Computer Immunology

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Intro

This talk is somewhat naturally divided into two parts.

The first is using artificial immune systems (AIS) to study the biological immune system. We discuss multiple methods of doing so throughout the talk.

The second is using AIS to study other non-biological computational problems. Here the principles of the immune system are used for other purposes. Think using ‘evolution’ to solve other problems in genetic algorithms.

The final section makes a swap back to some real world results using models.

ABM Approach to Immunology

- ABM - Agent Based Model
- Each entity is called an agent - represents a single cell or pathogen
- Computer program encodes an agent's behavior and rules for interacting with other agents
  - Cell death (deletion)
  - Division (copying)
  - Changing an internal state variable - for example to model cell activation or differentiation
- Each agent can have variables such as
  - Size
  - Location
  - Age
  - What receptors are on its surface

ABM Approach to Immunology (cont)

- Agents are assigned a section in memory
- Can interact locally with nearby agents, following the set of rule given by the program
  - Thus the behavior at the low level is prespecified
  - Interested in global behaviors

Why Use ABM to Study Immunology?

- The agent behaviors can directly incorporate biological knowledge or hypotheses about low-level components
  - even if they cannot be expressed mathematically
- Data from multiple experiments can be combined into a single simulation
  - to test for consistency across experiments
  - to identify gaps in our knowledge
- Easy to perform sensitivity testing of parameters

Biology Refresher

- B Cell - responsible for producing antibodies
- T Cell - type of white blood cell that circulate around our bodies, scanning for cellular abnormalities and infections
- When your body is infected with a particular germ, T- and B-cells will respond.
  - These selected cells then quickly multiply, creating an army of identical cells to fight the infection.
  - Special types of T- and B-cells 'remember' the invader, making you immune to a second attack.
- Antibody - Y shaped proteins that bind to antigens to inactivate it
- Antigen - any substance capable of triggering an immune response
  - Viruses, toxins, bacteria, etc.

Cellular Automata (CA) Models of the Immune System

We cover two:

1. IMMSIM
2. ma_immune

IMMSIM - Early CA Model of the Immune System

T-cells, B-cells, and other antigen-presenting cells were represented as bit strings.

Usually run on a small grid such as a 15x15 hexagonal grid.

B-cell receptors interact with ‘bare’ parts of an antigen. T-cell receptors interact with the pair of an antigen and molecule called MHC II.

Bindings are determined by the checking if two bits are complementary. 1 matches 0.

If the number of matches is passed some binding threshold (hyperparameter), then the agents interact.

In any given step, one potential action of an agent is chosen probabilistically. These include cell death, cell division, and antibody production.

ma_immune (CA model)

Study generic immune cells patrolling in a sample of tissue. Used for studying local tissue infections. (cells are immobile, packed, and infection spreads to neighbors)

Used to study the importance of spatial localization

Differential Equation models assume uniformly distributed populations. This is a fault that ma_immune addresses.

Found that grouping infected cells into patches rather than uniformly distributed better matches experimental data with influenza A infection data.

Hybrid Approaches - Simmune

Combine Differential Equation modelling with agent based models.

Simmune is a two-level immune system simulator. Lower level molecules dynamics are modeled using continuous differential equations. They move by diffusion rules.

At the higher level, cells are modeled using discrete ABM. Rules are specified by user.

Runs on a 3D grid. User defines compartments (thymus, lymph nodes). Diffusion rate, types of cells, etc. are hyperparameters defined by user.

Hybrid Approaches - CyCells

Similar to simmune with the same two level break up.

One difference is that the usage and its functions are better documented and it is open source.

CyCells uses the ‘sense-process-act’ abstraction where a user specifies a sensing procedure for a cell type, a processing function that describes how the cell is activated, and an action (like death or division).

Brief Aside for Performance - Lazy Evaluation

A person has an estimated 10^7 B cells and T cells combined.

The ABM models discussed so far only look at a small number of cell interactions (10-100 T or B cells) which is good for studying some questions but not good for cross-reactivity and alloreactivity.

Lazy Evaluation models only the 10^2 - 10^3 that actually have the affinity to participate at any time.

Complicates the programming. Reduces the time and memory required by a lot.

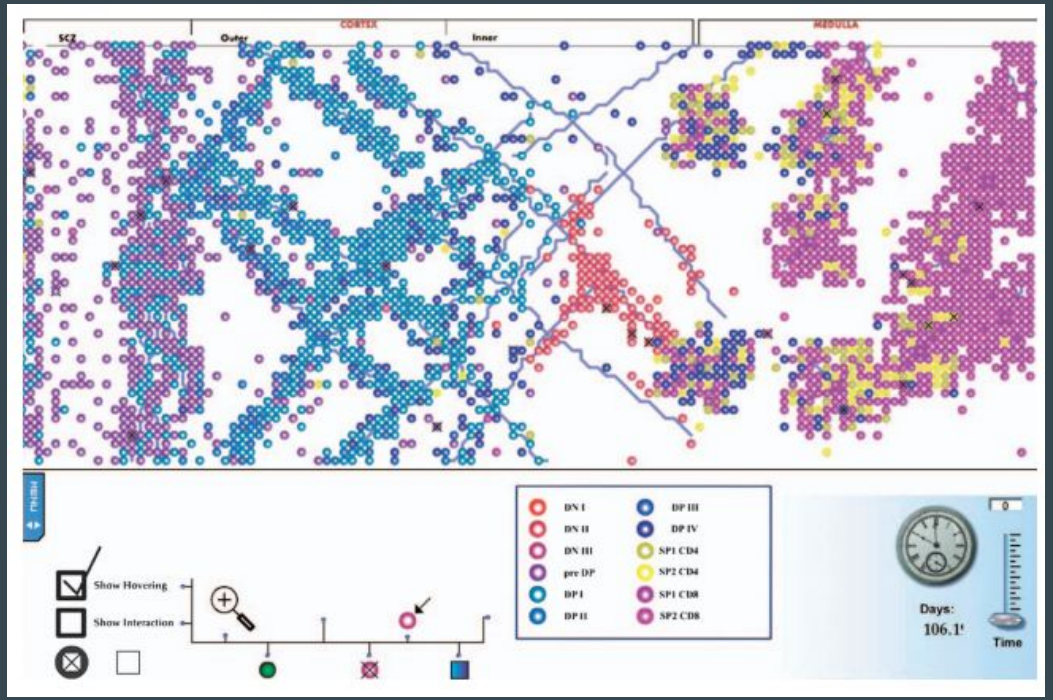
Statecharts - A visualization

Not a CA, not an ABM (In terminology or motivation). But similar.

Allows better collaborative communication.

Can move, zoom in, click on a particular agent to view status, etc.

Observe thymocytes and other interacting cells in the Thymus (The agents).



Non-Biological Applications

Immune System ideas have been used for:

- Control Engineering
- Robotics Scheduling
- Fault Tolerance
- Bioinformatics
- **Computer Security**

Computer Security = Computer Immune Systems

- Like the natural immune system there are computer defenses that correspond to non-specific and specific responses
  - Non-specific
    - Firewalls
    - access controls (logins/passwords)
  - Specific:
    - known as intrusion-detection systems(IDS), recognize active intrusions, including those that may not have been seen before
    - ‘anomaly’ IDS can detect novel forms of attack, while signature detection systems respond only to known attacks, corresponding to a secondary response
    - include injected foreign code (as in the case of viruses)
    - exploitation of vulnerabilities in existing code by illegitimate user

Computer Security = Computer Immune Systems

- Unit of protection - single computer
- Cell – each executing process
- Discrimination between normal and abnormal behavior is based on what functions (or subroutines) are normally invoked by the running program
  - Peptides – short 6-10 subsection of a program's system-call history, define normal behavior of the program
- Organism – local area network (LAN)
  - behavior of the protected system can be characterized by its normally occurring TCP/IP connections

Controlling Autoimmunity

- Avidity
  - A detector is required to accumulate enough matches to exceed the activation threshold to become active
  - Reduced autoimmunity significantly
  - Activation thresholds are analogous to avidity in the natural immune system, where multiple receptors on the lymphocyte must be bound simultaneously in order for it to become activated. Here, the integration of signals takes place over time instead of in space
- Costimulation
  - A human is needed to give the second signal once the first is triggered
  - If a detector received costimulation, it entered a competition to become a memory detector.

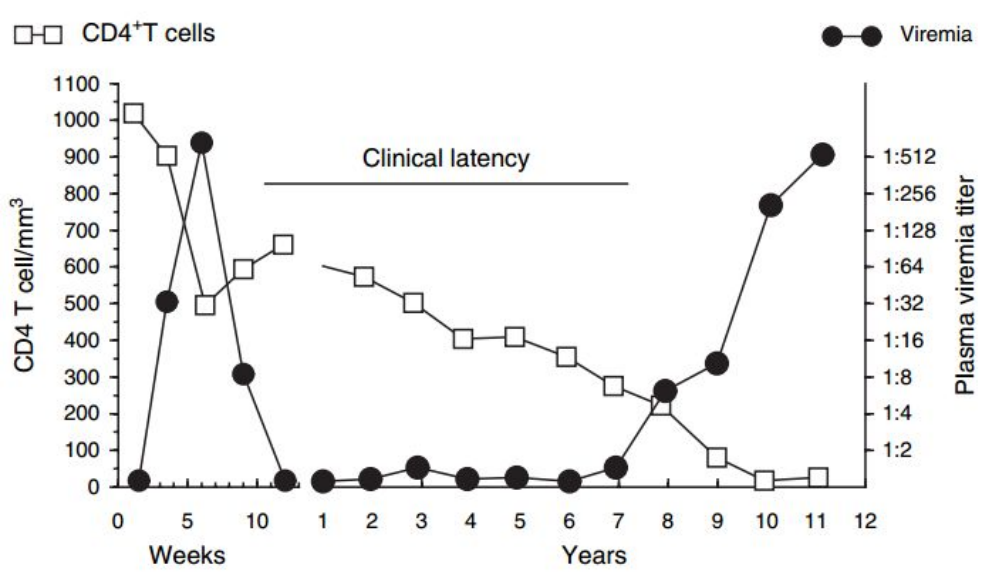
AIS applied to problems of Biomedical significance

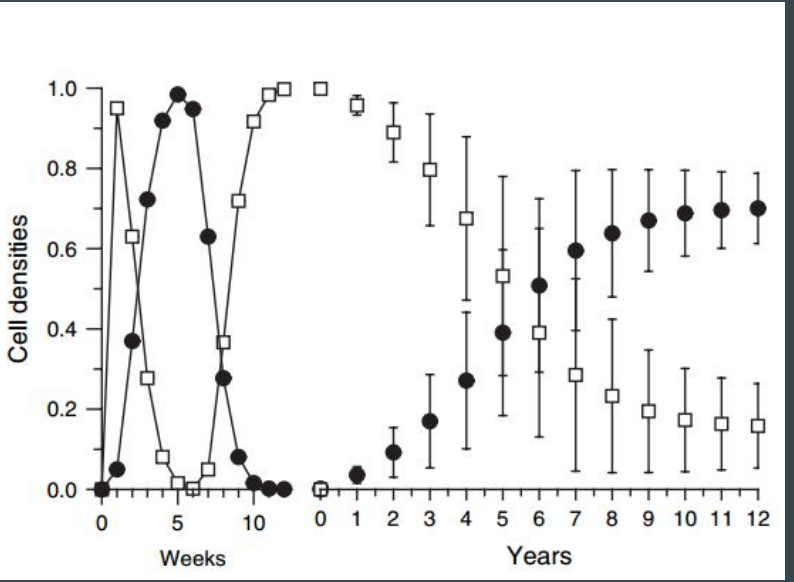
- HIV
- Mtb (Mycobacterium tuberculosis)
- Influenza (the Flu)

HIV

- Zorzenon dos Santos and Coutinho introduced a CA model
  - 2D
  - models HIV in lymph nodes
  - reproduces the two time scales of an HIV infection
    - short time scale (weeks) associated with the primary response
    - long one (years) associated with the clinical latency period and the onset of acquired immunodeficiency syndrome (AIDS)
- Strain et al
  - 3D
  - incorporates additional biophysical properties.
  - goal was to study the role of spatial effects in viral propagation (high density vs low density)

HIV - Zorzenon dos Santos and Coutinho





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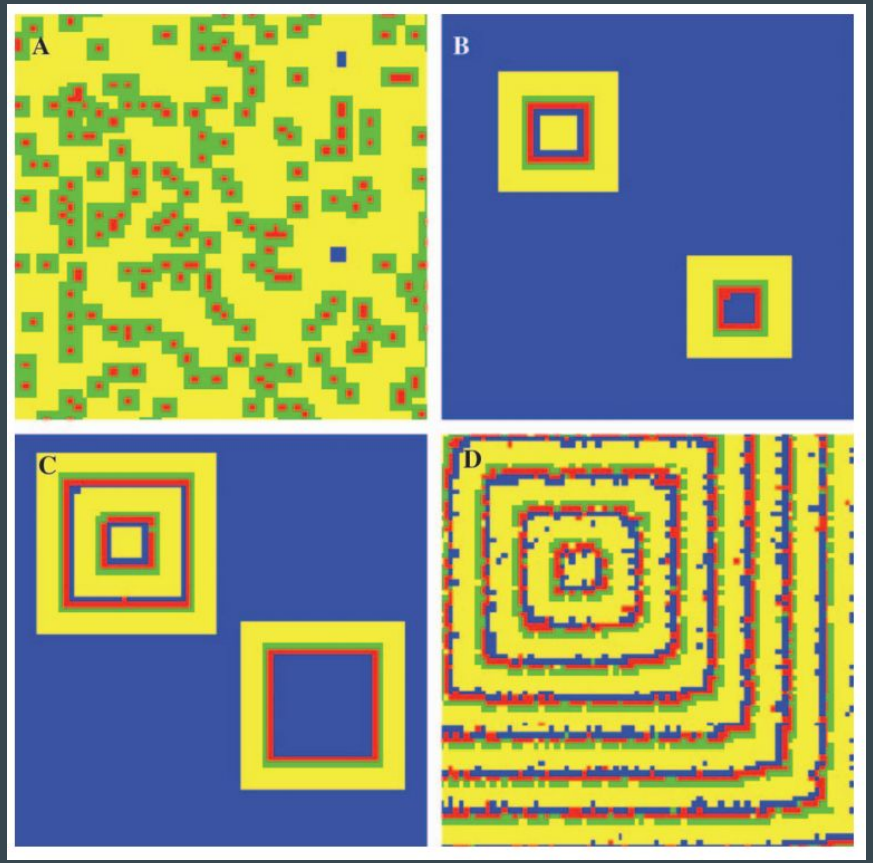


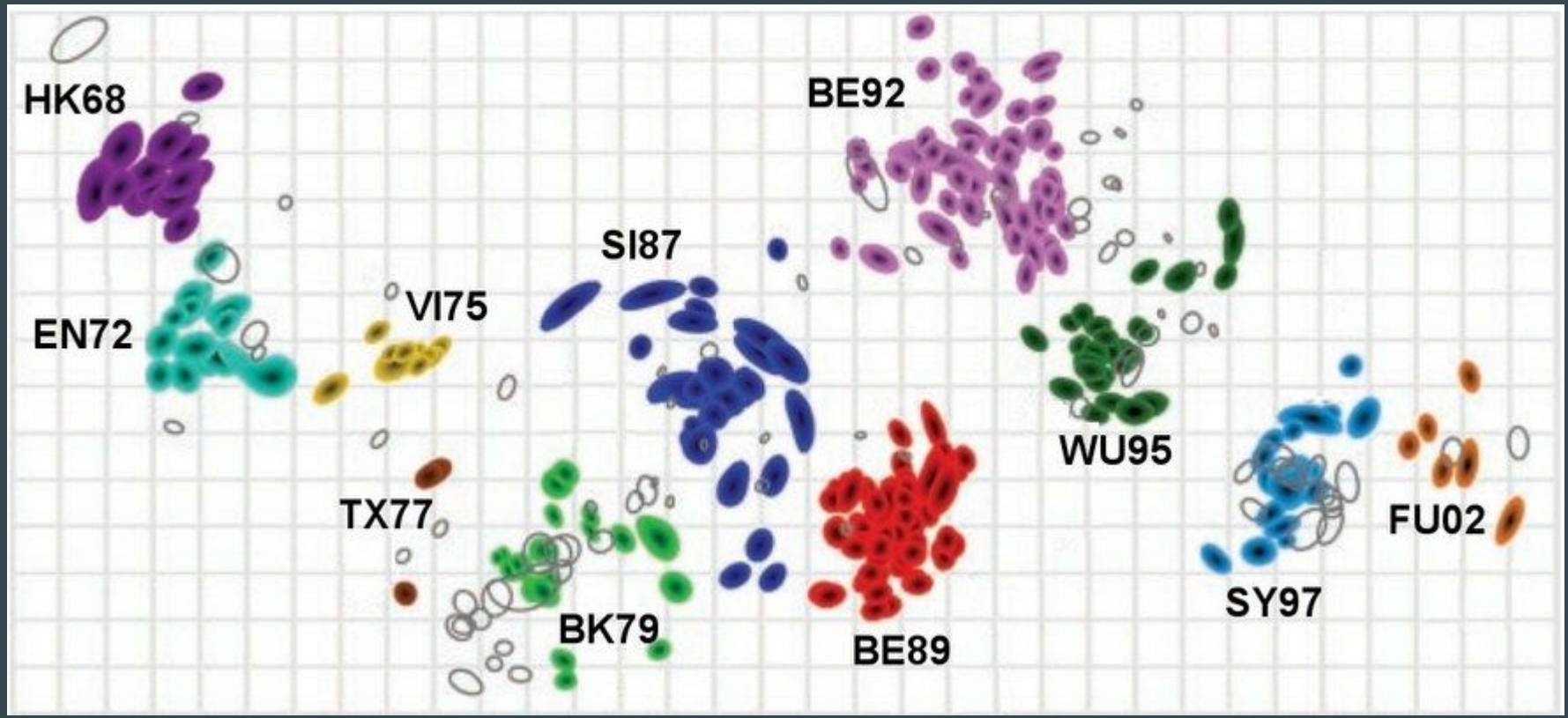
HIV Study Conclusions

- Neither model accounts for target cell movement
- Allowing the cells to move, for example, would prevent the formation of the perfect square waves, and it could potentially prevent the emergence of the more complicated square patterns that were interpreted as the onset of AIDS
- The second model is interesting because it highlights how ABM can be used to study the contribution of spatial effects on viral propagation
    - the basic reproduction ratio (R0) was calculated for HIV, taking into consideration the localized spatial nature of viral bursts.
    - The calculation predicts that viral propagation is limited by viral stability at low target cell density, and by geometry (target cell's radius) at high cell density

Other Applications

- Models of Mtb (Mycobacterium tuberculosis)
  - a two dimensional square grid with toroidal boundary conditions, representing a cross-section of alveolar lung tissue.
  - They (Segovia-Juarez) found that intracellular growth rate of Mtb is positively correlated with the number of extracellular Mtb at early times of the infection and at much later times post infection, but it is negatively correlated at intermediate times
- Influenza (the Flu)
  - led to the concept of ‘antigenic cartography’
  - We use antigenic cartography, along with genetic and population biology techniques, to study basic questions in pathogen evolution, and coevolution with the acquired immunity in host populations

Antigenic Cartography



Summary/Conclusions

- Computational immune systems are designed to behave analogously to the natural immune system
- Although the computational mechanisms are crude compared with their biological analogs, the resulting computer immune systems models can show surprisingly realistic behaviors and sometimes be calibrated closely with experimental data

Summary/Conclusions - Strengths/Limitations

- Limitations
  - It can be difficult to identify the proper level of abstraction, decide what aspects of the immune response are important and what their proper role or ‘purpose’ is, and how they should be translated into computation.
- Strengths
  - In spite of these limitations, computational abstractions and concepts have proved powerful enough to provide important insights into immunological processes and to solve challenging engineering problems.
  - By abstracting away from physical realism, AIS can enhance our understanding of the large-scale patterns of interaction that occur among the millions of individual components that comprise a natural immune system

Summary/Conclusions - Why Use ABM?

- if a synthetic computer model captures the relevant phenomena, it is much easier to perform experiments on the model than on the natural system
  - may be used to predict efficacy of new treatments and vaccines
- models can be flexible, allowing researchers to try out variations within the same framework and to add complexity to the model incrementally.
  - This greatly simplifies the work of testing alternative hypotheses

Summary/Conclusions - Why Computer Immune Systems

Limitations:

- Avoiding autoimmune responses when confronted with malware or viruses is difficult since program behavior can be so diverse.
- Deciding on the correct response to anomalies can be difficult (costimulation incurs a burden on users).

Strengths:

- Don’t need to update the software with new virus definitions constantly.
- Can attack intruders that have never been seen before.
- Can learn from new attacks and become better next time (adaptation)

Questions?