IL NUOVO CIMENTO Vol. 32 C, N. 1 Gennaio-Febbraio 2009
DOI 10.1393/ncc/i2009-10353-4

Colloquia: GCM8

# A three-dimensional model of a gap junction

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(ricevuto il 3 Aprile 2009; pubblicato online il 10 Luglio 2009)

**Summary.** — Gap junctions are effective electric couplings between neurons and form a very important way of communication between them. Since they can be considered as the points on the neuron's membrane on which for example dendrites of different cells become one piece, in three dimensions they can be modelled by observing this property in the created geometry. Thus they can be easily made part in an already existing 3-dimensional model for signal propagation on the neuron's membrane, if the geometries are chosen in such a way that they respect the blending of the membranes. A small network of two cells was created, which blend in their dendrites and a simulation of the three-dimensional model was carried out which reveals the fast transmission of the signal from one cell to the other.

PACS 87.16.A- – Theory, modeling, and simulations.
PACS 87.19.lb – Action potential propagation and axons.
PACS 87.19.lg – Synapses: chemical and electrical (gap junctions).

## 1. – Introduction

This paper introduces preliminary three-dimensional simulations of a small network between two cells which are coupled electrically by one *gap junction*. Our aim is to model a network of neurons by taking into account its full geometric properties, and to make simulations in order to examine how the extracellular potential and the three-dimensional extension of the neurons play a role in the procession of input signals. In this framework, our model provides a first approach. It is preliminary because the experimental evidence of its correctedness has still to be verified. However, we believe that it may provide qualitatively correct results.

A neuron is a nerve cell embedded in a substance called *neuroglia*. It can be understood as a system which serves as a building block of the nervous system. Although the neuron consists of different parts, we are interested in its cell body, its dendrites, and axons. While dendrites are ramified branches implanted in the cell body and serving as

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collectors of signals [1] from other neurons, there is one axon which juts from the cell body and conveys the cell's answer on input signals. Thus, the cell body receives all input signals from the dendrites and sums them up to "decide" whether to generate an output signal. This output signal travels along the axon, and reaches its end at which a synapse is formed. A synapse can be considered as a "device" forming at one end of the axon and pointing to another cell's dendrite. The synapse releases *neurotransmitter* after the signal has arrived. These neurotransmitters are chemical substances which cause a difference in the voltage at the dendrite's membrane of contact.

The signals are described electrically by the voltage which is built up on the membrane by means of ionic liquids filling the interior and the exterior of the neuron. This potential difference is often called *membrane potential*.

The neuron's membrane is an uncharged bilipid layer which separates these ionic liquids and can be thus regarded as a capacitor in an equivalent electric circuit model. These layers are infiltrated by proteins which serve as channels for the surrounding ions. The ions follow the electro-chemical gradient and thus build a potential difference across the membrane. In the situation in which the cell is not active this difference is around $-65\,\mathrm{mV}$. The cell is activated if the action potential is released. This happens if the membrane potential at the cell body exceeds a given threshold value, which is about $10\,\mathrm{mV}$ above the resting state. The triggering of an action potential is also often referred to as *firing* of the cell. In the generation of the action potential, two types of ion currents are basically involved, *i.e.* the sodium and potassium current. The latter one causes a decrease of the membrane potential, while the former causes an increase. If an initial increase of the membrane potential exceeds a certain threshold, more sodium channels open, so that the membrane voltage increases even more until it reaches a certain value at around $+40\,\mathrm{mV}$. At this value the sodium channels close again, the potassium channels open, and cause a decrease of the membrane potential. Since the sodium channels again open with some delay, the potential falls even below the resting potential before it goes over to its resting state. This mechanism governed by the time constants of the channels is described by the Hodgkin-Huxely model [2] which captures the dynamics of these currents mathematically by means of first-order differential equations of the following type:

$$\tau(V_m)\partial_t x = x_\infty - x, \tag{1}$$

where $x \in [0,1]$ determines the channel state, *i.e.* either open or closed, $V_m$ denotes the membrane potential, and $\tau(V_m)$ is a time constant which tells how fast a channel reaches its resting state, $x_\infty$.

While synapses described above account for a chemical mechanism of coupling between neurons, there are also electric couplings and these are effectively acheived by gap junctions. The most fundamental difference between these two couplings is that, in contrast to the chemical synapse, there is almost no delay in the signal transmission from one neuron to the other in the case of a gap junction. The gap junction can occur, for instance, between axons and axons as well as between dendrites and dendrites, and between axons and dendrites. The gap junction provides a direct coupling of two cells by means of channels which allow for a direct exchange of substances between two cells. The distance between the cells in the couplings is around $3\,\mathrm{nm}$. It is proposed that these couplings are responsible for fast synchronous oscillations within a network of neurons [3], and that these oscillations play a role in the detailed shaping of eliptogenic events [4].

The aim is to model the gap junctions in a three-dimensional already existing framework and to simulate the transmission of a signal through a gap junction.

## 2. – Model description and methods used for generating geometry

Inspired by the Hodgkin-Huxley model, which considered the neuron as a one-dimensional object, we developed a model [5] which incorporates the membrane's activity in three dimensions. Our model consists of the integro-differential equations written below, which were obtained by exploiting Maxwell's equations and the Hodgkin-Huxley model, *i.e.*

$$\int_B \operatorname{div}[\sigma \nabla \Phi] \mathrm{d}x = 0, \quad B \subset \Omega, \tag{2}$$

$$\int_\Gamma \left[ C \frac{\partial V_m}{\partial t} + j_{\mathrm{HH}} \right] \mathrm{d}S = \frac{1}{2} \left\{ \int_{\partial B_i \setminus \Gamma} \sigma \nabla \Phi_i \mathrm{d}S - \int_{\partial B_a \setminus \Gamma} \sigma \nabla \Phi_a \mathrm{d}S \right\}, \quad B \cap \Gamma \neq \emptyset, \tag{3}$$

subject to initial conditions

$$\begin{aligned} \Phi(x,0) &= \begin{cases} 0, & \forall\, x \in \partial\Omega_a \setminus \Gamma, \\ -65, & \forall\, x \in \Omega_i, \end{cases} \\ V_m(x,0) &= -65, \quad \forall\, x \in \Gamma, \end{aligned}$$

and boundary conditions

$$\Phi(x,t) = 0, \qquad \forall\, (x,t) \in \partial\Omega \times [0,\infty], \tag{4}$$

$$V_m(x,t) = \Phi_i(x,t) - \Phi_a(x,t), \quad \forall\, (x,t) \in \quad \Gamma \times [0,\infty]. \tag{5}$$

Here, $B \subset \Omega$ is a subset of the whole domain, $\Omega$, in which the neuron is embedded, and $\Gamma$ denotes the membrane of the neuron, which is treated as a two-dimensional manifold. We remark that all quantities in eqs. (2)–(5) are functions of space and time. In order to close the problem, the electric current $j_{\mathrm{HH}}$ is given through the Hodgkin-Huxley constitutive theory [2], *i.e.*

$$j_{\mathrm{HH}}(x,t) = \widehat{j}_{\mathrm{HH}}(V_m(x,t), n(x,t), m(x,t), h(x,t), t), \tag{6}$$

where functions $m$, $n$, and $h$ are the solutions of the following set of ordinary differential equations [REF]:

$$\frac{\mathrm{d}m(V_m(x,t),t)}{\mathrm{d}t} = \alpha_m(V_m(x,t))[1 - m(V_m(x,t),t)] - \beta_m(V_m(x,t))m(V_m(x,t),t), \tag{7}$$

$$\frac{\mathrm{d}h(V_m(x,t),t)}{\mathrm{d}t} = \alpha_h(V_m(x,t))[1 - h(V_m(x,t),t)] - \beta_h(V_m(x,t))h(V_m(x,t),t), \tag{8}$$

$$\frac{\mathrm{d}n(V_m(x,t),t)}{\mathrm{d}t} = \alpha_n(V_m(x,t))(1 - n(V_m(x,t),t)) - \beta_n(V_m(x,t))n(V_m(x,t),t), \tag{9}$$

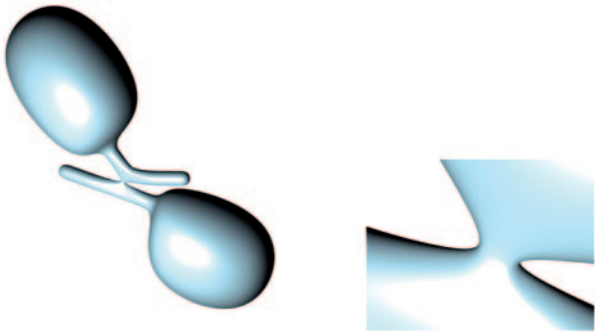

Fig. 1. – The left picture shows the geometry which represents two cells connected with a gap junction and created with Blender. The right zooms the gap junction of the geometry.

with initial conditions

$$m(V_m(x,0),0) = m(-65,0) = 0.052932485, \tag{10}$$

$$h(V_m(x,0),0) = h(-65,0) = 0.59120753, \tag{11}$$

$$n(V_m(x,0),0) = n(-65,0) = 0.317676914. \tag{12}$$

We notice that initial conditions (10)–(12) define the resting states of the variables $(\Phi, V_m, n, m, h)$.

The geometry (fig. 1) on which the simulation was carried out was created with Blender [6] and then adapted to the requirements of the simulation software uG [7]. Finally the software visit [8] was used in order to visualize the solution. The units of measure for the geometry are cm.

## 3. – Results

After one cell has been activated by means of a constant current applied over the period of 1 ms, it is possible to observe that the signal passes almost "instantaneously" to the cell body of the same neuron, as well as to the neighbouring one (fig. 2). In figs. 3, 4, which show recordings of both cell bodies, respectively, this fast transmission is visible. These figures show the time course of the membrane potential at a point of the membrane of the left and right cell body, respectively. It is possible to note that the maximum of the action potential was almost "instantanously" reached in both figures.

## 4. – Discussion

The main goal of this paper was to provide a three-dimensional model of a gap junction, which might be used for more complex systems of neurons building a realistic network. In order to do that, we firstly developed a model capable of describing the signal trasmission in a neuron of arbitrarily complicated geometry, and secondly we adapted our model to the case in which a gap junction between two neurons is present. We believe that our results provide a basis for studying, with a sufficient accuracy, the effect that the geometrical properties of a neuron, the presence of gap junctions among neurons, and the behaviour of the outer space potential have on the signal procession within a neuron network.

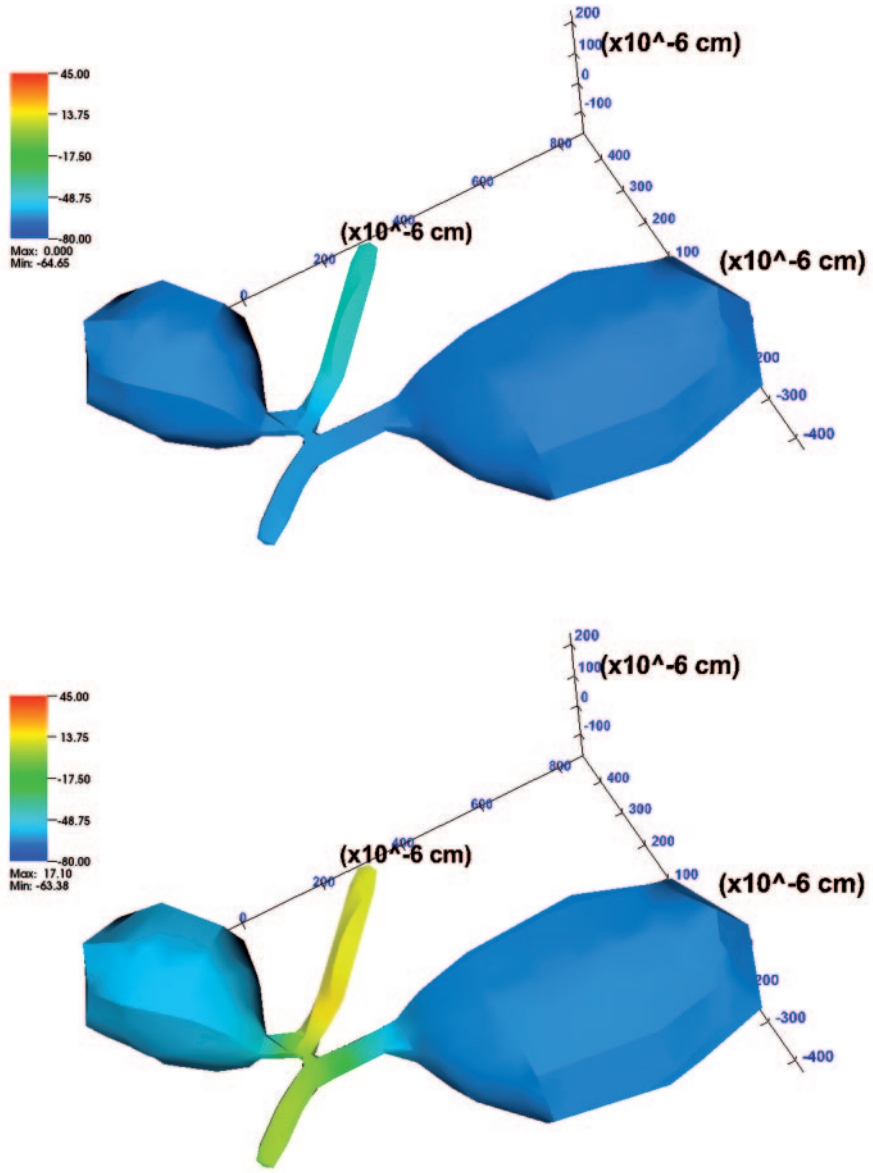


Fig. 2. – Excitation of a network and spread of the action potential in the presence of a gap junction. The time course with spacial dependence is recorded. A synchrony of activation is seen. The whole simulation represented 7.9 ms.

Our next steps towards the mathematical modelling of the neuron physiology are: i) the inclusion of chemical synapses, ii) the description of the effect of the myelin sheat, and iii) the use of a more realistic distribution of the sodium channels present in the neuron membrane. Indeed, sodium channels are not uniformly distributed on the neuron membrane, and feature higher density regions (for example, the area where an axon

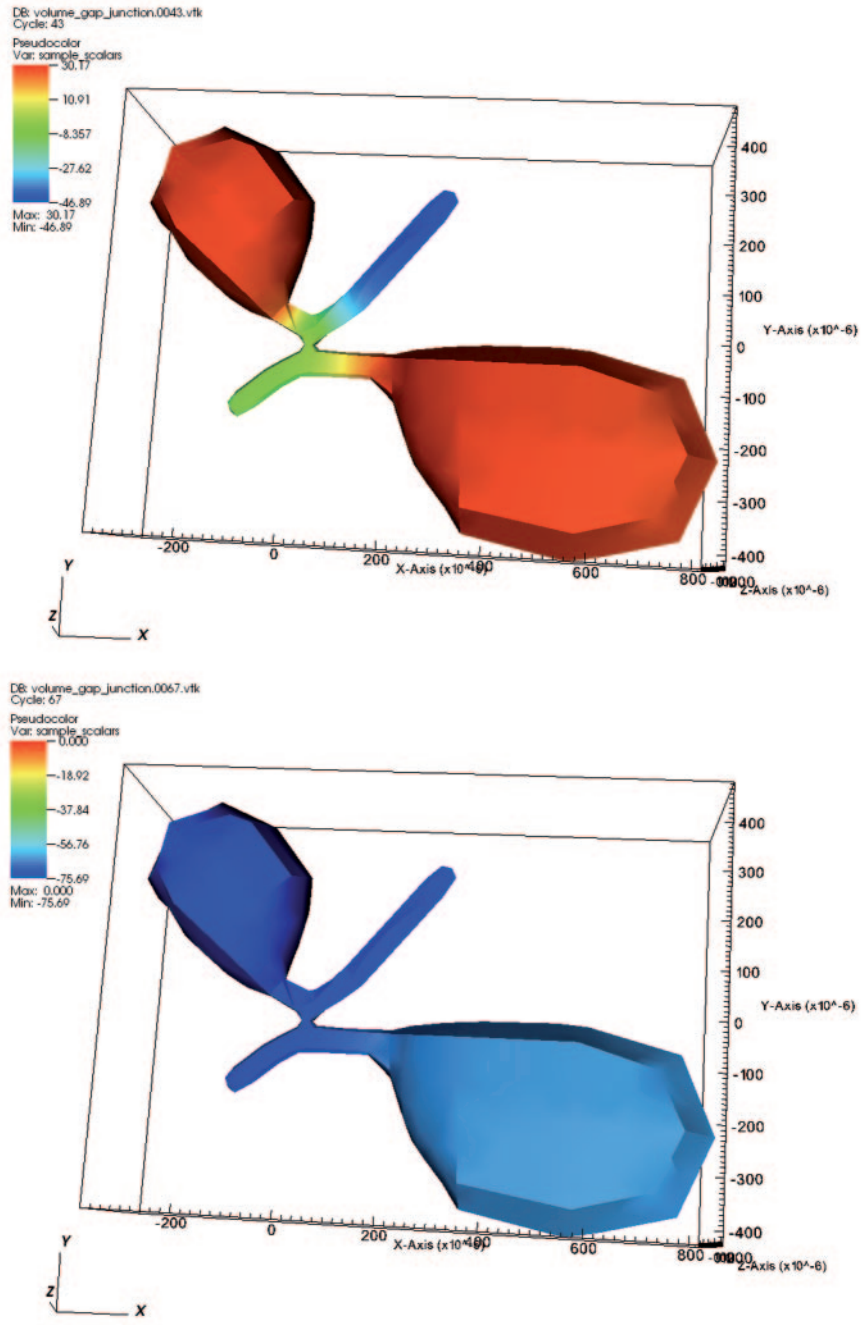


Fig. 2. – (*Continued.*)

origins, called Axon Hillock).

Simulating a small network of neurons and their connections already represents a difficult task. We hope that the approach presented in our paper may be considered a

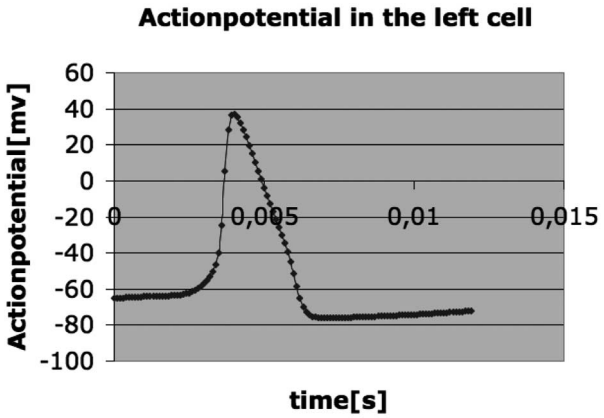


Fig. 3. – Action potential recorded on the membrane of the left cell.

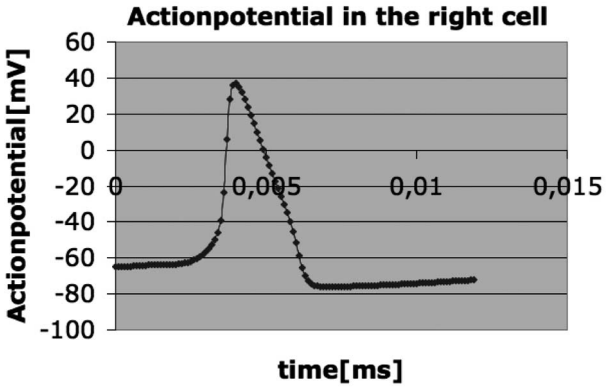


Fig. 4. – Action potential recorded on the membrane of the right cell. This graph is very similar to the time course of the action potential in the left cell and therefore shows that synchrony in firing of both cells has occurred.

preliminary step.

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We would like to thank A. Grillo whose inspiring cooperation made this paper finally possible. This work was supported by the German Ministry of Education and Research (Bundesministerium für Bildung und Forschung), program: Bernstein-Gruppe "Detailed Modeling of Signal Processing in Neurons".

REFERENCES

[1] London M. and Haeusser M., *Annu. Rev. Neurosci.*, **28** (2005) 503.
[2] Hodgkin A. L. and Huxley A. F., *J. Physiol.*, **117** (1952) 503.
[3] Traub R. D., Schmitz D., Jefferys J. G. R. and Draguhn A., *Neuroscience*, **92** (1999) 407.

[4] Traub R. D., Contreras M., Cunningham M. O., Murray H., LeBeau F. E. N., Roopun A., Bibbig A., Wilent W. B., Higley M. J. and Whittington M. A., *J. Neurophysiol.*, **93** (2005) 2194.
[5] Xylouris K., Diploma Thesis: Signalverarbeitung in Neuronen (2008).
[6] Blender Foundation, Blender, `www.blender.org` (2009).
[7] Bastian P., Birken K., Lang S., Johannsen K., Neuss N., Rentz-Reichert J. and Wieners C., *Comput. Visual Sci.*, (1997) 27.
[8] Lawrence Livermore National Laboratory, `wcl.llnl.gov/codes/visit` (2008).