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Comment on Falcke et al., "Polymerization, bending, tension: What happens at the leading edge of motile cells?"

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Abstract. Commentary on the contribution by M. Falcke and J. Zimmermann [1] in this special issue.

In their contribution, the authors review the implications of their model of cytoskeleton-membrane interaction for the force velocity relation of moving cells, as well as for cell oscillations and protrusion formation. Their model, which neglects spatial degrees of freedom, couples a small, anterior region of the lamellipodium, where a loose brush of actin filaments makes contacts with the membrane, to a gel-like region behind in the lamella. The model accounts in detail for several distinct processes and it is impressive in its power to reproduce experimental data.

Below we give a series of comments, questions and suggestions, related mostly to cell motility. We do not expect the authors to have clear-cut answers, of course, the aim is rather to stimulate further discussion and future research. **The gel and large deformations.** The gel is only accounted for via crosslinking rates and in the retrograde flow. The force transfer is not very transparent: is it sticking to the substrate or gliding? Most importantly, should it not enter the force balance as an elastic degree of freedom? For free protrusions this may be safely neglected (rigid boundary condition due to infinite stiffness compared to the semiflexible region). However, it may have important effects on the semiflexible region in geometries with large deformations, as occurring when a keratocyte is crawling against a AFM cantilever: one could measure, to some extent, the gel and not the semiflexible region. Possibly, this issue could be addressed in an extended model including spatial degrees of freedom?

Dynamic adhesion. An actively debated question in cell motility is the effect of adhesion on the motility modes and phenotype switches. Barnhart et al. [2] have shown that keratocytes show their "archetypical" persistent movement with constant crescent-like shape only for an intermediate adhesiveness of the substrate.

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For lower adhesiveness, they were almost round and moved erratically, while for higher adhesiveness their shape was very irregular and fluctuating, as was their motion. Similar conclusions were obtained in Ref. [3], namely a phenotypic switch in human neutrophils as a function of the density of adhesive ligands: It was shown that neutrophils adopt a well-spread morphology on moderate densities of adhesion ligands. As density increased, their morphology switched to classic amoeboid type and motion. This clearly shows that adhesion dynamics is an important factor for both the force-velocity relation and the protrusions. As the authors have a model at hand that describes both effects, it would be very interesting to see whether a generalization of the gel part towards adhesion (so far there is only friction, as well as a contribution in the retrograde flow stemming from "unsufficient adhesion") could account for such behaviors. One additional effect is stick-slip motion and stick-slip protrusions, which on a simpler level was discussed in [4] and on a coarse-grained, whole cell level in [5]. But even for stationary motion/protrusions one would expect that adhesion will interfere with the force-velocity relation as of the present model.

Coarse-grained model. To model the motion of a whole cell with all the concomitant additional complexity [6], it would be very valuable to have a simpler, coarse-grained picture of the complex leading edge dynamics. So far such models mostly account for a simple driving term and relate it to the ratcheting of actin polymerization, which may be not sufficient as the authors of [1] have shown. In view of the fact that the semiflexible region is small compared to the cell (a few hundred nanometers compared to tens of microns), would it be possible to derive a reduced – say two or three component model – that "lives" at the interface of the cell in the sense of the modular approach proposed and discussed in [7]? Possibly, dynamic equations for the distance between gel and leading edge, z, and one or two other degrees of freedom may be sufficient to recover the basic features at the front.

Continuum models and fluctuations. Finally, fluctuations have a profound role in all biological systems, from the most basic molecular, sub-cellular processes to the dynamics of tissues, organs, organisms and populations, see e.g. [8] for a recent review. The effect of fluctuations varies as well, sometimes playing a surprising role in accelerating transitions between dynamic states or enhancing intracellular transport of biomolecules. One of the most nontrivial manifestations of fluctuations in biological systems is associated with a relatively small number of particles (e.g. enzymes, reactants, ligands) participating in the biochemical inter-cellular reactions. As a result, even the stability of the most basic states in corresponding continuum models can be affected by a finite number of particles, e.g. increasing the occurrence of "rare events" like complete extinction [9]. While this is beyond the scope for phenomenological models, it would be interesting and valuable to validate the outcome of mean-field continuum models by corresponding stochastic systems with large yet finite number of particles.

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