Analytical Assessment of Kinetic Model Selection, Noise and Aliasing on Physiological Parametric Estimation in Dynamic Contrast-Enhanced MRI

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Introduction:

Using kinetic modeling, dynamic contrast-enhanced (DCE)-MRI has the potential of allowing investigators to infer physiological parameters such as perfusion, capillary permeability and blood volume. Accuracy and precision in parameter estimation in terms of model selection [1], noise and measurement error [2], and temporal sampling [3] have been evaluated in the past using computer simulations. Here, a detailed analysis covering these topics is presented using purely analytical arguments.

Theory:

Fourier Analysis of Linear Kinetic Models

Various models that describe tracer kinetics as linear, time-invariant systems can be generalized to the form $c_t(t) = c_p(t) \otimes h(t)$, where $h(t)$ is the *impulse residue function* of tissue to be estimated. Analysis is simplified by noting its Fourier pair is $C_t(\omega) = C_p(\omega)H(\omega)$, where $H(\omega)$ is the *transfer function* of tissue to be estimated. Since all unknown parameters to be estimated are entirely contained in the transfer function, accuracy of estimating parameters of a particular model depends on how well the transfer function of that model fits the true transfer function of actual tissue physiology. Three commonly used kinetic models of increasing complexity were chosen for analysis to illustrate conditions in which the models diverge. These are the same models compared by Buckley [1] using simulations:

	Integral Form	Impulse Residue Function, $h(t)$	Transfer Function, $H(\omega)$
Model 1[4]	$c_t(t) = K^{trans}\int_0^t c_p(\xi)e^{-K^{trans}(t-\xi)/v_e}d\xi$	$h(t) = K^{trans}e^{-K^{trans}t/v_e}u(t)$	$H(\omega) = \frac{v_e}{1+i\omega/k_{ep}}$, where $k_{ep} = K^{trans}/v_e$
Model 2[5]	$c_t(t) = v_p c_p(t) + K^{trans}\int_0^t c_p(\xi)e^{-K^{trans}(t-\xi)/v_e}d\xi$	$h(t) = v_p\delta(t) + K^{trans}e^{-K^{trans}t/v_e}u(t)$	$H(\omega) = v_p + \frac{v_e}{1+i\omega/k_{ep}}$
Model 3[6]	$c_t(t) = F\int_0^\tau c_p(t-\xi)d\xi + K^{trans}\int_\tau^t c_p(\xi)e^{-K^{trans}(t-\xi-\tau)/v_e}d\xi$	$h(t) = F(u(t)-u(t-\tau)) + K^{trans}e^{-K^{trans}(t-\tau)/v_e}u(t-\tau)$	$H(\omega) = \frac{F}{i\omega}\left(1-e^{-i\omega\tau}\right) + \frac{v_e}{1+i\omega/k_{ep}}e^{-i\omega\tau}$

Interpretation of physiological parameters is appreciated by graphing $|H(\omega)|$ of Models 1, 2 and 3 as log-log plots (*Bode plots*, Fig. 1). Corner frequencies $\omega_{c1} = K^{trans}/v_e$, $\omega_{c2} = K^{trans}/v_p$, and $\omega_{c3} = \pi/\tau$ define parameter boundaries of kinetic dominance: v_e mostly governs kinetics at frequencies $|\omega| << \omega_{c1}$, whereas K^{trans} mostly determines kinetics at frequencies $|\omega| >> \omega_{c1}$. The influence of v_p is seen at all frequencies but dominate at frequencies $|\omega| >> \omega_{c2}$, and τ determines kinetics at frequencies $|\omega| >> \omega_{c3}$. At near-steady state $|\omega| << \omega_{c1}$, $|H(\omega)| \approx v_e$ for Model 1, and $|H(\omega)| \approx v_e + v_p$ for Models 2 and 3. At high frequencies $|\omega| >> \omega_{c2}$, $|H(\omega)| \approx v_p$ for Model 2, whereas $|H(\omega)|$ of Model 3 closely approximates (but is always less than) that of Model 2. Only in the limit as $F \to \infty$ does $|H(\omega)|$ of Model 3 approach that of Model 2. Assuming Model 3 describes "true" tissue physiology, this explains why certain inaccuracies occur when Models 1 and 2 are used to estimate physiologic parameters. v_p is underestimated using Model 2 by the difference in $|H(\omega)|$ between Models 2 and 3, especially at frequencies $\omega_{c2} << |\omega| << \omega_{c3}$, which is related to the ratio PS/F (Fig. 2). Since $v_e + v_p$ is accurately estimated near steady state, underestimation of v_p leads to overestimation of v_e (which is most severe with Model 1 since v_p is not even considered in the model). As $\omega_{c1} = k_{ep} = K^{trans}/v_e$ is also accurately estimated, overestimation of v_e leads to overestimation of K^{trans} that is proportional to k_{ep} (Fig. 3).

Noise, Measurement Error and Bandwidth

For an arbitrary function $X(\omega)$, we define Ω_X (*bandwidth* of $X(\omega)$) as the maximum frequency that satisfies $\sigma/|X(\omega)| \le \varepsilon$ for $|\omega| \le \Omega_X$, where σ is the *upper bound absolute error* of $|X(\omega)|$ from noise and measurement errors, and ε is the *maximum tolerated relative error* of $|X(\omega)|$. If σ is the upper bound absolute error of both $C_p(\omega)$ and $C_t(\omega)$, and we set ε as the maximum tolerated relative error for defining their bandwidths, then we prove that $|\omega| \le \Omega_{Ct}$ is the frequency window at which the estimated $H(\omega)$ is reliable for estimating physiological parameters with a relative error of at most 2ε.

Sampling Theory, Aliasing and Essential Bandwidth

If an arbitrary function $x(t)$ is sampled regularly at an interval T_s, it is well known from sampling theory that aliasing occurs if $X(\omega)$ is non-zero for $|\omega| > \omega_N$, where $\omega_N = \omega_S/2$ is the *Nyquist frequency*, and $\omega_s = 2\pi/T_s$ is the *sampling frequency*. We define Ω_X (*essential bandwidth of* $X(\omega)$ *relative to* ω_0) by $\int_{|\omega|>\Omega_X}|X(\omega)|^2 d\omega \Big/ \int_{|\omega|>\omega_0}|X(\omega)|^2 d\omega = \varepsilon^2$, where $\Omega_X \ge \omega_0$, and ε^2 is the fraction of energy in $|\omega| > \Omega_X$ normalized by the energy in $|\omega| > \omega_0$. Choice of ω_0 used to define Ω_X depends on the parameter evaluated for aliasing ($\omega_0 = 0$ for v_e; $\omega_0 = \omega_{c1}$ for K^{trans}; $\omega_0 = \omega_{c2}$ for v_p; $\omega_0 = \omega_{c3}$ for τ). By using ω_0 and ε^2 to set the essential bandwidth of both $C_p(\omega)$ and $C_t(\omega)$, we prove that $2\varepsilon^2$ is the maximum fraction of energy attributable to aliasing if $\Omega_{Cp} \le \omega_N$. This can be used to define the minimum sampling rate $\omega_s \ge 2\Omega_{Cp}$ for reliable estimation of all parameters if physiological parameters are known *a priori*; choice of ω_0 used to define Ω_{Cp}, and therefore ω_s, is model dependent ($\omega_0 = \omega_{c1} = K^{trans}/v_e$ for Model 1; $\omega_0 = \omega_{c2} = K^{trans}/v_p$ for Model 2, and $\omega_0 = \omega_{c3} = \pi/\tau$ for Model 3). Application of simulated data yields results similar to that reported by Henderson, *et al.*[3]

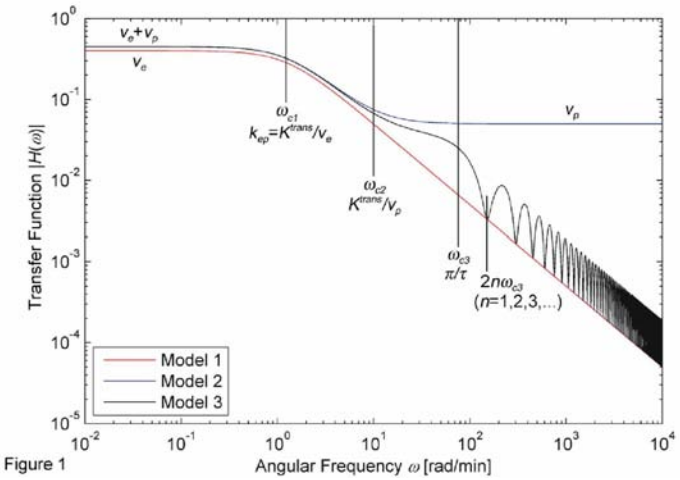

Figure 1

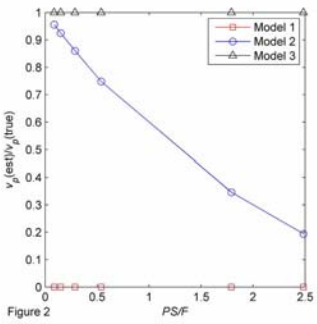

Figure 2

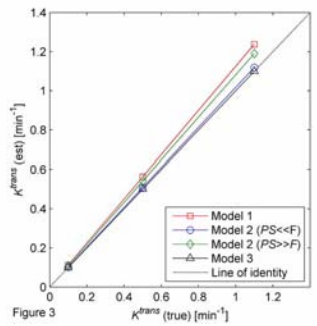

Figure 3

References:

1. Buckley DL. MRM 2002; 47:601-606.
2. Dale BM, et al. JMRI 2003; 18:575-584.
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4. Kety SS. Pharmacol Rev 1951; 3:1-41.
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