Analysis of signalling in large protein interaction networks

Ton Coolen

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Several research and teaching initiatives
at maths-computation-biomedicine interface
at King's College London

Dec 2011: Institute for Mathematical and Molecular Biomedicine

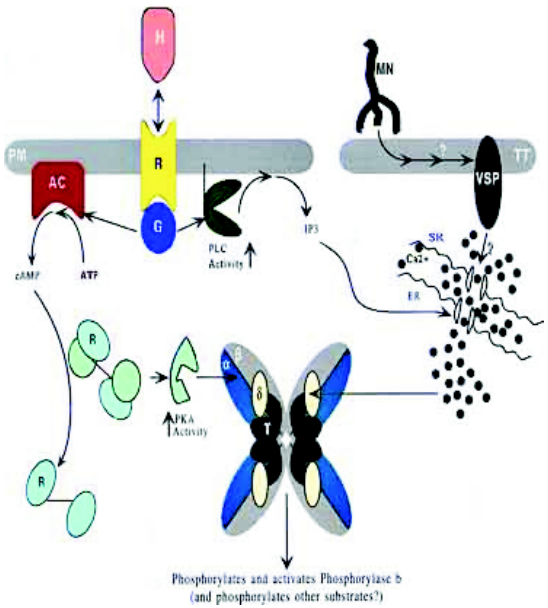
- biological networks:
  - graph theory for cellular signalling networks
  - network null models via MCMC processes
  - reaction dynamics in large protein interaction networks
- Bayesian analysis and biomedical statistics:
  - analysis of fluorescence lifetime data
  - clinical outcome prediction from biomarkers
  - survival analysis for heterogeneous cohorts with competing risks
- other topics:
  - theory of cell re-programming
  - immune networks

THIS TALK

- Problems with pathway analysis
- How to quantify protein network topology
- Analysis of signalling dynamics in large protein networks

Problems with proteomic pathway analysis

usual description:
reaction equations



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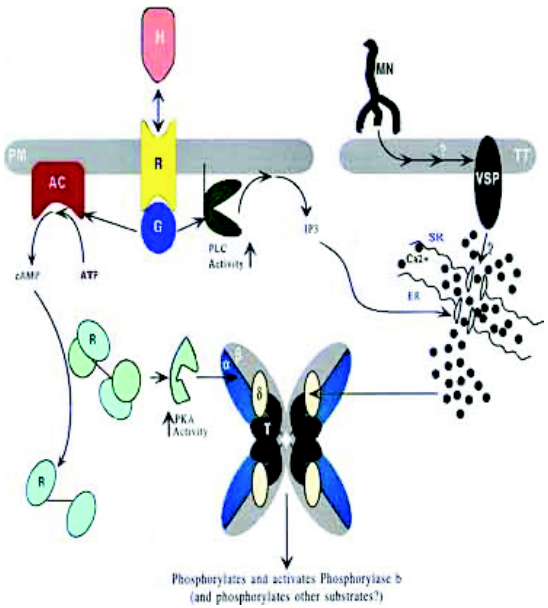

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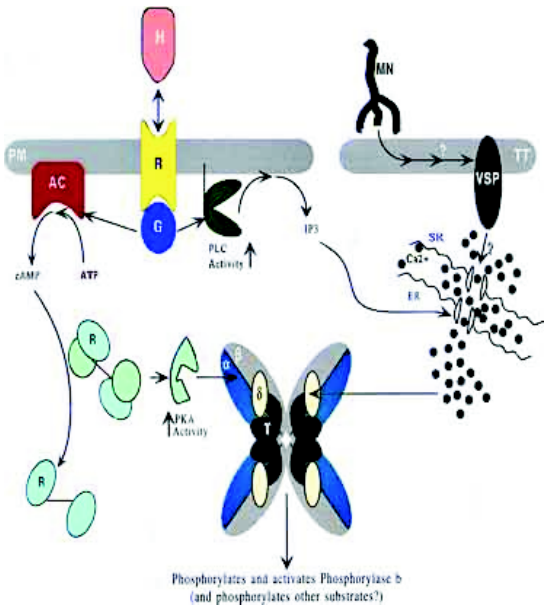

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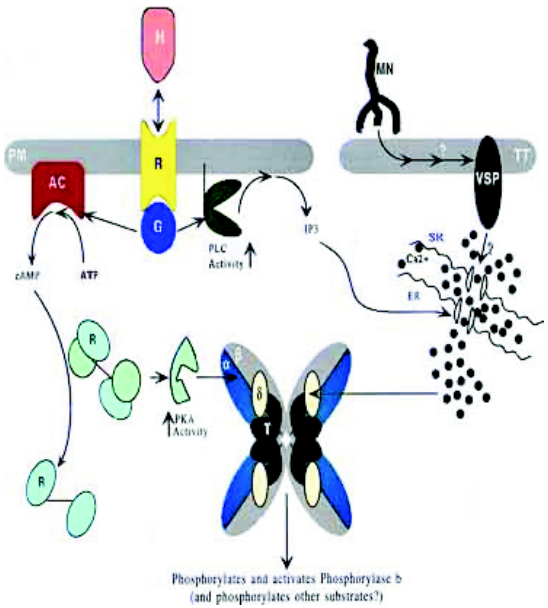

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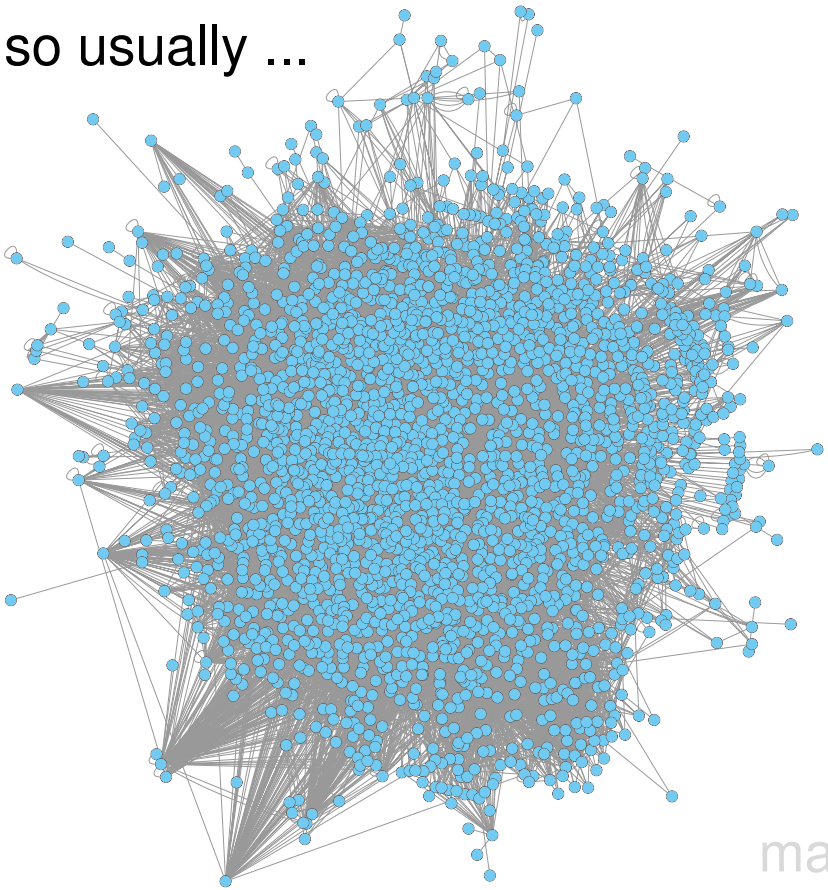
so usually ...



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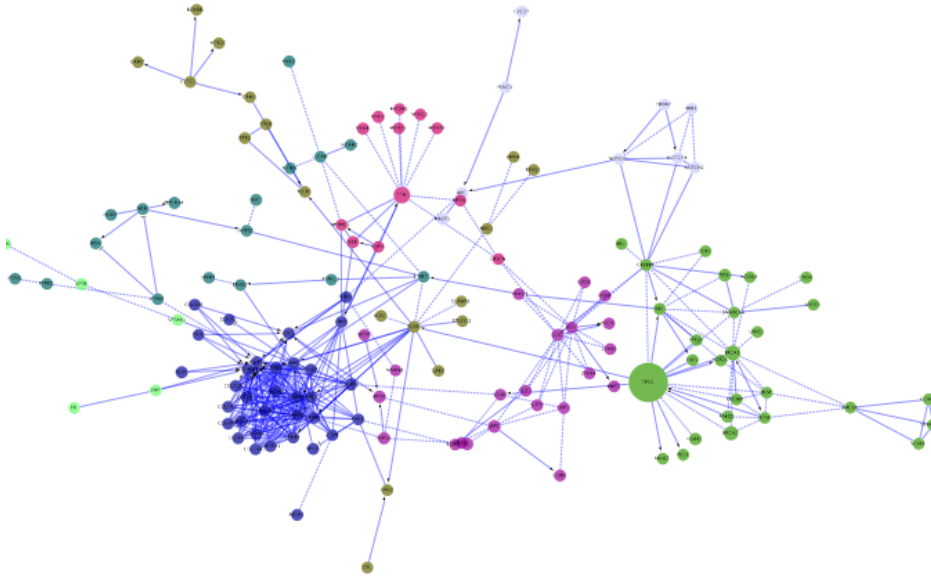

many-variable problem is not limited to biology
can we adapt methods from physics?

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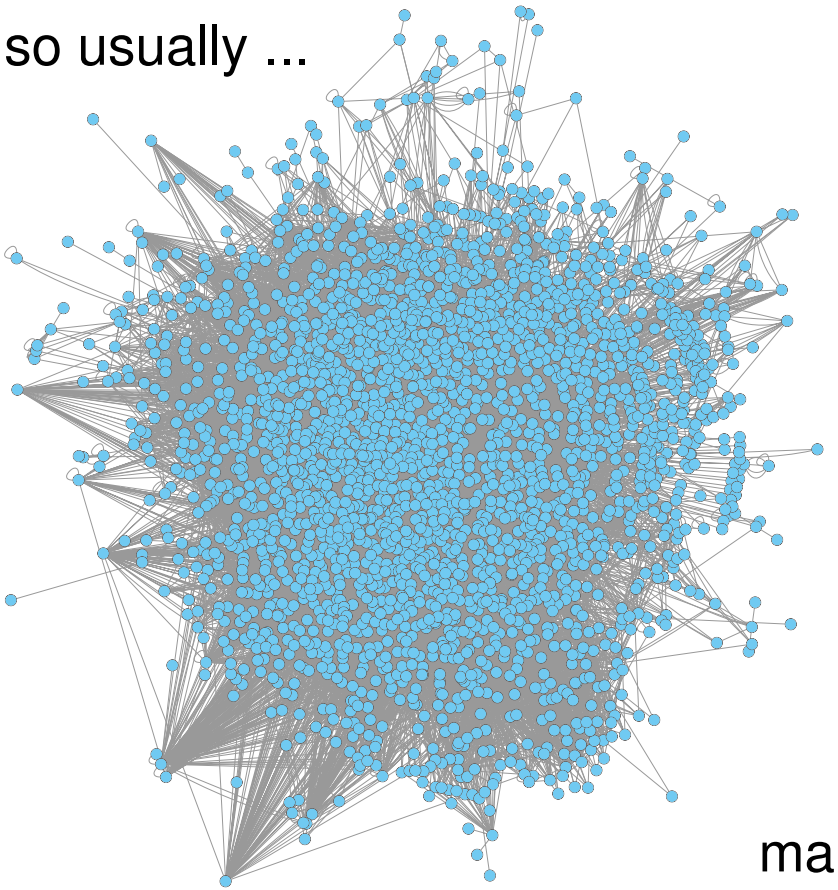

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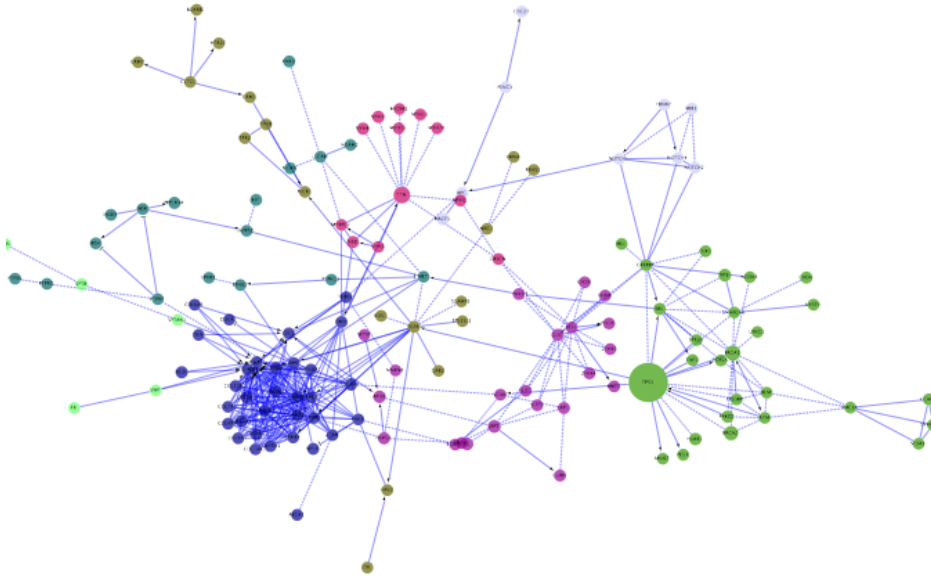

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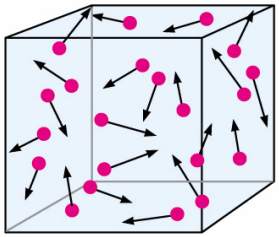
statistical physics



dynamical variables:

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

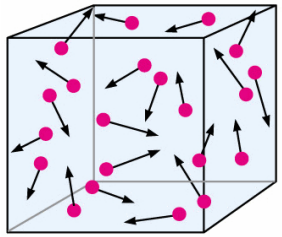
microscopic dynamics:

Newton's equations of motion
$\frac{d}{dt}(\vec{x}_1, \vec{v}_1) = \ldots,\ \frac{d}{dt}(\vec{x}_2, \vec{v}_2) = \ldots$ ← don't try to solve these!

macroscopic description:

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

statistical physics



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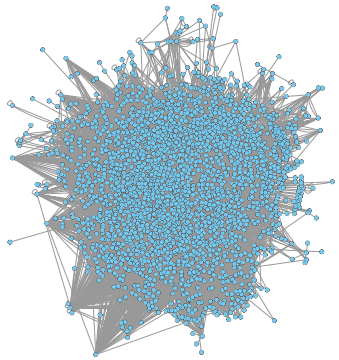
statistical biology?



dynamical variables:

concentr of proteins & complexes

$\vec{x}_1,\ \vec{x}_2,\ \vec{x}_3,\ \ldots$

microscopic dynamics:

reaction equations

$\frac{d}{dt}\vec{x}_1 = \ldots,\ \frac{d}{dt}\vec{x}_2 = \ldots, \frac{d}{dt}\vec{x}_3 = \ldots$

macroscopic description:

???

Proteome:

heterogeneous many-particle system,
small number of partners per node

- math methods since $\sim$1980/2000 (statics/dynamics)
- what is many? $N = 1000$ or more ...
- biology is not physics:
  no evolution to equilibrium, conservation laws ...

What should we expect to get out?

- predictions for **macroscopic** quantities in **typical** proteomes
  (correlation functions, response functions, ...)
- collective phenomena (e.g. phase transitions)
- not dependent on *details* of network or reaction rates,
  only on network and rate **statistics** ('self-averaging')

potential to address both of Kholodenko's fundamental problems

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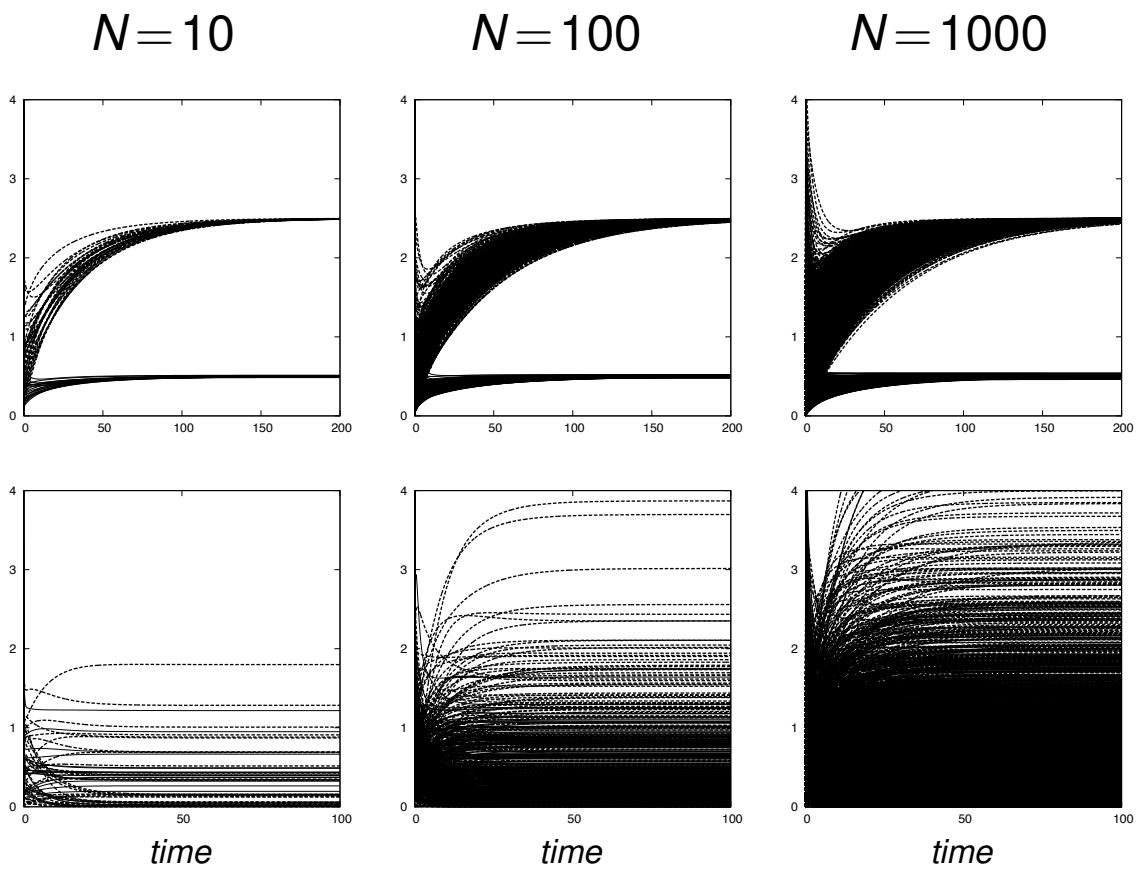
numerical illustration:

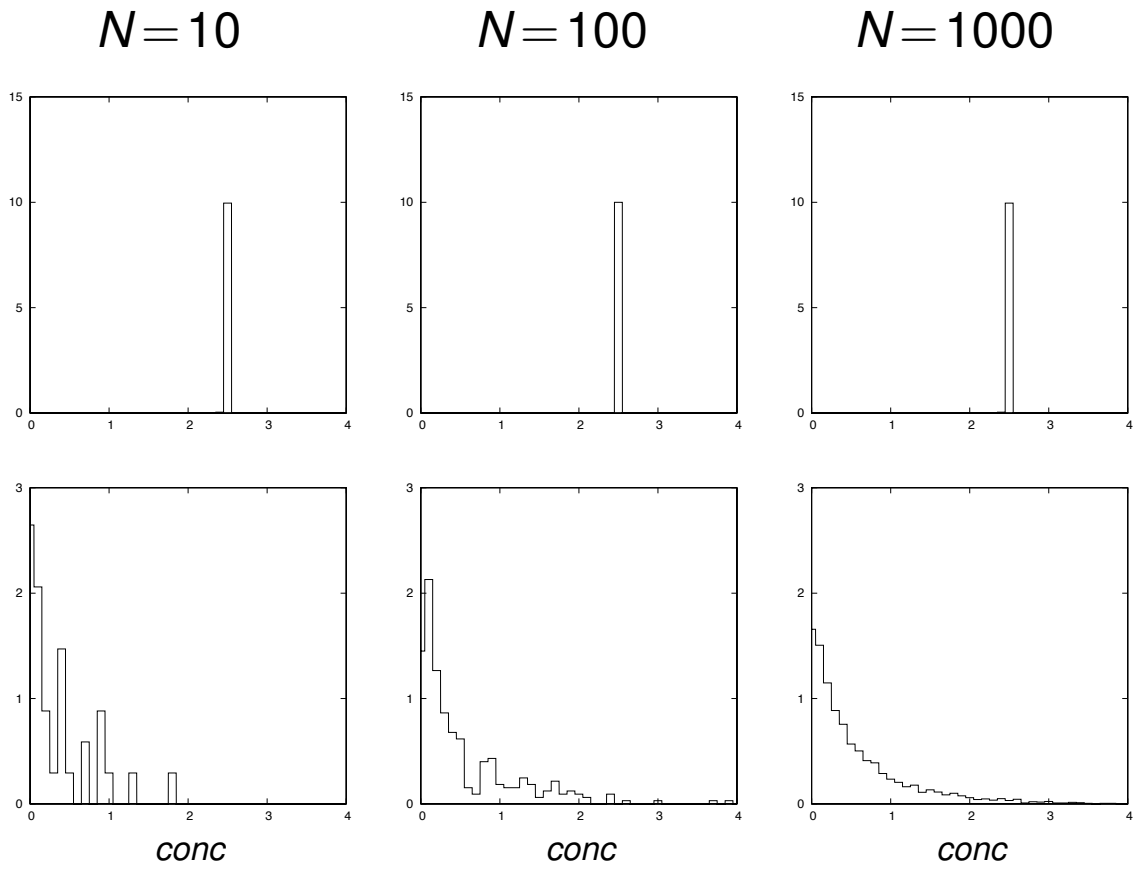
two states/protein,
binary complexes,

random topology,
average nr of partners: 7

dashed lines: conc of complexes
solid lines: conc of unbound proteins



e.g. distribution of complex concentrations in stationary state



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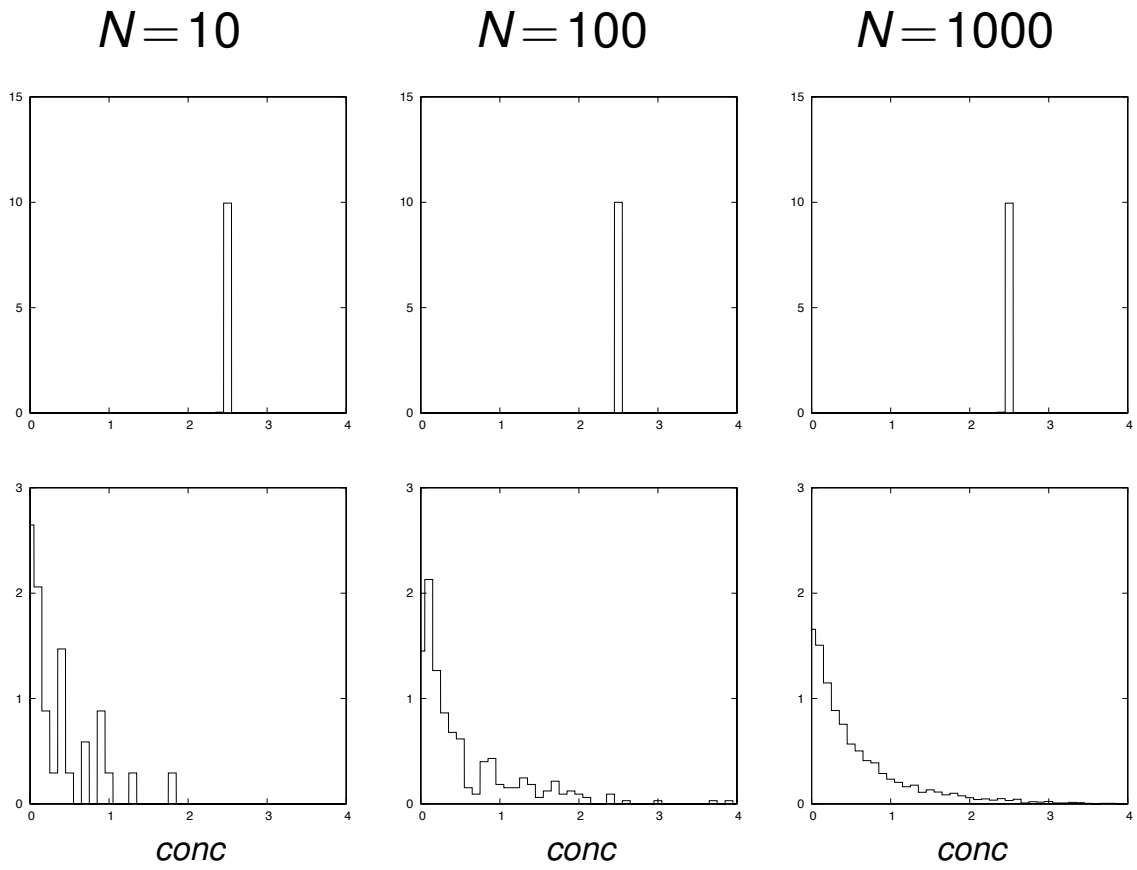

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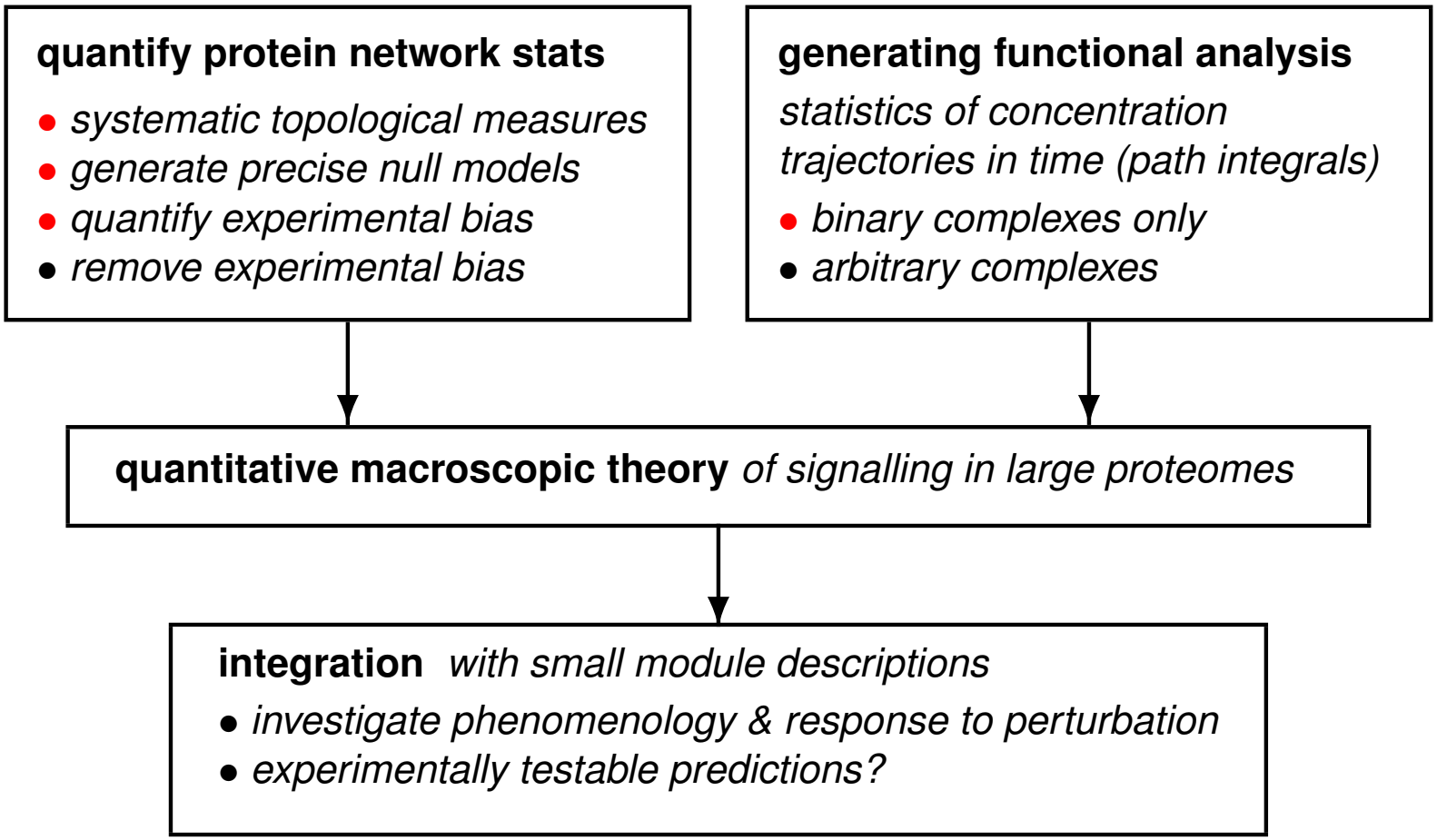
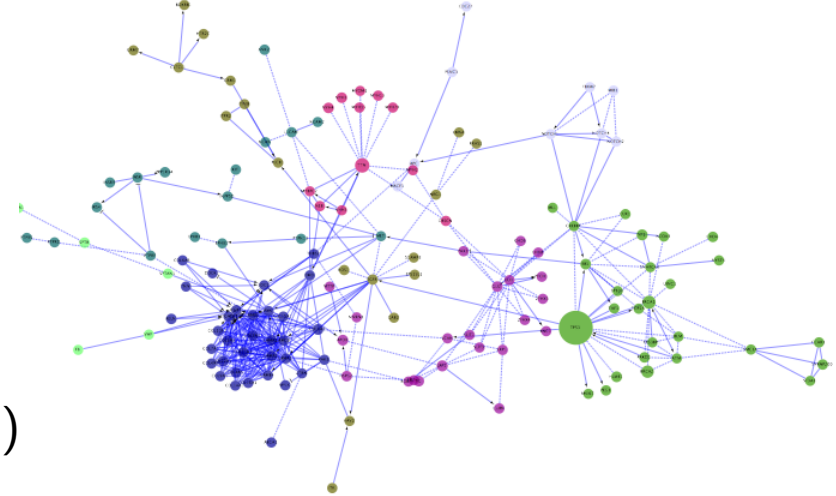
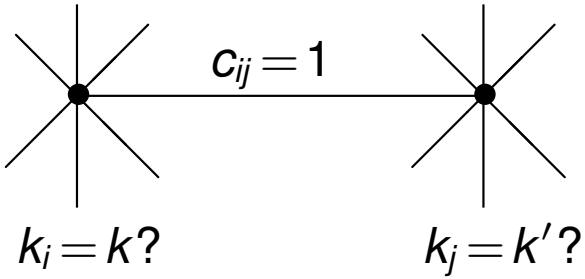
The research programme



Quantify protein network topology



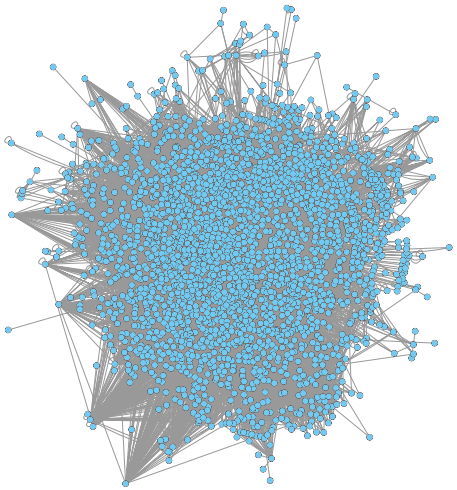
- Quantify topology beyond degrees:
  joint degree stats of connected nodes

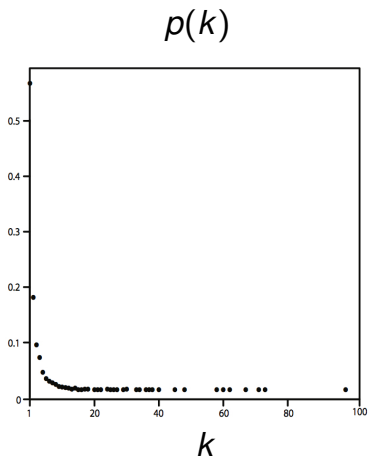


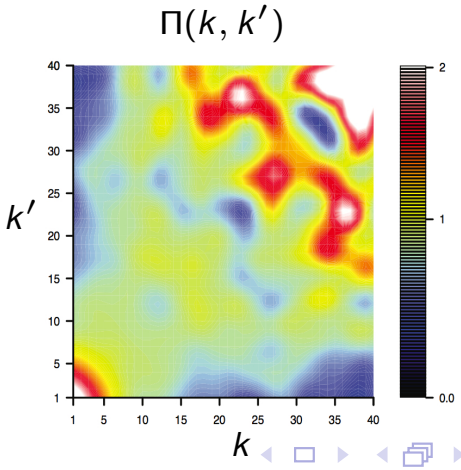
$W(k,k')$

- $W(k)=p(k)k/\langle k\rangle$: so use $\Pi(k,k')=W(k,k')/W(k)W(k')$

  $\Pi(k,k')\neq 1$:
  structural information in degree correlations

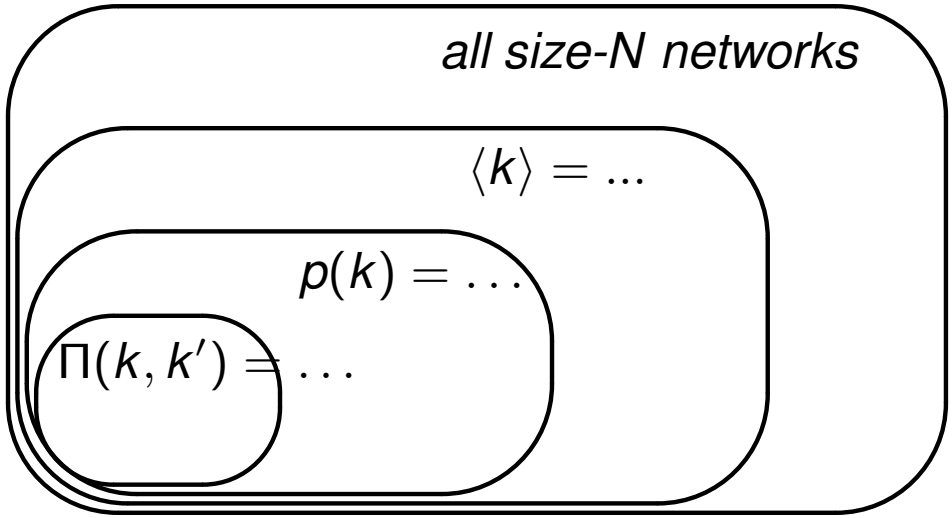






H sapiens
$N=9306$
$\langle k\rangle=7.53$

- network classification via increasingly detailed measurements



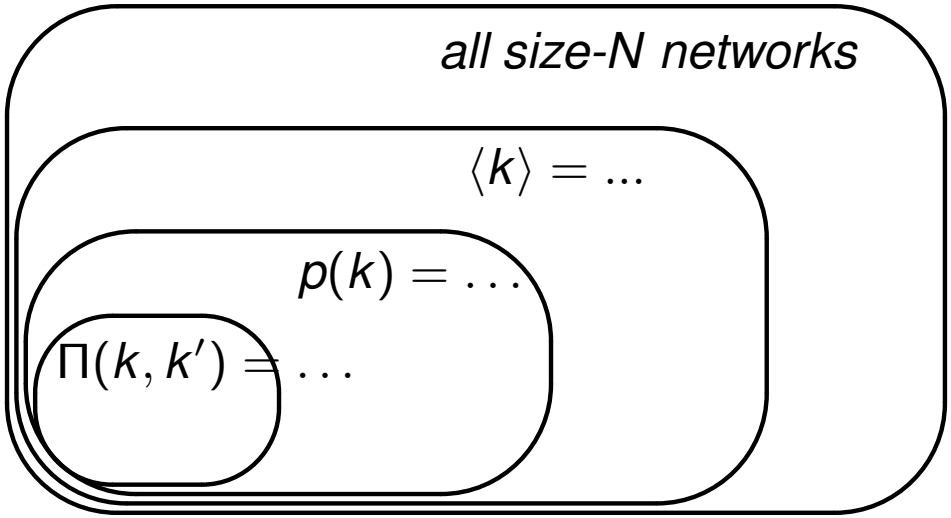
- Questions:
  - complexity: how many networks exist with given properties?
  - hypothesis testing: graphs with controlled features as null models (e.g. how 'special' are local modules?)
  - quantifying network dissimilarity

can al be done **analytically**
(information theory and statistical mechanics of complex graphs)

entropy & complexity in terms of $p(k)$ and $\Pi(k, k')$,
structural distances in terms of $p(k)$ and $\Pi(k, k')$

present focus: short loops

- network classification via increasingly detailed measurements



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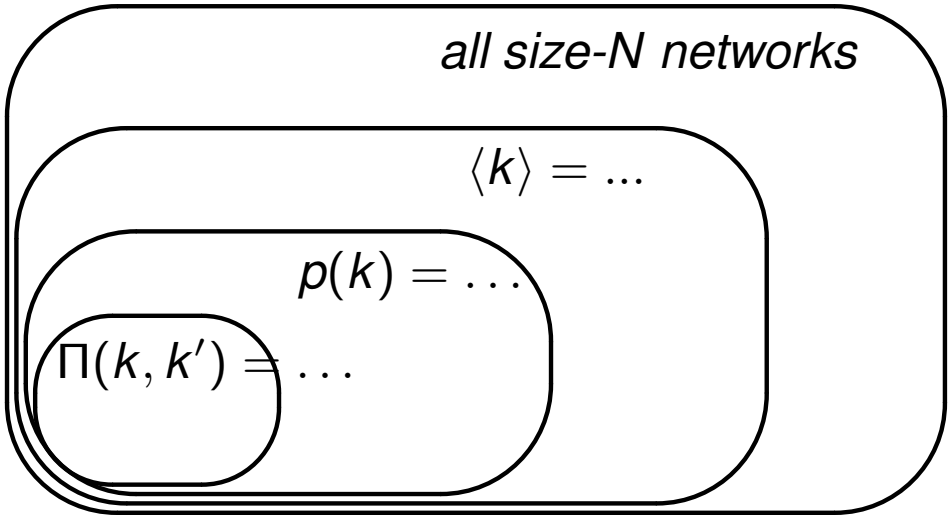
- network classification via increasingly detailed measurements



- Questions:
  - complexity: how many networks exist with given properties?
  - hypothesis testing: graphs with controlled features as null models (e.g. how 'special' are local modules?)
  - quantifying network dissimilarity

can al be done **analytically**
(information theory and statistical mechanics of complex graphs)

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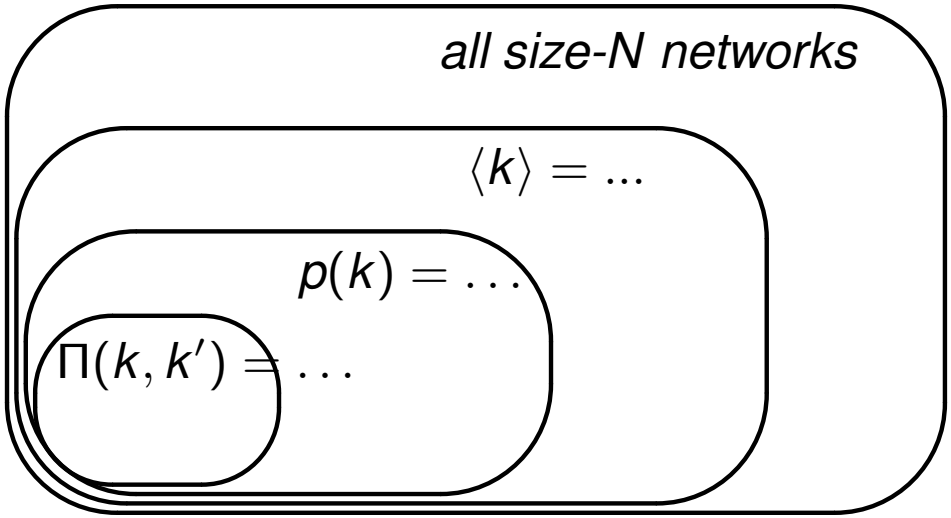

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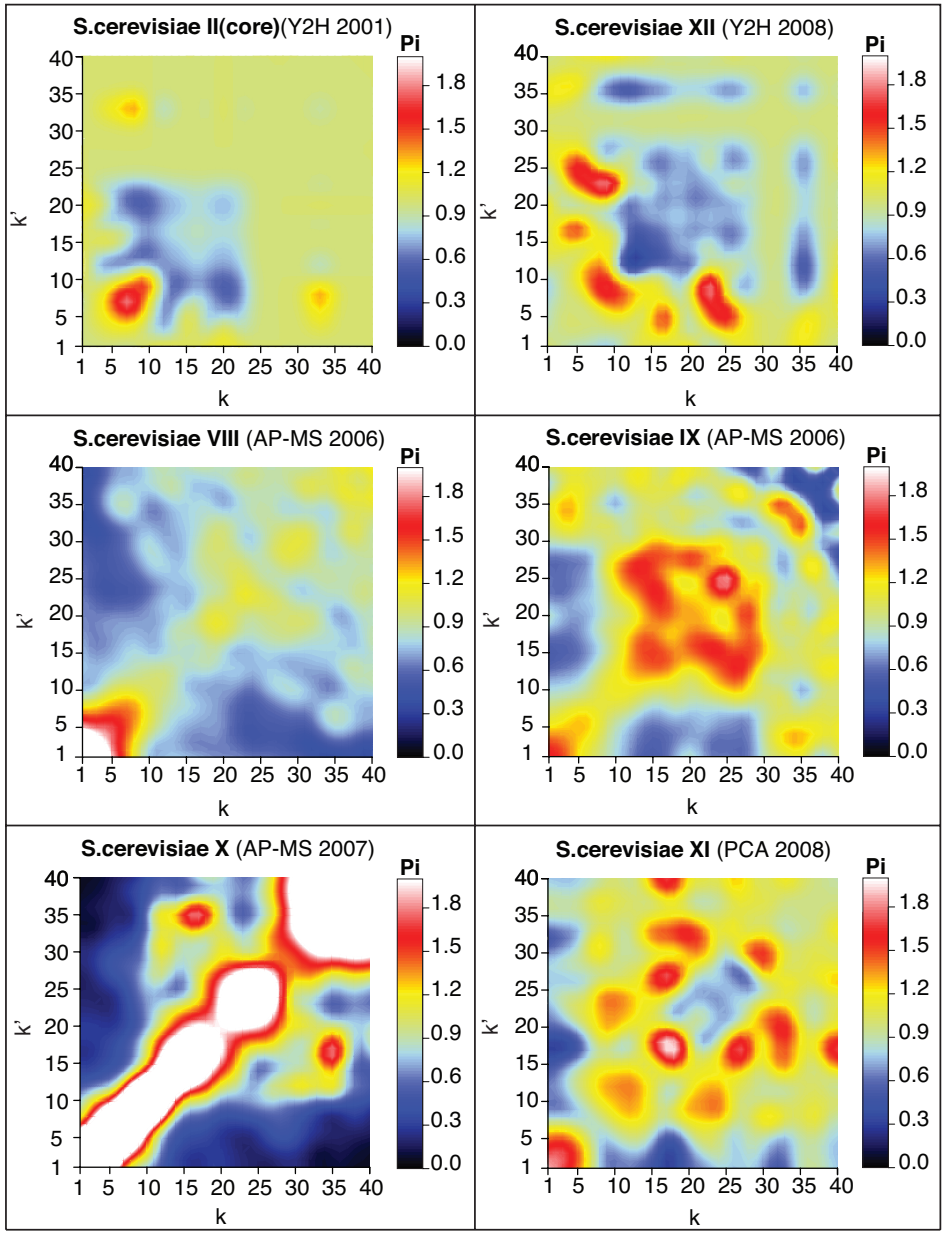
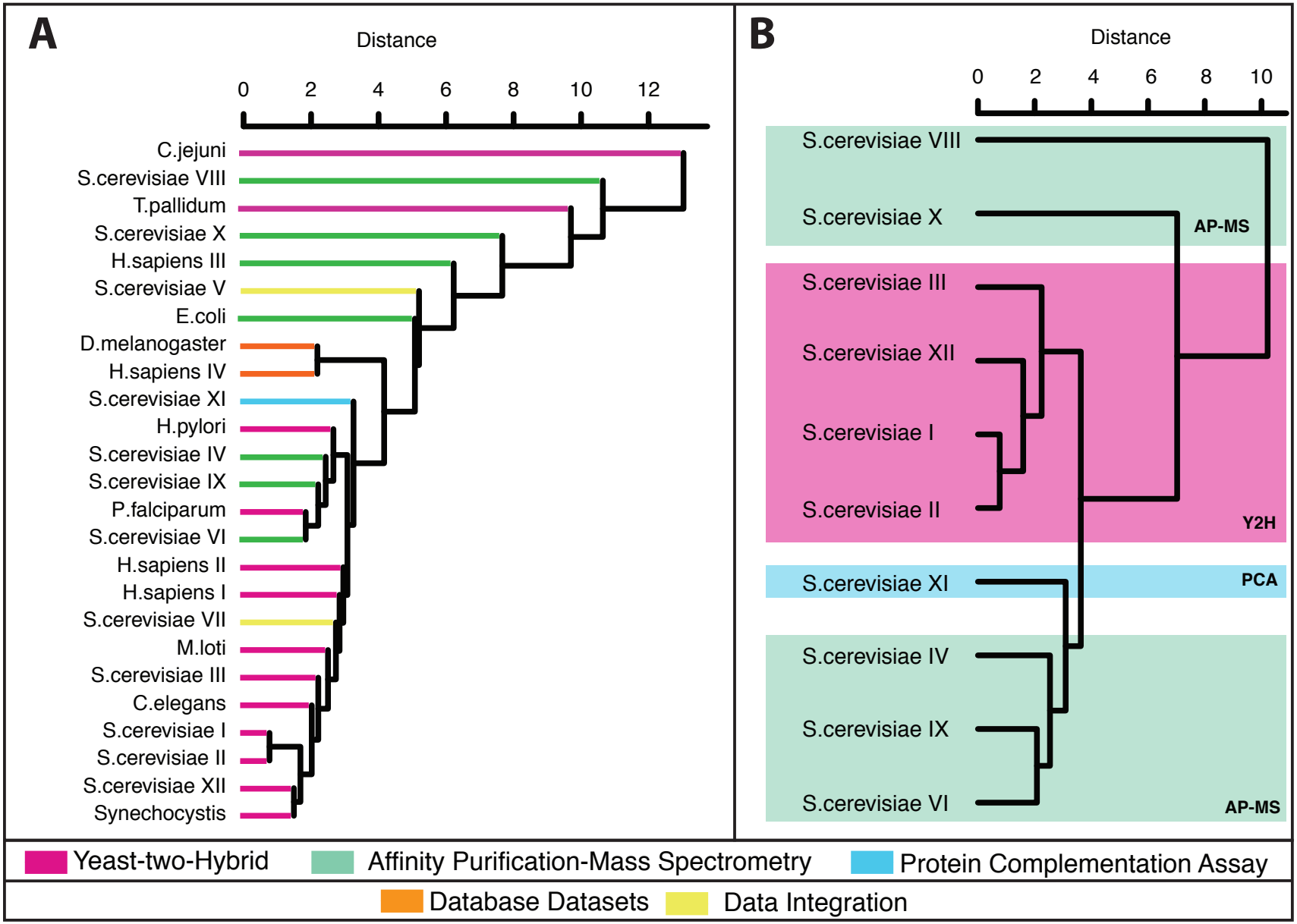
Can we trust protein interaction data?

e.g. yeast

$\Pi(k, k') \neq 1$:
degree-degree correlations





quantify sampling bias: see poster of Alessia Annibale

Signalling dynamics in the proteome

adapt techniques from many-particle physics
to do *many-particle biology*

- notation:

  $i = 1 \ldots N$ labels proteins
  x_i^α: concentr of protein i in state α
  x_{ij}: concentration of dimer $i \asymp j$

- events:

		rate:
complex formation:	$(i,\alpha) + (j,\beta) \to (i \asymp j)$	$k_{ij}^{\alpha\beta+} x_i^\alpha x_j^\beta$
complex dissociation:	$(i \asymp j) \to (i,\alpha) + (j,\beta)$	$k_{ij}^{\alpha\beta-} x_{ij}$
conformation change:	$(i,\alpha) \to (i,\beta)$	$\lambda_i^{\alpha\beta} x_i^\alpha$
protein degradation:	$(i,\alpha) \to \emptyset$	$\gamma_i^\alpha x_i^\alpha$
protein synthesis:	$\emptyset \to (i,\alpha)$	θ_i^α

- reaction eqns:

$$\frac{\mathrm{d}}{\mathrm{d}t}x_i^\alpha = \sum_j c_{ij} \overbrace{\sum_\beta [k_{ij}^{\alpha\beta-} x_{ij} - k_{ij}^{\alpha\beta+} x_i^\alpha x_j^\beta]}^{\textit{complex formation \& dissociation}} + \overbrace{\sum_\beta [\lambda_i^{\beta\alpha} x_i^\beta - \lambda_i^{\alpha\beta} x_i^\alpha]}^{\textit{post-transl modification}} + \overbrace{\theta_i^\alpha}^{\textit{synthesis}} - \overbrace{\gamma_i^\alpha x_i^\alpha}^{\textit{decay}}$$

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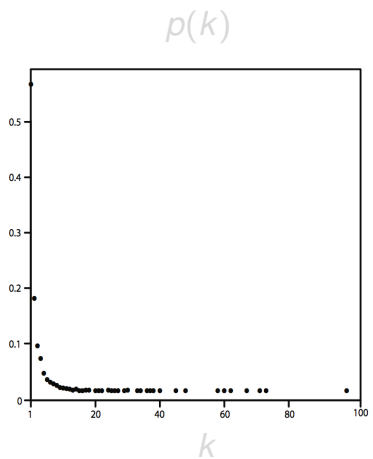
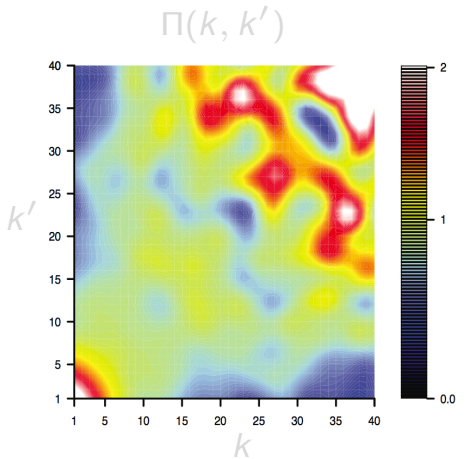
- tailored random interaction network,

  prescribed degrees $p(k)$,
  and degree correlations $W(k, k')$





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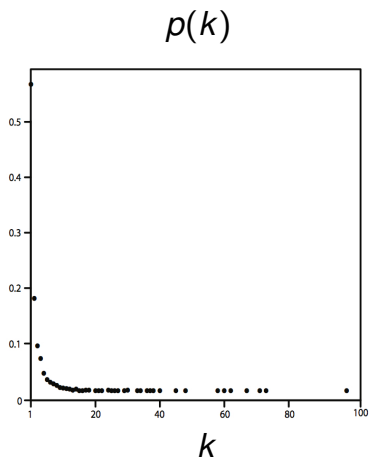

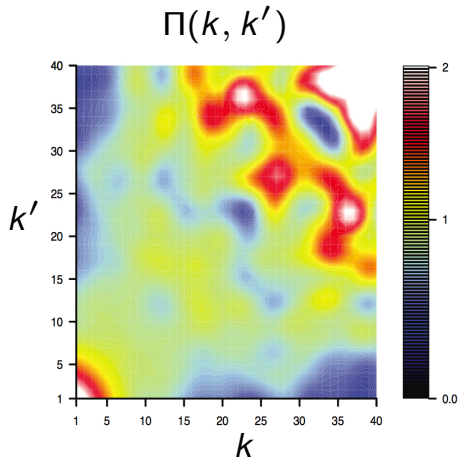

preparation:

- solve equations for $\{x_{ij}\}$:

$$\frac{\mathrm{d}}{\mathrm{d}t}x_i^\alpha(t) = F_i^\alpha[t,\{x\}]$$

$$F_i^\alpha[t,\{x\}] = \theta_i^\alpha - \gamma_i^\alpha x_i^\alpha + \sum_\beta [\lambda_i^{\beta\alpha} x_i^\beta - \lambda_i^{\alpha\beta} x_i^\alpha] + \sum_j c_{ij} \int \mathrm{d}s \sum_{\rho\lambda} \underbrace{W_{\alpha;\rho\lambda}(t-s|\mathbf{k}_{ij})\, x_i^\rho(t-s) x_j^\lambda(t-s)}$$

effective delayed free-protein interaction

$$W_{\alpha;\rho\lambda}(\tau|\mathbf{k}) = k^{\rho\lambda+}\Big[\sum_\beta k^{\alpha\beta-}\theta[\tau]\mathrm{e}^{-k^-\tau} - \delta_{\alpha\rho}\delta(\tau)\Big]$$

closed equations for unbound protein concentrations,
price paid: equations are nonlocal in time

generating functional analysis:

calculate correlations, response functions etc ...
without solving reaction equations!

- generating functional:

$$Z[\boldsymbol{\psi}] = \int \Big[\prod_{i\alpha t} \mathrm{d}x_i^\alpha(t)\Big]\; \mathrm{e}^{\mathrm{i}\sum_{i\alpha}\int \mathrm{d}t\;\psi_i^\alpha(t)x_i^\alpha(t)} \prod_{i\alpha t}\delta\Big[x_i^\alpha(t+\mathrm{d}t)-x_i^\alpha(t)-F_i^\alpha[t,\{x\}]\mathrm{d}t\Big]$$

path integral over all possible concentration trajectories in time

$$x_i^\alpha(t) = -\mathrm{i}\lim_{\boldsymbol{\psi}\to 0}\frac{\delta Z[\boldsymbol{\psi}]}{\delta\psi_i^\alpha(t)} \qquad x_i^\alpha(t)x_j^\beta(t') = -\lim_{\boldsymbol{\psi}\to 0}\frac{\delta^2 Z[\boldsymbol{\psi}]}{\delta\psi_i^\alpha(t)\delta\psi_j^\beta(t')}$$

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  $Z[\psi]$ will no longer depend on network details, just on statistics
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after further calculations ...
(path integral techniques, saddle-point integration, etc)

- key macroscopic quantities:

$$D[\{x\}|\{y\}] = \frac{1}{N}\sum_j \left\langle \delta[\{x\} - \{x_j\}] \right\rangle \Big|_{\theta_j^\alpha(t)\to\theta_j^\alpha(t)+y_\alpha(t)\ \forall\alpha}$$

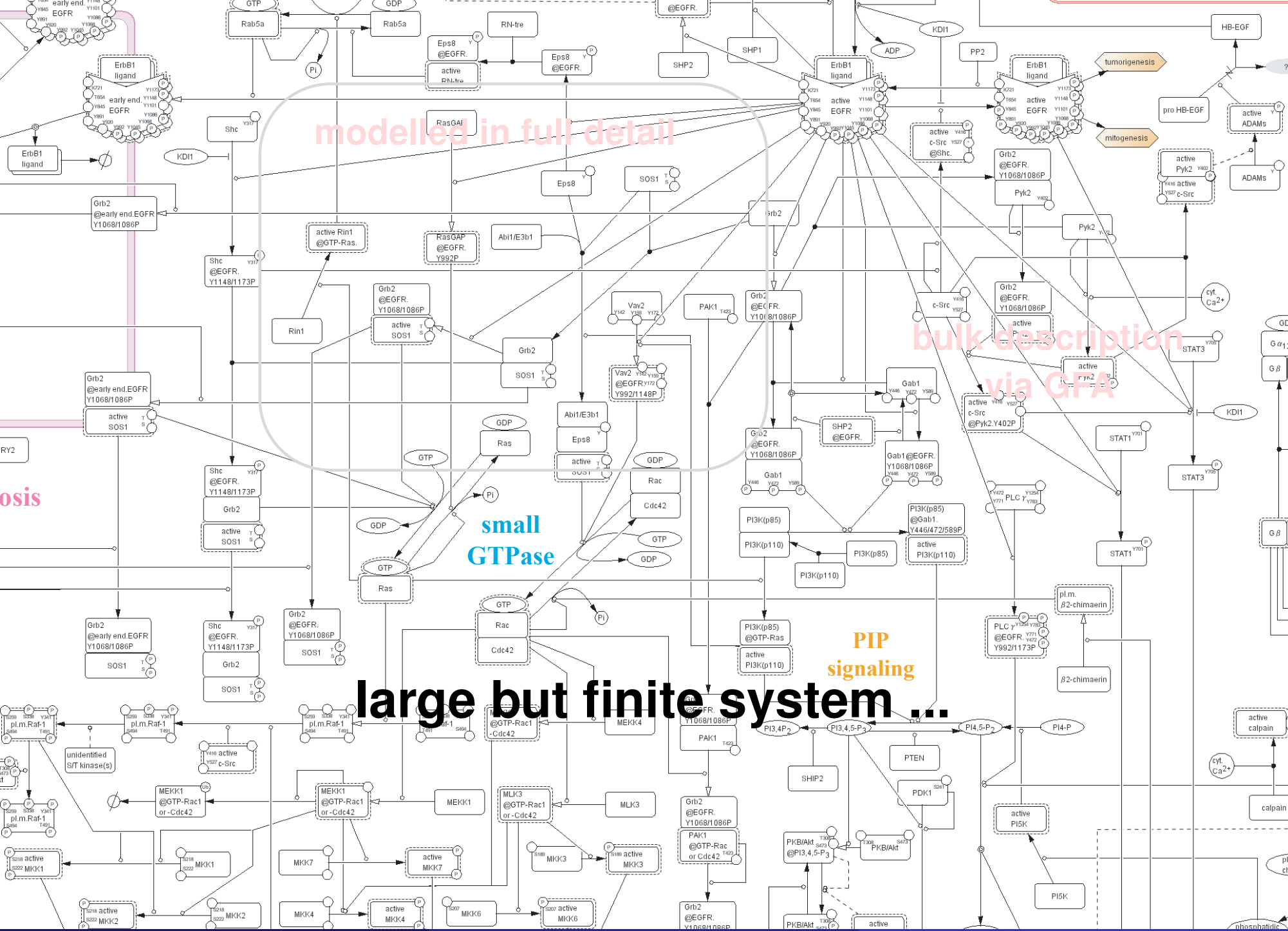
$$W[\{x\}|\{y\}] = \frac{1}{N}\sum_j \left\langle \delta[\{x\} - \{x_j\}] \right\rangle \Big|_{k_j\to k_j-1,\ \ \theta_j^\alpha(t)\to\theta_j^\alpha(t)+y_\alpha(t)\ \forall\alpha}$$

$\{x\}$ = trajectories $x_\alpha(t)$ for all α
$\{y\}$ = time dep production rate perturbations $y_\alpha(t)$ for all α

- macroscopic equations:

$$W = \mathcal{G}_1[W], \quad D = \mathcal{G}_2[W], \qquad \mathcal{G}_{1,2}: \ \textit{complicated but exact formulas}$$

equations interpreted in terms of
response to single-node perturbations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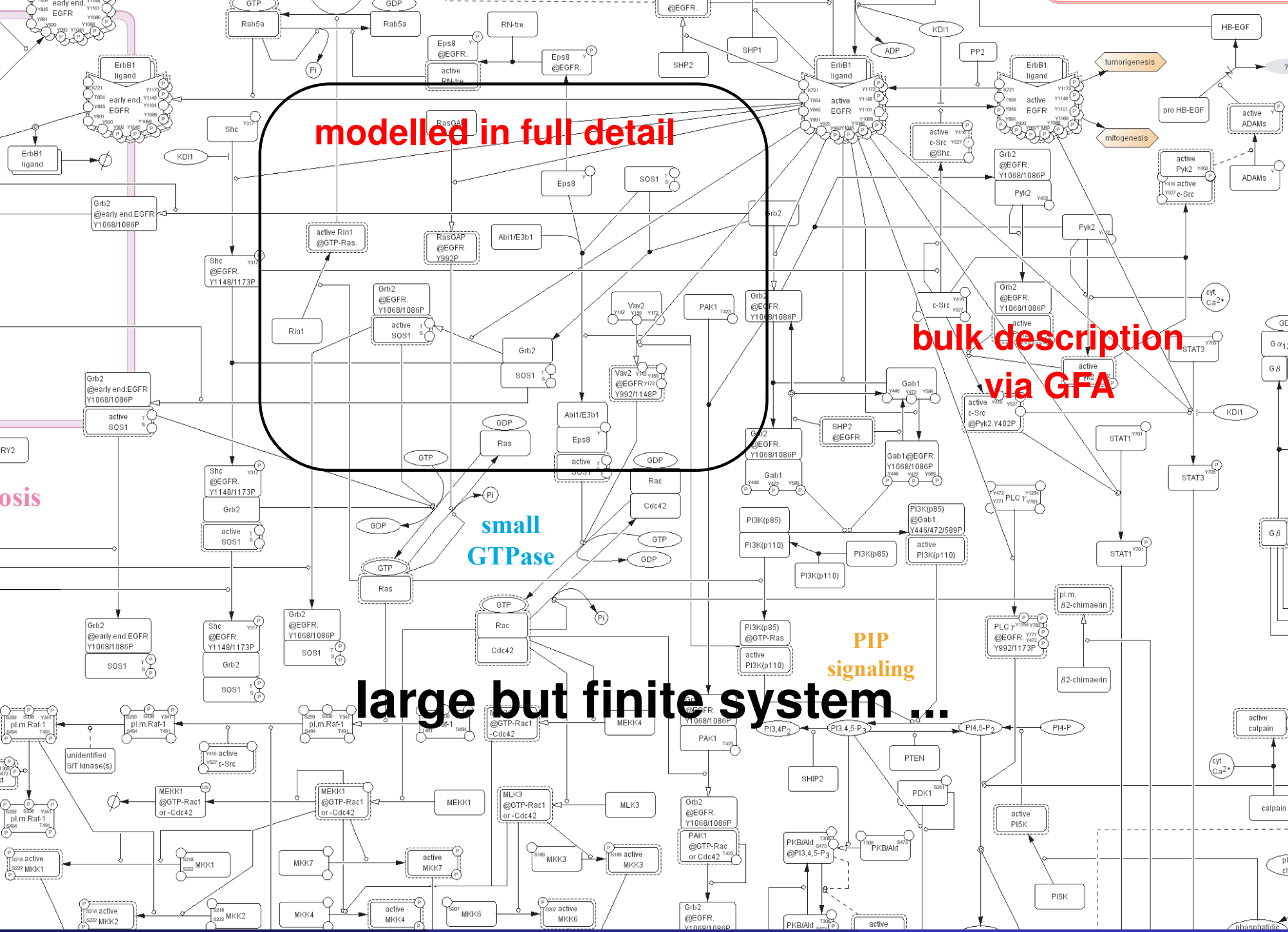
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  can be studied by adapting methods from many-particle physics
- requires systematic characterisation of network topologies
  (many spin-offs)
- macroscopic theory in terms of W and D
  (concentration trajectory response to time-dep perturbation)

- Ongoing:
  - solving equations for W and D
  - phase diagrams, analysis of instabilities
  - remove bias from protein network data
  - include short loops in network characterisation

- Next:
  - inclusion of higher order complexes
  - integration with 'small module' reaction equations
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