Towards Genome-scale Disease Progression Models

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1. Objective

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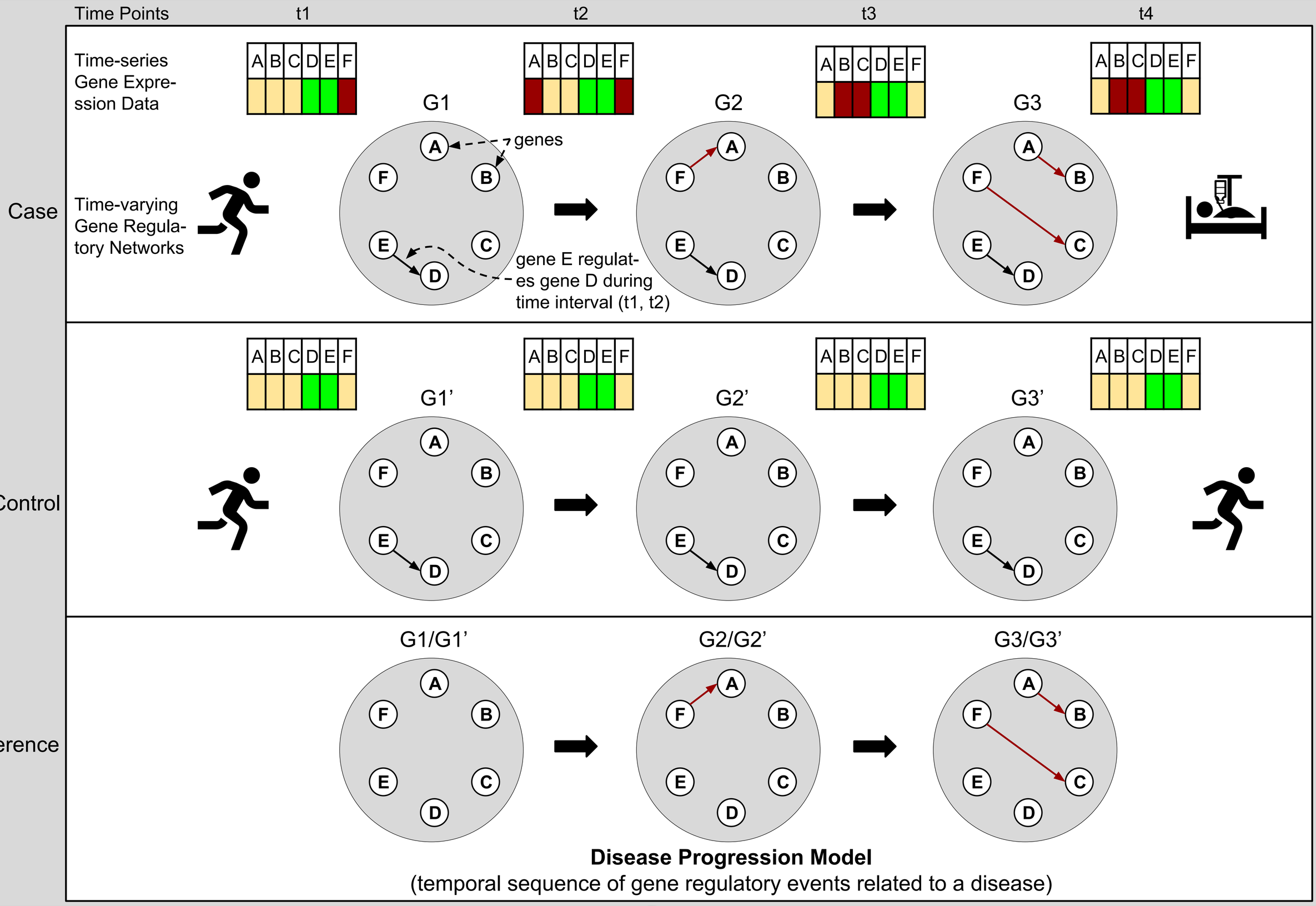
Discover how the genome-scale *gene regulatory network* changes with time during progression of a given disease.



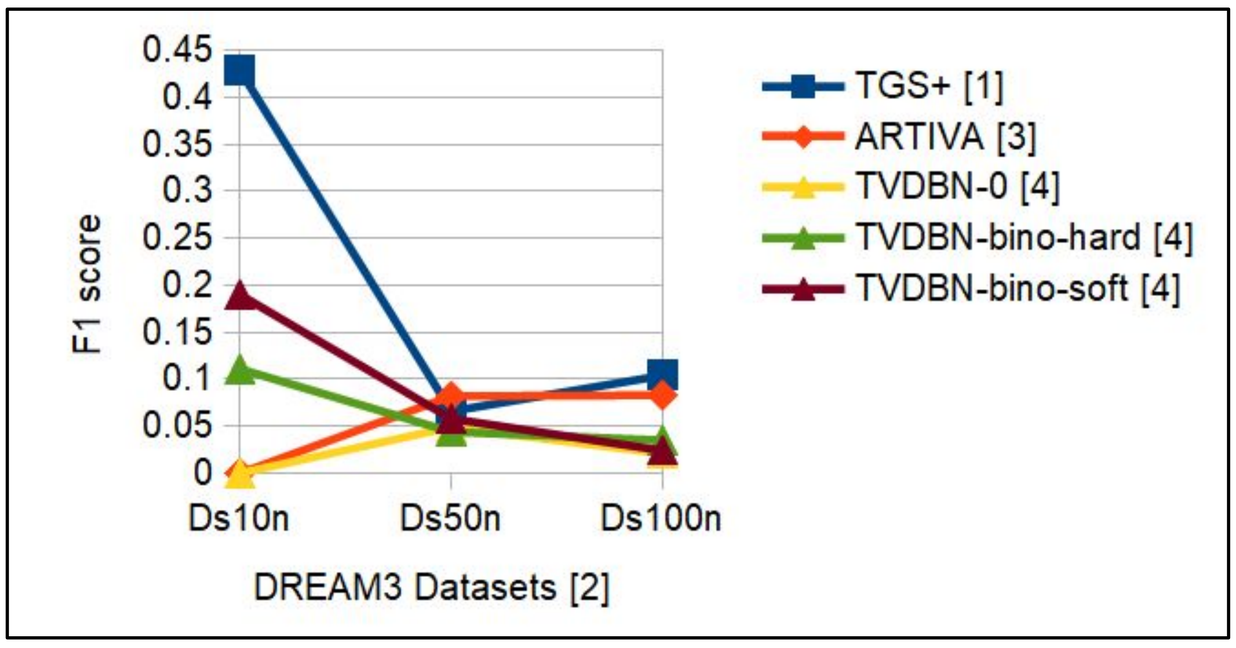
2. Challenges, Methods & Results

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 candidate 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.



#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

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.

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