Generating functional analysis of complex formation and dissociation in large protein interaction networks

A pilot study

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Outline

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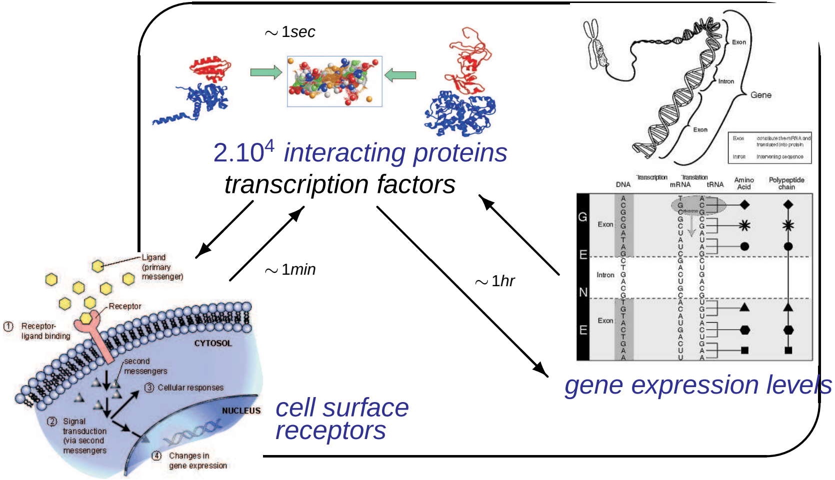
Introduction - signalling in the cell



$\sim 1sec$

2.10^4 *interacting proteins*

transcription factors

$\sim 1min$

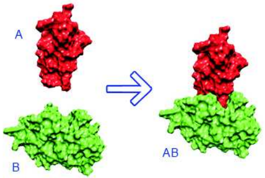
$\sim 1hr$

cell surface receptors

gene expression levels

Introduction - protein interaction networks

- *function* of a protein:
  controlled by *conformation* (3-dim shape)
- protein *interaction*:
  form *complexes*, trigger shape changes in other proteins via temporary *complexes*
- usual description:
  kinetic equations



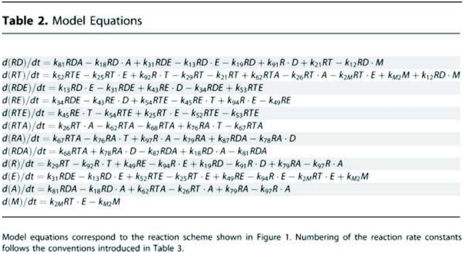


Table 2. Model Equations

$$d(RD)/dt = k_{81}RDA - k_{18}RD \cdot A + k_{31}RDE - k_{13}RD \cdot E - k_{19}RD + k_{91}R \cdot D + k_{21}RT - k_{12}RD \cdot M$$
$$d(RT)/dt = k_{52}RTE - k_{25}RT \cdot E + k_{92}R \cdot T - k_{29}RT - k_{21}RT + k_{62}RTA - k_{26}RT \cdot A - k_{2M}RT \cdot E + k_{M2}M + k_{12}RD \cdot M$$
$$d(RDE)/dt = k_{13}RD \cdot E - k_{31}RDE + k_{43}RE \cdot D - k_{34}RDE + k_{53}RTE$$
$$d(RE)/dt = k_{34}RDE - k_{43}RE \cdot D + k_{54}RTE - k_{45}RE \cdot T + k_{94}R \cdot E - k_{49}RE$$
$$d(RTE)/dt = k_{45}RE \cdot T - k_{54}RTE + k_{25}RT \cdot E - k_{52}RTE - k_{53}RTE$$
$$d(RTA)/dt = k_{26}RT \cdot A - k_{62}RTA - k_{68}RTA + k_{76}RA \cdot T - k_{67}RTA$$
$$d(RA)/dt = k_{67}RTA - k_{76}RA \cdot T + k_{97}R \cdot A - k_{79}RA + k_{87}RDA - k_{78}RA \cdot D$$
$$d(RDA)/dt = k_{68}RTA + k_{78}RA \cdot D - k_{87}RDA + k_{18}RD \cdot A - k_{81}RDA$$
$$d(R)/dt = k_{29}RT - k_{92}R \cdot T + k_{49}RE - k_{94}R \cdot E + k_{19}RD - k_{91}R \cdot D + k_{79}RA - k_{97}R \cdot A$$
$$d(E)/dt = k_{31}RDE - k_{13}RD \cdot E + k_{52}RTE - k_{25}RT \cdot E + k_{49}RE - k_{94}R \cdot E - k_{2M}RT \cdot E + k_{M2}M$$
$$d(A)/dt = k_{81}RDA - k_{18}RD \cdot A + k_{62}RTA - k_{26}RT \cdot A + k_{79}RA - k_{97}R \cdot A$$
$$d(M)/dt = k_{2M}RT \cdot E - k_{M2}M$$

Model equations correspond to the reaction scheme shown in Figure 1. Numbering of the reaction rate constants follows the conventions introduced in Table 3.

'The most significant challenges that face mechanistic modeling are the lack of quantitative kinetic data and the combinatorial increase in the number of distinct species ... of the protein network ...' (Kholodenko 2006)

Model definitions - elementary processes

- N protein species, labeled $i = 1, \ldots, N$
  post-translational states, labeled $\alpha = 1 \ldots, q$
  complex where i binds to j: $(i \asymp j)$
- concentration of (i, α): x_i^α
  concentration of $(i \asymp j)$: x_{ij} $\quad (x_{ij} = x_{ji})$
- elementary events:

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

- protein interaction network: $\mathbf{c} = \{c_{ij}\}$
  $c_{ij} = c_{ji} = 1$ if $(i \asymp j)$ possible
  $c_{ij} = c_{ji} = 0$ otherwise

Model definitions - microscopic equations

- Michaelis-Menten reaction equations:

$$\frac{\mathrm{d}}{\mathrm{d}t}x_i^\alpha = \sum_j c_{ij}\sum_\beta [k_{ij}^{\alpha\beta-}x_{ij} - k_{ij}^{\alpha\beta+}x_i^\alpha x_j^\beta] + \theta_i^\alpha - \gamma_i^\alpha x_i^\alpha$$

$$\frac{\mathrm{d}}{\mathrm{d}t}x_{ij} = c_{ij}\sum_{\alpha\beta}[k_{ij}^{\alpha\beta+}x_i^\alpha x_j^\beta - k_{ij}^{\alpha\beta-}x_{ij}]$$

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

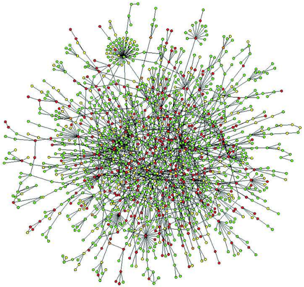
$$\frac{\mathrm{d}}{\mathrm{d}t}x_i^\alpha(t) = \sum_j c_{ij}\int \mathrm{d}s \sum_{\rho\lambda} W_{\alpha;\rho\lambda}(t-s|\mathbf{k}_{ij})x_i^\rho(s)x_j^\lambda(s) + \theta_i^\alpha(t) - \gamma_i^\alpha(t)x_i^\alpha(t)$$

effective protein interaction

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

limitations:
no higher order complexes, no spatial variation of concentrations

Model definitions - interaction network, reaction rates



- disordered system on
  finitely connected random graph
  disorder: $\{c_{ij}, k_{ij}^{\alpha\beta\pm}\}$
  $N \sim 2.10^4, \quad \langle k \rangle \sim 7$
- protein interaction network $\mathbf{c}$:
  degrees $\{k_i\}$ random, from realistic $p(k)$

$$P(\mathbf{c}) \;=\; \frac{1}{Z}\prod_i \delta_{k_i,\sum_{j\neq i} c_{ij}} \cdot \prod_i \Big[c_0\delta_{c_{ii},1} + (1-c_0)\delta_{c_{ii},0}\Big]$$

- 'on/off' rates $\mathbf{k}_{ij} = \{k_{ij}^{\alpha\beta\pm}\}$:
  random, from realistic $P(\mathbf{k})$

  necessary symmetry: $P(S\mathbf{k}) = P(\mathbf{k})$ for all $\mathbf{k}$
  where $(S\mathbf{k})^{\alpha\beta\pm} = k^{\beta\alpha\pm}$

Model definitions - can we trust network data?

Interactome data suffer from *methodological bias* ...

Species	Average Degree	Kmax	Detection Method	Reference
C.elegans	2.96	99	Y2H	Simonis et al. 2008
C.jejuni	17.5	207	Y2H	Parrish et al. 2007
D.melanogaster	6.85	176	DD	Stark et al. 2006
E.coli	7.05	641	AP-MS^1	Arifuzzaman et al. 2006
H.pylori	3.87	55	Y2H	Rain et al. 2001
H.sapiens I	3.37	125	Y2H	Rual et al. 2005
H.sapiens II	3.71	95	Y2H	Stelzl et al. 2005
H.sapiens III	5.67	314	AP-MS^1	Ewing et al. 2007
H.sapiens IV	7.52	247	DD	Prasad et al 2008
M.loti	3.43	401	Y2H	Shimoda et al. 2008
P.falciparum	4.17	51	Y2H	Lacount et al. 2005
S.cerevisiae I	1.82	24	Y2H	Uetz et al. 2000
S.cerevisiae II	1.91	55	Y2H	Ito et al. 2001(core)
S.cerevisiae III	2.69	279	Y2H	Ito et al. 2001
S.cerevisiae IV	4.58	62	AP-MS^1	Ho et al. 2002
S.cerevisiae V	9.05	118	DI	Von Mering et al. 2002
S.cerevisiae VI	4.73	53	AP-MS^1	Gavin et al. 2003
S.cerevisiae VII	3.61	32	DI	Han et al. 2004
S.cerevisiae VIII	16.77	955	AP-MS^2	Gavin et al. 2006
S.cerevisiael X	5.25	141	AP-MS^1	Krogan et al. 2006
S.cerevisiae X	11.15	127	AP-MS^2	Collins et al. 2007
S.cerevisiae XI	4.7	58	PCA	Tarassov et al. 2008
S.cerevisiae XII	2.34	86	Y2H	Yu et al. 2009
Synechocysti	3.25	51	Y2H	Sato et al. 2007
T.pallidum	10.01	285	Y2H	Titz et al. 2008

a

🟪 Yeast-two-Hybrid ⬜ Afinity Purification-Mass Spectrometry^1 🟧 Database Datasets

🟨 Data Integration 🟩 Afinity Purification-Mass Spectrometry^2 🟦 Protein Complementary Assay

GFA - the disorder-averaged functional

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

- De Dominicis:

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

- average over $\{c_{ij}, k_{ij}^{\alpha\beta\pm}\}$: $\quad Z[\psi] \to \overline{Z[\psi]}$
- calculate observables *without solving eqns*:

$$\overline{x_i^\alpha(t)} = -\mathrm{i}\lim_{\psi\to 0}\frac{\delta}{\delta\psi_i^\alpha(t)}\overline{Z[\psi]}$$

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

- statistical mechanics: calculate $\lim_{N\to\infty}\overline{Z[\psi]}$
(saddle-point integration, closed eqns for dynamical order parameters)

GFA - introduction of dynamical order parameters

- to achieve factorization in $\overline{Z[\psi]}$ we need

$$P[\{x,\hat{x}\}|\{\mathbf{x},\hat{\mathbf{x}}\},\boldsymbol{\omega}] = \frac{1}{N}\sum_i \prod_\alpha \delta[\{x_\alpha\}-\{x_i^\alpha\}]\delta[\{\hat{x}_\alpha\}-\{\hat{x}_i^\alpha\}]\mathrm{e}^{-\mathrm{i}\omega_i}$$

- for $\psi \to 0$:

$$\lim_{N\to\infty} N^{-1}\log\overline{Z[\psi]} = \mathrm{extr}_{\{P,Q\}}\Big\{\Psi[\{P,Q\}]+\Phi[\{P\}]+\Omega[\{Q\}]+\mathrm{const}\Big\}$$

$$\Psi = -\int\{\mathrm{d}x\,\mathrm{d}\hat{x}\}P[\{x,\hat{x}\}]Q[\{x,\hat{x}\}]-\frac{1}{2}\langle k\rangle$$

$$\Phi = \frac{1}{2}\langle k\rangle\int\{\mathrm{d}x\,\mathrm{d}\hat{x}\,\mathrm{d}x'\mathrm{d}\hat{x}'\}P[\{x,\hat{x}\}]P[\{x',\hat{x}'\}]\times$$

$$\Big\langle \mathrm{e}^{-\mathrm{i}\int \mathrm{d}t\mathrm{d}\tau \sum_{\rho\lambda}k^{\rho\lambda+}x_\rho(t-\tau)x'_\lambda(t-\tau)\big\{\theta[\tau]\mathrm{e}^{-k^-\tau}\sum_{\alpha\beta}k^{\alpha\beta-}[\hat{x}_\alpha(t)+\hat{x}'_\beta(t)]-\delta(\tau)[\hat{x}_\rho(t)+\hat{x}'_\lambda(t)]\big\}}\Big\rangle_{\mathbf{k}}$$

$$\Omega = \Big\langle \log\int_{-\pi}^{\pi}\frac{\mathrm{d}\omega}{2\pi}\mathrm{e}^{\mathrm{i}\omega k}\int\{\mathrm{d}x\,\mathrm{d}\hat{x}\}\;\mathrm{e}^{\mathrm{i}\int\mathrm{d}t\sum_\alpha \hat{x}_\alpha(t)\left[\frac{\mathrm{d}}{\mathrm{d}t}x_\alpha(t)-\theta_\alpha(t)+\gamma_\alpha(t)x_\alpha(t)\right]}$$

$$\times\mathrm{e}^{Q[\{x,\hat{x}\}]\mathrm{e}^{-\mathrm{i}\omega}}\Big\langle \mathrm{e}^{-\mathrm{i}s\sum_{\alpha\rho\lambda}\int\mathrm{d}t\mathrm{d}\tau\;W_{\alpha;\rho\lambda}(\tau|\mathbf{k})\hat{x}_\alpha(t)x_\rho(t-\tau)x_\lambda(t-\tau)}\Big\rangle_{\mathbf{k},s}\Big\rangle_{\{\theta,\gamma,k\}}$$

GFA - saddle-point equations

$$\frac{\delta}{\delta P[\{x,\hat{x}\}]}\Psi[\{P,Q\}]+\frac{\delta}{\delta P[\{x,\hat{x}\}]}\Phi[\{P\}]=0$$
$$\frac{\delta}{\delta Q[\{x,\hat{x}\}]}\Psi[\{P,Q\}]+\frac{\delta}{\delta Q[\{x,\hat{x}\}]}\Omega[\{Q\}]=0$$

- transform:

$$W[\{x\}|\{y\}] \;=\; \int\{\mathrm{d}\hat{x}\}P[\{x,\hat{x}\}]\mathrm{e}^{-\mathrm{i}\int\mathrm{d}t\,\sum_\alpha y_\alpha(t)\hat{x}_\alpha(t)}$$

- physical meaning:

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

pick randomly a species j, remove one binding partner,
and increase production rates of j by $\{y\}$
what is probability to observe for j the concentrations $\{x\}$?

- implications:
  $\int\{\mathrm{d}x\}\,W[\{x\}|\{y\}]=1$ for all $\{y\}$, and *causality*

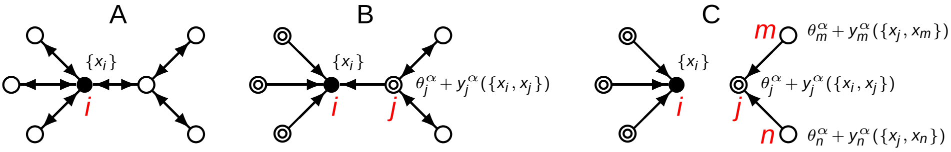
GFA - implications of causality

explicit closed eqn for $W[\{x\}|\{y\}]$,
exact for $N \to \infty$

$$\begin{aligned} W[\{x\}|\{y\}] \;=\; & \sum_k \frac{p(k+1)(k+1)}{\langle k\rangle} \Big\langle \int \prod_{\ell\leq k} \Big\{ \{\mathrm{d}x_\ell \mathrm{d}y_\ell\} W[\{x_\ell\}|\{y_\ell\}] \\ & \times \prod_{\alpha t} \delta\Big[y_{\ell\alpha}(t) - \int \mathrm{d}\tau \sum_{\rho\lambda} W_{\alpha;\rho\lambda}(\tau|S\mathbf{k}_\ell)\, x_{\ell\rho}(t-\tau)\, x_\lambda(t-\tau)\Big]\Big\} \\ & \times \prod_{\alpha t} \delta\Big\{ \mathrm{d}x_\alpha(t) - \mathrm{d}t\Big[\theta_\alpha(t) + y_\alpha(t) - \gamma_\alpha(t)x_\alpha(t) + \sum_{\rho\lambda} \int \mathrm{d}\tau\, x_\rho(t-\tau) \\ & \times \Big(sW_{\alpha;\rho\lambda}(\tau|\mathbf{k})\, x_\lambda(t-\tau) + \sum_{\ell\leq k} W_{\alpha;\rho\lambda}(\tau|\mathbf{k}_\ell)\, x_{\ell\lambda}(t-\tau)\Big)\Big]\Big\}\Big\rangle_{\mathbf{k},s;\{\mathbf{k}_\ell\},\{\theta,\gamma|k\}} \end{aligned}$$

physical measure without node removal: $D[\{x\}|\{y\}]$
eqn for D: replace $p(k+1)(k+1)/\langle k\rangle \to p(k)$ in RHS

GFA - cavity interpretation of order parameter eqns



- A: site i with four partners (the set ∂_i)
  B: modified graph: flow from $i \rightarrow \partial_i$ is prohibited (i effectively removed), production rates of *all* $j \in \partial_i$ adjusted to compensate

  compare A to B: eqn for $D[\{x\}|\{y\}]$ in terms of $W[\{x\}|\{y\}]$

- C: further modification: flow from $j \rightarrow \partial_j$ is prohibited (j is removed), production rates of nodes in $\partial_j = \{m, n\}$ adjusted to compensate

  compare B to C: eqn for $W[\{x\}|\{y\}]$ in terms of $W[\{x\}|\{y\}]$

argument requires:
tree-like nature of graph, absence of degree-degree correlations

Macroscopic equation to be solved

Exact for $N \to \infty$,
all ingredients have clear interpretation

$$
\begin{aligned}
{\color{red}W[\{x\}|\{y\}]} \;=\; & \sum_k \frac{p(k+1)(k+1)}{\langle k\rangle}\Big\langle \int \prod_{\ell\le k}\Big\{\{\mathrm{d}x_\ell \mathrm{d}y_\ell\}{\color{red}W[\{x_\ell\}|\{y_\ell\}]} \\
& \qquad \times \prod_{\alpha t}\delta\Big[y_{\ell\alpha}(t) - \int \mathrm{d}\tau \sum_{\rho\lambda} W_{\alpha;\rho\lambda}(\tau|S\mathbf{k}_\ell)x_{\ell\rho}(t-\tau)x_\lambda(t-\tau)\Big]\Big\} \\
\times \prod_{\alpha t}\delta\Big\{\mathrm{d}x_\alpha(t) - \mathrm{d}t\Big[& \theta_\alpha(t) + y_\alpha(t) - \gamma_\alpha(t)x_\alpha(t) + \sum_{\rho\lambda}\int \mathrm{d}\tau\, x_\rho(t-\tau) \\
& \times\Big(sW_{\alpha;\rho\lambda}(\tau|\mathbf{k})x_\lambda(t-\tau) + \sum_{\ell\le k} W_{\alpha;\rho\lambda}(\tau|\mathbf{k}_\ell)x_{\ell\lambda}(t-\tau)\Big)\Big]\Big\}\Big\rangle_{\mathbf{k},s;\{\mathbf{k}_\ell\},\{\theta,\gamma|k\}}
\end{aligned}
$$

Solution of macroscopic eqns - simplifying limits

- low connectivity, $p(k) \to \delta_{k1}$

$$\begin{aligned} W[\{x\}|\{y\}] &= \Big\langle \prod_{\alpha t} \delta\Big\{ \mathrm{d}x_\alpha(t) - \mathrm{d}t\Big[\theta_\alpha(t) + y_\alpha(t) - \gamma_\alpha(t)x_\alpha(t) \\ &\qquad + s\sum_{\rho\lambda}\int \mathrm{d}\tau\; W_{\alpha;\rho\lambda}(\tau|\mathbf{k})x_\rho(t-\tau)x_\lambda(t-\tau)\Big)\Big]\Big\}\Big\rangle_{\mathbf{k},s,\{\theta,\gamma\}} \end{aligned}$$

- high connectivity: $k^{\alpha\beta^+} = \tilde{k}^{\alpha\beta+}/\langle k\rangle,\ \langle k\rangle \to \infty$
  closed eqn for $W[\{x\}] = W[\{x\}|\{0\}]$

$$\begin{aligned} W[\{x\}] &= \Big\langle \prod_{\alpha t} \delta\Big[\mathrm{d}x_\alpha(t) - \mathrm{d}t\Big(\theta_\alpha(t) - \gamma_\alpha(t)x_\alpha(t) \\ &\qquad + s\sum_{\rho\lambda}\int \mathrm{d}\tau\; W_{\rho\lambda}(\tau|\mathbf{k})x_\rho(t-\tau)x_\lambda(t-\tau) \\ &\qquad + \sum_{\rho\lambda}\int \mathrm{d}\tau\; W_{\rho\lambda}(\tau|S\tilde{\mathbf{k}})x_\lambda(t-\tau)\int\{\mathrm{d}x'\}\; W[\{x'\}]x'_\rho(t-\tau)\Big)\Big]\Big\rangle_{s,\mathbf{k},\tilde{\mathbf{k}},\{\theta,\gamma\}} \end{aligned}$$

Solution of macroscopic eqns - ideas that don't work

- Numerical solution?

  $W[\{x\}|\{y\}]$: nr of order parameters grows exponentially with time
  here: arguments of $W[\{x\}|\{y\}]$ are *continuous* paths ...

- Variational methods?

  rationale: exploit origin of theory as a saddle-point eqns of functional
  apply transformations directly to $\Psi[\{P,Q\}]+\Phi[\{P\}]+\Omega[\{Q\}]$:

  kernel to specify protein-protein interaction

$$\begin{aligned}\mathcal{M}[\{x,y\};\{x',y'\}] &= \Big\langle \prod_{\alpha t}\delta\Big[y_\alpha(t)-\int\!\mathrm{d}\tau\sum_{\rho\lambda}W_{\alpha;\rho\lambda}(\tau|\mathbf{k})x_\rho(t-\tau)x'_\lambda(t-\tau)\Big] \\ &\quad\times\prod_{\alpha t}\delta\Big[y'_\alpha(t)-\int\!\mathrm{d}\tau\sum_{\rho\lambda}W_{\alpha;\rho\lambda}(\tau|S\mathbf{k})x'_\rho(t-\tau)x_\lambda(t-\tau)\Big]\Big\rangle_{\mathbf{k}}\end{aligned}$$

and $F[\{\theta\};s,\mathbf{k}]$ as soln of

$$\frac{\mathrm{d}}{\mathrm{d}t}x_\alpha(t) = \theta_\alpha(t)-\gamma_\alpha(t)x_\alpha(t)+s\sum_{\rho\lambda}\int\!\mathrm{d}\tau\; W_{\alpha;\rho\lambda}(\tau|\mathbf{k})x_\rho(t-\tau)x_\lambda(t-\tau)$$

Solution of macroscopic eqns - ideas that don't work

- surface being extremized:

$$
\begin{aligned}
\mathcal{L}[\{V,W\}] \;=\; & \frac{1}{2} - \int\{\mathrm{d}x\,\mathrm{d}y\}\, W[\{x\}|\{y\}]V[\{y\}|\{x\}] \\
& + \frac{1}{2}\int\{\mathrm{d}x\,\mathrm{d}y\,\mathrm{d}x'\mathrm{d}y'\}\, W[\{x\}|\{y\}]\,\mathcal{M}[\{x,y\};\{x',y'\}]\, W[\{x'\}|\{y'\}] \\
& + \sum_k \frac{p(k)}{\langle k\rangle}\Big\langle \log\int\{\mathrm{d}x\}\int\prod_{\ell\leq k}\Big[\{\mathrm{d}y_\ell\}V[\{y_\ell\}|\{x\}]\Big]\Big\langle\delta\Big[\{x\}-F\big[\{\theta+\sum_{\ell\leq k}y_\ell\};s,\mathbf{k}\big]\Big]\Big\rangle\Big\rangle
\end{aligned}
$$

- construct $\mathcal{L}[\{W\}]$ whose minimum gives true solution?
  systematic variational approximations of W?

  never possible!
  if W obeys causality: $\mathcal{L}[\{V,W\}]$ independent of $\mathcal{M}[.;.]$ ...

Solution of macroscopic eqns - alternative routes

iterative soln of $W[\{x\}|\{y\}]=\Omega[\{x\}|\{y\},W]$?

$$W_{n+1}[\{x\}|\{y\}]=\Omega[\{x\}|\{y\},W_n], \qquad W_0[\{x\}|\{y\}]=\delta[\{x\}]$$

- $n=1$: environment of ‘free’ nodes

$$W_1[\{x\}|\{y\}] \;=\; \sum_k \frac{p(k+1)(k+1)}{\langle k\rangle}\Big\langle \delta\Big[\{x\}-F\big[\{\theta+y\};s,\mathbf{k}\big]\Big]\Big\rangle_{\mathbf{k},s,\{\theta,\gamma|k\}}$$

- $n=2$: environment of interacting nodes

$$\begin{aligned}W_2[\{x\}|\{y\}] \;=\; &\sum_k \frac{p(k+1)(k+1)}{\langle k\rangle}\Big\langle \int \prod_{\ell\leq k}\Big\{\{\mathrm{d}x_\ell \mathrm{d}y_\ell\}W_1[\{x_\ell\}|\{y_\ell\}] \\ &\times\prod_{\alpha t}\delta\Big[y_{\ell\alpha}(t)-\int\!\mathrm{d}\tau\sum_{\rho\lambda}W_{\alpha;\rho\lambda}(\tau|S\mathbf{k}_\ell)x_{\ell\rho}(t-\tau)x_\lambda(t-\tau)\Big]\Big\} \\ \times\prod_{\alpha t}\delta\Big\{\mathrm{d}x_\alpha(t)-\mathrm{d}t\Big[&\theta_\alpha(t)+y_\alpha(t)-\gamma_\alpha(t)x_\alpha(t)+\sum_{\rho\lambda}\int\!\mathrm{d}\tau\; x_\rho(t-\tau) \\ &\times\Big(sW_{\alpha;\rho\lambda}(\tau|\mathbf{k})x_\lambda(t-\tau)+\sum_{\ell\leq k}W_{\alpha;\rho\lambda}(\tau|\mathbf{k}_\ell)x_{\ell\lambda}(t-\tau)\Big)\Big]\Big\}\Big\rangle\end{aligned}$$

Solution of macroscopic eqns - alternative routes

GFA is fully exact, but
nr of order parameters grows *exponentially* with time ...

Dynamical replica method (DRT)?

- choose macroscopic observables $\mathbf{\Omega}(\mathbf{x})=(\Omega_1(\mathbf{x}),\ldots,\Omega_k(\mathbf{x}))$
  formalism gives

  $$\mathrm{d}\mathbf{\Omega}/\mathrm{d}t=\mathcal{F}[\mathbf{\Omega}] \qquad \mathbf{\Omega}=\lim_{N\to\infty}\overline{\langle\mathbf{\Omega}(\mathbf{x})\rangle}$$

  best possible closed eqns for chosen observables
  but no direct prescription for choice ...
- Do observables $\mathbf{\Omega}(\mathbf{x})$ exists for which DRT is exact?
  yes! nr of order parameters grows *linearly* with time
- tasks:

  (i) connect two formalisms,

  $\mathbf{\Omega}$, DRT eqns $\Leftrightarrow$ $W[\{x\}|\{y\}]$, GFA eqns

  (ii) identify *simplest* observables $\mathbf{\Omega}(\mathbf{x})$

Summary

- GFA can be applied successfully to protein interaction networks
- stochastic process for nontrivial ‘effective single protein’
- order parameter $W[\{x\}|\{y\}]$ (path response function on cavity graph)
- present focus: solving closed eqn for $W[\{x\}|\{y\}]$

- Outlook
    - closed eqns for stationary state order parameters?
    - working out solutions for realistic choices of $p(k)$ and $P(\mathbf{k})$
    - phase diagrams, analysis of instabilities
    - inclusion of higher order complexes
    - connections with experiment, verifiable predictions
    - integration with ‘small module’ reaction equations
    - more sophisticated random graph ensembles