436i Cell Phase Mapping from Cytometry

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Quantitative systems biology models typically focus on single-cell or average-cell behavior. These models are sufficient for many purposes,but there are occasions where population models may be needed. Where the populations are small, or the effects are highly non-linear,especially with cell cycle or phase boundaries, such as the transition from maintenance to growing states, cancerous cells, or stem cell differentiation.

In the past years, tools have been developing that make viable population approaches to cellular systems. Simulation methods have been and are still being developed that allow the simultaneous solution of large numbers of cells, or entire cellular densities.Techniques such as flow cytometry allow the measurement of entire populations of cells, in addition to average measures, and allow sorting, and the measurement of a detailed proteome on subsets of the population. These tools allow the validation of cellular models at the population level, but few techniques have been developed for the use of such measurements in developing these models.

This work presents some very preliminary work towards generating relatively simple predictive models from cytometric data, focusing on the identification of phases. Cell phases can be defined most fundamentally by discontinuous changes in cell behavior. This is easily seen in the standard phases that make up the cell cycle, but also in cell maintenance states. While these correspond to the activation and expression of certain genes, triggered by internal or external stimuli, the behavior change is a commonality that links all phase changes and systems, and would be the first indication of new phases that were not yet recognized.

From a population viewpoint, a phase boundary corresponds to a discontinuous (or rapidly changing) jump in the vector field that defines individual cell behavior. This has a number of ramifications. The first is that the same models are unlikely to hold on either side of a phase boundary. This is to be expected, since the definition of a phase boundary was a change in the behavior, but it does mean that fitting a single model to cellular data from both sides is unlikely to work. Instead the boundaries must be recognized, and individual models prepared. The second implication is that for an initially smooth distribution of cell state, as is likely in most experiments, the discontinuity in the growth law will correspond to a discontinuity in the number density of the cells, and will show up as measured by cytometry. The mathematical basis for this is related to the evolution of the number density by characteristics, and the divergence of the vector field, but also corresponds to the problems considered for simulation across such boundaries.

The identification of these phase boundaries in cellular state space is a problem analogous to that of edge detection in pictures. A number of techniques are examined for extension from two to three and four dimensions, and tested on simulated data to judge the data requirements for measurements in prediction.

The automatic identification of phase boundaries is a necessary pre-requisite for techniques that extract data from cytometry. Future work is hoped to generate quantitative growth laws within these regions.