Ad hoc Constraints on Complex Liver DCE-MRI Models can Reduce Parameter Uncertainty

Mikael Fredrik Forsgren[1,2], Olof Dahlqvist Leinhard[1,2], Gunnar Cedersund[3,4], and Peter Lundberg[1,2]

[1]Depts of Radiation Physics, Linköping University and Radiation Physics, UHL County Council of Ostergotland, Linköping, Sweden, [2]Center for Medical Image Science and Visualization (CMIV), Linköping University, Linköping, Sweden, [3]Depts of Clinical and Experimental Medicine (IKE), Diabetes and Integrated Systems Biology, Linköping University, Linköping, Sweden, [4]School of Life Sciences, Freiburg Institute of Advanced Sciences, Freiburg, Germany

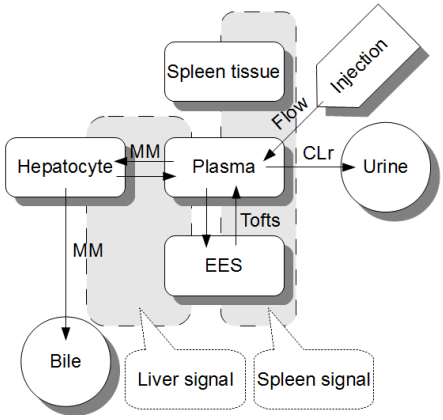

Fig. 1 *Diagram of the model equations with states (rounded rectangles), output (circles), transports with their respective base equations (arrows), input function (pointed rectangle) and measured MRI signals (shaded grey areas) reproduced from [3].*

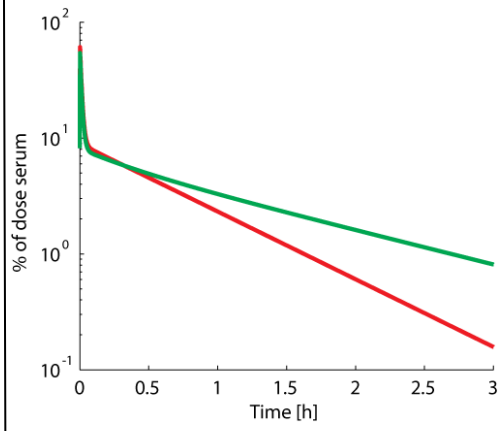

Fig. 2 *Simulated dose-normalized serum concentration time cure. The red line corresponds to the solution with lowest residual size (optimal) and the green line corresponds to a physiologically accurate solution as defined by the 3 h constraint.*

Introduction: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) using the hepatocyte specific contrast agent (CA) Gd-EOB-DTPA ('EOB') has been proposed as promising method for characterization of liver function [1, 2]. A human whole body pharmacokinetic model for analysis of DCE-MRI using EOB has previously been presented [3]. A problem with complex models in biology is that the solutions are not necessarily unique and identifiable [5, 7]. Furthermore mathematically optimal solutions in modelling, based on biological systems, are not automatically physiologically correct [7]. The aim of this study was to 1) evaluate the uniqueness of the solutions from a large scale model fitting and to improve the model structure, and to 2) evaluate *ad hoc* constraints on the model.

Table 1 *Simulated elimination fractions (median and range) as a percentage of the administered dose, before and after applying the 3 h constraint. The rightmost column presents some literature values (mean and standard deviation) for comparison.*

	Simulated (before)	Simulated (After)	Reported in literature	
Urine	26.1% (19.5-41.9%)	40.1% (40.1-41.9%)	48±5% [6]	43.6±8.6% [4]
Faeces	71.3% (39.0-79.9%)	41.4% (39.0-43.7%)	37±17% [6]	36.8±8.5% [4]

Materials and Methods: Signal intensities in regions of interests in the liver (n=7) and spleen (n=3) in T1-weighted DCE images (native, arterial and portal venous phase, 10, 20, 30 and 40 minutes) from 10 healthy volunteers following a bolus injection of EOB (0.025 mmol/kg BW) were converted into change in relaxivity [1]. Furthermore blood plasma concentrations following 10 min infusion of EOB from 18 subjects (Table 1 in [4]) were included in the data set (0.2, 0.35, 0.5 mmol/kg BW). The model has been described elsewhere [3], **Fig. 1** shows a schematic representation of the model. A Chi^2-test was used as metric for model error, and for evaluating the size of the residuals [5]. Evaluations of parameter values for all vectors passing a Chi^2-test in a large set of optimizations were used as a base for model reduction. The CA is assumed to be eliminated from the system once it enters the states 'Bile' and 'Urine' (**Fig.1**).

The flux between 'Hepatocyte' and 'Plasma' States (**Fig. 1**) were earlier described by Michaelis-Menten expressions [3]. Here we found that these rats operated in the linear regime, and the reactions were therefore replaced by mass-action based transport rates. Other improvements were that the optimization problem was simplified by assuming a fixed value for the renal clearance. The dose-normalized serum concentration in a healthy subject has been reported to be above 1% after 3h [4]. A recent study showed that in renal and/or hepatic impairment the amount EOB residing within the blood pool is higher than for healthy subjects [6].

Results: A Chi^2-test indicates that the new partly linearized model with high probability (P=0.05) explains the experimental data or doses up to 20 times the clinically used dose. Furthermore, using the proposed constraints on the simulated serum concentrations at 3 h (**Fig. 2**), well defined solutions were found (**Table 1**). As a further consequence of the constraints, the number of unique acceptable parameter vectors were reduced from an excess of 400 000 to 11. The acceptable solutions, according to the 3 h constraint, had an estimated urine elimination of 40.1% (range 40.1-41.9%) and biliary excretion of 41.4% (range 39.0-43.7%) of the administered EOB after 3h (**Table 1**).

Discussion and Conclusions: The use of *ad hoc* constrains on complex mathematical models used to understand CA dynamics can potentially yield more physiologically valid solutions. This study shows that the herein defined constraints are very efficient in reducing the acceptable parameter space, as defined by a Chi^2-test. The motivation for applying the constraint *ad hoc* is that computational time is drastically reduced, when only acceptable solutions are simulated for 3 h instead of the millions of vectors in a global optimization algorithm. Importantly, this proposed constraint is potentially applicable to other models which aim towards mimicking whole body dynamics. Prior to the use of such constraints the solutions contained cases where the elimination fractions were clearly faulty in the healthy case. Interestingly all solutions that passed the constraint provided a valid estimate of the eliminations. The 1% dose in serum at 3 h is a conservative constraint and serves as a lowest limit in the healthy subjects; this percentage has been shown to be higher in groups with renal or hepatic impairment [6].

References: [1] Dahlqvist Leinhard O *et al* Eur Radiol 2011 Oct. 9 [Epub ahead of print] [2] Tsuda N *et al* Eur J Radiol 2010;73:137-42 [3] Forsgren M F *et al* Proc. ISMRM 2011;5154 [4] Schuhmann-Giampieri G *et al* J Clin Pharmacol 1997;37:587-596, [5] Cedersund G & Roll J FEBS Journal 2009;276:903-22, [6] Gschwend *et al* Invest Radiol 2011 [Epub ahead of print] [7] Fernandez Slezak D *et al* PloS One 2010;5(10)p.e13283