A mathematical model of intestinal oedema formation

JENNIFER YOUNG AND BÉATRICE RIVIÈRE*

Computational and Applied Mathematics Department, Rice University, Houston, TX, USA

*Corresponding author: riviére@rice.edu

AND

CHARLES S. COX JR. AND KAREN URAY

*Center for Microvascular and Lymphatic Studies at the University of Texas-Houston Medical School,
Division of General and Thoracic Pediatric Surgery, Houston, TX, USA and DeBakey Institute at
Texas A&M University, College Station, TX, USA*

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Intestinal oedema is a medical condition referring to the build-up of excess fluid in the interstitial spaces of the intestinal wall tissue. Intestinal oedema is known to produce a decrease in intestinal transit caused by a decrease in smooth muscle contractility, which can lead to numerous medical problems for the patient. Interstitial volume regulation has thus far been modelled with ordinary differential equations, or with a partial differential equation system where volume changes depend only on the current pressure and not on updated tissue stress. In this work, we present a computational, partial differential equation model of intestinal oedema formation that overcomes the limitations of past work to present a comprehensive model of the phenomenon. This model includes mass and momentum balance equations which give a time evolution of the interstitial pressure, intestinal volume changes and stress. The model also accounts for the spatially varying mechanical properties of the intestinal tissue and the inhomogeneous distribution of fluid-leaking capillaries that create oedema. The intestinal wall is modelled as a multi-layered, deforming, poroelastic medium, and the system of equations is solved using a discontinuous Galerkin method. To validate the model, simulation results are compared with results from four experimental scenarios. A sensitivity analysis is also provided. The model is able to capture the final submucosal interstitial pressure and total fluid volume change for all four experimental cases, and provide further insight into the distribution of these quantities across the intestinal wall.

Keywords: fluid balance; interstitium; smooth muscle; poroelastic; oedema; intestine.

1. Introduction

Intestinal oedema refers to the excess accumulation of fluid in the interstitium (the spaces between cells) of the intestinal wall tissue (Granger & Barrowman, 1984; Dongaonkar *et al.*, 2008). This condition can arise in patients with gastroschisis, inflammatory bowel disease and cirrhosis (Moore-Olufemi *et al.*, 2009), as well as in patients receiving resuscitative treatments after traumatic injuries (Cox *et al.*, 2008). The presence of this excess fluid has been shown to cause ileus (oedema-induced intestinal contractile and transit dysfunction) due to a decrease in intestinal smooth muscle contraction (Moore-Olufemi *et al.*, 2005; Cox *et al.*, 2008). The oedema and subsequent delayed intestinal transit can lead to longer patient recovery times and hospital stays, as well as death (Dongaonkar *et al.*, 2008; Moore-Olufemi *et al.*, 2009).

Understanding the mechanics of intestinal oedema formation is an important ingredient to the future exploration of relationships between oedema and ileus. Significant experimental work has been done in the field of intestinal oedema (Moore-Olufemi *et al.*, 2005; Uray *et al.*, 2006, 2007; Cox *et al.*, 2008; Moore-Olufemi *et al.*, 2009). Theoretical work has been done on volume regulation, fluid balance and fluid transport in the interstitium (Taylor *et al.*, 1990; Gyenge *et al.*, 1999; Dongaonkar *et al.*, 2008, 2009), and some oedema models have been developed for other organs (Wiener *et al.*, 1983; Hempling & Katz, 1989; Nagashima *et al.*, 1990). However, these models neglect one or more factors, that are important for modelling oedema in the intestine. In Dongaonkar *et al.* (2008, 2009), Gyenge *et al.* (1999), Taylor *et al.* (1990), Wiener *et al.* (1983) and Hempling & Katz (1989) changes in the mechanical response (stress tensor) of the tissue that surrounds the interstitium are not explicitly evolved, but are represented with a pressure–volume compliance relationship. To provide a more detailed description of the tissue deformation, a model of oedema formation must include an equation describing the balance of forces from pressure gradients and mechanical stress. Also, the intestine has spatially varying mechanical properties and capillary distributions (Granger & Barrowman, 1984) which must be taken into consideration for a model. The models mentioned above do not account for such spatial variations in these properties. In the work presented here, we define and simulate a computational model of intestinal oedema development that addresses these issues in order to provide a thorough theoretical explanation of this phenomenon in this organ. Our model is able to correctly capture the pressure and volume changes seen in the four experimental scenarios presented in Cox *et al.* (2008). The model is also able to provide estimates of pressures and volume changes in the individual intestinal layers, quantities which have not yet been measured experimentally, but would certainly factor in to an explanation of the oedema–ileus relationship. In a broader sense, this model will serve as a general model of the intestine, capable of simulating the response of this organ to different stimuli under various conditions.

The small intestine is a multi-layered organ of the digestive system (Johnson, 1981). The lumen is the central cavity through which food passes, and is encased by the intestinal wall. Moving radially outward from the lumen, one finds the mucosa, submucosa, muscularis externa and serosa (Johnson, 1981). The mucosal layer makes up 60–80% of the intestinal wall thickness (Dou *et al.*, 2003) and contains circular folds and microvilli that project into the lumen to collect nutrients from passing food (Wilson & Wilson, 1983). It also contains blood and lymph capillary systems (Wilson & Wilson, 1983), as well as nerves and connective tissue (Johnson, 1981). The submucosa contains larger blood and lymph vessels, connective tissue and elastic fibres (Johnson, 1981), making it elastically more stiff than the mucosa (Cox *et al.*, 2008). The muscularis externa contains layers of circular and longitudinal smooth muscle cells, which contract and relax in a coordinated fashion to propel forward the contents of the lumen (Johnson, 1981). The muscularis externa also contains its own blood and lymph capillary systems. The final layer is the serosa, an outer membrane that encloses the intestinal wall (Johnson, 1981). The intestine is suspended in the abdomen by the mesentery (Johnson, 1981). This tissue anchors the intestine in place and contains the main blood and lymph vessels that supply the intestine (Granger & Barrowman, 1984). Figure 1 shows a circular cross-sectional diagram of the intestinal layers.

The interstitium is the space between tissue cells where extracellular and extravascular fluids can accumulate (Reed, 1995). Under homeostatic conditions, the fluid volume in the interstitium is kept relatively constant by a balanced fluid exchange between blood capillaries and lymphatics in the interstitium, controlled by hydrostatic and oncotic pressure gradients (Guyton (1995); Reed (1995); Dongaonkar *et al.* (2008)). Fluid tends to flow into the interstitium by filtering through the blood capillaries (Reed, 1995; Dongaonkar *et al.*, 2008). This fluid is removed from the interstitium by the lymphatics via a filling and pumping mechanism (Guyton, 1995). If J_V represents the rate at which fluid is

FIG. 1. Diagram of a circular cross section of the intestine.

added to the interstitium by the blood capillaries and J_L is the rate at which fluid is removed from the interstitium by the lymph capillaries, then under normal circumstances $J_V = J_L$. Oedema occurs if this balance is upset with the influx of fluid into the interstitium exceeding the outflow ($J_V > J_L$), creating a build-up of interstitial fluid (Guyton, 1995; Cox *et al.*, 2008). This extra fluid causes an increase in interstitial fluid pressure and volume (Guyton, 1995).

As mentioned in the introduction, the previous main modelling work on oedema was done for a general interstitial space (Taylor *et al.*, 1990; Gyenge *et al.*, 1999; Dongaonkar *et al.*, 2008, 2009). The model in Dongaonkar *et al.* (2008, 2009) describes the change in volume in the interstitium with the following ordinary differential equation:

$$\frac{\partial V}{\partial t} = J_V - J_L,$$

where V is the interstitial volume, and J_V and J_L are the rates previously described. These rates are defined using the Starling–Landis equation of microvascular fluid filtration (Dongaonkar *et al.*, 2008):

$$J_V = K_f((P_V - p) - \sigma(\Pi_V - \Pi_{\text{int}})) \quad (1)$$

and the Drake–Laine model of the lymph flow (Dongaonkar *et al.*, 2008):

$$J_L = \frac{1}{R_L}(p + P_p - P_L). \quad (2)$$

Here K_f is the microvascular filtration coefficient, P_V is the microvascular hydrostatic pressure, p is interstitial pressure, Π_V and Π_{int} are the microvascular and interstitial oncotic pressures, respectively, σ is the permeability of the blood capillaries to plasma proteins, R_L is the effective lymphatic resistance, P_p is the lymph system's pumping pressure and P_L is the hydrostatic pressure of the lymph capillaries.

A main limitation of the model in Dongaonkar *et al.* (2008, 2009) is that the interstitial pressure is updated with a piece-wise linear relationship with the current volume, and the modelling of the tissue's mechanical response is neglected. The model in Taylor *et al.* (1990) utilizes a similar idea, modelling

only a dilatational volume change as a function of the local hydrostatic pressure. Secondly, the models mentioned in the introduction cannot account for spatially varying concentrations of capillaries. It is known that the distribution of blood and lymph capillaries varies between and within the layers of the intestine (Granger & Barrowman, 1984). Such variation will impact how much fluid is added or removed from an area, and one would expect the contribution of $J_V - J_L$ to reflect these differences. For our model, the blood and lymph capillaries are the fluid sources and sinks that create the oedema, and so an accurate description of their location and density across the intestinal wall is a key ingredient to producing biologically relevant results.

The model developed in this work accounts for these issues, to present a more complete picture of the mechanics taking place during intestinal oedema formation.

2. Mathematical model

To simulate this biological process, the intestinal wall is modelled as a poroelastic medium with an interstitial fluid that completely fills the void spaces. The system of equations described here is based on the Biot model (Biot, 1941, 1955) with derivation details found in Bear & Bachmat (1990). The model will be developed with the following assumptions:

- (1) The interstitial fluid is incompressible.
- (2) The interface between the fluid and solid phases is impermeable.
- (3) The solid phase at the microscopic level preserves its volume.

As for the notation, boldface indicates vector or tensor quantities, and subscripts s and f refer to the solid and fluid phases, respectively.

The conservation of mass equations for the fluid and solid phases are given by:

$$\text{(Fluid)} \quad \frac{\partial(n\rho_f)}{\partial t} + \nabla \cdot [\rho_f(\mathbf{q}_r + n\mathbf{V}_s)] + \rho_f\phi(p) = 0, \quad (3)$$

$$\text{(Solid)} \quad \frac{\partial[(1-n)\rho_s]}{\partial t} + \nabla \cdot [(1-n)\rho_s\mathbf{V}_s] = 0, \quad (4)$$

where n is the porosity of the material (void volume fraction), t is time, ρ_f and ρ_s are the fluid and solid phase densities and $\mathbf{q}_r = n(\mathbf{V}_f - \mathbf{V}_s)$ is the relative fluid flux with $\mathbf{V}_f$ and $\mathbf{V}_s$ the fluid and solid phase velocity vectors. The term $\phi(p)$ is the pressure (p)-dependent source term representing fluid that is added or removed from the interstitium by the blood and lymph capillaries. It has the form $\phi(p) = \theta(x_0, y_0)(J_V - J_L)/V_0$, where J_V and J_L are as defined in the introduction, and V_0 is a unit volume, so that $\phi(p)$ has the correct units of time^{-1} to add to the mass balance equation. The quantity $\theta(x_0, y_0)$ represents the concentration of capillaries at the location (x_0, y_0) (subscript of 0 denotes the original position in the domain, not the deformed position). It takes values $[0, 1]$. The mucosal layer has the most capillaries (with higher concentrations near the lumen), whereas the submucosa has a much smaller concentration (Granger & Barrowman, 1984). The muscle layer is somewhere in between, having its own evenly distributed blood and lymph capillary systems (Granger & Barrowman, 1984). Figure 2 shows a plot of $\theta(x_0, y_0)$ utilized in our simulations.

FIG. 2. Capillary concentration $\theta(x_0, y_0)$.

By distributing the divergence operators in (3) and (4), $\nabla \cdot \mathbf{V}_s$ can be isolated in both equations and used to combine the two equations into one by its elimination:

$$\nabla \cdot \mathbf{q}_r + n \frac{1}{\rho_f} \frac{D_f \rho_f}{Dt} + \frac{1}{1-n} \frac{D_s n}{Dt} - \frac{n}{\rho_s} \frac{D_s \rho_s}{Dt} + \phi(p) = 0, \quad (5)$$

where $D_i x / Dt = \partial x / \partial t + \mathbf{V}_i \cdot \nabla x$ is the material derivative of variable x in phase i . The relative flux $\mathbf{q}_r$ can be written in terms of the pressure utilizing Darcy's law: $\mathbf{q}_r = -(k/\mu_f) \nabla p$ where k is the medium's permeability and μ_f is the fluid viscosity. Making this substitution, and invoking Assumptions 1 and 3, (5) becomes

$$-\frac{k}{\mu_f} \Delta p + \frac{1}{1-n} \frac{D_s n}{Dt} + \phi(p) = 0. \quad (6)$$

Next, the conservation of momentum equation is derived by summing all forces acting on a unit volume of porous medium. These forces may include inertial, viscous and pressure forces from the fluid as well as elastic stress from the solid phase. From poroelastic theory (Bear & Bachmat, 1990), inertial and viscous forces can be neglected if the following relationships are satisfied: $St \leq 1$ and $Re \cdot Da^{1/2} \ll 1$ where St is the Strouhal number, Re is the Reynolds number and Da is the Darcy number. These dimensionless quantities are defined in Bear & Bachmat (1990). Both relationships are satisfied for this problem. To validate this claim, we utilize our simulation parameters from Table 1 and the fluid density $\rho = 1000 \text{ kg/m}^3$ to estimate Re , Da and St . Re and Da were computed to be: 3.39×10^{-9} and 2.9×10^{-11} making $Re \cdot Da^{1/2} \ll 1$ true. St was estimated to be of the order of 0.46, satisfying the $St \leq 1$ criterion; thus both inertial and viscous terms were neglected from our model. Also neglected in this model are forces from muscle contractions. The focus of this first model is on oedema formation. The modelling of muscle contractions and the effect of oedema on them will be undertaken in future work.

The layers of the intestinal wall are known to have differing mechanical properties (Cox *et al.*, 2008); however, within each layer the material is assumed to be isotropic. The elastic stresses will thus be described by the Cauchy stress tensor for an isotropic solid: $\boldsymbol{\tau} = \mu_s(\nabla \mathbf{w} + (\nabla \mathbf{w})^T) + \lambda_s(\nabla \cdot \mathbf{w})\mathbf{I}$

TABLE 1 List of parameter values from experimental literature, along with the values within these ranges that were utilized in the model simulations

Parameter	Range of values from the literature	References	Value used in model
k/μ_f	$1.3\text{--}22 \times 10^{-13} \text{ m}^2/(\text{mmHg} \cdot \text{s})$	Reed (1995) and Beatty <i>et al.</i> (2002)	$5 \times 10^{-15} \text{ m}^2/(\text{Pa} \cdot \text{s})$
K_f	121–200 ml/mmHg · h	Gyenge <i>et al.</i> (1999) and Chapple <i>et al.</i> (1993)	121 ml/mmHg · h (low pres.) 160 ml/(mmHg · h) (high pres.)
σ	0.68–0.99	Granger & Barrowman (1984), Gyenge <i>et al.</i> (1999) and Chapple <i>et al.</i> (1993)	0.8
P_V (Normal)	10–12 mmHg	Cox <i>et al.</i> (2008) and Guyton & Guyton (2000)	12 mmHg
P_V (Elevated)	20 ± 3 mmHg	Cox <i>et al.</i> (2008)	20 mmHg
P_L	2 mmHg	Dongaonkar <i>et al.</i> (2011)	2 mmHg
P_p	10–30 mmHg	Guyton & Guyton (2000), Dongaonkar <i>et al.</i> (2011) and Unno <i>et al.</i> (2010)	15 mmHg (low pres.) 28 mmHg (high pres.)
Π_V (Normal)	20–25.9 mmHg	Gyenge <i>et al.</i> (1999) and Reed (1995)	21 mmHg
Π_V (HS)	+3–5 mmHg higher	Kinsky <i>et al.</i> (2000)	25 mmHg
Π_I	10–14.7 mmHg	Gyenge <i>et al.</i> (1999) and Reed (1995)	12 mmHg
$1/R_L$	43.1 ml/mmHg · h	Gyenge <i>et al.</i> (1999)	43.1 ml/mmHg · h
μ_{mucosa}	3 mmHg	Est. from Cox <i>et al.</i> (2008)	$\mu_1 = 3, \mu_2 = 1.5$ mmHg
$\mu_{\text{submucosa}}$	750–1050 mmHg	Est. from Cox <i>et al.</i> (2008) and Radhakrishnan <i>et al.</i> (2005)	$\mu_1 = 1050, \mu_2 = 750$ mmHg
μ_{muscle}	33–135 mmHg	Est. from Collinworth <i>et al.</i> (2002)	$\mu_1 = 120, \mu_2 = 60$ mmHg
E_{mucosa}	7.5 mmHg	Cox <i>et al.</i> (2008)	$E_1 = 7.5, E_2 = 3.75$ mmHg
$E_{\text{submucosa}}$	1875–2625 mmHg	Cox <i>et al.</i> (2008) and Radhakrishnan <i>et al.</i> (2005)	$E_1 = 2625, E_2 = 1875$ mmHg
E_{muscle}	82–337 mmHg	Collinworth <i>et al.</i> (2002)	$E_1 = 300, E_2 = 150$ mmHg
p_{thres}	0–4.5 mmHg	Granger & Barrowman (1984) and Guyton (1995)	2 mmHg

where $\mathbf{w}$ is the displacement vector, $\mathbf{I}$ is the identity matrix and μ_s and λ_s are the Lamé coefficients of the solid material. These two parameters have been shown experimentally to vary depending on the interstitial pressure (Granger & Barrowman, 1984; Radhakrishnan *et al.*, 2005). This is most likely due to the rupture of connective elastic fibres that occurs at higher pressures (Guyton, 1995; Radhakrishnan *et al.*, 2005). In this model, the elastic parameters will vary in a step-wise fashion between two values, depending on the pressure. For example,

$$\mu_s(p) = \begin{cases} \mu_1 & \text{if } p < p_{\text{thres}}, \\ \mu_2 & \text{if } p \geq p_{\text{thres}}, \end{cases}$$

with a similar expression for λ_s . Table 1 lists experimentally derived values for the shear modulus (μ_s) and Young's modulus, (E) of each layer for low (subscript 1) and high (subscript 2) pressures. Parameters μ_s and E can be used to determine λ_s via: $\lambda_s = \mu_s(E - 2\mu_s)/(3\mu_s - E)$. The conservation of momentum equation is thus

$$\nabla \cdot [\mu_s(p)(\nabla \mathbf{w} + (\nabla \mathbf{w})^T) + \lambda_s(p)(\nabla \cdot \mathbf{w})\mathbf{I}] - \nabla p = 0. \quad (7)$$

To close the system, one final relationship is needed between the porosity n and the displacement $\mathbf{w}$. From the solid phase conservation of mass equation (4), one sees that $\mathbf{V}_s$ can be written in terms of n . First

$$\begin{aligned} \rho_s \frac{\partial(1-n)}{\partial t} + (1-n) \frac{\partial \rho_s}{\partial t} + \rho_s \mathbf{V}_s \cdot \nabla(1-n) + (1-n) \rho_s \nabla \cdot \mathbf{V}_s + (1-n) \mathbf{V}_s \cdot \nabla \rho_s &= 0, \\ \rho_s \frac{D_s(1-n)}{Dt} + (1-n) \frac{D_s \rho_s}{Dt} + (1-n) \rho_s \nabla \cdot \mathbf{V}_s &= 0. \end{aligned}$$

Deleting the second term by Assumption 3, and dividing by $\rho_s(1-n)$ leaves

$$\frac{1}{1-n} \frac{D_s(n)}{Dt} = \nabla \cdot \mathbf{V}_s,$$

which can be related to $\mathbf{w}$ as

$$\nabla \cdot \mathbf{V}_s = \frac{\partial}{\partial t} (\nabla \cdot \mathbf{w}) = \frac{\partial \epsilon}{\partial t},$$

where $\epsilon = \nabla \cdot \mathbf{w}$. Substituting ϵ terms into (6)–(7) and applying the divergence operator in (7), we arrive at the following system of equations:

$$-\frac{k}{\mu_f} \Delta p + \frac{\partial \epsilon}{\partial t} + \phi(p) = 0, \quad (8)$$

$$\nabla \cdot \mathbf{w} = \epsilon, \quad (9)$$

$$-\mu_s(p) \Delta \mathbf{w} - (\nabla \mathbf{w} + (\nabla \mathbf{w})^T) \cdot \nabla \mu_s(p) - (\nabla \cdot \mathbf{w}) \mathbf{I} \cdot \nabla \lambda_s(p) + \nabla p = (\mu_s(p) + \lambda_s(p)) \nabla \epsilon. \quad (10)$$

In the following section, we discretize (8)–(10) by using discontinuous piecewise polynomials on a partition of the domain. Since λ_s and μ_s are piece-wise constant functions of p on each mesh element, the quantities $\nabla \mu_s(p) = \partial \lambda_s(p) / \partial p \nabla p$ and $\nabla \lambda_s(p) = \partial \mu_s(p) / \partial p \nabla p$ become zero in the discrete scheme. The momentum equation that is solved in our numerical simulations is thus reduced to

$$-\mu_s(p) \Delta \mathbf{w} + \nabla p = (\mu_s(p) + \lambda_s(p)) \nabla \epsilon. \quad (11)$$

2.1 Numerical methods

The system of (8), (9) and (11) includes both time and space derivatives. The evolution forward in time of this system will take place as a two-step process, with δt denoting the time step:

- (1) Given the pressure at time step m , ϵ^m will be updated to ϵ^{m+1} by utilizing (8), discretized in time

$$\frac{\epsilon^{m+1} - \epsilon^m}{\delta t} = -\phi(p^m) + \frac{k}{\mu_f} \Delta p^m \quad (12)$$

- (2) Next, ϵ^{m+1} from Step 1 will be utilized to compute the right-hand sides for (9) and (11), and solve these together for updated values of $\mathbf{w}$ and p at time $m + 1$:

$$\nabla \cdot \mathbf{w}^{m+1} = \epsilon^{m+1} \quad (13)$$

$$-\mu_s(p^m) \Delta \mathbf{w}^{m+1} + \nabla p^{m+1} = (\mu_s(p^m) + \lambda_s(p^m)) \nabla \epsilon^{m+1} \quad (14)$$

The computational domain for this model is a two-dimensional region, representing a circular cross section of the intestinal wall. This model contains three subdomains representing the mucosa, submucosa and muscle layers. The domain is discretized with triangular elements, and (12)–(14) are solved with a discontinuous Galerkin (DG) method (Rivière, 2008).

For the numerical simulations presented below, variables p , ϵ and $\mathbf{w}$ are initialized to zero across the domain. The outer circular and inner undulated boundaries are free to move, ($\boldsymbol{\sigma} \cdot \mathbf{n} = 0$, where $\boldsymbol{\sigma}$ is the Cauchy stress tensor and $\mathbf{n}$ is the normal vector). A vertical boundary, separating the left and right halves of the circular domain at the top is fixed in space ($\mathbf{w} = 0$) and impermeable to fluid, to represent the anchoring of the intestine by the mesentery. All interior mesh vertices are also free to move. The nodes begin the simulation in positions (x_0, y_0) . Their positions are updated after each time step utilizing the current displacement vector values. For example, after solving for $\mathbf{w}$ at time step m , new node positions are determined via

$$x_m = x_0 + \mathbf{w}_m(1)$$

$$y_m = y_0 + \mathbf{w}_m(2).$$

In preliminary model testing, mesh refinement was utilized to check convergence, and the DG scheme was found to be first order.

2.2 Set-up for simulations

To validate this mathematical model, it was tested against the experimental data of Cox *et al.* (2008). In this experimental work, male Sprague Dawley rats were divided into groups, and given one of four treatments: (1) elevated venous pressure (EVP) (meaning an increase in P_V) with an infusion of normal saline, (2) an infusion of hypertonic saline alone (HS), (3) EVP with an infusion of normal saline for a period of time, followed by an infusion of HS (EVP–HS) and (4) a control group given only normal saline (CG). EVP is known to induce intestinal oedema (4), and so case EVP is where we expect to see a large increase in pressure and volume in the intestinal wall. An infusion of HS increases the vascular oncotic pressure (Π_V) (Kinsky *et al.*, 2000) and has been shown to reduce interstitial fluid volume (Mazzoni *et al.*, 1988) and pressure (Fisher *et al.*, 1992) in oedematous tissue. The EVP–HS group

should experience oedema-like symptoms initially, but the increase in pressure and volume should be halted or reversed by the administration of HS.

After the procedures, the interstitial pressure in the submucosa was measured, as well as the gain in fluid weight, for all four groups. To recreate these experiments in the simulations, parameter values from Cox *et al.* (2008) and other experimental papers (see Table 1) were used in (8), (9), and (11). Ranges of values were found for several of the parameters in the literature as shown in Table 1. A set of parameter values were chosen from these ranges to best fit the pressure and volume gain results for the EVP and CG cases. The parameters of the EVP–HS and HS cases were not fit to match their results. EVP–HS and HS were simulated using the parameter values from the EVP and CG cases (except for the Π_V value, explained below). Therefore the results from the EVP–HS and HS simulations are predictive results from the model.

Parameter values for the four simulations were the same except for P_V , Π_V , K_f and P_p . For groups EVP and EVP–HS, $P_V = 20$ mmHg, whereas for HS and CG, $P_V = 12$ mmHg. For EVP, CG and EVP–HS (before HS administration), $\Pi_V = 21$ mmHg, whereas for HS and EVP–HS (during HS administration), $\Pi_V = 25$ mmHg. It has been shown experimentally that as P_V increases, P_p increases and K_f decreases (Guyton & Guyton, 2000). This will be represented in the simulations with K_f taking on the value 121 ml/mmHg · h for cases CG, HS and EVP–HS (during HS administration), and 160 ml/mmHg · h for cases EVP and EVP–HS (before HS administration). Similarly, P_p will be 15 mmHg for cases HS and CG, and 28 mmHg for cases EVP and EVP–HS.

3. Results

A comparison of the interstitial pressure in the submucosa among the four cases at the end of their simulations is shown in Fig. 3, alongside the experimental results. The EVP case had the highest final pressure value of 3.91 mmHg, followed by the EVP–HS and CG cases at 1.13 and 0.84 mmHg, respectively. The HS case had the lowest interstitial pressure at 0.68 mmHg. These results correlate well with those found in Cox *et al.* (2008), where final submucosal pressures were as follows: CG = 0.88 ± 0.13 mmHg, EVP = 3.80 ± 0.34 mmHg, HS = 0.5 ± 0.34 mmHg and EVP–HS = 1.0 ± 0.26 mmHg. The percent volume increase over the simulation was also computed for each case. Simulation EVP had the highest increase in volume at close to 16.1%. The other cases had volume increases of 5.0% (EVP–HS), 1.6% (CG) and 1.3% (HS). In Cox *et al.* (2008), the wet to dry ratio of the intestinal tissue, defined as (wet weight–dry weight)/dry weight, is measured. A wet to dry ratio of 5.37 ± 0.31 was measured for the EVP case, and a ratio of 4.15 ± 0.26 was measured for the CG case. We translated these data from a ratio to an estimate of percent volume increase. The result was an estimate of $19.8\% \pm 5\%$ volume increase for the experimental EVP case. In Fig. 3 we show a comparison of the percent volume change in the experimental and simulation EVP case.

Also tracked during the simulations were the average interstitial pressures in each of the three layers over time. Figure 4 shows this data. Pressures were highest in the submucosa, followed by the mucosa and muscle layers. Similarly, the percent change in volume in all three layers was also tracked. Figure 5 shows those results. The volume increased the most in the mucosa layer in each simulation, followed by the muscle layer and the submucosa. Figure 6 shows a snapshot of the computational domain representing the intestinal wall and the pressure contours at $t = 20$ s.

The venous pressure P_V is the main parameter whose value influences oedema formation. Now we examine what happens if we perform a perturbation of P_V for the EVP case. In the experiments in Cox *et al.* (2008), the measured P_V in the EVP and EVP–HS cases was 20 ± 3 mmHg. We utilized $P_V = 20$ for the EVP and EVP–HS simulations. Now we run the EVP simulation for

FIG. 3. Comparison of the final interstitial pressure in the submucosa between the experimental results of Cox *et al.* (2008) and the simulations for the four cases (left). Comparison of the percent volume increase in the whole domain between the experiment (Cox *et al.*, 2008) and simulation for the EVP case (right).

$P_V = [17, 23]$. Figure 7 shows the comparison of the final average submucosal pressure for the cases $P_V = 17, 18, 19, 20, 21, 22$ and 23. Also shown is the comparison of the total volume increase for the same seven cases. We know from the experimental results that the final submucosal pressure for the EVP group was 3.80 ± 0.34 mmHg, where 0.34 is the standard deviation. Our standard deviation was computed to be 0.82. If we drop the two extremes ($P_V = 17, 23$), the standard deviation is 0.43, which is close to the experimental one, but still larger. For the volume increase, the experimental EVP case results were $19.8\% \pm 5\%$. The standard deviation of our simulations was 6.63% and if we drop the two extremes, we have 5.1%, which is very close to the experimental value. We only changed P_V in these simulations. As mentioned previously, it is known that parameters such as K_f and P_p change with P_V (Guyton & Guyton, 2000), though the specific relationships are not clear. To achieve the standard deviation results seen in the experiments more precisely in our simulations, we would likely need to adjust other parameters as we adjust P_V .

4. Discussion

A computational model of oedema formation in the intestine was developed. By mathematically describing the intestine as a poroelastic medium, and utilizing parameters from experiments, we were able to model the build-up of fluid in the intestine that occurs as a result of elevated blood pressure. The interstitial pressure values in the submucosa and overall volume increases computed by the model correlate well with the experimentally measured values in Cox *et al.* (2008) for the four scenarios. Beyond these average quantities, the model is able to provide a detailed look at the pressure and change in volume distributions across the three main layers of the intestinal wall. The pressure is highest in the submucosa layer, which can be explained by this layer's high elastic moduli compared with the other two layers. It is more energetically costly for the submucosa to expand when fluid is added there, thus pressure builds up to a higher value. The same logic explains the variation in the volume increase seen across the layers. The mucosa has the lowest elasticity parameters and also receives a higher fraction of fluid from the source term, due to its extensive blood and lymph capillary systems; thus its volume increases the most during oedema. The submucosa and muscle layers are more stiff and also have less fluid-exchanging capillaries, and so their volumes increase at a much slower rate than the mucosa. These hypotheses

FIG. 4. The average pressure vs. time for the four cases in the individual layers: mucosa, submucosa and muscle.

provided by the model regarding pressure and volume changes in the individual layers will be tested in future experimental work.

Our model overcomes several limitations of past models. We take into account the mechanical response of the intestinal tissue, and its effect on the interstitial pressure and volume. We also include a concentration parameter that captures the varying distribution of capillaries found in the different layers of the intestine. Lastly, our PDE system includes the evolution of the interstitial pressure itself, so that one can compute the source term $\phi(p)$ with the most up-to-date pressure information at each time step.

In future work, we plan to utilize this model to explore possible mechanical triggers of ileus that oedema is capable of initiating. One hypothesis that warrants further exploration is that the increase in fluid volume in the interstitium causes an interruption in communication between nerves and muscle cells (Guyton, 1995; Veeraraghavana & Poelzing, 2010). For muscle cells in the intestine to contract, signals originating in enteric nerve cells and the interstitial cells of Cajal embedded in the muscle layer (Gregersen, 2003) are transmitted to muscle cells via the diffusion of neurotransmitters and ions through synapses (Alberts *et al.*, 1994; Gregersen, 2003), with diffusion distances of approximately

FIG. 5. The average percent increase in volume vs. time for the four cases in the individual layers: mucosa, submucosa and muscle.

15–30 nm (Devine *et al.*, 1971; Savtchenko & Rusakov, 2007). Muscle cells continue to propagate the signals to other muscle cells via gap junctions (Gregersen, 2003), (distances of 2–3 nm Alberts *et al.*, 1994). Gap junctions are thin, protein-walled channels directly connecting one cell's interior to another (Alberts *et al.*, 1994).

Using our model, we can make some preliminary predictions for this hypothesis. The force needed to rupture a gap junction is on the order of 10 nN for a patch of gap junctions 1–2 μm in diameter (Hoh *et al.*, 1993). This translates to a stress of approximately 22 mmHg, which is well above the interstitial fluid pressure measured in ileus-stricken tissue (Cox *et al.*, 2008). Gap junction rupture is not a likely candidate for muscle communication disruption. However, a synapse is not a protected channel but rather just open interstitial space. During oedema, as the interstitial volume increases, cells are pushed apart, increasing the distance over which diffusing ions must travel (Guyton, 1995). From the simulations, the percent change in the total volume in the muscle layer for the EVP case is approximately 1%. This small change in the overall volume translates to a much higher percent change in the interstitial fluid volume, since the muscle cells and connective tissue occupy a majority of the space (Guyton, 1995; Gregersen, 2003). Using the average size of a smooth muscle cell (2–4 μm wide, 150 μm long Lane,

FIG. 6. Pressure contours for the EVP case at $t = 20$ s. FIG. 7. Comparison of the average submucosal pressure for the EVP cases with $P_v = [17, 23]$ (left) and comparison of the total percent volume increase for the same cases over time.

1965) and average distance between neighbouring cells (2–30 nm; Devine *et al.*, 1971; Alberts *et al.*, 1994), we can estimate the average distance between cells after oedema, to be of the order of 30–60 nm, a 2- to 15-fold increase. Theoretical studies such as Savtchenko & Rusakov (2007) have shown that there exists a range of synapse lengths for optimal signal transmission (12–20 nm was considered optimal in Savtchenko & Rusakov 2007). Lengths outside this range, such as the 30–60 nm range estimated here, produce weaker signal transmissions (Savtchenko & Rusakov, 2007). The significant increase in the synapse length due to oedema is a potential instigator of muscle contraction signalling interruption.

This model of intestinal oedema development provides valuable insight into the mechanical basis of this phenomenon. The different elastic and structural properties of the intestinal layers utilized in the model provide a detailed look at the pressure and volume variation across the intestine during oedema formation. Future work will include additions to the model such as the forces from muscle contractions, as well as the fluid dynamics of the lumen. This model will be utilized to further explore oedema mechanics and to test the effect of various treatment methods for oedema.

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