Inférence de Réseaux bayésiens dynamiques à structure variant "progressivement" dans le temps

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Etude de différents modes de partage d'information entre les segments successifs

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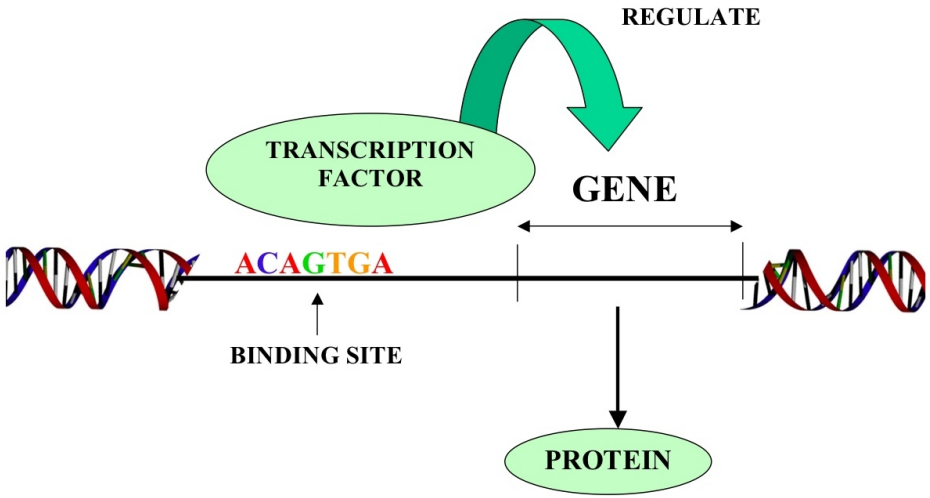
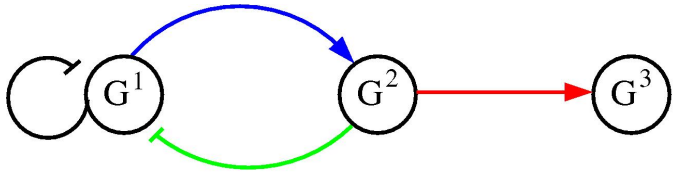
Outline

Recovering genes functions?

- Regulatory relationships:



  - up/down regulation
  - retroaction, feedforwards loops...

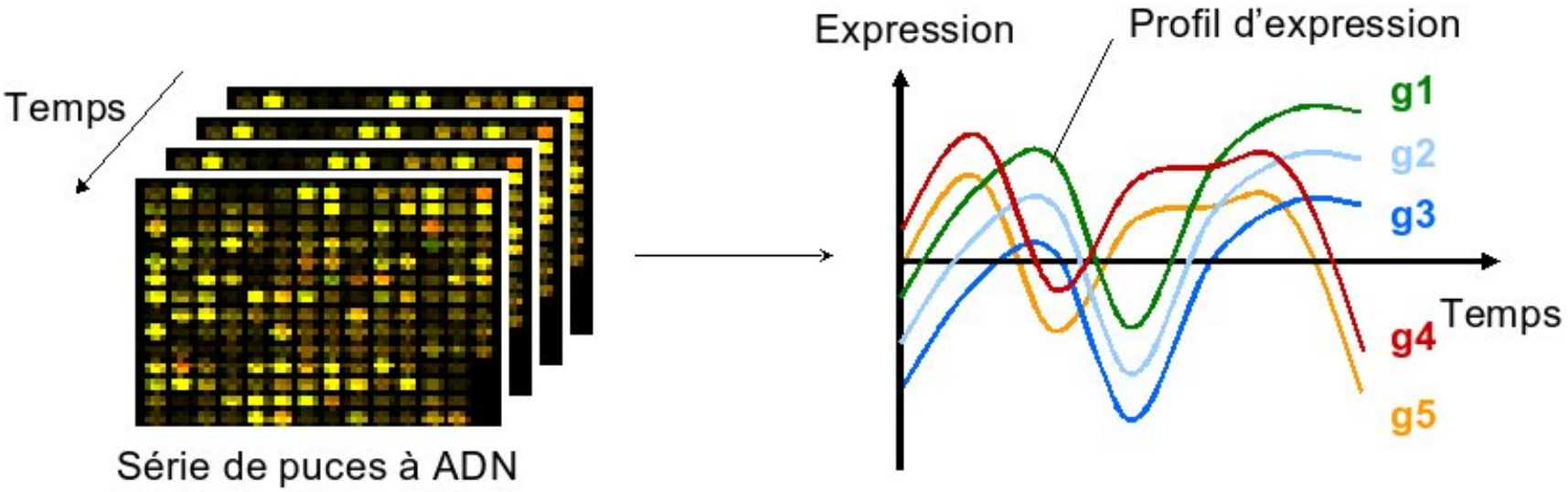


$\Rightarrow$ **Complex dynamic system**

- Objective: identifying this organisation in large scale.

Temporal gene expression data

- Microarrays:
  ⇝ **simultaneous** expression of **several thousands** of genes.



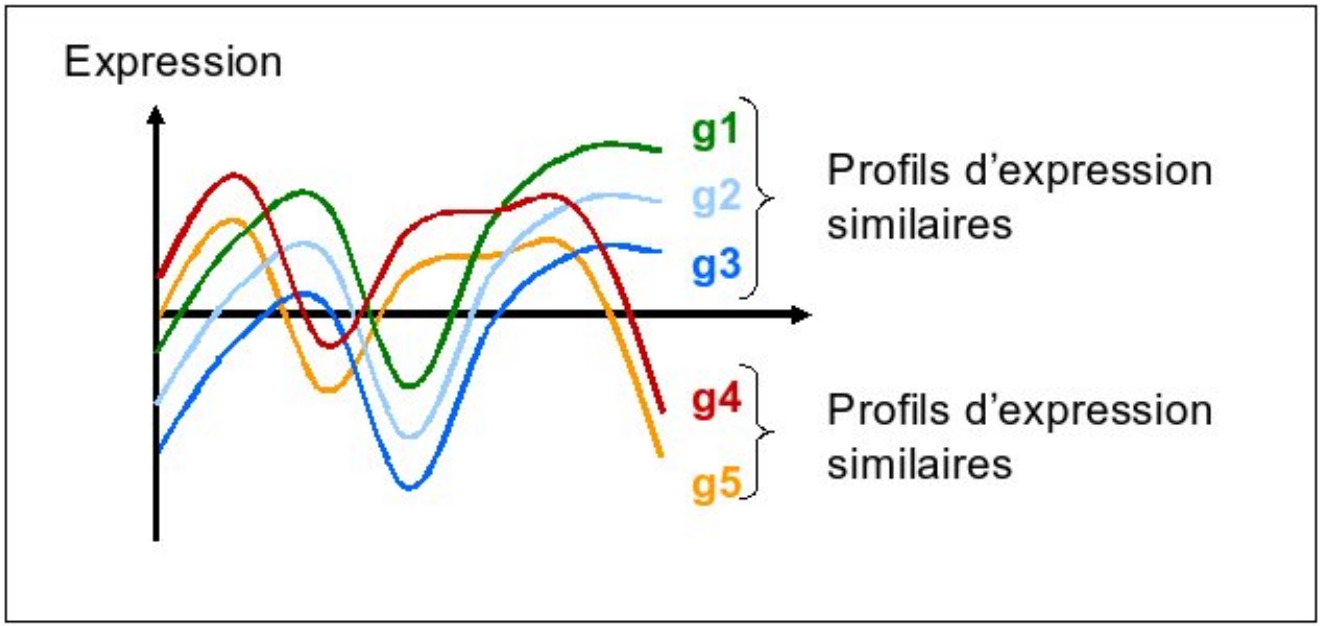
- Notations: we consider the stochastic process,

$$X = \{X_t^i;\ \forall i \in \{1, ..., p\}, \forall t \in \{1, ..., n\}\}$$

where X_t^i is the expression of gene i at time t,

What information extracting from expression profiles?

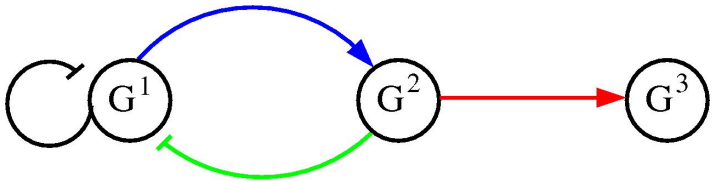
- Identifying coexpressed genes
  $\rightsquigarrow$ coregulated genes? $\rightsquigarrow$ same biological process?



- 2 main objectives:
  - Which genes work together?
  - At what time of the process?

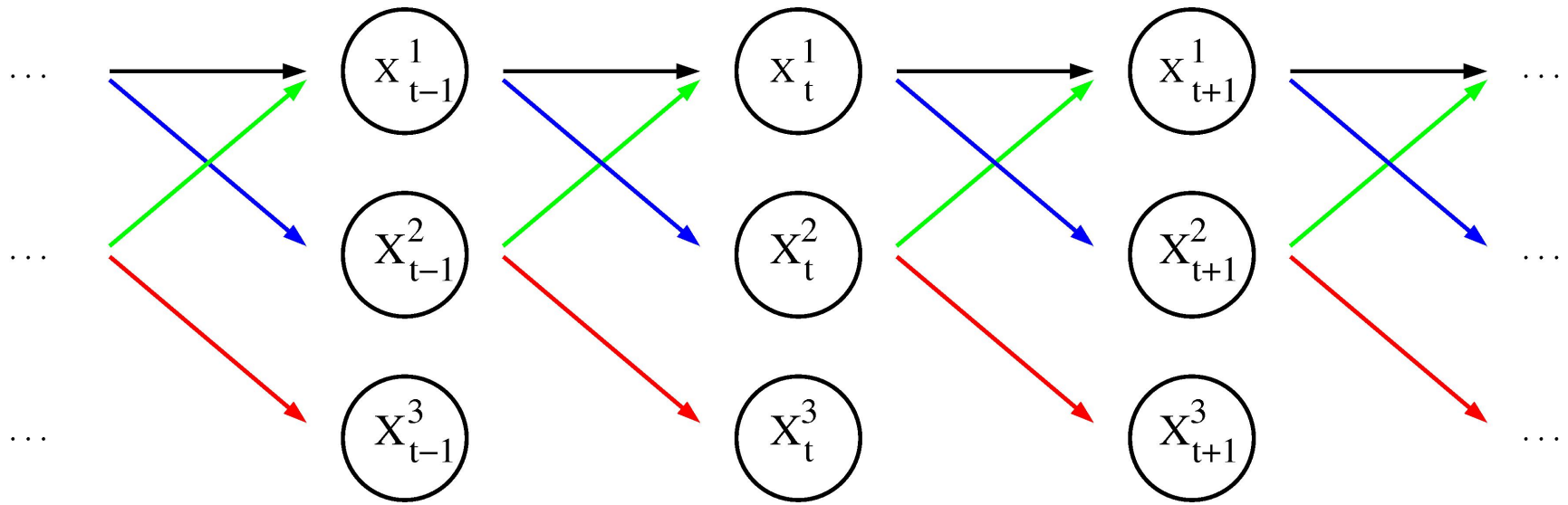
DBN modelling of biological motifs

- A biological motif



- Dynamic Bayesian Networks (DBNs)

  $\rightsquigarrow$ allow to model biological cycles



(Friedman et al. 1998, Murphy and Mian 1999)

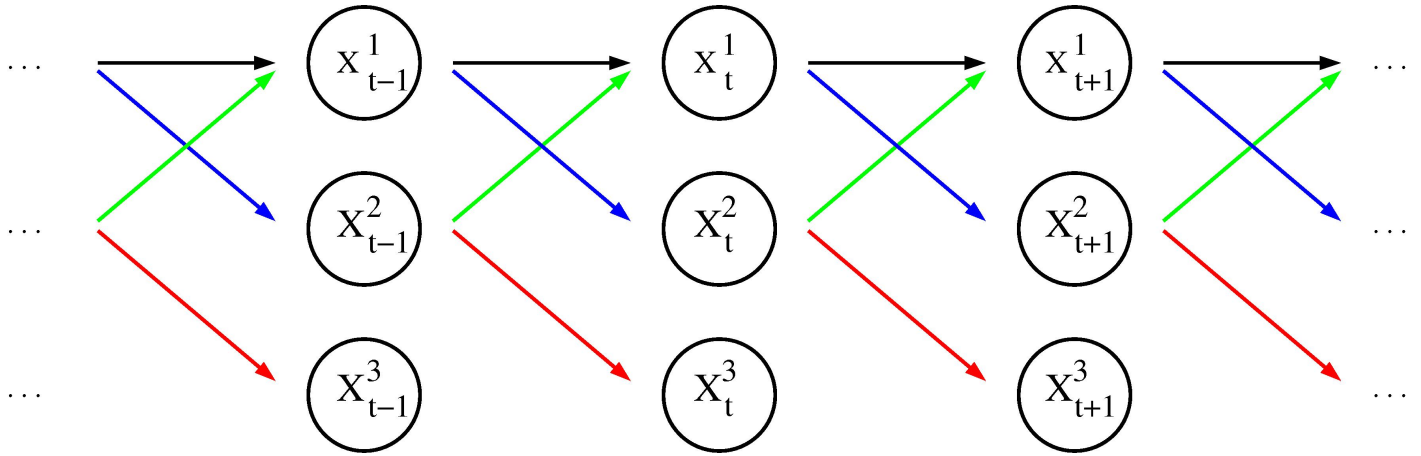
DBN modelling

Assumptions

- $(\mathcal{A}_1)$ 1^{st} *order Markov process*
- $(\mathcal{A}_2)$ *'simultaneous independence' given the past,*

$$\forall t > 1, \forall i, j \in N, \quad X_t^i \perp\!\!\!\perp X_t^j \mid X_{t-1}.$$

- $(\mathcal{A}_3)$ *time homogeneity*



$$f(X) = \prod_{1<t\leq n} f(X_t^1|X_{t-1}^1, X_{t-1}^2)\ f(X_t^2|X_{t-1}^1)\ f(X_t^3|X_{t-1}^2)$$

DAG $\tilde{\mathcal{G}}$ for a first order AR process

- AR(1) process: $\forall t \geq 1,\ X_t = AX_{t-1} + B + \varepsilon_t, \quad \varepsilon_t \sim \mathcal{N}(0, \Sigma)$

$$\begin{bmatrix} X_t^1 \\ \vdots \\ X_t^i \\ \vdots \\ X_t^p \end{bmatrix} = \begin{bmatrix} a_{11} & \cdots & a_{1j} & \cdots & a_{1p} \\ \vdots & & \vdots & & \vdots \\ a_{i1} & \cdots & a_{ij} & \cdots & a_{ip} \\ \vdots & & \vdots & & \vdots \\ a_{p1} & \cdots & a_{pj} & \cdots & a_{pp} \end{bmatrix} \begin{bmatrix} X_{t-1}^1 \\ \vdots \\ X_{t-1}^j \\ \vdots \\ X_{t-1}^p \end{bmatrix} + \begin{bmatrix} b_t^1 \\ \vdots \\ b_t^i \\ \vdots \\ b_t^p \end{bmatrix} + \begin{bmatrix} \varepsilon_t^1 \\ \vdots \\ \varepsilon_t^i \\ \vdots \\ \varepsilon_t^p \end{bmatrix}$$

Proposition

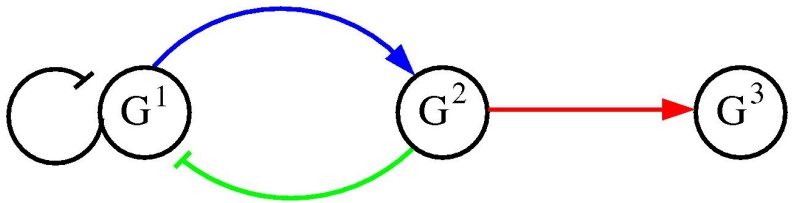
If $\Sigma = Var(\varepsilon_t)$ is diagonal then $\tilde{\mathcal{G}}_A := \{X_{t-1}^j \to X_t^i\} \Leftrightarrow a_{ij} \neq 0$.

DBN for a 1^{st} order auto-regressive process: AR(1).

- AR(1) process: $\forall t \geq 1,\ X_t = AX_{t-1} + B + \varepsilon_t,\quad \varepsilon_t \sim \mathcal{N}(0, \Sigma)$

$$\begin{bmatrix} X_t^1 \\ \cdot \\ \cdot \\ X_t^i \\ \cdot \\ \cdot \\ X_t^p \end{bmatrix} = \begin{bmatrix} a_{11} & \cdot & \cdot & \cdot & a_{1j} & \cdot & \cdot & a_{1p} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ a_{i1} & \cdot & \cdot & \cdot & a_{ij} & \cdot & \cdot & a_{ip} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ a_{p1} & \cdot & \cdot & \cdot & a_{pj} & \cdot & \cdot & a_{pp} \end{bmatrix} \begin{bmatrix} X_{t-1}^1 \\ \cdot \\ \cdot \\ \cdot \\ X_{t-1}^j \\ \cdot \\ \cdot \\ X_{t-1}^p \end{bmatrix} + \begin{bmatrix} b_t^1 \\ \cdot \\ \cdot \\ b_t^i \\ \cdot \\ \cdot \\ b_t^p \end{bmatrix} + \begin{bmatrix} \varepsilon_t^1 \\ \cdot \\ \cdot \\ \varepsilon_t^i \\ \cdot \\ \cdot \\ \varepsilon_t^p \end{bmatrix}$$

- Example:



$$A = \begin{pmatrix} a_{11} & a_{12} & 0 \\ a_{21} & 0 & 0 \\ 0 & a_{32} & 0 \end{pmatrix}$$

Inferring DBNs when $n << p$.

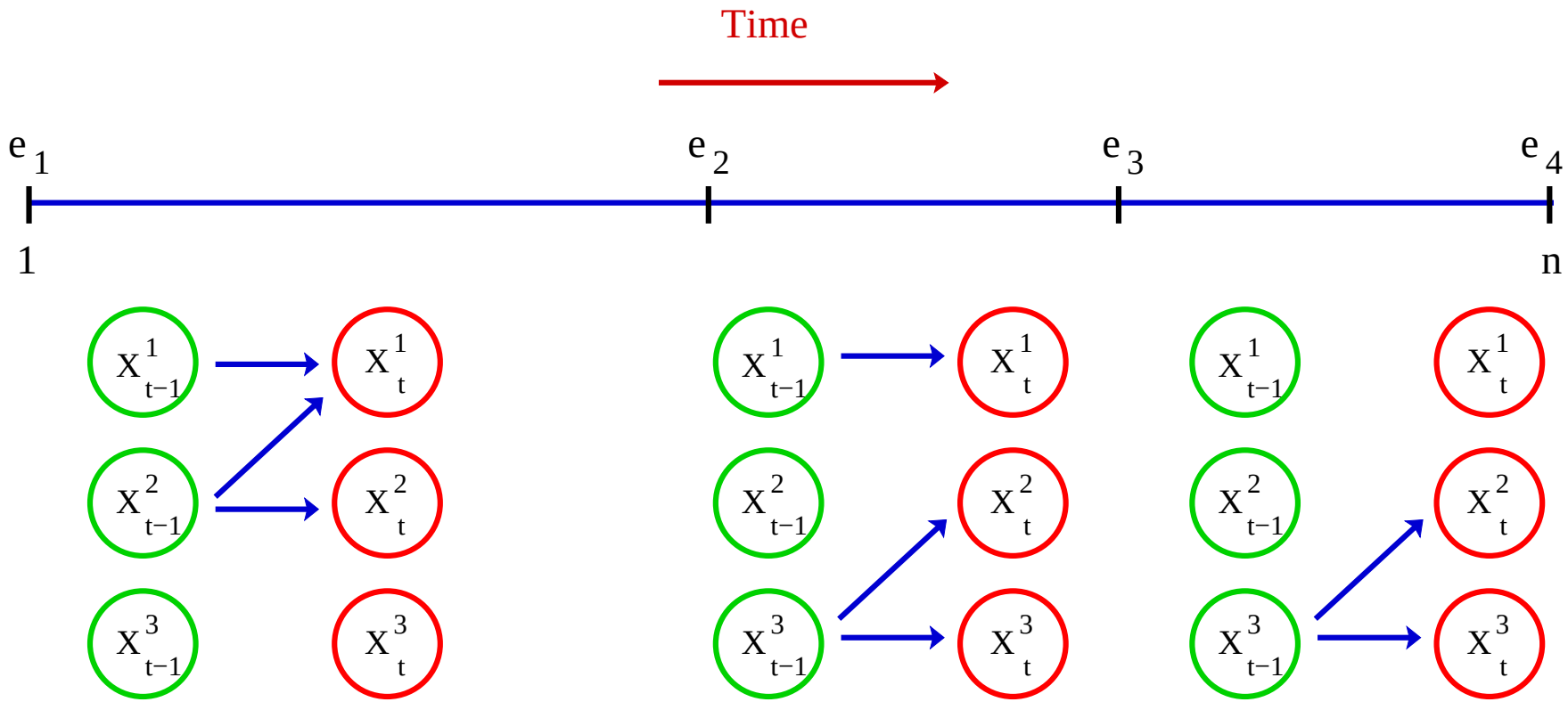
- **MCMC**, *The Bayes Net Toolbox for MATLAB*, Murphy (2001).
- **Lasso**, *High-dimensional graphs and variable selection with the Lasso*, Meinshausen and Bühlman (2006).
- **Shrinkage**, *Learning causal networks from systems biology time course data: an effective model selection procedure for the vector autoregressive process*, OpgenRhein and Strimmer (2007).
- **G1DBN**, *Inferring dynamic genetic networks with low order independencies,* Lèbre (2009).
- **SIMoNe**: *Statistical Inference for MOdular NEtworks*, Chiquet et al. (2009).

$\rightsquigarrow$ Time-homogeneous DBNs

$\rightsquigarrow$ Remove $(\mathcal{A}_3)$ time homogeneity ?

Time-varying dynamic Bayesian network model

- Introducing changepoints where the network topology changes.



$$X_t^1 = b^{10} + b^{11} X_{t-1}^1 + b^{12} X_{t-1}^2$$

$$X_t^1 = b^{10} + b^{11} X_{t-1}^1$$

$$X_t^1 = b^{10}$$

Previous work

- Undirected networks: Yoshida et al. (2005), Talih and Hengarten (2005), Xuan and Murphy (2007), Ahmed and Xing (2009).
- Directed networks:
  - First attempts ;
    - $\rightsquigarrow$ Fujita et al. (2007): wavelet, fixed network structure
    - $\rightsquigarrow$ Rao et al. (2007): CP/edges estimated separately
  - Most recent
    - $\rightsquigarrow$ Ahmed and Xing (2010): non-bayesian (parameter tuning, BIC, ...)
    - $\rightsquigarrow$ Robinson and Hartemink (2009, 2010): discrete network
    - $\rightsquigarrow$ Grzegorczyk and Husmeier (2009, 2011): fixed network structure

Outline

1. Modelling regulatory networks from gene expression time series with DBN
2. ARTIVA: Auto Regressive TIme VArying network
3. Gradually time varying structure: segment information coupling
4. Simulation study
5. Real data analysis

First step (2010)

- Auto Regressive TIme VArying (ARTIVA) network model
  Joint work with
  Gaëlle Lelandais, Frédéric Devaux, Jennifer Becq and Michael Stumpf
  $\rightsquigarrow$ BMC Systems Biology (2010)

- Our aims:
  $\rightsquigarrow$ Recover changepoints and edges simultaneously
  $\rightsquigarrow$ Gene specific segment transition
  $\rightsquigarrow$ Continuous data

ARTIVA network model definition.

p genes - n time points - k changepoint positions

For each gene i, $(1 \leq i \leq p)$,

- a **changepoint vector**
  $\xi_i = (\xi_i^1, ..., \xi_i^{h-1}, \xi_i^h, ..., \xi_i^{K^i+1}) \subseteq \{2, ..., n+1\}$
- in each segment h, (for all $\xi_i^h \leq t < \xi_i^{h+1}$),
  - a set of s_i^h **parents** $G_i^h = \{j_1, ..., j_{s_i^h}\} \subseteq \{1, ..., p\}$
  - and a set of **parameters** $((w_{ij}^h)_{j \in \{0,...,p\}}, \sigma_i^h)$,

define the regression model,

$$X_i(t) = w_{i0}^h + \sum_{j \in G_i^h} w_{ij}^h X_j(t-1) + \varepsilon_i(t), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma_i^h).$$

$\rightarrow$ number of segments K_i?

$\rightarrow$ number of edges s_i^h in each segment? unknown dimension...

Priors

- Multiple changepoint model:
  - Number of changepoints $K_i \sim \mathcal{P}(\lambda)$
  - Changepoints vector $\xi_i | K_i \sim \textit{Uniform}$
- Network model: (Andrieu and Doucet 1999)
  - Number of parents $s_i^h \sim \mathcal{P}(\Lambda)$
  - Set of parents $G_i^h | s_i^h \sim \textit{Uniform}$
  - Noise variance $(\sigma_i^h)^2 \sim \textit{Inverse Gamma}$
  - Regression coefficients $w_i^h | G_i^h, \sigma_i^h \sim \mathcal{N}\left(0, (\sigma_i^h)^2 \Sigma_{\mathcal{G}_i^h}\right)$

    where $\Sigma_{\mathcal{G}_i^h} = \delta^{-2} D_{G_i^h}^{\dagger}(x) D_{G_i^h}(x)$ and $D_{G_i^h}(x)$ has size $(\xi_i^h - \xi_i^{h-1}) \times (s_i^h + 1)$
- Hyperparameters:
  - $\lambda, \Lambda \sim \mathcal{G}a(0.5, 1) \rightsquigarrow$ expected number of CP/edges
  - $\delta^2 \sim \mathcal{IG}(2, 0.2) \rightsquigarrow$ expected signal-to-noise ratio

Posterior

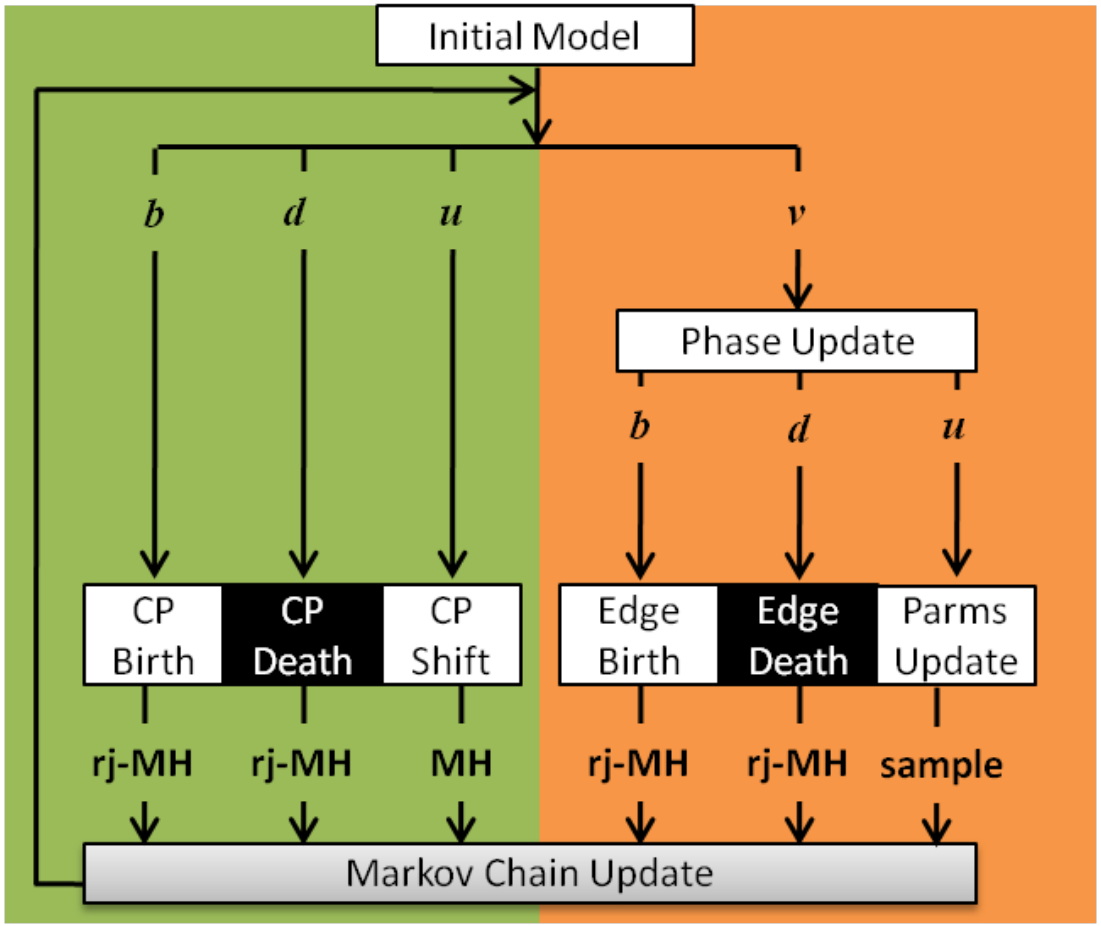
- From the AR model definition

$$P(x_i^h | G_i^h, a_i^h, \sigma_i^h) = \left(\sqrt{2\pi}\sigma_i^h\right)^{-\text{length}(x_i^h)} \exp\left(-\frac{(x_i^h - D_{G_i^h} a_{G_i^h})^\dagger \, (x_i^h - D_{G_i^h} a_{G_i^h})}{2(\sigma_i^h)^2}\right)$$

- Attractive feature (Andrieu and Doucet 1999): integration over parameters w and σ
  $\rightsquigarrow$ analytical expression of $P(k, \xi, G, \lambda, \Lambda, \delta^2 | x)$

Time-varying DBN inference with reversible jump MCMC

- Outline of the ARTIVA procedure:



⇝ Reversible jump MCMC (Green, 1995).

⇝ Model selection adapted from Andrieu and Doucet (1999).

Time-varying DBN inference with reversible jump MCMC

- 4 moves : Birth (b_k), Death (d_k), Position shift (u_k), Regression model update (v_k).

$$b_k + d_k + u_k + v_k = 1$$

- Moves probability

$$b_k = c \ \min\left\{1, \frac{P_{\overline{k}}(k+1)}{P_{\overline{k}}(k)}\right\}, \ d_k = c \ \min\left\{1, \frac{P_{\overline{k}}(k-1)}{P_{\overline{k}}(k)}\right\}, \ u_k = \frac{1}{2}(b_k + d_k).$$

$\rightsquigarrow$ keep c small (less CP moves)

Changepoint move

- Birth/death move
  - Acceptance ratio

    $R(\xi^+|\xi) = (\text{Likelihood ratio}) \times (\text{Prior ratio}) \times (\text{Proposal ratio}) \times (\text{Jacobian})$

  - (Likelihood ratio) $\perp\!\!\!\perp w, \sigma$ (Andrieu and Doucet, 1999)

    $\rightsquigarrow$ Acceptance ratio based on the network structure only

  - Acceptance probability $A(\xi^+|\xi) = \min\{1, R(\xi^+|\xi)\}$

    $\rightsquigarrow$ Ensures reversibility

- Shift move: standard Metropolis-Hastings step

  $$R(\tilde{\xi}|\xi) = (\text{Likelihood ratio}) \times (\text{Proposal ratio})$$

  (Prior ratio =1)

Edge birth/death move

- Moves probabilities : birth ($b_{s_i^h}$), death ($d_{s_i^h}$), Parameter update (u)

$$\text{with } b_{s_i^h} + d_{s_i^h} + u = 1$$

$$b_{s_i^h} = c_{s_i^h} \ \min\left\{1, \frac{P_{\bar{s}}(s_i^h+1)}{P_{\bar{s}}(s_i^h)}\right\}, \ d_{s_i^h} = c_{s_i^h} \ \min\left\{1, \frac{P_{\bar{s}}(s_i^h-1)}{P_{\bar{s}}(s_i^h)}\right\}$$

- Acceptance ratio

$$R(\tilde{G}_i^h | G_i^h) = \text{ (Likelihood ratio) } = \frac{P(x_i^h | \tilde{G}_i^h, \delta^2)}{P(x_i^h | G_i^h, \delta^2)}$$

as:

  - Prior ratio $\times$ Proposal ratio=1
  - Jacobian=1

ARTIVA network inference with reversible jump MCMC

- Reversible jump MCMC procedure
  - $\rightsquigarrow$ Generation of an ergodic Markov chain.
  - $\rightsquigarrow$ Reversible Markov chain: detailed balance satisfied.
  - $\rightsquigarrow$ Equilibrium distribution converges to the desired post-distribution,

$$P(k, \xi, s, G, w, \sigma | x).$$

- R package ARTIVA freely available (`http://cran.r-project.org`)
- Simulation study + real data analysis in :
  "Statistical inference of the time-varying structure of gene-regulation networks" Lèbre S, Becq J, Devaux F, Lelandais G, Stumpf M.
  BMC Systems Biology 4(130) 2010

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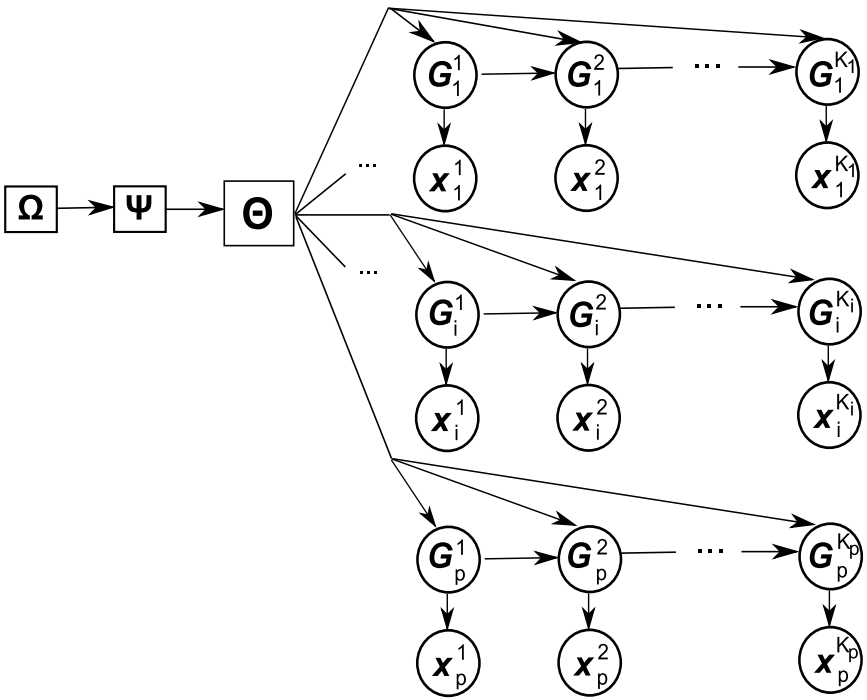
Improvement : information coupling between segments

- Assumptions: independence of the different segments
  - risk of over flexibility
  - not realistic in many cases
- Introducing information coupling between segments $\Rightarrow$ Various approaches
  - Inter-segment information coupling: Hierachical Bayesian model
  - Inter-node information: Hard coupling or Soft coupling
  - Prior distribution ?
    - Exponential distribution $\mathcal{E}xp(\beta)$
      $\rightsquigarrow$ 1 parameter
    - Binomial distribution $\mathcal{B}(a, b)$
      $\rightsquigarrow$ 2 parameters: 1 for edges similarity, 1 for non-edge similarity

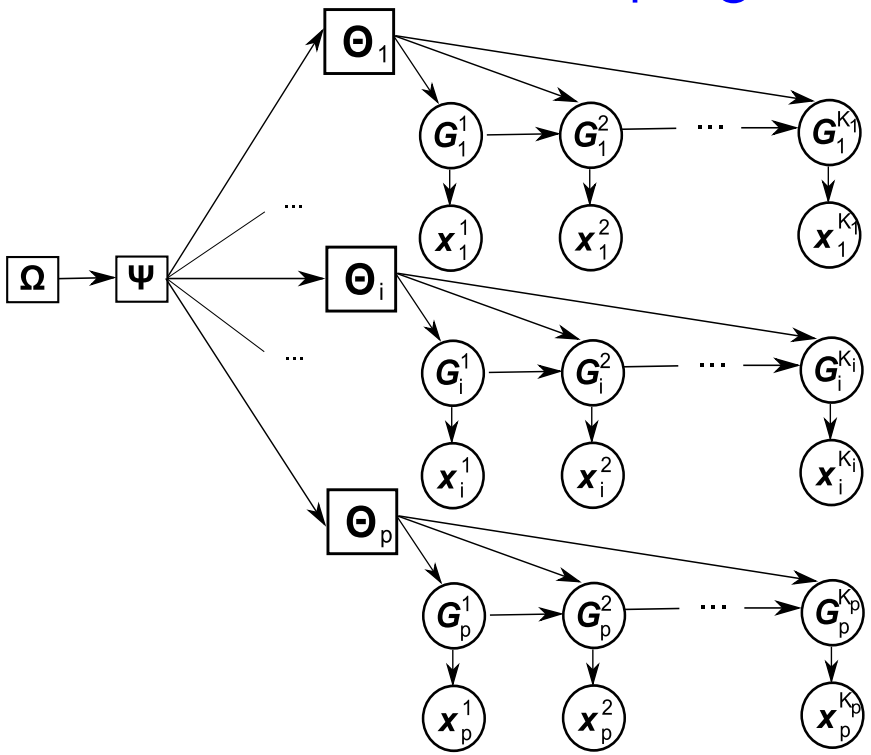
Hierachical Bayesian model for inter-segment information coupling

- Strength of the segment coupling: hyperprior Θ
- Level-2, level-3 hyperparameters: Ψ, Ω
- 2 schemes:

Hard coupling



Soft coupling



Hard information coupling based on an exponential prior

- Prior modification (Werlhi and Husmeier, 2008)
  For all $h \geq 2$,

$$P(G_i^h | G_i^{h-1}, \beta) = \frac{e^{-\beta \left| G_i^h - G_i^{h-1} \right|}}{Z(\beta, G_i^{h-1})}$$

  where
  - β defines the strength of the coupling between G_i^h and G_i^{h-1}
  - $|.|$ the Hamming distance
  - $Z(\beta, G_i^{h-1}) = \sum_{G_i^h \in \mathbb{G}} e^{-\beta \left| G_i^h - G_i^{h-1} \right|}$ is a normalizing constant also known as the partition function
- When ignoring fan-in restriction ($\overline{s}$): $Z(\beta, G_i^{h-1}) = Z(\beta) = (1 + e^{-\beta})^p$

$$\Rightarrow P(G_i^h | G_i^{h-1}, \beta) = \frac{e^{-\beta \left| G_i^h - G_i^{h-1} \right|}}{(1 + e^{-\beta})^p}$$

Easy to integrate to ARTIVA (Lebre et al. 2010)

- Changepoint birth/death acceptance ratio $\quad (\ G_i = \{G_i^h\}_{1 \leq h \leq K_i})$

$$\mathbb{R}(\tilde{\xi}|\xi) = \text{ (Likelihood ratio) } \times \frac{P(\tilde{G}_i)}{P(G_i)} \times \text{ (Proposal ratio)}$$

- Changepoint shift acceptance ratio : unchanged
- Edge birth/death ratio :

$$R(\tilde{G}_i^h|G_i^h) = \frac{P(x_i^h|\tilde{G}_i^h)}{P(x_i^h|G_i^h)} \times \frac{P(G_i^{h+1}|\tilde{G}_i^h,\beta)P(\tilde{G}_i^h|G_i^{h-1},\beta)}{P(G_i^{h+1}|G_i^h,\beta)P(G_i^h|G_i^{h-1},\beta)} \times \frac{Q(G_i^h|\tilde{G}_i^h)}{Q(\tilde{G}_i^h|G_i^h)}$$

- Parameter update : unchanged
- Additional MCMC step : sampling hyperparameter β
  With symmetric proposal probability,

$$R(\tilde{\beta}|\beta) = \frac{P(\tilde{\beta})}{P(\beta)} \prod_{i=1}^{p} \prod_{h=2}^{K_i} \frac{P(G_i^h|G_i^{h-1},\tilde{\beta})}{P(G_i^h|G_i^{h-1},\beta)}$$

$P(\beta) \sim \mathcal{U}[0, 20]$ in our study.

Soft information coupling: $\beta \rightarrow \beta_i$

- For each node i,

$$P(G_i^h | G_i^{h-1}, \beta_i) = \frac{e^{-\beta_i \left| G_i^h - G_i^{h-1} \right|}}{(1 + e^{-\beta_i})^p}$$

- Common gamma prior $\mathcal{G}a(\kappa, \rho)$

$$P(\beta_i) = P(\beta_i | \kappa, \rho) = \beta_i^{\kappa - 1} \frac{e^{-\beta_i / \rho}}{\rho^\kappa \Gamma(\kappa)}$$

- We set
  - $\rho = 0.1$ (mean $\mu = \kappa\rho$, variance $\sigma^2 = \kappa\rho^2$)
  - vague exponential prior on κ : $P(\kappa | \lambda_\kappa) = \lambda_\kappa e^{-\kappa / \lambda_\kappa}$ with $\lambda_\kappa = 10$ (prior ignorance)
    $\rightsquigarrow$ coupling strength between node defined by the coefficient of variation $\frac{\sigma}{\mu} = \frac{1}{\sqrt{\kappa}}$ (small coefficient $\rightarrow$ strong coupling)

Easy to integrate to ARTIVA (Lebre et al. 2010)

- Edge birth/death ratio :

$$R(\tilde{G}_i^h|G_i^h) = \frac{P(x_i^h|\tilde{G}_i^h)}{P(x_i^h|G_i^h)} \times \frac{P(G_i^{h+1}|\tilde{G}_i^h,\beta_i)P(\tilde{G}_i^h|G_i^{h-1},\beta_i)}{P(G_i^{h+1}|G_i^h,\beta_i)P(G_i^h|G_i^{h-1},\beta_i)} \times \frac{Q(G_i^h|\tilde{G}_i^h)}{Q(\tilde{G}_i^h|G_i^h)}$$

- Sampling hyperparameter β_i

$$R(\tilde{\beta}_i|\beta_i) = \frac{P(\tilde{\beta}_i)}{P(\beta_i)} \prod_{h=2}^{K_i} \frac{P(G_i^h|G_i^{h-1},\tilde{\beta}_i)}{P(G_i^h|G_i^{h-1},\beta_i)}$$

- Additional MCMC step: sampling κ
  With symmetric proposal probability,

$$R(\tilde{\kappa}|\kappa,\rho) = \frac{e^{-\tilde{\kappa}/\lambda_\kappa}}{e^{-\kappa/\lambda_\kappa}} \frac{P(\beta_i|\tilde{\kappa},\rho)}{P(\beta_i|\kappa,\rho)}$$

Binomial prior : 2 hyperparameters

- Binomial prior

$$P(G_i^h | G_i^{h-1}, a, b) = a^{N_1^1[h,i]}(1-a)^{N_1^0[h,i]} b^{N_0^0[h,i]}(1-b)^{N_0^1[h,i]}$$

  - $N_1^1[h,i]$ is the number of edges in G_i^{h-1} matched by an edge in G_i^h
  - $N_1^0[h,i]$ is the number of edges in G_i^{h-1} not matched by an edge in G_i^h
  - $N_0^1[h,i]$ is the number of edges in G_i^h not matched by an edge in G_i^{h-1}
  - $N_0^0[h,i]$ is the number of coinciding non edges in G_i^{h-1} and G_i^h

- Hyperparameter a, b prior :

$$P(a, b | \alpha, \overline{\alpha}, \gamma, \overline{\gamma}) \propto a^{\alpha-1}(1-a)^{\overline{\alpha}-1} b^{\gamma}(1-b)^{\overline{\gamma}-1}$$

Outline

Simulations

First evalution : topology inference performance

$\Rightarrow$ Changepoint fixed at their true value

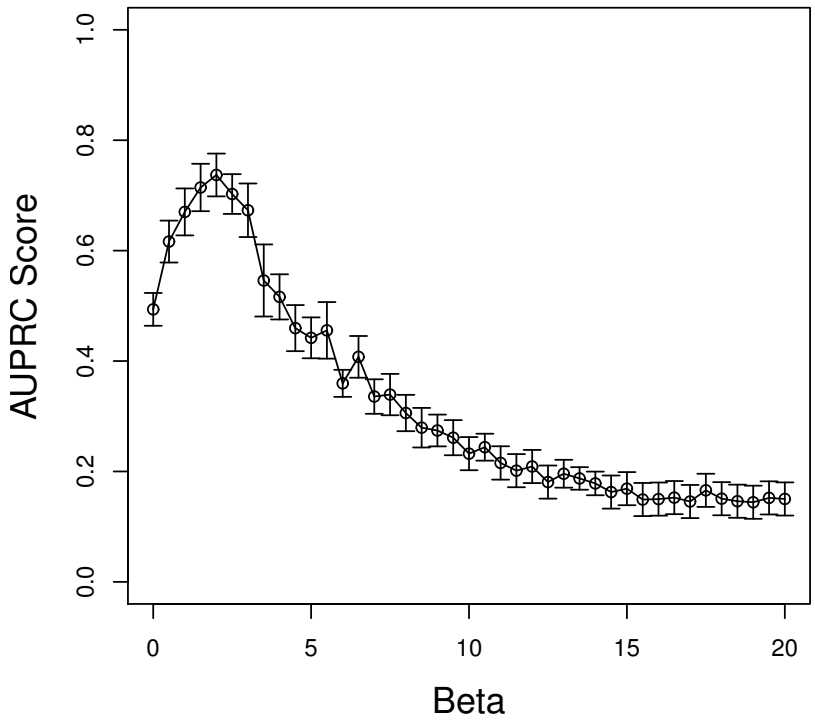
$\Rightarrow$ No structure change (only edges weights)

- 10 networks of 10 nodes
- number of parents : Poisson with mean $\lambda_{parent} = 3$
- 4 segments of length 15
- weights $w_{ij} \sim \mathcal{N}(0, 1)$
- noise $\varepsilon_i(t) \sim \mathcal{N}(0, 1)$

First evaluation: no structure change

- Exponential prior : $P(G_i^h | G_i^{h-1}, \beta) = \frac{e^{-\beta \left| G_i^h - G_i^{h-1} \right|}}{(1+e^{-\beta})^p}$

$\rightarrow$ high values of β?



$\rightsquigarrow$ performance deteriorates with larger values of the hyperparameter

$\rightsquigarrow$ poor MCMC mixing and convergence...

Conclusion: large coupling strength affects the mixing of the Markov chain

Alternative MCMC scheme : multi-segments moves

- Remark: CP moves unchanged
- Target-node specific
- 2 steps (for target node i)
  1. Sample *one* possible parent (j) for node i
  2. For each segment h of the K_i segments, flip the edge status between parent node and target-node i with probability q ($q = \frac{1}{2}$)
- Acceptance ratio (with $G_i = \{G_i^h\}_{1 \leq h \leq K_i}$)

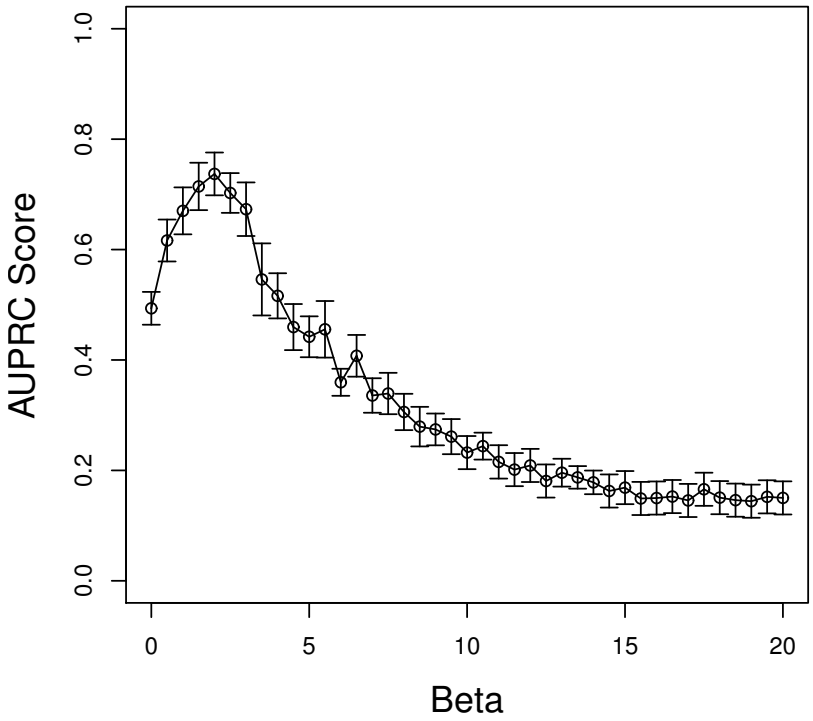
$$R(\tilde{G}_i|G_i) = R_{Likelihood}(\tilde{G}_i|G_i)\ R_{prior}(\tilde{G}_i|G_i)\ R_{Proposal}(\tilde{G}_i|G_i)$$

- $R_{Likelihood}(\tilde{G}_i|G_i) = \frac{P(x_i^h|\tilde{G}_i,\delta^2)}{P(x_i^h|G_i,\delta^2)}$
- $R_{prior}(\tilde{G}_i|G_i) = \frac{P(\tilde{G}_i)}{P(G_i)}$
- Probability of proposing $\tilde{G}_i$ given G_i: $\mathcal{Q}(\tilde{G}_i|G_i) = \frac{1}{p2^{K_i}}$

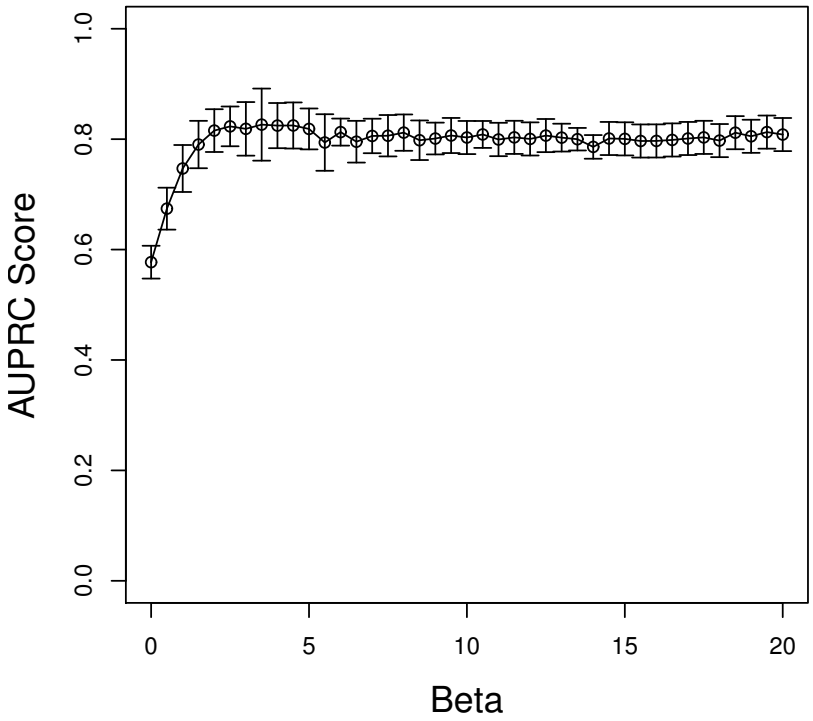
  $\Rightarrow R_{Proposal}(\tilde{G}_i|G_i) = 1$

First evaluation: no structure change

Before

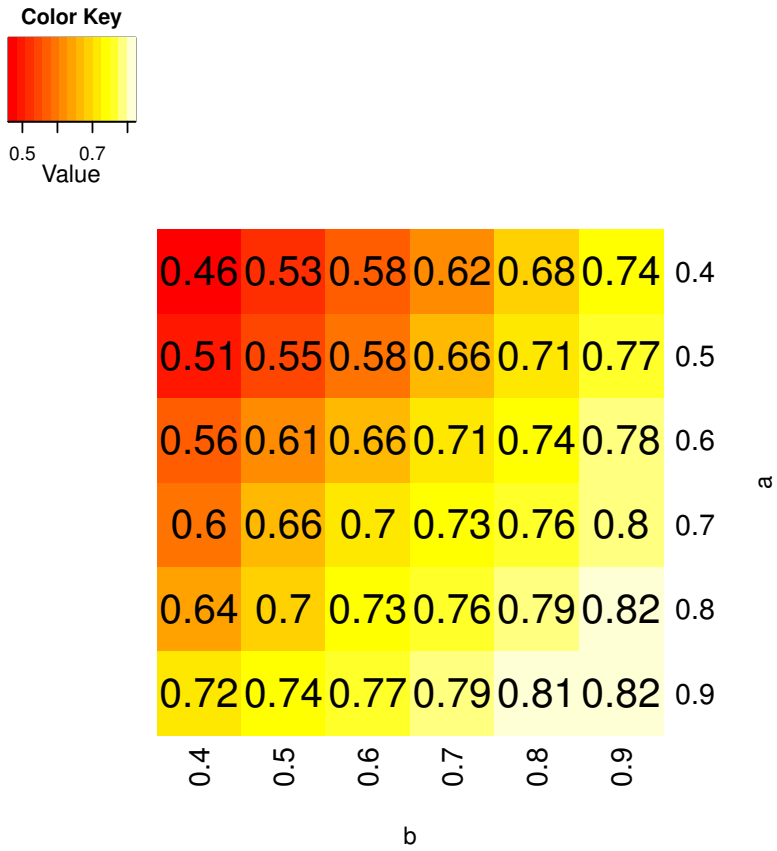


With multi-segs move

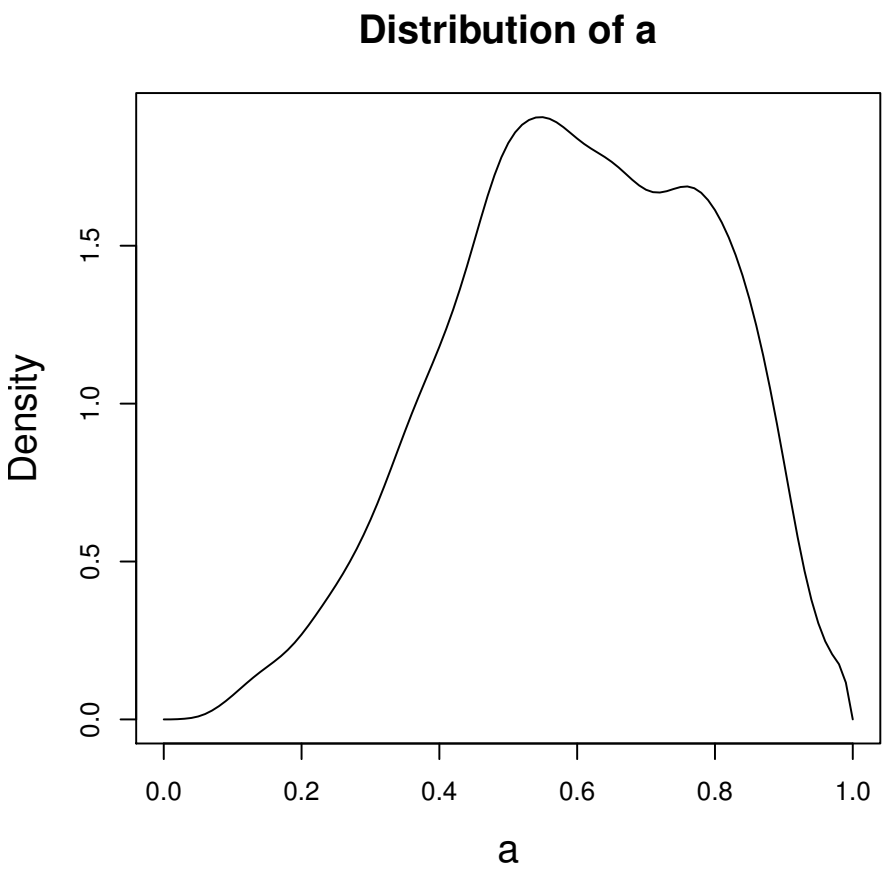


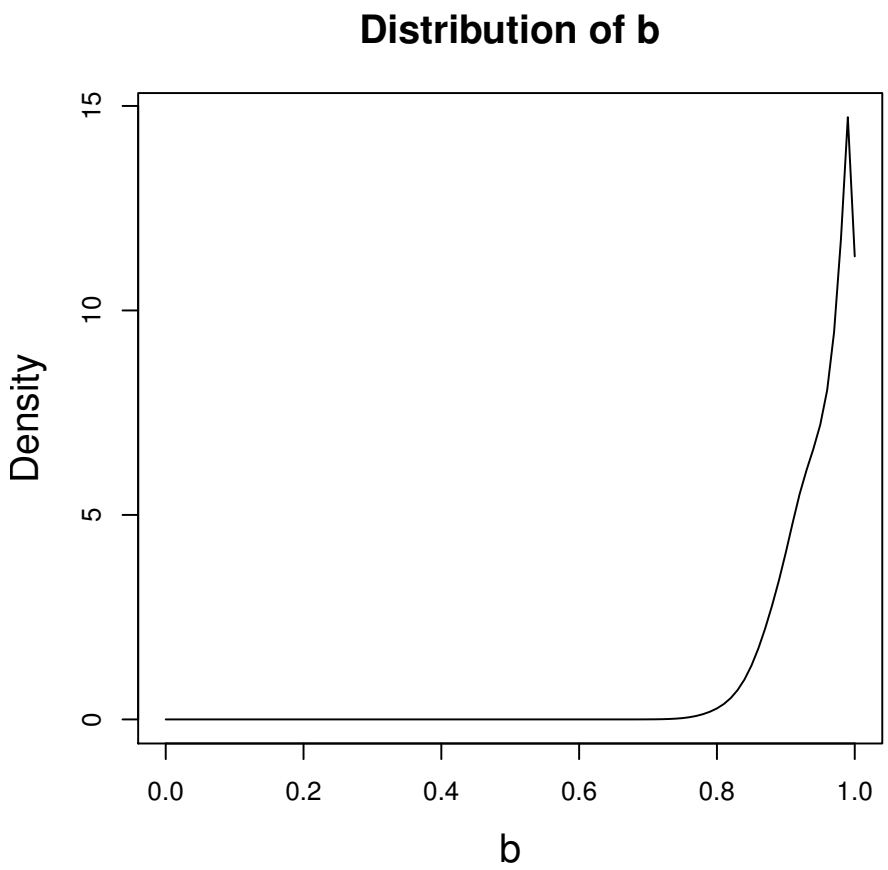
Binomial prior (no structure change)

- Area Under Precision Recall Curve (AUPRC)

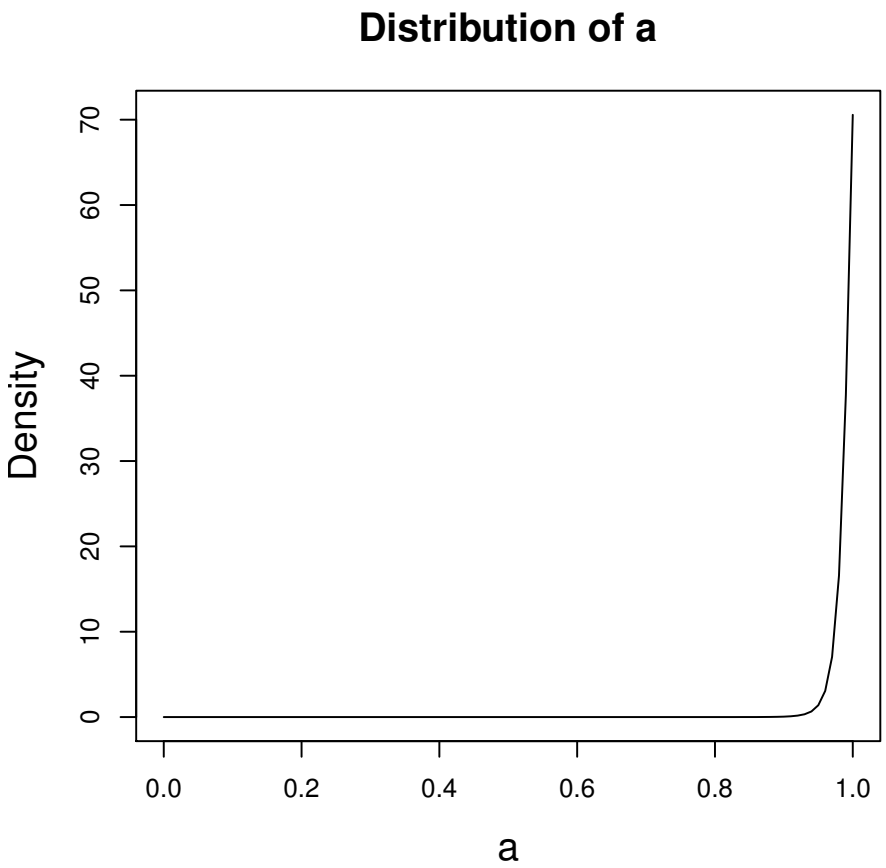


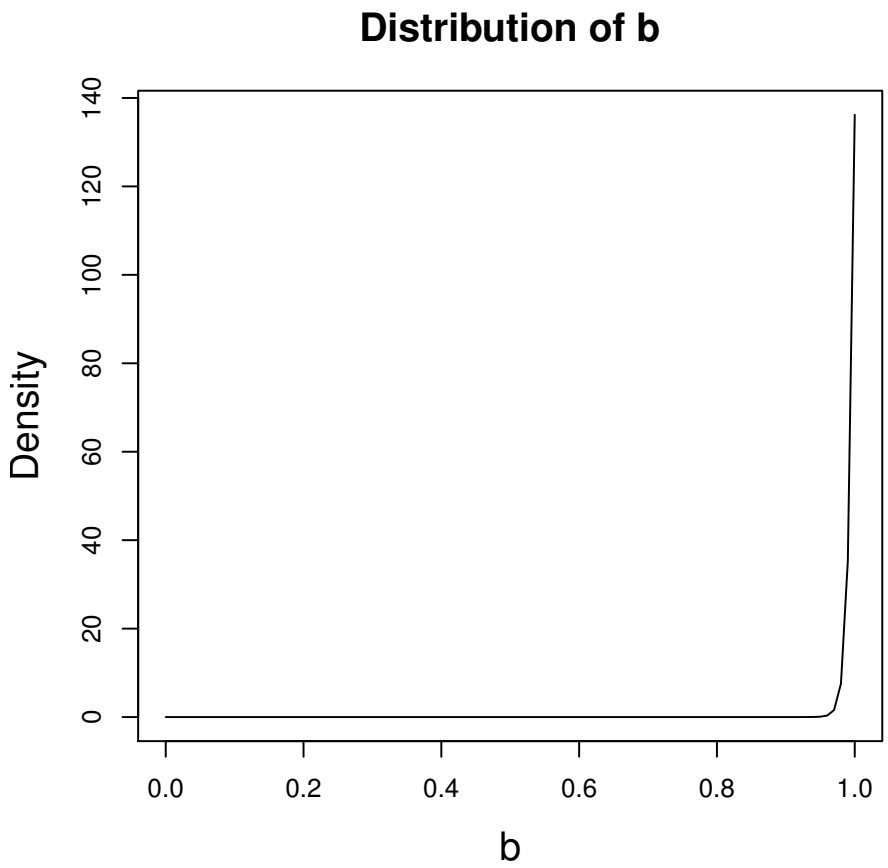
Binomial prior: original MCMC scheme + segment coupling





Binomial prior: with multi-segs moves



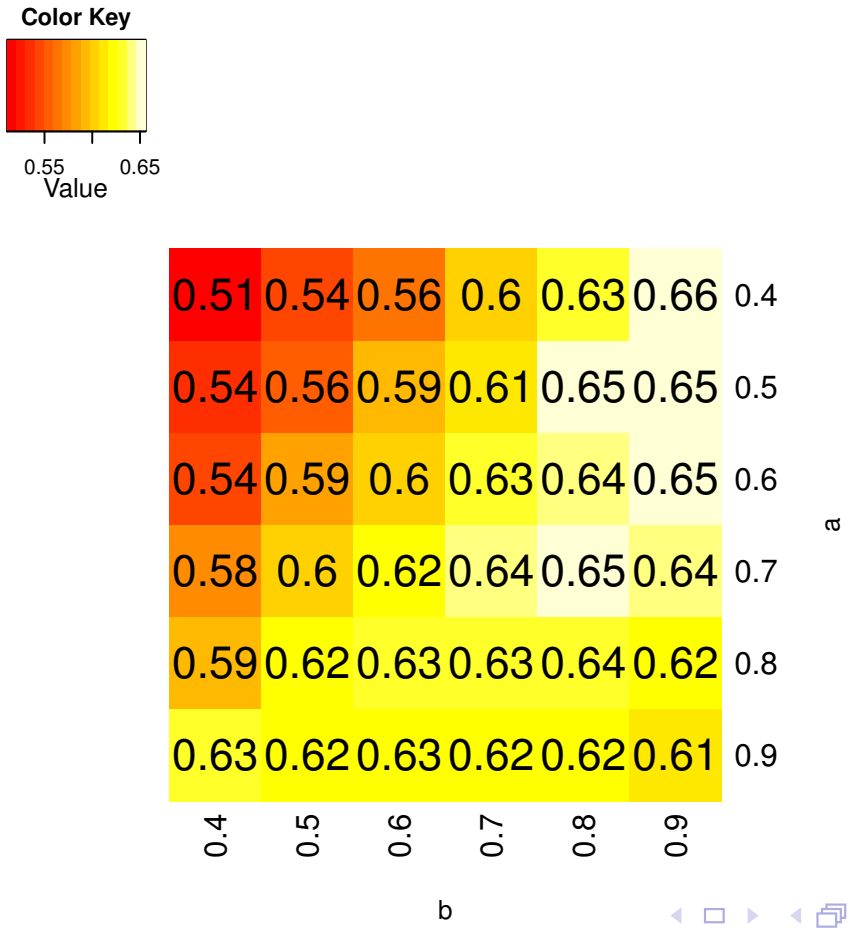


Simulations with structure changes

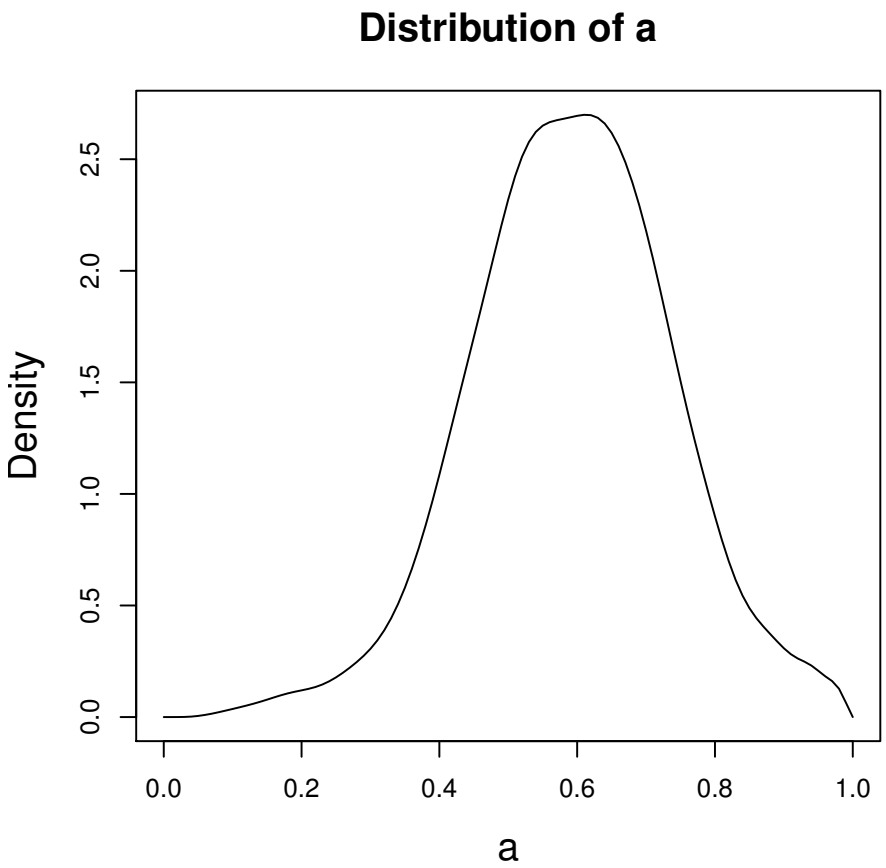
- Number of changes per node:

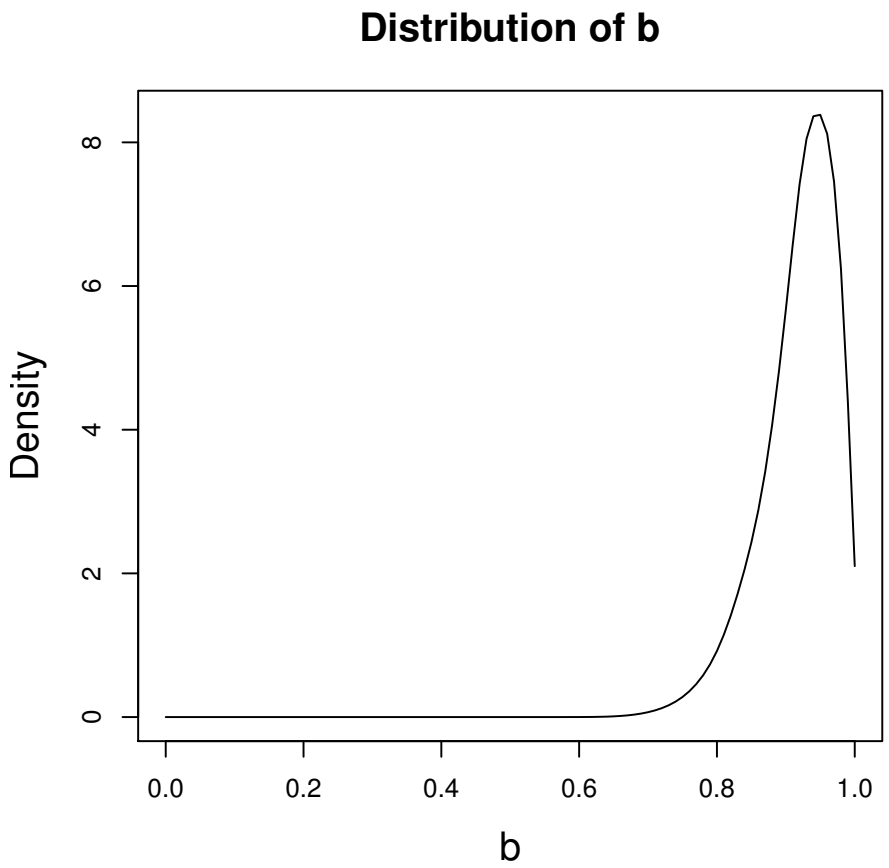
  Poisson with mean $\lambda_{changes} = 0.25, 0.5, 1$

- Binomial prior (hard coupling): AUPRC



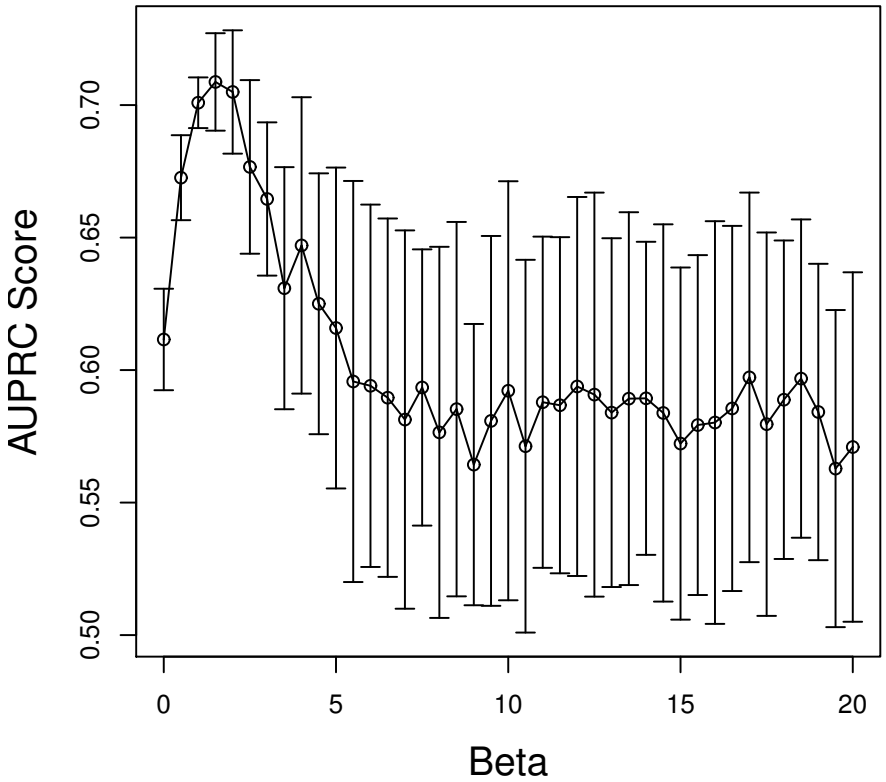
Binomial prior (hard coupling): with multi-segs move

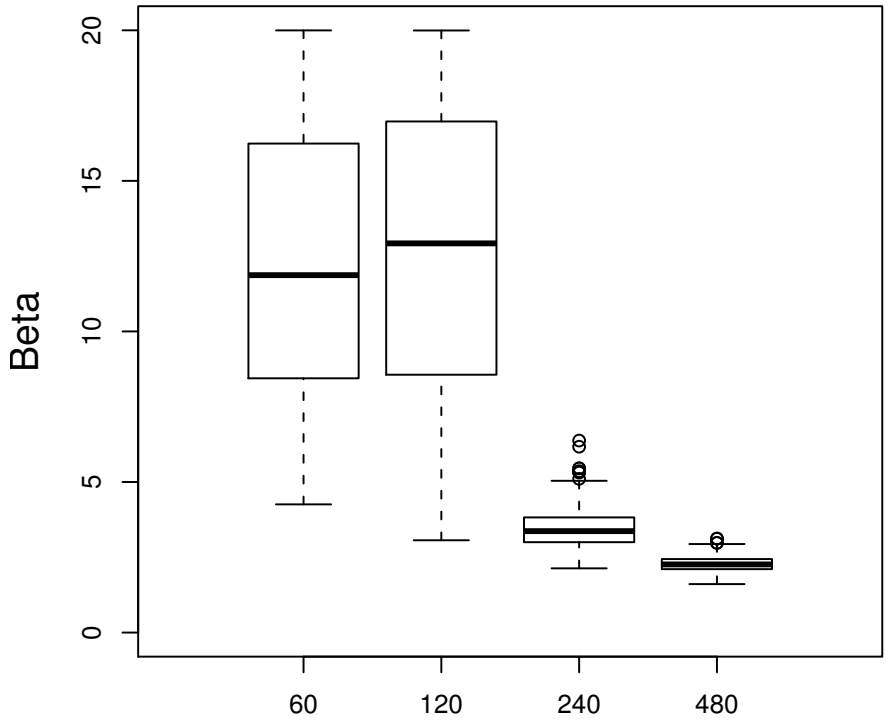




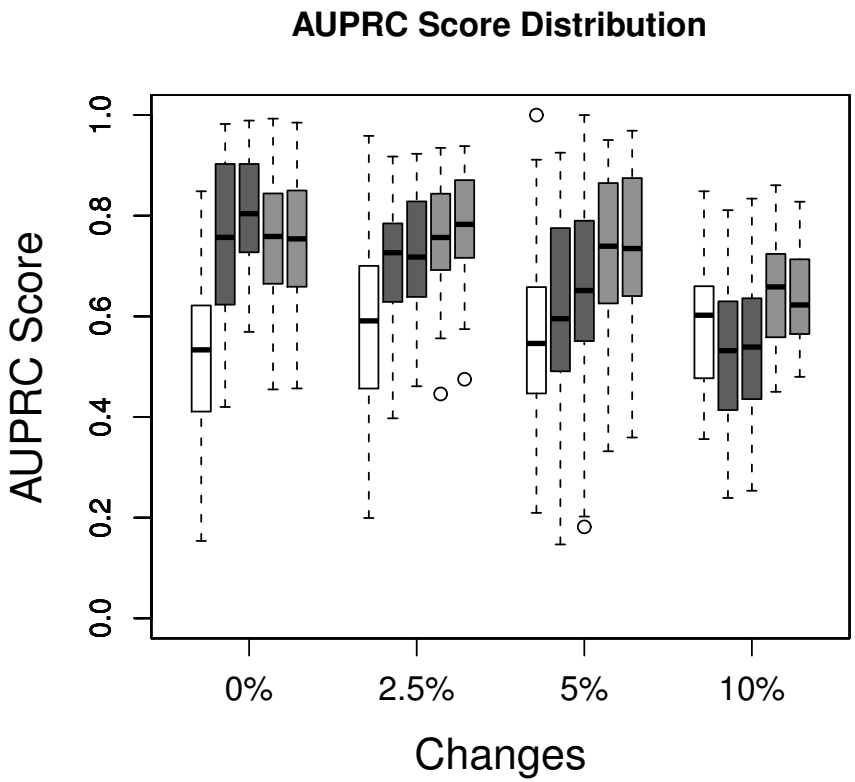
Exponential prior (hard coupling): with multi-segs move

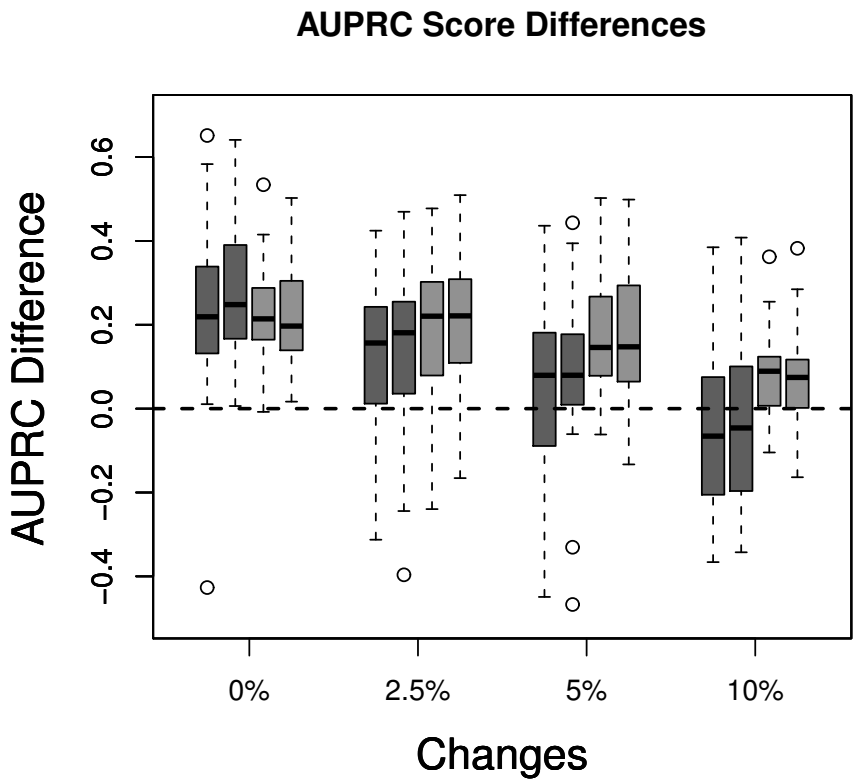
- Area Under Precision Recall Curve





Comprehensive simulation analysis





Left to right:

ARTIVA-0 Exp-Hard Exp-Soft Bin-Hard Bin-Soft

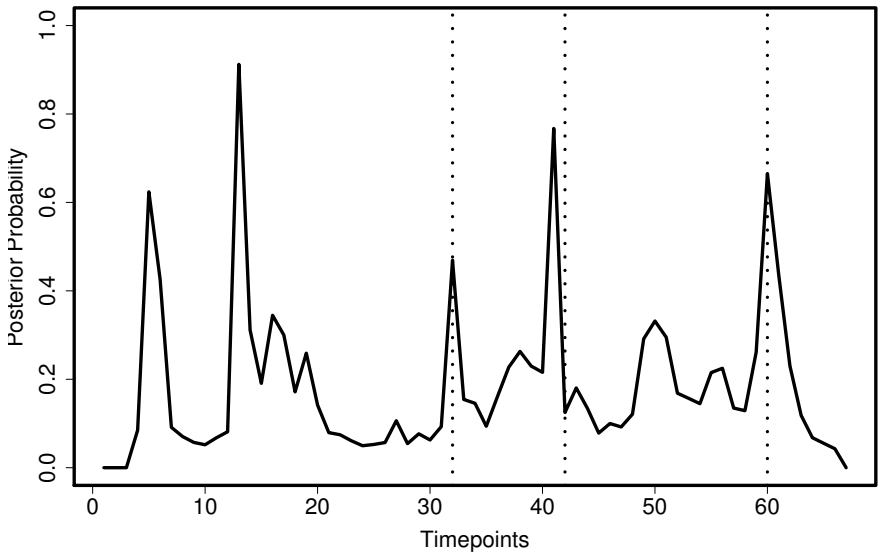
Outline

Drosophila melanogaster life cycle data

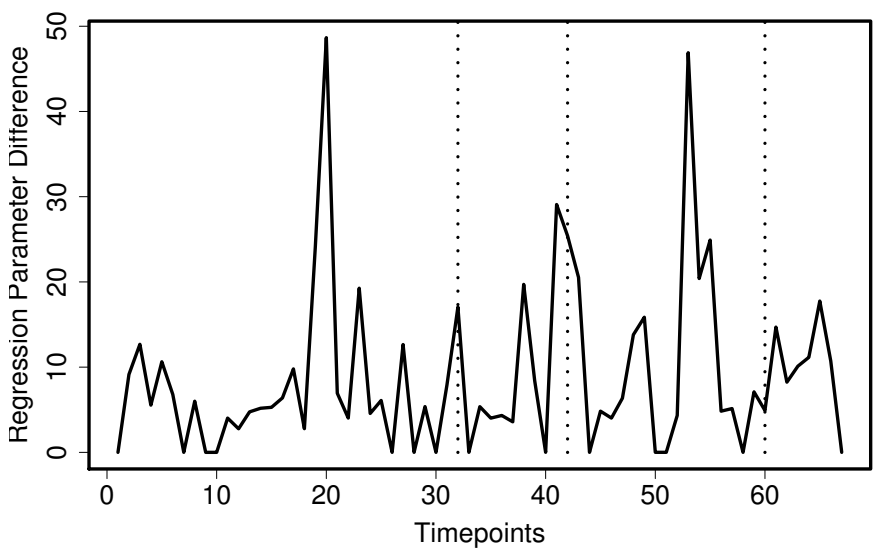
- Gene expression across the whole life cycle of *D. melanogaster* (Arbeitman et al., 2002)
  - 4028 genes
  - 67 successive time points
  - 4 temporal segments: Embryo - Larva - Pupa - Adult
- Comparison with previous work on 11 genes involved in muscle development
  - TESLA (Ahmed and Xing, 2009)
  - Robinson and Hartemink 2009, 2010.

Real data application

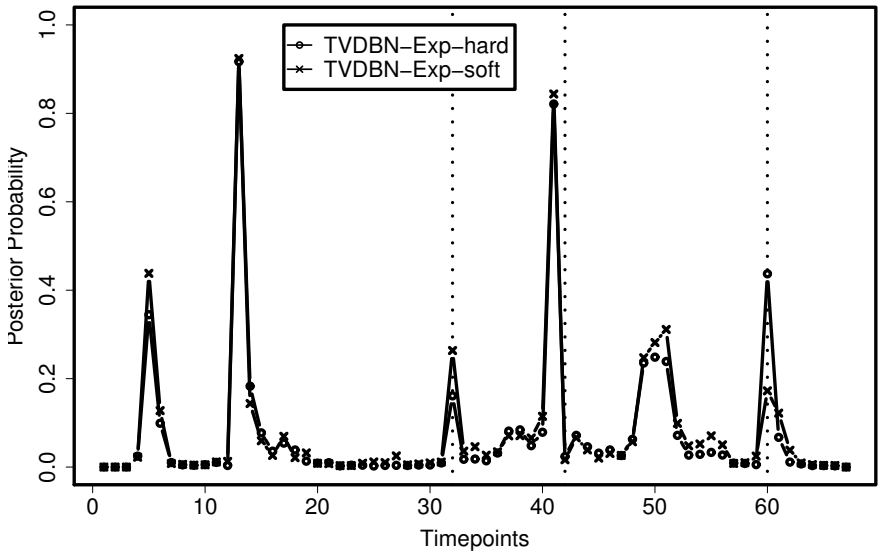
ARTIVA



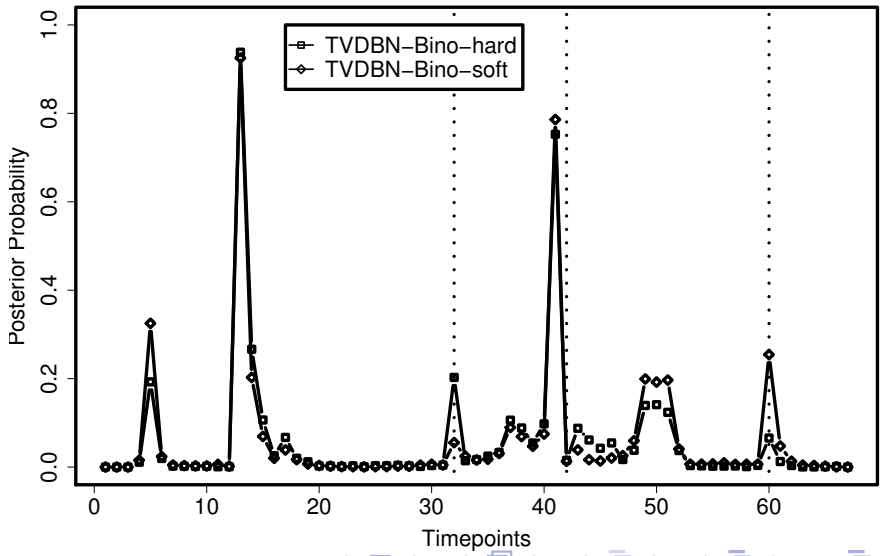
TESLA



Exponential prior



Binomial prior



Conclusion

ARTIVA segments coupling

- Advantages over existing methods:
  - no need to discretize the data ($\neq$ Robinson and Hartemink 2009, 2010)
  - allows structure changes ($\neq$ Grzegorczyk and Husmeier, 2009, 2011)
  - all hyperparameters inferred from the data via a consistent Bayesian inference scheme ($\neq$ Ahmed and Xing 2009)
  - includes four regularization coupling ($\neq$ ARTIVA, Lebre et al. 2010)

- Detailed investigation of the hyperparameter inference
  $\Rightarrow$ improved MCMC scheme for better convergence

- Difference hard/soft coupling seems negligeable in the investigated scenario...

Future work

- Investigate hard versus soft coupling
- Investigate other functional forms for information sharing

  e.g. recently Wang et al (2011) : exponential prior + additional parameter for sparsity prior
  Our approach : sparsity with truncated Poisson distribution
  $\Rightarrow$ explore the effect this additional sparsity parameter for gene network reconstruction

ARTIVA (2010)

Joint work with:

- Gaëlle Lelandais and Jennifer Becq

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ARTIVA with segment coupling:

Joint work with:

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- Dirk Husmeier
  School of Mathematics and Statistics, University of Glasgow
  and
  Biomathematics and Statistics Scotland (BioSS), University of Edinburgh

$\rightsquigarrow$ Submitted paper: *"Non-homogeneous dynamic Bayesian networks with Bayesian regularization for inferring gene regulatory networks with gradually time-varying structure"*