Pattern Regeneration in Coupled Networks

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Abstract

Many organisms such as planaria, axolotls and deer exhibit prodigious regenerative abilities, being capable of regenerating complex organs or entire body plans. An understanding of how these organisms store and modify their morphological patterning information is necessary to identify modes of control and intervention. Insight into this process is key to the development of novel biomedical applications. In this work, we present the CANN(k) model: an abstract computational model of pattern regeneration which couples an artificial neural network (ANN) with a k-color cellular automaton (CA). The ANN provides a global information processing system which generates state-dependent update rules for the CA. The CANN(k) models are constructed to generate target patterns which are stable under perturbations of the pattern. We generate ensembles of CANN(4) models for each of the 4-color patterns, assess their sensitivity to changes of the ANN structure. This provides a novel model for understanding the important biological phenomenon of neural control of cellular morphogenesis in development or regeneration.

Introduction

Many animals are capable of regenerating complex structures after amputation (Birnbaum and Sánchez Alvarado, 2008). For example, planaria can regenerate their entire body from a fragment as small as $1/279$ of the original animal (Handberg-Thorsager et al., 2008). Control of cellular activity toward the creation and repair of complex anatomical patterns is a central aspect of evolutionary biology as well as birth defects, traumatic injury and cancer. The ability to intervene upon and effectively control these processes is key to developing novel biomedical applications (Baddour et al., 2012; Levin, 2011). Modes of control over the process of large-scale, complex homeostasis are still lacking, despite significant development in our understanding of the molecular mechanisms necessary for these processes (Stocum and Cameron, 2011). Specifically, while it is known that the nervous system can guide complex morphogenesis (Herrera-Rincon et al., 2017), the control dynamics of this process are very poorly understood. An important open question is whether regenerative processes require large-scale information about the current state of the organism, or if information local to each cell or tissue is sufficient. The answer to this question will suggest the ideal level and method of intervention necessary to control regenerative processes.

This work presents an abstract model of pattern regeneration that combines both global information processing and local update rules to generate stable target patterns.

Methods and Results

The model of pattern regeneration considered here, referred to as a CANN(k) model, is composed of two parts: a k-color cellular automaton (CA), and a feed-forward artificial neural network (ANN). The k-color CA is a one-dimensional array of cells, each of which can be in one of k states (or colors). The state of each cell is updated according to a nearest-neighbor rule with the same rule applied to each cell concurrently. Traditionally, a fixed rule is applied at each time step, and the process is iterated to generate a *trajectory* of states that terminates in an attractor cycle, a sequence of states that repeats indefinitely. The distinguishing characteristic of a CANN(k) model is that the rule used at each time step is not fixed. Instead, the state of the CA is provided as input to the CANN(k)'s ANN which outputs the CA update rule to use at the current time step. Another important choice for these lattice-type models is the boundary conditions for the ends of the CA lattice. Here we employ a fixed, open boundary condition where each boundary cell uses an unchanging "white" cell for its missing neighbor's state. See Figure 1a for a schematic representation of a CANN(k) model.

The objective is to better understand how morphological patterns can be faithfully regenerated when the pattern is perturbed. We say that the pattern, or particular sequence of colored CA states, regenerates if it is recovered as a fixed-point attractor under the model's dynamics. If the pattern is perturbed, will the system ultimately return to and retain the desired pattern? In particular, given a desired target pattern and a set of perturbations, we wish to construct and analyze a CANN(k) model with the following three properties:

1. The target pattern is a fixed-point attractor of the dynamic.
2. Every admissible perturbation of the target pattern ultimately converges to that target pattern.

3. No cell that is colored becomes white in the next time step along any of the perturbed trajectories.

We employed a simulated annealing (SA) algorithm (Kirkpatrick et al., 1983) to construct CANN(k) models which satisfy all three criteria. The decision to employ SA for training was based primarily on the constraint-based specification of the problem. A deterministic algorithm, such as back-propagation, is ill-suited here as we are primarily interested in the final pattern generated rather than the particular sequence of states in the time series, and we do no have a well-defined training set. One advantage of the SA approach is each model is endowed with an *energy* which quantifies how well it solves the problem at hand. This provides a way of quantifying the difference in effectiveness between two models. This energy is, in our case, defined in terms of three factors which mirror the constraints above:

1. δ is the fraction of cells of the target pattern that are not fixed by the CANN(k) update rule.
2. κ is the fraction of observed states that do not transition into the target state after some number of time steps.
3. τ is the fraction of observed states which introduce new white cells.

We then define the energy as

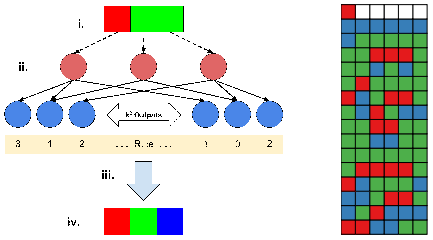
$$E = \alpha\delta + \beta\kappa + \gamma\tau \tag{1}$$

with $0 \leq \alpha, \beta, \gamma \leq 1$ and $\delta + \kappa + \gamma = 1$. For this work, we chose $\alpha = \beta = 4/9$, and $\gamma = 1/9$, though these can be adjusted freely. There is no strict guarantee that the SA algorithm will find a solution; however, the energy in eq. (1) ensures that the degenerate global minimum satisfies our desired heuristic properties.

We generated ensembles of 100 CANN(4) models for each of the 729 possible 6 cell, 4-color (■, ■, ■ and □) target patterns with no white cells. We limited the set of pattern perturbations which must converge to the target pattern to *amputations* of the desired pattern. An amputation is the removal of a contiguous region from either end of the target pattern, i.e. setting cells on either end of the array to white. This limited type of perturbation roughly models a common type of intervention biologists perform, and from which regenerative organisms should recover. An example of an amputation and regeneration process is depicted in Figure 1b.

We then assessed the sensitivity of the resulting CANN(4) models to small perturbations *of the underlying ANN*. This is defined as the average change in energy of the model when either one weight or one threshold of the ANN is modified, and is distinct from the types of perturbations applied to the CA state discussed above. We find that 6-cell CANN(4) models exhibit an average sensitivity of 0.020 ± 0.009. This suggests that the target pattern remains a fixed-point under small perturbations of the ANN, but that the system looses the ability to properly regenerate from all amputations.

Subsequent work will include improving the training algorithms, either by choosing an alternative approach or modifying the constraint-based energy function, assessing the scalability of this approach, and performing a detailed sensitivity analyses of generalized models.



(a) A CANN Model (b) Trajectory

Figure 1: (a) A 3-cell CANN(k) model consists of a cellular automaton (CA) and a feed-forward, artificial neural network. (i.) At each time step, the state of the CA is provided as input into the ANN. (ii.) The ANN processes that input and generates k^3 outputs with values $\{0, \ldots, k-1\}$. (iii.) The outputs are assembled into a CA rule and (iv.) used to update the state of the CA. (b) An Example 6-cell CANN(4) Trajectory. The top-most row represents an extreme amputation (setting colored cells to white) of the target pattern (bottom row). Each row from top to bottom represents successive updates of the state according to the underlying CANN(4) model. The final row is the fully regenerated, stable target pattern.

Acknowledgements

This work was supported by the Templeton Foundation (TWCF0089/AB55 and TWCF0140). M.L. gratefully acknowledges support by the Allen Discovery Center program through The Paul G. Allen Frontiers Group (12171).

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