Molecular Communication: Modeling and Simulations

Department of Chemical Engineering and Material Science*
School of Information and Computer Science**
University of California, Irvine

1. Introduction to the Proposed Summer Research

This proposal is intended to address research challenges in *Molecular Communication* [4], a new and interdisciplinary research area that spans the nanotechnology, bioengineering, and communication technology. Molecular communication allows nanomachines (e.g., nano-scale devices) to communicate using molecules as a communication carrier. One of the applications of molecular communication is to nano-medicine [2], where nanomachines use molecular communication to interact with cells and tissues at a molecular scale, or nanomachines do so to interact with other nanomachines. In drug delivery systems, (now highly recognized as a multidisciplinary research area [3]), molecular communication provides mechanisms to deliver drugs in a manner that is friendly to the biological systems. For instance, soft sender nanomachines may be embedded in a human body and emit drug to the targeted receiver cells.

In molecular communication, biological systems are artificially modified to function as networking devices that may perform error correction, collision avoidance, amplification, filtering, and routing. Molecular communication differs from electrical communication as shown in Table 1; and these differences create a challenge in designing molecular communication systems. This project is to test one type of molecular communication systems designed by Dr. Nakano through computer simulations.

Since December of 2004, I have been conducting simulation studies of molecular communication systems using cell simulation software, *CellWare* [5] and exploring a mathematical basis of simulation algorithms. The goal of my research is to design a realistic simulation model that takes stochastic aspects of living systems into

Data Communication		**Molecular Communication**
Electrical/optical signals	**Carrier**s	Chemical signals
Wires, airborne	**Environment**	Aqueous
High speed ($3x10^5$ km/s) and Long range (m – km)	**Communication Characteristics**	Slow (10^{-1} km/s) and short Range (nm – m)
High accuracy and high energy consumption	**System Characteristics**	Low accuracy due to stochastic Nature, and energy efficient

Table 1: Electrical Communication vs. Molecular Communication

consideration. The proposed project is currently being carried out by seven students; three Ph.D. students from information and computer science, two undergraduate students from biological sciences, one undergraduate student from electrical engineering, and myself from chemical engineering. A group meeting occasionally takes place, which provides an opportunity to exchange information among group members with different majors. By bringing all disciplines together, the proposed summer research is expected to develop a realistic simulation model that can be used to characterize molecular communication systems.

2. Research Objectives and Approaches: Modeling and Simulations

Molecular communication is engineered biological communication (e.g., cell-to-cell signaling) that allows nanomachines (e.g., engineered organisms) to communicate with each other in an aqueous environment. The major research issues in the filed of molecular communication include (1) system design and (2) characterization of designed systems. For (1), there are several molecular communication systems proposed and designed in the research group [4]. For (2), I have been using Cellware [5], a modeling and simulation tool for cellular transactions, to identify communication characteristics of the molecular communication systems designed in the research group. System characterization including identification of possible communication range, communication delay and communication speed provides a key to further improves the system design.

The specific goal of the proposed summer research is through simulations to provide an insight into the fundamental behavior of the designed systems (e.g., how the environmental factors such as pH level impact the system behavior and communication performance). In order to achieve the goal (using computer simulations to identify communication characteristics of molecular communication systems), I have first

surveyed various modeling and simulation tools of cellular processes, including BioGrid, Bio Sketch Pad, Jdesigner, JigCell, Monod, Pathway builder, Simpathica, Bio Spice, Cellware, Stochastirator, Sig Tran, Dynetica, M-Cell, Stochsim, and Dizzy.

After looking through their possible uses I tested a few of the simulators and Cellware [2] seemed to be able to model intercellular interactions. To test the capabilities of Cellware, I created a hypothetical system consisting of three cells that modeled Ca^{2+} and IP_3 diffusion through the cells following a model provided in [1]. The tested model describes intercellular Ca^{2+} waves in astrocytes. The model is described mathematically using a set of partial differential equations in the following manner:

- The model is represented by a system of equations dependent on four variables: cytoplasmic Ca^{2+} concentration [$\delta C/\delta t$], Endoplasmic Reticulum Ca^{2+} concentration [$\delta S/\delta t$], IP_3 concentration [$\delta I/\delta t$], and the active fraction of IP_3 receptors [$\delta R/\delta t$]. The model is being evaluated by comparing it to the results of the researchers who developed the proposed mathematical model of Ca^{2+} diffusion across gap junctions.
- IP_3 is the main cause of the propagating Ca^{2+} waves. The main source of IP_3 generation is when an agonist in the surrounding solution activates a protein in the cellular membrane, which ultimately activates phospholipase C in a cascading signaling pathway, which in turn activates IP_3 molecules. The other significant source of IP_3 activation is through the positive feedback loop that is between calcium ions and IP_3. This mechanism results in an increase in the concentration of IP_3 when the concentration of calcium ion increases.
- As IP_3 concentration increases in the cell it activates the gated calcium channels on the endoplasmic reticulum. Once activated, the proteins release calcium ions from the endoplasmic reticulum's high concentration reservoir. The other, less significant, source of calcium concentration increase is through the calcium pumps, which pump calcium out and into the cell from the surrounding solution.
- The calcium and IP_3 diffusion are the most significant mechanism in the entire model as it is the diffusion of IP_3 across gap junctions that is ultimately responsible for intercellular calcium waves. The diffusion of both molecules is modeled through double derivative equations involving concentrations, relative cell position, and intensity.

In implementing the above model, Cellware has proven to be user friendly because of its simple GUI; but it is difficult to simulate diffusion through cells. However, Cellware can

simulate reactions within a cell. It has become obvious that one simulator is not enough to model the entire system, but the use of two or more to simulate different sections of the system would provide more accurate results. Thus, in the proposed summer project, I will be working with other undergraduate researchers from the engineering department, who have been working on some other simulation tools.

3. Student's Responsibility

I am working with a group consisting of three Ph.D. students from ICS (Michael Moore, Ryota Egashira, Akihiro Enomoto), one under graduate majoring in mechanical engineering, and two under graduates majoring in biology, and myself, majoring in chemical and computer engineering.

The first step into modeling this potential communication system was to find an appropriate model for gap junction diffusion. The second step into modeling this potential communication system was to find a simulator that could model intercellular interactions; especially diffusion. The third step was to study the mathematical basis of the stochastic algorithms, since they provide more accurate data than deterministic algorithms. I have presented two group meetings, one on simulators, and the other on the mathematical algorithms. The presentation materials that I have created are attached to the end of this proposal. The last step is to create our own model and simulation algorithm that would correctly simulate the biological network we are trying to create.

In the above mentioned steps, I will be working closely with one of the undergraduates on creating the model using Cellware and E-Cell (the simulator that Omar is researching) and compare results to see which simulator produces the most accurate data. In particular, my responsibility is to create a working, accurate stochastic model. In preparation for creating a realistic model that takes a stochastic aspect of living organisms into account, I have studied the mathematical basis for those built-in stochastic algorithms: Gillespie's Stochastic Simulation Algorithm [3], the First Reaction Method [4], the Tau-Leap Method [5], Gibson's Next Reaction Method [4], and StochSim [5]. These algorithms are used to determine the evolution of a chemical species over time taking into consideration the randomness and natural fluctuations of a biological system. The deterministic and stochastic algorithms meet when the number of molecules becomes large.

The outcome of the proposed summer research is expected to help the researchers determine the best route for their research. The results will give the researchers an idea of what to expect when working in vivo. Part of my responsibility as well is to work closely with my fellow peers and overseers to achieve the best results. I will be meeting with Dr. Nakano weekly, and will occasionally have group meetings with the other members of the group.

4. Project Timeline

Table 1 shows the project milestones of 2005 summer months. Dr. Nakano will be leading the proposed project. I will meet with Dr. Nakano weekly to review progress and discuss the next steps. There will be occasional group meetings and other research members (undergraduate students, and Ph. D. students in the same research group) will be invited.

Table 1: Project Time Table

Week 1	Finish creating a working stochastic model to compare with a deterministic one. Keep all results well documented.
Week 2	Identify the strengths and weaknesses of a stochastic simulation versus a deterministic simulation; and determine which aspects of the simulation should be run stochastically and which should be run deterministically
Week 3	Make detailed simulation plans. Decide what performance measures to obtain through simulations. Create a detailed document with the simulation plans.
Week 4	Continue with simulation implementation and work out many of the bugs in the simulation
Weeks 5 and 6	Conduct extensive sets of simulations according to simulation plans made in the fall quarter, week 9 and 10 (including changing variables and experimental factors to observe the effect it has on calcium and IP_3 propagation.
Week 7	Analyze simulation results from weeks 2 to 6. For analysis, visualize emerging networks formed. Find out any correlation among the network conditions and network formation
Weeks 8 and 9	Organize simulation results, and start writing a project summary. Create presentation slides about this project and be prepared for a

	meeting scheduled at the final week.
Week 10	Provide a seminar and present research results to all members.

5. References

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