SAMBA, a recommendation system for biomarker discovery using metabolic networks

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Metabolomics is a cornerstone approach for biomarker discovery. Nevertheless, some important metabolites may be missed due to analytical, computational or biological reasons. To complement metabolomics-based biomarker discovery, we propose a constraint-based modelling approach which suggests *in silico* biomarkers that are more likely to be differentially abundant under metabolic perturbations (e.g. inborn errors of metabolism). The fluxes of exchange reactions in genome-scale metabolic networks can be simulated and compared between control and disease conditions in order to calculate changes in metabolite import and export. These import/export differences reflect changes in plasma levels of those metabolites, which can then be interpreted as potential biomarkers. Generally, Flux Variability Analysis (FVA) is used for this as it is fast computationally (*1*, *2*). However, FVA produces flux interval bounds without providing insight into the frequency of flux values between those bounds. Random sampling can be used to explore the solution space of each reaction's fluxes, therefore highlighting flux distributions for a more meaningful interpretation of metabolite changes. In this study, we present SAMBA (SAMpling Biomarker Analysis), an approach which simulates reaction fluxes following a metabolic perturbation using random sampling, and ranks suggested metabolites with the highest likelihood of being biomarkers for the perturbation. We compare simulated biomarkers with experimental biomarkers detected in plasma, such as patient data from OMIM (*3*), or metabolic trait-SNP associations using mGWAS data (*4*). These biomarker recommendations can provide insight into the underlying mechanism or metabolic pathway perturbation at the root of metabolic conditions, and suggest new metabolites as potential biomarkers for disease diagnosis.

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