Published in final edited form as:

Phys Life Rev. 2017 December ; 22-23: 120–122. doi:10.1016/j.plrev.2017.08.013.

How Can We Predict Cellular Mechanosensation?: Comment on “Cellular Mechanosensing of the Biophysical Microenvironment: A Review of Mathematical Models of Biophysical Regulation of Cell Responses” by Bo Cheng et. al

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Introduction

In this issue Cheng et al. [1] presents a great review of cutting edge modeling approaches in mechanobiology. This field continues to expand at a fantastic rate and keeping all of the most recent work in perspective is advanced tremendously by this review. The authors review a wide variety of important areas in this article including the influence of mechanical force, matrix shape and rigidity, and fluid flow and shear stress on the cell. The discussion and presentation of the dynamics involved are very essential due to the rapidly changing nature of biological sensing from a biophysics perspective. Furthermore, the direction of feedback and response in biology is particularly important. While feedback is a concept that is designed into many man-made systems, biology has innate feedback mechanisms already embedded within its structures. If we are to ever fully exploit biology to our benefit we must first be able to model and predict its feedback behavior. Figuring out the sophisticated ways that biology accomplishes feedback and control requires mathematical modeling as the authors present. Therefore, in this commentary we highlight the wonderful advances in mathematical modeling in mechanobiology through a variety of methods presented by the authors. These models will impact a variety of fields from heart disease to traumatic brain injury.

Modeling Mechanosensing in Response to External Mechanical Forces

Cheng et al. [1] explores mathematical models related to cellular mechanosensing that are essential to understanding how cells respond to its biophysical microenvironment. Although we do not cover every model presented in this article, we are highlighting a few selected major mathematical models that are important in the field. We begin our discussion with a chemo-mechanical model, that applies the Michaelis-Menten kinetics equation to determine the cellular mechanosensing response to cellular adhesion and adhesion cluster in stress fibers

[2]. This model describes the transduction of external, mechanical forces to chemical signals and an example is presented of how cells react to stretch. In the cellular signaling model, cellular mechanosensing in response to matrix rigidity is presented. The foundation of this model is built on cellular differential signaling [3] and cellular structural remodeling [4]. The cellular differential signaling model predicts that the regulation locations of YAP (Yes-associated protein) are provided by the tensional cytoplasmic protein F-actin, while another cellular restructuring model observes the lifetime of central dorsal ruffles (an actin-rich structure) based on actin filament stiffness [4]. Lastly in the gene circuit model synthesis and turnover rates of the cytoskeletal proteins myosin II and filamin-A are used to predict the cellular response to matrix rigidity, which is proposed to depend on the nuclear protein Lamin-A [5]. This model was recently partially validated using a developmental embryonic chick heart model [6], but additional work is needed as it has yet to be shown if increasing cytoskeletal tension will indeed inhibit Lamin-A degradation, leading to a stiffer nucleus.

Modeling Cellular Dynamic Response

Dynamic cellular processes such as cell migration and cell spreading are known to be important to cell behavior. To study these phenomenon experimentally micropatterning and microchannel techniques have been used extensively as they allow researchers to study cells using controlled and reproducible geometries [7]. This has allowed cell migration experiments to be conducted on either a 2D substrate [8] or 3D substrate [9] with the former being the most commonly used. However, regardless of the substrate used (2D vs. 3D) modeling cell migration is quite challenging. In the 3D integrated microfluid model, for example, Newton's second law is applied to solve for the displacement nodes between the plasma membrane and nuclear membrane to subsequently predict cell migration rate [10]. While the previously mentioned model predicts cell migration rate, it is believed to be the tractions exerted at the cell-substrate interface that allow the cell to propel itself through its environment. In this regard a notable model worth mentioning is the Cellular Potts Model [11]. This model utilizes, a quasi-static energy minimization equation to determine cell shape and cell tractions. Additional models that have advanced the field are the bio-chemo-mechanical models that have yielded prediction of migration and spreading in response to biochemical and mechanical cues. In Deshpande's model, a time-decaying activation signal, first-order kinetic equation for relative stress fiber concentration, and actin-myosin cross-bridge dynamics have been used to cell contraction on 2D and 3D substrates [12]. In addition, Shenoy's model utilizes principles from thermodynamics to explain durotaxis [13].

Conclusion

Cells have the uncanny ability to sense and respond to their microenvironment. This occurs despite the fact that they are constantly exposed to chemical, physical, and in some cases even electrical stimuli. Cheng et. al. [1] presents a very thorough and insightful review of mathematical models in the field and in doing so reveal that while much has been accomplished, there are many key questions that have yet to be answered. Some of these questions are: 1) Are cellular mechanosensing models conserved among all cell types (mammalian and non-mammalian cells), 2) How does the cell respond to multimodal modes of stimuli such as fluid shear stress and stretch, for example, and 3) How are multiple,

simultaneously occurring mechanosensing events integrated to influence overall tissue function. Questions such as these and others will continue to drive researchers both new and old to the field for years to come as they will undoubtedly lead to a greater understanding of the mechanobiology and the human body in general. This will have an impact on a range of biological systems ranging from human physiology and pathology to non-human systems such as microorganisms.

References

1. Cheng B, Lin M, Huang G, Li Y, Ji B, Genin GM, et al. Cellular mechanosensing of the biophysical microenvironment: A review of mathematical models of biophysical regulation of cell responses. *Phys Life Rev.* 2017
2. Kong D, Ji B, Dai L. Stability of adhesion clusters and cell reorientation under lateral cyclic tension. *Biophys J.* 2008; 95:4034–44. [PubMed: 18621806]
3. Sun M, Spill F, Zaman MH. A Computational Model of YAP/TAZ Mechanosensing. *Biophys J.* 2016; 110:2540–50. [PubMed: 27276271]
4. Zeng Y, Lai T, Koh CG, LeDuc PR, Chiam KH. Investigating circular dorsal ruffles through varying substrate stiffness and mathematical modeling. *Biophys J.* 2011; 101:2122–30. [PubMed: 22067149]
5. Kang J, Steward RL, Kim Y, Schwartz RS, LeDuc PR, Puskas KM. Response of an actin filament network model under cyclic stretching through a coarse grained Monte Carlo approach. *J Theor Biol.* 2011; 274:109–19. [PubMed: 21241710]
6. Dingal PC, Discher DE. Systems mechanobiology: tension-inhibited protein turnover is sufficient to physically control gene circuits. *Biophys J.* 2014; 107:2734–43. [PubMed: 25468352]
7. Kim MC, Neal DM, Kamm RD, Asada HH. Dynamic modeling of cell migration and spreading behaviors on fibronectin coated planar substrates and micropatterned geometries. *PLoS Comput Biol.* 2013; 9:e1002926. [PubMed: 23468612]
8. Palecek SP, Loftus JC, Ginsberg MH, Lauffenburger DA, Horwitz AF. Integrin-ligand binding properties govern cell migration speed through cell-substratum adhesiveness. *Nature.* 1997; 385:537–40. [PubMed: 9020360]
9. Tseng Q, Wang I, Duchemin-Pelletier E, Azioune A, Carpi N, Gao J, et al. A new micropatterning method of soft substrates reveals that different tumorigenic signals can promote or reduce cell contraction levels. *Lab Chip.* 2011; 11:2231–40. [PubMed: 21523273]
10. Irimia D, Toner M. Spontaneous migration of cancer cells under conditions of mechanical confinement. *Integr Biol (Camb).* 2009; 1:506–12. [PubMed: 20023765]
11. Albert PJ, Schwarz US. Dynamics of cell shape and forces on micropatterned substrates predicted by a cellular Potts model. *Biophys J.* 2014; 106:2340–52. [PubMed: 24896113]
12. Deshpande VS, McMeeking RM, Evans AG. A bio-chemo-mechanical model for cell contractility. *Proc Natl Acad Sci U S A.* 2006; 103:14015–20. [PubMed: 16959880]
13. Shenoy VB, Wang H, Wang X. A chemo-mechanical free-energy-based approach to model durotaxis and extracellular stiffness-dependent contraction and polarization of cells. *Interface Focus.* 2016; 6:20150067. [PubMed: 26855753]