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# Modeling the Interplay between Neurons and Glial Cells

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The traditional view of the glial cells as passive bystanders of neural transmission has been disproved by recent studies. A certain type of glial cell, the star shaped astrocyte, is now thought to play a number of active roles in its interplay with neurons. The aim of the neuron-glial project is to map out the different networks in the neuron-glial system and then develop mathematical models which are able to describe how these networks function, how they interact with each other, and predict how they react to stimuli. The long term goal of the modeling project is to obtain a physiologically based model that contributes to a better understanding of the biological processes and the mechanisms of diseases, and that can be applied to test the effects of drugs using computer simulations as a supplement to costly and time consuming biological experiments.

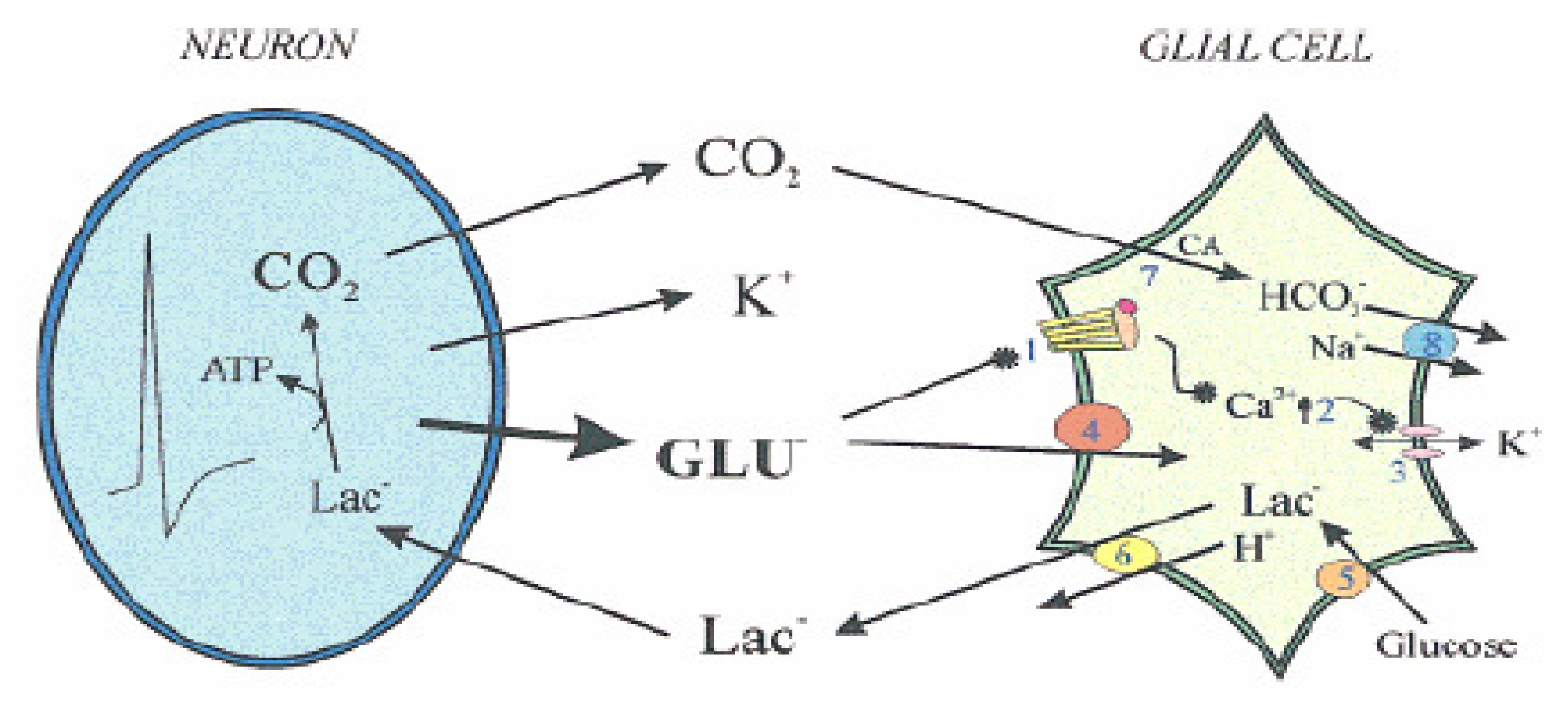
## Background

Neurons in the human brain are embedded in a web of glial cells. Contrary to earlier beliefs, glial cells are not passive bystanders to the information processing in the brain, but respond to the action potential signaling of neurons. To understand the principles of neural activity, and diseases such as epilepsy, the study of glial cells could therefore be very important. In [1] a hypothesis has been presented in which different components of the glial cell are thought to be functionally linked. In particular, a coupling between the NBC and the MCT1 membrane transport proteins is believed to increase the activity of the latter. As a first step towards a better understanding of the mechanisms behind the neuron-glial interplay on a systems level, the aim is to develop a mathematical model of the glial cell focusing on the kinetics of the above mentioned transport proteins and on other important reactions intertwined with these transporters. A vision in the long run is a detailed model of the complete system which also features the neuron.

## The Neuron-Glial Interplay

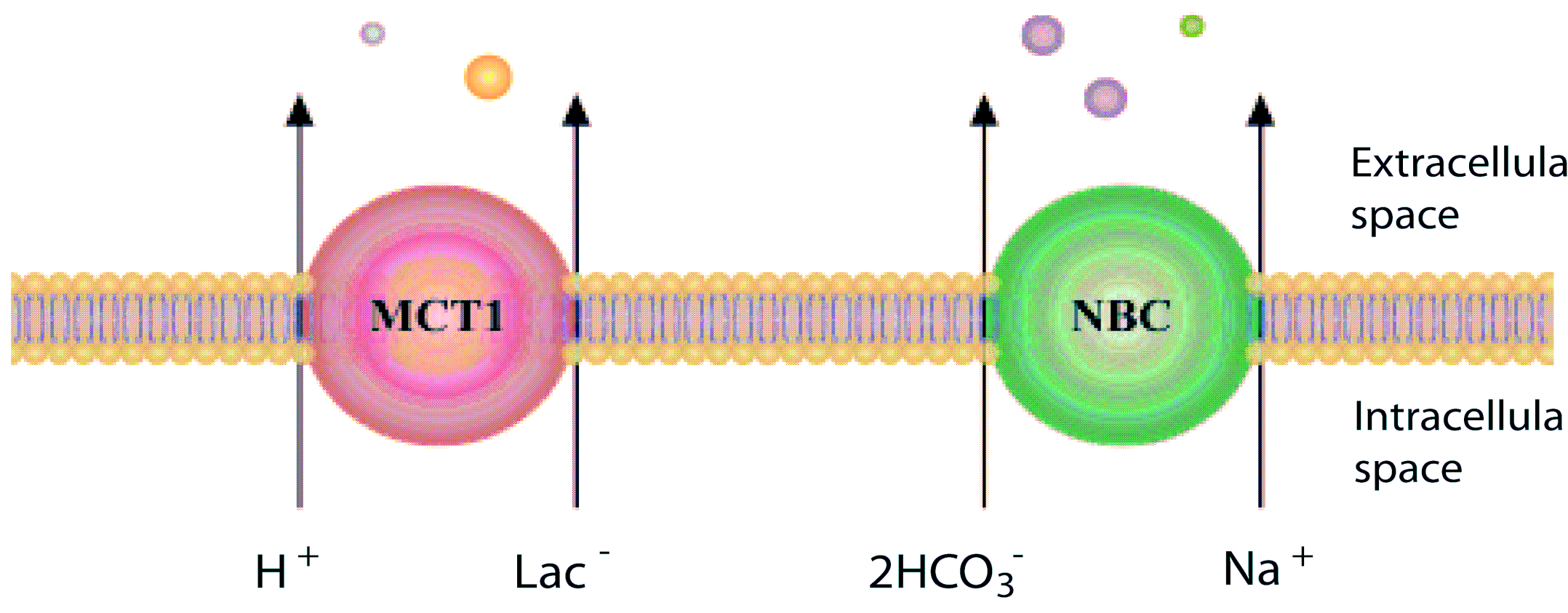
For every neuron in the human brain, there are approximately ten glial cells. The most abundant type of glial cell, the astrocyte, serves a variety of functions in the nervous system, including the regulation of the external chemical environment of neurons by removing excess ions, and recycling neurotransmitters released during synaptic transmission. They also provide neurons with nutrients such as lactate, working as a metabolic mediator between neurons and blood vessels. Figure 1 schematically displays the key elements of the neuron-glial interplay.

*Figure 1: The neuron-glial interplay*



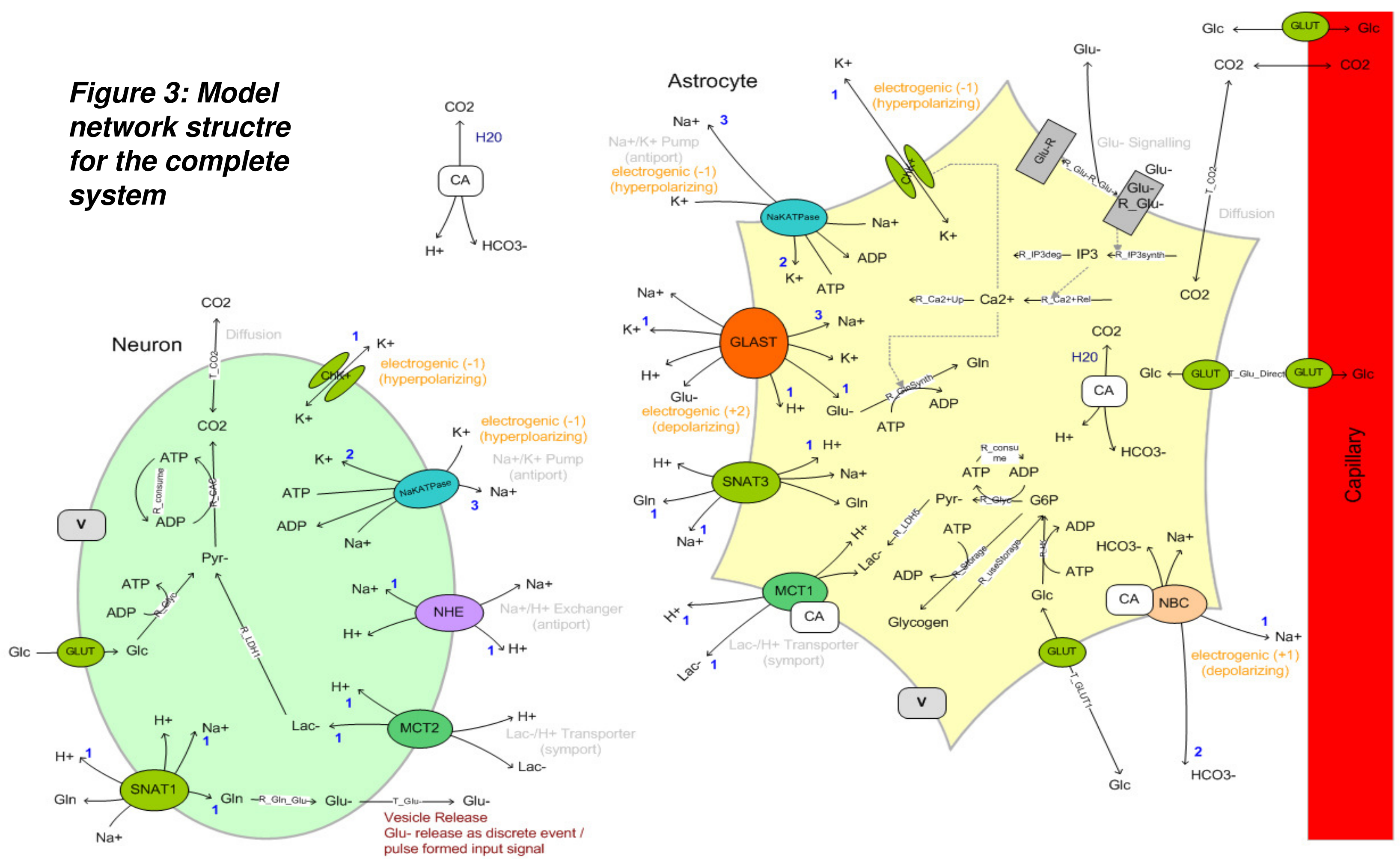
When neurons fire action potentials, glutamate and potassium is released into the extracellular space. Glutamate activates metabotropic receptors (1), which leads to calcium signaling (2) and, in turn, increases the potassium permeability (3). Glutamate is also taken up by the glial cell via the excitatory amino acid transporter (EAAT) (4). Glucose enters the glial cell from the blood vessels (5) and is stored as glycogen or converted to pyruvate through the glycolysis. The pyruvate is transported via the MCT1 as lactate to the extracellular space (6), where the MCT2 transports it to the neuron. Here, the pyruvate is metabolized in the citric acid cycle and the respiratory chain, leaving carbon dioxide and water as waste products. The carbon dioxide diffuses into the extracellular space, and further on into the glial cell (7). Aided by carbonic anhydrase, the carbon dioxide is converted into bicarbonate and a free proton, and the bicarbonate is transported out of the cell by the NBC transporter (8). Figure 2 shows the chemicals being transported by the NBC and MCT1 proteins, and the stoichiometry of the two transport processes.

***Figure 2: The electro-neutral MCT1 carries one hydrogen ion in co-transport with one lactate ion across the membrane. NBC on the other hand, transporting two bicarbonate ions and one sodium ion, is electrogenic and linked to the electric potential across the cell membrane.***



With PathwayLab, a graphical representation of the full astrocyte system was created. Figure 3 shows this graphical network structure which can be said to be the modelers view of the biological system in Figure 1. The network structure contain objects such as ion concentrations, compartments, membrane proteins, chemical reactions and diffusion processes, that are believed to be significant for the dynamics of the system.

***Figure 3: Model network structre for the complete system***



## The Oocyte Experimental System

To study the interaction between the two transporters MCT1 and NBC we use *Xenopus Laevis* oocytes, in which these transporters have been artificially expressed, as a model system. When performing an experiment, the oocyte is placed in a liquid bath. Different stimuli solutions, typically containing the substances that activates the transport proteins, are applied to the oocyte bath via pipes where they replace the current solution. Using ion sensitive micro electrodes, it is possible to continuously measure the resulting intracellular concentrations of sodium and protons inside the cell, and also the flow of electric current through the membrane.

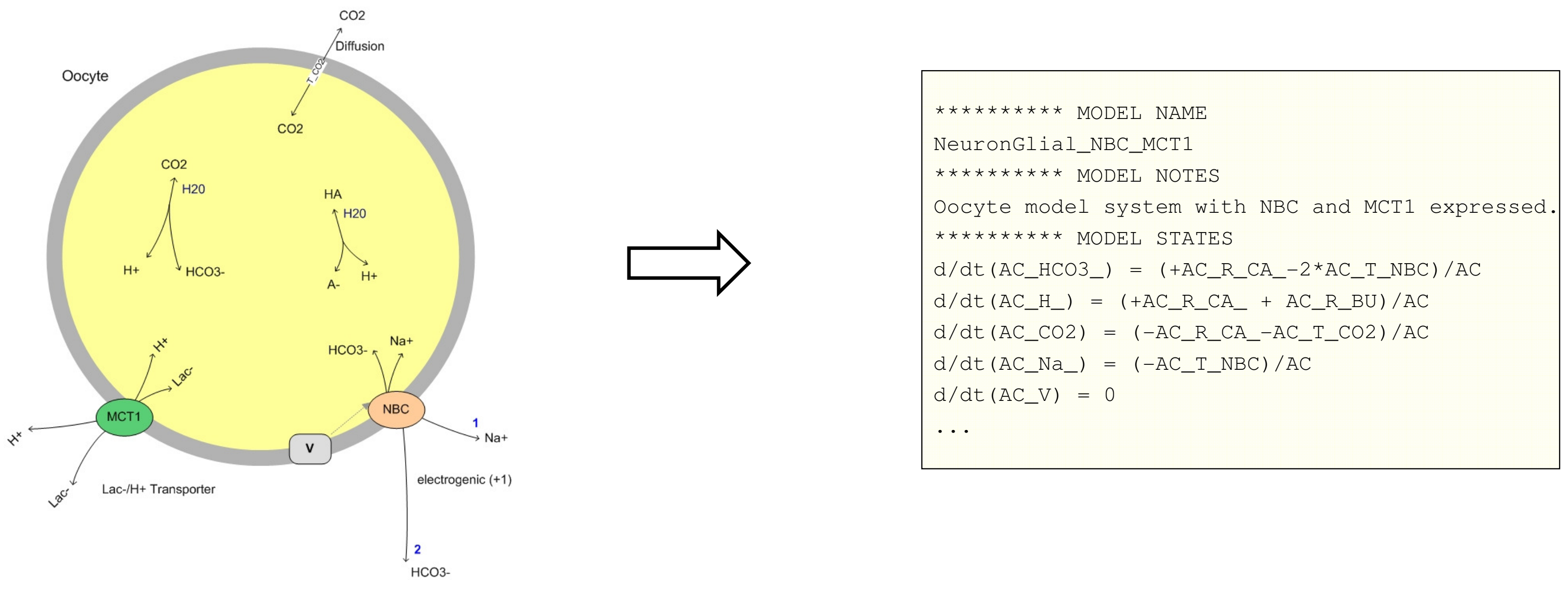
## The Oocyte Model

Figure 4 shows the graphical network structure for the reduced experimental system. Having defined the model network structure of the oocyte, the next step in the modeling process is the determination of the mathematical expressions that define the interactions between the different components of the network. This was done based on relevant theory from biology, chemistry and physics. As an example, the expression for the membrane current, $I_{NBC}$, caused by the NBC transporter were set to

$$I_{NBC} = g_{NBC}(V_m - E_{NBC})$$

$$E_{NBC} = \frac{RT}{z_{NBC}F}\ln\left(\frac{Na_i^+[HCO_{3i}^-]^2}{Na_o^+[HCO_{3o}^-]^2}\right)$$

where $V_M$ is the electric potential across the cell membrane, $E_{NBC}$ is the so called Nernst potential, depending on the intra and extracellular concentrations of sodium and bicarbonate, and $g_{NBC}$ is an unknown conductance factor. The network structure, includning the mathematical expressions, can be exported to the standardize SBML format [2] and then be imported to the Systems Biology Toolbox for Matlab [3], appearing as a system of ordinary differential equations. Once there, simulation, parameter estimation, model analysis, etc. can be performed.



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********** MODEL NAME
NeuronGlial_NBC_MCT1
********** MODEL NOTES
Oocyte model system with NBC and MCT1 expressed.
********** MODEL STATES
d/dt(AC_HCO3_) = (+AC_R_CA_-2*AC_T_NBC)/AC
d/dt(AC_H_) = (+AC_R_CA_ + AC_R_BU)/AC
d/dt(AC_CO2) = (-AC_R_CA_-AC_T_CO2)/AC
d/dt(AC_Na_) = (-AC_T_NBC)/AC
d/dt(AC_V) = 0
...
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***Figure 4: Model network structure for the reduced experimental oocyte system (left), and the model equations imported to the Systems Biology Toolbox (right)***

## Results

All unknown parameters of the model were estimated using the available measurement data. Figure 5 shows a plot of the measured (blue curve) and the simulated (red curve) membrane current for an oocyte subjected to the application and removal of two different extracellular levels of lactate concentration, first in nominal absence of $CO_2$ and then at a 5% $CO_2$ level.

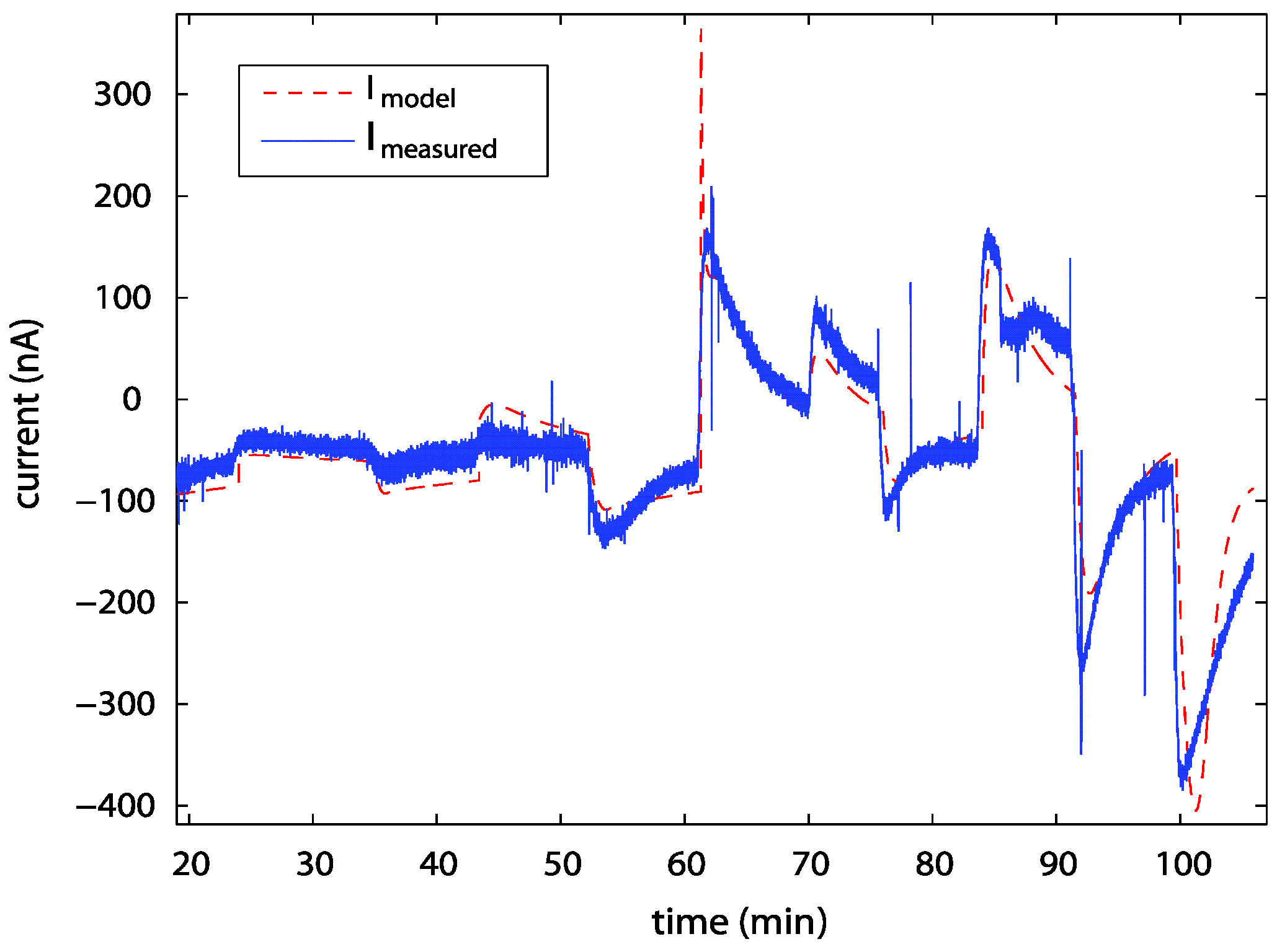
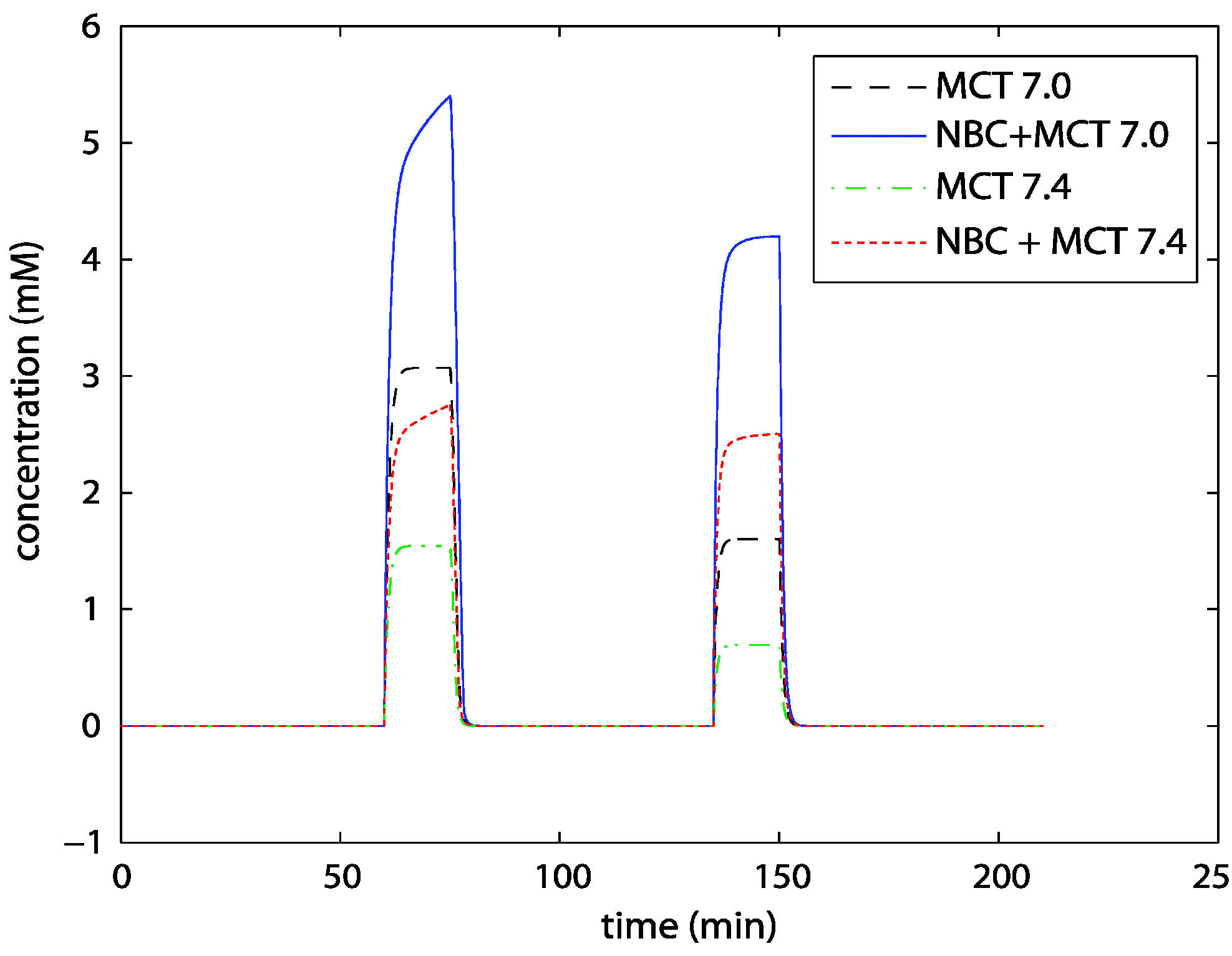


***Figure 5: Simulated and measured membrane current of the optimized oocyte model for a typical experiment***

***Figure 6: Simulated lactate concentration for different configurations of membrane transport proteins and pH levels***



Since lactate does not react with any of the present substances, its concentration is a direct measure of the MCT1 activity. To investigate the coupling between NBC and MCT1, simulations of lactate uptake for MCT1 alone was compared with the uptake for both proteins co-expressed. This was done for extracellular pH levels of 7.0 and 7.4, respectively. The simulated lactate concentrations of the optimized oocyte model in Figure 6 indicates that the presence of the NBC transporter distinctly increases the MCT1 activity, supporting the proposed coupling between the two transport proteins.

## PDE model

In a large cell such as the *Xenopus* oocyte, diffusion effects are most probably important. Therefore, an alternative model based on partial differential equations has also been used, in an attempt to describe these spatial dependences in a more realistic way. Figure 7 shows a simulation of the intracellular proton concentration as a function of both time and radial distance, assuming a spherically symmetric cell.

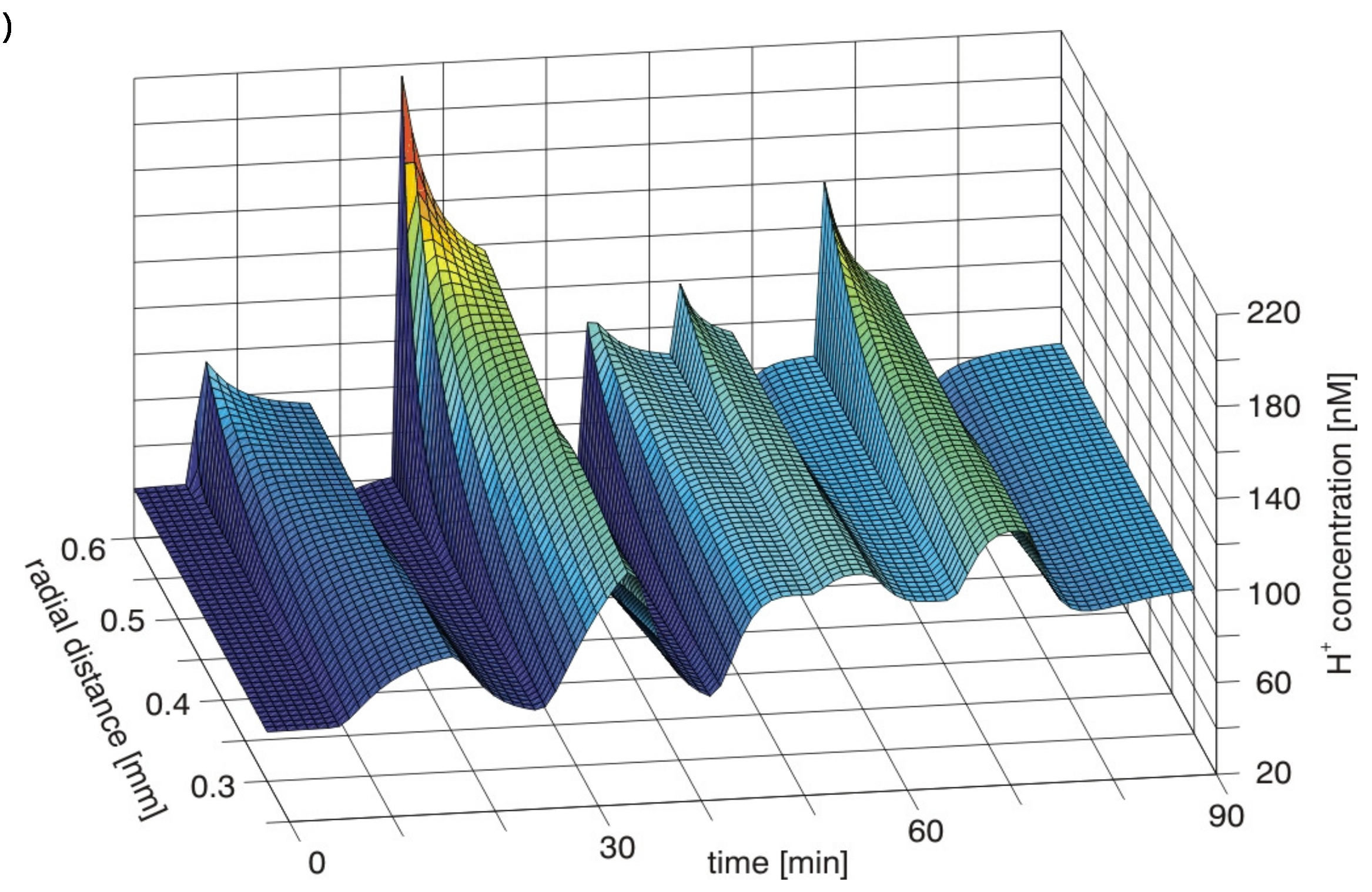


***Figure 7: Simulated intracellular proton concentration for a typical experiment using the PDE model***

*[1] J. Deitmer (2000) BioEssays, 22(8), 747–752*
*[2] M. Hucka, et al. (2003) Bioinformatics, 19(4), 524-531, http://sbml.org*
*[3] H. Schmidt, M. Jirstrand (2006) Bioinformatics, 22(4), 514-515,http://www.sbtoolbox.org*

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