AC 2010-1008: AN AGENT-BASED MODEL OF ION EQUILIBRIUM

Anca Stefan, Lawrence Technological University

Dr. Stefan earned a Diploma (1996) and M.S. (1997) in Electrical Engineering from the "Politehnica" University of Bucharest in Romania. She went on to earn a Ph.D. in Biomedical Engineering from The Ohio State University in 2005.

An agent-based model of ion equilibrium

Abstract

An agent-based model for ion equilibrium was constructed in order to enhance student understanding of how ions reach equilibrium as they flow through a permeable cell membrane. The topic is taught in a senior level course in Biomedical Engineering, which is a required course for the students in the electrical concentration of the program. The course, entitled Bioelectrical Engineer Physics, is also cross-listed as a Technical Elective in the Electrical and Computer Engineering curriculum. The purpose of the course is to teach the principles of bioelectricity and computer modeling of bioelectrical phenomena and is aimed at students with an electrical engineering background. Therefore, it is assumed that not all students have taken a course in Physiology. The model was designed to include both diffusion according to a chemical gradient (concentration) and flow according to an electrical gradient. Students were able to analyze the diffusion of ions due to the concentration gradient only, and then include the electrical gradient as well. Since the model allows the user to include interaction among ions, the students were able to understand that the mechanisms that lie at the origin of cellular excitability are more complex than the behavior predicted by the Nernst equation. They were also able to suggest improvements to the model, and point out some of its faults.

Introduction

This paper presents an agent-based model for equilibrium of charged particles (ions) that exist on either side of the mammalian cell membrane. Since some of the students enrolled in the class are not part of the Biomedical Engineering program, generally they have not taken more advanced life science courses, such as Physiology. Consequently, there is an increased need to facilitate their understanding of biological processes.

The Nernst equation is a mathematical expression of the equilibrium of one species of ions to which the cell membrane is permeable. The membrane voltage depends on the concentrations of ions in the intracellular and extracellular media:

$$V_m = \frac{60}{Z} \log_{10} \frac{[X]_e}{[X]_i} (mV) \qquad (1)$$

where V_m is the membrane voltage, defined as the potential difference between the intracellular and extracellular media, in this order, and $[X]_e$ and $[X]_i$ are the extracellular and intracellular concentrations of ion X, and Z is the valence of ion X.

The ions flow through the membrane according to an electrochemical gradient[1]. At equilibrium there is no net flow of ions, because the electrical gradient (created by charge) and the chemical gradient (created by ion concentration) compensate. It is known that the Nernst equation has a major limitation in that it can only take one ion species into account, whereas the membrane voltage at equilibrium is the interplay of several ion species, mainly sodium and potassium in certain excitable tissues. For this reason, the model in discussion was designed to incorporate at least one ion species.

Description of the model

Recently it became evident that the transport of ions across a membrane cannot be described as a flux of particles individually controlled by their interaction with the electric field, but as a cooperative process involving the ions, co-migrating water molecules and even atomic components of the channel (or pore), collectively generating a virtual entity named "permion"[2]. This 'quasi-particle' is the emergent result of a multi-body system, which classical electro-mechanics cannot account for. As a first step towards a novel modeling approach of these collective phenomena in ion transport, an agent-based platform was used here, designed for describing the swarming behavior, such as flocks of birds or schools of fish[3].

Agent-based modeling is a class of computational models that simulates the behavior of a system by modeling the actions and interactions of its individual constituents. The constituents are called agents, and they operate simultaneously and interact with each other. The simple rules that govern the behavior of the agents can generate very complex behaviors of the system as a whole.

A computer model was built using an agent-based modeling approach, and assigned as a class project. The software of choice was Netlogo[4], developed by the Center for Connected Learning and Computer-Based Modeling at Northwestern University (Evanston, IL). Netlogo was elected for classroom use because it was originally developed for educational purposes, and students find it accessible. It is also in use at many academic institutions. Moreover, it can be downloaded for free and installed easily. Thus, for our purpose, Netlogo has several advantages over other simulation software, such as Matlab (The Mathworks, Inc), for which a license must be purchased.

First, the students were presented with a simpler version of the model, consisting of only one species of ions. The model was further adapted to include two species, namely sodium and potassium. The cell was modeled as two compartments, the intracellular medium and the extracellular medium. The two compartments were separated by a membrane which allows ions to flow only through ion channels. The number of ion channels can be adjusted.

In search for emerging, collective properties of particle transport, the interaction amongst ions was modeled using an approach similar to that of the Flocking model from the Netlogo Model Library[5]. The Flocking model is an attempt to simulate the flocking of birds. It describes the interaction among the agents that form a system, based on several parameters: the minimum and maximum distance from the nearest neighbor, the amount of rotation for a certain agent to move towards or away from a neighbor, and the maximum distance at which an agent can "sense" its neighbors. The members of the system (the agents) interact by moving towards each other or away, if they come too close. Flocking is a behavior that can be extended to other dynamic systems, and the ability to manipulate the interaction parameters allows for flexibility in modeling. Therefore, this model was considered as an appropriate starting point to model the dynamics of the constituents of the cell.

The electrical gradient was implemented mathematically in the model as the electrostatic field created between a positive and negative charge. A similar approach can be found in OBS model

available from the Netlogo Community Models, which uses the potential field approach to avoid obstacles and find targets[6]. In the model described here, for each species of ions a corresponding electrostatic field was defined, its polarity depending on the Nernst equilibrium potentials: positive for sodium and negative for potassium. As an example, to describe the flow of potassium ions according to the electrical gradient, the field was created between a negative target situated in the intracellular medium and a positive target situated in the extracellular region. The ions move according to the direction of the electrostatic force. The other component of ion flow, the diffusion according to the chemical gradient, was simulated by setting the interaction parameters such that the tendency of the agents to aggregate did not overcome the random motion of the agents. Specifically, the minimum separation and the vision parameters were adjusted.

Results and Discussion

First, the students were allowed to become familiar with the model by experimenting with the version that included only one species of ions. The students worked in teams of two or four, with at least one biomedical engineering student in each group. The class size of this course is generally small, between 4 and 6 students, given that it is a senior level course in a new program. This year the mixture of students was interesting, two biomedical engineering students, one computer engineering student and one electrical and computer engineering student. They worked best in the four-people format. They were allowed 45 minutes to run an experiment and were asked to present their conclusions as a one or two-page report. Before running simulations, the students set up the model, by choosing the intracellular and extracellular concentrations, the electrical potential of the intracellular and extracellular region, the size and number of ion channels. In this model, concentrations are obtained simply by counting the number of ions.

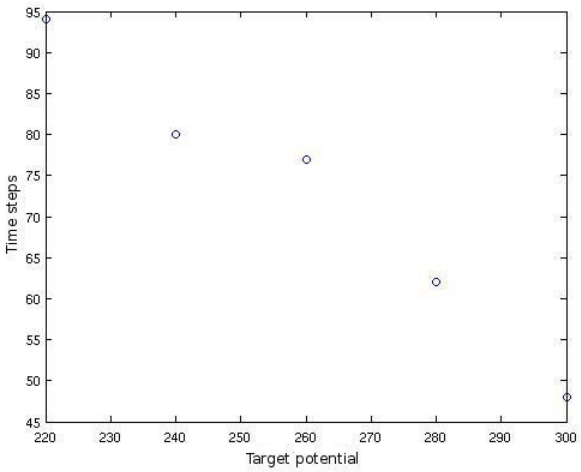

Figure 1. The relationship between the time steps needed for the system to reach equilibrium and the value of potential difference between the intracellular and extracellular medium.

The students observed that, as the potential difference between the intracellular region and extracellular region was increased, the time needed for the ions to flow from one chamber to the other decreased (Figure 1) and they correctly attributed it to the fact that the electrical force

dominated over the diffusion process. They also observed that running the simulation with two ion channels in the membrane did not significantly alter the time needed to reach equilibrium (when flow of ions stops) and they attributed that to the random nature of the model. The values ranged between 442 and 678 time steps for one channel, and between 410 and 586 for two channels.

Specific student suggestions included: the interaction among ions must be modeled as a weak interaction that does not force them to aggregate within a small region; the potential difference between the intracellular region must be changed depending on the concentration of ions, because the amount of charge in either of the regions depends on the number of ions present. Their comments showed that they indeed understood the relationship between the equilibrium potential and ion concentration, according to Nernst equation (1).

For their final project, the students were asked to experiment with a version of the model that included two ions, sodium and potassium. At this point, they were familiar enough with the model that they could attempt experiments on their own. In the first part of the project they removed the electrical gradient by setting the potential difference between the intracellular and extracellular chamber to zero. The diffusion process was analyzed. The students noticed that equilibrium of both species of ions was attained after approximately 500 time steps, when most ion flow stopped and intracellular and extracellular concentrations for both species were approximately equal. Fluctuations in the number of ions of either side of the membrane were observed, but considered small enough to be reasonable.

Time Steps	Intracellular Potassium	Extracellular Potassium	Intracellular Sodium	Extracellular Sodium
73	200	47	15	111
184	168	79	31	95
456	131	116	72	54
895	131	116	57	69
1400	142	105	64	62
2190	128	119	61	65
8380	145	102	57	69

Figure 2. The above table was compiled by one of the students. It shows values of the intracellular and extracellular concentrations of the two ions at different time steps. In this experiment, the ion flow was according to the chemical gradient only. The findings were consistent among all students that the values stabilize around 500 time steps.

In the second part of the project, the flow of ions due to both the electrical and chemical gradients was analyzed. The students were asked to vary the concentrations of sodium and potassium in both the extracellular and intracellular region and characterize the behavior of the system as a result of these variations. The first observation was that equilibrium was reached faster when both gradients (electrical and concentration) were active. Most students defined the time to reach equilibrium as the time when concentrations stabilize. This time was used as the output variable for each of their tests. It was interesting to note that they understood that concentrations of ions in both chambers do not have to be equal, because of the interplay between the two types of forces, chemical and electrical.

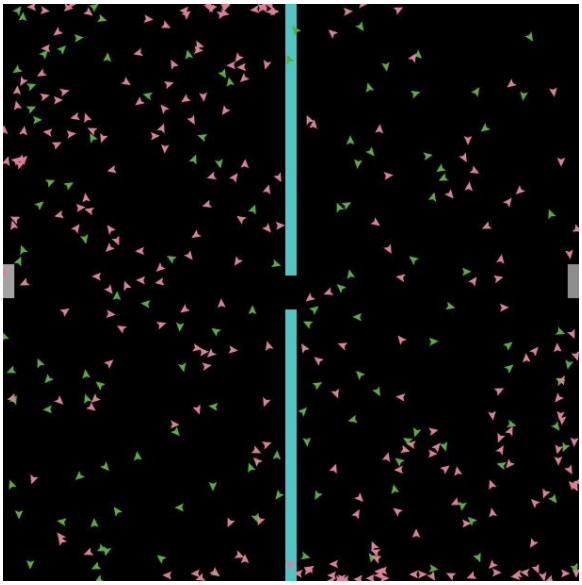

Figure 3. Shown is of the dynamic system in steady state. Both gradients were turned on. The green agents represent sodium ions, and the pink agents represent potassium ions. The left chamber represents the intracellular medium, and the right chamber represents the extracellular medium. The membrane is shown in blue, with one adjustable opening (ion channel selective to both sodium and potassium). The gray-filled rectangles represent the locations of the source and sink of the electric field.

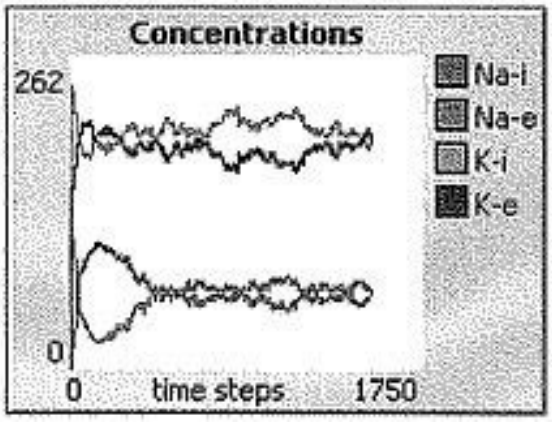

Figure 4. A student showed her results from one simulation experiment where the potassium extracellular concentration was increased. The student found that the system reached steady state after approximatively 400 steps. Na-i and Na-e denote the intracellular and extracellular sodium concentrations, and K-i and K-e denote the intracellular and extracellular potassium concentrations. The top two traces represent K-i and K-e, and the bottom two are Na-e and Na-i.

To analyze long term stability the students ran simulations for a long time. Some even chose to run for 24 hours. The common findings were that once stability is reached, it is maintained if no

other factors interfere. One student observed deterministic behavior in potassium ions and not sodium, and attributed it to additional factors involved with the potassium travel, and possibly the larger number of potassium ions. Another interesting issue that was raised was the fact that the model is spatially bounded, and changing the concentrations of ions should be done while keeping the total number of ions constant.

Suggestions for improvement of the model included: some indications regarding a better control of ion flow through the pore(s) in the membrane, and a suggestion to investigate certain repetitive patterns noticed after long simulation times.

The following learning outcomes were envisioned:
(1) help students understand a process that occurs at cellular level and is therefore difficult to observe. This is especially important for students without a biomedical engineering background.
(2) help students understand that in many dynamic systems, the behavior is a result of the interaction among components, and randomness is a fact of life.
(3) build teamwork skills by allowing students to work in teams and submit a common report.
(4) encourage creative thinking by allowing them define the parameters to be measured in their simulation experiments and by prompting them to submit suggestions for improvement of the software.

Based on the above mentioned observations, these outcomes were met. The students were able to obtain a better understanding of the topic, even though some of them had never taken a course in Physiology. They also obtained an insight of how dynamic systems work. The agent-based model stimulated creative thinking in that students were allowed some flexibility in how to change the parameters of the model and how to analyze the way a system reaches steady state. Moreover, the positive feedback received by the instructor confirmed that this was also an enjoyable experience for the students. Future improvements envision the inclusion of ion selective channels, which will make the model more realistic. With this modification, membrane permeability to various ions, as in the Goldman-Hodgkin-Katz equation, could be modeled.

Bibliography

1. Berne, R. and Levy, M., editors, Physiology, 4th edition, 1998 Mosby, Inc.
2. Elber, R. et al, Sodium in Gramicidin: An Example of a Permion, Biophysical Journal 68: 906-924 (1995)
3. Sklar, E, Software Review: NetLogo, a Multi-agent Simulation Environment, Artificial Life 13: 303 – 311 (2007)
4. *W*ilensky, U. (1999). NetLogo. http://ccl.northwestern.edu/netlogo. Center for Connected Learning and Computer-Based Modeling. Northwestern University, Evanston, IL.
5. Wilensky, U. (1998). NetLogo Flocking model. http://ccl.northwestern.edu/netlogo/models/Flocking. Center for Connected Learning and Computer-Based Modeling, Northwestern University, Evanston, IL.
6. http://ccl.northwestern.edu/netlogo/models/community/OBS