Organ(oid)-on-Chip Amplifies Diffusion Signals

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***Abstract*—Realistic models of the components and processes are required for molecular communication (MC) systems. In this abstract, a spheroidal receiver structure is proposed for MC that is inspired by the 3D cell cultures known as *spheroids* being widely used in organ-on-chip systems. The spheroidal receiver is modeled as a porous medium for diffusive signaling molecules, then its boundary conditions and effective diffusion coefficient are characterized. It is revealed that the spheroid amplifies the diffusion signal.**

I. Introduction

Molecular communication (MC) is a bio-inspired mechanism that is envisioned to realize micro- and nano-scale communication systems using molecules as information carriers [2]. Despite many efforts by the MC community to model the components of MC systems, more realistic models are required. Elements and structures of *in vitro* environments such as organs-on-chip could be used to improve model realism, potentially contribute to MC research and development, and to provide mechanistic insight into the biology of the organs (on the chip).

Previous related works have considered the receiver as a single cell (or machine) whose surface is reacting with molecules. However, cells do not normally live in isolation but in populations with other cells of the same or of different types. This is true *in vivo* but also in many *in vitro* systems. In particular, tissues and tumors in multi-cellular organisms and biofilms of microorganisms are common natural instances whereas spheroids, organoids, tumoroids, and cell islets are well-known instances in biological experimental setups. This inspires the design of MC transceivers based on a population of (biological or biosynthetic) cells.

One realistic receiver for MC is a spheroid structure, which is a 3D cell aggregation in a spherical shape that is widely used in organ-on-chip systems. Spheroids are constructed by various methods aiming to emulate the internal physiological activities of an organ [3]. In this abstract[1], we consider a diffusive MC system with a spheroidal receiver and a point source transmitter. We model the spheroidal receiver as a porous medium for the diffusion signal and characterize its effective diffusion coefficient and implied boundary conditions. We introduce and characterize *amplification* of the diffusion signal as an important processing feature of the spheroid. Our results are confirmed by a particle-based simulator (PBS).

[1]The extended version of this work will be presented at IEEE ICC 2023 [1].

II. System Model

A spheroid with radius R_s formed by N_c cells is considered. The spheroid interior space is comprised of the cells and the void space between the cells (i.e., extracellular environment). Given that the volume of a cell within the spheroid is V_c, the volumes of the cell matrix and the void space inside the spheroid are given by $V_c N_c$ and $V_s - V_c N_c$, respectively, where $V_s = \frac{4}{3}\pi R_s^3$ is the spheroid volume.

We model the spheroid structure as a porous medium with volume V_s whose porosity, ϵ, is defined as the ratio of the void space to the whole spheroid volume, i.e., $\epsilon = 1 - \frac{N_c V_c}{V_s}$.

We assume that the spheroid is in a fluid medium that surrounds it and fills its void space. The diffusive signaling molecules of type A in the medium can diffuse into the void space of the spheroid and stimulate the spheroid's cells through a transmembrane mechanism, e.g., by binding to receptors.

Inside the spheroid, the molecules diffuse via the curved paths of the void space among the cells, which leads to a shorter net displacement of the molecules in a given time interval. Thus, macroscopic diffusion within the spheroid effectively differs from the diffusion within the free fluid outside the spheroid. Since the molecules traverse a shorter net path within the spheroid, the effective diffusion coefficient is smaller than the diffusion coefficient in the free fluid medium and molecules are more likely to be observed and sensed by the spheroid's cells. Given the diffusion coefficient D for molecules A in the free fluid, the effective diffusion coefficient within the spheroid is given by $D_{\text{eff}} = \frac{\epsilon}{\tau} D$, where τ is the tortuosity, a measure of the transport properties of the porous medium, and is modeled as a function of spheroid porosity as $\tau = \frac{1}{\epsilon^{0.5}}$ [4].

To describe the environment geometry, we use the spherical coordinate system where (r, θ, φ) denote radial, elevation, and azimuth coordinates, respectively. At the border of the two diffusive environments with different diffusion coefficients, we have a flow continuity condition as $D_{\text{eff}} \frac{\partial c_s(\bar{r},t)}{\partial r} = D \frac{\partial c_o(\bar{r},t)}{\partial r}$,

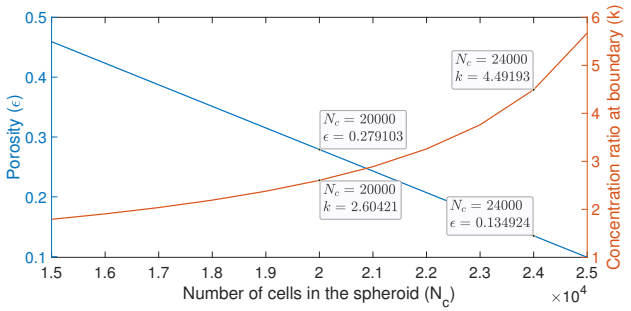

Fig. 1. Porosity (ϵ) and concentration ratio at the boundary (k) versus the number of cells inside the spheroid (N_c).

and another boundary condition that is generally modeled as [5, Ch. 3]

$$c_s(\bar{r}, t) = k c_o(\bar{r}, t), \tag{1}$$

where $\bar{r} \in \partial\Omega$, $\partial\Omega$ denotes the boundary region of the spheroid, and c_s and c_o denote the concentration function inside and outside the spheroid, respectively. The constant k is a function of porosity of the medium and should be determined experimentally. But, the literature on mathematical analysis of tumor spheroids simply assumes continuity of concentration, i.e., $k = 1$, by neglecting the porosity of the medium [6], [7]. However, in the results section, we show using a PBS that for two ideal diffusion environments with diffusion coefficients D and D_{eff}, we have $k = \sqrt{\frac{D}{D_{\text{eff}}}}$. Thus, for $k \neq 1$, a concentration discontinuity (i.e., jump) occurs at the boundary.

III. Results

Fig. 1 demonstrates the porosity (ϵ) and boundary concentration ratio (k) as a function of the number of the cells, $15000 < N_c < 25000$ in the spheroid when the spheroid radius and cell volume are assumed to be $R_s = 275\ \mu\text{m}$ and $V_c = 3.14 \times 10^{-15}\ \text{m}^3$, respectively [8]. As observed in Fig. 1, the boundary concentration ratio increases exponentially with an increase in N_c. For $N_c = 24000$, which is the approximate number of cells in HepaRG spheroids reported in [8], we have $\epsilon = 0.13$ and correspondingly $k = 4.49$. This value of k suggests a large concentration discontinuity at the spheroid boundary.

Using a particle-based simulator (PBS), Fig. 3 evaluates the boundary concentration ratio, k, for a MC system whose schematic illustration is represented in Fig. 2 when $N_c = 24000$ and the point source transmitter is located at $\bar{r}_{\text{tx}} = (500\ \mu\text{m}, \pi/2, 0)$. An irreversible first order reaction inside the spheroid is simply assumed to be $\text{A} \xrightarrow{\text{k}_\text{f}} \text{E}$ with $k_\text{f} = 0.01$ or $0.1\ \text{s}^{-1}$.

Fig. 3 shows the concentration at inner and outer boundary points $c_s(275^-\mu\text{m}, 0, 0)$ and $c_o(275^+\mu\text{m}, 0, 0)$ of the spheroid given the impulsive source at the transmitter obtained from the PBS when $N_c = 24000$. We have also plotted the concentration at the outer boundary scaled by the factor k to verify the boundary condition (1). The minor mismatch at the peaks is mainly due to the PBS procedure to approximate

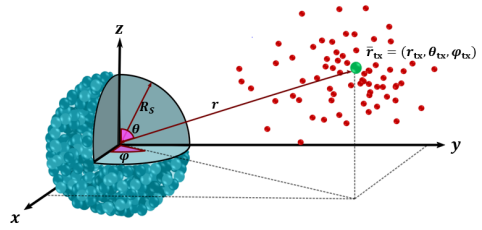

Fig. 2. System model schematic where the red, greenish-blue, and green spheres represent the signaling molecule, cell, and point source transmitter, respectively.

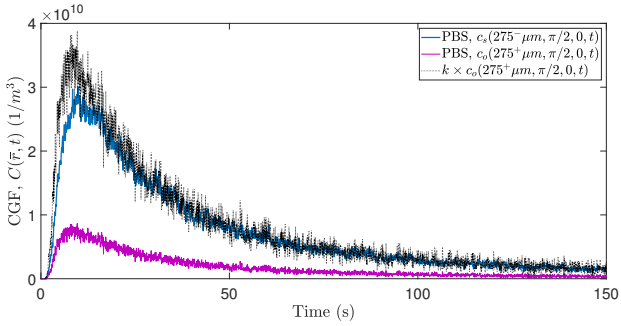

Fig. 3. CGF at the inner and outer boundaries versus time obtained from the PBS for $N_c = 24000$.

the concentration at a point. To compute the concentration at the boundary point $(275\ \mu\text{m}, 0, 0)$, we have assumed a transparent sphere of radius $10\ \mu\text{m}$ centered at the boundary point and have counted the molecules in the left and right hemisphere to approximate the concentration of the molecules at inner and outer points. This leads to slightly higher and lower approximations for the concentrations at the outer and inner boundary, respectively.

IV. Acknowledgement

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References

[1] H. Arjmandi, et. al., "Diffusive Molecular Communication with a Spheroidal Receiver for Organ-on-Chip Systems," To be presented in *IEEE International Conference on Communications*, Rome, Italy, 2023.

[2] N. Farsad, et. al., "A comprehensive survey of recent advancements in molecular communication," in *IEEE Communications Surveys & Tutorials*, vol. 18, no. 3, pp.1887-919, Feb. 2016.

[3] S. Daunys, et. al., "3D tumor spheroid models for in vitro therapeutic screening of nanoparticles," *InBio-Nanomedicine for Cancer Therapy*, Springer, Cham, pp. 243-270, 2021.

[4] F. Sharifi, B. Firoozabadi,K. Firoozbakhsh, "Numerical investigations of hepatic spheroids metabolic reactions in a perfusion bioreactor," *Frontiers in bioengineering and biotechnology*, vol. 7, p.221, Sep. 2019.

[5] J. Crank, *The mathematics of diffusion*, Oxford university press, 1979.

[6] J.J. Klowss, et al., "A stochastic mathematical model of 4D tumour spheroids with real-time fluorescent cell cycle labelling," *Journal of the Royal Society Interface*, vol. 19, no. 189, Apr. 2022.

[7] J. A. Bull, et al., "Mathematical modelling reveals cellular dynamics within tumour spheroids." *PLoS Computational Biology*, vol. 16, no. 8, Aug. 2020.

[8] S. Bauer, et al., "Functional coupling of human pancreatic islets and liver spheroids on-a-chip: Towards a novel human ex vivo type 2 diabetes model," *Scientific reports*, vol. 7, no. 1, pp. 1-11, Nov. 2017.