

MEMS WIRELESS SENSOR NETWORKS FOR SPACECRAFT AND VACUUM TECHNOLOGY

by

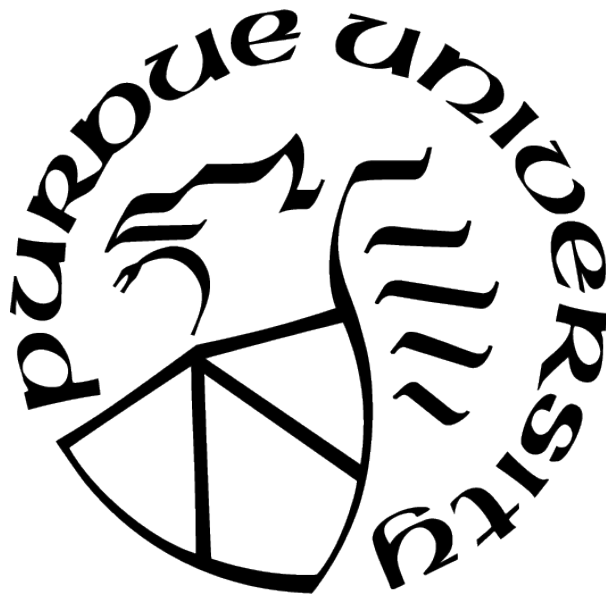
Andrew Strongrich

A Dissertation

Submitted to the Faculty of Purdue University

In Partial Fulfillment of the Requirements for the degree of

Doctor of Philosophy



School of Aeronautics and Astronautics

West Lafayette, Indiana

May 2021

**THE PURDUE UNIVERSITY GRADUATE SCHOOL
STATEMENT OF COMMITTEE APPROVAL**

Dr. Alina Alexeenko, Chair

School of Aeronautics and Astronautics

Dr. Sunil Bhawe

School of Electrical and Computer Engineering

Dr. Amy Marconnet

School of Mechanical Engineering

Dr. Steven Nail

Baxter BioPharma Solutions

Dr. Alexey Shashurin

School of Aeronautics and Astronautics

Approved by:

Dr. Gregory Blaisdell

ACKNOWLEDGMENTS

First and foremost, I would like to thank my advisor, Professor Alina Alexeenko, for her trust and support throughout my entire graduate career. She offered me the autonomy and freedom to explore wild ideas in her sandbox of labs, make a bunch of mistakes, and ultimately learn from them. This freedom was an invaluable part of my growth as an engineer, researcher, and mentor and I am eternally grateful to her for taking a chance on me. I am also grateful to the members of my committee for their open doors and for providing the feedback I needed to bring this work together.

I simply could not have achieved this goal without the help of those closest to me. Specifically, I would like to thank my parents for their unwavering patience, understanding, and sacrifice. They have stood behind me without question throughout my entire life and have always pushed me to swing for the fences, regardless of the challenge. I would also like to thank Arly Black for her endless support and encouragement throughout this journey. She was there for me every step of the way from the very beginning and I will be forever in her debt for all she has done. Dr. Tony Cofer is one of the most brilliant minds (both in depth and breadth) I've ever met. He was an incredible inspiration to me and his mentorship during my undergraduate career played a huge role in my decision to attend graduate school. He taught me more about what it means to be an engineer than any textbook ever has. I'd also like to thank Rishabh Tukra for his friendship and allowing me to bombard him with questions on all things pharmaceuticals. Finally, I would like to express my gratitude to those at Birck Nanotechnology Center for their assistance with our lab as well as all of the individuals associated with the Advanced Lyophilization Technology Hub (LyoHub).

TABLE OF CONTENTS

LIST OF TABLES	9
LIST OF FIGURES	11
LIST OF SYMBOLS	18
ABBREVIATIONS	20
ABSTRACT	21
1 INTRODUCTION	22
1.1 Motivation	24
1.2 Application of WSNs to Vacuum Technology	26
1.3 Application of WSNs to Aerospace	28
1.4 Objectives of the Thesis	29
2 THE LYOPHILIZATION PROCESS	31
2.1 Lyophilization Process Overview	32
2.1.1 Freezing	32
Ice Nucleation	32
2.1.2 Primary Drying	35
2.1.3 Secondary Drying	36
2.2 Configuration of a Modern Lyophilizer	37
2.3 Motivation	38
2.3.1 Applications of WSNs to Primary Drying	39
2.3.2 Applications of WSNs to Controlled Ice Nucleation	41
3 WIRELESS VACUUM AND TEMPERATURE SENSORS FOR LYOPHILIZA- TION PROCESS MONITORING	43
3.1 Wireless Sensor Design	44
3.1.1 Front End Design	50

	Signal Processing	51
	Power Conditioning	53
3.1.2	Sensor Packaging	53
3.2	Wireless Micro-Pirani Sensor Calibration	54
3.2.1	Temperature Calibration	55
	Materials and Methods	55
	Thermal Characterization Results	57
3.2.2	Pressure Calibration	59
	Materials and Methods	59
	Calibration Results	65
	Process Gas Composition Validation	65
3.2.3	Wireless MicroPirani Calibration Validation	71
3.3	Wireless MicroPirani Performance Characterization	71
3.3.1	Bridge Sensitivity Analysis	77
3.4	Gas Pressure Temperature Distribution Within Lyophilizer During Primary Drying	78
3.4.1	Materials and Methods	79
3.4.2	Pressure and Temperature Variation Within Vial Pack During Primary Drying	82
	Effect of Shelf Temperature	87
	Effect of Chamber Pressure	89
	Effect of Excipient	91
	Effect of Lyophilizer Configuration	93
3.5	Sublimation Rate and Product State Estimation During Primary Drying . .	96
3.5.1	Heat and Mass Transfer Model	96
3.5.2	Lyophilization Process Modeling Using Computational Fluid Dynamics	101
	Grid Convergence Study	104
	CFD Simulation Results	104
	Sublimation Rate Estimation Procedure	104
3.5.3	Heat and Mass Transfer Characterization	113

	Vial Heat Transfer Coefficient	113
	Product Mass Transfer Resistance	113
3.5.4	Product Temperature Estimation	114
3.5.5	Analytical Model to Estimate Local Sublimation Rate Based on Measured Gas Pressure and Temperature	116
	Governing Equations	116
	Boundary Conditions	119
	Solution of Inverse Problem	121
	Model Validation Using Computational Fluid Dynamics	124
	Grid Convergence	125
	Comparison to Flow Model to CFD Solution	126
	Flow Matching Validation	128
	Comparison to 3-dimensional CFD Model	134
	Non-Uniform Sublimation Rate	134
	Application to Experimental Measurements	136
4	WIRELESS PRESSURE AND TEMPERATURE SENSORS FOR THE CHARACTERIZATION OF RAPID DEPRESSURIZATION ICE NUCLEATION	138
4.1	Sensor Design	138
4.1.1	Signal Processing	142
4.1.2	Depressurization Modeling	143
	Supersonic Flow	145
	Subsonic Compressible Flow	146
4.2	Experimental Setup	150
4.2.1	Cycle Parameters	150
4.2.2	Sensor Measurement Verification	151
4.3	Results	153
4.3.1	Effect of Ballast Composition	153
4.3.2	Effect of Vial Type	160
4.3.3	Effect of Initial Discharge Pressure	162

4.4	Estimation of Gas Temperature During RD-CIN	166
4.4.1	Analytical Model Validation	170
4.4.2	2-Dimensional Finite Element Model Validation	172
4.4.3	Gas Temperature Estimation	176
5	APPLICATION OF WIRELESS SENSOR NETWORKS TO MICRONEWTON THRUST MEASUREMENT	180
5.1	Thruster Design	180
5.1.1	Signal Processing	182
5.2	Materials and Methods	184
5.3	Force Calibration	186
5.3.1	Estimation of Vacuum Chamber Volume	187
5.4	Results	189
5.4.1	Mass Flow Rate Estimate	189
5.5	System Modeling	192
5.5.1	Model Identification	192
	Estimation of System Parameters	193
5.5.2	State and Input Estimation Model	195
	PIO Model Validation	196
	Estimate of Transient Thrust Profile Using PIO Model	196
5.5.3	Thruster Performance	196
6	CONCLUSIONS	201
6.1	Outlook and Suggestions for Future Work	202
	REFERENCES	204
A	WIRELESS MICROPIRANI NOISE ANALYSIS	215
A.1	Forms of Electrical Noise	215
A.1.1	Noise Analysis of Bridge with Chopper-Stabilized Feedback	216

B	DERIVATION OF FINITE ROD MODEL WITH CONVECTIVE HEAT TRANS-	
FER		219

LIST OF TABLES

1.1	Comparison of common wireless sensor network communication protocols. . . .	25
1.2	Summary of wireless sensor technologies for lyophilization.	27
2.1	Comparison of common process monitoring methods used in pharmaceutical lyophilization.	38
3.1	Summary of measured bridge resistances for the WMP devices based on the schematic shown in Figure 3.2. All devices were designed for a nominal temperature offset of around 8°C. Sense and compensation filament measurements were taken at room temperature.	49
3.2	Power consumption estimates for WMP system.	53
3.3	Temperature coefficients of resistance for compensation filaments	59
3.4	Temperature coefficients of resistance for sense filament	59
3.5	Published mass-to-charge ratio and abundance values for nitrogen, water vapor, and oxygen [99].	69
3.6	Linear fit coefficients describing power dissipation as a function of pressure in the free-molecule regime.	75
3.7	Extracted (estimated) values of model parameters A , U_c , and ϵ , as determined by the least-squares minimization routine.	76
3.8	Summary of experiments performed using WMP devices. Cycle H was also used to investigate the influence of flow barriers. All temperature ramp rates are fixed at 1°C/min	80
3.9	Water vapor properties used in 3-dimensional CFD model	102
3.10	CFD sensitivity study conducted for 3D shelf domain	104
3.11	Results from 2-dimensional CFD grid convergence study for uniform and quadratic injection. The grid quality metric is the static pressure integrated over the injection boundary surface	125
3.12	Parameters used in CFD and 2-dimensional flow matching model.	126
3.13	Comparison of velocity profiles at different channel locations between the semi-analytical flow model and CFD results with and without boundary slip in terms of root-mean-square deviation	128
3.14	Comparison of flow matching accuracy when applied to “measured” data from CFD simulations.	131
4.1	Power consumption estimates for wireless RD-CIN system. Total estimated lifetime based on battery capacity is 86 hours.	142

4.2	Summary of RD-CIN experiments performed using wireless sensors. Indicated values are nominal.	151
4.3	Pressure calibration results for chamber (Device 2) and headspace (Device 1) devices.	152
4.4	Summary of parameters used in isentropic relations. The chamber volume to valve area ratio is applied as the fitting parameter to experimental data.	155
4.5	Entropy generated during the RD-CIN process based on the measured and estimated gas state prior to and following valve closure.	159
4.6	Summary of ice fog formation times for different initial charge pressures. No cloud was observed for a pressure of 10 psig.	165
4.7	Energy balance for each zone as indicated in Figure 4.17	171
4.8	Root-mean-square difference between the 2-dimensional axisymmetric finite difference model and analytical solution (Figure 4.18) at different instances of time for a uniform cylinder in crossflow	172
4.9	Parameters used during validation of 2-dimensional axisymmetric finite difference model.	173
4.10	Root-mean-square difference between 2-dimensional finite difference model and COMSOL finite element solution (Figure 4.19) at different instances of time for a thermocouple in crossflow	175
5.1	Estimated vacuum chamber volume from pressure-rise test.	188
5.2	Torsional balance model parameters derived from calibration	194
A.1	Johnson noise across bridge resistors	218
A.2	Noise at bridge amplifier inverting and non-inverting inputs.	218

LIST OF FIGURES

1.1	Wireless sensor network architecture. The sensor field is populated with nodes which are able to, in general, communicate with one another or to the gateway. The gateway consolidates the data and provides it to the user.	23
2.1	Lyophilization cycle displayed on water phase diagram. The sample is initially frozen to separate the solvent from the solute. Pressure is then reduced below the vapor pressure of the solvent to induce sublimation. Once the bulk material is removed the temperature is raised to promote desorption and further dehydration.	33
2.2	Illustration of lyophilization process from liquid fill to secondary drying.	33
2.3	Example of cake collapse (left), partial collapse (middle), and an acceptable cake with no collapse (right). Images taken from Patel et al. [63]	36
2.4	Schematic of typical lyophilization unit. The system is composed of process and condenser chambers connected by a duct. Solvent vapor sublimates and frosts on the condenser. The non-condensed ballast gas continues into the vacuum pump where it is removed and discharged to the atmosphere.	37
3.1	Schematic of Pirani gauge operation. The metal filament is enclosed inside of a chamber and is heated using electrical current. The heat dissipated by the filament depends on gas pressure, temperature, and composition.	43
3.2	Circuit used for constant-temperature operation. The operational amplifier ensures changes in the compensation filament resistance is reflected in the sensing element. Increasing gas temperature causes filament temperature to increase by an equal amount.	45
3.3	Schematic of typical MEMS Pirani gauge. The device contains both sense and compensation filaments to resolve ambient pressure over a range of gas temperatures. The sense filament is located on a thin diaphragm having low thermal resistance to the ambient gas.	46
3.4	Analog front end for wireless microPirani sensor.	50
3.5	Schematic of WSN topology used for the WMP devices. The sensor nodes are paired to a hub outside of the vacuum chamber which pushes all broadcasts to a central host. The host is responsible for unpacking data, displaying it to the user, and logging to a file.	52
3.6	Image of disassembled WMP sensor showing various internal components and 3D-printed housing.	54
3.7	Schematic of wireless thermoelectric controller setup used to maintain ambient temperature at a constant value during TCR characterization. The RTD was cemented directly to the housing of Pirani gauge on the DUT.	56

3.8	Image of the calibration setup used to compute filament TCR. The wireless thermoelectric controller receives setpoint information from an external host. The temperature of the Pirani gauge package (Vac03k) is monitored by the Pt1000 RTD (hidden).	57
3.9	Measured and fitted temperature coefficient of resistance data for sensing and compensating filaments on WMP1. The TCRs for both exhibit linear behavior over the measured temperature range.	58
3.10	Schematic of water vapor calibration apparatus. Water ice was frozen in a reservoir on a thermoelectric cold plate. The sublimed vapor was fed into the lyophilizer using a stepper motor-driven gate valve. The capacitance manometer on the lyophilizer provided the necessary feedback for pressure control.	60
3.11	Images of apparatus used to calibrate wireless microPirani devices.	61
3.12	Controller box electronics. The stepper motor driver circuitry is used for water vapor calibration and the proportional valve for non-condensable gas.	62
3.13	Machined aluminum choking plug used to restrict vapor flow through the lyophilizer during wireless microPirani calibration. The plug insert is 3D-printed to allow the effective duct diameter to be changed if larger pressure magnitudes are desired.	63
3.14	Aluminum fixture used for device calibration. Pirani and RTD filaments were fastened to ensure good thermal coupling. Fixture temperature was monitored using two T-type thermocouples. Thermal paste was applied to the thermocouples to ensure effective coupling	64
3.15	Calibration data for WMP1. Raw bridge outputs on the left axes are calibrated to chamber pressure and fixture temperatures on the right axes.	66
3.16	Calibration surface for WMP1. Arbitrary voltage measurements across the sense and compensation filaments may be interpolated to determine chamber pressure and ambient temperature.	67
3.17	Transpector Compact Process Monitor Residual Gas Analyzer (RGA) mounted to the upper surface of the process chamber. The RGA is able to measure process gas composition in real time, allowing water vapor purity to be quantified during the calibration process.	68
3.18	Raw RGA data from wireless microPirani calibration procedure. Several mass-to-charge ratios are shown.	70
3.19	Hexagonal sensor arrangement in vial pack during calibration validation experiment	71
3.20	Process data from calibration validation experiment. Sensors are arranged as indicated in Figure 3.19. The maximum difference among sensors during primary drying is approximately 0.4 mTorr.	72

3.21	Dissipated power from Pirani filament over a range of chamber pressures for ambient temperatures of 20C and -20C. A linear dependence on pressure is exhibited below 10 mTorr, indicating free-molecule behavior.	74
3.22	Variation in temperature offset between the Pirani filament and RTD during the power dissipation measurements. Peak-to-peak variations relative to the mean for 20C and -20C are 0.0098% and 0.011%, respectively.	74
3.23	Experimentally measured gaseous heat transfer coefficient for sense filament. Solid-state conduction and radiation contributions are eliminated using the least-squares minimization approach.	76
3.24	Sensitivity of compensation filament to changes in gas pressure and temperature offset. The chosen WMP sensitivity at an offset of 8°C is indicated by the solid line. Sensitivity is highest at low pressures and decreases monotonically as the gas enters the transitional rarefied regime.	79
3.25	Image and schematic of WMP sensor and thermocouple locations within vial pack.	81
3.26	Process data from cycle H in Table 3.8. Pressure data are indicated by solid lines and temperature by dashed. The indicated pressure is assumed absolute over the duration of primary drying (approximately 8-17 hours)	83
3.27	Surface and contour plots of measured pressure around 3 hours after the start of primary drying using cycle H.	85
3.28	Surface and contour plots of measured temperature around 3 hours after the start of primary drying using cycle H.	86
3.29	Effect of shelf temperature on a) gas pressure and b) temperature during primary drying using cycle H. Increasing shelf temperature increases sublimation rate which leads to a larger pressure drop from center to edge.	88
3.30	Effect of chamber pressure on a) gas pressure and b) temperature during primary drying using cycle H. Pressure data is expressed in terms of gauge pressure relative to the chamber to facilitate direct comparison. Increasing chamber pressure results in a decrease in pressure drop from center to edge due to the increase in density.	90
3.31	Effect of excipient on a) gas pressure and b) temperature during primary drying using cycle H. The excipient has a significant impact on sublimation rate due to the effects of pore size and microcollapse.	92
3.32	Surface and contour plots of measured pressure around 3 hours after the start of primary drying using cycle H with flow barriers.	94
3.33	Surface and contour plots of measured temperature around 3 hours after the start of primary drying using cycle H with flow barriers.	95

3.34	Effect of lyophilization chamber configuration (sidewalls) on a) gas pressure and b) temperature during primary drying using cycle H. The sidewalls prevent flow from exiting the shelf in its transverse direction and therefore produces a pressure drop 2.6 times greater from center to edge. The flow barriers have little influence on overall drying rate as indicated by nearly identical drying times.	97
3.35	Vial energy balance. Energy is provided to the cake via solid conduction, gaseous conduction, and radiation to offset the energy lost through sublimation.	98
3.36	Isometric (top) and top (bottom) views of domain used for CFD simulations. Pressure outlet, wall, and velocity inlet conditions are labeled in blue, green, and red, respectively.	103
3.37	Root mean-square error determined from pressure matching procedure for cycle H at an elapsed time of 11 hours.	105
3.38	Pathlines of sublimed vapor during primary drying of 5% w/v mannitol at 100 mTorr and 10°C (cycle H in Table 3.8) colored in terms of static (gauge) pressure	106
3.39	Pathlines of sublimed vapor during primary drying of 5% w/v mannitol at 100 mTorr and 10°C (cycle H in Table 3.8) colored in terms of speed	107
3.40	Comparison of pressure profile predicted using CFD and that which was measured during cycle H at an elapsed time of 11 hours.	109
3.41	Pathlines of sublimed vapor during primary drying of 5% w/v mannitol using cycle H with flow barriers. Pathlines are colored in terms of static (gauge) pressure	110
3.42	Pathlines of sublimed vapor during primary drying of 5% w/v mannitol using cycle H with flow barriers. Pathlines are colored in terms of flow speed	111
3.43	Comparison of pressure profile predicted using CFD and that which was measured during cycle H at an elapsed time of 11 hours using flow barriers.	112
3.44	Process data for cycle H in Table 3.8 showing predicted product temperature based on sublimation rate estimation procedure	115
3.45	Schematics of physical system (top) and idealized (bottom) flow model. Water vapor is injected into domain at southern boundary. The vial top surface is modeled as a porous wall with piecewise continuous injection profile.	117
3.46	Schematic of lyophilizer flow model. Water vapor is injected into domain at southern boundary.	121
3.47	Schematic of domain used for all CFD simulations	124
3.48	Contours of flow speed from CFD solution. Stream traces are shown in black emanating from lower boundary of simulation domain.	126
3.49	Contours of static pressure from CFD solution. Results indicate minimal pressure variation in the transverse direction.	127

3.50	Comparison of nondimensional axial and transverse velocity profiles for model and CFD solutions. Both slip and no-slip boundary condition results are provided for the CFD simulations.	129
3.51	Comparison of pressure profiles between model and CFD for uniform inlet velocity of 3 [m/s] and base pressure of 100 mTorr. The inclusion of slip boundary conditions reduces the pressure gradient from center to edge due to the reduction in shear stress magnitude at the wall.	130
3.52	Convergence history of static pressure and inlet velocity for $v_{sim}(\xi) = 3.5 + 10 \operatorname{erf}(\xi - 0.8)$	132
3.53	Converged solution for injection profile of the form $v_{sim}(\xi) = 3.0 + \xi^2$	133
3.54	Converged solution for injection profile of the form $v_{sim}(\xi) = 1.5 + 1.5 \sin(12\pi\xi)$	133
3.55	Pressure and corresponding sublimation flux estimate from flow matching procedure on CFD.	135
3.56	Pressure and corresponding sublimation flux estimate from flow matching procedure on cycle H in Table 3.8 using flow barriers. The total matched sublimation rate has a deviation of 19% relative to the gravimetric measurement. The difference is most likely due to the assumption of no-slip conditions at the solid boundaries as well as the measurement uncertainty intrinsic to the devices.	137
4.1	Electrical schematic of RD-CIN sensors.	139
4.2	Image and schematic of vial headspace pressure and temperature sensor used to monitor the RD-CIN process. The pressure sensor and thermocouple are inserted into the headspace through two holes drilled into the vial barrel.	140
4.3	Image and schematic of chamber pressure and temperature sensor used to monitor the RD-CIN process.	141
4.4	Schematic of software architecture for wireless controlled nucleation pressure and temperature sensor network. Data is collected by the central via the BLE link. The real-time stream is pushed to the host over the UART bus where it is processed, logged, and displayed to the user.	143
4.5	Schematic of the adiabatic decompression model domain.	144
4.6	Theoretical gas pressure and temperature during RD-CIN for different ballast compositions using isentropic model	148
4.7	Theoretical gas pressure and temperature during RD-CIN for different ballast compositions using isentropic model	149
4.8	Effect of ballast gas composition on RD-CIN response	154
4.9	Comparison of measured and theoretical gas pressure and temperature in chamber during RD-CIN using nitrogen ballast.	156

4.10	Comparison of measured and theoretical gas pressure and temperature in chamber during RD-CIN using argon ballast.	156
4.11	Comparison of measured and theoretical gas pressure and temperature in chamber during RD-CIN using helium ballast.	157
4.12	Effect of ballast gas composition on vial headspace pressure and temperature response during RD-CIN	161
4.13	Effect of vial size on RD-CIN response using nitrogen ballast	163
4.14	Effect of vial size on RD-CIN response using helium ballast	164
4.15	Effect of initial charge pressure on RD-CIN response	167
4.16	Computational domain (not to scale) for the axisymmetric thermocouple finite difference model.	168
4.17	Zone map used to construct energy balance for 2-dimensional thermocouple finite difference domain. Zone equations are provided in Table 4.7	170
4.18	Comparison between finite difference model and analytical solution at various times for thin rod shown in Figure B.1. Maximum root-mean square error is 1.9% and occurs 250ms.	173
4.19	Comparison between finite difference model and COMSOL solution at various times along the line of axisymmetry. Maximum root-mean square error is 2.2% and occurs 1s.	174
4.20	Estimate of true gas temperature during decompression using nitrogen ballast. .	177
4.21	Estimate of true gas temperature during decompression using argon ballast. . .	178
4.22	Estimate of true gas temperature during decompression using helium ballast. . .	178
5.1	Cross-sectional schematic of milliNewton evaporation thruster. Liquid water evaporates from the membrane and exits the nozzle to produce thrust	181
5.2	Image of assembled (bottom right) and exploded (top left) evaporation thruster. The device is controlled by an wireless transceiver module (not shown) that communicates with the host over a BLE link.	181
5.3	Electrical schematic of evaporation thruster.	183
5.4	Image of thrust stand with evaporation thruster installed. The response in terms of displacement is measured by the LVDT and correlated to applied force using a gravimetric calibration.	185
5.5	Schematic of microNewton torsional balance. The thruster induces a rotational displacement which is detected by a Linear Variable Differential Transformer (LVDT). Displacement is directly correlated to thrust using the calibrated spring stiffness.	185

5.6	MicroNewton torsional balance calibration data. The thrust stand displacement is highly linear with applied force.	187
5.7	Raw chamber pressure, chamber wall temperature, and torsional balance displacement following valve actuation using an orifice nozzle.	190
5.8	Comparison of measured and PIO-estimated displacement and electrostatic actuation force during calibration.	197
5.9	Comparison of estimated and measured thrust and torsional balance displacement using the PIO state model.	198
A.1	Schematic of bridge, filter, and follower network used for noise estimate of WMP device.	217
B.1	Schematic of analytical model domain. A thin rod of diameter D and length $2L$ and uniform temperature, T_0 , suddenly has its ends raised to temperature T_1 . Convective cooling is applied over the length of the rod for constant fluid temperature T_0	219

LIST OF SYMBOLS

α	Temperature Coefficient of Resistance <i>or</i> Thermal Diffusivity
A	Cross-Sectional Area
Bi	Biot Number
c	Aerodynamic Damping Coefficient
C_p	Specific Heat Capacity
D	Diameter
e	Velocity Profile Shaping Parameter
ϵ	Spectral Emissivity
F	Thrust
γ	Heat Capacity Ratio
h	Convective Heat Transfer Coefficient
H_{sub}	Latent Heat of Sublimation
I	Moment of Inertia
I_{sp}	Specific Impulse
J	Penalty Function
k	Spring Stiffness <i>or</i> Thermal Conductivity
k_B	Boltzmann Constant
K_v	Vial Heat Transfer Coefficient
Kn	Knudsen Number
λ	Molecular Mean-Free Path
L, l	Length
M	Mach Number
m	Molecular Mass
$\dot{m}$	Mass Flow Rate
μ	Dynamic Viscosity
Nu	Nusselt Number
Pr	Prandtl Number
p	Pressure

ψ	Stream Function
ρ	Density
r	Radial Distance
R	Electrical Resistance <i>or</i> Specific Gas Constant
Re	Reynolds Number
σ	Stefan-Boltzmann Constant <i>or</i> root-mean-square deviation
θ	Angular Displacement
T	Temperature
U	Conduction Heat Transfer Coefficient
u,v	Flow Velocities
V	Electrical Potential <i>or</i> Volume

ABBREVIATIONS

ADC	Analog-to-Digital Converter
BFGS	Broyden-Fletcher-Goldfarb-Shanno
BLE	Bluetooth Low-Energy
CFD	Computational Fluid Dynamics
CIN	Controlled Ice Nucleation
DUT	Device Under Test
LVDT	Linear Variable Differential Transformer
LR-WPAN	Low-Rate Wireless Personal Area Network
MCU	Microcontroller Unit
MEMS	Microelectromechanical System
PIO	Proportional-Integral Observer
RD-CIN	Rapid Depressurization Controlled Ice Nucleation
RGA	Residual Gas Analyzer
RMSE	Root-Mean-Square Error
RTD	Resistance Temperature Detector
SPI	Serial Peripheral Interface
TC	Thermocouple
TCR	Temperature Coefficient of Resistance
TWI	Two-Wire Interface
UART	Universal Asynchronous Receiver/Transmitter
UPW	Ultra-Pure Water
WMP	Wireless MicroPirani
WSN	Wireless Sensor Network

ABSTRACT

Wireless sensor networks are highly integrated across numerous industries from industrial manufacturing to personal health monitoring. They provide several key benefits over traditional wired systems including positioning flexibility, modularity, interconnectivity, and robust data routing schemes. However, their adoption into certain sectors such as vacuum and aerospace has been slow due to tight regulation, data security concerns, and device reliability.

Lyophilization is a desiccation technique used to stabilize sensitive food and drug products using vacuum sublimation. A series of wireless devices based on the Pirani architecture are developed to quantify the spatial variations in pressure and temperature throughout this process. The data is coupled to computational fluid dynamics simulations to estimate the sublimation rate over time. This information is then used to quantify the heat and mass transfer characteristics of the product, allowing estimates of product temperature and mass flux to be obtained for an arbitrary cycle. This capability is significant, having the ability to accelerate process development and reduce manufacturing time.

Drying performance during lyophilization is highly sensitive to the dynamics of the freezing process. This work therefore also develops a wireless network to monitor both gas pressure and temperature throughout the controlled ice nucleation process, a technique used to improve batch uniformity by inducing simultaneous and widespread ice nucleation via adiabatic decompression. The effects of initial charge pressure, ballast composition, and vial size are investigated. Experimental data is supported by numerical modeling to describe the evolution of the true gas temperature during the discharge event.

Finally, The mechanisms governing the lyophilization process are directly applied to the aerospace industry in the form of a novel milliNewton-class evaporation-based thruster concept. The device was tested under vacuum using a torsional balance and demonstrated peak thrust magnitudes on the order of 0.5 mN. A state observer model was then implemented to decouple the dynamics of the balance with the time-dependent thrust input. With this model the true time-dependent thrust output and corresponding thruster performance are analyzed.

1. INTRODUCTION

Over the last decade, Wireless Sensor Networks (WSNs) have become prolific in a broad range of applications. Tracing their origin to the Cold War, WSNs were first conceived under the U.S. Navy’s Sound Surveillance System (SOSUS) program to passively monitor coastal waters for signs of Soviet submarines[1]. Following their emergence, the development of innovative and low-cost microelectromechanical systems (MEMS), robust and secure wireless communication protocols, refinement of low-power digital electronics, and enhanced analytics have led to the rapid expansion of WSNs into the civilian domain. Today, WSNs have revolutionized the way people interact with the world.

The global WSN market is upwards of \$8 billion, growing at a rate around 27% annually[2]. Around 48% of the \$2 billion share in the Americas is captured by the home automation and smart buildings sector[3]. Common sensing tasks in this application include temperature, humidity, air quality (e.g. smoke and volatile organic compounds), energy, and security and access monitoring[4]. Other dominant sectors in order of market share include energy infrastructure, personal augmentation and health monitoring [5], [6], logistics and transport, ecology and agriculture, defense and surveillance, and industrial automation and process control[7]. Although it currently only captures 6% of the total market, ecology and agriculture is the fastest growing sector with a forecast annual rate of 14%[3]. Expansion in this domain has been driven primarily by the emergence of wireless protocols specifically designed for long-range (in the order of a few miles) communication, increased demands on food production and yield, and a heightened climate change awareness[8]–[11].

WSNs are comprised of a series of discrete, low-power, collaborative nodes that perform one or several sensing and/or actuation tasks in the physical world, manipulate and package data using simple computations, and relay the processed information to a nearby node or gateway via wireless broadcast. In general, nodes are equipped with their own sensor(s), actuator(s), radio, processor, memory, and power source in the form of a battery or energy harvesting system [12]. Common measurement applications include position, temperature, flow, level, imaging, chemical detection, pressure, and humidity[3]. The gateway has greater throughput and transmission performance (along with higher power consumption) than the

nodes and is responsible for packaging data and relaying it to the end user(s). Additionally, one or more nodes may be equipped with higher power transmission capabilities, allowing them to serve as local sinks for nearby devices. Many of the standard wireless protocols now include IP addressing capabilities, enabling convenient access to sensor information from anywhere in the world. In many cases the network is bi-directional, enabling the user to provide input that is subsequently propagated outward to the sensor field. This basic architecture of a WSN is outlined in Figure 1.1.

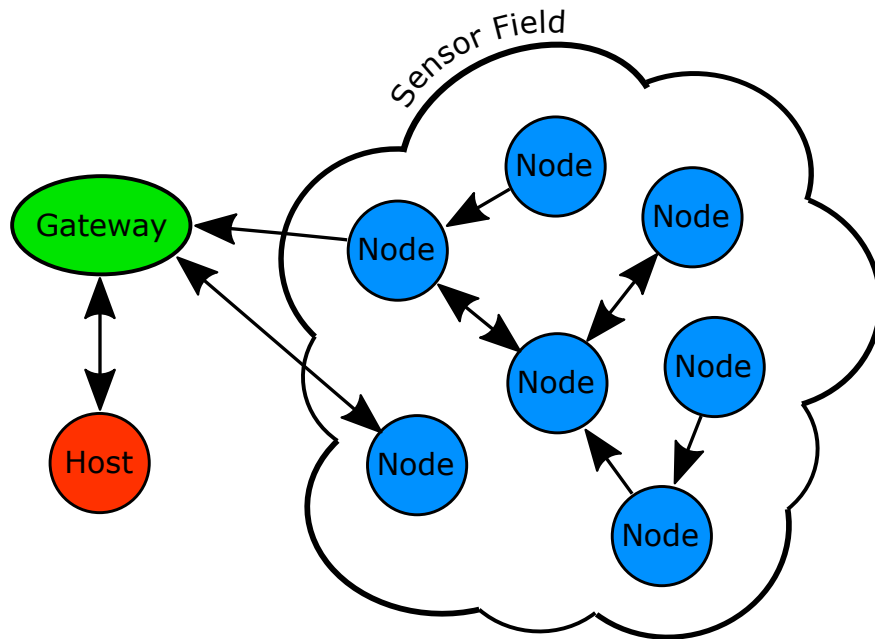


Figure 1.1. Wireless sensor network architecture. The sensor field is populated with nodes which are able to, in general, communicate with one another or to the gateway. The gateway consolidates the data and provides it to the user.

The nodes may be cast in either a structured or unstructured arrangement depending on the application's constraints. In a structured network, nodes are positioned in a pre-planned manner. This generally requires fewer sensors and less complicated data routing schemes. However, it is often limited in its flexibility. The unstructured or ad-hoc network is more complicated from a logistical standpoint but is more robust and better able to respond to events such as node additions (or failures), unplanned sensor movements, or congested communications[12].

Many of the common WSN communication protocols have been developed under the IEEE 802.15.4 standard for Low-Rate Wireless Personal Area Networks (LR-WPANs) [13]. This architecture specifies the configuration of the physical and data-link (specifically the MAC sublayer) layers and is optimized for low-power and low-throughput devices. Each protocol is defined by unique cross-layer interactions in the application, transport, and network layers, all three of which are unspecified under 802.15.4. Common examples of LR-WPANs based on 802.15.4 include 6LoWPAN, Wireless HART (Highway Addressable Remote Transducer), ISA100.11a, and ZigBee [12], [14].

Bluetooth Low Energy (BLE) is another popular WSN standard that emerged in response to the performance and success of other LR-WPAN protocols. BLE is largely based on the standard Bluetooth architecture but sacrifices throughput for improved power efficiency. BLE is defined and operated under the Bluetooth SIG standard. The IEEE 802.15.3 standard is similar 802.15.4 but is targeted towards high throughput applications using ultra wideband-compatible physical and data-link layers. Amendments have also been made in the realm of WiFi devices (IEEE 802.11ah) to support extended range networks while having power characteristics similar to that of standard Bluetooth. Other protocols such as ANT/ANT+, Z-Wave, Thread, LoRA/LoRAWAN, and DASH7 are proprietary and do not adhere to any regulated standards. The choice of protocol is application-specific, each having unique advantages in the realms of power consumption, node arrangement, transmission architecture, compatibility, payload capacity, range, and throughput. A summary of the characteristics associated with several common protocols is provided in Table 1.1.

1.1 Motivation

Despite numerous advantages, the adoption of WSN technology by the pharmaceutical manufacturing and aerospace sectors has been slow. The lack of penetration into these high-risk environments is largely due to concerns related to energy efficiency, interference and reliability, security, and data management[15]. Wired communication remains unparalleled in simplicity, reliability, and security. However, the increasing robustness sophistication of

Table 1.1. Comparison of common wireless sensor network communication protocols.

Protocol	Standard	Range	Throughput	Applications
Bluetooth Low Energy	Bluetooth SIG (2.45 GHz)	100 m	≈ 1 Mbps	Home Automation, Fitness/Health Monitoring, Localization, HID
6LoWPAN	802.15.4 (2.4 GHz)	100 m	250 kbps	Home Automation
Thread	802.15.4 (2.4 GHz)	100 m	100 kbps	Home Automation
ZigBee	802.15.4 (2.4 GHz/915 MHz)	100 m	250 kbps	Home Automation and Health Monitoring
Wireless HART	802.15.4 (2.4 GHz)	100 m	100 kbps	Industrial Process Monitoring/Automation
ISA100.11a	802.15.4 (2.4 GHz)	100 m	100 kbps	Industrial Process Monitoring/Automation
Z-Wave	Proprietary (908 MHz)	100 m	100 kbps	Home Automation
ANT/ANT+	Proprietary (2.45 GHz)	100 m	12.8 kbps	Fitness/Health Monitoring
LoRA	Proprietary (915 MHz)	2-15 km	100 kbps	Smart Cities, Agriculture, Logistics
DASH7	Proprietary (433 MHz)	5-10 km	200 kbps	Smart Cities, Logistics, Localization

wireless protocols is beginning to make them viable options as redundant systems or as a non-critical supplement to existing sensor networks.

1.2 Application of WSNs to Vacuum Technology

One of the key limitations of the current state-of-the-art in vacuum technology and measurement is accessibility. Most vacuum processing equipment and sensors are flange-mounted at the chamber wall and therefore limited in terms of their location. In dynamic low-pressure applications (i.e. flowing vapor), the highly viscous nature of these flows can lead to significant measurement uncertainty when data is taken far from the physical process.

Lyophilization, also known as freeze-drying, is one industrial vacuum process that will benefit significantly from the introduction of WSNs. Freeze-drying is a key unit operation in both the pharmaceutical and food manufacturing that is used to stabilize perishable goods using vacuum sublimation. The former focuses principally on product quality whereas the latter strives for volume or throughput. In either case, accurate determination of product state is critical to optimizing the process. Wireless devices are nearly unconstrained in terms of their placement, allowing measurements to be performed directly at the product location. This feature reduces uncertainty which ultimately enables faster processing times, better models, and improved efficiency or throughput. A handful of wireless sensors are currently available for lyophilization process monitoring. A summary of these technologies is presented in Table 1.2.

Most of the listed devices are targeted towards product temperature measurement as this is one of the most critical process variables. Although the ability to sample the temperature is desirable, measurement validity in this case is questionable due to the effect of parasitic heating on the samples. In principle, the local gas pressure and temperature can be used to infer the temperature, however no device is currently available to perform the quantitative measurements. Although seemingly worlds apart from the aerospace domain, lyophilization is performed under a combination of low pressures and low temperatures, making it a suitable analog when considering spacecraft operating environments.

Table 1.2. Summary of wireless sensor technologies for lyophilization.

Device	Frequency	Interval	Measurement Type
Tempris[16]	Proprietary	1 - 600 s	Product Temperature
WTMPlus[17]	2.4 GHz	-	Product Temperature
Ellab TrackSense[18]	Data Logger or 2.4 GHz	1s - 24hr	Product Temperature
Ellab TrackSense[18]	Data Logger or 2.4 GHz	1s - 24hr	Pressure (Gas-Dependent)
Wireless Multipoint 1[19]	2.4 GHz	5ms - 5s	Product Temperature
Wireless Multipoint 2[20]	2.4 GHz	5ms - 5s	Vial Temperature

1.3 Application of WSNs to Aerospace

The combined low weight, absence of wired connection, and remote locating potential of wireless sensors make WSNs a highly attractive alternative to conventional wired sensor arrays in aerospace applications. For instance, modern aircraft such as the Boeing 787 contain over 500 km of wiring, a 350% increase from a Boeing 767 in 1984. Integrating WSNs to these modern systems has the capability of shedding an estimated 1800 kg, roughly the weight of two dozen passengers [21]. The applications for wireless sensors in aircraft are widespread and range from cabin environment to fuel and hydraulic line pressure monitoring. Benefits of this weight reduction come in the form of increased passenger capacity, lower fuel consumption, and improved reliability.

WSNs will offer several advantages to future space applications including monitoring of astronaut biotelemetry, launch site propellant storage systems, inflatable habitats, large-scale experiments, and micrometeorite impact detection [15]. Current launch costs range from \$1k-30k per pound (depending on the provider), making even modest reductions in inert mass a high priority [22]. The benefits of WSNs will also be felt at the opposite end of the spectrum in the realm of thrust measurement and characterization for small-satellite propulsion systems[23]. The rise in small satellite technology has placed demands on the propulsion community to develop thrusters capable of generating small quantities of thrust (between 0.001mN to 1mN) for attitude control and deorbiting. Current micropropulsion concepts commonly rely on pressurized gas, liquid monopropellants, or ionized particles to generate thrust [24].

Measuring thruster performance at these small magnitudes requires a highly sensitive force balance. One recurring problem with testing thrusters on these devices is the error induced by the mechanical potential energy stored in electrical wires or propellant lines that interface with the thruster element. WSNs are able to mitigate these errors as all electrical hardware may be located on the thruster itself. Propellant storage, plumbing, and valving may also be stored directly on the thrust stand, completely decoupling the system from the support structure and eliminating unwanted displacement drift.

1.4 Objectives of the Thesis

The goal of this work is to integrate wireless MEMS sensor networks into low-pressure and low-temperature environments to describe the physical flow processes encountered in many vacuum and spacecraft applications. This goal will be accomplished through three discrete objectives.

The first objective is to design, calibrate, and integrate wireless microPirani sensors into the lyophilization process to measure the spatial variations of gas pressure and temperature throughout the lyophilizer during the primary drying (bulk sublimation) phase. The influence of chamber pressure, shelf temperature, formulation composition, and lyophilizer configuration are explored independently. The data are coupled to computational fluid dynamics simulations to predict the sublimation rate of water at several discrete points in time. This information, in turn, is used to extract heat and mass transfer parameters that are critical to product state monitoring and cycle optimization.

The drying performance of pharmaceutical products is highly sensitive to the dynamics of the freezing event. However, the freezing process is stochastic and can lead to significant variability in drying performance across the batch. The ice nucleation event can be induced using several commercially available methods, one of which relies on the rapid (adiabatic) depressurization of the gas surrounding a supercooled formulation. Under suitable conditions, the water vapor becomes saturated and condenses out of the gas where it is immediately frozen to form ice crystals. It is believed that these ice crystals contact the surface of the metastable formulation and serve as the primary nucleation mechanism. The second objective is therefore to develop a series of wireless devices to better understand the adiabatic depressurization by measuring the pressure and temperature of the gas throughout the process. The influence of the gas composition, initial charge pressure, and vial size on these process variables are investigated. Measured data are compared to isentropic theory and an inverse parameter estimation model is derived to estimate the true gas temperature.

Finally, many of the principles that govern the lyophilization process are identical to those found in aerospace propulsion applications. To illustrate these similarities, a third objective is pursued whereby a wireless evaporation thruster for microsatellite propulsion systems

is designed, fabricated, and tested. The device relies on the evaporation of water from a paper membrane inside of a plenum chamber and subsequent expansion through an orifice to produce thrust. The performance of the device in terms of thrust output and specific impulse is quantified through a combination of experimental measurements and numerical modeling.

2. THE LYOPHILIZATION PROCESS

Lyophilization, commonly referred to as freeze-drying, is a method of preserving perishable products or materials using sublimation. This desiccation method is one of the key unit operations in pharmaceutical manufacturing and is widely used for the stabilization of vaccines, proteins/peptides, or other injectables (e.g. small-molecule drugs)[25]. More recently, the scope has expanded to include orally disintegrating tablets[26], gene therapies[27], and biological standards[28].

Freeze-drying dates back to the time of the ancient Incan civilization who applied identical principles to the production of chuño. The villagers carried freshly harvested potatoes high into the Andes Mountains to freeze in the cool night air. During the day they were covered with straw to increase the temperature without direct exposure to the sunlight. The elevated temperature increases the vapor pressure of the ice to a level above that of the dry atmosphere at the high altitudes, leading to sublimation. The method is so effective that it is still practiced to this day [29], [30].

The modern era of lyophilization using purpose-built equipment began in the 1890's. Richard Altmann demonstrated the capability of drying biological products under application of sub-freezing temperatures and mild vacuum [31]. The benefits of this technique were not immediately apparent to the scientific community and over a decade passed until its preserving qualities were evaluated by L.F. Shackell [32]. Similar to Altmann, Shackell's system employed a mechanical pump to generate vacuum within a process chamber. The sublimed vapor passed through a duct into a second chamber which was filled with concentrated sulfuric acid. Sulfuric acid is naturally hygroscopic and has a vapor pressure of around 1 mTorr at room temperature. In this configuration, the water vapor is removed from the low-pressure gas and the liquid acid solution is able to exist without boiling. After passing the sulfuric acid bath the dried air entered the vacuum pump where it was evacuated from the system. Shackell demonstrated renewed biological activity of the dried specimens after re-introduction of water.

The true utility of lyophilization on a large commercial scale not fully realized until World War II, at which time the technique was applied to the preservation of blood plasma, plasma

supplements, and therapeutic agents [33]. Freeze-drying these life-saving treatments was shown to greatly improve stability, shelf-life, and portability, making them easily deployable to the front lines of the battlefield. Following the war, attention slowly shifted from food and blood preservation to pharmaceutical manufacturing. In the 1970’s, research efforts focused on heat transfer modeling and a critical product temperatures to better understand drying dynamics and improve yield. The 1980’s saw a shift towards process monitoring hardware and drying of blood derivatives. The 1990’s brought economic studies on lyophilized pharmaceuticals as well as advances in product formulation. Today, attention has turned to the development of “current Good Manufacturing Practices” (cGMP), closed-loop processing techniques, enhanced Process Analytical Technologies (PATs), and continuous manufacturing [34].

2.1 Lyophilization Process Overview

A typical lyophilization or freeze-drying cycle consists of three principal stages: freezing, primary drying, and secondary drying. The physical process is outlined in Figures 2.1 and 2.2.

2.1.1 Freezing

The lyophilization process begins by first filling the liquid formulation into vials at room temperature (point 1). The product is then frozen either on the shelves of the lyophilizer or externally by other means (point 2). The purpose of the freezing step is to separate the solvent from the solute, enabling selective extraction of the volatile compounds. In this way, freezing itself is a dehydration process. Freezing is a critical phase of lyophilization due to its influence on drying performance [35], batch homogeneity [36], and possible degradation in protein formulations [37]–[41]. One of the most important aspects of the freezing process is the ice nucleation event.

Ice Nucleation

A typical freezing process takes place in four discrete stages: supercooling, primary ice nucleation, secondary ice nucleation, and solidification[42]. During supercooling, the temper-

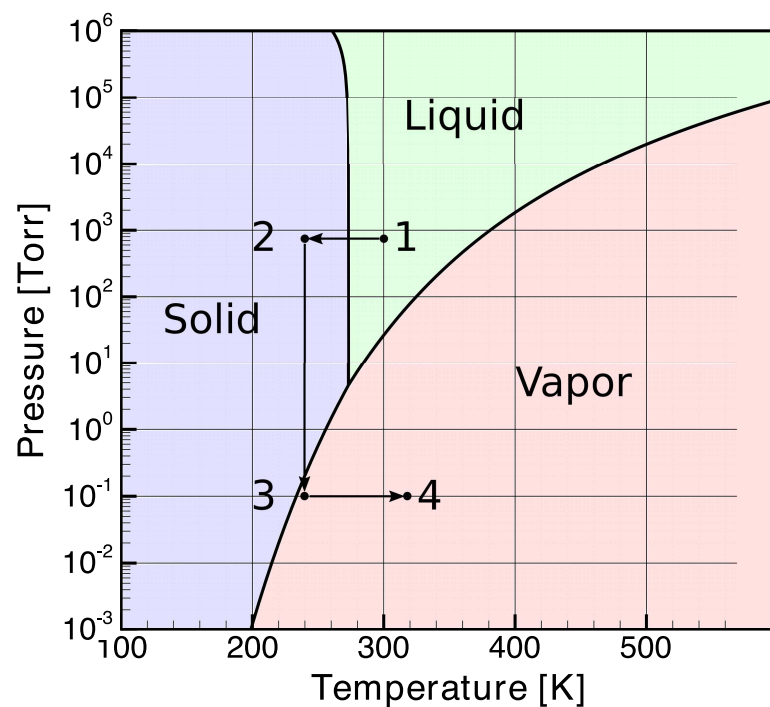


Figure 2.1. Lyophilization cycle displayed on water phase diagram. The sample is initially frozen to separate the solvent from the solute. Pressure is then reduced below the vapor pressure of the solvent to induce sublimation. Once the bulk material is removed the temperature is raised to promote desorption and further dehydration.

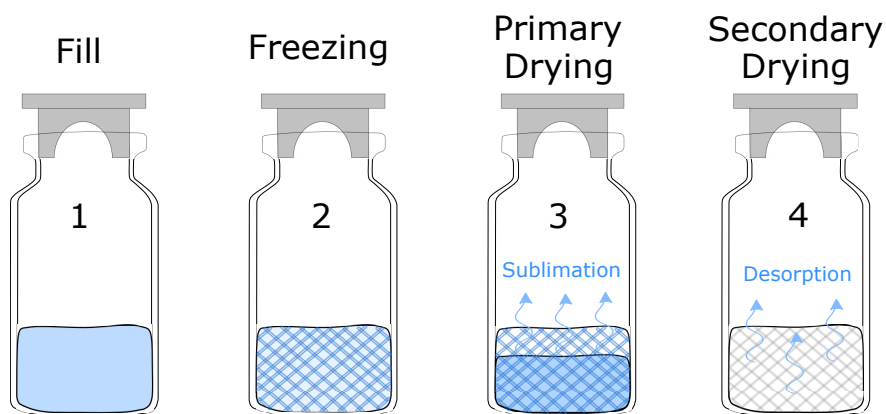


Figure 2.2. Illustration of lyophilization process from liquid fill to secondary drying.

ature of the sample is reduced below its equilibrium freezing temperature into a metastable state where ice-like nuclei repeatedly form, agglomerate, and dissolve. As the temperature is lowered, the density and size of these particles increases until a sufficient number coalesce to form a thermodynamically stable ice crystal. The emergence of this seed particle is referred to as primary nucleation and is stochastic in nature. Secondary ice nucleation is marked by the continued growth of the seed crystal and leads to a rapid rise in temperature of the bulk liquid to the equilibrium freezing point due to the release of latent heat at the liquid-ice interface [42]. The rate of growth is typically on the order of a few cm/s and the direction is against that of the thermal gradient[43]. The degree of bulk crystallization during secondary nucleation is directly related to the degree of supercooling (i.e. the temperature difference between the formulation and the equilibrium freezing temperature). Higher supercooling offsets the latent heat for a longer period of time and allows a larger portion of the formulation to crystallize before reaching the equilibrium freezing temperature. When the equilibrium freezing point is reached the energy release from crystallization balances the heat transfer out of the solution and the system transitions to the much slower solidification process. Crystal growth in this phase is once again against the direction of the temperature gradient and heat is transported through the previously frozen ice structure and bottom of the vial into the shelf [44]. Both solidification and secondary nucleation contribute significantly to the cake morphology and their relative contributions are largely dependent on the primary nucleation temperature [35], [42], [44]–[46].

The stochastic nature of the primary nucleation event leads to inconsistent nucleation temperatures within the batch. This behavior ultimately generates heterogeneity in drying characteristics among the vials and is highly undesirable [35]. Products have been shown to undergo primary ice nucleation at temperatures of -20°C in a laboratory environment and as low as -30°C at the manufacturing scale under standard ramped shelf freezing practices [47]. The high density of ice-like clusters at these low temperatures leads to many small nuclei distributed throughout the liquid solution during primary nucleation [48], [49]. Ice crystals rapidly grow into interconnected needle-like crystal filaments and produce low-conductance passages through which sublimed water vapor eventually flows [50]. The characteristics of this morphology can be predicted using computational methods [51]. However, in most cases,

small pores are unfavorable as they drive up primary drying time and increase frozen layer temperature. Some benefit is derived from the higher surface area during secondary drying in the form of lower residual moisture content but this typically does not offset the performance gains in primary drying and can be accounted for by increasing the secondary drying temperature [47]. Rapid freezing associated with deep supercooling has also been shown to place unwanted stresses on the product, potentially leading to protein denaturation [40], [41], aggregation, pH shifts [52], and phase separation [37]. In many cases the issue of small pore size can be rectified by annealing but this step comes at the cost of additional processing time [35].

To produce a cake morphology more favorable for lyophilization, nucleation should be induced simultaneously in all vials at a low degree of supercooling where crystals assume a more dendritic form with a larger cross section and greater conductance [50]. Controlled Ice Nucleation (CIN) refers to any process used to achieve this objective. Several techniques have been demonstrated in the literature for inducing ice nucleation [53] including “ice fog” [54], vacuum-induced surface freezing (also known as snap freezing) [55], ultrasound [56], electro-freezing [57], addition of nucleating agents [42], quench freezing, and rapid depressurization [58].

2.1.2 Primary Drying

After freezing, the process enters the primary drying phase. The low temperatures associated with the frozen product inhibit the natural evaporative tendencies of the solvent due to the reduction of vapor pressure at the solid-gas interface. To induce sublimation the process chamber pressure is reduced below the vapor pressure of the volatile compounds using a vacuum pump and cold trap. This event is indicated by the progression from points 2 to 3 on the phase diagram. Here, heat is supplied from the shelf (or some alternative means such as infrared or microwave radiation [59]) to offset the energy lost through the phase change. These conditions are maintained until the bulk frozen material is completely removed.

During primary drying it is imperative to keep the product temperature below that of the collapse or eutectic melting temperatures. Product collapse results from mobilization of

water that is contained in the interstitial layer due to an increase in temperature. The ability for the interstitial material to displace transforms the solid into a highly viscous liquid, allowing it to “collapse” under its own weight. Product collapse is considered catastrophic to the process and can lead to undesirable cake appearance, reduced drying rates, delayed reconstitution times, non-uniform sublimation, and poor shelf life [60]–[62]. Products which have exceeded their critical temperature are rejected at the time of inspection and, if widespread, can result in the discard of the batch as a whole. An example of cake collapse is presented in Figure 2.3.



Figure 2.3. Example of cake collapse (left), partial collapse (middle), and an acceptable cake with no collapse (right). Images taken from Patel et al. [63]

2.1.3 Secondary Drying

At the conclusion of primary drying the moisture content within the cake typically ranges between 1-10% [62]. At this point the water that remains is adsorbed on the product matrix and can only be relinquished by increasing product temperature, often to a value far higher than the freezing point [62], [64]. Secondary drying is indicated by movement from point 3 to 4 on the phase diagram. Typically, secondary drying produces a residual moisture content below 1% and leads to greatly improved product stability and shelf life of many formulations [52]. This is not always the case however as some drug products, specifically

those involving proteins, require elevated moisture levels on the order of 3% to prevent denaturation during storage [65].

2.2 Configuration of a Modern Lyophilizer

Since its discovery, great strides have been made in lyophilization technology on the fronts of process control, process modeling, and formulation development. However, the configuration of the lyophilizer itself has remain largely unchanged since the mid-20th century. A schematic of a typical lyophilizing unit is shown in Figure 2.4.

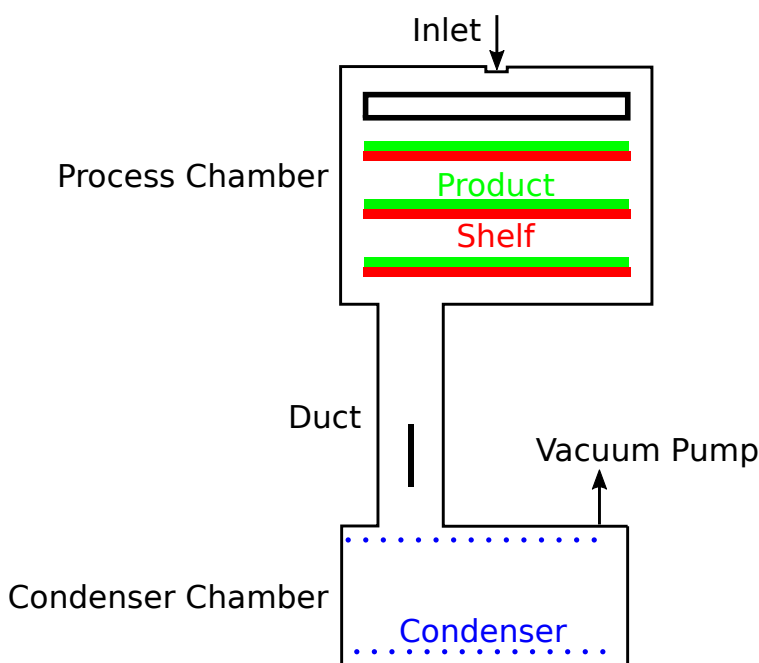


Figure 2.4. Schematic of typical lyophilization unit. The system is composed of process and condenser chambers connected by a duct. Solvent vapor sublimates and frosts on the condenser. The non-condensed ballast gas continues into the vacuum pump where it is removed and discharged to the atmosphere.

A typical lyophilizer contains a process chamber, condenser chamber, and a duct connecting the two. The product undergoing lyophilization is located in the process chamber on a series of shelves. Each shelf contains a serpentine channel system through which heat transfer fluid is circulated. The fluid temperature is precisely controlled in a push/pull sense by both a refrigeration system and heating element.

Table 2.1. Comparison of common process monitoring methods used in pharmaceutical lyophilization.

Attribute	Comparative Measurement	DP	TDLAS	MTM	Product Temperature	RGA	Heat Flux
Spatial Fidelity	×	✓	×	×	✓	×	✓
Steam-In-Place (SIP)	✓	×	✓	✓	✓	✓	✓
Product Temperature	×	×	✓	✓	✓	×	✓
Ease of Integration	✓	✓	×	✓	✓	×	×
Accurate	✓	×	×	×	✓	✓	✓
Non-invasive	✓	✓	✓	×	×	✓	✓
Cost	✓	✓	×	✓	✓	×	✓
Durable	✓	×	✓	✓	✓	✓	✓

The condenser chamber is responsible for maintaining vacuum inside of the process chamber. The condenser itself is maintained at a very low temperature (-60°C to -80°C in laboratory scale dryers) using a multi-stage refrigeration cycle. The vapor passing over the coil deposits onto the surface which provides a pumping action for condensable species. As a rule of thumb, the condenser coil should generally be kept at a temperature greater than 20°C below that of the solvent vapor to ensure a high probability of frosting [62]. The vacuum pump removes non-condensable species and lies downstream of the condenser to inhibit solvent vapor ingestion.

2.3 Motivation

Several technologies and methods are currently available to monitor the lyophilization process. The reader is referred to a thorough survey by Fissore et al. for an exhaustive overview [66]. Of the documented PAT methods, few are simultaneously practical in production environments, non-invasive, and able to provide spatially resolved measurements of the variable of interest. Common techniques employed today for process monitoring include: comparative measurement [67], dew point monitoring [68], [69], Tunable Diode Laser Absorption Spectroscopy (TDLAS) [70], Manometric Temperature Measurement (MTM) [71], product temperature monitoring, Residual Gas Analysis (RGA) [72], and heat flux monitoring [73]. A summary of the methods and their various attributes is summarized in Table 2.1.

One limitation common to many of the methods in Table 2.1 is the ability to capture batch-averaged properties only. The principle reason for this shortcoming is the inaccessibil-

ity of vacuum systems. The nature of WSNs allows them overcome this constraint, having nearly infinite positional flexibility within the process chamber. This capability is especially advantageous in production settings where accessibility is limited due to tightly regulated cGMP aseptic manufacturing protocols[74].

2.3.1 Applications of WSNs to Primary Drying

Primary drying is the most time consuming phase of the lyophilization process, taking anywhere from days to weeks to complete. Today, this problem is compounded by the fact that many lyophilization systems apply open-loop control architectures. That is, pre-programmed pressure and temperature setpoints are executed sequentially at specific times during the cycle until the expected moisture content is achieved. This “recipe” is often developed on small-scale laboratory lyophilizers which have substantially different heat and mass transfer characteristics relative to production equipment[75]. Uncertainties arising from scale-up are often accounted for using unnecessarily conservative cycles to ensure both the product and equipment capability limits are not exceeded. The application of mathematical modeling has helped bridge this gap and accelerate cycle development[68], [76]–[78]. However, theoretical treatments alone are insufficient and must be supplemented by physical measurements to improve the robustness of current PAT. WSNs applied to primary drying are able to provide localized real-time information to the operator. This capability, in principle, can be applied to closed-loop control schemes. From a quality control perspective, the spatially resolved measurements also provide quality assurance in the event of an unexpected system malfunction.

Gas pressure and temperature variations within the shelf networks of lyophilizers have been well-documented using a variety of analytical and numerical approaches. In 1971, Massey developed a 2-dimensional model of a semiporous channel to describe the distributions of gas pressure and product temperature along the length of the shelf in an industrial-scale freeze-dryer. The model was compared to experimental measurements collected during the drying of haddock samples with a high degree of accuracy [79], [80]. Variations of this approach have been developed (which are also applicable outside of freeze-drying) and gen-

eralize the injection boundary assumptions to include non-uniform profiles or 3-dimensional channels [81], [82]. A simplified analytical approach to the semiporous injection system was developed by Zhang who created a model to estimate the variation of water vapor pressure throughout the lyophilizer [83]. The model is based on a Poiseuille flow and includes an additional profile stretching term to account for the boundary mass injection. Although these analytical approximations are useful to gain a fundamental understanding between local gas pressure or temperature and product state, they are unable to account for the complex 3-dimensional geometries (e.g. vials and stoppers) found in real lyophilizers.

Computational Fluid Dynamics (CFD) allows many of the limitations associated with analytical methods to be overcome by simultaneously offering high degrees of flexibility, versatility, and accuracy. Numerous studies have applied CFD to the lyophilization process to describe the flow behavior at various locations throughout the system including the condenser [84], [85], duct [86], [87], and process chamber [77], [88]–[92]. Rasetto developed a dual-scale model using a combination of CFD and an analytical description of the vial sublimation and heat transfer characteristics to model heterogeneity in production-scale lyophilizers [89], [90]. Barresi later adapted the model to include gas mixtures (i.e. the effect of the inert ballast gas) and examined the effects of accounting for low-pressure boundary slip in both production and laboratory scales. The pressure drop across the shelf was shown to vary linearly with sublimation rate for a fixed pressure [88]. Similar results were obtained by Ganguly who investigated flow behavior in a laboratory-scale lyophilizer using a multi-species model to determine the parameters which contribute to pressure variation along the shelf [91]. The sublimation surface was assumed to be an ice slab having uniform temperature and sublimation rate. The results were compared to experimental measurements of the pressure difference between the center of a laboratory-scale lyophilizer and the edge. The tests employed an ice slab and false shelf inserted above the slab containing two pressure taps. The differential pressure measurement was shown to exhibit dependence on chamber pressure, shelf temperature, and the distance between the sublimation surface and shelf above [93]. In particular, the pressure difference was shown to be highly sensitive to the shelf spacing and varied in inverse proportion with this parameter.

The impact on spatial variations of gas pressure on drying performance at both the laboratory and production scales was briefly addressed by Sane [93]. In the laboratory setting the pressure variations are small relative to the base pressure and can generally be neglected. This behavior has been confirmed experimentally through adjustment of the shelf spacing [94]. At the large length scales encountered in a manufacturing environment the pressure variations increase significantly which leads to spatial variations in heat transfer characteristics. In some cases, these variations can be large enough to produce a higher drying rate in center vials due to the modulation of the vial heat transfer coefficient. In this way the pressure variations can be favorable and potentially lead to a more homogeneous process.

2.3.2 Applications of WSNs to Controlled Ice Nucleation

Rapid Depressurization CIN (RD-CIN) is one of the widely accepted CIN technologies and relies on the sudden discharge of pressurized inert gas to induce nucleation [58]. Under this method the samples are first supercooled in the pressurized chamber (typically on the order of 20-30 psig). Following equilibration at the target ice nucleation temperature, the ballast is suddenly released to the surrounding atmosphere, leading to a rapid decrease in chamber pressure and gas temperature. The timeframe for this process is on the order of one second at the laboratory scale and extends to a few seconds in manufacturing environments due to increasing chamber volume. The exact mechanism inducing primary ice nucleation using this technique has yet to be determined. However, current popular theories include gas bubble formation, accelerated supercooling, ice cloud formation [58], cooling due to evaporation at the liquid interface [95], and a combination of mechanical and acoustic shock [47]. The advent of Microelectromechanical Systems (MEMS) coupled with recent advances in wireless sensor networks have made the spatially and temporally resolved measurements of gas pressure and temperature in the vicinity of the vials during RD-CIN possible. This capability is highly desirable as it provides data which is used to better understand the mechanisms affecting ice nucleation performance under different process conditions. WSNs

may be directly integrated into the RD-CIN process to better understand the roles of the gas ballast composition and vial size on primary nucleation.

3. WIRELESS VACUUM AND TEMPERATURE SENSORS FOR LYOPHILIZATION PROCESS MONITORING

The Pirani gauge is a form of vacuum transducer first introduced in 1906 and still widely used today [96]. In its classical form, the Pirani gauge consists of a resistive metal filament (usually platinum or nickel) that is heated using electrical current. The power dissipated by the filament into the surrounding gas will vary with the pressure, temperature, and composition. A schematic of the device is shown in Figure 3.1.

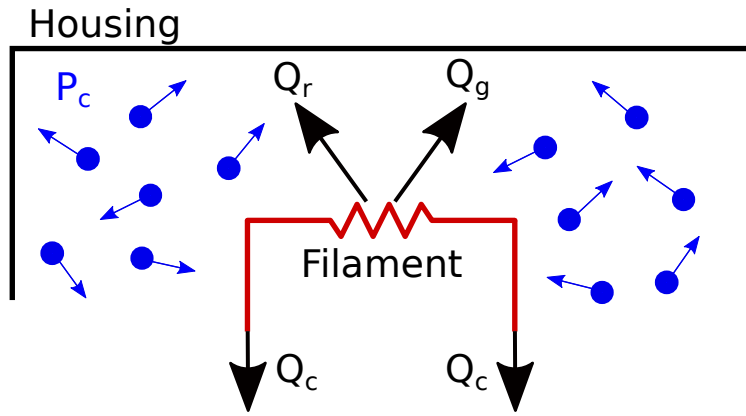


Figure 3.1. Schematic of Pirani gauge operation. The metal filament is enclosed inside of a chamber and is heated using electrical current. The heat dissipated by the filament depends on gas pressure, temperature, and composition.

The Pirani gauge correlates the power dissipated by the filament to the pressure of the gas assuming the composition is known and the temperature does not deviate strongly from that in which it was calibrated. Most Pirani devices operate in either a constant-bias or constant-temperature mode. In the constant-bias mode, a fixed current (or voltage) is applied to a filament (typically in a bridge configuration) and the corresponding changes in voltage (or current) are correlated to ambient pressure. The advantage of this technique lies in its simplicity, but comes at the expensive of a reduced partial pressure detection limit and lower overall full-scale range [97]. The constant-temperature mode is a closed-loop system that continuously adjusts input power to maintain the filament at a constant temperature relative to the ambient gas. This method is more complex than the constant

bias mode since it requires the addition of an external temperature-compensating element for feedback. However, the benefit is in the form of greater sensitivity, resistance to small changes in ambient temperature, and improved long-term drift resistance. In the steady state, electrical power applied to the filament in the constant-temperature mode balances the heat lost through gas conduction (Q_g), solid conduction (Q_c), and radiation (Q_r) such that the target filament temperature is maintained. If pressure is decreased, the efficacy of gas conduction is reduced and lower power is needed to sustain the filament temperature. Conversely, an increase in pressure requires a greater applied power. This trend is non-linear but monotonic, allowing ambient pressure to be uniquely correlated to applied power through calibration.

Closed-loop control of the Pirani filament temperature can be achieved in the analog domain using the self-balancing bridge architecture [98]. This configuration is illustrated in Figure 3.2. The bridge resistances determine the performance of the device and were designed to be most sensitive in conditions characteristic of lyophilization.

3.1 Wireless Sensor Design

The emergence of MEMS has enabled the miniaturization of Pirani gauges, leading to lower power consumption, greater sensitivity, faster response time, and smaller size than their macroscale counterparts. The Pirani gauge selected for the wireless vacuum and temperature sensor is the HVS Vac03k (Boston Electronics, Brookline, MA) due to its high sensitivity at pressures characteristic of lyophilization. The device contains two filaments, one for pressure measurement (sensing filament) and the other for temperature measurement (compensation filament). A rendering of a typical MEMS Pirani sensor is shown in Figure 3.3

The sensing filament is located on a diaphragm that is suspended between two planes. The compensation filament is deposited directly on the chip substrate and is exposed to the air. For the Vac03k sensors, the sense and compensation elements have equal nominal base resistances of $8.0\text{ k}\Omega$ and exhibit a positive Temperature Coefficient of Resistance (TCR).

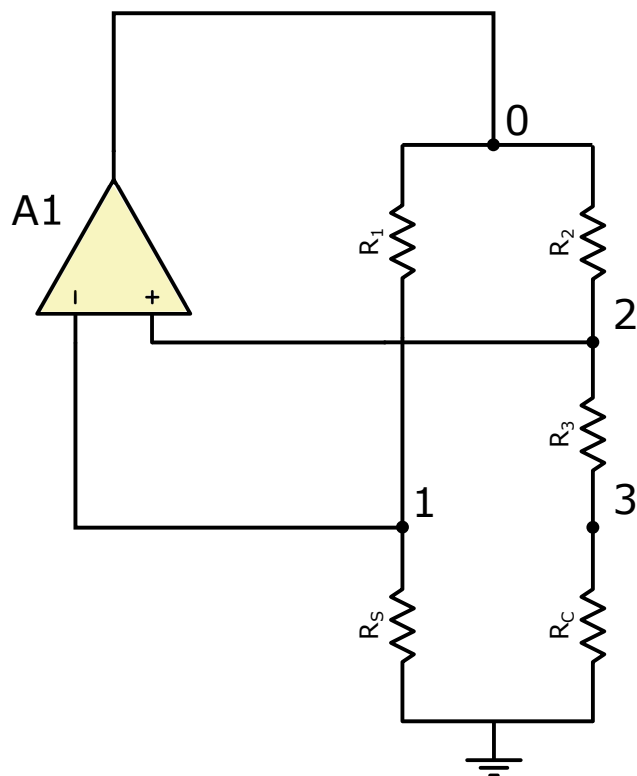


Figure 3.2. Circuit used for constant-temperature operation. The operational amplifier ensures changes in the compensation filament resistance is reflected in the sensing element. Increasing gas temperature causes filament temperature to increase by an equal amount.

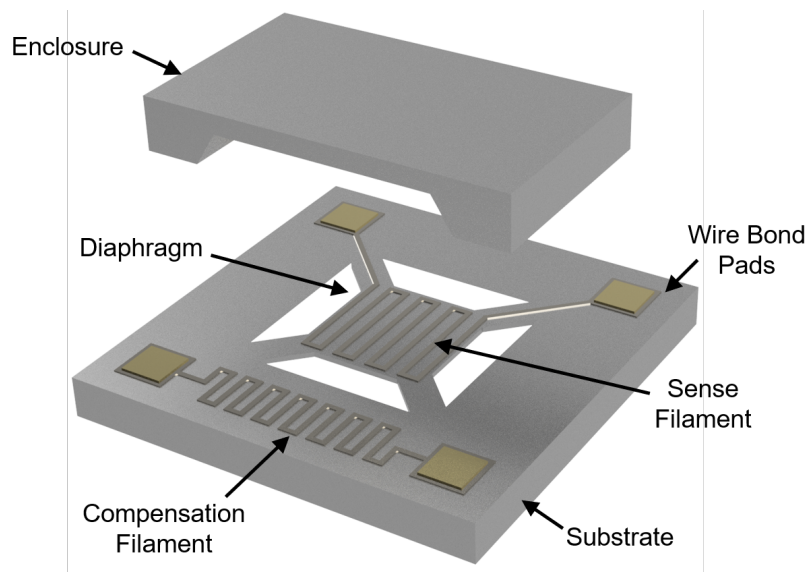


Figure 3.3. Schematic of typical MEMS Pirani gauge. The device contains both sense and compensation filaments to resolve ambient pressure over a range of gas temperatures. The sense filament is located on a thin diaphragm having low thermal resistance to the ambient gas.

The TCR is typically described using a polynomial fit but is often linear. Assuming quadratic behavior, the TCR can be described by

$$R(T) = R_0 \left(1 + \alpha_0(T - T_0) + \alpha_1(T - T_0)^2 \right) \quad (3.1)$$

The sensing (R_s) and compensating (R_c) filaments are placed on opposing legs of the bridge shown in Figure 3.2. At startup, the legs are imbalanced due to unequal resistance ratios. To compensate, the operational amplifier, A1, drives the output high. The sensing filament responds to the electrical current, causing it to warm and increase its resistance. The compensation filament is deposited directly on the silicon substrate (having a large relative mass) and therefore resists the Joule heating. The time scale of the lyophilization process is on the order of several hours to days so it is assumed that the die temperature is in equilibrium with the gas at any moment. The amplifier continues to increase output until the sensing filament resistance has risen to a level such that both legs are balanced (i.e. the differential voltage between the inverting and non-inverting terminals is zero). The magnitude of the temperature offset between filaments depends on the value of R_3 . If pressure changes at this equilibrium state the temperature of the sensing filament will either increase or decrease, pulling the bridge out of balance. The amplifier will adjust its output accordingly to restore the system back to equilibrium. Using basic bridge balance relations, the equilibrium (null condition) sense filament resistance is described by

$$R_S = \frac{R_2}{R_1} (R_3 + R_C) \quad (3.2)$$

Using equations 3.2 and 3.1 the equilibrium temperature for the sense resistor is given by

$$T_S = \frac{-\alpha_{S,0} + \sqrt{\alpha_{S,0}^2 - 4 \left(R_{S,0} - \frac{R_1}{R_2} (R_3 + R_{C,0} (1 + \alpha_{C,0}T_\infty + \alpha_{C,1}T_\infty^2)) \right) \alpha_{S,1}}}{2\alpha_{S,1}} \quad (3.3)$$

The magnitudes of R_1 and R_2 are determined by first balancing the bridge at the prescribed filament operating temperature. The general bridge equations are given by

$$\begin{aligned}\frac{V_0 - V_1}{R_1} &= \frac{V_2}{R_S} \\ \frac{V_0 - V_2}{R_2} &= \frac{V_2}{R_3 + R_C}\end{aligned}\tag{3.4}$$

Solving each of the equations for V_0 , invoking the ideal op-amp null state voltage constraint ($V_1 = V_2$), and applying equation 3.1 to the sensing and compensation filaments the system reduces to

$$\begin{aligned}\frac{R_2}{R_1} R_{S,0} \left(1 + \alpha_{S,0}(T_{S,1} - T_{S,0}) + \alpha_{S,1}(T_{S,1} - T_{S,0})^2 \right) = \\ R_3 + R_{C,0} \left(1 + \alpha_{C,0}(T_{\infty,1} - T_0) + \alpha_{C,1}(T_{\infty,1} - T_0)^2 \right)\end{aligned}\tag{3.5}$$

Temperature variation in the bridge balance equation 3.5 is analyzed by considering a change in ambient temperature from $T_{\infty,1}$ to $T_{\infty,2}$. This results in an increase in sensing filament temperature to $T_{S,2}$ since maintaining the constant temperature condition necessitates $T_{\infty,1} - T_{\infty,2} = T_{S,1} - T_{S,2}$.

$$\begin{aligned}\frac{R_2}{R_1} R_{S,0} \left(1 + \alpha_{S,0}(T_{S,2} - T_{S,0}) + \alpha_{S,1}(T_{S,2} - T_{S,0})^2 \right) = \\ R_3 + R_{C,0} \left(1 + \alpha_{C,0}(T_{\infty,2} - T_0) + \alpha_{C,1}(T_{\infty,2} - T_0)^2 \right)\end{aligned}\tag{3.6}$$

Taking the difference of equations 3.5 and 3.6 and accounting for unequal TCRs leads to the relation

$$\frac{R_1}{R_2} = \frac{R_{S,0}}{R_{C,0}} \frac{\alpha_{S,0} + \alpha_{S,1}(T_{\infty,1} - T_{\infty,2})}{\alpha_{C,0} + \alpha_{C,1}(T_{\infty,1} - T_{\infty,2})}\tag{3.7}$$

The nonlinear resistance profiles of the sensing and compensating filaments result in a temperature-dependent R_1/R_2 resistance ratio. The total resistance ratio difference between the highest and lowest typical operating temperature in lyophilization (-40°C to 40°C) is in the realm of 0.05%. For this reason, a constant resistance ratio is acceptable and the quadratic contribution can be neglected.

$$\frac{R_1}{R_2} \approx \frac{R_{S,0}}{R_{C,0}} \frac{\alpha_{S,0}}{\alpha_{C,0}} \quad (3.8)$$

The high-side resistors, R_1 and R_2 , were both chosen to be 1 k Ω to limit the current flowing through the bridge. The final resistor, R_3 , is used to set the resistance (temperature) offset between the sense and compensation filaments. Casting equation 3.2 in terms of temperature and solving for R_3 yields

$$R_3 = \frac{R_1}{R_2} R_{S,0} (1 + \alpha_{S,0} T_S + \alpha_{S,1} T_S^2) - R_{C,0} (1 + \alpha_{C,0} T_\infty + \alpha_{C,1} T_\infty^2) \quad (3.9)$$

The values of R_3 for each of the devices was selected based on the specified maximum operating voltage of the Vac03k sensor (3.2 V). To meet this constraint, the nominal offset temperature was selected as 8°C. A table of measured resistances for the six Wireless Micro-Pirani (WMP) devices is provided in Table 3.1.

Table 3.1. Summary of measured bridge resistances for the WMP devices based on the schematic shown in Figure 3.2. All devices were designed for a nominal temperature offset of around 8°C. Sense and compensation filament measurements were taken at room temperature.

WMP	R_1 [Ω]	R_2 [Ω]	R_3 [Ω]	R_S [Ω]	R_C [Ω]
1	999.8	1000.1	37.8	7775	8069
2	999.9	999.8	239.8	7945	8022
3	999.6	1000.1	268.4	8393	8412
4	1000.2	1000.2	149.7	7651	7816
5	998.1	1000.1	269.7	7495	7525
6	1000.3	1000.1	14.8	8471	8772

3.1.1 Front End Design

The analog front end used to measure sensing and compensation filament voltages is composed of the bridge circuit from Figure 3.2, a filter network, buffer amplifiers, and an Analog-to-Digital Converter (ADC). The schematic representation of the complete front end is shown in Figure 3.4.

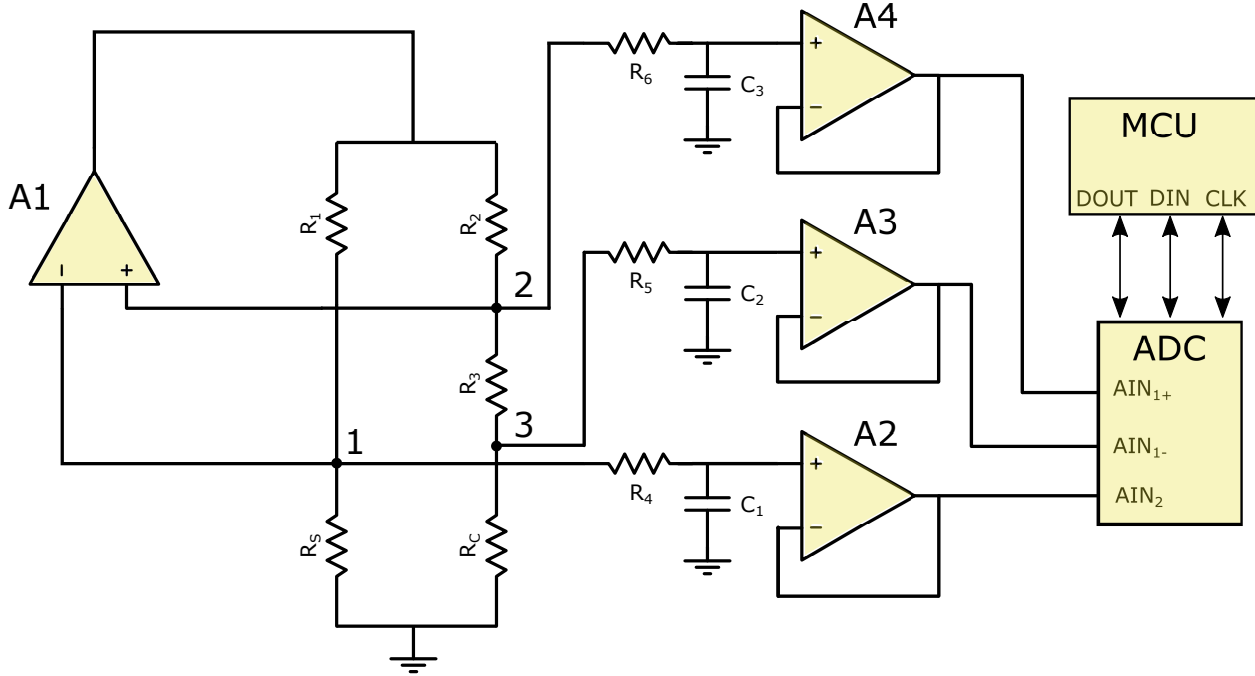


Figure 3.4. Analog front end for wireless microPirani sensor.

The ADC (AD7787, Analog Devices, Norwood, MA) has two analog inputs, one purely differential and the other single-ended. Input 1 measures the differential voltage across the ballast resistor, R_3 , and input 2 provides the single-ended measurement across the sense filament. All ADC inputs are sampled at 4.17 Hz and passively filtered at a cutoff frequency of 10 Hz (equivalent noise bandwidth of 15.7 Hz) with a 20 dB/decade rolloff. The inputs are operated in an unbuffered configuration since the impedance of the voltage followers prevents DC attenuation. This design choice was made to enable full rail-to-rail operation of the ADC. The ADC samples input voltages against a 3.0V low-dropout precision external reference (MAX3071, Maxim, San Jose, CA), providing large full-scale range while maintaining an estimated peak-to-peak resolution (based on datasheet specifications) of around 4 μ V. The

voltage reference is generated by a shunt-type circuit, having a a voltage noise of around 3 μV peak-to-peak and temperature variation of 8 ppm/ $^{\circ}\text{C}$ from -40°C to 125°C . In this case, the reference voltage can be expected to drift by up to 1mV over the full-scale temperature range. However, this effect is largely accounted for during calibration since the device experiences similar temperature swings to those encountered during the experiments. The chopper-stabilized operation of A1-A4 (AD8554, Analog Devices, Norwood, MA) ensures the amplifier has minimal drift and input offset due to ambient temperature variations. Using the listed components, the estimated root mean square noise generated in the bridge by the amplifiers and resistors is on the order of 1 μV . A derivation of the noise estimate is provided in detail in Appendix [A](#).

Signal Processing

The digital signal processing architecture consists of a BC832 (Fanstel, Scottsdale, AZ) transceiver module and the 24-bit Σ - Δ ADC. The BC832 is built around the Nordic NRF52832 chipset, a highly versatile, power-optimized, multiprotocol system-on-a-chip having an embedded 2.45 GHz radio. The microcontroller is based on the 32-bit ARM M4 architecture and was flashed with the s212 softdevice (ANT protocol stack). When power is applied, the system is in a power saving sleep state with a running sleep timer. Upon timer expiration the MCU wakes up, queries measurements from the ADC over the SPI bus, packages and wirelessly broadcasts data, resets the timer, and returns to sleep until the next timeout event. Each 3-byte measurement is packaged along with a device identifier, resulting in a packet size of 7 bytes. The ANT+ protocol is used for wireless transmission due to the low bandwidth constraints and capability of accommodating a large number of devices on a single channel. The host node consists of a PC connected to an ANT+ transceiver hub that operates in a continuous scanning mode. When a new measurement is received from one of the sensor nodes, it pushes data to the data acquisition software via a UART bus where it is displayed to the user and logged to a file. A schematic of the wireless star network configuration is shown in Figure [3.5](#).

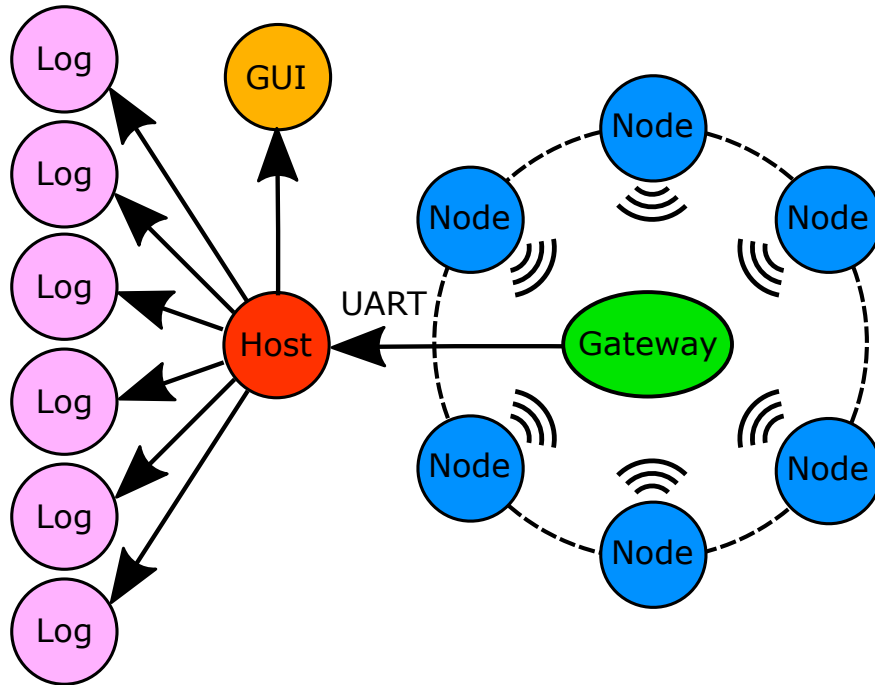


Figure 3.5. Schematic of WSN topology used for the WMP devices. The sensor nodes are paired to a hub outside of the vacuum chamber which pushes all broadcasts to a central host. The host is responsible for unpacking data, displaying it to the user, and logging to a file.

Power Conditioning

Power is supplied to the electronics module via a 3.7V lithium polymer battery pack (LP561836JU, Villingen-Schwenningen, Germany) having a capacity of 350 mAh. The module contains a low dropout 3.3V voltage regulator (MCP1700, Microchip, Chandler, AZ) to supply power to the board. A table of power profiling under the maximum power condition can be seen in Table 3.2. Bias currents associated with the LDO regulator have been neglected. Estimates for the CPU are based on an average current draw for the idle, active, and transmission windows over the 5-second sampling interval.

Table 3.2. Power consumption estimates for WMP system.

Component	Current Draw
CPU	7.9 μ A
ADC	75 μ A
Voltage Reference	260 μ A
Bridge Amplifier	950 μ A
Buffer Amplifiers	2.854 mA
Bridge	711 μ A
Total	4.858 mA

Using the battery specifications and power estimate from Table 3.2, the estimated device lifetime under full power operation is 72 hours. According to the estimates, significant improvements in device lifetime can be quickly achieved using power-optimized operational amplifiers. The devices implemented in the WMP sensors were selected for their high auto-zeroing and modest drive performance.

3.1.2 Sensor Packaging

The WMP devices were installed into a 3D-printed housing as shown in Figure 3.6. The base and lid are composed of ABS plastic and incorporate integral bracket structures for securing the various components. This material is selected due to its transparency in the RF broadcast spectrum and resistance to lyophilization conditions. The diameter of the package was 30mm, having an identical footprint to a standard 20R glass tubing vial. This

feature allows the sensor package to be placed directly into the vial pack with no special accommodations. Threaded inserts are press-fit into the base and lid for fastening various components.

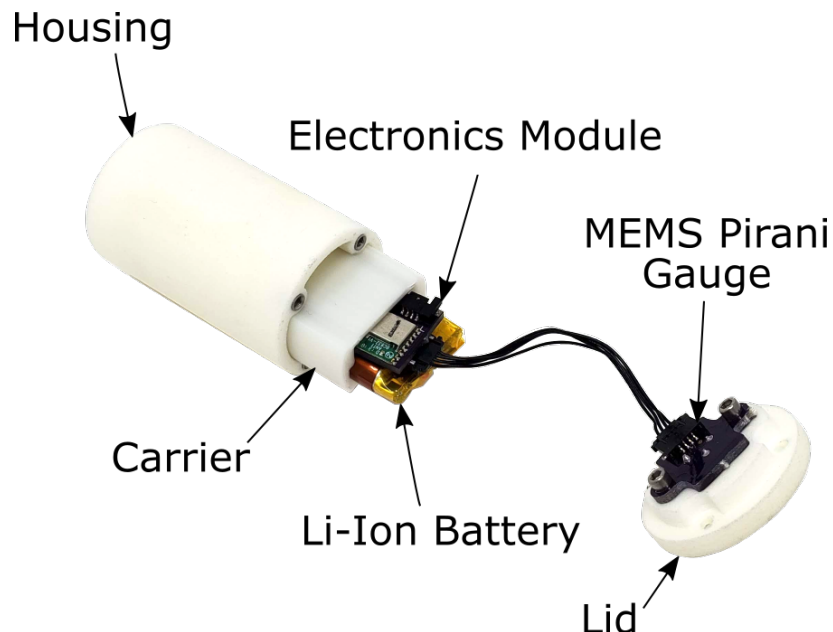


Figure 3.6. Image of disassembled WMP sensor showing various internal components and 3D-printed housing.

3.2 Wireless Micro-Pirani Sensor Calibration

The WMP sensors correlate the power required to maintain a silicon diaphragm at a specified temperature relative to the ambient. The dependence of a device's output on the thermal conductivity of the surrounding gas necessitates calibration over an appropriate range of temperatures, pressures, and compositions. In the case of lyophilization, pressure magnitudes typically span 50 to 250 mTorr and temperatures from -40°C to $+40^{\circ}\text{C}$. It can also be assumed that the gas composition within the shelf system is 100% water vapor as the highly laminar flow and favorable pressure gradient strongly inhibit upstream diffusion of ballast gas.

3.2.1 Temperature Calibration

The sensing and compensation filaments were first calibrated to enable a quantitative measure of gas temperature. The calibration procedure was performed by evaluating the resistances of the sensing and compensation filaments over a range of temperatures. The results were then fit to equation 3.1 to determine the TCRs.

Materials and Methods

The TCRs of the sense filament and compensation filaments were determined using a voltage divider technique to avoid parasitic Joule heating under typical ohmmeter bias currents (in the range of 10 μ A in the 10 kOhm range). All tests were performed inside of a REVO[®] (Millrock Technologies, Kingston, NY) lyophilizer at a pressure of 500 mTorr, allowing the temperatures to extend well below the dew point at atmospheric pressures. The lyophilizer has the capability of regulating shelf temperature. However, this method was insufficient for TCR calibration as the control system lacks the authority to regulate the temperature of the Device Under Test (DUT) directly. A custom wireless thermoelectric controller was developed to overcome this limitation. An electrical schematic of the controller is provided in Figure 3.7. The RTD was attached directly to the housing of the DUT (Vac03k) using adhesive to ensure proper thermal coupling.

The controller consists of a BC832 module (Fanstel, Scottsdale, AZ) built around the Nordic Semiconductor BLE microcontroller chipset. The device receives setpoint data, measures process variables, computes control outputs based on a proportional-integral architecture, and broadcasts temperature data to a central host. Setpoint, controller gain, and enable/disable information is received from a master device located outside of the lyophilizer. Upon reception of data, the controller samples temperature from the Pt1000 RTD (Honeywell, Charlotte, NC) shown in Figure 3.7. The RTD is biased using a constant current source of 100 μ A. Bias current is set using the resistor, R_1 , from the figure. The output determined by the controller is passed to a digital-to-analog converter (AD7787, Analog Devices, Norwood, CA) which drives the input pin on the switch-mode thermoelectric driver (MAX1968, Maxim, San Jose, CA). The amplifier operates in a bipolar mode, enabling push/pull con-

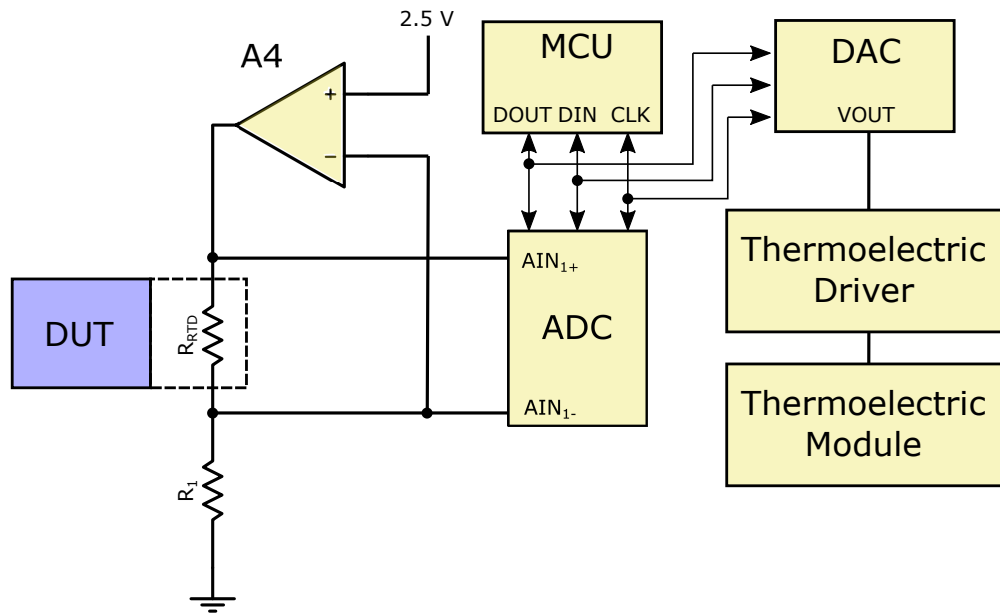


Figure 3.7. Schematic of wireless thermoelectric controller setup used to maintain ambient temperature at a constant value during TCR characterization. The RTD was cemented directly to the housing of Pirani gauge on the DUT.

trol action with a drive current of up to $\pm 3\text{A}$. The thermoelectric cooler (Laird Thermal Systems, Morrisville, NC) is fixed between the shelf and the copper mounting block with a thermal adhesive. Copper was selected to minimize thermal gradients and provide a stable reference environment for the gas surrounding the DUT. An image of the setup used for TCR measurement is shown in Figure 3.8. The TCR calibration was carried out at three points, -20°C , 0°C , and 20°C , allowing linearity to be assessed over a wide temperature range.

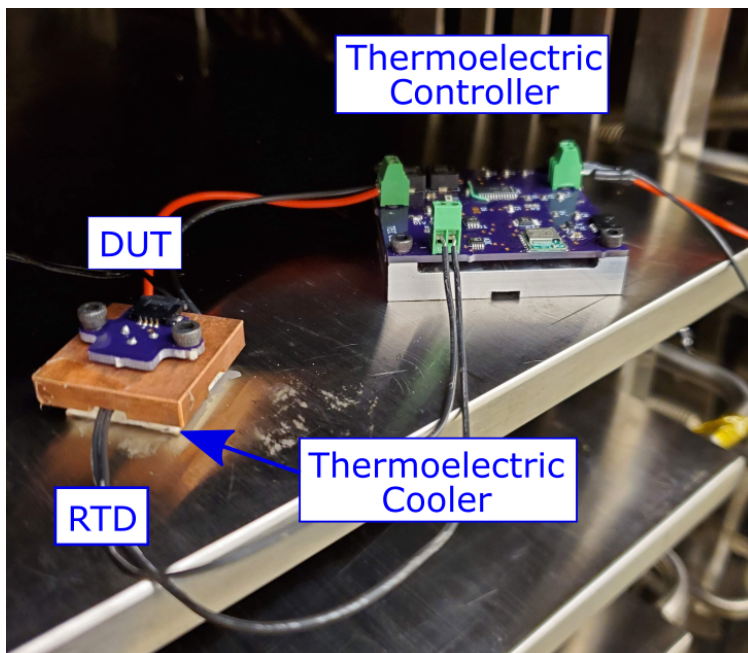


Figure 3.8. Image of the calibration setup used to compute filament TCR. The wireless thermoelectric controller receives setpoint information from an external host. The temperature of the Pirani gauge package (Vac03k) is monitored by the Pt1000 RTD (hidden).

Thermal Characterization Results

A plot summarizing the resistance change as function of temperature for both the sense and compensation filaments is shown in Figure 3.9. The TCR data exhibit a negligible degree of nonlinearity with temperature, making a linear fit from equation 3.1 appropriate. The coefficient of determination, R^2 , values for the sense and compensation resistors are equal with a magnitude of 0.9998.

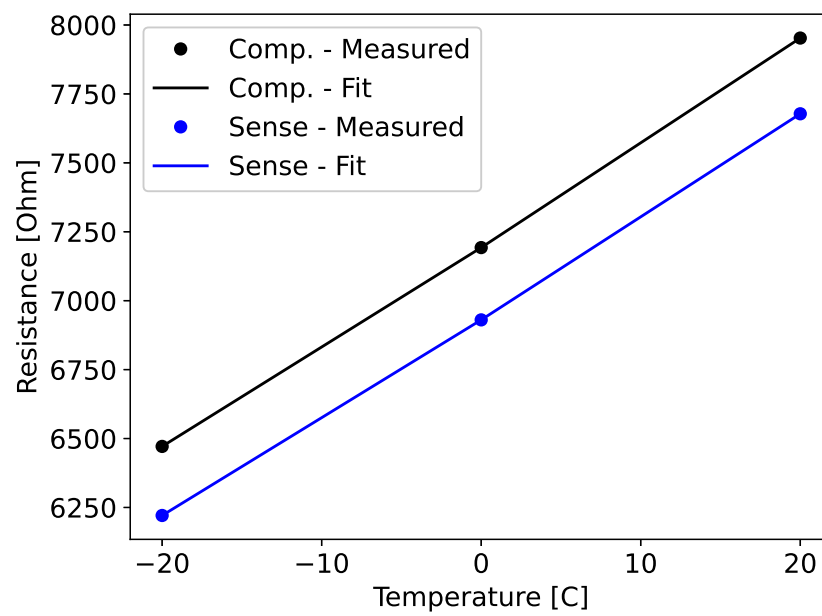


Figure 3.9. Measured and fitted temperature coefficient of resistance data for sensing and compensating filaments on WMP1. The TCRs for both exhibit linear behavior over the measured temperature range.

The measurement results for sense and compensation filament temperature coefficient measurements are provided in Tables 3.3 and 3.4, respectively. Uncertainty values at each temperature setpoint are also included. The linear portion of the TCRs for the sense and compensation filaments show a difference from the mean of around 2%, allowing them to be assumed equal. This assumption simplifies the design and analysis of the bridge in equation 3.7.

Table 3.3. Temperature coefficients of resistance for compensation filaments

Compensation Filament				
Temperature [°C]	Uncertainty [°C]	Base Resistance [Ω]	α_0 [1/°C]	α_1 [1/°C ²]
19.99	0.028	7952.6	0.00515	6.74e-6
-0.017	0.017	7192.6		
-20.01	0.025	6471.4		

Table 3.4. Temperature coefficients of resistance for sense filament

Sensing Filament				
Temperature [°C]	Uncertainty [°C]	Base Resistance [Ω]	α_0 [1/°C]	α_1 [1/°C ²]
20.00	0.004	7677.9	0.00526	6.85e-6
0.00	0.008	6930.4		
-20.02	0.006	6220.9		

3.2.2 Pressure Calibration

Following the thermal characterization all devices were calibrated against a series of ambient pressures characteristic to lyophilization.

Materials and Methods

Pirani-type devices must be calibrated in the medium in which they will operate to obtain a measure of absolute pressure. For this work, this necessitates introduction of pure water vapor into the lyophilizer in a controlled manner. This task can be accomplished by either raising the temperature of the water to saturation conditions at a given pressure or lowering

the ambient pressure to that of the vapor pressure at the interface. Boiling water leads to large perturbations and condensation in the plumbing which may damage the regulating valve. For this reason, the latter option was pursued. A schematic of the apparatus used to perform the pressure-regulating operation is shown in Figure 3.10 and an image of the setup in Figure 3.11.

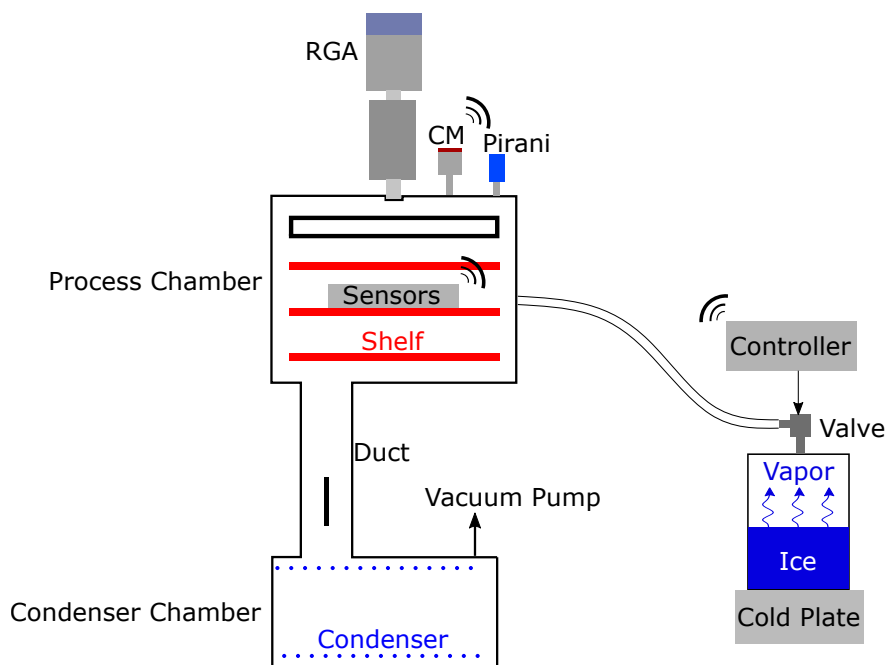
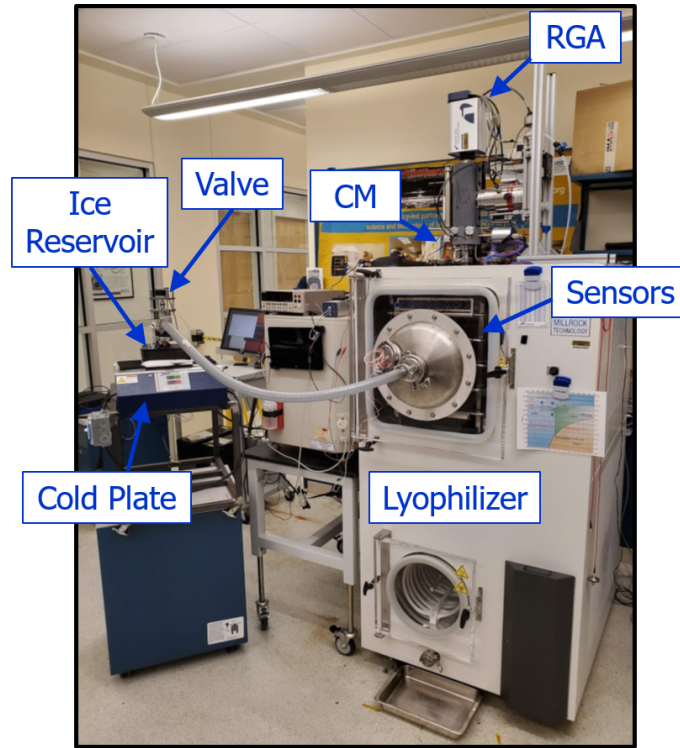
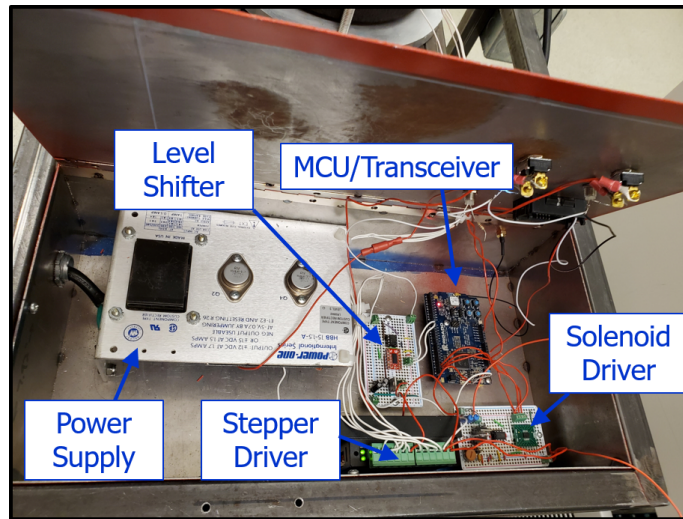


Figure 3.10. Schematic of water vapor calibration apparatus. Water ice was frozen in a reservoir on a thermoelectric cold plate. The sublimed vapor was fed into the lyophilizer using a stepper motor-driven gate valve. The capacitance manometer on the lyophilizer provided the necessary feedback for pressure control.

The control box contained a microcontroller and wireless transceiver that received set-point and controller gain values in real time from an external host. Measured chamber pressure data was simultaneously received from a transceiver affixed to a capacitance manometer. The box had the capability of using either water vapor or dry compressed gases as a calibration medium. If water vapor was selected, the output was routed to the level shifter and stepper controller. The stepper, in turn, actuated a gate valve to regulate vapor flow. For dry compressed gases, the output was sent to the solenoid controller which drove a proportional valve. The proportional valve had much lower conductance than the stepper-controlled



(a) Image of experimental setup used to calibrate wireless vacuum gauges



(b) Controller used for device calibration. The MCU receives setpoint and controller gain information wirelessly. The control loop is then executed and the output is pushed to either the stepper or solenoid controller depending on calibration gas.

Figure 3.11. Images of apparatus used to calibrate wireless microPirani devices.

gate valve and could therefore only be used with gases at pressures far above those in the lyophilization chamber. The control loop was based on a proportional-integral architecture. A schematic of the controller box electronics is shown in Figure 3.12

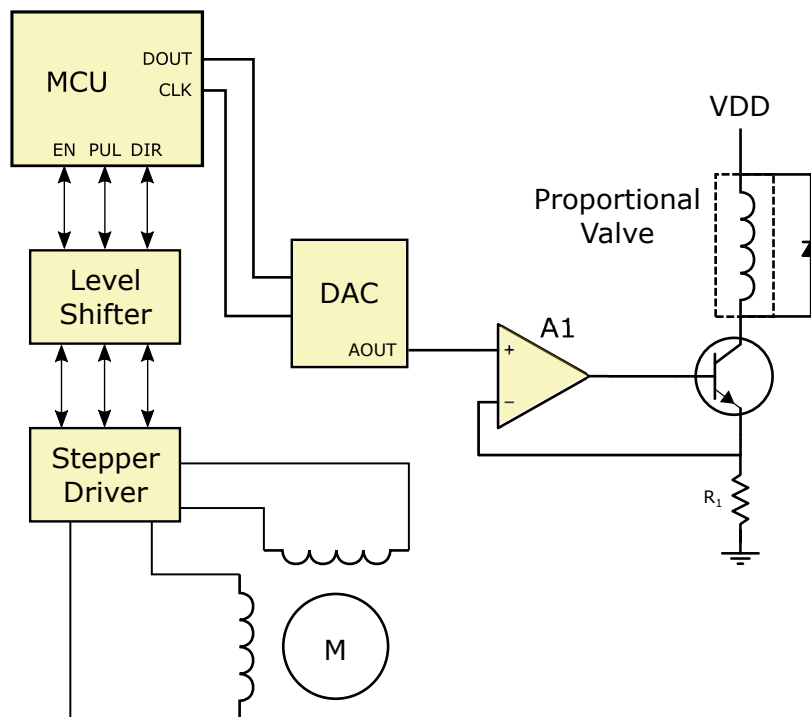


Figure 3.12. Controller box electronics. The stepper motor driver circuitry is used for water vapor calibration and the proportional valve for non-condensable gas.

The water vapor source consisted of an insulated reservoir initially filled with liquid water. A leak check was performed prior to installation by submerging the reservoir in liquid water under positive pressure. The absence of bubbles indicated that no significant leaks were present. Before calibration, the water was frozen by placing the reservoir on a thermoelectric cooling plate which maintained a surface temperature of -10°C . A frozen state was necessary to prevent boiling as well as suction of liquid water through the vacuum line into the lyophilizer. Both effects would inhibit the ability to regulate pressure in a controlled manner. The temperature of the ice set the vapor pressure within the reservoir and the flow rate of vapor was governed by a digitally controlled valve located at the reservoir outlet. An aluminum plug orifice with o-ring seal was inserted into the duct of the lyophilizer to limit

vapor flow rate and increase pressure span. The plug reduced the effective duct diameter from 5" to 1". A series of 3D printed plugs lowered this diameter further to finely tune the usable range. The largest plug that allowed the pressure to be controlled between the target range was selected to maximize water vapor concentration. An image of the plug with 3D printed orifice inserted is shown in Figure 3.13.

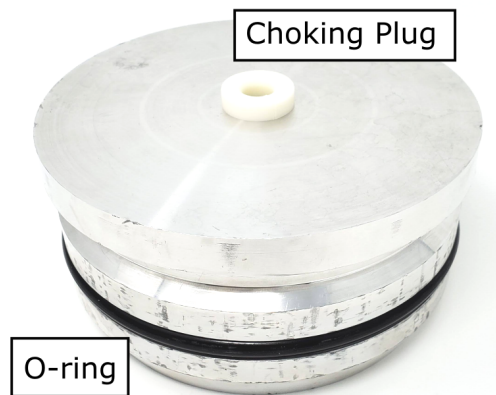


Figure 3.13. Machined aluminum choking plug used to restrict vapor flow through the lyophilizer during wireless microPirani calibration. The plug insert is 3D-printed to allow the effective duct diameter to be changed if larger pressure magnitudes are desired.

The wireless microPirani sensors were installed on a machined aluminum fixture. The fixture contained two 40 gauge thermocouples (Omega Engineering, Norwalk, CT) for temperature monitoring and is shown in Figure 3.14.

At the start of the calibration the pressure within the lyophilizer was reduced to its ultimate vacuum to reduce the presence of impurities. The valve connecting the chamber to the water vapor reservoir was then opened and controlled around the first setpoint using the real-time broadcast from the CM as the process variable. The shelf temperature was simultaneously adjusted to its first setpoint. The sensors were allowed to equilibrate to the shelf temperature for a duration of 5 hours. Following this soak period, the water vapor pressure was incremented to the next setpoint for 20 minutes. This process continued until all pressure setpoints were cycled. The shelf temperature was then adjusted to its new setpoint and the entire process was repeated. The devices were calibrated in pressures between 50

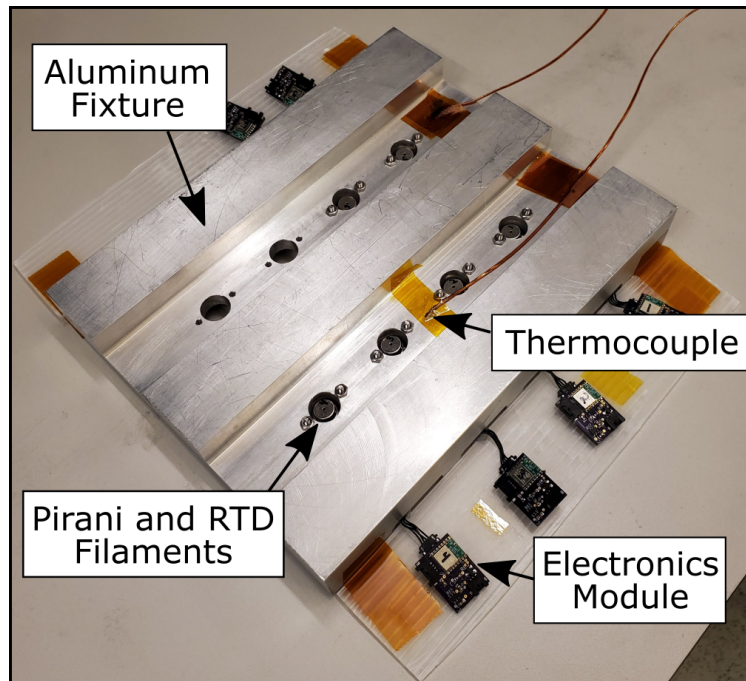


Figure 3.14. Aluminum fixture used for device calibration. Pirani and RTD filaments were fastened to ensure good thermal coupling. Fixture temperature was monitored using two T-type thermocouples. Thermal paste was applied to the thermocouples to ensure effective coupling

mTorr and 160 mTorr in increments of 5 mTorr and shelf temperatures between -33°C to +33°C in increments of 11°C. The upper limit of calibration pressure was limited by the shelf temperature as regulating around a setpoint higher than the vapor pressure would lead to frost formation within the process chamber.

Sensors were calibrated by correlating measured absolute pressure of pure water vapor and device temperature directly to bridge voltages at junctions 1 and 2 (see Figure 3.4). The final 50 samples (a duration of around 4.2 minutes) at each pressure setpoint were averaged to reduce the influence of noise. Outlying peaks were discarded based on the moving Z-score with normalized absolute deviation greater than 3.0 as these represent unsuccessful broadcast attempts or bad data.

Calibration Results

A calibration data sample for WMP1 is presented in Figure 3.15. The results of the calibration procedure were used to form a 3D surface plot which can be interpolated for arbitrary chamber pressures. The calibration for WMP1 is shown in Figure 3.16. The surface is monotonic and can therefore be used to uniquely determine gas pressure using both bridge junction measurements.

Conversion of raw measurement data into calibrated pressure values was accomplished using a 3rd-order bivariate spline surface. The temperature data was extracted by assuming all sensors are at the same temperature while installed into the aluminum calibration fixture. This assumption was validated by comparison of the two thermocouples installed on the jig, having a variation of up to 1°C over the entire duration of the calibration procedure. Using this approach, WMPs 2-6 are referenced via a quadratic fit to the temperature measured by WMP1 as the TCR of this sensor was calibrated directly in section 3.2.1.

Process Gas Composition Validation

Accuracy of the Pirani vacuum gauge is highly dependent on the process gas composition. A Residual Gas Analyzer (RGA) was therefore used during the calibration procedure to verify

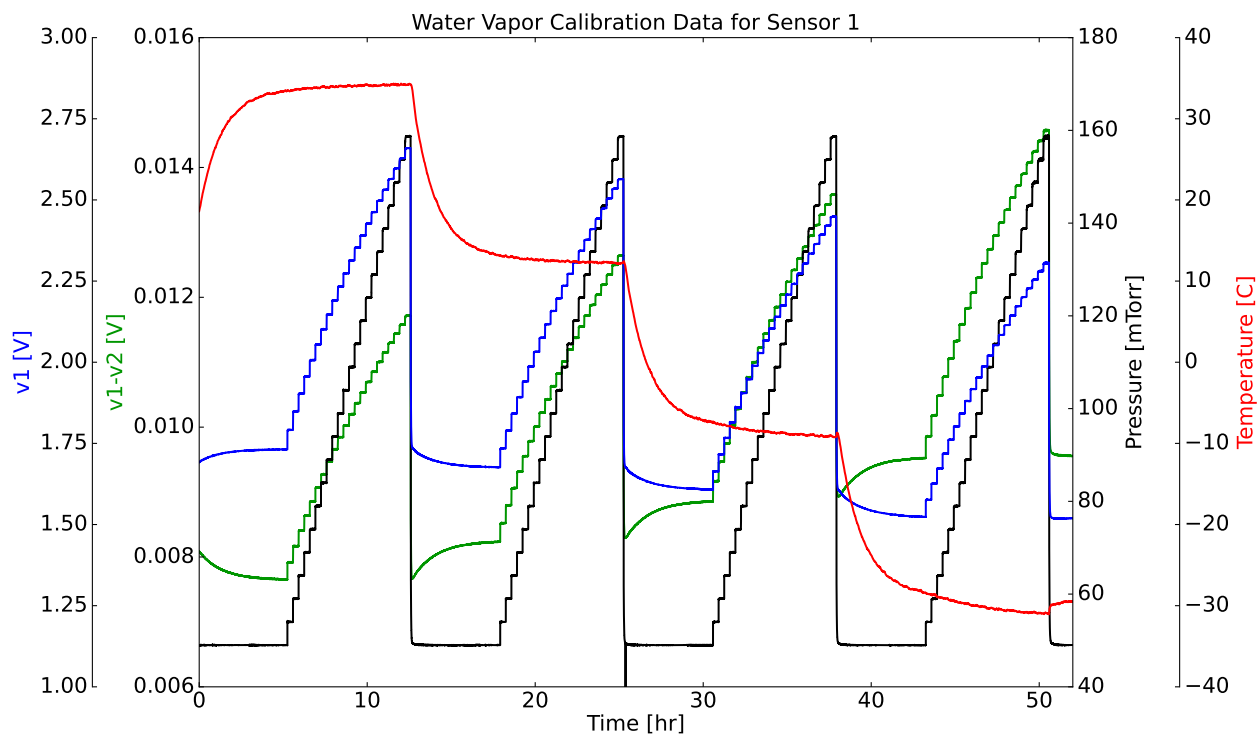


Figure 3.15. Calibration data for WMP1. Raw bridge outputs on the left axes are calibrated to chamber pressure and fixture temperatures on the right axes.

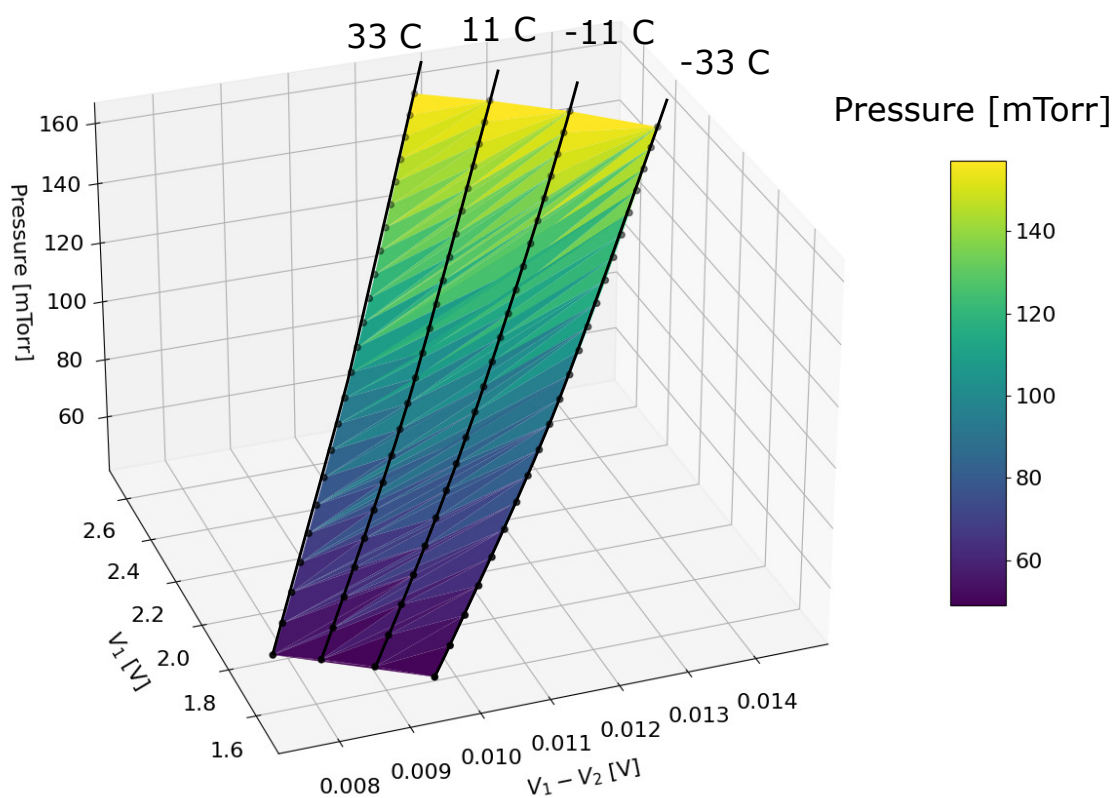


Figure 3.16. Calibration surface for WMP1. Arbitrary voltage measurements across the sense and compensation filaments may be interpolated to determine chamber pressure and ambient temperature.

purity. The RGA used for this process was the Transpector 3 Compact Process Monitor (Inficon, Bad Ragaz, Switzerland). An image of the setup is shown in Figure 3.17

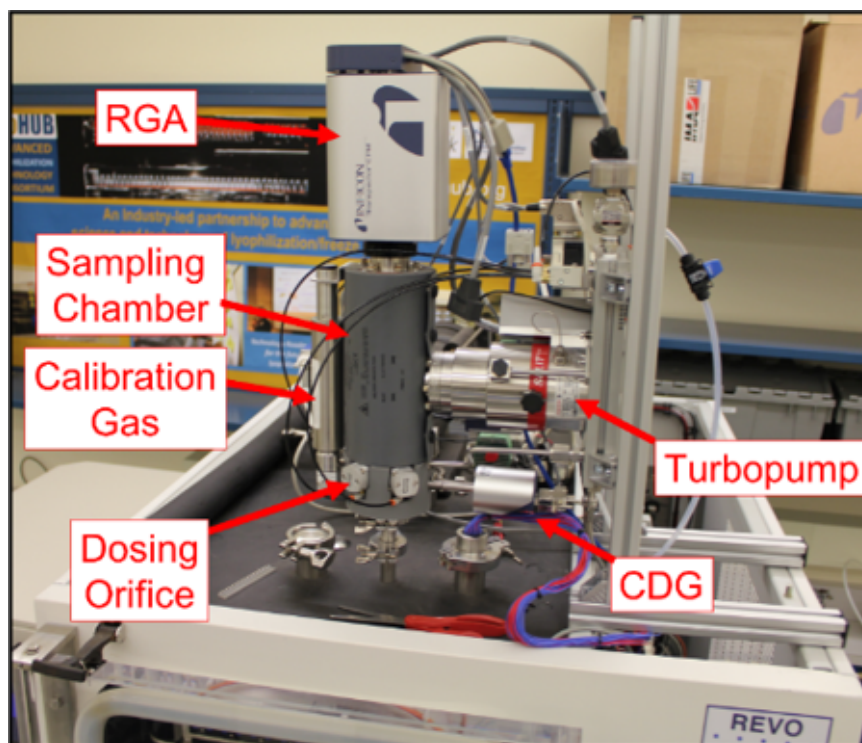


Figure 3.17. Transpector Compact Process Monitor Residual Gas Analyzer (RGA) mounted to the upper surface of the process chamber. The RGA is able to measure process gas composition in real time, allowing water vapor purity to be quantified during the calibration process.

The RGA system uses a quadrupole mass filter to sample gas mass-to-charge ratios in the range of 0-200 mass-to-charge ratio (m/z) in increments of 0.1 m/z . A total of 10 measurements were sampled and averaged at each m/z location. Species are ionized and fragmented using a thermionic emission source. The quadrupole filters these compounds using a combination of RF and DC bias, permitting only those with the correct mass-to-charge ratio to collide with the Faraday cup. The dosing orifice system is used to restrict flow rate of the process gas into the sampling chamber, maintaining it safely in high-vacuum while enabling safe operation at lyophilization chamber pressure up to 1 Torr. The device contains a heating jacket used for bakeout of adsorbed water vapor prior to calibration as well as a calibration gas standard for system tuning.

In many cases, the raw data received from the RGA does not provide an absolute measurement of composition as species within the sampling chamber are both ionized (not always singly) and fragmented into smaller compounds. Further complicating the process, the m/z ratio of the fragmented species may overlap for different base compounds (e.g. nitrogen and carbon monoxide). Nevertheless, the RGA may be used to obtain an estimate of the partial pressures of nitrogen and water vapor during calibration. Fragmentation patterns for these species as published by NIST are provided in Table 3.5. The patterns are highly dependent on the equipment used but they are useful in identifying species of interest. The summarized raw output from the water vapor calibration is shown in Figure 3.18.

Table 3.5. Published mass-to-charge ratio and abundance values for nitrogen, water vapor, and oxygen [99].

Compound	m/z	Relative Abundance
N_2	28	1.0
	14	0.138
	29	0.0074
H_2O	18	1.0
	17	0.212
	16	0.009
	19	0.005
	20	0.003
O_2	32	1.0
	16	0.218

As expected, the principal water trace at 18 m/z is the dominant signal throughout the calibration procedure. The 32 m/z signal likely arises from the fragmentation of water and recombination of the resulting atomic oxygen (O) to form O_2 . This result is also supported by the inverse relationship to the $m/z=28$ trace. The $m/z=28$ trace represents the nitrogen signal and has a maximum magnitude of around 0.5% of $m/z=18$. It can therefore be assumed that the composition in the lyophilization chamber throughout the process is pure water vapor. The presence of nitrogen is most likely due to a small leak in the chamber or atmosphere backstreaming through the vacuum pump, a conclusion supported by the decrease in signal as the water partial pressure is increased.

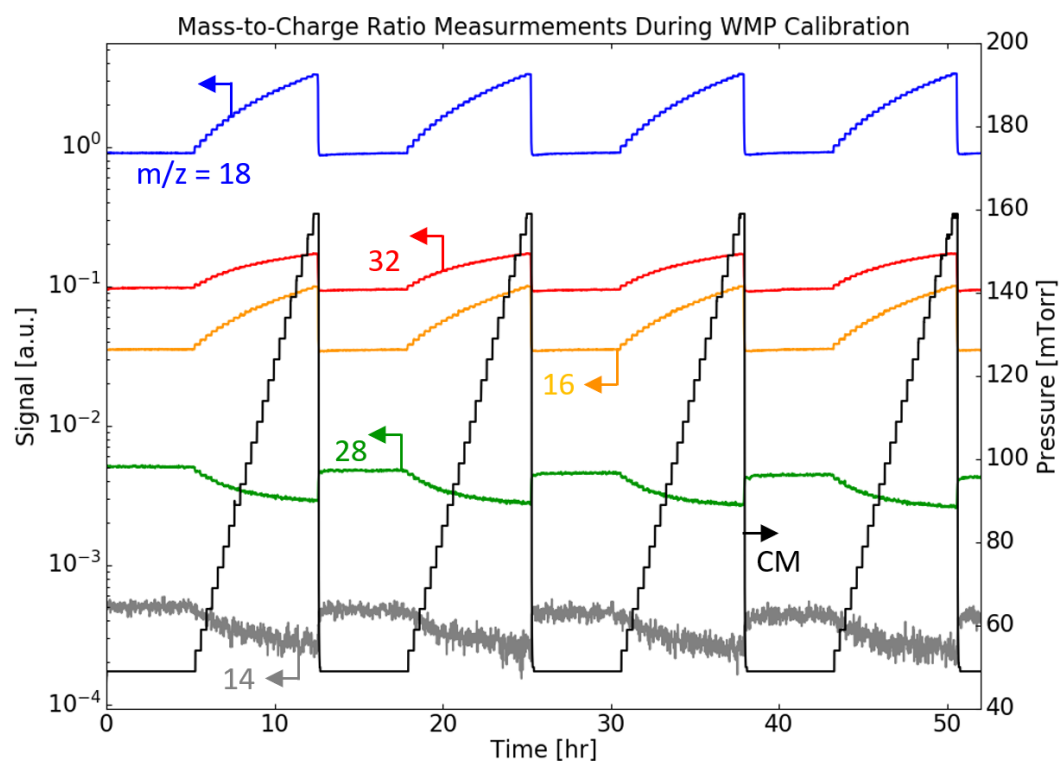


Figure 3.18. Raw RGA data from wireless microPirani calibration procedure. Several mass-to-charge ratios are shown.

3.2.3 Wireless MicroPirani Calibration Validation

To validate the sensor calibration the WMP sensors were arranged in a hex pattern at the center of a full rack of 20cc vials as shown in Figure 3.19. The vials were filled with 5 mL of ultra-pure water ($>18.2 \text{ M}\Omega\text{-cm}$). The water was frozen at -40°C and sublimed at a shelf temperature of 10°C and chamber pressure of 100 mTorr. No secondary drying was applied due to the absence of excipients. The process and WMP data is shown in Figure 3.20 and indicate a strong agreement among the devices in terms of both pressure and temperature. The maximum difference occurs between WMP1 and WMP2 at 7 hours and assumes a magnitude of 0.4 mTorr. In terms of temperature, the maximum difference occurs at 6.2 hours and is 6.7°C .

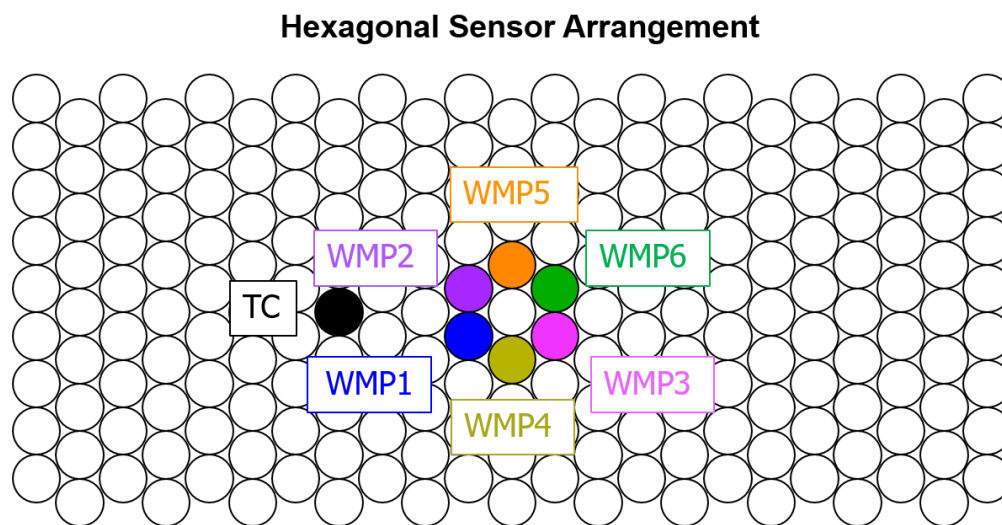


Figure 3.19. Hexagonal sensor arrangement in vial pack during calibration validation experiment

3.3 Wireless MicroPirani Performance Characterization

The sensitivity of the WMP devices as a function of ambient gas pressure is the primary metric of performance and can be estimated through consideration heat flow surrounding the sense filament. Under application of electrical current, heat loss from the sensor will occur through a combination of gas conduction, solid-state conduction, and radiative pathways as

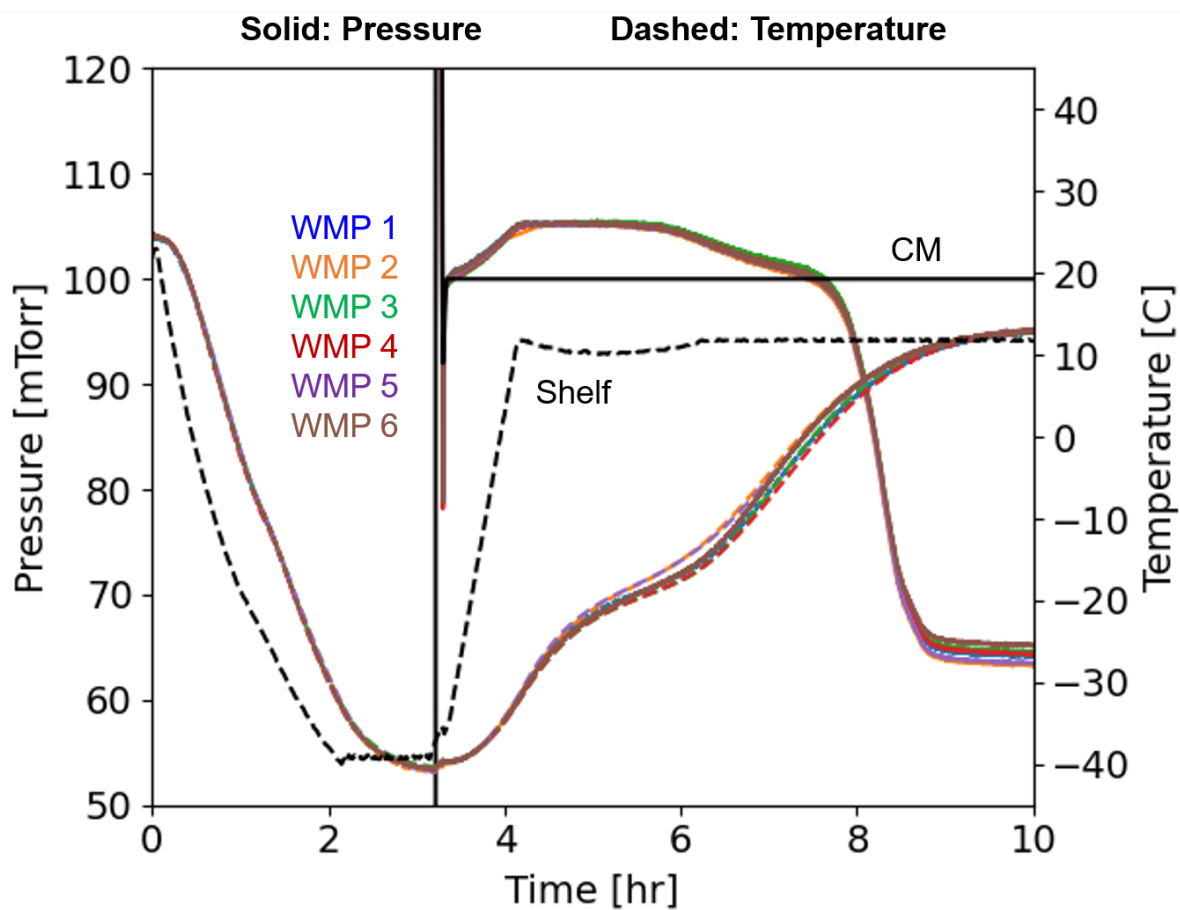


Figure 3.20. Process data from calibration validation experiment. Sensors are arranged as indicated in Figure 3.19. The maximum difference among sensors during primary drying is approximately 0.4 mTorr.

illustrated in Figure 3.1. At a given temperature and pressure, the overall heat balance at the sense filament is given by

$$Q = h_g A (T - T_\infty) + U_c (T - T_\infty) + \epsilon \sigma A (T^4 - T_\infty^4) \quad (3.10)$$

WMP sensor performance is evaluated by measuring the geometrical and heat transfer properties of the device. These components are determined through a combination of kinetic theory and experimental measurements of power dissipation. To evaluate the heat transfer characteristics of the sense filament the device was placed inside of the lyophilization chamber and the gas was evacuated to an ultimate pressure of around 4 mTorr. The filament temperature was then biased using the self-balancing bridge architecture from Figure 3.2, increasing its temperature to 8°C above the ambient. After a stabilization period the sense filament power dissipation and compensation filament temperature were averaged over 5 minutes with sampling rate of 0.2 Hz. Once complete, the pressure was advanced and the process was repeated. The experimental data for ambient pressures between 4 mTorr and 270 mTorr and shelf temperatures of 20°C and -20°C are shown in Figure 3.21. The influence of ambient temperature is clearly seen, confirming the need to calibrate under a variety of conditions. The temperature offset variation over the course of the test is shown in Figure 3.22. From the figure, the temperature offset between sense and compensation filaments is verified to be independent of both gas pressure and temperature. Peak-to-peak variations relative to the mean for 20C and -20C are 0.0098% and 0.011%, respectively.

Extraction of the convective heat transfer properties requires that the experimental measurements be made in the free-molecule regime. The Knudsen number, Kn , is used to determine if the operating conditions are appropriate and is defined as the ratio of the molecular mean-free path to the system's characteristic dimension, l_c .

$$Kn = \frac{\mu}{Pl_c} \sqrt{\frac{\pi k_b T}{2m}} \quad (3.11)$$

where μ is the gas viscosity at temperature T , P is ambient pressure, k_b is Boltzmann's constant, and m is the molecular mass. [100]. In this case, the characteristic dimension is the separation between the suspended diaphragm and the device substrate. This dimension

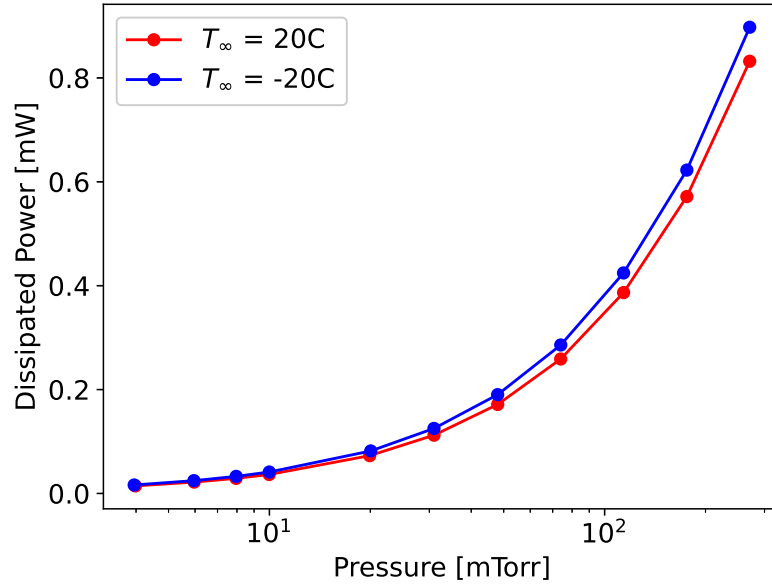


Figure 3.21. Dissipated power from Pirani filament over a range of chamber pressures for ambient temperatures of 20C and -20C. A linear dependence on pressure is exhibited below 10 mTorr, indicating free-molecule behavior.

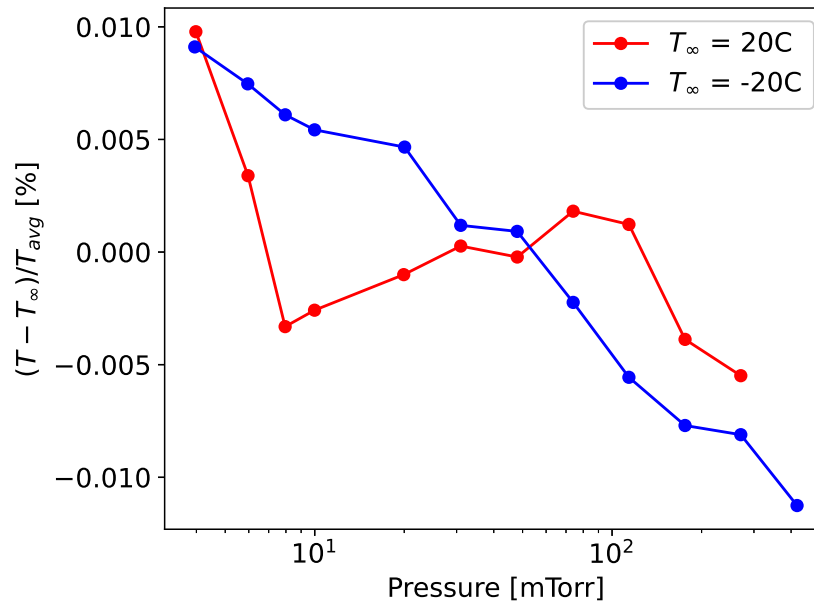


Figure 3.22. Variation in temperature offset between the Pirani filament and RTD during the power dissipation measurements. Peak-to-peak variations relative to the mean for 20C and -20C are 0.0098% and 0.011%, respectively.

is unknown but is approximated to be on the order of 0.5mm. Typically, a gas is considered collisionless, or free-molecular, for $Kn > 10$. In this regime it can be shown that the heat flux, $Q_{FM,gas}$, dissipated by a body of uniform temperature T to the gas and surrounding bodies at temperature T_∞ varies linearly with ambient pressure[101].

$$Q_{FM,gas} = 4P_\infty A \sqrt{\frac{8k_b T_S T_\infty}{\pi m}} \left(\frac{\sqrt{T} - \sqrt{T_\infty}}{T_S + T_\infty} \right) \quad (3.12)$$

Equation 3.12 assumes complete thermal accommodation between the gas and solid boundaries. Combining the free-molecule solution with solid-state conduction and radiation, the total energy balance surrounding the sense filament becomes

$$Q_{FM} = Q_{FM,gas} + U_c (T - T_\infty) + \epsilon \sigma A (T^4 - T_\infty^4) \quad (3.13)$$

The radiation and conduction components are independent of pressure (and therefore constant due to the constant temperature and constant offset conditions), allowing all unknown parameters to be extracted through application of a linear fit to the power dissipation data in the free-molecule regime. Assuming the calibration takes place in a known composition, equation 3.13 contains three unknown parameters: A , U_c , and ϵ . The surface area was evaluated from the slope of the linear fit at a shelf temperature of 20°C, leaving two pressure-independent unknowns, U_c , and ϵ . These values were determined from the intercept by performing the calibration procedure at a different ambient temperature (i.e. at 20°C). The fitting coefficients for the two tests are provided in Table 3.6. As expected from equation 3.12, the slope of the power dissipation increases with decreasing ambient temperature. Additionally, the intercepts agree to within 4%.

Table 3.6. Linear fit coefficients describing power dissipation as a function of pressure in the free-molecule regime.

Ambient Temperature [C]	Slope [W/mTorr]	Intercept [W]
20	2.77e-5	8.37e-5
-20	3.13e-5	8.01e-5

Combining the results of Table 3.6 with equation 3.13, the surface area of the sense filament diaphragm is estimated to be 2.05 mm². Assuming a square planform, the total length is 1.43 mm, 37% of the total device die length. The parameters U_c and ϵ are determined by simultaneously solving equation 3.13 at zero pressure, producing values of 8.09e-6 [W/K] and 0.067, respectively. A summary of the estimated parameters is shown in Table 3.7.

Table 3.7. Extracted (estimated) values of model parameters A , U_c , and ϵ , as determined by the least-squares minimization routine.

Design Variable	Value
A	2.05 [mm ²]
U_c	8.09e-6 [W/K]
ϵ	0.067

Elimination of the conduction and radiation components from equation 3.10 provides the gas heat transfer coefficient for the sense filament as a function of the ambient pressure. The results of this procedure are provided in Figure 3.23.

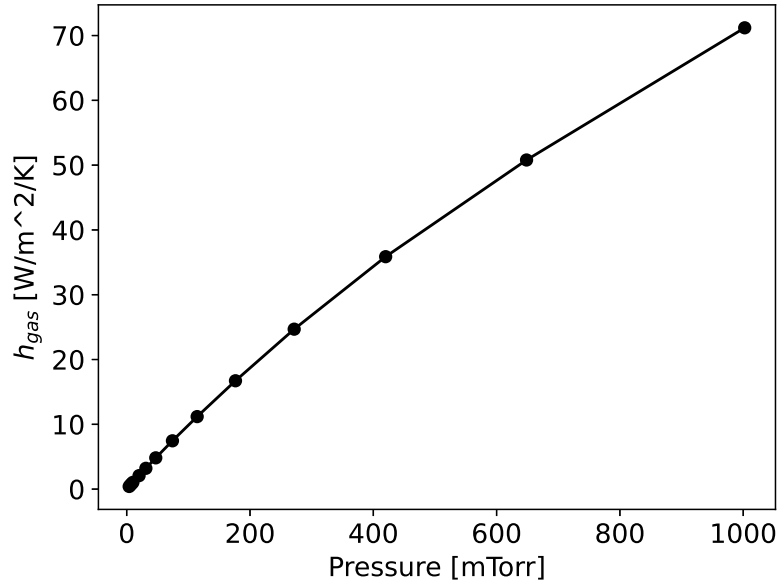


Figure 3.23. Experimentally measured gaseous heat transfer coefficient for sense filament. Solid-state conduction and radiation contributions are eliminated using the least-squares minimization approach.

The data in Figure 3.23 exhibits non-linear but monotonic behavior. In the free-molecule regime below roughly 10 mTorr, the gaseous heat transfer coefficient varies linearly with pressure. At higher pressures, the flow enters the transitional regime where the mean-free path is comparable to the sense filament dimensions.

3.3.1 Bridge Sensitivity Analysis

The potential differences across the sense and compensation filaments determine the ambient pressure and temperature. Using equation 3.13 together with Ohm's law of power

$$Q = \frac{V^2}{R} \quad (3.14)$$

the voltage output of the filament based on the extracted heat flow parameters is described by

$$V_1 = \sqrt{R_{S,0} (1 + \alpha_1 T + \alpha_2 T^2) h_g A (T - T_\infty) + U_c (T - T_\infty) + \epsilon \sigma A (T^4 - T_\infty^4)} \quad (3.15)$$

With equations 3.1, 3.10, and 3.15 sensitivity of the potential across the sense filament with respect to the ambient pressure is described by

$$\frac{\partial V_1}{\partial P} = \frac{1}{2} \sqrt{\frac{R_{S,0} (1 + \alpha_1 T + \alpha_2 T^2)}{h_g A (T - T_\infty) + U_c (T - T_\infty) + \epsilon \sigma A (T^4 - T_\infty^4)}} \frac{\partial h_{gas}}{\partial P} A (T - T_\infty) \quad (3.16)$$

The sensitivity of the gaseous conduction heat transfer coefficient is determined by taking the numerical gradient of the experimental data in Figure 3.23. Applying the bridge balance relations, the voltage across the resistance thermometer is

$$V_2 = \frac{V_1}{1 + \frac{R_3}{R_C}} \quad (3.17)$$

According to equations 3.16 and 3.17, the sensitivity with respect to pressure across the compensation filament will always be lower in magnitude than the sense filament. Since

both V_1 and V_2 are used together to determine pressure, V_2 represents the critical design sensitivity.

$$\frac{dV_2}{dP} = \frac{dV_1}{dP} \frac{1}{1 + \frac{R_3}{R_{RTD}}} \quad (3.18)$$

The sensitivity of the compensation filament with respect to pressure is presented in Figure 3.24. Additional curves demonstrating the effect of sense filament temperature offset are also shown. The data indicate a high sensitivity to ambient pressure, ranging from 15.7 mV/mTorr at the lowest pressure to 1.4 mV/mTorr at the highest. The decreasing sensitivity with pressure is expected based on the experimental data shown in Figure 3.23 and results from the flow transitioning to a continuum where the heat transfer performance is comparatively insensitive to pressure. The sensitivity of the potential across the filaments also exhibits dependence on the temperature offset. However, the range of offset temperature finite and is limited by the supply voltage. The WMP devices sample sense and compensation filaments with a specified peak-to-peak resolution of 19.5 bits, leading to a measurement uncertainty of around 4 μ V over the full-scale 3.0V range. In terms of pressure, this accuracy corresponds to an uncertainty between 2.55e-4 mTorr and 0.003 mTorr over the range of pressures in Figure 3.23 which is 2-3 orders of magnitude below the published uncertainty of the Baratron reference gauge. Therefore, the accuracy of the WMP sensors is limited primarily by errors in indicated pressure measurement during calibration.

3.4 Gas Pressure Temperature Distribution Within Lyophilizer During Primary Drying

Following calibration, the WMP devices were applied to various representative lyophilization cycles to quantify the gas pressure and temperature variations in the vicinity of the vials during primary drying. It was assumed that the gas composition over the entire shelf during primary drying was pure water vapor. This assumption is reinforced by the favorable pressure gradient and low Reynolds number in the gap region between the vials and the shelf which act to prevent upstream diffusion of ballast nitrogen. For this reason, the pressure

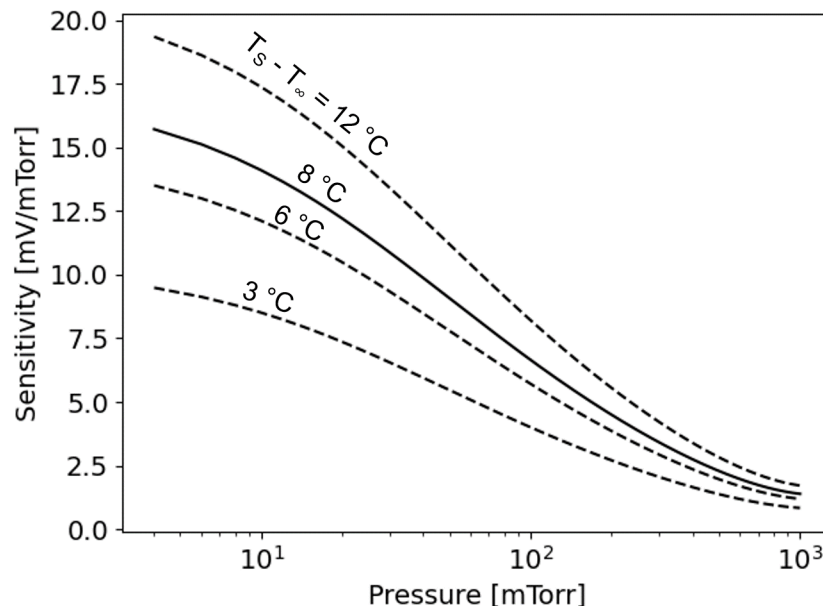


Figure 3.24. Sensitivity of compensation filament to changes in gas pressure and temperature offset. The chosen WMP sensitivity at an offset of 8°C is indicated by the solid line. Sensitivity is highest at low pressures and decreases monotonically as the gas enters the transitional rarefied regime.

measured by the WMP devices during primary drying following the water vapor calibration procedure is taken as absolute.

3.4.1 Materials and Methods

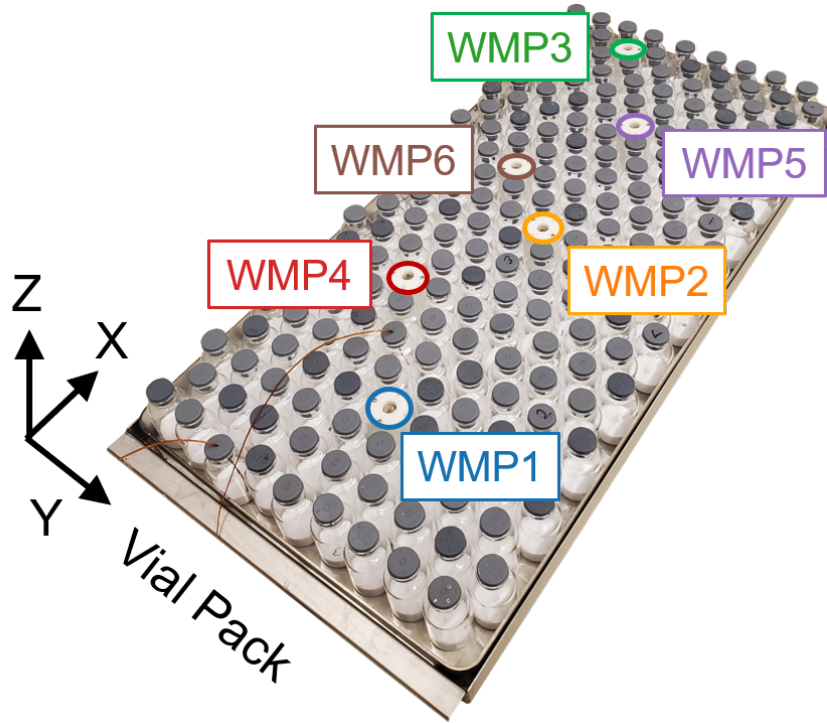
All tests were conducted in a REVO[®] (Millrock, Kingston, NY) laboratory-scale lyophilizer. A summary of the formulations and process parameters used in the experiments are shown in Table 3.8. Sucrose (Sigma-Aldrich, St. Louis, MO) and D-mannitol (Phansteil, Waukegan, IL) excipients were used. The solvent for all studies was ultra-pure water (UPW) having resistivity greater than 18.2 MΩ-cm. Experiments were performed using 201 20mL type 1 glass tubing vials (Schott, Lebanon, PA), each having a fill volume of 5mL. This vial quantity corresponds to one fully-loaded shelf when the six WMP devices are installed. All vials were partially stoppered prior to testing and the top shelf was used for all cycles. Product temperature measurements were performed using two 40 gauge T-type thermocouples

(Omega Engineering, Norwalk, CT). Both thermocouples were placed in center vials and one was located adjacent to one of the wireless sensors to evaluate the influence of parasitic heating. Care was taken to ensure the thermocouple junction was located at the bottom center of the vial. The WMP sensors were arranged in a staggered linear arrangement as shown in Figure 3.25 to facilitate measurement of both axial and transverse pressure and temperature gradients.

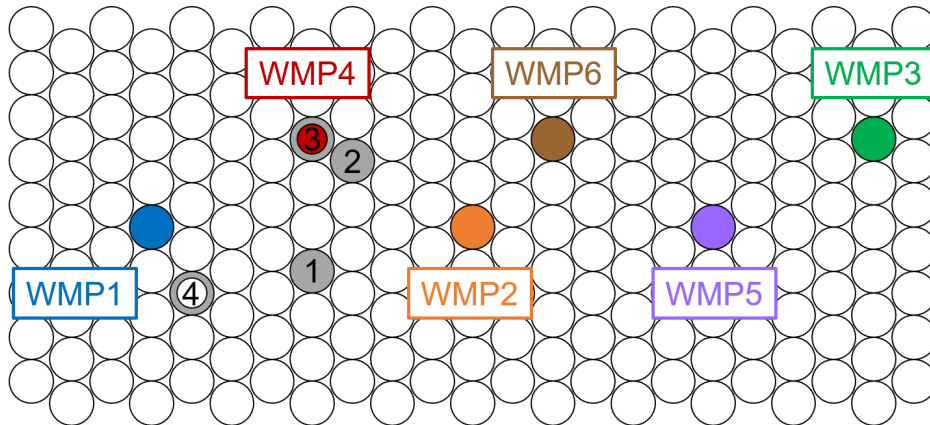
The configuration of the lyophilization process chamber varies between manufacturers. The REVO[®] unit used here contains several cutouts in the shelf support system which ultimately provide a high conductance path for vapor to leave the shelf system. To investigate the influence of these cutouts on the process variables, two polycarbonate walls (hereafter referred to as flow barriers) were installed along the sides of the shelf to force the flow to exit the front and rear exits. The barriers were only used when indicated in Section 3.4.2

Table 3.8. Summary of experiments performed using WMP devices. Cycle H was also used to investigate the influence of flow barriers. All temperature ramp rates are fixed at 1°C/min

Cycle	Formulation	Fill Volume	Freezing Shelf	Primary Drying Pressure	Drying Shelf	Secondary Drying Pressure	Drying Shelf
A	Water	5 mL	1 hr @ -40°C	70 mTorr	-20°C	N/A	N/A
B	5% w/v Sucrose	5 mL	1 hr @ -40°C	70 mTorr	-20°C	70 mTorr	40°C
C	5% w/v Sucrose	5 mL	1 hr @ -40°C	70 mTorr	-10°C	70 mTorr	40°C
D	5% w/v Sucrose	5 mL	1 hr @ -40°C	70 mTorr	10°C	70 mTorr	40°C
E	5% w/v Sucrose	5 mL	1 hr @ -40°C	100 mTorr	10°C	100 mTorr	40°C
F	5% w/v Sucrose	5 mL	1 hr @ -40°C	150 mTorr	10°C	150 mTorr	40°C
G	5% w/v Mannitol	5 mL	0 hr @ -40°C 3 hr @ -15°C 1 hr @ -40°C	70 mTorr	-20°C	70 mTorr	40°C
H	5% w/v Mannitol	5 mL	0 hr @ -40°C 3 hr @ -15°C 1 hr @ -40°C	100 mTorr	10°C	100 mTorr	40°C



(a) Image of sensors loaded in vial pack in staggered linear arrangement.



(b) Schematic illustrating sensor locations in staggered linear arrangement. Thermocouples 1 and 2 were located at the bottom center of the frozen product whereas thermocouples 3 and 4 were affixed to the outside of WMP4 and a vial, respectively.

Figure 3.25. Image and schematic of WMP sensor and thermocouple locations within vial pack.

3.4.2 Pressure and Temperature Variation Within Vial Pack During Primary Drying

The WMP sensor and lyophilizer process data for Cycle H (see Table 3.8) are shown in Figure 3.26. During freezing, the WMP devices closely track the measured shelf and thermocouple temperatures. Freezing is conducted at half atmospheric pressure and it can therefore be assumed that the thermal coupling between the shelf and the gas is not significantly attenuated. WMP1 and WMP3 register a constant offset of around 4-5°C greater than the rest of the group due to their exposure to radiation and convective currents along the chamber wall at their locations near the edge of the pack.

At the onset of primary drying at 7.5 hours the pressure surrounding the vials begins to increase in response to the shelf temperature ramp. Initially, the indicated pressure is lower than the absolute measurement from the capacitance manometer due to the presence of nitrogen in the shelf network. During the ramp, water vapor gradually replaces the inert ballast and the pressure gradient from center to edge rises. Over the course of primary drying, all sensors show a gradual decrease in local pressure and an approximately constant offset relative to one another. The decreasing pressure gradient indicates a decreasing sublimation rate since a lower vapor load requires a smaller actuating force. This behavior results from the growing dry layer thickness as the drying process proceeds. The dry layer contains a tortuous network of passages of finite conductance which act to restrict mass transfer [91], [93]. Near the end of primary drying at around 18.5 hours the pressure indicated by the WMP devices falls rapidly as the bulk ice is completely removed. Here, nitrogen ballast fills the chamber and ingresses towards the center of the shelf. In experiments taking time-lapsed videos with pure water, it was observed that the drop in Pirani gauge pressure at this location corresponds to the disappearance of bulk ice in the edge vials. The second inflection at 23 hours was correlated to the disappearance in center vials. Following primary drying, most of the initial water content is removed and the WMP sensors read erroneously low due to the lower heat transfer efficacy of nitrogen (a factor of 1.25 if temperatures, pressures, and thermal accommodation coefficients are assumed to be equal)[102], [103]. It should be noted that WMP data in this region are extrapolated and therefore exhibit an offset relative to

one another. The secondary drying phase between 27 and 30 hours is met with an increase in the indicated pressure signal due to the desorption of water vapor from the dry layer, however these measurements are not absolute and provide only an indication of when the secondary drying process is complete.

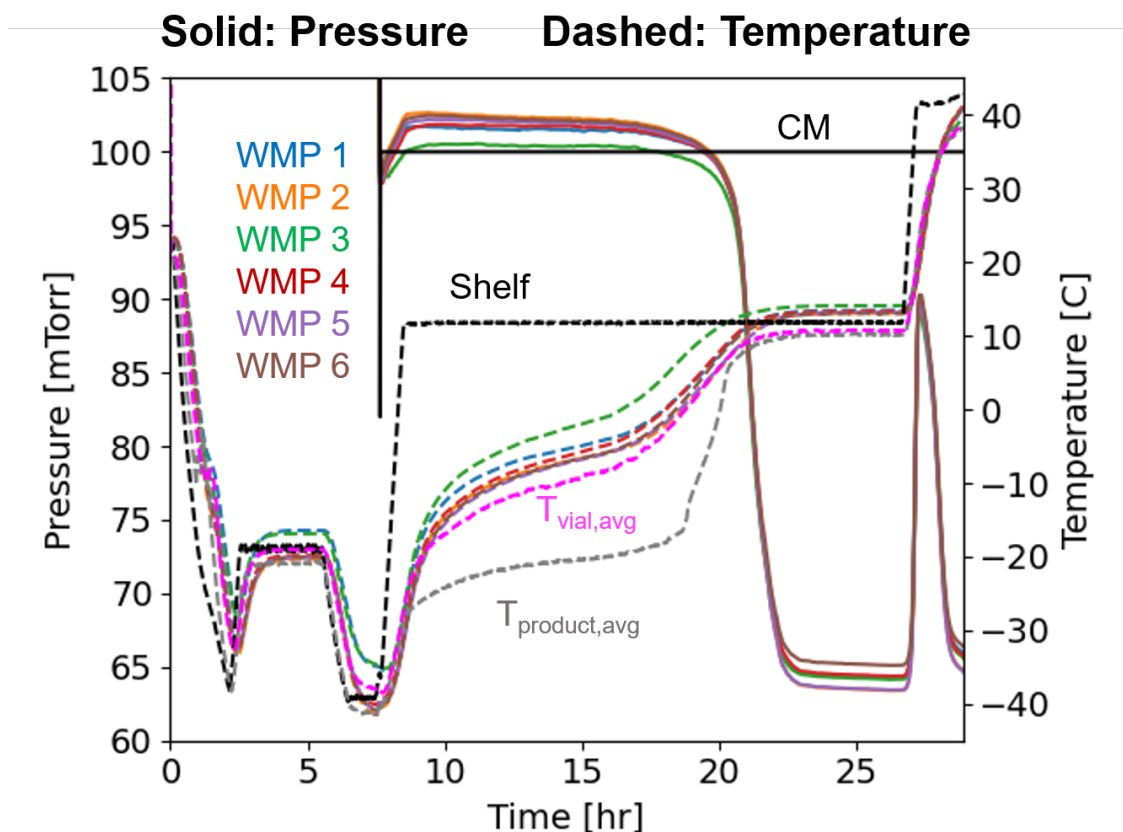


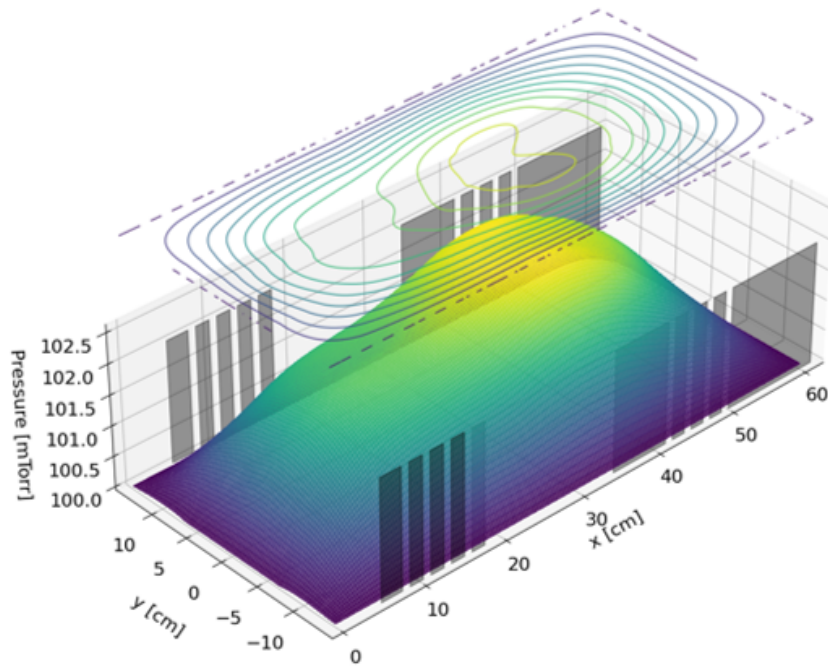
Figure 3.26. Process data from cycle H in Table 3.8. Pressure data are indicated by solid lines and temperature by dashed. The indicated pressure is assumed absolute over the duration of primary drying (approximately 8-17 hours)

In terms of measured gas temperature, all devices except WMP1 and WMP3 produce readings within approximately 1°C over the course of primary drying. Similar to freezing, WMP1 and WMP3 measure higher temperatures than the rest of the group due to the well-known radiative and convective heating action near the edge of the shelf [75], [104]. WMP3 is closest to the edge and is therefore most affected. Regardless, all wireless sensors lie roughly halfway between the product and shelf temperatures.

Thermocouples were used to evaluate the effect of parasitic heating of the WMP sensors on the product in adjacent vials. TC 1 was placed in an isolated center vial and TC 2 was located in a vial adjacent to WMP4 (see Figure 3.25). The two probes showed no greater than a $\pm 2^{\circ}\text{C}$ offset throughout the entire process which suggests the heating effect of the WMP sensors is small. For clarity, the displayed product temperature represents the average of the two. Thermocouples 3 and 4 were attached to the external surfaces of the WMP enclosure and isolated center vial, respectively. These probes also exhibited nearly identical behavior, having a variation of 2.5°C over the course of primary drying.

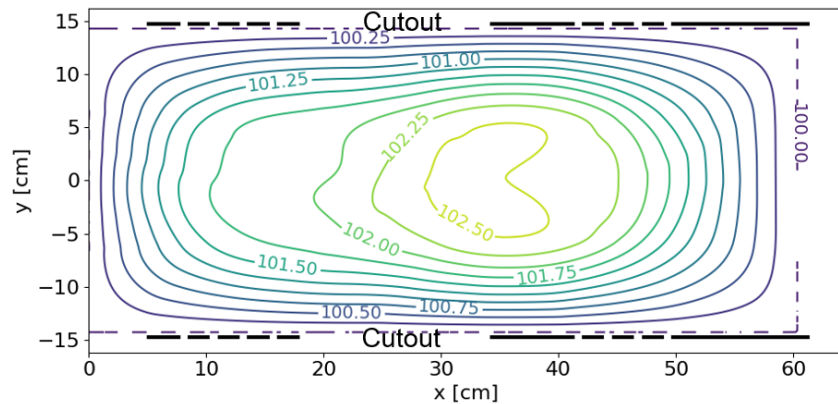
Cycle H was duplicated with all sensor positions shifted two vial spaces along the y-direction to enable a high resolution mapping of gas pressure and temperature to be determined over the shelf. The linear staggered arrangement is maintained. Measurements from both runs are combined at a process time of 11 hours to form surface and contour data of pressure and temperature in Figures 3.27 and 3.28, respectively. The chamber pressure of 100 mTorr is imposed at the shelf boundaries to fill the map. Temperatures at these locations are unknown and thus only a partial distribution can be obtained. Locations closer to the sidewall were considered invalid as the effects of local ballast diffusion (e.g. through turbulent mixing) into the shelf area are unknown. Solid portions of the sidewalls are indicated in the figure by the gray shaded regions.

The data in Figure 3.27 demonstrate a smoothly varying pressure distribution over the area of the shelf with a maximum slightly aft of center and minimum along the periphery. The mild asymmetry between the front and rear of the shelf is most likely due to the outlets in the supporting sidewalls between 18cm and 34cm. The locations of these features are indicated in the contour data. The pressure gradients with respect to the y-coordinate near the outlets are 24% larger than those in the x-direction and tend to draw the vapor away from the centerline. The outlets reduce mass flow demands in the x-direction and ultimately lower the gradient towards the front half of the shelf. Asymmetries can also arise due to the location of the duct that separates the process and condenser chambers [88], [90]. Regardless of the cause, gravimetric data reveal that the measured spatial variations in pressure have negligible impact on the sublimation rate at the laboratory scale. However, these variations will tend to grow with increasing shelf length and will potentially affect drying rate in a



(a) Surface plot illustrating variation of measured pressure over shelf surface for cycle G. The sidewall cutouts between 18 cm and 34 cm shifts the location of maximum pressure aft of the center point. Pressure magnitude smoothly decreases from this location to the edges.

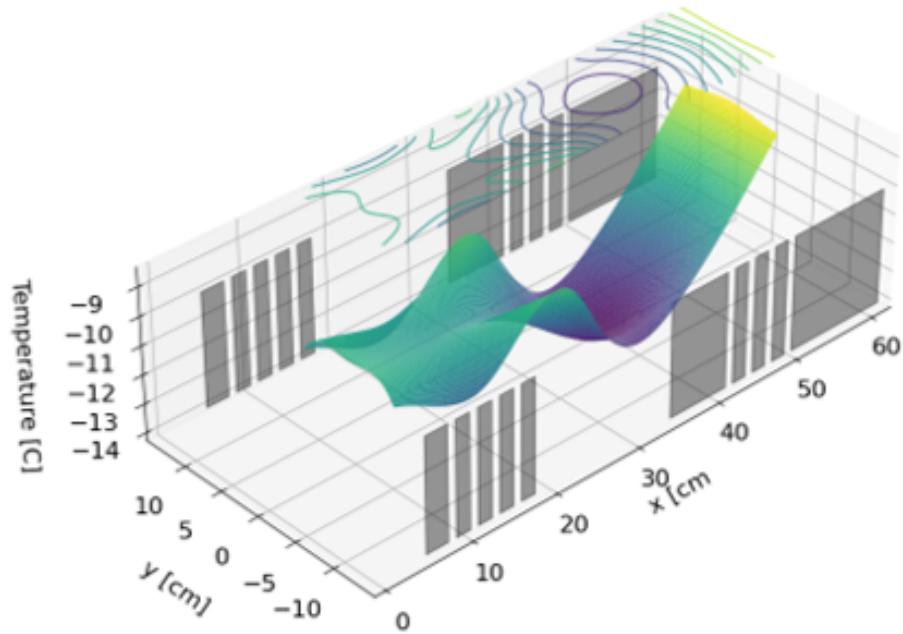
Contours of Static Pressure



* All units in mTorr

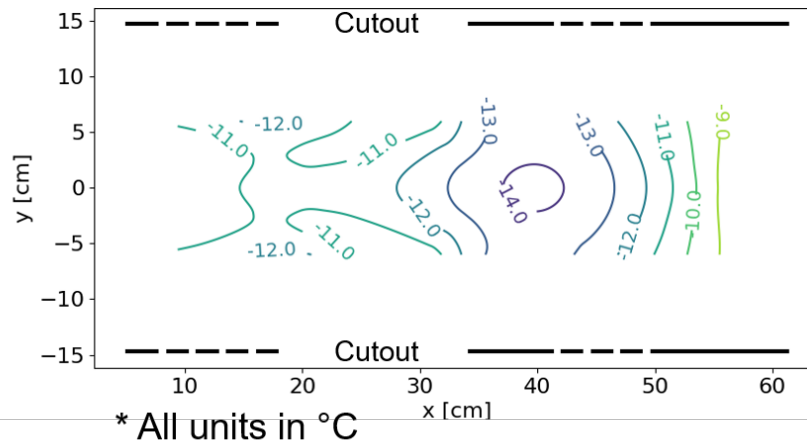
(b) Contour plot of measured pressure over the shelf surface for cycle G. The sidewall cutouts produce strong pressure gradients in the y-direction and cause the flow to preferentially flow towards these features.

Figure 3.27. Surface and contour plots of measured pressure around 3 hours after the start of primary drying using cycle H.



(a) Surface plot illustrating variation of measured temperature over shelf surface for cycle H. The sidewall cutouts between 18 cm and 34 cm shifts the location of minimum temperature aft of the center point. The cutouts lead to local maxima due to the radiative and convective heating outside of the shelf.

Contours of Gas Temperature



(b) Contour plot of measured gas temperature over the shelf surface for cycle H. The increase in temperature towards the shelf exits is due to the convective heating from the shelf as well as the edge effect.

Figure 3.28. Surface and contour plots of measured temperature around 3 hours after the start of primary drying using cycle H.

production setting where characteristic sizes are on the order of a few meters. In some cases, it is expected that the center vials will dry at the same or even faster rates relative to edge vials. Such behavior could potentially be exploited to improve overall batch uniformity [93].

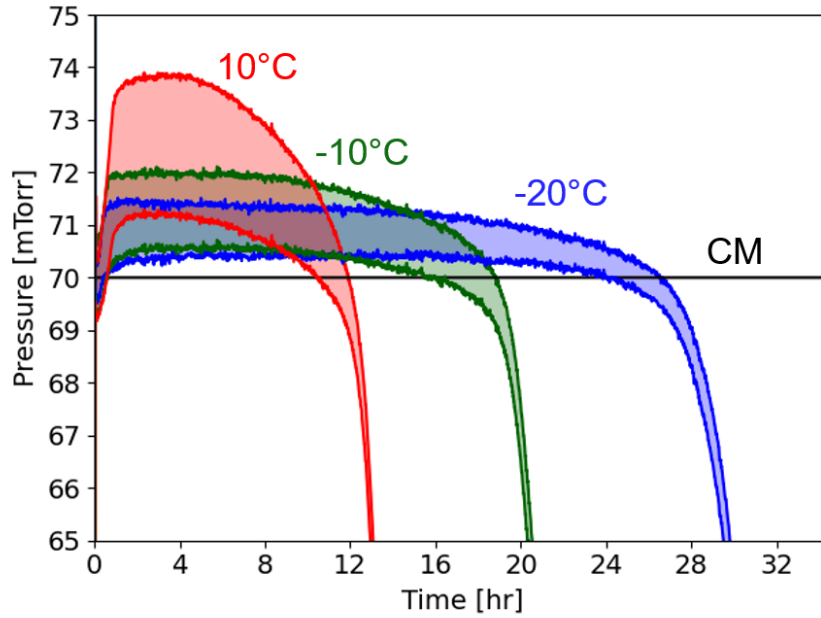
The temperature data in Figure 3.28 indicate a minimum temperature near the location of maximum pressure. It is expected that the gas temperature increases towards the outlets due to the influence of shelf convection and the edge vial effect [75]. The temperature near the sidewall outlets is comparable to the shelf fore and aft exits, suggesting the edge vial effect is enhanced for samples in this area. From gravimetric calibration data, the vials in the shelf cutout region dried an average of 8% faster than the average of the center vials. Samples at the shelf fore and aft exits dried 15-20% faster than the center vials, supporting published results that these areas are most affected by the phenomenon [75].

Effect of Shelf Temperature

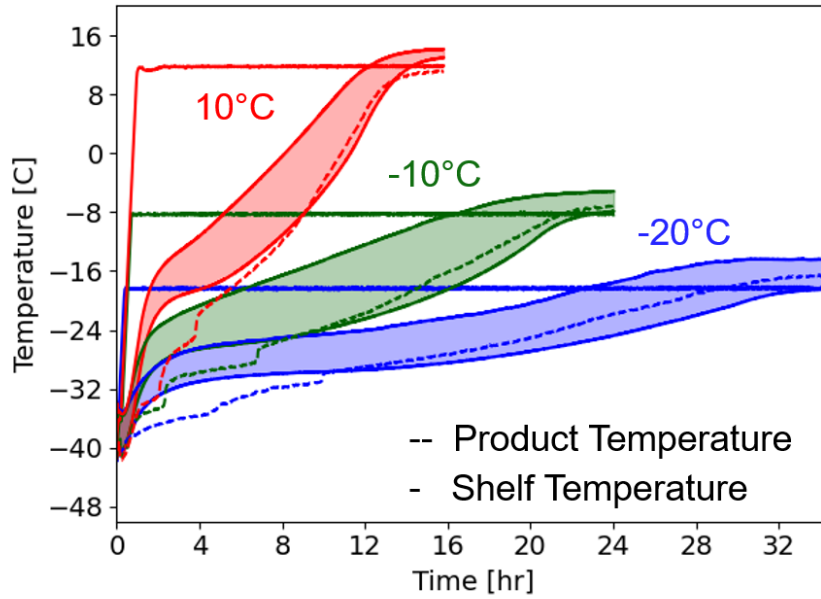
Raising the shelf temperature increases the heat flow into the cake which provides additional energy to offset that which is lost through sublimation. The effect of shelf temperature on measured local gas pressure and temperature for a formulation of 5% w/v sucrose is shown in Figure 3.29 for center (WMP2) and edge (WMP3) vials. The cycles represented are B, C, and D in Table 3.8.

The pressure difference from center to edge at a fixed pressure of 70 mTorr increases with increasing shelf temperature. This behavior can be explained by the increase in mass flow rate between the shelves. As vapor is introduced to this region the principle of mass conservation requires an increase in flow velocity and stretching of the profile. The shear stress (viscous dissipation) scales with the velocity gradient normal to the solid surfaces. Therefore, as velocity increases the shear stress increases and the system must apply a larger pressure gradient to maintain the target mass flow rate.

The gas temperature in Figure 3.29 at the onset of primary drying experiences a rapid increase as the shelf temperature is raised to its target setpoint. During this period the sublimation rate is low and the heat transfer into the gas is dominated by conduction from the shelves. As the setpoint is approached, the cold subliming water vapor enters the shelf



(a) Center-to-edge pressure difference



(b) Center-to-edge temperature difference

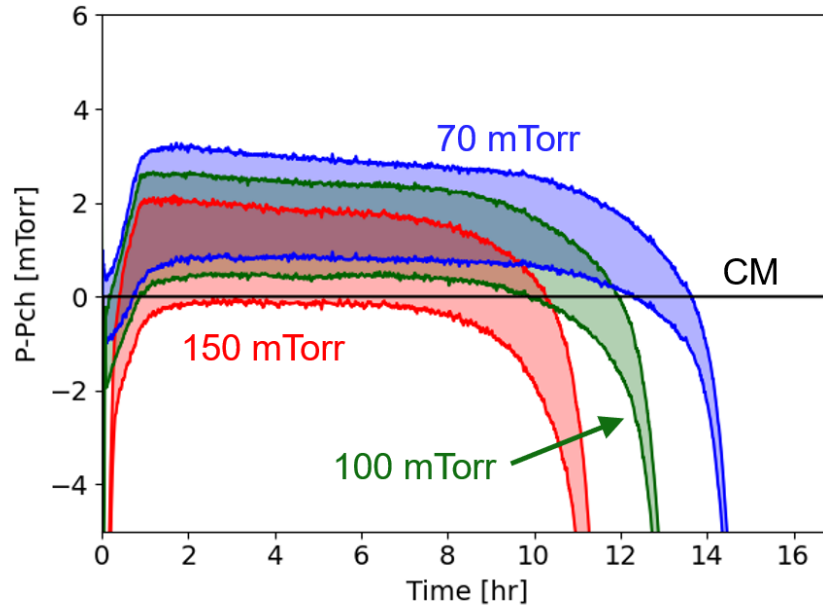
Figure 3.29. Effect of shelf temperature on a) gas pressure and b) temperature during primary drying using cycle H. Increasing shelf temperature increases sublimation rate which leads to a larger pressure drop from center to edge.

network and begins to offset the heating. This behavior is indicated by the deceleration of the measured gas temperature near the 1-2 hour mark. As primary drying proceeds the sublimation rate decreases due to the increasing dry layer resistance and the gas temperature once again accelerates. The conclusion of primary drying is indicated by the second deceleration of the gas temperature as it approaches the shelf setpoint. The thermocouple measurements demonstrate an offset relative to the gas temperature at the beginning of primary drying. At some point, all data experience an abrupt increase and track inside of the envelope formed by the center and edge gas temperatures. This sudden change is a result of the sublimation front crossing the thermocouple junction. As a result, the product temperature measurement after this time is no longer valid as the measurement is that of the dry layer.

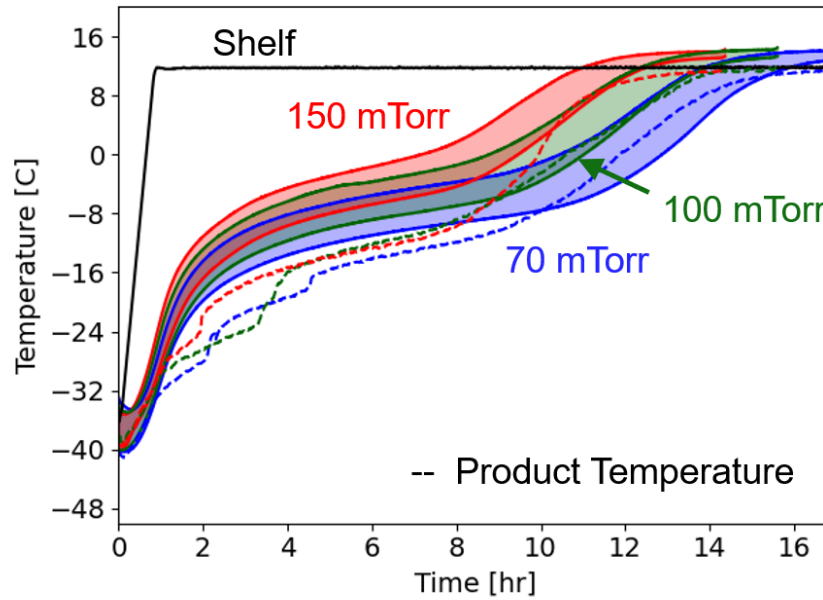
Effect of Chamber Pressure

The chamber pressure influences the efficacy of heat transfer to the vial in the form of gas conduction and therefore contributes significantly to the sublimation rate. The heat transfer performance is usually determined empirically and is accounted for in the form of the vial heat transfer coefficient [68]. To observe the effect of the chamber base pressure, a series of experiments using a 5% w/v sucrose formulation are carried out using cycles C, D, and E in Table 3.8. The experimental data is illustrated in Figure 3.30. Here, the pressure is expressed in terms of the gauge pressure relative to the process chamber setpoint to facilitate direct comparison between experiments.

The data in Figure 3.30 demonstrate a direct relationship between chamber pressure and sublimation rate as is evidenced by the relative times of convergence (i.e. a precipitous drop in indicated pressure and simultaneous equilibration with the shelf temperature). The clearance between the bottom of the vials used in this study and the shelf is assumed to be on the order of a few hundred microns, making it comparable to the molecular mean free path at pressures commonly applied in lyophilization. In this transitional rarefied regime, gas conduction heat transfer exhibits a nonlinear dependence on pressure which acts to modulate the heat transfer rate into the cake. For a fixed pressure, an increase in mass



(a) Center-to-edge pressure difference



(b) Center-to-edge temperature difference

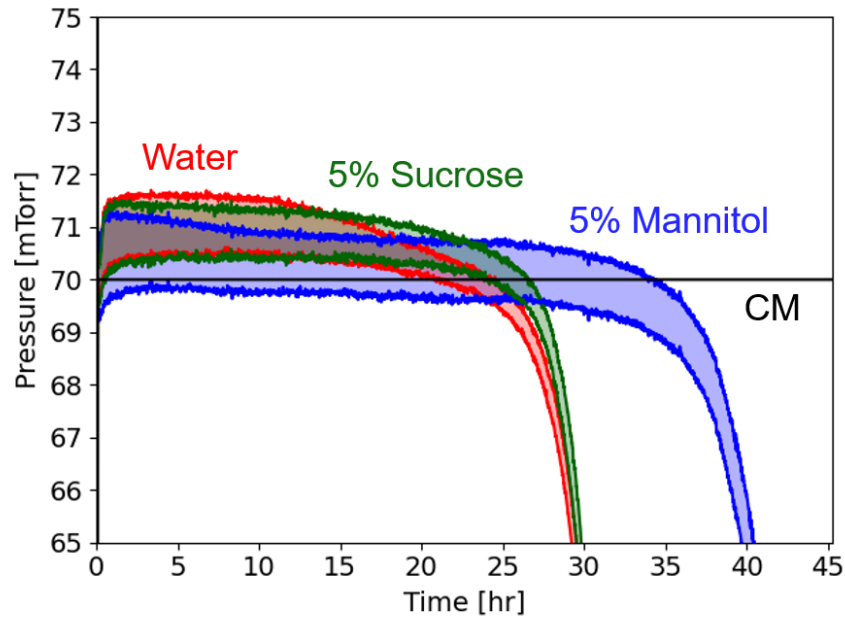
Figure 3.30. Effect of chamber pressure on a) gas pressure and b) temperature during primary drying using cycle H. Pressure data is expressed in terms of gauge pressure relative to the chamber to facilitate direct comparison. Increasing chamber pressure results in a decrease in pressure drop from center to edge due to the increase in density.

transfer rate was shown in Figure 3.29 to increase the pressure gradient from center to edge. However, as chamber pressure increases at a constant shelf temperature the pressure difference from center to edge in Figure 3.30 decreases. This inverse variation with bulk density is in qualitative agreement with the analytical model proposed by Massey for a channel flow with semi-porous membrane [79]. The physical explanation for this trend lies in the Reynolds number, a non-dimensional variable defined as the ratio of the inertial to viscous forces. In lyophilization, the Reynolds number in the shelf section is on the order $O(1)$ which suggests that local turbulent fluctuations are heavily dampened and the flow will exhibit laminar behavior. As Reynolds number is increased (e.g. by increasing density, mass flow rate, or channel height), the inertial forces grow relative to the viscous forces and the flow more readily overcomes the energy loss through viscous dissipation. As a result, a lower pressure gradient is required to transport the given quantity of fluid from the center of the shelf to the edge.

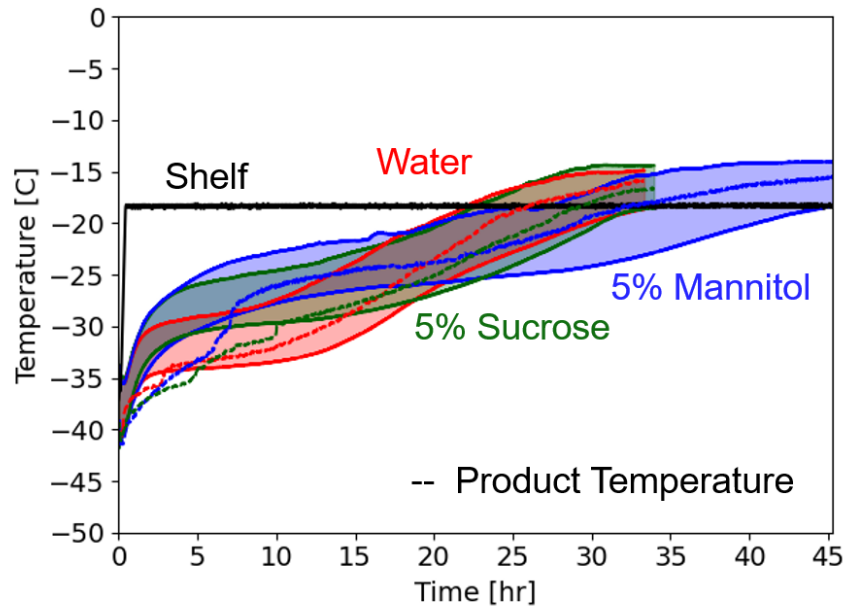
Effect of Excipient

The excipient composition and concentration affect the mass transfer resistance and the pressure variation over the vial pack. To examine the influence of different excipients a series of tests are carried out using UPW, 5% w/v sucrose, and 5% w/v D-mannitol. These cycles are given by A, B, and G in Table 3.8, respectively. A comparison of measured gas pressure and temperature at the center and edge of the vial pack for each excipient over the course of lyophilization is shown in Figure 3.31.

The UPW samples dry most quickly due to the absence of a dry layer. The pressure difference is nearly constant over the first half of primary drying, suggesting the sublimation rate in this interval is also constant. As the ice front approaches the bottom of the vial in the latter half of primary drying it assumes a hemispherical shape and recedes inwards towards the axis. The reduction in surface area leads to reduction in sublimation rate and ultimately in the pressure difference from center to edge. The behaviors of sucrose and mannitol are also shown in Figure 3.31. The 5% w/v sucrose formulation produces a drying time very close to that of pure water due to its low mass transfer resistance with respect



(a) Center-to-edge pressure difference



(b) Center-to-edge temperature difference

Figure 3.31. Effect of excipient on a) gas pressure and b) temperature during primary drying using cycle H. The excipient has a significant impact on sublimation rate due to the effects of pore size and microcollapse.

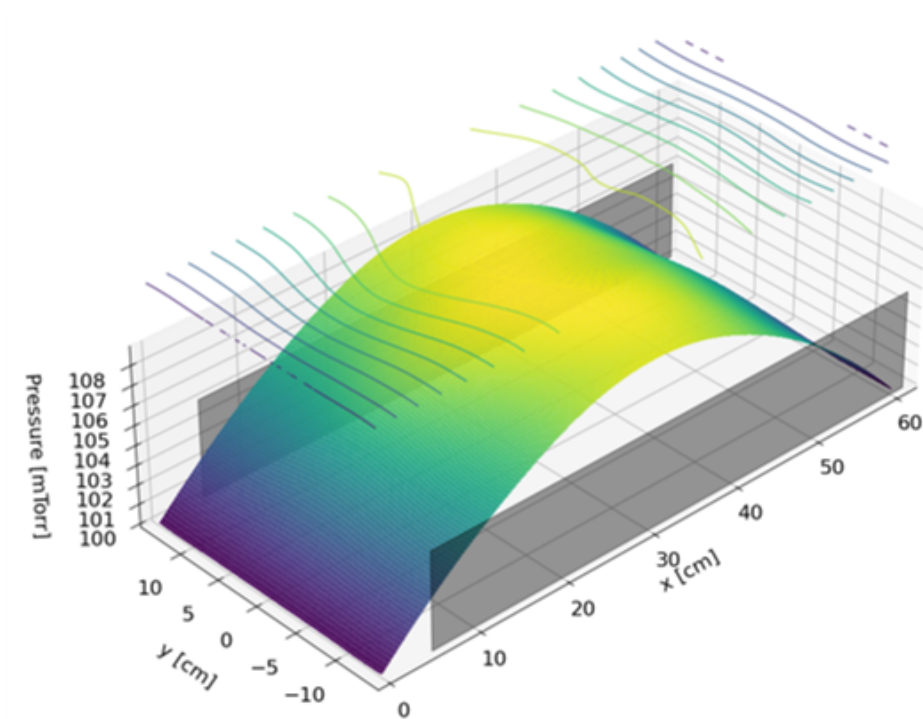
to dry layer thickness. It has been shown that the low critical temperature of sucrose leads to microcollapse of the partially dried layer as the sublimation front progresses, resulting in a nearly linear increase in pore size with dry layer thickness [105]. Gas conductance in the rarefied flow regime (i.e. when the molecular mean free path is much larger than the pore diameter) is proportional to the pore diameter and inversely proportional to the channel length, resulting in competing mechanisms over the course of primary drying. The high critical temperature of mannitol formulations inhibits this effect, resulting in a constant pore diameter and constant conductance throughout the drying process. Therefore, for a given shelf temperature and chamber pressure, mannitol formulations will have increased drying times and lower sublimation rates than sucrose at similar concentrations.

Effect of Lyophilizer Configuration

Lyophilizers come in a wide array of sizes and configurations from laboratory to production scale. One feature that has a pronounced effect on the gas pressure in the vicinity of the vials is the shelf support system. To examine the relative influence of the sidewall outlets a pair of polycarbonate barriers are installed to constrain vapor flow along the length of the shelf. Two tests are performed using cycle H from Table 3.8. The sensors are moved between the tests to capture the spatial variations in pressure assuming drying performance is unchanged. The resulting pressure and temperature surface data and contours are shown in Figures 3.32 and 3.33. The solid sidewalls are indicated by the gray shaded regions.

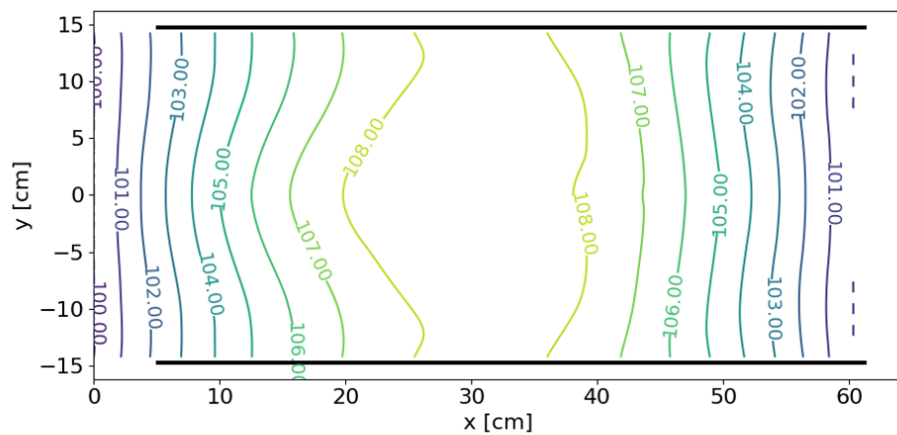
The influence of the flow barriers is clear when comparing the results from Figure 3.27 to those in Figure 3.32. The flow barriers constrain the vapor to move along the length (x-axis) of the shelf only. In this case, the transverse flow component is negligible and there exists no pressure gradient in this direction. The location of maximum pressure lies closer to the true center of the shelf and the variation on either side of this location is highly symmetric.

The gas temperature data also exhibit symmetric behavior. However, in this case, the distribution is parabolic. The temperature rises as the gas proceeds away from the center point due to the radiative and convective heat transfer. The measured gas temperatures along the flow barriers are comparable to those measured at the fore and aft ends of the



(a) Surface plot illustrating variation of pressure over shelf surface for cycle H with flow barriers. The flow is constrained to move along the x-direction only which acts to eliminate the pressure gradient in the y-direction.

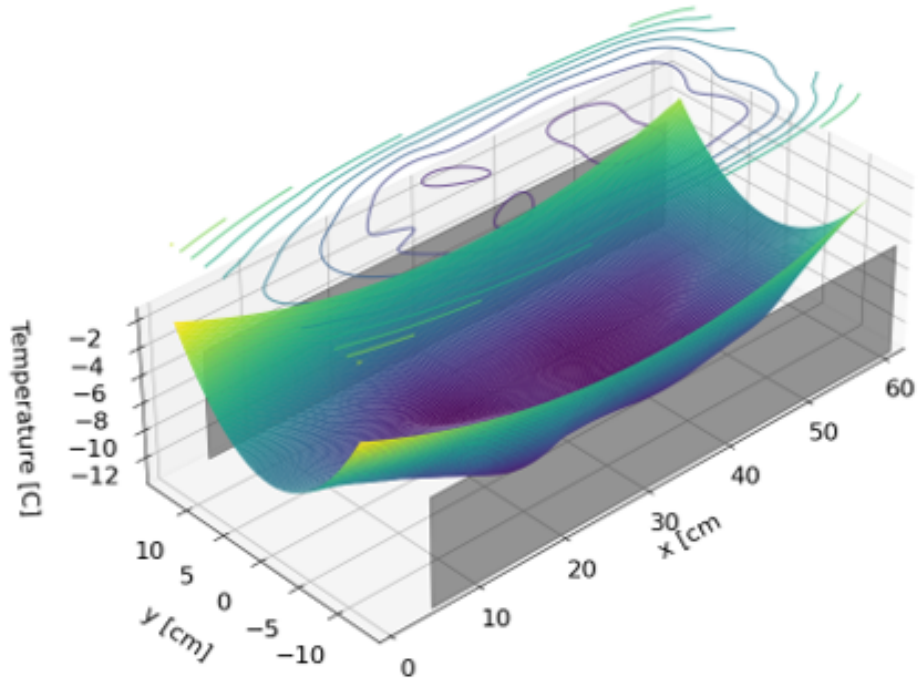
Contours of Static Pressure



* All units in mTorr

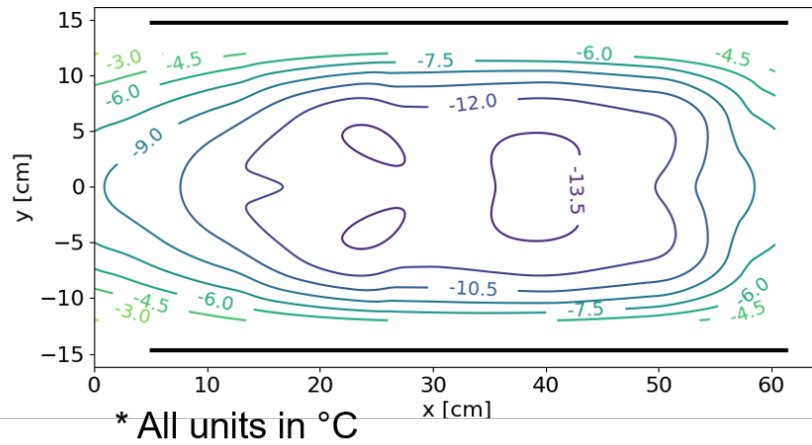
(b) Contour plot of pressure over the shelf surface for cycle H with flow barriers.

Figure 3.32. Surface and contour plots of measured pressure around 3 hours after the start of primary drying using cycle H with flow barriers.



(a) Surface plot illustrating variation of temperature over shelf surface for cycle H with flow barriers.

Contours of Gas Temperature



(b) Contour plot of temperature over the shelf surface for cycle H with flow barriers. The increase in temperature towards the shelf exits is due to the convective heating from the shelf as well as the edge effect.

Figure 3.33. Surface and contour plots of measured temperature around 3 hours after the start of primary drying using cycle H with flow barriers.

shelf. In contrast to the measurements without the flow barriers, the variation is smooth along the entire edge.

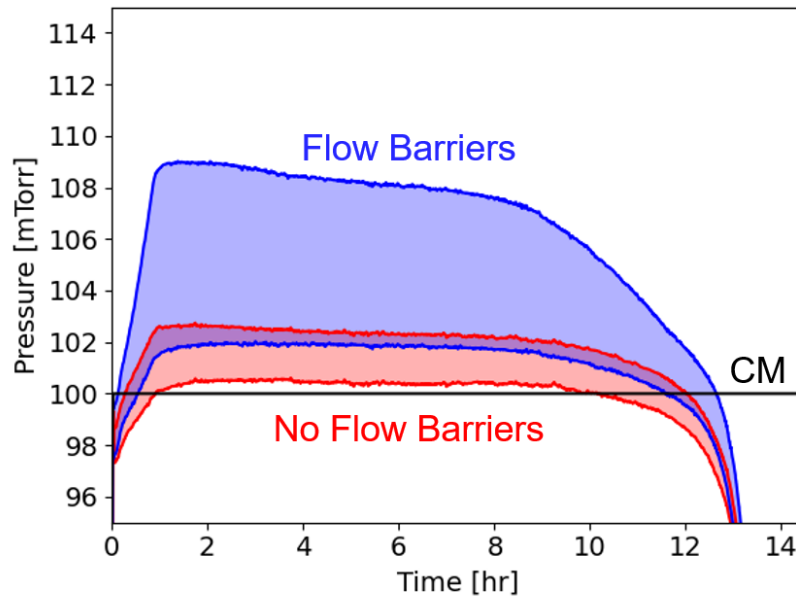
A comparison of the pressure and temperature variation from the center of the shelf to the edge for cycle H with and without sidewall flow barriers is shown in Figure 3.34. Constraining the flow to move along the length of the shelf has a significant influence on the pressure difference, moving from 2.6 mTorr with cutouts to 9 mTorr without. Although local pressure is higher with the false walls installed there is no observable effect on sublimation rate as indicated by the relative convergence times of the WMP devices. The influence of these variations on heat transfer performance are likely too small (on the order of a few percent) to have an appreciable effect on the sublimation rate [93]. The gas temperature over the course of primary drying also exhibits almost no dependence on the flow barriers, further supporting the observation that the sublimation rates for both cases are nearly identical.

3.5 Sublimation Rate and Product State Estimation During Primary Drying

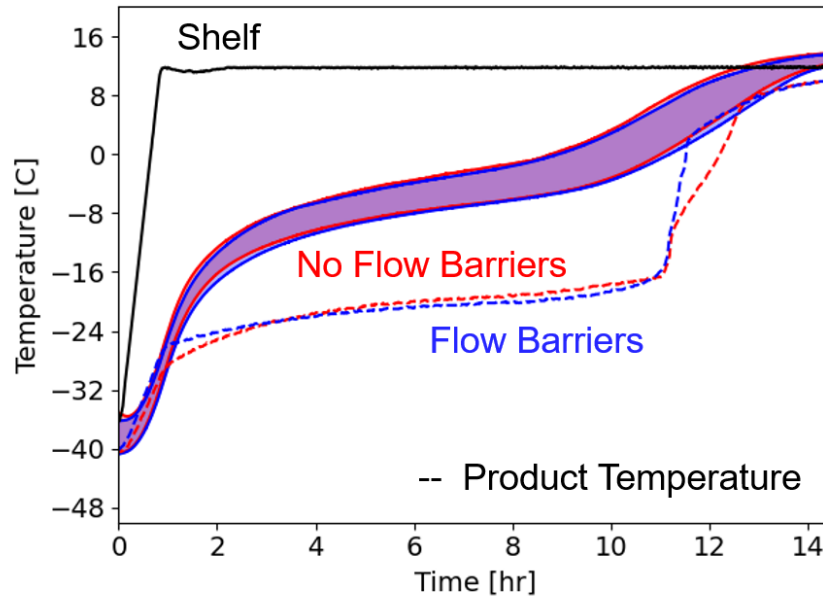
The WMP devices measure local gas pressure and temperature throughout the primary drying process. This information is useful from the standpoint of process monitoring, control, and heat and mass transfer characterization. Two mathematical models have been developed to estimate drying performance during primary drying. The first employs Computational Fluid Dynamics (CFD) to provide a high-fidelity estimate of flowfield behavior. The results are combined with experimental data to determine the sublimation rate, heat and mass transfer properties, and product temperature throughout the process. The second is based on a simplified two-dimensional representation of the flow within the shelf network and uses local pressure measurements to determine the spatial variation in sublimation rate in the inverse sense.

3.5.1 Heat and Mass Transfer Model

The sublimation rate represents one of the most significant process variables in lyophilization due to its ability to capture relevant variables including product temperature, heat trans-



(a) Center-to-edge pressure difference



(b) Center-to-edge temperature difference

Figure 3.34. Effect of lyophilization chamber configuration (sidewalls) on a) gas pressure and b) temperature during primary drying using cycle H. The sidewalls prevent flow from exiting the shelf in its transverse direction and therefore produces a pressure drop 2.6 times greater from center to edge. The flow barriers have little influence on overall drying rate as indicated by nearly identical drying times.

fer performance, and mass transfer resistance. The magnitude of the sublimation rate relies on a coupled exchange of mass and energy that is schematically represented in Figure 3.35.

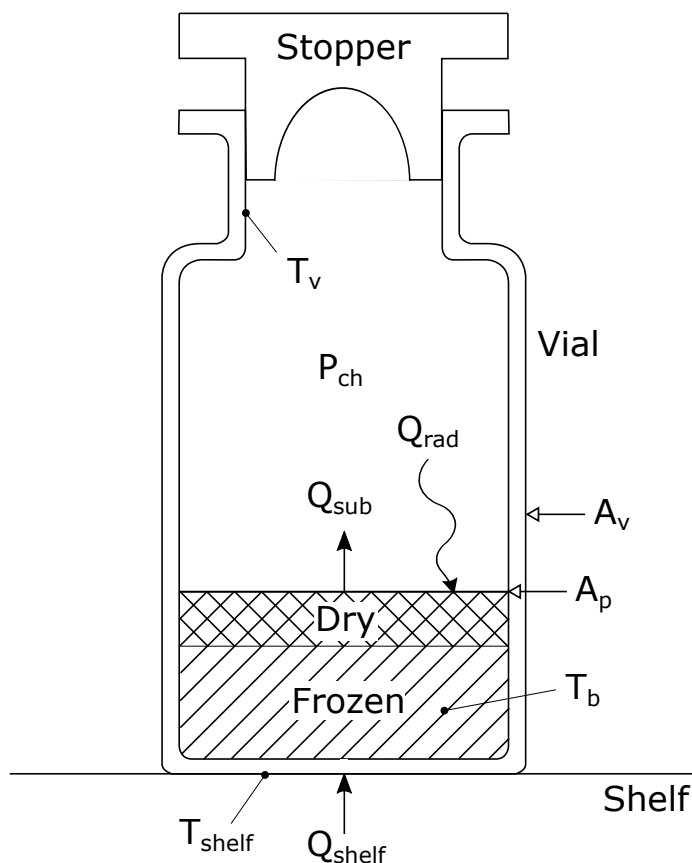


Figure 3.35. Vial energy balance. Energy is provided to the cake via solid conduction, gaseous conduction, and radiation to offset the energy lost through sublimation.

Following freezing, the gas in the process chamber is evacuated using a vacuum pump. As the chamber pressure approaches the saturated vapor pressure of the solvent the system attempts to maintain equilibrium between the solid and vapor phases through sublimation. The sublimation process is endothermic and therefore provides a cooling effect on the product as mass is removed. To offset the cooling, the temperature of the shelf is raised above the temperature of the frozen solid. Energy is transferred from the shelf to the frozen product

through the bottom of the vial via gas conduction, solid-state conduction, and radiation. Assuming a quasi-steady state, the overall energy balance from Figure 3.35 is simply

$$\frac{dQ}{dt} = Q_{shelf} + Q_{rad} - Q_{sub} = 0 \quad (3.19)$$

The sublimation energy, Q_{sub} , is dominated by the latent heat of sublimation which is around two orders of magnitude greater than the sensible contribution. The overall energy transfer out of the system is then

$$Q_{sub} = \dot{m}_{sub} H_{sub} \quad (3.20)$$

The shelf and radiation terms are frequently combined into a linear form to simplify the analysis. Under this method the energy entering the system becomes

$$Q_{shelf} + Q_{rad} \approx K_v A_v (T_s - T_b) \quad (3.21)$$

The heat transfer coefficient, K_v , is dependent on both the vial geometry and chamber pressure and must be determined through calibration. The vial-specific empirical fit expression is often given by

$$K_v(p_{ch}) = K_C + \frac{K_P p_{ch}}{1 + K_D p_{ch}} \quad (3.22)$$

The constant portion of the heat transfer coefficient represents the solid state conduction and radiation between the shelf and glass vial. The pressure-dependent term is a result of the non-linear heat transfer associated with the transition from the free-molecule to continuum regimes. The transition region is generally described in terms of the Knudsen number, Kn . For Knudsen numbers greater than 10, the flow is considered collisionless and the heat transfer between the shelf and the bottom of the vial varies linearly with pressure. Conversely, as the Knudsen number approaches zero the heat transfer becomes largely independent of pressure. The gap between the bottom of the vial and the shelf is typically on the order of a few hundred microns which leads to a Knudsen number near unity. This transitional regime

branches the free-molecule and continuum regimes and is reasonably approximated by the form given in equation 3.22.

During primary drying, the heat from the shelf moves upwards through the ice layer towards the sublimation interface. The finite thermal conductivity of the frozen formulation leads to a temperature gradient between upper and lower surfaces. This variation is linear and can be expressed simply using Fourier's law.

$$Q_{cond} = k_{ice} A_p \frac{T_b - T_{sub}}{l_d - l_0} \quad (3.23)$$

where k_{ice} is the thermal conductivity of the frozen layer, A_p is the product (ice) cross sectional area, l_d is the dry layer thickness, l_0 is the initial fill height, and T_{sub} is the ice temperature at the ice/gas interface. Typical temperature variations within the frozen layer during primary drying are on the order of one or two degrees. As the water vapor leaves the sublimation interface it must pass through the dry porous layer on its way into the process chamber. This layer introduces a resistance to mass transfer and therefore requires a pressure gradient for actuation. The mass flow rate through the dry layer is expressed as

$$\dot{m} = A_p \frac{p_{vap}(T_{sub}) - p_{ch}}{R_p} \quad (3.24)$$

Here, p_{vap} is the saturated vapor pressure at the sublimation interface (and is a function of ice temperature) and R_p is the empirical product resistance which depends both on the dry layer pore density and thickness. Generally, R_p assumes the form

$$R_p = R_0 + \frac{R_1 l_d}{1 + R_2 l_d} \quad (3.25)$$

The coefficients, R_0 , R_1 , and R_2 are product-dependent (and, in many cases, process-dependent) and evaluated through calibration. The pressure at the interface depends on the ice temperature so the mass transfer becomes coupled directly to the heat transfer. Combining equations 3.22, 3.23, and 3.25, the product temperature at the base of the vial (representing the highest and therefore most critical temperature in the system) is determined by discretizing the dry layer and iteratively stepping through its thickness [76].

If the sublimation rate is known, equations 3.19-3.25 can be used to estimate either the heat and mass transfer properties or the product temperature in a non-invasive way. This capability holds several advantages over existing lyophilization PAT, especially in the production setting where large length scales and aseptic manufacturing protocols severely limit accessibility to the product.

3.5.2 Lyophilization Process Modeling Using Computational Fluid Dynamics

Flow within the shelf network was modeled using the commercial software package Fluent (ANSYS, Canonsburg, PA). The 3-dimensional incompressible Navier-Stokes equations were solved using a pressure-based steady-state solver with full pressure-velocity coupling and second-order upwind differencing. Buoyancy effects were neglected and the gas was assumed to be pure water vapor. The fluid viscosity, heat capacity, and thermal conductivity were determined from empirical correlations provided in the literature[106]. A summary of the flow parameters used in the simulations is provided in Table 3.9. The flow was also assumed to be laminar and a low-pressure velocity and temperature slip correction was applied at the solid boundaries. Justification for these models can be made through consideration of the relevant non-dimensional parameters, namely the Reynolds and Knudsen numbers. The accommodation coefficients for momentum and energy were assumed to be unity and the Lennard-Jones characteristic length was determined through an iterative estimation procedure to be $2.644\text{\AA}$. A schematic of the computational domain is shown in Figure 3.36.

A total of 201 vials were modeled (representing a load of one full shelf with the inclusion of the WMP devices) and a uniform mass flux was applied across all vials at the ice/vapor interface. The temperature at the vapor inlets was assigned based on the measured thermocouple readings. The outlets were set to a constant pressure equal to that of the measured chamber pressure. The product, vial wall, shelf, and side wall temperatures were specified independently and based directly on the lyophilizer process data.

Table 3.9. Water vapor properties used in 3-dimensional CFD model

Parameter	Symbol	Value
Pressure	P	100 [mTorr]
Density	ρ	$\frac{P}{RT}$ [kg/m ³]
Dynamic Viscosity	μ	$1 \times 10^{-4} \frac{T}{647.096} \left(1.67752 + \frac{1426.601}{T} + \frac{2.6659 \times 10^5}{T^2} - \frac{6.5465 \times 10^7}{T^3} \right)^{-1}$ [Pa-s]
Thermal Conductivity	k	$0.0088 - 1 \times 10^{-5}T + 1.4 \times 10^{-7}T^2$ [W/m-K]
Specific Heat Capacity	C_p	$1875.711 - 0.3465T - 5.919 \times 10^{-4}T^2 + 7.240 \times 10^{-6}T^3$ [J/kg-K]
Lennard-Jones Characteristic Length	σ	2.644 [Å]
Thermal Accommodation Coefficient	α_T	1.0
Momentum Accommodation Coefficient	α_M	1.0

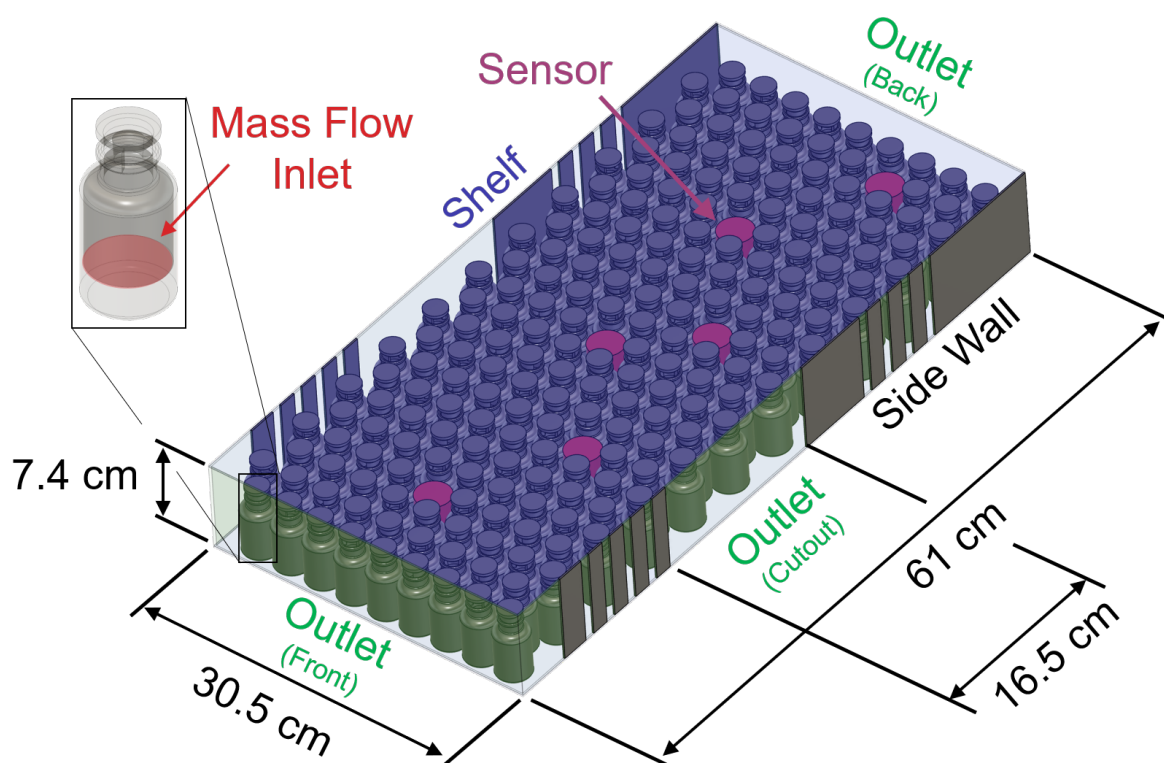


Figure 3.36. Isometric (top) and top (bottom) views of domain used for CFD simulations. Pressure outlet, wall, and velocity inlet conditions are labeled in blue, green, and red, respectively.

Grid Convergence Study

A mesh sensitivity study was performed across five meshes of increasing cell density prior to simulation. The convergence criterion was based on the relative change in pressure magnitude at the center of the shelf (location of WMP2). A summary of the study results is provided in Table 3.10. A scaled residual convergence of $1e-5$ was achieved in all cases. Mesh D was selected from this study based on considerations of accuracy and computational time.

Table 3.10. CFD sensitivity study conducted for 3D shelf domain

Mesh	# Elements	Center Pressure [mTorr]	Relative Difference to Mesh E [%]
A	3808243	2.329	4.5
B	6214726	2.369	2.9
C	11491306	2.422	0.7
D	15756677	2.432	0.3
E	21639052	2.439	-

CFD Simulation Results

The CFD model was applied to cycle H in Table 3.8 to develop a deeper understanding of flow behavior within the lyophilizer shelf network. With the chamber pressure and boundary temperatures known, the sublimation rate was estimated using a pressure matching procedure.

Sublimation Rate Estimation Procedure

The pressure matching procedure was carried out by first selecting a time point from the experimental data and assigning the measured boundary temperatures and chamber pressure. A series of simulations were then performed at sublimation rates ranging from 0.358 g/hr/vial to 0.627 g/hr/vial and the resulting pressure distributions at each of the

assigned sublimation rates were compared directly to the experimental data in the form of the root-mean square error, σ .

$$\sigma = \sqrt{\sum_{i=1}^N \frac{(p_{meas,i} - p_{sim,i})^2}{N}} \quad (3.26)$$

A spline fit was applied to the error distribution and the location of the minimum (i.e. the best match in terms of pressure between CFD and experimental data) was assumed to be the true sublimation rate. Once found, a new time point with new measured temperatures was assigned to the CFD model and the procedure was repeated. A plot of the error distribution as a function of sublimation rate is shown in Figure 3.37. The RMS difference at the minimum location was 0.06 mTorr.

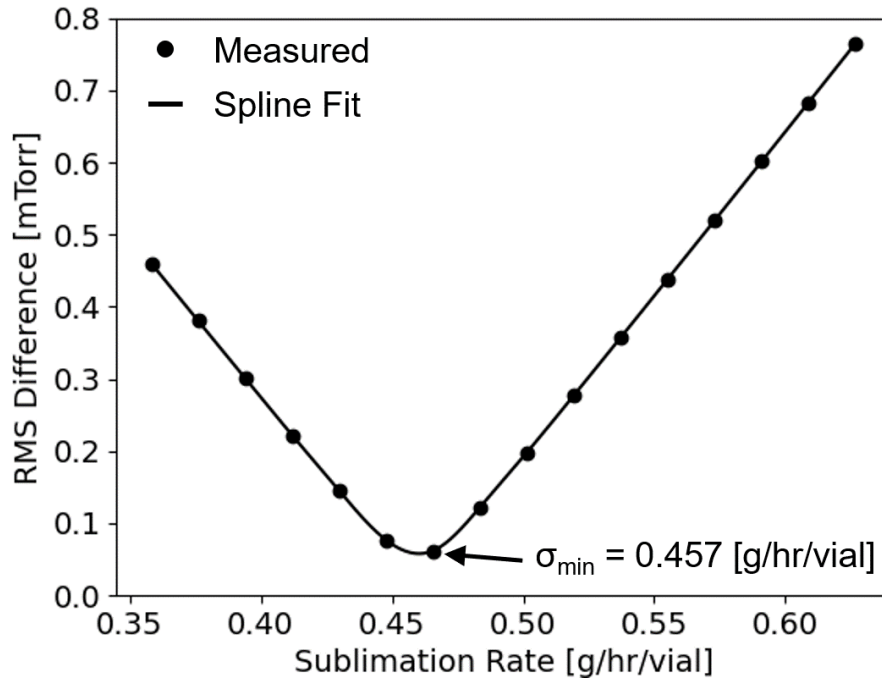


Figure 3.37. Root mean-square error determined from pressure matching procedure for cycle H at an elapsed time of 11 hours.

Matched flowfield results in terms of static pressure and velocity magnitude 2.4 hours after the beginning of primary drying (11 hours elapsed) for cycle H are shown in Figures 3.38 and 3.39. The data in terms of pressure are quantitatively similar to the experimentally

measured distribution seen in Figure 3.27b. The estimated sublimation rate at this time is 0.475 g/hr/vial from the pressure matching procedure. The average mass flow rate was confirmed experimentally using two gravimetric measurement cycles. The first cycle was stoppered 2.5 hours after the start of primary drying and the second was stoppered after 4.2 hours. A total of 6 center vials were weighed before and after the cycles and the positions of the vials were maintained between tests. The average change in mass over the 1.72 hour interval (assuming mass flow rate is constant during this period) was 0.786g with a standard deviation of 0.12g, resulting in an average sublimation rate of 0.457 ± 0.07 g/hr/vial. Comparison to the CFD prediction at this time point leads to a difference of 3.9%.

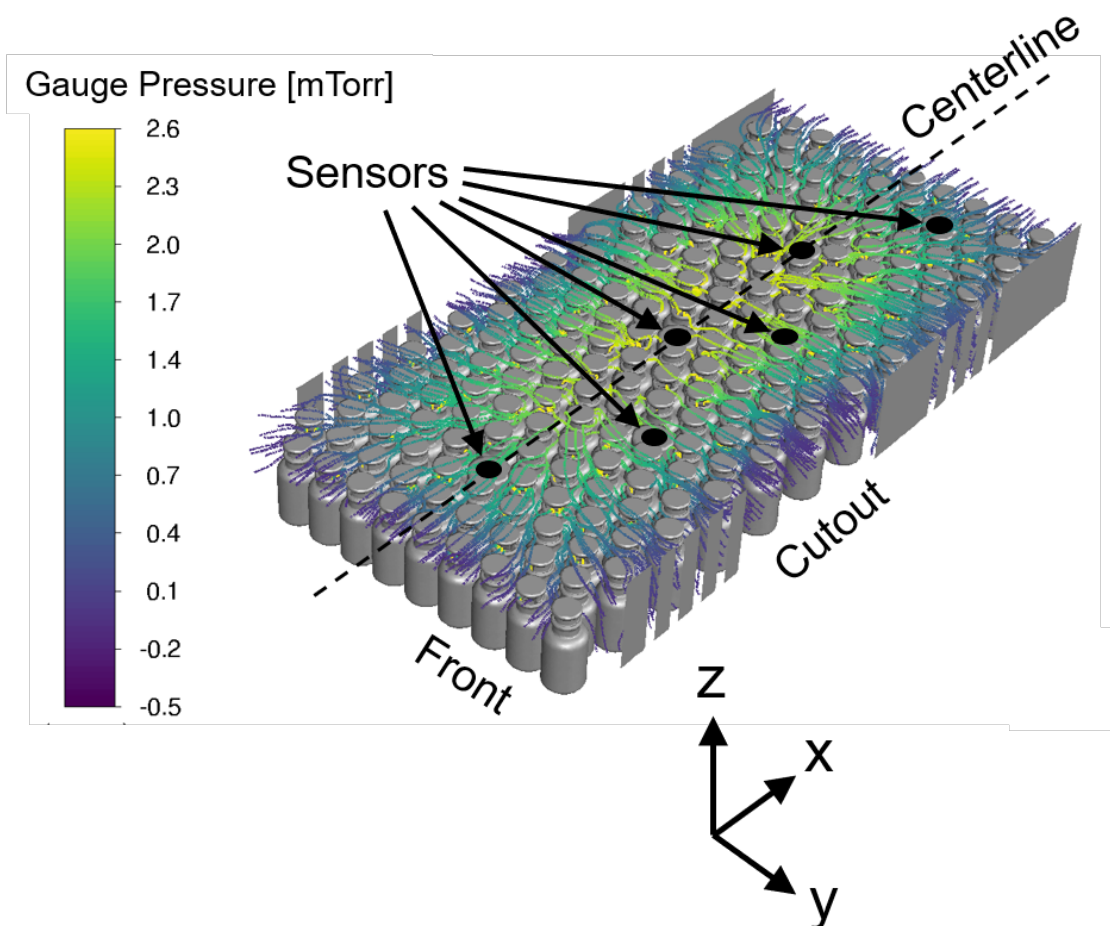


Figure 3.38. Pathlines of sublimed vapor during primary drying of 5% w/v mannitol at 100 mTorr and 10°C (cycle H in Table 3.8) colored in terms of static (gauge) pressure

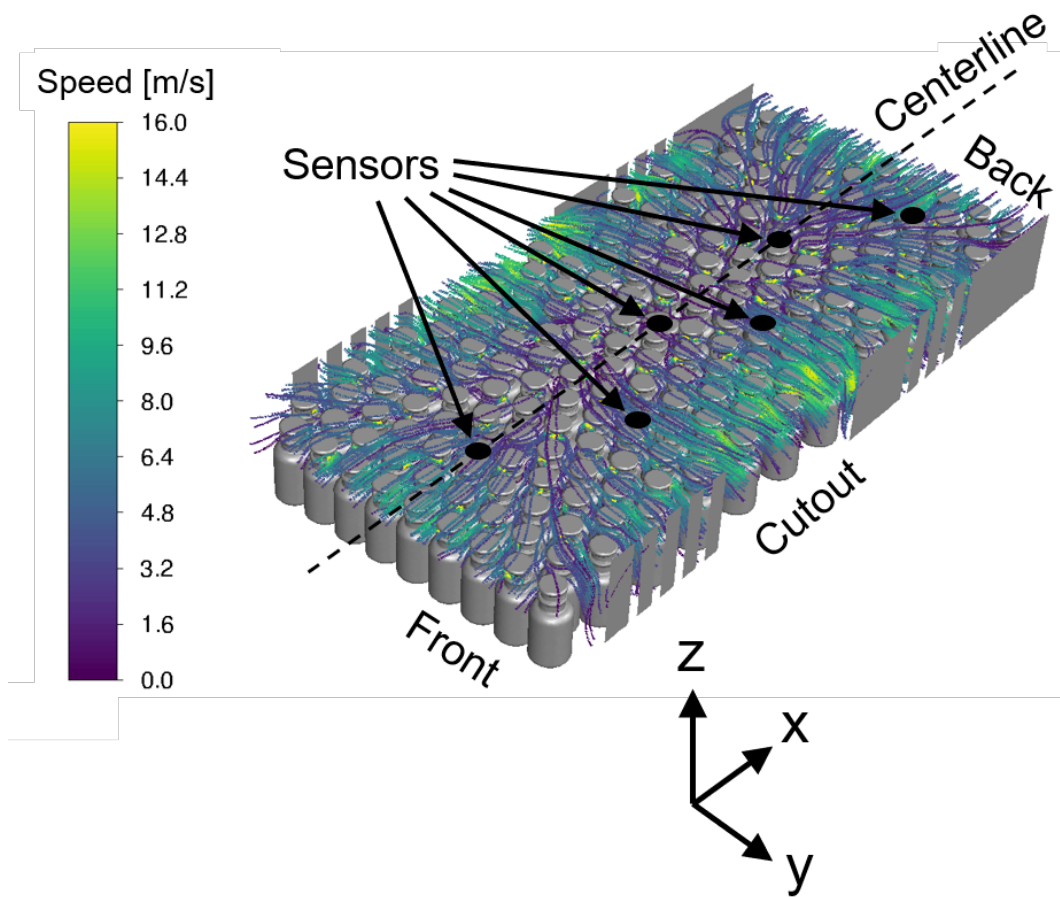


Figure 3.39. Pathlines of sublimed vapor during primary drying of 5% w/v mannitol at 100 mTorr and 10°C (cycle H in Table 3.8) colored in terms of speed

The vapor flow within the shelf network is actuated by the pressure gradients and will tend to follow the path of steepest descent (perpendicular to the isobars). The directional gradients near the center of the shelf are strongest towards the sidewall cutouts, causing the flow to accelerate towards these features and exit the domain. The sidewall outlets experience the highest fluid velocity upon exit relative to the other boundaries due to these gradients. In the fore and aft sections of the shelf the vapor preferentially exits in the x-coordinate directions since the axial gradients at these locations are either comparable or larger than the transverse.

A comparison of the measured pressure and that which is estimated from the CFD solution at the sensor locations is shown in Figure 3.40. The total root mean square deviation between the data sets at the locations of the sensors is 0.07 mTorr. Roughly 40% of the error contribution is from the sensor (WMP3) located closest to the edge of the shelf. This reading was verified as repeatable by performing a duplicate experiment with a different sensor (WMP5) at this location. One possible cause for the discrepancy near the edge of the shelf is the local mixing of nitrogen with the water vapor [88]. As the vapor passes over the final row of vials just upstream of the exit it encounters a strongly adverse pressure gradient and will tend to separate from the stoppers. This sets up a vortical region near the base of the vial which is sustained by the shearing action of the separated bulk flow. As the nitrogen ballast flows downwards past the aft exit of the shelf on its way to the duct it is likely that some of this gas becomes intermixed with water vapor in the vortex region and gets transported a small distance upstream through the gaps between the vials. This slow moving flow would likely be drawn upwards on account of the static pressure difference. Due to this mixing action, the assumption of pure water vapor near the edge vial region would be expected to break down and produce an erroneously low indicated pressure. If the measurement from WMP3 is ignored, the deviation is reduced to 0.29 mTorr. With WMP3 removed, most of the discrepancy is from WMP4 and WMP6. These devices are located off of the centerline where the transverse pressure gradients are large. The vial packing during loading was somewhat loose, so it is possible that the devices shifted slightly from their nominal positions when loading the tray. The difference between the CFD solution and measurements at these locations based on local gradient values corresponds to a position uncertainty of around 0.8 cm.

The CFD model was also applied to cycle H using the polycarbonate sidewall flow barriers. The pressure and velocity magnitude flowfields at an elapsed cycle time of 11 hours is shown in Figures 3.41 and 3.42. Boundary temperatures were set based on experimental measurements at this time. The pressure-matching procedure was used to estimate the sublimation rate and was determined to be 0.430 g/hr/vial, a 10% decrease from the case without flow barriers. The flow barriers force the vapor to exit the domain at the fore and aft exits and significantly reduce the transverse pressure gradients observed in Figures 3.27a and 3.38.

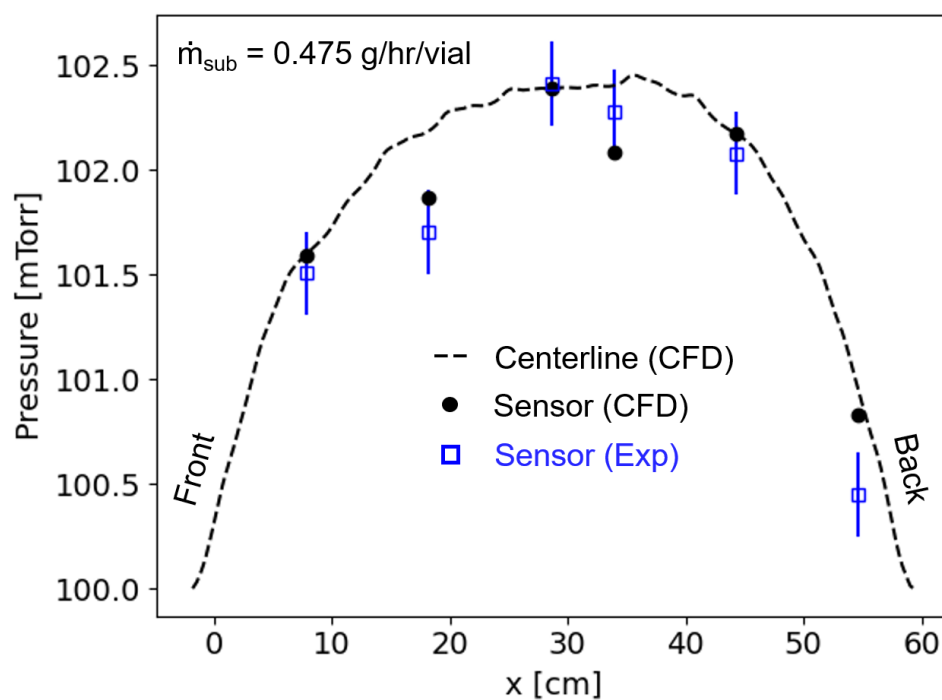


Figure 3.40. Comparison of pressure profile predicted using CFD and that which was measured during cycle H at an elapsed time of 11 hours.

This increases flow rate demands on the fore and aft exits which ultimately increases the shear stress and requires a larger pressure gradient for actuation.

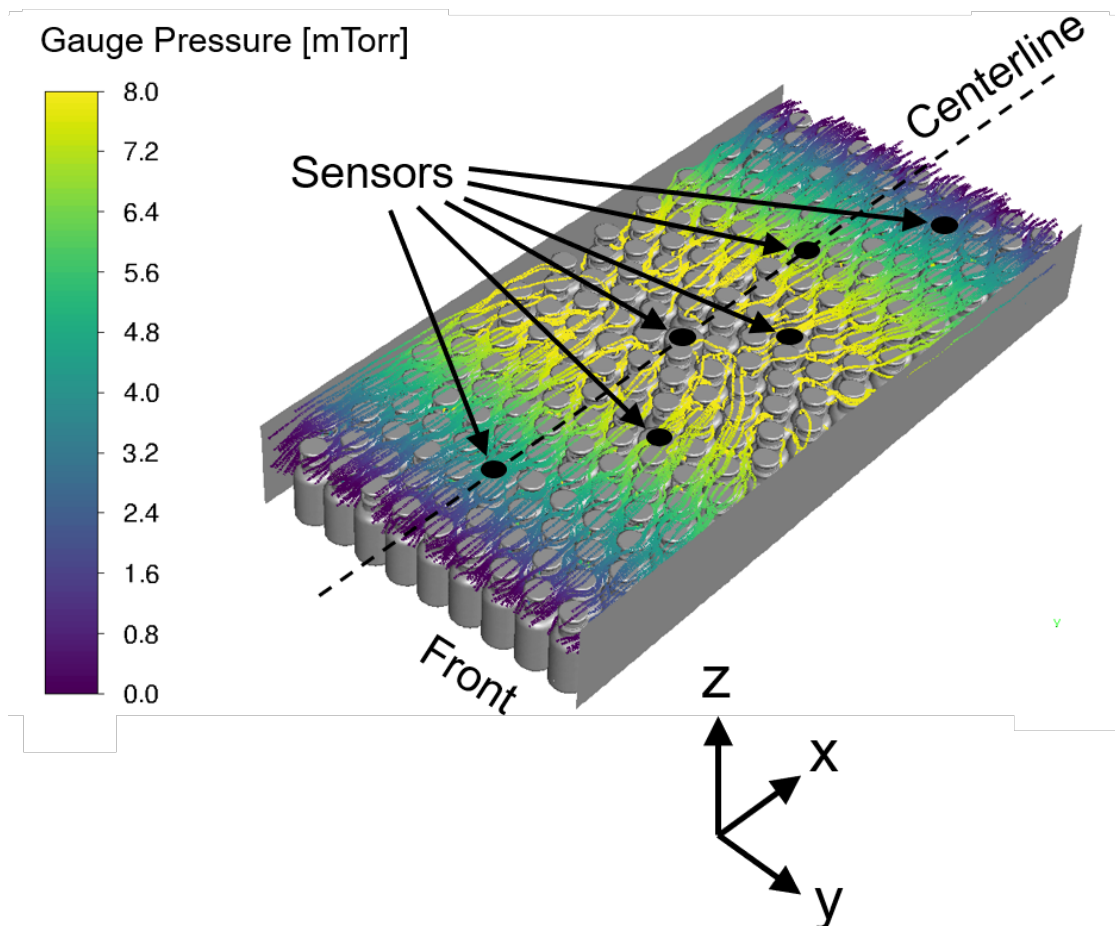


Figure 3.41. Pathlines of sublimed vapor during primary drying of 5% w/v mannitol using cycle H with flow barriers. Pathlines are colored in terms of static (gauge) pressure

The comparison between the CFD solution and experimental measurements at each of the sensor locations at an elapsed time of 11 hours using flow barriers is shown in Figure 3.43. The agreement between the simulation and measurements is improved by 16% relative to the case without flow barriers, having a mean-square deviation of 0.06 mTorr. The measurements from WMP3, WMP4, and WMP6 move closer to the centerline pressure due to the significant reduction in transverse pressure gradient.

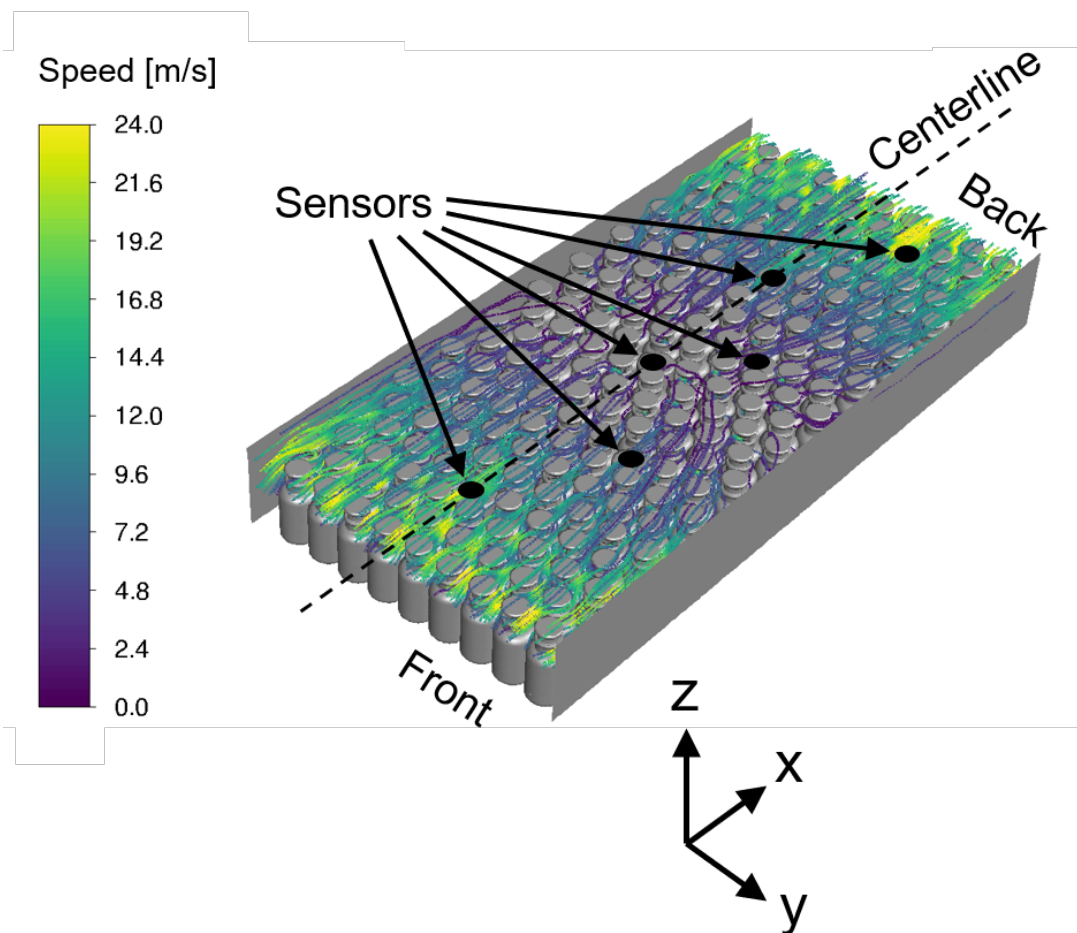


Figure 3.42. Pathlines of sublimed vapor during primary drying of 5% w/v mannitol using cycle H with flow barriers. Pathlines are colored in terms of flow speed

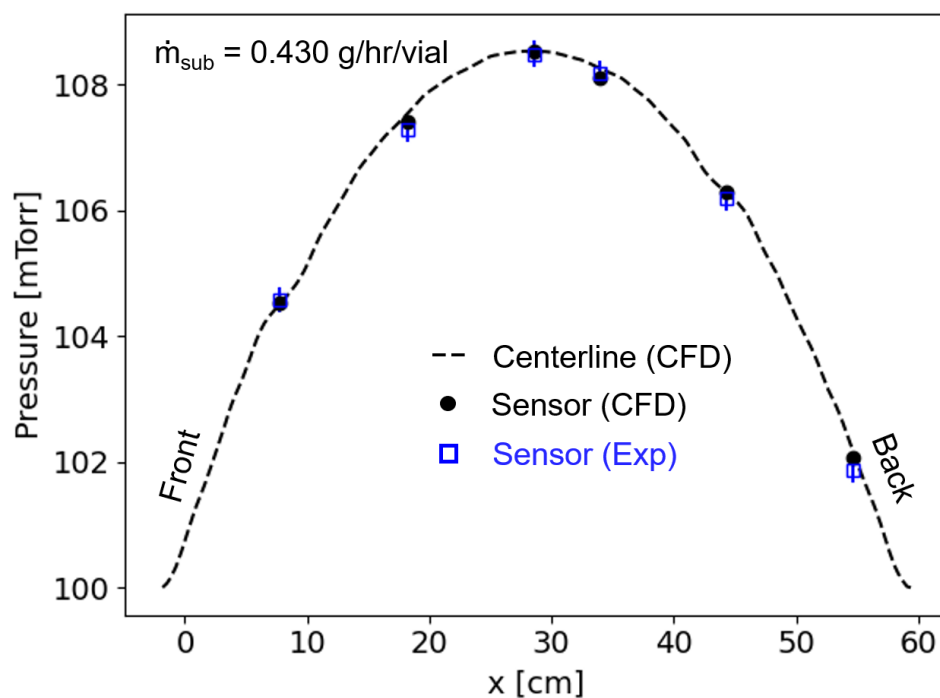


Figure 3.43. Comparison of pressure profile predicted using CFD and that which was measured during cycle H at an elapsed time of 11 hours using flow barriers.

3.5.3 Heat and Mass Transfer Characterization

The results provided by the sublimation rate estimation procedure provides the necessary information to characterize the heat and mass characteristics of the product during primary drying. Several different techniques have been developed for this purpose. Direct methods obtain sublimation directly and include gravimetric measurement[107], tunable diode laser absorption spectroscopy[108], and the use of a microbalance[109]. Indirect methods couple a heat and mass transfer model with an optimization routine to empirically determine relevant parameters [105] .

Vial Heat Transfer Coefficient

The vial heat transfer coefficient for the 20cc vials used during cycle H was determined using the estimated sublimation rate of 0.475 g/hr/vial. With equations 3.21 and 3.20 and the temperatures and vial cross sectional area known, the heat transfer coefficient is computed to be 15.6 +/- 0.33 W/m²/K for the chamber pressure of 100 mTorr. Most of the uncertainty in heat transfer coefficient is derived from the unequal heat transfer between center and edge vials. In many cases, the rate differences between these two regions can vary between 30-40% [75].

Product Mass Transfer Resistance

The product resistance was determined by applying the sublimation rate matching procedure at several discrete time points throughout the cycle. The empirical relation in equation 3.25 depends on the instantaneous dry layer thickness which can be estimated from the sublimation rate information. In discrete form,

$$l_i = l_{i-1} + \frac{\dot{m}_{sub,i} (t_i - t_{i-1})}{\rho_{ice} A_p} \quad (3.27)$$

The product resistance at these time points was found using equation 3.24 and exhibits a nearly linear dependence on dry layer length. This behavior is most likely attributed

to the lack of microcollapse associated with mannitol [110]. Setting the coefficient R_2 in equation 3.25 to zero leads to a product resistance fit of the form

$$R_p = 1.05e5 + 7.92e7l_d \text{ [m/s]}$$

Once the heat and mass transfer properties of the system are known, equations 3.19- 3.25 may be used to determine the unknown product temperature in an arbitrary cycle provided the vials and product formulation remain constant.

3.5.4 Product Temperature Estimation

The product temperature model was applied to cycle H to evaluate its accuracy. The sublimation rate and product temperature were computed over the course of primary drying by iterating over dry layer thicknesses from zero to the fill height. The experimentally measured modeled bottom product temperature and sublimation rate over the course of primary drying are shown in Figure 3.44. Uncertainty bounds are indicated by the shaded envelope surrounding the product temperature estimate. Estimated product temperature, $T_{b,est,ref68}$, based on a product resistance model from the literature is also shown [68].

The estimated product temperature demonstrates good agreement with the corresponding measurements over the course of primary drying. Additionally, the measured data fall within the uncertainty envelope of the model throughout the entire process. The endpoint predicted by the model (i.e. when the iterated dry layer length reaches the fill height) is located within the Pirani gauge convergence region and agrees well with the sublimation rate determined from the pressure matching procedure, suggesting the estimate is feasible.

The characterization of heat and mass transfer performance using the WMP devices holds a few key advantages over current state-of-the-art methods. Specifically, the wireless sensors have the capability of providing shelf-wise information. In large-scale systems, drying performance can vary significantly between the shelves and therefore batch-averaged properties (e.g. using TDLAS or MTM) are not necessarily representative of those on a more local scale. More localized techniques such as gravimetric measurements overcome this limitation,

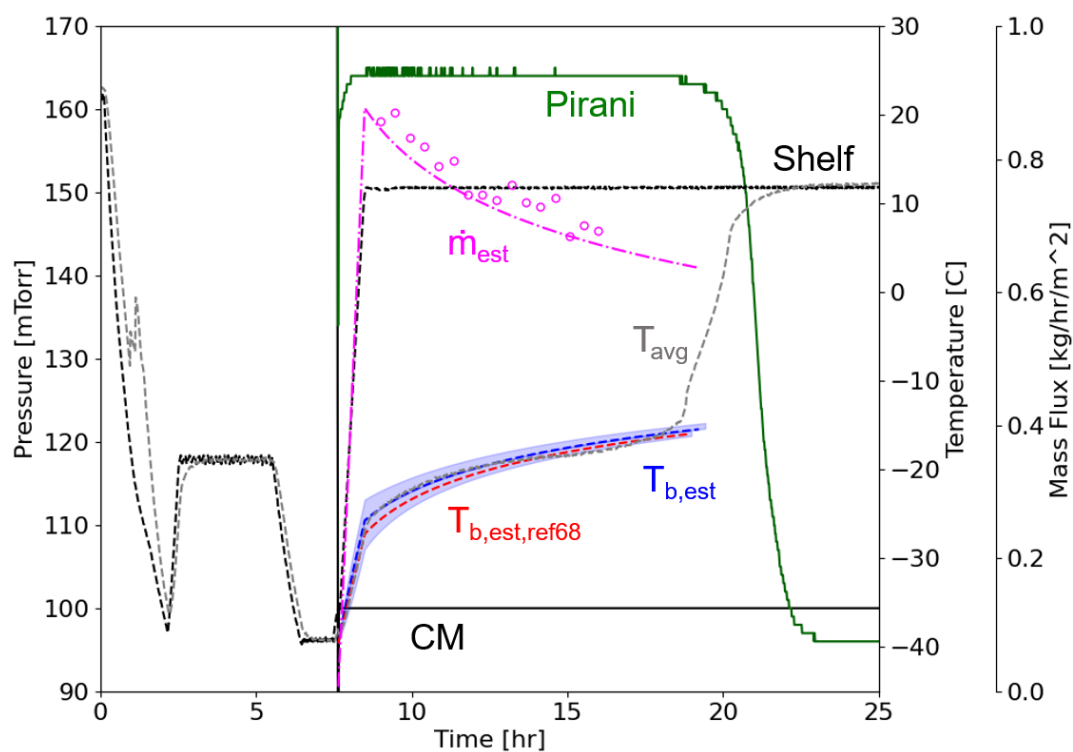


Figure 3.44. Process data for cycle H in Table 3.8 showing predicted product temperature based on sublimation rate estimation procedure

however the application is time consuming and often requires several experiments and/or specialized hardware (e.g. a sample thief).

3.5.5 Analytical Model to Estimate Local Sublimation Rate Based on Measured Gas Pressure and Temperature

The flow within the lyophilizer's shelf system was modeled as a 2-dimensional channel flow with a porous inlet on the lower boundary, a solid upper wall, and outlets at the left and right edges of the domain. A general schematic of both the physical and the model problems with spatially varying transverse and axial velocities are shown in Figure 3.45. Here, the top of the stopper in the physical domain was taken as the porous lower boundary. The symmetry of the problem allowed the centerline to be imposed with a zero-flux condition. Further, the injection surface was assumed to be continuous whereas in the physical system the boundary is composed of discrete inlets. A no-slip assumption was applied to all solid surfaces.

Governing Equations

The low-speed, low-density, near-continuum nature of the flowfield in the shelf network permits application of the incompressible Navier-Stokes system of equations. Following the analysis of Berman[111], the differential forms of the continuity and momentum in the x and y-coordinate directions are given by 3.28-3.30.

$$\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} = 0 \quad (3.28)$$

$$u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} = -\frac{1}{\rho} \frac{dp}{dx} + \frac{\mu}{\rho} \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) \quad (3.29)$$

$$u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} = -\frac{1}{\rho} \frac{dp}{dy} + \frac{\mu}{\rho} \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} \right) \quad (3.30)$$

Here, μ is the dynamic viscosity, ρ is the density, p is the local pressure, and u and v represent the flow velocity in the x and y-directions, respectively. To simplify the above

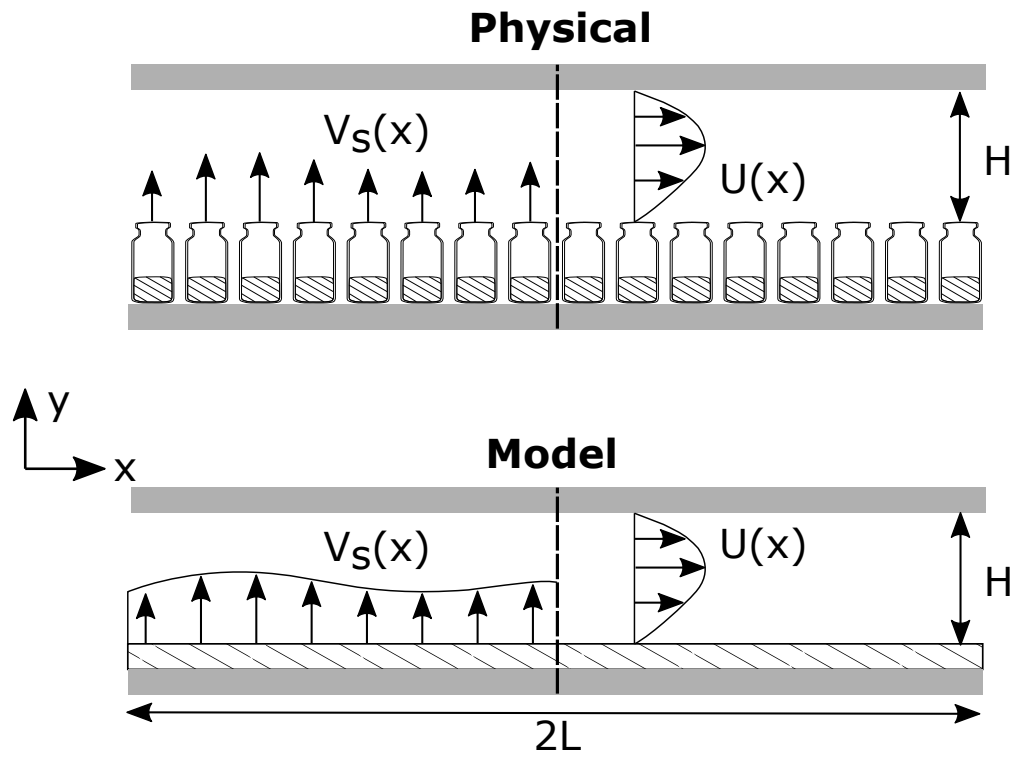


Figure 3.45. Schematics of physical system (top) and idealized (bottom) flow model. Water vapor is injected into domain at southern boundary. The vial top surface is modeled as a porous wall with piecewise continuous injection profile.

system of equations and reduce its order the number of velocity terms is reduced to a single variable through introduction of a stream function, $\psi(\xi, \eta)$.

$$\psi(\xi, \eta) = X(\xi)Y(\eta)$$

where ξ represents the non-dimensional coordinate in the x-direction and η in the y-direction. Application of the stream function to the velocity terms yields

$$u = \frac{1}{H} \frac{\partial \psi}{\partial \eta} \quad v = -\frac{1}{L} \frac{\partial \psi}{\partial \xi} \quad (3.31)$$

Substituting the above expressions for velocity into 3.29 and 3.30 and assuming that transverse gradients are negligible, the x-momentum and y-momentum equations become

$$\frac{1}{H^2 L} (X X' Y'^2 - X X' Y Y'') = -\frac{1}{\rho L} \frac{dp}{d\xi} + \frac{\mu}{\rho} \left(\frac{1}{H^2 L} X'' Y' + \frac{1}{H^3} X Y''' \right) \quad (3.32)$$

$$\frac{1}{H^2 L} (X'^2 Y Y' - X X'' Y Y') = -\frac{1}{\rho H} \frac{dp}{d\eta} - \frac{\mu}{\rho} \left(\frac{1}{L^3} X''' Y + \frac{1}{L H^2} X' Y'' \right) \quad (3.33)$$

Pressure-velocity coupling is used to reduce the system to a single unknown. Taking the derivative of equation 3.32 with respect to η and equation 3.33 with respect to ξ and combining, the pressure terms can be equated to form a single equation.

$$\begin{aligned} & \frac{1}{H^2} (2X X' Y' Y'' - X X' (Y' Y'' + Y Y''')) - \frac{1}{L^2} (2X' X'' Y Y' - Y Y' (X' X'' + X X''')) \\ & - \frac{\mu}{\rho} \left(\frac{1}{H L} X'' Y'' - \frac{L}{H^3} X Y^{(4)} - \frac{H}{L^3} X^{(4)} Y - \frac{1}{H L} X'' Y'' \right) = 0 \end{aligned} \quad (3.34)$$

The original system of three equations has been reduced to a single equation with two unknowns. Further simplification is possible through assumption of the velocity profile shape and application of the appropriate boundary conditions. Equation 3.34 is fourth-order in Y and third-order in X , requiring seven boundary conditions in total.

Boundary Conditions

To capture the effects of the asymmetric injection, the axial velocity profile, $u(\xi, \eta)$ is modeled by a third-order polynomial. According to equation 3.31, Y will be a fourth-order expression in terms of η .

$$Y(\eta) = a + Hb\eta + \frac{H^2}{2}c\eta^2 + \frac{H^3}{3}d\eta^3 + \frac{H^4}{4}e\eta^4 \quad (3.35)$$

Equation 3.35 is reduced to a single parameter through introduction of the appropriate boundary conditions. Assuming no-slip conditions at the south and north boundaries, the boundary conditions become

$$u(\xi, 0) = 0 \quad u(\xi, 1) = 0 \quad v(\xi, 0) = v_w\xi \quad v(\xi, 1) = 0$$

Or in terms of Y ,

$$Y(0) = -1 \quad Y(1) = 0 \quad Y'(0) = 0 \quad Y'(1) = 0$$

Introducing the velocity profile terms to equation 3.35 reduces Y to a single unknown, e . Following substitution and simplification of the boundary condition system, expressions for Y and its derivatives are provided below.

$$\begin{aligned} Y(\eta) &= -1 + (3 + H^4e)\eta^2 - (2 + 2H^4e)\eta^3 + eH^4\eta^4 \\ Y'(\eta) &= 2(3 + H^4e)\eta - 3(2 + 2H^4e)\eta^2 + 4eH^4\eta^3 \\ Y''(\eta) &= 2(3 + H^4e) - 6(2 + 2H^4e)\eta + 12eH^4\eta^2 \\ Y'''(\eta) &= -6(2 + 2H^4e) + 24eH^4\eta \\ Y^{(4)}(\eta) &= 24eH^4 \end{aligned} \quad (3.36)$$

The X term in equation 3.5.5 is determined by invoking the principle of continuity. Results for X and its derivatives become

$$\begin{aligned}
X(\xi) &= L \int v_w(\xi) d\xi \\
X'(\xi) &= Lv_w(\xi) \\
X''(\xi) &= Lv'_w(\xi) \\
X'''(\xi) &= Lv''_w(\xi) \\
X^{(4)}(\xi) &= Lv'''_w(\xi)
\end{aligned} \tag{3.37}$$

The equation set 3.36 and 3.37 are substituted into equation 3.34 to yield an expression for e in terms of the channel dimensions, transverse coordinate, η , and the injection profile, $v_w(\xi)$. Similar to the Karman-Polhausen boundary layer method [112] the properties within the boundary layer are averaged by integrating over η , reducing the system to a single unknown. Assuming the injection profile is prescribed, the unknown shaping variable, e , is given by

$$e(\xi) = \frac{15}{H^3} \left(\frac{H^3 \nu X^{(4)} - H^2 L X X''' + H^2 X' X'' - 12 L^3 X X'}{H^4 \nu X^{(4)} + 60 H L^3 X X' + 720 L^4 \nu X} \right) \tag{3.38}$$

With the velocity boundary and its derivatives known, stream function computation is straightforward using equations 3.36-3.38. Returning to equation 3.29, the pressure gradient term is solved for and integrated over η and ξ to yield

$$P(\xi) = \int_0^\xi \int_0^1 \left(\frac{\rho}{H^2} (X X' Y Y'' - X X' Y'^2) + \frac{\mu}{H L} X'' Y' + \frac{\mu L}{H^3} X Y''' \right) d\eta d\xi + P_{ch} \tag{3.39}$$

Here, it is assumed that no pressure variation exists between the channel outlet and the pressure transducer on the upper surface of the lyophilizer. The pressure distribution in equation 3.39 is non-linear in the velocity inlet boundary condition along the lower wall, requiring an iterative solver to invert. The flow matching procedure is therefore classified as an inverse parameter estimation problem.

Solution of Inverse Problem

Computation of measurable flow parameters using the above analysis requires knowledge of the injection profile. In many internal flow applications such as lyophilization the boundary information is unknown and a direct solution is not possible. Under the inverse method, the boundary conditions are first assumed and are used to predict the state variables. Comparison of the solution to the known values produces an error which is minimized by iteratively adjusting the boundary conditions until the desired tolerance is met. The flow matching problem is established by assuming a piecewise continuous injection velocity profile with slopes, a_i . Other profiles (e.g. based on polynomial or Fourier series expansions) are also possible, however for simplicity they are not considered here. An example of the linearly segmented profile is shown in Figure 3.46. In vector form, the injection surface is represented by

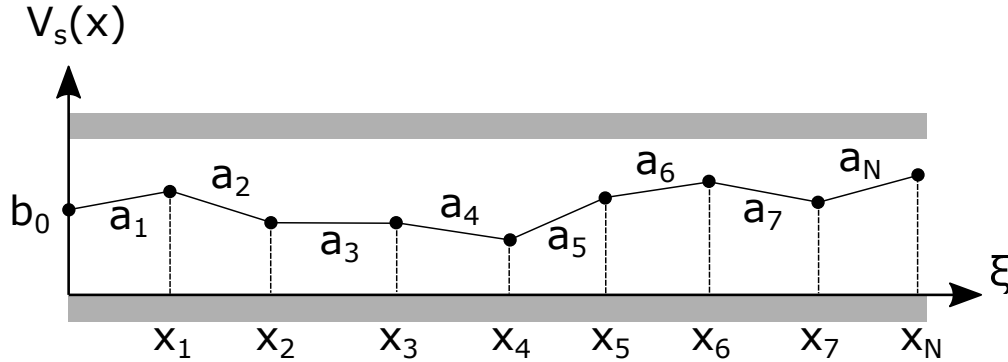


Figure 3.46. Schematic of lyophilizer flow model. Water vapor is injected into domain at southern boundary.

$$v_s(\xi) = \begin{pmatrix} 0 & a_0 & 0 & \cdots & 0 \\ 0 & a_0 - a_1 & a_1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_0 - a_1 & a_1 - a_2 & \cdots & a_N \end{pmatrix} \begin{pmatrix} x_0 \\ x_1 \\ \vdots \\ x_N \end{pmatrix} + \begin{pmatrix} b_0 \\ b_0 \\ \vdots \\ b_0 \end{pmatrix}$$

To obtain the stream function, derivatives of the assumed injection velocity profile are taken. For linear segmentation, all derivatives second-order and higher are identically zero, leaving only the first-order terms.

$$\frac{dv_w}{d\xi} = \begin{pmatrix} 0 & a_0 & 0 & \cdots & 0 \\ 0 & a_0 - a_1 & a_1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_0 - a_1 & a_1 - a_2 & \cdots & a_N \end{pmatrix}$$

The velocity profile and its derivatives are used to solve for the static pressure from equation 3.39 at each node using equation 3.39. The computed pressure is compared to the measured distribution in terms of the square error, forming the objective function, J .

$$J = \frac{1}{2} \int (P - P_{meas})^2 d\xi \approx \frac{1}{2} \sum (P_n - P_{meas,n})^2 \Delta\xi \quad (3.40)$$

Minimization of the objective function is performed using any multivariate optimizer (BFGS, Nelder-Mead, etc.). The solution procedure is as follows:

1. Guess the unknown coefficients for the piecewise continuous injection velocity profile, $v_s(\xi)$
2. Solve the flow model and compute the corresponding pressure distribution from equation 3.39.
3. Compute the cost function from equation 3.40 using the results from Step (2).
4. Determine cost function sensitivities using finite-differencing relative to the inputs (i.e. velocity profile coefficients).
5. Execute optimization algorithm to find the new search direction
6. Compute updated injection profile using the results from (5)
7. Repeat Steps (2)-(6) until the desired first-order optimality tolerance is reached

In this work, the Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm is selected as the optimization routine due to its fast convergence and ability to numerically approximate the Hessian of the cost function[113]. The algorithm uses complex first-order finite-differencing to approximate the Jacobian of the objective function at each optimization interval.

$$\frac{\partial J}{\partial x} = \frac{J(p(\tilde{v}), v^{(m)}) - J(p(v^{(m)}), v^{(m)})}{\tilde{v} - v^{(m)}}$$

Under traditional real-valued differencing, the gradient near the optimum point does not always satisfy first-order optimality conditions. That is, the gradient of the objective function with respect to the design variables is close to zero. To rectify this limitation, a modified complex-step form is applied for more accurate estimates of the sensitivities [114]. With this approach, the finite differences become:

$$\frac{\partial J}{\partial x} = \text{Im} \left(\frac{J(p(v^{(m)} + i\delta), v^{(m)}) - J(p(v^{(m)}), v^{(m)})}{\delta} \right) \quad (3.41)$$

Here, δ represents the perturbation applied to each injection site and carries a magnitude of 1e-20. According to equations 3.5.5 and 3.41, computation of the Jacobian requires $N+1$ flow solves where N represents the number of linear spline segments. For the simple 2D domain discussed here the computational cost of the finite-differencing scheme is justified by its simplicity. For more complex domains, the Jacobian is more realistically determined via an adjoint approach, requiring only 2 solutions. In either case, the inverse Hessian, $\mathbf{B}$ is approximated from the Jacobian and design variables using the standard method as described in the original work[113].

$$\mathbf{B} = \frac{\sigma + \tau}{\sigma^2} \mathbf{p} \mathbf{p}^T - \frac{1}{\sigma} \left(\mathbf{B}^* \mathbf{y} \mathbf{p}^T + \mathbf{p} (\mathbf{B}^* \mathbf{y})^T \right) \quad (3.42)$$

where the operator “*” represents values from the previous iteration and

$$\mathbf{y} = \mathbf{x} - \mathbf{x}^* \quad (3.43)$$

$$\mathbf{p} = \nabla f(\mathbf{x}) - \nabla f(\mathbf{x}^*) \quad (3.44)$$

$$\sigma = \mathbf{p}^T \mathbf{y} \quad (3.45)$$

$$\tau = \mathbf{y}^T \mathbf{B}^* \mathbf{y} \quad (3.46)$$

The optimization routine is carried out until first-order optimality conditions are met. With no constraints imposed on the problem this condition achieved when the maximum absolute Jacobian value, $|\nabla f(\mathbf{x})|$, at each index is less than $1\text{e-}12$.

Model Validation Using Computational Fluid Dynamics

Validation of the numerical method for computing the unknown injection boundary given the measured flow properties was carried out using commercial Computational Fluid Dynamics (CFD) software Fluent (ANSYS, Canonsburg, PA). To perform the validation, an injection profile was applied to the CFD domain and the resulting flowfield static pressure was computed. The pressure distribution then served as the “measured” variable and the flow matching algorithm was executed using the process outlined above. That is, the true (known) injection profile was found by minimizing the difference between iteration output and the “measured” pressure distribution. A schematic of the simulation domain is shown in Figure 3.47.

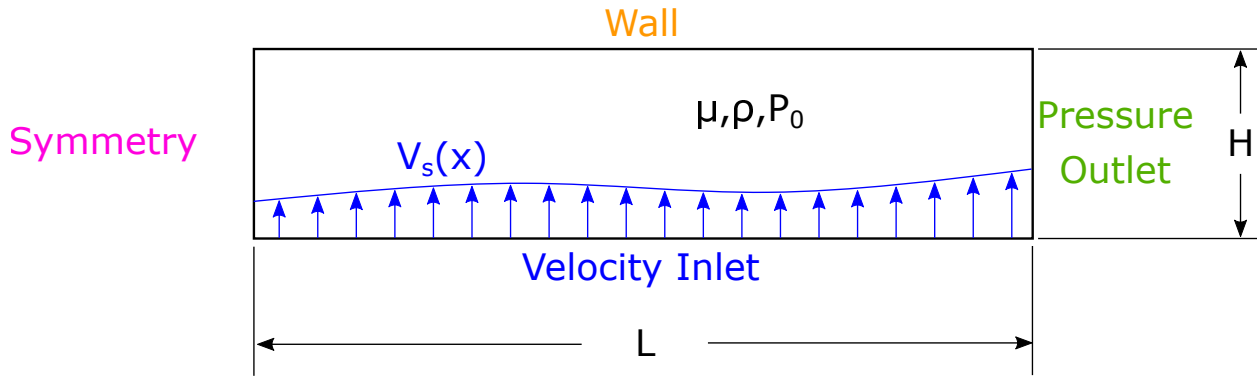


Figure 3.47. Schematic of domain used for all CFD simulations

Laminar flow and incompressibility were assumed throughout the domain for the purpose of comparison with the model. These assumptions are considered valid as the Reynolds and Mach numbers encountered within the shelf system during lyophilization are typically on the order of 1-100 and 0-0.1, respectively. All solid boundaries were assumed adiabatic and the no-slip condition was enforced. In reality, the low speed and low pressure flow encountered in lyophilization can produce conditions in which velocity and temperature slip

effects become significant. The slip regime is defined in terms of the the Knudsen number (see equation 3.11) and is generally considered over the range $0.01 < \text{Kn} < 0.1$. For this reason, additional simulations were carried out with slip effects to evaluate its influence on solution behavior.

Grid Convergence

A standard grid convergence study was performed prior to comparison with the simplified model to ensure accuracy of the CFD solution. The performance metric was stated in terms of the static pressure integrated over the injection surface ($\int P(x,0)dx$) for two separate injection profiles, uniform and quadratic. This attribute was selected due to its relevance to the cost function presented above in equation 3.40. The uniform injection had a magnitude of 3m/s and the quadratic was described by $x^2 + 3\text{m/s}$. Results are tabulated in Table 3.11. All domains were constructed using rectangular cells.

Table 3.11. Results from 2-dimensional CFD grid convergence study for uniform and quadratic injection. The grid quality metric is the static pressure integrated over the injection boundary surface

Grid Size	Uniform (3 m/s) [Torr-m]	Quadratic ($x^2 + 3$ m/s) [Torr-m]
Low (100×12)	-2.9448	-3.1404
Medium (200×25)	-2.9740	-3.1711
High (400×50)	-2.9811	-3.1782

Grid convergence results demonstrate a relative change in accuracy of 0.24% and 0.22% between the medium and high density meshes for the uniform and quadratic profiles, respectively. To ensure accuracy, the high density mesh was selected as the additional computational time is insignificant.

Comparison to Flow Model to CFD Solution

The results of the semi-analytical flow model are compared directly to the CFD simulations for the fine mesh in Figure 3.50 with a uniform inlet velocity of 3 m/s. The flow parameters used for both simulations are listed in Table 3.12.

Table 3.12. Parameters used in CFD and 2-dimensional flow matching model.

Parameter	Symbol	Value
Chamber Pressure	p_{ch}	100 [mTorr]
Temperature	T	233.5 [K]
Density	ρ	1.236e-4 [kg/m ³]
Dynamic Viscosity	μ	5.532e-6 [Pa-s]

The 2-dimensional velocity and pressure contours corresponding to the CFD solution are presented in Figures 3.48 and 3.49. As expected, pressure is highest near the center of the channel and the fluid accelerates towards the outlet as mass is introduced from the lower boundary [79], [81], [112]. One of the assumptions made during model development is that of a negligible transverse pressure gradient. Using the data from Figure 3.49, the transverse pressure gradient along the length of the channel is constant at -0.36 mTorr/m. For the specified channel height of 2 cm, the expected pressure drop along the vertical axis is 7 microTorr, 0.007% of the base pressure. Therefore, this assumption is considered valid.

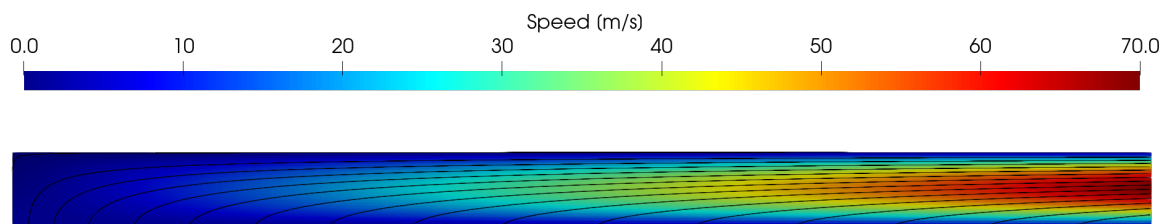


Figure 3.48. Contours of flow speed from CFD solution. Stream traces are shown in black emanating from lower boundary of simulation domain.

A direct comparison between the model and CFD solutions was carried out using the extracted axial velocity profiles. For comparison, additionally CFD solutions were performed

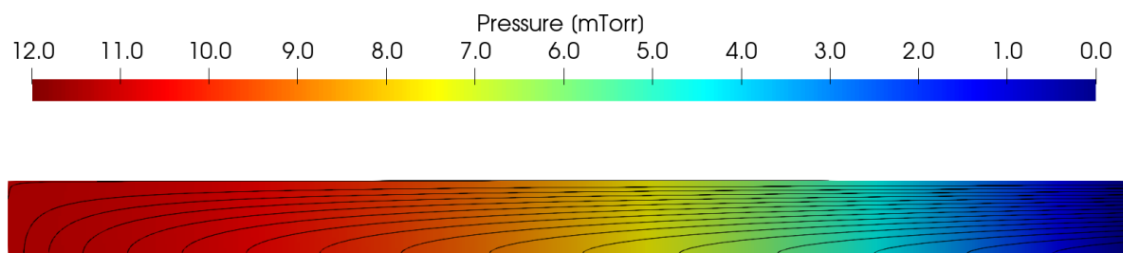


Figure 3.49. Contours of static pressure from CFD solution. Results indicate minimal pressure variation in the transverse direction.

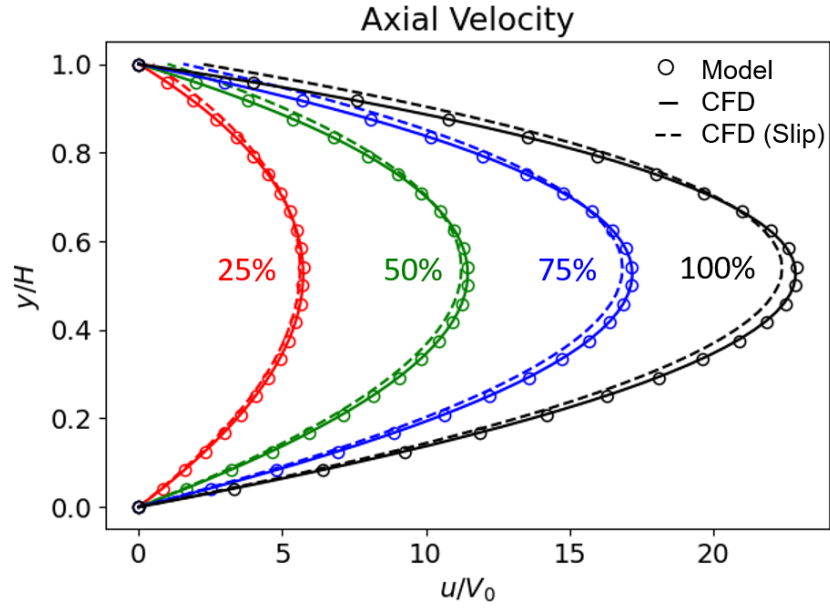
using the Maxwell slip model. Profiles were selected at intervals of $0.25L$, $0.50L$, $0.75L$, and $1.0L$ and overlaid to determine agreement. The data shown in Figure 3.50 demonstrate a strong agreement between the two solutions. The root-mean-square deviations between intervals are presented in Table 3.13. The maximum error occurs at the outlet of the domain in the axial non-dimensional velocity component for both slip and no-slip cases and assumes values of 0.0077 and 0.133, respectively. The pressure distribution displays similar agreement and can be found in Figure 3.51. Total root-mean-square difference between model and CFD solutions over the entire inlet surface is $7.95e-5$ for the no-slip case and 0.004 with slip included. Although the slip effects lead to a $50\times$ greater error between the model and CFD solutions they are nevertheless assumed negligible during subsequent application of the 2-dimensional flow model. Additionally, the velocity and pressure profile agreement between the present model and the CFD solution combined with the validated hypothesis of negligible transverse pressure gradient justify the assumptions made during derivation and provide confidence that the flow matching procedure will represent the physical flow with reasonable accuracy.

Table 3.13. Comparison of velocity profiles at different channel locations between the semi-analytical flow model and CFD results with and without boundary slip in terms of root-mean-square deviation

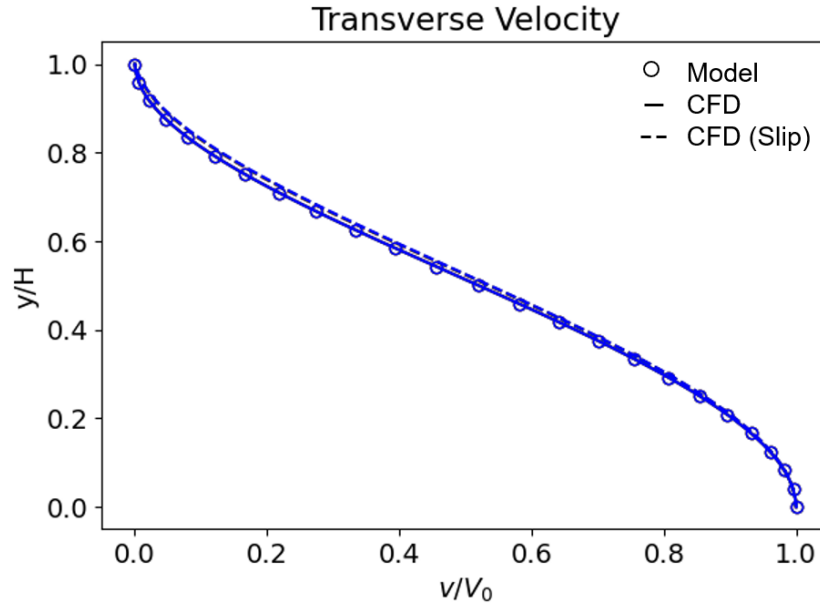
Slice	No-Slip		Slip	
	RMSE(U) []	RMSE(V) []	RMSE(U) []	RMSE(V) []
L/4	0.0013	0.001	0.030	0.002
L/2	0.0027	0.001	0.061	0.002
3L/4	0.0040	0.001	0.094	0.02
L	0.0077	0.001	0.133	0.004

Flow Matching Validation

Following validation against CFD solutions, the semi-porous injection model was applied to the flow matching problem. The CFD model was used to generate “measured” pressure data using a known injection boundary condition. During lyophilization, it can generally be expected that the sublimation rate (injection velocity) will vary across the length of the



(a) Comparison of nondimensional axial velocity profiles for model and CFD solutions. Inclusion of slip effects reduces centerline velocity and skews the profile towards the solid boundary.



(b) Comparison of nondimensional transverse velocity profiles for model and CFD solutions.

Figure 3.50. Comparison of nondimensional axial and transverse velocity profiles for model and CFD solutions. Both slip and no-slip boundary condition results are provided for the CFD simulations.

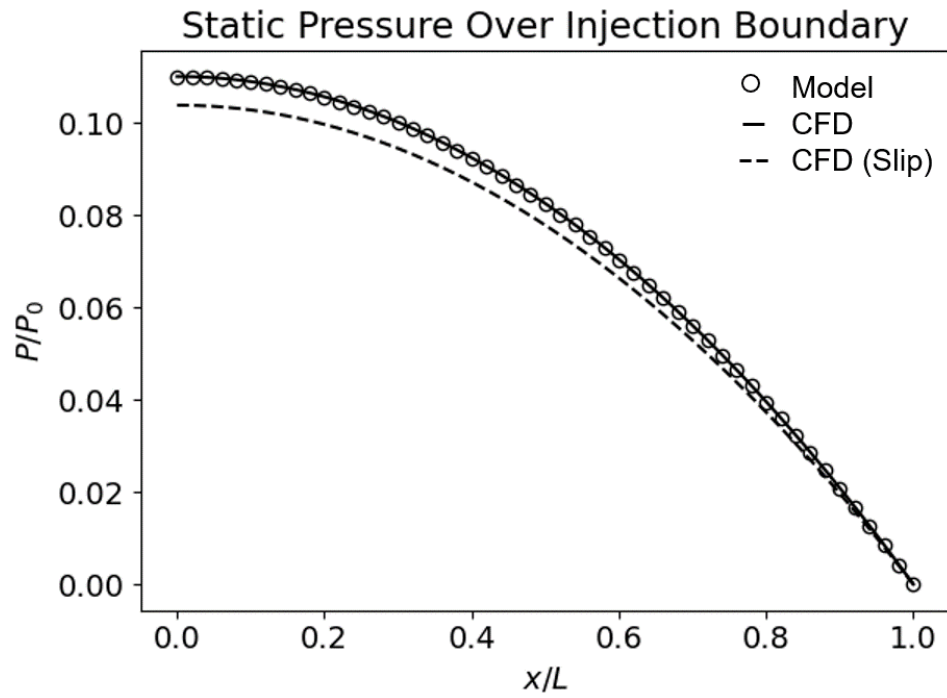


Figure 3.51. Comparison of pressure profiles between model and CFD for uniform inlet velocity of 3 [m/s] and base pressure of 100 mTorr. The inclusion of slip boundary conditions reduces the pressure gradient from center to edge due to the reduction in shear stress magnitude at the wall.

shelf due to variations in heat transfer performance[75], [104]. To approximate this behavior an injection profile with smooth velocity step near the edge was assumed.

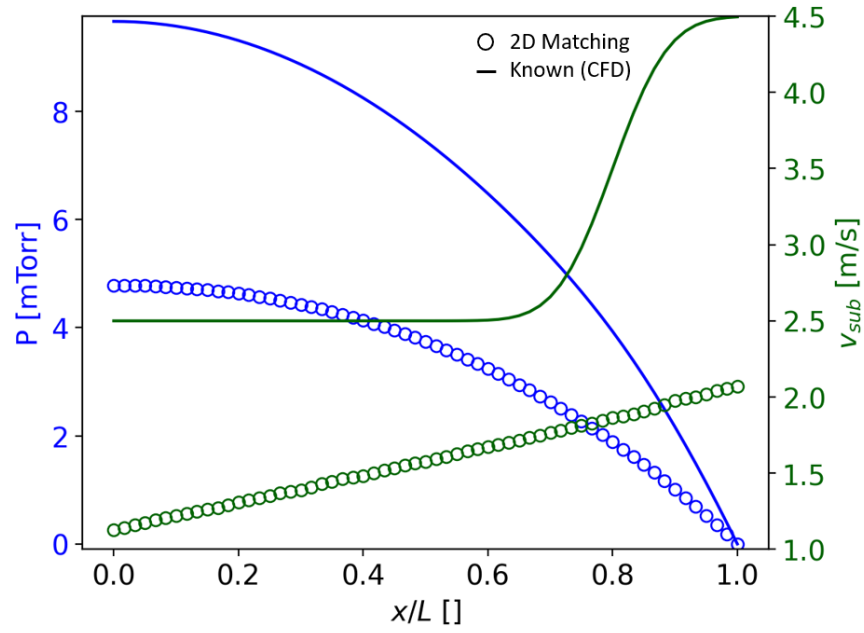
$$v_{inj}(x) = a + \text{erf}(b(\xi - c))$$

The coefficient terms a,b, and c, were taken as 3.5, 10, and 0.8, respectively. The domain was discretized into 61 cells and initial inlet velocity coefficients were assigned a random slope value of $1 + \text{rand}/5$. The optimization procedure outlined in Section 3.5.5 was then carried out until converged. Initial and final iterations were extracted and are plotted in Figure 3.52.

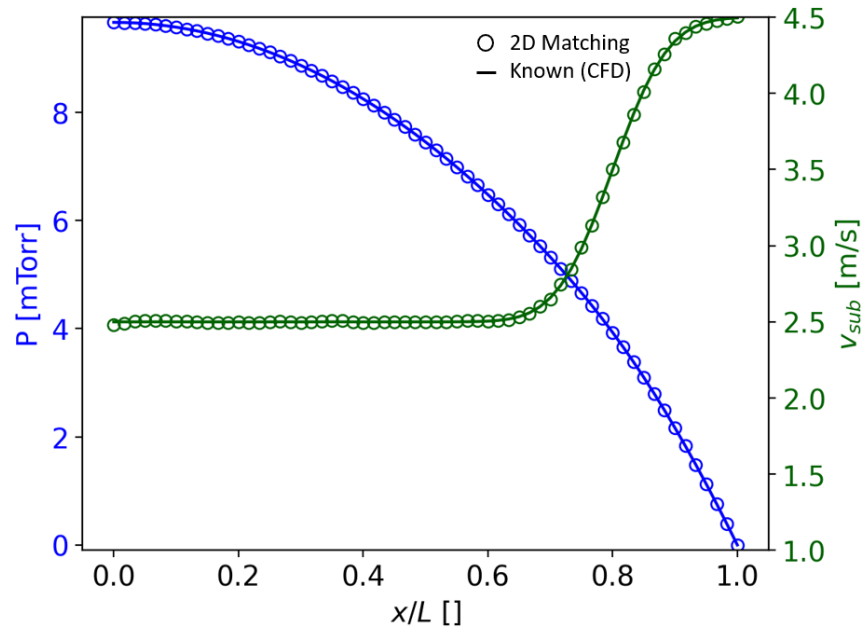
Results of Figure 3.52 demonstrate convergence at an objective function value of 6.41e-13 after 283 iterations with a maximum Jacobian magnitude, $|\nabla f(\mathbf{x})|$, of 5.02e-13. This result is assumed sufficient in terms of first-order optimality. To quantify the model’s ability to capture several variations in injection profile the flow matching method was also applied to both quadratic and sinusoidally varying boundary velocities. The converged solution for these inputs are provided in Figures 3.53 and 3.54, respectively. Convergence for the quadratic profile is achieved after 322 iterations and the sinusoidal after 592. The RMS error between the “measured” and computed velocity profiles are provided in Table 3.14. Overall, the flow matching model is able to capture the known injection boundary variation with an acceptable degree of accuracy.

Table 3.14. Comparison of flow matching accuracy when applied to “measured” data from CFD simulations.

$v_{sim}(\xi)$	RMSE(U) [m/s]	RMSE(P) [mTorr]
3.0	0.0169	0.001
$3.5 + 10 \text{erf}(\xi - 0.8)$	0.0084	0.001
$3.0 + \xi^2$	0.0169	0.001
$1.5 + 1.5 \sin(12\pi\xi)$	0.0253	0.001



(a) Static pressure and inlet velocity at iteration 0



(b) Static pressure and inlet velocity at iteration 283 (final)

Figure 3.52. Convergence history of static pressure and inlet velocity for $v_{sim}(\xi) = 3.5 + 10 \operatorname{erf}(\xi - 0.8)$

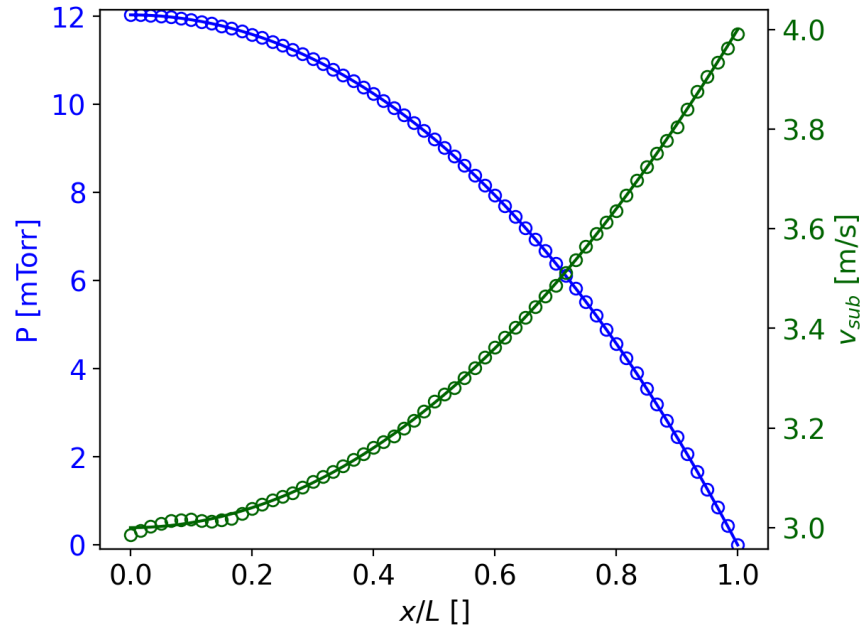


Figure 3.53. Converged solution for injection profile of the form $v_{sim}(\xi) = 3.0 + \xi^2$

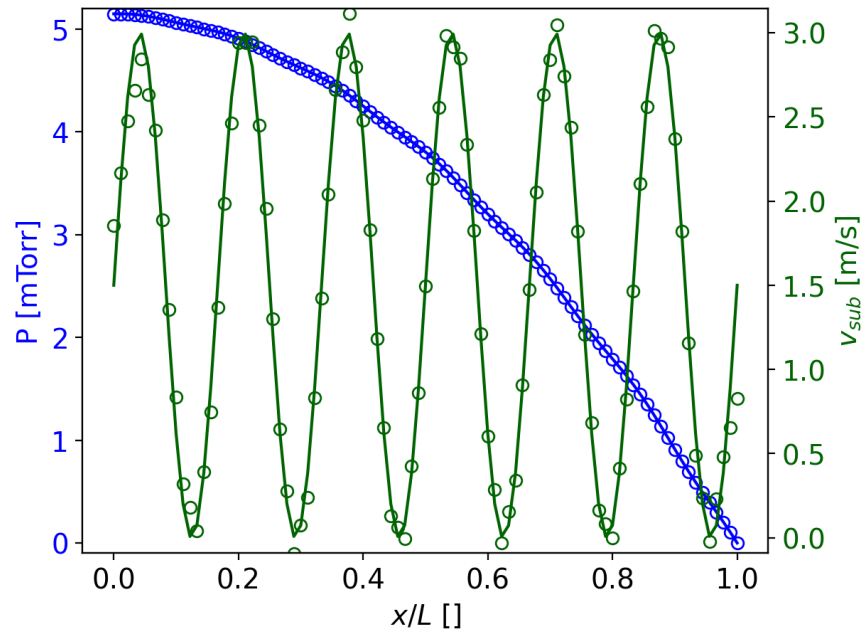


Figure 3.54. Converged solution for injection profile of the form $v_{sim}(\xi) = 1.5 + 1.5 \sin(12\pi\xi)$

Comparison to 3-dimensional CFD Model

The simplified 2-dimensional model does not account for the influence of the 3-dimensional vial and stopper geometries. The effective channel gap must therefore be determined using a separate matching procedure. The process was carried out using data manufactured from the 3-dimensional CFD flow model outlined in Section 3.5.2 using flow barriers (i.e. the cutouts are defined as solid boundaries). The solution to the CFD model was then obtained assuming a uniform injection rate in each vial. In this case, the flow density and viscosity were set to constant values of $1.15\text{e-}4 \text{ kg/m}^3$ and $8.33\text{e-}6 \text{ Pa-s}$, respectively. The resulting pressure distribution along the vial pack centerline was then extracted and compared to the 2-dimensional model pressure profile for a range of gap sizes. The root-mean-square difference between the model and CFD solutions at each gap height was then fit with a spline curve. The gap that minimized the difference between the models represents the effective gap height and was determined to be 1.59 cm. The true measured distance between the upper shelf and the top of the stoppers is around 1.4 cm, 12% smaller than the effective value.

Non-Uniform Sublimation Rate

After the effective gap was determined the 2-dimensional sublimation rate estimation process was compared to the 3-dimensional CFD results for a quadratic injection velocity profile. Flow parameters were identical to those established in the effective gap estimation procedure. The discrete velocities ranged from 1 m/s at the center of the vial pack to 2 m/s at the edge, producing a total batch mass flow rate of 68.1 g/hr. The resulting CFD pressure distribution was then fit with a 5th-order polynomial to reduce high-frequency oscillations and the flow matching procedure was carried out. The results of the procedure are shown in Figure 3.55.

The pressure fit captures the trend of the mass flux over the length of the shelf but is resistant to the large velocity oscillations on account of the low-order polynomial fit. The estimated total mass flow rate into the domain was 66.7 g/hr, a difference of 2% relative to the known CFD solution.

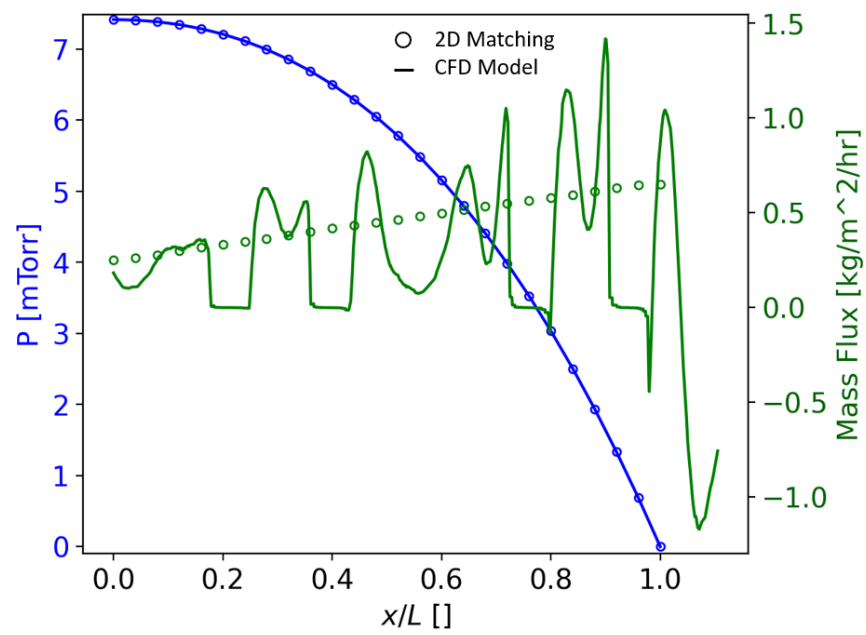


Figure 3.55. Pressure and corresponding sublimation flux estimate from flow matching procedure on CFD.

Application to Experimental Measurements

Finally, the 2-dimensional flow model was applied to experimental data from cycle H in Table 3.8 with flow barriers installed in the sidewalls. The addition of these boundaries diminishes the transverse flow component and allows the physical system to be assumed 2-dimensional. Due to calibration limitations, the pressure data from the WMP sensors has a resolution of ± 0.2 mTorr. Additionally, the pressure distribution along the length of the shelf is relatively insensitive to the injection velocity magnitude. Therefore, even the small pressure variations associated with calibration accuracy will lead to significant noise in the predicted boundary velocity. To overcome this limitation, the pressure data is fitted with a 5th-order polynomial shape function and the inverse parameter estimation procedure is carried out as usual. The fitting was conducted using a linear least-squares method and the linear coefficient of the polynomial was set to zero to enforce the symmetry constraint. The measured pressure distribution over the length of the shelf and the corresponding fit are shown in Figure 3.56.

The total estimated sublimation rate is 74.5 g/hr as calculated by numerical integration of the flux over the length of the shelf. The measured rate at a cycle time of 11 hours was 91.9 g/hr, leading to a relative estimation error of 19%. Errors of this magnitude are expected due to the assumption of a no-slip at all solid boundaries. According to Figure 3.51, the inclusion of slip leads to a lower pressure gradient for a given sublimation rate. Therefore, if slip effects were accounted for, the sublimation rate in Figure 3.56 would necessarily be larger, placing the total rate estimate closer to the measured value. Nevertheless, the results demonstrate the capability of using the measured pressure distribution to evaluate local variations in sublimation flux. If desired, this method may be directly applied to higher fidelity CFD simulations to obtain more accurate results.

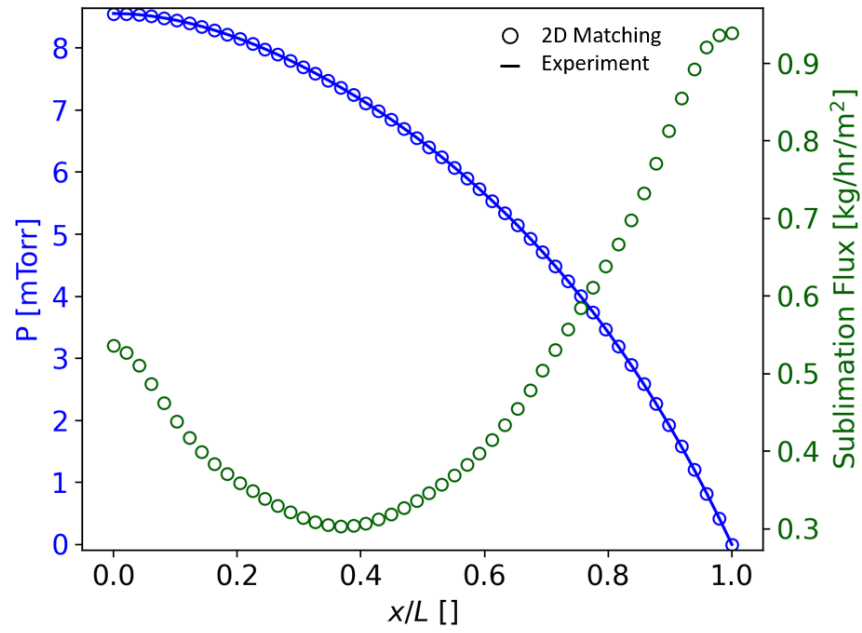


Figure 3.56. Pressure and corresponding sublimation flux estimate from flow matching procedure on cycle H in Table 3.8 using flow barriers. The total matched sublimation rate has a deviation of 19% relative to the gravimetric measurement. The difference is most likely due to the assumption of no-slip conditions at the solid boundaries as well as the measurement uncertainty intrinsic to the devices.

4. WIRELESS PRESSURE AND TEMPERATURE SENSORS FOR THE CHARACTERIZATION OF RAPID DEPRESSURIZATION ICE NUCLEATION

Wireless gas pressure and temperature sensors were designed and fabricated for the purpose of monitoring the Rapid Depressurization Controlled Ice Nucleation (RD-CIN) process. The devices measured both the chamber and vial headspace properties during the discharge and are used to better understand the mechanisms contributing to the nucleation event.

4.1 Sensor Design

The depressurization event takes roughly one second to complete at the laboratory scale and is characterized by pressure and temperature swings on the order of two atmospheres and 50°C, respectively. Temperature measurements were performed by both devices using 40-gauge T-type thermocouples (Omega Engineering, Norwalk, CT). High-gauge lead wires were selected to minimize thermal mass and lead conduction. The amplifiers (Max31855T, Maxim, San Jose, CA) were electronically cold-junction compensated with an internal reference to resist fluctuations in ambient temperature. The favorable response time of MEMS diaphragm-based sensors made them ideally suited for pressure measurement during RD-CIN. Pressure sensors are commercially available off the shelf and are available in a wide assortment of measurement types and ranges. The pressure sensor used in the chamber measured absolute pressure with a range of 0-60 psia and uncertainty of 0.6 psi (HSC-MANN060PA2A3, Honeywell, Charlotte, NC). The vial headspace sensor measured gauge pressure (relative to the instantaneous chamber pressure) with a range of 0-0.36 psig and uncertainty of 0.01 psi (HSCMANN010NDSA3, Honeywell, Charlotte, NC). The published response time of both devices is 1ms. An electrical schematic of the devices is shown in Figure 4.1.

Vial headspace pressure and temperature measurements are accessed by drilling two 3/16" holes into the barrels of each vial type at roughly 2/3 the total barrel height. This configuration eliminates the introduction of external flow disturbances in the vial neck area

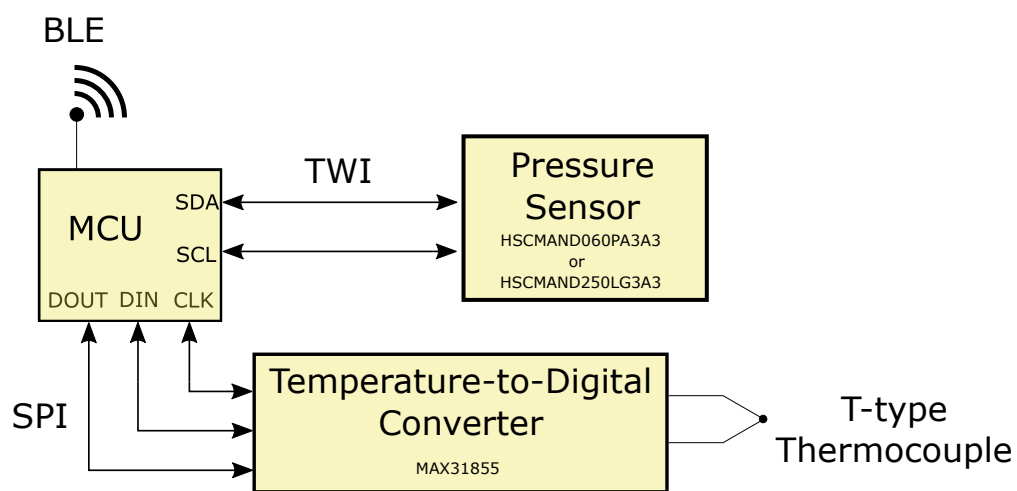


Figure 4.1. Electrical schematic of RD-CIN sensors.

while still sitting above the liquid water line. The vials are sealed from the chamber at the sensor inlet ports using a buna rubber o-ring. To accommodate the thermocouple, a custom plug is fabricated out of ABS plastic. The channel in which the thermocouple passes in this fixture is sealed using epoxy compound. Images of the devices as well as schematics illustrating their configurations are provided in Figures 4.2 and 4.3.

Headspace Sensor

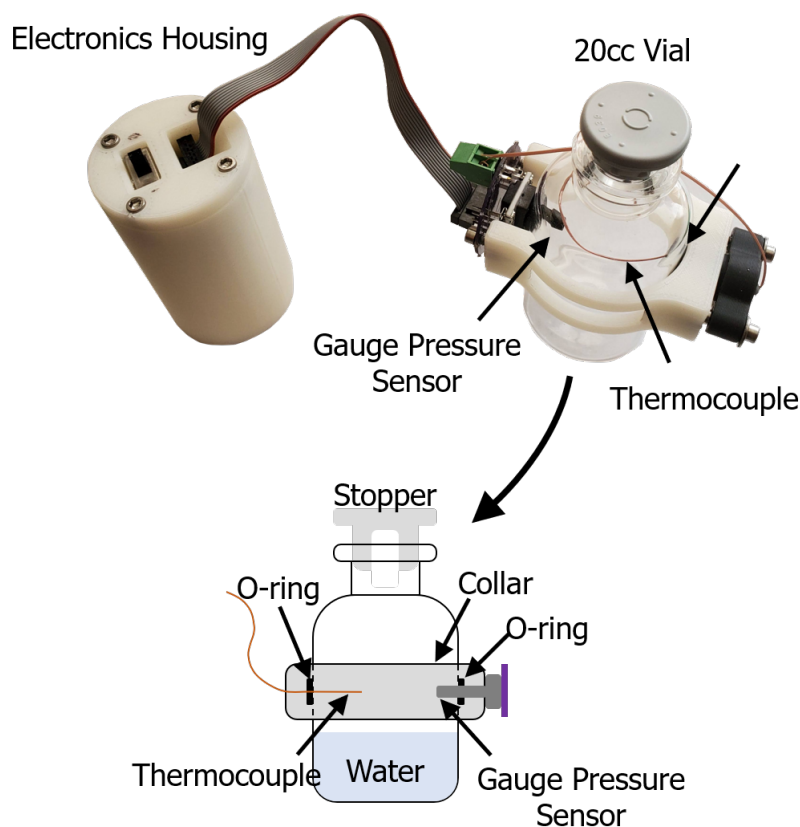


Figure 4.2. Image and schematic of vial headspace pressure and temperature sensor used to monitor the RD-CIN process. The pressure sensor and thermocouple are inserted into the headspace through two holes drilled into the vial barrel.

The Nordic Semiconductor nrf52832 MCU and transceiver provided the primary signal processing and communication functions for the wireless devices (see Section 3.1.1 for system details). Bluetooth Low Energy (BLE) is selected as the wireless protocol to accommodate the throughput demands required by the RD-CIN process. BLE achieves low power con-

Chamber Sensor

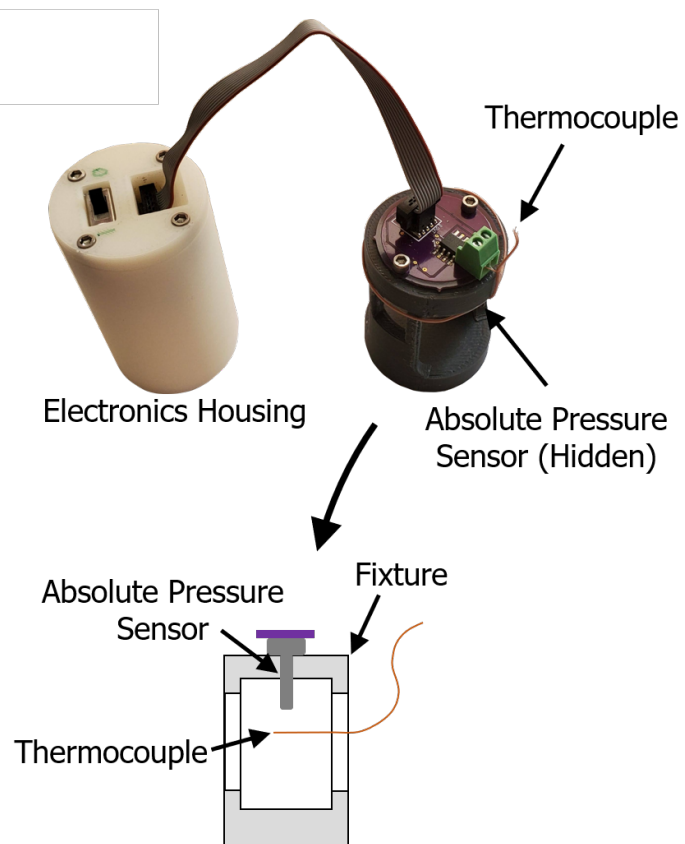


Figure 4.3. Image and schematic of chamber pressure and temperature sensor used to monitor the RD-CIN process.

sumption rates by intermittently checking for and pushing new data out to the central node during a defined connection interval. The connection interval is negotiated by the host and peripheral prior to the bonding event and can be modified by the central node if necessary. The minimum connection interval for BLE is 7.5 ms, more than double the sampling time of the sensor node. To accommodate the connection interval limitation the data is buffered between notifications. A total of 10 bytes are stored every 3 ms and a transmission packet consists of 5 samples, resulting in a broadcast interval of 15 ms. Data is relayed from the peripherals to the central over the Nordic BLE UART service and service characteristic notifications are enabled and disabled on the host side via a graphical user interface. The pressure sensor communication protocol is the Serial Peripheral Interface (SPI) and the thermocouple amplifier is two-wire interface. Power is supplied to the board using a 350 mAh lithium polymer battery pack (LP561836JU, Villingen-Schwenningen, Germany). Power draw estimates for the RD-CIN sensor components are provided in Table 4.1, producing a nominal expected lifetime of around 86 hours.

Table 4.1. Power consumption estimates for wireless RD-CIN system. Total estimated lifetime based on battery capacity is 86 hours.

Component	Current Draw
CPU	833 μ A
Pressure Sensor	2.3 mA
TC amplifier	900 μ A
Total	4.033 mA

4.1.1 Signal Processing

The central node receives notification data from each peripheral and immediately relays the information to the host processor via the UART bus at a baud rate of 460800. On the host side the data packet is identified, passed to its respective thread, and written to a log file. Every 33rd packet is returned to the primary process for display to the user. Time stamping is performed on the peripheral side with a resolution of 30 microseconds and is

included in the standard 10-byte packet. A schematic of the software architecture is shown in Figure 4.4.

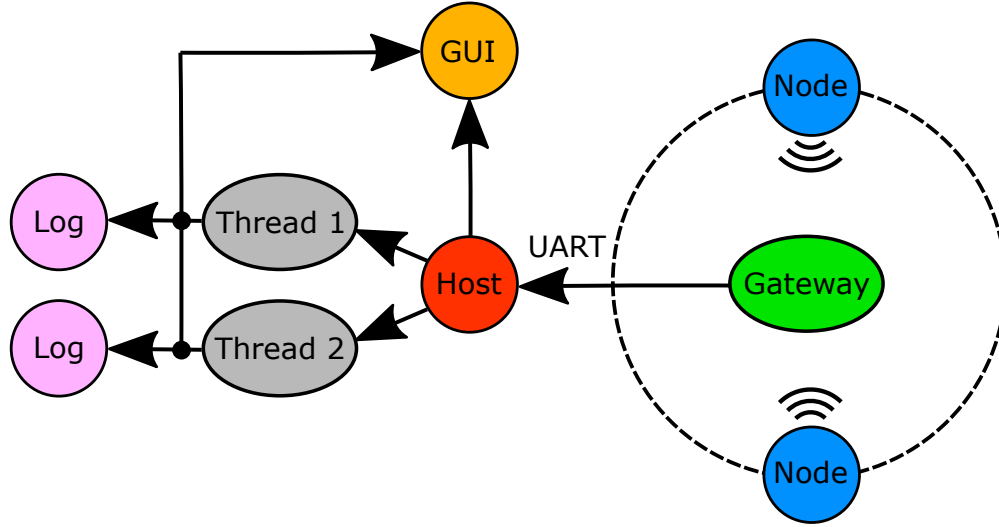


Figure 4.4. Schematic of software architecture for wireless controlled nucleation pressure and temperature sensor network. Data is collected by the central via the BLE link. The real-time stream is pushed to the host over the UART bus where it is processed, logged, and displayed to the user.

4.1.2 Depressurization Modeling

The fast decompression process allows the discharge process to be modeled as adiabatic. A schematic of the model domain is provided in Figure 4.5. To enable use of the isentropic flow relations the discharges are also assumed reversible. In reality, the heat transfer from the chamber components, viscous effects within the valve, and phase change associated with the condensation of water vapor challenge the validity of this assumption. However, it is still useful to compare discharge conditions on a purely theoretical basis.

For isentropic compressible flows the pressure, temperature, and density are related through the well-known relations [115].

$$\left(\frac{p}{p_0}\right) = \left(\frac{T}{T_0}\right)^{\frac{\gamma}{\gamma-1}} = \left(\frac{\rho}{\rho_0}\right)^{\gamma} \quad (4.1)$$

List of Variables/Parameters

Variable/Parameter	Description
P	Pressure
T	Temperature
V	Chamber Volume
A	Cross Sectional Area
γ	Specific Heat Ratio
$\mathcal{M}$	Molecular Mass

List of Subscripts

Subscript	Description
c	Chamber
0	Stagnation
e	Exit (Ambient)

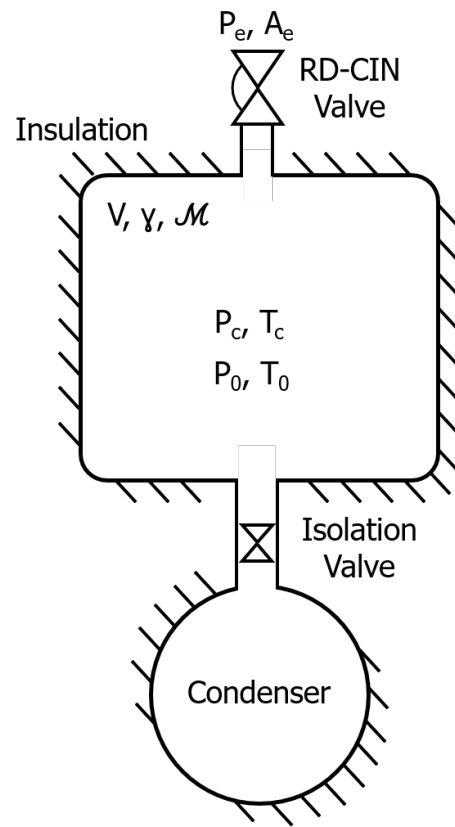


Figure 4.5. Schematic of the adiabatic decompression model domain.

where p , T , ρ , and γ represent pressure, temperature, density, and specific heat capacity ratio of the gas, respectively. The The pressure ratio is defined in terms of Mach number, M , using

$$\frac{p}{p_0} = \left(1 + \frac{\gamma - 1}{2} M^2\right)^{\frac{-\gamma}{\gamma - 1}} \quad (4.2)$$

The common pressure magnitudes encountered in RD-CIN cause the system to experience both choked and unchoked flow conditions throughout the process. The choking limit defining this transition is found by inserting a Mach number of unity into equation 4.2. The critical pressure ratio is gas-dependent and defined by

$$\frac{p_e}{p_c} = \left(\frac{\gamma + 1}{2}\right)^{\frac{-\gamma}{\gamma - 1}} \quad (4.3)$$

The development of the adiabatic decompression model begins by assuming a choked condition upon valve actuation. As the mass exits the chamber the pressure ratio falls until the critical ratio is met. At this point the flow transitions to subsonic and becomes dependent on the valve exit conditions. The entire process is modeling under the assumption of a quasi-steady state. That is, the composition, pressure, and temperature at any instant of time are considered perfectly mixed.

Supersonic Flow

The time-dependent pressure within the chamber while the system is choked is determined using the continuity equation.

$$V \frac{\partial \rho_c(t)}{\partial t} = -\rho_e(t) v_e(t) A_e \quad (4.4)$$

where V represents the volume of the chamber, $\rho(t)$ the density of the gas, v the average velocity across the cross section, and A the local cross sectional area of the chamber. Subscripts c and e define chamber and exit conditions, respectively. For choked flow,

equations 4.1 and 4.3 are inserted into equation 4.4, leading to the well-known Fliegner's formula [116].

$$V \frac{\partial \rho_c(t)}{\partial t} = - \frac{P_c A_e}{\sqrt{RT_c}} \sqrt{\gamma} \left(\frac{\gamma + 1}{2} \right)^{\frac{-(\gamma+1)}{2(\gamma-1)}} \quad (4.5)$$

where R represents the specific gas constant. From here, the isentropic relations are once again applied to express equation 4.5 in terms of the stagnation or chamber conditions.

$$V \frac{\partial (P_c/P_0)^{\frac{1}{\gamma}}}{\partial t} = - \frac{\sqrt{\gamma RT_0} A_e}{V} \left(\frac{P_c}{P_0} \right)^{\frac{1+\gamma}{2\gamma}} \left(\frac{\gamma + 1}{2} \right)^{\frac{-(\gamma+1)}{2(\gamma-1)}} \quad (4.6)$$

Equation 4.6 is integrated using substitution of variables to yield the chamber pressure as a function of discharge time.

$$P_c = P_0 \left(t \frac{A_e}{V} \sqrt{\gamma RT_0} \left(\frac{\gamma + 1}{2} \right)^{\frac{(\gamma+1)}{2(\gamma-1)}} \frac{\gamma - 1}{2} + 1 \right)^{\frac{-2\gamma}{\gamma-1}} \quad (4.7)$$

For a given gas, the time at which the flow in the duct transitions from choked to unchoked is determined by rearranging equation 4.7 and substituting the critical pressure ratio. The conditions at this time are used as initial conditions for the subsonic regime.

Subsonic Compressible Flow

As the flow becomes subsonic the Mach number is no longer unity and the chamber pressure is influenced by the conditions at the valve exit. Returning to equation 4.4, the velocity term is eliminated by applying the definition of the Mach number at the exit.

$$v_e = M_e a_e = M_e \sqrt{\gamma RT_e}$$

Invoking the assumption of an isentropic fluid, the exit properties are related to the chamber or stagnation conditions via equation 4.1. For the adiabatic and reversible fluid the stagnation temperature and pressure remain constant throughout the discharge process. Additionally, the exit mach number is related to the pressure ratio in equation 4.2.

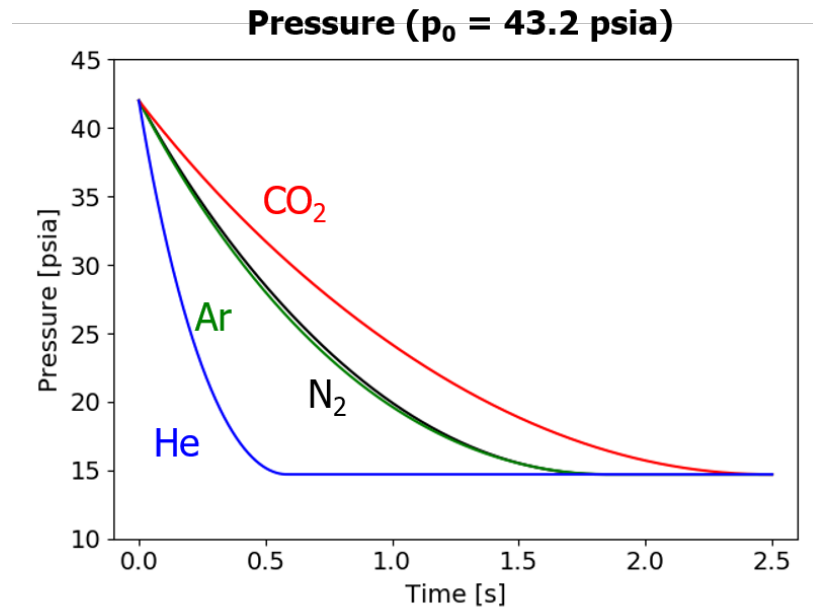
$$M_e = \sqrt{\frac{2\gamma}{\gamma-1} \left(1 - \left(\frac{P_e}{P_c} \right)^{\frac{\gamma-1}{\gamma}} \right)}$$

Substituting the above relations and applying the ideal gas equation to 4.4 to eliminate density terms gives

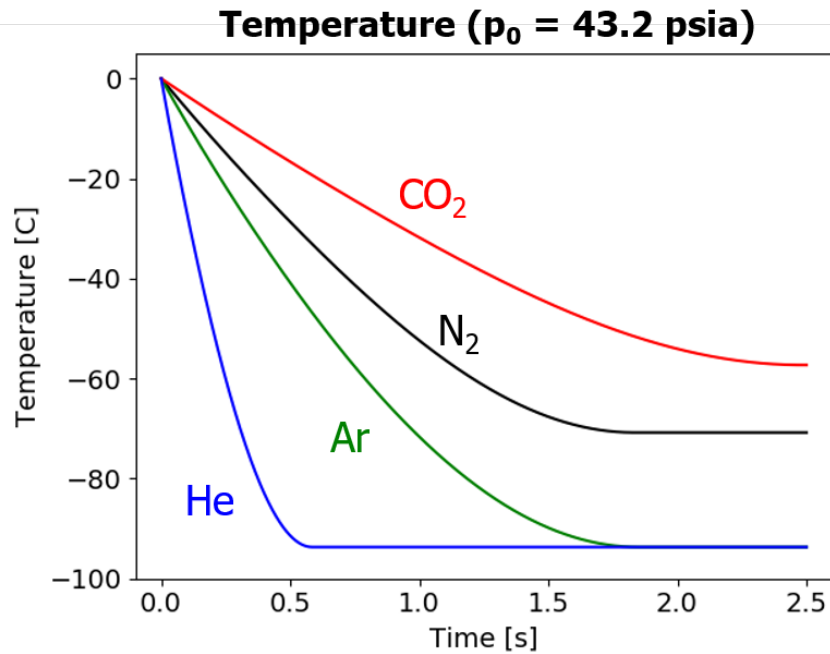
$$\frac{d(P_c/P_e)}{dt} = -\frac{A_e}{V} \gamma \sqrt{\gamma R T_0} \left(\frac{P_e}{P_0} \right)^{\frac{\gamma-1}{2\gamma}} \sqrt{\frac{2}{\gamma-1} \left(\left(\frac{P_c}{P_e} \right)^{\frac{\gamma-1}{\gamma}} - 1 \right)} \quad (4.8)$$

Equation 4.8 is in the form of an ordinary differential equation which is solved numerically. In this case, the solution is carried out using a 4th order Runge-Kutta scheme. Initial conditions are defined by the end states computed from the choked model. The variable V/A_e is unknown and is adjusted to fit the isentropic model to experimental data. With pressure known, the chamber gas temperature in both the choked and unchoked flows is found using the isentropic relation in equation 4.1.

The theoretical gas pressure and temperature during depressurization for different ballast gases are shown in Figure 4.6. Monoatomic gases tend to produce the greatest temperature drop between initial and final states due to their comparatively large heat capacity ratio. The mass of the gas influences the rate of pressure drop which, in turn, reduces the losses associated with heat transfer to the chamber surfaces. The influence of initial charge pressure on the RD-CIN process for nitrogen ballast according to the isentropic formulation is provided in Figure 4.7. The results demonstrate that the magnitude of the temperature drop tends to increase with charge pressure. This effect is due to the additional energy stored at higher pressures for a given initial temperature. Therefore, from a theoretical standpoint, it can be stated that low mass monatomic gases at high pressure are most optimal for RD-CIN processes. In practice, this statement may not be true as helium has a very high thermal conductivity relative to the other species, allowing it to wick heat from the warm surroundings much more effectively. The transfer of heat generates entropy which will tend to invalidate the primary assumption postulated during the derivation.

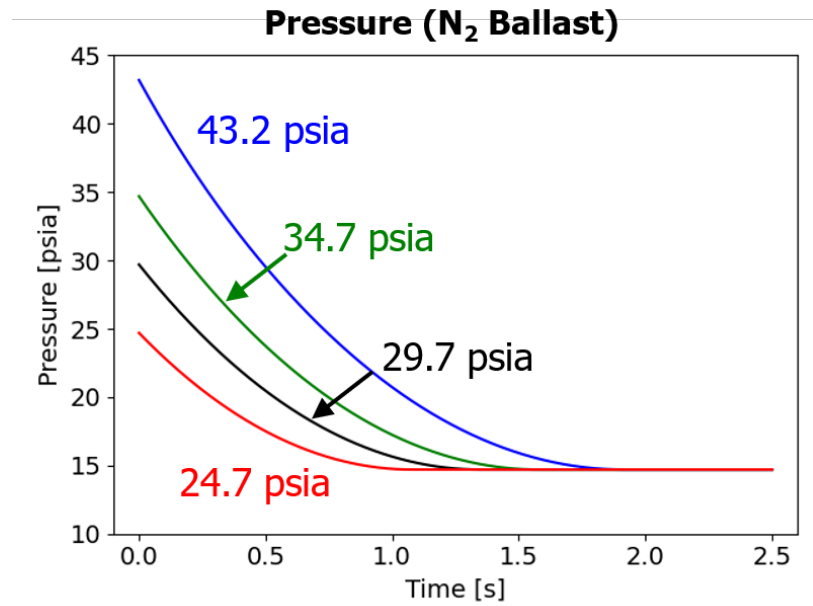


(a) Theoretical chamber pressure during RD-CIN assuming isentropic discharge

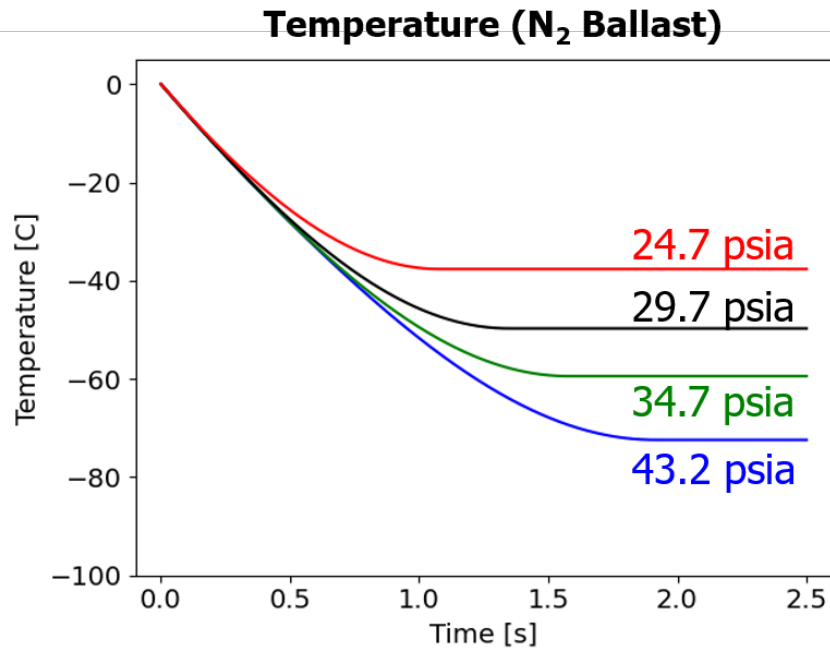


(b) Theoretical chamber temperature during RD-CIN assuming isentropic discharge

Figure 4.6. Theoretical gas pressure and temperature during RD-CIN for different ballast compositions using isentropic model



(a) Theoretical chamber pressure during RD-CIN assuming isentropic discharge



(b) Theoretical chamber temperature during RD-CIN assuming isentropic discharge

Figure 4.7. Theoretical gas pressure and temperature during RD-CIN for different ballast compositions using isentropic model

4.2 Experimental Setup

All CIN experiments were conducted in a LyoStar 3 lyophilizer (SP Scientific , Warminster, PA) outfitted with ControLyo[®] technology. ISO standard 6cc, 20cc, and 100cc Type I glass serum vials (Schott, Lebanon, PA) with 20 mm neck diameter were used. The number of vials for 6cc, 20cc, and 100cc sizes were 52, 20, and 111, respectively. Vials were partially stoppered using two-legged lyophilization style rubber stoppers and coated with a fluoropolymer (Daikyo Seiko, Sano, Japan). The upper two shelves of the LyoStar 3 were anchored in place against the upper support structure for all tests in order to accommodate the large 100cc vials. Ultra-pure semiconductor-grade water meeting SEMI standard Type E1.2 (18.2 M Ω -cm at 25°C) was used for all samples. No excipients were included during the study as the addition of these materials have little influence on the depressurization process [58]. In theory, they may affect the nucleation behavior by adjusting the freezing point or equilibrium vapor pressure however these effects are out of the scope of this study. Fill volumes for the 6cc, 20cc, and 100cc vials were 2cc, 5cc, and 40cc, respectively. In terms of measured fill height these volumes correspond to 0.7 cm, 0.8 cm, and 2.7 cm and were chosen to be representative of common manufacturing fill levels. Bottled helium and argon (Indiana Oxygen, Lafayette, IN) were sourced high-pressure bottles (>99.999% purity) and the nitrogen ballast was boiled off from the in-house liquid nitrogen supply (Linde, Lafayette, IN).

4.2.1 Cycle Parameters

All CIN experiments in this study employed an identical CIN cycle, independent of the vial type or charge gas. Initially, the samples were brought to 20°C and held for 28 minutes. Following this equilibration step, the chamber pressure was increased to the target setpoint and shelf temperature was reduced to -8°C at 1°C/min. Once at the setpoint, the conditions were held for 3 hours. This time scale was selected to ensure the solution and gas in the chamber are in equilibrium prior to depressurization. Following the soak period, the chamber pressure was released to a setpoint of 2 psig. The cycle was then stopped, the chamber opened, and the sensors shut down. Both wireless pressure and gas temperature

sensors were deployed in the first row of the vial pack. A summary of the experimental conditions is provided in Table 4.2.

Table 4.2. Summary of RD-CIN experiments performed using wireless sensors. Indicated values are nominal.

Cycle	Ballast	Vial Size	Temperature [°C]	Charge Pressure [psig]
A	N ₂	6cc	-8.0	28.5
B	N ₂	20cc	-8.0	28.5
C	N ₂	100cc	-8.0	28.5
D	Ar	20cc	-8.0	28.5
E	He	20cc	-8.0	28.5
F	N ₂	20cc	-8.0	20.0
G	N ₂	20cc	-8.0	15.0
H	N ₂	20cc	-8.0	10.0

4.2.2 Sensor Measurement Verification

Measurement accuracy of both thermocouples was verified in an ultra-pure frozen water ice bath prior to testing and demonstrated an average temperature of $-0.06^{\circ}\text{C} \pm 0.13^{\circ}\text{C}$. The absolute pressure sensor accuracy was verified against a NIST-traceable Ashcroft 2089 test gauge (Stratford, CT) with an accuracy of 0.05% and full-scale range of 60 psig. The verification process was performed by loading the sensors, sealing the chamber, and pressurizing to a range of target setpoints. Absolute and gauge pressure measurements from the wireless sensor were logged throughout the entire process and the shelf temperature was maintained at 20°C . Although the gauge sensor could not be calibrated in this manner it was nevertheless included to verify an average and invariant pressure near zero throughout the entire procedure. A table summarizing pressure calibration results is provided in Table 4.3. The maximum and minimum errors between Device 2 (absolute sensor) and the reference are 0.32% and 0.12% at target chamber pressures of 10 and 15 psig, respectively.

Table 4.3. Pressure calibration results for chamber (Device 2) and headspace (Device 1) devices.

Target [psig]	Reference [psig]	Device 2 [psia]	Device 1 [psig]
10	10.527	10.561	-0.0568
15	15.432	15.413	-0.0568
20	20.372	20.320	-0.0476
28.5	28.806	28.766	-0.0293

4.3 Results

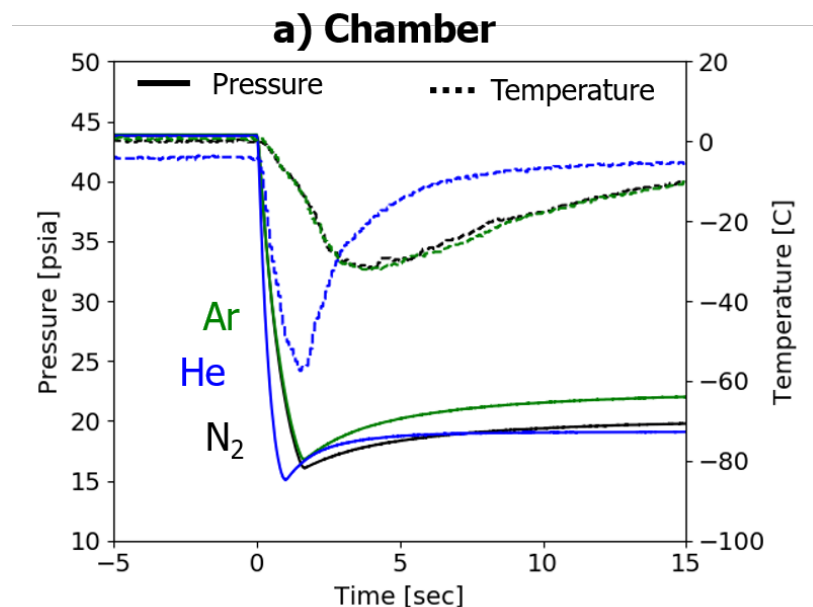
A series of RD-CIN experiments were conducted for the purpose of quantifying flow characteristics in the vicinity of the vial and within the headspace. Each vial type was tested using both nitrogen and helium ballast. The 20cc vial was also tested with argon.

4.3.1 Effect of Ballast Composition

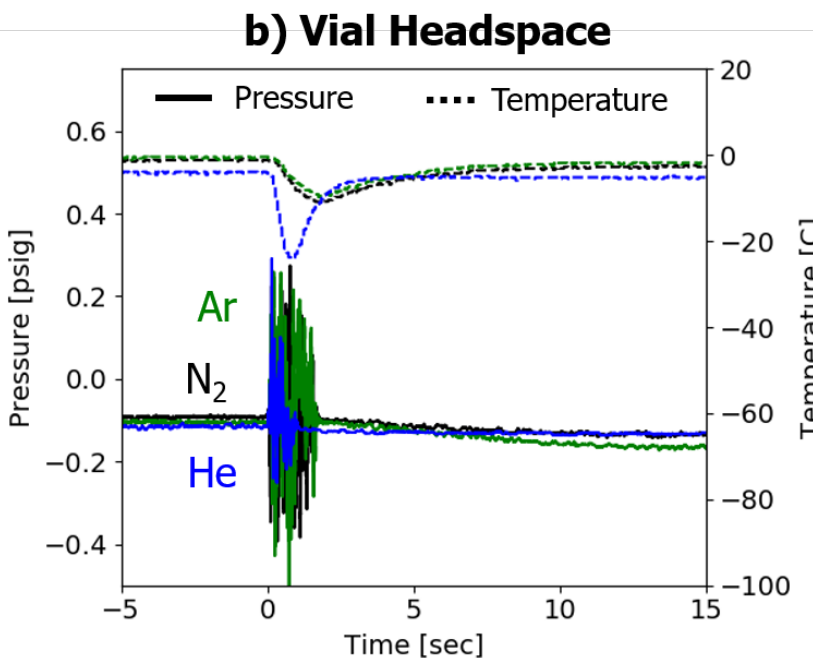
The experimental data for cycles A, D and E from Table 4.2 are shown in Figure 4.8. The discharge time is synchronized for all tests to facilitate direct comparison. Complete nucleation was achieved in all vials across all tests.

In terms of pressure, the helium discharge is most rapid. This result agrees with the isentropic predictions in Figure 4.6. Argon and nitrogen exhibit similar depressurization rates, taking around 60% longer than helium to complete. Here, the depressurization time is based on the chamber pressure and is taken as the time between the valve opening and the minimum measured pressure. After RD-CIN valve closure the pressure rises by roughly 5 to 7 psi, depending on the gas. The recovery action is due to the gradual warming of gas back to its initial state as a result of the heat transfer from the chamber walls, vials, shelves, and supporting structure. Helium exhibits the fastest recovery due to its high thermal conductivity whereas argon is slowest. The headspace pressure data in Figure 4.8b has been moving average-filtered with a window of 15 samples to reduce noise. The data exhibit large oscillations during the depressurization and the average pressure is nearly zero for all species. It is speculated that this behavior could be due to turbulence, mechanical vibration, diaphragm resonance or a combination of all three. This conclusion is supported by the uniform spectrum below 166 Hz when evaluating the spectral components via Fast Fourier Transform (FFT). Common resonant frequencies for MEMS diaphragms devices are on the order of 10 kHz (30 times greater than the sampling rate) and are therefore inaccessible to a spectral analysis.

The isentropic model equations were applied to the experimental data and the chamber volume to RD-CIN valve throat area, V/A_e , was used as the fitting parameter. The optimal ratio was solved using a univariate minimization technique, taking the mean-square error



(a) Effect of ballast gas composition on chamber pressure and temperature during RD-CIN



(b) Effect of ballast gas composition on vial headspace pressure and temperature during RD-CIN

Figure 4.8. Effect of ballast gas composition on RD-CIN response

between model and pressure data during the discharge as the cost function. Optimal values for nitrogen, argon, and helium are 349, 377, and 566 m, respectively. The scatter in the geometric parameter between gases is attributed to the viscous losses within the RD-CIN valve body. The isentropic model in equations 4.7 and 4.8 were derived assuming an ideal orifice flow, however in reality the RD-CIN valve is a finite length tube with an unknown series of bends or obstructions that both impart viscous and kinetic losses. Combined, these effects weaken the isentropic assumption in the RD-CIN valve region, leading to the observed gas dependence. In other words, a change in composition or discharge rate will make the valve more or less restrictive and will have the same effect as a changing the exit orifice area if the flow were purely inviscid. Following the fitting process, the experimental pressure data for cycles A, D, and E show good agreement to the fitted isentropic model. A comparison of the measured and estimated pressure and temperature during depressurization is shown in Figures 4.9-4.11. Parameters used in the model equations 4.7, 4.8, and 4.1 are provided in Table 4.4. In terms of RMS error, the deviation is 0.267, 0.316, and 0.336 psi over the duration of the discharge for nitrogen, argon, and helium, respectively.

Table 4.4. Summary of parameters used in isentropic relations. The chamber volume to valve area ratio is applied as the fitting parameter to experimental data.

Gas	γ	R [J/kg-K]	P_e [psia]	P_0 [psia]	T_0 [°C]	V/A_e [m]
Nitrogen	1.4	296.9	14.7	43.2	0.18	349
Argon	1.66	207.9	14.7	43.1	0.68	377
Helium	1.66	2078.6	14.7	43.3	-3.46	566

The isentropic theory in equation 4.1 predicts a direct correlation from gas pressure to temperature. However, a time lag between these measurements was observed in all cases. This time lag is defined as the span between the locations of minimum pressure and temperature during a discharge event. The adiabatic cooling effect must cease at valve closure (minimum pressure) but the measured temperature continues to decrease beyond this point. In all cases the minimum temperature is achieved later than the minimum pressure, indicating the gas is cooler than what is measured both during and for a short time after depressurization. Therefore, it can be assumed that the cause of the disagreement between

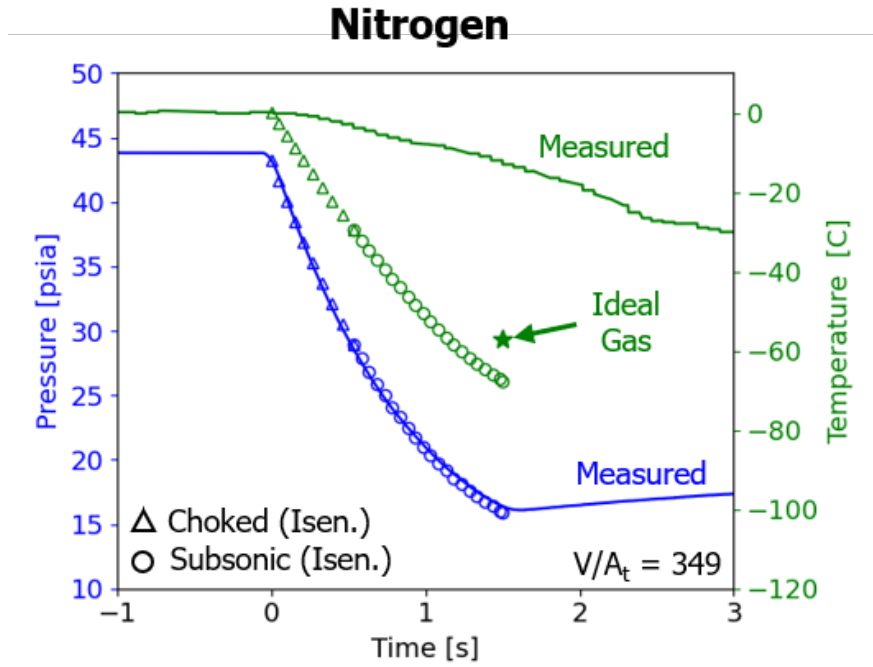


Figure 4.9. Comparison of measured and theoretical gas pressure and temperature in chamber during RD-CIN using nitrogen ballast.

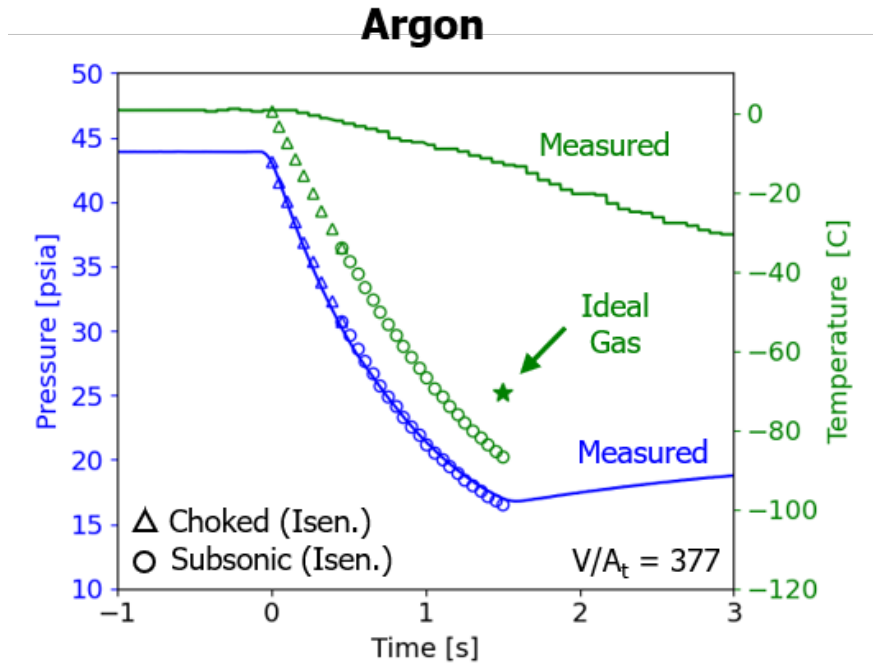


Figure 4.10. Comparison of measured and theoretical gas pressure and temperature in chamber during RD-CIN using argon ballast.

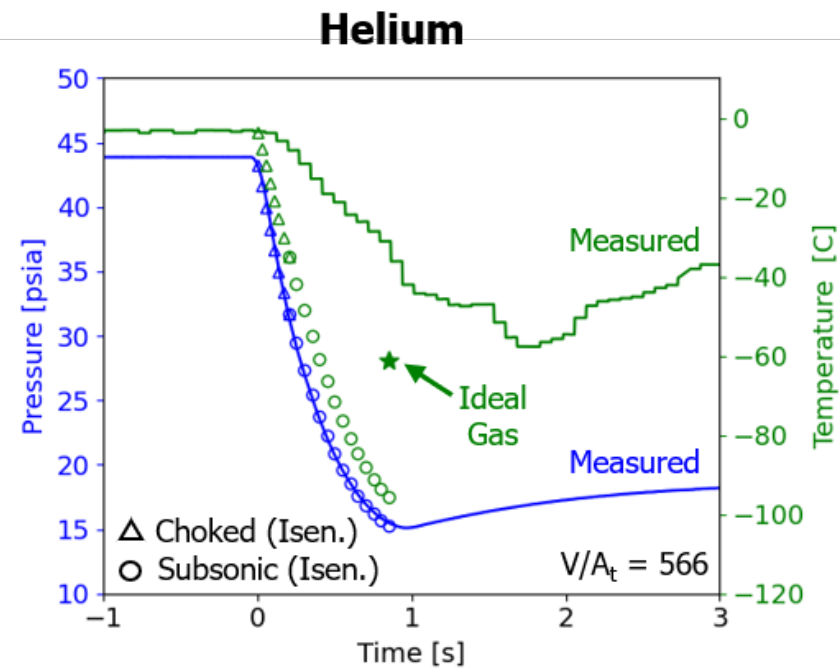


Figure 4.11. Comparison of measured and theoretical gas pressure and temperature in chamber during RD-CIN using helium ballast.

measurements and theory is due to the thermal inertia of the thermocouple. This conclusion can also be reached through application of the ideal gas law. At the time of valve closure the density (mass) of the gas in the chamber becomes constant. The post-discharge density is computed following equilibration of pressure and temperature around 19 seconds after the valve closure (not shown in the span of the plot data). It can safely be assumed based on estimates of partial pressure that the mass of the water vapor in the gas is negligible relative to the charge gas (estimated to be have a theoretical maximum of 0.4% w/w at the end of depressurization based on considerations of saturated vapor pressure) and is therefore ignored. With density and pressure known, the temperature of the gas in the chamber is computed at the time of valve closure. The estimated minimum temperatures for nitrogen, argon, and helium are -56.9°C, -70.6°C, and -61.2°C, respectively. These values are indicated in Figures 4.9-4.11 by the “Ideal Gas” markers and indicate that the actual gas temperature lies between the isentropic solution and that measured by the thermocouple at the conclusion of the depressurization event.

Comparison of the relative magnitudes under ideal gas predictions demonstrates that argon achieves the lowest temperature during depressurization. This result is supported by the experimental evidence that argon was more effective than both nitrogen and helium at achieving widespread nucleation [47], [58]. One explanation for this behavior is the low thermal conductivity of argon relative to the other species. Argon is less effective at wicking heat from the chamber walls, shelf support structure, etc. and therefore better approximates an adiabatic system. This conclusion is also supported by considering the entropy difference between initial and final states. Working with the ideal gas temperatures shown in Figures 4.9-4.11, argon produces 76% and 77% of the specific entropy generated by nitrogen and helium, respectively. A summary of the entropy generated during the discharge for different ballast gases based on the ideal gas estimates is provided in Table 4.5. Here, the subscripts 0 and 1 represent the gas state just prior to and immediately following valve closure.

During the experimental studies it was noticed that a vapor cloud filled the chamber near the end the discharge process (i.e. the valve closure event). The formation of this cloud results from the saturated vapor pressure falling below the partial pressure (dew point) on

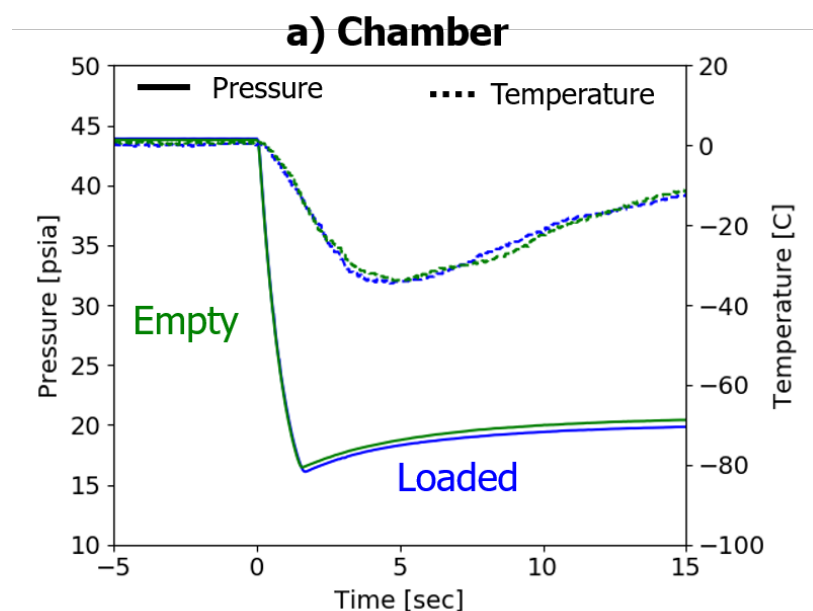
Table 4.5. Entropy generated during the RD-CIN process based on the measured and estimated gas state prior to and following valve closure.

Gas	P_0 [psia]	P_1 [psia]	T_0 [°C]	T_1 [°C]	Δs [J/kg-K]
N ₂	43.82	16.27	0.11	-54.47	63.9
Ar	43.90	16.72	0.61	-68.92	48.5
He	43.82	14.96	-4.23	-63.08	63.3

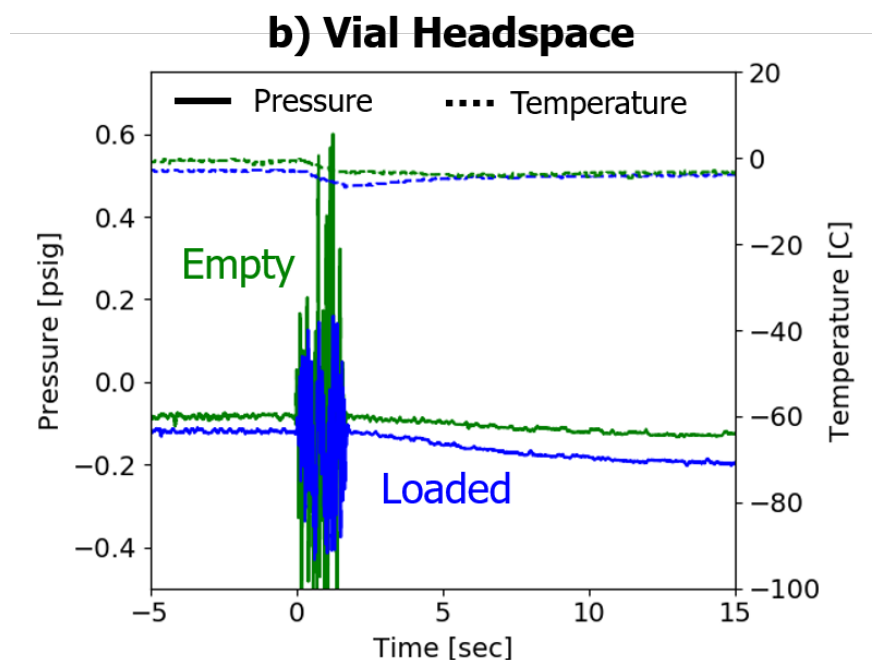
account of the rapidly decreasing temperature. At this point the liquid water condenses out the gas and quickly freezes to form ice nuclei. It was speculated that the latent heat generated by the condensing liquid could also contribute to the observed deviations from the isentropic process in Figures 4.9-4.11. However, identical experiments performed with and without liquid water in the chamber demonstrate similar temperature responses. These results are provided in Figure 4.12 and suggest the latent heat effect is minimal and can be neglected. The water vapor in the charge gas could be sourced from the vapor in the gas prior to depressurization, evaporation from the supercooled liquid during depressurization[58], or a combination of both. Regardless of the source, it is believed that the ice particles eventually deposit onto the supercooled liquid surface and induce nucleation. Although the pressure gradients in the system tend to result in the migration of ice nuclei out of the vials into the chamber it is reasonable to assume that those forming near the liquid surface will contact the interface through turbulent mixing, buoyancy-driven vortex structures, etc.

4.3.2 Effect of Vial Type

Comparisons of the measured chamber and headspace pressures and temperature for cycles B and E from Table 4.2 are shown in Figures 4.13 and 4.14, respectively. According to the data, vial type (in the studied range of 6cc to 100cc vial size) has no influence on chamber depressurization rate. The 100cc vial demonstrates a positive average gauge pressure relative to the chamber during depressurization, achieving a magnitude of around 0.2 psig in both cases. This result is supported by the larger vial barrel volume to stopper outlet area ratio. From this data it is concluded that flow is subsonic at the stopper vent throughout the entire process, forcing the pressure at this location to be equal to that of the chamber. To meet this condition, the mass flow rate out of the larger volume must be larger than that of the smaller volume. A larger mass flow rate necessitates a greater differential pressure for a given neck size and stopper outlet area (identical among all vials tested), the result of which is observed directly in the figure. Chamber temperature profiles indicate an independence of vial size during depressurization but some scatter upon valve closure. This behavior is most likely due to convection and radiation from the vials as the chamber gas equilibrates with its



(a) Comparison of chamber gas pressure and temperature with empty and loaded process chamber.



(b) Comparison of vial headspace gas pressure and temperature with empty and loaded process chamber.

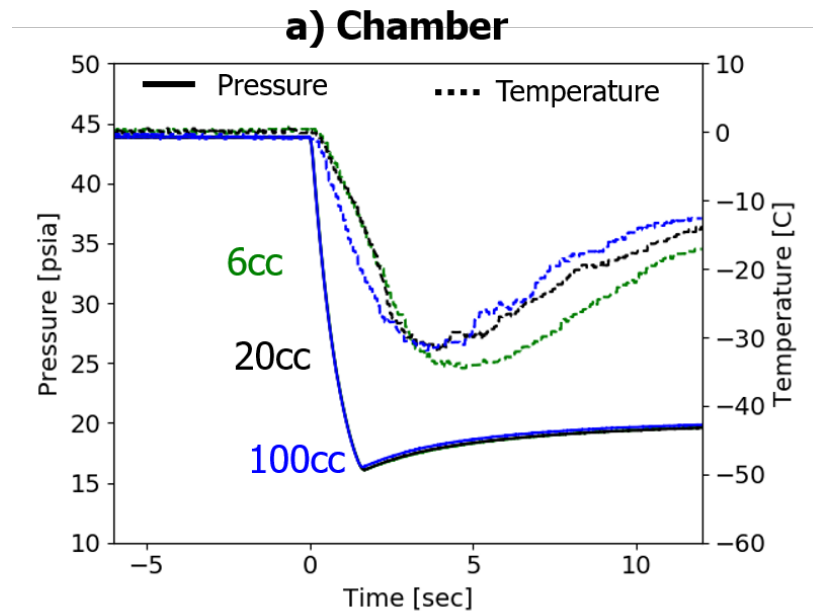
Figure 4.12. Effect of ballast gas composition on vial headspace pressure and temperature response during RD-CIN

surroundings, but additional experiments are required to provide conclusive evidence. Exact thermocouple placement relative to the vials also likely plays a major role.

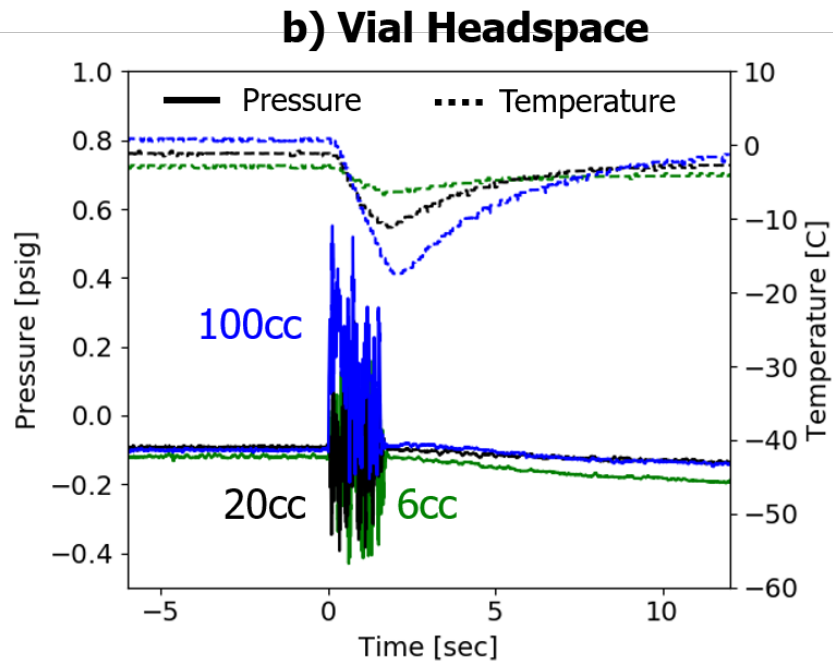
Figures 4.13 and 4.14 demonstrate that the smallest vial volume leads to the smallest decrease in headspace temperature. These measurements support the empirical observation that smaller vials are more difficult to nucleate under RD-CIN[117]. One possible explanation for the headspace temperature vial dependence is the heat capacity of the gas. The 6cc vial necessarily contains a smaller mass of gas just prior to depressurization than the 20cc or 100cc vials and therefore has a shorter thermal time constant. Assuming the walls of the borosilicate vials remain at a constant temperature during the discharge it is expected that the temperature of headspace gas in small vials maintain a higher temperature throughout depressurization. It could also be expected that the relative differences in flow rate out of the vials would impart an effect on the measured temperature drop. However, the flow velocity in the vial is highly dependent on the location and therefore makes a direct comparison difficult. The thermocouple responds much more quickly during helium depressurization due to the higher thermal conductivity and lower temperature magnitude (as indicated in Figure 4.10 relative to 4.9 and 4.11). The temperature recovery following RD-CIN valve closure is also much more rapid for helium, equilibrating around 66% faster than the other species.

4.3.3 Effect of Initial Discharge Pressure

The discharge pressure is critically important to the RD-CIN process and can be used to increase the probability of widespread nucleation by modulating the gas temperature drop. This capability is explored by cycles B, F, G, and H from Table 4.2 and the corresponding results are provided in Figure 4.15. The thermocouple measurements during the RD-CIN process indicate that the overall temperature drop grows as the initial charge pressure is raised. This result is in agreement with the isentropic relation from equation 4.1. The temperatures in the vial headspace display a similar behavior. However, as previously discussed, the measurements are consistently lower than those in the chamber due to the greater heat transfer in this region. A similar effect was observed while investigating the effect of the

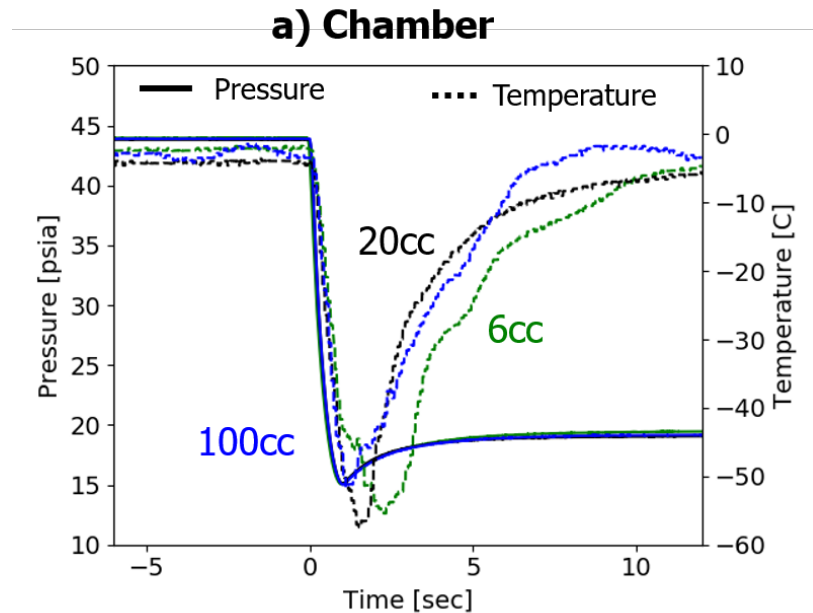


(a) Effect of vial size on chamber pressure and temperature during RD-CIN using nitrogen ballast

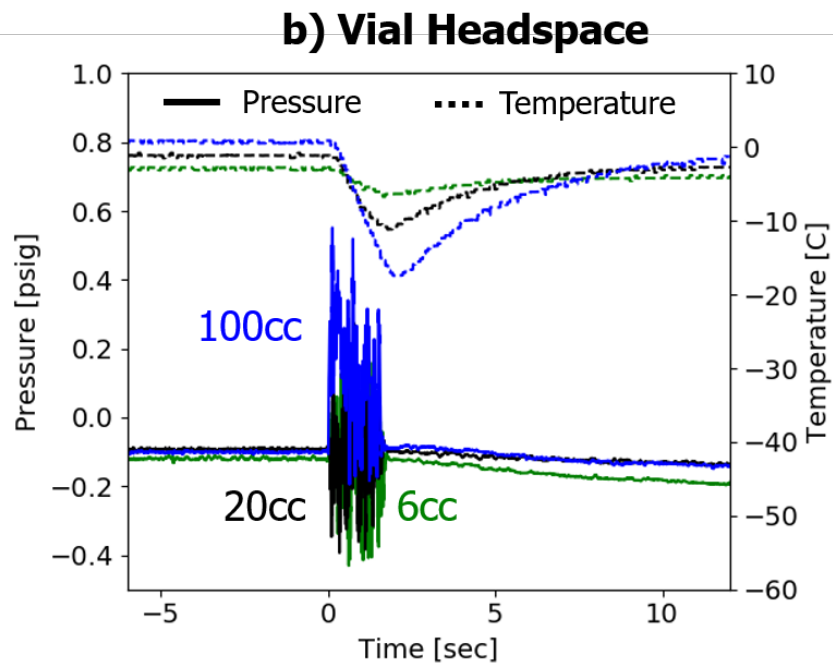


(b) Effect of vial size on vial headspace pressure and temperature during RD-CIN using nitrogen ballast

Figure 4.13. Effect of vial size on RD-CIN response using nitrogen ballast



(a) Effect of vial size on chamber pressure and temperature during RD-CIN using helium ballast



(b) Effect of vial size on vial headspace pressure and temperature during RD-CIN using helium ballast

Figure 4.14. Effect of vial size on RD-CIN response using helium ballast

ballast composition (Figure 4.8). Terminal gas temperature estimates using the ideal gas equation at valve closure are indicated by the symbols.

Following valve closure, the chamber pressure exhibits a pressure recovery period due to the cessation of mass transfer out of the chamber and the gradual warming of the gas as it equilibrates with the chamber walls and internal structure (shelf, supports, etc.). The magnitude of the temperature rise varies proportionally with the initial charge pressure due to the increased temperature difference at the conclusion of the discharge. All thermocouples approach identical limiting values which further supports the assumption that the chamber internal structure and glass vials maintain a constant value throughout the process.

A vapor cloud was formed during the experiments at 28.5, 20, and 15 psig and all vials appeared to undergo nucleation simultaneously. No visible cloud or nucleation event was observed for the charge pressure of 10 psig which suggests that the temperature drop for this charge pressure was not sufficient for the inert gas to become saturated. This behavior further supports the hypothesis that the nucleation mechanism relies on the seeding of the metastable liquid with ice nuclei. To characterize the relative cloud formation times a LED was placed in parallel with the valve relay. All processes were filmed and synchronized to the actuation signal. A summary of the observed cloud formation and nucleation times is presented in Table 4.6. The valve closure times are also indicated and based off of the LED extinguish event.

Table 4.6. Summary of ice fog formation times for different initial charge pressures. No cloud was observed for a pressure of 10 psig.

Charge Pressure [psig]	Cloud Visible [s]	LED off [s]	Nucleation [s]
28.5	0.87	1.27	1.77
20	0.9	0.93	1.76
15	0.97	0.77	1.8
10	-	0.54	-

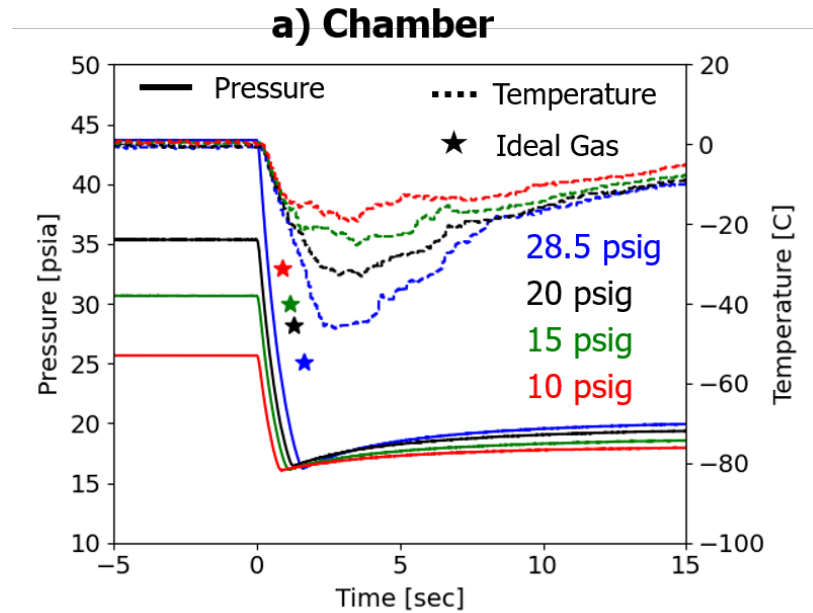
In all cases, the ice nucleation event occurs after the formation of the ice cloud. Initial charge pressure scales in inverse proportion to the appearance of the ice cloud. That is, a larger charge pressure causes the cloud to form sooner after the valve is opened. This result is expected since the rate of the gas temperature change scales with the initial charge pressure

(see equations 4.6 and 4.1). The nucleation times occur an average of 1.78 ± 0.01 seconds after the valve opening event, regardless of the initial pressure. One commonly proposed explanation for the nucleation mechanism is convective cooling of the liquid surface as the gas temperature drops. If this explanation were true, and dependence on charge pressure would likely be observed since the difference in heat transfer rates between charge pressures (due to differences in gas temperature) would be significant. Another proposed mechanism is the local cooling at the meniscus due to evaporation. Evaporation is driven by concentration gradients at the interface. If this explanation holds, a dependence on chamber pressure should also be observed since the relative vapor discharge rates out of the lyophilizer will be different. The evaporation rates over time, and hence the relinquished latent heats, would therefore also be different. Additionally, the camera footage show nucleation beginning near the center of the formulation. If evaporation were indeed the mechanism it would be expected that the nucleation front start at the edge.

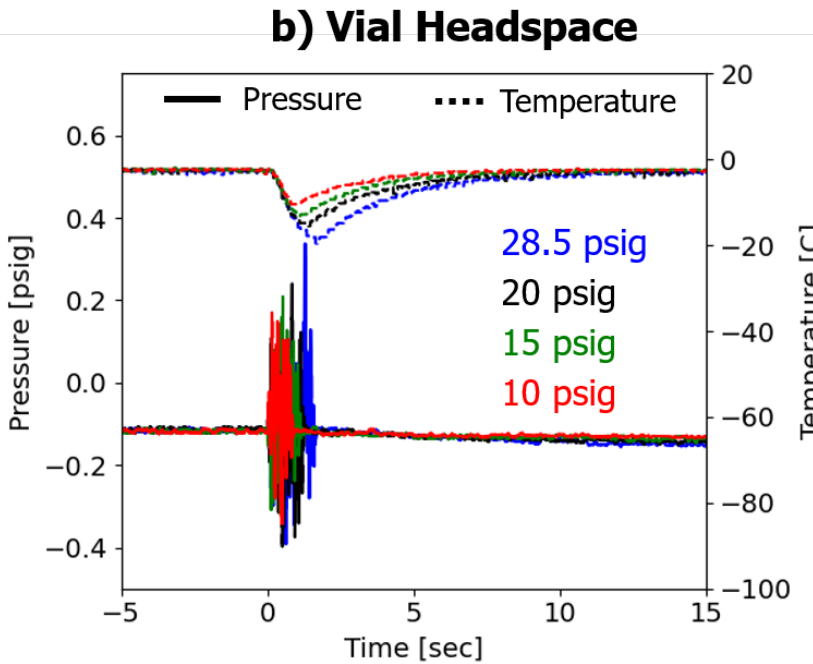
4.4 Estimation of Gas Temperature During RD-CIN

The thermocouple measurement lag during RD-CIN in both the chamber and vial headspace is attributed to the finite response time (thermal inertia) of the thermocouple. To account for this effect and estimate the true gas temperature during the discharge the thermocouple was modeled numerically using a 1st-order finite difference method. A schematic of the model domain is shown in Figure 4.16.

The system was assumed to be 2-dimensional and axisymmetric. The domain was discretized using a uniform cell spacing where the cell size is based on the radius of the thermocouple wire (0.025 mm). The thermal properties of copper and constantan were applied to the lead wires. Perfluoroalkoxy (PFA) insulation covers all but 4 mm of the lead wires at the junction and has a measured radius of 0.25 mm. Thermal properties for all materials are listed in Table 4.9. Convection boundary conditions were applied to all exposed zones and radiation was neglected. Empirical Nusselt number correlations were taken from the literature assuming forced convection around a cylinder[118]. The influence of the weld bead



(a) Effect of initial charge pressure on chamber pressure and temperature during RD-CIN using nitrogen ballast



(b) Effect of initial charge pressure on vial headspace pressure and temperature during RD-CIN using nitrogen ballast

Figure 4.15. Effect of initial charge pressure on RD-CIN response

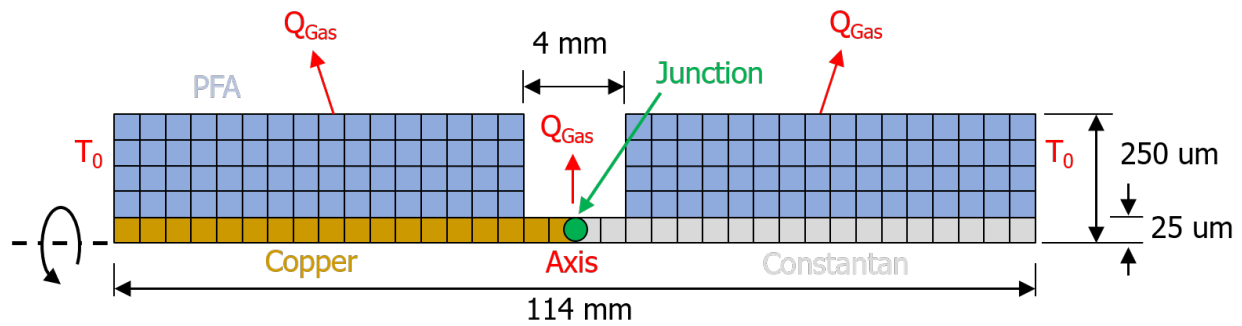


Figure 4.16. Computational domain (not to scale) for the axisymmetric thermocouple finite difference model.

at the junction was neglected as its radius was comparable to the copper and constantan lead wires[119].

$$Nu_D = 0.3 + \frac{0.62Re^{0.5}Pr^{0.33}}{\left(1 + \left(\frac{0.4}{Pr}\right)^{0.66}\right)^{0.25}} \left(1 + \left(\frac{Re}{282000}\right)^{0.625}\right)^{0.8} \quad (4.9)$$

The variables Re and Pr are the Reynolds and Prandtl numbers, respectively.

$$Re = \frac{\rho v D}{\mu}$$

$$Pr = \frac{\nu}{\alpha}$$

where ρ is the gas density, v is the bulk velocity, D is the local solid diameter, μ is the dynamic viscosity, ν is the kinematic viscosity and α is the thermal diffusivity of the gas. All gas properties are evaluated at the film temperature, T_f , which represents the average of the solid and gas temperatures.

$$T_f = \frac{T + T_\infty}{2}$$

The temperature and pressure-dependent gas properties, specifically thermal conductivity, heat capacity, and viscosity, were accounted for via interpolation from a lookup table at each time step [120]. Gas density was computed using the ideal gas law. The ends of the thermocouple were mounted into a terminal block on the circuit board and were therefore assumed isothermal during the discharge. The velocity of the gas, v , over the course of the discharge was estimated from the continuity and ideal gas equations.

$$v = -\frac{V}{A} \frac{T}{P} \frac{d(P/T)}{dt} \quad (4.10)$$

Here, V is the volume of the lyophilization chamber and A is its cross sectional area perpendicular to the flow. The temperature field was solved implicitly to ensure solution

stability. Under this method, the temperature at each node in the $m \times n$ domain was determined simultaneously.

$$\mathbf{A}T = \mathbf{b} \quad (4.11)$$

The $p \times p$ ($p = m \times n$) coefficient matrix, $\mathbf{A}$, was constructed by performing an energy balance at each node in Figure 4.17. Results for each zone are summarized in Table 4.7. At each time step the sparse linear system was solved to determine the temperature at the next time step. These results were then used to form the solution array, $\mathbf{b}$, and the process was repeated until the desired solution time was reached. The time step of 2 ms was selected by reducing step size over successive simulations until an invariance in predicted junction temperature was achieved.

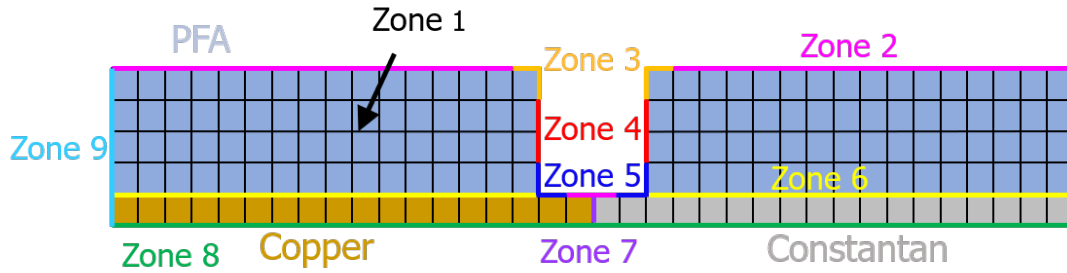


Figure 4.17. Zone map used to construct energy balance for 2-dimensional thermocouple finite difference domain. Zone equations are provided in Table 4.7

4.4.1 Analytical Model Validation

The 2-dimensional finite difference model was first validated through comparison against an analytical model. The axisymmetric model was developed for a thin rod of length L as shown in Figure B.1. A convective boundary condition exists over the length of the rod, dissipating heat into the surroundings of constant temperature, T_∞ . The rod is initially at a uniform temperature, T_∞ and the ends are set to T_0 . A detailed derivation can be found in Appendix B. The resulting temperature distribution in the rod is given by

Table 4.7. Energy balance for each zone as indicated in Figure 4.17

Zone 1:	$\left(\frac{1}{F_o} + \frac{2r_1\Delta x}{r_2^2 - r_1^2} + 2\right) T_{m,n}^{p+1} - \left(\frac{2r_1\Delta x}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} - \left(\frac{2r_2\Delta x}{r_2^2 - r_1^2}\right) T_{m+1,n}^{p+1} - T_{m+1,n+1}^{p+1} = T_{m,n}^p \left(\frac{1}{F_o}\right)$
Zone 2:	$\left(\frac{1}{F_o} + \frac{2r_1\Delta x}{r_2^2 - r_1^2} + \frac{2r_2\Delta x Bi}{r_2^2 - r_1^2} + 2\right) T_{m,n}^{p+1} - \left(\frac{2r_1\Delta x}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} - T_{m,n-1}^{p+1} = \left(\frac{1}{F_o}\right) T_{m,n}^p + \left(\frac{2r_2\Delta x Bi}{r_2^2 - r_1^2}\right) T_{\infty}$
Zone 3:	$\left(\frac{1}{2F_o} + \frac{r_1\Delta x}{r_2^2 - r_1^2} + 1 + Bi \left(\frac{r_2\Delta x}{r_2^2 - r_1^2} + 1\right)\right) T_{m,n}^{p+1} - \left(\frac{r_1\Delta x}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} - T_{m,n-1}^{p+1} = \left(\frac{1}{2F_o}\right) T_{m,n}^p + Bi \left(\frac{r_2\Delta x}{r_2^2 - r_1^2} + 1\right) T_{\infty}$
Zone 4:	$\left(\frac{1}{2F_o} + \frac{r_1\Delta x}{r_2^2 - r_1^2} + 1 + Bi + \frac{r_1\Delta x}{r_2^2 - r_1^2} + \frac{r_2\Delta x}{r_2^2 - r_1^2}\right) T_{m,n}^{p+1} - \left(\frac{r_1\Delta x}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} - \left(\frac{r_2\Delta x}{r_2^2 - r_1^2}\right) T_{m+1,n}^{p+1} = \left(\frac{1}{2F_o}\right) T_{m,n}^p + Bi T_{\infty}$
Zone 5:	$\left(\frac{1}{F_{o1}} + \frac{\beta}{2F_{o2}} + 2 + \frac{2r_1 + \Delta x}{r_2^2 - r_1^2} + \frac{Bi_1 \bar{r} \Delta x}{r_2^2 - r_1^2} + \beta \left(1 + \frac{r_2 \Delta x}{r_2^2 - r_1^2} + Bi_2\right)\right) T_{m,n}^{p+1} - \left(\frac{2r_1 \Delta x}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} - (1 + \beta) T_{m,n+1}^{p+1} - \left(\frac{r_2 \Delta x \beta}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} = \left(\frac{1}{2F_o}\right) T_{m,n}^p + Bi \left(\frac{r_2 \Delta x}{r_2^2 - r_1^2} + 1\right) T_{\infty}$
Zone 6:	$\left(\frac{1}{F_{o1}} + \frac{\beta}{F_{o2}} + 2 + \frac{2r_1 + \Delta x}{r_2^2 - r_1^2} + \frac{2r_2 \Delta x \beta}{r_2^2 - r_1^2} + 2\beta\right) T_{m,n}^{p+1} - \left(\frac{2r_1 \Delta x}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} - T_{m,n-1}^{p+1} - (1 + \beta) T_{m,n+1}^{p+1} - \left(\frac{2r_2 \Delta x \beta}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} = \left(\frac{1}{F_{o1}} + \frac{\beta}{F_{o2}}\right) T_{m,n}^p$
Zone 7/2:	$\left(\frac{1}{2F_{o1}} + \frac{\beta}{2F_{o2}} + 1 + \gamma + (1 + \gamma) \frac{r_1 + \Delta x}{r_2^2 - r_1^2} + (Bi_1 + \gamma Bi_2) \frac{r_2 \Delta x}{r_2^2 - r_1^2}\right) T_{m,n}^{p+1} - \left(\frac{r_1 \Delta x}{r_2^2 - r_1^2}\right) T_{m-1,n}^{p+1} - T_{m,n-1}^{p+1} - \beta T_{m,n+1}^{p+1} = \left(\frac{1}{2F_{o1}} + \frac{\beta}{2F_{o2}}\right) T_{m,n}^p + (Bi_1 + \gamma Bi_2) \left(\frac{r_1 \Delta x}{r_2^2 - r_1^2}\right) T_{\infty}$
Zone 7/8:	$\left(\frac{1}{2F_{o1}} + \frac{\gamma}{2F_{o2}} + 1 + \gamma + \frac{(1 + \gamma) \Delta x}{r_2}\right) T_{m,n} - \left(\frac{(1 + \gamma) \Delta x}{r_2}\right) T_{m+1,n}^{p+1} - T_{m,n-1}^{p+1} - \gamma T_{m,n+1}^{p+1} = \left(\frac{1}{F_{o1}} + \frac{\gamma}{2F_{o2}}\right) T_{m,n}^p$
Zone 8:	$\left(\frac{1}{F_o} + 2 + \frac{2\Delta x}{r_2}\right) T_{m,n}^{p+1} - \left(\frac{2\Delta x}{r_2}\right) T_{m+1,n}^{p+1} - T_{m,n-1}^{p+1} - T_{m,n+1}^{p+1} = \left(\frac{1}{F_o}\right) T_{m,n}^p$
Zone 9:	$T_{m,n}^{p+1} = T_0$

$$\begin{aligned}
T(z, t) = & \frac{T_0}{2} e^{\alpha t} \left(e^{-\sqrt{\frac{\alpha}{k}}((2n+1)L-z)} \operatorname{erfc} \left(\frac{((2n+1)L-z)}{2\sqrt{kt}} - \sqrt{\alpha t} \right) \right. \\
& \left. + e^{\sqrt{\frac{\alpha}{k}}((2n+1)L-z)} \operatorname{erfc} \left(\frac{((2n+1)L-z)}{2\sqrt{kt}} + \sqrt{\alpha t} \right) \right) + \\
& \frac{T_0}{2} e^{\alpha t} \left(e^{-\sqrt{\frac{\alpha}{k}}((2n+1)L+z)} \operatorname{erfc} \left(\frac{((2n+1)L+z)}{2\sqrt{kt}} - \sqrt{\alpha t} \right) \right. \\
& \left. + e^{\sqrt{\frac{\alpha}{k}}((2n+1)L+z)} \operatorname{erfc} \left(\frac{((2n+1)L+z)}{2\sqrt{kt}} + \sqrt{\alpha t} \right) \right) \quad (4.12)
\end{aligned}$$

A graphical comparison of the analytical and finite difference model at different time points is provided in Figure 4.18 and a summary of the parameters in Table 4.9. The number of cells used in the discretization was 96 and were applied uniformly. The RMS difference at each time step is provided in Table 4.8. The models demonstrate good agreement throughout the transient cooling process with decreasing error as the solution approaches a steady state.

Table 4.8. Root-mean-square difference between the 2-dimensional axisymmetric finite difference model and analytical solution (Figure 4.18) at different instances of time for a uniform cylinder in crossflow

Time [ms]	RMS Difference [°C]
250	0.019
500	0.015
750	0.013
1000	0.013

4.4.2 2-Dimensional Finite Element Model Validation

Following benchmarking against the simplified analytical model the 2-dimensional finite difference model was validated using the commercial multiphysics solver COMSOL. The domain is identical to that shown in Figure 4.16 and all material properties were derived from Table 4.9. The system was initially at a temperature of 20°C and the surrounding gas was suddenly lowered to 0°C. Validity was established by comparing the computed temperature along the axis from both solution methods. In both cases, the solution was

Table 4.9. Parameters used during validation of 2-dimensional axisymmetric finite difference model.

Parameter	Value	Unit
k_{copper}	407.0	[W/m/K]
$C_{p,\text{copper}}$	386.0	[W/m/K]
ρ_{copper}	8960.0	[kg/m ³]
$k_{\text{constantan}}$	21.2	[W/m/K]
$C_{p,\text{constantan}}$	390.0	[W/m/K]
$\rho_{\text{constantan}}$	8908.0	[kg/m ³]
k_{PFA}	0.195	[W/m/K]
$C_{p,\text{PFA}}$	1172.0	[W/m/K]
ρ_{PFA}	2150.0	[kg/m ³]
h	100	[W/m ² /K]
D_{TC}	0.05	[mm]
D_{PFA}	0.50	[mm]
L	50.75	[mm]
L_{PFA}	48.7	[mm]
T_1	20.0	[°C]
T_∞	0.0	[°C]
T_0	20.0	[°C]

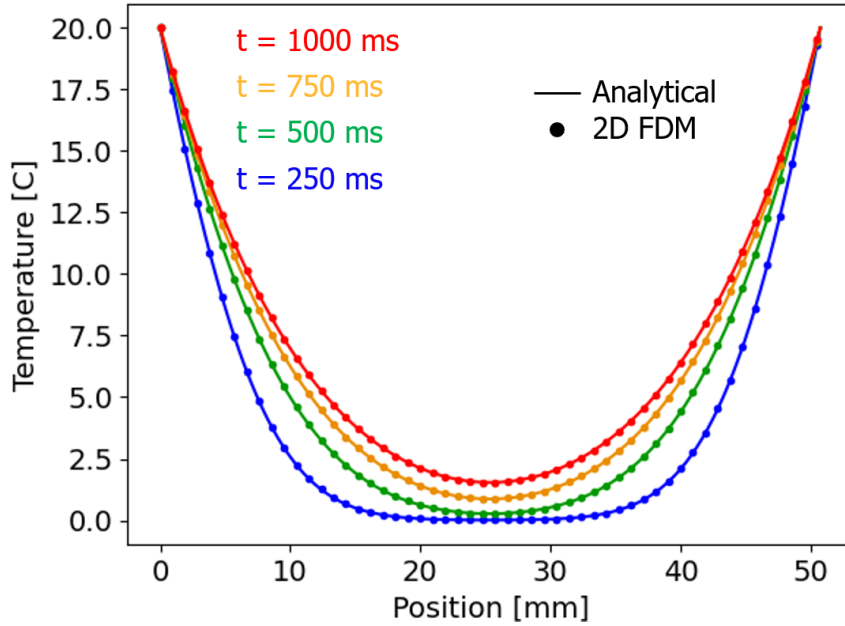


Figure 4.18. Comparison between finite difference model and analytical solution at various times for thin rod shown in Figure B.1. Maximum root-mean square error is 1.9% and occurs 250ms.

carried out to a stopping point of 1 second as this represents the typical depressurization time during RD-CIN. The results are shown in Figure 4.19.

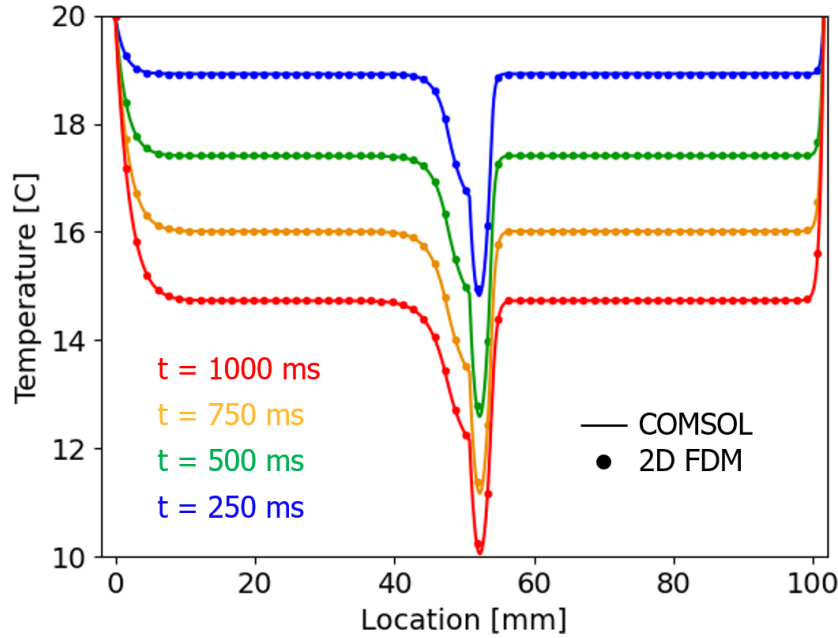


Figure 4.19. Comparison between finite difference model and COMSOL solution at various times along the line of axisymmetry. Maximum root-mean square error is 2.2% and occurs 1s.

Similar to the comparison against the analytical solution the accuracy of the model was established by taking the root-mean-square difference over the entire axis. The results are provided in Table 4.10. The temperature profiles display an asymmetry across the thermocouple junction due to the large differences in thermal conductivity (roughly 20 times) between copper and constantan. Copper spreads heat much more readily and therefore produces a much wider temperature profile along the axis near the junction. The minimum temperature exists in the constantan lead at around 50% of the exposed length. However, the actual measured temperature at the welded junction is higher in magnitude.

The agreement with the simplified analytical and high-fidelity COMSOL models suggest the 2-dimensional finite difference model is able to accurately approximate the temperature distribution within the thermocouple for arbitrary gas temperatures and discharge times.

Table 4.10. Root-mean-square difference between 2-dimensional finite difference model and COMSOL finite element solution (Figure 4.19) at different instances of time for a thermocouple in crossflow

Time [ms]	RMS Difference [°C]
250	0.009
500	0.016
750	0.019
1000	0.022

4.4.3 Gas Temperature Estimation

The finite difference model establishes the direct problem. That is, the temperature distribution throughout the thermocouple is computed from a known time-dependent gas temperature. To determine the unknown gas temperature the model was applied as an inverse parameter estimation problem. Estimation of the true gas temperature was carried out using a univariate minimization algorithm (Brent's method[121]). At each time step a new gas temperature was assumed and the finite-difference equations were solved to provide the temperature distribution within the thermocouple. The junction temperature was compared to the experimentally measured temperature in a root-mean-square error sense and passed to the minimization algorithm.

The estimated gas temperature was assumed to be the true temperature. When the error between computed solution at the junction and the measured value was minimized. The isentropic and measured chamber temperature data served as the solution bounds. Once the true gas temperature was found the time step was incremented and the “true” temperature from the previous iteration was used to compute the gas properties in the current iteration. The solution procedure is listed below:

1. Guess the value of the true gas temperature. Typically taken as the result from the previous iteration.
2. Solve the 2-dimensional finite-difference model to determine the temperature at the thermocouple junction.
3. Compute the cost function using the results from Step (2) and the measured thermocouple temperature.
4. Execute optimization algorithm to find the new search direction
5. Compute updated gas temperature using the results from (4)
6. Repeat Steps (2)-(5) until first-order optimality is achieved

The estimated junction, estimated gas, measured junction, and isentropic gas temperatures for each ballast gas are shown in Figures 4.20-4.22. Here, the estimated junction temperature was determined through application of a 4th-order polynomial fit to provide a smoothly varying response. The simulations are carried out until the time at which the valve began to close since the quasi-steady assumption at this time begins to break down. The valve closure point was determined directly from the estimated flow velocity and was marked by a rapid decrease in this variable. The junction temperature represents that which is predicted by the model and is provided for comparison to the measured values.

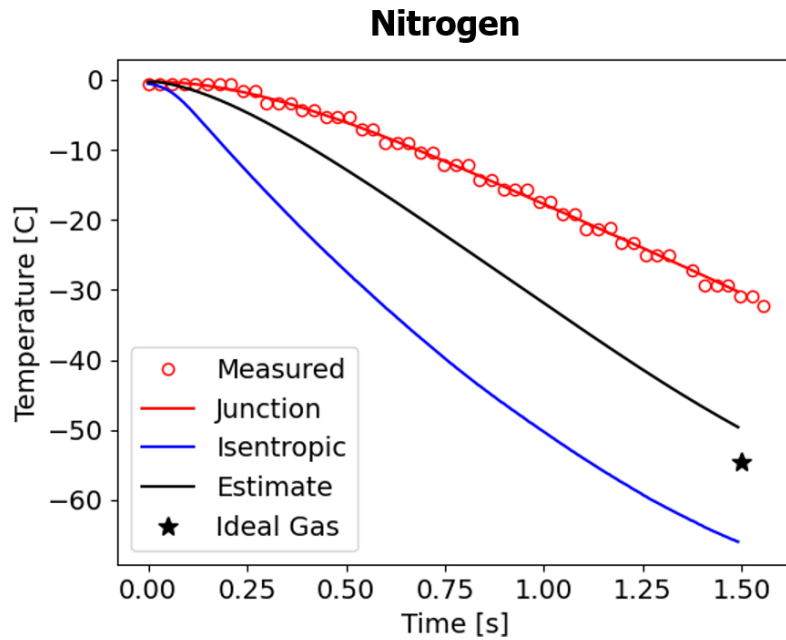


Figure 4.20. Estimate of true gas temperature during decompression using nitrogen ballast.

In all cases, the estimated gas temperature lies between the isentropic solution and experimental (and modeled) measurements. The deviation from the isentropic temperature solution results from the combined convective and radiative heat transfer during depressurization which act to weaken the isentropic assumption. According to the model data, argon produced the lowest gas temperature at the time of valve closure whereas nitrogen had the highest. This result is in qualitative agreement with the ultimate temperature estimated using the ideal gas equation. Helium produced the strongest deviation from the isentropic

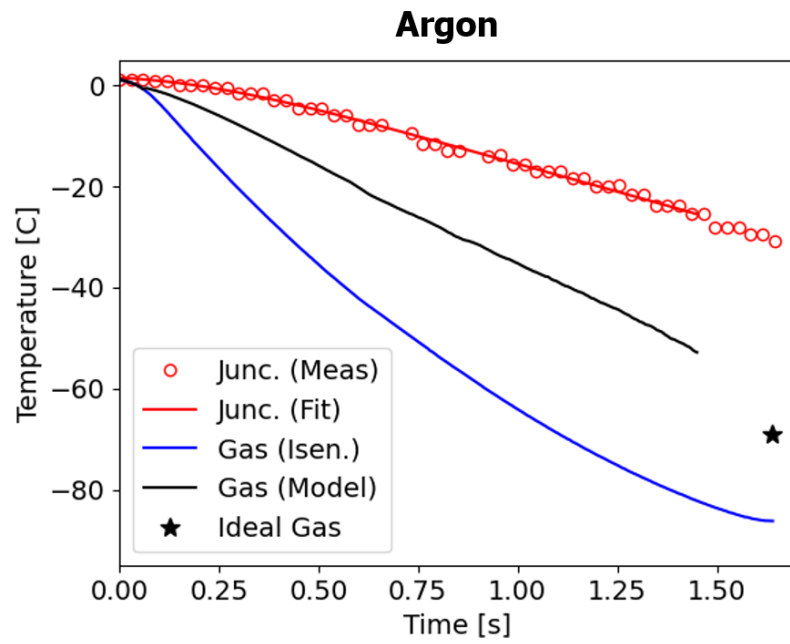


Figure 4.21. Estimate of true gas temperature during decompression using argon ballast.

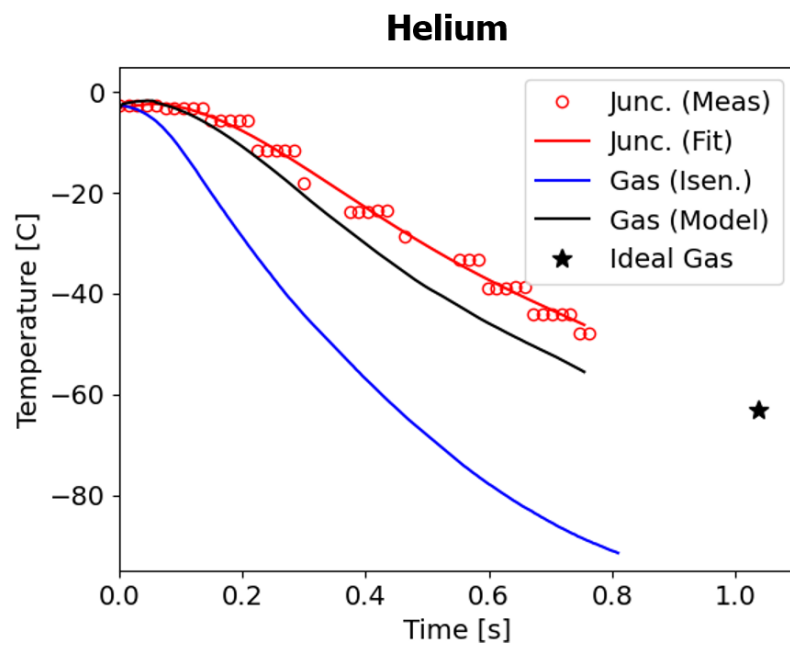


Figure 4.22. Estimate of true gas temperature during decompression using helium ballast.

solution, owing to its high thermal conductivity. This conclusion suggests that, of the three ballast species investigated, argon is the most optimal choice in terms of the temperature drop magnitude.

5. APPLICATION OF WIRELESS SENSOR NETWORKS TO MICRONEWTON THRUST MEASUREMENT

The principles of heat and mass transfer common to lyophilization are directly transferable to the design of a small-satellite propulsion systems. The growing popularity of microsatellites in the 1-20 kg mass class has been met with a corresponding demand in small thruster technology for attitude control in earth-orbiting bodies and course corrections for interplanetary vehicles [122].

5.1 Thruster Design

An evaporation-based thruster was designed and fabricated to meet the ongoing propulsion needs of microsatellites. The design is represented schematically in Figure 5.1. The corresponding image containing the assembled and exploded device is provided in Figure 5.2. The thruster has a wet chamber volume of 16 cm³ and an empty mass of 193g. Volume was measured by filling the thrust chamber with pure water and weighing the change in mass. The default throat diameter is 12 mm and accommodates nozzle inserts of various dimensions and configurations to quantify performance. The thrust chamber is composed of a copper pipe and statically sealed using two machined aluminum end caps, each containing a buna o-ring. The solenoid is fixed to the aft end cap and actuates a plunger with a silicone gasket. The plunger is spring-loaded and seals against the fore end cap in its default state to minimize power draw.

The device relies on the evaporation of liquid propellant from a thin paper membrane adhered to the inner wall of the thrust chamber and is analogous to the operation of larger solid rocket motors found on launch vehicles. Water was selected as the propellant due to its natural abundance, reasonably high vapor pressure at room temperature, high density, and low toxicity. The paper membrane was saturated with liquid water to provide a large surface area for evaporation. To produce thrust, the plunger sealing the thrust chamber from the external environment is retracted using a solenoid. The high pressure water vapor exits the nozzle, leading to a reduction in pressure. In an attempt to re-establish equilibrium, water

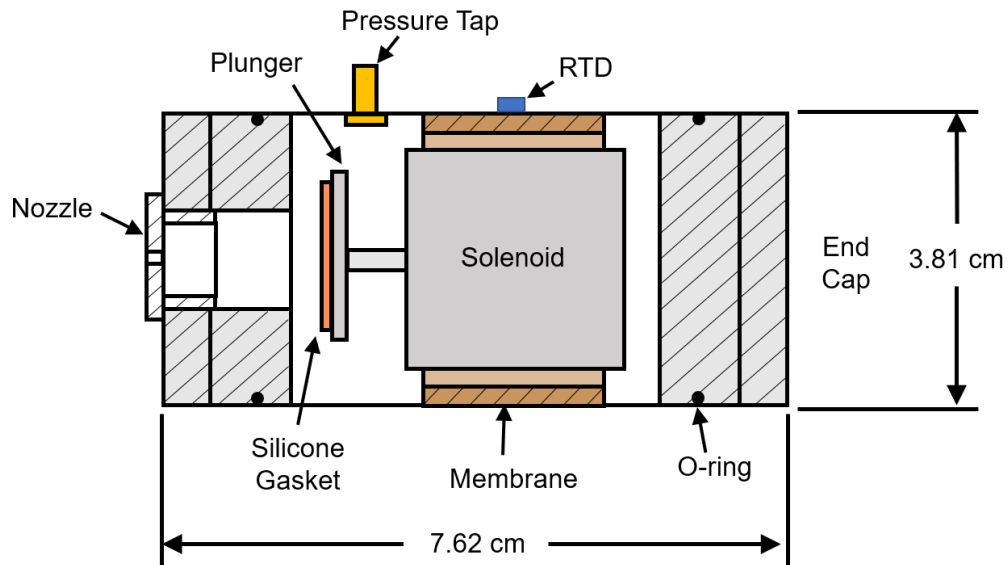


Figure 5.1. Cross-sectional schematic of milliNewton evaporation thruster. Liquid water evaporates from the membrane and exits the nozzle to produce thrust

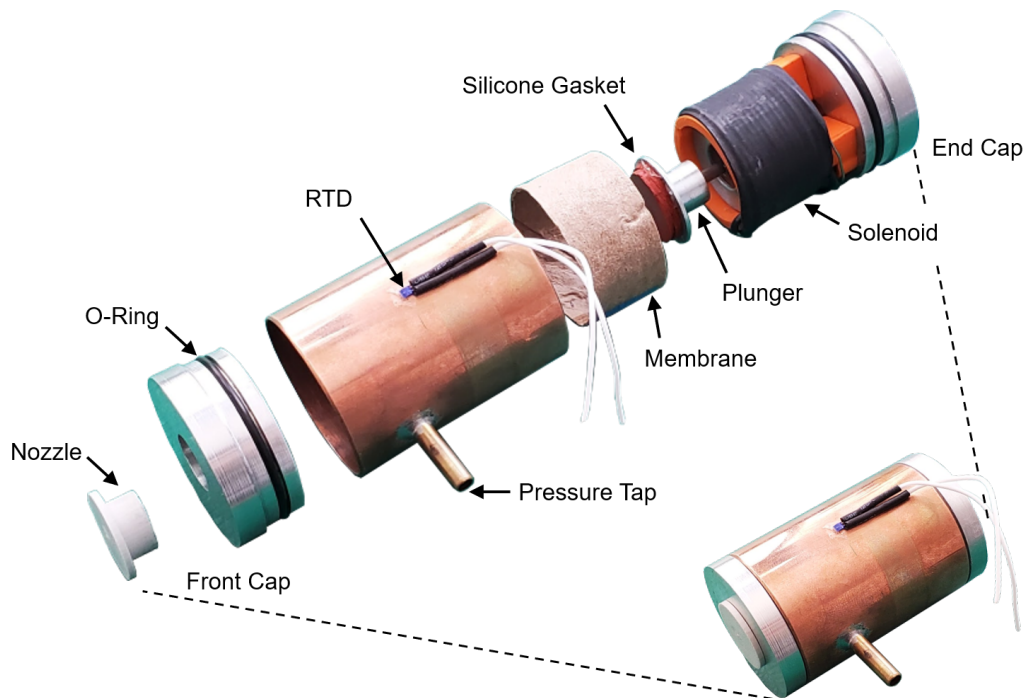


Figure 5.2. Image of assembled (bottom right) and exploded (top left) evaporation thruster. The device is controlled by an wireless transceiver module (not shown) that communicates with the host over a BLE link.

vapor evaporates from the membrane into the thrust chamber. The latent heat required for evaporation produces a cooling effect which lowers the saturated vapor pressure of the water vapor. A heating element surrounding the solenoid was therefore included to allow the membrane temperature to be controlled at a target setpoint. A RTD affixed to the outer surface of the thrust chamber provided the necessary feedback for thermal actuation. Chamber pressure is monitored through the static port via a rubber hose using a MEMS differential pressure transducer.

5.1.1 Signal Processing

The Nordic Semiconductor nrf52832 MCU (see Section 3.1.1 for system details) was used to collect thrust chamber pressure and temperature data, actuate the solenoid and heater, and communicate with a central host node over a BLE link. The connection between host and peripheral was established using the Nordic UART service with both transmit and receive characteristics. Upon power-up the thruster advertises its services and connects to the host if able. After pairing, characteristic notifications are enabled and the thruster starts broadcasting measurements to the host at a rate of 2 Hz. The device also monitors the receive buffer on each connection interval (between 20-40ms, depending on the negotiated value) for a change in commanded solenoid or heater state from the host. A schematic of the thruster electronics is provided in Figure 5.3.

If the trigger event is detected, the MCU toggled the solenoid through a gate driver which, in turn, fed the N-channel MOSFET. The thruster chamber pressure was measured relative to the ambient at the pressure tap via a differential pressure transducer (HSC-MANN010ND2A3, Honeywell, NC) over a two-wire interface. It is reasonable to assume that the pressure is spatially uniform throughout both the vacuum and thrust chambers. Therefore, the thrust chamber pressure is simply the sum of the differential pressure and the absolute pressure that is measured by the capacitance manometer. Chamber wall temperature in contact with the membrane is monitored using a Pt1000 RTD (Honeywell, Charlotte, NC). Due to the low thermal resistance the temperature indicated by the RTD is assumed to be the temperature of the membrane. The RTD is biased with a 300 μ A constant-current

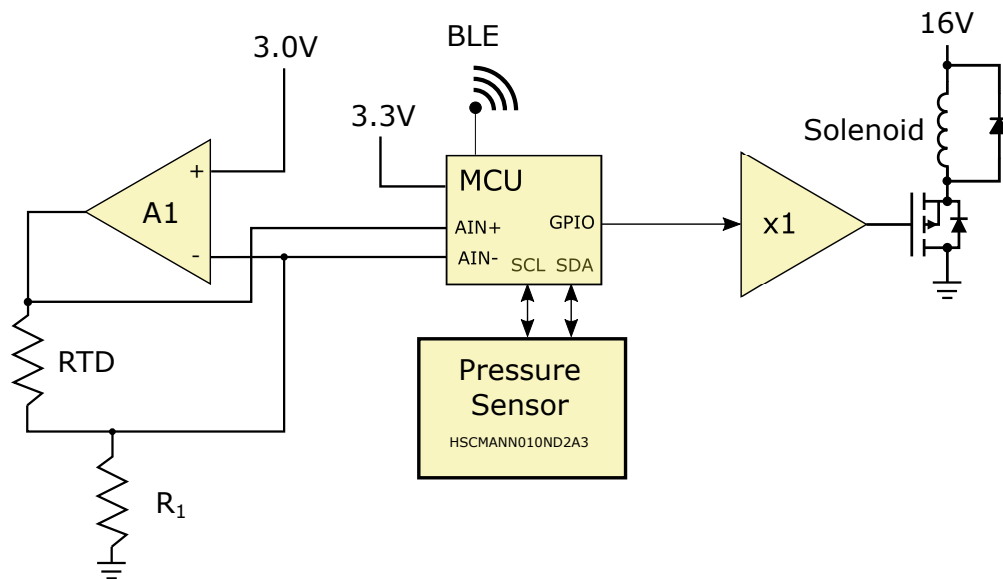


Figure 5.3. Electrical schematic of evaporation thruster.

source formed using a zero-drift operational amplifier, A1. The RTD bias voltage is measured using a 12-bit successive approximation ADC native to the nrf52832 chipset. The RTD provided the necessary feedback to regulate the chamber wall temperature via the heating element. However, this capability was not explored in this work.

5.2 Materials and Methods

The water vapor thruster was mounted on a microNewton torsional balance inside of a nominal 4.2 m^3 vacuum chamber at Purdue University’s High Vacuum Laboratory (HVL)[23]. Vacuum was generated by a DK200 rotary vane and WAU2001 blower pump array (Oerlikon, Cologne, Germany), providing ultimate vacuum in the range of $1\text{e-}4$ mbar. The HVL large chamber has a $20,000\text{L/min}$ diffusion pump which can extend this range down to $1\text{e-}5$ mbar. However, this system was not used as the high expected thruster flow rates would likely lead to stall and potential silicone oil contamination. Background chamber pressure was monitored using a Baratron 626B (MKS, Andover, MA) having a full-scale range of 100 mTorr and accuracy of 0.25% full-scale. An image of the experimental setup is shown in Figure 5.4.

The microNewton balance was installed on a spring-dampened table to minimize the influence of mechanical vibrations from the vacuum pumps. Additional dampening was provided by magnets which induced eddy currents as the thrust stand displaced under the influence of an external force. In this configuration the unit was capable of resolving thrust with a full-scale range of 1.8 mN and a resolution of ± 0.003 mN. A schematic of the balance is provided in Figure 5.5. Weights were added on the torsion arm opposing the thruster to null any off-axis external moments.

Locating the torsional balance inside of the the vacuum chamber allowed the pressure surrounding the device to be lowered far below the vapor pressure of the water (at room temperature), simulating high altitude flight. When the operating pressure was reached the plunger was actuated using the solenoid, exposing the thrust chamber to the vacuum. The expulsion of the water vapor out of the nozzle produces thrust which can then be used for attitude adjustments or deorbiting. Nozzles were 3D printed and installed into the fore end

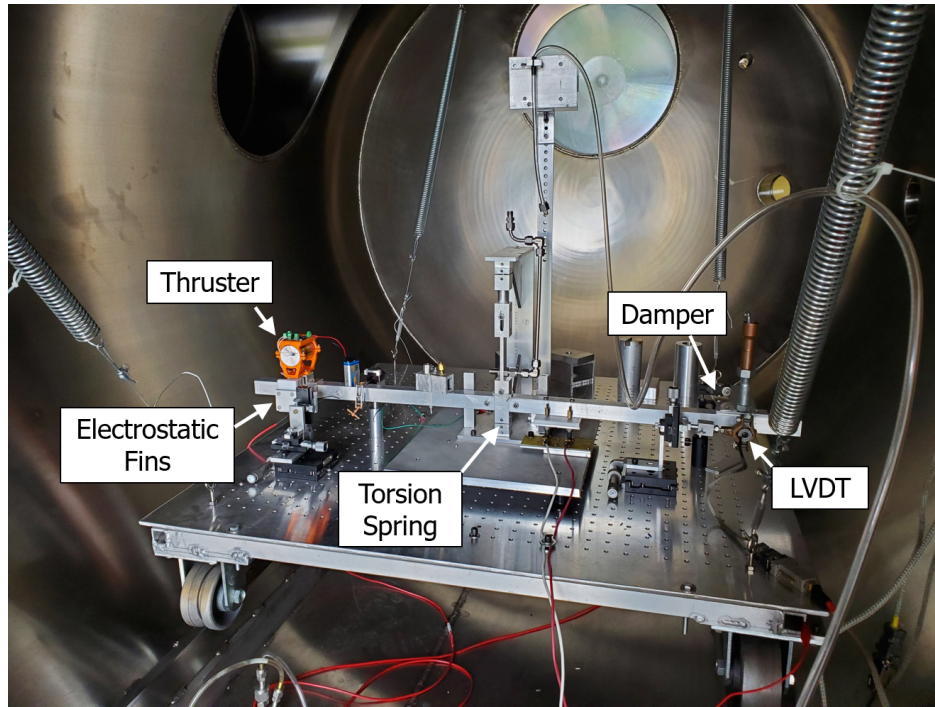


Figure 5.4. Image of thrust stand with evaporation thruster installed. The response in terms of displacement is measured by the LVDT and correlated to applied force using a gravimetric calibration.

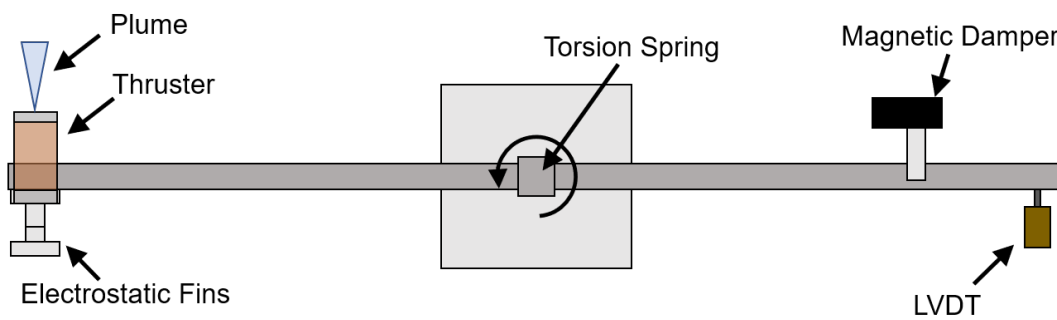


Figure 5.5. Schematic of microNewton torsional balance. The thruster induces a rotational displacement which is detected by a Linear Variable Differential Transformer (LVDT). Displacement is directly correlated to thrust using the calibrated spring stiffness.

cap using an interference fit. A silicone gasket was placed between the thruster face plate and nozzle flange to ensure water vapor could pass through the nozzle only. This configuration enabled the nozzle geometry to be quickly and easily changed between tests. An orifice having a diameter of 0.66mm and thickness of 1.6mm was used for all tests.

The experiments began by first dispensing liquid water onto the paper membrane using a syringe. The mass of the syringe before and after this procedure was noted. Following propellant loading the thrust chamber was assembled and sealed. The thruster was then mounted onto the torsional balance and connected to a 16V power source. Power was delivered by an external supply through two gallium pools, one serving as a common and the other as the bias voltage. Although power was supplied by a wired connection, all data was transmitted via a wireless broadcast. After power-up the BLE link was established between the peripheral and host and the data transfer began. Once operational the chamber was sealed and vacuum was pulled. The solenoid was actuated periodically throughout the pumpdown process to relieve excess pressure in the thrust chamber. Once at the target pressure of 5 mTorr the plunger was retracted and the torsional balance deflected in response to the thrust. The plunger remained in this state until the chamber pressure registered a differential pressure close to zero, indicating water is no longer evaporating.

5.3 Force Calibration

The microNewton torsional balance was calibrated prior to testing to allow the measured displacement to be directly correlated to the (unknown) applied force. The force produced by a thrusting body on one arm of the thrust stand induces a rotational torque about the pivot axis. A torsional spring (F10, C-Flex, Frankfort, NY) located in the column counteracts the thrust and attempts to restore the system to its original position. The offset from the equilibrium state is directly proportional to the thrust and is measured using a Linear Variable Differential Transformer (LVDT) with a sensitivity of 228 mV/V/mm (HR-050, Schaevitz, Bloomfield Hills, MI). The spring characteristics were evaluated prior to the test using a gravimetrically-calibrated electrostatic fin array. During calibration, the fins were biased between 100 and 1000 V in increments of 100 V. A summary of the calibration data

is provided in Figure 5.6. The maximum force produced by the electrostatic fin array was 0.76 mN. To enable interpolation at intermediate thrust levels the data was fit with a 2nd-order polynomial. The LVDT had a full-scale output of 20V, corresponding to a maximum displacement of +/-0.89mm.

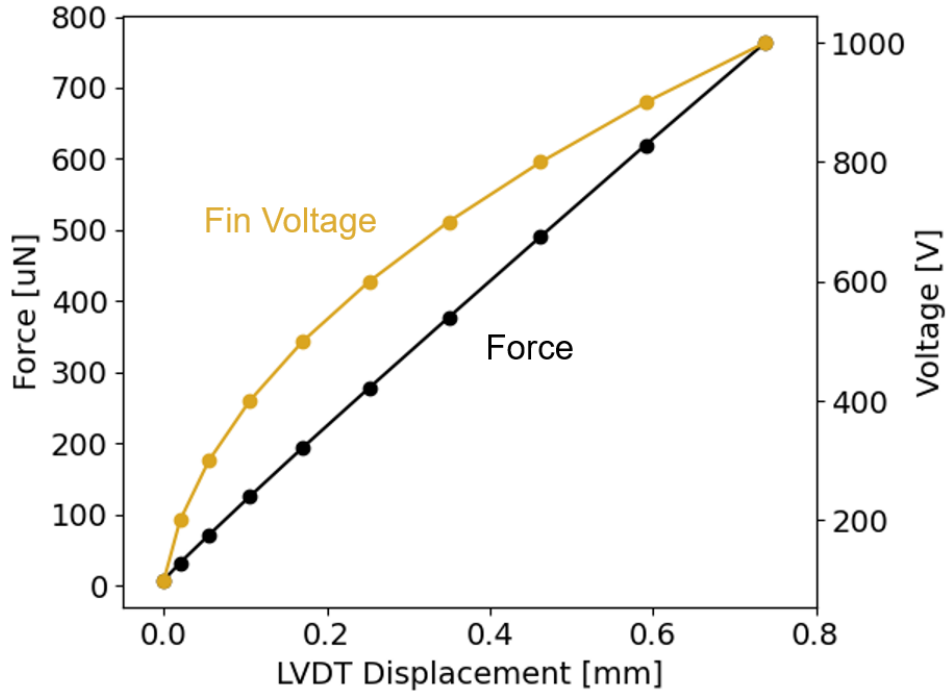


Figure 5.6. MicroNewton torsional balance calibration data. The thrust stand displacement is highly linear with applied force.

The electrostatic force exerted by the comb array is independent of the comb engagement (and hence, the thrust stand displacement) and was gravimetrically calibrated in prior work using a microgram balance. A detailed description of the setup and procedure can be found in the literature[23].

5.3.1 Estimation of Vacuum Chamber Volume

The vacuum chamber volume is needed to determine the mass flow of water vapor exiting the evaporation thruster. Volume was estimated by observing the pressure response to a known gas flow. To perform this measurement, the vacuum chamber was evacuated to a

pressure of around 1 mTorr. Once stabilized, the gate valve between the chamber and the vacuum pumps was closed to establish the baseline leak rate. In this case, the leak rate is found through a simple mass balance. Invoking the ideal gas law, the balance becomes

$$\frac{dm}{dt} = \frac{V}{RT} \frac{dp}{dt} = \dot{m}_{leak} \quad (5.1)$$

where V is the chamber volume, R is the gas constant, and T is the gas temperature (assumed constant). The pressure gradient is nearly linear following valve closure and was therefore determined through a simple linear least-squares fit over the time interval. Following leak characterization, the process was repeated and a known flow rate of atmospheric air was introduced into the chamber. The rate was controlled using a proportional valve and monitored by a 0-500 sccm programmable mass flow meter (M-500SCCM-D/5M, Alicat, Marana, AZ). Similar to the leak rate procedure in equation 5.1, the overall pressure rise can be correlated to the known flow rates. In this case, the only unknown is the chamber volume and was determined using

$$V = \frac{\dot{m}_{in}RT}{\left(\frac{dp}{dt}\right)_{in} - \left(\frac{dp}{dt}\right)_{leak}} \quad (5.2)$$

To ensure repeatability, the pressure rise characterization was performed under two different mass flow loads. The results are provided in Table 5.1. The average chamber volume from the two tests is $4.8465 \pm 0.006 \text{ m}^3$. With this estimate, the mass flow rate of water vapor can be determined using the same procedure.

Table 5.1. Estimated vacuum chamber volume from pressure-rise test.

Mass Flow Rate [mg/s]	Temperature [°C]	dp/dt [Pa/s]	Volume [m ³]
0.44	24.4	0.0081	4.841
0.97	24.4	0.0174	4.852

5.4 Results

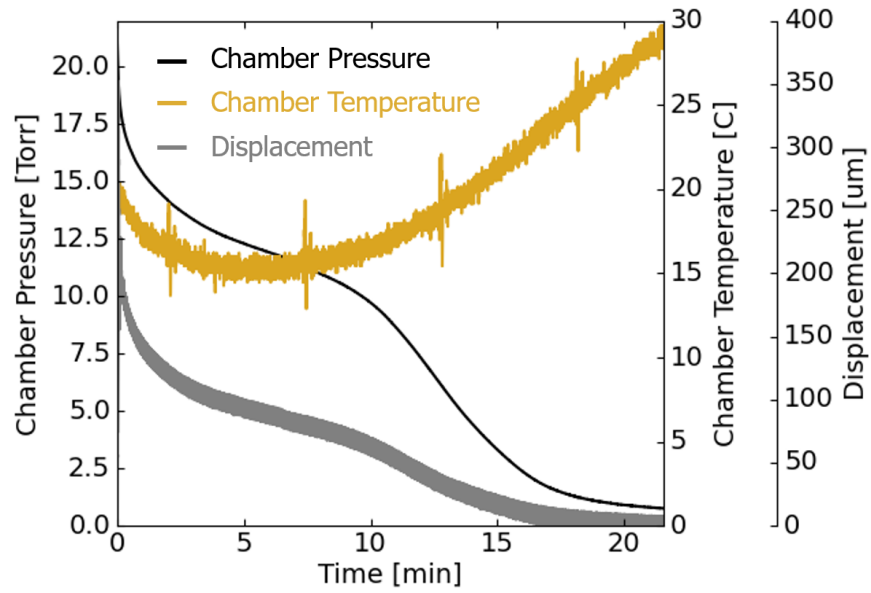
The evaporation thruster was tested using the microNewton torsional balance under a vacuum level between 5 and 10 mTorr. The thrust chamber pressure and wall temperature were broadcast to the external host and the LVDT measurement was logged separately. The datasets were merged and synchronized to the valve actuation event. A summary of the measured data over the entire test using the orifice nozzle is shown in Figure 5.7a. Figure 5.7b provides the initial response from 0-36 seconds.

Prior to valve actuation the thrust chamber pressure was on the order of 20 Torr, corresponding well with the equilibrium vapor pressure at room temperature. Following actuation, the pressure drops precipitously at a rate of 0.8 Torr/s. The ejection of water vapor induces a moment on the torsional balance that results in a measurable displacement away from the equilibrium position. The peak displacement occurred 2.4s after the actuation and had a magnitude of 0.35 mm. As the pressure in the thrust chamber falls, the system attempts to restore it back to the equilibrium vapor pressure through evaporation of liquid water. Transporting mass through this process requires energy and therefore leads to reduction in temperature. The equilibrium vapor pressure scales approximately exponentially with temperature, resulting in a reduction in thrust output (as indicated by the displacement).

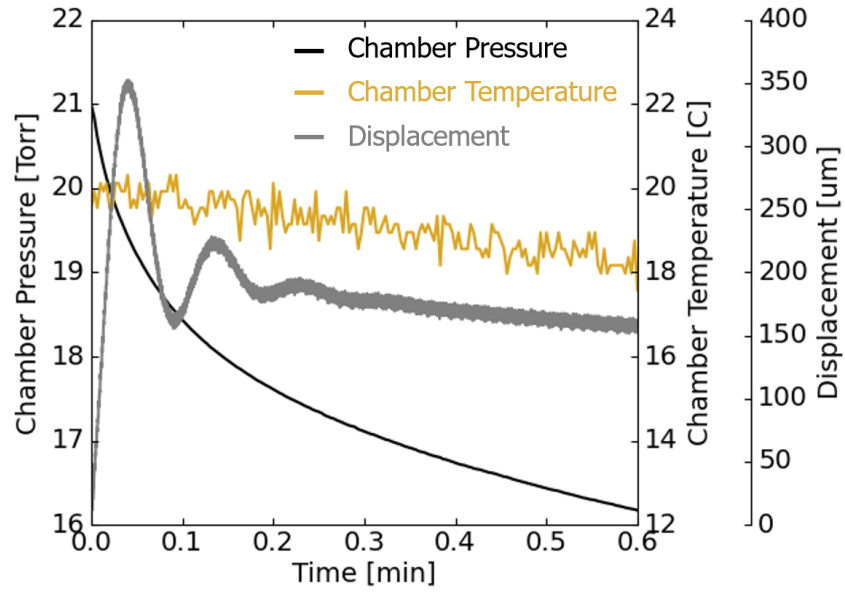
The bulk water contained in the membrane is nearly relinquished 5 minutes following the actuation signal as indicated by the minimum value of temperature. Here, the evaporative energy losses diminish and the system begins to warm under the influence of convection and radiation. It is reasonable to assume that the chamber pressure between 5-10 minutes is sustained by the desorption of bound water from the membrane. At the 10-minute mark all water has been removed and the thrust chamber pressure accelerates downwards towards the vacuum baseline level of 10 mTorr.

5.4.1 Mass Flow Rate Estimate

The mass flow rate exiting the thruster nozzle represents a critical thruster performance parameter but cannot be measured directly. To determine this value experimentally, the pressure rise procedure outline in Section 5.3.1 is applied. Here, the chamber volume known



(a) Raw data from complete test.



(b) Raw data up to 36 seconds after valve actuation.

Figure 5.7. Raw chamber pressure, chamber wall temperature, and torsional balance displacement following valve actuation using an orifice nozzle.

and the mass flow rate of water vapor leaving the nozzle for the production of thrust is found using

$$\dot{m}_{thrust} = \frac{V}{RT} \frac{dp}{dt} - \dot{m}_{leak} - \dot{m}_{quiescent} \quad (5.3)$$

Since the exact composition of the gas in the vacuum chamber is unknown, application of the method in equation 5.3 assumes that the vacuum chamber contains only water vapor. The validity of this assumption can be determined through consideration of the relative flow rates. The estimated flow rate can be compared to the isentropic estimate using Fliegner's formula.

$$\dot{m}_{isen} = \frac{p_c A_t}{\sqrt{T_c}} \sqrt{\frac{2\gamma}{R(\gamma+1)} \left(\frac{\gamma+1}{\gamma-1}\right)} \quad (5.4)$$

Using the measured chamber pressure and temperature just prior to valve actuation, the isentropic mass flow rate of water vapor out of the nozzle is 4.06 μ kg/s. Comparing this value to the experimentally estimated value of 1.46 μ kg/s yields a difference of 64%. In other words, the estimated discharge coefficient for the nozzle at the time of valve actuation is 0.36. Much of this discrepancy is likely influenced by the finite orifice, having a length-to-diameter ratio of 2.5. The Reynolds number at the measured conditions is around 370, suggesting the flow is highly viscous. As the vapor passes through the finite-length orifice it develops a boundary layer which acts to reduce the effective area. This ultimately leads to a reduction in flow rate for a given set of upstream chamber conditions due to the formation of a vena contracta. Applying the flow conductance correlation of Yang for thick orifices, the estimated mass flow rate based on the measured chamber pressure, temperature, and orifice dimensions is 1.50 μ kg/s, a difference of around 3% from the experimentally estimated mass flow rate[123].

Actuation of the thruster valve produces an impulse that leads to a damped oscillatory response from the torsional balance. This behavior is illustrated in Figure 5.7b between 0-0.3 minutes. The chamber pressure evolution is monotonic so it is therefore expected that

the thrust will behave in a similar manner. By developing a system model for the torsional balance, the true thrust output over the duration of the test may be extracted.

5.5 System Modeling

The force produced by the evaporative thruster generates a deflection of the torsional balance that is measured using a LVDT. When the thrust magnitude is constant, the balance responds to the input and settles in a position where all torques are balanced. This steady-state deflection can then be used to infer the unknown force magnitude using the gravimetric calibration. For transient thrust profiles having a characteristic time much shorter than that of the balance the true thrust cannot be directly extracted from the LVDT signal since the impulse response of the system is convolved with the input. These effects may be decoupled through appropriate system modeling.

5.5.1 Model Identification

The dynamics of the torsional balance are reasonably approximated by a 2nd-order system. Working in the body-fixed frame, the equation of motion for the rigid body is described by the balance between the rate of change of angular momentum and the sum of external torques acting on the balance.

$$I\ddot{\theta} = r_F F - r_d c\dot{\theta} - k\theta \quad (5.5)$$

where I and $\ddot{\theta}$ are the moment of inertia and angular acceleration around the pivot axis, respectively. The external torques acting on the balance are in the form of the thrust, $r_T T$, magnetic damping, $c r_d \dot{\theta}$, and restoring spring force, $c\theta$. The influence of aerodynamic damping is neglected in the model.

The 2nd-order system in equation 5.5 can be expressed as an equivalent 1st-order system of linear equations. Under the continuous state model, the system becomes

$$\dot{x}(t) = \mathbf{A}x(t) + \mathbf{B}u(t) \quad (5.6)$$

$$y(t) = \mathbf{C}x(t) + \mathbf{D}u(t) \quad (5.7)$$

where

$$\mathbf{A} = \begin{bmatrix} 0 & 1 \\ -\frac{k}{I} & -\frac{cr_D}{I} \end{bmatrix} \quad \mathbf{B} = \begin{bmatrix} 0 \\ \frac{r_F}{I} \end{bmatrix} \quad \mathbf{C} = \begin{bmatrix} 1 & 0 \end{bmatrix} \quad \mathbf{D} = 0$$

Under this model, the internal system states, x , are driven by arbitrary inputs, u . The array, y , represents the measured outputs. The response of the torsional balance was measured at a fixed sampling rate of 1 kHz. The continuous linear time invariant system in equation 5.7 can be represented in a discrete form under the following transformations.

$$\mathbf{A}_d = e^{\mathbf{A}T} \quad \mathbf{B}_d = \int_0^T e^{\mathbf{A}\tau} d\tau \quad \mathbf{C}_d = \mathbf{C} \quad \mathbf{D}_d = \mathbf{D}$$

The discrete state space representation then becomes a set of difference equations.

$$\begin{aligned} \dot{x}(k+1) &= \mathbf{A}_d x(k) + \mathbf{B}_d u(k) \\ y(k) &= \mathbf{C}_d x(k) + \mathbf{D}_d u(k) \end{aligned} \quad (5.8)$$

The inertia, damping, and spring constants are unknown parameters which were determined using an iterative minimization approach.

Estimation of System Parameters

The unknown model parameters were estimated using a multivariate optimization technique. A calibration cycle was performed prior to the estimation procedure to provide reference values. This cycle was performed under atmospheric pressure to prevent the electrical breakdown in the surrounding gas at high calibration voltages. Calibrating at atmospheric pressures also carries the advantage of reduced mechanical noise since the vacuum pumps

were not active. Estimation validity at these pressures was confirmed by direct comparison to the same procedure at pressures between 5 and 10 mTorr. All coefficients agree to within 3%. Using this measured data, the penalty function was formed by taking the root-mean square error between observation and prediction.

$$J = \frac{1}{2} \int (\theta - \theta_{meas})^2 dt \approx \frac{1}{2} \sum (\theta_n - \theta_{meas,n})^2 \Delta t \quad (5.9)$$

The estimation was then performed by iteratively adjusting parameter values and solving the continuous LTI system in equation 5.7. The solution at each iteration was computed numerically using a Runge-Kutta 5th-order solver. The process was as follows:

1. Guess initial values for inertia, damping, and stiffness parameters
2. Simulate system response using continuous LTI system model in equation 5.7.
3. Compute the cost function from equation 5.9 using the results from Step (2).
4. Determine cost function sensitivities using finite differencing relative to the inputs
5. Execute optimization algorithm to find the new search direction
6. Compute updated thrust arm position
7. Repeat Steps (2)-(6) until the desired first-order optimality tolerance is reached

The best-fit values for the inertia, gas damping, and spring stiffness determined through the optimization are provided in Table 5.2.

Table 5.2. Torsional balance model parameters derived from calibration

Parameter	Value
I	0.1446 [kg-m ²]
c	0.2378 [kg-m/s]
k	0.1681 [kg-m ² /s ²]

5.5.2 State and Input Estimation Model

with the discrete LTI system parameters in equation 5.8 known, the model was applied to decouple the true thrust (or force) input from the response on the torsional balance. The discrete LTI system is observable and therefore its full state may be estimated. With the states and outputs known, the system's response may be used to infer any unknown disturbance. Estimation of the input vector was accomplished using a Proportional-Integral Observer (PIO)[124]. The PIO requires that the sampling interval, Δt , be small enough such that the disturbance at each step is small. Further, the following condition must hold

$$\text{rank} \left(\begin{bmatrix} \mathbf{A}_d - \mathbf{I}_n & \mathbf{E}_d \\ -\mathbf{C}_d & \mathbf{0} \end{bmatrix} \right) = n + l$$

Following Chang's method, the discrete PIO can be written as

$$\begin{aligned} \dot{x}(k+1) &= \mathbf{A}_d x(k) + \mathbf{B}_d u(k) + \mathbf{L}_1 (y(k) - \hat{y}(k)) + \mathbf{E}_d q(k) \\ q(k+1) &= q(k) + \mathbf{L}_2 (y(k) - \hat{y}(k)) \\ y(k) &= \mathbf{C}_d x(k) \end{aligned} \tag{5.10}$$

The stabilizing gain matrices are determined such that the poles of $(\mathbf{M} - \mathbf{L}\mathbf{G})$ where

$$\mathbf{M} = \begin{bmatrix} \mathbf{A}_d & \mathbf{E}_d \\ \mathbf{0}_d & \mathbf{I}_n \end{bmatrix} \quad \mathbf{L} = \begin{bmatrix} \mathbf{L}_1^T \\ \mathbf{L}_2^T \end{bmatrix} \quad \mathbf{G} = \begin{bmatrix} \mathbf{C}_d & \mathbf{0} \end{bmatrix}$$

The poles are chosen to reside at $\lambda = \{0.6, 0.7, 0.8\}$ based on a trial and error approach (with the constraint that all poles must reside in the unit circle to be stable), producing the gain matrices

$$\mathbf{L}_1 = \begin{bmatrix} 0.8750 \\ 5.6950 \end{bmatrix} \quad \mathbf{L}_2 = \begin{bmatrix} 5.7618 \end{bmatrix}$$

PIO Model Validation

To validate the input estimation routine the PIO system was applied to the calibration process. Force inputs are assumed to be in the form of a step function. The measured and estimated torsional balance displacement and force loading are shown in Figure 5.8.

The estimated state and force input agree well with the known values. The largest error occurs at the highest calibration voltage (force), having a difference of 1%. Following the validation procedure the PIO model is applied to the experimental measurements using the evaporation thruster.

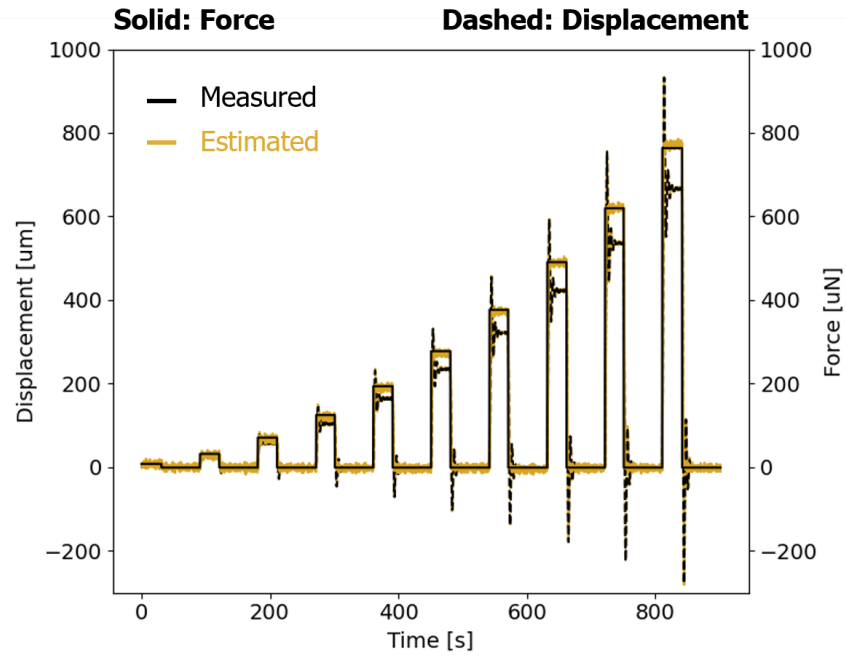
Estimate of Transient Thrust Profile Using PIO Model

Following validation against the calibration dataset the PIO model was applied to the measured data in Figure 5.7. The estimated thrust and deflection profiles are shown in Figure 5.9 for the period between 0-1 minutes after plunger actuation.

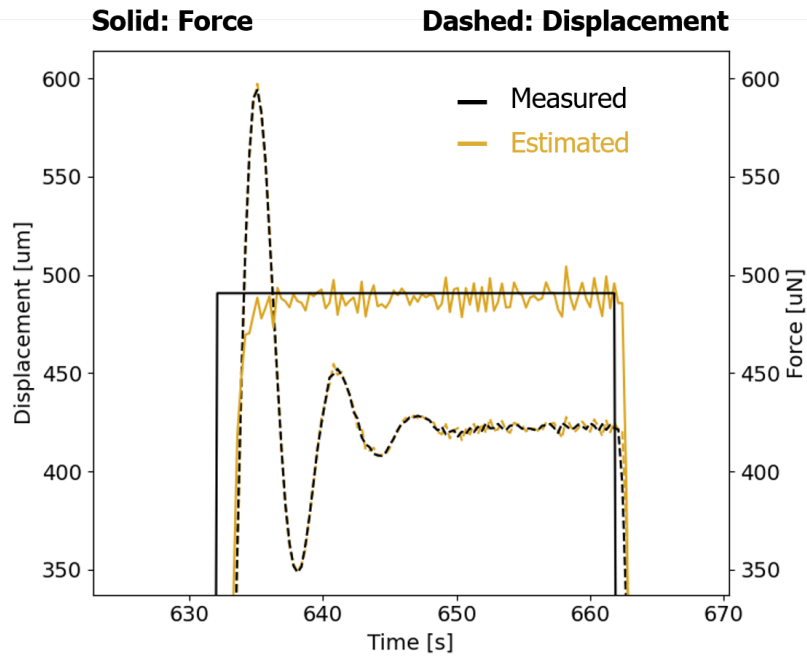
The state model accurately predicts the displacement of the torsional balance under the application of thrust throughout the duration of the test. The thrust used to produce the simulated response has a peak magnitude around 17% greater than that measured by the balance. Following the initial impulse, the indicated thrust undergoes two additional oscillations before achieving a quasi-steady state at a time of around 0.3 minutes. The period of these oscillations is identical to those observed during the calibration tests (5.9s), suggesting the balance is operating at its damped resonant frequency. The estimated thrust input exhibits monotonic behavior following the initial impulse and is in qualitative agreement with the thrust chamber pressure data. Additionally, the estimated thrust intercepts and agrees with the indicated measurement after the 0.3 minute mark.

5.5.3 Thruster Performance

The low thrust chamber pressures (relative to traditional space propulsion systems) combined with small orifice dimensions produce viscous effects which can degrade overall system performance. In many cases, it has been shown that the performance gains achieved by gas



(a) Complete calibration



(b) Comparison at 800V pulse

Figure 5.8. Comparison of measured and PIO-estimated displacement and electrostatic actuation force during calibration.

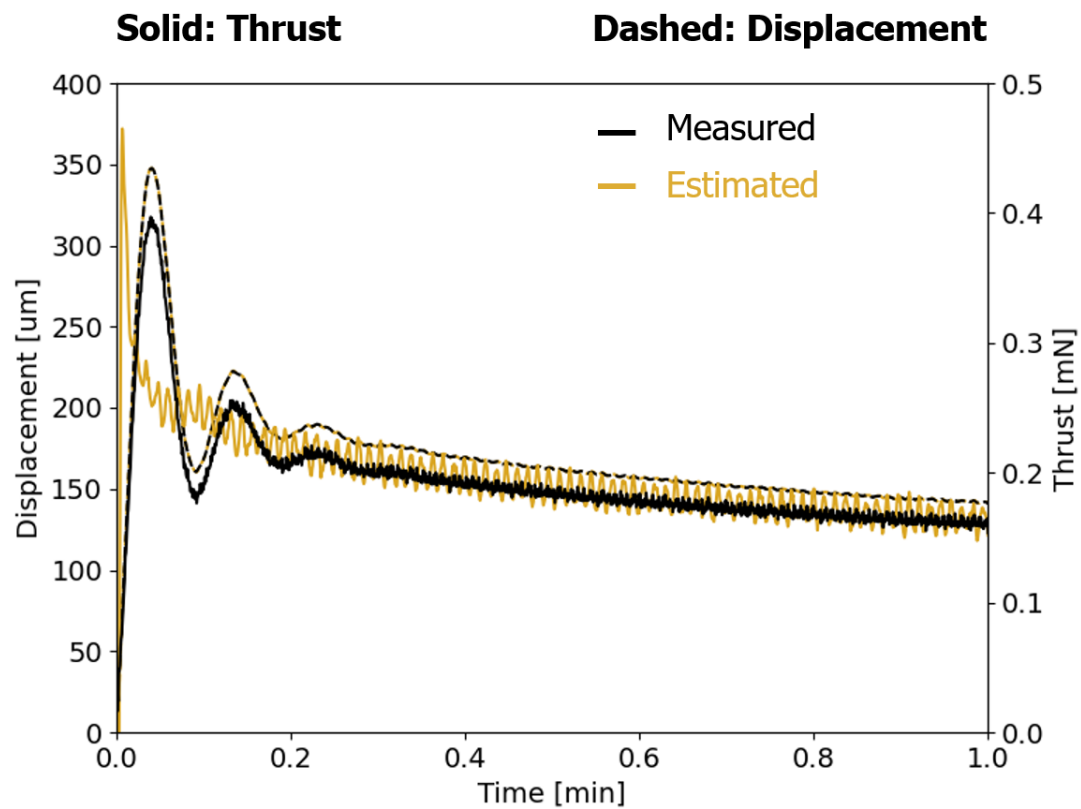


Figure 5.9. Comparison of estimated and measured thrust and torsional balance displacement using the PIO state model.

expansion are largely offset by the viscous losses. The orifice geometry is therefore the most optimal for thrusters operating at low Reynolds numbers[125].

Specific impulse (I_{sp}) is the primary performance metric when comparing the efficiency of various thruster architectures. Using the thrust output from the PIO model combined with the mass flow estimate from the pressure-rise experiment, the I_{sp} is calculated using

$$I_{sp} = \frac{F}{\dot{m}g} \quad (5.11)$$

The estimated I_{sp} was computed 16 seconds after the valve actuation and had a value of 21 seconds. It has been shown that measured thrust under these conditions is significantly affected by the background pressure due to scattering of molecules near the orifice exit. As the underexpanded jet leaves the orifice it tends to spread radially outwards, displacing the background gas and creating a localized low-pressure area on the front face of the thruster. This leads to an induced force between the front and rear faces of the thruster body and diminishes the jet thrust relative to its magnitude in pure vacuum [126], [127]. The vacuum thrust level may be estimated through consideration of the effective thruster face area. Following the results of Brook, the effective face area, A_{eff} , is estimated using

$$A_{eff} = 2\pi \int_0^{r_T} \left(1 - e^{-\frac{r_{p,sfc}}{r}}\right) r dr \quad (5.12)$$

where r_T is the radius of the thrust chamber and $r_{p,sfc}$ is the radius of penetration of the background gas into the jet plume. The latter variable was estimated using the experimental and theoretical data provided by Brook [126]. With equation 5.12, the reduction in thrust due to background gas scattering is given by

$$\Delta F = p_c A_{eff} \quad (5.13)$$

The force deficit predicted by equation 5.13 at the time of mass flow measurement is 0.42mN, around two times greater than the measured force. The scattered area corresponding to this is 3.2cm², 70% of the total face area. Using these estimates, the vacuum thrust

generated by the device is 0.662mN, resulting in a corrected specific impulse of 58 seconds. An I_{sp} value of this magnitude is characteristic of cold gas thrusters in the same class[\[128\]](#).

6. CONCLUSIONS

The utility of wireless sensor networks in terrestrial applications is evidenced by their rapid growth across numerous industries. Two sectors which have been slow to adopt wireless technologies are pharmaceutical manufacturing and aerospace.

Lyophilization is a desiccation technique used to preserve sensitive food and pharmaceutical products. The method is applied under low pressures and low temperatures and was therefore used as a wireless sensor demonstration platform. A series of wireless microPirani gauges were fabricated, calibrated, and applied to various lyophilization cycles to characterize the gas pressure and temperature distributions during primary drying. The sensors were encapsulated in an enclosure having an identical footprint to a 20R pharmaceutical vial, allowing the devices to be placed at any location within the vial pack. The influence of shelf temperature, process pressure, formulation, and lyophilizer configuration were explored experimentally. Computational Fluid Dynamics (CFD) simulations were performed and the results were compared to measurements to elucidate flow behavior. A pressure-matching algorithm using the CFD model was then developed to estimate the sublimation rate over the course of primary drying. A 2-dimensional inverse parameter estimation model was also derived to predict the spatial variation of sublimation rate based on its influence on the local pressure measurements. Using the rate information the heat and mass characteristics of the vial and product were extracted and applied to simple 1-dimensional heat transfer model for a mannitol formulation. The product temperature was simulated for different process conditions and compared directly to experimental data with acceptable accuracy. The ability to rapidly estimate these quantities from a single experiment is highly desirable and can significantly reduce overall cycle development time and effort.

A separate WSN using gas pressure and temperature sensors was applied to the Rapid Depressurization Controlled Ice Nucleation (RD-CIN) process. Experimental measurements were performed to investigate the effects of charge gas composition, pre-discharge pressure, and vial size on the depressurization event. Results combined with an isentropic pressure vessel discharge model demonstrate that monatomic species with low thermal conductivity under high pressure are likely most optimal for the RD-CIN process due to the combined

large drop in temperature and low heat transfer with the solid boundaries (i.e. vials, shelf, chamber walls, etc.). It is proposed that mechanism of nucleation under RD-CIN results from the reduction of gas temperature below the saturated vapor pressure of water, forcing it to condense out of the bulk and freeze. The frozen ice crystals form an ice fog which, upon contact with the supercooled liquid, induce nucleation. Experimental measurements were supported by a 2-dimensional finite-difference heat transfer model which was applied to estimate the true gas temperature during the discharge.

Finally, a wireless sensor system was applied to microNewton thrust characterization for small satellite propulsion systems. A thruster based on the evaporation of water in vacuum was developed and characterized. The experimental data was applied to the development of a system model based on a proportional-integral observer. The model was capable of decoupling the thrust output from the torsional balance impulse response, allowing true force output to be predicted. The influence of the background gas on thrust attenuation was addressed and an estimate for the vacuum thrust level was computed. The specific impulse of the thruster was determined using the force and mass flow estimates based on a pressure-rise test and carried a value of 58 seconds.

6.1 Outlook and Suggestions for Future Work

Wireless sensors show great promise for spatially-resolved high-fidelity measurement in both vacuum and spacecraft applications. Several potential avenues exist to expand upon the work completed here.

In terms of lyophilization, inferring local sublimation rates from the pressure distribution requires a high degree of precision since the pressure variation is relatively insensitive to the sublimation rate. The WMP devices developed during this study have a theoretical resolution capable of meeting this requirement. However, the uncertainty associated with the calibration (due to limits imposed by the capacitance manometer's resolution) did not permit thorough investigation. The computational cost needed to perform the parameter estimation on a case-by-case basis is prohibitively expensive and requires an alternate solution.

One potential alternative would be to apply a supervised learning algorithm (e.g. using an artificial neural network) to develop a model capable of performing estimates in the loop.

For spacecraft technology, the high degree of regulation surrounding radio frequency emissions will inevitably delay integration of WSNs into flight system. Small satellites are a natural starting point due to their low-cost, short lifetime, and low-risk characteristics. The thruster developed in this study could be applied for attitude adjustment or controlled deorbiting at end-of-life. Additional research must first be performed related to the optimal nozzle geometry, throttling capabilities, and the prevention of quiescent propellant losses.

REFERENCES

- [1] I. Khemapech, I. Duncan, and A. Miller, “A survey of wireless sensor networks technology,” in *6th Annual Postgraduate Symposium on the Convergence of Telecommunications, Networking and Broadcasting*, vol. 13, 2005.
- [2] S. Ramamurthy, “Wireless sensors: Technologies and global markets,” Tech. Rep., Sep. 2016.
- [3] K. Arun, “Wireless sensors: Technologies and americas markets,” Tech. Rep., Dec. 2018.
- [4] D.-M. Han and J.-H. Lim, “Smart home energy management system using ieee 802.15.4 and zigbee,” *IEEE Transactions on Consumer Electronics*, vol. 56, no. 3, pp. 1403–1410, 2010.
- [5] H. Alemdar and C. Ersoy, “Wireless sensor networks for healthcare: A survey,” *Computer networks*, vol. 54, no. 15, pp. 2688–2710, 2010.
- [6] D. Malan, T. Fulford-Jones, M. Welsh, and S. Moulton, “Codeblue: An ad hoc sensor network infrastructure for emergency medical care,” in *International workshop on wearable and implantable body sensor networks*, Boston, MA; vol. 5, 2004.
- [7] V. C. Gungor and G. P. Hancke, “Industrial wireless sensor networks: Challenges, design principles, and technical approaches,” *IEEE Transactions on industrial electronics*, vol. 56, no. 10, pp. 4258–4265, 2009.
- [8] M. Castillo-Effer, D. H. Quintela, W. Moreno, R. Jordan, and W. Westhoff, “Wireless sensor networks for flash-flood alerting,” in *Devices, Circuits and Systems, 2004. Proceedings of the Fifth IEEE International Caracas Conference on*, IEEE, vol. 1, 2004, pp. 142–146.
- [9] K. K. Khedo, R. Perseedoss, A. Mungur, *et al.*, “A wireless sensor network air pollution monitoring system,” *arXiv preprint arXiv:1005.1737*, 2010.
- [10] A. Mainwaring, D. Culler, J. Polastre, R. Szewczyk, and J. Anderson, “Wireless sensor networks for habitat monitoring,” in *Proceedings of the 1st ACM international workshop on Wireless sensor networks and applications*, Acm, 2002, pp. 88–97.
- [11] J. Burrell, T. Brooke, and R. Beckwith, “Vineyard computing: Sensor networks in agricultural production,” *IEEE Pervasive computing*, vol. 3, no. 1, pp. 38–45, 2004.

- [12] J. Yick, B. Mukherjee, and D. Ghosal, "Analysis of a prediction-based mobility adaptive tracking algorithm," in *Broadband Networks, 2005. BroadNets 2005. 2nd International Conference on*, IEEE, 2005, pp. 753–760.
- [13] *Ieee 802.15 wpan task group 4 (tg4)*. [Online]. Available: <https://www.ieee802.org/15/pub/TG4.html>.
- [14] I. F. Akyildiz and M. C. Vuran, *Wireless sensor networks*. John Wiley & Sons, 2010, vol. 4.
- [15] W. Wilson and G. Atkinson, "Wireless sensing opportunities for aerospace applications," 2007.
- [16] *Tempris*, <https://www.tempris.com/>.
- [17] *Wtmplus*, <https://www.martinchrist.de/en/freeze-drying/wtmplus/>.
- [18] *Tracksense pro wireless data logger*, <https://www.ellab.com/>.
- [19] N. Raghunathan, X. Jiang, A. Ganguly, and D. Peroulis, "An ant-based low-power battery-free wireless cryogenic temperature probes for industrial process monitoring," in *2016 IEEE SENSORS*, IEEE, 2016, pp. 1–3.
- [20] X. Jiang, T. Zhu, T. Kodama, N. Raghunathan, A. Alexeenko, and D. Peroulis, "Multi-point wireless temperature sensing system for monitoring pharmaceutical lyophilization," *Frontiers in chemistry*, vol. 6, p. 288, 2018.
- [21] H. Canaday, "War on wiring," *AEROSPACE AMERICA*, vol. 55, no. 5, pp. 24–27, 2017.
- [22] T. Roberts, "Space launch to low earth orbit: How much does it cost?" *CIVIL AND COMMERCIAL SPACE, SPACE SECURITY*, 2020.
- [23] A. G. Cofer, S. D. Heister, and A. Alexeenko, "Improved design and characterization of micronewton torsional balance thrust stand," in *49th AIAA/ASME/SAE/ASEE Joint Propulsion Conference*, 2013, p. 3856.
- [24] R. S. Legge, E. B. Clements, and A. Shabshelowitz, "Enabling microsatellite maneuverability: A survey of microsatellite propulsion technologies," in *2017 IEEE MTT-S International Microwave Symposium (IMS)*, IEEE, 2017, pp. 229–232.
- [25] J. C. Kasper, G. Winter, and W. Friess, "Recent advances and further challenges in lyophilization," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 85, no. 2, pp. 162–169, 2013.

- [26] C. Dexiang, *Fast-dissolving tablet vaccines for enteric and other mucosal pathogens made by lyophilization—a case study in vaccine stabilization*, 2012.
- [27] S. D. Allison and T. J. Anchordoquy, “Lyophilization of nonviral gene delivery systems,” in *Nonviral vectors for gene therapy*, Springer, 2001, pp. 225–252.
- [28] P. Matejtschuk, M. Stanley, and P. Jefferson, “12 freeze-drying of biological standards,” *Freeze Drying/Lyophilization of Pharmaceutical and Biological Products*, p. 317, 2010.
- [29] R. W. Werge, “Potato processing in the central highlands of peru,” *Ecology of food and nutrition*, vol. 7, no. 4, pp. 229–234, 1979.
- [30] J. A. Christiansen, *The utilization of bitter potatoes to improve food production in the high altitude of the tropics*. Cornell University, Jan., 1977.
- [31] R. Altmann, *Die Elementarorganismen und ihre Beziehungen zu den Zellen*. Veit, 1894.
- [32] L. Shackell, “An improved method of desiccation, with some applications to biological problems,” *American Journal of Physiology—Legacy Content*, vol. 24, no. 3, pp. 325–340, 1909.
- [33] D. Varshney and M. Singh, “History of lyophilization,” in *Lyophilized Biologics and Vaccines*, Springer, 2015, pp. 3–10.
- [34] F. Franks and T. Auffret, *Freeze-drying of pharmaceuticals and biopharmaceuticals*. royal Society of Chemistry, 2008.
- [35] J. A. Searles, J. F. Carpenter, and T. W. Randolph, “Annealing to optimize the primary drying rate, reduce freezing-induced drying rate heterogeneity, and determine tg? in pharmaceutical lyophilization,” *Journal of pharmaceutical sciences*, vol. 90, no. 7, pp. 872–887, 2001.
- [36] F. Franks, “Freeze-drying of bioproducts: Putting principles into practice,” *European journal of Pharmaceutics and BioPharmaceutics*, vol. 45, no. 3, pp. 221–229, 1998.
- [37] D. Awotwe-Otoo, C. Agarabi, E. K. Read, S. Lute, K. A. Brorson, M. A. Khan, and R. B. Shah, “Impact of controlled ice nucleation on process performance and quality attributes of a lyophilized monoclonal antibody,” *International journal of pharmaceutics*, vol. 450, no. 1-2, pp. 70–78, 2013.

- [38] B. M. Eckhardt, J. Q. Oeswein, and T. A. Bewley, "Effect of freezing on aggregation of human growth hormone," *Pharmaceutical research*, vol. 8, no. 11, pp. 1360–1364, 1991.
- [39] S. Jiang and S. L. Nail, "Effect of process conditions on recovery of protein activity after freezing and freeze-drying," *European journal of pharmaceuticals and biopharmaceutics*, vol. 45, no. 3, pp. 249–257, 1998.
- [40] B. S. Chang, B. S. Kendrick, and J. F. Carpenter, "Surface-induced denaturation of proteins during freezing and its inhibition by surfactants," *Journal of pharmaceutical sciences*, vol. 85, no. 12, pp. 1325–1330, 1996.
- [41] A. Arsiccio, J. McCarty, R. Pisano, and J.-E. Shea, "Heightened cold-denaturation of proteins at the ice–water interface," *Journal of the American Chemical Society*, vol. 142, no. 12, pp. 5722–5730, 2020.
- [42] J. A. Searles, J. F. Carpenter, and T. W. Randolph, "The ice nucleation temperature determines the primary drying rate of lyophilization for samples frozen on a temperature-controlled shelf," *Journal of pharmaceutical sciences*, vol. 90, no. 7, pp. 860–871, 2001.
- [43] C. Lindenmeyer, G. Orrok, K. Jackson, and B. Chalmers, "Rate of growth of ice crystals in supercooled water," *The Journal of Chemical Physics*, vol. 27, no. 3, pp. 822–822, 1957.
- [44] M. Kochs, C. Körber, I. Heschel, and B. Nunner, "The influence of the freezing process on vapour transport during sublimation in vacuum-freeze-drying of macroscopic samples," *International Journal of Heat and Mass Transfer*, vol. 36, no. 7, pp. 1727–1738, 1993.
- [45] A. Arsiccio, A. A. Barresi, and R. Pisano, "Prediction of ice crystal size distribution after freezing of pharmaceutical solutions," *Crystal Growth & Design*, vol. 17, no. 9, pp. 4573–4581, 2017.
- [46] K. Nakagawa, A. Hottot, S. Vessot, and J. Andrieu, "Modeling of freezing step during freeze-drying of drugs in vials," *AIChE Journal*, vol. 53, no. 5, pp. 1362–1372, 2007.
- [47] A. K. Konstantinidis, W. Kuu, L. Otten, S. L. Nail, and R. R. Sever, "Controlled nucleation in freeze-drying: Effects on pore size in the dried product layer, mass transfer resistance, and primary drying rate," *Journal of pharmaceutical sciences*, vol. 100, no. 8, pp. 3453–3470, 2011.
- [48] R. Pisano, "Alternative methods of controlling nucleation in freeze drying," in *Lyophilization of pharmaceuticals and biologicals*, Springer, 2019, pp. 79–111.

- [49] G. Petzold and J. M. Aguilera, “Ice morphology: Fundamentals and technological applications in foods,” *Food Biophysics*, vol. 4, no. 4, pp. 378–396, 2009.
- [50] A. Shibkov, Y. I. Golovin, M. Zheltov, A. Korolev, and A. Leonov, “Morphology diagram of nonequilibrium patterns of ice crystals growing in supercooled water,” *Physica A: Statistical Mechanics and its Applications*, vol. 319, pp. 65–79, 2003.
- [51] L. C. Capozzi and R. Pisano, “Looking inside the ‘black box’: Freezing engineering to ensure the quality of freeze-dried biopharmaceuticals,” *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 129, pp. 58–65, 2018.
- [52] X. C. Tang and M. J. Pikal, “Design of freeze-drying processes for pharmaceuticals: Practical advice,” *Pharmaceutical research*, vol. 21, no. 2, pp. 191–200, 2004.
- [53] R. Geidobler and G. Winter, “Controlled ice nucleation in the field of freeze-drying: Fundamentals and technology review,” *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 85, no. 2, pp. 214–222, 2013.
- [54] S. Rambhatla, S. Tchessalov, and M. J. Pikal, “Heat and mass transfer scale-up issues during freeze-drying, iii: Control and characterization of dryer differences via operational qualification tests,” *Aaps Pharmscitech*, vol. 7, no. 2, E61–E70, 2006.
- [55] M. Kramer, B. Sennhenn, and G. Lee, “Freeze-drying using vacuum-induced surface freezing,” *Journal of Pharmaceutical Sciences*, vol. 91, no. 2, pp. 433–443, 2002.
- [56] A. Hottot, K. Nakagawa, and J. Andrieu, “Effect of ultrasound-controlled nucleation on structural and morphological properties of freeze-dried mannitol solutions,” *Chemical engineering research and design*, vol. 86, no. 2, pp. 193–200, 2008.
- [57] A. Petersen, H. Schneider, G. Rau, and B. Glasmacher, “A new approach for freezing of aqueous solutions under active control of the nucleation temperature,” *Cryobiology*, vol. 53, no. 2, pp. 248–257, 2006.
- [58] T. Gasteyer, R. Sever, B. Hunek, N. Grinter, and M. Verdone, “Lyophilization system and method,” *Patent US20070186437*, 2007.
- [59] T. Percy and R. Lentz, *Microwave lyophilization method*, US Patent App. 09/864,862, Nov. 2002.
- [60] G. Adams and L. Irons, “Some implications of structural collapse during freeze-drying using erwinia caratovorale-asparaginase as a model,” *Journal of Chemical Technology and Biotechnology*, vol. 58, no. 1, pp. 71–76, 1993.

- [61] R. J. Bellows and C. J. King, "Freeze-drying of aqueous solutions: Maximum allowable operating temperature," *Cryobiology*, vol. 9, no. 6, pp. 559–561, 1972.
- [62] T. A. Jennings, *Lyophilization: introduction and basic principles*. CrC Press, 1999.
- [63] S. M. Patel, S. L. Nail, M. J. Pikal, R. Geidobler, G. Winter, A. Hawe, J. Davagnino, and S. R. Gupta, "Lyophilized drug product cake appearance: What is acceptable?" *Journal of pharmaceutical sciences*, vol. 106, no. 7, pp. 1706–1721, 2017.
- [64] M. Pikal, S. Shah, M. Roy, and R. Putman, "The secondary drying stage of freeze drying: Drying kinetics as a function of temperature and chamber pressure," *International journal of pharmaceuticals*, vol. 60, no. 3, pp. 203–207, 1990.
- [65] L. R. Rey *et al.*, "Aspects théoriques et industriels de la lyophilisation," 1964.
- [66] D. Fissore, R. Pisano, and A. A. Barresi, "Process analytical technology for monitoring pharmaceuticals freeze-drying—a comprehensive review," *Drying Technology*, vol. 36, no. 15, pp. 1839–1865, 2018.
- [67] S. Nail and W. Johnson, "Methodology for in-process determination of residual water in freeze-dried products.," *Developments in biological standardization*, vol. 74, pp. 137–50, 1992.
- [68] M. Pikal, M. Roy, and S. Shah, "Mass and heat transfer in vial freeze-drying of pharmaceuticals: Role of the vial," *Journal of pharmaceutical sciences*, vol. 73, no. 9, pp. 1224–1237, 1984.
- [69] M. L. Roy and M. J. Pikal, "Process control in freeze drying: Determination of the end point of sublimation drying by an electronic moisture sensor," *PDA Journal of Pharmaceutical Science and Technology*, vol. 43, no. 2, pp. 60–66, 1989.
- [70] H. Gieseler, W. J. Kessler, M. Finson, S. J. Davis, P. A. Mulhall, V. Bons, D. J. Debo, and M. J. Pikal, "Evaluation of tunable diode laser absorption spectroscopy for in-process water vapor mass flux measurements during freeze drying," *Journal of Pharmaceutical Sciences*, vol. 96, no. 7, pp. 1776–1793, 2007.
- [71] N. Milton, M. J. Pikal, M. L. Roy, and S. L. Nail, "Evaluation of manometric temperature measurement as a method of monitoring product temperature during lyophilization," *PDA Journal of Pharmaceutical Science and Technology*, vol. 51, no. 1, pp. 7–16, 1997.
- [72] J. P. Connelly and J. V. Welch, "Monitor lyophilization with mass spectrometer gas analysis," *PDA Journal of Pharmaceutical Science and Technology*, vol. 47, no. 2, pp. 70–75, 1993.

- [73] R. Chen, N. K. Slater, L. A. Gatlin, T. Kramer, and E. Y. Shalaev, "Comparative rates of freeze-drying for lactose and sucrose solutions as measured by photographic recording, product temperature, and heat flux transducer," *Pharmaceutical development and technology*, vol. 13, no. 5, pp. 367–374, 2008.
- [74] A. A. Barresi, S. A. Velardi, R. Pisano, V. Rasetto, A. Vallan, and M. Galan, "In-line control of the lyophilization process. a gentle pat approach using software sensors," *International Journal of Refrigeration*, vol. 32, no. 5, pp. 1003–1014, 2009.
- [75] M. J. Pikal, R. Bogner, V. Mudhivarthi, P. Sharma, and P. Sane, "Freeze-drying process development and scale-up: Scale-up of edge vial versus center vial heat transfer coefficients, kv," *Journal of pharmaceutical sciences*, vol. 105, no. 11, pp. 3333–3343, 2016.
- [76] G. Shivkumar, P. S. Kazarin, A. D. Strongrich, and A. A. Alexeenko, "Lyopronto: An open-source lyophilization process optimization tool," *AAPS PharmSciTech*, vol. 20, no. 8, pp. 1–17, 2019.
- [77] T. Zhu, E. M. Moussa, M. Witting, D. Zhou, K. Sinha, M. Hirth, M. Gastens, S. Shang, N. Nere, S. C. Somashekar, *et al.*, "Predictive models of lyophilization process for development, scale-up/tech transfer and manufacturing," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 128, pp. 363–378, 2018.
- [78] A. Hottot, R. Peczalski, S. Vessot, and J. Andrieu, "Freeze-drying of pharmaceutical proteins in vials: Modeling of freezing and sublimation steps," *Drying Technology*, vol. 24, no. 5, pp. 561–570, 2006.
- [79] W. Massey Jr and J. Sunderland, "Heat and mass transfer in semi-porous channels with application to freeze-drying," *International Journal of Heat and Mass Transfer*, vol. 15, no. 3, pp. 493–502, 1972.
- [80] G. Lusk, S. GOLDBLITH, and M. KAREL, "Thermal conductivity of some freeze-dried fish," *Food technology*, vol. 18, no. 10, p. 1625, 1964.
- [81] Y. Song and K. Sundmacher, "Approximation of laminar flow field in rectangular channels with suction/injection along one wall," *Chemical Engineering Communications*, vol. 197, no. 4, pp. 551–570, 2009.
- [82] Y. Cheng and G. Hwang, "Experimental studies of laminar flow and heat transfer in a one-porous-wall square duct with wall injection," *International journal of heat and mass transfer*, vol. 38, no. 18, pp. 3475–3484, 1995.
- [83] S. Zhang and J. Liu, "Distribution of vapor pressure in the vacuum freeze-drying equipment," *Mathematical Problems in Engineering*, vol. 2012, 2012.

- [84] A. Ganguly and A. A. Alexeenko, "Modeling and measurements of water-vapor flow and icing at low pressures with application to pharmaceutical freeze-drying," *International Journal of Heat and Mass Transfer*, vol. 55, no. 21, pp. 5503–5513, 2012.
- [85] M. Petitti, A. A. Barresi, and D. L. Marchisio, "Cfd modelling of condensers for freeze-drying processes," *Sadhana*, vol. 38, no. 6, pp. 1219–1239, 2013.
- [86] D. L. Marchisio, M. Galan, and A. A. Barresi, "Use of computational fluid dynamics for improving freeze-dryers design and process understanding. part 2: Condenser duct and valve modelling," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 129, pp. 45–57, 2018.
- [87] A. A. Alexeenko, A. Ganguly, and S. L. Nail, "Computational analysis of fluid dynamics in pharmaceutical freeze-drying," *Journal of pharmaceutical sciences*, vol. 98, no. 9, pp. 3483–3494, 2009.
- [88] A. A. Barresi, V. Rasetto, and D. L. Marchisio, "Use of computational fluid dynamics for improving freeze-dryers design and process understanding. part 1: Modelling the lyophilisation chamber," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 129, pp. 30–44, 2018.
- [89] V. Rasetto, D. L. Marchisio, D. Fissore, and A. A. Barresi, "Model-based monitoring of a non-uniform batch in a freeze-drying process," in *Proceedings of 18th European Symposium on Computer Aided Process Engineering-ESCAPE18 (edited by B. Braunschweig, X. Joulia)*, 2008, pp. 1–4.
- [90] V. Rasetto, D. L. Marchisio, D. Fissore, and A. A. Barresi, "On the use of a dual-scale model to improve understanding of a pharmaceutical freeze-drying process," *Journal of pharmaceutical sciences*, vol. 99, no. 10, pp. 4337–4350, 2010.
- [91] A. Ganguly, N. Varma, P. Sane, R. Bogner, M. Pikal, and A. Alexeenko, "Spatial variation of pressure in the lyophilization product chamber part 1: Computational modeling," *AAPS PharmSciTech*, vol. 18, no. 3, pp. 577–585, 2017.
- [92] A. A. Barresi, R. Pisano, V. Rasetto, D. Fissore, and D. L. Marchisio, "Model-based monitoring and control of industrial freeze-drying processes: Effect of batch nonuniformity," *Drying Technology*, vol. 28, no. 5, pp. 577–590, 2010.
- [93] P. Sane, N. Varma, A. Ganguly, M. Pikal, A. Alexeenko, and R. H. Bogner, "Spatial variation of pressure in the lyophilization product chamber part 2: Experimental measurements and implications for scale-up and batch uniformity," *AAPS PharmSciTech*, vol. 18, no. 2, pp. 369–380, 2017.

- [94] L. A. Wegiel, S. J. Ferris, and S. L. Nail, “Experimental aspects of measuring the vial heat transfer coefficient in pharmaceutical freeze-drying,” *AAPS PharmSciTech*, vol. 19, no. 4, pp. 1810–1817, 2018.
- [95] J. Luoma, G. Magill, L. Kumar, and Z. Yusoff, “Controlled ice nucleation using controlyo® pressurization-depressurization method,” in *Lyophilization of Pharmaceuticals and Biologicals*, Springer, 2019, pp. 57–77.
- [96] M. v. Pirani, “Selbstzeigendes vakuum-messinstrument,” *Verhandl. deut. Physik Ges*, vol. 8, p. 686, 1906.
- [97] P. K. Weng and J.-S. Shie, “Micro-pirani vacuum gauge,” *Review of scientific instruments*, vol. 65, no. 2, pp. 492–499, 1994.
- [98] M. D. Borenstein, *Technique for improving pirani gauge temperature compensation over its full pressure range*, US Patent 7,331,237, Feb. 2008.
- [99] *Nist chemistry webbook*, <http://webbook.nist.gov/>.
- [100] F. Sharipov and V. Seleznev, “Data on internal rarefied gas flows,” *Journal of Physical and Chemical Reference Data*, vol. 27, no. 3, pp. 657–706, 1998.
- [101] G. A. Bird, “Molecular gas dynamics and the direct simulation of gas flows,” 1994.
- [102] Y. Sone, *Molecular gas dynamics: theory, techniques, and applications*. Springer Science & Business Media, 2007.
- [103] L. Lees and C.-Y. Liu, “Kinetic-theory description of conductive heat transfer from a fine wire,” *The Physics of Fluids*, vol. 5, no. 10, pp. 1137–1148, 1962.
- [104] S. Rambhatla and M. J. Pikal, “Heat and mass transfer scale-up issues during freeze-drying, i: Atypical radiation and the edge vial effect,” *Aaps Pharmscitech*, vol. 4, no. 2, pp. 22–31, 2003.
- [105] W. Y. Kuu, S. L. Nail, and G. Sacha, “Rapid determination of vial heat transfer parameters using tunable diode laser absorption spectroscopy (tdlas) in response to step-changes in pressure set-point during freeze-drying,” *Journal of pharmaceutical sciences*, vol. 98, no. 3, pp. 1136–1154, 2009.
- [106] W. Wagner and A. Pruß, “The iapws formulation 1995 for the thermodynamic properties of ordinary water substance for general and scientific use,” *Journal of physical and chemical reference data*, vol. 31, no. 2, pp. 387–535, 2002.

- [107] D. E. Overcashier, T. W. Patapoff, and C. C. Hsu, “Lyophilization of protein formulations in vials: Investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse,” *Journal of pharmaceutical sciences*, vol. 88, no. 7, pp. 688–695, 1999.
- [108] W. Y. Kuu, K. R. O’Bryan, L. M. Hardwick, and T. W. Paul, “Product mass transfer resistance directly determined during freeze-drying cycle runs using tunable diode laser absorption spectroscopy (tdlas) and pore diffusion model,” *Pharmaceutical development and technology*, vol. 16, no. 4, pp. 343–357, 2011.
- [109] M. Pikal, S. Shah, D. Senior, and J. Lang, “Physical chemistry of freeze-drying: Measurement of sublimation rates for frozen aqueous solutions by a microbalance technique,” *Journal of pharmaceutical sciences*, vol. 72, no. 6, pp. 635–650, 1983.
- [110] M. Pikal, “Use of laboratory data in freeze drying process design: Heat and mass transfer coefficients and the computer simulation of freeze drying,” *PDA Journal of Pharmaceutical Science and Technology*, vol. 39, no. 3, pp. 115–139, 1985.
- [111] A. S. Berman, “Laminar flow in channels with porous walls,” *Journal of Applied physics*, vol. 24, no. 9, pp. 1232–1235, 1953.
- [112] W. M. Massey, “Heat and mass transfer in semi-porous channels,” Ph.D. dissertation, Georgia Institute of Technology, 1968.
- [113] R. Fletcher, *Practical methods of optimization*. John Wiley & Sons, 2013.
- [114] J. A. Snyman, *Practical mathematical optimization*. Springer, 2005.
- [115] J. D. Anderson Jr, *Fundamentals of aerodynamics*. Tata McGraw-Hill Education, 2010.
- [116] J. A. Owczarek, *Fundamentals of Gas Dynamics*. International textbook, 1964.
- [117] J. Luoma, E. Ingham, C. Lema Martinez, and A. Allmendinger, “Comparison of techniques to control ice nucleation during lyophilization,” *Processes*, vol. 8, no. 11, p. 1439, 2020.
- [118] V. T. Morgan, “The overall convective heat transfer from smooth circular cylinders,” in *Advances in heat transfer*, vol. 11, Elsevier, 1975, pp. 199–264.
- [119] C. Petit, P. Gajan, J.-C. Lecordier, and P. Paranthoen, “Frequency response of fine wire thermocouple,” *Journal of Physics E: Scientific Instruments*, vol. 15, no. 7, p. 760, 1982.

- [120] P. Linstrom, “Nist standard reference database number 69,” *NIST Chemistry Web-Book*, 2003.
- [121] R. P. Brent, “An algorithm with guaranteed convergence for finding a zero of a function,” *The Computer Journal*, vol. 14, no. 4, pp. 422–425, 1971.
- [122] J. Mueller, “Thruster options for microspacecraft-a review and evaluation of existing hardware and emerging technologies,” in *33rd joint propulsion conference and exhibit*, 1997, p. 3058.
- [123] F. Yang, G. Li, D. Hu, and T. Kagawa, “A new method for calculating the sonic conductance of airflow through a short-tube orifice,” *Advances in Mechanical Engineering*, vol. 9, no. 2, p. 1687814016687264, 2017.
- [124] J.-L. Chang, “Applying discrete-time proportional integral observers for state and disturbance estimations,” *IEEE Transactions on Automatic Control*, vol. 51, no. 5, pp. 814–818, 2006.
- [125] A. D. Ketsdever, M. T. Clabough, S. F. Gimelshein, and A. Alexeenko, “Experimental and numerical determination of micropropulsion device efficiencies at low reynolds numbers,” *AIAA journal*, vol. 43, no. 3, pp. 633–641, 2005.
- [126] J. Brook, B. Hamel, and E. Muntz, “Theoretical and experimental study of background gas penetration into underexpanded free jets,” *The Physics of Fluids*, vol. 18, no. 5, pp. 517–528, 1975.
- [127] A. D. Ketsdever, “Facility effects on performance measurements of micropropulsion systems that utilize gas expansion,” *Journal of propulsion and power*, vol. 18, no. 4, pp. 797–804, 2002.
- [128] E. G. Lightsey, T. Stevenson, and M. Sorgenfrei, “Development and testing of a 3-d-printed cold gas thruster for an interplanetary cubesat,” *Proceedings of the IEEE*, vol. 106, no. 3, pp. 379–390, 2018.
- [129] P. Horowitz, W. Hill, and I. Robinson, *The art of electronics*. Cambridge university press Cambridge, 2015, vol. 3.
- [130] H. S. Carslaw and J. C. Jaeger, *Conduction of heat in solids*, BOOK. Clarendon press, 1992.

A. WIRELESS MICROPIRANI NOISE ANALYSIS

Accurate quantification of ambient pressure and temperature necessitates evaluation of noise within the system. Each component generates its own form of noise and can be classified as either intrinsic or extrinsic. The large temperature swings encountered in lyophilization must also be accounted for as drift effects in semiconductors contribute substantially to measurement performance.

A.1 Forms of Electrical Noise

Several forms of noise are present in any electrical system. The most prominent include Johnson, shot, and 1/f noise. The relative contribution of each noise type varies based on construction, age, temperature, and frequency, etc. The goal of any circuit is to minimize this unwanted contribution over the operating conditions of interest.

Johnson noise results from the fluctuations in electron energy in response to changes in temperature. These fluctuations are white (constant noise density over the frequency spectrum) and are reflected in all resistive elements including the Pirani filament, RTD, and ballast resistors [129]. The RMS noise density of the signal measured across a noisy resistor in $V/\sqrt{Hz}$ is given by

$$e_J = \sqrt{4k_b T R} \text{ [V}/\sqrt{\text{Hz}}] \quad (\text{A.1})$$

Johnson noise may also be expressed in terms of current as

$$i_J = \sqrt{\frac{4k_b T}{R}} \text{ [A}/\sqrt{\text{Hz}}] \quad (\text{A.2})$$

Shot noise is another form of white noise in certain electrical elements and results from the discrete flow of charges through the system. Shot noise grows with decreasing current as the effects of each charge become more significant.

$$v_S = \sqrt{2q I_{DC} R} \text{ [V}/\sqrt{\text{Hz}}] \quad (\text{A.3})$$

where $q = 1.60 \times 10^{-19}$ coulomb and I_{DC} is the current flowing through the element. Shot noise is only found in situations where electrons are crossing a potential barrier, such as a p-n junction in semiconductor components. This effect is included in manufacturer specifications and is therefore neglected in the present analysis.

The final common form of electrical noise arises from the nature of the device under consideration and exhibits dependence on bandwidth. This form is referred to as 1/f or flicker noise and attains highest power at low frequencies. In the case of DC measurements 1/f noise contributes significantly to the measurement and should be minimized. For integrated circuits, these contributions cannot be directly estimated and instead are provided by the manufacturer. Chopper-stabilized amplifiers are a form of operation amplifier which have the advantage of eliminating 1/f noise at the cost of increased wideband noise. For slow sampling rates, this drawback is of little significance. These devices are also capable of auto-zeroing and generally have very low temperature drift, ideal for the wide temperature swings encountered in lyophilization. For these reasons a chopper-stabilized amplifier is selected as the feedback mechanism in the bridge circuit.

A.1.1 Noise Analysis of Bridge with Chopper-Stabilized Feedback

The bridge circuit used to analyze the noise performance of the modified microPirani is shown in Figure A.1.

The noise contributions from each of the resistive elements can be estimated from equation A.2. The process is carried out by considering each resistor in parallel with a noisy current source and assuming the others are noiseless. The results are expressed as a voltage noise at the amplifier output. The Johnson noise contributions at this point from each resistor are summarized in Table A.1. Minimization of Johnson noise corresponds to a minimization of resistance. In typical bridge circuits the fixed resistors are selected to achieve a minimum common mode level. For the Pirani bridge, the low gain coupled with the high common mode rejection ratio allow amplifier input voltages to be closer to the positive rail. This has the added benefit of enabling higher drive current to the Pirani gauge. For this reason, R1 and R2 are selected to have a resistance of 1000Ω with 0.1% tolerance.

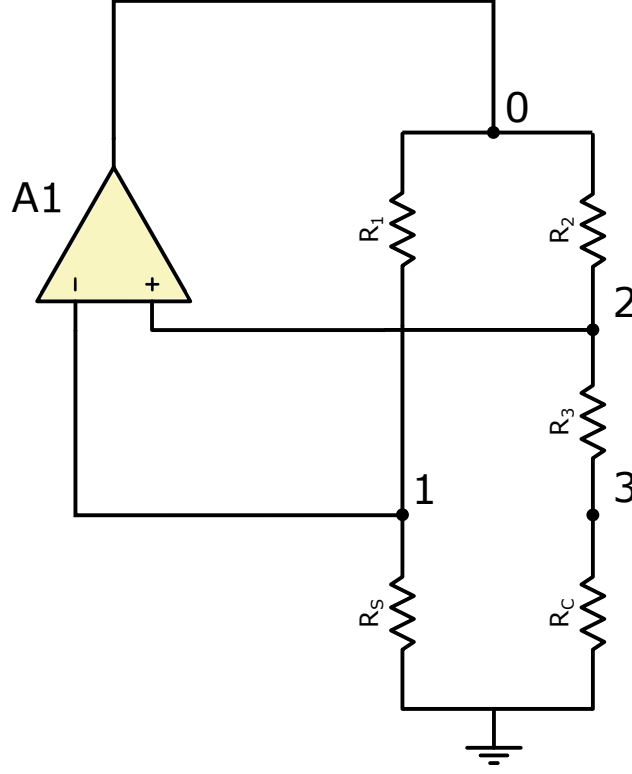


Figure A.1. Schematic of bridge, filter, and follower network used for noise estimate of WMP device.

The amplifier itself generates 294 nV_{RMS} ($1.94 \text{ }\mu\text{V}_{pp}$) of intrinsic noise at its input terminals from 0.1 to 10 Hz. These can be modeled as noise generators in series with the respective ports. The rms contribution of all noise sources at the terminals are amplified and appear at the top of the bridge. A summary of these noise sources is shown in Table A.2.

With all noise sources quantified the total RMS voltage noise at the bridge amplifier, A1, output is given by

$$E_t = \sqrt{E_{in+}^2 + E_{in-}^2 + E_{R1}^2 + E_{R2}^2 + E_{R3}^2 + E_{RP}^2 + E_{RTD}^2} \quad (\text{A.4})$$

Table A.1. Johnson noise across bridge resistors

Resistor	Amplifier Output Noise [V/ $\sqrt{\text{Hz}}$]
E_{R1}	$\frac{R_P(1+R_2/(R_3+R_{RTD}))}{1-R_2R_P/R_1(R_3+R_{RTD})} i_{1,J}$
E_{R2}	$\frac{(R_3+R_{RTD})(1+R_1/R_P)}{1-R_1(R_3+R_{RTD})/R_2R_P} i_{2,J}$
E_{R3}	$\frac{1+R_1/R_P}{R_1/R_2/R_P+R_{RTD}R_1/R_2R_PR_3-1/R_3} i_{3,J}$
E_{RP}	$\frac{R_P(1+R_2/(R_3+R_{RTD}))}{R_2R_P/R_1(R_3+R_{RTD})-1} i_{P,J}$
E_{RRTD}	$\frac{1+R_1/R_P}{R_1/R_2R_P+R_1R_3/R_P R_{RTD}R_2-1/R_{RTD}} i_{RTD,J}$

Table A.2. Noise at bridge amplifier inverting and non-inverting inputs.

Resistor	Amplifier Output Noise [nV/ $\sqrt{\text{Hz}}$]
E_{in+}	$\frac{1+R_1/R_P}{e_{in}}$
E_{in-}	$\frac{1+R_2/(R_3+R_{RTD})}{e_{in}}$

As the voltage Pirani and RTD filaments are located on the lower legs of the bridge the amplifier output noise must be divided and considered there. The noise at the Pirani filament input is given by

$$E_{Pirani} = \frac{E_t}{1 + R_1/R_P} \quad (\text{A.5})$$

Upstream of the RTD is a ballast resistor used for controlling the Pirani temperature. Taking this element into account the RTD noise is

$$E_{RTD} = \frac{E_t}{1 + (R_2 + R_3)/R_{RTD}} \quad (\text{A.6})$$

The total noise at the Pirani and RTD filaments is dictated by the temperature of the board as well as the resistance values across the bridge. The resistances R_1 and R_2 are selected to be 1 k Ω to limit drive current at full output. The value R_3 varies based on the Pirani and RTD resistances.

B. DERIVATION OF FINITE ROD MODEL WITH CONVECTIVE HEAT TRANSFER

The heat equation for the model in Figure B.1 is written as

$$\frac{\partial T}{\partial t} = \alpha \frac{\partial^2 T}{\partial z^2} + 2h\pi DL(T - T_\infty) \quad (\text{B.1})$$

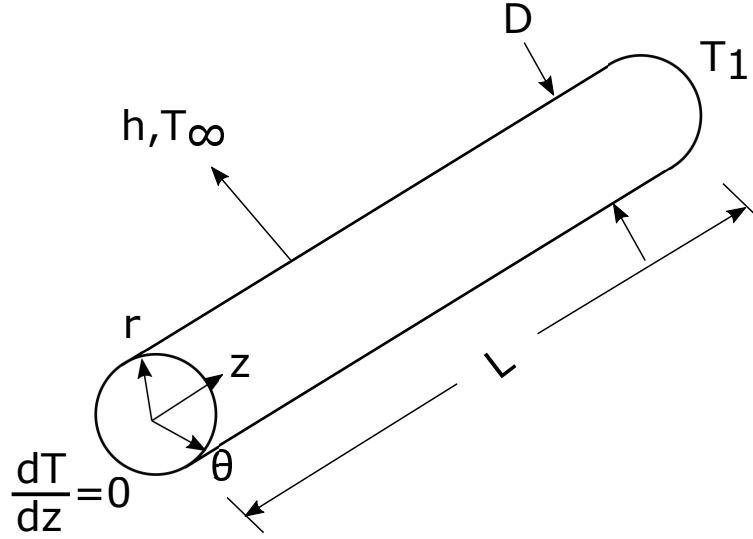


Figure B.1. Schematic of analytical model domain. A thin rod of diameter D and length $2L$ and uniform temperature, T_0 , suddenly has its ends raised to temperature T_1 . Convective cooling is applied over the length of the rod for constant fluid temperature T_0 .

The parameter T_∞ was set to zero without loss of generality. This also set the initial rod temperature to zero. Equation B.1 is made separable under the following substitution

$$u(z, t) = T(z, t)e^{-\alpha t}$$

Application of this expression to B.1 yields the standard form heat equation.

$$\frac{\partial u}{\partial t} = \alpha \frac{\partial^2 u}{\partial z^2} \quad (\text{B.2})$$

The solution to equation B.2 was carried out using the Laplace transform.

$$\bar{u}(s) = \int_0^\infty u(t)e^{-st}dt \quad (\text{B.3})$$

Alternatively, the solution to equation B.2 may be determined by application of Duhamel's theorem for the time-dependent boundary conditions. Substituting equation B.3 into the heat equation converts it to a homogeneous ordinary differential equation

$$\frac{\partial^2 \bar{u}}{\partial z^2} - \frac{s}{\alpha} \bar{u} = 0 \quad (\text{B.4})$$

Using equation B, the boundary conditions at the rod ends are

$$\frac{d\bar{u}(x=0)}{dz} = 0 \quad (\text{B.5})$$

$$u(L) = \frac{T_0}{s - \alpha} \quad (\text{B.6})$$

Applying the boundary conditions to the solution of the ODE yields

$$\bar{u} = \frac{T_0}{s - \alpha} \frac{e^{\mu(z-L)} + e^{-\mu(z+L)}}{1 + e^{-2\mu L}} \quad (\text{B.7})$$

To facilitate the inverse transform $\bar{u}$ was expressed in terms of a geometric series to remove the exponential terms from the denominator.

$$\bar{u} = \frac{T_0}{s - \alpha} \sum e^{q(z-L(2n+1))} + \sum e^{q(z+L(2n+1))} \quad (\text{B.8})$$

The inverse transform was computed using the tabulated solution [130].

$$\mathcal{L}^{-1} \left\{ \frac{e^{-\mu z}}{s - \alpha} \right\} = \frac{1}{2} e^{\alpha t} \left(e^{-\sqrt{\frac{\alpha}{k}} z} \operatorname{erfc} \left(\frac{z}{2\sqrt{kt}} - \sqrt{\alpha t} \right) + e^{\sqrt{\frac{\alpha}{k}} z} \operatorname{erfc} \left(\frac{z}{2\sqrt{kt}} + \sqrt{\alpha t} \right) \right) \quad (\text{B.9})$$

Applying the inversion in equation B.9 to equation B.8 the time-dependent rod temperature becomes

$$\begin{aligned}
T(z, t) = & \frac{T_0}{2} e^{\alpha t} \left(e^{-\sqrt{\frac{\alpha}{k}}((2n+1)L-z)} \operatorname{erfc} \left(\frac{((2n+1)L-z)}{2\sqrt{kt}} - \sqrt{\alpha t} \right) \right. \\
& \left. + e^{\sqrt{\frac{\alpha}{k}}((2n+1)L-z)} \operatorname{erfc} \left(\frac{((2n+1)L-z)}{2\sqrt{kt}} + \sqrt{\alpha t} \right) \right) + \\
& \frac{T_0}{2} e^{\alpha t} \left(e^{-\sqrt{\frac{\alpha}{k}}((2n+1)L+z)} \operatorname{erfc} \left(\frac{((2n+1)L+z)}{2\sqrt{kt}} - \sqrt{\alpha t} \right) \right. \\
& \left. + e^{\sqrt{\frac{\alpha}{k}}((2n+1)L+z)} \operatorname{erfc} \left(\frac{((2n+1)L+z)}{2\sqrt{kt}} + \sqrt{\alpha t} \right) \right) \quad (\text{B.10})
\end{aligned}$$

Andrew Strongrich

Education

Purdue University

Doctor of Philosophy, *Aeronautical and Astronautical Engineering*
Thesis: MEMS Wireless Sensor Networks for Spacecraft and Vacuum Technology
Advisor: Dr. Alina Alexeenko
G.P.A.: 4.0
Expected: May 2021

Master of Science, *Aeronautical and Astronautical Engineering*
Thesis: Microscale Radiometer Based on the Knudsen Thermal Force
Advisor: Dr. Alina Alexeenko
G.P.A.: 4.0
Received: December 2015

Bachelor of Science, *Aeronautical and Astronautical Engineering*
G.P.A.: 3.97
Received: May 2013 (with highest distinction)

Work and Research Experience

- Graduate Research Fellow*, Purdue University, West Lafayette, IN 8/2013 to present
- Fabricate wireless gas and temperature sensors into lyophilization process to provide high-fidelity product state estimates and improve cycle performance
 - Designed and created novel MEMS sensor to produce and resolve Knudsen forces at the microscale
- LyoHUB Demo Facility Laboratory Manager*, Purdue University, West Lafayette, IN 1/2016 to present
- Train and qualifying users on equipment in lyophilization demonstration facility
 - Supervise engineering team that supports LyoHUB client projects
- Graduate Student Intern*, Baxter BioPharma Solutions, Bloomington, IN 5/2019 to 8/2019
- Developed graphical design tool for simulating lyophilization process
- Undergraduate Student Intern*, NASA Jet Propulsion Laboratory, Pasadena, CA 6/2012 to 8/2012
- Undergraduate Student Intern*, NASA Dryden Flight Research Center, Edwards, CA 1/2012 to 5/2012
- Undergraduate Research Assistant*, Purdue University, West Lafayette, IN 8/2011 to 5/2013

Mentoring and Volunteer Experience

- Undergraduate Research Supervisor*, Purdue University, West Lafayette, IN 8/2013 to present
- SURF Graduate Mentor*, Purdue University, West Lafayette, IN 6/2014 to present
- Volunteer*, Feast of the Hunter's Moon (Boy Scout Troop 322) 6/2018 to present
- Science Demonstration Volunteer* Purdue NanoDays 6/2016 to present

Awards, Honors, and Scholarships

- Purdue Forever Fellowship Awarded: 5/2018
- Dr. Thomas Jennings Best Poster Award, International Society of Lyophilization - Freeze-Drying (ISLFD) Awarded: 4/2018
- Dr. Thomas Jennings Best Poster Award, ISLFD Awarded: 4/2016
- National Science Foundation GRFP Honorable Mention Awarded: 4/2014
- Frederick N. Andrews Research Fellowship Awarded: 4/2013
- Indiana Space Grant Consortium Scholarship Awarded: 6/2012
- NASA Dryden Peer Award Awarded: 4/2012
- NASA Undergraduate Student Research Program Scholarship Awarded: 1/2012
- Boeing Undergraduate Scholarship Awarded: 9/2011
- A.T.K. Space Award Awarded: 5/2011
- Bruce Reese Aeronautics and Astronautics Scholarship Awarded: 1/2011
- Purdue University Dean's List (7/7 undergraduate semesters)
- Purdue University Semester Honors (7/7 undergraduate semesters)

Technical Skills

- Python, C, MATLAB, Simulink, Fortran, UNIX, LabVIEW, Ansys Workbench (FLUENT/Mechanical), COMSOL, EES, SPARTA, TecPlot, AutoCAD, Fusion 360, SolidWorks, G-Code, SPICE, Eagle, CoventorWare, Star-CCM+, $\text{\LaTeX}$
- Milling (CNC and vertical), turning, MIG/TIG welding, plasma cutting, additive manufacturing, PCB design, microelectromechanical system design and fabrication, forging, and woodcraft
- FAA-licensed private pilot (VFR-ASEL)

Publications

Journal Publications

1. Shivkumar, G., Kazarin, P., Strongrich, A., Alexeenko, A., “LyoPRONTO: an Open-Source Lyophilization Process Optimization Tool.” *AAPS PharmSciTech*, 20.8, 2019
2. Jaiswal, Shashank, Sebastiao, I.B., Strongrich, A., Alexeenko, A., “Quantification of thermally-driven flows in microsystems using Boltzmann equation in deterministic and stochastic contexts.” *Physics of Fluids*, 31.8, (2019).
3. Pikus, A., Sebastião, I. Borges, Strongrich, A. and Alexeenko, A., “Characterization of a Knudsen force based vacuum sensor for N₂H₂O gas mixtures”, *Vacuum*, 161, 130-137.
4. Leichty, E., Strongrich, A., Moussa, E., Topp, E., Alexeenko, A., “In-Situ Molecular Vapor Composition Measurements During Lyophilization”, *Pharmaceutical Research*, 25, p.115, 2018.
5. Strongrich, A., Pikus, A., Sebastiao, I.B., Alexeenko, A., “Microscale In-Plane Knudsen Radiometric Actuator: Design, Characterization, and Performance Modeling”, *Journal of Microelectromechanical Systems*, 26(3), 528-538.
6. Strongrich, A., Pikus, A., Sebastiao, I., Peroulis, D., Alexeenko, A., “Microscale Actuation and Gas Sensing by the Knudsen Thermal Force”, *Applied Physics Letters*, 107(19), 193508.
7. Strongrich, A., Cofer, A., O'Neill, W., Alexeenko, A., “Experimental Measurements and Numerical Simulations of Knudsen Force on a Non-Uniformly Heated Beam”, *Vacuum*, 109, 405-416.

In Preparation

1. Strongrich, A., Lim, F., Kumar, L., Alexeenko, A., “Rapid Depressurization Controlled Ice Nucleation in Pharmaceutical Freeze-Drying: The Roles of the Ballast Gas and the Vial”, *Journal of Pharmaceutical Sciences*, 2021 (Under Review).
2. Strongrich, A., Alexeenko, A., “Application of Wireless Sensor Networks to Lyophilization PAT: Measurement and Modeling of Local Gas Pressure and Temperature During Primary Drying”, *European Journal of Pharmaceutics and Biopharmaceutics*, 2021 (Under Review).

Invited and Published Conference Proceedings (* Denotes Speaker)

1. Strongrich, A.*, Alexeenko, A., “Next-Generation Process Monitoring for Lyophilization - Applications for Wireless Sensor Networks,” *SP Scientific LyoLearn Webinar Series*, 2020 (Invited).
2. Strongrich, A.*, Alexeenko, A., “IOT PAT for Lyophilization,” *International Society of Lyophilization - Freeze-Drying (ISLFD)*, Gent, Belgium, 2019 (Invited).
3. Strongrich, Andrew D., Gayathri, S.*, Alexeenko, A., “Dark-to-Arc Transition in Air for Planar Electrodes with Microscale Gaps.” *IEEE International Conference on Plasma Science*, IEEE, 2017.
4. Alexeenko, A.*, Strongrich, A., Cofer, A., Pikus, A., Sebastiao, I. B., Tholeti, S., Shivkumar, G., “Microdevices Enabled By Rarefied Flow Phenomena”, *AIP Conference Proceedings*, Vol. 1786. No. 1. AIP Publishing, 2016 (Invited).
5. Fowee, K.*, Ibrayeva, A., Strongrich, A., Alexeenko, A., “Experimental Measurements and Numerical Modeling of a Thermostress Convection-Based Actuator”, *The 30th International Symposium of Rarefied Gas Dynamics*, Victoria, Canada, 2016.
6. Pikus, A.*, Sebastiao, I., Strongrich, A., Alexeenko, A., “DSMC Simulation of Microstructure Actuation By Knudsen Thermal Forces Including Binary Mixtures”, *The 30th International Symposium of Rarefied Gas Dynamics*, Victoria, Canada, 2016.

7. Strongrich, A.*, Alexeenko, A., “Low-pressure Gas Sensor Exploiting the Knudsen Thermal Force: DSMC Modeling and Experimental Validation,” *IEEE MEMS 2016* (pp. 828-831), Shanghai, China, 2016.
8. Strongrich, A.*, Alexeenko, A., “Convective Cooling in the Transitional Rarefied Flow Regime,” *International Mechanical Engineering Congress & Exposition*, Montreal, Canada, 2014. pp. V08AT10A033-V08AT10A033
9. Strongrich, A.*, Alexeenko, A., “Knudsen Thermal Force Generation at the Microscale,” *International Mechanical Engineering Congress & Exposition*, Montreal, Canada, 2014.
10. Strongrich, A., Alexeenko, A.*, “Experimental Measurements and Modeling of Convective Cooling in the Transitional Rarefied Regime,” *29th International Symposium on Rarefied Gas Dynamics*, Xi’an, China, 2014.
11. O’Neill W., Wada, M., Strongrich, A., Cofer, A., Alexeenko, A.*, “Amplification and Reversal of Knudsen Force by Thermoelectric Heating,” *29th International Symposium on Rarefied Gas Dynamics*, Xi’an, China, 2014.

Patents

1. A. Strongrich, A. Alexeenko, “Microelectromechanical Gas Sensor Based on Knudsen Thermal Force”, U.S. Patent 10,161,818, 25 December 2018.
2. A. Strongrich, A. Alexeenko, “Method for Measuring Rapid Decompression Ice Nucleation in Lyophilization”, U.S. Patent Application No. 63/112,089, Filed 10 November 2020.
3. A. Strongrich, A. Alexeenko, “Process Monitoring and Control for Lyophilization Using a Wireless Sensor Network”, U.S. Patent Application No. 62/838,959, Filed 27 April 2020.