



An Investigation of Gene Regulatory Network State Space Variability



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Definitions

- A **gene** is a segment of DNA that encodes the instructions for making proteins and RNA
- A set of genes that interact with each other to control cell function is a **gene regulatory network**. Denoted (GRN)
 - Gene networks
 - Regulate expression
 - Help organisms adapt to environments
 - Aid development

Goal

Capture variation between gene state transitions using three different methods

- Other models focus on finding variation in the entire network
- Here we focus on variation contained in one transition
- Data obtained from a single cell can have large amounts of noise and variation [3]
- Noise from gene expression data can be as large as 30% [3]
- Different feedback loops can amplify or dampen variation in networks [4]
- Genetically identical cells may show cell-cell differences by more than 10%

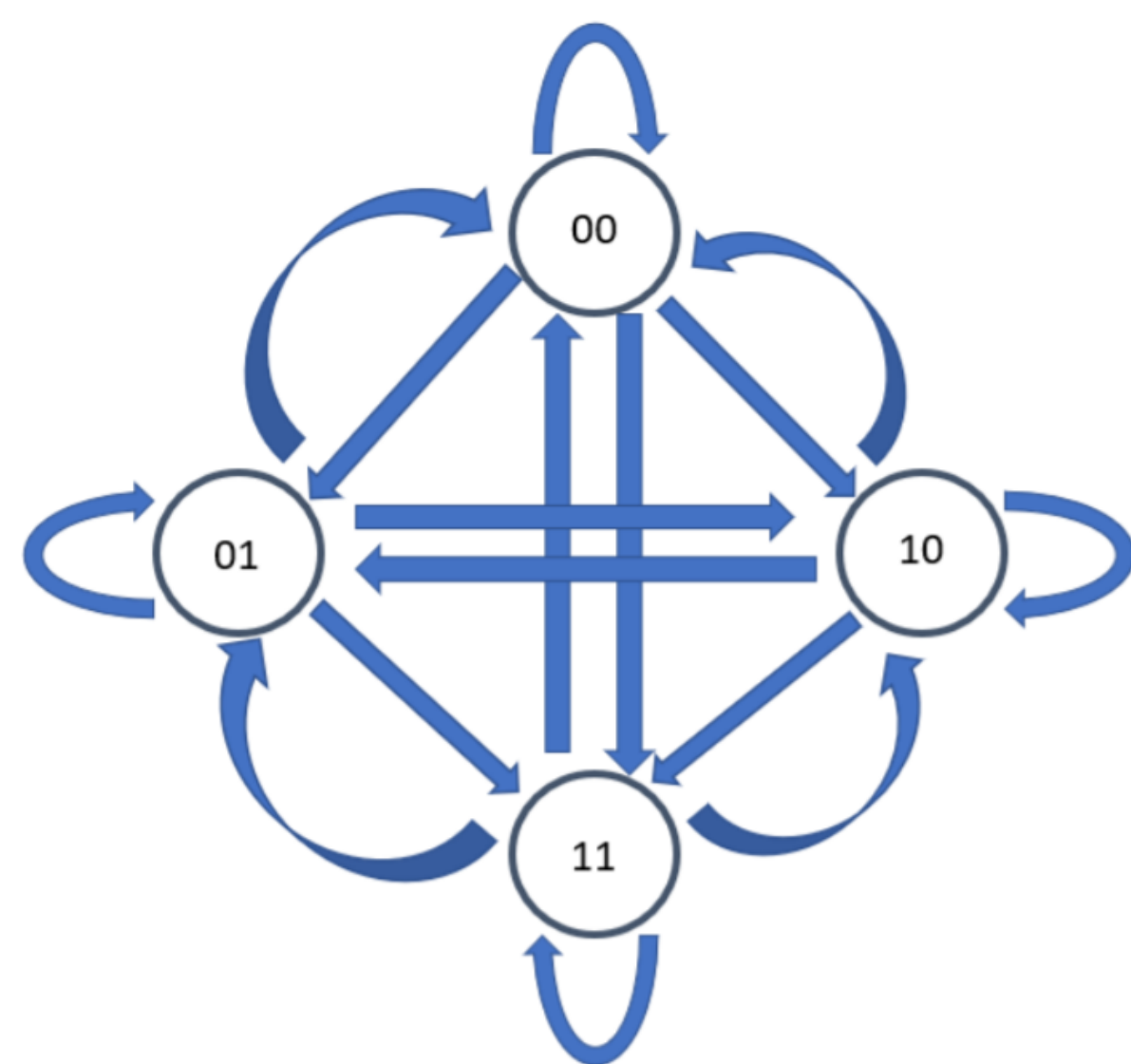


Figure: Boolean Network of two genes; 0 → A gene is off ; 1 → A gene is on.

Table: Transition Matrix of State Update Propensities

| In \ Out | 00 | 01 | 10 | 11 |
|----------|--|--|--|--|
| 00 | $(1 - p_1^\uparrow)(1 - p_2^\uparrow)$ | $(1 - p_1^\uparrow)(p_2^\uparrow)$ | $(p_1^\uparrow)(1 - p_2^\uparrow)$ | $(p_1^\uparrow)(p_2^\uparrow)$ |
| 01 | $(1 - p_1^\uparrow)(p_2^\downarrow)$ | $(1 - p_1^\downarrow)(1 - p_2^\downarrow)$ | $(p_1^\downarrow)(p_2^\downarrow)$ | $(p_1^\downarrow)(1 - p_2^\downarrow)$ |
| 10 | $(p_1^\downarrow)(1 - p_2^\downarrow)$ | $(p_1^\downarrow)(p_2^\downarrow)$ | $(1 - p_1^\downarrow)(1 - p_2^\downarrow)$ | $(1 - p_1^\downarrow)(p_2^\downarrow)$ |
| 11 | $(p_1^\downarrow)(p_2^\downarrow)$ | $(p_1^\downarrow)(1 - p_2^\downarrow)$ | $(1 - p_1^\downarrow)(p_2^\downarrow)$ | $(1 - p_1^\downarrow)(1 - p_2^\downarrow)$ |

Model Assumptions

- Intrinsic variation
- Well-mixed
- Discrete
- Stochastic

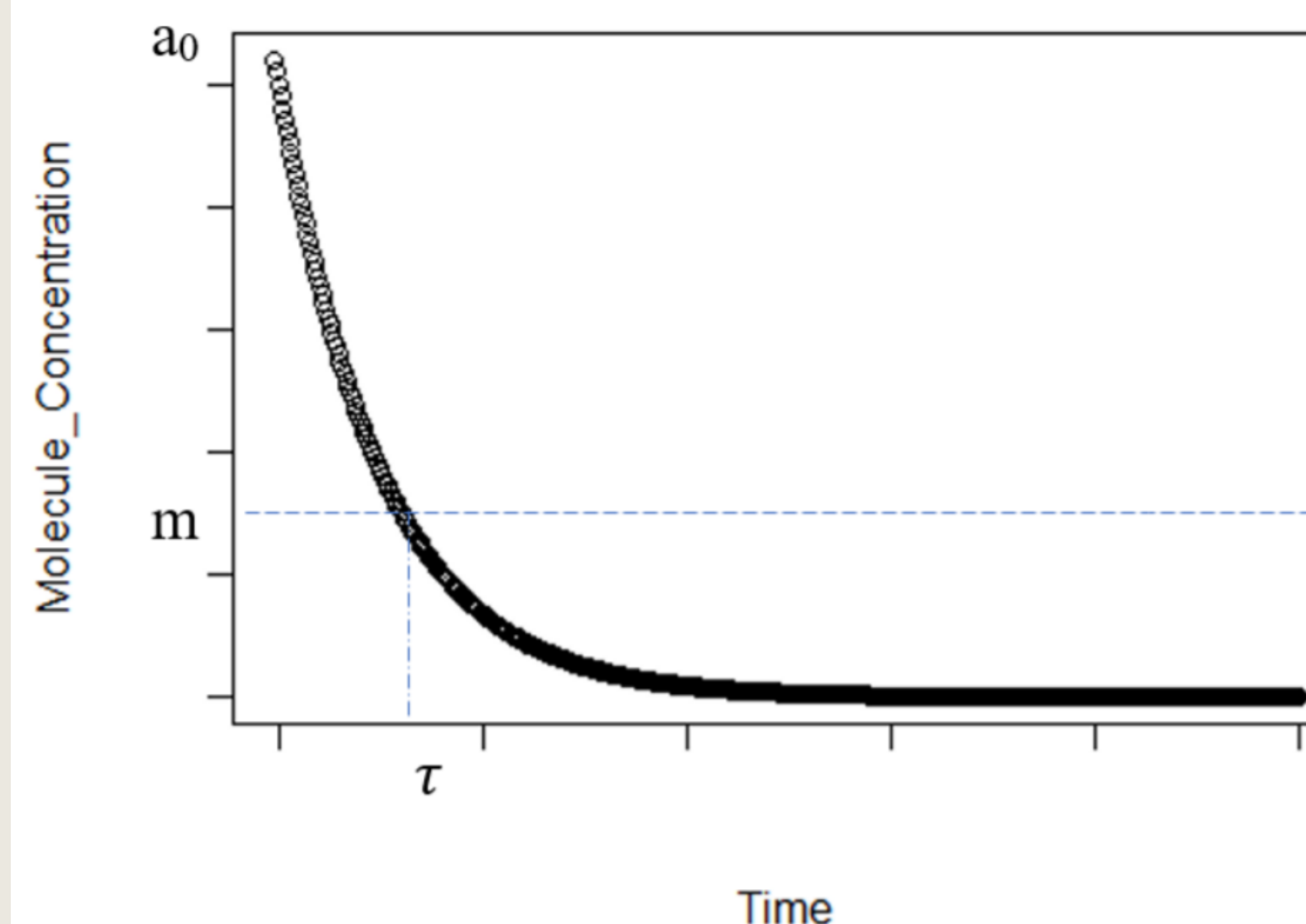
Transition Function

$$f(t) = a_0 e^{-kt}, t \geq 0 \quad (1)$$

Thresholds

$$x_i = \begin{cases} 1 & \text{if } t < \tau \\ 0 & \text{if } t \geq \tau \end{cases}$$

Transition Function with Threshold



Methods

- Transition Function
- Beta Distribution
- Spectral Density

Transition Function Conclusions

- Describes qualitative behavior for transitions that can be confirmed by literature: highly responsive systems have less variation than systems with lower response rates
- Not all systems can be highly responsive because responsiveness requires more energy [24]
- Useful if we know qualitative properties about the molecules needed for transition
 - It is difficult to obtain data for rates of change of molecule concentration
 - This is difficult to incorporate into a large network

Beta Distribution Conclusions

- Variation is highest when there is a mix of genes that update approximately 75% and 100% of the time
- The beta distribution is a natural way to distribute probabilities
- Nadarajah and Kotz in 2005 and Krysicki in 1999 showed that the product of beta distributions is a beta distribution when the shape and rate parameters have certain properties
 - There is no clear natural explanation to the behavior of the beta distribution results
 - Does not incorporate the transition function
 - Variation caused by the differences in shape parameters is biologically unclear

Spectral Density Conclusions

- The distribution of k does not have a large impact on variation
- Higher rates of decay have less variation
 - A network will likely require large amounts of data
 - Negative and imaginary variation can be difficult to interpret

Overall Conclusions

- Useful if we know qualitative properties about the molecules needed for transition
- Variation is highest when there is a mix of genes that update approximately 75% and 100% of the time
- Nadarajah and Kotz in 2005 and Krysicki in 1999 showed that the product of beta distributions is a beta distributions when the shape parameters have certain properties
- The distribution of k does not have a large impact on variation
- Higher rates of decay have less variation and are more responsive than genes that are slower to respond