Cluster Gauss-Newton method and its potential application to optimal experimental design in drug discovery

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Inspired by the Cluster Newton method for an underdetermined inverse problem [1], we have constructed a variant that can be used to conduct a bootstrap analysis on an over-determined inverse problem [2]. The resulting method is more efficient compared to a conventional approach. We then demonstrate how this quick bootstrap method can potentially be used for the optimal experimental design workflow in preclinical drug discovery studies.
In such studies, *in vivo* experiments for a drug candidate are typically run in series, and we can refine the subsequent experiments using the experimental data from the previous experiments. On the other hand, the time we can spend to design an experiment is very limited and a computationally efficient algorithm is therefore necessary. We propose an experimental design workflow where we conduct bootstrap analysis using the data from previously ran experiments using the Cluster Gauss-Newton method to obtain the parameter and its estimation uncertainty and then use these information to compute a robust optimal design (ED optimal design) for the subsequent experiments.
Finally, we demonstrate PopED lite which is an optimal design software for preclinical studies [3].

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Improvements to the Cluster Newton Method for Underdetermined Inverse Problems

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Keywords: Cluster Newton method; Underdetermined inverse problem; Beta distribution; Pharmacokinetics

The Cluster Newton method (CN method) has proved to be very efficient at finding multiple solutions to underdetermined inverse problems. In the case of pharmacokinetics, underdetermined inverse problems are often given extra constraints to restrain the variety of solutions. In this presentation, we introduce an algorithm based on the two parameters of the Beta distribution to find families of solution near a solution of interest. This allows for a much greater control of the variety of solutions that can be obtained with the CN method. In addition, this algorithm facilitates the task of obtaining pharmacologically feasible parameters.

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Application of Cluster Newton Method for the physiologically-based pharmacokinetic analyses of drug-drug interactions

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Keywords: drug–drug interactions, pharmacokinetics, PBPK model

Pharmacokinetic drug–drug interactions (DDIs) are one of the major causes of unexpected change of pharmacological/toxicological effects of victim drugs. For the analyses and predictions of DDIs, physiologically-based pharmacokinetic (PBPK) models are widely used in the process of drug development. However, reliable estimations of parameters in PBPK models remain difficult, due to the difficulties in rationally setting up model parameters only from in vitro experimental results or estimating the values of large number of unknown parameters. To overcome these issues, we introduced Cluster Newton Method (CNM) [1,2] in PBPK analyses of DDIs. We analyzed two types of DDIs that are difficult to analyze with conventional parameter optimization methods: (1) a hepatic transporter-mediated DDI between pitavastatin and cyclosporine A, and (2) DDIs involving the inhibition of various cytochrome P450 (CYP) enzymes with pharmacokinetic alterations of the metabolites of victim drugs. As a result, we could successfully obtain multiple parameter sets reproducing clinical observations. Inhibition constants (K_i), which are important in the prediction of new DDI cases, were estimated well, while most of the other parameters had certain deviations in estimated values. Further application of the CNM may improve in vitro-in vivo extrapolations of K_i, which can lead to the accurate preclinical prediction of DDIs.

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