Title: Interacting Cell Systems

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Interacting Cell Systems

Synonyms

ICS, Interacting particle system, IPS

Definition

An interacting cell system (ICS) is a spatial modeling framework that allows to analyze the collective spatio-temporal behavior (collective behavior, spatio-temporal pattern formation) of biological cell populations which emerges from local intercellular interactions. The model is a systems biology adaption of interacting particle systems (IPS) which have been used in non-equilibrium statistical physics. Mathematically, ICSs refer to a class of stochastic processes, more specific Markov processes (Markov process), in which time is continuous and space is discretized, the latter resembled by a regular lattice or a more general graph structure (Liggett 1985). Each spatial location can be in one of a discrete number of states — interpreted, for instance, as the state or type of a cell at that location. The dynamics is described by specifying the transition rules for changing a configuration of cells within small subregions. Those transitions may depend strongly on the details of the cell configuration found in close vicinity of the considered

region but only weakly on remote cell states and numbers. ICSs are closely related to (time-discrete) Cellular Automata (Cellular Automaton) with fully asynchronous update. The available analytical methods for ICSs range from computer simulations (Klauss and Voss-Böhme 2008) to approximative numerical methods (e.g. Marro and Dickman (1999)) up to the mathematically rigorous analysis of suitably simplified systems (Liggett 1985).

Characteristics

Problem

Biological structure and function often results from the complex interaction of a large number of components. When spatio-temporal pattern formation (spatio-temporal pattern formation) in cellular populations or tissues is considered, one is often interested in concluding characteristics of the global, collective behavior (collective behavior) of cell configurations from the individual properties of the cells and the details of the intercellular interaction. However, even if the basic cell properties and interactions are perfectly known, it is possible that – due to the complex structure of the system – the collective traits cannot be directly extrapolated from the individual properties. Therefore, appropriate mathematical models need to be designed and analyzed that help to accomplish this task on a theoretical basis. A particular suitable modeling framework in this respect are Interacting Cell Systems. Being well-amenable to precise analysis as well as to numerical and computer simulation methods, they allow to derive collective properties of interacting cell systems at the tissue scale from their specific features of interaction at the cellular scale.

Example [Cell Sorting Model]. Cell sorting is a biological process where heterotypic cell

populations in composite aggregates segregate into spatially confined homotypic cell clusters. It is widely assumed that the observed bulk behavior of the cell populations results from type-dependent differences in individual cell properties. In particular, cell-type dependent disparities in the expression of molecules that regulate intercellular adhesion are held to be responsible for cell sorting (Differential Adhesion Hypothesis). By means of an suitable ICS and its analysis, it becomes possible to explore the tissue-scale consequences of the assumed intercellular interaction and thereby provide a theoretical basis to test the Differential Adhesion Hypothesis (Voss-Böhme and Deutsch 2010).

The Model

State space

An ICS assigns a value $\eta(x)$ from a set W to each site x of a countable set S. The set S resembles the possible spatial position of cells. It is often chosen as a two- or three-dimensional regular lattice, but the framework characterized below can be extended to a more general spatial graph structure, as well. The set W of all considered cell types or states (orientation, mass, cell cycle phase, sensitivity, etc) is assumed to be finite. The state of the system as a whole is described by *configurations* $\eta \in \mathbb{X} = W^S$. This means that $\eta = (\eta(x))_{x \in S}$, where $\eta(x)$ describes the state or type of a cell at node x. The value 0 is assigned to a given node, if this node is not occupied by any cell. Since at most one cell is allowed per node, a *volume exclusion* principle is inbuilt.

Example [Cell Sorting Model]. It is assumed that each site of the lattice S is occupied by exactly one cell which can be of one out of two cell types, called type A or type B. Thus, we set $W := \{1, 2\}$ with the interpretation that $\eta(x) = 1$ if the cell at site x is

of type A and $\eta(x) = 2$ if the individual at x is of type B, see Fig. 1.

Transitions

ICSs evolve in continuous time according to Markovian transition rules. In each transition, a global configuration $\eta \in \mathbb{X}$ is altered only within a certain spatial region $T \subset S$. Such a transition $\eta \to \tau_T(\eta, v)$ consists of replacing the values $\{\eta(x)\}_{x\in T}$ by new values $\{v(x)\}_{x\in T}$ chosen from W:

$$\tau_T : W^S \times W^T \to W^S : \tau_T(\eta, v)(x) := \begin{cases} v(x), & x \in T \\ \eta(x), & x \notin T. \end{cases}$$

It is always assumed that T is a finite set. Often further restrictions are posed on the set of possible T. For instance one allows T to consist only of one single site or to consist only of pairs of neighboring nodes. The set of all finite $T \subset S$ is denoted by $\mathscr{T}$, whereas the set of all finite $T \subset S$, which are allowed as transition areas is denoted by $\mathscr{T}_0$.

Example [Cell Sorting Model]. Only transitions where two neighboring cells located at $x \in S$ and $y \in S$ interchange their positions are considered, see Fig. 1. This means that transitions take place on pairs of adjacent nodes, i.e.

$$\mathscr{T}_0 := \{\{x, y\}; x \text{ and } y \text{ are adjacent lattice sites}\}.$$

The transitions are described by

$$\tau_{x,y}(\eta)(z) = \begin{cases} \eta(z) & z \neq x, y \\ \eta(y) & z = x \\ \eta(x) & z = y \end{cases}, \quad \eta \in \mathbb{X},\ \{x, y\} \in \mathscr{T}_0.$$

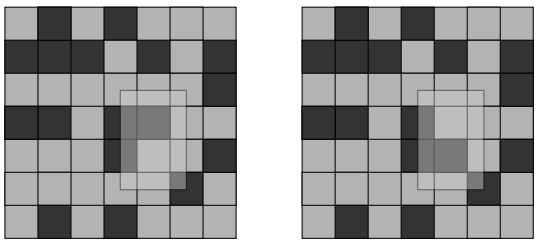

Fig. 1. Migration transition in the Cell Sorting Model.

Type-A cells (dark gray) and type-B cells (light gray) are arranged on a two-dimensional square lattice. Left: The dark cell located within the shadowed area adheres to one dark cell and three light cells. The light cell adheres to two dark and two light cells. Therefore the rate for a transition into the state shown at the right-hand side is $\exp\{-\beta_{11} - \beta_{22} - 5\beta_{12}\}$.

Transition Rates

By associating weights to the different possible transitions, the stochastic dynamics is specified. The system's dynamics is *Markovian*, which means that the rate for a transition from the actual configuration η to a new configuration $\tau_T(\eta, v)$ does not depend on the temporal history of the system but on the present configuration η and the future configuration $\tau_T(\eta, v)$. The rate for a transition $\eta \to \tau_T(\eta, v)$ is denoted by $c_T(\eta, v)$. One can think of the rates as a weighting of the possible transitions. The dynamics of the system is completely described by the family $\mathscr{T}_0$ of possible spatial transition regions and an associated family $(c_T(\eta, \cdot))_{\eta \in \mathbb{X}, T \in \mathscr{T}_0}$ of transition rates. Note that

$$c_T : \mathbb{X} \times W^T \to [0, \infty), \quad T \in \mathscr{T}_0.$$

Example [Cell Sorting Model]. It is assumed that the cells are the less mobile the more they adhere to the neighboring cells. Let β_{ij} denote the type-specific adhesive affinity

between two cells of type $i \in W$ and $j \in W$, respectively. Then, the rate for a transition $\eta \to \tau_{x,y}\eta$ is can be modeled, for instance, by $c_{x,y}(\eta)$, where

$$c_{x,y}(\eta) = \begin{cases} \exp\left\{-\sum_{z\in\mathcal{N}(x)} \beta_{\eta(x)\eta(z)} - \sum_{z\in\mathcal{N}(y)} \beta_{\eta(y)\eta(z)}\right\}, \\ \qquad \text{if } x \text{ and } y \text{ are neighbors,} \\ 0, \qquad \text{otherwise.} \end{cases}$$

Here $\mathcal{N}(x)$ denotes the set lattice sites that are adjacent to x.

In the case that the spatial lattice S is finite, the above transition rates supplemented with boundary conditions lead to a well-defined interacting particle system. However, many analytical properties of such a particle system are only revealed if the corresponding system on the infinite lattice S_∞ is studied (e.g. Voss-Böhme and Deutsch (2010)). Since the state space W^{S_∞} is not countable even for finite W, special care has to be taken that the rates lead to a well-defined Markov process for an infinite lattice. A sufficient condition for this is the *finite range condition* which essentially says that (1) the transition rates depend only on the states close to the considered transition region but not on the states of remote cells and (2) the transition regions are small (Liggett 1985). In many applications, particularly those where the consequences of local, microscopic interactions are studied on a global, macroscopic scale, this condition is fulfilled quite naturally. This condition can even be considerably relaxed, see Liggett (1985) for details. The latter reference is a standard work on the mathematical foundation of IPS and the analytic tools available for suitably simplified systems.

Applications

ICSs and their algorithmic, time-discrete counterparts have been successfully applied to a number of biological pattern formation problems, such as cell sorting (Voss-Böhme

and Deutsch 2010), collective motion of oriented cells (Peruani et al 2011), mesoscale patterning in motile cell populations (Simpson et al 2010) or tumor cell migration (Deroulers et al 2009). Due to the fact that they are both analytically tractable and easy to simulate, they attract interest from biologically motivated researchers and rather theoretically working scientists, as well. There are some well studied simplified models which can hint to the expected qualitative behavior of a given ICS, as well as general methods for the analysis of IPS. The latter comprise, for instance, limit procedures to derive partial or ordinary differential equations that describe the temporal evolution of macroscopic variables. They can be obtained by moment closure methods such as mean field or pair approximations (Marro and Dickman 1999; Durrett and Levin 1994) or by mathematically well-founded hydrodynamic limit procedures (DeMasi and Presutti 1991; Kipnis and Landim 1999). If this approach is successful, systems of differential equations can be derived that directly relate to the individual intercellular interaction. Since, of course, the analysis of more complicated systems is often of a delicate nature, the theoretical analysis of suitably simplified systems is in many applications complemented by computer simulations. Here a method can be used which is an adaption of the classical Gillespie algorithm to IPS (Klauss and Voss-Böhme 2008). The resulting time-discrete model is essentially a Cellular Automaton Model.

Example [Cell Sorting Model]. The ICS developed by Voss-Böhme and Deutsch (2010) has been analyzed by studying its asymptotic properties when suitable spatio-temporal limit procedures are applied. Thereby, the geometry of cell segregation could be described as a function of the intercellular adhesion parameters.

It is important to understand that IPS are dynamic models where the details of the temporal evolution are directly modeled by specifying the transition rates. In

contrast, there are methods, so-called Markov chain Monte Carlo methods such as the Metropolis algorithm (Metropolis algorithm), where transition rates are constructed in such a way that the process samples configurations of a pre-defined equilibrium model on a lattice. The resulting Markov chain algorithm is an auxiliary means to analyze the equilibrium model. If its temporal evolution is interpreted as a model of the dynamics of a biological system, it is not immediately clear to which extent it resembles actual biological behavior. Instead, the model's appropriateness has to be justified by additional arguments. This approach has been pursued, for instance, in the Cellular Potts Model (Cellular Potts Model).

Conclusion

Interacting Cell Systems are spatial models that allow to predict characteristics of the collective cell behavior from the properties of the individual cell and the intercellular interaction. Although the models that can be studied in detail are often considerably simplified representations of nature, they may capture some of the essential features responsible for spatio-temporal pattern formation in biological tissues. ICS can be analyzed by mathematically well-founded theoretical as well as approximative numerical methods and computer simulations. They attract interest from both theoreticians and more biologically motivated researchers in systems biology.

Cross-references

Markov process; Metropolis algorithm; Differential Adhesion Hypothesis; Lattice-Gas Cellular Automaton Models for Biology; spatio-temporal pattern formation; collective behavior; Cellular Automaton; Cellular Potts Model

References

DeMasi A, Presutti E (1991) Mathematical methods for hydrodynamic limits. Springer

Deroulers C, Aubert M, Badoual M, Grammaticos B (2009) Modeling tumor cell migration: From microscopic to macroscopic models. Phys Rev E 79

Durrett R, Levin S (1994) The importance of being discrete (and spatial). TheorPopulBiol 46(3):363–394

Kipnis C, Landim C (1999) Scaling limits of interacting particle systems. Springer-Verlag

Klauss T, Voss-Böhme A (2008) Modelling and simulation by stochastic interacting particle systems. In: Mathematical Modeling of Biological Systems, Birkhauser, vol II, pp 353–367

Liggett TM (1985) Interacting Particle Systems. Springer

Marro J, Dickman R (1999) Nonequilibrium Phase Transitions in Lattice Models. Cambridge University Press

Peruani F, Klauss T, Deutsch A, Voss-Böhme A (2011) Traffic jams, gliders and bands in the quest for collective migration. Phys Rev Lett (in press)

Simpson MJ, Landman KA, Hughes BD, Fernando AE (2010) A model for mesoscale patterns in motile populations. Physica A: Statistical Mechanics and its Applications 389(7):1412 – 1424

Voss-Böhme A, Deutsch A (2010) On the cellular basis of cell sorting kinetics. J Theor Biol 263(4):419–436