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**The mechanics of cell protrusion<sup>1</sup>**

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The protrusion of the cell edge is the first step in a cycle of molecular processes that drive cell movements during development, immune responses, wound healing and many other physiological functions. It is also the earliest pathological event observed during metastasis of cancer. Textbook models associate protrusion with the assembly of an actin polymer network subadjacent to the cell plasma membrane. However, for this process to be transformed into edge advancement, polymerization-induced forces need to be balanced by adhesion complexes that link the actin network to the extracellular domain. Also, the effectiveness of network assembly in mediating forward movement of the cell edge depends on how contraction forces pull the network in the cell front retrogradely towards the cell center. Thus, what is observed in a microscope as cell protrusion reflects the kinematic output of at least three space- and time-modulated mechanisms of force generation. The coordination of these machineries is thought to be regulated by a complex network of mechano-chemical signals. Our goal is to establish the contributions of each those mechanisms and their control by reconstructing the spatiotemporal distribution of intracellular forces via inverse dynamics and molecular intervention with the relevant signalling pathways. To this end, we have developed quantitative Fluorescent Speckle Microscopy (qFSM) which provides high-resolution spatiotemporal measurements of actin network deformation and material properties in migrating cells. In addition, qFSM delivers maps of cytoskeleton assembly and disassembly, so that we can infer the plasticity of the material in situ. Together, this data allows us to deduce intracellular force distributions from the constitutive laws of strain and stress in the actin polymer network. Using this approach we discovered that unperturbed cells protrude in a dynamic steady state where periodic patterns of network assembly, adhesion formation, and cytoskeleton transport are tightly connected to protrusion waves. We exploited the sub-cellular heterogeneity of these patterns to identify the causality and timing between dynamic events in the actin network, leading towards a first integral view of the mechano-chemical process interaction in the protrusion machinery.

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