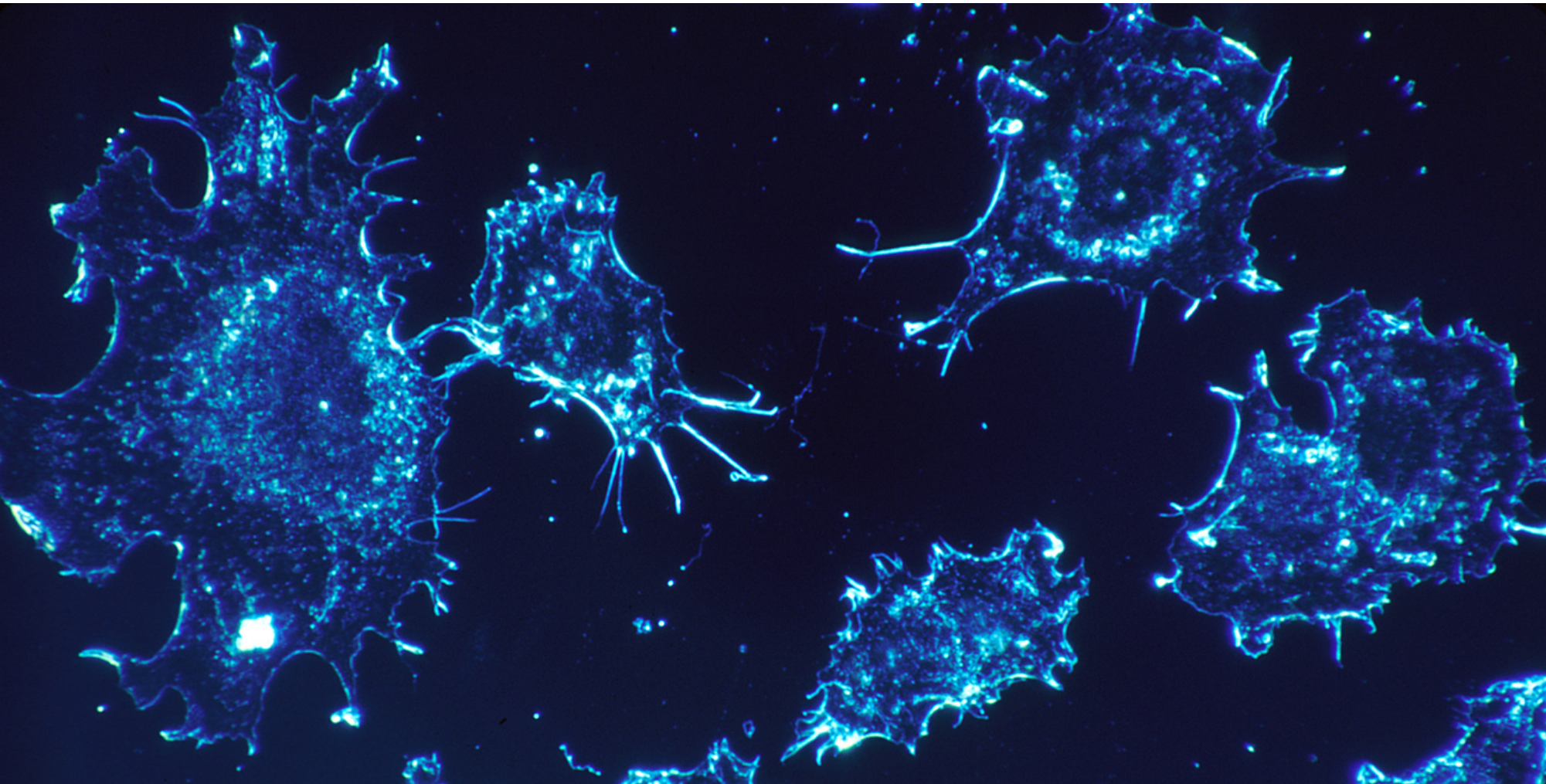
# Neural networks versus immune networks

## interesting observations and new questions

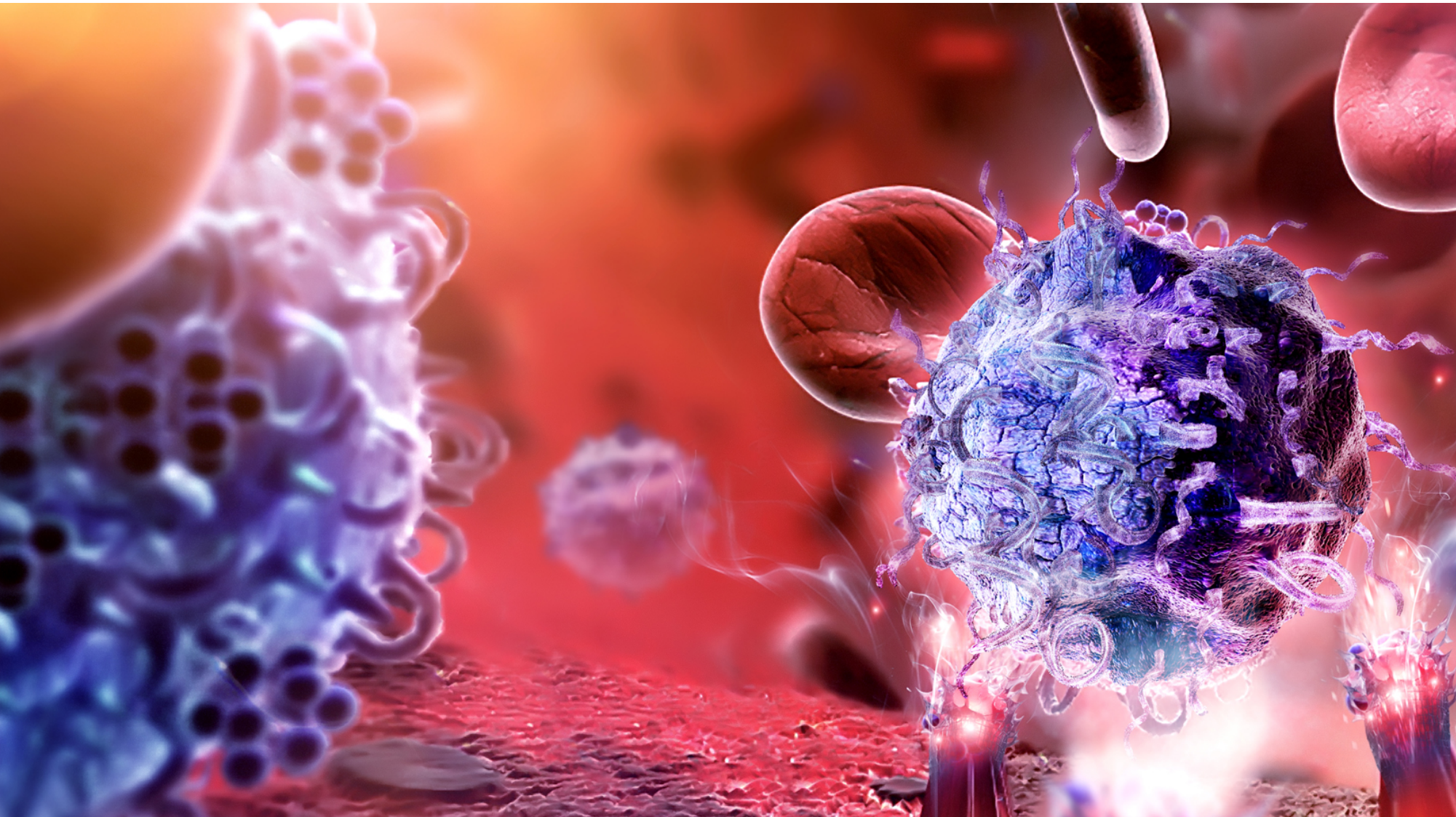
ACC Coolen, King's College London

Barcelona 31/8 2017



# Outline

# Immunology in a nutshell



# Role of the immune system

protect organism from invaders (e.g. bacteria, viruses)
or from degenerated host cells (e.g. cancer)

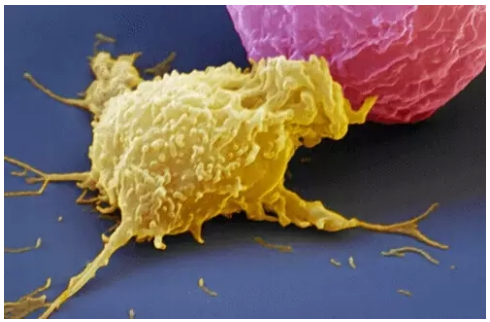
## Innate immune system

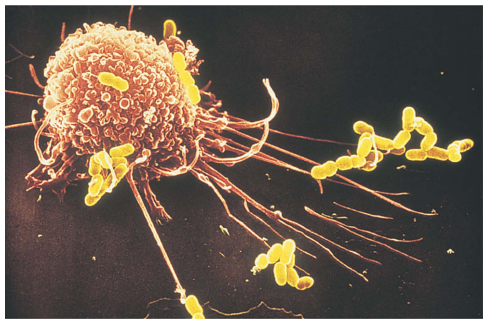
- generic short-term response to infections (hours),
  found in all plants and animals

  – recruit immune cells to infection site, via cytokines
  – create physical and chemical barriers for bacteria
  – sensitize pain receptors
  – activate adaptive immune system

  'inflammation'

- involves immune cells that are not pathogen-specific
  (natural killer cells, mast cells, macrophages, dendritic cells, ...)





## Adaptive immune system

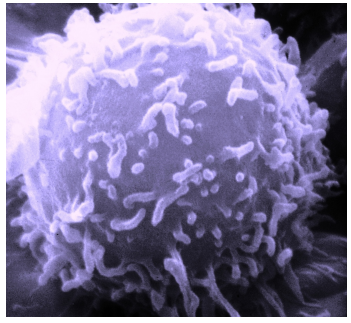
- more sophisticated response to pathogens (days), appeared later in evolution (vertebrates only)

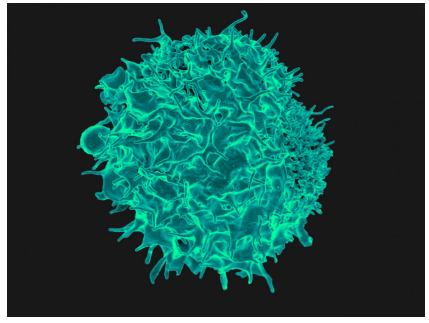
  – develop highly pathogen-specific responses
  – learning and memory mechanisms
  – tune receptors via hypermutation and genetic recombination
  – sophisticated cell-cell communication

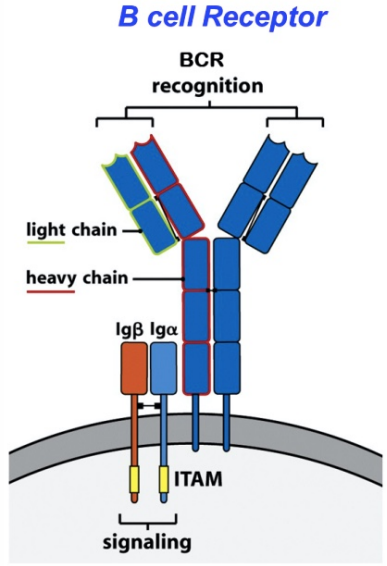
  result: enhanced secondary response,
  and acquired immunity

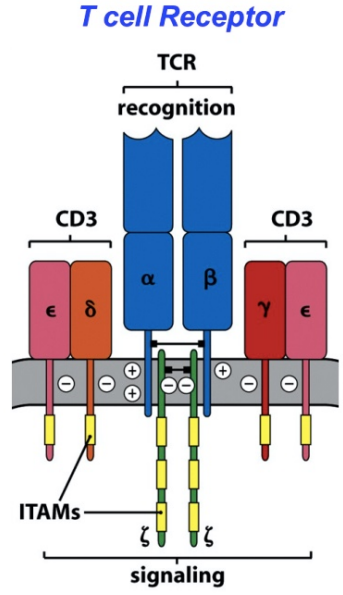
- involves cells ('lymphocytes') with *adaptive pathogen-specific receptors*

  B-cells, born in bone marrow
  T-cells, born in thymus







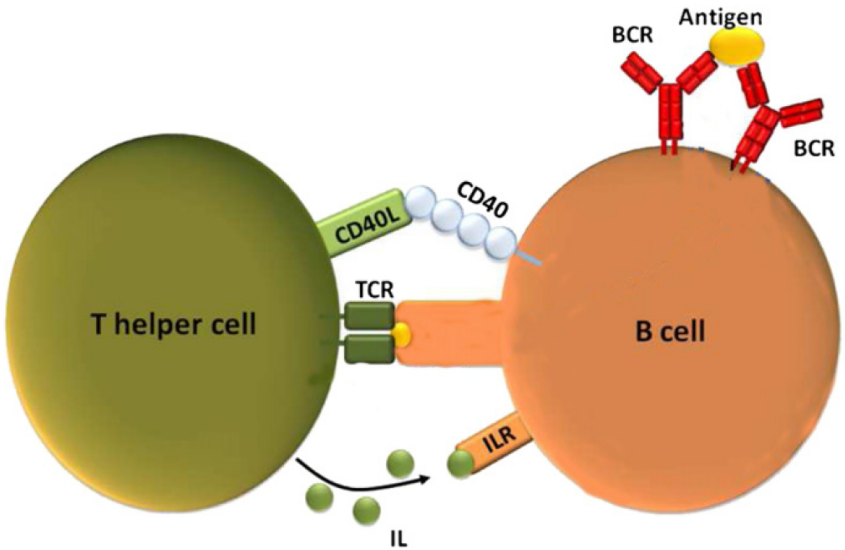



- Strategy of *adaptive* immune system: mark the enemy

  – B-cells can recognize specific ‘antigen’
  – if activated: secrete antigen-specific antibodies
  – antibodies ‘stick’ to the enemy
  – antibody-tagged objects are removed by the innate immune system

- Controlling the process

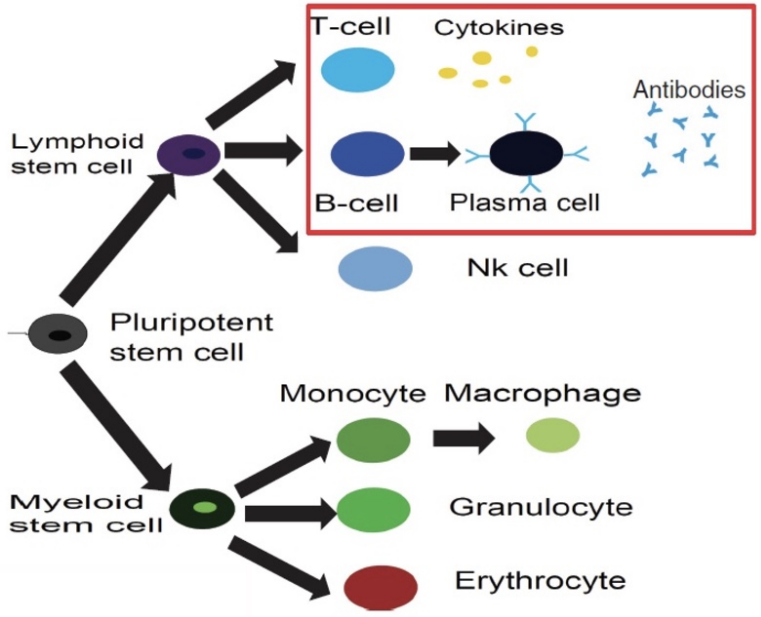
  – B-cells require activation signal from T-cells
  – helper T-cells: activate B-cells
  – regulator T-cells: de-activate B-cells
  – T-cells require antigen parts being ‘presented’ to them by other cells

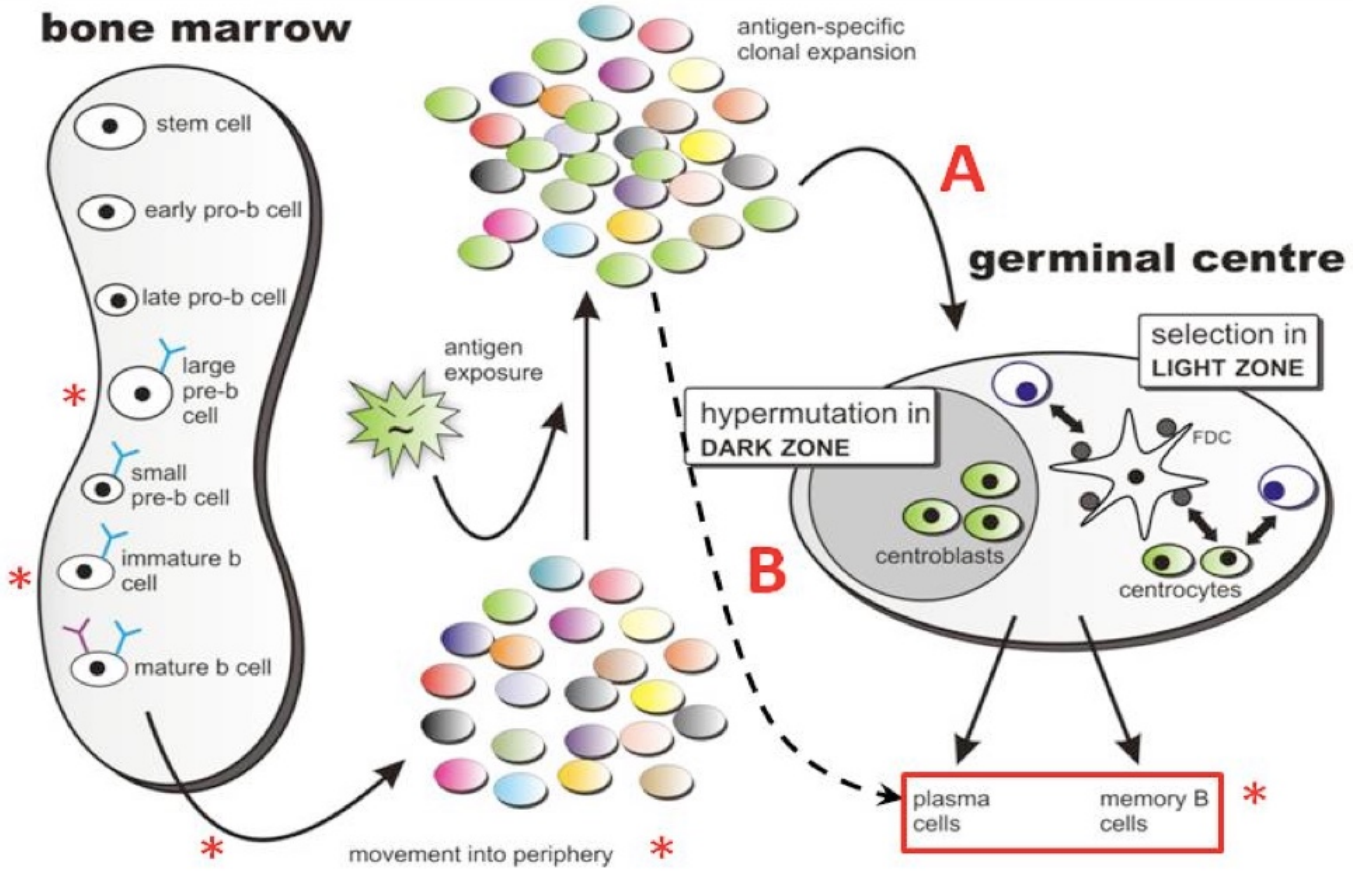



B-T communication via cytokines and antigen presentation

Lymphocyte lineage
and development

naive B-cell → mature B-cell → plasma cell
naive T-cell → 'armed' effector T-cell



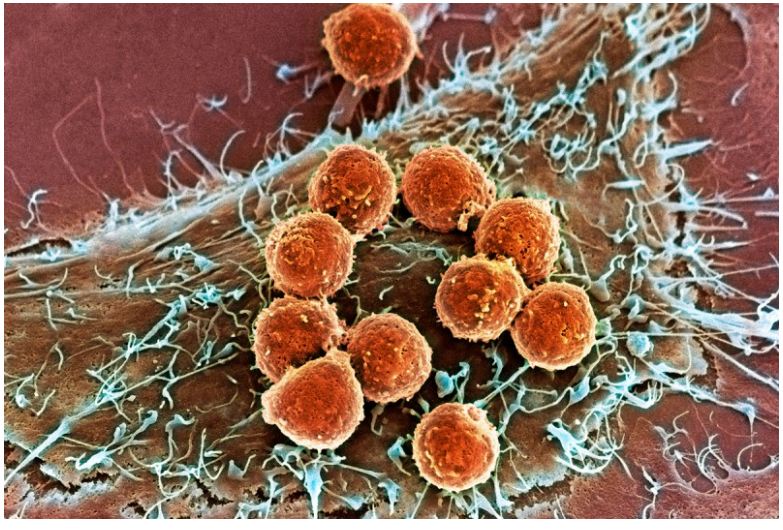



‘with great power comes great responsibility’

## The self-nonself problem

How to prevent the adaptive immune system from classifying healthy hosts cells accidentally as enemies to be destroyed?

- false positives: auto-immune diseases
- false negatives: fatal infections
- cancer: is enemy, but looks like self

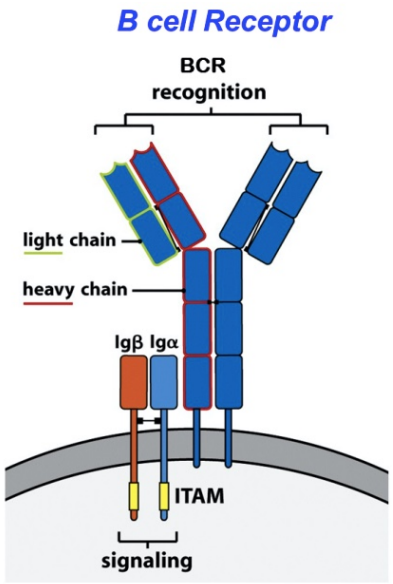


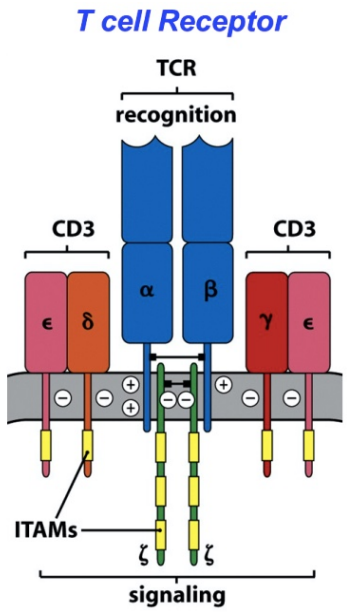
- Why learning is essential

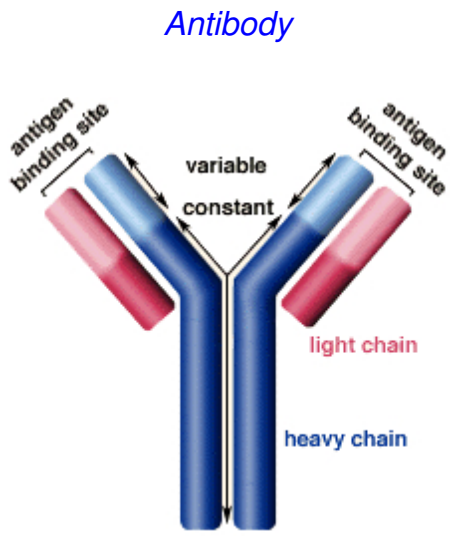
  – resource limitations: cannot maintain receptors for all possible antigen shapes, ‘learn’ the relevant ones
  – improve efficacy of B/T/antibody binding to relevant antigen
  – ‘learn’ to distinguish between friend and foe ...

- The mechanism of learning

  – hypersomatic mutation and selection of high-affinity receptors
  – deselection of B/T cells that respond significantly to self-antigen
  – B-cells that are never or chronically triggered die ...



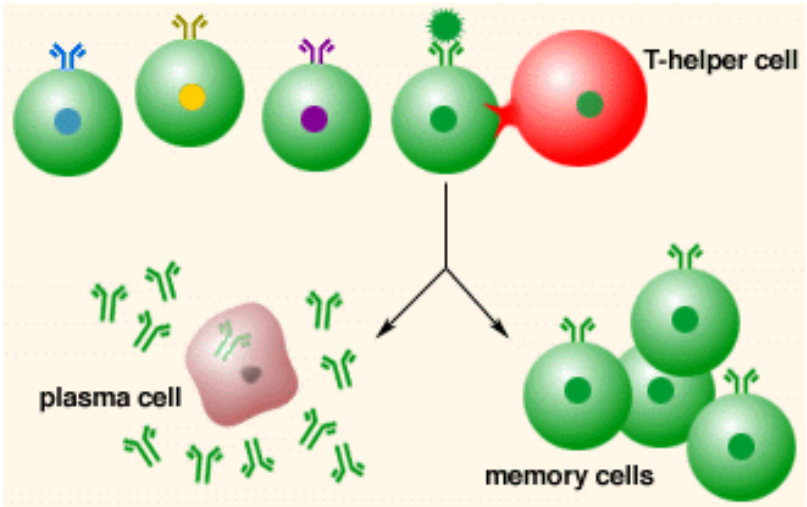
## clones

families of B- or T-cells that are activated by the same antigen
(i.e. have identical antigen receptors)

- Memory in the adaptive immune system
  - – previously encountered antigens are memorized,
    so that secondary response is more swift and strong
  - – how? no full consensus yet ...

current dogma:

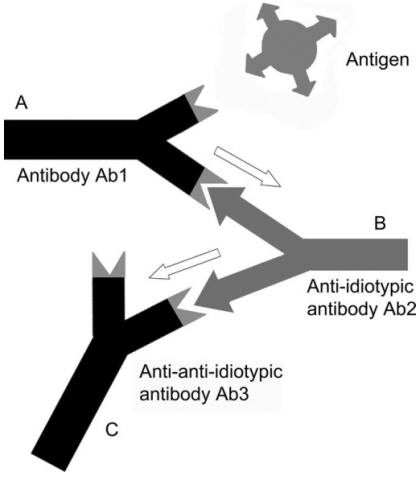
after immune response,
B-cells of activated clones
become long-lived
'memory cells'

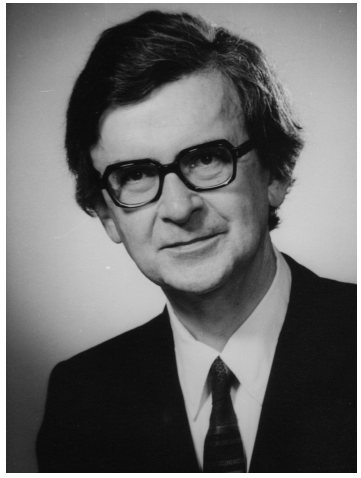


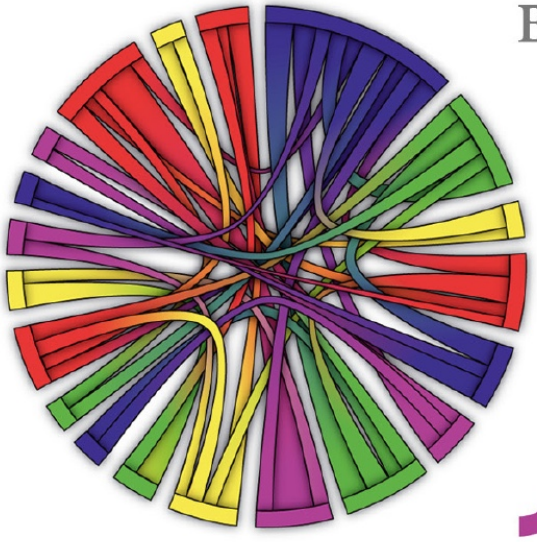
alternative explanation
for immunological memory:

Jerne's 'idiotypic networks' 1974
1984 Nobel prize ...

(developed further by
Varela & Coutinho, 1991)





B-B network

B clones

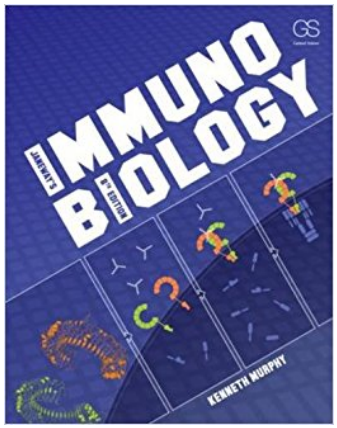
Nobel award premature?

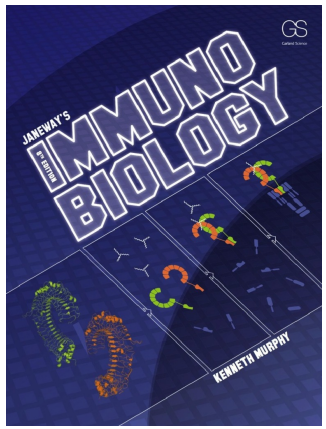
immunology:
relatively young compared to neuroscience ...

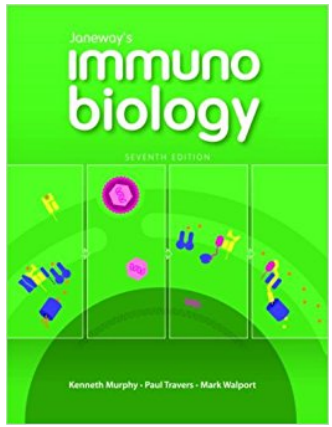
1938: antigen-antibody hypothesis
1948: B-cells produce antibodies
1957: clonal selection theory
1964: T and B cell cooperation

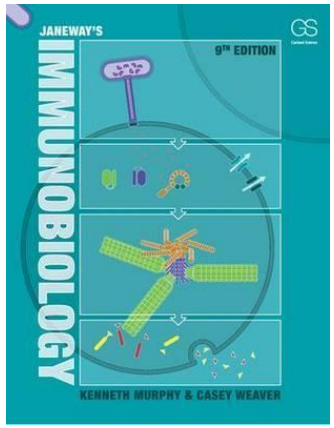
1978: first mathematical models

1983: discovery of T-cell antigen receptor
1995: discovery of regulatory T-cells










each new edition of Janeway's handbook:
new players and new mechanisms

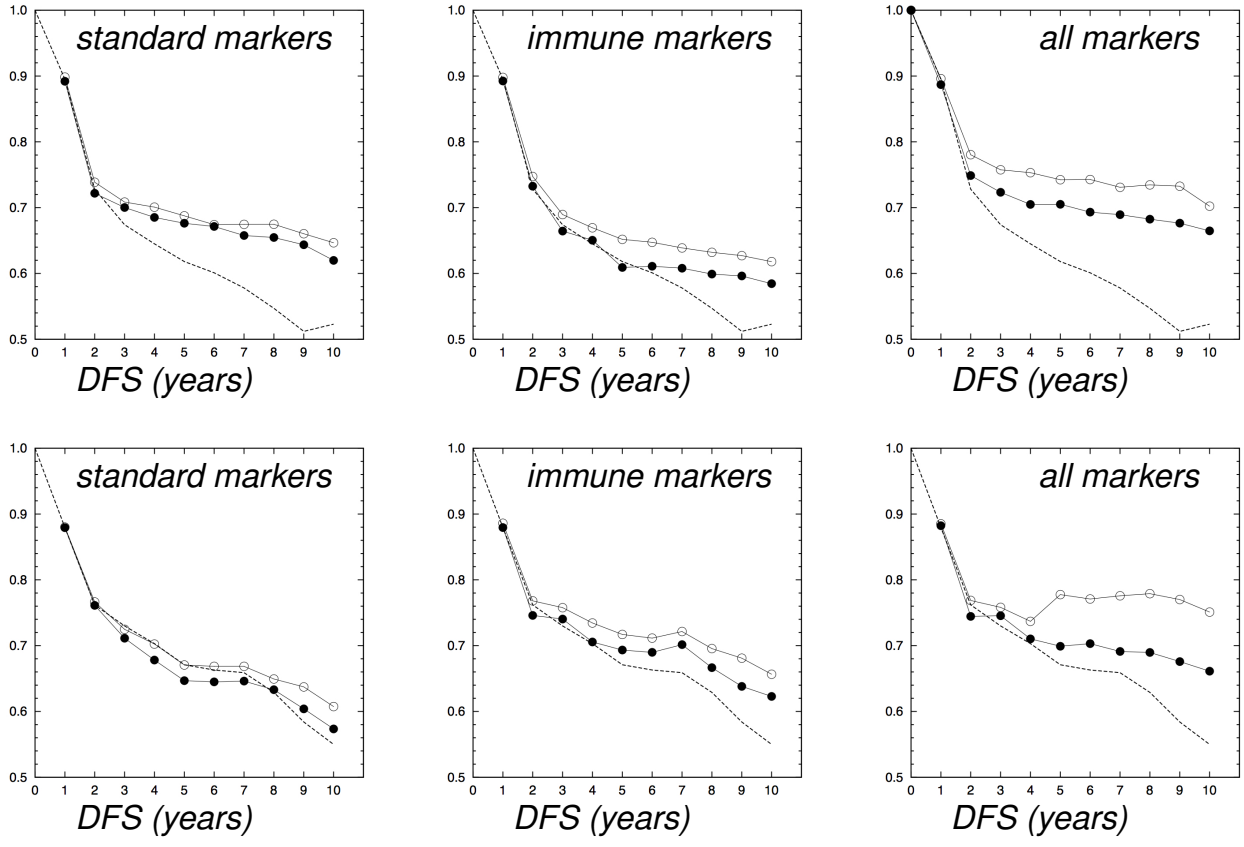
# Prognostic power of immunological markers in cancer medicine

*DFS:*
*disease-free survival*

All breast cancer types

TN breast cancer only

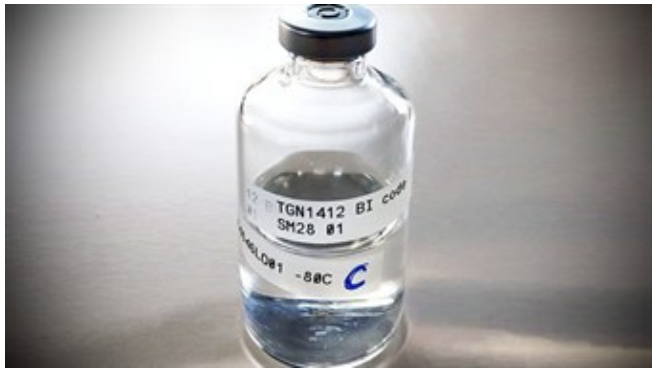
fraction correct




*standard markers: tumour size, grade, nr of lymph nodes affected ...*

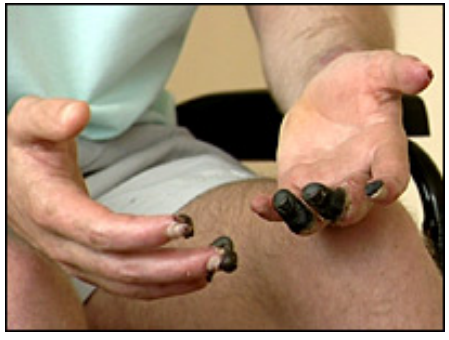
*immunological markers: lymphocyte counts and distributions, even in unaffected lymph nodes*

# The TGN1412 trial (2006)




TGN1412: genetically engineered antibody that can activate T-cells without needing antigen receptor signal ...

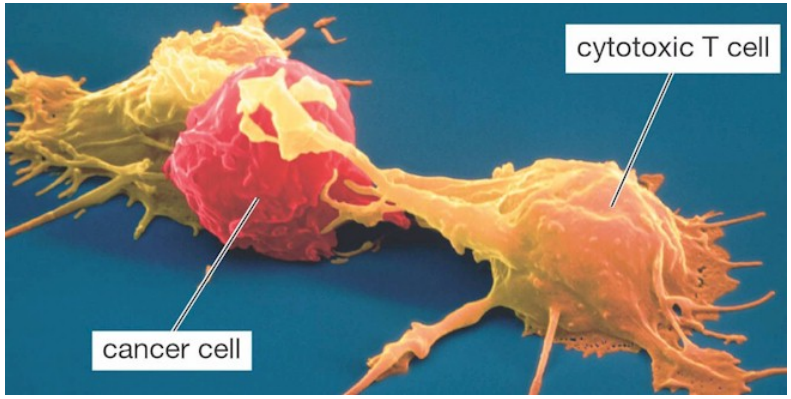
- six volunteers given the drug ...
  - within 1 hour, all seriously ill
  - within 16 hours, all in intensive care
  - 'cytokine storm', multiple organ failures
  - only barely kept alive ...



- long term effects
  - lost fingers and toes
  - chronically low numbers of regulatory T-cells
  - auto-immune diseases, cancer risks
- looking back ...
  - naive extrapolation of 'safe' dose from animal studies
  - gave drug to all volunteers at the same time

  but what actually happened? still not clear ...

# Cancer immunotherapy




increase efficacy of natural killer cells
and cytotoxic T-cells in docking to
and killing tumour cells

e.g. CART
(chimeric antigen receptor Tcell)

high affinity antigen receptor, tailored to specific antigen
expressed by the *patient's* tumour, plus co-stimulatory signals

- successful in leukemia and lymphoma types
- tricky to control dose, CARTs multiply ...
  - cytokine storms ...
  - uncontrolled macrophage proliferation ...
  - tumour lysis syndrome when CARTs work too well ...

# Novartis CAR-T cell therapy CTL019 unanimously (10-0) recommended for approval by FDA advisory committee to treat pediatric, young adult r/r B-cell ALL

JUL 13, 2017

- *Recommendation based on review of CTL019 r/r B-cell ALL development program, including the pivotal Phase II global ELIANA trial*
- *A Biologics License Application (BLA) for this indication is under FDA priority review; if approved, CTL019 could become first CAR-T cell therapy available*
- *Positive ODAC recommendation is latest milestone for CTL019 program that started through collaboration with the University of Pennsylvania*

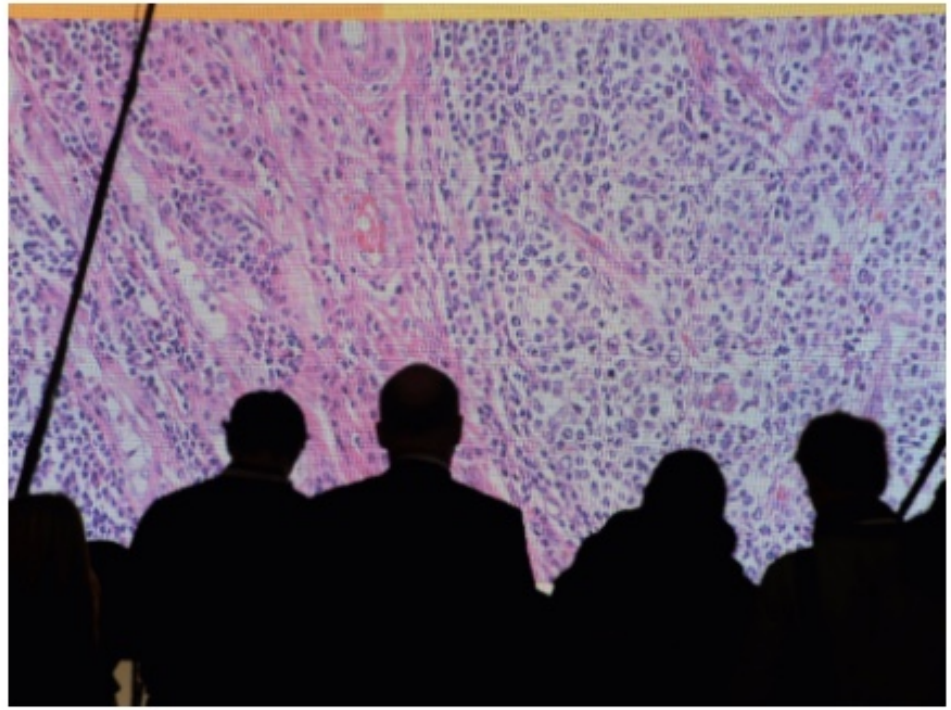
**Basel, July 12, 2017 -** Novartis announced today that the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) unanimously (10-0) recommended approval of CTL019 (tisagenlecleucel), an investigational chimeric antigen receptor T cell (CAR-T) therapy, for the treatment of relapsed or refractory (r/r) pediatric and young adult patients with B-cell acute lymphoblastic leukemia (ALL).

The US Food and Drug Administration just approved a cutting-edge cancer therapy.

On Wednesday, the FDA approved Novartis's Kymriah, also known as tisagenlecleucel, a treatment for pediatric acute lymphoblastic leukemia.

"I think this is the most exciting thing I've seen in my lifetime," said Dr. Tim Cripe, an oncologist who was part of the FDA advisory committee panel that voted in favor of approving the drug in July.

The highly personalized treatment is called CAR T-cell therapy. It's a type of cancer immunotherapy — or a therapy that harnesses the body's immune system to take on cancer cells.



**Cancer cells are seen on a large screen connected to a microscope at the CeBit computer fair in Hanover, Germany, March, 6, 2012.** Reuters

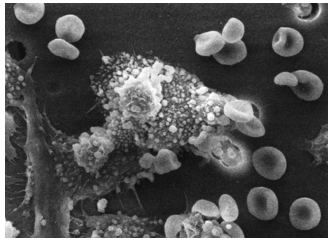


"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," the FDA commissioner, Scott Gottlieb, said in a statement. "New technologies such as gene and cell therapies hold out the potential to transform medicine

# Similarity between immune and neural networks

- recurrent many-variable systems, with parallel dynamics
- adaptive interactions between components
- distributed storage and processing of information

## immune networks

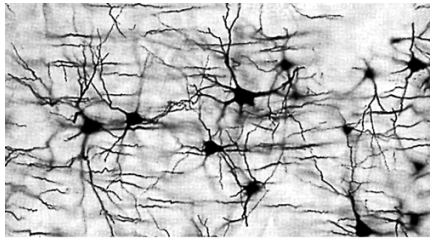


$10^8$ B/T-clones
concentrations
hours

parallel
adaptive links
connectivity low

equations?

## neural networks

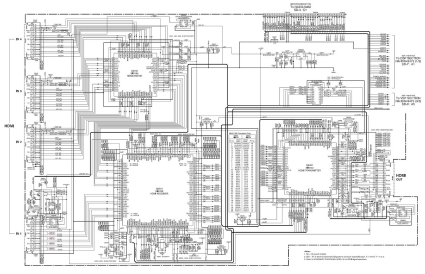


$10^{11}$ neurons
spike trains
msecs

parallel
adaptive links
connectivity high

equations known
since 1940s/1950s

## computers



$10^{10}$ logical gates
0/1 states
nsecs

sequential
fixed links
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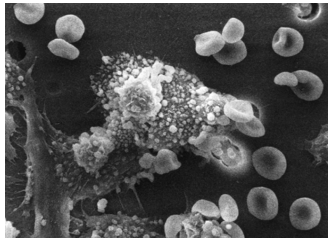

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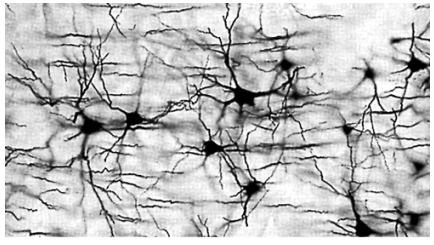

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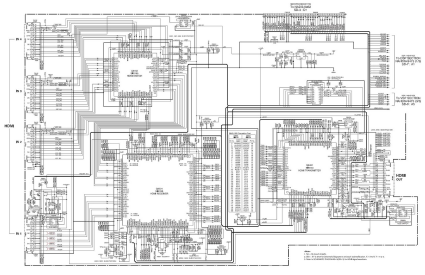

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We know in principle how to program
and reprogram recurrent neural networks:
(Hebbian-type rules, in $\pm 1$ notation)

$$\Delta J_{ij} = \eta_i \xi_j : \quad \textit{if in state } (\xi_1, \ldots, \xi_N) \textit{ go to state } (\eta_1, \ldots, \eta_N)$$
$$\Delta J_{ij} = -\eta_i \xi_j : \quad \textit{if in state } (\xi_1, \ldots, \xi_N) \textit{ do not go to state } (\eta_1, \ldots, \eta_N)$$

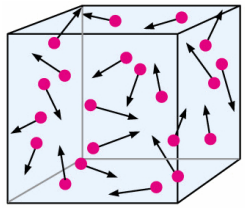
i.e. we can manipulate the dynamics ...
learn, unlearn, control response to triggers

## Future immune therapies ...

- using intuition, experience and techniques
  of recurrent neural networks ...
- can we reprogram the adaptive immune system?
  e.g. manipulate self-nonself dividing line?
  ('switching' as in alopacia)
- learning and unlearning requires *theory*,
  e.g. immunological equivalent of Hebb rule ...

# Modelling complex many-variable processes

# statistical mechanics



$\sim 10^{24}$ positions, velocities

$(\vec{x}_1, \vec{v}_1),\ (\vec{x}_2, \vec{v}_2),\ \ldots$

Newton's equations

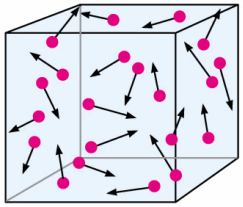
$\frac{d}{dt}(\vec{x}_1, \vec{v}_1) = \ldots,\ \frac{d}{dt}(\vec{x}_2, \vec{v}_2) = \ldots$ $\leftarrow$ don't try to solve these!

*macroscopic theory:*

densities, correlation functions,
perturbation response functions,
phase transitions ...

large systems: 'self-averaging', macroscopic theory
only dependent on *statistics* of model parameters ...

## statistical mechanics



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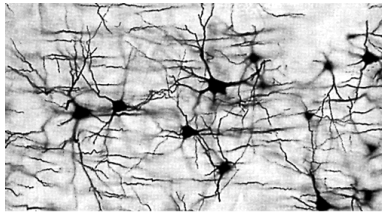
## recurrent neural networks



$\sim 10^{11}$ neuronal firing states

$S_1,\ S_2,\ S_3,\ \ldots$

simplified Hodgkin-Huxley equations

$\frac{\mathrm{d}}{\mathrm{d}t} S_i = g(\sum_j J_{ij} S_j + \theta_i) - \mu S_i$

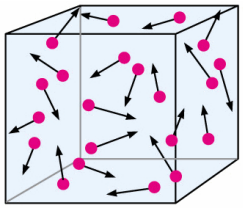
*macroscopic theory:*

overlaps, correlation functions,
response functions (to perturbations),
phase transitions ...

large systems: 'self-averaging', macroscopic theory
only dependent on *statistics* of model parameters ...

1980s onwards

## statistical mechanics



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densities, correlation functions,
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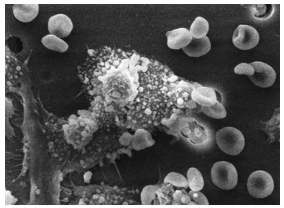
phase transitions ...

## immune networks



$\sim 10^{8}$ B/T clone concentrations

$B_1,\ B_2,\ B_3, \ldots, T_1, T_2, T_3, \ldots$

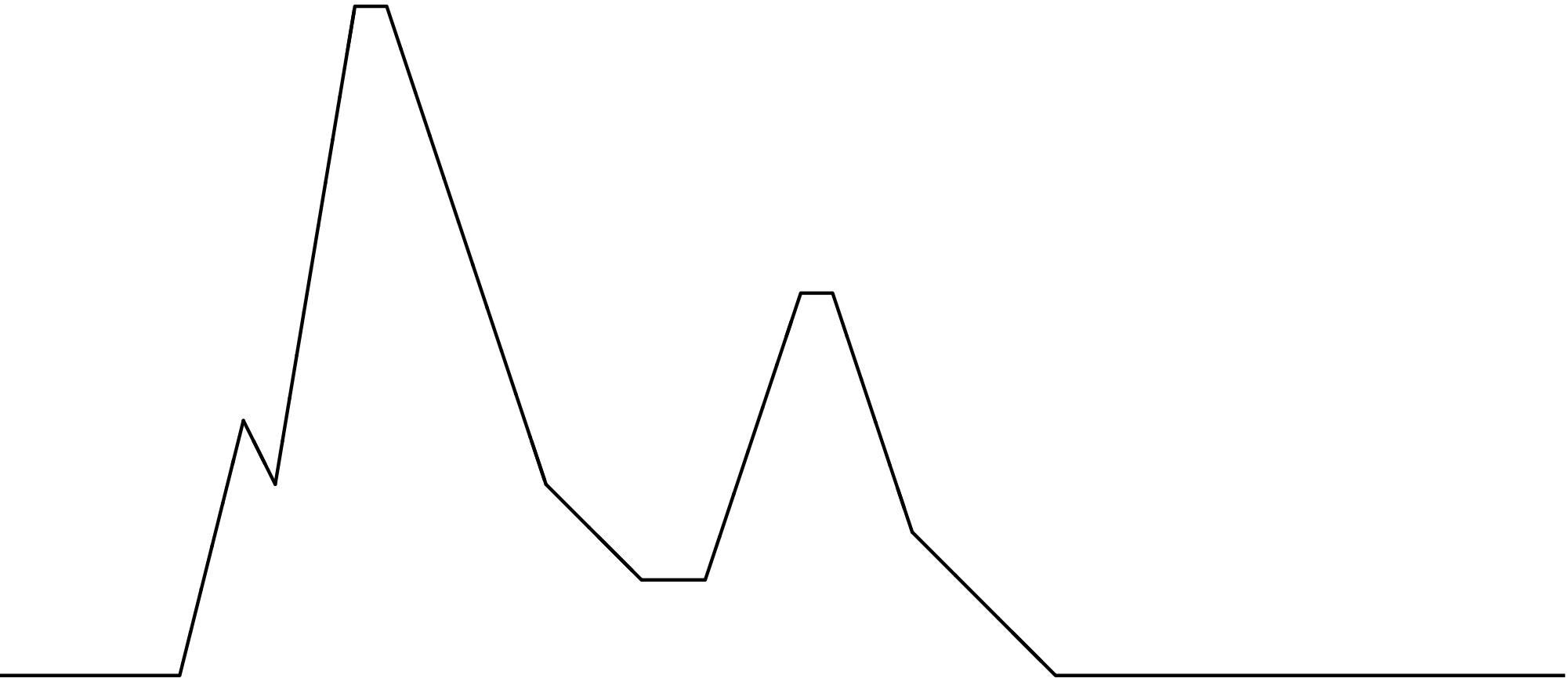
equations?

*experiments tricky ...*
*reliable data scarce ...*
*confusion about lymphocyte types ...*
*mostly single clone models ...*

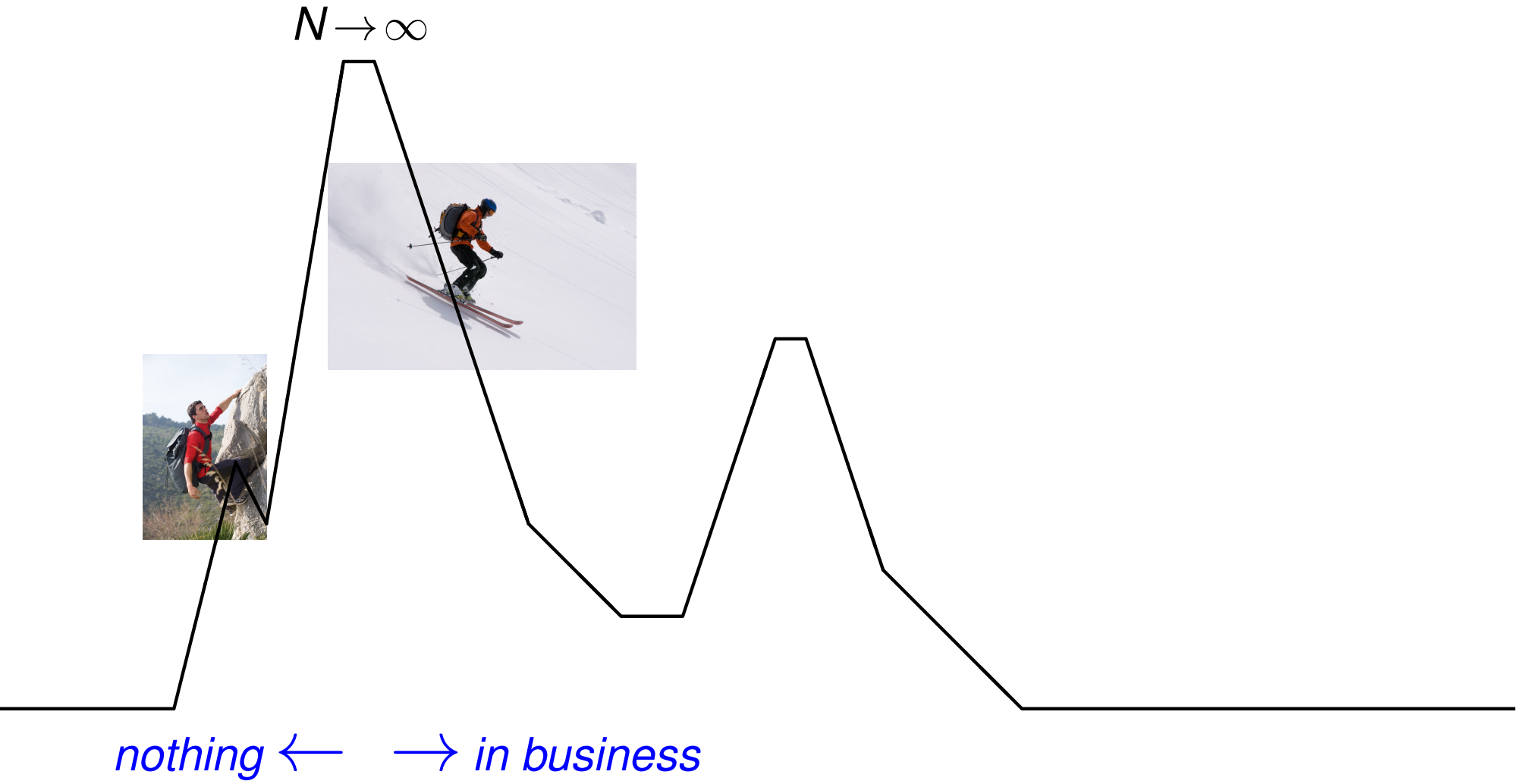
?

large systems: 'self-averaging', macroscopic theory
only dependent on *statistics* of model parameters ...

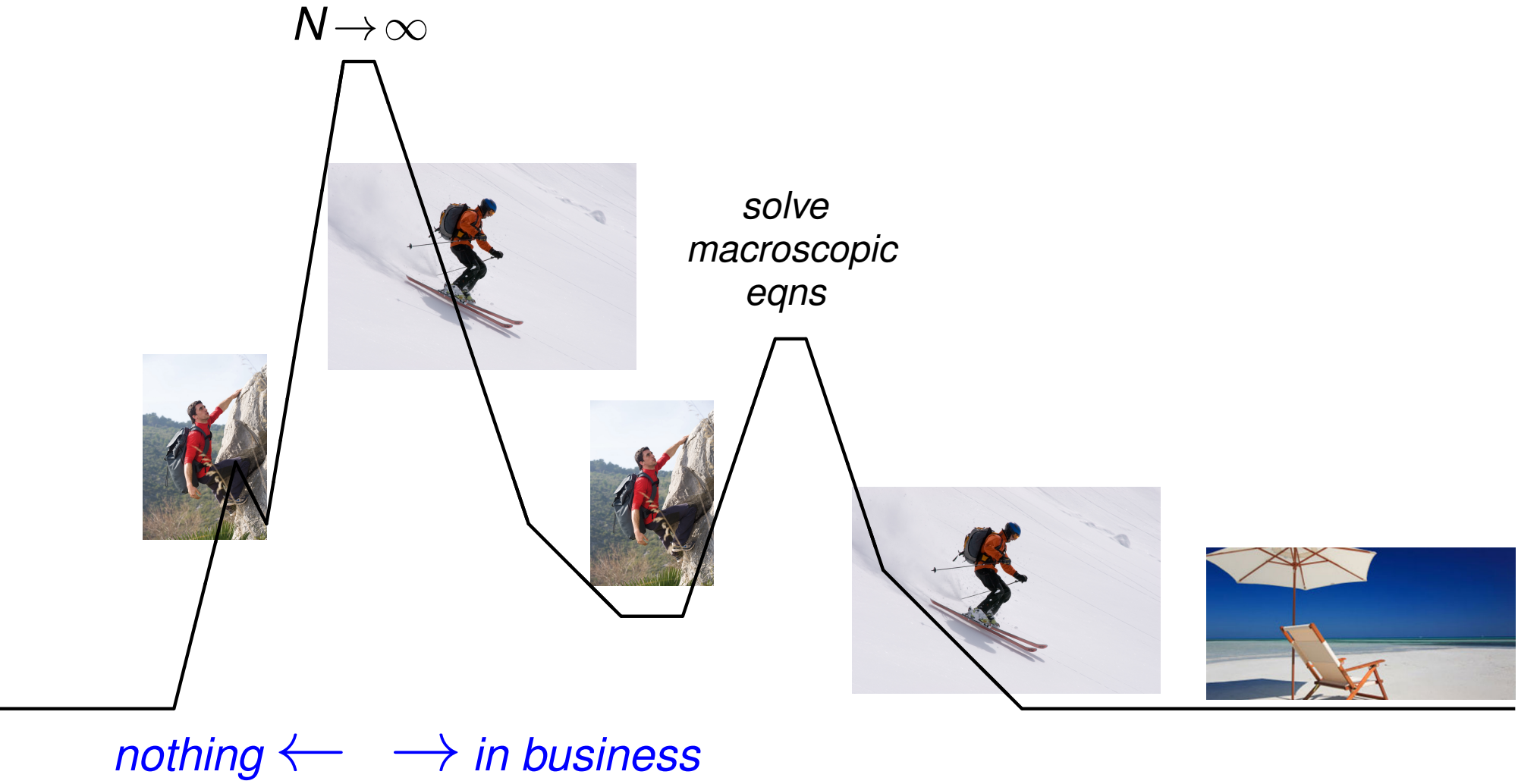
statistical mechanics of
many-variable systems



statistical mechanics of
many-variable systems



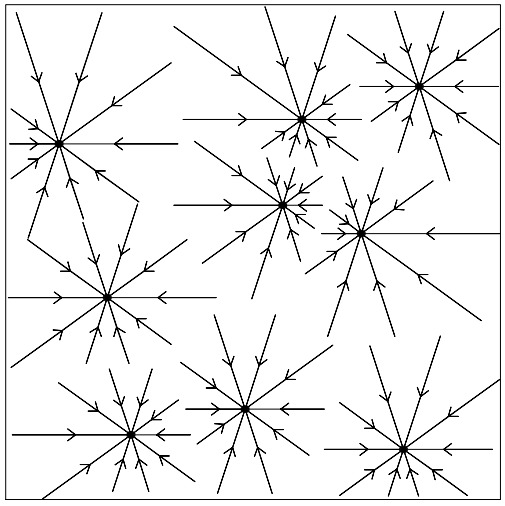
statistical mechanics of
many-variable systems




*nothing* ⟵ ⟶ *in business*

# Analysis of recurrent neural networks the frontline 1970–1985

full connectivity, Hebbian synapses:
attractor neural networks



- 1972: Amari, Kohonen and others

combine McCulloch Pitts
(i.e. binary) neurons
with Hebbian synapses

$$x_i(t+1) = \mathrm{sgn}\Big(\sum_j w_{ij} x_j(t)\Big)$$

$$\overbrace{w_{ij} = \sum_{\mu=1}^{p} s_i^\mu s_j^\mu}^{\textit{creates fixed point attractors}} \quad \text{or} \quad \overbrace{w_{ij} = \sum_{\mu=1}^{p} s_i^{\mu+1} s_j^\mu}^{\textit{creates dynamical attractors}}$$

- 1982: Hopfield

  if symmetric synapses:
  equivalence with models of magnetism,

  studied memory capacity
  via simulations: $\alpha = p/N \sim 0.14$

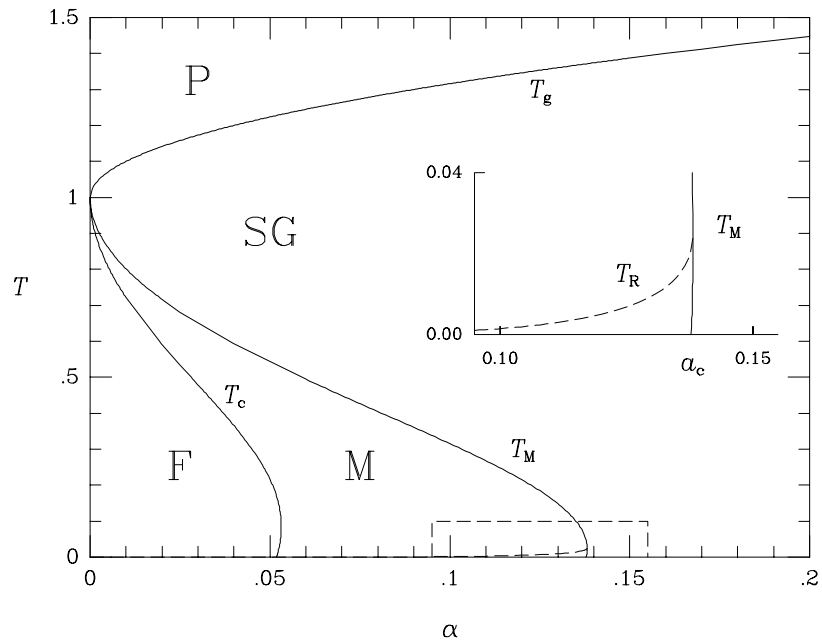
following Hopfield's paper in PNAS,
and recent progress in analysis of
heterogeneous many-particle systems,
physicists became interested ...

- 1985: Amit, Gutfreund, Sompolinsky

  full equilibrium stat mech analysis,
  computed phase diagram
  of stochastic Hopfield model

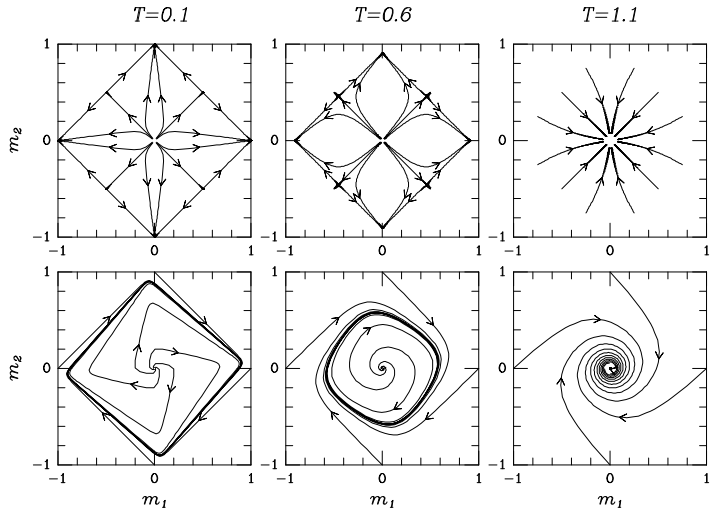
- 1987: Derrida, Gardner, Zippelius

  similar solution for randomly
  diluted Hebbian synapses



# Analysis of recurrent neural networks the frontline 1985–2000

generalizations,
analysis of dynamics ...




- 1987,1988: Buhmann et al, Coolen et al, Van Hemmen et al

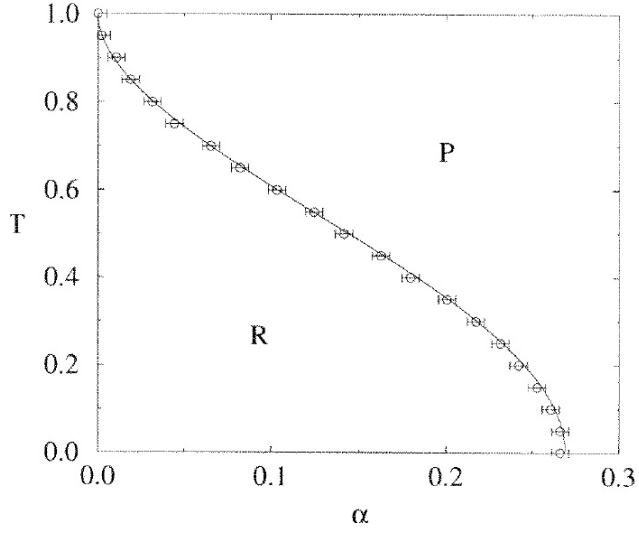
  pattern recall dynamics away from saturation

- 1988–1993: Amari & Maginu, Horner et al, Coolen et al

  pattern recall dynamics near saturation (using approximations)

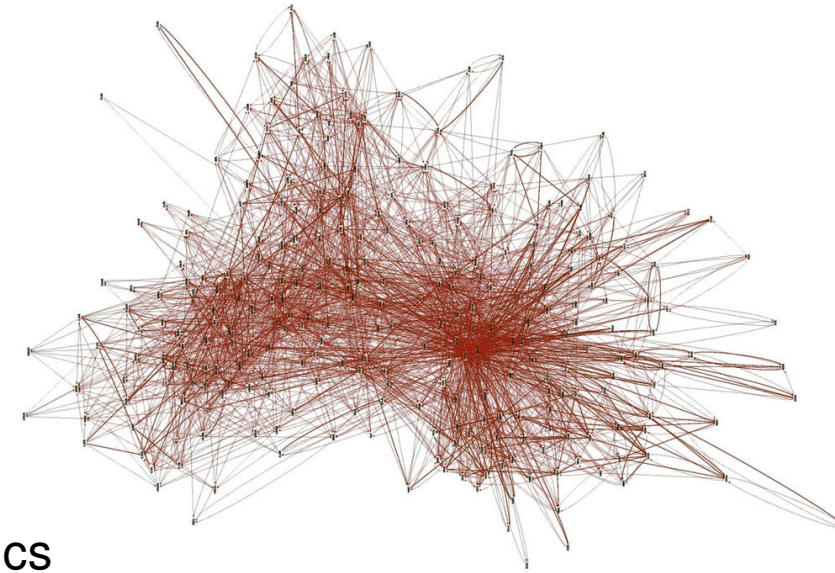
- 1998: Düring, Coolen, Sherrington

  exact phase diagram of sequence processing model near saturation



# Analysis of recurrent neural networks the frontline 2000-onwards

processes on *finitely connected graphs*
with specified statistical features



- 2003: Wemmenhove, Coolen

  Attractor network, Hebbian synapses
  on finitely connected random graph: statics

$$\sigma_i(t+1) = \mathrm{sgn}\Big(\sum_j J_{ij}\sigma_j(t) + \mathrm{noise}\Big)$$

$$J_{ij} = c_{ij}\phi\Big(\sum_\mu \xi_i^\mu \xi_j^\mu\Big), \qquad \begin{array}{l}\mathrm{Prob}(c_{ij}=1) = c/N \\ \mathrm{Prob}(c_{ij}=0) = 1-c/N\end{array}$$

- 2004, 2005: Hatchett et al, Coolen et al

  Attractor network on finitely connected random graph: dynamics
  Generalisation of statics analysis to coupled oscillators

- now: processes on topologies with many short loops

*tools for finitely connected systems:*
*time to return to immune networks*

# Modeling immune networks the Roman way

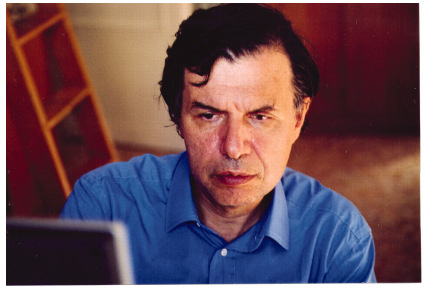
# Immune network model of Agliari and Barra *et al*

2011 onwards ...

builds on a 1990 paper by Parisi

(before discovery of regulatory T-cells ...)





SAPIENZA
UNIVERSITÀ DI ROMA

forget (for now) about B-cell and T-cell subtypes,
forget (for now) about hypersomatic mutation,
forget (for now) about antigen dynamics

focus on B-T interaction,
find simplest possible *solvable* model
that describes many interacting clones

remember lessons from modelling recurrent neural networks ...

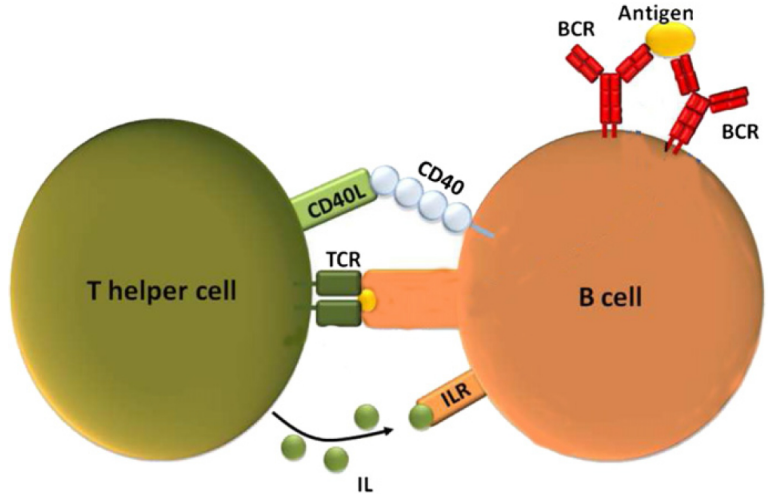
# model of Agliari and Barra *et al*

- B-cell *clones* $b_\mu$

  each B-clone can recognise and attack *specific* antigen $a_\mu$

- T-cell *clones* $\sigma_i$

  coordinate B-clones via cytokine signals $\xi_i^\mu = -1, 0, 1$ ($-1$: contract, $+1$: expand)




- Phenomenological eqn for evolution of B-clones:

$$\frac{\mathrm{d}}{\mathrm{d}t} b_\mu = \overbrace{\lambda_\mu a_\mu + \sum_{i=1}^{N_T} \xi_i^\mu \sigma_i}^{\text{expansion force}} - \overbrace{b_\mu}^{\text{decay}} + \overbrace{\chi_\mu(t)}^{\text{noise}}$$

evolution of T-clones?
not known ...

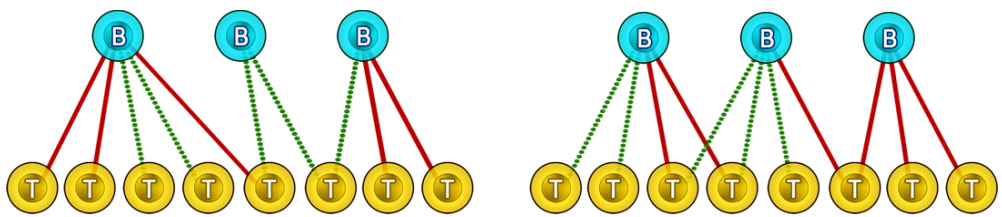
# lymphocyte promiscuity

randomly drawn cytokine variables:
(bi-partite random graph)

$$p(\xi_i^\mu) = \frac{c}{2N}\left[\delta_{\xi_i^\mu,1} + \delta_{\xi_i^\mu,-1}\right] + (1-\frac{c}{N})\delta_{\xi_i^\mu,0}$$

$c$: *promiscuity*

average nr of T-clones
interacting with each B-clone




$N_B = \alpha N \sim 10^8$

$N \sim 2.10^8$

# Evolution of T-clones?

- Observation:

  B-dynamics is
  noisy gradient descent

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}b_\mu &= \lambda_\mu a_\mu + \sum_{i=1}^{N_T}\xi_i^\mu\sigma_i - b_\mu + \chi_\mu(t)\\ &= -\frac{\partial}{\partial b_\mu}E(\mathbf{b},\boldsymbol{\sigma}) + \chi_\mu(t)\end{aligned}$$

  with

$$E(\mathbf{b},\boldsymbol{\sigma}) = \frac{1}{2}\sum_{\nu=1}^{N_B}b_\nu^2 - \sum_{\nu=1}^{N_B}b_\nu\left(\lambda_\nu a_\nu + \sum_{i=1}^{N_T}\xi_i^\nu\sigma_i\right)$$

- Assume:

  also T-dynamics is
  noisy gradient descent

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\sigma_i &= -\frac{\partial}{\partial\sigma_i}E(\mathbf{b},\boldsymbol{\sigma}) + \eta_i(t)\\ &= \sum_{\mu=1}^{N_B}\xi_i^\mu b_\mu + \eta_i(t)\end{aligned}$$

Consequence:

if noise is Gaussian,
system evolves to equilibrium
with state probabilities

$$p(\boldsymbol{\sigma},\mathbf{b}) = \frac{1}{Z}\mathrm{e}^{-\beta E(\mathbf{b},\boldsymbol{\sigma})}$$

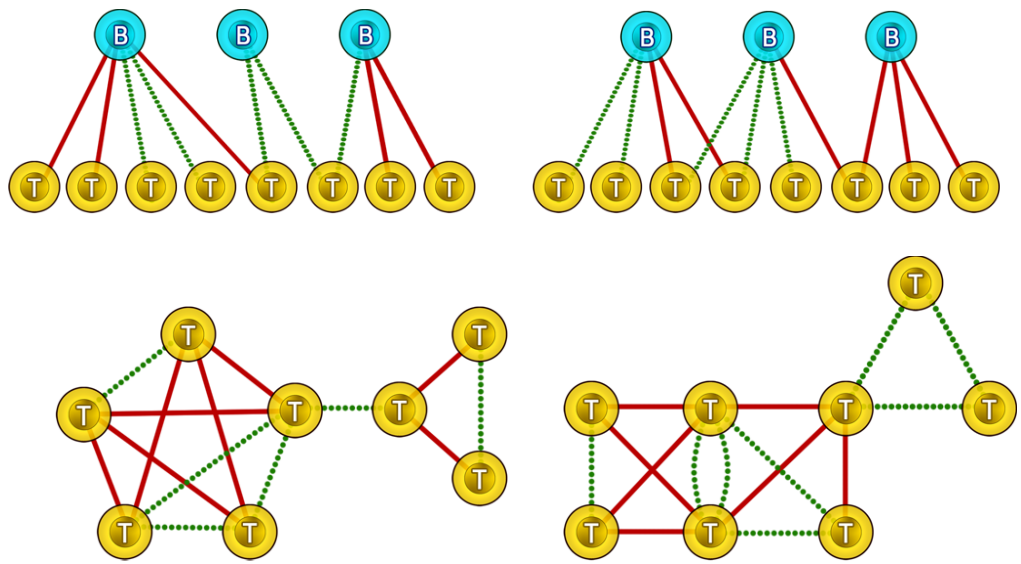
another observation ...

'integrate out' the B-clones:

$$p(\boldsymbol{\sigma}) = \int \mathrm{d}\mathbf{b}\; p(\mathbf{b},\boldsymbol{\sigma}) = \frac{1}{Z}\int \mathrm{d}\mathbf{b}\; \mathrm{e}^{-\beta E(\mathbf{b},\boldsymbol{\sigma})}$$

$$= \frac{1}{Z}\int \mathrm{d}\mathbf{b}\; \mathrm{e}^{-\frac{1}{2}\beta\sum_{\nu=1}^{N_B} b_\nu^2 + \beta\sum_{\nu=1}^{N_B} b_\nu\left(\lambda_\nu a_\nu + \sum_{i=1}^{N_T}\xi_i^\nu\sigma_i\right)} = \frac{\mathrm{e}^{-\beta E_{\mathrm{eff}}(\boldsymbol{\sigma})}}{Z_T}$$

$$E_{\mathrm{eff}}(\boldsymbol{\sigma}) = -\frac{1}{2}\sum_{i,j=1}^{N}\sigma_i\sigma_j\sum_{\mu=1}^{\alpha N}\xi_i^\mu\xi_j^\mu - \sum_{i=1}^{N}\sigma_i\sum_{\mu=1}^{\alpha N}\lambda_\mu a_\mu\xi_i^\mu$$



# Immune and neural networks: beyond similarity

both store and recall information ...
now also *mathematically* very similar ...

$$p(\boldsymbol{\sigma}) = \frac{\mathrm{e}^{-\beta E(\boldsymbol{\sigma})}}{Z_T} \qquad E(\boldsymbol{\sigma}) = -\frac{1}{2}\sum_{i,j=1}^{N} \sigma_i \sigma_j J_{ij} - \sum_{\mu=1}^{\alpha N} \psi_\mu \sum_{i=1}^{N} \sigma_i \xi_i^\mu$$

- Immune model: pattern dilution

$$J_{ij} = \sum_{\mu=1}^{\alpha N} \xi_i^\mu \xi_j^\mu, \qquad p(\xi_i^\mu) = \frac{c}{2N}\left[\delta_{\xi_i^\mu,1} + \delta_{\xi_i^\mu,-1}\right] + (1-\frac{c}{N})\delta_{\xi_i^\mu,0}$$

*simultaneous recall of $\mathcal{O}(N)$ c-bit cytokine patterns essential for survival!*

- diluted Hopfield model: bond dilution

$$J_{ij} = c_{ij}\sum_{\mu=1}^{\alpha N} \xi_i^\mu \xi_j^\mu, \qquad \xi_i^\mu = \pm 1, \qquad p(c_{ij}) = \frac{c}{N}\left[\delta_{c_{ij},1} + (1-\frac{c}{N})\delta_{c_{ij},0}\right]$$

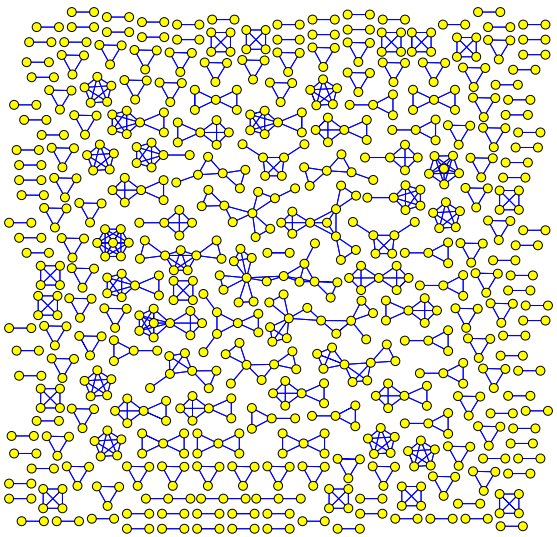
*recall of $\mathcal{O}(c)$ N-bit neuronal firing patterns*

# topological features
## of the effective T-T interaction graph

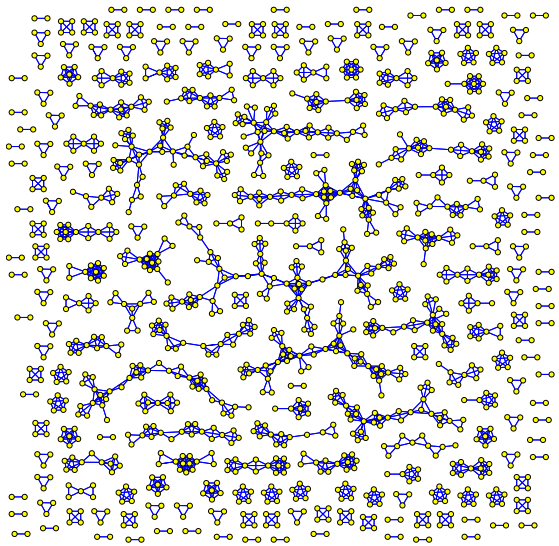
$J_{ij} = \sum_{\mu=1}^{\alpha N} \xi_i^\mu \xi_j^\mu$

$c$: promiscuity of $B$-clones

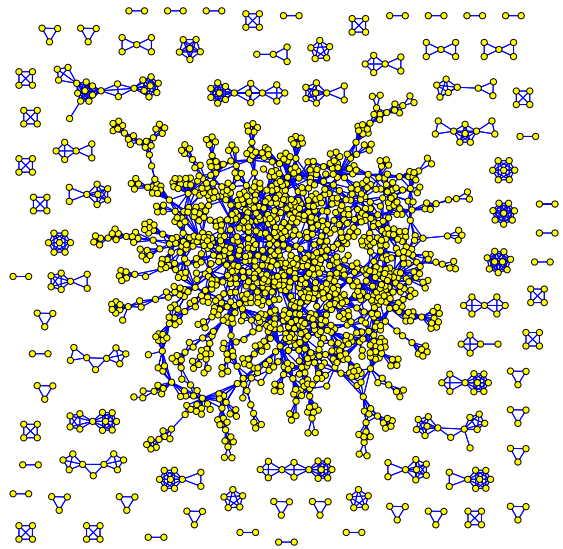
$\alpha c^2 < 1$



$\alpha c^2 = 1$



$\alpha c^2 > 1$



percolation transition: $\alpha c^2 = 1$

unlike diluted Hopfield model:
many short loops and cliques

so analysis significantly harder ...

# Statistical mechanical analysis

$$E(\boldsymbol{\sigma}) = -\frac{1}{2c}\sum_{\mu=1}^{\alpha N} M_\mu^2(\boldsymbol{\sigma}) - \sum_{\mu=1}^{\alpha N}\psi_\mu M_\mu(\boldsymbol{\sigma}), \qquad M_\mu(\boldsymbol{\sigma}) = \sum_{i=1}^{N}\xi_i^\mu\sigma_i$$

$M_\mu(\boldsymbol{\sigma}) > 0$: pos signal to B-clone, $b_\mu \uparrow$
$M_\mu(\boldsymbol{\sigma}) < 0$: neg signal to B-clone, $b_\mu \downarrow$

$\psi_\mu$: antigen trigger

- To calculate:

$$f = -\lim_{N\to\infty}\frac{1}{\beta N}\Big\langle \log Z_N\Big\rangle_{\boldsymbol{\xi}}, \qquad Z_N = \sum_{\boldsymbol{\sigma}} e^{\frac{\beta}{2c}\sum_\mu M_\mu^2(\boldsymbol{\sigma}) + \beta\sum_\mu \psi_\mu M_\mu(\boldsymbol{\sigma})}$$

$$\mathcal{P}(M|\psi) = \Big\langle\Big\langle \frac{1}{\alpha N}\sum_{\mu=1}^{\alpha N}\delta_{M,M_\mu(\boldsymbol{\sigma})}\delta(\psi-\psi_\mu)\Big\rangle\Big\rangle$$

*prob of clonal activation M, given antigen trigger* $\psi$

- tricky but feasible calculation ...
  combination of replica method, path integrals,
  and steepest descent integration

## final macroscopic theory

$$W(h) = \mathrm{e}^{-c} \sum_{k\geq 0} \frac{c^k}{k!} \mathrm{e}^{-\alpha c k} \sum_{r\geq 0} \frac{(\alpha c)^r}{r!} \int_{-\infty}^{\infty} \Big[ \prod_{s\leq r} \mathrm{d}h_s W(h_s) \Big] \sum_{\ell_1 \ldots \ell_r \leq k} \int \mathrm{d}\psi \; P(\psi)$$

$$\times \sum_{\tau=\pm 1} \delta \left[ h - \tau\psi - \frac{1}{2\beta} \log \left( \frac{\sum_{\sigma_1 \ldots \sigma_k = \pm 1} \mathrm{e}^{\beta (\sum_{\ell\leq k} \sigma_\ell)^2/2c + \beta (\sum_{\ell\leq k} \sigma_\ell)(\psi + \tau/c) + \beta \sum_{s\leq r} h_s \sigma_{\ell_s}}}{\sum_{\sigma_1 \ldots \sigma_k = \pm 1} \mathrm{e}^{\beta (\sum_{\ell\leq k} \sigma_\ell)^2/2c + \beta (\sum_{\ell\leq k} \sigma_\ell)(\psi - \tau/c) + \beta \sum_{s\leq r} h_s \sigma_{\ell_s}}} \right) \right]$$

$W(h)$: clonal cross-talk interference distribution

$$P(M|\psi) = \sum_{k\geq 0} p(k) P(M|k,\psi), \qquad p(k) = \mathrm{e}^{-c} c^k / k!$$

$$P(M|k,\psi) = \mathrm{e}^{-\alpha c k} \sum_{r\geq 0} \frac{(\alpha c)^r}{r!} \int_{-\infty}^{\infty} \Big[ \prod_{s\leq r} \mathrm{d}h_s W(h_s) \Big] \sum_{\ell_1 \ldots \ell_r \leq k}$$

$$\times \left\{ \frac{\sum_{\sigma_1 \ldots \sigma_k = \pm 1} \delta_{M, \sum_{\ell\leq k} \sigma_\ell} \; \mathrm{e}^{\beta (\sum_{\ell\leq k} \sigma_\ell)^2/2c + \beta\psi \sum_{\ell\leq k} \sigma_\ell + \beta \sum_{s\leq r} h_s \sigma_{\ell_s}}}{\sum_{\sigma_1 \ldots \sigma_k = \pm 1} \mathrm{e}^{\beta (\sum_{\ell\leq k} \sigma_\ell)^2/2c + \beta\psi \sum_{\ell\leq k} \sigma_\ell + \beta \sum_{s\leq r} h_s \sigma_{\ell_s}}} \right\}$$

## state without clonal cross-talk

$W(h) = \delta(h)$,
always a soln, for any choice of model parameters

$k > 0$ :

$$P(M|k,\psi) = \mathrm{e}^{-\alpha c k} \sum_{r\geq 0} \frac{(\alpha c)^r}{r!} \sum_{\ell_1 \ldots \ell_r \leq k} \left\{ \frac{\sum_{\sigma_1 \ldots \sigma_k = \pm 1} \delta_{M,\sum_{\ell\leq k}\sigma_\ell} \mathrm{e}^{\frac{\beta}{2c}(\sum_{\ell\leq k}\sigma_\ell)^2 + \beta\psi \sum_{\ell\leq k}\sigma_\ell}}{\sum_{\sigma_1 \ldots \sigma_k = \pm 1} \mathrm{e}^{\frac{\beta}{2c}(\sum_{\ell\leq k}\sigma_\ell)^2 + \beta\psi \sum_{\ell\leq k}\sigma_\ell}} \right\}$$

at $T = 0$ (no noise):

$\psi \neq 0$ : $\quad P(M|k,\psi) = \delta_{M,k\ \mathrm{sgn}(\psi)}$

*i.e. error free activation or inhibition*
*of stored strategy with k nonzero entries*

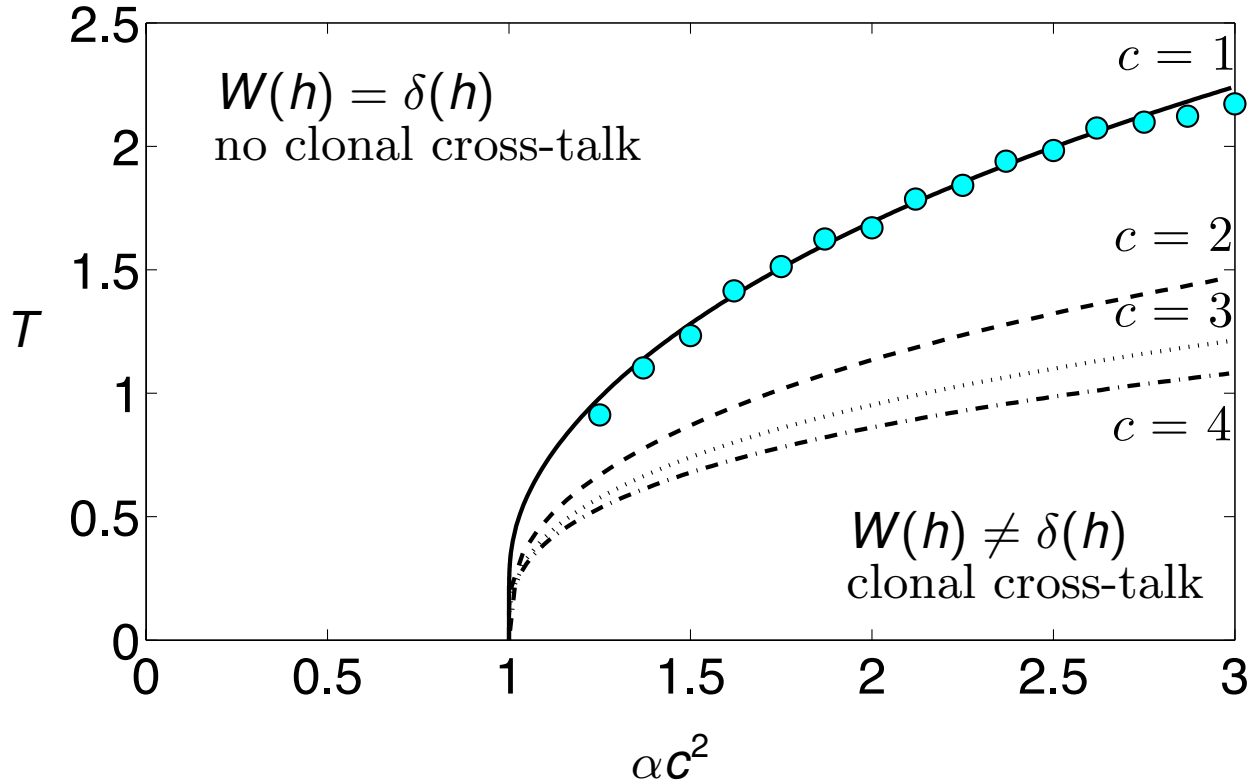
$\psi = 0$ : $\quad P(M|k,\psi) = \frac{1}{2}[\delta_{M,k} + \delta_{M,-k}]$

*weak ergodicity breaking*,
*clone oscillates randomly between* $M_\mu > 0$ *and* $M_\mu < 0$ *states*,
*important for homeostasis*!

# Phase diagram

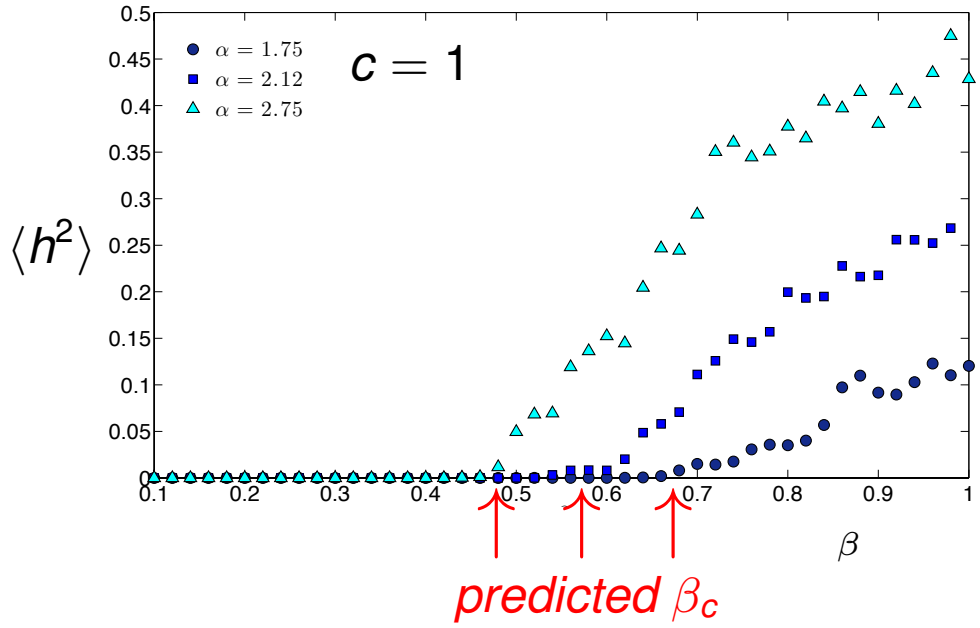
continuous bifurcations
away from $W(h) = \delta(h)$:

$$1 = \alpha c^2 \sum_{k\geq 0} \mathrm{e}^{-c}\,\frac{c^k}{k!}\left\{\frac{\int \mathrm{d}z\ \mathrm{e}^{-\frac{1}{2}z^2}\tanh(z\sqrt{\beta/c}+\beta/c)\cosh^{k+1}(z\sqrt{\beta/c}+\beta/c)}{\int \mathrm{d}z\ \mathrm{e}^{-\frac{1}{2}z^2}\cosh^{k+1}(z\sqrt{\beta/c}+\beta/c)}\right\}^2$$

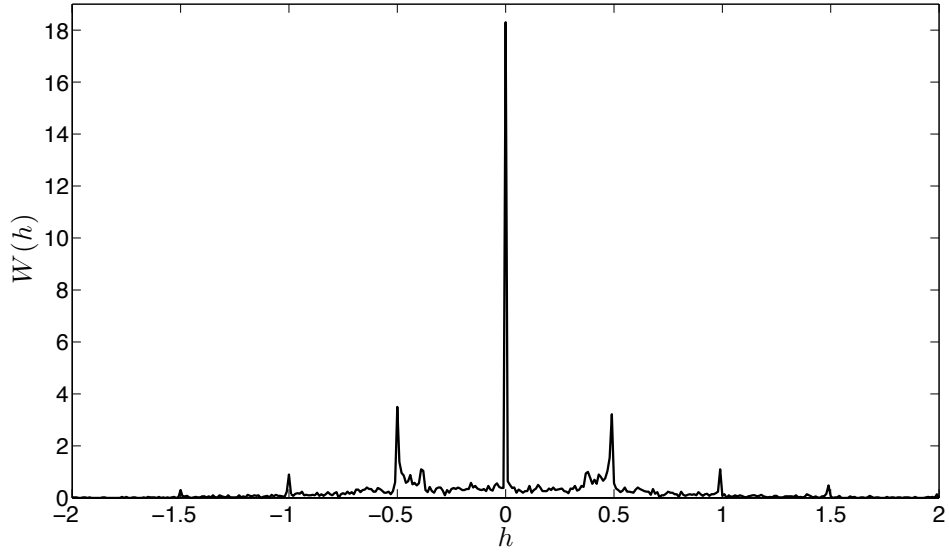



*circles: numerical soln of $W(h)$ eqn for $c=1$*

numerical soln of eqn for $W(h)$
via population dynamics
algorithm



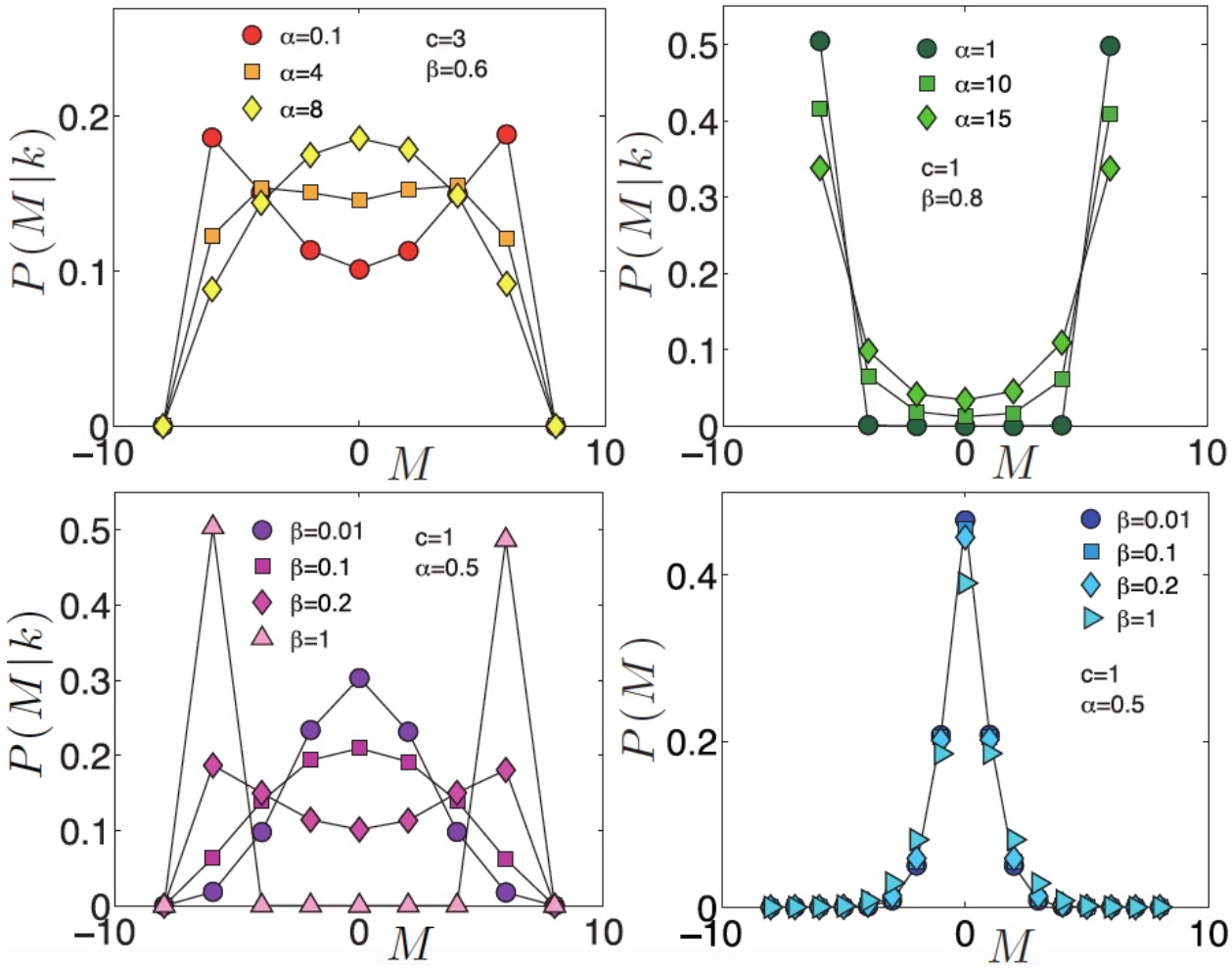

clonal cross-talk interference
distribution $W(h)$
below $T_c$
($c=2$, $\alpha=2$, $\beta=6.2$)



clonal activation statistics
in absence of antigen

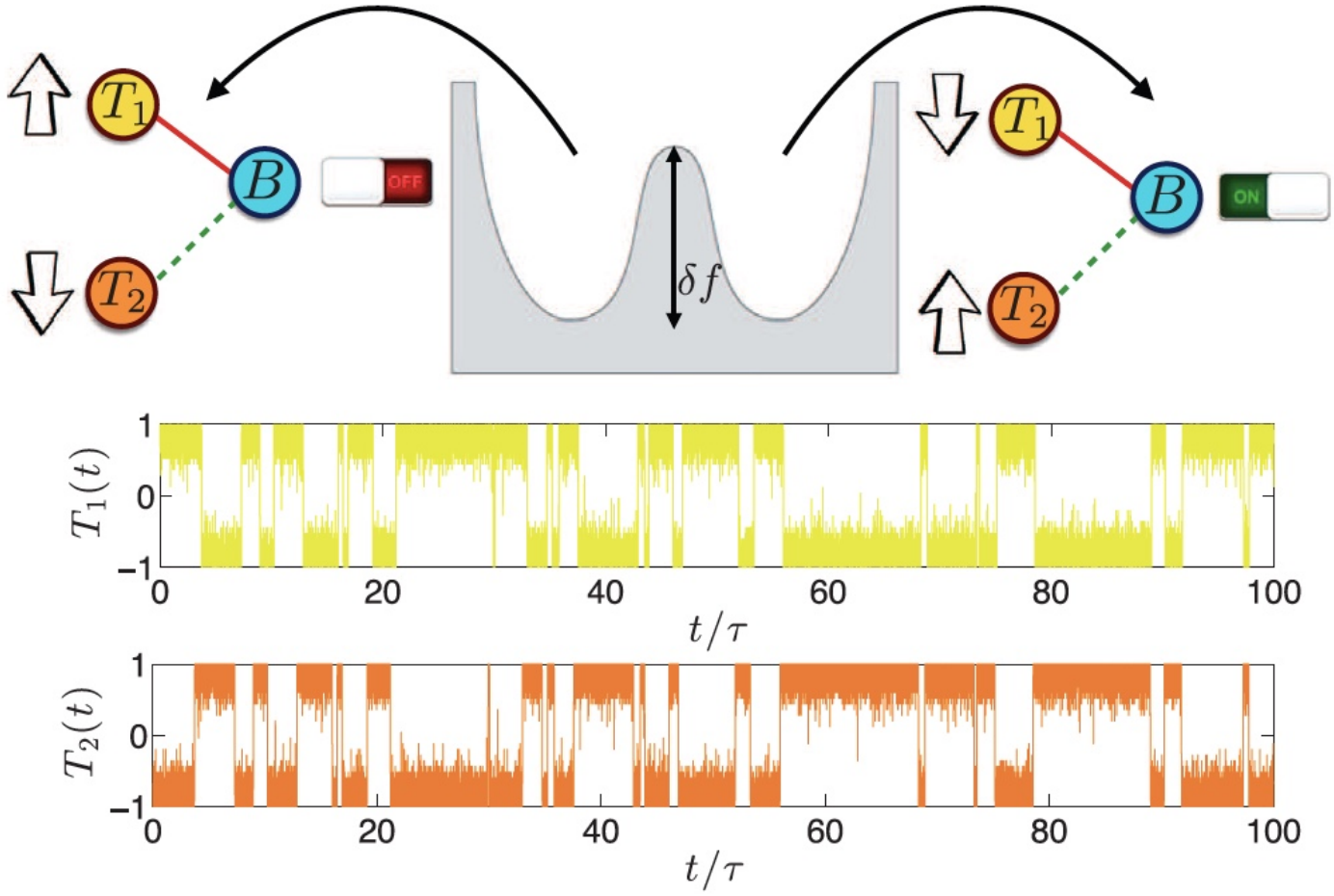
*transitions into cross-talk regime*

*no cross-talk*



consequence of finite
connectivity in the model:

## homeostasis




*important property,*
*since permanently inactive clones die ...*

# Further developments

Imperfections of the
Agliari-Barra model

- Convenient short-cuts in modelling ...

  – no biological motivation for the T-clone equation
  – $b_\mu \in \mathbb{R}$ but $\sigma_i \in \{-1, 1\}$
  – identical noise levels for *B*-clones and *T*-clones
  – no dynamical analysis

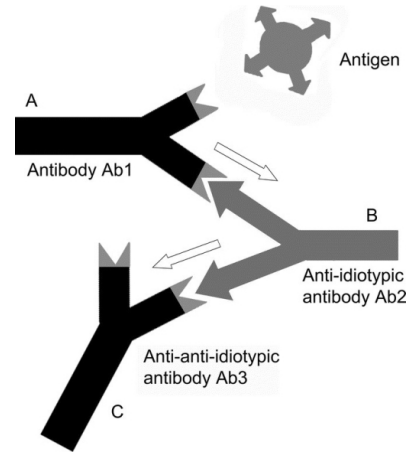
- Level of biological detail ...

  – no distinction between T-helpers and T-regulators
  – no B-cell subtypes
  – no other lymphocyte types
  – primitive definition of interaction network

- Relevant timescales ...

  – no antigen dynamics
  – no hypersomatic mutation

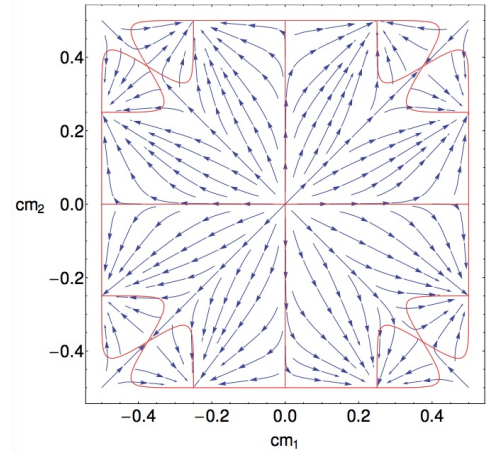
# more recent studes




- Include idiotypic interactions:
  *B*-clones come in complementary pairs, $(\mu, \bar{\mu})$

$$\frac{\mathrm{d}}{\mathrm{d}t} b_\mu = \lambda_\mu a_\mu + \sum_{i=1}^{N_T} \xi_i^\mu \sigma_i - b_\mu + k b_{\bar{\mu}} + \chi_\mu(t)$$

  increased danger of auto-immune disease ...

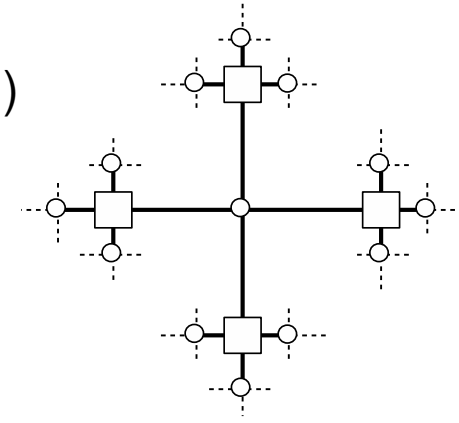


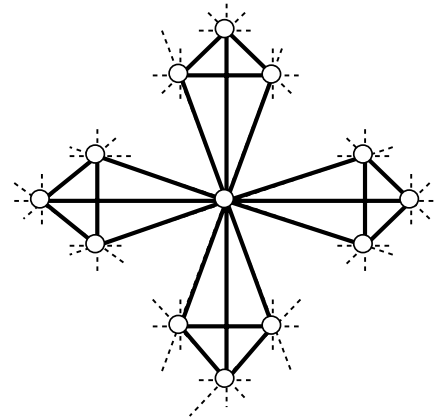

- Dynamical analysis:
  so far only in extensively connected regime,
  i.e. few B-clones, extensively many T-clones

  flow diagrams very similar to overlap dynamics
  in standard non-diluted Hopfield model

- Alternative (regular or random)
  interaction topologies
  for B-T lymphocytes:

  no qualitative changes





- More realistic equations

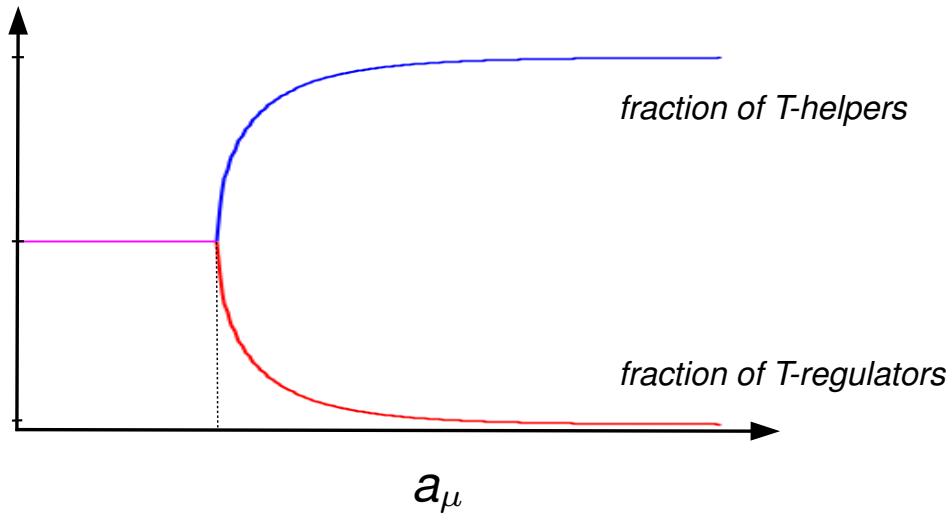
  – representation of activation: multiplicative,
  – distinct helper- and activator T-clones: $\xi_i^\mu = \pm 1$, $\sigma_i \geq 0$,
  – distinct T-clone and B-clone noise levels,
  – arbitrary topology: interaction partner sets $\partial_i$ and $\partial_\mu$

$$\tau_b \frac{\mathrm{d}}{\mathrm{d}t} b_\mu = a_\mu \Big( \sum_{i \in \partial_\mu} \xi_i^\mu \sigma_i + \theta_\mu \Big) - \rho b_\mu + \chi_\mu(t)$$

$$\tau_\sigma \frac{\mathrm{d}}{\mathrm{d}t} \sigma_i = \sum_{\mu \in \partial_i} a_\mu \xi_i^\mu b_\mu - \frac{\partial}{\partial \sigma_i} V(\boldsymbol{\sigma}) + \eta_i(t)$$

*transitions between low dose tolerance state, and vigorous immune response state*

*auto-immune pathologies, or immune switch-off ...*



# Discussion

- Similarity between immune and neural networks

  – large nr of interacting variables
  – adaptive links between components
  – learn and recall distributed information

  neuroscience: high connectivity, equations known
  immunology: low connectivity, equations unclear

- Using post-2000 statistical mechanics tools:
  more realistic solvable immunological models

  Mathematically *nearly identical* to diluted
  Hopfield model of recurrent neural networks

  Experience with recurrent neural networks
  extremely helpful in immunological modeling

- Rich phenomenology

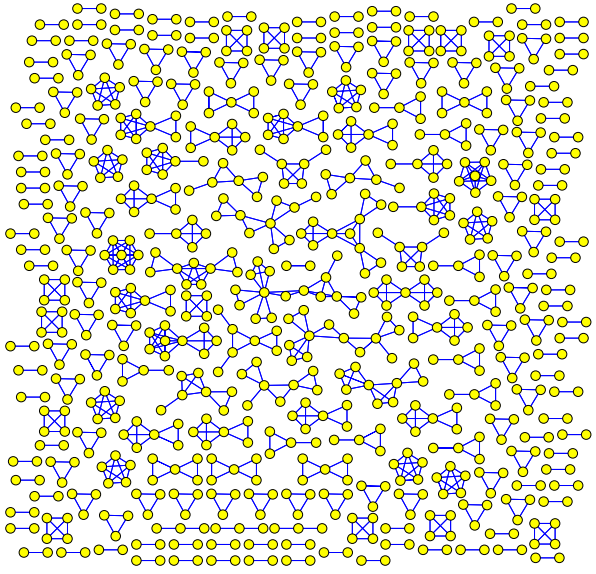
  – clonal cross-talk transitions
  – clonal on/off switching in absence of antigen (homeostasis)
  – low tolerance states
  – autoimmunity due to percolation

# Possible benefits to neuroscience

transfer of mathematical methods

- Ability to solve models analytically in terms of statistical features of (finite) connectivity graph
  - impact of recurrent network topology on operation (degree distribution, correlations, modularity, ...)
  - impact of short loops
  - extend to models with spike trains and phases (e.g. coupled oscillators)
  - extend to models with (Hebbian) synaptic adaptation (finite $n$ replica method)
  - application to neural activity dynamics on functional connectivity graphs

suggestions of
new functionality



- Recall simultaneously $\sim N$ sub-patterns, each with finite nr of bits, with controlled linking between sub-patterns (percolation transition)
- Oscillation between metastable states, in absence of input, with controlled durations in individual attractors

  – equivalent phenomena in neuroscience?
  – memory homeostasis?
  – brain activity during sleep?

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https://toncoolen.wixsite.com/accc

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# Selected references

- Recurrent neural network modelling prior to 2000:

  ACCC, 2001, *chapters 14+15, Handbook of Biol Physics Vol 4 (Elsevier)*
  S-I Amari, 2013, *Neural Networks 37*

- Immune modelling prior to 2000:

  G Parisi, 1990, *Proc Natl Acad USA 87*
  RJ De Boer, L Segel, AS Perelson, 1992, *J Theor Biol 155*
  AS Perelson, G Weisbuch, 1997, *Rev Mod Phys 69*

- Immune modelling after 2000:

  E Agliari, A Barra, F Guerra, F Moauro, 2011, *J Theor Biol 287*
  E Agliari, A Annibale, A Barra, ACCC, D Tantari, 2013, *J Phys A 46*
  S Bartolucci, A Annibale, 2015, *J Stat Mech: Theory Exp P08017*
  A Mozeika, ACCC, 2017, *J Phy A 50*