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Compartmental Modelling of the Pharmacokinetics of an Efflux Transporter

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A mathematical model has been developed describing the pharmacokinetics of Hoechst 33342 following administration into a culture medium containing a population of transfected cells (HEK293 hBCRP) with a potent inhibitor of the BCRP, Fumitremorgin C (FTC), present. FTC is reported to almost completely annul resistance mediated by BCRP *in vitro.* The non-linear and multi-compartmental model describes the relationship between the concentration of Hoescht 33342 and FTC initially spiked in the medium and the observed change in fluorescence due to Hoescht 33342 binding to DNA. This model has been extended to consider multi-cell, multi-input responses.

Structural identifiability arises from the inverse problem of inferring from the known properties of a biomedical or biological system a suitable model structure and estimates for the corresponding rate constants and other parameters. Structural identifiability analysis considers the uniqueness of the unknown model parameters from the input-output structure corresponding to proposed experiments to collect data for parameter estimation. This is an important theoretical prerequisite to experiment design, system identification and parameter estimation, since numerical estimates for unidentifiable parameters are effectively meaningless. If parameter estimates are to be used to inform about intervention or inhibition strategies, or other critical decisions, then it is essential that the parameters be uniquely identifiable. Such analysis is highly relevant to large-scale, highly complex systems, typical in chemical kinetics and systems biology.

Structural identifiability analysis has been performed on the Hoechst 33342 pharmacokinetic models developed using a method based on the similarity transformation/exhaustive modelling approach. The analysis demonstrated that all models derived are uniquely identifiable for the experiments/observations available. This permitted subsequent numerical parameter estimation to be performed with greater confidence.

A kinetic modelling software package, FACSIMILE (MPCA Software, UK), was used to obtain numerical solutions for the system equations and for parameter fitting. Model fits gave very good agreement with in-vitro data provided by AstraZeneca across a variety of experimental scenarios. This should ultimately permit predictive analysis to be performed using the model in an attempt to optimise targeting of the compound to cancerous tumours.

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