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The Role of Cell Geometry over Transport and Reaction Processes

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Cell morphology is commonly approximated using simple regular models. This approach, while didactic for academic purposes, may not turn out to be the most suitable for sound studies. This oversimplification of the cell geometry leads to incorrect estimations of general mass transport from the cellular membrane to the core. We have carried out numerical simulations of intracellular mass transport in both idealized and realistic models of human cell geometries in order to assess the suitability of the former to study biological transport phenomena. Our results indicate that in general the use of regular geometric models does not satisfactorily reproduce the results from more realistic geometries. In fact, the partial agreement between idealized and realistic representations of the cells is found to be highly dependent upon transport and reaction conditions, in specific of the Biot number and Thiele modulus values. This work should prevent future studies to avoid as much as possible oversimplifying the cell geometry when performing intracellular simulations as well as experimental designs.

1. Introduction

Cells are generally exposed to several types of particles, which may come from a wide variety of sources in their natural environments. The particular matter (PM) is usually nanometric, and therefore liable to be transported within a current flow to different regions of the human body (Chirino *et al.* 2010). Currently, there is a great interest in studying the effects of PMs in different tissues of human organisms (Clare *et al.* 2006, Campbell *et al.* 2009) in view of the fact that some PMs can trespass the cell membrane and integrate themselves into the organelles (Chirino *et al.* 2010).
Phagocitosis is one of the main forms of interaction between cells and particles and it is strongly dependent on cellular geometry. Mathematical modeling has aided understanding the influence of the particle geometry over the interaction with different organisms.

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Recently, Decuzzi *et al.* (2009) compared the flow dynamics of spherical and ellipsoidal particles, and observed that the latter presented a larger adhesion to endothelial cells in blood vessels than the former. In addition, Champion and Mitragotri (2006) studied the role of geometry in phagocytosis both experimentally and theoretically considering spherical, cylindrical, oval and elliptic discs. These authors conclude that both PMs shape and size are critical issues in phagocitosis processes.
Regarding cellular morphology, it seems to be a common practice to treat the cells as spheres when performing mathematical modeling of transport phenomena in this type of systems (see e.g. Truskey *et al.* 2009). While the use of simple regular geometries is a reasonable approach for didactic purposes, the same may not be true in realistic studies, because most cells exhibit irregular geometries. Cellular geometry may be determinant in modeling transport and reaction of PMs at the cell level, which is intrinsically related to experimental design and upscaling processes among other research activities.
This work is aimed to investigate the extents and limitations of simple geometrical models for describing mass transport and reaction of PMs in human cells. The choice of human cells is based upon two reasons: *i*) the intrinsic relevance of transport phenomena within the human body and *ii*) the availability of good quality photographs for different human tissues (Japanese Collection of Research Bioresources 2010). The considered images correspond to the most studied zones of the human body, namely, liver, bladder, heart, finger skin, lung and kidney. To evaluate the pertinence of using idealized geometries, we consider the real geometries of the aforementioned cells and compare both results in terms of PMs concentration profiles and effectiveness factor predictions under several transport and reaction conditions. These conditions are tuned by changing the ratios of the speed of diffusion with respect to the speed of reaction (Thiele modulus) and the speed of extracellular transport with respect to intracellular diffusion (Biot number).

2. Mathematical Modeling and Image Processing

We have considered mass transport of a reactant (species A) within a single cell which may correspond to PM as discussed in the introduction. To simplify the analysis, we adopt the following assumptions:

- An effective-medium model is applicable, involving an average diffusivity coefficient, D, which accounts for the cell tortuosity and it is assumed to be position-independent.
- The reactant is sufficiently dilute (i.e., its mole fraction is much less than one) in order to use Fick's law justifiably.
- Convective effects are negligible with respect to diffusion within the cell.
- Cell-cell interaction as well as cellular growth and death are neglected. This is a reasonable assumption since the rate of mass transport and reaction is several orders of magnitude larger than the cell cycle.
- Receptors are sufficiently far apart from each other so that the binding of a ligand to a receptor does not deplete the concentration of ligands near other receptors in accordance with Berg and Purcell's supposition (Berg and Purcell 1977). The nature of the binding process of the PMs and the receptors determine the values of the interfacial mass transport coefficient.
- The reaction rate follows Michaelis-Menten kinetics. Although, this type of kinetics is typical for enzymatic kinetics, we use it in our model due to its

successful application in biological transport studies (Choi *et al.* 2001, Truskey *et al.* 2009, Yamaguchi *et al.* 2010).

The dimensionless governing equation for mass transport of the reactant inside the cell (i.e., $\mathbf{x}\in\Omega$) is given by

$$\frac{\partial U}{\partial \tau}=\nabla^2 U-\underbrace{\frac{\Phi^2 U}{K+U}}_{R(U)}, \qquad \text{in } \Omega$$

with U and K being the dimensionless concentration distribution and Michaelis-Menten constant respectively and Φ denoting the Thiele modulus. The corresponding boundary and initial conditions are

$$-\mathbf{n}\cdot\nabla U=Bi\left(U-1\right), \qquad \text{at } \partial\Omega$$

$$U=U_0, \text{ when } \tau=0$$

where Bi is the Biot number and U_0 denotes the dimensionless initial concentration distribution. Due to the nonlinearity of the reaction kinetics, it is not possible to obtain explicit analytical solutions of the reactant concentration. Instead, numerical methods are employed, involving sufficient mesh nodes to guarantee stability and unicity of the predictions. Once the intracellular concentration profiles are obtained, they are used to compute the cell effectiveness factor, which is defined as

$$\eta=\frac{\int\limits_{\mathbf{x}\in\Omega} R\left(U\right)dV\left(\mathbf{x}\right)}{\int\limits_{\mathbf{x}\in\Omega} R\left(U\big|_{\mathbf{x}\in\partial\Omega}\right)dV\left(\mathbf{x}\right)}$$

This parameter is known to be highly dependent on the Thiele modulus and the Biot number and only mildly dependent on the system geometry (Levenspiel 1998). The selected images from the Cell Line Distribution Center (Japanese Collection of Research Bioresources 2010), were digitally processed using a Matlab routine.

3. Results and Discussion

Here, we present the analysis of the influence of transport conditions (intracellular diffusion and extracellular transport) and geometry upon the concentration profiles and effectiveness factor predictions using *realistic* and *idealized* models of cell morphologies. In this context, we use the words realistic and idealized models only in terms of cell geometry. It should be clear that our model is already idealized due to the assumptions previously adopted. For the developments that follow, let us constrain the analysis to steady-state conditions, so that the only degrees of freedom are the Biot number, the Thiele modulus and the cell geometry.

Figure 1 shows the concentration profiles for the six cell geometries here considered along with those for a unit circle and an ellipse with eccentricity equal to $\sqrt{3}/2$ (ellipse-1). In all cases, the Biot number and Thiele modulus are arbitrarily held

constant and equal to 5; in addition K = 1 in all simulations. These parameters were fixed to these values because they allow comparing diffusion transport with the reaction rate as they take place within the cells. The results clearly show that the use of a unit circle or an ellipse is somewhat reasonable only when comparing with liver and bladder cells. For the other cell geometries it was necessary to include another scale to better appreciate the results since they were plausibly different from those shown in Figure 1 a)-d). It should be noticed that due to the irregular geometry of some cells, one may appreciate not-uniform distributions of the reactant at the boundaries; this behavior is practically impossible to reproduce by regular geometries. Furthermore, the poor agreement between the idealized geometries and those corresponding to Figs. 1e)-h) can be attributed to the fact that every inner point of those cells is fairly close to the membrane as opposed to the circle and the ellipse. Interestingly, the location of the lowest concentration values is around the cell nucleus. This is biologically appealing in virtue of the natural protection of the nucleus, and therefore of the genetic material, from external agents.

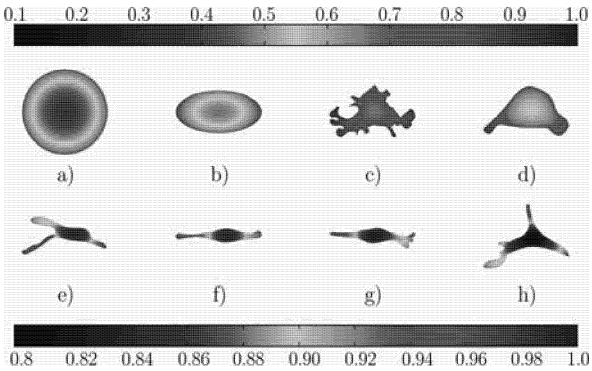

Figure 1: Influence of geometry over the concentration profiles for a) circle, b) ellipse and cells of c) liver, d) bladder, e) heart, f) finger skin g) lung and h= kidney for =5 and Bi = 5. The scale indicates the value of U in Eq. (1). The upper color scale is used for a)-d) while the lower is used for e-h).

Figure 2 displays the effectiveness factor dependence upon the Biot, number and Thiele modulus for the geometries considered in Figure 1 with the addition of an ellipse with eccentricity $\sqrt{15}/4$ (ellipse-2). Regarding the results in Fig. 2, the following comments are in order:

- A circle is, overall, the worst representation of the cell geometries here studied. In contrast, the elliptical models are closer to the realistic cell structures.
- For cases in which mass transport is dominated by reaction (i.e., $\Phi < 1$), all the models yield η = 1. On the other hand, when diffusion is the controlling transport mechanism (i.e., $\Phi > 10$), the geometry plays a crucial role over the effectiveness factor predictions.
- On the basis of the similarities in the results for realistic cell geometries, two groups of results are identified: one includes liver and bladder (group A) and the second one encompasses heart, skin, lung and kidney (group B). The results corresponding to ellipse-1 are closer to those from group A whereas

the ellipse-2 is closer to group B. However neither of them reproduced satisfactorily any of the results from realistic cells in the complete range of *Bi* and Φ here considered.

- It is interesting to notice in Fig. 2a that the results from ellipse-2 are in agreement with those for the liver. However, from Fig. 2b, we observe that this match only takes place for Bi > 10. When this is not the case, the results from ellipse-2 are in better agreement with those from group B. Similarly, the predictions arising from ellipse-1 match those for bladder cells only for Bi < 1.

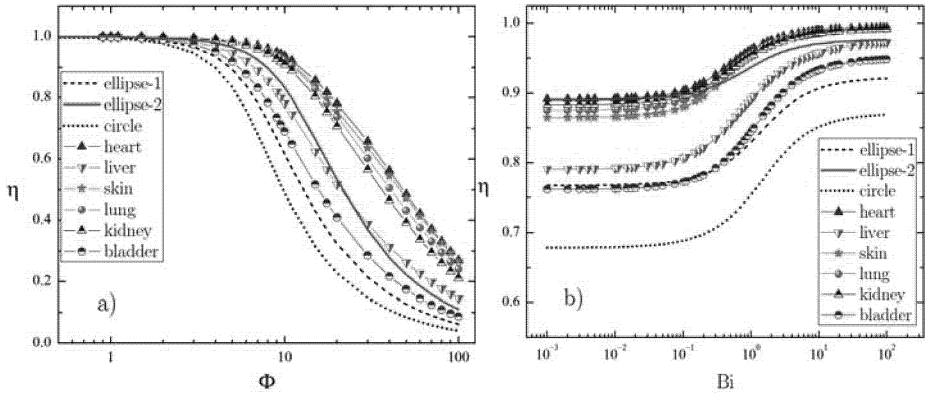

Figure 2: Cell effectiveness factor for the geometries in Figure 1 as functions of a) Thiele modulus and b) Biot number taking Bi = 5 and Φ =5, respectively.

4. Conclusions

This work addresses the question of whether or not simple geometrical models reproduce mass transport and reaction simulations in realistic representations of human cells. Our analysis was directed at two levels of scale, the first one deals with the PMs concentration profiles at each point of the cells and the second one corresponds to the average reaction rate within the cell, via the effectiveness factor.

We found that the use of simple regular geometric models did not appear to satisfactorily reproduce the results from more realistic cell geometries. In other words, the fact that a relatively simple cell model may reproduce the results from the more realistic geometries for certain values of the Biot number and the Thiele modulus does not guarantee that the agreement will prevail under different transport conditions.

Numerical simulations carried out in this work have been limited to simple transport and reaction conditions that may turn out to be over simplistic. Nevertheless, the results from this work (see Fig. 2) should prevent future studies to avoid as much as possible modeling cellular geometries with regular structures for biological transport phenomena.

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