

Inferring Cellular Mechanistic Models from Perturbation Data

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At least 60% percent of all cancers (90% for pancreatic cancer) are the result of mutations that occur in protein signaling pathways resulting in errors in signal processing that leads to uncontrolled growth. One of the objectives of systems biology is to develop mechanistic predictive models of protein signaling networks that can be used to develop more intelligent drug therapies and thus more efficiently treat cancer. Unfortunately developing models that can be used in this way is very hard to do. The problem stems for the complexity of the networks, the sparseness of data, the nonlinearity in the processes and noise in the measurements. Interestingly, similar problems confront weather forecasting. The strategy used in weather forecasting is to employ model ensembles in order to capture the uncertainties in our knowledge of the weather. We feel a similar approach could be used to model complex protein signaling pathways. In this poster we will describe efforts to create the initial ensemble for subsequent work.

We propose an evolutionary algorithm designed to generate an ensemble of detailed mechanistic models from perturbation data which can be obtained experimentally. An evolutionary algorithm is a population-based heuristic optimization algorithm where the population goes through reproduction, mutation, recombination, and selection processes from generation to generation. Our implementation of mutates the network topology, rate laws and parameter values while at the same time running parameter fitting, and exploring orthogonal search spaces at the same time. We show that the method, even in the presence of experimental noise, is able to correctly capture test networks. Moreover, we have found that model averaging over the ensemble generates much better predictions and any single model in the ensemble.