A statistical model of hepatic blood flow: application to normal and fibrotic livers

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Target audience: Clinicians and researchers interested in the changes in hepatic blood flow in the presence of fibrosis.

Purpose: Chronic damage to the liver causes fibrosis, stiff tissue, that replaces hepatocytes and hepatic sinusoids. This can lead to hepatic dysfunction, portal hypertension and ultimately cirrhosis[1]. The portal vein, which carries nutrient rich blood from the intestines, normally supplies 75% of the blood to the liver; the remaining blood is supplied by the hepatic artery. Gadolinium (Gd) enhanced MRI can be used to study the dynamics of blood flow in the liver[2] without having to perform an invasive catheterization. Here we model the liver's uptake of Gd using a system of ordinary differential equations and estimate model parameters using a Bayesian approach, allowing us to obtain not only appropriate model parameters that fit that the data, but their uncertainties as well. The Bayesian framework incorporates data from Gd MRI and some prior information on the model parameters, which are subsequently estimated using Markov Chain Monte-Carlo estimation. We use the parameter estimates to investigate the relative contribution of the hepatic artery to the total blood flow in the liver in non-fibrotic versus fibrotic subjects.

Methods: *Subjects and Data* Gd enhanced MRI was performed on 13 healthy liver donors and 16 subjects with biopsy-diagnosed liver fibrosis. After Gd injection, data was acquired using a 3D stack of variable density spiral sequence reconstructed at a high temporal frame rate using the TRACER method[5]. Time courses of Gd concentration were obtained from these images (assuming a linear relationship between T1 signal and Gd concentration) for liver tissue, hepatic artery and portal vein.

Model Construction We modeled two liver compartments, blood (C_b) and tissue (C_t), using a similar approach to that described previously[3]. The concentration change of Gd in the blood compartment is due to three terms (Eq. 1) while the rate of change of concentration in tissue is due only to one term (Eq. 2). F_a and F_p are the blood flow values from the hepatic artery and portal vein while $C_a(t)$ and $C_p(t)$ denote their concentrations over time; $V_b$and V_t are the volumes of the respoctive copartments, The dynamic expression for facilitated bidirectional transport between compartments is given by (Eq 3), with α and β the kinetic parameters of the transport:

$$V_b\frac{dC_b}{dt} = F_a(C_a(t) - C_b(t)) + F_p(C_p(t) - C_b(t)) - V_tJ^{b\to t}(t) \quad \text{(Eq. 1)} \qquad \frac{dC_t}{dt} = J^{b\to t}(t) \quad \text{(Eq. 2)} \qquad J^{b\to t}(t) = \alpha\big(C_b(t) - C_t(t)\big)/(\beta + C_b(t) + C_t(t)) \quad \text{(Eq. 3)}$$

Our data from the perfusion experiments consisted of N sampled points in time of the concentration of Gd in the liver tissue, contained in $C_t(t_{data}) = y$. The parameters that needed to be estimated are collected in $\theta = [F_a, F_p, \alpha, \beta, C_b(0)]$. If we let $f(C(\theta, t_{data})) = f(\theta)$ and assume an independent Gaussian additive noise model $y = f(\theta) + \epsilon$, then our likelihood is

$$\pi(\epsilon) = \pi(y|\theta) \propto \exp\left(-\frac{1}{2}\big(y - f(\theta)\big)^T\Gamma_\epsilon^{-1}(y - f(\theta))\right), \quad \text{(Eq. 4)}$$

where Γ_ϵ is a diagonal covariance matrix, empirically estimated to be the signal variance within the liver tissue ROI. Our priors $\pi(\theta)$ consist of positivity constraints on θ and a Gaussian prior on the initial blood concentration of Gd, i.e. $C_b(0) \sim N(\mu, \sigma)$. Bayes theorem states that the posterior density $\pi(\theta|y)$ is proportional to the likelihood $\pi(y|\theta)$ times the prior $\pi(\theta)$.

Parameter Estimation Our posterior density $\pi(\theta|y)$ cannot be solved for analytically, so we used delayed-rejection Metropolis-Hastings[4] (MH) sampling to explore its shape and location. We initialized our sampling at the same point for each subject and produced a sample size of 10000 or more, depending on the convergence of the sample (assessed visually) for that particular subject. The delayed-rejection component of the MH sampling consisted of proposing a smaller step upon rejection of the full proposal step. The proposal density was a Gaussian centered at the current point, with a standard deviation that varies according to the level of acceptance. If the acceptance became too low (<15%), we reduced the step size in order to increase acceptance; if the acceptance rate became too high (>50%), we increased the step size so that the MH sampler could fully explore the parameter space. Once the parameters were estimated, we calculated the percent contribution of aorta to overall blood flow[6]: $R_a = F_a/(F_a + F_p)$ and looked at the histograms of these values for each individual. We investigated the differences between normal and fibrotic cases by performing a t-test of the mean R_a in normal versus fibrotic cases.

Results: The result of sampling is a set of M parameters θ for each subject, with each θ corresponding to a different forward model that produces time curves for $C_b$and C_t. The sampling results for a healthy subject are given in Figure 1 (left panel), with the corresponding distribution of R_a in the bottom right plot in red. Figure 1 shows the corresponding M time curves as a light blue envelope that contains 90% of the forward models (median in red). In Figure 1 we also plot the empirical liver tissue curve (blue error bars) along with the aorta (black curve) and portal vein (green curve) as measured from the MRI. The model prediction matches well the empirical data for this particular subject; this level of model agreement with the data is similar across the population. Between populations, the values of R_a were significantly higher in fibrotic subjects (59±31%) versus controls (23±14%), with $p = 8.6\times10^{-4}$ and $t = 3.7$.

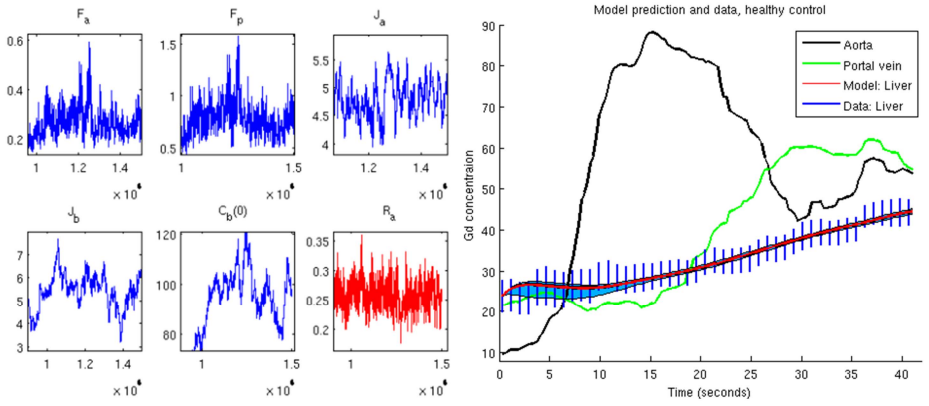

Figure 1: (left panel) Sampling results for the 5 model parameters and the corresponding $R_a$for a particular fibrotic subject. (right panel) The timecourse of the Gd signal in aorta (black), portal vein (green), liver (blue error bars), as well as light blue envelopes encompassing 90% of the model predictions for Gd tissue concentration. The median model prediction is plotted in red.

Discussion Numerical sampling techniques can be used to explore complicated posterior densities that cannot be solved analytically. Another advantage of using sampling as opposed to other optimization strategies is that the result is a distribution of possible models, not a single model. This distribution can be used to infer uncertainty in the parameters and model estimates by inspecting the width of the parameter histograms or model prediction curves; the wider the curves and histograms, the less certain we are of their value. Estimates of arterial supply R_a show that this value is statistically larger in fibrotic subjects versus healthy controls, where it was a value we would expect. Further work will explore construction of different priors that can encode knowledge gained in normal populations.

Conclusion Statistical modeling of Gd uptake in the liver can provide insight as to the status of the patient's liver tissue health. The preliminary results shown here provide evidence that this type of model and parameter estimation approach may be used to detect fibrosis without an invasive biopsy or catheterization.

References 1. Friedman SL. Hepatic fibrosis - overview. *Toxicology*. 2008;254(3):120–9. 2. Faria SC, Ganesan K, Mwangi I, et al. *Radiographics*. 2009;29(6):1615–35. 3. Kuceyeski AF. Efficient Computational and Statistical Models of Hepatic Metabolism. *PhD Thesis*. 2009. 4. Green PJ, Mira A. *Biometrika*. 2001;88(4):1035–1053. 5. Xu, B. et al. Mag.Res.Med. 2013;69(2):370-381. 6. Miles KA et al, Radiology 1993; 188:405-411.