

Parallel Simulation of Immune System Modeling a prospectus

J.P. Daigle

Department of Computer Science
Georgia State University

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Outline

Parallel Simulation

Simulating the Immune System

The Immune System
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iC2MPI

IMMSIM

Conclusion

overall conclusions
For Further Reading

1 Simulating the Immune System

- The Immune System
- Simulation Challenges

2 Parallel Simulation

- PDES
- iC2MPI

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4 Conclusion

- overall conclusions

Motive

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Our motives for wanting to simulate the immune system are:

- 1 To cure cancer: immune system specific challenges
- 2 To make power grids more stable: applying the lessons to other physical systems.
- 3 Complex adaptive systems are just an interesting challenge

Understanding the Immune System

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The immune system of vertebrates consists of two parts
Innate Immune System The innate immune system is the first line of defense against common infections.

Includes:

- skin, saliva, mucos, outer barriers
- macrophages, phagocytes, non-discriminate inner barriers

Adaptive Immune System The adaptive immune system acquires new information over an organisms life.

Includes:

- bone marrow
- the lymphatic system (lymph, lymphatics, lymph nodes, spleen, thymus, etc.)
- specialized cells (T-Cells, B-Cells, mast cells, macrophages, dendritic cells, more)

The Adaptive Immune System

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The adaptive immune system is what we are interested in simulating. In particular, we are interested in acquired immunity, such as for chicken pox. This is a complicated process that involves many different components, all with a lifecycle and a variety of different states.

The Immune Response

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A simple view of an immune response:

- 1 A novel *pathogen* enters the body, through a breach in the skin or other outer defense.
- 2 The innate immune system begins responding to the invader. Dendritic cells engulf the pathogen and carry antigen to the lymph nodes.
- 3 The dendritic cells present antigen to T-Cells in the lymph nodes.
- 4 The T-Cells activate B-Cells, which in turn produce antibodies.
- 5 The antibodies return to the site of the infection and destroy the pathogens

Adaptation

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What is missing from the previous slide is the knowledge that the immune system will respond much more quickly to a known pathogen than a novel pathogen. This is because some B-cells become *memory cells*, which retain the ability to quickly make particular antibodies. For new antibodies, populations of B-Cells have to undergo mutation in order to “find” the correct antibody.

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- A typical immune response involves about 10^{12} cells of different kinds.
- Large populations are traditionally simulated through the use of ordinary differential equations, which average the behavior of large populations.
- Many systems are discrete and history sensitive.
- Another approach is needed.

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Discrete Event Simulation

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- Models each event at a particular level of granularity separately
- Draws on fields such as cellular automata and Object Oriented Programming
- Drawbacks include loss of efficiency
- Advantages include increase in accuracy

Parallel Discrete Event Simulation

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- Cellular Automata is a Common Approach
- Issues Include...
 - Load balancing
 - synchronization

Optimistic or Conservative?

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Getting Out of Sync

Optimization of a parallel or distributed simulation includes allowing different processes to move at different speeds. Relaxing this time step constraint can have large benefits. But it can cause problems if a process executes before it gets important information from another, slower, process.

Optimistic PDES Based on **rollback**, the simulation proceeds as if there are no sync issues, deals with problems if they arise.

Conservative PDES Based on **lookahead**, the simulation guarantees that there will be no sync issues.

We Can't all be Experts

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The who with the what now?

A persistent problem in modeling and simulation is that the system experts are not simulation experts, and simulation experts do not always know the physical systems well. In Parallel simulation, this traditional problem is even worse.

- Optimistic or Pessimistic
- Knowing how to write parallel code
- Understanding event windows

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The iterative C to MPI platform is an experimental parallelization Engine being developed at GSU by Harnish Botadra and Sushil Prasad. The goal is to solve one level of the experts problem.

- Generates MPI code from C code.
- May handle load balancing
- Does not handle lookahead or Rollback?

Requirements

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iC2MPI cannot take random C code and generate MPI code from it. There are restrictions and requirements for the User.

- C code must be iterative
- Simulation must be grid partitionable, CA work best
- The user must plug in the program graph, node data structures, and the node computation function.

Simulating the Immune System with IMMSIM

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- The first DES for the IS: 1992 (Kleinstein and Seiden)
- Based on a modified cellular automaton
- Focuses on a particular behavior, the original scope is limited to portions of individual lymph nodes

IMMSIM

IMMSIM is represented as a triangular lattice, each node of which may contain 0 or more entities such as T-Cells, B-Cells, antibodies, or antigens.

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Cellular Automata

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Cellular Automata

- consist of a discrete lattice of sites
- evolve in discrete time steps
- each site takes on a finite set of possible values
- each site evolves according to the same *deterministic rules*
- The rules for evolution depend on a states in the *local neighborhood*

IMMSIM

- consists of a triangular lattice of sites
- evolves in discrete time steps
- each site takes on a finite set of possible values
- each site evolves according to the same *probabalistic rules*
- The rules for evolution depend on the state of the site

Other parts of the simulation

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Entities

IMMSIM defines 6 cellular and 5 molecular entities. Cellular entities can be viewed as *stochastic finite state machines*. Simply, the state of an entity is determined by a probability function on its current state and a molecular input.

Repertoire

- binding cells have a receptor, a bit string of length l
- all entities have a number of distinct classes, equal to $2^{N_e l}$ where N_e is the number of receptors for the cell type.
- There are potentially 2^{21} different classes of B and T cells in the simulation. This is less than the natural lower limit of 2.5×10^7 , but its a start!

mutation

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- Each B-Cell produces antibodies, which must match a given antigen. This is accomplished by measuring the Hamming Distance between two strings, but...
- In the real IS, cells mutate to match antigens
- This must be simulated as well

the process of the simulation

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- 1 population & antigen inputs chosen
- 2 all possible interactions in a site are examined
- 3 a subset of of interactions are simulated
- 4 new cells are born, divide, or die
- 5 diffusion of entities into neighboring sites
- 6 repeat from step two

iC2MPI and ImmSim

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iC2MPI

- requires an iterative input
- must be grid partitionable
- discrete and easily identifiable node-computation functions

IMMSIM

- iterative computation
- divided into a triangular lattice
- node based data structures
- most computations seem to be stepwise enacted on each node

ImmSim seems to be an appropriate candidate for testing the iC2MPI platform. It remains to be seen how well this can be done, however.

The to-do list

- Make sure ImmSim compiles and runs correctly on a Parallel Machine
- Establish a solid group of test inputs
- Create a canonical, simple C program as an iC2MPI tutorial
- Create the user inputs for ImmSim
- Test and write up
- There exists a PVM version of ImmSim, it would be nice to acquire it as well.

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For Further Reading II

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