Published in final edited form as:

Magn Reson Med. 2018 April ; 79(4): 2415–2421. doi:10.1002/mrm.26888.

VASTLY ACCELERATED LINEAR LEAST SQUARES FITTING WITH NUMERICAL OPTIMIZATION FOR DUAL INPUT DELAY COMPENSATED QUANTITATIVE LIVER PERFUSION MAPPING

Ramin Jafari, MS¹, Shalini Chhabra, MD², Martin R. Prince, MD, PhD, FACR², Yi Wang, PhD^{1,2}, and Pascal Spincemaille, PhD²

¹Meinig School of Biomedical Engineering, Cornell University, Ithaca, NY

²Department of Radiology, Weill Cornell Medicine, New York, NY

Abstract

Purpose—To propose an efficient algorithm to perform dual input compartment modeling for generating perfusion maps in the liver.

Methods—We implemented whole field of view linear least squares (LLS) to fit a delay compensated dual input single compartment model to very high temporal resolution (4 frames per second) contrast enhanced 3D liver data in order to calculate kinetic parameter maps. Using simulated data and experimental data in healthy subjects and patients, whole-field LLS was compared to the conventional voxel-wise nonlinear least squares (NLLS) approach in terms of accuracy, performance and computation time.

Results—Simulations showed good agreement between LLS and NLLS for a range of kinetic parameters. The whole-field LLS method allowed generating liver perfusion maps about 160-fold faster than voxel-wise NLLS, while obtaining similar perfusion parameters.

Conclusion—Delay compensated dual input liver perfusion analysis using whole-field LLS allows generating perfusion maps with a considerable speedup compared to conventional voxel-wise nonlinear fitting.

Keywords

Dynamic contrast-enhanced MRI; Hepatic Lesion Perfusion Analysis; Linear and Nonlinear Least Squares Fitting; Bolus Arrival Time; Linear Inversion

INTRODUCTION

In dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), a differential equation based on conservation of mass relates the temporal dynamics of contrast agent concentration to perfusion parameters that describe the transport processes within the tissue. Nonlinear least squares (NLLS) techniques are used to derive perfusion parameters by fitting enhancement curves to the integral solution of the differential equation (1). This approach is

computationally expensive and requires a good initial guess or multiple starting points to avoid convergence to local minima. An alternative to this nonlinear method is to fit the differential equation directly in a linear least squares (LLS) sense. Solving the differential equation directly instead of working with the integral solution has been applied to Positron Emission Tomography (PET)(2–6) demonstrating efficient performance for data acquired with high temporal resolution. Implementation and comparison of LLS and NLLS techniques have similarly been investigated in DCE-MRI (7–12) again demonstrating increased efficiency while maintaining accuracy.

Estimating and correcting the input function delay is important, since ignoring it can introduce large errors in the true value of perfusion parameters, such as up to 35% underestimation of flow, and up to 60% of overestimation of mean transit time (13). Materne et al. implemented a delay compensated dual input model using nonlinear fitting. In this approach, the nonlinear fit is repeated for several time shifted input functions and the delay that minimizes the residual error is selected (14). Accurate liver perfusion quantification requires correction for both arterial input function (AIF) and portal venous input function (PVIF) delays (15). This, however, considerably increases the computational cost for the current NLLS fitting approach because of the many combinations of delays for which a NLLS fit needs to be carried out. Therefore, a dual delay correction is performed only on a region-of-interest (ROI) basis, and not for whole liver perfusion mapping (16).

The current work proposes a whole-field LLS method that uses efficient large scale solvers to fit the perfusion parameters for all voxels within the field of view simultaneously (17). Additionally, a method is proposed to efficiently combine this with dual input function delay compensation. This method is demonstrated for high spatial and temporal 4D liver contrast enhanced data(18–20). Compared to NLLS, LLS is shown to drastically decrease computational cost, making delay correction practical.

METHODS

Signal intensity was converted to relative enhancement assuming a linear relationship between relaxation rate and concentration. Conversion from signal intensity (S) to enhancement (Ξ) for a spoiled gradient echo sequence (SPGR) is given by (21):

$$\Xi = \frac{S(t)_{post} - S(t)_{pre}}{S(t)_{pre}}, \quad [1]$$

where $S(t)_{pre}$ and $S(t)_{post}$ denote signal intensity before and after the arrival of contrast agent. Signal enhancement was further converted from blood to plasma assuming a hematocrit of 45% (22). Routine clinical image data acquired for 7 liver donors and 7 patients with liver lesions including metastasis (1), adenoma (1), focal nodular hyperplasia (1), and hepatocellular carcinoma (4) were included in this study after removing all patient identifiers. T1-weighted images using 3D stack of spiral sequence (18) were acquired at 1.5 Tesla (GE Healthcare) before and after the injection of contrast agent (10 ml gadoxetate at 1 ml/s). Whole liver 4D images with 5 mm slice thickness at a temporal frame rate of 0.23

seconds, and duration of 67 seconds were reconstructed using the Patch Based Reconstruction of Undersampled Data (PROUD) algorithm (20) for enhanced signal-to-noise ratio and high temporal frame rate. Image parameters included: 15° flip angle, 1.56×1.56×5 mm³ voxel size, TR 6 ms, TE 0.6 ms. Slices with the most prominent tumors (size and enhancement) were selected by a radiologist with 4 years of experience (SC).

In this liver perfusion study, we incorporated a dual input single compartment model with both AIF and PVIF delays (τ_a, τ_p) to account for input functions transit time:

$$\frac{dC(t)}{dt} = k_a C_a(t - \tau_a) + k_p C_p(t - \tau_p) - k_2 C(t), \quad [2]$$

where changes of contrast agent concentration $C(t)$ during the time course equals ingoing contrast agent concentration from the aorta $C_a(t)$ and portal vein $C_p(t)$ multiplied with the corresponding flow rate constants (k_a, k_p) minus the outgoing concentration multiplied with the outflow rate constant (k_2). We minimized the cost function:

$$\text{argmin}_{k_a, k_p, k_2, \tau_a, \tau_p} \varepsilon(\mathbf{k}, \boldsymbol{\tau}) = \text{argmin}_{k_a, k_p, k_2, \tau_a, \tau_p} \sum_t \|\dot{C}(t) - k_a C_a(t - \tau_a) - k_p C_p(t - \tau_p) + k_2 C(t)\|_2^2. \quad [3]$$

$\dot{C}(t)$ denotes the time derivative of $C(t)$. Here, the spatial dimension is implied in the L2 norm. Equation [2] is a function of both perfusion parameters $\mathbf{k} = (k_a, k_p, k_2)$ and delays $\boldsymbol{\tau} = (\tau_a, \tau_p)$. We minimize the cost function by setting its gradient to zero with respect to $\mathbf{k}$ (perfusion parameters) for known delays ($\boldsymbol{\tau}$):

$$\nabla_{\mathbf{k}} \varepsilon(\mathbf{k}, \boldsymbol{\tau}) = 0 \quad [4]$$

This forms an overdetermined linear inverse problem which was solved numerically by taking the integral of both sides in equation (2) and forming matrices comprising of enhancement profile time series with n time points. A matrix representation of the problem is

$$\underbrace{\begin{bmatrix} C(t_1) \\ \vdots \\ C(t_n) \end{bmatrix}}_b = \underbrace{\begin{bmatrix} \bar{C}_a(t_1), & \bar{C}_p(t_1), & \bar{C}(t_1), \\ \vdots & \vdots & \vdots \\ \bar{C}_a(t_n), & \bar{C}_p(t_n), & \bar{C}(t_n), \end{bmatrix}}_A \underbrace{\begin{bmatrix} k_a \\ k_p \\ -k_2 \end{bmatrix}}_x, \quad [5]$$

where A denotes the system matrix which relates measurements (b) to model parameters (x) and overbar indicates numerical integration. While previous approaches have solved the

linear system in Eq. 5 of voxel by voxel basis, a conjugate gradient method is used to solve Eq. 5 for the whole field of view simultaneously. This formulation is referred to for the remainder of the text as whole-field LLS. This method has the advantage of allowing adding additional regularizations, such as spatial smoothing. In this work, however, we use Tikhonov regularization with a small regularization parameter λ :

$$X = (A^T A + \lambda I)^{-1} A^T b. \quad [6]$$

The use of a small regularization parameter was empirically found to accelerate convergence while obtaining a solution that was nearly identical to the $\lambda=0$ case.

Once rate constants (k_a, k_p, k_2) were calculated, maps of the arterial fraction ($AF = k_a / (k_a + k_p)$), extracellular volume ($ECV = (k_a + k_p) / k_2$) and mean transit time ($MTT = 1 / k_2$) were computed as follows:

$$\operatorname{argmin}_{AF} \|(k_a + k_p)AF - k_a\|_2^2, \operatorname{argmin}_{ECV} \|k_2 \cdot ECV - (k_a + k_p)\|_2^2, \operatorname{argmin}_{MTT} \|k_2 \cdot MTT - 1\|_2^2$$

[7]

The second part of this problem consists of finding optimum delays. Minimizing the cost function (Eq. [3]) with respect to delays is nonconvex and forms a nonlinear inverse problem which is dependent on the initial guess and may suffer from convergence to local minima. To overcome this, a discrete set of physiological delays for both AIF and PVIF ranging between 0 to 20 seconds with 1.15-second intervals (a multiple of the temporal frame rate) were considered (16). For a pair of input function delays (one for AIF and one for PVIF), a whole-field LLS problem was solved assuming that each voxel had the same given pair of input function delays. The L2 norm between the measured and the calculated enhancement curves was used to compute a residual for each voxel for this particular pair of delays. After repeating this whole field of view calculation for all considered pairs of delays, the smallest residual and corresponding delays were selected for each voxel separately across all obtained solutions.

To compare the performance of voxel-wise LLS and voxel-wise NLLS methods, synthetic data were generated under different scenarios including variation of temporal resolution and contrast-to-noise ratio (CNR) for two typical cases. The first case represented a hypervascular tumor such as hepatocellular carcinoma and assumed $AF=90\%$, $ECV=80 \text{ ml}/100\text{ml}$ and $MTT=10 \text{ s}$. The second case represented healthy liver with $AF=30\%$, $ECV=30 \text{ ml}/100\text{ml}$, and $MTT=30 \text{ s}$. The curves were reconstructed at 4 frames per second and 67-second duration to mimic acquisition protocol in the experimental data. Input (AIF, PVIF) curves and corresponding tissue enhancement curves are shown in Supporting Figure S6. Next noise was simulated by adding complex Gaussian noise to these curves and taking the absolute value. CNR was defined as the peak of tissue enhancement

curve divided by the standard deviation of the added Gaussian noise. CNR was varied between 10 to 100 and fitting was repeated 100 times for each CNR. Relative error for each perfusion parameters was recorded and averaged over the repetitions. Next this simulation was repeated by introducing a pair of delays for the tumor case (AIF delay=0 s, PVIF delay=12 s) and for the healthy liver case (AIF delay=12 s, PVIF delay=0 s). Finally, noiseless data was downsampled to study the effect of temporal resolution which ranged from 0.23 to 4 seconds.

To investigate the effect of input function delays on the estimated perfusion parameters, noisy synthetic curves (CNR=50) were generated (see above) now using various combinations of delays ranging from 0 to 16 seconds with 2-second intervals for both AIF and PVIF. Average error for each perfusion parameter across 100 repetitions was recorded for each pair of delays and compared between voxel-wise LLS and voxel-wise NLLS.

To compare voxel-wise LLS to whole-field LLS, noisy synthetic tissue curves were generated with variable CNR ranging from 10 to 100 for various combinations of delays ranging from 0 to 16 seconds (for both AIF and PVIF) similar to the simulations above. For each of the 100 repetitions, a single image was constructed containing all possible combinations of delays and solved using both whole-field LLS and voxel-wise LLS. The estimation error for each perfusion parameter was then averaged across all delays and all 100 repetitions for both methods.

To compare voxel-wise LLS and voxel-wise NLLS fitting in experimental data, ROI-based analysis was performed on the images acquired in the 7 healthy subjects and 7 patients described above. In each subject, 3 masks including the lesion (patient) or liver (healthy subject), hepatic artery, and portal vein were drawn (SC), and corresponding enhancement curves were obtained. These curves were selected to calculate perfusion parameters and delays. Finally, for one healthy subject (liver donor) and one metastasis patient, perfusion parametric maps were generated using both whole-field LLS and voxel-wise NLLS fitting. All algorithms (<https://github.com/RaminJafari/DCEMRI>) were implemented in MATLAB (Mathworks, Natick, MA) and calculations were performed on a 64-bit Windows Machine with 6 cores (Intel i7-3.3 GHz) and 64 GB of RAM.

RESULTS

Computation time in estimating delays and perfusion mapping for a slice with 256×256 voxels and 288 time frames, was 146 hrs for voxel-wise NLLS, 8.5 hrs for voxel-wise LLS (resulting in a 17 fold speed-up) and 0.88 hrs for whole-field LLS (resulting in a 166 fold speed-up).

Figure 1 compares the performance of voxel-wise LLS and voxel-wise NLLS as a function of CNR for a simulated tumor enhancement curve without AIF or PVIF delays (Fig. 1a) and with delays (Fig. 1b). Supporting Figure S1 in the Supplementary Information shows the corresponding results for a healthy liver. These figures show that for high enough CNR (>30), the relative error in the estimated perfusion parameters are small and similar for both methods. Arterial fraction and mean transit time generally have higher relative error

compared to extracellular volume fraction. Adding delay in Fig 1b increases uncertainty in parameter estimation by introducing additional unknowns to equation (2). For high CNR (>30), the AIF delay error is smaller compared to PVIF delay error since the tissue is mostly arterially supplied ($AF=90\%$). Dependency of voxel-wise LLS and voxel-wise NLLS methods on temporal resolution is shown in Supporting Figure S5 in the Supplementary Information. Higher temporal resolution is associated with perfusion parameter estimation accuracy. Among the perfusion parameters, extracellular volume is the least susceptible to changes in temporal resolution and fitting method.

Figure 2 compares the errors in estimated perfusion parameters between voxel-wise LLS (Fig. 2a) and voxel-wise NLLS (Fig. 2b) for a simulated tumor for various pairs of true AIF and PVIF delays. While there is no error in AIF delay maps, the larger PVIF delay error has limited effect on perfusion estimation since with $AF=90\%$ the portal vein minimally supplies the tissue. Overall, voxel-wise LLS and voxel-wise NLLS agree well with the extracellular volume yielding the lowest error. Supporting Figure S2 in the Supplementary Info shows the corresponding results for the simulated healthy liver case. Errors in the estimated delays for both AIF and PVIF are below 3s in absolute terms, while the error in estimated AF is slightly larger compared to the tumor case. Again, overall performance was very similar between voxel-wise LLS and voxel-wise NLLS.

Figure 3 shows a comparison between whole-field LLS and voxel-wise LLS for the simulated tumor case as a function of CNR. Extracellular volume is the most robust in low CNR followed by mean transit time and arterial fraction. For each CNR the results are averaged over the range of AIF and PVIF delays. Supporting Figure S3 in the Supplementary Info shows the corresponding results for the simulated healthy liver case. Overall, estimation performance is nearly identical between whole-field LLS and voxel-wise LLS.

Table 1 shows a comparison of voxel-wise LLS and voxel-wise NLLS applied on the single curves obtained after ROI averaging. Good agreement is observed in the estimated perfusion parameters between voxel-wise LLS and voxel-wise NLLS fitting. Although delays change from one subject to another within each category, AIF delays tend to be larger in healthy liver compared to lesions while the opposite trend is observed for the PVIF delays. A Wilcoxon signed rank test fail to reject the hypothesis that difference between NLLS and LLS perfusion parameters come from a distribution with zero median for each perfusion parameters with the p-values shown in Table 1.

Figure 4 shows a comparison of perfusion parametric maps superimposed on the first frame of the dynamic DCE MR acquisition for the metastasis patient using whole-field LLS (a) and voxel-wise NLLS (b). Overall a good agreement between the two methods is observed across the liver. The AIF delay in the lesion (arrows) is lower (~ 5 s) compared to the surrounding liver (~ 15 s). The opposite trend is observed in the PVIF delay maps. The metastasis, compared to surrounding liver, had an average extracellular volume that was about 3 times larger, an average arterial fraction that was about 4 times higher, ranging between 45% to 80% and indicating that the tumor was supplied by the hepatic artery (23), and a mean transit time that was 2 times higher. NLLS fitting was limited to the voxels

within the liver ROI and required 32 hrs of computation time. Whole-field LLS required 55m of computation time but only the results within the liver ROI are shown in Figure 4. The corresponding result for a healthy subject is shown in Supporting Figure S4 with obtained perfusion parameters in agreement with normal values reported in the literature. Again, good agreement was observed across the liver between whole-field LLS and voxel-wise NLLS.

DISCUSSION

The results in this work demonstrate the feasibility of significantly accelerating the fitting of DCE-MRI of the liver to a delay compensated dual input single compartment model. The proposed whole field LLS method uses conjugate gradient to reduce computation time by a factor of about 160 as compared to voxel-wise nonlinear least squares fitting. The estimates obtained using the whole-field LLS method are similar to the ones obtained using the current NLLS method. The whole-field LLS method enables liver perfusion mapping with corrected dual arterial and portal venous delays, going beyond limited ROI analysis in practice, and allowing investigating heterogeneity of the perfusion parameters within liver lesions.

The speedup in computation has two factors. First the use of linear fitting is shown here to be more efficient for the dual input model compared to nonlinear fitting, confirming similar results in the literature (7,9,24). The second factor in this speedup lies in the fitting for all voxels simultaneously exploiting efficient large scale numerical solvers, such as the conjugate gradient method used in this work. On the other hand, estimation of input function delay is critical for the accuracy of perfusion quantification (13,15,25,26) but consumes a significant amount of time. The proposed method provides a means to efficiently account for input delays for whole-field fitting.

Perfusion quantification using whole-field LLS is an efficient method to generate perfusion maps. The significant increase of computation time when using NLLS fitting limits its use to ROI-based analysis in practice. Despite effectiveness in suppressing noise and motion artifacts by averaging enhancement curves within the ROI, this approach produces one set of perfusion parameters for the whole region. However, lesions tend to be heterogeneous and this ROI-based method inhibits clinicians from observing details of tissue structure and anatomy within the perfusion parameter maps. Galban et al. quantified local hemodynamic changes of brain tumors before and after radiation therapy treatment using a voxel-wise approach that maintains spatial information with successful prediction of survival in patients with high-grade glioma (27). Conversely, the same analysis using an ROI-based technique did not provide voxel-wise sensitivity in mapping perfusion changes in response to treatment. Model-free analysis is another common technique that is used in DCE-MRI to generate perfusion maps in which a deconvolution problem is formed that involves estimation of tissue residue function. Performing deconvolution between a known input function (blood supply) and a tissue enhancement curve estimates the kernel, which is the tissue residue function (7–9). However, since the liver has dual inputs, the unknown arterial fraction of input functions combined with the unknown tissue residue function forms a blind deconvolution problem which is challenging to solve because it involves the simultaneous estimation of both unknowns.

There are a number of limitations to this study. First, estimating the input function delays remains a challenge. Initially, we defined delay as a nonconvex optimization problem and solved for it using the Gauss Newton method. However, depending on the initial guess, perfusion results were different and there was no guarantee for finding a global minimum despite reducing computation time by another order of magnitude (data not shown here). In this study, a voxel dependent optimal delay is found by repeating the whole-field LLS for a set of delay pairs (fixed across the field of view) and selecting the smallest residual for each voxel across this set. It is desirable to make the delay search interval as small as possible to ensure finding the global minimum. However, the cost associated with the computation time makes the choice of search interval a tradeoff between accuracy vs. efficiency. This tradeoff is identical to the one faced by current nonlinear fitting techniques. Second, computation time remains a challenge to be addressed for clinical applications. Further reduction from the ~50 minutes reported in this study may be achieved through implementing the algorithm in a compiled programming language, using parallel processing and/or GPUs. Third, although in this study, the input function delay induced by the traveling of the bolus from hepatic artery and/or portal vein to the tissue of interest was estimated, the corresponding dispersion remains ignored. Furthermore, in compartmental modeling, the input function is assumed to have the same shape across voxels, which ignores the spatial dynamics of the input function and communication between voxels: the output of one voxel is part of the input to a neighboring voxel.

CONCLUSION

A delay compensated whole-field linear least squares perfusion quantification method is shown to be significantly faster compared to the conventional voxel-wise non-linear fitting approach, while obtaining similar perfusion parameters. This method enables liver perfusion mapping with corrected dual arterial and portal venous delays.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by NIH grants R01CA181566, R01NS072370, R01NS090464, and R01NS095562.

References

1. Ahearn TSS, Staff RTT, Redpath TWW, Semple SIKIK. The use of the Levenberg-Marquardt curve-fitting algorithm in pharmacokinetic modelling of DCE-MRI. *Phys Med Biol* [Internet]. 2005; 50:N85–92. DOI: 10.1088/0031-9155/50/9/N02
2. Blomqvist G. On the Construction of Functional Maps in Positron Emission Tomography. *J Cereb Blood Flow Metab* [Internet]. 1984; 4:629–632. DOI: 10.1038/jcbfm.1984.89
3. Feng D, Huang SC. A study on statistically reliable and computationally efficient algorithms for generating local cerebral blood flow parametric images with positron emission tomography. *IEEE Trans Med Imaging*. 1993; 12:182–188. DOI: 10.1109/42.232247 [PubMed: 18218406]
4. Feng D, Ho D, Chen K, Wu LC, Wang JK, Liu RS, Yeh SH. An evaluation of the algorithms for determining local cerebral metabolic rates of glucose using positron emission tomography dynamic data. *IEEE Trans Med Imaging* [Internet]. 1995; 14:697–710. DOI: 10.1109/42.476111

5. Zhou Y, Huang SC, Bergsneider M. Linear ridge regression with spatial constraint for generation of parametric images in dynamic positron emission tomography studies. *IEEE Transactions on Nuclear Science*. 2001; 48:125–130. DOI: 10.1109/23.910842
6. Feng D, Ho D, Lau KK, Siu WC. GLLs for optimally sampled continuous dynamic system modeling: Theory and algorithm. *Comput Methods Programs Biomed*. 1999; 59:31–43. DOI: 10.1016/S0169-2607(98)00099-6 [PubMed: 10215175]
7. Kallehauge JF, Sourbron S, Irving B, Tanderup K, Schnabel JA, Chappell MA. Comparison of linear and nonlinear implementation of the compartmental tissue uptake model for dynamic contrast-enhanced MRI. *Magn Reson Med* [Internet]. 2016; doi: 10.1002/mrm.26324
8. Murase K. Efficient method for calculating kinetic parameters using T1-weighted dynamic contrast-enhanced magnetic resonance imaging. *Magn Reson Med* [Internet]. 2004; 51:858–62. DOI: 10.1002/mrm.20022
9. Flouri D, Lesnic D, Sourbron SP. Fitting the two-compartment model in DCE-MRI by linear inversion. *Magn Reson Med* [Internet]. 2015; 0:n/a-n/a. doi: 10.1002/mrm.25991
10. Miyazaki S, Yamazaki Y, Murase K. Error analysis of the quantification of hepatic perfusion using a dual-input single-compartment model. *Phys Med Biol* [Internet]. 2008; 53:5927–5946. DOI: 10.1088/0031-9155/53/21/003
11. Wang C, Yin F-F, Chang Z. An efficient calculation method for pharmacokinetic parameters in brain permeability study using dynamic contrast-enhanced MRI. *Magn Reson Med* [Internet]. 2015; 0:739–749. DOI: 10.1002/mrm.25659
12. Cárdenas-Rodríguez J, Howison CM, Pagel MD. A linear algorithm of the reference region model for DCE-MRI is robust and relaxes requirements for temporal resolution. *Magn Reson Imaging*. 2013; 31:497–507. DOI: 10.1016/j.mri.2012.10.008 [PubMed: 23228309]
13. Calamante F, Gadian DG, Connelly A. Delay and dispersion effects in dynamic susceptibility contrast MRI: simulations using singular value decomposition. *Magn Reson Med*. 2000; 44:466–473. doi: 10.1002/1522-2594(200009)44:3<466::AID-MRM18>3.0.CO;2-M. [PubMed: 10975900]
14. Materne R, van Beers BE, Smith AM, Leconte I, Jamart J, Dehoux JP, Keyeux A, Horsmans Y. Non-invasive quantification of liver perfusion with dynamic computed tomography and a dual-input one-compartmental model. *Clin Sci (Lond)* [Internet]. 2000; 99:517–525. DOI: 10.1042/CS20000080
15. Miyazaki S, Murase K, Yoshikawa T, Morimoto S, Ohno Y, Sugimura K. A quantitative method for estimating hepatic blood flow using a dual-input single-compartment model. *Br J Radiol* [Internet]. 2008; 81:790–800. DOI: 10.1259/bjr/52166324
16. Sourbron S, Sommer WH, Reiser MF, Zech CJ. Combined Quantification of Liver Perfusion and Function with Dynamic Gadoteric Acid-enhanced MR Imaging. *Radiology*. 2012; 263:874–883. DOI: 10.1148/radiol.12110337 [PubMed: 22623698]
17. Saad Y. Iterative Methods for Sparse Linear Systems. *Notes* [Internet]. 2003; 3 xviii+528. doi: 10.1137/1.9780898718003
18. Xu B, Spincemaille P, Chen G, Agrawal M, Nguyen TD, Prince MR, Wang Y. Fast 3D contrast enhanced MRI of the liver using temporal resolution acceleration with constrained evolution reconstruction. *Magn Reson Med*. 2013; 69:370–381. DOI: 10.1002/mrm.24253 [PubMed: 22442108]
19. Brodsky EK, Bultman EM, Johnson KM, Horng DE, Schelman WR, Block WF, Reeder SB. High-spatial and high-temporal resolution dynamic contrast-enhanced perfusion imaging of the liver with time-resolved three-dimensional radial MRI. *Magn Reson Med*. 2014; 71:934–941. DOI: 10.1002/mrm.24727 [PubMed: 23519837]
20. Cooper MA, Nguyen TD, Xu B, Prince MR, Elad M, Wang Y, Spincemaille P. Patch based reconstruction of undersampled data (PROUD) for high signal-to-noise ratio and high frame rate contrast enhanced liver imaging. *Magn Reson Med* [Internet]. 2014; 0:1587–1597. DOI: 10.1002/mrm.25551
21. Schabel MC, Parker DL. Uncertainty and bias in contrast concentration measurements using spoiled gradient echo pulse sequences. *Phys Med Biol* [Internet]. 2008; 53:2345–2373. DOI: 10.1088/0031-9155/53/9/010

22. Brix G, Kiessling F, Lucht R, Darai S, Wasser K, Delorme S, Griebel J. Microcirculation and microvasculature in breast tumors: Pharmacokinetic analysis of dynamic MR image series. *Magn Reson Med*. 2004; 52:420–429. DOI: 10.1002/mrm.20161 [PubMed: 15282828]
23. Thng CH, Koh TS, Collins DJ, Koh DM. Perfusion magnetic resonance imaging of the liver. *World J Gastroenterol*. 2010; 16:1598–1609. DOI: 10.3748/wjg.v16.i13.1598 [PubMed: 20355238]
24. Garpebring A, Löfstedt T. Parameter estimation using weighted total least squares in the two-compartment exchange model. *Magn Reson Med* [Internet]. 2017; n/a–n/a. doi: 10.1002/mrm.26677
25. Mehrtash A, Gupta SN, Shanbhag D, Miller J V, Kapur T, Fennessy FM, Kikinis R, Fedorov A. Bolus arrival time and its effect on tissue characterization with dynamic contrast-enhanced magnetic resonance imaging. *J Med Imaging* [Internet]. 2016; 3:14503.doi: 10.1117/1.JMI.3.1.014503
26. Chouhan, Manil D., Bainbridge, Alan, Atkinson, David, Punwani, Shonit, Mookerjee Rajeshwar, P., Lythgoe Mark, F., SAT. Estimation of Contrast Agent Bolus Arrival Delays for Improved Reproducibility of Liver DCE MRI. *Phys Med Biol*. 2016; 61(19)
27. Galbán CJ, Chenevert TL, Meyer CR, et al. The parametric response map is an imaging biomarker for early cancer treatment outcome. *Nat Med* [Internet]. 2009; 15:572–576. DOI: 10.1038/nm.1919

Figure 1. Simulation results for a simulated hypervascular tumor (AF=90%, ECV=80 ml/100ml, MTT=10 s) comparing performance of voxel-wise LLS vs. voxel-wise NLLS as a function of CNR. Shown are relative errors (%) for ECV (Extracellular volume), AF (Arterial Fraction), MTT (Mean Transit Time) and errors (s) for AIF (Arterial Input Function) delay and PVIF (Portal Venous Input Function) delay a) without delay b) with AIF delay=0 s, PVIF delay=12 s.

Figure 2.

Comparison of voxel-wise LLS (a) and voxel-wise NLLS (b) methods for a simulated tumor case (AF=90%, ECV=80 ml/100ml, MTT=10 s) including delays at CNR = 50. The horizontal and vertical axes indicate the true PVIF and AIF delays, respectively. Shown are the mean relative error (%) for the perfusion parameters and corresponding mean error (s) in the estimated AIF and PVIF delays.

Figure 3.

Comparison of whole-field LLS and voxel-by-voxel LLS in estimating perfusion parameters and associated input function delays for a hypervascular tumor (AF=90%, ECV=80 ml/100ml, MTT=10 s) as a function of CNR. Note that for each CNR, the results are averaged over a range of AIF and PVIF delays (see text for details).

Figure 4.

Comparison of perfusion parameters using whole-field LLS (a) and voxel-wise NLLS (b) methods in the metastasis subject (see Table 1). Perfusion parameters in metastasis (white arrows in a) reveal increased extracellular volume (ml/100ml), arterial fraction (%), and mean transit time (s) in the tumor compared to the surrounding liver. Arterial input function delay (s) is smaller in the metastasis compared to the liver and opposite trend is observed in the portal venous input function delay (s). Good agreement was found between whole-field LLS and voxel-wise NLLS in perfusion parametric maps.

Table 1
Comparison between LLS and NLLS of ROI-based perfusion parameters for 7 healthy liver donors and 7 patients.

Lesion	MTT (s)		ECV (ml/100ml)		AF (%)		AIF Delay (s)		PVIF Delay (s)	
	NLLS	LLS	NLLS	LLS	NLLS	LLS	NLLS	LLS	NLLS	LLS
Healthy Liver	30.7	32.6	17.7	17	18	21.1	3.2	0	0	0
Healthy Liver	22.8	29.8	37.8	42.9	48.4	44.4	4.6	4.1	0	2
Healthy Liver	13.1	14.3	18.4	19.3	22.1	23.1	0	0	0	2.3
Healthy Liver	46.3	43.5	24.4	22.1	27.6	23.3	7.3	6.9	0	0
Healthy Liver	25.3	23.9	31.4	33.6	15.3	17.2	2.3	2.3	3.4	3.5
Healthy Liver	21.7	18.9	15.9	14.8	19.3	19	2.3	2.3	0	0
Healthy Liver	19.5	23.8	31.9	31.4	18.5	20.1	4.6	4.3	0	0
Metastasis	8	11.2	17.14	17.17	36.3	40	0	0	15.2	15
Adenoma	11.1	11.3	29.6	28.5	79.3	80	2.3	2	14.9	11.5
FNH	8.7	8.9	64.9	65.4	69	72.2	0	0.9	15.2	15.2
HCC	13.2	12.3	91	89.3	91.6	90	0	0	11.5	11.5
HCC	7.4	10.1	35.5	37.4	30	33.8	14.9	15	0	0
HCC	38.8	36.5	38.8	39	94	90	0	0	14.9	15.1
HCC	10.1	15	43.4	48.6	85.5	89.5	10.3	8.9	15.2	15.2
P-Value	0.26		0.64		0.59		0.15		1	