Comprehensive Modeling of the Spatiotemporal Distribution of PET Tracer Uptake in Solid Tumors based on the Convection-Diffusion-Reaction Equation


Abstract— In this paper, the distribution of PET tracer uptake is elaborately modeled via a general equation used for solute transport modeling. This model can be used to incorporate various transport parameters of a solid tumor such as hydraulic conductivity of the microvessel wall, transvascular permeability as well as interstitial space properties such as pressure. This is especially significant because tracer delivery and drug delivery to solid tumors are determined by similar underlying tumor transport phenomena, and quantifying the former can enable enhanced prediction of the latter. First, based on a mathematical model of angiogenesis, the capillary network of a solid tumor and normal tissues around it were generated. The coupling mathematical method, which simultaneously solves for blood flow in the capillary network as well as fluid flow in the interstitium, is used to compute pressure and velocity distributions. Subsequently, we applied a comprehensive convection-diffusion-reaction equation to accurately model distribution of PET tracer uptake, specifically FMISO in this work, within solid tumors. The abovementioned use of partial differential equations (PDEs), beyond ordinary differential equations (ODEs) as commonly invoked in tracer kinetic modeling, enables simultaneous modeling of tracer distribution over both time and space. For different angiogenetic structures, the intravascular pressure and interstitial pressure were elaborately calculated across the domain of interest, and used as input to model tracer distribution. The results can be utilized to comprehensively assess the impact of various parameters on the spatiotemporal distribution of PET tracers.

I. INTRODUCTION

Molecular imaging methods especially utilizing positron emission tomography (PET) have found increasing applications in a variety of cancers, including diagnosis, initial staging, restaging, prediction and monitoring of treatment response, surveillance and prognostication [1]. Routine clinical applications include qualitative interpretation of PET studies. At the same time, PET imaging also enables quantitative measurements of radioactivity concentrations over time across the body and in the tumor(s) of interest. The most commonly utilized techniques include (i) static (single time-frame) imaging invoking the standardized uptake value (SUV), and (ii) dynamic imaging, invoking simplified tracer kinetic modeling using Patlak modeling [2]–[7].

Critical knowledge of the tumor environment can be obtained by linking the tissue time activity curve (TAC) to the underlying tumor physiology, which in turn can help determine the most sensible course of action. Patlak plots [8] and conventional compartment models [9], [10] have the limitation that they do not model movement of tracer between compartments at different physical locations, e.g., through diffusion or convection. Furthermore, it is difficult to use these models to investigate the consequences of perturbing the underlying physiology, since actual physical quantities, such as permeability and the local vascular supply, can be hidden within compound parameters. The solute transport equation which includes diffusion, convection and reaction is widely used to simulate drug delivery [11], referred to as the convention-diffusion-reaction (CDR) equation. Baxter and Jain, based on the theoretical framework in their 1D mathematical method, found the effective factors on drug delivery [12]–[15]. Wang and Li [10] used modified MRI images and convection-diffusion equation for tumor geometry. They considered interstitial fluid flow with blood and lymphatic drainage in their model. Wang et al. [11] studied the effect of elevated interstitial pressure, convective flux, and blood drainage on the delivery of specified solute to brain tumors. Magdoom et al. [16] used a simplified model of CDR for predicting albumin tracer distribution in the lower limb of a mouse. They used a dynamic contrast enhanced (DCE)-MRI based computational model [17], [18] to estimate the spatial variation of transport properties in intestinal space. Stylianopoulos and Jain [19] used the CDR equation to investigate effects of vascular normalization for improving perfusion and drug delivery in solid tumors. They extent their work by considering the surface charge of the drug and the resulting electrostatic relations [20].

The ability to predict sensitivity of a given tumor to specific therapeutic agents is the "holy grail" in personalized cancer medicine. We note that tracer delivery and drug delivery to solid tumors, the former used in diagnostic imaging and the latter in therapy, are determined by similar underlying tumor transport phenomena. To this end, we have utilized the CDR equation that we have previously used for assessment of drug delivery [11], [19], to comprehensively model the spatiotemporal distribution of PET tracers in solid tumors, focusing in the present work on the tracer FMISO.
This approach is based on the use of partial differential equations (PDEs), in contrast to ordinary differential equations (ODEs) as commonly utilized for tracer kinetic modeling, and enables the assessment of tracer distribution in both time and space. This in turn allows quantification of the impact of various parameters, including tumor angiogenic factors, microvessel and interstitial pressures, and hydraulic conductivity and permeability, amongst others, on the distributions. Such comprehensive modeling may then be utilized in inverse methods, including the use of dynamic FMISO imaging, potentially aided by other modalities such as CT or MRI, to enable enhanced prediction of drug delivery to solid tumors.

There have been few works in this area. Kelly et al. [21] used a simplified form of the CDR equation for investigation of FMISO distribution. Monnich et al. [22], [23] modified Kelly’s approach to investigate the influence of acute hypoxia on FMISO retention and the potential to distinguish between retention from chronic and acute hypoxia in serial (or single dynamic) clinical PET scans. In the above works, the spatial scale was in the order of a few millimeters. Furthermore, the applications did not include convection transport from vessel to tissue or within tissue. Finally, the dynamic (spatially variable) structure of the microvascular networks was not incorporated to compute the variable pressure/flow distributions across the networks. The present study by contrast uses a general, comprehensive framework that includes a dynamic microvascular structure, and the effects of both intravascular and extravascular flow and their stimuli, including both diffusion and convection, are incorporated. This framework is applicable to different tracers, and tumors of varying sizes, and for images spanning short, intermediate or long durations of time post-injection.

In Section 2, we discuss our overall methods for modeling fluid flow in the interstitium and the microvessel network as developed in our previous work [11], [24], and using these for computation of tracer distribution based on the CDR equation. In section 3, we show our results and various analyses to assess performance of our framework. Sections 4 and 5 discuss and conclude the work, respectively.

II. METHODS

A. Solute transport in tissue:

In the macroscopic solute transport model, the variations on the length scale of capillary distances are not included, but averaged over some region that is small compared to the length scale of the tumor radius. The general model for solute transport in tissue includes transport in interstitium, reaction mechanism (binding to the cancer cells/matrix). The derivation of this model is elaborated in Appendix A, to which the reader is referred.

General form of Solute transport equation: The general form of solute transport in tissue involves the diffusive and convective transport of the free tracer within the tumor interstitium as well as reaction rate (CDR equation) [17], [19], [20], as derived in Appendix A:

\[
\frac{\partial C_j}{\partial t} = \nabla \cdot (D_{ij} \nabla C_j) - v_i \nabla (C_j) + \frac{K_{ij}}{V_L} \frac{N_j}{C_j} + \frac{k_{ij}}{V_L} \frac{N_j}{C_j} + \frac{C_j}{t_{on}} + \frac{-k_{ij}}{t_{off}}
\]

(1)

B. Compartmental model and spatiotemporal distribution mode

In this section, our main framework to model spatiotemporal distribution based on the CDR equation is compared to the compartmental model. The CDR equation involves solute transport between blood and lymphatic vessels and interstitium, solute transport between free solute and produced or bound solute due to reaction, as well as spatiotemporal distribution of solute in interstitium. It is comparable with the traditional model for solute distribution, namely the compartmental model.

The compartmental model is a commonly invoked approach to model and quantify solute transport. In this framework, concentration in each region of interest (ROI; e.g. an entire organ, or as small as a voxel of interest) is assumed to be independently distributed. Subsequently, ordinary differential equations are utilized to model the distribution of activity over time in each ROI. By contrast, in the CDR model, distributions in space are not modeled as independent from one another, and partial different equations, involving both time and space, are invoked, to collectively model solute distribution over time and space.

To see this better, let us consider a commonly invoked form of solute transport in compartmental modeling involving four compartments, also referred to as the three-tissue compartmental model (shown in Figure 1). From arterial blood, the solute passes into the second compartment, known as the free compartment. The third compartment is the region of specific binding. The fourth compartment is a nonspecific-binding compartment that exchanges with the free compartment. For more simplicity, it is commonly assumed that there is rapid exchange between the free and nonspecifically bound compartments, and that these two compartments can be combined together [25]. Therefore the three tissue compartmental model is changed to the two tissue compartmental model (Figure 2). This model fits many radioligand tracers well such as [18F] FMISO which is considered in this study.

The CDR model is related to the two-tissue compartmental model with some differences in the free compartment. For the free compartment, it is considered that the solute is redistributed in time and space. Figure 3 demonstrates how the CDR equation is related to a two-tissue compartment reversible binding model [9]. Movement between plasma, free and bounds states is governed by four parameters, \(L_1, L_2, L_3\) and \(L_4\), analogous to the rate constants \(K_1, K_2, K_3\) and \(K_4\) seen in conventional compartmental models (e.g., [25]). The parameters in Figure 3 are defined as follow:
\[ L_1 = \left( \frac{L_p S}{V} (P_v - P_i - \sigma_i (\pi_v - \pi_i)) (1 - \sigma_i) + \frac{P_n S}{V} P_e \rho e^{-\frac{1}{a}} \right) \]  
(2)

\[ L_2 = \left( \frac{P_n S}{V} P_e \right) + \phi_i \]  
(3)

\[ L_3 = k_{oa} \]  
(4)

\[ L_4 = k_{ef} \]  
(5)

where \( \phi_i = \left\{ \begin{array}{l} \frac{L_{pg} S_L}{V} (P_v - P_L) \quad \text{Normal Tissue} \\ 0 \quad \text{Tumor Tissue} \end{array} \right. \)

and the various terms are defined in Tables 1 and 2. Based on the elaborate form of the CDR equation (Appendix A), Equation (1) is given by:

\[ \frac{\partial C_f}{\partial t} = D_{eff} \nabla^2 C_f - \nabla \cdot (v_c C_f) + L_{ec} C_f - L_{ec} C_f - L_{ec} C_f + L_{ec} C_f \]

\[ \frac{\partial C_b}{\partial t} = L_{ec} C_f - L_{ec} C_f \]

By contrast, the standard two-tissue compartmental model (shown in Figure 3) is given by [26], [27]:

\[ \frac{\partial C_f}{\partial t} = K_1 C_p - k_2 C_f - k_3 C_f + k_4 C_f \]

\[ \frac{\partial C_b}{\partial t} = k_3 C_f - k_4 C_f \]

If the spatial redistribution terms (i.e. diffusion and convection; the first and second terms in the right hand side of in Equation (6)), are neglected, it will resemble Equation (7).

Table 1. Summary of parameters related to normal and tumor tissues, and typical values used in our simulations [11]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pi_p ) mmHg</td>
<td>Osmotic pressure of the plasma</td>
<td>20(normal) 20(tumor)</td>
</tr>
<tr>
<td>( \pi_i ) mmHg</td>
<td>Osmotic pressure of the interstitial fluid</td>
<td>10(normal) 15(tumor)</td>
</tr>
<tr>
<td>( S/V ) cm(^{-4})</td>
<td>Surface area per unit volume for transport</td>
<td>70(normal) 200(tumor)</td>
</tr>
<tr>
<td>( \sigma_s )</td>
<td>Average osmotic reflection coefficient</td>
<td>0.91(normal) 0.82(tumor)</td>
</tr>
<tr>
<td>( L_{ec} ) cm/mmHg s</td>
<td>Hydraulic conductivity of the microvascular wall</td>
<td>0.36×10(^{-7})(normal) 2.80×10(^{-7})(tumor)</td>
</tr>
<tr>
<td>( P_i ) [mmHg]</td>
<td>Hydrostatic pressure of the lymphatic</td>
<td>0 (normal)</td>
</tr>
<tr>
<td>( L_{pg} S_L/V ) [1/mmHg s]</td>
<td>Lymphatic filtration coefficient</td>
<td>1.33×10(^{-5})(normal)</td>
</tr>
</tbody>
</table>

Table 2. Summary of parameters related to tracer transport, and typical values used in our simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_{eff} ) (mm(^2)/s)</td>
<td>Effective diffusion coefficient</td>
<td>0.7×10(^{-5})(n) 2.5×10(^{-5})(t)</td>
</tr>
<tr>
<td>( P_n ) (m/s)</td>
<td>Transvascular permeability of the vessel to the tracer</td>
<td>2.4×10(^{-5})(n) 9.4×10(^{-5})(t)</td>
</tr>
<tr>
<td>( K_1 ) (1/min)</td>
<td>Constant transport rate from blood to tissue</td>
<td>0.45 calculated</td>
</tr>
<tr>
<td>( K_2 ) (1/min)</td>
<td>Constant transport rate from tissue to blood</td>
<td>0.45 calculated</td>
</tr>
<tr>
<td>( k_{of} ) or ( k_f ) (1/min)</td>
<td>Association (binding) rate</td>
<td>8×10(^{-3})(hypoxia) 1×10(^{-3})(normoxia)</td>
</tr>
<tr>
<td>( k_{of} ) or ( k_f ) (1/min)</td>
<td>Dissociation rate</td>
<td>0</td>
</tr>
</tbody>
</table>

C. Computational domain and mathematical equation:

As mentioned before, FMISO is considered as tracer of interest in this study.
The 2D domain (shown in Figure 4) considered for computational simulation is a 6×3 cm² rectangle. The tumor is located at the center of the domain with the radius of 1.2 cm. The two parent vessels from which the vascular network grows are located at the left and right edges of the domain.

![Figure 4. A schematic of the solution domain.](image)

For capillary network, an elaborative model is incorporated based on our previous work [24], [30], [31] to generate a microvascular network induced by tumor angiogenesis. This mathematical model captures the capillary formation by tracking the motion of endothelial cells in capillary sprout tips. On both sides of the domain, parent vessels are considered to be sources of new capillaries. Capillaries start to migrate within the domain and reach the tumor. The details of rules for sprouting angiogenesis and algorithms for this method are outlined in our previous work [32], and by Anderson and Chaplain [33], and some results are shown in result section.

**Intravascular and interstitial flow:** Some of the parameters in Equation (1) are related to fluid flow in interstitium and blood flow in capillaries. An advanced mathematical model is used to calculate interstitial velocity and pressure and intravascular pressure. The details and mathematics of the framework are explained in our previous studies [11], [24], [30], [31], [34], [35].

**D. General equation for tracer transport**

**CDR equation:** In the modeling of tracer distribution in tissue with capillary network, the third and fourth terms of Equation (1) are implemented wherever the capillary exists and for other places these terms are zero. To show this more systematically, the mathematical form of our elaborate tracer transport model in tissue is given by:

\[
\begin{align*}
\frac{\partial C}{\partial t} &= D_{\text{eff}} \nabla^2 C_j - \nabla \cdot \left( \mathbf{v} C_j \right) \\
&+ L_i C_j - L_i C_j + L_k C_k \quad \text{where blood source exists} \\
\frac{\partial C_j}{\partial t} &= D_{\text{eff}} \nabla^2 C_j - \nabla \cdot \left( \mathbf{v} C_j \right) \\
&- L_i C_j + L_i C_i \\
\frac{\partial C_i}{\partial t} &= L_i C_i - L_i C_i \\
C_{\text{total}} &= C_j + C_k
\end{align*}
\]  

(8)

where \( L_i \) and \( L_k \) were defined previously.

**Solution of Kinetic model:** The Solution of Equation (7) yields to the following expression for \( C_{\text{total}} \):

\[
C_{\text{total}} = \frac{K_{0}}{\alpha_2 - \alpha_1} \left[ (k_1 + k_4 - \alpha_1) e^{-\alpha_1 t} + (\alpha_2 - k_1 - k_4) e^{-\alpha_2 t} \right] \otimes C_r
\]

(9)

where \( \otimes \) denotes the convolution operation, and

\[
\alpha_{1,2} = \left[ k_2 + k_3 + k_4 + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_3} \right] / 2
\]

(10)

**E. Oxygen pressure distribution:**

In the case of FMISO, tracer uptake rate is modulated by oxygen distribution. The oxygen distribution in tissue with capillary network can be modeled via a reaction-diffusion model [36]. Oxygen pressure is used instead of concentration due to the direct relationship between \( O_2 \) concentration and partial pressure (Henry’s law):

\[
\frac{\partial P_{O_2}}{\partial t} = D_{o_2} \nabla^2 P_{O_2} - q_{\text{met}} + F_s
\]

(11)

where

- \( P_{O_2} \): Oxygen pressure in tissue.
- \( D_{o_2} \): The diffusion coefficient of oxygen.
- \( q_{\text{met}} \): The rate of oxygen metabolism as a function of oxygen pressure.
- \( F_s \): The rate of oxygen supplied from the blood vessels.

The constitutive equation for \( F_s \) is given by Equation (12) [36]:

\[
F_s = \frac{P_{\text{mos}} S}{V} \left( P_{O_2,\text{tissue}} - P_{O_2} \right) \quad \text{for existence of blood source}
\]

(12)

where

- \( P_{\text{mos}} \): The transvascular permeability of \( O_2 \).
- \( P_{O_2,\text{tissue}} \): The oxygen pressure in the vessels.

\( q_{\text{met}} \) is calculated based on the most common model (Michaelis-Menten) [36]:

\[
q_{\text{met}} = \frac{q_{\text{max}} P_{O_2}}{P_{O_2} + P_0 a_2}
\]

(13)

where

- \( q_{\text{max}} \): Maximum \( O_2 \) consumption rate.
- \( P_0 a_2 \): The oxygen pressure at which \( q_{\text{met}} \) is half-maximal (Michaelis-Menten coefficient).

The values used in oxygen distribution are summarized in Table 3. The \( k_{\text{on}} \) or \( k_s \) for FMISO depends non-linearly on the local oxygen concentration, as follows [22], [23]:

\[
k_3 = F_1(P) \cdot F_2(P)
\]

(14)

\[
F_1(P) = \frac{k_{\text{max}} P}{P + P_1}
\]

(15)

\[
F_2(P) = \left( \frac{P}{P + P_2} \right)^\alpha
\]

(16)

**F. Model parameterization and simulation details**

The parameters used in Equation (8) as related to tumor or normal tissues were listed in Table 1, and the parameters of tracer transport were listed in Table 2. Table 3 lists...
parameters related to oxygen transport, and values utilized in our simulations.

Table 3. Summary of parameters related to oxygen transport

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Refer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D_{o_2}) (m²/s)</td>
<td>Diffusion coefficient of oxygen</td>
<td>2\times10^{-3}</td>
<td>[37]</td>
</tr>
<tr>
<td>(Pm_{o_2}) (m/s)</td>
<td>transvascular permeability of (O_2)</td>
<td>4.1\times10^{4}</td>
<td>[36]</td>
</tr>
<tr>
<td>(q_{\text{max}}) (mmHg)</td>
<td>Max. (O_2) consumption rate</td>
<td>15</td>
<td>[38]</td>
</tr>
<tr>
<td>(P_{\text{D}O_2}) (mM)</td>
<td>Michaelis-Menten coefficient</td>
<td>2</td>
<td>[36], [38]</td>
</tr>
<tr>
<td>(P_{O_2,\text{vessel}}) (mmHg)</td>
<td>Vessel oxygen pressure</td>
<td>40</td>
<td>[39]</td>
</tr>
<tr>
<td>(k_{\text{max}}) (1/a)</td>
<td>Maximum binding rate</td>
<td>1.7\times10^{4}</td>
<td>[23]</td>
</tr>
<tr>
<td>(P_1)</td>
<td>(P_o) inhibiting binding by 50%</td>
<td>1.5mmHg</td>
<td>[40]</td>
</tr>
<tr>
<td>(P_2)</td>
<td>(P_o) inducing 50% necrosis</td>
<td>0.1mmHg</td>
<td>[23]</td>
</tr>
<tr>
<td>(k)</td>
<td>Determines step width at (P_2)</td>
<td>0.3</td>
<td>[23]</td>
</tr>
</tbody>
</table>

The boundary conditions considered for intravascular flow are:

\[ \begin{align*}
P_{\text{vessel 1}} &= 25\text{mmHg} \\
P_{\text{vessel 2}} &= 5\text{mmHg}
\end{align*} \]

For the boundary between tumor and normal tissues, the continuity of concentration and its flux are considered as boundary conditions:

\[ \begin{align*}
\left( D_{\text{eff}} \nabla C + v_C \right)_i &= \left( D_{\text{eff}} \nabla C + v_C \right)_t \\
C_i &= C_t
\end{align*} \]  

(17)

The open boundary condition is used for the edges of domain. The open boundary is used to set up mass transport across boundaries where both convective inflow and outflow can occur and defined by Equation (18):

\[ -\mathbf{n} \cdot \nabla C = 0 \]  

(18)

where \(\mathbf{n}\) is the normal vector.

III. INVERSE METHOD (PARAMETER ESTIMATION)

In what we will refer to as “forward modeling”, we assume that all physical parameters are known and can thus use appropriate physical laws and scientific theories to predict responses to stimuli. Most well-known numerical models are built to be used as forward models—that is, their input includes parameter estimates and their output is a prediction of system response. By contrast, inverse modeling is concerned with those cases where we have already measured actual responses to stimuli in the field or in laboratory, and would like to work backwards, or “invert”, from the data to estimate the physical parameters of the system (this is also referred to as parameter estimation, history matching, or data fitting.)

The present work is primarily concerned with establishing the forward model using the CDR framework in the context of radiotracer distribution, emphasizing that tracer delivery and drug delivery to solid tumors, the former used in diagnostic imaging and the latter in therapy, are determined by similar underlying tumor transport phenomena. At the same time, this framework renders itself to enhanced parameter estimates. Two important outcomes are expected in the context of the inverse problem: enhanced parameter estimates (\(K_1\)-\(K_3\)), as well as estimation of the diffusion coefficient from radiotracer imaging, which has not been performed, to our knowledge, in past studies. This is subject of ongoing work, and detailed analysis. However, we show some preliminary results in the present work.

We consider that the diffusion coefficient (\(D_{\text{eff}}\)) in the tumor region (Equation (8)) is unknown, and concentration of tracer over time in the tumor region is available via imaging data. Gaussian-distributed noise was added to imaging data, to simulate varying levels of noise present in imaging. Given a set of experimental data of tracer concentration (\(C_i(x_j, y_j, t_j)\)) at N sampling points and M time step, the following nonlinear least squares objective function is defined:

\[ S = \sum_{j=1}^{M} \sum_{i=1}^{N} (C_i(x_j, y_j, t_j) - Y(x_j, y_j, t_j, D_{\text{eff}}))^2 \]

(19)

where \(Y(x_j, y_j, t_j, D_{\text{eff}})\) is the calculated tracer concentration based on equations (8). By minimizing \(S\), a set of optimal values of the parameter were obtained. The Levenberg-Marquardt method was utilized in this study in order to minimize the objective function \(S\). The LM method is an iterative technique which finds the unknown parameters as the minimum point of function \(S\) is reached. The inverse algorithm used in this work is shown in Figure 5.

IV. RESULTS

Two different networks generated via the discrete angiogenesis method are used in the calculations. One of the networks is produced by 3 sprouts as initial condition and modifying tumor angiogenic factor (TAF) conditions in the tumor region for generation less uniform tumoral coverage. The other network is initialized by 10 sprouts in two parent vessels for producing particular angiogenetic capillary network in tumor domain like as experimental observation. The intravascular pressure distributions in the network and interstitial pressure in tissues are shown in Figure 6 and...
The interstitial pressure has its greatest value in the tumor region, since in this region there is no lymphatic system, and blood vessels are highly leaky. The maximum interstitial pressure for both networks is around 2000Pa.

The resulting oxygen distributions for the two different networks are shown in Figure 8 and Figure 9. Since the oxygen distribution reaches steady state condition very soon, the results are nearly independent of time. The simulated $PO_2$ strongly decreases with increasing distance from the vessels. Therefore, the close up of the results near the vessel is also shown in Figure 8 and Figure 9. The oxygen pressure profile from vessel into tissue is shown in Figure 10.

Tracer distribution: In this section, the tracer distribution of FMISO is investigated. A plasma activity as obtained from Backes et al. [42] was used in this part of the analysis. The spatiotemporal concentration distributions of FMISO at different post injection times for networks 1 and 2 are shown in Figure 12 and Figure 13, respectively. The second network shows more uniform distribution than network 1. This is due to a higher number of vessels in the network, which act as source terms for the tracer. The increasing of effect C1 in areas distant from vessels observed in Figure 12 and Figure 13 would not have been observed if interstitial transport (diffusion, convection) was not considered, as there is no other means for tracers in the vicinity of vessels to make it to hypoxic regions.

Figure 14 depicts the average FMISO uptake, respectively, across the tumor tissue. The results include those from the proposed comprehensive CDR-based approach. Furthermore, the results are compared with the conventional analytical method (standard kinetic modeling) using ODEs, though the latter lacks sophistication of simultaneous spatiotemporal modeling. Since the ODE-based analytical method in conventional kinetic modeling gives tracer activity levels that are spatially independent, the CDR results were also averaged in space to eliminate dependency of tracer value on position thus obviously lacking the details shown in previous images. The results show that the trend of the graphs for the conventional analytical method and the proposed CDR model is the same. The differences between the analytical method and current approach in network 1 (sparse network) is more than that of network 2.

CDR model validation: We utilized experimental observations of Bruehlmeier et al [41]. Figure 11 shows comparison of average concentration of FMISO in tumor region with experimental data. The CDR equation produces results that are in good agreement with experimental data. We emphasize that this comparison with experimental data is for demonstration purposes, and that future work (see discussion) consists of focusing on the inverse problem, namely to estimate micro-parameters that produce fits to experimental data. At the same time, in the next part, we perform further analysis including comparisons with conventional ODE-based analytical methods, with similar modeled parameters.
Since averaging the tracer activity across the tumor oversimplifies the available information, we also investigated the tracer activity at some specified points across the tumor. These points are shown in Figure 15. The results of C1 and C2 are shown in Figure 16. The results show that tracer distribution especially for C1 is highly spatially dependent. However, at points close to vessels, tracer uptake for both networks is nearly the same. The comparison of results between conventional analytic vs. comprehensive model shows that the tracer uptake better agrees at points near the vessels.

Parameter estimation:
As mentioned in section 4, it is assumed that the diffusion coefficient is unknown. The concentration of points at network 2 shown in Figure 15 is used as experimental data. Three sets of data examined in this study include:
(1) Noise-free data,
(2) Realizations of data containing 1% Gaussian-distributed noise, and
(3) Realizations of data containing 10% Gaussian-distributed noise.
The inverse problem results obtained are listed in Table 4. The estimated parameters are implemented in the direct code with previous plasma activity for comparison of the results with new estimated parameters and real values. The maximum error \(\left|\frac{C_{\text{estimated}} - C_{\text{real}}}{C_{\text{real}}}\right|\) in the results based on estimated parameter and results based on real value is 4.2%.

V. DISCUSSION
In our general CDR expression, all terms related to solute transport from vessels to tissue or vice versa, as well as within tissue, and tracer binding to cells/matrix are considered. The interstitial fluid flow coupled with intravascular flow through a tumor induced dynamic capillary network (adaptable size of capillaries diameter based on different stimuli) is also modeled and is used in the CDR equation.
The elevated interstitial pressure in tumor region is also shown in experimental observation of Huber et al. [43]. They measured the IFP for different tumors between 1.1 kPa to 1.8 kPa. Since the FMISO uptake depends on the oxygen levels in the tissue, the oxygen distribution has to be solved first in this part of the study. The oxygen distribution shows that the Po2 decreases to low values around 2 mmHg at a distance of about 150 μm from vessels. empirical data [37], [44], [45] confirm this observation. The low diffusivity of oxygen is the reason that in the first network the hypoxia region is much larger than what occurs in the second one.

Tracer distribution is both time and space dependent. This spatiotemporal distribution enables the investigation of the relationship between image data and molecular processes. The incorporation of both transport phenomena (diffusion and convection) enables application of our overall framework to PET studies of tumors with varying extents and as acquired over short or long durations of time. Radiolabeled antibodies and tyrosine kinase inhibitors (i.e. immune-PET and TKI-PET) pose another great area of application, for better understanding of the in vivo behavior and efficacy of monoclonal antibodies (MAbs) and TKI targeted drugs in individual patients and for more efficient drug development [46].

The tracer distribution in time has agreement with the general trends of experimental data [47], [48]. The activity level of tissue follows plasma activity level in the early stages. In early stages, the free concentration is dominant. The binding portion has significant value only at later stages. The comparison of our CDR model vs. the analytical method based on kinetic compartment method shows that two methods predict similar patterns for tracer distribution. However, the results of these two methods have differences. The results of the analytical method are similar to network 2 (dense network). Generally, the results (Figure 14) demonstrate that the tracer distribution depends on the structure of the microvascular network. The evaluation of the spatially averaged results shows that the dependency of FMISO uptake in the first tissue compartment C₁ on the microvascular network reduces as time goes on. Since the total concentration value at increasing time steps is more dominated by the bound state than the free state of the tracer, and since FMISO binding for the hypoxic region (the region distant from the network) is higher than for normoxic region, overall FMISO uptake in very considerable at points distant from blood vessels at later times.

Results of FMISO uptake show that the activity level of FMISO in hypoxic regions is high which has been reported in [21], [49], which is a very good motivation for the use of FMISO in the study of hypoxia [28], [29]. The result of the first network with more hypoxic regions shows this effect clearly (Figure 12).

The comparison of the average uptake for FMISO demonstrates that the activity level depends on the network structure as well. This is because our approach incorporates the impact of interstitial diffusion and convection. For the 1st network, due to the highly inhomogeneous angiogenic structure, tracer delivery to some cells are limited, lowering uptake.

Our ongoing work focuses on detailed analysis of the inverse problem of estimating parameters of interest from imaging data. This includes modeling of the various PET detection and degradation processes [50], [51], leading to image blur and noise, and constructing appropriate numerical non-linear regression paradigms incorporating the comprehensive solute transport model within it to estimate the parameters of interest.

### VI. Conclusion

A comprehensive numerical approach which couples the mathematical model of the microvascular network and the interstitial flow with the mathematical model of general solute transport was utilized to study the distribution of PET tracers. The tracer distribution model incorporated convection and diffusion transport from vessels to tissue and within tissue, as well as the reaction mechanism. The present work focused on the application of the framework to FMISO, demonstrating the ability of this approach to shed light on the spatiotemporal distribution of PET tracers, beyond the usage of conventional methods. The proposed methodology enables assessment of the impact of various tumor related parameters and phenomena on tracer distribution, thus providing a condition to analyze sensitivity of tracer distributions upon physiological parameters. Furthermore, this framework can be utilized in an inverse model for potentially enhanced estimation of parameters of interest, as the forward-model is more accurate, as well as estimation of the diffusion coefficient from PET tracers, which, to our knowledge, has not been achieved in the past. Overall, the proposed model provides a framework for the analysis of PET tracer distribution that moves beyond conventional computational methods including ODE-based kinetic compartment modeling.

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Diffusion and convection:

For fluid flow in a porous medium, free solute transports are due to two important mechanisms: diffusion and convection. The solute mass flux \( J \) which includes both diffusion and convection is obtained by Fick’s first law \([52]\). Then, by applying Fick’s second law, mass conservation is obtained \([53]–[55]\) (Equation (1)):

\[
\nabla \cdot \vec{J} = -\frac{\partial}{\partial t} \left( C_f \right)
\]

(20)

where \( \vec{J} \) is the solute mass flux, and \( C_f \) is the free solute concentration.

Equation (1) simply states that the net mass output per unit volume is equal to the time rate of change of mass within the volume.

The solute mass flux \( \vec{J} \) has both diffusion and advection fluxes \([53]\):

\[
\vec{J} = -D \nabla C_f + v_i (C_f)
\]

(21)

The first term on the right hand side is the diffusion flux, in which \( D \) is the diffusion coefficient. The second term is the convection flux, due to \( v_i \), the velocity of the fluid flow. Substituting Equations (21) into Equation (1) results in

\[
\nabla \cdot \nabla \left( D \nabla C_f \right) - \nabla \cdot \left[ v_i (C_f) \right] = \frac{\partial C_f}{\partial t}
\]

(22)

The second term on the left hand side of Equation (5) can be written as

\[
\nabla \cdot \left[ v_i (C_f) \right] = \nabla \cdot \left( v_i \nabla C_f \right) + v_i \nabla \cdot \left( C_f \right)
\]

(23)

If there is no changes in fluid density because of the solute transport process, the solute transport does not have any effects on the flow velocity field, \( v_i \), and \( v_i \) can be calculated independent of the solute concentration field. In a steady fluid flow field, the governing equation is simplified to Darcy’s law \( v_i = -\kappa \nabla P \) \([52]\) where \( \kappa \) is hydraulic conductivity and \( \nabla P \) is the pressure gradient. In this case, the divergence of the fluid velocity field vanishes, as in the Equation (24),

\[
\nabla \cdot v_i = \nabla \cdot \left( -\kappa \nabla P \right) = 0
\]

(24)

Under the steady state flow assumption, Equation (23) is simplified to

\[
\frac{\partial C_f}{\partial t} = \nabla \cdot \left( D \nabla C_f \right) - v_i \cdot \nabla \left[ C_f \right]
\]

(25)

Equation (25) is the governing equation for solute transport in a steady fluid flow field. In a porous media, the same equation can be applied, if there is no solute source or solute sink. However, in the most biological tissues there are sources and sinks. For example, between interstitial space and the blood or lymph vessels fluid is exchanged; therefore, the steady state form of the Equation (25) in this case can be written as \([56]\):

\[
\frac{\partial C_f}{\partial t} = \nabla \cdot \left( D \nabla C_f \right) - v_i \cdot \nabla \left[ C_f \right] + \Phi_r - \Phi_L + R
\]

(26)

where \( \Phi_r \) is the rate of solute transport per unit volume from blood vessels into the interstitial space, \( \Phi_L \) is the rate of solute transport per unit volume from the interstitial space into lymph vessels, and \( R \) is the rate of solute production and consumption per unit volume due to chemical reactions. In following, the source and sink and also chemical reaction are defined.

Solute transport across vessel:

Solute transport across the vessel walls and through the interstitium is because of both diffusion and convection. Concentration gradients result in the diffusive transport. Movement of fluid molecules caused by pressure gradients results in the convective transport of solute molecules. If the diffusion is the mechanism of transvascular flow, the diffusive solute flux is given by\([57]\):

\[
J_s = PS \left( C_p - C_f \right)
\]

(27)

where \( J_s \) is the net flow of solute from vessel, \( P \) is the diffusive permeability, \( S \) is the surface area of the vessel, \( C_p \) is the plasma concentrations of the solute, and \( C_f \) is the free concentrations of the solute. By considering convection transport from microvessel wall, the total solute flow is given by the Staverman-Kedem-Katchalsky equation \([58]–[59]\):

\[
J_s = PS \left( C_p - C_f \right) + J_r \left( 1 - \sigma_f \right) \Delta C_{in}
\]

(28)

where: \( \sigma_f \) is the solvent-drag reflection coefficient, and \( 1 - \sigma_f \) is a measure of coupling between fluid and solute transport. \( \Delta C_{in} \) is the log-mean concentration within the pore \([57]\):

\[
\Delta C_{in} = \frac{C_p - C_f}{\ln \left( C_p/C_f \right)}
\]

(29)

\( J_r \) is the volume flow of fluid across the vessel wall. According to Starling’s law, net fluid flow across a vessel wall is given by \([60]\):

\[
J_r = L_p S \left[ (P_v - P_i) - \sigma (\pi_v - \pi_i) \right]
\]

(30)

where \( L_p \) is the hydraulic conductivity (or the filtration coefficient) of the vessel, \( P_v \) and \( P_i \) are the intravascular and interstitial fluid pressures, \( \pi_v \) and \( \pi_i \) are the colloid-osmotic pressures in plasma and interstitial fluid, and \( \sigma \) is the osmotic reflection coefficient \([53]\).

A complete description of the solute transport based on the pore model of membrane is given by the so-called Patlak equation \([61]\):

\[
J_s = J_r \left( 1 - \sigma_f \right) \frac{(C_p - C_f) e^{-P_v}}{1 - e^{-P_v}}
\]

(31)

This equation can be easily partitioned into the diffusive and convective components as shown below:

\[
J_s = PS \left( C_p - C_f \right) \left[ \frac{Pe}{e^{Pe} - 1} \right] + J_r \left( 1 - \sigma_f \right) C_p
\]

(32)
where: \( Pe \) is referred to as the Peclet number, and is given by:
\[
Pe = \frac{J_r (1 - \sigma_r)}{PS}
\]
(33)
The Peclet number indicates the importance of convective transport with respect to diffusive transport. The rate of solute transport per unit volume from blood vessels into the interstitial space is obtained by [11], [62]:
\[
\Phi_r = \frac{J_r}{V} = PS \left[ C_p - C_r \right] \left[ \frac{Pe}{e^{Pe} - 1} \right] + \left[ P_r - P_i \right] \left[ \sigma (\pi_r - \pi_i) \right] (1 - \sigma_r) C_p
\]
(34)
The solute transport rate across the lymphatic vessels can be considered as [18]
\[
\Phi_L = \phi_L C
\]
(35)
where \( \phi_L \), the drainage term, i.e. elimination by lymphatic system, is calculated by:
\[
\phi_L (r) = \frac{L_{PS} S_L}{V} \left( P_r - P_L \right)
\]
(36)
\[
\frac{L_{PS} S_L}{V} \text{ is the lymphatic filtration coefficient, and } P_L \text{ is the hydrostatic pressure of the lymphatic system.}
\]
The general form of free solute transport in tissue is then given by:
\[
\frac{\partial C}{\partial t} = \frac{D_{eff} V}{V} C_r - v \cdot \nabla C_r + \Phi_{r - L} + \Phi_L + R
\]
(7)
\[
\text{Diffusion transport in interstitium} \quad \text{Convection transport in interstitium} \quad \text{Vascular term} \quad \text{Lymphatic term} \quad \text{Reaction rate}
\]
Chemical reaction rate:
The free solute is consumed and produced due to chemical reaction in biological tissue. The reaction mechanism can be binding to cell membrane [63] or other mechanism such as phosphorylation. Reaction of solute increases the retention and accumulation of tracer/drug in tumors, but reduces the amount of free solute available for interstitial transport and results in uneven distribution [64]. The schematic of reaction is shown in Figure 17. The schematic of reaction of free solute is similar to the compartments model in kinetic modeling.

![Figure 17. Schematic of reaction of free solute in interstitium [25].](image)

The rate of consumption and production of free solute [52]:
\[
R = k_{off} C_b - k_{on} C_f
\]
(38)
And the mass balance for \( C_b \) is [52]:
\[
\frac{\partial C_b}{\partial t} = k_{on} C_f - k_{off} C_b
\]
(39)
where
\[
k_{on} \text{: Association rate constant,} \quad k_{off} \text{: Dissociation rate constant, and} \quad C_b \text{: produced or bound solute concentration.}
\]

REFERENCES


