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Upscaling diffusion and reaction processes in multicellular systems considering different cell populations

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HIGHLIGHTS

- A local mass equilibrium model for multicellular systems is derived.
- The effective diffusivity is computed theoretically through a closure problem.
- The effective diffusivity depends on the proportion between living and dead cells.
- Theoretical percent errors are computed when only one type of cell is considered.
- There is a range of parameter values in which the percent errors are at least 10%.

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ABSTRACT

In this work, we derive a mass equilibrium model to describe the diffusion and reaction processes in a cell cluster composed of different cell populations. This study extends previous ones in which the existence of only one type of cell population was considered. The microscopic description is used to derive an upscaled model for diffusion and reaction in multicellular systems using the method of volume averaging. The effective diffusivity coefficient that appears in the upscaled equation is predicted by solving a closure problem in simple 2D unit cells. This effective coefficient depends on the volumetric fraction of the cells, the cell distribution, and the ratios of microscopic diffusivities, permeabilities and solubilities that measure the differences between the physical properties of living cells. It was found that there is a wide range of these parameter values in which the effect of considering different cell populations is important, leading to errors in the predictions of the effective diffusivity with respect to those resulting from assuming that there is only one type of cell population.

1. Preliminaries

Multicellular systems have important applications in a variety of technologies such as water treatment and purification (Lewandowski and Boltz, 2011), environmental processes, biotechnology (Nielsen, 2003), biomedical science and engineering (Eibl et al., 2009; Minchinton and Tannock, 2006), aquaculture (Scryver et al., 2008), among others. All of these applications are based on both laboratory and large-scale cultures with different types of microorganisms or eukaryotic cells. Despite the biochemical, morphological and physiological differences between all these cells, most of them tend to form discrete aggregates of packed cells (also known as cell clusters) with similar structures under which mass transport can be studied.

One of the principal features of multicellular systems is their *hierarchical nature* (Cushman, 1990), i.e., both physical and biochemical processes take place in more than one scale level and the description of each level is determined by the processes that occur in the lower ones. In general, we have recognized four scale levels that are represented by an interval of characteristic lengths, as sketched in Fig. 1. Level I or the field scale, corresponds to the length scale with an order of magnitude larger than 10^{-3} m, which might represent the total size of the system under study, for instance, the subsurface heterogeneities that comprise an aquifer in bioremediation processes, a bioreactor, an organ, a tumor, etc. At Level II, or the Darcy-scale, many multicellular systems has a complex structure consisting of cell clusters, channels and voids that contain a fluid phase (Costerton et al., 1994; DeBeer et al.,

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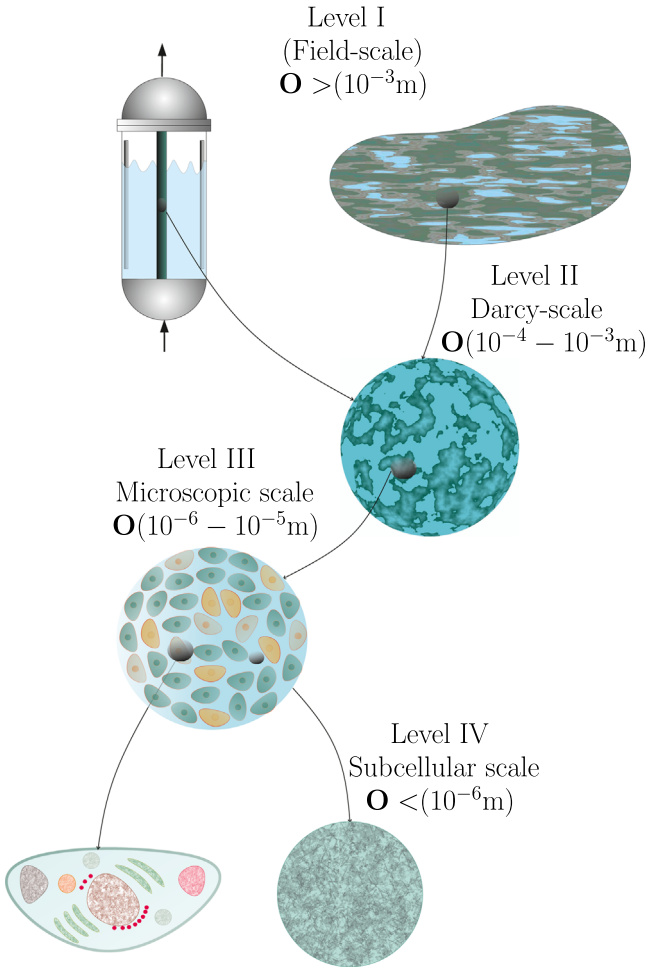

Fig. 1. Characteristic length-scales of a cell-based system.

1994b, 1996). The characteristic length of the Darcy-scale ranges from 10^{-4} to 10^{-3} m and some examples could be biofilms and tissues. Cell clusters are described at Level III or the microscopic scale, which involves hundreds of cells embedded in an extracellular matrix commonly composed of proteins, polysaccharides, lipids and cell lysis (Branda et al., 2005; Costerton et al., 1994; Sing et al., 2006). At this level, a pronounced heterogeneity of cell populations have been observed, i.e., living cells with different metabolic activities, different microorganisms or animal cells of different histological origin and functions, and dead cells (Mueller-Klieser, 2000; Scryver et al., 2008; Webb et al., 2003). The characteristic length of the microscale is about $10^{-6}-10^{-5}$ m. Finally, Level IV or the subcellular scale, is represented by a characteristic length smaller than 10^{-6} m that corresponds to the size of both intracellular components (organelles, plasmatic membrane and macromolecules) and extracellular components (protein fibers found in the extracellular matrix).

Some studies have hypothesized that cell growth depends strongly on mass transport taking place inside of many multicellular systems (Araujo and McElwain, 2004; Chung et al., 2006; Galban and Locke, 1997; Wood and Whitaker, 1999). In fact, the estimate of cell growth rate is the final goal in most of applications mentioned above. For this reason, a proper description of mass transport and reaction processes occurring at the different length-scales is crucial. At Level II, two dominant processes are described: the advective fluxes in voids and/or channels around the cell clusters and the diffusion and reaction inside of agglomerates. Whereas, the mechanisms occurring at Level III are three: diffusion in an extracellular region, transport across the cell membrane, and diffusion and reaction in the intracellular region.

Many efforts have been made to describe mass transport and reaction in systems at Level II. There is a fair number of mathematical models that have been formulated heuristically, where the associated parameters are assumed to be known *a priori*. The primary assumption associated with these models is that the system at this scale is treated as a continuum medium (Ebigbo et al., 2013; Kiran et al., 2009; Matson and Characklis, 1976; Stein et al., 1971; Wanner and Gujer, 1986). However, several studies have pointed out that the heterogeneous structure of many multicellular systems at the microscopic scale plays an important role in the transport process at the Darcy-scale (DeBeer et al., 1994b, 1994a; Mueller-Klieser, 2000). Therefore, it is convenient to have an upscaling technique that allows to relate the transport processes that take place at the different scale levels. In this context, we refer to upscaling as the systematic filtering of information from a lower scale level to a higher one (Wood, 2009).

Derivation of the theory that connects the descriptions of diffusion and reaction between the Darcy and microscopic scales in homogeneous cellular media has been the subject of several investigations (Kapellos et al., 2007; Ochoa-Tapia et al., 1986, 1987; Wood and Whitaker, 1998, 2000; Wood et al., 2002). In these studies, the method of volume averaging was used to derive effective-medium equations, which are valid only for the cell clusters at the Darcy-scale. In this upscaling technique, the non-redundant information from the microscopic scale is captured by the parameters involved in the effective-medium equations (Wood, 2009). In recent years, the volume averaging method has been already applied to describe larger scale levels where the convective mass transport in the voids and channels formed between the cell clusters is considered (Davit et al., 2010; Golfier et al., 2009; Lasseux et al., 2004; Orgozozo et al., 2010).

Unlike the heuristic formulation, in which the model is postulated, upscaling using the volume averaging method allows to derive the effective-medium equations from the governing equations at the microscale. In addition, the associated time and length-scale constraints that bound the validity of the model are clearly identified. Lastly, a salient feature of this methodology is that it involves a closure scheme that leads to a theoretical prediction of the associated effective-medium coefficients.

On the basis of the method of volume averaging, mass transport and reaction in cellular media have been studied under two approaches based on the pertinence (or not) of the principle of local mass equilibrium. To be precise about the meaning of this principle, it should be noted that, under conditions of *thermodynamic equilibrium*, there are no Darcy-scale concentration gradients and consequently no mass transport takes place. This suggests that all the Darcy-scale concentrations relative to each region can be represented by a single average concentration. Even if the thermodynamic equilibrium is not of interest in many systems, there are situations close enough to this condition for which the use of a single average concentration (solving a one-equation model) is an acceptable approximation. When this is true, the *local mass equilibrium principle* is said to be valid. This approximation requires imposing additional constraints to those already adopted in the upscaling process. However, for situations in which these constraints are too difficult to satisfy, a *non-equilibrium model*, involving coupled effective-medium equations for each region, should be used to properly represent the mass and reaction processes in multicellular systems. Although the latter approach is less restrictive than the equilibrium model, in practice it is more common to find models for multicellular systems formulated in terms of an equilibrium model due to the simplicity that it implies (Araujo and McElwain, 2004; Ebigbo et al., 2013; Yu, 2012).