Protein interaction networks via Tailored graph ensembles: a study of sampling

A Annibale

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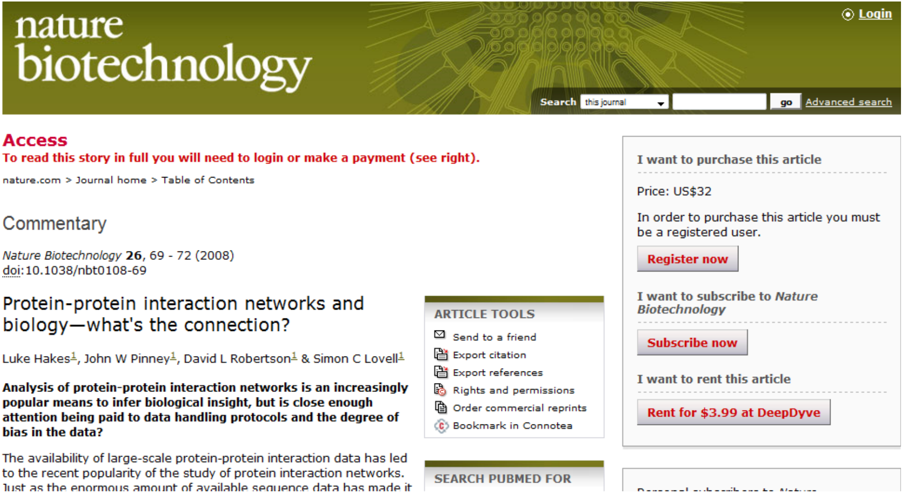
Outline

1. Motivation
2. Quantifying biases
   - Tailored random graph ensembles
   - Sampling protocols
   - Results
3. Inferring the true network from imperfect data
   - Bayesian analysis

Motivation



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Commentary

Nature Biotechnology **26**, 69 - 72 (2008)
doi:10.1038/nbt0108-69

Protein-protein interaction networks and biology—what's the connection?

Luke Hakes[1], John W Pinney[1], David L Robertson[1] & Simon C Lovell[1]

Analysis of protein-protein interaction networks is an increasingly popular means to infer biological insight, but is close enough attention being paid to data handling protocols and the degree of bias in the data?

The availability of large-scale protein-protein interaction data has led to the recent popularity of the study of protein interaction networks. Just as the enormous amount of available sequence data has made it

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- Large-scale PIN dataset are available nowdays
- Data are biased and incomplete

Is it possible to use the available data reliably?

Yes, if we understand the relation between the patterns of a real graph and those of a graph sample

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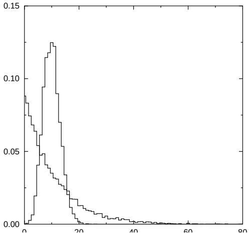

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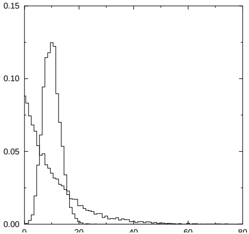
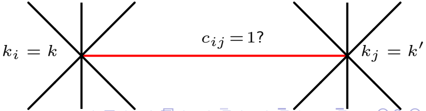


- Degree correlation

$$W(k,k') = \frac{\sum_{ij} c_{ij} \delta_{k,k_i} \delta_{k',k_j}}{\sum_{ij} c_{ij}}$$



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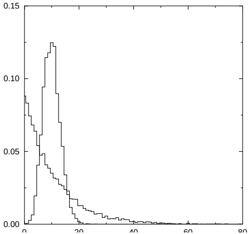

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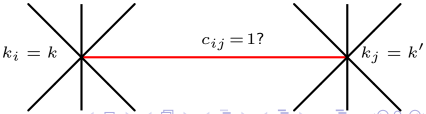

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$\Pi\neq 1$ signals presence of structure beyond degrees statistics

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Numerical sampling of $\omega_\mu(\mathbf{\Omega})$ hard for sophisticated $\mathbf{\Omega}$, but analytical progress feasible for suitable choices and N large!

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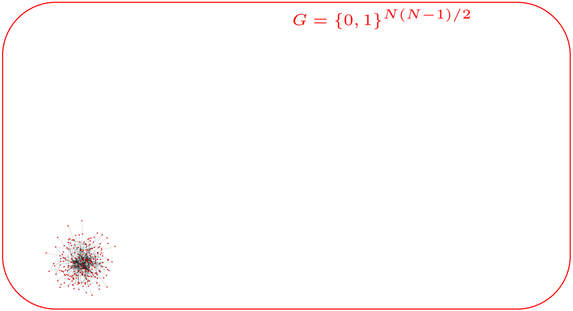

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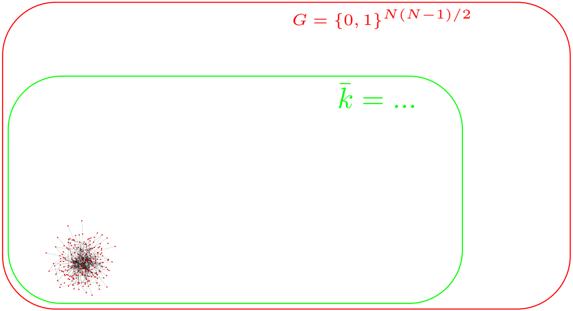

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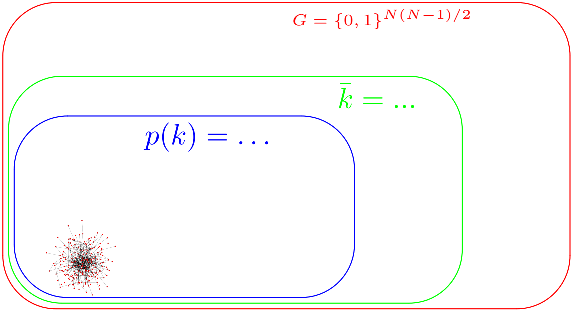

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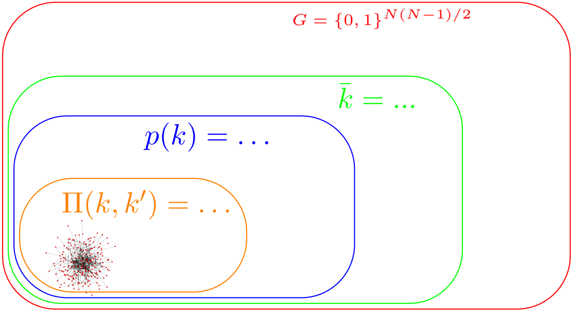

Hierarchy of ensembles

(i) prescribe only $\langle k\rangle$ Erdös-Renyi graphs

$$P(\mathbf{c}|\bar{k}) = \prod_{i<j}\left[\frac{\bar{k}}{N}\delta_{c_{ij},1} + \left(1-\frac{\bar{k}}{N}\right)\delta_{c_{ij},0}\right] \qquad \text{(soft)}$$

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$$P(\mathbf{c}|\mathbf{k}, Q) = \frac{\delta_{\mathbf{k},\mathbf{k}(\mathbf{c})}}{Z(\mathbf{k}, Q)} \prod_{i<j} \left[\frac{\langle k \rangle}{N} Q(k_i, k_j) \delta_{c_{ij},1} + \left(1 - \frac{\langle k \rangle}{N} Q(k_i, k_j)\right) \delta_{c_{ij},0} \right]$$

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Right choice:
$Q(k,k') = \Pi(k,k')kk'/\langle k\rangle^2$

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$Q(k, k') = \Pi(k, k') k k' / \langle k \rangle^2 = W(k, k') / p(k) p(k')$

Modelling biological networks

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[A Annibale, ACC Coolen, LP Fernandes, F Fraternali J Kleinjung *J. Phys. A: Math. Theor. 42 485001* (2009)]

Distance between networks

Information theory

⇓

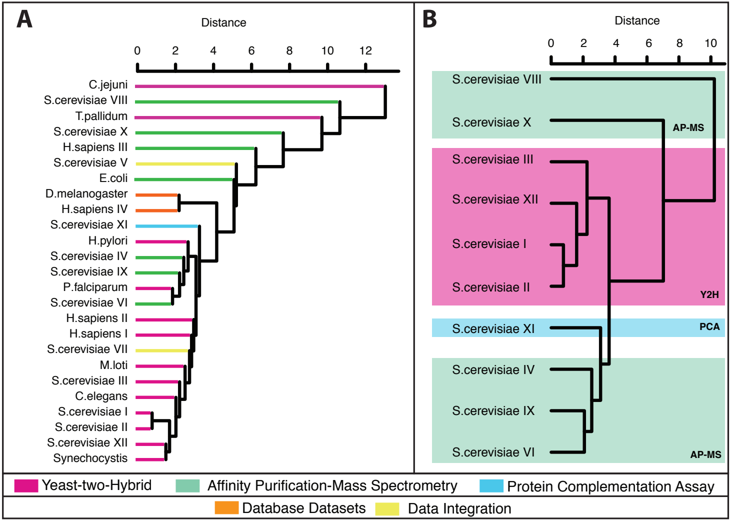
Distance between $\mathbf{c}_A$ and $\mathbf{c}_B$

$$D_{AB} = \frac{1}{2N}\sum_{\mathbf{c}} P(\mathbf{c}|p_A, W_A)\log\frac{P(\mathbf{c}|p_A, W_A)}{P(\mathbf{c}|p_B, W_B)}$$

$$+\frac{1}{2N}\sum_{\mathbf{c}} P(\mathbf{c}|p_B, W_B)\log\frac{P(\mathbf{c}|p_B, W_B)}{P(\mathbf{c}|p_A, W_A)}$$

$$= f(p_A, p_B, W_A, W_B)$$

Dendrograms



[LP Fernandes, A Annibale, J Kleinjung, ACC Coolen, F Fraternali *PLoS ONE 5(8): e12083* (2010)]

Accounting for biases

$$\begin{tikzcd}
\mathbf{c} \arrow[r, "\text{sampling}"] \arrow[d] & \mathbf{c}' \arrow[d] \\
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So far:

- only p' was studied and
- only for random node sampling

Accounting for biases

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\mathbf{c} \arrow[r, "\text{sampling}"] \arrow[d] & \mathbf{c}' \arrow[d] & \text{Microscopic} \\
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$$\sigma_i = \begin{cases} 1 & \text{node i detected} \qquad\qquad x \\ 0 & \text{otherwise} \qquad\qquad 1-x \end{cases}$$

- bond undersampling: $c'_{ij} = \tau_{ij} c_{ij}$

$$\tau_{ij} = \begin{cases} 1 & \text{bond } i-j \text{ detected} \qquad\qquad y \\ 0 & \text{otherwise} \qquad\qquad 1-y \end{cases}$$

- bond oversampling: $c'_{ij} = c_{ij} + (1-c_{ij})\lambda_{ij}$

$$\lambda_{ij} = \begin{cases} 1 & \text{bond } i-j \text{ created} \\ 0 & \text{otherwise} \end{cases}$$

$$\Downarrow \qquad \text{in combination}$$

$$c'_{ij} = \sigma_i \sigma_j [\tau_{ij} c_{ij} + (1-c_{ij})\lambda_{ij}]$$

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Macroscopic features

$$\mathbf{c} \xrightarrow{\boldsymbol{\sigma},\,\boldsymbol{\tau},\,\boldsymbol{\lambda}} \mathbf{c}'$$

Macroscopic features

$$\begin{tikzcd} \mathbf{c} \arrow[r, "{\boldsymbol{\sigma}, \boldsymbol{\tau}, \boldsymbol{\lambda}}"] \arrow[d] & \mathbf{c}' \\ p_0, W_0 & \end{tikzcd}$$

Macroscopic features

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p_0, W_0 & p, W
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$$p(k|\mathbf{c}') = \frac{\sum_i \sigma_i \delta_{k,\sum_j c_{ij'}}}{\sum_i \sigma_i}$$

$$W(k, k'|\mathbf{c}') = \frac{\sum_{ij} c'_{ij} \delta_{k,\sum_\ell c'_{i\ell}} \delta_{k',\sum_\ell c'_{j\ell}}}{\sum_{ij} c'_{ij}}$$

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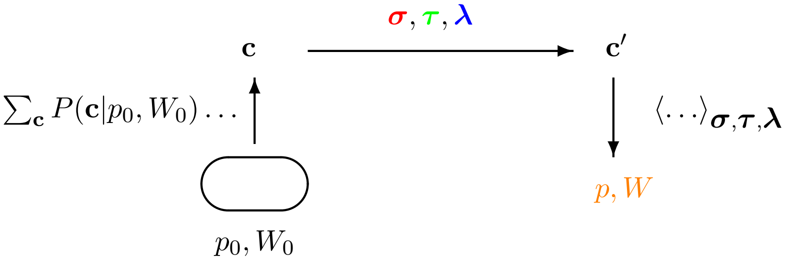
Macroscopic features



$\boldsymbol{\sigma}, \boldsymbol{\tau}, \boldsymbol{\lambda}$

$\mathbf{c}$

$\mathbf{c}'$

$\sum_{\mathbf{c}} P(\mathbf{c}|p_0, W_0) \ldots$

$\langle \cdots \rangle_{\boldsymbol{\sigma},\boldsymbol{\tau},\boldsymbol{\lambda}}$

p, W

p_0, W_0

$$p(k|x,y,z) = \lim_{N\to\infty} \sum_{\mathbf{c}} P(\mathbf{c}|p_0, W_0) \left\langle \frac{\sum_i \sigma_i \delta_{k,\sum_j c_{ij'}}}{\sum_i \sigma_i} \right\rangle_{\boldsymbol{\sigma},\boldsymbol{\tau},\boldsymbol{\lambda}}$$

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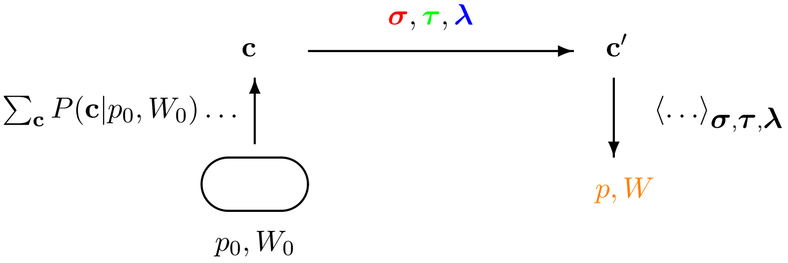
Macroscopic features



$\boldsymbol{\sigma}, \boldsymbol{\tau}, \boldsymbol{\lambda}$

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$\Rightarrow$ Statistical mechanics techniques $\Rightarrow$

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Outline

1. Motivation
2. Quantifying biases
    - Tailored random graph ensembles
    - Sampling protocols
    - Results
3. Inferring the true network from imperfect data
    - Bayesian analysis

Results

$$p(k|x,y,z) = \frac{\sum_q x(q)p(q)\Big\{a(q)\mathcal{J}(k|q) + qb(q)\mathcal{L}(k|q)\Big\}}{k\sum_q p(q)x(q)}$$

$$W(k,k'|x,y,z) = \frac{\sum_{q,q'>0} x(q)x(q')\Big\{p(q)p(q')z(q,q')\mathcal{J}(k|q)\mathcal{J}(k'|q') + \overline{k}W(q,q')y(q,q')\mathcal{L}(k|q)\mathcal{L}(k'|q')\Big\}}{\bar{k}(x,y,z)\sum_q p(q)x(q)}$$

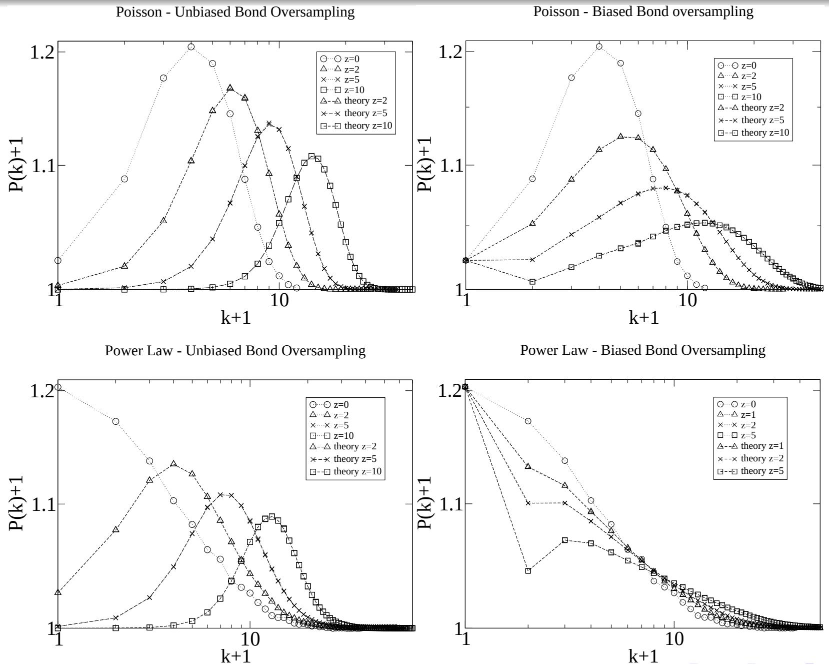
$$\bar{k}(x,y,z) = \sum_k k\,p(k|x,y,z) = \frac{\sum_q x(q)p(q)[a(q) + q\,b(q)]}{\sum_q p(q)x(q)}$$

with

$$\mathcal{J}(k|q) = e^{-a(q)} \sum_{n=0}^{\min\{k-1,q\}} \left(\begin{array}{c} q \\ n \end{array}\right) \frac{a^{k-1-n}(q)}{(k-1-n)!} b^n(q)(1-b(q))^{q-n}$$

$$\mathcal{L}(k|q) = e^{-a(q)} \sum_{n=0}^{\min\{k-1,q-1\}} \left(\begin{array}{c} q-1 \\ n \end{array}\right) \frac{a^{k-1-n}(q)}{(k-1-n)!} b^n(q)(1-b(q))^{q-1-n}$$

$$a(q) = \sum_{q'\geq 0} p(q')x(q')z(q,q'), \qquad b(q) = \frac{\overline{k}}{qp(q)} \sum_{q'\geq 0} x(q')y(q,q')W(q,q')$$



Poisson - Unbiased Bond Oversampling

Poisson - Biased Bond oversampling

Power Law - Unbiased Bond Oversampling

Power Law - Biased Bond Oversampling

Random sampling from Elegans: degree correlations

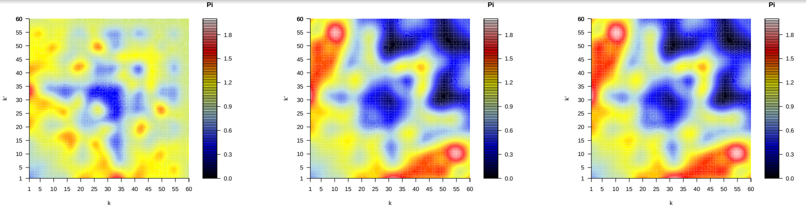


Figure: Random bond undersampling $x = 1, y = 0.9, z = 0,\ N = 3512,\ \bar{k} = 3.72$

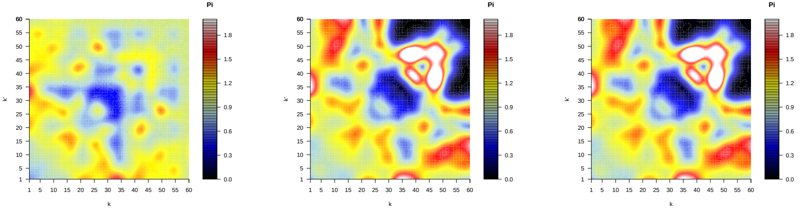


Figure: Random bond oversampling $x = 1, y = 1, z = 1,\ N = 3512,\ \bar{k} = 3.72$

[A Annibale, ACC Coolen *Interface Focus December 6, 2011 1:836-856*]

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Bayesian analysis

- $\ell = 1, ..., L$ species

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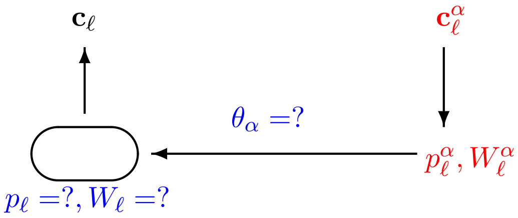

$\mathbf{c}_\ell$

$\mathbf{c}_\ell^\alpha$

$\theta_\alpha =?$

$p_\ell^\alpha, W_\ell^\alpha$

$p_\ell =?, W_\ell =?$

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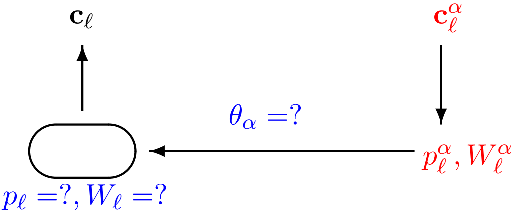

- Maximize $p(\{\theta_\alpha\}, \{p_\ell\}, \{W_\ell\} | \{\mathbf{c}_\ell^\alpha\})$ over $p_\ell, W_\ell, \theta_\alpha$

- Uniform choice for prior

$$p(p_\ell, W_\ell), \quad p(\theta_\alpha)$$

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- Likelihood:

$$p(\mathbf{c}_\ell^\alpha|\theta_\alpha, p_\ell, W_\ell) = \sum_{\mathbf{c}_\ell} P(\mathbf{c}_\ell|W_\ell, p_\ell)\ p(\mathbf{c}_\ell^\alpha|\theta_\alpha, \mathbf{c}_\ell)$$

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with

$p(\mathbf{c}_\ell^\alpha|\theta^\alpha, \mathbf{c}_\ell)$ determined from relation between $\mathbf{c}_\ell$ and $\mathbf{c}_\ell^\alpha$ (known!)

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- Calculate $\langle p(\mathbf{c}_\ell^\alpha|\theta^\alpha, \mathbf{c}_\ell)\rangle$ via statistical mechanics
- Maximise posterior using Lagrange multipliers to handle constraints

$$\sum_k p_\ell(k) = 1 \qquad \sum_q W_\ell(k,q) = kp_\ell(k)/\bar{k}_\ell$$

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- get a set of equations for p_ℓ, W_ℓ and $x^\alpha, y^\alpha, z^\alpha$ in terms of the observed $p_\ell^\alpha, W_\ell^\alpha$

Conclusions

- Tailored random graphs ensemble can be used to model complex networks and quantify distances between them.
- Tailored graph ensembles can be used to quantify sampling effects on degree distributions and degree correlations for general sampling protocols (simulations match theory!)
- Underway: Bayesian inference of macroscopic features of biological networks and sampling parameters of different experiments given the observed networks
- Future: go all the way back to the original matrices

Aknowledgements

- ACC Coolen (maths)
- LP Fernandes, F Fraternali, J Kleinjung (bioinformatics)

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A. Annibale, ACC Coolen

Infering protein interactions networks from biased experimental data (in preparation).