Spontaneous Plasticity in the Causal Networks of Cell Migration

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Abstract

Cell Migration is a complex, dynamic and heterogeneous phenomenon that emerges over multiple spatial and temporal scales. Such heterogeneity is often considered noise and is under-represented in the understanding of migration, partly because common aggregative experimental approaches impose insensitivities to natural variability. Furthermore, even given high target specificity, perturbation-based methods used to dissect such complex processes may induce systemic distortions due to dense regulatory interdependencies – potentially undermining functional inferences. To address these two common limitations, we have developed a Systems Microscopy research framework that instead *leverages natural heterogeneity* to reveal functional networks underlying the cell migration system, *without dependence on experimental perturbations*. This is enabled by acquisition of quantitative data simultaneously defining numerous features of migration system organization and behavior, capturing macromolecular- (adhesions, F-actin, membranes) and cellular-scales (morphology, polarity, motility). This multi-scale data, acquired on a time-resolved, single cell basis, facilitates diverse statistical investigations, including mapping networks of causal influence between recorded features using Granger causality analysis (used in econometrics and neuronal network mapping). Thus, we recently provided proof-of-principle that causal interactions display plasticity in response to strong molecular perturbations (http://goo.gl/c2Jilq). We now extend this unique methodology, revealing that natural heterogeneity in unperturbed cell behavior corresponds to *spontaneous* plasticity in causal interaction networks, such that these networks undergo progressive re-wiring as migration speed changes. Hence regulatory interactions appear both condition- and behavior-dependent, not universal. Furthermore, we show this approach is stringent against purely correlative relationships, capturing directionally specific information transmissions embedded in the cell migration system. We also map the time-dependence of causal interactions, revealing differential influence timings and rates of influence-decay, suggesting that several dynamic regulatory regimes underlie the migration system. Overall, we describe an extensible research strategy that provides a complement to perturbation-driven methods for the study of cell migration and similar complex, dynamic and heterogeneous processes.