A new model selection framework to quantify microvascular liver function in hepatocellular carcinoma using gadoxetate-enhanced MRI

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Introduction

Hepatocellular carcinoma (HCC) most common primary liver cancer

- Most often occurs with chronic liver diseases

Gadoxetate-enhanced MRI used regularly in clinical assessment of chronic liver disease and cancer

- Actively transported by hepatocytes
- Allows more direct investigation of liver function than standard agents

First study to apply tracer-kinetic modelling of gadoxetate in HCC

Data

10 patients with HCC

- No prior local* (apart from one patient…) or systemic therapy
- At least one measurable lesion (according to RECIST)

Coronal 3D FLASH DCE-MRI protocol of the liver

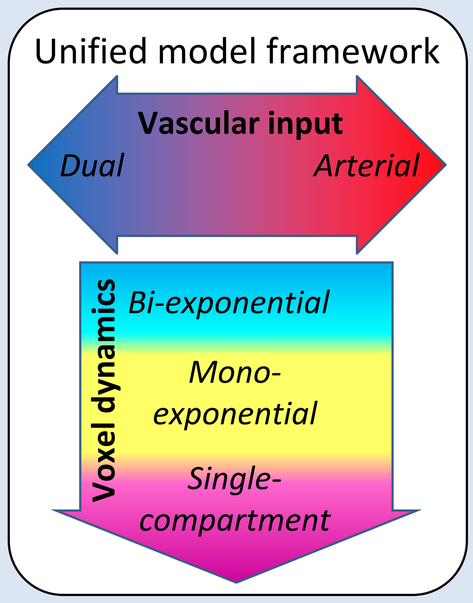
- Siemens 1.5 T Avanto system
- 100 time-points; temporal resolution 3.8 s; field-of-view 35.0 x 27.5 x 20.0 cm; spatial resolution 2.73 x 2.73 x 5.00 mm

Baseline T_1 estimated using variable flip angles, 3D FLASH

Gadoxetate acid (*Gd-EOB-DTPA*, Primovist™/Eovist™, Bayer)

- 8th time point using a power injector
- Dose 0.1 mmol/kg; flow rate of 3 ml/s

Tracer-kinetic modelling



Top-level: 2-compartment, bi-exponential model $I_4(t) = \alpha_+ \cdot e^{-t\beta_+} + \alpha_- \cdot e^{-t\beta_-}$

Functional form for **2CXM** and a Gadoxetate specific **active uptake + efflux model**

Simplified by setting β_+=0 then α_+=0

3 models of reducing complexity, each can be combined with single or dual-input vascular supply giving 6 models

Functional parameters of each model can be converted to physiological parameters for either **active** or **exchange** regime

Methods

Active transport of gadoxetate and varying vascular input produce different dynamic time-series in healthy liver, diseased tissue, tumour

To account for these variations, use 6 tracer-kinetic models:

- varying functional form cross-matched with single/dual vascular input
- generalises previously applied models into a single unified framework

Models fitted to each patient dataset, Aikake Information Criterion used to determine most statistically probable at each voxel

Physiological parameters derived from the models in two distinct regimes: active transport vs passive exchange

- Physiological constraints on $\boldsymbol{v_e}$ and $\boldsymbol{v_p}$ determine valid interpretation

ROI summary statistics liver vs tumour computed using only those voxels with a valid physiological interpretation for each regime.

Proportion of voxels selected for each model/physiological regime further characterise disease status.

Results

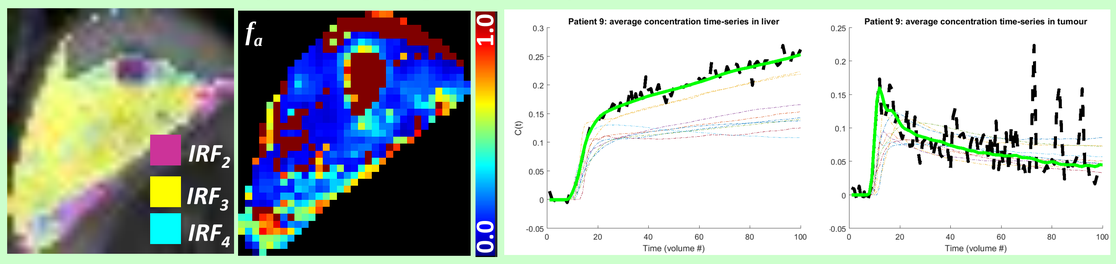
		Patient										
	Model %	1*	2	3	4	5†	6	7	8	9	10	All‡
IRF form	$\%L_2$	6.6	3.0	28.4	25.2	12.6	13.0	3.7	54.5	15.4	9.9	17.7
	$\%T_2$	0.0	40.2	34.8	28.3	21.2	22.4	77.3	62.2	46.0	39.8	31.8
	$\%L_3$	84.9	88.1	66.9	66.3	79.5	70.6	90.7	43.5	77.8	79.2	74.5
	$\%T_3$	100.0	59.1	62.4	65.2	64.7	34.0	18.7	34.1	20.0	52.0	45.3
	$\%L_4$	8.5	8.9	4.7	8.5	7.9	16.4	5.6	2.0	6.8	10.9	7.8
	$\%T_4$	0.0	0.6	2.8	6.5	14.0	43.6	4.0	3.7	34.0	8.1	22.9
Input	$\%L_d$	60.4	58.0	69.0	35.0	75.2	48.8	22.4	30.3	44.6	11.8	48.6
	$\%T_d$	75.0	16.5	59.7	23.5	43.5	46.1	37.1	19.8	34.0	13.8	40.0
Regime	$\%L_a$	84.9	86.8	83.1	95.3	78.1	45.1	81.9	65.5	97.2	97.1	82.5
	$\%T_a$	75.0	59.1	64.1	49.0	55.7	13.6	20.8	13.3	2.0	53.7	32.2

Table 1: Percentage of voxels in non-tumorous liver (white rows) and tumour (shaded rows) selected by functional form ($\%L_{2,3,4}$, $\%T_{2,3,4}$), dual-input supply ($\%L_d$, $\%T_d$), and under the active-uptake interpretation ($\%L_a$, $\%P_a$) for each patient. ◯ highlight abnormalities presented below in pink box.

1. Over 10 patient cohort, basic hypothesis holds

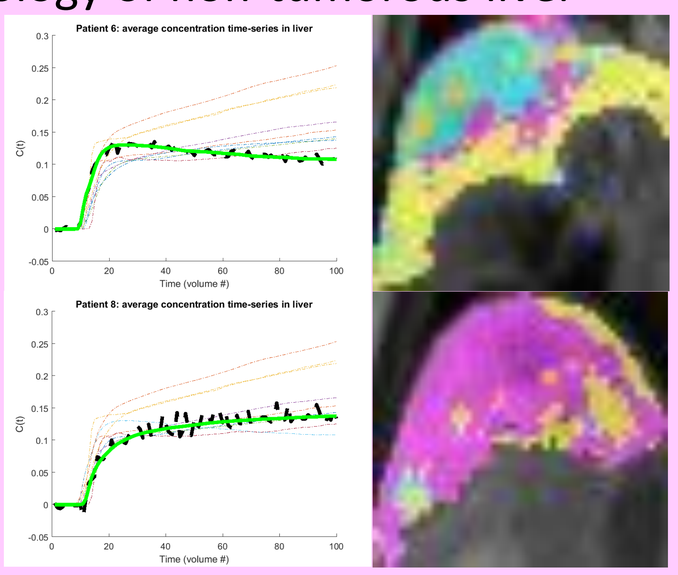
Active regime preferred in **82.1%** of liver voxels vs **40.8%** in tumours

- Arterial fraction f_a significantly higher in tumours (0.66 vs 0.32),
- Arterial delay time τ significantly shorter (0.07 min vs 0.17 min)



2. Pathophysiology of non-tumorous liver

- Abnormally high efflux
- Patient had previous localised treatment (TARE 90)
- Reduced hepatocyte function
- Patient has chronic haemochromatosis



3. Hepatocyte function within tumours

Active regime still accounts for **40.8% tumour** voxels

Active model parameters differ significantly in tumours vs liver

- Higher arterial and lower portal vein supply
- Reduced rate of hepatocyte uptake

Conclusion

Model selection and parameters:

- match previously described behaviour of gadoxetate contrast in liver imaging
- produce spatially consistent maps that correlate with the clinical presentation of patients in the study

Motivates application of the method in further comprehensive, longitudinal studies of HCC.

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