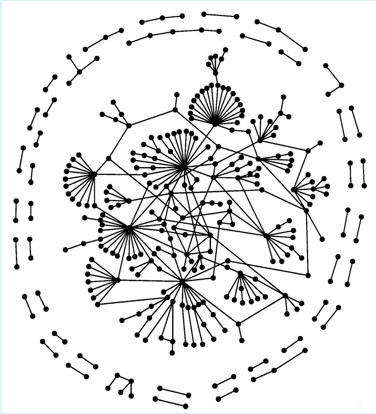
Collective Phenomena in Biological Systems
The Toolbox of Statistical Mechanics



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Mathematics, KCL

‘Claim: a statistical mechanical analysis of protein networks is feasible and timely’

Statistical mechanics

objective and philosophy
relation with systems biology
‘large is beautiful’: universality and phase transitions

Modern statistical mechanics – dynamics and disorder

inhomogeneous/disordered systems
interdisciplinary applications
complex networks

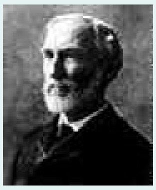
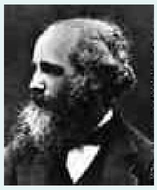
Signalling networks in biology

neural versus proteomic networks
macroscopic descriptions
modulation and control of global processes

Statistical mechanics of proteomic networks

potential and limitations
the language of the theory

Theory of many-particle systems:
'statistical mechanics'


(Boltzmann, Gibbs, Maxwell, Einstein)

Objective (Baxter):

> *'predict the relations between the observable macroscopic properties of the system, given only a knowledge of the microscopic forces between the components'*

- *equilibrium* ($\pm$1870)

$$\text{Prob[state]} = \frac{e^{-E(\text{state})/kT}}{\sum_{\text{states}} e^{-E/kT}}$$

E : energy
T : temperature

e.g.

molecules	$\longrightarrow$	*pressure/temp/volume, gas-liquid-solid transitions*
atomic electrons	$\longrightarrow$	*magnetism*
cells in suspensions	$\longrightarrow$	*blood rheology, visco-elastic properties*

- *non-equilibrium* ($\pm$1905)

Systems biology:

*'the study of the emergence of functional properties
that are present in a biological system
but not in its individual components'*

Statistical mechanics:

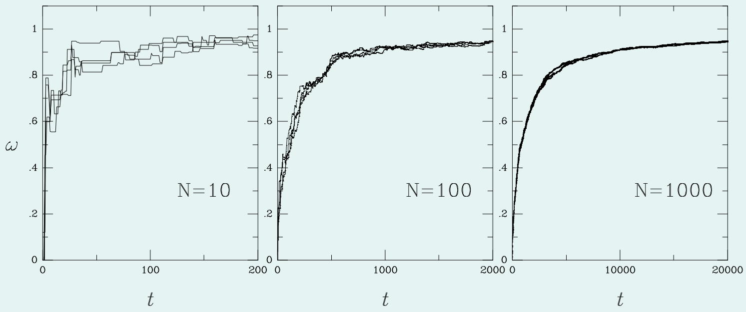
*'predict the relations between the observable macroscopic
properties of the system, given only a knowledge of the
microscopic forces between the components'*

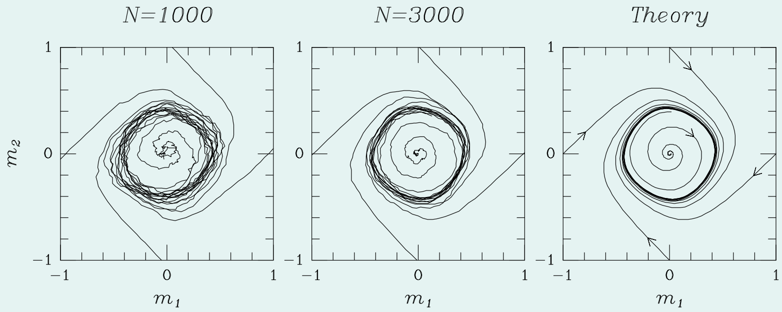
- *objectives of systems biology and of statistical mechanics are very similar*
- *it is irrelevant to the mathematical methods of statistical mechanics what the microscopic components* **represent**, *as long as there are many ...*

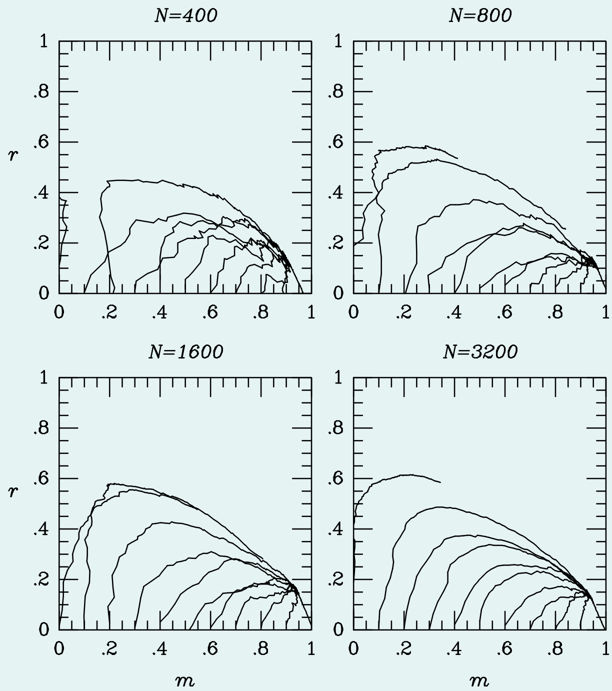
  e.g. inorganic molecules (or atomic magnets), organic molecules (amino-acids), living cells (blood cells, immune cells, neurons), computer hardware (processors), people (market models) ...
- *statistical mechanics: more than a century's worth of experience and specific mathematical methods and tricks*

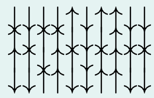
‘large is beautiful’ – universality and phase transitions

emerging deterministic macroscopic laws in large systems
independent of most microscopic details









Some jargon ...

Dynamical equations plus noise: stochastic process

Phase transition: drastic change in the system's macroscopic behaviour
at a specific value of a global control parameter
(collective phenomenon: can happen only in large systems !)

How large is large ?

stat mech: finds the macroscopic laws for infinitely large systems
real systems: always of finite size ...
why can we get away with it ?

effects of finite size N on observed macroscopic quantities:

- *fluctuations around 'infinite system' values:* $\Delta x/x \sim 1/\sqrt{N}$
- *'escape' time from 'infinite system' trajectories:* $t_{\rm esc} \sim e^N \tau$
  (τ: typical microscopic time scale)

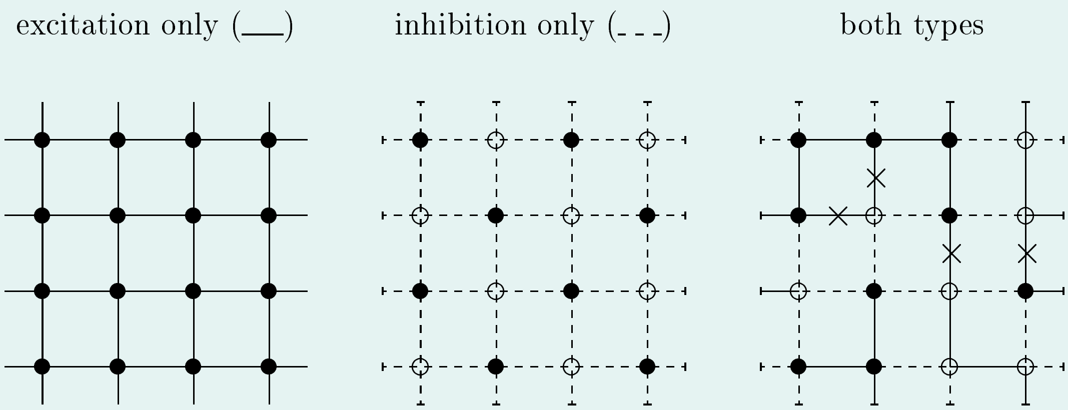
  example: $\tau \approx 10^{-15}$ *sec,* $N = 1000 \quad \rightarrow \quad \Delta x/x \approx 0.03, \;\; t_{\rm esc} \approx 10^{400}$ *sec*
  (age of universe $\approx 4.10^{17}$ sec)

Modern statistical mechanics – dynamics and disorder

Complex dynamics due to disorder or diversity

Simple example:
two-state neurons

○*: neuron active* ●*: neuron inactive*



Right diagram:
there is no state in which all 'instructions' are satisfied

'frustrated' neuron pairs: $\times$

Interdisciplinary applications of statistical mechanics to disordered many-particle systems

- *many structurally similar interacting microscopic elements*
- *noisy dynamics*
- *diversity, or (pseudo-) randomness in mutual forces*

↓↓↓↓↑↓↑↑↓↓
↑↓↑↑↓↓↓↑↓↓
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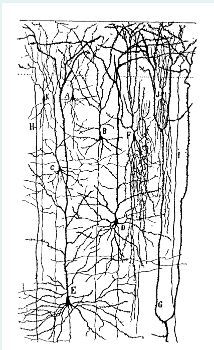
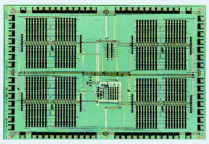
10^{24}
magnets

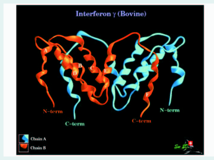


$10^4 - 10^8$
neurons

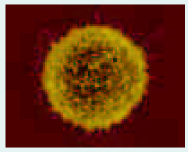


$10^4 - 10^6$
processors

$10^2 - 10^5$
traders



$10^3 - 10^4$
amino-acids



$10^8 - 10^{12}$
lymphocytes

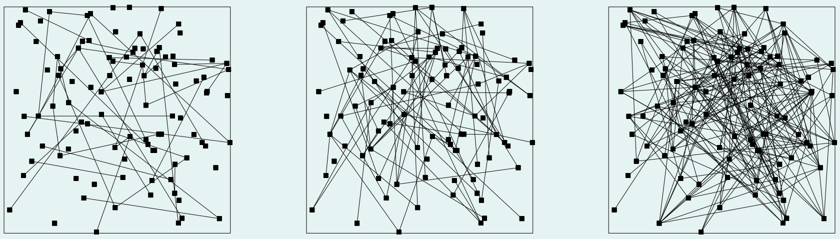
homogeneous many-particle systems: theory since ± 1870
disordered many-particle systems: theory since ± 1970

Modern statistical mechanics – large complex networks

N nodes, with links

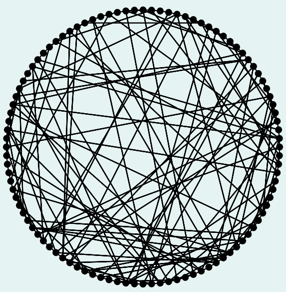
- *simple (Poissonnian) networks*
  for each pair (i, j): form a link with probability c/N

$N = 100$:

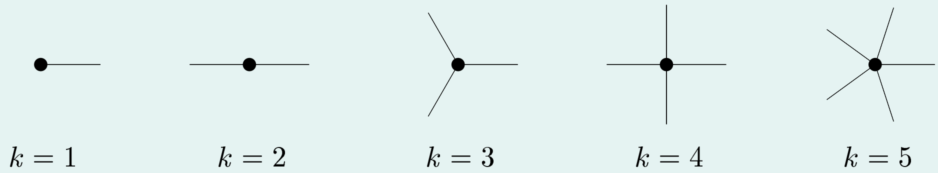


$c = 1$ $c = 2$ $c = 4$

- *'small-world' networks'*
  (epidemics, etc)

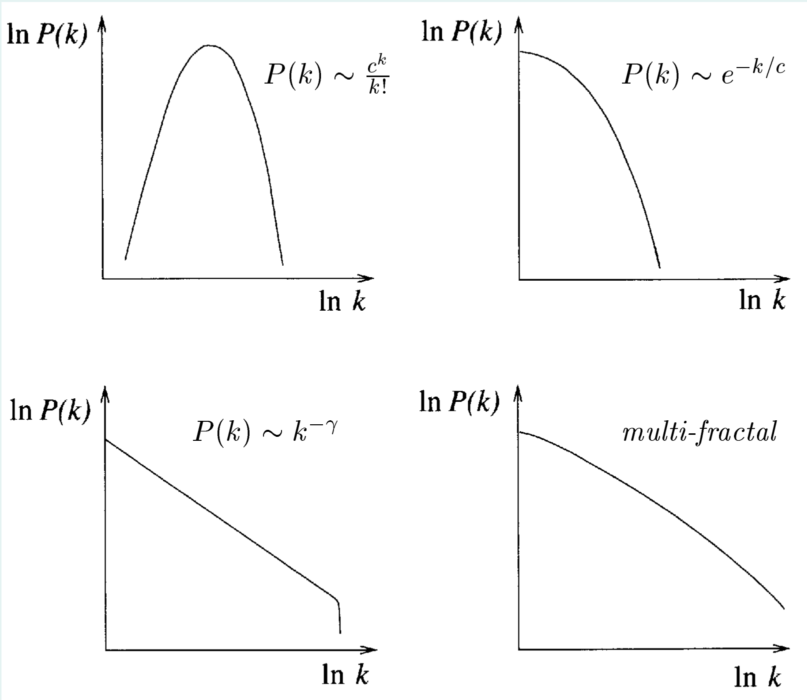


degree k of a node: nr of links to that node
degree distribution $P(k)$: statistics of the N degrees



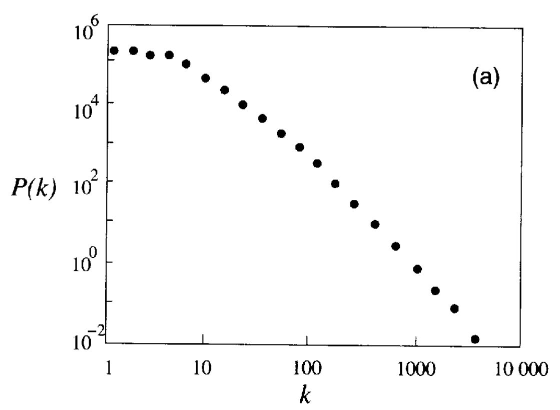
simple networks:

'scale-free' networks:

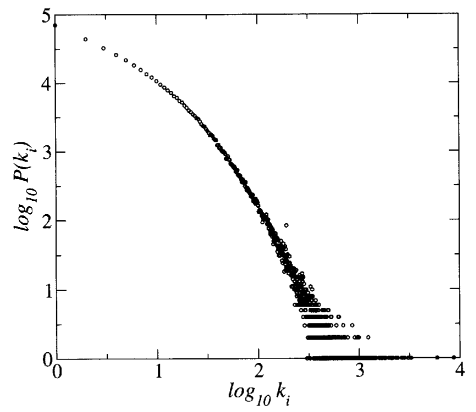


Social networks in science

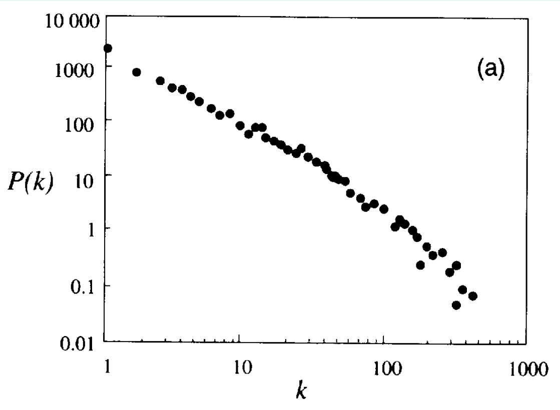
author networks:



citation networks:

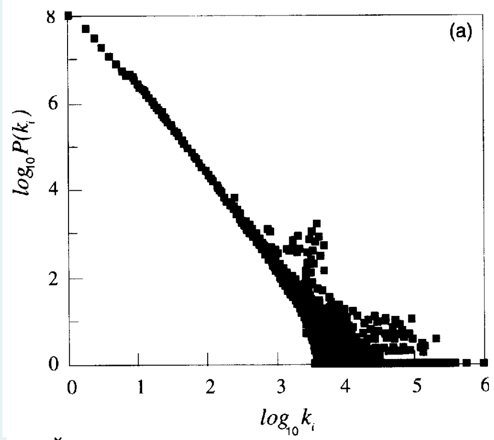


E-mail networks:

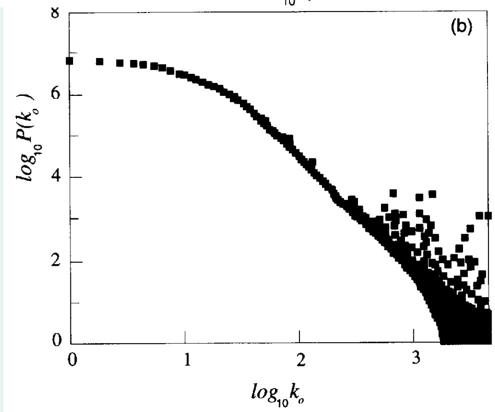


Internet

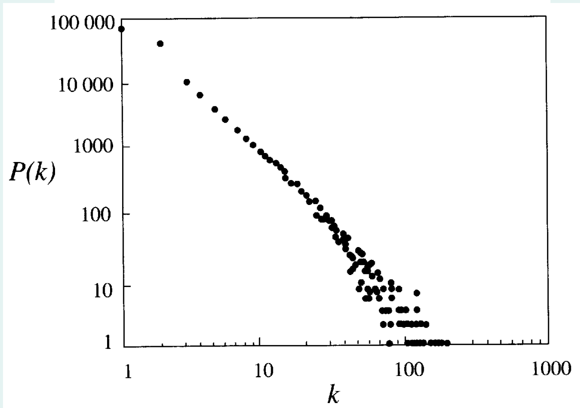
WWW in-links:



WWW out-links:

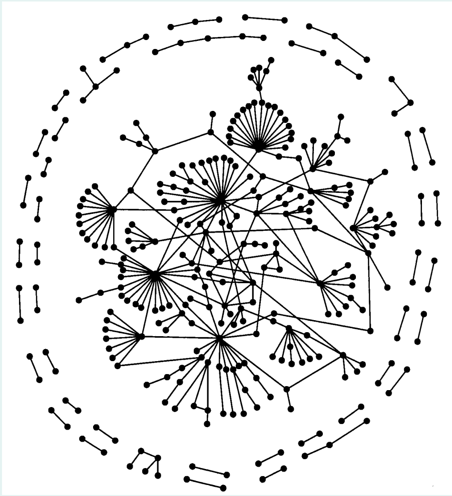


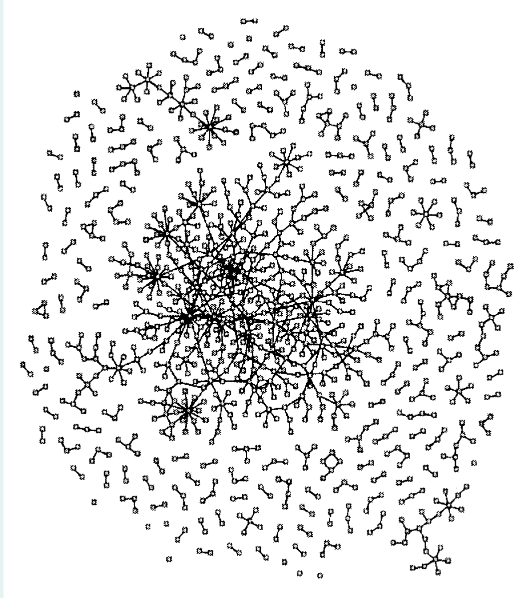
WWW routers:

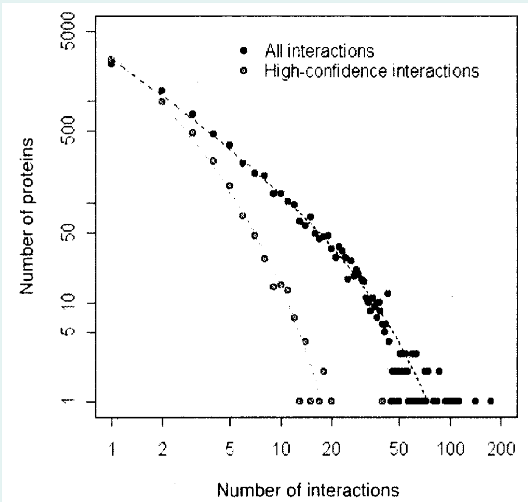


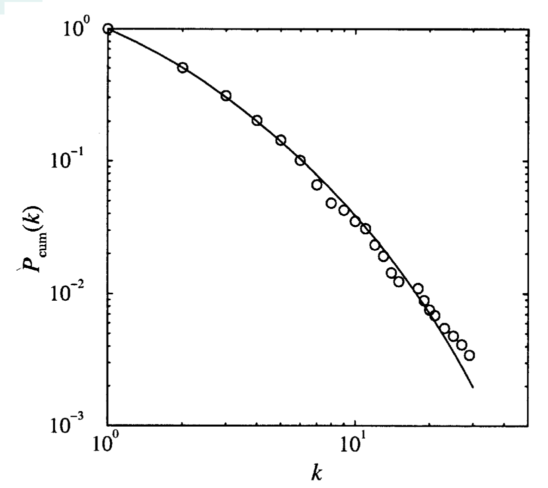
Protein interaction networks

yeast two-hybrid method









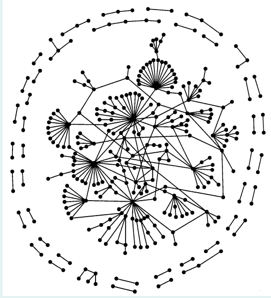
Giot et al (Science, 2003)

Jeong et al (Nature, 2001)

Signalling networks in biology

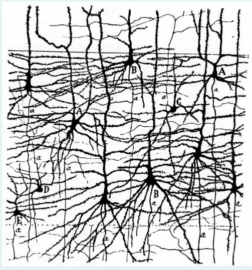
- **protein interaction networks***:*

  $N \approx 10^4$
  links: $\langle k \rangle \approx 2 - 7$
  scale-free, complex ('hub' proteins, etc)
  chemical conservation laws
  interactions static



- **neural networks***:*

  $N \approx 10^4 - 10^8$
  links: $\langle k \rangle \approx 10^2 - 10^4$
  random (hippocampus) to regular (cerebellum)
  no conservation laws
  interactions time-dependent

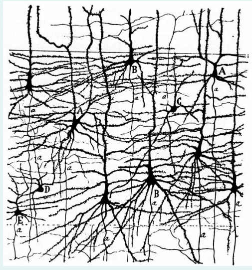


both examples: nontrivial emergent collective processes

statistical mechanical theory:

$\pm$ *1975: disordered systems with large connectivity*
$\pm$ *1990: statics of disordered systems with low connectivity*
$\pm$ *2002: dynamics of disordered systems with low connectivity*

Statistical mechanical modelling of neural networks



Examples of microscopic laws:

- N *binary neuron state variables* $\sigma_i = \pm 1$
  reacting to incoming signals V_i
  '1': firing, '-1': rest

$$\sigma_i(t+1) = \begin{cases} 1 & \text{if} \quad V_i(t) > \theta_i + \eta_i(t) \\ -1 & \text{if} \quad V_i(t) < \theta_i + \eta_i(t) \end{cases} \qquad V_i(t) = \sum_j J_{ij}\sigma_j(t)$$

  $\eta_i(t)$ *denotes noise*

- N *neuron voltages* V_i

$$\frac{d}{dt}V_i(t) = \sum_j J_{ij}\tanh[\gamma V_j(t)] - V_i(t) + \theta_i + \eta_i(t)$$

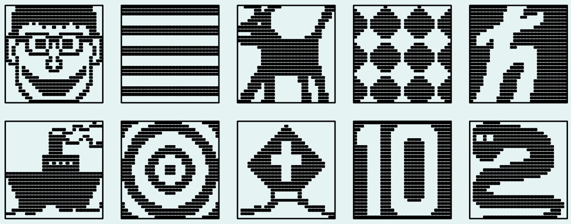
- N *coupled neural oscillators, with phases* ϕ_i

$$\frac{d}{dt}\phi_i(t) = \omega_i + \sum_j J_{ij}\sin[\phi_j(t) - \phi_i(t)] + \eta_i(t)$$

Attractors

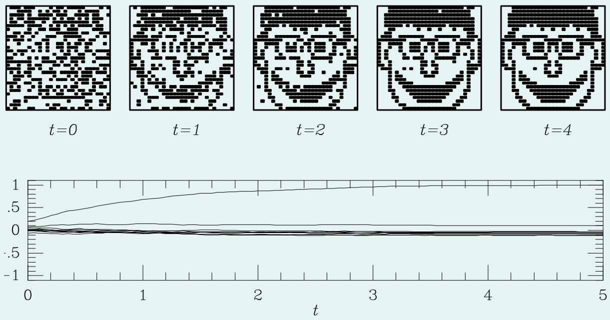
Information processing based on suitable interactions between the nodes

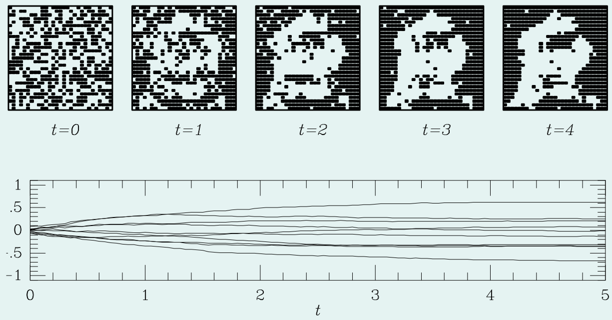
Desired attractors:
10 special network states $\boldsymbol{\xi}^\mu = (\xi_1^\mu, \ldots, \xi_N^\mu)$
$\xi_i = 1 : \ \bullet$
$\xi_i = -1 : \ \circ$



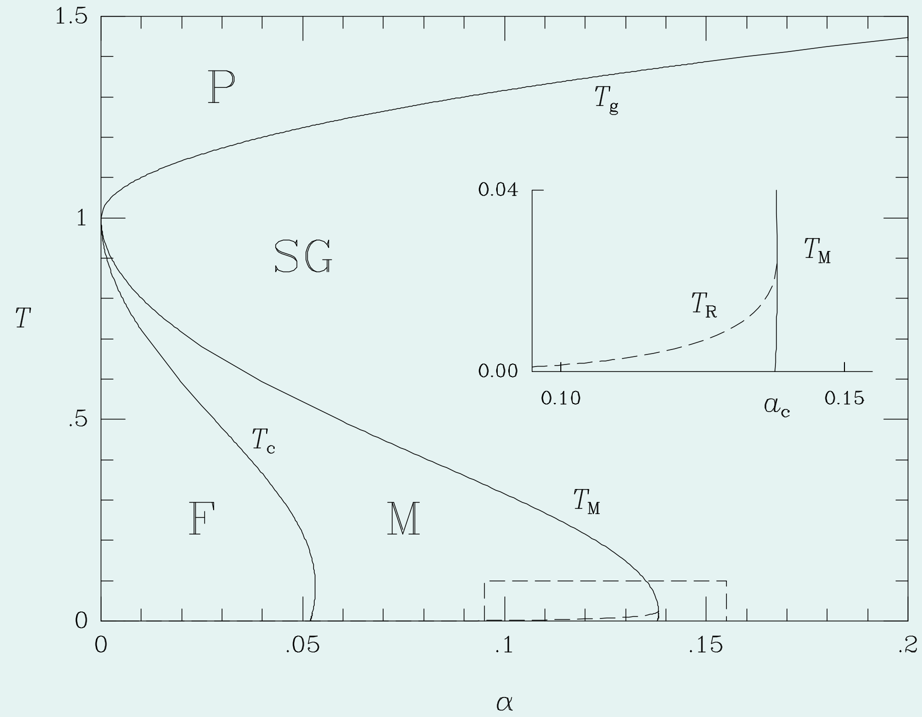
Possible choice: $$J_{ij} = \sum_{\mu=1}^{10} \xi_i^\mu \xi_j^\mu$$

macroscopic quantities: $$m_\mu = \frac{1}{N} \sum_{i=1}^{N} \xi_i^\mu \sigma_i$$





Deliverables of statistical mechanics: phase diagrams



example: memory with $p = \alpha N$ stored random patterns
control parameters: T neuronal noise level, α loading level
phases: P random dynamics, F/M recall, SG complex frozen state (overload)

Deliverables of statistical mechanics:
understanding the phenomenology of memory quantitatively

principles

- *'learning' by synapse adaptation, categorization*
- *associative recall*

'graceful degradation'

- *robustness against cutting links randomly*
- *robustness against link degradation*
  e.g. $J_{ij} \to \text{sgn}[J_{ij}]$
- *robustness against unreliable components*
- *noise eliminates unwanted system states*

pathologies

- *reproduction of specific lesion-induced memory disorders*
- *chemical modulators and related disorders*

Deliverables of statistical mechanics: macroscopic laws

$$J_{ij} = \frac{1}{N} \sum_{\mu\nu=1}^{p} \xi_i^\mu A_{\mu\nu} \xi_j^\nu$$

If $p \ll \sqrt{N}$*:*

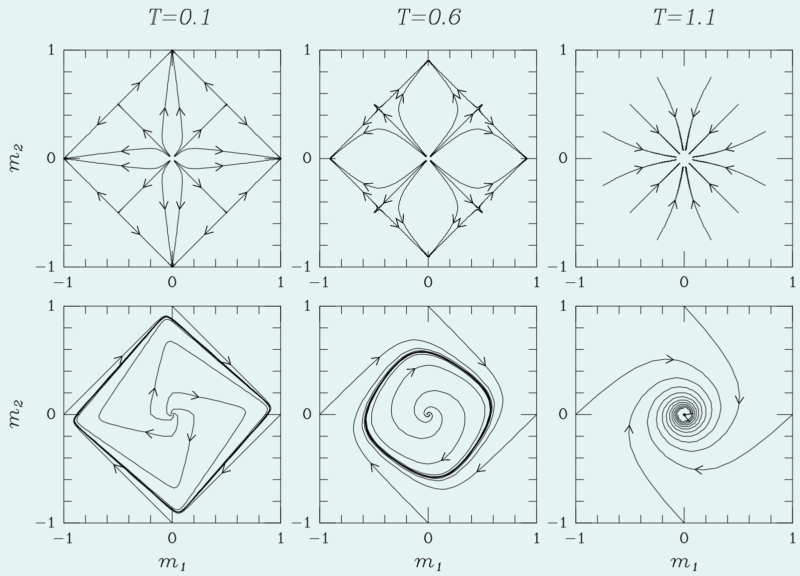
$$\frac{d}{dt}\boldsymbol{m} = \langle \boldsymbol{\xi} \tanh[\boldsymbol{\xi} \cdot A\boldsymbol{m}/T] \rangle_{\boldsymbol{\xi}} - \boldsymbol{m} \qquad \boldsymbol{m} = (m_1, \ldots, m_p)$$

Example:

$$A = \begin{pmatrix} 1 & \kappa \\ -\kappa & 1 \end{pmatrix}$$

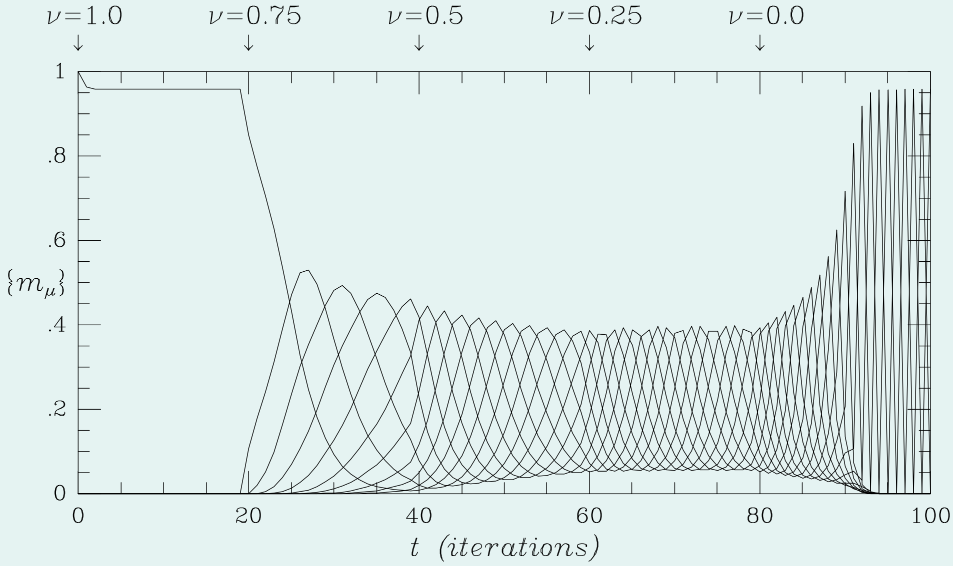
$\kappa = 0$

$\kappa = 1$



Modulation and control:
chemical modulators in neural networks

- *switching between possible global modes of operation*
- *control of periods of global oscillations*
- *theory allows for 'what if' approach*



Evolution of $\{m_\mu\}$, for $J_{ij} = \frac{\nu}{N}\sum_\mu \xi_i^\mu \xi_j^\mu + \frac{1-\nu}{N}\sum_\mu \xi_i^{\mu+1}\xi_j^\mu$, with 10 stored patterns at $T = 0.5$.

Statistical mechanics of proteomic networks

why stat mech ?

- *large numbers of interacting microscopic components*
- *systems biology: desire to explain macroscopic from microscopic laws, and to understand control and modulation of macroscopic processes*
- *proteomic networks appear to be 'scale-free'*
- *focus in modern stat mech: disorder (1975-), complex networks(2000-)*

deliverables of stat mech

- *phase diagrams, transitions between modes of operation*
- *macroscopic laws for self-averaging quantities*
- *insight into mechanisms, potential for 'inverse engineering'*

limitations of stat mech

- *generally no predictions for individual protein concentrations*
- *simplified mathematical representations of microscopic elements*
- *no solutions for spatial problems involving localized elements*

The language of disordered systems theory

core problem: carrying out disorder averages in probabilistic dynamical equations

'replica theory'

(statics: ±1975*, dynamics:* ±1993*)*

$$\langle \text{Prob}(x|y,\text{disorder})\rangle_{\text{disorder}} = \left\langle \frac{\text{Prob}(x,y|\text{disorder})}{\sum_{x'}\text{Prob}(x',y|\text{disorder})}\right\rangle_{\text{disorder}}$$

$$= \lim_{n\to 0}\left\langle \text{Prob}(x,y|\text{disorder})\left[\sum_{x'}\text{Prob}(x',y|\text{disorder})\right]^{n-1}\right\rangle_{\text{disorder}}$$

$$= \lim_{n\to 0}\sum_{x_2,\ldots,x_n}\langle \text{Prob}(x_1,y|\text{disorder})\ldots\text{Prob}(x_n,y|\text{disorder})\rangle_{\text{disorder}}$$

result mathematically equivalent to having n *copies (replicas) of the system*

- *one disordered system* $\Rightarrow$ n *coupled homogeneous systems*
- *new forces between pairs and quartets of elements*

however: $n \to 0$ **!!**

At end of the calculation:

$$f = \lim_{n\to 0} \text{ extr } \mathcal{F}[\boldsymbol{q}]$$

$n \times n$ matrix, $q_{\alpha\beta} \in \mathbb{R}$
zero diagonal elements:

$$\boldsymbol{q} = \begin{pmatrix} 0 & q_{1,2} & \cdots & q_{1,n-1} & q_{1,n} \\ q_{2,1} & 0 & & & q_{2,n} \\ \vdots & & \ddots & & \vdots \\ q_{n-1,1} & & & 0 & q_{n-1,n} \\ q_{n,1} & q_{n,2} & \cdots & q_{n,n-1} & 0 \end{pmatrix}$$

calculus in $n(n-1)$ dimensions (number of non-zero entries)
$n(n-1)$ is **negative** *as soon as $0 < n < 1$!*

Many peculiarities, e.g.
choose $q_{\alpha\beta} = q$ for all $\alpha \neq \beta$:

$$\sum_{\alpha\neq\beta}^{n} q_{\alpha\beta}^2 = n(n-1)q^2 < 0$$

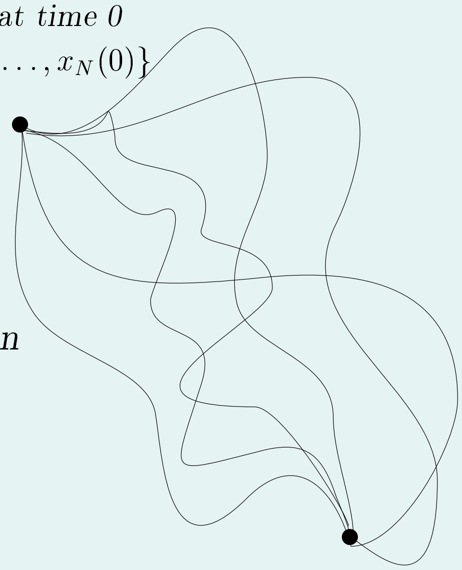
'generating functional analysis' (± 1975)

Interpret dynamics of N-particle system $\{x_1(t),\ldots,x_N(t)\}$ as a 'path' of a single particle in an N-dimensional 'world'

target:

generating functional

$$\mathcal{Z}[\psi] = \langle\langle e^{i\int_0^t ds \sum_{i=1}^N \psi_i(s)x_i(s)}\rangle_{\rm paths}\rangle_{\rm disorder}$$



'generates' all relevant macroscopic multiple-time observables via (functional) differentiation

e.g.

$$\langle\langle x_i(t)\rangle_{\rm paths}\rangle_{\rm disorder} = -i\lim_{\psi\to 0}\frac{\delta\mathcal{Z}[\psi]}{\delta\psi_i(t)}$$

$$\langle\langle x_i(t)x_j(t')\rangle_{\rm paths}\rangle_{\rm disorder} = -\lim_{\psi\to 0}\frac{\delta^2\mathcal{Z}[\psi]}{\delta\psi_i(t)\delta\psi_j(t')}$$

- *theory involving ‘path-integrals’*
- *disordered system* $\Rightarrow$ *one non-disordered ‘effective’ component*
- *new forces: non-trivial noise, retarded self-interaction (component ‘remembers’ its history)*
- *closed laws for e.g. covariance and response functions:*

$$C(t,t') = \frac{1}{N}\sum_{i=1}^{N}\langle\langle x_i(t)x_i(t')\rangle_{\rm paths}\rangle_{\rm disorder}$$

$$G(t,t') = \frac{1}{N}\sum_{i=1}^{N}\langle\langle \frac{\delta x_i(t)}{\delta x_i(t')}\rangle_{\rm paths}\rangle_{\rm disorder}$$