Methods for Characterizing Convective Cryoprobe Heat Transfer in Ultrasound Gel Phantoms

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While cryosurgery has proven capable in treating of a variety of conditions, it has met with some resistance among physicians, in part due to shortcomings in the ability to predict treatment outcomes. Here we attempt to address several key issues related to predictive modeling by demonstrating methods for accurately characterizing heat transfer from cryoprobe, report temperature dependent thermal properties for ultrasound gel (a convenient tissue phantom) down to cryogenic temperatures, and demonstrate the ability of convective exchange heat transfer boundary conditions to accurately describe freezing in the case of single and multiple interacting cryoprobe(s). Temperature dependent changes in the specific heat and thermal conductivity for ultrasound gel are reported down to -150°C for the first time here and these data were used to accurately describe freezing in ultrasound gel in subsequent modeling. Freezing around a single and two interacting cryoprobe(s) was characterized in the ultrasound gel phantom by mapping the temperature in and around the "iceball" with carefully placed thermocouple arrays. These experimental data were fit with finite-element modeling in COMSOL Multiphysics, which was used to investigate the sensitivity and effectiveness of convective boundary conditions in describing heat transfer from the cryoprobes. Heat transfer at the probe tip was described in terms of a convective coefficient and the cryogen temperature. While model accuracy depended strongly on spatial (i.e., along the exchange surface) variation in the convective coefficient, it was much less sensitive to spatial and transient variations in the cryogen temperature parameter. The optimized fit, convective exchange conditions for the single-probe case also provided close agreement with the experimental data for the case of two interacting cryoprobes, suggesting that this basic characterization and modeling approach can be extended to accurately describe more complicated, multiprobe freezing geometries. Accurately characterizing cryoprobe behavior in phantoms requires detailed knowledge of the freezing medium's properties throughout the range of expected temperatures and an appropriate description of the heat transfer across the probe's exchange surfaces. Here we demonstrate that convective exchange boundary conditions provide an accurate and versatile description of heat transfer from cryoprobes, offering potential advantages over the traditional constant surface heat flux and constant surface temperature descriptions. In addition, although this study was conducted on Joule-Thomson type cryoprobes, the general methodologies should extend to any probe that is based on convective exchange with a cryogenic fluid. [DOI: 10.1115/1.4023237]

Keywords: cryosurgery, cryotherapy, cryoablation, thermal properties, heat transfer modeling, clinical modeling

Introduction

Cryosurgery is a minimally invasive technique in which freezing temperatures are used to destroy tissue in the body to treat various conditions, including cancer (prostate, kidney, liver, and lung) [1–4], cardiovascular disorders (arterial and pulmonary) [5,6], and neurological disorders (neuro analgesia and plantar fasciitis) [7,8]. The main benefit of cryosurgical approaches is the ability to treat a volume of target tissue without completely disrupting the surrounding structures [9]. This can lead to reduced risk and recovery times over some traditional surgical approaches. Intraoperative imaging also allows direct visualization of the iceball, however, temperatures well below freezing are needed to completely destroy the tissue [10]. This gap in monitoring treatment outcome is a challenge to the field that can be approached

through predictive modeling. The relevance of these models is critically related to three main factors: (i) accurately accounting for changes in the freezing medium properties (both phase change and with temperature), (ii) accurately modeling heat transfer at the cryoprobe freezing interface, and (iii) using the appropriate temperature-time thresholds to predict cell death. This work highlights the importance of the first two, in the context of the ability of numerical modeling to predict the temperature distribution around a freezing cryoprobe. Here we demonstrate a general methodology for accurately characterizing the heat transfer from a convectively cooled Joule-Thomson cryoprobe, present for the first time the temperature dependent thermal properties of ultrasound gel phantoms, and discuss their impact on the accuracy of modeling in cryosurgery. The ability of modeling to describe freezing in cases of multiple, interacting cryoprobes is also investigated, which is of critical importance considering that clinical approaches often utilize arrays of probes to create larger treatment areas or modified freeze geometries. Then in the iceball, cell death is generally described by the concept of lethal threshold

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temperatures. Estimates of these threshold temperatures can range from -20°C to -40°C [10,11] and new preconditioning techniques utilizing adjuvants have demonstrated the potential to raise this limit up to as high as 0°C [12,13]. While biological freeze destruction is an important area of research, there are multiple mechanisms at the cellular, vascular, and even immunological level that contribute, putting this topic beyond the scope of this current work. Interested readers should consult reviews on the subject [10,11], but we will continue here with considerations related to predicting the temperatures achieved around freezing cryoprobes.

Modeling of cryosurgical processes is not a new topic and there has been significant and ongoing work in this area. Some of the first approaches used quasi-steady approximations of transient iceballs [14,15] or focused mainly on the challenges of incorporating phase change into numerical schemes [16]. These methods typically used the thermal properties of water and ice as first cut approximations for the unfrozen and frozen states and temperature dependence was ignored. As modeling became more sophisticated, latent heat evolution was employed using enthalpy and apparent heat capacity methods [17,18]. Gradually, temperature dependent properties were incorporated but often not directly for the tissue or phantom used in the study [19].

Although thermal property treatments have seen a gradual increase in sophistication, descriptions of the heat transfer from the cryoprobe have remained fairly consistent. While the thermodynamic mechanisms of cooling can vary significantly between different cryosurgical platforms (including liquid nitrogen phase change, Joule–Thomson effect, etc.) [20], a limited number of boundary conditions are generally employed in describing heat transfer at their freezing interfaces. Table 1 highlights the range of boundary conditions that have been employed throughout literature. These can generally be grouped into constant surface temperature, constant heat flux, and surface convection conditions. While these approximations have met with some success in previous modeling attempts, the use of external surface conditions suffers from an inherent limitation—the surface conditions will vary for different freezing environments. Different freezing media and different multiprobe configurations will draw different heat loads and produce different temperature distributions (on and around the probes). In addition, the use of constant boundary conditions does not provide for any variation in the heat transfer along the length of the probe, which can be significant as demonstrated in our results. Table 1 also notes any use of temperature dependent thermal properties in the studies described.

The Joule–Thomson cryoprobes studied here function on heat exchange with compressed argon gas flow inside the probe tip. Although the actual probe tip features a complicated internal exchange geometry, it was approximated by simple, cylindrical,

Fig. 1 Simplified internal exchange flow for the 1.5 mm diameter IceSeed (Galil Medical Inc., Arden Hills, MN) cryoablation needle studied here. Compressed argon gas flows down through a center channel and impinges on the top of a stainless steel tip, where significant heat exchange occurs. Convective exchange continues up the walls of the probe for 12 mm, at which point the cryoprobe is insulated for the remainder of the shaft.

convective exchange surfaces, as illustrated in Fig. 1. Since this internal geometry is fixed and the flow is controlled by pressure regulators, these convective exchange conditions should not vary significantly with the external freezing environment and should be valid for a broad range of freezing configurations (including cases of interacting probes, where the local temperatures will be lower than for a single probe).

To accurately characterize these convective exchange conditions, numerical modeling was fit with experimental temperature mapping around one and two (interacting) cryoprobes during freezing. These experiments were conducted in ultrasound gel, which is becoming a popular phantom for cryosurgical studies, both due to the convenience of use and close mimic of tissue thermal properties [26,28,33]. However, accurate modeling also requires accurately accounting for changes in the freezing medium's thermal properties (with phase and temperature). We, therefore, report for the first time here the specific heat and thermal conductivity of ultrasound gel in the cryogenic and suprazero regimes. The model sensitivity to phase change, temperature dependent thermal properties, and the heat transfer boundary conditions was investigated and the optimal fit for the single-probe case was applied in modeling the dual-probe configuration. Close agreement with the experimental data was demonstrated for both cases, suggesting the ability of convective heat transfer boundary conditions to accurately describe more complex freezing geometries. In addition, since a majority of cryoprobes fundamentally operate based on convective exchange with some type of cryogenic fluid (i.e., compressed gas, subcooled liquids, phase-change mixtures), both the experimental methodology and approaches for more accurately describing cryoprobe heat transfer demonstrated here should extend throughout the field. And this focus on improving model inputs (i.e., thermal properties and convective exchange boundary conditions) should be easily implemented in

Table 1 Heat transfer boundary conditions and thermal properties employed in cryosurgical modeling by various groups [21–31]. Adapted from Zhang et al. [32]. All the studies listed accounted for phase change in the frozen/unfrozen states, but only half accounted for variations in the thermal properties with temperature

Heat transfer boundary conditions	Thermal properties	References
Constant surface temperature	Constant	[21]
	Constant	[22,23]
	$c_p(T)$, $k(T)$	[24]
	Constant	[26]
Constant surface heat flux	$c_p(T)$, $k(T)$	[27]
	$c_p(T)$, $k(T)$	[28]
Convective exchange	Constant	[29]
	$c_p(T)$, $k(T)$	[30]
	$k(T)$	[31]

most current modeling approaches, greatly enhancing the current body of literature rather than providing an alternative path.

Method of Approach

Characterizing Ultrasound Gel Thermal Properties. Since Aquasonic, clear ultrasound gel (Parker Laboratories Inc., Fairfield, NJ) was used as the tissue phantom in these studies, we characterized its specific heat and thermal conductivity through the full range of expected temperatures. Methods for characterizing biomaterial thermal properties have been discussed in great detail elsewhere [34], but a brief description is provided below.

The apparent specific heat capacity of ultrasound gel was measured with a Diamond differential scanning calorimeter (DSC) (PerkinElmer Inc., Waltham, MA) from -150°C to 40°C at a heating/cooling rate of $5^{\circ}\text{C}/\text{min}$. Ten milligram samples were placed in aluminum sample pans. Water, sapphire, and an empty sample pan were used as calibration standards. The measurements were repeated for $n = 3$. Separation of the latent and specific heats from the measured apparent specific heat will be discussed in more detail in the Results and Discussion section.

The thermal conductivity was measured in the sub- and supra-zero regimes (-125°C to 40°C). In both cases, measurements were made with 7.5 mL samples contained in cryotubes, utilizing heated thermistor techniques. For the frozen-state measurements, the pulse-decay method (PDM) was employed, in which the thermistor is pulse heated and the thermal decay is measured to determine the thermal conductivity [34,35]. Measurements were made at temperatures ranging from -125°C to -25°C , at increments of 20°C . A Kryo 10 controlled-rate freezer (Planer PLC, Middlesex, UK) was used to cool the samples in an ethanol bath down to the desired temperatures, with typical equilibration times on the order of 5–8 h. Measurements were also made for ice, to provide a reference standard, and all measurement points were repeated for $n = 4$ or 5. In the unfrozen state, measurements were made with the constant power method [36], where the thermal decay was monitored as a constant power was applied to the thermistor for several seconds. This method requires comparator reference standards, for which glycerol and 1% agarose gel were used [34,37]. Measurements were repeated for $n = 3$ at -2°C , 18°C , and 38°C , equilibrating in a heated/cooled, Neslab RTE 740 ethanol recirculating bath (Thermo Scientific Corp., Essex, UK). In both measurement cases, the thermistor is assumed to be a spherical heat source and analytical approximations are used to

estimate the surrounding thermal conductivity based on the transient solutions, which have previously been described in detail [34–36].

Measuring Temperature Distribution Around a Freezing Cryoprobe. Freezing around the 17-gauge IceSeed cryoablation needles (Galil Medical Inc., Arden Hills, MN) was characterized by measuring the temperature at various locations around the probes during cooling, following similar methods to those applied by Kim et al. and Zhang et al. [27,32]. A jig was machined out of polypropylene, to allow accurate placement of one or two cryoprobes at a spacing of 10 mm and an array of thermocouples at radial distances of $r = 2.5, 5.0$, and 10.0 mm and across axial planes at $z = 0, 4, 8, 12$, and 15 mm, as illustrated in Fig. 2. The 40-gauge thermocouples were threaded through and fixed with epoxy at the tip of 1.27 mm outer diameter glass capillary tubes to facilitate accurate positioning.

The assembly was placed in a 1 L glass beaker filled with ultrasound gel and equilibrated to 37°C in an Isotemp water bath (Fisher Scientific, Essex, UK). Care was taken in pouring the ultrasound gel to avoid formation of any large air bubbles and any small air bubbles that were entrained diffused to negligible sizes during warming. Temperature measurements were recorded every second for 10 min of freezing, using a NI cDAQ-9172 data acquisition system (National Instruments Inc., Austin, TX). This system featured enough thermocouple inputs to allow simultaneous measurement at all radial points on a single axial (z) plane. The thermocouples were calibrated at 37°C (heated water bath), 0°C (ice slush bath), and -72°C (ethanol freezer bath), on a weekly basis. The beaker radius was approximately 5 cm, which is more than five times larger than the maximum iceball radius and the final simulated temperature at a distance of 3 cm from the probe dropped by only half a degree Celsius, so this container should provide a test bed free of significant edge effects.

Two probes were chosen for repeated use throughout the characterization studies, based on similar/consistent performance (i.e., temperature distributions around the freezing probes). Although the probes are recommended for single use in the clinic, this is largely due to concerns over sterility and great care was taken to minimize any physical wear due to the repeated use. The probes were flushed with helium gas for several minutes after every run and placed in sealed storage when not in use. For the single-probe studies, placement was randomized between the two jig positions.

Fig. 2 Experimental setup. An array of thermocouples was positioned around the cryoprobe(s) during freezing at different radial positions (r) and on different measurement planes (z). The temperature distribution was measured for both single- and dual-probe cases using the same placement jig.

Fig. 3 Model setup for 2D, axisymmetric, single-probe case (a). The temperature (T) distribution around the freezing cryosurgical probe is numerically solved using the described boundary conditions and heat transfer equations. The dual-probe case is modeled using the same heat transfer conditions, but utilizes a 3D geometry with symmetry planes ((b), symmetry highlighted in green on near and left-hand faces).

Measurements on each plane were repeated for $n = 4$. This process was then performed with both probes being simultaneously cooled (dual-probe setup), again for $n = 4$ on each plane.

Modeling Cryoprobe Freezing. COMSOL version 4.2 a (COMSOL Inc., Burlington, MA) running on a Dell Precision 490 workstation (2.33 GHz, 16GB RAM) was used to numerically model the single- and dual-probe freezing configurations. A 2D, axisymmetric, transient case was used to model single-probe freezing, whereas a 3D, transient case with two symmetry planes was used to model dual-probe freezing.

Figure 3 includes a complete description of the model definition. Convective exchange occurs across the top of the conical probe tip and along a 12 mm section up the probe shaft. The exchange parameters can be described by the argon temperature ($T_{ar}(z)$) and convective heat transfer coefficient ($h(z)$), which will vary axially along the probe. The remainder of the probe length is insulated by a trapped layer of gas, so very little heat transfer should occur across this boundary. Heat transfer in the ultrasound gel is governed by the standard heat diffusion equation [38], with the thermal properties input as interpolation functions based on the measured ultrasound gel thermal property data. The apparent heat capacity method was employed to approximate freezing, where the latent heat was distributed on top of the specific heat across a “mushy zone” temperature interval. The probe tip consists of a conical section of stainless steel. The temperature dependent thermal properties for stainless steel were taken from literature [39,40] and again implemented as interpolation functions. The top surface of the ultrasound gel is in contact with the polypropylene jig and was approximated as an insulating surface. The side and bottom surfaces of the sample beaker were submerged in the controlled water bath and were approximated as fixed temperature boundaries at 37°C .

All initial conditions were set to 37°C . A 5 s linear ramp period was used at the convective exchange boundary (from zero to maximum exchange conditions), to account for equilibration of flow through the system and alleviate numerical convergence issues. The model simulated 600 s of freezing.

The geometric mesh was refined at the heat transfer boundary, to provide an element size between 0.05 to 0.2 mm. An element growth rate of ≤ 1.04 produced a coarser mesh moving out into the heat transfer medium (where the thermal gradients decreased). The total number of elements was 16,601 in the 2D case and 1,133,418 for the 3D case.

The model was fit to optimize agreement with the experimentally measured data. An overall regression coefficient was, thus, used to optimize the fitting at each axial/radial location:

$$R_{r,z}^2 = \left(1 - \frac{\sum_{t=600} (T_{\text{meas}} - T_{\text{num}})^2}{\sum_{t=600} (T_{\text{meas}} - \bar{T}_{\text{meas}})^2} \right) \quad (1)$$

where $T_{\text{meas}}(r, z, t)$ and $T_{\text{num}}(r, z, t)$ are the measured and predicted temperatures at a given position and time, respectively, and $\bar{T}_{\text{meas}}(r, z)$ is the average temperature measured over all the time points at a given position. The overall regression coefficient was then taken as the average across all the measurement locations.

The convective coefficient ($h(z)$) was fit at five locations up the shaft length ($z = 3, 4, 8, 12$, and 15 mm) and interpolated between these points. A more detailed description of the fitting approach is included in Appendix A.

The cryoprobe manufacturer suggested an initial cryogen temperature of -130°C and gas flow of approximately $5.52 \times 10^{-4} \text{ kg/s}$ ($\dot{m}_{ar}$). This applies some constraints to fitting the cryogen temperature and an iterative approach was required. The numerical model also allows the total heat load ($\bar{Q}$) to be calculated, and with this the temperature increase of the cryogen gas (ΔT_{ar}) across the exchange region can be approximated from a basic energy balance, so that

$$\Delta T_{ar} = \frac{\bar{Q}}{c_{p,ar} \dot{m}_{ar}} \quad (2)$$

where $\bar{Q}$ is the average calculated heat load across all time points and $c_{p,ar}$ is the specific heat of argon gas at the flow temperature and pressure (approximately 1100 J/kg-K at 143 K and 225 bar [41]). These conditions are expected to match those at the end of the probe during expansion, but some drop in pressure is likely along the probe annulus. This may affect the $c_{p,ar}$ by up to 30%, depending on the pressure drop, but a constant value was assumed for this approximation.

In addition to characterizing the temperatures around the freezing cryoprobes, ultrafine gauge copper wire was used to tightly wrap thermocouples at various locations along the exchange surface and it was determined that the surface temperature varied roughly linearly across this region. By extension, we assumed the same for the cryogen temperature. With this assumption in place it was not then necessary to independently fit the cryogen

Fig. 4 Measured ultrasound gel specific heat (a) and thermal conductivity (b). Reference values for water and ice were included for comparison [42].

temperature since we impose the inlet temperature (at $z = 0$) and can calculate the outlet temperature (at $z = 15$ mm) using Eq. (2) and the numerically calculated heat load.

Results and Discussion

Ultrasound Gel Thermal Properties. The apparent specific heat and thermal conductivity of ultrasound gel were experimentally characterized through the cryogenic regime. Figure 4 includes the measured results with reference values for water and ice for comparison. Although the data were input in COMSOL as interpolation functions, piecewise linear fits are also shown. The measured data values and these piecewise fit equations have been included in Appendix B.

Figure 4(a) plots the specific heat of ultrasound gel from $-130^{\circ}C$ to $40^{\circ}C$. An approximate latent heat of fusion of $h_{fg} = 259 J/g$ (which is 77.5% that of water) is also indicated in the figure. In DSC freeze-thaw measurements, the latent heat of fusion appears over a wide temperature range corresponding to a mushy zone with a peak in the apparent specific heat around the melting point. Negative two degrees Celsius was assumed as the melting point for ultrasound gel because this is where the peak apparent specific heat occurred. However, there was a small amount of residual latent heat observed beyond this melting point, assumed to be due to lag associated with the finite heating rate. Additional approximations were invoked to separate the latent heat of fusion from the apparent specific heat [34,35]. The specific heat curve follows a nearly perfect linear trend between $-85^{\circ}C$ and $-50^{\circ}C$, so it was assumed that the latent heat effects were absent in this range. The specific heat was approximated in the mushy zone by first extending this linear trend up to the melting point. Then the offset between the frozen and unfrozen states was smoothed based on the proportion of latent heat observed below that temperature, with the latent heat being calculated as the discrete integral between the apparent specific heat curve and the assumed specific heat curve.

Figure 4(b) includes the thermal conductivity values measured for ultrasound gel and water. The values for ice demonstrate close agreement to the expected values, supporting the relevance of the PDM technique in characterizing low-temperature thermal conductivities. Although the ingredients of the ultrasound gel are proprietary, the manufacturer does indicate that it consists largely of water, with a "humectant" (likely propylene glycol) listed as the next most substantial component. Figure 4(b) then also includes a "fit" for the ultrasound gel thermal conductivity, assuming a 65%/35% mass-averaged thermal conductivity for a binary mixture of water and propylene glycol. This fit was calculated based on reference thermal conductivity values for water through the low-temperature regime [42] and the thermal conductivity of pure propylene glycol at

$-20^{\circ}C$ [34,43]. Lower temperature data were not available for propylene glycol, but the thermal conductivity of glycols are generally fairly flat until their glass transition [34]. This approximation shows close agreement until around $-90^{\circ}C$, where the measured values level off. The same behavior was observed for (pure) glycol/water mixtures in the low temperature regime, where a similar leveling occurs around their frozen glass transition [34]. A minor peak in the apparent specific heat was observed around $-105^{\circ}C$ (Fig. 4(a)), which suggests a glass transition in the frozen ultrasound gel. This correlates closely with the glass transition temperature of pure propylene glycol, $-101^{\circ}C$ [44]. In addition, similar plateau behavior and magnitudes for specific heat and thermal conductivity are observed for a range of tissues [34], again highlighting the value of ultrasound gel as a cryogenic tissue phantom.

The ultrasound gel manufacturer lists a room temperature density of $1.02 g/cm^3$, which is within 1% of the mass-averaged value for a 65%/35% binary, water/propylene glycol mixture (density of propylene glycol is $1.033 g/cm^3$ at $26^{\circ}C$ [45]). The same mass-average approach described above was, therefore, used to estimate the temperature dependent density of ultrasound gel throughout the range of expected temperatures and piecewise fit equations have been included in Appendix B. These estimated values were used in the numerical modeling but did not vary significantly from those of pure water.

Measured Temperature Distributions Around Cryoprobes.

Figure 5 includes the transient temperature profiles at a number of the measured locations, with a comparison between the temperatures observed in the single- and dual-probe cases. As expected, the temperatures were lower in the dual-probe case.

While the described methods provide accurate temperature distributions around the cryosurgical probes, they are also time intensive and great care must be taken to ensure proper thermocouple placement. Although cryosurgery is not widely monitored by magnetic resonance (MR) imaging, MR-compatible cryoprobes are available [46] and some groups have demonstrated the ability to measure temperatures in frozen tissues through MR-based thermometry [47]. This approach could provide an opportunity to generate even more accurate temperature distribution maps (i.e., fully concurrent 3D maps versus a series of point measurements) and greatly facilitate characterizing cryoprobe heat transfer, but significant developments for MR measurements in the frozen state would be necessary.

Modeling Temperature Distributions Around Cryoprobes.

Numerical modeling utilizing the measured ultrasound gel thermal property data was used to fit the experimentally observed temperature distributions around the freezing cryosurgical probe(s). For the

Fig. 5 Measured temperature profiles at the $z = 4$ mm plane and various radial distances for the single- and dual-probe cases (b–d). The single-probe case is plotted as the black curve for each radial distance. Colored curves correspond to the thermocouple grid locations (a), as first described in Fig. 2.

single-probe case, the average regression coefficient described in Eq. (1) was optimized for each of the fitting cases of interest, with sensitivity analyses being used to investigate the effects of the thermal properties and heat transfer boundary conditions on the accuracy of the modeling.

While the regression coefficient provided the best indicator of fit with the measured temperature data, an additional metric was defined to provide a more practical gauge of accuracy. Displacement error (DE) was defined to reflect the spatial error associated with the offset between the predicted and measured isotherms. This value was calculated as

$$DE_{r,z} = \frac{|T_{\text{meas}} - T_{\text{num}}|_{t=600}}{|\nabla T_{\text{num}}|_{t=600}} \quad (3)$$

where $\nabla T_{\text{num}}(r, z, t)$ is the modeled temperature gradient. Previous modeling techniques have often investigated model accuracy based on the displacement of the iceball edge (or other isotherms) [24,25,48] and so DE should provide a relevant base of comparison. Lethal tissue damage usually begins around -20°C , so this is one of the most relevant isotherms. In our case, this isotherm had a radius of about 5 mm, so the DE is reported based on the average value at $r = 5$ mm.

The model solve time was also included as a performance indicator. Increasing the complexity of a model can increase the computational requirements (and the time required to solve) and so this should be an important consideration when the end-goal is real-time clinical planning and monitoring. A summary of the results for the single-probe case is included in Table 2.

While a majority of the modeling cases incorporated the temperature dependent thermal properties measured for ultrasound gel, case B in Table 2 held these values constant in the frozen and unfrozen states (i.e., no temperature dependence outside of phase change). The constant thermal properties estimated from our measured values closely matched the approximations developed by Magalov et al. [26] except here we used 259 J/g for the latent heat

of fusion. A significant drop in model accuracy is observed for the constant property case, demonstrating the importance of including temperature dependence in the freezing medium thermal properties. Beyond fundamental characterization studies conducted in tissue phantoms, this also highlights the importance of efforts to develop thermal property databases for the tissues encountered in clinical cryosurgery applications [34]. Finally, Appendix A includes an analysis of the phase change treatment, in which it was determined that a 20°C mushy zone was the most appropriate temperature interval for freezing.

A sensitivity analysis was also performed to highlight the significance of accurately reflecting the heat transfer at the exchange boundary (Table 2). Both the convective coefficient and cryogen temperature were varied as a function of axial position and/or held constant. In addition, the cryogen temperature was fit as a function of time, where the heat load ($Q(t)$) input into Eq. (2) was solved on a transient basis, rather than taking the average value ($\bar{Q}$).

The most significant effect on model accuracy came from the spatial fit for the convective coefficient (i.e., $h(z)$). The fitted values for case 4 are included in Fig. 6. The predicted increase in the cryogen temperature across the exchange region is only about 13°C , compared to an order of magnitude variation in the convective coefficient, so it is not surprising that $h(z)$ dominates the model accuracy.

While an impinging jet will produce very high rates of convective heat transfer, $40 \text{ kW/m}^2\text{-K}$ is higher than would be expected in most realistic applications. However, Martin et al. has provided analytical expressions for predicting the convective heat transfer coefficient of a constrained impinging jet [49]. These relations can be evaluated for our simplified geometry and estimated argon gas flow, predicting a convective coefficient on the order of $20 \text{ kW/m}^2\text{-K}$ (see Appendix C). Yet it should be noted that the impinging surface was approximated as flat. If the actual exchange surface is curved or textured, this could account for a factor of two difference in the area and explain the numerical overestimation of the convective coefficient.

Also, in the simplified model, one might expect the cryogen flow to become developed moving up the exchange region, in which case, the increase in h at $z = 15$ mm might be questioned. However, it

Table 2 Thermal property and heat transfer boundary condition sensitivity analyses for the single-probe case. Model accuracy is indicated by the average regression coefficient (R^2 , Eq. (1)) and displacement error (DE , Eq. (2)).

Thermal property sensitivity					
Case	Mushy zone interval	Thermal properties	Average R^2 -fit	DE $r = 5.0$ mm	Solve time
A	20 °C	f (T)	0.968	0.13 mm	36 s
B	20 °C	Constant	0.924	0.65 mm	37 s

Heat transfer boundary condition sensitivity					
Case	Convective coefficient	Cryogen temperature	Average R^2 -fit	DE $r = 5.0$ mm	Solve time
1	Constant	Constant	0.835	0.46 mm	45 s
2	Constant	$T_{Ar}(z)$	0.861	0.39 mm	42 s
3	$h(z)$	Constant	0.966	0.12 mm	37 s
4	$h(z)$	$T_{Ar}(z)$	0.968	0.13 mm	36 s
5	$h(z)$	$T_{Ar}(z, t)$	0.968	0.12 mm	56 s
6	Constant Q_{surf}		0.891	0.41 mm	43 s
7	Constant T_{surf}		0.921	0.20 mm	85 s

Fig. 6 Fitted values for the convective heat transfer boundary conditions for case 4 (see Table 2)

again should be emphasized that the model is a simplification and the actual internal exchange geometry is much more complicated. A convergence in the flow as it moves into the insulated region or conduction along the probe shaft could account for an increase in h . Additionally, the same two probes were used for all the repeated measurements and it is possible that the insulated region experienced some wear over time, despite the efforts to prevent this.

Finally, cases 6 and 7 provide a base of comparison with the constant surface load and constant surface temperature descriptions of cryoprobe heat transfer. It is apparent that the spatially fit convective descriptions provide a significant advantage over the constant surface descriptions, based on R^2 and DE . However, it is likely that the accuracy of the surface conditions could be improved by a similar spatial fitting approach where the surface heat flux or temperature could be varied along the exchange length. However, one of the other potential advantages of the internal convective boundary condition is lower sensitivity to the external freezing environment. This has the highest relevance in cases of simulating freezing for multiprobe configurations, where the interactions between the probes can significantly lower the local temperatures versus an isolated probe. Therefore, the model heat transfer parameters ($h(z)$ and $T_{Ar}(z)$) optimized for the single-probe case 4 (see Table 2 and Fig. 6), were used to predict freezing in the case of two cryoprobes positioned at a spacing of 10 mm. This modeling was compared with the experimental data and the results are included in Fig. 7. The heat transfer

Fig. 7 Comparison of single- and dual-probe model results. Note the difference in isotherm shapes between the left and right sides of the probe. Isotherms on the left side are *strongly* influenced by the presence of the second probe and interactions between the probes results in expanded isotherms on the right side as well.

parameters characterized for the single-probe case also demonstrated good agreement for the dual-probe case, with an average R^2 of 0.954.

A significant difference in the average heat load extracted between the two cases was observed (a 12% decrease for the dual-probe case). This would likely lead to deviations from modeled behavior if a constant heat load is assumed between single- and multiprobe freezing geometries. The drop in surface temperature was not as significant (a difference of 4 °C between the two cases), suggesting that surface temperature boundary conditions are less sensitive to changes related to interacting probe behavior. However, higher differences could be expected in cases involving more cryoprobes or due to heat transfer behavior in different types of tissue (due to differences in thermal conductivity).

These results also begin to highlight the advantage of using multiple probes in cryosurgical applications. Use of multiple probes not only allows the surgeon to produce more complicated treatment geometries than an ellipsoidal iceball, but the interactions between the probes produce a synergistic effect where the relative volume affected by each probe increases dramatically

with a concomitant drop in temperature within the bulk of the iceball. In the simulated dual-probe case, the iceball volume per probe increases by 47% versus the single-probe case (and the -40°C isovolume almost doubles). This is a significant advantage, but the dramatic difference between the cases also highlights the importance of modeling that can accurately account for these interactions in multiprobe treatment cases.

Finally, the difference in the computation times between the single- and dual-probe cases should be highlighted. In moving from 2D to 3D modeling, the solution time increased from 35 s to almost 2 h. This again emphasizes the importance of balancing model complexity and accuracy. Although computational efficiency was not a major focus in this study, it is certainly an area of interest and importance in the field [25,28,48].

Conclusions

While cryosurgery has established itself as a viable treatment for a number of conditions and continues to find new applications, there are shortcomings in the current capabilities to predict treatment outcomes. Here we attempt to address some of the issues related to predictive modeling by demonstrating methods for accurately characterizing convective heat transfer from cryoprobes, report temperature dependent thermal properties for ultrasound gel (a convenient tissue phantom) through the cryogenic regime, and demonstrate the ability of the convective heat transfer boundary conditions to accurately describe freezing in the case of multiple, interacting probes.

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Appendix A: Fitting Convective Heat Transfer Boundary Parameters and Phase Change

A.1 General Fitting Procedure. The following describes the optimization routine employed for the most complicated modeling cases. Simpler cases followed the same general methodology but required a subset of the steps described below.

Optimized fitting was achieved through a series of iterative, parametric studies. COMSOL's Parametric Study solver was used to facilitate this approach. Each case was first solved for an overall average convective coefficient (h_{avg}) by varying this parameter at five to eight levels iteratively, across a narrowing range, to optimize the overall R^2 regression value. Spatial fitting of $h(z)$ values for $z=3, 4, 8, 12$, and 15 mm was then investigated by implementing a two-level, factorial design in varying these individual fit parameters around the initial average value (h_{avg}). Iterating the two-level, factorial approach led to a roughly optimal value

Table 3 Phase change model sensitivity analysis results

Case	Phase change sensitivity				
	Mushy zone interval	Thermal properties	Average R^2 -fit	DE $r=5.0\text{ mm}$	Solve time
A-1	2°C	f (T)	0.961	0.60 mm	29.5 min
A-2	5°C	f (T)	0.964	0.60 mm	365 s
A-3	10°C	f (T)	0.960	0.62 mm	94 s
A-4	20°C	f (T)	0.968	0.13 mm	36 s
A-5	40°C	f (T)	0.962	0.26 mm	36 s

for each of the $h(z)$ parameters, but fine tuning was then made by individually varying each at five to eight levels for several iterations.

A.2 Modeling the Phase Change Interval. While freezing is generally considered a discrete transition for pure substances, phase change in mixtures (and biological tissues) often occurs over a range of temperatures (especially in cases of rapid freezing) [24,34]. Table 3 illustrates the effects of phase change treatment on model accuracy. Cases A-1 through A-5 compare different temperature intervals for applying the latent heat of fusion in the ultrasound gel (for the apparent heat capacity method). Some level of effects from the latent heat was observed in the DSC apparent specific heat measurements up to almost 50°C and so the size of the freezing mushy zone was investigated across 2°C , 5°C , 10°C , 20°C , and 40°C gaps.

Optimal values of $h(z)$ and $T_{ar}(z)$ were fit for phase change intervals of 5°C , 10°C , 20°C , and 40°C , based on the procedure described in Appendix A.1. Sharp phase transitions created convergence issues in the numerical solver and required very long solve times. Although it was possible to solve parametric cases with durations less than 5°C , solve times increased significantly, which did not permit an iterative approach and so the 2°C case was not included in this parametric analysis step. Nominal variation was observed for the $h(z)$ and $T_{ar}(z)$ fit parameters between the different phase change interval cases. The values were averaged and this average fit was used as the basis for comparing the accuracy of each phase change interval. The results are included in Table 3.

Although all the cases demonstrated good regression fits, the highest R^2 value occurred for the 20°C phase change interval. This case also demonstrated very low displacement error at $r=5\text{ mm}$, a short solve time, and agrees with previous descriptions of freezing in biological tissues [24,25].

Appendix B: Measured Data and Piecewise Fits for Ultrasound Gel Thermal Properties

Included in this section are tabulated data for the apparent specific heat (Table 4) and thermal conductivity measured (Table 5) for ultrasound gel. Approximate piecewise fitting functions have also been included to provide the readers an easy way to implement the temperature dependent thermal properties in future modeling.

Temperature Dependent, Piecewise Fitting Equations for Specific Heat (Without h_{fg})

$$c_p(T^{\circ}\text{C}) = \left\{ \begin{array}{ll} 0.0126 * T + 2.709 & -150^{\circ}\text{C} < T \leq -20^{\circ}\text{C} \\ 0.0742 * T + 3.939 \text{ J/g} - K, & \text{for } -20^{\circ}\text{C} < T < -2^{\circ}\text{C} \\ -0.0031 * T + 3.861 & -2^{\circ}\text{C} \leq T < 40^{\circ}\text{C} \end{array} \right\}$$

$$k(T^{\circ}\text{C}) = \begin{cases} 2.28 & T < -85^{\circ}\text{C} \\ -0.0138 * T + 1.122 & \text{W/m-K, for } -85^{\circ}\text{C} \leq T < -2^{\circ}\text{C} \\ 0.0012 * T + 0.481 & -2^{\circ}\text{C} \leq T < 40^{\circ}\text{C} \end{cases}$$

$$\rho(T^{\circ}\text{C}) = \begin{cases} -0.0684 * T + 958.15 & T < -2^{\circ}\text{C} \\ -0.091 * T + 1011.9 & T \geq -2^{\circ}\text{C} \end{cases} \text{ kg/m}^3$$

Appendix C: Analytically Estimating Impinging Heat Transfer Coefficient

Martin et al. has provided analytical expressions for predicting the convective heat transfer of a constrained impinging jet, where the average convective coefficient across the impinging surface ($\bar{h}$) can be calculated from [49]

Table 4 Measured apparent specific heat values for ultrasound gel at temperatures ranging from -149°C to 39°C . The listed DSC values include the distributed latent heat of fusion. Measurements were taken at increments of 1°C , but the values are reported below at approximately 10°C increments, for simplicity

Temperature ($^{\circ}\text{C}$)	DSC measured apparent specific heat (J/g-K)
-149	0.94 ± 0.11
-140	1.02 ± 0.10
-130	1.10 ± 0.12
-121	1.17 ± 0.12
-111	1.27 ± 0.14
-100	1.45 ± 0.14
-90	1.51 ± 0.15
-80	1.59 ± 0.16
-70	1.74 ± 0.16
-60	1.90 ± 0.16
-50	2.06 ± 0.16
-40	2.28 ± 0.17
-30	2.73 ± 0.26
-20	3.72 ± 0.59
-10	7.54 ± 1.65
-5	17.69 ± 3.69
-2	34.08 ± 8.35
10	3.84 ± 0.25
20	3.82 ± 0.28
30	3.78 ± 0.25
39	3.70 ± 0.18

Table 5 Measured thermal conductivity values for ultrasound gel at temperatures ranging from -125°C to 38°C

Temperature ($^{\circ}\text{C}$)	Thermal conductivity (W/m-K)
-125	2.28 ± 0.06
-105	2.27 ± 0.08
-85	2.30 ± 0.04
-65	2.04 ± 0.07
-45	1.71 ± 0.04
-25	1.49 ± 0.04
-2	0.47 ± 0.02
18	0.52 ± 0.02
38	0.52 ± 0.03

Table 6 Estimated values for calculating the average impinging convective heat transfer coefficient

Parameter	Value
D^b	0.37 mm
H^b	0.75 mm
S^a	1.49 mm
$\dot{m}_{ar}^c$	5.52×10^{-4} kg/s
k_{ar}^d	0.08 W/m-K
μ_{ar}^d	1.04×10^{-4} Pa-s
$c_{p,ar}^d$	1100 J/kg-K
ρ_{ar}^d	1150 kg/m ³

Note: The thermophysical property values of argon gas were estimated at 143 K and 225 bar.

^aMeasured.

^bEstimated from the probe geometry.

^cProvided by the manufacturer.

^dReference values from literature [41].

$$\bar{h} = 0.5 \left(\frac{k_{ar}}{D} \right) \left(1 + \left(\frac{H/D}{0.6A_r^{0.5}} \right)^6 \right)^{-0.05} \times \left(2A_r^{0.5} \left(\frac{1 - 2.2A_r^{0.5}}{1 + 0.2A_r(H/D - 6)} \right) \right) \text{Re}^{\frac{1}{3}} \text{Pr}_{ar}^{0.42} \quad (\text{C1})$$

$$A_r = \frac{\pi D^2}{2\sqrt{3}S^2} \quad (\text{C2})$$

$$\text{Re} = \frac{\rho_{ar} U_{ar} D}{\mu_{ar}}, \quad \dot{m}_{ar} = \rho_{ar} U_{ar} \left(\frac{\pi D^2}{4} \right) \rightarrow \text{Re} = \frac{\pi \dot{m}_{ar}}{4D\mu_{ar}} \quad (\text{C3})$$

$$\text{Pr}_{ar} = \frac{c_{p,ar} \mu_{ar}}{k_{ar}} \quad (\text{C4})$$

where k_{ar} is the thermal conductivity of the argon gas, D is the outlet diameter of the impinging jet, H is the outlet height from the impinging surface, A_r is normalized area parameter, Re is the Reynolds flow number, Pr_{ar} is the Prandtl number of the argon gas, S is the diameter of the probe, ρ_{ar} is the density of the argon gas, U_{ar} is the velocity of the impinging jet, μ_{ar} is the dynamic viscosity of the argon gas, $\dot{m}_{ar}$ is the mass flow rate of the argon gas, and $c_{p,ar}$ is the specific heat of the argon gas. Based on the values estimated in Table 6, the expected impinging convective coefficient will be 17.4 kW/m²-K.

References

- [1] Onik, G. M., Cohen, J. K., Reyes, G. D., Rubinsky, B., Chang, Z., and Baust J., 1993, "Transrectal Ultrasound-Guided Percutaneous Radical Cryosurgical Ablation of the Prostate," *Cancer*, 72(4), pp. 1291–1299.

- [2] Uchida, M., Imaide, Y., Sugimoto, K., Uehara, H., and Watanabe H., 1995, "Percutaneous Cryosurgery for Renal Tumours," *Brit. J. Urology*, **75**(2), pp. 132–137.
- [3] Ravikumar, T. S., Kane, R., Cady, B., Jenkins, R., Clouse, M., and Steele, G. Jr., 1991, "A 5-Year Study of Cryosurgery in the Treatment of Liver Tumors," *Arch. Surgery*, **126**(12), pp. 1520–1524.
- [4] Maiwand, M. O., and Asimakopoulos G., 2004, "Cryosurgery for Lung Cancer: Clinical Results and Technical Aspects," *Tech. Cancer Res. Treat.*, **3**(2), pp. 143–150.
- [5] Cox, J. L., Ferguson, T. B. Jr., Lindsay, B. D., and Cain M. E., 1990, "Perinodal Cryosurgery for Atrioventricular Node Reentry Tachycardia in 23 Patients," *J. Thorac. Cardio. Sur.*, **99**(3), pp. 440–449.
- [6] Avitall, B., Urboniene, D., Rozmus, G., Lafontaine, D., Helms, R., and Urbonas A., 2003, "New Cryotechnology for Electrical Isolation of the Pulmonary Veins," *J. Cardiovasc. Electr.*, **14**(3), pp. 281–286.
- [7] Barnard, D., Lloyd, J., and Evans J., 1981, "Cryoanalgesia in the Management of Chronic Facial Pain," *J. Maxillofac. Surg.*, **9**, pp. 101–102.
- [8] Allen, B. H., Fallat, L. M., and Schwartz S. M., 2007, "Cryosurgery: An Innovative Technique for the Treatment of Plantar Fasciitis," *J. Foot Ankle Surg.*, **46**(2), pp. 75–79.
- [9] Rubinsky B., 2000, "Cryosurgery," *Ann. Rev. Biomed. Eng.*, **2**(1), pp. 157–187.
- [10] Gage, A. A., and Baust J., 1998, "Mechanisms of Tissue Injury in Cryosurgery," *Cryobiology*, **37**(3), pp. 171–186.
- [11] Hoffmann, N. E., and Bischof J. C., 2002, "The Cryobiology of Cryosurgical Injury," *Urology*, **60**(2), pp. 40–49.
- [12] Baust, J. G., Gage, A. A., Klossner, D., Clarke, D., Miller, R., Cohen, J., Katz, A., Polascik, T., Clarke, H., and Baust J. M., 2007, "Issues Critical to the Successful Application of Cryosurgical Ablation of the Prostate," *Tech. Cancer Res. Treat.*, **6**(2), pp. 97–109.
- [13] Jiang, J., Goel, R., Schmechel, S., Vercellotti, G., Forster, C., and Bischof J., 2010, "Pre-Conditioning Cryosurgery: Cellular and Molecular Mechanisms and Dynamics of TNF-Alpha Enhanced Cryotherapy in an *In Vivo* Prostate Cancer Model System," *Cryobiology*, **61**(3), pp. 280–288.
- [14] Cooper, T. E., and Trezek G. J., 1970, "Analytical Prediction of the Temperature Field Emanating From a Cryogenic Surgical Cannula," *Cryobiology*, **7**(2), pp. 79–83.
- [15] Cooper, T. E., and Trezek G. J., 1971, "Rate of Lesion Growth Around Spherical and Cylindrical Cryoprobe," *Cryobiology*, **7**(4), pp. 183–190.
- [16] Bischof, J. C., Bastacky, J., and Rubinsky B., 1992, "An Analytical Study of Cryosurgery in the Lung," *J. Biomech. Eng.*, **114**, pp. 467–472.
- [17] Schweikert, R. J., and Keanini R. G., 1999, "A Finite Element and Order of Magnitude Analysis of Cryosurgery in the Lung," *Int. Commun. Heat Mass Transf.*, **26**(1), pp. 1–12.
- [18] Wan, R., Liu, Z., Muldrew, K., and Rewcastle J., 2003, "A Finite Element Model for Ice Ball Evolution in a Multi-probe Cryosurgery," *Comp. Meth. Biomech. Biomed. Eng.*, **6**(3), pp. 197–208.
- [19] Rabin Y., 2000, "The Effect of Temperature-Dependent Thermal Conductivity in Heat Transfer Simulations of Frozen Biomaterials," *Cryo Lett.*, **21**(3), pp. 163–170.
- [20] Aus G., 2006, "Current Status of HIFU and Cryotherapy in Prostate Cancer—A Review," *Eur. Urology*, **50**(5), pp. 927–934.
- [21] Baissalov, R., Sandison, G., Donnelly, B., Saliken, J., McKinnon, J., Muldrew, K., and Rewcastle J., 2000, "A Semi-Empirical Treatment Planning Model for Optimization of Multiprobe Cryosurgery," *Phys. Med. Biol.*, **45**, pp. 1085–1098.
- [22] Rewcastle, J. C., Sandison, G. A., Hahn, L. J., Saliken, J. C., McKinnon, J. G., and Donnelly B. J., 1998, "A Model for the Time-Dependent Thermal Distribution Within an Iceball Surrounding a Cryoprobe," *Phys. Med. Biol.*, **43**, pp. 3519–3534.
- [23] Rewcastle, J. C., Sandison, G. A., Muldrew, K., Saliken, J. C., and Donnelly B. J., 2001, "A Model for the Time Dependent Three-Dimensional Thermal Distribution Within Iceballs Surrounding Multiple Cryoprobes," *Med. Phys.*, **28**, pp. 1125–1137.
- [24] Rossi, M. R., and Rabin Y., 2007, "Experimental Verification of Numerical Simulations of Cryosurgery With Application to Computerized Planning," *Phys. Med. Biol.*, **52**, pp. 4553–4567.
- [25] Rossi, M. R., Tanaka, D., Shimada, K., and Rabin Y., 2007, "An Efficient Numerical Technique for Bioheat Simulations and Its Application to Computerized Cryosurgery Planning," *Comp. Meth. Prog. Biomed.*, **85**(1), pp. 41–50.
- [26] Magalov, Z., Shitzer, A., and Degani D., 2007, "Isothermal Volume Contours Generated in a Freezing Gel by Embedded Cryo-Needles With Applications to Cryo-Surgery," *Cryobiology*, **55**(2), pp. 127–137.
- [27] Kim, C., O'Rourke, A. P., Mahvi, D. M., and Webster J. G., 2007, "Finite-Element Analysis of Ex Vivo and *In Vivo* Hepatic Cryoablation," *Biomed. Eng. IEEE Trans.*, **54**(7), pp. 1177–1185.
- [28] Blezek, D. J., Carlson, D. G., Cheng, L. T., Christensen, J. A., Callstrom, M. R., and Erickson B. J., 2010, "Cell Accelerated Cryoablation Simulation," *Comp. Meth. Prog. Biomed.*, **98**(3), pp. 241–252.
- [29] Keanini, R. G., and Rubinsky B., 1992, "Optimization of Multiprobe Cryosurgery," *ASME J. Heat Trans.*, **114**(4), pp. 796–801.
- [30] He, X., and Bischof, J. C., 2005, "Analysis of Thermal Stress in Cryosurgery of Kidneys," *J. Biomech. Eng.*, **127**, pp. 656–661.
- [31] Zhang, J., Sandison, G. A., Murthy, J. Y., and Xu L. X., 2005, "Numerical Simulation for Heat Transfer in Prostate Cancer Cryosurgery," *J. Biomech. Eng.*, **127**, pp. 279–294.
- [32] Zhang X., 2008, "Multi-Probe Cryosurgical Treatments: An Experimental and Computational Study Confirms Probe Cooling Power is Probe Number and Placement Dependent," M.S., University of Minnesota, Minneapolis, MN.
- [33] Young, J. L., Kolla, S. B., Pick, D. L., Sountoulides, P., Kaufmann, O. G., Ortiz-Vanderdys, C. G., Huynh, V. B., Kaplan, A. G., Andrade, L. A., Osann, K. E., Louie, M. K., McDougall, E. M., and Clayman, R. V., 2010, "*In Vitro*, Ex Vivo and *In Vivo* Isotherms for Renal Cryotherapy," *J. Urology*, **183**(2), pp. 752–758.
- [34] Choi, J., and Bischof J. C., 2010, "Review of Biomaterial Thermal Property Measurements in the Cryogenic Regime and Their Use for Prediction of Equilibrium and Non-Equilibrium Freezing Applications in Cryobiology," *Cryobiology*, **60**(1), pp. 52–70.
- [35] Choi, J. H., and Bischof J. C., 2008, "A Quantitative Analysis of the Thermal Properties of Porcine Liver With Glycerol at Subzero and Cryogenic Temperatures," *Cryobiology*, **57**(2), pp. 79–83.
- [36] Patel, P. A., Valvano, J. W., Pearce, J. A., Pahl, S. A., and Denham C. R., 1987, "A Self-Heated Thermistor Technique to Measure Effective Thermal Properties From the Tissue Surface," *J. Biomech. Eng.*, **109**, pp. 330–335.
- [37] Zhang, M., Che, Z., Chen, J., Zhao, H., Yang, L., Zhong, Z., and Lu J., 2011, "Experimental Determination of Thermal Conductivity of Water-Agar Gel at Different Concentrations and Temperatures," *J. Chem. Eng. Data*, **56**(4), pp. 859–864.
- [38] Bergman T. L., Lavine A. S., Incropera F. P., and DeWitt D. P., 2011, *Fundamentals of Heat and Mass Transfer*, John Wiley & Sons, Hoboken, NJ.
- [39] Reed R. P., and Horiuchi T., 1983, *Austenitic Steels at Low Temperatures*, Plenum Publishing Corp., New York.
- [40] Jensen, J. E., Tuttle, W. A., Stewart, R. B., Brechna, H., and Prodell A. G., 1980, *Brookhaven National Laboratory Selected Cryogenic Data Notebook: Volume I*, Sections 1–9, Brookhaven National Lab., Upton, NY.
- [41] Rabinovich V. A., and Selover T. B., 1988, *Thermophysical Properties of Neon, Argon, Krypton, and Xenon*, Hemisphere PubCorp, Berlin, New York, Washington, DC.
- [42] Harvey A. H., 2012, "Properties of Ice and Supercooled Water," *CRC Handbook of Chemistry and Physics 2012–2013*, CRC Press, Boca Raton, FL, pp. 6–12.
- [43] Li C., 1976, "Thermal Conductivity of Liquid Mixtures," *AIChE J.*, **22**(5), pp. 927–930.
- [44] Angell, C. A., and Smith D. L., 1982, "Test of the Entropy Basis of the Vogel-Tammann-Fulcher Equation. Dielectric Relaxation of Polyols Near T_g ," *J. Phys. Chem.*, **86**(19), pp. 3845–3852.
- [45] Sun, T., and Teja A. S., 2003, "Density, Viscosity, and Thermal Conductivity of Aqueous Ethylene, Diethylene, and Triethylene Glycol Mixtures Between 290 K and 450 K," *J. Chem. Eng. Data*, **48**(1), pp. 198–202.
- [46] Silverman, S. G., Tuncali, K., Adams, D. F., vanSonnenberg, E., Zou, K. H., Kacher, D. F., Morrison, P. R., and Jolesz F. A., 2000, "MR Imaging-Guided Percutaneous Cryotherapy of Liver Tumors: Initial Experience," *Radiology*, **217**(3), pp. 657–664.
- [47] Wansapura, J. P., Daniel, B. L., Vigen, K. K., and Butts K., 2005, "*In Vivo* MR Thermometry of Frozen Tissue Using R2* and Signal Intensity," *Acad. Radiol.*, **12**(9), pp. 1080–1084.
- [48] Rossi, M. R., Tanaka, D., Shimada, K., and Rabin Y., 2008, "Computerized Planning of Cryosurgery Using Bubble Packing: An Experimental Validation on a Phantom Material," *Int. J. Heat Mass Transf.*, **51**(23), pp. 5671–5678.
- [49] Martin H., 1977, "Heat and Mass Transfer Between Impinging Gas Jets and Solid Surfaces," *Adv. Heat Transf.*, **13**, pp. 1–60.