Performance and breakdown of the immune system from a statistical mechanics perspective

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Statistical Mechanics and Theoretical Immunology

Immune system devoted to protect host body against damaging substances

Made up of a huge number of different kinds of cells and messengers, which must be properly orchestrated to ensure safe performance

Pattern recognition, memory storage, self/non-self discrimination are cooperative features

Statistical mechanics
Systemic viewpoint to evidence emergent properties and the key mechanisms underlying (mis)functioning of the system
B cells make up a “ferromagnetic network”

**Experimental facts**

B lymphocytes are dichotomic → $\sigma = \pm 1$

Each lymph. carries a specificity → $\xi = \{1, 0, ..., 1\}$

Clone ($\xi_i$) ↔ Specific antibody ($\xi_i$)

Several ($N$) different clones → $\{\xi_1, \xi_2, ..., \xi_N\}$

**Model 0**

System of $N \times M$ spins

$N$ order parameters: $m_i(t) = \sum_a \sigma_{i}^a(t)/M$

$\rightarrow c_i(t) \sim \exp[ m_i(t)/\tau ]$

Antigenic stimulation ↔ External local field $h_i$

$$H_0 = -c_{Ag} \sum_i h_i m_i$$

$c_{Ag}$ is antigenic concentration

Burnet’s (Nobel Prize 1960) clonal expansion theory
Model 0
System of NxM spins
N order parameters: \( m_i(t) = \sum_a \sigma_i^a(t)/M \rightarrow c_i(t) \sim \exp[ m_i(t)/\tau] \)
Antigenic stimulation \( \leftrightarrow \) External local field \( h_i \)

\[
H_0 = - c_{Ag} \sum_i h_i m_i
\]
c_{Ag} is antigenic concentration

Model 1
System of NxM spins
N order parameters: \( m_i(t) = \sum_a \sigma_i^a(t)/M \rightarrow c_i(t) \sim \exp[ m_i(t)/\tau] \)
Exp. findings & “Small” repertoire \( \rightarrow \) Functional network

\[
H_1 = - 1/N \sum_{i,j} J_{ij} m_i m_j
\]
\( J_{ij} \) measures affinity between clones \( i \) and \( j \)

Jerne’s (Nobel Prize 1984) idiotypic network theory
The two approaches are synergic

\[ H = H_0 + H_1 = -c_A g \sum h_i m_i - \frac{1}{N} \sum_{i,j} J_{ij} m_i m_j \]

# Complementary matches

\[ c_{ij} = \sum_{\mu=1}^{L} [\xi_i^\mu (1 - \xi_j^\mu) + \xi_j^\mu (1 - \xi_i^\mu)] \]

Attractive vs Repulsive interaction \( \rightarrow \) weight \( \alpha \geq 0 \)

\[ f_{\alpha,L}(\xi_i, \xi_j) \equiv \alpha c_{ij} - (L - c_{ij}) \in [-L, \alpha L] \]

\[ J_{ij} = \Theta(f_{\alpha,L}(\xi_i, \xi_j)) \exp[f_{\alpha,L}(\xi_i, \xi_j)] / \bar{J} \]

\( \Rightarrow \) Ferromagnetic Correlated-Random-Bond Net

Coupling distribution

\[ P(J_{ij}) = \begin{cases} 
\frac{1}{2} \left( \frac{L}{(J_{ij} + L)/(1 + \alpha)} \right) & \text{if } J > 0 \\
1 - p & \text{if } J_{ij} = 0 
\end{cases} \]

\[ z_i = \sum_{j=1}^{N} A_{ij} = \sum_{j=1}^{N} \left\lfloor J_{ij} \right\rfloor \text{ Coordination number} \]

\[ w_i = \sum_{j=1}^{N} J_{ij} \quad \text{Weighted Coordination number} \]
Cooperative features of the idiotypic network

- Low-Dose Tolerance
- Bell-shape response
- Memory Effects

Self-NonSelf Discrimination

Surviving self-reacting clones are quiescent due to the interaction with the network (over which information is spread)

Negative selection in bone marrow: most self-reacting clones are deleted

\[ \varphi_i = \sum_j J_{ij} m_j + h_i, \quad c_i(t) \equiv \exp \left[ \frac{(m_i(t) + 1)}{2} \right] \]

High weighted connectivity (low reactivity) group → self addressed
Low weighted connectivity (high reactivity) group → non-self addressed

Interaction matrix [Kearney et al.]
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Negative selection in bone marrow: most self-reacting clones are deleted

Simulation of negative selection yields to correlation between $w$ and self-affinity

Negative selection is automatically accounted in our network
Helper cells make the system complex

**Th lymphocytes**
- No effector functions
- Receive first signal from APC
- Release/Absorb regulatory agents (cytokines)

**Tk lymphocytes**
- Induce death of dangerous cells
- Need signal of chemical messengers from Th

**Cytokines**
- Auto-, Para-, Endocrine effects
- Induce differentiation/growth/death
- Balance is crucial!

**B lymphocytes**
- Play as APC
- Make specific Abs
- Need signal of chemical messengers from Th
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Th lymphocytes
Each clone $h_i = \pm 1$, $i = 1,\ldots,H$
Actual concentration $\sim \Sigma_i \exp(h_i)$

B lymphocytes
Self-regulatory effects
Each clone $b_i \sim \mathcal{N}(0,1)$, $i = 1,\ldots,B$
Actual concentration $\sim \Sigma_i \exp(b_i)$

Tk lymphocytes
Self-regulatory effects
Each clone $k_i \sim \mathcal{N}(0,1)$, $i = 1,\ldots,K$
Actual concentration $\sim \Sigma_i \exp(k_i)$

Cytokines
$\xi_{i\mu}$ cytokine acting between $h_i$ and $b_\mu$ ($k_\mu$), assumed symmetric
$\xi_{i\mu} = \pm 1$ for excitatory/inhibitory stimulation, $P(\xi_{i\mu} = +1) = P(\xi_{i\mu} = -1) = 1/2$
$\{\xi\}$ quenched and encodes proper “strategies”

3-partite SG
$$H(h, k, b; \xi, \eta) = \frac{-1}{\sqrt{H}} \sum_{i,\mu} \xi_{i,\mu} h_i k_\mu - \frac{1}{\sqrt{H}} \sum_{i,\nu} \xi_{i,\nu} h_i b_\nu.$$
\[ \mathcal{H}(h, k, b; \xi, \eta) = -\frac{1}{\sqrt{H}} \sum_{i,\mu}^{H,K} \xi_{i,\mu} h_i k_{i\mu} - \frac{1}{\sqrt{H}} \sum_{i,\nu}^{H,B} \xi_{i,\nu} h_i b_{i\nu}. \]

**Partition function:**

\[ Z_{H,K,B}(\beta) = \sum_{h} \int \prod_{\nu} d\mu(b_{\nu}) \int \prod_{\mu} d\mu(k_{\mu}) \exp\left(\frac{\beta}{\sqrt{H}} \sum_{i,\mu}^{H,K} \xi_{i,\mu} h_i k_{i\mu} + \frac{\beta}{\sqrt{H}} \sum_{i,\nu}^{H,B} \xi_{i,\nu} h_i b_{i\nu}\right). \]

**Gauss-integrate**

\[ Z_{H,B,K} = \sum_{\{h\}} \exp(-\mathcal{H}_{\text{Hopfield}}(h; \zeta)). \]

\[ \mathcal{H}_{\text{Hopfield}}(h; \zeta) = -\frac{\beta}{H} \sum_{i<j}^{H} \left( \sum_{\mu=1}^{K} \xi_{i,\mu} \xi_{j,\mu} + \sum_{\nu=1}^{B} \xi_{i,\nu} \xi_{j,\nu} \right) h_i h_j. \]

**n-partite spin-glass** \(\leftrightarrow\) **Sum of n-1 independent neural networks**

**Helpers promote/suppress, via cytokines, the effectors branches** \(\leftrightarrow\) **Cytokines directly connect helpers via Hebbian interaction, making them able to learn, store, retrieve patterns**
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\[ J_{ij} = \sum_{\mu = 1}^{p} \zeta^\mu_i \zeta^\mu_j \]
Mattis magnetization for the $\mu$-th state

\[ m^\mu = \frac{1}{H} \sum_{i=1}^{H} \xi_i^\mu h_i \]

Retrieval pattern $\xi^1 \Leftrightarrow$ Stimulation $b_1$

As a result of a learning process, cytokines ensures the dynamic stability of certain helper configuration, corresponding to stimulation of certain $b_i$
Scaling for subset size (high load) \( \alpha, \gamma \) standard hematological markers

As the amount of patterns increases, the network fails retrieval

CD4/CD8 <1 \( \rightarrow \) HIV progression in AIDS

“Inverted ratio” reduces lymphocyte activity and responsiveness to foreign antigens

System actually always subjected to external stimuli (viruses, bacteria, tumor cells) on effector branches \( \rightarrow \) positive mean activity \( k_0 \) [polyclonal expansion]

\[
Z_{N,K,B}(\beta, \alpha, \gamma) = \sum \int \prod db \ e^{-\sum (b)^2/2} \int \prod dK \ e^{-\sum (K - k_0)^2/2} e^{-\beta H(\sigma, k, b; \xi)}
\]

\[
y_\mu = k_\mu - k_0, \quad \int dy_\mu e^{-y_\mu^2/2} e^{\sqrt{\beta H} \sum \xi^\mu_i h_i y_\mu} e^{\sqrt{\beta k_0} \sum \xi^\mu_i h_i}
\]

\[
\tilde{H}(\xi; \xi) = -\beta \frac{1}{H} \sum \left( \sum \xi^\mu_i \xi^\mu_j + \sum \xi^\mu_i \xi^\mu_j h_i h_j \right) - \sqrt{\beta k_0} \sqrt{\alpha} \sum \chi_i h_i
\]

Random field \( \rightarrow \mathcal{N}(0,1), \) TDL

consistent with low-titer self-Abs
\[ \beta \tilde{H}(h; \xi, \Phi) = \beta \frac{H}{\sum_{i<j} \sum_{\mu \in \{1\}} \sum_{\nu \in \{1\}} \xi_{i}^{\mu} \xi_{j}^{\mu} + \sum_{\nu \in \{1\}} \xi_{i}^{\nu} \xi_{j}^{\nu}} h_i h_j + \sqrt{\beta \Phi \sum_{i=1}^{H} \chi_i h_i} \]

\(\beta\) noise level

\(\Phi\) rescaled measure of mean activity

\(\alpha/\gamma\) lymphocyte ratios

Ordered work (organized effector activation) \(\sim t\)

\(\rightarrow\) introduction of disorder within the system \(\sim \sqrt{t}\)

\[ f(\alpha, \beta, \gamma, \Phi; m, q) \rightarrow \text{minimize RS free-energy w.r.t. order parameters} \rightarrow \text{self-consistent equations for} \]

\[ M(\alpha, \beta, \gamma, \Phi; m, q) \]

\[ Q(\alpha, \beta, \gamma, \Phi; m, q) \]

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Emergence of pathologies as retrieval failure

Abnormal lymphocyte accumulation (e.g. ALPS, leukemia) → severe autoimmune phenomena

Φ >> 1 RF phase prevails against retrieval phase

Free-radicals, cholesterol, damage accumulation, debris from lysis → slow down in recognition processes and speed up other pathologies

PM emergence and retrieval failure
Fast noise prevails

HIV to overt AIDS [HIV infect and kill h]
EBV [immortalize B cells] → populations imbalance yields reduced immune functions and responsiveness

SG emergence and retrieval failure
Slow noise prevails
Recovering the system as a dynamical process

\[ \tau \frac{db_v}{dt} = -\frac{1}{B} \sum_{l=1}^{B} f_v^{(b)} b_v - \frac{\beta}{\sqrt{H}} \sum_{i=1}^{H} \xi_i^v h_i - \sqrt{\eta_v^{(b)}} \]

Ornstein-Uhlenbeck process

Mean-Field approximations assuming \( \langle J \rangle \) exists strictly positive

\[ \frac{1}{B} \sum_{\nu} \frac{J_{\mu \nu} b_{\nu}}{J_{\mu \nu}} \sim b_{\mu} \]

\[ T \frac{db_{\mu}}{dt} = -W_{\mu} b_{\mu} - \frac{1}{\sqrt{H}} \sum_i \xi_i^\mu h_i + \sqrt{T} \eta_{\mu} \]

\[ H_{\text{tot}} = -\frac{1}{2B} \sum_\mu W_{\mu} b_{\mu}^2 - \frac{1}{\sqrt{H}} \sum_{i\mu} \xi_i^\mu h_i b_{\mu} \]

\[ H(h; \xi) = -\frac{1}{\sqrt{H}} \sum_{i,j}^H (\sum_\mu \frac{\xi_i^\mu \xi_j^\mu}{W_\mu}) h_i h_j. \]

Gaussian effectors activity with variance given by weighted connectivity

Agreement between idiotypic and tripartite approaches

Agreement between systemic and dynamical approaches

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Getting close to biology
Cytokines
\(\{\xi\}\) quenched
Excitatory/inhibitory/absent stimulation
\[P(\xi_{i\mu} = +1) = P(\xi_{i\mu} = -1) = (1-d)/2\]
\[P(\xi_{i\mu} = 0) = d\]

Finite degree of dilution h-h still FC
Network more effective
Parallel retrieval occurs
Critical parameters are corrected
Intermediate dilutions SG phase emerges
Extremely high dilution h-h network diluted
Conclusions

- Unifying picture including Burnet and Jerne theories

- Idiotypic network based on eliciting, complementarity-based couplings recovers basic facts in immunology

- Self/Non-self discrimination merges experimental results and ontogenesis features

- Learning and Memory needs complex interactions yielded by a “central control” provided by Th

- Errors ≠ Spurious states → Realize overlap of several strategies hence response hires several correlated lymphocytes

- Auto-immune diseases related to a few main sources of “noise”

- The tripartite system is consistent with idiotypic-network as well as dynamical approaches
Work in collaboration with:
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(Sapienza, Università di Roma)
Raffaella Burioni, Aldo Di Biasio (Università di Parma)
Silvio Franz, Thiago Sabetta (Université Paris-Sud, Orsay)

List of related publications:
EA, A. Barra, A Hebbian approach to complex network generation, EPL (2011)
A. Barra, EA, Solving statistical mechanics on complex topologies through neural network techniques, JStat (2011)
A. Barra, EA, A. Galluzzi, F. Guerra, F. Moauro, Parallel Processing Immune Networks, (2011)
EA, C. Cioli, E. Guadagnini, Percolation on correlated random networks, PRE (2011)
1. The B cell finds an antigen which matches its receptors.
2. It waits until it is activated by a helper T cell.
3. Then the B cell divides to produce plasma and memory cells.
4. Plasma cells produce antibodies that attach to the current type of invader.
5. “Eater cells,” prefer intruders marked with antibodies, and “eat” loads of them.
6. If the same intruder invades again, memory cells help the immune system to activate much faster.
Cooperative features of the idiotypic network

Low-Dose Tolerance \( c h_k^i > \frac{w_k}{N} \)

In “healthy state”, antigenic concentration to elicit response is lower-bounded
Cooperative features of the idiotypic network

Low-Dose Tolerance
Bell-shape response

First and second best matching antibody reacting with the antigen

Pathological example of a chronic response
Cooperative features of the idiotypic network

Low-Dose Tolerance

Bell-shape response

Memory Effects

Antigen $\sim \sigma_1(\text{Ab}) \sim \sigma_2(\bar{\text{Ab}}) \sim \sigma_3(\bar{\bar{\text{Ab}}})$

Circuit of length $\ell$: $\ell = \{i_1, i_2, ..., i_{\ell}\}$

Overall strength $J_\ell = l^{-1}\sum_{k=1}^{\ell} J_{i_k,i_{k+1}}$

$\rightarrow$ intrinsic robustness of $\ell$

Overall weight $w_\ell = l^{-1}\sum_{k=1}^{\ell} w_{ik}$

$\rightarrow$ influence of ext environment on $\ell$

The less diluted the network the smaller the region where memory effects may emerge

Region centered on $\langle k \rangle = O(10^{12}) \rightarrow L = O(10^2)$ consistent with experiments
Cooperative features of the idiotypic network

- Low-Dose Tolerance
- Bell-shape response
- Memory Effects
- Self-NonSelf Discrimination

Robustness under Ab correlation

Hypersomatic mutations in germinal centers
Evolution not completely random
Selective specification

\[ P(\xi=\pm 1) = \frac{1\pm a}{2} \]
\[ a \in [-1, +1] \]
(ageing)

Correlation first induces fringes and then breaks down connectivity

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Small (w.r.t. ER) frequency of short loops in underpercolated regime

- N=10000, L=64, a=0.570000, Α=0.700000. 9098 nodi isolati.
- N=10000, L=64, a=0.590000, Α=0.700000. 9472 nodi isolati.
- N=10000, L=64, a=0.610000, Α=0.700000. 9787 nodi isolati.
- N=10000, L=64, a=0.630000, Α=0.700000. 9896 nodi isolati.
La funzione di entropia è:

\[ H(h,k,b;\xi,\eta) = \frac{-1}{\sqrt{H}} \sum_{i,\mu} \xi_{i,\mu} h_i k_\mu - \frac{1}{\sqrt{H}} \sum_{i,\nu} \xi_{i,\nu} h_i b_\nu. \]
Standard ($\Phi=0$) phase diagram for Hopfield model

P: paramagnetic phase, $m=q=0$

SG: spin-glass phase, $m=0$, $q\neq 0$

F: pattern recall phase (pure states minimize $f$), $m\neq 0$, $q\neq 0$

M: mixed phase (pure states are local but not global minima)

$T_g$: second order, $T_M$ and $T_c$: first order
Fig. 4. From left to right: Solutions of the RS self-consistency equations for \( \Phi = 0.5, \alpha + \gamma = 0.01 \). Red line: solution of \( m \rightarrow m(m,q,\alpha + \gamma,\Phi,\beta) = 0 \). Blue line: solution of \( q - Q(m,q,\alpha + \gamma,\Phi,\beta) = 0 \). (a) \( 1/\beta = 0.8 \). Only the upper branch counts, under the value \( q = 1 - 1/\beta \) the free energy has only complex values. (b) \( 1/\beta = 0.6 \). In this particular point \( \alpha + \gamma,\Phi,\beta^{-1} \) a pure state solution \( m > 0 \) appears as the two contour-plot lines—for \( m \) and for \( q \)—are tangent. (c) \( 1/\beta = 0.5 \). Solution of the RS self-consistency equations for \( \Phi = 0.5, \alpha + \gamma = 0.01 \). Free energy is complex along the lower branches which are therefore rejected (note that they never cross in fact). Above two intersections appear. Only the higher \( m,q \) intersection is the thermodynamical pure state solution because it is coupled with the lower free energy. (d) \( 1/\beta = 0.2 \). Note that lowering the noise (for \( \alpha + \gamma < (\alpha + \gamma)_c = 0.138 \)) we always find the pure state retrieval solution. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 5. Left: RS amplitudes of the Mattis order parameter of the pure states at \( \Phi = 0.5 \) as function of the noise. From top to bottom: \( \alpha + \gamma = 0.01 - 0.05 \), \( (\alpha + \gamma)_c = 0.01 \). Right: Solid lines represent free energies of the pure states (PS) for \( \alpha + \gamma = 0.01 - 0.05 \) at \( \Phi = 0.5 \). Dashed lines represent free energies of the spin-glass (SG) states for \( \alpha + \gamma = 0.01 - 0.05 \) at \( \Phi = 0.5 \). Each different \( \alpha + \gamma \) is called simply \( \alpha \) in the plots and each couple of same lines has a different color for comparison. The higher \( 1/\beta \) of the PS line defines \( \beta_m \) point at each \( \alpha + \gamma \). The PS and spin-glass lines cross in the \( \beta_c \) point for each \( \alpha + \gamma \).