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Reply to comment

Energetics: An emerging frontier in cellular mechanosensing Reply to comments on "Cellular mechanosensing of the biophysical microenvironment: A review of mathematical models of biophysical regulation of cell responses"

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Abstract

How do cells can sense the substrate stiffness? Our recent review highlighted a range of theoretical models and simulations that have been proposed to answer this important question. In response to this review, three leading groups in the field noted some important omissions not only from our review itself but also from the field. These groups noted, correctly, that much of our understanding of cellular mechanosensing arises from models that take advantage of equilibrium thermodynamics, and that this is inappropriate because living cells are never in thermodynamic equilibrium. In this response, we highlight some promising research aimed at resolving this conundrum.

Keywords: Molecular clutch model; Stiffness sensing; Mechanobiology

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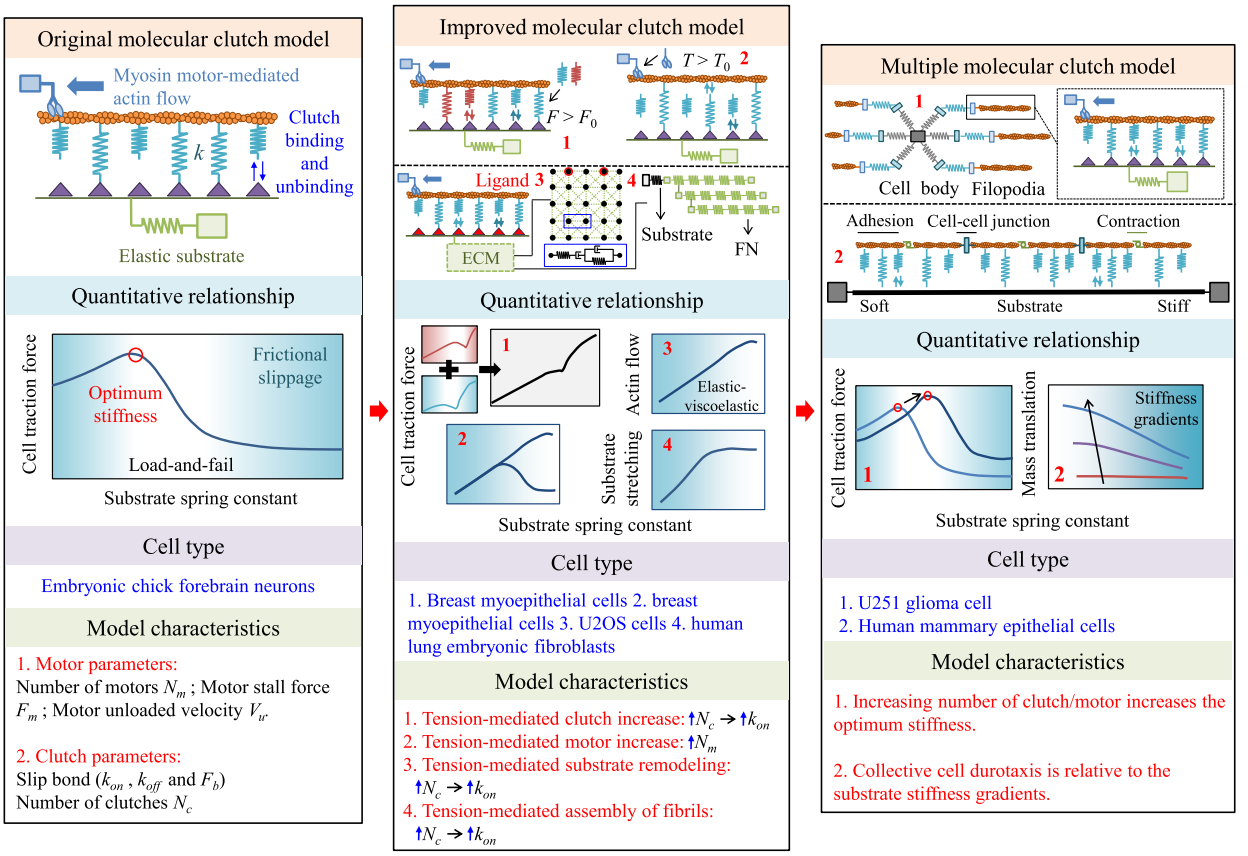

Fig. 1. The history of molecular clutch models.

Major advances in the field of mechanobiology have arisen from discussions of how complex behaviors might arise from a handful of simple principles, and we are honored to have the opportunity to reply to the three insightful commentaries of Nicolas [1], Spill et al. [2], and Wu et al. [3] that advance this discourse far beyond our short review [4]. These authors each noted that living cells exist outside of thermal equilibrium, and that the state-of-the-art models presented in our review must be called into question because they do not account for this.

1. Molecular clutch models and non-equilibrium steady states

A main focus of our review was molecular clutch models based upon the Mitchison and Kirschner [5] hypothesis that adhesion proteins are motor clutches that connect the actin cytoskeleton to the extracellular matrix (ECM), enabling transmission of forces from cells to ECM. We begin by reinforcing the observation that, despite their neglect of energetics, these models and their extensions provide valuable predictions.

The original molecular clutch model of Chan and Odde [6] models an elastic substrate loaded, through engaged molecular clutches, by myosin-mediated contraction and retrograde actin flow. Neither the model nor its inputs – motor and clutch parameters (**Fig. 1**) – account for energetics. However, predicted relationships between the cell traction and substrate stiffness match direct experimental observations, revealing a biphasic relationship consistent with the dynamics of single filopodial in embryonic chick forebrain neurons (ECFNs). However, this biphasic relationship is observed neither in EFCN growth cones, axons and neuronal soma, nor in 3T3 fibroblasts [7].

One possibility is certainly that an aspect of the non-equilibrium steady state character of living cells is not sustained outside of filopodial. The idea that energy supply to filopodial is enhanced by some kind of vesicle transport absent in these other parts of the neuron is certainly valid. As discussed in more detail in the final section of this commentary, such circular fluxes in non-equilibrium steady states are extraordinarily difficult to quantify. The ba-

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