II.1 Magnetization to Morphogenesis: A Brief History of the Glazier–Graner–Hogeweg Model

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Abstract. This chapter discusses the history and development of what we propose to rename the Glazier-Graner-Hogeweg model (GGH model), starting with its ancestors, simple models of magnetism, and concluding with its current state as a powerful, cell-oriented method for simulating biological development and tissue physiology. We will discuss some of the choices and accidents of this development and some of the positive and negative consequences of the model’s pedigree.

1. Introduction

Living cells, despite their great internal molecular complexity, do a few basic things. They stick to each other, move actively up and down gradients in their external environment, change shape and surface properties, exert forces on each other and their environment, secrete and absorb materials, differentiate, grow, divide, and die. A few may send electrical signals or perform other specialized functions. Many approaches to building physical models of tissues are possible.

The GGH model uses a framework derived from statistical mechanics to describe cell behavior, a choice which is not at all obvious at first glance.

The GGH model is a cell-oriented, as opposed to a continuous or pointillistic model. Continuum models ignore cells and treat tissues as continuous materials with specific mechanical properties, completely ignoring the division of tissues into cells. Pointillistic models treat biological tissues as collections of point-like cells, ignoring many cell characteristics that are important to biological behaviors, such as cell geometry and the adhesive interactions between cells at their membranes.

While both approaches are convenient and have had many successes in explaining tissue development and physiology [33, and references therein], many biological structures have length scales of a few cell diameters, e.g., capillaries or pancreatic islets, and thus require explicit spatial descriptions of cells.

The GGH model is actually a framework for defining biological models rather than a single model. GGH models define a biological structure consisting of the configuration of a set of generalized cells, each represented on a cell lattice as a
domain of lattice sites sharing the same cell code (generalized cells may represent all or part of a real cell or any non-cellular material in the simulation). a set of internal cell states for each cell (which may be gene complexes), and a set of auxiliary fields (which may include diffusing chemicals, extracellular matrix (ECM), gravity, etc.). the heart of the GGH model is an effective energy or Hamiltonian, which encapsulates almost all interactions between model elements, and optionally a set of partial differential equations (PDEs) and boundary conditions to describe the evolution of the fields, and optionally the evolution of the internal cell states. Terms in the effective energy often take the form of potential energies and elastic constraints. we call the energy effective because its terms primarily describe responses, which may not result from external forces (e.g., when a cell uses its internal motile apparatus to move up or down a gradient of a chemical diffusing in its extracellular space (e.g., adhesion to a substrate (hapten)). the GGH model also uses a few extra mechanisms, the most important of which is division. the generalized-cell configuration evolves through stochastic changes at individual lattice sites to minimize the effective energy. the classical GGH model uses a modified Metropolis algorithm for this evolution. since the GGH model uses the cell as its natural level of abstraction and treats subcellular behaviors phenomenologically, it reduces the interactions among the 10^-10^-10 gene products within each cell to a set of governing equations for the variation of the roughly ten phenomenological behaviors we mentioned above. a key benefit of the GGH formalism is that we can includes almost any biological mechanism or cell behavior we like, simply by adding appropriate terms to the effective energy. the GGH model then automatically handles the interactions between mechanisms (though we may be aware that its choices may not be the ones that we expect or want). thus, the GGH model provides a compact and efficient way to describe complex biological phenomena.

the global parameters of the effective energy and those describing the properties of cell may be static, or evolve according to simple or complex descriptions of biological or non-biological processes. e.g., the adhesion of cells might depend on a model of cell signaling written in the form of reaction-diffusion (RD) coupled ordinary differential equations (ODEs), or the growth of cells might depend on a neural-network model of genetic regulatory pathways. the GGH model itself is agnostic about the models run inside each cell or outside the cell lattice, using its Hamiltonian to translate the information those models provide into physical structure and physiological behaviors [8, 19].

glacier and François grauer derived their model as an extension of the large Potts model of statistical mechanics [17, 16], calling it the extended Potts model (CPM). the names Potts and associates the CPM with statistical models of equilibrium domain formation, which was appropriate to Glacier and Grauer's simple version. later extensions to the model to describe cell behavior means that it now has little in common with its Potts ancestor. key differences between the Potts and GGH models include:

1. a shift from calculating static equilibrium statistics to kinetics. while the modified Metropolis dynamics (which the GGH model uses to evolve a single configuration of predetermined) derivatizes from the Metropolis algorithm traditionally used with the Potts model, it does not obey the detailed-balance conditions required to generate equilibrium ensembles.

2. initial conditions simulating a particular biological configuration rather than random initial conditions.

3. a shift from physically motivated to biologically motivated domain properties. e.g., biological cells remain cells, even when they do not, so GGH models often include mechanisms to enforce domain connectivity. because the GGH model's behavior and goals are almost totally different from those of the Potts model, the analogy, which the Potts name suggests is misleading. therefore, we propose to name it after its originators, glacier and grauer and the person who has done the most to extend it and bring it to its current prominence in biological modeling, Paulien Hogeweg. from its ancestors, the GGH model has inherited a number of peculiarities; we will discuss several of these and possible solutions to some in sections 6 and 7. because of its flexibility, extensibility and ease of use, the GGH model has become the single most widely used cell-level model of tissue development [8, 19, 20, 21, 31, 32, 30].

1. historical origins of the glacier-grauer-hogeweg model

the GGH model began as an extension of the large-Potts model itself, an extension of the Ising model, a simple early model of ferromagnetism based on the magnetic moments, or spins (σ), of individual atoms and their interaction energies (J). the interaction between a single pair of neighboring spins is often called a bond, or a bond. spins interact via an energy function called a Hamiltonian. historical usage explains many of the otherwise obscure choices of terms and symbols in the mathematical formalism of the GGH model. we begin our historical survey with a note of the model, the Ising model of magnetism.

2. ferromagnetism and the ising model

2.1. ferromagnetism. Ferromagnetic materials develop a permanent magnetic field from a net orientation of the quantum-mechanical spin (σ) of their component atoms. the main goal of early statistical-mechanical models of magnetism was to explain the first-order (continuous) phase transition which occurs in iron at the Curie temperature (Tc). Below this temperature, materials such as iron are ferromagnetic. in ferromagnetic materials, stable domains (connected, spatially extending areas with collinear spins) form without an external field, giving a net
magnetic polarization. For temperatures above \( T_D \), thermal energy disrupts domain formation, the material becomes paramagnetic and its spontaneous magnetization drops suddenly to zero.

2.1.2. The Ising model. Ernst Ising constructed a simple model of magnetization by making four radical simplifications [24]:

1. His atoms reside at regularly spaced points \( i \) on a lattice (throughout this chapter, the symbols \( i, j, k \) will denote two or three-dimensional \((2D \text{ or } 3D)\) vectors of positive integers indexing lattice sites, e.g., \( i=(k,l,m) \); \( k, l, m \in \mathbb{Z} \)).
2. Spins have only two allowed orientations, up \( (s=1) \) and down \( (s=-1) \).
3. Each atom only interacts with its nearest neighbors on the lattice.
4. The interactions are classical, rather than quantum-mechanical, so the spins obey Boltzmann statistics.

According to item 4 the relative probability of any configuration of spins \( \{s_i\} \) is its Boltzmann probability, which depends on the configuration energy, or (Hamiltonian), \( \mathcal{H}(\{s_i\}) \):

\[
P_i(s_i) = e^{-\beta \mathcal{H}(s_i)}
\]

where \( k \) is Boltzmann’s constant and \( T \) is the temperature in degrees Kelvin.\(^3\)

Thus, the higher the energy of a configuration, the less probable it is. In the absence of any external field, the Ising Hamiltonian is the sum of interactions \( J(s_i,s_j) \) between all pairs of spins \( (i,j) \) that are nearest neighbors \( (\mid i-j \mid=1) \):

\[
\mathcal{H}_{\text{Ising}} = \frac{1}{2} \sum_{\langle i,j \rangle \text{ neighbors}} J(s_i,s_j).
\]

The factor of \( \frac{1}{2} \) comes because the summation double counts the interactions. In the Ising model \( J(s_i,s_j) \) favors co-aligned spins (energy \( -J \)) and penalizes anti-aligned neighbors (energy \( +J \)), so we can write Eq (2) as:

\[
\mathcal{H}_{\text{Ising}} = -\frac{1}{2} \sum_{\langle i,j \rangle \text{ neighbors}} J(s_i,s_j).
\]

Leo Ossenner analytically solved the Ising model in 2D and showed that the expected ferromagnetic phase transition did occur [38]. No analytical solution is known in 3D, however, a ferromagnetic phase transition still occurs for \( T_c > 0 \).

In the Ising model, the transition between ferromagnetic and paramagnetic states occurs because each unit of boundary between domains of opposite spin costs an energy \( 2J \), so configurations with connected domain boundaries and many domains have higher energies than those with fewer, smoother domains. On the other hand, the number of configurations composed of many connected domains is much larger than the number composed of a few smooth domains. If we pick a configuration at random from such an ensemble of configurations distributed

\[\text{according to the Boltzmann probability in Eq (1), the domain structure we expect to find depends on the product of the multiplicity of the structure with the Boltzmann probability. If } T \gg 2J, \text{ the greater number of random configurations wins out over their smaller Boltzmann factors, so random configurations are much more probable. At low temperatures, the cost of domain boundaries is so high that the lower Boltzmann probabilities of random configurations overcomes their large number, and large-domain configurations dominate. In the limit that } T \to 0, \text{ the most probable state has all the spins in the same direction (one infinite domain).} \]

2.1.3. Summary. The Ising model contains two key ideas that carry forward to the GGH model:

1. The energy of anti-aligned links between neighboring spins on a lattice represents the energy per unit length of the boundaries between domains.
2. A temperature or fluctuation amplitude determines the probability of a configuration.

However, the Ising model is far from being a model of biological cells because:

1. It lacks dynamics.
2. Many domains may share the same spin, while for biological modeling we need a unique label for each cell.

2.2. The Potts Model

Renfrey B. Potts, in his PhD thesis, described a simple extension of the Ising model which allowed multiple degenerate values of the spin, i.e., the energy of a link depends only on whether the neighboring spins are the same or different and not on their particular values [40, 41]. We can write the Potts version of Eq (2) as:

\[
\mathcal{H}_{\text{Potts}} = J \sum_{\langle i,j \rangle \text{ neighbors}} (1 - \delta(s_i,s_j)),
\]

where \( \delta(x,y) = 0 \text{ if } x \neq y \text{ and } 1 \text{ if } x = y \). We denote the number of possible spin values by \( q \). The Potts model has ferromagnetic and other phase transitions [6, 11]. In the limit of large \( q \), the Potts model can have many coexisting domains at low temperatures, but multiple domains can still share the same spin and it still lacks the concept of dynamics.

2.2.1. Summary. The Potts model contains two key ideas for biological simulations:

1. Individual domains can have individual spins (which in CPN and GGH simulations we refer to as cell indices.)
2. Domains have a boundary energy that can be used to model adhesivity.

However, the Potts model still has several shortcomings as a basic biological simulation:

1. It still lacks dynamics.
2. Many domains can share a single spin. In biological simulations we require that each separate domain represent a unique object, such as a biological cell or part of one.
3. The Potts model specifies only a single contact energy between all spin values.
4. The Potts model does not have a way to control domain size and shape.

2.2. From Statistics to Statistical Mechanics

According to statistical mechanics, the distribution of equilibrium configurations of a set of classical spins depends only on the Hamiltonian and the temperature. Mathematically, we enumerate the statistics for all configurations in the partition function, which sums the Boltzmann probability of every configuration:

\[ Z = \sum_{\{\sigma\}} e^{-\beta H_{\text{total}}} \]

(5)

Then the expectation value for any function \( f(\{\sigma\}) \) is:

\[ \langle f \rangle = \frac{\sum_{\{\sigma\}} f(\{\sigma\}) e^{-\beta H_{\text{total}}}}{Z} \]

(6)

2.3.1 Monte Carlo methods

Unless the partition function and the relevant expectation values are analytically tractable, it is necessary to use Monte Carlo methods to evaluate them numerically, which is effectively impossible because of the enormous number of configurations to enumerate (in the Potts model, \( 2^N \), where \( N \) is the number of spins in the lattice). Computationally, A. Ott and Teller showed that we can neglect the vast majority of configurations which have high energies and thus very low probabilities, making the calculation tractable [5]. In their Monte Carlo method, we start with any lattice configuration and jump\(^2\) randomly from configuration to configuration with probabilities chosen so that the number of times we visit a configuration is proportional to its Boltzmann probability. If we then average the values of \( f \) that we calculate for such a sequence of configurations, the average converges to \( \langle f \rangle \). In effect, we have replaced an integral over configurations with a time average. However, because the A. Ott and Teller method allows jumps between any two configurations, it is likely that we will never arrive at a stable configuration. Therefore, the method requires that kinetic models be considered. The required probability for a transition between configurations \( \{\psi(0)\} \) and \( \{\psi(1)\} \) is:

\[ \frac{\psi(1) - \psi(0)}{\psi(0) - \psi(1)} \]

(7)

This condition is called detailed balance. Monte Carlo methods do not obey detailed balance at \( T > 0 \).

2.2.2. The Metropolis algorithm

The Metropolis algorithm [5] randomly modifies the A. Ott and Teller method because it is local, i.e., instead of allowing transitions between any two configurations, it allows transitions only between configurations differing in their spin values at a single lattice site. We can think of the Metropolis algorithm as diffusion in configuration space. This local behavior allows a natural time ordering of configurations, because any configuration retains a memory of past configurations, and limits allowed future configurations. The Metropolis algorithm for a Hamiltonian \( H \) is:

II.1. Magnetization to Morphogenetic A History of GGR Model

1. Choose a lattice site at random. We call this the target site, which we will denote \( S_{\text{target}} \) and its spin, the target spin, which we will denote \( S_{\text{target}} \).
2. Pick any value of spin at random. We call this the trial spin and denote it \( S_{\text{trial}} \).
3. Compute the current configuration energy, \( E_{\text{current}} \), and the energy of the configuration if the target spin were changed to the trial spin value, \( E_{\text{target}} \).
4. Calculate the expected acceptance probability. If the new energy is lower, accept the change with probability \( p = e^{-\Delta E / kT} \), where \( \Delta E = E_{\text{target}} - E_{\text{current}} \). If the new energy is higher, accept it with probability \( p(1 - \exp(-\Delta E / kT)) \). This is called a spin flips attempt.
5. Go to 1. If all sites are visited, we have completed a spin flips attempt.

On a lattice with \( N \) sites, we define one Monte Carlo step (MCS) as \( N \) spin flips attempts. We also define the acceptance rate to be the average ratio of the number of spin flips accepted to the number of spin flips attempted. If the acceptance rate is small (as a rule of thumb, the acceptance rate should be greater than 0.01), the Monte Carlo method is inefficient and we say that the computation is sti for that Hamiltonian. Clearly, the acceptance rate increases as \( T \) increases. For \( T > 0 \) (because the transition probability, Eq. (7), the long-term distribution of configurations obeys Boltzmann statistics, Eq. (1)).

2.3.3. The use of the Metropolis algorithm for quasi-deterministic kinetics

Two behaviors suggest the possibility of using the Metropolis algorithm for kinetic simulations:

1. While the long-time behavior of the Metropolis algorithm is purely statistical, at low temperatures, over short times, the transition probability tends to lower the configuration energy.
2. For \( T > 0 \), the Metropolis algorithm does not produce a statistical equilibrium. Instead it drives the configurations down energy gradients to a local energy minimum, where evolution stops.

Consider a sequence of configurations, differing by one spin value, \( (S_{1}, \ldots, S_{N-1}, S_{N}) \), with associated energies, \( (H_{1}, H_{2}, \ldots, H_{N}) \). Then the rate of transition (the difference between the forward and backward transition probabilities):

\[ r(S_{N} \rightarrow S_{N-1}) = e^{K_{D} \beta^{-1} \left( E_{\text{current}} - E_{\text{target}} \right)} \]

(10)

If we choose \( T \) such that \( e^{-K_{D} \beta / T} \) is small, but not too small, for all \( i \), then, for \( T \rightarrow 0 \),

\[ e^{-K_{D} \beta / T} \approx \frac{N_{c} - N_{d}}{T} \]
so the net rate:

\[ r_{\text{eff}}(S_i, S_{i+1}) \sim \bar{\Delta}c \cdot \Delta N_{i+1} \]  

(12)

In this case, if we take one spin-copy attempt as our time unit, the average speed from \( S_i \rightarrow S_{i+1} \) is:

\[ \bar{\Delta}c(S_i, S_{i+1}) = 2 \cdot \bar{\Delta}N(S_i, S_{i+1}). \]

(13)

Thus, the average time evolution of the configuration obeys the Aronhadouz or overdensity force-velocity relation:

\[ \bar{\Delta}N = \bar{F} = \bar{\rho} \Delta \bar{c}, \]

(14)

where \( \rho \) is an effective mobility. The movements of individual boundary elements of a domain may be quite random, but the average velocities of large domains will be deterministic when the argument of the exponential in Eq. (10) is not too large.4

When the argument is small enough, which is in the case for at least biological simulations, the deterministic velocity relationship is indeed linear and obeys Eq. (14), [70] (see also chapter II.B by Marie et al.). This result is the fundamental justification for using Metropolis-like dynamics in kinetic simulations. Changing the dynamics, e.g., from Metropolis to Glauber, will change the result in complex and sometimes unpredictable ways [70].

Using Metropolis dynamics for kinetic simulations causes a number of problems. That Eq. (13) requires that the argument of the exponential in Eq. (10) be small, makes our original use of the Boltzmann factor in Eq. (9) questionable. However, no one has studied the effects of GHH modeling of switching to a different weighting factor in Eq. (9).

The exact relation between Monte-Carlo spin-copy attempts and continuous time are still the subject of debate and are a persistent source of criticism of kinetic applications of Metropolis-like algorithms in GHH simulations. In addition, because of the time-averaged movement obeys the deterministic kinetics, the time order of events occurring at different lattice sites is ambiguous over short times. Several more sophisticated approaches to dynamics are possible (see chapter II.B, section 3.1).

3. Kinetic Potts Simulations – From Metal Grain to Foams

3.1. From the Potts Model to Coarsening

The use of Metropolis methods to reveal the quasi-isothermal kinetic of coarsening evolving under a Hamiltonian, led to a great expansion of the range of questions that Monte-Carlo methods could address. One new area of interest in the early 1980s was the kinetics of metallic grain growth. Most simple metals are composed of microcrystals, or grains, each of which has a particular crystalline lattice orientation. The atoms at the surface of these grains have a higher energy than those in the bulk because of their missing neighbors. We can characterize this

\[ \text{excess energy as a boundary energy. Atoms in convex regions of a grain's surface have a higher energy than those in concave regions, in particular than those in the concave face of an adjoining grain, because they have more missing neighbors. Thus, an atom at a convex curved boundary can reduce its energy by "hopping" across the grain boundary to the concave side. The movement of atoms, which we can equivalently view as the movement of grain boundaries, lowers the net configuration energy, but requires thermal activation because an atom has a higher energy when it is in the space between grains than when it is part of one. Thus, while grains are stable at low temperatures, at high temperature metallic microstructure changes through coarsening or coarsening with the net size of grains growing because of grain disappearances.} \]

3.1.1. The Extensive model of grain growth. In the early 1980s, a group of researchers at Exxon Research, Michael P. Anderson, Gary S. Greet, Pardeep S. Sahni, and David J. Stehrkot, noticed that the Potts Hamiltonian used 3 times the total boundary length of the configuration [45, 44, 46]. They drew an analogy between grain growth and the Potts model, where they took the lattice sites to correspond to atoms, the specific spin values to different crystalline orientations, and links between different spin domains to grain boundaries. They usually assumed that domains were initially connected and compact, with a different spin assigned to each grain to avoid grain coalescence.6

In grain growth heterogeneous nucleation does not occur, i.e. a spin of type \( \sigma \) will not suddenly appear in the middle of a domain of spin \( \sigma' \). Since the Metropolis algorithm allows heterogeneous nucleation, the Extinct group modified the Metropolis algorithm to prevent it by selecting the trial spin from the neighborhood of the target spin. We will call the lattice site of the trial spin \( \sigma' \) and its value \( \sigma_{\text{trial}} \). Though they did not recognize it at the time, the concept of a copy of lattice value with a source and target implied a copy direction, which proved crucial for later development of the GHH model. Forbidding heterogeneous nucleation means that evolution occurs only at domain boundaries. It also violates detailed balance, a further move away from statistical mechanics and towards purely kinetic modeling.

For low T, the Potts Hamiltonian and the modified Metropolis dynamics, individual domains evolve in a manner that resembles the growth of metallic grains during annealing at high temperature. The simulated evolution of the distributions of domain sizes, shapes and correlations agreed very well with experiments in metals [66].

3.1.2. Coarsening in foams. Glaser, working with the Exxon group, later showed that the simulated evolution also closely matched the experimental evolution of bubbles in 2D liquid soap froths, where gas diffuses across soap films depending on their curvature [13, 15]. In this case, a link between two different spin directions represents

4Like a Brownian, the CPF has a critical temperature analogous to the Curie temperature (see section 6.1). Quasi-deterministic motion occurs only for temperatures well below this critical temperature.

5Allowing multiple spins to have the same spin allows coalescence, which occurs in some metals since grain boundaries are simply lines between lattice sites with different spins, when two grains with the same spins come into contact, they immediately fuse into one large grain.
3.1.4. Summary. The Exxon simulations introduced many key ideas - the use of uniquely-labeled coarse domains to identify different grains, the study of domain kinetics under the influence of boundary energy and fluctuations, the use of mismatched links to represent membranes, and the modification of the Metropolis algorithm to prevent heterogeneous nucleation. They also resolved the problem of lattice anisotropy, which still afflicts GGH simulations.

3.2. From Grain to Relaxed Foams - Constraints in an Extended Potts Model
One significant difference between foams and metallic grains is that the growth rate and relaxation rate of boundary shape of a metallic grain are the same, while in foams boundary relaxation is much faster than growth. The result is that grains can have irregular shapes, while foam boundary walls (soap films) are near-perfect minimal surfaces (circular arcs in 2D). In a brilliantly-preserved and careful study, Weeks and Kerneved extended the Potts model using constraints to stimulate courting in 2D liquid foams [67, 68].

3.2.1. Constraints. The use of constraints to describe interactions comes from classical mechanics. E.g., we can describe circular motion by imposing the constraint that a particle remains a constant distance from a specified point. We use the calculation of variations to derive equations of motion under a constraint, by minimizing an integral of a Hamiltonian (or Lagrangian) with an added physical constraint condition, which is the product of a Lagrange multiplier, \( \lambda \) (the generalized force needed to maintain the constraint), with a function which is minimal when the constraint is satisfied.

In the context of Monte-Carlo dynamics, we can write a constraint energy in a general elastic form: \( k_{\text{value}} = \text{target value}^2 \). This constraint is zero if \( \text{value} = \text{target value} \) and grows as \( \text{value} \) diverges from \( \text{target value} \). We call the constraint elastic, because the exponent of 2 occurs in ideal springs and elastic solids (we could, in principle, use any positive even integer). Because the constraint energy decreases smoothly to a minimum when the constraint is satisfied, the modified Metropolis algorithm automatically drives any configuration towards one that satisfies the constraint. In the presence of multiple terms in a Hamiltonian, no constraint is usually satisfied exactly, because no configuration will satisfy
all constraints and minimizes all energies simultaneously (see chapter II, section 5). While increasing the appropriate λ can force the configuration to satisfy any constraint to any desired accuracy, increasing J/λ reduces the acceptance rate, which slows the simulation timescale and makes it computationally inefficient. If J/λ becomes too large, the simulation will freeze and only limited configuration evolution will occur. In the context of numerically solving differential equations, such constraints are appropriately called stiff since we can make value depend on the configuration in any way we want, and also make target values very in any way we like in space or time, we can impose almost any behavior using constraints (although its expression may be cumbersome).

3.2.1. The Wester- Kermode model for soap froths. Because Wester and Kermode wanted dense domains that were compared to boundary relaxation and because they did not know the domains in the large-g Potts model already obeyed von Neumann’s law [60], they added an elastic constraint on the volume of each domain and evolved the target volume very slowly according to this law. They then used a Potts boundary-energy term in their Hamiltonian to impose an effective surface tension on their domains, causing boundaries to relax towards four-like minimal-surface shapes [69]:

$$N = \sum_{\langle ij \rangle \in \text{domains}} \left( \lambda - \rho(\sigma_i, \sigma_j) \right) + \sum_{\sigma} \delta(\sigma) - V(\sigma) \right)^2 \right)$$

where λ is an inverse gas compressibility, ρ(σ) is the number of lattice sites in the domain with spin σ, and V(σ) is the target number of sites for that domain. One useful result from this constraint formalism is that $P = -2\lambda (\rho(\sigma) - V(\sigma))$ is the pressure inside the domain. A domain with $\sigma > \rho$ has a positive internal pressure, while a domain with $\sigma < \rho$ has a negative pressure.

The shapes of the simulated domains in the Wester–Kermode model were much more foam-like than those in Glover’s simulations. Unfortunately, this pioneering work was not followed up.

3.2.2. Summary. With Wester and Kermode’s extension of the Potts model to include a volume constraint [69], all that a model of biological cells still needed was a boundary energy that depended on domain type, an idea that goes back to the Heitmann model of magnetism [72].

4. The Origin of the Cellular Potts Model

In this section we discuss the origin of the type-dependent boundary energies between cells used in the CPM and GCG model and write the full Hamiltonian for the CPM. The inspiration for the CPM came from experimental and theoretical work by the biologist Malcolm S. Steinberg at Princeton University on biological cell-surfing experiments and from his experiments on segregation in aggregates of hydro cells (Hidro cypridum) by the biophysicist Yuzo Sawada at Tohoku University, Sendai, Japan [48, 5, 12, 4].

4.1. Cell Adhesion and Cell Sorting

Cell adhesion is fundamental to multicellular organisms, and to many unicellular organisms as well [10]. If cells could not stick to each other and to extracellular materials, building complex life would be impossible. Adhesion also provides a mechanism for controlling structures, as well as holding them together once they have formed. In the late 1960s, Steinberg, while trying to understand how differences in gene expression between cells could translate into complex structures in embryos, noticed that during embryonic development, the behavior of aggregates of cells resembled the behavior of visco elastic fluids. For example, a random mixture of embryos—cells of two types, when formed into a 3D aggregate, reorganized into a compact ball with the more cohesive cell type surrounded by the less cohesive cell type in a phenomenon known as cell sorting [4, 12]. Differences in cohesion resulting from differences in the numbers and types of cell adhesion molecules on cell surfaces [11, 12] could also explain the layered structure of the embryonic retina and the segmentation of a more cohesive tissue by a less cohesive tissue. Steinberg’s Differential Adhesion Hypothesis (DAH) proposed that the final configuration of an initially arbitrary configuration of embryonic cells minimized their total free energy, so tissue really did behave like visco elastic fluids [54, 55, 56, 57].

The many families of adhesion molecules (CAMs, catheterins, etc.) provided a mechanism for embryos to control the relative adhesiveness of their various cell types to each other and to the extracellular ECM surrounding them, and thus to build complex structures. However, like the ising model, the DAH was concerned only with equilibrium configurations, not kinetics.

4.2. The Cellular Potts Model

In 1991, Glover joined the Sawada laboratory at Tohoku University in Sendai, Japan, which was famous for its studies on the regeneration of adult Hydra from randomly mixed aggregates of their dissociated cells [48, 47, 49, 2, 53, 42, 43]. There, Glover met Goyal, who was studying the first phase of Hydra regeneration, when endodermal cells sorted to the center of the aggregate and ectodermal cells to the surface [54]. Goyal wanted to see if the DAH explained his results. Glover realized that he could extend his foam simulations with the Exxon group to explore the kinetics and thermodynamics of biological cell sorting, e.g. to determine whether the cell sorting that Steinberg and Armstrong had observed experimentally required active cell motility, which would imply that the energy landscape of the configuration space was rough, with many local minima, or could occur in the absence of fluctuations, which would imply that the energy landscape was smooth, with a single global minimum for the sorted state.

Glover also realized that the domains could represent more than biological cells—in particular he introduced the concept of a domain as a generalized cell, which could take on different properties and behaviors depending on the specific conditions of the experiment.
which could be a biological cell, a sub-element of a cell, allowing compartmentalized cell models, or part of the extracellular medium, a fluid or a solid, depending on the domain's characteristics. This redefinition of everything in the simulation to be composed of generalized cells allows the same model to treat very different types of objects, greatly simplifying model building.

Glister and Gruner's model discretized the continuous cell configuration onto a square lattice. A collection of nodes with the same index represented a generalized cell, as shown in Fig. 2, with a unique index for each cell r(t) ∈ {1, 2, N} defined at each lattice site I, and a cell type r(t) for each cell. Links between different indices represented regions of contact between two cell membranes. From now on, we will drop the confusing term spin and refer to cell indices, since spin has no meaning in our biological context.

Since the cell volumes were constant and uniform in cell-sorting experiments, Glister and Gruner used an elastic volume constraint based on Weaire and Kermode's work on foams [68] to maintain the size of the biological cells. To represent variations in adhesion between cells of different types, they defined a Potts-like boundary energy which depended on the cell types at a link, J(r(t), r(t')) (see Fig. 2), so the boundary term in the Potts model (equation 4) became:

$$\gamma_{boundary} = \sum_{(I,J) neighbors} J(r(t), r(t'))[(1 - \delta(r(t), r(t')))],$$

(16)

where the boundary energy coefficients are symmetric,

$$J(r', t) = J(r, t).$$

Glister and Gruner assumed that the boundary energies were positive ($J > 0$), which proved to have unfortunate consequences (see section 6.2 below). The full Hamiltonian for Glister and Gruner's CPM is:

$$\gamma_{CPM} = \sum_{(I,J) neighbors} J(r(t), r(t'))[(1 - \delta(r(t), r(t')))] + \sum_{(I,J) neighbors} \lambda \Delta r(t), r(t')(r(t), r(t'))^2,$$

(18)

where $r(t)$ is the volume in lattice sites of cell $I$, $V_I$ its target volume, and $\lambda \Delta r(t)$ the strength of the volume constraint. In Glister and Gruner's original papers, the value of $V_I$ was constant for all biological cells and the volume of the generalized cell representing the surrounding medium was unconstrained ($\lambda \Delta r(\text{medium}) = 0$) [17, 16].

If we add a constant to all $J$-s and also add the same constant to the interaction energy between like indices (which is 0 if $\gamma_{boundary}$ in Eq. 18) and require us to change the form of the equation), the evolution is unchanged. Since the kinetics in the modified Metropolis algorithm depends only on two things, the sign of $\Delta N$ and the value of $\Delta N/T$ (see Eq. 9), if we multiply all the terms in the Hamiltonian by a positive constant and multiply the temperature as well, the evolution of configurations remains unchanged. Therefore, we have two degrees of freedom, one additive and one multiplicative, in setting the scale for the CPM parameters (see chapter II.1, section 4.3).

Since biological cells move actively (in the case of vertebrate cells usually by extending and retracting their membrane using their cytoskeletons), these membrane fluctuations are very roughly isothermal (through they have a non-thermal origin) and since cells do not suddenly appear inside other cells, Glister and Gruner used the modified Metropolis algorithm of the Exxon Group for the dynamics of their model.

4.3.1. Smoothing ("smoothening"). The CPM runs with $T > 0$ and the usual values of $\Delta N/T$ are fairly small. Thus fluctuations are large, especially for more cohesive cells (those with lower $J$ values) and cell boundaries can become highly contorted. In this case, cells can become disconnected by spinning off small (usually single lattice-site) blobs (we take the name from the small membrane-encased blobs of cytoplasm which migrating cells sometimes leave behind). Neither blobs nor contorted boundaries are biologically realistic. Both can affect calculations of surface areas, neighbors and volumes. In Glister and Gruner's original papers, before they calculated statistics for a configuration, they eliminated disconnected blobs and smooth cell boundaries by running their simulation with $T = 0$ for five, or more, MCS, using the normal Hamiltonian and modified Metropolis dynamics. Rather confusingly, they called this smoothing annealing, even though it is not the same as normal annealing in metals. Later studies have generally not needed smoothing to reproduce biologically-observed behaviors.
5. Classical CPM Results

Because of Glazer and Graner’s backgrounds in physics, their initial studies of cell sorting simulations resembled in many ways the Foucault group’s statistical mechanics studies of grain growth. They first validated the use of the CPM as a biological context by studying its phase transitions and the behaviors of stimulated cells of a single type as a function of individual spatial parameters (e.g., to establish the optimum range for J/T and to check for excessive inertia/antipathy effects). They then tried to simulate Steinberg and Armstrong’s experiments on cell sorting, studying the behavior of mixtures of two types of cells: high-boundary-energy, low-adhesion cells, and low-boundary-energy, high-adhesion cells, surrounded by a single generalized cell representing fluid medium.

A key result was that cell sorting is an activated process requiring membrane fluctuations [16]. In their CPM simulations at low temperatures, cells clustered but clusters could not coalesce. This observation was a good example of the way that simulations can clarify a complex experimental situation. Experiments had previously shown (and later verified) that introducing drugs which blocked membrane fluctuations into the fluid medium containing the cell aggregates inhibited cell sorting [4, 36]. However, the drugs used interfered with the cells’ cytoskeleton. Since the adhesion molecules, which determine cell-adhesion behavior, bind to the cytoskeleton and change their adhesivity when the cytoskeleton is disrupted, the experiments could not determine definitively whether the failure to observe sorting was due to lack of cell motility or to changes in cell-cell adhesivity. As in this case, biological experiments often lack clear control parameters. In their simulations, Glazer and Graner were able first to change cell motility while keeping adhesion constant and then to change cell adhesion while keeping cell motility constant. By comparing the results in these two cases, they were able to show that loss of cell motility indeed prevented sorting.

They then examined the various possible hierarchies of boundary energies (J/T) to characterize the classes of typical patterns which they could obtain. The variety of outcomes, even in this very simple situation, showed the power of variations in the expression of cell adhesion molecules to control embryonic morphogenesis (see a simulation Movie II.1 from the accompanying DVD).

6. Peculiarities of the CPM

Glazer and Graner were trying to build a model so simple that they could understand the physics of all of its components. Thus the CPM has certain peculiarities, which, while not generally critical to biological simulations, may cause confusion and artefacts. If we are aware of these potential problems, we can usually take steps to make sure that they do not mitigate our results.

II.1 Magnetization to Morphogenesis: A History of GGH Model

8.1. Temperature

We mentioned in section 5 that cell sorting (and indeed any interesting biological phenomenon we might want to investigate) requires cell motility both experimentally and in simulations. Thus we must pick a dynamic to go with our Hamiltonian. From a physical point of view, the modified Metropolis algorithm is the simplest choice.

Temperature can cause problems in a number of contexts in the CPM (see chapter II.2, section 6). The CPM has several phase transitions in temperature, three of which, in particular, are wholly non-biological and limit the range of temperatures which simulations can use. As a rough guide for picking appropriate values of J to avoid it < 0°c, we want to accept a significant fraction of index-copy attempts but not so many that the lattice pattern melts. Thus we need 0.2 < ΔJ/T < 2. If the number of neighbors per lattice site is n, the typical fluctuation energy per index-copy is ΔJ/T, so we need to pick all of our J values such that 0.2 < J/T < 2, which may not always be possible. If J is too large relative to T the boundaries of the cell will become rough and the cell will shed blocks. If J is too small relative to T the cell boundaries will become stiff and align with the lattice's preferred directions.

Only for small bacteria are actual thermal fluctuations important to motility. In all other cases, motility depends on molecular motors of varying kinds. The motivation for the use of the modified Metropolis dynamics was amorphous motion of the mesenchymal cells in Steinberg and Armstrong's experiments, where fluctuations in a cell's cytoskeleton cause its membrane to ripple, moving gently back and forth in a random manner. However, in most cases, cell motility results from different mechanisms [3], the geometries of which differ greatly from that of the typical membrane fluctuations in CPM cells.

Because active molecular motors drive all of these movements, the typical energy spectrum of membranes or cell movements need not follow the Boltzmann distribution of modified Metropolis dynamics. If the fluctuation spectrum of the movements matches the depth of local minima in a configuration-energy landscape, rearrangements may happen much faster than they would for thermal fluctuations, speeding the rate of configuration evolution. Worse, in almost every biological case, movements in a given direction tend to persist for fairly long times (up to a minute), because assembling and disassembling the molecular machinery responsible for cell movement takes time. Thus the assumption that motion is temporally uncorrelated, fails. We will discuss in chapter II.4, section 1.3 some ways to put these correlations back into GGH models. Sometimes these correlations have no significant effect. Unfortunately, when an energy landscape is rough, as it is for most biologically interesting problems, correlations and non-thermal fluctuation spectra can change not only time scales but time ordering [64]. Thus, in some cases, our assessment of the feasibility of a biological mechanism based on simulations may be incorrect.
Ironically, given these issues, the use of T in GGH simulations has almost never been a significant limitation. Where it has, simple fixes like including an inertial constraint (see chapter II.4, section 1.1) seem to have solved the problem. Nevertheless, improving the realism of GGH kinetics is worthy of attention, experimentally (to characterize actual kinetics), computationally and theoretically (to understand the significance of different kinetic behaviors to configuration evolution and scaling).

6.2. Diffusion, Energy and Parameter Choices

Glacier and Grasser's original model, following the physical reality in forms and metallic glasses, assumed that boundary energies were positive, so the boundary energy term served both to minimize boundary areas and to determine the optimal arrangement of cells. A negative J results in the cell boundaries breaking up to maximize their boundaries. When Glacier and collaborators began studying cell diffusion rates, they found that more cohesive cells (smaller J > 0) had more cramped surfaces, larger membrane fluctuations, and diffused further than less cohesive cells, exactly the opposite of the expected result [61]. Since biological cells usually have adhesive interactions with each other and the ECM, the correct way to solve this problem is to use negative J and constrain the surface area separately (see section 7.1.1). Equivalently, Hoggart further modified the modified Metropolis dynamics by shifting the Boltzmann probability in Eq (9) to negative $\Delta E_{b}$, which gives the same effect:

$$K_{E}(\sigma, \gamma) = K_{E}(\sigma', \gamma') = \begin{cases} 1 & \text{if } \Delta E_{b} \leq 0, \\ \exp\left(-\frac{\Delta E_{b}}{k_{B}T}\right) & \text{if } \Delta E_{b} \geq 0. \\ \end{cases}$$ (19)


We can equivalently view this modified dynamics as introducing an extra dissipation energy per index copy [31, 32]. Negative $J_{s}$ give correct diffusion hierarchies [42]. Since the configurations observed are independent of the sign of $J$ (only the diffusion constants are wrong), many researchers continue to use simple $J > 0$ models, when they do not care about relative rates.

While relating GGH parameters to experimentally-meaningful material properties has proved difficult, the recent development of the continuous limit of the CPM may help to connect simulation and physical parameters [65].

6.3. Intrinsic Dispersion and Viscosity

To make CPM simulations mechanistically realistic, we would like to be able to specify the resistance to motion that cells experience when moving through a fluid due to dispersion and viscosity. Dispersion is the loss of energy due to motion, i.e. resistance to all motion. Viscosity is dissipation which results from velocity gradients. The CPM is intrinsically dispersive, but not viscous. Consider a channel filled with CPM cells, which strongly adhere to the walls of the channel (small J). If we push the cells through the channel by applying a gradient, the cells will experience plug flow, i.e. all cells move with the same average velocity. The cells touching the walls do not move slower than those in the center of the channel, so

In certain situations, strong binding between cells can lead to cytokinetic changes which increase cell motility, in which case using positive energies may be more appropriately biological.

II.1 Magnetization to Morphogenesis: A History of GGH Model

we would expect in a viscous fluid. We can implement viscosity in the CPM (see chapter II.4, section 1.2.1) to produce the correct velocity profile. However, an object moving through a fluid with CPM viscosity experiences both viscous and intrinsic dissipation, while a real fluid has no intrinsic dissipation.

7. From the CPM to the GGH Model

The basic CPM models only the effects of differential adhesion, cell volume and fluctuations. The GGH model adds many of the other biological mechanisms we discussed in section 1 and also addresses some of the issues in section 6.

7.1. Simple Extensions to the Hamiltonian

7.1.1. Surface area constraints and negative boundary energies. Biological cells have a defined amount of cell membrane, which we can represent with a surface area constraint:

$$N_{surf} = \sum_{\sigma} \alpha_{s}(\sigma) = \alpha_{s}(\sigma)$$ (20)

where $\alpha_{s}(\sigma)$ is the surface area of cell $\sigma$ and $S_{t}$ is its target surface area in lattice sites. Changing the ratio:

$$\mu_{s} = \frac{3}{V_{s}}$$ (21)

changes the rigidity of the cell. Like a slowly inflated balloon (which corresponds to decreasing $\mu_{s}$), for $R > 1$ the cell is floppy, while for $R < 1$ it is spherical and for $R \leq 1$ increasingly rigid. While $\alpha_{s}(\sigma)$ is the simplest form of surface area constraint, other forms are possible and may be preferable, e.g.:

$$N_{surf} = \sum_{\sigma} \alpha_{s}(\sigma) = \alpha_{s}(\sigma)^{3/2} - \alpha_{s}(\sigma)^{3}$$ (22)

keeps the $R$ of a cell constant as it grows. Constraining the cell surface area leaves us free to define cells' boundary energies $J$ to be either positive or negative, depending on their real biological values, eliminating the diffusion-hierarchy problem we noted in section 6.2.

7.2. Non-Hamiltonian Extensions

7.2.1. Cell growth and proliferation. The simplest way to simulate the growth of cells is to allow $V_{t}$ and $S_{t}$ to increase gradually with time from a given initial values $V_{0}$ and $S_{0}$, to double that value, $2V_{0}$ [7], at a rate proportional to the concentration of a nutrient or growth factor $C$ [39], see also a simulation ModVII.1.2 from the accompanying DVD:

$$\frac{dt}{\alpha_{t}} \propto C_{t}$$ (23)

For large $C$, a real cell's growth rate saturates, which we can include by replacing $C$ by a Michaelis-Menten or Hill form $\frac{aC}{b + C}$, where $a$ and $b$ are constants depending on cell type. Cells can also grow when they are stretched [42, 48].
7.2.2. Cell division. To model cell division (mitosis) when a cell \( x \) reaches a given doubling volume, we assign a new index \( x \) to half of the existing cell's lattice sites, dividing the cell either along the cell's axis or randomly. The CPM automatically handles contact forces between cells. However, we might like to describe other influences on cell movement as well, for instance, external physical forces, or indirect effects like chemotaxis. In the context of the GGM model, we implement any influence on cell movement either through a generalized potential energy added to the Hamiltonian or by direction biasing of index copy acceptance probabilities. The latter has the form of a generalized force (chapter II.2, section 3).

The primary use of fields is to record the concentration of signaling chemicals or other biomolecules, which we will usually denote \( C(x) \), that may diffuse and react (section 7.3.2) and influence cell behavior via chemotaxis (section 7.3.1) or in other ways. Usually simple fields are thought of as occupying the same space as the cell lattice (i.e., cells do not exclude fields), although we can use repulsive haptotaxis to keep cells and fields spatially distinct. Fields may also be attached to cells or subcells rather than to the lattice (see chapter II.4, section 2.3) in which case we denote the field \( C(x) \) and its value at a lattice site as:

\[
(C(x) = C(u(x)))
\]

i.e., the amount of chemical at a particular lattice site equals the amount in the cell divided by the cell volume.

In some simple cases, we can represent the field as an analytic function of position. E.g., a gravitational field in direction \( \mathbf{e} \) produces a gravitational potential energy:

\[
\Phi_{\text{grav}} = -\sum_{i} \mu_{\text{grav}}(r(x)) \cdot C(x) \cdot \mathbf{e} \cdot \mathbf{d},
\]

where \( \mu_{\text{grav}}(r(x)) \) is the density of cell \( x \).

Yi Ji in her PhD thesis [27] applied these forces directly to cells by including a term in the Hamiltonian of form:

\[
H = \sum_{i} \Phi_{i}(x, \mathbf{e}, \mathbf{d})
\]

The force can depend on position, cell type and time.
cell, or a combination. Depending on the particular biological situation, different choices may be appropriate. For example, when a cell forms a leading edge, it typically responds to chemical concentration changes at the leading edge only and not at the trailing edge, in which case we will want to consider the chemoattractant response of the source cell only.

The most direct way to implement the phenomenological ideas expressed in Eq. (28) is to use a Hamiltonian term of the form [27].

\[ \Delta S_{\text{chemotaxis}} = \mu(\text{target}) \mathcal{C}(\text{target}). \]  

(29)

This reflects the potential energy form of Eq. (28), which makes it an equation of state. However, this form of chemotaxis also acts only at boundaries between diffusively chemotaxing cells. Thus, a big block of identically chemotaxing cells will respond vertically to the edges only since the chemical field at their edges.

In practice, Eq. (29) leads to

\[ \Delta S_{\text{chemotaxis}} = \langle \mu(\text{target}) \rangle - \mu(\text{source}) \mathcal{C}(\text{target}). \]  

(30)

Savill and Hogeweg [56], in their models of Dictyostelium discoideum chemotaxis, used an energy change proportional to the difference between the local chemical concentrations at the destination and source sites:

\[ \Delta S_{\text{chemotaxis}} = \mu(\text{source}) (\mathcal{C}(\text{source}) - \mathcal{C}(\text{target})). \]  

(31)

An advantage of this form is that a cell responds to a chemical field in the same way, regardless of what types of neighbors it has. Merks also used this form of his model of endothelial vasculogenesis. However, he enforced contact inhibition, i.e., chemorotors only at cell-cell interfaces, not at cell-medium interfaces [34] by only applying this energy at cell-medium interfaces when cells of type medium are not the source. To express this mathematically, one can multiply Eq. (31) by

\[ \mathcal{C}(\text{source}) = \text{median(chemical)} \mathcal{C}(\text{target}). \]  

(32)

All of the above methods are currently implemented in ComputeCHEM [10] (see chapter II 4, section 5.1.1 and also a simulation Movil1.1.3 from the accompanying DVD).

We know that for large \( C \) or \( \mathcal{C} \), the cell’s response saturates. We can include this effect using a Michaelis-Menten or Hill form:

\[ \Delta S_{\text{chemotaxis}} = \mu(\text{target}) \mathcal{C}(\text{source}) \mathcal{C}(\text{target}). \]  

(33)

Since all of these options may be appropriate in different biological circumstances, we propose to encapsulate all of them in a general term:

\[ \Delta S_{\text{chemotaxis}} = \langle \mu(\text{target}) \rangle + \mu(\text{source}) (\mathcal{C}(\text{source}) - \mathcal{C}(\text{target})), \]  

(34)

where \( a, b, c, d, \beta \) and \( \alpha \) are constants. In particular, \( \alpha \) is the Hill coefficient, which determines response rates at the threshold value \( C = \beta \). To model haptotaxis [62, 73], we can use a chemotactic form with a non-diffusing \( C \) or make the surface energies \( f(\tau(\phi_0), \tau(\phi)) \) depend on the concentration \( C \). The simplest form is

\[ f(\tau(\phi_0), \tau(\phi)) = f(\tau(0), \tau(\phi)) = \beta \frac{C - C_0}{C_0 + C_0^2}. \]  

(35)

where \( \beta \) is a positive constant. The linear decrease of the values of \( f^\ast \), as the concentration of the chemical corresponding to cell adhesion molecules grows, leads to observed density-dependent patterns in mesenchymal condensation in vitro where the average size of clusters is smaller at higher concentrations of these molecules [73].

7.2.2. Diffusion on external-field lattices. Cells respond to diffusible signals from other cells or external sources. Typically, we implement diffusion using a separate solver which acts on the external fields, which we call a certain number of times per MCS. The simplest method, the forward-Euler method, evolves the diffusion equation by redistributing concentration between neighbor lattice sites from those with higher concentrations to those with lower concentrations. The proportion of concentration redistributed at each step relates to the diffusion constant for that substance. The Euler method is unstable when the ratio \( D(\Delta t)/\Delta t^2 \) is bigger than about 1/25, where \( d \) is the dimension of the space, but we can maintain stability by calling the diffusion solver multiple times per MCS and using a smaller \( \Delta t \) each time.

An advantage of forward-Euler and other finite-difference schemes (for example, Crank-Nicholson) is that regions of the external field lattice corresponding to different cell types can have different diffusion rates, decay rates and diffusion constants, including no diffusion and anisotropic diffusion. Since these properties correspond to individual cells (see section 7.4), which can move, we gain some of the benefits of advection-diffusion, at very little computational expense. For example, one iteration of a 2D diffusion equation with local decay rate \( d(\phi,j) \) would be:

\[ C(x,j,t+\Delta t) = C(x,j,t) \]  

\[ +D(x,j)C(x,j,t+\Delta t) + D(x,j)C(x,j,t), \]  

\[ +D(x,j)C(x,j,t+\Delta t) \]  

\[ -D(x,j)C(x,j,t) \]  

\[ -D(x,j)C(x,j,t) \]  

\[ f(x,j), \]  

(36)

where \( f(x,j) \) describes secretion, absorption and reaction of the chemical. This formula multiplies the concentration by the diffusion, secretion and decay rates site-by-site over the whole lattice prior to the iteration, which we sometimes call applying a mask. As the cell lattice evolves, the diffusion, secretion and decay rates update automatically.

7.4. Internal Cell States

As researchers have attempted more realistic biological simulations, they have devised methods to impart specific biological behaviors to individual cells. As a result, GGH simulations have focused more on the properties and interactions of generalized cell and less on the properties of individual lattice sites, though, of course, the actual movement of cells still occurs at the lattice-site level. This
change in focus has inspired methods to describe and generate increasingly complex internal cell states and to describe generalized-cell interactions. We call this general class of approaches, off-lattice extensions of the GGH.

In Hogeweg’s model of genetic evolution [18, 19, 21, 25], cells have simple models of a genome and intergenic pathways that determine cell-cell adhesion, cell division and death. Between cell generations, the genetic code of each cell evolves via gene mutations. The evolving regulatory pathways create cell volumes with unique morphogenetic tendencies, including many experimentally observed morphogenetic mechanisms and morphologies. Alternative methods for cell differ-
entiation use preprogrammed type changes of the cells [31].

8. Outlook

The great advantages of the GGH model are its simplicity and extensibility, which have made it one of the widely-used approaches to cell-level modeling biology. GGH cells move according to effective-energy gradients \( F \times \nabla E \), which means that \( F \times \nabla E \) as in biological experiments. As in experiments, the position and movement of membranes determine cell dynamics. Adding new biological mechanisms is as simple as adding new potential energies or constraints to the Hamiltonian. While the lattice discretization and modified Metropolis dynamics of the GGH model can cause certain artifacts, these rarely cause serious troubles. Recent extensions of the GGH using subcells to model the behavior of fluids [9] and elastic media have addressed many of these issues (see chapter II.4, section 1). We discuss additional extensions to the GGH, which use generalized cells to provide many off-lattice modifications to the GGH without abandoning the convenience of the GGH’s underlying fixed lattice, in chapter II.4. As our understanding of the GGH model improves, we expect to be able to further improve both its accuracy and the range of biological problems it can address (see chapters II.2 and II.3) and to see it even more widely adopted.

This chapter has focused on the origin and development of the GGH model without discussing the computer-engineering aspects of its implementation. One of the most important developments in GGH modeling in the past few years has been the creation and release of open-source modeling packages like the “Lattice Simulation Toolkit” (LST) [38], or CompuCell [25], which provide standard platforms for model development (see the accompanying DVD for tutorial video: Mov11.1, Mov11.2 and Mov11.3). The use of one of these standard packages allows users to reproduce published results and share new algorithms relatively painlessly, and opens the field of GGH modeling to a much broader audience.

References


[56] M. S. Steinberg. Dose differential adhesions govern self-assembly processes in histo-


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