Combinatorics from biology: inference functions and sequence alignment

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Cambridge University Press is pleased to announce...

Algebraic Statistics for Computational Biology

Lior Pachter, *University of California, Berkeley*
Bernd Sturmfels, *University of California, Berkeley*

The quantitative analysis of biological sequence data is based on methods from statistics coupled with efficient algorithms from computer science. Algebra provides a framework for unifying many of the seemingly disparate techniques used by computational biologists. This book offers an introduction to this mathematical framework and describes tools from computational algebra for designing new algorithms for exact, accurate results. These algorithms can be applied to biological problems such as aligning genomes, finding genes, and constructing phylogenies.

The first part of this book consists of four chapters on the themes of Statistics, Computation, Algebra, and Biology offering speedy, self-contained introductions to the emerging field of algebraic statistics and its applications to genomics. In the second part, the four themes are combined and developed to tackle real problems in computational genomics. As the first book in this exciting and dynamic area, it will be welcomed as a text for self-study or for advanced undergraduate and beginning graduate courses.

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Introduction

- In biology, an important source of data is the genome, which is a long sequence of letters $\mathtt{A}, \mathtt{C}, \mathtt{G}$ and $\mathtt{T}$.
- In computational biology, one tries to analyze this data and obtain information from it:
  - evolution of species (phylogenetic trees),
  - structure of the genome,
  - ...
- Statistical models are used to analyze these sequences and draw conclusions from them.

Example 1: sequence alignment

- It is used to determine the similarity between biological sequences.
- It gives information about how a sequence evolved into another by a sequence of insertions, deletions, and mutations.
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Consider the sequences $S = \mathtt{AGGAATTCG}$ and $T = \mathtt{GGACGGTAT}$.

Which of the following two alignments is better?

$S_1 = \mathtt{AGGA{-}ATTCG}$	$S_2 = \mathtt{{-}{-}A{-}GGAATTCG}$
$T_1 = \mathtt{{-}GGACGGTAT}$	$T_2 = \mathtt{GGACGGTAT{-}{-}{-}}$

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$S_1 =$ AGGA-ATTCG

$T_1 =$ -GGACGGTAT

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One possible model: matches are rewarded by 1,
mismatches are penalized by α,
insertions are penalized by β.

$4 - 4\alpha - \beta \quad \longleftarrow \quad$ score:$= z - x\alpha - y\beta \quad \longrightarrow \quad 5 - \alpha - 3\beta$

- An *optimal alignment* is one with highest score.

  Optimality depends on the values of the parameters α and β.

  Example:

  $$4 - 4\alpha - \beta > 5 - \alpha - 3\beta \quad \text{if} \quad \alpha = 0.3, \;\; \beta = 1, \quad \text{but}$$
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  Such a map is called an *inference function*.

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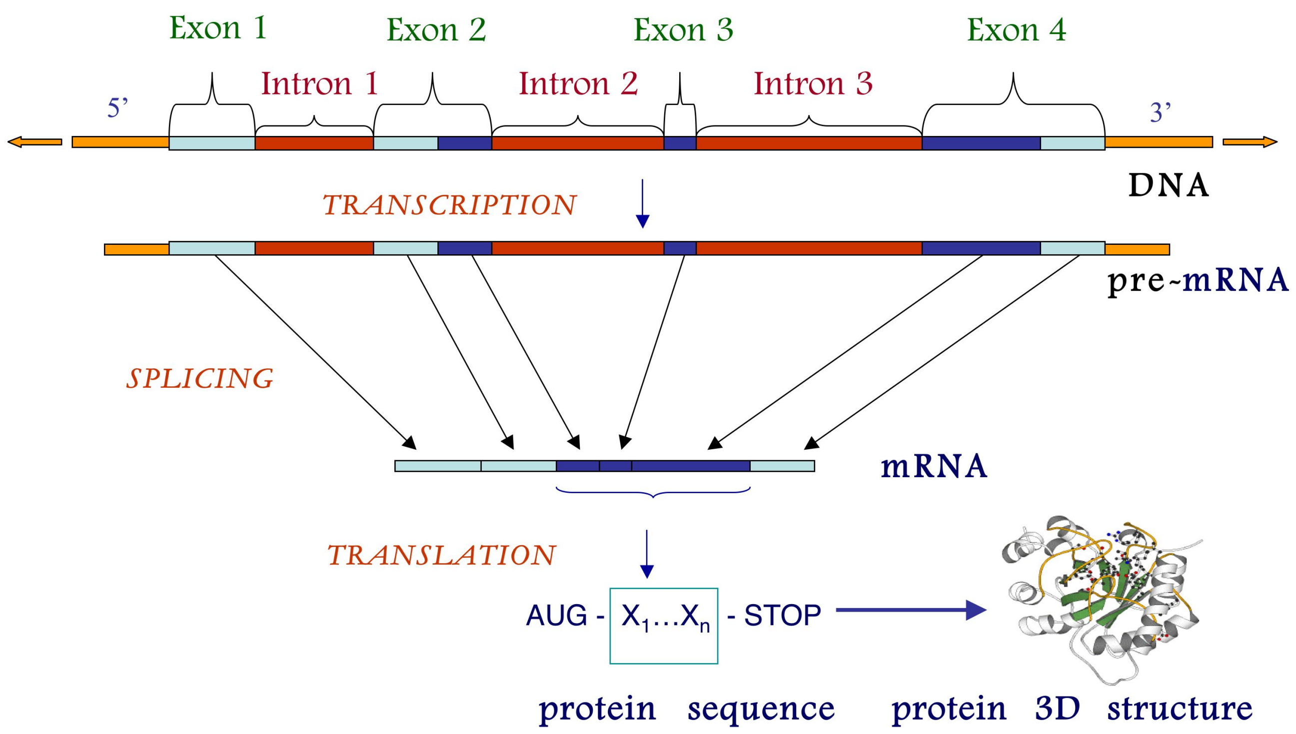
Problem: How many of them are inference functions?

Example 2: gene finding functions

A problem in biology is to distinguish introns from exons in the genome.



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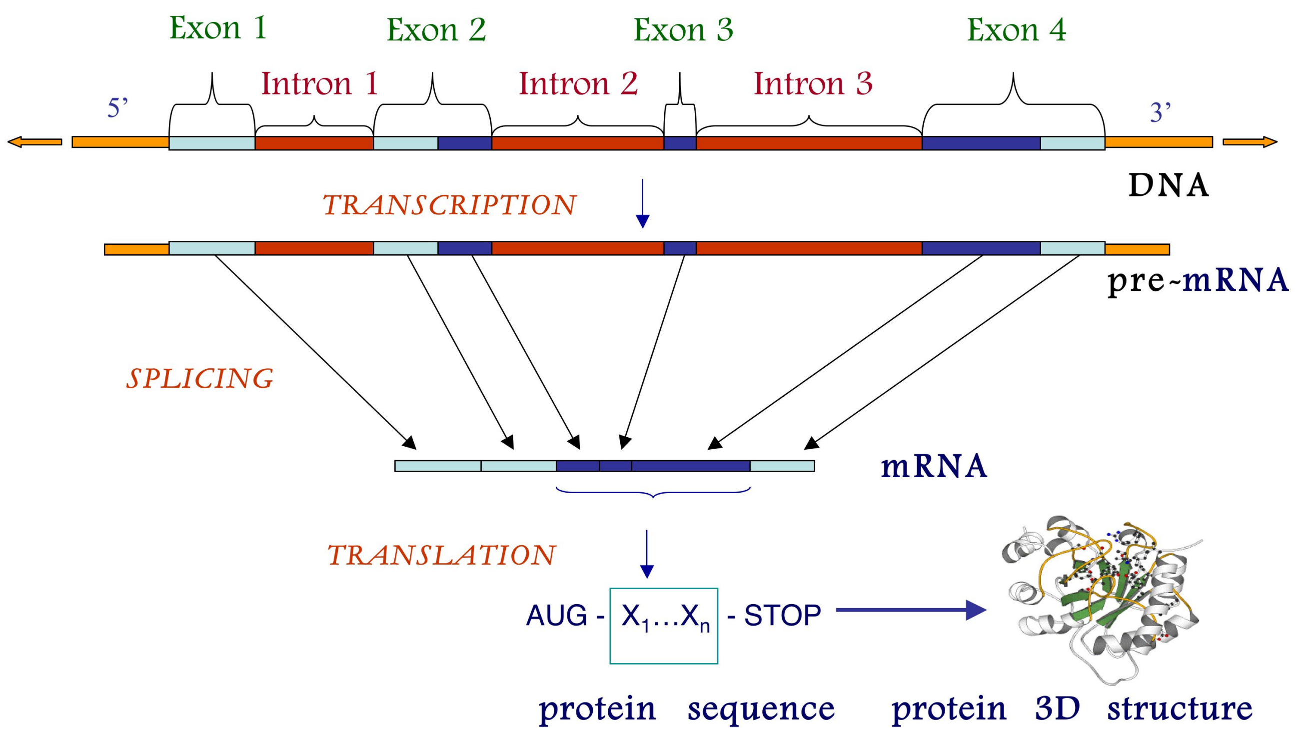

Exons are translated intro proteins, but introns are spliced out before the translation.

Example 2: gene finding functions

- A *gene finding function* is a map

$$\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}^n \longrightarrow \{\mathrm{in}, \mathrm{ex}\}^n$$

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An *algebraic statistical model* arises as the image of a polynomial map

$$\mathbf{f}: \begin{array}{ccc} \mathbb{R}^d & \longrightarrow & \mathbb{R}^m \\ \underbrace{\theta = (\theta_1, \ldots, \theta_d)}_{\text{model parameters}} & \mapsto & \underbrace{(f_1(\theta), f_2(\theta), \ldots, f_m(\theta))}_{\text{probability distribution}} \end{array}$$

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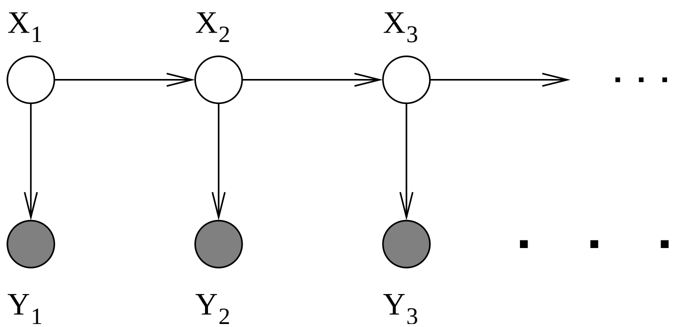
Each coordinate f_i is a polynomial in the d parameters, representing the probability of a certain outcome.

Example: hidden Markov model



} *hidden variables* $X_i \in \Sigma$

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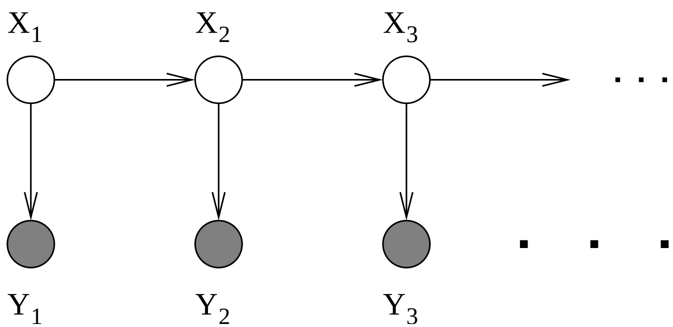

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Transition probabilities: for $i, j \in \Sigma$, $\ell \in \Sigma'$,

$$\theta_{ij} = \mathrm{Prob}(X_{k+1} = j \mid X_k = i)$$

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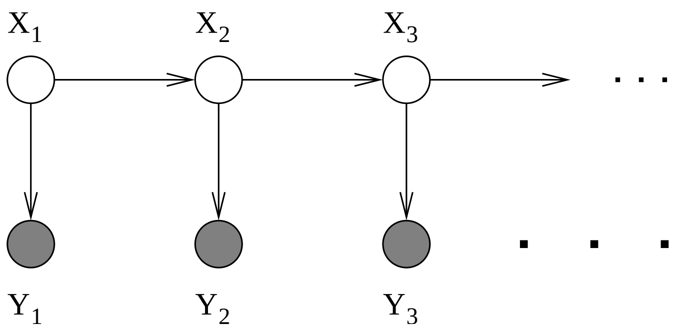

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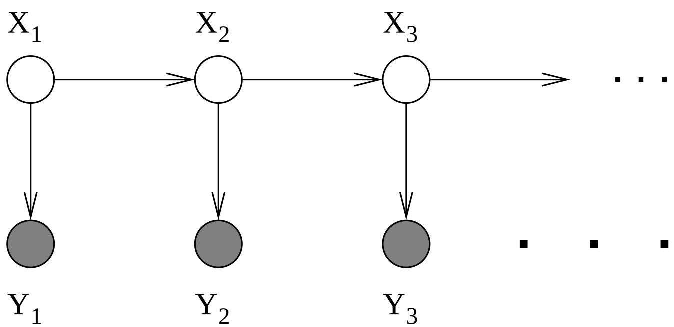

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- The only information that we see are the values of $Y_1, Y_2, \ldots$. We want to guess the most likely values of $X_1, X_2, \ldots$
- This model can be used to determine what parts of the genome are introns and what parts are exons.

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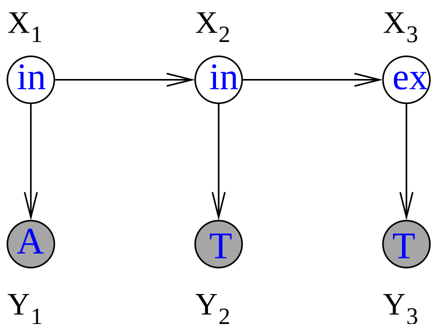

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- The model is represented by a polynomial map

$$\begin{array}{rccc} \mathbf{f}: & \mathbb{R}^{12} & \longrightarrow & \mathbb{R}^{64} \\ & (\theta_{\mathrm{in},\mathrm{in}}, \theta_{\mathrm{in},\mathrm{ex}}, \theta_{\mathrm{in},\mathtt{A}}, \ldots) & \mapsto & (f_{\mathtt{AAA}}, f_{\mathtt{AAC}}, f_{\mathtt{AAG}}, f_{\mathtt{AAT}}, f_{\mathtt{ACA}}, \ldots) \end{array}$$

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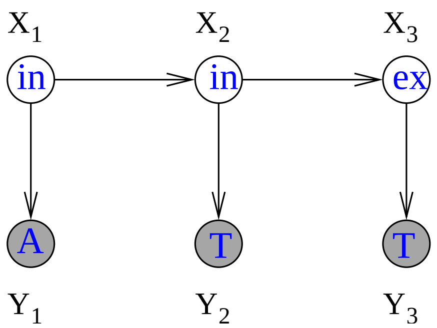

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$$f_{\mathtt{ATT}} = \underbrace{\frac{1}{2}\theta_{\mathrm{in},\mathtt{A}}\theta_{\mathrm{in},\mathrm{in}}\theta_{\mathrm{in},\mathtt{T}}\theta_{\mathrm{in},\mathrm{in}}\theta_{\mathrm{in},\mathtt{T}}}_{X_1=X_2=X_3=\mathrm{in}} + \underbrace{\frac{1}{2}\theta_{\mathrm{in},\mathtt{A}}\theta_{\mathrm{in},\mathrm{in}}\theta_{\mathrm{in},\mathtt{T}}\theta_{\mathrm{in},\mathrm{ex}}\theta_{\mathrm{ex},\mathtt{T}}}_{X_1=X_2=\mathrm{in},\ X_3=\mathrm{ex}} + \cdots$$

(assuming $\mathrm{Prob}(X_1 = \mathrm{in}) = \mathrm{Prob}(X_1 = \mathrm{ex}) = \frac{1}{2}$)

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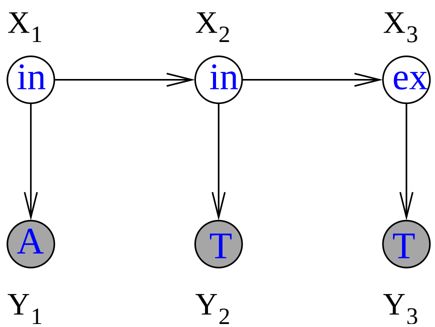

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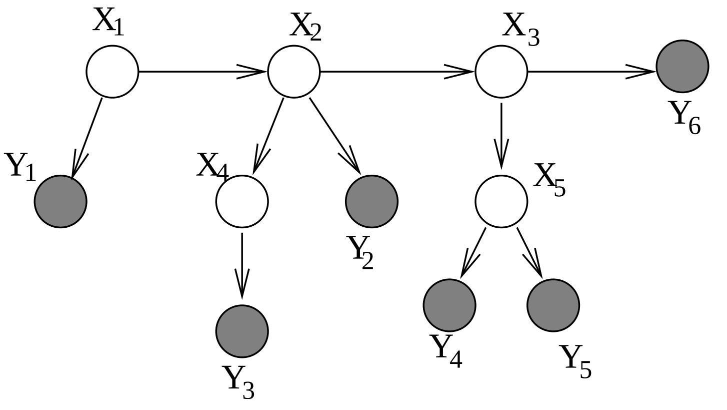
(assuming $\mathrm{Prob}(X_1 = \mathrm{in}) = \mathrm{Prob}(X_1 = \mathrm{ex}) = \frac{1}{2}$)

- Given an observation (e.g. $\mathbf{Y} = \mathtt{ATT}$), we want to find the most likely values of X_1, X_2, X_3.

Graphical models

More generally:



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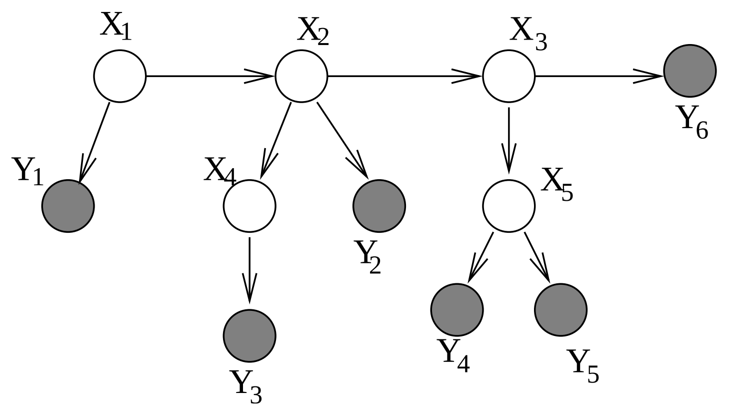

- Hidden random variables: $X_1, X_2, \ldots, X_q \in \Sigma$
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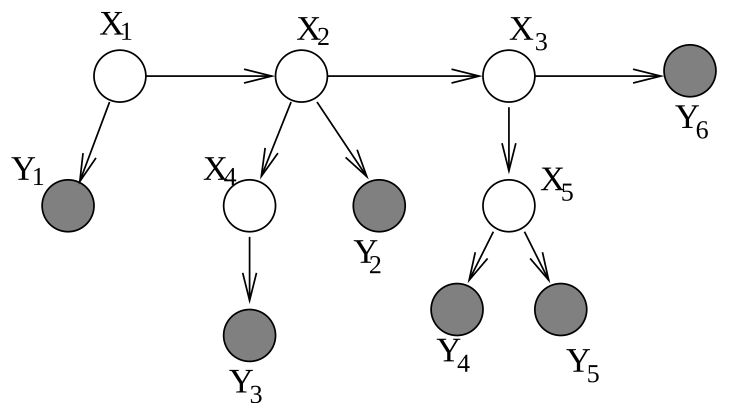

- Hidden random variables: $X_1, X_2, \ldots, X_q \ \in \Sigma$
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- Transition probabilities among states are given by parameters $\theta_1, \theta_2, \ldots, \theta_d$.

The coordinates of the map $\mathbf{f} : \mathbb{R}^d \longrightarrow \mathbb{R}^{(l')^n}$ are

$$f_{\tau} = \mathrm{Prob}(\mathbf{Y} = \tau) = \sum_{\mathbf{h} \in \Sigma^q} \underbrace{\mathrm{Prob}(\mathbf{X} = \mathbf{h}, \mathbf{Y} = \tau)}_{\text{monomial in } \theta_1, \theta_2, \ldots, \theta_d}$$

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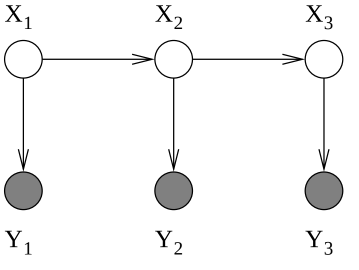
Example: Inference functions of the previous HMM are *gene finding functions*

$$\{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}^n \longrightarrow \{\mathrm{in}, \mathrm{ex}\}^n.$$



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Main Theorem. Fix $d > 0$. Consider a graphical model with d parameters, and let E be the number of edges of the underlying graph. Then, the number of inference functions of the model is at most

$$O(E^{d(d-1)}).$$

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However, most of these maps are not inference functions for any value of the parameters.

Problem: How many of them are inference functions?

Main Theorem. Fix $d > 0$. Consider a graphical model with d parameters, and let E be the number of edges of the underlying graph. Then, the number of inference functions of the model is at most

$$O(E^{d(d-1)}).$$

In most graphical models, E is a linear function of n, so the number of inference functions is $O(n^{d(d-1)})$.
For example, in the HMM, $E = 2n - 1$.

Geometric interpretation of the inference problem

For fixed parameters and a given observation τ, the inference problem is equivalent to find:

$$\boxed{\text{The explanation } \widehat{\mathbf{h}} \text{ that maximizes } \mathrm{Prob}(\mathbf{X} = \mathbf{h}, \mathbf{Y} = \tau).}$$

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$$\updownarrow \qquad v_i := \log(\theta_i)$$

The monomial of f_τ whose exponent vector $(a_{1,i}, a_{2,i}, \ldots, a_{d,i})$ maximizes the linear expression $v_1 x_1 + \ldots + v_d x_d$.

Definition. The *Newton polytope* of

$$f_{\tau}(\theta_1, \theta_2, \ldots, \theta_d) = \sum_i \theta_1^{a_{1,i}} \theta_2^{a_{2,i}} \cdots \theta_d^{a_{d,i}},$$

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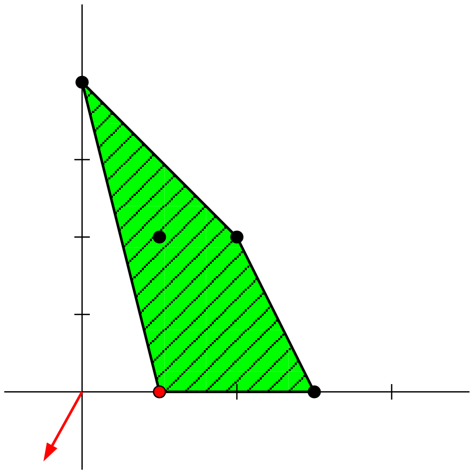
Example.

$$f(\theta_1, \theta_2) = \theta_1^3 + \theta_1^2\theta_2^2 + \theta_1\theta_2^2 + \theta_1 + \theta_2^4$$

$$\theta_1 = 0.6, \quad \theta_2 = 0.4,$$
$$\mathrm{v} = (\log\theta_1, \log\theta_2) = (-0.51, -0.92)$$



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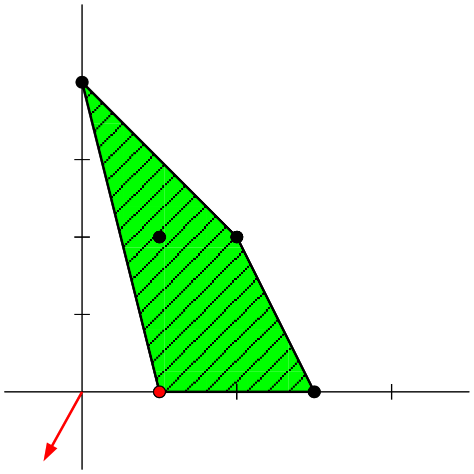

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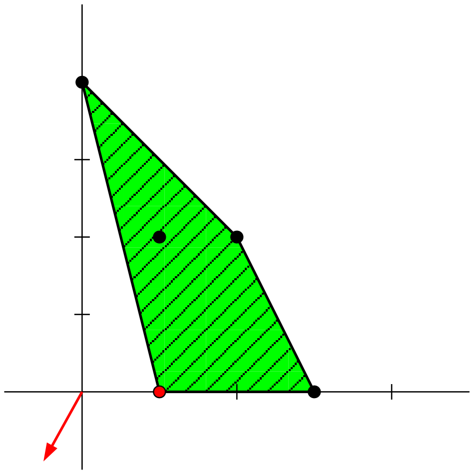

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The inference problem for fixed parameters is a linear programming problem.

- Let
$$\Phi_{\mathbf{v}} : (\Sigma')^n \longrightarrow \Sigma^q$$
denote the inference function where $\mathbf{v} = (\log(\theta_1), \ldots, \log(\theta_d)) \in \mathbb{R}^d$.

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The normal fan

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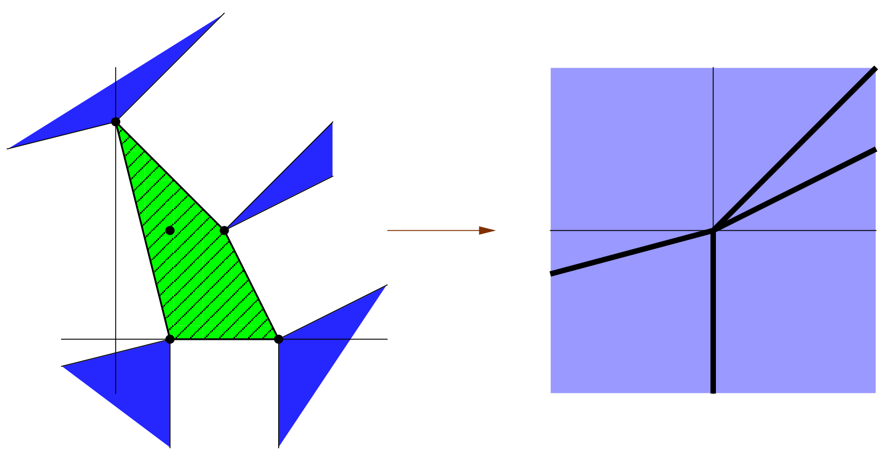

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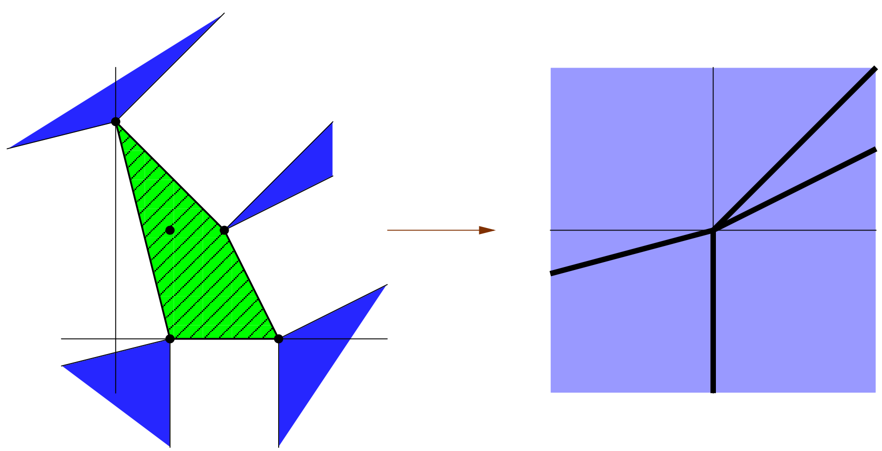

$\Phi_{\mathbf{v}}(\tau) = \Phi_{\mathbf{v}'}(\tau)$ iff $\mathbf{v}$ and $\mathbf{v}'$ belong to the same cone of $\mathcal{F}(\mathrm{NP}(f_\tau))$.

Vectors and inference functions

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How many different inference functions can a graphical model have?

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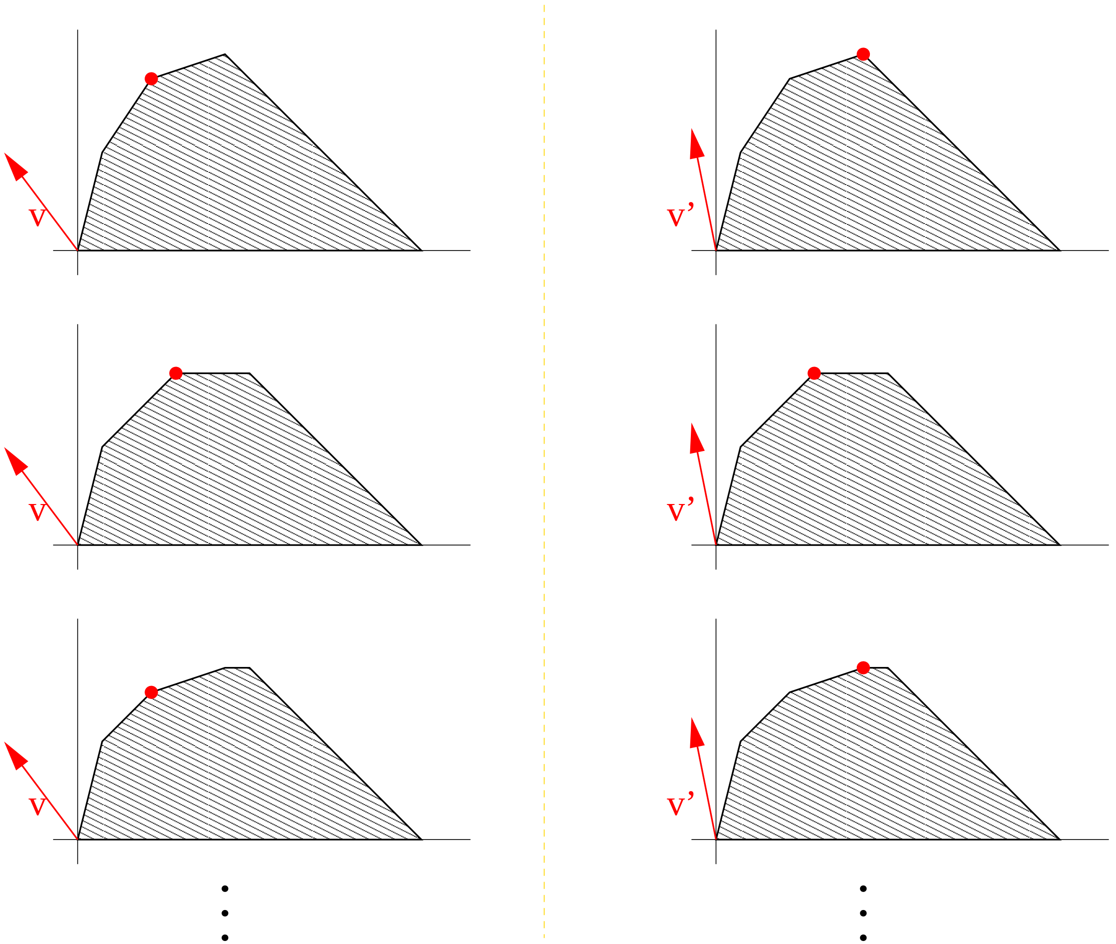

Common refinement of fans

$$\Phi_{\mathbf{v}}(\tau) = \Phi_{\mathbf{v}'}(\tau) \quad \Longleftrightarrow \quad \begin{array}{c}\mathbf{v} \text{ and } \mathbf{v}' \text{ belong to the} \\ \text{same cone of } \mathcal{F}(\mathrm{NP}(f_\tau))\end{array}$$

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The number of inference functions equals the **number of cones in the common refinement of fans.**

- The common refinement of the normal fans is the normal fan of the Minkowski sum of polytopes:

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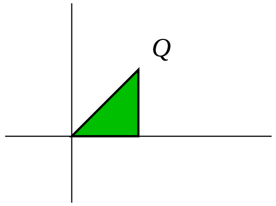

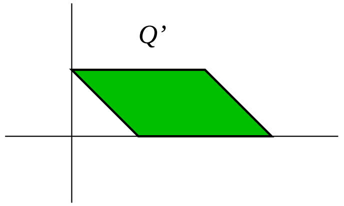

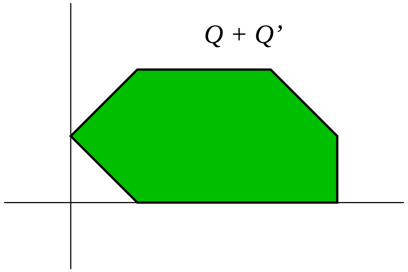

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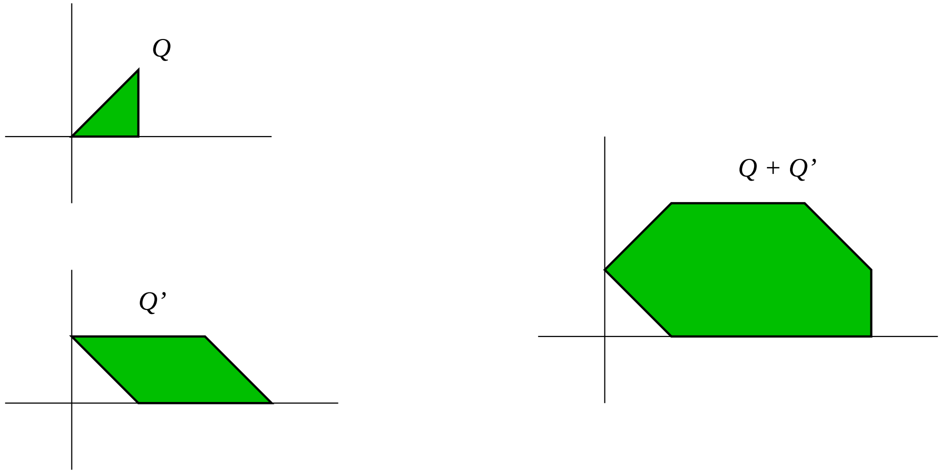

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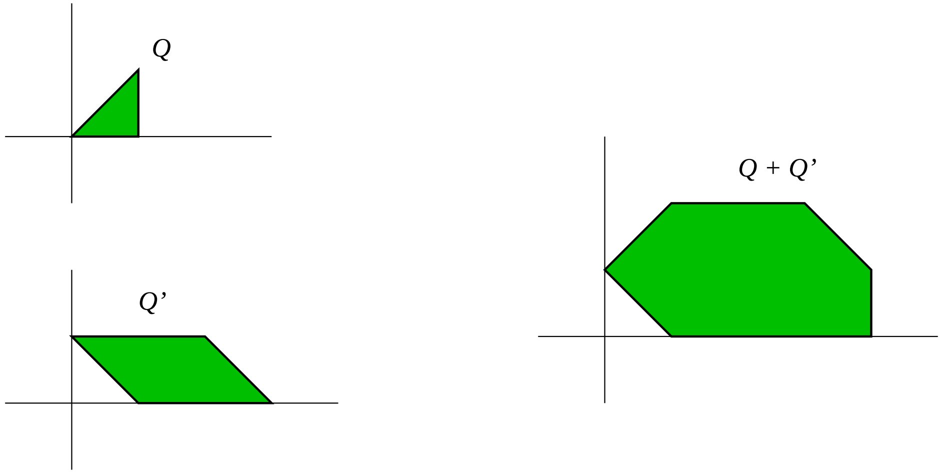

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The number of inference functions is $O(E^{d(d-1)})$. $\square$

Application to sequence alignment

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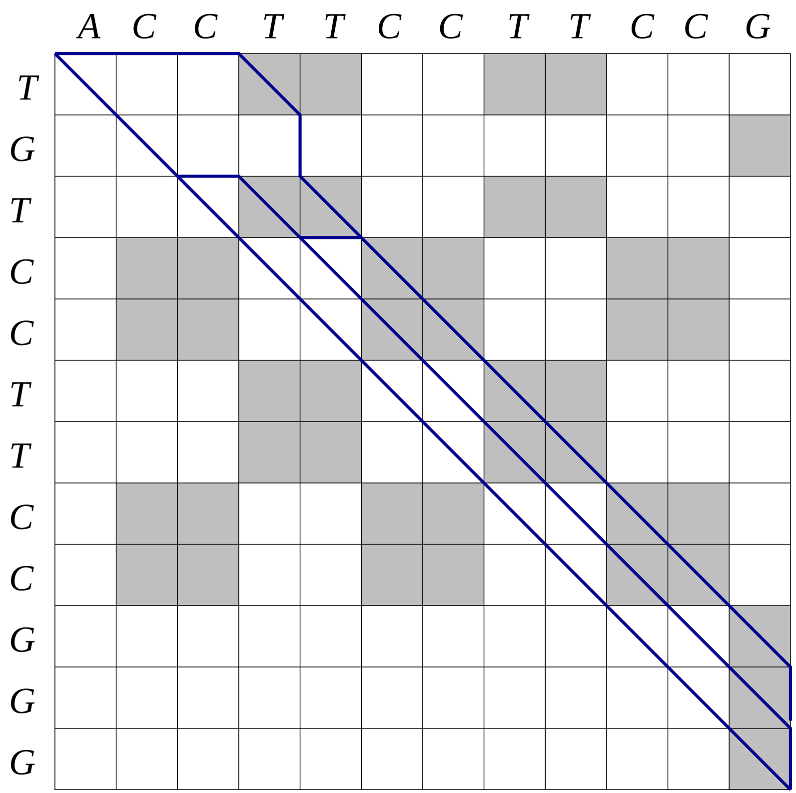
Newton polytope $\mathrm{NP}(f_\tau)$	$\longleftrightarrow$	convex hull of points (x, y, z) where $x = \#$mismatches, $y = \#$insertions, $z = \#$matches for each alignment (this polytope lies on the plane $x + y + z = n$)

- Alignments can be represented as paths from the upper-left to the lower-right corner in the alignment graph:



x	y	z

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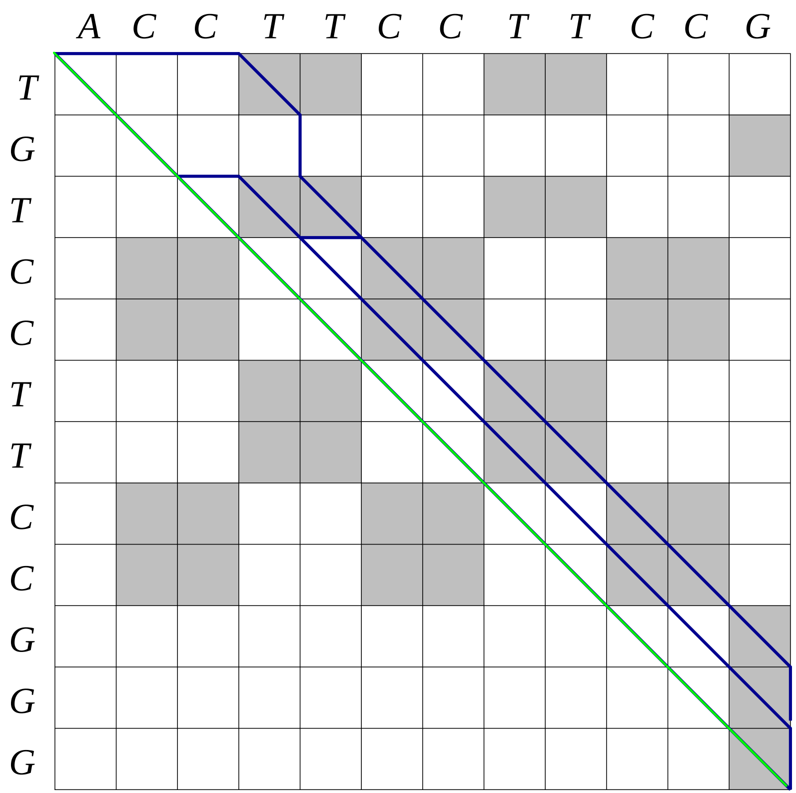

x	y	z
11	0	1

TGTCCTTCCGGG

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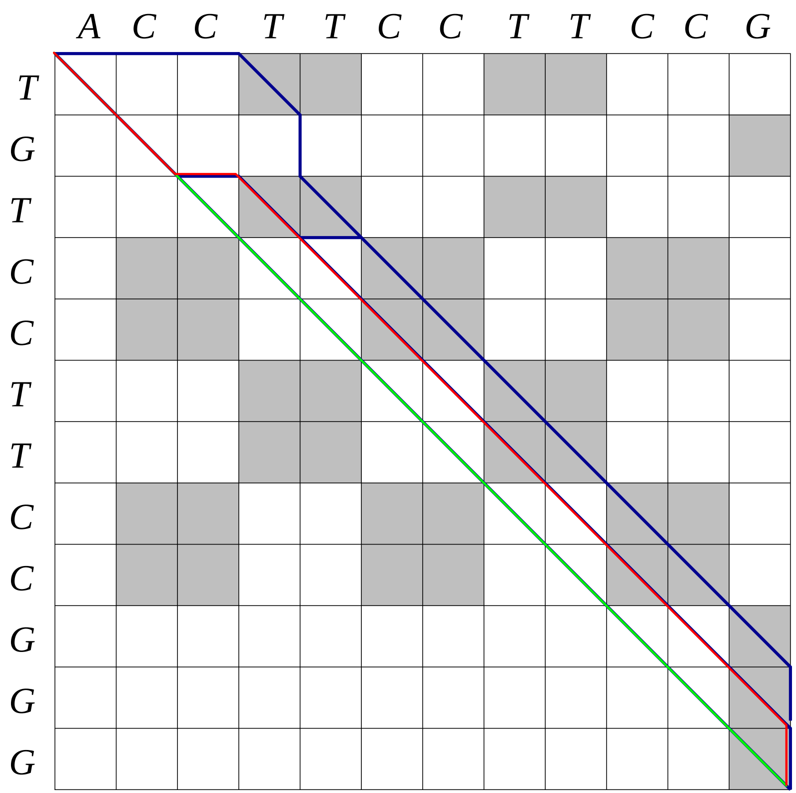

x	y	z
11	0	1
6	1	5

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TGTCCTTCCGGG    TG-TCCTTCCGGG
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```

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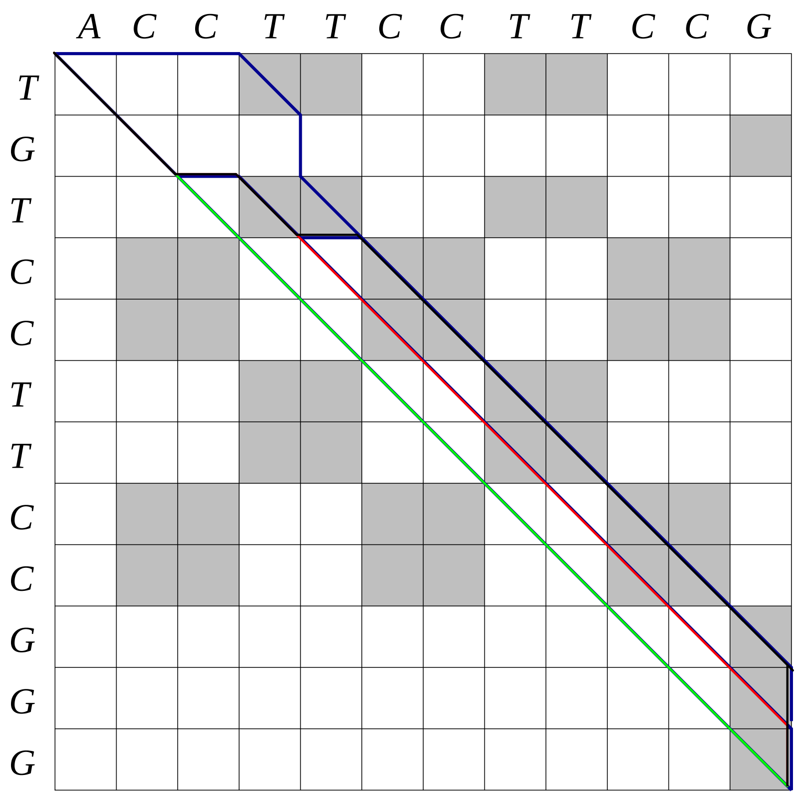

x	y	z
11	0	1
6	1	5
2	2	8

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TGTCCTTCCGGG    TG-TCCTTCCGGG    TG-T-CCTTCCGGG
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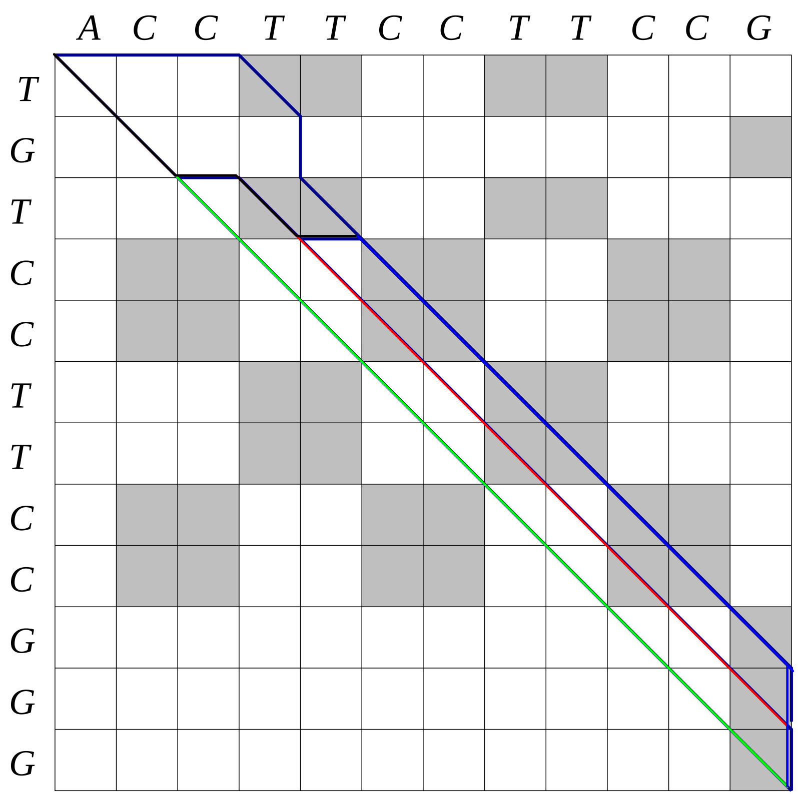

x	y	z
11	0	1
6	1	5
2	2	8
0	3	9
⋮	⋮	⋮

```
TGTCCTTCCGGG
ACCTTCCTTCCG
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TG-TCCTTCCGGG
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```

```
TG-T-CCTTCCGGG
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```

```
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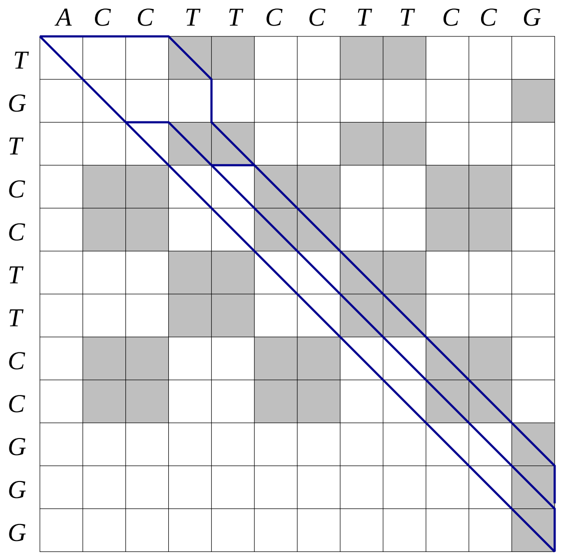
The Newton polytope of a pair of sequences



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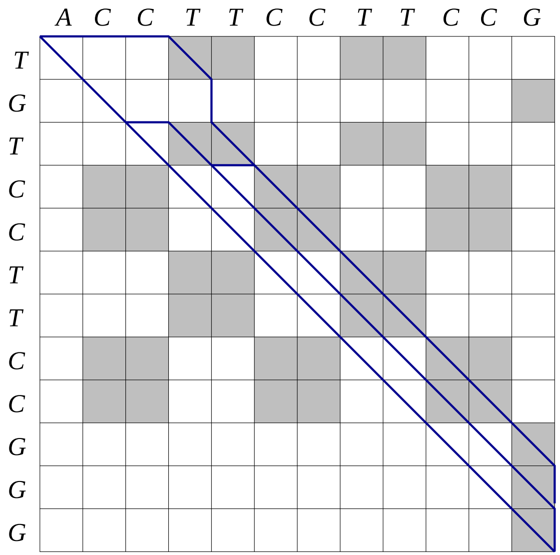

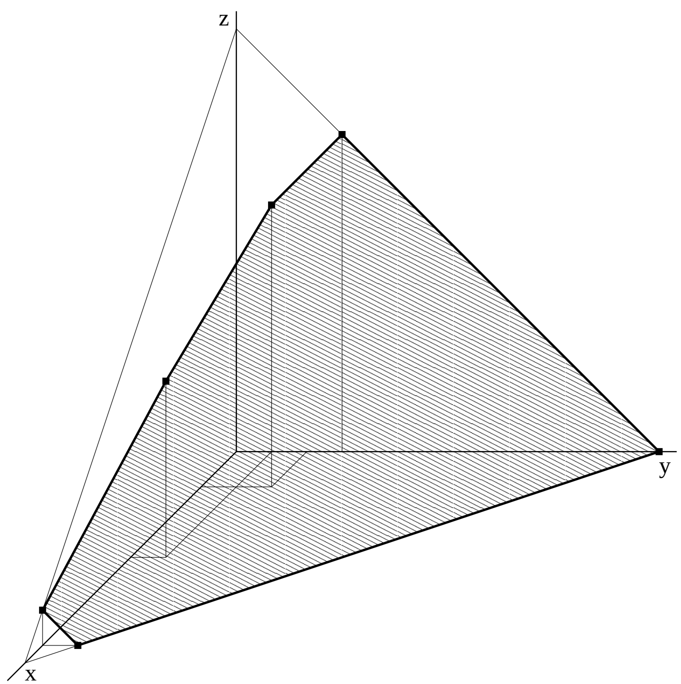

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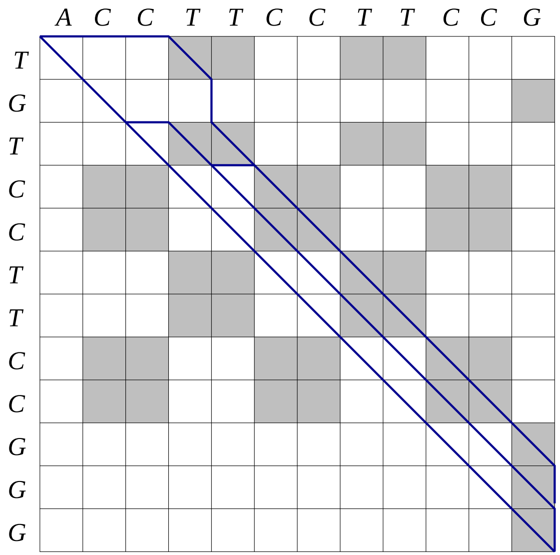

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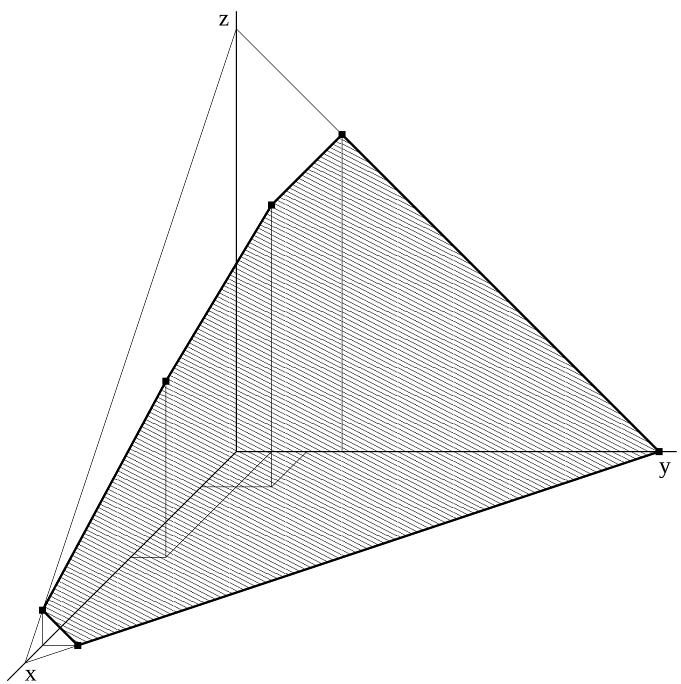

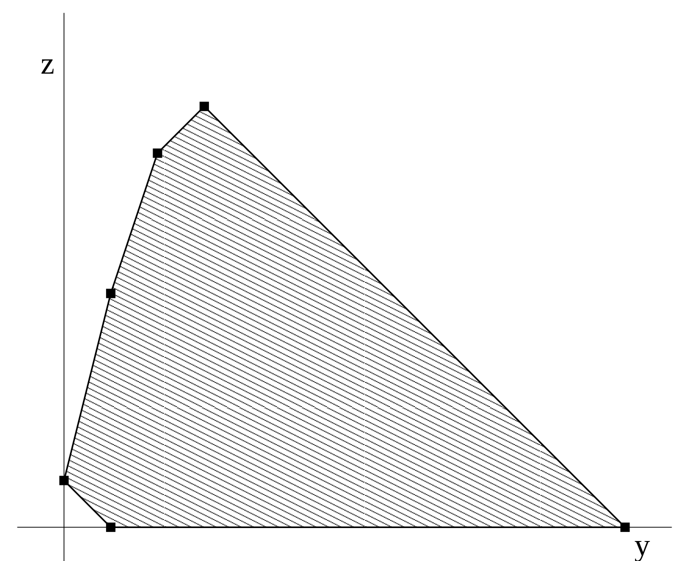

Bound on the number of inference functions

Let $\tau = (S, T)$ (sequences of length n).

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It can be shown that this bound is tight, i.e.,

$$P = \bigodot_{\tau=(S,T)\in\{0,1\}^{2n}} \mathrm{NP}(f_\tau) \quad \text{has } \Theta(n^2) \text{ vertices.}$$

Open problems

- The bound of $O(E^{d(d-1)})$ on the number of inference functions is tight for $d = 2$.

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- In the 2-parameter model for sequence alignment,

  $$P = \bigodot_{\tau \in \{0,1\}^{2n}} \mathrm{NP}(f_\tau) \text{ has } \Theta(n^2) \text{ vertices } (= \# \text{ inference functions}).$$

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  Conjecture: It is $O(\sqrt{n})$ for binary sequences.