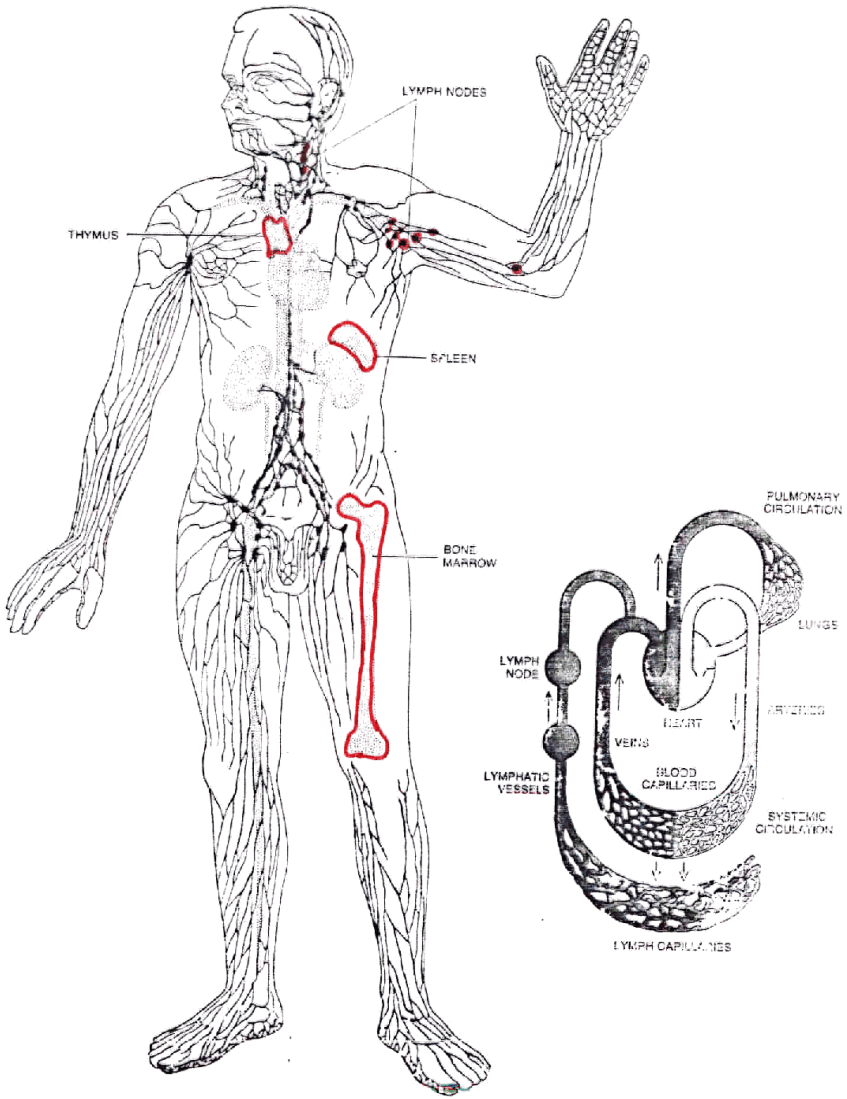
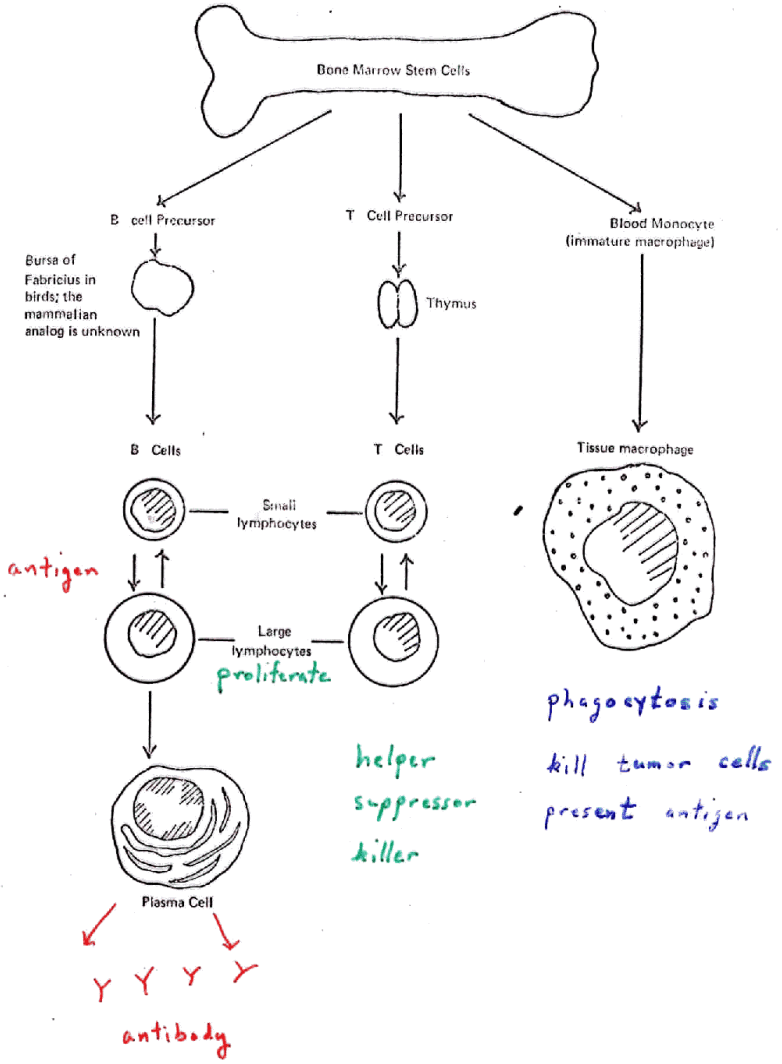
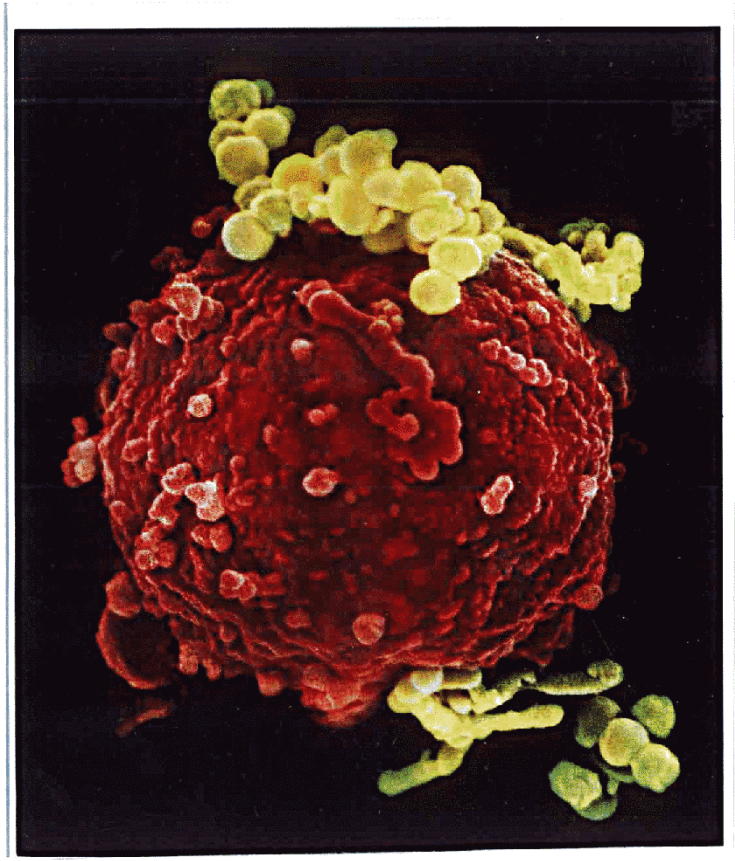
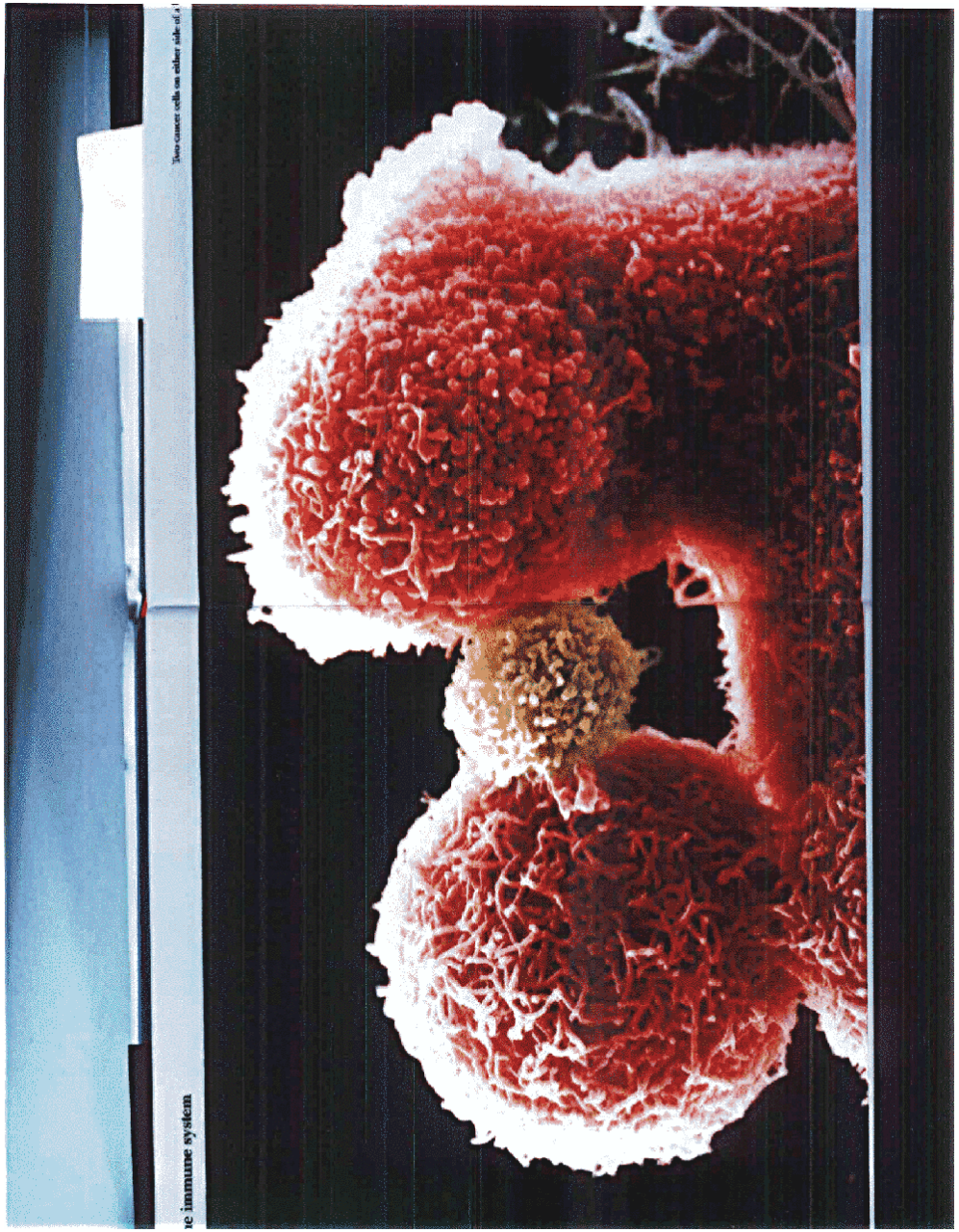
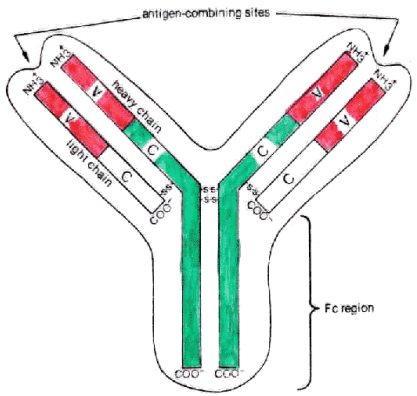

LYMPH NODES
THYMUS
SPLEEN
BONE MARROW
PULMONARY CIRCULATION
LUNGS
LYMPH NODE
ARTERIES
HEART
VEINS
LYMPHATIC VESSELS
BLOOD CAPILLARIES
SYSTEMIC CIRCULATION
LYMPH CAPILLARIES

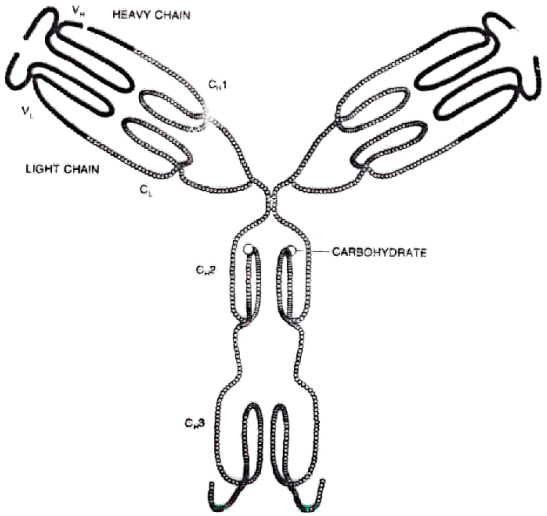

Bone Marrow Stem Cells
B cell Precursor
T Cell Precursor
Blood Monocyte (immature macrophage)
Bursa of Fabricius in birds; the mammalian analog is unknown
Thymus
B Cells
T Cells
Tissue macrophage
Small lymphocytes
antigen
Large lymphocytes
proliferate
helper
suppressor
killer
phagocytosis
kill tumor cells
present antigen
Plasma Cell
antibody

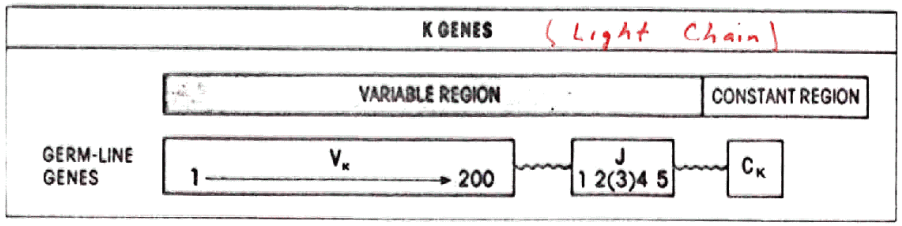


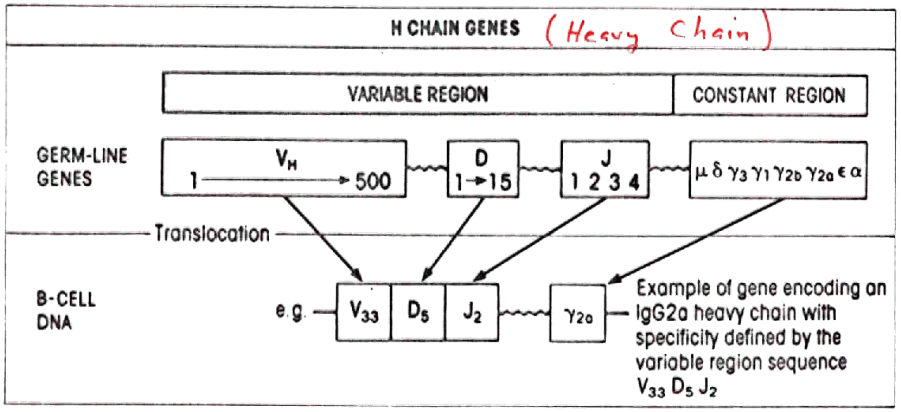


Antibody









Immune system uses combinatorics to generate large number of antibodies from few genes:

heavy chains : $500 \times 15 \times 4 = 3 \times 10^4$

light chains : $200 \times 5 = 10^3$

antibody : heavy × light = 3×10^7

plus point mutation, errors in joining gene segments

The Fundamental Problem of Immunology:

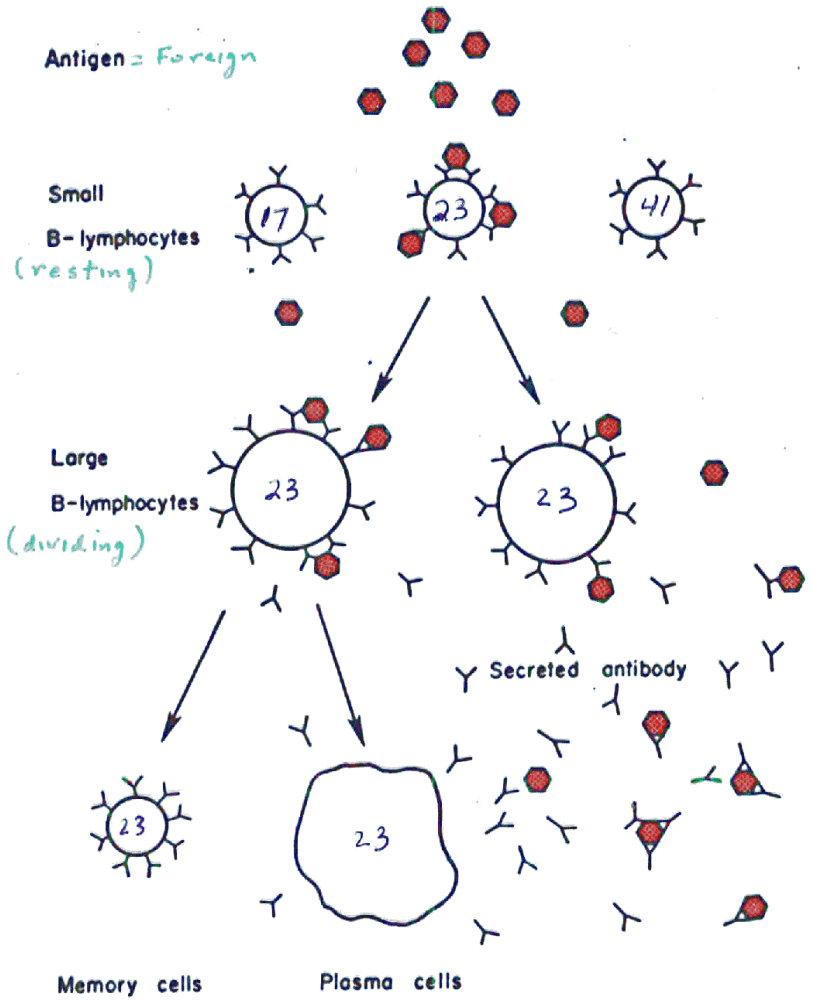
How do you recognize every possible pathogen -

even pathogens that have never existed before in all of evolutionary history, such as a new strain of flu or HIV?

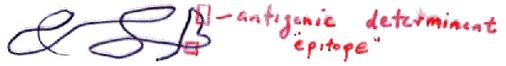
Solution: Clonal Selection

Make (sloppy) detectors (receptors) at random.

Select and amplify the useful ones.

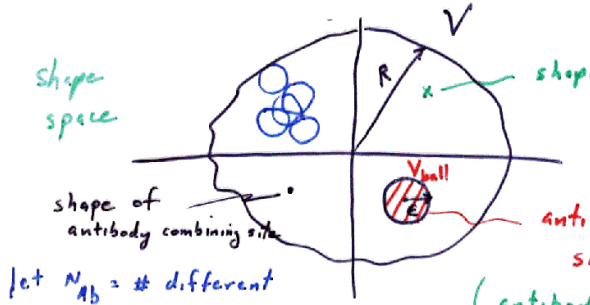


Recognition of Foreign Molecules by Antibody (Perelson + Oster J. Theoret. Biol. 1979)



Assume generalized shape of an antigenic determinant

determined by N characteristics, e.g. length, width, height, charge

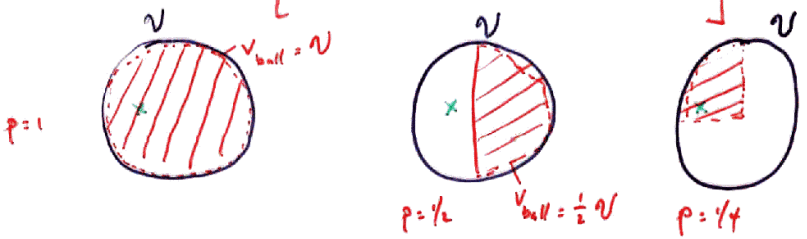


let N_{Ab} = # different antibody balls

antibodies complementary to antigenic determinant; for simplicity assume complementarity map = identity map

probability an antibody recognizes a foreign shape

$$p = V_{ball}/V \left[= \left(\frac{\epsilon}{R}\right)^N \text{ if Euclidean} \right]$$



Expt Expose B cells to a foreign antigen
(dropping antibody ball on antigen x)

Measure fraction of B cells that respond to antigen
This fraction is an estimate of p!

$$p \approx 10^{-5}$$

Probability antigen escapes detection if there are N_{Ab} different antibodies in the repertoire

$$P_{escape} = (1-p)^{N_{Ab}} \simeq e^{-N_{Ab}p}$$

If $N_{Ab} = 10^8$ then $P_{escape} = e^{-10^8 \cdot 10^{-5}} = e^{-1000}$

i.e. $P_{escape} = 10^{-430}$!! everything recognized!

Smallest known immune system
young tadpole $N_{Ab} \approx 10^5 - 10^6$

$\therefore P_{escape} = e^{-1} = .37$ barely works!

if $N_{Ab} = 10^6$: $e^{-10} = 5 \times 10^{-5}$ works fine

with $p = 10^{-5}$

	N_{Ab} = repertoire size	P_{escape}
tadpole	10^5	.37
	10^6	5×10^{-5}
mouse	10^7	3×10^{-44}
	10^8	10^{-430}

- If repertoire is 10^8 then only necessary that a small fraction of repertoire be generated at <u>random</u> for this to still work

e.g. 1% random $\Rightarrow N_{Ab} \approx 10^6$

- If $N_{Ab} = 10^8$ and $p = 10^{-5}$ then total volume of all antibody balls, $N_{Ab} V_{ball}$, is 1000 times volume of shape space

$$N_{Ab} p = N_{Ab} \frac{V_{ball}}{V} = 10^3$$

$\Rightarrow$ on average each point of shape space covered by 1000 antibody balls

<u>response is highly redundant</u>

average connectivity of network element : 1000!

Impose Dynamics on Algorithm

- antibody of a given type is rare

  mice - 10^8 lymphocytes 10^7-10^8 types

  humans - 10^{12} lymphocytes "

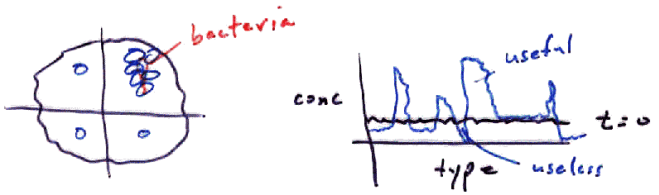
⟹ 1) If antibody is useful, i.e. detects something, make more of them

System has finite size

⟹ 2) If antibody useless, over some time period, eliminate it (>10^6 cells/sec !!)

⟹ 3) Immune Forgetting

1) + 2) ⟹ concentrations of different detectors will vary

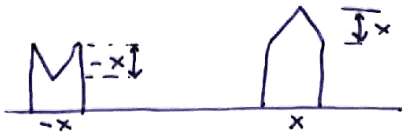


System can "learn" which detectors are useful. Must "remember" this information.

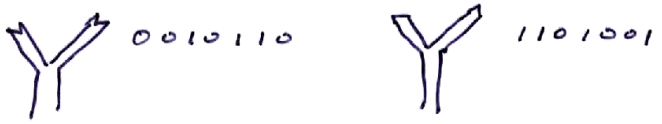
Approaches to Network Topology

1. Study fixed topologies — trees, different lattices, etc. Compare results, look for generic behavior

2. Geometric (Shape Space) Models



3. Bitstring Model



32 bits = repertoire 4×10^9

4. Random Networks - Connection matrix J_{ij} random $\{0, 1\}$ matrix

5. Experimentally Derived Matrix

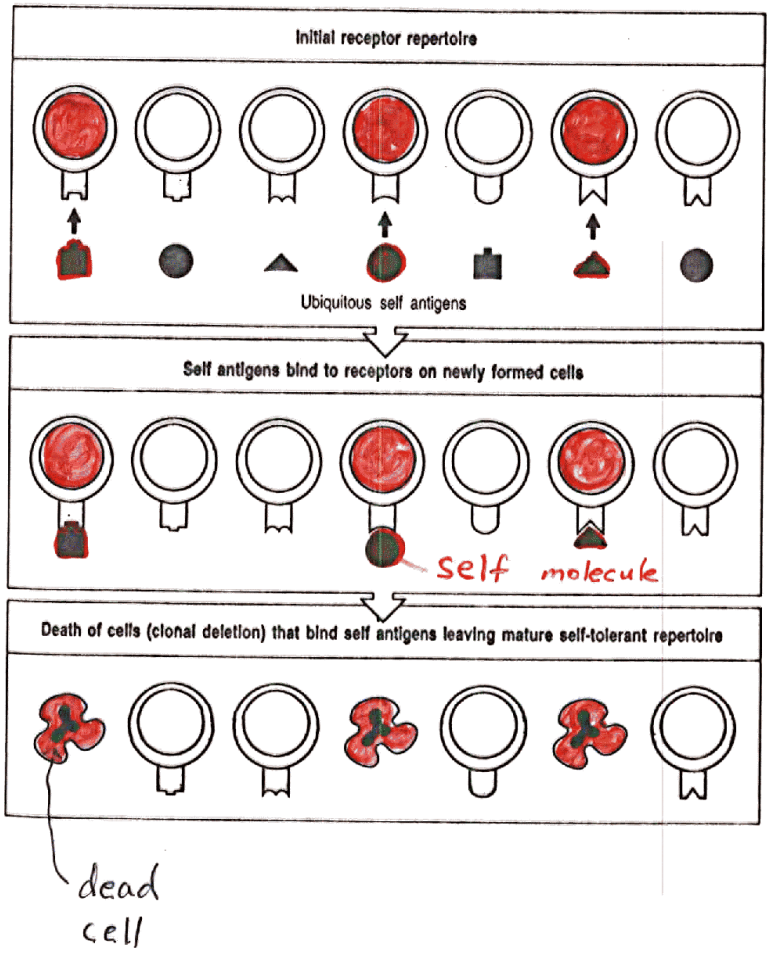
PROBLEM: Clonal selection is too good!

Everything is recognized including self.

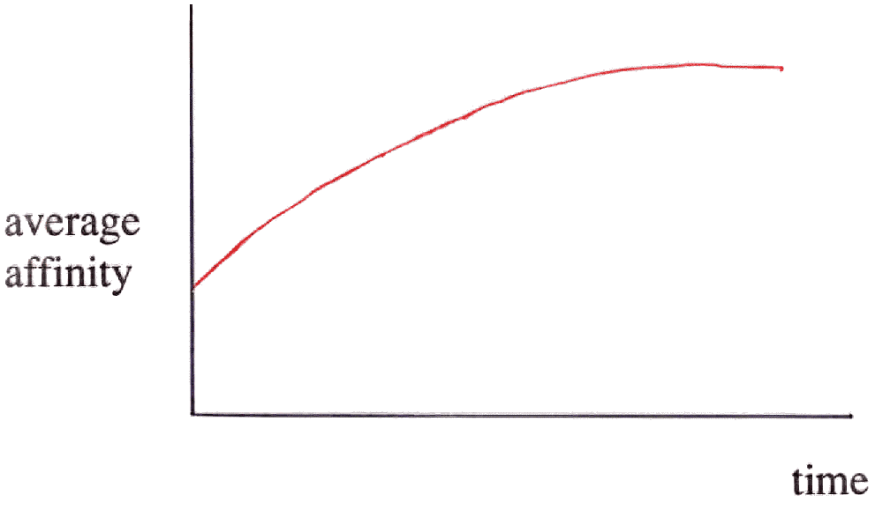
Solution: Delete clones that recognize self.

2) Fine tune recognition specificity

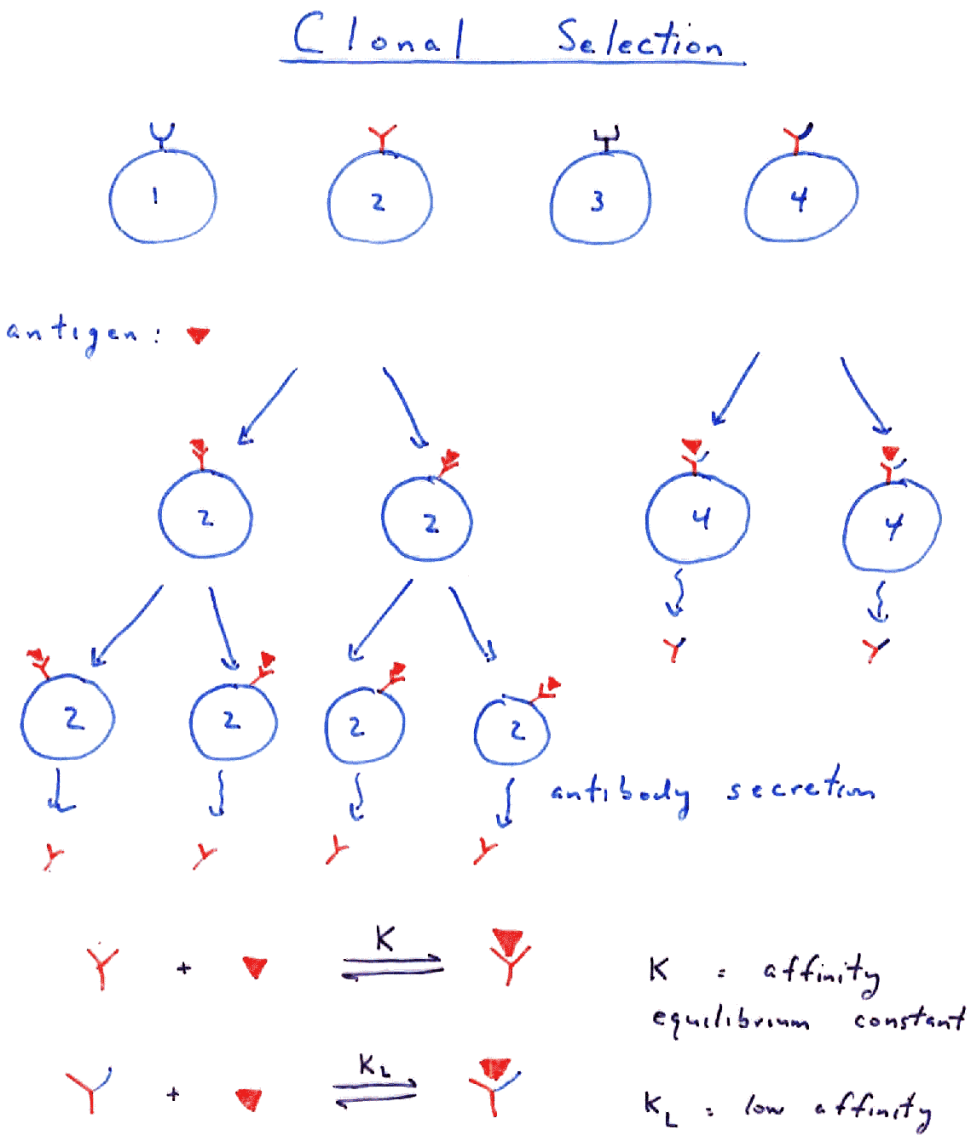
Clonal Deletion



Maturation of the Immune Response



Classical explanation: competition for limiting amounts of antigen causes low affinity cells to drop out of the response, leaving only high affinity B cells.



Somatic Mutation

Antibody Gene

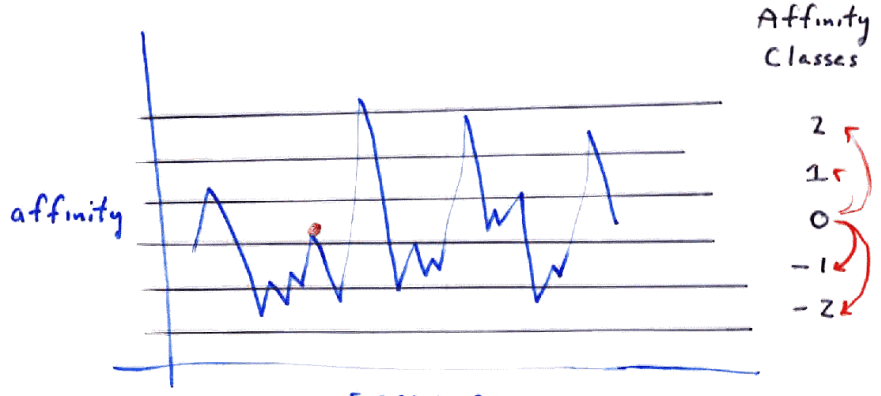
...AAT AAT GGT...*germline gene*

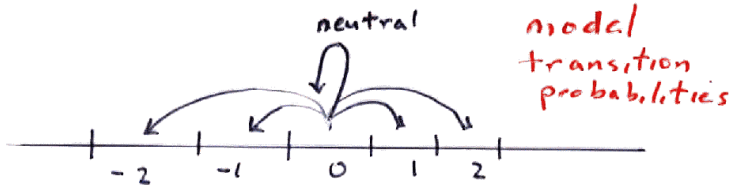
↓ *mutation*

AAT ATT GGT

↓ *mutation*

GAT ATT GGT





model transition probabilities

Affinity Classes

Build stochastic or deterministic models for population dynamics

Models can be simple enough to study control of mutations

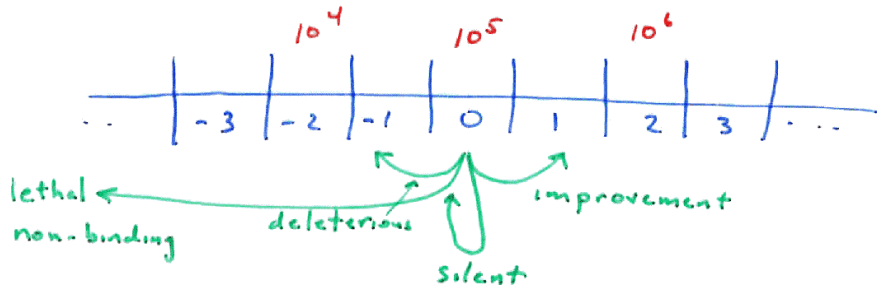
Kepler + Perelson

J. Theoret. Biol. 164, 37 (1993)

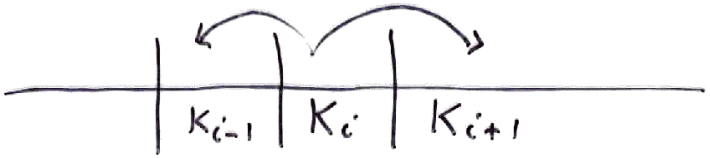
Immunol. Today 14, 412 (1993)

Proc. Natl. Acad. Sci. US (1995)

Affinity Classes



Affinity Classes



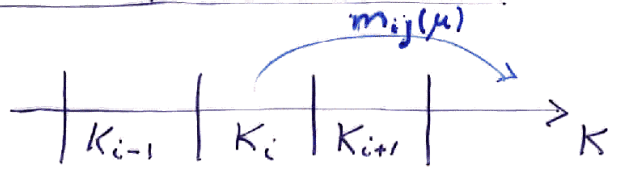
Population Dynamics

b_i = # B cells in affinity class i

$$\frac{db_i}{dt} = \text{growth} - \text{death} - \text{loss by mutation into classes } i+1, i-1, \ldots + \text{gain by mutation of cells in other classes}$$

growth – competition for antigen
high K_i cells grow better

AFFINITY CLASSES



Population Dynamics

$$\frac{db_i}{dt} = b_i \Theta_i \left[k_p h_i (2m_{ii} - 1) - k_d (1 - h_i) \right] + 2k_p \sum_{j \neq i} m_{ji} b_j h_j \Theta_j$$

growth; fraction stimulated; death; unstimulated; either of 2 daughter cells of type j can mutate into i; j mutates into i

where

$$\Theta_i \equiv \begin{cases} 1 & \text{if } b_i \geq 1 \\ 0 & \text{if } b_i < 1 \end{cases}$$

$$h_i = \frac{K_i a}{1 + K_i a}$$

antigen; fraction bound; receptors

Antigen conserved on surface of FDC

$$a + \sum_i b_i h_i \sigma_i = a_0$$

σ_i: receptors / cell / vol.

Assume evolution has optimized the performance of the immune system.

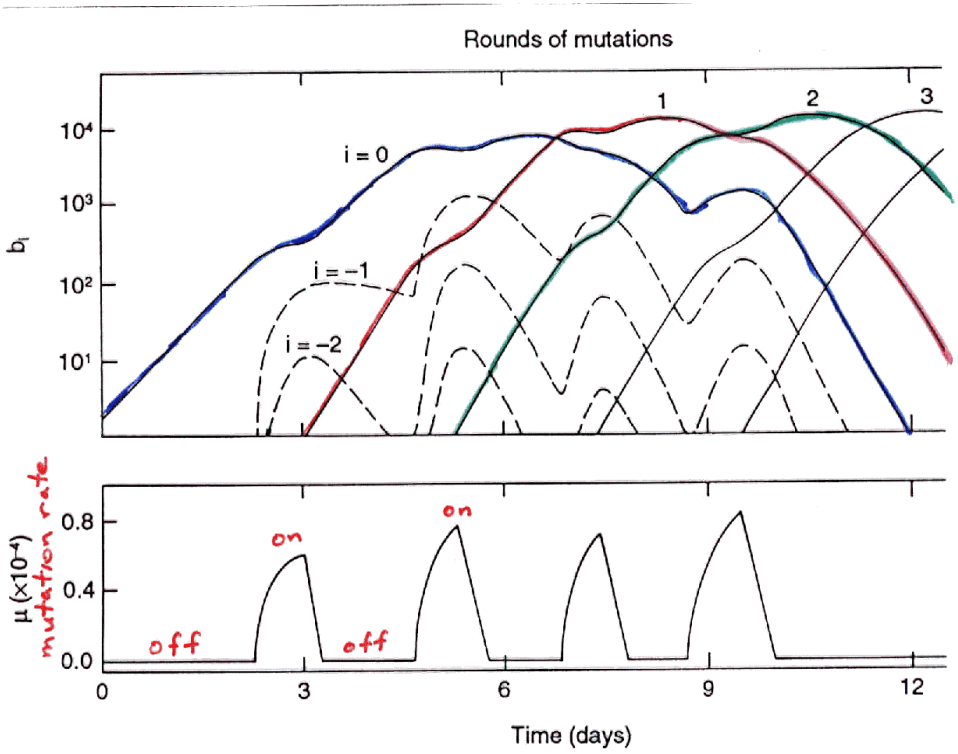
Maximize $A(t) = \sum_i b_i(t) K_i$ at $t = T$ e.g. 14 days

b_i: # of B cells of type i

K_i: affinity of antibody i

What mutation rate $\mu(t)$ maximizes $A(t)$?

$m_{ij} = m_{ij}(\mu(t))$



Mutation should be phasic

How can the immune system implement phasic mutation?

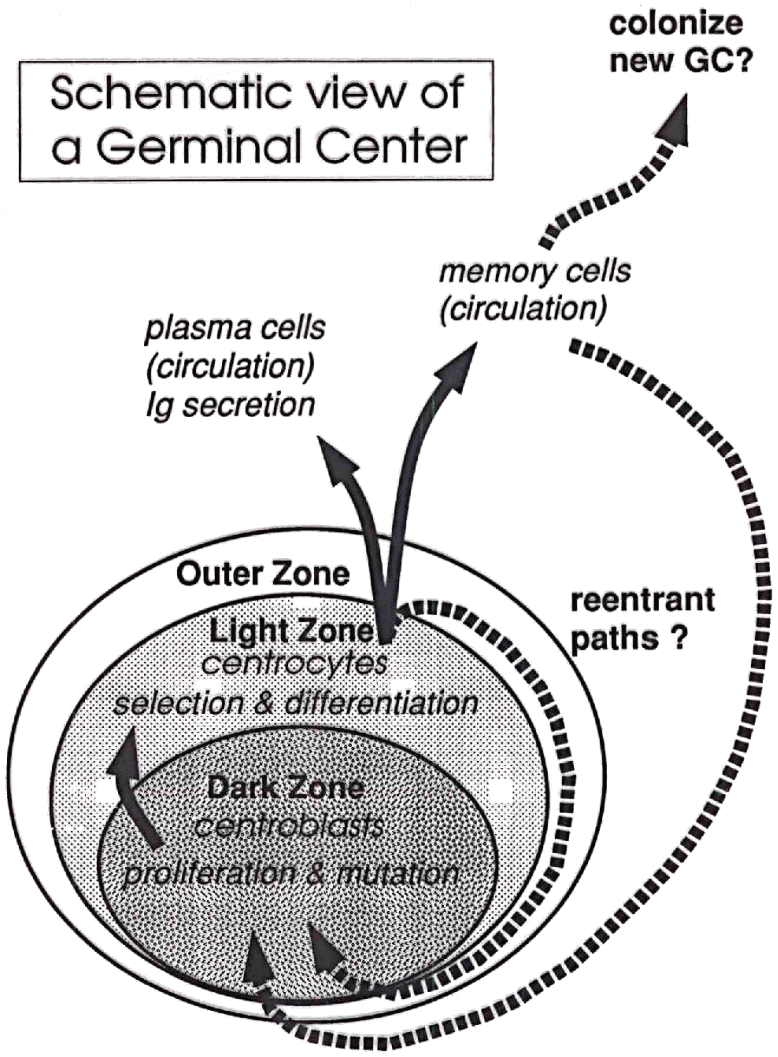
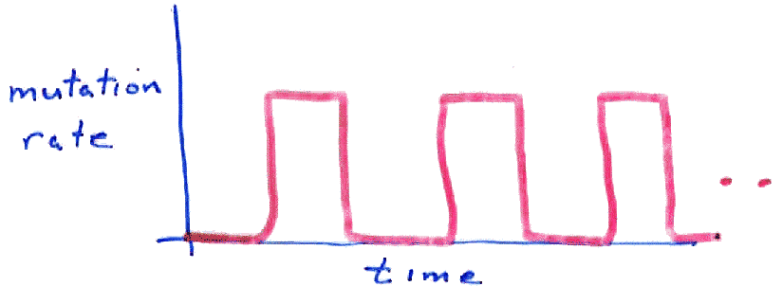


Fig. 5

RESULTS

- In evolving systems based on replication, mutation and selection of fitter variants, mutation should not be "on" all of the time – it should be phasic

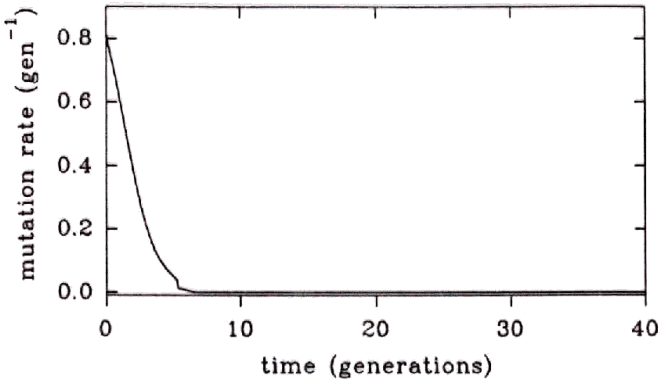


As soon as mutation is turned "on", all possible mutant species are populated – mutation travels with infinite propagation speed through (sequence) species space.

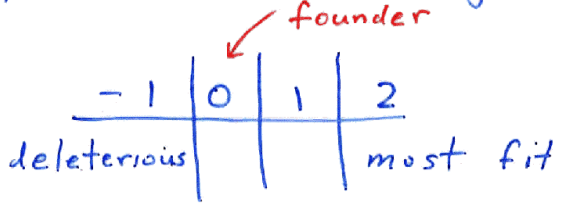
With strong selection model can pick out best possible variant – unrealistic

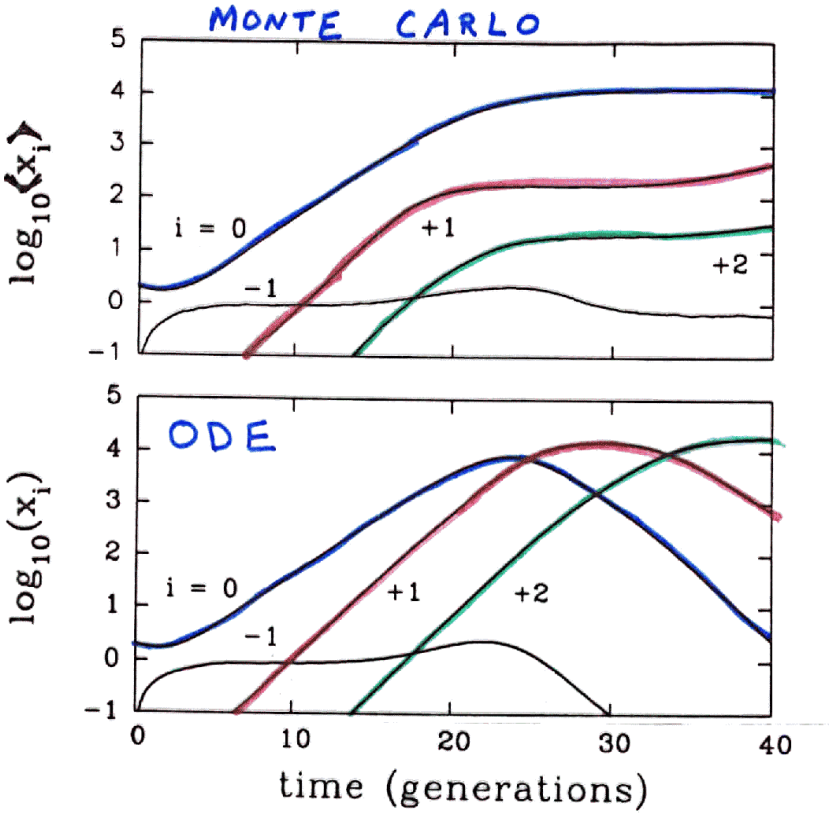
Simple Example

burst of mutation



4 species (or affinity classes)





10,000 Monte Carlo replicates

only in 0.2% of runs was a +2 mutant created.

Hybrid Model

$P_i(t)$ = probability that the i^{th} class not populated at time t

$$P_i(t+\Delta t) = P_i(t)\left(1 - \sum_{j \neq i} m_{ji}\, X_j(t)\,\Delta t\right)$$

m_{ji}: mutation rate from class j to class i

stochastic $$\frac{dP_i}{dt} = -P_i \sum_{j \neq i} m_{ji}\, X_j(t)$$

deterministic $$\frac{dx_i}{dt} = [\text{growth} - \text{death} - \text{loss by mutation}]\,\Theta(t-t_i) + \delta(t-t_i)$$

t_i = time of creation of i^{th} species

$$\Theta(t-t_i) = \begin{cases} 1 & \text{if } t-t_i > 0 \\ 0 & \text{otherwise} \end{cases}$$

Threshold Model

Replace stochastic arrival time t_i by real indicator variable τ_i, e.g.

$$P_i(\tau_i) = 1/e$$

τ_i similar to median $\left[P_i(\tau_i) = \frac{1}{2} \right]$

Solve $$\frac{dP_i}{dt} = -P_i \sum_{j \neq i} m_{ji} X_j$$

until $P_i = 1/e$, then populate i^{th} class and solve

$$\frac{dX_i}{dt} = \cdots \quad , t > \tau_i$$

$$X_i(\tau_i) = 1$$

Equation for P_i and X_i never solved simultaneously!

Let

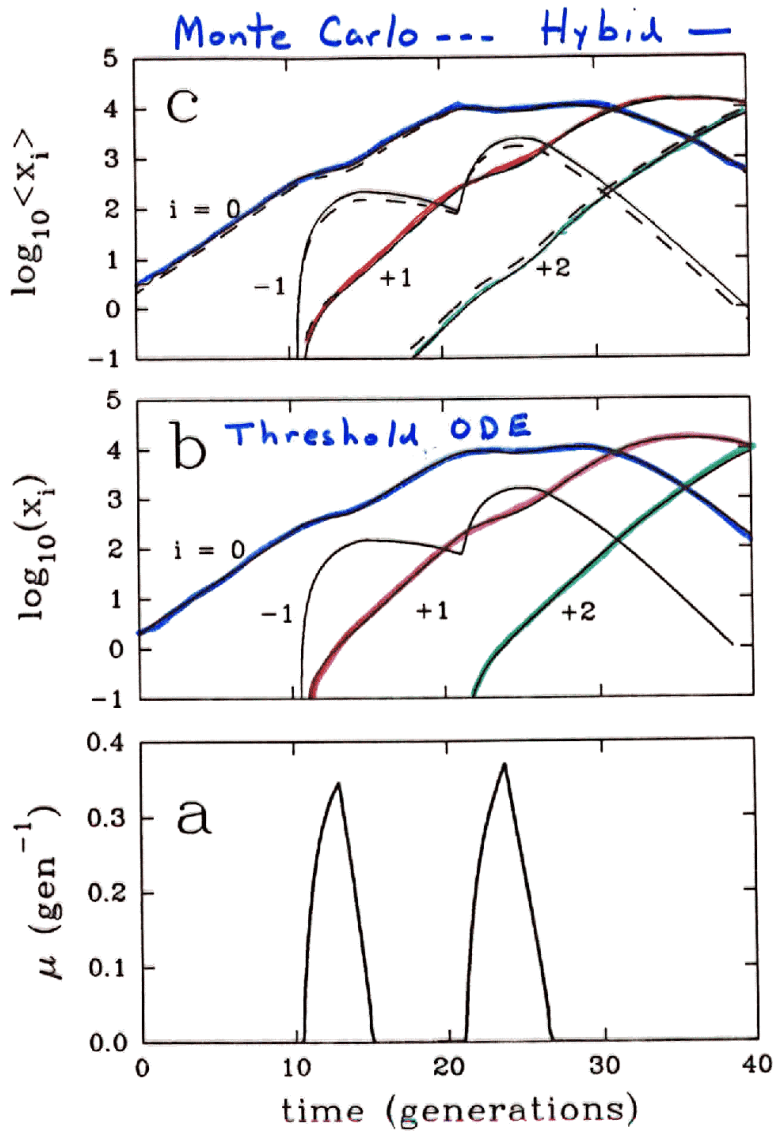
$$\xi_i = -\ln P_i \qquad t \leq \tau_i$$

$$= X_i \qquad t > \tau_i$$

at τ_i, $P_i(\tau_i) = 1/e \Rightarrow \xi_i = 1$

$$\frac{d\xi_i}{dt} = [\text{growth} - \text{death}]\,\theta(\xi_i - 1) + \sum_{j \neq i} m_{ji}\,\xi_j\,\theta(\xi_j - 1)$$

Thus single ode valid for all time.


Monte Carlo --- Hybrid —
c
b
Threshold ODE
a
i = 0
−1
+1
+2
$\log_{10}\langle x_i \rangle$
$\log_{10}(x_i)$
μ (gen^{-1})
time (generations)