

# Towards Genome-scale Disease Progression Models

Saptarshi Pyne, Alok Ranjan Kumar and Ashish Anand

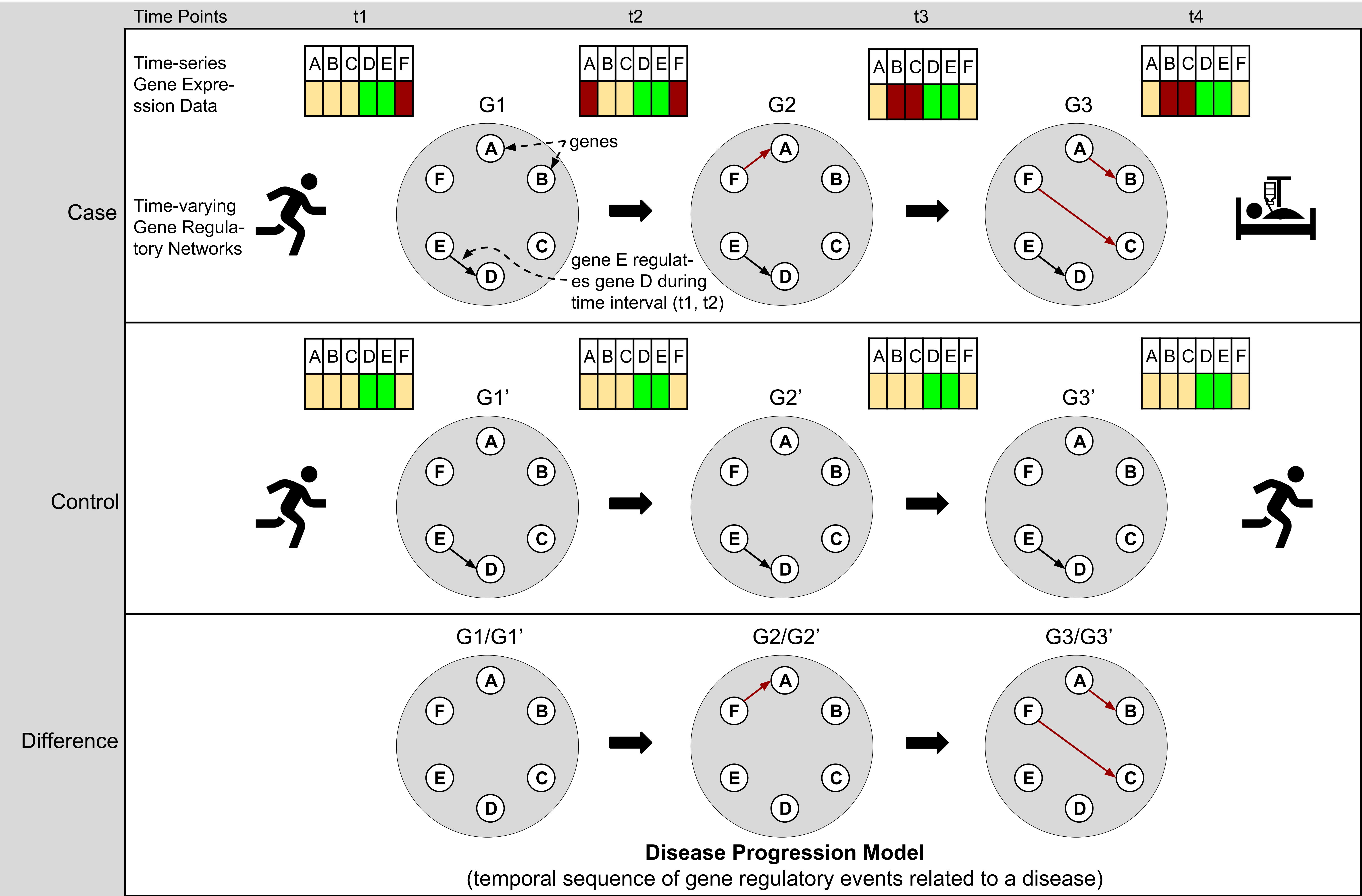
Department of Computer Science and Engineering, Indian Institute of Technology Guwahati, Guwahati, India 781039



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## 1. Objective

Discover how the genome-scale *gene regulatory network* changes with time during progression of a given disease.



## 2. Challenges, Methods & Results

### Challenges

- Estimation of a large number of parameters which also necessitates high computation time and memory
- Integration of auxiliary data, e.g., TF binding site information, to enhance accuracy

### Methods and Results

- A novel algorithm, namely ‘an algorithm for reconstructing Time-varying Gene regulatory networks with Shortlisted candidate regulators (TGS) plus (TGS+), is proposed [1]. TGS+ provides the state-of-the-art computational speed and accuracy (F1 score) w.r.t. three in-silico DREAM3 [2] benchmark datasets having 10, 50 and 100 genes.
- TGS+ has two steps. In step 1, for each gene, a shortlist of its candid-

ate regulators is inferred through an information theoretic pipeline. In step 2, the shortlisted candidates are evaluated within a Bayesian network framework to identify the true regulators among them.

## 3. Conclusions & Future Directions

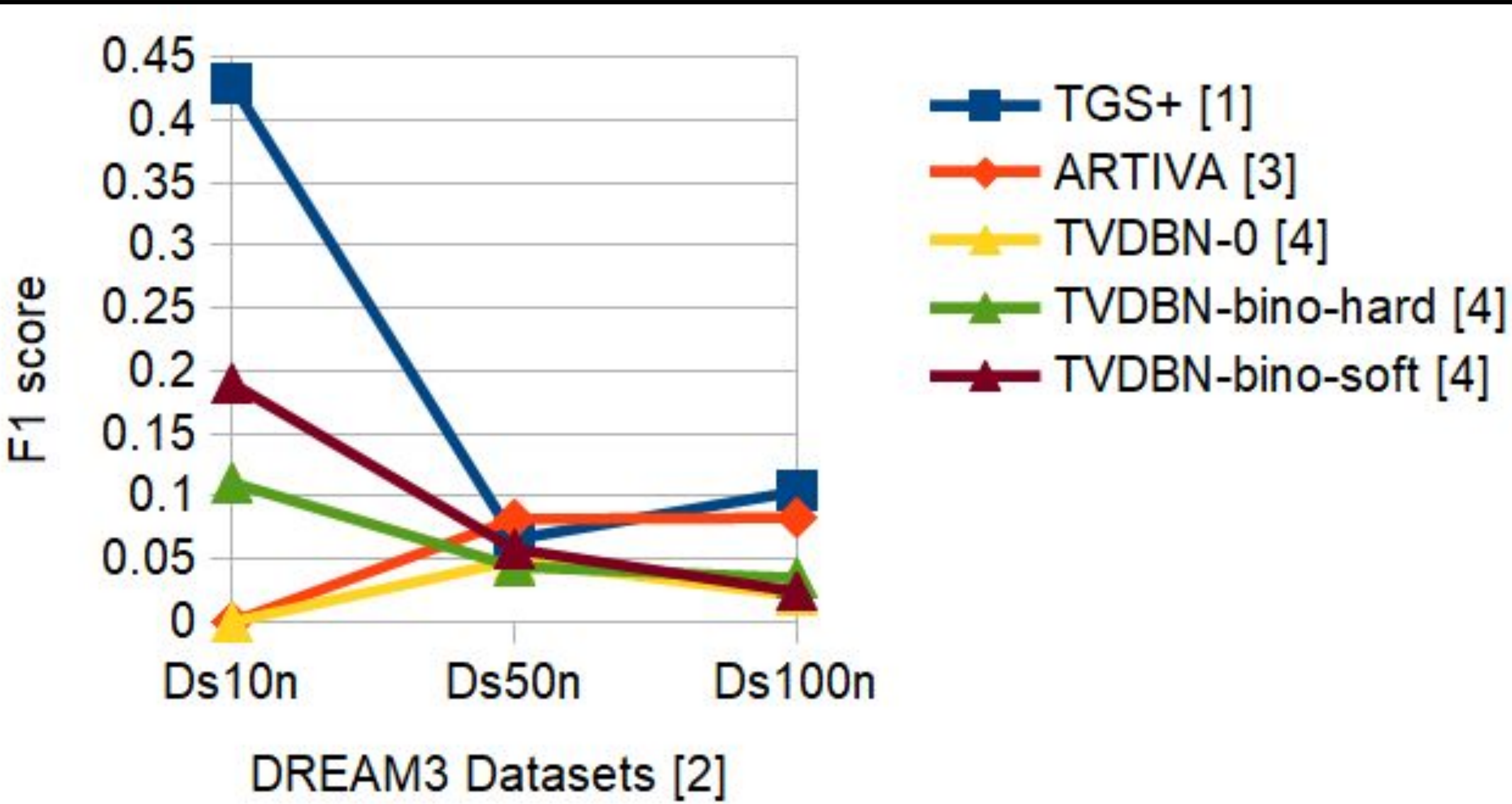
- A novel algorithm, TGS+, is proposed to reconstruct *time-varying gene regulatory networks* from *time-series gene expression datasets*. It provides the state-of-the-art computational speed and accuracy w.r.t. three benchmark in-silico DREAM3 datasets.
- TGS+ also reconstructs a biologically significant *D. melanogaster* (Dm) aka ‘fruit fly’ life cycle model in sub-30 mins when applied on a Dm developmental life cycle dataset with 588 genes and 66 time points.
- However, main memory (RAM) consumption of TGS+ increases exponentially with the number of genes. Reducing its memory requirement remains an important challenge.
- Moreover, TGS+ can be extended to incorporate auxiliary regulatory evidences, e.g., TF binding site information, for enhancing accuracy.

## 4. References

1. Pyne et al. ‘Rapid Reconstruction of Time-varying Gene Regulatory Networks’. TCBB, 2018. <https://ieeexplore.ieee.org/document/8423706/>
2. DREAM3 - In Silico Network Challenge. <https://www.synapse.org/#!/Synapse:syn2853594/wiki/71567>
3. Lèbre et al. ‘Statistical inference of the time-varying structure of gene-regulation networks’. BMC Syst Biol, vol 4, no 1, p130, Sep 2010.
4. Dondelinger et al. ‘Non-homogeneous dynamic Bayesian networks with Bayesian regularization for inferring gene regulatory networks with gradually time-varying structure’. Mach Learn, vol 90, no 2, p191–230, 2013.

## 5. Contacts

AA: [anand.ashish@iitg.ernet.in](mailto:anand.ashish@iitg.ernet.in), SP: [saptarshipyne01@gmail.com](mailto:saptarshipyne01@gmail.com)



#Genes\Algo	TGS+	ARTIVA	TVDBN-0	TVDBN-bino-hard	TVDBN-bino-soft
10	6 sec	10 min	2 min	2 min	2 min
50	22 sec	5 hrs	12 min	10 min	8 min
100	1 min	32 hrs	52 min	3 hrs	17 min