Simulating Physiological Behaviour of Neurons

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Abstract

We present a simulation system dedicated to the simulation of temporally changing biological cellular structures. It is based on the theory of *cellular hypergraphs* for modeling arbitrary spatial structures. Our approach not only allows us to simulate temporal changes of concentrations of biologically relevant substances, but it furthermore enables us to model structural changes of cellular structures which are relevant for investigations in the field of morphogenesis. In order to demonstrate the applicability of our system, we have modeled a neural system already described in literature, the dendritic tree of a single Purkinje cell. The efficiency of our simulations is higher than that obtained with other special purpose simulators like the *GENESIS* system [1]. Future activities will concentrate on the application of the specific strong points: the usage of replacement systems for formulating morphogenetic effects and for automatically improving accuracy.

1 Introduction

Knowledge about the physiological behavior of individual neurons is essential for various fields such as understanding of local information processing and neural morphogenesis. We present a framework for dynamic models of neurons which can be used to formulate contemporary knowledge about physical and biochemical processes. Such a model can synthesize a complex system from a multitude of special biological research results, such that it offers novel methods for the verification and integration of different disciplines. The models are based on the theory of *cellular hypergraphs* and *parallel replacement systems* [5].

Our cellular hypergraphs constitute a versatile instrument for describing the spatial structure of each neuron and the interconnections between neurons to an arbitrary level of abstraction: neurons can be modeled as abstract building blocks in a complex network, the effect of the spatial form of the axon and dendrites may be used, or the model may even be extended to the level of intracellular structural components like cytoskeleton and organelles. A powerful addressing model developed for these graphs [4] is used to associate state values (expressing physical or biochemical properties) with a given location in the graph. This addressing model constitutes the basis for formulating computations (the effect of physical and biochemical processes) of any complexity.

In addition to the dynamics of state values, the replacement systems allow us to apply these models to questions where the *spatial dynamics* need to be investigated, i.e. the simulation of morphogenesis and of guided growth experiments. The productions of a replacement system describe how the structure of parts of the neuron are altered as a response to state changes, i.e. intra- or extra-cellular signals. So the productions represent processes like cell proliferation, cell growth, cell death or establishing new interneural connections.

2 Cellular hypergraphs and replacement systems

Cellular hypergraphs (CHG) [5] are a generalization of graphs where edges express relationships between some objects represented by vertices. The more general *hypergraphs* allow us to assign an arbitrary subset of vertices to an edge rather than exactly two terminal vertices.

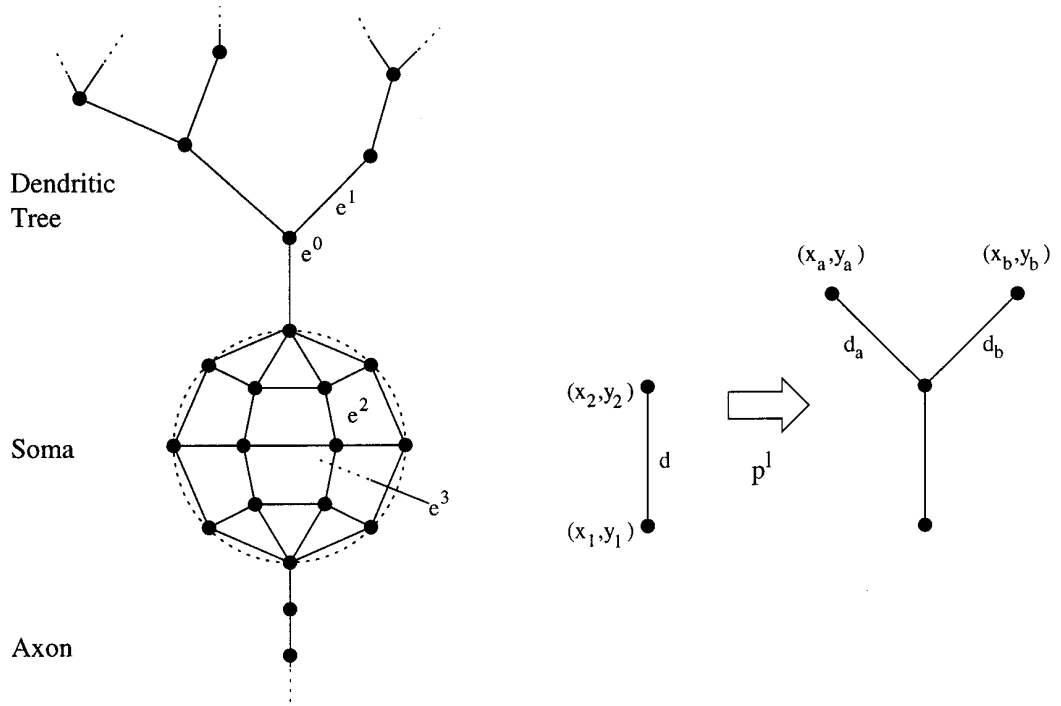

Figure 1: Sketch of how to represent a neuron's structure with a cellular hypergraph (left-hand side). The right-hand side illustrates how a production describing the construction of the dendritic tree might look like. The thickness d_a and d_b as well as the positions of the new terminal vertices (x_a, y_a) and (x_b, y_b) are a function of the original segment's data (d, (x_1, y_1) and (x_2, y_2), respectively).

We use CHGs to describe spatial structures (for instance, single neurons or aggregates of neurons) on a high level of abstraction and in a unified way. The vertices of the graph are associated with selected points of the original structure. Each edge is labeled with an integral number denoting its *dimensions*. In this way each edge represents a finite element of the spatial structure, i.e. 1-dimensional edges stand for line segments, 2-dimensional edges for faces, and 3-dimensional edges for solids. The vertices contained in an edge denote the corners of such a finite element. In the simple case, properties of the compartments like diameter, conductivity etc. can be noted as attributes with the edges. But one major advantage of CHGs over other data structures is the possibility to use the so called *component types* for representing the state of the cytosol and the polar cell walls intuitively and more adequately.

Figure 1 sketches out how a single neuron can be modeled with a CHG. The 0-dimensional edges, which are equivalent to the vertices of the graph, are drawn as dots (i.e. e^0) and the 1-dimensional edges as lines (e^1). 2-dimensional edges exist whenever line segments enclose some face (e^2), and the same holds for solids enclosed by a set of faces (e^3). The dendritic

tree and the axon consist of 0- and 1-dimensional edges, while the soma is represented by a three-dimensional edge with 2-dimensional edges representing faces on its surface.

The advantage of using CHGs over other approaches is that arbitrary structures can be modeled in a unified way. Furthermore, *parallel replacement systems* can be formulated for a CHG based model. Such a replacement system consists of a collection of productions; one sample production is sketched out on the right-hand side of figure 1. This production might represent how a segment of the tree can be replaced by a subtree, which describes the generation of the dendritic tree (for applications, see discussion below).

3 Implementation of an example

In order to demonstrate the applicability of our simulator to biologically relevant systems, we implemented the simulation of the dendritic tree of a cerebellar Purkinje cell. This tree-like structure has been modeled using a 1-dimensional CHG where each edge represents a segment of the dendritic tree and where the edges are labeled with the diameter of such a segment. The data for the geometrical positions of the vertices have been taken from three sample Purkinje cells, published by Rapp et.al. [7][1].

We have selected this system for its non-trivial electrochemical behavior. The passive electrochemical properties of neurons are described well by the cable equation, modelling each neural segment or compartment by an equivalent electrical circuit. Active voltage and calcium concentration components are also present, adding a complex dynamic component to the simulation (all data about the active channels in this model were derived from the work of *de Schutter and Bower* [2]). Possible extensions of this (structurally relatively simple) model are subject of future work.

3.1 The simulation system

The implementation has been performed in the object-oriented language *Smalltalk* [3], a well-known descendant from *Simula*. One intention of the presented work was to achieve a combination of *Smalltalk*'s favorable characteristics (support of graphical user interfaces, short turnaround times and the possibility to let users install their own object classes interactively), which simplifies the description of complex natural systems, with high system performance. In order to overcome the slow performance of the *Smalltalk* interpreter, it has been complemented with a library optimized for solving neural cable equations.

We have tested our simulation system running on an *Intel Pentium* single processor machine with a clock rate of 133 MHz. De Schutter and Bower performed their simulations on a cluster of 8 *Sun SPARC* workstations. They optimized the original input data of 2107 dendritic segments to obtain 1600 compartments. They state that a simulation should span a total time interval of $550msec$, and they use a time interval of $20\mu sec$ between each two simulation steps. A complete simulation run needs approximately 1 hour of runtime on their workstation cluster.

Our corresponding simulation based on the original set of 2107 segments requires approximately the same execution time (1 hour). The higher performance is a consequence of optimization strategies discussed below.

[1]The database can be accessed via the URL `http://www.ls.huji.ac.il/~rapp/reconst.html`

	Deviance from asymptote		
Limit	2	3	4
0.1%	$+0.64mV$ (+1.78%)	$-0.04mV$ (−0.16%)	$-0.72mV$ (−4.33%)
1%	$+3.39mV$ (+9.42%)	$+0.8mV$ (+3.24%)	$-2.53mV$ (−15.2%)
10%	$+6.22mV$ (+17.3%)	$+1.02mV$ (−4.13%)	$-11.8mV$ (−71.0%)

Table 1: Influence of the elimination of coefficients involved in the cable equation on the accuracy of a simulation, error weighted relative to the difference between the asymptote and the resting potential. Data is evaluated at different nodes 2, 3 and 4.

3.2 Optimization strategies for the simulation

The computations of the cable equations consist of two phases which are both subject to optimization strategies: (a) the initial solution of differential equations resulting in the coupling factors between adjacent dendritic segments, and (b) the iterative application of the resulting finite difference equations as well as the equations determining the activity state of ion channels. We have applied those strategies presented in [6] and improved them with respect to the specific problem domain.

In phase (a), for each of the compartments a set of relevant adjacent compartments is assembled based on a heuristic strategy taking the electrotonic length λ of the segments, derived from their passive resistance and capacitance, into account. The corresponding system of linear equations is constructed and solved making use of the optimization proposed by Hines [6]. The resulting set of coefficients describing the intensity of coupling with adjacent compartments is stored with each compartment. This procedure has an advantage over solving the complete linear equations system at once, because it scales linearly (instead of cubicly) with the problem size. In the case of 2107 compartments, we observed approximately 10^9 instead of 10^{10} arithmetic operations. Hines method which makes use of the matrix' tridiagonal shape reduces the computational load further by a factor of 16. This preprocessing phase requires approximately 60 seconds execution time on our system.

Those coefficients which are lower than a given relative limit are omitted from later computations. The influence of this optimization on the accuracy is documented within table 1. The percentage given in the first column denotes the limit for extraction coefficients with minor influence: the higher this value, the more coefficients are ignored. Figure 2 displays a screenshot from this experiment. The data is based on a simulation where a voltage step is input at a terminal compartment (node 1). The table documents for different compartments (nodes 2, 3 and 4) to what extent the correct asymptotic voltage level is achieved. The shape of the curves has been compared with the exact solution, too, but even under extreme conditions we could only detect neglectible deviation.

Phase (b) consists of the iterated evaluation of the cable equations, the evaluation of the activation of the channels as well as the influence of the active channels on the basal voltage. In the case of a dendritic tree having 2107 compartments, approximately 7 iterations can be performed within each second of simulation time.

4 Conclusions and future work

Based on the new paradigm of *cellular hypergraphs* and *parallel replacement systems*, which is of general utility for the simulation of the spatio-temporal development of cellular structures, a simulation system has been introduced. One possible field of applications, the simulation of the physiological behaviour of single neurons, has been studied. The simulations have shown that no restrictions result from the usage of the CHG paradigm. Optimization according to the necessary amount of computations has been investigated and rated according to the resulting accuracy.

Our simulation system represents an efficiently usable tool for investigations in the behaviour of individual neurons. To date we have applied techniques for numerically solving the differential equations relevant for neurons, but significant improvements can be expected when replacement systems are added.

Available data from examined neurons rarely constitutes a well prepared input for simulations. The compartments should have a electrotonic length which optimizes both aspects, accuracy as well as efficiency of the simulation [2]. Productions of a replacement system can automate the preparation of data since they can describe how to refine or how to combine the compartments.

Furthermore, if the influence of the dendritic tree's structure on its characteristics is to be investigated, a replacement system can act as a generator for a multitude of differerent neuron types. For this purpose we will need to abtain characteristic data from sample neurons. Productions that correspond to such a set of characteristic measures can be constructed straightforwardly.

Limitations became obvious which actually result from the quality of available structural and neurophysiological data: The implementation of a realistic system has revealed that, although further investigations need to be performed in various fields, such simulations can guide natural scientists in future studies. In the past simulations have demonstrated the need of unifying the diverse approaches and to express neuro-physiological observations in a unified nomenclature. If this is done, results from several sources can be combined to form a single model which helps to reveal contradictions and open questions. And a simulation can support our understanding of the complex interplay between different units of a neuron such as dendrites, the soma, the axon hillock, the axon and the terminal synapses.

These results provide a concrete demonstration of an application of cellular hypergraphs in the simulation of the physiology of a single Perkinje cell. The system that has been developed is however very general and easily modifiable to solve problems in a wide variety of fields where complex geometry and dynamical behavior are manifest.

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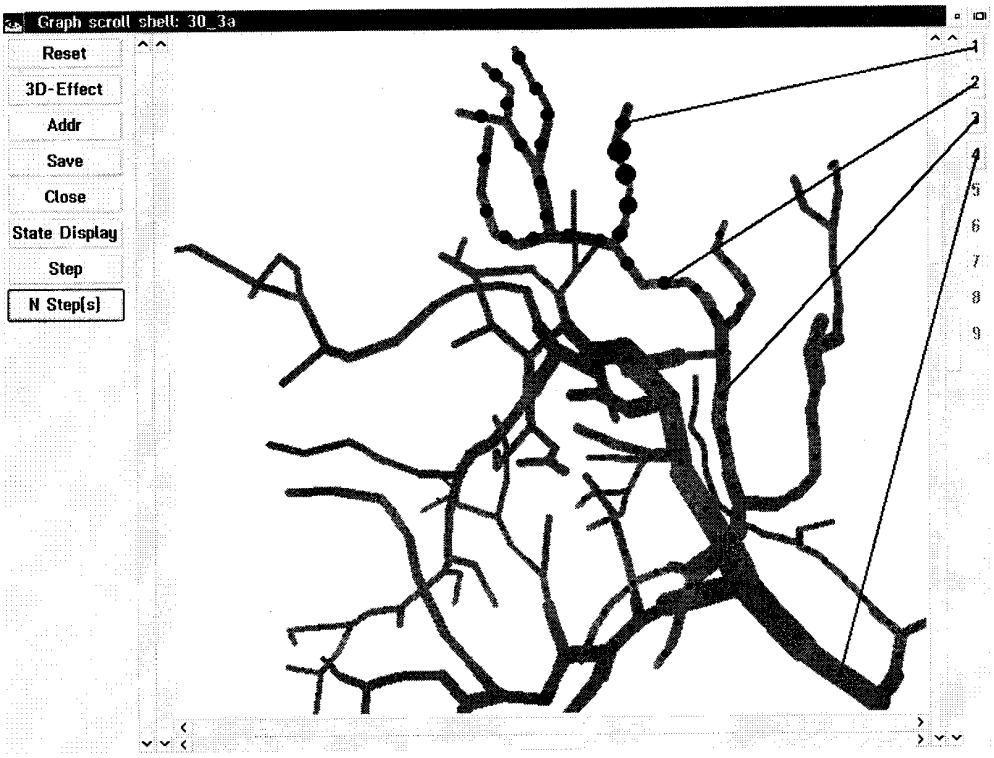

Figure 2: Screenshot of the simulator. The simulator supports different graphical views for i.e. displaying and altering the graph (center), introducing tools for observing selected compartments (buttons on the right-hand side), or steering the experiment (buttons on the left-hand side). In this experiment, voltage is injected via node 1 and recorded at nodes 2, 3 and 4. The potential of the segments can be visualized differently, for instance via the diameter of the black dots.