

Models from experiments: combinatorial drug perturbations of cancer cells



We present a novel method for deriving network models from molecular profiles of perturbed cellular systems. The network models aim to predict quantitative outcomes of combinatorial perturbations, such as drug pair treatments or multiple genetic alterations. Mathematically, we represent the system by a set of nodes, representing molecular concentrations or cellular processes, a perturbation vector and an interaction matrix. After perturbation, the system evolves in time according to differential equations with built-in nonlinearity, similar to Hopfield networks, capable of representing epistasis and saturation effects. For a particular set of experiments, we derive the interaction matrix by minimizing a composite error function, aiming at accuracy of prediction and simplicity of network structure. To evaluate the predictive potential of the method, we performed 21 drug pair treatment experiments in a human breast cancer cell line (MCF7) with observation of phospho-proteins and cell cycle markers. The best derived network model rediscovered known interactions and contained interesting predictions. Possible applications include the discovery of regulatory interactions, the design of targeted combination therapies and the engineering of molecular biological networks.

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Result Testing modeling power for combinatorial perturbations in breast cancer cells. Dual drug perturbation experiments in MCF7 breast cancer cells To directly test **PDF(455K) - Wiley Online Library**