

Development and Validation of a Novel Inverse Heat Transfer Model for Cryosurgical Tumor Characterization

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Abstract—This study aimed at developing an inverse heat transfer approach for predicting the time-varying freezing front and the temperature distribution of tumors during cryosurgery. Using a temperature probe pressed against the layer of tumor, the inverse approach is able to predict simultaneously the metabolic heat generation and the blood perfusion rate of the tumor. Once these parameters are predicted, the temperature-field and time-varying freezing fronts are determined with the direct model. The direct model rests on one-dimensional Pennes bioheat equation. The phase change problem is handled with the enthalpy method. The Levenberg-Marquardt Method (LMM) combined to the Broyden Method (BM) is used to solve the inverse model. The effect (a) of the thermal properties of the diseased tissues; (b) of the initial guesses for the unknown thermal properties; (c) of the data capture frequency; and (d) of the noise on the recorded temperatures is examined. It is shown that the proposed inverse approach remains accurate for all the cases investigated.

I. INTRODUCTION

CRYOSURGERY has become a well-established technique for the ablation of undesirable tissues such as tumors and cancers. It is an effective treatment for external tumors such as ear tumors and skin tumors, and for internal tumors such as lung tumors and breast tumors. Cryosurgery is often preferred to the traditional surgery due to the fact that it is minimally invasive and the hospitalization time is reduced.

Cryosurgery resorts to extreme cold for destroying diseased tissues. It works by taking advantage of the destructive effect of freezing temperatures on living cells. The instrument used to freeze the tissues is a cryoprobe. The low temperatures are obtained by circulating liquid nitrogen through the cryoprobe.

As illustrated in Fig. 1, the cryoprobe is inserted in such a way as to optimize the freezing of the tumor. When the rate of cooling is very high, ice crystals form inside the cells. These ice crystals damage the cell membrane and lead to the destruction of the tumor. Furthermore, the formation of ice crystals harms the blood vessels that supply the tumor tissue.

Destroying the diseased tissues while minimizing the damages to the surrounding healthy tissues is however a

challenging task. Sophisticated imaging techniques such as Magnetic Resonance Imaging (MRI) or ultrasounds must be used to guide the cryoprobe and monitor the freezing of the cells [1], [2]. But, these imaging techniques are often unavailable. Moreover, they cannot reproduce the timevarying temperature distribution inside the layer of tissue.

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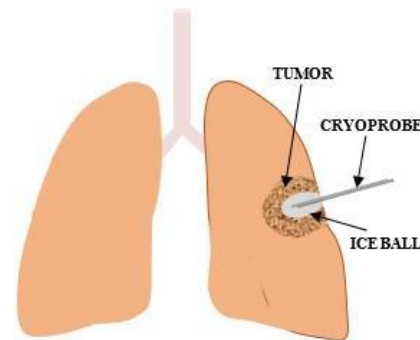


Fig. 1 Cryosurgery of lung tumor

An alternative to MRI or ultrasounds is the mathematical modeling of the heat transfer and the freezing processes that take place inside the tissues [3]-[6]. But, in order to perform the mathematical analysis, the thermal properties of the tissues, such as the metabolic heat generation and the blood perfusion, must be known. Measuring these properties with experimental techniques is however a complicated task [7], [8]. They require sophisticated equipment that can hardly be employed during cryosurgery. This is where inverse heat transfer methods come to the rescue [9]. In these methods, the unknown thermal properties may be determined by means of temperatures recorded by a temperature probe pressed against the layer of tissue.

Many studies based on inverse methods have been carried out in the past for predicting the blood perfusion coefficient [10], the unknown time-dependent surface heat flux in a living skin tissue [11], and the size and the location of the tumor [12]-[16]. Studies also focused on the

simultaneous estimation of various other thermo-physical properties using inverse approach [17]-[21].

In all the aforementioned investigations however, the prediction of the thermal properties of the biological tissues during cryosurgery was not carried out.

The main purpose of the present paper is to pursue the aforementioned studies by developing an inverse method capable of estimating the unknown metabolic heat generation rate and the blood perfusion rate during cryosurgery. Once these unknown parameters are determined, the temperature-field and the moving freezing front are predicted. Overall, the proposed method may become, one day, a viable alternative to more expensive imaging techniques that are used in cryosurgery.

This paper is organized as follows. First, a one-dimensional finite-volume model based on the Pennes bioheat equation and the non-isothermal phase change enthalpy method is developed. The model is then validated with an analytical solution available in the open literature. Second, an inverse procedure based on the Levenberg-Marquardt Method (LMM) combined to the Broyden Method (BM) is presented. Finally, the proposed inverse procedure is thoroughly tested for several freezing scenarios.

II. PROBLEM STATEMENT AND ASSUMPTIONS

Fig. 2 illustrates the one-dimensional phase change problem for cryosurgery. Three regions are considered: (1) the frozen zone whose time-varying interface position is $s(t)$, (2) the mushy zone and (3) the intact (unfrozen) zone. The lower and upper phase change interfaces are defined as the distance that separates the cryoprobe from the solidus temperature T_{sol} and the liquidus temperature T_{liq} , respectively. A freezing temperature T_c , which represents the temperature of the cryoprobe, is imposed on the left boundary condition (at $x = 0$). At the right boundary ($x=L_t$), the temperature gradient is set equal to zero. No heat is transferred as this boundary is far removed from the cryoprobe. The thickness of the tissue is set equal to $L_t=0.05$ m.

The mathematical model of cryosurgery rests on the following assumptions:

- Heat is predominantly transferred from the tissue to the cryoprobe. Thus, a one-dimensional heat transfer model can be applied [22].
- The blood perfusion rate and the metabolic heat generation are assumed to be uniform through time and space.

- The blood perfusion rate and the metabolic heat generation are set equal to zero in the frozen and in the mushy regions.
- The blood temperature is set equal to $T_b=37$ °C.
- The phase change of the diseased tissue is non-isothermal. The freezing process is characterized by three zones: a frozen solid zone, a mushy zone, and an unfrozen zone (Fig. 2).
- The liquidus temperature T_{liq} (the upper limit) and the solidus temperature T_{sol} (the lower limit) of the biological tissue are set equal to -1 °C and -8 °C, respectively [23], [24].
- The heat transfer inside the diseased tissue is conduction dominated [25], [26].
- The effect of large blood vessels is neglected [27], [28].

III. THE DIRECT PROBLEM

For the direct problem, all the thermo-physical properties, the initial and the boundary conditions are known. The mathematical model for the heat transfer inside the biological tissue is given by the fundamental Pennes bio-heat equation [29]:

$$\rho c \frac{\partial T}{\partial t} = \frac{\partial}{\partial x} \left(k \frac{\partial T}{\partial x} \right) + \omega_b \rho_b c_b (T_b - T) + Q_m - \delta H \frac{\partial f_s}{\partial t} \tag{1}$$

ρ , c , and k are the density, the specific heat, and the thermal conductivity of the tissue, respectively. The subscript ‘b’ refers to the blood characteristics. ω_b and Q_m represent the blood perfusion rate and the metabolic heat generation in the tissue, respectively. T is the tissue temperature, and T_b is the arterial blood temperature.

The last term on the right-hand side of (1) represents the liquid/solid phase change of the tissue during cryosurgery. δH and f_s are the enthalpy and the solid fraction during the phase change, respectively. The enthalpy δH is defined as $\delta H = (C_{solid} - C_{liquid})T$, and the solid fraction may be expressed as

$$f_s = \begin{cases} 0 & T > T_{liq} \text{ (Liquid)} \\ \frac{T - T_{sol}}{T_{liq} - T_{sol}} & T_{liq} > T > T_{sol} \text{ (Mushy regions)} \\ 1 & T < T_{sol} \text{ (Solid)} \end{cases} \tag{2}$$

At each time-step, the solid fraction f_s is updated iteratively according the following approximation

$$(3) \frac{d}{dt} \left(\int_{s(t)}^L k \frac{\partial T}{\partial x} dx \right) + \int_{s(t)}^L f_s dx = \rho c_p \frac{ds}{dt} + \int_{s(t)}^L f dx$$

F is a function of the temperature T . F^{-1} is the inverse function of F .

The boundary conditions at the right and left sides of Fig. 2 are defined by:

$$(4) \begin{cases} T(x=L, t) = T_c & \text{Right boundary} \\ T(x=0, t) = T_c & \text{Left boundary} \end{cases}$$

The initial condition is given by:

$$(5) T(x, t=0) = 37 \text{ }^\circ\text{C}$$

IV. THE INVERSE PROBLEM

In the inverse model, it is assumed that (1) the blood perfusion rate w_b and (2) the metabolic heat generation Q_m are unknown. They are estimated from the inverse method and then fed to the direct model that calculates the temperature distributions $T(x,t)$ and the phase change interface position $s(t)$. Therefore, the objective of the inverse method is to determine the unknown coefficients $P = (w_b, Q_m)$ by using temperature measurements taken from a temperature probe pressed against the diseased tissue (Fig. 4).

The estimation of these thermal properties can be constructed as a problem of minimization of the least square norm $\|Y - TtP\|_2$

$$(6) \min_P \|Y - TtP\|_2^2$$

where $P = (w_b, Q_m)$ is the set of unknown thermal parameters. I is the total number of measurements. $Y(t_i)$ are the temperatures (also called the direct temperatures) measured with the temperature probe. In the present study, these temperatures are 'generated' from the solution of the direct problem wherein the parameters $P = (w_b, Q_m)$ are specified.

The one-dimensional Pennes bio-heat equation (1) is solved by using a finite-volume method. The scheme adopted for the time discretization is implicit. The resulting set of algebraic equations is then solved by using the Tri-Diagonal-MatrixAlgorithm (TDMA) [30].

The mathematical model accuracy was validated by comparing it to the Neumann's solution. The freezing temperature was set equal to $T_c = -196 \text{ }^\circ\text{C}$. The metabolic heat generation and blood perfusion rate were set equal to zero. Fig. 3 compares the upper phase change interface position (liquidus temperature T_{liq}) predicted by the present model to the Neumann's solution. The agreement between both solutions is excellent.

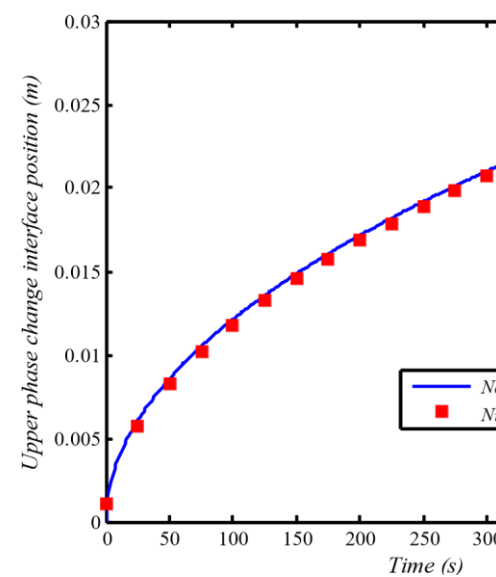


Fig. 3 Comparison of the FVM with Neumann's solution

$T(t, P)$ are the estimated temperatures from the inverse problem. Thus, the solution of the inverse problem is obtained when the least square norm (6) is minimized.

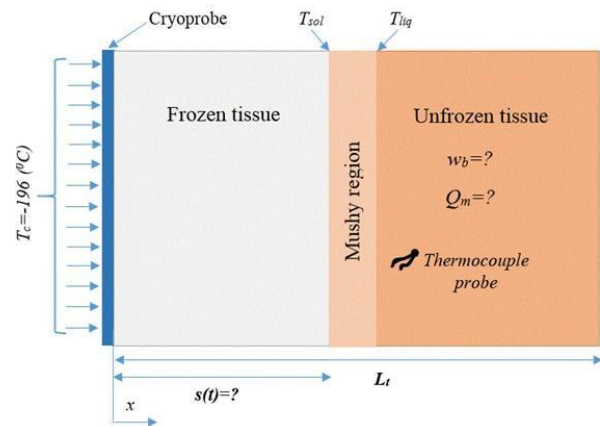


Fig. 4 Inverse problem of cryosurgery. w_b and Q_m are unknown. They are estimated from temperature measurements provided by a temperature probe

The *Levenberg–Marquardt* method is used for the solution of the present inverse problem. This method has been successfully applied to inverse problems in the past [31], [32]. In this iterative method, the incremental value of the unknown parameters ΔP , is written as:

$$\Delta P = - (J^T J + \alpha I)^{-1} J^T (T - T^e) \quad (7)$$

α is a positive scalar, called the ‘damping parameter’. The choice and the update of this parameter are discussed in

[33]. $I = \text{diag} \{J_{11}^2, J_{12}^2, \dots, J_{1N}^2\}$ is a diagonal matrix.

J_{ij} is the ‘sensitivity matrix’, also called the ‘Jacobian matrix’

$$J = \begin{bmatrix} T_1 & T_1 \\ w_b & Q_m \\ \vdots & \vdots \\ T_2 & T_2 \\ w_b & Q_m \end{bmatrix} \quad (8)$$

The *Jacobian matrix* plays a crucial role in the estimation of the thermal parameters. In fact, there are several approximations for computing the Jacobian matrix [9]. In the current study, the Jacobian matrix is approximated with a finite difference approximation

$$J_{ij} = \frac{\partial T_i}{\partial P_j} = \frac{T(t_i, x_i; P_1, \dots, P_j + \Delta P_j, \dots, P_N) - T(t_i, x_i; P_1, \dots, P_j, \dots, P_N)}{\Delta P_j} \quad (9)$$

The subscripts i and j represent the time and the parameter, respectively. The parameter perturbation ΔP_j is set to ϵP_j , where ϵ is an arbitrary small number.

In order to reduce the computational effort, the Jacobian matrix is updated using the *Broyden* method [34].

$$J_{k+1} = J_k + \frac{(T_{k+1} - T_k) - J_k \Delta P_k}{\Delta P_k^T \Delta P_k} \Delta P_k \quad (10)$$

ΔP_k is the incremental value of the unknown parameters. T_k are the estimated temperatures. Further details about this

inverse method are provided in [35]-[38].

The main steps involved in the computational procedure for the direct and the inverse problems are summarized in Figs. 5 and 6, respectively.

V. RESULTS AND DISCUSSION

In order to evaluate the temperature distribution $T(x,t)$ and the time-varying phase change interface position $s(t)$, the unknown thermal properties of the biological tissue must first be determined. To achieve this task, the above inverse procedure (Fig. 6) was implemented. It predicts simultaneously the metabolic heat generation Q_m and the blood perfusion rate w_b . Once these thermal parameters are obtained, the temperature distribution $T(x,t)$ and the timevarying phase change interface position $s(t)$ are calculated with the direct model described in Section III.

The freezing temperature was fixed at $T_c = -196$ °C, and the thickness of tissue was set equal to 0.05 m. The duration of cryosurgery was set equal to $t = 500$ s. The total number of measurements (temperatures recorded by the temperature probe during cryosurgery) is set equal to $I = 50$.

All simulations presented here were conducted with a grid space of $dx = 2.5 \cdot 10^{-4}$ m and a time step of $dt = 10$ s. Additional simulations were conducted to make sure that the predictions are grid space and time step independent. All simulations were performed using the MATLAB software running on an Intel® Core(TM) i5-2520M CPU@ 2.50 GHz.

In order to demonstrate the ability of the inverse method for determining the blood perfusion rate and the metabolic heat generation, two different diseased tissues (lung tumor and breast tumor) were considered. The thermal-physical properties of these diseased tissues are summarized in TABLE I [39]-[41].

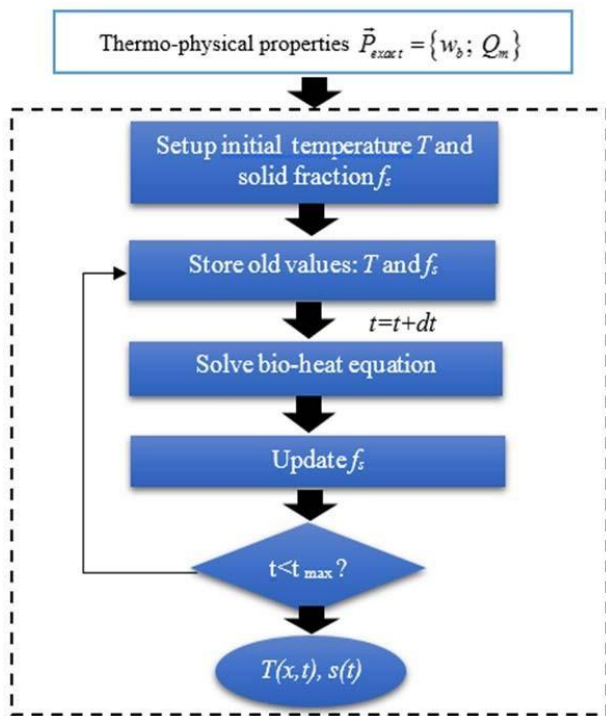


Fig. 5 The direct problem

To characterize the accuracy of the proposed inverse method, two relative errors ‘for the blood perfusion rate and the metabolic heat generation’ are used. These errors are defined as

$$Error_{w_b} \% = 100 \left| \frac{w_b^{exact} \cdot w_b^{inverse}}{w_b^{exact}} \right| \quad (11)$$

$$Error_{Q_m} \% = 100 \left| \frac{Q_m^{exact} \cdot Q_m^{inverse}}{Q_m^{exact}} \right| \quad (12)$$

The superscripts ‘exact’ and ‘inverse’ refer to the exact solution obtained with the direct model and the inverse

solution predicted by the inverse model, respectively.

TABLE I
THERMO-PHYSICAL PROPERTIES OF

	Symbol	Unit
Specific heat of unfrozen tumor tissue	c_u	J/kg·K
Specific heat of frozen tumor tissue	c_f	J/kg·K
Thermal conductivity of unfrozen tumor tissue	k_u	W/m·K
Thermal conductivity of frozen tumor tissue	k_f	W/m·K
Density of unfrozen tumor tissue	ρ_u	kg/m ³
Density of frozen tumor tissue	ρ_f	kg/m ³
Lower phase transition temperature	T_{sol}	°C
Upper phase transition temperature	T_{liq}	°C
Latent heat of freezing	L	J/kg
Blood temperature	T_b	°C
Blood specific heat capacity	c_b	J/kg·K
Blood density	ρ_b	kg/m ³
Blood perfusion rate	w_b	ml/ml.t.s
Metabolic heat generation	Q_m	W/m ³

w_b (ml/ml.t.s)

The effect of the initial guess values of the blood perfusion rate and of the metabolic heat generation on the convergence of the inverse model is shown in Figs. 7 and 8, respectively. The initial guesses for *test#1*, *test#2*, *test#3*, and *test#4* were set equal to 1/3, 1/5, 1/7, and 1/9 of that of the exact value, respectively. It is seen that the convergence of the inverse method is excellent in all cases.

The results of the inverse predictions are summarized in Table II. Examination of this table reveals that the prediction of the blood perfusion rate and of the metabolic heat generation are good for the both tumors. The maximum recorded error is less than 0.7%.

Fig. 7 Convergence of blood perfusion rate (lung tumor)

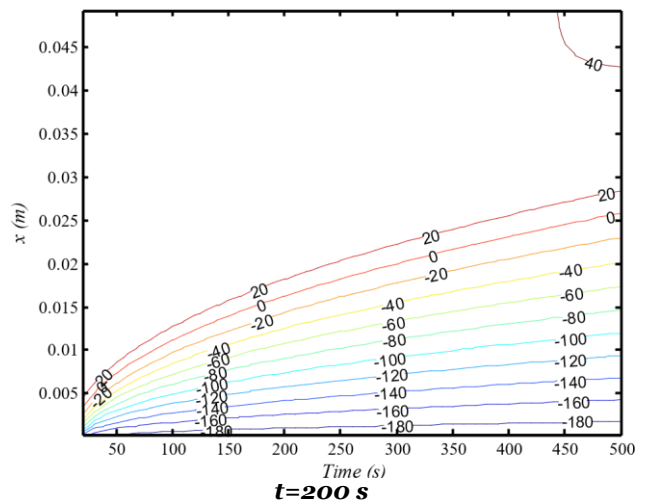
$\times 10^4$

Fig. 9 compares the exact and the estimated motion of the lower phase change interface $s(t)$ during the freezing process for the both tumors. It is seen that the inverse solution (the solution obtained from the inverse model) and the exact solution (the solution provided by the direct model) are in perfect agreement. One may observe that the phase change interface position in the lung tumor gets ahead of the breast tumor. This is due the smaller blood perfusion rate of the lung tumor (0.002 ml/s.ml) compared with the breast tumor (0.009 ml/s.ml).

TABLE II
INVERSE PREDICTION OF BLOOD PERFUSION AND METABOLIC HEAT GENERATION

	<i>Parameter</i>	P_{Exact}	$P_{Inverse}$	<i>Error%</i>
Lung cancer	w_b	$2 \cdot 10^{-3}$	$2.0 \cdot 10^{-3}$	0
	Q_m	$4.2 \cdot 10^4$	$4.18 \cdot 10^4$	0.48
Breast tumor	w_b	$9 \cdot 10^{-3}$	$9 \cdot 10^{-3}$	0
	Q_m	$2.9 \cdot 10^4$	$2.88 \cdot 10^4$	0.69

for both tumors are also presented in Fig. 10.



Time (s)

Fig. 11 Effect of cryosurgery duration on temperatures distribution

Fig. 10 Temperature distribution for both tumors

on The temperature contours predicted with the inverse model the inverse predictions. The duration of cryosurgery was set equal to 200, 500, and 800 s. It is seen that the inverse predictions of the metabolic heat generation and of the blood perfusion rate are good for all cases. The relative error recorded is less than 0.5%. The corresponding temperature contours are depicted in Fig. 11. As expected, the freezing region expands with increasing duration of cryosurgery.

TABLE III EFFECT OF CRYOSURGERY DURATION ON INVERSE PREDICTIONS

Time (s)	Parameter	$P_{inverse}$	Error%
200	w_b	$2.0 \cdot 10^{-3}$	0
	Q_m	$4.198 \cdot 10^4$	0.2
500	w_b	$2.0 \cdot 10^{-3}$	0
	Q_m	$4.18 \cdot 10^4$	0.4
800	w_b	$2.0 \cdot 10^{-3}$	0
	Q_m	$4.19 \cdot 10^4$	0.2

A. Effect of Noise on the Inverse Predictions

In this section, the temperatures recorded by the temperature probe were contaminated with measurement errors (or noise) using a random number generator ($randn$). These measurement errors are added to the recorded temperatures (the exact temperatures T_{exact} provided by the direct model):

$$T_{noise}(t_i) = T_{exact}(t_i) + \sigma \cdot randn_i \quad (13)$$

σ is the standard deviation of the measurement errors. The value for σ is arbitrarily set equal to 2% T_{max} and to 4% T_{max} . T_{max} is the maximum temperature measured by the temperature probe.

Table IV summarizes the effect of the noise and of the total number of measurements I on the inverse predictions. As expected, when the noise level rises from 2% T_{max} to 4% T_{max} , the relative errors on the predicted blood perfusion rate and metabolic heat generation increase. Nevertheless, the inverse method remains stable and accurate. On the other hand, when the total number of measurements is increased from $I=50$ to $I=100$, the relative errors drop.

TABLE IV EFFECT OF NOISE AND OF I ON THE INVERSE PREDICTIONS

TABLE III presents the effect of cryosurgery duration

		$I=50$	$I=100$
$\sigma=0\%$ (no noise)	$Error_{wb}$	0	0
	$Error_{Qm}$	0.48	0.23
$\sigma=2\%$	$Error_{wb}$	7.11	5.10
	$Error_{Qm}$	18.05	7.04
$\sigma=4\%$	$Error_{wb}$	31.56	5.41
	$Error_{Qm}$	36.55	18.39

VI. CONCLUSION

This paper presented an inverse heat transfer approach for predicting the time-varying phase change interface and the temperature distribution of diseased tissue during cryosurgery. Using a temperature probe pressed against the layer of diseased tissue, the inverse approach is able to determine simultaneously the metabolic heat generation and the blood perfusion rate. Once these thermal properties are obtained, the temperature distribution and the time-varying phase change interface may be predicted with the direct model. The direct problem is handled with the Pennes bioheat equation and the enthalpy method. The inverse model rests on the LevenbergMarquardt Method (LMM) combined to the Broyden Method (BM). The effect (1) of the initial guesses for the unknown thermal properties; (2) of the thermal properties of the diseased tissues; (3) of the data capture frequency; and (4) of the noise on the recorded temperature was investigated. It was shown that the proposed inverse method remains accurate and stable for all the cases investigated.

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NOMENCLATURE

- c specific heat [J/kg°C]
- dt time step [s]
- fs solid fraction
- I total number of measurements
- J Jacobian matrix
- k thermal conductivity [W/m°C]
- L latent heat of freezing [J/kg]
- L_t thickness of tissue [m]
- N number of unknown parameters
- P vector of unknown parameter
- Q_m metabolic heat generation [W/m³]
- $Error$ estimation errors [%]
- $s(t)$ freezing front position [m]
- t time [s]

\hat{T}	estimated temperature [$^{\circ}\text{C}$]
T_b	arterial blood temperature [$^{\circ}\text{C}$]
T_c	cryogenic probe temperature
$[\text{C}] x$	cartesian spatial coordinate [m]
Y	measured temperature [$^{\circ}\text{C}$]
	w_b blood perfusion rate [ml/s ml]

A. Greek Symbols

•	small number
•	damping parameter
•	density of tissue [kg/m^3]
•	standard deviation of the measurement error
•	sum of squares norm
•	small number
• H	enthalpy [J/m^3]
•	difference
• k	diagonal matrix
•	random number

B. Subscripts

b	blood
$exact$	exact solution
f	frozen region
liq	liquidus
max	maximum
u	unfrozen region
P	parameter
sol	solidus
T	temperature

C. Superscripts

k	time iteration number
T	transposed matrix
\square	estimated parameter
\square	vector
\square	matrix

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