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Temporal resolution and SNR requirements for accurate DCE-MRI data analysis using the AATH model

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Abstract

Dynamic contrast-enhanced MRI has been used in conjunction with tracer kinetics modelling in a wide range of tissues for treatment monitoring, oncology drug development and investigation of disease processes. Accurate measurement of model parameters relies on acquiring data with high temporal resolution and low noise, particularly for models with large numbers of free parameters, such as the adiabatic approximation to the tissue homogeneity (AATH) model for separate measurements of blood flow and vessel permeability. In this simulation study, accuracy of the AATH model was investigated, examining the effects of temporal resolution, noise levels, and error in the measured arterial input function (AIF). A temporal resolution of 1.5 s and high SNR (noise sd = 0.05) were found to ensure minimal bias (<5%) in all four model parameters (extraction fraction, blood flow, mean transit time and extravascular-extracellular volume), and the sampling interval can be relaxed to 6 s if the transit time need not be measured accurately (bias becomes >10%). A 10% error in the measured height of the AIF first pass peak resulted in an error of at most 10% in each model parameter.

Key words: AATH model, DCE-MRI, temporal resolution, arterial input function (AIF), accuracy, blood flow
Introduction

Modelling of tracer kinetics in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has become increasingly common in oncology drug development (see (1) and references therein), investigation of pathophysiology (2-5) and monitoring of treatment effect (6-8). In contrast to semi-quantitative measures of tracer uptake (e.g. the area under the uptake curve (9)), which are reproducible (10) but dependent on the protocol used, tracer kinetics model parameters are intended to reflect underlying physiological properties of the tissue and are, therefore, valuable for their insensitivity to differences in protocol and equipment. The most commonly-used model in DCE-MRI data analysis is the Kety model (11), which allows estimation of the transfer constant (\(K_{\text{trans}}\)), the size of the extravascular extracellular space (\(v_e\)) and also the blood volume (\(v_b\)) when using the modified version (12). A major disadvantage of this model is that it does not directly estimate perfusion, and it assumes that the time taken for blood to pass from the arterial to the venous side of the capillary bed (the transit time \(T_c\)) is negligibly short. This assumption is unsuitable for many tissues where \(T_c\) is long (e.g. in the prostate (13)). A more accurate description of underlying tissue physiology is possible using models more complex than the Kety model (14-16) that include the effects of a finite transit time and allow a distinct measurement of perfusion. A more realistic physiological representation often results in a better fit to the data (17). However, increased model complexity requires higher quality data measurements (in terms of temporal resolution and signal to noise ratio) to maintain parameter accuracy and precision. An investigation of the data quality required for accurate parameter estimates for a particular model is, therefore, important in order to exploit the full potential of tracer kinetics modelling to measure tissue physiology.

The performance of any tracer kinetics model is dependent on a number of factors. Two major influences on parameter accuracy are the temporal resolution and the noise level in the acquired data. Another potential source of error is the arterial input function (AIF) that describes the concentration of contrast agent in a blood vessel feeding the tissue of interest. Accurate measurement of the AIF is challenging due to the very rapid concentration changes in the first pass, and the high peak concentrations (18). Partial volume effects, inflow of unsaturated spins, temporal undersampling, (i.e. using a temporal resolution too low to capture the first pass peak accurately), and signal saturation due to very high concentrations can all corrupt the AIF measurement (19). The data fitting process can also influence parameter accuracy, because as the number of free parameters increases, the fitting algorithm must search an extra dimension in parameter space, making it more difficult to find the optimum solution. Whether it is better to fit all parameters freely...
or fix certain parameters to reduce the number of free parameters for the fitting algorithm to search through remains unclear.

Several studies have investigated the requirements for model parameter accuracy and reproducibility, though most of this work has focussed on the Kety model (11,12). In these previous studies, parameter repeatability (6,20), accuracy (21) and temporal resolution requirements (22) for both the tissue uptake curve and the AIF were considered. Similar studies are lacking for more complex models such as the four-parameter tissue homogeneity model proposed by Johnson and Wilson (14) and its adiabatic approximation (the AATH model) (15), and it is inappropriate to apply the same requirements derived for a simpler model. For example, a minimum temporal resolution of 4 s for the uptake curve and 1 s for the AIF to ensure less than 10% error in parameter estimates, as found by Henderson et al (22) for the modified Kety model, is likely to be inadequate for these distributed parameter tracer kinetics models that include a vascular transit time. A handful of previous investigations have examined the precision and repeatability of these models (13,23-27), but parameter accuracy and its dependence on temporal resolution and signal to noise ratio (SNR) have not, to our knowledge, been considered. Accuracy is as important as parameter precision, if not more, in models aiming to measure absolute physiological parameters.

In this study, the accuracy of the AATH model was investigated. The influence of temporal resolution and noise was examined over physiological values relevant for a range of tissue types. The impact of an incorrect AIF was considered, specifically incorrect measurement of the peak height, which is most susceptible to errors from signal saturation and temporal undersampling. The curve fitting process was also systematically assessed, comparing two alternatives that have been used in the literature for fitting the AATH model: allowing all four parameters to vary freely, or fixing the mean transit time at several different values and fitting the remaining three parameters.

Methods

**Tracer kinetics models**

Three models were used in this work: the Johnson and Wilson model (14) for generating tissue uptake curves, and the modified Kety (11,12) and AATH (15) models for curve fitting. Generally, the concentration of contrast agent in the tissue as a function of time \( C(t) \) can be written as the convolution of the arterial input function \( C_p(t) \) (the concentration of contrast agent in blood plasma
as a function of time $t$ (min)) with an impulse response function $R(t)$, multiplied by blood plasma flow $F_p$ (ml (ml tissue)$^{-1}$ min$^{-1}$), as shown in Eq. [1]).

$$C_t(t) = F_p C_p(t) \otimes R(t) \tag{1}$$

The impulse response function describes the response of the tissue to a delta function input of contrast agent, and each model used in this work has a different form for $R(t)$ (Fig. 1). The impulse response function for the modified Kety model ($R_{K}(t)$) is shown in Eq. [2] and Fig. 1a.

$$R_{K}(t) = E \exp \left(\frac{-EF_p}{v_e} \right) + \frac{v_p}{F_p} \delta(t) \tag{2}$$

where $E$ is the extraction fraction (the fraction of tracer extracted from the intravascular to extravascular extracellular space (EES) in the first pass of the tracer through the capillary bed), $v_e$ is the volume of the EES (ml (ml tissue)$^{-1}$), $v_p$ is the plasma volume (ml (ml tissue)$^{-1}$) and $\delta$ is the Dirac delta function. In the original Kety model, the blood volume was assumed to be negligible, hence $R(t)$ contained only the exponential term. When the convolution in Eq. [1] is evaluated using $R_{K}(t)$, the delta function term results in the addition of the term $v_p C_p(t)$, the vascular concentration of contrast agent. Since $F_p$ is always multiplied by the extraction fraction $E$ in the full expression for $C_t(t)$, the three free parameters in this model are $EF_p$ (also known as $K^\text{trans}$) (ml (ml tissue)$^{-1}$ min$^{-1}$), $v_e$ and $v_p$.

The impulse response function for the Johnson and Wilson model, $R_{JW}(t)$, is shown in Eq. [3], derived from (28). This model includes a vascular mean transit time $T_c$ (min), which is related to the plasma flow and plasma volume by $v_p = T_c F_p$. The mean transit time takes into account the gradient in concentration down the length of a capillary, rather than assuming it to be negligibly short as in the modified Kety model. At times shorter than $T_c$, $R_{JW}(t)$ is a constant, reflecting the idea that at very short times after a bolus injection of contrast, all the contrast agent is contained in the tissue since it has not yet had time to transit the capillary bed. This results in a total tissue concentration equal to the total inflow of tracer in that time. After $T_c$, tracer that has not been extracted into the EES leaves the tissue, resulting in the sudden drop at $t = T_c$ seen in Fig. 1b.
\[ R_{JW}(t) = u(t) - u(t - T_c)(1 - E) \left\{ 1 + \int_0^{t-T_c} (1 - E)^{\frac{x}{v_e}} \sqrt{\frac{v_e}{v_c}} \ln(1 - E) \right\} \right( 2 \ln(1 - E) \right) \right( \frac{v_e^2}{v_c} \right) d\tau \right. \]  

[3]

In this model, \( I_1 \) is the modified Bessel function, \( u(t) \) is the Heaviside unit step function, and \( \tau \) is a dummy integration variable. The four free parameters are \( E, F, T_c \) and \( v_e \).

To simplify the Johnson and Wilson model an adiabatic approximation can be assumed, i.e. that the concentration in the EES changes much more slowly than the concentration in the blood plasma.

This leads to the impulse response function \( R_{\text{AATH}}(t) \), shown in Eq. [4] and Fig. 1c. This model also includes \( T_c \), and for \( t > T_c \) the impulse response function is identical to that in the Kety model. The free parameters are the same as those in the Johnson and Wilson model.

\[ R_{\text{AATH}}(t) = \begin{cases} 
0 & t \leq 0 \\
1 & 0 < t \leq T_c \\
E \exp \left( -EF \frac{v_e}{v_c} (t - T_c) \right) & t > T_c 
\end{cases} \]  

[4]

**Arterial input function**

An AIF representative of that measured in a well-designed (high temporal resolution, low noise) human DCE-MRI study was used to generate simulated tissue uptake curves (shown as the solid line in Fig. 2). This AIF was derived from the mean of AIFs measured in a previous study (27), where rapidly-sampled (time resolution = 1.5 s) input functions were obtained from the external iliac artery in 13 patients each imaged twice. The mean AIF was calculated across all patients and visits after conversion from signal intensity to change in \( 1/T_1 \) as described in (29). A smooth function was fitted to this AIF to remove the influence of AIF noise. The fitted AIF function was adapted from Ref (18) and consisted of several components as described in Eqs. [6]-[10], listed below.

1. An exponential modulated by a sigmoid to describe the first pass peak:
\[ F_1(t) = \frac{A_1 e^{-\beta_1 t}}{1 + e^{-\gamma_1 (t - T_1)}} \]  
\[ \text{where } t \text{ represents time (s), } A_1 (s^{-1}) \text{ is the amplitude of the exponential, } \beta_1 (s^{-1}) \text{ is the time constant of the exponential, and } s_1 (s^{-1}) \text{ and } T_1 (s) \text{ are the width and centre of the sigmoid, respectively.} \]

2. A Gaussian to describe the second pass peak:
\[ F_2(t) = \frac{A_2}{\sigma_2 \sqrt{2\pi}} e^{-(t-T_2)/\sigma_2^2} \]  
\[ \text{where } A_2, (\text{dimensionless}), T_2, (s) \text{ and } \sigma_2, (s) \text{ are the amplitudes, centres and widths of the two Gaussians.} \]

3. A Gaussian to describe the early portion of the curve:
\[ F_3(t) = \frac{A_3}{\sigma_3 \sqrt{2\pi}} e^{-(t-T_3)/\sigma_3^2} \]  
\[ \text{where } A_3, (\text{dimensionless}), T_3, (s) \text{ and } \sigma_3, (s) \text{ are the amplitudes, centres and widths of the two Gaussians.} \]

4. An exponential to describe the tail of the AIF:
\[ F_4(t) = A_4 e^{-\beta_4 t} \]  
\[ \text{where } A_4 (s^{-1}) \text{ is the amplitude and } \beta_4 (s^{-1}) \text{ is the time constant of the exponential.} \]

5. A sigmoid to ensure that the curve rises smoothly from zero at \( t = 0 \):
\[ F_5(t) = \frac{1}{1 + e^{-s_5 (t - T_5)}} \]  
\[ \text{where } s_5 (s^{-1}) \text{ and } T_5 (s) \text{ are the width and centre of the sigmoid, respectively.} \]

The fitted AIF, in units of \( s^{-1} \) (i.e. measured as the change in relaxivity \( R_1 \)), was obtained by summing \( F_1 \) to \( F_4 \) and multiplying by \( F_5 \), using the parameters shown in Table 1.

\[ \text{The AIF and all tissue uptake curves were simulated for a total time of 7 min. This AIF was also used in the curve fitting, except in the simulations investigating an overestimate or underestimate of first pass peak height (see below).} \]

\[ \text{Note that there is no physiological interpretation of these parameters or the AIF functional form; they were simply chosen to fit a smooth curve to the measured data.} \]
Comparison of AATH curve fitting methods

The aim of the first simulation was to determine which of two approaches for fitting the AATH model gave more accurate parameter estimates: either fitting all model parameters at once, or holding T\(_c\) constant at several values. Noiseless curves were simulated using the AIF described above, the Johnson and Wilson model and the parameters shown in Table 2. These parameters were chosen to broadly cover the expected range for prostate tumour, normal tissue, benign prostatic hyperplasia and internal obturator muscle (23,27). A total of 1680 different noiseless curves were simulated, using the same temporal resolution as for the AIF (1.5 s). The median curve is shown along with the AIF used to generate it in Fig. 2. Noise was added to each point by choosing randomly from a Gaussian distribution with zero mean and standard deviation 0.05, which is typical of baseline DCE-MRI concentration curves from the prostate (from data in (27)).

The AATH model was fitted to the simulated curves by first fitting the modified Kety model to obtain estimates of EF\(_p\), v\(_e\) and v\(_p\). Two approaches were then used, the first involved fitting all four model parameters by using initial guesses of 0.5 for E, 2*EF\(_p\) from the Kety model fit for F\(_p\) and v\(_e\) from the Kety model fit for v\(_e\). For T\(_c\), thirty different starting guesses (from 0.01 to 1.5 min) were used, and once a minimum had been found the fit was restarted with the fitted parameters changed by 5%. The fit from the second set of 30 fits that gave the lowest chi-squared value was chosen as the final fit (23). All parameter values were constrained to be positive (lower bounds of 10\(^{-4}\) for each parameter) with upper limits of 1 (E), 10 ml (ml tissue) \(^{-1}\) min \(^{-1}\) (F\(_p\)), 5 min (T\(_c\)), and 1 (v\(_e\)). The second fitting method used fixed values for T\(_c\) with only E, F\(_p\) and v\(_e\) as free parameters in an attempt to constrain the fit more effectively (24,30,31). Values for T\(_c\) ranged from 0.01 to 1.5 min in 0.01 min steps. Starting guesses and limits for E, F\(_p\) and v\(_e\) were the same as the first method. The fit that gave the lowest chi-squared value from these 150 fits was chosen as the final fit. In both cases the fitting algorithm for the AATH model was a nonlinear constrained fitting algorithm from the NAG toolbox for Matlab (Numerical Algorithms Group, Oxford, UK and The Mathworks, Natick, MA) which uses a sequential quadratic programming approach (32).
Investigation of temporal resolution and SNR requirements

To investigate temporal resolution and SNR requirements for reliable fitting of the AATH model, a range of sampling intervals (1.5, 3, 4.5 and 6 s) and SNRs (noise sd = 0, 0.02, 0.05, and 0.1) encountered in DCE-MRI experiments were considered. Curves were initially simulated without noise at 1.5 s temporal sampling using the 1680 parameter combinations shown in Table 2. Both the AIF and the simulated curves were then resampled to lower resolution of 3, 4.5 and 6 s and noise was added as described above to achieve different SNR and temporal resolution conditions. The AATH model was fitted to these curves using the fixed Tc method described above and parameter estimates were compared against their simulated values.

Investigation of AIF peak height influence

The impact of an inaccurate AIF measurement was examined by altering the first pass peak height, which shows the greatest sensitivity to signal saturation, temporal undersampling, inflow and partial volume. To create AIFs with an underestimate or overestimate of the first pass peak height, the parameter A1 in Eq. [6] was varied between 5 and 10, resulting in a peak height change of -25% to +25%. All other parameters remained constant. Curves were simulated for 1680 parameter sets as before, using a temporal resolution of 1.5 s and noise sd = 0.05 to represent data from a well-designed DCE-MRI experiment. Each curve was fitted using the fixed Tc method as before but using the AIFs with different peak heights rather than the AIF used to generate the curves.

Comparison of Kety and AATH parameter estimates

We chose to investigate data simulated for a well-designed DCE-MRI experiment to highlight the differences in parameter errors when using the AATH model and the simpler Kety model. For curves with 1.5 s temporal resolution and noise sd of 0.05, the parameter values from the initial fit to the Kety model (Ktrans, ve and vp) were compared directly with the values for these parameters derived from the AATH model fit, i.e. Ktrans was calculated for each fit as E multiplied by Fp, and vp was calculated as Tc multiplied by Fp.

Results

A comparison of the two AATH curve fitting methods, fitted Tc and fixed Tc, is shown in Fig. 3. The fixed Tc method is seen to reduce the median error in E and the interquartile range of error in all
parameters. This reduction is largest in $T_c$, where the range of errors is reduced by a factor of 2.5 in noiseless data and by a factor of 2 in noisy (sd=0.05) data; therefore, the fixed $T_c$ method was used in all subsequent simulations.

The influence of temporal resolution and SNR on the fitted AATH parameters is shown in Figs. 4 and 5. In Fig. 4 for each temporal sampling regime and noise level the median percentage errors and interquartile ranges are shown for each parameter, averaged over all parameter values. All parameters were relatively robust to temporal undersampling and noise. The median errors remained below 10% at 1.5 s temporal sampling across all noise levels, and below 20% up to 6 s sampling. $T_c$ was the least robust, with both the median error and the interquartile range increasing with noise level and with sampling slower than 1.5 s. In Fig. 5, percentage errors are plotted as a function of parameter magnitude for two scenarios: good quality DCE-MRI data (1.5 s sampling and noise sd = 0.05) and poor quality data (6 s sampling and noise sd = 0.1). The parameter $F_p$ showed a small constant bias over all flow rates considered, and decreasing interquartile range of errors for larger flows. The other parameters showed biases that were dependent on parameter magnitude. $T_c$ was highly sensitive to poor temporal resolution and low SNR, particularly when $T_c < 0.45$ min, while $v_e$ was least sensitive.

The influence of an AIF peak height error on AATH parameters is shown in Fig. 6. Under the conditions of a low-noise, high temporal resolution experiment, the error in parameters is seen to be a monotonic function of error in AIF. The higher the AIF peak, the lower the $F_p$ and the higher the other three parameters. In general, all parameters remain within 10% error when the AIF peak is measured to within 10% of its true value. Note that although the interquartile range of errors increases with AIF peak height error, it reaches a minimum not at the correct AIF but for AIF peak height overestimates between 0 and 15%.

A comparison of the AATH and Kety models is shown in Fig. 7. The Kety fitted parameters ($K_{\text{trans}}$, $v_o$, and $v_p$) are compared with the same parameters derived from the AATH model, with the additional AATH parameters $E$ and $F_p$ also shown. Even for good quality data (1.5 s temporal sampling and noise sd = 0.05), the Kety model gives inaccurate parameter estimates in comparison with the AATH model, with a systematic underestimate of $v_o$, overestimate of $K_{\text{trans}}$ and wide spread in fitted values for $v_p$. These parameters are measured with greater accuracy when the AATH model is used, with the additional advantage of separate estimates of blood flow and permeability.
Discussion

This simulation study investigated the influence of three key factors (temporal resolution, noise level, AIF peak height measurement) on parameter accuracy for the AATH model, which allows separate measurement of blood flow and permeability not possible with the more common and simpler Kety model. Although the AATH model has been used in several previous studies, expected parameter accuracy has remained unclear since absolute requirements in terms of temporal resolution and so forth have not to date been systematically characterized. Similar previous investigations are not directly relevant, as these focus mainly on the Kety model, (for example, temporal resolution and SNR requirements were investigated by Henderson et al (22)). In this study, it is shown that temporal resolution is the dominant determinant of AATH parameter accuracy. A temporal resolution of 1.5 s is required if all parameters of the AATH model are to be measured with minimal bias (< 5% bias in all four parameters for noise sd = 0.05). However, the temporal resolution can be relaxed to 6 s if $T_c$ need not be measured accurately (bias becomes >10% even for noise sd = 0.05 and interquartile range of errors is 4.6 - 40%) and small amounts of bias in $E$ and $F_p$ can be tolerated. If an accurate measurement of $T_c$ is required, the sampling interval must be sufficiently small to detect the sudden onset of outflow from the vasculature (which occurs at the discontinuity $t = T_c$ in the impulse response function). Signal to noise ratio did not have a large influence on parameter accuracy, with errors remaining within ±10% for all noise levels at 1.5 s temporal sampling. Errors in the measurement of the AIF peak height propagated into errors in AATH model parameter estimates, with a 10% error in peak height resulting in an error of at most 10% in each parameter. Two different methods for fitting the AATH model were also considered, and it was found that a fixed $T_c$ approach improved parameter accuracy compared to allowing all four parameters to vary freely. Finally, the AATH model was shown to provide much more accurate estimates of the Kety model parameters $v_e$, $v_p$ and $K_{trans}$ than the Kety model itself, with the additional advantage of separate estimates of blood flow and permeability.

Optimisation of the curve fitting process is particularly relevant for the AATH model due to the difficulty of fitting large numbers of free parameters. Previous authors have used two broadly similar methods in order to find a fit that represents a global minimum for the chi-squared value. Both approaches employ a similar optimisation algorithm (24,25) and use multiple fits before choosing the best final fit (21,24,30,31). The first approach steps through several initial values for $T_c$ and allows all four parameter values to vary freely (21,23). The second allows only $E$, $F_p$ and $v_e$ to vary freely, whilst $T_c$ is held fixed, again at several values (24,30,31). The performance of these two methods has not been directly compared, but in this study the fixed $T_c$ method is shown to give the
smallest errors, particularly in the $T_c$ parameter. Figure 3 shows that the choice of fitting method makes more difference to the fitted parameters than the noise level, highlighting the importance of optimising the fitting technique.

Much of the parameter behaviour observed can be appreciated from the fundamental dynamics of tissue contrast uptake. General trends in errors with temporal sampling and noise level, i.e. increased bias and standard deviation of errors with decreasing temporal resolution, are similar to those found for the Kety model (22), although much larger biases and range of errors for temporal resolutions under 6 s were observed. Amongst the four parameter estimates, $T_c$ showed the largest bias and range of errors and the greatest sensitivity to temporal sampling and noise. This result is consistent with previous studies showing large uncertainties (>100%) in $T_c$ for an individual fit (13,23,25) and emphasises the need for a sampling interval smaller than or comparable with $T_c$ (15) to capture information about the initial transit through the vasculature. Since $T_c$ represents the onset of outflow, detecting the time of this onset is also dependent on the tissue curve dynamics and is difficult for smoothly varying tissue curves that do not contain a well defined vascular peak. The plasma flow rate $F_p$ was the most robust parameter. Its measurement depends primarily on adequate characterisation of the initial rise of the tissue curve, as evident from model sensitivity curves (25). Even at a slow sampling rate of 6 s, $F_p$ was overestimated by only ~10%. The second most robust parameter was $v_e$, which can be appreciated from the extended washout time interval over which $v_e$ exerts an effect and can be measured. Generally, larger biases were associated with large $v_e$ (Fig. 5: $t_{ri} = 1.5$ s and noise sd = 0.05), since equilibrium is not reached by the end of the dynamic acquisition (27,33). The only unanticipated finding was reduced bias in $v_e$ with slower sampling. A plausible explanation is parameter covariance with $E$ and $F_p$. When sampling is rapid, to properly characterise early tissue uptake, $E$ and $F_p$ can be fitted more accurately at the expense of increased bias in $v_e$. On the other hand, with slow sampling, where $E$ and $F_p$ cannot be accurately measured, $v_e$ is estimated more accurately.

An accurate AIF measurement is recognized to be difficult, and the rapidly-changing first pass peak is the most challenging due to the potential for temporal undersampling and signal saturation, in addition to other errors, such as in-flow and partial volume effects, that also affect the later portions of the AIF. The impact of a poorly-measured AIF peak has been investigated for the Kety model (34) but not, to our knowledge, for the AATH model. Similar to the findings of Cheng (34), $E$ and $F_p$ were found to be most sensitive to peak height error while $v_e$ was the least sensitive. The inverse relationship between peak height and blood flow is expected since $F_p$ is the scaling factor for the AIF in the convolution (Eq. [6]). What is unexpected is that the interquartile range of errors reached a
minimum not at the correct AIF but for AIF peak height overestimates between 0 and 15%. This
behaviour is most evident for the extraction fraction E. Further investigation is required to
investigate this finding.

Comparison between the AATH and Kety models (Fig. 7) showed that fitted parameter values
derived from the AATH model were much more accurate than those found from fitting the Kety
model directly. Similar to previous findings, the Kety model severely underestimated $v_p$ and
overestimated $E_{F_p}$ (15,21). The underpinnings of these behaviours have been extensively
investigated by Cheng (34) and are related mainly to the assumption of $T_c = 0$ in the Kety model. In
Ref. (34) a finite transit time is shown to lower and widen the vascular phase ($t < T_c$) of the tissue
curve. Since the $v_p$ estimate is sensitive to the amplitude of the vascular phase, this curve lowering
leads to an underestimate of $v_p$. However, as $E_{F_p}$ is also sensitive to the vascular phase, parameter
coupling results in an $E_{F_p}$ overestimation to compensate for an underestimated $v_p$. It is important also
to note that parameter precision between the AATH and Kety models is expected to be different and
would be difficult to compare due to intrinsic model differences. The AATH impulse function has a
discontinuity at $t = T_c$ and is, therefore, susceptible to fitting instability. On the other hand, Kety
model parameters are inherently more precise, because a continuous impulse response function
enables the fitting algorithm to find a stable fit at the global minimum. However, improved
precision is of limited value when parameters cannot provide accurate absolute physiological
measurements in tissues where the transit time is not negligible.

Numerous factors not considered in this investigation can also influence parameter accuracy. For
example, a noiseless AIF was used in order to isolate errors due to noise in the uptake curve. In
future, noise in the AIF also needs to be considered since it is more practical to use a raw measured
AIF rather than fitting a smooth function that requires a large number of free parameters for an
adequate description. Another assumption in this work is the use of the Johnson and Wilson model
for curve simulation and a simpler model for curve fitting. This approach was adopted in an attempt
to mirror real DCE-MRI experiments where a model is fitted to data arising from a more complex
system. Other sources of error in real DCE-MRI data are partial volume effects, inaccurate
conversion from signal intensity to concentration, and the time offset between the AIF and the
tissue uptake curve (the bolus arrival time) due to the finite time required for contrast agent to
travel from the feeding vessel to the tissue of interest (22,35). Finally, although a broad range of
parameter values has been considered here, there may be tissues with values outside of this range.
In conclusion, obtaining data with a high temporal resolution is the most critical factor in ensuring accurate parameter estimates using the AATH model, but this requirement can be relaxed if larger biases can be permitted and $T_1$ need not be accurately measured. The trends observed and the data requirements recommended in this study are applicable to implementations of the AATH model in both MRI and CT data.

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We thank Prof David Buckley for providing AIF and uptake curve data.
References


8. Kershaw LE, Logue JP, Hutchinson CE, Clarke NW, Buckley DL. Late tissue effects following radiotherapy and neoadjuvant hormone therapy of the prostate measured with quantitative magnetic resonance imaging. Radiother Oncol 2008;88:127-134.


Figure captions

Figure 1 – Impulse response functions for the modified Kety model (a), Johnson and Wilson model (b) and AATH model (c) for the parameters $E = 0.5$, $F_p = 0.5$ ml (ml tissue)$^{-1}$ min$^{-1}$, $T_c = 1$ min, $v_e = 0.5$ ml (ml tissue)$^{-1}$.

Figure 2 – Simulated uptake curve using the median parameter values from Table 2 (dashed line), and the AIF used to generate it (divided by ten for clarity).

Figure 3 – Comparison of AATH model fitting approaches. The fitted $T_c$ (x) and fixed $T_c$ (o) methods are compared on noiseless (a) and noisy (noise sd = 0.05) (b) data. Median % errors in parameter estimates and interquartile range are shown.

Figure 4 – Errors in fitted AATH parameters under different temporal resolutions and noise levels. Time resolutions are: 6 s (a), 4.5 s (b), 3 s (c), and 1.5 s (d). Noise levels are: noiseless (x), noise sd = 0.02 (o), noise sd = 0.05 (.), noise sd = 0.1 (Δ). Median % errors in parameter estimates and interquartile range are shown.

Figure 5 – Trends in AATH parameter error as a function of parameter magnitude. Illustrated are good quality data (x) [temporal resolution = 1.5 s, noise sd = 0.05] and poor quality data (o) [temporal resolution = 6 s, noise sd = 0.1] for $E$ (a), $F_p$ (b), $T_c$ (c) and $v_e$ (d). Median % error in parameter estimates and interquartile range are shown.

Figure 6 – Effect of AIF peak height measurement error on AATH parameter estimates. Illustrated is a DCE-MRI experiment with temporal resolution = 1.5 s, noise sd = 0.05, and AIF peak heights measured with ±25% error. Median % error in parameter estimates and interquartile range are shown for $E$ (a), $F_p$ (b), $T_c$ (c), and $v_e$ (d).

Figure 7 – Comparison of parameters from AATH (top row) and Kety (bottom row) models. Fitted parameters are plotted against simulated parameters for curves with temporal resolution = 1.5 s and noise sd = 0.05. Dotted lines show the line of identity.
### Table 1 – parameters used to generate the smooth AIF curve

<table>
<thead>
<tr>
<th>Parameter / units</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1 , s^{-1}$</td>
<td>7.5</td>
</tr>
<tr>
<td>$s_1 , s^{-1}$</td>
<td>0.5</td>
</tr>
<tr>
<td>$T_1 , s$</td>
<td>15</td>
</tr>
<tr>
<td>$\beta_1 , s^{-1}$</td>
<td>0.083</td>
</tr>
<tr>
<td>$A_2$</td>
<td>13</td>
</tr>
<tr>
<td>$\sigma_2 , s$</td>
<td>4.2</td>
</tr>
<tr>
<td>$T_2 , s$</td>
<td>34</td>
</tr>
<tr>
<td>$A_3$</td>
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<tr>
<td>$\sigma_3 , s$</td>
<td>66</td>
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<tr>
<td>$T_3 , s$</td>
<td>36</td>
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<tr>
<td>$A_4 , s^{-1}$</td>
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<tr>
<td>$\beta_4 , s^{-1}$</td>
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<tr>
<td>$T_4 , s$</td>
<td>5.4</td>
</tr>
<tr>
<td>$s_5 , s^{-1}$</td>
<td>1.33</td>
</tr>
</tbody>
</table>
Table 2 – model parameters used to simulate tissue uptake curves

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraction fraction (E)</td>
<td>0.5, 0.6, 0.7, 0.8, 0.9</td>
</tr>
<tr>
<td>Plasma flow ($F_p$)</td>
<td>0.03, 0.09, 0.15, 0.21, 0.27, 0.39, 0.51, 0.63</td>
</tr>
<tr>
<td>/ ml (ml tissue)$^{-1}$ min$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>Mean transit time ($T_c$)</td>
<td>0.05, 0.25, 0.45, 0.65, 0.85, 1.05, 1.25</td>
</tr>
<tr>
<td>/ min</td>
<td></td>
</tr>
<tr>
<td>Extravascular-Extracellular volume ($v_e$)</td>
<td>0.1, 0.2, 0.3, 0.4, 0.5, 0.6</td>
</tr>
<tr>
<td>/ ml (ml tissue)$^{-1}$</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1 – Impulse response functions for the modified Kety model (a), Johnson and Wilson model (b) and AATH model (c) for the parameters $E = 0.5$, $F_p = 0.5 \text{ ml (ml tissue)}^{-1}$ min$^{-1}$, $T_c = 1$ min, $v_e = 0.5 \text{ ml (ml tissue)}^{-1}$. 57x21mm (600 x 600 DPI)
Figure 2 – Simulated uptake curve using the median parameter values from Table 2 (dashed line), and the AIF used to generate it (divided by ten for clarity).

52x36mm (600 x 600 DPI)
Figure 3 – Comparison of AATH model fitting approaches. The fitted $T_\text{c}$ (x) and fixed $T_\text{c}$ (o) methods are compared on noiseless (a) and noisy (noise sd = 0.05) (b) data. Median % errors in parameter estimates and interquartile range are shown.

57x42mm (600 x 600 DPI)
Figure 4 – Errors in fitted AATH parameters under different temporal resolutions and noise levels. Time resolutions are: 6 s (a), 4.5 s (b), 3 s (c), and 1.5 s (d). Noise levels are: noiseless (x), noise sd = 0.02 (o), noise sd = 0.05 (□), noise sd = 0.1 (∆). Median % errors in parameter estimates and interquartile range are shown.

93x68mm (600 x 600 DPI)
Figure 5 – Trends in AATH parameter error as a function of parameter magnitude. Illustrated are good quality data (x) [temporal resolution = 1.5 s, noise sd = 0.05] and poor quality data (o) [temporal resolution = 6 s, noise sd = 0.1] for E (a), Fp (b), Tc (c) and vₑ (d). Median % error in parameter estimates and interquartile range are shown.

83x45mm (600 x 600 DPI)
Figure 6 – Effect of AIF peak height measurement error on AATH parameter estimates. Illustrated is a DCE-MRI experiment with temporal resolution = 1.5 s, noise sd = 0.05, and AIF peak heights measured with ±25% error. Median % error in parameter estimates and interquartile range are shown for E (a), $F_p$ (b), $T_c$ (c), and $v_e$ (d).

108x76mm (600 x 600 DPI)
Figure 7 – Comparison of parameters from AATH (top row) and Kety (bottom row) models. Fitted parameters are plotted against simulated parameters for curves with temporal resolution = 1.5 s and noise sd = 0.05. Dotted lines show the line of identity.

66x28mm (600 x 600 DPI)