

# VORLESUNG 15

Vorlesung  
Humboldt-Universität zu Berlin  
Institut für Physik

## Biologische Physik

Die Dynamik biologischer Prozesse im menschlichen Körper

Richard Weinkamer

Max Planck Institute of Colloids and Interfaces  
Department of Biomaterials  
Potsdam

[richard.weinkamer@mpikg.mpg.de](mailto:richard.weinkamer@mpikg.mpg.de)



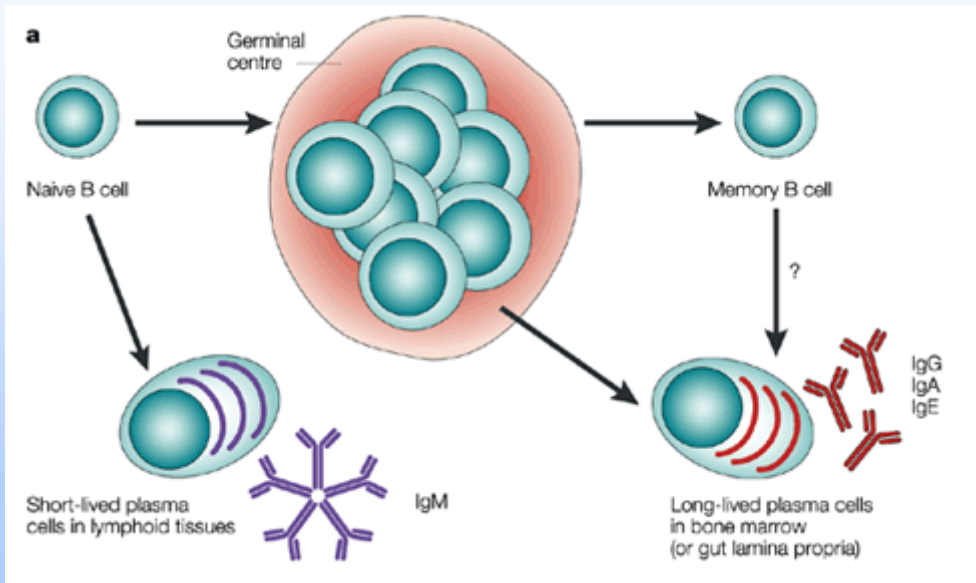
**Max Planck Institute  
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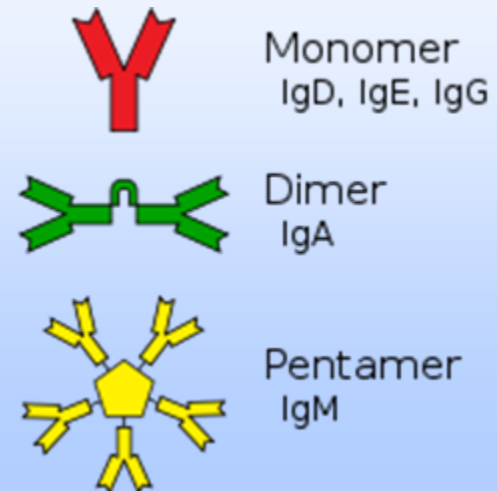
## 7.2 The Humoral Immune Response

the "life"  
of B cells:

- virgin B cell coming from the bone marrow
- **ACTIVATION** of a B cell requires two keys: crosslinking of BCRs and a „co-stimulatory“ key (e.g., by helper T cells, „battle cytokines“ from innate immune system)
- production of IgM antibodies – class switching of antibody to produce most effective antibody
- selection for **PROLIFERATION** and somatic hypermutation results in a collection of B cells whose BCRs bind more tightly to an invader
- final „career **CHOICE**“: plasma cell (antibody factories) or a memory B cell



memory B cell





## 7.2 The Humoral Immune Response

BELL's model: four different population of B cells:

- small (virgin) B cells  $S$  : 
$$\frac{dS}{dt} = m(t) - F(R) S / T_1$$
- large (proliferating) B cells  $L$  : 
$$\frac{dL}{dt} = G(R) S / T_1 + H(R) L / T_2 - L / T_2'$$
- plasma cells  $P$  : 
$$\frac{dP}{dt} = \left( \frac{1 - H(R)}{2} \right) L / T_2 - P / T_3$$
- memory cells  $M$  : 
$$\frac{dM}{dt} = \left( \frac{1 - H(R)}{2} \right) L / T_2 - M / T_4$$

$R$  ... average number of occupied receptor sites per cell

- free antibodies  $F$  :  
(internal production, external injection, binding to receptors, decay) :

$$\frac{dF}{dt} = c_2 L + c_3 P + s_F - J(R) F / T_5 - F / T_5'$$

- amount of antigen  $A$  and free antigen  $FA$  :  
(influx, decay, „receptor kinetics“ – affinity of the receptors)

$$\frac{dFA}{dt} = s_{FA} - FA / T_6 - \text{receptor term}$$





## 7.2 The Humoral Immune Response

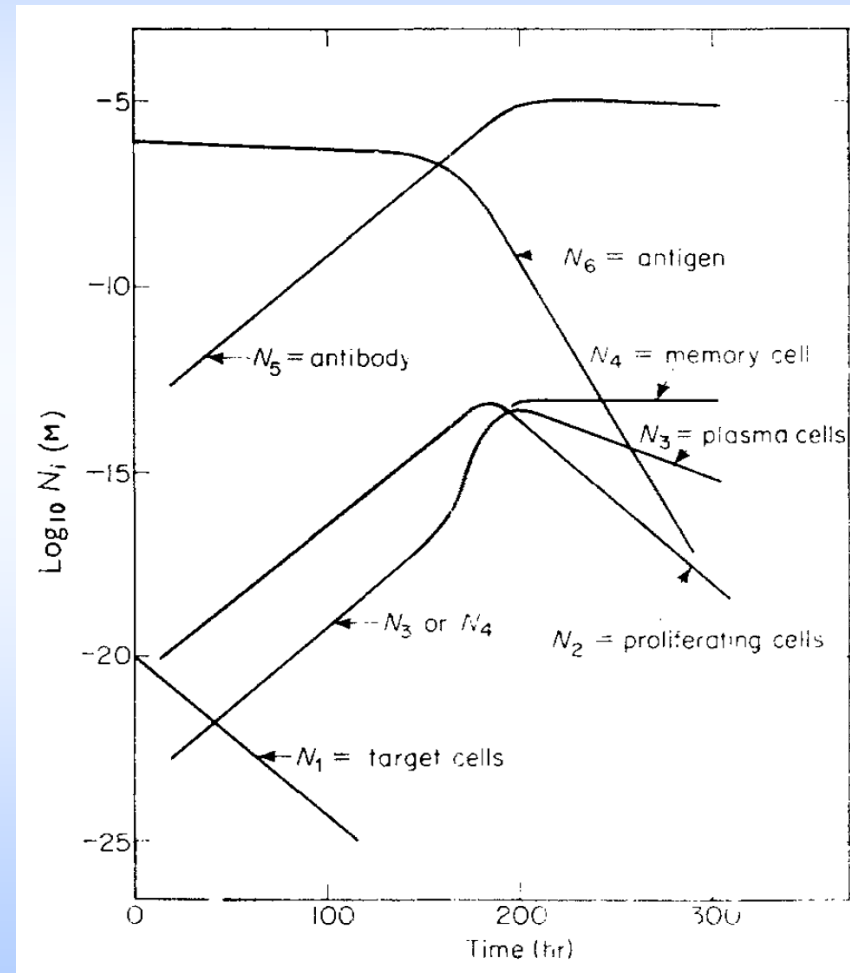
### BELL's model:

simulation consists of the following steps:

- 1) specify values for parameters and initial conditions
- 2) determine the FA and R
- 3) numerically solve the differential equations for the cell populations
- 4) repeat steps 2 and 3 until the desired time is reached (the "action" is over)

### QUESTIONS:

- different initial dose of antigen
- one-shot versus continuous antigen source
- secondary immune response





## 7.2 The Humoral Immune Response

QUESTION: what is the optimal strategy in dividing the task of overpowering between proliferating B cells and plasma cells  
simplified BELL's model:

only 3 populations: large B cells, plasma cells, antibody

important quantity:  $\frac{dA}{dt} = k(L + \gamma P)$   
 $u(t)$  ... fraction of proliferating B cells  
 $1-u(t)$  ... fraction of plasma cells

how should  $u(t)$  be chosen in order to minimize the time needed to secrete the amount of antibody  $A^*$  required to neutralize a given dose of antigen

$\min \int_0^T dt$  minimization over all functions  $u$ ,  
where the final time  $T$  is defined by  $A(T) = A^*$

answer obtained by optimal control theory:

- if  $\gamma$  is too small  $\Rightarrow u^*(t) = 1 \quad 0 \leq t \leq T$
- if  $A^*$  is too small  $\Rightarrow u^*(t) = 0 \quad 0 \leq t \leq T$
- if  $A^*$  is large  $\Rightarrow u^*(t) = \begin{cases} 1 & 0 \leq t \leq t^* \\ 0 & t^* \leq t \leq T \end{cases}$



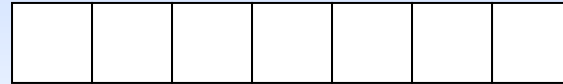


# cellular automata

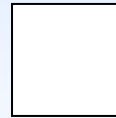
- ✗ simplicity
- ✗ versatility

## simplest cellular automaton:

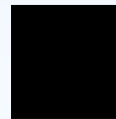
✗ 1-dimensional



✗ only two-states

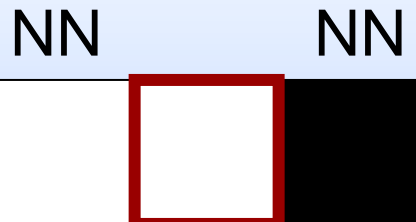


0, white, healthy, ...



1, black, diseased, ...

✗ only local nearest-neighbour transformation rules (NN rules)

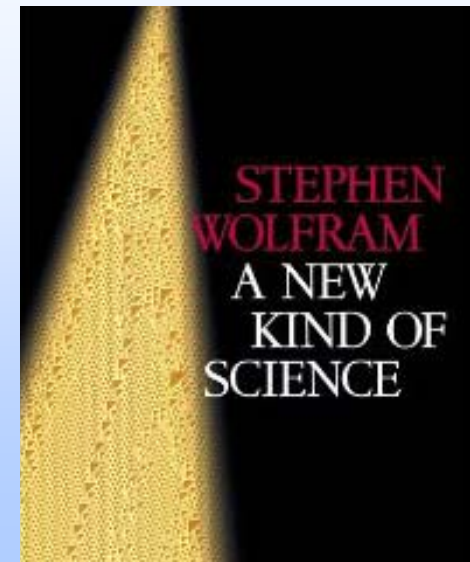


time evolution



timestep t

timestep t+1

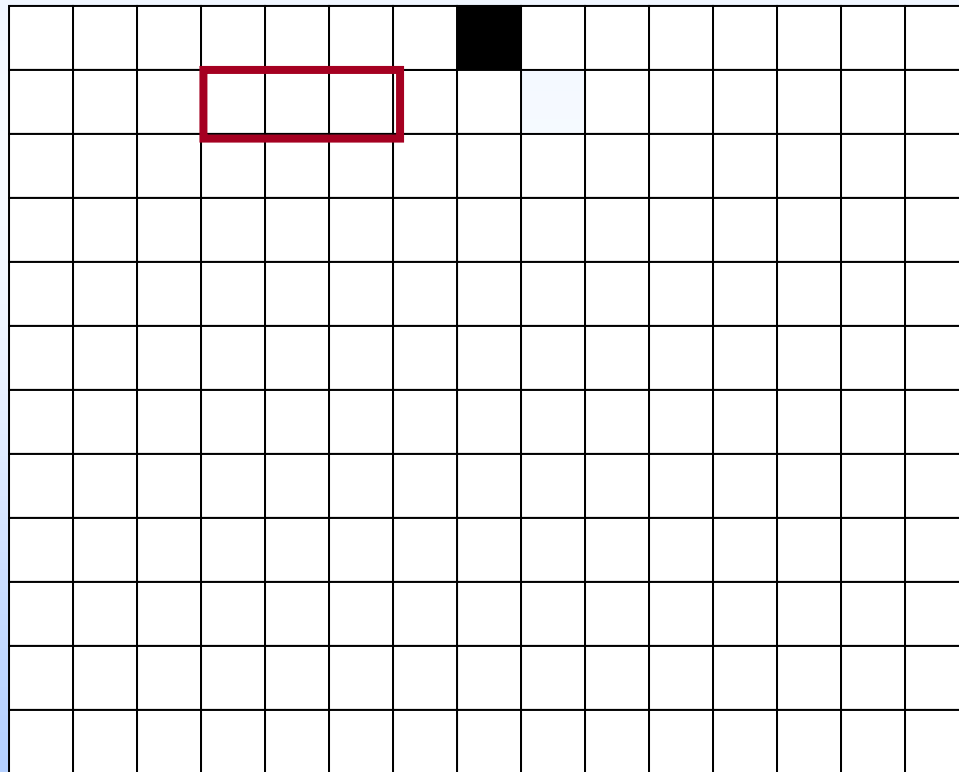
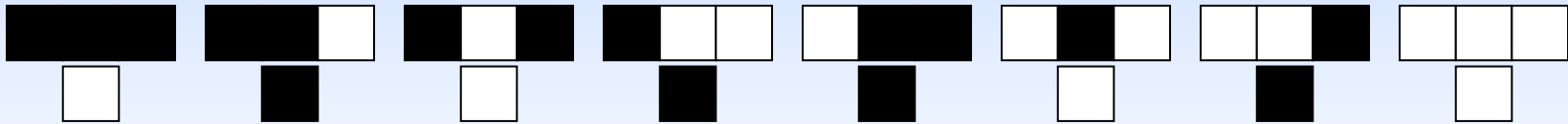




# cellular automata

first example:

$2^3 = 8$  rules have to specified

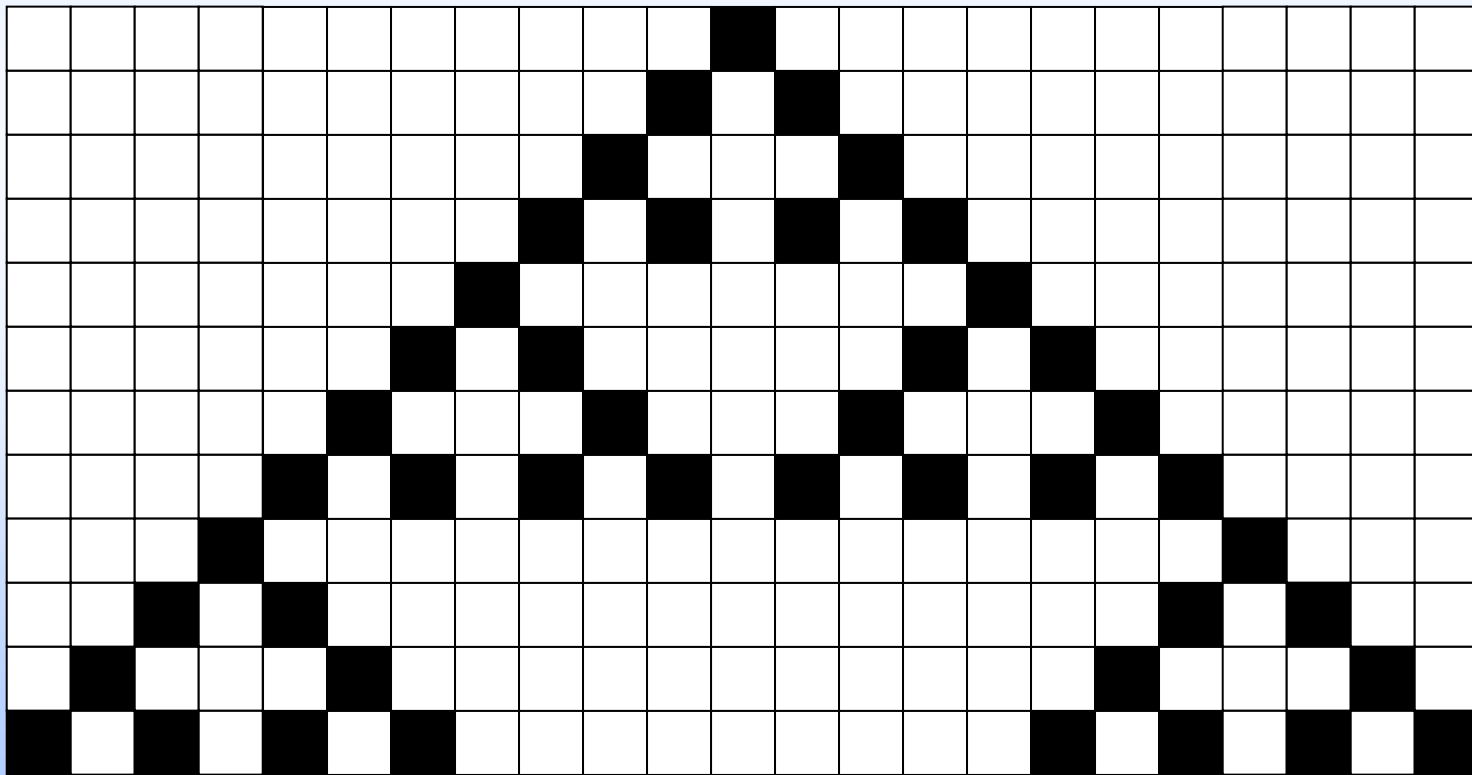
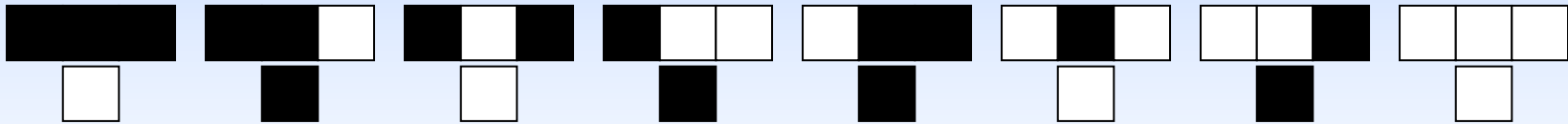




# cellular automata

first example:

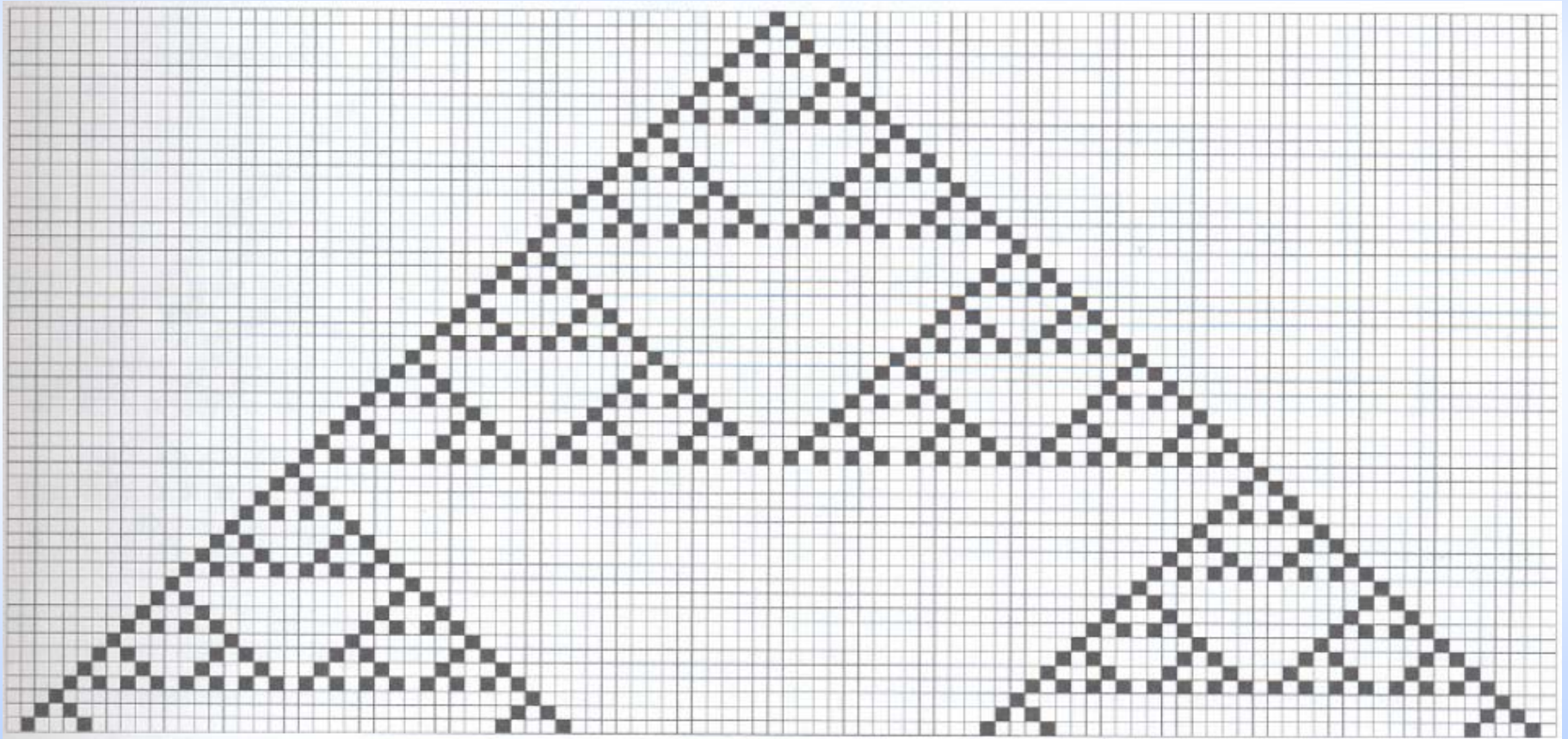
$2^3 = 8$  rules have to specified





# cellular automata

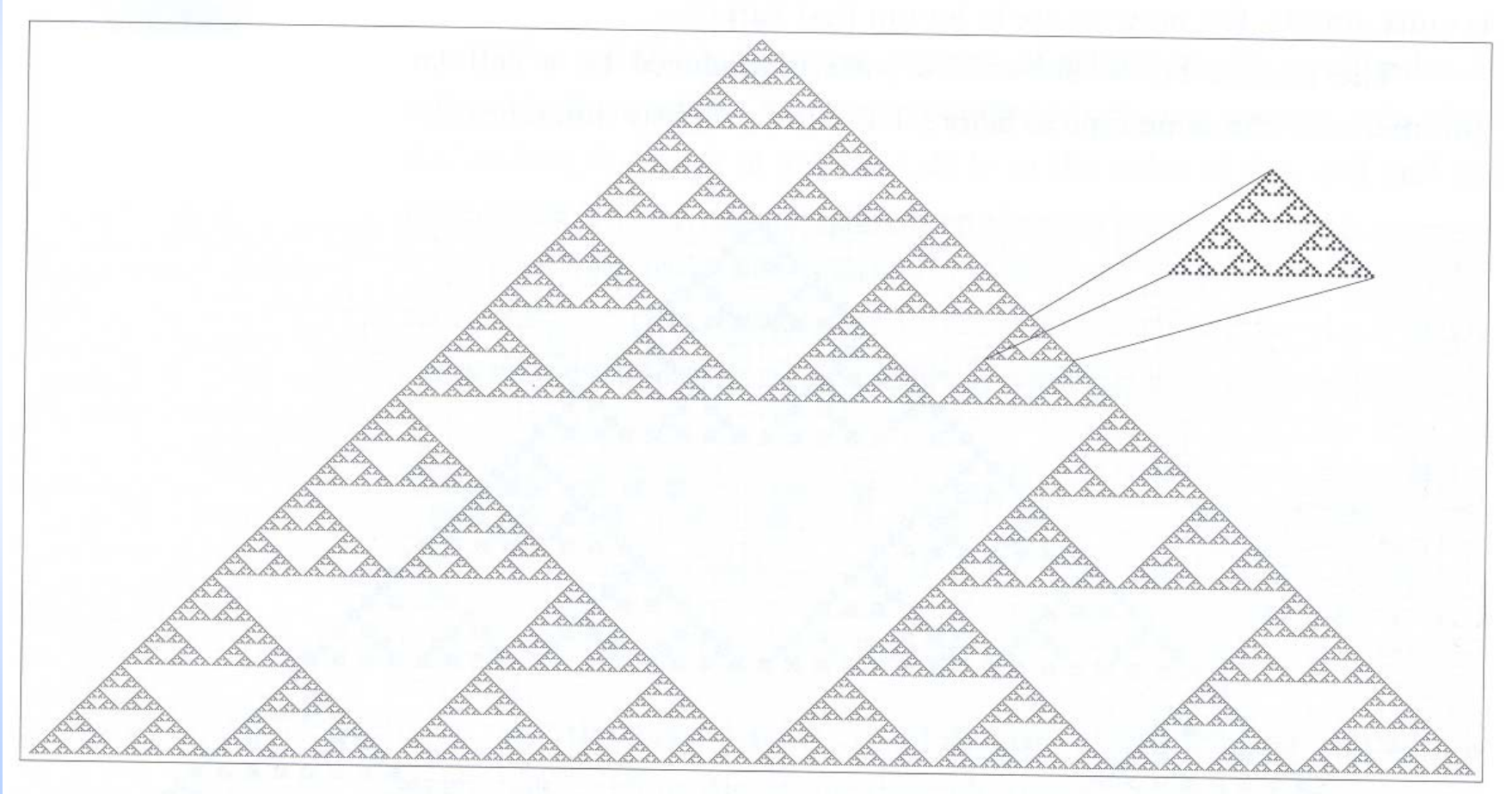
first example:





# cellular automata

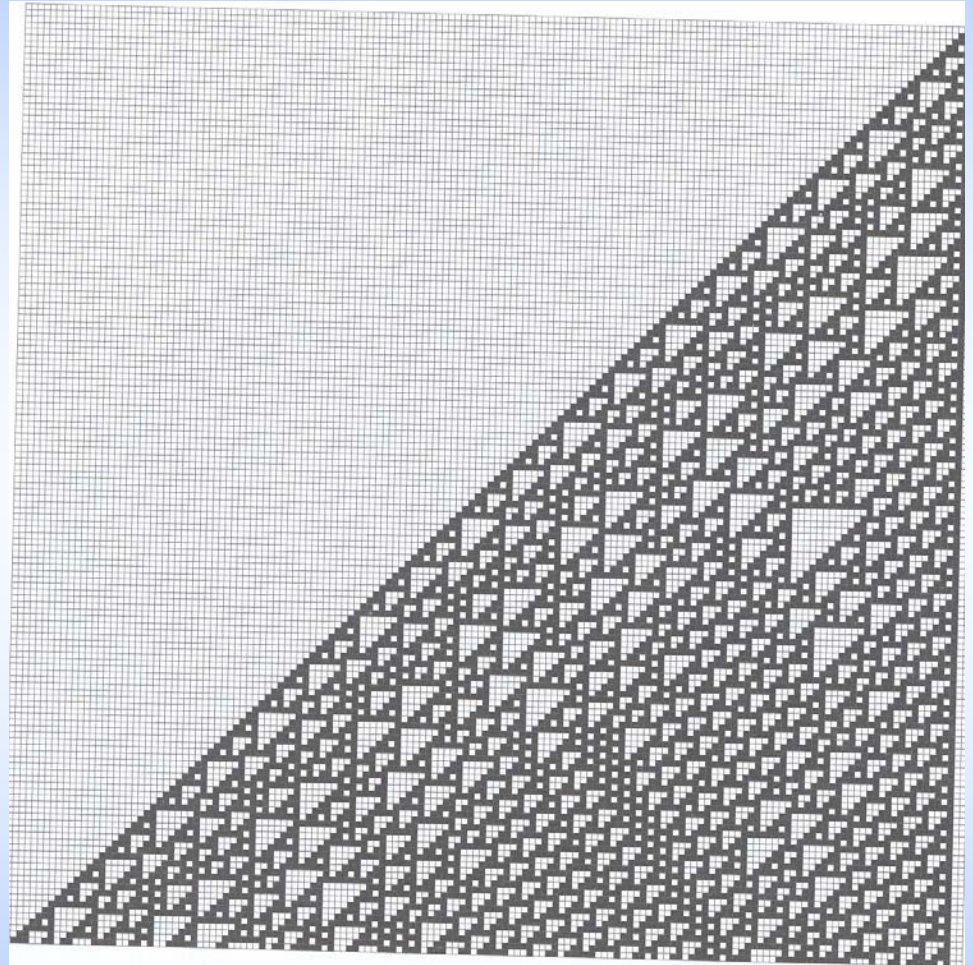
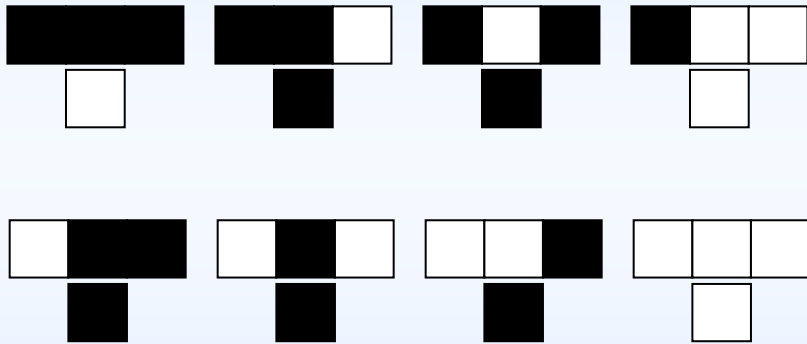
first example:





# cellular automata

second example:





# cellular automata

second example:





# cellular automata

second example:





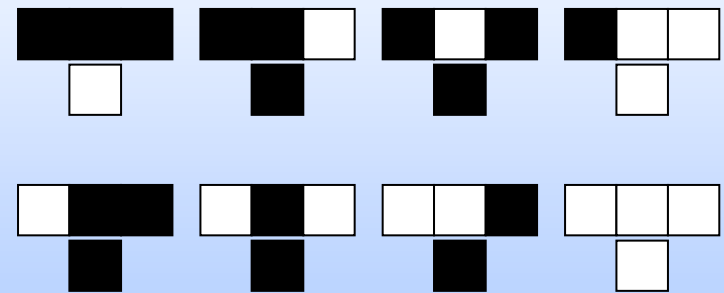
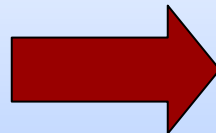
# cellular automata

## conclusion:

simple rules can result in extremely complex, unforeseeable behavior

## even more important:

observed complex behavior can have their origin in astonishing simple rules



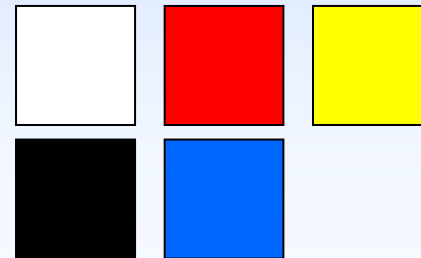


# cellular automata

## straightforward extensions:

✘ 2-dimensional, 3-dimensional – general lattices

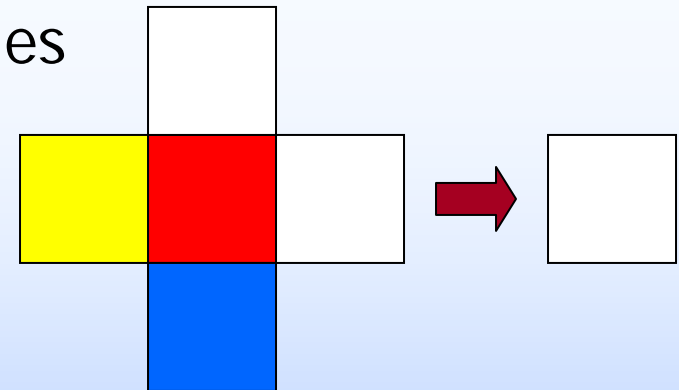
✘ more than two-states  
(infinite: number)



✘ also global transformation rules

✘ memory effects

(not only the last state of the system  
is decisive for the future)



✘ stochastic elements

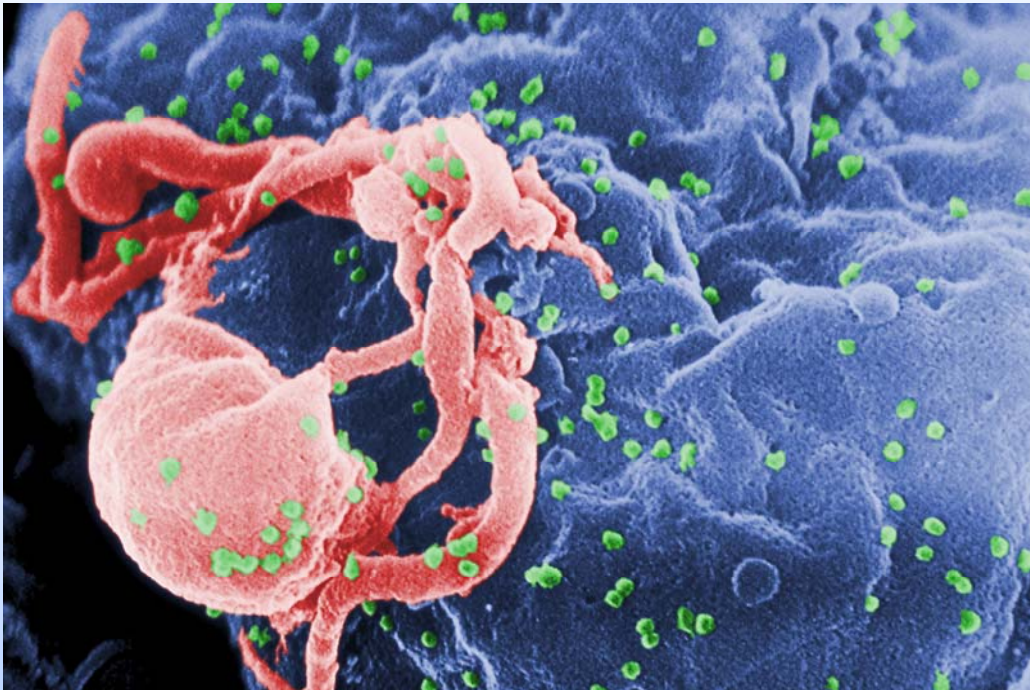
(random selection of a lattice site,  
probabilistic transformation rules)



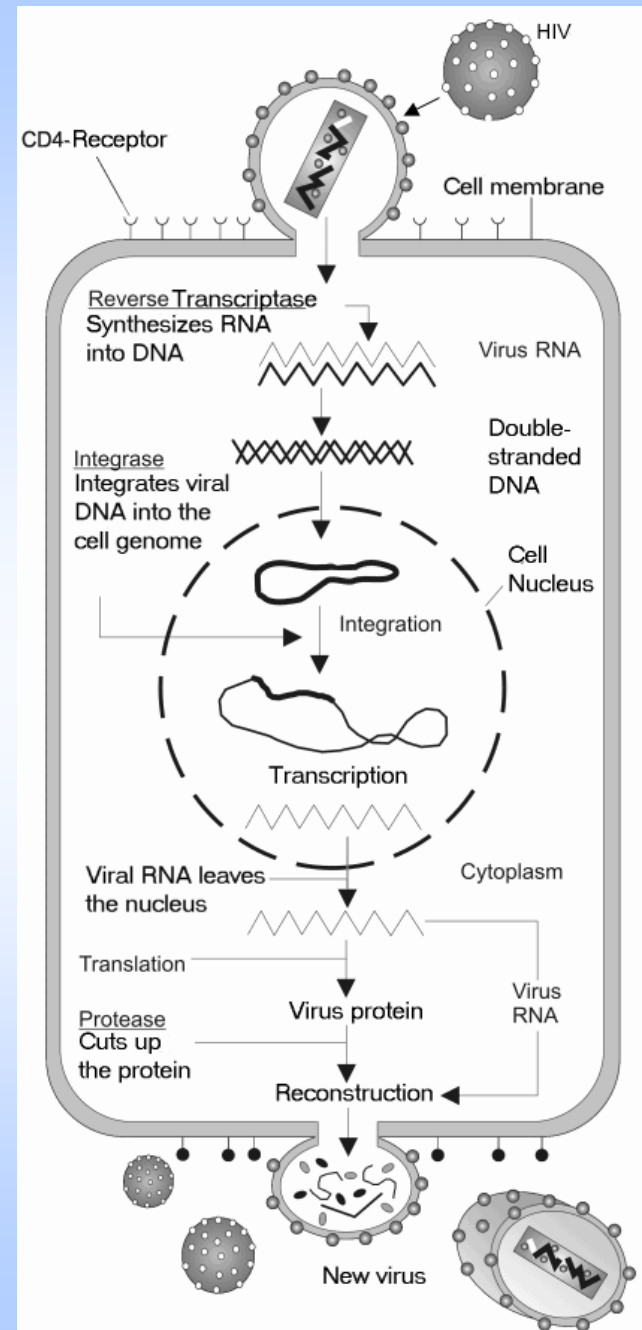


## 7.3 Viral Infection - AIDS

AIDS ... acquired immune deficiency syndrome set of symptoms and infections resulting from the damage to the human immune system caused by the human immunodeficiency virus (HIV)



HAART ... highly active antiretroviral therapy

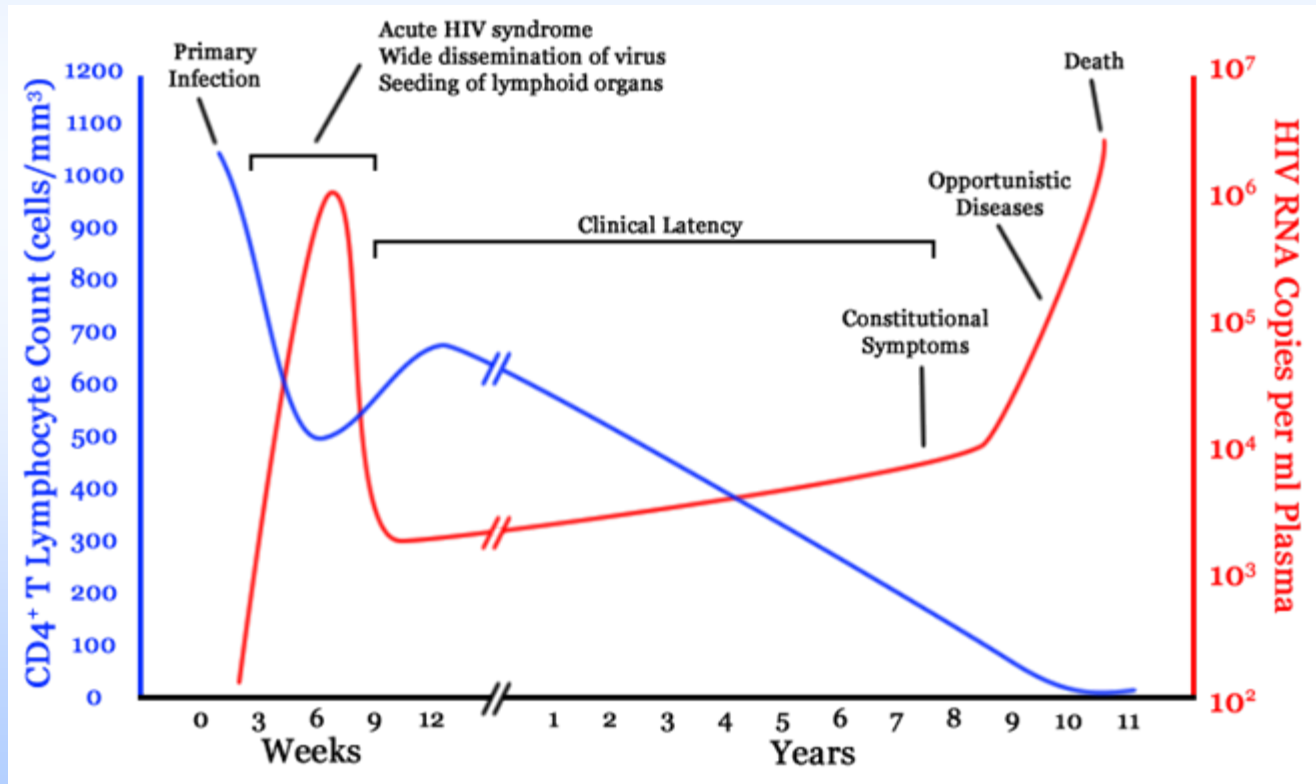




## 7.3 Viral Infection - AIDS

HIV infection leads to low levels of helper T cells (CD4+ T cells) due to:

- direct viral killing of infected cells
- increased rates of apoptosis in infected cells
- killing of infected cells by killer T cells





## 7.3 Viral Infection - AIDS

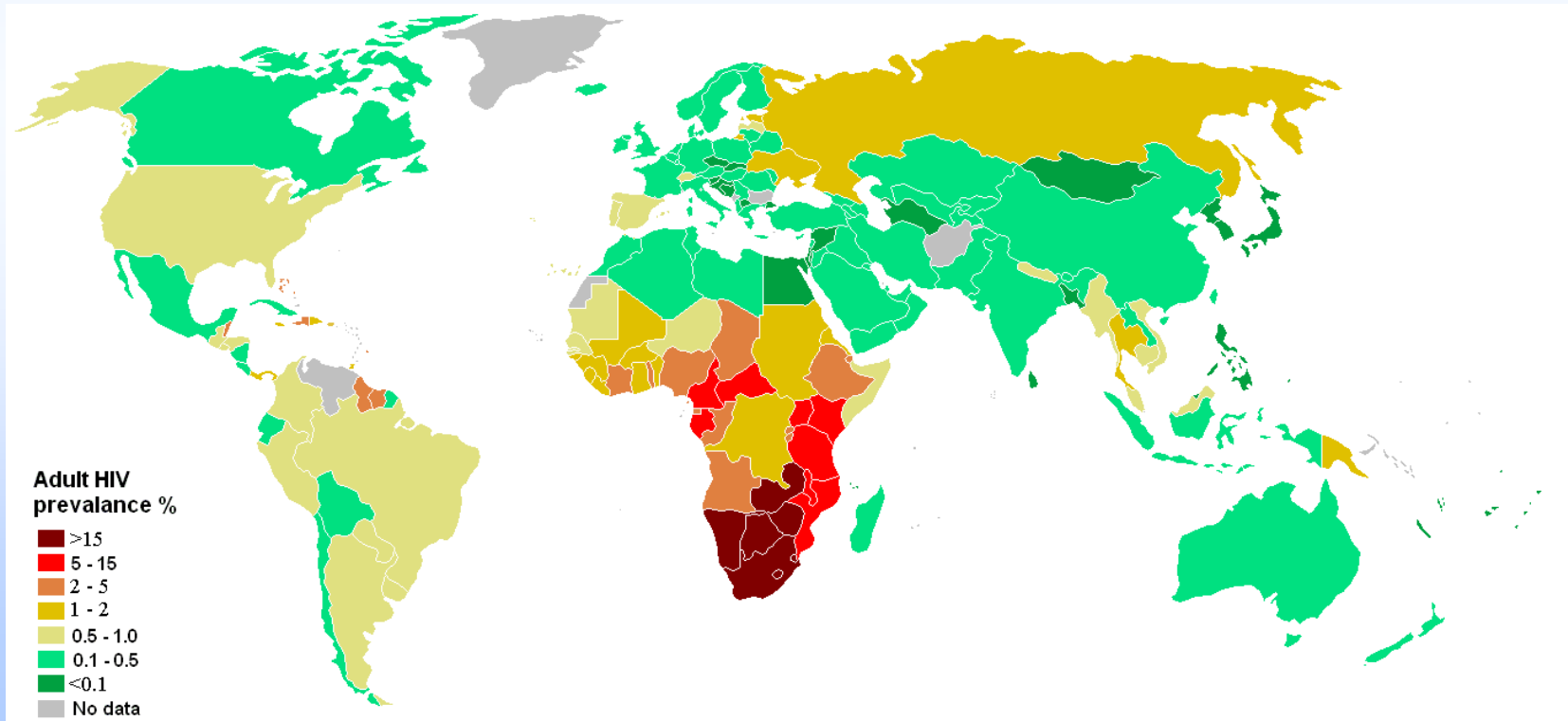
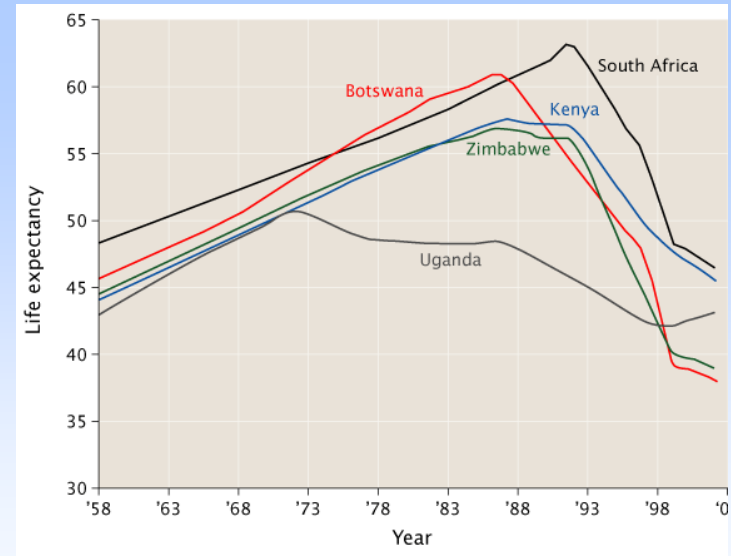
AIDS is now a pandemic

in 2007

30.6 – 36.1 million people are infected by HIV

2.1 million people died

2.5 million new infections





## 7.3 Viral Infection - AIDS

Worldwide mortality due to infectious diseases<sup>[9]</sup>

Rank	Cause of death	Deaths 2002	Percentage of all deaths	Deaths 1993	1993 Rank
N/A	All infectious diseases	14.7 million	25.9%	16.4 million	32.2%
1	Lower respiratory infections <sup>[10]</sup>	3.9 million	6.9%	4.1 million	1
2	HIV/AIDS	2.8 million	4.9%	0.7 million	7
3	Diarrheal diseases <sup>[11]</sup>	1.8 million	3.2%	3.0 million	2
4	Tuberculosis (TB)	1.6 million	2.7%	2.7 million	3
5	Malaria	1.3 million	2.2%	2.0 million	4
6	Measles	0.6 million	1.1%	1.1 million	5
7	Pertussis	0.29 million	0.5%	0.36 million	7
8	Tetanus	0.21 million	0.4%	0.15 million	12
9	Meningitis	0.17 million	0.3%	0.25 million	8
10	Syphilis	0.16 million	0.3%	0.19 million	11
11	Hepatitis B	0.10 million	0.2%	0.93 million	6
12-17	Tropical diseases (6) <sup>[12]</sup>	0.13 million	0.2%	0.53 million	9, 10, 16-18

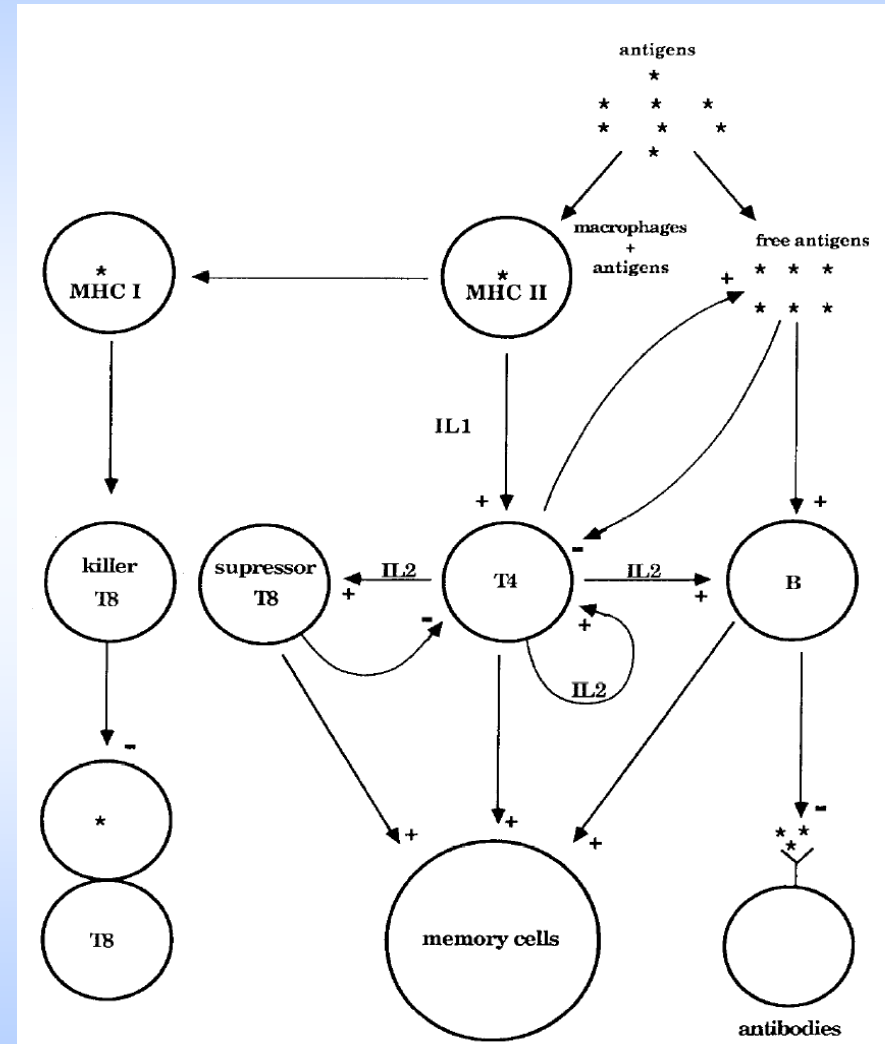




## 7.3 Viral Infection - AIDS

### OBSERVATIONS:

- introduction of HIV into the immune system, causing a non-specific immune response from the macrophages; some macrophages become infected
- macrophages present components of the virus to helper T cells
- infection and subsequent destruction of helper T cells by HIV virus
- proliferation of killer T cells in response to the lymphokines released by the helper T cells
- destruction of infected cells by the killer T cells
- spread of the virus by rapid or slower growth





## 7.3 Viral Infection - AIDS

Pandey, Physica A 179  
(1991) 442

### MODELING:

#### 4 cell types considered:

- $M(t)$  ... stimulated macrophages
- $T4(t)$  ... healthy helper T cells
- $T8(t)$  ... killer T cells
- $V(t)$  ... virions (= cells infected by HIV or free virus particles)

#### dynamical rules:

##### **RAPID MODE:**

$$M(t+1) = M(t) \text{ OR } V(t)$$

$$V(t+1) = [V(t) \text{ OR } M(t) \text{ OR } T4(t)] \text{ AND } [NOT T8(t)]$$

$$T4(t+1) = [M(t) \text{ OR } T4(t)] \text{ AND } [NOT V(t)]$$

$$T8(t+1) = T4(t) \text{ AND } M(t) \text{ AND } V(t)$$

##### **SLOW MODE:**

$$M(t+1) = M(t) \text{ OR } V(t)$$

$$V(t+1) = [V(t) \text{ OR } T4(t)] \text{ AND } [NOT [T4(t) \text{ AND } T8(t)]]$$

$$T4(t+1) = [T4(t) \text{ OR } [M(t) \text{ AND } V(t)]] \text{ AND } [NOT V(t)]$$

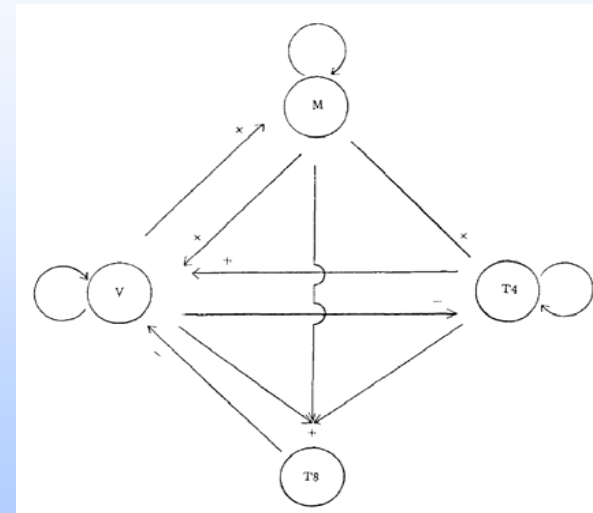
$$T8(t+1) = T8(t) \text{ OR } [T4(t) \text{ AND } M(t) \text{ AND } V(t)]$$

#### binary code:

- 1 ... high population of a specific cell type
- 0 ... low or absent cell population

#### example:

$$[M, V, T4, T8] = 1100 = 12$$





# 7.3 Viral Infection - AIDS

## RESULTS:

mean-field approximation

### RAPID MODE:

Flow	Fixed point	Biomedical interpretation	Probability
1 → 0	0 = (0000)	fully immunocompetent	$\frac{1}{8}$
	12 = (1100)	fully immunodeficient	$\frac{5}{16}$
	14 = (1110) 13 = (1101) 8 = (1000)	infected badly infected susceptible	$\frac{9}{16}$

### SLOW MODE:

Flow	Fixed point	Biomedical interpretation	Probability
1 → 0	0 = (0000)	fully immunocompetent	$\frac{1}{8}$
	12 = (1100)	fully immunodeficient	$\frac{1}{4}$
	3 = (0011)	susceptible	$\frac{1}{16}$
	13 = (1101)	badly infected	$\frac{1}{4}$
	9 = (1001)	susceptible	$\frac{3}{16}$
	8 = (1000)	susceptible	$\frac{1}{16}$
	11 = (1011)	susceptible	$\frac{1}{16}$

Pandey, Physica A 179  
(1991) 442





## 7.3 Viral Infection - AIDS

Pandey, Physica A 179  
(1991) 442

**RESULTS:** three-dimensional model of HIV infection

cubic lattice with nearest neighbor interaction

each time step:

- (i) applications of cell transport between cubes
- (ii) application of rules for cell interaction within cubes

crossover from "immunodeficient" to "immunocompetent" state for  $P$  (initial probability of host cells),  $P = 0.07$

probability  $B$  that virus is not dormant (dilution model)

