Stochastic Processes on Large Random and/or Complex Biological Networks

ACC Coolen

with

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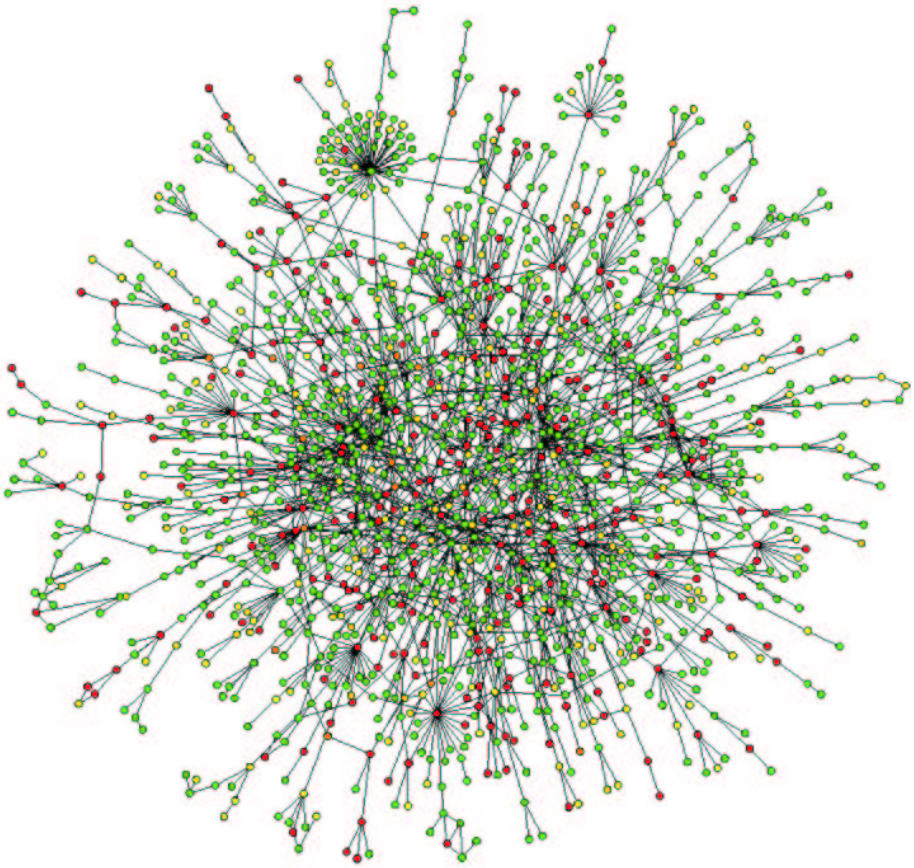


OVERVIEW

Stochastic processes on large networks in biology

interacting cells	(neural & immune networks)
interacting proteins	(proteomic networks)
interacting genes	(gene regulation networks)
interacting amino-acids	(protein folding)

Complex networks – definitions, characterization

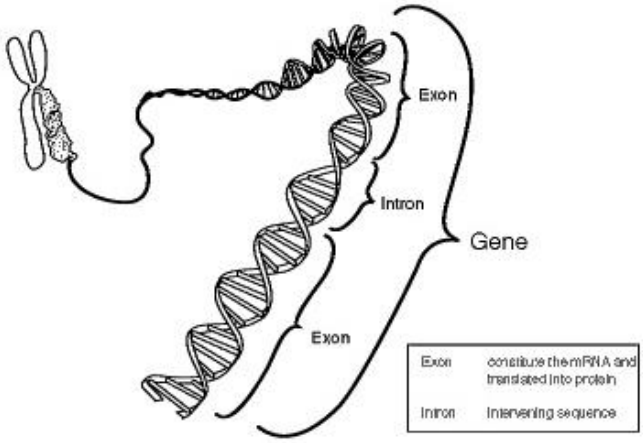
random graphs, degree distribution
small-world networks
scale-free networks

Theory of processes on large complex networks

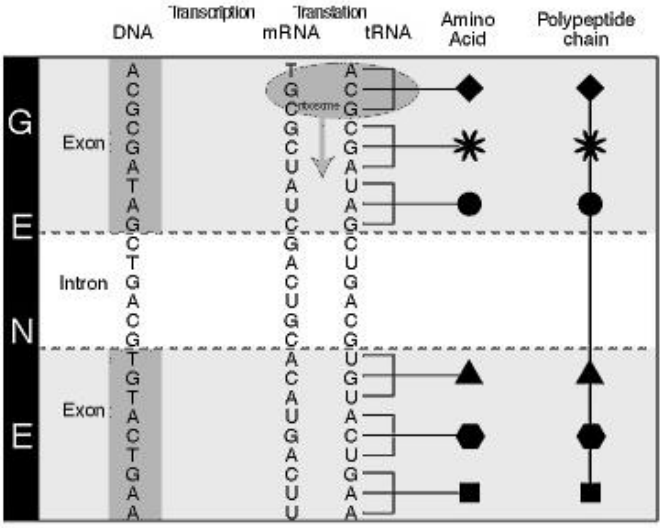
methods and their applicability
statics – finite connectivity replica theory
dynamics – generating functional analysis
dynamics – dynamical replica & cavity techniques

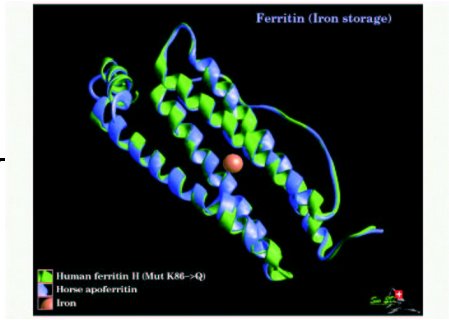
PROCESSES ON LARGE NETWORKS IN BIOLOGY

networks: defined functionally, by interaction partners

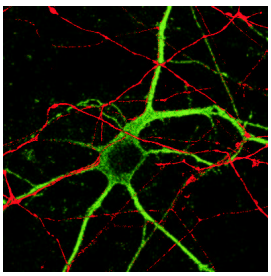


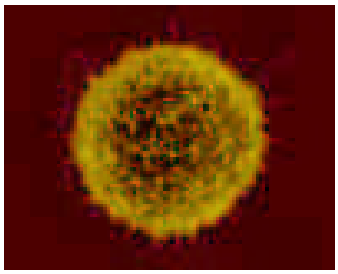
- *gene level*
- *amino-acid level*
- *protein level*
- *cell level*





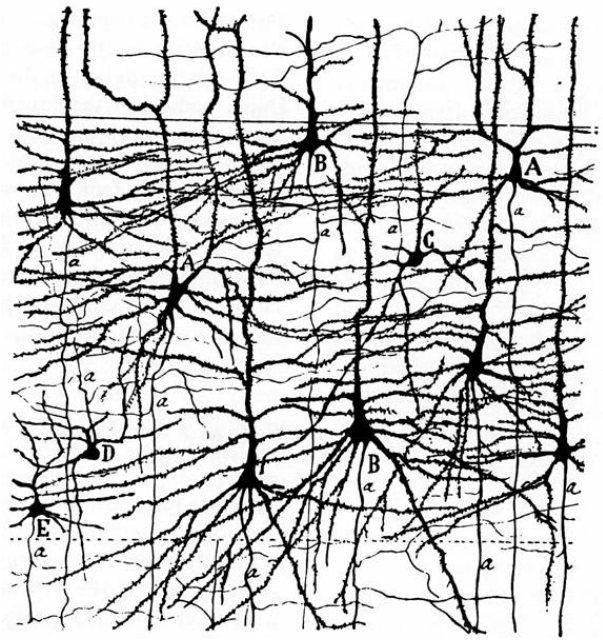
organism ←

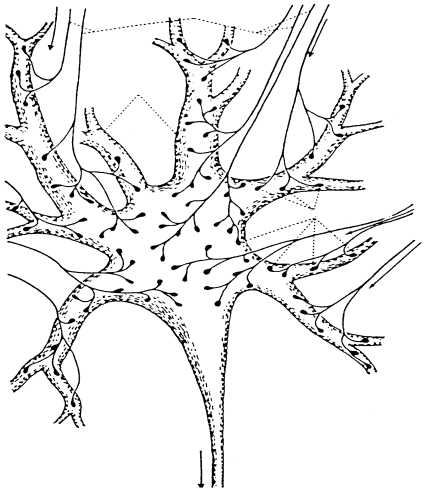




NEURAL NETWORKS

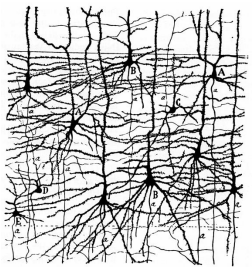
Dense networks of $\sim 10^4 - 10^8$ brain cells (neurons)
connected via electro-chemical terminals (synapses)





conventional computers	neural networks
processors *clock speed* $\sim 10^9 Hz$ *signal/noise* $\sim \infty$ *signal velocity* $\sim 10^8 m/sec$ *connections* ~ 10	neurons *clock speed* $\sim 10^2 Hz$ *signal/noise* ~ 1 *signal velocity* $\sim 1 m/sec$ *connections* $\sim 10^4$
sequential operation program & data external programming	parallel operation synaptic connections self-programming, adaptation
hardware failure: fatal no unforseen data	hardware failure: robust messy, unforseen data

Mathematical models of neural networks



network:
represented by matrix $\{J_{ij}\}$

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

Examples of microscopic dynamical laws:

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

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

  $\eta_i(t)$: noise

- neuron voltages V_i

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

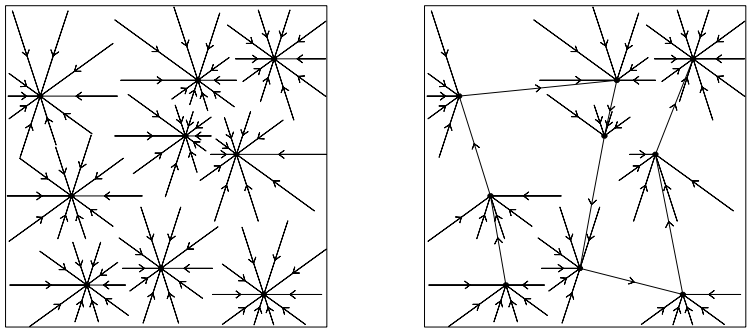
- coupled neural oscillators, with phases ϕ_i

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

Attractors

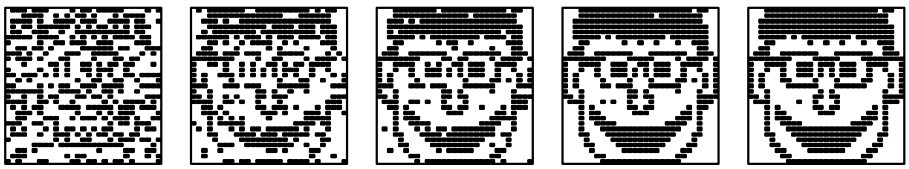
Information processing based on
'tayloring' the system's dynamical properties:

'mould' attractor landscape in state space
by creating suitable bonds $\{J_{ij}\}$ between the nodes



e.g. parallel dynamics,
binary neuron states $\sigma_i \in \{-1, 1\}$:
(●, ○)

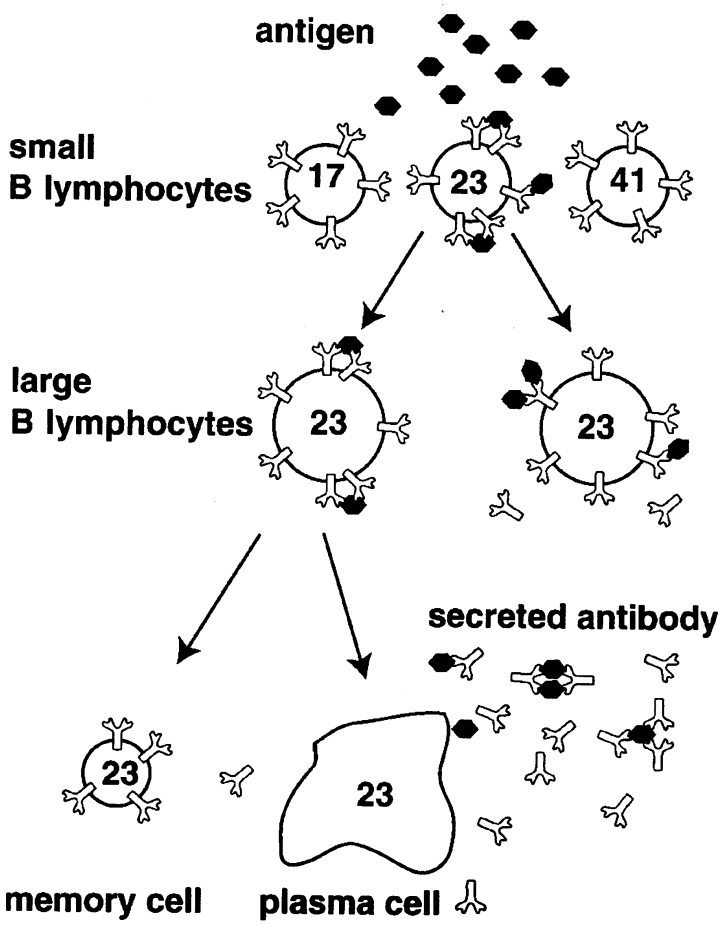
$$\begin{aligned} \text{dynamical 'instruction'}: &\quad \text{if in state } \boldsymbol{\sigma}^a \text{ go to state } \boldsymbol{\sigma}^b \\ \text{implementation}: &\quad J_{ij} \to J_{ij} + \sigma_i^b \sigma_j^a \end{aligned}$$



IMMUNE NETWORK

the enemy:

invaders,
abnormal cells
(antigen)

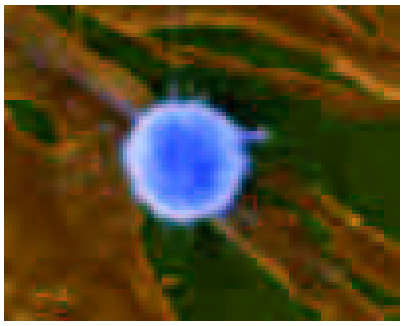


the defense:

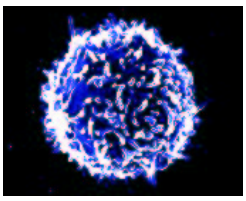
lymphocytes (white blood cells)

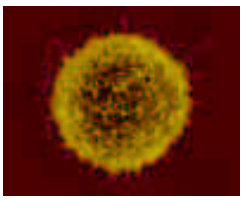
B-cells: secrete tags (antibodies)
helper T-cells: assist B-cells
cytotoxic T-cells: cell killers

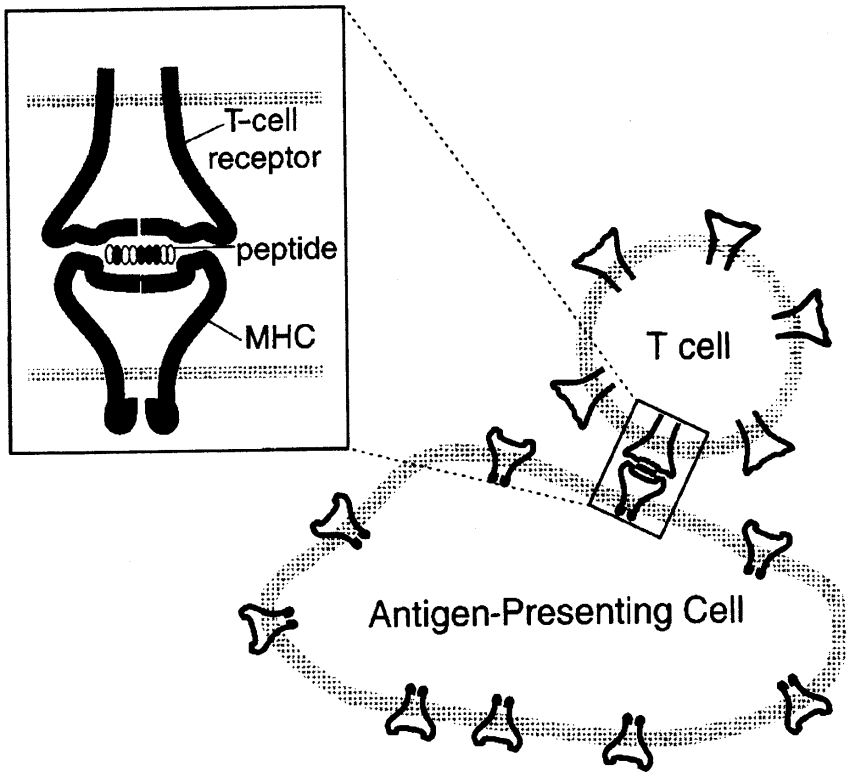
phagocytic cells: vacuum cleaners
(eat anything tagged ...)



Lymphocytes recognize
surface shapes of antigens







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

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 response to antigen i

- first $b_i \uparrow$, then $f_i \uparrow$

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:

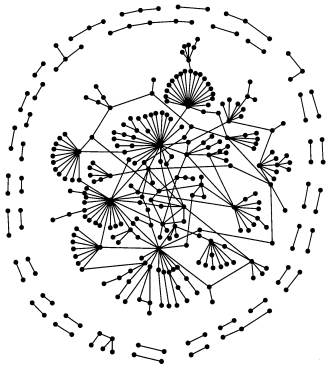
- network of antibody clones with negative mutual interactions
- clone-anticlone pairs support *stable* $(\uparrow,\downarrow)$ and $(\downarrow,\uparrow)$ states

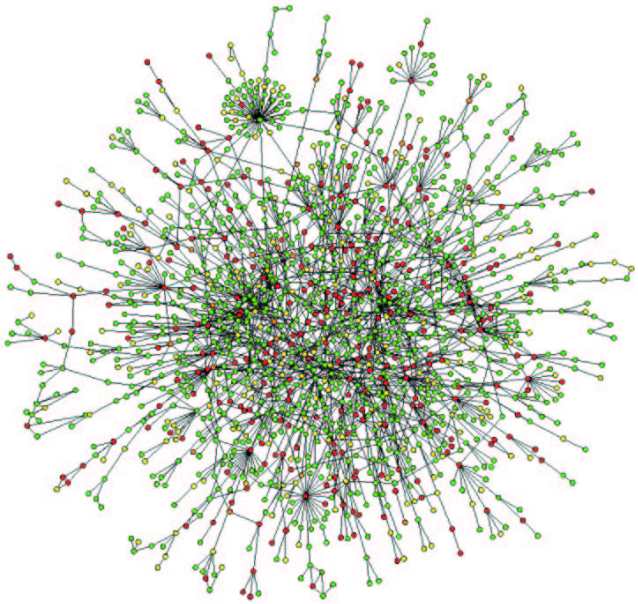
GENE REGULATION & PROTEOMIC NETWORKS

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

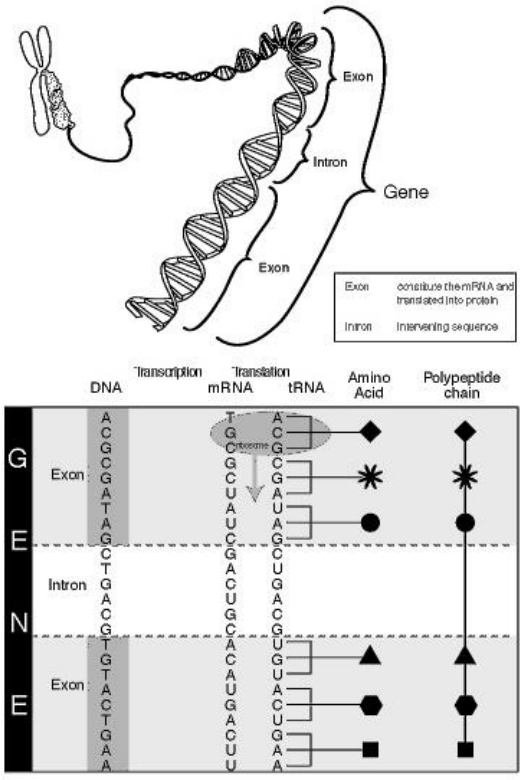
$$\frac{d}{dt} f_i \;=\; \sum_j J_{ij} f_j + \sum_{jk} J_{ijk\ell} f_j f_k + \sum_{jk\ell} J_{ijk\ell} f_j f_k f_\ell + \ldots$$

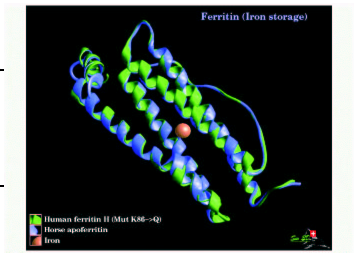
in addition:

- 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 & explain cell differentiation





gene expression:
conversion of info
into protein production

- expression level of a gene: controlled by specific proteins
- protein concentrations: controlled by
  - ⋆ other proteins
  - ⋆ other expressed genes
  - ⋆ external stimuli
- GRNs:
  - ⋆ 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)

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

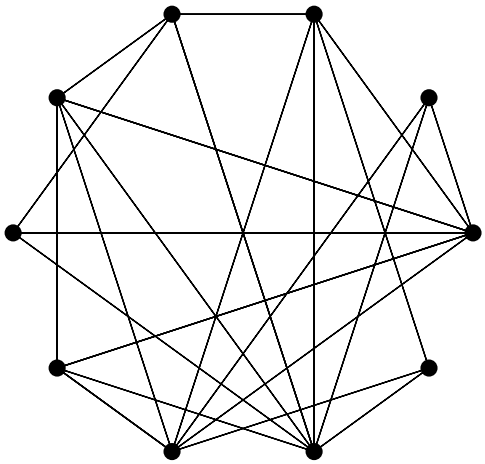
dynamics:

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

each i:

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

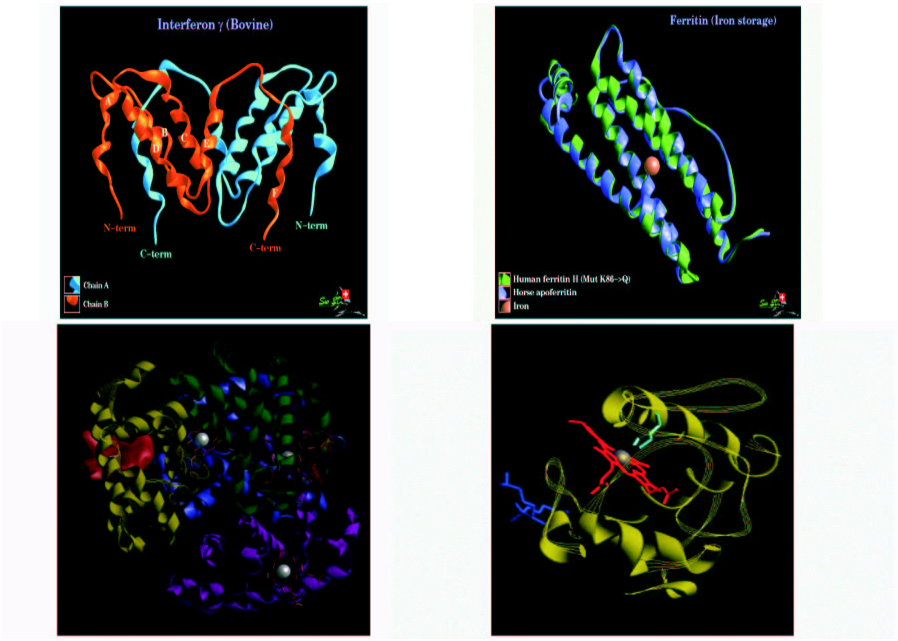
$$\mathcal{F}_i : \{0,1\}^k \to \{0,1\} \qquad \text{random function, Prob}(\mathcal{F} = 0) = p$$



- 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?

PROTEIN FOLDING

Terminology



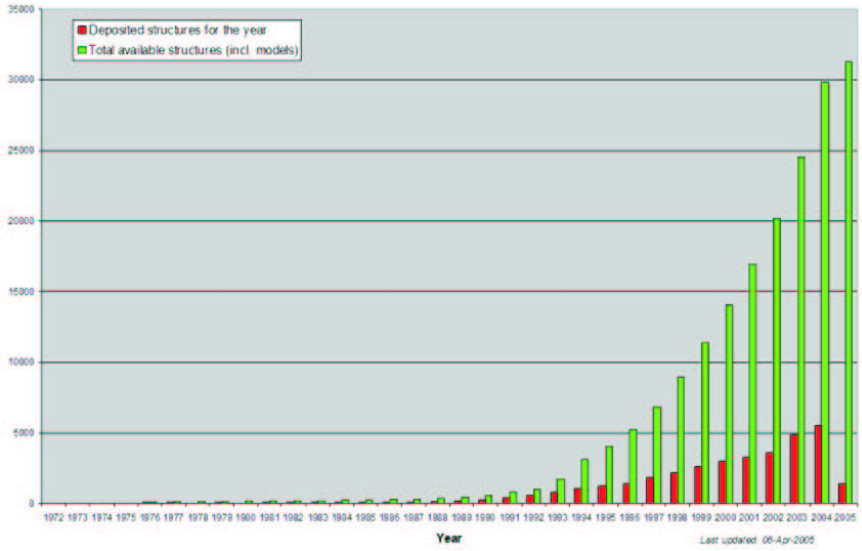
Primary structure:
amino-acid sequence

Secondary structure:
local conformation of α-helices, β-sheets, etc

Tertiary structure:
3D arrangement of secondary structure elements

'Knowledge of a protein's tertiary structure is a prerequisite for the proper understanding and engineering of its function'

'This makes the [protein] folding problem, the successful prediction of a protein's tertiary structure from its amino-acid sequence, central to rapid progress in post-genomic biology'



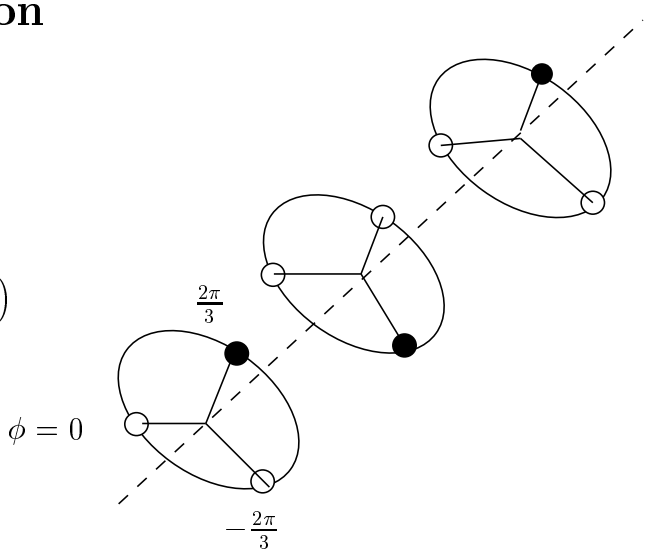
known sequences: $\pm\, 2.10^6$

known tertiary structures: $\pm\, 3.10^4$ (growing at $\pm 5.10^3$/year)

Secondary structure formation in hetero-polymers

$$\phi_i \in [0, 2\pi], \quad \boldsymbol{\phi} = (\phi_1, \ldots, \phi_N)$$

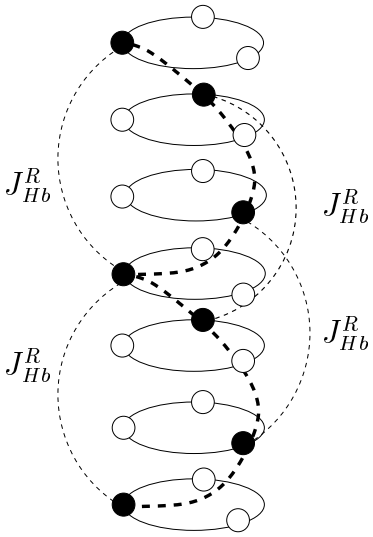
$$H(\boldsymbol{\phi}) = H_{\rm s}(\boldsymbol{\phi}) + H_{\rm p}(\boldsymbol{\phi}) + H_{\rm Hb}(\boldsymbol{\phi})$$

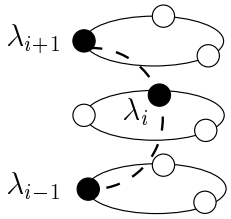


polarity energy (hydrophobic/philic)
steric energy (mechanical constraints)
hydrogen bonding energy

short-range
1-dim interactions:

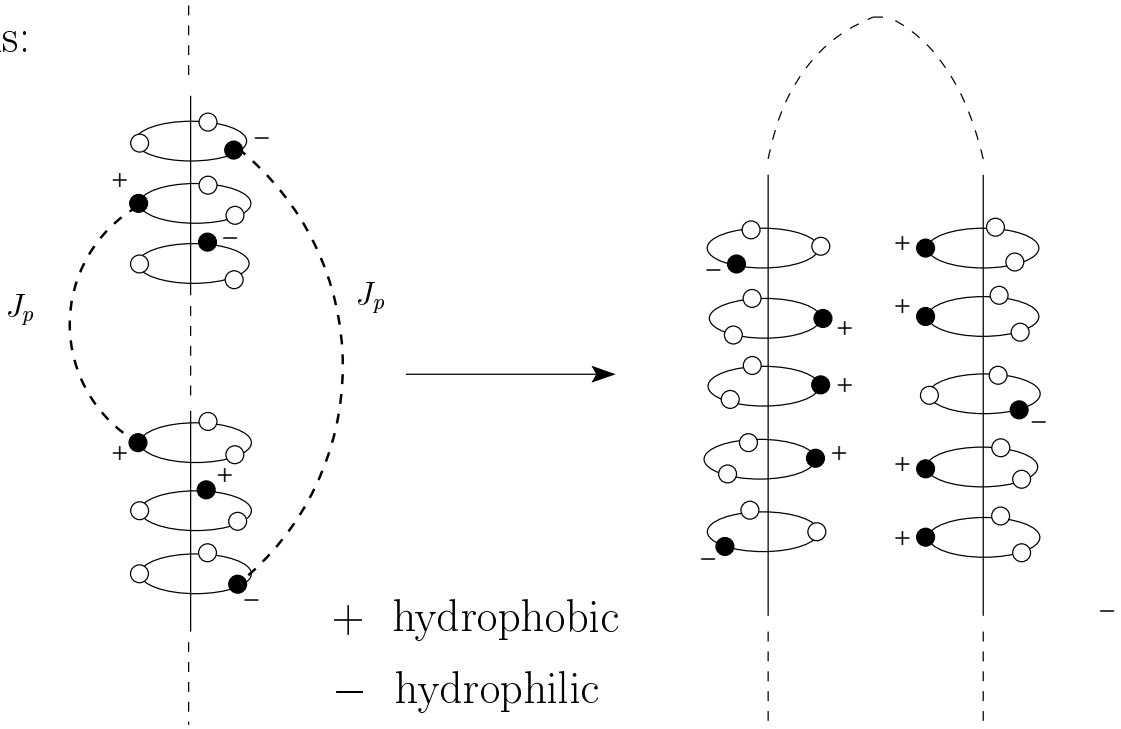
$H_{\rm s}(\boldsymbol{\phi}),\ H_{\rm Hb}(\boldsymbol{\phi})$





long-range
interactions:

$H_{\rm p}(\boldsymbol{\phi})$



- amino-acid 'interaction network':
  superposition of 1-dim short range links and long-range links

COMPLEX NETWORKS

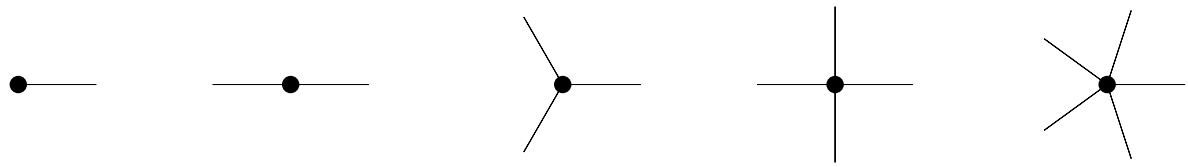
Networks – definition and characterization

⋆ nodes and links:

$$\text{nodes}: \quad i = 1, \ldots, N$$

$$\text{links}: \quad c_{ij} \in \{0, 1\} \qquad \begin{array}{ll} c_{ij} = 1: & \text{link } j \to i \text{ present} \\ c_{ij} = 0: & \text{link } j \to i \text{ absent} \end{array}$$

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



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

⋆ 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 the $\frac{1}{2}N(N-1)$ distances ℓ_{ij}

mean path-length:

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

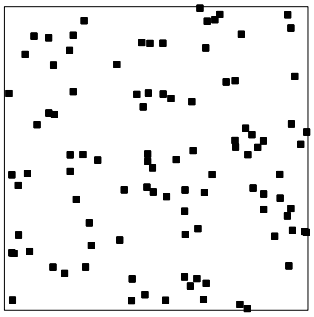
Examples

- disconnected nodes:

  $k_i = 0$ for all i

  $C_i = 0$ for all i

  $\ell_{ij} = \infty$ for all (i,j)

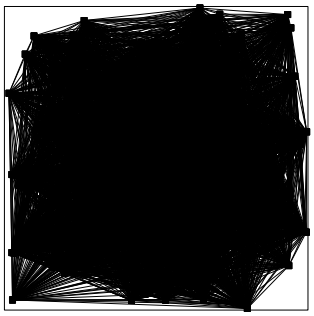


- fully connected network:

  $k_i = N$ for all i

  $C_i = 1$ for all i

  $\ell_{ij} = 1$ for all (i,j)



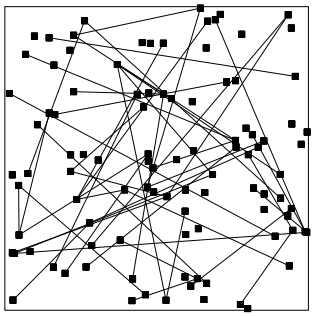
- Poissonnian (Erdos-Renyi) random networks
  for each pair (i,j): form a link with probability c/N

  k_i random for all i

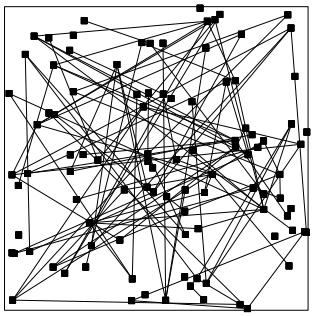
  N large : $\quad P(k) = c^k e^{-c}/k! \qquad c = \Sigma_{k\geq 0}\, P(k)k$

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

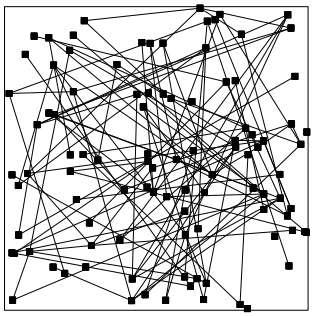
$N = 100$:



$c = 1$



$c = 2$

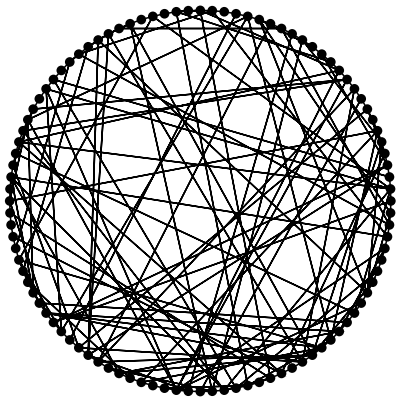


$c = 3$

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

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

  $k_i = 2+$ Poisonnian random number



'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)*

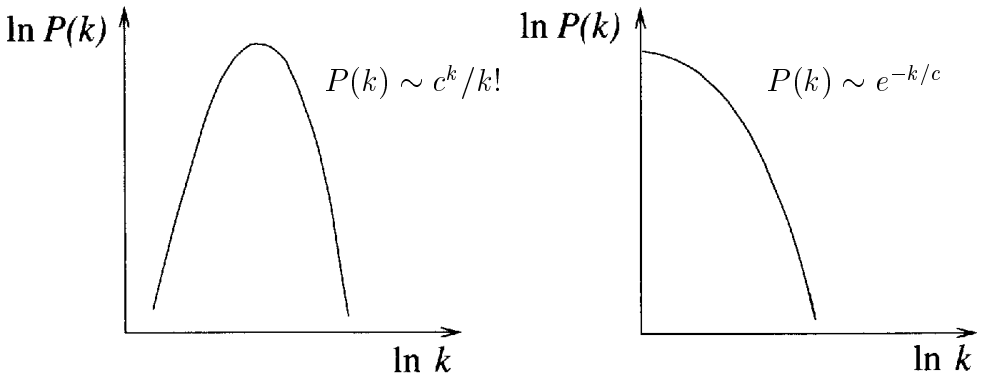
Simple network:

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

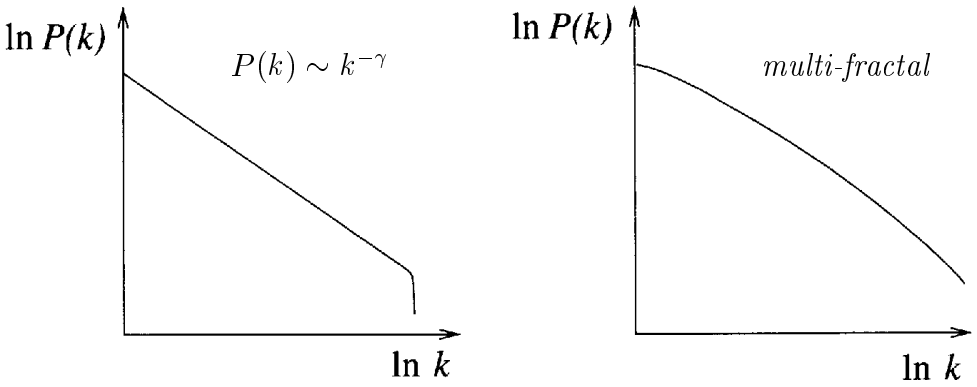
Complex (or 'scale-free') network:

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

simple:



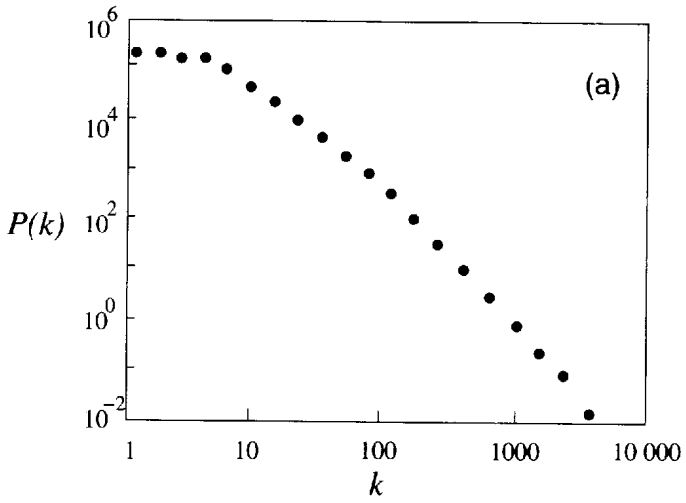
complex:



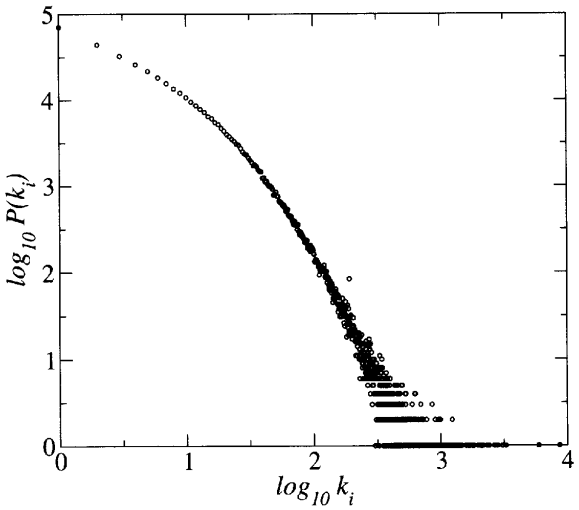
mechanism:
growth with preferential attachment

Social networks

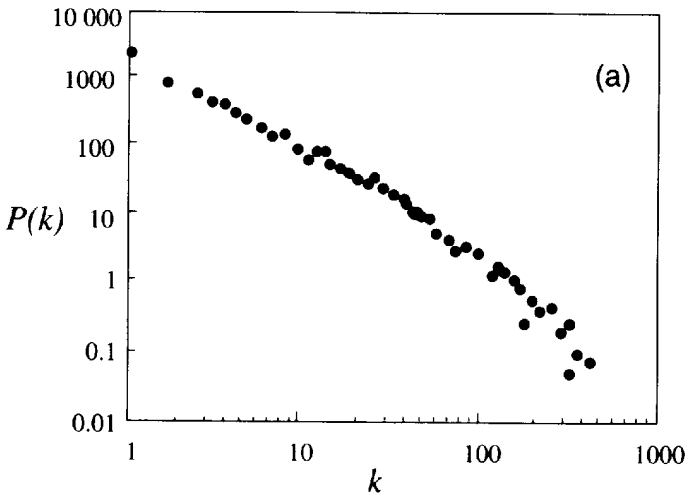
author networks:



citation networks:

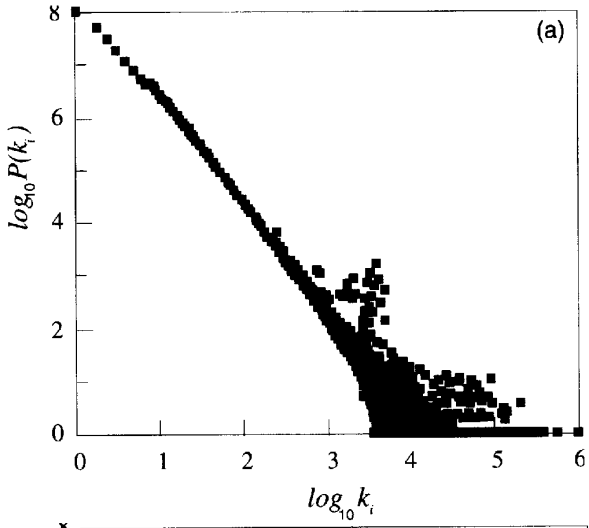


E-mail networks:

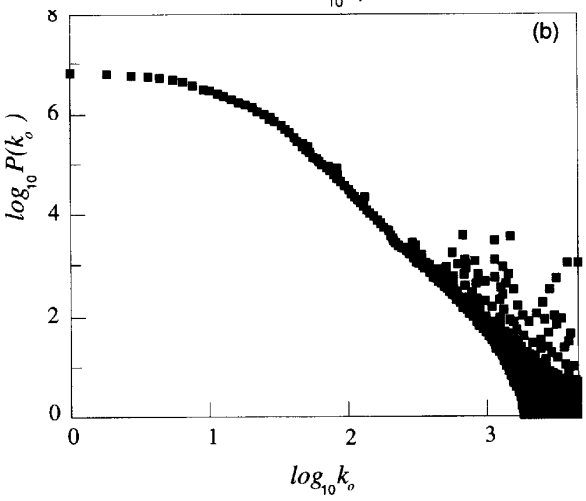


Internet

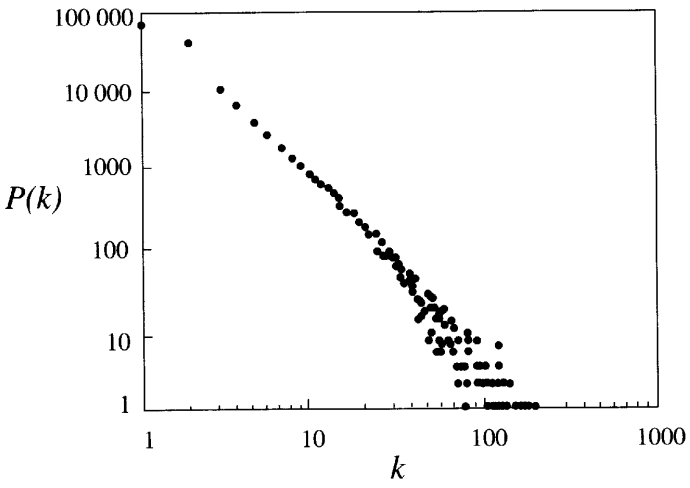
WWW in-links:



WWW out-links:

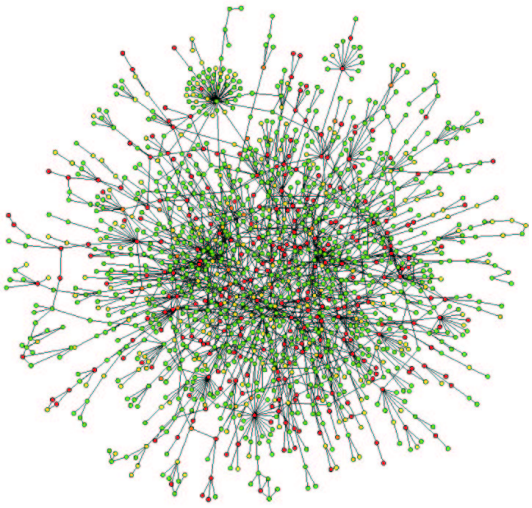


WWW routers:

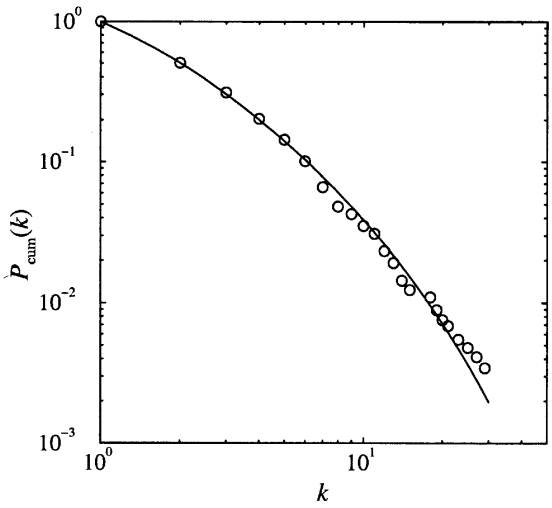


Protein interaction networks

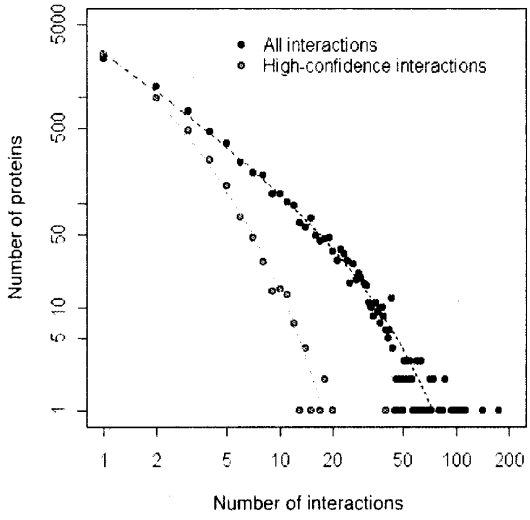
(yeast two-hybrid method)



Jeong et al (Nature, 2001)



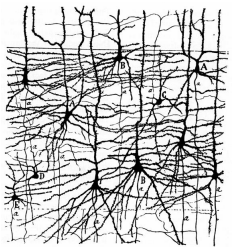
Giot et al (Science, 2003)



CHARACTERISTICS OF BIOLOGICAL NETWORKS

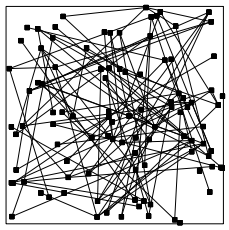
- **neural networks**:

  $N \sim 10^4$-10^8, $\langle k \rangle \sim 10^2$-$10^4$
  random (hippocampus) to regular (cerebellum)
  link strengths time-dependent



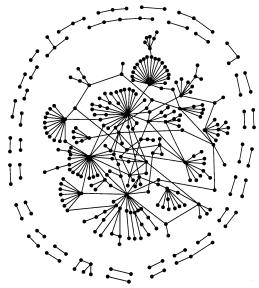
- **immune networks**:

  $N \sim 10^6$-10^7, $\langle k \rangle \sim$ small ?
  narrow distribution $P(k)$?
  link strengths symmetric



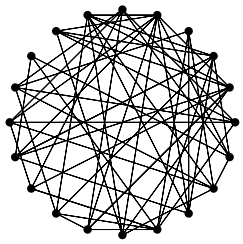
- **protein interaction networks**:

  $N \sim 10^4$, $\langle k \rangle \sim 2-7$?
  scale-free, complex ('hub' proteins, etc)
  chemical conservation laws



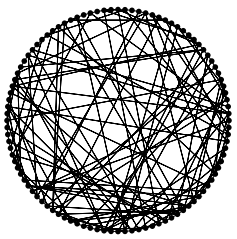
- **gene regulation networks**:

  $N \sim 10^4$, $\langle k \rangle \sim$ 1-10?
  structure? complexity?
  Kauffman model: $P(k) = \delta_{k,k^\star}$



- **protein folding**:

  $N \sim 10^3$-10^4, $\langle k \rangle \sim$?
  small-world type structure:
  short-range 1D + long range links



ANALYSIS OF STOCHASTIC PROCESSES ON LARGE RANDOM NETWORKS

state-of-the-art in the relevant mathematical theory:

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 processes)

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

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

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 ($\pm$1870)

$$\text{Prob[state]} = \frac{e^{-E(\text{state})/kT}}{\sum_{\text{states}} e^{-E/kT}} \qquad \begin{array}{ll} E: & \text{energy} \\ T: & \text{temperature} \end{array}$$

  e.g.

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

- non-equilibrium ($\pm$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

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:

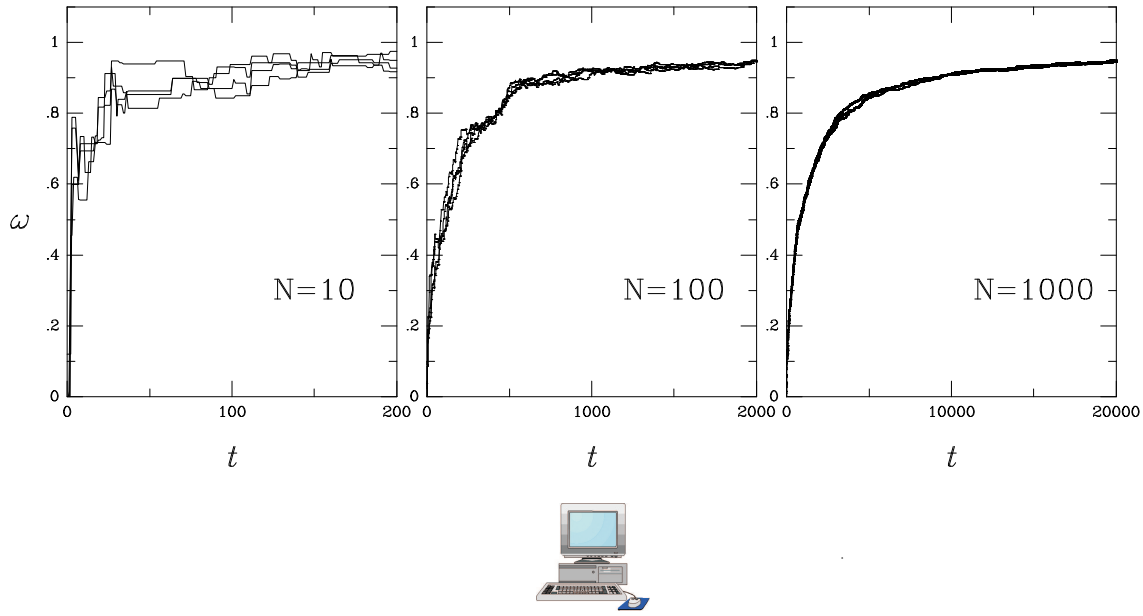
'predict the relations between the observable macroscopic properties of the system, given only a knowledge of the microscopic forces between the components'

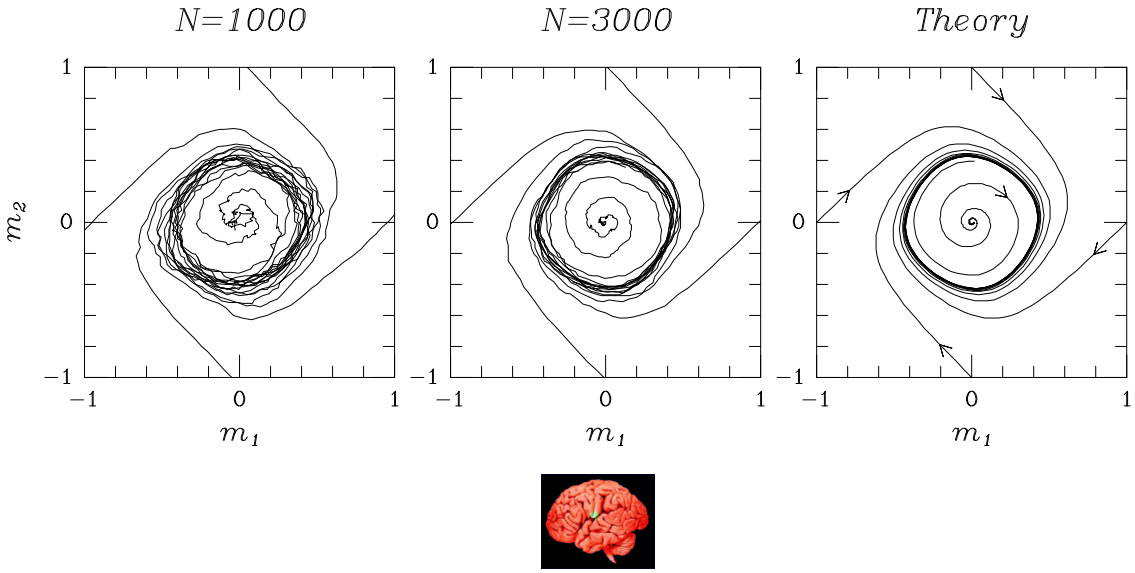
- objectives of systems biology and of statistical mechanics are very similar
- it is irrelevant to the mathematical methods of statistical mechanics what the microscopic components **represent**, as long as there are many ...

  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, these laws are independent of most microscopic details





Some jargon ...

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: $\tau \sim 10^{-15}$ sec, $N = 1000$

$$\Delta x/x \sim 0.03, \qquad t_{\rm esc} \sim 10^{400} \text{ sec}$$

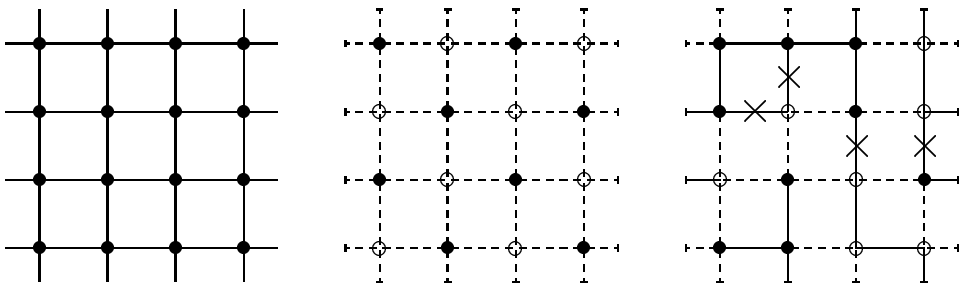
$$(\text{age of universe } \sim 4.10^{17}\text{sec})$$

DISORDERED MANY-PARTICLE SYSTEMS

- (pseudo-) randomness in microscopic parameters
- no microscopic periodicity
- high degree of frustration, incompatible forces

example: disordered spin systems
(spin = microscopic magnet)

ferro (—) anti-ferro (- - -) both types



○: spin up ●: spin down

- many relevant time-scales
- many techniques no longer applicable
- even simple models are non-trivial

physics:	spin-glasses, glasses
biology:	neural networks, proteins, immune networks
IT:	machine learning, error-correcting codes
economics:	agent-based market models

The language of disordered systems theory

core problem: carrying out disorder averages in probabilistic dynamical equations

The replica trick/method (Hardy & Littlewood, 1934)

statics: ± 1975
dynamics: ± 1993

$$\Big\langle \sum_x f(x,\mathrm{dis}) P(x|y,\mathrm{dis}) \Big\rangle_{\mathrm{dis}} = \Big\langle \frac{\Sigma_x f(x,\mathrm{dis}) P(x,y|\mathrm{dis})}{\Sigma_x P(x,y|\mathrm{dis})} \Big\rangle_{\mathrm{dis}}$$

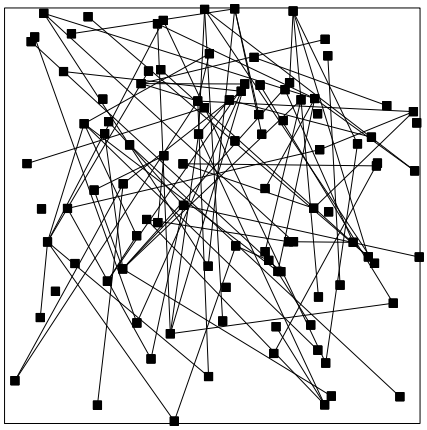
$$= \lim_{n\to 0} \Big\langle \sum_x f(x,\mathrm{dis}) P(x,y|\mathrm{dis}) \Big[\sum_{x'} P(x',y|\mathrm{dis}) \Big]^{n-1} \Big\rangle_{\mathrm{dis}}$$

$$= \lim_{n\to 0} \sum_{x_1,\ldots,x_n} \big\langle f(x_1,\mathrm{dis}) P(x_1,y|\mathrm{dis}) \ldots P(x_n,y|\mathrm{dis}) \big\rangle_{\mathrm{dis}}$$

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 $n \to 0$!

FINITE CONNECTIVITY STATICS



$N = 100,\ c = 2$

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

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

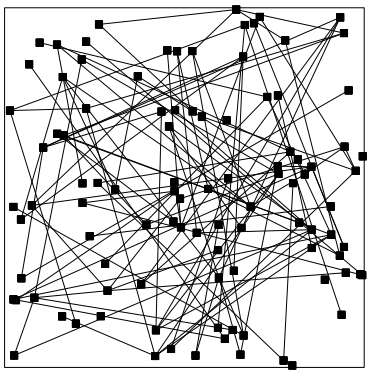
- $P(c_{ij}) = \frac{c}{N}\delta_{c_{ij},1} + (1 - \frac{c}{N})\delta_{c_{ij},0}, \quad c = \mathcal{O}(N^0)$
- indep random bonds J_{ij}
- disorder: $\{c_{ij}, J_{ij}\}$

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, $W[\{P\}]$

Example: attractor neural networks on scale-free graphs



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

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

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:

$$\mathcal{P}(\boldsymbol{c}) = \frac{[\,\Pi_{i<j}\,\mathcal{P}(c_{ij})\;\delta_{c_{ij},c_{ji}}][\,\Pi_i\,\delta_{k_i,\sum_{j\neq i} c_{ij}}]}{\Sigma_{\boldsymbol{c}'}\,[\,\Pi_{i<j}\,\mathcal{P}(c'_{ij})\;\delta_{c'_{ij},c'_{ji}}][\,\Pi_i\,\delta_{k_i,\sum_{j\neq i} c'_{ij}}]}$$

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

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)

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

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

Noise resilience of scale-free networks

Single pattern retrieval phase boundary:

$$\beta_{\rm crit} = -\frac{\langle k\rangle}{2} \log\left(1 - \frac{2\langle k\rangle}{\langle k^2\rangle}\right)$$

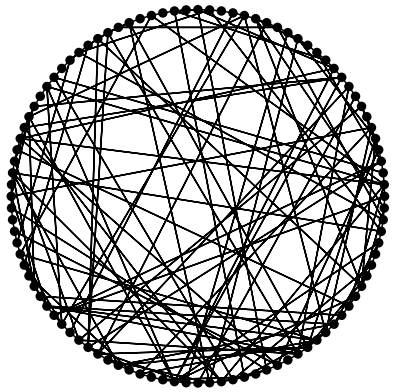
- simple Poissonnian network $P(k) = e^{-c}c^k/k!$:
  $\langle k\rangle = c, \quad \langle k^2\rangle = c^2 + c$

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

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

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

Example: 'small world' networks



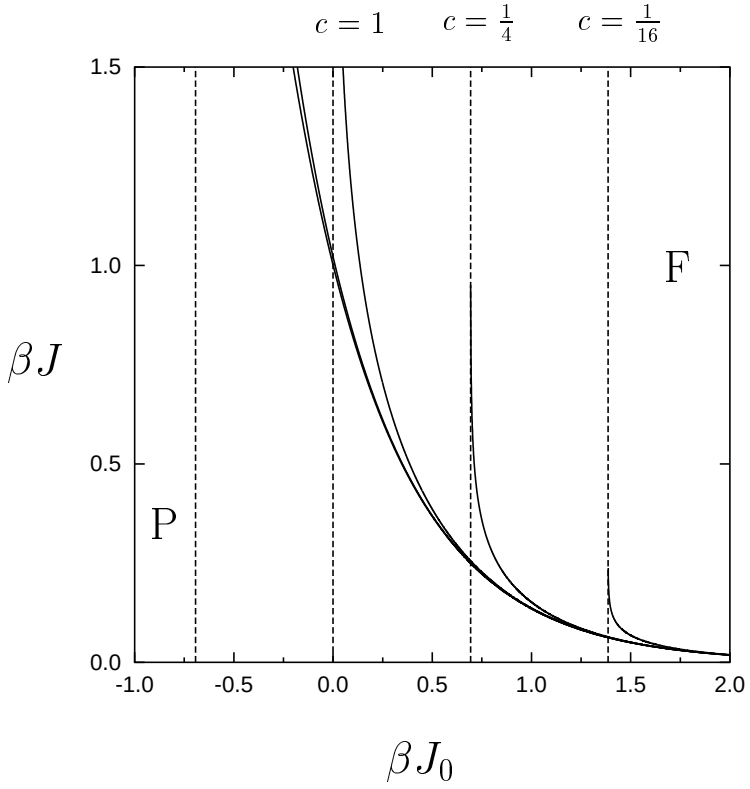
$$H = -J_0 \sum_i \sigma_i \sigma_{i+1} - \frac{J}{c} \sum_{i<j} c_{ij} \sigma_i \sigma_j$$

with Poissonnian random graph $\{c_{ij}\}$

Phase diagram

based on diagonalization of
RS replicated transfer matrix

$$\text{P} \to \text{F}: \qquad 1 = c \tanh(\frac{\beta J}{c}) \left[\frac{1 + \tanh(\beta J_0)}{1 - \tanh(\beta J_0)} \right]$$

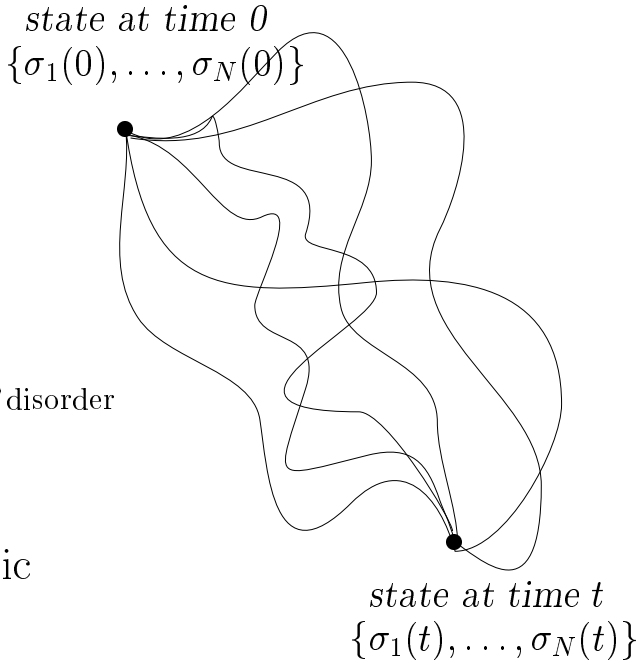


solid:
P→F transition
for $c = \frac{1}{16}, \frac{1}{4}, 1, 4, 16$

dashed:
$\beta J_0 = \log(1/\sqrt{c})$
for $c = \frac{1}{16}, \frac{1}{4}, 1, 4, 16$

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

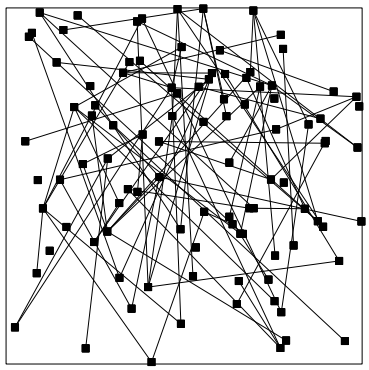
'generates' all relevant macroscopic multiple-time observables via (functional) differentiation
e.g.

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

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

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

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:

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

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

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

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 $\boldsymbol{\theta} = (\theta(0), \theta(1),\ \theta(2), \ldots)$

$$P(\boldsymbol{\sigma}|\boldsymbol{\theta}) \ = \ p_0(\sigma(0))e^{-c} \times$$

$$\left\{ \prod_t \left[\frac{e^{\beta\sigma(t+1)\theta(t)}}{2\cosh[\beta\theta(t)]} \right] + \sum_{k>0} \frac{c^k}{k!} \int dJ_1 P(J_1) \ldots dJ_k P(J_k) \sum_{\boldsymbol{\sigma}'_1 \ldots \boldsymbol{\sigma}'_k} \right.$$

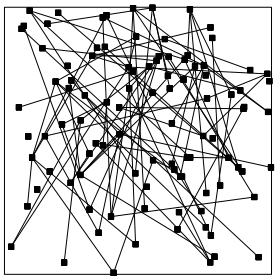
$$\times \prod_{\ell=1}^{k} \left[(1-\epsilon_1) P(\boldsymbol{\sigma}'_\ell|\mathbf{0}) + \epsilon_1 \left[\epsilon_2 P(\boldsymbol{\sigma}'_\ell|J_\ell\boldsymbol{\sigma}) + (1-\epsilon_2) \langle P(\boldsymbol{\sigma}'_\ell|J'\boldsymbol{\sigma}) \rangle_{J'} \right] \right]$$

$$\left. \times \prod_t \frac{e^{\beta\sigma(t+1)[\theta(t)+\sum_{\ell\leq k} J_\ell \sigma'_\ell(t)]}}{2\cosh[\beta[\theta(t) + \Sigma_{\ell\leq k}\, J_\ell \sigma'_\ell(t)]]} \right\}$$

$\epsilon_1 \in [0,1]$: 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 $\quad m(\boldsymbol{\sigma}) = N^{-1}\,\Sigma_i\, s_i$
and internal energy $\quad e(\boldsymbol{\sigma}) = N^{-1}\,\Sigma_{i<j}\, c_{ij}J_{ij}s_is_j$

exact macroscopic laws:

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

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

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)

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

- use replica identity for graph & bond disorder averages

resulting closed laws:

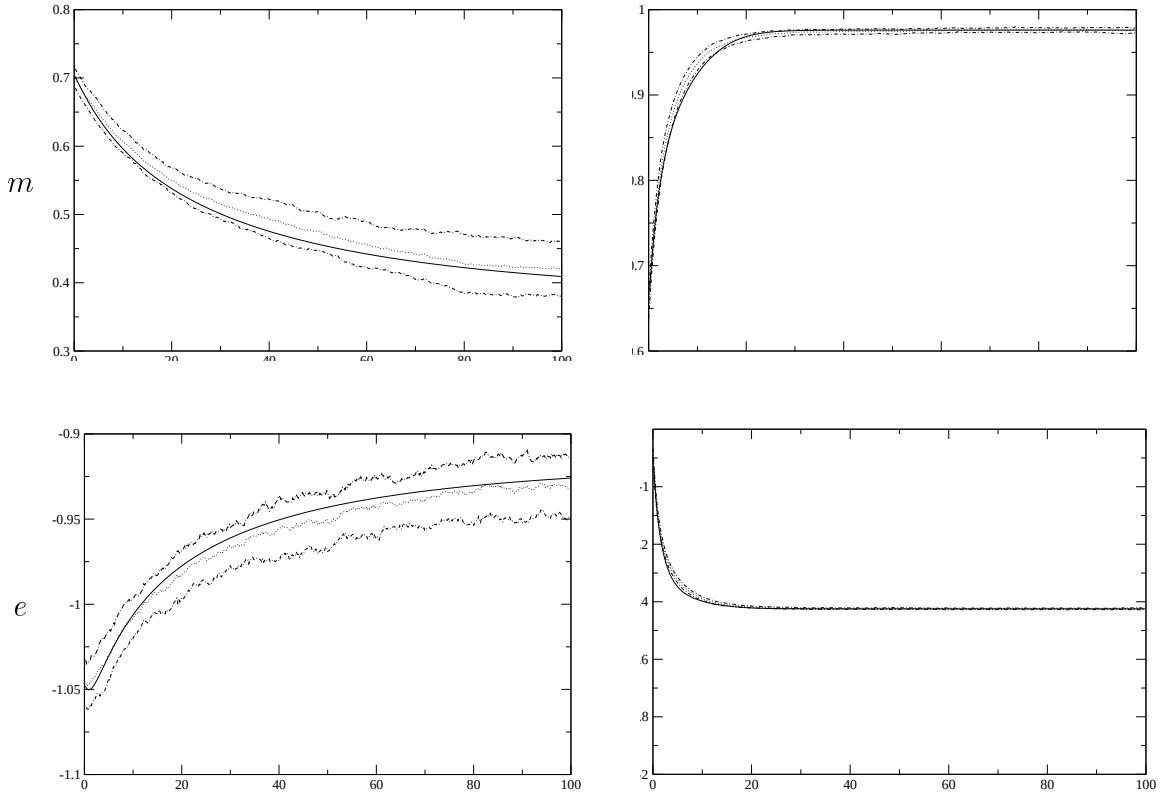
$$\frac{d}{dt}m = -m + \int dh\; D(h|m,e)\tanh(\beta h)$$
$$\frac{d}{dt}e = -2e - \int dh\; D(h|m,e)h\tanh(\beta h)$$

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

$$= \lim_{N\to\infty}\frac{1}{N}\sum_{i=1}^{N}\Big\langle\; \frac{\Sigma_{\boldsymbol{\sigma}}\,\delta[m - m(\boldsymbol{\sigma})]\delta[e - e(\boldsymbol{\sigma})]\delta[h - h_i(\boldsymbol{\sigma})]}{\Sigma_{\boldsymbol{\sigma}}\,\delta[m - m(\boldsymbol{\sigma})]\delta[e - e(\boldsymbol{\sigma})]}\;\Big\rangle_{\rm disorder}$$

random bonds, uniform degrees

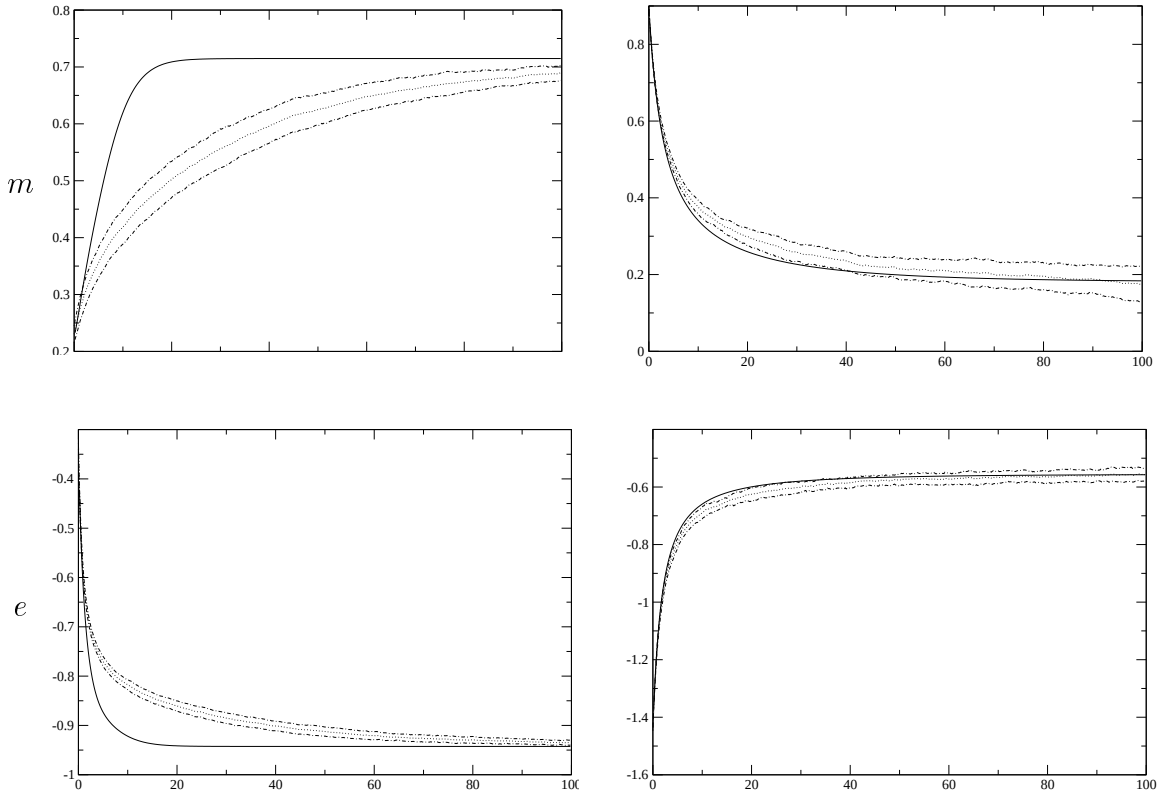
$$P(k) = \delta_{k,3} \qquad Q(J) = \eta\delta(J-1) + (1-\eta)\delta(J+1)$$



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

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, protein folding, ...)

- 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