Wang-Landau and Path Sampling of Biopolymers

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Outline

1 Biopolymer models

2 Energy landscapes

3 Barrier tree dynamics

4 Wang-Landau sampling

5 RNA refolding

6 Summary

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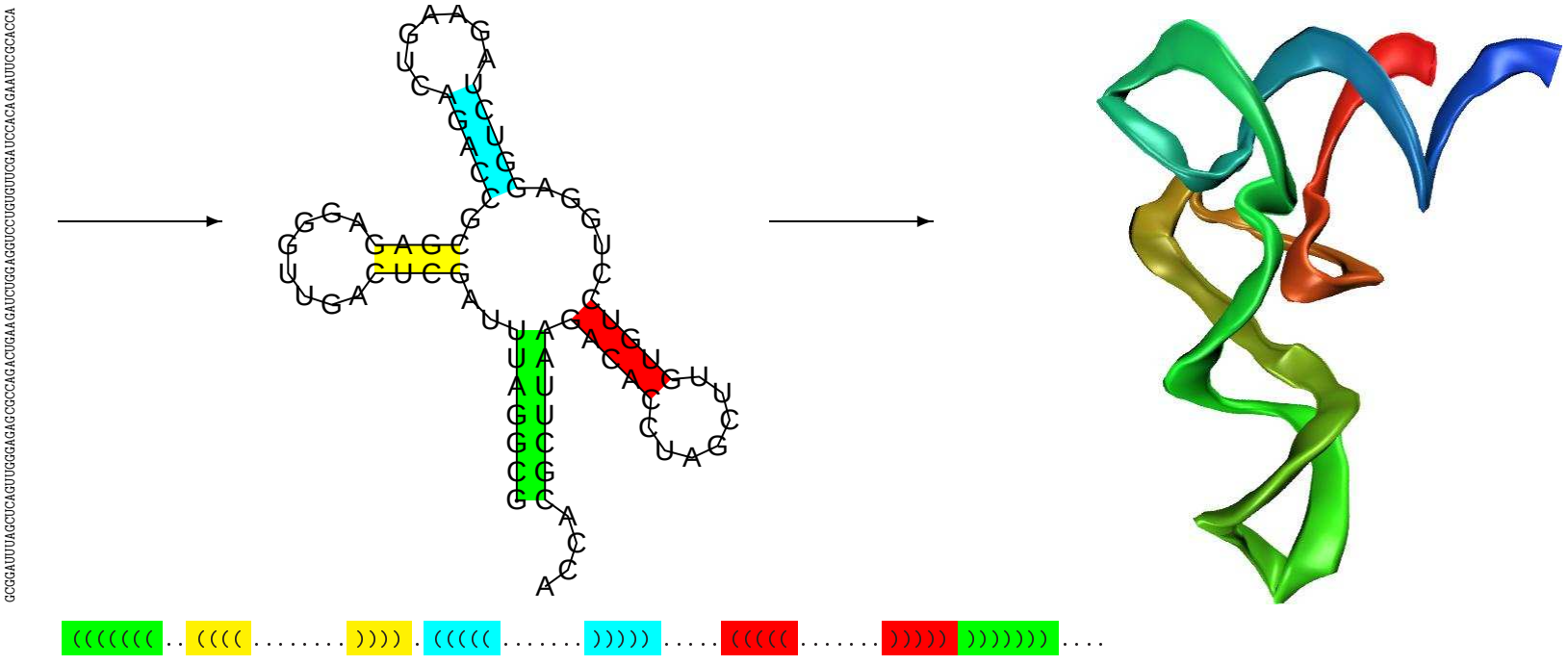
The RNA model



A secondary structure is a list of base pairs that fulfills two constraints:

- A base may participate in at most one base pair.
- Base pairs must not cross, i.e., no two pairs (i,j) and (k,l) may have $i < k < j < l$. (no pseudo-knots)

The optimal as well as the suboptimal structures can be computed recursively.

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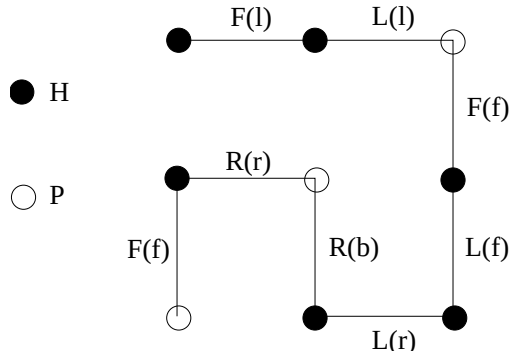
The HP-model

In this *simplified model*, a conformation is a *self-avoiding walk (SAW)* on a given lattice in 2 or 3 dimensions. Each bond is a straight line, bond angles have a few discrete values. The 20 letter alphabet of amino acids (monomers) is reduced to a two letter alphabet, namely **H** and **P**. H represents hydrophobic monomers, P represents hydrophilic or *polar* monomers.

Advantages:

- lattice-independent folding algorithms
- simple energy function
- hydrophobicity can be reasonably modeled



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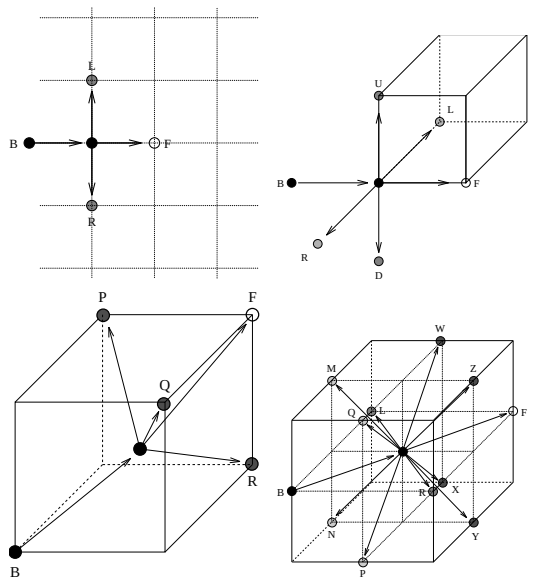

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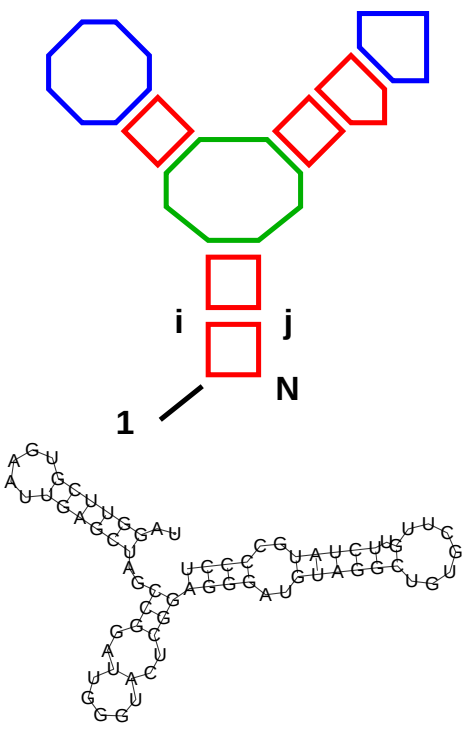
Energy functions

RNA

The standard energy model expresses the free energy of a secondary structure S as the sum of the energies of its loops l

$$E(\mathrm{S}) = \sum_{l \in \mathrm{S}} E(l)$$



$E = -17.5 kcal/mol$

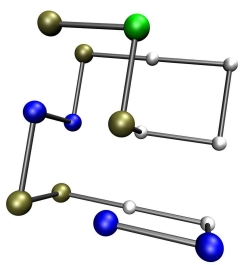
Lattice Proteins

The energy function for a sequence with n residues $\mathfrak{S} = \mathfrak{s}_1\mathfrak{s}_2\ldots\mathfrak{s}_n$ with $\mathfrak{s}_i \in \mathscr{A} = \{a_1, a_2, \ldots, a_b\}$, the alphabet of b residues, and an overall configuration $x = (\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_n)$ on a lattice $\mathscr{L}$ can be written as the sum of pair potentials

$$E(\mathfrak{S}, x) = \sum_{\substack{i < j-1 \\ |\mathbf{x}_i - \mathbf{x}_j| = 1}} \Psi[\mathfrak{s}_i, \mathfrak{s}_j].$$

	H	P
H	-1	0
P	0	0

	H	P	N	X
H	-4	0	0	0
P	0	1	-1	0
N	0	-1	1	0
X	0	0	0	0



$E = -16$

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Folding landscape - energy landscape

The energy landscape of a biopolymer molecule is a complex surface of the (free) energy versus the conformational degrees of freedom.

Number of RNA secondary structures

$c_n \sim 1.86^n \cdot n^{-\frac{3}{2}}$

dynamic programming algorithms available

Number of LP structures

$c_n \sim \mu^n \cdot n^{\gamma-1}$

problem is NP-hard

dim	Lattice Type	μ	γ
2	SQ	2.63820	1.34275
	TRI	4.15076	1.343
	HEX	1.84777	1.345
3	SC	4.68391	1.161
	BCC	6.53036	1.161
	FCC	10.0364	1.162

Formally, three things are needed to construct an energy landscape:

- A set X of configurations
- an energy function $f : X \to \mathbf{R}$
- a symmetric neighborhood relation $\mathfrak{N} : X \times X$

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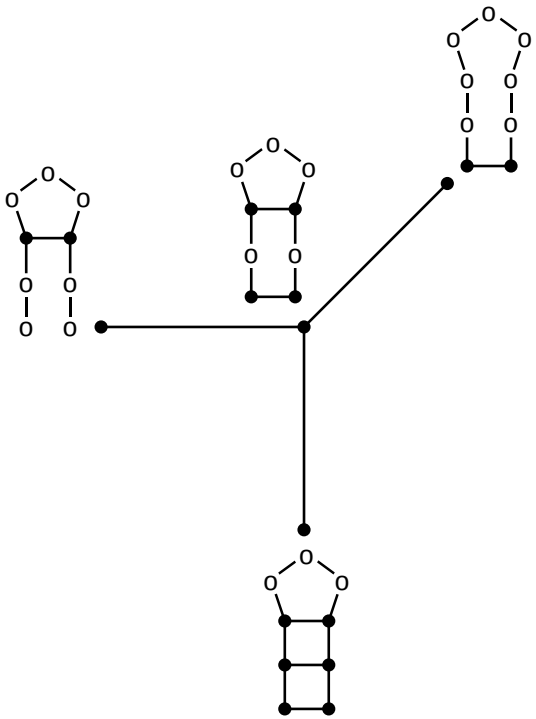
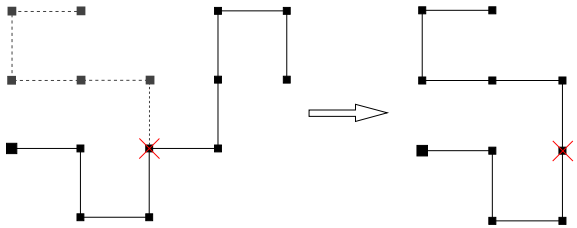
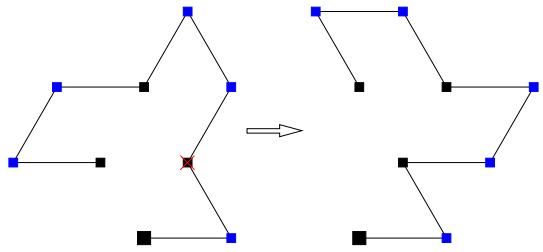
The move set







- For each move there must be an inverse move
- Resulting structure must be in X
- Move set must be *ergodic*

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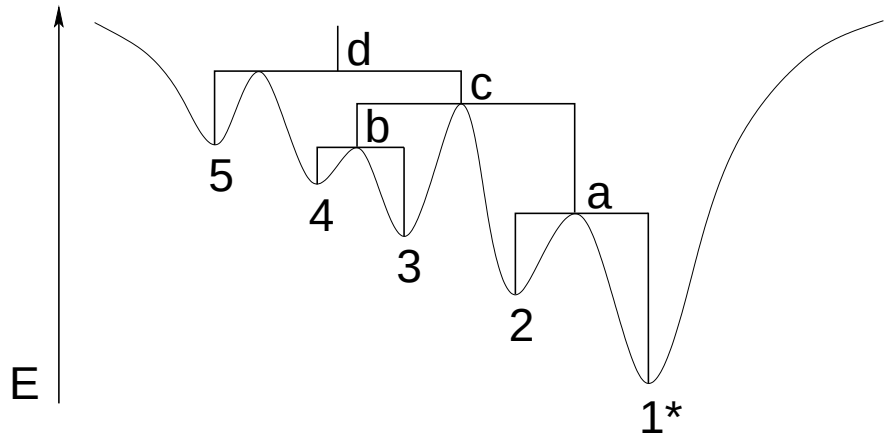
Energy barriers and barrier trees

Some topological definitions:

A structure is a

- local minimum if its energy is lower than the energy of **all** neighbors
- local maximum if its energy is higher than the energy of **all** neighbors
- saddle point if there are at least two local minima thar can be reached by a downhill walk starting at this point



C. Flamm, I. L. Hofacker, P. F. Stadler, and M. T. Wolfinger.
Barrier trees of degenerate landscapes.
Z. Phys. Chem., 216:155–173, 2002.

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The algorithm of Barriers

Barriers

Require: all suboptimal secondary structures within a certain energy range from mfe

```
 1: 𝓑 ⇐ ∅
 2: for all x ∈ subopt do
 3:    𝓚 ⇐ ∅
 4:    𝓝 ⇐ generate_neighbors(x)
 5:    for all y ∈ 𝓝 do
 6:       if b ⇐ lookup_hash(y) then
 7:          𝓚 ⇐ 𝓚 ∪ b
 8:       end if
 9:    end for
10:    if 𝓚 = ∅ then
11:       𝓑 ⇐ 𝓑 ∪ {x}
12:    end if
13:    if |𝓚| ≥ 2 then
14:       merge_basins(𝓚)
15:    end if
16:    write_hash(x)
17: end for
```

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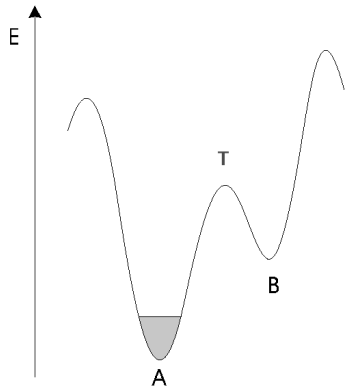
The flooding algorithm



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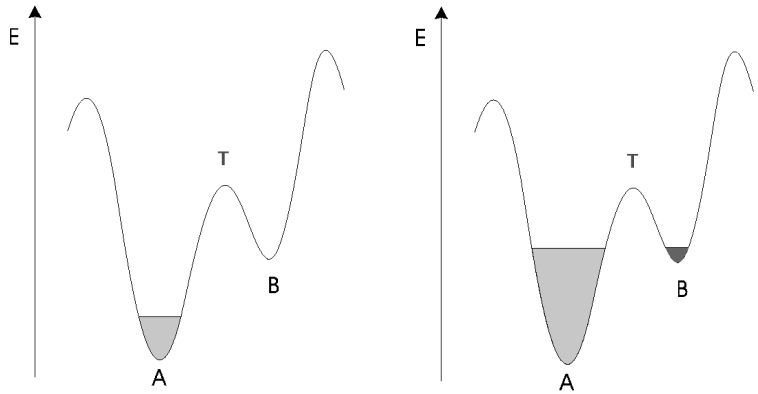
The flooding algorithm



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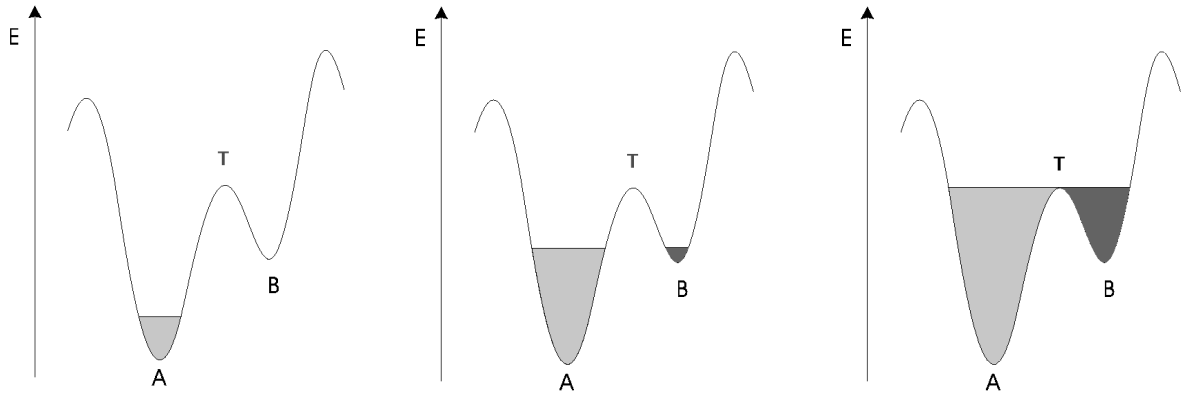

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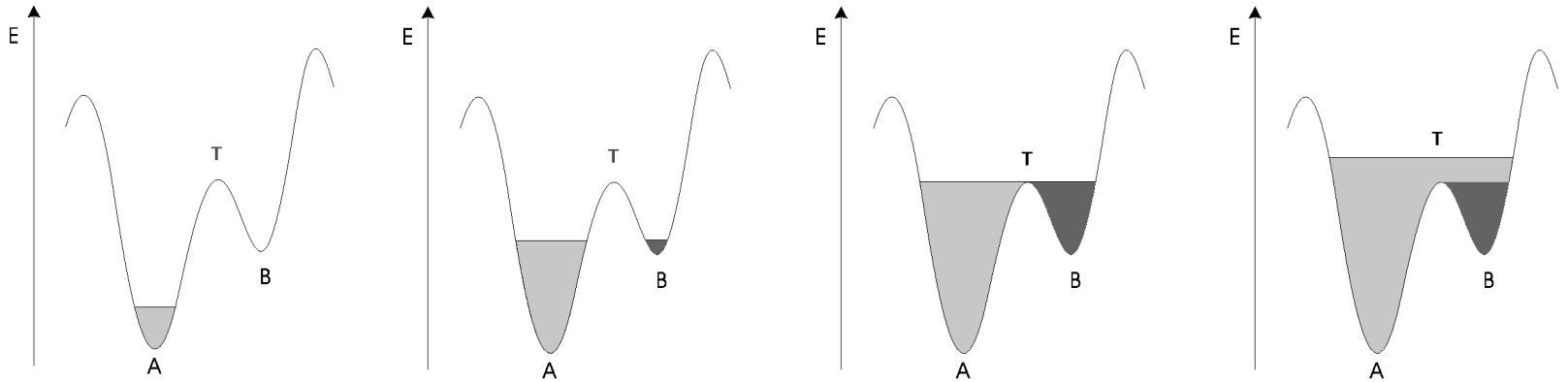
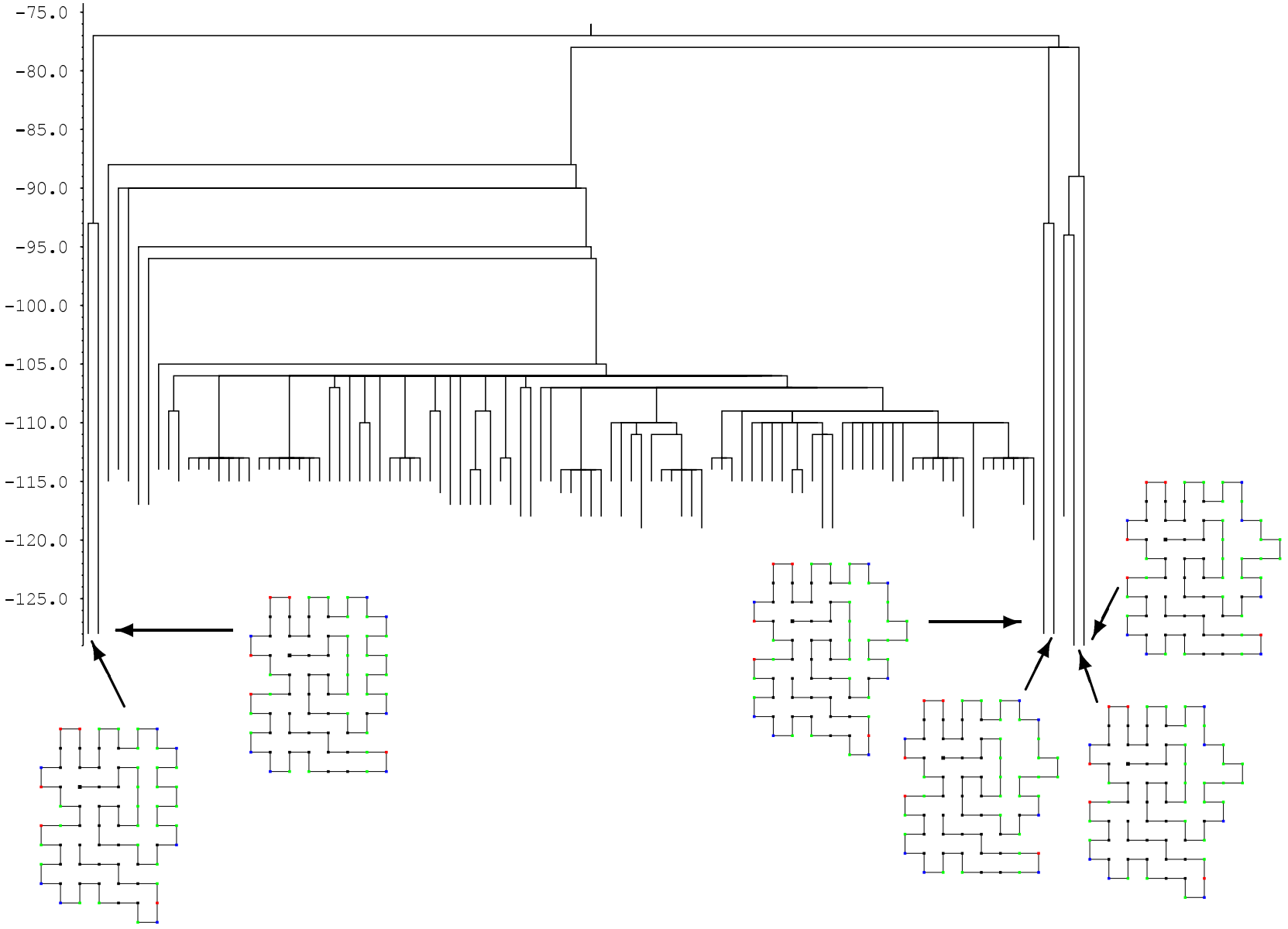


Barrier tree example



Information from the barrier trees

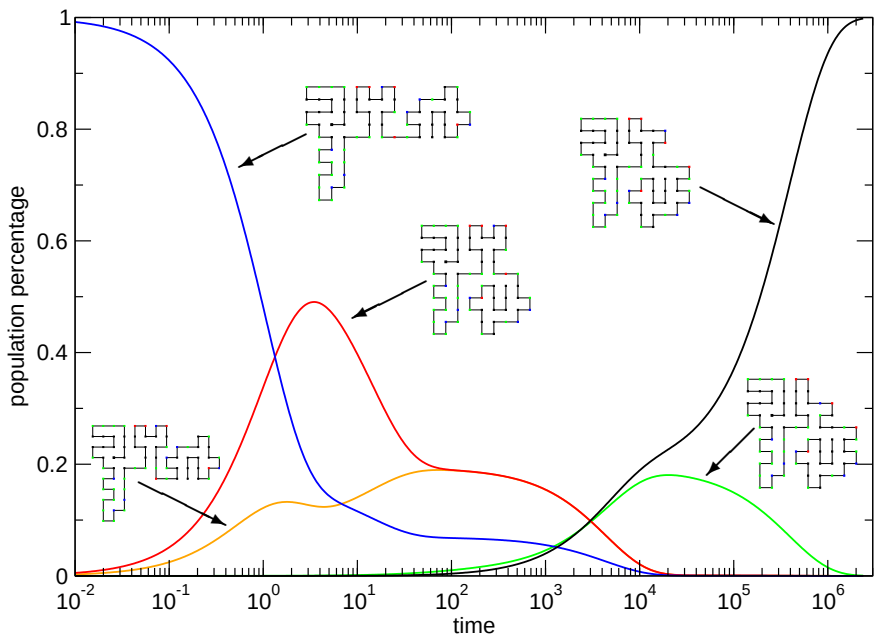
- Local minima
- Saddle points
- Barrier heights
- Gradient basins
- Partition functions
- Free energies of (gradient) basins

With this information, a reduced dynamics can be formulated as a Markov process by means of macrostates (i.e. basins in the barrier tree) and Arrhenius-like transition rates between them.

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

- macro-states form a partition of the full configuration space
- transition rates between macro-states

$$r_{\beta\alpha} = \Gamma_{\beta\alpha} \exp\left(-(E^*_{\beta\alpha} - G_\alpha)/kT\right)$$



M. T. Wolfinger, W. A. Svrcek-Seiler, C. Flamm, I. L. Hofacker, and P. F. Stadler.
Efficient computation of RNA folding dynamics.
J. Phys. A: Math. Gen., 37(17):4731–4741, 2004.

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Barrier tree dynamics - problems and pitfalls

The method works fine for moderately sized systems.

Currently, we consider approx. 100 million structures within a single run of BARRIERS to calculate the topology of the landscape.

However, we are interested in larger systems:

- biologically relevant RNA switches
- large 3D lattice proteins

The next steps:

- use high-level diagonalization routines for sparse matrices
- calculate low-energy structures
- sample (thermodynamics properties of) individual basins
- sample low-enery refolding paths

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Wang-Landau sampling

"A dynamic Monte Carlo algorithm to estimate the density of states by performing a random walk in energy space with a flat histogram"

F. Wang and D. P. Landau.
Efficient, Multiple-Range Random Walk Algorithm to Calculate the Density of States.
Phys. Rev. Lett., 86:2050–2053, 2001.

The classical partition function can be written as the sum over all states, *or* over all energies, i.e.

$$Z = \sum_i e^{-E_i/kT} \equiv \sum_E g(E) e^{-E/kT}$$

Wang-Landau sampling estimates $g(E)$ directly, instead of trying to extract it from a 'standard' Monte Carlo probability distribution.

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Monte Carlo basics

Generally, any (probability) distribution can be sampled by a Monte Carlo-type algorithm. Prerequisites: Detailed Balance

$$\pi(x)\, p(x \to y) = \pi(y)\, p(y \to x)$$

The probability of state x occuring in a classical system, is $\pi(x) = \frac{1}{Z} e^{-E_x/kT}$ ("Boltzmann-sampling")

Metropolis rule:

$$p(x \to y) = \min\left(1, \frac{\pi(y)}{\pi(x)}\right)$$

In Wang-Landau sampling, we have $\pi(x) = \frac{1}{g(E_x)}$ and thus

$$p(x \to y) = \min\left(1, \frac{g(E_x)}{g(E_y)}\right)$$

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Wang-Landau basics

Wang-Landau sampling assumes a crude 'guess' for the density of states, i.e. $g(E_x) = 1$ for all x.
Starting from an (arbitrary) initial state, a random neighbor is chosen with a transition probability

$$p(x \to y) = \min\left(1, \frac{g(E_x)}{g(E_y)}\right)$$

- If the move is accepted, the value of $g(E_y)$ is multiplied with a modfication factor $f > 1$ and the histogram entry $h(E_y)$ is updated.
- If the move is rejected, $g(E_x)$ is multiplied with f and $h(E_x)$ is incremented.

In practice, we work with the logarithm of the density of states, i.e. an update of the density of states yields $ln[g(E)] \to ln[g(E)] + ln(f)$.

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Wang-Landau continued

A reasonable initial value for the modification factor is $f = e^1 \simeq 2.71828$. The random walk is continued until the histogram $h(E)$ is 'flat'[1], which is typically checked for every 10^6 iterations.
$\rightarrow$ all energy bins have been visited an euqal number of times.
$\rightarrow$ the density of states converges to the true value prop. $ln(f)$.

Then, f is reduced to $f^{1/2}$, i.e. $f_1 = \sqrt{f_0}$ and $h(E)$ is reset to 0.

The random walk is continued, until the histogram becomes 'flat' again, in which case we reset $h(E)$ and modify f to $\sqrt{f}$. This is done, until a final value of $f = \exp(10^{-8}) \simeq 1.00000001$ is reached.

After many iterations, $g(E)$ converges to the true value as f approaches 1. At that point, the random walk satifies detailed balance:

$$\frac{1}{g(E_x)} p(E_x \rightarrow E_y) = \frac{1}{g(E_y)} p(E_y \rightarrow E_x)$$

[1] 'flat' means that $h(E) \geq 0.8 \langle h(E) \rangle$ for all E

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Wang-Landau sampling - pseudocode

Require: a start structure x compatible with sequence $\mathfrak{S}$
Ensure: **for all** E : $g(E) \leftarrow 1$ and **for all** E : $h(E) \leftarrow 0$

1: $f \leftarrow f_0 = exp(1)$
2: $E_1 \leftarrow \text{energy}(x)$
3: $\mathcal{N} \leftarrow \text{generate\_neighbors}(x)$
4: **repeat**
5: $y \leftarrow \text{get\_random\_neighbor}(\mathcal{N})$
6: $E_2 \leftarrow \text{energy}(y)$
7: $\xi \leftarrow g(E_1)/g(E_2)$
8: $r \leftarrow \text{random\_number}()$ // from $[0;1]$
9: **if** $r < \xi$ **then** // accept the move
10: $E_1 \leftarrow E_2$
11: $\mathcal{N} \leftarrow \text{generate\_neighbors}(y)$
12: **end if**
13: $g(E_1) \leftarrow g(E_1) * f$
14: $h(E_1) \leftarrow h(E_1) + 1$
15: **if** histogram_is_flat() **then**
16: $f \leftarrow f^{1/2}$
17: reset_histogram()
18: **else**
19: goto 5
20: **end if**
21: **until** $f \leftarrow f_{min} \sim exp(10^{-8})$

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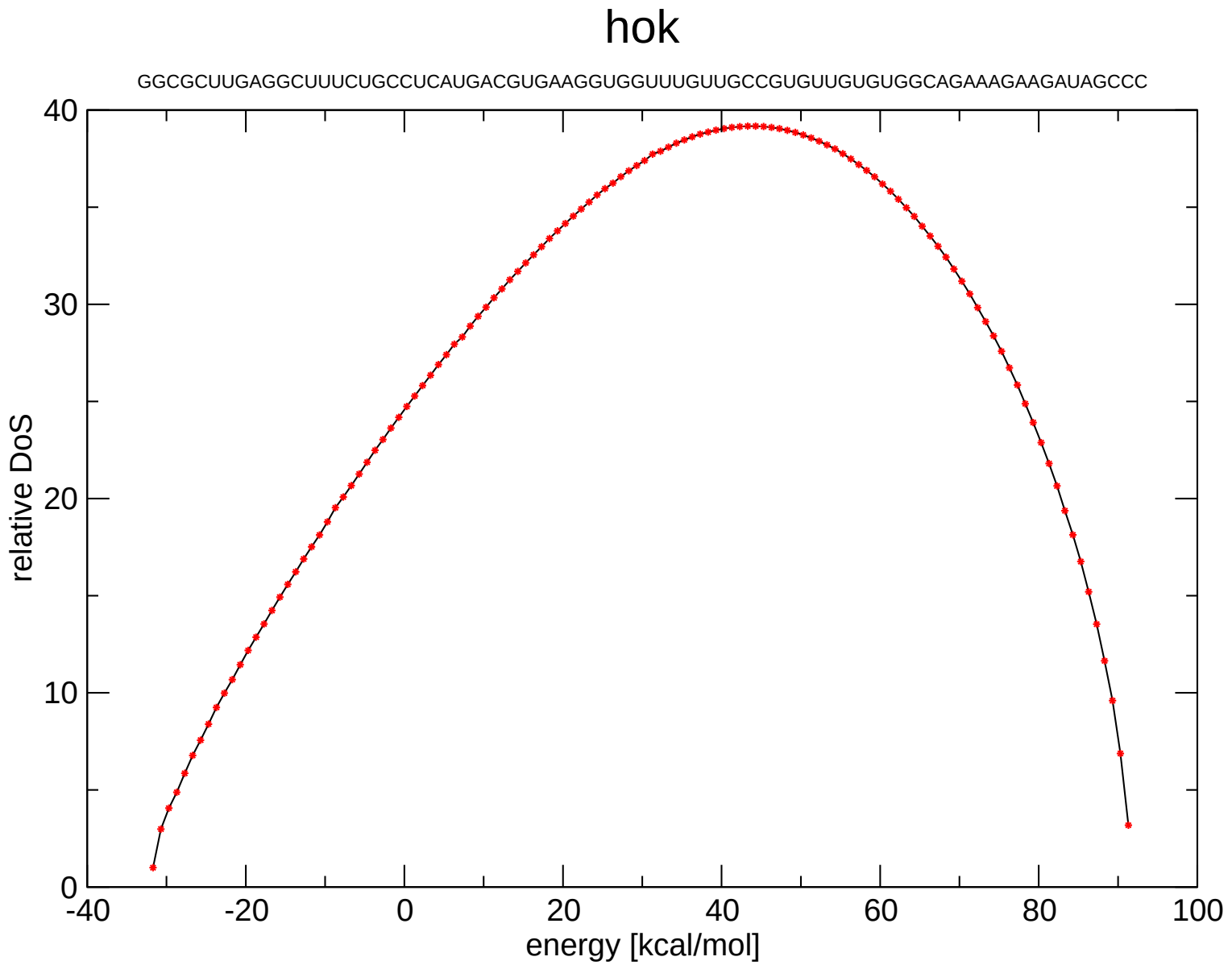
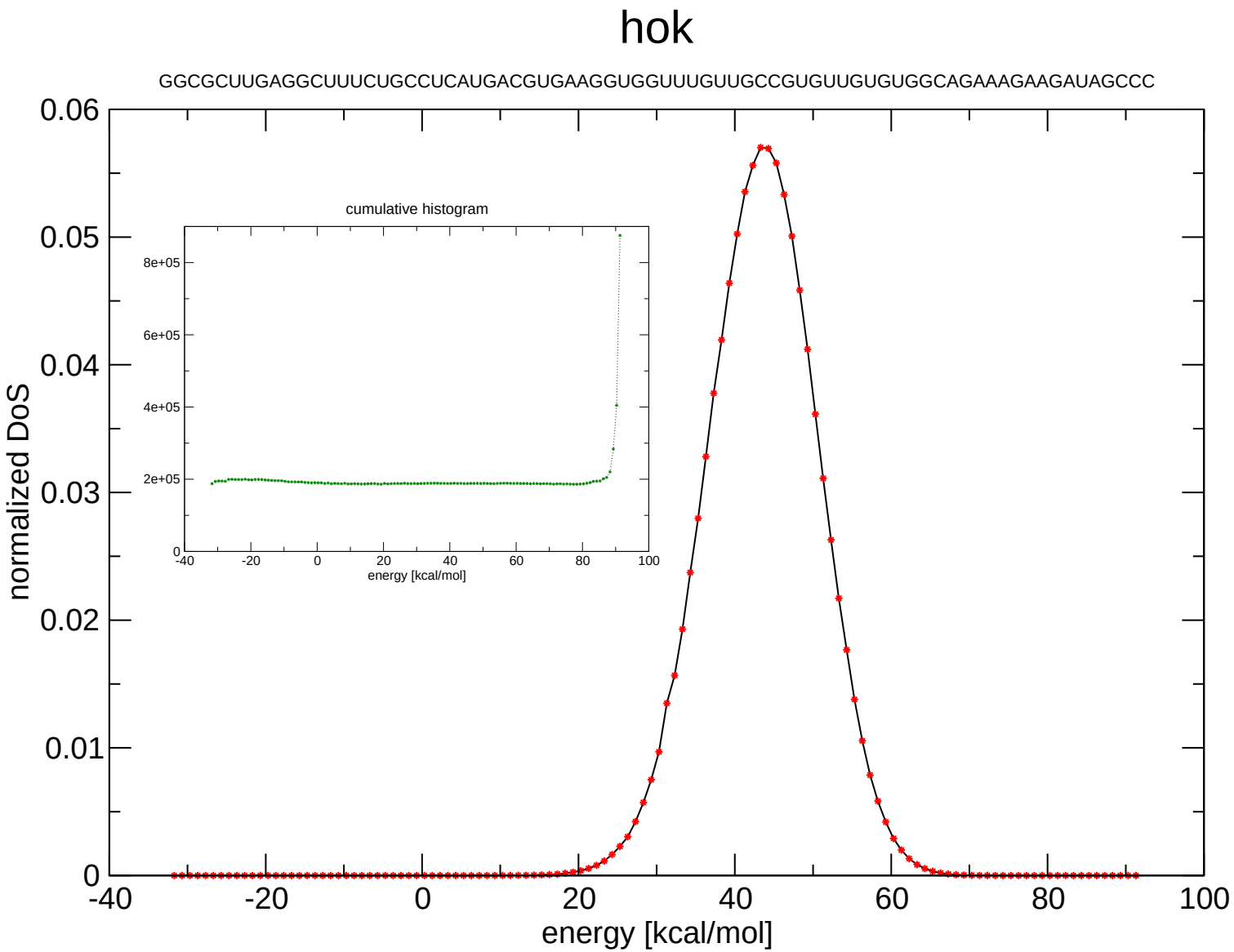
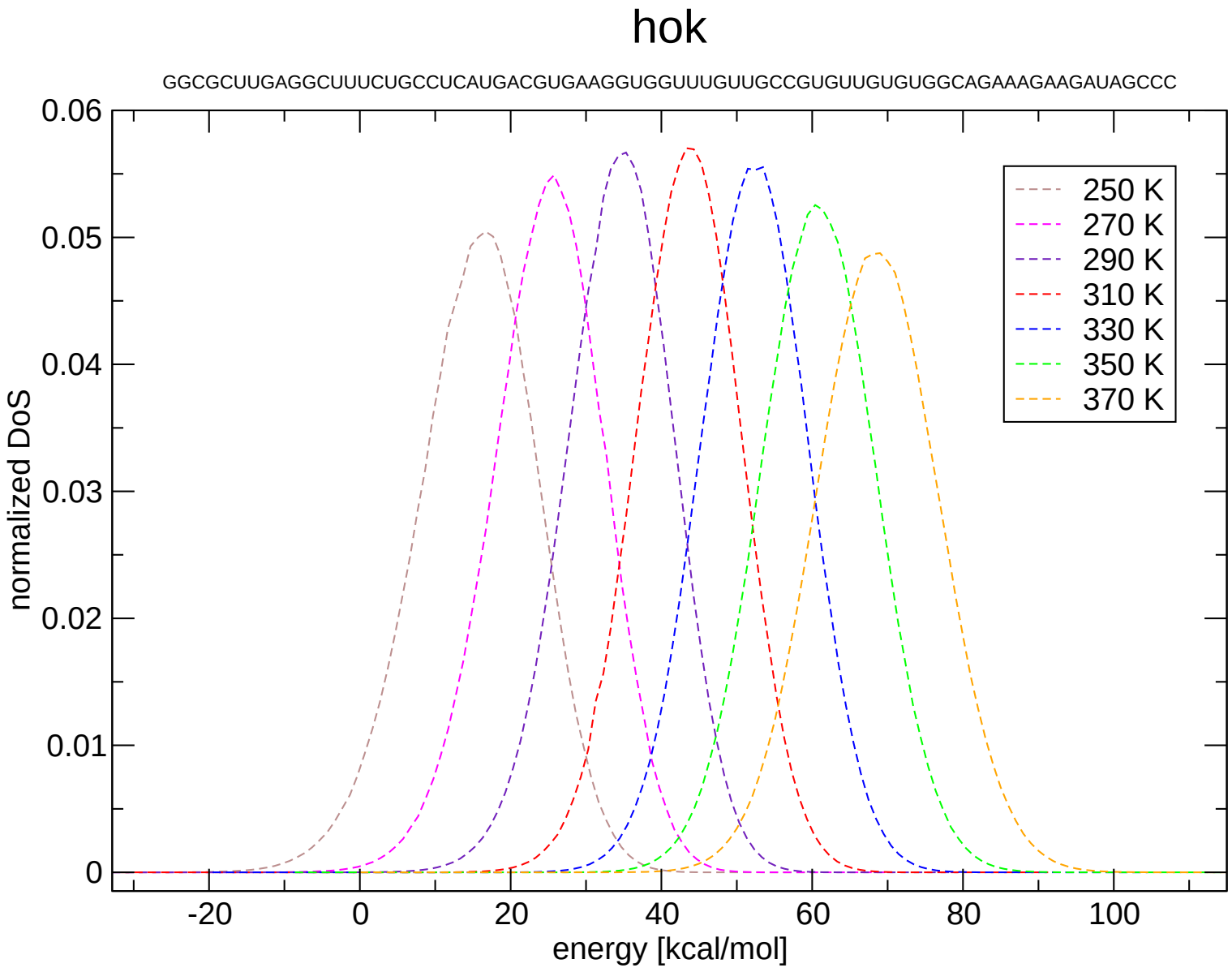
Wang-Landau - RNA example



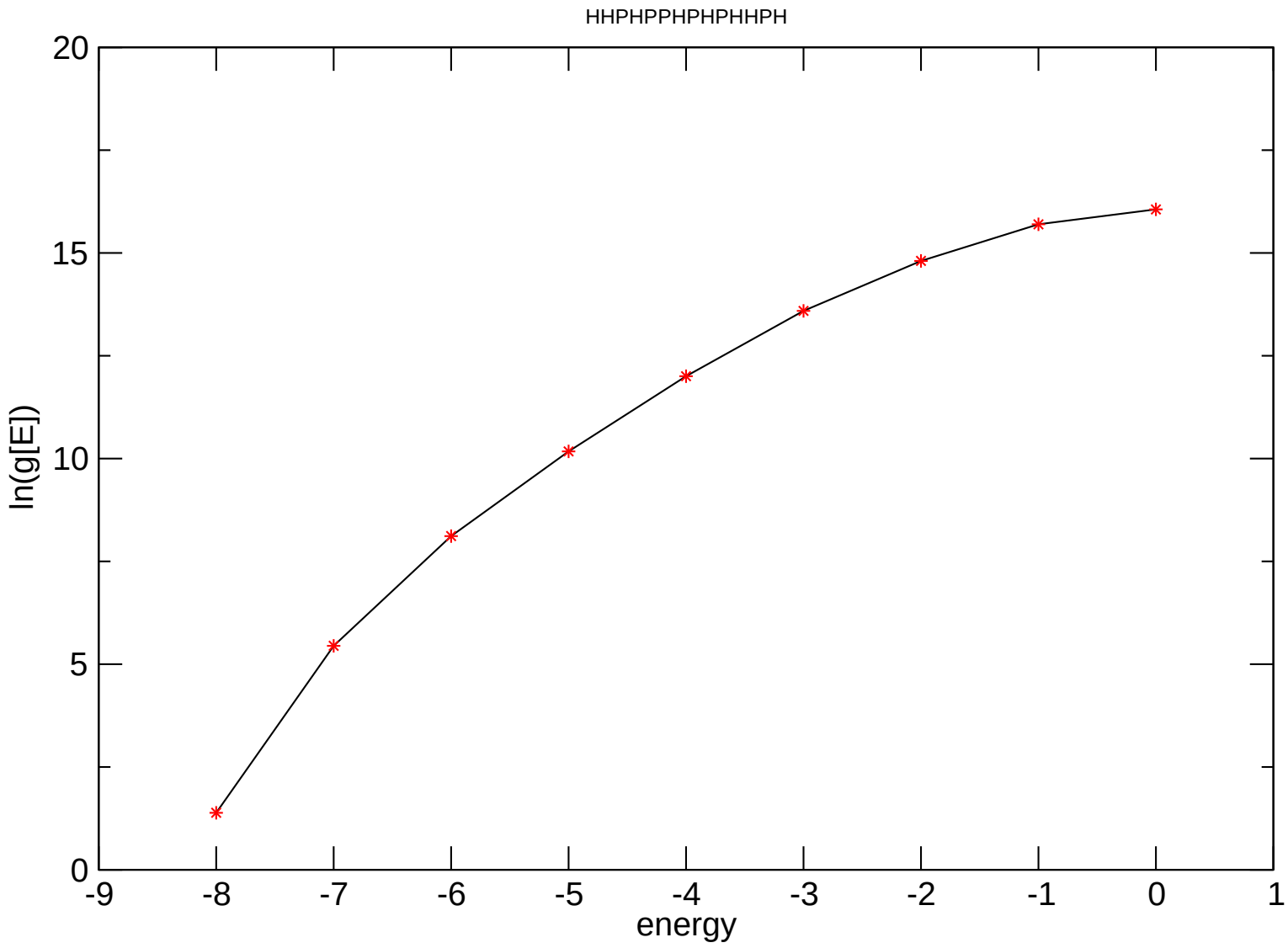
Wang-Landau - Density of States



Wang-Landau - DoS at different T



Wang-Landau - LP example



Thermodynamics

Relevant thermodynamic quantities can easily be calutaed from the DoS

$$U(T) = \frac{\sum_E E\, g(E)\, e^{-E/kT}}{\sum_E g(E)\, e^{-E/kT}} \equiv \langle E \rangle_T$$

$$C(T) = \frac{\partial U(T)}{\partial T} = \frac{\langle E^2 \rangle_T - \langle E \rangle_T^2}{kT^2}$$

$$F(T) = -kT \ln(Z) = -kT \ln\left(\sum_E g(E)\, e^{-E/kT}\right)$$

$$S(T) = \frac{U(T) - F(T)}{T}$$

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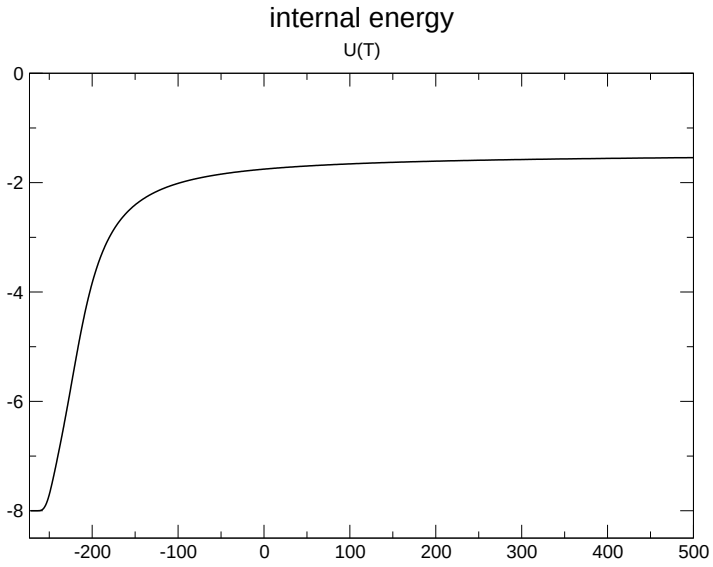
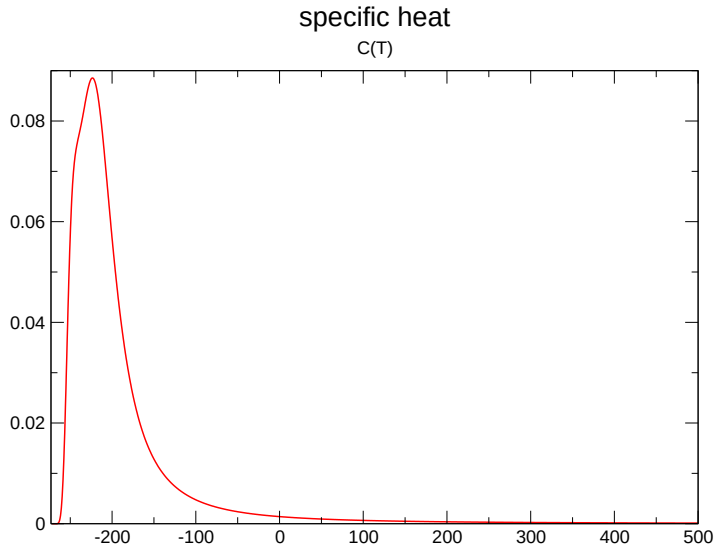
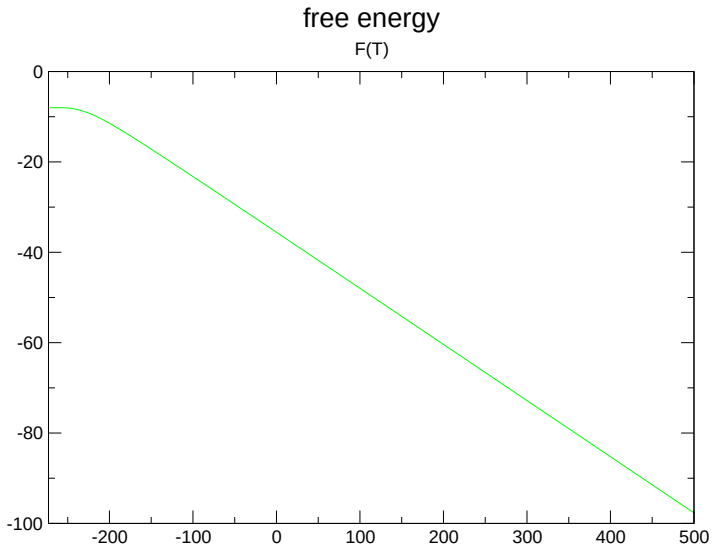
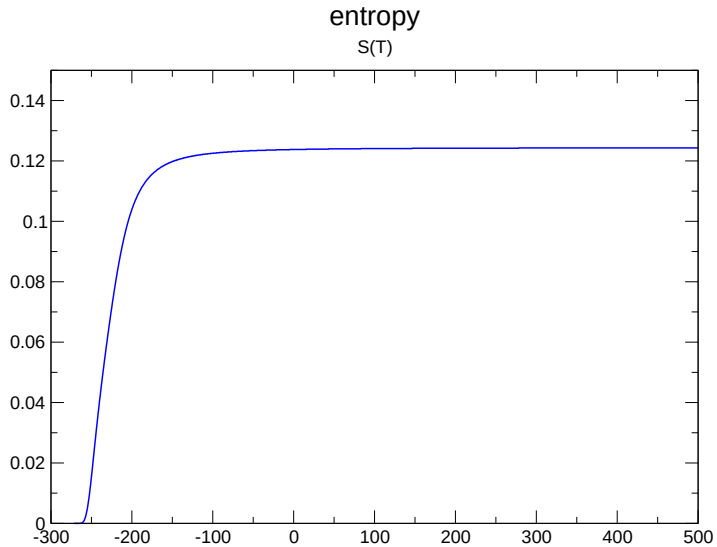
Thermodynamics of a short, artificial LP

HHPHPPHPHPHHPH $n = 14$

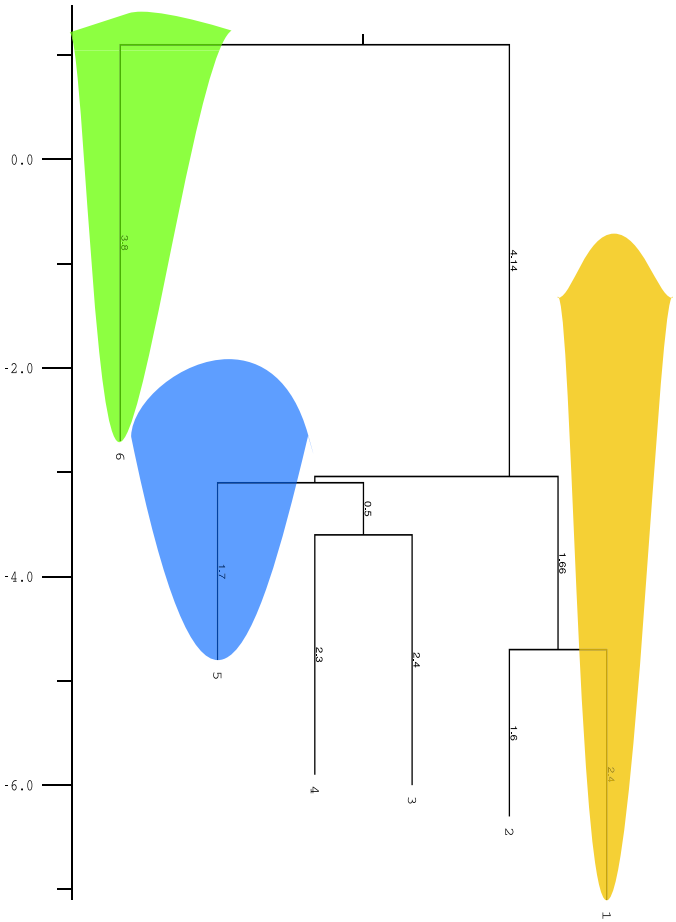








Basin sampling



1: $f \leftarrow f_0 = exp(1)$
2: $E_1 \leftarrow \text{energy}(x)$
3: $\alpha \leftarrow \text{get\_gradient\_basin}(x)$
4: $\mathcal{N} \leftarrow \text{generate\_neighbors}(x)$
5: **repeat**
6: $y \leftarrow \text{get\_random\_neighbor}(\mathcal{N})$
7: $E_2 \leftarrow \text{energy}(y)$
8: $\xi \leftarrow g(E_1)/g(E_2)$
9: $r \leftarrow \text{random\_number}()$ // from $[0;1]$
10: **if** $r < \xi$ **then** // accept the move
11: $\beta \leftarrow \text{get\_gradient\_basin}(y)$
12: **if** $\alpha != \beta$ **then**
13: **continue**
14: $E_1 \leftarrow E_2$
15: $\mathcal{N} \leftarrow \text{generate\_neighbors}(y)$
16: **end if**
17: $g(E_1) \leftarrow g(E_1) * f$
18: $h(E_1) \leftarrow h(E_1) + 1$
19: **if** histogram_is_flat() **then**
20: $f \leftarrow f^{1/2}$
21: reset_histogram()
22: **else**
23: goto 6
24: **end if**
25: **until** $f \leftarrow f_{min} \sim exp(10^{-8})$

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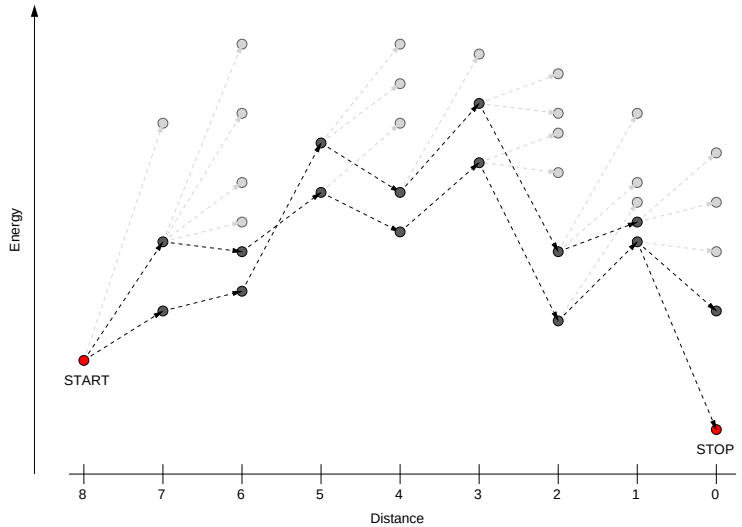
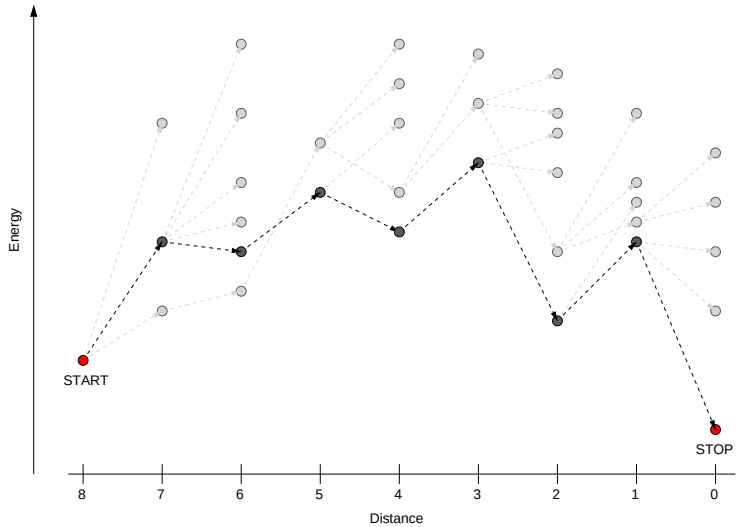
The PathFinder tool

A heuristic approach to efficiently estimate low-energy refolding paths

Overall procedure for direct paths:

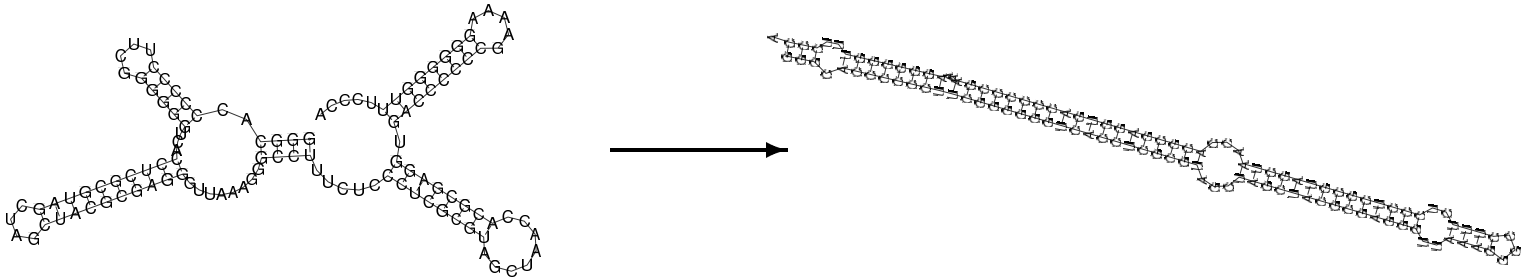
1. Calculate distance bewteen start and target structure
2. Generate all neighbors of the start structure whose distance to the target is less than the distance of the start structure
3. Sort those neighbor structures by their energies
4. Take the *n* energetically best structures, take them as new starting points and repeat the procedure until the stop structure is found
5. If a path has been found, try to find another one with lower energy barrier





PathFinder example - SV11

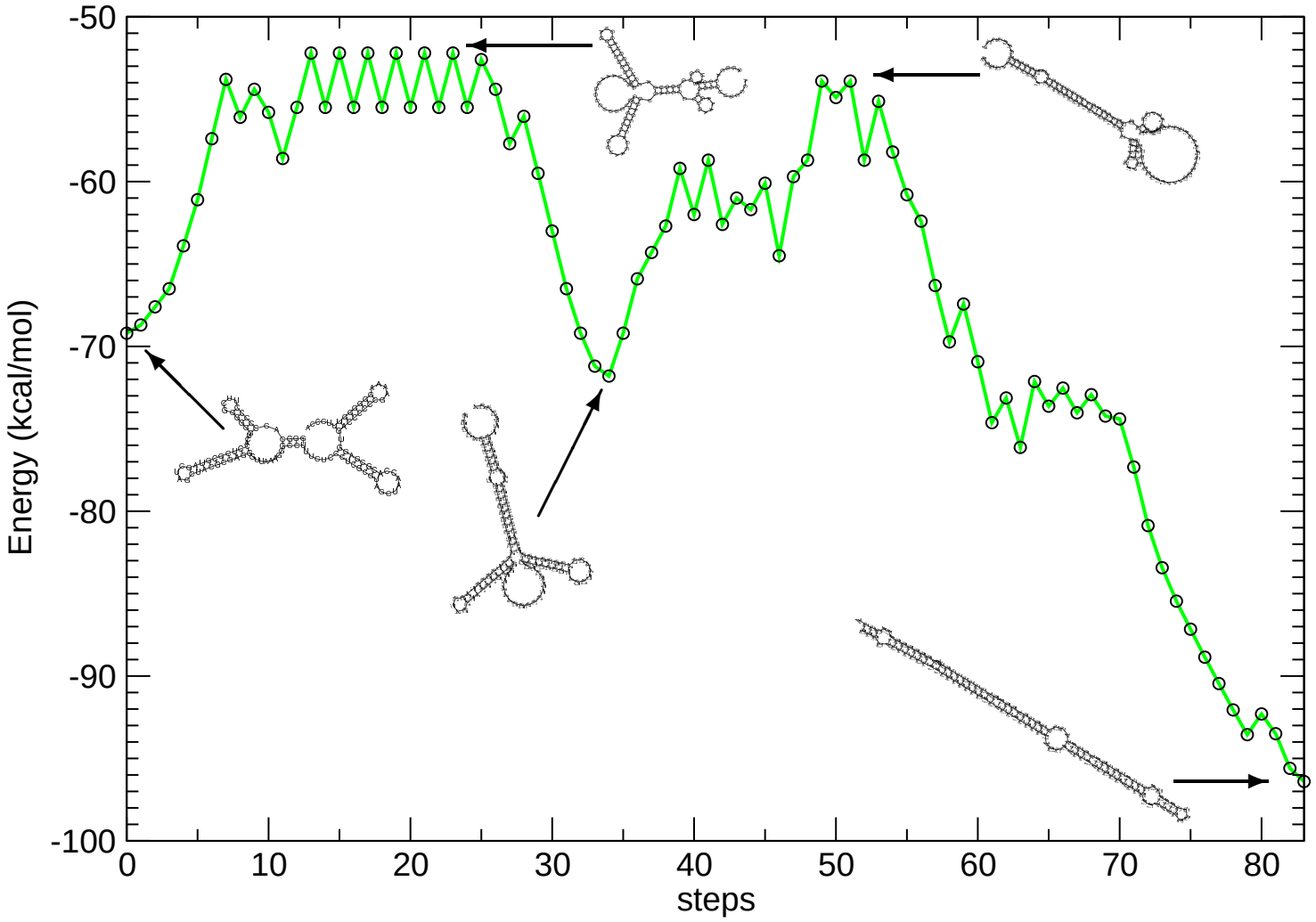
SV11 is a RNA switch of length 115



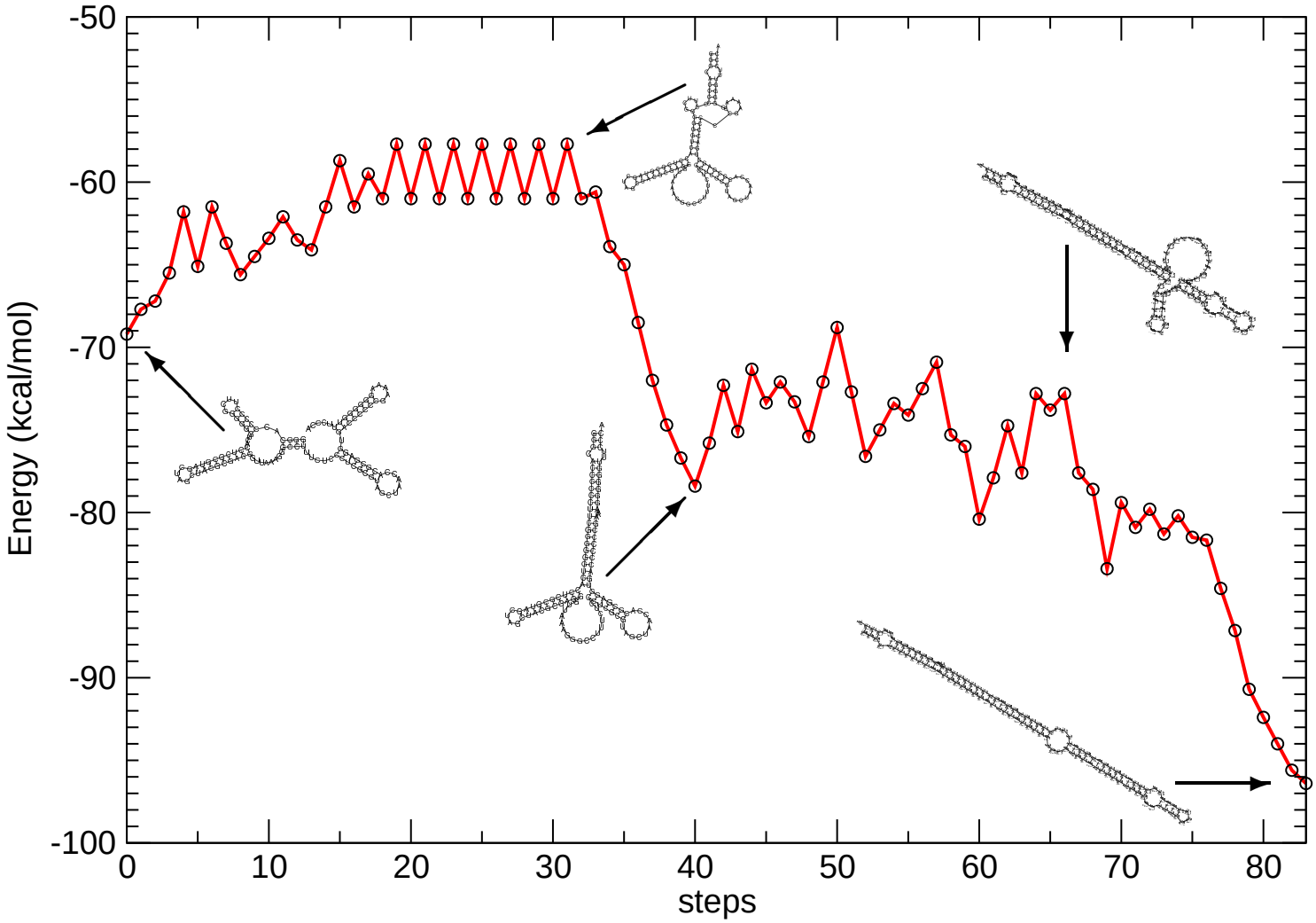
$E = -69.2$ kcal/mol
metastable
template for Qβ replicase

$E = -96.4$ kcal/mol
stable
not a template

SV11 refolding path 1/3: $E_{\text{saddle}} = -52.2\,\text{kcal/mol}$



SV11 refolding path 2/3: $E_{\text{saddle}} = -57.7$ kcal/mol



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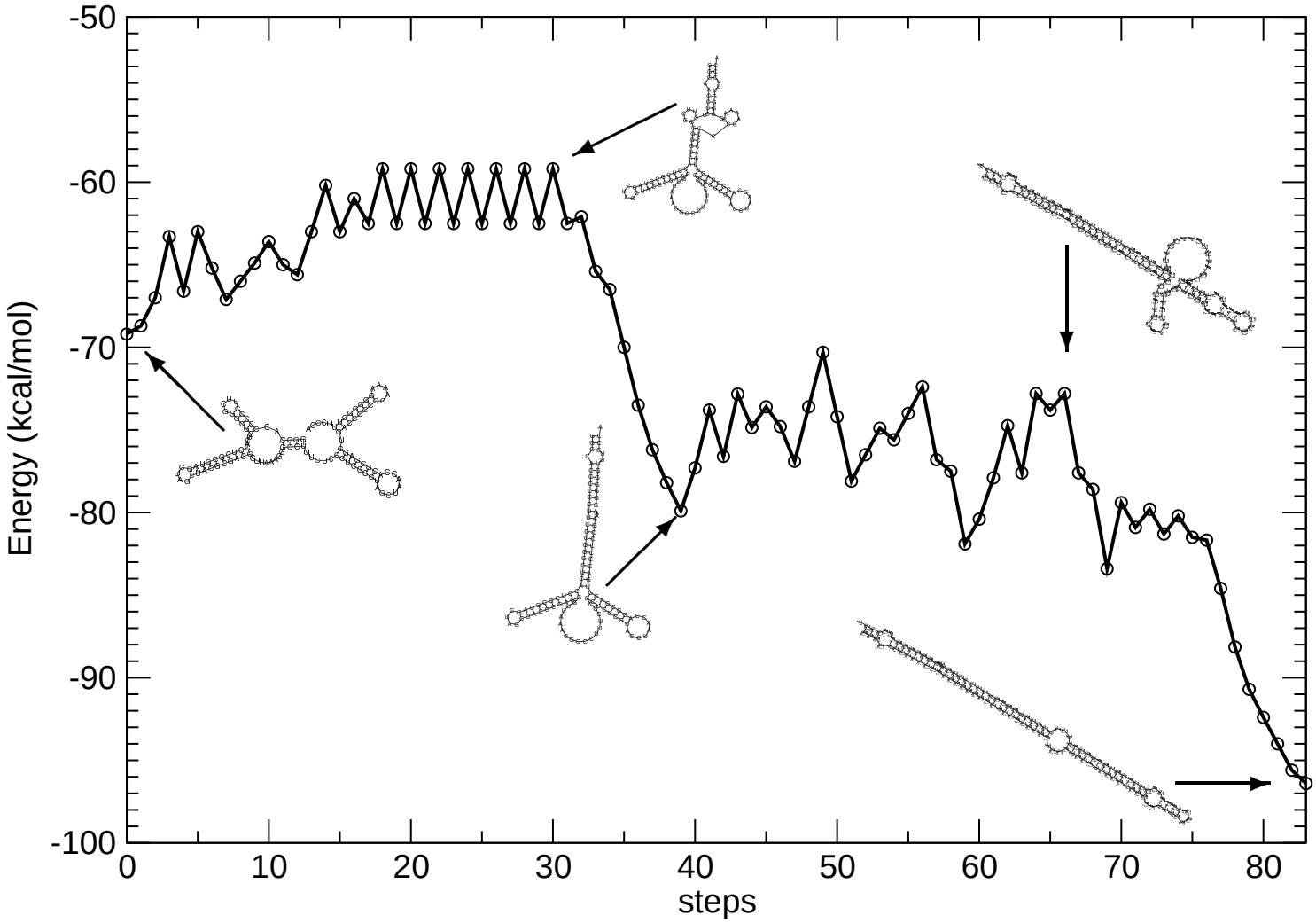
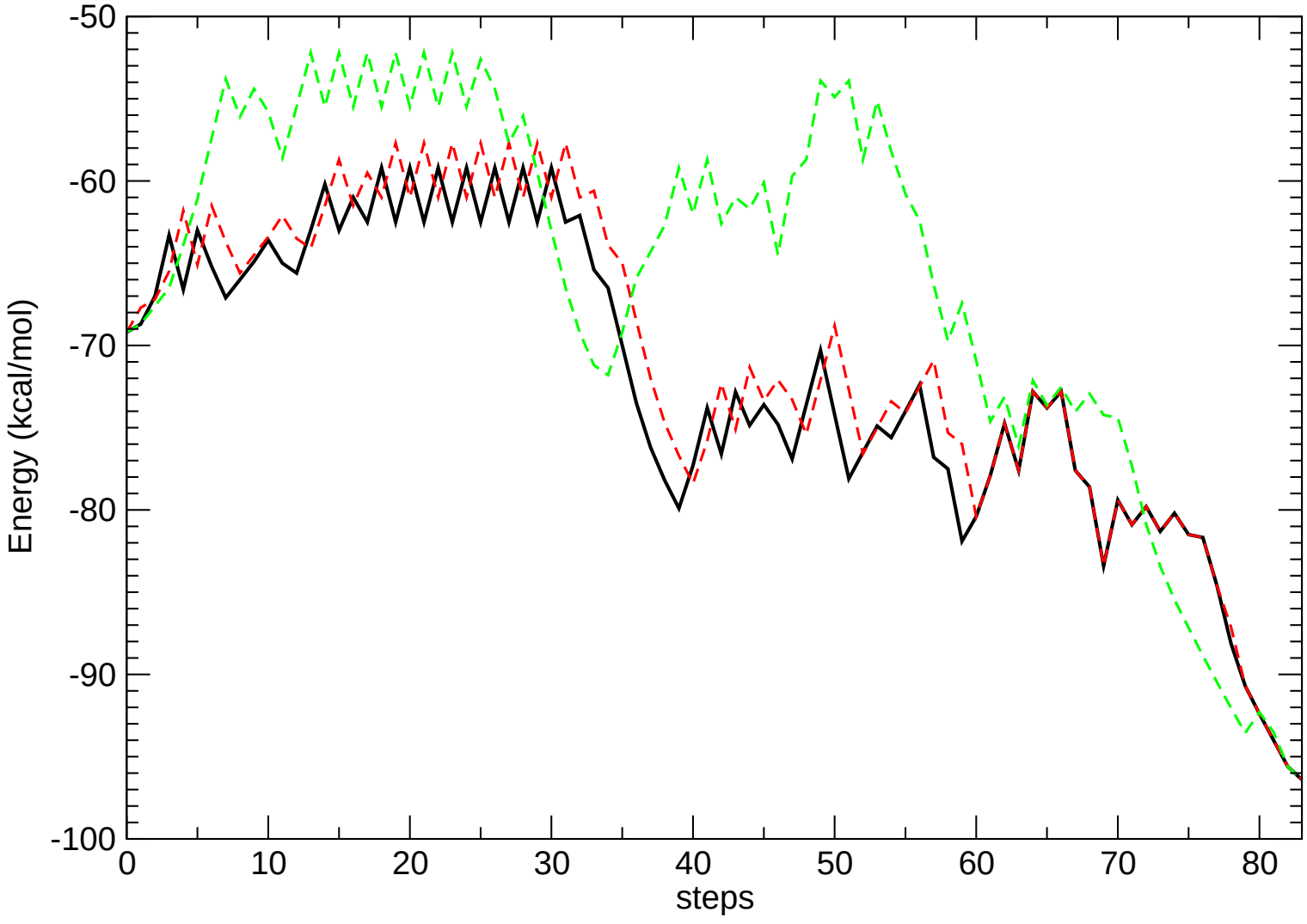
SV11 refolding path 3/3: $E_{\text{saddle}} = -59.2\,\text{kcal/mol}$



SV11 refolding paths



`libPF` - a generic path sampling library

- In practice, this path sampling heuristics is implemented as a C library
- All structures along a path are stored in a hash and therefore available for the next iterations
- Heuristics routines are strictly separated from model-dependent routines, i.e. the library is completely generic
- Currently, RNA secondary structures and lattice proteins are implemented
- It is easy to extend the functionality to other discrete systems

Current applications:

1. `PathFinder`
2. `Kinwalker`
3. `...`

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Conclusion

- Discrete models allow a detailed study of the energy surface
- Barrier trees represent the landscape topology
- A macrostate approach of folding kinetics reduces simulation time drastically
- Wang-Landau sampling approximates the density of states and allows the calculation of basin properties
- A path sampling approach yields low-energy refolding paths and is a valuable tool for further kinetics studies

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Acknowledgments & References

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