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(Article begins on next page)

In silico model of colon electromechanics for manometry prediction *after* laser tissue soldering

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Abstract

The present study introduces an advanced multi-physics and multi-scale modeling approach to investigate *in silico* colon motility. We introduce a generalized electromechanical framework, integrating cellular electrophysiology and smooth muscle contractility, thus advancing a first-of-its-kind computational model of *colon motility after intraluminal* laser tissue soldering. The proposed theoretical framework comprises three main elements: a microstructural material model describing intestine wall geometry and composition of reinforcing fibers, with four fiber families, two active-conductive and two passive; an electrophysiological model describing the propagation of slow waves, based on a fully-coupled nonlinear phenomenological approach; and a thermodynamical consistent mechanical model describing the hyperelastic energetic contributions ruling tissue equilibrium under diverse loading conditions. The active strain approach was adopted to describe tissue electromechanics, thus solving the governing equations via a staggered finite element scheme. The computational framework was fine-tuned according to state-of-the-art experimental evidence, and extensive numerical analyses *were conducted to compare and contrast clinical* manometric traces. The model proved capable of reproducing both qualitatively and quantitatively high or low-amplitude propagation contractions *demonstrating that material*

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properties of the deposited tissue are critical to restoring a proper peristaltic activity.

Keywords: colon motility, colonic manometry, active strain, finite element, finite elasticity, laser tissue soldering.

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1. Introduction

Anastomotic leakage following resection of gastrointestinal (GI) lesions is a primary source of concern for clinicians and patients alike [1]. Nowadays, developing techniques to improve tissue resection and sealing, thus reducing leakage rates, are essential to increase the reliability of interventions in a clinical setting. Current methods of tissue fixation, such as sutures or staples, exert tensile and compressive forces on the attached tissue, potentially forming gaps in the anastomotic line, resulting in anastomotic leakage and/or pathological scars [2, 3, 4]. In recent years, laser technology has been used as an alternative method for tissue bonding in different tissues such as skin, cornea, buccal mucosa, and even nerves using laser tissue soldering (LTS) and laser tissue welding (LTW) [5, 6, 7] principally. The advantage of these techniques is that they allow to glue tissues that have been bio-printed [8]. In this regard, patches can be 3D printed externally, or, thanks to new emerging technologies protected by patents [9], they can directly bio-printed within the organs thanks to a new generation of endoscopes.

However, bonding requires great dexterity on the part of the clinician and the robots, as parameters such as compressive force, welding material, and laser temperature must be taken into account for the operation to be successful [10, 11]. Moreover, after such an operation, there is always a risk of local inflammation and scarring of the surrounding tissues [12]. This inflammatory response can lead to muscle fibrosis in the colon, resulting in increased muscle stiffness surrounding the welding tissue. On the other hand, it can happen that after LTS, the weld area is not effective enough (not fully cellularized and/or integrated) to withstand the burst pressure or that the weld eventually ruptures at very low pressure [13, 14, 12, 15]. Such a condition generally happens when the compressive force during LTS, the soldering time, and the laser power are not properly designed for the patient.

Therefore, there is an urgent need to develop a high-fidelity *in silico* model of the colon that can be exploited to simulate and predict the response of the organ after such interventions, understand how to optimize the 3D bio-

32 printed patch, and identify potential critical issues. A [validated in silico](#)
33 model can effectively enable digital technology to accelerate the move from
34 the technological proof of concept to the clinical setting.

35 In order to provide data of clinical use, any [in silico](#) model designed
36 for such a purpose should be able to accurately predict the effect of tis-
37 sue resection and repairing on High-Resolution Manometry (HRM). HRM is
38 a standard GI motility diagnostic system that measures intraluminal pres-
39 sure activity in the GI tract using a series of closely spaced pressure sensors
40 [16, 17, 18]. Displayed and interpreted by intraluminal pressure topography
41 (EPT) spatiotemporal patterns, HRM/EPT provides a detailed assessment
42 of GI function that is critical in evaluating patients with nonobstructive dys-
43 phagia. Accordingly, esophageal motility diagnoses are determined system-
44 atically by applying objective metrics of peristaltic function to the Chicago
45 Classification of Motility Disorders [19, 20]. In general, intestinal dysmotil-
46 ity is characterized by altered motility patterns that result in compromised
47 transit of luminal contents accounting for 30-45% of gastrointestinal condi-
48 tions globally [21]. It is worth noticing that, in clinical practice, HRM is
49 the primary method used to evaluate GI motor function invasively. In the
50 case of colon assessment, HRM involves inserting a catheter with 36 pressure
51 transducers spaced 1 cm or 2 cm apart, sometimes for hours.

52 Regarding the underlying biophysics mechanisms, colon contraction is
53 ruled by electrophysiological slow waves generated by the coordination be-
54 tween interstitial cells of Cajal (ICCs) and smooth muscle cells (SMCs)
55 [22, 23, 24, 25]. Several electrical models have been proposed in the literature
56 to reproduce the complex spatiotemporal phenomenology of gastrointestinal
57 excitation [26, 27, 28, 29, 30, 31, 32]. Moreover, the mechanical activity of
58 the gastrointestinal system is ensured by the interaction between ICCs and
59 SMCs from the cellular to the organ level [33, 34, 35, 36, 37, 38]. The electric
60 waves produced by ICCs propagate to the surrounding SMCs via dedicated
61 gap junctions proteic nanostructures [39]. These localized plasma membrane
62 fusions provide direct electrical cell-cell coupling, forming what is known as
63 a functional syncytium. SMC contraction occurs when neuronal/hormonal
64 signals coincide with slow wave electrical phases. In particular, voltage mem-
65 brane depolarisation activates L-type voltage-gated calcium channels [23],
66 which is the initial event triggering complex mechanisms on several scales:
67 the opening of the Calcium channels triggers the entry of Calcium ions, lead-
68 ing to the contraction of the smooth muscle that deforms the GI wall.

69 The GI wall is a complex multilayered structure (see Fig. 1) comprising:

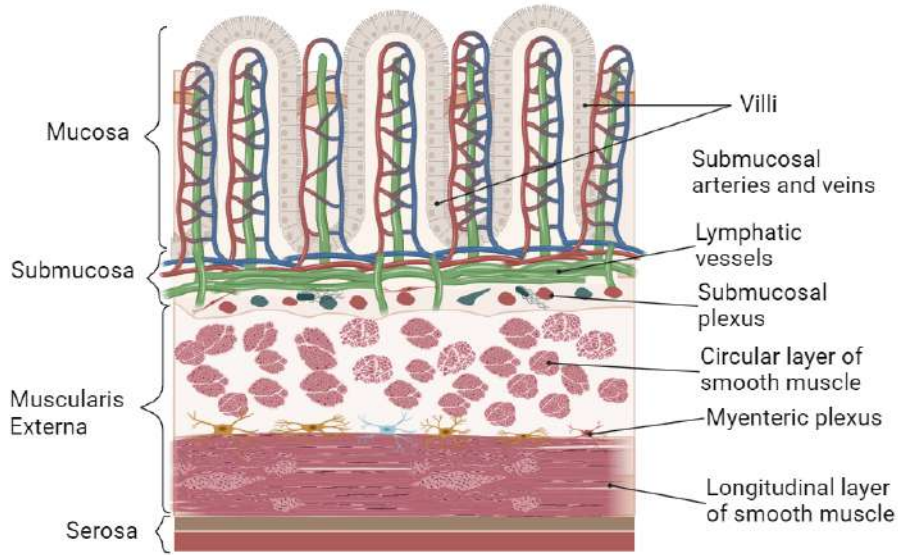


Figure 1: Structure of the Gastrointestinal wall highlighting the different layers with their internal microstructure.

70 serosa (outermost layer), a simple epithelium secreting serous fluid; mus-
 71 cularis externa, containing longitudinal and circular SMC fibers; Auerbach’s
 72 plexus containing enteric neurons; submucosa, a dense layer of connective tis-
 73 sues containing large blood and lymphatic vessels; mucosa, formed by three
 74 sublayers (epithelium, lamina propria, and muscularis mucosae) and con-
 75 taining villi and microvilli to maximise the exchange surface. Accordingly,
 76 various constitutive models have been proposed to reproduce the electromechanical
 77 behavior of the different GI sections, e.g., stomach [37, 40, 41, 42],
 78 small intestine [28, 38, 43, 44], and colon [45, 46, 47]. Though active elec-
 79 tromechanics has been proposed in few cases, most of the literature is based
 80 on the active stress approach disregarding multiple anisotropic components
 81 and lacking a robust numerical implementation.

82 We assume the constitutive model for the passive part as an exponential
 83 Holzapfel-type material models described in [48, 49] since these structure-
 84 based approaches account for directional fiber reinforcements. Overall, ex-
 85 ponential anisotropic constitutive laws have been shown to characterize well
 86 the mechanical behavior of several intact GI segments (esophagus, small in-
 87 testine, large intestine, and rectum), validating their performances against
 88 uniaxial (planar uniaxial extension, planar shear) and biaxial tests (planar

89 biaxial extension and tubular inflation-extension).

90 To the best of the authors' knowledge, a comprehensive computational
91 study investigating the mechanical effects of the LTS procedure on colonic
92 motility and dysmotility, addressing the resulting manometry patterns, [has](#)
93 [yet to be proposed in the literature](#). We advance a detailed mathematical
94 modeling of colon motility to fill this gap. The main contribution of the
95 present work consists in coupling different available models in the GI context,
96 the application and validation of the results with experimental data, and
97 finally, the analysis of an important clinical application.

98 In detail, we propose an active strain electromechanical model of colon
99 motility considering an anisotropic hyperelastic constitutive law consisting
100 of four reinforcing microstructures (embedding two active muscle fibers–
101 longitudinal and circumferential–and the two passive collagen sheets present
102 in the submucosa layer), coupled with a phenomenological electrophysiolog-
103 ical model that finely reproduces SMCs and ICCs spatiotemporal dynamics.
104 The proposed multi-field model is employed to numerically study the effect
105 of deposited bio-printed material or albumin due to LTS endoscopic resection
106 represented by an elliptical portion of [colon endothelium](#) and characterized
107 by altered material properties. In particular, we show that the computational
108 framework is able to reproduce the intraluminal pressure maps corresponding
109 to HRM data, both health and disease.

110 The manuscript is organized as follows. In section 2, the active strain
111 electromechanical formulation for colon motility is presented. In section 3,
112 the strong form of the problem is derived, and the finite element discretiza-
113 tion and associated staggered solver are presented. In section 4, numerical
114 analyses are carried out, as well as the exploitation of the [in silico](#) model to
115 investigate the effect of laser tissue soldering on colon motility. Conclusions,
116 limitations, and perspectives are discussed in section 5.

117 2. Electromechanical constitutive modeling of colon motility

118 In this section, we [briefly](#) recall the governing equations for active strain
119 finite deformations coupled with GI electrophysiology.

120 We represent a scalar, a vector, and a second-order tensor with the low-
121 ercase letters (a), lowercase bold letters (\mathbf{a}) and capital bold letters (\mathbf{A}),
122 respectively, and (\mathbf{A}^T) stands for the transpose of a tensor. According to the
123 tensor notation, we indicate the scalar product with (\cdot) , the double contrac-
124 tion with $(:)$, and the dyadic product with (\otimes) . Moreover, ∇ , $\nabla \cdot$ and ∇^2

125 represent the gradient, divergence, and Laplace operator, respectively.

126 2.1. Finite kinematics

127 The kinematics of the deformable GI tissue is embedded in the classical
 128 description of continuum mechanics under the assumption of finite elasticity
 129 [50]. We denote with \mathbf{X}, \mathbf{x} the material position vector in the reference,
 130 current configuration $\Omega_0, \Omega_t \subset \mathbb{R}^d$, $d = 2, 3$, respectively, the deformation
 131 gradient tensor and its Jacobian with $\mathbf{F} = \partial \mathbf{x} / \partial \mathbf{X}$ and $J = \det \mathbf{F} > 0$,
 132 the left Cauchy-Green deformation tensor with $\mathbf{C} = \mathbf{F}^T \mathbf{F}$, the first isotropic
 133 invariant of deformation with $I_1(\mathbf{C}) = \text{tr}(\mathbf{C})$, where $\text{tr}(\cdot)$ denotes the trace
 134 operator, and the fourth anisotropic pseudo-invariant with $I_4(\mathbf{C}) = \mathbf{C} : \mathbf{G}$,
 135 where \mathbf{G} denotes the structure tensor [48, 51]

136 The contraction of an excitable biological tissue combines active and pas-
 137 sive behaviours, nonlinearly coupling electrophysiological cellular dynamics
 138 with a material hyperelastic response. According to the active strain ap-
 139 proach [37, 52, 53, 54], a multiplicative decomposition of the deformation
 140 gradient tensor into an elastic, \mathbf{F}_e , and an inelastic, \mathbf{F}_a , part is put forward:

$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_a. \quad (1)$$

141 Such an approach allows to apply multiscale and multiphysics couplings in a
 142 homogenised continuum framework over the local active deformation map.

143 Stemming from the gastric microstructural approach detailed in [37], and
 144 according to the active strain kinematics, we consider longitudinal and cir-
 145 cumferential SMC directions as contractile units ruled by the active part of
 146 the deformation gradient:

$$\mathbf{F}_a = \mathbf{I} - \gamma(V)(\alpha_c \mathbf{n}_c \otimes \mathbf{n}_c + \alpha_l \mathbf{n}_l \otimes \mathbf{n}_l) + \gamma_n \mathbf{n}_n \otimes \mathbf{n}_n, \quad (2)$$

147 where \mathbf{n}_c , and \mathbf{n}_l are the orthonormal unit vectors in the circumferential and
 148 longitudinal direction, respectively, while $\mathbf{n}_n = \mathbf{n}_c \times \mathbf{n}_l$ represents the unit
 149 vector orthogonal to their plane. In Eq. (2), α_c and α_l stand for material
 150 parameters ruling the amount of contraction in a certain direction, while γ_n
 151 enforces the incompressibility constraint in such a way that $\det(\mathbf{F}_a) = 1$, i.e.:

$$\gamma_n = \frac{1 - (1 - \gamma\alpha_c)(1 - \gamma\alpha_l)}{(1 - \gamma\alpha_c)(1 - \gamma\alpha_l)}. \quad (3)$$

152 The excitation function $\gamma(V)$ couples the mechanical problem with the
 153 electrophysiological one via a smooth activation function, defined in [48],

154 dependent on the active membrane potential V crossing the smooth muscle
 155 layer:

$$\gamma(V) = (1 - e^{1-\beta_1(V-V_{th})})(1 - e^{1-\beta_2(V-V_{th})})H(V - V_{th}), \quad (4)$$

156 where, β_1 , β_2 , and V_{th} are the material parameters linked to the intracellular
 157 Ca^{2+} dynamics, while $H(V - V_{th})$ is a Heaviside step function switching on
 158 active contraction whenever the threshold V_{th} is reached.

Parameters of $\gamma(V)$ and \mathbf{F}_a can be found in Table 1.

Table 1: Material parameters of the active strain model [37].

α_c	α_l	β_1	β_2	V_{th}
0.2	0.2	10	10	50% V

159

160 2.2. GI electrophysiological model

161 The electrophysiological model adopted in [38] is herein recalled and gen-
 162 eralized. The SMC and ICC layers are labeled with indices s and i , respec-
 163 tively. The resulting system of nonlinear partial differential reaction-diffusion
 164 equations describe the coupled dynamics between the transmembrane poten-
 165 tial variables, u_s, u_i , and the slow currents ones, v_s, v_i :

$$\frac{\partial u_s}{\partial t} = f(u_s) + D_s \nabla^2 u_s - v_s + F_s(u_s, u_i) + I_{stim}^s \quad \text{on } \Omega_0 \times [0, T], \quad (5a)$$

$$\frac{\partial v_s}{\partial t} = \epsilon_s [\lambda_s (u_s - \beta_s) - v_s] \quad \text{on } \Omega_0 \times [0, T], \quad (5b)$$

$$\frac{\partial u_i}{\partial t} = g(u_i) + D_i \nabla^2 u_i - v_i + F_i(u_s, u_i) + I_{stim}^i \quad \text{on } \Omega_0 \times [0, T], \quad (5c)$$

$$\frac{\partial v_i}{\partial t} = \epsilon_i (z) [\lambda_i (u_i - \beta_i) - v_i] \quad \text{on } \Omega_0 \times [0, T], \quad (5d)$$

166 where:

$$f(u_s) = k_s u_s (u_s - a_s) (1 - u_s), \quad F_s(u_s, u_i) = \alpha_s D_{si} (u_s - u_i), \quad (6a)$$

$$g(u_i) = k_i u_i (u_i - a_i) (1 - u_i), \quad F_i(u_s, u_i) = \alpha_i D_{is} (u_s - u_i). \quad (6b)$$

167 Here, I_{stim}^s and I_{stim}^i are the stimulation currents applied to the SMC and
 168 ICC respectively; D_s, D_i are the diffusivities (assumed isotropic); λ_s, λ_i are
 169 the coupling factors between the membrane potential and recovery variable;
 170 D_{si}, D_{is} are the diffusivities of the gap junctions between the two cell species;

171 $k_i, k_s, a_s, a_i, \alpha_s, \alpha_i$ are phenomenological model parameters and their values
 172 are provided in Table. 2. The parameter $\epsilon(z)$, which is proportional to the os-
 173 cillation frequency of the ICCs cells, represents a space-dependent excitability
 174 function, decreasing with distance from the pylorus [36].

Table 2: Electrophysiological parameters adapted from [36, 38].

SMC layer		ICC layer	
$k_s=10$	$a_s=0.06$	$k_i=7$	$a_i=0.5$
$\beta_s = 0$	$\lambda_s=8$	$\beta_s = 0.5$	$\lambda_i=8$
$\epsilon_s=0.15$	$\alpha_s=1$	$\epsilon_i=\epsilon_i(z)$	$\alpha_i=-1$
$D_{si}=0.3$	$D_s=0.4$	$D_{is}=0.3$	$D_i=0.04$

175 In view of coupling the electrophysiological model with the active defor-
 176 mation map via $\gamma(V)$ in Eq. (4), the action potential V is identified with the
 177 transmembrane voltage dynamics u_s passing through the SMC layer.

178 2.3. Constitutive mechanical model of the GI system

179 Considering a structure-based constitutive formulation, we proceed with
 180 an additive decomposition of the elastic strain energy density into isotropic
 181 and anisotropic parts, $\Psi = \Psi^{\text{iso}} + \Psi^{\text{aniso}}$, where the isotropic contribution is
 182 related to the passive mechanical response of the non-collagenous components
 183 of the tissue (matrix) [49, 55]. For the sake of clarity, and with no loss of
 184 generality (other options could be made with similar results [56]), in the
 185 following we restrict our analysis to the Neo-Hookean material model, $\Psi^{\text{iso}} =$
 186 $\mu(I_1 - 3)$, where μ is the passive isotropic stiffness.

187 The anisotropic energetic component presents, in general, passive and
 188 active contributions. The passive part is associated with the mechanical
 189 response of directional collagen fibers. These are assumed to mimic the
 190 submucosa reinforcement, d_1 and d_2 , oriented with an angle θ according to the
 191 circumferential directions (see Fig. 2). The active anisotropic contribution is
 192 due to the presence of SMC fibers in the longitudinal, l , and circumferential,
 193 c , direction, respectively:

$$\begin{aligned} \Psi^{\text{aniso}} &= \Psi_{\text{p}}^{\text{aniso}} + \Psi_{\text{act}}^{\text{aniso}} \\ &= \sum_{i \in \{d_1, d_2\}} \frac{k_1^i}{4k_2^i} [e^{k_2^i (I_4^i - 1)_+^2} - 1] + \sum_{i \in \{l, c\}} \frac{k_1^i}{4k_2^i} [e^{k_2^i (I_4^i - 1)_+^2} - 1]. \end{aligned}$$

194 Here, the notation $(y)_+ := y$ if $y \geq 0$ reproduces the tension-compression
 195 switch approximation [48] and the anisotropic fourth invariant $I_4^j = \mathbf{C} :$
 196 $(\mathbf{n}_j \otimes \mathbf{n}_j)$ is distinguished for each fiber family $j \in \{l, c, d_1, d_2\}$.

197 The material parameters k_1^j (stiffness-like) and k_2^j (nondimensional) are
 198 associated with the directional behavior of the material. According to previ-
 199 ous studies [49, 55, 56], diagonal fibers are assumed identical. Furthermore,
 200 a preliminary tuning analysis was conducted to identify experimental-based
 201 material stiffness as explained in Appendix B. Material parameters are pro-
 202 vided in Table B.5.

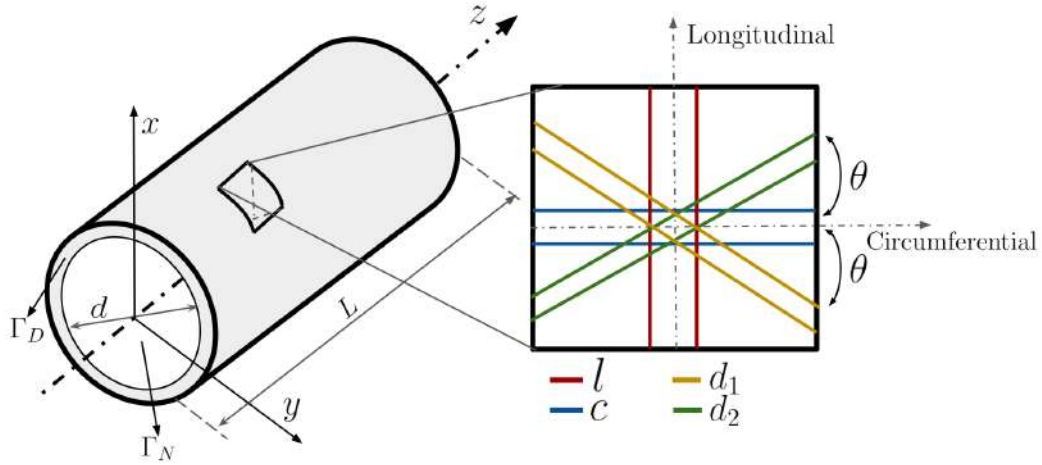


Figure 2: Idealized colon segment with length L and diameter d . The zoomed cross-section represents the wall microstructure, which is composed of four families of fibers embedded in an isotropic elastin matrix. The directions of the fibers are uniquely defined with respect to the circumferential direction by the angle θ ; l represents the external longitudinal muscular layer, c the internal circumferential muscular fiber, d_1 and d_2 are the submucosa helically collagen fibers.

203 According to the given prescriptions, the first Piola-Kirchhoff stress tensor
 204 is derived under variational principles as:

$$\mathbf{P} = \frac{\partial \Psi}{\partial \mathbf{F}} - pJ\mathbf{F}^{-T} = \det(\mathbf{F}_a) \left(\frac{\partial \Psi^{\text{iso}}}{\partial \mathbf{F}_e} + \frac{\partial \Psi^{\text{aniso}}}{\partial \mathbf{F}_e} \right) \mathbf{F}_a^{-T} - pJ\mathbf{F}^{-T}, \quad (7)$$

205 where p stands for the solid hydrostatic pressure.

206 It is worth mentioning that from a numerical viewpoint, the precise cre-
 207 ation of the fibrous structure of the GI tract is crucial. Due to their com-
 208 plex structure and strong layer adhesion, a homogenized layer was chosen

209 for fiber generation throughout the thickness of the wall. Similarly to the
 210 method presented in Piersanti et al. [57], we adopted and customized a rule-
 211 based algorithm [58], originally proposed for cardiac fibers, to reproduce
 212 colon microstructure and generate muscle fibers throughout all the simula-
 213 tions (detailed explanation is provided in Appendix C). We used this tech-
 214 nique to generate longitudinal, circumferential, and helical fibers, enabling
 215 us to mimic the colon histology by assuming fibers spread within the entire
 216 wall, as shown in Fig. C.20.

217 It is worth mentioning that multiple families of reinforcing muscular fibers
 218 are peculiar to the present GI wall model. Generalizing the concept of fiber
 219 sheet direction used in the cardiac ventricular wall [54], for the GI system,
 220 we introduce two active families of fibers, namely circumferential and longi-
 221 tudinal, and two additional passive diagonal ones.

222 3. Numerical implementation

223 3.1. Strong form of the problem

224 The strong form of the problem is given by the following set of nonlinear
 225 coupled partial differential equations prescribing mechanical equilibrium in
 226 terms of displacement field \mathbf{u} and pressure p variables, defined in the unde-
 227 formed colon domain Ω_0 :

$$\nabla \cdot \mathbf{P} = \mathbf{0}, \quad \text{on } \Omega_0 \times [0, T] \quad (8a)$$

$$J - 1 = 0, \quad \text{on } \Omega_0 \times [0, T] \quad (8b)$$

228 complemented with electrophysiological balance laws Eq. (5), solved for the
 229 electrophysiological variables u_s, v_s, u_i, v_i .

230 Mixed boundary conditions of normal displacement and traction close the
 231 system:

$$\mathbf{u} \cdot \mathbf{n} = 0, \quad \text{on } \Gamma_D \times [0, T] \quad (9a)$$

$$\mathbf{P}\mathbf{n} - p_0 J \mathbf{F}^{-T} \mathbf{n} = \mathbf{0}, \quad \text{on } \Gamma_N \times [0, T] \quad (9b)$$

232 being Γ_D and Γ_N a disjoint partition of the boundary. Condition Eq. (9a)
 233 constrains normal motion along the surface Γ_D . The term p_0 in Eq. (9b) de-
 234 notes a prescribed (possibly time-dependent) boundary load (normal stress-
 235 pressure) associated with the presence of digesta within the lumen. In the
 236 present case, such a load is assumed uniform over the deformed counterpart

237 of Γ_N , and applied in the normal direction to the internal surface of the colon
 238 in the deformed configuration.

239 Finally, no flux boundary conditions are considered for the electrophysi-
 240 ological problem:

$$D_s \nabla u_s \cdot \mathbf{n} = 0, \quad D_i \nabla u_i \cdot \mathbf{n} = 0 \quad \text{on} \quad \partial\Omega_N, \quad (10)$$

241 where $\partial\Omega_N$ stands for the Neumann boundary (the whole boundary for the
 242 electrophysiological problem).

243 3.2. Mixed-primal weak variational form

244 The trial spaces, where the solution of the weak form of the problem is
 245 defined, are given by:

$$\mathbf{u} \in \mathbf{V} := L^2(0, T; \mathbf{H}^1(\Omega_0)), \quad p \in Q := L^2(0, T; L^2(\Omega_0)), \quad (11)$$

246 for displacements and pressure and

$$(u_s, u_i, v_s, v_i) \in V^4 := [L^2(0, T; H^1(\Omega_0))]^4, \quad (12)$$

247 for the electrophysiological variables. The virtual displacements for the me-
 248 chanical problem are introduced as $\delta\mathbf{u} \in \mathbf{V}_0$, as well as the test functions for
 249 the pressure $\delta p \in Q_0$ and $(\delta u_s, \delta u_i, \delta v_s, \delta v_i) \in (V_0)^4$ for the electrophysiologi-
 250 cal problem, defined on the spaces of the corresponding fields, and vanishing
 251 on the Dirichlet part of the boundary. Multiplying Eq. (8) by a virtual dis-
 252 placement, using the divergence theorem and the boundary conditions in
 253 Eq. (9), the weak form of the mechanical problem is:

254 find displacement $\mathbf{u} \in \mathbf{V}$ and pressure $p \in Q$ such that

$$\int_{\Omega_0} \mathbf{P} : \nabla \delta \mathbf{u} - \int_{\Gamma_N} p_0(t) J \mathbf{F}^{-T} \mathbf{n} \cdot \delta \mathbf{u} = 0, \quad \forall \delta \mathbf{u} \in \mathbf{V}_0, \quad (13a)$$

$$\int_{\Omega_0} (J - 1) \delta p + \int_{\Omega_0} \zeta_{stab} \nabla p \cdot \nabla \delta p = 0, \quad \forall \delta p \in Q_0, \quad (13b)$$

255 where ζ_{stab} is a positive pressure stabilization parameter used as a locking-
 256 free parameter to enhance the stability of the discrete problem [59]. The
 257 mechanical problem can be rewritten in a more compact form as:

258 find displacement and pressure \mathbf{u} and p such that

$$\begin{aligned} \mathcal{M}(\mathbf{u}, p; \delta \mathbf{u}, \delta p) := & \int_{\Omega_0} \mathbf{P} : \nabla \delta \mathbf{u} - \int_{\Gamma_N} p_0(t) J \mathbf{F}^{-T} \mathbf{n} \cdot \delta \mathbf{u} + \\ & \int_{\Omega_0} (J - 1) \delta p + \int_{\Omega_0} \zeta_{stab} \nabla p \cdot \nabla \delta p = 0, \quad (14) \end{aligned}$$

259 for all test functions $\delta \mathbf{u}$ and δp . Analogously, multiplying the rest of Eq. (8)
 260 by test functions $(\delta u_s, \delta v_s, \delta u_i, \delta v_i) \in (V_0)^4$, applying the divergence theorem
 261 and the condition of zero flux at the boundary in Eq. (10), the weak form
 262 of the electrophysiology problem can be written as it follows: at each time
 263 step $t^{n+1} = t^n + \Delta t$ of an equispaced partition of the time interval $[0, T]$,
 264 given the solution of the electrophysiology problem at the previous timestep
 265 $(u_s^n, v_s^n, u_i^n, v_i^n) \in V^4$ find the vector $(u_s^{n+1}, v_s^{n+1}, u_i^{n+1}, v_i^{n+1}) \in V^4$ at the
 266 current timestep t^{n+1} such that it is satisfied

$$\int_{\Omega_0} \frac{u_s^{n+1} - u_s^n}{\Delta t} \delta u_s + \int_{\Omega_0} D_s \nabla u_s^{n+1} \cdot \nabla \delta u_s = \int_{\Omega_0} I_{ion}^s(u_s^n, v_s^n, u_i^n) \delta u_s, \quad (15a)$$

$$\int_{\Omega_0} \frac{v_s^{n+1} - v_s^n}{\Delta t} \delta v_s = \int_{\Omega_0} R_s(u_s^n, v_s^n) \delta v_s, \quad (15b)$$

$$\int_{\Omega_0} \frac{u_i^{n+1} - u_i^n}{\Delta t} \delta u_i + \int_{\Omega_0} D_i \nabla u_i^{n+1} \cdot \nabla \delta u_i = \int_{\Omega_0} I_{ion}^i(u_s^n, v_i^n, u_i^n) \delta u_i, \quad (15c)$$

$$\int_{\Omega_0} \frac{v_i^{n+1} - v_i^n}{\Delta t} \delta v_i = \int_{\Omega_0} R_i(u_i^n, v_i^n) \delta v_i, \quad (15d)$$

267 for all test functions $(\delta u_s, \delta v_s, \delta u_i, \delta v_i) \in (V_0)^4$, where:

$$I_{ion}^i(u_s, v_i, u_i) = g(u_i) - v_i + F_i(u_s, u_i) + I_{stim}^i, \quad (16a)$$

$$R_i(u_i, v_i) = \epsilon_i(z) [\lambda_i(u_i - \beta_i) - v_i], \quad (16b)$$

$$I_{ion}^s(u_s, v_s, u_i) = f(u_s) - v_i + F_s(u_s, u_i) + I_{stim}^s, \quad (16c)$$

$$R_s(u_s, v_s) = \epsilon_s [\lambda_s(u_s - \beta_s) - v_s]. \quad (16d)$$

268 The implicit Euler scheme for the discretization of the time derivative has
 269 been adopted in Eqs. (15), while an explicit treatment of the reaction terms
 270 has been used. In a more compact notation, the electrophysiology problem
 271 can be written as: find u_s, u_i, v_s and v_i such that

$$\mathcal{E}(u_s, u_i, v_s, v_i; \delta u_s, \delta u_i, \delta v_s, \delta v_i) := \mathcal{E}_1 + \mathcal{E}_2 + \mathcal{E}_3 + \mathcal{E}_4 = 0, \quad (17)$$

272 for all test functions $\delta u_s, \delta u_i, \delta v_s, \delta v_i$, where:

$$\mathcal{E}_1 = \mathcal{E}_1(u_s, u_i, v_s; \delta u_s, \delta u_i, \delta v_s), \quad (18)$$

$$\mathcal{E}_2 = \mathcal{E}_2(u_s, v_s; \delta u_s, \delta v_s), \quad (19)$$

$$\mathcal{E}_3 = \mathcal{E}_3(u_s, u_i, v_i; \delta u_s, \delta u_i, \delta v_i), \quad (20)$$

$$\mathcal{E}_4 = \mathcal{E}_4(u_i, v_i; \delta u_i, \delta v_i), \quad (21)$$

273 are respectively the residuals of Eqs. (15).

274 3.3. Finite element discretization

275 The computational domain Ω_0 has been discretized into tetrahedral finite
 276 elements and the unknowns have been approximated using Lagrangian shape
 277 functions \mathbb{P}_2 and \mathbb{P}_1 for the two variational problems defined by Eqs. (14) and
 278 (17), respectively. The problem has been implemented in the open-source fi-
 279 nite element software **FEniCS** [60]. A splitting scheme was adopted to solve
 280 separately the mechanical problem Eq. (14) and the electrophysiology prob-
 281 lem Eq. (17), the nonlinear mechanical problem is solved using the Newton-
 282 Raphson method and, at each Newton's iteration, the resulting linear system
 283 given by $d\mathcal{M}(\Delta \mathbf{u}, \Delta p; \delta \mathbf{u}, \delta p) = -\mathcal{M}(\mathbf{u}_k^{n+1}, p_k^{n+1}; \delta \mathbf{u}, \delta p)$ for the corrections
 284 $\Delta \mathbf{u}$ and Δp is solved using a **BiCGStab** (Biconjugate Gradient Stabilised)
 285 method preconditioned with **ILU** (Incomplete LU factorization). The tangent
 286 operator $d\mathcal{M}$ associated to the nonlinear variational mechanical problem in
 287 Eq. (14) has been computed via the symbolic derivative **derivative**. For
 288 the solution of electrophysiological problem, the **PETSc** library (Portable, Ex-
 289 tensible Toolkit for Scientific Computing) has been used. The algorithm for
 290 the solution of the coupled electromechanical problem describing the colonic
 291 motility is detailed in Alg. 1.

Algorithm 1 Algorithm for the electromechanical motility of a GI tract

- 1: **Input** Initial and boundary conditions for displacement, pressure and electrophysiological variables:
 - 2: **while** $t^n < T$ **do**
 - 3: **Given:** displacement and pressure \mathbf{u}^n, p^n solve the linear electrophysiology problem: $\mathcal{E}(u_s^{n+1}, u_i^{n+1}, v_s^{n+1}, v_i^{n+1}; \delta u_s, \delta u_i, \delta v_s, \delta v_i) = 0$
 - 4: **Update** EP solutions $(u_s^n, u_i^n, v_s^n, v_i^n) \leftarrow (u_s^{n+1}, u_i^{n+1}, v_s^{n+1}, v_i^{n+1})$
 - 5: **Given:** the electrophysiological variables $(u_s^{n+1}, u_i^{n+1}, v_s^{n+1}, v_i^{n+1})$, solve the mechanical problem via Newton-Raphson procedure:
 - 6: **for** a given Newton iteration k **do**
 - 7: **Given:** \mathbf{u}_k^{n+1} and p_k^{n+1} solve the linearized mechanical problem:
 $d\mathcal{M}(\Delta \mathbf{u}, \Delta p; \delta \mathbf{u}, \delta p) = -\mathcal{M}(\mathbf{u}_k^{n+1}, p_k^{n+1}; \delta \mathbf{u}, \delta p)$
 - 8: **Set:** $\mathbf{u}_{k+1}^{n+1} = \Delta \mathbf{u} + \mathbf{u}_k^{n+1}$ and $p_{k+1}^{n+1} = \Delta p + p_k^{n+1}$
 - 9: **if** $\|\mathbf{u}_{k+1}^{n+1} - \mathbf{u}_k^{n+1}\| < tol$ **then**
 - 10: **Update** the Newton solutions $\mathbf{u}_k^{n+1} \leftarrow \mathbf{u}_{k+1}^{n+1}$ and $p_k^{n+1} \leftarrow p_{k+1}^{n+1}$
 - 11: **else** $k \leftarrow k + 1$
 - 12: **end if**
 - 13: **Update** mechanical solutions $\mathbf{u}^{n+1} \leftarrow \mathbf{u}_{k+1}^{n+1}$ and $p^{n+1} \leftarrow p_{k+1}^{n+1}$
 - 14: **end for**
 - 15: **Update time:** $t \leftarrow t + \Delta t$
 - 16: **Output:** Displacement \mathbf{u}^{n+1} , pressure p^{n+1} and electrophysiological variables $(u_s^{n+1}, v_s^{n+1}, u_i^{n+1}, v_i^{n+1})$ at the current time t^{n+1}
 - 17: **end while**
-

292 **4. Exploitation of the *in silico* model**

293 Several numerical experiments are herein presented to characterize the
 294 mechanical and electrophysiological response of an idealized tract of the hu-
 295 man colon. The present tests aim to investigate and compare colon motility in
 296 healthy and post-surgical conditions where a region of the computational do-
 297 main, corresponding to a lesion in the colon endothelium, has been removed
 298 after a representative endoscopic submucosal dissection (ESD) [60] and thus
 299 replaced with an implant consisting of a patch of 3D printed material. Nu-
 300 merical results are analyzed in terms of topography maps of intraluminal
 301 pressure and compared to existing data on colonic high-resolution manome-
 302 try. Electrophysiological and mechanical constitutive parameters used in the
 simulations can be found in Tab.s 2 and 3, respectively.

Table 3: Mechanical constitutive parameters.

μ [kPa]	k_1^l [kPa]	k_2^l [-]	k_1^c [kPa]	k_2^c [-]	k_1^d [kPa]	k_2^d [-]	θ [-]
2.5	5.43	1.19	0.78	0.02	3.65	0.31	39.5

303

304 *4.1. Idealized colon geometry model*

305 The computational domain consists of a hollow cylinder with typical di-
 306 mensions of a human colon geometry. According to colonoscopy and surface
 307 data [61, 62], the diameter of the colon varies between 4.8 cm and 6 cm, while
 308 the length of its transverse part is around 50 cm. For the present study, a
 309 diameter of 5 cm, a length of 50 cm, and a thickness of 0.5 cm have been
 310 considered. Figure 3 shows a sketch of the geometry used with associated
 311 boundary conditions.

312 The red elliptic region, with axes r_{\min} , r_{\max} and thickness $h = 0.3$ cm, rep-
 313 represents a patch of bio-printed material (e.g., albumin). Two representative
 314 geometries for the implanted patch have been considered, fixing the value of
 315 the minor axis, $r_{\min} = 2$ cm, and varying $r_{\max} \in \{2, 3\}$ cm. The bio-printed
 316 region was modeled using a Neo-Hookean material model, assuming perfect
 317 contact between the tissue-patch boundary, thus representing the clinical sit-
 318 uation when a healthy bond appears during the healing process. The elastic
 319 modulus of the implanted patch, μ_p , has been varied with respect to the
 320 elastic modulus of the surrounding healthy tissue, μ_t , as $\mu_p \in \{\mu_t/2, \mu_t, 2\mu_t\}$.

321

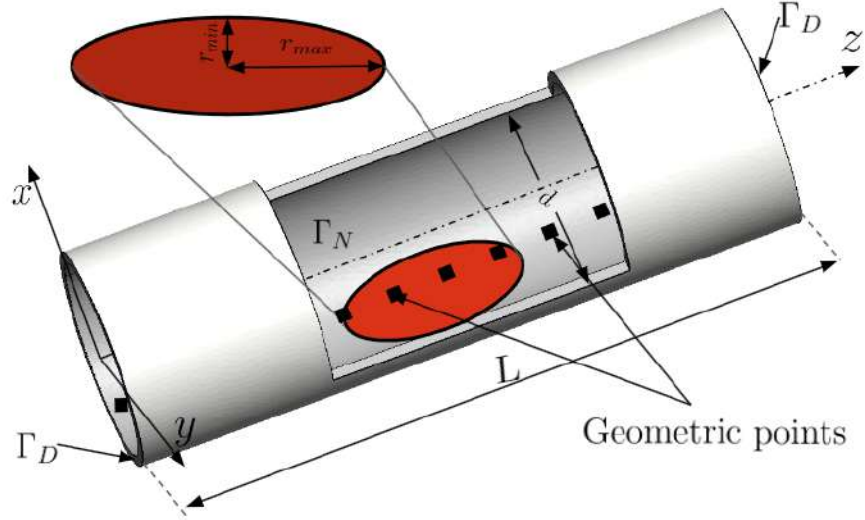


Figure 3: Sketch of the computational domain used in the numerical simulations with length $L = 50$ cm, diameter $d = 5$ cm, thickness 0.55 cm. Dirichlet (Γ_D) and Neumann (Γ_N) boundary conditions. The red ellipsoidal region with axes r_{\max} , r_{\min} , and thickness $h = 0.3$ cm represents the bio-printed patch.

322 The intraluminal pressure due to mechanical contraction has been evalu-
 323 ated according to Lamé's theory of stresses in thick-walled cylinders [28, 63,
 324 64]. Accordingly, a direct comparison with experimental manometry record-
 325 ings was conducted. The circumferential stresses (σ_c) in the cylinder wall
 326 were calculated using internal (p_i) and external (p_o) pressures, and internal
 327 (r_i) and external (r_o) radii of the hollow cylinder, readily:

$$\sigma_c = \frac{p_i r_i^2 - p_o r_o^2}{r_o^2 - r_i^2} - \frac{r_i^2 r_o^2 (p_o - p_i)}{r (r_o^2 - r_i^2)}, \quad (22)$$

328 where r is the radial coordinate (computed from the Cartesian reference
 329 system aligned with the cylinder centerline). For simplicity and with no loss
 330 of generality, in the present study, we assumed the external pressure p_o due
 331 to surrounding tissues and organs as a null reference value (fulfilling material
 332 equilibrium withstanding with colon cylindrical shape). Because the active
 333 fibers on the inner surface of the colon are aligned in the circumferential
 334 direction, the intraluminal pressure calculated at $r = r_i$ can therefore be
 335 expressed as follows:

$$p_i = \sigma_c \frac{r_o^2 - r_i^2}{r_o^2 + r_i^2}, \quad (23)$$

336 such that, after solving electromechanical equilibrium, σ_c is known and the
337 intraluminal pressure can be estimated.

338 The topographic maps of intraluminal pressure simulating high-resolution
339 manometry were created according to the clinical protocol described in [16,
340 18]: the intraluminal pressure has been evaluated at 36 geometric points
341 along the computational domain in the numerical simulations; after comput-
342 ing p_i values, an in-house code was written in `Matlab2022` to display the
343 results of the simulations.

344 4.2. The role of implant material on intraluminal pressure

345 *Healthy case.* The first numerical test is aimed to simulate the electrome-
346 chanical behavior of a healthy colonic tract (corresponding to the condition
347 $\mu_p = \mu_t$). Figure 4 shows the numerical results obtained by finite element
348 simulations for two representative snapshots (a zoomed clip of the region of
349 interest is shown in Fig. D.21). In particular, the spatial distribution of SMC
350 transmembrane potential u_s (first row) and hydrostatic pressure p (second
351 row) are shown on the deformed/contracted state. According to the active
352 strain constitutive modeling assumptions (2), the deformation is in phase
353 with the peak of slow wave activity. After a transient period of system sta-
354 bilization (see Appendix A for details), multiple slow waves coexist on the
355 domain and propagate in the axial direction, correctly reproducing healthy
356 colon peristalsis.

357 Besides, manometry maps (Fig. 4) and pressure topography maps (Fig. 5)
358 provide a faithful representation of the intraluminal pressure generated by
359 muscle contraction. Manometry map analysis reveals qualitative agreement
360 with clinical data from the literature [65], as illustrated in Fig. 4 for the
361 healthy case. Specifically, the space-time diagram highlights the intensity
362 and speed of propagation (slope computed as space/time) of p_i field (23).
363 As observed in clinical data, a stronger intraluminal pressure is measured
364 according to the excitation wave speed, thus changing along the GI tract in
365 favor of the mixing function. Moreover, it is worth mentioning that in the
366 healthy case, the motility pattern follows the propagating waves smoothly
367 without impediments or gaps.

368 The differences observed between the clinical data and the simulated pre-
369 dictions are due to several factors. Clinical manometry readings are neces-
370 sarily influenced by the position of the sensor and the length covered by the
371 sensor in the colon. Figure 4 shows the manometric readings in the colonic
372 system from the cecum to the rectum, representing virtually the entire colon

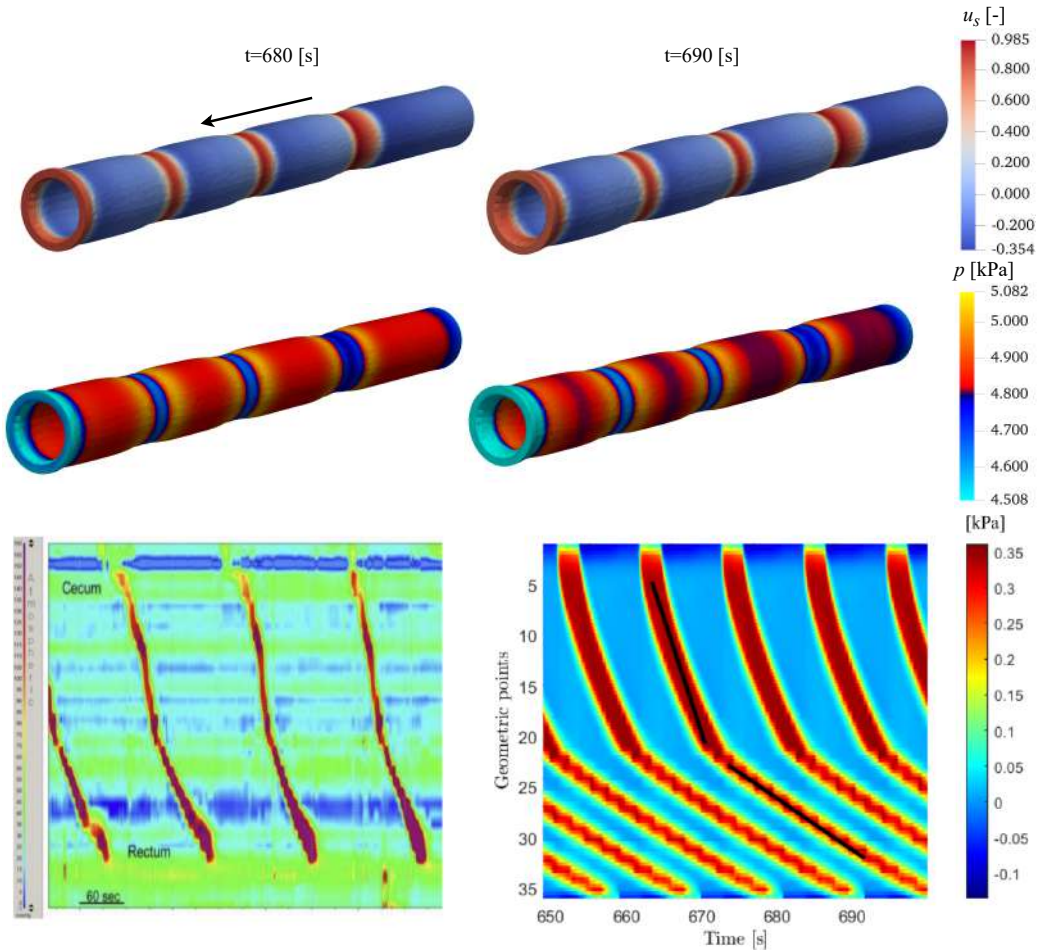


Figure 4: (Top) Temporal evolution of the SMC transmembrane potential u_s and hydrostatic pressure p in the healthy condition ($\mu_p = \mu_t$). The arrow represents the direction of propagation. (Bottom) Topography map of the intraluminal pressure p_i corresponding to HRM map in a healthy colon tract: (a) clinical results taken from [65], (b) numerical model with $\mu_p = \mu_t$. Black lines represent the slope, i.e., conduction velocity, in the space-time diagram.

373 length. However, the simulated results provide a first-of-its-kind informa-
 374 tive representation of the corresponding pressure topography manometric
 375 patterns. Moreover, due to the difficulty of accessing clinical data related
 376 to post-surgical endoscopic situations, the model has been validated against
 377 manometric data corresponding to healthy conditions, which are available in
 378 the literature.

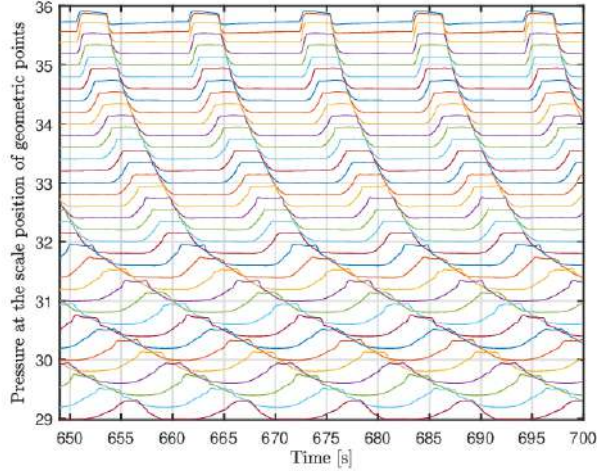


Figure 5: Pressure topography map corresponding to the numerical manometry in Fig. 4.

379 *The role of patch geometry and stiffness.* In this section, we provide a prelim-
 380 inary parametric analysis comparing different properties of the bio-printed
 381 patch, namely geometry and stiffness. Figure 6 shows a graphical repre-
 382 sentation of the numerical results obtained varying the size of the elliptical
 383 region $r_{\max} \in \{2, 3\}$ cm and considering a stiffer patch material other than
 384 the surrounding tissue, namely $\mu_p = 2\mu_t$.

385 It can be noticed that although the slow wave propagation is not consid-
 386 erably altered by the presence of the patch (representative of the case when
 387 the implant is fully cellularized), such that only geometrical couplings are
 388 implied, the intraluminal pressure distribution critically changes due to the
 389 presence of a stiff patch. In particular, the overall patch area shows much
 390 higher p_i levels (from about 5 kPa in the healthy case to more than 7 kPa in
 391 the stiff patch case), concurring to increase the stress state of the surrounding
 392 tissue and thus enhancing the development of pathological scars [2, 4].

393 Figure 7 shows analyses conducted varying patch size $r_{\max} \in \{2, 3\}$ cm
 394 but considering a softer material other than the host surrounding tissue,
 395 namely $\mu_p = \mu_t/2$. As expected, a similar behavior is obtained for the SMC
 396 voltage field, i.e., the voltage field only experiences geometric coupling, but,
 397 in this case, the intraluminal pressure lowers (from about 5 kPa in the healthy
 398 case to less than 3 kPa in the soft patch case) on the overall patch region.
 399 Such a general stress mismatch could affect the stability of the implant (it

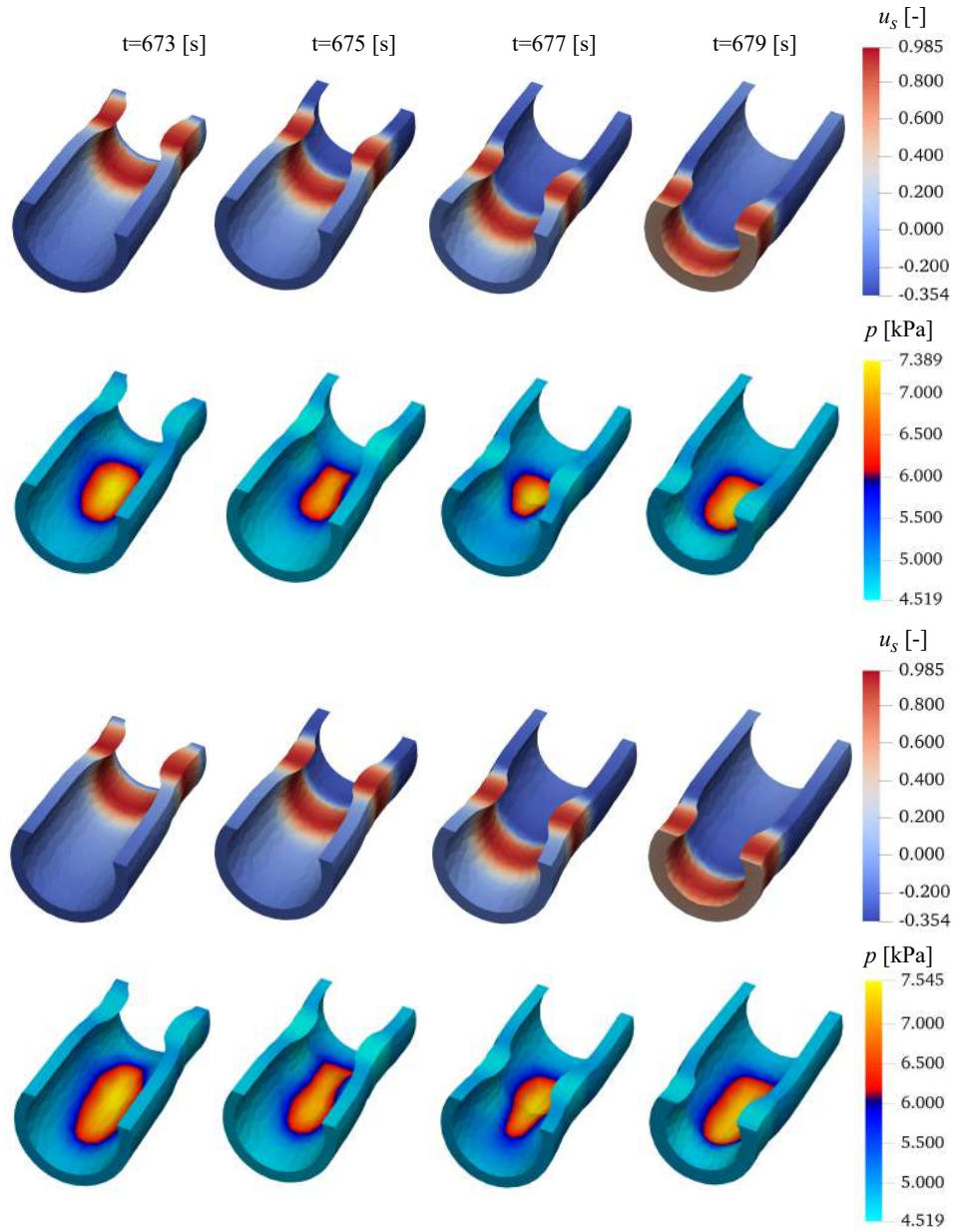


Figure 6: Temporal evolution of SMC transmembrane voltage u_s and hydrostatic pressure p in proximity of the patch region with parameters $r_{\max} = 2, r_{\min} = 2, \mu_p = 2\mu_t$ (top), and $r_{\max} = 3, r_{\min} = 2, \mu_p = 2\mu_t$ (bottom).

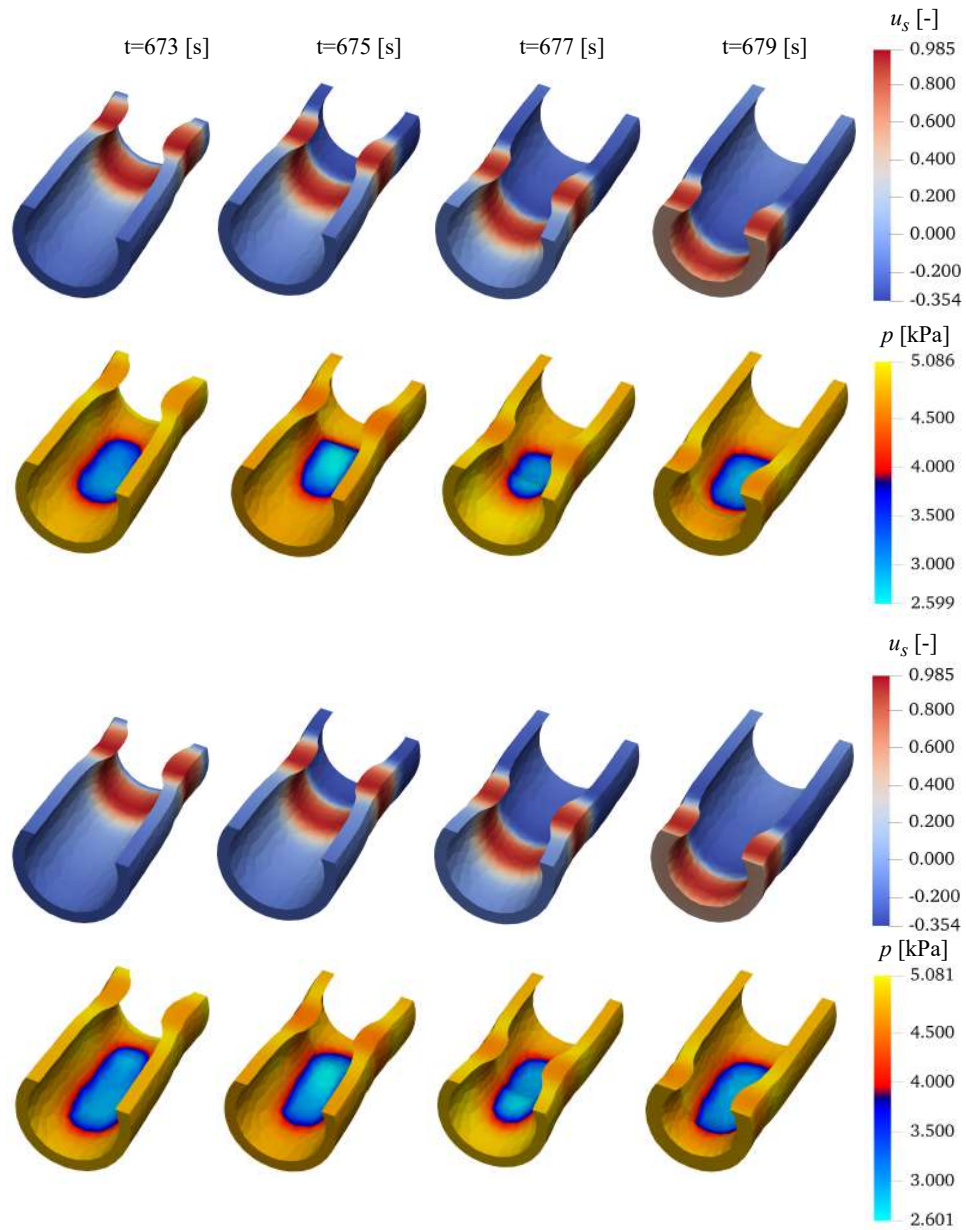


Figure 7: Temporal evolution of SMC transmembrane voltage u_s and hydrostatic pressure p in proximity of the patch region with parameters $r_{\max} = 2, r_{\min} = 2, \mu_p = 0.5\mu_t$ (top), and $r_{\max} = 3, r_{\min} = 2, \mu_p = 0.5\mu_t$ (bottom).

400 may lose its position) with concurrent loss of contractility efficiency.

401 To further emphasize the critical role of material stiffness in the over-
 402 all colon motility, we discuss the resulting topography maps for the selected
 403 pathological cases, as shown in Fig. 8 and Fig. 9. A direct comparison with
 404 the healthy case provided in Fig. 4 highlights that the region surrounding the
 405 patch material reduces its contractility for a stiffer or softer patch. Moreover,
 406 a critical gap can be observed in the intraluminal pressure profiles that break,
 407 thus reducing the lateral wall displacement. Such a contractility impairment
 408 is more evident in the case of the stiff patch, concurring to a wrong scar re-
 409 modeling in the long-term tissue adaptation. Contrarily, selected differences
 410 in patch size do not alter the resulting motility behavior, which seems to be
 411 ruled by the patch material properties other than its geometrical features.

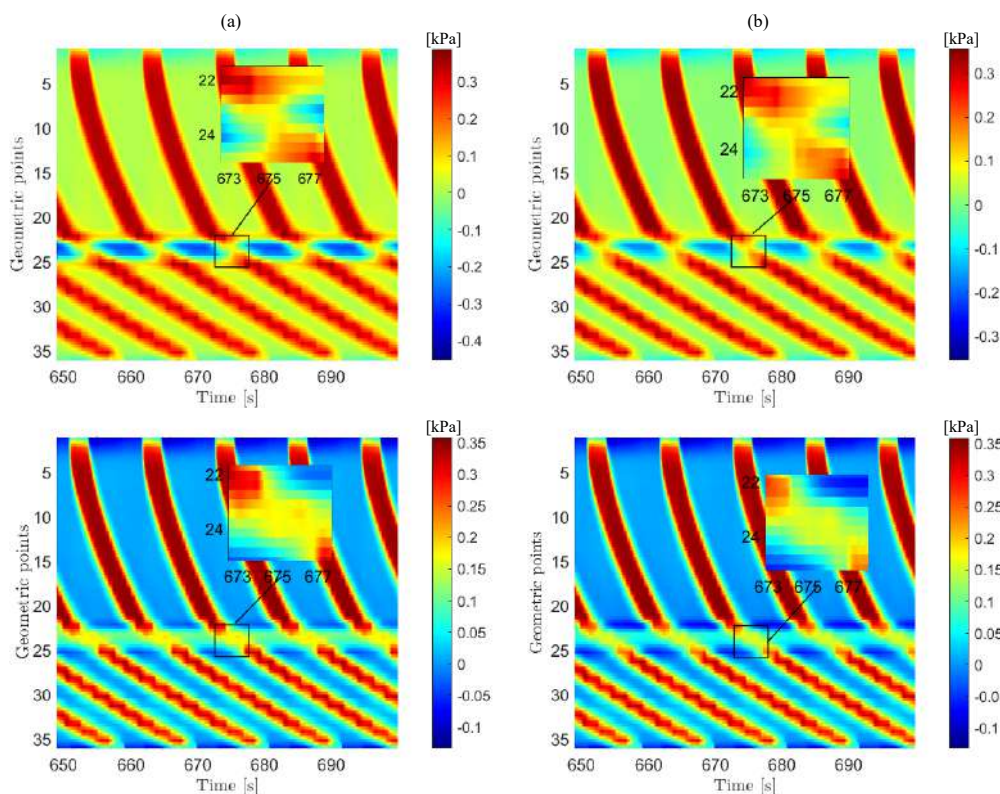


Figure 8: HRM maps for two implant configurations after the LTS with parameters $\mu_p = 2\mu_t$ (top) and $\mu_p = 0.5\mu_t$ (bottom). Columnwise discriminates between $r_{\max} = 2, r_{\min} = 2$ (a) and $r_{\max} = 2, r_{\min} = 3$ (b).

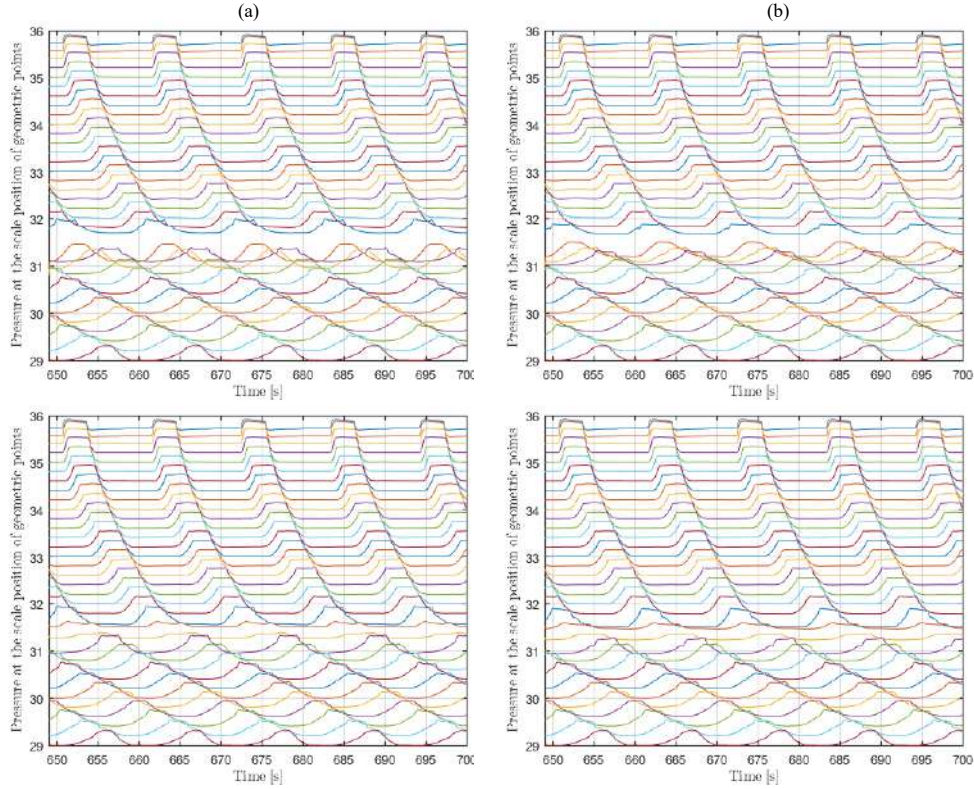


Figure 9: Topography pressure maps for the HRM in Fig. 8 two implant configurations after the LTS with parameters $\mu_p = 2\mu_t$ (top) and $\mu_p = 0.5\mu_t$ (bottom). Columnwise discriminates between $r_{\max} = 2, r_{\min} = 2$ (a) and $r_{\max} = 2, r_{\min} = 3$ (b).

412 *The role of patch electrical conductivity.* In this numerical test, the elec-
 413 trophysiological properties of the implant are varied from those of the sur-
 414 rounding host tissue; namely, the SMC and ICC electrical conductivity in the
 415 patch, D_s^p, D_i^p , are ten times lower than those in the tissue, D_s^t, D_i^t . The size
 416 of the elliptical region is fixed at $r_{\min} = 2$ cm and $r_{\max} = 3$ cm and material
 417 stiffness is considered $\mu_p = 2\mu_t$.

418 Figure 10 shows the evolution of the hydrostatic pressure p in the sur-
 419 roundings of the implant, where no significant variations can be observed
 420 compared to the previous analysis in Fig. 6. However, because of the altered
 421 electrophysiological properties, the slow wave spatiotemporal distribution
 422 changes, and, in particular, the conduction velocity of the excitation wave
 423 lowers by enlarging the action potential wavelength when passing across the

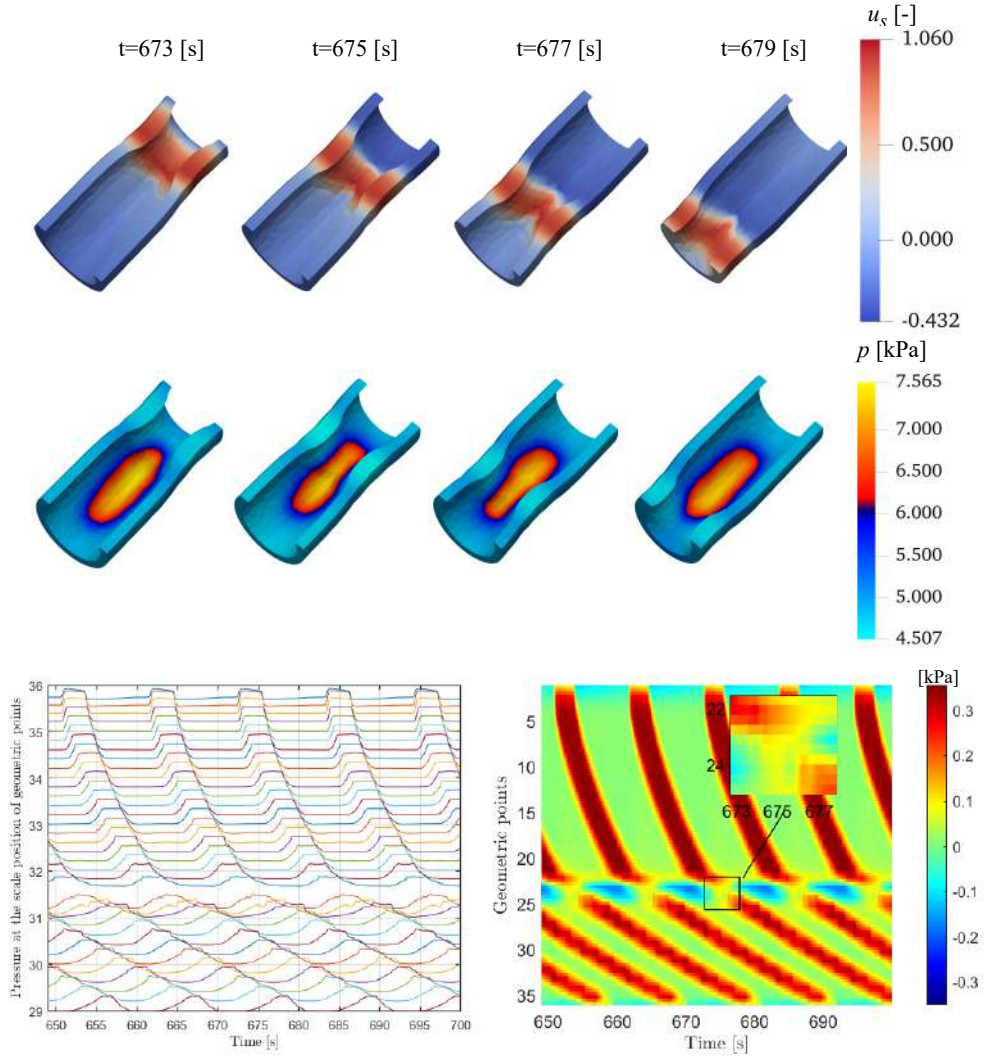


Figure 10: Temporal evolution of SMC transmembrane voltage u_s and hydrostatic pressure p around the patch region with parameters $r_{\max} = 3$ and $r_{\min} = 2$ with stiffness $\mu_p = 2\mu_t$ and the diffusion coefficients $D_s^p = 0.1D_s$ and $D_i^p = 0.1D_i$. HRM map with $\mu_p = 2\mu_t$ with in-homogeneous diffusivity $D_s^p = 0.1D_s$ and $D_i^p = 0.1D_i$.

424 implant. Such a perturbation affects the overall displacement field inducted
 425 on the colon surrounding the patch, concurring with an altered pattern obtained
 426 for the intraluminal pressure map. Accordingly, such a preliminary
 427 analysis, in conjunction with the topographic pressure profiles in Fig. 10, con-

428 firms the sensitivity of colon motility to material stiffness and excitability.
 429 The gap in the p_i map is more pronounced than the case in Fig. 8 because
 430 the contraction of the tissue surrounding the patch is delayed. To better
 431 understand the effect of diffusivity, we repeated the simulation by reducing
 432 again the diffusivity of the patch by ten, and the results are presented in
 433 [Appendix E](#). The results confirm no significant difference with those pro-
 434 vided in Fig. 10, which means that diffusivity alone has a minor effect on the
 435 overall material behavior.

436 *The role of patch contractility.* In this numerical test, the implant electro-
 437 physiological properties and contractility vary from the surrounding host tis-
 438 sue. Namely, the SMC and ICC electrical conductivity in the patch, D_s^p, D_i^p ,
 439 are a hundred times lower than those in the tissue, D_s^t, D_i^t , and the ampli-
 440 tude of contractility in Eq. (2), α_i^p, α_c^p , is reduced as by 50%. The size of the
 441 elliptical region is fixed at $r_{\min} = 2$ cm and $r_{\max} = 3$ cm and material stiffness
 442 is considered $\mu_p = 2\mu_t$.

443 Figure 11 shows the evolution of the hydrostatic pressure p in the sur-
 444 roundings of the implant. It is worth noting that due to the reduction of
 445 contractility, significant variations can be observed in hydrostatic pressure
 446 compared to the case in Fig. 6. As electrophysiological properties are al-
 447 tered, the slow wave spatiotemporal distribution changes, and, in particular,
 448 the conduction velocity of the excitation wave lowers by enlarging the action
 449 potential wavelength when passing across the implant. The two contributions
 450 notably affect the overall displacement field u where a low displacement of
 451 0.4 cm is observed around the patch (see third row in Fig. 10), enforcing
 452 an altered motility pattern demonstrated by a clear gap in the intraluminal
 453 pressure profile in Fig. 11—a p_i gap more pronounced compared to the case in
 454 Fig. 10. Accordingly, such analysis confirms the sensitivity of colon motility
 455 to material stiffness, excitability, and contractility.

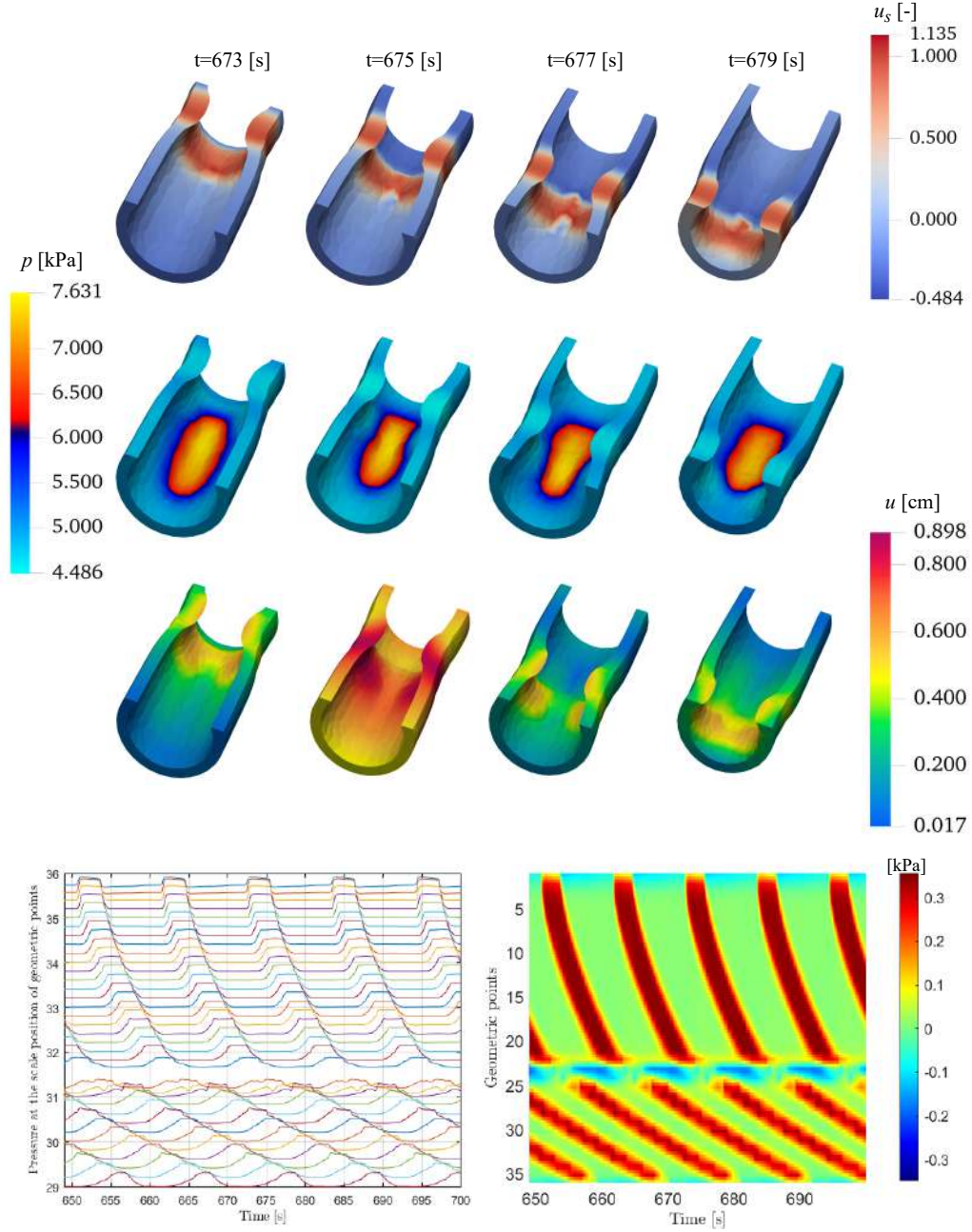


Figure 11: Temporal evolution of SMC transmembrane voltage u_s , of hydrostatic pressure p and the displacement u around the patch region with parameters $r_{\max} = 3$ and $r_{\min} = 2$ with stiffness $\mu_p = 2\mu_t$ and the diffusion coefficients $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$. HRM map with $\mu_p = 2\mu_t$ with in-homogeneous diffusivity $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$ and the contractility $\alpha_l^p = 50\%\alpha_l$ and $\alpha_c^p = 50\%\alpha_c$.

456 *The role of a non-cellularized patch.* In this numerical test, we consider a
457 patch not yet fully cellularized (representative of an early healing stage) with
458 altered electrophysiological properties. Namely, the SMC and ICC electrical
459 conductivity D_s^p, D_i^p are 10^2 times lower than those in the tissue, D_s^t, D_i^t ,
460 and the reaction terms Eq. (16) are 10^3 times lower (i.e., the reaction terms
461 are multiplied by a constant 10^{-3} factor). The patch size and stiffness are
462 maintained as in the previous case.

463 Figure 12 shows the evolution of the hydrostatic pressure p in the sur-
464 roundings of the implant. Though no significant variations are observed
465 compared to the case in Fig. 6, altered electrophysiological properties induce
466 a critical change in slow wave spatiotemporal dynamics leading to wave-
467 breaks around the patch (no closed rings). In particular, the excitation wave
468 is slowed, and its amplitude is reduced, thus flattening and prolonging the
469 duration of SMC action potential. The two reaction-diffusion contributions
470 affect the colon wall overall motility, leading to an altered pattern of intralu-
471 minal pressure maps: a clear gap in the recorded traces is representative of
472 no contraction. Such analysis is aligned with the topographic pressure pro-
473 files presented in Fig. 12, further confirming the sensitivity of colon motility
474 to bio-printed material cellular viability.

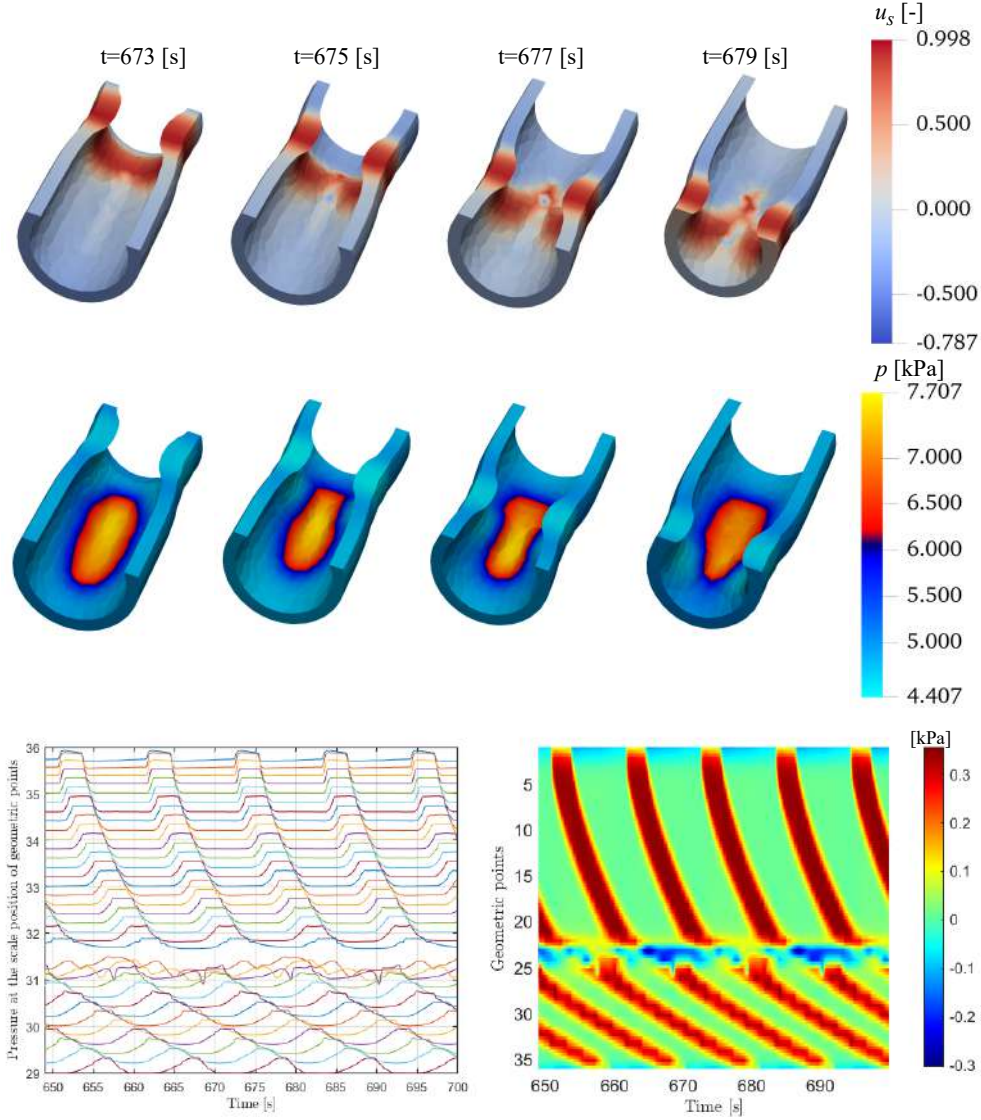


Figure 12: Temporal evolution of SMC transmembrane voltage u_s and hydrostatic pressure p around the patch region with parameters $r_{\max} = 3$ and $r_{\min} = 2$ with stiffness $\mu_p = 2\mu_t$ and the diffusion coefficients $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$. HRM map with $\mu_p = 2\mu_t$ with in-homogeneous diffusivity $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$ with the reaction terms (Eq. (16)) 10^3 times lower inside the patch.

475 *The role of patch contractility and altered electrophysiology.* In the last nu-
476 merical test, we combine the multiple cases discussed before by considering
477 a not fully cellularized patch (reducing the reaction terms by 10^{-3} and the
478 diffusion coefficients by 10^{-2}) but also considering a reduced material con-
479 tractility via α_i^p, α_c^p lowered by 50%. Size and stiffness of the patch are
480 maintained as in the previous case.

481 Figure 13 shows the results of the combined ill cases. As expected, hydro-
482 static pressure and slow waves are affected similarly, as well as the displace-
483 ment field u , which is practically two times lower than the case in Fig. 11.
484 However, regarding the HRM and topography maps, no contraction is asso-
485 ciated with a reduced displacement to 0.006 cm complemented with a larger
486 gap in the p_i map comprising a wider region around the patch. Such a
487 comprehensive analysis confirms the role and sensitivity of colon motility to
488 bio-printed material properties in various features.

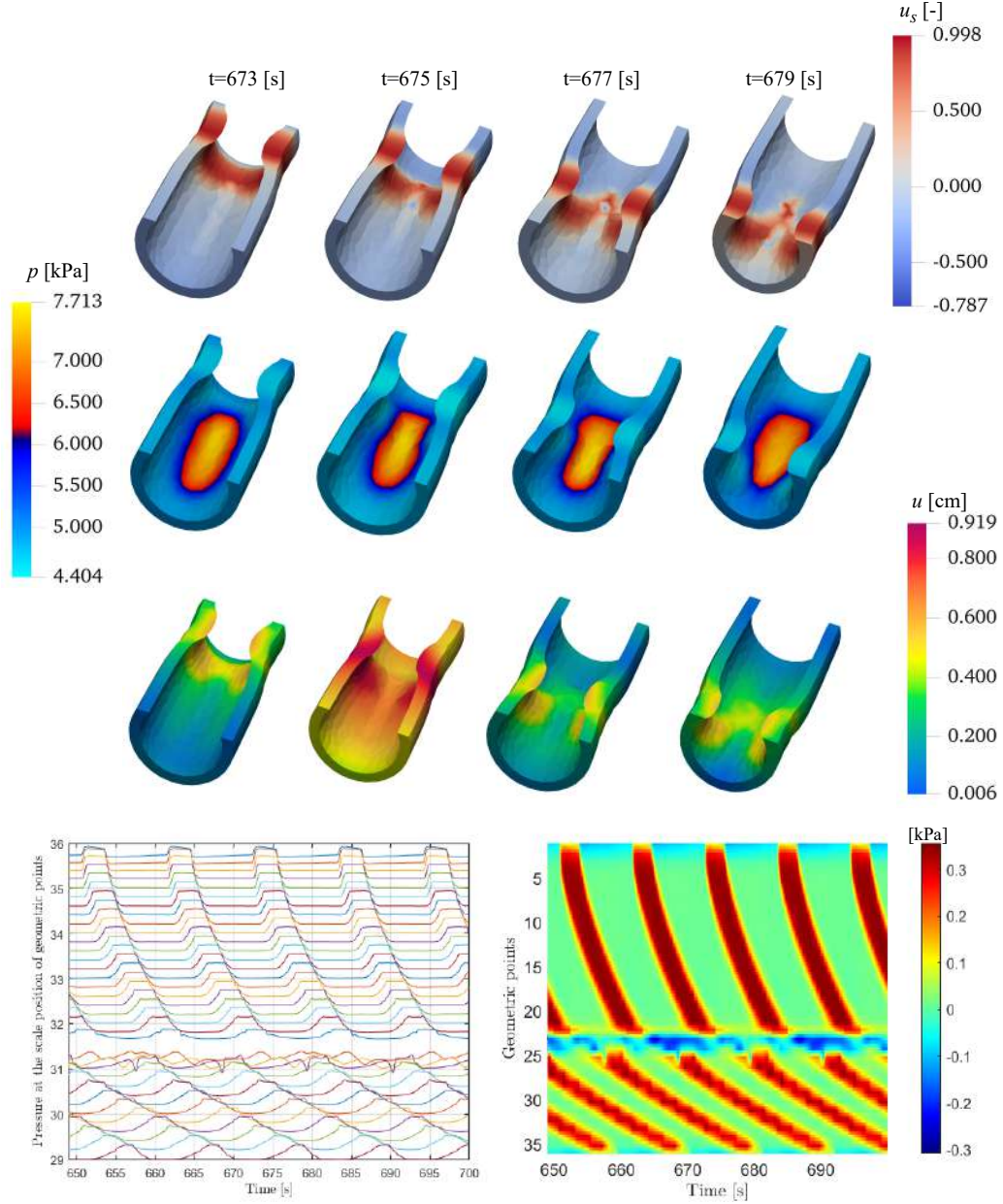


Figure 13: Temporal evolution of SMC transmembrane voltage u_s , the hydrostatic pressure p and the displacement u around the patch region with parameters $r_{\max} = 3$ and $r_{\min} = 2$ with stiffness $\mu_p = 2\mu_t$ and the diffusion coefficients $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$. HRM map and the pressure map with $\mu_p = 2\mu_t$ with in-homogeneous diffusivity $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$ and the contractility $\alpha_l^p = 50\%\alpha_l$ and $\alpha_c^p = 50\%\alpha_c$ and the reaction terms (Eq. (16)) 10^3 times lower inside the patch.

489 **5. Conclusion**

490 Several factors still hinder the advancement of GI electromechanics. These
491 include the intricate and historically poorly understood GI electrophysiology,
492 the complex mechanics of digesta (food undergoing digestion) tightly coupled
493 to its electrical features, and the limited knowledge of neural and hormonal
494 mechanisms regulating GI motility. Over the past decade, significant strides
495 have been made in all these areas, and the exponential growth in computa-
496 tional power now enables tackling even intricate multiphysics problems.

497 This paper presented a comprehensive multi-field computational frame-
498 work to model colonic motility, incorporating active strain electromechan-
499 ics, tissue anisotropy, and cellular electrophysiology. The obtained **in sil-**
500 **ico** has been exploited to characterize colon contractility in the presence of
501 bio-printed deposited materials, e.g., by LTS procedures, assumed to bond
502 perfectly to the surrounding healthy tissue.

503 The fully coupled system was numerically solved via a custom finite ele-
504 ment staggered scheme to exchange information among the electrophysiology-
505 ical and mechanical solvers efficiently. An extended calibration activity was
506 preliminarily conducted to provide a robust and reliable **in silico** model, thus
507 performing several benchmark tests: (i) the study of transmembrane action
508 potential conduction velocity; (ii) the entrainment frequency and stability
509 of ICCs and SMCs temporal dynamics; (iii) the fine-tuning of strain energy
510 material parameters upon multiaxial experimental data.

511 As an additional modeling step, the numerical values of intraluminal pres-
512 sures generated by colon contractions have been compared to high-resolution
513 manometry patterns, showing qualitative and quantitative agreement with
514 clinical data and providing a novel **in silico** characterization of colon motility
515 in health and disease. Accordingly, a series of parametric numerical analyses
516 revealed that excessive or reduced patch stiffness could affect the capability
517 of the colon to generate effective muscle contractions, resulting in impaired
518 motility. Furthermore, altered electrophysiological properties, also connected
519 with muscular contractility ruled by the active deformation gradient, con-
520 firmed the critical role of a cellularized patch. In particular, the proposed **in**
521 **silico model** is able to identify the possible outcomes of altered motility due
522 to LTS at different stages of the patch healing process.

523 *5.1. Limitations and perspectives*

524 The present model can reproduce contraction patterns of a colon tract by
525 embedding one single type of contraction wave, either high (HAPCs) or low
526 (LAPCs) amplitude propagation contractions [17, 18]. Such a limitation is
527 linked to the physiological onset of excitation waves, often initiated by the
528 enteric nervous system (ENS), not modeled in the present work [66, 67, 68].
529 In a forthcoming study, we are considering extending the present formulation
530 to account for ENS in a reliable and robust numerical implementation.

531 We considered a perfectly bounded patch representative of a correct heal-
532 ing process. Though not exploited, the *in silico* model has already been
533 formulated to account for generalized contact mechanics problems. In par-
534 ticular, irregular or localized faults can be considered in future studies.

535 As a modeling assumption, the four fiber families have been homogenized
536 within the thickness of the colon, limiting our ability to control the move-
537 ments of each muscle layer. In such a perspective, we are already working
538 to avoid such a limitation by implementing curvilinear thickness-dependent
539 anisotropies, mimicking rotational anisotropy patterns known for the cardiac
540 ventricular wall [69] and considering distributed fiber reinforcement [45].

541 With no loss of generality, we considered a simplified Neo-Hookean ma-
542 terial model as a basic modeling assumption. Several other choices could
543 be considered in the present case. Of particular interest for the GI tissues
544 is a poroelastic formulation [70, 71, 72], which should account for the high
545 permeability of the multiple GI wall layers that embed filtration as a key
546 function. Furthermore, active strain poroelasticity generalizes soft tissue in-
547 compressibility and stress-assisted electrophysiology diffusion [73, 74], which
548 may result in unrealistic for the GI wall.

549 In view of a preliminary parametric analysis and the lack of dedicated
550 data, we assumed uniform external pressure representative of an elastic and
551 isotropic surrounding tissue. A possible extension of the study should also
552 consider a cohesive zone model and material remodeling to reproduce the
553 multiple interfaces and loading acting on the external colon wall, affecting
554 internal pressure, re-absorption, and healing.

555 Finally, fluid-structure interaction is foreseen by coupling active strain
556 electromechanics with advanced fluid dynamics models [75], further modu-
557 lating the intraluminal pressure profile and critically affecting the shear stress
558 on the patch profile.

559 **Declaration of competing interest**

560 All co-authors have endorsed the manuscript's content, and no financial
561 interests need to be disclosed. We assert that this submission represents
562 original work and is not concurrently under review by any other publication.

563 **Data availability**

564 All the data utilized are detailed within this article.

565 **Acknowledgement**

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568 **References**

- 569 [1] F. E. Turrentine, C. E. Denlinger, V. B. Simpson, R. A. Garwood,
570 S. Guerlain, A. Agrawal, C. M. Friel, D. J. LaPar, G. J. Stukenborg,
571 R. S. Jones, Morbidity, mortality, cost, and survival estimates of gas-
572 trointestinal anastomotic leaks, *Journal of the American College of*
573 *Surgeons* 220 (2015) 195–206.
- 574 [2] A. Gizzi, C. Cherubini, N. Pomella, P. Persichetti, M. Vasta, S. Filippi,
575 Computational modeling and stress analysis of columellar biomechanics,
576 *Journal of the Mechanical Behavior of Biomedical Materials* 15 (2012)
577 46–58.
- 578 [3] S. A. Chadi, A. Fingerhut, M. Berho, S. R. DeMeester, J. W. Fleshman,
579 N. H. Hyman, D. A. Margolin, J. E. Martz, E. C. McLemore, D. Molena,
580 et al., Emerging trends in the etiology, prevention, and treatment of gas-
581 trointestinal anastomotic leakage, *Journal of Gastrointestinal Surgery*
582 20 (2016) 2035–2051.
- 583 [4] P. Simone, C. Carusi, F. Segreto, R. Iannuzzi, S. Buscaglione, A. Gizzi,
584 S. Giannitelli, A. Rainer, S. Filippi, P. Persichetti, Postbariatric brachio-
585 plasty with posteromedial scar: physical model, technical refinements,
586 and clinical outcomes, *Plastic and Reconstructive Surgery* 141 (2018)
587 344–353.
- 588 [5] A. Y. Gerasimenko, E. A. Morozova, D. I. Ryabkin, A. Fayzullin, S. V.
589 Tarasenko, V. V. Molodykh, E. S. Pyankov, M. S. Savelyev, E. A.
590 Sorokina, A. Y. Rogalsky, et al., Reconstruction of soft biological tissues
591 using laser soldering technology with temperature control and biopoly-
592 mer nanocomposites, *Bioengineering* 9 (2022) 238.
- 593 [6] M. A. Birkelbach, R. Smeets, I. Fiedler, L. Kluwe, M. Wehner, T. Trebst,
594 P. Hartjen, In vitro feasibility analysis of a new sutureless wound-closure
595 system based on a temperature-regulated laser and a transparent colla-
596 gen membrane for laser tissue soldering (Its), *International Journal of*
597 *Molecular Sciences* 21 (2020) 7104.
- 598 [7] S. Basov, D. Varssano, M. Platkov, I. Gabay, M. Rosner, I. Barequet,
599 M. Rattunde, J. Wagner, M. Harlev, D. Ofer, et al., Strong bonding of
600 corneal incisions using a noncontact fiber-optic laser soldering method,
601 *Journal of Biomedical Optics* 24 (2019) 128002–128002.

- 602 [8] F. Chirianni, G. Vairo, M. Marino, Development of process design tools
603 for extrusion-based bioprinting: From numerical simulations to nomo-
604 grams through reduced-order modeling, *Computer Methods in Applied*
605 *Mechanics and Engineering* 429 (2024) 116685.
- 606 [9] P. Alduini, Endoscopic system, 2021. WO2021152530A1.
- 607 [10] I. Nisky, Y. Che, Z. F. Quek, M. Weber, M. H. Hsieh, A. M. Okamura,
608 Teleoperated versus open needle driving: Kinematic analysis of experi-
609 enced surgeons and novice users, in: 2015 IEEE International Confer-
610 ence on Robotics and Automation (ICRA), IEEE, 2015, pp. 5371–5377.
- 611 [11] Y. Sharon, I. Nisky, Expertise, teleoperation, and task constraints affect
612 the speed–curvature–torsion power law in ramis, *Journal of Medical*
613 *Robotics Research* 3 (2018) 1841008.
- 614 [12] H.-C. Huang, C. R. Walker, A. Nanda, K. Rege, Laser welding of rup-
615 tured intestinal tissue using plasmonic polypeptide nanocomposite sol-
616 ders, *ACS Nano* 7 (2013) 2988–2998.
- 617 [13] I. Ashbell, N. Agam, A. Katzir, S. Basov, M. Platkov, I. Avital, I. Nisky,
618 U. Netz, Laser tissue soldering of the gastrointestinal tract: A systematic
619 review lts of the gastrointestinal tract, *Heliyon* 9 (2023) e16018.
- 620 [14] R. Urie, S. Quraishi, M. Jaffe, K. Rege, Gold nanorod-collagen
621 nanocomposites as photothermal nanosolders for laser welding of rup-
622 tured porcine intestines, *ACS Biomaterials Science & Engineering* 1
623 (2015) 805–815.
- 624 [15] M. Mushaben, R. Urie, T. Flake, M. Jaffe, K. Rege, J. Heys, Spatiotem-
625 poral modeling of laser tissue soldering using photothermal nanocom-
626 posites, *Lasers in Surgery and Medicine* 50 (2018) 143–152.
- 627 [16] J. Conklin, M. Pimentel, E. Soffer, *Color atlas of high resolution manom-*
628 *etry*, Springer, 2009.
- 629 [17] P. G. Dinning, E. Carrington, S. Scott, The use of colonic and anorectal
630 high-resolution manometry and its place in clinical work and in research,
631 *Neurogastroenterology & Motility* 27 (2015) 1693–1708.

- 632 [18] Y.-W. Li, Y.-J. Yu, F. Fei, M.-Y. Zheng, S.-W. Zhang, High-resolution
633 colonic manometry and its clinical application in patients with colonic
634 dysmotility: A review, *World Journal of Clinical Cases* 7 (2019) 2675.
- 635 [19] R. Yadlapati, P. J. Kahrilas, M. R. Fox, A. J. Bredenoord,
636 C. Prakash Gyawali, S. Roman, A. Babaei, R. K. Mittal, N. Rommel,
637 E. Savarino, et al., Esophageal motility disorders on high-resolution
638 manometry: Chicago classification version 4.0©, *Neurogastroenterol-
639 ogy & Motility* 33 (2021) e14058.
- 640 [20] J. H. Noh, K. W. Jung, I. J. Yoon, H. K. Na, J. Y. Ahn, J. H. Lee, D. H.
641 Kim, K. D. Choi, H. J. Song, G. H. Lee, et al., Comparison of diagnosis
642 of esophageal motility disorders by chicao classification versions 3.0 and
643 4.0, *Journal of Neurogastroenterology and Motility* 29 (2023) 326.
- 644 [21] R. R. Rai, V. M. Prasad, Prokinetics in the management of upper
645 gastrointestinal motility disorders: an indian expert opinion review, *In-
646 ternational Journal of Advances in Medicine* 8 (2021) 1442.
- 647 [22] J. D. Huizinga, W. J. Lammers, Gut peristalsis is governed by a mul-
648 titude of cooperating mechanisms, *American Journal of Physiology-
649 Gastrointestinal and Liver Physiology* 296 (2009) G1–G8.
- 650 [23] K. M. Sanders, Y. Kito, S. J. Hwang, S. M. Ward, Regulation of gas-
651 trointestinal smooth muscle function by interstitial cells, *Physiology* 31
652 (2016) 316–326.
- 653 [24] K. M. Sanders, S. D. Koh, S. M. Ward, Interstitial cells of cajal as
654 pacemakers in the gastrointestinal tract, *Annu. Rev. Physiol.* 68 (2006)
655 307–343.
- 656 [25] P. Tremain, C.-H. A. Chan, D. Rowbotham, G. Lim, G. O’Grady, L. K.
657 Cheng, J. McKeage, T. R. Angeli-Gordon, Endoscopic mapping of bio-
658 electric slow waves in the gastric antrum, *Device* (2024) 100292.
- 659 [26] M. L. Buist, Y. C. Poh, An extended bidomain framework incorporating
660 multiple cell types, *Biophysical journal* 99 (2010) 13–18.
- 661 [27] P. Du, G. O’Grady, J. B. Davidson, L. K. Cheng, A. J. Pullan, Mul-
662 tiscala modeling of gastrointestinal electrophysiology and experimental
663 validation, *Critical Reviews™ in Biomedical Engineering* 38 (2010).

- 664 [28] P. Du, J. Lim, L. K. Cheng, A model of electromechanical coupling in
665 the small intestine, *Multiscale Computer Modeling in Biomechanics and*
666 *Biomedical Engineering* (2013) 179–207.
- 667 [29] R. Lees-Green, P. Du, G. O’Grady, A. Beyder, G. Farrugia, A. J. Pullan,
668 Biophysically based modeling of the interstitial cells of cajal: current
669 status and future perspectives, *Frontiers in Physiology* 2 (2011) 29.
- 670 [30] A. Corrias, P. Du, M. L. Buist, Modelling tissue electrophysiology in
671 the gi tract: past, present and future, *New Advances in Gastrointestinal*
672 *Motility Research* (2013) 167–195.
- 673 [31] O. N. Athavale, R. Avci, L. K. Cheng, P. Du, Computational models
674 of autonomic regulation in gastric motility: Progress, challenges, and
675 future directions, *Frontiers in Neuroscience* 17 (2023) 1146097.
- 676 [32] O. N. Athavale, R. Avci, A. R. Clark, M. R. Di Natale, X. Wang, J. B.
677 Furness, Z. Liu, L. K. Cheng, P. Du, Neural regulation of slow waves
678 and phasic contractions in the distal stomach: a mathematical model,
679 *Journal of Neural Engineering* 20 (2024) 066040.
- 680 [33] A. Corrias, M. L. Buist, A quantitative model of gastric smooth muscle
681 cellular activation, *Annals of Biomedical Engineering* 35 (2007) 1595–
682 1607.
- 683 [34] A. Corrias, M. L. Buist, Quantitative cellular description of gastric
684 slow wave activity, *American Journal of Physiology-Gastrointestinal*
685 *and Liver Physiology* 294 (2008) G989–G995.
- 686 [35] J. W. Yeoh, A. Corrias, M. L. Buist, Modelling human colonic smooth
687 muscle cell electrophysiology, *Cellular and Molecular Bioengineering* 10
688 (2017) 186–197.
- 689 [36] R. R. Aliev, W. Richards, J. P. Wikswo, A simple nonlinear model of
690 electrical activity in the intestine, *Journal of Theoretical Biology* 204
691 (2000) 21–28.
- 692 [37] S. Brandstaeter, A. Gizzi, S. L. Fuchs, A. M. Gebauer, R. C. Aydin,
693 C. J. Cyron, Computational model of gastric motility with active-strain

- 694 electromechanics, ZAMM-Journal of Applied Mathematics and Mechan-
695 ics/Zeitschrift für Angewandte Mathematik und Mechanik 98 (2018)
696 2177–2197.
- 697 [38] A. Gizzi, C. Cherubini, S. Migliori, R. Alloni, R. Portuesi, S. Filippi,
698 On the electrical intestine turbulence induced by temperature changes,
699 Physical Biology 7 (2010) 016011.
- 700 [39] M. Hanani, G. Farrugia, T. Komuro, Intercellular coupling of interstitial
701 cells of cajal in the digestive tract, International Review of Cytology
702 242 (2005) 249–282.
- 703 [40] S. Papenkort, M. Borsdorf, M. Böl, T. Siebert, A geometry model of the
704 porcine stomach featuring mucosa and muscle layer thicknesses, Journal
705 of the Mechanical Behavior of Biomedical Materials 142 (2023) 105801.
- 706 [41] I. Toniolo, C. G. Fontanella, M. Foletto, E. L. Carniel, Coupled ex-
707 perimental and computational approach to stomach biomechanics: To-
708 wards a validated characterization of gastric tissues mechanical proper-
709 ties, Journal of the Mechanical Behavior of Biomedical Materials 125
710 (2022) 104914.
- 711 [42] S. J. Friis, T. S. Hansen, M. Poulsen, H. Gregersen, A. Brüel, J. V.
712 Nygaard, Biomechanical properties of the stomach: A comprehensive
713 comparative analysis of human and porcine gastric tissue, Journal of
714 the Mechanical Behavior of Biomedical Materials 138 (2023) 105614.
- 715 [43] H. S. Hosseini, J. S. Taylor, L. S. Wood, J. C. Dunn, Biomechanics
716 of small intestine during distraction enterogenesis with an intraluminal
717 spring, Journal of the Mechanical Behavior of Biomedical Materials 101
718 (2020) 103413.
- 719 [44] R. Aydin, S. Brandstaeter, F. Braeu, M. Steigenberger, R. Marcus,
720 K. Nikolaou, M. Notohamiprodjo, C. Cyron, Experimental character-
721 ization of the biaxial mechanical properties of porcine gastric tissue,
722 Journal of the Mechanical Behavior of Biomedical Materials 74 (2017)
723 499–506.
- 724 [45] A. Pandolfi, A. Gizzi, M. Vasta, Coupled electro-mechanical models
725 of fiber-distributed active tissues, Journal of Biomechanics 49 (2016)
726 2436–2444.

- 727 [46] A. Pandolfi, A. Gizzi, M. Vasta, Visco-electro-elastic models of fiber-
728 distributed active tissues, *Meccanica* 52 (2017) 3399–3415.
- 729 [47] S. Johnson, M. Schultz, M. Scholze, T. Smith, J. Woodfield, N. Hammer,
730 How much force is required to perforate a colon during colonoscopy? an
731 experimental study, *Journal of the Mechanical Behavior of Biomedical*
732 *Materials* 91 (2019) 139–148.
- 733 [48] B. Patel, A. Gizzi, J. Hashemi, Y. Awakeem, H. Gregersen, G. Kassab,
734 Biomechanical constitutive modeling of the gastrointestinal tissues: A
735 systematic review, *Materials & Design* 217 (2022) 110576.
- 736 [49] S. Puértolas, E. Peña, A. Herrera, E. Ibarz, L. Gracia, A compara-
737 tive study of hyperelastic constitutive models for colonic tissue fitted to
738 multiaxial experimental testing, *Journal of the Mechanical Behavior of*
739 *Biomedical Materials* 102 (2020) 103507.
- 740 [50] G. A. Holzapfel, *Nonlinear solid mechanics: a continuum approach for*
741 *engineering science*, 2002.
- 742 [51] G. A. Holzapfel, R. W. Ogden, Constitutive modelling of arteries, *Pro-*
743 *ceedings of the Royal Society A: Mathematical, Physical and Engineer-*
744 *ing Sciences* 466 (2010) 1551–1597.
- 745 [52] C. Cherubini, S. Filippi, P. Nardinocchi, L. Teresi, An electromechani-
746 cal model of cardiac tissue: Constitutive issues and electrophysiological
747 effects, *Progress in biophysics and molecular biology* 97 (2008) 562–573.
- 748 [53] D. Ambrosi, G. Arioli, F. Nobile, A. Quarteroni, Electromechanical
749 coupling in cardiac dynamics: the active strain approach, *SIAM Journal*
750 *on Applied Mathematics* 71 (2011) 605–621.
- 751 [54] R. Ruiz-Baier, A. Gizzi, A. Loppini, C. Cherubini, S. Filippi, Thermo-
752 electric effects in an anisotropic active-strain electromechanical model,
753 *Commun Comput Phys* 27 (2020) 87–115.
- 754 [55] D. P. Sokolis, Variation of passive biomechanical properties of the small
755 intestine along its length: microstructure-based characterization, *Bio-*
756 *engineering* 8 (2021) 32.

- 757 [56] S. Nagaraja, K. Leichsenring, M. Ambati, L. De Lorenzis, M. Böl, On
758 a phase-field approach to model fracture of small intestine walls, *Acta*
759 *Biomaterialia* 130 (2021) 317–331.
- 760 [57] R. Piersanti, P. C. Africa, M. Fedele, C. Vergara, L. Dedè, A. F. Corno,
761 A. Quarteroni, Modeling cardiac muscle fibers in ventricular and atrial
762 electrophysiology simulations, *Computer Methods in Applied Mechanics*
763 *and Engineering* 373 (2021) 113468.
- 764 [58] S. Rossi, T. Lassila, R. Ruiz-Baier, A. Sequeira, A. Quarteroni, Ther-
765 modynamically consistent orthotropic activation model capturing ven-
766 tricular systolic wall thickening in cardiac electromechanics, *European*
767 *Journal of Mechanics-A/Solids* 48 (2014) 129–142.
- 768 [59] K. S. Chavan, B. P. Lamichhane, B. I. Wohlmuth, Locking-free finite ele-
769 ment methods for linear and nonlinear elasticity in 2d and 3d, *Computer*
770 *Methods in Applied Mechanics and Engineering* 196 (2007) 4075–4086.
- 771 [60] M. Alnæs, J. Blechta, J. Hake, A. Johansson, B. Kehlet, A. Logg,
772 C. Richardson, J. Ring, M. E. Rognes, G. N. Wells, The fenics project
773 version 1.5, *Archive of Numerical Software* 3 (2015).
- 774 [61] C. M. Stauffer, C. Pfeifer, *Colonoscopy*, StatPearls Publishing, Treasure
775 Island (FL), 2023.
- 776 [62] H. F. Helander, L. Fändriks, Surface area of the digestive tract—revisited,
777 *Scandinavian Journal of Gastroenterology* 49 (2014) 681–689.
- 778 [63] S. Choudhury, Stress analysis of thick walled cylinder, Ph.D. thesis,
779 2013.
- 780 [64] M. R. Lindeburg, *PPI Mechanical Engineering Reference Manual*, eText-
781 6 Months, 1 Year, Simon and Schuster, 2019.
- 782 [65] R. A. Arbizu, S. Nurko, N. Heinz, M. Amicangelo, L. Rodriguez,
783 Prospective evaluation of same day versus next day colon manometry
784 results in children with medical refractory constipation, *Neurogastroen-*
785 *terology & Motility* 29 (2017) e13050.
- 786 [66] C. Fung, P. Vanden Berghe, Functional circuits and signal processing
787 in the enteric nervous system, *Cellular and Molecular Life Sciences* 77
788 (2020) 4505–4522.

- 789 [67] B. B. Barth, C. S. Henriquez, W. M. Grill, X. Shen, Electrical stimu-
790 lation of gut motility guided by an in silico model, *Journal of Neural*
791 *Engineering* 14 (2017) 066010.
- 792 [68] B. B. Barth, X. Shen, Computational motility models of neurogastroen-
793 terology and neuromodulation, *Brain Research* 1693 (2018) 174–179.
- 794 [69] S. Land, V. Gurev, S. Arens, C. M. Augustin, L. Baron, R. Blake,
795 C. Bradley, S. Castro, A. Crozier, M. Favino, et al., Verification of car-
796 diac mechanics software: benchmark problems and solutions for testing
797 active and passive material behaviour, *Proceedings of the Royal So-*
798 *ciety A: Mathematical, Physical and Engineering Sciences* 471 (2015)
799 20150641.
- 800 [70] R. Oyarzúa, R. Ruiz-Baier, Locking-free finite element methods for
801 poroelasticity, *SIAM Journal on Numerical Analysis* 54 (2016) 2951–
802 2973.
- 803 [71] N. A. Barnafi, B. Gómez-Vargas, W. d. J. Lourenço, R. F. Reis, B. M.
804 Rocha, M. Lobosco, R. Ruiz-Baier, R. W. dos Santos, Finite element
805 methods for large-strain poroelasticity/chemotaxis models simulating
806 the formation of myocardial oedema, *Journal of Scientific Computing*
807 92 (2022) 92.
- 808 [72] W. d. J. Lourenço, R. F. Reis, R. Ruiz-Baier, B. M. Rocha, R. W.
809 Dos Santos, M. Lobosco, A poroelastic approach for modelling myocar-
810 dial oedema in acute myocarditis, *Frontiers in Physiology* 13 (2022)
811 888515.
- 812 [73] D. E. Hurtado, S. Castro, A. Gizzi, Computational modeling of non-
813 linear diffusion in cardiac electrophysiology: A novel porous-medium
814 approach, *Computer Methods in Applied Mechanics and Engineering*
815 300 (2016) 70–83.
- 816 [74] C. Cherubini, S. Filippi, A. Gizzi, R. Ruiz-Baier, A note on stress-driven
817 anisotropic diffusion and its role in active deformable media, *Journal of*
818 *Theoretical Biology* 430 (2018) 221–228.
- 819 [75] N. Palmada, S. Hosseini, R. Avci, J. Cater, V. Suresh, L. Cheng, A sys-
820 tematic review of computational fluid dynamics models in the stomach
821 and small intestine, *Applied Sciences* 13 (2023) 6092.

- 822 [76] A. Quarteroni, T. Lassila, S. Rossi, R. Ruiz-Baier, Integrated
823 heart—coupling multiscale and multiphysics models for the simulation
824 of the cardiac function, *Computer Methods in Applied Mechanics and*
825 *Engineering* 314 (2017) 345–407.
- 826 [77] K. M. Sanders, S. M. Ward, S. D. Koh, Interstitial cells: regulators of
827 smooth muscle function, *Physiological Reviews* 94 (2014) 859–907.
- 828 [78] D. P. Sokolis, S. G. Sassani, Microstructure-based constitutive modeling
829 for the large intestine validated by histological observations, *Journal of*
830 *the Mechanical Behavior of Biomedical Materials* 21 (2013) 149–166.

831 **Appendix A. Entrainment analysis of the ICC cells and mesh con-**
832 **vergence analysis**

833 Entrainment is one of the most significant mechanisms in gastrointestinal
834 electrophysiology. This phenomenon is inherent. The excitability parame-
835 ter and, consequently, the intrinsic frequency of electrical oscillations at the
836 cellular level are larger in the upper than in the lower portion of the gastroin-
837 testinal tract. Excitability and frequency in the stomach are obviously higher
838 in the proximal region than in the distal region near the pylorus. Similarly,
839 the pylorus has a greater frequency than the duodenum, which has a higher
840 frequency than the jejunum and we have the same behavior in the colon.
841 This implies that the oscillation frequencies of the ICCs in these areas would
842 differ greatly if they were isolated. However, the ICCs in the lower region
843 are trained due to the cellular interaction at the tissue and organ level and
844 for good movement coordination. To put it another way, the high-frequency
845 cells and the low-frequency cells are compelled to vibrate at about the same
846 frequency.

847
848 In accordance with this theory, we ran a simulation for 1000 s on a com-
849 putational domain. In order to determine the frequency, we then extracted
850 the data along a line that extended from [0,50] cm. Fig .A.14 depicts the
851 frequency gradient's temporal progression. Initially, every point exhibits its
852 own frequency of oscillation. As a result, at $t = 0s$, there is a noticeable fre-
853 quency gradient throughout the domain. Gradient reduces with time. The
854 electrical oscillations of the ICC demonstrate nearly constant frequency from
855 $t = 550s$, which is the same as the ICC's initial frequency in the top region
856 of the domain (i.e. at $z = 0$).

857
858 This suggests that these pacemaker ICCs in the upper portion of the do-
859 main have driven the ICCs at the other end. Horizontal straight lines show
860 that training from $t = 550s$ is consistent throughout the domain. This out-
861 come ensures that the model can replicate a physiological entrainment proce-
862 dure. In order to validate this behavior, we present in Fig.A.15 the progres-
863 sion of the phase portrait for the two electrophysiological state variables for
864 SMC and ICC from their intrinsic to entrained states. The last 450 seconds,
865 which we have highlighted in red, demonstrate how both cell types form a
866 stable limit cycle. This indicates that, after 550 seconds, the system has sta-
867 bilized. Brandstaeter et al. [37] was the first to perform this kind of analysis.

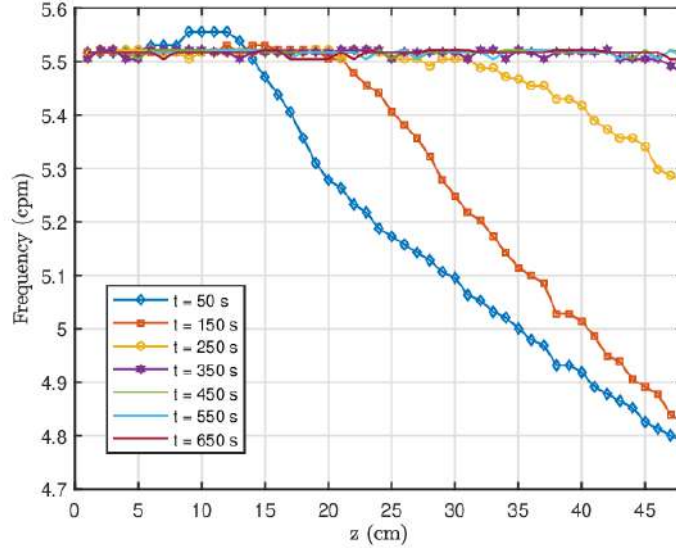


Figure A.14: Temporal evolution of the frequency of the ICC at each point

868 This analysis's ability to solve the electrophysiological problem alone for up
 869 to 550 seconds before linking it to the mechanics problem is a crucial feature.
 870 To assess the accuracy of the numerical scheme described in the previous sec-
 871 tion, a series of numerical tests is carried out. The first test aims to study
 872 the convergence of the electrophysiological solver towards the physical solu-
 873 tion as a function of mesh size or degree of freedom (DoF). For this purpose,
 874 we consider the same cylindrical domain as in the previous. For simplicity
 875 and to facilitate the implementation of this test, the domain is constructed
 876 directly in `FEniCS` and triangular Lagrangian finite elements and a homo-
 877 geneous mesh of size are used. Different refinements are considered based
 878 on the number of subdivisions $N \in [50, 100, 150, 200, 250, 300, 350, 400, 450]$.
 879 Each simulation runs for a total duration $t = 800s$ with a constant time step
 880 $\Delta t = 0.1s$.

881

882 It is well known that the conduction velocity of reaction-diffusion systems
 883 generally depends on the numerical scheme. This analysis aims to obtain a
 884 physiologically acceptable conduction velocity (CV). [76].

885

886 We calculated the conduction velocity at a point located in the middle

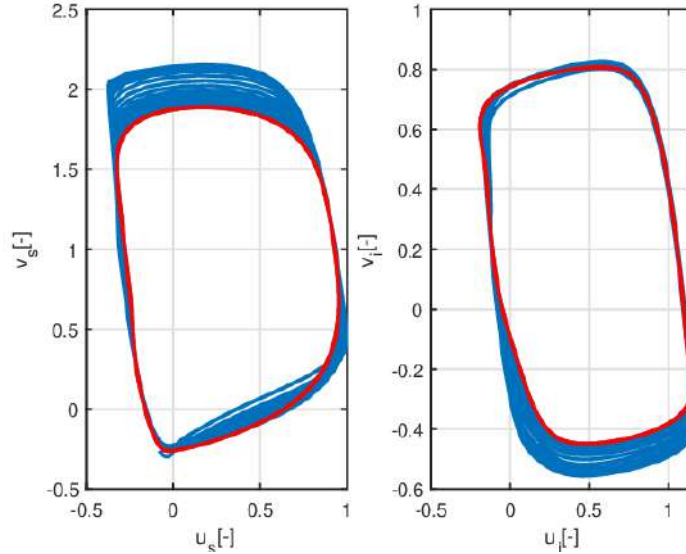


Figure A.15: Development of the phase portraits from the intrinsic to the entrained state of ICCs (right) and SMCs (left) located in the middle of the domain at $z = 25cm$. The resulting stable limit cycle is shown in red.

887 of the domain to avoid contamination of the boundary conditions. Fig.A.16
 888 shows us the evolution of the conduction velocity as a function of the degree
 889 of freedom. we see that a coarse mesh tends to overestimate the conduction
 890 velocity. the more the number of degrees of freedom increases, the more
 891 the conduction velocity tends towards a stable value. This simulation also
 892 shows us that the conduction velocity is within the range of physiologically
 893 acceptable values [77].

894 Appendix B. Tuning of mechanical parameters

895 To calibrate our passive material model and associated code, we under-
 896 took a series of tests to calibrate the model parameters. These tests include
 897 a uniaxial test based on Nagaraja data [56], and a triaxial test using cylinder
 898 occlusion based on Sokolis data [78]. We would like to point out that as
 899 we did not have the original experimental data, we were content to validate
 900 part of the authors' experimental curve. To this end, we have extracted data
 901 from their figure to use it as a reference. About the uniaxial test, most of
 902 the parameters were taken from Nagaraja et al. [56] study, which we then

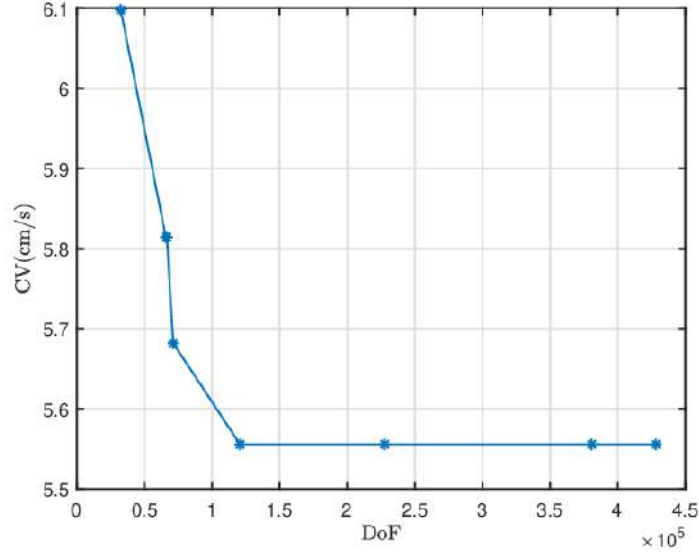


Figure A.16: conduction velocity analysis

903 used as a basis for approximating certain points in Sokolis and Sassani [78]
 904 experimental data.

905

906 We began by attempting to reproduce Nagaraja’s experimental results
 907 with our model. To this end, we performed a uniaxial test aimed at reproduc-
 908 ing Nagaraja’s experimental results for the case where β (the cutting angle
 909 of the sample.) is equal to 90° . This test was performed for the maximum
 910 and minimum values of the parameters, and some parameters were adjusted
 911 to approximate the experimental values. Figure B.17 below illustrates the
 912 comparison between the model and the experimental. We can see that the
 913 model comes closer to the experimental curve for the minimum parameters.
 914 This shows that these parameters can be used without causing errors in the
 915 code. The calibrated data are summarised in the following table B.4.

To be more consistent about the model’s performance, we carried out a

Table B.4: Table of Material used for the uni-axial test [56]

sets	$\mu[kPa]$	$k_1^l[kPa]$	$k_2^l[-]$	$k_1^c[kPa]$	$k_2^c[-]$	$k_1^d[kPa]$	$k_2^d[-]$	$\theta[^\circ]$
max	5	77.35	1.04	0.95	0.06	7.38	0.6	39.78
min	5	5.14	1.19	0.78	0.02	3.65	0.31	38.18

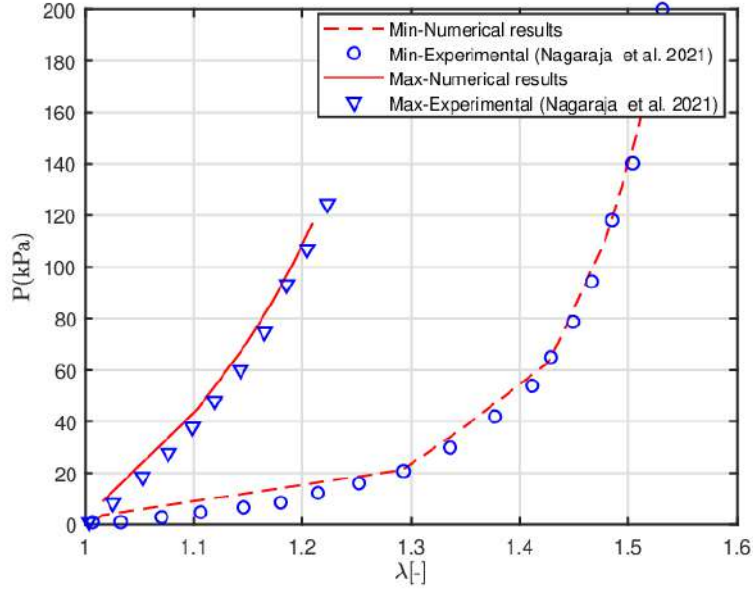


Figure B.17: Comparison between simulation of the uni-axial test and experimental data.

916
 917 carefully calibrated inflation test. As shown in the figure B.18, a 3.5 cm long
 918 cylinder was used for this purpose [78]. Pressure was applied to the inner
 919 surface of the cylinder, while both ends were clamped. After each inflation,
 920 the parameters were carefully adjusted to reproduce the experimental data
 921 faithfully and to extract the outer radius. The agreement between the model
 922 and the experimental data from [78] is clearly demonstrated in the figure
 923 below. The parameters obtained after calibration are detailed in Table B.5.
 These data will be crucial for all future simulations.

Table B.5: Table of Material used for the three-axial test

parameters	$\mu[kPa]$	$k_1^l[kPa]$	$k_2^l[-]$	$k_1^c[kPa]$	$k_2^c[-]$	$k_1^d[kPa]$	$k_2^d[-]$	$\theta[^\circ]$
values	2.5	5.4324	1.19	0.78	0.02	3.65	0.31	39.5

924

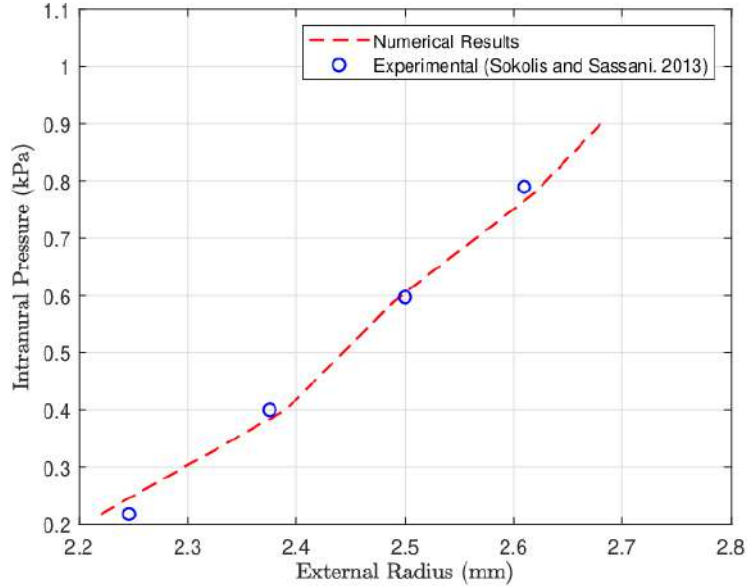


Figure B.18: Comparison between simulation of the three-axial test and experimental data.

925 Appendix C. Fibers generation procedure

926 We start by the configuration show in Figs C.19. The curvilinear coordinates are obtained by solving the stationary modified scalar diffusion with
 927 the corresponding boundary conditions.
 928

$$\nabla^2 \zeta = 0 \quad \text{on} \quad \Omega_0 \quad (\text{C.1a})$$

$$\zeta = \zeta_0 \quad \text{on} \quad \partial\Gamma_D \quad (\text{C.1b})$$

$$\mathbf{n} \cdot \nabla \zeta = 0 \quad \text{on} \quad \partial\Gamma_N \quad (\text{C.1c})$$

929 where ζ is an arbitrary scalar field, ζ_0 is the value prescribed on the Dirichlet
 930 boundary ($\partial\Gamma_D$), and \mathbf{n} is the unit vector of the surface normal. The discrete longitudinal vector field $\nabla\zeta_z$ is obtained by solving Eqs. C.1 with the
 931 Neumann boundary condition prescribed on the inner and outer surfaces, together with the Dirichlet boundary condition prescribed on both end surfaces
 932 as shown in Figs. C.19. The final longitudinal fiber direction is obtained by
 933 the normalisation $\mathbf{n}_l = \nabla\zeta_z / \|\nabla\zeta_z\|$.
 934
 935 The radial vector direction \mathbf{n}_r is obtained similarly, only the Neumann and
 936

937 Dirichlet boundary conditions must be interchanged. Then, the circumferen-
 938 tial fiber direction \mathbf{n}_c is defined as a cross product of the unitary radial and
 939 longitudinal vector fields, \mathbf{n}_r and \mathbf{n}_l . Regarding the helical fiber direction,
 940 two additional parameters are necessary, a unit vector \mathbf{r}_0 aligned with the
 941 centreline and the angle θ that will determine the rotational anisotropy from
 942 the circumferential direction. Once the radial direction has been computed,
 943 we project the centreline on the normal direction and compute the so-called
 944 flat fiber field \mathbf{r}_f [54]. Then the diagonal fibers are obtained by using the
 945 Rodrigues rotation formula.

$$\mathbf{n}_{d1} = \mathbf{r}_f \cos(\theta) + (\mathbf{n}_l \times \mathbf{r}_f) \sin(\theta) + \mathbf{n}_l(\mathbf{n}_l \cdot \mathbf{r}_f)(1 - \cos(\theta)) \quad (\text{C.2})$$

a similar expression can be derived for \mathbf{n}_{d2} .

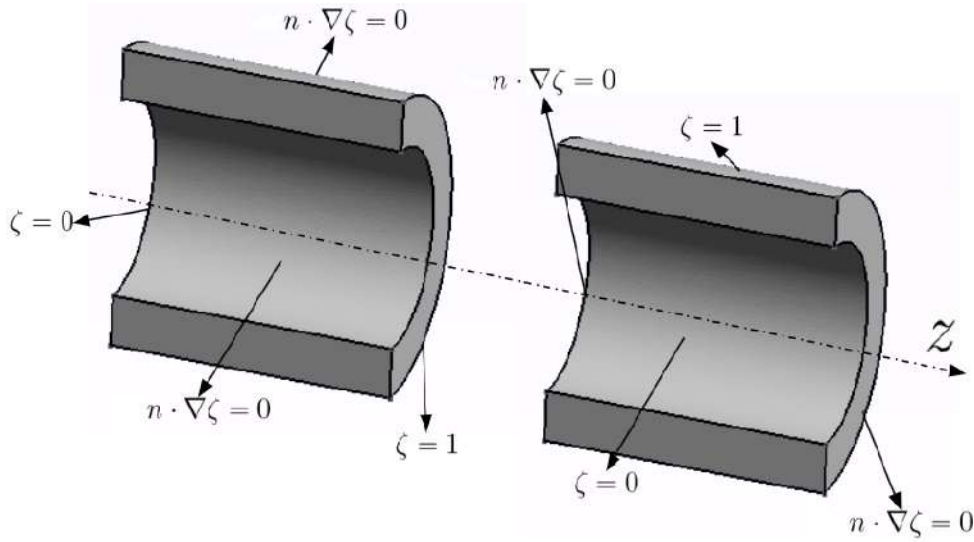


Figure C.19: Configuration used to compute fiber orientation in the colon, left represents the configuration for the longitudinal fibers and right the configuration for the radial fibers.

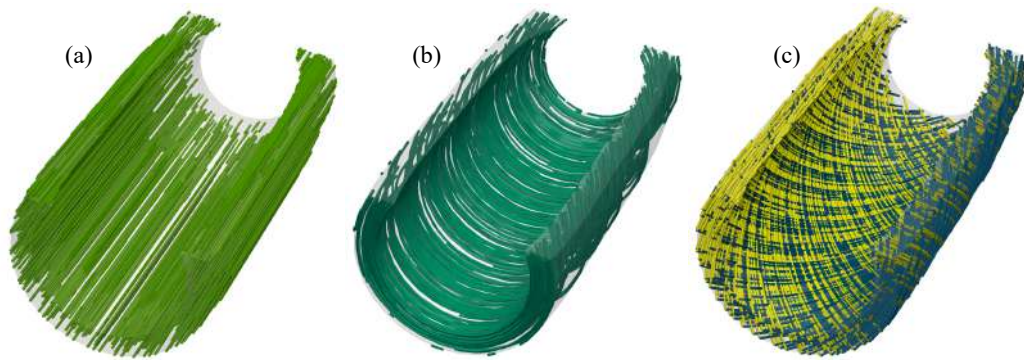


Figure C.20: Result of the fiber structure used for all simulations (a) the longitudinal fiber, (b) circumferential fibers, and (c) the diagonal fibers. All the fiber families are homogenised throughout all the thicknesses.

947 **Appendix D. Zoomed clip of the region of interest where the patch**
948 **is located**

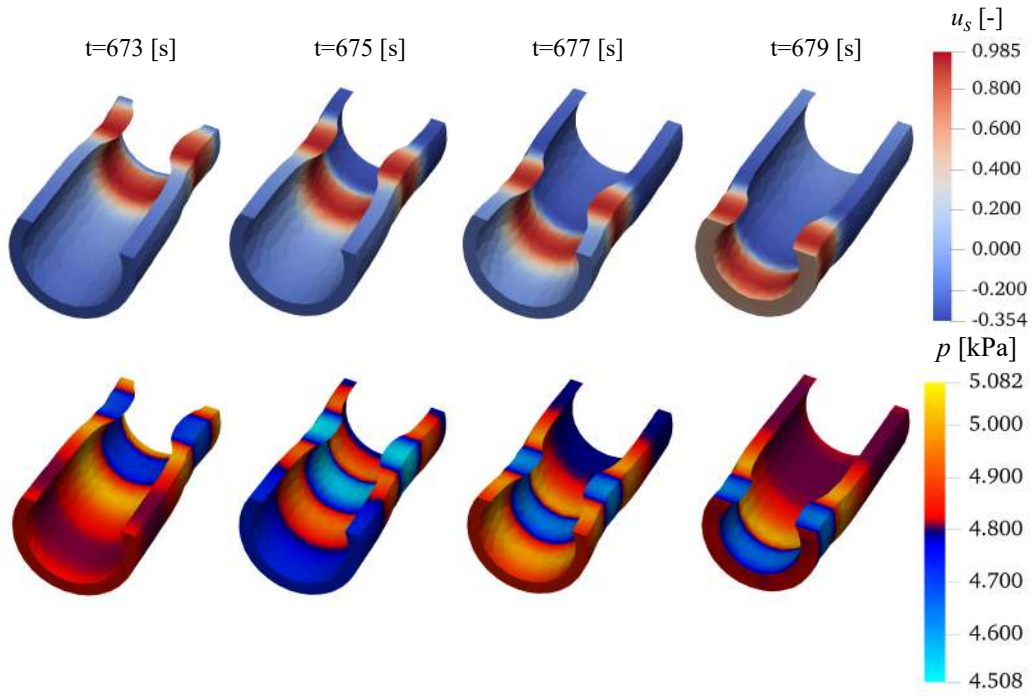


Figure D.21: Temporal evolution of the hydrostatic pressure p , the action potential in the smooth muscle layer u_s , and the longitudinal and circumferential fibers distribution in the deformed domain corresponding to healthy condition ($\mu_p = \mu_t$).

949 **Appendix E. Numerical solution of the nonlinear diffusivity with**
 950 $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$

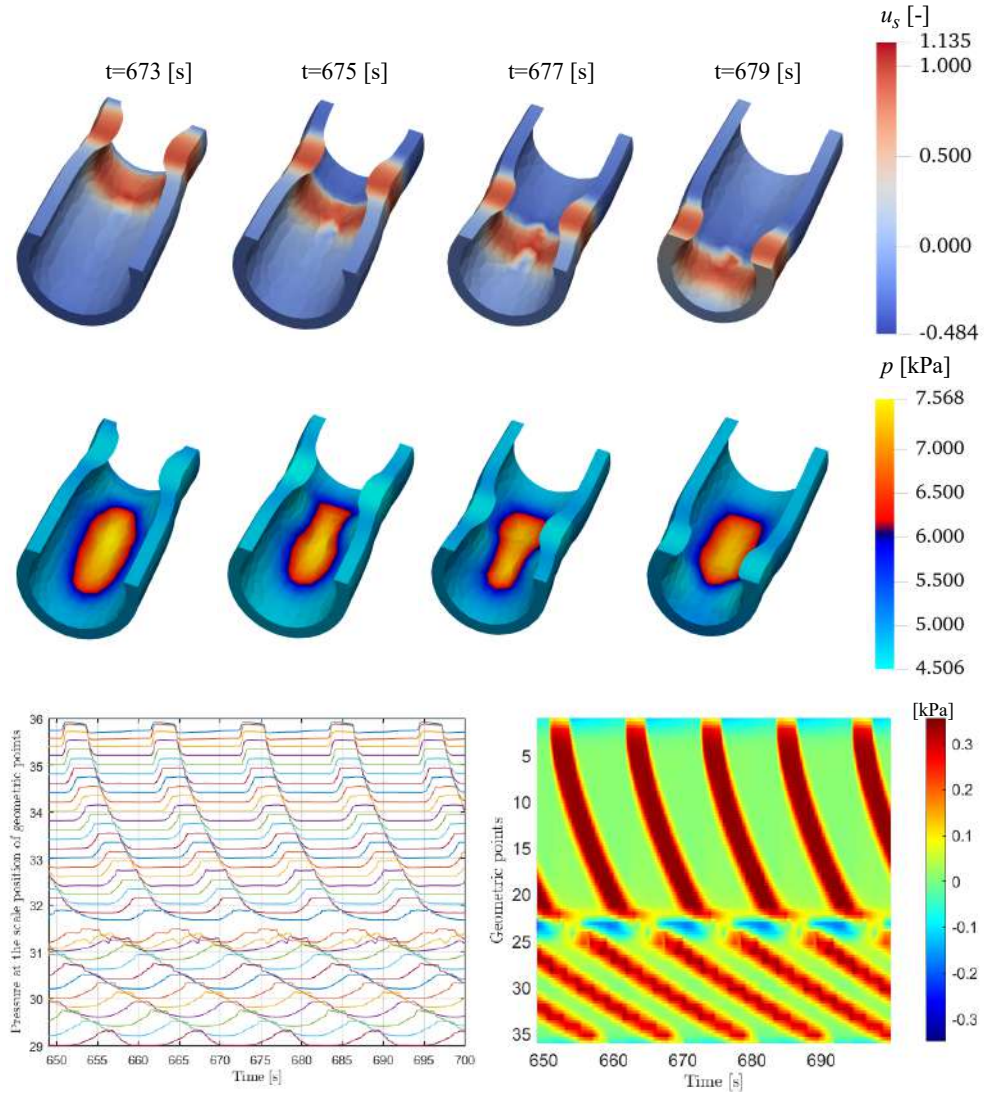


Figure E.22: Temporal evolution of hydrostatic pressure p and the action potential in the smooth muscle layer u_s in a region around an elliptical geometry of radii $r_{\max} = 3$ and $r_{\min} = 2$ with stiffness $\mu_p = 2\mu_t$ and the diffusion coefficients $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$. HRM map with $\mu_p = 2\mu_t$ with in-homogeneous diffusivity $D_s^p = 0.01D_s$ and $D_i^p = 0.01D_i$