Generating Structures of Likely Metabolites Based on Predicted Cytochrome P450 Regioselectivity

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The metabolic fate of xenobiotics such as drugs and agrochemicals impacts their safety and efficacy, because biotransformation of small organic molecules can generate metabolites with substantially different biological and physicochemical properties compared to the parent compound. [1] Prediction of regioselectivity of metabolizing enzymes, specifically the prediction of the atom positions in a molecule where metabolic reactions are initiated (sites of metabolism), is a popular computational approach to studying metabolism and can be used as a stepping stone for the prediction of the chemical structures of metabolites.

We have developed a strategy for metabolite structure prediction that is based on FAME 2, [2] our recently-developed and highly effective machine learning method for human cytochrome P450 (CYP) regioselectivity prediction. By applying known CYP-mediated reactions to the sites of metabolism predicted by FAME 2, we are able to correctly predict the vast majority of known metabolites while keeping false-positive prediction rates low. Applying the site of metabolism predictions as a preceding filter results in an approximately ten-fold reduction in the number of false positive metabolite predictions on average as compared to CYP-mediated reactions applied to all atom positions in a parent compound.

[1] J. Kirchmair, A. H. Göller, D. Lang, J. Kunze, B. Testa, I. D. Wilson, R. C. Glen, G. Schneider, *Nature Rev Drug Discov* **2015**, 14, 387-404.
[2] M. Šícho, C. de Bruyn Kops, C. Stork, D. Svozil, J. Kirchmair, *J Chem Inf Model* **2017**, 57, 1832-1846.