# Kinetic Backtracking of RNA folding

### Michael Geis

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Algorithm

- Select set of states
- Find starting structure
- Extending the Front
- Saddle Height

# 3 Future Work

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#### Leipzig Group

Chair of Bioinformatics Konstantin Klemm: Networks Matthias Kruspe: Sequence Alignments Christoph Flamm: RNA Folding Dynamics, Energy Landscapes

Chair of parallel Computing and Complex Systems Michael Geis: RNA Folding, Swarm Intelligence

Chair of Image Processing Christian Heine: BarVis Sebastian Poetzsch: PinfoldVis



#### Aim: Simulate the folding path of an RNA molecule

=> start at random coil=> end at minimum free energy (mfE)

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## **Essential components:**

Select a set of states

Model state transitions

Main issue: How to calculate energy barriers between states.

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#### How do we get from A to B?



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Select set of states Find starting structure Extending the Front Saddle Height

Calculate the suboptimal structures

- 1. Find mfE via DP and backtrack suboptimal structures
- This yields an upper triangular matrix with entry (i,j) denoting the free energy of the suboptimal structure on the subsequence (i,j)
- 3. Filter out subsequences, in which base i and j pair.

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Select set of states Find starting structure Extending the Front Saddle Height

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Select set of states Find starting structure Extending the Front Saddle Height

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Select set of states Find starting structure Extending the Front Saddle Height

### Determine the initial energy front

- 1. Rank extrema by
  - i) diagonal
  - ii) distance from edge of matrix
  - iii) 5' before 3'
- 2. Find the diagonal closest to the main diagonal that is not empty
- 3. Add substructures in that diagonal to the front if there is no conflict

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Select set of states Find starting structure Extending the Front Saddle Height



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Select set of states Find starting structure Extending the Front Saddle Height

### **Conflict**

A substructure (i,j) determines how the bases in that subsequence pair. Once (i,j) is part of the front, a pair (k,l) can only be added if  $[i, j] \cap [k, l] = \emptyset$ 

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Select set of states Find starting structure Extending the Front Saddle Height

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Select set of states Find starting structure Extending the Front Saddle Height

## Algorithm

 $\begin{aligned} & saddleheight = 0 \\ & Front \ F = initial \ structure \\ & while(F! = mfE) \\ & increment \ saddleheight \\ & for \ x \ in \ extrema \\ & calculate \ saddle \ point \ S \ between \ x \ and \ F \\ & if(E(S) - E(F) < saddleheight) \\ & extend \ F \ by \ x \\ & remove \ all \ x \ in \ extrema \ that \ conflict \ with \ F \end{aligned}$ 

Select set of states Find starting structure Extending the Front Saddle Height

## **Extend Front**

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Select set of states Find starting structure Extending the Front Saddle Height

## **Extend Front**

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Select set of states Find starting structure Extending the Front Saddle Height

# **Final Front**

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Select set of states Find starting structure Extending the Front Saddle Height

## Saddle Height

To go from conformation A to B, there are  $(A \Delta B)!$  direct paths.

The best path does not have to be direct.

The saddle height is the highest energy of the lowest path:

$$S = min_{P: A \rightarrow B}max_{x \in P}E(x)$$

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Current Heuristic: Morgan-Higgs(1998)

- 1. Rank the elements in  $B \setminus A$  by conflict
- 2. For each x in  $B \setminus A$ 
  - i) Remove the base pairs in A that conflict with x
  - ii) Add x
  - iii) Add all other elements in  $B \setminus A$  that can be added now
  - iv) Record the energies of the traversed states
- 3. Take the highest recorded energy as saddle energy

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### Future Work

Experiment with different heuristics for saddle heights

In Particular:

What is the lowest saddle point for n extensions of the front?

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## Acknowledgments

Christoph Flamm, Peter Stadler



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