Doctoral Thesis

Biophysical models of neurons

Petr Maršálek

Faculty of Mathematics and Physics, Charles University
Prague, Czech Republic

1999

Petr Maršálek

April 23, 1999

[1] Faculty of Mathematics and Physics, Charles University
Ke Karlovu 3 (CZ 121 16) Prague 2, Czech Republic
e-mail: marsalek@karlin.mff.cuni.cz
[2] Institute of Physiology, Czech Academy of Sciences
Vídeňská 1083 (CZ 142 20) Prague 4, Czech Republic
phone: ++(420)(2) 475 2539
[3] Department of pathological physiology, 1st Medical Faculty, Charles University
U nemocnice 5 (CZ 128 53) Prague 2, Czech Republic
phone: ++(420 2) 2491 4929, 2491 2835, fax: ++(420 2) 2491 2834
[4] http://www.karlin.mff.cuni.cz/~marsalek
[5] Advisor: Dr. Petr Lánský, Institute of Physiology, CAS

Contents

Abstract

Several problems from biophysics of neurons are addressed. Four types of neurons are studied: the pyramidal cells in neocortex, and in CA1 area in hippocampus, cells in the nucleus laminaris in avian auditory pathway, and the receptor cells in olfactory epithelium. Detailed and reduced models of these cells are used. Detailed models are based on the formalism of the Hodgkin-Huxley equations. Reduced models range from the stochastic two-point model, through the leaky integrator model to the simplest, perfect integrator model. The thesis is divided into parts 1-5. (1) In the first part we introduce all the mathematical tools for next parts and the basics of biology of neurons. (2) We study the dependence of the level of intracellular calcium on the previous firing in pyramidal cells. (3) Two-point stochastic model describes firing of olfactory cell in dependence on the odorant concentration. (4) Using several models we study spike timing in neocortex. In particular the question of the functional relationship between synaptic input jitter, and spike output jitter in individual pyramidal cells in neocortex. The term jitter means a standard deviation of events centered around some mean time. (5) Along with the discussion of results, several experimental methods, which are the sources of data for our models, are commented.

R.P. Feynman: If our small minds, for some convenience, divide this glass of wine, this universe, into parts — physics, biology, geology, astronomy, psychology, and so on — remember that nature does not know it! So let us put it all back together, not forgetting ultimately what is it for. Let it give us one more final pleasure: drink it and forget it all!

C. Koch: Science is a social endeavor; many, if not most, new ideas are born out of discussions with colleagues, reading books and papers, attending seminars and so on. We are often not even explicitly aware of these influences, but they are there none-the-less. It is to acknowledge this that I use the pluralis modestati *form of the "we"...*

Introduction

Organization of this thesis

This thesis is organized into five parts. It contains three articles already published and parts of work in preparation. We added an introductory text to all three papers. In this **part 1**, we introduce variables and equations used throughout the thesis. **Part 2** contains an article studying rise of intracellular calcium following backpropagating action potential in pyramidal neurons. The core of this part is in reproducing in model some phenomena discovered using calcium imaging techniques. From the model we propose that the function of calcium channels can be predicted from a small number of parameters. In **part 3** we show how a stochastic model can be applied to the description of a phylogenetically simple neuron, the olfactory cell. The goal of **part 4** is to give a theoretical background to the observation of the fast signal propagation in primate visual cortex. We propose the explanation for this high speed of the signal propagation based on investigations of single cell responses using three different models of a single pyramidal cell. The closing part, **part 5**, contains the conclusion and the discussion.

This thesis is submitted to the board for the subject "Physics of Molecular and Biological Structures" following paragraph 22.4 of regulations of graduate studies at the Faculty of Mathematics and Physics, Charles University, from 1991.

Notation, definitions, and conventions

Literature citations throughout the text refer to four lists of references ((2), (3), (4), at the end of each paper, and (5) at the end of the thesis), which are cited as follows [Migliore, 1996, 2], [Wiener, 1958, 3], and [Konishi, 1990]. In the paper presented as part 4, the references are cited by numbers, like ref.5, therefore we add this number to the citation, [Abeles, 1982, 4.5]. Sometimes, a page reference is added. The same notation referring to parts applies to equations, figures and tables. References to equations and tables throughout part 1 are denoted by number 1 (e.g. 1.5, and references to equations and tables in papers (2), (3), (4), are made accordingly).

1 Single neurons

Abstract of part 1

In this part, all the mathematical tools for next parts are introduced. (1) The equations for the passive properties of the neuronal membrane are shown. These are the linear differential equations for the RC-circuit, and the cable equation. (2) The equations for the active, membrane voltage dependent properties, are shown. These include the Hodgkin-Huxley equations (a system of nonlinear differential equations), two examples of synaptic functions, and one example introducing the threshold behavior in reduced neuronal models. (3) Models are classified into the detailed models, and the reduced models. Examples of them and of their particular implementation are given. (4) In a short review, biological information necessary for understanding the rest of the thesis is discussed. This includes the morphology of

neurons, and the physiology of both the membrane potential and the calcium intracellular level. (5) The introductory part of the thesis is closed by references to the results of other groups working on the modeling of single neurons.

1.1 Passive membrane properties

In the introductory part 1 we start with basic equations and proceed to the Hodgkin-Huxley equations. The Hodgkin-Huxley equations are the key mathematical tool used in this thesis. We are aware that it is impossible to reduce a biological level of description to the physical level of description without loss of some details. Yet the mathematical and physical level of description can proceed further without loss of generality. Therefore we attempted to describe all models in the unifying biophysical approach of writing equations for membrane electricity. We tried to illustrate terms from neuroscience by simple examples. The following equations are based on measurements of single cell activity. When during electrophysiological measurements action potentials, or spikes [1] are omitted (or filtered out using low pass filters), the response of a cell is similar to an RC-circuit, [Koch, 1999]. An introduction to the thesis from the biological point of view can be found in this part 1 in section named Biology of neurons.

RC-circuit

Assume charging an RC-circuit by input current I and measuring the voltage V (at some parts of the thesis denoted V_m, membrane voltage).

$$\frac{dV}{dt} = -\frac{V}{RC} + \frac{I}{C}, \tag{1.1}$$

(see further equations (2.7), (4.8)), where R is resistance, and C capacitance, t time. The time constant of the circuit is $\tau = RC$. For the solution of this equation we have to provide initial value of V, in models based on RC-circuit we set usually $V(0) = 0$ to the origin of coordinate system. As an input current to the RC-circuit, an arbitrary function I can be used. We will give one example now. After switching DC current on, i.e. when I is a step function, the RC-circuit reaches a steady state, with a speed given by the time constant τ.

$$V_\infty = I_\infty R. \tag{1.2}$$

When we denote the sustained current value $I_\infty = I$, the capacitor becomes charged and voltage V asymptotically reaches the steady state value V_∞.

Dimensions of parameters and variables expressed in basic units in SI are: $[C] = \mathrm{F} = \mathrm{m}^{-2}\mathrm{kg}^{-1}\mathrm{s}^4\mathrm{A}^2$, $[R] = \Omega = \mathrm{m}^2\mathrm{kg}^1\mathrm{s}^{-3}\mathrm{A}^{-2}$, $[V] = \mathrm{V} = \mathrm{m}^2\mathrm{kg}^1\mathrm{s}^{-4}\mathrm{A}^{-1}$, and $[I] = \mathrm{A}$. However, appropriate multiples and fractions of these units, μF, MΩ, or kΩ, mV, and nA are used in the literature on neural systems and throughout this thesis. Typical values in RC-circuit model are like: $\tau = 10$ ms, $C = 1$ nF, $R = 10$ MΩ, $V_\infty = 10$ mV, $I_\infty = 1$ nA. Sign convention in measurements: sign of cell potential is measured from intracellular space to outside. It is negative at rest. Current injected into a cell in order to depolarize this cell is thus positive. Equation 1.1 is a linear differential equation. From this viewpoint the cell basically behaves as a linear system (as we noted already, under the assumption that action potentials are omitted, [Koch, 1999]).

Cable equation

A typical neuron consists of many tiny cylindrical processes. They branch in functionally distinct **axonal**, and **dendritic**[1] arborizations. Diameter of these processes changes slowly. In an equivalent electrical model they can be replaced by series of equivalent cylinders connected together.

[1] For the explanation of biological terms, see the section **Biology of neurons**.

The electrical properties of these cylinders are described by the cable equation. The cable equation with absolute (not related to spatial dimensions) parameters is:

$$\frac{\partial V}{\partial t} = \frac{1}{r_i c_m}\frac{\partial^2 V}{\partial x^2} - \frac{V}{r_m c_m} + \frac{I}{c_m}. \tag{1.3}$$

Compared to the ordinary differential equation 1.1, we have one more term on the right side of this partial equation, called the space term. Equation 1.1 is then sometimes called a one compartment, or one-point model. Separate cylinders are called **compartments** in this context. Again, V is the voltage variable, and x is the space variable. I is input current, t is time, r_m, and c_m are the membrane resistance, and capacitance, and r_i is the axial resistance of the cylinder.

Let us note that such a cylinder is covered by the membrane possessing a specific capacitance and resistance per unit of area and its volume is filled with intracellular medium with a specific resistance. Equation 1.3 can be parameterized by the diameter d and the length l of the cylinder. We will denote specific capacitances and resistances by capitals. [2] We will introduce specific parameters with following dimensions: membrane capacitance $[C_m] = \mathrm{F\ cm^{-2}}$, membrane resistance $[R_m] = \Omega\ \mathrm{cm}^2$ and axial resistance $[R_i] = \Omega$ cm. We will substitute for r_m, c_m and r_i into equation 1.3: $c_m = C_m \pi d l$, $r_m = R_m/(\pi d l)$ and $r_i = R_i 4l/(\pi d^2)$. We get:

$$\frac{\partial V}{\partial t} = \frac{d}{4l^2 R_i C_m}\frac{\partial^2 V}{\partial x^2} - \frac{V}{R_m C_m} + \frac{I}{C_m \pi d l}. \tag{1.4}$$

We have to add initial and boundary conditions for a solution of these equations 1.3 and 1.4. The time constant has the same meaning as in equation 1.1, ($[\tau] = \mathrm{ms}$). It is:

$$\tau = r_m c_m = R_m C_m.$$

The length constant λ is such a length, within which a voltage command drops to e^{-1}, i.e. 0.368 of its original value for the open end boundary condition. (Open end boundary condition means that that the cylinder goes to infinity at both its ends.) λ ($[\lambda] = \mathrm{cm}$) is calculated as:

$$\lambda = l\sqrt{\frac{r_m}{r_i}} = \frac{1}{2}\sqrt{\frac{R_m d}{R_i}}.$$

In this passive version of the cable equation, other derived parameters can be introduced, for example: input resistance, [Tuckwell, 1988, 2, vol.1, p.143], and higher order time constants, [Koch et al., 1996, 4.8]. Typical values of parameters in squid and cat are shown in Table 1.1.

	animal	squid	cat	cat
variable	units	giant axon	motoneuron	pyr. cell
R_m	$\mathrm{k\Omega cm^2}$	1	2.5	11-100
C_m	$\mu\mathrm{Fcm^{-2}}$	1	2	1
τ	ms	1	5	11-100
R_i	Ωcm	30	70	200
d	μm	500	10	0.1-10

Table 1.1: Values of passive parameters

The values for the giant axon of the squid giant neuron can be found in [Hodgkin and Huxley, 1952]. The values for a primary dendrite of cat spinal motoneurons are described in [Tuckwell, 1988, 2, vol.1, p.138],

[2] In [Tuckwell, 1988, 2, vol.1] and [Koch, 1999] the use of uppercase and lowercase notation for the parameters is just the opposite. We follow here a notation from a shorter introduction to the topic, [Koch, 1990].

data on cat pyramidal cell dendrites from both brain slices and whole animal recordings are in [Koch et al., 1995, 4.18]. [3]

1.2 Active membrane properties

The ability of a membrane to respond to voltage and ion concentration changes in a nontrivial manner is in physiology called the excitability of a membrane. The electrical properties of membrane are the substrate for its excitability. The division of membrane properties into passive and active is borrowed from electrical engineering. Some elements of an electrical circuit which cannot be described by linear differential equations like 1.1, 1.3, and 1.4, are called **active** elements (for example transistors and diodes), compared to **passive** elements (resistors, capacitors, and inductances).

The active elements of neural membranes are **ion channels** and **ion pumps**. Channel openings influence membrane voltage by changing ion distributions. Setting a voltage using an external source, a voltage command, can also change the membrane voltage. The command voltage, under which ion flow through ion channel changes direction, is called **the reversal potential**. The reversal potentials of basic ions in examples of neurons are listed in Table 1.2.

Table 1.2: Reversal potentials of ions

	potentials [V_{ion}] = mV		
ion	squid	snail	cat, chicken
Na^+	115	50	50
K^+	-12	-68	-95
Ca^{2+}	-	64	115
Leak	10	-44	-66

The ionic composition of squid giant neuron is taken from [Tuckwell, 1988, 2, vol.1, p.69]. The snail neuron is a burster neuron, one of 20,000 central neurons in marine snails *Aplysia californica*, or *Aplysia limacina*, [Bower and Beeman, 1995, p.123]. Cat pyramidal cells in neocortex, [Koch et al., 1995, 4.18], and chicken neurons in nucleus laminaris [Reyes et al., 1994] have the same ion compositions.

The Hodgkin-Huxley equations

The regenerative events of membrane excitation are described by the Hodgkin-Huxley equations. We will not write these equations in their most general form, like equations (2.1), instead a simpler example is given. The following system differs from the original set [Hodgkin and Huxley, 1952], [Tuckwell, 1988, 2] in one regard; it has voltage independent time constants, τ_j. The one point (space clamped) system is written:

$$\begin{aligned} C\frac{dV}{dt} &= G_{Na}m_{Na}^2 h_{Na}(V_{Na}-V) + G_K m_K^2 h_K (V_K - V) + G_L(V_L - V) + I, \\ \frac{dj}{dt} &= \frac{j_{\text{ss}} - j}{\tau_j} \quad \text{for} \quad j = m_{Na}, h_{Na}, m_K, h_K, \end{aligned} \tag{1.5}$$

where V, C, I and t are as in equation 1.1, G_{Na}, G_K and G_L are maximal **sodium (Na^+)**, **potassium (K^+)** ion channel, and "leakage" (L) [4] conductances (reciprocals to resistances), V_{Na}, V_K, and V_L are the corresponding reversal potentials (example values are in Table 1.2 for cat and chicken). The second equation represents the system of four equations for activation and inactivation of voltage sensitive ion channels. Activation (m) and

[3] I depends on how long compartments we choose to model.

[4] Leakage conductance is mediated by **chloride (Cl^-)** and a mixture of all ions.

inactivation (h) variables are for both Na^+ and K^+ ions. They are denoted $j = m_{Na}, h_{Na}, m_K, h_K$. Their time constants are τ_j and steady state voltage dependences j_{ss} are given by the sigmoideal (Boltzmann) curves:

$$j_{\text{ss}} = \frac{1}{1+\exp\left((V_{j,\text{half}} - V)/K_j\right)}, \tag{1.6}$$

where $V_{j,\text{half}}$ is the half-activation voltage and K_j is the slope coefficient of the Boltzmann curve. $G_L = 1$ nS and the rest of active parameters are in Table 1.3. In contrast to the usual potassium current, the current used here inactivates and thus has both m_K, and h_K variables. When starting from initial conditions: $V(0) = -66$ mV, $m_{Na}(0) = 0.14,\ h_{Na}(0) = 1,\ m_K(0) = 1,\ h_K(0) = 0$, which are close to steady state values, the system stays at rest. This time the convention is not to move the initial condition to the origin of coordinates, $[t, V] = [0, 0]$, as we did under equation 1.1, because there is a stronger physiological context, and therefore the baseline value of V is set to the absolute value of membrane potential measured from the intracellular side of membrane, here $V(0) = -66$ mV. [5] When a short duration current pulse with suprathreshold amplitude (see below) is delivered, the system elicits an action potential and then returns to resting values.

constant	units	m, Na	h, Na	m, K	h, K
$V_{j,\text{half}}$	mV	-40	-45	-54	-50
K_j	mV	3	-3	6.5	-6.5
τ_j	ms	0.05	0.5	0.43	1.2
G_{ion}	nS	200	200	120	120

Table 1.3: Example parameters of the Hodgkin-Huxley equations

This set of equations uses parameters from the chicken nucleus laminaris neurons, [Reyes et al., 1994], [Reyes et al., 1996]. In comparison to neocortical pyramidal cell, these neurons do not have any adaptation current. Therefore they can be described by one of the simplest Hodgkin-Huxley equations among all neurons in higher animals. Anyway, the set of equations describing this model, and virtually all models containing Hodgkin-Huxley equations, have to be solved numerically.

In analogy to equation 1.1, this example of a Hodgkin-Huxley system is a one point system. The system of these equations can be rewritten to its cable version, in a manner analogous to going from equation 1.1 to equations 1.3, or 1.4. There is, however, one difficulty. At this point we have to consider the detailed morphology of the cell, because the densities of ion channels (G_{ion}) vary in relation to different parts of a neural cell. We will mention the distinguished morphological parts of neurons, **axons, dendrites and synapses** briefly here and we will return to them in the section named **Biology of neurons**.

Axons

Axons possess a collection of ion channels such that a brief and acute depolarization pulse to positive values of V does not decrement with distance, thus there is no length constant λ (defined below 1.4). The depolarization wave holds its shape and propagates along the axon fiber in one direction with a constant speed. Such an event is frequently called a traveling wave in physics, in physiology it is called an **action potential**, or spike. Once this wave reaches a **synapse**, the electrical signal is transduced to another cell.

Dendrites

At this another cell, a signal is transduced by **dendrites**. In dendrites, the depolarization wave spreads with decrement. From this fact it can be concluded that dendrites either consist of passive membrane, or that the

[5] When starting from any V in a meaningful range from -100 to +50 mV, the system reaches its stable point -66 mV after some time.

active part of dendritic ion channels is weaker compared to axon, see [Maršálek and Santamaría, 1998].

Synapses

At the target cell, action potential transmitted by synapse can cause hyperpolarization, or depolarization. A synaptic depolarization is called an excitatory postsynaptic potential, EPSP. Accordingly, a hyperpolarization is called an inhibitory postsynaptic potential, IPSP. A synaptic response can be modeled by the following synaptic functions. The alpha function is $f_{\text{syn}} = te^{-t/\tau_1}$ [Jack et al., 1975]. Double exponential function is $f_{\text{syn}} = (1 - e^{-t/\tau_1})e^{-t/\tau_2}$ [Bower and Beeman, 1995, 2]. τ_1 and τ_2 are time constants of synaptic events. The alpha function has to be multiplied by a constant with dimension [s^{-1}] in order to get a dimensionless function. Both the hyper- and de-polarizing action of synapses is a conductance change for an appropriate ion:

$$I = f_{\text{syn}} G_{\max}(V_{\text{ion}} - V), \tag{1.7}$$

where f_{syn} is a synaptic function, $G_{\max}$ is a maximal synaptic conductance and V_{ion} is the reversal potential of the synaptic current. Typical values of τ_1 and τ_2 are milliseconds or tens of milliseconds. A typical amplitude of $G_{\max}$ in this equation can be about one millivolt. The sign of the term $(V_{\text{ion}} - V)$ determines, whether the synapse causes depolarization, or hyperpolarization (EPSP, or IPSP). Current I is then added to the net current on the right side of the principal Hodgkin-Huxley equation, for example in 1.5.

Threshold properties

How is the action potential generated? When enough excitatory postsynaptic potentials are integrated, the membrane voltage reaches a threshold and elicits the short event, called the action potential, or the spike, that was introduced in previous subsection. In the Hodgkin-Huxley equations, an action potential is obtained as a solution to depolarizing current input (sufficient enough to elicit a spike), [Cronin, 1987]. This was one of the tests of the validity of the original Hodgkin-Huxley model. All parameters were fitted to values obtained from observations of the steady state voltage, as in equations 1.6 and 1.2. Yet the same system was then capable of reproducing an action potential, a physiological event observed at a much faster time scale. In the RC-circuit model, in the equation 1.1, a threshold V_{th} can be introduced as follows:

$$\begin{aligned} \frac{dV}{dt} &= -\frac{V}{RC} + \frac{I}{C}, && \text{for } V < V_{\text{th}} \\ V(t) &= 0, && \text{for } V \geq V_{\text{th}} \end{aligned} \tag{1.8}$$

see [Tuckwell, 1988, 2, vol.1, p.86], and [Maršálek and Santamaría, 1998], compare to equation 2.7. When the voltage V reaches the threshold V_{th}, it is reset to 0 using the second branch of this equation 1.8. This reset mimics the spiking, or firing, of the cell. Therefore this model is called the leaky integrate-and-fire unit, or **leaky integrator**. The leaky integrator can be charged to the threshold voltage by three means. The first one (1) is trivial: when a voltage signal is delivered from the voltage source, the unit fires whenever the voltage exceeds the threshold. The second one (2) is bringing the unit to firing using the "long" lasting "lower" current source. The "lower" value means that it is comparable to the value of I_∞ from equation 1.2. When $V_\infty < V_{\text{th}}$, the unit remains silent. We shall skip the asymptotic case $V_\infty = V_{\text{th}}$, when the unit is not firing in a finite time. Thus we are left with the obvious condition $V_\infty > V_{\text{th}}$ for this second type of firing initiation, and the threshold (asymptotic) value of I is from the equation 1.2 directly: $I_{\text{th},\infty} = V_{\text{th}}/R$. The third way (3) of stimulating the unit is bringing the unit to firing using the short pulse of "higher" current source. Given the pulse duration Δt and assuming that voltage decay is during this "short" time negligible, we can determine

the "short" time current threshold $I_{\text{th}}(\Delta t)$. The charge threshold (not applicable to detailed models, see [Koch et al., 1995, 4.18]), is $Q_{\text{th}} = CV_{\text{th}}$ and from this $I_{\text{th}} = Q_{\text{th}}\Delta t$. The analogous behavior in response to voltage command (1), "lower" current command (2) and "higher" current command (3) can be described in a detailed model using Hodgkin-Huxley equations. Let us give one example with numerical values here. In a cable version of the Hodgkin-Huxley equations with parameters in Table 4.4 (from pyramidal cell model, see the next section), the threshold properties are: (1) For a voltage command, the threshold is $V_{\text{th}} = -50$, (2) for a sustained current injection its threshold value is $I_{\text{th},\infty} = 0.3$ nA and (3) $\Delta t = 0.5$ ms lasting current pulse has its threshold value $I_{\text{th}} = 10$nA. , see [Koch et al., 1995, 4.18].

1.3 Models of neurons

Example of a detailed model and its implementation

In the thesis we refer at several places to detailed models (**L5**, or neocortical pyramidal cell in **L**ayer **5**; **CA1**, or hippocampal pyramidal cell in a structure **C**ornu **A**mmonis **1**), which serve as workbenches for our numerical investigations. For example, the model L5 of a cortical pyramidal cell is based on morphometrical and electrophysiological data originally measured in the laboratory of R. Douglas, [Douglas et al., 1991, 4.9] [6]. The cable equation was solved by simulation packages GENESIS, [Bower and Beeman, 1995, 2], and NEURON, [Hines, 1989, 4.19]. Output data were post-processed by various software: free software GNUplot, Octave, and a commercial software Matlab, Lotus-1-2-3, and IslandDraw, [Kay et al., 1984]. As operating systems we used UNIX clones running on various hardware architectures (we used SunOS on SUN SparcStation, Linux on IBM PC pentium, HP-UX on HP series 730 machines, OSF1 on DEC alpha), [Minasi, 1992] [7]. In recent years we moved to Linux systems on both IBM PC pentiums, and on SUN SparcStations, [Alper, 1998].

Other than detailed models

The process of integrating excitatory and inhibitory postsynaptic potentials, (EPSPs and IPSPs), on a postsynaptic neuron cell is rather a complicated one and not yet known in detail. We can build models with equations simpler than equations 1.1, 1.3, 1.4 and 1.5, or conceptually different from it. In [Maršálek et al., 1997], here part 4, we use the **perfect integrator** model. An equivalent electrical circuit for this model is just a capacitor element, with the threshold mechanism. We can obtain the perfect integrator model from the set of equations 1.8, when omitting the "leak" term. The first equation in 1.8 becomes $V = \int_0^T (I(t)/C)dt$, from time $t = 0$ to time $t = T$. Equation 1.7 is simplified to $I(t) = af_{\text{syn}}(t - t_i)$, or even to $I(t) = a\delta(t - t_i)$, where a is the amplitude of PSP, t_i is the time of PSP arrival and δ is Dirac delta function. The perfect integrator model can be written in its discretized version, where V has to count n_{th} excitatory steps to reach the threshold V_{th}. This notation is used between equations 4.3 and 4.4. The computational use of this model is in defining appropriate synaptic input.

The randomness of a trajectory of V can be grasped when considering V as a random variable in **stochastic models**. In our first work in studying single cell models we tested a stochastic model of a phylogenetically simple neuron, the olfactory cell, [Maršálek, 1994b], here part 3. A bandpass random signal can be used in electrophysiological experiments, see for example [Mainen and Sejnowski, 1996, 2], where the bandpass white noise current is injected into the neuron. The appropriate mathematical model of this experimental

[6] This model was maintained and developed by several people in the software laboratory of C. Koch - Ö. Bernander, G. Holt, and F. Santamaría.

[7] Electronic computer is like a cathedral holding together by the hidden contribution of art and experience of thousands of engineers and masons. ... *ars longa* and there are in each generation heroes like N. Wiener, J. von Neuman, A. M. Turing, D. E. Knuth, N. Wirth, R. Stallman, L. Torvalds, and so on ...

situation uses a concept of random signals as random variables. This is a natural correspondence between stochastic models and experiments.

1.4 Biology of neurons

We have intentionally restricted sections on active and passive membrane properties to presenting a theory with its equations and with a minimal set of biological terms. They should be understood in the physical context and should not require understanding of underlying biological reality. In this section we will add the biological context to the emerging picture of neurons, following biological introductions from [Tuckwell, 1988, 2, vol.1] and [Amit, 1989].

Morphology

The basic functional elements of neural tissue are neurons [8]. In an optic microscope, when visualized by an appropriate staining, neurons look like trees and bushes. What concerns their connectivity, neurons with all their processes just resemble the wiring of some ancient electronic device where everything is connected by thin wires to everything. In the analogy we can describe parts of neurons as parts of wood. An ordinary tree consists of roots (1), stump part (2), stem (3), branches (4), and leaves (5); a typical neuron consists of dendrites (1), soma (or cell body)(2), axon (3), axonal branches (4), and axonal terminals (5). The signal processing in neuron proceeds in the same order, in which neuron parts were named here. In Figures 2.1 and 4.2 C, only dendrites are shown, because we investigated in our models dendritic processing. Dendrites (1) are attached to soma. Soma (2) contains the cell nucleus, governing all the cell's life. Another trunk-like structure, axon (3), different from dendrites, grows from the soma at the point distinguished in some cells as an axonal hillock. The axon branches and its branching (4) ends with axonal terminals (5). Under physiological conditions, various cell processes convey signals in determined directions. It is generally assumed that dendrites serve as input and processing devices, the axon is a fiber that transmits a signal to remote locations, ending with synaptic boutons (output devices) at the axonal arborization. This direction is called orthodromic in physiology, in contrast to the reverse, antidromic direction.

Connections between neurons are made by synapses. The fine structure of synapses can be seen under higher resolution, in an electron microscope. Synapses consist from presynaptic membrane, synaptic cleft, and postsynaptic membrane. Presynaptic membrane belongs to axonal terminals of the presynaptic cell. Postsynaptic membrane is a dendritic membrane of the postsynaptic cell, the target cell of the synapse. Axonal terminals, or synaptic boutons are spherical drumsticks made of presynaptic membrane, attached to the postsynaptic cell. They contain vesicles with a signal chemical, transmitter. At the synaptic bouton, the electrical signal is transduced into chemical, and then back to the electrical signal at a postsynaptic membrane again. At the postsynaptic membrane, transmitter binding causes depolarization and hyperpolarization, as was mentioned in the subsection on **neural elements**.

Electrophysiology

The living membrane separates two compartments, distinguished as the intracellular and extracellular spaces. Even a cellular membrane endowed only with voltage independent (thus passive) ion channels will be charged at rest because of concentration differences of ions inside and outside a membrane. These concentration differences exist because the electrochemical equilibrium is balanced by larger charged molecules which do not pass through the membrane. These molecules are mainly negatively charged intracellular proteins, therefore the voltage from inside to outside is negative at rest. Each ion species would charge

[8] There are other types of cells in neural tissue - supportive cells, named glial cells. They provide energy, mechanical support and electrical insulation for neurons. They are assumed not to be transmitting signals using action potentials.

membrane to a different voltage, if it alone were distributed across the membrane. The resulting membrane voltage is a net voltage combining effects of all ions. [9] The additional concentration differences are maintained by ion pumps, which are powered by universal cellular battery, adenosintriphosphate, ATP. Ion pumps add a small voltage change to the membrane voltage compared to its value without the pumps. Such resulting potential, measured at rest, is called resting potential. From the baseline of resting potential, membrane can be hyper- or depolarized, mainly by the action of synapses.

In the neuron, the synaptic depolarization signal flows in the direction from the dendrites through the soma, further through the axon to the synaptic boutons (terminals). The signal is then transmitted from one cell to another, and to the next cell, in a chain of cells, named neural pathway. There is an ongoing signal processing along the pathway. Let us look at one cycle of signal transmission from one cell to another and at the action potential generation.

We are beginning a description of the spike (pulse, action potential) transmission cycle at the axon. The axon functions as a pulse transmitting circuit. It can be in two possible states only. In a resting state it is ready to propagate a passing spike further. In a depolarization state it is just transmitting a spike. This spike has a uniform shape, duration, and propagation speed. It has the amplitude in tens of millivolts. The spike duration is about one millisecond, in smaller axonal fibers longer. After the spike there is a refractory period, lasting from one to several milliseconds. During the refractory period the axon is unable to transmit another spike. Therefore the frequency of transmitted spikes is bandlimited. At branching points the spike is replicated to both branches, see [Manor et al., 1991, 4.27].

As the spike reaches axon terminals, it causes transmitter vesicles to release their content into synaptic cleft. The diameter of area of contact of pre- and postsynaptic membrane ranges from 0.5 to 2 μm. The width of synaptic cleft measures fractions of μm. The distance and the time the transmitter has to diffuse before binding to postsynaptic membrane receptors is therefore negligible. The binding of transmitter causes ion channel opening or closing, or an intracellular response activating intracellular signaling system called second messenger. One of these three effects causes de-, or hyper-polarization, (EPSP, or IPSP), of postsynaptic membrane see equation 1.7.

The postsynaptic potential (PSP) spreads in a graded manner (compared to all-or-none axonal spike propagation). Thousands of PSPs are integrated in the dendritic tree. This integration is very probably a substrate of rich signal processing capabilities of single cells. The signal processing in dendrites is still poorly understood, see [Yuste and Tank, 1996, 2]. From both morphology and electrophysiology, predilecting sites for excitatory and inhibitory synapses are described. Excitatory synapses connect to the target cell usually with uniform, or similar to uniform densities along all the dendritic structures, frequently a specific input from a specific neural pathway is confined to a specific part of the dendritic tree. For example, a strong thalamic input from the thalamo-cortical neural pathway connects to pyramidal cells at their part laying in the layer 4 of neocortex. In general, inhibitory synapses have the highest spatial probability density of connection in the neighborhood of the soma.

Moreover, the soma is the place of the last stage of PSP processing in the single cell. With the respect to the sign of PSP change, PSPs are summed, integrated, added up. Their net potential yields the potential at the place decisive for the single cell response, at the axonal hillock, where the axon stems from the soma. In the electrophysiology, a concept of the voltage threshold was coined. If the net voltage at the hillock reaches the value of voltage threshold, an all-or-none event, the spike, is triggered. The rest of the excitation cycle proceeds, as described above. Once the spike is triggered, it travels from the hillock along the axon with an uniform shape and speed. The physiological direction of spike travel is centrifugal, sometimes called orthodromic. If the inhibition prevails and the net voltage does not reach the threshold, the cell remains silent.

The whole cycle from the time of spike emission at one (presynaptic) cell to the spike at the next

[9] After the death of the cell, all molecules start mix freely and the concentration differences disappear.

(postsynaptic) cell can take 1-2 ms. The longest pathway the spike has to travel in the brain itself is the cortico-cortical associative neural pathway. The maximal length of its fibers is not exceeding 10 cm. [10] Since the membrane of both the hillock and the axon is after-hyperpolarized (= after the spike), a refractory period follows the spike emission. It takes some time, typically one, or few ms, before the membrane is ready to emit another spike. This sets a maximal frequency of spike transmission rate to 1 kHz, or less. Various cells differ substantially in the maximal firing rate they can produce, from this 1 kHz down to the units of Hz. A typical maximal rate of all neurons investigated in this thesis is several hundreds of Hz.

Physiology of calcium ion

As important for the cell, as membrane voltage V, is intracellular concentration of **calcium ion (Ca^{2+})**. This value is considered to be another cellular signal integrating several functions of a single cell. According to accumulated experimental evidence, summarized for example in [Ghosh and Greenberg, 1995], neuronal activity can lead to marked increase in the concentration of intracellular calcium. Intracellular calcium then functions as an intracellular hormone (second messenger) that mediates a wide range of cellular responses. This hormone like action of calcium can lead to proteosynthesis, and other events occurring in a time range of tens of minutes. This time range is beyond the scope of this thesis. We have to think of it, however, when debating the physiological consequences of calcium signaling. Calcium binds to a protein named calmodulin and stimulates the activity of a variety of enzymes, including calcium calmodulin kinases and calcium sensitive adenylate cyclases. These enzymes transduce the calcium signal and effect short term biological responses, such as modifications of synaptic functions and longer lasting neuronal responses. The recordings of calcium levels is now possible with the same temporal and even higher spatial accuracy, compared to the accuracy of membrane potential measurement.

1.5 Current development in modeling neurons

RC-circuit was used in description of neuronal activity already by [Lapicque, 1907, 4.10]. There were two breakthroughs in the understanding of cell excitability, the first one using the voltage clamp technique by A.L. Hodgkin, A.F. Huxley with J.C. Eccles, [Hodgkin and Huxley, 1952], and the second one introduced by the patch clamp technique by B. Sakmann, [Stuart and Sakmann, 1994, 2], see further the section on **Experimental data** [11]. Since works of both of these groups introduced new methods, an amount of experimental data started to grow after major discoveries of both groups. Recently theoretical electrophysiology and biophysics of neurons are dividing from the experimental research, in analogy, as it happened with the theoretical and experimental physics at the beginning of the century.

A typical challenge to a theoretical biophysics in recent years is a wide variety of ion channels. A biotechnology available around year 2K brings to us cloning of ion channels from their genes as a standard technique. Ion channels are expressed in a frog oocytes and this way isolated for the investigation by the patch clamp technique. A reconstruction of a secondary and higher structure of ion channel protein molecules simulated in protein folding program connects the structure with the function of ion channels. Ion channels are depicted as tiny automata. As it is calculated in computer it leaves virtually fewer jobs for experiments. A detailed description of a single ion channel only contributes to the concept of how single cell functions and does not allow to explain a single cell behavior. The level of description has to move (from a channel to a cell) one level higher. And the question of a cell connected into the network moves us again one level higher.

[10] In the spinal cord this path can be as long as the spinal cord itself is, i.e. about 1 m.

[11] Both groups of A.L. Hodgkin, A.F. Huxley with J.C. Eccles in sixties, and a group of B. Sakmann in eighties, were awarded by Nobel prize for the development of the voltage clamp recording techniques.

A current boom of neural modeling studies in neuroscience is made possible by revolutionary development in scientific and technical computing. All the differential equations were already at hand for a long time. Numerical methods were tailored to fit compartmental modeling [Koch, 1999], together with the specialized software applications, [Bower and Beeman, 1995, 2], [Hines, 1989, 4.19]. Without the attempt to get completeness, we list seven groups working on the topics of single cell modeling here [12]. A group of L. Abbott, at the Brandeis University, works together with the experimental group, see for example [Abbott and Kepler, 1990]. J. Bower group is at the California Institute of Technology (Caltech), [Bower and Beeman, 1995, 2], where F. Santamaríis planing to submit his thesis next year, [Maršálek and Santamaría, 1998]. In a next building there is a C. Koch group, both groups are parts of the Computation and Neural Systems Program at Caltech. C. Koch, [Koch, 1999], maintains two theoretical groups, the informal labels to them could be the software and the hardware labs [13]. B. Mel, [Mel, 1993, 2], at the University of Southern California, is a former postdoctoral fellow of C. Koch. I. Segev group works at the Hebrew University, [Segev, 1992]. T. Sejnowski, at the Salk Institute, is maintaining the experimental laboratory together with the theoretical laboratory, see the review [Sejnowski et al., 1988], or a less technical and more ideological review [Churchland et al., 1990]. A group of K. Stratford and G. Major, with J. Jack [Jack et al., 1975], collects experimental data as well, at the Oxford University.

A monograph with several original results and a glossary of many recent achievements in the field is [Koch, 1999]. It came out just ten years after the paper [Sejnowski et al., 1988]. This paper from 1988, is a "Science" review. It can be called the inaugural address of computational neuroscience. Choosing several topics from the book [Koch, 1999] and finding them in retrospective in [Sejnowski et al., 1988], one can asses the distance that computational neuroscience reached in last ten years. The growth of experimental data available, even online, is enormous. The proceedings of the theory itself are much modest. Several classical problems mentioned in [Sejnowski et al., 1988] are staying to be a rich ground for a current research. For example, [Koch et al., 1996, 4.8] revisited the old problem of time constant in neurons. A part of a contemporary research is focused to phenomena newly described in experiments, for example the background synaptic input, [Bernander et al., 1991], [Rapp et al., 1996, 2], and the backpropagating spike train, [Migliore, 1996, 2]. For further and concluding comments we refer to the **Open problems** section. A review of single cell modeling is in [Segev, 1992]. For a special review on a dendritic function, see [Yuste and Tank, 1996, 2].

Further references to part 1

Modeling electrical membrane events in neurons is one subject of this thesis. Equations describing these events can be found in [Koch, 1999]. A collection of examples of programming and numerical solution of these equations is [Koch and Segev, 1998], or [Bower and Beeman, 1995, 2]. A quantitative description of neural circuits at the subcellular level can be found in [Shepherd, 1990]. A short review on computational models is [Sejnowski et al., 1988]. Methodical questions on the relation between models of neurons and experiment can be found in [Bower and Koch, 1992]. Physiological functions of human and primate neurons are described in [Kandel et al., 1991]. An introduction to physiology of nucleus laminaris in birds can be found in [Konishi, 1990]. The classical Hodgkin-Huxley equations were first presented in [Hodgkin and Huxley, 1952]. They are studied in detail in [Tuckwell, 1988, 2] and [Cronin, 1987]. This thesis was put together following examples of PhD theses by [Bernander, 1993] and [Boogaard, 1985]. A current Czech language review on the subjects studied in this thesis can be found in [Wünsch, 1998]. As an introduction to problems of contemporary neuroscience we recommend [Crick, 1994], which recently came out in a Czech translation, [Crick, 1997]. Further we may suggest two short news on recent advancements

[12] Compare to the footnote [7].

[13] At the "software" lab, part of this thesis was written under kind supervision of C. Koch, see **Acknowledgments**

in computing technology and in neuromorphic engineering, [Alper, 1998], [Watson, 1997]. In the following parts we address several specific questions of how neurons process information.

2 On Ca^{2+} influx to neurons

Introduction to the paper

In the paper [Maršálek and Santamaría, 1998], models described by the formalism of the Hodgkin-Huxley equations are used to approach the following problems from the physiology of neurons. It is known that synapses can strengthen or depress their $G_{\max}$ as a consequence of cell spiking activity. How can the signal of cell spiking reach postsynaptic sites the on dendritic membrane? How it is possible that an action potential originates in the soma? What are similarities among pyramidal cells in neocortex and hippocampus? To answer these questions we studied the effect of a backpropagating spike train on intra-cellular calcium dynamics. We used two models of pyramidal cells, a L5 from neocortex and a CA1 from hippocampus. Several experimental findings for apical dendrites were reproduced qualitatively in computer simulations. 1) The active backpropagation of action potentials to the apical dendrite, 2) the dynamics of intra-cellular calcium in the proximal part of the dendrite, 3) the accumulation of calcium along the apical trunk.

We found that 1) the backpropagation of trains of action potentials can be explained using only sodium and calcium channels along the apical dendrite; 2) the accumulation of calcium depends mainly on the diameter of the dendrite while the homogeneous distribution of calcium channels is sufficient for explaining various experimental observations; 3) the concentration of sodium and potassium channels modulates the efficiency of the backpropagating train; 4) The dynamics of the instantaneous calcium concentration is different in the proximal and in the distal part; 5) We have demonstrated in the model that all the phenomena observed in slices have a common denominator in the coupling of active, calcium and sodium channels in the dendritic tree. Our results unified in model different experimental protocols of stimulation and recording in brain slices. In this paper, morphological data, and biophysical data on ion channels were used. We attempted to maintain a complete description of all the parameters and the computation procedures in order to make our results reproducible. The last goal was to unify our approach to pyramidal cells in both major cortical structures in mammals, in neocortex and in hippocampus.

3 Two-point model

Introduction to the paper

The paper [Maršálek, 1994b] is our first work in the field of modeling neurons. It is more theoretical than later papers. In the choice of topic, the influence of [Lansky and Rospars, 1993, 3] can be clearly recognized. In this work we have tested several tools, which we employed later on. It contains a lot of material and tools, used by [Rospars and Lansky, 1993, 3] in their long term collaboration. This work was inspired by recordings of the activity of olfactory cells in frogs. We did not use these data directly, however. Yet from that time we are trying to relate our modeling effort to physiological recordings.

What we found interesting in connection to the rest of this thesis is Fig. 1, in this part 3. This figure shows a relationship, known elsewhere as the F-I curve [Koch, 1999]. The F-I curve is a dependence of cell firing frequency F (frequency of action potentials) on sustained (DC) input current I. In the original set of the Hodgkin-Huxley equations, this curve is discontinuous. When considering DC current input as one parameter to the Hodgkin-Huxley equations, the discontinuity is a Hopf bifurcation type, [Cronin, 1987], [Koch, 1999]. When other slower ion channels are added to the original set of equations, the F-I curve becomes continuous again, as can be seen in the example of L5 model.

Channel activation and inactivation can be described by chemical kinetics. Recently this approach is used by [Schneidman et al., 1998]. They decompose the Hodgkin-Huxley equations by adding kinetic equations for ion channels. They use this approach to address the issue of spike timing in single cell. [14] In their work there is a straightforward correspondence between a kinetic description of ion channel activation and the Hodgkin-Huxley equations.

The derivation of Michaelis-Menten kinetics from more detailed kinetic equations is another example of this type of calculation. Such a calculation is shown for example in [Murray, 1990, 3]. We find Michaelis-Menten kinetics important, because it is general and simple enough. It can be applied to events where small molecules, like ions, or neuromediators, interact with much larger molecules, like protein receptors. Using equations like (3.12), we can reach the biophysically (or biochemically) relevant level of description of a physiological event, binding of the odorant to receptors on the olfactory cell.

[14] They cite our spike timing paper, [Maršálek et al., 1997].

4 On I/O jitter in neurons

Introduction to the paper

A detailed model with L5 morphology in the paper [Maršálek et al., 1997] is the most complicated set of the Hodgkin-Huxley equations used in this thesis. Methodical questions are in the paper rather suppressed but we will discuss them here. Appropriate numbers can be found in [Koch et al., 1995, C 18], or are discussed in detail in [Bernander, 1993]. We list them in the table below.

Table 4.4: Parameters of the Hodgkin-Huxley equations used in L5 model

		Na	Na	NaP	Ca	DR	AHP	AR	AR	K	A	A
constant	units	m^2	h	m^2	m^2	m^2	m^2	h_1	h_2	m	m^2	h
$V_{j,\mathrm{half}}$	mV	-40	-45	-40	-25	-40	NA	-82	-82	-55	-65	-60
K_j	mV	-3	3	-7	-4	-3	NA	7	7	-10	-2	4
τ_j	ms	0.05	0.5	2	2	2	2	40	300	20	20	100
G_{ion}	nS	200	200	1	0.6	120	45	1	1	0.6	1	1

Names of ion currents: m are activation, and h inactivation variables of ion channels. Na and DR are spiking mechanism channels, sodium, and Delayed Rectifier potassium currents. NaP is sodium Persistent, Ca is calcium current, AHP is potassium AfterHyperPolarization current, AR stands for potassium and sodium Anomalous Rectifier current, K is potassium M- current and A is potassium A- current. For completeness we will add from [Koch et al., 1995, 4.18] some more notes. Ion currents are used as in the Hodgkin-Huxley set 1.5 and in particle equations (those with dj/dt) in place of j are used all abovementioned currents with exponents as in the Table 4.4 and with following adjustments. Opening of channel described by m_{AHP} is dependent on intracellular calcium concentration $[\mathrm{Ca}^{2+}]_i$, instead of V. AHP Activating curve is written like $m_\infty = [\mathrm{Ca}^{2+}]_i/([\mathrm{Ca}^{2+}]_i + 4\times 10^{-5})$, $[\mathrm{Ca}^{2+}]_i$ measured in mols. Calcium influx is given by a current named here Ca. Calcium extrusion is given by equation (2.6) with $\tau_{\mathrm{Ca}} = 50$ ms in simulations in this part 4. For the two currents in Anomalous Rectifier, the appropriate term in principal equation is written: $G_{\mathrm{AR}}(0.8h_1 + 0.2h_2)(V_{\mathrm{AR}} - V)$, and the reversal potential V_{AR} is set to -50 mV. Rest of V_{ion} potentials are as in Table 1.2 and the leak conductance is $G_L = 1$nS.

The majority of these so called adaptation currents do not influence our results. Our results are dependent on eliciting single spikes and not on the mean firing frequency of the cell. Using a simplified morphology, as used for example by [Migliore, 1996, 2], should give similar results. A simplified set of ion currents, as used in part 2, would probably yield similar results, as well.

5 Discussion

Abstract of part 5

Since the work presented in the thesis is a theoretical work, the discussion of experiments as sources of data was postponed into the closing part. Unlike in the classical physics, many experimental approaches to the measurement of a single biophysical value are yielding different results. The origin of such differences is in the control of experimental conditions influencing the measurement. The better control of experimental conditions is allowed in recordings *in vitro*, mainly in brain slices, yet the conditions are less natural, compared to the *in vivo* recordings. *In vivo* recordings can be made either in the anesthetized, or even in the awake animal with chronically implanted recording and/or stimulating electrodes. Recording and stimulation can be extracellular and intracellular. Examples of all abovementioned techniques together with the procedure of obtaining the cell morphology are given in the closing part of the thesis. Results in computational models are discussed from the unifying point of view. Finally a list of selected open problems is given.

We presented several models of electrical activity of single neurons here. They made together three special parts, which followed after a general introduction, part 1. They are not ordered chronologically, in the order that they were built and published. Their ordering here reflects rather a succession from the use of more straightforward computation techniques to more complicated ones. In part 2, a study of calcium influx to neurons, we used neuronal morphologies and biophysical parameters. A relatively simple method, constructing a detailed model, led us to reproduce experimental results from measurements in single cells. In part 3, in a two-point model neuron simulation, the relationship to experiment results was looser. Our main results described a stochastic mathematical model itself. In part 4, on I/O jitter in neurons, both of the abovementioned methods, detailed and stochastic models, were used. As a result, a high speed of signal processing in a neocortical neuron was demonstrated. All models presented here react to experiments and are attempting to reproduce or predict the results of experiments. As mass storage technology develops with an astonishing speed, it is easier than ever to have access to experimental data. But the time of division of labor between theory and experiment has yet to come into the field of neuroscience. In the mean time we process data from experiments. When some of the quantities can be measured, it is important to discuss how they can be measured and what values they really have. Therefore we start the discussion with the section on experimental data.

5.1 Experimental data used in models

We will start with a **brain slices** recording. Brain slices are prepared on special devices, microtomes, vibratomes. Brain slice thickness ranges from 70 to 400 μm, [Kandel et al., 1991]. In the slice preparation, neurons can be directly visualized by intracellular injection of indicator dye usable in living cells, for example "Lucifer yellow". A functional cell type can be sometimes identified using its shape, **the morphology**, shown by the dye. The cell can be filled by horse radish peroxidase (HRP) after the recordings are made. HRP is transported by the intracellular transportation system. When a fixed preparation of the slice is made, cell parts are colored by the reaction of HRP and can be scanned using methods of optical microscopy. Optical scans can be used for computer aided reconstruction of a cell's 3D morphology. Our morphological data were collected using these techniques on L5, [Douglas et al., 1991, 4.9], and on CA1, [Wathey et al., 1992, 2]. From these reconstructions we got diameters d and lengths l (as below equation 1.3) for our compartmental models. Two photon laser scanning microscopy enables to visualize even finer details of living cell morphology, see below.

Let us return for a moment to Tables 1.3 and 4.4. They list values for equations 1.5 and 2.1. These values were measured in brain slices by the patch clamp technique. The patch clamp technique is a miniature version of a classical **voltage clamp** experiment developed by [Hodgkin and Huxley, 1952]. Both methods allow V to be kept at a fixed value and to measure the opening and closing of ion channels in dependence on V. The classical voltage clamp used intracellular, and extracellular wire electrodes. Using a feedback system of amplifiers, the current flowing through the membrane was injected back to the system, keeping fixed V. Repeating the experiment for different values of V gives the fraction of opened channels. These fractions are the activation and inactivation variables j from equation 1.5 and tables 1.3 and 4.4. A fit of these data to Boltzmann curves, described by parameters $V_{j,half}$ and K_j, can be made. From the time of reaching the steady state, τ_j can be inferred. In cells of higher animals, much smaller than squid giant axon, all the abovementioned parameters can be measured by the **patch clamp** technique. In such a preparation, a patch clamp pipette isolates a patch of membrane and enables measurement of transmembrane potential from inside to the outside of a pipette. With amplifiers sensitive enough, individual ion channels, which are trapped in the patch, can be measured. From the count of channel opening and closing pulses, a proportion of channels opened under a given transmembrane voltage V can be inferred. In brain slices from different brain regions, $V_{j,half}$, K_j, and τ_j can be measured on individual channels, using this patch clamp technique.

Various ion channels can be included or excluded in patch clamp experiments using drugs acting as **channel blockers**, or by changing the ionic composition of cellular fluids. Membrane currents and their appropriate ion channels are usually identified using specific blockers of these channels. Fish poison tetrodotoxin (TTX) blocks sodium channels responsible for action potentials. Tetraethylammonium chloride (TEA) blocks a potassium current, the second ion current in the classical Hodgkin-Huxley equations. To block some types of potassium channels, α-dendrotoxin (DTX) can be used. Changing the ionic composition of the intra- and extra-cellular fluid changes the contribution of individual ions. Even non-physiological ions, like cadmium (Cd^{2+}) can be introduced into cellular fluids. Cadmium, administered as cadmium chloride, $CdCl_2$, competes with calcium. Conductances (g_{ion} in the general version of the Hodgkin-Huxley equations, see equations 2.1) reflect both the contribution of a given ion species to the potential, and the density of ion channels per membrane area.

As ions in neurons are tracked in smaller and smaller amounts, they can be visualized using **optical** methods in living tissue. Calcium influx into cells can be visualized using the fluorescent dye, "fura-2". Dyes sensitive to several other ions are available. Two photon laser scanning microscopy enables simultaneous recording of intracellular calcium changes with detail as small as one dendritic spine (less than 1 μm), within a 125 μs time window and together with an intracellular electrode V recording at the same time. [Svoboda et al., 1997, 2] were able to record these values not only in slices, but in anesthetized rats. In [Maršálek and Santamaría, 1998] we modeled events which are recorded by this technique.

From these local signals, a net signal can be constructed. One signal characterizing global cell activity, can be the net intracellular calcium accumulation. Another global signal can be V at the axonal hillock, [Mainen et al., 1995, 2], where the action potential is generated. **Recording** a train of individual action potentials, or spikes, can be made using **intracellular**, or **extracellular** electrodes. Intracellular recordings have lower noise, and about a decade or two higher voltage amplitude compared to extracellular recordings. However intracellular recording destroys the cell and does not last too long. It is more difficult to pick a cell using an intracellular electrode. For extracellular recordings it is enough to put the electrode tip close to the recorded cell. Both intra, and extracellular recordings can be used in both preparations, in slices, or in a whole animal. For examples of extracellular *in vivo* recordings visit [Bair and Newsome, 1996] and see [Bair and Koch, 1996, 4.1], or [Bair et al., 1994, 4.2]. Or see [Maunsell and Gibson, 1992, 4.4], their data from macaque monkey are shown in this thesis in Fig. 4.1.

Slice recording is performed *in vitro*. [15] *In vitro* experimental techniques are the most immediate

[15] *In vitro* means in a dish. *In vivo* means in a living animal.

counterpart to the theoretical work presented here. The isolated individual neurons in brain slices are not under the synaptic barrage, compared to *in vivo* conditions. The elimination of as many poorly defined factors as possible is crucial for all experiments. This fact is generally acknowledged among physicists. Surprisingly, in the field of neurophysiology, brain slice recording is frequently criticized. One standpoint of such a critic is that a neuron firing in a slice does not reflect any "reasonable" cell activity. Then the modeling approach, as an anecdote termed *in computo*, [Bower and Beeman 1995, 2], can bridge the differences between responses of cells *in vivo* and *in vitro*. To make results from *in vivo* and *in vitro* experiments comparable, one has to model all the inputs which are assumed to supply a cell connected to a network of other cells *in vivo* and which are in brain slices disconnected. There is an experimental approach to the comparison of results *in vivo* and *in vitro*: one has to redo experiments as similar as possible under these two setups. Let us give one example of such an experiment: [Svoboda et al., 1997, 2], discussed here in part 2.

There is a final question closing this subsection on experiments. This is a question of extrapolating lower animal, even primate data, to humans. Experiments on humans are limited by strict ethical considerations. There is one advantage, however. Compared to animals, on humans one can use a conscious response of an experimental subject. The experimental approach relying on a subjective (behavioral) response is called psychophysics. What is psychophysics? Psychophysics is a part of sensory physiology, dealing with the quantitative relation between stimulus and sensation [Schmidt, 1978]. Why is psychophysics important? Because psychophysics bridges many levels of description. See the following subsection on I/O jitter discussion for an example of how psychophysical results can be compared to results obtained in single cell recording.

For a recent and general introduction to methods and questions of neuroscience in general, not only of cognitive theories, see [Crick, 1994], or its Czech version, [Crick, 1997].

5.2 Computational models

The goal of the theory - describing biophysical phenomena by sets of equations - is sometimes not the ultimate result. Another power of biophysical models is seen in the numerical simulations, reproducing experiments. The choice of model parameters is based on experimental data. These data are collected throughout the experimental literature and are contradictory, sometimes. There is usually a trade off between the known cellular complexities and simplifications in order to make the numerical solutions robust. Models cannot reproduce all the known data. Some subset of the observed phenomena is chosen as a skeleton for the model. Then some tests are run. Finally, questions known as open problems from the literature are asked. To predict the results of some future experiments is really the ultimate goal of biophysical models. However, even an agreement with experiments which are not used for fitting the data used as an input to the model is very important. This shows a proof of the concept of a current theoretical explanation of a single cell's physiology.

The passive propagation of membrane depolarization is governed by the same equation, as diffusion of ions. The diffusion equation and the cable equation are two versions of one common parabolic equation. With variables and parameters renamed, this equation is called the one dimensional heat conduction equation [Rektorys, 1969, 4.13]. One space dimension, x, is natural here. The analogy of the cable and diffusion equations can be extended one step further. Branched cable for the potential conducted by the cable is the same structure, as the cable tubing for diffusible ions. All the appropriate equations and their analogies, are developed in [Zador and Koch, 1994], focused on the intracellular calcium diffusion in neurons.

Ca^{2+} influx to neurons

Our modeling study [Maršálek and Santamaría, 1998] attempted to unify some of recent experimental results related to backpropagating dendritic action potentials and Ca^{2+} entry. We were inspired by the recent and popular experimental findings of [Helmchen et al., 1996, 2], and [Svoboda et al., 1997, 2]. We investigated the attenuation of a train of action potentials, which we did not include in the final manuscript. Independently, [Migliore, 1996, 2] described the attenuation mechanism in a more realistic way. He predicted the presence of a sodium channel with a slower inactivation, which indeed was later found in experiment of [Jung et al., 1997]. He further suggested the role of potassium channel regulation. This role was experimentally demonstrated by [Hoffman et al., 1997, 2].

The most difficult part in designing the model was the choice of parameters - channel densities and activation curves. Even when these numbers passed a peer review process, this does not mean that they fit all experimental conditions. We refer here to the abovementioned example of model of [Migliore, 1996, 2]. Following his predictions, experiments revealed finer structure of various channel densities along the dendritic tree in hippocampal pyramidal cells. Knowledge of all the particular numbers develops quickly. Yet some basic facts do not change. From the speed of spike propagation along the axon the higher density of sodium channels in axon compared to the rest of the cell can be inferred. Depolarizing sodium current and repolarizing potassium current maintain the shape of an action potential. Calcium influx is caused by the action potential wave opening voltage activated calcium channels. Considering these basic facts without any quantitative consideration, some nontrivial questions can be asked anyway. For example: Is there a saturation of level of accumulated calcium.

There are a long series of simplified, and more detailed, models of calcium accumulation in neurons. Some include calcium diffusion. Diffusion of ions in cells is of several orders slower than the action potential propagation. Calcium diffusion was thoroughly discussed in the literature anyway. There are dendritic spines, where the effect of longer path for the calcium to diffuse may be considered. In our work, we studied intracellular calcium rise without considering synaptic events, therefore calcium diffusion in our models can be neglected. It is generally assumed that diffusion of sodium and potassium ions does not influence events associated with action potentials. Diffusion of all ions involved can be neglected then.

Stochastic models of neurons

Sometimes it is appropriate to think of a stochastic nature of dendritic membrane voltage. First, there are many synaptic events (or receptor interactions in the example of the olfactory cell). Second, they cause PSPs with some jitter in time. Third, the exact spatial structure of these events is not known, or is not relevant. Thus we have some dispersion of many inputs to neuron in both time and space. It is useful to look at them from a statistical perspective. In order to make the trajectory of the dendritic signal more tractable, diffusion approximation of the dendritic signal is used, [Tuckwell, 1988, 2]. Throughout this thesis we used some of results of the theory of random processes like an user picking them up for applied calculations. All technical details and journal references can be found in our primary source, [Tuckwell, 1988, 2].

The parameter space of statistical models is usually not as complex, as is the parameter space of detailed models. Statistical models consider a spatial variable from some biophysical problem rarely. From the point of view of numerical simulation, it is hard to simulate them, compared to the Hodgkin-Huxley equations. The leaky integrator model, used in parts 2, and 4, can be regarded as a simplified ancestor to both the Hodgkin-Huxley equations, and to the stochastic equations. The analytically rigorous reduction of the Hodgkin-Huxley equations to the leaky integrator model can be found in [Abbott and Kepler, 1990]. We presented some more calculations with the two-point stochastic model on a poster at the meeting of the Czech Neuroscience Society, [Maršálek, 1994a]. Particularly, the relation to the Hodgkin-Huxley equations was discussed. For further reading on comparison of the classical Hodgkin-Huxley equations to their

reduced and stochastic versions see [Schneidman et al., 1998] and [Abbott and Kepler, 1990].

I/O jitter in neurons

In the paper [Maršálek et al., 1997] we tried to derive some analytical estimate for the expression of timing variance in a leaky integrator model. In the first published report on this work, [Maršálek and Koch, 1996], we put a stress to the calculations with a stochastic model. In the next development of our solution to the problem, we have got some formula for the jitter level, but we were unable to prove that the formula is correct. Finally we solved this problem as follows: For a leaky integrator model we simulated it, and this way we got some putative result of the formula numerically. Then we derived the formula for a special case of a leaky integrator, perfect integrator, analytically, where we got comparable result. In current works of [Elston and Bulsara, 1997] and [Kempter et al., 1998], it can be seen that the analytical treatment of the leaky integrator model is still a rich source of open problems. Later on, following our paper, [Feng, 1997] has shown some particular results on the way towards obtaining some analytical estimate. He has found several solutions to the special case, the perfect integrator model, in the study of extremes of random processes. He substituted appropriate values to the formulas found in a theory of random processes. He arrived to the same numbers as we did with our numerical simulations. This way he has shown by independent calculations that our numerical results in simplified model are correct.

At this point we want to stress that our debate of event timing in cortical cells is restricted to single cell events. It is possible that other mechanisms that keep spike timing are involved as well. Two examples: first, cortical cells may be synchronized by the oscillatory activity, or by the other than principal inputs. They can be synchronized by the nonspecific input from the nuclei of reticular formation. Second, the timing can be preserved by the feedback cortico-cortical connections that have different conduction velocity than the principal feed-forward connections.

Let us comment now the range of biophysical parameters we use. It appears that different results are obtained when varying biophysical parameters of the cable equation. One example for all - the time constant, $\tau = R_m C_m$, [Koch et al., 1996, 4.8], dependent on membrane capacitance C_m, and membrane resistance R_m. Membrane capacitance C_m of the lipid bilayer membrane should be uniform in the particular clone of neural cells. What can vary dramatically is membrane resistance, R_m. Net cell resistance is dependent on both net resistance of the voltage dependent membrane channels and on resistance of the synaptically driven channels. Thus changing the principal input, or the neuromodulatory input to cells can change the solution of the corresponding set of equations dramatically, [Bernander et al., 1991]. Further, the use of detailed morphologies raises methodical questions of reproducibility of results. At a small database of 3D reconstructions of cells, we have a couple of cells at our hand. Our detailed simulation usually works with some three to four different cells, [Bernander, 1993]. Is it sufficient to present results obtained at one particular morphology? At this point, however, the positive answer is more straightforward. Sometimes, biological results are demonstrated on a small set of experiments only. It is left for a scientific community as a homework to reproduce them and to increase this way the number of experimental samples. The models are more advantageous. As all parameters used are either published, or available at request together with cell morphologies, and source codes, simulations can be reproduced quite efficiently. In fact we started our work on the paper [Maršálek and Santamaría, 1998] with reproducing results of [Mainen et al., 1995, 2].

In the subsection of the methods we listed psychophysics at the very end among the methods. Very similar psychophysical experiments can be used in both monkeys and humans. In monkeys they are called behavioral tests. They can be done together with simultaneous electrode recording from the brain. In humans, a *less invasive* recording method, like **EEG** (Electro-EncephaloGraphy) can be used together with the psychophysical experiment. We give here an example of such a psychophysical experiment with electric potential recordings. [Thorpe et al., 1996] recorded behavioral, and EEG responses in human paid volunteers to the "rapid serial visual presentation task". Their results support the concept of cortical processing, originally

formulated by [Abeles, 1990, 4.6]. Abeles based his theory on recordings from monkey frontal and auditory cortices. We mention it here as an alternative approach to the description of the fast feedforward spread of a visual signal in cortical projection areas, which was a motivation for the paper [Maršálek et al., 1997]. At the same time, when we were processing data from J.H.R. Maunsell, [deCharms and Merzenich, 1996] found similar rises of activity in the auditory cortex of the marmoset monkey. We can generalize these observations to the proposal that the fast processing of some cortical signal may occur in all stages and different projection systems in the neocortex.

Open problems

The motivating goal for investigating our neuronal models is clear: to understand how signal processing, or computation, is accomplished at the level of single cell. The single cell can be isolated in experiments by several ways. The cells can grow in a tissue culture. Or the cells can be kept alive for some time in a cerebrospinal fluid like liquid in a brain slice. Or various inputs to the cell can be knocked out by applying drugs into brain tissue of otherwise intact, maybe anesthetized animals. The electric stimulation can be delivered to the cell. All these experimental techniques record intra- or extracellular electrical signals in isolated cells. In all of these preparations, the input to the cell is made somewhat simpler, compared to the *in vivo* situation. The output, usually action potentials, can be measured with a limited precision. In models we are trying to design more interesting inputs, which are still far from the simplest experimental reality. We can enjoy *ad libitum* precision of computations of outputs, compared to experiments.

We can hardly make inputs more realistic, because we do not know, how the higher functional units, neural circuits, compute their outputs, whatever they compute. They compute, indeed, for they process images, and sounds, and execute (motor) programs. We do not even know how this works in lower animals, for example in invertebrates, in flies. The majority of neurons in several favorite experimental fly species can be listed. Fly neurons are confined to their anatomical place and they have the name and they possess some hypothetical function. It ranges from the difficult to the impossible to describe how different subdivisions of fly brain work. It seems to us that choosing the right paradigm for deciding what is important in the single cell can really help in current neurophysiological research. Let us look at the closing chapter of [Koch, 1999]. In this closing chapter there are seven numbered strategic open questions. We will not list all these open questions here. We will reformulate two of them and show their context with the work presented here.

One of the questions can read like: What is the meaningful time and amplitude resolution in the single cell? In other words, how can we estimate information throughput in the single cell, what are the sources of noise and how the noise compromises signal processing at the single cell level? In the discussion of I/O jitter in neurons we have shown that single cells can operate very fast. The time constant of the whole cell, as the number obtained in measurements, probably does not have a value for an estimate how fast can voltage of some functional unit of membrane change [Koch et al., 1996, 4.8].

Surprisingly, one of these seven questions is quite special. What are all the functions of the apical dendrite in pyramidal cells? In our work on calcium accumulation in pyramidal cells, [Maršálek and Santamaría, 1998], we repeat a basic comment of [Helmchen et al., 1996, 2] that one of the phenomena observed in the apical dendrite is the firing frequency integration using the calcium signal. In [Ghosh and Greenberg, 1995] we can find that such a calcium signal can have more then ten functional consequences executed at a molecular level in the single cell.

Some phenomena which require longer time scales, like learning at the single cell level, were omitted in this thesis. We are aware of the fact that synapses are far more complicated than one-point devices described by the equation 1.7. Just compare experimental findings at single synapses to one-point one-value synaptic weights in learning algorithms in attractor neural networks. Clearly, the time of learning algorithms for neural networks multi-level in time domain has not come yet.

Further, there is no functional classification of neurons according to their morphologies. In constructing detailed models, we still do not know what features of cellular morphology of the cell are important and what are not. Some statistical distributions of different synapses along the dendritic tree are known. Specifically, the inhibitory synapses are usually located in the neighborhood of the soma, while the excitatory and modulatory synapses follow uniform, or anatomically predilected distributions. This issue is intimately connected to questions about the development of neuronal wiring. Neurons are guided during the development by the exact program for making connections. The aspect of development, as well as the aspect of synaptic plasticity, were not studied in this thesis.

Rereading the thesis now. It is like hearing some learned reader suggesting to change the title of the thesis to "Solving the Hodgkin-Huxley equations numerically". It is simply necessary to use these equations when calculating nonlinear neuronal membrane events. The Hodgkin-Huxley equations became the standard in the description of membrane voltage gated by the ion channels. From the fit to the limited number of experiments the Hodgkin-Huxley equations predict several physiological properties of the nerve fiber. At the activation and inactivation variables in equations 1.5 and 2.1 there are exponents which are the results of the best fit of the steady state curves in the voltage clamp experiments. It was shown later that these exponents correspond to the number of protein subunits which are necessary for proper ion channel function.

There is urgent need for some higher level standard neuronal models, maybe including the Hodgkin-Huxley equations. In [Shepherd, 1990] and in [Koch, 1999] there are some models called canonical models. Under the term canonical models we understand the models with some desired level of biophysical validity on one hand, and generality on the other. Canonical models should comprise only a representative selection of elements crucial for neuronal function. Similarly as for the more biological neural learning algorithms, the time for canonical single cell models has not come yet.

Concluding remarks

Numerical solving of equations with a lot of parameters like these used in the thesis is far from elegant. When comparing the state of our knowledge of neuronal coding to the state of the knowledge of coding in the DNA, the lack of preciseness in neuroscience is striking. Collecting biophysical properties of different neurons can be compared to collecting X-ray diffraction snapshots of nucleic acids in the times before the discovery of their double helix structure. It is possible that the time of discovery of the neuronal code is coming now, soon after the turn of the millennium. There are signs that, maybe, something interesting is going on. In individual experimental preparations, especially in lower animals, I/O function in the single cell can be reconstructed using signal processing techniques. The linear, and even the nonlinear kernels are reconstructed; after convolution of the input with them, the output is obtained. Signal reconstruction algorithms can unify the theory of information processing in the single neural cell by the same means, as the Hodgkin-Huxley equations did unify the theory of the action potential fifty years ago. Or the Hodgkin-Huxley equations may show to be the necessary prerequisite for generalizing signal reconstruction approach. Or maybe nothing from the above mentioned possibilities will happen and the solution to the neuronal coding problem will come out using different techniques. In any case, many unanswered questions are still tempting our curiosity.

Acknowledgments

Let me first thank the coauthors. Below, I pinpoint their individual roles and direct contributions to the thesis. Thanks to my advisor, P. Lánský. All the thesis with the exception of papers in parts 2 and 4 was written under his kind supervision. Thanks to F. Santamaría for an implementation of our model in part 2. In part 4, the division of labor was, briefly: P. Maršálek - computing, equations, figures, C. Koch - narrative, J. Maunsell - data. J. Maunsell, the only experimentalist among the coauthors, formulated a problem addressed in this part in a letter to C. Koch. Thanks to him and to all his collaborators for the animal recordings in part 4. Thanks to C. Koch for rewriting my dumb writings

in part 4 into clearly written and vivid communication. Special thanks belong to C. Koch for being *éminence grise* in directing my work presented in this thesis. I am indebted to him for all his support during my stay at the California Institute of Technology.

Thanks to all anonymous referees. Thanks to all my colleagues and teachers. It would be too long to list their efforts: giving professional and inspiring advice, making their own results available, spending time as members of exam committees, and especially reading, rereading and commenting on parts of this thesis... I am giving their incomplete list in alphabetical order below. Our huge brains work in such a way that they forget this and that time by time, yet they are also able to forgive. Those, whom I forgot, will sure forgive me. Thanks to M. Abeles, D.G. Amaral, P. Bělíček, Ö. Bernander, J. Beran, F. Bochníček, A. Borst, J.M. Bower, J. Bureš, V. Čápek, A. Drápal, K. Drbohlav, P. Erdi, A.A. Fenton, D. Flowers, J. Firth, B. Holcová, G.R. Holt, T. Hromádka, O. Jelínek, T. Kepka, D.T. Kewley, A. Křepinská, W.W. Lytton, P. Mareš, C.J. McAdams, Z. Mainen, M. Migliore, R. Murphy, D. Mumford, D. Obdržálek, J. Obdržálek, J. Plášek, J.-P. Rospars, I. Segev, D.K. Smetters, N. Spruston, M. Stemmler, J. Sýkora, O. Ulrych, and Z. Wünsch.

Thanks to my close family members. To acknowledge all their love and moral support I was given to finish all my studies is impossible. Thanks to them, for they accept me, regardless of how bizarre my occupation.

Thanks to several Institutions for their support: Grant Agency of the Charles University, for Grants number 182/1994, and 242/1995; National Institute for Mental Health for the support through the Center for Neuroscience Research at Caltech. Special thanks to the Faculty of Mathematics and Physics, Charles University.

References

[Abbott and Kepler, 1990] Abbott, L. F. and Kepler, T. B. (1990). Model neurons: from Hodgkin-Huxley to Hopfield. In Davids, L., editor, *Statistical Mechanics of Neural Networks*. Springer-Verlag.

[Alper, 1998] Alper, J. (1998). From army of hackers, an upstart operating system. *Science*, 282:1976–1979.

[Amit, 1989] Amit, D. J. (1989). *Modelling brain function, The world of attractor neural networks*. Cambridge University Press, New York, USA.

[Bair and Newsome, 1996] Bair, W. and Newsome, W. T. (1996). Checked: April 20, 1999.
See URL `http://www.cns.nyu.edu/home/wyeth/data/newsome/newsome.html`.

[Bernander, 1993] Bernander, Ö. (1993). *Synaptic Integration and its Control in Neocortical Pyramidal Cells*. PhD thesis, California Institute of Technology, URLs checked: April 20, 1999,
Available at `ftp://ftp.klab.caltech.edu/pub/ojvind/thesis-bernander.tar.Z`
Information at `http://www.klab.caltech.edu/~ojvind/pub.info.thesis.html`.

[Bernander et al., 1991] Bernander, Ö., Douglas, R., Martin, K., and Koch, C. (1991). Synaptic background activity determines spatio-temporal integration in single pyramidal cells. *Proc. Natl. Acad. Sci. USA*, 88:1569–1573.

[Boogaard, 1985] Boogaard, H. (1985). *Neural interaction equations*. PhD thesis, Catholic University of Nijmegen.

[Bower and Koch, 1992] Bower, J. M. and Koch, C. (1992). Experimentalists and modelers: can we just get along? *TINS*, 15. 458-461.

[Churchland et al., 1990] Churchland, P. S., Koch, C., and Sejnowski, T. J. (1990). What is computational neuroscience? In Schwartz, E. L., editor, *Computational Neuroscience*, pages 46–55. MIT Press.

[Crick, 1994] Crick, F. (1994). *The Astonishing Hypothesis. The Scientific Search for the Soul*. Simon and Schuster, London, UK.

[Crick, 1997] Crick, F. (1997). *Věda hledá duši*. Mladá fronta, Prague, CZ. Translated into Czech by František Koukolík.

[Cronin, 1987] Cronin, J. (1987). *Mathematical aspects of Hodgkin-Huxley neural theory*. Cambridge University Press, Cambridge, UK.

[deCharms and Merzenich, 1996] deCharms, R. C. and Merzenich, M. M. (1996). Primary cortical representation of sounds by the coordination of action-potential timing. *Nature*, 381:610–613.

[Elston and Bulsara, 1997] Elston, T. C. and Bulsara, A. R. (1997). First passage statistics of periodically driven models for neural dynamics. *BioSystems*, 40:37–43.

[Feng, 1997] Feng, J. (1997). Behaviors of spike output jitter in the integrate-and-fire model. *Physical Review Letters*, 79:4505–4508.

[Ghosh and Greenberg, 1995] Ghosh, A. and Greenberg, M. E. (1995). Calcium signaling in neurons: Molecular mechanisms and cellular consequences. *Science*, 256:239–247.

[Hodgkin and Huxley, 1952] Hodgkin, A. L. and Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve, *reprinted* in (1990) *Bulletin of Math. Biol.,* 52:25–71, originally published in 1952. *J. Physiol.*, 117:500–544.

[Jack et al., 1975] Jack, J. J. B., Noble, D., and Tsien, R. W., editors (1975). *Electric current flow in excitable cells*. Oxford University Press, Oxford, UK.

[Jung et al., 1997] Jung, H.-Y., Mickus, T., and Spruston, N. (1997). Prolonged sodium channel inactivation contributes to dendritic action potential attenuation in hippocampal pyramidal neurons. *Journal of Neuroscience*, 17:6639–6646.

[Kandel et al., 1991] Kandel, E. R., Schwartz, J. H., and Jessell, T. M., editors (1991). *Principles of neural science*. Prentice Hall Int., London, UK.

[Kay et al., 1984] Kay, A., Wirth, N., Tesler, L. G., Denning, P. J., Brown, R. L., Winograd, T., van Dam, A., Lesk, M., Spector, A. Z., Wolfram, S., and Lenat, D. B. (1984). Special issue on computer software. *Scientific American*, 251(3):40–160.

[Kempter et al., 1998] Kempter, R., Gerstner, W., and von Hemmen, J. L. (1998). How the threshold of a neuron determines its capacity for coincidence detection. *BioSystems*, 48:105–112.

[Koch, 1990] Koch, C. (1990). Biophysics of computation: Toward the mechanisms underlying information processing in single neurons. In Schwartz, E. L., editor, *Computational Neuroscience*, pages 97–113. MIT Press.

[Koch, 1999] Koch, C. (1999). *Biophysics of Computation: Information Processing in Single Neurons*. Oxford University Press, New York.

[Koch and Segev, 1998] Koch, C. and Segev, I., editors (1998). *Methods in Neuronal Modeling*. MIT Press, Cambridge, MA, USA.

[Konishi, 1990] Konishi, M. (1990). Similar algorithms in different sensory systems and animals. In *Cold Spring Harbor Symposia on Quantitative Biology*, pages 575–583. CSH Laboratory, New York.

[Maršálek, 1994a] Maršálek, P. (1994a). Application of the two-point stochastic neuronal model. In *Abstracts*, 1st Conference. Czech Neuroscience Society.

[Maršálek, 1994b] Maršálek, P. (1994b). A simulation approach to the two-point stochastic model of olfactory neurons. *Gen. Physiol. Biophys.*, 13:341–356.

[Maršálek and Koch, 1996] Maršálek, P. and Koch, C. (1996). Beyond the spontaneous activity - the application of stochastic model in neocortical cell. *Soc. Neuroscience Abstr.*, 22.

[Maršálek et al., 1997] Maršálek, P., Koch, C., and Maunsell, J. (1997). On the relationship between synaptic input and spike output jitter in individual neurons. *Proc. Natl. Acad. Sci. USA*, 94:735–740.

[Maršálek and Santamaría, 1998] Maršálek, P. and Santamaría, F. (1998). Investigating spike backpropagation induced Ca^{2+} influx in models of hippocampal and cortical pyramidal neurons. *BioSystems*, 48:147–156.

[Minasi, 1992] Minasi, M. (1992). *IBM PC, hardware*. Grada, Prague, CZ. Czech translation of an English original.

[Reyes et al., 1994] Reyes, A. D., Rubel, E. W., and Spain, W. J. (1994). Membrane-properties underlying the firing of neurons in the avian cochlear nucleus. *Journal of Neuroscience*, 14:5352–5364.

[Reyes et al., 1996] Reyes, A. D., Rubel, E. W., and Spain, W. J. (1996). In-vitro analysis of optimal stimuli for phase-locking and time-delayed modulation of firing in avian nucleus laminaris neurons. *Journal of Neuroscience*, 16:993–1007.

[Schmidt, 1978] Schmidt, R. F., editor (1978). *Fundamentals of Sensory Physiology*. Springer-Verlag, London, UK.

[Schneidman et al., 1998] Schneidman, E., Friedman, B., and Segev, I. (1998). Ion channel stochasticity may be critical in determining the reliability and precision of spike timing. *Neural Computation*, 10:1679–1704.

[Segev, 1992] Segev, I. (1992). Single neurone models: oversimple, complex, and reduced. *TINS*, 15:414–421.

[Sejnowski et al., 1988] Sejnowski, T. J., Koch, C., and Churchland, P. S. (1988). Computational neuroscience. *Science*, 241:1299–1306.

[Shepherd, 1990] Shepherd, G., editor (1990). *The synaptic organization of the brain, 2nd ed.* Oxford University Press, Oxford, UK.

[Thorpe et al., 1996] Thorpe, S., Fize, D., and Marlot, C. (1996). Speed of processing in the human visual system. *Nature*, 381:520–522.

[Watson, 1997] Watson, A. (1997). Why can't computer be more like a brain. *Science*, 277:1934–1936.

[Wünsch, 1998] Wünsch, Z. (1998). Dendrity, neurony a simulační modely. *Časopis lékařů českých*, 137:131–136.

[Zador and Koch, 1994] Zador, A. and Koch, C. (1994). Linearized models of calcium dynamics: Formal equivalence to the cable equation. *Journal of Neuroscience*, 14:4705–4715.