Learning drug targets in the signaling network context

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***Short Abstract* — We present a probabilistic modeling approach for deciphering the effects of drugs on proteins in signaling networks, based on multivariate, high throughput single cell measurements of proteins in cells treated with varying drug doses. Our approach provides a high resolution understanding of drug effects, enabling improved prediction of drug efficacy and potential toxicity.**

***Keywords* — drug discovery, drug screening, drug development, probabilistic models, signaling pathways, Bayesian networks**

I. Motivation

Drug development and discovery is an important goal for virtually every human disease. For potential drug candidates, an important challenge lies in determining protein targets, to assess potential efficacy as well as undesired off target effects leading to toxicity. Although it is reasonably straightforward to determine which proteins (and mRNA abundances) are affected by application of a drug, it is difficult to assess which of the affected proteins are actual drug targets and which are not bound by the drug, but are themselves affected by drug targets, constituting indirect drug targets. A high resolution mapping of drug effects, at the signaling network level, will provide greater insight towards assessing efficacy and toxicity. Such a systems understanding of drug targets might also enable complex strategizing for optimizing drug effects, such as prediction of effective combination therapies.

II. Modeling approach

In spite of the benefits of a network-level mapping, such an understanding is hard to achieve, in particular because it is difficult to determine which drug targets are direct versus indirect, and, even if the indirect targets are known, it is difficult to know by what path they were affected. Towards this goal, we have developed a probabilistic method that determines drug effects at the signaling network level.

We previously developed an approach to map signaling pathways employing high throughput, multivariate flow cytometric measurements of signaling pathway molecules.[1] We now extend this approach to include information regarding drug effects directly in the signaling pathway map.

As in previous work, we employ a multivariate approach: we measure a set of signaling pathway proteins (the entire set simultaneously) in the presence of varying inhibitor doses using multidimensional flow cytometry, then we take advantage of the multivariate data to determine which proteins are affected by drug dose and which are affected by the drug targets (or by targets of drug targets, and so on). Our method employs a probabilistic graphical model (a Bayesian network) in which queried drugs are included as (root) nodes. We employ the Bayesian network structure learning algorithm to determine the pathway structure downstream of the drug nodes, revealing direct and indirect targets. Because flow cytometry is limited in the number of parameters it can measure simultaneously, we discuss extensions of this approach to handle protein sets that include a number of proteins larger than the number that can be measured simultaneously by a flow cytometer.

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