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Letter to Editor

Reducing discrepancies between 3D and 2D simulations due to cell packing density

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ABSTRACT

Modelling all three spatial dimensions is often much more computationally expensive than modelling a two-dimensional simplification of the same system. Researchers comparing these approaches in individual-based models of microbial biofilms report quantitative, but not qualitative, differences between 2D and 3D simulations. We show that a large part of the discrepancy is due to the different space packing densities of circles versus spheres, and demonstrate methods to compensate for this: the internal density of individuals or the distances between them can be scaled. This result is likely to be useful in similar models, such as smoothed particle hydrodynamics.

1. Letter

Simplification of the mental model one has of a real-life system is practically unavoidable when translating that mental model into a mathematical model: simpler models tend to be more analytically tractable or less computationally expensive. This is particularly true when the system belongs to biology (Gunawardena, 2014). A typical example of model simplification is using fewer spatial dimensions than the realistic three. This is justified when some dimensions may be considered as equivalent to each other, and when there is no need to consider navigation of fluids or objects around obstacles. Relevant examples where reduced dimensionality is assumed include smooth particle hydrodynamics of viscous media (Lu et al., 2005) and Monte Carlo simulations of protein interactions (Woodard et al., 2016).

While such simplification of a model is useful, it can introduce bias and so affect results. Bacterial cells are often modelled as hard spheres (three-dimensional) or hard circles (two-dimensional). We show that a bias is introduced when simplifying a model of spheres to a model of circles, which does affect results in simulations of biofilm growth and may also affect simulations of other systems. A method to compensate for the bias is developed from first principles and its efficacy demonstrated in biofilm simulations.

Biofilms are communities of microorganisms growing in close proximity, attached to some solid surface or interface, and are important habitats in the study of microbial ecology and for microbes themselves (Allison and Gilbert, 1992; Costerton et al., 1995). Microorganisms in aqueous biofilms consume nutrients dissolved in the fluid, grow and reproduce, and so cause the expansion of the entire community. Dissolved nutrients and other chemicals are typically referred to as solutes. Fluid flow is obstructed within the biofilm and its immediate surroundings so much that the motion of solutes is dominated by diffusion and advection can be ignored (Manz et al., 2003; Neu et al., 2010).

The two dimensions parallel to the solid surface are often considered equivalent, since the concentration gradient is typically strongest along the axis orthogonal to the surface and the gradient primarily determines biofilm morphology. In the previous studies on biofilm simulation referenced in this work, the key focus is often the qualitative, emergent behaviour of microbial populations rather than quantitatively precise prediction of biofilm growth. Other systems may be translationally invariant along one dimension, such as the azimuthal when considering flow along a pipe.

A toy model of biofilm growth (single solute and single biomass type) illustrates the key processes. The diffusion-reaction equation describes the dynamics of solute concentration:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + f(c, X) \tag{1}$$

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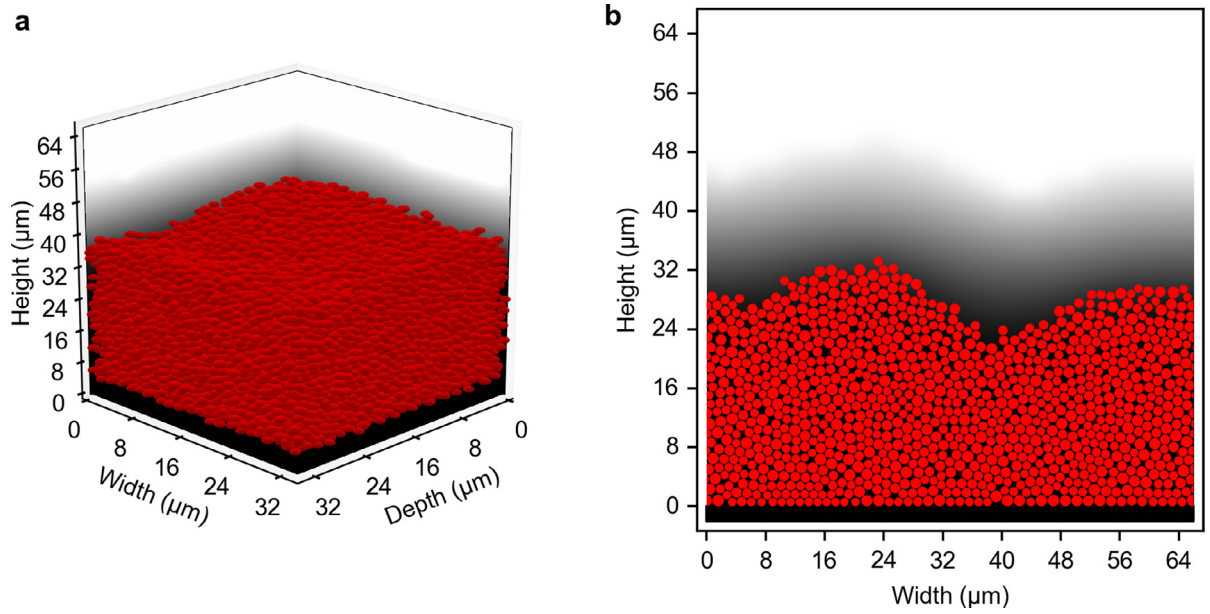

Fig. 1. Biofilm simulations. (A,B) Typical biofilm structures simulated using the parameters given in Supplementary File 2. Cells are shown in red and the solute concentration in greyscale: white for the maximum concentration in the bulk liquid (c_b, 1 mg L^{-1}) and black for no solute (0 mg L^{-1}). The solid surface is shown as a black region at the bottom of each panel. (A) is three-dimensional; (B) two-dimensional, using the unscaled values of ρ and s_f.

where c is the solute concentration, D the diffusivity, X the biomass concentration, and function f the combined rates of production (positive) and of consumption (negative) by chemical reactions (Wanner et al., 2006; Horn and Lackner, 2014). In the simulations reported later, diffusion-reaction is assumed to operate on a far shorter timescale than growth, and so the former is taken to be at steady-state when the latter is considered: in the context of Eq. (1), this means that the time-derivative on the left-hand side is set to zero (Lardon et al., 2011).

The distribution of biomass is given in more general terms:

$$\frac{\partial X}{dt} = growth(c, X) + movement(X). \tag{2}$$

The *growth* term is linked to the reactions described by function f in (1), and the *movement* term depends on further details of the model. The exact forms of functions f, *growth* and *movement* used in simulations here are described in **Supplementary File 1.** Numerical solution of (1) and (2) may require spatial discretisation of continuous fields, e.g., into rectilinear grids.

Individual-based modelling has proven a popular method of investigating biofilms, particularly since the heterogeneity within clonal populations of microorganisms became apparent (Kreft et al., 2013; Ackermann and Schreiber, 2015; Hellweger et al., 2016). Of these, hybrid models are among the most realistic; these treat microorganisms as discrete, non-overlapping particles, and solutes as continuous scalar fields. The rule that particles may not overlap leads to the *movement* part of (2), since cells push away their neighbours as they grow and divide (Kreft et al., 1998). The biomass concentration field and/or field for reaction rates must be updated at each time step by mapping the biomass and/or reaction rates of each microbial cell onto the grid voxel(s) corresponding to its location. Particles have internal biomass density, ρ, and fill the space with packing density, η. In a grid voxel $\boldsymbol{i}$, the fraction of space occupied by biomass is described by $\eta_{\boldsymbol{i}} \in [0, 1]$ and the fraction that is fluid is therefore given by $(1-\eta_{\boldsymbol{i}})$: this is also known as the porosity. The local biomass concentration is then $X_{\boldsymbol{i}} = \rho\ \eta_{\boldsymbol{i}}$.

Individual microbial cells are often represented as hard spheres in three-dimensional space and as hard circles in two-dimensional space (Fig. 1A,B). Where physically realistic parameters (e.g. density as mass per volume) require inclusion of an extrusive third dimension, circles are typically extended to cylinders with co-parallel axes of identical length (Picioreanu et al., 1998a, 1998b; Alpkvist et al., 2006; Lardon et al., 2011; Ardré et al., 2015). Furthermore, the thresholds in cell radius that trigger events such as division and death are consistent between simulations in 2D and in 3D: if thresholds of volume or mass were used, the cell radii at these events would vary according to the length of this third dimension (Lardon et al., 2011). In two-dimensional simulations this approach ensures that cell radii, and so the overall shape and size of the biofilm, are unaffected by the choice of extrusion thickness. Where these simplifications are made, and two- and three-dimensional simulations of the same system compared, authors observe quantitative differences but little or no qualitative differences. Picioreanu et al. (2004) modelled a multispecies nitrifying biofilm: compared to biofilms simulated in 3D, those in 2D grew more quickly in terms of total biomass per unit surface area and caused ammonium concentrations in the bulk fluid to decline more rapidly, but the overall trends were the same. Alpkvist et al. (2006) built on the work of Picioreanu et al. (2004), expanding the model to include extracellular polymeric substance (EPS): they also reported quantitative differences that did not significantly change the conclusions, but did not describe these differences in any detail.

We point to the different packing densities of circles and of spheres as the source of these quantitative differences. The maximal packing density of spheres of equal radius is

$$\eta_{sphere} = \frac{\pi}{3\sqrt{2}} \approx 0.74 \tag{3}$$

(Hales, 1992) and the equivalent packing density for circles is

$$\eta_{circle} = \frac{\pi}{2\sqrt{3}} \approx 0.91 \tag{4}$$

(Tóth, 1972). Given that simulated cells in a biofilm are growing, they will have different radii and are unlikely to achieve optimal packing. However, the packing achieved by random close-packed circles and spheres fall short of the maximum packing by a similar degree in two- and in three-dimensional simulations:

$$\hat{\eta}_{sphere} \approx 0.64 \tag{5}$$