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 1. Introduction

Anastomotic leakage following resection of gastrointestinal (GI) lesions is 2 a primary source of concern for clinicians and patients alike [1]. Nowadays, 3 developing techniques to improve tissue resection and sealing, thus reduc-4 ing leakage rates, are essential to increase the reliability of interventions in 5 a clinical setting. Current methods of tissue fixation, such as sutures or 6 staples, exert tensile and compressive forces on the attached tissue, potentially forming gaps in the anastomotic line, resulting in anastomotic leakage 8 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 10 as skin, cornea, buccal mucosa, and even nerves using laser tissue soldering 11 (LTS) and laser tissue welding (LTW) [5, 6, 7] principally. The advantage of 12 these techniques is that they allow to glue tissues that have been bio-printed 13 [8]. In this regard, patches can be 3D printed externally, or, thanks to new 14 emerging technologies protected by patents [9], they can directly bio-printed 15 within the organs thanks to a new generation of endoscopes. 16

However, bonding requires great dexterity on the part of the clinician 17 and the robots, as parameters such as compressive force, welding material, 18 and laser temperature must be taken into account for the operation to be 19 successful [10, 11]. Moreover, after such an operation, there is always a 20 risk of local inflammation and scarring of the surrounding tissues [12]. This 21 inflammatory response can lead to muscle fibrosis in the colon, resulting 22 in increased muscle stiffness surrounding the welding tissue. On the other 23 hand, it can happen that after LTS, the weld area is not effective enough 24 (not fully cellularized and/or integrated) to withstand the burst pressure or 25 that the weld eventually ruptures at very low pressure [13, 14, 12, 15]. Such 26 a condition generally happens when the compressive force during LTS, the 27 soldering time, and the laser power are not properly designed for the patient. 28 Therefore, there is an urgent need to develop a high-fidelity in silico model 29 of the colon that can be exploited to simulate and predict the response of 30 the organ after such interventions, understand how to optimize the 3D bio-31

printed patch, and identify potential critical issues. A validated in silico
model can effectively enable digital technology to accelerate the move from
the technological proof of concept to the clinical setting.

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

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

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.

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

We assume the constitutive model for the passive part as an exponential Holzapfel-type material models described in [48, 49] since these structurebased approaches account for directional fiber reinforcements. Overall, exponential anisotropic constitutive laws have been shown to characterize well the mechanical behavior of several intact GI segments (esophagus, small intestine, large intestine, and rectum), validating their performances against uniaxial (planar uniaxial extension, planar shear) and biaxial tests (planar ⁸⁹ biaxial extension and tubular inflation-extension).

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

In detail, we propose an active strain electromechanical model of colon 98 motility considering an anisotropic hyperelastic constitutive law consisting 90 of four reinforcing microstructures (embedding two active muscle fibers-100 longitudinal and circumferential-and the two passive collagen sheets present 101 in the submucosa layer), coupled with a phenomenological electrophysiolog-102 ical model that finely reproduces SMCs and ICCs spatiotemporal dynamics. 103 The proposed multi-field model is employed to numerically study the effect 104 of deposited bio-printed material or albumin due to LTS endoscopic resection 105 represented by an elliptical portion of colon endothelium and characterized 106 by altered material properties. In particular, we show that the computational 107 framework is able to reproduce the intraluminal pressure maps corresponding 108 to HRM data, both health and disease. 109

The manuscript is organized as follows. In section 2, the active strain electromechanical formulation for colon motility is presented. In section 3, the strong form of the problem is derived, and the finite element discretization and associated staggered solver are presented. In section 4, numerical analyses are carried out, as well as the exploitation of the in silico model to investigate the effect of laser tissue soldering on colon motility. Conclusions, limitations, and perspectives are discussed in section 5.

117 2. Electromechanical constitutive modeling of colon motility

In this section, we briefly recall the governing equations for active strain finite deformations coupled with GI electrophysiology.

We represent a scalar, a vector, and a second-order tensor with the lowercase letters (a), lowercase bold letters (a) and capital bold letters (A), respectively, and (A^T) stands for the transpose of a tensor. According to the tensor notation, we indicate the scalar product with (\cdot), the double contraction 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

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

The contraction of an excitable biological tissue combines active and passive behaviours, nonlinearly coupling electrophysiological cellular dynamics with a material hyperelastic response. According to the active strain approach [37, 52, 53, 54], a multiplicative decomposition of the deformation gradient tensor into an elastic, F_e , and an inelastic, F_a , part is put forward:

$$\boldsymbol{F} = \boldsymbol{F}_e \boldsymbol{F}_a \,. \tag{1}$$

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

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

$$\boldsymbol{F}_{a} = \boldsymbol{I} - \gamma(V)(\alpha_{c}\boldsymbol{n}_{c} \otimes \boldsymbol{n}_{c} + \alpha_{l}\boldsymbol{n}_{l} \otimes \boldsymbol{n}_{l}) + \gamma_{n}\boldsymbol{n}_{n} \otimes \boldsymbol{n}_{n}, \qquad (2)$$

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

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

The excitation function $\gamma(V)$ couples the mechanical problem with the electrophysiological one via a smooth activation function, defined in [48], dependent on the active membrane potential V crossing the smooth muscle layer:

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

where, β_1 , β_2 , and V_{th} are the material parameters linked to the intracellular Ca²⁺ dynamics, while $H(V - V_{th})$ is a Heaviside step function switching on active contraction whenever the threshold V_{th} is reached.

Parameters of $\gamma(V)$ and \boldsymbol{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

The electrophysiological model adopted in [38] is herein recalled and generalized. The SMC and ICC layers are labeled with indices s and i, respectively. The resulting system of nonlinear partial differential reaction-diffusion equations describe the coupled dynamics between the transmembrane potential variables, u_s, u_i , and the slow currents ones, v_s, v_i :

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

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

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

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

166 where:

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

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

Here, I_{stim}^{s} and I_{stim}^{i} are the stimulation currents applied to the SMC and ICC respectively; D_{s}, D_{i} are the diffusivities (assumed isotropic); λ_{s}, λ_{i} are the coupling factors between the membrane potential and recovery variable; D_{si}, D_{is} are the diffusivities of the gap junctions between the two cell species; $k_i, k_s, a_s, a_i, \alpha_s, \alpha_i$ are phenomenological model parameters and their values are provided in Table. 2. The parameter $\epsilon(z)$, which is proportional to the oscillation frequency of the ICCs cells, represents a space-dependent excitability function, decreasing with distance from the pylorus [36].

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

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

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

178 2.3. Constitutive mechanical model of the GI system

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

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

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

Here, the notation $(y)_+ := y$ if $y \ge 0$ reproduces the tension-compression switch approximation [48] and the anisotropic fourth invariant $I_4^j = \mathbf{C}$: $(\mathbf{n}_j \otimes \mathbf{n}_j)$ 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 crosssection 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.

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

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

where p stands for the solid hydrostatic pressure.

It is worth mentioning that from a numerical viewpoint, the precise creation of the fibrous structure of the GI tract is crucial. Due to their complex structure and strong layer adhesion, a homogenized layer was chosen

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

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

222 **3.** Numerical implementation

223 3.1. Strong form of the problem

The strong form of the problem is given by the following set of nonlinear coupled partial differential equations prescribing mechanical equilibrium in terms of displacement field **u** and pressure p variables, defined in the undeformed colon domain Ω_0 :

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

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

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

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

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

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

being Γ_D and Γ_N a disjoint partition of the boundary. Condition Eq. (9a) constraints normal motion along the surface Γ_D . The term p_0 in Eq. (9b) denotes a prescribed (possibly time-dependent) boundary load (normal stresspressure) associated with the presence of digesta within the lumen. In the present case, such a load is assumed uniform over the deformed counterpart of Γ_N , and applied in the normal direction to the internal surface of the colon in the deformed configuration.

Finally, no flux boundary conditions are considered for the electrophysiological problem:

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

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

243 3.2. Mixed-primal weak variational form

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

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

²⁴⁶ for displacements and pressure and

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

for the electrophysiological variables. The virtual displacements for the mechanical problem are introduced as $\delta \boldsymbol{u} \in \mathbf{V}_0$, as well as the test functions for 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 electrophysiological problem, defined on the spaces of the corresponding fields, and vanishing on the Dirichlet part of the boundary. Multiplying Eq. (8) by a virtual displacement, using the divergence theorem and the boundary conditions in Eq. (9), the weak form of the mechanical problem is:

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

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

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

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

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

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

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

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

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

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

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

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

$$I_{ion}^{i}(u_{s}, v_{i}, u_{i}) = g(u_{i}) - v_{i} + F_{i}(u_{s}, u_{i}) + I_{stim}^{i}, \qquad (16a)$$

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

$$I_{ion}^{s}(u_{s}, v_{s}, u_{i}) = f(u_{s}) - v_{i} + F_{s}(u_{s}, u_{i}) + I_{stim}^{s}, \qquad (16c)$$

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

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

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

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

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

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

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

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

are respectively the residuals of Eqs. (15).

274 3.3. Finite element discretization

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

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

²⁹² 4. Exploitation of the in silico model

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

Table 3: Mechanical	$\operatorname{constitutive}$	parameters.
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μ [kPa]	$k_1^l [\mathrm{kPa}]$	$k_2^l\left[- ight]$	$k_1^c [\mathrm{kPa}]$	$k_2^c\left[- ight]$	$k_1^d [\mathrm{kPa}]$	$k_2^d\left[- ight]$	$\theta\left[- ight]$
2.5	5.43	1.19	0.78	0.02	3.65	0.31	39.5

303

304 4.1. Idealized colon geometry model

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

The red elliptic region, with axes r_{\min} , r_{\max} and thickness h = 0.3 cm, rep-312 resents a patch of bio-printed material (e.g., albumin). Two representative 313 geometries for the implanted patch have been considered, fixing the value of 314 the minor axis, $r_{\min} = 2$ cm, and varying $r_{\max} \in \{2, 3\}$ cm. The bio-printed 315 region was modeled using a Neo-Hookean material model, assuming perfect 316 contact between the tissue-patch boundary, thus representing the clinical sit-317 uation when a healthy bond appears during the healing process. The elastic 318 modulus of the implanted patch, μ_p , has been varied with respect to the 319 elastic modulus of the surrounding healthy tissue, μ_t , as $\mu_p \in \{\mu_t/2, \mu_t, 2\mu_t\}$. 320 321



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.

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

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

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

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

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

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

344 4.2. The role of implant material on intraluminal pressure

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

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

The differences observed between the clinical data and the simulated predictions are due to several factors. Clinical manometry readings are necessarily influenced by the position of the sensor and the length covered by the sensor in the colon. Figure 4 shows the manometric readings in the colonic 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.

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



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

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

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

Figure 7 shows analyses conducted varying patch size $r_{\text{max}} \in \{2, 3\}$ cm but considering a softer material other than the host surrounding tissue, namely $\mu_p = \mu_t/2$. As expected, a similar behavior is obtained for the SMC voltage field, i.e., the voltage field only experiences geometric coupling, but, in this case, the intraluminal pressure lowers (from about 5 kPa in the healthy case to less than 3 kPa in the soft patch case) on the overall patch region. 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 $r_{\text{max}} = 2, r_{\text{min}} = 2, \mu_p = 2\mu_t$ (top), and $r_{\text{max}} = 3, r_{\text{min}} = 2, \mu_p = 2\mu_t$ (bottom).



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

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

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



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 $r_{\text{max}} = 2, r_{\text{min}} = 2$ (a) and $r_{\text{max}} = 2, r_{\text{min}} = 3$ (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 $r_{\text{max}} = 2, r_{\text{min}} = 2$ (a) and $r_{\text{max}} = 2, r_{\text{min}} = 3$ (b).

The role of patch electrical conductivity. In this numerical test, the electrophysiological properties of the implant are varied from those of the surrounding host tissue; namely, the SMC and ICC electrical conductivity in the patch, D_s^p , D_i^p , are ten times lower than those in the tissue, D_s^t , D_i^t . The size of the elliptical region is fixed at $r_{\min} = 2 \text{ cm}$ and $r_{\max} = 3 \text{ cm}$ and material stiffness is considered $\mu_p = 2\mu_t$.

Figure 10 shows the evolution of the hydrostatic pressure *p* in the surroundings of the implant, where no significant variations can be observed compared to the previous analysis in Fig. 6. However, because of the altered electrophysiological properties, the slow wave spatiotemporal distribution changes, and, in particular, the conduction velocity of the excitation wave 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 $D_i^p = 0.1D_i$.

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

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

The role of patch contractility. In this numerical test, the implant electrophysiological properties and contractility vary from the surrounding host tissue. Namely, the SMC and ICC electrical conductivity in the patch, D_s^p, D_i^p , are a hundred times lower than those in the tissue, D_s^t, D_i^t , and the amplitude of contractility in Eq. (2), α_l^p, α_c^p , is reduced as by 50%. The size of the elliptical region is fixed at $r_{\min} = 2 \text{ cm}$ and $r_{\max} = 3 \text{ cm}$ and material stiffness is considered $\mu_p = 2\mu_t$.

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



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 $\alpha_c^p = 50\%\alpha_c$.

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

Figure 12 shows the evolution of the hydrostatic pressure p in the sur-463 roundings of the implant. Though no significant variations are observed 464 compared to the case in Fig. 6, altered electrophysiological properties induce 465 a critical change in slow wave spatiotemporal dynamics leading to wave-466 breaks around the patch (no closed rings). In particular, the excitation wave 467 is slowed, and its amplitude is reduced, thus flattening and prolonging the 468 duration of SMC action potential. The two reaction-diffusion contributions 460 affect the colon wall overall motility, leading to an altered pattern of intralu-470 minal pressure maps: a clear gap in the recorded traces is representative of 471 no contraction. Such analysis is aligned with the topographic pressure pro-472 files presented in Fig. 12, further confirming the sensitivity of colon motility 473 to bio-printed material cellular viability. 474



Figure 12: Temporal evolution of SMC transmembrane voltage u_s and hydrostatic pressure p around the patch region with parameters $r_{\text{max}} = 3$ and $r_{\text{min}} = 2$ 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)) 10³ times lower inside the patch.

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

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



Figure 13: Temporal evolution of SMC transmembrane voltage u_s , the hydrostatic pressure p and the displacement u around the patch region with parameters $r_{\text{max}} = 3$ and $r_{\text{min}} = 2$ 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

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

This paper presented a comprehensive multi-field computational framework to model colonic motility, incorporating active strain electromechanics, tissue anisotropy, and cellular electrophysiology. The obtained in silico has been exploited to characterize colon contractility in the presence of bio-printed deposited materials, e.g., by LTS procedures, assumed to bond perfectly to the surrounding healthy tissue.

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

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

⁵²³ 5.1. Limitations and perspectives

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

We considered a perfectly bounded patch representative of a correct healing process. Though not exploited, the in silico model has already been formulated to account for generalized contact mechanics problems. In particular, irregular or localized faults can be considered in future studies.

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

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

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

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

559 Declaration of competing interest

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

563 Data availability

All the data utilized are detailed within this article.

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Appendix A. Entraiment analysis of the ICC cells and mesh convergence analysis

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

847

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

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



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

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

881

It is well known that the conduction velocity of reaction-diffusion systems generally depends on the numerical scheme. This analysis aims to obtain a 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.

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

⁸⁹⁴ Appendix B. Tuning of mechanical parameters

To calibrate our passive material model and associated code, we under-895 took a series of tests to calibrate the model parameters. These tests include 896 a uniaxial test based on Nagaraja data [56], and a triaxial test using cylinder 897 occlusion based on Sokolis data [78]. We would like to point out that as 898 we did not have the original experimental data, we were content to validate 890 part of the authors' experimental curve. To this end, we have extracted data 900 from their figure to use it as a reference. About the uniaxial test, most of 901 the parameters were taken from Nagaraja et al. [56] study, which we then 902



Figure A.16: conduction velocity analysis

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

905

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

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

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

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



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

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carefully calibrated inflation test. As shown in the figure B.18, a 3.5 cm long
cylinder was used for this purpose [78]. Pressure was applied to the inner
surface of the cylinder, while both ends were clamped. After each inflation,
the parameters were carefully adjusted to reproduce the experimental data
faithfully and to extract the outer radius. The agreement between the model
and the experimental data from [78] is clearly demonstrated in the figure
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

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

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

$$\zeta = \zeta_0 \quad on \quad \partial \Gamma_D \tag{C.1b}$$

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

where ζ is an arbitrary scalar field, ζ_0 is the value prescribed on the Dirichlet boundary ($\partial \Gamma_D$), and \boldsymbol{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 Neumann boundary condition prescribed on the inner and outer surfaces, together with the Dirichlet boundary condition prescribed on both end surfaces as shown in Figs. C.19. The final longitudinal fiber direction is obtained by the normalisation $\boldsymbol{n}_l = \nabla \zeta_z / \| \nabla \zeta_z \|$.

⁹³⁶ The radial vector direction n_r is obtained similarly, only the Neumann and

Dirichlet boundary conditions must be interchanged. Then, the circumferen-937 tial fiber direction n_c is defined as a cross product of the unitary radial and 938 longitudinal vector fields, \boldsymbol{n}_r and \boldsymbol{n}_l . Regarding the helical fiber direction, 939 two additional parameters are necessary, a unit vector r_0 aligned with the 940 centreline and the angle θ that will determine the rotational anisotropy from 941 the circumferential direction. Once the radial direction has been computed, 942 we project the centreline on the normal direction and compute the so-called 943 flat fiber field $r_f[54]$. Then the diagonal fibers are obtained by using the 944 Rodrigues rotation formula. 945

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

a similar expression can be derived for 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.

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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.

Appendix D. Zoomed clip of the region of interest where the patch 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 ($\mu_p = \mu_t$).

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



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 $r_{\rm max} = 3$ and $r_{\rm min} = 2$ 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 $D_i^p = 0.01D_i$