Determining tumor blood flow parameters from dynamic image measurements

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Abstract. Many recent cancer treatments focus on preventing angiogenesis, the process by which a tumor promotes the growth of large and efficient capillary beds for the increased nourishment required to support the tumor’s rapid growth[1]. To measure the efficacy of these treatments in a timely fashion, there is an interest in using data from dynamic sequences of contrast-enhanced medical imaging, such as MRI and CT, to measure blood flow parameters such as perfusion, permeability-surface-area product, and the relative volumes of the plasma and extracellular-extravascular space. Starting with a two compartment model presented by the radiology community[2], this work challenges the application of a simplification to this problem, which was originally developed to model capillary reuptake[3]. While the primary result of this work is the demonstration of the inaccuracy of this simplification, the remainder of the paper is dedicated to presenting alternative methods for calculating the perfusion and plasma volume coefficients. These methods are applied to model data sets based on real patient data, and preliminary results are presented.

1. Introduction and Motivation
Many modern approaches to cancer treatment focus on the prevention of further cancer growth, specifically by arresting angiogenesis, the process by which a tumor actively promotes the development of a highly efficient capillary bed to feed itself. The goal of this research is to reduce the time it takes to measure the efficacy of such treatments from a timescale of months to a timescale of weeks or even days. In lieu of using static measurement techniques that look at the size of a tumor, this work supports the idea of using time-sequence data to measure the blood flow to the tumor.

Typically, upon the discovery and classification of a cancerous tumor, the patient undergoes a test involving either Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT). In either case, a contrast agent is injected into the patients bloodstream while a sequence of images in the region of interest captures the flow of the tracer. A radiologist looks at these images and tries to estimate the size of the tumor. Upon the recommendation of the oncologist, the patient begins a treatment regiment, and after three to six months, the radiologist repeats the test. If the treatment is working, then the tumor will not have grown since the previous test. However, if the treatment is not working, the patient will have dealt with the devastating side effects of a treatment that has not helped on top of losing six months of treatment time in his or her battle with cancer. Additionally, the high financial cost of cancer treatments lends further justification to determine their efficacy in a timely fashion.
The goal of this research is to use all the time-data from the sequence of images to identify parameters that indicate how blood is flowing in the region of the tumor, such as perfusion, permeability-surface-area product, and relative volumes of the plasma and extracellular-extravascular space. Therefore, if a treatment only takes a few days to start impacting blood flow to the tumor, the efficacy of this treatment can be measured almost immediately.

2. Presentation of the Problem
2.1. Two Compartment Model
Radiologists have already begun research in this area, and in an effort to make this work accessible to the radiology community, the model used is generally accepted as the building block for research in this field [2].

![Diagram of Two Compartment Model](image.png)

**Figure 1.** This quasi-1D model has two compartments through which contrast agent flows in time and space, the plasma compartment inside the capillary and the extracellular-extravascular space (EES) immediately surrounding the capillary.

The flow of contrast agent into, through, and out of an average capillary and surrounding tissue is modeled using a simple two compartment model. The tracer enters the capillary through the arteriole. The tagged blood flows along the length of the capillary, and due to the concentration gradient, oncotic pressure pushes the tracer out of the capillary into the EES compartment. Note the arrow in Figure 1 between the two compartments is bidirectional; this is because as time progresses, the oncotic pressure will be reversed and the capillary will reabsorb the tracer from the EES compartment. This behavior is mathematically represented using basic mass transport equations, resulting in a linear system of two partial differential equations (PDEs).

\[
\begin{align*}
v_p \frac{\partial c_p(x,t)}{\partial t} &= -F L \frac{\partial c_p(x,t)}{\partial x} - P (c_p(x,t) - c_e(x,t)) \\
v_e \frac{\partial c_e(x,t)}{\partial t} &= P (c_p(x,t) - c_e(x,t)),
\end{align*}
\]

subject to: \(c_p(x, t = 0) = 0, c_e(x, t = 0) = 0,\) and \(c_p(x = 0, t) = c_A(t),\) where \(c_p(x,t)\) is the concentration of contrast agent in the plasma, \(c_e(x,t)\) is the concentration of contrast agent in the EES, \(F\) is the blood flow perfusion, \(L\) is the length of the capillary, \(P\) is the permeability surface area product, \(v_p\) is the volume fraction of plasma compartment in the region of interest, and \(v_e\) is the volume fraction of EES compartment in the region of interest. Without loss of generality, the problem can be scaled to the length of the capillary, \(L = 1.\) For the time period of the imaging, it is assumed that \(F, P, v_p,\) and \(v_e\) are constant.

Due to the simplicity of the model relative to the geometric complexity of the body, there is no strong correlation between any spatial data in the test images and the spatial relationships in the model. To create a correlation, each pixel intensity is summed over the whole image for each time step to give the signal intensity, \(S(t).\) The equations are spatially integrated along the length of the capillary, resulting in a system of ordinary differential equations (ODEs). In the equations below, the bars indicate spatial averages.

\[
v_p \frac{d \bar{c}_p(t)}{dt} = F(c_A(t) - c_V(t)) - P(\bar{c}_p(t) - \bar{c}_e(t))
\]

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\[ v_e \frac{d\bar{c}_e(t)}{dt} = P(\bar{c}_p(t) - \bar{c}_e(t)), \quad (4) \]

subject to: \( \bar{c}_e(x, t = 0) = 0 \) and \( \bar{c}_p(x = 0, t) = 0 \), where \( c_A(t) = c_p(x = 0, t) \) is the flow into the model capillary from the arteriole and \( c_V(t) = c_p(x = L, t) \) is the flow from the capillary out of the model into the venule. These equations can be related back to the signal intensity of the sequence of images through following relationship, as the signal intensity of the entire image is given by the sum of the contrast agent in each of the two compartments:

\[ S(t) = v_p \bar{c}_p(t) + v_e \bar{c}_e(t). \quad (5) \]

### 2.2. Morales and Smith Simplification

The left boundary condition, \( c_A(t) \), is known; it is the amount of tracer injected into the capillary as a function of time. Also, the sum of the solution to the ODEs, weighted by the relative volume of each compartment, is also discretely known in time, as this can be determined from the sum of the signal intensity of the pixels in the images in the region of interest. However the right boundary condition, \( c_V(t) \), is not known, and it cannot be explicitly measured easily. Much of the work that has been done on this problem makes an assumption on the right-hand boundary condition to simplify the problem; specifically using the mathematical representation of capillary re-uptake as proposed by Morales and Smith in 1948\(^3\) and applied to this problem by Brix et al. in 1999\(^2\):

\[ c_A(t) - c_V(t) = \frac{1}{r} \left( c_A(t) - \bar{c}_p(t) \right), \quad (6) \]

where \( r \) is a constant between zero and one. By substituting this assumption into the ODEs, one obtains the following modified system of equations

\[ v_p \frac{d\bar{c}_p(t)}{dt} = f(c_A(t) - \bar{c}_p(t)) - P(\bar{c}_p(t) - \bar{c}_e(t)) \quad (7) \]
\[ v_e \frac{d\bar{c}_e(t)}{dt} = P(\bar{c}_p(t) - \bar{c}_e(t)), \quad (8) \]

where \( f = \frac{E}{r} \) is the apparent flow rate. This modified system has been the starting point for a lot of work in this field. Radiologists and mathematicians have proposed various methods to improve parameter measurements starting with this modified system of equations, ranging from enhancing the model with more compartments\(^4\) to more mathematically stable methods\(^5\) to solve the inverse problem of determining the coefficients given weighted information for the sum of the \( \bar{c}_p(t) \) and \( \bar{c}_e(t) \).

While this simplification has many advantages, including the ability to directly solve the resulting ODEs, the assumption seems to be invalid for this application. To illustrate, several sets of model data were created by numerically integrating the original PDEs (1) and (2), using \( c_A(t) = -(t - 0.5)^2 + 0.25 \) as the left boundary condition. This boundary condition was chosen to emulate the parabolic shape that naturally occurs in actual patient data as shown in Figure 2 and Figure 3\(^5\); the time is scaled such that the contrast agent is injected over a time period of 1.

Results are presented for two sets of data, the parameters of which are defined in Table 1.

Using these model parameters and the defined boundary condition \( c_A(t) \), \( \bar{c}_p(t) \) and \( c_V(t) \) are calculated at each time step. Solving (6) for \( r \),

\[ r = \frac{c_A(t) - \bar{c}_p(t)}{c_A(t) - c_V(t)}. \quad (9) \]

By definition, \( r \) should be a constant between 0 and 1, however, by computing the right hand side of (9), it is shown in Figure 4 and Figure 5 that this assumption is not valid.
Figure 2. Actual patient data. Dashed line: injected $c_A(t)$. Solid line: $S(t)$.

Figure 3. Model data. Dashed line: injected $c_A(t)$. Solid line: $S(t)$.

Table 1. Parameter Values for Two Sets of Model Data.

| Data Set | $F$ | $P$ | $v_p$ | $v_e$ |
|----------|-----|-----|-------|-------|
| A        | 2.0 | 1.0 | 0.5   | 0.7   |
| B        | 1.0 | 0.05| 0.5   | 0.7   |

Figure 4. Plot of $r$ given by (9) for Model Data Set A.

Figure 5. Plot of $r$ given by (9) for Model Data Set B.

2.3. Introduction to the Inverse Problem

In the actual medical imaging application, the contrast agent entering the capillary can be measured at each time step. Additionally, the signal intensity of each pixel in a single image can be summed to calculate the total signal intensity $S(t)$ at each time step. Using this information, the problem is to determine the parameters that characterize the blood flow in the region: perfusion, the permeability of the capillaries, and the relative volumes of the capillaries and the surrounding tissue. Correlating this back to the original system of PDEs (1) and (2), given the boundary condition $c_A(t)$ and signal intensity $S(t)$, which is the weighted sum of the integrated solutions $\bar{c}_p(t)$ and $\bar{c}_e(t)$, the problem is to determine the constant coefficients $F$, $P$, $v_p$, and $v_e$. 
3. Determining Unknowns Without Using Morales and Smith Simplification

As illustrated in Figure 4 and Figure 5, the Morales and Smith simplification is not valid for this application. Therefore, the ODEs (3) and (4) are used in lieu of those given by (7) and (8). This section describes methods for accurately calculating two of the four blood flow parameters, along with a method for determining $c_V(t)$. The presented results use data from the two model data sets, A and B. For each of the two data sets, a high fidelity set of truth data is calculated through numerically integrating the PDEs (1) and (2), using $c_A(t) = -(t-0.5)^2 + 0.25$ as the left boundary condition. Subsets of the resulting $c_A(t)$ and $S(t)$ truth data representing $N$ equally spaced time steps are then passed into the algorithms described in the following subsections. This method of downsampling the truth data is used to represent the discrete nature of the image capture process during an actual medical imaging test, but it does not account for noise in the signal. In these preliminary results, noise is not considered, but additional work is in process to measure the sensitivity of these methods to noise.

3.1. Perfusion Coefficient

The perfusion coefficient, $F$, represents the flow rate of the contrast agent along the length of the capillary. This parameter is isolated through algebraic manipulations of the equations. First, (3) and (4) are added to get:

$$v_p \frac{dc_p(t)}{dt} + v_e \frac{dc_e(t)}{dt} = F(c_A(t) - c_V(t)),$$

where the left side is exactly equal to $\frac{dS(t)}{dt}$. Writing the left side as $S'(t)$ and solving (10) for $F$ results in:

$$F = \frac{S'(t)}{c_A(t) - c_V(t)}.$$  \hspace{1cm} (11)

$c_A(t)$ is known for each time step, and $S'(t)$ is calculated numerically for each time step using only the $N$ data points. Instead of using the Morales and Smith simplification to eliminate $c_V(t)$ from (11)[2, 5], it is assumed that $c_V(t) = 0$ for exactly the time it takes for the tracer to travel along the length of the capillary. While this time is not known a priori, (11) can be solved for $F$ by setting $c_V(t) = 0$ for all $t$. Plotting the resulting values of $F$ as a function of $t$, it is clear that the correct value can be extracted before the assumption of $c_V = 0$ becomes invalid. Figure 6 and Figure 7 show the results for Model Data Sets A and B respectively each with $N = 100$, and Table 2 shows the exact and calculated results for both data sets using $N = 100$ and $N = 1000$ time steps.

Figure 6. Plot of $F$ given by (11) for Model Data Set A. The horizontal line represents the actual value of $F$.

Figure 7. Plot of $F$ given by (11) for Model Data Set B. The horizontal line represents the actual value of $F$. 
### Table 2. Actual versus Calculated Values of $F$.

| Data Set | $N$ | Actual $F$ | Calculated $F$ | %-error |
|----------|-----|------------|----------------|---------|
| A        | 100 | 2.0        | 2.04           | 2.0%    |
| A        | 1000| 2.0        | 2.01           | 0.5%    |
| B        | 100 | 1.0        | 1.01           | 1.0%    |
| B        | 1000| 1.0        | 1.00           | 0.0%    |

#### 3.2. Concentration of Contrast Agent Exiting the Capillary via the Venule

Recall that the reason for invoking the Morales and Smith simplification was the difficulty of measuring $c_V(t)$ [2]. Instead, $c_V(t)$ can be directly calculated using the value of $F$ computed using the method described in the previous section. Solving (11) for $c_V(t)$ gives

$$c_V(t) = c_A(t) - \frac{S'(t)}{F}$$

where the entire right hand side is known. Figure 8 and Figure 9 show the comparison between the truth data for $c_V(t)$ and the values calculated using (12) for Model Data Sets A and B, $N = 100$.

#### 3.3. Volume of the Plasma Compartment

The first step to recover the coefficient that represents volume of the plasma compartment is to determine the time, $t^*$, it takes for the contrast agent to travel along the length of the capillary. The value of $t^*$ is found by examining the calculated data for $c_V(t)$ to find the first time the data is greater than some threshold, $\epsilon$, greater than zero.

Dividing the original PDE (1), by $v_p$ and recalling that the problem is scaled to the length of the capillary, $L = 1$,

$$\frac{\partial c_p(x,t)}{\partial t} = -\frac{F}{v_p} \frac{\partial c_p(x,t)}{\partial x} - \frac{P}{v} \left( c_p(x,t) - c_e(x,t) \right),$$

where $\frac{F}{v_p}$ is the rate at which the contrast agent travels along the length of the capillary. Relating this rate, $\frac{F}{v_p}$, with the time, $t^*$, and again recalling $L = 1$,

$$v_p = Ft^*.$$
Table 3 presents the calculated value of $t^*$ along with the actual and calculated values of $v_p$ with the percent error for both Model Data Sets A and B, using $N = 100$. The results presented in Table 3 for both the actual and calculated values of $t^*$ were recovered using a threshold of $\epsilon = 0.005$.

Table 3. Actual versus Calculated Values of $t^*$ and $v_p$.

| Data Set | Actual $t^*$ | Calculated $t^*$ | $t^*$-%-error | Actual $v_p$ | Calculated $v_p$ | $v_p$-%-error |
|----------|--------------|------------------|--------------|-------------|-----------------|---------------|
| A        | 0.2572       | 0.2500           | 2.80%        | 0.5         | 0.5100          | 2.00%         |
| B        | 0.4942       | 0.4900           | 0.85%        | 0.5         | 0.4949          | 1.02%         |

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