Available online at www.sciencedirect.com
ScienceDirect
Neurocomputing 71 (2008) 963–972
NEUROCOMPUTING
www.elsevier.com/locate/neucom

EvOL-Neuron: Neuronal morphology generation

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Received 12 May 2006; received in revised form 14 February 2007; accepted 18 February 2007
Communicated by R. Koetter
Available online 7 April 2007

Abstract

Virtual neurons are essential in computational neuroscience to study the relation between neuronal form and function. One way of obtaining virtual neurons is by algorithmic generation from scratch. However, a main disadvantage of current available generation methods is that they impose a priori limitations on the outcomes of the algorithms. We present a new tool, EvOL-Neuron, that overcomes this problem by putting a posteriori constraints on generated virtual neurons. We present a proof of principle and show that our method is particularly suited to investigate the neuronal form–function relation.
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Keywords: Virtual neuron; Neuronal morphology; Computational neuroanatomy

1. Introduction

Virtual neurons are digitized descriptions of biological neurons, with an emphasis on their morphology. In computational neuroscience their use is at least twofold. First, they compensate for the lack of vast amounts of morphometric data and are used for extensive modelling studies [3,5,36]. Second, their synthesized nature enables the experimenter to have full control over morphometric parameters [22], which is required in the study of morphological effects on the neuronal function. In this article we present a new tool for the generation of virtual neurons: EvOL-Neuron.

An adequate description of neuronal morphology is required for studies investigating the influence of morphology on information processing capabilities of neurons. Up to date, three main methods exist to obtain realistic virtual neurons: tracing, algorithmic reconstruction, and generation from scratch (for a review see [5]). We argue that most of these methods suffer from the fact that they are biased by current biological knowledge about neuronal morphology in the generation phase: the algorithms are devised in such a way that only 3D structures (i.e., virtual neurons) can be generated that reflect current insights and opinions. Intuitively, this seems to be a virtue but it seriously restricts the adaptivity of the generation algorithm to new biological detail (or evidence). Furthermore, current knowledge of neuronal morphology is too limited to claim that we know all data (i.e., properties or measurements) from which realistic virtual neurons can be generated. While several groups succeeded in reconstructing specific characteristics of neuronal morphology (e.g., dendritic branching patterns [27,35]), it remains difficult to generate complete virtual neurons with both adequate topological (i.e., order and degree) and metrical (i.e., length and size) properties. More precisely, all variations on the morphometric properties make up a large *parameter space*. Existing generation methods specify the generation of virtual neurons in terms of these morphological properties. Consequently, the generated virtual neuron is always limited to combinations of known values of these properties, or to put it differently, limited to a small subset of the parameter space.

We propose a new methodology for generating virtual neurons that explores the immense parameter space for morphologies, that conform to current knowledge (rather than exploring specific parts of this space only). Our aim is to find an algorithmic description to generate virtual neurons that share the same morphological properties with

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doi:10.1016/j.neucom.2007.02.016

a single (experimentally reconstructed) prototype neuron. L-Systems are used to generate candidate morphologies and evolutionary computation (EC) to guide the exploration in search for accurate morphologies. As mentioned before, existing methods for the generation of virtual neurons are limited to the generation of virtual neurons from a small part of the parameter space. We call this the *a priori limitation strategy* as the specification of virtual neurons is limited to combinations of statistically determined values of morphological properties. Thus, only a particular part of the parameter space is reached due to the limitation or bias inherent to the generation algorithm. Contrastingly, our method adopts a so-called *a posteriori constraining strategy* in which we consider all structures in the parameter space as a candidate virtual neuron, and explore this parameter space until a structure is found that complies with specific morphological properties.

Two main advantages of our method stand out. First, the exploratory capabilities of our method allow us to search the whole parameter space for structures that conform to current biological knowledge. This means that all possible outcomes are considered, and that the potential outcome is not limited in advance. It can be argued that a large potential parameter space is not advantageous as most of this space consists of biologically unrealistic morphologies. However, generally the exploration algorithm moves quickly to subsets of the parameter space where neuron-like structures can be found. This subset is not necessarily equal to the solution space of existing methods as EvOL-Neuron can find all subspaces of the parameter space where structures obey specific criteria. Second, our method is highly adaptive to new biological insights and evidence since we only need to update the exploration criteria. We do not need to redesign and implement a new algorithm to be in accordance to biological data.[1]

The remainder of this paper is outlined as follows. The next section presents a brief overview of relevant techniques that are related to our method. Section 3 provides a detailed description of our method, and Section 4 is dedicated to how we select and validate generated virtual neurons. Results are presented in Section 5 and we conclude with a discussion in Section 6.

2. Related methods

The generation of morphologically accurate virtual (or synthetic) neurons has been studied for the past three decades. Advances in computational power in the last decade have boosted the power of these generation techniques.

A first step toward the generation of virtual neurons was taken by Hillman in 1979 who experimentally described *fundamental parameters* of neuronal morphology [19]. Hillman concluded that seven morphometric properties were sufficient to describe (and classify) all types of neuronal morphologies, and, that realistic neuronal morphologies could be generated algorithmically by obeying these seven properties. More recently, a range of tools or methods based on Lindenmayer systems (L-Systems) were introduced. The first applications of L-Systems for generation of neuronal morphologies can be traced back to Hamilton [18] and McCormick and Mulchandani [28]. Both used an extended version of L-Systems; Hamilton used a dedicated grammar to support neuronal structures while McCormick and Mulchandani introduced stochastic L-Systems to generate neuronal structures. Despite the promising initial results with L-Systems it was not until the release of L-Neuron that the idea of L-Systems modelling to generate virtual neurons became popular. L-Neuron, a highly successful tool, was created by Ascoli and Krichmar [4]. It relies on taking samples from density distributions (the so-called parameter sampling) describing neuronal morphology as arguments for L-Systems to generate highly accurate and realistic virtual neurons. Several tools followed the same principle as L-Neuron and combined L-Systems with parameter sampling, i.e., Neuron PRM [25] and NeuGen [15]. Both programs are designed to generate networks of morphologically realistic virtual neurons. All these methods rely on the a priori limitation strategy in which the specification of virtual neurons is limited to combinations of statistically determined values of morphological properties. As a consequence they are biased by the sparse data on neuronal morphology.

Our review of morphology generation tools is mainly restricted to those based on L-Systems. However, it is important to note that this is by no means an exhaustive review of generation techniques. Contrary to the use of L-Systems to describe (and generate from scratch) neuronal morphology, techniques exist that use a stochastic description generated by Monte Carlo models [9] or hidden Markov models [31]. And contrary to generating morphologies from scratch, some techniques perform an algorithmic tracing of microscopic images [17] or raw anatomical preparations [32] to reconstruct neuronal morphology in a digitized way. A final type of generation method builds only particular branching patterns and are non-descriptive but include underlying mechanism in their modelling studies, e.g., [34,35].

3. Methodology: EvOL-Neuron

We propose a new methodology to generate virtual neurons from scratch without putting a priori limitations on the candidate virtual neurons. The methodology is implemented in a computer program called EvOL-Neuron. The name of our method, EvOL-Neuron refers to our two-step methodology to generate virtual

[1] A drastic example would be the existence of trifurcations in neuronal morphologies. Despite the fact that in the current opinion about neuroanatomy trifurcations do not occur, several studies do report there existence (e.g., [16,23]). As most generation algorithms are based on branching probability [14] the revelation of new biological detail might require a complete new design of most algorithms.

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