Geometric combinatorics and RNA folding algorithms

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Introduction

I am a 4th-year PhD student at Clemson University, interested in combinatorics, computational algebra, and mathematical biology.

Current research projects

- **Applying geometric combinatorics (polytopes) and parametric inference to RNA folding**. [What I'll talk about today] With MRC 2014 research group led by Christine Heitsch & Svetlana Poznanovikj.
- *k*-**canalizing Boolean functions**. With Matthew Macauley & Elena Dimitrova. [See my poster!]
- **Data identification using Gröbner normal forms**. With Elena Dimitrova & Brandy Stigler.

Advertisments

- I am co-organizing (with Raina Robeva & Andy Jenkins) a mini-symposium on discrete and algebraic biology at the 2015 Biomathematics and Ecology Education and Research (BEER) Symposium in October 2015.
- I am the organizing chair of the 12th Graduate Students Combinatorics Conference which will be at Clemson in March 2016!
- I will be on the job market next year. Know of anyone looking for a postdoc?

What is RNA?

RNA (*Ribonucleic acid*) are biological molecules built from strings of nucleotides.

adenine (**A**), *guanine* (**G**), *cytosine* (**C**), *thymine* (**T**), *uracil* (**U**)

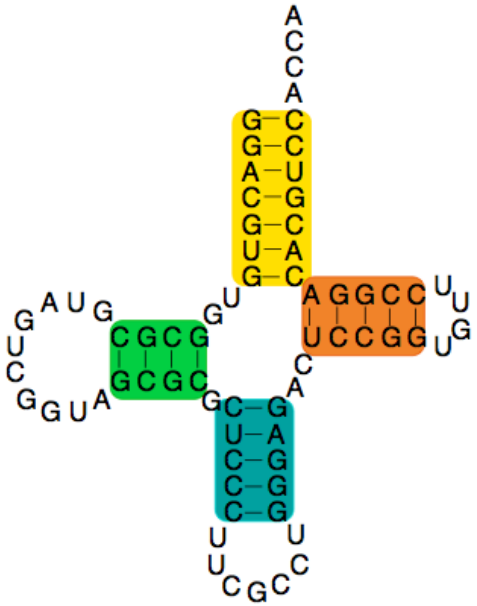
RNA strands consist of **A**, **C**, **G**, and **U**.

Combinatorially, an RNA strand is a length-n sequence, over the alphabet $\{\mathbf{A}, \mathbf{C}, \mathbf{G}, \mathbf{U}\}$.

RNA sequences via base pairings

Primary sequence $\longrightarrow$ Secondary structure $\longrightarrow$ 3D molecule

GGGCGUAUGGCG
CGUAGUCGGUAG
CGCGCUCCCUUC
GCCUGGGAGACU
CCGGUGUUCCGG
ACACGUCCACCA

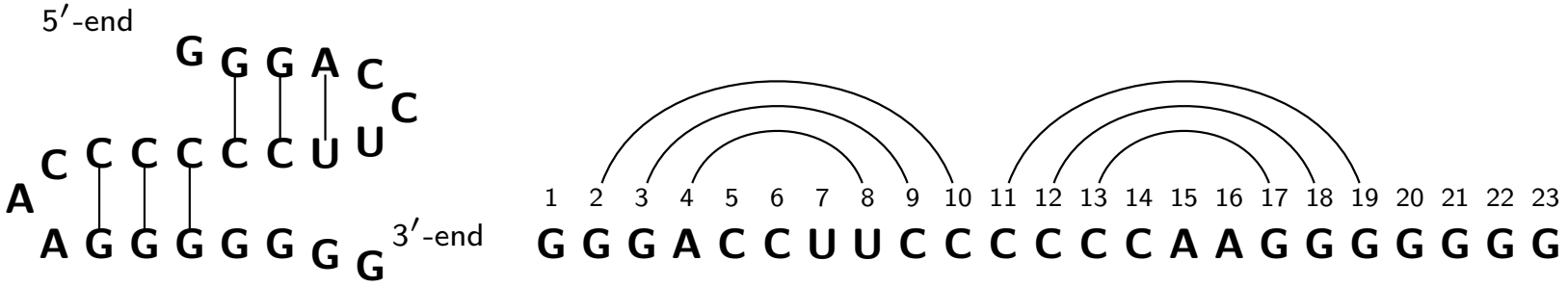


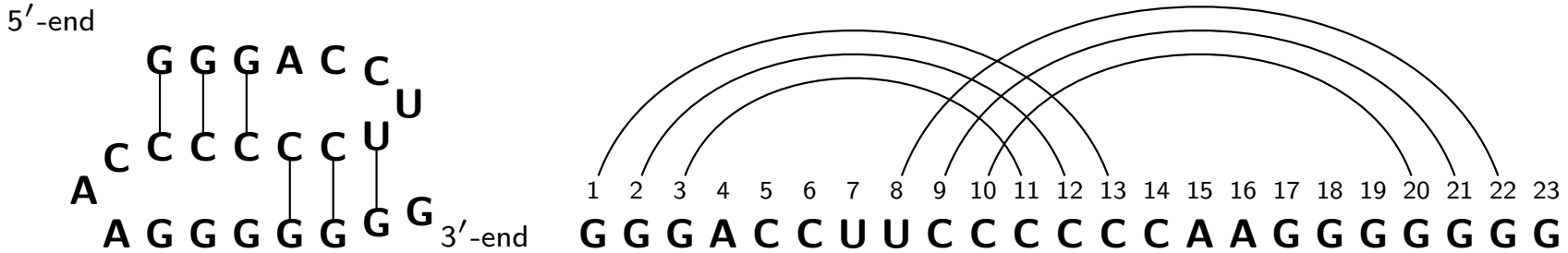
RNA secondary structures balance energetically favorable helices (consecutive base pairs) against destabilizing loops (single-stranded bases).

Secondary structure & pseudoknots

Here are two folds of the same RNA strand, and the corresponding arc diagrams.

The first is a secondary structure and the second is a pseudoknot.





The problem

For a given sequence, there are many possible secondary structures into which it can fold. *What is the most 'likely' one?*

Minimal free energy (mfe) model

The optimal secondary structure minimizes the free energy, ΔG.

Example energy model

Given an RNA sequence $S = b_1 b_2 \cdots b_n$, let

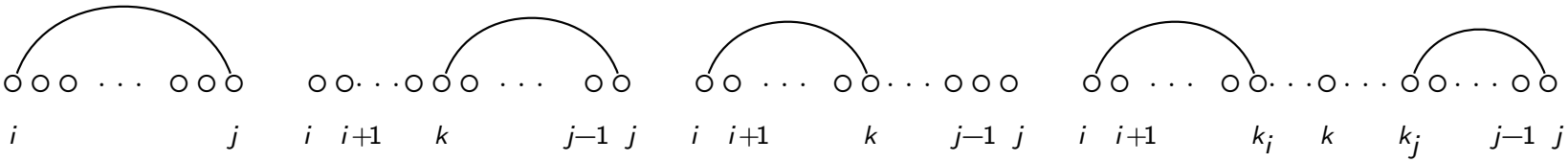
$$\delta g(i,j) = \begin{cases} -3 & \{b_i, b_j\} = \{\mathbf{C}, \mathbf{G}\} \text{ and } i \leq j-4 \\ -2 & \{b_i, b_j\} = \{\mathbf{A}, \mathbf{U}\} \text{ and } i \leq j-4 \\ -1 & \{b_i, b_j\} = \{\mathbf{G}, \mathbf{U}\} \text{ and } i \leq j-4 \\ 0 & \text{otherwise.} \end{cases}$$

be the free energy of the potential bond between b_i and b_j. Find the structure that minimizes ΔG, the sum of the energies of the base pairs.

This can be done using dynamic programming (DP) to recurse on the substructures.

There are 4 ways to recurse on the substructure $S_{i,j} = b_i b_{i+1} \cdots b_{j-1} b_j$.

These correspond to the following 4 cases about how bases b_i and b_j can bond:



Thus the optimal energy score $\Delta G(i,j)$ of subsequence $S_{i,j}$ is given by:

$$\Delta G(i,j) = \min \begin{cases} \Delta G(i+1, j-1) + \delta g(i,j) \\ \Delta G(i+1, j) \\ \Delta G(i, j-1) \\ \min\limits_{i<k<j} \Delta G(i,k) + \Delta G(k+1, j). \end{cases}$$

Our final goal is to compute $S_{1,n}$.

A toy example: $S =$ **GGGACCUUCC**

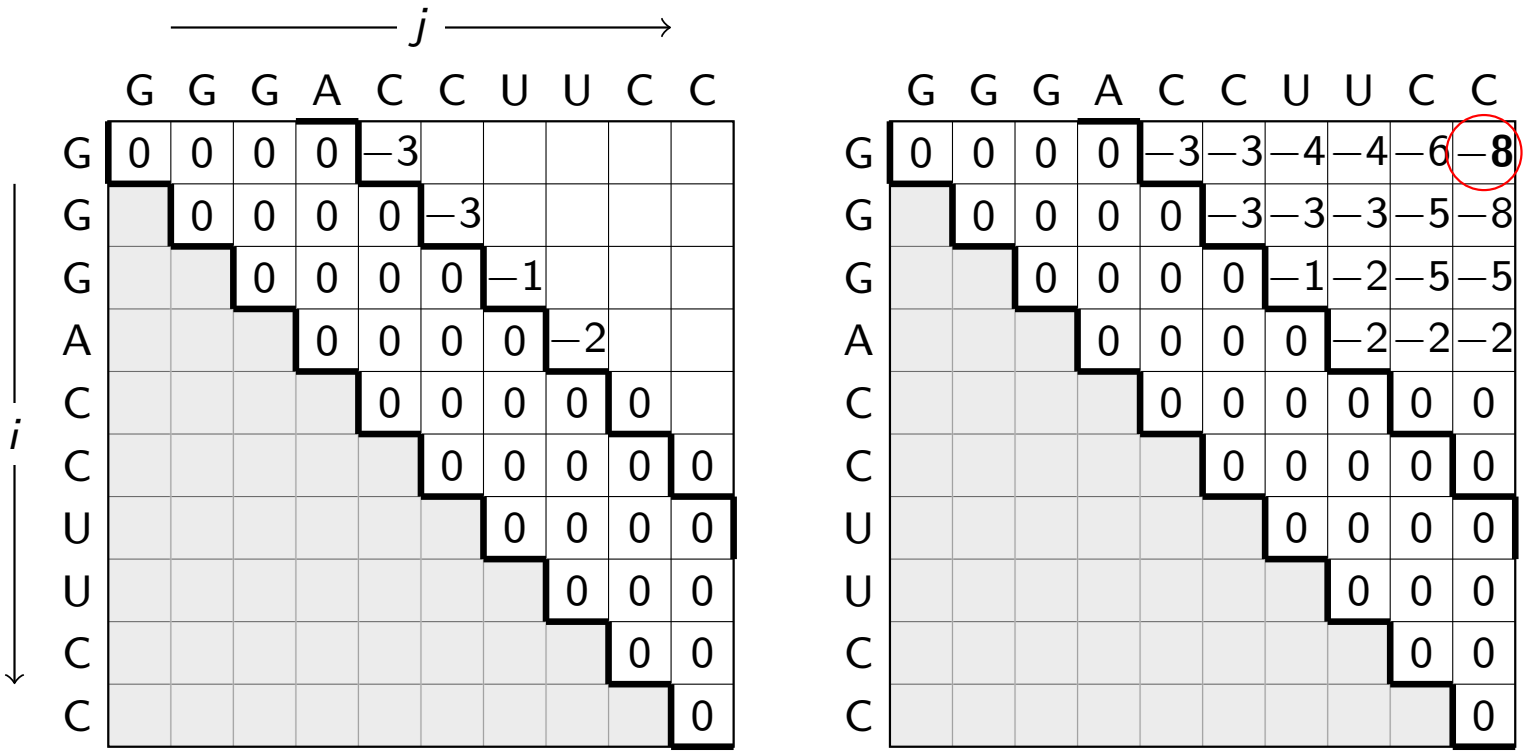
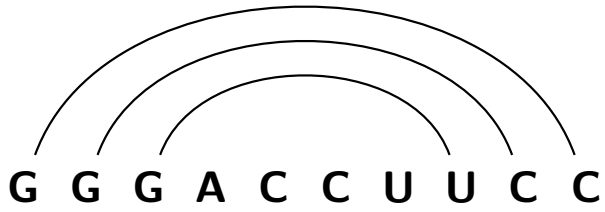


Figure: Recording the optimal scores in a table during a DP routine.



$\Delta G(S) = -8$

MFE folding: toy example

We can use the language from OR to describe RNA folding folding problems.

In our toy example of $S = \mathbf{GGGACCUUCC}$, the problem can be rephrased as:

$$\min \Delta G = -3k_1 - 2k_2 - k_3,$$

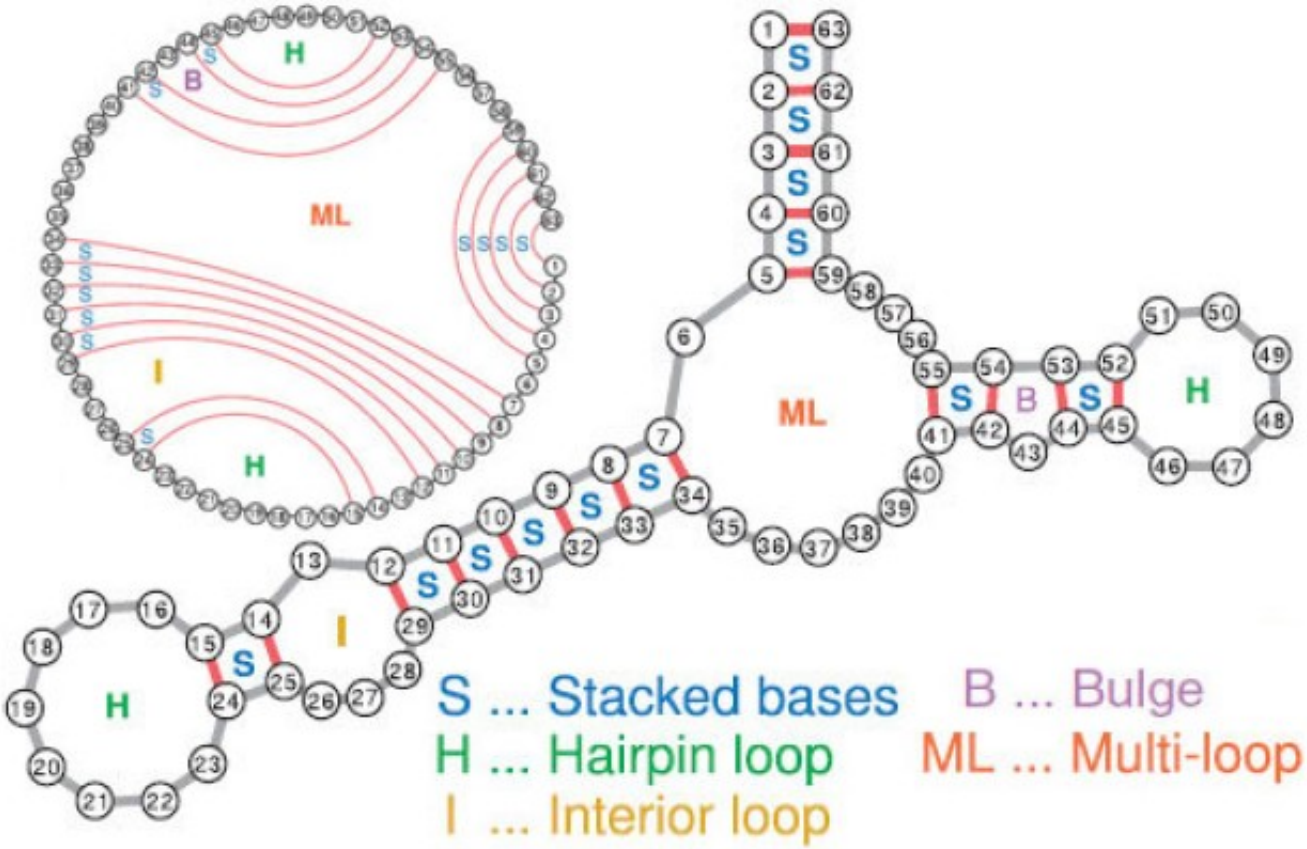
such that,

there exist a 'valid' structure T on S with

- k_1 **CG** pairs,
- k_2 **AU** pairs,
- k_3 **GU** pairs.

We know little about the *feasible region* of this optimization problem, but we know it is finite.

Nearest neighbor thermodynamic model: linear objective function with over 7,000 parameters (Turner99 database)!



GTfold: DP algorithm based on NNTM (using Turner99 database) to minimize the free energy and provide optimal RNA folding structure.

DP solves discrete optimization efficiently, but quality of free energy approximation by the NNTM objective function varies widely.

Abbreviation	Sequence	Length (nt)	MFE accuracy
T1	*H. sapiens* (AC004932_g)	72	0.00
T2	*S. tokodaii* (BA00002_e)	74	0.26
T3	*S. tokodaii* (BA000023_b)	74	0.45
T4	*L. delbrueckii* (CP000412_o)	72	0.75
T5	*O. nivara* (AP006728_af)	73	1.00
S1	*E. coli* (V00336)	120	0.26
S2	*G. arboreum* (U31855)	120	0.47
S3	*A. tabira* (AB015591)	120	0.59
S4	*S. cerevisiae* (X67579)	118	0.71
S5	*D. mobilis* (X07545)	135	0.88

What might go wrong?

Multibranch loop parameters

For computational efficiency, only 3 parameters are used to govern multibranch loops. Even worse: they are almost purely 'made up'.

Multibranch loop parameters

- a: energy penalty for a multibranch loop.
- b: energy for each unpaired nucleotide in a multibranch loop.
- c: energy for each branching helix in a multibranch loop.

Question

How do multibranch loop parameters (a, b, c) affect the optimal structure?

Multibranch loop parameters

We want to run parametric analysis on (a, b, c), but we don't know how 'wrong' they are.

Answer?

We need to construct the convex hull (a polytope) of the feasible region.

The optimal value should exist on an extreme point of the feasible region (a vertex of this polytope).

The real problem

The dimension of this polytope is over 7,000 and we know little about the feasible region.

Dimension reduction

For a given structure T, we can write its free energy as:

$$\Delta G(T) = ax_T + by_T + cz_T + w_T,$$

where

- x_T: number of multibranch loops in T,
- y_T: number of unpaired nucleotides in multibranch loops in T,
- z_T: number of branching helices in multibranch loops in T,
- w_T: energy of the remaining structures using Turner99 parameters.

The *profile space* is (x_T, y_T, z_T, w_T), and we introduce a dummy variable d:

$$\Delta G(T) = ax_T + by_T + cz_T + dw_T.$$

Question

How do multibranch loop parameters (a, b, c, d) affect the optimal structure?

The real problem

How to compute the convex hull of an implicit finite feasible region?

Answer!

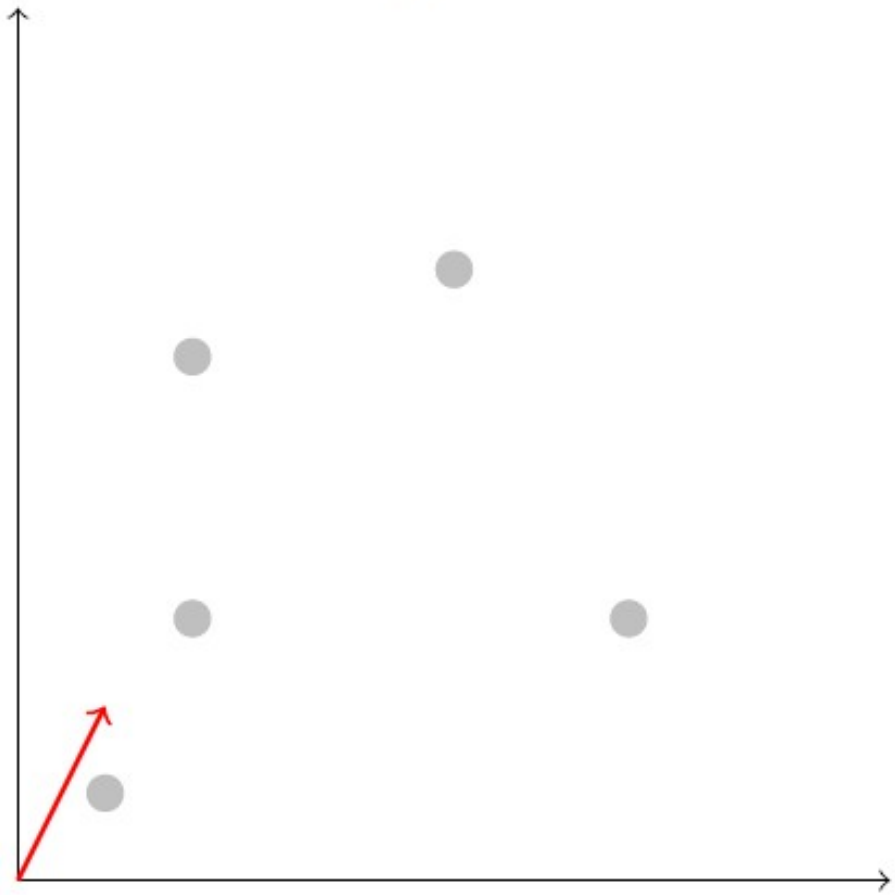
Let GTfold do it for us!

iB4e and beneath-beyond method

iB4e: given a solver for maximization of linear objective functions over an implicit finite feasible region, iB4e builds the convex hull of the feasible region incrementally, by systematically finding new vertices and facets.

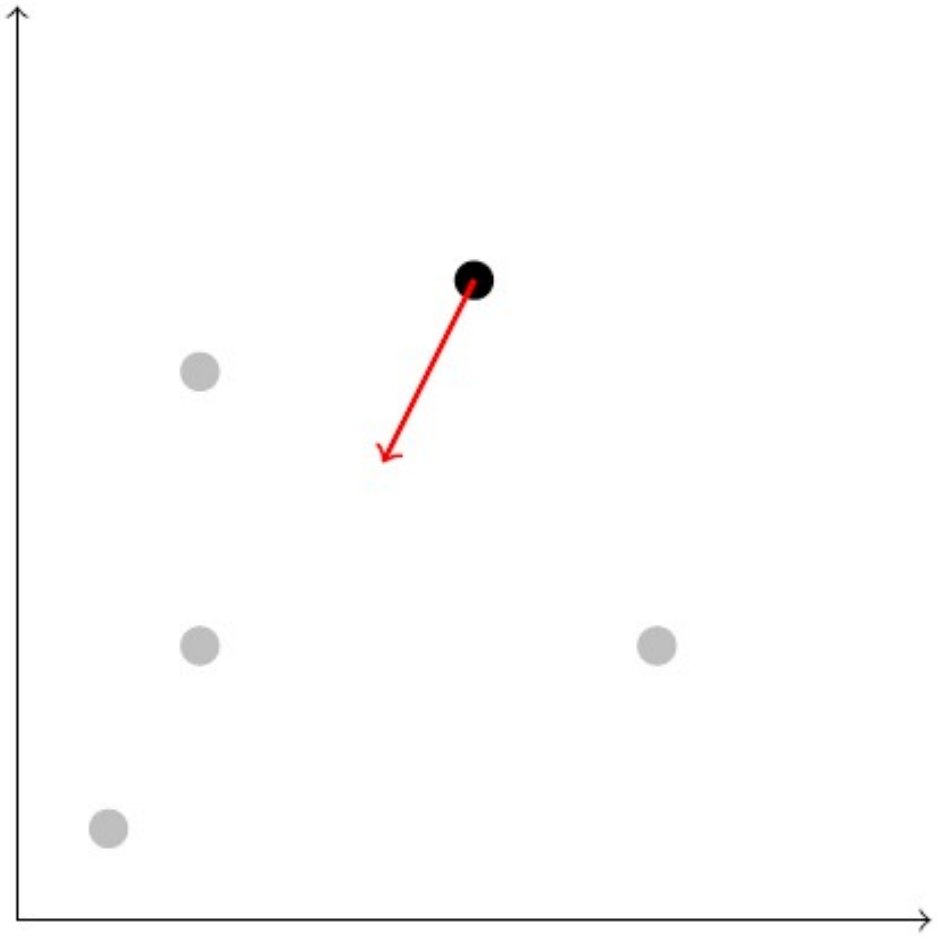
Step 1: find the affine hull of the feasible region.

iB4e generates a vector v and asks another program to find the $\mathbf{x}$ that optimizes $v \bullet \mathbf{x}$.



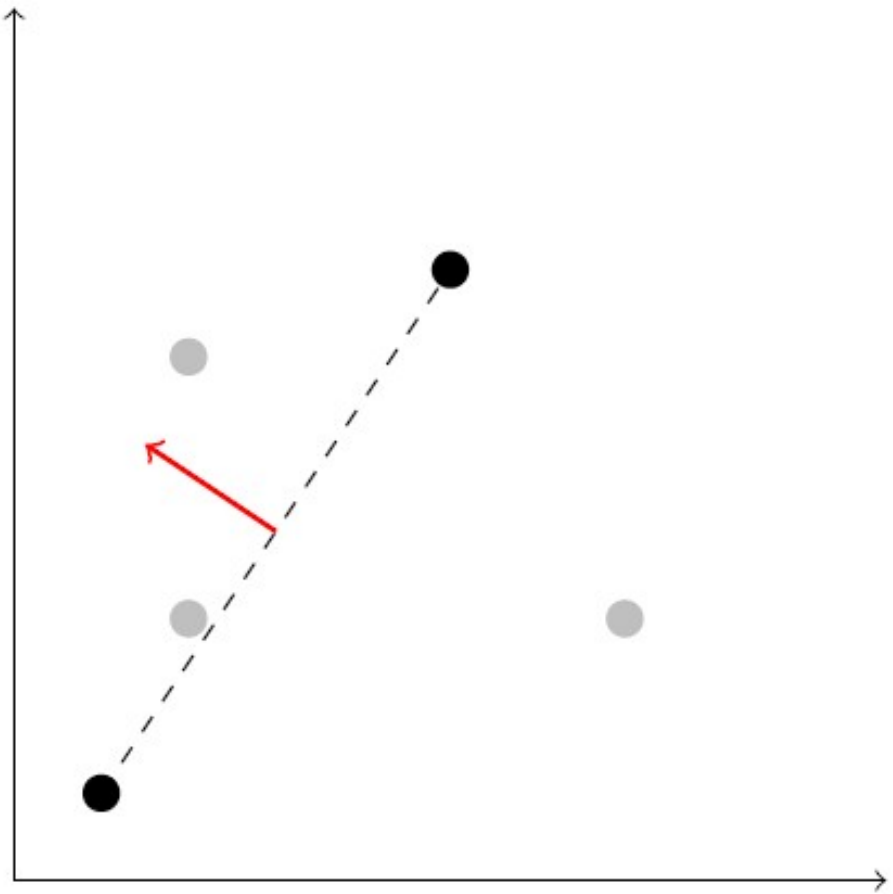
Step 1: find the affine hull of the feasible region.

iB4e asks the program to find the $\mathbf{x}$ that optimizes $-v \bullet \mathbf{x}$.



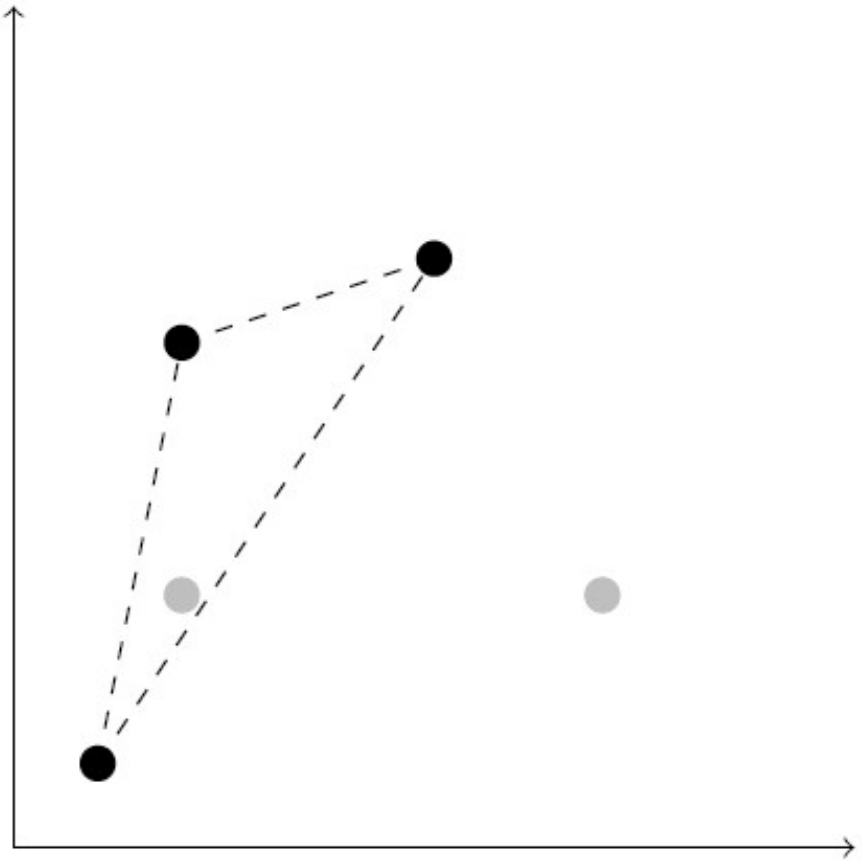
Step 1: find the affine hull of the feasible region.

iB4e computes the affine hull of the existing vertices.
It generates a vector orthogonal to that hull.



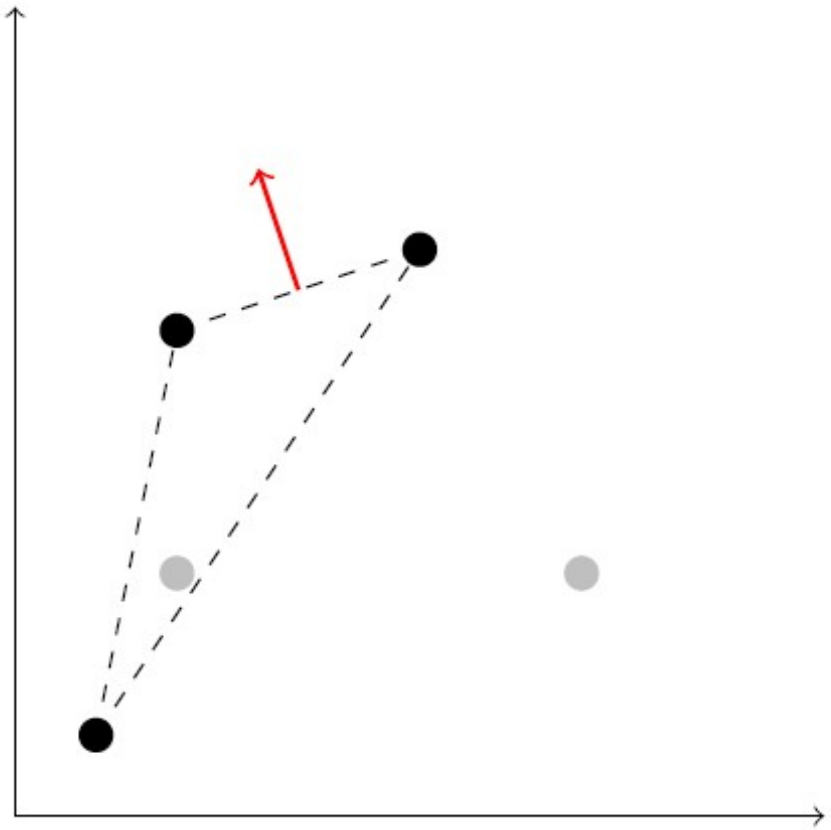
Step 1: find the affine hull of the feasible region.

If iB4e finds a point not in the face, it computes a new affine hull with temporary faces.



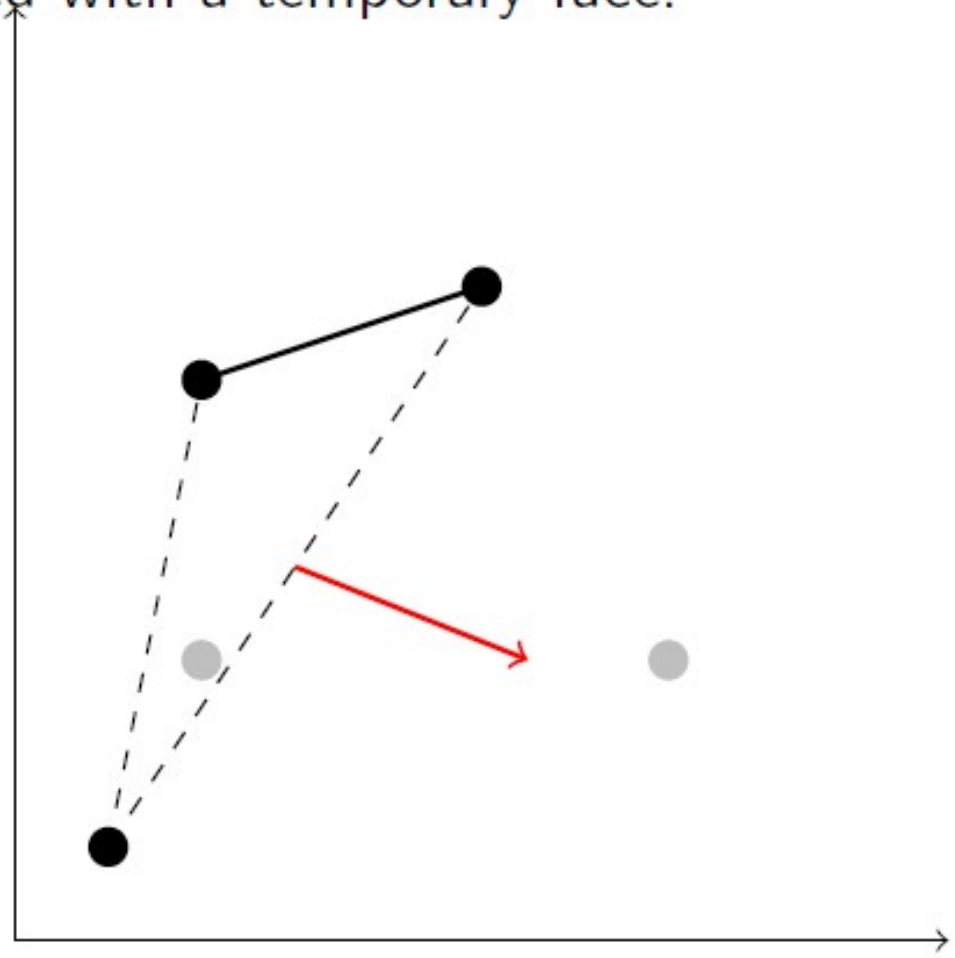
Step 2: build the polytope incrementally.

iB4e repeats the process with one of the temporary faces.



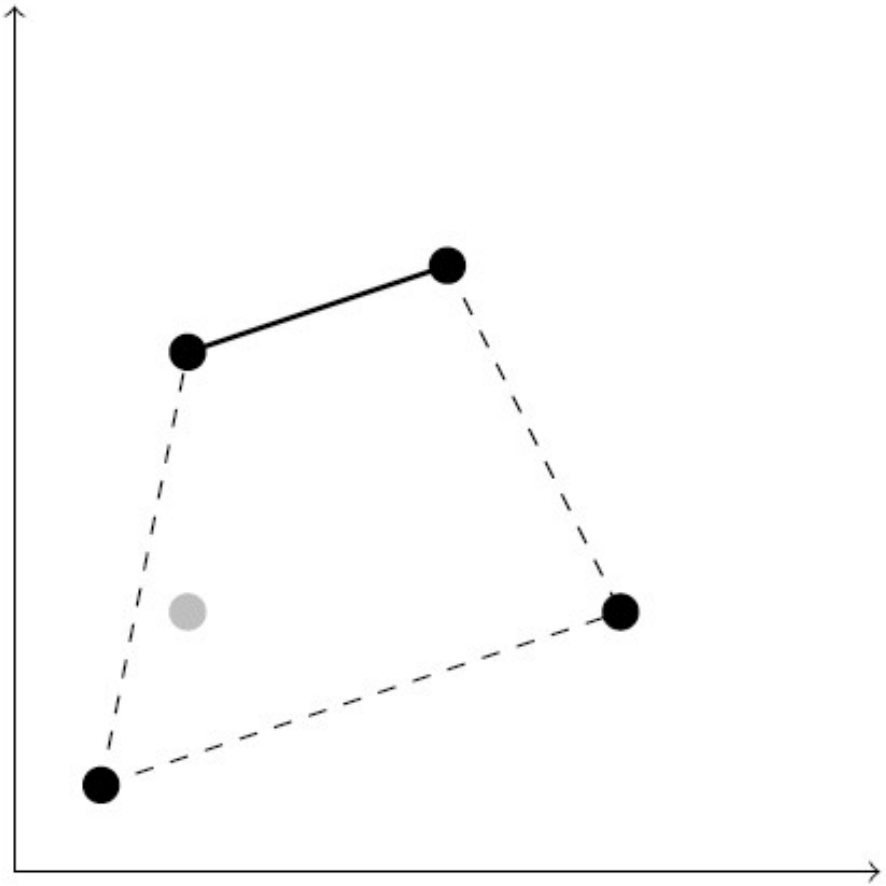
Step 2: build the polytope incrementally.

If no new vertex outside of the face is found, that face becomes a confirmed face and the process is restarted with a temporary face.



Step 2: build the polytope incrementally.

The process is repeated until all faces are confirmed.



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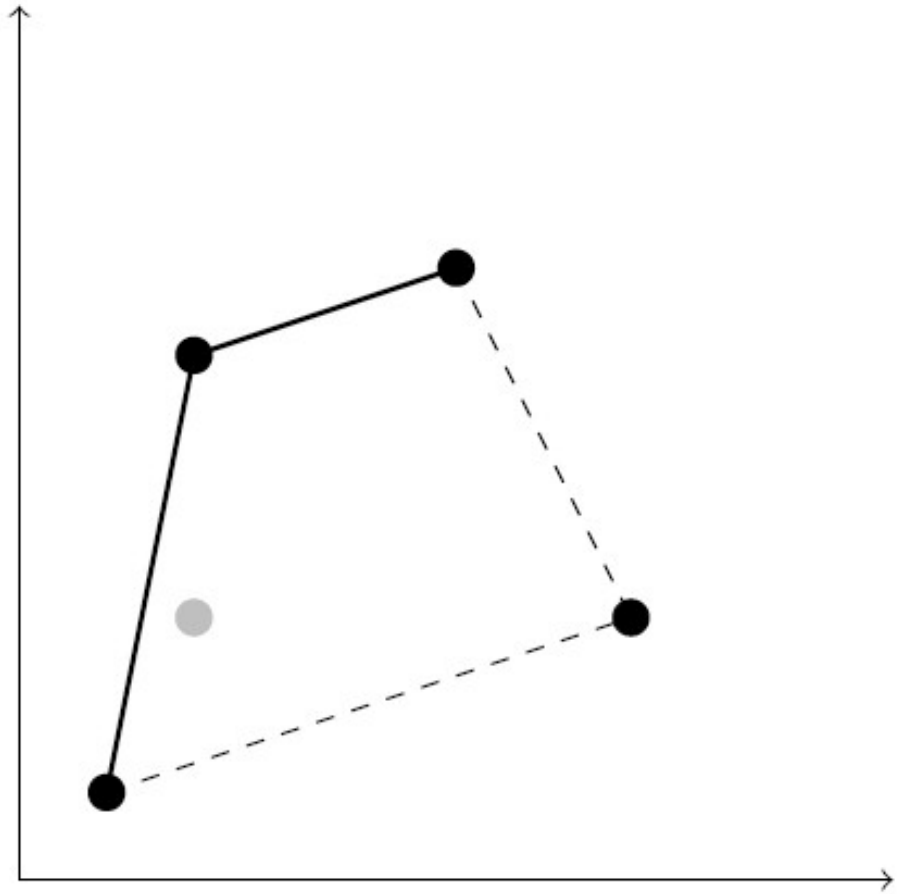

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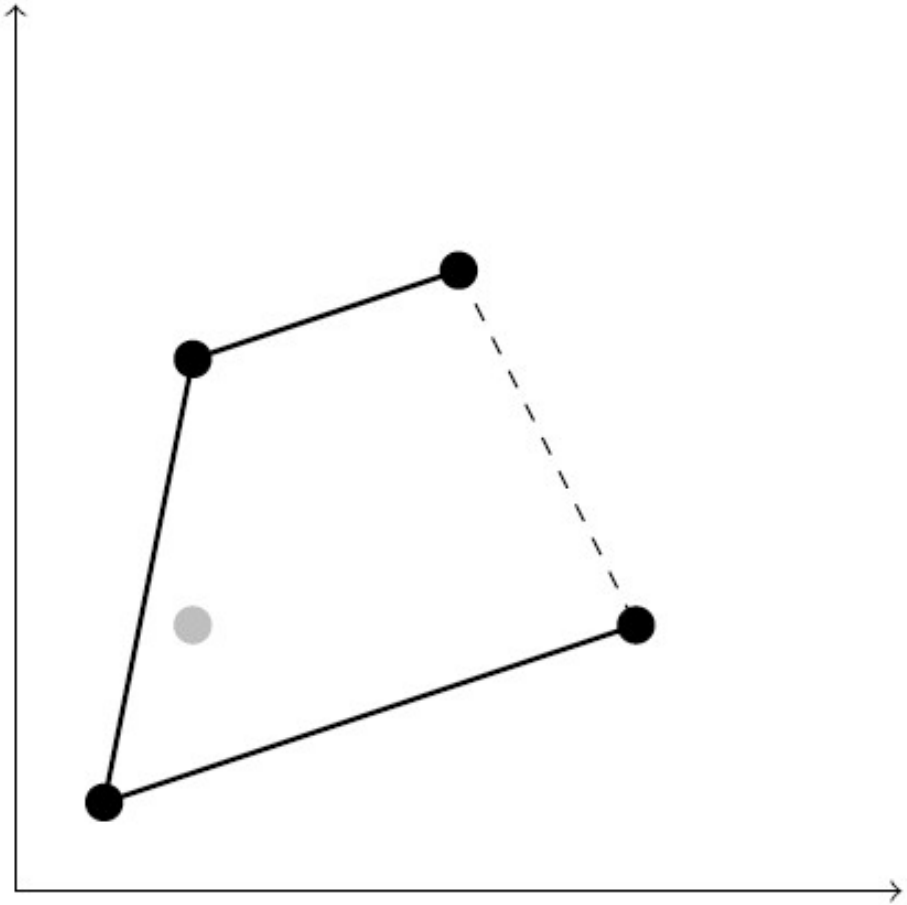

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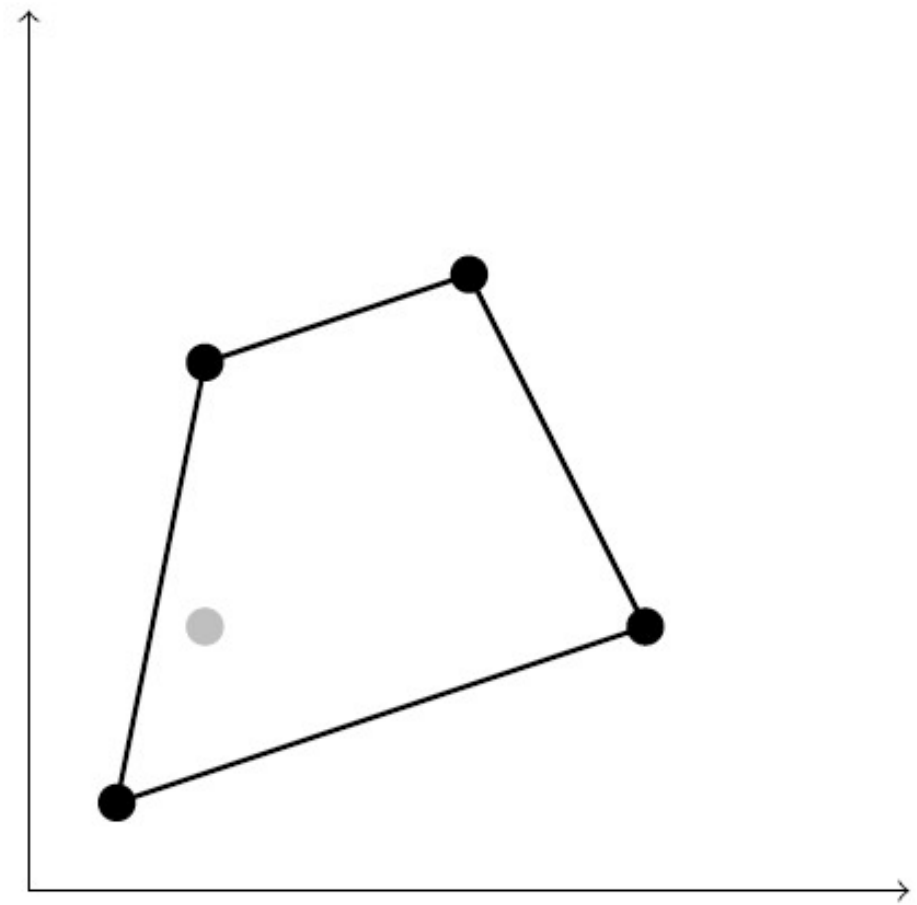
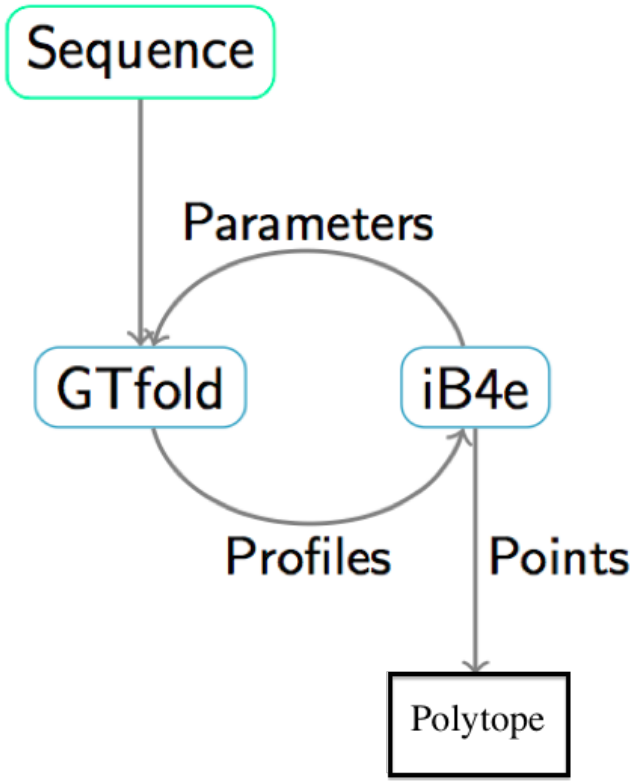
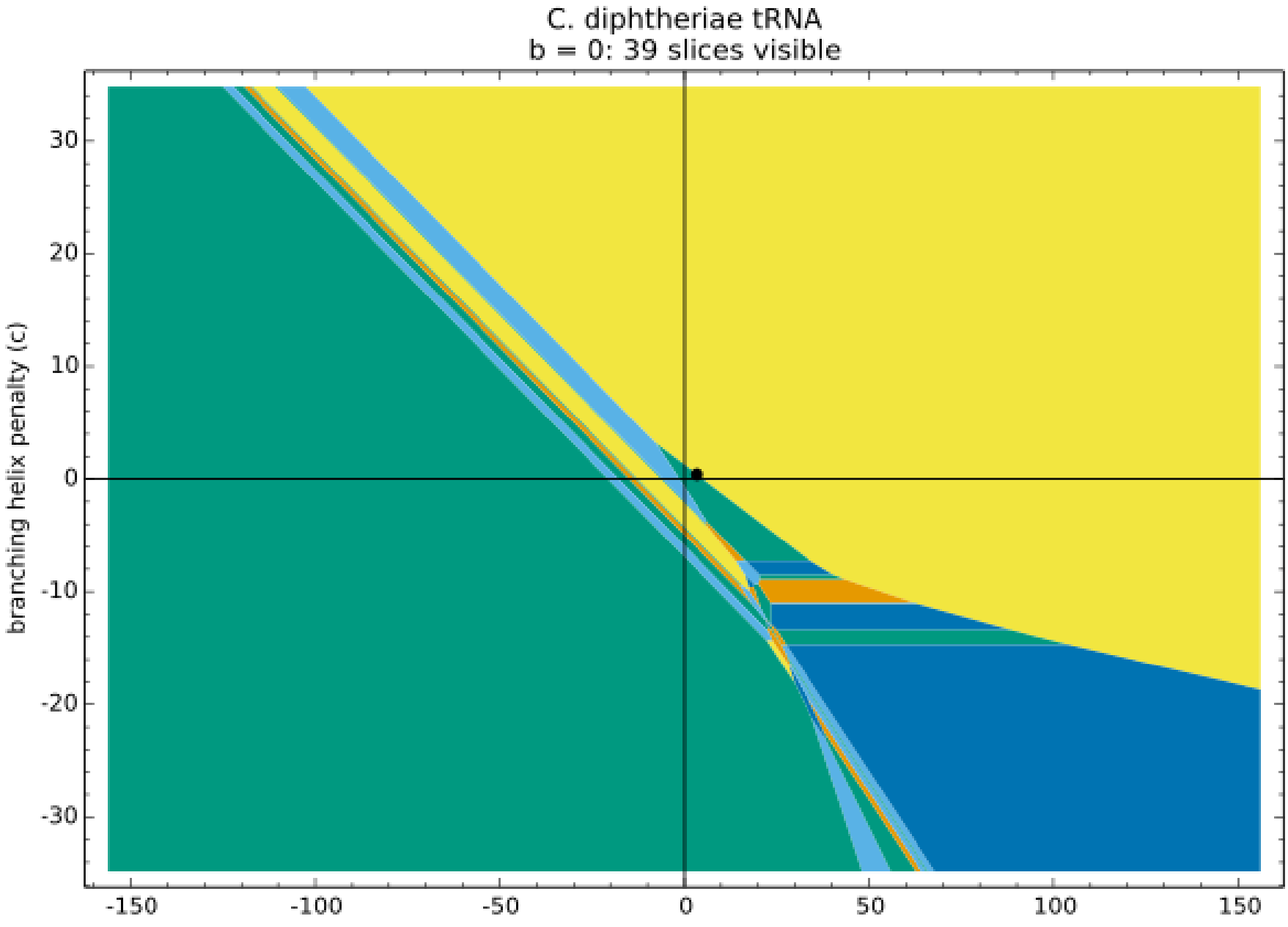


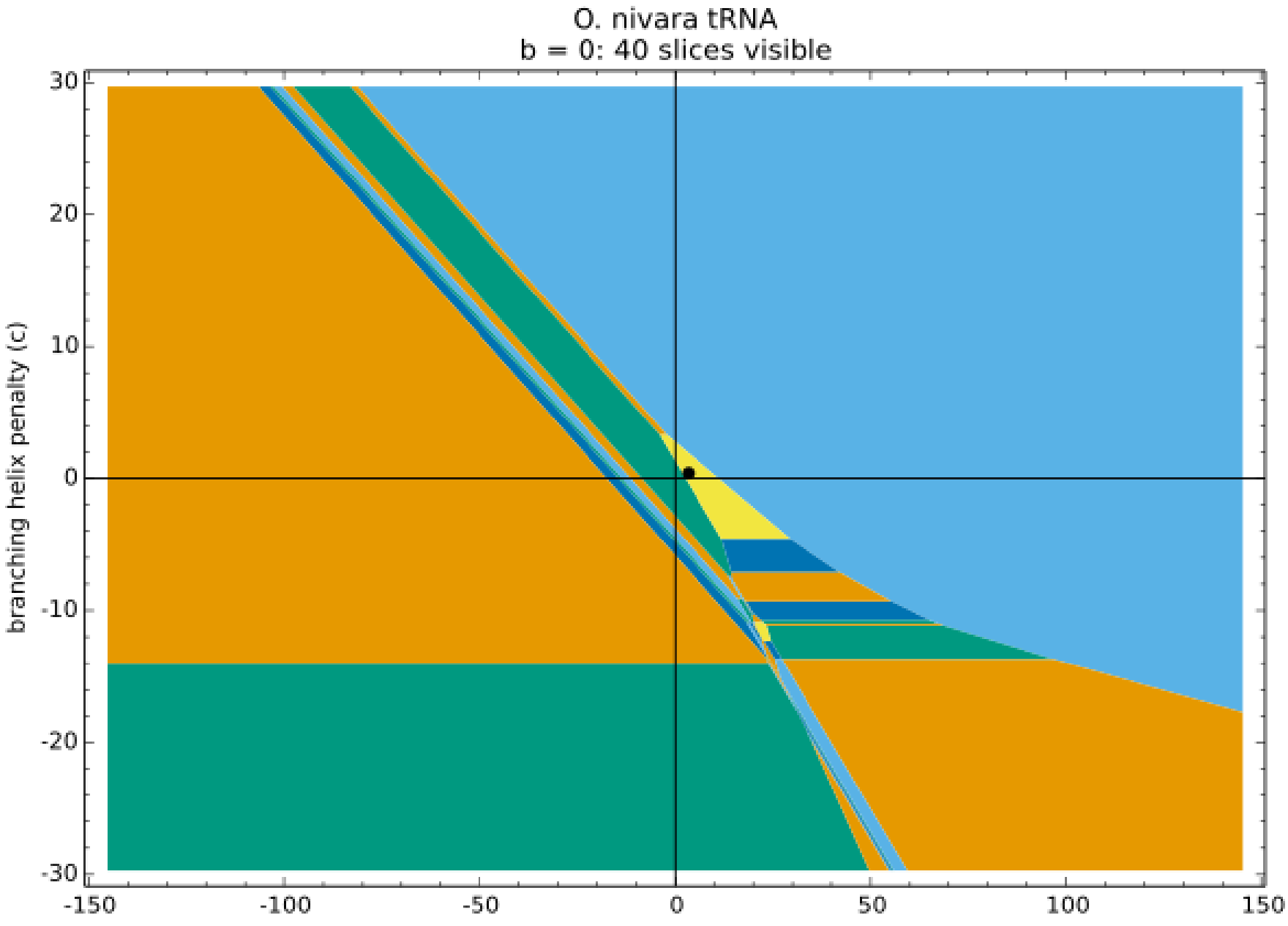
iB4e and beneath-beyond method



Example


C. diphtheriae tRNA
b = 0: 39 slices visible
branching helix penalty (c)
30
20
10
0
-10
-20
-30
-150
-100
-50
0
50
100
150

Example


O. nivara tRNA
b = 0: 40 slices visible
branching helix penalty (c)
30
20
10
0
-10
-20
-30
-150
-100
-50
0
50
100
150

Future work

- Further develop our software to make it more stable and convenient.
- Run sensitivity analysis on our current multibranch loop parameters.
- Improve prediction to known structures by modifying multibranch loop parameters.
- Predict unknown structures with desired parameters.

Thank you!

References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