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Analyse statistique de réseaux biologiques

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Statistical analysis of biological networks.

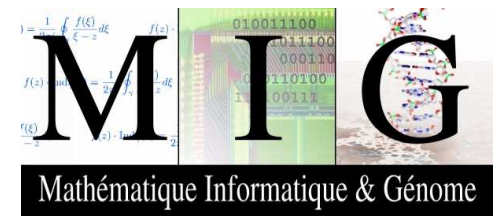
Assessing the exceptionality of network motifs

S. Schbath

SSB
for
statistics systems iology

Jouy-en-Josas/Evry/Paris, France

<http://genome.jouy.inra.fr/ssb/>



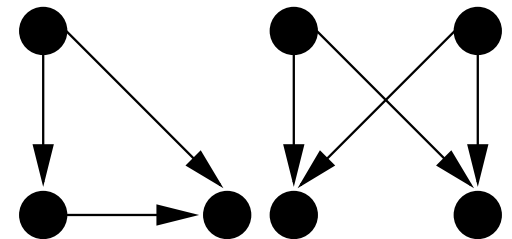
The network revolution



- **Nature of the data:**
 - n individuals (n large),
 - but also n^2 couples.
- **Many scientific fields:**
sociology, physics, "internet", biology.
- **Biological networks :**
protein-protein interaction networks, regulatory networks, metabolic networks.
- **Statistical aspects:**
 - network inference,
 - statistical properties of given networks (degrees, diameter, clustering coefficient, modules, motifs etc.),
 - random graph models.

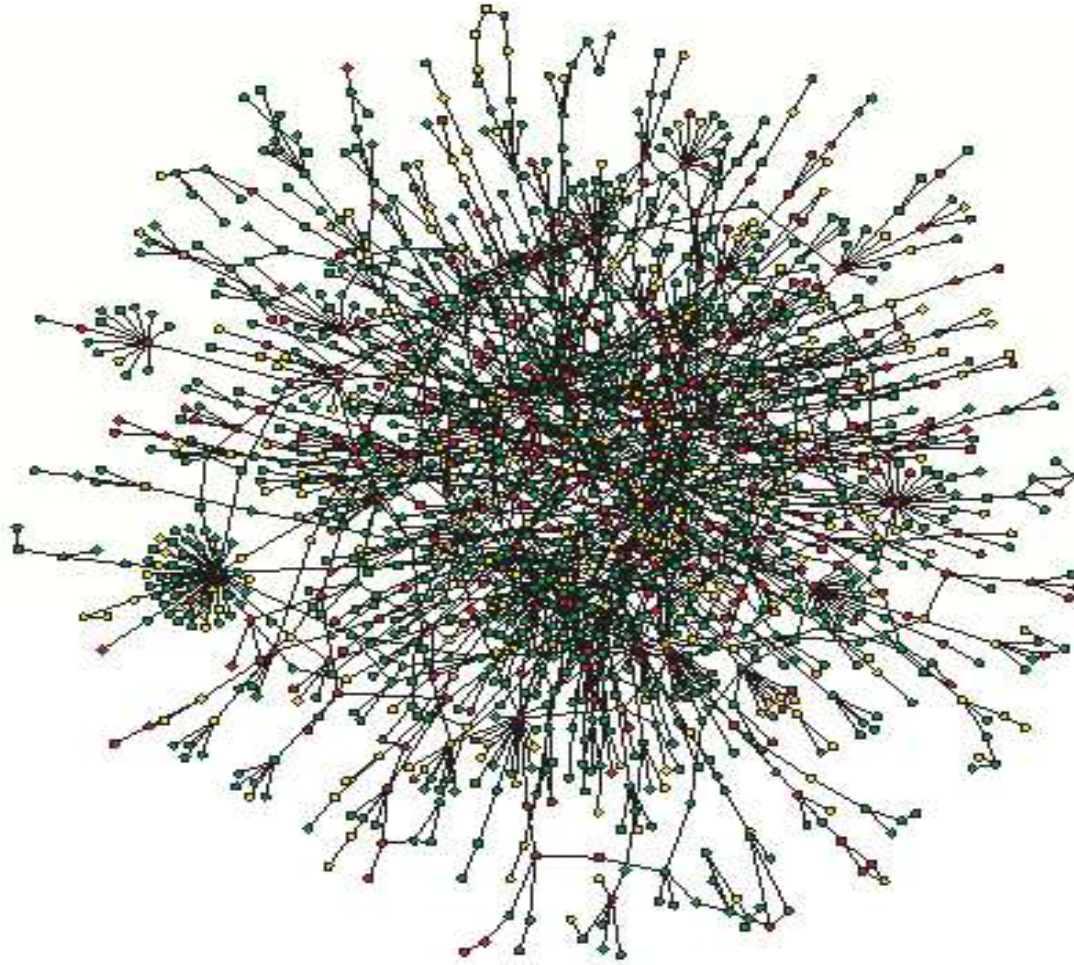
Looking for local structures

- Breaking-down complex networks into functional modules or **basic building blocks**: [Shen-Orr et al. (02)]
→ patterns of interconnection, **topological motifs**.
- **Focus on exceptional motifs** = motifs appearing more frequently than **expected**. [Milo et al. (02), Shen-Orr et al. (02), Zhang et al. (05)]
- **Interpretation**:
 - they are thought to reflect functional units which combine to regulate the cellular behavior as a whole,
 - mathematical analysis of their dynamics are required. [Mangan and Alon (03), Prill et al. (05)]
- **Transcriptional regulatory networks**:
particular regulatory units (e.g. feed-forward loop, bi-fan).



Other kind of motifs

If the nodes are colored (e.g. GO term, EC number etc.):

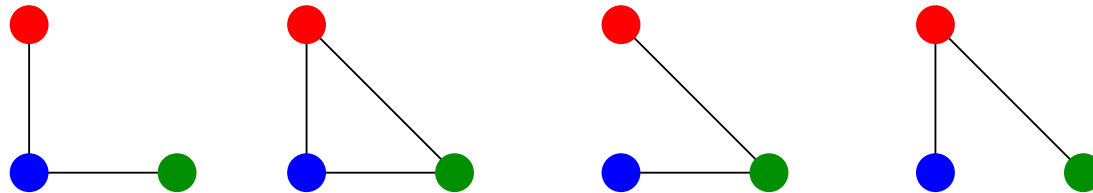


From Barabasi et al.(2004)

Other kind of motifs

If the nodes are colored (e.g. GO term, EC number etc.):

- **Colored motifs** [Lacroix et al. (05, 06)]
 - no topological constraint
 - only a connectedness constraint



- **Topological colored motifs** [Lee et al. (07), Taylor et al. (07)]

How to assess the exceptionality of a motif?



Step 1 To count the observed number of occurrences $N_{\text{obs}}(\mathbf{m})$ of a given motif \mathbf{m} (out of my scope)

Its significance is assessed with the p -value $\mathbb{P}\{N(\mathbf{m}) \geq N_{\text{obs}}(\mathbf{m})\}$
(*the probability to get as much occurrences at random*)

Step 2 To choose an appropriate **random graph model**

Step 3 To get the **distribution** of the count $N(\mathbf{m})$ under this model

State of the art (1/2)



Analytical approaches:

- The most popular random graph model is the **Erdős-Rényi model** (nodes are connected independently with proba p)
- Some theoretical works exist on Poisson and Gaussian approximations of topological motif count distribution [Janson et al. (00)]

BUT

- only for particular motifs,
- the Erdős-Rényi model is not a good model for biological networks (e.g. it does not fit the degrees).

State of the art (2/2)



Simulated approaches:

- Random networks are generated by edge swapping, (degrees are preserved)
- Empirical distributions for motif counts are obtained leading either to p -values or to z -scores

BUT

- huge number of simulations required to estimate tiny p -values,
- z -scores are compared to $\mathcal{N}(0, 1)$ which is not always appropriate,
- Edge swapping does not define a probabilistic random graph model.

Our contributions (1/2)



- To propose probabilistic random graph models
 - adapted for biological networks,
 - allowing probabilistic calculations,
 - with efficient estimation procedures.

Daudin, Picard, Robin (08) *A mixture model for random graphs*. Statis. Comput.

Birmelé (07) *A scale-free graph model based on bipartite graphs*. Disc. Appl. Math.

Daudin, Picard, Robin (07) *Mixture model for random graphs: a variational approach*, SSB preprint 4

Zanghi, Ambroise, Miele (07) *Fast online graph clustering via Erdős-Rényi mixture*, SSB preprint 8.

Mariadassou, Robin (07) *Uncovering latent structure in valued graphs: a variational approach*, SSB preprint 10.

Our contributions (2/2)



- To provide general analytical results on motif count distribution:
 - mean and variance of the count in a wide class of random graph models,
 - relevant distribution to approximate the count distribution.

Matias, Schbath, Birmelé, Daudin and Robin (06) *Network motifs: mean and variance for the count*, REVSTAT. 4 31–51.

Picard, Daudin, Schbath and Robin (08) *Assessing the exceptionality of network motifs*, J. Comput. Biol.

Schbath, Lacroix and Sagot *Assessing the exceptionality of coloured motifs in networks*, submitted.



Random graph models

Random graphs

- A random graph G is defined by:
 - a set \mathcal{V} of fixed vertices with $|\mathcal{V}| = n$,
 - a set of random edges $\mathbf{X} = \{X_{ij}, (i, j) \in \mathcal{V}^2\}$ such that

$$X_{ij} = \begin{cases} 1 & \text{if } i \text{ and } j \text{ are connected,} \\ 0 & \text{otherwise} \end{cases}$$

- and a distribution on X_{ij} .
- Examples:
 - the Erdős-Rényi model,
 - the Mixture model for random graph (Mixnet/ERMG),
 - the Expected Degree Distribution model.

Example 1: Erdős-Rényi model



- Edges X_{ij} 's are independent ...
- ... and identically distributed according to $\mathcal{B}(p)$

$$\mathbb{P}(X_{ij} = 1) = p$$

- Degrees are Poisson distributed

$$K_i := \sum_{j \neq i} X_{ij} \sim \mathcal{B}(n - 1, p) \approx \mathcal{P}((n - 1)p)$$

- It does not fit with biological networks.
The main reason is: heterogeneity.

Example 2: Mixture model for random graphs

- Vertices are spread into Q groups.
- Conditionally to the group of vertices, edges are independent and

$$X_{ij} \mid \{i \in q, j \in \ell\} \sim \mathcal{B}(\pi_{q,\ell})$$

$\pi_{q,\ell}$ is the connection probability between groups q and ℓ .

- Degrees are distributed according to a Poisson mixture

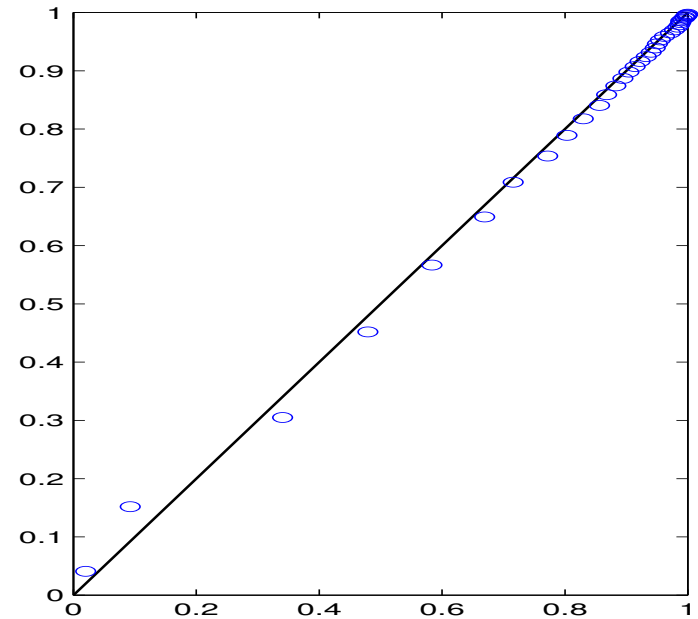
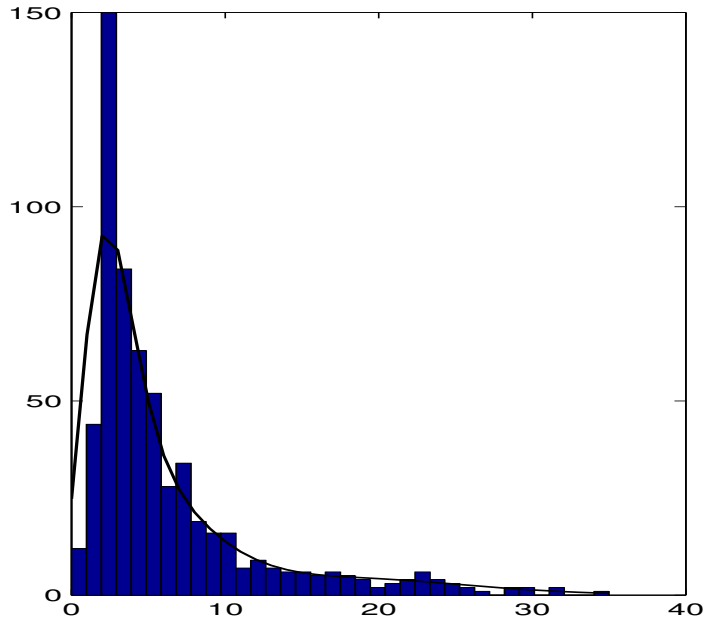
$$K_i \sim \sum_q \alpha_q \mathcal{B}(n-1, \bar{\pi}_q) \text{ with } \bar{\pi}_q = \sum_\ell \alpha_\ell \pi_{q,\ell}$$

- Better fit to biological networks.

Mixnet fit

- *E. coli* reaction network: 605 vertices, 1782 edges.
(data curated by V. Lacroix and M.-F. Sagot).
- **Degrees:** Poisson mixture versus empirical distribution

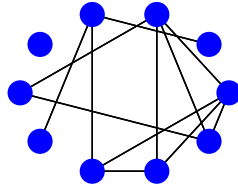
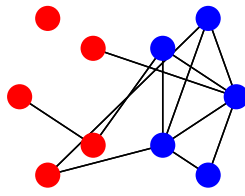
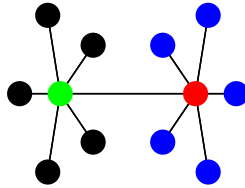
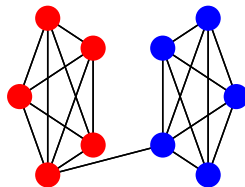
PP-plot



- **Clustering coefficient:**

Empirical	Mixnet ($Q = 21$)	ER ($Q = 1$)
0.626	0.544	0.0098

Mixnet flexibility

Examples	Network	Q	π
Erdős-Rényi		1	p
Independent model (product connectivity)		2	$\begin{pmatrix} a^2 & ab \\ ab & b^2 \end{pmatrix}$
Stars		4	$\begin{pmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{pmatrix}$
Clusters (affiliation network)		2	$\begin{pmatrix} 1 & \varepsilon \\ \varepsilon & 1 \end{pmatrix}$

Mixnet: estimation procedure

- The aim is to maximize the log-likelihood $\mathcal{L}(\mathbf{X})$,
- ... but $\mathcal{L}(\mathbf{X})$ is not calculable because of hidden groups (\mathbf{Z} , Z_i is the group of node i).
- EM algorithm is classical to fit mixture models,
- ... but cannot be used because $\mathbb{P}(\mathbf{Z} | \mathbf{X})$ is not computable (all vertices are potentially connected, no local dependence)
- Strategy = **variational approach**
 - maximization of $\mathcal{L}(\mathbf{X}) - KL(\mathbb{P}(\mathbf{Z} | \mathbf{X}), Q_R(\mathbf{Z}))$ where Q_R is the best approximation of $\mathbb{P}(\mathbf{Z} | \mathbf{X})$ within a class of 'nice' distributions. \Rightarrow estimator of $\mathbb{P}(Z_i = q | \mathbf{X})$.
 - iterative algorithm
- Heuristic penalized likelihood criterion inspired from BIC (ICL)

[Daudin, Picard and Robin (07)]

Example 3: Expected Degree Distribution model



- Let f be a given distribution and D_i 's i.i.d. $D_i \sim f$.
- Conditionally to the D_i 's, edges X_{ij} 's are independent and

$$\mathbb{P}(X_{ij} = 1 \mid D_i, D_j) = \gamma D_i D_j$$

- A suitable value for γ ensures that $\mathbb{E}(K_i \mid D_i) = D_i$.
- This model generates graphs whose degrees follow a given distribution.

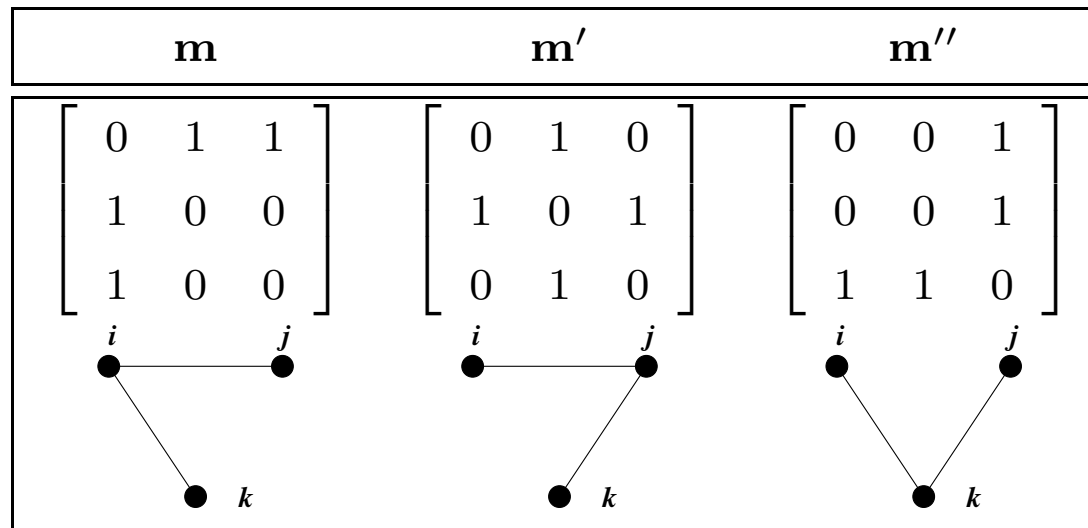


Occurrences of topological motifs

Topological motifs

Let \mathbf{m} be a motif of size k (connected graph with k vertices, $k \ll n$).

- \mathbf{m} is defined by its adjacency matrix (also denoted by \mathbf{m}):
 $\mathbf{m}_{uv} = 1$ iff nodes $u \leftrightarrow v$ ($\mathbf{m}_{uv} = 0$ otherwise).
- Let $\mathcal{R}(\mathbf{m})$ be the set of non redundant permutations of \mathbf{m} (so-called “versions”).
- Ex: 3 versions of the V motif at a **fixed** position (i, j, k) .



Occurrences of a motif

- Let $\alpha = (i_1, \dots, i_k) \in I_k$ be a possible position of \mathbf{m} in G .
 G_α denotes the subgraph $(V_{i_1}, \dots, V_{i_k})$.

- Non strict occurrences:

$$\mathbf{m} \text{ occurs at position } \alpha \Leftrightarrow \mathbf{m} \subseteq G_\alpha$$

- Random indicator of occurrence: $Y_\alpha(\mathbf{m})$

$$Y_\alpha(\mathbf{m}) = \mathbf{1}\{\mathbf{m} \text{ occurs at position } \alpha\} = \prod_{1 \leq u, v \leq k} X_{i_u i_v}^{m_{uv}}.$$

- The total count $N(\mathbf{m})$ of motif \mathbf{m} is then:

$$N(\mathbf{m}) = \sum_{\alpha \in I_k} \sum_{\mathbf{m}' \in \mathcal{R}(\mathbf{m})} Y_\alpha(\mathbf{m}')$$

- Warning: $N(\mathbf{m}) \neq$ number of induced subgraphs (“ $\mathbf{m} = G_\alpha$ ”).

Expected count of a motif

Recall that
$$N(\mathbf{m}) = \sum_{\alpha \in I_k} \sum_{\mathbf{m}' \in \mathcal{R}(\mathbf{m})} Y_\alpha(\mathbf{m}')$$

- Under “stationarity” assumption on the random graph model, the distribution of $Y_\alpha(\mathbf{m})$ does not depend on α and let us define

$$\mu(\mathbf{m}) := \mathbb{E}Y_\alpha(\mathbf{m}'), \quad \forall \alpha, \forall \mathbf{m}' \in \mathcal{R}(\mathbf{m}).$$

- The expectation of $N(\mathbf{m})$ is then:

$$\mathbb{E}N(\mathbf{m}) = \binom{n}{k} |\mathcal{R}(\mathbf{m})| \mu(\mathbf{m}).$$

Variance for the count

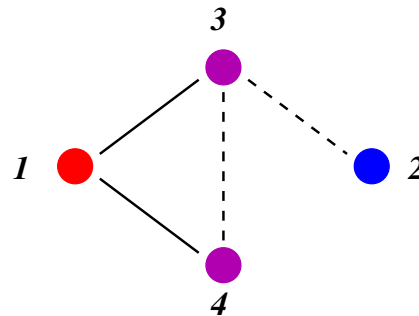
By definition $\text{Var}N(\mathbf{m}) = \mathbb{E}N^2(\mathbf{m}) - [\mathbb{E}N(\mathbf{m})]^2$. We then calculate

$$\begin{aligned}\mathbb{E}N^2(\mathbf{m}) &= \mathbb{E} \left(\sum_{\alpha, \beta \in I_k} \sum_{\mathbf{m}', \mathbf{m}'' \in \mathcal{R}(\mathbf{m})} Y_\alpha(\mathbf{m}') Y_\beta(\mathbf{m}'') \right), \\ &= \mathbb{E} \left(\sum_{s=0}^k \sum_{|\alpha \cap \beta| = s} \sum_{\mathbf{m}', \mathbf{m}'' \in \mathcal{R}(\mathbf{m})} Y_{\alpha \cup \beta}(\mathbf{m}' \Omega_s \mathbf{m}'') \right) \\ &= \sum_{s=0}^k C(n, k, s) \sum_{\mathbf{m}' \Omega_s \mathbf{m}''} \mu(\mathbf{m}' \Omega_s \mathbf{m}''),\end{aligned}$$

where $\mathbf{m}' \Omega_s \mathbf{m}''$ is a **super-motif** composed of the union of two overlapping occurrences of \mathbf{m}' and \mathbf{m}'' sharing s common vertices.

Super-motifs

- Example for the V motif:



- m occurs at $\alpha = (1, 3, 4)$, m' occurs at $\beta = (2, 3, 4)$,
 - in this case $\alpha \cap \beta = (3, 4)$ and $s = 2$.
-
- The adjacency matrix of the super-motifs $m' \underset{s}{\Omega} m''$ can be easily derived from the adjacency matrices of m' and m'' [Picard et al. (07)].

Occurrence probability for mean and variance

The following expressions for the mean and variance of $N(\mathbf{m})$ are valid under any stationary random graph model:

$$\mathbb{E}N(\mathbf{m}) = \binom{n}{k} |\mathcal{R}(\mathbf{m})| \mu(\mathbf{m})$$
$$\text{Var}N(\mathbf{m}) = \sum_{s=0}^k C(n, k, s) \sum_{\mathbf{m}' \Omega_s \mathbf{m}''} \mu(\mathbf{m}' \Omega_s \mathbf{m}'') - [\mathbb{E}N(\mathbf{m})]^2.$$

The final point is now the calculation of the occurrence probability $\mu(\cdot)$ given the adjacency matrix of a motif.

Calculating $\mu(\mathbf{m})$

- The probability of occurrence of a given motif depends on the distribution of the X_{ij} 's.
- Stationary assumption: $\mu(\mathbf{m})$ does not depend on the position of the motif
- In the **Erdős-Rényi model**: $\mu(\mathbf{m}) = \pi^{v(\mathbf{m})}$, with $v(\mathbf{m})$ the number of edges in \mathbf{m} .
- In the **Mixnet** model with Q groups with proportion $\alpha_1, \dots, \alpha_Q$:

$$\mu(\mathbf{m}) = \sum_{c_1=1}^Q \dots \sum_{c_k=1}^Q \alpha_{c_1} \dots \alpha_{c_k} \prod_{1 \leq u < v \leq k} \pi_{c_u, c_v}^{m_{uv}}.$$

- In the **EDD** model ($D \sim f$): $\mu(\mathbf{m}) = \gamma^{m_{++}/2} \prod_{u=1}^k \mathbb{E} D^{m_u}$

Motif count distribution



- Exact distribution unknown.
- Several approximations exist (or are used) in the literature:
 - Gaussian distribution
 - Poisson distribution

Motif count distribution



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 - Gaussian distribution
BUT not adapted for rare motifs
 - Poisson distribution
BUT mean \neq variance

Motif count distribution



- Exact distribution unknown.
- Several approximations exist (or are used) in the literature:
 - Gaussian distribution
BUT not adapted for rare motifs
 - Poisson distribution
BUT mean \neq variance
 - \Rightarrow Compound Poisson distribution?

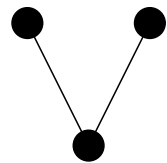
Compound Poisson distribution

- Distribution of $\sum_{i=1}^Z T_i$ when $Z \sim \mathcal{P}(\lambda)$ and T_i 's iid.
- Particularly adapted for the count of clumping events: Z is the number of clumps and T_i is the size of the i -th clump.
- All network motifs are overlapping: they occur in clumps.
- We proposed to use a **Geometric-Poisson**(λ, a) distribution, i.e. when $T_i \approx \mathcal{G}(1 - a)$
 - analogy with sequence motifs [Schbath (95)],
 - (λ, a) can be calculated according to $\mathbb{E}N(\mathbf{m})$ and $\text{Var}N(\mathbf{m})$.

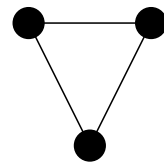
Simulation study

- Aim: to compare the Gaussian, Poisson and Geometric-Poisson approximations for the motif count distribution.
- Random graph model: Mixnet with 2 groups.
- Simulation design:
 - the number of vertices $n = 20, 200$
 - the mean connectivity $\bar{\pi} = 1/n, 2/n$
 - the within/between group connectivity $\gamma = 0.1, 0.5, 0.9$
 - the proportion of the groups $\alpha = 0.1, 0.9$

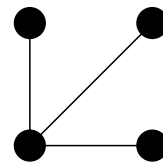
- 4 motifs:



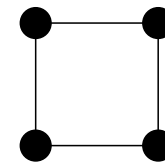
V



triangle



4-star

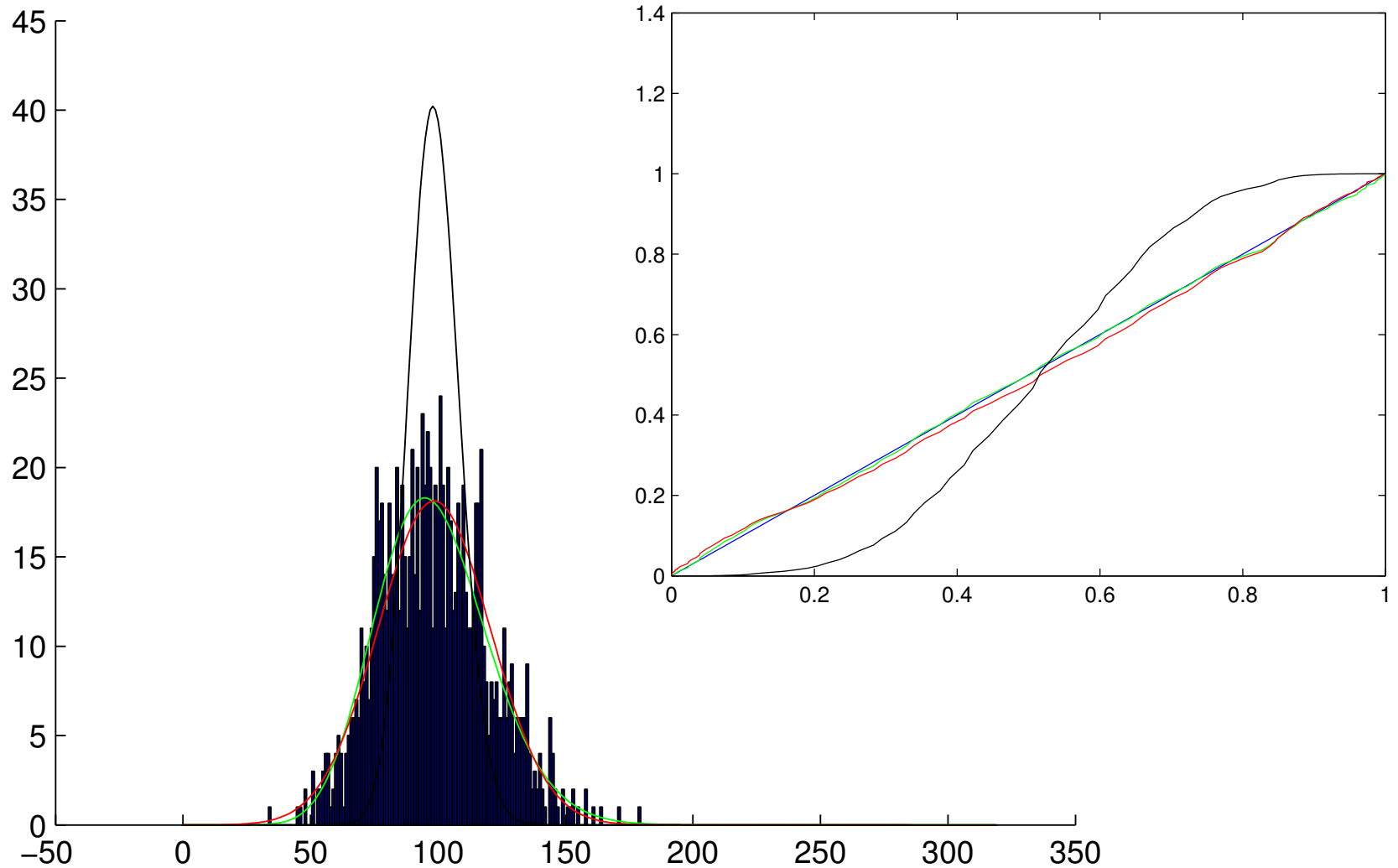


square

- We cover a large range for $\mathbb{E}N(\mathbf{m})$ (from 0.07 to 1075.5).

Expectedly frequent motif count distribution

Gaussian (—), Poisson (—) and Geometric-Poisson (—)



Approximation for expectedly frequent motif

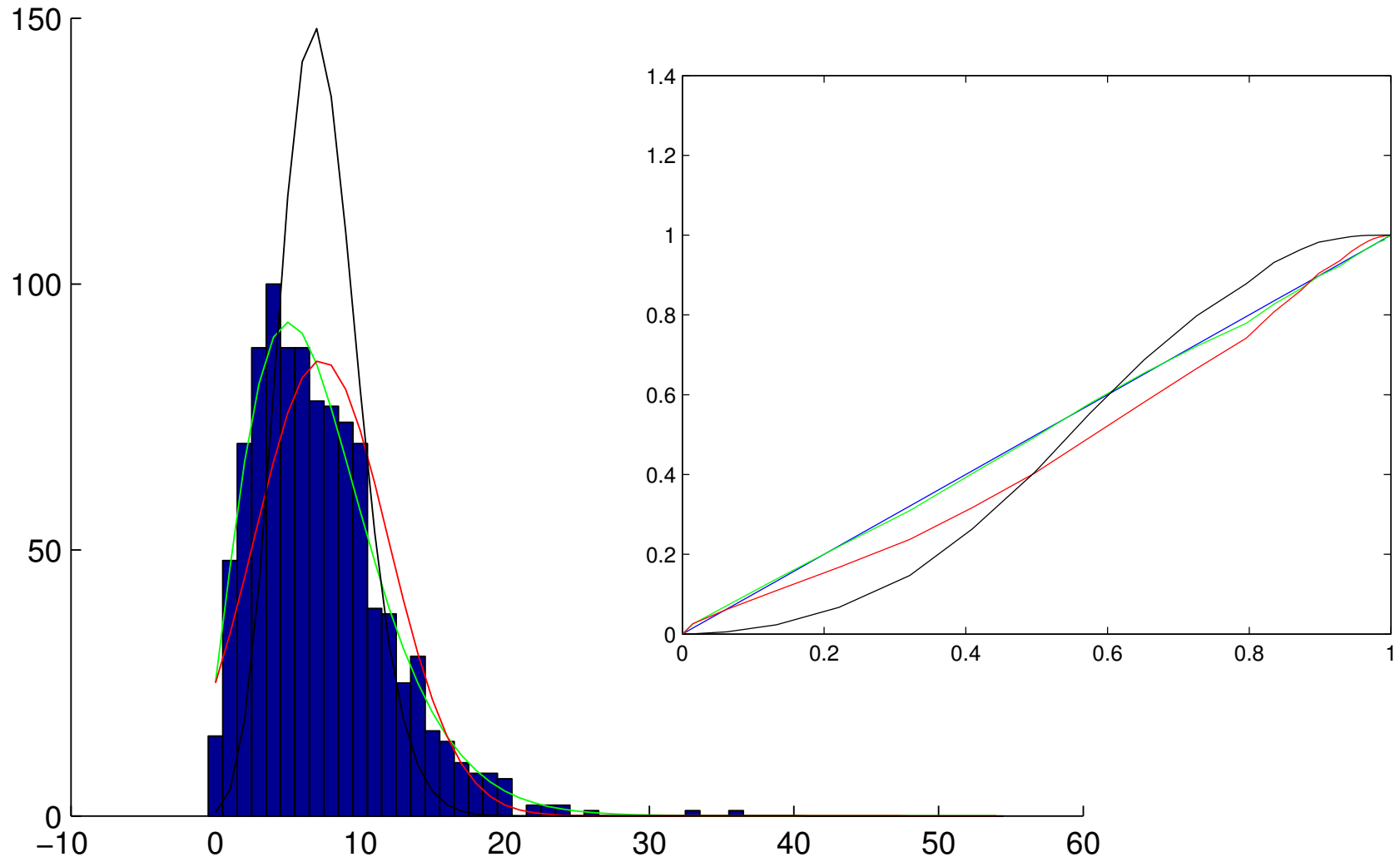
simulation parameters				motif V							
n	$\bar{\pi}$	α (%)	γ (%)	\mathbb{E}	\mathbb{V}	λ	$\frac{1}{1-a}$	D_G	D_{GP}	\hat{F}_G	\hat{F}_{GP}
200	0.5	10	10	159.5	2034.0	23.1	6.66	20.4	19.7	2.5	1.6
200	0.5	10	90	104.9	590.5	31.6	3.33	15.2	14	1.9	1.2
200	0.5	50	10	98.5	484.0	33.3	2.27	13.1	12.6	1.1	0.7
200	0.5	50	50	98.5	484.0	33.2	2.27	14.3	13.2	1.6	1.1
200	0.5	50	90	98.5	488.4	33.1	2.27	14.5	14.8	2.5	0.9

Criteria to assess the goodness-of-fit:

- D_G (resp. D_{GP}): **total variation distance** between the empirical dist. and the Gaussian (resp. Geometric-Poisson) dist.
- \hat{F}_G (resp. \hat{F}_{GP}): **empirical proba. of exceeding the 0.99 quantile** of the Gaussian (resp. Geometric-Poisson) dist.

Expectedly rare motif count distribution

Gaussian (—), Poisson (—) and Geometric-Poisson (—)



Approximation for expectedly rare motif

simulation parameters				motif \square							
n	$\bar{\pi}$	α (%)	γ (%)	\mathbb{E}	\mathbb{V}	λ	$\frac{1}{1-a}$	D_G	D_{GP}	\hat{F}_G	\hat{F}_{GP}
200	1	10	10	7.31	21.72	3.68	2	11.8	5.4	3.2	0.9
200	1	10	90	2.57	3.42	2.21	1.16	9.3	2.7	3.6	0.5
200	1	50	10	2.74	3.69	2.33	1.17	12.3	3.6	4.7	1.2
200	1	50	50	1.94	2.40	1.74	1.11	11.3	2.0	3.2	1.6
200	1	50	90	2.74	3.72	2.32	1.17	10.8	4.5	3.7	0.7

Criteria to assess the goodness-of-fit:

- D_G (resp. D_{GP}): total variation distance between the empirical dist. and the Gaussian (resp. Geometric-Poisson) dist.
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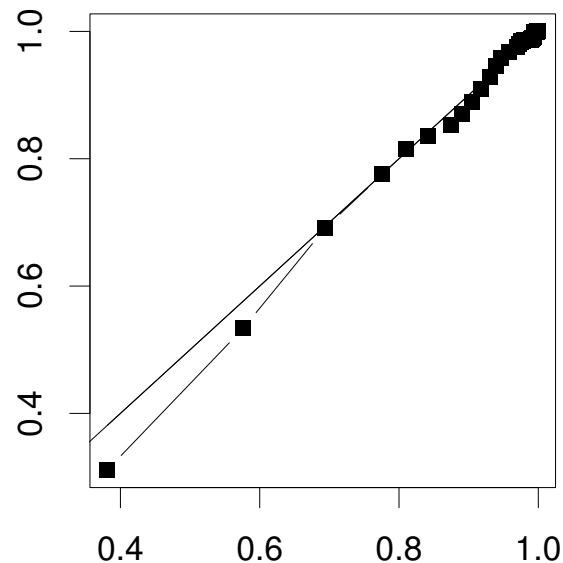
Conclusions for the simulation study











- Validation of our analytical expressions for $\mathbb{E}N$ and $\text{Var}N$.
- The Poisson approximation is not satisfactory.
- The Geometric-Poisson approximation outperforms the Gaussian approximation for both criteria in all cases, especially for “rare” motifs.
- The 0.99 quantile is underestimated by the Gaussian approximation:
→ false positive results.
- The total variation distance is high for both approximations in some cases, especially for frequent and highly self overlapping motifs.
- The clumps size distribution is probably not geometric . . .

Application to the *H. pylori* PPI network

- Protein-protein interaction network: 706 proteins (nodes) and 1420 interactions (edges).
- Mixnet was fitted to the network and 4 groups of connectivity were selected using a model selection criterion.
- Goodness-of-fit for the degree distribution (PP-plot):

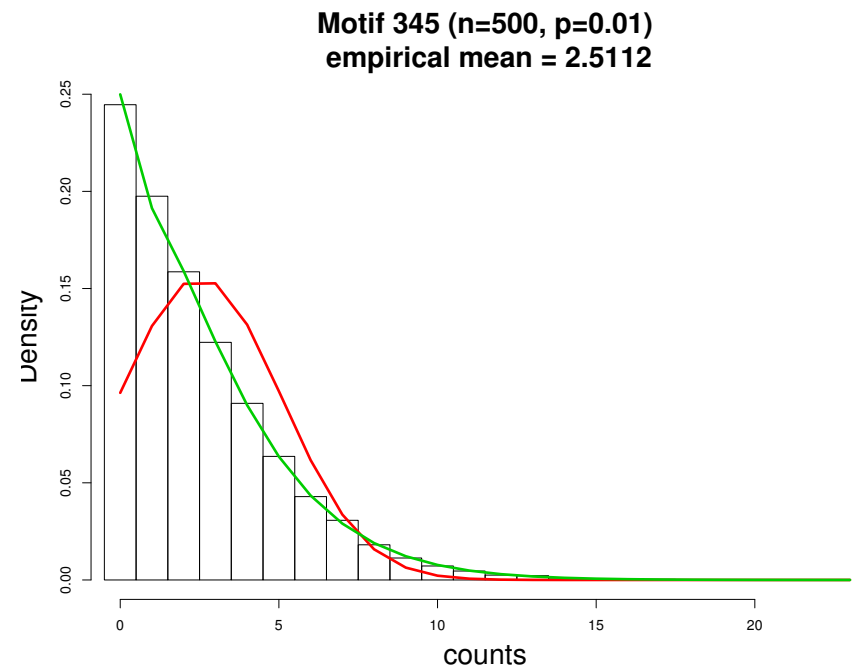
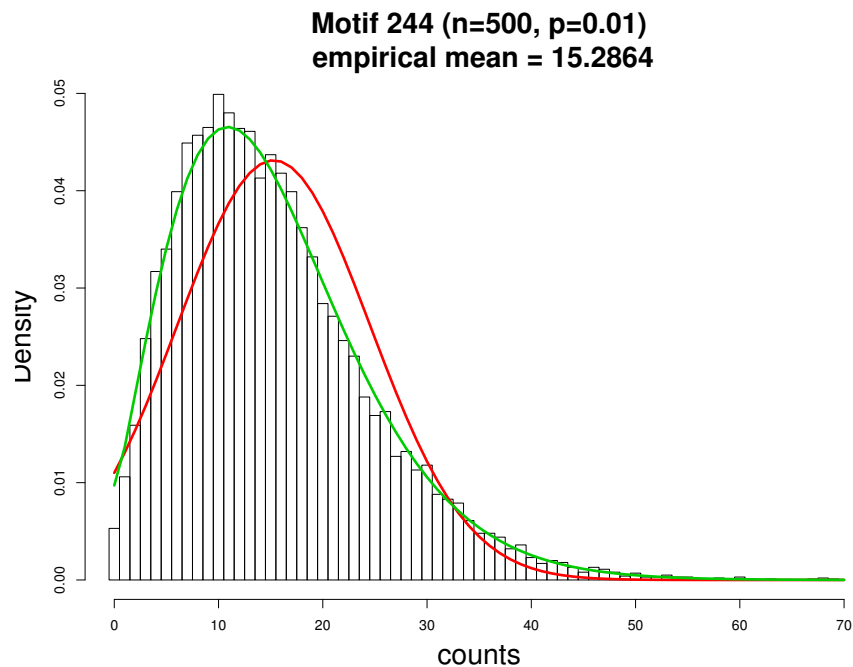


Exceptional motifs of size 3 and 4

Motif	N_{obs}	$\mathbb{E}_{\text{mixnet}} N$	$\sigma_{\text{mixnet}}(N)$	$\mathbb{P}(\mathcal{GP} \leq N_{\text{obs}})$	$\mathbb{P}(\mathcal{GP} \geq N_{\text{obs}})$
	14113	13602	2659		$4.06 \cdot 10^{-1}$
	75	66.9	20.4		$3.31 \cdot 10^{-1}$
	98697	94578	27039		$4.12 \cdot 10^{-1}$
	112490	93741	27257		$2.34 \cdot 10^{-1}$
	1058	516.6	208.7		$1.33 \cdot 10^{-2}$
	3535	2897	1120		$2.63 \cdot 10^{-1}$
	79	34.8	20.0		$3.11 \cdot 10^{-2}$
	0	0.17	0.45	$8.5 \cdot 10^{-1}$	

What about colored motifs?

- Ongoing work : colored Erdős-Rényi model.
- Analytical mean and variance for motifs of size up to 5 (difficulty in the variance: connectivity term).
- Simulations: Geometric-Poisson distribution performs better than the Gaussian one.



Conclusions & future directions



- We have proposed a flexible mixture model to fit biological networks.
- We proposed statistical methods to assess the exceptionality of network motifs *without simulations*.
- The Geometric-Poisson approximation for the count distribution works well (better than the Gaussian) on simulated data.
- For topological motifs:
 - The method to calculate the moments of the count is general and can be applied to any random graph model with stationary distribution.
 - Results can be easily generalized to directed motifs.

Directions:

- Distribution of the clump size.
- For colored motifs:
 - General formula for the variance.
 - Generalization to Mixnet.

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Mixnet: model selection procedure

- Heuristic penalized likelihood criterion inspired from BIC (ICL)
- The completed log-likelihood $\mathcal{L}(\mathbf{X}, \mathbf{Z})$ is the sum

$$\sum_i \sum_q \mathbf{1}\{Z_i = q\} \log \alpha_q \quad + \quad \sum_{i,j>i} \sum_{q,\ell} \mathbf{1}\{Z_i = q\} \mathbf{1}\{Z_j = \ell\} \log b(X_{ij}; \pi_{q,\ell})$$

$(Q - 1)$ independent proportions α_q 's and n terms

$Q(Q + 1)/2$ probabilities $\pi_{q,\ell}$'s and $n(n - 1)/2$ terms

- The heuristic criterion is then:

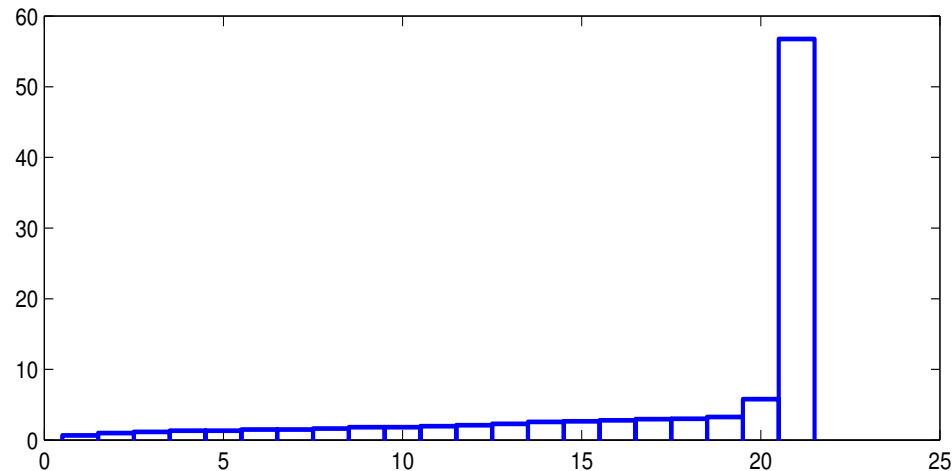
$$-2\widehat{\mathcal{L}}(\mathbf{X}, \mathbf{Z}) + (Q - 1) \log n + \frac{Q(Q + 1)}{2} \log \left[\frac{n(n - 1)}{2} \right].$$

Illustration of Mixnet

The Mixnet has been adjusted to

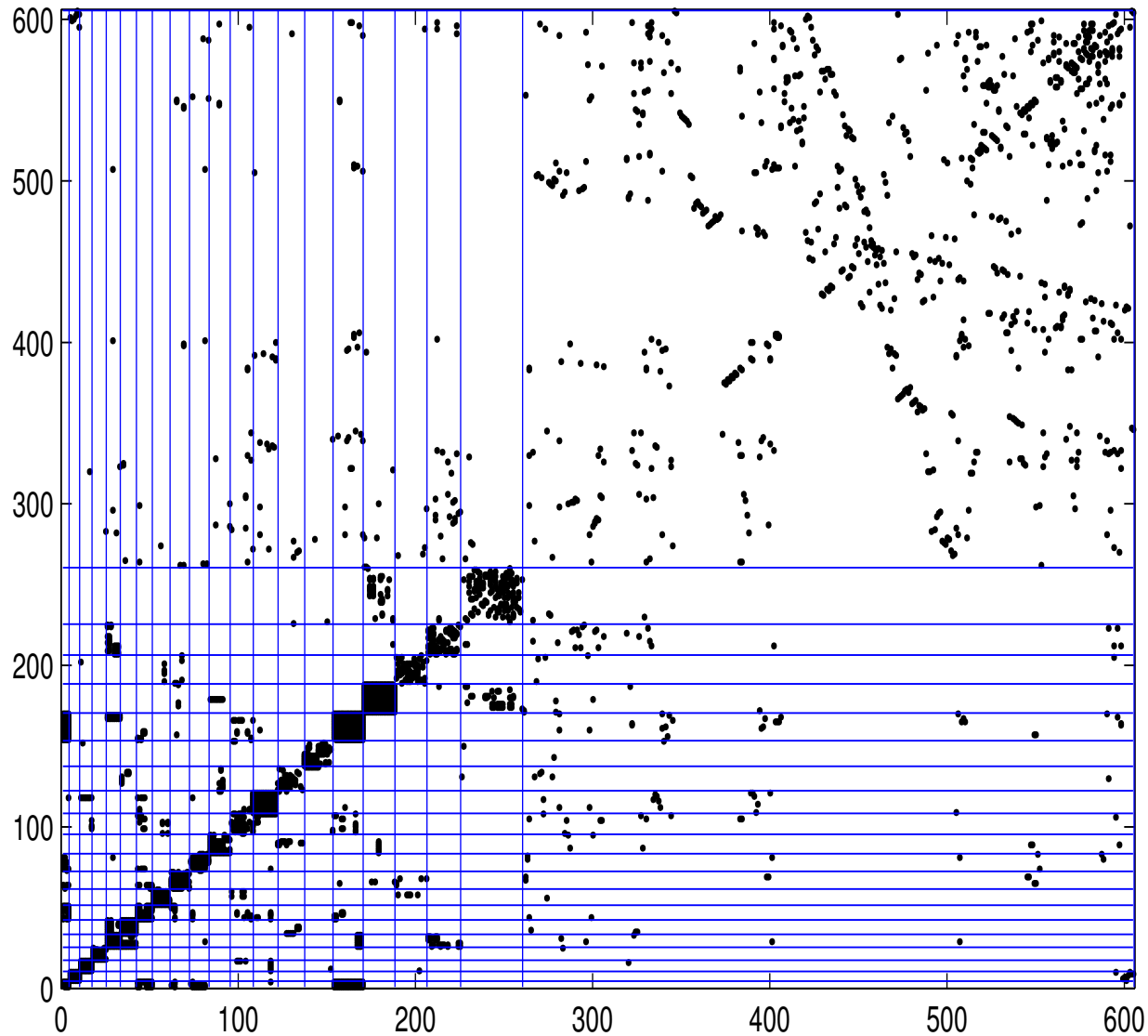
- *E. coli* reaction network: 605 vertices, 1782 edges. (data curated by V. Lacroix and M.-F. Sagot).
- $Q = 21$ groups selected

Group proportions $\hat{\alpha}_q$ (%).



- Many small groups correspond to cliques or pseudo-cliques.

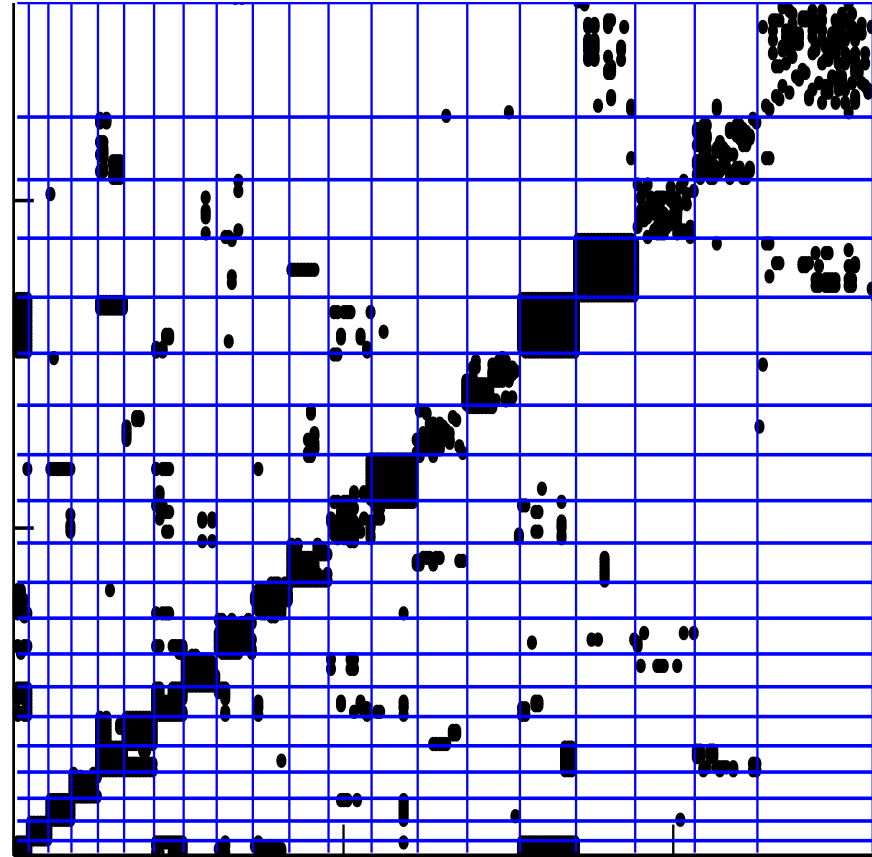
Dot plot representation of the network



Dot plot representation (zoom)

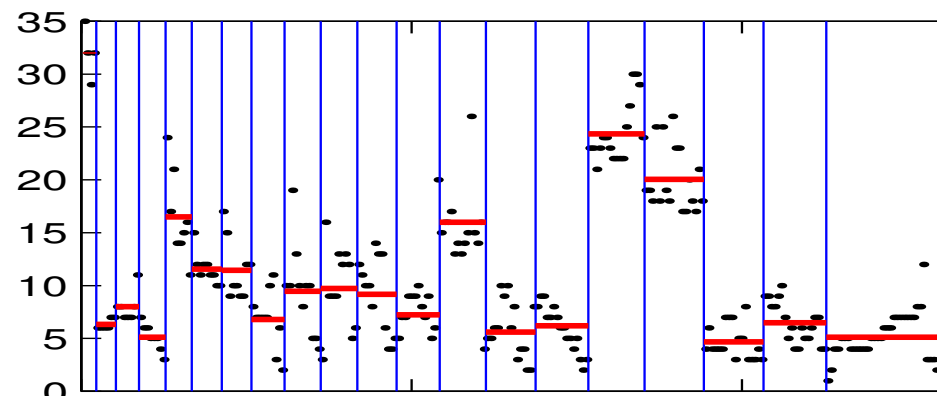
Sub-matrix of π :

q, ℓ	1	10	16
1	1.0		
10	.43	.67	
16	1.0	0	1.0



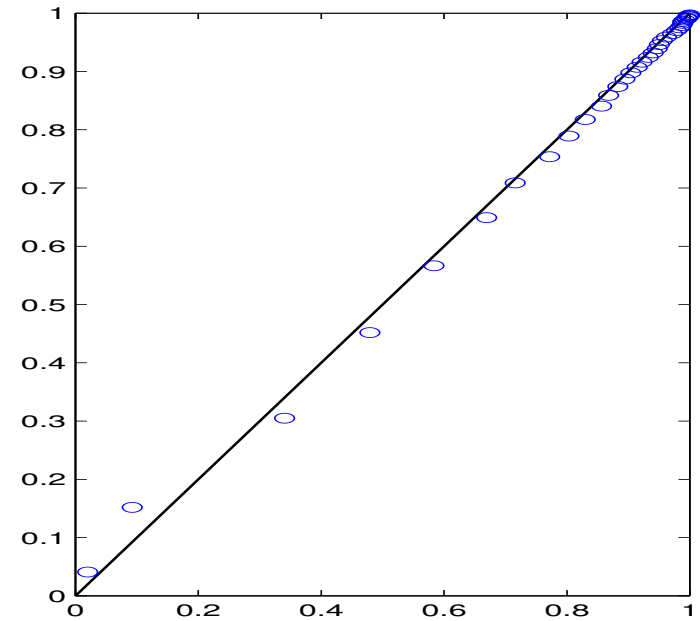
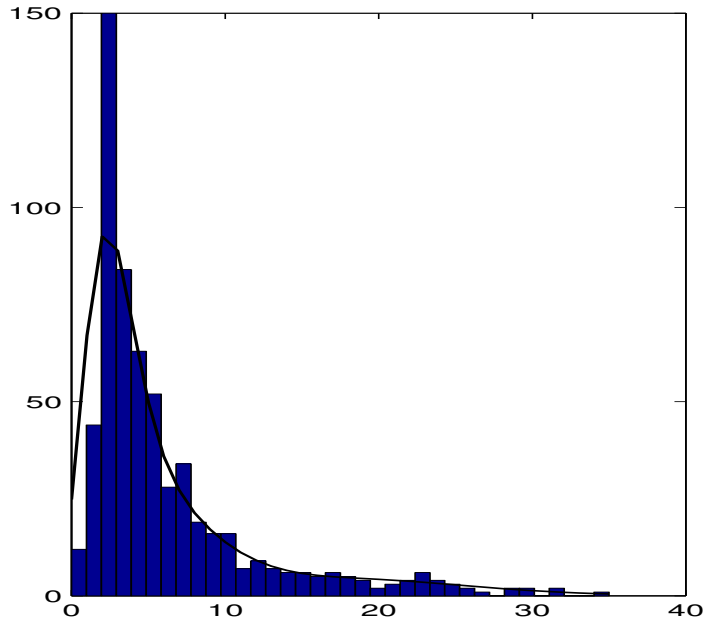
Vertex degrees K_i 's.

Mean degree in the last group: $\overline{K}_{21} = 2.6$



Model fit

- **Degrees:** Poisson mixture versus empirical distribution
PP-plot



- **Clustering coefficient:**

Empirical	Mixnet ($Q = 21$)	ER ($Q = 1$)
0.626	0.544	0.0098