Spatial Patterning with the Rule of Normal Neighbors

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Abstract

Based on developmental biology's Rule of Normal Neighbors, we develop a new mechanism for spatial patterning, exhibiting spontaneous symmetry breaking, regeneration, and approximate scale invariance. The desired pattern is represented as a topological adjacency graph, yielding an energy function that cells minimize through local interactions. Combined with a controller manipulating cells' mechanical properties, we demonstrate programmable geometric homeostasis for 3D cellular surfaces via simultaneous patterning and deformation.

Introduction

How might one assemble a pattern from un-differentiated tissue or regenerate a missing piece lost to injury? A common theme seen in developmental biology is the Rule of Normal Neighbors (Mittenthal, 1981): a point in a patterned tissue knows what elements of the pattern belong adjacent to it, its "normal neighbors". If it finds its neighbors are wrong, it takes steps to correct the situation, such as re-growing a more appropriate neighbor or changing its own fate to better fit its environment. This general rule captures many striking experimental results, such as the growth of inverted segments in cockroach limbs when the distal portions of the limbs are excised and replaced with longer explants (French, 1981).

In recent work (Brodsky, 2014a), we propose one possible mechanism by which patterning and pattern repair under the rule of normal neighbors can be implemented, with only local computation and minimal resources. We represent the topology of a desired pattern as an adjacency graph over discrete pattern states. Based on this graph, we construct an energy function using local interactions for which the desired pattern is (usually) a minimum. Cells can then explore this potential by a process mathematically analogous to thermal (and simulated) annealing, seeking a minimum.

The result is a spatial patterning mechanism that demonstrates spontaneous symmetry breaking, regeneration, and approximate scale invariance. In conjunction with control algorithms for cell-cell traction and bending forces, it has been used to generate self-stabilizing 3D geometries within a simplified model of embryonic tissue. This serves a primitive artificial demonstration of morphological homeostasis.

Energy specification

The core idea of the rule of normal neighbors is purely topological: what can lie adjacent to what. This alone is not enough to form a pattern, but it's a good starting place. In our formalism, each region of the pattern is assigned a discrete state, and the adjacency graph captures the neighbor relationships between homogeneous regions of a single state (see Figure 1). An implicit self-edge exists for each state, in order that the representation be scale-invariant and meaningful both in continuum and on a discrete lattice.

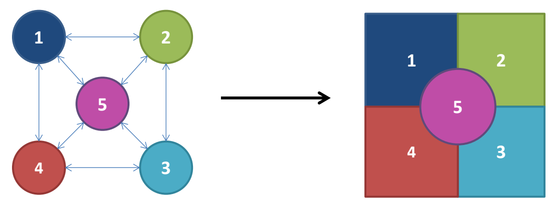

Figure 1 – Example adjacency graph (left), associated desired pattern (right).

A variety of other patterns will satisfy the same adjacency graph, however, indeed, any arbitrary continuous distortion of the original pattern. Furthermore, any simply connected (but possibly overlapping) cut through the pattern, such as a spiral that repeatedly cut through the same regions, will still satisfy as well, albeit with some regions and neighbor contacts duplicated and others absent.

In order to avoid arbitrarily pathological deformations, we favor compact, blob-like regions by including a virtual "surface tension" self-affinity term in the energy function. To avoid arbitrary cuts with missing regions, we can either impose boundary conditions that force every region contacting the boundary to appear in the pattern, or we can add per-region quorum sensing. The former will ensure that all boundary-contacting regions are present, although the sizes of non-boundary-associated regions will be unstable, and they may shrink to a sliver or disappear entirely. Alternatively, quorum sensing adds complexity but can ensure the stability of region sizes and, in conjunction with surface tension, strongly discourage the presence of duplicate regions.

Energy minimization

For suitably-constructed energy functions such as sketched above, gradient descent can be implemented purely locally, with local information and local updates. However, spatial patterns are prone to local minima, and gradient descent fails almost immediately. Instead, a probabilistic strategy is quite successful. Energetically favorable transitions are made with high probability and unfavorable transitions are made with low probability. With appropriate choice of weights (i.e. the

Boltzmann distribution), this becomes analogous to natural and simulated annealing, complete with a "temperature" parameter.

The algorithm sketched thus far works fairly well. However, it is noisy and has no clear termination condition. As an alternative, we can formulate a "thermodynamic limit" to the stochastic algorithm, where fluctuating discrete states are replaced by mean field values. The result is somewhat analogous to loopy belief propagation and produces clean, robust patterns even at significant temperatures, suitable for driving downstream actuators.

Regulating Geometry

Ultimately, the goal of patterning is to spatially choreograph phenotypic properties. These properties may be simple and self-contained (e.g. "color"), or they may be disruptive and far-reaching, such as the geometry of the substrate itself. With substrate manipulations, the patterning process is not a feed-forward cascade but is in general a large feedback loop, changes to geometry rearranging and disrupting the original pattern. However, given a suitably robust and self-stabilizing patterning mechanism such as above, combined with suitable closed-loop controllers for geometric features, self-stabilizing geometry that is faithful to the pattern can be demonstrated. With a simple embryonic epithelium model (Brodsky, 2014b), actuation mechanisms that combine curvature sensing, intrinsic forcing (e.g. purse-string), and extrinsic bending (apical/basal constriction) have been shown to be successful.

Results

Several successful patterns and their associated adjacency graphs are illustrated in Figure 2, using the mean field algorithm. These patterns can self-organize on a variety of domain shapes and sizes and can self-repair in response to large sections being erased. Temperature was selected or annealed as appropriate for the size of the domain and the complexity of the pattern; under poor temperature conditions or with certain pathological patterns, topological defects can arise, particularly twinning (duplication of regions and sub-patterns) and twisting (irreconcilable partial mirror inversions). The rightmost example illustrates a case of the algorithm operating on and directing a dynamically deforming surface (Brodsky, 2014b), such that the overall shape is determined by the underlying pattern. Under the direction of the algorithm, cells flow and rearrange themselves to produce the desired structure. Such self-organizing, self-stabilizing geometries are the subject of ongoing work.

Acknowledgments

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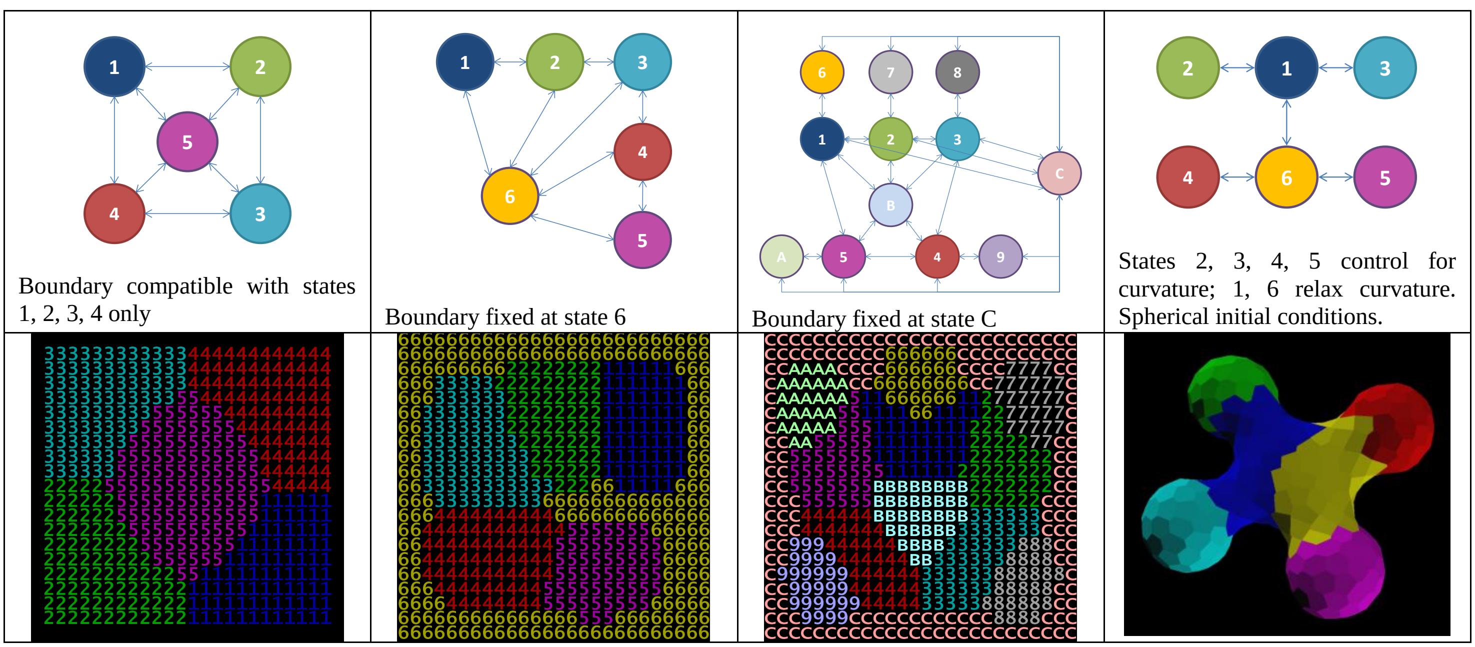

Figure 2 – Example successful results – exhibiting exactly one instance of every region, each contacting every normal neighbor and no spurious neighbors – achieved under appropriate annealing conditions. Left three are on rectangular lattices, while rightmost is on an irregular, dynamically changing cellular mesh of spherical overall topology.