Identifying network topologies that conform with steady state data

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The malignant properties of many types of cancer rely on alterations within key signaling pathways. Even if a resulting cancerous signaling response can initially be counteracted by targeted therapy, the plasticity of the kinase interaction network has shown to evolve resistance to such treatments. Clearly, detailed knowledge of the network topology and its modifications helps to reveal the mechanisms of cancer, to understand the appearance of resistance and to develop novel treatments. As direct experimental measurements of interaction strengths are not available, we require a computational method that reconstructs the network from more indirect measurements. A common approach to study biological networks is to analyse the response of the involved units to external perturbations. For signaling pathways we can apply it by measuring the change in equilibrium concentrations of phosphorylated kinases in reaction to various stimulations and inhibitions. In contrast to many existing network-inference methods that make use of such data in order to fit continuous network parameters to a given dynamical model, we strive to identify the unweighted network topologies that are in principal able to able to produce the observed data without having to specify any dynamical properties. Our approach interprets the perturbed equilibrium concentrations as changes of the steady states of an unspecified ODE system. Assuming the perturbations to be sufficiently mild, certain groups of steady states are elements of subspaces in a transformed data space. The hierarchical set of such subspaces can be translated into constraints which rule out all network topologies that can not generate the observed steady states. Further filtering to incorporate prior structural knowledge typically leaves us with only a few or a single remaining network topology that is conform with the data.