A Beginner's Guide to Simulation in Immunology

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Outline

- Introduction
  - Motivation
- What is Simulation?
  - Simulation approaches
- The need of simulation for immunology
- A framework for the development of simulation for the immune system
  - Challenges and pitfalls
- The potential contribution of system dynamics
- Conclusions and future work

Introduction

- Immune system is a set of biological structures and processes within an organism that protects it against disease by identifying and killing pathogens and eliminating danger.
- Immunology can benefit of simulation because:
  - Compared with real-world experimentation, simulation is time and cost-effective.
  - Laboratory experiments are expensive and have to be in agreement with ethical specifications.
  - The accuracy of the results of *in vitro testing relies on environmental conditions,* the quality of the material collected and the appropriate procedure to conduct experiments.

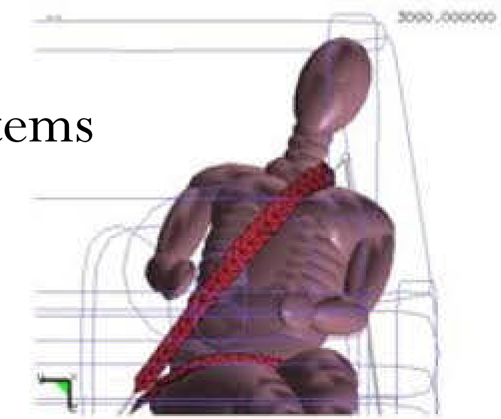
What is Simulation?

- "*imitation (on a computer) of a system as it progresses through time*"
- Purpose:
  - understand, change, manage and control reality
  - Better understanding of the system and/or to identify improvements to a system
- Focus on the main aspects of the real system
- Models exclude unnecessary details of the original system
- Predicts the performance of a system given a specific set of inputs.
- Experimental approach to modelling a "*what-if*" analysis tool
- User determines scenarios and simulation predicts outcomes
- Decision support tool

What can I Simulate?

- Natural systems: systems whose origins lie in the origins of the universe
  - atoms, molecules and galactic systems

- Physical systems designed by humans
  - cars, mobile phone networks and computers
- Abstract systems designed by humans
  - mathematical models
- Human activity systems
  - family, schools, cities and criminal justice systems



Characteristics of the Simulation Approaches

- Static or dynamic (time representation)
- Stochastic or deterministic (probability)
- Continuous or discrete (how variables change)
- Top-down or bottom-up

Simulation Approaches

- Mathematical (numerical) simulation (characteristics??)
- Monte Carlo simulations
- System Dynamics simulation
- Discrete-event simulation
- Agent-based simulation

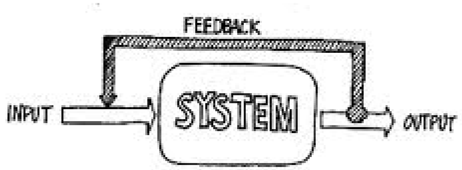
These are the approaches of our interest

Simulation Approaches

…That one is easy:

- Suitable for system simulation
- No need for indepth understanding of mathematics
- Some approaches allow individual behaviour, memory, spatial localization
- I can see what is going on over time

System Dynamics

- Continuous top-down approach
- uses stocks , flows and feedback loops 

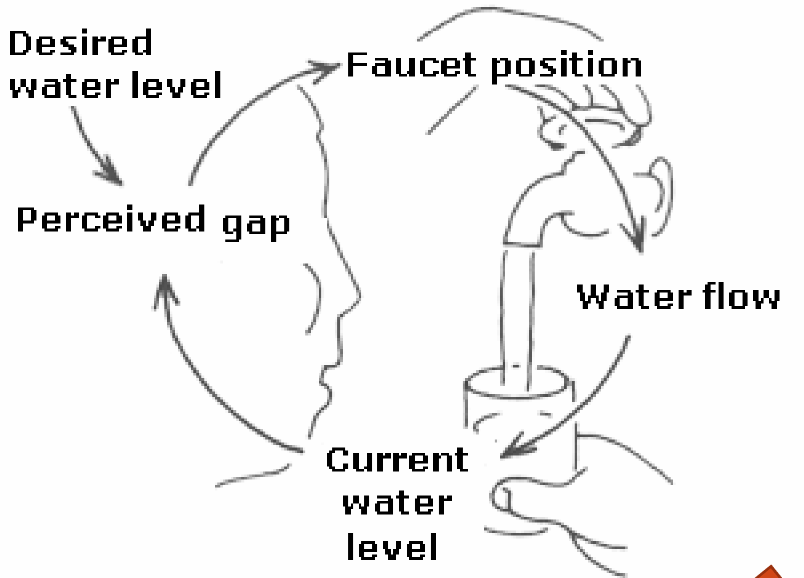
as concepts to model the behaviour of complex systems

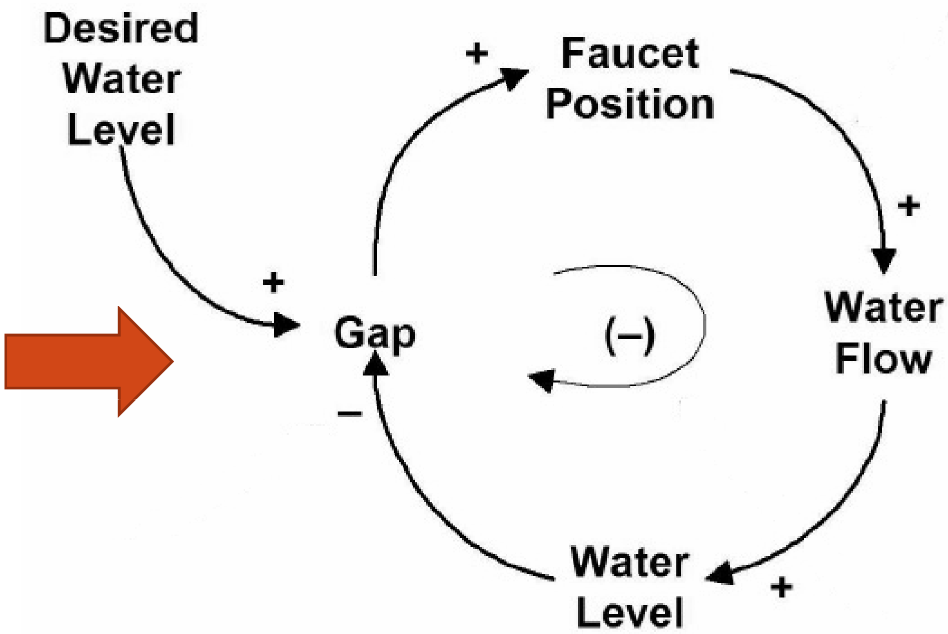
- Based on systems theory
- Initially: understand complex aggregate behaviours in industry
- Currently: any complex system with interdependency, mutual interaction, information feedback and circular causality
- Implementation: differential equations solved for a time interval
- Few studies apply it to immune problems

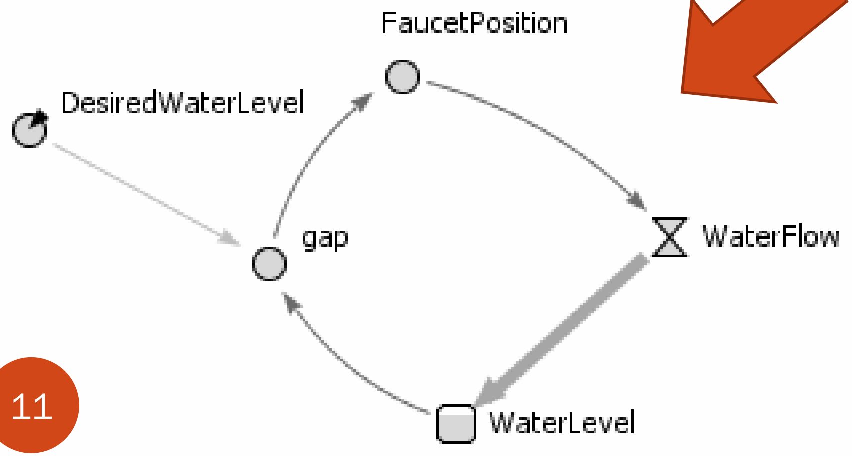
System Dynamics vs ODEs

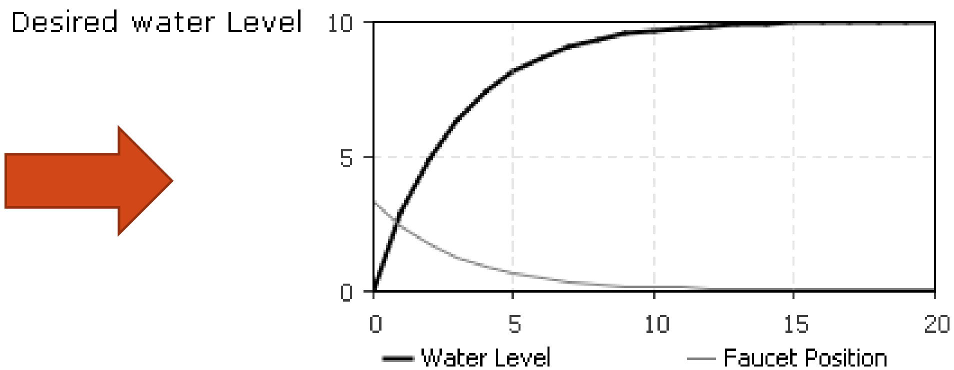
- Ordinary differential equation models are more commonly used
- System Dynamics encompasses mathematical formulations and of keep info of how the elements change over time
- No need for an indepth understanding of mathematics to formulate a model (for many cases)
  - The differential equations are implicit in the system's structure
  - Relationships between the elements modelled can be established with experimental data

System Dynamics – An Example









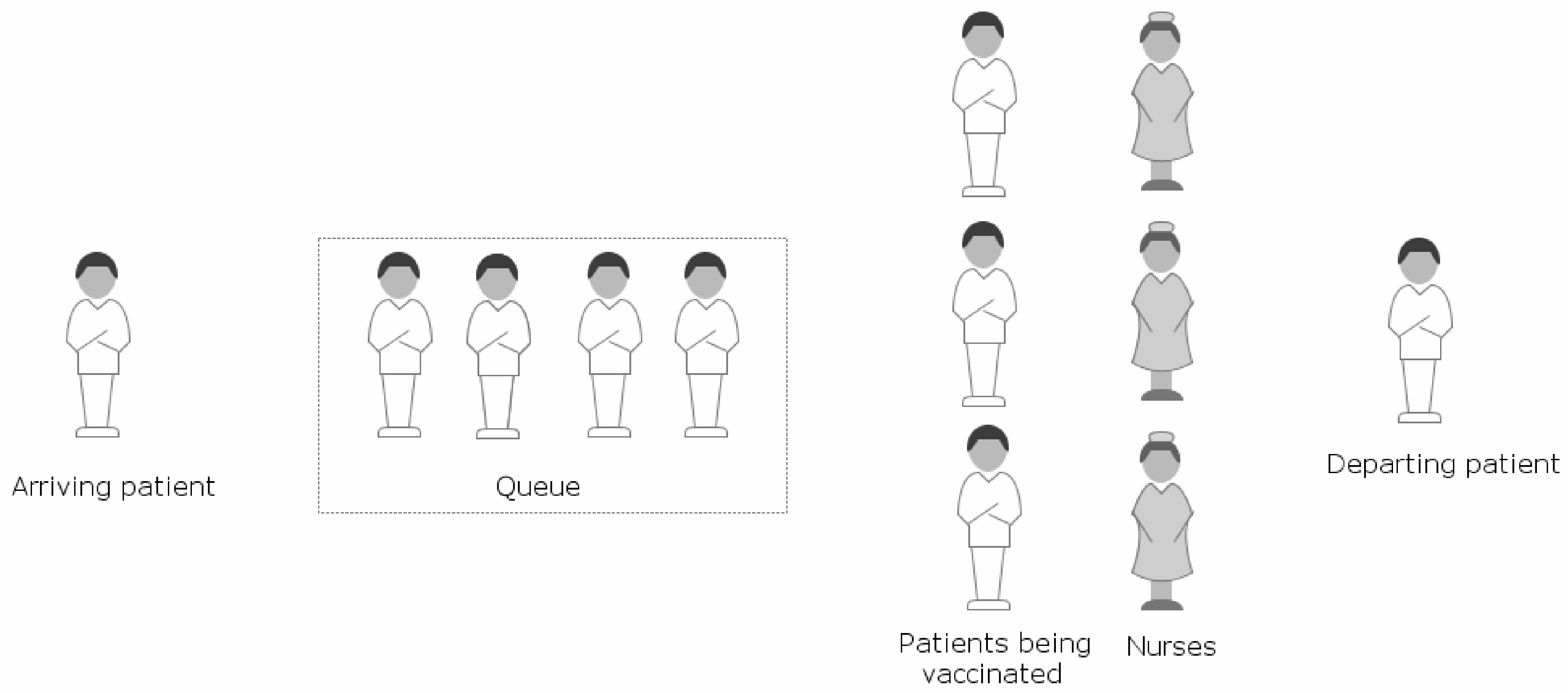
Discrete-event Simulation

- Top-down approach
- Set of entities being processed and evolving over time according to the availability of resources and the triggering of events
- The simulator maintains an ordered queue of events
- Each event occurs at an instant in time and marks a change of state in the system.
- Process-oriented
- Passive entities (no proactivity)
- Entities individually represented and tracked over time
- Stochastic

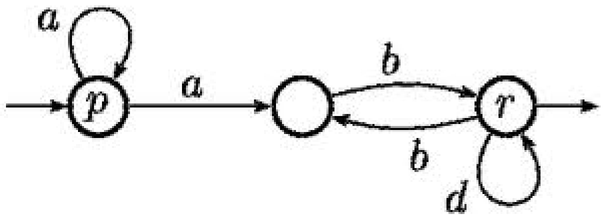
Discrete-event Simulation – Main Loop

```
// Initialization phase
EndingCondition = FALSE;
Initialize system state variables;
Initialize Clock (usually starts at simulation time zero);
Schedule an initial event (i.e., put some initial event into the Events List);

// Main Loop
while EndingCondition == FALSE do
Set clock to next event time;
Do next event and remove from the Events List;
Update statistics;
end

// Output phase
Generate statistical report;
```

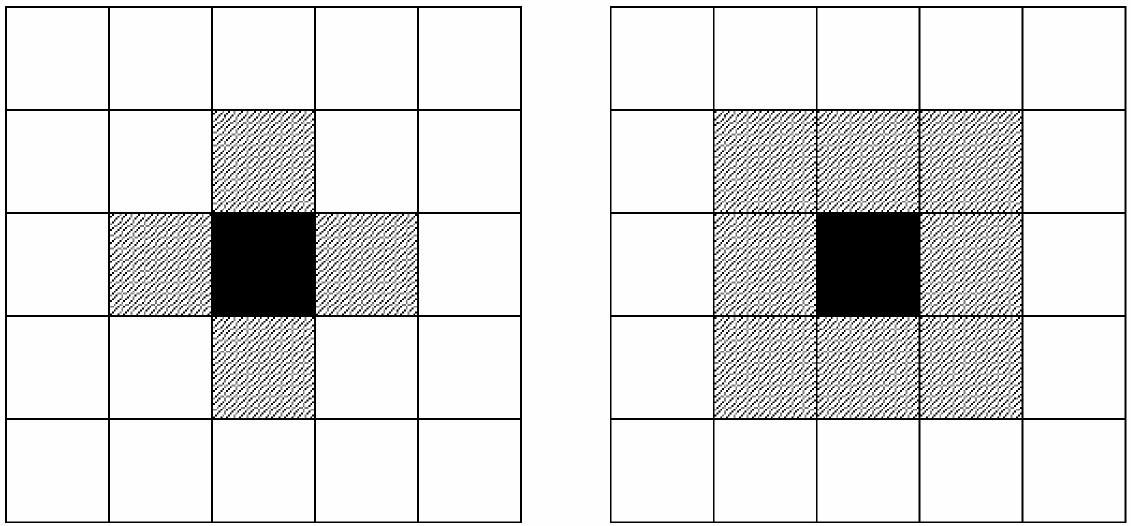
Discrete-event Simulation – Example



Agent-based Simulation: Cellular Automata

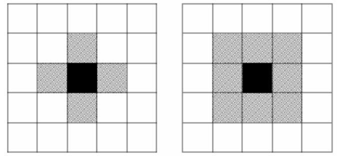


- Regular grid of cells
- cell: finite states and dimensions
- For each cell, a neighbourhood of other cells is defined
- Any automata: initial state and the subsequent states will defined by some fixed rule



(a) Von Neumann (b) Moore

Cellular Automata - Example



(a) Von Neumann (b) Moore

- Conway's Game of Life:
  - No players
  - evolution determined initial state, defined by the user.
  - The universe: infinite 2D orthogonal grid of square cell
  - Cell is either in the state live or dead and has eight neighbours: cells that are horizontally, vertically, or diagonally adjacent.
  - At each step:
    - cell with fewer than two live neighbours dies
    - cell with two or three live neighbours lives on to the next generation
    - cell with more than three live neighbours dies.
    - dead cell with exactly three live neighbours becomes a live cell.
- http://en.wikipedia.org/wiki/Conway's_Game_of_Life

Agent-based Simulation

- Autonomous agents that interact with each other.
- The agents' behaviour: rules determine how they learn, interact with each other and adapt.
- Overall system behaviour arises from the agents' individual dynamics and their interactions (EMERGENCE)

Agent-based Simulation

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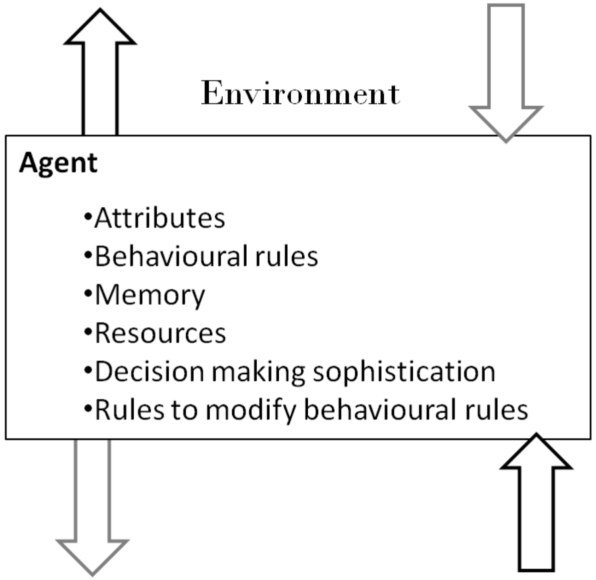
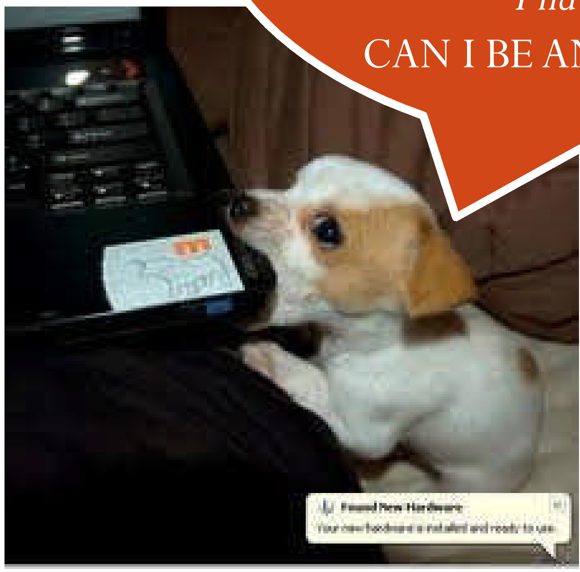
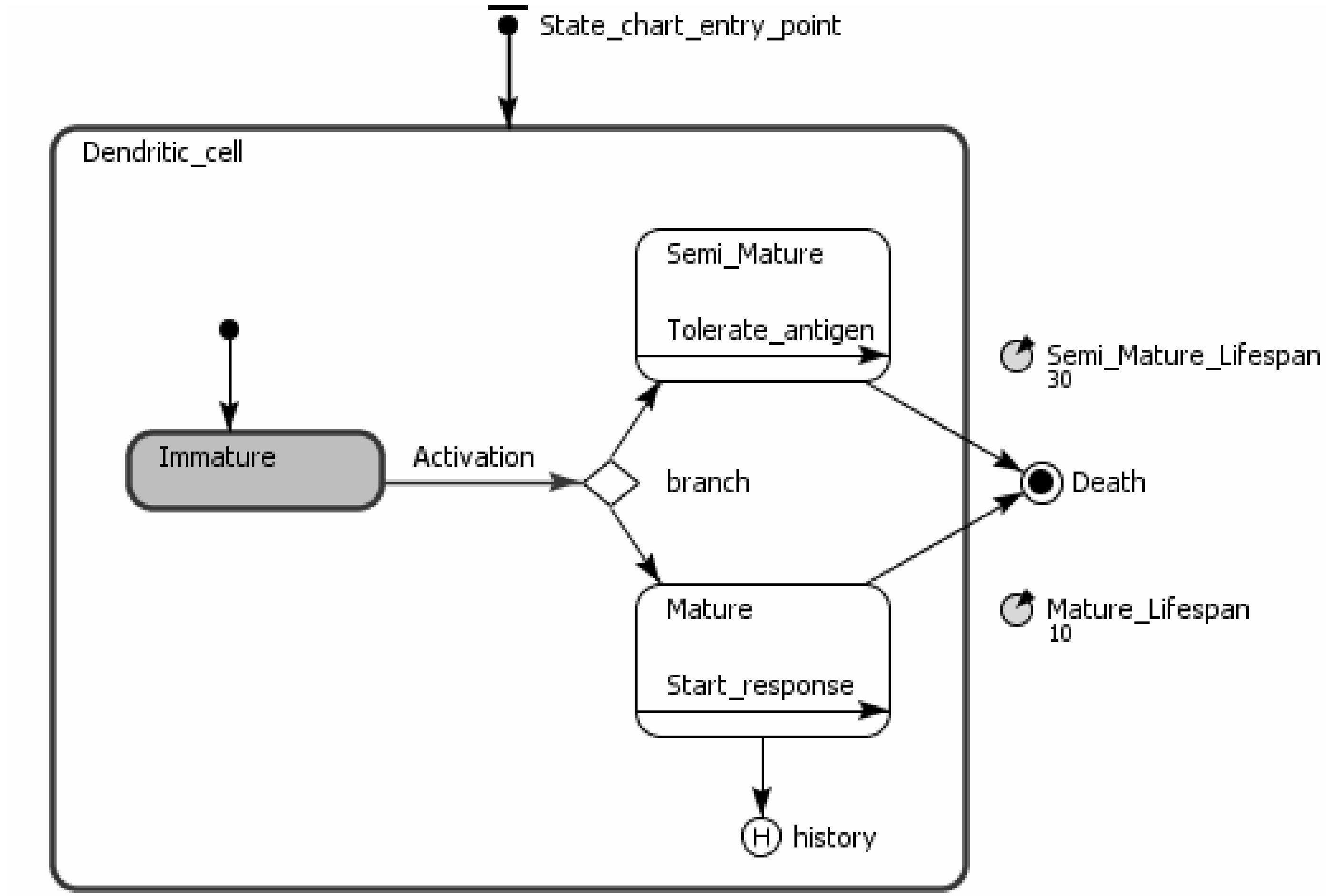




Agent-based Simulation – An example

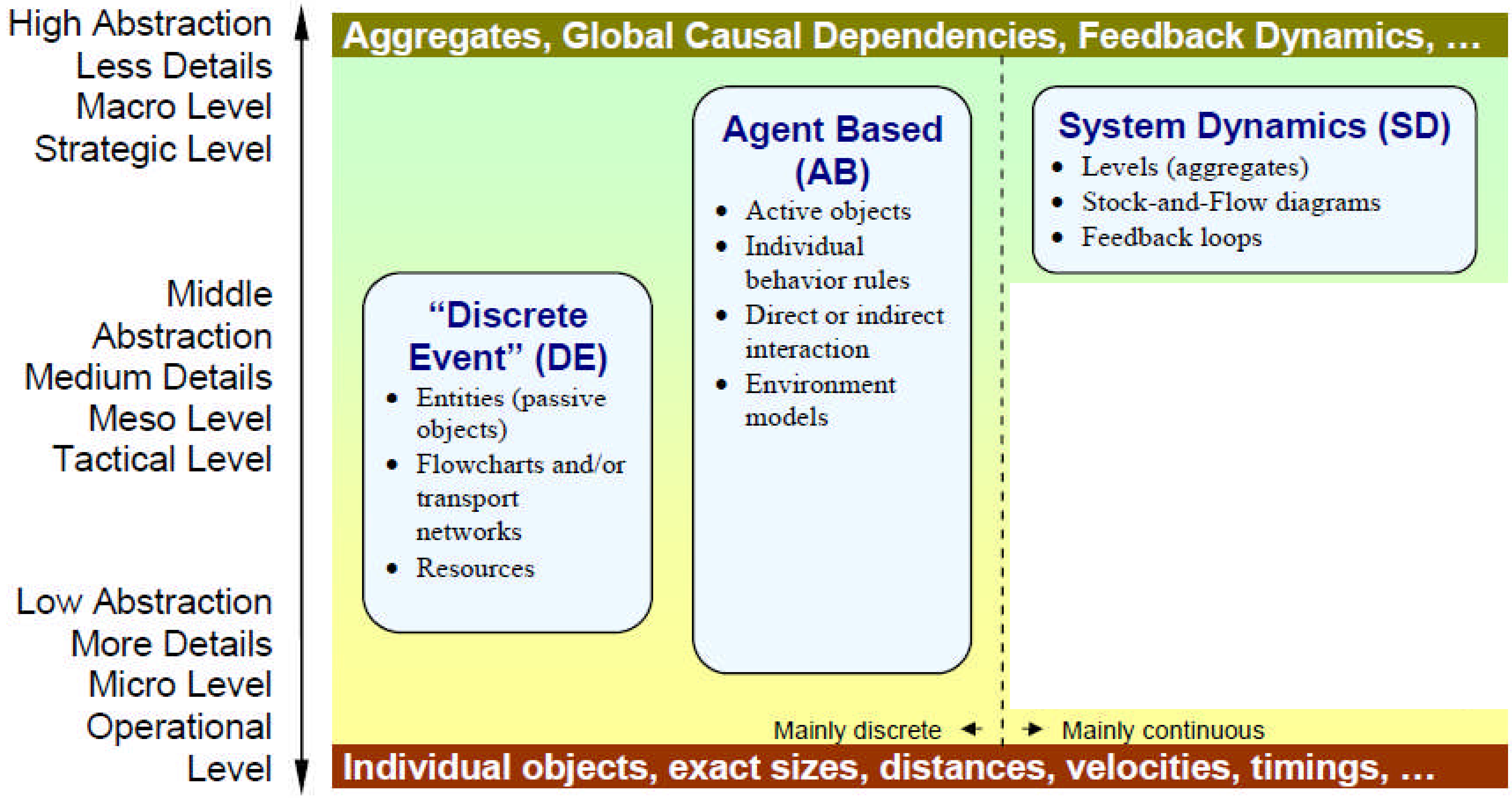
- Dendritic cells (DCs) are immune cells that search for signs of danger (possible antigen) in the organism.
- Initially: immature state until contact with a possible antigen, where they become activated.
- Then DC investigates if it is a real danger or not.
- If yes, the dendritic cell becomes mature; otherwise, semi-mature
- Mature: immune response should be triggered and information about the antigen should be kept as history.
- Semi-mature: the foreign material should be tolerated
- DCs in an active state have a lifespan of days, while immature cells exist for longer
- For our example, we consider ten days for active cells and thirty days for immature cells

Agent-based Simulation – DC State Chart



And what now? Which one should I pick?

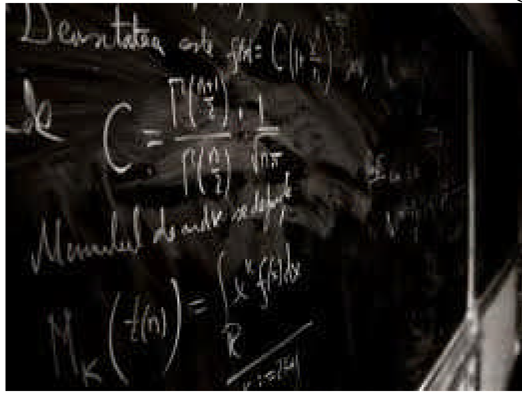
The choice of a modelling technique for a problem is driven by the resources available such as experimental data, understanding of the mechanisms involved, the hypothesis to be tested and the level of abstraction needed to test the hypothesis



High Abstraction
Less Details
Macro Level
Strategic Level
Middle Abstraction
Medium Details
Meso Level
Tactical Level
Low Abstraction
More Details
Micro Level
Operational Level
Aggregates, Global Causal Dependencies, Feedback Dynamics, …
Agent Based (AB)
Active objects
Individual behavior rules
Direct or indirect interaction
Environment models
System Dynamics (SD)
Levels (aggregates)
Stock-and-Flow diagrams
Feedback loops
"Discrete Event" (DE)
Entities (passive objects)
Flowcharts and/or transport networks
Resources
Mainly discrete
Mainly continuous
Individual objects, exact sizes, distances, velocities, timings, …

The Need for Simulation of the Immune System

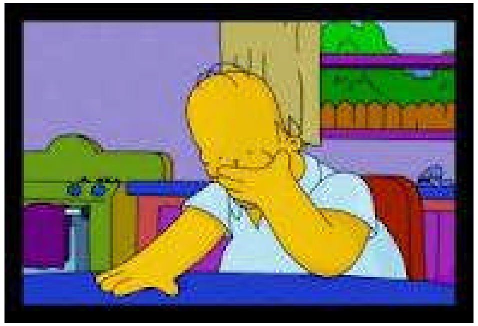
Is Mathematics Enough?



- Most work is based on math equations
- Mathematical models have enabled biologists and immunologists to improve their comprehension of models and methods
- Over 200 models developed
- Mostly ODEs
- However:
  - limits the modelling effort to simple dynamics involving few immune elements such as cells or molecules
  - Only allows analysis at an aggregate level
  - Determine outputs given inputs (I cant see what is going on)
  - Not trivial to model problems involving individual localisation, memory and emerging properties
  - Simulation overcomes these limitations!

What about Reductionism?

- in reductionism *"the dynamics of a system is understood from studying the properties of its parts. Once one knows the parts, the dynamics of the whole can be derived"*
- The problem is: in immunology its not always possible to know the parts



- … and reductionism does not represent emergence

OK, Simulation! But how do I start?

1. Define the Objectives:

- validate a theory (based on experimental data or an intuition of what might happen in reality)
- current models do not match realworld experimentation further investigation
- New hypothesis and research questions defined with immunologists as simulation goals.
- The objectives come from real-world observation (previously performed by immunologists)

OK, Simulation! But how do I start?

2. Describe the system:

- Documents (immunology books, articles, interview with experts, etc.) on how immune elements work and interact
- The description is generally based on knowledge acquired by theoretical work, real-world observation and laboratory experimentation
- Due to the complexity of the elements knowledge is mostly scarce.
- The immune system is far from being fully knowable, and the descriptions
- found in literature are only partial representations and assumptions of what occurs in reality

…and that's when the problems for computer scientists begin

And?

3. Investigate existing theories and established models

- Mostly mathematical models describing the phenomenon
- Verified using experimental data
- Existing models their hypothesis, objectives, validation process and limitations.
- new model: improvement of what has already been done

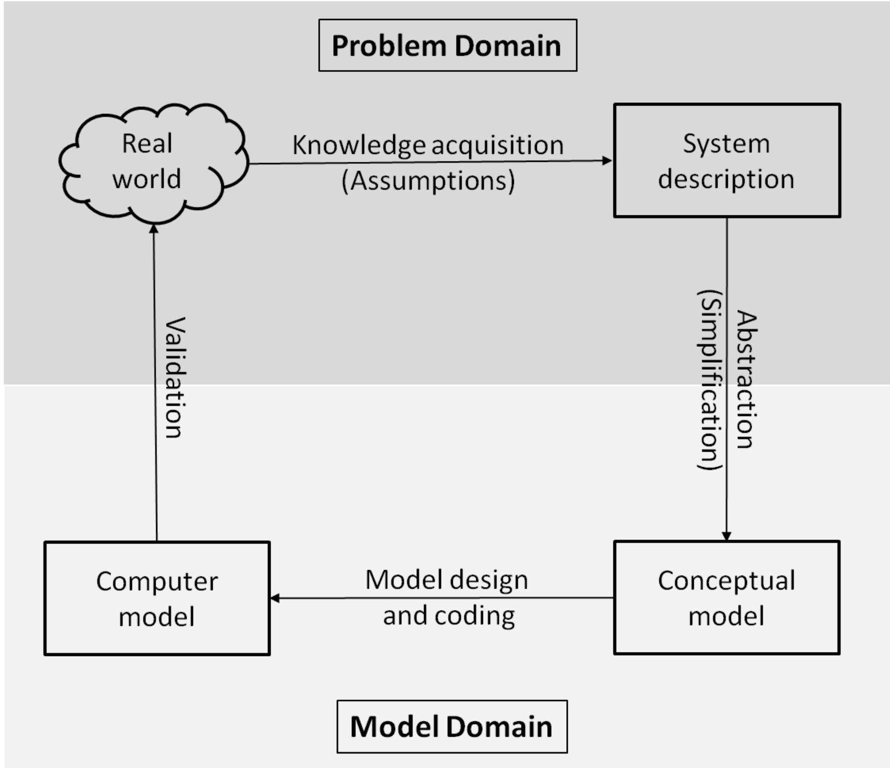
4. **Use experimental data**

- Most simulation models are built based on real-world experimentation
- Cases where no data is available: based on theoretical assumptions to provide more insights about the real world
- No data: lack of understanding of a process, difficulty/impossibility to collect information with current technology.
- A hypothesis is first formulated and it needs experimental data to confirm it.

Next step...

5. Build conceptual model

abstraction intended to contain the principal aspects observed in the real world, considering the necessary level of details



<u>Challenges:</u>

- ✓Keep it simple
- ✓Work with information available
- ✓Hierarchical charadteristics of the Immune System
- ✓Field constantly gathering information needs frequent updates

Now the Simulation

6. Identify elements, parameters, aggregates, etc. already established in theory and real-world data
7. Decide the appropriate simulation approach
8. Represent elements, parameters, etc. using the appropriate simulation approach
9. Build the simulation model
10. Verify the model (Do I model the thing right?)
11. Validate the model with existing theories and, if available, real-world data. (Do I model do the right thing?)

Bear in mind that:

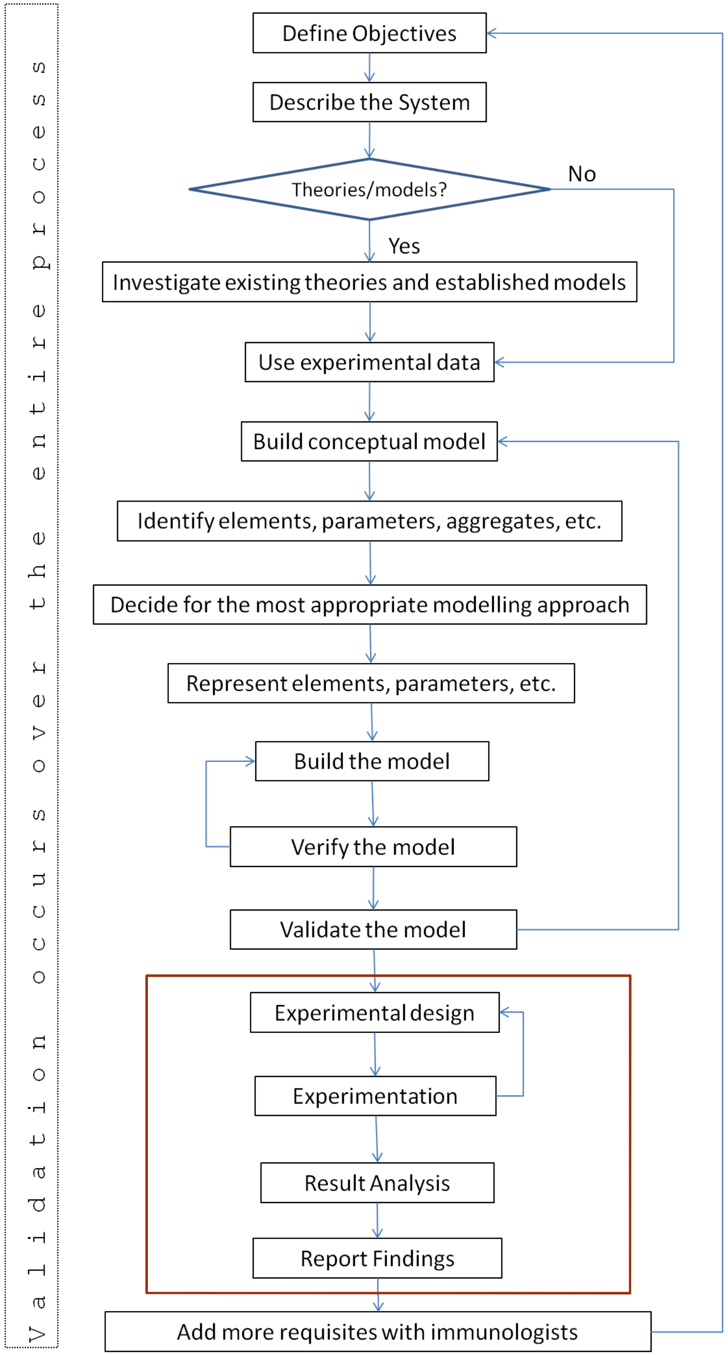
For immunology models are not 100% accurate for a number of reasons:

(1) there is no real world data to compare against,

(2) there is little data,

(3) real-world data is inaccurate,

(4) even if the data is accurate, the real world data is only a sample, which in itself creates inaccuracy.


Validation occurs over the entire process
Define Objectives
Describe the System
Theories/models?
No
Yes
Investigate existing theories and established models
Use experimental data
Build conceptual model
Identify elements, parameters, aggregates, etc.
Decide for the most appropriate modelling approach
Represent elements, parameters, etc.
Build the model
Verify the model
Validate the model
Experimental design
Experimentation
Result Analysis
Report Findings
Add more requisites with immunologists

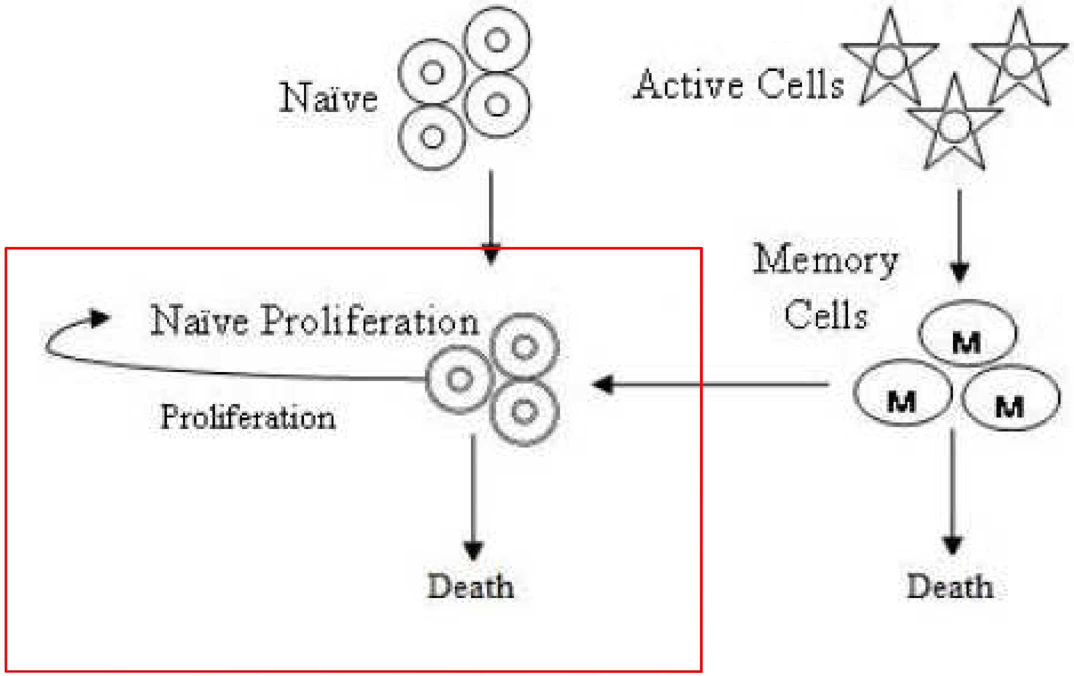
Building a Simulation

- Let us build a simulation from scratch and see

- What do we have to do to define simulation a problem?

Building a Model from Scratch

Objective: understand peripheral naive T cell repertoire dynamics over time.



Building a Model from Scratch

Describe the System:

- There is a type of white blood cell, naive T cell, which plays an important role in the immune system by responding to new infections.
- Before the age of 20, the set of naive T cells is sustained primarily from thymic output.
- In middle age there is a change in the source of naive T cells: as the thymus involutes, there is a considerable shrinkage in its T cell output, which means that new T cells are mostly produced by peripheral expansion.
- There is also a belief that some memory T cells have their phenotype reverted back to the naive proliferation cells type
- Furthermore, memory cells are originated from active T cells.

Building a Model from Scratch

Investigate existing theories and models:

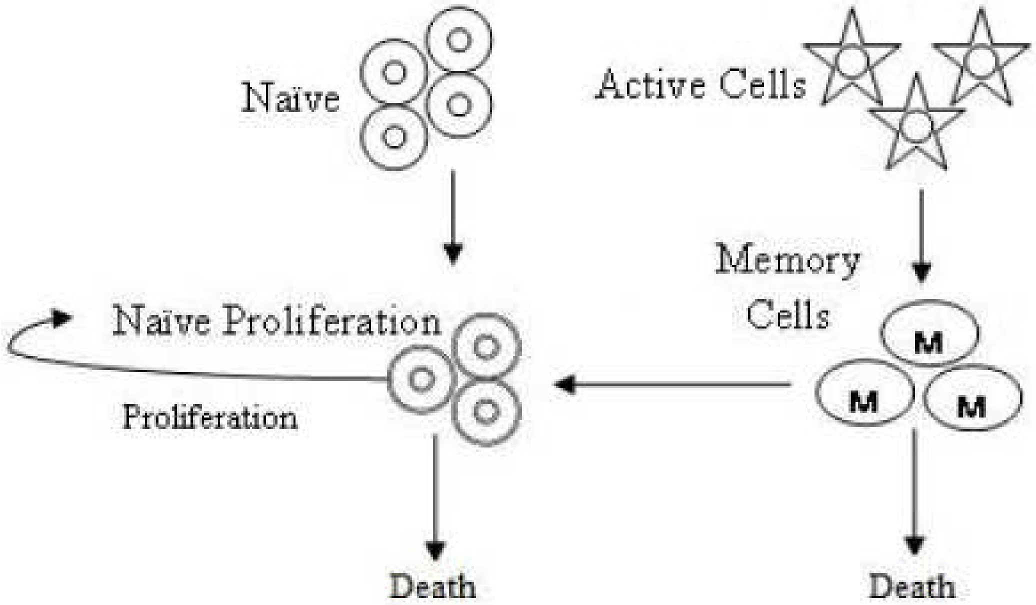
- Immunologists found out that thymic contribution in an individual are quantified by the level of a biological marker called 'T cell receptors excision circle' (TREC).
- TREC is circular DNA originated during the formation of the T-cell receptor.
- The percentage of T cells possessing TRECs decays with shrinkage of thymic output, activation and reproduction of naive T cells
- This means that naive T cells originating from the thymus have a greater percentage of TREC than those originating through other proliferation.

Building a Model from Scratch

- Experimental data:
- There is TREC data collected by immunologists *(Murray* et al., 2003), which also develops a mathematical model for the dynamics of peripheral naive T cells.
- Furthermore, the authors provided us with data on active cells and total naive T cells in individuals with age ranging from 1 to 55 years.
- Assuming that this data has been validated, we can use it to continue our simulation

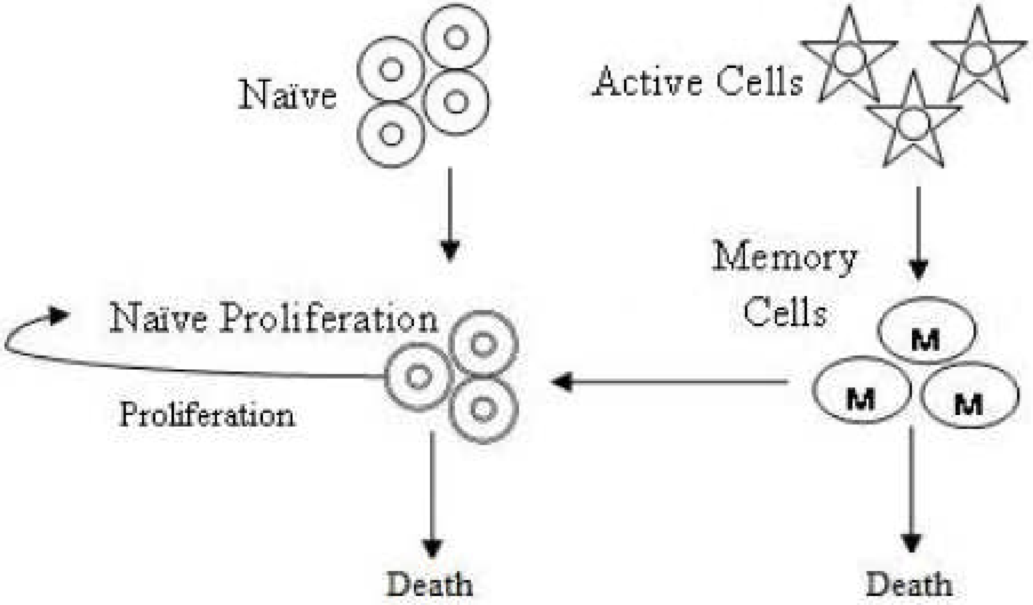
Building a Model from Scratch

- Conceptual model: can you help me with this one?

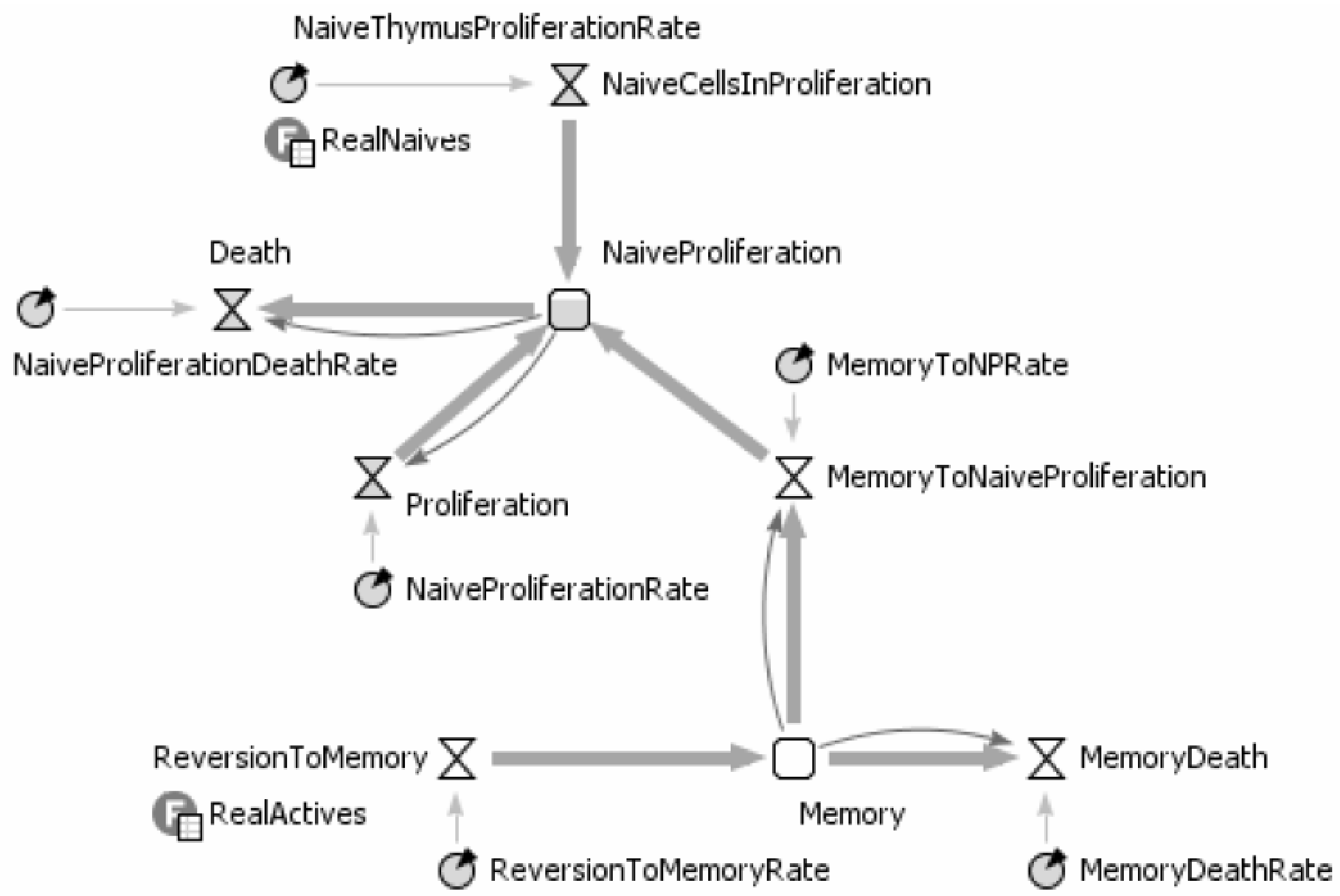


Building a Model from Scratch

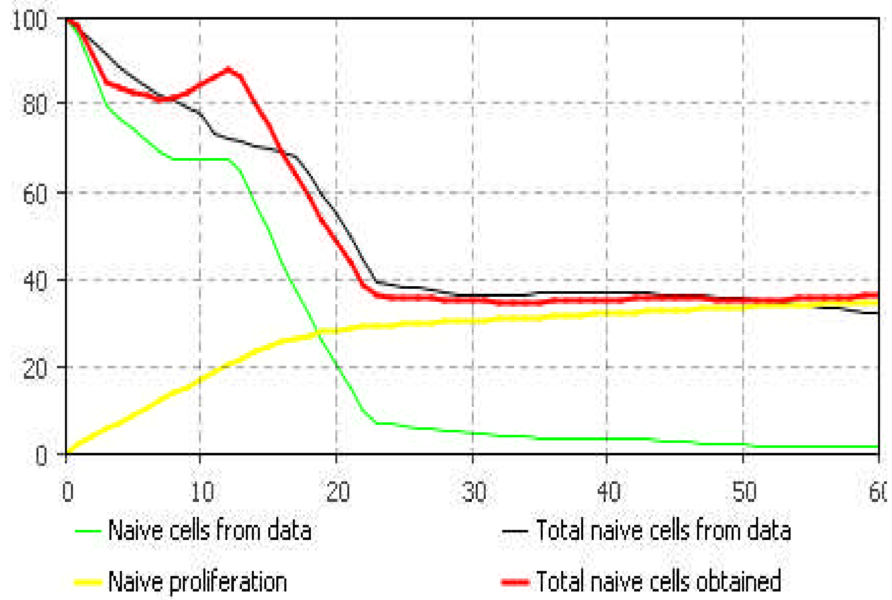
- Best simulation approach and parameters?

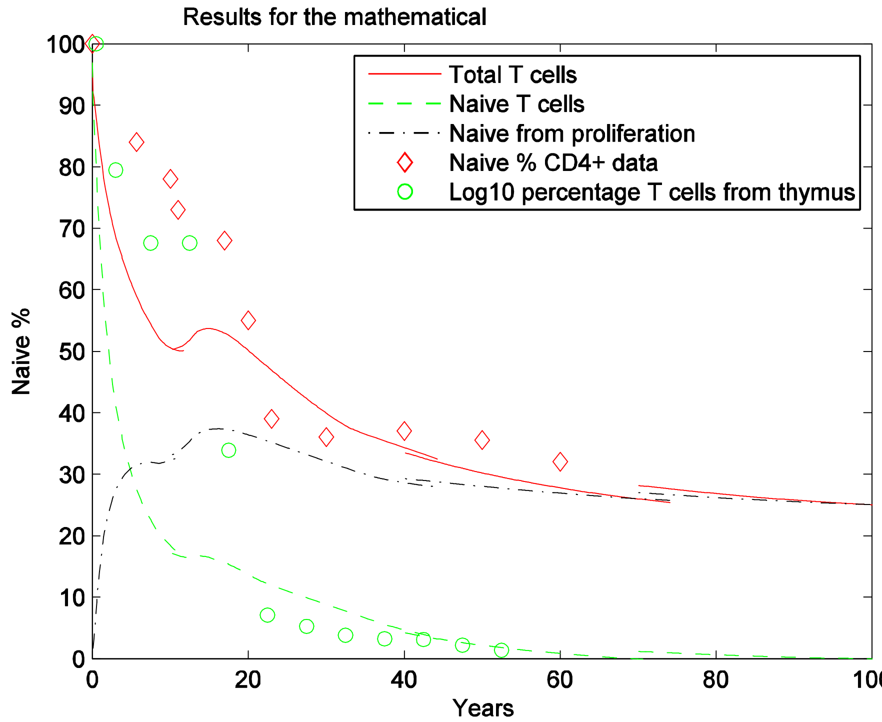


System Dynamics



System Dynamics - Results





Conclusions

- Summary of simulation and its main approaches
- The importance of simulation for immunology
- Framework to help with the development of simulations for immunology
- We demonstrated the importance of SD in immunological research
- Working now on the conversion between approaches (Future talk)

Questions?