

Simulation of Biological Neural Networks

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1 Mathematical modeling of biological systems

The list of success stories of the use of mathematics and mathematical simulation in physics, chemistry and engineering is endless. In the biological sciences the situation is different. The training of students in biology or medicine traditionally puts little emphasis on mathematics and physics, and skepticism towards any benefits of mathematics in describing living systems prevails in the biological and medical research communities.

Neuroscience is maybe the biological subdiscipline where the use of mathematical techniques is most established and recognized. An important reason for this is the success of Hodgkin and Huxley [1] 50 years ago of describing signal transport in a single neuron (nerve cell) as a modified electrical circuit where the charge carriers are Na^+ , K^+ , Ca^{++} , Cl^- and other ions flowing through the neuron cell membrane. This mathematical formulation, known as Hodgkin-Huxley theory, could not only account for the results from experiments used to construct the model and fit the model parameters. From their model they could also predict the shape and velocity of the so called *action potential* which is a pulse-like electrical disturbance which travels down thin outgrowths, called *axons*, of neurons. From their model they calculated the propagation velocity of the action potential down their experimental system, the squid giant axon, to be 18.8 m/s (at 18.3°C) which was roughly 10% off the experimental value of 21.2 m/s. Such quantitatively accurate model predictions are rare in theoretical biology. (Thorough introductions to mathematical modeling of single neurons, including Hodgkin-Huxley theory, can be found in Refs. [2, 3, 4]).

The success story of the Hodgkin-Huxley model has for two reasons made the life for theoretical neuroscientists easier than for modelers in other branches of biology: First, it has given the modelers a relatively firm starting point for mathematical explorations of both single neurons and neural networks. Secondly, experimental neuroscientists may have a more positive view on the potential benefit of mathematical modeling than their colleagues working in other fields of biology where such an example of a successful mathematical theory is still lacking. Moreover, due to its obvious success in describing action potentials, the Hodgkin-Huxley model has opened up for mathematical analysis of a variety of cell membrane phenomena. One example is the compartmental modeling of propagation of synaptic signals to the soma which is crucial for understanding the information processing properties of a single neuron [5, 6]. It has also opened up for mathematical analysis of membrane phenomena outside the nervous system, e.g., in the heart [7].

Since 1996 a research program in computational neuroscience has been established at the Agricultural University of Norway (NLH) in connection with the establishment of siv. ing. and cand. scient. programmes in environmental physics. Specifically we focus on mathematical modeling, including simulation, of biologically realistic networks of neurons. So far, our research has mainly focused on the early visual pathway and has been done in close collaboration with the experimental group of Professor Paul Heggelund at the Department of Physiology at the University of Oslo.

2 The visual pathway

When light hits the eye, neurons in the retina on the back side of the eye get excited. Several types of neurons are involved in the signal processing in the retina, but the output signal which is transmitted towards cortex, leaves from so called *retinal ganglion cells*. The ganglion cell axons (long, thin neuronal out-growths which propagate the signal to other neurons) constitute the optical nerve which transmits visual information to a part of the brain called *dorsal lateral geniculate nucleus (dLGN)* which is a part of thalamus. The main function of thalamus is to transmit sensory stimuli from the outer sensory systems to cortex. The so called *relay cells* in LGN receive visual signals from ganglion cells and transmit processed information to the primary visual cortex. From primary visual cortex the signals are then transmitted to other parts of cortex, and this eventually results in a visual perception of the surrounding world.

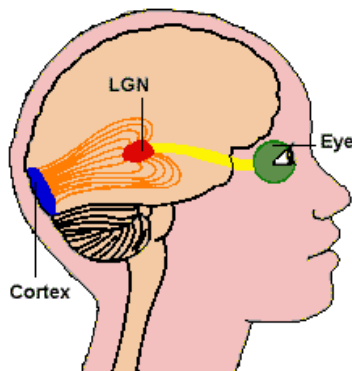


Figure 1: Sketch of the early visual pathway

Neurons which responds to light spots in this way are called *on-cells*. *Off-cells* have opposite response, i.e., they have largest activity when a dark spot covers the receptive field center. The antagonistic center-surround organization makes the system more suited to detect changes in the light intensity than the absolute magnitude of the intensity.

An important notion in studies of the visual system is the *receptive field*. This term refers to the limited area in the retina of the eye which when stimulated by light (or darkness) influences the firing of action potentials in a neuron. For retinal ganglion cells and dLGN relay cells the receptive fields are small, roughly circular, areas, and they exhibit so called center-surround antagonism. This means that the cells have highest response when stimulated by a circular spot of light (on a dark background) which exactly covers the so called *receptive-field center*. Illumination of an area outside this receptive-field center, on the other hand, will contribute to reducing the activity. Therefore, the receptive field can be described as a circular excitatory area surrounded by a ring-shaped inhibitory area.

3 Mathematical modeling of the early visual pathway

The mathematical models used in neuroscience can be categorized into three types: *Descriptive*, *mechanistic*, and *interpretive* models [4]. The goal of *descriptive*, or *statistical*, models is to summarize experimental data compactly yet accurately. Even though such models may be motivated by knowledge about the underlying neuronal circuitry, the goal

of such a model is to account mathematically for a phenomenon, not to explain it. In *mechanistic* modeling one attempts to account for nervous system activity on the basis of neuronal morphology, physiology and circuitry. In its approach this type of modeling follows the traditional physics approach to mathematical modeling of natural systems. In *interpretive* modeling the goal is to model the functional roles of neural systems, i.e., relating neuronal responses to the task of processing useful information for the animal. This type of modeling is unique to biological systems which have developed under evolutionary pressure. While it makes sense to ask, e.g., *why* the receptive field of retinal ganglion cells exhibits center-surround antagonism, the question on, e.g., *why* an apple falls to the ground is not fruitful.

Mechanistic modeling in the early visual pathway has mainly focused on (i) modified electrical-circuit models (of the Hodgkin-Huxley type) for single neurons or (ii) modelling of subcellular processes to account for, e.g., photoreceptor adaptation to changing light conditions (day vs. night) [8]. To understand the behavior of neural systems one must generally consider networks of neurons, i.e., *neural networks*, and until now biological neural networks have predominantly been addressed with descriptive and interpretive models.

An example of a commonly used descriptive model in the early visual system is the difference-of-Gaussians (DOG) model introduced by Rodieck 35 years ago [9] to describe the spatial aspect of the receptive-field structure in retinal ganglion cells. Rodieck mathematically described the small, roughly circular receptive fields of these cells as a difference of two circularly symmetric and concentric Gaussians. This choice is mathematically convenient, and allowed Rodieck to derive an analytical solution for the response to moving bars for cells with this type of receptive field. Later, Enroth-Cugell and Robson [10] calculated the spatial frequency response to sinusoidal stimuli for cells with receptive fields described by the DOG model. This solution is the basis for the *spatial frequency analysis* method which has been widely applied in the study of receptive fields during the last decades [11]. Such frequency response methods have a long tradition in engineering where it is a part of what is known as *systems theory*, alternatively *filter theory* or *cybernetics*.

The lack of detailed information about the neuronal circuitry has to a large extent prohibited mechanistic modeling of neuronal circuits in the visual pathway. During the last decades major progress has been made in mapping out the properties of the neurons in the dorsal lateral geniculate nucleus (dLGN) and their synaptic connections (for an overview see the new book by Sherman and Guillery [12]). The dLGN is a, relatively speaking, simple system with few cell types and, compared to cortex, modest divergence and convergence of synaptic connections (a schematic overview over the neurons in the dLGN circuit and their synaptic connections are shown in Fig. 2). This limited complexity makes a mathematical analysis more tractable. More importantly it reduces the number of unknown model parameters and thus limits the number of mechanistic models which need to be explored. Further, a lot of both physiological and anatomical studies have been done on the dLGN circuit, and such data are necessary to falsify the suggested mechanistic models.

4 Rate-based modeling of the lateral geniculate nucleus

At NLH we have focused on the development of *mechanistic* mathematical models of the signal processing properties of the dorsal lateral geniculate nucleus (dLGN). In the initial phase we have developed *rate-based* models, i.e., models for the firing *frequency* of neurons, for the receptive-field organization of relay cells and so-called *interneurons* in the dLGN [13, 14, 15].

In a first project [14] our starting point was data from experiments from dLGN on cats from Heggelund's laboratory at University of Oslo. Ruksenas, Fjeld and Heggelund [16] recorded action potentials of a class of dLGN relay cells (X, nonlagged) as well as so-called s-potentials corresponding to input action potentials from retinal ganglion cells. Circular light or dark spots of different diameters were used as visual stimuli, and the

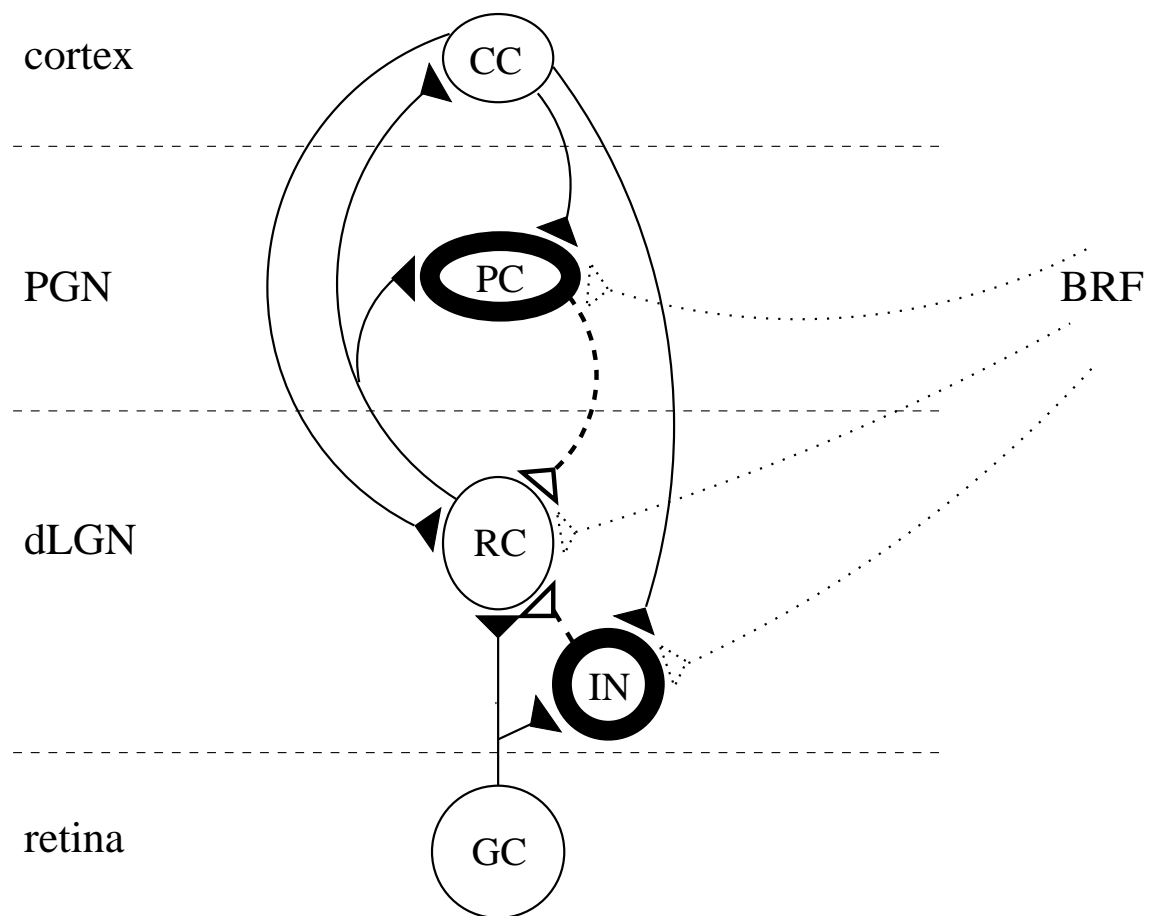


Figure 2: Schematic overview over the dLGN circuit involving feedforward inputs from the retina and feedback inputs from the cortex and the perigeniculate nucleus (PGN). The neurons involved are retinal ganglion cells (GC), geniculate relay cells (RC), intrageniculate interneurons (IN), perigeniculate cells (PC), and cortical cells (CC). Excitatory connections (*increasing* the probability for the receiving cells to fire an action potential) are shown as solid lines. Inhibitory connections (*decreasing* the probability for the receiving cells to fire an action potential) are shown with dashed lines. In addition the geniculate and perigeniculate cells receive *modulating* inputs from the brainstem reticular formation (BRF).

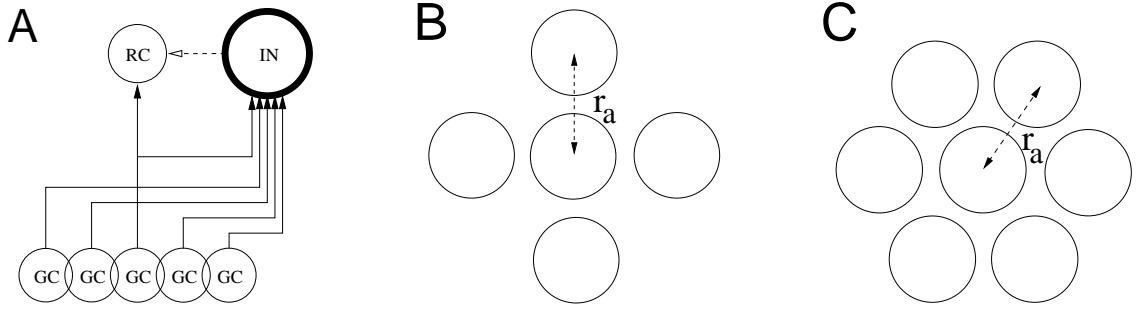


Figure 3: A: Schematic drawing of couplings at the geniculate level assumed in the model with a single excitatory input with weight and n inputs to a single interneuron (IN) for the specific example $n = 5$. B: Illustration of *square* model ($n = 5$) for spatial distribution of inputs from retinal ganglion cells to interneuron. The circles correspond to ganglion-cell receptive-field centers which are set unrealistically small and non-overlapping for reasons of figure clarity. C: Illustration of alternative *hexagonal* model ($n = 7$) for spatial distribution of inputs from retinal ganglion cells to interneuron.

number of action potentials during the on-time of the stimuli (500 ms), was used as a measure of neuronal response.

Circular spot stimuli evokes little firing activity in the cortical and perigeniculate cells feeding back to relay cells and interneurons. Thus data from circular spot experiments are well suited to study the feedforward aspects of the geniculate circuitry (cf. Fig. 2).

In our model we made the following initial assumptions motivated by physiological and anatomical observations [12]: (1) A relay cell receives a single excitatory input from a retinal ganglion cell. (2) A relay cell also receives indirect feedforward inhibition, via a single intrageniculate interneuron, from n retinal ganglion cells of the same class (X) and type (on/off). Further we had to specify the number and spatial positions of the retinal ganglion cells providing excitatory input to the interneuron. Anatomical studies [17] revealed a disordered grid of retinal ganglion cells with typically 4-6 nearest neighbors of the same type. Physiological studies [18] indicated that an interneuron receives excitation from a similar number of retinal ganglion cells. As a simple choice for the spatial distribution of ganglion-cell inputs to the interneuron we thus assumed that (1) the retinal ganglion cell which provides the excitatory input to the relay cell, also excites the interneuron. (2) the other $n - 1$ ganglion cells are positioned at $n - 1$ nearest-neighbor positions. The nearest-neighbor distance is denoted r_a . An illustration of the model for the choices $n = 5$ (square model) and $n = 7$ (hexagonal model) is given in Fig. 3.

We will not go into the details of (i) the mathematical derivations of the relay-cell and interneuron response within a firing-rate based formalism, or (ii) the detailed comparison with experiments from Heggelund's laboratory. A thorough presentation of this can be found in Ref. [14]. However, our conclusions can be summarized as follows: Our simple feedforward model accounts well for the results from the 22 recordings for nonlagged X cells reported in the experiments of Rukxenas *et al.* [16] Moreover, *predictions* regarding (1) distances between neighboring retinal ganglion cells providing input to interneurons, (2) receptive-field center sizes of interneurons, and (3) the amount of center-surround antagonism for interneurons compared to relay cells, were all found to be compatible with data available in the literature.

A model claiming general validity should have a high predictive power, i.e., it should

be able to predict correctly results from several types of experiments. Moreover, correct predictions of experimental results for situations very different from the experiments *on which the model is based*, are the most convincing.

To test the model presented here further, one thus should look for other types of experimental tests. In Ref. [15] we described how data from experiments with drifting (moving) sinusoidal gratings can be used to test this and other mechanistic models for the geniculate circuitry. A good approach for testing models for the geniculate circuitry would be to record the response of single neurons to both circular-spot and drifting-grating stimuli. Then a mathematical model fitted to experimental results for, e.g., circular-spot stimuli for one particular cell pair, would produce testable predictions for the experimental response when drifting-grating stimuli are presented to the same cell pair. At present we await such “combined” experimental data so that such a test can be performed.

5 Spike-based simulations of the dLGN

The advantage of rate-based modeling compared to simulations of networks of spiking neurons (i.e., neuron models where the generation of each action potential, or spike, is included) is that one can obtain (approximate) analytical expressions which are more transparent than numerical data. However, the rate-based approach has limitations since it is unclear to what extent all information in a spike train is carried by the firing rate. If the detailed timing between consecutive spikes matters, a spike-based model is necessary. Further, the parameters in spike-based models are generally more easily extracted from physiological experiments than the corresponding parameters in rate-based models.

Presently we are thus building a simulation model for a patch of the visual field where the basic simulation units are the known neurons in the dLGN (and an associated brain area called the perigeniculate nucleus, PGN). The construction of the model is based on the shape and properties of the individual neurons taken from anatomical and physiological studies, and the model will be tested (and modified) by comparing with a variety of electrophysiological studies both on living animals (*in vivo*) and preparations of neural tissue in a glass dish (*in vitro*).

For the simulation of the dLGN network we use the SYNOD simulator [19] (for more information, see www.synod.uni-freiburg.de). This simulator models neurons as pulse-emitting point neurons and is therefore well suited to the simulation of neuronal *coding* and signal processing in large neuronal networks. In future work we plan to develop a parallel version of the simulator relying on the message passing interface (MPI) to allow for the simulation of large, biological neuronal networks. Development will proceed in close contact with the original NEST development group at Universität Freiburg, Honda R&D Europe, Offenbach, and Max-Planck-Institut für Strömungsforschung, Göttingen in Germany.

5.1 Model design

The goal of our current modeling efforts is to explore the functional significance of peculiarities of thalamic nuclei, namely (i) the ability of thalamic neurons to fire either in a burst or a tonic manner, and (ii) triadic synapses that connect axons of retinal ganglion cells with both a geniculate relay cell dendrite and an interneuron dendrite, and which include inhibitory dendro-dendritic synapses. Interneurons participating in such triads may

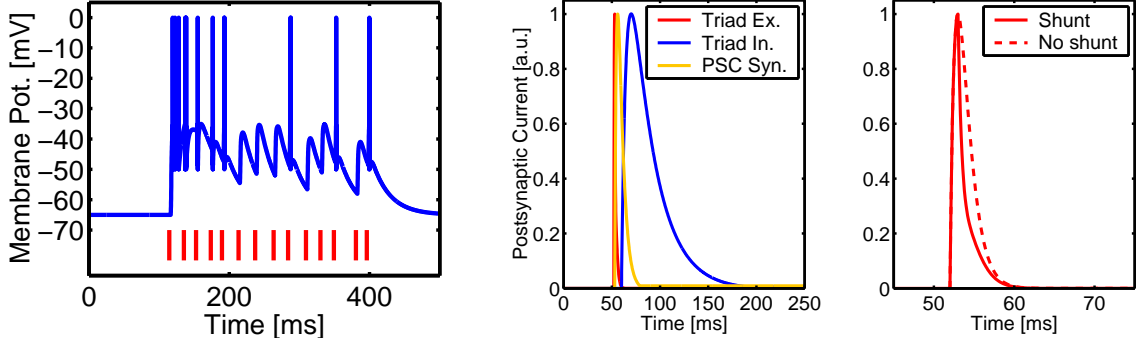


Figure 5: Left: Response of the LIFB model neuron to the 50Hz Γ -spike train indicated below the membrane potential trace. Center: The three types of synaptic input used in the model, triadic excitation to the relay cell, triadic excitation to the interneuron mediated by metabolic receptors, and fast, normal synapses. Right: Close-up of triadic excitatory input, showing the effect of shunting. Amplitudes are normalized.

synapse from interneuron to relay cell. The latter effectively shunts the excitatory input to the relay cell [23]. The net input to the relay cell can thus be modeled as

$$\begin{aligned}
 I_{\text{triad}}(t) &= I_{\alpha}(t)(1 - s(t - \Delta)) \\
 I_{\alpha}(t) &\sim te^{-t/\tau} \\
 s(t) &= s_{\max}(e^{-t/\tau_{\text{decay}}} - e^{-t/\tau_{\text{rise}}}) .
 \end{aligned}$$

The effect of triadic excitatory input on the interneuron is modeled via a standard synapse. The implementation of the triad is discussed in detail by V. Strengen, see Ref. [24].

5.2 Modeling responses to spot stimuli

As a first application, we have used our model to simulate the responses to spot stimuli, as they were used by Heggelund in his *in vivo* experiments [16]. The network was stimulated with circular spots of light, concentric to the receptive field of the central neuron in the network. Ganglion cell activity was modeled as a Γ -process with firing rates estimated from a rate-based, linear model [14]. Responses of the central neuron in the network were fit to responses measured in X-on cells of cat dLGN, as shown in Fig 6. The fit was obtained by adapting only synaptic weights using a Nelder-Mead minimization routine.

6 Perspectives

Our model of the retinogeniculate circuit presented here is currently in an early stage of development towards a biologically realistic model of the early visual pathway. We hope to close many of the open issues concerning connectivity, especially of interneurons, the selection of realistic parameter values, interaction between X- and Y-pathways, and feedback from both the perigeniculate nucleus, and cortex, in the foreseeable future. When the model will have been sufficiently validated against experimental findings, it will be an ideal system for *in silico* experiments exploring the role of particular properties of thalamic circuitry. A feature we consider particularly intriguing is the finding that

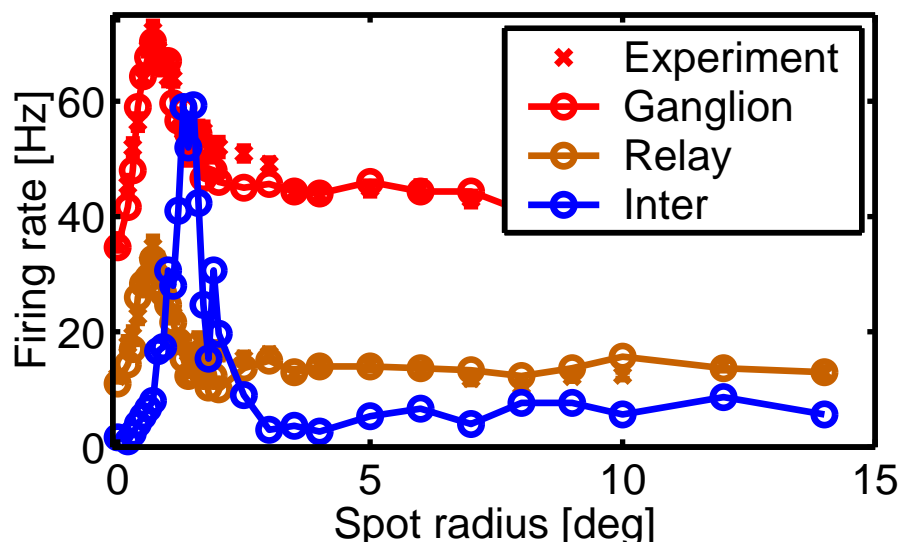


Figure 6: Firing rate vs. spot diameter for a typical geniculate relay cell (“middle”), the retinal geniculate cell providing the driving input to the relay cell (“top”, measured as s-potentials), and the pertaining interneuron (sharply peaked curve). Circles indicate simulation results, crosses experimental data. No experimental data is available for the interneuron.

cholinergic input to interneurons, arising from the brainstem, can shunt triadic input to interneurons [25]. The dLGN may thus work in a regime of either localized or globally coupled inhibition to relay cells. We plan to investigate the functional significance of this finding once the model is well established.

Acknowledgments

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