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ORIGINAL ARTICLE

How to Build a Multiscale Model in Biology

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Abstract Biological processes span several scales in space, from the single molecules to organisms and ecosystems. Multiscale modelling approaches in biology are useful to take into account the complex interactions between different organisation levels in those systems. We review several single- and multiscale models, from the most simple to the complex ones, and discuss their properties from a multiscale point of view. Approaches based on master equations for stochastic processes, individual-based models, hybrid continuous-discrete models and structured PDE models are presented.

Keywords Multiscale model · Master equation · Reaction-diffusion equation · Hybrid modelling · Individual-based modelling · Structured PDE

1 Introduction

Multiscale modelling first appeared in material engineering problems in the 1990's. Modellers in biology have since adapted multiscale techniques to study cancer and other complex biological systems (Gatenby and Gawlinski 1996; Lesart et al. 2012; Powathil et al. 2012; Schnell et al. 2007; Spencer et al. 2006; Zhang et al. 2009).

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Here we present a few approaches to multiscale modelling in biology. Biological processes span several scales in space, from the single molecules to organisms and ecosystems, and time, from the nanosecond for protein folding, to hours for cellular processes up to years or longer for population evolution (Qu et al. 2011). In single-scale models, processes are well separated in time and space. However, in practice, it is difficult to keep scales separated, for several reasons. 1. There can be a mismatch between the available biological data or knowledge and the process of interest, so that one has to include many scales to take full account of the data. An example is the problem of predicting the effect of a cancer treatment on a tumour based on a molecular profile (organisation scale mismatch), or to assess the likelihood of a species going extinct based on short time observations. 2. It is now recognised that heterogeneity is a integral part of any biological system, and that many systems are driven by outliers that cannot be taken into account by averaged models (Wilkinson 2009). Multiscale approaches allows the modeller to include relevant biological information from one scale without having to guess what the effect is at the other scales.

This paper is a short tutorial, aimed at giving an overview of how to build a multiscale model. Because of the inherent complexity of multiscale models, it is not possible to introduce all details here. Instead, we try to identify desirable properties such as description at many scales and interactions among and between scales. We proceed stepwise, beginning with classical models in mathematical biology, and introducing progressively richer structures that share more of the features of a multiscale model. We begin with the Lotka-Volterra predator-prey equations (Kaplan and Glass 1995). We then introduce the Turing equations for pattern formation (Turing 1952), and the Keller-Segel equations for chemotaxis (Keller and Segel 1970). We present contemporary approaches for multiscale modelling: master-equation-based models, individual-based models, hybrid models, and structured PDE models. Examples include multiscale models used to probe cancer growth and treatment strategies (Anderson et al. 2006; Ribba et al. 2006); models for the cell cycle (Bekkal Brikci et al. 2008; Doumic 2007) and cell differentiation (Hoffmann et al. 2008); and spatial multi-scale models for tissue and cancer growth (Drasdo and Höhme 2005; Drasdo et al. 1995; Drasdo and Loeffler 2001; Galle et al. 2005). We specifically focus on scales in space and organisation, rather than time (Françoise 2005, Gunawardena 2012, Lahutte-Auboin et al. 2013), although different time scales are implicitly assumed. Finally, we propose two properties any model should possess to be multiscale.

2 From Single-scale to Multiscale Models

2.1 A Basic Population Model: Predator-Prey Interaction

Lotka-Volterra equations are a system of two nonlinear ordinary differential equations describing the interaction between two species, a predator and a prey (Kaplan and Glass 1995). Their first use in biology date back to 1925 (Lotka) and 1926 (Volterra). The dynamical variables are the populations (numbers) of preys

(x) and predators (y). Preys find enough food at all times, and predators feed on prey. The populations evolve according to the equations

$$x' = x(a - by), \tag{1}$$

$$y' = y(dx - c). \tag{2}$$

(Here and in the following, time derivatives in ODEs are denoted by the symbol $'$ and all coefficient are positive.) At the population scale, Eqs. (1–2) state that the growth rate of the prey population is constant (a) and the death rate of the preys is proportional to the number of predators ($b\ y$). The death rate of the predators is constant (c) and the growth rate of the predator population is proportional to the prey number ($d\ x$). The positive fixed point $(x, y) = (\frac{c}{d}, \frac{a}{b})$ is unstable (it is a centre). The predator-prey population oscillate around the fixed point along closed trajectories (Fig. 1).

This is an example of a population model, and it involves interactions between objects at a lower scale: individuals. Yet this is clearly not a multiscale model. A multiscale model should be able to provide information at more than one scale, for instance, on population ("is the wolf population declining?") and on the individual themselves ("which wolves find prey?"). The first question can be answered, while the second one cannot. All the wolves are the same, so are all the hares. What is missing to the predator-prey model is the ability to characterise individuals. One can make the predation rates depend on physiological traits of the preys or the predators. Examples include body-size effect on anti-predator behaviours and foraging strategies of the preys (Dial et al. 2008), or the fight or flight behaviour in moose and roe deer (Wikenros et al. 2009).

This example shows that two populations with simple interactions can display a complex dynamics, oscillations in their number (Fig. 1). It is not multiscale because there is a single scale, the population, even though the model rests on assumptions on interactions between individuals. Modelling is about describing interactions between single objects. By considering a large number of these objects, we obtain

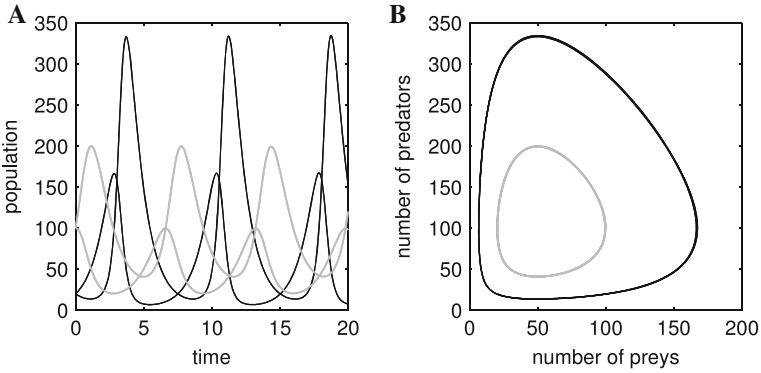

Fig. 1 Lotka-Volterra predator-prey system (1), with $a = c = 1$, $b = 0.01$ and $d = 0.02$, for two different initial conditions: $x_0 = 20$, $y_0 = 20$ (*black*) and $x_0 = 100$, $y_0 = 100$ (*grey*). **a** Time evolution of preys and predators numbers. **b** Solutions shown in *panel A* lie on distinct, closed trajectories

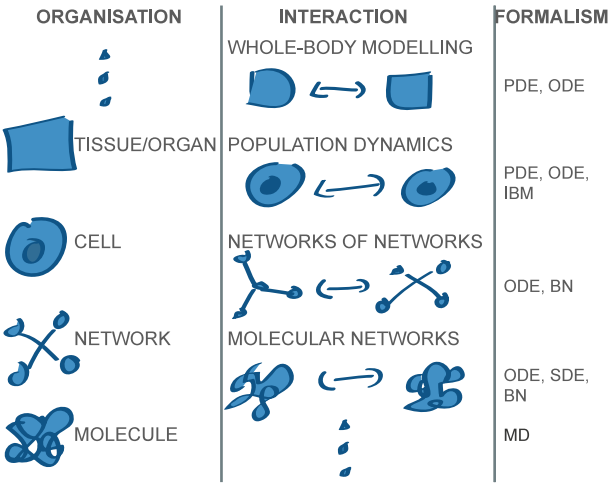

Fig. 2 Organisation scales in biology. Single-scale model equations are determined by the interactions at the lower scale. For example, molecular networks are described by the interaction between molecules. From this point of view, a tissue is a collection of cells interacting together; a cell is a collection of networks interacting together; a molecular network is a collection of molecules interacting together. Scales can go lower (atoms/ions interacting in a single molecule) or higher (organisms interaction in an ecosystem). *ODE* ordinary differential equations, *PDE* partial differential equations, *SDE* stochastic differential equations, *IBM* individual-based modelling, *BN* boolean network, *MD* molecular dynamics

population equations. It turns out that this link between organisation at one scale and the interaction at the lower scale is always present (Fig. 2).

2.2 A Spatial Differentiation Model: Pattern Formation

Alan M. Turing introduced in 1952 a system of two reaction-diffusion equations to show how spatial patterns (spatially heterogeneous solutions) could arise from diffusion of chemical substances, when diffusion was thought to promote homogeneous solutions. In his paper (Turing 1952), Turing discusses a system of two morphogens regulating each other and diffusing in space. One is an activator and the other one is an inhibitor. The activator, u, activates itself and the inhibitor. The inhibitor, v, inhibits itself and the activator. The concentrations of u and v can show spatial instabilities if the diffusion rate of the activator is much smaller than the diffusion rate of the inhibitor. When the activation/inhibition are linear, the equations are

$$u_t = D_u u_{xx} + f_u u - f_v v, \tag{3}$$

$$v_t = D_v v_{xx} + g_u u - g_v v. \tag{4}$$

We can coarse-grain the space x to consider, for instance, cells, located at x, characterised by certain amounts of activator and inhibitors. Spatial instabilities, or Turing patterns, offer an example of lasting heterogeneity, by which cells can be distinguished or differentiated (Fig. 3). Turing equations provide the first model to show how a complex pattern at the tissue level can be generated by interaction

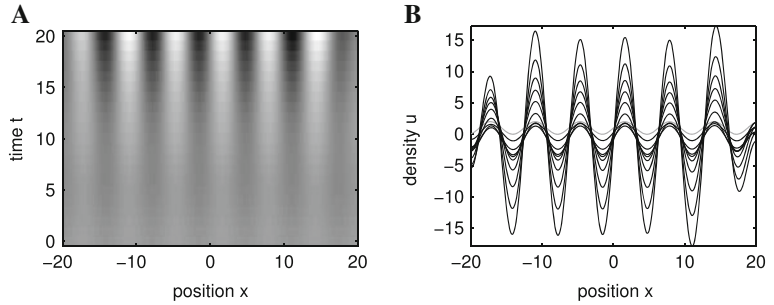

Fig. 3 Solution to the Turing equations, with $f_u = 0.4$, $f_v = 0.5$, $g_u = 1$, $g_v = 0.5$, $D_u = 0.2$, $D_v = 10$, initial conditions $(u_0(x), v_0(x)) = (1 + \sin(x), 1 + \cos(x))$ and Neumann boundary conditions (no flux). **a** Density plot of the solution $u(t, x)$, with increasing concentration values from *black to white*. **b** Solution in x at successive, fixed times. The initial condition is outlined in *grey*

between molecules, two scales down. However, cells are introduced artificially and they do not interact. Turing equations are not yet multiscale.

2.3 A Cell Movement Model: Chemotaxis

In the multiscale interpretation of the Turing system, cells are static objects. It would be better if they could move and interact, for instance. Chemotaxis is the phenomenon by which cells move according to concentration gradients in their environment. They could be attracted by food, or repelled by poisons. If the cells themselves secrete chemotactic molecules, we can describe the movement of the cells by a model Keller and Segel developed in 1970 (Keller and Segel 1970),

$$u_t = du_{xx} - (uv_x)_x, \tag{5}$$

$$v_t = \epsilon v_{xx} + u - av. \tag{6}$$

The Keller-Segel equations include two scales: cell density (u) and molecule concentration (v). Interaction between cells is based on the chemoattractant

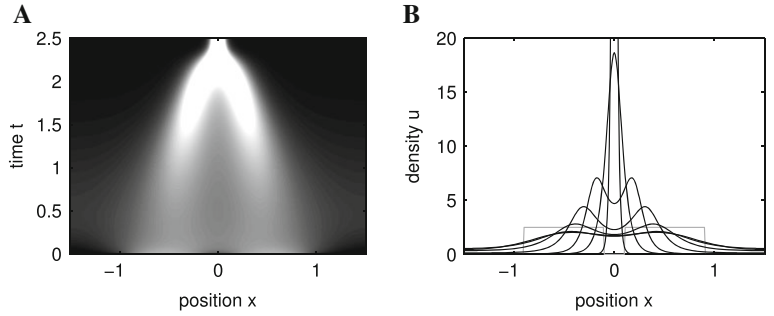

Fig. 4 Solution to the Keller-Segel equations (5–6), with $d = 0.5$, $\epsilon = 0.05$, $a = 0.1$, initial conditions $(u_0(x), v_0(x)) = 2.5\left(\mathbf{1}_{[-0.9,-0.1]} + \mathbf{1}_{[0.1,0.9]}, 0\right)$ and Neumann boundary conditions (no flux). **a** Density plot of the solution $u(t, x)$, with increasing values from *black to white*. *White* indicates $u \geq 4.0$. **b** Solution in x at successive, fixed times. The initial condition is outlined in *grey*. Solution at $t = 2.5$ is out of bound

concentration they produce (Fig. 4). Yet, the two scales are not nested, they live in the same world. Cells and chemoattractant are modelled at the same level, like the predator and the prey in the Lotka-Volterra model. We do not have yet a multiscale model.

3 Master Equation-Based Models

To build a simple multiscale model, we proceed in three steps:

1. We consider an individual deterministic or stochastic process $y(t)$.
2. We obtain the master equation by taking a large population of size $N\,(y_i(t))_{i\in\{1,\ldots,N\}}$ of these processes (N can be infinite) and consider what happens as the population evolve in time. We assume that there is some source of variability between different individual processes. We get a system with two scales of description, but there is not interaction between individuals yet.
3. We obtain a multiscale formulation by adding interaction between individuals and between the individuals and the population. More scales can be added by repeating these steps.

3.1 Individual Process

We consider $y(t) \in \Gamma \subset \mathbb{R}$the state of a system at time t at a particular scale. If we describe a single cell, y could be mRNA or protein levels, cell mass or gene expression profile. If we describe a cell population, y could be numbers of quiescent cells, stem cells, differentiated or tumour cells. We assume that y fluctuates around a value given by the nonlinear deterministic equation $y' \simeq F(y)$. We add a noise term to get a nonlinear Langevin equation (Van Kampen 1992),

$$y' = f(y) + g(y)\xi(t). \tag{7}$$

The noise component $\xi(t)$ is usually a white noise, that is, a time-uncorrelated noise with zero mean and finite variance, often chosen Gaussian.

3.2 Master Equation

We consider a population of N independent processes $(y_i(t))_{i\in\{1,\ldots,N\}}$ described by Langevin equations of the form (7). The probability density function for any y_i at time t, $P(y, t)$ is given by the Fokker-Planck equation

$$P_t(y,t) + [f(y)P(y,t)]_y = \frac{1}{2}[g(y)^2 P(y,t)]_{yy}. \tag{8}$$

Fokker-Planck equations and Langevin equations are mathematically equivalent formulations (Van Kampen 1992). When the population N is large, the Fokker-Planck equation can be interpreted as a population density, i.e. $\int_A P(y,t)dy$ is the fraction of individual processes in state $y \in A$. (It is also possible to consider

Fokker-Planck and Langevin equations in many variables $y \in \mathbb{R}^n$.) The Fokker-Planck equation is a special kind of *master equation* used as an approximate description of a Markov process in which jumps are small and the nonlinearities f and g are smooth. When this is not the case, the formulation by the Fokker-Planck and Langevin equation duet is not valid. The more general master equation can be used to describe the probability density of a Markov process. The master equation is a differential equation local in time but nonlocal in space Γ.

$$P_t(y,t) = \int_\Gamma \{W(y|z)P(z,t) - W(z|y)P(y,t)\}dz. \tag{9}$$

The kernel W describes the transition rates (or jumps) from state z to state y, and it is related to the function f and g, as detailed below. The master equation is a gain-loss equation for the probability of each state y.

3.3 Multiscale Formulation

The master Eq. (9) is a conservation equation (with appropriate boundary conditions), the total normalised population is constant $\int P(y,t)dt = 1$. We now modify it to allow individual processes to be removed or added; hence we will allow the total population to fluctuate.

As an illustration of the master equation approach, we study a model in which cell differentiate by diffusing (i.e. non-directed random movement) into a differentiation space $y \in \mathbb{R}$ (Hoffmann et al. 2008). The cell population density $n(y, t)$ obeys an equation derived from a master equation,

$$n_t(y,t) = \int_\Gamma p(y|z)R(z)n(z,t)dz - R(y)n(y,t) + r(y)n(y,t). \tag{10}$$

The distribution $p(y|z)$ of jumps in the differentiation space is Gaussian, with a nonlinear, space-dependent variance $\sigma^2(z)$. The rate of jumps is given by $R(y)$, which is assumed to be correlated to the cell proliferation rate $r(y)$. The differentiation domain $\Gamma = \mathbb{R}$. The associated Fokker-Planck-like equation is found by calculating the first two jump moments (Van Kampen 1992). The first jump moment, $\int_\Gamma rp(y+r|y)R(y)dr = 0$, vanishes, and the second moment, $a_2(y) = \int_\Gamma r^2 p(y+r|y)R(y)dr = R(y)\sigma^2(y)$. The Fokker-Planck-like equation associated to Eq. (10) is then

$$n_t(y,t) = \frac{1}{2}\left\{R(y)\sigma^2(y)n(y,t)\right\}_{yy} + r(y)n(y,t).$$

Denote by $N_A(t)$ the number of cells with $y \in A$, where $A \subseteq \mathbb{R}$ is a subset of cells of interest:

$$N_A(t) = \int_A n(y,t)dy. \tag{11}$$

We introduce a logistic growth in the following way:

$$n_t(y,t) = \frac{1}{2}\left\{R(y)\sigma^2(y)n(y,t)\right\}_{yy} + r(y)\left(1 - \frac{N_A(t)}{K}\right)n(y,t). \tag{12}$$

K is the carrying capacity for population A. Cell number is regulated at the cell population scale through the term $N_A(t)$, while the single-cell scale defines how cells move in Γ. The associated single-cell Langevin equation is

$$y' = \sqrt{R(y)}\sigma(y)\xi(t). \tag{13}$$

The Langevin equation only describes part of Eq. (12): cell movement in Γ. Arguably, Eqs. (11–12) form a simple multiscale model. They describe a system at two organisation scales: the cell (with $y \in \Gamma$) and the population (with $N_A(t)$), and the interaction between the two scale through the logistic term. The two scales are nested, N_A is formed directly by the density n. For the numerical simulation, we take $\Gamma = [0, 1]$ and $A = [0.8, 1] \subset \Gamma$ (Fig. 5). The state $y \in A$ corresponds to differentiated (mature) cells, and $y \in \Gamma \backslash A$ to progenitor (non-mature) cells. The logistic term in Eq. (12) controls the global proliferation rate (Fig. 5a). The number of progenitors increases until $N_A(t)$ is sufficiently large and then falls off (Fig. 5b, c). The behaviour of single cells differs from the process described by the Langevin Eq. (13) alone (Fig. 5d).

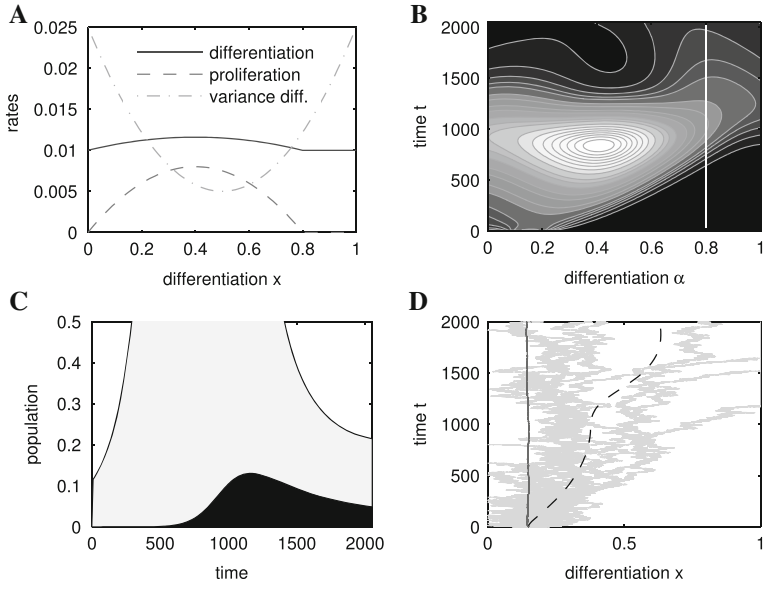

Fig. 5 Solution to the multiscale Eqs. (11–12) derived from the Fokker-Planck equation. The domain is $\Gamma = [0, 1]$, and $A = [y_N, 1]$. Functions are $R(y) = r_0 + r_1\ r(y)$, $r(y) = 4r_{max}\ y\ (1 - y/y_N)\ \mathbf{1}_{[0,y_N]}$, $\sigma^2(y) = s_0 + 4s_1\ (y - 1/2)^2$. Parameter values are $r_0 = 0.01$, $r1 = 0.20$, $r_{max} = 0.01$, $s_0 = 0.005$, $s_1 = 0.02$, $K = 0.05$, $y_N = 0.8$. **a** Rate functions. **b** Density plot of the solution $n(y, t)$, with increasing values from black to white. **c** $N_{[0,\ 1]}(t)$ (*grey*) and $N_A(t)$ (*black*). **d** Some realisations of Langevin equation (*grey*) and their mean (*black*) compared to the mean differentiation value of the solution $n(y, t)$ (*dashed line*)

4 Individual-Based Models

Individual-based modelling (IBM), or agent-based modelling, has been used in computer science, social sciences, ecology (Railsback and Grimm 2011) and more recently in biology (Chauvière et al. 2009). Models are composed of many agents who can make decisions, learn and adapt, and interact with other agents and the environment (Macal and North 2005). They are not necessarily multiscale, but they are flexible enough to allows a multiscale description.

Drasdo and colleague have developed a methodology for simulating proliferating cells (Drasdo et al. 1995). Cells are modelled as oriented, deformable spheroids that can move, rotate, change shape, grow in volume and divide into two daughter cells. Cells interacts mechanically and biochemically through membrane surface molecules. Internal properties of the cell regulate how fast cells grow and divide, and which type of surface molecules are expressed. Although simulations can be computationally costly, this kind of modeling is needed to reproduce some of the key features of a growing tissue, such a 3D cell alignment and movement. This type of single-cell-based model has had many applications: epithelium (Drasdo et al. 1995; Galle et al. 2005), tumors (Drasdo and Höhme 2005; Ramis-Conde et al. 2009) and more recently liver regeneration (Hoehme et al. 2010). A related method has been proposed (Newman and Grima 2004).

5 Hybrid Continuous-Discrete Models

This is a popular approach to multiscale modelling, in which cells are discrete entities and molecular concentrations are given by continuous equations. The space contains a coarse-grained lattice. At each node, one or many cells can be present. Each cell is represented individually and is endowed with relevant property: shape, intracellular state, cycling status, mutation, etc. Cells can move, replicate, die and interact with other cells, directly, or via an extracellular medium.

Ribba and colleagues have proposed a multiscale model for cancer growth, with the purpose of optimising therapeutic irradiation protocols (Ribba et al. 2006). The model incorporates gene regulation, cell kinetics, tissue dynamics, macroscopic tumour evolutions and radio-sensitivity dependence on cell cycle phase. Intracellular interactions are modelled by a boolean network. The state of the boolean network determines how cells progress in the cell division cycle and their fate. Cell can either divide, stop in a quiescent phase, or die by apoptosis. Cell cycle progression, arrest or death is monitored by a cell cycle status. Cell are laid on a lattice and are subject to a changing environment, consisting in the local cell density and the oxygen concentration. Cell fate depends on the local environment. On a tissue level, a fluid dynamics model is used to describe cell movement. Radiation therapy affects the molecular network, which in turn affect cell fate, and tumour progression. Although the model is too complex to reproduce here, we can identify the multiscale features of the model. The model spans three organisation scales: genetic/molecular networks, cells and tissues and interactions between scales are

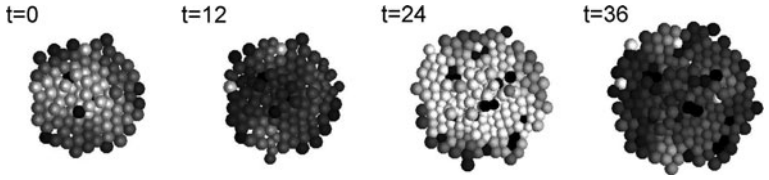

Fig. 6 Synchronisation of circadian clocks in dividing cells induced by cell-cell contact interaction. Cells (*small spheres*) move freely, but tend to stay in contact with each other, and express a clock marker (*dark: low, light: high levels*). Each cell is represented physically by a visco-elastic ball interacting with direct neighbours. A system of 13 differential equations in each cell describes the cell division cycle (Battogtokh et al. 2006), the circadian clock (Bernard et al. 2007) and cell death. Intracellular clocks are coupled by surface contact, and synchronise with each other

modelled explicitly. This formalism has been applied to other anti-cancer therapies (Billy et al. 2009).

Anderson and colleagues have developed a multiscale model for tumour morphology and phenotypic evolution, in which phenotypic mutations and selection drive the tumour morphology evolution (Anderson 2005; Anderson et al. 2006). Discrete cell are laid on a square lattice. Cells are characterised by a life cycle governing proliferation and death, and by a phenotype with traits describing key properties of cancer cells like propensity to proliferate or cell-cell adhesion. Cell can undergo phenotypic mutations that will affect their ability to proliferate and move. Because resources (space, oxygen) are limited, phenotypic selection operates and defines the dynamics of tumour evolution. Oxygen and extracellular matrix concentrations are modelled with PDEs.

A feature of hybrid models is their ability to reproduce relevant biological phenomena, including spatial and intercellular heterogeneities. To illustrate the potential of hybrid models, we show how discrete cells with molecular network of circadian clocks can communicate and synchronise their clocks (Fig. 6). The circadian clock model is a set of 10 ODEs, which produce damped oscillations in isolated single cells. Cells integrate clock signals from their neighbours. Provided there are enough neighbours, the intracellular clock model starts oscillating, ensuring synchrony (Bernard et al. 2007).

6 Structured PDE Models

Population models structured by molecular content are becoming increasingly popular (Magal et al. 1936). Structured equations can be derived from Fokker-Planck equations without noise (for instance, Eqs. (7) and (8) with $g = 0$).

Doumic presented and analysed a model structured by age a and molecular content x (Doumic 2007). The equation describes the evolution of the density $n(t, a, x)$ at time t, of cells aged a with molecular content x. The evolution of the molecular content x, the structure, and the age are given by a system of ODEs, $x' = F(a, x)$ and $a' = 1$. Cells are lost with a rate $B(a, x)$ and a boundary conditions at $a = 0$ defines the birth rate of new cells. The structured equation is a birth-death

transport equation describing how cells move, die and are born in the age/structure space (a, x).

$$n_t + n_a + \{F(a,x)n\}_x + B(a,x)n = 0,$$

$$n(t, a = 0, x) = 2 \int_0^\infty \int_\Gamma b(a,x,y)n(t,a,y)dyda.$$

This system of equations involves two scales: the molecular scale given by the equation $x' = F(a, x)$ and the population scale, with the death term $B(a, x)$ and the boundary condition. This model is a simplified version of a population model structured by cyclins with explicit cell cycle phases (Bekkal Brikci et al. 2008). Other structured equation models for cell population dynamics have been proposed (Benzekry 2011; Friedman et al. 2009; Friedman et al. 2012).

7 Discussion and Conclusion

We have presented here several approaches to multiscale modelling, from master equation-based approaches to individual-based and hybrid models to structured models. Stochastic and multiscale formalisms share many attributes. Depending on the point of view, the same equation can describe a stochastic or a multiscale phenomenon, as with the Fokker-Planck equation. In both multiscale and stochastic models, there are at least two distinct scales. The choice of the scales is left to the modeller, but many models incorporate scales ranging from molecules to the tissue, with the cell as the fundamental modelling unit. One consequence of multiscale modelling is the need to have a detailed but simple description of the intracellular dynamics, with mechanisms to create heterogeneity between cells. Stochastic processes are compatible with the multiscale framework developed here and have been well studied in the context of intracellular networks (Kærn et al. 2005; Kepler and Elston 2001; Paulsson 2005; Perkins and Swain 2009; Ribeiro et al. 2009). In a recent review, Byrne and Drasdo discussed the merits of individual-based models and continuum models of cell populations (Byrne and Drasdo 2009). More approaches to multiscale modelling and examples of applications can be found in recent books (Chauvière et al. 2009; Cristini and Lowengrub 2010; Deisboeck and Stamatakos 2010; Treuil et al. 2008). Based on the discussions presented here and elsewhere (IMAG 2012) we propose two properties a computational or mathematical model should possess to be a multiscale model

- *At least two nested organisation scales* We should be able to distinguish attributes of objects at each scale. The lower scale should be imbedded into the higher scale.
- *Interaction between and among scales* Emerging behaviour (higher scale) of interacting particles (lower scale) is not sufficient, the emergent behaviour should interact with the particles themselves.

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