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Multiscale Modeling of Biological Pattern Formation

Ramon Grima
Institute for Mathematical Sciences, Imperial College, London SW7 2PG, United Kingdom

In the past few decades, it has become increasingly popular and important to utilize mathematical models to understand how microscopic intercellular interactions lead to the macroscopic pattern formation ubiquitous in the biological world. Modeling methodologies come in a large variety and presently it is unclear what is their interrelationship and the assumptions implicit in their use. They can be broadly divided into three categories according to the spatial scale they purport to describe: the molecular, the cellular and the tissue scales. Most models address dynamics at the tissue-scale, few address the cellular scale and very few address the molecular scale. Of course there would be no dissent between models or at least the underlying assumptions would be known if they were all rigorously derived from a molecular level model, in which case the laws of physics and chemistry are very well known. However in practice this is not possible due to the immense complexity of the problem. A simpler approach is to derive models at a coarse scale from an intermediate scale model which has the special property of being based on biology and physics which are experimentally well studied. In this article we use such an approach to understand the assumptions inherent in the use of the most popular models, the tissue-level ones. Such models are found to invariably rely on the hidden assumption that statistical correlations between cells can be neglected. This often means that the predictions of these models are qualitatively correct but may fail in spatial regions where cell concentration is small, particularly if there are strong long-range correlations in cell movement. Such behavior can only be properly taken into account by cellu-

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lar models. However such models unlike the tissue-level models are frequently not easily amenable to analysis, except when the number of interacting cells is small or when the interactions are weak, and thus are rather more suited for simulation. Hence it is our conclusion that the simultaneous theoretical and numerical analysis of models of the same biological system at different spatial scales provides a more robust method of understanding biological systems than the utilization of a single scale model. In particular this enables one to clearly separate nonphysical predictions stemming from model artifacts from those due to genuine physiological behavior.

I. Introduction

Cell migration is at the basis of much of pattern formation in nature. Cell movement particularly that directed by extracellular chemical signals, e.g., chemotaxis and haptotaxis, plays a fundamental role in a wide range of developmental processes, a few examples being: primordial germ cell migration in the chick, mouse and zebrafish embryos (Reichman-Fried *et al.*, 2004; Weidinger *et al.*, 2002); gastrulation and limb development in the chick embryo (Li and Muneoka, 1999; Yang *et al.*, 2002); attraction of sperm to the ova or oviducts in a diverse range of invertebrates and vertebrates (Ralt *et al.*, 1994; Xiang *et al.*, 2004; Yoshida *et al.*, 1993); the wiring of the developing nervous system (Ming *et al.*, 2002). Its significance is however not restricted to the developing embryo, but is also of crucial importance in disease (Ridley *et al.*, 2003), e.g., cancer and arthritis, and in biofilm dynamics (Hall-Stoodley *et al.*, 2004), a subject of current technological importance.

The study of cell movement has a long history, starting with Anthony van Leeuwenhoek who in 1674 was the first to observe swimming cells in a drop of water using a primitive microscope. Since then, advances in microscope technology have enabled us to study in detail the mechanics of individual cell motion. This has shed light on how the coupling of intracellular processes such as actin polymerization (in amoeboid cells) and receptor activation are responsible for how cells alter their movement in response to external stimuli (Bray, 2001). Having made substantial progress in understanding the basic units of life, the primary challenge ahead lies in understanding how these units, the cells, interact with each other to produce the large-scale organization typical of tissues. Studies which directly address such problems can be experimental or theoretical, the latter only coming into fashion in the last half of the twentieth century. In this article we will discuss the multiscale modeling of tissue, in particular focusing on how the choice of the mathematical approach to the problem depends on the questions of interest and on the spatial and temporal length scales inherent to the biological processes under investigation.

In the last fifty years, the role of mathematical modeling in biology has vastly increased in scope and application, and nowadays it is considered an important tool

to interpret experimental data and also to test hypotheses and generate new predictions (Mogilner *et al.*, 2006; Schnell *et al.*, 2007). One may ask why there is the need at all of such modeling when the basic details about the fundamental units, the cells, and their interactions are well known. The answer is that a system of discrete entities (these can represent molecules, cells or whole organisms) interacting with each other via very simple rules can produce incredibly complex and intricate behavior which generally is difficult or impossible to predict by "simply thinking about it." An example of this is Conway's Game of Life (Gardner, 1970). This is a two-dimensional computer simulation (a cellular automaton) in which two types of discrete entities, here referred to as A and B, are placed on a square grid and interact via four rules: (i) if an A has less than two A neighbors then it changes to B, (ii) if an A has more than three A neighbors it changes to B, (iii) if A has two or three A neighbors then it remains unchanged, (iv) if a B has exactly three A neighbors then it changes to A. These rules are very simple but when they are iterated it is found that the system exhibits a large number of different life-like behaviors such as the appearance of still and oscillating ordered patterns from initially random ones and arrangements of entities which glide over the grid. These nontrivial patterns can be qualitatively predicted in many instances by theory (Deutsch and Dormann, 2005). Simple cellular automaton models such as the above illustrate the need of computer simulation and mathematical modeling in understanding how cell–cell interactions at the microscopic level lead to the macroscopic form and order which is ubiquitous in nature.

The remainder of this article is organized as follows. In Section II we discuss how mathematical models of biological systems can be constructed at various spatial scales of interest and how these models can, separately or combined, provide insight in the system under study. In Section III we illustrate the process of model building at two different scales for a rudimentary chemotactic intercellular communication system which incidentally is a popular abstraction of a number of different biological systems. In Section IV we discuss the relationship of models at different scales to each other in the framework of mean-field theory. This sheds light on the models' range of validity and applicability. We conclude in Section V by showing how multiple scale analysis of the same biological system is more robust then single scale analysis. Such an analysis enables one to weed out nonphysical predictions due to model artifacts and hence to build a coherent picture of the biological dynamics.

II. Quantitative Modeling

Mathematical models can be constructed at various scales of interest. Three common spatial scales which are of experimental relevance are the molecular, the cellular and the supercellular or tissue scale. In principle, given complete knowledge of the molecular-level processes occurring inside a cell, one can construct a model which is

correct and valid for all spatial scales of interest. However, in practice, because this knowledge is incomplete and also because of the immense number of equations (one needs equations for the position and velocity of each individual molecule in a cell!) needed to encode such detail, it is not feasible to build and analyze such detailed microscopic models of cell movement. We shall not treat such models further but instead focus on cellular and tissue models.

By cellular models, we mean those which precisely describe the movement of each individual cell. In these models, the natural spatial scale is set by the size of the cell and so chemical molecules which are much smaller than this scale are modeled by means of a continuum concentration field, not as discrete entities. In this description, a colony of N cells interacting via M different chemicals would be modeled by $3N$ equations of motion for the cells in terms of the position and velocities of their center of mass and M equations describing how the chemical concentrations vary with space and time. These models can be based on cellular automata (Deutsch and Dormann, 2005) or lattice-free Monte Carlo simulations (Drasdo *et al.*, 1995; Grima, 2007; Newman and Grima, 2004; Grima and Schnell, 2007).

Tissue-level models are even coarser than cellular models. The spatial scale is here much larger than that of a cell, meaning that one cannot distinguish between individual cells or molecules. These are population-type models in which one is interested in the collective dynamics of the colony rather than in its individual components. Hence in this case, both cells and chemicals are modeled by means of continuum concentration fields. A colony of N cells interacting via M different chemicals would be described by just $1 + M$ equations, a substantial reduction in complexity compared to the cellular model. Tissue-level models are by far the most common in the scientific literature mainly owing to the fact that they are based on sets of coupled ordinary or partial differential equations for which many methods of analysis are available (Murray, 2002; Murray, 2003). The differences between cell and tissue-level modeling are illustrated in Fig. 1.

It is to be emphasized that models can be built at other scales, for example, one could construct sub-cellular models in which the relevant spatial scale is a fraction of the cell diameter. Examples of such models are the Cellular Potts model (Graner and Glazier, 1992), Hyphasma (Meyer-Hermann and Maini, 2005), the SubCellular Element Model (Newman, 2005), and continuum models based on a viscoelastic description of the intracellular environment (Gracheva and Othmer, 2004). These models are currently for the most part more phenomenological than cellular models due to the large detail involved in describing the intracellular environment.

Models at different scales can also be combined in a module-like fashion to form a supermodel which describes in an approximate way a biological system over a wide range of spatial and temporal scales. These models are not usually amenable to mathematical analysis but are suitable for studying, via computer simulation, very complex processes such as those involved in cancer (Alarcon *et al.*, 2004).

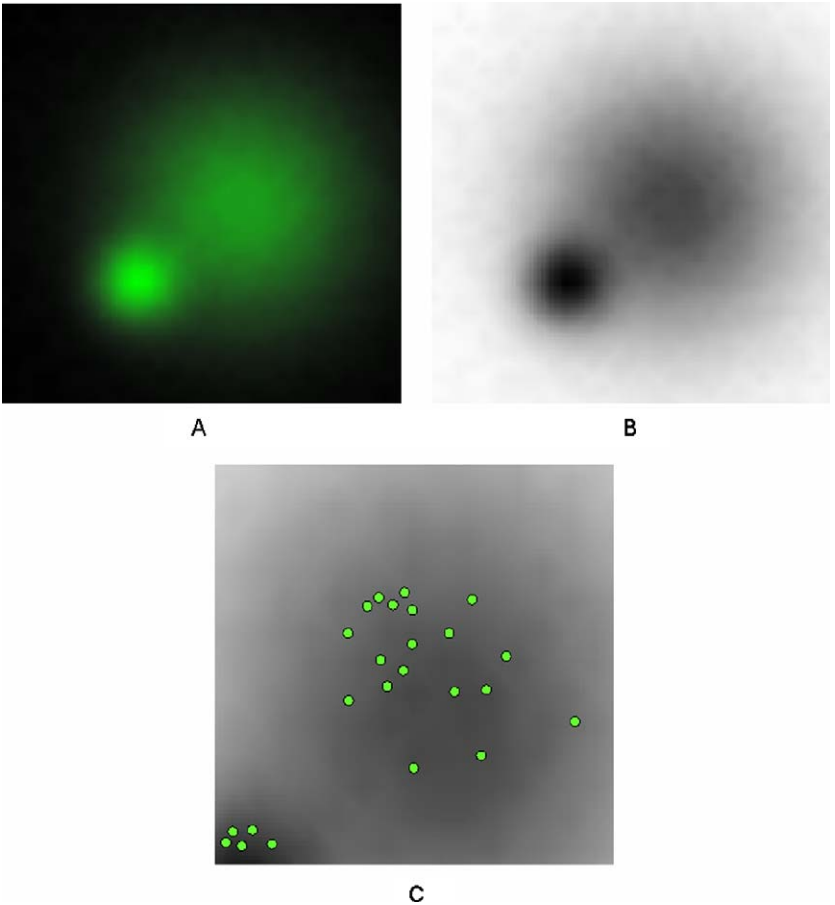

Figure 1 Schematic illustrating tissue (A and B) and cellular models (C). Tissue-level models are at a scale much larger than that of an individual cell and so the only variables are cell concentration (shown by the intensity of the color green in A) and chemical concentration (shown by the gray scale in B where white denotes regions of high chemical concentration). Note that in this example, chemical is absorbed by cells and thus regions of large cell concentration correspond to regions of low chemical concentration. However generally the relationship between the two is much more complex. Cellular-level models are at a much finer spatial scale such that individual cells (solid green circles in C) can be distinguished; molecules are much smaller than cells and hence only a chemical concentration can be defined at this level (represented by gray-scale background in C). See color insert.

III. Building Cellular and Tissue-Level Models for a Simple Biological System

In this section we illustrate the process of model building at two different spatial scales, namely at the cellular and tissue scales. To make our discussions concrete,

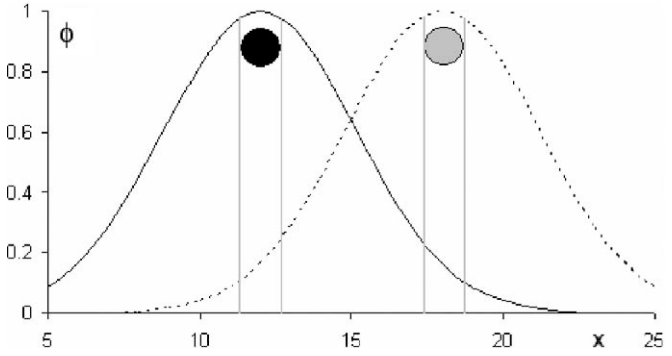

Figure 2 Two chemotactic cells interacting via chemical fields. The cells continuously secrete chemical which then diffuses and decays at a later time. Thus at a snapshot in time, t, the chemical concentration ϕ around a cell due to its own secretion is a Gaussian (solid and dashed curves). Each cell measures the difference in chemical concentration across its body; the black cell senses a chemical gradient pointing towards the gray cell (difference in concentration indicated by points where the solid vertical gray lines intersect with dotted and vertical Gaussians). The same is valid for the gray cell. Hence cells will move towards or away from each other, depending on whether they are positively or negatively chemotactic.

we consider a simple biological system composed of cells which continuously secrete a chemical at a constant rate and which chemotactically respond to it by moving up (positive chemotaxis) or down (negative chemotaxis) the local chemical gradient present across the cell. The chemical diffuses and degrades in solution after some time. This is amongst the simplest examples of a cell–cell communication system. If the cells are strongly chemotactic then the expected net result is aggregation if the cells are positively chemotactic and dispersion if they are negatively chemotactic (Fig. 2).

This simple system was originally postulated as a crude model for the aggregation stage of the life-cycle of the slime mold (Keller and Segel, 1970). In that case, chemotaxis is strictly positive and the secreted chemical is cAMP. By adding more processes to the core model described above, one finds that it describes a wide range of biological systems. It can be applied to model the preaggregation stage of the slime mold where the amoeboid cells secrete a chemorepellent, i.e., a chemical to which they do negative chemotaxis to, while simultaneously performing positive chemotaxis to folic acid trails left by their food source, bacteria. Other examples in which the model finds use are: (a) the formation of plaques in Alzheimer's disease, which form by aggregation of microglia (Edelstein-Keshet and Spiros, 2002), (b) the formation of regular striking patterns of bacterial colonies of *Escherichia coli* and *Salmonella typhimurium* feeding on intermediates of the tricarboxylic acid cycle (Murray, 2003), (c) the dynamics of blood vessel formation (Gamba *et al.*, 2003).

A. Tissue-Level Modeling

The tissue-level model for this simple biological system was first written down by Keller and Segel (1970) in the context of slime mold aggregation. It has two main variables: the chemical concentration Φ and the cell number density or concentration ρ. These two completely define the state of the system at a given time and point in space. The equations defining the model are:

$$\frac{\partial \rho}{\partial t} = D_0 \nabla^2 \rho - \alpha \nabla \cdot \rho \nabla \Phi, \tag{1}$$

$$\frac{\partial \Phi}{\partial t} = D_1 \nabla^2 \Phi - \lambda \Phi + \beta \rho. \tag{2}$$

The second equation follows directly from well-known physical principles. This is a reaction–diffusion equation modeling the diffusion of chemical with diffusion coefficient D_1, its decay or degradation in solution at a rate λ and chemical secretion by cells at a rate β.

The first equation was written down as an approximate phenomenological description of the average movement of a colony of cells with time. This was done by analogy with two physical laws, namely those governing diffusion and heat transfer (Keller and Segel, 1971). The first term on the right of Eq. (1) represents cell motion in the absence of chemotaxis while the second term takes into account chemotaxis. In the absence of a chemical gradient, $\nabla \Phi = 0$, the equation becomes identical to the diffusion equation. This models the fact that in the absence of chemotaxis, the random motion of cells appears to be similar to that of molecules. In this case D_0 is a measure of the space spanned by motile cells per unit time, otherwise called the cell diffusion coefficient. The second term which describes chemotaxis can be deduced by analogy with Fourier's law of heat conduction which states that the heat flux through a material is proportional to the temperature gradient. In a similar way one can hypothesize that cell flux due to chemotaxis is proportional to the chemical gradient. The parameter α is the chemotactic sensitivity which is analogous to conductivity in heat transfer problems; it is positive for positive chemotaxis and negative for negative chemotaxis. We note that this model has not been derived from a finer-scale model or from first principles but rather by analogy with unrelated though qualitatively similar physical phenomena. This is a general common problem to many tissue-models which means that frequently the assumptions implicit in such models are not exactly known, a topic we address in detail in Section IV.

B. Cell-Level Modeling

We now consider a cellular model for the above biological system. As we have previously remarked this approach consists of writing down equations describing the movement of each individual cell rather than a population-type description as for the

tissue-level model. If we set the spatial scale of interest to be about an order of magnitude larger than the cell diameter then small scale details such as the actual cell shape can be ignored meaning that the dynamics of the cell's center of mass is the only relevant process for modeling purposes. As we now show, the model can be rigorously built using experimental data of single cell motion in the absence and presence of chemotaxis.

Experiments show that in the absence of chemical or adhesion gradients, cell velocities are correlated for some short time τ (which varies with the cell type) and uncorrelated for times longer than τ (Mombach and Glazier, 1996; Rieu *et al.*, 2000). Hence provided τ is sufficiently small, cells can be considered to perform random walks and their movement statistics to be analogous to the statistics of the Brownian motion of molecules in solution. Thus by analogy cells have a diffusion coefficient D_0 characterizing their diffusion-like motion. Note that the origin of the random walk behavior of cells has physically nothing to do with that of molecules; the two simply share a common mathematical underpinning. For cells, D_0 simply reflects the incessant fluctuations in the actin polymerization dynamics of their cytoskeleton while for solute molecules it reflects the rate of collision of the smaller solvent molecules with them (Rieu *et al.*, 2000). Typically the cell diffusion coefficient is one to two orders of magnitude smaller than the chemical diffusion coefficient of free molecules in dilute solutions.

It thus follows from experiment that a cell can be modeled as a random walker. Using Newton's second law one can then immediately deduce that the equation of motion for the center of mass coordinates, $\vec{x}_i(t) = \{x_i(t), y_i(t), z_i(t)\}$, of a single cell, labeled i, is given by:

$$m\frac{\partial^2 \vec{x}_i(t)}{\partial t^2} = -k\frac{\partial \vec{x}_i(t)}{\partial t} + \vec{\eta}_i(t) + F_c\big(\vec{x}_i(t), t\big). \tag{3}$$

The forces acting on the cell are the viscous drag force, $k\frac{\partial \vec{x}_i(t)}{\partial t}$, due to the surrounding fluid, a stochastic force, $\vec{\eta}_i(t)$, which takes into account the cell's apparent random motion and a force F_c which directs the cell towards or away from the source of the chemotactic stimulus. The stochastic force term is usually modeled as white noise which has two main statistical properties, namely that both the mean force and the correlation time τ are zero. This is appropriate for modeling cells with small τ. A more general description involves using colored noise instead of white noise which has a nonzero correlation time.

Cells and microorganisms live in an environment with different hydrodynamic properties than the one we experience in our every day life. Viscous forces dominate their movement whereas inertia is an insignificant factor for cell motility (Berg, 1993; Bray, 2001; Purcell, 1977). Practically speaking this means that water jet propulsion is not efficient for cells and that streamlined shapes are also of no help to their movement. More importantly for our discussion this means that the acceleration term on the left hand side of Eq. (3) is negligible compared to the viscous drag force term and

so it can be neglected, leading to a simplified model equation:

$$\frac{\partial \vec{x}_i(t)}{\partial t} = \vec{\eta}_i(t) + F_c\big(\vec{x}_i(t), t\big). \tag{4}$$

The last task in completing the mathematical description of individual cell movement involves specifying the chemotactic force, F_c. It is experimentally found that in the presence of a chemical gradient, the diffusion-like behavior persists but the mean-velocity of chemotactic cells, which was zero in the absence of chemotaxis, is now a function of the magnitude of the local chemical gradient and of the absolute value of the local chemical concentration (Lewus and Ford, 2001; Tranquillo *et al.*, 1988). If the chemical concentration is not too large, it is found that this mean velocity is directly proportional to the chemical gradient but independent of the absolute value of the chemical concentration. From Eq. (4) it follows that the mean cell velocity is proportional to the chemotactic force and thus to comply with experiment, we set $F_c = \alpha \nabla_i \phi$, where the subscript i denotes that the gradient is evaluated at the current position of cell i. Hence the equations of motion for a cell colony composed of N cells are:

$$\frac{\partial \vec{x}_i(t)}{\partial t} = \vec{\eta}_i(t) + \alpha \nabla_i \phi, \quad i = 1, \ldots, N. \tag{5}$$

Note that each cell in the colony has associated with it a distinguishing index i. Note also that in the tissue-level model the concentration field was denoted by Φ rather than ϕ as in Eq. (5). The reason for the use of this notation will become clear in the next section. The chemotactic sensitivity α is a measure of an individual cell's response to an external chemical stimulus.

To complete the cellular model one needs to specify an equation for how the chemical concentration varies in time and space due to the three processes of diffusion, decay and secretion by the cells. This follows straightforwardly from well-known physical principles:

$$\frac{\partial \phi}{\partial t} = D_1 \nabla^2 \phi - \lambda \phi + \beta \sum_{i=1}^{N} \delta\big(\vec{x} - \vec{x}_i(t)\big). \tag{6}$$

Note that chemical is actually secreted by cells on their surface but since we are assuming that the spatial scale is an order of magnitude or so greater than cell size, this is effectively the same as saying that secretion occurs at the current position of their center of mass coordinates. This is the reasoning behind the delta function term on the right-hand side of the above equation.

The cellular model is now complete. It is fully described by the $3N + 1$ equations given by Eqs. (5) and (6). Note that there is a one-to-one correspondence between all the parameters in the cellular and tissue models. The cellular model was introduced and first studied by Newman and Grima (2004).

IV. Mean-Field Theory and the Interrelationship of Models at Different Spatial Scales

As we saw in Sections II and III there are many varied modeling methodologies for studying biological systems. Each modeling approach has its strengths and limitations and naturally is only valid provided certain conditions are satisfied. Presently much work is being done to understand the assumptions implicit in such approaches, how different models are related to each other and how to separate results due to model artifacts from those due to genuine physiological processes. For example, model results can in some instances be highly sensitive to the topology of an artificial spatial grid on which simulation of molecular or cellular movement occurs (Deutsch and Dormann, 2005; Grima and Schnell, 2006). Of course there would be no dissent between models at different scales if they were all rigorously derived from a molecular level model, in which case the laws of physics and chemistry are very well understood. However in practice this is not possible. A simpler approach is to derive models at a coarse scale from an intermediate scale model which has the special property of being based on biology and physics which are experimentally well studied. In this section we use such an approach to understand the assumptions inherent in the use and application of the tissue-level model of our simple biological system. This will involve the derivation of this phenomenological model from the experimentally based and finer scale cell-level model introduced in the previous section.

A. Coarse Graining

The process of deriving models at a certain scale from those at a finer model is called coarse-graining. This usually implies performing some form of averaging of the dynamics of interaction over a certain length scale. Examples from statistical mechanics would be the derivation of the macroscopic ideal-gas laws and the stress-strain constitutive relations (Goldhirsch and Goldenberg, 2002) starting from the microscopic equations of motion for individual molecular motion. The process of going from the cellular model to the tissue-level model involves going from a description in terms of the $3N$ positions and velocities of individual cells to one in terms of a single parameter, the average number density (or concentration) of cells ρ. The definition of the number density is based on the idea of an ensemble average from statistical mechanics. Consider M separate biological systems (or experiments) which initially at $t = 0$ are all identical, meaning that they have the same exact spatial distribution of cells. Each cell's movement is described by an equation of motion as in our cellular model. Then as time progresses, the spatial distribution of cells in each of the systems is not anymore the same due to the inherent stochasticity in each cell's movement. The average cell concentration at a given point in space and time, $\rho(\vec{x}, t)$, can then be obtained by counting the total number of cells at time t having center of mass coordinates in a small volume ΔV centered about $\vec{x}$ in all the biological systems and dividing by

$M\Delta V$. This is the basic idea behind ensemble averaging, which is mathematically encapsulated by the equation:

$$\rho(\vec{x}, t) = \left\langle \sum_{i=1}^{N} \delta\left(\vec{x} - \vec{x}_i(t)\right) \right\rangle. \tag{7}$$

Note that the ensemble average is denoted by the angular brackets. Taking the time derivative of Eq. (7) one obtains an equation for the time evolution of the cell concentration as a function of the positions and velocities of all cells:

$$\frac{\partial \rho}{\partial t} = -\sum_{i=1}^{N} \nabla \cdot \left\langle \frac{\partial \vec{x}_i(t)}{\partial t} \delta\left(\vec{x} - \vec{x}_i(t)\right) \right\rangle. \tag{8}$$

This equation provides the link between the tissue-level parameter, ρ, and the cell-level parameters which are the cell position and velocity. By substituting the equations defining our cellular model, Eqs. (5) and (6) in Eq. (8), one obtains the coarse-grained version of the cellular model (a detailed derivation can be found in Newman and Grima, 2004). We shall call this derived model, Model A, as opposed to the tissue-model written down directly using phenomenological arguments, defined by Eqs. (1) and (2), which we refer to as Model B.

The question of interest here is whether Models A and B are the same. The answer is no, except under certain conditions. The general, nonintuitive conclusion of the coarse-graining procedure is that generally it is not possible to derive a tissue-level model, i.e., a model in terms of only the concentrations of chemicals and cells. In particular it is found that the exact determination of how the cell concentration varies with time requires full knowledge of the statistical correlations between cells, i.e., the two-cell joint probability distribution, the three-cell joint probability distribution functions, etc. This fact suggests that Model B is an approximate description which results from Model A by making some assumptions regarding the nature of cell–cell correlations.

Statistical correlations between cells depend sensitively on a number of factors. Each cell's motion has two components; one is stochastic which models the incessant actin polymerization dynamics of their cytoskeleton (cell diffusion) while the other component leads to directed movement up or down chemical gradients (chemotaxis). Since cells themselves produce the chemotactic chemical, it follows that the second component of their motion leads to correlations between different cells. On the contrary the first component of their motion dilutes intercell correlations. Hence the strength of statistical correlations between cells depends on the relative strengths of cell diffusion and chemotaxis. Similarly one expects that if cells have a large space in which to roam then their correlations are bound to be less important than if they were constrained to move in a smaller space. If the number of cells is particularly large then it is plausible that the correlations between any two cells i and j is small. This is since the chemical field sensed by cell i will be due to the sum total of chemical secreted by all other cells at all previous times, which effectively swamps the chemical

specifically secreted by cell j. However it must be emphasized that since chemotaxis is a long-range force, the magnitude of intercell correlations in our biological system is always appreciable particularly when compared to other biological systems in which cell interaction occurs only via contact-mediated forces such as adhesion. Note that in the latter case there are only correlations between nearest neighboring cells rather than between all cells as in the case of chemotaxis.

It can be shown that by assuming that cell–cell statistical correlations are very weak or negligible, one recovers Model B from Model A (similar conclusions are also borne out by a different derivation using a different model due to Stevens, 2000). Without this assumption, it is not generally possible to derive a tissue-level model from a finer scale one. This conclusion is true not only for our simple biological chemotactic system but is generally valid. It is a statement following from many-body theory, which is a general mathematical framework for studying systems consisting of many interacting discrete entities (Mattuck, 1992). The weak correlation assumption inherent in the tissue-model implies that such models are only valid for modeling biological systems where there are large numbers of cells and where chemotaxis and other-long range forces are weak compared to local forces due to neighboring cells. Another situation where the use of such models is warranted is when a chemical gradient is set up by some artificial means in a laboratory, e.g., Boyden chamber experiments. In such a case the chemical providing the stimulus is not produced by the cells and thus there cannot be any cell–cell correlations due to chemotaxis. The use of tissue-level models is suspicious for understanding the biological dynamics in spatial regions where cell concentration is low, for example, at the edges of a cell colony or regions where the cell death rate is high or situations where interactions are limited to few hundreds of cells. The use of such models is also problematic in cases where (i) the effective dimensionality of the environment in which cells move is less than three dimensions, e.g., haptotactic cell motion, which restricts cell movement to following adhesive gradients on surfaces, (ii) the extracellular chemical signals secreted by cells decay slowly compared to the typical timescale of cell movement. In such cases it would be wise to compare the predictions of tissue-level models with those of a finer scale model such as a cellular model before making any final conclusions.

B. Mean-Field Theory

Models which are obtained by neglecting correlations between interacting entities are generally called mean-field theories (or self-consistent field theories) in the physical sciences. Though this idea is new to biology and mathematical biology, mean-field theory (MFT) has been extensively used and its implications investigated in various fields of physics particularly in statistical mechanics (Kadanoff, 2001). The idea behind MFT is to make the approximation that each entity behaves as if it was an independent entity sitting in a mean field produced by all other entities. Note that the mean referred to in this case is the average field computed by: (i) calculating the total

field due to all other entities in a set of N independent realizations at a time t which leads to the quantities $\phi_1(t), \phi_2(t), \ldots, \phi_N(t)$; (ii) calculating the average of the latter quantities leading to $\Phi(t)$. Since realizations are independent from each other, an entity is uncorrelated with the mean field $\Phi(t)$ produced by all the other entities.

MFT is expected to be correct when fluctuations in the field, i.e., the standard deviation of the set of values $\phi_1(t), \phi_2(t), \ldots, \phi_N(t)$, are much smaller than its mean value, $\Phi(t)$. This condition is usually satisfied provided the number of interacting entities is particularly large. Thus it is generally found that MFT provides a qualitatively correct picture of the dynamics of fluids provided they are not near their critical points. At these points, phase transitions occur and due to the strong fluctuations in mass density, the predictions of MFT are incorrect in both two and three dimensions. Indeed this is the underlying reason why the Van der Waals theory of fluids fails to describe the experimental data of fluid behavior near the critical points (Kadanoff, 2001).

The main difference between MFT applied to cellular models to understand tissue dynamics and that applied to molecular models of fluids is that the latter involves Avogadro number of interacting molecules whereas the former frequently involves few hundreds or thousands of cells. This suggests that fluctuations in the chemical fields through which cells interact may play an important role in determining the overall behavior of a multicellular system and that mean-field theories such as the tissue model previously introduced may not be able to effectively capture such behavior. The chemical field sensed by cells in the tissue-models is an ensemble averaged field, Φ, and hence is an artificially smooth field devoid of any local spatial fluctuations whereas the chemical field in the cellular model, ϕ, contains such fluctuations. Note that the cellular model itself is the result of the application of the mean-field assumption on a molecular-level model and hence in reality the tissue-model represented by the Keller–Segel equations, Eqs. (1) and (2), encapsulates two consecutive and separate mean-field assumptions, as illustrated in Fig. 3.

Unfortunately it is frequently difficult to develop a tractable analytical theory for strongly correlated behavior and indeed to date most attempts at understanding such behavior have been via direct computer simulation. The mathematical tools to understanding such systems include diagrammatic perturbation methods (Mattuck, 1992), field theory and renormalization group theory (Cardy, 1997) and small noise perturbation theories (Gardiner, 2004). In the next section we discuss some of the effects that fluctuations bear on model predictions.

V. Multiple Scale Analysis

In this section we discuss the effects of cell correlations in the simple biological example introduced in previous sections. In particular we investigate the validity of the mean-field assumption inherent in tissue-level models. Depending on whether

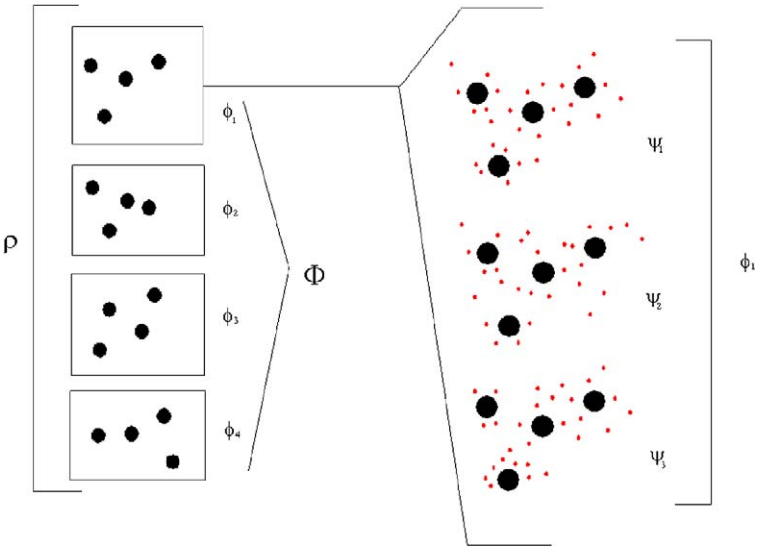

Figure 3 Schematic showing a pictorial representation of a tissue-level model in the framework of mean-field theory. The black circles are cells and the smaller red circles are chemical molecules. We show a system of four interacting cells. At each instant in time, the variables of the tissue-level model (ρ, Φ) are derived by averaging an ensemble of similar cellular-scale models each one having slightly different positions for the four cells. Each of the cellular models has associated with it a mesoscopic chemical field ϕ_i which is dependent on the spatial configuration of cells. The ensemble average over this field gives the macroscopic field Φ while the density field ρ results from the ensemble average of the spatial configuration of cells. In a similar manner, the cellular models are related to the microscopic models: the ensemble average over the microscopic field ψ_j produced by the different spatial configurations of the chemical molecules in a molecular-level model leads to the mesoscopic fields. See color insert.

the chemotaxis is positive or negative, cells either aggregate or disperse. Aggregation leads to progressively higher cell concentrations suggesting that the Keller–Segel tissue-model (MFT) is at least overall qualitatively correct in predicting the dynamics. The converse is true of chemotaxis-induced dispersion; in such a case it is not immediately clear as to how trustworthy is MFT.

A. Weak Intercellular Interactions

We first consider the case of weak chemotactic signaling between the cells. Consider an experimental setup in which initially cells are confined to a small volume. Given this setup, what is the qualitative and quantitative temporal dynamics of cell motility? The cells will experience two forces: a cohesive (dispersive) force due to positive (negative) chemotaxis and a dispersive force due to cell diffusion.

In the absence of chemotaxis, it is clear that only cell diffusion is present and thus the outer edge of the cell aggregate will necessarily increase as the square root of time elapsed, at a rate determined by the cell diffusion coefficient. When chemotaxis is turned on, albeit very weakly, it is found that this behavior is qualitatively unchanged. This is predicted by both cellular and tissue-level models (Newman and Grima, 2004). However tissue-level models predict that the rate at which the outer edge of the aggregate outwardly expands is also unchanged whereas cellular models predict a smaller rate when chemotaxis is positive (cohesive forces act against cell diffusion) and larger when chemotaxis is negative (dispersive forces enhance cell diffusion). These results are illustrated in Fig. 4. The discrepancies between the two models can be shown to arise due to the fact that for very weak chemotaxis the cells primarily interact with their own secreted chemical rather than with that of other cells. The mean-field approach underestimates effects due to self-interaction since its main underlying assumption, namely that it is valid in the limit of a very large number of interacting cells, also implies that the self-interaction is negligible compared to that due to all other cells. The above results are obtained via perturbation analysis in the strength of cell–cell coupling. By the term "coupling" here we mean how strongly cells feel each other through chemical fields or other forces. For example, the coupling strength in our simple biological system would be proportional to the product of the chemotactic sensitivity and the chemical secretion rate, $\varepsilon = \alpha\beta$.

Thus in the case of weak intercellular interactions the MFT assumption leads to a qualitatively correct picture but quantitatively incorrect predictions. This we expect to generally be the case when modeling cells which are interacting solely through local forces such as adhesion or through weak long-range interactions. This statement is particularly true when the strength of these cell–cell interaction forces are small compared to those stemming from the incessant fluctuations in the actin polymerization dynamics of the cell's cytoskeleton. Another instance when the MFT assumption holds is when cells are only chemotactic for periodic short spans of time, in between of which cell motion is random and completely unaffected by external chemical stimuli (pure cell diffusion). These conjectures have been directly or implicitly verified for models of tissue growth (Deutsch and Dormann, 2005) and of in vitro monolayer cultures (Drasdo, 2005).

B. Strong Intercellular Interactions

Perturbation analysis is typically not useful for strongly-coupled many-body systems which in general elude analysis and their exploration is thus presently for the most part confined to computer simulation. We shall describe two complimentary approximate analytical methods which can afford insight into such problems. The first assumes that there is a very high average cell concentration in the system such that MFT can be directly applied whilst the second assumes that the cell concentration is so low that a single-cell model captures the dynamics. These two approaches are extremes and

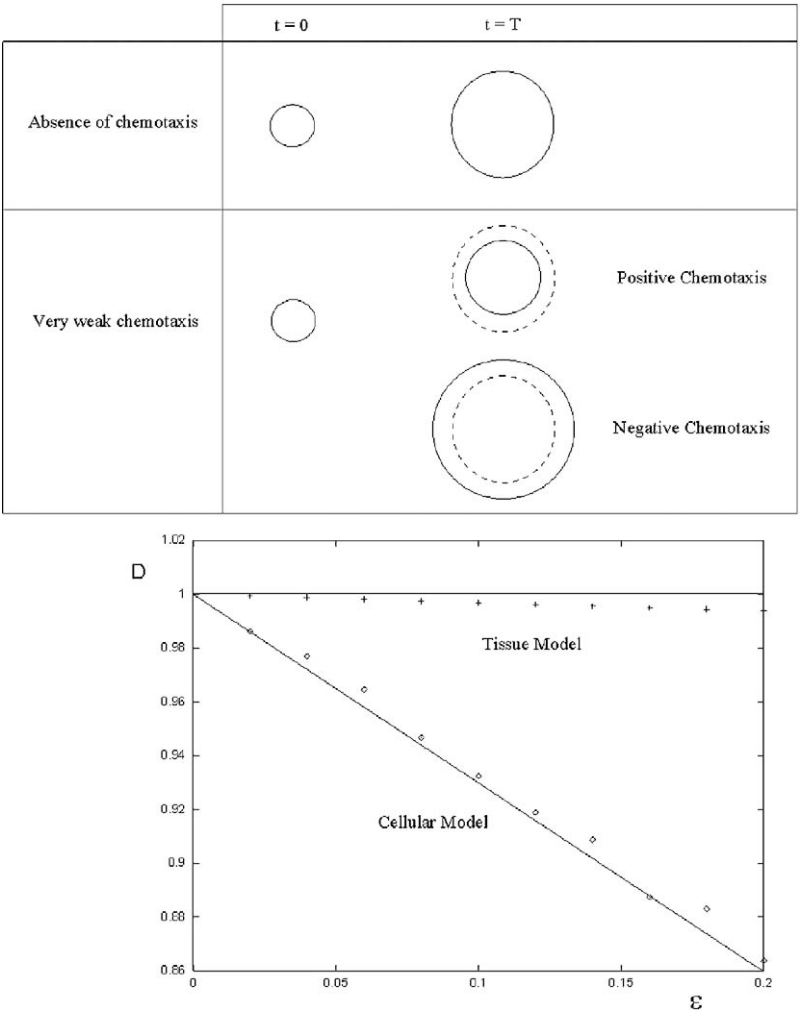

Figure 4 Differences in prediction between cellular and tissue-level models for a simple biological system consisting of chemotactic cells which are constantly secreting a chemoattractant (positive chemotaxis) or a chemorepellent (negative chemotaxis). The cells at $t = 0$ occupy a small compact volume. In the absence of chemotaxis, as time progresses the cells diffuse and the cell aggregate becomes correspondingly larger; the size of the predicted aggregate in this case is the same for both models at any point in time (shown for $t = T$). However when very weak chemotactic forces are present, the predictions of the two models at later times disagree (solid circles represent the prediction of the cellular model whereas dashed circles represent those of the tissue model). The graph at the bottom of the figure compares the predictions for the effective cell diffusion coefficient D using both theory (solid curves) and computer simulation (data points) for the case of positive chemotaxis. The parameters are $D_0 = D_1 = 1$, $\lambda = 0.05$ and the number of realizations is 10^5. The models disagree because the tissue model incorrectly ignores cell–cell correlations induced by chemotactic signaling.

hence in reality the dynamics of the tissue will be exactly described by neither but will be approximated by both, in a manner dependent on the actual cell concentration. The single cell approach can sometimes properly take into account cell–cell correlations even when strong but its predictions may quantitatively (and maybe qualitatively as well) fail when there are large numbers of interacting cells. The MFT approach cannot take into account cell–cell correlations but since effects due to the latter are diluted for large cell concentrations it may offer a picture of the dynamics in such a limit. The two approaches are thus complimentary in many ways.

1. Mean-Field Analysis

Analysis of MFT is frequently a necessary first step in shedding light on the complex dynamics. This is since many methods from the general theory of ordinary and partial differential equations, the building blocks of mean-field models, can be brought to bear on the problem. The most common and popular technique is that of stability analysis (phase-plane analysis) about the equilibrium points of the system (Deutsch and Dormann, 2005; Murray, 2002). For our simple biological system, the equilibrium point corresponds to the case when the cells and the chemical are uniformly distributed all over space such that the rate of chemical secretion by the cells equals exactly the rate of chemical degradation. In such a case the system neither aggregates nor disperses but if fluctuations in cell density occur then it is plausible that the system will move away from this equilibrium state. Stability analysis indicates that such fluctuations will cause positively chemotactic cells to aggregate provided the chemotactic coupling between them is sufficiently large. In particular, for cells constrained to move in a very thin capillary, i.e., a one-dimensional space, aggregation occurs only if the chemotactic sensitivity, α, satisfies the condition:

$$\alpha > \frac{D_0}{\beta\rho_0}\left(\frac{4D_1^2\pi^2}{\Lambda^2} + \lambda\right), \tag{9}$$

where Λ is the spatial wavelength of the fluctuations in the cell concentration. If this condition is not satisfied then any fluctuations in cell concentration will die away by cell diffusion thus reverting the system back to the equilibrium state. Of course if the cells are negatively chemotactic then the system always goes back to its equilibrium state as the chemotaxis-induced dispersion enhances the effects of cell diffusion. It must be borne in mind that these conclusions are correct for our simple biological system initially set up such that cells and chemical are uniformly distributed all over space in equilibrium. A more general realistic initial condition is one in which cells occupy a certain finite spatial region of size L. In such a case and for positive chemotaxis, aggregation occurs if Eq. (9) with $\Lambda = L$ is approximately satisfied. For negative chemotaxis, the cells will invariably disperse themselves over a larger region than L at a rate larger than that solely due to cell diffusion.

Whether these predictions hold or not for the strongly-coupled many-cell case can be ascertained by simultaneous computer simulation of the cellular and tissue

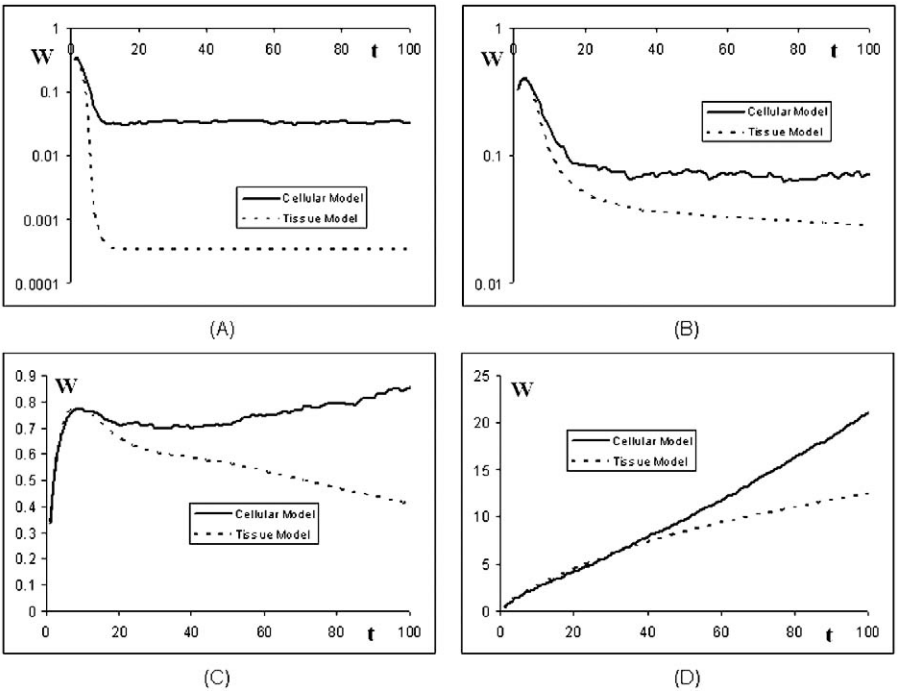

Figure 5 Comparison of cellular and tissue-model predictions for the temporal variation of the size W of a strongly coupled aggregate of twenty positively chemotactic cells. The cells are initially uniformly distributed over the spatial region $[-1, 1]$. W is the standard deviation of the cell positions. The parameters are $D_1 = \alpha = \beta = \lambda = 1$ and the cell diffusion coefficient is $D_0 = 0.05$ (A), $D_0 = 0.5$ (B), $D_0 = 1.0$ (C) and $D_0 = 2$ (D). The data for the tissue-model is obtained by numerical integration of Eqs. (1) and (2), while the data from the stochastic cellular model defined by Eqs. (5) and (6) is obtained by averaging simulation data for 1000 independent realizations. Proper convergence of results with decreasing size of time step, δt, has been verified by repeating simulations using various values of δt; data shown is using $\delta t = 0.005$ or 0.01. There is qualitative agreement between the two models except when the parameters are such that the multicellular system is close to the transition from aggregative behavior to dispersive behavior (C).

models for the same set of parameters. Such a comparison is shown in Fig. 5 for the case of twenty positively chemotactic cells which are initially uniformly distributed in a region of length two spatial units in a one-dimensional space. Note that in the cellular model the cells aggregate when the cell diffusion coefficient, D_0, is less than some critical value between 0.5 and 1, and disperse otherwise. Given the parameters $\alpha = \beta = D_1 = \lambda = 1$ used in the simulation, the stability analysis on the mean-field (tissue) model, i.e., Eq. (9), predicts aggregation if D_0 is less than 0.9. Hence in this case the mean-field analysis has fared remarkably well even though the system consists of a small number of strongly-interacting cells.

Note that qualitative differences between cellular and tissue-models are present only when the parameters force the system to be close to the transition between aggregative and dispersive behavior (Fig. 5C), a phenomenon which indeed parallels the breakdown of mean-field models of fluid phase transitions, i.e., near their critical points. In all other cases, there is qualitative but not necessarily quantitative agreement. Generally it is found that tissue-level models predict artificially small cell aggregate sizes, particularly when aggregation is strong, e.g., the final aggregate size for the tissue model in Fig. 5A is approximately 100 times smaller than that predicted by the cellular model. This can be explained by the following thought experiment. Consider the case where positively chemotactic cells at some point in time are exactly distributed according to a Gaussian distribution; this we call Case A. This case is not really achievable in practice. The real case, Case B, would have small cell concentration fluctuations about the Gaussian distribution of Case A. Indeed Case A is the ensemble average of a large number of Case B systems. Since the chemotactic chemical is produced by the cells, then the chemical concentration will have an identical spatial distribution as the one for cell concentration. Hence in Case A, cells on both sides of the central peak of the Gaussian distribution will invariably sense a chemical gradient directed towards this peak. This is not the situation in Case B, where cells will sense chemical gradients both towards and away from the central peak according to the local fluctuations (the local minima and maxima) in chemical concentration. This naturally implies that in the real case, Case B, cells will not be as strongly attracted to the global cell concentration peak as in Case A, which explains the observed differences in final aggregate width in Fig. 5.

There is another reason supporting such observations. A cell, due to its own constant secretion and positive chemotaxis to its own chemical, will tend to stay in the region of space which it presently occupies; this self-interaction opposes the aggregation of the multicellular system. However this behavior is counteracted by the response to the chemical secreted by other cells which favors aggregation. The mean-field approach is strictly valid in the limit of a very large number of interacting cells in which case the self-interaction is negligible compared to that due to all other cells. Hence MFT has to predict artificially stronger aggregation than cellular models. This shows one of the implications of assuming cell sensitivity to a mean chemical field (tissue-level model) as opposed to sensitivity to the actual field (cellular model).

2. The Single-Cell Approach

The single-cell system is not always amenable to analysis, but in cases where it is, it can provide useful insight into the strongly-coupled dynamics of cell movement. This approach takes into account the self-interaction but ignores interaction with other cells and hence is the polar opposite of the mean-field approach. The two methods are thus complimentary and together they give a more complete picture of the dynamics than that obtained solely from one approach.

For a single noninteracting cell, the model reduces to that of a pure random walker. For a cell interacting via positive or negative chemotaxis to its own secreted chemical, it reduces to a consideration of self-attracting or self-repelling random walks, the study of which is indeed a subject in its own right. One may rightly wonder what is the use of studying the dynamics of a self-interacting cell since such a model appears at first sight far fetched from reality. Besides the obvious fact that understanding a one cell, strongly-coupled system paves the way for understanding strongly-coupled many-body effects, such a simple model finds direct application in certain types of autocrine signaling (Alberts *et al.*, 1994) as well as modeling the movement of a single cell in a spatial region characterized by a low cell concentration. In the latter context, cells respond to chemical gradients which are primarily generated by themselves while gradients generated by other cells must have less important, secondary effects. The critical cell concentration below which such circumstances occur can be estimated as follows. Cells typically diffuse an order of magnitude or more slower than chemicals in solution. Thus the chemical concentration due to a single cell at position x at any given time t is to a good approximation given by considering the cell to be fixed at this position while secreted chemical diffuses at a rate determined by its diffusion coefficient D_1 and decays in solution at a rate λ. This implies that the typical distance traveled by the chemical away from the cell, before it decays, is of the order $L_c = \sqrt{D_1/\lambda}$ (this is called the Kuramoto length; see, for example, Togashi and Kaneko, 2004). Hence cell–cell interactions via chemotaxis will dominate over self-interaction if the average intercellular distance is smaller than L_c. If the intercell distance is larger than L_c then cells will primarily interact with their self-generated chemical, in which case the single-cell approach will approximate the dynamics of cell movement better than the mean-field approach.

It turns out that even the single self-interacting cell problem is nontrivial. The cell constantly modifies its physical environment through its continuous chemical secretion and simultaneously reacts to its environment via chemotactic sensing and directed motion. This feedback gives the cell memory of its past movements since the chemical field sensed at a particular time is due to secretion at all previous spatial locations which the cell visited. This nonMarkovian behavior (Gardner, 2004) is generally not possible to analyze unless some further assumptions are made about the problem. One reasonable assumption is that the cell diffusion coefficient is much smaller than its chemical counterpart. In such a case one can make progress by use of small noise perturbation methods (Grima, 2005) which leads to the following two main results: (i) for positive chemotaxis, a cell's motion is always (in the presence or absence of chemotaxis) similar to diffusion, i.e., its mean square displacement is proportional to time; (ii) for negative chemotaxis, the cell's motion is akin to that of diffusion when the coupling is less than a certain threshold (weak interaction) and ballistic, i.e., its mean square displacement is proportional to time squared, when the threshold is exceeded (strong interaction). Thus if Λ is the power that time is raised to in the expression for the mean-square displacement (*msd*), i.e., $msd \propto t^{\Lambda}$, then the single-cell approach predicts a transition from $\Lambda = 1$ to $\Lambda = 2$ as the coupling strength is increased. This

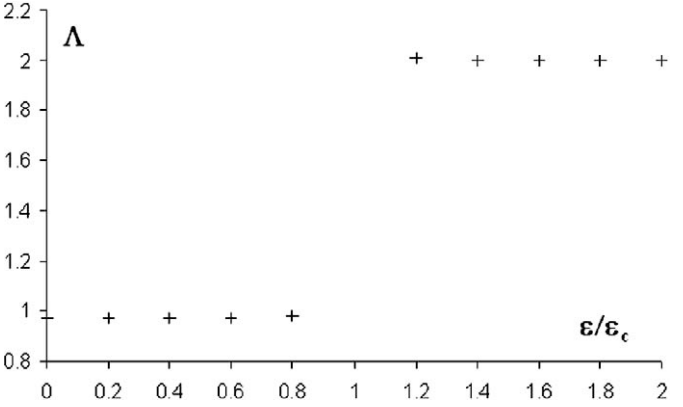

Figure 6 Graph showing the variation of the exponent Λ with the relative strength of coupling ϵ/ϵ_c for a single cell in one dimension (data from numerical simulations). Λ is the power that time is raised to in the expression for the mean-square displacement (*msd*), i.e., $msd \propto t^{\Lambda}$. The critical coupling strength at which the transition is predicted to occur by theory is denoted by ϵ_c. The parameters are $D_0 = 0.001$, $D_1 = 1$ and $\lambda = 0.1$. The *msd* is obtained by averaging the square of the single cell displacement from 1000 independent numerical simulations of the cellular model; Λ is then extracted from the slope of log–log plots of *msd* versus time for data in the time range: $t \in [500, 50000]$. The cell behavior is similar to diffusion for low coupling strength ($\epsilon < \epsilon_c$) and ballistic otherwise.

conjecture for negative chemotaxis is verified by simulation (Fig. 6). Note that this behavior is not transient. The cell's motion is ballistic after a time of the order of $1/\lambda$ has elapsed since chemical secretion started.

We note that transitions of this kind cannot be predicted by stability analysis of mean-field models. These transitions occur in all dimensions. It is found that the sharpness of the transition apparent in Fig. 6 occurs only for cell diffusion coefficients which are approximately two orders of magnitude smaller than the chemical diffusion coefficient. For larger ratios of the cell to chemical diffusion coefficients, the transition occurs but is not sharp, meaning that for intermediate coupling the cell's movement is neither diffusion nor ballistic but rather superdiffusive, $1 < \Lambda < 2$. The physical and biological implications of this transition can be appreciated by plotting typical cell trajectories for different coupling strengths (Figs. 7A–7C). Note that the cell direction changes very frequently for low coupling strength but for high coupling strength the cell moves in a certain randomly chosen direction for a significant amount of time before changing direction. This shows that the statistics of cell movement, in particular the correlation time T_c, is sensitively dependent on the feedback between cytoskeletal dynamics and surface receptor activation by chemorepellents (Fig. 7D).

As we now show, the possible biological relevance of this phenomenon lies in enabling cells to optimize their search strategy for catching moving prey or for finding target areas. Simulations (Viswanathan *et al.*, 1999; Bartumeus *et al.*, 2002) show that in general for searchers faster than their targets, the optimal searching strategy is for

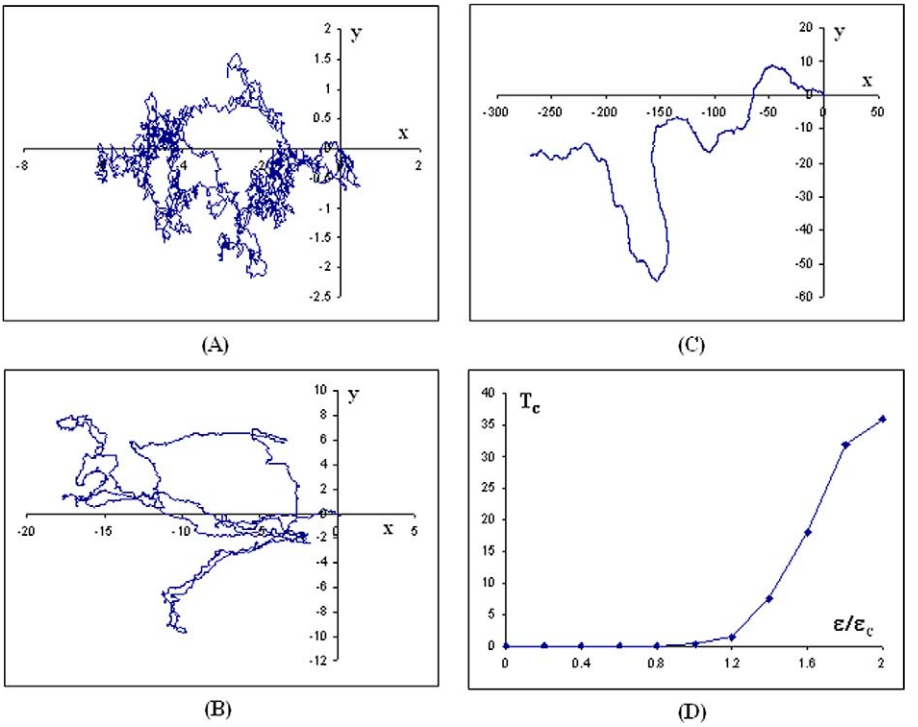

Figure 7 Sample trajectory of a cell self-interacting through negative chemotaxis in two dimensions in the time period: $t \in [0, 300]$. The parameters are $D_0 = 0.01$, $D_1 = 1$, and $\lambda = 0.1$. We show the cell behavior for (A) $\epsilon = 0.5$, (B) $\epsilon = \epsilon_c$, (C) $\epsilon = 2\epsilon_c$. Note how as the transition from diffusive to ballistic behavior occurs, the cell tends to move for longer times in one direction before switching to a new random direction. This phenomenon is quantified by plotting the correlation time T_c versus the coupling strength (D). T_c is extracted from the velocity autocorrelation data.

searchers to have a mean square displacement which scales quadratic in time (ballistic motion, also called Levy walks with $\mu = 2$); if the searchers are slower than their targets then searching is optimal if the searcher's mean square displacement scales linearly with time (Brownian motion). Note that here by the word "searchers" we do not specifically mean a chemotactic cell but rather any entity which through a random walk of some sort aspires to find its target or prey. In the light of these results, the previous prediction of a transition in cell motility acquires biological meaning. Cells dispersing through negative chemotaxis (such as the slime mold in its preaggregative life stage) can fine tune their optimal strategy to find their prey by controlling the rate of chemorepellent secretion: low secretion rate is effective for finding fast moving targets and high secretion rate for finding slow moving targets.

Our results are based on the stochastic cellular model defined by Eqs. (5) and (6) which assume that the mean chemotactic velocity of a cell is directly proportional

to the local chemical gradient sensed by the cell. As previously remarked this "assumption" agrees with experiment provided the absolute value of the local chemical concentration is not too large. For large concentrations, the chemotactic response saturates and may, for example, become logarithmic (this is referred to as the Weber–Fechner law; see, for example, Brown and Berg, 1974). For such cases, the transition in cell motility for negative chemotaxis still holds (Grima, 2006).

We note that for the case of negative chemotaxis, independent of the initial cell concentration, the repulsive effects between cells will invariably lead to a gradual increase in the intercell distance suggesting that the transition predicted by the single-cell approach is as well valid for this many-cell situation. Such can explain why in-vitro experiments investigating the negative chemotaxis phase of an initially compact aggregate of *Dictyostelium discoideum*, show that the edge of the aggregate grows proportional to time (ballistic behavior) and not to the square root of time (diffusive behavior) as normal nonchemotactic cells do (Keating and Bonner, 1977).

We finish this section by noting that mean-field models cannot generally easily capture the qualitative and quantitative behavior predicted by the single-cell approach. This is since at the low-cell concentrations at which the latter approach is valid, the chemical concentration sensed by the cells will exhibit wild spatial fluctuations not the smooth behavior implicit in the application of mean-field modeling. The discrepancy between mean-field and discrete stochastic models is not limited to models of tissue but also appears at the molecular scale (Togashi and Kaneko, 2004) in reaction–diffusion phenomena and also in the large scale population dynamics of predator–prey systems (Durrett and Levin, 1994; McKane and Newman, 2004).

VI. Discussion

In this article, motivated by the complexity inherent in the biological world, we have discussed how mathematical models can be constructed at different spatial scales to provide insight into the fundamental biological processes at the heart of pattern formation and also to assist experimental data interpretation. In particular we have illustrated model construction at the cell and tissue-level scales for a simple multicellular chemotactic system which finds broad application by itself or in conjunction with other processes in understanding a wide range of phenomena. The crucial feature which makes this system have broad appeal is the fact that it is amongst the simplest biological systems in which the individual cell dynamics are regulated via interaction with other cells; such feedback is at the heart of the large scale self-organization of tissue.

The process of model building at a particular relevant spatial scale should in principle result from a rigorous derivation starting from a molecular level model. However in practice this is not possible due to the huge complexity of the processes involved. This has led to model development based on phenomenology, namely biological processes are modeled by similarity with other well understood physical processes. There are many ways in which this can be done and thus it is not always clear if the prediction

of a model is genuine or if it is due to artifacts introduced by the particular phenomenological approach. One approach to solving this problem is to derive models at a coarse scale from an intermediate scale model which has the special property of being based on biology and physics which are experimentally well studied.

In this article starting from a cellular model we have used such an approach to understand the assumptions implicit in using tissue-level models, which are the dominant modeling methodology in biology and mathematical biology. Such models are found to be correct only when statistical correlations between cells are ignored which limits their application to weakly-interacting multicellular systems. Hence tissue-models based on sets of coupled partial differential equations for the cell and chemical concentrations are akin to mean-field theories in the physical sciences. This suggests that tissue-level models break down when the fluctuations in cell and chemical concentrations become comparable to their average, a situation which would be expected to occur for biological systems with few hundreds of strongly-interacting cells. Nevertheless for our simple biological system it is found that tissue-level models do generally correctly capture some of the major qualitative features though they may fare badly in predicting the correct quantitative details. Theoretical and numerical analysis of the corresponding cellular models provides the missing quantitative information. This suggests that the simultaneous use of multiple modeling methodologies at different spatial scales is useful to weed out model artifacts and to ensure both qualitative and quantitative accuracy in model prediction.

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