# *Programming* Biological Time Machines: Lecture I[1]

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[1]Based on: Kocuk, B. (2022). Optimization problems involving matrix multiplication with applications in materials science and biology. Engineering Optimization, 54(5), 786-804.

# Disclaimer

- I am, by no means, a "biology guy". In fact, biology was my least favorite topic in high school!
- I will explain the problem the way I understand it, that is, from an operations research/optimization point of view.
- I concur that the mathematics in this presentation is not very deep but it combines a few tricks nicely to solve an interesting problem.

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- Can you give an upper bound on the number of ways you can organize your knapsack?
- What are the best items to select?
- Do you think this is an *easy* problem or a *hard* problem to solve if we have *many* items?

# A Motivating Example: Knapsack Problem

- Here is some notation (*parameters* of the problem):
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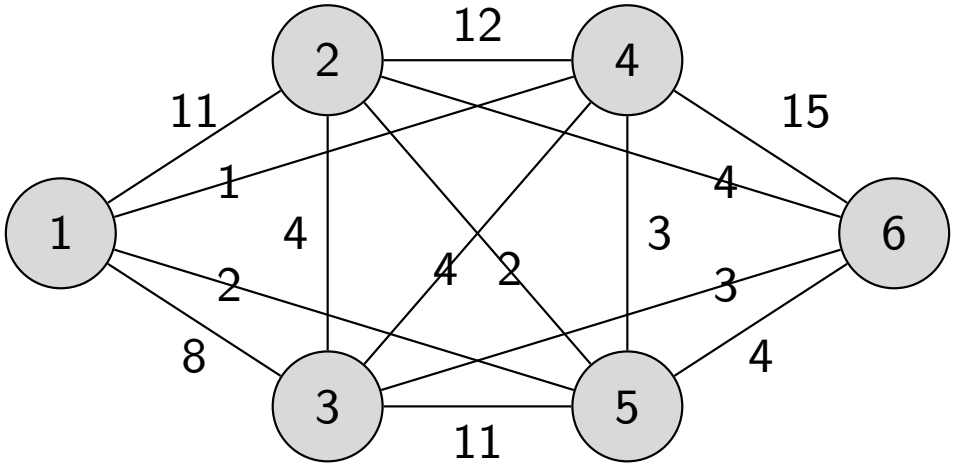
- There are efficient and general-purpose solvers for *this kind* of problems!

# Two More Motivating Examples



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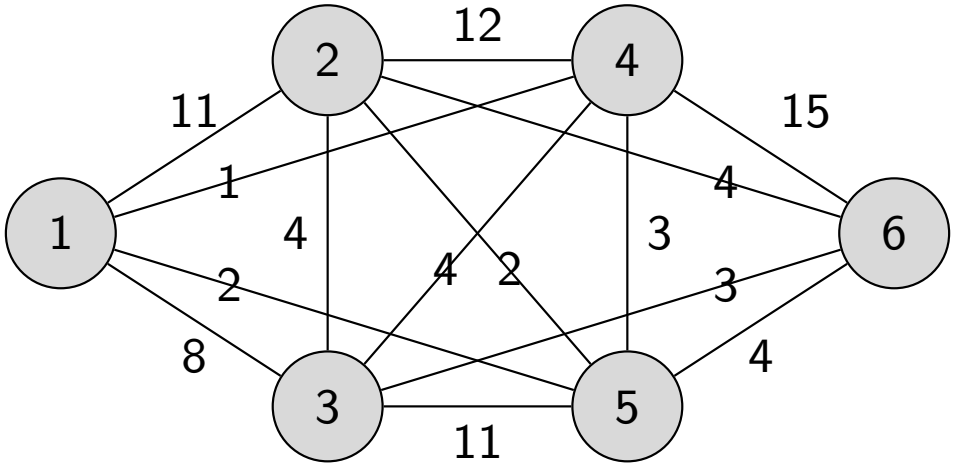


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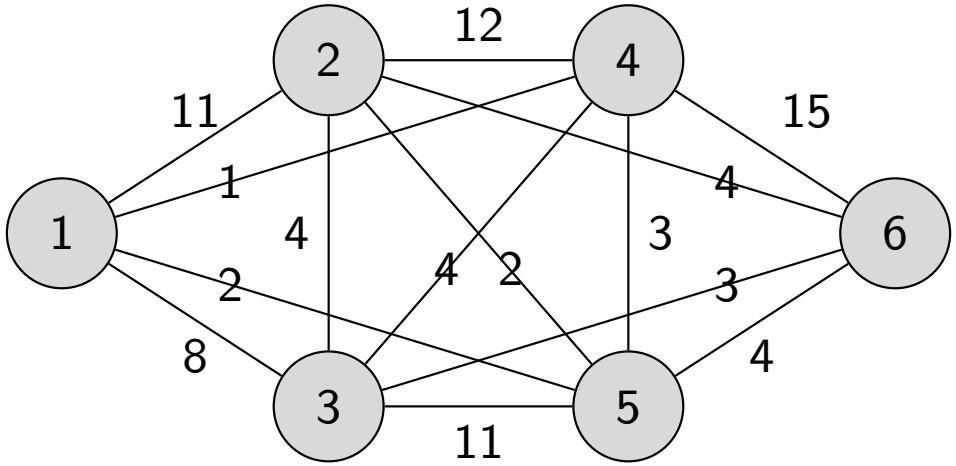


- Shortest Path Problem: Given a network, a source and a sink, find the shortest path.
  - Easy in theory (polynomially solvable) and also in practice.
- Traveling Salesperson Problem: Given a network, find the shortest tour that visits all the nodes exactly once.
  - Difficult in theory (NP-Hard) but large instances (tens of thousand of nodes) can be solved optimally.

# What is Optimization/Mathematical Programming?

George B. Dantzig: "If the system exhibits a structure which can be represented by a mathematical equivalent, called a mathematical model, and if the objective can be also so quantified, then some computational method may be evolved for choosing the best schedule of actions among alternatives. Such use of mathematical models is termed mathematical programming."

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A generic optimization problem looks like this:

$$\begin{aligned} \min_x \ & f(x) && && \text{(objective function)} \\ \text{s.t. } & g_i(x) \leq 0 && i = 1, \ldots, m && \text{(inequality constraints)} \\ & h_l(x) = 0 && l = 1, \ldots, k && \text{(equality constraints)} \\ & x \in \mathbb{R}^{n_1} \times \mathbb{Z}^{n_2}. && && \text{(decision variable domain)} \end{aligned}$$

Here, the functions $f$, $g_i$, $h_l$ are real-valued and well-defined.

# Solving an Optimization Problem

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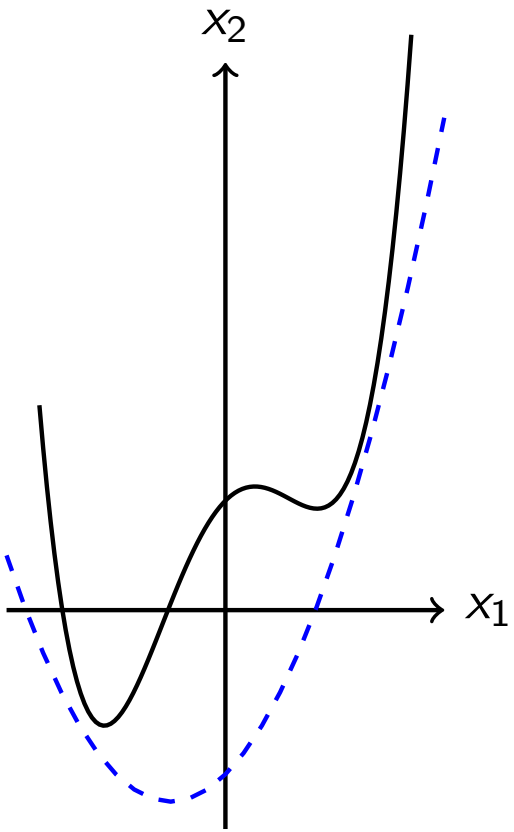
- Solving an optimization problem means finding an optimal solution (and proving its optimality).
- An engineer might be satisfied with a feasible solution that "looks good".
  - Domain knowledge, local solvers, discretization, heuristics,...
- An optimizer would not be completely satisfied without a certificate of (near-) optimality.
  - Relaxation, convexification, (spatial) branch-and-bound, cutting planes,...

# The Concept of Relaxation

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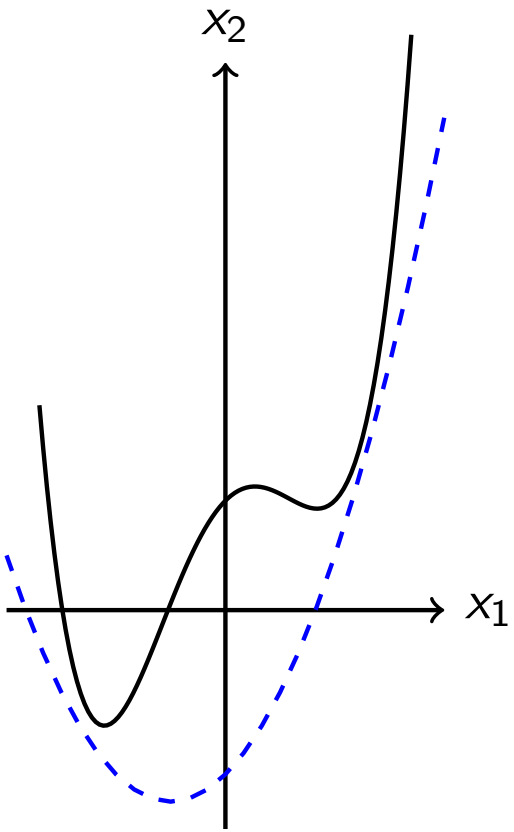


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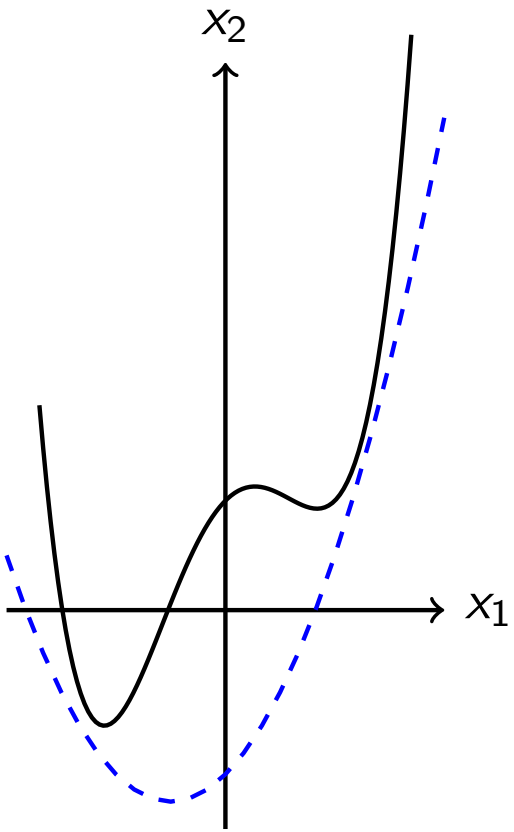


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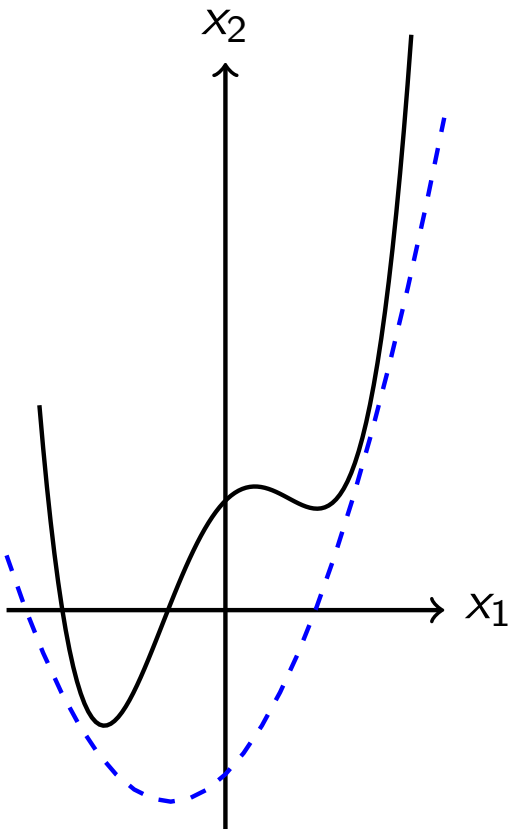


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- We can divide the domain into subdomains and obtain a global optimization algorithm.
- Relaxations allow us to prove (near-) optimality WITHOUT exploring all solutions!

# When is an Optimizer Happy/Hopeful?

- Recall the problem

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- Relevance to Time Machines: The static-deterministic version can be formulated as an MILP!

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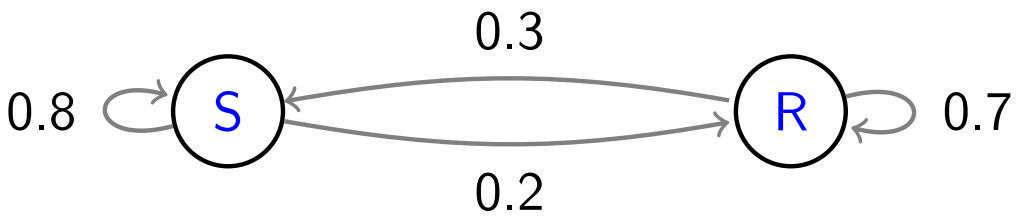

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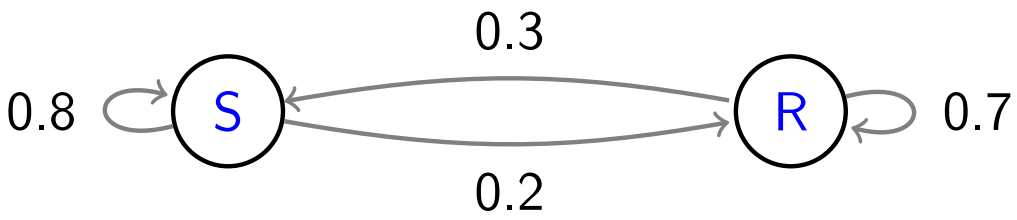


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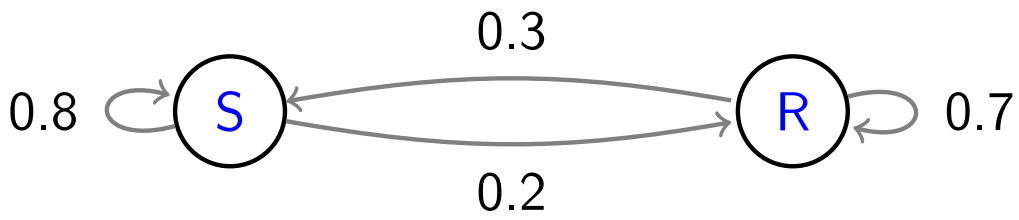


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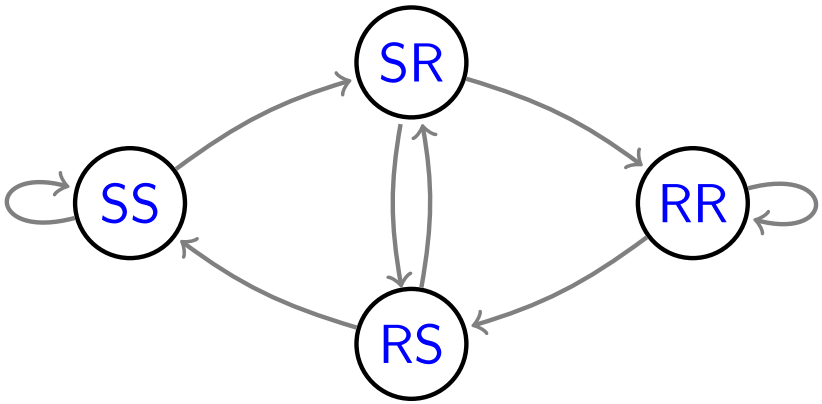
- A possible transition diagram looks like this:



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- Given an initial state of a Markov chain, one might be interested in questions of the following sort:
  - What is the probability of being in a certain state after a specified number of transitions?
  - What is the probability of being in a certain state on the long run?
  - What is the probability of being "absorbed" in a certain state eventually?

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  - What is the probability of being in a certain state on the long run?
  - What is the probability of being "absorbed" in a certain state eventually?
- Relevance to Time Machines: Transition from one genotype to another under the effect of an antibiotic is modelled as a DTMC!

# Outline

# Antibiotics Time Machine

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- *Antibiotics Time Machine* is an important problem to understand this issue and how it can be reversed.
- **Idea**: Apply known antibiotics in a way that the resistance can be reversed *so we go back in time*.
  - Mira et al. (2015, 2017); Nichol et al. (2018, 2019); Maltas et al. (2019, 2021, 2023); Aulin et al. (2021); Batra et al. (2021); ...

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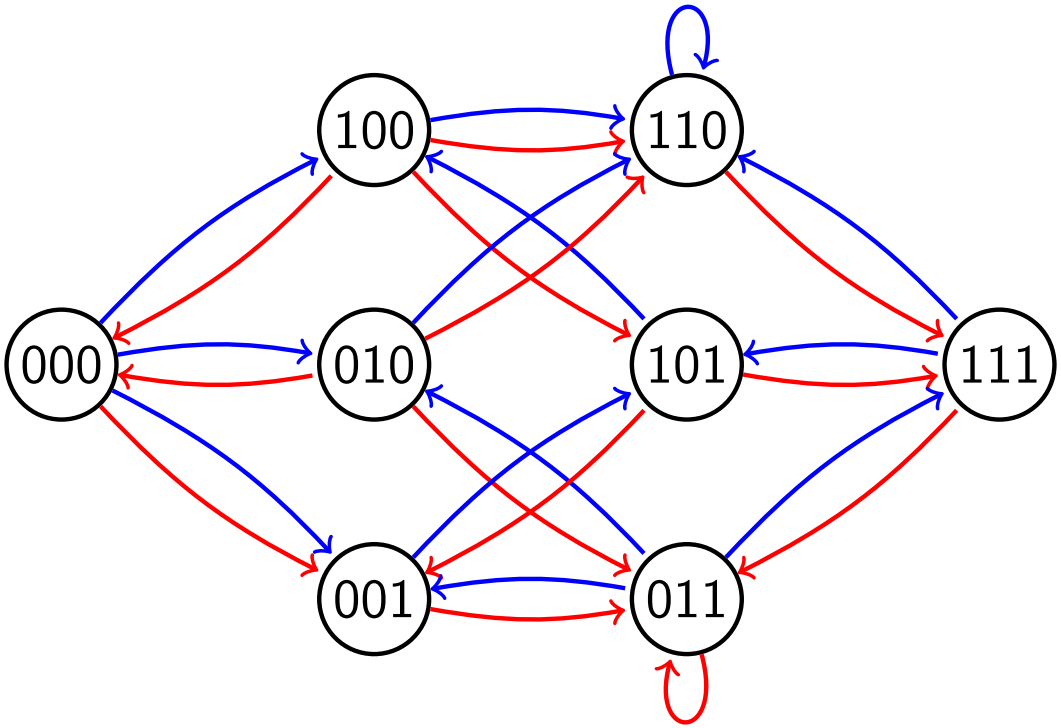
  - Suppose, for now, that $\boldsymbol{M^k}$ matrices are certain.
- The aim is to maximize the probability of going from a certain state to the wild type in $N$ steps using any sequence of $K$ drugs.
  - Suppose, for now, that the sequence should be determined at the beginning.

# An Example with $a = 3$ and $K = 2$ Drugs

- Think of each color (Red and Blue) as a different antibiotic/drug.
- Observe that a single drug is not enough to go from state 111 to state 000.
- If $N = 3$ steps are allowed, administering Blue, Blue, Red or Red, Blue, Red gives a positive probability of going from 111 to 000.



# Problem Definition: *Static Deterministic* Version

- Let $\boldsymbol{p} \in \mathbb{R}^d$ ($\boldsymbol{q} \in \mathbb{R}^d$) be the given initial (desired) probability distribution vectors.
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- This version is *static* since the antibiotic sequence is decided at the beginning (out of $K^N$ possible such sequences).

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- Recently, a mixed-integer linear programming (MILP) formulation was proposed (Kocuk, 2022), which outperforms complete enumeration (as expected).

# Outline

# An Example with $a = 2$, $K = 2$ and $N = 2$ (initial $= 11$)

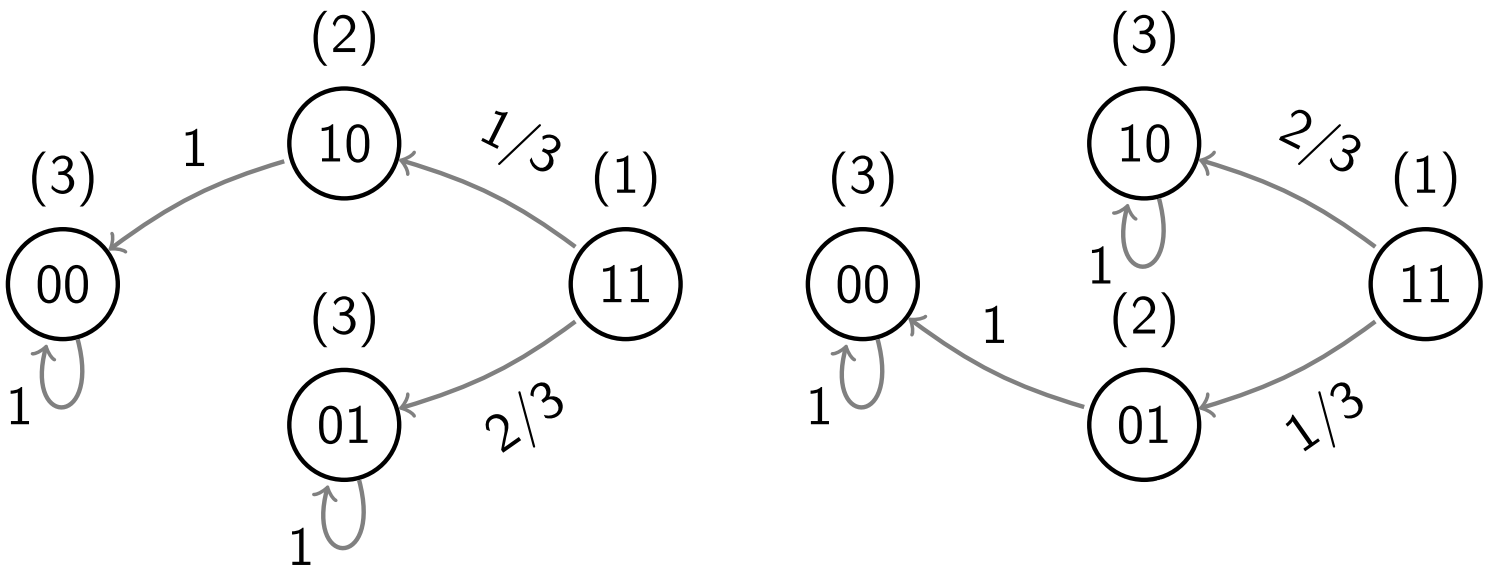


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Figure: Markov chains corresponding to two antibiotics.

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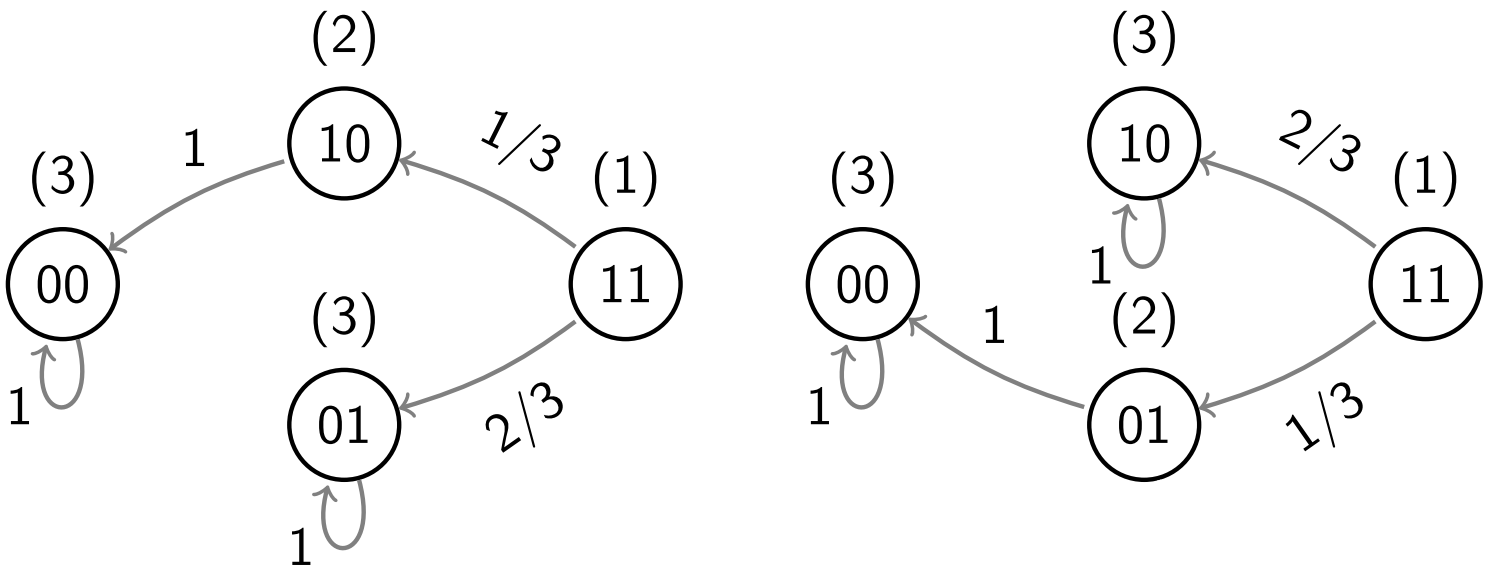


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Figure: Markov chains corresponding to two antibiotics.

*Static*: 4 possible sequences
Optimal Value: 2/3
Optimal Sequence: I-II or II-I

# Problem Definition

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Given $K$ antibiotics with their transition probability matrices $\boldsymbol{M^k}$, $k = 1, \ldots, K$, the length of the treatment plan $N$ and the initial distribution $\boldsymbol{p}$, determine a *sequence* of antibiotics to be applied so that the probability of reaching the desired final distribution $\boldsymbol{q}$ is maximized.

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- We compute the transition probabilities as a function of the measured **growth rates** $\boldsymbol{\omega} \in \mathbb{R}_{+}^{d}$ of genotypes under each antibiotic (Mira et al., 2015).

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- For a pair of neighbors $(j, j') \in J$ for antibiotic $k$, the transition probability from genotype $j$ to genotype $j'$ is

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- Following Mira et al. (2015), we consider two models regarding how the precise transition probabilities are computed.

# Transition Probability Matrix Computation

- Correlated Probability Model (CPM): In this model, the elements of the transition probability matrix are computed as

$$C_{j,j'}(\boldsymbol{\omega}) := \frac{\max\{0, \omega_{j'} - \omega_j\}}{\sum_{j'':(j'',j)\in J} \max\{0, \omega_{j''} - \omega_j\}}, \quad (j, j') \in J.$$

- Equal Probability Model (EPM): In this model, the elements of the transition probability matrix are computed as

$$E_{j,j'}(\boldsymbol{\omega}) := \frac{\mathbf{1}(\omega_{j'} > \omega_j)}{\sum_{j'':(j'',j)\in J} \mathbf{1}(\omega_{j''} > \omega_j)}, \quad (j, j') \in J.$$

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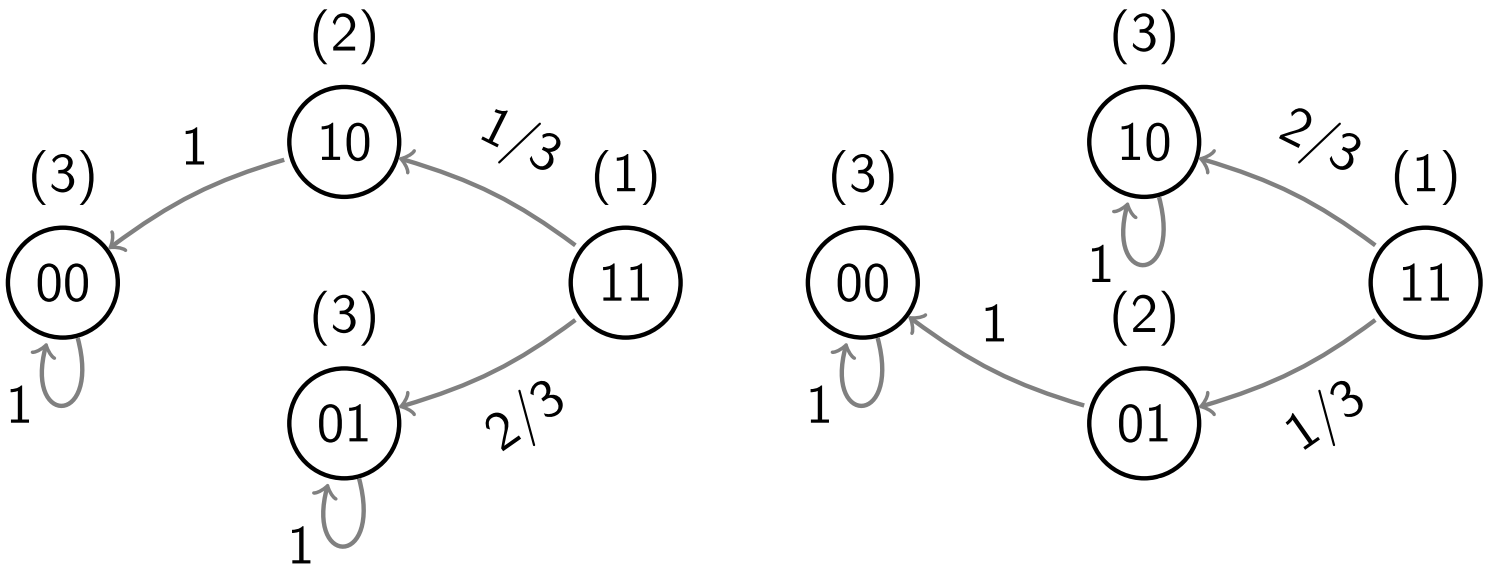
For each antibiotic $k$, we will denote its growth rate vector as $\boldsymbol{\omega}^{\boldsymbol{k}}$, and set the probability transition matrix $\boldsymbol{M}^{\boldsymbol{k}} = \boldsymbol{C}(\boldsymbol{\omega}^{\boldsymbol{k}})$ if CPM is used and $\boldsymbol{M}^{\boldsymbol{k}} = \boldsymbol{E}(\boldsymbol{\omega}^{\boldsymbol{k}})$ if EPM is used.

# Transition Probability Matrix Computation

In this example with $a = 2$ and $K = 2$, the CPM is used to compute the transition probabilities (the numbers near nodes are the growth rates).

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**Problem (Static Deterministic Version)**

Given $K$ antibiotics with their transition probability matrices $\boldsymbol{M^k}$, $k = 1, \ldots, K$, the length of the treatment plan $N$ and the initial distribution $\boldsymbol{p}$, determine a *sequence* of antibiotics to be applied so that the probability of reaching the desired final distribution $\boldsymbol{q}$ is maximized.

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Nonlinear Formulation:

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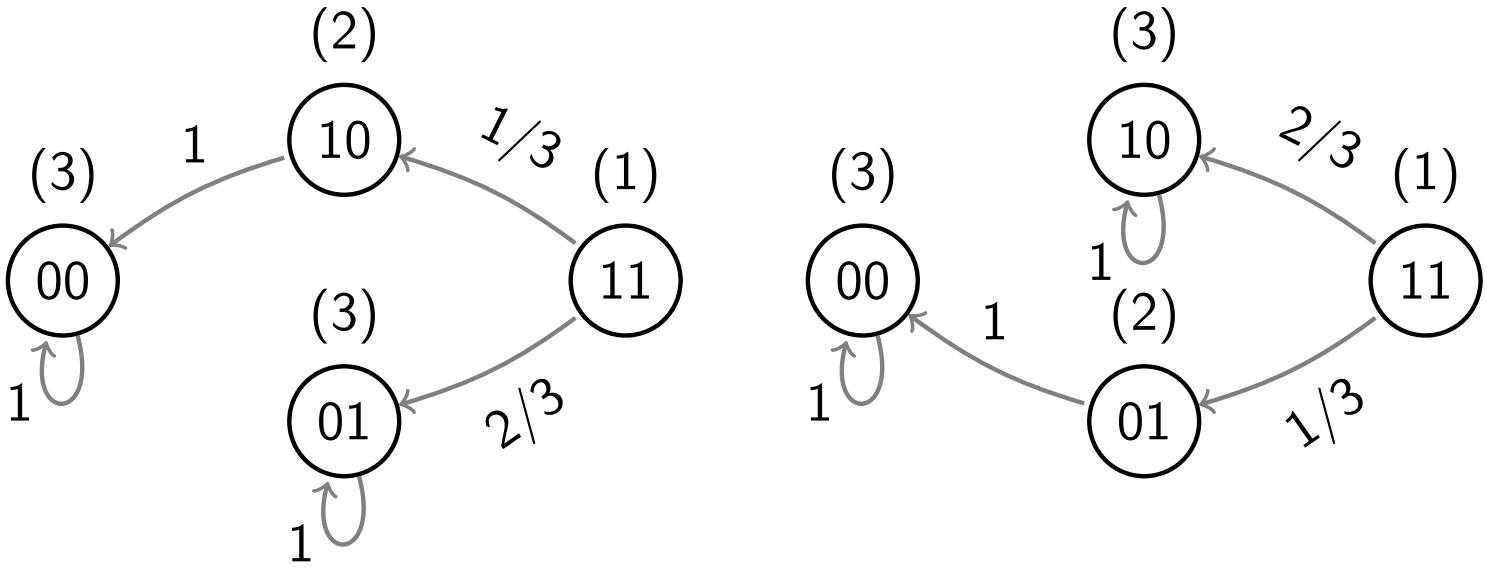

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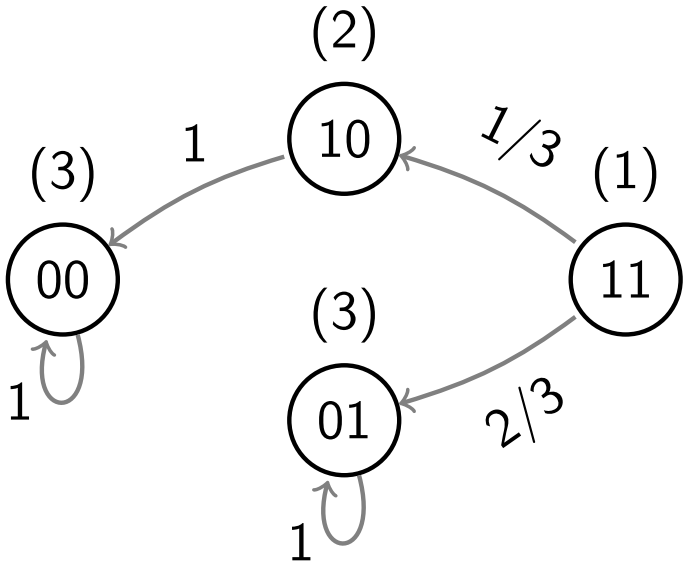


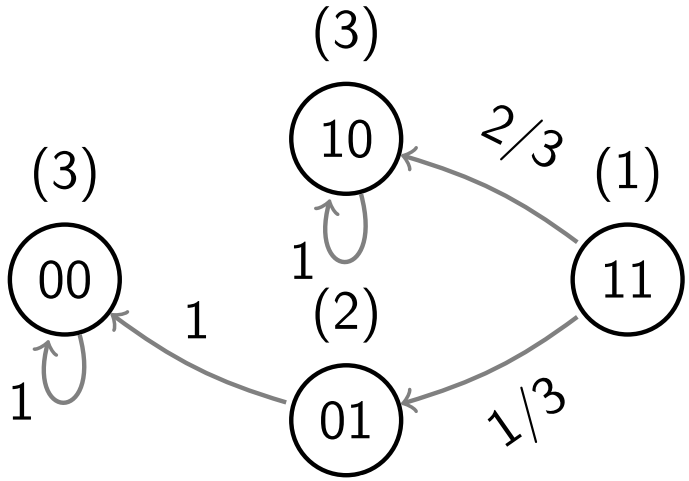


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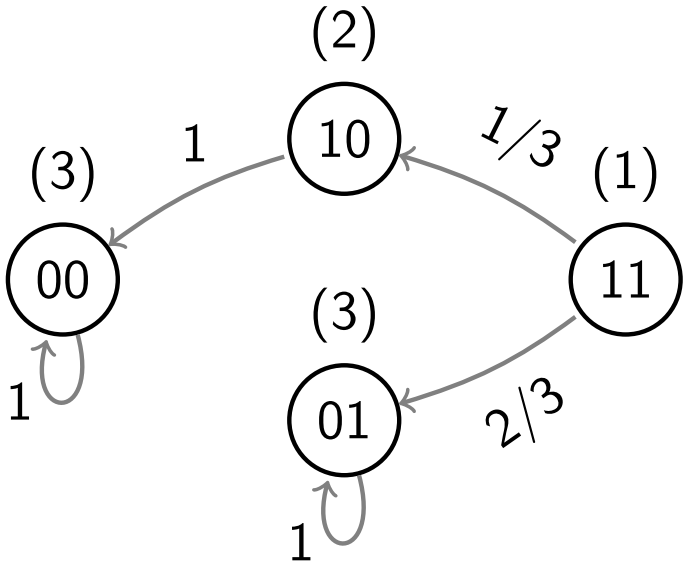


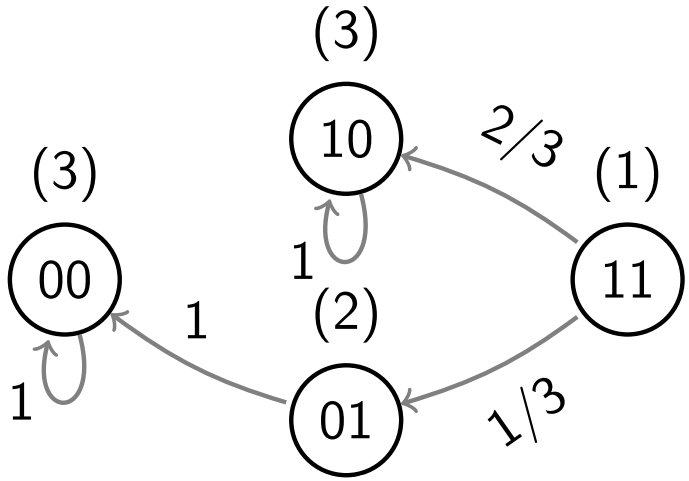


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$$\textbf{SOLVE} \ \max \left\{ \boldsymbol{p}^{\top} \left( \boldsymbol{T}_1 \boldsymbol{T}_2 \right) \boldsymbol{q} : \boldsymbol{T}_1, \boldsymbol{T}_2 \in \{ M^{\mathrm{I}}, M^{\mathrm{II}} \} \right\},$$

where $\boldsymbol{p}^{\top} = \begin{array}{c} \begin{array}{cccc} 00 & 10 & 01 & 11 \end{array} \\ \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$ and $\boldsymbol{q}^{\top} = \begin{array}{c} \begin{array}{cccc} 00 & 10 & 01 & 11 \end{array} \\ \begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix} \end{array}$.

# Static Optimization: MILP Formulation (Kocuk, 2022)

- The key idea is to define two sets of decisions variables:
  - $x_{n,k}$: one if antibiotic $k$ is applied in step $n$ and zero otherwise
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- This relation is linearized using a disjunctive formulation by defining copy variables $\boldsymbol{v_{n,k}} \in \mathbb{R}^d_+$, which take value $\boldsymbol{u_{n-1}}$ if $x_{n,k} = 1$.

# Static Optimization: MILP Formulation

Let $\boldsymbol{e}$ be the vector of ones.

$$\max_{\boldsymbol{u},\boldsymbol{v},\boldsymbol{x}} \boldsymbol{q}^\top \boldsymbol{u_N} \qquad \text{(maximize probability)}$$

$$\text{s.t. } \boldsymbol{u_0} = \boldsymbol{p} \qquad \text{(initial condition)}$$

$$\sum_{k=1}^{K} \boldsymbol{v_{n-1,k}} = \boldsymbol{u_{n-1}} \qquad \forall n \qquad \text{(disjunction-1)}$$

$$\sum_{k=1}^{K} \boldsymbol{v_{n-1,k}}^\top \boldsymbol{M^k} = \boldsymbol{u_n}^\top \qquad \forall n \qquad \text{(disjunction-2)}$$

$$\boldsymbol{e}^\top \boldsymbol{v_{n-1,k}} = x_{n,k} \qquad \forall n, k \qquad \text{(disjunction-3)}$$

$$\sum_{k=1}^{K} x_{n,k} = 1 \qquad \forall n \qquad \text{(one drug/step)}$$

$$\boldsymbol{v_{n-1,k}} \in \mathbb{R}^d_+, \boldsymbol{u_n} \in \mathbb{R}^d_+, \; x_{n,k} \in \{0,1\} \qquad \forall n, k \qquad \text{(domains)}$$

"Proposition": For each $n$, our extended (disjunctive) formulation gives the convex hull of the recursive relation.

# Outline

# Computational Setting

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- We utilize Gurobi 9 to solve the MILPs with the default settings (except the absolute optimality gap parameter is set to 0.001).

# EPM Results

| Initial | $N=4$ | $N=5$ | $N=6$ | $N=7$ | $N=8$ | $N=9$ | $N=12$ | $N=15$ |
|---|---|---|---|---|---|---|---|---|
| **1000** | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| **0100** | 0.375 | 0.458 | 0.458 | 0.463 | 0.463 | 0.471 | 0.515 | 0.520 |
| **0010** | 0.500 | 0.500 | 0.500 | 0.512 | 0.512 | 0.515 | 0.520 | 0.532 |
| **0001** | 0.667 | 0.667 | 0.667 | 0.690 | 0.690 | 0.693 | 0.696 | 0.704 |
| **1100** | 0.389 | 0.389 | 0.458 | 0.458 | 0.463 | 0.463 | 0.479 | 0.520 |
| **1010** | 0.583 | 0.583 | 0.587 | 0.587 | 0.591 | 0.591 | 0.601 | 0.606 |
| **1001** | 0.667 | 0.667 | 0.690 | 0.690 | 0.693 | 0.693 | 0.700 | 0.704 |
| **0110** | 0.333 | 0.375 | 0.458 | 0.458 | 0.463 | 0.463 | 0.479 | 0.520 |
| **0101** | 0.458 | 0.458 | 0.463 | 0.463 | 0.471 | 0.479 | 0.515 | 0.526 |
| **0011** | 0.500 | 0.500 | 0.500 | 0.502 | 0.531 | 0.539 | 0.557 | 0.562 |
| **1110** | 0.333 | 0.333 | 0.375 | 0.458 | 0.458 | 0.463 | 0.479 | 0.515 |
| **1101** | 0.375 | 0.458 | 0.458 | 0.463 | 0.463 | 0.471 | 0.515 | 0.520 |
| **1011** | 0.333 | 0.389 | 0.417 | 0.458 | 0.458 | 0.475 | 0.481 | 0.515 |
| **0111** | 0.198 | 0.333 | 0.375 | 0.458 | 0.458 | 0.463 | 0.479 | 0.515 |
| **1111** | 0.333 | 0.375 | 0.458 | 0.458 | 0.463 | 0.463 | 0.479 | 0.520 |
| MILP(s) | 0.14 | 0.25 | 0.42 | 0.6 | 0.96 | 1.96 | 14.96 | 165.86 |
| BBNode | 4 | 43 | 168 | 448 | 1002 | 2380 | 22676 | 125473 |
| Enum(s) | 0.94 | 16.46 | 273.02 | $4 \cdot 10^3$ | $6 \cdot 10^4$ | $9 \cdot 10^5$ | $3 \cdot 10^9$ | $1 \cdot 10^{13}$ |

- Probabilities of going from initial state to wild type (0000) are reported.
- MILP (sec): Avg. CPU time of Gurobi (absolute opt. gap is set to 0.001).
- Enum (sec): Avg. (serial) time of the enumeration (estimated for $N > 6$).

# CPM Results

| Initial | $N = 4$ | $N = 5$ | $N = 6$ | $N = 7$ | $N = 8$ | $N = 9$ | $N = 12$ | $N = 15$ |
|---|---|---|---|---|---|---|---|---|
| **1000** | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| **0100** | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| **0010** | 0.715 | 0.715 | 0.715 | 0.715 | 0.715 | 0.715 | 0.715 | 0.715 |
| **0001** | 0.592 | 0.726 | 0.726 | 0.729 | 0.729 | 0.729 | 0.731 | 0.733 |
| **1100** | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| **1010** | 0.715 | 0.715 | 0.715 | 0.715 | 0.715 | 0.715 | 0.715 | 0.715 |
| **1001** | 0.726 | 0.726 | 0.729 | 0.729 | 0.729 | 0.729 | 0.732 | 0.733 |
| **0110** | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| **0101** | 0.612 | 0.612 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| **0011** | 0.586 | 0.600 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| **1110** | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| **1101** | 0.592 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| **1011** | 0.532 | 0.684 | 0.690 | 0.691 | 0.693 | 0.694 | 0.695 | 0.697 |
| **0111** | 0.600 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| **1111** | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 | 0.617 |
| MILP(s) | 0.12 | 0.19 | 0.41 | 0.63 | 1.01 | 1.42 | 10.21 | 147.29 |
| BBNode | 2 | 8 | 26 | 84 | 252 | 602 | 8093 | 97275 |
| Enum(s) | 0.94 | 16.46 | 272.12 | $4 \cdot 10^3$ | $6 \cdot 10^4$ | $9 \cdot 10^5$ | $3 \cdot 10^9$ | $1 \cdot 10^{13}$ |

- Probabilities of going from initial state to wild type (0000) are reported.
- MILP (sec): Avg. CPU time of Gurobi (absolute opt. gap is set to 0.001).
- Enum (sec): Avg. (serial) time of the enumeration (estimated for $N > 6$).