Modelling of thermally induced electrical instabilities in intestine using Comsol Multiphysics

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Abstract: Postoperative or paralytic ileus (PI) is a temporary aftermath of major abdominal surgeries. PI prevents the passage of food throughout the lumen leading to bloating, distension, emesis and pain. A plausible mathematical model for this phenomenology physiologically fine tuned including thermal variations, is presented here. Using COMSOL Multiphysics the existing intestinal ionic model have been implemented in three-dimensions.

Keywords: Mathematical modelling, FEM, Intestine tissue, Thermo-ionic coupling

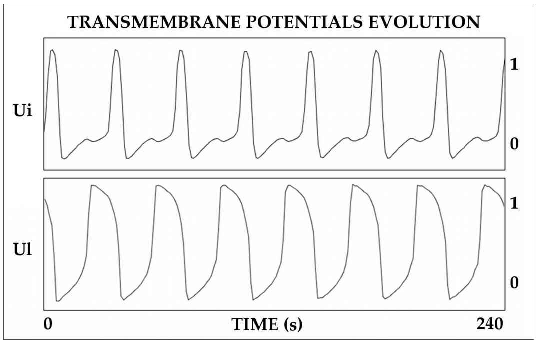

Figure 1: Time evolution of the transmembrane potentials at fixed position $x = 120\,cm$.

1 Introduction

Many interacting factors (surgical trauma and inflammatory reactions as examples [1, 2]) contribute to paralysis of the intestine known as paralytic ileus (PI). Currently, no drugs are available to fully treat this condition and little is known about the pathogenesis of this disorder. Anatomically intestine integrates the functions of many types of different cells and tissues [3]. Focusing on the first part of small intestine (duodenum) the electrophysiological regime is governed by an excitable double layered structure: longitudinal muscle (LM) and interstitial cells of Cajal (ICC). In most regions of the gastrointestinal tract (GI), an interconnected network of ICC generates pacemaker potentials which conduct the signal passively to the adjacent longitudinal and circular muscle layers where they produce rhythmical waves of membrane depolarization [4]. In this paper we discuss implementation via COMSOL Multiphysics of the mathematical model introduced in Ref. [5].

2 Governing Equations

The electrical activity of the small intestine in humans consists of repetitive depolarizations which act by changing the excitability of intestinal muscles producing spikes and contractile responses [6]. Electric dynamics in the intestine layers is here described by a pair of PDEs for each layer as reported in the Aliev-Richards-Wikswo ionic model [7]. Based on a FitzHugh-Nagumo type structure [8], which is widely used to simulate as a first step the dynamics of many excitable biological tissues [9], the first equation of each pair has a characteristic N-like nullcline [10] and describes the dynamics of the transmembrane potential; the second equation describes slow transmembrane currents ensuring membrane repolarization. Indicating with subscription "l" and "i" the two layers (LM and ICC respectively) and with Δ the Laplace operator in Cartesian coordinates, we consider an homogenous and isotropic tissue (in reason of lack in experimental data) writing down the following reaction-diffusion system

$$\begin{aligned}\partial_t U_l &= f\left(U_l\right) + D_l \Delta U_l - V_l + F_l\left(U_l, U_i\right)\\ \partial_t V_l &= Q_{10}\left(T\right)\zeta_l[\delta_l\left(U_l - \alpha_l\right) - V_l]\\ \partial_t U_i &= g\left(U_i\right) + D_i \Delta U_i - V_i + F_i\left(U_l, U_i\right)\\ \partial_t V_i &= Q_{10}\left(T\right)\zeta_i\left(z\right)\left[\delta_i\left(U_i - \alpha_i\right) - V_i\right] \qquad (1)\end{aligned}$$

where

$$f\left(U_l\right) = \gamma_l U_l\left(U_l - b_l\right)\left(1 - U_l\right) \qquad (2)$$

$$F_l\left(U_l, U_i\right) = \mu_l D_{li}\left(U_l - U_i\right) \qquad (3)$$

$$g\left(U_i\right) = \gamma_i U_i\left(U_i - b_i\right)\left(1 - U_i\right) \qquad (4)$$

$$F_i\left(U_l, U_i\right) = \mu_i D_{il}\left(U_l - U_i\right). \qquad (5)$$

Variables U and V stand for non dimensional transmembrane potentials and slow currents, respectively (time is measured in seconds and space in centimeters) although it is possible to obtain physical dimensions related to human or animal tissue by appropriate mappings. In figure (1) the time evolution of the two non dimensional transmembrane potentials is reported. The excitability parameter for the ICC layer is a function of the distance from pylorus, i.e. in agreement with experimental interpolation plot reported in [7]. Specifically we were able to extract its analytical form as (6).

$$\zeta_i\left(z\right) = 0.032 + 0.05\exp\left(-\frac{z}{68}\right) \qquad (6)$$

Heat transfer in biological systems is relevant in many diagnostic, surgical and therapeutic applications [11]. This class of problems has been traditionally addressed using Pennes bioheat equation (BHE) [12]. Heat conduction and perfusion contributions are combined here in a generalized BHE [13, 14]

$$\partial_t T = \Gamma \Delta T + \Omega\left(T_a - T\right) + Q \qquad (7)$$

where model parameters are reported in Appendix and in Ref. [15]. Electro-thermal coupling in biological media is introduced following the traditional formulation used in electrophysiological models [16] as shown in equation (1). We adopted the exponential form $Q_{10} = B\exp\left[\left(T - T_a\right)/10°C\right]$ where $T_a = 37°C$ is the reference tissue temperature and $B = 2.6$ is the physiologically tuned parameter.

3 Numerical Models with COMSOL Multiphysics

The spatial domain is characterized by the two LM and ICC layers physically distinct but mathematically coincident, thus identifying a single frame of reference. Uniform constant fields are assumed as initial value for both the problems while boundary values have been imposed as Nuemann zero flux for the ionic model (1) and Dirichlet time-dependent conditions for the thermal one (7) (see ref. [5] for clinical reasons of this choice). An example of the latter boundary condition is

$$T_{Eb} = T_E + \left(T_a - T_E\right)\exp(-t/\tau) \qquad (8)$$

where $\tau = 400\,s$ represents the time constant by which tissue temperature decreases towards thermal regime; T_E is the asymptotic values reached after about $3 \times \tau$ time in the subdomain. The model has been explored specifically through a General Form and time-dependent COMSOL Multiphysics code. We adopted Lagrange quadratic tetrahedral elements with Linear system Geometric Multigrid solver and a BDF method to minimize the amount of RAM required. A schematic representation of the adopted mesh and geometry model, together with the main modelling applications is reported in figures (2) and (3).

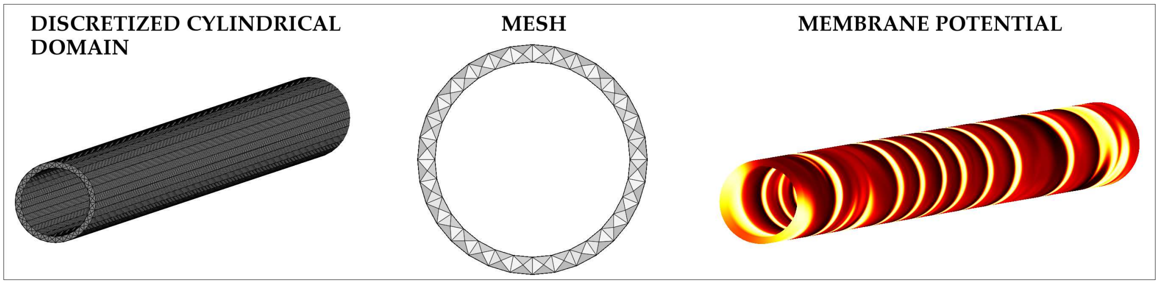

Figure 2: 3D geometry, mesh and membrane potential evolution. A thin cylindrical layer $[240 \times 10 \times 0.2]\,cm$ has been discretized through an adapted mesh method which leads to about 3×10^4 nonlinear quadratic elements (about 8×10^5 degrees of freedom). Color map shows U_l waves with action potentials in yellow.

The discretized domain structure is showed from two different perspectives in order to give a better representation of the adopted geometry. The solutions have been performed using a UMFPACK FEM solver requiring a reduced amount of RAM and CPU. The 3D multiphysics study needs a finite thickness ($0.2\,cm$) to impose internal and external thermal boundary conditions as well as to represent physical gradients inside the tissue. In the latter case, a thin cylindrical tube has been taken as evolution domain and we assumed constant lumen diameter, internal and external radii. The 3D FEM model consisted of about 8×10^5 degrees of freedom with 3×10^4 Lagrange quadratic tetrahedral elements generated by a swept mesh method. Numerical calculations have required about 5Gb of RAM on an Intel Xeon dual core workstation on which we were able to simulate about $60\,s$ of evolution per day of computation.

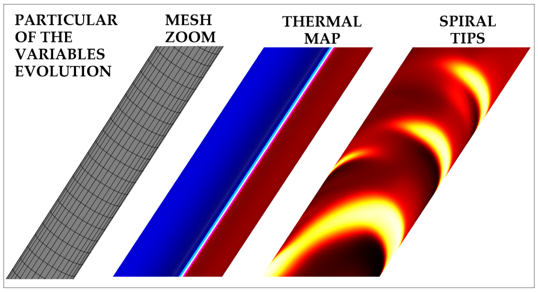

Figure 3: 3D particular of the adopted swept mesh, thermal map and spiral waves. Numerical results of the adopted ionic model in higher dimensions showed as temperature gradients induces action potential instabilities leading to turbulent persistent spiral behavior.

4 Results and Discussion

The proposed modelling achieved using COMSOL Multiphysics can be considered an extension of the 1D Aliev-Richards-Wikswo model to higher dimensions as well as an interesting multiphysics problem by coupling heat transfer equation with GI ionic activity (for more applications see [17, 18]). Steep electrical tissue stimulations as well as thermal cooling showed sustained turbulent electrical patterns as a result of the multiphysics mathematical implementation obtained in COMSOL 3.5a. Intestinal activities gave rise to spiral wave behaviors both in two and three dimensions, which are a well known problem in many biological and clinical contexts and may be experimentally associated with the destabilization of the physiological motility following abdominal surgery [19, 20]. The proposed thermoionic study can be widely generalized to any kind of biological modelling using the direct implementation available in COMSOL Multiphysics.

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Appendix

LM layer		**ICC layer**	
$\gamma_l = 10$	$b_l = 0.06$	$\gamma_i = 7$	$b_i = 0.5$
$\alpha_l = 0$	$\delta_l = 8$	$\alpha_i = 0.5$	$\delta_i = 8$
$\zeta_l = 0.15$	$\mu_l = 1$	$\zeta_i = \zeta_i(x)$	$\mu_i = -1$
$D_{li} = 0.3$	$D_l = 0.4$	$D_{il} = 0.3$	$D_i = 0.04$

Table 1: Aliev-Richards-Wikswo DML intestine ionic model parameters [7].

Parameter	**Value**
L	$240.0\,cm$
R_i	$1.8\,cm$
R_e	$2.0\,cm$
U	$[-0.4 \div 1]$
V	$[-0. \div 1]$
T	$[20 \div 37]°C$
T_a	$37°C$
Γ	$1.4 \times 10^{-3}\,cm^2 s^{-1}$
Ω	$6.9 \times 10^{-3}\,s^{-1}$
Q	$1.62 \times 10^{-4}\,°C s^{-1}$

Table 2: Geometrical domain dimensions, model variables and model parameters referred to human abdominal core and whole blood ($Hct = 40\%$) adopted to perform numerical simulations [15, 17].