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Laboratory for Statistical Artificial InteLligence & INtegrative Genomics

Time (and Space)-Varying Networks:

Reverse engineering rewiring social and genetic interactions

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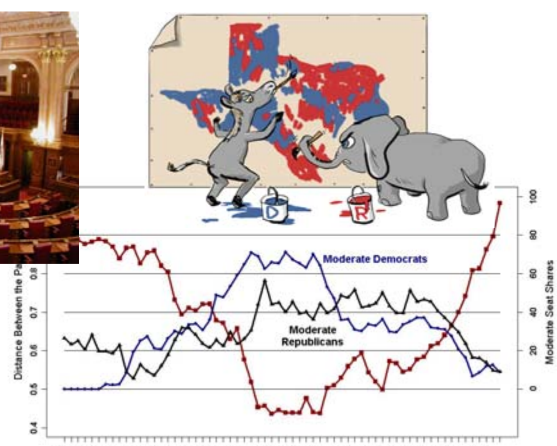
Changing Social Networks



Corporativity,

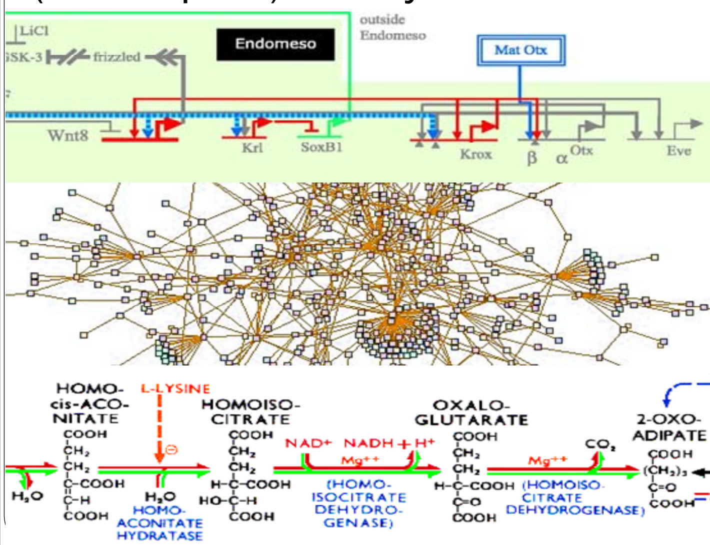
Antagonism,

Cliques,

…

over time?

Regulation of cell response to stimuli is paramount, but we can usually only measure (or compute) steady-state interactions

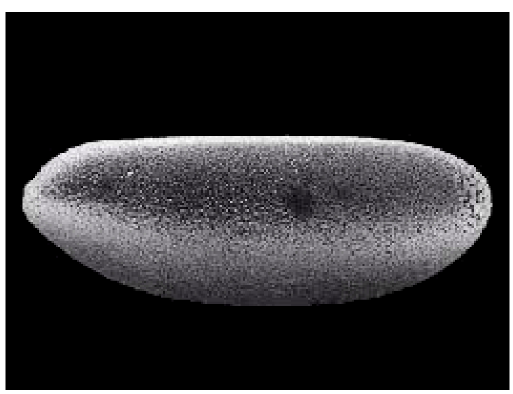


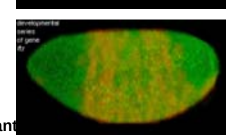
Transcriptional interactions
- ▲ Chromatin IP
- ▲ Microarrays

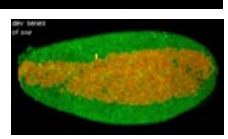
Protein—protein interactions
- ▲ Protein coIP
- ▲ Yeast two-hybrid

Biochemical reactions
- ▲ Metabolic flux measurements

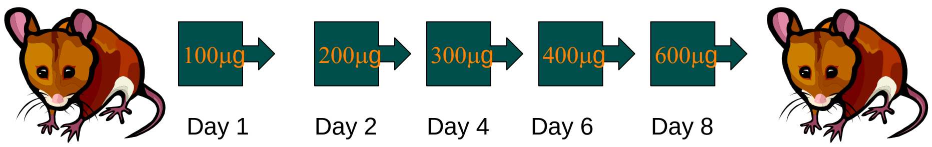
Biological regulations may be transient (in time and space) …

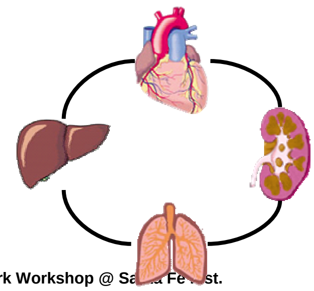


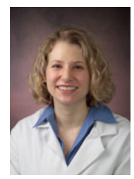




Example II: Inflammatory Response in Endotoxinated Mice



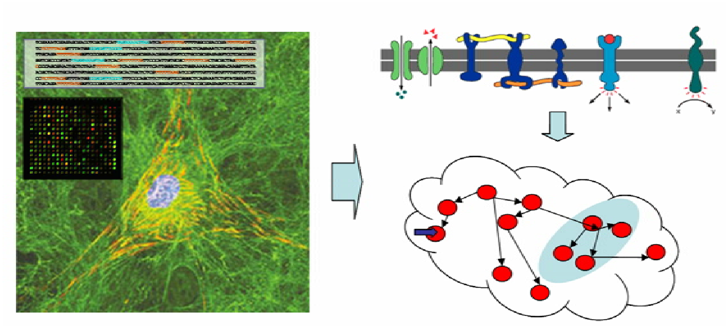




Judie Howrylak MD, UPMC

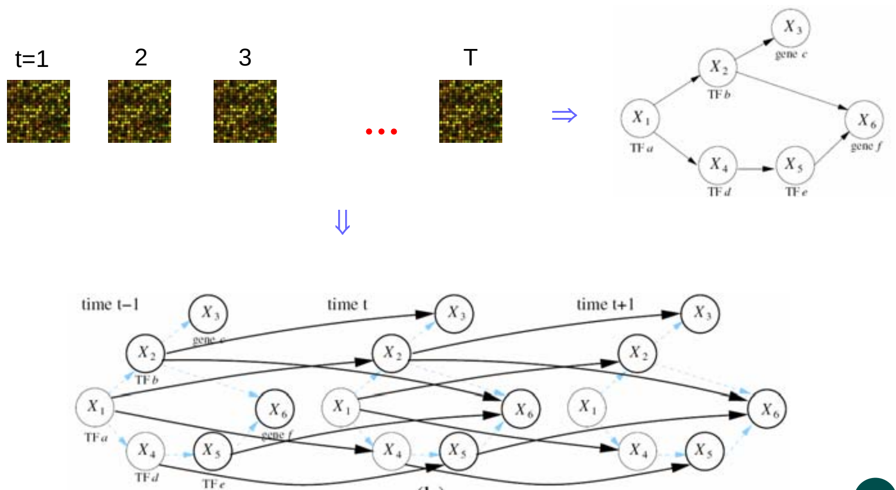
The Big-Picture Questions

- What pathway is active under certain extra-cellular stimuli or a certain point of a dynamic process?

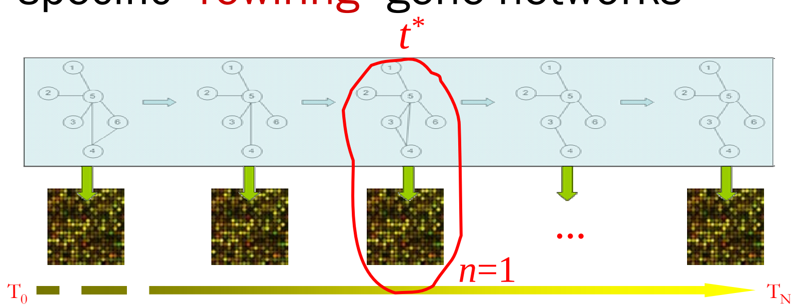


- How does the network response to environmental perturbation and biomolecular/genetic therapy?

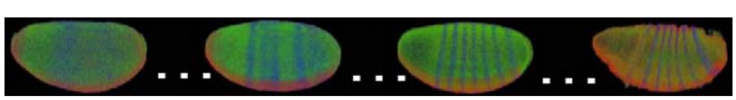
Current Practice …



Reverse engineer temporal/spatial-specific "rewiring" gene networks

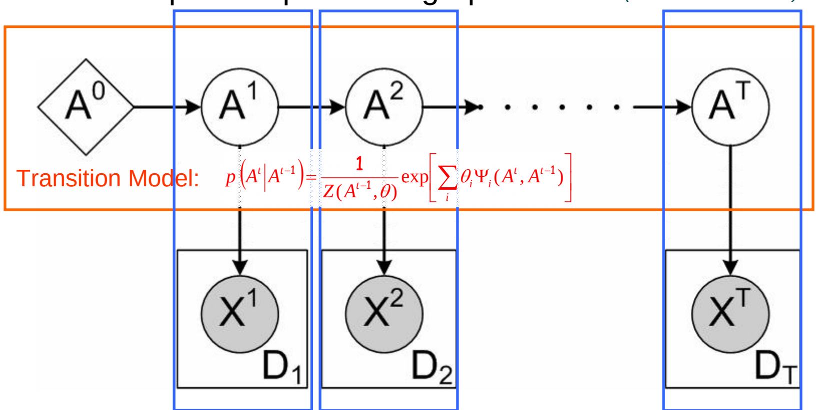


Drosophila development



Modeling Time-Varying Graphs

- The temporal exponential graph models *(Fan et al. ICML 2007)*



Transition Model: $p\left(A^t \middle| A^{t-1}\right) = \frac{1}{Z(A^{t-1}, \theta)} \exp\left[\sum_i \theta_i \Psi_i (A^t, A^{t-1})\right]$

Emission Model: $p\left(x^t \middle| A^t, \Lambda\right) = \frac{1}{Z(A^t, \Lambda, \eta)} \exp\left[\eta \sum_{ij} \Phi_{ij}(x_i^t, x_j^t, A_{ij}^t, \Lambda_{ij})\right]$

"Dynamic" Potentials

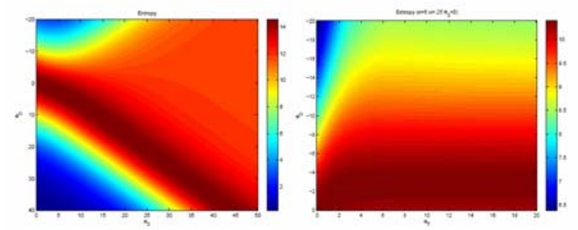
$$P\left(A^t \middle| A^{t-1}\right) = \exp\left\{\theta \cdot \Psi\left(A^t, A^{t-1}\right) - \ln Z\left(\theta, A^{t-1}\right)\right\}$$

- "Continuity": $\Psi_1\left(A^t, A^{t-1}\right) = \sum_{ij}\left(A_{ij}^t A_{ij}^{t-1} + \left(1 - A_{ij}^t\right)\left(1 - A_{ij}^{t-1}\right)\right)$
- "Reciprocity": $\Psi_2\left(A^t, A^{t-1}\right) = \sum_{ij} A_{ij}^t A_{ji}^{t-1}$
- "Transitivity": $\Psi_3\left(A^t, A^{t-1}\right) = \frac{\sum_{ijk} A_{ij}^t A_{ik}^{t-1} A_{kj}^{t-1}}{\sum_{ijk} A_{ik}^{t-1} A_{kj}^{t-1}}$
- "Density": $\Psi_4\left(A^t, A^{t-1}\right) = \sum_{ij} A_{ij}^t$

A tERGM is non-degenerate

- **Theorem 1**: when the transition distribution factors over the edges, a tERGM is non-degenerate:

$$H(A^t) \geq \sum_{i,j} H(A^t_{i,j}|A^{t-1}) \geq p \ln \frac{1}{p} + (1-p) \ln \frac{1}{(1-p)}$$



- → Maximum likelihood estimator exists!

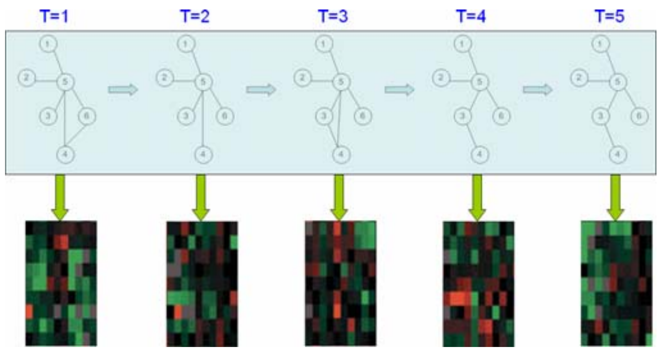
  (actually should not be taken for granted for arbitrary models, be careful!)

What's it good for?

- Hypothesis Testing
- Data Exploration (e.g., node-classification)
- Foundation for Learning
  - Current approaches:
    - Time invariant structures
    - Global optimality?
    - Consistency guarantee?

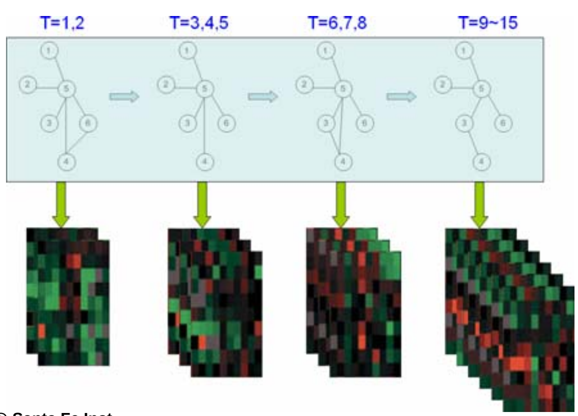
Inferring Rewiring Biological Networks

- Networks rewire over discrete time-steps



Inferring Rewiring Biological Networks

- Networks rewire over epochs



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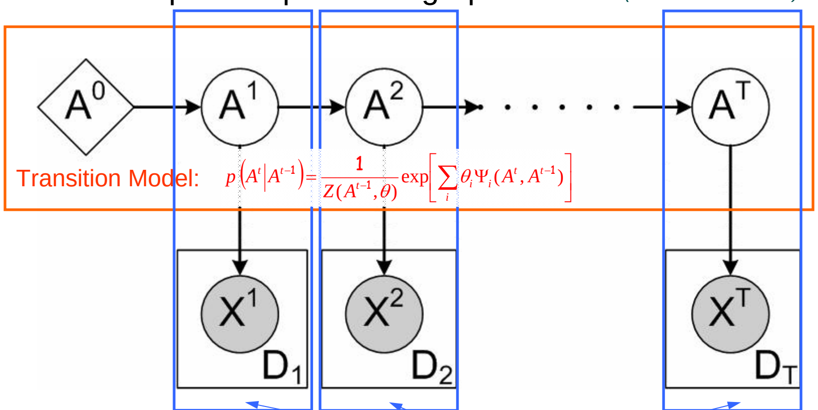
Modeling Time-Varying Graphs

- The temporal exponential graph models *(Fan et al. ICML 2007)*



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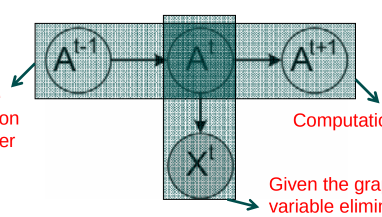
Inference (1)

$P(\text{Network}|\text{Data})$?

- Gibbs sampling:
  - Need to evaluate the log-odds

$$\mu_{ij}^t = \log \frac{P(A_{ij}^t = 1 | A_{t-1}, A_{-ij}^t, A^{t+1}, x^t)}{P(A_{ij}^t = 0 | A_{t-1}, A_{-ij}^t, A^{t+1}, x^t)}$$
$$= \log \frac{P(A_{-ij}^t, A_{ij}^t = 1 | A^{t-1})}{P(A_{-ij}^t, A_{ij}^t = 0 | A^{t-1})} + \log \frac{P(A^{t+1} | A_{-ij}^t, A_{ij}^t = 1)}{P(A^{t+1} | A_{-ij}^t, A_{ij}^t = 0)} + \log \frac{P(x^t | A_{-ij}^t, A_{ij}^t = 1)}{P(x^t | A_{-ij}^t, A_{ij}^t = 0)}$$

  - Difficulty: Evaluate the ratio of Partition function $Z(A') = \Sigma_A \exp(\theta \Phi(A, A'))$
  - So far scale to ~20 genes



Straightforward -- tractable transition model; the partition function is the product of per edge terms

Computation is non-trivial

Given the graphical structure, run variable elimination algorithms, works well only for small graphs

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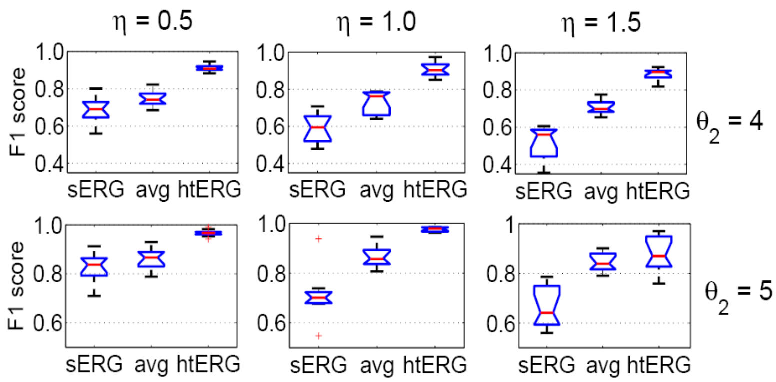
Results on Simulated Data

- F1 scores on different parameter settings (varying θ_2, η)

$(\theta_1 = -0.5, \theta_3 = 4, D = 5, \text{100k iterations of Gibbs sampling, 10 repetitions})$



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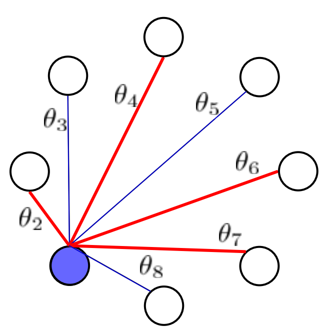
Graph Regression

$$\mathbf{X}^t \sim \frac{1}{Z}\exp\{\sum_i \theta_i^t x_i^t + \sum_{i<j}\theta_{i,j}^t x_i^t x_j^t\}$$

Markov Random Fields

$$\mathbf{X}^t \sim \frac{1}{(2\pi)^{\frac{d}{2}}|\Sigma^t|^{\frac{1}{2}}}\exp\{-\frac{1}{2}\mathbf{x}^{\prime t}(\Sigma^t)^{-1}\mathbf{x}^t\}$$

Graphical Gaussian Model



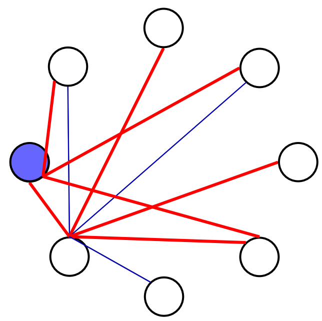
$$\Theta^t \equiv (\Sigma^t)^{-1}$$

contains both the structure and parameters

Lasso:

$$\hat{\theta} = \arg\min_{\theta} \sum_{t=1}^{T} l(\theta) + \lambda_1 \|\theta\|_1$$

Graph Regression



$\Theta^t \equiv (\Sigma^t)^{-1}$

contains both the structure and parameters

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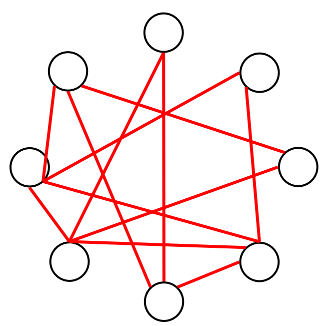
Graph Regression



$\Theta^t \equiv (\Sigma^t)^{-1}$

contains both the structure and parameters

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Inference II

- **TESLA**: Temporally Smoothed L_1-regularized logistic regression

$$\hat{\theta}_i^1, \ldots, \hat{\theta}_i^T = \arg\min_{\theta_i^1,\ldots,\theta_i^T} \sum_{t=1}^{T} l_{avg}(\theta_i^t) + \lambda_1 \sum_{t=1}^{T} \| \theta_{-i}^t \|_1 + \lambda_2 \sum_{t=2}^{T} \| \theta_i^t - \theta_i^{t-1} \|_q^q,$$

$$\text{where } l_{avg}(\theta_{\mathbf{i}}^{\mathbf{t}}) = \frac{1}{N^t} \sum_{d=1}^{N^t} \log P(x_{d,i}^t | \mathbf{x}_{\mathbf{d},-\mathbf{i}}^{\mathbf{t}}, \theta_{\mathbf{i}}^{\mathbf{t}}).$$

- Constrained convex optimization
  - Now scale to ~5000 nodes, how about 20K+ ?

Inference III

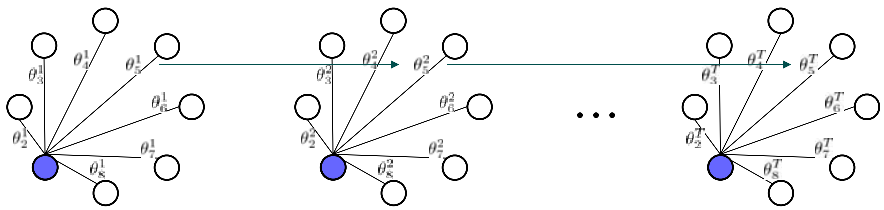
- Kernel Weighting (Kolar and Xing, 2008):

$$\hat{\theta}_i^1, \ldots, \hat{\theta}_i^T = \arg\min_{\theta_i^1,\ldots,\theta_i^T} \sum_{t=1}^{T} l_w(\theta_i^t) + \lambda_1 \sum_{t=1}^{T} \| \theta_{-i}^t \|_1$$

$$\text{where } l_w(\theta_i^t) = \sum_{t'=1}^{T} w(\mathbf{x}^{t'}; \mathbf{x}^t) \log P(x_i^{t'} | \mathbf{x}_{-i}^{t'}, \theta_i^t).$$

- Constrained convex optimization
  - Could scale to ~10^4 genes, but under stronger smoothness assumptions

Temporally Smoothed Graph Regression



TESLA:

$$\min_{\substack{\theta_i^1,\dots,\theta_i^T \\ \mathbf{u}_i^1,\dots,\mathbf{u}_i^T;\mathbf{v}_i^2,\dots,\mathbf{v}_i^T}} \sum_{t=1}^{T} \ell(\mathbf{x}^t;\theta_i^t) + \lambda_1 \sum_{t=1}^{T} \mathbf{1}'\mathbf{u}_i^t + \lambda_2 \sum_{t=2}^{T} \mathbf{1}'\mathbf{v}_i^t$$

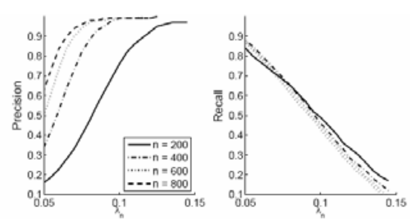
$$\text{s.t.} \quad -u_{i,j}^t \le \theta_{i,j}^t \le u_{i,j}^t,\ t=1,\dots,T,\ \forall j \in V \setminus i,$$

$$\text{s.t.} \quad -v_{i,j}^t \le \theta_{i,j}^t - \theta_{i,j}^{t-1} \le v_{i,j}^t,\ t=2,\dots,T,\ \forall j \in V \setminus i,$$

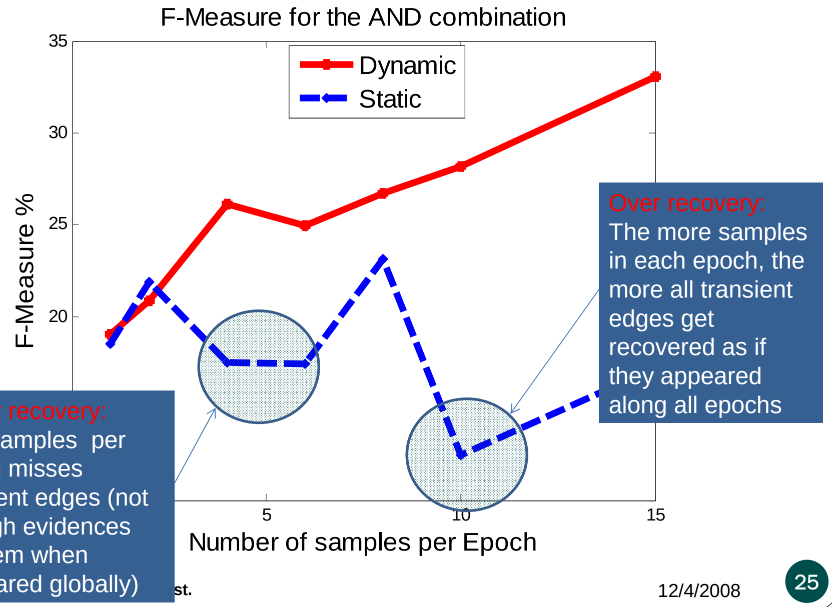
Consistency

- **Theorem 2**: for the kernel weighting method, under certain verifiable conditions (omitted here for simplicity):

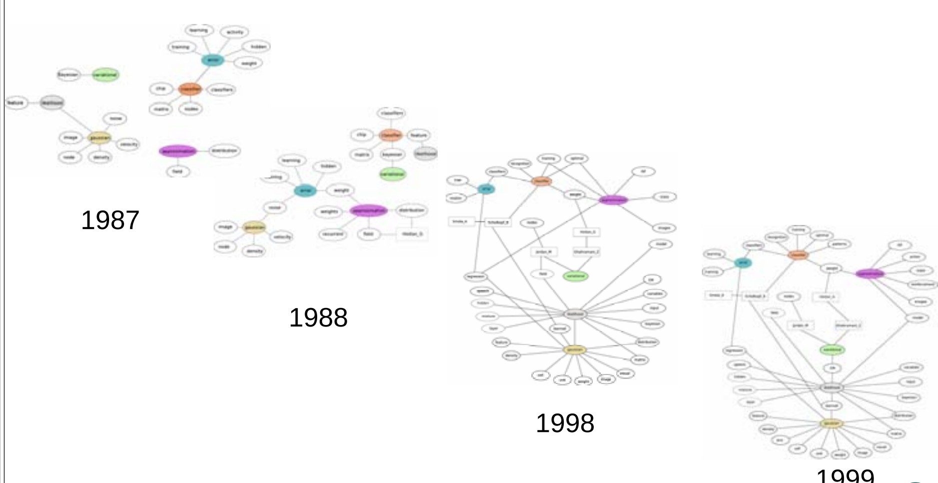
$$\mathbb{P}\left[\hat{G}(\lambda_n, t_0) \neq G^{t_0}\right] = \mathcal{O}\left(\exp\left(-C\frac{nh_n}{s_n^3} + C'\log p\right)\right) \to 0$$

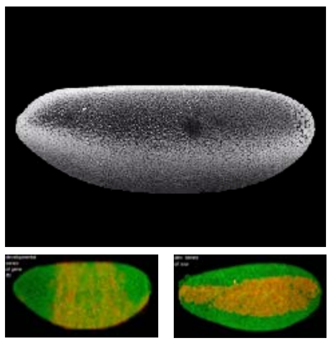


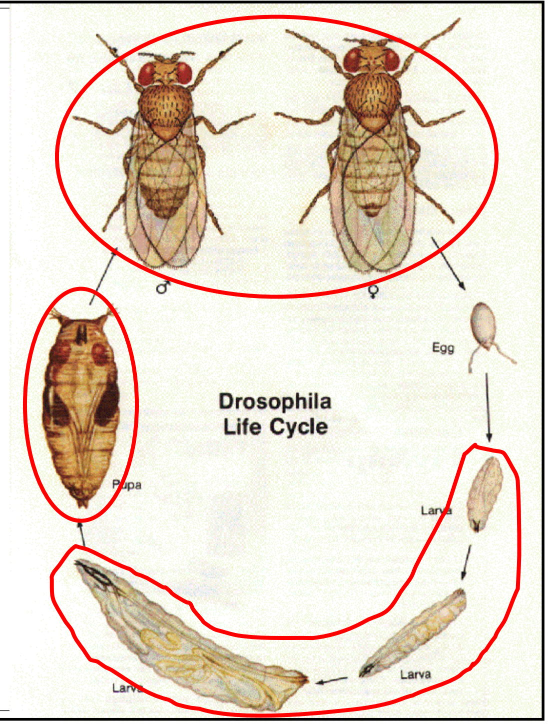
- Consistency for TESLA is yet to be proven! (very hard!)

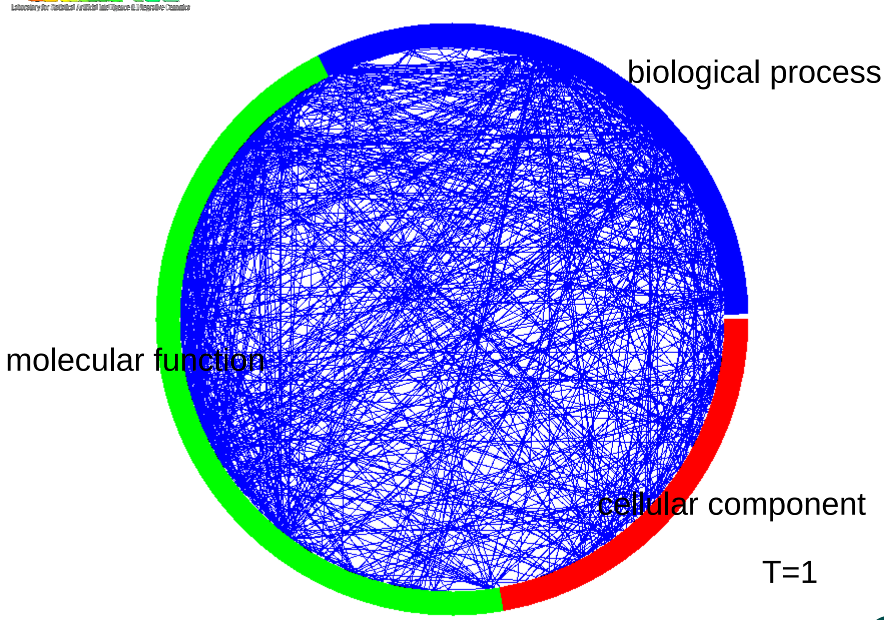


NIPS academic social network






Drosophila
Life Cycle
Egg
Larva
Larva
Larva
Pupa
♂
♀


biological process
molecular function
cellular component
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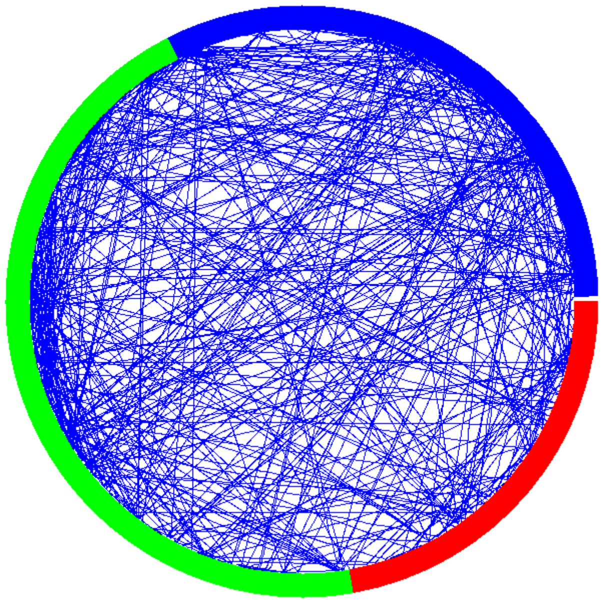

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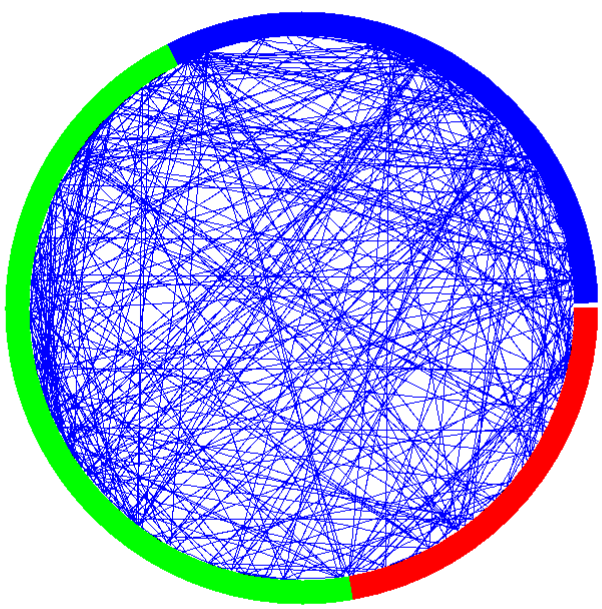

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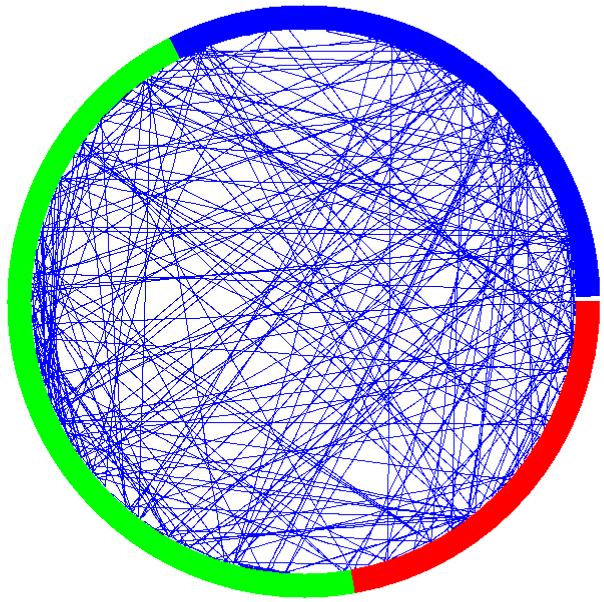

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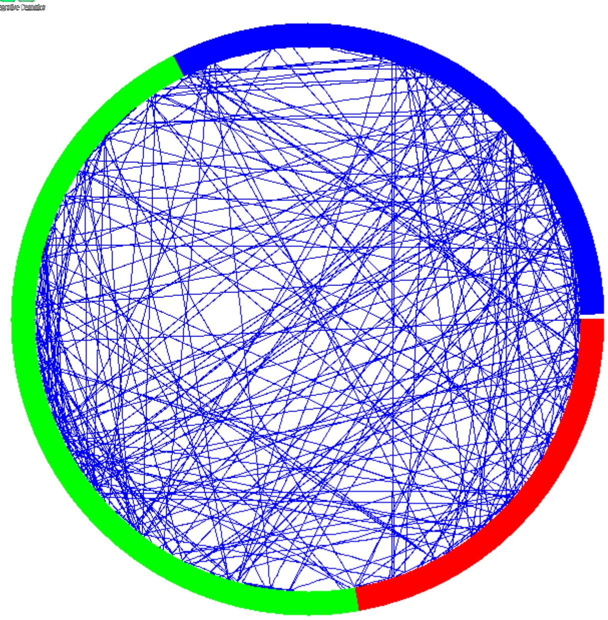

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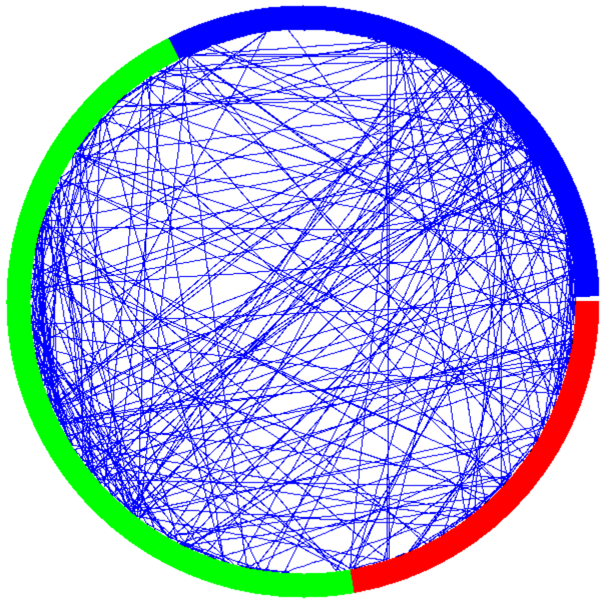

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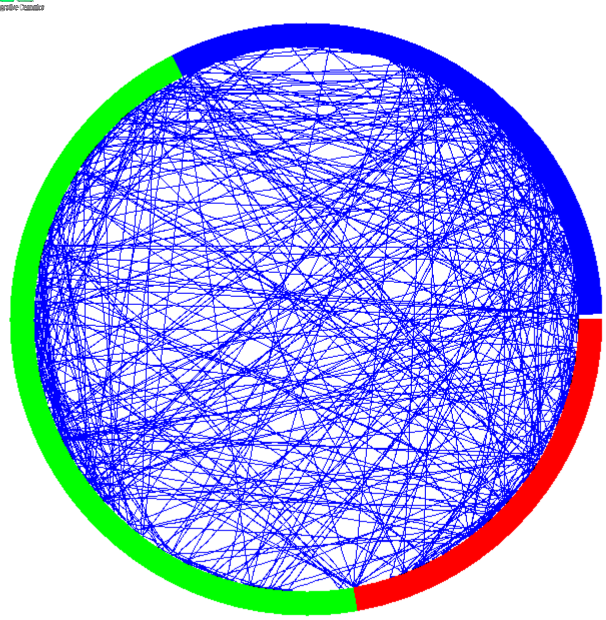

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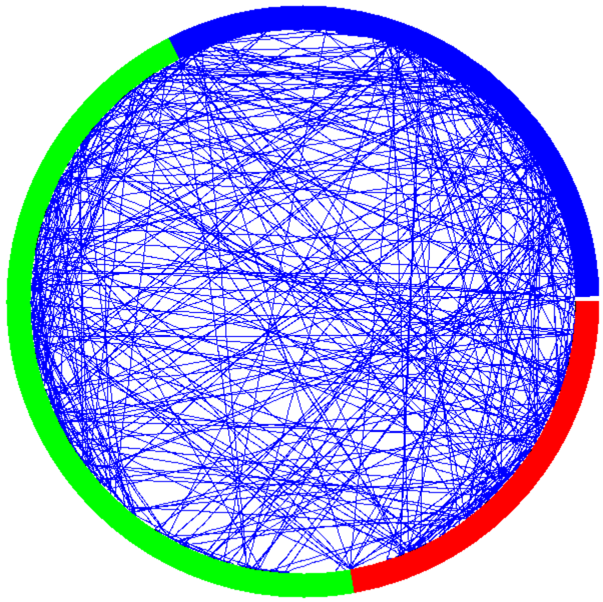

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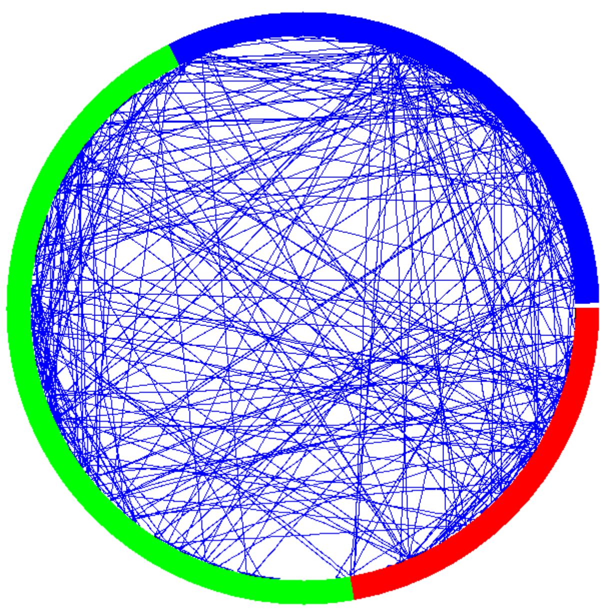

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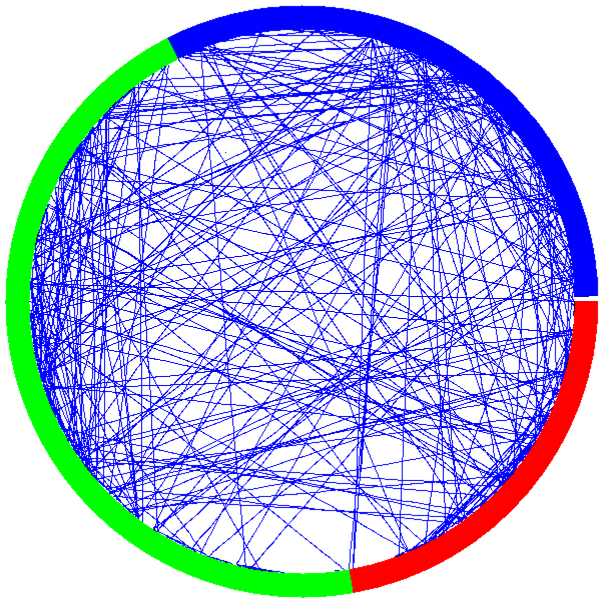

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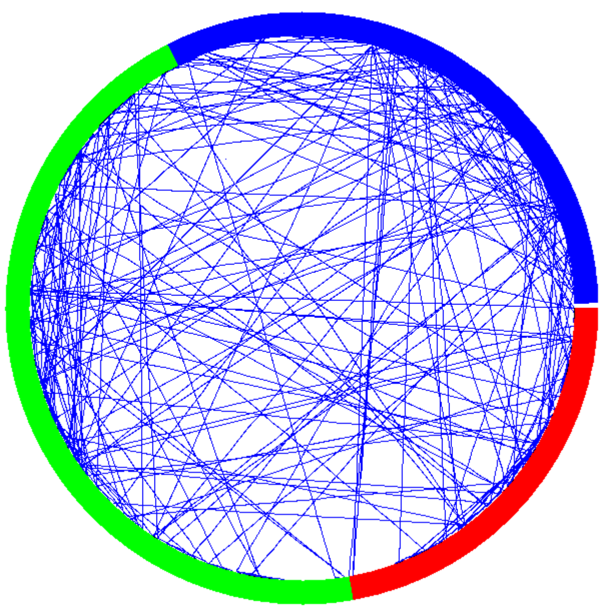

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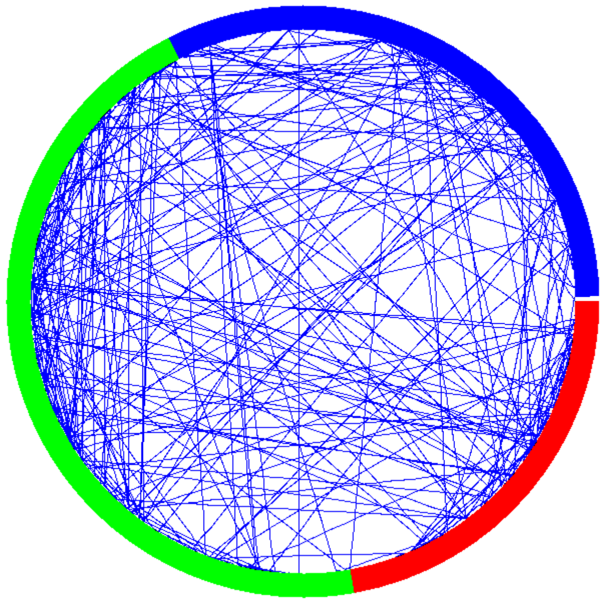

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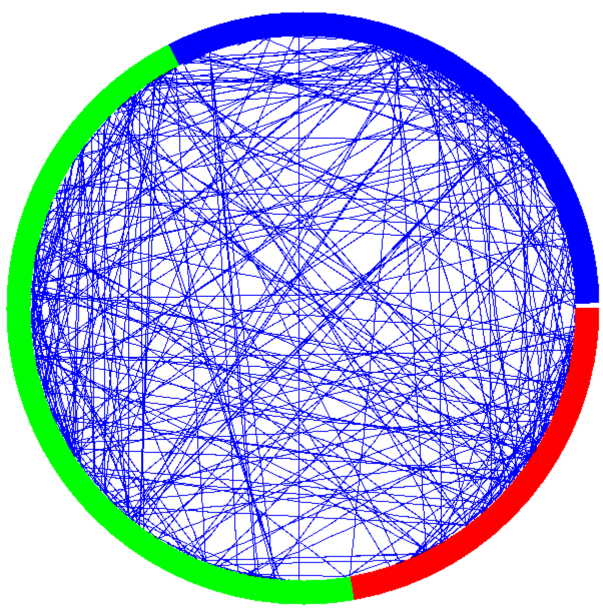

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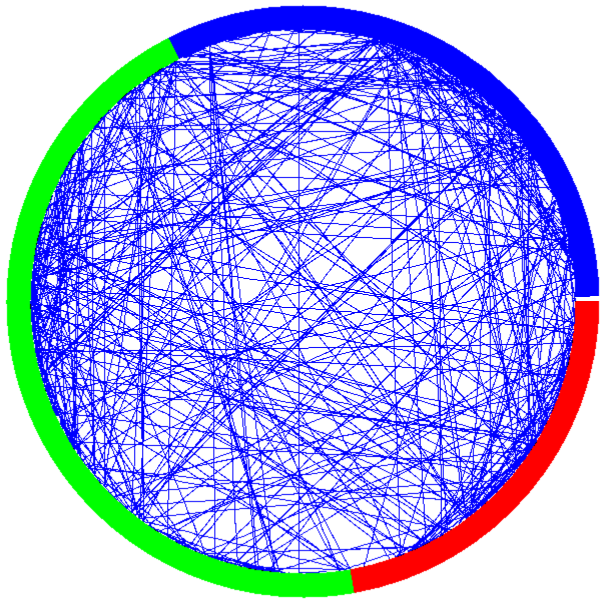

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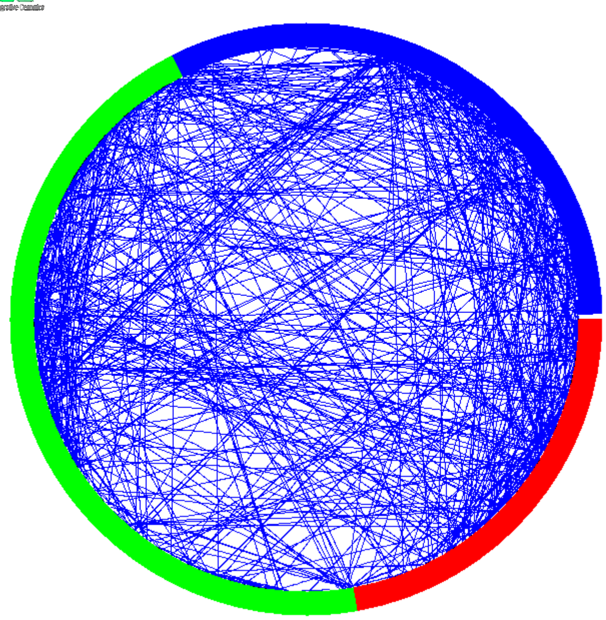

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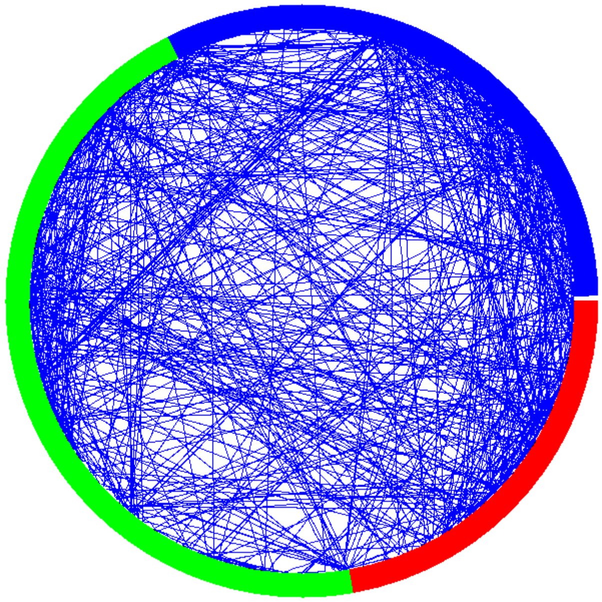

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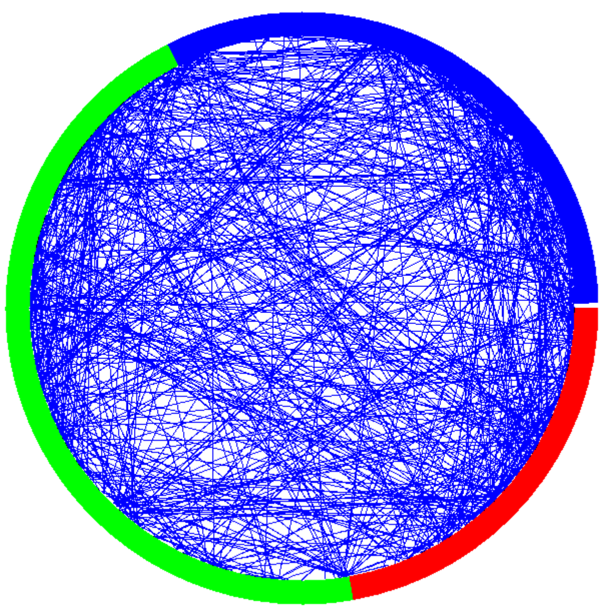

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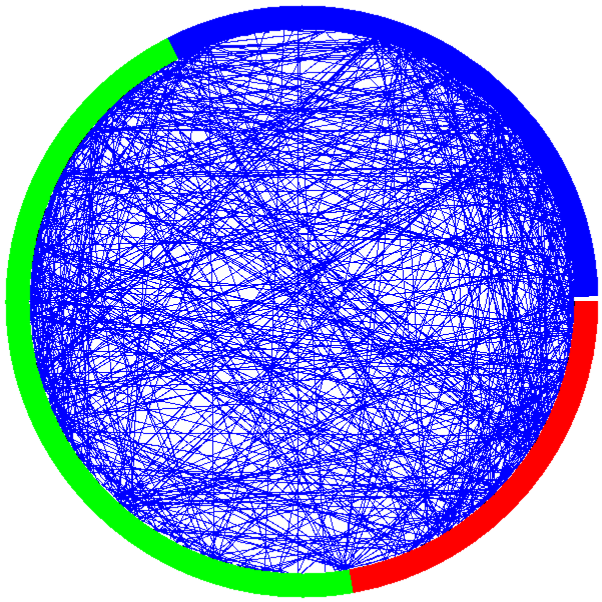

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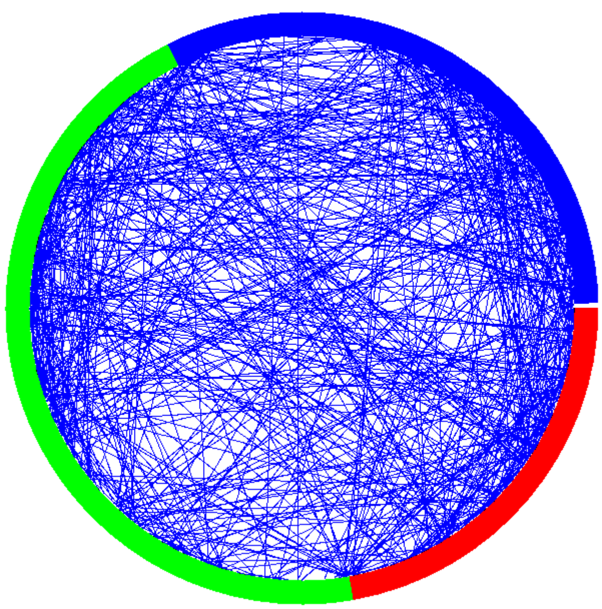

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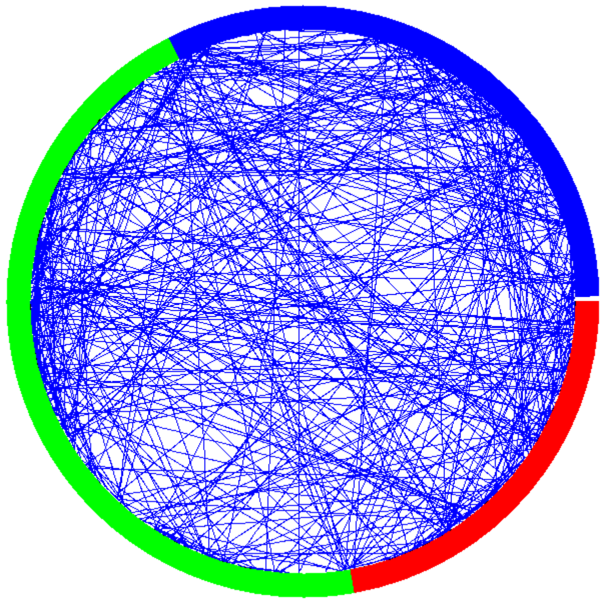
46



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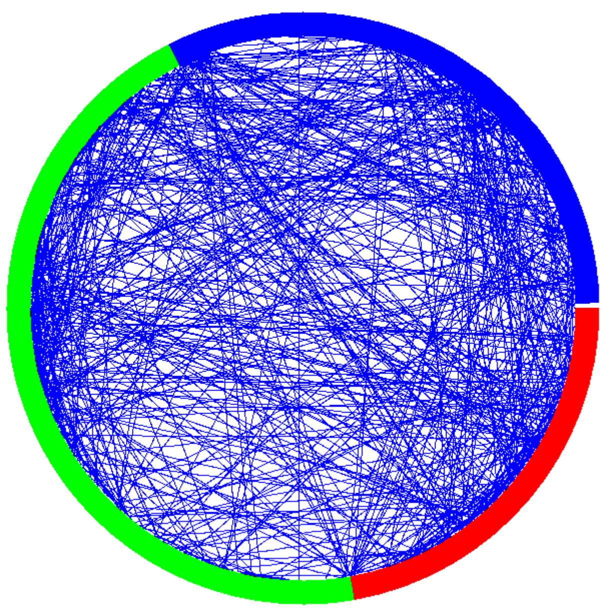
Network Workshop @ Santa Fe Inst. 12/4/2008 47



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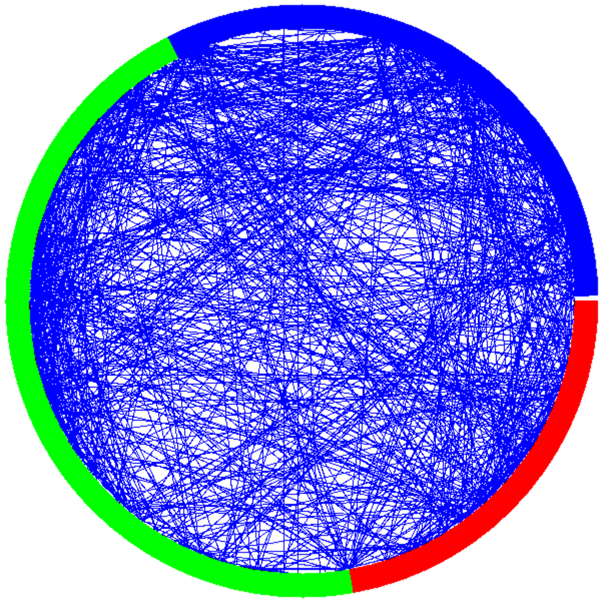

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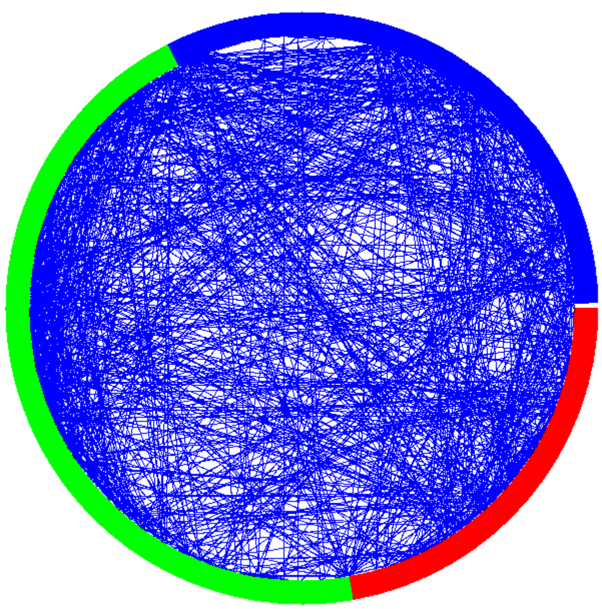

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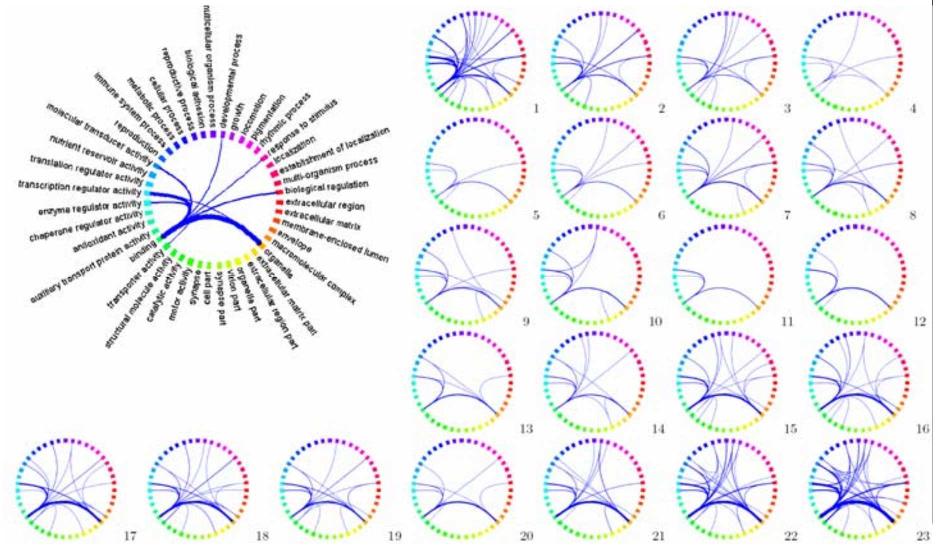
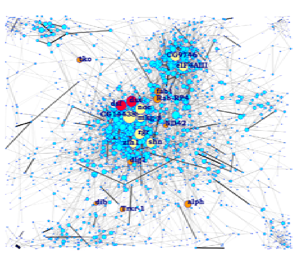
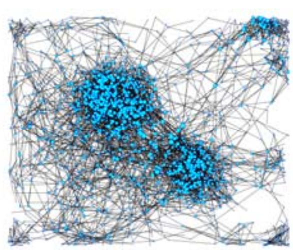
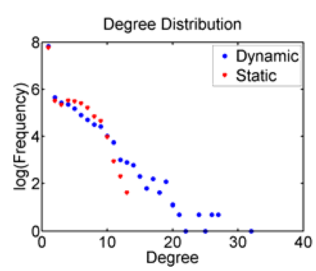
Transient Interaction



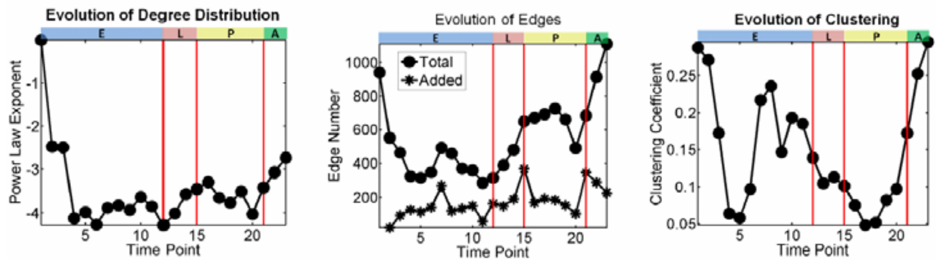
Static Versus Dynamic



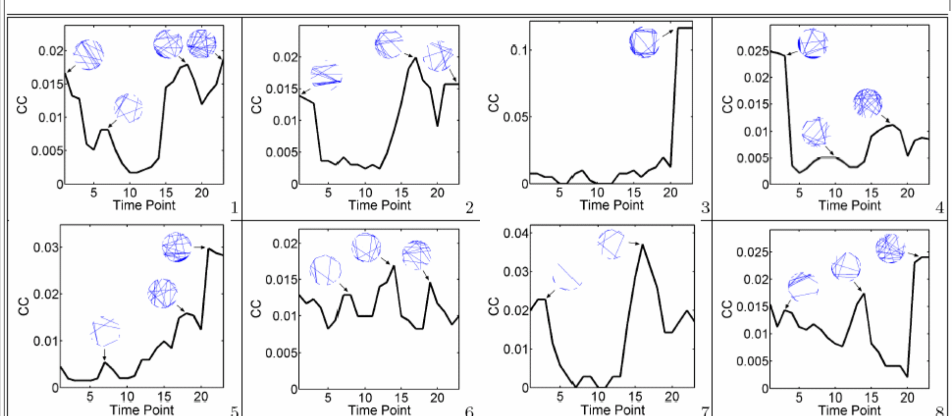




Evolution of Network Signatures



Transient Subgraph

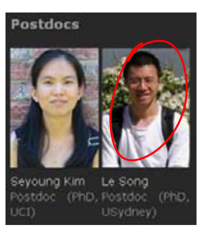


Future Work

- Analyzing time-space data in biological processes
  - Drosophila life cycle
  - Breast cancer progression and reversal
  - Inflammatory response in endotoxinated mice
- Other dynamic behaviors of networks
  - Differentiation: tree of networks
  - Detection of sudden changes
  - Active learning – when to get more samples
- Open theoretical issues
  - Consistence (pattern, value, …)
  - Confidence
  - Stability
  - Sample complexity

Acknowledgement

Laboratory for Statistical Artificial InteLligence & INtegrative Genomics



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