The ViennaRNA Websuite: barriers webserver

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1. Barrier trees
   - Fitness landscape
   - Free energy landscape of RNA secondary structures
   - The flooding algorithm `barriers`
   - Re-folding pathway between local minima
   - Transition rates

$$\text{Landscape} = \{\mathcal{X}, \mathcal{H}, f\}$$

$\mathcal{X}$ . . . set of configurations
$\mathcal{H}$ . . . topological structure on $\mathcal{X}$ that determines accessibility
f . . . fitness/energy function with $f : \mathcal{X} \rightarrow \mathbb{R}$

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find local minima, gradient basins and saddle points

- build up gradient basins/macrostates $B(s)$, *i.e. collections of configurations arround local minima*
  if y is local minimum of $B(s)$ then

$$x \in B(s) \Leftrightarrow \exists p \in \mathbb{P}_{xy} : \forall z \in p : f(z) \leq f(x)$$

- saddle points s are configurations where more than one local minimum is reachable along such a path p , *i.e. saddle points connect basins* $B_k(s)$
- all configurations in $B(s)$ are mutually connected by paths that dont exceed $f(s)$
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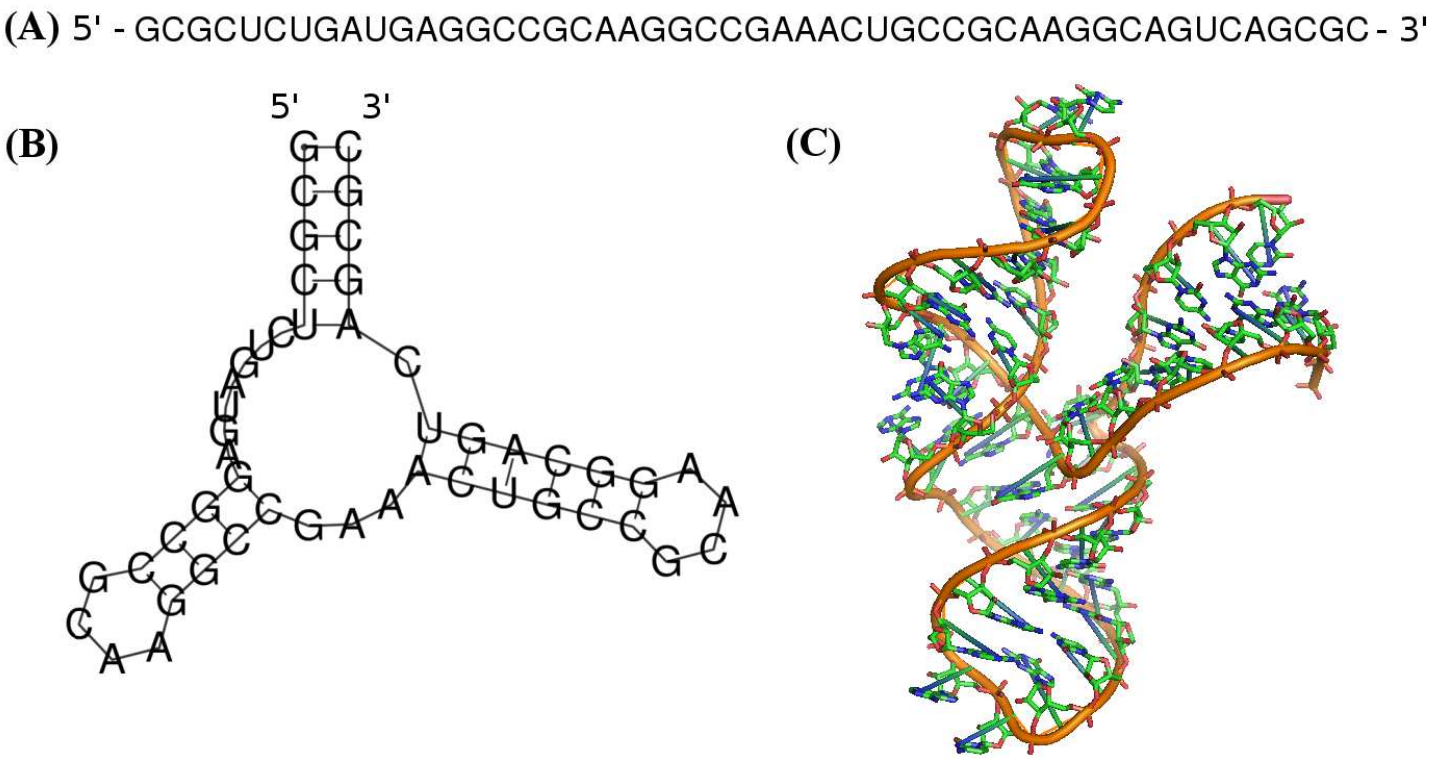
- all configurations in $B(s)$ are mutually connected by paths that dont exceed $f(s)$
- results in a hierarchical structure of basins and saddle points
- barriers $f^{\mathcal{B}}(x, y)$ between two local minima x, y:

$$f^{\mathcal{B}}(x, y) = \min_{p \in \mathbb{P}_{xy}} \max_{z \in p} f(z)$$

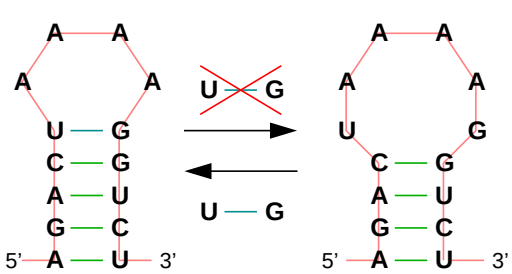
Energy landscape of biopolymers play important role

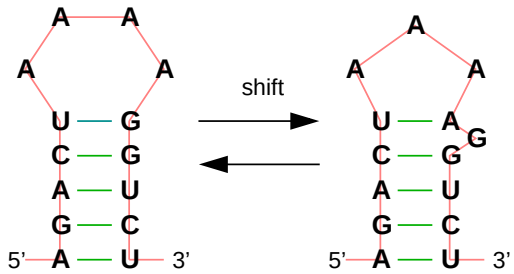
- RNA is one of the most important building blocks in living cells
- ncRNA structure conformation crucial for regulation of cellular processes



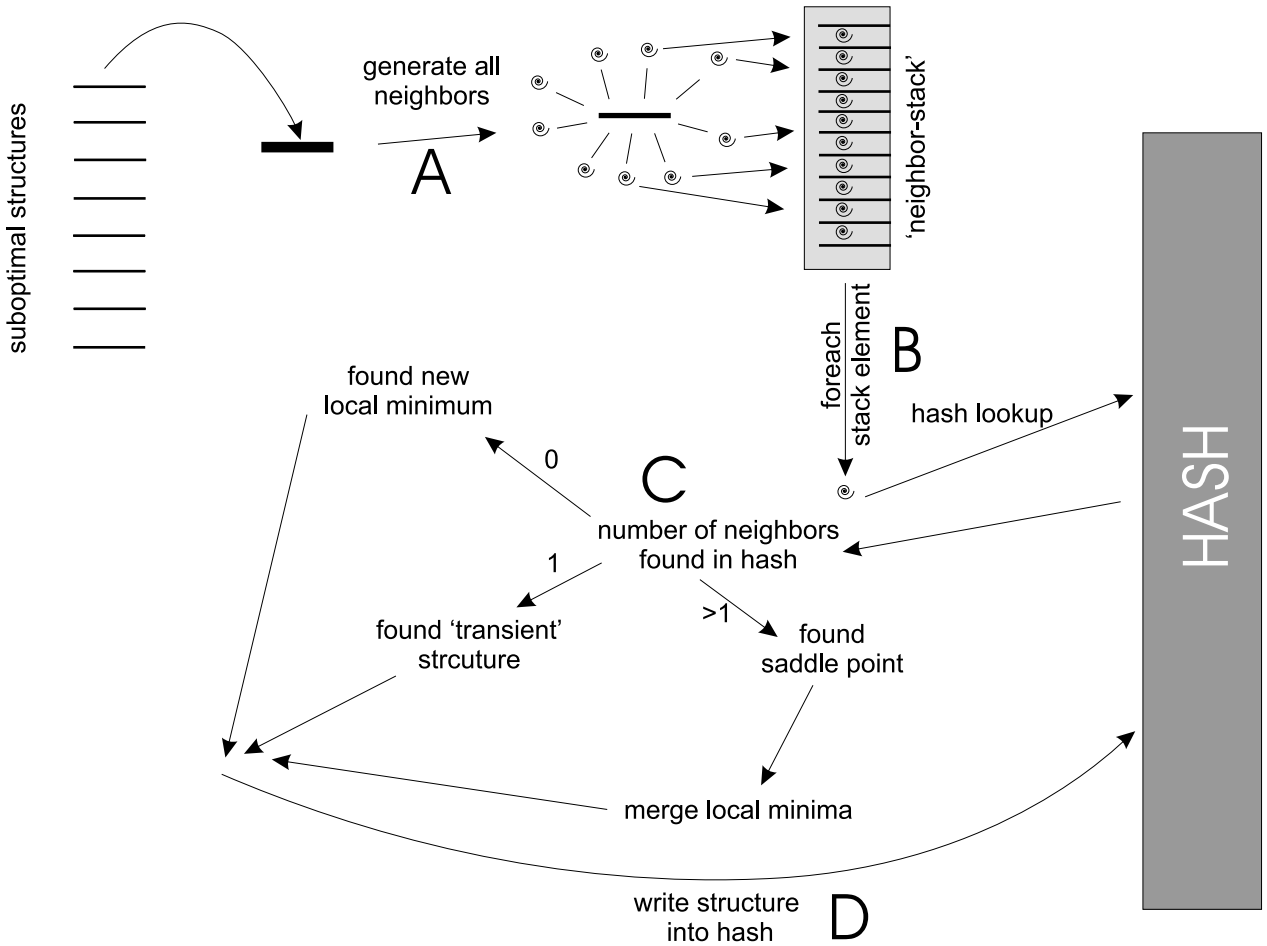
Free energy landscape of RNA secondary structures

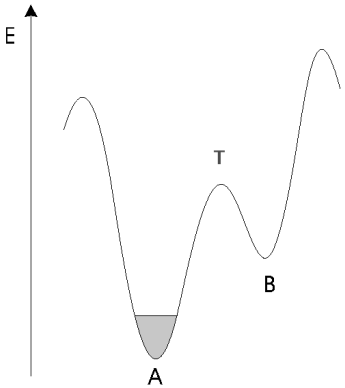
- **Configurations:**
  complete set of suboptimal secondary structures arround energy range δ of MFE structure (e.g. obtained by `RNAsubopt`)
- **Topology/move set:**
  base pair delete, base pair insert, shift move





- **Fitness function:**
  free energy of secondary structure


suboptimal structures
generate all neighbors
A
'neighbor-stack'
foreach stack element
B
found new local minimum
hash lookup
HASH
0
C
number of neighbors found in hash
1
>1
found 'transient' strcuture
found saddle point
merge local minima
write structure into hash
D



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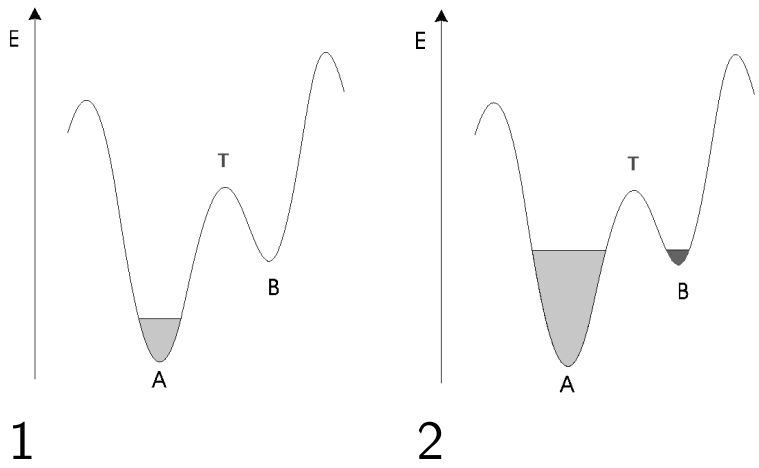
E
T
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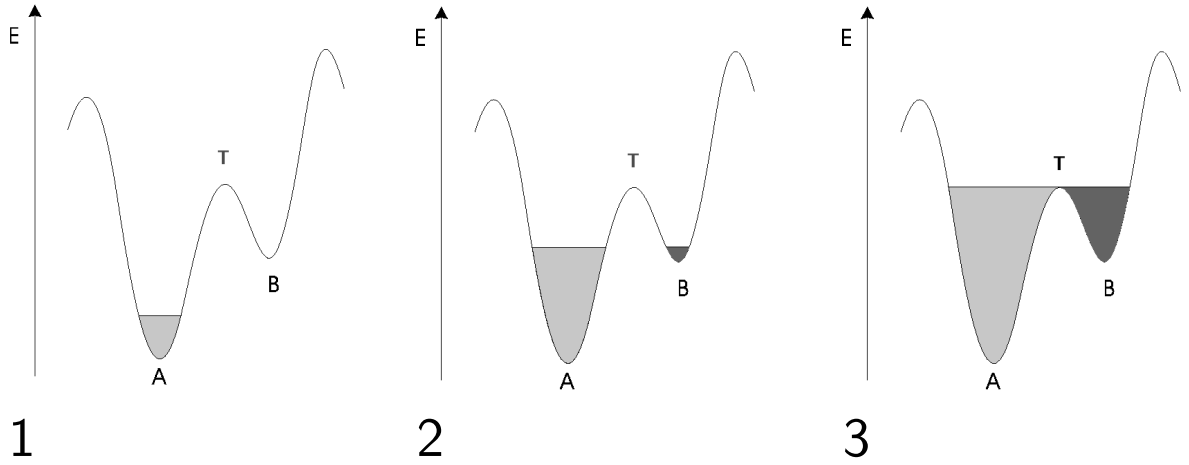
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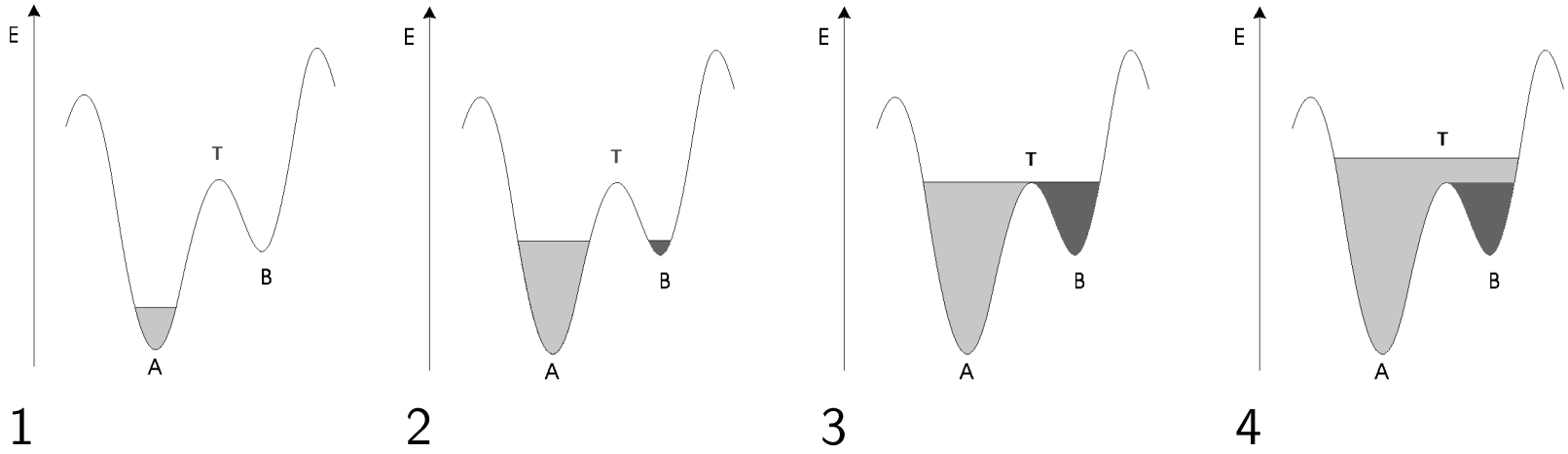
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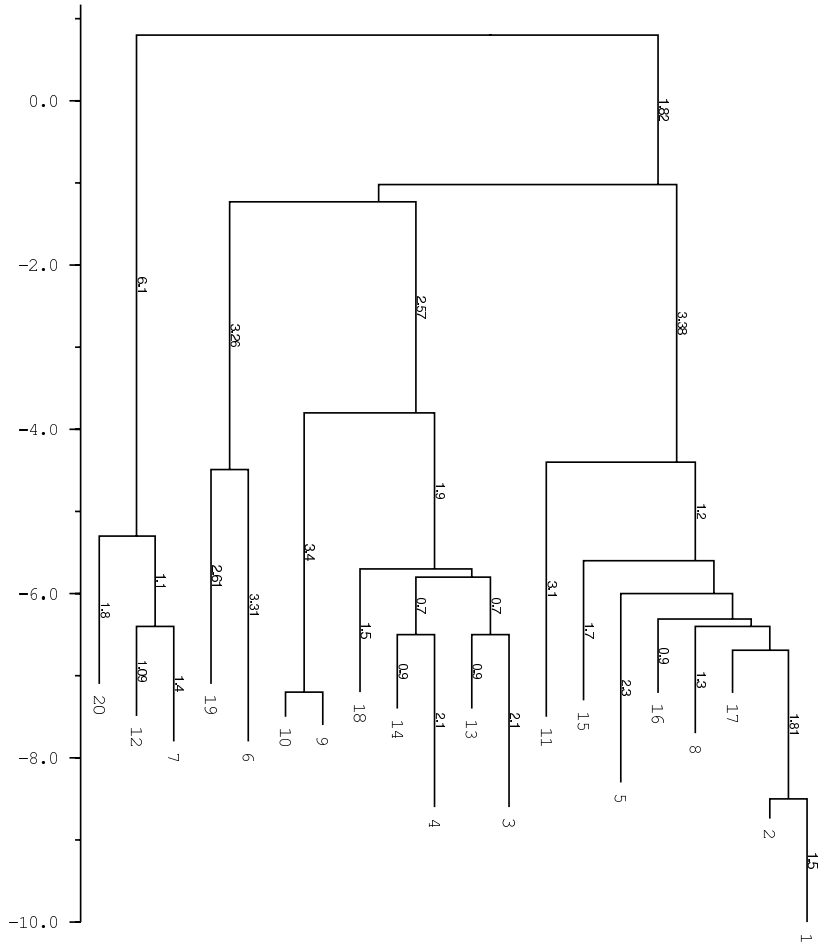
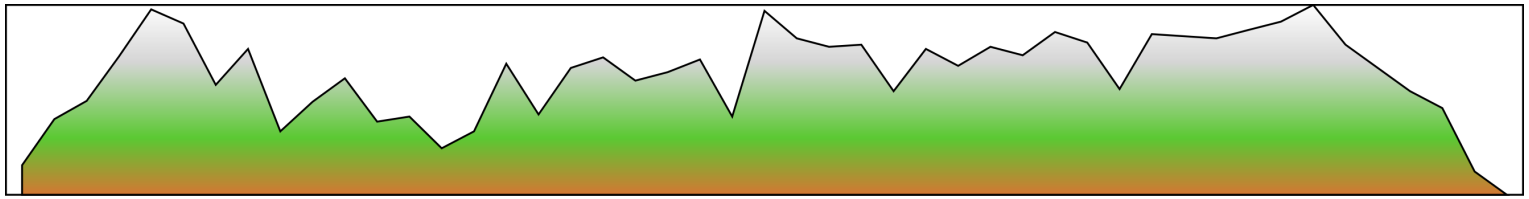
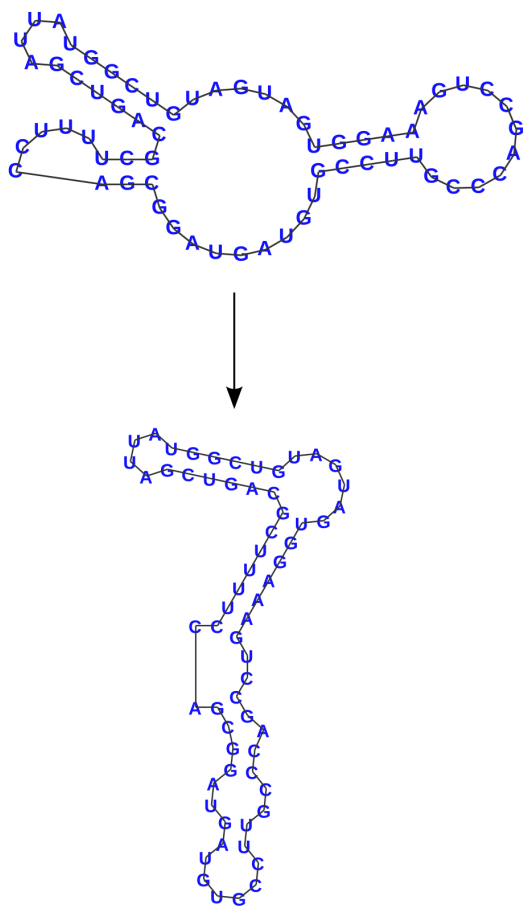


sR29 sRNA of Pyrococcus furiosus





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- transition of the sytem from basin/macro state α into basin/macro state β
- the barrier tree generation is a partitioning of the state space

$$Q_\alpha = \sum_{j \in \alpha} e^{-E_j/kT}, G_\alpha = -kT \cdot lnQ_\alpha$$

$$Q = \sum_\alpha Q_\alpha$$

- the equilibrium distribution of state α is given by

$$\pi_\alpha = \frac{Q_\alpha}{Q}$$

- to take reversibility of the system into account, $\forall \beta, \alpha$

$$r_{\beta\alpha}\pi_\alpha = r_{\alpha\beta}\pi_\beta$$

$$\frac{r_{\beta\alpha}}{r_{\alpha\beta}} = \frac{e^{-G_\beta/kT}}{e^{-G_\alpha/kT}}$$

$$\frac{r_{\beta\alpha}}{r_{\alpha\beta}} = \frac{e^{-(Es_{\alpha\beta}-G_\alpha)/kT}}{e^{-(Es_{\alpha\beta}-G_\beta)/kT}}$$

- transition rate to reach state β from state α

$$r_{\beta\alpha} = \Gamma_{\alpha\beta} \cdot e^{-(Es_{\alpha\beta}-G_\alpha)/kT}$$

RNA folding can be modeled as a *Markov process*

The probability distribution P of structures as a function of time is ruled by a set of forward equations, also known as the master equation

$$\frac{dP_t(x)}{dt} = \sum_{y \neq x} [P_t(y)k_{yx} - P_t(x)k_{xy}]$$

Given an initial population distribution P_0, how does the system evolve in time?

$$\frac{d}{dt}P_t = \mathbf{U}P_t \quad \Longrightarrow \quad P_t = e^{t\mathbf{U}}P_0$$

- Coarse grained approach
- Conformation space is mapped onto macro states of the barrier tree
- Transition rates for matrix U are available after applying barriers algorithm
- Deterministic process

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Starting at a specific local minimum of the barrier tree how long does the sytem takes to reach an equilibrium state?

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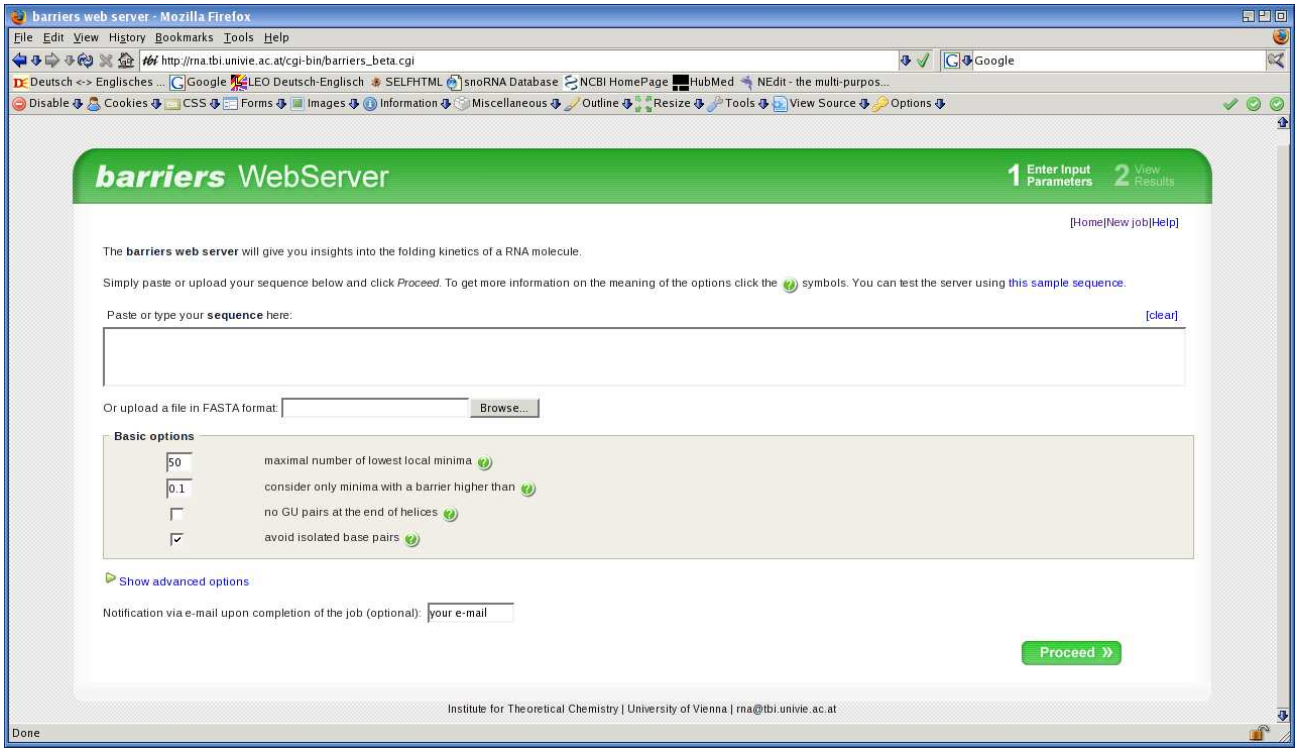
- Conformation space is mapped onto macro states of the barrier tree
- Transition rates for matrix U are available after applying barriers algorithm
- Deterministic process

Starting at a specific local minimum of the barrier tree how long does the sytem takes to reach an equilibrium state?

How much are other local minima populated on the way from a start structure to the local minimum?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Disable Cookies CSS Forms Images Information Miscellaneous Outline Resize Tools View Source Options
barriers WebServer
1 Enter Input Parameters
2 View Results
[Home|New job|Help]
The barriers web server will give you insights into the folding kinetics of a RNA molecule.
Simply paste or upload your sequence below and click Proceed. To get more information on the meaning of the options click the symbols. You can test the server using this sample sequence.
Paste or type your sequence here:
[clear]
Or upload a file in FASTA format:
Browse...
Basic options
50
maximal number of lowest local minima
0.1
consider only minima with a barrier higher than
no GU pairs at the end of helices
avoid isolated base pairs
Show advanced options
Notification via e-mail upon completion of the job (optional):
your e-mail
Proceed »
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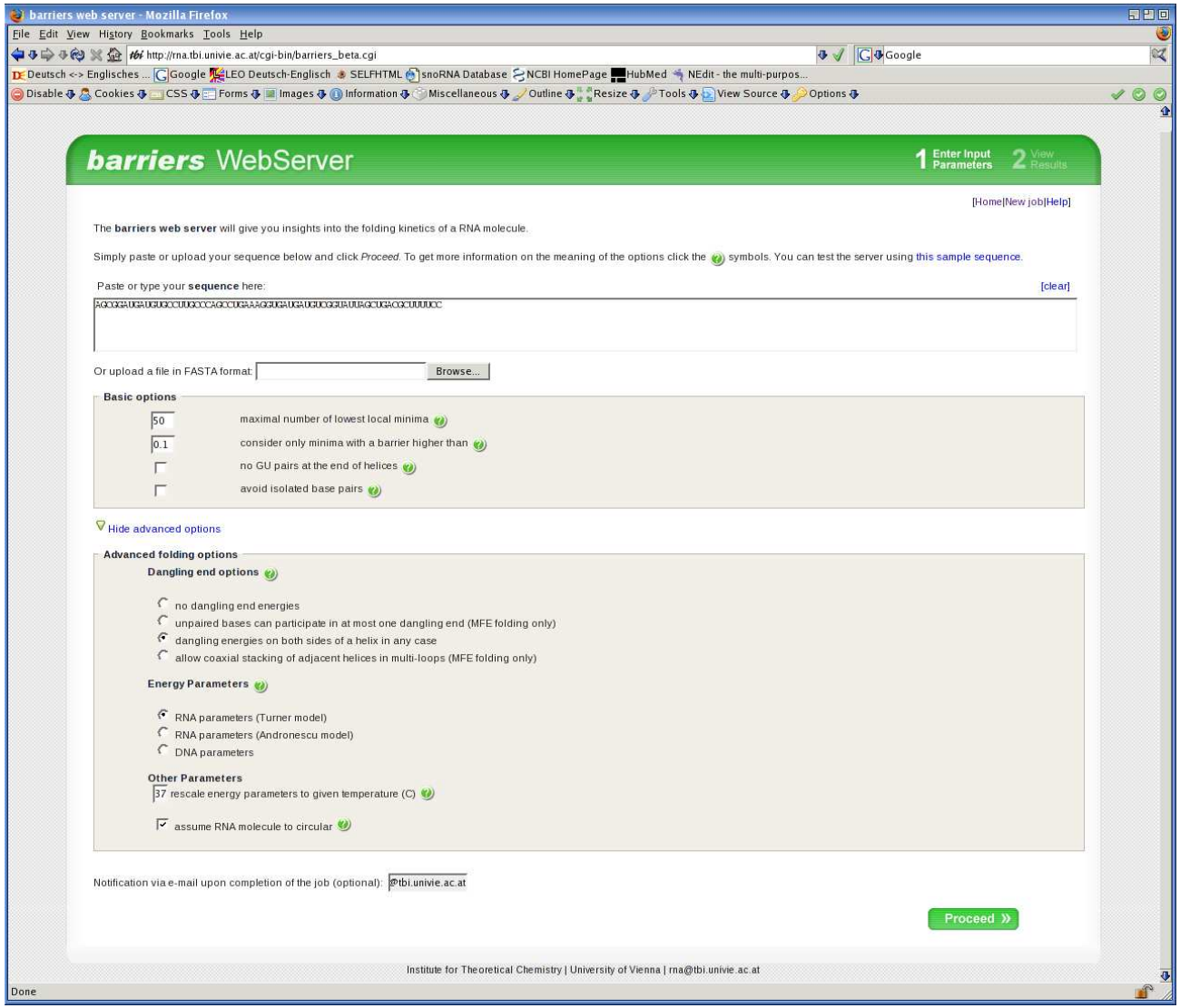
Done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http://rna.tbi.univie.ac.at/cgi-bin/barriers_beta.cgi
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Paste or type your sequence here:
[clear]
Or upload a file in FASTA format:
Browse...
Basic options
50 maximal number of lowest local minima
0.1 consider only minima with a barrier higher than
no GU pairs at the end of helices
avoid isolated base pairs
Hide advanced options
Advanced folding options
Dangling end options
no dangling end energies
unpaired bases can participate in at most one dangling end (MFE folding only)
dangling energies on both sides of a helix in any case
allow coaxial stacking of adjacent helices in multi-loops (MFE folding only)
Energy Parameters
RNA parameters (Turner model)
RNA parameters (Andronescu model)
DNA parameters
Other Parameters
37 rescale energy parameters to given temperature (C)
assume RNA molecule to circular
Notification via e-mail upon completion of the job (optional):
@tbi.univie.ac.at
Proceed »
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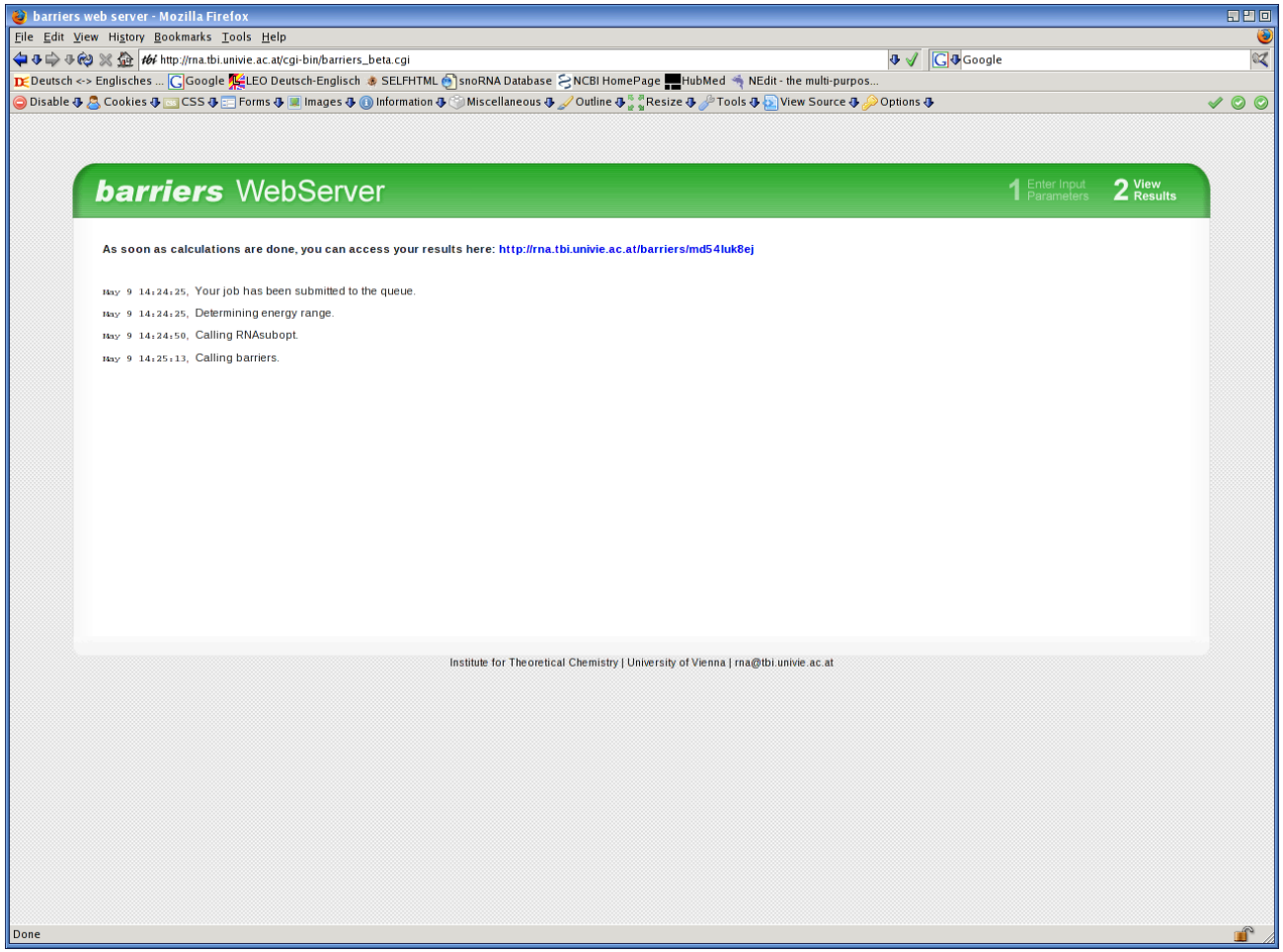
Done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http://rna.tbi.univie.ac.at/cgi-bin/barriers_beta.cgi
barriers WebServer
1 Enter Input Parameters
2 View Results
As soon as calculations are done, you can access your results here: http://rna.tbi.univie.ac.at/barriers/md54luk8ej
May 9 14:24:25, Your job has been submitted to the queue.
May 9 14:24:25, Determining energy range.
May 9 14:24:50, Calling RNAsubopt.
May 9 14:25:13, Calling barriers.
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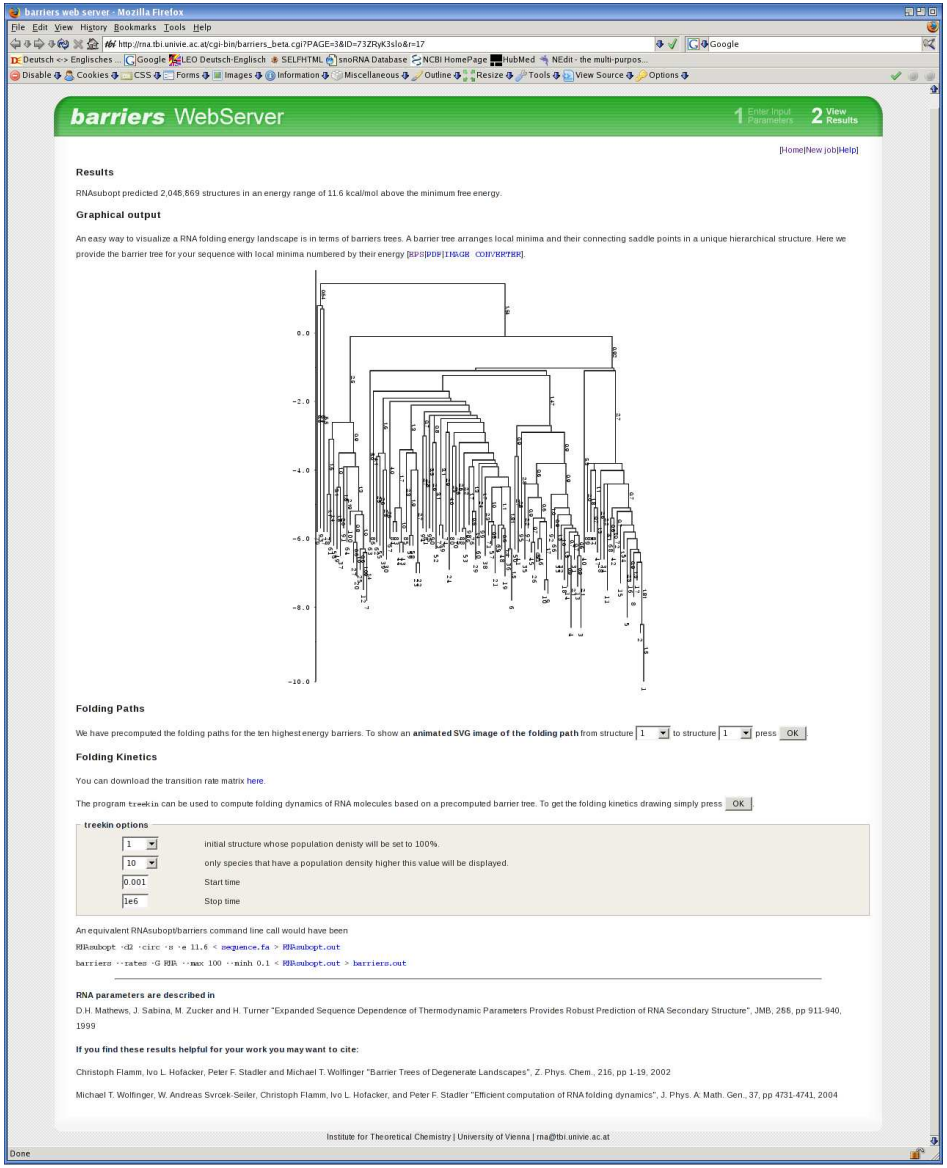
Done


barriers web server - Mozilla Firefox
barriers WebServer
1 Enter Input Parameters
2 View Results
[Home|New job|Help]
Results
RNAsubopt predicted 2,048,869 structures in an energy range of 11.6 kcal/mol above the minimum free energy.
Graphical output
An easy way to visualize a RNA folding energy landscape is in terms of barriers trees. A barrier tree arranges local minima and their connecting saddle points in a unique hierarchical structure. Here we provide the barrier tree for your sequence with local minima numbered by their energy [EPS|PDF|IMAGE CONVERTER].
Folding Paths
We have precomputed the folding paths for the ten highest energy barriers. To show an animated SVG image of the folding path from structure 1 to structure 1 press OK
Folding Kinetics
You can download the transition rate matrix here.
The program treekin can be used to compute folding dynamics of RNA molecules based on a precomputed barrier tree. To get the folding kinetics drawing simply press OK
treekin options
initial structure whose population denisty will be set to 100%.
only species that have a population density higher this value will be displayed.
Start time
Stop time
An equivalent RNAsubopt/barriers command line call would have been
RNAsubopt -d2 -circ -s -e 11.6 < sequence.fa > RNAsubopt.out
barriers --rates -G RNA --max 100 --minh 0.1 < RNAsubopt.out > barriers.out
RNA parameters are described in
D.H. Mathews, J. Sabina, M. Zucker and H. Turner "Expanded Sequence Dependence of Thermodynamic Parameters Provides Robust Prediction of RNA Secondary Structure", JMB, 288, pp 911-940, 1999
If you find these results helpful for your work you may want to cite:
Christoph Flamm, Ivo L. Hofacker, Peter F. Stadler and Michael T. Wolfinger "Barrier Trees of Degenerate Landscapes", Z. Phys. Chem., 216, pp 1-19, 2002
Michael T. Wolfinger, W. Andreas Svrcek-Seiler, Christoph Flamm, Ivo L. Hofacker, and Peter F. Stadler "Efficient computation of RNA folding dynamics", J. Phys. A: Math. Gen., 37, pp 4731-4741, 2004
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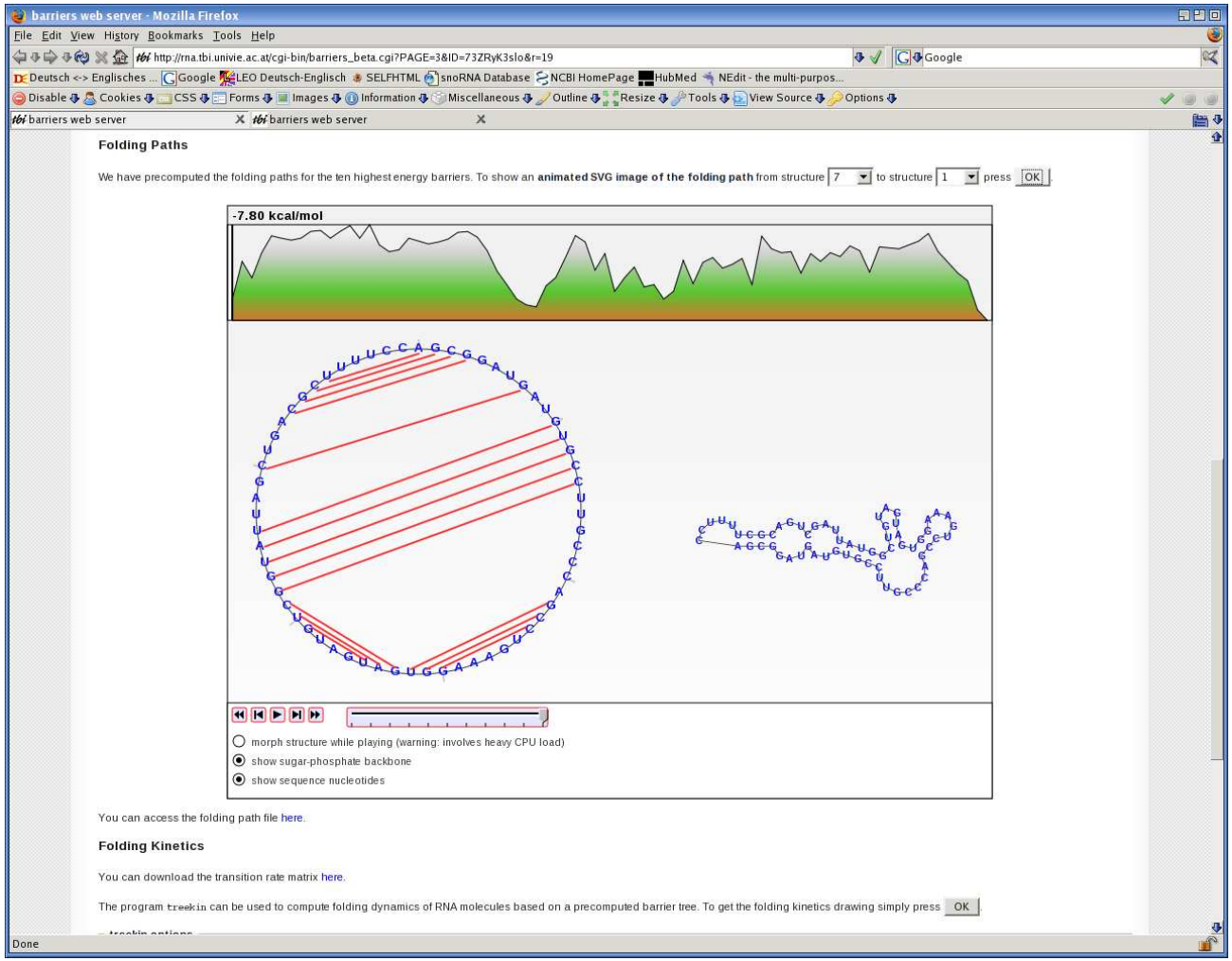
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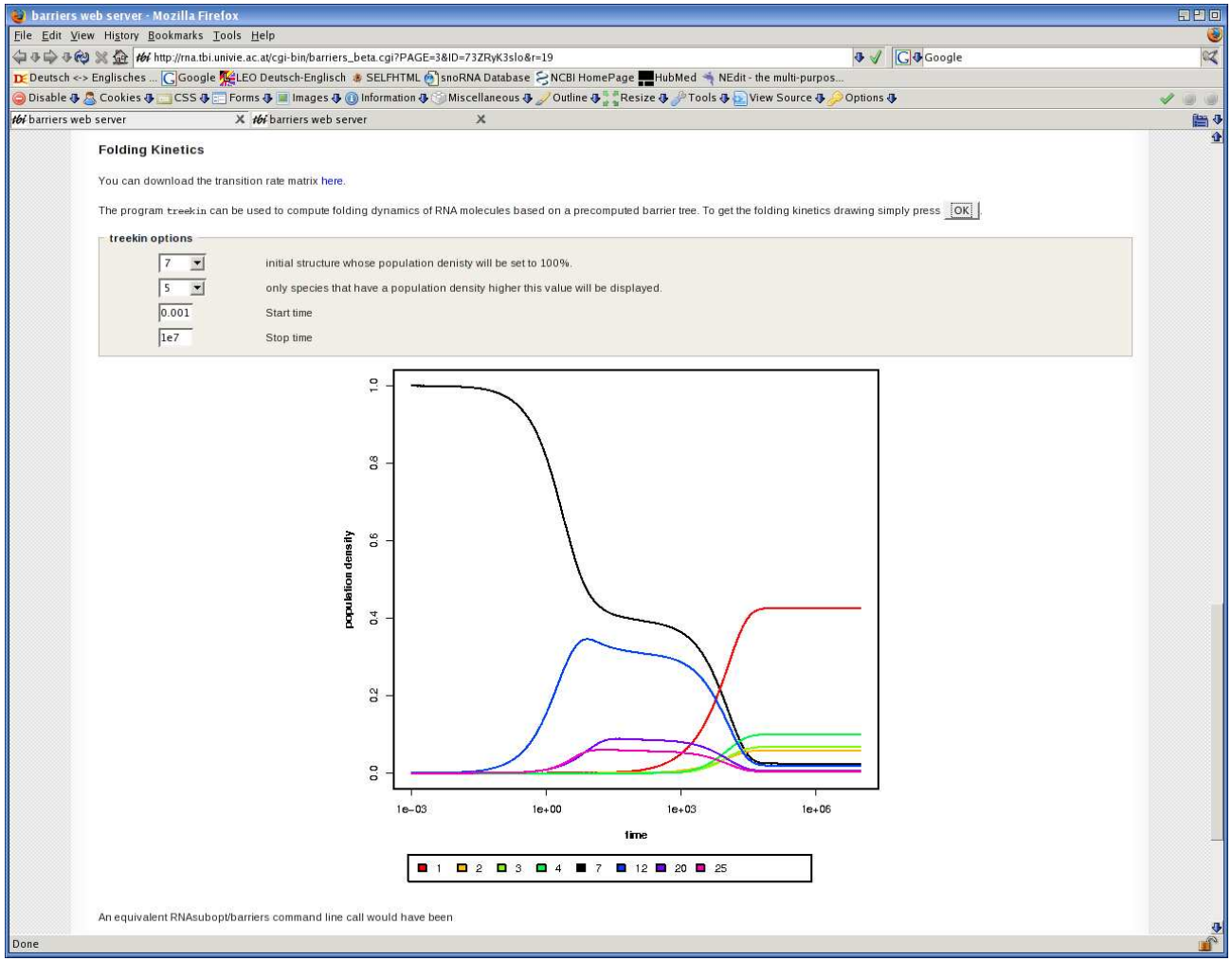
http://rna.tbi.univie.ac.at/cgi-bin/barriers_beta.cgi?PAGE=3&ID=73ZRyK3slo&r=19
barriers web server
Folding Paths
We have precomputed the folding paths for the ten highest energy barriers. To show an animated SVG image of the folding path from structure 7 to structure 1 press OK
-7.80 kcal/mol
morph structure while playing (warning: involves heavy CPU load)
show sugar-phosphate backbone
show sequence nucleotides
You can access the folding path file here.
Folding Kinetics
You can download the transition rate matrix here.
The program treekin can be used to compute folding dynamics of RNA molecules based on a precomputed barrier tree. To get the folding kinetics drawing simply press OK
Done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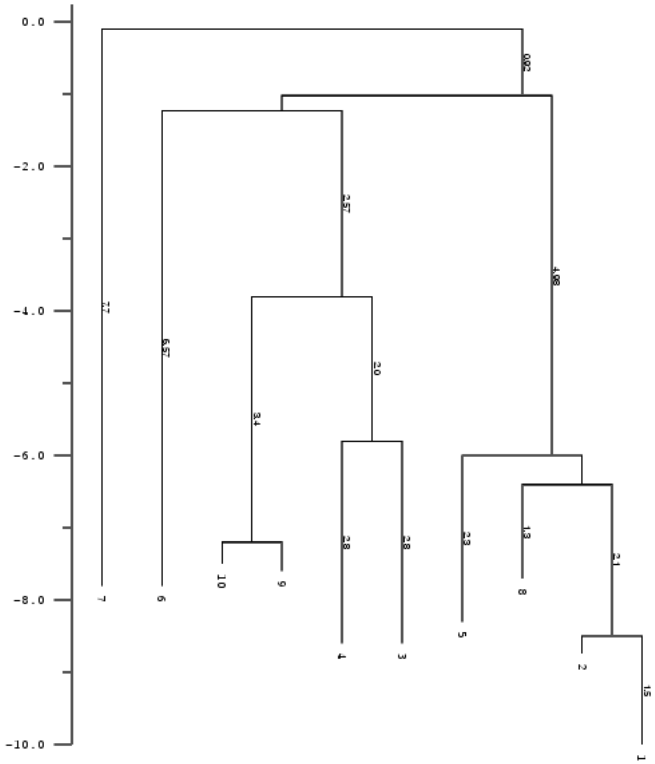
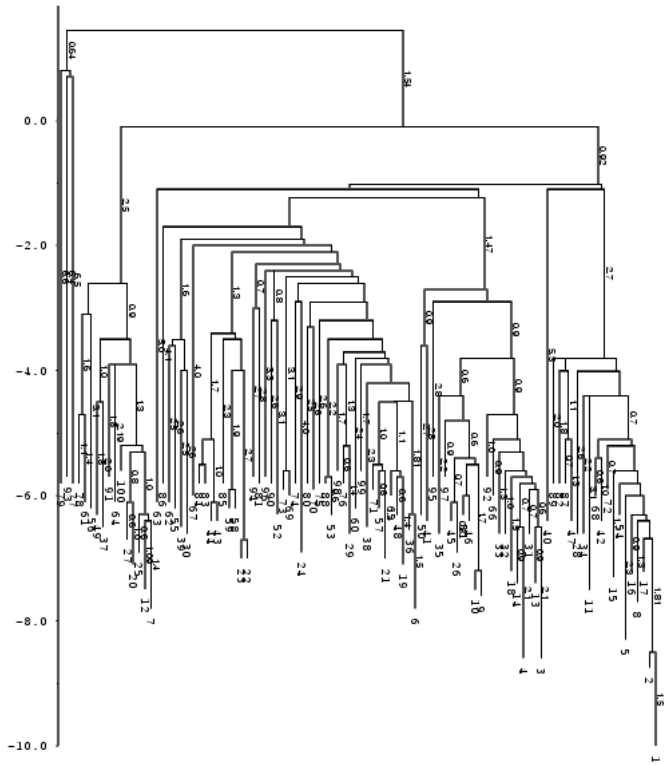
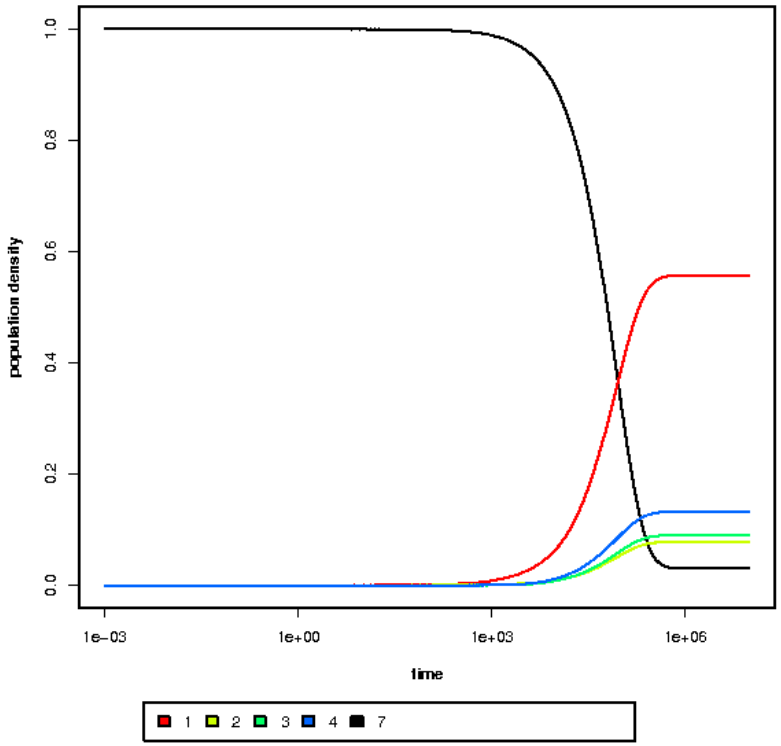
treekin options
7
initial structure whose population denisty will be set to 100%.
5
only species that have a population density higher this value will be displayed.
0.001
Start time
1e7
Stop time
population density
0.0
0.2
0.4
0.6
0.8
1.0
1e−03
1e+00
1e+03
1e+06
time
1 2 3 4 7 12 20 25
An equivalent RNAsubopt/barriers command line call would have been
Done



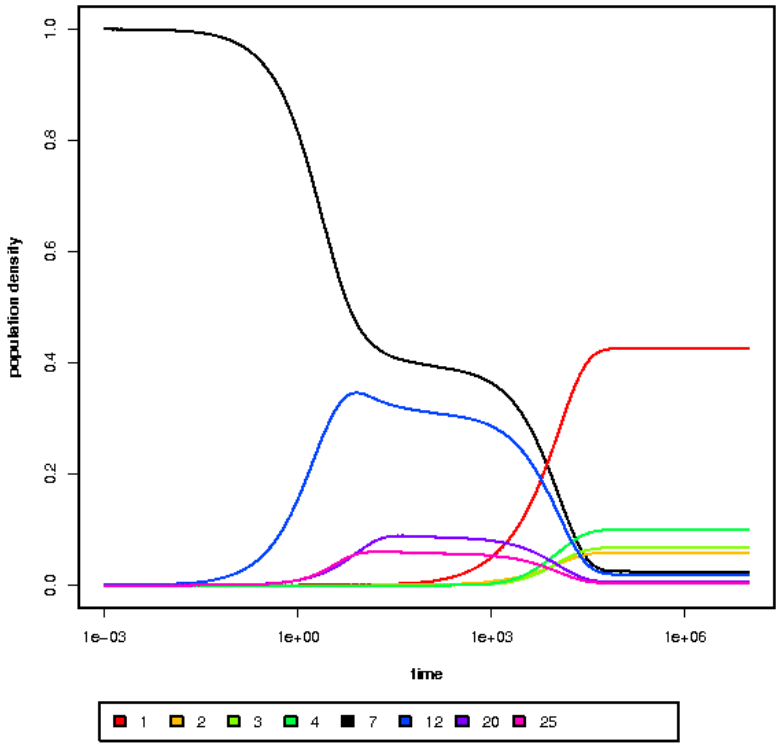
10 macro states



100 macro states



10 macro states



100 macro states

Thanks to:

Stephan Bernhart
Lukas Endler
Christoph Flamm
Andreas Gruber
Ivo Hofacker
Richard Neuböck
Peter Stadler
Michael Wolfinger

The audience for listening