Computational design of a circular RNA with prion-like behavior

Stefan Badelt[1], Christoph Flamm[1] and Ivo L. Hofacker[1,2]

{stef,xtof,ivo}@tbi.univie.ac.at

[1]**Institute for Theoretical Chemistry**, University of Vienna,
Währingerstraße 17/3, A-1090 Vienna, Austria
[2]**Research Group Bioinformatics and Computational Biology**,
University of Vienna, Währingerstraße 29, A-1090 Vienna, Austria

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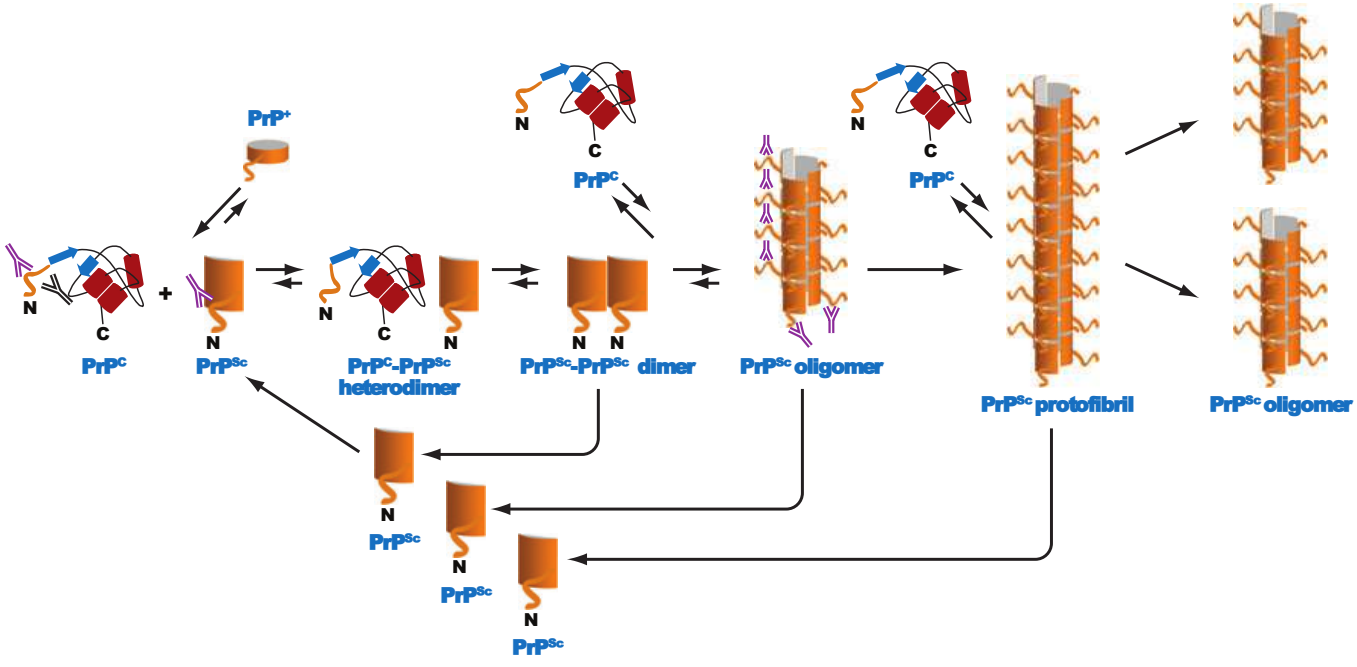
Prions and conformational self-replication

Prions are proteins known to be the infectious agents for several neurological diseases (e.g. Altzheimer, Creuzfeld-Jakob, ...)

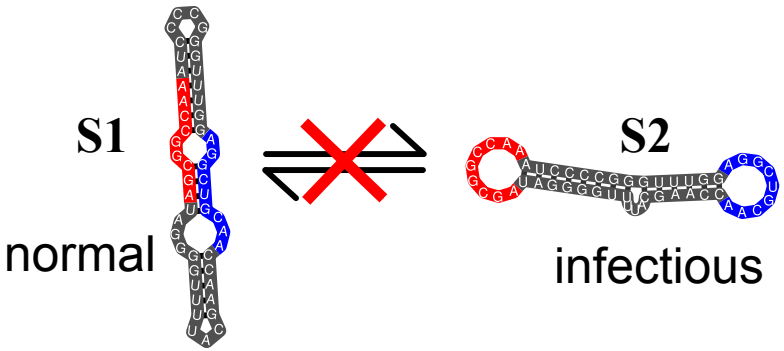
The "*protein only hypothesis*" states that a single mis-folded infectious prion can convert the other correctly folded proteins to the infectious agent.



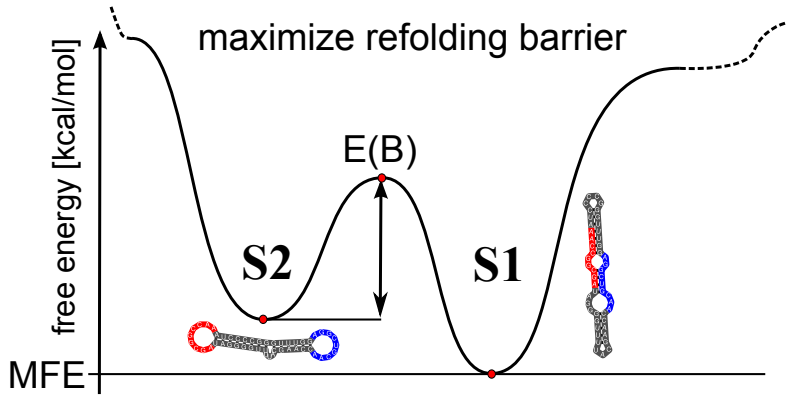
Can we design a minimal RNA with prion-like behavior?

Prions and conformational self-replication

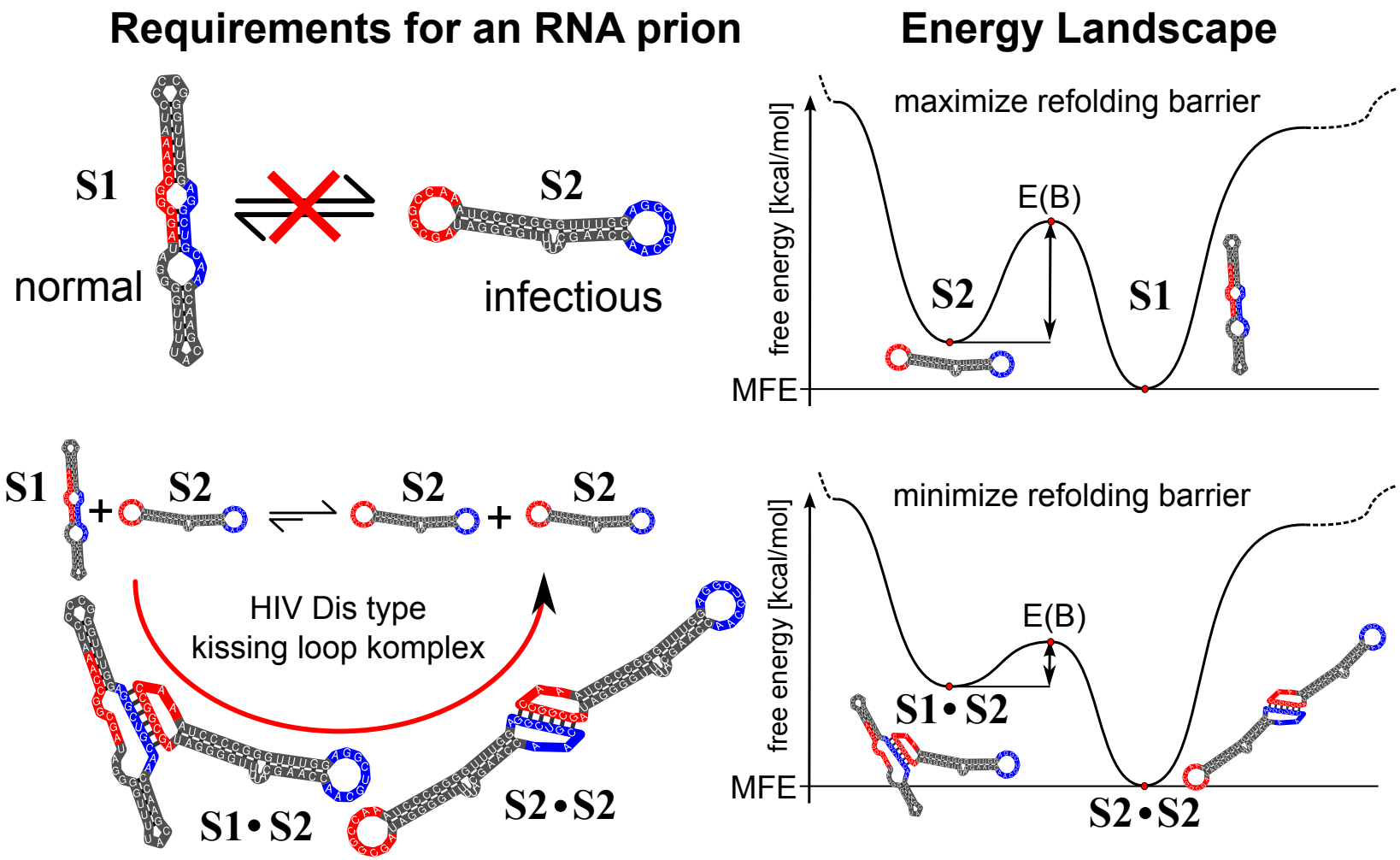
Requirements for an RNA prion



Energy Landscape

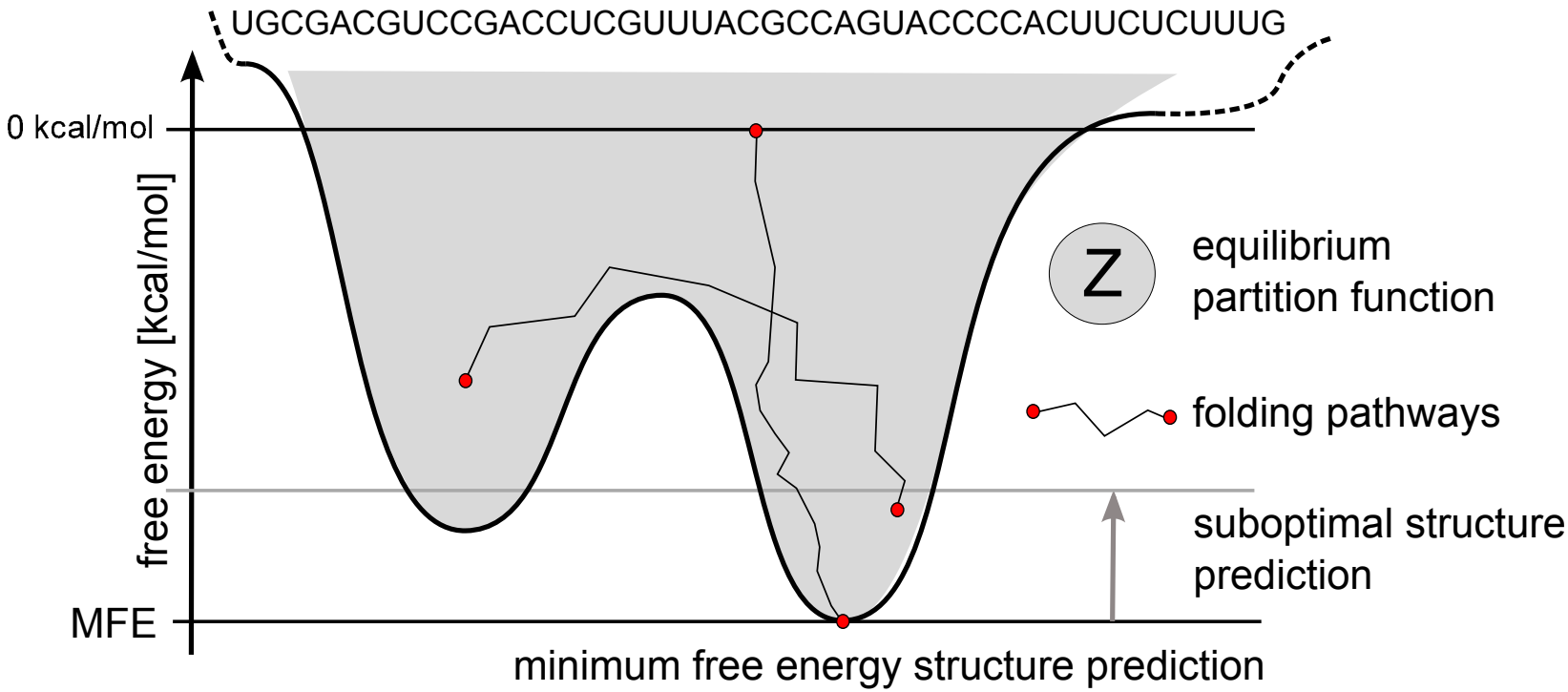


Prions and conformational self-replication



Computational RNA folding

Sequence $\Rightarrow$ Structure



$$G = -kTln(Z) \quad Z = \sum_{S \in \Omega} e^{\frac{-E(S)}{kT}} \quad P(S) = \frac{e^{\frac{-E(S)}{kT}}}{Z}$$

Computational RNA design

Structure $\Rightarrow$ Sequence (inverse of RNA folding problem)

Simplest case: Find a sequence that forms a predefined structure

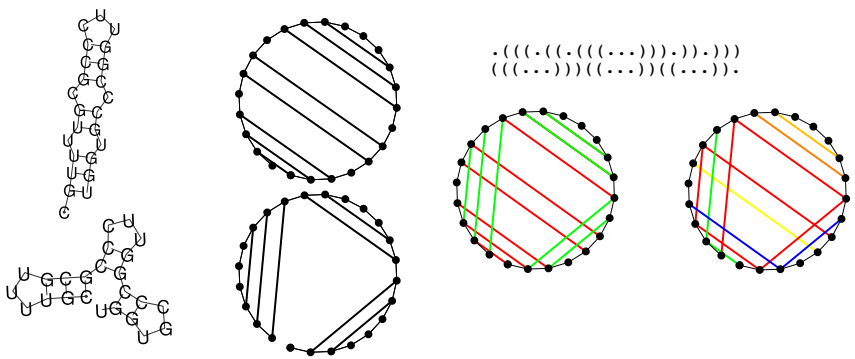
$\Rightarrow$ structure is the MFE of the designed sequence

$\Rightarrow$ maximize probability of the desired structure

$\Rightarrow$ sequence must be biologically reasonable (GC content)

Even harder: Find a sequence that forms two predefined structures

$\Rightarrow$ sequence must be bi-stable (like a Prion)



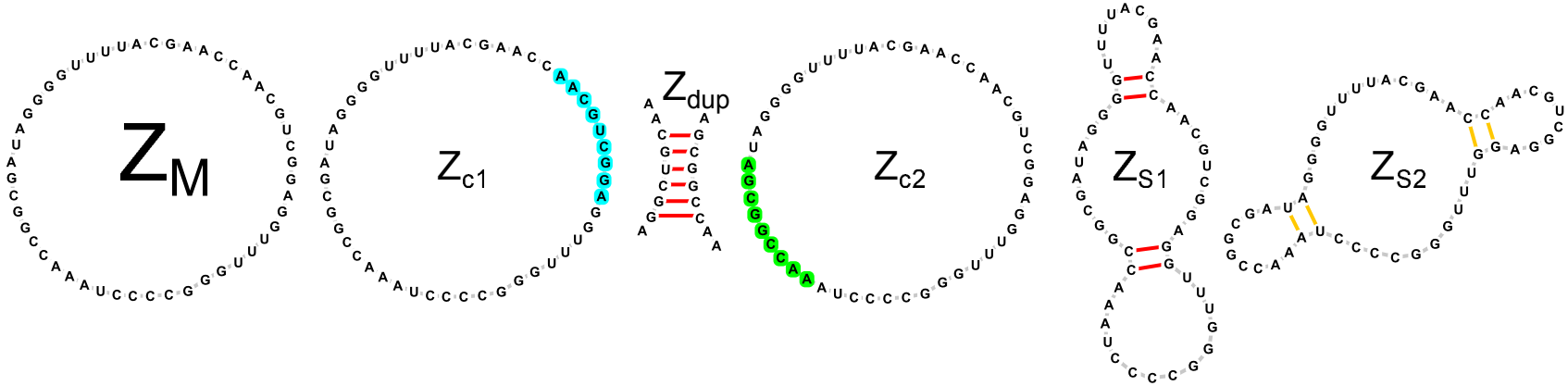
Computational Prion design

- `switch.pl` with two conformations and HIV-Dis loop

```
....((((((..((((...((((...))))))...))))..))))))).
((((((.........)))))))....((((((.........))))))).
NNNNNNNAACCGACGANNNNNNNNNNNNNNNNNAACGUCGGANNNNNNN
```

- Generate lots of sequences (128 different results)
- Select candidate with required prion features

Evaluation of prion-like behavior



Partition function of the Dimer:

$$Z_D = Z_{c1} * Z_{c2} * Z_{dup} \tag{1}$$

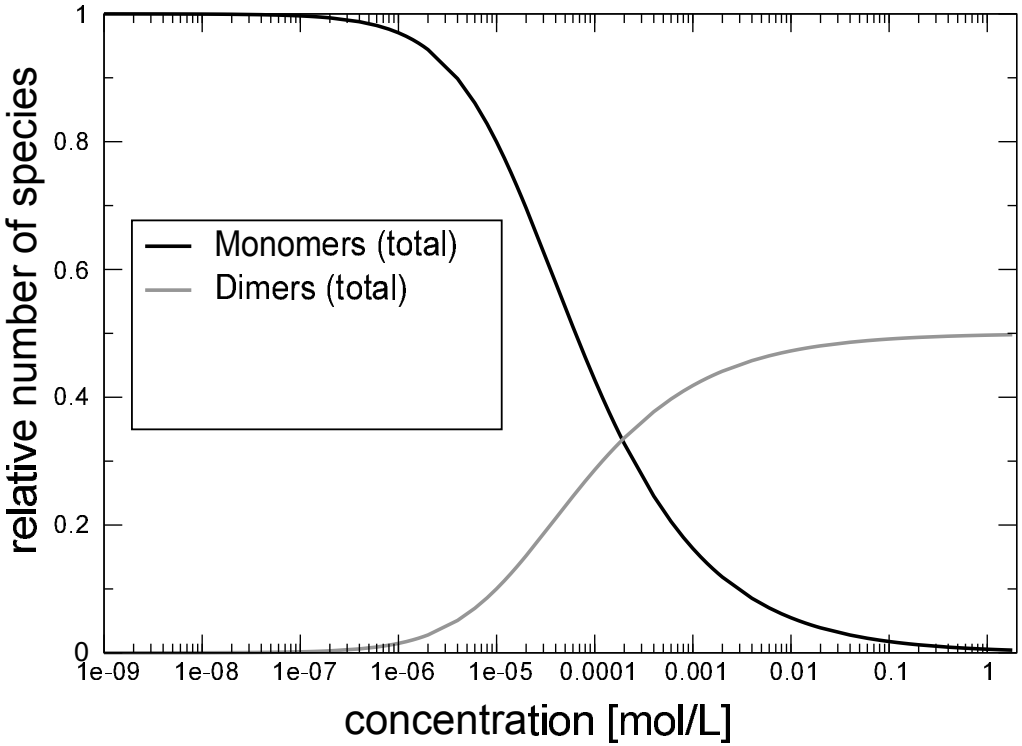
Partition function of all Structures that are neither $S1$ nor $S2$:

$$Z_{!S1\ \&\ !S2} = Z_M - Z_{S1} - Z_{S2}$$

Equilibrium Constant for Dimerization: [M]+[M] $\Leftrightarrow$ [D]

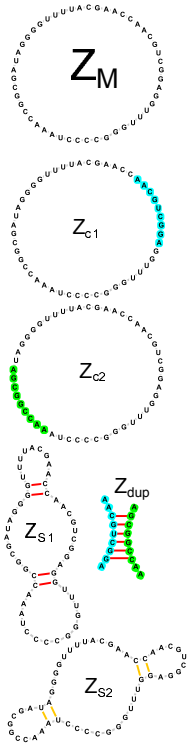
$$K = \frac{[D]}{[M]^2} = \frac{Z_D}{Z_M^2}$$

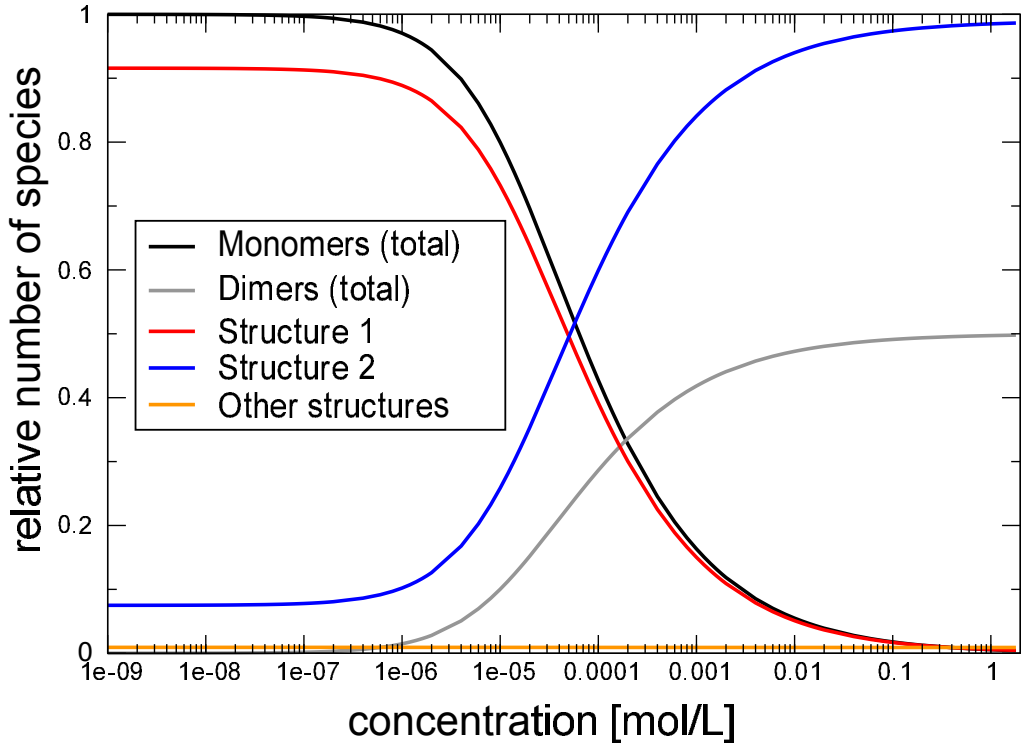
Evaluation of prion-like behavior



$$K[D] = [M] * [M]$$

Evaluation of prion-like behavior



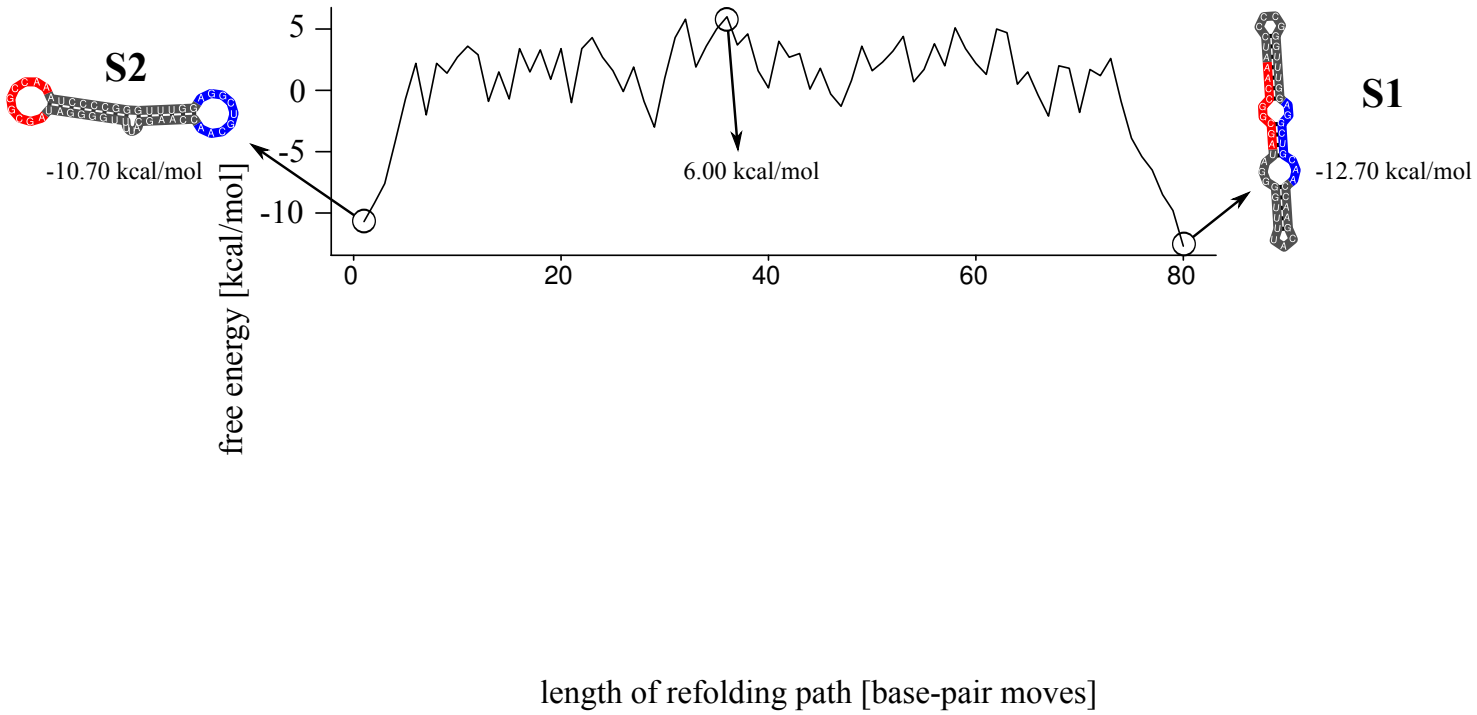


$$[S1] = \frac{Z_{S1}}{Z_M} \cdot [M] + \left(\frac{Z_{S1+c1}}{Z_{c1}} + \frac{Z_{S1+c2}}{Z_{c2}} \right) \cdot [D] \qquad (2)$$

$$[S2] = \frac{Z_{S2}}{Z_M} \cdot [M] + \left(\frac{Z_{S2+c1}}{Z_{c1}} + \frac{Z_{S2+c2}}{Z_{c2}} \right) \cdot [D]$$

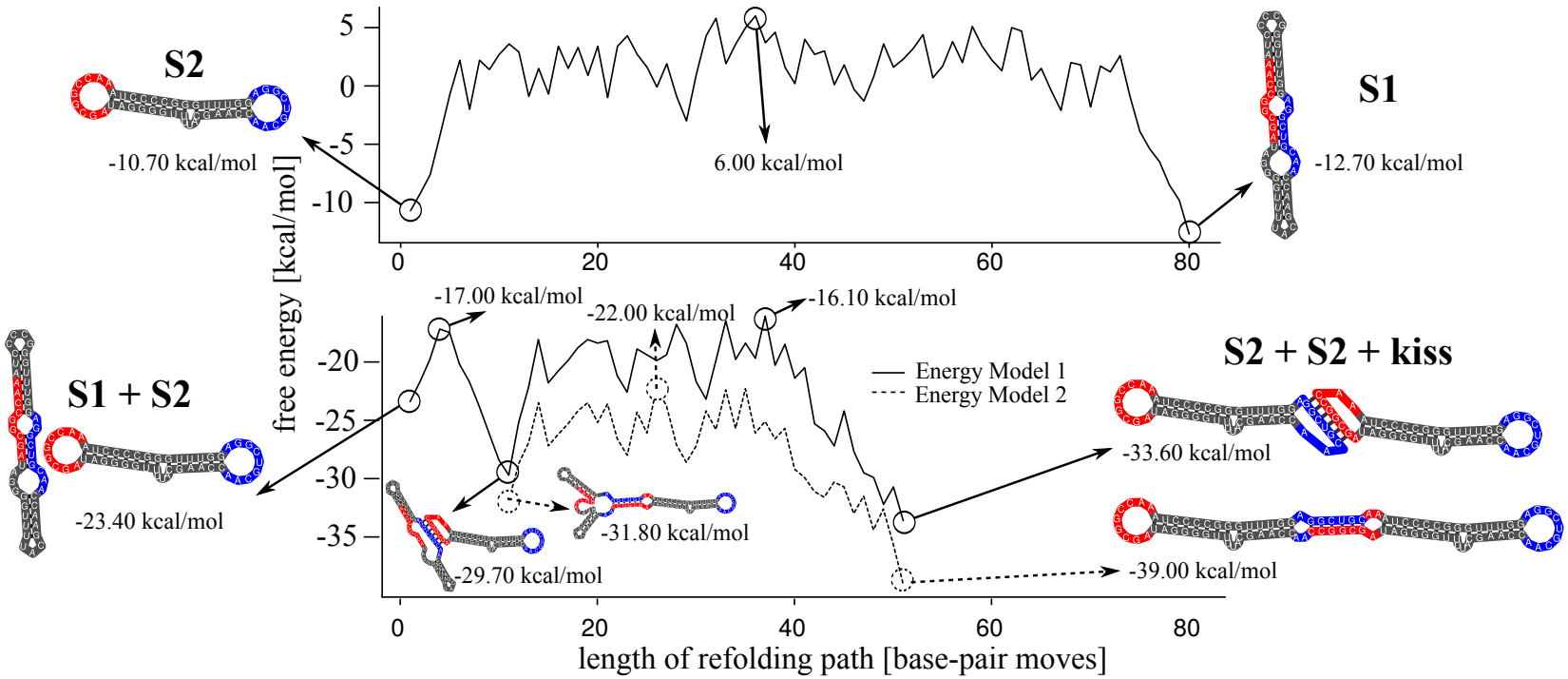
Evaluation of prion-like behavior

S1 and S2 are separated by a high energy barrier:



Evaluation of prion-like behavior

S2 catalyzes reaction from S1 to S2:



Evaluation of prion-like behavior

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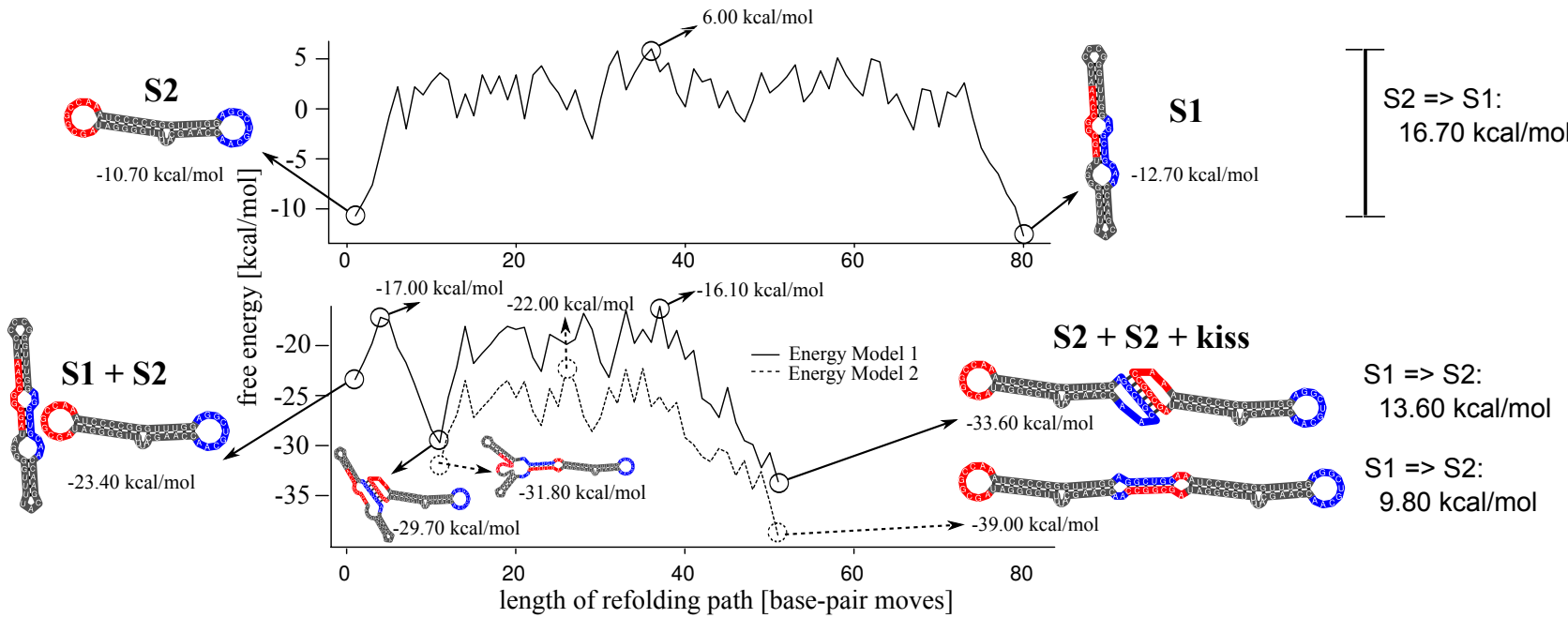

Summary

- RNAprions are a from of conformational self-replication
- Computatinal RNA folding and design
- HIV-Dis loops can be used to favor the infectious conformation for dimers
- Different energy models for refolding pathways all show that S2 can act as a catalyst

thanks to

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the TBI group

Badelt et al. (2014) **Design of a circular RNA with prion-like behavior**
Flamm et al. (2001) **Design of multi-stable RNA Molecules**
Weixlbaumer et al. (2004) **Determination of Thermodynamic Parameters for HIV-1 DIS Type Loop-Loop Kissing Complexes**
Lorenz et al. (2011) **ViennaRNA Package 2.0**

tbi universität wien DK rna Biology FWF Der Wissenschaftsfonds.

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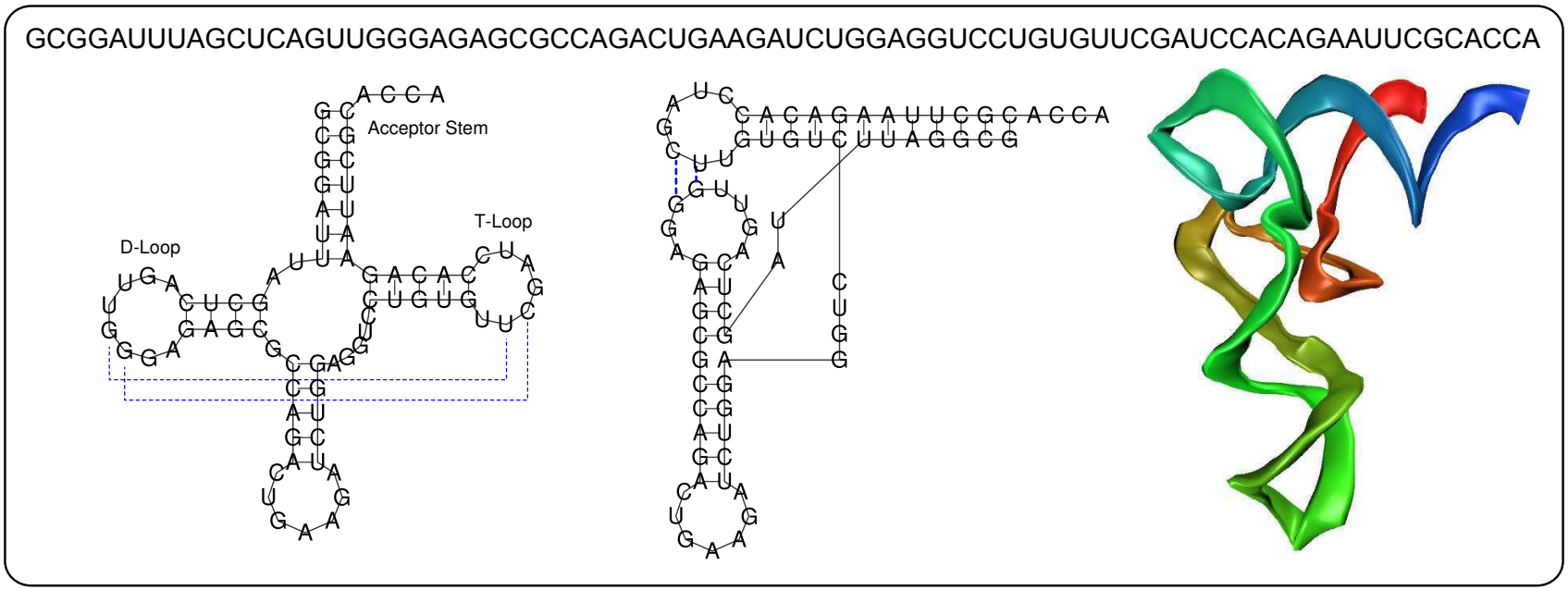
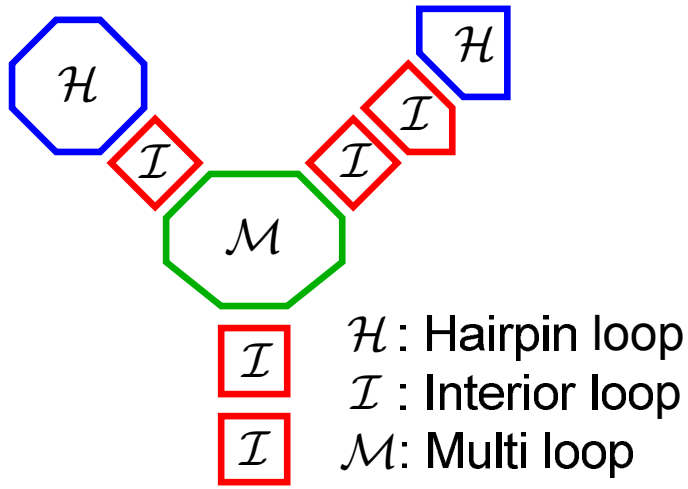
Computational RNA folding



A secondary structure is a list of base pairs (i, j), where:

- 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 $i < k < j < l$.
- Only isosteric base-pairs GC, CG, AU, UA, GU, UG are allowed.
- Hairpin loops have at least length 3 ($|j - i| > 3$)

Computational RNA folding



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

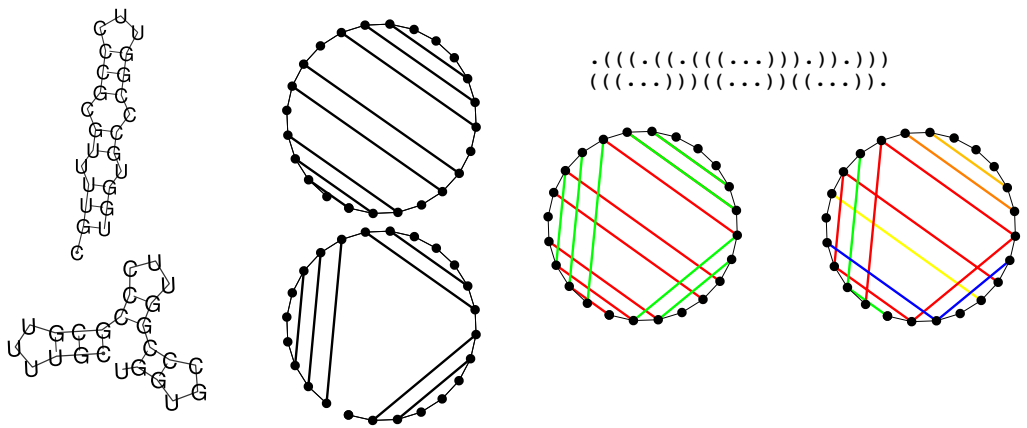
Nearest Neighbor Energy Model: The free energy E of a secondary structure $\mathcal{S}$ is the sum of the energies of its loops l

- Energies depend on loop type and size, with some sequence dependence.
- Most relevant parameters are measured experimentally.

Computational RNA design

`switch.pl` in a nutshell:

- build a dependency graph
- mutate an initial sequence guided by dependency graph
- accept/reject mutations according to a cost function



Cost Function:

$$\Rightarrow\ E(x, S_1) + E(x, S_2) - 2G(x) + \xi(E(x, S_1) - (E(x, S_2) + \epsilon))^2$$