Development and clinical applications of the time intensity curve shape analysis in dynamic contrast enhanced MRI: a pixel-by-pixel approach
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CHAPTER 6


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ABSTRACT

It is widely recognised that the measurement of the Arterial Input Function (AIF) is a key issue and a major source of errors in the pharmacokinetic modelling of Dynamic Contrast Enhanced (DCE)-MRI data, and the modality of the AIF determination is still a matter of debate.

In this study we addressed the problem of the intrinsic variability of the AIF within the imaged volume of a DCE-MRI scan by systematically investigating the change in the concentration of contrast agent over time and the fit parameters of the derived Vascular Input Function (VIF) obtained from the Superior Sagittal Sinus (SSS) of a patient population that was scanned longitudinally during treatment for high grade glioma.

From a total of 82 scanning sessions we compared the results obtained with three different DCE-MRI protocols and between two different fitting functions. We applied a correction algorithm to the measured concentration-time curves (CTC) to minimize the effect of the low temporal resolution on the VIF, and investigated the effect of this algorithm on the reproducibility. Finally, where possible, we compared the signal obtained in the SSS to the signal obtained in the Middle Cerebral Artery (MCA).

We found a good intra-patient reproducibility of both the measured Gd concentrations and VIF parameters, and that the variation of the parameters due to slice location within a patient was significantly lower than the intra patient variation. Intra-patient, Inter-scan differences were significantly less marked than inter-patient differences showing a good Intraclass Correlation Coefficient. We did encounter a MRI-protocol dependence of the VIF fitting parameters. The correction algorithm significantly improved the reproducibility of the fitting parameters.

These results support the idea that the use of a patient specific measured AIF, not necessarily averaged over a large volume, offers a significant benefit with respect to an external AIF or a measured cohort average AIF.
INTRODUCTION
The use of pharmacokinetic models for quantifying tissue permeability from DCE-MRI data is widespread and of high clinical relevance [1, 2, 3].
A requirement of the most used models (e.g. Tofts [4]) is that the Arterial Input Function (AIF) be known. The issue of selecting the correct AIF is not yet settled and represents one of the major obstacles to a correct determination of the pharmacokinetic parameters of the above-mentioned models [5]. The most common way of obtaining an AIF is through sampling in a vessel close or distal to the to-be-analysed tissue. Uncertainty remains in the clinical practice as to which vessel should be sampled and how.
Ideally the AIF should be measured (possibly with a high temporal resolution) in a feeding vessel close (physiologically, not just anatomically) to the tissue to be analysed. This is very often, if not always, unrealistic since not always a feeding vessel is visible in the field of view and, if so, not always is the SNR or the temporal resolution of the scan sufficient to map the quickly varying behaviour of signal in the vessel. Sometimes saturation problems intervene to prevent the correct determination of contrast agent concentration.
In practice, often a vessel is chosen in the same slice where the quantification is performed, or in a slice in the middle of the scan [6]; sometimes it is averaged from different vessels from different slices [7,8]. Other strategies are also used such as sampling in a large close [9] or distal vessel [10], or the use of a “standard” AIF, such as, for example, the Weinmann function [11,12,13] or a measured cohort-averaged AIF as for example one obtained by a study population [14, 15]. Automatic extraction techniques have been developed [16-18] to automatically recognise vessels. Where the temporal resolution allows it, more sophisticated methods are used to infer the AIF directly from tissue data, such as the reference tissue/region based methods [19]. The latter is though not suited for use in brain scans, as in healthy brain (reference tissue) there is no signal uptake after Gadolinium (Gd) injection. In clinical brain studies it is still common to extract the AIF from the signal in the sagittal sinus [6, 20], in which case the signal is not arterial but venous, or from an averaged signal arising from different locations in the brain obtained via a segmentation process [7, 8].
It is known that the AIF can vary significantly between different patients and within patients between different sessions, due to differences in cardiac output, kidney
function, body fat etc., making an ad-hoc measurement of the AIF preferable over a patient averaged AIF. Also when an AIF is truly measured during the same scan, the choice of the vessel, as well as the level where the AIF should be measured can be a large source of uncertainty.

In order to address the reproducibility of the AIF, we have systematically investigated the behaviour of the Concentration Time Curves (CTC) measured in the Superior Sagittal Sinus (SSS), a large and easily visible vessel that spans across a large FOV in the cranio-caudal direction. Though the SSS lends well to serve as AIF (it is always apparent on an axial scan, independent of which level in the brain the scan is acquired), it contains venous blood and therefore data extracted from the sinus cannot be properly classified as “arterial” input. From now on we will therefore describe the fitting function of the CTC as Vascular Input Function (VIF). For this reason we also compared the difference between the signal in the SSS and the Middle Cerebral Artery (MCA), when this was possible.

We assessed the variability of the CTCs within a single scan (differences across slices – also referred to as “intra-scan” variability), and we compared it with the CTCs variability longitudinally across scans (“intra-patient” variability) and across the study (“inter-scan”, “inter-patient” variability). For this purpose, in this work we have analysed the data extracted from the SSS of 23 different patients who were included in the protocol of a brain study on recurrent glioma and who underwent repeated MRI scans, for a total of 82 scans, and then tested the stability of the CTC fitting parameters. We have used and compared three different MR protocols and two different fitting functions, the first fitting only the CTC decay, and the other comprising also the wash-in part of the CTC.

We have developed an algorithm to try and compensate for the loss of information arising from the relatively low temporal resolution of the dynamic scan. We have compared the effect of this correction method on the reproducibility of the VIF.

MATERIALS AND METHODS

2.1 Patients.

Twenty-two patients were recruited in the frame of a study aimed at investigating the effect of metronomic temozolomide (daily, 50mg/m2 orally) combined with bevacizumab infusions (10 mg/kg every 3 weeks) on recurrent glioma [21]. Another patient (patient 23) with the same pathology was included in this work with the purpose of comparing MRI protocols, though this patient did not undergo the above
mentioned bevacizumab/temozolomide treatment. A total of 82 scans were acquired. This study was approved by the local medical ethical committee, and all patients gave informed consent for the participation in this study.

In the scatter plots the results from the 23 patients are given individually and shown in the x axis. Patient 23 and 24 are the same individual, but the results refer to data obtained from two different vessels, as it will be specified further on. Patients underwent the first scan one day before the start of the treatment, and a 2\textsuperscript{nd}, 3\textsuperscript{rd} and 4\textsuperscript{th} scan respectively after 3, 21 and, when possible, 80 days after start of treatment. Details of the patient population and treatment are given elsewhere [21]

2.2 MRI:

DCE-MRI was performed on a 1.5 Tesla Siemens Avanto clinical system while a bolus of 0.1 mmol/Kg Gd (Gadovist® 1.0 M) was injected at a speed of 5 ml/sec through a 20G needle in the antecubital vein followed by a 12 ml saline chase. Three DCE protocols were run using a phased array 4-channel coil, and the MRI parameters were set as follows:

Protocol 1: 2D T1w GRE, TE/TR = 3.31/140 ms flip angle = 70 deg, spatial resolution = 0.89 × 1 × 4 mm, Time resolution 15.74 s, 28 acquisitions. Matrix size = 256x256, No Partial Fourier and no asymmetric echo. BW= 260 Hz/Pix, Parallel acquisition with acceleration factor 2 (GRAPPA).

Protocol 2: 2D T1w GRE, same parameters as above, but spatial resolution = 0.89 ×1.8 × 3 mm, Time resolution 13.49s.

Protocol 3: 3D T1-w GRE (TE/TR= 4.76/7.65 flip angle = 30, spatial resolution = 0.45 × 0.61 × 3 mm), Time resolution = 20 sec, 20 acquisitions. Matrix Size 256x256x24, partial Fourier imaging in slice direction 6/8, no partial Fourier in phase direction, no asymmetric echo, BW=300 Hz/pix.

Protocol 1 and 2 only differed in spatial/ time resolution, and therefore, most importantly, in SNR (protocol 2 had a lower SNR). Protocol 3 differed substantially as it used a 3D acquisition with a very short TR.

Patients 1 to 9 underwent protocol 1. Patient 10 to 22 underwent protocol 2. Patient 23 underwent protocol 3.

The choice of the 2D dynamic protocols was made in order to match the IR images. These were chosen in order to acquire good quality T1 maps which were later used for the measurement of Gd concentration for pharmacokinetic modelling of the tumour [21].
2.3 TIC analysis.
An automated vessel segmentation procedure was applied to the whole scan according to the classification algorithm described in [18]. This resulted in a number of vessels being identified, such as the SSS, the sinus rectus and transverse sinus. The MCA showed enhancement during contrast agent injection on the 3D Dynamic GRE MRI scan, whereas it did not in the 2D FGRE scan, possibly because of the more pronounced inflow effects in the 2D scan, for which the MCA signal was hyper-intense also before contrast injection.

From all the resulting segmented vessels, the SSS and MCA were manually selected by drawing ROIs around the area of the sinus in 6 to 9 slices (we avoided slices at the edge of the scan) in the Head-Foot direction.

For all the patients the results are presented for the SSS. Patient 23 and 24 are the same individual, but patient 23 represents the results from the SSS and patient 24 represents the results from the MCA.

2.4 Analysis of the Gd concentration-time curves.
Concentration-Time Curves (CTC) were obtained from all the TICs according to Equation 1

$$[Gd(t)] = - \frac{1}{TR \cdot \Re} \ln \left\{ \frac{S10(t) \cdot (1 - E) - (1 - a \cdot E)}{E \cdot (S10(t) \cdot a \cdot (1 - E) - (1 - a \cdot E))} \right\}$$

(1)

where $S10(t)=S(t)/S(0)$ and $S(0)$ is the average baseline signal $S(T_{10})$ ($T_{10}$ being the native $T_I$, before contrast enhancement), $E=\exp(-TR \cdot R0)$ $a=\cos(\alpha)$ with $\alpha$ the flip angle, and $\Re$ is the relaxivity ($\Re=4.5 \text{ s}^{-1}\text{mM}^{-1}$) [15], $R0=1/T_{10\text{blood}}$ where $T_{10}$ is the $T_I$ of blood before contrast injection.

As the measured blood $T_I$ was underestimated on the $T_I$ maps (which we obtained from multiple IR images) due to inflow effect [22] we used a fixed value of $T_I=1540$ ms [23].
Eq. (1) is the exact solution of $S_{10}(t) = f(\alpha, T_{10}, TR, T_1(t))$ (see appendix) with

$$S(t) = N_0 \sin \alpha \frac{1 - \exp(-TR/\tau_1(t))}{1 - \cos \alpha \cdot \exp(-TR/\tau_1(t))} \cdot \exp(-TE/T_2^* \cdot t) \ [24],$$

where $N_0$ is the spin density, and with the assumption of negligible $T_2^*$ effects and of a linear relationship between $1/T_1$ and $[\text{Gd}]$ : $1/T_1 = 1/T_{10} + R[\text{Gd}]$ (for the derivation of [Eq. (1)] see Appendix A1). Equation 1 does not require the approximation $TR/T_1 << 1$ to be valid [25], nor a normalization factor [26].

As concentrations in capillaries differ from concentration in venous blood due to the different hematocrit, we rescaled the measured venous Gadolinium Concentration [Gd] by a factor $(1 - Hc(\text{cap})/(1 - Hc(\text{ven})))$ with $Hc(\text{Cap}) = 0.25$ being the hematocrit in the capillaries, and $Hc(\text{ven}) = 0.45$ in venous blood [27, 28]. In this way the presented concentration values reflect the AIF as it would be used for pharmacokinetic modelling.

All the individual TICs (or TIC$_{\text{slice}}$) were converted to a set of CTCs (which will be denoted CTC$_{\text{slice}}$). Then we averaged the individual TICs generated in all slices, transformed the averaged TIC (TIC$_{\text{volume}}$) into a CTC (CTC$_{\text{volume}}$).

### 2.4.1 fitting of the CTCs

From each of these original CTCs we generated two new datasets in the following way.

CTC1: The first data-point was set to start at time 0, defined as the time point when the curve reaches the top point. Only the decay is visible.

CTC2: The CTCs were stripped of the baseline except the last baseline point (intensity = 0), for which the initial raise of the concentration remains visible [see Figure1].

Type CTC1 datasets were fitted to a bi-exponential as in Eq. (2):

$$C_p(t) = \sum_{i=1}^{2} a_i \cdot e^{-m_it} \ (2)$$

where, in this paper, $a_i$ and $m_i$ will refer to the fast decay component, and $a_2$ and $m_2$ will refer to the slow decay component.

Type CTC2 datasets were fitted to Eq. (3), a convolution as in Model 2 in [28].

$$C_p(t) = C_b(t) + C_d(t) \otimes B(t) \ (3),$$

where $\otimes$ represents convolution.
Eq. (3) can be solved in closed form to obtain

\[ C_p(t) = b \cdot mb^2 \cdot t \cdot e^{-mb \cdot t} \]

\[ B(t) = a \cdot e^{-ma \cdot t} \]

Eq. (3) can be solved in closed form to obtain

\[ C_p(t) = b \cdot mb^2 \left( \alpha \cdot t \cdot e^{-mb \cdot t} - \beta \cdot e^{-mb \cdot t} + \beta \cdot e^{-ma \cdot t} \right) \]  

(4)

with

\[ K_b = b \cdot mb^2 \]

\[ \beta = \frac{a}{(ma - mb)^2} \]

\[ \alpha = \left[ 1 + \frac{a}{(ma - mb)} \right] \]

(see Appendix A2 for derivation).

The parameters \( ma, mb \) as in Eq. (4) describe respectively the slow exponential decay and “sharpness” of the initial peak. All CTCs generated in each individual slice (CTC\(_{\text{slice}}\)) as well as in each volume CTC (CTC\(_{\text{volume}}\)), were converted to both CTC1 and CTC2 and fitted individually with the above functions, in an unconstrained fashion. In total we calculated 8 fitting parameters for each CTC, both for the individual slices,

\[ \text{Slice}\_\text{Par}_{[1..8]} = (a_1, a_2, m_1, m_2, a,b, ma, mb)_{\text{slice}} \]

and for the averaged CTCs (CTC\(_{\text{volume}}\)) (average over all the slices)

\[ \text{Vol}\_\text{Par}_{[1..8]} = (a_1, a_2, m_1, m_2, a,b, ma, mb)_{\text{volume}} \]

Note that the averaged parameter over the individual (slice based) CTC\(_{\text{slice}}\)s need not coincide with the parameters calculated form the averaged CTC\(_{\text{volume}}\). As the latter is originated from averaging all the individual TICs and only then transformed into a CTC, it results in a better SNR, and therefore in, possibly, different fit results.

2.4.2 CTC Correction algorithm.

We corrected the native CTCs with an algorithm which we developed based on the following observations.

The typical arterial CTC presents itself with an initial spike, followed by a slow decay [29]. Sometimes, at high temporal resolutions, a second spike (recirculation) can be visible [15]. In our scans the “real” maximum concentration in the vessel after injection is missed most of the time, because of the low temporal resolution (= 13 to 20 ms, according to protocol) of the dynamic scan, and therefore the fact that
the scanning grid can be misaligned with respect to the top concentration point. However we assumed that, because of the different moment of the dynamic timepoint at which each slice of the 2D scan is acquired, there will be at least one slice whose maximum intensity of the CTC will best approach the maximum vessel Gd concentration. From each slice, we therefore calculated the ratio “iRTS” (Ratio Top Slow of the $i^{th}$ slice) between the Gd concentration at the top point and that at the beginning of the slow decay. We assumed that the largest value among all the iRTS within one scan was the most probable ratio between the maximum achievable (top) concentration and the concentration at the beginning of the slow decay. We multiplied this by 1.2 (arbitrary number) to compensate for a possible under-estimation of the measured peak due to other causes such as saturation effects, and we named this value RTS.

For each individual CTC, we performed multiple non linear regressions of the CTC to model Equation 3, while continuously shifting the time axis, thus “moving” the CTC with respect to the zero time-point. Of all the fitted curves we kept the one which showed a peak value whose ratio with respect to the baseline was the one calculated before (RTS). We added then an “artificial” point to the native CTC, corresponding to this new top of the CTC, in the position determined by the best fit. The “corrected” CTC consists therefore of the original CTC to which a top point, of an intensity equal to the slow decay of the CTC times RTS, has been added in the location chosen by the above fitting –selecting algorithm.

The corrected CTCs (corrCTC) were then analysed again according to the same algorithm in 2.4.1, and therefore fitted to both Eq 2 and 3.

2.5 Calculation of the relative Standard Deviations

We aimed at understanding the variability of the CTC fit parameters within the imaged volume (across slices within a scan session) and compare this to the variability within a patient and across the study. To do this we first calculated the mean, the standard deviation and the relative standard deviations (RSD) of the parameters over all the CTCs in the measured volume (mean and STD over $M$ slices of the same scan)

$$RSD_{scan}(\text{SlicePar}_i)_j = \frac{\text{STD}(\text{SlicePar}_i)_{\text{slic}1...M}}{\text{mean}(\text{SlicePar}_i)_{\text{slic}1...M}}$$

for each individual scan session $j$. This provides a measure of the variance of the measured parameter within each scan (variability due to slice position).
Then for each patient we calculated the mean, the standard deviation and the relative standard deviation of the mean volume-originate parameters \( Vol_{Par} \), calculated over all CTC \(_{volume}\)s from the different scan sessions of the same patient. This provides a measure of the variance of the parameters within each \( k^{th} \) patient.

\[
RSD_{pat} (Vol_{Par})_k = \frac{STD(Vol_{Par})_{scan1..N}}{mean(Vol_{Par})_{scan1..N}}
\]

where \( N \) is the total number of scans the \( k^{th} \) patient underwent.

Of the relative standard deviations \( RSD_{scan}(Slice_{Par})_j \) and \( RSD_{pat}(Vol_{Par})_j \) we calculated an average value respectively over all the scan sessions and all the patients as described below. We calculated the results separately for patients undergoing the three different protocols.

\[
\text{av}_j \ RSD_{scan} (slice_{Par})_j = \frac{\sum_{j=1}^{J} RSD_{scan}(Slice_{Par})_j}{J}
\]

where \( j \) is the counter over all individual scans (\( J=34 \) for protocol 1, \( J=46 \) for protocol 2 and \( J=4 \) for protocol 3).

The average RSD over all patients is given by

\[
\text{av}_K \ RSD_{pat} (Vol_{Par})_k = \frac{\sum_{k=patient1.K} RSD_{pat} (Vol_{Par})_k}{K}
\]

where \( K \) is the number of patients undergoing each protocol (\( K=9 \) in protocol 1, \( K=13 \) in protocol 2, \( K=1 \) in Protocol 3). As protocol 3 was only used for one patient, we have omitted the statistical calculation (RSD) for patient 23.

Finally we calculated the RSD over the whole study as

\[
RSD_{study} (Vol_{Par})_j = \frac{STD(Vol_{Par})_{scan1..J}}{mean(Vol_{Par})_{scan1..J}}
\]

\( J \) is the total number of scans with each protocol (\( J=34 \) for protocol 1, \( J=44 \) for Protocol 2, \( J=4 \) for protocol 3).

In short, \( \text{av}_j \ RSD_{scan} \) represents the intrinsic RSD of the slice parameters within an individual scan, averaged over all the scans, \( \text{av}_K \ RSD_{patient} \) represents the RSD of the volume parameters across each individual patient, averaged over all the
patients and $RDS_{study}$ represent the RSD of the parameters of all the scans pooled together.

We calculated a patient Intraclass Correlation Coefficient $ICC_{patCTC}$, calculated according to

$$ICC(VolPar) = \frac{\left(\text{STD}(VolPar)_{study}\right)^2}{\left(\text{STD}(VolPar)_{study}\right)^2 + \left(Av_{-}\text{STD}(VolPar)_{pat}\right)^2}$$

The ICC is commonly used to assess consistency or reproducibility of quantitative measurements that are organized into groups. It describes how strongly measures obtained in the same group resemble each other, with respect to the measurement of all the groups together. Value 0 reflects a low resemblance, whereas 1 represents a high reproducibility.

**Figure 2** Intensity in mMol/l of the Sagittal sinus CTC at peak value and at the beginning of the slow decay, shown per patient. Vertical lines separate patients undergoing different protocols. Patient 1 to 9 were scanned with protocol 1, patient 10 to 22 with protocol 2 and patient 23 with protocol 3. Patient 24 refers to the CTC in the MCA.

**RESULTS**

We first present the fit parameters of the volume-averaged CTCs and their STDs to address the protocol dependence of the VIF determination. We then compare the individual study results, and at the same time observe the difference in parameters obtained in another vessel (the MCA).

We compare the variability (measured with the RSDs) of the CTCs fit parameters within each individual scan, across scans within the same patient, and throughout the study to infer a measure of reproducibility of the VIF. We also investigate its protocol dependence. Finally, we address the problem of the uncertainty on the
temporal jitter and how the correction method affected the results. In all cases we compare results obtained using an uncorrected and a corrected CTC.

3.1 CTC characteristics and fit parameters.
The characteristics of the CTCs, namely the highest value and the amplitude at the beginning of the slow decay, are shown in Figure 2 for both corrected and uncorrected data. The plot shows that the amplitude of the slow decay, which is the parameter least affected by the low temporal resolution of the scan, is well reproducible within the same patient. The maximum amplitude of the CTC is, conversely, highly variable. The correction method, which results in larger top CTC values, does not significantly change the intra-patient variability of the top values.

3.1.1 Protocol dependence of the fit parameters
To analyse the protocol dependency of the fit parameters we calculated average values of the fit parameters of the CTC\text{volume} (a1,m1,a2,m2 and a,ma,b,mb) across the whole study (independent of patient grouping). These, together with their STDs are shown in Table 1.

We found the slow decay component values (ma) to lie around the value of 0.07-0.11 min\(^{-1}\), according to protocol, in accordance with the literature. Both the uncorrected and corrected averaged CTC fit parameters are shown separately for comparison in Table 1. We could observe a difference in the results obtained with the different protocols. By looking at the relative STD (in brackets, expressed in percentage) it can be seen that the correction algorithm significantly stabilises the fit parameters, resulting in lower rSTD in the parameters of the corrected data, especially those of the fast decay m1 and mb, resulting in lower RSD in each of the three protocols.

The details of the individual results of the decay per patient are given in Figure (3), where we compare the parameters m1 and m2 (the fast and slow bi-exponential decay rates of the corrected and uncorrected CTC in a scatter-plot).

In this plot it is possible to appreciate the difference between the fit parameters in the SSS and in the MCA by looking at patient 23 and 24, showing that the decay parameters m1 and m2 in the SSS and in the MCA were comparable.

3.2 Variance of the CTC fit parameters within each scan and across the study.
In order to assess the reproducibility of the VIFs, we have investigated the distribution of the CTC\text{slice} fit parameters across the individual slices, and compared it with the distribution of the fit parameters of the CTC generated by a slice-averaged signal (CTC\text{volume}) across the patients and with the study RSD. The
results of these (averaged) relative STDs (Av_RSD\textsubscript{scan}, Av_RSD\textsubscript{patient} and RSD\textsubscript{study}) are presented in Table 2 and are expressed in percentages. For each parameter, we have reported the results referring to the two 2D protocols (1 (first line) and 2 (second line)).

![Figure 3](image.png)

**Figure 3.** Fitting parameters of parameters m1 and m2 of the bi-exponential fit. Fits of both corrected and uncorrected CTC results are displayed. Bars separate data acquired with different protocols (1, 2, and 3).

Comparison between “scan”, “patient” and “study” columns in Table 2 show that the parameters RSD calculated across slices within one scanning session is, on average, smaller than the average RSD of the parameter across different scans of the same patient, which in turn is smaller than the study RSD. This confirms the fact that VIF are well reproducible within the same scan, and within the same patient. The small spread in the parameters value across the slices (“RSD\textsubscript{scan}”) suggests that the parameters do indeed vary much less within the imaged volume than within the same patient across different scans. This suggests that selecting a VIF in a single slice instead of a whole volume could be an acceptable approximation. The values of the ICC also indicate a good correlation. The fit parameters describing the slow component of the decay are relatively insensitive to the random, unknown delay in the alignment of the data sampling grid with respect to the start of the signal enhancement (or temporal jitter [30]), and are therefore more stable. Conversely the fast decay component m1, is highly unstable (RSD\textsubscript{study} varying up to 102%, using protocol 2) because of the random temporal jitter combined with the low temporal resolution.

The fit parameters of the convolved function ($b, mb, a, ma$) (Eq. (3)) appear to be slightly more stable than the fit parameters of the bi-exponential function.
(a1,m1,a2,m2), showing on average lower STDs. In the left column the results are presented of the corrected CTCs, showing that the correction effectively works towards the stabilisation of the fit parameters describing the fast decay (m1, mb), whereas results referring to the slow decay are only very slightly affected.

3.3 Uncertainty in the temporal jitter.

Due to the relatively low temporal resolution of the Dynamic MR protocol (13, 15 and 20 seconds in each protocol respectively) the maximum amplitude of the CTC (peak value) was expected to vary significantly between scans because of the random delay in the start of the sampling grid with respect to the injection (“temporal jitter” [30]). The ratio RTS between the CTC maximum intensity and the initial value at the beginning of the slow decay (see 2.4.2), plotted in Figure 4, remained stable. For comparison, in Figure 4 we also show the average ratio between the maximum of the averaged CTC (without correction) and the beginning of the slow decay.

![Figure 4](image)

**Figure 4.** RTS (see 2.4.2) and the ratio between max and the beginning of the smooth decay of the averaged CTC (cross).

In published data [29] this value approximates 4 -5, while in our study it did not vary sensibly between the scans, almost never reaching values larger than twice the tail onset, except in the 3D scan in the sagittal sinus (patient 23). This underestimation was most probably not a reflection of the true Gd concentration, but a saturation effect, which was difficult to estimate theoretically. Although the correction algorithm could not stabilise the max value, it did improve the estimation of the
3.4 Correlation of the parameters with patient characteristics and treatment.
In this study contrast medium dose was adjusted according to patient weight. We
cHECKED if any parameters showed any relation with the patient weight, but no
significant relation was found.
Despite the fact that the patients underwent anti-angiogenic treatment, affecting the
micro and macro vascularity, no trend in any of the AIF parameters was observed
during treatment, and no significant difference was observed between pre- and
after- treatment. Conversely, the $K_{trans}$ measured in the tumour was significantly
affected by the treatment [21].

<table>
<thead>
<tr>
<th></th>
<th>Protocol 1</th>
<th>Protocol 2</th>
<th>Protocol 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>0.26 ± 0.15 (57)</td>
<td>0.153 ± 0.12 (78)</td>
<td>0.89 ± 0.39 (44)</td>
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<tr>
<td>$m_1$ (min$^{-1}$)</td>
<td>7.19 ± 2.55 (35)</td>
<td>7.83 ± 2.4 (30)</td>
<td>6.77 ± 1.31 (19)</td>
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<tr>
<td>$a_2$</td>
<td>0.27 ± 0.11 (40)</td>
<td>0.15 ± 0.08 (53)</td>
<td>0.43 ± 0.105 (24)</td>
</tr>
<tr>
<td>$m_2$ (min$^{-1}$)</td>
<td>0.078 ± 0.028 (36)</td>
<td>0.093 ± 0.032 (34)</td>
<td>0.11 ± 0.038 (34)</td>
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<tr>
<td>$b$</td>
<td>0.086 ± 0.048 (56)</td>
<td>0.043 ± 0.025 (58)</td>
<td>0.26 ± 0.093 (35)</td>
</tr>
<tr>
<td>$m_b$ (min$^{-1}$)</td>
<td>15.49 ± 3.84 (24)</td>
<td>16.4 ± 2.63 (16)</td>
<td>12.86 ± 1.8 (14)</td>
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<tr>
<td>$a$</td>
<td>3.627 ±1.048 (28)</td>
<td>3.84 ± 0.70 (18)</td>
<td>1.8 ± 0.21 (11)</td>
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<tr>
<td>$m_a$ (min$^{-1}$)</td>
<td>0.082 ± 0.027 (33)</td>
<td>0.09 ± 0.032 (36)</td>
<td>0.11 ± 0.041 (37)</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>0.14 ± 0.094 (67)</td>
<td>0.076 ± 0.05 (65)</td>
<td>0.44 ± 0.16 (36)</td>
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<tr>
<td>$m_1$ (min$^{-1}$)</td>
<td>6.72 ± 6.56 (97)</td>
<td>5.97 ± 6.13 (102)</td>
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<td>$a_2$</td>
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<td>$m_2$ (min$^{-1}$)</td>
<td>0.072 ± 0.026 (36)</td>
<td>0.087 ± 0.031 (35)</td>
<td>0.11 ± 0.04 (36)</td>
</tr>
<tr>
<td>$b$</td>
<td>0.117 ± 0.065 (55)</td>
<td>0.05 ± 0.039 (78)</td>
<td>0.42 ± 0.15 (35)</td>
</tr>
<tr>
<td>$m_b$ (min$^{-1}$)</td>
<td>20.45 ± 15.59 (76)</td>
<td>35.07 ± 21.37 (60)</td>
<td>7.87 ± 1.9 (24)</td>
</tr>
<tr>
<td>$a$</td>
<td>2.85 ± 1.1 (38)</td>
<td>3.66 ± 1.05 (28)</td>
<td>1.12 ± 0.28 (25)</td>
</tr>
<tr>
<td>$m_a$ (min$^{-1}$)</td>
<td>0.083 ± 0.026 (31)</td>
<td>0.09 ± 0.037(41)</td>
<td>0.11 ± 0.038 (35)</td>
</tr>
</tbody>
</table>

Table 1: average values and STD of the CTC$_{voume}$ fit parameters. The average and standard
deviations (RSD in % is given in brackets) are calculated over all the 34 scans in Protocol 1
(all patients grouped together), 44 scans in Protocol 2, and 4 scans in Protocol 3. Results
are presented for corrected and uncorrected data.
DISCUSSION
The choice of the arterial input function for use in PK modelling is still an unsettled issue. The use of a measured AIF is generally considered to be the first choice, but which vessel should be used is difficult to assess. Not always vessels feeding the ROI in which PK modelling is performed are visible, and often the visible vessels are (physiologically) quite distant from the feeding vessels. Often, as suitable AIF, a vessel is chosen in the same slice where the quantification is performed. This raises the question whether this arbitrary choice can introduce further bias.
In this work we have investigated the sensitivity of the AIF to the spatial location of the vessel sampling. Namely, we investigated how the TICs and CTCs obtained from an easily identifiable vessel, the superior sagittal sinus, which spans over a large cranio-caudal distance and whose dynamic behaviour should be independent of the sampling location, can vary within a patient depending on the slice location. We compared these variations with the variations through a series of longitudinal scans and across a study. We found that the differences we observed in the calculated VIF parameters across the imaged volume were less pronounced than the differences that occurred between volume averaged parameters over different scans, yielding a good Intraclass Correlation Coefficient. Moreover, volume averaged parameters tended to be relatively stable within each patient across different sessions (compared to the overall STD of the study), suggesting that an ad-hoc measured VIF is a sensible choice, and that a CTC averaged over the volume is to be preferred. The correction algorithm we proposed effectively improved the reproducibility.
However, we did find differences in the results produced by fitting the CTCs from data obtained by the two 2D different, though similar, protocols which only differed in time and spatial resolution. Most probably the different slice thickness of the two protocols led to different flow effects [31]. The lower SNR of protocol 2 could have made the determination of the baseline and top point more uncertain, therefore indirectly affecting the values of the CTC.
In this study we used a 2D dynamic MR protocol whose use was justified by the necessity of matching the 2D scans which we performed in order to calculate good quality (IR-generated) T1 maps for the main study [21]. The choice of a 2D protocol resulted in the MCA not producing measurable enhancement, possibly a cause of a larger inflow effect in the vessels because of the repetitive excitation and concomitant flow of blood across the slice direction [35]. In order to relate our
results to the more commonly used 3D protocols, we included a patient in this study who underwent a 3D-DCE protocol (protocol 3). This allowed us to compare results of the SSS with those obtained in the MCA. We did observe a difference in the fitting parameters between the results in the SSS between the 3D and 2D protocol, though there was not a large one between the SSS and the MCA (Figure 3).

### 4.1 Selection of the SSS and MCA

We selected voxels belonging to vascular space according to a selection scheme based on TIC pattern recognition [18]. We also investigated the effect of a further voxel selection to avoid possible contamination from voxels suffering partial volume effect, which were expected to limit the intensity of the peak of the TIC, using a procedure similar, though not identical, to that presented by Parker [16]. In the interest of space we did not present the results in this paper, though we were able to observe that the difference in the final parameters was not significant. We decided to only present the results of the averaged data arising from all pixels classified as vascular, without the above-mentioned selection, as the higher SNR showed to result in lower RSD, and thus better reproducibility.

<table>
<thead>
<tr>
<th></th>
<th>Average RSD, Corrected CTC</th>
<th>ICC</th>
<th>Average RSD, Uncorrected CTC</th>
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<tr>
<td></td>
<td>Scan</td>
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<td>Study</td>
<td>Scan</td>
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<td>a1</td>
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<td>32%</td>
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<tr>
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</tr>
<tr>
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<tr>
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<td>30%</td>
</tr>
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</tr>
<tr>
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<tr>
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<td></td>
<td>Prot 2</td>
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<td>26%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Table 2. Comparison between the average RSD of the parameters across the slices, across sequential scans of the same patient, and across different patients. In the last column the patient ICC is shown.
4.2 Amplitude of the CTCs

TICs were transformed into CTCs using Eq. 1. The transformation of signal intensity into concentration-time curves is meant to standardise data originating from different protocols, and obtained quantitative information about Gd concentrations.

Unfortunately we observed that small differences in the protocol did result in different fitting parameters, and that large differences in the acquisition protocol, as it occurs in or 3D and 2D protocols, resulted in different CTC fitting parameters.

Equation 1, which we used to convert the TICs into CTCs, is the exact solution of the ratio between the enhanced signal and the pre-contrast signal, where the expression for the signal intensity was the steady state signal function for gradient echo sequences [24], neglecting $T_2^*$ decay. It is therefore, in principle, not sensitive to the size of the ratio $TR/T_1$, as in the (first order) approximation as in [25], though still sensitive to changes in $T_2^*$.

The rescaling factor we used to take into account the different hematocrit in capillary and major vessel is an approximation. It assumes that the relaxivity in whole blood and in pure plasma is the same. A more accurate calculation has been discussed by [32], but for the purpose of this study the simple rescaling was considered sufficient.

The slow decay of the CTCs we obtained was in both approaches consistent with previously published CTCs with a comparable contrast agent dosage [29], with intensities in the range of 0.4-0.7 mM and decay rates of 0.08-0.11 min$^{-1}$. The initial peak was, in contrast, lower than the expected value. From previous literature values we know that top Gd concentration of a fast bolus injection can reach from 2 to up to 5 times the slow decay [15,29,33,34]. Though one possible reason could have been the low temporal resolution, (insufficient temporal sampling) we observed that if this was the case, a large peak should have been visible at least once because of the large amount of scans (the time shift is per se random). This did not seem to be the cause, as all peak values tend to be stable (see Figure 4). Apparently, other problems appeared to limit the sensitivity of the scan at high concentrations of Gd. We associated this effect to a combination of flow and $T_1/T_2^*$ saturation effects. The transformation from Signal intensity into Concentration [see Eq. (1)], though not using an approximated form, is most probably not valid for the TIC peak area because of $T_2^*$ saturation effects (at high Gd concentration the approximation of negligible $TE/T_2^*$ fails) and because of lack
of linearity of between $R1(t)$ and $C(t)$ at high Gd concentrations (the linearity of $R1(t) = \Re \times C(t) + R10$ fails to hold at high contrast agent concentrations [27]), both effects occurring when measuring AIF in a major artery such as the aorta [35].

This underestimation of the peak amplitude occurred in both GRE sequences, 2D and 3D, with large (140ms) and short (7.9ms) TR, but was more marked in the 2D protocol. Although the relationship between Signal amplitude and Gd Concentration [see Eq. (1)] approximates less well a linear relationship in the 2D protocol, the function described in Eq. (1) did not plateau at the concentration we were estimating in the SSS.

We concluded that it was not the low temporal resolution in sampling that caused the scan to “miss” the top point, but rather other effects such as flow or $T2^*$ decay. Other independent observation in AIFs acquired with high temporal resolution (not shown here) confirmed this hypothesis.

The correction method we applied only partly compensate for this problem. Although the correction algorithm we used did not stabilise the maximum CTC intensity (see Figure 2), it helped stabilizing the fit parameters. This is a consequence of the improved placing of the position of the top, a result of the algorithm. These results suggest that more attention should be paid to the reliability of the actual transformation from signal intensities to Concentration Time curves, and that an algorithm to correct for saturation problems is desirable.

4.3 Fitting functions of the CTC

In this study we used two different fitting functions for the CTCs (CTC1 and CTC2), the more commonly used bi-exponential, and a recently proposed convolution [28]. In this way we wanted to investigate whether keeping the initial rise would improve stability of the fitting parameters. In both cases, fitting of the initial peak was uncertain due to the few sampling points, though we observed that the fitting parameters had a smaller STD using the convolution form, which also takes into account the up-rise of the AIF. This functional form of the AIF can be solved in closed form, and can be inserted into models such as Tofts’ and still result in a closed form solution.

Though the differences were not large, the results are in favour of the convolved function. Again, the correction method improved fitting to both model functions. VIFs were fitted in an unconstrained fashion. Although constrained fitting may help correct the VIF by assigning the peak value of contrast agent [6], it could not be
applied to our data, because this “artificial” peak value would not match the other measured points measured in the initial CTC spike.

CONCLUSIONS
In this work we have investigated how a Vascular Input Function obtained in the SSS varies within a scan as a result of position, across scans within a patient, and across patients within a study. We have found that the individual CTC are well reproducible within the same patient at different sessions though the measured fitting parameters of the measured CTCs are dependent on the protocol parameters, as well as through the type of acquisition used (2D/3D).
We also found that the stability of the fitting parameters of the VIF is dependent on the fitting function: the use of a bi-exponential to fit only the CTC decay appears less stable than fitting the initial peak with a fitting function that models also the wash-in phase.
The lack of temporal information is not the limiting factor in determining the amplitude of the initial spike in the AIF, but it does significantly hamper the determination of the peak position, resulting in oscillating fit parameters of the quick decaying component of the CTC.
It is advisable to use a correction method when using CTCs with low temporal resolutions, as this might improve greatly the fit of the fast decay parameters.
On the basis of this study, and on the fact that we observed protocol dependent differences in the fitted parameters, we conclude that a patient-specific VIF represent a significant advantage over a standard (patient averaged) VIF, and that selecting one slice instead of an averaged signal to reduce computation time is a reasonable approximation. Further research is needed to correct for saturation effect affecting the calculation of the contrast agent concentration.

APPENDIX
A1. Derivation of the Gd Concentration from the Signal ratio
The ratio between the signal intensity after contrast delivery at time \( t \) \((S(t))\) and the signal before delivery \((S(0))\) in a gradient echo sequence can be expressed (neglecting T2* effects) as
\[
\frac{S(t)}{S(0)} = \frac{1 - \exp(-TR/T_1)}{1 - \cos \alpha \cdot \exp(-TR/T_1)} \cdot \frac{1 - \cos \alpha \cdot \exp(-TR/T_{10})}{1 - \exp(-TR/T_{10})}
\]
Assuming linearity between Gd concentration and \( 1/T_1 \),
$1/T_1 = 1/T_{10} + R[Gd]$,

equation A1 can be rewritten as:

$$\frac{S(t)}{S(0)} = \frac{1 - \exp(-TR \cdot (R0 + R[Gd]))}{1 - \cos \alpha \cdot \exp(-TR / T_{10})} \cdot \frac{1 - \exp(-TR / T_{10})}{1 - \cos \alpha \cdot \exp(-TR \cdot (R0 + R[Gd]))}$$

or, with the following substitutions:

$$E = \exp(-TR \times R0)$$

$$RR = \exp(-TR \times R \times [Gd])$$

$$a = \cos(alpha)$$

$$S10 = S(t) / S(0)$$

$$S10(t) = \frac{1 - RR(t) \cdot E}{1 - a \cdot RR(t) \cdot E} \cdot \frac{1 - a \cdot E}{1 - E}$$

the solution of which is

$$RR(t) = -\frac{S10 - S10 \cdot E - 1 + a \cdot E}{E \cdot (S10 \cdot a \cdot E - S10 \cdot a + 1 - a \cdot E)}$$

resulting in

$$TR \cdot R \cdot [Gd] = -\ln\left\{\frac{S10 - S10 \cdot E - 1 + a \cdot E}{E \cdot (S10 \cdot a \cdot E - S10 \cdot a + 1 - a \cdot E)}\right\}, \text{ or}$$

$$[Gd(t)] = -\frac{1}{TR \cdot R} \ln\left\{\frac{S10(t) \cdot (1 - E) - (1 - a \cdot E)}{E \cdot (S10(t) \cdot a \cdot (1 - E) - (1 - a \cdot E))}\right\}$$

A2. Convolution of Equation 3.

The convolution of Eq. (3) $C_p(t) = C_b(t) + C_b(t) \otimes B(t)$

where

$$C_p(t) = b \cdot mb^2 \cdot t \cdot e^{-mb \cdot t}$$

$$B(t) = a \cdot e^{-ma \cdot t}$$

can be developed as follows:

By posing $K_b := b \cdot mb^2$,

$$C_p(t) = b \cdot mb^2 \cdot t \cdot e^{-mb \cdot t} + \int_0^t b \cdot mb^2 \cdot u \cdot e^{-mb \cdot u} \cdot a \cdot e^{-ma(t-u)} du$$

$$C_p(t) = K_b \left\{t \cdot e^{-mb \cdot t} + a \cdot e^{-ma \cdot t} \int_0^t u \cdot e^{-(mb-ma) \cdot u} \cdot du\right\}$$

$$C_p(t) = K_b \left\{t \cdot e^{-mb \cdot t} + a \cdot e^{-ma \cdot t} \left\{\frac{e^{-(mb-ma) \cdot u}}{-(mb-ma)} \left(u - \frac{1}{-(mb-ma)}\right)\right\}_0^t\right\}$$
CHAPTER 6

Reproducibility of the AIF

\[
C_p(t) = K_b \left\{ e^{-mb \cdot t} \left\{ t + \frac{a}{(ma - mb)} \cdot t - \frac{a}{(ma - mb)^2} \right\} + e^{-ma \cdot t} \cdot \frac{a}{(ma - mb)^2} \right\}
\]

With the substitution

\[
\beta := \frac{a}{(ma - mb)^2}
\]

\[
\alpha := 1 + \frac{a}{(ma - mb)}
\]

Eq. (3) can be written as

\[
C_p(t) = K_b \left( \alpha \cdot t \cdot e^{-mb \cdot t} - \beta \cdot e^{-mb \cdot t} + \beta \cdot e^{-ma \cdot t} \right).
\]

REFERENCES


15. Parker, GJM; Roberts, C; Macdonald, A.; Buonaccorsi, G; Cheung, SW; Buckley, DL; Jackson, A.; Watson, Y; Davies, KE; Jayson, G. Experimentally-derived functional form for a population-averaged high temporal resolution arterial input function for dynamic contrast-enhanced MRI Magn Reson Med 2006; 56: 993-1000.


