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2 Cellular Potts Model

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7 Synonyms

8 CPM; Glazier–Graner–Hogeweg model; Potts model,
9 cellular/extended

10 Definition

11 A cellular Potts model (CPM) is a spatial lattice-based
12 formalism for the study of spatiotemporal behavior of
13 biological cell populations. It can be used when the
14 details of intercellular interaction are essentially deter-
15 mined by the shape and the size of the individual cells
16 as well as the length of the contact area between
17 neighboring cells.

18 Formally, a cellular Potts model is a time-discrete
19 Markov chain (► [Markov process](#)). It is a lattice model
20 where the individual cells are simply connected
21 domains of nodes with the same cell index. A CPM
22 evolves by updating the cells' configuration by one
23 pixel at a time based on probabilistic rules. These
24 dynamics are interpreted to resemble membrane fluc-
25 tuations, where one cell shrinks in volume by one
26 lattice site and a neighboring cell increases in volume
27 by occupying this site. The transition rules follow
28 a modified ► [Metropolis algorithm](#) with respect to
29 a Hamiltonian.

Characteristics

30

Problem

31

32 The biological structure and function typically result
33 from the complex interaction of a large number of
34 components. When ► [spatiotemporal pattern forma-](#)
35 [tion](#) in cellular populations or tissues is considered,
36 one is often interested in concluding characteristics of
37 the global, ► [collective behavior](#) of cell configurations
38 from the individual properties of the cells and the
39 details of the intercellular interaction. However, even
40 if the basic cell properties and interactions are per-
41 fectly known, it is possible that – due to the complex
42 structure of the system – the collective traits cannot be
43 directly extrapolated from the individual properties.
44 Therefore, appropriate mathematical models need to
45 be designed and analyzed that help to accomplish this
46 task on a theoretical basis. Cellular Potts models con-
47 stitute a modeling framework that is applicable when
48 the details of intercellular interaction are essentially
49 determined by the shape and the size of the individual
50 cells as well as the length of the contact area between
51 neighboring cells.

52 This model class has been developed by Glazier and
53 Graner (1993) in the context of cell sorting. The latter
54 refers to the observed segregation of heterotypic cell
55 aggregates into spatially confined homotypic cell clus-
56 ters. The CPM was introduced to explore the tissue-
57 scale consequences of the differential adhesion
58 hypothesis (► [Differential Adhesion Hypothesis](#)) that
59 holds that cell-type-dependent disparities in the
60 expression of molecules that regulate intercellular
61 adhesion are responsible for cell sorting. Since then,
62 this formalism has been elaborated and applied to

63 study a wide range of morphogenetic phenomena in
 64 developmental biology.

65 **The Model**

66 **State Space**

67 A CPM assigns a value $\eta(x)$ from a set
 68 $W = \{0, 1, \dots, n\}$ to each site x of a countable set S ,
 69 cp. Fig. 1. The set S resembles the discretized space
 70 and is often chosen as a two- or three-dimensional
 71 regular lattice. The set $W = \{0, 1, \dots, n\}$ contains the
 72 so-called cell indices, where $n \in \mathbb{N}$ is the absolute
 73 number of cells that are considered in the model. The
 74 state of the system as a whole is described by *config-*
 75 *urations* $\eta \in X = W^S$. Given a configuration $\eta \in X$,
 76 a *cell* is the set of all points in S with the same cell
 77 index, $\text{cell}_w := \{x \in S : \eta(x) = w\}$, $w \in W \setminus \{0\}$. The
 78 value 0 is assigned to a given node, if this node is not
 79 occupied by a cell but by medium. Each cell is of
 80 a certain *cell type*, which determines the migration
 81 and interaction properties of the cell, the set of all
 82 possible cell types being denoted by A . Denote by
 83 $\tau : W \rightarrow A$ the map that assigns each cell its cell
 84 type. A cell with index $w \in W$ has *volume* (for the
 85 Kronecker symbol δ it holds that $\delta(u, v) = 1$ if $u = v$
 86 and $\delta(u, v) = 0$ otherwise)

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

87 and *surface length*

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

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

91 **Dynamics**

92 A cellular Potts model (CPM) is a time-discrete
 93 Markov chain (► [Markov Process](#)) with state space
 94 X , where the transition probabilities are specified
 95 with the help of a *Hamiltonian*. The latter is
 96 a function $H: X \rightarrow \mathbb{R}$ which often has a special struc-
 97 ture. Usually, it is the sum of several terms that control
 98 single aspects of the cells' interdependence structure.
 99 The standard CPM uses the following two terms. First
 100 a *surface interaction term*

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

is specified. Here, $J: A \times A \rightarrow \mathbb{R}$, the matrix of so- 101
 called surface energy coefficients, is assumed to be 102
 symmetric. Second the *volume constraint* 103

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

is used. Here V_τ , the target volume, and λ_τ , the strength 104
 of the volume constraint, are cell-type-specific param- 105
 eters, $\tau \in A$. Depending on the phenomenon under 106
 investigation, further summands can be included. For 107
 instance, a constraint can be put on the surface length 108
 (Ouchi et al. 2003) 109

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

Again m_τ , the target surface length, and α_τ , the strength 110
 of the surface constraint, are parameters, $\tau \in A$. Thus, 111
 the typical structure of a CPM-Hamiltonian is 112

$$H = H_s + H_v + H_0, \quad (4)$$

where H_s, H_v are given in (1) and (2) and $H_0: X \rightarrow \mathbb{R}$ is 113
 a model-specific addend. See the section “Extensions 114 [Au2](#)
 and Applications” for additional examples of H_0 . 115

Transitions from one configuration to another fol- 116
 low a special rule which is called *modified Metropolis* 117
algorithm (► [Metropolis Algorithm](#)). First, two addi- 118
 tional parameters are specified: a so-called temperature 119
 $T > 0$, which is a biological analogue of the energy of 120
 thermal fluctuations in statistical physics and is 121
 a measure of cell motility, and the *transition threshold* 122
 h , which accounts for energy dissipation during forma- 123
 tion and breaking of intercellular bonds and avoids 124
 oscillatory behavior (Savill and Hogeweg 1997; 125
 Ouchi et al. 2003). Then, the following algorithm is 126
 performed (1): 127

1. Start with configuration η . 128
2. Pick a target site $x \in S$ at random with uniform 129
 distribution on S . 130
3. Pick a neighbor y of x at random with uniform 131
 distribution among all lattice neighbors of x . 132
4. Calculate the energetic difference 133
 $\Delta H_x^y := H(\eta_x^y) - H(\eta)$ of a transition $\eta \rightarrow \eta_x^y$, 134

135 where $\eta_x^y(z) := \eta(y)$ if $z = x$ and $\eta_x^y(z) := \eta(z)$
 136 otherwise.

137 5. Accept the transition by setting $\eta := \eta_x^y$ with prob-
 138 ability $p(\Delta H_x^y)$, or ignore the transition with proba-
 139 bility $1 - p(\Delta H_x^y)$, where

$$140 \quad p(\Delta H_x^y) = \begin{cases} 1 & \text{if } \Delta H_x^y < h \\ e^{-(\Delta H_x^y - h)/T} & \text{otherwise} \end{cases}$$

141 5. Go to 1 or end the algorithm.

142 Consequently, only such transitions are possible
 143 where the index of at most one lattice site is changed,
 144 resulting in a shift of the cell's center of mass. The new
 145 assignment to this lattice site is chosen from the cell
 146 indices of the neighboring lattice sites. These dynam-
 147 ics are interpreted to resemble membrane fluctuations,
 148 where one cell shrinks in volume by one lattice site and
 149 a neighboring cell increases in volume by occupying
 150 this site.

151 To complete the model, appropriate boundary condi-
 152 tions must be specified. If the influence of the bound-
 153 ary shall be neglected, periodic boundary conditions
 154 are used. This means that the space can be thought of as
 155 being mapped onto a torus. However, fixed boundary
 156 conditions, where the interaction between cell surfaces
 157 and confining environment is explicitly modeled, can
 158 be defined as well.

159 Extensions and Applications

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

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

$$\Delta H_{\text{inertia}}(t) = \sum_{w \in W} \lambda_{\text{inertia}}(w) \|\vec{vel}(w, t) - \vec{vel}(w, t - \Delta t)\|^2, \quad (5)$$

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

185 *Cell shapes* arise in the CPM implicitly from satisf-
 186 ying the volume constraint. In the two-dimensional
 187 CPM, cells adopt approximately hexagonal shapes,
 188 producing a space tiling pattern comparable to epithe-
 189 lial tissues. Elongated cell shapes can be modeled by
 190 imposing a cell length constraint which renders the
 191 major axis of the ellipsoidal approximation of the
 192 cell's shape to be close to a predefined target length
 193 or ratio (Zajac et al. 2003). Rod cell shapes with
 194 particular stiffness have been modeled using
 195 a compartmentalized cell concept, where each cell
 196 consists of a row of standard CPM cells (Starruß
 197 et al. 2007).

198 *Chemotactic response* to some field $c: S \rightarrow [0, \infty)$ of
 199 signals can be modeled in the simplest form by an
 200 addend $H_{\text{chemo}} = \sum_{w \in W \setminus \{0\}} \lambda_{\text{chemo}}(w) \sum_{x \in \text{cell}_w} c(x)$ to
 201 the Hamiltonian, where λ_{chemo} is possibly a cell-type-
 202 specific chemotactic response parameter (Glazier et al.
 203 2007). If $\lambda_{\text{chemo}} < 0$, the cells prefer to move up the
 204 chemotactic gradient, for $\lambda_{\text{chemo}} > 0$ they prefer to
 205 move down the gradient. There have been several
 206 more refined extensions to the CPM that model che-
 207 motaxis (Glazier et al. 2007). One example is the
 208 following kinetic extension used by Savill and
 209 Hogeweg (1997), where the positions of the target
 210 spin x and the trial spin y in a proposed transition
 211 $\eta \rightarrow \eta_x^y$ are taken into account,

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

212 *Hybrid and multiscale modeling*: The CPM can be
 213 coupled to auxiliary formalisms, typically using sys-
 214 tems of differential equations. A hybrid approach
 215 enables multiscale modeling in which molecular spe-
 216 cies are represented as continuous quantities, and cells
 217 are treated as discrete entities. For instance, CPM
 218 parameters pertaining to cellular properties can be

219 under the control of ordinary differential equations,
 220 representing subcellular processes such as gene
 221 regulation. CPM cell behavior can also be linked to
 222 lattice-based reaction-diffusion systems representing
 223 the biochemical microenvironment through, for
 224 example, chemotaxis. A similar approach can be
 225 adopted to spatially represent the intracellular bio-
 226 chemistry that exerts influence on the protrusions and
 227 retractions in the CPM by kinetic modulation of tran-
 228 sition probabilities (Marée et al. 2006).

229 Implementations

230 When applied to specific biological problems, the
 231 CPM framework is typically used with several exten-
 232 sions and modifications. Its analysis comprises exten-
 233 sive numerical simulation studies. In an effort to
 234 provide a common implementation for CPM simula-
 235 tions, CompuCell3D has been developed ([www.compu-
 237 cell3d.org](http://www.compu-

 236 cell3d.org)). This open source software imple-
 238 ments a large number of common CPM extensions and
 provides a graphical modeling interface.

239 Limitations and Merits

240 From a theoretical perspective, the CPM is poorly
 241 understood. Hence, the analysis of CPM models can
 242 effectively only be performed by numerical simula-
 243 tion. Important mathematical methods, such as rigor-
 244 ous spatiotemporal limit procedures to derive the laws
 245 that guide the behavior of certain macroscopic vari-
 246 ables, are not yet available. Since the classical Metrop-
 247 olis algorithm (► [Metropolis algorithm](#)) is modified in
 248 the CPM, these models differ in essential aspects from
 249 classical equilibrium models. In addition, CPMs have
 250 been criticized because their calibration is often
 251 nontrivial. Cellular behaviors are specified in an indi-
 252 rect or phenomenological manner via the Hamiltonian
 253 and the modified Metropolis algorithm. Consequently,
 254 the relation between the parameters that control the
 255 dynamics of the CPM and the biological-physical
 256 quantities they represent often remains allusive.

257 Despite these limitations, the CPM formalism has
 258 found applications in many topics, mainly in the field
 259 of developmental biology. Its spatial and cell-centered
 260 nature renders it suitable for the study of phenomena
 261 where a mesoscopic description of individual cell
 262 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 explo-
 ration of the complex interplay between several factors
 at different biological scales, acting at the intracellular,
 the intercellular, and the tissue level.

Cross-References

- [Collective Behavior](#) 270
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- [Markov Process](#) 272
- [Metropolis Algorithm](#) 273
- [Spatiotemporal Pattern Formation](#) 274

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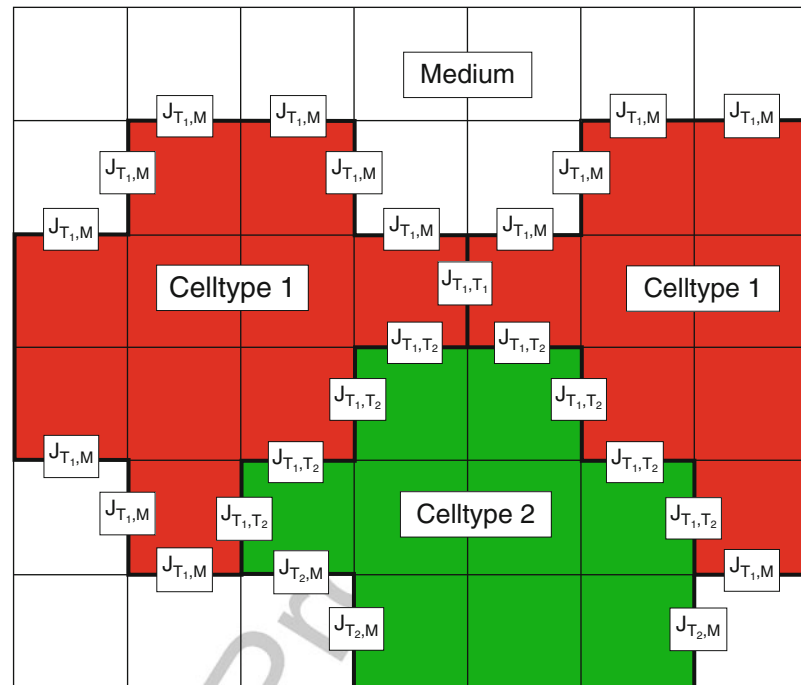
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Cellular Potts Model,

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 T1 depicted in *red*, type T2 in *green*. There are also interactions between the cells and the medium (*white*)



Galley Proof

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