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Challenges in Characterizing and Controlling Complex Cellular Systems[1]

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Multicellular dynamic biological processes such as developmental differentiation, wound repair, disease, aging, and even homeostasis can be represented by trajectories through a phase space whose extent reflects the genetic, post-translational, and metabolic complexity of the process - easily extending to tens of thousands of dimensions. Intra- and inter-cellular sensing and regulatory systems and their nested, redundant, and non-linear feed-forward and feed-back controls create high-dimensioned attractors in this phase space. Metabolism provides free energy to drive non-equilibrium processes and dynamically reconfigure attractors. Studies of single molecules and cells provide only minimalist projections onto a small number of axes. It may be difficult to infer larger-scale emergent behavior from linearized experiments that perform only small amplitude perturbations on a limited number of the dimensions. Complete characterization may succeed for bounded component problems, such as an individual cell cycle or signaling cascade, but larger systems problems will require a coarse-grained approach. Hence a new experimental and analytical framework is needed. Possibly one could utilize high-amplitude, multi-variable driving of the system to infer coarse-grained, effective models, which in turn can be tested by their ability to control systems behavior. Navigation at will between attractors in a high-dimensioned dynamical system will provide not only detailed knowledge of the shape of attractor basins, but also measures of underlying stochastic events such as noise in gene expression or receptor binding and how both affect system stability and robustness. Needed for this are wide-bandwidth methods to sense and actuate large numbers of intracellular and extracellular variables and automatically and rapidly infer dynamic control models. The success of this approach may be determined by how broadly the sensors and actuators can span the full dimensionality of the phase space.

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