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Precise estimation of the contribution of CYP enzymes to overall metabolism from in vivo information: application of Cluster Newton Method

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Drug–drug interactions (DDIs) are a major cause of adverse drug reactions and subsequent withdrawal of new drugs from the market. For DDIs mediated by the inhibition of drug metabolisms, there are two key determinants of the degree of these interactions: inhibition constants (K_i) of coadministered drugs and fraction metabolized (f_m) by individual metabolic enzymes in the overall metabolism of substrate drugs.

In this study, we performed physiologically-based pharmacokinetic (PBPK) analyses of DDIs to determine "in vivo" f_m values. For the precise determination of f_m values, analyses of pharmacokinetic alterations in both parent drug and metabolites are essential. Since the pharmacokinetic analyses of metabolites are difficult with conventional parameter optimization methods owing to the lack of information on feasible initial parameters, we utilized Cluster Newton Method [1-2] to estimate solution spaces of pharmacokinetic parameters.

PBPK analyses were performed for the DDIs involving lansoprazole, lidocaine, or oxycodone, whose major clearance pathways are CYP2C19 and CYP3A4, CYP1A2 and CYP3A4, or CYP2D6 and CYP3A4, respectively. DDI data were retrieved from the University of Washington Metabolism and Transport drug interaction database (http://www.druginteractioninfo.org). As a result, f_m of each CYP enzyme was determined with small variations, only when we included metabolites' pharmacokinetic alterations in the analyses. Application of the proposed method may improve in vitro-in vivo extrapolations of f_m values, which can lead to the accurate preclinical prediction of DDIs involving the inhibition of metabolisms.

[1] Aoki, Y., *et al.*, Cluster Newton Method for Sampling Multiple Solutions of an Underdetermined Inverse Problem: Parameter Identification for Pharmacokinetics, *NII Technical Report*, NII, NII-2011-002E, 2011.
[2] Yoshida, K., *et al.*, Estimation of feasible solution space using Cluster Newton Method: application to pharmacokinetic analysis of irinotecan with physiologically-based pharmacokinetic models, *BMC Systems Biology*, 7(Suppl 2):S3, 2013.