Statistical Mechanics of Signaling Processes on Complex Biological Networks

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with

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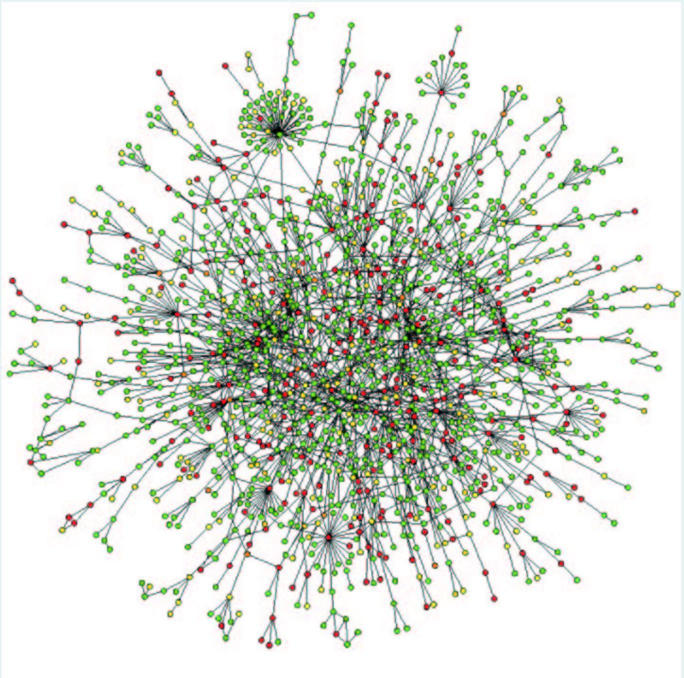


OVERVIEW

Stochastic processes on large networks in biology

interacting cells *(neural & immune networks)*
interacting proteins *(proteomic networks)*
interacting genes *(gene regulation networks)*

Complex networks – definitions, characterization

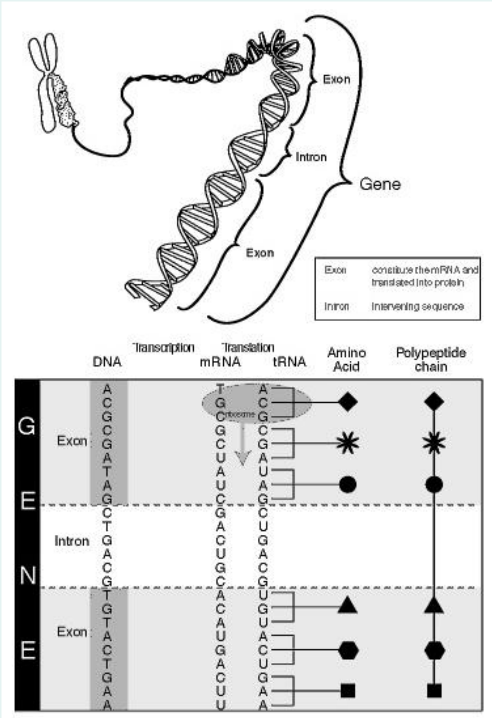
random graphs, degree distribution
small-world networks
scale-free networks

Theory of processes on large complex networks

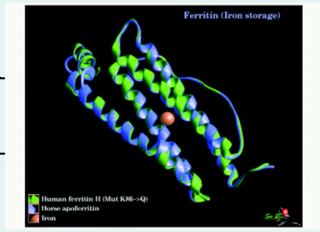
methods and their applicability
statics – finite connectivity replica theory
dynamics – generating functional analysis
dynamics – dynamical replica & cavity techniques

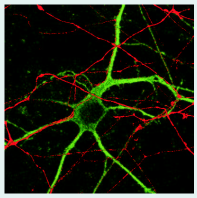
PROCESSES ON LARGE NETWORKS IN BIOLOGY

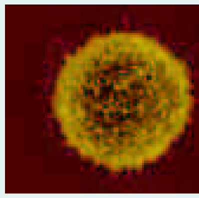
networks: defined functionally, by interaction partners

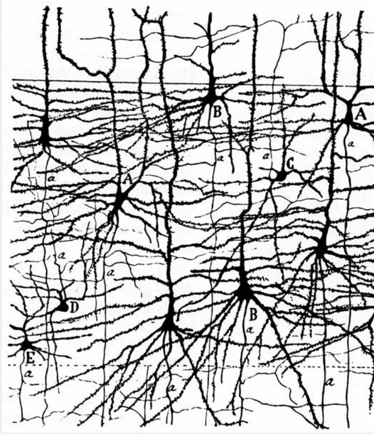


- *gene level*
- *protein level*
- *cell level*









NEURAL NETWORKS

Dense networks of $\sim\ 10^4 - 10^8$ *brain cells (neurons)*
connected via electro-chemical terminals (synapses)

models

$$J_{ij} = c_{ij} K_{ij} \qquad \begin{cases} c_{ij} \in \{1,0\} & \text{bond } j \to i \text{ present/absent (architecture)} \\ K_{ij} \in \mathbb{R} & \text{strength \& type of bond} \end{cases}$$

- *binary variables* $\sigma_i = \pm 1$,
  reacting to incoming signals V_i

$$\sigma_i(t+1) = \text{sgn}\Big[\sum_j J_{ij}\sigma_j(t) + \theta_i + \eta_i(t)\Big]$$

  $\eta_i(t)$: *noise*

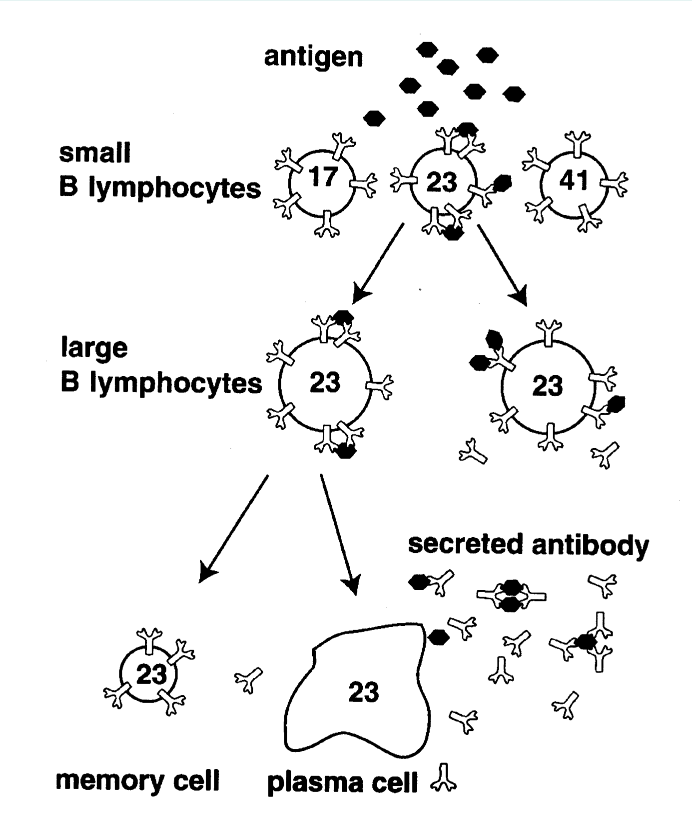
- *neuron voltages* V_i

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

- *coupled oscillators, phases* ϕ_i

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

IMMUNE NETWORKS



the enemy:

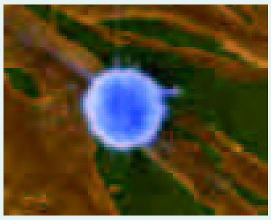
invaders, abnormal cells (antigens)

the defense:

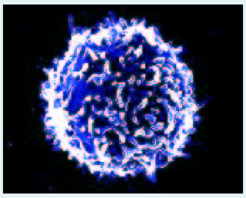
lymphocytes (white blood cells)

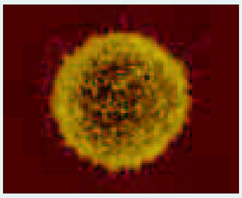
B-cells: secrete tags (antibodies)
helper T-cells: assist B-cells
cytotoxic T-cells: cell killers

phagocytic cells: vacuum cleaners
(eat anything tagged ...)

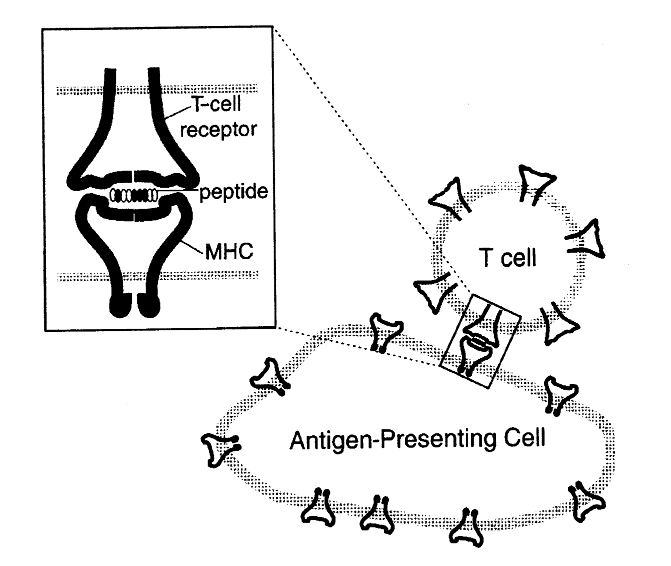


Lymphocytes recognize
surface shapes *of antigens*





- *each lymphocyte has surface receptors of a specific type*
- *antigen binding to receptor triggers the lymphocyte into reproducing*
- *shapes of encountered antigens are memorized*
- *recognize as many shapes as possible but* **not** *healthy self molecules ...*



models of the immune system:

dynamics of concentrations of many different competing cell types

How is memory achieved in the immune system?

Jerne (1974): network models of the immune system
Varela et al (1991): 2nd generation immune network theory

$$\frac{d}{dt}f_i = -K_1 f_i h_i - K_2 f_i + K_3 b_i M(h_i) + \text{ noise}$$
$$\frac{d}{dt}b_i = -K_4 b_i + K_5 b_i P(h_i) + K_6 + \text{ noise}$$

$$h_i = \sum_j c_{ij} f_j + \theta_i \quad \text{`activation' of clone } i$$

f_i : concentration of antibody (idio)type i
b_i : concentration of B−cell (idio)type i
θ_i : concentration of antigen type i
$M(.),\ P(.)$: nonnegative bell−shaped functions

single-clone stationary states:

- *non-suppressed clone:* $h_i \ll 1,\ f_i \sim 1$
- *suppressed clone:* $h_i \gg 1,\ f_i \sim 0$

net result:

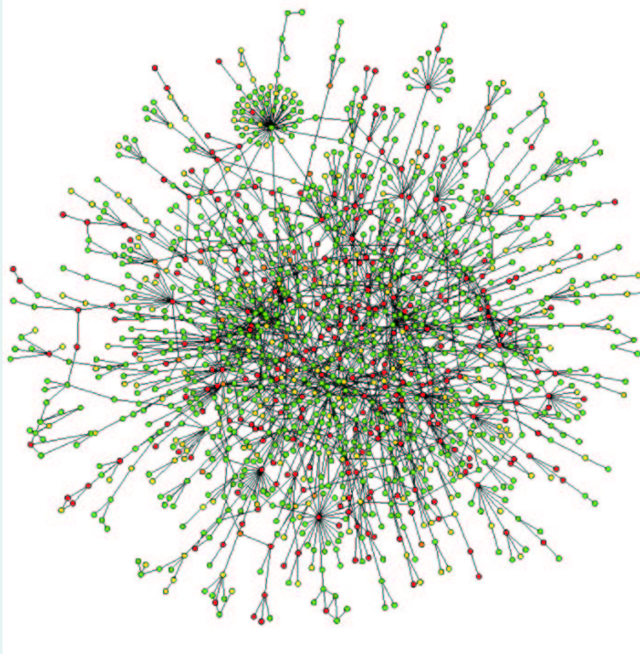
- *network of antibody clones with negative mutual interactions*
- *clone-anticlone pairs support stable* $(\uparrow,\downarrow)$ *and* $(\downarrow,\uparrow)$ *states*

GENE REGULATION & PROTEOMIC NETWORKS

protein interaction networks

('yeast two-hybrid method')

nodes: protein species
links: direct physical pair-interaction



simple models:

f_i: *concentration of i-th protein type*

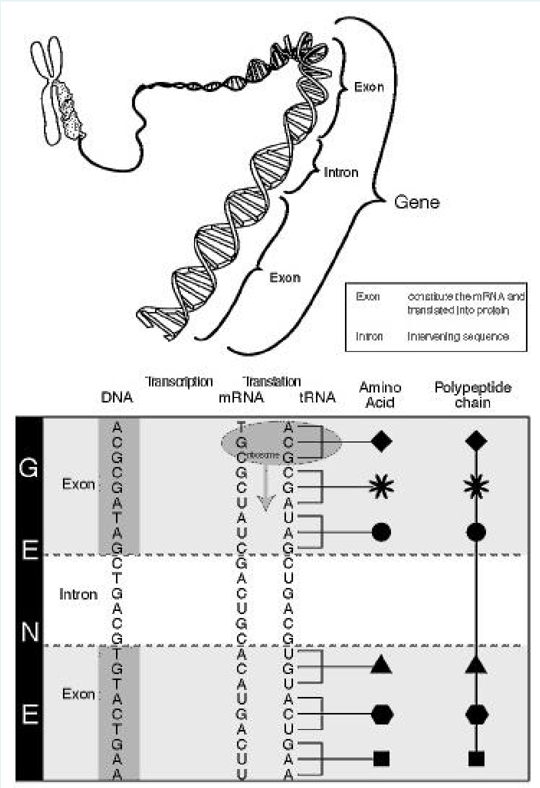
$$\frac{d}{dt}f_i = \sum_j J_{ij}f_j + \sum_{jk} J_{ijk\ell}f_j f_k + \sum_{jk\ell} J_{ijk\ell}f_j f_k f_\ell + \ldots$$

in addition:

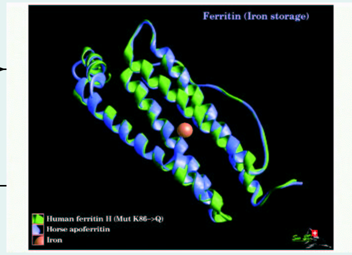
- *indirect interactions via regulation of gene expression*
- *conformation changes of proteins*
- *spatial effects (localized proteins, diffusion, ...)*
- *conservation laws*
- *functional versus actual interactions*

Gene regulation networks

Initial objective: understand and explain cell differentiation



- *gene expression:*
  conversion of information into protein production
- *expression level of a gene:*
  controlled by specific proteins
- *protein concentrations controlled by:*
  other proteins, other expressed genes, external stimuli



Models of Gene Regulation Networks:

- *basic variables are expression levels of genes (e.g. on/off)*
- *replace genes→proteins→genes feedback loop*
  by effective gene→gene interactions

The Kauffman model (1969)

$$N \text{ Boolean genes}: \quad \begin{cases} \sigma_i = 0 & \text{gene } i \text{ switched off} \\ \sigma_i = 1 & \text{gene } i \text{ switched on} \end{cases}$$

dynamics:

$$\sigma_i(t+1) = \mathcal{F}_i[\sigma_{j_1(i)}(t), \ldots, \sigma_{j_k(i)}(t)]$$

each i:

$$j_1(i), \ldots, j_k(i) \qquad \text{drawn randomly from } \{1, \ldots, N\}$$

$$\mathcal{F}_i : \{0,1\}^k \to \{0,1\} \qquad \text{random function, } \operatorname{Prob}(\mathcal{F} = 0) = p$$

- *critical connectivity:* $k_c = [2p(1-p)]^{-1}$
- $k < k_c$*: frozen phase (trajectories end in fixed-points)*
- $k > k_c$*: chaotic phase (limit cycles, diverging trajectories)*
- *number, length of attractors? dependence on* N*?*

COMPLEX NETWORKS

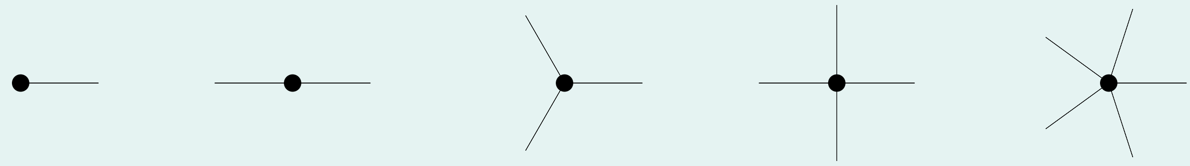
Networks – definition and characterization

⋆ *nodes and links:*

nodes : $i = 1, \ldots, N$

links : $c_{ij} \in \{0, 1\}$ $\quad$ $c_{ij} = 1$: link $j \to i$ present; $c_{ij} = 0$: link $j \to i$ absent

⋆ *degree k of a node:*
total nr of links to that node



$k = 1$ $\qquad$ $k = 2$ $\qquad$ $k = 3$ $\qquad$ $k = 4$ $\qquad$ $k = 5$

⋆ *degree distribution $P(k)$:*
histogram of the N degrees $\{k_1, k_2, \ldots, k_N\}$

average connectivity:

$$c = \frac{1}{N}\sum_{i=1}^{N} k_i = \sum_{k \geq 0} P(k)k$$

⋆ *clustering coefficient of node i:*

$$C_i = \frac{\text{actual nr of links amongst the } k_i \text{ neighbours of } i}{\text{possible nr of links amongst the } k_i \text{ neighbours of } i}$$

⋆ *distance between nodes* (i,j)*:* ℓ_{ij}
length of the shortest path connecting nodes (i,j)

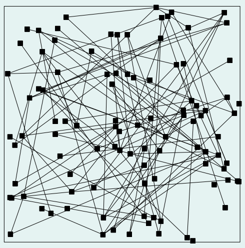
distance distribution $\Pi(\ell)$*: histogram of distances* ℓ_{ij}

mean path-length:

$$\overline{\ell} = \sum_{\ell \geq 0} \Pi(\ell)\ell$$

Examples

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

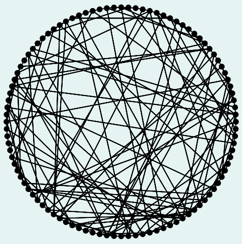


k_i random for all i

N large : $\quad P(k) = c^k e^{-c}/k! \qquad c = \sum_{k\geq 0} P(k)k$

$$\overline{\ell} \sim \log(N)$$

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



e.g. connect nearest neigbours on a ring
+
Poissonnian random graph

'small world effect':

due to even very small *number of random links*
(i) reduction of distances: $\overline{\ell} \sim \mathcal{O}(N) \ \rightarrow \ \overline{\ell} \sim \mathcal{O}(\log N)$
(ii) greater robustness of processes against noise

complex network *(definition in a nutshell)*

Simple network:

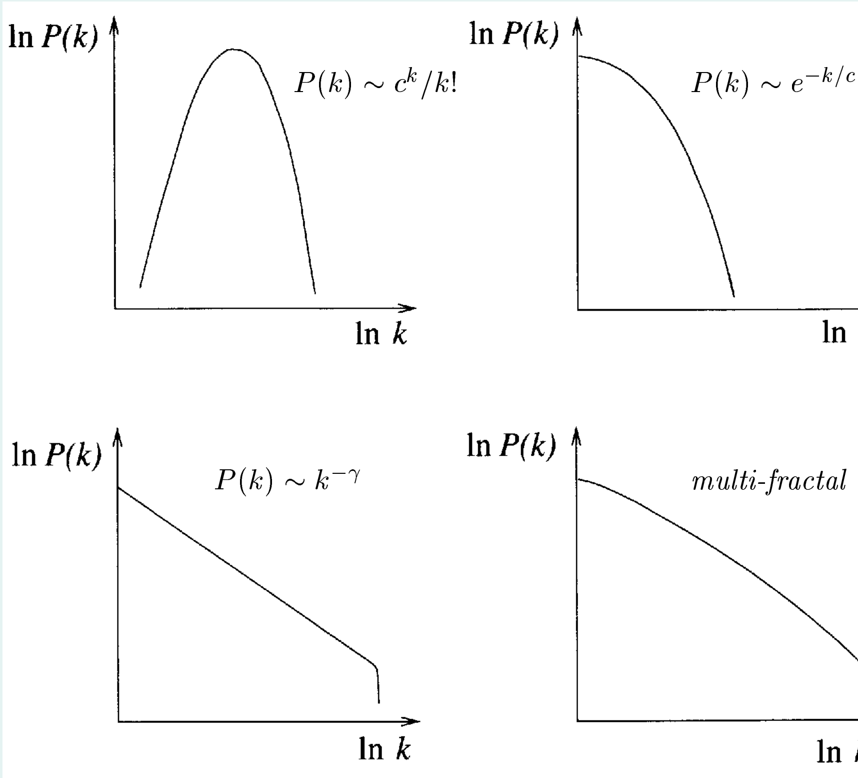
- *degree distribution $P(k)$ decays faster than power law*
- *clustering coeff C_i independent of degrees k_i*
- *conventional path lengths $\overline{\ell} \sim \log(N)$*

Complex ('scale-free') network:

- *degree distribution $P(k)$ decays according to power law*
- *clustering coeff C_i positively correlated with degrees k_i*
- *shorter path lengths*

simple:

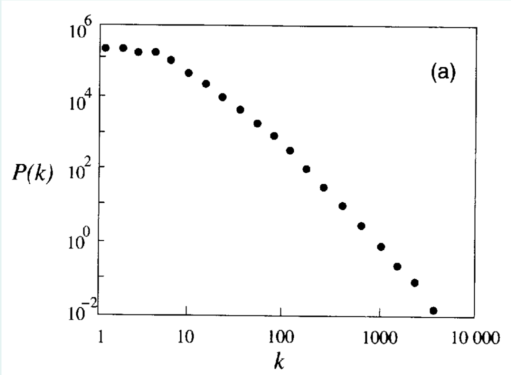
complex:



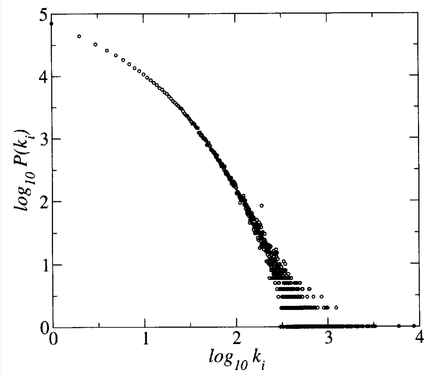
mechanism:
growth with preferential attachment

Social networks

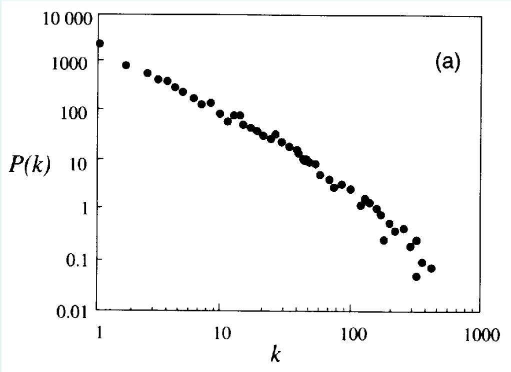
author networks:



citation networks:

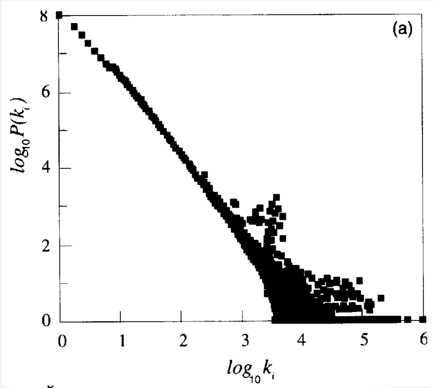


E-mail networks:

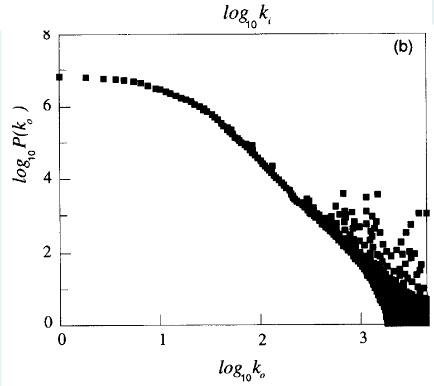


Internet

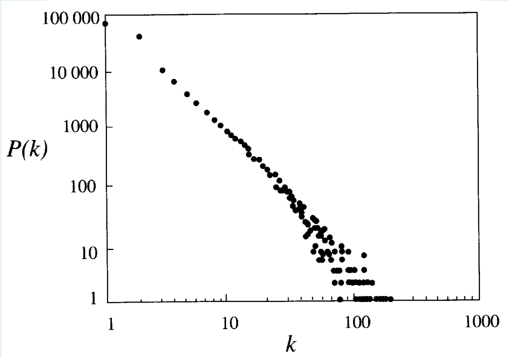
WWW in-links:



WWW out-links:

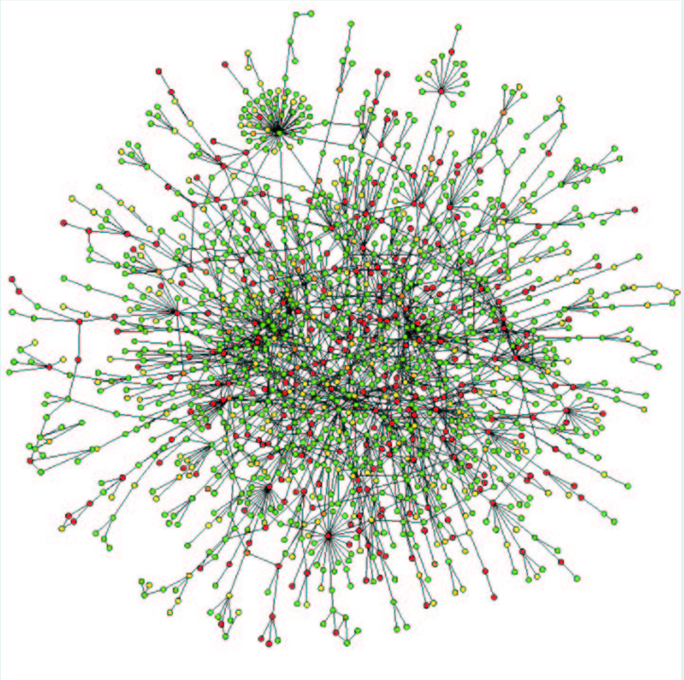


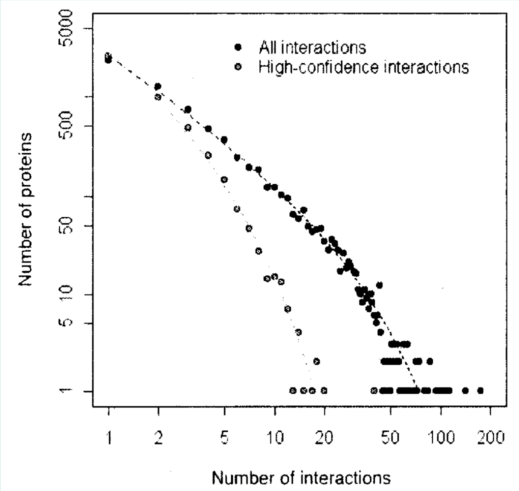
WWW routers:

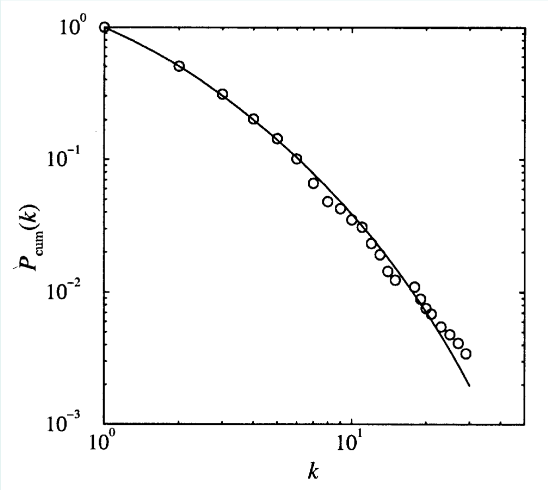


Protein interaction networks

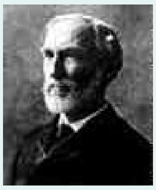
(yeast two-hybrid method)







Theory of many-particle systems: 'statistical mechanics'

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* (± 1870)

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

E : energy
T : temperature

e.g.

molecules	$\longrightarrow$	*pressure/temp/volume phase diagrams, gas-liquid-solid transitions*
atomic electrons	$\longrightarrow$	*magnetism (ferro, anti-ferro, para)*
cells in suspensions	$\longrightarrow$	*blood rheology, visco-elastic properties*

- *non-equilibrium* (± 1905)
- *statistical mechanics of disordered (or complex) systems*

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

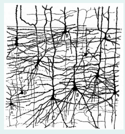
Applicability of statistical mechanics – how large is large?

stat mech: finds macroscopic laws for $N \to \infty$
effects of finite N *on macroscopic quantities:*

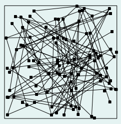
- *fluctuations around 'infinite system' values:* $\Delta x/x \sim 1/\sqrt{N}$
- *'escape' time from 'infinite system' trajectories:* $t_{\rm esc} \sim e^N \tau$
  (τ*: typical microscopic time scale)*

Example: $\tau \sim 10^{-15}$ *sec,* $N = 1000$ $\Delta x/x \sim 0.03$, $t_{\rm esc} \sim 10^{400}$ sec

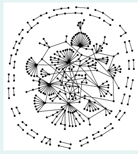
- **neural networks***:*
  $N \sim 10^4$-10^8, $\langle k\rangle \sim 10^2$-$10^4$
  random (hippocampus) to regular (cerebellum)



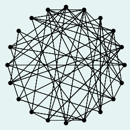
- **immune networks***:*
  $N \sim 10^6$-10^7, $\langle k\rangle \sim$ *small ?*
  narrow distribution $P(k)$ *?*



- **protein interaction networks***:*
  $N \sim 10^4$, $\langle k\rangle \sim 2-7$ *?*
  scale-free, complex ('hub' proteins, etc)



- **gene regulation networks***:*
  $N \sim 10^4$, $\langle k\rangle \sim$ 1-10?
  structure? complexity?



ANALYSIS OF STOCHASTIC PROCESSES ON LARGE RANDOM NETWORKS

state-of-the-art in statistical mechanics

Equilibrium methods

	asymmetric	*partially symm*	*symmetric*
$\langle k \rangle \sim N$	–	–	*ok*
$1 \ll \langle k \rangle \ll N$	–	–	*ok*
$\langle k \rangle \sim 1$	–	–	*hard*

Dynamical methods

	asymmetric	*partially symm*	*symmetric*
$\langle k \rangle \sim N$	*ok*	*hard*	*hard*
$1 \ll \langle k \rangle \ll N$	*ok*	*hard*	*hard*
$\langle k \rangle \sim 1$	*ok*	–/*hard*	–/*hard*

mundane definition of complexity, at the workfloor level ...
(for those who study stochastic processes on networks)

Simple network:
connectivity $\langle k \rangle$ *diverges as* $N \to \infty$

Complex network:
connectivity $\langle k \rangle$ *does not grow with* N

The language of disordered systems theory

core problem: carrying out disorder averages
of macroscopic ensemble averages

replica trick/method
(Hardy & Littlewood, 1934)

statics: ±1975
dynamics: ±1993

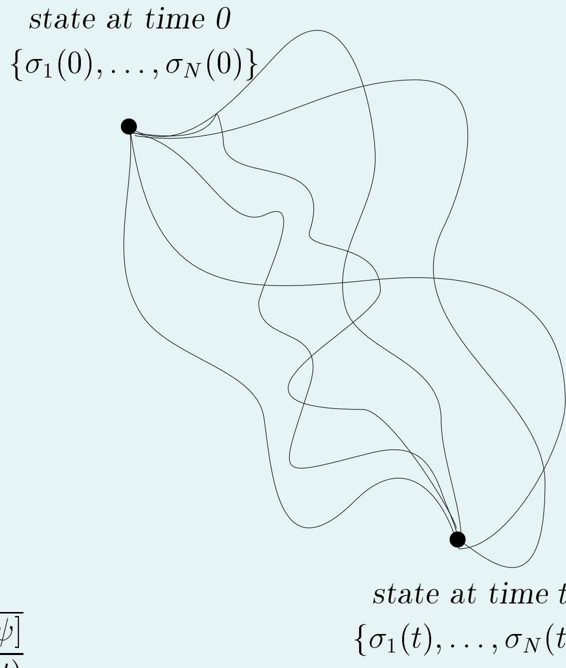
$$
\begin{aligned}
\left\langle \sum_x f(x,\mathrm{dis}) P(x|y,\mathrm{dis}) \right\rangle_{\mathrm{dis}} &= \left\langle \frac{\sum_x f(x,\mathrm{dis}) P(x,y|\mathrm{dis})}{\sum_x P(x,y|\mathrm{dis})} \right\rangle_{\mathrm{dis}} \\
&= \lim_{n\to 0} \left\langle \sum_x f(x,\mathrm{dis}) P(x,y|\mathrm{dis}) \left[\sum_{x'} P(x',y|\mathrm{dis}) \right]^{n-1} \right\rangle_{\mathrm{dis}} \\
&= \lim_{n\to 0} \sum_{x_1,\ldots,x_n} \langle f(x_1,\mathrm{dis}) P(x_1,y|\mathrm{dis}) \ldots P(x_n,y|\mathrm{dis}) \rangle_{\mathrm{dis}}
\end{aligned}
$$

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: at the end $n \rightarrow 0$!*

Dynamics: generating functional analysis

Interpret dynamics of N-particle system $\{\sigma_1(t), \ldots, \sigma_N(t)\}$ as a 'path' of a single particle in an N-dimensional 'world'



target:
generating functional

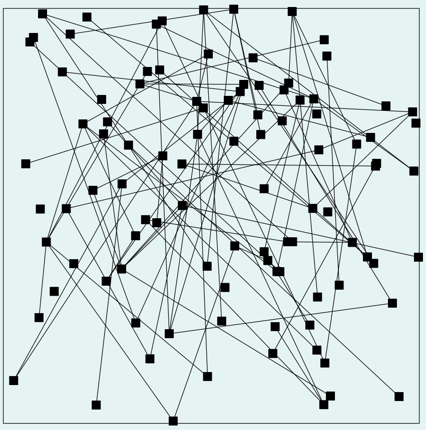
$$\overline{\mathcal{Z}[\psi]} = \langle\langle e^{i\int_0^t ds \sum_{i=1}^N \psi_i(s)\sigma_i(s)} \rangle_{\text{paths}}\rangle_{\text{disorder}}$$

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

$$\begin{aligned}
\langle\langle \sigma_i(t)\rangle_{\text{paths}}\rangle_{\text{disorder}} &= -i \lim_{\psi\to 0} \frac{\delta \overline{\mathcal{Z}[\psi]}}{\delta\psi_i(t)} \\
\langle\langle \sigma_i(t)\sigma_j(t')\rangle_{\text{paths}}\rangle_{\text{disorder}} &= -\lim_{\psi\to 0} \frac{\delta^2 \overline{\mathcal{Z}[\psi]}}{\delta\psi_i(t)\delta\psi_j(t')}
\end{aligned}$$

- *theory involving 'path-integrals'*
- *disordered system → non-disordered 'effective' particle*
- *new forces: non-trivial noise, retarded self-interaction*

FINITE CONNECTIVITY STATICS



$N = 100,\ c = 2$

N spins on random graph, $c_{ij} \in \{0, 1\}$

$$H = -\sum_{i<j} c_{ij} J_{ij} \sigma_i \sigma_j + \sum_i V(\sigma_i)$$

- $P(c_{ij}) = \frac{c}{N}\delta_{c_{ij},1} + (1 - \frac{c}{N})\delta_{c_{ij},0}, \quad c = \mathcal{O}(N^0)$
- *indep random bonds* J_{ij}
- *disorder:* $\{c_{ij}, J_{ij}\}$

Replica theory order parameters

Dependence on connectivity c
(average number of bonds/spin)

connectivity	*variables*	*order param*	*RS ansatz*
$c = N$	*discrete*	$\{q_{\alpha\beta}\}$	*numbers, e.g.* q
$c = N$	*continuous*	$\{q_{\alpha\beta}\}$	*numbers, e.g.* q
$1 \ll c \ll N$	*discrete*	$\{q_{\alpha\beta}\}$	*numbers, e.g.* q
$1 \ll c \ll N$	*continuous*	$\{q_{\alpha\beta}\}$	*numbers, e.g.* q
$c = \mathcal{O}(1)$	*discrete*	$P(\sigma_1, \ldots, \sigma_n)$	*functions,* $P(h)$
$c = \mathcal{O}(1)$	*continuous*	$P(\sigma_1, \ldots, \sigma_n)$	*functionals,* $W[\{P\}]$

CASE STUDY – STATICS

N Kuramoto-type oscillators,
$\phi_i \in [0, 2\pi]$, $\boldsymbol{\phi} = (\phi_1, \ldots, \phi_N)$

$$H(\boldsymbol{\phi}) = -J \sum_{i<j} c_{ij} \cos(\phi_i - \phi_j - \omega_{ij}), \qquad J > 0$$

- *network connectivity: random variables* $c_{ij} \in \{0, 1\}$
  finite connectivity regime: $k_i = \sum_j c_{ij} = \mathcal{O}(N^0)$
  degree distribution: $p_k = N^{-1} \sum_i \delta_{k,k_i}$

  $$P(c_{ij}) = \frac{c}{N}\delta_{c_{ij},1} + (1 - \frac{c}{N})\delta_{c_{ij},0} \quad \text{for all} \ \ i < j$$

  $c = \mathcal{O}(N^0)$

  $p_k = e^{-c}c^k/k!$ *for* $N \to \infty$

- *random interactions between oscillators:* $\omega_{ij} \in [0, 2\pi]$
  independently drawn from $P(\omega)$*, with* $P(-\omega) = P(\omega)$
  e.g.

  $$\begin{array}{lll} \omega_{ij} = 0 & \rightarrow & \text{synchronization of oscillators } (i,j) \\ \omega_{ij} = \pi & \rightarrow & \text{antisynchronization of oscillators } (i,j) \end{array}$$

Strategy

- *calculate disorder-averaged free energy per oscillator*

$$\overline{f} = -\lim_{N\to\infty} (\beta N)^{-1}\overline{\log Z}, \qquad Z = \int d\boldsymbol{\phi}\; e^{-\beta H(\boldsymbol{\phi})}$$

  $\overline{\cdots}$: *average over* $\{c_{ij}, \omega_{ij}\}$

- *use replica identity*

$$\overline{\log Z} = \lim_{n\to 0} n^{-1} \log \overline{Z^n}$$

- *evaluate* $\overline{Z^n}$ *for integer* n*, in terms of* n *system copies, and evaluate disorder average first:*

$$\overline{Z^n} \;=\; \int d\boldsymbol{\phi}^1 \ldots d\boldsymbol{\phi}^n \overline{e^{-\beta\sum_{\alpha=1}^n H(\boldsymbol{\phi}^\alpha)}}$$

- *In result:*
  exchange the limits $N \to \infty$ *and* $n \to 0$

$$\begin{aligned}
\overline{f} &= -\lim_{N\to\infty} (\beta N)^{-1}\overline{\log Z} \\
&= -\lim_{N\to\infty} (\beta N)^{-1} \lim_{n\to 0} n^{-1} \log \overline{Z^n} \\
&= -\lim_{N\to\infty} (\beta N)^{-1} \lim_{n\to 0} n^{-1} \log \int d\boldsymbol{\phi}^1 \ldots d\boldsymbol{\phi}^n \overline{e^{-\beta\sum_{\alpha=1}^n H(\boldsymbol{\phi}^\alpha)}} \\
&= \lim_{n\to 0} n^{-1} \left\{ -\lim_{N\to\infty} (\beta N)^{-1} \log \int d\boldsymbol{\phi}^1 \ldots d\boldsymbol{\phi}^n \overline{e^{-\beta\sum_{\alpha=1}^n H(\boldsymbol{\phi}^\alpha)}} \right\}
\end{aligned}$$

Replica calculation of the disorder-averaged free energy

Disorder-averaged free energy per oscillator:

$$\overline{f} = \lim_{n\to 0}\frac{1}{n}\left\{-\lim_{N\to\infty}\frac{1}{\beta N}\log\int d\boldsymbol{\phi}^1\ldots d\boldsymbol{\phi}^n\overline{e^{-\beta\sum_{\alpha=1}^n H(\boldsymbol{\phi}^\alpha)}}\right\}$$

Disorder average:

$$\overline{e^{-\beta\sum_{\alpha=1}^n H(\boldsymbol{\phi}^\alpha)}} = \prod_{i<j}\overline{e^{\beta J\sum_{\alpha=1}^n c_{ij}\cos(\phi_i^\alpha-\phi_j^\alpha-\omega_{ij})}}$$

$$= \exp\left\{\frac{c}{2N}\sum_{ij}\left[\int d\omega\ P(\omega)e^{\beta J\sum_{\alpha=1}^n\cos(\phi_i^\alpha-\phi_j^\alpha-\omega)}-1\right]+\mathcal{O}(N^0)\right\}$$

replica-order parameter:
$\boldsymbol{\phi}=(\phi_1,\ldots,\phi_n)$, $\boldsymbol{\phi}_i=(\phi_i^1,\ldots,\phi_i^n)$

$$P(\boldsymbol{\phi})=\frac{1}{N}\sum_i\delta[\boldsymbol{\phi}-\boldsymbol{\phi}_i]$$

$$\overline{e^{-\beta\sum_{\alpha=1}^n H(\boldsymbol{\phi}^\alpha)}} = \exp\left\{\frac{cN}{2}\int d\boldsymbol{\phi}d\boldsymbol{\phi}'P(\boldsymbol{\phi})P(\boldsymbol{\phi}')\left[\int d\omega\ P(\omega)e^{\beta J\sum_\alpha\cos(\phi_\alpha-\phi'_\alpha-\omega)}-1\right]+\mathcal{O}(N^0)\right\}$$

minor technicalities

- *discretize domain* $[0, 2\pi]^n$ *of* $\boldsymbol{\phi}$
- *insert appropriate functional* δ*-distributions*
  to isolate order parameter function $P(\boldsymbol{\phi})$
  integral representations: conjugate functions $\hat{P}(\boldsymbol{\phi})$
- *take continuum limit for domain* $[0, 2\pi]^n$ *of* $\boldsymbol{\phi}$,
  gives path integral measure:

$$\prod_{\boldsymbol{\phi}}[dP(\boldsymbol{\phi})d\hat{P}(\boldsymbol{\phi})/2\pi] = \{dPd\hat{P}\}$$

$$\begin{aligned}\overline{f} \;\; = \;\; & -\lim_{n\to 0}\lim_{N\to\infty}\frac{1}{\beta Nn}\log\int\{dPd\hat{P}\}\; e^{iN\int d\boldsymbol{\phi}\;\; P(\boldsymbol{\phi})\hat{P}(\boldsymbol{\phi})+N\log\int d\boldsymbol{\phi}\;\; e^{-i\hat{P}(\boldsymbol{\phi})}} \\ & \times\exp\left\{\frac{cN}{2}\int d\boldsymbol{\phi}d\boldsymbol{\phi}' P(\boldsymbol{\phi})P(\boldsymbol{\phi}')\Big[\int d\omega\;\; P(\omega)e^{\beta J\sum_\alpha \cos(\phi_\alpha-\phi'_\alpha-\omega)}-1\Big]\right\}\end{aligned}$$

$N \to \infty$*:*

$$\begin{aligned}\overline{f} \;\; = \;\; & -\lim_{n\to 0}\frac{1}{\beta n}\text{extr}_{\{P,\hat{P}\}}\Big\{i\int d\boldsymbol{\phi}\;\; P(\boldsymbol{\phi})\hat{P}(\boldsymbol{\phi})+\log\int d\boldsymbol{\phi}\;\; e^{-i\hat{P}(\boldsymbol{\phi})} \\ & +\frac{1}{2}c\int d\boldsymbol{\phi}d\boldsymbol{\phi}' P(\boldsymbol{\phi})P(\boldsymbol{\phi}')\Big[\int d\omega\;\; P(\omega)e^{\beta J\sum_\alpha \cos(\phi_\alpha-\phi'_\alpha-\omega)}-1\Big]\Big\}\end{aligned}$$

saddle-point eqns:

$$P(\boldsymbol{\phi}) = \frac{e^{c\int d\boldsymbol{\phi}'\, P(\boldsymbol{\phi}')[\int d\omega\;\; P(\omega)e^{\beta J\sum_\alpha \cos(\phi_\alpha-\phi'_\alpha-\omega)}-1]}}{\int d\boldsymbol{\phi}' e^{c\int d\boldsymbol{\phi}''\;\; P(\boldsymbol{\phi}'')[\int d\omega\;\; P(\omega)e^{\beta J\sum_\alpha \cos(\phi'_\alpha-\phi''_\alpha-\omega)}-1]}}$$

Replica symmetric theory

$$P(\phi_1,\ldots,\phi_n) = \frac{1}{N}\sum_i \prod_{\alpha=1}^{n} \delta[\phi_\alpha - \phi_i^\alpha]$$

next:
limit $n \to 0$ in saddle-point eqns
RS ansatz for continuous variables?

$$P_{\rm RS}(\phi_1,\ldots,\phi_n) = \int \{dP\}\ W[\{P\}]\ \prod_\alpha P(\phi_\alpha)$$

RS order parameter:

functional measure $W[\{P\}]$

interpretation:

$$\int \{dP\}\ W[\{P\}] \prod_\alpha \left[\int d\phi\ P(\phi) f_\alpha(\phi)\right] = \lim_{N\to\infty} \frac{1}{N}\sum_i \overline{\prod_\alpha \langle f_\alpha(\phi_i)\rangle}$$

RS saddle-point eqns:

$$\begin{aligned} W[\{P\}] \ &= \ \sum_{k\geq 0} \frac{e^{-c}c^k}{k!} \int \prod_{\ell\leq k} [\{dP_\ell\} W[\{P_\ell\}] d\omega_\ell P(\omega_\ell)] \\ &\quad \times \prod_{\phi\in[0,2\pi]} \delta\left[P(\phi) - \frac{\prod_{\ell=1}^k \int d\phi' P_\ell(\phi') e^{\beta J\cos(\phi-\phi'-\omega_\ell)}}{\int d\phi'' \prod_{\ell=1}^k \int d\phi' P_\ell(\phi') e^{\beta J \cos(\phi''-\phi'-\omega_\ell)}}\right] \end{aligned}$$

PHASE DIAGRAMS

bifurcation analysis of order parameter eqn:

$$W[\{P\}] = \sum_{k\geq 0} p_k \int \prod_{\ell\leq k} [\{dP_\ell\} W[\{P_\ell\}] d\omega_\ell P(\omega_\ell)]$$
$$\times \prod_{\phi\in[0,2\pi]} \delta\left[P(\phi) - \frac{\prod_{\ell=1}^k \int d\phi' P_\ell(\phi') e^{\beta J\cos(\phi-\phi'-\omega_\ell)}}{\int d\phi'' \prod_{\ell=1}^k \int d\phi' P_\ell(\phi') e^{\beta J\cos(\phi''-\phi'-\omega_\ell)}}\right]$$

$\beta = 0$:

$$\text{paramagnetic state}: \quad W[\{P\}] = \prod_{\phi\in[0,2\pi]} \delta\left[P(\phi) - \frac{1}{2\pi}\right]$$

phase transitions

Continuous bifurcations away from paramagnetic state located by Guzai (i.e. functional moment) expansion

- *transform:*

$$P(\phi) \to \frac{1}{2\pi} + \Delta(\phi), \qquad \int_0^{2\pi} d\phi\ \Delta(\phi) = 0, \qquad W[\{P\}] \to \tilde{W}[\{\Delta\}]$$

- *expand saddle-point eqns in functional moments*

$$\int \{d\Delta\} \tilde{W}[\{\Delta\}] \Delta(\phi_1)\ldots\Delta(\phi_r)$$

- *assume: close to continuous bifurcation $\exists \epsilon \ll 1$ such that*

$$\int \{d\Delta\} \tilde{W}[\{\Delta\}] \Delta(\phi_1)\ldots\Delta(\phi_r) = \mathcal{O}(\epsilon^r)$$

Lowest order bifurcation ϵ^1

$$\Psi(\phi) = \frac{c}{2\pi I_0(\beta J)} \int_0^{2\pi} d\phi' \int d\omega \; P(\omega) e^{\beta J \cos(\phi - \phi' - \omega)} \Psi(\phi') \qquad \int_0^{2\pi} d\phi \; \Psi(\phi) = 0$$

$c = \sum_k p_k k$

$I_k(z)$: *modified Bessel functions*

- *solution: Fourier modes* $\Psi(\phi) = e^{ik\phi}$
  transition:
  $$c = \min_{k>0} \left\{ \frac{I_k(\beta J)}{I_0(\beta J)} \int_{-\pi}^{\pi} d\omega \; P(\omega) \cos(k\omega) \right\}^{-1}$$

- *bifurcating state:*
  $$\lim_{N\to\infty} \frac{1}{N} \sum_i \overline{\langle \begin{pmatrix} \cos(\phi_i) \\ \sin(\phi_i) \end{pmatrix} \rangle} \; = \; \frac{1}{2}\epsilon \; \delta_{k1} \begin{pmatrix} \cos(\lambda) \\ \sin(\lambda) \end{pmatrix} + \ldots$$

- $k = 1$: *global synchronization*
  $k > 1$: *no global synchronization*

$$\text{P} \to \text{F} : \qquad c = \left\{ \frac{I_1(\beta J)}{I_0(\beta J)} \int_{-\pi}^{\pi} d\omega \; P(\omega) \cos(\omega) \right\}^{-1}$$

$$\text{KT} : \qquad c = \min_{k>1} \left\{ \frac{I_k(\beta J)}{I_0(\beta J)} \int_{-\pi}^{\pi} d\omega \; P(\omega) \cos(k\omega) \right\}^{-1}$$

Lowest order bifurcation ϵ^2

$$\Psi(\phi_1,\phi_2) \;=\; c\int \frac{d\phi_1' d\phi_2'}{[2\pi I_0(\beta J)]^2}\left[\int d\omega\; P(\omega) e^{\beta J\cos(\phi_1-\phi_1'-\omega)+\beta J\cos(\phi_2-\phi_2'-\omega)}\right]\Psi(\phi_1',\phi_2')$$

$$\int d\phi_1\;\Psi(\phi_1,\phi_2)=\int d\phi_2\;\Psi(\phi_1,\phi_2)=0$$

- *solution: Fourier modes* $\Psi(\phi_1,\phi_2)=e^{i(k_1\phi_1+k_2\phi_2)}$
  transition:
  $$c=\min_{k_1\neq 0,\;k_2\neq 0}\left\{\frac{I_{k_1}(\beta J)I_{k_2}(\beta J)}{I_0^2(\beta J)}\int d\omega\;P(\omega)\cos[(k_1+k_2)\omega]\right\}^{-1}$$
  min: $k_1=-k_2=1$
  $$\mathrm{P}\to\mathrm{SG}:\qquad c=I_0^2(\beta J)/I_1^2(\beta J)$$

- *bifurcating state: no global synchronization, yet*
  $$\lim_{N\to\infty}\frac{1}{N}\sum_i\left[\overline{\langle\cos(\phi_i)\rangle^2}+\overline{\langle\sin(\phi_i)\rangle^2}\right]>0$$

- *P→SG bifurcation precedes P→KT*
  physical transitions away from P: *P→F, P→SG*

Phase diagrams

phases:

P: *paramagnetic state, no freezing of oscillator phases*

F: *synchronized state, coherent oscillations*

SG: *spin-glass state, frozen relative phases but incoherent*

transitions:

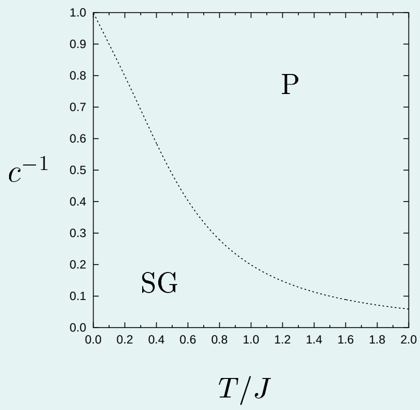
$$\mathrm{P} \rightarrow \mathrm{F}: \qquad c^{-1} = [I_1(\beta J)/I_0(\beta J)] \int_{-\pi}^{\pi} d\omega \; P(\omega) \cos(\omega)$$

$$\mathrm{P} \rightarrow \mathrm{SG}: \qquad c^{-1} = [I_1(\beta J)/I_0(\beta J)]^2$$

$$\mathrm{F} \rightarrow \mathrm{SG}: \qquad \text{cannot yet calculate, Parisi} - \text{Toulouse hypothesis ?}$$

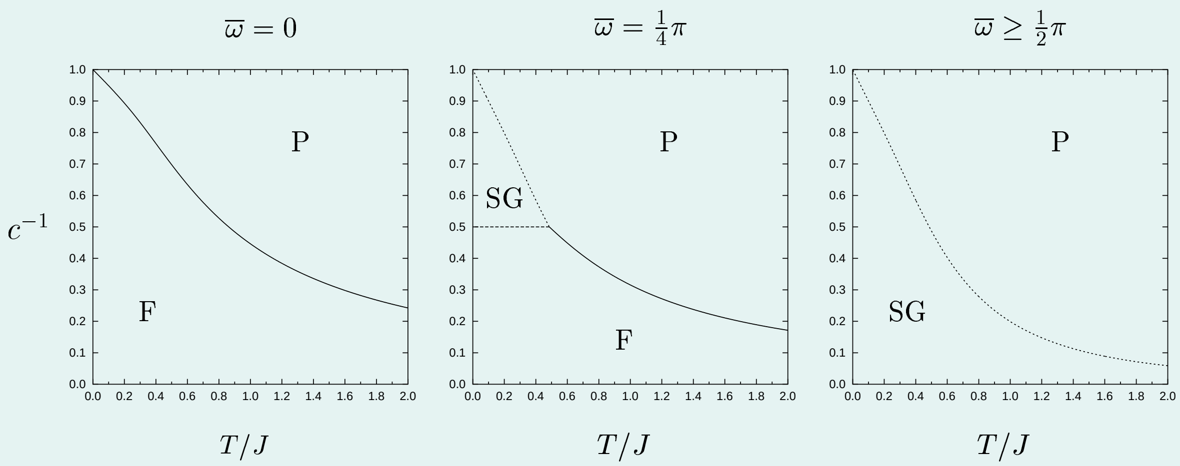
Example:

$P(\omega) = 1/2\pi$



Example:

$P(\omega) = \frac{1}{2}\delta(\omega - \overline{\omega}) + \frac{1}{2}\delta(\omega + \overline{\omega})$



THEORY VERSUS SIMULATIONS

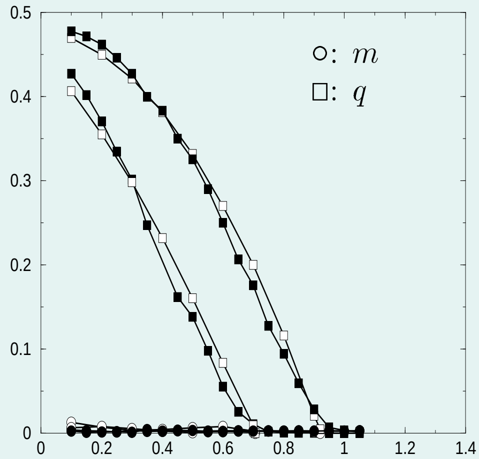
Numerical solution of order parameter equations (via truncated parametrizations) versus simulations

$$m^2 = \left[\frac{1}{N}\sum_i \overline{\langle\cos(\phi_i)\rangle}\right]^2 + \left[\frac{1}{N}\sum_i \overline{\langle\sin(\phi_i)\rangle}\right]^2$$

$$q = \frac{1}{2N}\sum_i \left[\overline{\langle\cos(\phi_i)\rangle^2} + \overline{\langle\sin(\phi_i)\rangle^2}\right]$$

P : $q = m = 0$
F : $q > 0,\ m > 0$
SG : $q > 0,\ m = 0$

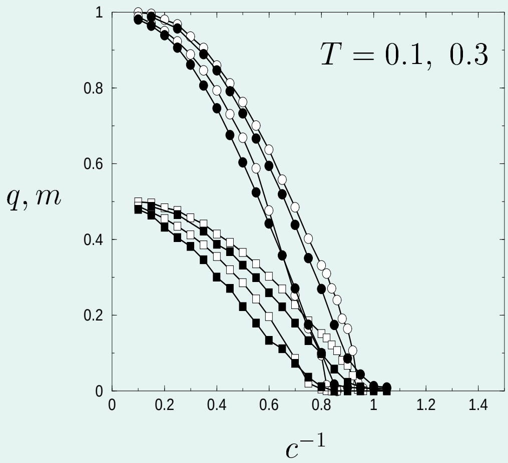
Example:
$P(\omega) = 1/2\pi$

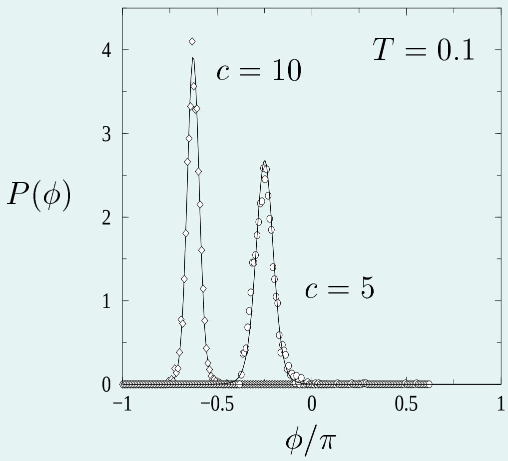


c^{-1}

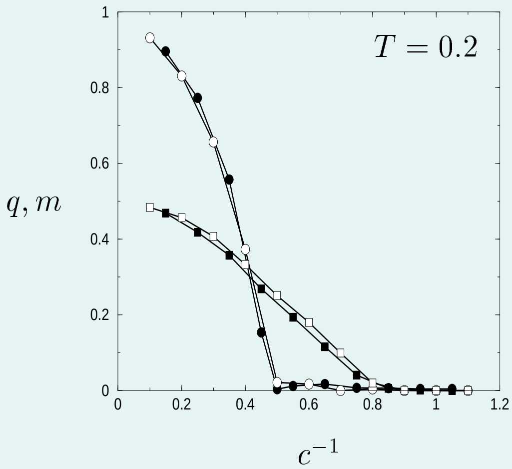
upper: $T = 0.1$
lower: $T = 0.3$

Example:
$P(\omega) = \delta(\omega)$

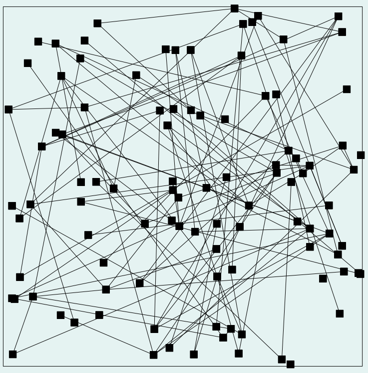




Example:
$P(\omega) = \frac{1}{2}\delta(\omega - \frac{\pi}{4}) + \frac{1}{2}\delta(\omega + \frac{\pi}{4})$



confirms Parisi-Toulouse for F→SG transition



Example: attractor neural networks on scale-free graphs

neurons: $\sigma_i \in \{-1, 1\}$

$$H = -\sum_{i<j} \sigma_i c_{ij} J_{ij} \sigma_j, \qquad J_{ij} = \frac{1}{\langle k \rangle} \phi\Big(\sum_{\mu=1}^{p} \xi_i^\mu \xi_j^\mu\Big)$$

p stored patterns: $(\xi_1^\mu, \ldots, \xi_N^\mu)$

$\phi(-x) = -\phi(x), \quad \phi(1) = 1$

e.g. Hopfield model on graph: $\phi(x) = x$

random graph:

$$\mathcal{P}(\boldsymbol{c}) = \frac{\Big[\prod_{i<j} \mathcal{P}(c_{ij})\ \delta_{c_{ij},c_{ji}}\Big]\Big[\prod_i \delta_{k_i, \sum_{j\neq i} c_{ij}}\Big]}{\sum_{\boldsymbol{c}'} \Big[\prod_{i<j} \mathcal{P}(c'_{ij})\ \delta_{c'_{ij},c'_{ji}}\Big]\Big[\prod_i \delta_{k_i, \sum_{j\neq i} c'_{ij}}\Big]}$$

$$\mathcal{P}(c_{ij}) = \frac{\langle k \rangle}{N} \delta_{c_{ij},1} + \Big(1 - \frac{\langle k \rangle}{N}\Big) \delta_{c_{ij},0}$$

degree distribution:

$$\lim_{N\to\infty} \frac{1}{N} \sum_i \delta_{k,k_i} = P(k)$$

Phase diagram

based on finite connectivity RS replica theory
& sublattice partitioning (for random patterns)

$$\mathrm{P} \to \mathrm{R}: \quad \frac{\langle k^2\rangle - \langle k\rangle}{\langle k\rangle} 2^{-p} \sum_{n=0}^{p} \binom{p}{n} (1 - \frac{2n}{p}) \tanh\Big[\frac{\beta\phi(p-2n)}{\langle k\rangle}\Big] = 1$$

$$\mathrm{P} \to \mathrm{SG}: \quad \frac{\langle k^2\rangle - \langle k\rangle}{\langle k\rangle} 2^{-p} \sum_{n=0}^{p} \binom{p}{n} \tanh^2\Big[\frac{\beta\phi(p-2n)}{\langle k\rangle}\Big] = 1$$

Noise resilience of scale-free networks

Single pattern retrieval phase boundary:

$$\beta_{\mathrm{crit}} = -\frac{\langle k\rangle}{2} \log\Big(1 - \frac{2\langle k\rangle}{\langle k^2\rangle}\Big)$$

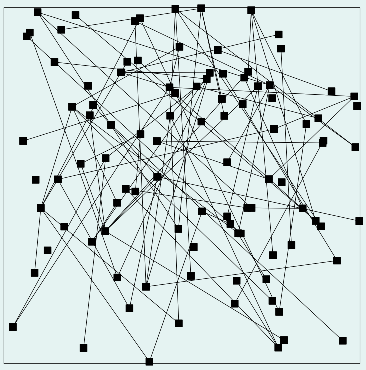
- *simple Poissonnian network* $P(k) = e^{-c} c^k / k!$:
  $\langle k\rangle = c, \quad \langle k^2\rangle = c^2 + c$

$$T_{\mathrm{crit}} = \frac{1}{2} c \log\Big(\frac{c+1}{c-1}\Big) \qquad \begin{array}{ll} c = 1: & T_{\mathrm{crit}} = 0 \\ c = 2: & T_{\mathrm{crit}} = 1/\log 3 \\ c \to \infty: & T_{\mathrm{crit}} = 1 \end{array}$$

- *scale-free network* $P(k) \sim k^{-\gamma}, \quad \gamma > 2$:
  if $\gamma \leq 3$: $\quad \langle k^2\rangle = \infty$

$$T_{\mathrm{crit}} = \infty, \quad \text{order at any noise level, for any } c > 0 \text{ !}$$

Example: parallel dynamics on finitely connected random graphs



finitely connected Ising model with parallel stochastic dynamics:

$$p_{t+1}(\boldsymbol{\sigma}) = \sum_{\boldsymbol{\sigma}'} W_t[\boldsymbol{\sigma};\boldsymbol{\sigma}']p_t(\boldsymbol{\sigma}')$$

$$W_t[\boldsymbol{\sigma};\boldsymbol{\sigma}'] = \prod_i \frac{e^{\beta\sigma_i h_i(\boldsymbol{\sigma}';t)}}{2\cosh[\beta h_i(\boldsymbol{\sigma}';t)]}$$

local fields:

$$h_i(\boldsymbol{\sigma};t) = \sum_{j\neq i} c_{ij}J_{ij}\sigma_j + \theta(t)$$

controlled symmetry:

$$i<j: \qquad \mathrm{Prob}(c_{ij}) = W(c_{ij})$$
$$i>j: \qquad \mathrm{Prob}(c_{ij}) = \epsilon_1\delta_{c_{ij},c_{ji}} + (1-\epsilon_1)W(c_{ij})$$

$$i<j: \qquad \mathrm{Prob}(J_{ij}) = P(J_{ij})$$
$$i>j: \qquad \mathrm{Prob}(J_{ij}) = \epsilon_2\delta[J_{ij}-J_{ji}] + (1-\epsilon_2)P(J_{ij})$$

$$W(x) = \frac{c}{N}\delta_{x,1} + (1-\frac{c}{N})\delta_{x,0} \qquad c = \mathcal{O}(N^0)$$

detailed balance & equil stat mech:

$$\epsilon_1 = \epsilon_2 = 1$$

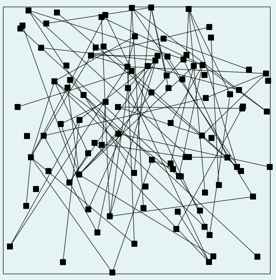
effective single spin problem

$P(\boldsymbol{\sigma}|\boldsymbol{\theta})$: *fraction of sites i which exhibit*
a single spin path $\boldsymbol{\sigma}=(\sigma(0),\sigma(1),\sigma(2),\ldots)$
given a field path $\boldsymbol{\theta}=(\theta(0),\theta(1),\ \theta(2),\ldots)$

$$
\begin{aligned}
P(\boldsymbol{\sigma}|\boldsymbol{\theta}) \;=\; & p_0(\sigma(0))e^{-c}\left\{\prod_t\left[\frac{e^{\beta\sigma(t+1)\theta(t)}}{2\cosh[\beta\theta(t)]}\right]+\sum_{k>0}\frac{c^k}{k!}\int dJ_1P(J_1)\ldots dJ_kP(J_k)\sum_{\boldsymbol{\sigma}'_1\ldots\boldsymbol{\sigma}'_k}\right. \\
& \times\prod_{\ell=1}^{k}\Big[(1-\epsilon_1)P(\boldsymbol{\sigma}'_\ell|\mathbf{0})+\epsilon_1\left[\epsilon_2P(\boldsymbol{\sigma}'_\ell|J_\ell\boldsymbol{\sigma})+(1-\epsilon_2)\langle P(\boldsymbol{\sigma}'_\ell|J'\boldsymbol{\sigma})\rangle_{J'}\right]\Big] \\
& \left.\times\prod_t\frac{e^{\beta\sigma(t+1)[\theta(t)+\sum_{\ell\leq k}J_\ell\sigma'_\ell(t)]}}{2\cosh[\beta[\theta(t)+\sum_{\ell\leq k}J_\ell\sigma'_\ell(t)]]}\right\}
\end{aligned}
$$

$\epsilon_1\in[0,1]$: *graph symmetry*
$\epsilon_2\in[0,1]$: *bond value symmetry*

DYNAMICS
DYNAMICAL REPLICA METHOD



$$\frac{d}{dt}p_t(\boldsymbol{\sigma}) = \sum_{k=1}^{N}[p_t(F_k\boldsymbol{\sigma})w_k(F_k\boldsymbol{\sigma}) - p_t(\boldsymbol{\sigma})w_k(\boldsymbol{\sigma})]$$

$$F_k\boldsymbol{\sigma} = (\sigma_1, \ldots, -\sigma_k, \ldots, \sigma_N)$$

$$w_k(\boldsymbol{\sigma}) = \frac{1}{2}\{1 - \sigma_k \tanh[\beta h_k(\boldsymbol{\sigma})]\} \qquad h_i(\boldsymbol{\sigma}) = \sum_{j\neq i} c_{ij}J_{ij}s_j + \theta$$

macroscopic variables:

average activity $m(\boldsymbol{\sigma}) = N^{-1}\sum_i s_i$
and internal energy $e(\boldsymbol{\sigma}) = N^{-1}\sum_{i<j} c_{ij}J_{ij}s_is_j$

exact macroscopic laws:

$$\frac{d}{dt}m = -m + \int dh\ D_t(h|m,e)\tanh(\beta h)$$
$$\frac{d}{dt}e = -2e - \int dh\ D_t(h|m,e)h\tanh(\beta h)$$

$$D_t(h|m,e) = \lim_{N\to\infty}\left\langle \sum_{\boldsymbol{\sigma}}\ p_t(\boldsymbol{\sigma}|m,e)\ \frac{1}{N}\sum_{i=1}^{N}\delta[h - h_i(\boldsymbol{\sigma})]\ \right\rangle_{\text{disorder}}$$

dynamical replica method:

- *assume macroscopic laws are self-averaging*
- *approximate in macroscopic laws:* $p_t(\boldsymbol{\sigma}|m,e) \to p(\boldsymbol{\sigma}|m,e)$ *(maximum entropy)*

$$p(\boldsymbol{\sigma}|m,e) = \frac{\delta[m-m(\boldsymbol{\sigma})]\delta[e-e(\boldsymbol{\sigma})]}{\sum_{\boldsymbol{\sigma}'}\delta[m-m(\boldsymbol{\sigma}')]\delta[e-e(\boldsymbol{\sigma}')]}$$

- *use replica identity for graph & bond disorder averages*

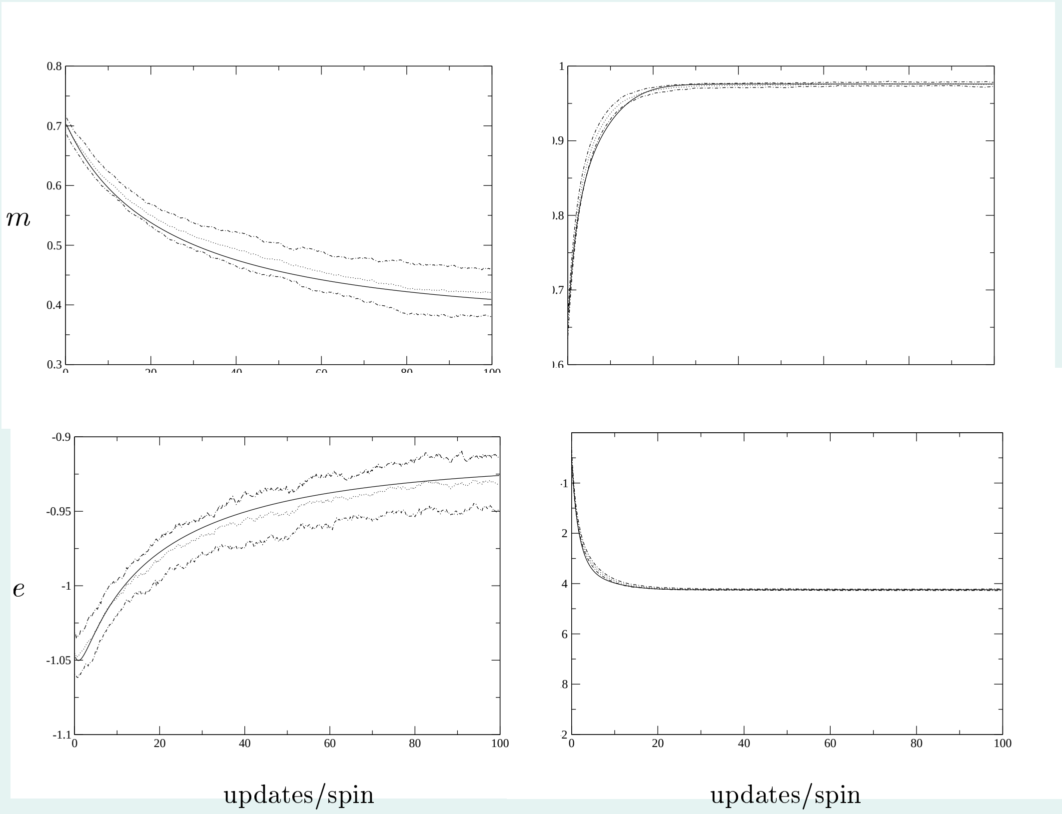
resulting closed laws:

$$\begin{aligned}\frac{d}{dt}m &= -m + \int dh\; D(h|m,e)\tanh(\beta h)\\ \frac{d}{dt}e &= -2e - \int dh\; D(h|m,e)h\tanh(\beta h)\end{aligned}$$

$$\begin{aligned}D(h|m,e) &= \lim_{N\to\infty}\frac{1}{N}\sum_{i=1}^{N}\left\langle \sum_{\boldsymbol{\sigma}}\; p(\boldsymbol{\sigma}|m,e)\;\delta[h-h_i(\boldsymbol{\sigma})]\right\rangle_{\rm disorder}\\ &= \lim_{N\to\infty}\frac{1}{N}\sum_{i=1}^{N}\left\langle \frac{\sum_{\boldsymbol{\sigma}}\delta[m-m(\boldsymbol{\sigma})]\delta[e-e(\boldsymbol{\sigma})]\delta[h-h_i(\boldsymbol{\sigma})]}{\sum_{\boldsymbol{\sigma}}\delta[m-m(\boldsymbol{\sigma})]\delta[e-e(\boldsymbol{\sigma})]}\right\rangle_{\rm disorder}\end{aligned}$$

random bonds, uniform degrees

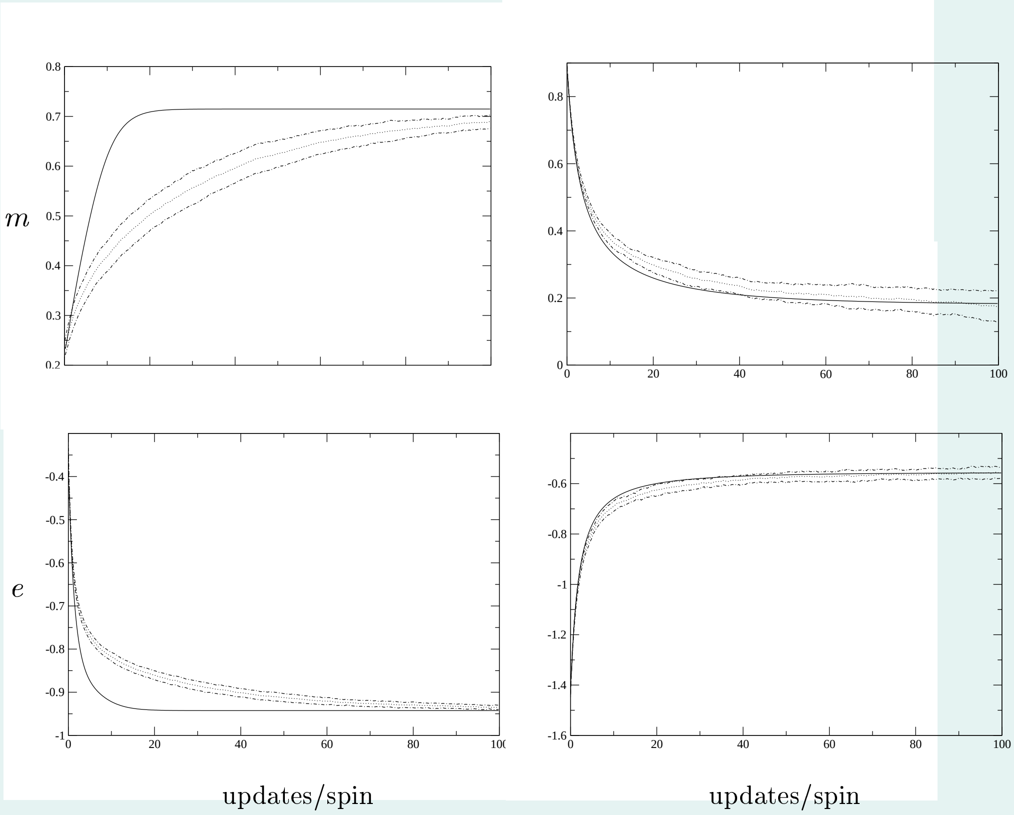
$$P(k) = \delta_{k,3} \qquad Q(J) = \eta\delta(J-1) + (1-\eta)\delta(J+1)$$



$\eta = 0.95,\ \beta = 0.65$ $\qquad$ $\eta = 0.97,\ \beta = 1.2$

Poissonnian random degrees, uniform bonds

$$P(k) = e^{-c}c^k/k!$$



$c = 2$ $c = 3$

SUMMARY

- *In biology one finds many instances of process control by large random and/or complex interaction networks*

  (e.g. neural networks, immune networks, protein networks, gene regulation networks, ...)

- *Except perhaps for neural networks, most such networks are of the finite connectivity type.*

  (large number N of nodes, finite number of links k_i per node)

- *In the mathematical analysis of stochastic processes on random and/or complex networks the regime of finite connectivity is the most demanding*

- *The latter regime is one of increased research activity in disordered systems theory. We are now beginning to acquire the necessary mathematical tools to solve both statics and dynamics.*

  - *equilibrium replica theory*
  - *cavity techniques*
  - *diagonalization of replicated transfer matrices*
  - *generating functional analysis*
  - *dynamical replica theory*

The GUZAI Initiative (2003–present)

ACC Coolen, JPL Hatchett, T Nikoletopoulos, I Perez-Castillo,
CJ Perez-Vicente, NS Skantzos, B Wemmenhove

statics

- *Finite connectivity attractor neural networks. J. Phys. A 36 (2003) 9617*
- *The Little-Hopfield model on a sparse random graph. J. Phys. A 37 (2004) 9087*
- *Analytic solution of attractor neural networks on scale-free graphs. J. Phys. A 37 (2004) 8789*
- *Replicated transfer matrix analysis of Ising spin models on 'small world' lattices.*
  J. Phys. A 37 (2004) 6455
- *Finitely connected vector spin systems with random matrix interactions. preprint* `cond-mat/0504690`

dynamics

- *Parallel dynamics of disordered Ising spin systems on finitely connected random graphs.*
  J. Phys. A 37 (2004) 6201
- *Dynamical replica analysis of disordered Ising spin systems on finitely connected random graphs.*
  preprint `cond-mat/0504313`

systems with evolving bonds

- *Slowly evolving connectivity in recurrent neural networks I: the extreme dilution regime.*
  J. Phys. A 37 (2004) 7653
- *Slowly evolving random graphs II: adaptive geometry in finite connectivity Hopfield models.*
  J. Phys. A 37 (2004) 7843