Simplified model for Gd-EOB-DTPA DCE-MRI liver function analysis

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Target audience: This work is of interest to researchers working on estimating liver function using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

Purpose: DCE-MRI using the hepatocyte specific contrast agent Gd-EOB-DTPA has been proposed as a promising method for characterization of liver function, for instance in liver disease [1, 2] and drug induced liver injury in pre-clinical trials [3]. Recently a model based approach to assess liver function in rats was published [3]. The model allows for separation between hepatocyte uptake and subsequent efflux into bile of Gd-EOB-DTPA, providing a method for evaluating clinically important transport mechanisms in the hepatocytes (MRP2 and OATP).

There is a body of evidence that the efflux of Gd-EOB-DTPA into the bile, facilitated by MRP2, is a saturable process (described by Michaelis-Menten (MM) kinetics). However, when using complex mathematical models in biology it is desirable to have as few estimated parameters and nonlinearities as possible since parameters in these models often suffer from identifiability issues, *i.e.* not having finite or sufficiently small parameter confidence intervals given the data [4, 5]. Furthermore, MM rate kinetics are approximately linear for substrate concentrations below K_M, and it has been shown in another model based method for analyzing Gd-EOB-DTPA that it is possible to do a linear approximation of the MM rate equation describing the kinetics of MRP2 in humans [6].

The purpose of this study was to assess if it is possible to linearize the rate equation for Gd-EOB-DTPA efflux in the recently published model for rats [3], and how this linearization affects the parameters and the ability of the linearized model to separate between normal and reduced liver function.

$$\mathcal{M}_1: \frac{dC_{hep}(t)}{dt} = k_1 C_{ES}(t) - \frac{V_{max} C_{hep}(t)}{K_M + C_{hep}(t)}$$

$$\mathcal{M}_2: \frac{dC_{hep}(t)}{dt} = k_1 C_{ES}(t) - k_2 C_{hep}(t)$$

Figure 1 *Model equations, the original model with Michaelis-Menten based Gd-EOB-DTPA efflux into the bile* (M_1) *and the linearized model* (M_2)

Materials and Methods: DCE-MRI data of 30 rats was acquired from a recent study [3]. In short, the rats were divided into 5 groups and 4 of these groups received chemokine receptor antagonist (CKA) that inhibits biliary transport activity (at different doses per group; 20, 200, 500 & 2000 mg/kg). The remaining group was used as control. Subsequently all rats were imaged for 60 min using a 4.7 T Avance III, Bruker Biospin MR-scanner combined with an injection of Gd-EOB-DTPA equal to 0.025 mmol/kg. The data was then converted into contrast agent concentrations. Further description of the experimental setup and data post-processing can be found in [3].

The models used herein are shown in Fig. 1, where M_1 is from [3]. The models were implemented in Mathematica 9, which was furthermore used for model fitting and statistical analysis. A global optimization algorithm was used to identify optimal parameter values. Linear regression was used to test if the contrast agent uptake (k_1) was affected by the linearization, and finally ANOVA with Tukeys post-test was used to test the linearized model's ability to separate between the groups based on contrast agent efflux (k_2 in M_2).

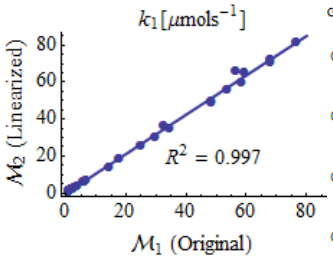

Figure 2 *Scatterplot of the estimated values for the uptake of contrast agent (k_1) for the two model variants* M_1 *(x-axis) and* M_2 *(y-axis).*

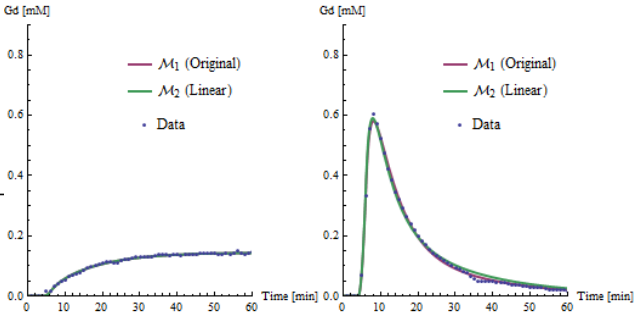

Figure 3 *Example of simulated hepatocyte concentration of Gd-EOB-DTPA for both models versus data. The left panel shows a rat subjected to 2000 mg/kg CKA and the right panel shows a control.*

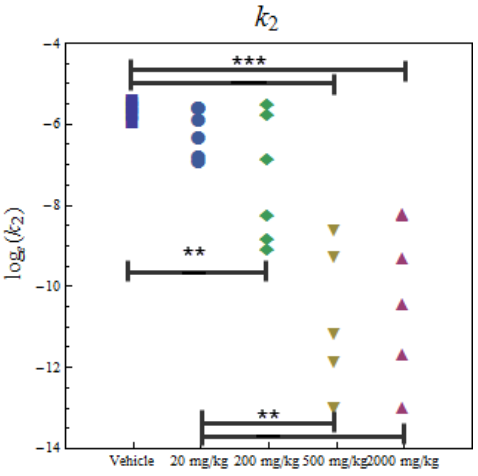

Figure 4 *Fitted parameter values for the efflux to the bile via MRP2 using the linear model* (M_2) *in the five CKA dose groups. The vertical bars indicate significance level on group difference using ANOVA with Tukeys post-test; *** p<0.001, ** p<0.01*

Results: The fitted values for contrast agent uptake (k_1) correlates well between the two model variants (R^2=0.997, slope = 1.06 (p<0.001, 95% CI:{1.04;1.08}), intercept = 0.00 (p=0.33), see Fig. 2). The linearized model was able to describe data, see Fig. 3. Significant group differences were found in the hepatocyte efflux (k_2) of the contrast agent using the linearized model (M_2), see Fig. 4.

Discussion and Conclusions: The main result is that it is possible to do a linearization of the model that seems to describe the data sufficiently well. The contrast agent uptake into the hepatocyte was practically unaffected by the linearization of the efflux, indicating that the concentration ranges *in vivo* are likely in the approximately linear region of the MM transfer rates for MRP2, specifically in the case of reduced function. As can be seen in Fig. 2, the values for the uptake deviates in the higher range, corresponding to a normal liver function, were likely the high contrast concentration in the hepatocytes pushes the transfer rate into the more nonlinear range of the MM rate equation.

Importantly, the linearized description of contrast agent transfer by MRP2 still allowed for significant group separation. A linear model would likely allow for a more robust analysis, with fewer parameters to fit and interpret. Also, only using linear equations allows for faster data analysis since more numerical and analytical methods becomes available. Furthermore, parameters uncertainties, given the data, are likely reduced, which is often the case in model reduction and linearization. Estimating the parameter uncertainties formally requires additional work; but initial tests indicate that the linear model has lower parameter uncertainties.

References: [1] Tsuda N *et al* Eur J Radiol 2010;73:173-42, [2] Dahlqvist Leinhard O *et al* Eur Radiol 2012;22:642-53, [3] Ulloa J L *et al* NMR Biomed 2013;26:1258-70, [4] Cedersund G & Roll j FEBS Journal 2009;276-:903-22, [5] Raue A *et al* Bioinformatics 2009;25:1923-29, [6] Forsgren M F *et al* Proc. ISMRM 2012;20:1911