Dynamic Contrast-Enhanced Magnetic Resonance Imaging for Oncology in R

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data analysis that delivers

Outline

Goal

dcemriS4 provides a collection of functions/subroutines that move experimental data through all steps of the data analysis pipeline, using standard data formats.

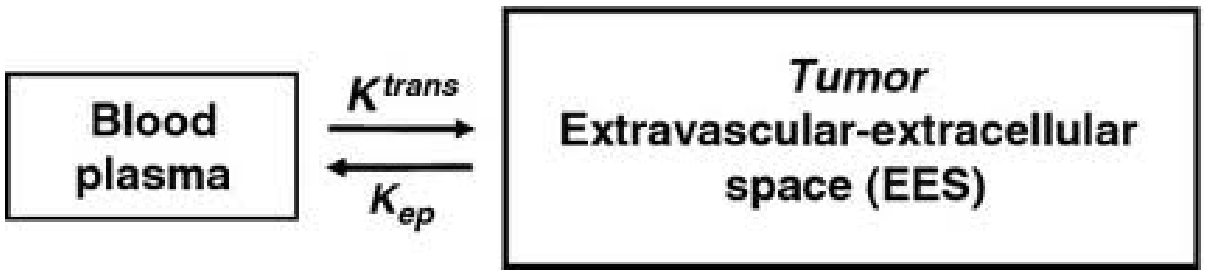
- Understand the experimental design involved in acquiring DCE-MRI data.
- Understand the steps involved in performing a fully quantitative analysis using parametric models.
- Understand the (dis)advantages of various approaches to perform kinetic parameter estimation.

Dynamic Contrast-Enhanced MRI

Usually in MR, one cites Kety (1951) for the model.

- "By building on the derivations of Bohr and Krogh it was possible to derive an expression for the exchange of an inert but diffusible tracer between flowing capillary blood and the surrounding tissue in terms of perfusion rate, the capillary diffusing surface, and the diffusion coefficient of the tracer through the capillary membrane (Kety, 1951)."

The History of Neuroscience in Autobiography, V1, (ed) LR Squire



Data Analysis Pipeline

The quantitative analysis of DCE-MRI data in **dcemriS4** consists of the following steps

1. Pre-processing of the T1 signal (e.g., motion correction, co-registration, correction of the B1 field)
2. Estimation of voxel-wise contrast agent concentration time curves
3. Determination of the arterial input function (AIF), either from the literature or by data-driven methods
4. Parameter estimation for a given compartmental model
5. Statistical inference on kinetic parameters for differences between scans of a single patient or between distinct patients

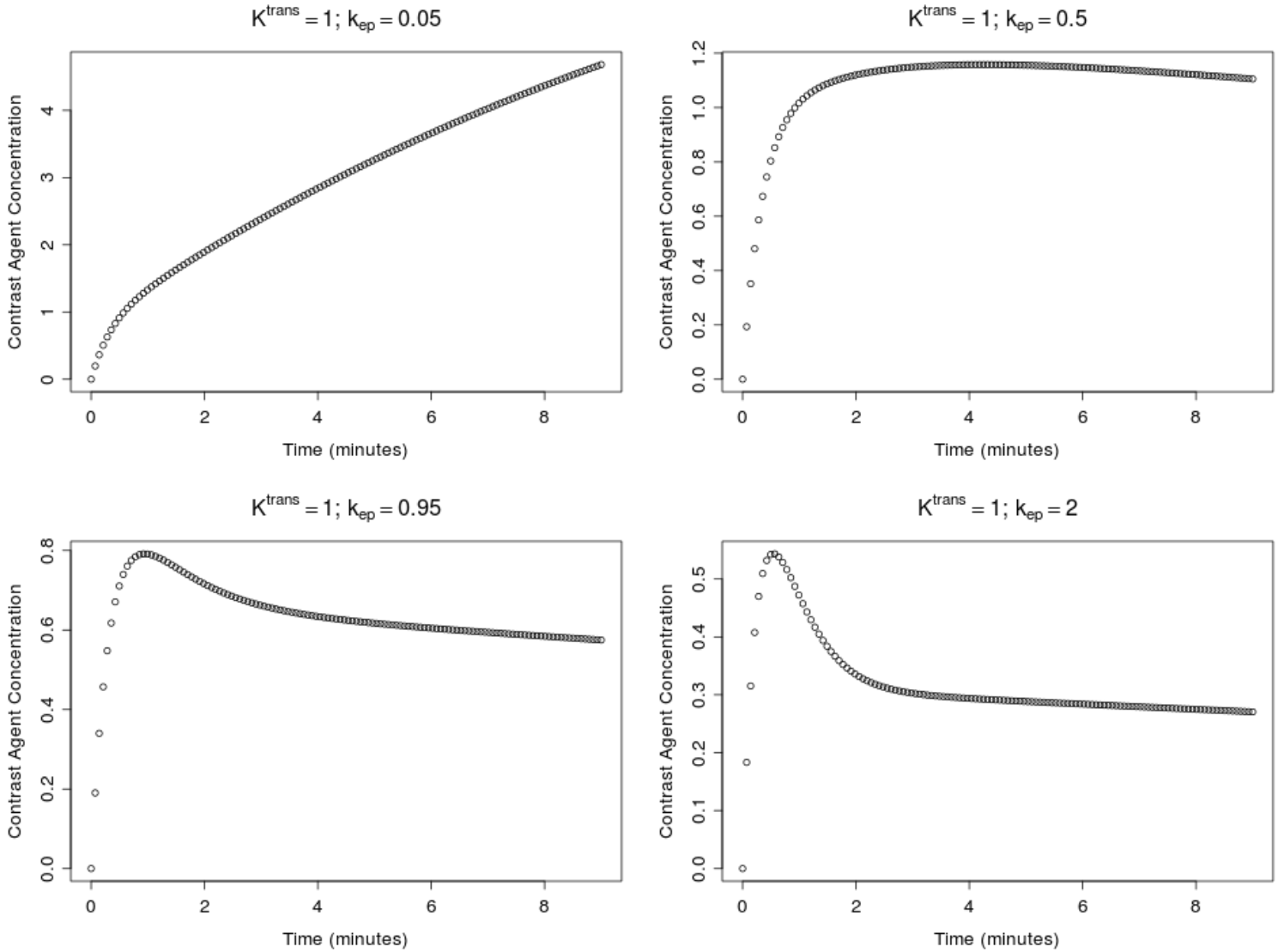
Parametric Models

Whereas qPET studies routinely perform arterial cannulation to characterize the arterial input function (AIF) directly, it has been common to use literature-based AIFs in the quantitative analysis of DCE-MRI.
Data driven AIFs are also utilized

$$C_p(t) = D\left(a_1 e^{-m_1 t} + a_2 e^{-m_2 t}\right).$$

The contrast agent concentration time curve at each voxel in the region of interest (ROI) is approximated using

$$\begin{aligned} C_t(t) &= K^{\text{trans}}\left[C_p(t) \otimes e^{-k_{\text{ep}} t}\right], \\ C_t(t) &= v_{\text{p}} C_p(t) + K^{\text{trans}}\left[C_p(t) \otimes e^{-k_{\text{ep}} t}\right]. \end{aligned}$$


$K^{trans} = 1; k_{ep} = 0.05$
$K^{trans} = 1; k_{ep} = 0.5$
$K^{trans} = 1; k_{ep} = 0.95$
$K^{trans} = 1; k_{ep} = 2$
Contrast Agent Concentration
Time (minutes)

T1 Estimation

Multiple flip-angle acquisitions are commonly used to estimate the intrinsic relaxation rate maps $\{m_0, R_{10}\}$ of the tissue

- m_0 is the equilibrium signal intensity, and
- R_{10} is the pre-injection longitudinal relaxation rate.

The non-linear equation

$$S(\theta) = \frac{m_0 \sin(\theta)(1 - E_{10})}{1 - \cos(\theta) E_{10}},$$

where $E_{10} = \exp(-\mathrm{TR} \cdot R_{10})$, relates the observed signal intensity $S(\cdot)$ with the parameters of interest when varying the flip angle θ prior to the injection of the contrast agent.

Contrast Agent Concentration

The final step of the conversion process to contrast agent concentration, using the CA.fast() function, is

$$C_t(t) = \frac{1}{r_1}\left(\frac{1}{T_1} - \frac{1}{T_{10}}\right)$$

- r_1 is the spin-lattice relaxivity constant (depends on the gadolinium chelate and magnet field strength),
- $T_{10} = 1/R_{10}$ is the spin-lattice relaxation time in the absence of contrast media (Buckley and Parker 2005).

Arterial Input Function I

Literature-based AIFs in the quantitative analysis of DCE-MRI, examples include

$$C_p(t) = D\left(a_1 e^{-m_1 t} + a_2 e^{-m_2 t}\right),$$

- $D = 0.1\,\text{mmol/kg}$
- $\mathbf{a} = (3.99, 4.78)\,\text{kg/l}$; $\mathbf{m} = (0.144, 0.0111)\,\text{min}^{-1}$

(Weinmann et al. 1984; Tofts and Kermode 1984)

- $D = 1.0\,\text{mmol/kg}$
- $\mathbf{a} = (2.4, 0.62)\,\text{kg/l}$; $\mathbf{m} = (3.0, 0.016)\,\text{min}^{-1}$

(Fritz-Hansen et al. 1996)

Arterial Input Function II

Recent models include a mixture of Gaussians (Parker et al. 2006) and sums of exponentials (Orton et al. 2008). **dcemriS4** has incorporated the sums-of-exponentials model

$$C_p(t) = A_B t e^{-\mu_B t} + A_G \left(e^{-\mu_G t} + e^{-\mu_B t} \right)$$

(Orton et al. 2008), where the unknown parameters $\beta = (A_B, \mu_B, A_G, \mu_G)$ may be estimated using nonlinear regression.

Kinetic Parameter Estimation

Parameter estimation in **decmriS4** may be performed using one of four options:

1. dcemri.lm(): Non-linear regression using non-linear least squares (Levenberg-Marquardt optimization),
2. dcemri.map(): Bayesian *maximum a posteriori* (MAP) estimation (Nelder-Mead algorithm)
3. dcemri.bayes(): Fully Bayesian inference using Markov chain Monte Carlo (MCMC) (Schmid et al. 2006),
4. dcemri.spline(): Deconvolution via non-parametric curve fitting using Bayesian penalized splines (with MCMC) (Schmid et al. 2009).

Non-Linear Regression

The convolution of a one-compartment model with the literature-based AIF produces the following statistical model

$$C_t(t) = De^{\theta_1} \sum_{i=1}^{2} \frac{a_i\{e^{-m_i t} - e^{-e^{\theta_2} t}\}}{e^{\theta_2} - m_i} + \epsilon(t),$$

- $\epsilon(t)$ is the observational error at time t with $E(\epsilon) = 0$,
- $\theta_1 = \log(K^{\text{trans}})$ and $\theta_2 = \log(k_{\text{ep}})$.

The parametrization (θ_1, θ_2) is used instead of $(K^{\text{trans}}, k_{\text{ep}})$ to ensure positive values for both transfer rates.
The parameter $v_e = K^{\text{trans}}/k_{\text{ep}}$.

Non-Linear Regression Function

dcemri.lm()

Voxel-wise nonlinear regression model is applied to the contrast agent concentration time curves.

- Estimation, along with asymptotic standard errors, obtained via Levenberg-Marquardt algorithm in **minpack.lm**.
- For the typical number of time points used in DCE-MRI, the estimation procedure is not well-behaved asymptotically and, thus, the asymptotic standard errors may not be accurate.

Bayesian Model

- **Data model**: we assume a signal-plus-noise model

$$C_t(t) \sim N(f(K^{\text{trans}}, k_{\text{ep}}, t), \sigma^2).$$

- **Process model**: we use the single-compartment

$$f(K^{\text{trans}}, k_{\text{ep}}, t) = DK^{\text{trans}} \sum_{i=1}^{2} \frac{a_i(e^{-m_i t} - e^{-k_{\text{ep}} t})}{k_{\text{ep}} - m_i}.$$

  - $\log(K^{\text{trans}}) \sim N(a(K^{\text{trans}}), b(K^{\text{trans}}))$,
  - $\log(k_{\text{ep}}) \sim N(a(k_{\text{ep}}), b(k_{\text{ep}}))$,
  - $a(K^{\text{trans}}) = a(k_{\text{ep}}) = 0$, and
  - $b(K^{\text{trans}}) = b(k_{\text{ep}}) = 1$.

- **Prior parameters**: $\sigma^2 \sim IG(a(\sigma^2), b(\sigma^2))$, with default parameters $a(\sigma^2) = 1$ and $b(\sigma^2) = 0.001$.

Bayesian Functions

dcemri.map()

Voxel-wise *maximum a posteriori* (MAP) estimators using the Nelder-Mead algorithm provided in optim().

- No standard errors are provided with this method.

dcemri.bayes()

Voxel-wise posterior median estimates of $(K^{\text{trans}}, k_{\text{ep}}, v_{\text{p}})$, and the posterior standard error for all statistics, via MCMC.

- All samples from the joint posterior distribution may be saved using the option “samples=TRUE”.
- It may be useful to retain all samples from the joint posterior when one wants to construct, for example, voxel-wise credible intervals on the kinetic parameters.

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Help

- `http://www.dcemri.org`
- `http://dcemri.sourceforge.net`
- `http://sourceforge.net/projects/dcemri/support`
- `dcemri-help@lists.sourceforge.net`

Volume 44 in the *Journal of Statistical Software*

Special volume on "Magnetic Resonance Imaging in R"

- 13 articles on fMRI, DTI, DCE-MRI, etc.
- `http://www.jstatsoft.org/v44`

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R Package: **dcemriS4**

- **Title:** A Package for Medical Image Analysis (S4)
- **Description:** A collection of routines and documentation that allows one to perform voxel-wise quantitative analysis of dynamic contrast-enhanced or diffusion-weighted MRI data.
- **Depends:** R ($>=$ 2.14.0), grDevices, graphics, methods, oro.nifti ($>=$ 0.2.8), parallel, utils
- **Suggests:** bitops, minpack.lm, splines, XML, oro.dicom
- **License:** BSD
- **URL:** `http://www.dcemri.org/`