A Three-State Thermal Cell Death Model for the Assessment of Esophageal Damage in Cardiac Ablation

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Abstract

Radiofrequency ablation is widely used for treating atrial arrhythmias, but unintended thermal exposure of the esophagus can lead to severe complications such as atrioesophageal fistula. Existing computational models predict thermal damage based on Arrhenius kinetics but do not capture tissue recovery processes.

We propose a three-state cell death model that distinguishes native, unfolded, and denatured esophageal cells, and incorporates a gamma-distributed recovery function to represent tissue regeneration. The model is calibrated using published experimental thresholds of esophageal damage and reproduces both reversible and irreversible responses across clinically relevant thermal exposures.

We integrate the model into a patient-specific ablation simulation framework. Results demonstrate that the method can differentiate between transient and permanent injury, thereby improving the predictive capability of computational tools for esophageal safety assessment during ablation procedures.

1. Introduction

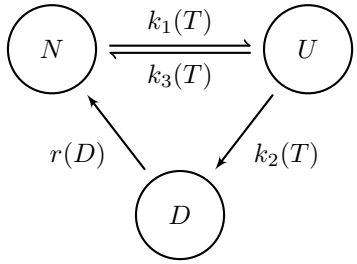
Radiofrequency ablation is a common treatment for cardiac arrythmias. Although a generally safe procedure, it is not exempt from complications. In particular, during pulmonary vein isolation or when the ablation is performed on the left atrial posterior wall, a non-negligible risk for hyperthermic exposure of proximal tissues, most notably the esophagus and adjacent connective tissue, exists. In the worst case scenario, it can lead to the formation of an atrioesophageal fistula, a complication which affects less than 0.1% of patients, but whose associated mortality rate is more than 71% [1].

To date, no reliable computational framework exists for predicting esophageal thermal injury during ablation procedures. Previous work, such as the Arrhenius-based damage model proposed in [2], provides a first step toward quantifying esophageal injury, but it does not incorporate key biological processes such as cellular turnover and tissue recovery. In this study, we introduce a three-state model that explicitly accounts for these processes, and we calibrate the model specifically for esophageal tissue.

2. Methods

2.1. Three-state model with recovery

We develop a three-state cell death model to estimate the risk of damage to the esophagus during radiofrequency ablation to prevent the formation of atrial-esophageal fistula in the recovery period. An extension of the established cell death model for cardiac cells [1] is proposed to capture the regenerative capabilities of esophageal tissue, by introducing a tissue condition dependent regeneration term. We denote by N, U and D the cells in the native, unfolded and denaturated state respectively. The model is summarized as



where the transition rates $k_i(T)$, $i = 1, 2, 3$ depend on the temperature T, and follow an Arrhenius type equation

$$k_i(T) = A_i \cdot e^{-\Delta E_i/(RT)}, i = 1, 2, 3,$$

with A_i being the frequency factor, ΔE_i the activation energy and R the universal gas constant; $r(D)$ is the proposed recovery function of the esophageal cells. The governing system of differential equations is

$$\begin{aligned}\frac{dN}{dt} &= -k_1(T)\,N + k_3(T)\,U + r(D),\\ \frac{dU}{dt} &= k_1(T)\,N - (k_2(T) + k_3(T))\,U,\\ \frac{dD}{dt} &= k_2(T)\,U - r(D).\end{aligned} \tag{1}$$

2.2. State conservation

The values for N, U, D are to be understood as percentages of the considered unit of tissue at different states. Therefore, the state conservation condition $1 = N+U+D$ is applied, assuming that the total amount of cells in a tissue area remain constant. Additionally, the system is initialized by assuming all cells to be in their natural state $(N, U, D) = (1, 0, 0)$.

2.3. Recovery function

Crucial for this approach to work is the way in which the recovery term depends on the number of denatured cells. To preserve the state conservation, the recovery function needs be zero when there are no cells in the denatured compartment, $p(0) = 0$, and further $\lim_{D\to 1} p(D) \to 0$. Additionally, to match the physiological tissue response, the model should remain stable around $(1, 0, 0)$ at physiological condition ($T = 37\,^\circ\mathrm{C}$), which means a rather strong recovery is needed for low values of D.

Following these considerations, the best suited recovery function follows the probability density function of the Gamma distribution, and is written as

$$r(D) = A_4 \cdot \frac{\beta^\alpha}{\Gamma(\alpha)} D^{(\alpha-1)} e^{-\beta D},$$

where A_4 is the frequency factor, and α and β are shape parameters of the recovery function.

2.4. Lesion estimation

As there is no data available for the identification of esophageal lesions, the approach in [3] following the data presented in [4] is considered. In particular, all cells below the threshold of $N_{thr} = 0.8$ at the final time are considered irreversibly damaged. The final time considered corresponds to the cellular turnover period of 2 weeks.

3. Results

The proposed 3-state model is numerically solved using a first order implicit-explicit scheme, treating the nonlinear term explicitly and the other terms implicitly in time. A finer time step-size of $\Delta t = 0.1\,\mathrm{s}$ is considered for the first $500\,\mathrm{s}$, followed by a coarser one of $\Delta t = 10\,\mathrm{s}$ until the final time of $14\,\mathrm{days}$.

3.1. Model calibration

The proposed model has been calibrated to obtain physiological response for esophageal tissue cells. In particular, following the relevant literature, the criteria below were established:

- Healthy condition at temperatures of $37\,^\circ\mathrm{C}$, i.e. $(N, U, D) = (1, 0, 0)$,
- No noticeable differences at $40\,^\circ\mathrm{C}$ for any reasonable time period [5],
- No damage at $50\,^\circ\mathrm{C}$ for $30\,\mathrm{s}$, light and moderate damage for $60\,\mathrm{s}$ and $90\,\mathrm{s}$ respectively [5],
- Critical damage for temperatures above $50\,^\circ\mathrm{C}$ [6],
- Severe damage at $60\,^\circ\mathrm{C}$ [5],
- Reversible damage after two weeks for short exposure time at $60\,^\circ\mathrm{C}$ [6],
- Esophageal cells 11-day turnover rate of more than 80% under physiological conditions [7].

Table 1. Calibrated parameter values for esophageal damage using the proposed three-state model with recovery.

Name	Unit	Value	
A_1	(s^{-1})	2×10^{73},	$T \leq 55\,^\circ\mathrm{C}$
		3.56×10^{22},	$T > 55\,^\circ\mathrm{C}$
A_2	(s^{-1})	5.35×10^{11}	
A_3	(s^{-1})	1.6×10^{15}	
ΔE_1	$(\mathrm{J/mol})$	467.6×10^3,	$T \leq 55\,^\circ\mathrm{C}$
		144.7×10^3,	$T > 55\,^\circ\mathrm{C}$
ΔE_2	$(\mathrm{J/mol})$	87×10^3	
ΔE_3	$(\mathrm{J/mol})$	105.1×10^3	
A_4	(s^{-1})	7.891×10^{-7}	
α	(-)	1.5	
β	(-)	6	

To match the literature physiological response, a similar approach as in [3] is followed, imposing a constant temperature for a given amount of time and then allowing for

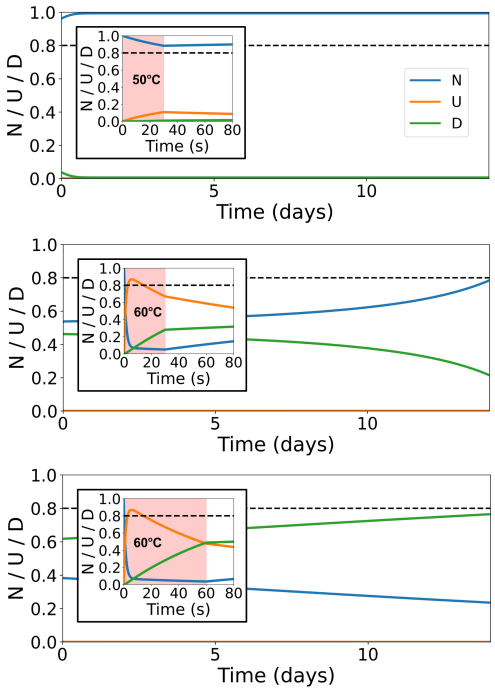


Figure 1. The native N, unfolded U and denaturated D states of esophageal cells under a fixed temperature for 30 or 60 seconds (shaded red area) acutely and after 2 weeks.

tissue recovery by imposing $37\,^{\circ}\mathrm{C}$. The calibrated parameters appear in Table 1.

The model response for applications of $50\,^{\circ}\mathrm{C}$ for $30\,\mathrm{s}$, and $60\,^{\circ}\mathrm{C}$ for $30\,\mathrm{s}$ and $60\,\mathrm{s}$ appears in Figure 2. Following the patient data from [6], we observe that the esophageal tissue recovers for exposures of $60\,^{\circ}\mathrm{C}$ up to $30\,\mathrm{s}$ within 2 weeks, while longer exposures result in irreversible damage.

3.2. A patient-specific application

Computational domain. A 3D torso model of a 73 years old male patient from the Hospital de la Santa Creu and Sant Pau in Barcelona (Spain) was developed for a previous study of our group [8]. The torso accounts for 38 distinct and labeled subdomains, all equipped with specific conductivities. The catheter (featuring a spherical tip electrode of $7\,\mathrm{F}$ and $3.5\,\mathrm{mm}$ length, common in the market) traverses at the centerline of the inferior vena cava, enters the right atrium (RA), pierces the interatrial septum and is placed on the posterior wall of the left atrium, the most at-risk position for esophageal damage. Finally, a a dispersive patch of $8 \times 16.75\,\mathrm{cm}^2$ was placed horizontally in the center of the back of the patient, a standard approach in the clinic.

A tetrahedral mesh of the multi-labeled segmentation of the torso was obtained with Studio software from NumeriCor GmbH (`www.numericor.at`), while the catheter and electrode geometries were created using the Salome software (`https:www.salome-platform.org`).

We refer the reader to [8] for a detailed description of the computational domain and its characteristics.

Mathematical model. A modified Penne's bioheat equation models the temperature changes in the system, with an electric heat source. The cooling effect of the blood flow and the irrigated saline are lumped via a penalization term in the blood subdomain. The electrical potential follows a quasi-static elliptic equation augmented with a power constraint and is solved along with the bioheat equation in the entire domain. The system reads as:

$$\rho c \frac{\partial T}{\partial t} - \operatorname{div}(k \nabla T) = \sigma |\nabla \Phi|^2 - \gamma\,(T - T_X) - Q_p$$

$$\operatorname{div}(\sigma \nabla \Phi) = 0 \qquad \int_\Omega \sigma \nabla \Phi \cdot \nabla \Phi \, dx = P.$$

In the above system, T is the temperature, Φ is the electrical potential, ρ is the density, c is the specific heat, k and σ are thermal and electrical conductivities, T_X is a penalization term in the blood and electrode subdomains ($T_b = 37\,^{\circ}\mathrm{C}$, $T_e = 38\,^{\circ}\mathrm{C}$), $\gamma = 4 \times 10^7\,\mathrm{J/(m^3 sK)}$ is a scaling factor, $Q_p = \rho c \omega_b (T - T_b)$ is the cardiac tissue perfusion, $\omega_b = 1.4 \times 10^{-2}\,\mathrm{s}^{-1}$ is the perfusion rate, Ω is the computational domain, while P is the power dissipated in the system, which depends on the ablation protocol. All parameters are both temperature and subdomain dependent, and their values come from the IT'IS database [9].

A voltage $\Phi = V_0$ is applied at the upper boundary of the electrode, and tuned to satisfy the power constraint [8]. A ground condition ($\Phi = 0$) at the dispersive patch closes the circuit, while the remaining torso boundary and the catheter body are considered insulated ($\partial\Phi/\partial n = 0$). Body temperature of $37\,^{\circ}\mathrm{C}$ is applied to the exterior of the torso. The simulations were conducted using our in-house developed AblaFEMx library, which is built on the open-source FEniCSx software. An open access version of the library can be found in `https://linzlabinsilmed.github.io/`.

Results. An ablation protocol of $25\,\mathrm{W}$ for $30\,\mathrm{s}$ [10] is simulated, followed by a $30\,\mathrm{s}$ relaxation. The 3-state system is then solved for all the affected esophageal cells for the 2 weeks turnover period. Figure 2 shows the results of the simulation. Some esophageal damage is observed, which is transient and recovers within the turnover period of the esophageal cells.

4. Conclusions

Our study presents a new model for the estimation of esophageal cell thermal damage that accounts for cellular turnover. The model has been calibrated to reproduce well

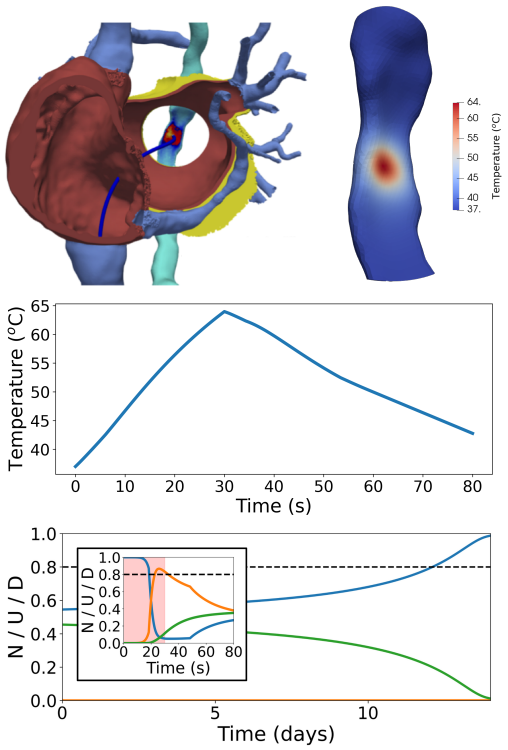


Figure 2. Top: position of the electrode on the posterior wall and temperature distribution in the esophagus. Mid: evolution of max temperature in the esophagus. Bottom: native N, unfolded U and denaturated D cell in the position corresponding to the max temperature reached by the esophagus during ablation.

understood physiological aspects of thermal damage to the esophageal tissue. We also showed how the model can complement existing computational frameworks for ablation simulations in order to estimate the esophageal damage. effectively improving their predictive capability, and enhancing treatment planning and safety.

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