Engineering Genetic Circuits

Chris J. Myers

Lecture 6: Logical Abstraction
Somebody who thinks logically is a nice contrast to the real world.
Example Electrical Circuits

Intel 4004 (1971)
2,300 xtors / 108 KHz

42 million xtors / 1.5 GHz

(Courtesy of the Intel Museum)
Example Electrical Circuits

Intel 4004 (1971)
2,300 xtors / 108 KHz
If cars improved similarly, could now drive from SF to NYC in 13 seconds!
(Courtesy of the Intel Museum)

42 million xtors / 1.5 GHz
Electrical engineers routinely analyze circuits with thousands or even millions of interconnected complex components.

Logical abstraction is essential to reason about such complex systems.

Can logical abstraction be applied to biochemical circuits?

Regulation of genetic circuits controlled by Hill functions.

In the limit, these Hill functions become step functions which can be encoded logically.
Overview

- Logical encoding
- Piecewise models
- Stochastic finite-state machines
- Markov chain analysis
- Qualitative logical models
Electrical circuits often classified as being either *analog* (i.e., having continuous valued states) or *digital* (i.e., having discrete valued states).

Analog circuits must be analyzed using ODEs while digital circuits can be analyzed using *switch-level simulation*.

Digital circuits are actually also analog circuits, but logical abstraction reduces their complexity of analysis.

Logical abstraction essential since complex integrated circuits cannot be efficiently analyzed using ODEs.

Can the efficiency of genetic circuit analysis also be improved using such a logical abstraction?
Hill Functions

- Inhibition and activation can be modeled with Hill functions:

\[
\frac{1}{1 + K_j^n x_j^n} \quad \text{OR} \quad \frac{K_j^n x_j^n}{1 + K_j^n x_j^n}
\]

where \( \theta_j = \sqrt[n]{a/(K_j - aK_j)} \) is the critical threshold where the change occurs, and \( a \) is an amplifier in the range of \([0.5, 1.0)\).

- As \( n \) increases, time spent in the transition region decreases and the function begins to behave like a step function.

- In this case, \( x_j \) could be encoded using a binary variable which is false when \( x_j < \theta_j \) and true when \( x_j \geq \theta_j \).
Activity of the $P_{RM}$ Promoter

$[CI_2]$ cannot be mapped into a single binary variable.
Assume that species $x_j$ has $N_j$ thresholds $\theta^1_j, \ldots, \theta^i_j, \ldots, \theta^N_j$ that satisfy:

$$\theta^0_j < \theta^1_j < \ldots < \theta^i_j < \ldots < \theta^N_j < \theta^{N_j+1}_j$$

where $\theta^0_j = 0$ and $\theta^{N_j+1}_j = \infty$.

States partitioned into *critical intervals* $(A^0_j, A^1_j, \ldots, A^{N_j}_j)$ where

$A^i_j = [\theta^i_j, \theta^{i+1}_j)$.

An $n$-ary variable $b_j$ is created which can take any value in $\{0, 1, \ldots, N_j\}$.

Initial value of $b_j$ is the largest $i$ such that $[x^0_j]_0 \geq \theta^i_j$ where $[x^0_j]_0$ is the initial concentration of $x_j$.

Critical thresholds divide space into $n$-dimensional *regulatory domains* that are separated by hyperplanes $x_j = \theta^i_j$.

The total number of these $n$-dimensional domains is:

$$\prod_{j=1}^n (N_j + 1)$$

An assignment to each $b_j$ uniquely selects an individual domain.
Regulatory Domains

![Diagram of regulatory domains with axes labeled as $x_1$, $x_2$, $x_3$, $\theta_1$, $\theta_2$, $\theta_3$]
Example Encoding for CI/CII Portion of Phage $\lambda$

- **Abstracted model:**

\[
\frac{d[CI]}{dt} = np \frac{P_{RE}RNAP(k_bK_{o1} + k_aK_a[CII])}{1 + K_{o1}RNAP + K_aRNAP[CII]} - k_d[CI]
\]

\[
\frac{d[CII]}{dt} = np \frac{k_0P_RK_{o2}RNAP}{1 + K_{o2}RNAP + K_rK_d[CI]^2} - k_d[CII]
\]

- **Critical thresholds and intervals assuming the amplifier, $a$, is 0.5:**

\[
\theta_{CI}^1 = \frac{1}{\sqrt{K_rK_d}} = 7, \quad \theta_{CII}^1 = \frac{1}{K_aRNAP} = 21
\]

\[
A_{CI}^0 = [0, 7), A_{CI}^1 = [7, \infty), \quad A_{CII}^0 = [0, 21), A_{CII}^1 = [21, \infty)
\]
Piecewise Linear Differential Equations

- **Piecewise linear differential equation (PLDE):**

\[
\frac{dx_j}{dt} = f_j(x) - g_j(x)x_j \quad j = 1, \ldots, n
\]

where \( f_j \) and \( g_j \) are piecewise constant functions and \( x = [x_1, \ldots, x_n] \) is a vector of species concentrations.

- Each \( f_j \) and \( g_j \) changes value when a \( x_j \) crosses a threshold \( \theta_j \).

\[
f_j(x) = \sum_{l \in L} \alpha_{jl} B_{jl}(x) \geq 0
\]

where \( \alpha_{jl} \) is a constant, and \( B_{jl} \) is composed of a conjunction of terms of the form \( (b_k = i) \).

- Example:

\[
\frac{d[CI]}{dt} = np \, P_{RE}(k_b + k_a(b_{CII} = 1)) - k_d[CI]
\]

\[
\frac{d[CII]}{dt} = np \, k_o P_R(b_{CI} = 0) - k_d[CII]
\]
Inside each domain $B$, behavior is linear and quite simple. 

$B$ is defined by a Boolean formula of the form: $(b_1 = i_1) \land \ldots \land (b_n = i_n)$ and denoted by a state vector of the form $(i_1 \ldots i_n)$.

Denote $f = [f_1, \ldots, f_n]$ within $B$ by $f^B$, and $g = [g_1, \ldots, g_n]$ by $g^B$.

Within domain $B$, the behavior of $x$ reduces to the simple linear differential equation $\frac{dx}{dt} = f^B - g^B x$ which has the solution:

$$X(t) = \Phi^B + (X(t_0) - \Phi^B) e^{\gamma(t_0-t)} \quad \text{where} \quad \Phi^B = f^B / g^B$$
The domains are (00), (01), (10), and (11).

The solutions are:

\[
\Phi^{00} = \left( \frac{np \, k_o \, P_R}{k_d}, \frac{np \, k_b \, P_{RE}}{k_d} \right) = (19, 0.05)
\]

\[
\Phi^{01} = \left( 0, \frac{np \, k_b \, P_{RE}}{k_d} \right) = (0, 0.05)
\]

\[
\Phi^{10} = \left( \frac{np \, k_o \, P_R}{k_d}, \frac{np \, P_{RE}(k_b + k_a)}{k_d} \right) = (19, 20)
\]

\[
\Phi^{11} = \left( 0, \frac{np \, P_{RE}(k_b + k_a)}{k_d} \right) = (0, 20)
\]
As $t \to +\infty$, $X(t)$ approaches $\Phi^B$ until it reaches a boundary.

If $\Phi^B$ is within $B$, then $X(t)$ reaches a stable stationary point at $\Phi^B$.

Assuming that $B$ is bounded between $\theta^i_j$ and $\theta^{i+1}_j$:

- If $\Phi^B < \theta^i_j$, all trajectories in $B$ that reach $x_j = \theta^i_j$ are leaving $B$.
- If $\Phi^B > \theta^{i+1}_j$, all trajectories in $B$ that reach $x_j = \theta^{i+1}_j$ are leaving $B$.
- If $\theta^i_j < \Phi^B < \theta^{i+1}_j$, all trajectories that reach $x_j = \theta^i_j$ or $x_j = \theta^{i+1}_j$ enter $B$.

A boundary between two domains is *transparent* if trajectories enter one domain and leave the other domain through this boundary.

A boundary is *black* if trajectories leave both domains from this boundary.

A boundary is *white* if trajectories enter both domains from this boundary.

If a boundary is black or white, the result is a *sliding motion*.

If the boundary is black, then the solution proceeds along the boundary until it either reaches another boundary or a stable point on the boundary.

If the boundary is white, the solution can either proceed sliding along the boundary or leave it at any point, since a white wall is unstable.
Example Flow Graph for CI/CII Portion of Phage \( \lambda \)

\[
\begin{array}{c|c|c|c}
\theta^2_{CI} & \Phi^{10} & \Phi^{01} & \Phi^{00} \\
\hline
\Phi^{11} & (01) & (00) \\
\hline
\theta^1_{CI} & (11) & (10) \\
\hline
\end{array}
\]
Hybrid Petri nets can represent piecewise differential equation models. HPNs include both a discrete part that can model discrete states such as the current regulatory domain that the system is in as well as a continuous part that can model continuous quantities like species concentrations.

Numerous ways to add continuous quantities to Petri nets.

Labeled hybrid Petri nets (LHPNs) add the continuous values as auxiliary variables that evolve over time.

These variables can be sampled in enabling conditions on transitions.

Their rates of change can be modified by assignments on transitions.
LHPN Model of the CI/CII Portion of Phage λ

\[
\begin{align*}
\frac{dCII}{dt}: & = 0.14, \\
CII < 21: & \quad \left\langle \frac{dCI}{dt} : = -0.05, \frac{dCII}{dt} : = 0 \right\rangle, \\
CI \geq 8: & \quad \left\langle \frac{dCI}{dt} : = -0.05, \frac{dCII}{dt} : = 0 \right\rangle, \\
CI < 6: & \quad \left\langle \frac{dCI}{dt} : = 0.0004, \frac{dCII}{dt} : = 0.14 \right\rangle, \\
CI \geq 7: & \quad \left\langle \frac{dCI}{dt} : = 0.1, \frac{dCII}{dt} : = -0.16 \right\rangle, \\
CI \geq 8: & \quad \left\langle \frac{dCI}{dt} : = 0.0004, \frac{dCII}{dt} : = 0.14 \right\rangle, \\
CII \geq 23: & \quad \left\langle \frac{dCI}{dt} : = 0.15, \frac{dCII}{dt} : = -0.02 \right\rangle, \\
CII < 19: & \quad \left\langle \frac{dCI}{dt} : = 0.0004, \frac{dCII}{dt} : = 0.14 \right\rangle
\end{align*}
\]
Piecewise Model for the Phage λ Decision Circuit
Stochastic Finite-State Machines

- Piecewise models still track exact concentrations of each species making their state space infinite.

- A *stochastic finite-state machine* (FSM) only tracks the n-ary encoding value for each species.

- Creates a purely logical representation of the genetic circuit.

- Analysis of a stochastic FSM can be accomplished using either stochastic simulation or Markov chain analysis.

- A stochastic FSM can often be efficiently analyzed while maintaining the high-level quantitative behavior.
SAC model transformation requires reaction model to satisfy the property that all reactions have either one reactant or one product, but not both. Often true after applying the reaction-based abstractions, but if not, it can be made to hold using *reaction splitization*. 
Reaction Splitization Example

\[ f([s_1],[s_2]) \]

\[ S_1 \quad r \quad S_2 \]

\[ S_3 \quad p \quad S_4 \]
Reaction Splitization Example

\[ f([s_1],[s_2]) \]
Reaction Splitization Example

\[
f([s_1], [s_2]) \quad \text{and} \quad f([s_1], [s_2]) \quad \text{and} \quad f([s_1], [s_2])
\]

\[
S_1 \quad m \quad S_2
\]

\[
S_3 \quad m \quad S_4
\]

\[
s_3 \quad p \quad s_4
\]
Reaction Splitization Example

\[ f([s_1],[s_2]) \]

\[ f([s_1],[s_2]) \]

\[ f([s_1],[s_2]) \]

\[ f([s_1],[s_2]) \]

\[ s_1 \]

\[ s_2 \]

\[ p \]

\[ p \]

\[ s_3 \]

\[ s_4 \]
Guarded Commands

- A stochastic FSM is specified using a set of *guarded commands*. Each guarded command, $c_k \in C$, has a form:

$$G_k(b) \xrightarrow{q_k} b_j := i$$

where the function $G_k(b)$ is the *guard*, $q_k$ is the transition rate, and $i$ is the n-ary value assigned to $b_j$ as a result of $c_k$.

- A guard is a conjunction of literals of the form $(b_j = i)$.

- Each guarded command, $c_k$, is required to monotonically change the state of some variable in $b$.

- If $b_j$ is assigned to $i$ by $c_k$, then the guard must include a term of the form $(b_j = i - 1)$ or $(b_j = i + 1)$. 

Chris J. Myers (Lecture 6: Abstraction)
Guarded Command Generation: CI

• Production of CI:

\[
\begin{align*}
    b_{CI} = 0 \land b_{CII} = 0 & \quad \xrightarrow{q_1} \quad b_{CI} := 1 \\
    b_{CI} = 1 \land b_{CII} = 0 & \quad \xrightarrow{q_2} \quad b_{CI} := 2 \\
    b_{CI} = 0 \land b_{CII} = 1 & \quad \xrightarrow{q_3} \quad b_{CI} := 1 \\
    b_{CI} = 1 \land b_{CII} = 1 & \quad \xrightarrow{q_4} \quad b_{CI} := 2 \\
    b_{CI} = 0 \land b_{CII} = 2 & \quad \xrightarrow{q_5} \quad b_{CI} := 1 \\
    b_{CI} = 1 \land b_{CII} = 2 & \quad \xrightarrow{q_6} \quad b_{CI} := 2 \\
    b_{CI} = 0 \land b_{CII} = 3 & \quad \xrightarrow{q_7} \quad b_{CI} := 1 \\
    b_{CI} = 1 \land b_{CII} = 3 & \quad \xrightarrow{q_8} \quad b_{CI} := 2
\end{align*}
\]

• Degradation of CI:

\[
\begin{align*}
    b_{CI} = 2 & \quad \xrightarrow{q_9} \quad b_{CI} := 1 \\
    b_{CI} = 1 & \quad \xrightarrow{q_{10}} \quad b_{CI} := 0
\end{align*}
\]
Guarded Command Generation: CII

- **Production of CII:**

  \[ b_{CI} = 0 \land b_{CII} = 0 \quad \xrightarrow{q_{11}} \quad b_{CII} := 1 \]
  \[ b_{CI} = 0 \land b_{CII} = 1 \quad \xrightarrow{q_{12}} \quad b_{CII} := 2 \]
  \[ b_{CI} = 0 \land b_{CII} = 2 \quad \xrightarrow{q_{13}} \quad b_{CII} := 3 \]
  \[ b_{CI} = 1 \land b_{CII} = 0 \quad \xrightarrow{q_{14}} \quad b_{CII} := 1 \]
  \[ b_{CI} = 1 \land b_{CII} = 1 \quad \xrightarrow{q_{15}} \quad b_{CII} := 2 \]
  \[ b_{CI} = 1 \land b_{CII} = 2 \quad \xrightarrow{q_{16}} \quad b_{CII} := 3 \]
  \[ b_{CI} = 2 \land b_{CII} = 0 \quad \xrightarrow{q_{17}} \quad b_{CII} := 1 \]
  \[ b_{CI} = 2 \land b_{CII} = 1 \quad \xrightarrow{q_{18}} \quad b_{CII} := 2 \]
  \[ b_{CI} = 2 \land b_{CII} = 2 \quad \xrightarrow{q_{19}} \quad b_{CII} := 3 \]

- **Degradation of CII:**

  \[ b_{CII} = 3 \quad \xrightarrow{q_{20}} \quad b_{CII} := 2 \]
  \[ b_{CII} = 2 \quad \xrightarrow{q_{21}} \quad b_{CII} := 1 \]
  \[ b_{CII} = 1 \quad \xrightarrow{q_{22}} \quad b_{CII} := 0 \]
For each guarded command $c_k$ that increases $b_j$ to $i$:

$$q_k = \frac{m \cdot f_j(\Theta)}{\theta_i - \theta_i^{-1}}$$

where $m$ is the stochiometry of $s$ in the corresponding reaction, $f(\Theta)$ is the rate law for this reaction, and $\Theta$ is the critical levels that satisfy $G_k(b)$.

For each guarded command $c_k$ that decreases $b_j$ to $i$:

$$q_k = \frac{m \cdot f_j(\Theta)}{\theta_{i+1} - \theta_i}$$
Transition Rate Generation Example: CI

- **Production of CI:**

  \[ b_{CI} = 0 \land b_{CII} = 0 \quad q_1 \rightarrow b_{CI} := 1 \quad q_1 = 10 \cdot f_3(0)/\theta_1^{CI} \]

  \[ b_{CI} = 1 \land b_{CII} = 0 \quad q_2 \rightarrow b_{CI} := 2 \quad q_2 = 10 \cdot f_3(0)/(\theta_2^{CI} - \theta_1^{CI}) \]

  \[ b_{CI} = 0 \land b_{CII} = 1 \quad q_3 \rightarrow b_{CI} := 1 \quad q_3 = 10 \cdot f_3(\theta_1^{CII})/\theta_1^{CI} \]

  \[ b_{CI} = 1 \land b_{CII} = 1 \quad q_4 \rightarrow b_{CI} := 2 \quad q_4 = 10 \cdot f_3(\theta_1^{CII})/(\theta_2^{CI} - \theta_1^{CI}) \]

  \[ b_{CI} = 0 \land b_{CII} = 2 \quad q_5 \rightarrow b_{CI} := 1 \quad q_5 = 10 \cdot f_3(\theta_2^{CII})/\theta_1^{CI} \]

  \[ b_{CI} = 1 \land b_{CII} = 2 \quad q_6 \rightarrow b_{CI} := 2 \quad q_6 = 10 \cdot f_3(\theta_2^{CII})/(\theta_2^{CI} - \theta_1^{CI}) \]

  \[ b_{CI} = 0 \land b_{CII} = 3 \quad q_7 \rightarrow b_{CI} := 1 \quad q_7 = 10 \cdot f_3(\theta_3^{CII})/\theta_1^{CI} \]

  \[ b_{CI} = 1 \land b_{CII} = 3 \quad q_8 \rightarrow b_{CI} := 2 \quad q_8 = 10 \cdot f_3(\theta_3^{CII})/(\theta_2^{CI} - \theta_1^{CI}) \]

- **Degradation of CI:**

  \[ b_{CI} = 2 \quad q_9 \rightarrow b_{CI} := 1 \quad q_9 = f_2(\theta_2^{CI})/(\theta_2^{CI} - \theta_1^{CI}) \]

  \[ b_{CI} = 1 \quad q_{10} \rightarrow b_{CI} := 0 \quad q_{10} = f_2(\theta_1^{CI})/\theta_1^{CI} \]
If the process being modeled is in the state $b$, $c_k$ can be executed if its guard is satisfied (i.e., $G_k(b)$ evaluates to true).

The result of executing the guarded command is that a new state $b'$ is reached in which $b'_j = i$ and $b'_l = b_l$ and for all $l \neq j$.

The probability that $c_k$ is executed is:

$$P(c_k) = G_k(b) \cdot q_k \cdot \Delta t$$

where $\Delta t$ must be small enough such that the probability that two or more commands are executed in that time interval is negligible.

The probability that no transition is taken in a $\Delta t$ time step is:

$$\left(1 - \left(\sum_{k=0}^{\left|C\right|} G_k(s) \cdot q_k \cdot \Delta t\right)\right)$$
A stochastic FSM can be analyzed using multiple stochastic simulation runs beginning in state $b_0$.

In each state, simulation process determines whether or not to execute a guarded command in the next $\Delta t$.

If guarded command executed, assignment is performed resulting in a new state, and transition probabilities are recalculated.

Process continues until desired simulation time has been reached.

This process is inefficient, since for small $\Delta t$, number of simulation steps that do not result in a state change increases significantly.

More efficient to use SSA to jump to time of the next state change.

Can also be efficiently analyzed using Markov chain analysis.
Markov processes satisfy the Markov property:

\[ Pr[X(t+\tau) \leq y \mid X(s) = x(s), \forall s \leq t] = Pr[X(t+\tau) \leq y \mid X(\tau) = x(\tau)], \quad \forall \tau > 0 \]

Process is memoryless (i.e., the time that will be spent in a state is independent of the time already spent there).

A homogeneous Markov process does not depend on the time \( t \):

\[ Pr[X(t+\tau) = y \mid X(\tau) = x] = Pr[X(\tau) = y \mid X(0) = x(0)], \forall t, \tau > 0 \]

A Markov chain is a Markov process with a discrete state space.
Discrete-Time Markov Chains (DTMC)

- States observed only at discrete time points.
- Homogenous DTMC’s specified by a \textit{transition probability matrix}, \( P \), composed of \textit{single-step transition probabilities} of this form:
  
  \[ p_{ij} = Pr[X_{n+1} = j \mid X_n = i], \text{ for all } n = 0, 1, \ldots \]

  where \( 0 \leq p_{ij} \leq 1 \) and \( \sum_{\text{all } j} p_{ij} = 1 \).
- Weather in Salt Lake City, Utah in January (snowy, overcast, clear):
  
  \[
  P = \begin{pmatrix}
  0.4 & 0.4 & 0.2 \\
  0.7 & 0.3 & 0.0 \\
  0.3 & 0.2 & 0.5 
  \end{pmatrix}
  \]
$n$-Step Transition Probabilities

- $n$-step transition probabilities can be obtained as follows:

$$P^n = PP^{(n-1)}$$

- Example:

$$P^2 = \begin{pmatrix} 0.5 & 0.32 & 0.18 \\ 0.49 & 0.37 & 0.14 \\ 0.41 & 0.28 & 0.31 \end{pmatrix}$$
\( n \)-Step Transition Probabilities

- \( n \)-step transition probabilities can be obtained as follows:

\[
P^n = PP^{(n-1)}
\]

- Example:

\[
P^6 = P^\infty = \begin{pmatrix}
0.48 & 0.33 & 0.19 \\
0.48 & 0.33 & 0.19 \\
0.48 & 0.33 & 0.19
\end{pmatrix}
\]
Classifications of States

- A state is *transient* when there is a non-zero probability that the DTMC will at some point never return to that state.
- A state is *recurrent* when the DTMC is guaranteed to return to this state at some point in the future.
- A state is *positive-recurrent* when its mean time to revisit is finite.
- A state is *null-recurrent* when its mean time to revisit is infinite.
- In a finite Markov chain, all states are transient or positive-recurrent.
- A state \( j \) is *periodic with period* \( p \) when upon leaving \( j \) it can only be returned to after a number of transitions that is a multiple of \( p > 1 \).
- A state with \( p = 1 \) is *aperiodic*.
- An *ergodic* Markov chain is positive-recurrent and aperiodic.
- A DTMC is *irreducible* if every state can be reached by every other state.
- A finite, aperiodic, irreducible Markov chain is ergodic.
Often interested in determining the probability of being in a state:

\[ \pi_i(n) = Pr[X_n = i] \]

Probability vector for all states is written as follows:

\[ \pi(n) = [\pi_1(n), \pi_2(n), \ldots, \pi_i(n), \ldots] \]

The limit as \( n \) goes to \( \infty \) is the \textit{limiting distribution}:

\[ \pi = \lim_{n \to \infty} \pi(n) \]

In an ergodic Markov chain, limiting distribution is also known as a \textit{steady-state distribution} and satisfies:

\[ \pi = \pi P \]
Can multiply $P$ by itself repetitively or squaring the matrix.

Drawback is the time and memory requirements for matrix multiplication.

$P$ is typically a very large and sparse matrix (i.e., many entries are zero).

After squaring, zero entries take non-zero values.

If kept sparse, $P$ can be represented with sparse matrix data structure.

Numerous methods developed to find the steady-state distribution.

Two types of methods presented here:

- Direct methods
- Iterative methods
Direct Methods

- Solve system of equations given by $\pi = \pi P$.
- Use Gaussian elimination or other methods.
- Example:

\[
\begin{bmatrix}
s & o & c \\
\end{bmatrix}
= \begin{bmatrix}
s & o & c \\
\end{bmatrix}
\begin{pmatrix}
0.4 & 0.4 & 0.2 \\
0.7 & 0.3 & 0.0 \\
0.3 & 0.2 & 0.5 \\
\end{pmatrix}
\]
Direct Methods

- Solve system of equations given by $\pi = \pi P$.
- Use Gaussian elimination or other methods.
- Example:

$$\begin{bmatrix} s & o & c \end{bmatrix} = \begin{bmatrix} (0.4s + 0.7o + 0.3c)(0.4s + 0.3o + 0.2c)(0.2s + 0.5c) \end{bmatrix}$$
Direct Methods

- Solve system of equations given by $\pi = \pi P$.
- Use Gaussian elimination or other methods.
- Example:

\[
\begin{align*}
  s &= 0.4s + 0.7o + 0.3c \\
  o &= 0.4s + 0.3o + 0.2c \\
  c &= 0.2s + 0.5c 
\end{align*}
\]
Direct Methods

- Solve system of equations given by $\pi = \pi P$.
- Use Gaussian elimination or other methods.
- Example:

$$s = 0.48$$
$$o = 0.33$$
$$c = 0.19$$
Iterative Methods

- Iterate using $\pi_n = \pi_{n-1}P$ until convergence.
- Convergence can be slow and periodicity must be determined.
- Convergence rate dependent on initial state vector.
- Example:

$$
\pi(1) = \begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix} \begin{pmatrix} 0.4 & 0.4 & 0.2 \\ 0.7 & 0.3 & 0.0 \\ 0.3 & 0.2 & 0.5 \end{pmatrix}
$$

$$
\pi(1) = \begin{bmatrix} 0.4 & 0.4 & 0.2 \end{bmatrix}
$$
Iterative Methods

- Iterate using $\pi_n = \pi_{n-1} P$ until convergence.
- Convergence can be slow and periodicity must be determined.
- Convergence rate dependent on initial state vector.
- Example:

\[
\begin{align*}
\pi(2) &= [0.4 \ 0.4 \ 0.2] \begin{pmatrix} 0.4 & 0.4 & 0.2 \\ 0.7 & 0.3 & 0.0 \\ 0.3 & 0.2 & 0.5 \end{pmatrix} \\
\pi(2) &= [0.5 \ 0.32 \ 0.18]
\end{align*}
\]
Iterate using $\pi_n = \pi_{n-1} P$ until convergence.

Convergence can be slow and periodicity must be determined.

Convergence rate dependent on initial state vector.

Example:

$$\pi(3) = [0.5 \ 0.32 \ 0.18] \begin{pmatrix} 0.4 & 0.4 & 0.2 \\ 0.7 & 0.3 & 0.0 \\ 0.3 & 0.2 & 0.5 \end{pmatrix}$$

$$\pi(3) = [0.48 \ 0.33 \ 0.19]$$
Iterate using $\pi_n = \pi_{n-1} P$ until convergence.

Convergence can be slow and periodicity must be determined.

Convergence rate dependent on initial state vector.

Example:

$$\pi(4) = \begin{bmatrix} 0.48 & 0.33 & 0.19 \end{bmatrix} \begin{pmatrix} 0.4 & 0.4 & 0.2 \\ 0.7 & 0.3 & 0.0 \\ 0.3 & 0.2 & 0.5 \end{pmatrix}$$

$$\pi(4) = \begin{bmatrix} 0.48 & 0.33 & 0.19 \end{bmatrix}$$
When iterations are converging rapidly, can check:

$$\| \pi(k) - \pi(k - 1) \| < \varepsilon$$

where \( \|x\| = \sqrt{x_1^2 + \ldots + x_n^2} \) and \( \varepsilon \) is the desired accuracy.

When iterations are converging slowly, it is better to check:

$$\| \pi(k) - \pi(k - m) \| < \varepsilon$$

where \( m \) should be set based on the convergence rate.

Problems occur when probabilities are small, so should normalize:

$$\max_i \left( \frac{\left| \pi_i(k) - \pi_i(k - m) \right|}{|\pi_i(k)|} \right) < \varepsilon$$
The period of a irreducible Markov chain is:

\[ p = \gcd(l_1, \ldots, l_i, \ldots, l_c) \]

where \( \gcd \) is the greatest common divisor, \( l_i \) is the length of the \( i^{th} \) cycle in the Markov chain, and \( c \) is the total number of cycles.

A periodic Markov chain (i.e., \( p > 1 \)) does not converge for all \( m \).

Example:

\[
\begin{align*}
\pi(1) & = [1.0 \ 0.0 \ 0.0] \begin{pmatrix} 0.0 & 0.7 & 0.3 \\ 1.0 & 0.0 & 0.0 \\ 1.0 & 0.0 & 0.0 \end{pmatrix} \\
\pi(1) & = [0.0 \ 0.7 \ 0.3]
\end{align*}
\]
The period of an irreducible Markov chain is:

\[ p = \gcd(l_1, \ldots, l_i, \ldots, l_c) \]

where \( \gcd \) is the greatest common divisor, \( l_i \) is the length of the \( i^{th} \) cycle in the Markov chain, and \( c \) is the total number of cycles.

A periodic Markov chain (i.e., \( p > 1 \)) does not converge for all \( m \).

Example:

\[
\pi(2) = \begin{bmatrix} 0.0 & 0.7 & 0.3 \\ 1.0 & 0.0 & 0.0 \\ 1.0 & 0.0 & 0.0 \end{bmatrix}
\]

\[
\pi(2) = \begin{bmatrix} 0.0 \\ 0.0 \\ 0.0 \end{bmatrix}
\]
The period of a irreducible Markov chain is:

\[ p = \gcd(l_1, \ldots, l_i, \ldots, l_c) \]

where gcd is the greatest common divisor, \( l_i \) is the length of the \( i^{th} \) cycle in the Markov chain, and \( c \) is the total number of cycles.

A periodic Markov chain (i.e., \( p > 1 \)) does not converge for all \( m \).

Example:

\[
\begin{align*}
\pi(3) &= [1.0 \ 0.0 \ 0.0] \begin{pmatrix}
0.0 & 0.7 & 0.3 \\
1.0 & 0.0 & 0.0 \\
1.0 & 0.0 & 0.0
\end{pmatrix} \\
\pi(3) &= [0.0 \ 0.7 \ 0.3]
\end{align*}
\]
Periodicity: Simple Solution

- Check convergence only after each $p$ steps.
- When converged, combine steady state distributions from last $p$ steps.
- Normalize by $p$.
- Example:

$$
\pi = \frac{[1.0 \ 0.7 \ 0.3]}{2} = [0.5 \ 0.35 \ 0.15]
$$
Continuous-Time Markov Chains (CTMC)

- States can change at any arbitrary point in time.
- Specified using a *transition rate matrix* rather than a transition probability matrix which is defined as follows for a homogeneous CTMC:

\[
p_{ij}(\tau) = Pr[X(s + \tau) = j \mid X(s) = i]
\]

\[
q_{ij} = \lim_{\Delta t \to 0} \left\{ \frac{p_{ij}(\Delta t)}{\Delta t} \right\}, \text{ for } i \neq j
\]

\[
q_{ii} = -\sum_{j \neq i} q_{ij}
\]

- Example:

\[
Q = \begin{pmatrix}
-6 & 4 & 2 \\
4 & -4 & 0 \\
4 & 4 & -8
\end{pmatrix}
\]
Can find the steady-state distribution of a CTMC using its discrete-time *embedded Markov chain* (EMC).

\[
\pi = \frac{-\phi D_Q^{-1}}{\| \phi D_Q^{-1} \|_1}
\]

where \( \phi \) is steady-state distribution for the EMC, \( D_Q^{-1} \) is the inverse of the diagonal matrix of \( Q \), and \( \| \phi D_Q^{-1} \|_1 \) is the norm of the \( \phi D_Q^{-1} \) vector.

Probabilities for an EMC for \( Q \) are defined as follows:

\[
s_{ij} = \begin{cases} 
q_{ij} / \sum_{i \neq j} q_{ij}, & i \neq j \\
0, & i = j
\end{cases}
\]
Embedded Markov Chain Example

\[ Q = \begin{pmatrix}
-6 & 4 & 2 \\
4 & -4 & 0 \\
4 & 4 & -8
\end{pmatrix} \]
Embedded Markov Chain Example

\[ Q = \begin{pmatrix} -6 & 4 & 2 \\ 4 & -4 & 0 \\ 4 & 4 & -8 \end{pmatrix} \]

\[ S = \begin{pmatrix} 0 & 0.67 & 0.33 \\ 1 & 0 & 0 \\ 0.5 & 0.5 & 0 \end{pmatrix} \]
Embedded Markov Chain Example

\[ S = \begin{pmatrix}
0 & 0.67 & 0.33 \\
1 & 0 & 0 \\
0.5 & 0.5 & 0
\end{pmatrix} \]

\[ \phi = (0.46, 0.39, 0.15) \]
\[ Q = \begin{pmatrix} -6 & 4 & 2 \\ 4 & -4 & 0 \\ 4 & 4 & -8 \end{pmatrix} \]

\[ -D_Q^{-1} = \begin{pmatrix} 0.167 & 0 & 0 \\ 0 & 0.25 & 0 \\ 0 & 0 & 0.125 \end{pmatrix} \]
\[ \phi = (0.46, 0.39, 0.15) \]

\[ - D_Q^{-1} = \begin{pmatrix} 0.167 & 0 & 0 \\ 0 & 0.25 & 0 \\ 0 & 0 & 0.125 \end{pmatrix} \]

\[ - \phi D_Q^{-1} = (0.08, 0.1, 0.02) \]
Embedded Markov Chain Example

\[- \phi D_Q^{-1} = (0.08, 0.1, 0.02)\]

\[\| \phi D_Q^{-1} \|_1 = 0.2\]
\[- \phi \hat{Q}^{-1} = (0.08, 0.1, 0.02)\]

\[\| \phi \hat{Q}^{-1} \|_1 = 0.2\]

\[\pi = \frac{-\phi \hat{Q}^{-1}}{\| \phi \hat{Q}^{-1} \|_1} = (0.4, 0.5, 0.1)\]
Guarded Commands for CI

- Production of CI:

  \[ b_{CI} = 0 \land b_{CII} = 0 \xrightarrow{q_1} b_{CI} := 1 \]
  \[ q_1 = 10 \cdot f_3(0)/\theta_{CI}^1 \]

  \[ b_{CI} = 1 \land b_{CII} = 0 \xrightarrow{q_2} b_{CI} := 2 \]
  \[ q_2 = 10 \cdot f_3(0)/(\theta_{CI}^2 - \theta_{CI}^1) \]

  \[ b_{CI} = 0 \land b_{CII} = 1 \xrightarrow{q_3} b_{CI} := 1 \]
  \[ q_3 = 10 \cdot f_3(\theta_{CII}^1)/\theta_{CI}^1 \]

  \[ b_{CI} = 1 \land b_{CII} = 1 \xrightarrow{q_4} b_{CI} := 2 \]
  \[ q_4 = 10 \cdot f_3(\theta_{CII}^1)/(\theta_{CI}^2 - \theta_{CI}^1) \]

  \[ b_{CI} = 0 \land b_{CII} = 2 \xrightarrow{q_5} b_{CI} := 1 \]
  \[ q_5 = 10 \cdot f_3(\theta_{CII}^1)/\theta_{CI}^1 \]

  \[ b_{CI} = 1 \land b_{CII} = 2 \xrightarrow{q_6} b_{CI} := 2 \]
  \[ q_6 = 10 \cdot f_3(\theta_{CII}^2)/(\theta_{CI}^2 - \theta_{CI}^1) \]

  \[ b_{CI} = 0 \land b_{CII} = 3 \xrightarrow{q_7} b_{CI} := 1 \]
  \[ q_7 = 10 \cdot f_3(\theta_{CII}^3)/\theta_{CI}^1 \]

  \[ b_{CI} = 1 \land b_{CII} = 3 \xrightarrow{q_8} b_{CI} := 2 \]
  \[ q_8 = 10 \cdot f_3(\theta_{CII}^3)/(\theta_{CI}^2 - \theta_{CI}^1) \]

- Degradation of CI:

  \[ b_{CI} = 2 \xrightarrow{q_9} b_{CI} := 1 \]
  \[ q_9 = f_2(\theta_{CI}^2)/(\theta_{CI}^2 - \theta_{CI}^1) \]

  \[ b_{CI} = 1 \xrightarrow{q_{10}} b_{CI} := 0 \]
  \[ q_{10} = f_2(\theta_{CI}^1)/\theta_{CI}^1 \]
Reachable State Space

\[ \text{Cl, CII} \]

Diagram showing transitions between states:
- From Cl, CII to 00
- From 00 to 01 via q11
- From 00 to 10 via q10
- From 00 to 20 via q9
- From 00 to 03 via q22
- From 01 to 02 via q12
- From 01 to 11 via q21
- From 01 to 21 via q15
- From 01 to 03 via q6
- From 02 to 03 via q20
- From 02 to 12 via q10
- From 02 to 22 via q16
- From 02 to 03 via q8
- From 03 to 02 via q7
- From 03 to 13 via q10
- From 03 to 23 via q19
- From 10 to 11 via q10
- From 10 to 21 via q4
- From 10 to 13 via q14
- From 10 to 20 via q17
- From 11 to 12 via q10
- From 11 to 22 via q18
- From 11 to 13 via q9
- From 11 to 21 via q22
- From 11 to 13 via q22
- From 12 to 13 via q9
- From 12 to 23 via q19
- From 12 to 22 via q20
- From 13 to 10 via q14
- From 13 to 20 via q8
- From 13 to 21 via q22
CTMC Transition Rates

<table>
<thead>
<tr>
<th>State</th>
<th>Transition Rate</th>
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<tbody>
<tr>
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<td>0.13</td>
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<tr>
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<td>0.07</td>
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<td>0.0003</td>
</tr>
<tr>
<td>23</td>
<td>0.035</td>
</tr>
</tbody>
</table>
EMC Transition Probabilities

\[
\begin{array}{cccc}
10 & 11 & 12 & 13 \\
00 & 0.01 & 0.00004 & 0.08 & 0.99 \\
01 & 0.13 & 0.54 & 0.04 & 0.57 \\
02 & 0.02 & 0.06 & 0.75 & 0.93 \\
03 & 0.24 & 0.01 & 0.1 & 0.91 \\
20 & 0.01 & 0.00004 & 0.08 & 0.99 \\
21 & 0.13 & 0.54 & 0.04 & 0.57 \\
22 & 0.02 & 0.06 & 0.75 & 0.93 \\
23 & 0.24 & 0.01 & 0.1 & 0.91 \\
\end{array}
\]
State Probabilities

\[ n = 1 \]

\[ \text{CI, CII} \]

\begin{align*}
\text{0.00} & \quad 0.999999 \quad 0.08 \quad 0.000001 \quad 0.08 \quad 0.99 \quad 0.02 \quad 0.00 \quad 0.9 \quad 0.57 \quad 0.06 \quad 0.24 \quad 0.01 \quad 0.07 \\
\text{0.00} & \quad 0.08 \quad 0.000001 \quad 0.00 \quad 0.00 \quad 0.02 \quad 0.00 \quad 0.00 \quad 0.93 \quad 0.9 \quad 0.75 \quad 0.54 \quad 0.06 \quad 0.04 \quad 0.01 \\
\text{0.00} & \quad 0.13 \quad 0.99 \quad 0.00 \quad 0.00 \quad 0.02 \quad 0.00 \quad 0.00 \quad 0.99 \quad 0.01 \quad 0.05 \quad 0.3 \quad 0.06 \quad 0.04 \quad 0.08 \\
\text{0.00} & \quad 0.01 \quad 0.08 \quad 0.00 \quad 0.00 \quad 0.02 \quad 0.00 \quad 0.00 \quad 0.1 \quad 0.99 \quad 0.67 \quad 0.05 \quad 0.06 \quad 0.04 \quad 0.08 \\
\text{0.00} & \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \\
\end{align*}
State Probabilities

\[ n = 6 \]

The diagram shows a state transition model with probabilities for each state transition. The states are labeled as CI, CII, with the transition probabilities indicated by arrows between them. The probabilities are as follows:

- From CI to CII: 0.999999
- From CI to 0.00: 0.08
- From CII to CI: 0.99
- From CII to 0.20: 0.08
- From 0.00 to CI: 0.13
- From 0.00 to 0.20: 0.08
- From 0.20 to 0.00: 0.99
- From 0.20 to 0.04: 0.04
- From 0.04 to 0.00: 0.99
- From 0.04 to 0.02: 0.08
- From 0.02 to 0.00: 0.99
- From 0.02 to 0.04: 0.08
- From 0.04 to 0.00: 0.99
- From 0.00 to 0.04: 0.07
- From 0.00 to 0.01: 0.01
- From 0.01 to 0.00: 0.01
- From 0.01 to 0.08: 0.08
- From 0.08 to 0.00: 0.99
- From 0.08 to 0.04: 0.99
- From 0.04 to 0.00: 0.99
- From 0.04 to 0.02: 0.08
- From 0.02 to 0.00: 0.99
- From 0.02 to 0.04: 0.08
- From 0.04 to 0.00: 0.99
- From 0.04 to 0.01: 0.01
- From 0.01 to 0.00: 0.01
State Probabilities

\[ n = 7 \]

\[ \text{CI, CII} \]

\[
\begin{array}{cccc}
\text{CI} & \text{CII} \\
0.00 & 0.00 & 0.00 & 0.01 \\
0.03 & 0.37 & 0.33 & 0.00 \\
0.00 & 0.15 & 0.00 & 0.01 \\
0.00 & 0.00 & 0.00 & 0.01 \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{CI} & \text{CII} \\
0.00 & 0.99999 & 0.99 & 0.19 \\
0.08 & 0.02 & 0.06 & 0.24 \\
0.08 & 0.04 & 0.05 & 0.01 \\
0.08 & 0.04 & 0.05 & 0.01 \\
\end{array}
\]
State Probabilities

\[ n = 8 \]

\[ \begin{align*}
CI, CII & \\
0.03 & \quad 0.99999 & \quad 0.9 \\
0.00 & \quad 0.08 & \quad 0.02 \\
0.00 & \quad 0.00001 & \quad 0.57 \\
0.04 & \quad 0.01 & \quad 0.06 \\
0.00 & \quad 0.00004 & \quad 0.13 \\
0.00 & \quad 0.01 & \quad 0.75 \\
0.00 & \quad 0.08 & \quad 0.54 \\
0.00 & \quad 0.01 & \quad 0.54 \\
0.00 & \quad 0.08 & \quad 0.87 \\
0.00 & \quad 0.08 & \quad 0.87 \\
0.00 & \quad 0.00 & \quad 0.99 \\
0.00 & \quad 0.00 & \quad 0.99
\end{align*} \]
State Probabilities

\[
\begin{align*}
\text{CI, CII} & \quad 0.00 & \quad 0.31 & \quad 0.00 & \quad 0.09 \\
0.00 & \quad 0.08 & \quad 0.02 & \quad 0.01 \\
0.03 & \quad 0.99 & \quad 0.75 & \quad 0.1 \\
0.00 & \quad 0.08 & \quad 0.67 & \quad 0.08 \\
\end{align*}
\]

\[n = 9\]
State Probabilities

\[ n = 10 \]

\[
\begin{array}{c}
\text{Cl, CII} \\
0.02 \\
0.00 \\
0.00 \\
0.06 \\
0.00 \\
0.00 \\
0.00 \\
0.00 \\
0.04 \\
\end{array}
\]

Probabilities:

- \( \text{CI} \rightarrow \text{CI} \): 0.99999
- \( \text{Cl} \rightarrow \text{CI} \): 0.08
- \( \text{CI} \rightarrow \text{Cl} \): 0.08
- \( \text{Cl} \rightarrow \text{Cl} \): 0.99
- \( \text{CI} \rightarrow \text{CI} \): 0.00001
- \( \text{Cl} \rightarrow \text{Cl} \): 0.13
- \( \text{CI} \rightarrow \text{CI} \): 0.00004
- \( \text{Cl} \rightarrow \text{Cl} \): 0.01
- \( \text{CI} \rightarrow \text{CI} \): 0.01
- \( \text{Cl} \rightarrow \text{Cl} \): 0.25
- \( \text{CI} \rightarrow \text{Cl} \): 0.87
- \( \text{Cl} \rightarrow \text{Cl} \): 0.99

State Probabilities

\[ n = 13 \]
$n = 14$

The diagram illustrates the state probabilities for a system with $n = 14$. The state probabilities are given for each state, and the arrows indicate the transition probabilities between states. The diagram shows the transition probabilities as fractions, with arrows pointing from the current state to the next state, and the probability values are labeled on the arrows.
State Probabilities

\[ n = 15 \]
State Probabilities

\[ n = 18 \]
State Probabilities

\[ n = 19 \]

\[ CI, CII \]

\[
\begin{align*}
&0.00 & 0.99999 & 0.08 & 0.02 & 0.06 & 0.24 & 0.01 & 0.07 \\
&0.03 & 0.99 & 0.08 & 0.57 & 0.06 & 0.75 & 0.1 & 0.01 \\
&0.00 & 0.13 & 0.04 & 0.54 & 0.05 & 0.91 & 0.01 & 0.08 \\
&0.00 & 0.99 & 0.08 & 0.67 & 0.57 & 0.87 & 0.08 & 0.99 \\
&0.00 & 0.25 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\
&0.00 & 0.01 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\
&0.04 & 0.19 & 0.93 & 0.01 & 0.07 & 0.08 & 0.00 & 0.00 \\
\end{align*}
\]
State Probabilities

\[ n = 20 \]

\[
\begin{array}{cccc}
0.01 & 0.99999 & 0.00 & 0.19 \\
0.08 & 0.00 & 0.9 & 0.00 \\
0.00001 & 0.08 & 0.57 & 0.24 \\
0.00 & 0.02 & 0.06 & 0.01 \\
0.01 & 0.08 & 0.75 & 0.08 \\
0.00004 & 0.08 & 0.54 & 0.08 \\
0.01 & 0.004 & 0.00 & 0.01 \\
0.005 & 0.00 & 0.00 & 0.07 \\
0.12 & 0.99 & 0.08 & 0.03 \\
0.00 & 0.13 & 0.54 & 0.3 \\
0.00004 & 0.08 & 0.05 & 0.08 \\
0.25 & 0.67 & 0.87 & 0.99 \\
0.00 & 0.04 & 0.3 & 0.08 \\
\end{array}
\]
State Probabilities

\[ n = 21 \]

\[
\begin{array}{c}
\text{Cl,CI} \\
\text{0.00} \quad \text{0.14} \\
0.03 \quad 0.00 \quad 0.25 \\
0.01 \\
\end{array}
\]

\[
\begin{array}{c}
\text{0.04} \\
\text{0.00} \quad \text{0.00} \\
0.01 \quad 0.07 \\
\end{array}
\]

\[
\begin{array}{c}
\text{0.08} \\
0.08 \\
0.04 \\
\end{array}
\]

\[
\begin{array}{c}
0.99999 \\
0.99 \\
0.99 \\
\end{array}
\]

\[
\begin{array}{c}
0.08 \\
0.08 \\
0.08 \\
\end{array}
\]

\[
\begin{array}{c}
0.00001 \\
0.00004 \\
0.00004 \\
\end{array}
\]

\[
\begin{array}{c}
0.02 \\
0.04 \\
0.04 \\
\end{array}
\]

\[
\begin{array}{c}
0.57 \\
0.54 \\
0.54 \\
\end{array}
\]

\[
\begin{array}{c}
0.06 \\
0.05 \\
0.05 \\
\end{array}
\]

\[
\begin{array}{c}
0.24 \\
0.3 \\
0.3 \\
\end{array}
\]

\[
\begin{array}{c}
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0.91 \\
0.91 \\
\end{array}
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\[
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0.1 \\
0.1 \\
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0.01 \\
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State Probabilities

\[ n = 23 \]

\[ \text{Ci,Cii} \]

\begin{align*}
0.00 & \xrightarrow{0.08} 0.00 \\
0.00 & \xrightarrow{0.02} 0.00 \\
0.00 & \xrightarrow{0.06} 0.00 \\
0.00 & \xrightarrow{0.24} 0.00 \\
0.00 & \xrightarrow{0.54} 0.00 \\
0.00 & \xrightarrow{0.3} 0.00 \\
0.00 & \xrightarrow{0.01} 0.00 \\
0.00 & \xrightarrow{0.08} 0.00 \\
\end{align*}

\begin{align*}
0.03 & \xrightarrow{0.99} 0.13 \\
0.13 & \xrightarrow{0.08} 0.00 \\
0.00 & \xrightarrow{0.75} 0.24 \\
0.24 & \xrightarrow{0.91} 0.00 \\
0.04 & \xrightarrow{0.67} 0.53 \\
0.53 & \xrightarrow{0.87} 0.00 \\
0.00 & \xrightarrow{0.99} 0.04 \\
\end{align*}
State Probabilities

\[ n = 24 \]

\[ 0.01 \quad 0.00 \quad 0.16 \quad 0.00 \]

\[ 0.00 \quad 0.21 \quad 0.00 \quad 0.03 \]

\[ 0.13 \quad 0.00 \quad 0.47 \quad 0.00 \]

\[ 0.00 \quad 0.00 \quad 0.00 \quad 0.00 \]

\[ 0.99999 \quad 0.9 \quad 0.19 \quad 0.005 \]

\[ 0.08 \quad 0.57 \quad 0.24 \quad 0.005 \]

\[ 0.00001 \quad 0.02 \quad 0.06 \quad 0.01 \]

\[ 0.08 \quad 0.75 \quad 0.24 \quad 0.01 \]

\[ 0.00004 \quad 0.04 \quad 0.05 \quad 0.01 \]

\[ 0.08 \quad 0.67 \quad 0.08 \quad 0.08 \]

\[ 0.25 \quad 0.54 \quad 0.87 \quad 0.99 \]

\[ 0.01 \quad 0.91 \quad 0.99 \quad 0.00 \]
State Probabilities

\[ n = 25 \]

\[ \text{Cl, CII} \]

\[ 0.00 \]

\[ 0.03 \]

\[ 0.01 \]

\[ 0.00 \]

\[ 0.00 \]

\[ 0.11 \]

\[ 0.02 \]

\[ 0.08 \]

\[ 0.99999 \]

\[ 0.08 \]

\[ 0.99 \]

\[ 0.08 \]

\[ 0.00 \]

\[ 0.06 \]

\[ 0.02 \]

\[ 0.00001 \]

\[ 0.01 \]

\[ 0.13 \]

\[ 0.08 \]

\[ 0.00 \]

\[ 0.75 \]

\[ 0.57 \]

\[ 0.19 \]

\[ 0.93 \]

\[ 0.24 \]

\[ 0.07 \]

\[ 0.00 \]

\[ 0.00 \]

\[ 0.00 \]

\[ 0.04 \]

\[ 0.04 \]

\[ 0.08 \]

\[ 0.08 \]

\[ 0.00 \]

\[ 0.87 \]

\[ 0.67 \]

\[ 0.1 \]

\[ 0.91 \]

\[ 0.91 \]

\[ 0.01 \]

\[ 0.01 \]

\[ 0.08 \]

\[ 0.08 \]

\[ 0.04 \]
State Probabilities

\[ n = 26 \]

\[ C_1, C_{II} \]

\[
\begin{align*}
C_1 &\rightarrow 0.01, & 0.99999, & 0.08, & 0.00, & 0.9, & 0.19, & 0.00, \\
0.00 &\rightarrow 0.00, & 0.02, & 0.57, & 0.06, & 0.24, & 0.01, & 0.03, \\
0.14 &\rightarrow 0.14, & 0.01, & 0.00004, & 0.08, & 0.04, & 0.54, & 0.3, \\
0.00 &\rightarrow 0.00, & 0.00001, & 0.08, & 0.05, & 0.87, & 0.08, & 0.00, \\
0.01 &\rightarrow 0.00, & 0.08, & 0.08, & 0.00, & 0.00, & 0.08, & 0.00.
\end{align*}
\]
State Probabilities

\[ n = 27 \]

The diagram illustrates state transitions with probabilities labeled on the arrows. For example, the transition from state 0.00 to state 0.03 has a probability of 0.99999. Each state is labeled with a probability, and the diagram shows the probability of transitioning from one state to another. The diagram is labeled with "CI, CII" at the top left, indicating the context or variable in the study.
State Probabilities

\[ n = 28 \]

\[ \text{CI, CII} \]

- \( 0.01 \) to \( 0.00 \) with probability \( 0.99999 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.9 \)
- \( 0.14 \) to \( 0.00 \) with probability \( 0.19 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.93 \)
- \( 0.03 \) to \( 0.00 \) with probability \( 0.91 \)
- \( 0.14 \) to \( 0.20 \) with probability \( 0.75 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.57 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.06 \)
- \( 0.48 \) to \( 0.00 \) with probability \( 0.87 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.3 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.01 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.08 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.99 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.99 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.99 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.01 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.08 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.99 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.99 \)
- \( 0.00 \) to \( 0.00 \) with probability \( 0.99 \)
State Probabilities

\[ n = 29 \]

\[ \text{CI}, \text{CII} \]

\[
\begin{array}{cccccc}
0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\
0.03 & 0.10 & 0.23 & 0.00 & 0.00 & 0.04 \\
0.00 & 0.57 & 0.00 & 0.00 & 0.00 & 0.00 \\
0.00 & 0.00 & 0.24 & 0.00 & 0.00 & 0.00 \\
0.00 & 0.00 & 0.01 & 0.00 & 0.00 & 0.00 \\
0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\
\end{array}
\]

Transitions:

- CI to CI: 0.999999
- CI to CII: 0.08
- CII to CI: 0.00001
- CII to CII: 0.08

- CI to CI: 0.99
- CI to CII: 0.13
- CII to CI: 0.01
- CII to CII: 0.01

- CI to CI: 0.99
- CI to CII: 0.25
- CII to CI: 0.25
- CII to CII: 0.25

- CI to CI: 0.75
- CI to CII: 0.54
- CII to CI: 0.54
- CII to CII: 0.54

- CI to CI: 0.67
- CI to CII: 0.87
- CII to CI: 0.87
- CII to CII: 0.87

- CI to CI: 0.08
- CI to CII: 0.99
- CII to CI: 0.99
- CII to CII: 0.99
State Probabilities

\[ n = 30 \]

\[ CI, CIi \]

\[
\begin{align*}
CI &\quad 0.01 &\quad 0.00 &\quad 0.13 &\quad 0.00 \\
CII &\quad 0.00 &\quad 0.20 &\quad 0.00 &\quad 0.03 \\
\end{align*}
\]

Transitions:

- From CI to CII with probability 0.08
- From CI to CI with probability 0.99
- From CII to CI with probability 0.13
- From CII to CII with probability 0.99

Probabilities:

- CI: 0.01
- CII: 0.99

Transition Probabilities:
State Probabilities

\[ n = 31 \]

\[ CI, CII \]

\[ 0.00 \quad 0.99999 \quad 0.08 \quad 0.02 \quad 0.57 \quad 0.06 \quad 0.24 \quad 0.01 \quad 0.07 \]

\[ 0.03 \quad 0.13 \quad 0.08 \quad 0.04 \quad 0.75 \quad 0.54 \quad 0.3 \quad 0.01 \quad 0.08 \]

\[ 0.00 \quad 0.19 \quad 0.24 \quad 0.3 \quad 0.08 \quad 0.99 \quad 0.91 \quad 0.01 \quad 0.08 \]

\[ 0.03 \]
Steady-State Distribution of the EMC

Chris J. Myers  (Lecture 6: Abstraction)  Engineering Genetic Circuits
Steady-State Distribution of the CTMC

Chris J. Myers  (Lecture 6: Abstraction)  Engineering Genetic Circuits
Fraction of Lysogens vs. API

- Estimated Fraction of Lysogens
- Average Phage Input (API)

- Stochastic Asynchronous Circuit (starved)
- O- Experimental (starved)
- P- Experimental (starved)
Fraction of Lysogens vs. API

Stochastic FSM results generated in only 7 minutes.
Fraction of Lysogens vs. API

Stochastic FSM results generated in only 7 minutes.
Models typically require the estimation of binding affinities and kinetic parameters which are often difficult to obtain for genetic circuits.

Systems, however, are often quite robust to parameter variation.

May be possible to make reasonable behavioral predictions with only qualitative information.

A **qualitative logical model** is similar to the stochastic FSM model except that no rate parameters are provided.

Note that while a stochastic FSM may potentially enter any state, it would not be informative if a qualitative logical model also could reach any state.

Qualitative logical models only describe the most likely states and state transitions.
Qualitative logical model for the CI/CII portion of the phage $\lambda$:

\[
\begin{align*}
    b_{CII} &:= (b_{CI} = 0) \\
    b_{CI} &:= (b_{CII} = 1)
\end{align*}
\]

where CI and CII are binary encoded variables.

In order to analyze a qualitative logical model, one first finds all reachable states using a depth first search assuming some initial state.
State Graph for the CI/CII Portion of the Phage λ Model

Note that this represents only the most likely scenario as it is potentially possible that through basal production of CI, that it goes to a high concentration before CII increases.
The full phage λ decision circuit can be represented logically as follows:

- \( b_N \) := \((b_{CI} \neq 2) \land (b_{Cro} = 0)\)
- \( b_{CIII} \) := \((b_N = 1) \land (b_{CI} \neq 2) \land (b_{Cro} = 0)\)
- \( b_{CII} \) := \((b_N = 1) \land (b_{CIII} = 1) \land (b_{CI} \neq 2) \land (b_{Cro} = 0)\)
- \( b_{CI} \) := \(((b_{CII} = 1) \land (b_{CI} = 0)) + 2(b_{CI} \neq 0)) \land (b_{Cro} = 0)\)
- \( b_{Cro} \) := \((b_{CI} \neq 2)\)

where \( N, CII, CIII, \) and \( Cro \) are binary and \( CI \) is a ternary variable.
Partial State Graph for the Complete Phage λ Model
Sources

- Relation of electrical and biochemical circuits:

- Piecewise models:
  - Hybrid Petri nets - Matsuno et al. (2000) and Little et al. (2006).

- Stochastic FSMs:

- Markov Chains:
  - Stewart (1994).

- Qualitative logical models:
  - Qualitative differential equations - DeJong et al. (2001).