Dynamic modelisation of transcriptional regulatory networks in yeast

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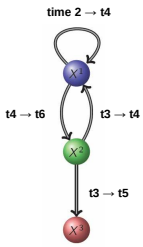
Introduction

Biological networks are highly dynamic and change in response to environmental and biological cues. This variability is in contrast to usual analyses of biological networks which employ static graph models. Here we develop a new method, the time-varying dynamic Bayesian network formalism, which allows us to learn temporally varying gene-regulation networks from biological time-course data. The performance of the method are presented according to the input data. The method is then applied to unravel the *pleiotropic drug resistance* network involved in yeast resistance to the presence of a toxic component in the environment.

Time-varying Dynamic Bayesian Network (tvDBN)

Biological process:
Time-varying regulatory motif between genes

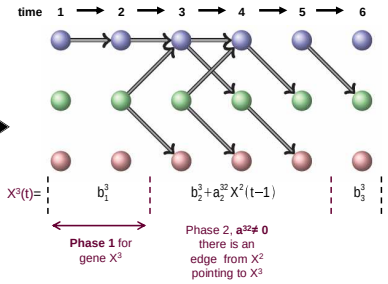


Dynamic Bayesian Networks:
each node corresponds to a gene at a specific timepoint

Use of a **regression model** to capture the dependency structure:

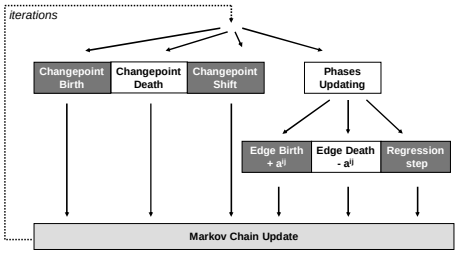
$X(t) = A.X(t-1) + B + \varepsilon$

with $\varepsilon \sim \mathcal{N}(0,\Sigma)$



Use of a **rj-MCMC algorithm**[1,2] to determine for each gene:
– the vector of **changepoints** (*i.e. the* position of phases)
– the set of **edges** (*i.e.* the transcription factors that regulate the gene) for each phase

rjMCMC =
reversible jump Markov Chain – Monte Carlo algorithm

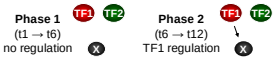


Evaluate performance of tvDBN with simulations

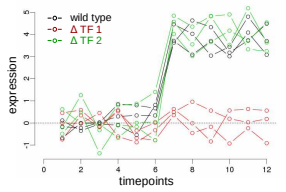
Simulations protocole

- Modify 2 parameters, all others are fixed for perfect results
- Simulate 100 expression profiles for which the dynamic network is known
- Count # of changepoints correctly detected
- Count # of edges correctly detected

Example of a simulated dynamic network



Simulated profiles associated



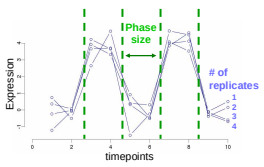
Parameters evaluated

Data parameters:
- Intensity of noise
- Difference in levels of expression
- Number of timepoints
- Number of replicates
- Number of transcription factors
- Number of edges between transcription factors and target genes
- Lag between transcription factor expressions and target gene expression

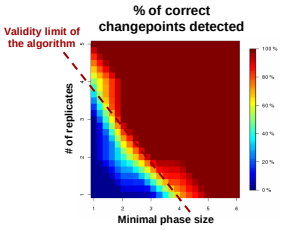
Algorithm parameters:
- Number of iterations
- Lag parameter

RESULTS

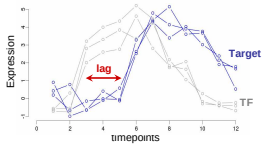
Minimal phase size versus # of replicates

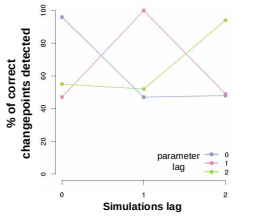


% of correct changepoints detected



Simulation lag versus tvDBN lag parameter

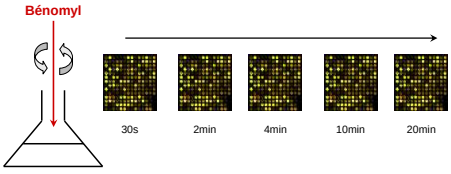




The lag must be known *a priori*

Application: yeast response to benomyl stress[3]

Gene expression profiles for *S. cerevisiae* grown under **benomyl-induced stress** conditions, measures made at 5 successive **timepoints: 30s, 2min, 4min, 10min and 20min**



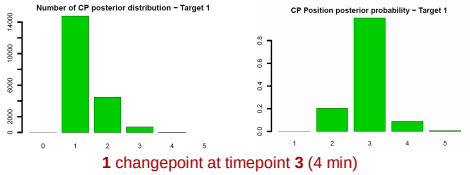
mRNA expression levels where measured in the **wild-type** and in **knock-out strains** for the genes coding for the transcription factors **YAP1, PDR1, PDR3 and YRR1**, known to influence drug response

We selected **78 genes** for which sufficient expression data were available in each genetic context.

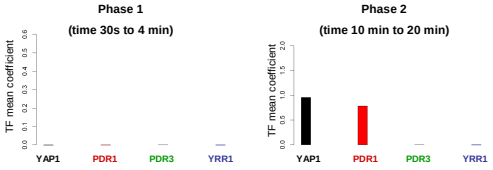
Hierarchical cluster analysis identified **18 clusters** of genes with concordant transcription profiles.

Each cluster was independently analyzed using tvDBN.

tvDBN results for cluster 6 (genes RTN2, SNQ2 and PDR5)



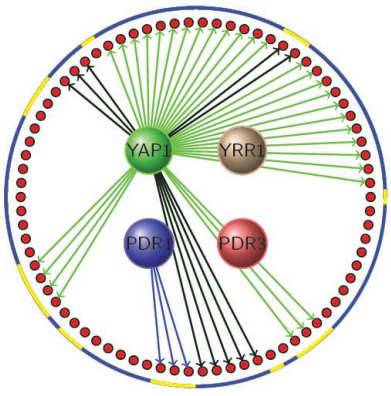
1 changepoint at timepoint **3** (4 min)



No regulation

Regulation by **YAP1** and **PDR1**

Global view of tvDBN results for the 78 genes



30s to 4 min
10 min to 20 min
4 min to 10 min

Conclusion & Perspectives

Changes in the regulatory network are an essential aspect of these dynamics and turning on (or off) the transcription of a gene will often trigger more regulatory, metabolic or signaling events downstream. The tvDBN approach extracts information about time-variability from the data and generates a range of testable hypotheses. Analysis of the yeast "Pleiotropic Drug Resistance" (PDR) network is still in its infancy, but we are currently using the tvDBN method to propose time-varying dynamical models of the transcriptional regulatory networks involved in the response of several chemical components (benomyl [3], fluphenazine [4], progesterone [5] and selenium [6]).

References

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