BIOMATH
www.biomathforum.org/biomath/index.php/biomath
Biomath Forum

ORIGINAL ARTICLE

Mechanotransduction caused by a point force in the extracellular space

Bradley J. Roth
Department of Physics, Oakland University
Rochester, MI, USA
roth@oakland.edu

Received: 16 January 2018, accepted: 19 October 2018, published: 27 October 2018

***Abstract*—The mechanical bidomain model is a mathematical description of biological tissue that focuses on mechanotransduction. The model's fundamental hypothesis is that differences between the intracellular and extracellular displacements activate integrins, causing a cascade of biological effects. This paper presents analytical solutions of the bidomain equations for an extracellular point force. The intra- and extracellular spaces are incompressible, isotropic, and coupled. The expressions for the intra- and extracellular displacements each contain three terms: a monodomain term that is identical in the two spaces, and two bidomain terms, one of which decays exponentially. Near the origin the intracellular displacement remains finite and the extracellular displacement diverges. Far from the origin the monodomain displacement decays in inverse proportion to the distance, the strain decays as the distance squared, and the difference between the intra- and extracellular displacements decays as the distance cubed. These predictions could be tested by applying a force to a magnetic nanoparticle embedded in the extracellular matrix and recording the mechanotransduction response.**

***Keywords*-analytical solution; extracellular matrix; integrin; intracellular cytoskeleton; mathematical model; mechanotransduction; mechanical bidomain model; point source.**

I. Introduction

Mechanotransduction is the process by which biological tissues grow and remodel in response to mechanical signals. One cause of mechanotransduction might be a cascade of biological responses triggered by activation of integrin molecules in the cell membrane [2], [3], [16]. A force acting on the extracellular matrix is transmitted to the cytoskeleton via these integrins, thereby coupling the intra- and extracellular spaces. Much research on mechanotransduction is qualitative, but to predict quantitatively how tissue responds to applied forces we need a mathematical model [12]. Many studies in mechanobiology analyze individual cells and molecules, but to describe tissues and organs we require a macroscopic model that averages over the cellular and molecular scales. Yet, this macroscopic model must predict the activation of integrin molecules.

One mathematical model that describes mechanotransduction is the mechanical bidomain model

Citation: Bradley J. Roth, Mechanotransduction caused by a point force in the extracellular space, Biomath 7 (2018), 1810197, http://dx.doi.org/10.11145/j.biomath.2018.10.197

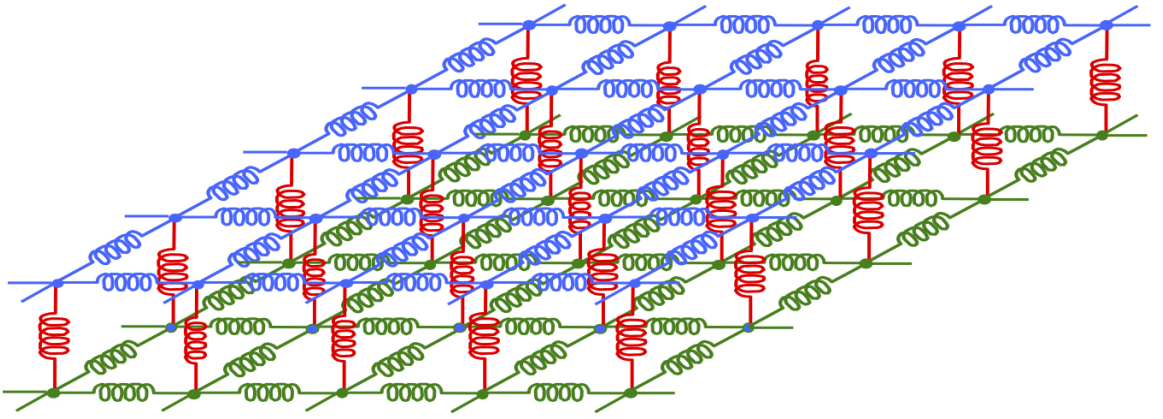

Fig. 1. A schematic illustration of the mechanical bidomain model. The green springs represent the intracellular cytoskeleton, the blue the extracellular matrix, and the red the integrins. The figure illustrates a two-dimensional version of the model, but this article analyzes a three-dimensional version.

[11], [15]. It predicts displacements of the intra- and extracellular spaces individually. The difference between the intra- and extracellular displacements results in a force on the integrins that couple the two spaces. A schematic illustration of the model is shown in Figure 1. One of the most important properties of a mathematical model is how it responds to a point source. Often complicated responses can be expressed as a convolution of the point source response, so knowing how tissue responds to a point force provides insight into its general behavior.

In this paper, I derive analytical expressions describing how the mechanical bidomain model responds to a point source in the extracellular space. Experimentally, this could be approximated by, for instance, applying a magnetic force on a superparamagnetic nanoparticle [7], [8]. Magnetic tweezers [5] have been used to exert forces on single cells or individual molecules. The technique, however, could be applied to intact tissue where a nanoparticle is embedded in the extracellular matrix. When a force is exerted by the nanoparticle it pulls on the matrix, which stretches the integrins embedded in the membranes of nearby cells, triggering mechanotransduction [9].

II. Methods

I assume the intra- and extracellular spaces are incompressible and isotropic, and their strains are small and linear. Incompressibility implies that the intracellular displacement **u** and the extracellular displacement **w** are both divergenceless. I use spherical coordinates (r, θ, ϕ) with the force applied at the origin and acting along the z axis (θ = 0). By symmetry there are no displacements or derivatives in the ϕ direction. In that case **u** and the intracellular strain ϵ_i are related by [10]

$$\epsilon_{irr} = \frac{\partial u_r}{\partial r}, \tag{1}$$

$$\epsilon_{i\theta\theta} = \frac{1}{r}\frac{\partial u_\theta}{\partial \theta} + \frac{u_r}{r}, \tag{2}$$

$$\epsilon_{i\phi\phi} = \frac{u_\theta}{r}\cot\theta + \frac{u_r}{r}, \tag{3}$$

$$\epsilon_{ir\theta} = \frac{1}{2}\left(\frac{1}{r}\frac{\partial u_r}{\partial \theta} + \frac{\partial u_\theta}{\partial r} - \frac{u_\theta}{r}\right), \tag{4}$$

with analogous relationships in the extracellular space. The intracellular stress τ_i and the intracellular strain are related by

$$\tau_{irr} = -p + 2\nu\epsilon_{irr}, \tag{5}$$

$$\tau_{i\theta\theta} = -p + 2\nu\epsilon_{i\theta\theta}, \tag{6}$$

$$\tau_{i\phi\phi} = -p + 2\nu\epsilon_{i\phi\phi}, \tag{7}$$

$$\tau_{ir\theta} = 2\nu\epsilon_{ir\theta}, \tag{8}$$

where p is the intracellular pressure and ν is the intracellular shear modulus. Similar stress-strain relationships exist for the extracellular pressure q and extracellular shear modulus μ. The equations of mechanical equilibrium are [10], [15]

$$-\frac{\partial p}{\partial r} + 2\nu\left[\frac{\partial \epsilon_{irr}}{\partial r} + \frac{1}{r}\frac{\partial \epsilon_{ir\theta}}{\partial \theta} + \frac{1}{r}\Big(2\epsilon_{irr} - \epsilon_{i\theta\theta} - \epsilon_{i\phi\phi} + \cot\theta\ \epsilon_{ir\theta}\Big)\right] = K\left(u_r - w_r\right), \tag{9}$$

$$-\frac{1}{r}\frac{\partial p}{\partial \theta} + 2\nu\left[\frac{\partial \epsilon_{ir\theta}}{\partial r} + \frac{1}{r}\frac{\partial \epsilon_{i\theta\theta}}{\partial \theta} + \frac{1}{r}\Big(\left(\epsilon_{i\theta\theta} - \epsilon_{i\phi\phi}\right)\cot\theta + 3\epsilon_{ir\theta}\Big)\right] = K\left(u_\theta - w_\theta\right), \tag{10}$$

$$-\frac{\partial q}{\partial r} + 2\mu\left[\frac{\partial \epsilon_{err}}{\partial r} + \frac{1}{r}\frac{\partial \epsilon_{er\theta}}{\partial \theta} + \frac{1}{r}\Big(2\epsilon_{err} - \epsilon_{e\theta\theta} - \epsilon_{e\phi\phi} + \cot\theta\ \epsilon_{er\theta}\Big)\right] + F\delta\left(r\right)\cos\theta = -K\left(u_r - w_r\right), \tag{11}$$

$$-\frac{1}{r}\frac{\partial q}{\partial \theta} + 2\mu\left[\frac{\partial \epsilon_{er\theta}}{\partial r} + \frac{1}{r}\frac{\partial \epsilon_{e\theta\theta}}{\partial \theta} + \frac{1}{r}\Big(\left(\epsilon_{e\theta\theta} - \epsilon_{e\phi\phi}\right)\cot\theta + 3\epsilon_{er\theta}\Big)\right] - F\delta\left(r\right)\sin\theta = -K\left(u_\theta - w_\theta\right), \tag{12}$$

where K is the integrin spring constant coupling the two spaces, F is the force applied to the extracellular space, and $\delta(r)$ is the delta function. I assume that the displacements and pressures go to zero at large r.

To picture the problem physically, imagine that in Figure 1 a point in the extracellular matrix (one of the blue dots) is pulled to the right by an attached nanoparticle. This force would displace the extracellular matrix (blue springs), which would stretch the integrins coupling the two spaces (red springs). The integrins would then pull on the cytoskeleton, causing the intracellular space to be displaced.

III. Results

Equations 9-12 were solved using the method of undetermined coefficients. The solution is

$$u_r = \frac{F}{8\pi\left(\nu+\mu\right)}\cos\theta \left\{\frac{2}{r} - \frac{4\sigma^2}{r^3} + 4\left[\frac{\sigma^2}{r^3} + \frac{\sigma}{r^2}\right]\mathrm{e}^{-\frac{r}{\sigma}}\right\}, \tag{13}$$

$$u_\theta = \frac{F}{8\pi\left(\nu+\mu\right)}\sin\theta \left\{-\frac{1}{r} - \frac{2\sigma^2}{r^3} + 2\left[\frac{\sigma^2}{r^3} + \frac{\sigma}{r^2} + \frac{1}{r}\right]\mathrm{e}^{-\frac{r}{\sigma}}\right\}, \tag{14}$$

$$w_r = \frac{F}{8\pi\left(\nu+\mu\right)}\cos\theta \left\{\frac{2}{r} + \frac{\nu}{\mu}\frac{4\sigma^2}{r^3} - 4\frac{\nu}{\mu}\left[\frac{\sigma^2}{r^3} + \frac{\sigma}{r^2}\right]\mathrm{e}^{-\frac{r}{\sigma}}\right\}, \tag{15}$$

$$w_\theta = \frac{F}{8\pi\left(\nu+\mu\right)}\sin\theta \left\{-\frac{1}{r} + \frac{\nu}{\mu}\frac{2\sigma^2}{r^3} - 2\frac{\nu}{\mu}\left[\frac{\sigma^2}{r^3} + \frac{\sigma}{r^2} + \frac{1}{r}\right]\mathrm{e}^{-\frac{r}{\sigma}}\right\}, \tag{16}$$

$$p = 0, \tag{17}$$

$$q = \frac{F}{4\pi}\frac{\cos\theta}{r^2}. \tag{18}$$

Each expression for the displacement contains a monodomain term (first term in the brace) that is the same in the intra- and extracellular spaces, and two bidomain terms that are different in the two spaces (one is -ν/μ times the other). The first bidomain term is proportional to σ^2, where $\sigma = \sqrt{\frac{\nu\mu}{K(\nu+\mu)}}$ is a length constant characteristic of the mechanical bidomain model [15]. The exponential in the second bidomain term decays with length constant σ.

The displacements (Eqs. 13-16) have interesting properties as r goes to zero. If you expand the exponential as a Taylor series, you will find that the terms in the expression for the intracellular displacement that are singular at the origin cancel and it remains finite there. The extracellular displacement, however, diverges at the origin as $1/r$ as expected for a delta function source in the extracellular space. At large distances ($r \gg \sigma$) bidomain terms decay more rapidly than monodomain terms.

The fundamental hypothesis of the mechanical bidomain model is that mechanotransduction depends on the difference **u** - **w** [15]. The monodomain terms are the same in the two spaces and do not contribute to **u** - **w**; only the bidomain terms generate the displacement difference that drives mechanotransduction,

$$u_r - w_r = \frac{F}{8\pi\mu}\cos\theta\left\{-\frac{4\sigma^2}{r^3}+4\left[\frac{\sigma^2}{r^3}+\frac{\sigma}{r^2}\right]\mathrm{e}^{-\frac{r}{\sigma}}\right\},$$

$$u_\theta - w_\theta = \frac{F}{8\pi\mu}\sin\theta\left\{-\frac{2\sigma^2}{r^3}+2\left[\frac{\sigma^2}{r^3}+\frac{\sigma}{r^2}+\frac{1}{r}\right]\mathrm{e}^{-\frac{r}{\sigma}}\right\}.$$

For $r \gg \sigma$ the exponentials are negligible and the difference in displacements falls as $1/r^3$.

Figure 2 shows the extracellular displacement, **w**, the intracellular displacement, **u**, and their difference, **u** - **w**, in the plane corresponding to a constant angle ϕ. Near the source, **u** - **w** resembles -**w**. Far from the source, **u** - **w** is small compared to **u** and **w** individually.

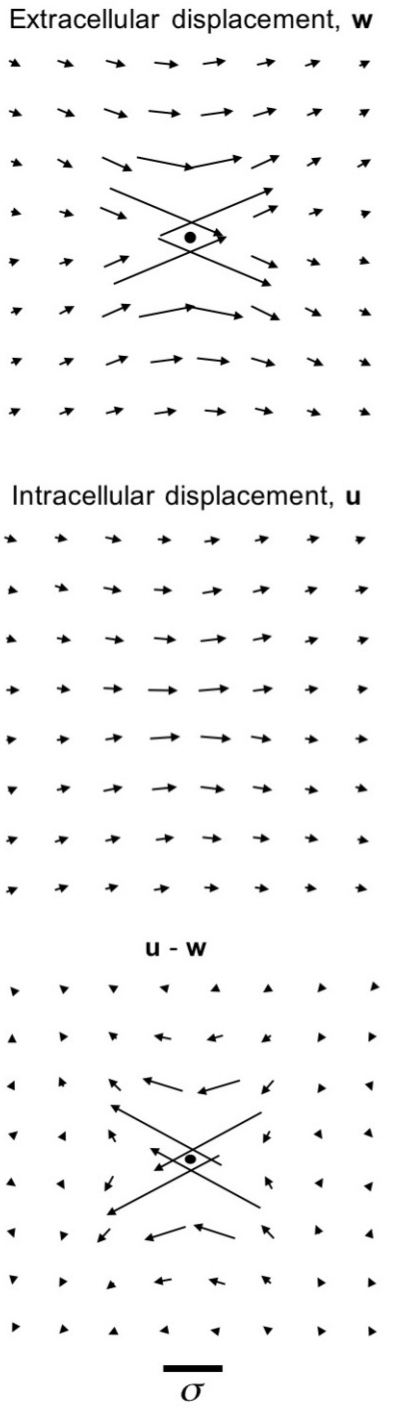

Fig. 2. The extarcellular displacement, **w**, the intracellular displacement, **u**, and their difference, **u**-**w**. The calculation assumes $\nu = \mu$. The black dot indicates the position of the point source, corresponding to an applied force F acting to the right.

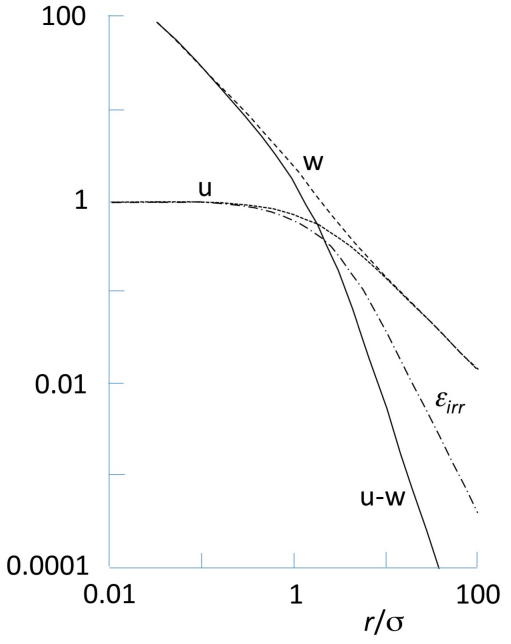

Fig. 3. u_r, w_r, u_r - w_r, and ϵ_{irr} as functions of r/σ, for $\theta = 0$; u_r is indicated by short dashes, w_r by long dashes, u_r - w_r by a solid line, and ϵ_{irr} by dash-dot. All quantities are normalized so that the intracellular displacement and strain are equal to one at the origin.

Figure 3 plots the intra- and extracellular displacements and their difference along the direction of the applied force. It also shows the intracellular strain, ϵ_{irr}. At large distances, the displacements fall as $1/r$, the strain as $1/r^2$, and the difference in the displacements as $1/r^3$. This result is a testable prediction. If mechanotransduction depends on the strain it decays relatively slowly, as $1/r^2$. If, however, mechanotransduction depends on **u** - **w** it decays relatively rapidly, as $1/r^3$.

IV. Discussion

Most biomechanical models treat tissue as a single phase: a monodomain. These mathematical models are often valuable tools for predicting tissue displacements, stresses, and strains [4]. If, however, mechanotransduction is triggered by activation of integrins, and integrins are activated by differences between the displacements of the intra- and extracellular spaces, then a bidomain model is essential for predicting where mechanotransduction occurs. The activation of integrins could in principle be determined by measuring the intra- and extracellular displacements individually, and then taking their difference. In practice, however, this difference is very small compared to the displacements themselves, and a better strategy would be to measure a mechanotransduction effect caused by integrin activation, such as tissue growth, remodeling, or genetic changes associated with these processes.

The monodomain solution for a point source is $u_r = w_r = \frac{F}{8\pi(\nu+\mu)}\frac{2\cos\theta}{r}$ and $u_\theta = w_\theta = -\frac{F}{8\pi(\nu+\mu)}\frac{\sin\theta}{r}$. This solution is the same as the expression for the velocity caused by a point force in an incompressible fluid at low Reynolds number [10], sometimes referred to as a Stokeslet. When σ is small the Stokeslet approximates the displacements in the intra- and extracellular spaces, but it provides no information about where mechanotransduction occurs because it contributes nothing to **u** - **w**. The monodomain term can be represented in Fig. 3 as a line that matches the **u** and **w** curves at large radii, and is extrapolated back linearly at smaller radii.

A key parameter in the model is the length constant σ, which depends on the bidomain constant K coupling the intra- and extracellular spaces. In monolayers of stem cells, σ is about 150 microns [1], which is larger than a cell and much larger than a nanoparticle, implying that a macroscopic model should be valid.

The mechanical bidomain model has many similarities to the electrical bidomain model [6] used to describe pacing and defibrillation of the heart. My analysis of the mechanical bidomain model's response to a point force is analogous to the calculation of the transmembrane potential produced by a point current using the electrical bidomain model [13]. In the electrical model, unequal anisotropy ratios for the intra- and extracellular conductivities plays a crucial role in determining the transmembrane potential distribution. Similar effects might arise in the mechanical model if it were made anisotropic.

What experiment can test the predictions of this

model? One suggestion is to grow a large cluster of epithelial cells, with a magnetic particle at its center. Alternatively, tissue engineering techniques could be used to grow cells in an extracellular substrate containing a magnetic particle. Then, a force could be applied to the particle, and the mechanotransduction response could be imaged by monitoring a second messenger activated by the integrins, or the turning on of a gene associated with cell growth.

The bidomain model has several limitations. It assumes a linear relationship between displacement and strain, which is only appropriate for small strains [10]. In my solution, the extracellular displacement and strain diverge at the origin, so the small strain assumption is violated there. However, the delta function is an approximation that breaks down on a distance scale similar to the radius of the magnetic nanoparticle used to exert the force. As long as the strains are small at this scale, the linear approximation should be valid. I assume the stress-strain relationships are linear, whereas in tissue these relationships can be nonlinear [4]. If the strains are small enough, however, a linear approximation should suffice. I assume that the tissue is isotropic, but tissues such as muscle are anisotropic and the model needs to be extended to account for anisotropy. I assume both the intra- and extracellular spaces are incompressible. Because both spaces contain mostly water, the incompressible assumption should be accurate [14]. My model is for steady-state. If the applied force varies with time, the solution might be invalid over short times because of the propagation of sound waves, or over long times because of viscoelasticity or tissue growth and remodeling. Finally, and fundamentally, I assume that mechanotransduction depends on the difference in the displacements, **u** - **w**. If it depends on other factors, such as the intracellular stress or strain, or some microscopic behavior that is not included in this macroscopic model, the results might not describe mechanotransduction correctly.

The model could be extended to avoid some of my limiting assumptions, but in that case an analytical solution might not exist. Analytical solutions can provide insight into the model behavior and are valuable even when the model is only an approximation. Moreover, analytical solutions are useful for testing limiting cases of complex models and for evaluating the accuracy of numerical methods.

V. Conclusion

The mechanical bidomain model makes testable predictions about where mechanotransduction occurs. In particular, the model predicts that the distribution of mechanotransduction in response to a point source in the extracellular space falls off with distance more rapidly if mechanotransduction is driven by the difference in the intra- and extracellular displacements, and less rapidly if mechanotransduction is driven by intra- or extracellular strain. This prediction could be tested by measuring how the tissue responds to a force applied using a magnetic nanoparticle embedded in the extracellular space.

References

[1] Auddya D, Roth BJ (2017) A mathematical description of a growing cell colony based on the mechanical bidomain model. *J Phys D* 50:105401.

[2] Chiquet M (1999) Regulation of extracellular matrix gene expression by mechanical stress. *Matrix Biology* 18:417-426.

[3] Dabiri BE, Lee H, Parker KK (2012) A potential role for integrin signaling in mechanoelectrical feedback. *Prog Biophys Mol Biol* 110:196-203.

[4] Fung YC (1981) *Biomechanics: Mechanical Properties of Living Tissues*. Springer, New York.

[5] Gosse C, Croquette V (2002) Magnetic tweezers: Micromanipulation and force measurement at the molecular level. *Biophys J* 82:3314-3329.

[6] Henriquez CS (1993) Simulating the electrical behavior of cardiac tissue using the bidomain model. *Crit Rev Biomed Eng* 21:1-77.

[7] Hughes S, McBain S, Dobson J, El Haj AJ (2007) Selective activation of mechanosensitive ion channels using magnetic particles. *J R Soc Interface* 5:855-863.

[8] Ingber DE (2009) From cellular mechanotransduction to biologically inspired engineering. *Ann Biomed Eng* 38:1148-1161.

[9] Kresh JY, Chopra A (2011) Intercellular and extracellular mechanotransduction in cardiac myocytes. *Pflugers Arch Eur J Physiol* 462:75-87.

[10] Love AEH (1944) *A Treatise on the Mathematical Theory of Elasticity*. Dover, New York.

[11] Roth BJ (2013) The mechanical bidomain model: A review. *ISRN Tissue Engineering* 2013:863689.

[12] Schwarz US (2017) Mechanobiology by the numbers: A close relationship between biology and physics. *Nat Rev Mol Cell Biol* 18:711-712.

[13] Sepulveda NG, Roth BJ, Wikswo JP (1989) Current injection into a two-dimensional anisotropic bidomain. *Biophys J* 55:987-999.

[14] Sharma K, Roth BJ (2014) How compressibility influences the mechanical bidomain model. *BIOMATH* 3:141171.

[15] Sharma K, Al-asuoad N, Shillor M, Roth BJ (2015) Intracellular, extracellular, and membrane forces in remodeling and mechanotransduction: The mechanical bidomain model. *Journal of Coupled Systems and Multiscale Dynamics* 3:200-207.

[16] Sun Y, Chen CS, Fu J (2012) Forcing stem cells to behave: A biophysical perspective of the cellular microenvironment. *Annu Rev Biophys* 41:519-542.