A gene regulatory network model for axon guidance

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Abstract. During development, axons follow various cues to determine their path, forming the structure of the nervous system. The axon growth cone uses local chemical signals and neural activity to determine its movement. While the axon guidance process is integral to developmental cognition, it is not yet fully understood and there are few in-silica models of this process. In this work, a model of axon guidance using artificial gene regulatory networks (AGRNs) is presented. An AGRN is optimized through artificial evolution to control glial cells, which secrete morphogens in a 3D space, and axon growth cones, which follow these morphogenetic cues to eventually connect with other neurons.

Keywords: Axon guidance; Neural development; Gene regulatory networks

1 Introduction

Axon guidance is at the base of neural topology. The structure of the brain, within the central nervous system and as connections are made to sensory organs and other parts of the body, is the result of axons being guided by a variety of cues. These mechanisms are beginning to be understood in biology, with examples such as the visual system providing insight to this complex process [3].

Both genetic factors and morphogenetic cues, such as netrins, are important in axon guidance. However, despite the seemingly concrete nature of neural topology, (eyes must connect to the visual cortex, which must then connect to other specific sections of the brain, for example), neural activity has also been shown to play an important role in axon guidance [5].

In this work, we create a model of axon guidance which relies on these three factors: morphogenetic signals, gene expression, and neural activity. The model is an abstraction, with a parameterized number of morphogens which don't represent any specific axon guidance protein and an evolved artificial gene regulatory network (AGRN). This abstraction allows for flexibility of applying the model to different experimental configurations, where the number of axon guidance cues is known, and to allow artificial evolution to determine the relationship between an artificial morphogen and its biologic counterpart, if any. In this work, AGRNs are evolved to replicate the experiment observed in [5] , where neural activity disrupts the differentiation of axonal projections from the eyes into the visual cortex.

2 Artificial Gene Regulatory Network

Artificial GRNs were first proposed using a binary encoding of proteins with specific start and stop codons, similar to biological genetic encoding [1], and have since been used in a number of domains. Finding similar use to their biological inspiration, AGRNs have controlled the design and development of multi-cellular creatures [2] and of artificial neural networks (ANNs) [6].

An AGRN is composed of multiple artificial proteins, which interact via evolved properties. Each protein has a concentration, representing the use of this protein and providing state to the network. For *input* proteins, the concentration is given by the environment and is unaffected by other proteins. *output* protein concentrations are used to determine actions in the environment; these proteins do not affect others in the network. The bulk of the computation is performed by *regulatory* proteins, an internal protein whose concentration is influenced by other *input* and *regulatory* proteins.

3 Axon guidance model

The model simulates cells and morphogens in a 3D space. Two cell types are simulated: glial cells and neurons. Glial cells regulate morphogen concentrations in the environment and neurons project axons, which navigate within the environment.

Each morphogen is modeled by a concentration c_i at discrete points in the environment. This morphogen grid is then used to construct a continuous 3D morphogen space using linear interpolation. The concentration is bound between $[0, 1]$ and decays exponentially to model natural absorption.

Glial cells diffuse morphogens based on output proteins of their AGRN, d_i. The morphogen grid is updated based on the euclidean distance, D of each point in the grid, $[x, y, z]$ to the glial cell, $[x_g, y_g, z_g]$:

$$\frac{dc_i[x, y, z]}{dt} = \frac{e^{-\beta_{diffusion} D d_i}}{\tau_{diffusion}} \tag{1}$$

Neurons are modeled in two distinct parts: axon and soma. Somata are fixed in space and receive dendritic input from other neurons or direct stimulation. The membrane potential V of each soma is modeled using a leaky integrate and fire (LIF) model with conductance-based synapses.

A neuron spikes when its membrane potential exceeds V_{thresh}. This spike propagates down the axon and is used by the growth cone to decide movement. Dendrites are not considered in the model for simplicity.

Axon growth cones follow morphogen gradients to move in the space. Based on their AGRN outputs, at each timestep the axons can rotate towards or away from a morphogen gradient, move in their current direction, or rest. When in proximity to a soma in the visual cortex, they can form a synapse. In order to do this, they must rest at least one timestep near the target soma to approach it; if they continue to move they will not connect. Once connected, axons cannot

disconnect. Axon growth cone branching and pruning were not considered in this model. The connection is considered a permanent synapse, and any firing from the presynaptic neuron activates the postsynaptic neuron.

The glial cells and neurons share the same AGRN, but the inputs and outputs are separated for the two different cell types. Certain glial cells are placed directly on somata, and in this case, the membrane potential of the soma and the neuron type (visual cortex or eye) are given as an inputs to the glial cell's AGRN. Both cells types receive the morphogen concentrations as inputs, and the axon also receives as input the dot product of its current direction with the different morphogen gradients. A final input is given to both types to indicate the cell type; 0 for neurons and 1 for glial cells.

4 Experiments

The point of this experiment is to see if this artificial axon model changes behavior based on neural activity, as in [5]. For this reason, four different neural activity cases are considered. Each eye receives either periodic neural activity, which comes in waves of strong synaptic input, or non-periodic activity, which causes spiking following a uniform distribution. The four cases are therefore periodic activity in both eyes, only in the left or only in the right, and non-periodic activity in both eyes.

As in biology, the expected outcome is that the axonal projections differentiate in the visual cortex during periodic activity but fail to differentiate under non-periodic activity. The evolutionary fitness is therefore based on replicating this effect, in a score composed of four parts: the percentage of connections formed, differentiation from the right eye, from the left eye, and distance between the different projection clusters when both eyes have periodic activity.

5 Results and conclusion

The evolved behavior led to a mostly distributed connection scheme, even in the case of periodic neural activity. While this may be the cause of the evolutionary fitness function, which evaluated the case of no periodic activity first, neural activity did have a result on the final activity of the growth cones. Interestingly, the best evolved individual used neural activity in the axons to decide to rest, leading the periodic activity to have large-scale connection events, whereas the non-periodic activity caused connections to be formed sporadically. This lead to more tightly clustered connections during periodic activity, although not to the level of differentiation seen in biology.

The demonstration of activity-based topology formation is interesting for the case of developing artificial neural networks (ANNs) for use in computational problems. While the structure of ANNs is often static, developmental structures have been used [4]. A remaining challenge in evolving developmental structures is the responsiveness of development to neural activity. Previous work has shown that evolution can easily develop a static structure optimized for the problem

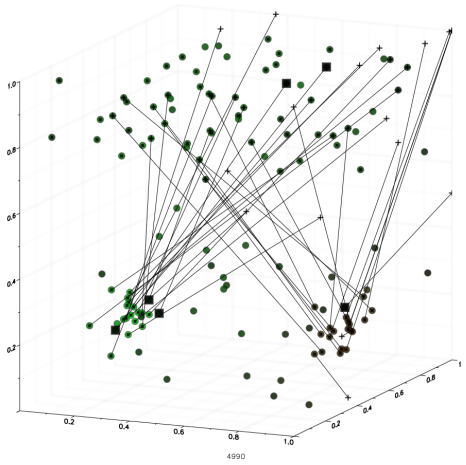

Fig. 1: Evolved axon connection behavior. Axons from both eyes connect throughout the visual center based on non-periodic spiking activity in the eyes.

at hand, without relying on neural activity. In future work, this model will be applied to ANN development for computational problems, as it has shown capabilities for activity based development.

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