

AC 2010-1687: A COMPUTER MODEL OF CELL DYNAMICS USING AGENTS

Anca Stefan, Lawrence Technological University

Dr. Stefan earned a Diploma and M.S. 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.

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Abstract

An agent-based model for cellular dynamics was constructed to be used as a simulation tool in a senior level course in Biomedical Engineering. 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. Given that the student body includes students with no biomedical background, there is an increased need to facilitate the understanding of biological processes.

The students were able to experiment with different parameters of the model and were also allowed to criticize it. They were able to see the necessity of including more complex factors, in order to create a more realistic model of ionic equilibrium.

The model can be further extended to simulate other dynamic processes at cellular level and therefore represents a useful teaching tool. Finally, it was interesting to see how this class project stimulated creative thinking and helped build teamwork skills, as well.

Description of the model

Agent-based modeling is a computational tool that simulates the behavior of a system by modeling the actions and interactions of its individual constituents. These individual constituents are called agents, and by modeling the interaction among them, a complex behavior of the system as a whole can be described. The model discussed here was built using NetLogo¹, developed by the Center for Connected Learning and Computer-Based Modeling at Northwestern University (Evanston, IL). NetLogo was selected for classroom use because it was originally developed for educational purposes, and students find it accessible. It can be downloaded for free and installed easily, and thus has an advantage over other simulation software, for which a license must be purchased. NetLogo comes with a vast models library, and community developed models are also available. Users can also benefit from the netlogo-educators group².

The main purpose of this model was to help students with a variety of backgrounds to understand electrophysiological processes that lie at the foundation of cellular excitability. The main players are ions that are present inside the cell (the intracellular medium) and outside the cell (the extracellular medium) which flow across the membrane under certain conditions. The membrane is said to be permeable to these ions. The flow of ions is caused by two phenomena. One is the difference in the concentration of ions in each of the two compartments, called chemical gradient. Ions diffuse from areas of higher concentration to areas of lower concentration. The other cause is the voltage established across the membrane, referred to as the membrane voltage or the electrical gradient. This voltage is created by the distribution of charged particles on either side of the membrane. The resulting electric field exerts a force upon any charged particles. The

direction of ion flow due to the electrical gradient is opposite to that of the chemical diffusion. Equilibrium of ions occurs when their net flow across the membrane ceases.

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 caused by the unequal distributions of ions in the intracellular and extracellular media, is given by³:

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

where V_m is the membrane voltage, defined as the potential difference between the intracellular and extracellular media, and $[X]_e$ and $[X]_i$ are the extracellular and intracellular concentrations of ion X. Ion X can be either positively or negatively charged, and Z is its valence.

In its initial form the model was designed to simulate the flow of one species of ions from one cellular compartment to another according to an electrical gradient. The flow of ions is allowed through one or more channels in the membrane. The agent-based model consists of two bounded compartments, one representing the intracellular medium and the other representing the extracellular medium. The two compartments are separated by the membrane. One or more openings in the membrane, called pores or ion channels, can be modeled. The size of channels can be adjusted. In NetLogo language, the two compartments form the world, and the ions represent the agents. The world is physically made up of patches, thus all geometrical dimensions are expressed in terms of these units. The model can be run either with one species of ions, or two. The two species represent the sodium and potassium ions, which are the main players in establishing the membrane voltage.

In the model, the electrical gradient is described mathematically as the electrostatic field created between a positive and negative charge. A similar approach can be found in one of the NetLogo Community Models, the OBS model, which uses the potential field approach to avoid obstacles and find targets⁴. In the model presented here, each species of ions moves according to its own electrostatic field. The polarity of this field depends on the polarity of the Nernst equilibrium potentials as given by equation (1): positive for sodium and negative for potassium. For example, to describe the flow of potassium ions according to the electrical gradient, the field is created between a negative target situated in the intracellular region and a positive target situated in the extracellular region. The ions move in the direction of the electrostatic force. Furthermore, the electrostatic field changes as the distribution of charge changes due to the flux of ions from one compartment to the other.

The model has an option to include interaction among the agents. The interaction is modeled using an approach similar to that of the Flocking model from the NetLogo Model Library⁴, where the agents must keep a certain distance among them and are able to move away from each other when this distance reaches a minimum value, called minimum separation. Other parameters that describe the interaction are 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, called vision. The reason for introducing this interaction is because agents represent positive ions, which repel each other. Also, the model can be extended to simulate other types of cell dynamics. The interaction parameters can be adjusted such that ions form clusters. The diffusion of ions due to the

chemical gradient is simulated by setting the interaction parameters such that the tendency to aggregate does not overcome the random motion of the agents. In the experiments performed by the students, diffusion was most easily obtained by setting the vision to zero.

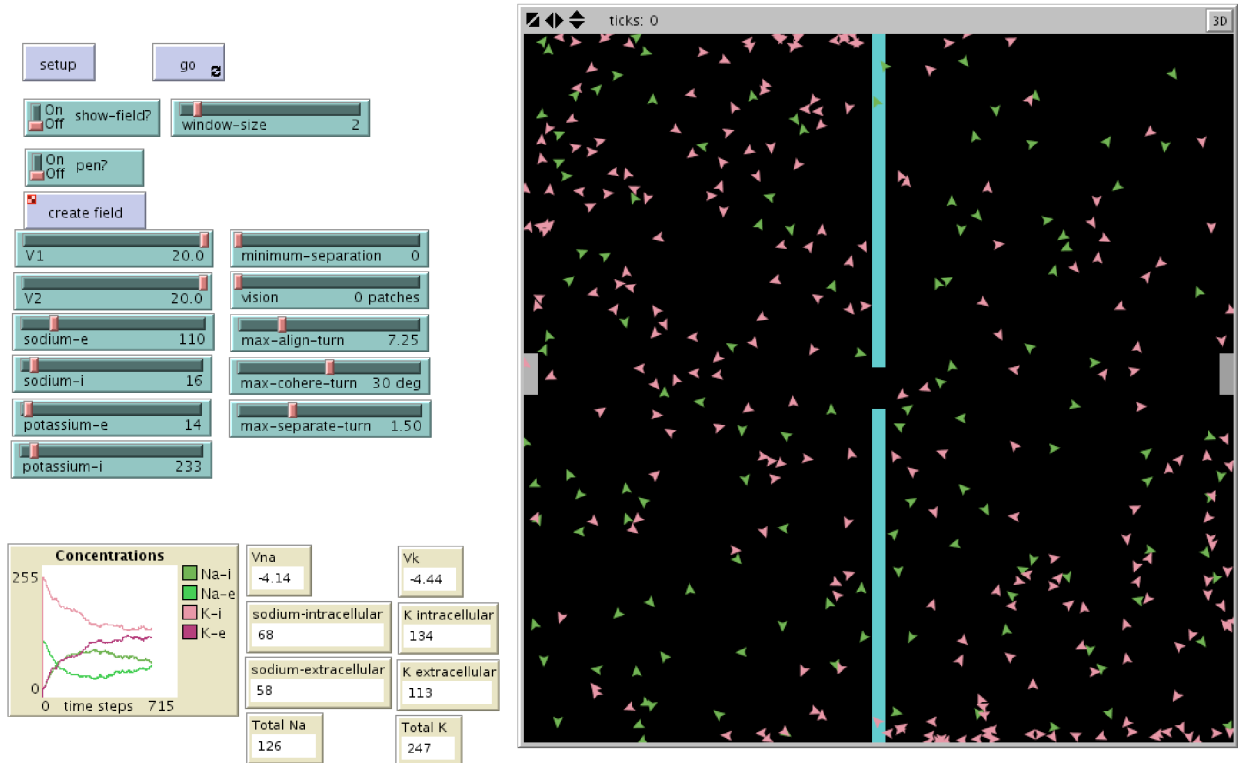


Figure 1. The interface of the model built with NetLogo.

Figure 1 shows the interface of the agent-based model presented to the students. On the left half of the interface are the parameters that can be adjusted. The leftmost stack consists of the electrochemical parameters: the potentials V1 and V2 that generate the electrostatic field (their locations are shown in gray in the view on the right), and concentrations of the two types of ions. The stack on the right represents the interaction parameters. The parameter “window-size” adjusts the size of the pore(s) in the membrane. The number of pores can be controlled from the software. The membrane is shown in blue and separates the two compartments: the intracellular medium (left chamber) and the extracellular medium (right chamber). The model is two-dimensional. The agents are represented by the colored arrows; the green agents are the sodium ions and the pink agents are the potassium ions. The default values for concentrations are such that the intracellular potassium concentration is larger than the extracellular one. For sodium, the situation is reversed. Typical concentration values for the squid axon are 400 mM intracellular and 10 mM extracellular for potassium and 50 mM intracellular and 460 mM extracellular for sodium. In the model the concentrations can be adjusted for more realistic values, but increasing the number of ions (agents) will increase computational time, since each agent must perform certain actions. In this model, concentration of an ion species is calculated as the number of ions.

Results and Discussion

In their class project, the students first simulated the diffusion process, by removing the electrostatic fields (the values of the potentials that generate the fields were set to 0). Figure 2 shows the initial state of the system and figure 3 shows the dynamic system after concentrations have stabilized and diffusion has ended. The students chose to monitor the values of ion concentrations in order to estimate the time when the system reached equilibrium. They considered a certain level of fluctuation of the values to be normal, given the randomness of the system.

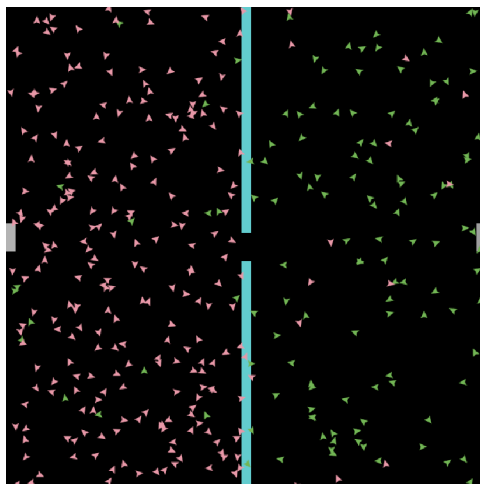


Figure 2. Initial setup for diffusion.

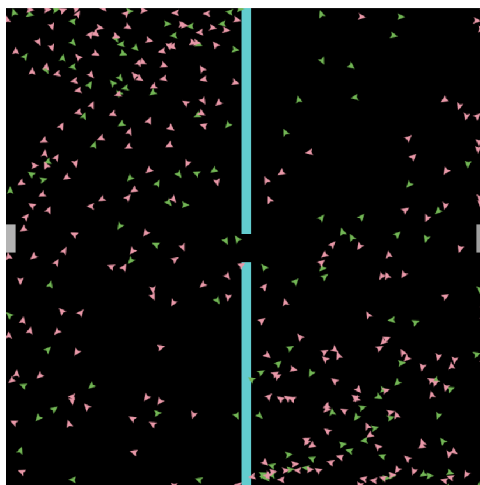


Figure 3. The diffusion process has ended. Intracellular and extracellular concentrations are approximately equal for both species of ions.

Furthermore, the students were asked to manipulate some of the interaction parameters to see how they influenced the aggregation of ions. One parameter that was easy to manipulate was the vision, which represents the maximum distance at which an ion “senses” its neighbors. As

mentioned before, the geometrical dimensions are expressed in terms of patches. Figure 4 shows the results of setting the vision parameter to a non-zero value, meaning that ions are able to “see” the presence of their neighbors within a certain range. The ions tended to form clusters.

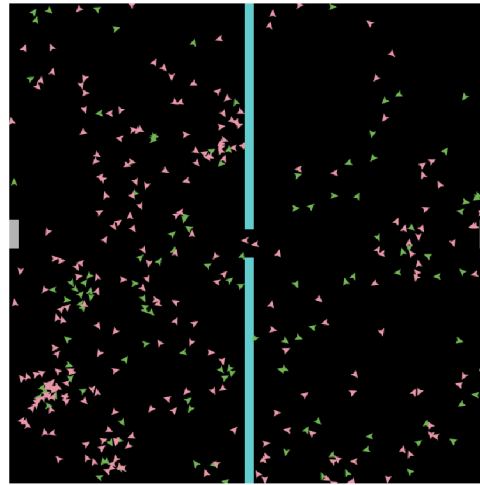


Figure 4. Steady state of the dynamic system with the vision parameter set to a non-zero value (2 in this case). If the vision is small enough, the ions tend to diffuse, rather than aggregate.

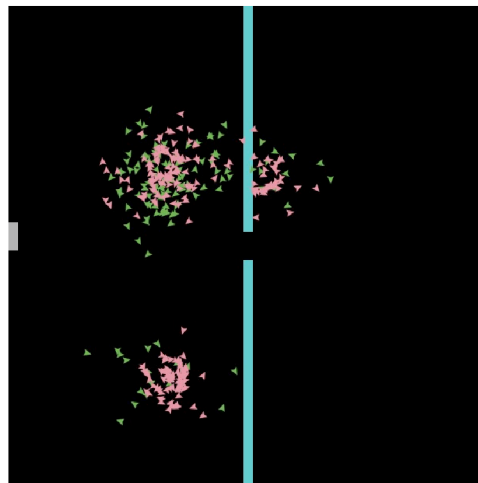


Figure 5. Steady state of the dynamic system with the vision parameter set to 10. The ions form clusters.

When the value of the vision was increased, the ions formed clusters, as shown in figures 5 and 6. Due to the randomness of the motion of ions, the composition of the clusters (namely the amount of sodium and potassium ions), their size and location differed from one simulation to another. In figures 4 through 6, the results are shown for the same number of simulation steps (1200).

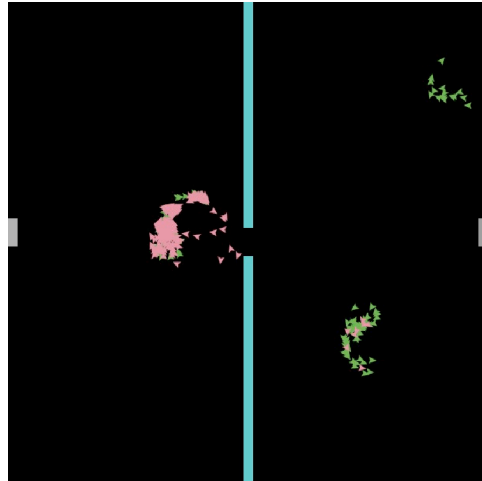


Figure 6. Another simulation of the diffusion process with the vision parameter set to 10.

The students were then asked to simulate the movement of ions due to both diffusion and electrical gradient and include interaction among agents as well. The vision parameter was set to a larger value (10 patches, which is about $\frac{1}{4}$ of the size of the world) and one result is shown in Figure 7. The students noticed that the tendency of the ions to aggregate, was not as pronounced as in Figure 6, where the electrical fields were set to zero.

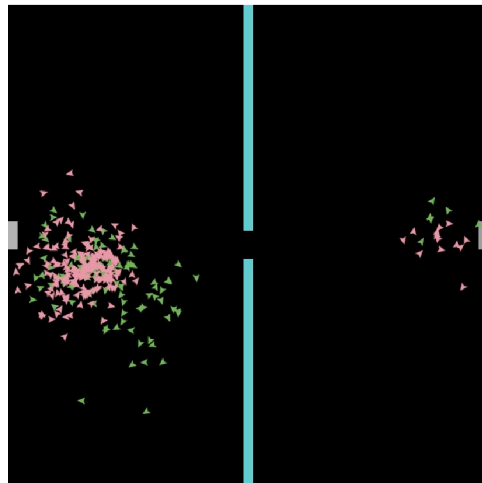


Figure 7. Flow of ions due to the electrochemical gradient and interaction parameters turned on.

Finally the students were asked to add one more variable into the picture. The parameter that defined the minimum distance that can be kept among agents, called the minimum-separation was set to a small non-zero value, as in Figure 8. The students observed a lesser tendency of ions to aggregate. At the same time there was less spreading of the ions as compared to figure 9, where the ion flow was due to the electrochemical gradient only, without interaction.

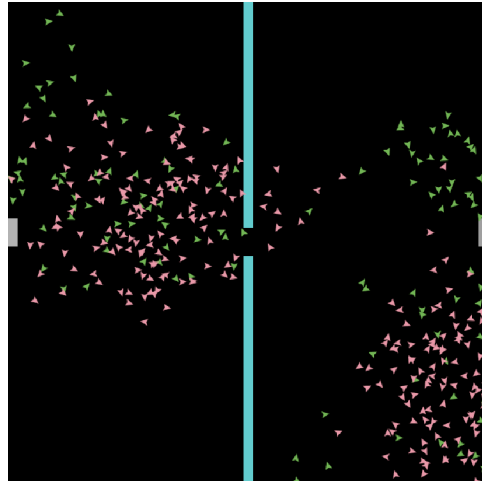


Figure 8. Ion flow due to electrochemical gradient. Interaction among ions is modeled by setting the vision parameter to 10 and the minimum-separation to 1.

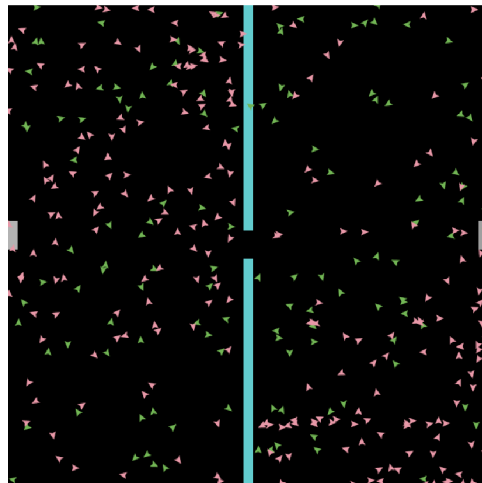


Figure 9. Ion flow due to electrochemical gradient, with no interaction among ions modeled.

From the instructor's point of view, this project was an enjoyable experience for the students, who interacted well and came up with interesting suggestions. For example, among the comments they made were (1) the observation that the variability of the ion concentration should be limited by the fact that this model simulates a spatially bounded medium, and (2) some cyclic or repetitive patterns in the motion of ions were noticed after long simulation times, and their cause should be investigated. Finally, by experimenting with different aspects of ion interaction, such as minimum allowable distance among ions (called minimum-separation in the model), or maximum distance at which an ion can “see” its neighbors (called vision in the model), the students noticed significant changes in the dynamic pattern of ions. Thus, they were able to get an insight of the complexity of the underlying mechanisms of cellular dynamics.

Bibliography

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