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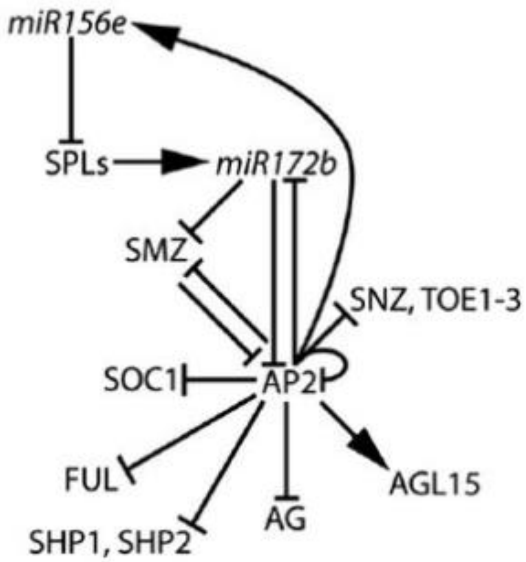
Popular biological networks

Gene Regulatory Networks



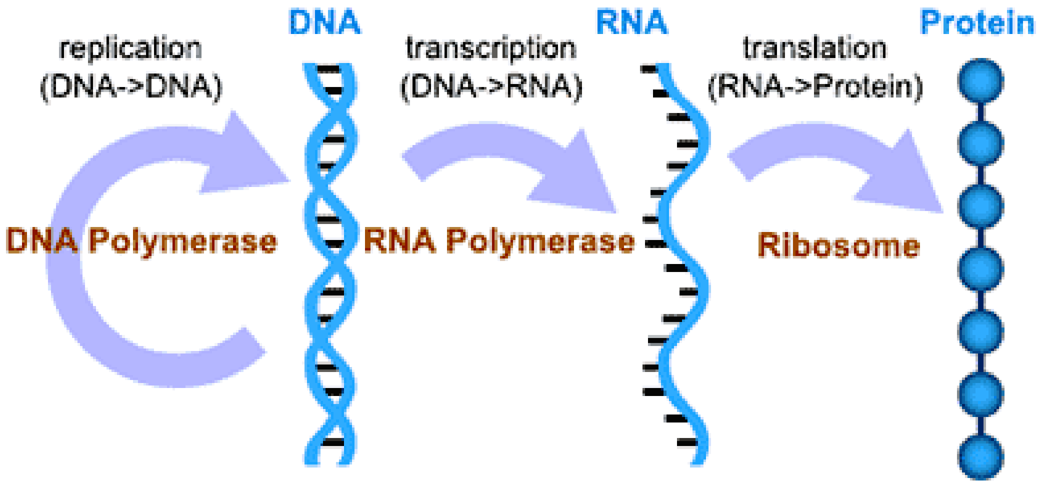
Sadegh Sulaimany

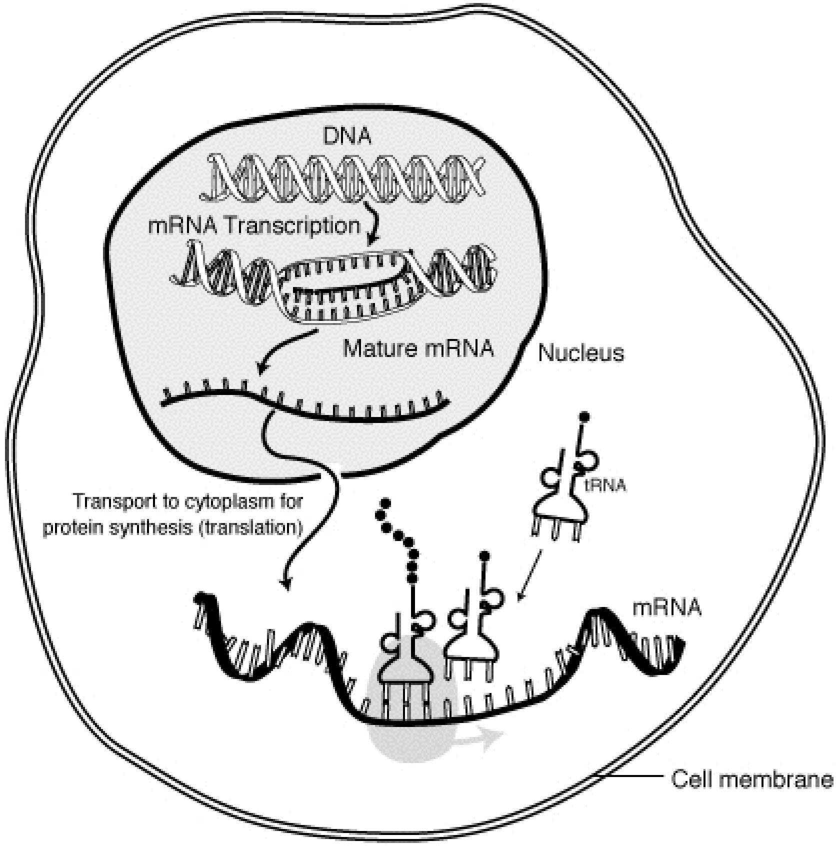
Biological network analysis course

Agenda

- Gene Regulatory Network (GRN)
  - Review
  - Gene Regulation
  - Modeling
    - Boolean network
    - Bayesian network
    - Petri nets
    - Differential equation modeling
  - Tools
  - Some surveys
  - Conclusion

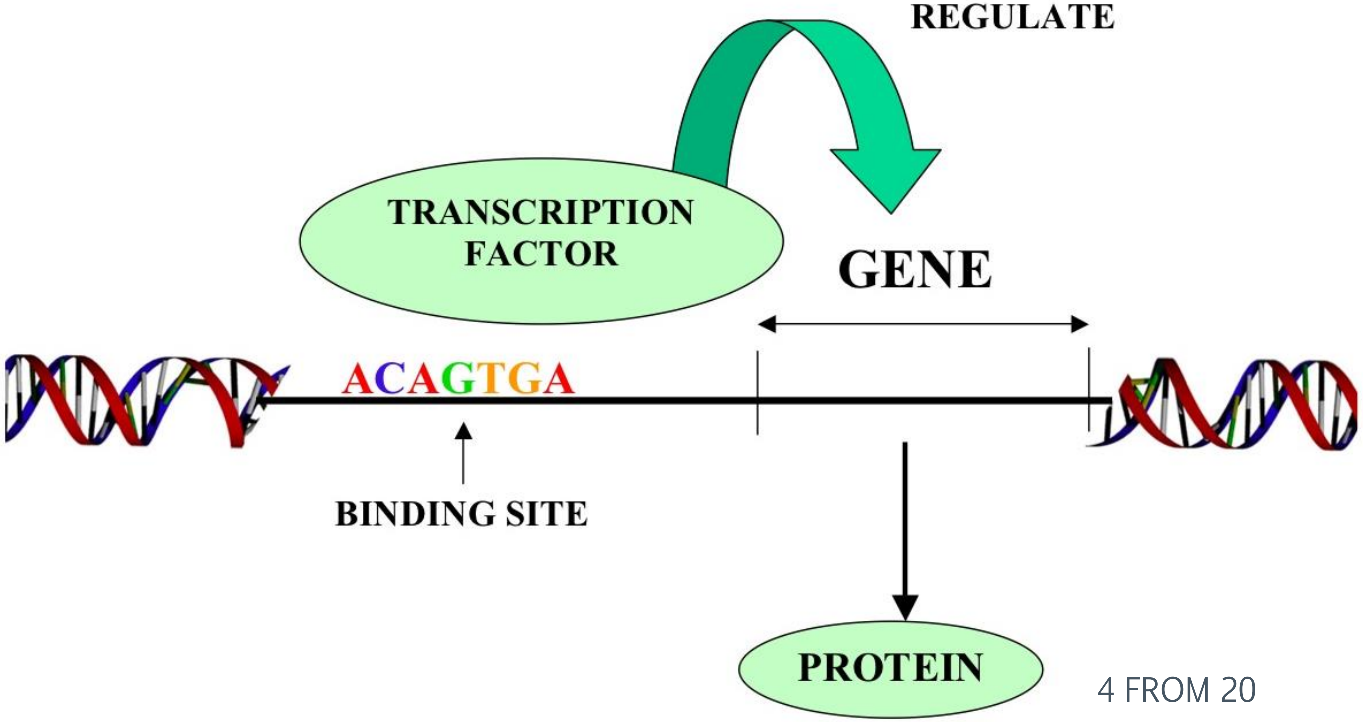
Review – Central dogma





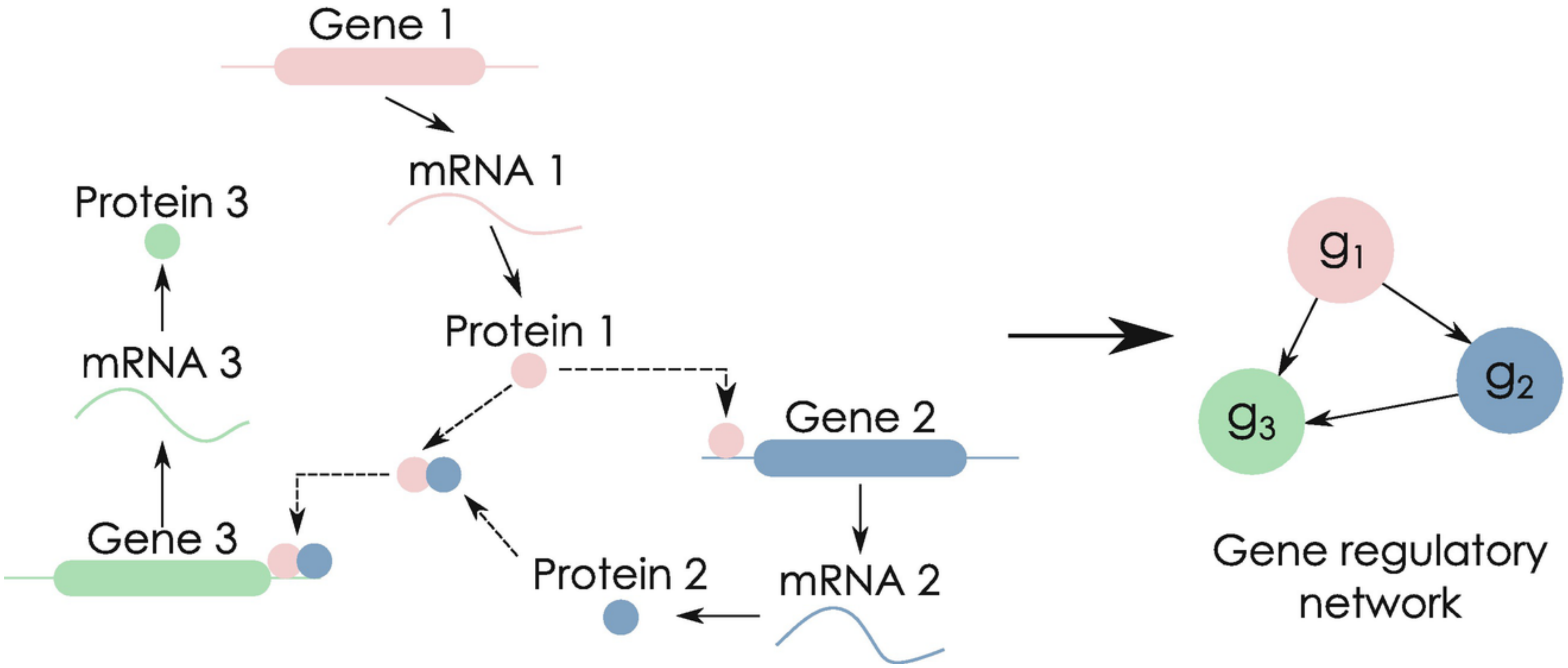
Gene Regulatory

- Transcription
  - Transcription factors are proteins that help turn specific genes "on" or "off" by binding to nearby DNA
    - bind to a specific sequence of DNA referring to the genes that they regulate
      - activate (or upregulate) or inhibit (or downregulate) the production of another protein



Gene Regulatory Networks

- genes inside cells interact with each other via intermediate transcription factors to influence each others expression



Gene Regulatory Networks

- regulation process can involve more than one transcription factor
  - a gene product can indirectly downregulate or upregulate another gene product through a chain of regulations
  - It can generate feedback loops
    - gene product can downregulate or upregulate its own production

- Signaling pathway
  - some proteins resulting from the activation due to some transcription factors can pass through cell membranes and create signaling paths to other cells

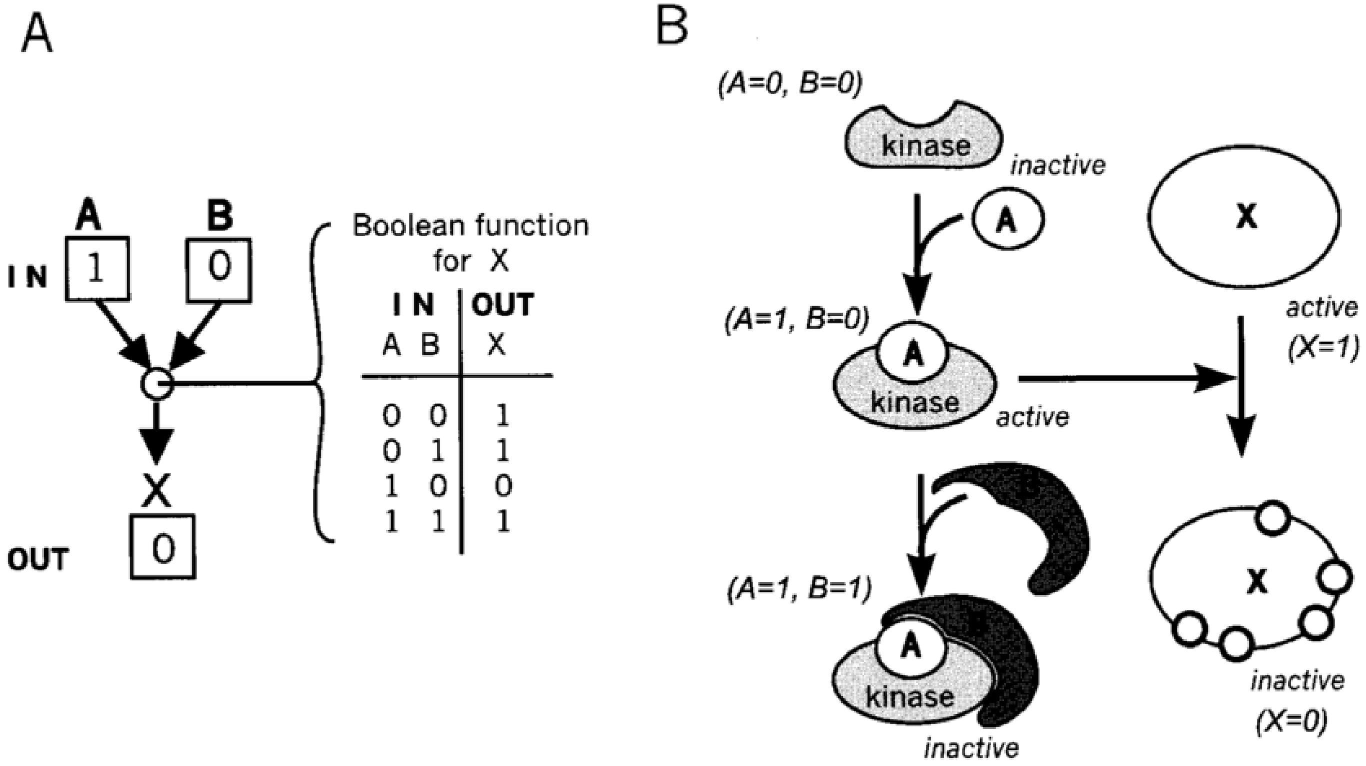
  - The set of genes interactions, both activations and inhibitions, inside the cell
    - is referred to as the gene regulatory network

Modeling GRN

- Three classes
  1. logical models
     - qualitative point of view
       - can only answer qualitative questions
         - if a gene is activated or not at some stage of the life of the system
  2. Continuous models
     - finer grain analysis
     - when also quantitative information are needed
       - e.g., the concentrations of molecules
  3. Single molecule level models
     - takes into account the noise that can affect the functionality of regulatory networks

Logical modeling of GRN

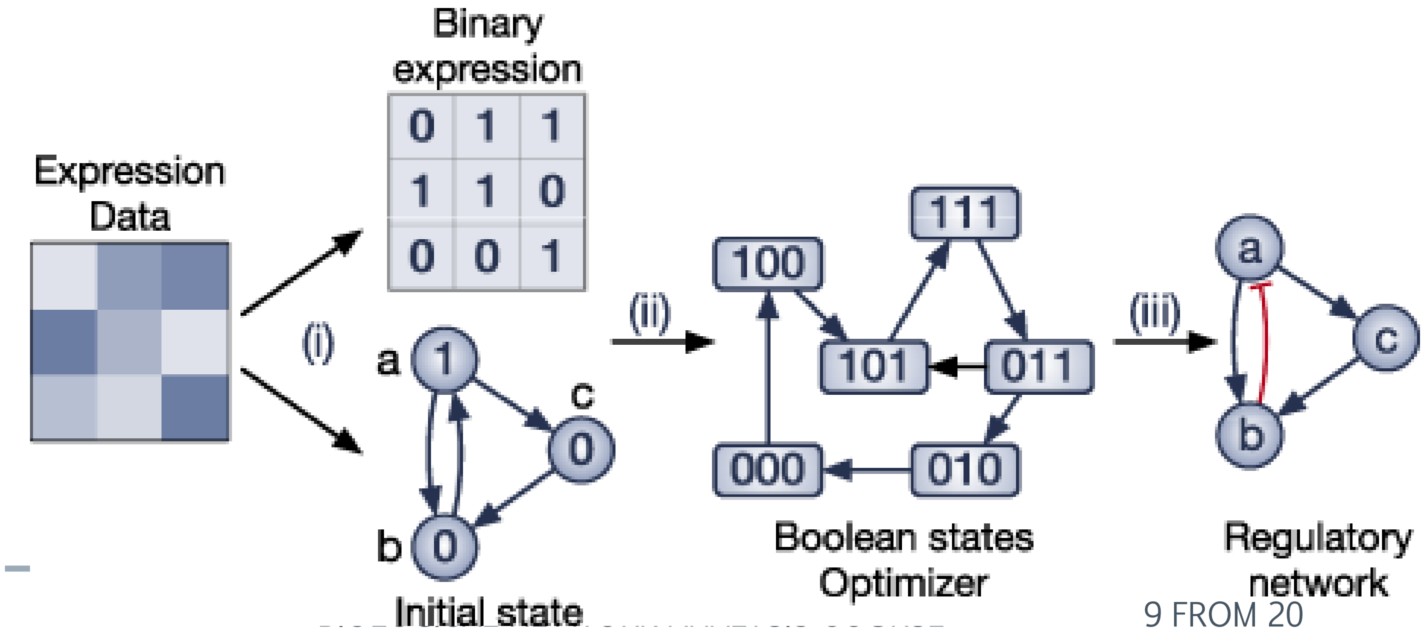
- represent GRN as a Boolean network
  - a directed graph the nodes of which are in one-to-one correspondence with genes and have associated Boolean variables
  - 0: not expressed
  - 1: expressed



IN		OUT
A	B	X
0	0	1
0	1	1
1	0	0
1	1	1

Boolean GRN modelinh

- The overall workflow of methods using the boolean model.
  - (i) These methods first binarize the gene expression data and then generate the initial boolean states.
  - (ii) The methods optimize the states of the model with respect to the binary values.
  - (iii) The methods output the GRN with activation and repression edges or a set of boolean functions



0	1	1
1	1	0
0	0	1

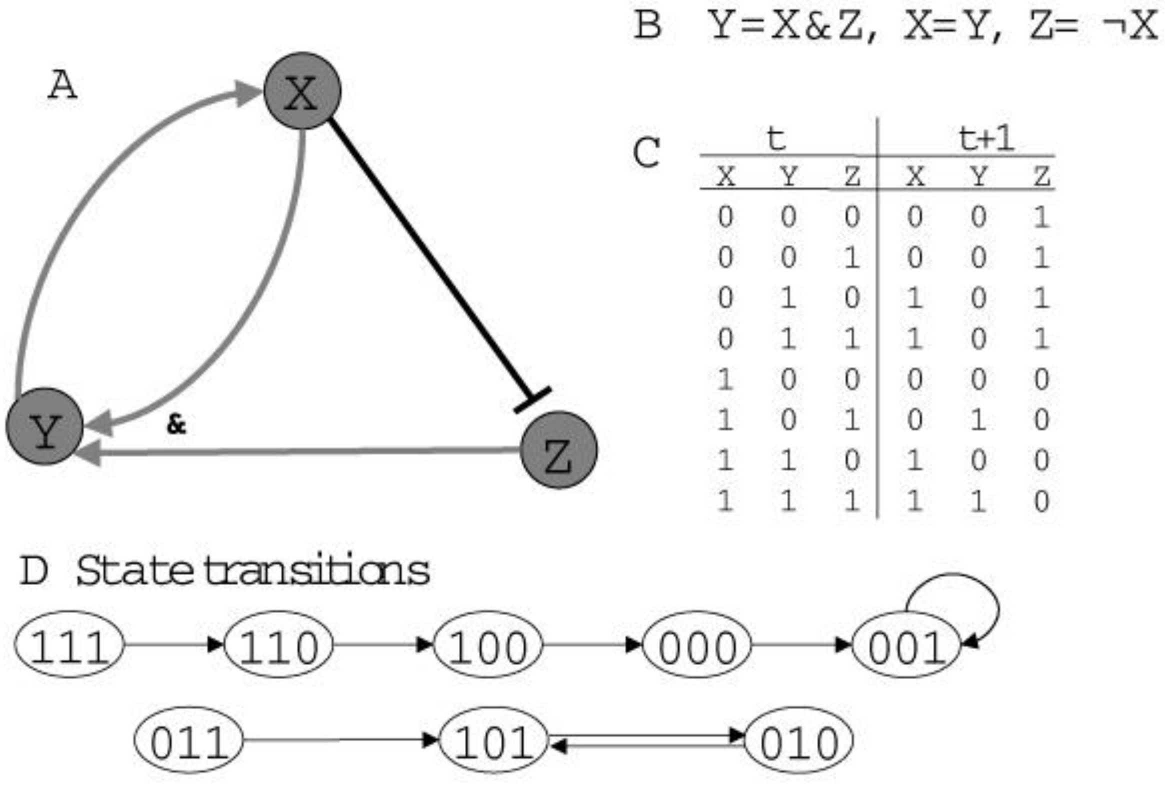
Probabilistic Boolean network

- Boolean networks
  - allow to use one function only per gene
  - very often, due to insufficient understanding of the biological system to model, for each node in the network
    - there is more than one possible boolean function that generate a state

  - *Probabilistic Boolean networks*
    - Modify Boolean networks by associating to each node several regulation Boolean functions each of which has associated a probability.
      - at each time step the function to apply at each node is determined randomly according to the given probabilities

Probabilistic Boolean network

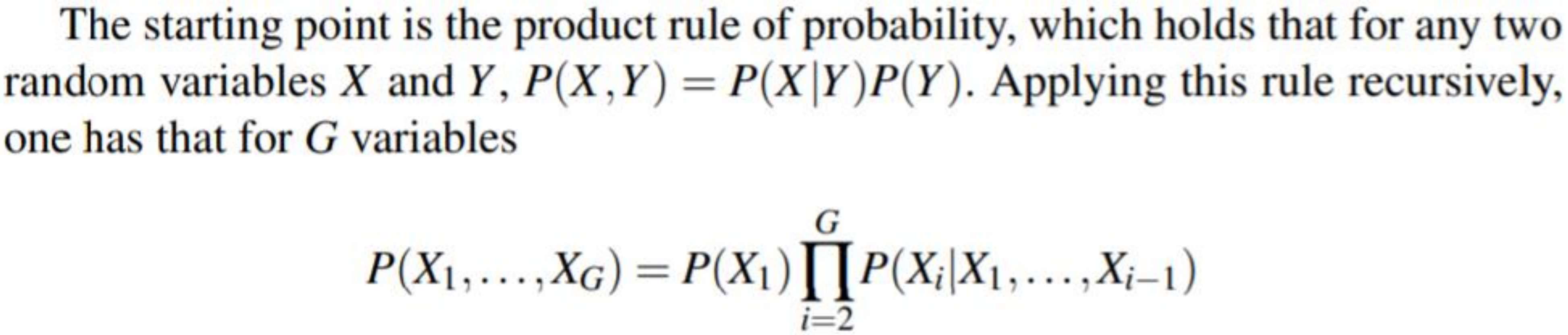
- There is at least
  - Two probable state transition path



t			t+1		
X	Y	Z	X	Y	Z
0	0	0	0	0	1
0	0	1	0	0	1
0	1	0	1	0	1
0	1	1	1	0	1
1	0	0	0	0	0
1	0	1	0	1	0
1	1	0	1	0	0
1	1	1	1	1	0

Bayesian network

- probabilistic directed acyclic graph model
- represent a set of random variables via a directed acyclic graph
  - (i.e., the genes' expressions)
  - and their conditional dependencies (i.e., activation or inhibition)

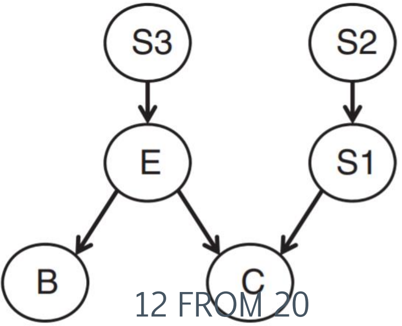


The starting point is the product rule of probability, which holds that for any two random variables X and Y, $P(X,Y) = P(X|Y)P(Y)$. Applying this rule recursively, one has that for G variables

$$P(X_1,\ldots,X_G) = P(X_1)\prod_{i=2}^{G} P(X_i|X_1,\ldots,X_{i-1})$$

Example

$$P(S1,S2,S3,E,B,C) = P(B|E)\cdot P(C|E,S1)\cdot P(E|S3)\cdot P(S1|S2)\cdot P(S3)\cdot P(S2)$$

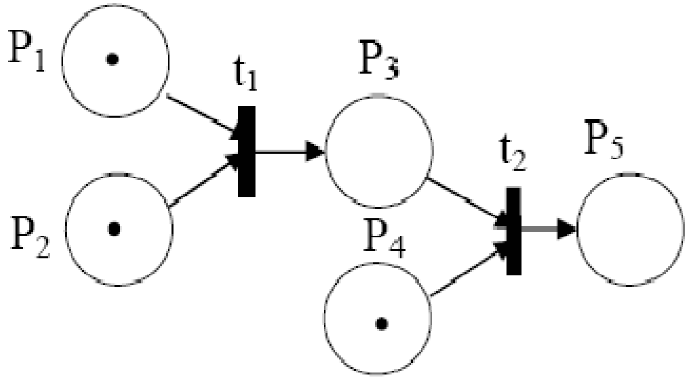


Petri nets

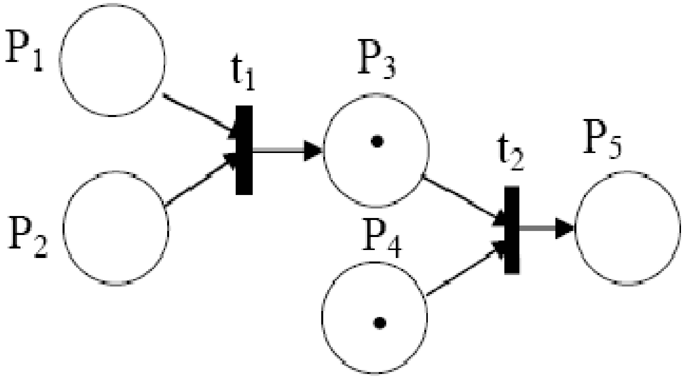
- analyze the dynamics of gene regulatory network
  - Powerful model
  - a directed bipartite network
  - having two types of nodes
    - transitions, represented by bars
    - places, represented by circles
  - The directed arcs
    - denoted by arrows
    - describe which places are pre- and/or post-conditions for which transitions
    - Arcs run from a place to a transition or vice versa
  - Moreover
    - tokens, represented by black dots inside some places, enable transitions to fire

Petri net

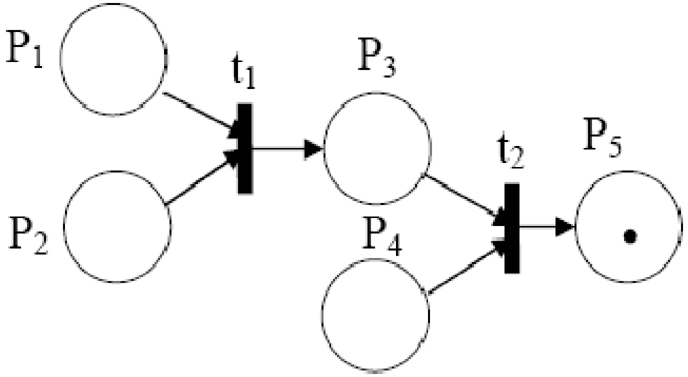
- Example



a) **Initial Marking**



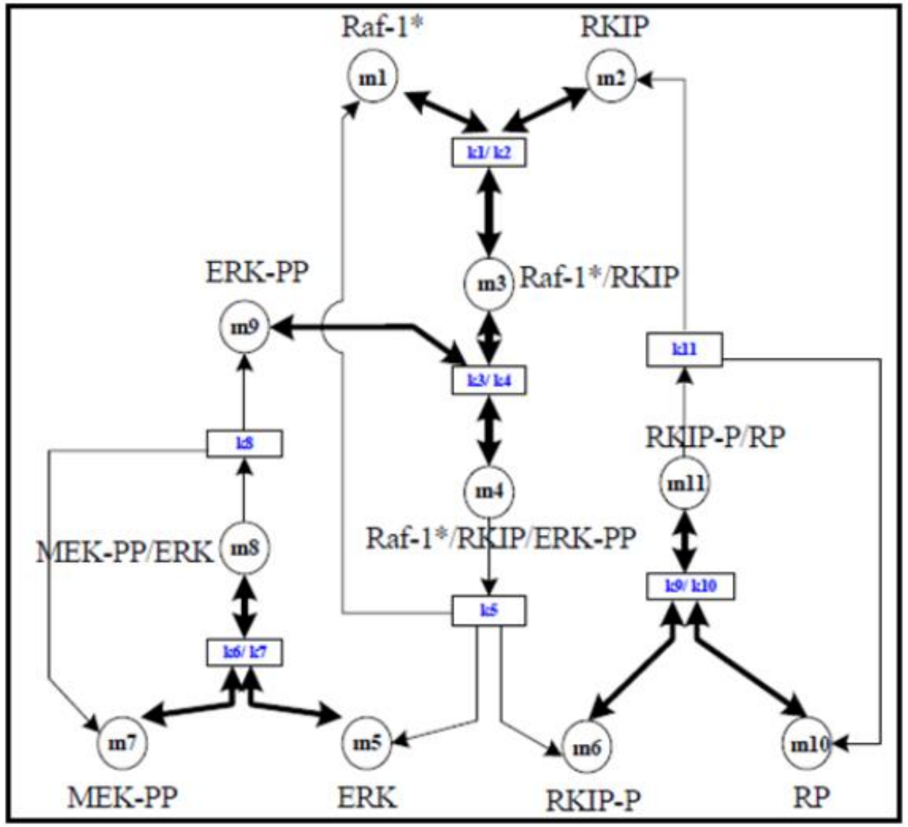
b) **Marking after t_1 fires**



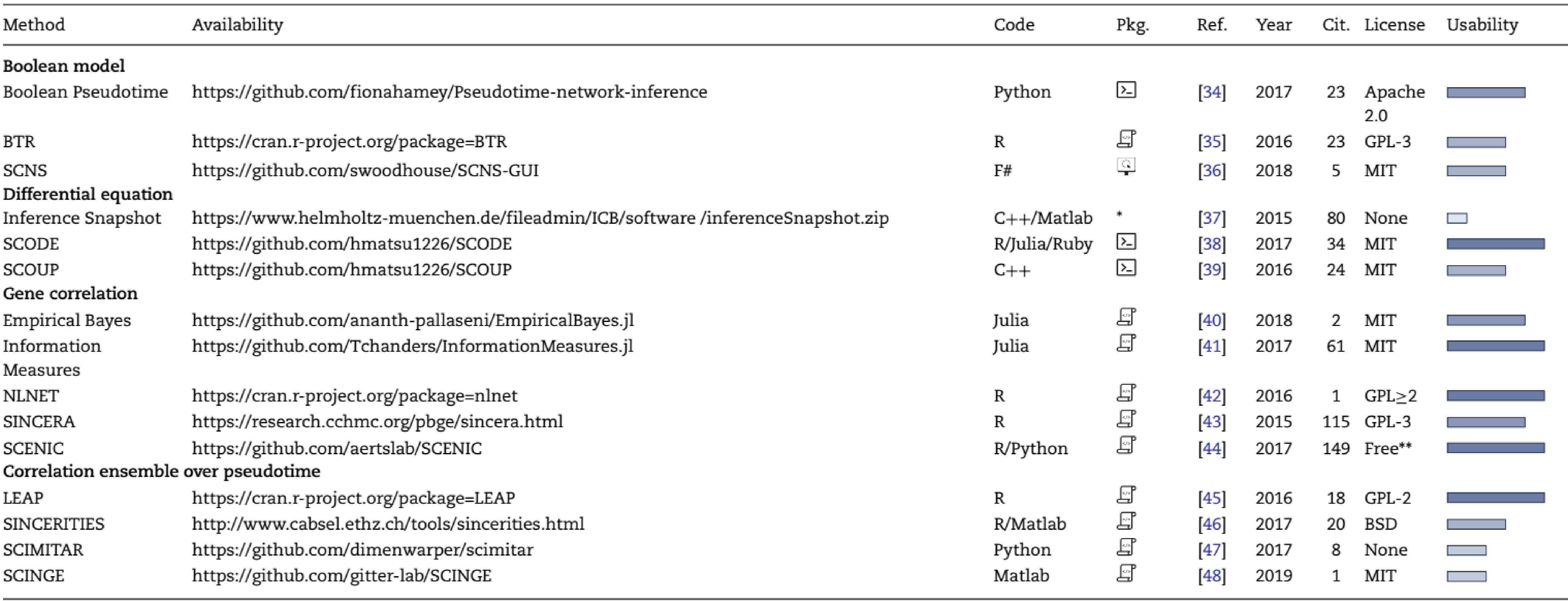
c) **Marking after t_2**

Differential equation model

- allow to explicitly model the concentration changes of molecules over time
  - better model to study the dynamics of the network



Tools



Method	Availability	Code	Pkg.	Ref.	Year	Cit.	License	Usability
Boolean model								
Boolean Pseudotime	https://github.com/fionahamey/Pseudotime-network-inference	Python	>_	[34]	2017	23	Apache 2.0	▬▬▬▬
BTR	https://cran.r-project.org/package=BTR	R	📜	[35]	2016	23	GPL-3	▬▬▬
SCNS	https://github.com/swoodhouse/SCNS-GUI	F#	🖥	[36]	2018	5	MIT	▬▬▬
Differential equation								
Inference Snapshot	https://www.helmholtz-muenchen.de/fileadmin/ICB/software /inferenceSnapshot.zip	C++/Matlab	*	[37]	2015	80	None	▬
SCODE	https://github.com/hmatsu1226/SCODE	R/Julia/Ruby	>_	[38]	2017	34	MIT	▬▬▬▬▬
SCOUP	https://github.com/hmatsu1226/SCOUP	C++	>_	[39]	2016	24	MIT	▬▬▬
Gene correlation								
Empirical Bayes	https://github.com/ananth-pallaseni/EmpiricalBayes.jl	Julia	📜	[40]	2018	2	MIT	▬▬▬▬
Information Measures	https://github.com/Tchanders/InformationMeasures.jl	Julia	📜	[41]	2017	61	MIT	▬▬▬▬▬
NLNET	https://cran.r-project.org/package=nlnet	R	📜	[42]	2016	1	GPL≥2	▬▬▬▬▬
SINCERA	https://research.cchmc.org/pbge/sincera.html	R	📜	[43]	2015	115	GPL-3	▬▬▬▬
SCENIC	https://github.com/aertslab/SCENIC	R/Python	📜	[44]	2017	149	Free**	▬▬▬▬▬
Correlation ensemble over pseudotime								
LEAP	https://cran.r-project.org/package=LEAP	R	📜	[45]	2016	18	GPL-2	▬▬▬▬▬
SINCERITIES	http://www.cabsel.ethz.ch/tools/sincerities.html	R/Matlab	📜	[46]	2017	20	BSD	▬▬▬
SCIMITAR	https://github.com/dimenwarper/scimitar	Python	📜	[47]	2017	8	None	▬▬
SCINGE	https://github.com/gitter-lab/SCINGE	Matlab	📜	[48]	2019	1	MIT	▬▬

- https://academic.oup.com/view-large/209215716

Conclusion

- it has been observed that
  - behavior of biological systems is not deterministic
    - it can evolve differently even starting from the same initial state
  - non-determinisms can be modeled by stochastic approaches
    - Taking into account the probability

  - Background knowledge is deterministic for model selection
  - Every biological network has it own charactersitics

Some recent review papers

Cornell University

the

arXiv.org > q-bio > arXiv:1801.04087

Search...

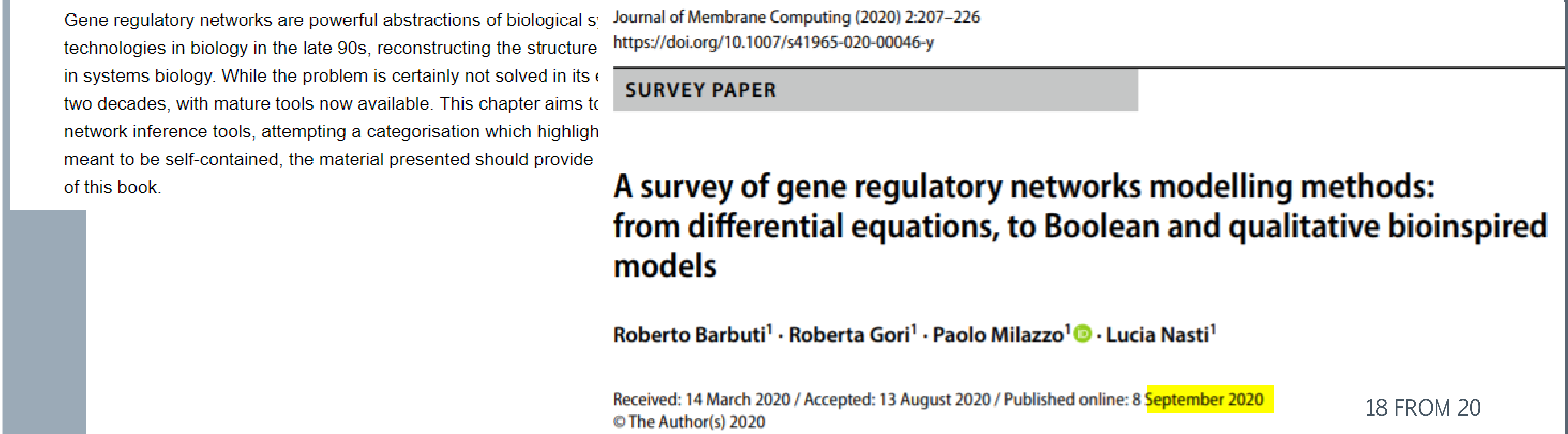
Help | Advar

Quantitative Biology > Quantitative Methods

[Submitted on 12 Jan 2018 (v1), last revised 19 Dec 2018 (this version, v2)]

Gene regulatory network inference: an introductory survey

Vân Anh Huynh-Thu, Guido Sanguinetti



Gene regulatory networks are powerful abstractions of biological s
technologies in biology in the late 90s, reconstructing the structure
in systems biology. While the problem is certainly not solved in its
two decades, with mature tools now available. This chapter aims to
network inference tools, attempting a categorisation which highligh
meant to be self-contained, the material presented should provide
of this book.

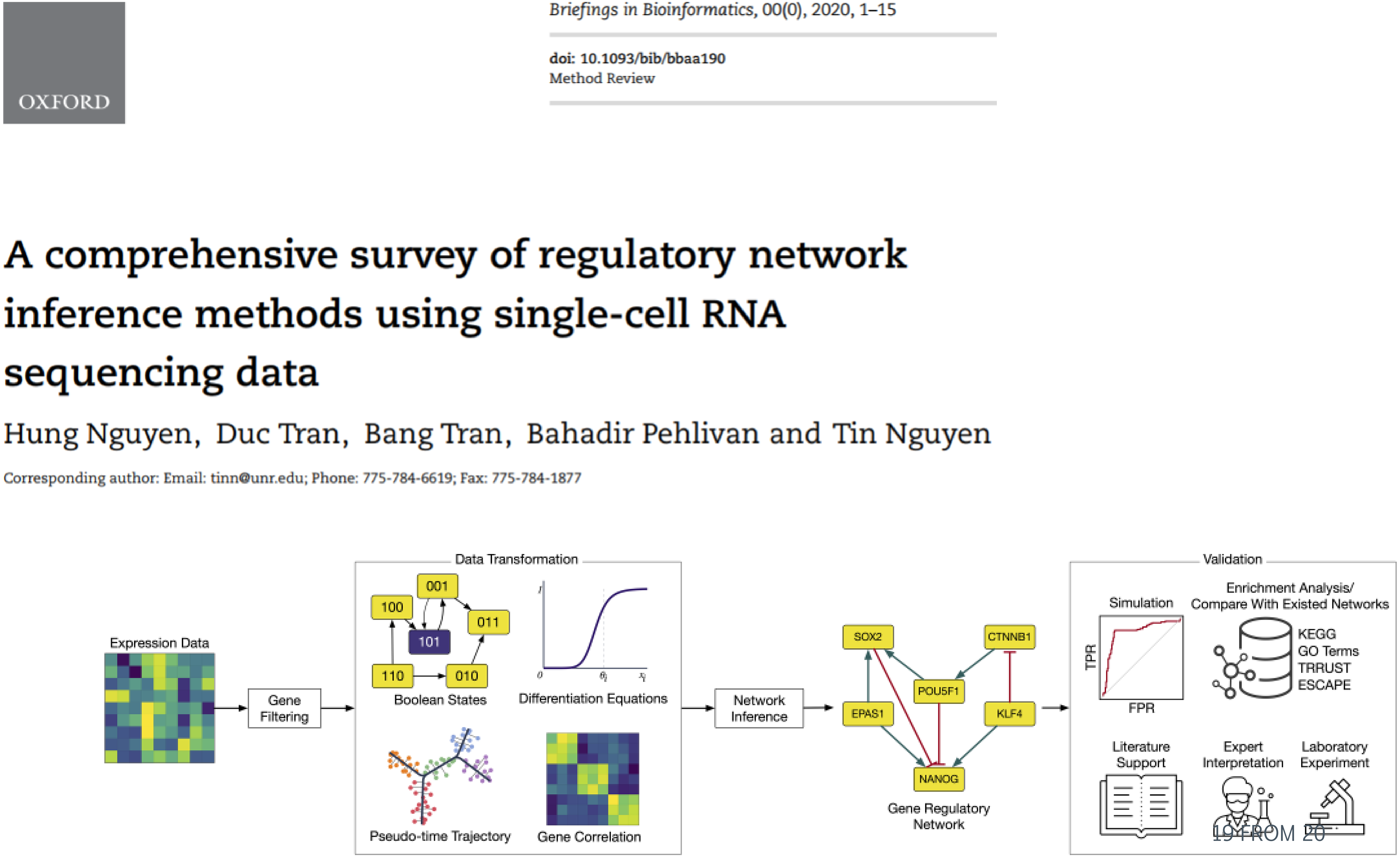
Journal of Membrane Computing (2020) 2:207–226
https://doi.org/10.1007/s41965-020-00046-y

SURVEY PAPER

A survey of gene regulatory networks modelling methods: from differential equations, to Boolean and qualitative bioinspired models

Roberto Barbuti[1] · Roberta Gori[1] · Paolo Milazzo[1] · Lucia Nasti[1]

Received: 14 March 2020 / Accepted: 13 August 2020 / Published online: 8 September 2020



OXFORD

Briefings in Bioinformatics, 00(0), 2020, 1–15

doi: 10.1093/bib/bbaa190
Method Review

A comprehensive survey of regulatory network inference methods using single-cell RNA sequencing data

Hung Nguyen, Duc Tran, Bang Tran, Bahadir Pehlivan and Tin Nguyen

Corresponding author: Email: tinn@unr.edu; Phone: 775-784-6619; Fax: 775-784-1877

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