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Adhesion and volume constraints via nonlocal interactions determine cell organisation and migration profiles

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ABSTRACT

The description of the cell spatial pattern and characteristic distances is fundamental in a wide range of physio-pathological biological phenomena, from morphogenesis to cancer growth. Discrete particle models are widely used in this field, since they are focused on the cell-level of abstraction and are able to preserve the identity of single individuals reproducing their behavior. In particular, a fundamental role in determining the usefulness and the realism of a particle mathematical approach is played by the choice of the intercellular pairwise interaction kernel and by the estimate of its parameters. The aim of the paper is to demonstrate how the concept of H-stability, deriving from statistical mechanics, can have important implications in this respect. For any given interaction kernel, it in fact allows to *a priori* predict the regions of the free parameter space that result in stable configurations of the system characterized by a finite and strictly positive minimal interparticle distance, which is fundamental when dealing with biological phenomena. The proposed analytical arguments are indeed able to restrict the range of possible variations of selected model coefficients, whose exact estimate however requires further investigations (e.g., fitting with empirical data), as illustrated in this paper by series of representative simulations dealing with cell colony reorganization, sorting phenomena and zebrafish embryonic development.

1. Introduction

An accurate description of the spatial pattern of cell aggregates is a fundamental issue in theoretical biology. The spatial cell configuration and characteristic distances are in fact at the basis of a wide range of biological processes, i.e., from morphogenesis to cancer growth and invasion. For example, defects in the spatial organization of multipotent stem cells in animal embryos lead to severe malformations of adult organs (Ilina and Friedl, 2009). Further, the compact configuration of epithelial monolayers is fundamental in wound healing scenarios. Finally, the dispersion of highly motile malignant individuals triggers the metastatic transition of tumor progression (Friedl and Wolf, 2003).

From a mathematical point of view, the spatial distribution of cells forming aggregates can be well approximated by discrete models, which actually approach the biological problem focusing on the cell-level of abstraction and preserve the identity and the behavior of individual elements (for comprehensive reviews the reader is referred to Alber et al. (2003); Anderson and Rejniak (2007); Deutsch et al. (2007); Drasdo (2003b)). In more details, these techniques represent biological elements as one or a set of discrete units, being individual morphology restricted according to some underlying assumptions. Among discrete approaches, we here focus on particle-based models, where the biological individual is represented by a material point with concentrated mass and identified by its position in space, in contrast to methods that allow for a description of the cell membrane and its morphology as vertex-based models (Fletcher et al., 2014) or Cellular Potts Models (CPM, see Balter et al. (2007); Glazier et al. (2007)). For particle or agent-based models, the cells move according to ordinary differential equations (ODEs), with the phenomenological postulation of either acceleration (second-order models) or velocity (first-order models) contributions. In both cases, among the possible migratory components that can be included, one of the main important model ingredients is the term relative to direct intercellular pairwise interactions that can be described by a proper kernel (potential). This contribution in cell behavior is typically the combination of adhesive/repulsive mechanisms and can lead to unrealistic cell collapse or dispersion or more realistic patterns with optimal individual spacing.

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The definition of proper interaction kernels, as well as an accurate estimate of the relative parameters, is therefore mandatory when developing a particle model for biological problems. In particular, the issue relative to the parameter estimate is very relevant in theoretical biology. In fact, regardless of the specific implemented approach, a direct one-to-one correspondence between all the model parameters and experimental quantities is not straightforward (as commented also in Balter et al. (2007); Glazier et al. (2007); Merks and Koolwijk (2009), in the case of CPM). The different model coefficients often interfere with each other in an intricate way, and therefore simultaneous parameter fittings are typically needed, which can be done with large-scale massive preliminary simulations.

Objective of the work. The main objective of this paper is indeed to propose a procedure that improves the strategy to choose proper adhesive/repulsive kernels by identifying a physically admissible subset of the free parameter space which gives rise to realistic system configurations in terms of inter-agent spacing. In order to do this, we will take advantage of the concept of H-stability of particle interaction kernels and potentials, defined in the statistical mechanics (Ruelle, 1969), and already used in the modeling of swarming and collective migration of animal population (Carrillo et al., 2010b; Kolokolnikov et al., 2013). The determination of the H-stability properties allows in fact to predict the stable configurations, in terms of particle spacing, of the system of interest. Of particular relevance is the fact that the H-stability condition of interaction kernels translates into a constraint involving the values of the relative interaction parameters, therefore reducing the range of their possible variations if we want to obtain realistic patterns. It is useful to clarify that the proposed analytical results do not shed light either on the dynamics of the aggregate or on the exact position of the single agents at the equilibrium.

Structure of the work. The rest of the paper is then organized as it follows. In Section 2, we will present a general first-order particle model (formally derived by a second-order approach) and discuss some possible velocity contributions that can be included in the modeling framework. In Section 3, we will focus on the interaction velocity term. In this respect, we will propose a class of interaction kernels/potentials, commenting the underlying biological hypothesis and, in Section 3.2, we will introduce the concept of H-stability of the system and its implications in the classification (in terms of agent spacing) of the stable configurations of a particle system and on the estimate of the interaction parameters. In Section 3.3, such analytical results will be supported by proper sets of simulations. Section 3.4 will instead show that, once restricted the free space of the interaction model parameters, a more detailed coefficient estimate can only result by a data fitting with experimental/biological quantities. Finally, in order to not remain on a pure conceptual level, we will finally show in Section 4 that the proposed analytical procedure can be important also in the case of more realistic biological applications: for instance, we will reproduce the early migration of the zebrafish lateral line primordium, whose dynamics are fundamental for the correct embryonic development of the animal, and show how the use of H-stable interaction potentials is crucial to reproduce typical migration patterns.

2. Basic Mathematical Model

We start by considering a biological system composed by N cells of the same phenotype/lineage, i.e., characterized by the same biophysical properties (mass and dimension) and behavior. We anticipate that in the following sections, we will extend such a model framework in the case of multiple differentiated cell populations. As previously introduced, each individual is here represented as a discrete entity, i.e., as a material particle with concentrated mass, say m, and characterized by its position in space, $\mathbf{x}_i(t) \in \mathbb{R}^2$ with $i = 1, \dots, N$, assuming a planar cell distribution. The configuration of the overall system at a given instant t can therefore be given by the vector:

$$\mathbf{X}(t) = \{\mathbf{x}_1(t), \dots, \mathbf{x}_N(t)\} \in \mathbb{R}^{2N}, \qquad \forall\ t \in \mathbb{R}_+.$$

To approach the dynamics of a generic cell i, we start from a general second-order particle model:

$$m\frac{d^2\mathbf{x}_i}{dt^2}(t) + \lambda_i^{cs}\frac{d\mathbf{x}_i}{dt}(t) + \sum_{\substack{j=1\\ j\neq i}}^{N}\lambda_{ij}^{cc}\left(\frac{d\mathbf{x}_i}{dt}(t) - \frac{d\mathbf{x}_j}{dt}(t)\right) = \mathbf{F}_i(t). \qquad (1)$$

The second and the third terms on the left hand side of Eq. (1) describe damping mechanisms related to the friction forces resulting from the contact of cell i with, respectively, the substrate and the other individuals, as λ_i^{cs} and λ_{ij}^{cc} are the corresponding coefficients (which may be, for instance, constant parameters in common for all cells (Costanzo et al., 2015) or time-dependent individually-specific tensors (Liedekerke et al., 2015)). These contributions have the effect to slow down individual movement and eventually to increase the characteristic time scale of the overall cell collective patterning. On the right hand side, $\mathbf{F}_i$ instead denotes the sum of all forces influencing cell behavior. However, in order to simplify the picture, we can first notice that cells move in extremely viscous environments, characterized by very small Reynolds numbers: inertial effects in cell dynamics can therefore be neglected, if a sufficiently large observation time is considered (Liedekerke et al., 2015; Odell et al., 1981). In fact, in these conditions, biological cells can maintain a persistent ballistic locomotion only for a substantially small time, giving rise to straight displacements shorter than their typical dimensions. These considerations allow to drop the inertial term in (1) and to employ a first-order model, where the velocity of an individual, and not its acceleration, is proportional to the acting forces. Such a relation, called *overdamped force-velocity response*, is at the basis of a number of other discrete/IBM approaches (see Drasdo (2003b); Scianna and Preziosi (2012) and references therein for comments). As seen, cell-cell friction is in principle an important contribution: however, such a damping term is of particular relevance in the case of three-dimensional settings, where the adhesive surface between cells is significantly large (Drasdo, 2003b). In fact, in planar domains, as those considered in this work, cell membranes are instead mainly in contact with extracellular elements, e.g., flat matrix substrates. It is further not too restrictive to assume, at least in a first approximation and in a more conceptual work, that the relative velocity between pairs of cells is negligible with respect to cell-substrate friction. For these reasons, we opt to neglect also the third term on the left hand side of Eq. (1), thereby obtaining the following law of cell motion:

$$\lambda_i^{cs}\frac{d\mathbf{x}_i}{dt}(t) = \mathbf{F}_i(t) \qquad \Rightarrow \qquad \frac{d\mathbf{x}_i}{dt}(t) = \frac{\mathbf{F}_i(t)}{\lambda_i^{cs}} = \underbrace{\mathbf{v}_i(t)}_{\substack{\text{cell}\\ \text{velocity}}}. \qquad (2)$$

Eq. (2) implies indeed that cell dynamics can be described by a direct phenomenological postulation of the velocity contributions, which have to take into account of the cell-substrate friction coefficient, possibly included within their characteristic parameters. It is finally useful to remark that, once cells move with constant velocity, the shape of their migration profile is given by the stationary states of the model (2): they derive from the balance of forces acting on each individual (i.e., $\mathbf{F}_i(t) = 0$ for all i) and are exactly the same that would result by the corresponding second-order approach.

We now assume that the velocity of each cell i results from the superimposition of different, biologically reasonable, contributions: