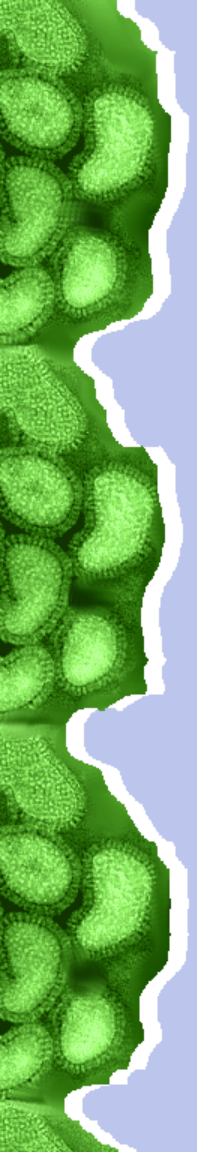

A Simple Cellular Automaton Model for Influenza A Viral Infections

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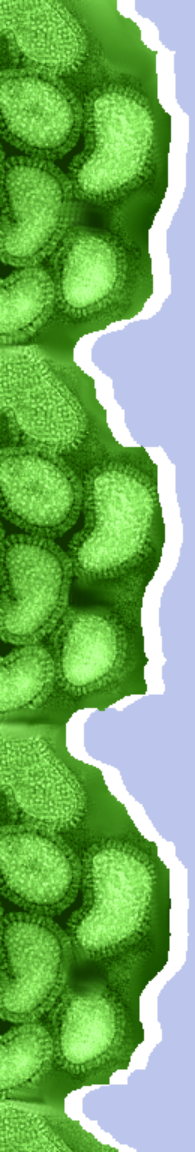


The simple CA model for viral infection

Project:

- Build a simple CA model which can reproduce experimental results of an uncomplicated viral infection with Influenza A.

Motivations:

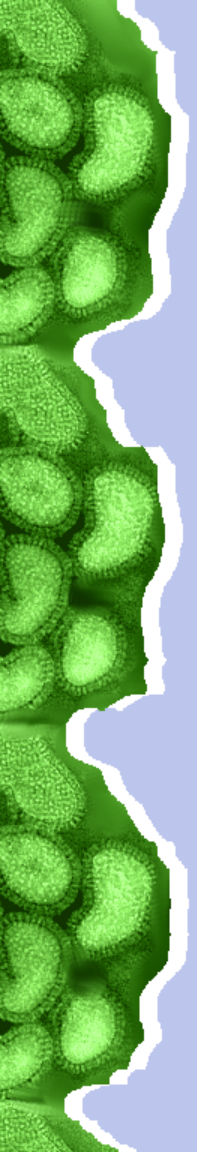
- Current CA models, like `CImmSim`, are too complex and not well calibrated enough;
- Differential equation models of viral infection are typically spatially homogeneous and few include delays or age classes.

Why a CA?

- Why not? A CA offers a natural description of the physical system. There is good correspondance between the CA's parameters and measurable quantities.

Ultimate objective:

- Explore whether spatial pattern formation affects the development and outcome of a viral infection.



The CA model of influenza A

- The model considers 2 species:

  Epithelial cells, which are the target of the viral infection, and;
  Immune cells, which fight the infection.

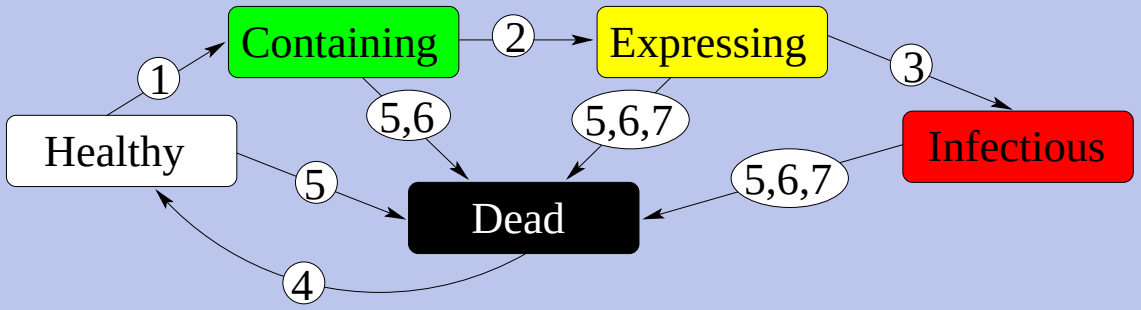
- The CA is run on a 2-D square lattice where
  - each site represents one epithelial cell; and
  - immune cells are mobile, moving from one lattice site to another.

- Update rules: synchroneous updating.

- Boundary conditions: toroidal for both cell types.

- The virus particles are not explicitly considered, rather the infection is modelled as spreading directly from one epithelial cell to another.

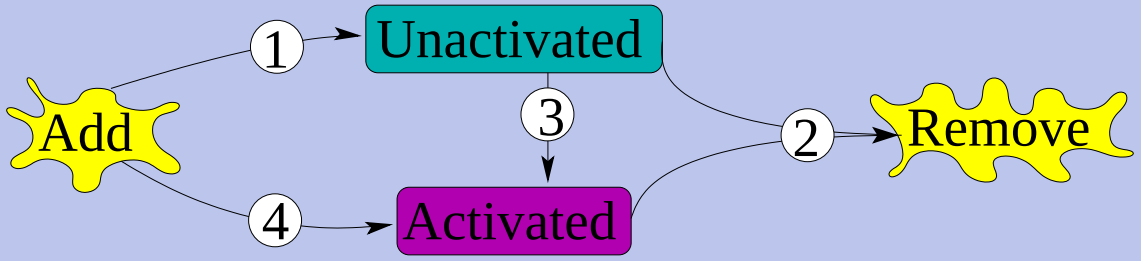
Rules for the epithelial cells



1. with probability `INFECT_RATE` for each infectious Moore neighbour.
2. after infected for `EXPRESS_DELAY` $= 4$ h.
3. after expresssing for `INFECT_DELAY` $= 2$ h.
4. at a rate `DIVISION_TIME`$^{-1} \times$ # healthy/# dead.
5. after `CELL_LIFESPAN` $= 380$ h.
6. after infected for `INFECT_LIFESPAN` $= 24$ h.
7. when “recognized” by an immune cell.

Rules for the immune cells

Immune cells move randomly on the CA lattice at a speed of one lattice site per time step.



1. at random lattice sites as needed to maintain a minimum density of `BASE_IMM_CELL` $= 1.5 \times 10^{-4}$ unactivated immune cells.
2. when older than `IMM_LIFESPAN` $= 168$ h.
3. when it first occupyies an expressing or infectious lattice site.
4. If an activated cell is occupying an expressing or infectious lattice site, it kills the epithelial cell and `RECRUITMENT` activated immune cells are added at random sites after `RECRUIT_DELAY` $= 7$ h.

The non-tuning parameters

Parameter	Value	Bio. Range	Source
grid_width	440		
grid_height	280		
CELL_LIFESPAN	380 h	160 – 600 h	Piao 01
INFECT_LIFESPAN	24 h	unknown	Bocharov 94
EXPRESS_DELAY	4 h	unknown	Bocharov 94
INFECT_DELAY	2 h	unknown	Bocharov 94
BASE_IMM_CELL	1.5×10^{-4}	$\frac{15}{100} \times 100 \times 10^{-5}$	Westermann 92, Bocharov 94, Klinman 75
IMM_LIFESPAN	168 h	48 – 480 h	Bocharov 94
RECRUIT_DELAY	7 h	2 – 12 h	Bocharov 94

Sensitive parameters (Bocharov 94)

FLOW_RATE = 6 time steps/h

Speed of immune cells (biol. range = 2–20 time steps/h).

DIVISION_TIME = 12 h

Duration of epithelial cell division (biol. range = 7–24 h).

INFECT_INIT = 0.01

Fraction of cells initially infected (biol. range = 0.001–0.1).

RECRUITMENT = 0.25

Number of immune cells recruited when one recognizes the virus

INFECT_RATE = 2 h^{-1}

Rate of infection of the Moore neighbours

Initialization

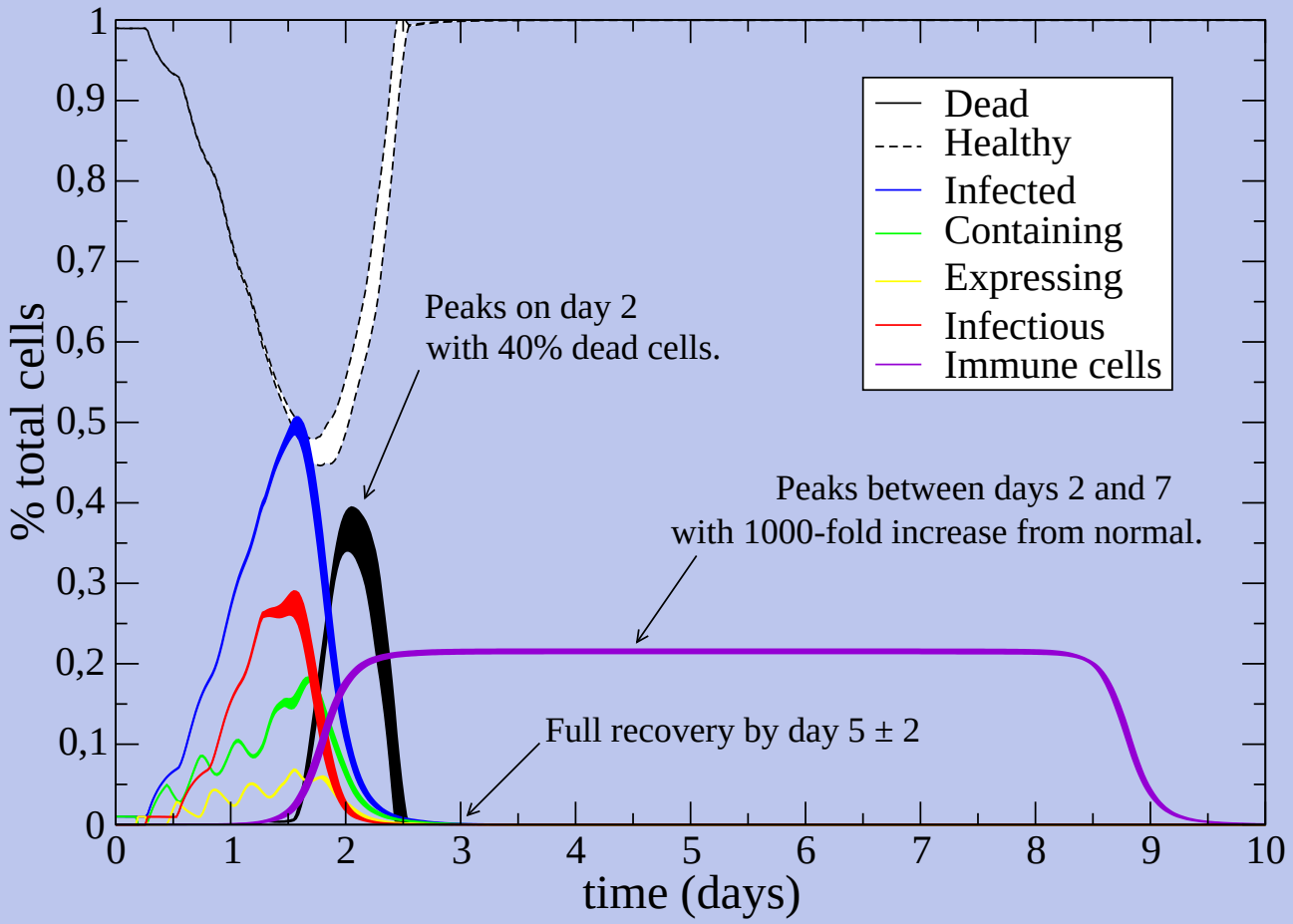
Epithelial cells All are assigned a random age and are set to the Healthy state, except for a fraction `INFECT_INIT` = 0.01 which, chosen at random, are set to the Containing state.

Immune cells A density of `BASE_IMM_CELL` unactivated immune cells are placed at random locations on the CA lattice, each with a random age.

Comparing against experimental data

1. The infection should peak on day 2.
2. Over the course of the infection, the fraction of epithelial cells that are dead should be as follows:
   (a) 10% on day 1;
   (b) 40% on day 2;
   (c) 10% on day 5.
3. From Fritz et al. 1999, experimental data recovered from 8 volunteers indicated that virus shedding persisted for 5 ± 2 d.
4. The number of immune cells should peak anywhere between day 2 (macrophages' peak) and day 7 (cytotoxic T cells' and B cells' peak).
5. At their peak, the number of B cells, helper T cells, and cytotoxic T cells should be 100-fold greater than their normal concentration, while that of plasma cells should be 10^4-fold greater. This corresponds to 0.015 – 1.5 immune cells / epithelial cells for our parameters.

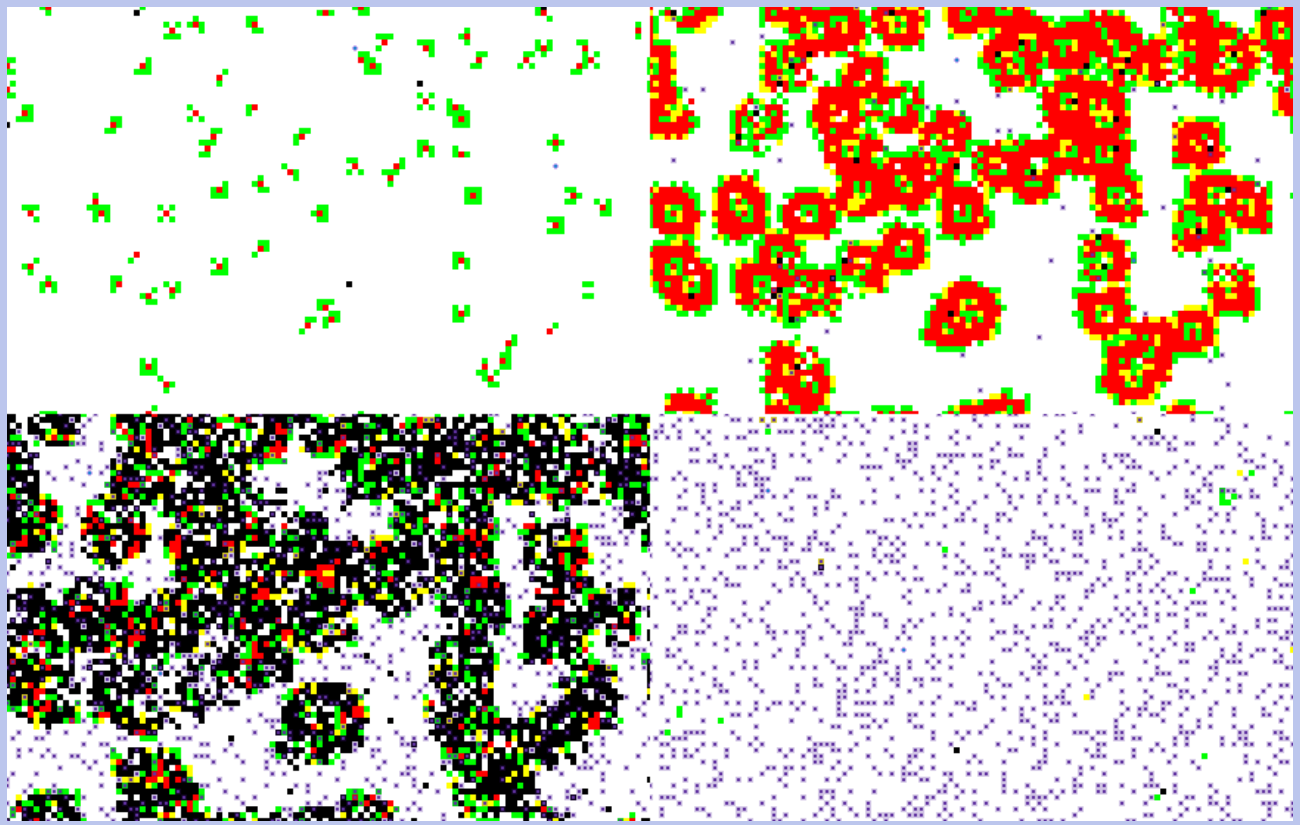
Results from the CA model



How good is this?

- We have introduced a 7 state variables and 12 parameters CA model of influenza A.
- To keep parameters within biological range, only 5 of the 12 could be used to tune the dynamics.
- Our model fits well 5 of the 7 available characteristics of the infection.
- Comparaison to Bocharov 94 model:
  - It is a 13 state variable and 60 parameters ODE model with delays.
  - It has more cell types, but not various infection cell classes.
  - At infection peak, 70% of cells are infected vs 50% for ours.
  - After the parameter fit, 9 of the 60 parameters were outside biological range, one of them was 10^6-fold greater and two were 10^3-fold greater.
- To our knowledge, our model and that of Bocharov 94 are the only models on influenza A.

Visualizing the simulations with MASyV



At 9 h, 37 h, 48 h, and 62 h after start of infection.

Where to find information and links

My personal webpage
http://www.phys.ualberta.ca/∼cbeau/

MASyV on Sourceforge and movie files from ma_immune
http://masyv.sourceforge.net

The article on simple CA model of influenza A
http://www.arxiv.org/abs/q-bio.CB/0402012

A good intro. to immunology for physicists and mathematicians:

A.S. Perelson, G. Weisbuch. **Immunology for physicists**, *Reviews of Modern Physics*, 69(4):1219-1267, 1997.

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