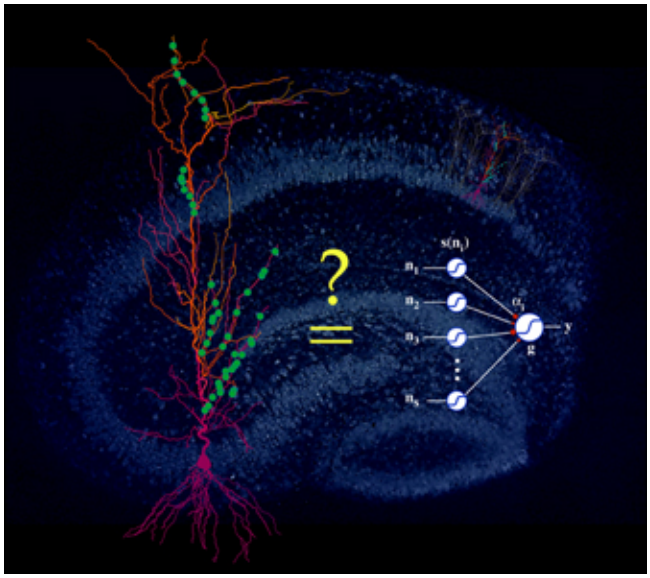
MSc thesis proposal:
Multi-scale simulation of neurons

Mikael Djurfeldt and Michael Hanke



1 Background

This MSc thesis proposal aims to advance the available techniques for simulating neurons. Within a volume of 1400 cm^3, the human brain packs 20 billion neurons and a vast network, made of millions of kilometers of axons, carrying their signals. The brain provides a computing capacity surpassing that of todays supercomputers by several magnitudes while consuming a power of only 20 W, and solves, on an everyday basis, many problems for which there exist no known human engineering solutions.

A century of neuroscience research has produced volumes of knowledge about the brain, but, due to its rich structure and dynamics, its secrets have just begun to unravel. The last 20 years of research has seen a strong growth of the sub-discipline *computational* neuroscience in which the dynamics of the brain is studied using mathematical tools and computer simulation. In 1952, Alan L. Hodgkin and Andrew F. Huxley described the interaction of ion channels in a patch of neuronal membrane using a set of coupled non-linear ordinary differential equations and could explain and quantitatively reproduce the basic features of the unit of neuronal signalling, the action potential—a work for which they were awarded the Nobel Prize in medicine 1963. Via the equivalent

cylinder model of the dendrite (branching outgrowth of a neuron), described by Wilfrid Rall in 1959, developments led to the first models of the dynamics of neocortical neurons towards the end of the 1970s.

During the 1980s, personal computers became powerful enough to solve models of single neurons quickly enough to allow for numerical experiments. With a growing computing power, it soon became possible to simulate networks of neurons and several neuronal network simulation softwares, like Genesis, NEURON and NEST were developed. During the 2000s, the first large-scale simulations of brain networks were made using parallel supercomputers, encompassing tenths of millions of neurons.

We are now confronting two unsolved problems:

1. While the increasing available computing power allows us to start simulating nervous systems composed of multiple areas and nuclei, we lack tools to handle the complexity of such models.

2. Hitherto, most models have encompassed few levels of organization (e.g. describing the electrical processes of one neuron and its dendritic compartment or a local network composed of point neurons). But many phenomena of the brain can only be described by models spanning several levels of organization. We need tools to handle well models spanning multiple spatial and temporal scales as well as different categories of physics (e.g. electrical and chemical processes).

The MUSIC framework, described below, addresses the first problem by allowing multiple models of local brain networks to be connected into a larger model and simulated in a parallel computer. This thesis work aims to develop a tool, either as an extension to MUSIC or stand-alone, which addresses the second problem. The tool should work as a communication interface between neuron simulators aimed at different scales or physics, allowing the simultaneous numerical simulation of a model composed of components simulated by the participating simulators.

2 Simulation of a multi-scale, multi-physics model

As an example problem, consider a model of neuron with one dendritic spine. Most neurons in the brain carry tens of thousands of small appendages, spines, on their dendrites. The purpose of a dendritic spine seems to be to create a local, partially isolated, electo-chemical module which receives signals to the neuron through synaptic transduction. Processes local to the spine are, for example, the basis for learning.

It is common to discretize the volume enclosed by the neuronal cell membrane into compartments. Using the Hodgkin-Huxley formalism, the membrane potential, $V(t)$, of a compartment is expressed as a differential equation

$$C_m \frac{dV}{dt} = I_{comp} + I_{cond} + I_{syn} \tag{1}$$

where C_m is the membrane capacitance, I_{comp} the sum of currents from adjacent compartments, I_{cond} the sum of ionic currents through channels in the cell membrane, and I_{syn} the sum of synaptic currents. The electrical behavior of

the cell is determined by by the ionic currents which are described through *activation* and *inactivation* functions.

The single spine of our model can be separated into an electrical and a chemical regime. Electrically, the spine can be described just as yet another compartment according to the formalism above. In order to account for diffusion and the effect of organelles such as local calcium stores, the spine should chemically be discretized into a set of volumes.

In the chemical regime, modelled using the Gillespie algorithm, we want to describe diffusion of ions, such as calcium, and biochemical reactions, for example the phosphorylation of AMPA-type glutamate receptors. An ionic current in the Hodgkin-Huxley formalism above, belonging to the electrical regime, will have an effect both in the electrical and chemical regime. Conversely, the phosphorylation of the glutamate receptor, a process belonging to the biochemical regime, will have an effect in the electrical regime, through the modification of the conductance of associated ion channel.

3 Available tools

The electrical regime of the model described above can be simulated in the neuron simulator NEURON. An existing neuron model can be used as a starting point. The chemical regime can be simulated using a software called NeuroRD. The challenge of this project is to develop the mathematical and software framework required for the numerically correct simultaneous simulation of these two regimes. As a starting point, the existing MUSIC framework can be used to connect the two softwares. MUSIC, the multi-simulation coordinator, enables different large-scale parallel simulators to exchange data on-line, between eachother or with other applications, within a computer cluster.

In the context of this project, there is a need of a kind of simulator interaction not yet supported by MUSIC: an integration of the solvers of the simulators which allows for tightly coupled models. Such interaction may also involve spatio-temporal filtering, providing a convenient interface between different spatial and temporal scales.

4 Prerequisites

- Advanced course in mathematical analysis
- Advanced course in numerical analysis, with emphasis on numerical methods for the solution of differential equations
- Programming skills in C++ and experience of Matlab
- An interest in biological applications

5 Practical considerations

The MSc thesis project will be supervised by Mikael Djurfeldt (mikael@djurfeldt.com) and Michael Hanke (hanke@csc.kth.se). The student will receive financial support from PDC, KTH.