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An evolutionary developmental approach for generation of 3D neuronal morphologies using gene regulatory networks

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ABSTRACT

Computational modeling of neuronal morphologies is significant for understanding structure-function relationships and brain information processing in computational neuroscience. Using a gene regulatory network model, an evolutionary developmental approach is presented for efficient generation of 3D virtual neurons. This approach describes the developmental process of dendritic morphologies by locally intercorrelating morphological variables which can be represented by the dynamics of gene expression. Then, the multi-objective evolutionary algorithm with gene segmental duplication and divergence operators is applied to evolve the virtual neurons, which aims at generating virtual neurons that are as good as the experimentally traced real neurons in terms of statistical morphological measurements. We experimentally generated motoneurons and statistically compared between the real neurons and the generated virtual neurons by measuring a series of emergent morphological features. The results show that the generated virtual neurons are seemingly realistic, accurate, and further suggest that this approach is an efficient tool for understanding neural development and investigating the relation of neuronal structure to function in particular.

1. Introduction

The brain, with billions of neurons and trillions of connections, is the most complex organ in the body and it will be a long time before we understand all its mysteries. Neurons are the basic building blocks of the nervous system and thus constitute the computational units of the brain. Dendritic and axonal trees stemming from the soma develop an extremely complex pattern of branching that occupies and fills three-dimensional (3D) space. Understanding the morphology and function of the brain from a neuroscience point of view, requires adequate computational descriptions of biological neurons, with an emphasis on their morphologies. Dendrites and axons define the connectivity of the brain [1,2] and contribute to understand neuronal information processing at the single cell level [3,4].

Computational models are important tools for investigating neuronal morphologies and their effects during normal brain function, development, and pathologies [5]. Therefore, 3D digital reconstructions of neuronal morphology are indispensable for exploring neural function [6,7]. This process consists of tracing the axonal and dendritic arbors of neurons imaged by optical microscopy into a geometrical format suitable for quantitative analysis. Digital reconstructions can be obtained either with dedicated computer-microscope interfaces or with semi-automatic reconstruction software tools such as NeuroLucida [8] or Neuromantic [9]. However, these procedures are often time-consuming and laborious, the data compression and amplification that can be acquired with these techniques are also considerable advantage [10,11]. For this reason, the algorithmic generation of neurons has become increasingly important in the computational neuroscience. The computational approaches have been used to measure geometric parameters of real neuronal arborizations and simulate realistic virtual neurons and even networks that are extremely accurate in terms of biological detail.

Currently, there are two main classes of computer algorithms to generate virtual neurons with similar shape properties as their empirically observed counterparts: reconstruction algorithms and growth algorithms. Reconstruction algorithms measure relevant variables from real neurons and use the empirical distribution functions for geometrical properties to generate neuronal morphologies by a repeated process of random sampling of these distributions. In general, they are descriptive algorithms and can generate complete neuronal morphologies. The parameter algorithms use the statistical distributions of some basic parameters to

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generate virtual dendrites [12–15]. However, fitting the probability distribution model to the prototype data requires a priori knowledge of the number and types of distributions. The simple parametric distributions might not accurately capture the distributions of morphological measurements of real neurons. To avoid this limitation, some non-parametric algorithms have been proposed. Lindsay et al. [16] applied kernel density estimation (KDE) to generate 2D dendritic tree structure. Torben-Nielsen et al. [17] proposed KDE-Neuron, a generic non-parametric 3D reconstruction algorithm that is based on KDEs to model the distribution of morphological properties. Other reconstruction methods have also been proposed for the simulation of 3D dendritic morphologies. These methods use computational models such as Monte Carlo model [18], hidden Markov model [19] or Bayesian network model [20], to capture the interactions between the variables in the problem domain. Most of the above approaches are successful in generating virtual neurons, but they provide very little insight into the fundamental growth mechanisms.

In contrast, growth algorithms aim at modeling neuronal morphologies from principles of neuronal development, and use the hypothetical growth rules for branching and elongation in the generation of dendritic and axonal trees. These algorithms estimate the branching and elongation probabilities by taking into account some of the different factors of neuronal development [21,22]. They can simulate neuronal morphologies at different stages of growth. In short, growth algorithms are grow models based on developmental processes in an abstract but biologically plausible manner. The growth algorithms have been applied in the last few decades and usually consider various aspects of neuronal development, e.g., molecular gradients [23,24], neurite tension [25,26], neurotrophic particles [27], cell proliferation [28] and migration [29], and gene regulation [30], etc. There are some studies to describe the simulation tools (e.g., CX3D [31] and NETMORPH [32]) for modeling the development of large realistic neural networks. In these models, as in biology, neurons arise by the replication and migration of precursors, which mature into cells able to extend axons and dendrites.

In addition, variations of L-Systems have been successfully used in neuronal morphology modeling [33]. An L-system is a parallel rewriting system and a type of formal grammar [34]. McCormick and Mulchandani [35] applied stochastic L-Systems to generate neuronal morphologies. L-Neuron [36] is a software tool for the generation of anatomically plausible neuronal analogs. It is built on a range of rewrite rules that parsimoniously describe neuronal geometry and topology by locally relevant morphological parameters. More importantly, evolutionary computation has also been used to output L-Systems that generate realistic neuronal morphologies [37]. Interestingly, L-Systems are not initially designed to be evolved. Thus, a potential problem for virtual neurons based on L-systems is that the capacity to describe neuronal morphologies does not necessarily imply a capability to evolve neuronal morphologies.

In this paper, using the artificial genome model as a framework for describing gene regulatory networks (GRNs), the dynamics of gene expression can be used for the control of segment bifurcation or elongation. We propose a novel methodology for evolution and development of 3D neuronal morphologies. The goal is to simulate virtual neurons that share the same morphological properties with a kind of (experimentally reconstructed) real ones. Our proposal can be classed as a growth algorithm, and the gene activations of GRNs are used to generate candidate morphologies. Because mutation operators of GRNs reprogram neuronal development trajectories, evolutionary algorithm is to guide the exploration in search for accurate neuronal morphologies.

There are a number of advantages in our algorithm. Firstly, GRNs are biological interaction networks, the genes in a chromosome encode a particular type of protein called transcription factors, which regulate (either inhibit or enhance) the expression of other genes. The activation state vector of GRN output nodes is used for the control of branching and elongation in the generation of dendritic trees. We model the basic developmental control mechanisms: symmetric and asymmetric bifurcations. Secondly, we apply segmental duplication and divergence mechanism to evolve GRNs, and use multi-objective functions to evaluate the generated virtual neurons. It is able to solve practical problems by means of adopting the ideas and principles of biological evolution. So it is highly adaptive to new biological detail and evidence since we only need to update the exploration criteria. In short, we can search the most ideal virtual neurons by exploration the whole parameter space. Thirdly, this method uses experimental distributions of parameters from real cell anatomical data to generate different cell types. For this reason, it can be applied to any neuronal class without the need for any modification.

The rest of this paper is organized as follows. In Section 2 we analyze the morphological values of real motoneurons, including the basic variables and emergent features. In Section 3 we construct the evolutionary developmental approach for generation of 3D virtual neurons based on the GRN model and multi-objective evolutionary algorithm. In Section 4 the flexibility and power of our approach are showcased by the generated virtual neurons. The discussion and conclusion are presented in Section 5.

2. Morphological data of real neurons

The 3D morphological structure of neurons can be described by the standard SWC file format, which has been widely used for analyzing neuronal morphologies or sharing neuron reconstructions [38]. According to the SWC model, a neuron is defined as a sequence of interconnected cylindrical segments (compartments). Each segment in the neuron is characterized by only seven values, corresponding to the numerical tag, the type of neuronal segment (to distinguish soma, axon, dendrite, apical dendrite, etc), the three Euclidean coordinates (x, y, and z), the radius of its ending location, and the tag of the "parent" segment. The digitally reconstructed neurons are publicly available at the online NeuroMorpho.Org (http://www.neuromorpho.org), which is the collection of publicly accessible 3D neuronal reconstructions and associated metadata [39]. We can read SWC morphology files by the publicly available tool Neuromantic [9]. Additionally, our method outputs the generated virtual neuron which is interpreted to SWC format file.

In this paper, we have used a set of 3D reconstructions of 6 motor cells from cat spinal cord, which are regarded as real neurons (or standard) [40,41]. These typical motor neurons are obtained from Burke's laboratory archive at the online NeuroMorpho.org. The two kinds of morphological properties are adopted in our algorithm: basic variables and emergent features. These basic variables can be usually measured from the digital files of the experimental traced neurons. The ranges of the 13 basic morphological variables for motoneurons are presented in Table 1. The parameter values of basic variables are computed by the output node activations of a GRN within the given ranges, which use to control the developmental processes of virtual neurons.

The emergent features are not explicitly specified in a neuronal growth algorithm, but emerge from the interaction between the basic variables. For example, the total number of branches and the total number of terminations in a neuron are both emergent features, but they are different from the number of stems in that neuron, which is a basic variable. We typically use some emergent features as evaluation to compare virtual and real neurons. Table 2 shows the selected 12 emergent morphological features of 6 motoneurons from Burke's laboratory [18,39].