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Comment on Machado et al., "Cytoskeletal turnover and myosin contractility drive cell autonomous oscillations in a model of Drosophila dorsal closure"

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Abstract. A commentary on the contribution of Machado et al. [1] in this special issue.

In this contribution, the authors present a mathematical model for the oscillation of amnioserosa cells with apical constriction during dorsal closure (DC) of the *Drosophila* embryo. Their model extends a recent study of the actin cortex in dividing animal cells by Sedzinski et al. [2] This study found that stability of the two poles of a dividing cell depends on a cortical actin cytoskeleton with sufficient turnover and an even distribution over each pole. With cortical stabilization or perturbation at one pole, the cells adopt a dramatic oscillatory behaviour during which the poles undergo cycles of anti-phase bulging and retraction relative to the equatorial cytokinetic ring. In the dividing cell, the difference between a persistent actin cortex and pulsatile actin cortex is the result of experimental manipulation, or rare events in normal cells. During the apical constriction of amnioserosa cells, a transition from pulsatile to persistent behaviour is a normal part of the developmental process. The differences between these amnioserosa cell behaviours are the subject of the model by Machado et al. [1] Their model further argues that local actin turnover helps promote widespread persistence of the cytoskeletal cortex.

In the model, cells are represented as polygons, with vertex motion governed by the total forces on spokes emanating from the cell centre to each vertex. The forces on these spokes include an active myosin-induced contractile force and a passive elastic force, and spoke lengths are gradually reduced as an internal ratchet. The key idea of the model is actin turnover on the spokes that is coupled to the cell area. With fast myosin on-off kinetics, the coupled system of ordinary differential equations exhibits steady-state equilibrium, oscillatory and unstable solutions. These are interrogated over a reasonable parameter ranges for connections to *in vivo* and *in vitro*

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observations. Comparing simulations of single cells to a full multicellular sheet of cells revealed similar results, arguing that mechanisms controlling the cell behaviours are largely cell autonomous.

The model offers an alternative to a recently proposed one [3] that relies on a feedback loop between a putative signaling molecule and myosin attachment and detachment. The actin turnover mechanism in the present model is attractive in that it highlights how the rate of the turnover affects the period of the cell oscillation. Experimental observations indicate a decaying amplitude and period of cell oscillation in the later stage of DC. In the model, such an outcome calls for an increasing rate of actin turnover and an increasing myosin contractile force. Both seem consistent with experimental evidence. Moreover, as Machado et al. discuss, myosin activity could explain both the increase to actin turnover (through breaking actin filaments) and the increase to contractility (through pulling on remaining actin filaments). Thus, the model suggests links between biological observations, and constitutes a welcome contribution to the literature.

At the end of the paper, the authors note that a key assumption of the model, the coupling between actin turnover and cell area, may not be realistic. This bespeaks the phenomenological nature of the model. In reality, DC proceeds under the direction of signaling proteins. A logical next step is to determine what these signaling molecules are, how they interact to form signaling pathways, and how such biochemistry is coupled with the mechanical movement and contraction of each cell. Mathematical modeling such as presented here will likely form essential components of the answers. That idea motivated Wang et al. [3] to postulate a feedback loop between myosin and a hypothetical signaling molecule. Experimentally, progress has been made in identifying the signaling proteins and understanding their interactions.

In the case of the dividing cell, Sedzinski et al. [2] have discussed how the polar actin cortices could be regulated by cross-talk with the major organizers of the cell: the mitotic spindle extending to each pole and the cytokinetic actomyosin ring between the poles. In the case of amnioserosa cells, cross-talk between the apicomedial actomyosin networks and the major organizers of apical-basal epithelial cell polarity is an attractive hypothesis. Indeed, David et al. [4] reported prominent roles of partitioning defective (Par) proteins in regulating the apicomedial actomyosin pulse during DC. In particular, atypical protein kinase C (aPKC) tends to inhibit actomyosin network contraction, while Par-3/Bazooka has the opposite effect. Furthermore, David et al. [5] showed that the actomyosin network recruits the Par-6-aPKC complex onto the apicomedial domain. aPKC in turn recruits Bazooka and phosphorylates it for a dynamic interaction. This suggests a tantalizing picture in which Bazooka acts as a competitive inhibitor to reduce aPKC phosphorylation of cytoskeletal regulators and thus its antagonism of apicomedial actomyosin networks. Elucidating this picture calls for quantitative modeling of the interactions among the signaling species as well as the coupling between mechanics and biochemistry.

Finally, another important outstanding issue is the mechanism that induces actomyosin networks to change their behaviour from pulsatile to persistent. Are the changes non-cell autonomous, the result of an open regulatory loop, or cell autonomous, the result of a closed regulatory loop? In both the models of Machado et al. [1] and Wang et al. [3] transitions are induced by outside modifications to players in the simulation. *In vivo*, cytoskeletal behaviour could also be changed by a stage-specific change in inter-cellular signaling or transcription (outside influences on pre-existing cytosolic machinery). Alternately, cytoskeletal change could emerge from feedback loops within the initiating cytosolic cytoskeletal and signaling complexes themselves. Further modeling is needed to help distinguish these possibilities.

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