# Biomechanical constitutive modeling of the gastrointestinal tissues: where are we?
# SUPPLEMENTAL MATERIAL

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## S1. Constitutive modeling of cell electrophysiology

In view of active models of GI tissues provided in Section 6, we briefly introduce GI electrophysiology for the sake of clarity. The active component of GI constitutive models depends on cellular electrophysiology. Interstitial cells of Cajal (ICC) and smooth muscle cells (SMCs) electrical activity dictates GI motility [1]. Here, plasma membrane proteins, acting as selective voltage-dependent ion channels (gates), rule inward and outward ionic fluxes and allow large excursions of the transmembrane voltage, known as action potential (AP). Unlike the heart, the generation and propagation of slow excitation waves in GI are realized by ICC. SMCs, then, get electrically excited, transforming these stimuli into mechanical responses upon threshold activation. Accordingly, the multiple lengths and time scales involved rely on simplified phenomenological approaches or detailed biophysical models [2]. We provide a concise basis of cell electrophysiology constitutive modeling within deformable substrate.

At the cell level, electrophysiological constitutive models are based on Kirchhoff's balance low (principle of conservation of total current), assuming the cell membrane composed by the superposition of capacitive and resistive contributions. When the tissue level is considered, such local representation is extended into a space-dependent constitutive description in which ion flux balances are homogenized into the so-called *cable equa-*

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*tion* (or *monodomain model*): this is a diffusive Fourier-like PDE accounting for resistive inter-cellular connections included in the conductivity tensor $\boldsymbol{\Sigma}$. In general, the cell-cell conductivity incorporates heterogeneous and anisotropic features, e.g., a function of local spatial coordinate $\mathbf{x}$ and material direction $\mathbf{n}$, respectively [3–11]. Recently, the active strain approach described in Section 6.2 has been coupled to gastric electrophysiology and successfully implemented in large-scale finite element models [12]. Such a multiphysics framework requires the pull-back operation applied on the monodomain model framing the current (deformed) configuration, in which constitutive laws are assigned, into a material (undeformed) reference configuration, amenable of numerical implementation frame invariance.

The cable equation in the material framework reads:

$$C_m \frac{\partial V}{\partial t} = \frac{1}{J} \nabla \cdot J \mathbf{C}^{-1} \boldsymbol{\Sigma}(\mathbf{x}, \mathbf{n}) \, \nabla V + I_{\text{ion}}(V, \mathbf{y}) \tag{1}$$

with $J = \det(\mathbf{F})$ and $\mathbf{C} = \mathbf{F}^T\mathbf{F}$ the right Cauchy-Green deformation tensor, $C_m$ the membrane capacitance, $I_{\text{ion}}$ the sum of the ionic currents contributing to the membrane potential $V$, $\mathbf{y}$ a list of local kinetics associated with voltage- or ion-dependent channels regulated by specific reaction rates, and $\mathbf{g}(V, \mathbf{y})$ is a vector of coupled nonlinear functions, readily:

$$\frac{\mathrm{d}\mathbf{y}}{\mathrm{d}t} = \mathbf{g}(V, \mathbf{y}) \tag{2}$$

Other general models proposed to reproduce GI electrical behavior comprise the *bidomain*, and *extended bidomain* (also named tridomain) models [13], further incorporating the inter-cellular space among two different cell types. These generalized constitutive descriptions allow investigating advanced phenomena, e.g., external electric stimulation of the tissue, though poorly applied in the GI context [14].

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**List of Tables**

Table S1: Search terms and combinations used on PubMed to identify relevant studies for each GI organ.

| **Organ** | **Search terms and combinations** |
|---|---|
| Esophagus | (constitutive AND (model OR modeling OR modelling)) OR (mechanical AND (model OR modeling OR modelling)) OR (mechanical AND (active OR passive)) OR (mechanical AND stress AND strain) OR (strain AND energy) OR (finite AND element) OR ((viscoelastic OR viscoelasticity) AND (model OR modeling OR modelling)) AND (esophagus OR esophageal) |
| Stomach | (constitutive AND (model OR modeling OR modelling)) OR (mechanical AND (model OR modeling OR modelling)) OR (mechanical AND (active OR passive)) OR (mechanical AND stress AND strain) OR (strain AND energy) OR (finite AND element) OR ((viscoelastic OR viscoelasticity) AND (model OR modeling OR modelling)) AND (stomach OR (gastric AND tissue)) |
| Small intestine | (constitutive AND (model OR modeling OR modelling)) OR (mechanical AND (model OR modeling OR modelling)) OR (mechanical AND (active OR passive)) OR (mechanical AND stress AND strain) OR (strain AND energy) OR (finite AND element) OR ((viscoelastic OR viscoelasticity) AND (model OR modeling OR modelling)) AND (small intestine OR duodenum OR jejunum OR ileum) |
| Large intestine | (constitutive AND (model OR modeling OR modelling)) OR (mechanical AND (model OR modeling OR modelling)) OR (mechanical AND (active OR passive)) OR (mechanical AND stress AND strain) OR (strain AND energy) OR (finite AND element) OR ((viscoelastic OR viscoelasticity) AND (model OR modeling OR modelling)) AND (large intestine OR colon OR sigmoid OR cecum) |
| Rectum | (constitutive AND (model OR modeling OR modelling)) OR (mechanical AND (model OR modeling OR modelling)) OR (mechanical AND (active OR passive)) OR (mechanical AND stress AND strain) OR (strain AND energy) OR (finite AND element) OR ((viscoelastic OR viscoelasticity) AND (model OR modeling OR modelling)) AND (rectum OR rectal) |

Table S2: List of studies where a hyperelastic Fung-type model is presented. We refer to Equation (8) and Equation (10) in the manuscript for the definitions of the parameters $a$ and $b$, respectively. The numbers of parameters $a$ and $b$ correspond to the best performing model in case multiple configurations were tested.

| **Study** | **Organ** | **Test protocol** | **Modeled entity** | **Number of parameters $a$ (and $b$ when applicable)** |
|---|---|---|---|---|
| Miftakhov & al. (1994) [15] | Small intestine | Numerical adjustment | Intact tissue | 3 (3) |
| Dou & al. (2003) [16] | Small intestine | Tubular inflation | Intact tissue | 3 |
| Liao & al. (2003) [17] | Esophagus | Tubular inflation | Intact tissue - Individual layer | 6 |
| Zhao & al. (2003) [18] | Small intestine | Tubular inflation | Intact tissue | 3 |
| Yang & al. (2004) [19] | Esophagus | Tubular extension - Tubular inflation - Tubular torsion | Intact tissue | 3 |
| Zeng & al. (2004) [20] | Esophagus | Tubular extension - Tubular inflation - Tubular torsion | Intact tissue | 3 |
| Stavropoulou & al. (2009) [21] | Esophagus | Tubular extension - Tubular inflation | Individual layer | 3 |

| | | | | |
|---|---|---|---|---|
| Liao & al. (2010) [22] | Small intestine | Tubular extension - Tubular inflation | Intact tissue | 6 |
| Sokolis & al. (2010) [23] | Esophagus | Tubular extension - Tubular inflation | Intact tissue - Individual layer | 3 |
| Bellini & al. (2011) [24] | Small intestine | Planar biaxial | Intact tissue | 3 |
| Sokolis & al. (2011) [25] | Large intestine & Rectum | Tubular extension - Tubular inflation | Intact tissue | 3 |
| Stavropoulou & al. (2012) [26] | Esophagus | Planar uniaxial | Individual layer | 3 |
| Aydin & al. (2017) [27] | Stomach | Planar biaxial | Intact tissue | 3 |
| Sokolis (2017) [28] | Small intestine | Tubular extension - Tubular inflation | Intact tissue | 3 (3) |
| Sun & al. (2017) [29] | Small intestine | Tubular extension - Tubular inflation - Tubular torsion | Intact tissue | 7 |

Table S3: List of studies where an isotropic hyperelastic phenomenological model is proposed.

| **Study** | **Organ** | **Test protocol** | **Modeled entity** | **Hyperelastic model type** |
|---|---|---|---|---|
| Gao & al. (2008) [30] | Stomach | Planar uniaxial | Intact tissue | Ogden |
| Boubaker & al. (2009) [31] | Rectum | Planar uniaxial | Intact tissue | Ogden |
| Tran & al. (2011) [32] | Large intestine | Compression - Planar uniaxial | Intact tissue | Ogden |
| Rubod & al. (2012) [33] | Rectum | Planar uniaxial | Intact tissue | Mooney-Rivlin |
| Puértolas & al. (2013) [34] | Large intestine | Planar uniaxial | Intact tissue | Mooney-Rivlin |
| Boubaker & al. (2015) [35] | Rectum | Planar uniaxial | Intact tissue | Ogden |
| Dargar & al. (2016) [36] | Stomach | Compression | Individual layer (mucosa, submucosa, and muscle) | 2nd order reduced polynomial |
| Zhou & al. (2018) [37] | Large intestine | Planar uniaxial | Intact tissue | Mooney-Rivlin extended |

Table S4: List of studies where a Holzapfel-type hyperelastic model is proposed.

| **Study** | **Organ** | **Test protocol** | **Modeled entity** | **Number of fiber families (details about directions)** |
|---|---|---|---|---|
| Ciarletta & al. (2009) [38] | Large intestine | Planar uniaxial - Planar shear | Intact tissue | 4 (longitudinal, circumferential, and two symmetrical directions) |
| Sokolis & al. (2013) [39] | Esophagus | Tubular extension - Tubular inflation | Intact tissue - Individual layer (mucosa and mucosa-submucosa) | 3 (longitudinal and two symmetrical directions) |
| | | | Individual layer (muscle) | 4 (longitudinal, circumferential, and two symmetrical directions) |
| Sokolis & al. (2013) [40] | Large intestine & Rectum | Tubular extension - Tubular inflation | Intact tissue | 3 (longitudinal and two symmetrical directions) |
| Sommer & al. (2013) [41] | Esophagus | Planar uniaxial - Planar biaxial - Tubular extension - Tubular inflation | Individual layer (mucosa-submucosa and muscle) | 1 |
| Patel & al. (2018) [42] | Large intestine | Tubular extension - Tubular inflation | Intact tissue | 3 (longitudinal and two symmetrical directions) |

| | | | | |
|---|---|---|---|---|
| Puertolas & al. (2019) [43] | Large intestine | Planar biaxial | Intact tissue | 4 (longitudinal, circumferential, and two symmetrical directions) |
| Zhao & al. (2020) [44] | Large intestine & Rectum | Planar biaxial - Tubular inflation | Individual layer (mucosa-submucosa and muscle) | 1 |
| Sokolis (2021) [45] | Small intestine | Tubular inflation - Tubular extension | Intact tissue | 2 (longitudinal and circumferential) |

Table S5: List of studies where Natali-type hyperelastic model is presented.

| **Study** | **Organ** | **Test protocol** | **Modeled entity** |
|---|---|---|---|
| Natali & al. (2009) [46] | Esophagus | Planar uniaxial | Individual layer (mucosa-submucosa and muscle) |
| Carniel & al. (2013) [47] | Large intestine | Planar uniaxial | Intact tissue |
| Carniel & al. (2014) [48] | Large intestine | Planar uniaxial | Intact tissue |

Table S6: List of studies where a visco-hyperelastic model is presented.

| Study | Organ | Test protocol | Modeled entity | Hyperelastic model type | Viscous model type |
|---|---|---|---|---|---|
| Higa & al. (2007) [49] | Large intestine | Tubular inflation | Intact tissue | Neo-Hookean | Convolution integral |
| Fontanella & al. (2019) [50] | Stomach | Tubular inflation | Intact tissue | Natali | Viscous variables |
| Panda & al. (2019) [51] | Small intestine | Tubular inflation | Intact tissue | Neo-Hookean | Panda type linear and non linear |
| | Large intestine | Tubular inflation | Intact tissue | Fung | Panda type linear |
| | Rectum | Tubular inflation | Intact tissue | Neo-Hookean | Panda type linear |

Table S7: List of studies where an active model is presented.

| Study | Organ | Test protocol | Modeled entity | Hyperelastic model category | Viscous model type | Active model category |
|---|---|---|---|---|---|---|
| Yang & al. (2007) [52] | Esophagus | Planar uniaxial - Tubular inflation - Other | Intact tissue - Individual layer (mucosa-submucosa and muscle) | Structure-based | NA | Active stress |
| Yassi & al. (2009) [53] | Esophagus | NP | Individual layer (muscle) | Phenomenological | NA | Active stress |
| Gao & al. (2009) [54] | Small intestine | Impedance planimetry | Intact tissue | NA | NA | Active stress |
| Altomare & al. (2014) [55] | Large intestine | Planar uniaxial - Other | Individual layer (muscle) | Structure-based | | Active strain |
| Kou & al. (2015) [56] | Esophagus | NA | Individual layer | NA | NA | Active stress |
| Gizzi & al. (2016) [57] | Small intestine | Planar biaxial | Intact tissue (muscosa-submucosa and muscle) | Structure-based | Neo-Hookean | Active electromechanics |

| | | | | | | |
|---|---|---|---|---|---|---|
| Peirlinck & al. (2018) [58] | Esophagus | Planar uniaxial - Planar biaxial - Tubular extension - Tubular inflation | Individual layer (mucosa, submucosa, and muscle) | Structure-based | NA | Active strain |
| Brandstaeter & al. (2018) [14] | Stomach | NA | Intact tissue | Phenomenological | NA | Active strain |
| Klemm & al. (2020) [59] | Stomach | Planar uniaxial | Individual layer (muscosa-submucosa and muscle) | Structure-based | NA | Active stress |

Table S8: List of studies where a model is developed based on human tissue testing.

| Study | Organ | Test protocol | Modeled entity | Hyperelastic model category | Viscous model type | Active model category |
|---|---|---|---|---|---|---|
| Boubaker & al. (2009) [31] | Rectum | Intact tissue | Ex vivo | Ogden | NA | NA |
| Gao & al. (2009) [54] | Small intestine | Intact tissue | In vivo | NA | NA | Active stress |
| Rubod & al. (2012) [33] | Rectum | Intact tissue | Ex vivo | Mooney-Rivlin | NA | NA |
| Puértolas & al. (2013) [34] | Large intestine | Intact tissue | Ex vivo | Mooney-Rivlin | NA | NA |
| Altomare & al. (2014) [55] | Large intestine | Individual layer (muscle) | Ex vivo | Holzapfel | NA | Active strain |
| Panda & al. (2019) [51] | Small intestine | Intact tissue | Ex vivo | Neo-Hookean | Panda-type linear and nonlinear | NA |