Improved Simulation Algorithms for Agent Based Models of the Immune Response

Johannes Textor *Institut für Theoretische Informatik*
Björn Hansen *Universität zu Lübeck, Germany*

EMCSR 2008 Vienna

Outline

1 Introduction

The Immune System, Very Briefly

- The Immune System (IS) is a classifying system:
  - Self (your body) is tolerated
  - Non-Self (everything else) is attacked

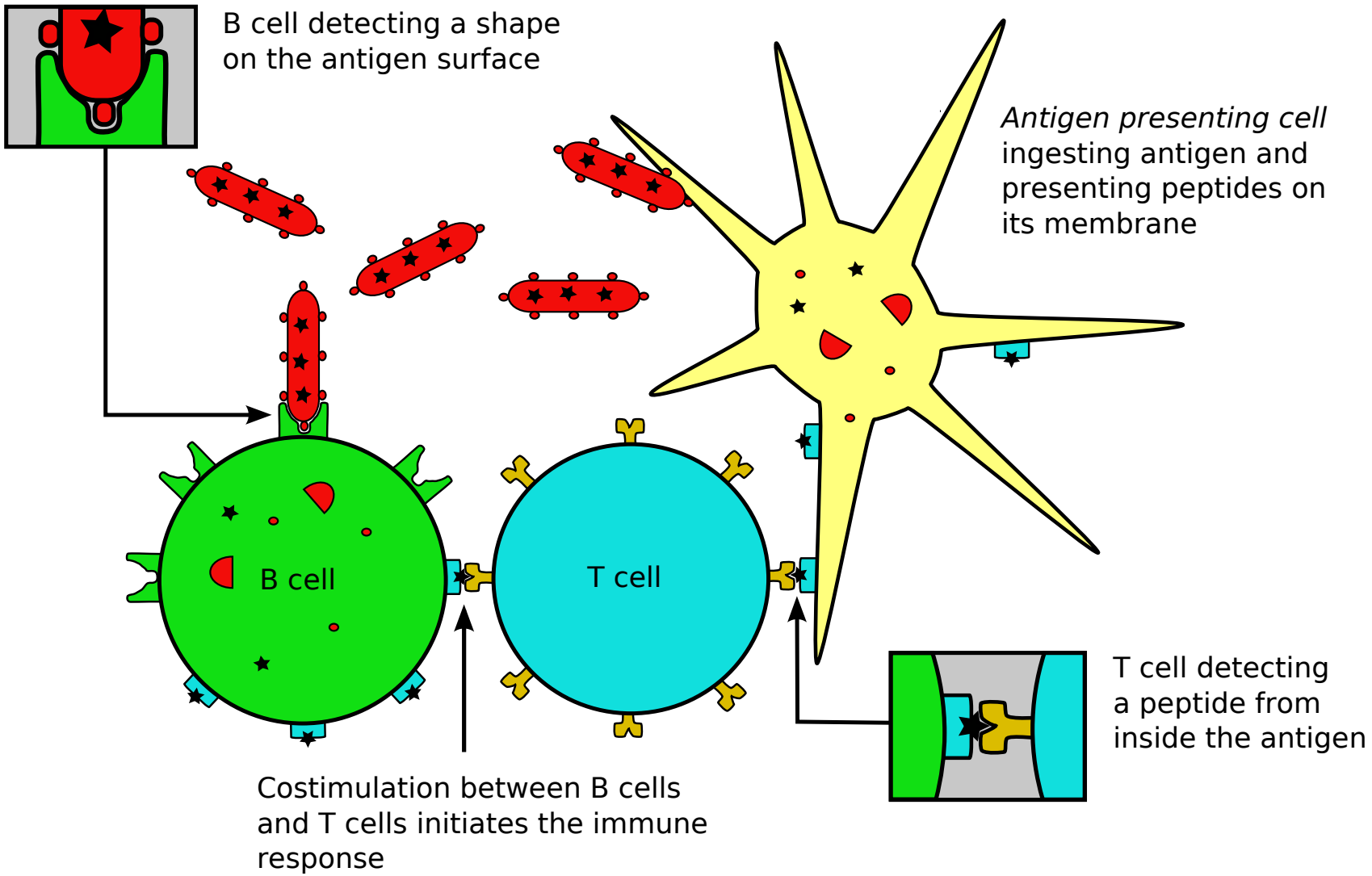
  Attacked non-self = antigen: bacteria, virus, implanted organ, ...

- Two complementary sets of shape detectors:
  - B-Cells detect shapes on the surface of an antigen
  - T-Cells detect shapes from the inside of an antigen

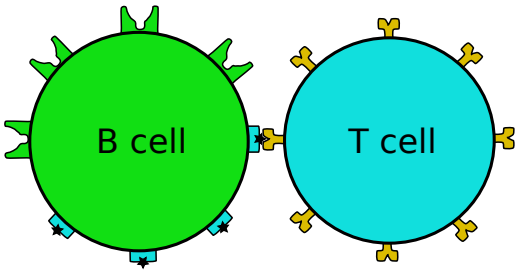
- B and T cells are randomly generated:
  - Possible antigens: $\approx 10^{11}$, human DNA: $3 \cdot 10^9$ bp
  - Evolutionary pressure by mutation of pathogens

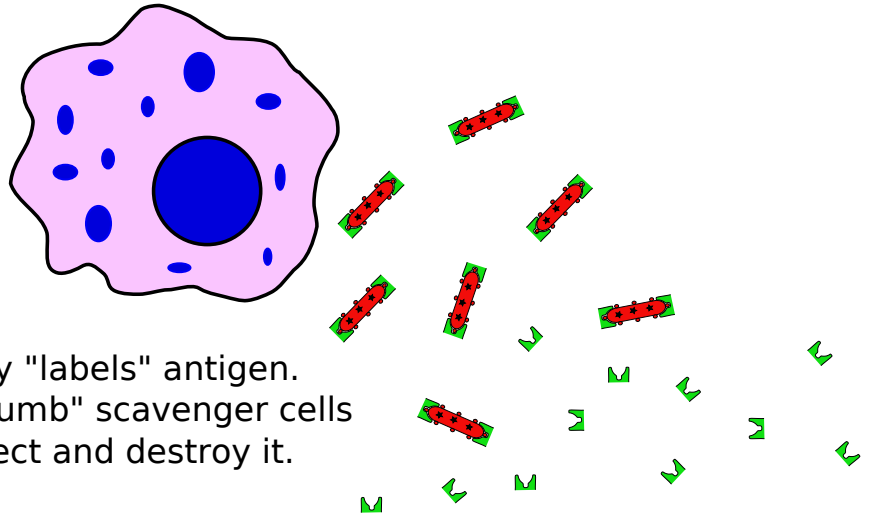
- Humoral Immune Response (HIR): subsystem of the IS that produces antibody

The Humoral Immune Response



The Humoral Immune Response

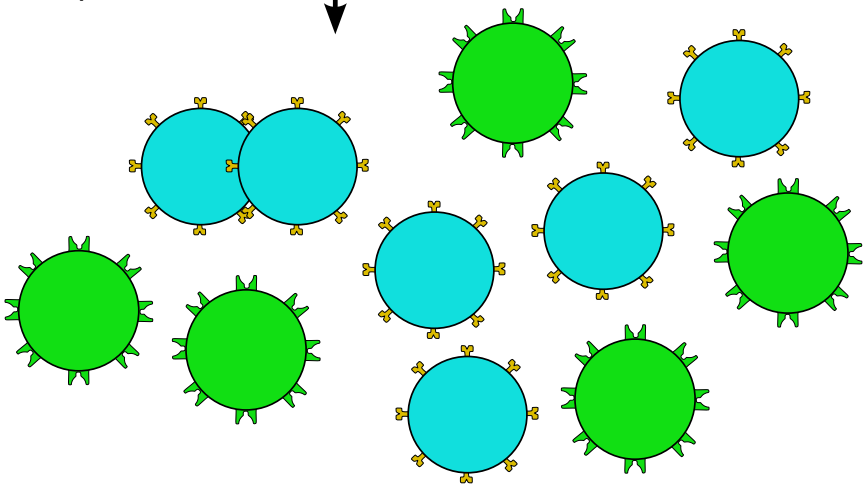


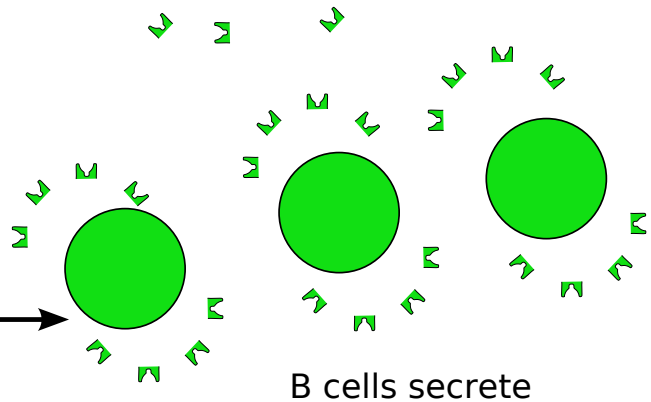


Antibody "labels" antigen.
Now, "dumb" scavenger cells
can detect and destroy it.

Antibody: Secreted B cell receptor

Clonal selection:
costimulated cells
become activated
and proliferate



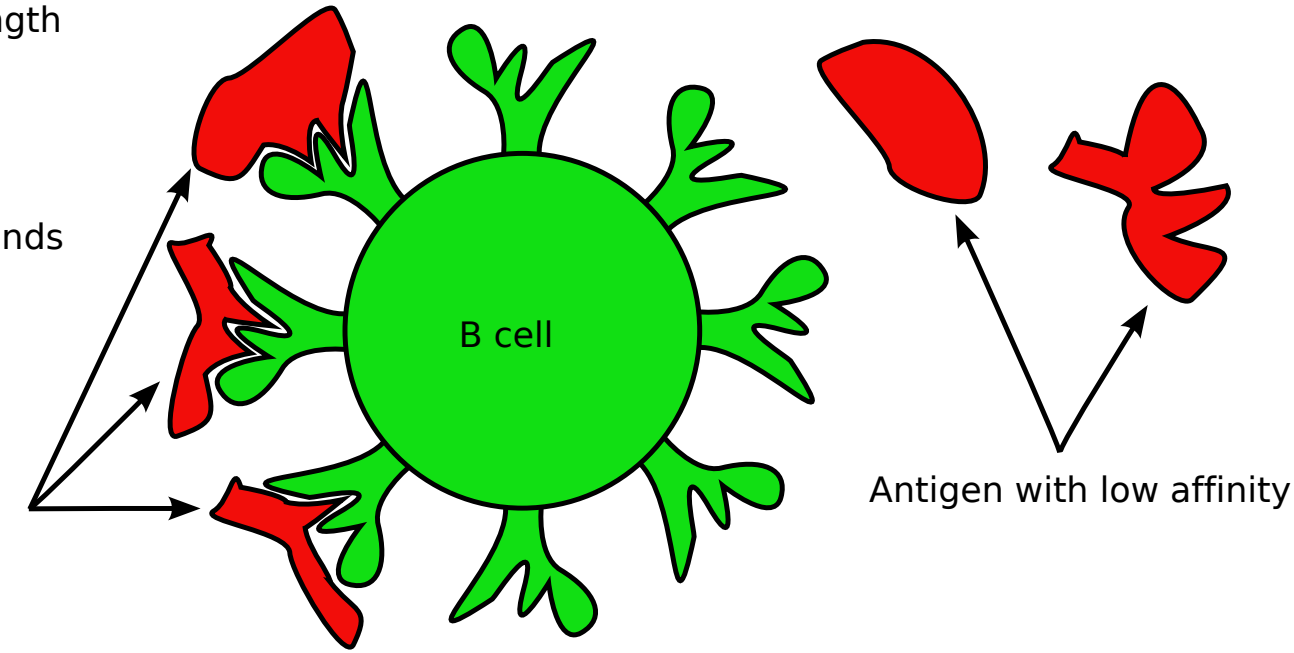


B cells secrete
their receptors

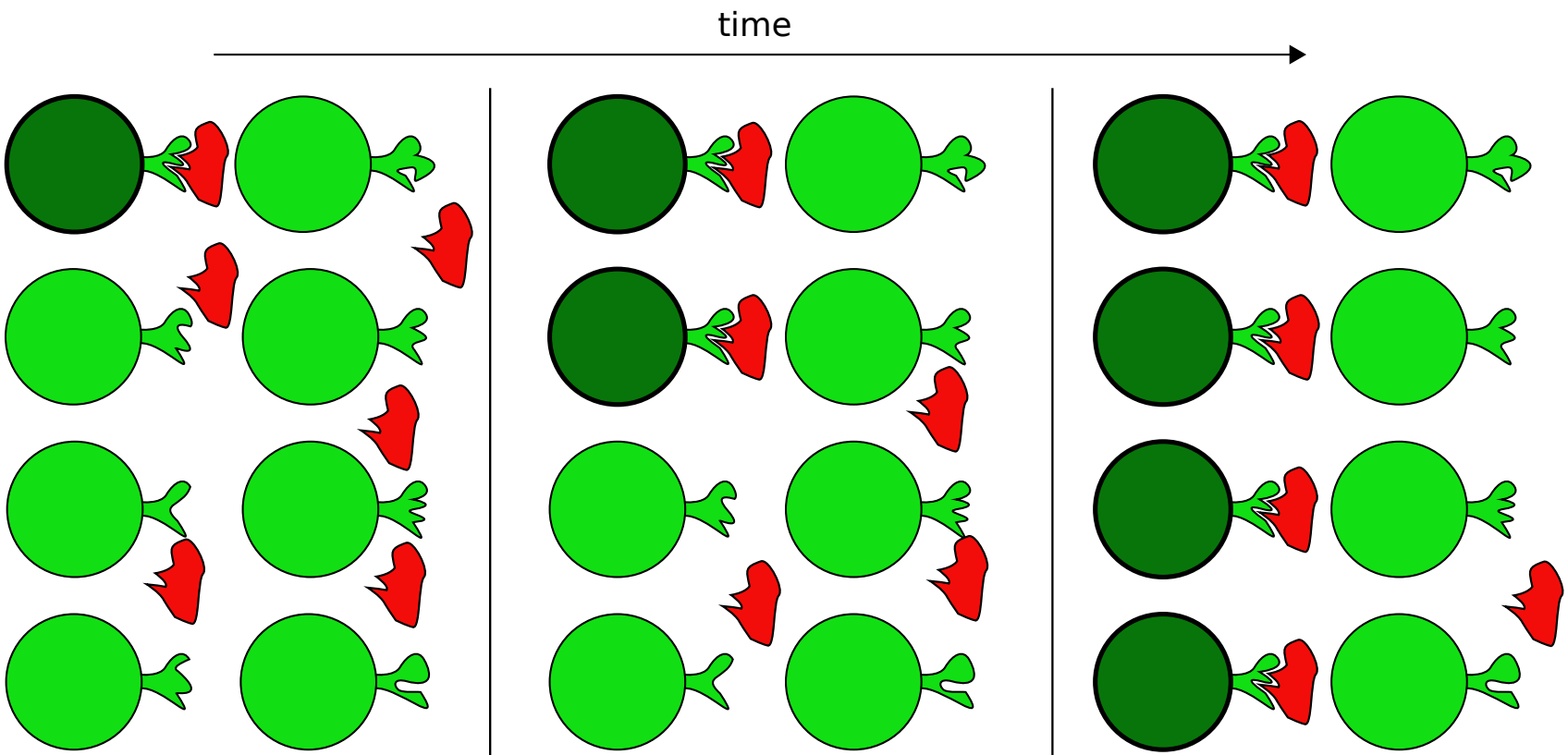
The Humoral Immune Response

Affinity: Binding strength between antigen and B Cell receptor

Epitope: Shape on antigen surface that binds to a B Cell receptor



The Humoral Immune Response



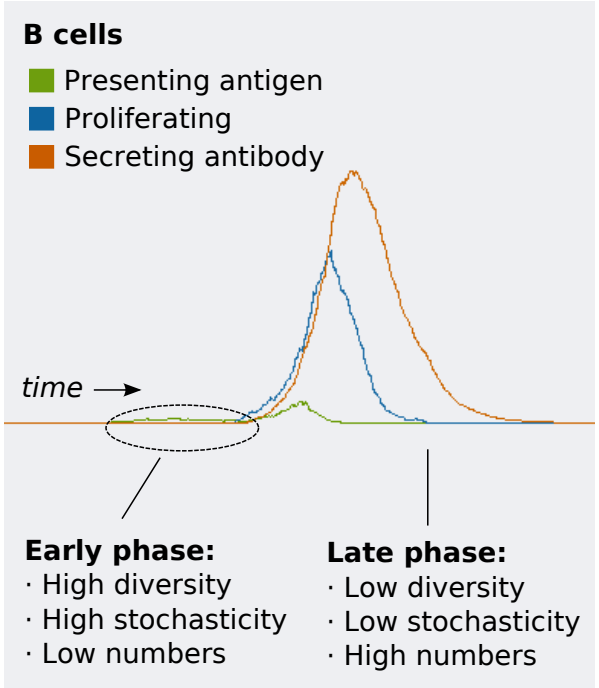
Initially: Large number of different clones, few highly affine cells

Clonal selection: B cells compete for antigen. Only highly affine cells are allowed to proliferate

Result: Highly affine clones are largely amplified, only a few types of antibody

How Do We Model the Humoral Immune Response?

- Agent Based Modelling (ABM)
  - Diversity and randomness are easy
  - Valid for both small and large numbers of agents
  - Difficult to analyze mathematically
- Partial Differential Equations (PDE)
  - Dominating in immunology
  - Rich, but complicated methodology
  - Valid for large particle numbers only



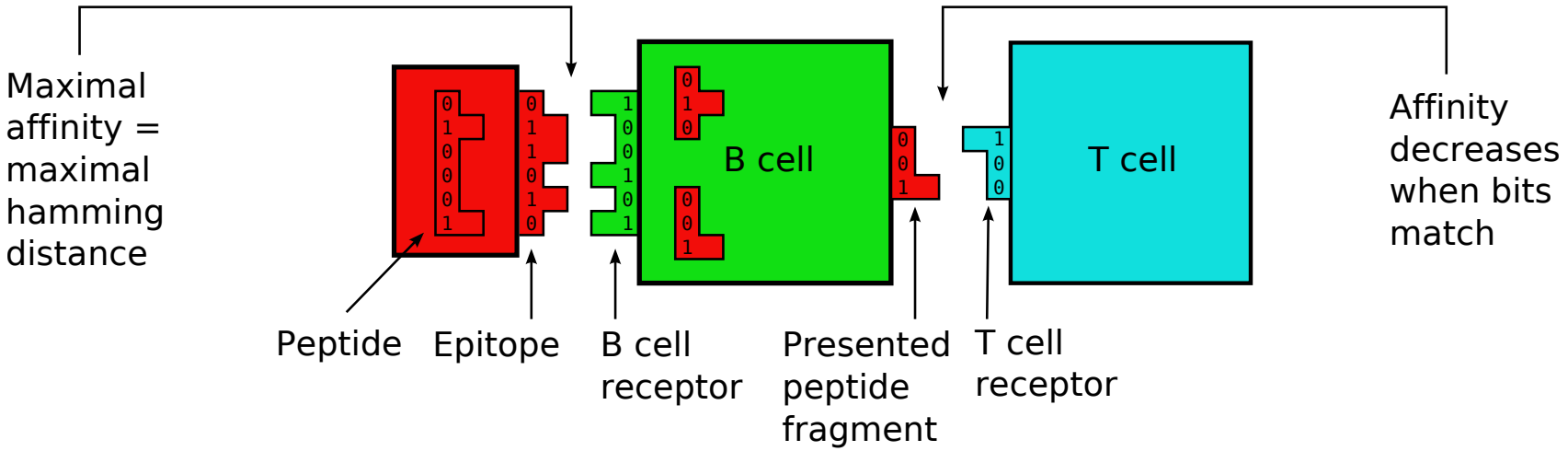
Hybrid approach: Use ABM, switch to PDE for large numbers!

- Combines strengths of both approaches
- Facilitates comparison to existing PDE models

2 The Celada / Seiden Model

The Celada / Seiden Model

Key idea of the CS model: Represent shapes of epitopes, peptides and receptors as bit strings!



Straightforward implementation of diversity, random repertoire generation, affinity, and mutations.

The Celada / Seiden Model

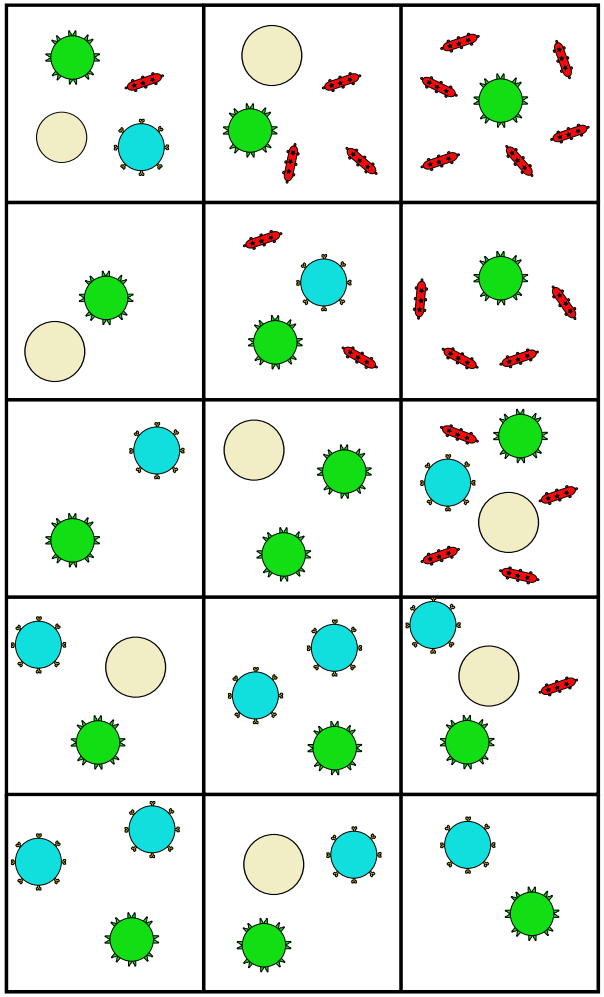
"Generalized Cellular Automaton"

[Celada, Seiden, J Immunol (1992)]

2D grid evolves in discrete time steps:

1. Interaction phase
   Cell-cell-interactions, Cell-molecule-interactions, proliferation, cell death, ...
   All interactions are local (same site only) and probabilistic.
2. Diffusion phase
   "Cells move from site to site"

Similar to stochastic simulation of a (huge) reaction-diffusion-system!



What Do We Want?

- CS model is (still) the most popular ABM of the humoral immune response
  Implementations: ImmSim [Kleinstein], C-ImmSim [Castiglione], ...

- Problems with the CS model
  - Often dismissed as “too complex”, “toy model”
  - Hard to compare results to other (PDE) models
  - Unnecessary slowdown as cells proliferate
- Our approach
  - Identify and analyze basic simulation algorithms
  - Link these algorithms to PDE models
  - Switch to PDE / deterministic algorithm for large numbers

3 Simulation Algorithms for the Immune Response

Simulation Algorithms in the CS model

Diffusion algorithm

- Moves particles from site to site

Interaction algorithm

- Interactions implement the domain knowledge
  B cell samples antigen, APC stimulates T cell, ...
- Base algorithm determines pairs of agents which interact
- Interaction may change internal state of agents, destroy agents, create new agents

Proliferation algorithm

- Growth of stimulated B cells, T cells and antigen

Desired features:

- Stochastic and deterministic mode should be available
- Should correspond to “reasonable” PDE model
- Should be aware of spatiotemporal model resolution

Celada / Seiden Diffusion Algorithm

Probabilistic discrete version

---

for each site S
  for each particle π at S
    if COIN$\left(\quad \mathcal{D} \right)$
      move π to random neighbour of S
    else
      do not move π

Celada / Seiden Diffusion Algorithm

Probabilistic discrete version

for each site S
  for each particle π at S
    if COIN$\left(\frac{\Delta t}{(\Delta s)^2}\mathcal{D}\right)$
      move π to random neighbour of S
    else
      do not move π

Expected outcome

$\tau^{(t)}(S)$: Concentration of particles τ at site S at time t

$$\tau^{(t+1)}(S) = \tau^{(t)}(S) + \frac{\mathcal{D}\Delta t}{4(\Delta s)^2}\left(\sum_{S' \in N(S)} \tau^{(t)}(S) - \tau^{(t)}(S')\right)$$

Celada / Seiden Diffusion Algorithm

Probabilistic discrete version

for each site S
  for each particle π at S
    if COIN$\left(\frac{\Delta t}{(\Delta s)^2}\mathcal{D}\right)$
      move π to random neighbour of S
    else
      do not move π

PDE version

$$\frac{\partial \tau}{\partial t} = \frac{\mathcal{D}_\tau}{4}\nabla^2\tau$$

Diffusion equation

Expected outcome

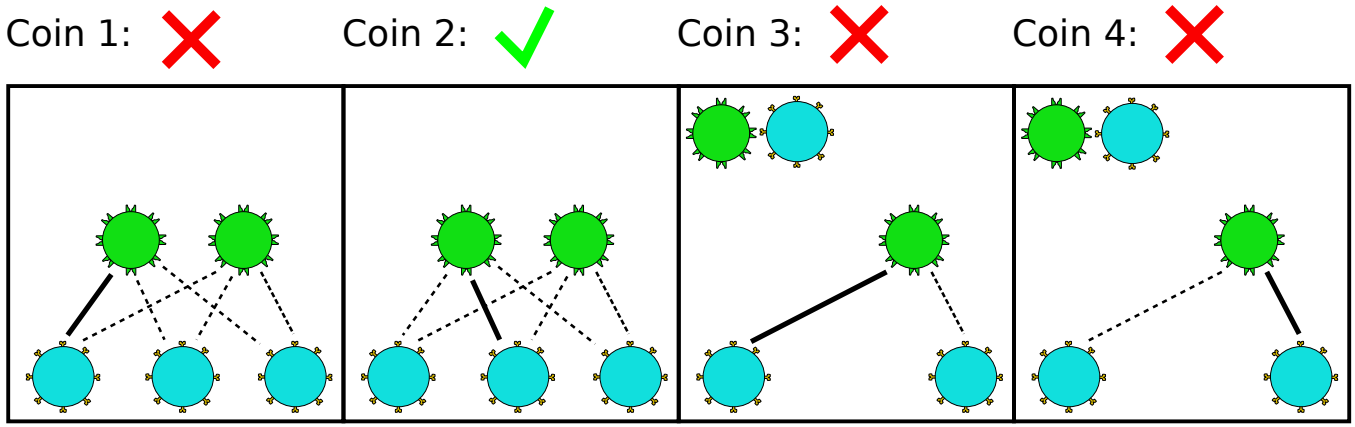
$\tau^{(t)}(S)$: Concentration of particles τ at site S at time t

$$\tau^{(t+1)}(S) = \tau^{(t)}(S) + \frac{\mathcal{D}\Delta t}{4(\Delta s)^2}\left(\sum_{S' \in N(S)} \tau^{(t)}(S) - \tau^{(t)}(S')\right)$$

Celada / Seiden Interaction Algorithm

Probabilistic discrete version

for each site S
  for each pair (π, π') at S **where**
    type(π)=τ **and** type(π')=τ'
  if COIN($\mathcal{I}_{\tau,\tau'}$)
    perform interaction, flag π
    and π' as unavailable for
    further interactions



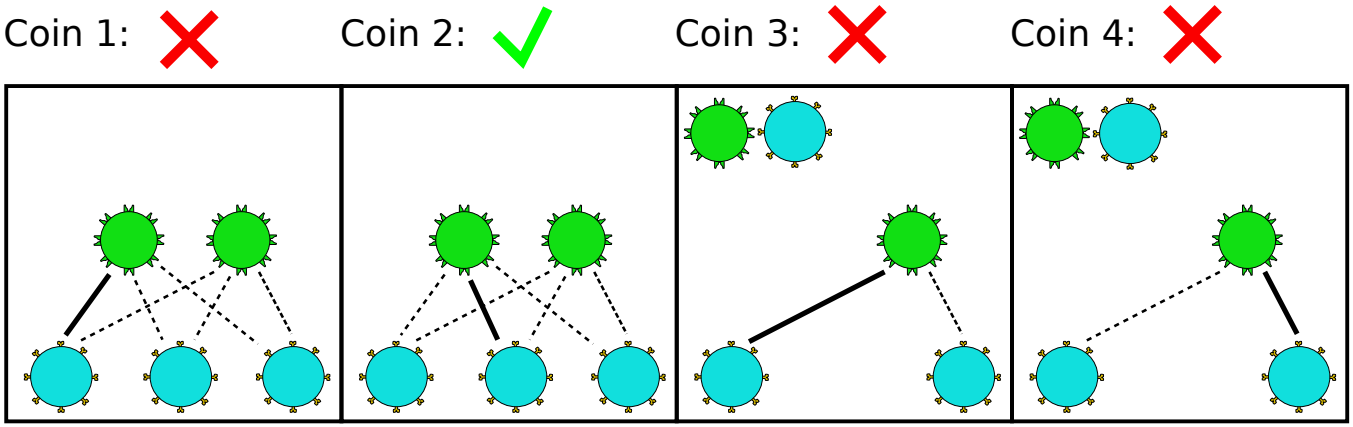
Celada / Seiden Interaction Algorithm

Probabilistic discrete version

for each site S
  for each pair (π, π') at S **where**
    type(π)=τ **and** type(π')=τ'
  if COIN($\mathcal{I}_{\tau,\tau'}$)
    perform interaction, flag π
    and π' as unavailable for
    further interactions

PDE version

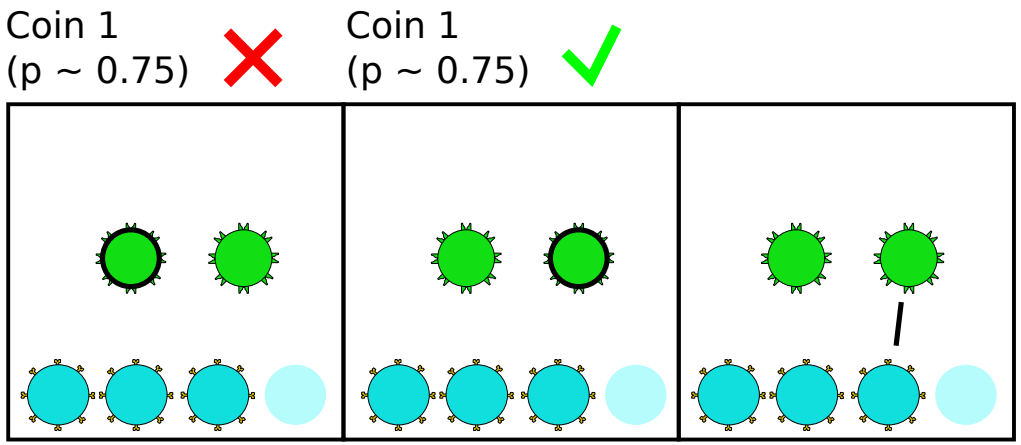
- *No PDE form known*
- *Non-linear kinetics*
- *Not biophyisically motivated*



Our Interaction Algorithm

Probabilistic discrete version

for each site S
  $\rho \leftarrow \text{count}(\tau', S) / C_{\max}$
  for each particle π at S **where**
    type(π)=τ
      if COIN($\Delta t \cdot \rho \cdot \mathcal{I}_{\tau,\tau'}$)
        perform interaction between
        π and some particle π' of
        type τ' at S



Our Interaction Algorithm

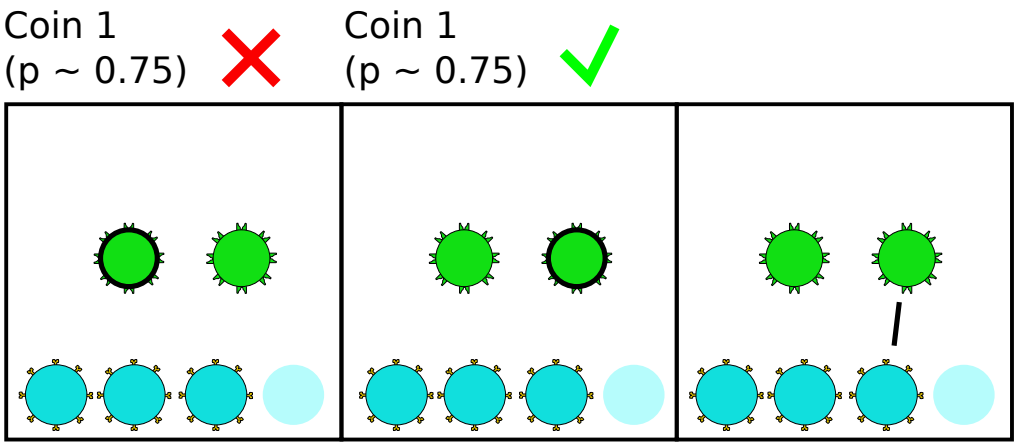
Probabilistic discrete version

for each site S
  $\rho \leftarrow \text{count}(\tau', S) \,/\, C_{\max}$
  for each particle π at S **where**
    type(π)=τ
      if COIN($\Delta t \cdot \rho \cdot \mathcal{I}_{\tau,\tau'}$)
        perform interaction between π and some particle π' of type τ' at S

PDE version

$$\frac{\partial \tau}{\partial t} = \mathcal{I}_{\tau,\tau'} \cdot \tau \cdot \tau'$$

Law of mass action: Interaction rate is proportional to the concentrations of the interacting particles



Celada / Seiden Proliferation Algorithm

---

for each site S
  for each π at S **where** type(π)=τ
    if COIN$\left(e^{-(\text{count}(\tau,S)/\mathcal{P}_\tau)^2}\right)$
      clone π

[Castiglione, Int J Mod Phys C (1997)]

Celada / Seiden Proliferation Algorithm

Probabilistic discrete version

for each site S
  for each π at S **where** type(π)=τ
    if COIN$\left(e^{-(\text{count}(\tau,S)/\mathcal{P}_\tau)^2}\right)$
      clone π

[Castiglione, Int J Mod Phys C (1997)]

PDE version

$$\frac{\partial \tau}{\partial t} = e^{-(\frac{\tau}{\sigma})^2}\tau$$

- *Biophysical meaning unclear*
- *Although growth is damped, population on a lattice site may grow arbitrarily (immigration from neighbouring sites!)*

Our Proliferation Algorithm

Probabilistic discrete version

for each site S
  $\rho \leftarrow \text{count}(\pi, S) \,/\, C_{\max}$
  for each π at S **where** type(π)=τ
    if COIN($|\Delta t \cdot \mathcal{P}_\tau \cdot (1 - \rho)|$)
      if $1 - \rho > 0$
        clone π
      else
        kill π

Our Proliferation Algorithm

Probabilistic discrete version

for each site S
  $\rho \leftarrow$ count(π, S) / $C_{\max}$
  for each π at S **where** type(π)=τ
    if COIN($|\Delta t \cdot \mathcal{P}_\tau \cdot (1 - \rho)|$)
      if $1 - \rho > 0$
        clone π
      else
        kill π

PDE version

$$\frac{\partial \tau}{\partial t} = \mathcal{P}_\tau \tau \frac{C_{\max} - \tau}{C_{\max}}$$

Logistic equation for constrained growth process

Summary

Diffusion algorithm

- Valid probabilistic version of diffusion equation
- Not changed

Interaction algorithm

- No simple formula for expected outcome
- Biophysical motivation unclear
- Changed to probabilistic version of mass-action law

Proliferation algorithm

- Exponential growth damped with gaussian kernel
- Biophysical motivation unclear
- Changed to probabilistic version of logistic equation

Hybrid mode: For large particle numbers, directly use expected outcome of probabilistic algorithms.

4 Experimental Results

Experiments

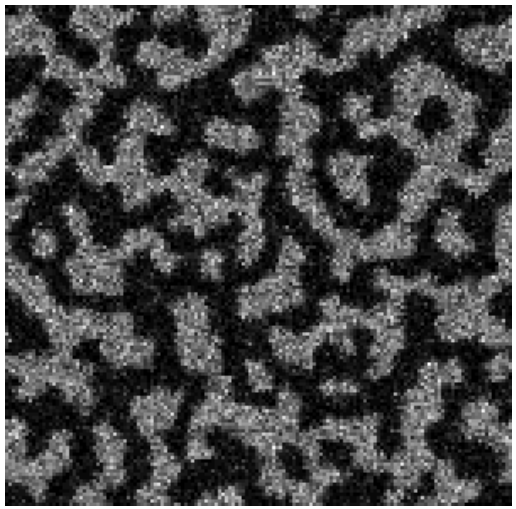
1. Simulation of a bistable chemical system
   - “Sandbox” to test algorithms
   - Verify parameter translation between continuous and discrete modes
   - Analyze effects of randomness in simple system
2. Simulation of the humoral immune response
   - “Complete” implementation of humoral immune response
   - Transition between stochastic and deterministic simulation mode controlled by thresholds
   - Multithreaded for parallel computers
   - OO approach to ease extension

Simulation of a Bistable Chemical System

- Imaginary chemical system exhibiting Turing patterns
- PDE description and reference stochastic implementation available
  [Malevanets, Kapral, Phys Rev Lett (1997)]
- Testcase for interaction and diffusion algorithms

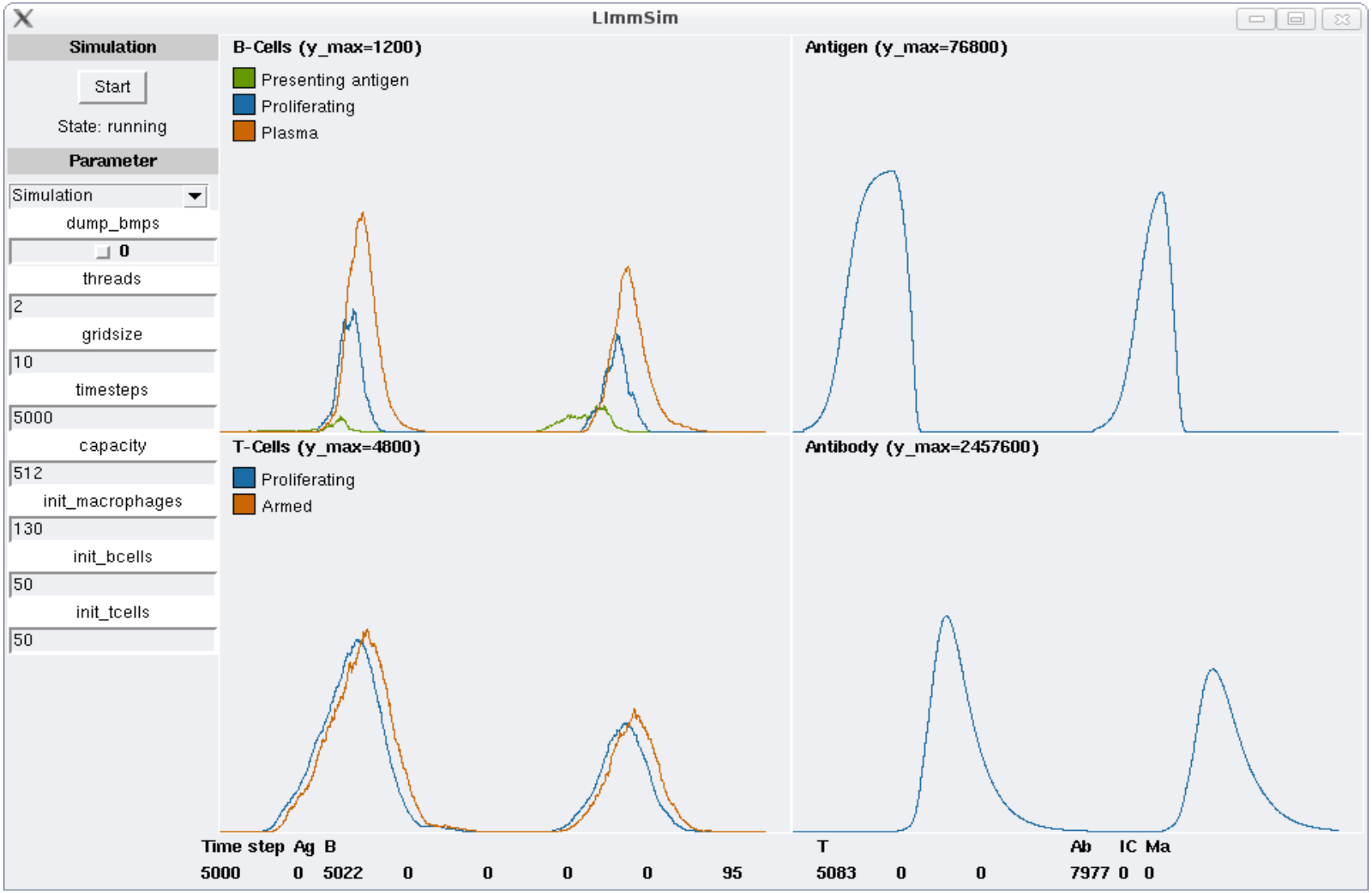
$$
\begin{array}{lcl}
2A + A^* & \longrightarrow & 3A \\
2A^* + A & \longrightarrow & 3A^* \\
A^* + B & \longrightarrow & A + B \\
\uparrow & & \downarrow \\
A^* + B^* & \longleftarrow & A + B^*
\end{array}
$$

PDE integration



Proposed algorithms

Simulation of the Immune Response

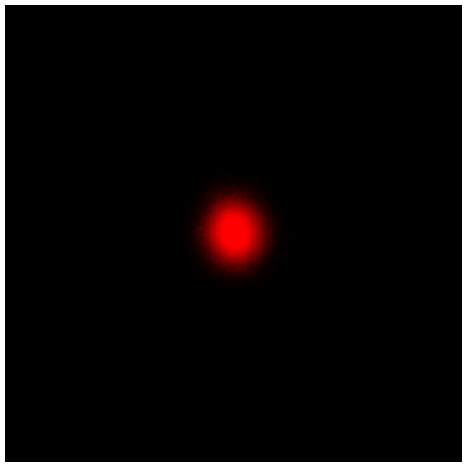


Simulation of the Immune Response

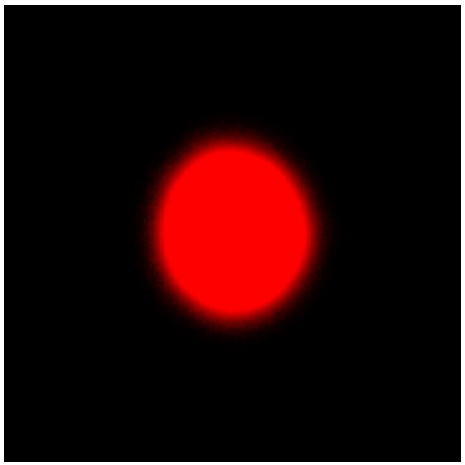
Hybrid simulations on 10x10 grid, max. 512 cells per grid point:

	first ab (t)	*last ag (t)*	*max. ag (count)*	*max. B (count)*	*max. T (count)*	*max. Ab (count)*
1	469	796	50902	7411	10783	2494584
2	926	1202	50971	6415	7742	1658143
3	597	1126	50946	5770	6670	934892
4	340	741	50086	7243	9750	2453614
5	471	694	50889	9192	13758	4550016
6	705	1277	50971	5557	6191	594443
7	546	810	50932	6441	9248	1753319
8	600	932	50955	6438	9058	1896623
9	601	988	50945	5919	7892	1049920
10	634	927	50964	5883	7588	888509
μ	589	949	50856	6627	8868	1827406
σ	149	189	258	1031	2107	1099618

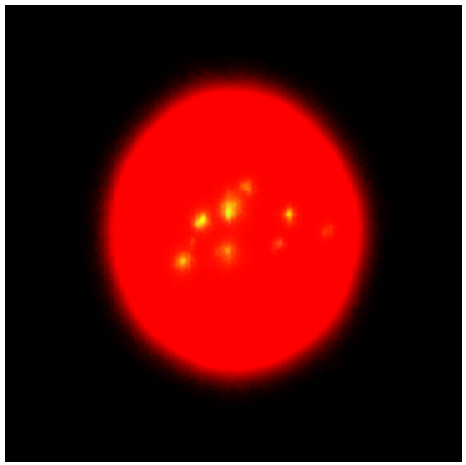
Simulation of the Immune Response



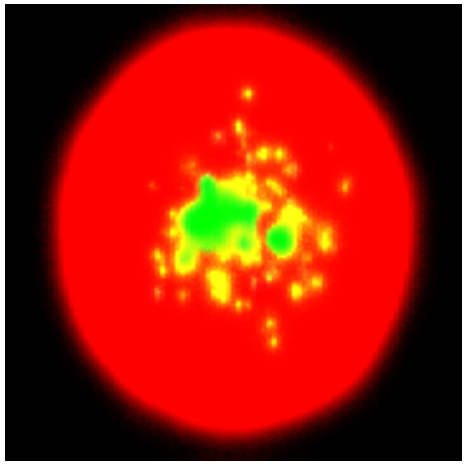
t=250



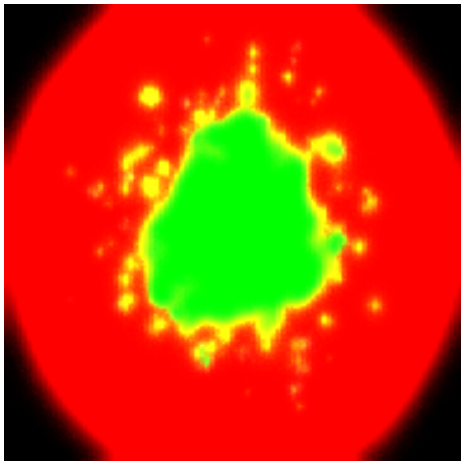
t=500



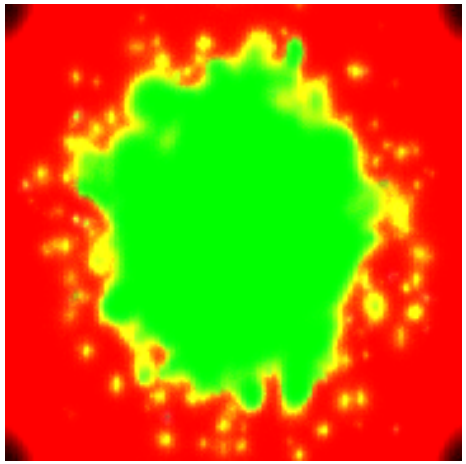
t=750



t=1000



t=1250



t=1500

Conclusions

- A hybrid model of the humoral immune response based on the Celada / Seiden model was developed
- The simulation can switch between probabilistic and deterministic mode

  Deterministic mode = approximation of corresponding PDE
- A multithreaded, object-oriented, open-source implementation is available:

  `http://www.tcs.uni-luebeck.de/forschung/software/limmsim/`

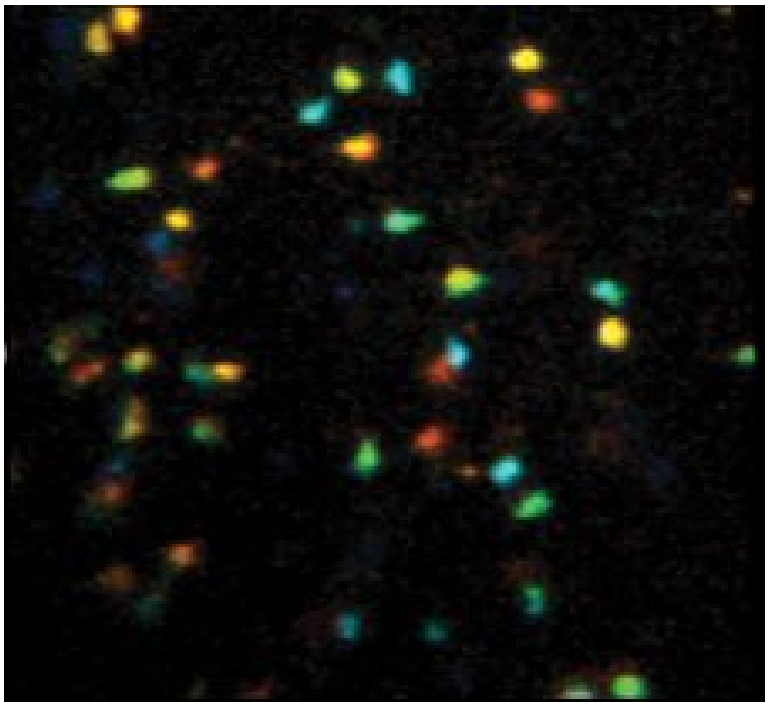
Random Walk of Real T Cells

Simulation space in CS model not meant to imitate a real space *[Puzone]*

In 2002, Miller et al. first observed individual T and B cells in the living lymph node. The result was a surprise to many immunologists:

The motion of T and B cells in their search for antigen is best described as a random walk!

CS model is similar to a real lymph node!



[Miller, Wei, Cahalan, Parker, PNAS (2003)]