Review Article
The Mechanical Bidomain Model: A Review

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The mechanical bidomain model is a new mathematical description of the elastic behavior of cardiac tissue. Its primary advantage over previous models is that it accounts for forces acting across the cell membrane arising from differences in the displacement of the intracellular and extracellular spaces. In this paper, I describe the development of the mechanical bidomain model. I emphasize new predictions of the model, such as the existence of boundary layers at the tissue surface where the membrane forces are large, and pressure differences between the intracellular and extracellular spaces. Although the theoretical analysis is quite mathematical, I highlight the types of experiments that could be used to test the model predictions. Finally, I present open questions about the mechanical bidomain model that may be productive future directions for research.

1. Introduction

This paper focuses on a quantitative analysis of the biomechanical forces acting on the intracellular and extracellular spaces of cardiac tissue, and especially on the coupling of these two spaces across the cell membrane. Our understanding of these forces is rudimentary, yet they may play a vital role in tissue engineering and mechanobiology. This paper concentrates on the mechanical behavior of cardiac tissue, although the results may apply to many other tissues. Before presenting a mathematical model that describes membrane forces in cardiac tissue, let us consider the biological and biomedical problems that motivate this research.

Chiquet [1] reviewed remodeling of the extracellular matrix and identified integrin proteins as playing a crucial role, because “they physically link the extracellular matrix to the cytoskeleton and hence are responsible for establishing a mechanical continuum by which forces are transmitted between the outside and the inside of cells.” Chiquet et al. [2] compare integrins and associated focal adhesion proteins to “molecular springs” coupling mechanical forces in the intracellular and extracellular spaces. Integrins may be important in tumor biology and cancer therapy [3].

The interaction of intracellular and extracellular forces plays a role in cardiac tissue remodeling. Kresh and Chopra [4] conclude that “ultimately, understanding how the highly interactive mechanical signaling can give rise to phenotypic changes is critical for targeting the underlying pathways that contribute to cardiac remodeling associated with various forms of dilated and hypertrophic myopathies, myocardial infarction, heart failure, and reverse remodeling.” Mechanotransduction refers to the mechanism by which mechanical forces trigger tissue remodeling and may be particularly important in the heart [5]. Furthermore, mechanical forces may cause remodeling of cardiac tissue in the border zone adjacent to an ischemic region [6]. They may even trigger mesenchymal stem cell differentiation [7].

Another important consequence of mechanical forces is the opening of stretch-activated ion channels. Mechanical feedback in cardiac tissue is well established [8], may be responsible for stretch-induced arrhythmias [9], and could impact defibrillation efficacy [10, 11]. One interesting feature of stretch-activated channels is that their mechanism of activation is unclear. These ion channels may respond to membrane forces, or they may be controlled by stretch sensors in the intracellular space [12]. A method to distinguish between these two cases would be valuable.

Engineered cardiac tissue is becoming increasingly important in therapeutic applications [13, 14]. In fact, tissue engineering in general often requires careful manipulation of mechanical forces. In vitro tissue engineering relies on the prefabrication of replacement tissue [15], typically grown on
some extracellular matrix [16], and the mechanical stresses that the tissue experiences during growth influence its structure and function [17, 18].

All these examples have one feature in common: they focus on how the intracellular and extracellular spaces interact across the cell membrane. Numerous studies have examined these interactions at the molecular level, from the perspective of biochemistry or gene expression. Such views are important, but so is information provided by tissue biomechanics. Unfortunately, most mechanical models of tissue do not emphasize, nor do they even include, the forces acting on and across the membrane. What is needed is a macroscopic mathematical model of biomechanics that highlights the coupling between intracellular and extracellular spaces, and that focuses on the forces across the cell membrane. Such a model has been developed recently: the mechanical bidomain model [19].

2. Development of the Mechanical Bidomain Model

The development of the mechanical bidomain model was guided by the existing and well-known electrical bidomain model, which has been used for decades to describe the electrical behavior of cardiac tissue [20–22]. This model accounts for the anisotropic electrical properties of the intracellular and extracellular spaces and their coupling by current crossing the cell membrane. The electrical bidomain model is the preferred model for simulating electrical stimulation of the heart, such as during cardiac pacing or defibrillation, whereas the mechanical bidomain model may be similarly useful when describing mechanical events in which the key consideration is mechanical forces acting on and across the membrane.

The development of the mechanical bidomain model was motivated in part by the Ohayon and Chadwick [25] model of cardiac tissue, which has three terms contributing to stress in the tissue: (1) an anisotropic tension acting along the myocardial fibers arising from the interaction of actin and myosin [26], (2) a hydrostatic pressure introduced because the tissue is primarily water, and (3) an isotropic shear force caused by the network of collagen fibers in the extracellular space. Ohayon and Chadwick represented the tissue as a single material (a monodomain), but Puwal and I extended the model to a bidomain representation [19]. We assigned the myocardial fiber tension to the intracellular space, the collagen matrix to the extracellular space, and a hydrostatic pressure to each space. In addition (and this is the key element of the bidomain model), we added a coupling of the two spaces across the membrane by a spring obeying Hooke’s law. The resulting bidomain equations were

\[
\begin{align*}
\frac{\partial p}{\partial x} + \gamma \frac{\partial^2 u_x}{\partial x^2} + \frac{\partial T}{\partial x} &= K (u_x - w_x), \\
\frac{\partial p}{\partial y} &= K (u_y - w_y) 
\end{align*}
\]

where \( u \) and \( w \) are the intracellular and extracellular displacements, \( p \) and \( q \) are the intracellular and extracellular pressures, \( T \) is the intracellular active tension produced by the fibers, \( \gamma \) is the Young’s modulus of the intracellular space along the fibers, and \( K \) is the shear modulus of the extracellular space. The new parameter in the bidomain model is \( K \), the spring constant coupling the two spaces. Equations (1)–(4) imply that the net force on a small volume of either the intracellular or extracellular space is zero (each space is in mechanical equilibrium). The first two equations are for the intracellular space, and the second two for the extracellular space. Equations (1) and (3) describe forces in the \( x \) direction, and (2) and (4) describe forces in the \( y \) direction. We have already made a few assumptions when deriving these equations: we only consider a two-dimensional model \((x, y)\), the fibers are taken as straight and aligned with the \( x \)-axis, and the intracellular and extracellular spaces are each incompressible so their displacements have zero divergence (\( \text{div} u = 0 \) and \( \text{div} w = 0 \)).

More recent calculations [27, 28] suggest that terms representing an isotropic shear should be included in the intracellular space as well as the extracellular space, making the bidomain equations have the slightly more general form

\[
\begin{align*}
\frac{\partial q}{\partial x} + \mu \left( \frac{\partial^2 w_x}{\partial x^2} + \frac{\partial^2 u_x}{\partial y^2} \right) &= -K (u_x - w_x) \\
\frac{\partial q}{\partial y} + \mu \left( \frac{\partial^2 w_y}{\partial x^2} + \frac{\partial^2 u_y}{\partial y^2} \right) &= -K (u_y - w_y),
\end{align*}
\]

where \( \mu \) is the intracellular shear modulus.

A few implications of this model became apparent immediately [19]. First, the intracellular and extracellular displacements can be different, and it is this difference that causes the mechanical forces on the cell membrane. If both the intracellular and extracellular spaces undergo a complicated displacement that strains the tissue, but if these displacements are identical in both spaces, then there is no membrane force \((u - w = 0)\). When the difference between \( u \) and \( w \) does not vanish, the membrane force can be significant, especially if \( K \) is large. Second, a pressure difference can exist between the intracellular and extracellular spaces \((p \neq q)\). Third, a new length scale arises from the model, which Puwal and Roth [19] specified as equal to \( \sqrt{\mu/K} \). Although I do
not have a good estimate of the value of $K$, I expect $K$ is large and therefore this length scale will be small. Many of the interesting effects that are unique to the bidomain model arise within a few length constants of the tissue surface [19]. We will consider all three of these effects, and others, in more detail later in this paper.

### 3. Incompressibility and Stream Functions

The displacements $u$ and $w$ are both divergenceless, implying that both spaces are individually incompressible. Therefore, these vectors can be described in terms of stream functions $\phi$ and $\eta$, such that $u_x = \partial \phi / \partial y$, $u_y = -\partial \phi / \partial x$, $w_x = \partial \eta / \partial y$, and $w_y = -\partial \eta / \partial x$ [29]. Using these stream functions, we can recast the mechanical bidomain equations in a somewhat more elegant form. For example, we can add the $x$-derivative of (5) and the $y$-derivative of (6), obtaining

$$\nabla^2 p = \mu \frac{\partial^4 \phi}{\partial x^4} + \frac{\partial^2 T}{\partial x^2}. \quad (9)$$

Similarly, we can take the $y$-derivative of (5) and subtract the $x$-derivative of (6), thereby eliminating $p$ as

$$\nabla^4 \psi + \frac{\partial^4 \phi}{\partial x^4 \partial y^2} + \frac{\partial^2 T}{\partial x^2 \partial y} = K (\nabla^2 \phi - \nabla^2 \eta). \quad (10)$$

Repeating the same process for the extracellular space, we find

$$\nabla^2 q = 0, \quad (11)$$

$$\mu \nabla^4 \eta = -K (\nabla^2 \phi - \nabla^2 \eta). \quad (12)$$

These four equations (9)–(12) govern the four scalar functions $\phi$, $\eta$, $p$, and $q$.

### 4. Separation of Bidomain and Monodomain Behavior

Punala and I recast the bidomain equations (1)–(4) in dimensionless form [29], and I will follow a similar procedure for (5)–(8). First, the primary goal of the mechanical bidomain model is to focus attention on differences between the intracellular and extracellular displacements. Therefore, let us define a new stream function $\lambda$ that is the difference between the intracellular and extracellular stream functions, $\lambda = \phi - \eta$. The membrane forces are then specified entirely by $\lambda$, which plays a fundamental role in the mechanical bidomain model analogous to the role played by the transmembrane potential in the electrical bidomain model. Let us carry the analogy between the mechanical and electrical bidomain models one step further and introduce a second stream function, $y$ [30], so that $\lambda$ and $y$ are related to $\phi$ and $\eta$ by

$$\lambda = \phi - \eta, \quad (13)$$

$$y = \phi + \mu \eta, \quad (14)$$

The physical meaning of $y$ is not immediately clear, but we will eventually show that it highlights the "monodomain" behavior of the displacement, whereas $\lambda$ highlights the "bidomain" behavior [20]. We can invert (13) to obtain

$$\phi = \frac{y}{\mu + \nu} \left( y + \frac{\mu}{\nu} \lambda \right), \quad (15)$$

$$\eta = \frac{y}{\mu + \nu} (y - \lambda). \quad (16)$$

Next, assume that length $a$ is characteristic of the tissue (e.g., $a$ might specify the size of the tissue sheet). We can then define nondimensional distances $X = x/a$ and $Y = y/a$. Furthermore, we introduce three dimensionless parameters $\varepsilon$, $\zeta$, and $\sigma$, defined as

$$\varepsilon = \frac{\mu \nu}{K (\mu + \nu) a^2} \quad (17)$$

$$\zeta = \frac{\nu}{\mu + \nu} \quad (18)$$

$$\sigma = \frac{\mu}{\nu}. \quad (19)$$

Adding (10) and (12) and rewriting them in terms of dimensionless parameters leads to

$$\varepsilon \nabla^4 \psi + \zeta \frac{\partial^4 \psi}{\partial X^4 \partial Y^2} + \mu \frac{\partial^4 \lambda}{\partial X^4 \partial Y^2} + \frac{\partial^2 T}{\nu \partial X^2} = 0. \quad (20)$$

Multiplying (12) by $\nu / \mu$ and subtracting the result from (10) leads to

$$\varepsilon \nabla^4 \lambda - \zeta \frac{\partial^4 \lambda}{\partial X^4 \partial Y^2} + \mu \frac{\partial^4 \lambda}{\partial X^4 \partial Y^2} + \frac{\partial^2 T}{\nu \partial X^2} = \lambda. \quad (21)$$

At the first glance, (18) and (19) do not appear to be any simpler than (10) and (12). However, on closer inspection one sees that when deriving (18) the right-hand sides of (10) and (12) cancel. Therefore, (18) does not contain the coupling spring constant $K$ (nor its nondimensional counterpart, $\varepsilon$). In contrast, (19) does depend on $\varepsilon$. Additional insight can be gained if, for the moment, we set $\zeta$ equal to zero. In that case, (18) and (19) reduce to

$$\varepsilon \nabla^4 \psi = -\frac{a^2}{\nu} \frac{\partial^2 T}{\partial X^2}, \quad (22)$$

$$\varepsilon \nabla^4 \lambda = \frac{a^2}{\nu} \frac{\partial^2 T}{\partial X^2}. \quad (23)$$

The two partial differential equations are now uncoupled, with (20) determining $\psi$ and not depending on the coupling constant $K$, and (21) determining $\lambda$ and depending sensitively on $K$. In fact, (20) is what one gets using a monodomain model of the tissue, like that presented by Ohayon and Chadwick [25]. From (14), we find that if $\lambda$ is zero, the stream functions in the intracellular and extracellular spaces are identical, both equal to $(y/(\mu + \nu))\psi$. We say that $y$ specifies the "monodomain" behavior of the tissue, in which
the displacements are the same in both spaces. On the other hand, (21) depends only on \( \lambda \) (specifying the difference between the intracellular and extracellular displacements). It is independent of \( \psi \) and depends on the parameter \( \varepsilon \). Therefore, \( \lambda \) specifies the "bidomain" behavior of the tissue. It contains all the new behavior predicted by the mechanical bidomain model.

5. Intracellular and Extracellular Anisotropy

If we relax our assumption that \( \zeta = 0 \), we find that (18) and (19) do not uncouple. In this case, the "bidomain" and "monodomain" behaviors influence each other. This coupling arises because of the tissue anisotropy. Equations (18) and (19) assume that the extracellular space is isotropic and the intracellular space has both an isotropic shear and an anisotropic stiffness that develops only along the fibers. Therefore, intracellular anisotropy arises because of a nonzero value of \( \zeta \). Does the difference in anisotropy between the intracellular and extracellular spaces lead to new behavior? One suspects the answer is yes because of the analogous property of the electrical bidomain model. Many of the most interesting results of that model—such as the presence of hyperpolarized regions near a unipolar stimulating electrode [31] and the polarization of curved fibers in a uniform electric field [32]—are caused by cardiac tissue having unequal anisotropy ratios: the electrical anisotropy is different in the intracellular and extracellular spaces [21]. I was able to derive approximate analytical solutions to the electrical bidomain equations using a perturbation expansion in terms of a parameter measuring the difference in anisotropy between the two spaces [33]. A similar approach with the mechanical bidomain model—using a perturbation expansion in the dimensionless parameter \( \zeta \)—may provide insight into new behavior arising because of differences in mechanical anisotropy in the intracellular and extracellular spaces. However, the assumption in (7) and (8) that the extracellular space is isotropic may be invalid, and the mechanical bidomain equations may need to be extended further to account for anisotropy in both spaces. This is a topic that needs more study.

6. What Does “\( K \) Is Large” Mean?

As I mentioned earlier, the parameter \( K \) coupling the intracellular and extracellular spaces is probably large. Large compared to what? To answer that question, let us examine the definition of the dimensionless parameter \( \varepsilon \) of (15) in more detail. Because \( a \) has the units of distance, the quantity \( \sqrt{\mu v / K (\mu + v)} \) must also have units of distance (else \( \varepsilon \) is not dimensionless). This quantity is the new distance scale introduced by the bidomain model. As \( K \) goes to infinity, \( \sqrt{\mu v / K (\mu + v)} \) goes to zero. Therefore, to say that “\( K \) is large” really means that the new bidomain distance scale is small compared to other distance scales within the tissue. But earlier we said that the tissue was characterized by distances of size \( a \), so the assumption that “\( K \) is large” really means \( \sqrt{\mu v / K (\mu + v)} \ll a \). In other words, \( \varepsilon \ll 1 \).

Let me stress that we do not have any measurements of \( K \) yet, so claiming \( \varepsilon \ll 1 \) is more of a conjecture than a fact. Nevertheless, this conjecture emphasizes one goal of future experiments: determine the size of \( \varepsilon \). To the extent that the mechanical bidomain model has any validity or usefulness, the measurement of \( \sqrt{\mu v / K (\mu + v)} \) will be key for understanding bidomain behavior.

7. Boundary Layers

Equation (19) is a partial differential equation containing a small parameter \( \varepsilon \), which suggests that perturbation theory may be useful for analyzing the equation. Punal and I applied perturbation theory to the mechanical bidomain equations [29]. We started with (1)–(4), so our results did not contain the intracellular shear modulus \( \nu \) and our small parameter \( \varepsilon \) was given by \( \mu / K a^2 \) rather than by (15), but the essential idea could easily be applied to the full bidomain equations, (5)–(8). Without rederviving the entire mathematical analysis here, let me summarize the key results. The zeroth order term in the perturbation expansion was the “monodomain” result. The zeroth order contribution to \( \lambda \) vanished, so to a lowest order approximation the intracellular and extracellular spaces move together. Only in the first order did we obtain a nonvanishing value for \( \lambda \), implying that there could be relative displacements between the intracellular and extracellular spaces, but these would be small. Specifically, these terms are multiplied by the small parameter \( \varepsilon \). The calculation predicted the detailed distribution of intracellular displacement \( \mathbf{u} \) and extracellular displacement \( \mathbf{w} \), and therefore specified the spatial distribution of membrane forces \( K (\mathbf{u} - \mathbf{w}) \). Interestingly, the distribution of membrane forces was very different than the distribution of other quantities, such as the strain along the fibers. The model thus provides definite predictions that could assist experimentalists in testing hypotheses about what causes certain behaviors such as tissue remodeling or stretch-induced ion channel opening: is it bidomain membrane forces, strain along the fibers, or some other quantity?

Mathematicians will notice how \( \varepsilon \) enters (19) (more clearly evident in (21)); it multiplies the highest derivative, the 4th-derivative biharmonic operator \( \nabla^4 \). When a small parameter multiplies the highest order derivative in a differential equation, the analysis often requires “singular perturbation theory” [34, 35]. In the analysis of fluid dynamics of a nearly inviscid fluid, singular perturbation theory results in a thin boundary layer appearing near a fluid-solid interface [36]. Viscosity can be neglected throughout the fluid except near the boundary, where a large velocity gradient is required in order to meet the no-slip boundary condition at the surface. By analogy, we expect that boundary layers will be predicted by the mechanical bidomain model. Such “boundary layers” are also evident in the electrical bidomain model: the transmembrane potential falls off exponentially from a source with a length constant. Trayanova et al. [32] found that when an electrical shock was applied to the
heart, the transmembrane potential was large within a few length constants from the heart surface, but was small deeper throughout the heart wall. Similar behavior almost certainly arises in the mechanical bidomain model, given the similar structure of the equations in the two models.

Recently, I have found examples of boundary layers predicted by the mechanical bidomain model [27, 28]. In one case [28] I was able to solve what may be the simplest biomechanical problem analytically. Consider a two-dimensional sheet of cardiac tissue, with its edges free (zero stress at the boundary). When at rest, the tissue is a circle with radius \(a\). However, active tissue generates a tension \(T\) along its fibers, causing the fibers to contract. Because the tissue is incompressible, the tissue also bulges in the direction perpendicular to the fibers. Such behavior was predicted by the “monodomain” part of the mechanical bidomain model.

The “bidomain” behavior was restricted to a boundary layer of thickness \(\sqrt{\mu/v/K(\mu + v)}\) at the tissue edge. The membrane forces are the largest at the tissue boundary, but are negligible throughout the rest of the tissue sheet. This calculation predicts that membrane forces are often the largest in a thin boundary layer at the tissue surface. If membrane forces are important for remodeling or mechanotransduction, the tissue surface is the place to look for such effects.

8. Strain Energy

Numerical simulations that use a realistic three-dimensional heart geometry require finite element calculations [37, 38]. The finite element model is typically based on a strain-energy formulation of elasticity. One area of future work will be to recast the mechanical bidomain model in terms of elastic energy [39]. An important question is as follows: do (5)–(8) describe a hyperelastic material (one in which the stresses are derivable from a strain-energy function, \(W\))? If we only allow \(W\) to depend on the intracellular and extracellular strains, then clearly our model is not hyperelastic. A uniform displacement of the intracellular space relative to the extracellular space causes no intracellular or extracellular strains, but would certainly produce energy in the springs coupling the two spaces. How to recast the mechanical bidomain model in terms of a strain-energy function is currently an open question.

One virtue of adopting an energy formulation is that it lends itself to large strains. The linear elasticity theory used in (5)–(8) is appropriate for small strains, but in cardiac tissue the strain can be large, and a nonlinear finite strain theory is necessary [39]. With large strains, you must distinguish between Green’s strain tensor (derivatives of the displacement are taken with respect to the original state) and Almansi’s strain tensor (derivatives of the original position are taken with respect to the displaced state). The constitutive law relating to stress and strain is often taken to be exponential [39], which reduces to the linear model only for small strains. Analysis based on (5)–(8) is useful for providing physical insight into the new features of the bidomain model, but careful comparison to experiment will require accounting for large strains. How to extend the mechanical bidomain model to large strains is another open question.

Equations (5)–(8) are based on several additional assumptions, such as that the tissue is two-dimensional and that the fibers are uniform and straight. The heart is actually a three-dimensional tissue with a complicated fiber geometry [40]. Extending the model to three dimensions should be easy; two equations like (6) and (8) could be added for the \(z\)-direction. One challenge would arise from the use of stream functions, which are more appropriate for two dimensions. Chadwick [26] has shown how a complex fiber geometry can be incorporated into (5)–(8). Numerical methods to solve the mechanical bidomain equations need to be developed in order to predict the mechanical behavior using a realistic model of a heart.

9. The Macroscopic/Microscopic Connection

In order to obtain a complete understanding of the mechanical bidomain model, we need to analyze how this macroscopic continuum representation of the tissue relates to the microscopic cellular properties of the intracellular and extracellular spaces. Such an analysis was crucial to obtaining a complete understanding of the electrical bidomain model [41]. We begin by imagining the tissue as a collection of cylindrical fibers, having intracellular volume fraction \(\theta_i\) and extracellular volume fraction \(\theta_e\) \((\theta_i + \theta_e = 1)\). The macroscopic tension \(T\) can be related to the microscopic tension developed in a single fiber \(T_{\text{micro}}\) by \(T = \theta_i T_{\text{micro}}\). This relationship makes sense, because if the tissue consisted of only a few fibers \((\theta_i \ll 1)\) then the net macroscopic force produced by the tissue would be small. Similarly, \(y = \theta_i y_{\text{micro}}\), \(v = \theta_i v_{\text{micro}}\), and \(\mu = \theta_i \mu_{\text{micro}}\). Interestingly, this analysis implies that the macroscopic pressures, \(p\) and \(q\), are not the same as the microscopic pressures: \(p = \theta_i p_{\text{micro}}\) and \(q = \theta_i q_{\text{micro}}\). However, the macroscopic displacements \(u\) and \(w\) are the same as the microscopic displacements (just as in the electrical bidomain model, the macroscopic and microscopic potentials are the same).

One of the unresolved questions about the mechanical bidomain model is the physical interpretation of pressure differences between the intracellular and extracellular spaces [19, 29]. Intuitively, such pressure differences should be accompanied by fluid flow into or out of the cells. Our microscopic analysis implies that it is not \(p - q\) that should drive fluid flow across the membrane, but \(p_{\text{micro}} - q_{\text{micro}}\). We can recast the bidomain equations in terms of two new variables, \(P = p + q\) and \(Q = p - \theta_i p_{\text{micro}}\). \(P\) is the “monodomain” pressure (i.e., the pressure that would correspond to a model like Ohayon and Chadwick’s), and \(Q\) is proportional to the difference between the microscopic intracellular and extracellular pressures, or the “bidomain” pressure. It may be that our mechanical bidomain equations, (5)–(8), are applicable only for rapid displacements, and longer-term displacements are accompanied by fluid flow between the intracellular and extracellular spaces, driven by \(Q\).
10. Incompressibility

In our past analysis of the mechanical bidomain model, we have assumed that the intracellular and extracellular spaces are each individually incompressible. This assumption may not be essential, particularly if there is fluid flow across the cell membrane. One could generalize the mechanical bidomain model to allow changes in the intracellular and extracellular volume fractions, while keeping the total volume of the tissue fixed. This approach is similar to that taken by Dembo and Harlow when analyzing interpenetrating reactive flow through contractile biopolymer networks [42, 43]. Their model is similar to ours, but focused on fluid flow as opposed to elastic behavior. Dembo and Harlow cast their model with the intracellular volume fraction \( \theta_i \) as a variable. Such a model may help us better explain the physical interpretation of differences in the microscopic pressures \( p_{\text{micro}} \) and \( q_{\text{micro}} \): they drive flow that changes the volume fraction of the two spaces.

One source of insight into the mechanical bidomain model is Mow’s biphasic model of cartilage [44, 45]. Cartilage is represented as a biphasic system, with a fluid phase and a solid phase. Moreover, a coupling term is introduced between the phases originating from viscous fluid flow, which is proportional to the difference between the fluid and solid velocities. This mathematical formulation is similar to the mechanical bidomain model (compare (6) in [44] with (5)–(8)). Exactly how the mechanical bidomain model relates to Mow’s biphasic model remains unresolved, but the similar mathematical formulations imply that a careful study of Mow’s work may provide new insights into the mechanical bidomain model.

11. Shear Waves

Equations (5)–(8) are based on mechanical equilibrium (sum of the forces is zero). We can also examine acoustic wave propagation if we relax this assumption and use Newton’s second law (sum of the forces equals mass times acceleration). We have made an initial study of shear wave solutions to the mechanical bidomain equations [46] and found they come in two types. First there is a monodomain solution, in which the two spaces oscillate in phase. Second, there is a bidomain solution, in which the two spaces oscillate out of phase. The bidomain solution is a new type of wave, never before examined.

12. Experiments

Currently the main weakness of the mechanical bidomain model is that its predictions have not been tested experimentally. Perhaps the most essential future research is experimental verification of the model. The first experiments to consider are those that can determine the coupling constant \( K \). One way to accomplish this goal would be to determine the width of a boundary layer at the edge of the tissue. Cardiac tissue can be grown in tissue culture with a specified fiber geometry [47, 48], which may provide a reproducible and controllable environment for performing these experiments.

Another way to determine \( K \) is to measure the intracellular and extracellular displacements individually. If \( K \) is large, the difference between these displacements will be small. Because the difference in displacements will likely be much smaller than the displacements themselves, direct measurement of the intracellular and extracellular displacements using a microscope or other imaging device probably will be unproductive. Instead, methods are needed to measure the displacement difference directly, without measuring the intracellular and extracellular displacements individually. This would be analogous to optical mapping of cardiac electrical activity [49], in which the transmembrane potential is measured directly without recording the intracellular and extracellular potentials individually. One way to accomplish this mechanically might be to use an experimental method that is sensitive to molecular displacement, such as fluorescence resonance energy transfer (FRET).

Another prediction of the mechanical bidomain model is that fluid pressure can be different in the intracellular and extracellular spaces. Methods must be developed to measure tissue pressure locally, and to distinguish intracellular from extracellular pressure. If pressures or pressure differences cannot be measured directly, fluid flow in response to pressure differences might be modeled and measured.

One prediction of the mechanical bidomain model is that when the springs connecting the intracellular and extracellular spaces are broken, \( K \) will be reduced (or go to zero). If experimentalists can identify drugs that modify intracellular-extracellular coupling (perhaps by disrupting integrin molecules in the cell membrane), they will have a powerful pharmacological tool to test many specific predictions of the model.

The hypothesis underlying the mechanical bidomain model is that membrane forces should lead to phenomena such as mechanotransduction, tissue remodeling, and stretch-induced ion channel opening. I should stress that this hypothesis is, as yet, unproven, and even untested. Equations (5)–(8) allow one to design experiments in which membrane forces are large in a well-defined location and small elsewhere. If such an experiment is performed, one could search for tissue remodeling or mechanotransduction at those locations, either by monitoring tissue growth over long periods of time, or detecting a biochemical signature over shorter periods. There is much to be gained from experiments that can test the mechanical bidomain model unambiguously, determining if the qualitative predictions of the model are correct. Comparisons between theory and experiment can be difficult [50], but they are essential for moving the field forward. The most important contribution of mathematical modeling in biology and medicine is to make predictions that can then motivate and guide experimentalists.

13. Conclusion

To appreciate the broader impact of the mechanical bidomain model, let me quote the conclusion of a paper by Butler et al. [51] as follows:
“In conclusion, biomechanical factors have a significant, yet incompletely understood influence on tissue growth, development, maintenance, degeneration, and repair. Recent advances in our understanding of the role of biomechanics in normal physiology and pathophysiology have begun to be harnessed to develop regenerative strategies to restore damaged or diseased tissues in vivo and create living tissue replacements in vitro. Many challenges remain, especially in relation to complex tissues, but the potential impact on health care is enormous.”

I believe that the mechanical bidomain model will significantly impact biomechanics and tissue engineering, which are important and growing areas of research.

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