Title: Cellular Potts Model

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Synonyms

Glazier-Graner-Hogeweg model; Potts model, cellular / extended; CPM

Definition

A Cellular Potts Model (CPM) is a spatial lattice-based formalism for the study of spatio-temporal behavior of biological cell populations. It can be used when the details of intercellular interaction are essentially determined by the shape and the size of the individual cells as well as the length of the contact area between neighboring cells.

Formally, a Cellular Potts Model is a time-discrete Markov chain (Markov process). It is a lattice model where the individual cells are simply-connected domains of nodes with the same cell index. A CPM evolves by updating the cells' configuration by one pixel at a time based on probabilistic rules. These dynamics are interpreted to resemble membrane fluctuations, where one cell shrinks in volume by one lattice site and a neighboring cell increases in volume by occupying this site. The transition rules follow a modified Metropolis algorithm with respect to a Hamiltonian.

Characteristics

Problem

Biological structure and function typically result from the complex interaction of a large number of components. When spatio-temporal pattern formation in cellular populations or tissues is considered, one is often interested in concluding characteristics of the global, 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. Cellular Potts models constitute a modeling framework that is applicable when the details of intercellular interaction are essentially determined by the shape and the size of the individual cells as well as the length of the contact area between neighboring cells.

This model class has been developed by Glazier and Graner (1993) in the context of cell sorting. The latter refers to the observed segregation of heterotypic cell aggregates into spatially confined homotypic cell clusters. The CPM was introduced to explore the tissue-scale consequences of the Differential Adhesion Hypothesis (Differential Adhesion Hypothesis) that holds that cell type-dependent disparities in the expression of molecules that regulate intercellular adhesion are responsible for cell sorting. Since then, this formalism has been elaborated and applied to study a wide range of morphogenetic phenomena in developmental biology.

The Model

State space

A CPM assigns a value $\eta(x)$ from a set $W = \{0, 1, ..., n\}$ to each site x of a countable set S, cp. Fig.1. The set S resembles the discretized space and is often chosen as a two- or three-dimensional regular lattice. The set $W = \{0, 1, ..., n\}$ contains so-called *cell indices*, where $n \in \mathbb{N}$ is the absolute number of cells that are considered in the model. The state of the system as a whole is described by *configurations* $\eta \in \mathbb{X} = W^S$. Given a configuration $\eta \in \mathbb{X}$, a *cell* is the set of all points in S with the same cell index, $\text{cell}_w := \{x \in S : \eta(x) = w\}, w \in W\backslash\{0\}$. The value 0 is assigned to a given node, if this node is not occupied by a cell but by medium. Each cell is of a certain *cell type*, which determines the migration and interaction properties of the cell, the set of all possible cell types being denoted by Λ. Denote by $\tau : W \to \Lambda$ the map that assigns each cell its cell type. A cell with index $w \in W$ has *volume*[1]

$$V_w(\eta) := \sum_{x \in S} \delta(w, \eta(x)),$$

and *surface length*

$$M_w(\eta) := \frac{1}{2} \sum_{\text{interfaces } \{x,y\}} \delta(w, \eta(x)).$$

The sum in the last term is taken over all *interfaces* of a given configuration η, that are all pairs of lattice neighbors which do not belong to the same cell.

Dynamics

A cellular Potts model (CPM) is a time-discrete Markov chain (Markov process) with state space $\mathbb{X}$, where the transition probabilities are specified with the help of a *Hamiltonian*. The latter is a function $H : \mathbb{X} \to \mathbb{R}$ which often has a special structure. Usually, it is the sum of several terms that control single aspects of the cells' interdependence

[1] For the Kronecker symbol δ it holds that $\delta(u, v) = 1$ if $u = v$ and $\delta(u, v) = 0$ otherwise.

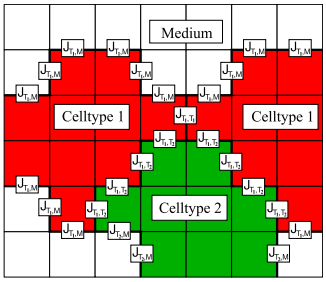

Fig. 1. Cell-surface interaction in the Cellular Potts Model. Three cells, each one covering several lattice sites, interact with each other at the cell surfaces. The strength J of the interaction depends on the cell types, type T_1 depicted in red, type T_2 in green. There are also interactions between the cells and the medium (white).

structure. The standard CPM uses the following two terms. First a *surface interaction term*

$$H_s(\eta) = \sum_{\text{interfaces } \{x,y\}} J(\tau(\eta(x)), \tau(\eta(y))), \quad \eta \in \mathbb{X}, \tag{1}$$

is specified. Here, $J : \Lambda \times \Lambda \to \mathbb{R}$, the matrix of so-called *surface energy coefficients*, is assumed to be symmetric. Second the *volume constraint*

$$H_v(\eta) = \sum_{w \in W} \lambda_{\tau(w)} (V_w(\eta) - v_{\tau(w)})^2, \quad \eta \in \mathbb{X}. \tag{2}$$

is used. Here v_τ, the target volume, and λ_τ, the strength of the volume constraint, are cell type-specific parameters, $\tau \in \Lambda$. Depending on the phenomenon under investigation, further summands can be included. For instance, a constraint can be put on the surface length (Ouchi et al 2003)

$$H_m(\eta) = \sum_{w \in W} \alpha_{\tau(w)} (M_w(\eta) - m_{\tau(w)})^2, \quad \eta \in \mathbb{X}. \tag{3}$$

Again m_τ, the target surface length, and α_τ, the strength of the surface constraint, are parameters, $\tau \in \Lambda$. Thus, the typical structure of a CPM-Hamiltonian is

$$H = H_s + H_v + H_0, \tag{4}$$

where H_s, H_v are given in (1) and (2) and $H_0 : \mathbb{X} \to \mathbb{R}$ is a model-specific addend. See the paragraph 'Extensions' below for additional examples of H_0.

Transitions from one configuration to another follow a special rule which is called *modified Metropolis algorithm* (Metropolis algorithm). First two additional parameters

are specified. A so-called *temperature* $T > 0$, which is a biological analogue of the energy of thermal fluctuations in statistical physics and is a measure of cell motility, and the *transition threshold* h, that accounts for energy dissipation during formation and breaking of intercellular bonds and avoids oscillatory behavior (Savill and Hogeweg 1997; Ouchi et al 2003). Then, the following algorithm is performed:

(0) Start with configuration η.

(1) Pick a target site $x \in S$ at random with uniform distribution on S.

(2) Pick a neighbor y of x at random with uniform distribution among all lattice neighbors of x.

(3) Calculate the energetic difference $\Delta H_x^y := H(\eta_x^y) - H(\eta)$ of a transition $\eta \to \eta_x^y$, where $\eta_x^y(z) := \eta(y)$ if $z = x$ and $\eta_x^y(z) := \eta(z)$ otherwise.

(4) Accept the transition by setting $\eta := \eta_x^y$ with probability $p(\Delta H_x^y)$, or ignore the transition with probability $1 - p(\Delta H_x^y)$, where

$$p(\Delta H_x^y) = \begin{cases} 1 & \text{if } \Delta H_x^y < h \\ e^{-(\Delta H_x^y - h)/T} & \text{otherwise} \end{cases}$$

(5) Go to 1 or end the algorithm.

Consequently, only such transitions are possible where the index of at most one lattice site is changed, resulting in a shift of the cell's center of mass. The new assignment to this lattice site is chosen from the cell indices of the neighboring lattice sites. These dynamics are interpreted to resemble membrane fluctuations, where one cell shrinks in volume by one lattice site and a neighboring cell increases in volume by occupying this site.

To complete the model, appropriate boundary conditions must be specified. If the influence of the boundary shall be neglected, periodic boundary conditions are used. This means that the space can be thought of as being mapped onto a torus. However,

fixed boundary conditions, where the interaction between cell surfaces and confining environment is explicitly modeled, can be defined as well.

Extensions and applications

The CPM model formalism has been used for several problem-specific extensions. In general, this is done by including additional terms into the Hamiltonian (4). In some cases, these additional terms also depend on the chosen target spin, thereby changing the weights for the acceptance of a proposed transition in the modified Metropolis algorithm. The latter extensions are called *kinetic extensions*, since they directly affect the transition rates.

Cell motility emerges in the CPM implicitly from the fluctuations of the cells' center of masses. To explicitly model physical characteristics of cell motility such as cell persistence and inertia, additional terms that constrain the cell displacement per time step can be added to the difference ΔH of the standard CPM-Hamiltonian (4) that is calculated in step (3) of the modified Metropolis algorithm. Inertia, for example, has been modeled by constraining the cell velocity increment via the term

$$\Delta H_{inertia}(t) = \sum_{w \in W} \lambda_{inertia}(w) \left\| \overrightarrow{vel}(w,t) - \overrightarrow{vel}(w, t-\Delta t) \right\|^2, \tag{5}$$

where $\overrightarrow{vel}(w,t)$ denotes the instantaneous center-of-mass velocity of the cell w at time t, $\lambda_{inertia}(w)$ is a cell-specific parameter and Δt is one or more Monte Carlo steps (Balter et al 2007). Since the increment of the Hamiltonian depends on the proposed transition, this is a kinetic extension of the CPM.

Cell shapes arise in the CPM implicitly from satisfying the volume constraint. In the two-dimensional CPM, cells adopt approximately hexagonal shapes, producing a space tiling pattern comparable to epithelial tissues. Elongated cell shapes can be modeled by imposing a cell length constraint which renders the major axis of the ellipsoidal

approximation of the cell's shape to be close to a predefined target length or ratio (Zajac et al 2003). Rod cell shapes with particular stiffness have been modeled using a compartmentalized cell concept, where each cell consists of a row of standard CPM cells (Starruß et al 2007).

Chemotactic response to some field $c : S \to [0, \infty)$ of signals can be modeled in the simplest form by an addend $H_{chemo} = \sum_{w \in W \setminus \{0\}} \lambda_{chemo}(w) \sum_{x \in \text{cell}_w} c(x)$ to the Hamiltonian, where λ_{chemo} is a possibly cell type-specific chemotactic response parameter (Glazier et al 2007). If $\lambda_{chemo} < 0$, the cells prefer to move up the chemotactic gradient, for $\lambda_{chemo} > 0$ they prefer to move down the gradient. There have been several more refined extensions to the CPM that model chemotaxis (Glazier et al 2007). One example is the following kinetic extension used by Savill and Hogeweg (1997) where the positions of the target spin x and the trial spin y in a proposed transition $\eta \to \eta_x^y$ are taken into account,

$$\Delta H_{chemo} = \sum_{w \in W} \lambda_{chemo}(w)(c(y) - c(x)). \tag{6}$$

Hybrid and multiscale modeling: The CPM can be coupled to auxiliary formalisms, typically using systems of differential equations. A hybrid approach enables multiscale modeling in which molecular species are represented as continuous quantities, and cells are treated as discrete entities. For instance, CPM parameters pertaining to cellular properties can be under the control of ordinary differential equations, representing subcellular processes such as gene regulation. CPM cell behavior can also be linked to lattice-based reaction-diffusion systems representing the biochemical microenvironment through e.g. chemotaxis. A similar approach can be adopted to spatially represent the intracellular biochemistry that exerts influence on the protrusions and retractions in the CPM by kinetic modulation of transition probabilities (Marée et al 2006).

Implementations

When applied to specific biological problems, the CPM framework is typically used with several extensions and modification. Its analysis comprises extensive numerical simulation studies. In an effort to provide a common implementation for CPM simulations, CompuCell3D has been developed (www.compucell3d.org). This open source software implements a large number of common CPM extensions and provides a graphical modeling interface.

Limitations and merits

From a theoretical perspective, the CPM is poorly understood. Hence, the analysis of CPM models can effectively only be performed by numerical simulation. Important mathematical methods, such as rigorous spatio-temporal limit procedures to derive the laws that guide the behavior of certain macroscopic variables, are not yet available. Since the classical Metropolis algorithm (Metropolis algorithm) is modified in the CPM, these models differ in essential aspects from classical equilibrium models. In addition, CPMs have been criticized because their calibration is often non-trivial. Cellular behaviors are specified in an indirect or phenomenological manner via the Hamiltonian and the modified Metropolis algorithm. Consequently, the relation between the parameters that control the dynamics of the CPM and the biological-physical quantities they represent often remains allusive.

Despite these limitations, the CPM formalism has found application in many topics, mainly in the field of developmental biology. Its spatial and cell-centered nature renders it suitable for the study of phenomena where a mesoscopic description of individual cell shape and motility is important. It provides a flexible modeling framework that allows incorporation of problem-specific extensions. Moreover, coupling the CPM to auxiliary model formalisms enables the exploration of the complex interplay between

several factors at different biological scales, acting at the intracellular, the intercellular and the tissue level.

Cross-references

Markov process; Metropolis algorithm; Differential Adhesion Hypothesis; collective behavior; spatio-temporal pattern formation

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