General Molecular Communication Model in Multi-Layered Spherical Channels

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***Abstract*—Spherical multi-layered structures are prevalent in numerous biological systems and engineered applications, including tumor spheroids, layered tissues, and multi-shell nanoparticles for targeted drug delivery. Despite their widespread occurrence, there remains a gap in modeling particle propagation through these complex structures from a molecular communication (MC) perspective. This abstract introduces a generalized analytical framework for modeling diffusion-based molecular communication in multi-layered spherical environments. The framework is capable of supporting an arbitrary number of layers and flexible transmitter-receiver positioning. However, in this study, we focus on the three-layer sphere, which is particularly relevant for different biological models such as tumor spheroids. The analytical results are validated using particle-based simulation (PBS) in scenarios that have short inter-layer distances. The findings reveal that the characteristics of each layer significantly impact molecule propagation throughout the entire structure, making their consideration crucial for designing targeted therapies and optimizing drug delivery systems.**

I. Introduction

Molecular communication (MC) via diffusion uses the Brownian motion of molecules to transmit information [1]. Although this field has been well-studied in simple, homogeneous environments, many practical biological applications involve complex structures, such as tumors, where molecules must traverse multiple layers with distinct diffusion properties.

Based on our work to be presented at [2], this study implements an analytical framework for MC in multi-layered channels. The framework investigates particle propagation in multi-layered spherical structures, generalizing solutions for diffusion problems regardless of layer numbers or transmitter-receiver positions, with full mathematical derivations contained in [2]. The versatility of our approach facilitates its application to various diffusion-dominated mass transfer problems. However, our focus in this paper is on MC systems within large spheroids – 3-D cellular aggregations in a spherical shape – which are fundamental components in organ-on-chip systems. Large spheroids are ideal examples due to their complex, multi-layered structure: an outer layer of loosely-attached cells surrounds intermediate layers with tighter cell packing and a denser extracellular matrix. This arrangement hinders oxygen diffusion to the core, potentially causing necrosis (death) of the cells in the center [3]. We specifically explore the diffusion problem in a three-layer model, given its prevalence in applications such as tumor modeling and drug delivery systems. To validate our analytical results, we use particle-based simulation (PBS). Our PBS approach is novel because it accommodates short distances between layers via continuous diffusion coefficient updates.

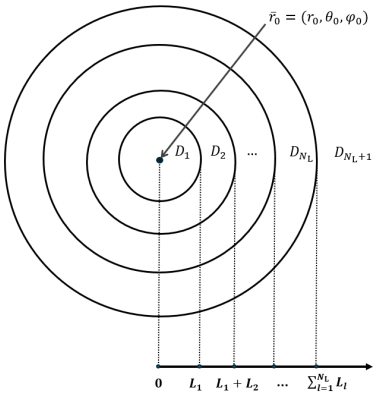

Fig. 1: Cross-section of a multi-layer spherical structure with N_{L} layers. Each layer i is characterized by a diffusion coefficient D_i and radial thickness L_i.

II. System Model

Our system model has a non-homogeneous porous sphere consisting of N_{L} finite layers each with radial thickness L_i, $i \in \{1, 2, 3, ..., N_{\mathrm{L}}\}$, enclosed within an additional infinite layer (i.e., the space outside the sphere is unbounded). This yields a system with a total of $N_{\mathrm{L}} + 1$ layers, as shown in Fig. 1. The *porosity parameter* of each layer, ε_i, serves as the ratio of the extracellular space of the corresponding layer to its overall volume, i.e., $\varepsilon_i = 1 - \frac{N_{\mathrm{c},i} V_{\mathrm{c},i}}{V_{\mathrm{L},i}}$, where $N_{\mathrm{c},i}$, $V_{\mathrm{c},i}$, and $V_{\mathrm{L},i}$ are the number of cells within layer i, volume of each cell, and volume of layer i, respectively. We consider an impulse source (transmitter) to be located within any of these layers. We assume that the sphere is immersed in an unbounded fluid medium with zero flow rate[1] that fills its extracellular space. The effective diffusion within the whole porous sphere volume is reduced compared to the free fluid diffusion outside [4]. Each layer has its own molecule degradation rate k_i and effective molecule diffusion coefficient $D_{\mathrm{eff},i}$, simply D_i for the rest of the abstract, according to its porosity parameter ε_i. D_i can be determined from the molecules' free fluid diffusion coefficient D, i.e., $D_i = \frac{\varepsilon_i}{\tau_i} D$, where τ_i is the tortuosity of layer i and it refers to the degree of path irregularity or

[1]The model is also extendable to a system with convection.

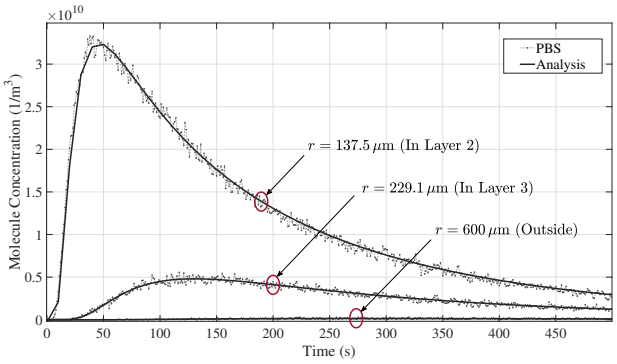

Fig. 2: Concentration profiles at the centers of three distinct spheroid layers for a spheroid with radius $275\,\mu$m. A point transmitter is located at $\bar{r}_0 = (L_1/2\,\mu\text{m}, \pi/2, \pi/2)$.

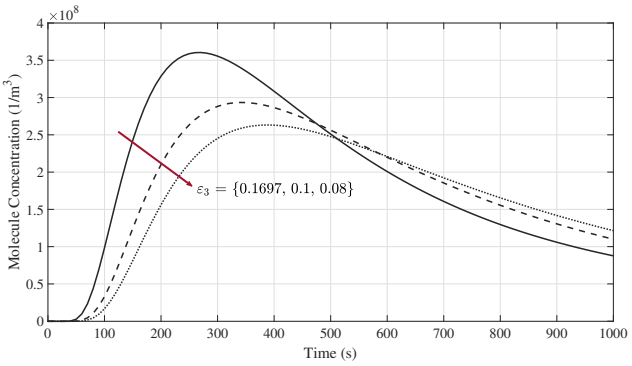

Fig. 3: Impact of the third (outer) layer porosity on molecular diffusion within the first (inner) layer of a three-layer spheroid, with the transmitter at $\bar{r}_0 = (600\,\mu\text{m}, \pi/2, \pi/2)$.

curvature experienced by a molecule while it traverses through the extracellular space of each layer of the spheroid [5]. τ_i is a function of porosity, i.e., $\tau_i = \frac{1}{(\varepsilon_i)^{0.5}}$.

To describe the environment geometry, we use the spherical coordinate system. The system origin is positioned at the center of the multi-layered structure, with $\bar{r} = (r, \theta, \varphi)$ representing radial, elevation, and azimuthal coordinates, respectively. At the interface between two diffusive environments that have different diffusion coefficients, a non-homogeneous continuity condition for flow must be satisfied, which is expressed as

$$D_i \frac{\partial c_i(\bar{r}, t)}{\partial r} = D_{i+1} \frac{\partial c_{i+1}(\bar{r}, t)}{\partial r}, \quad i \in \{1, 2, ..., N_\text{L}\}, \quad (1)$$

and another non-homogeneous boundary condition for a fully permeable interface (i.e., molecules crossing an interface are assumed to pass through without reflecting off of the interface) that is generally modeled as [6, Ch. 3]

$$c_i(\bar{r}, t) = \kappa_i c_{i+1}(\bar{r}, t), \qquad i \in \{1, 2, ..., N_\text{L}\}, \quad (2)$$

must also be satisfied, where $\bar{r} \in \partial\Omega$, $\partial\Omega$ denotes the sphere boundary region, Ω is the spheroid region, and c_i is the concentration function inside layer i. The constant κ_i is found as $\sqrt{\frac{D_{i+1}}{D_i}}$, for $i \in \{1 : N_\text{L}\}$ [4]. Thus, for $\kappa_i \neq 1$, a concentration discontinuity (i.e., jump) occurs at the boundary.

III. Results

This section presents the outcomes derived from the analytical model detailed in Section II. It is important to emphasize that our model is designed for application to a wide range of spherical multi-layer structures. However, for demonstration and validation, we apply the model to a large, non-homogeneous spheroid with distinct layers of varying porosity. Our model incorporates the average of radially-dependent porosity values for each layer from [7] to account for this heterogeneity. To clarify the presentation, we focus on a three-layer spheroid with radius $275\,\mu$m, where the porosities of the layers of the same thickness are $\varepsilon_1 = 0.2964$, $\varepsilon_2 = 0.1196$, and $\varepsilon_3 = 0.1697$, respectively.

Fig. 2 illustrates the concentration at the center of three layers within the spheroid, given an instantaneous point transmitter at $\bar{r}_0 = (L_1/2\,\mu\text{m}, \pi/2, \pi/2)$, where L_1 is the radial thickness of layer 1. As observed over a sufficiently long measurement period, the analytical results are fully supported by PBS. The concentration peak is highest near the source and decreases with distance, approaching zero at the spheroid periphery due to the low porosity of the outer layers.

Fig. 3 shows how reduced porosity in the outer layer (e.g., layer 3) of the multi-layer spherical model affects molecular diffusion to inner layers (e.g., layer 1). In this scenario, the transmitter is positioned outside the spheroid at $\bar{r} = (600\,\mu\text{m}, \pi/2, \pi/2)$. Lower outer porosity results in delayed signals, lower peaks, and increased dispersion in inner layers due to the increased difficulty for molecules to enter and exit the spheroid through less porous outer layers.

In summary, these findings highlight the importance of outer layer porosity in molecular transport within and around multi-layered spheroids, crucial for optimizing drug release and minimizing toxicity. Future work will extend the framework to non-parallel geometries and explore layer-specific drug release mechanisms, such as pH in cancer spheroids.

References

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