Kinetic Backtracking of RNA folding

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1. Introduction
2. Algorithm
   - Select set of states
   - Find starting structure
   - Extending the Front
   - Saddle Height
3. Future Work

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)

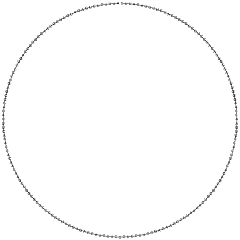
Essential components:

Select a set of states

Model state transitions

Main issue: How to calculate energy barriers between states.

How do we get from A to B?



Calculate the suboptimal structures

1. Find mfE via DP and backtrack suboptimal structures
2. 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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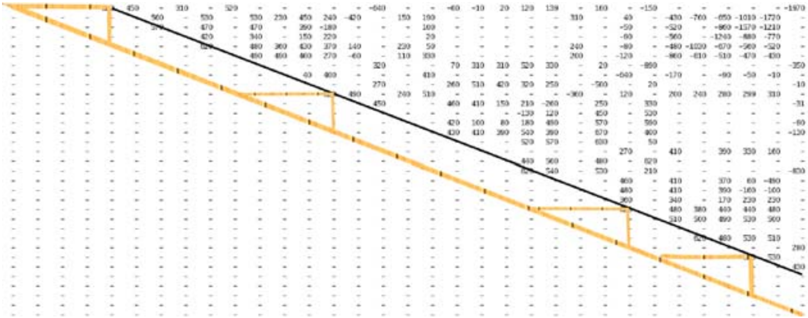
Determine the initial energy front

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



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 $[i,j] \cap [k,l] = \emptyset$

GUCCUUGCGUGAGGACAGCCCUUAUGUGAGGGC

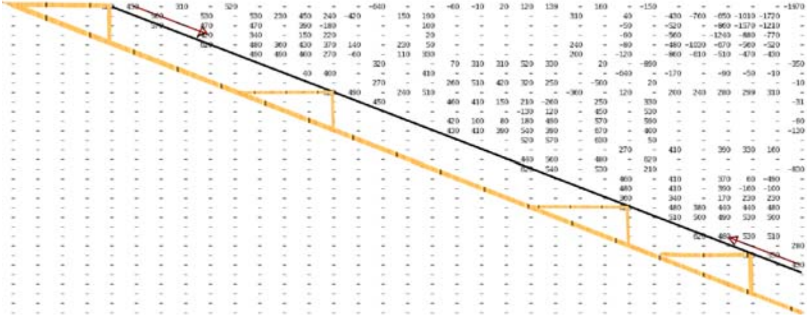
```
.................................
(...)............................   ( 1, 5)
.........(...)...................   (10,14)
.....................(...).......   (22,26)
..........................(...)..   (27,31)
(...)....(...).......(...)(...)..
```

Algorithm

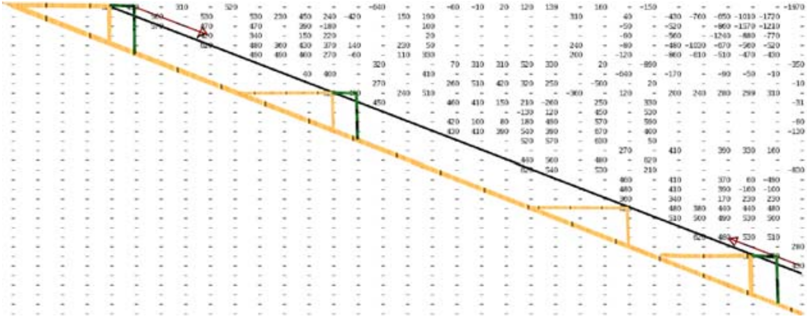
$saddleheight = 0$
$Front\ F = initial\ structure$

$while(F\,! = mfE)$
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

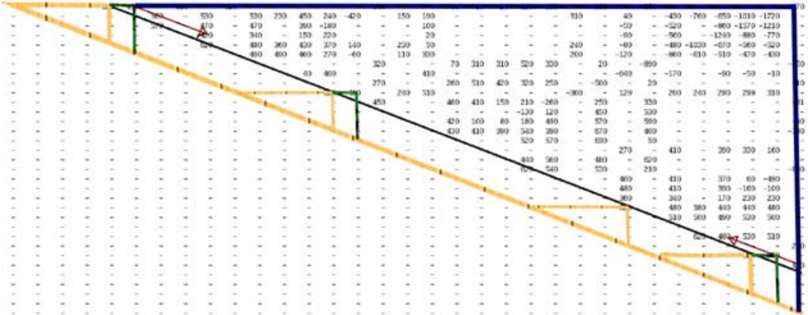
Extend Front



Extend Front



Final Front



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:

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

Current Heuristic: Morgan-Higgs(1998)

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

Future Work

Experiment with different heuristics for saddle heights

In Particular:

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

Acknowledgments

Christoph Flamm, Peter Stadler