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Bayesian generative modeling based on Pathways for drug repositioning and personalised medicine

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Abstract

Matching drugs to the right diseases is the key in drug development and personalised medicine. Regardless of the actual mechanisms, traditional computational methods assume similar drugs are likely to be used for similar diseases. Even though high predictive power, it is tricky to incorporate other prior knowledge in biology to improve our understandings and model performance. In contrast, our studies allow exploring the mechanistic how drugs act on diseases. This can be achieved by Bayesian generative modeling techniques.

Here we will present a suite of probabilistic generative models for understanding the interactions between drugs and diseases. To begin with, our methods incorporate curated pathways (gene sets) as *a priori* since pathways are individually interpretable. Unlike gene-wise analysis, pathway approaches can reduce the ambiguity for genes in multiple functions and can detect modest changes but huge impact. As a result, pathway crosstalks and perturbed pathways by drug treatment or disease intervention were identified using Bayesian factor models and latent Dirichlet allocation. Such resulted pathway networks lead to the additional three applications - disease comorbidity through pathway-based interactions where one step closer to in personalised medicine, drug repositioning via pathway-based interlinks, and tissue comparative analysis of pathway crosstalks.

As Bayesian generative modeling provides a straightforward framework to implement biological assumptions mathematically, the models can be enhanced when new prior knowledge is available. We also present our recent project where we are aiming to predict drug sensitivity across different diseased cell lines using the hypothesis of the underlying mechanisms between drugs and diseases. We assume that the degree of treatment effectiveness depends on how efficient the drug perturbs the same sets of pathways caused by diseases. The novel sophisticated model is resulted from combining the aforementioned two models with probabilistic multivariate regression. More importantly, we can elucidate the degrees of pathway contribution or engagement for the sensitivity in each interaction of drug-disease pair. This interpretation does not come along with prediction tasks if using discriminative models such as support vector machine and neural networks.