Sequences, structures, shapes, and conformations

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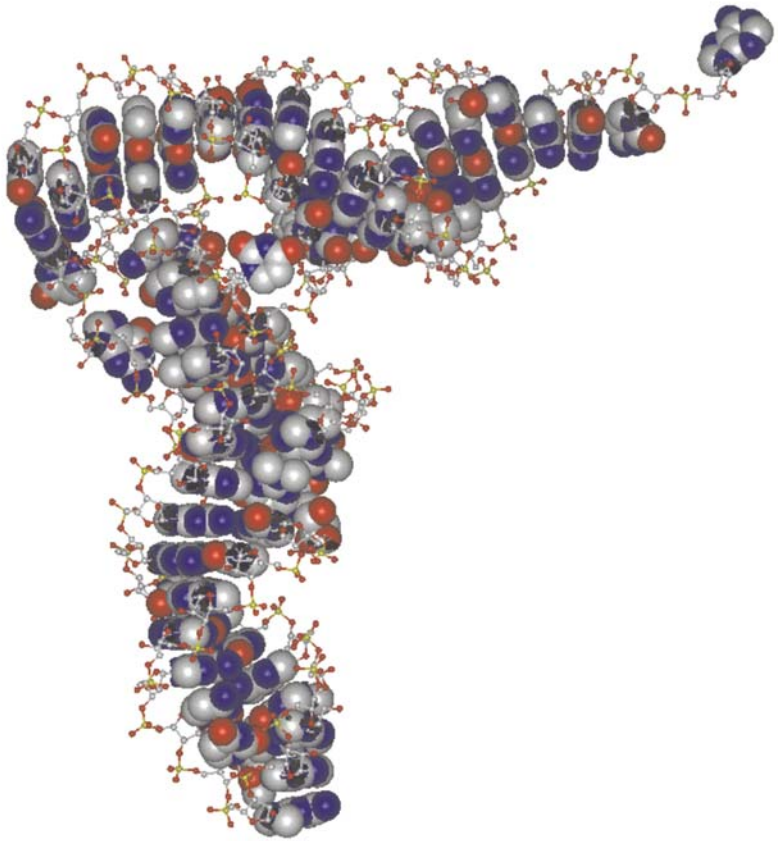
Web-Page for further information:

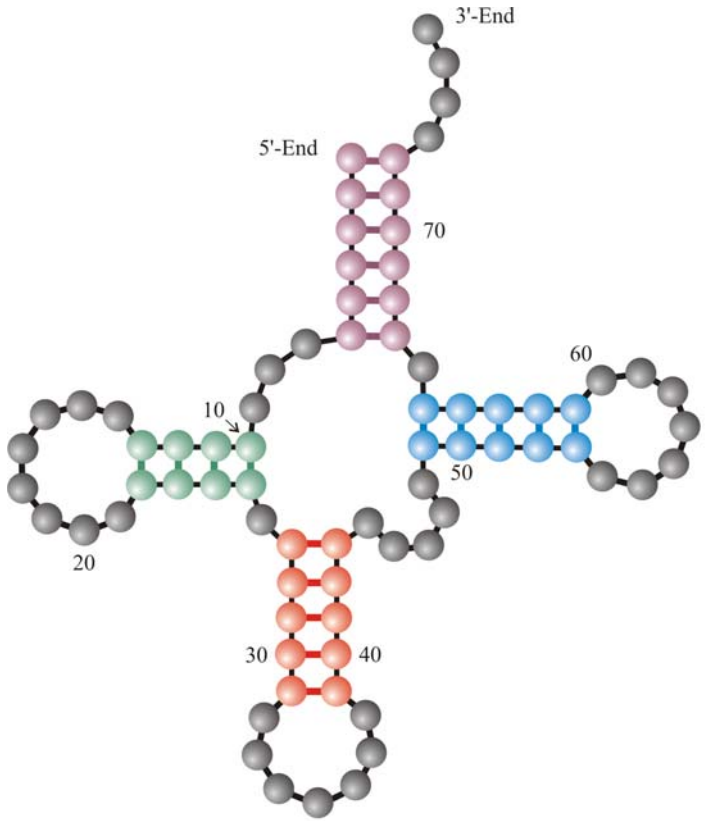
http://www.tbi.univie.ac.at/~pks

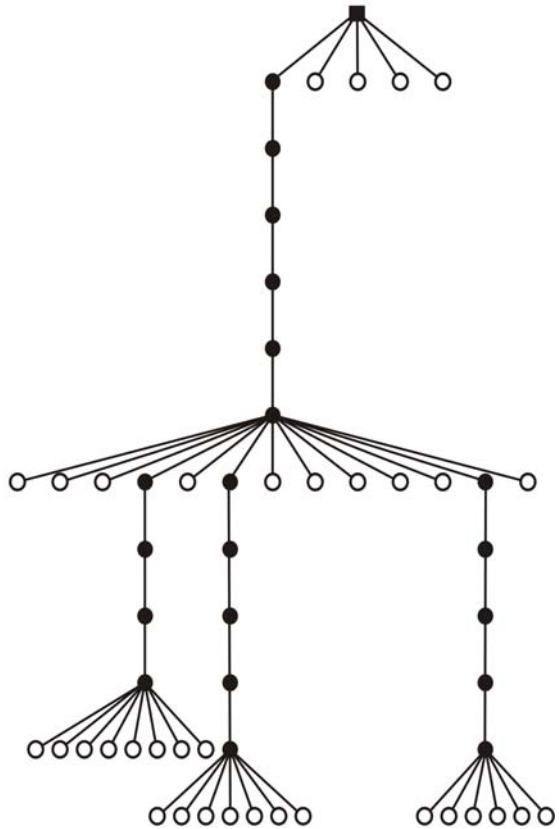
5'-end GCGGAUUUAGCUCAGUUGGGAGAGCGCCAGACUGAAGAUCUGGAGGUCCUGUGUUCGAUCCACAGAAUUCGCACCA 3'-end



tRNA^{phe}: sequence and molecular structure

5'-end GCGGAUUUAGCUCAGUUGGGAGAGCGCCAGACUGAAGAUCUGGAGGUCCUGUGUUCGAUCCACAGAAUUCGCACCA 3'-end





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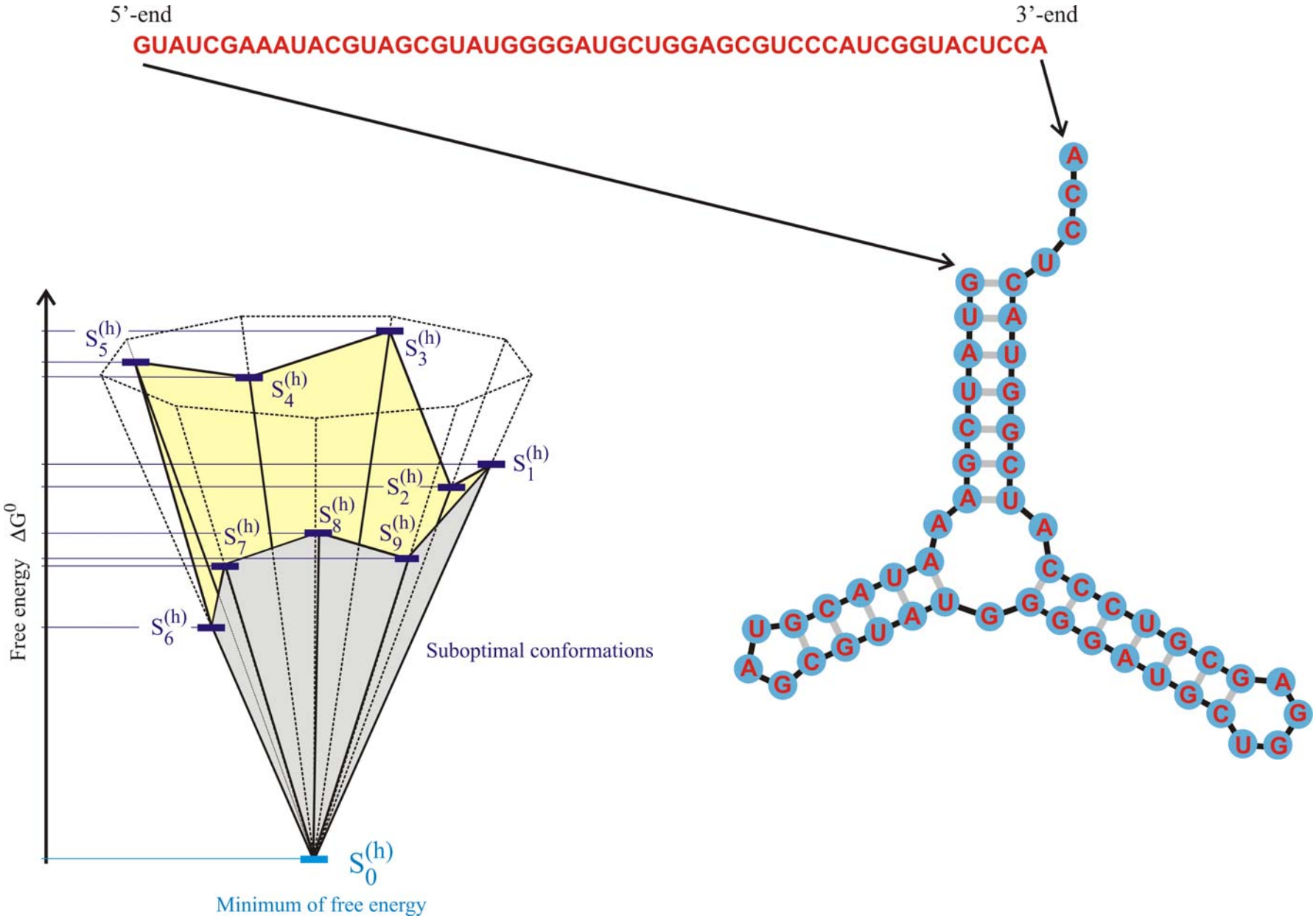
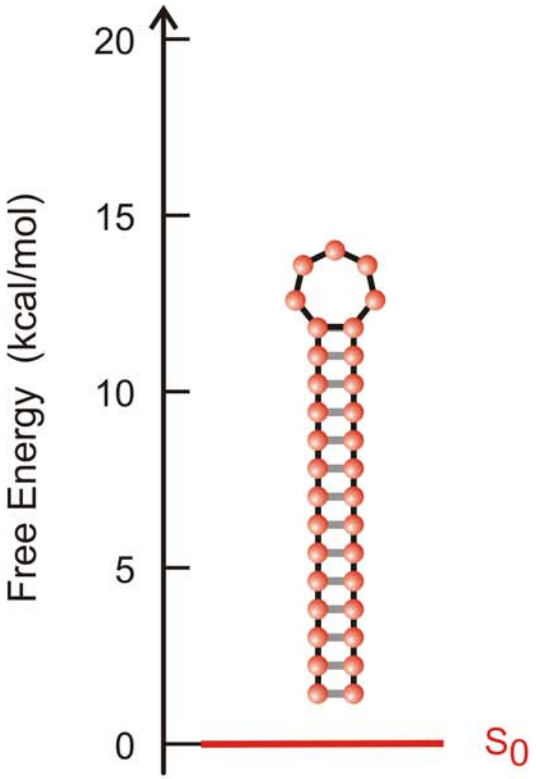
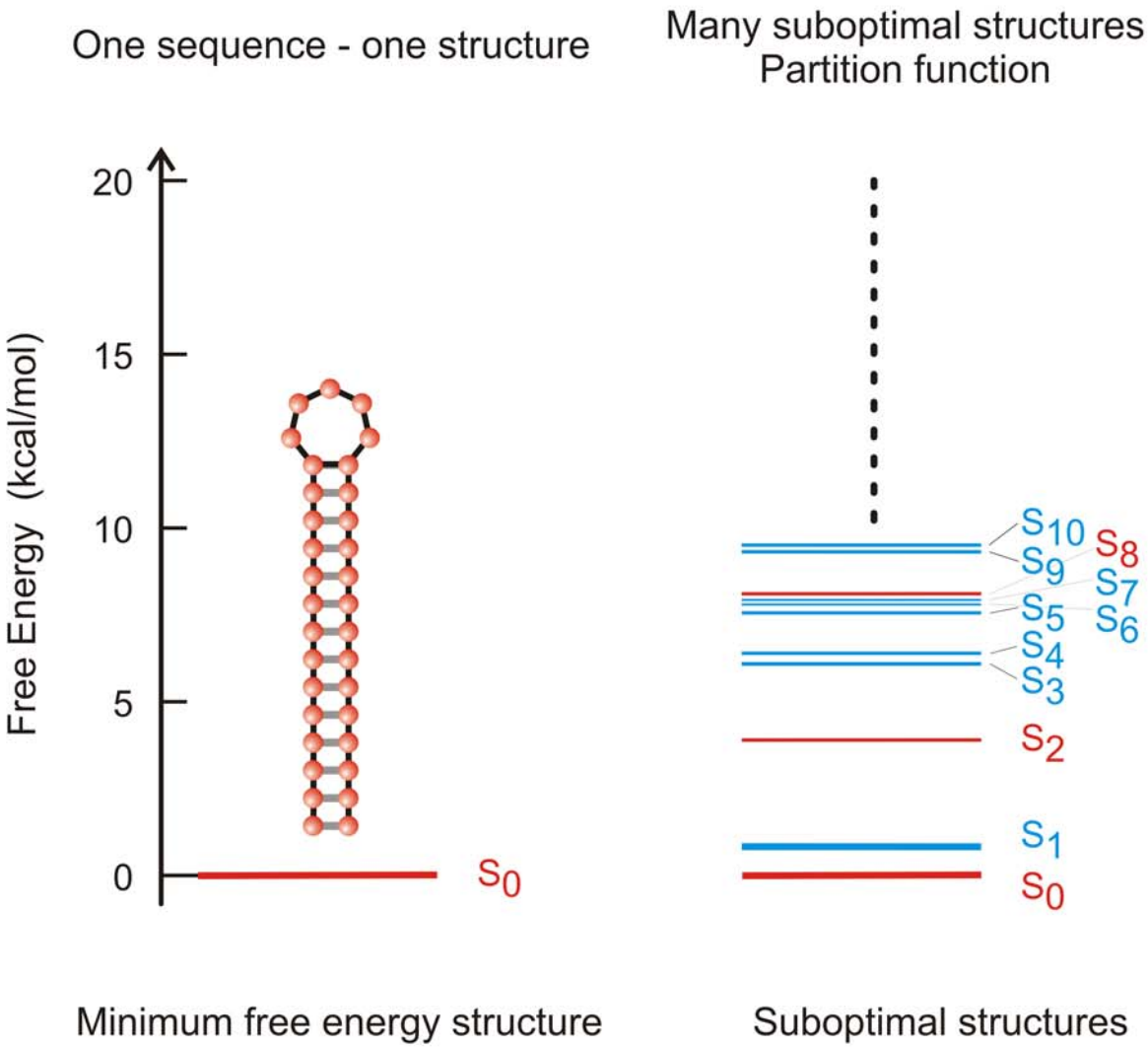
tRNA^{phe}: secondary structure is a **shape**

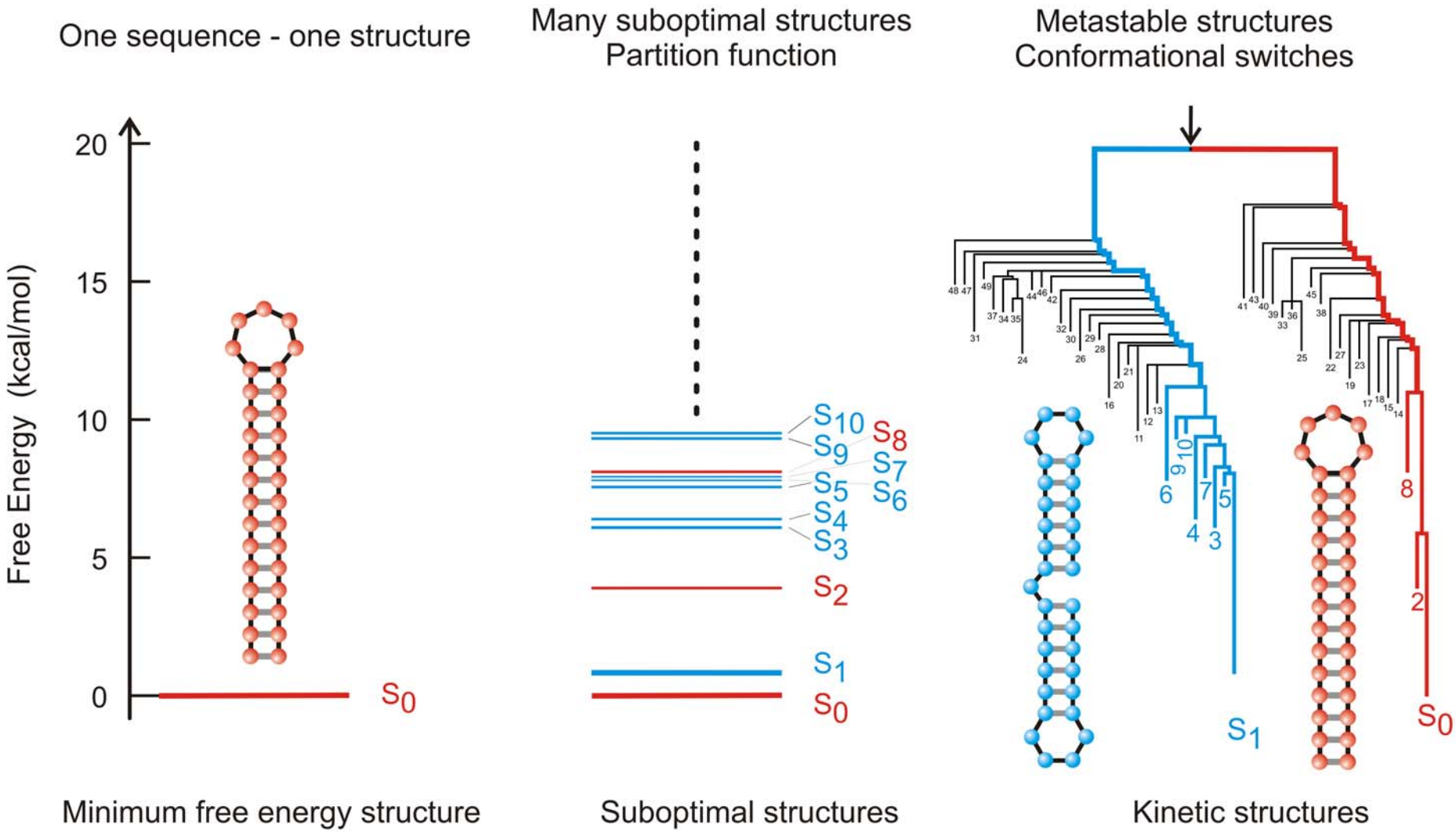

5'-end
3'-end
GUAUCGAAAUACGUAGCGUAUGGGGAUGCUGGAGCGUCCCAUCGGUACUCCA
Free energy ΔG0
S5(h)
S3(h)
S4(h)
S1(h)
S2(h)
S8(h)
S7(h)
S9(h)
S6(h)
Suboptimal conformations
S0(h)
Minimum of free energy

One sequence - one structure



Minimum free energy structure


One sequence - one structure
Many suboptimal structures
Partition function
Free Energy (kcal/mol)
20
15
10
5
0
S_0
S_{10}
S_9
S_8
S_7
S_5
S_6
S_4
S_3
S_2
S_1
S_0
Minimum free energy structure
Suboptimal structures

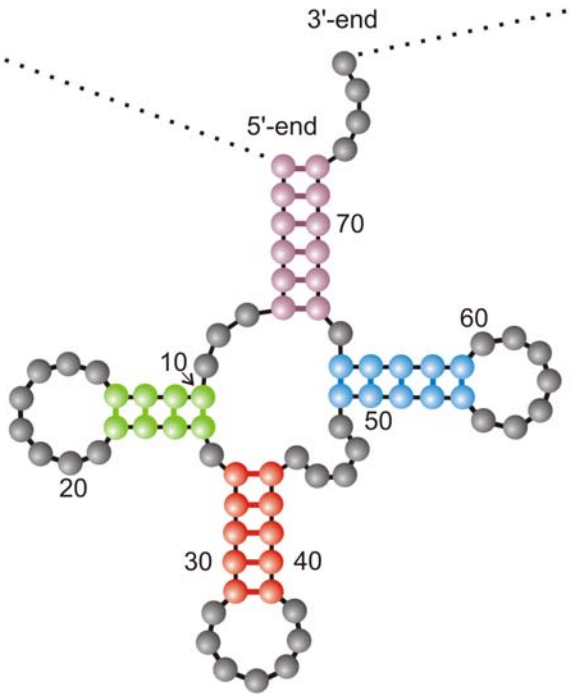

One sequence - one structure
Many suboptimal structures
Partition function
Metastable structures
Conformational switches
Free Energy (kcal/mol)
20
15
10
5
0
S0
S10
S9
S8
S7
S5
S6
S4
S3
S2
S1
S0
Minimum free energy structure
Suboptimal structures
Kinetic structures

Sequence

5'-End GCGGAUUUAGCUCAGDDGGGAGAGCMCCAGACUGAAYAUCUGGAGMUCCUGUGTPCGAUCCACAGAAUUCGCACCA 3'-End

$N = 4^n$

Secondary structure



Symbolic notation

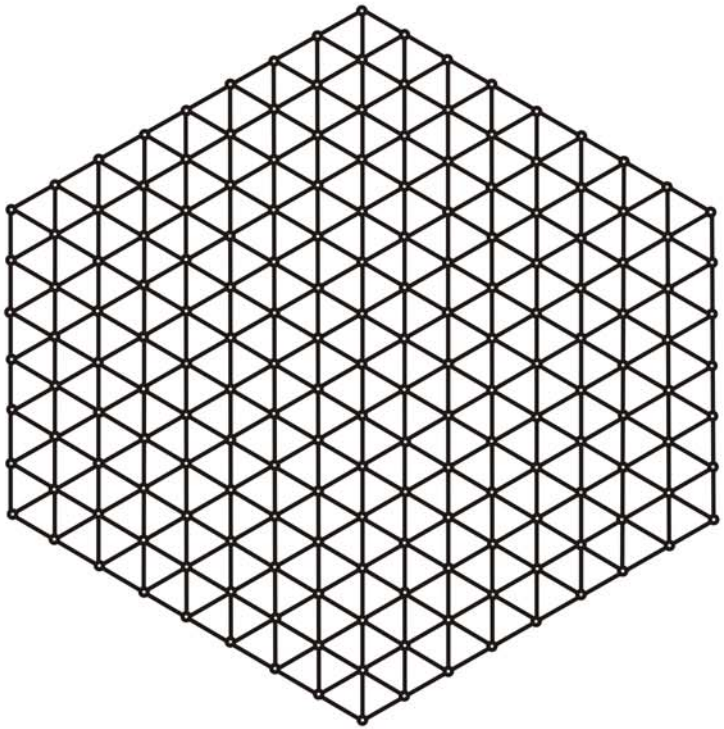
5'-End ((((((···((((·····))))·((((·····))))·····((((·····))))·))))))···· 3'-End

$N_S < 3^n$

Criterion: Minimum free energy (mfe)

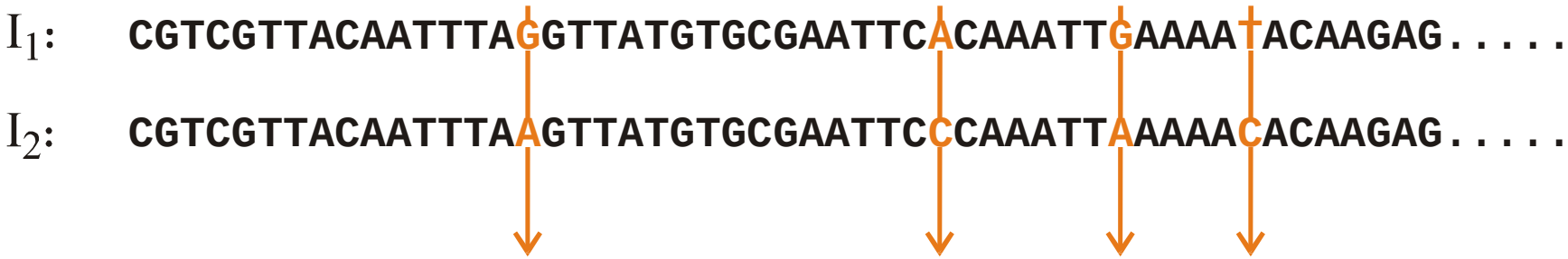
Rules: _ (_) _ ∈ {AU,CG,GC,GU,UA,UG}

A symbolic notation of RNA secondary structure that is equivalent to the conventional graphs



Sequence space

Sequence space



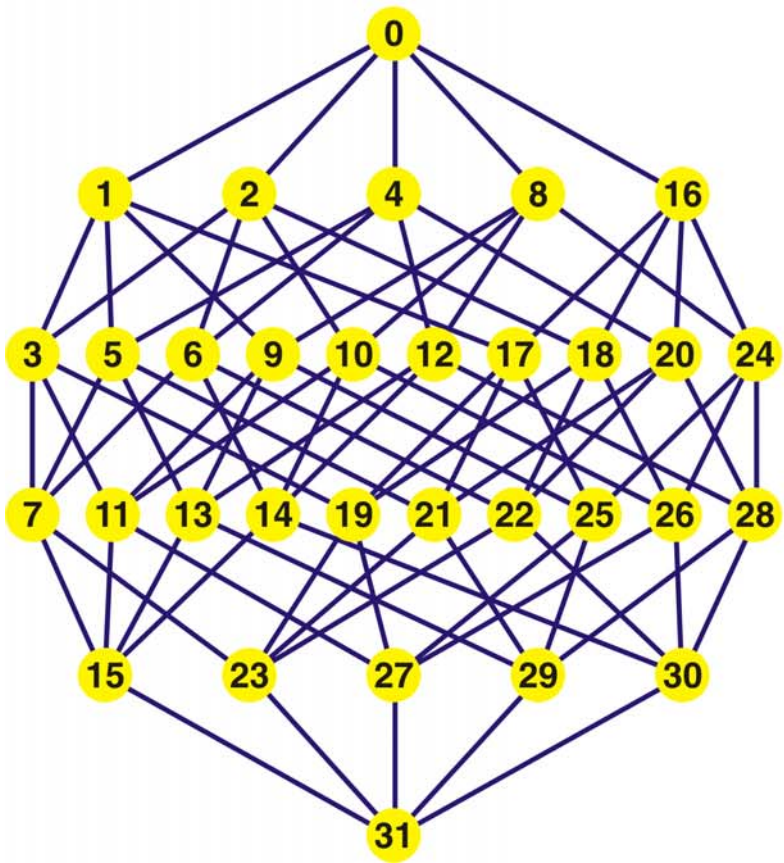
Hamming distance $d_H(I_1,I_2) = 4$

(i) $d_H(I_1,I_1) = 0$

(ii) $d_H(I_1,I_2) = d_H(I_2,I_1)$

(iii) $d_H(I_1,I_3) \leq d_H(I_1,I_2) + d_H(I_2,I_3)$

The Hamming distance between sequences induces a metric in sequence space



Binary sequences can be encoded by their decimal equivalents:

C = 0 and **G = 1**, for example,

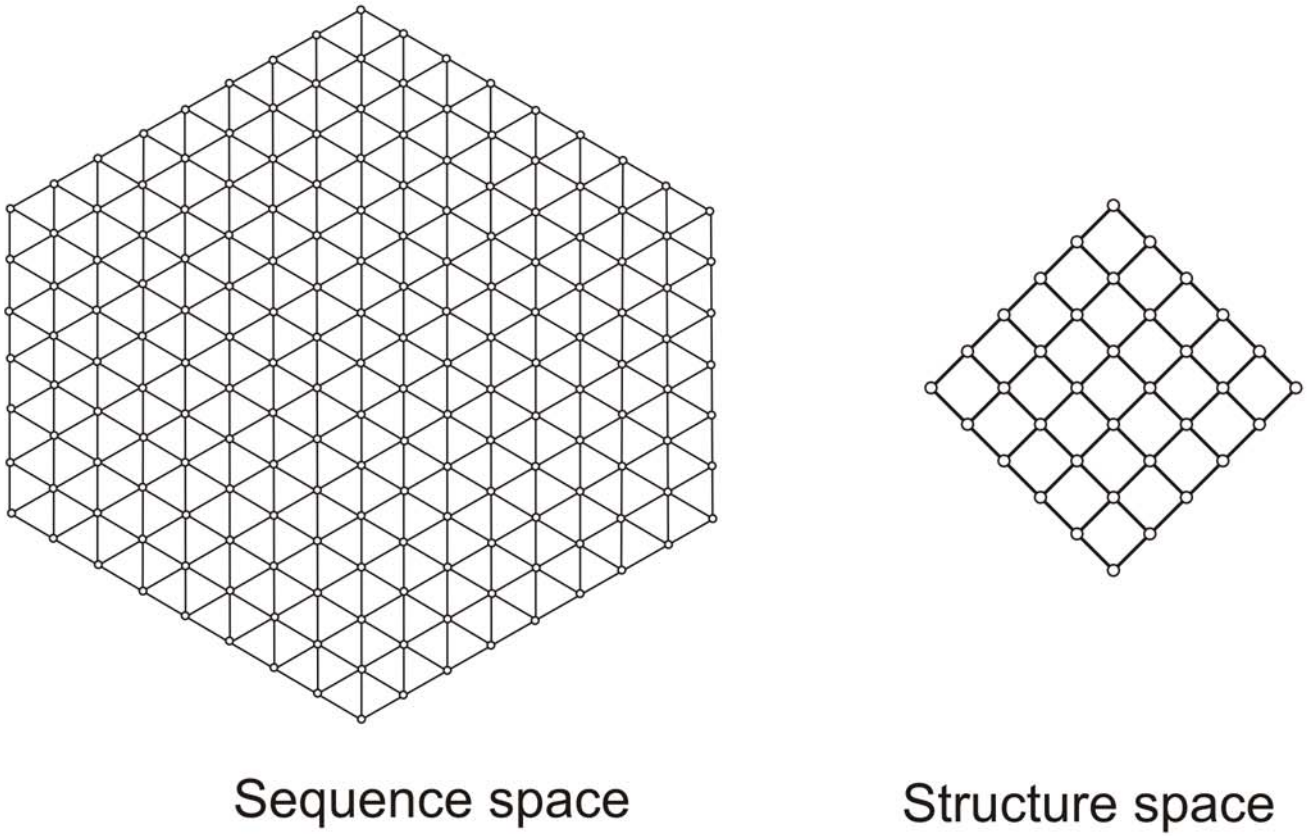
"0" ≡ 00000 = CCCCC,

"14" ≡ 01110 = CGGGC,

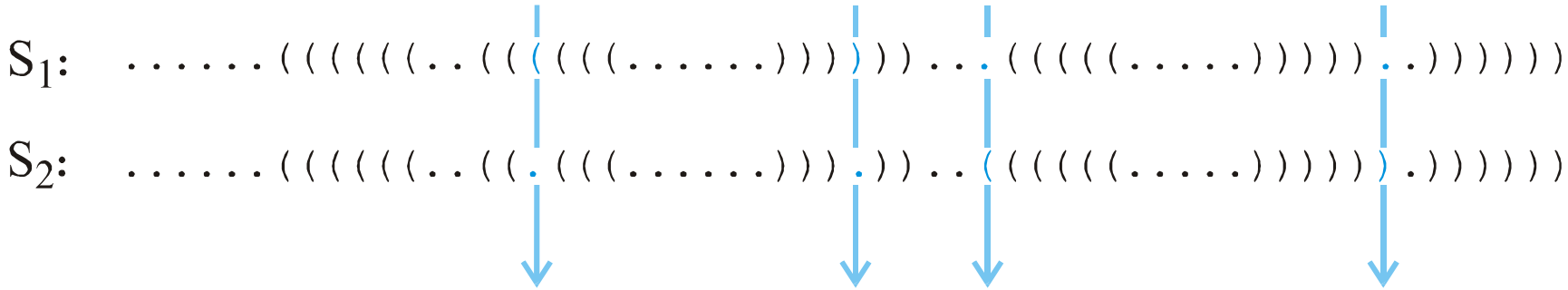
"29" ≡ 11101 = GGGCG, etc.

Every point in sequence space is equivalent

Sequence space of binary sequences with chain length $n = 5$



Sequence space and structure space



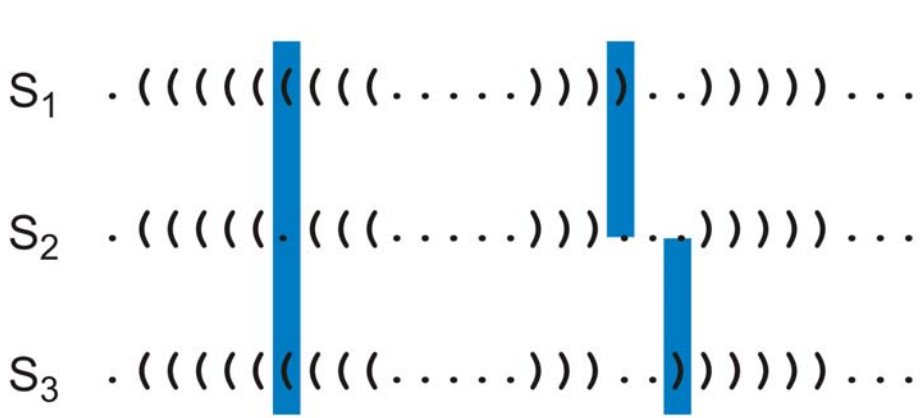
Hamming distance $d_H(S_1,S_2) = 4$

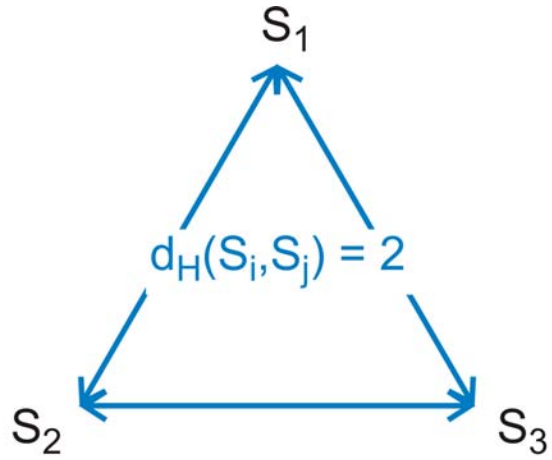
(i) $d_H(S_1,S_1) = 0$

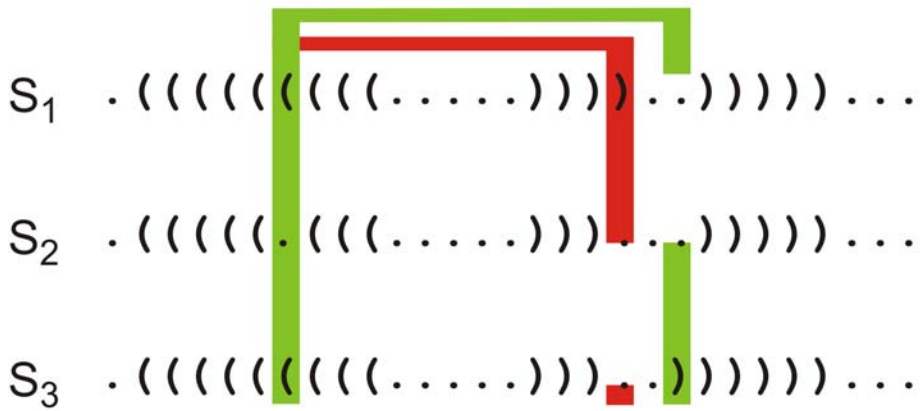
(ii) $d_H(S_1,S_2) = d_H(S_2,S_1)$

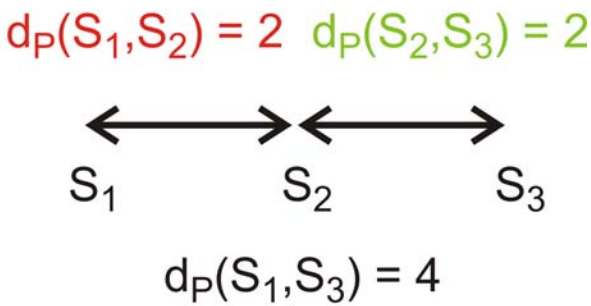
(iii) $d_H(S_1,S_3) \leq d_H(S_1,S_2) + d_H(S_2,S_3)$

The Hamming distance between structures in parentheses notation forms a metric in structure space



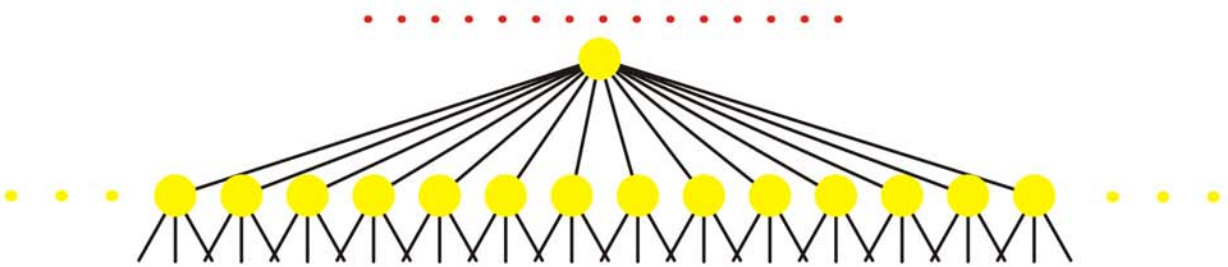






Two measures of distance in shape space:

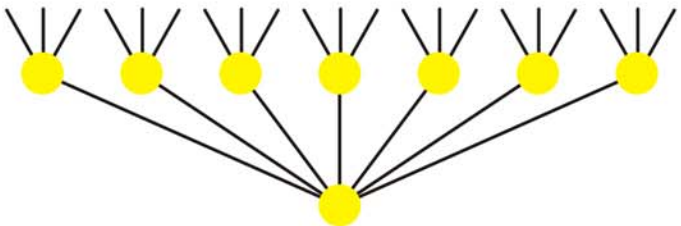
Hamming distance between structures, $d_H(S_i,S_j)$ and base pair distance, $d_P(S_i,S_j)$



open chain

number of edges $\frac{n\,(n-7)}{2}+6$

66 for n = 15



7 for n = 15

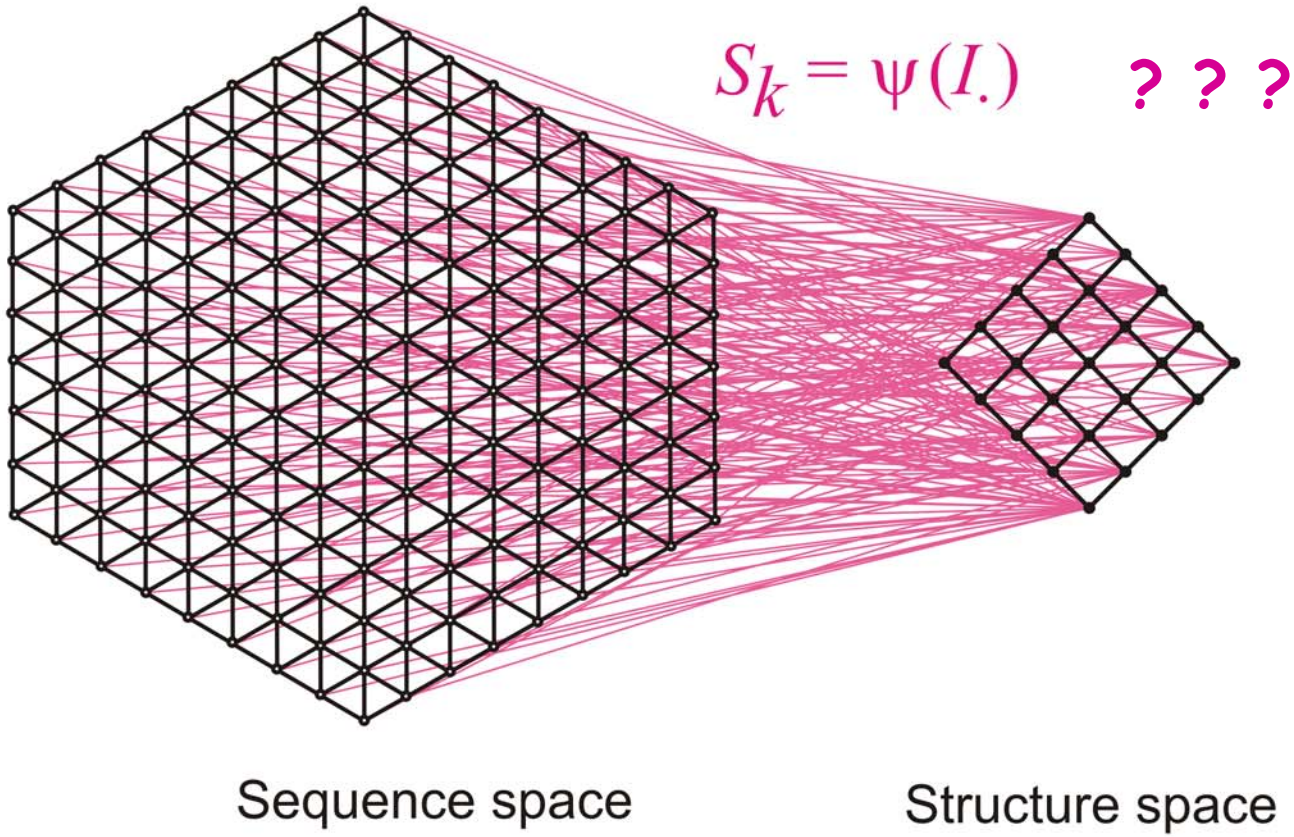
number of edges $\left\lfloor \frac{n-3}{2} \right\rfloor$

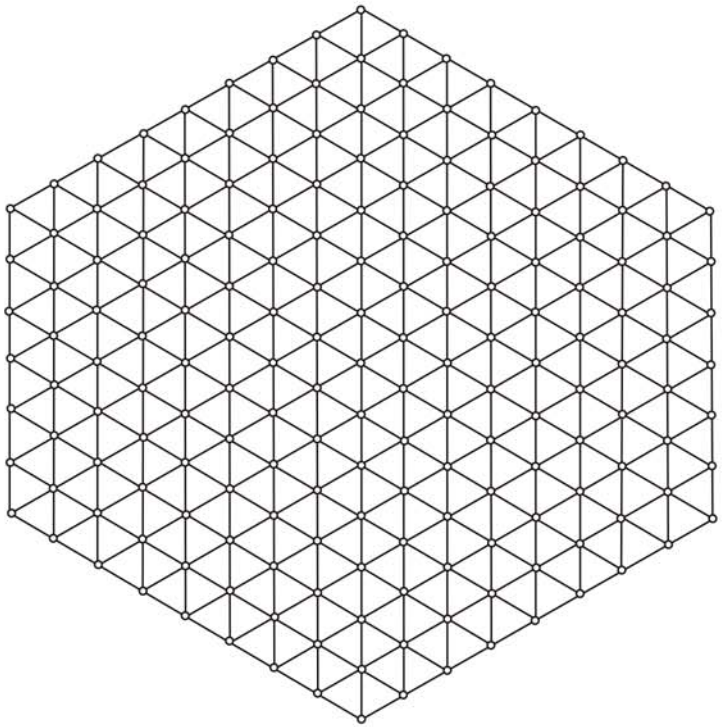
(((((((. . .)))))))

longest stack

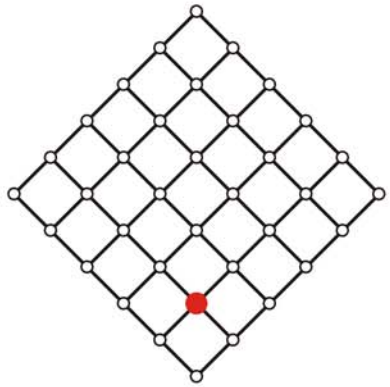
Structures are not equivalent in structure space

Sketch of structure space

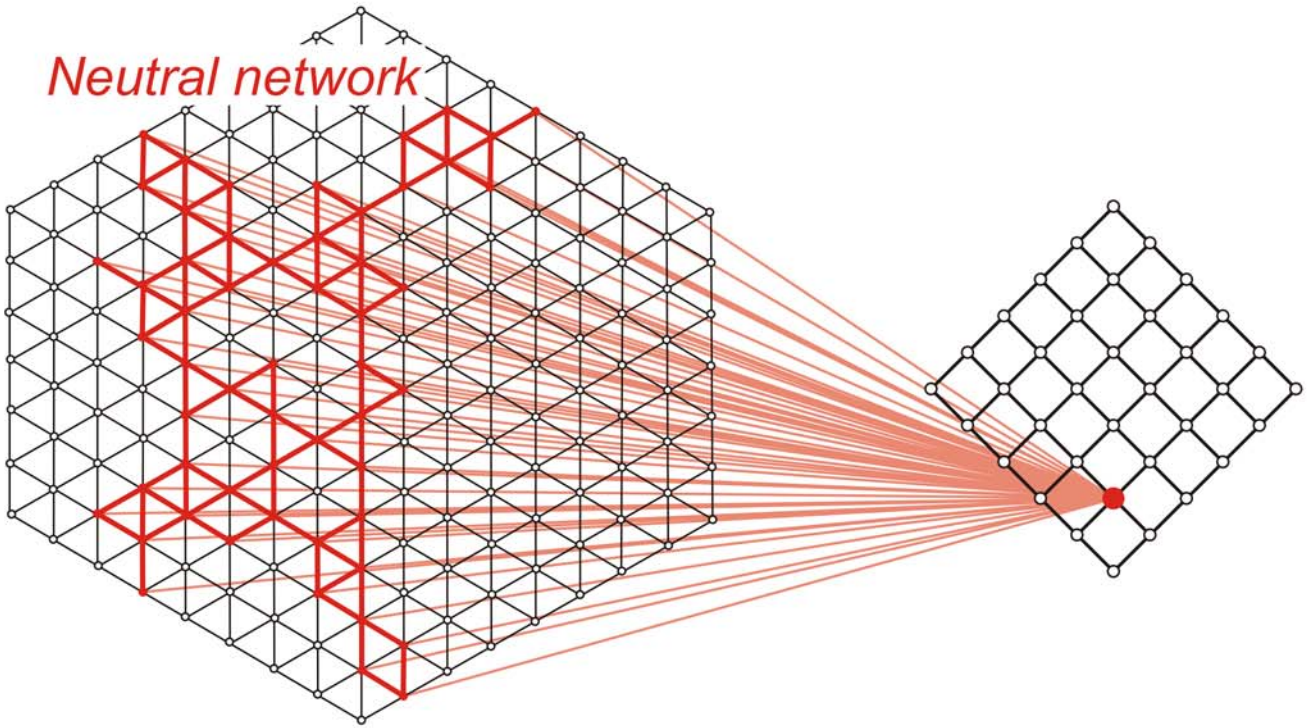

$S_k = \psi(I_.)$
? ? ?
Sequence space
Structure space

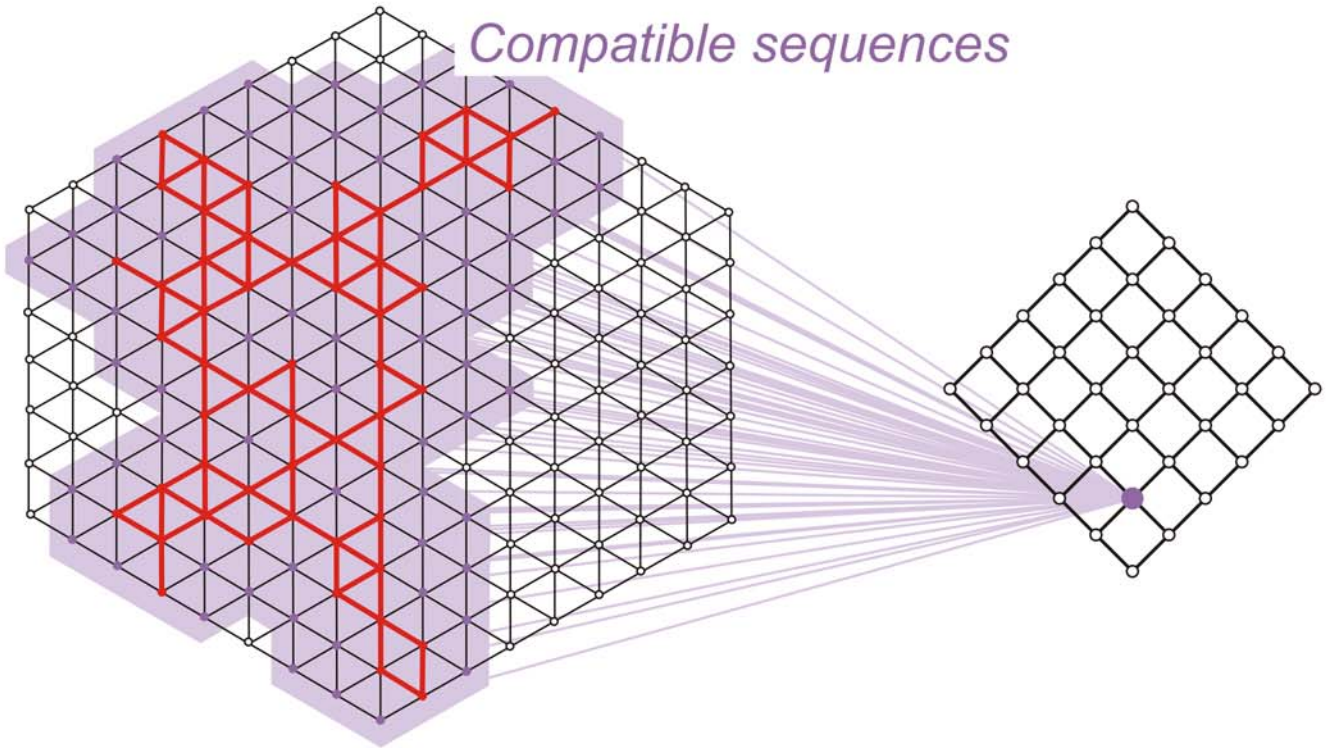


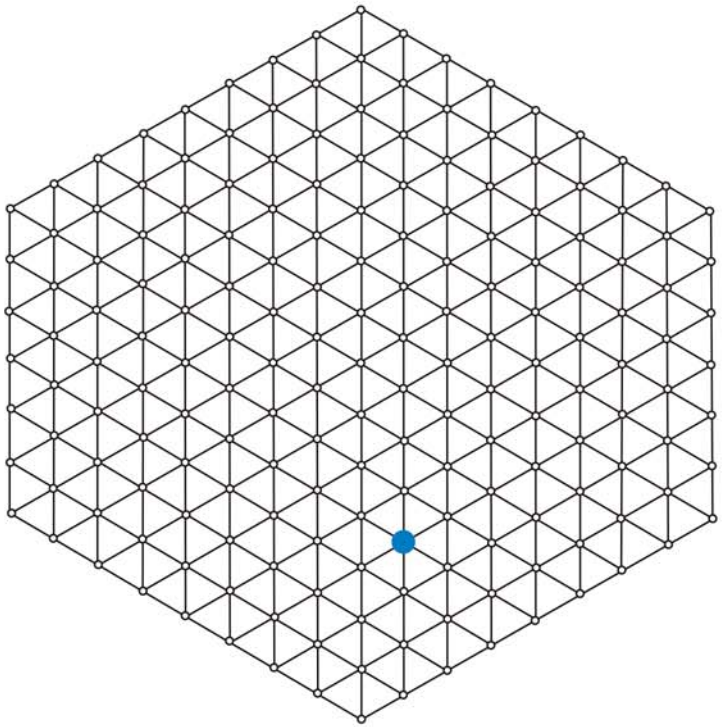
Sequence space



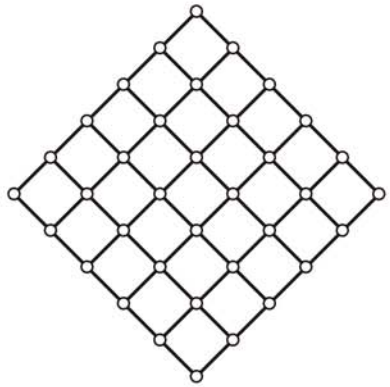
Structure space


Neutral network
Sequence space
Structure space

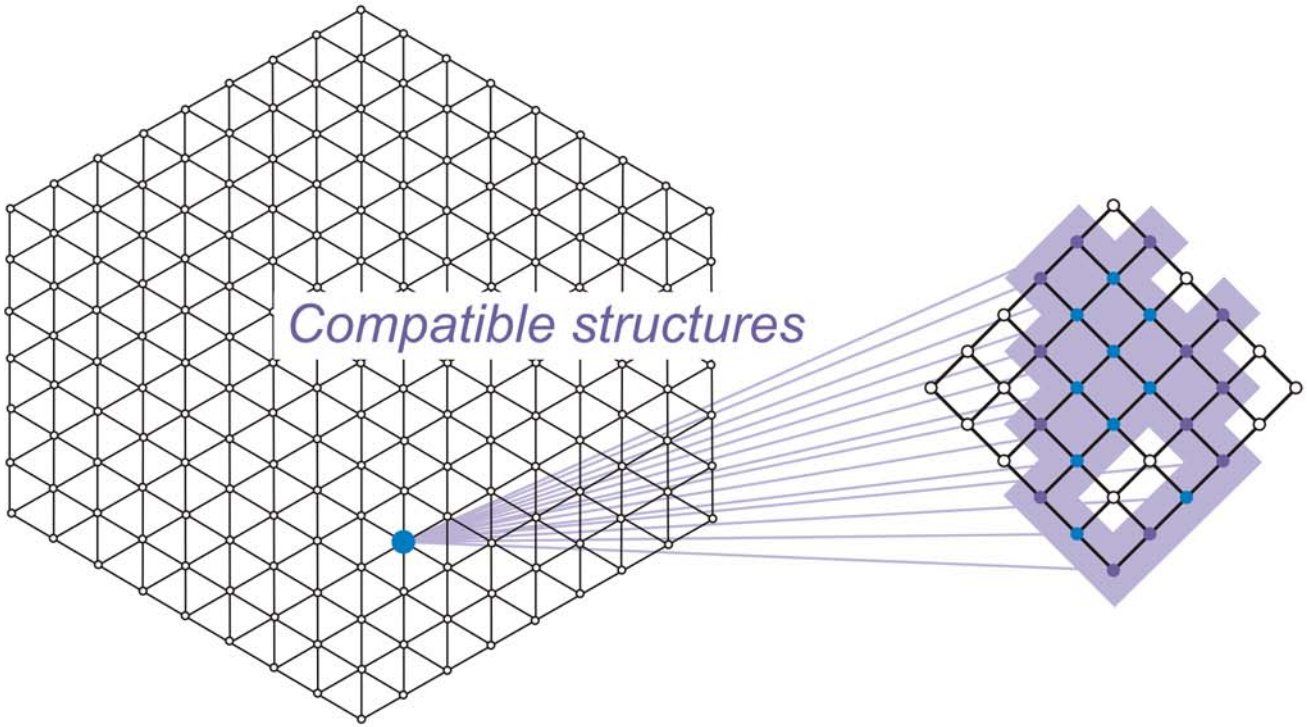

Compatible sequences
Sequence space
Structure space



Sequence space



Structure space



Compatible structures ≡ Suboptimal conformations

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GENERIC PROPERTIES OF COMBINATORY MAPS: NEUTRAL NETWORKS OF RNA SECONDARY STRUCTURES[1]

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Random graph theory is used to model and analyse the relationships between sequences and secondary structures of RNA molecules, which are understood as mappings from sequence space into shape space. These maps are non-invertible since there are always many orders of magnitude more sequences than structures. Sequences folding into identical structures form *neutral networks*. A neutral network is embedded in the set of sequences that are *compatible* with the given structure. Networks are modeled as graphs and constructed by random choice of vertices from the space of compatible sequences. The theory characterizes neutral networks by the mean fraction of neutral neighbors (λ). The networks are connected and percolate sequence space if the fraction of neutral nearest neighbors exceeds a threshold value ($\lambda > \lambda^*$). Below threshold ($\lambda < \lambda^*$), the networks are partitioned into a largest "giant" component and several smaller components. Structures are classified as "common" or "rare" according to the sizes of their pre-images, i.e. according to the fractions of sequences folding into them. The neutral networks of any pair of two different common structures almost touch each other, and, as expressed by the conjecture of *shape space covering* sequences folding into almost all common structures, can be found in a small ball of an arbitrary location in sequence space. The results from random graph theory are compared to data obtained by folding large samples of RNA sequences. Differences are explained in terms of specific features of RNA molecular structures. © *1997 Society for Mathematical Biology*

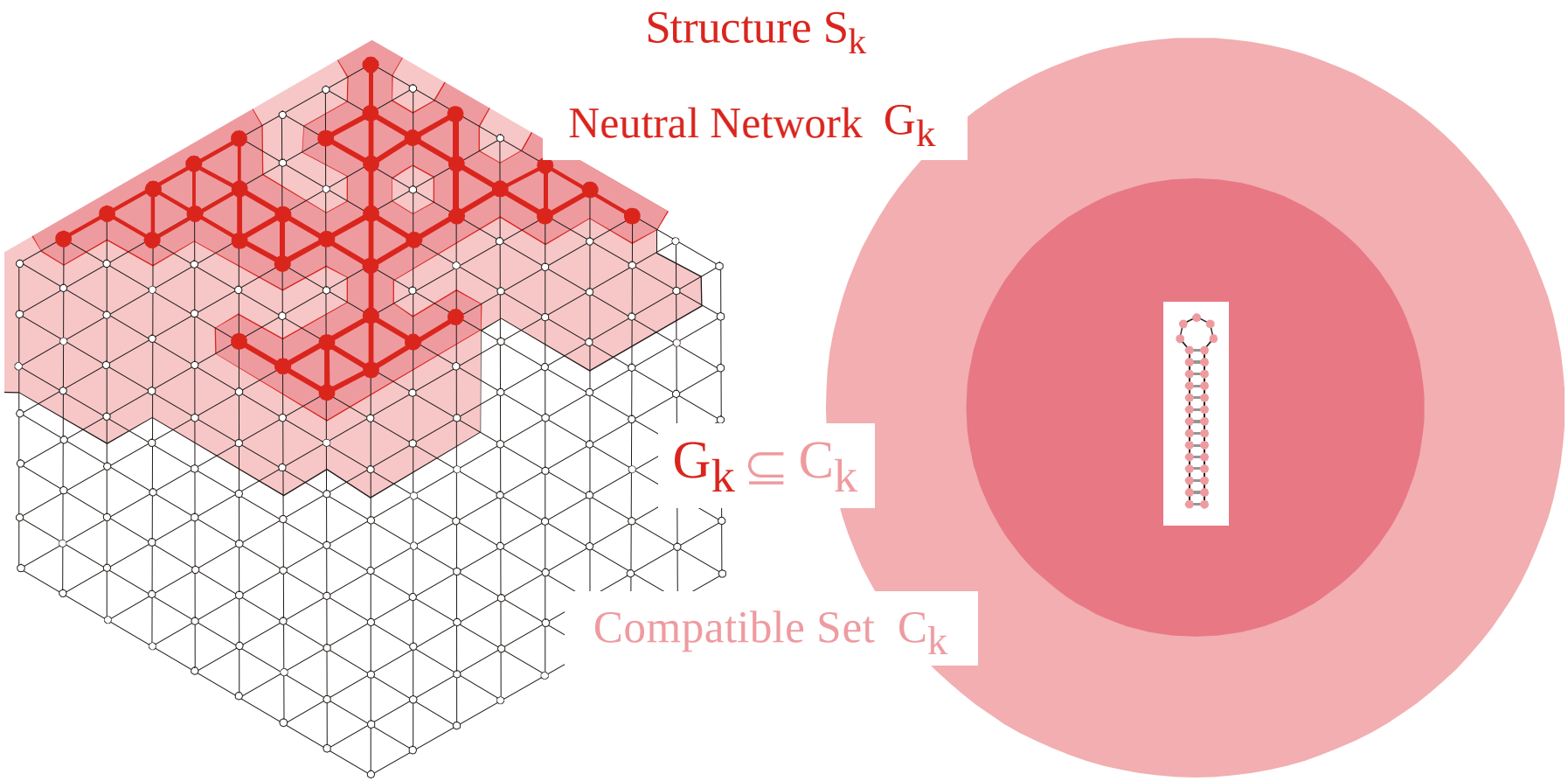
THEOREM 5. INTERSECTION-THEOREM. *Let* s *and* s′ *be arbitrary secondary structures and* **C**[s], **C**[s′] *their corresponding compatible sequences. Then,*

$$\mathbf{C}[s] \cap \mathbf{C}[s'] \neq \emptyset.$$

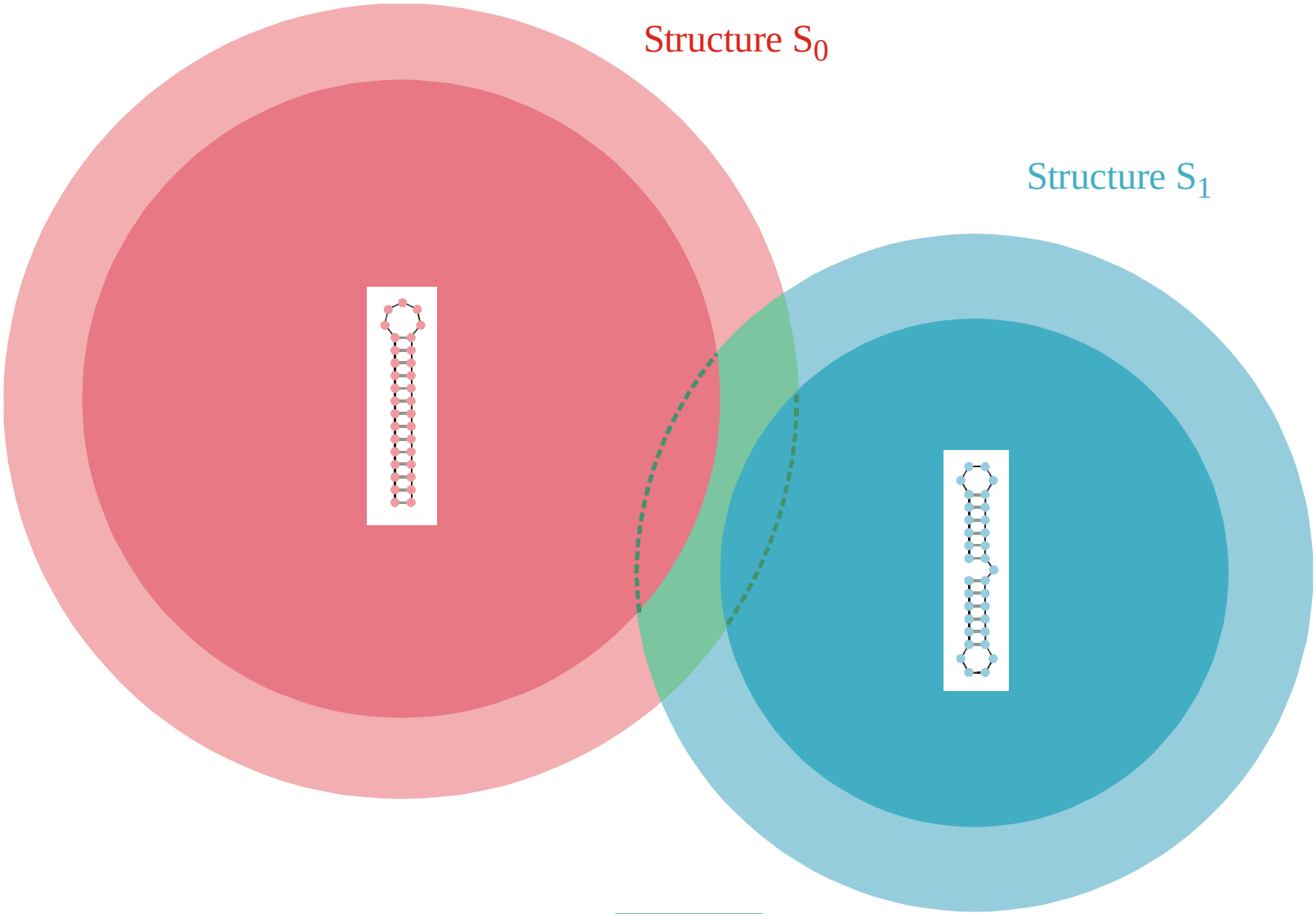
Proof. Suppose that the alphabet admits only the complementary base pair $[XY]$ and we ask for a sequence x compatible to both s and s'. Then $\gamma(s, s') \cong D_m$ operates on the set of all positions $\{x_1, \ldots, x_n\}$. Since we have the operation of a dihedral group, the orbits are either cycles or chains and the cycles have even order. A constraint for the sequence compatible to both structures appears only in the cycles where the choice of bases is not independent. It remains to be shown that there is a valid choice of bases for each cycle, which is obvious since these have even order. Therefore, it suffices to choose an alternating sequence of the pairing partners X and Y. Thus, there are at least two different choices for the first base in the orbit. ■

Remark. A generalization of the statement of theorem 5 to three different structures is false.

Reference for the definition of the intersection and the proof of the **intersection theorem**



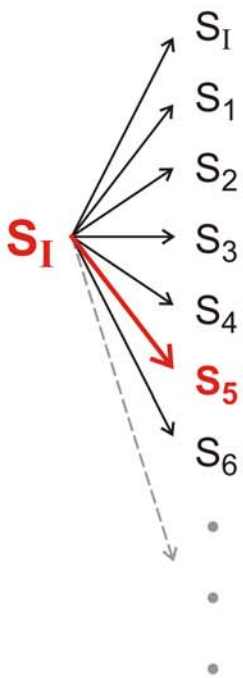
The **compatible set C_k** of a structure **S_k** consists of all sequences which form **S_k** as its minimum free energy structure (the neutral network **G_k**) or one of its suboptimal structures.



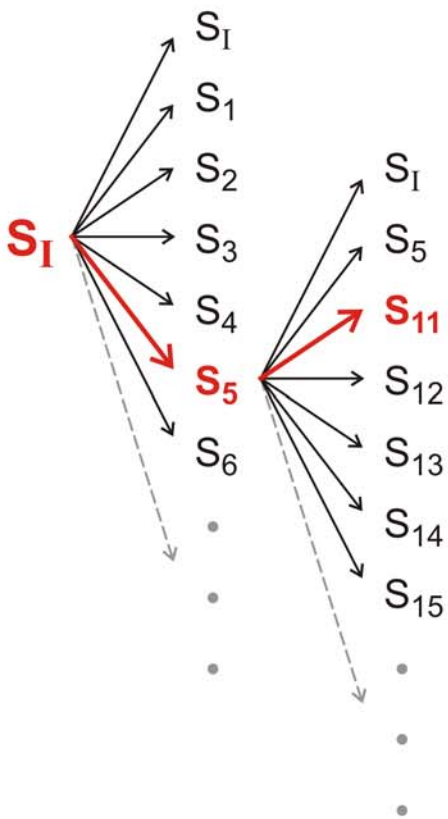
Intersection of two compatible sets: $C_0 \cap C_1$

The intersection of two compatible sets is always non empty: $C_0 \cap C_1 \notin \varnothing$

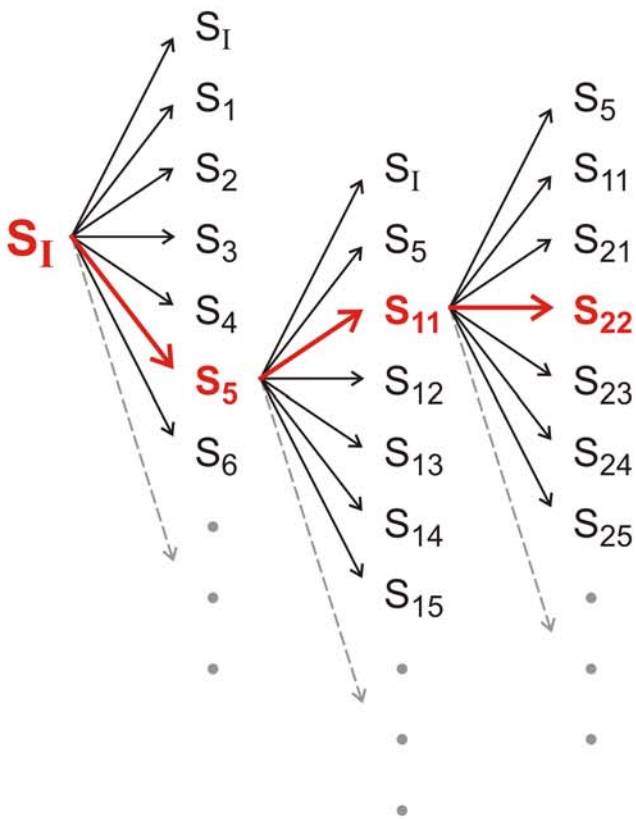
Kinetic folding of RNA as a Markow process



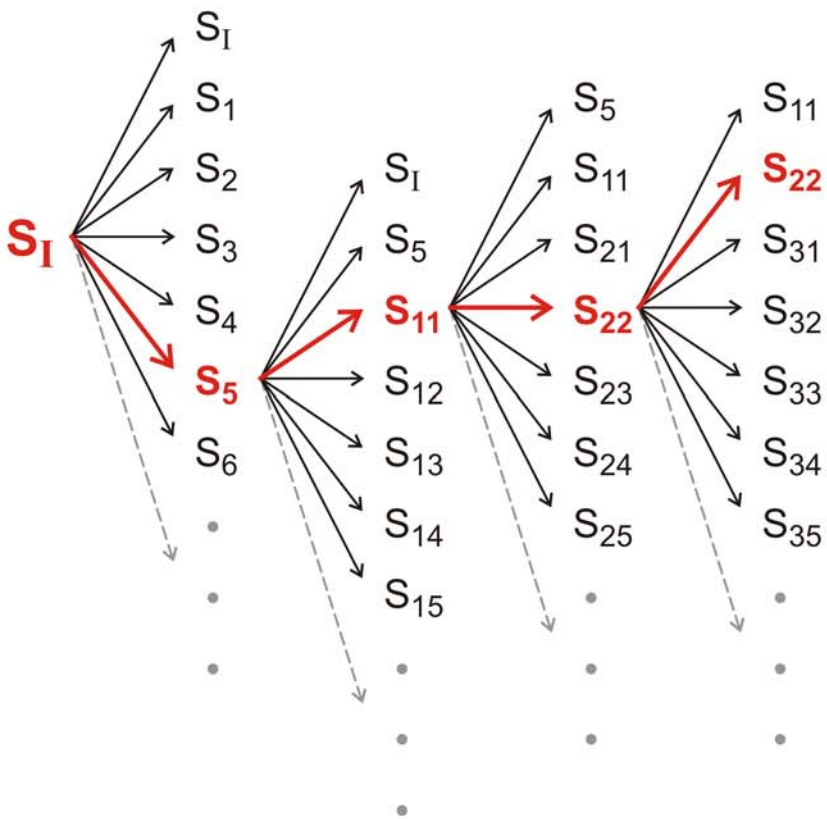
Kinetic folding of RNA as a Markow process



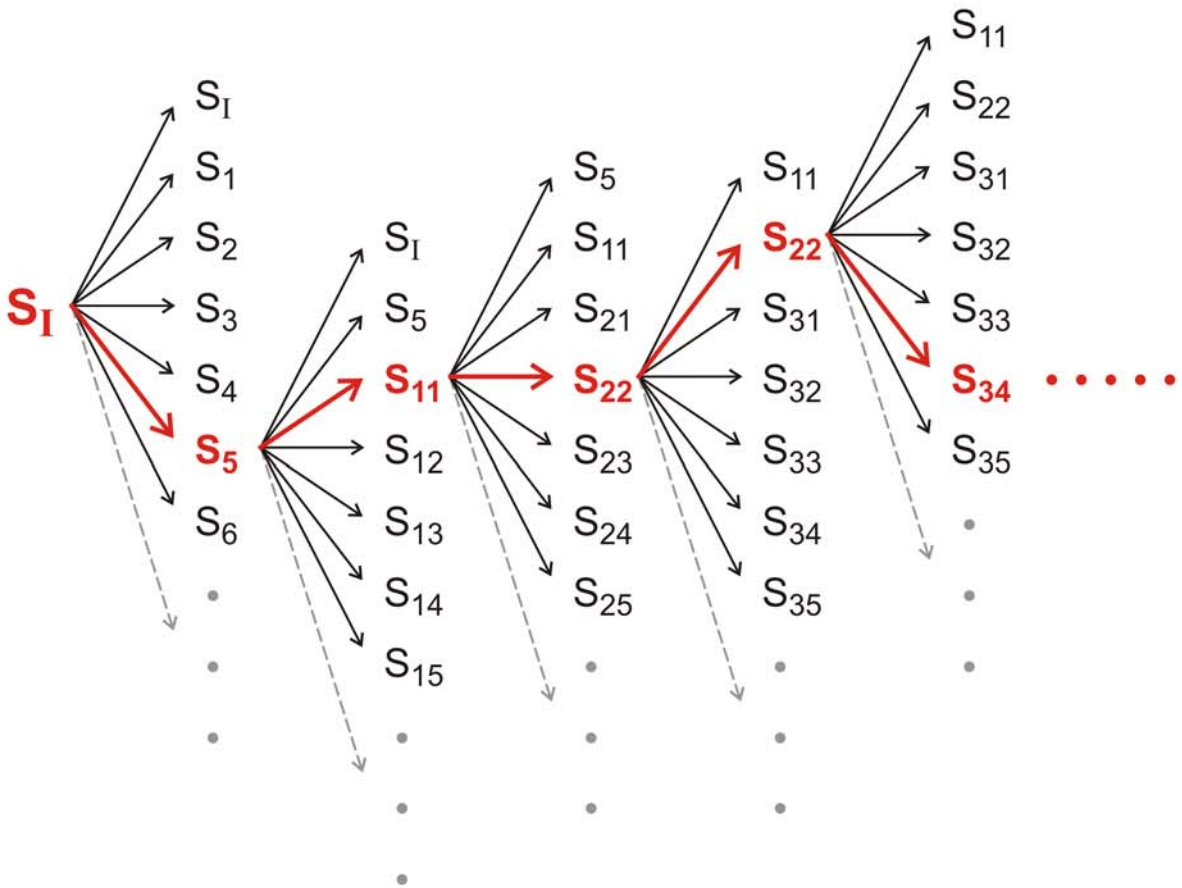
Kinetic folding of RNA as a Markow process



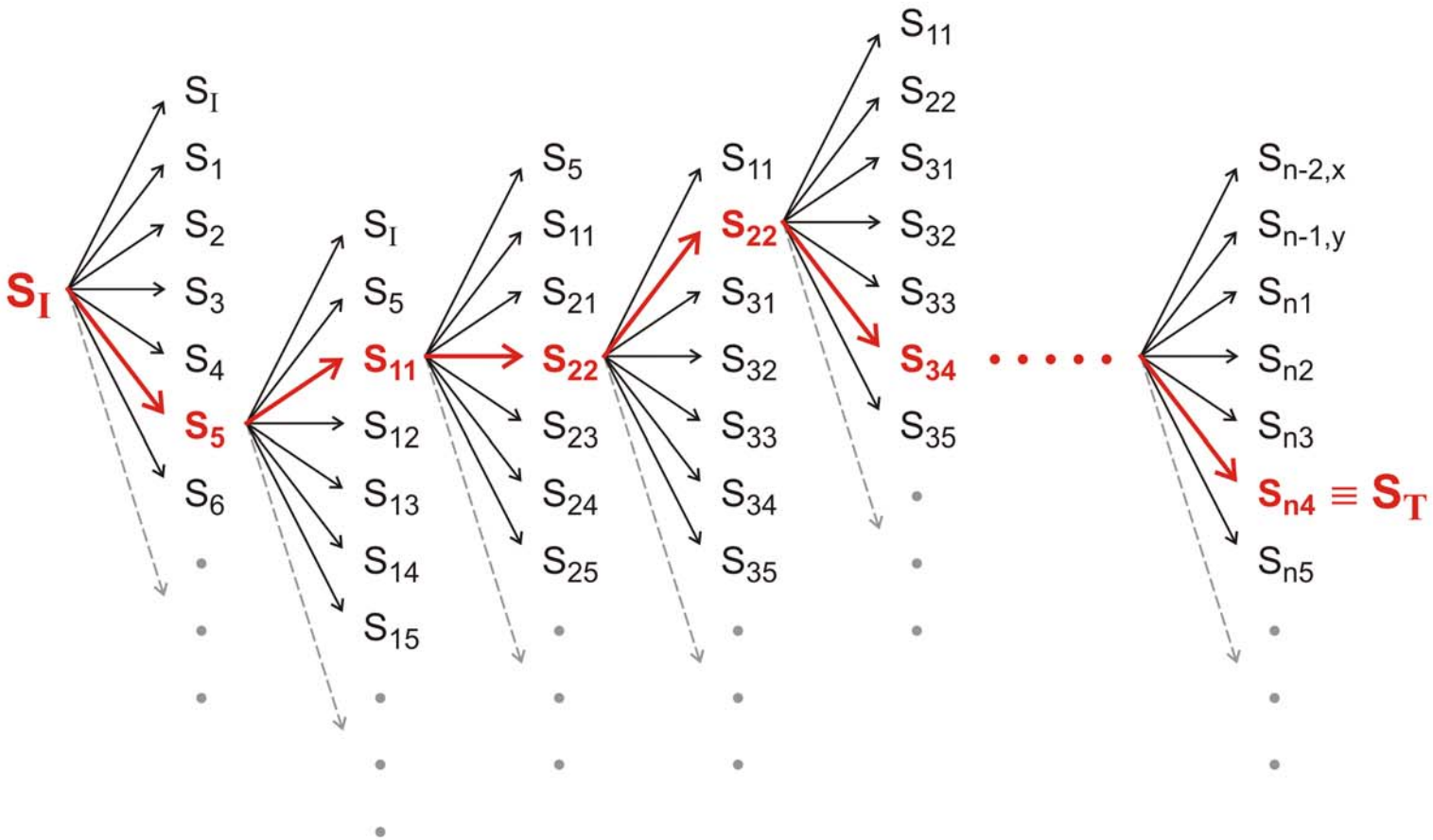
Kinetic folding of RNA as a Markow process



Kinetic folding of RNA as a Markow process



Kinetic folding of RNA as a Markow process



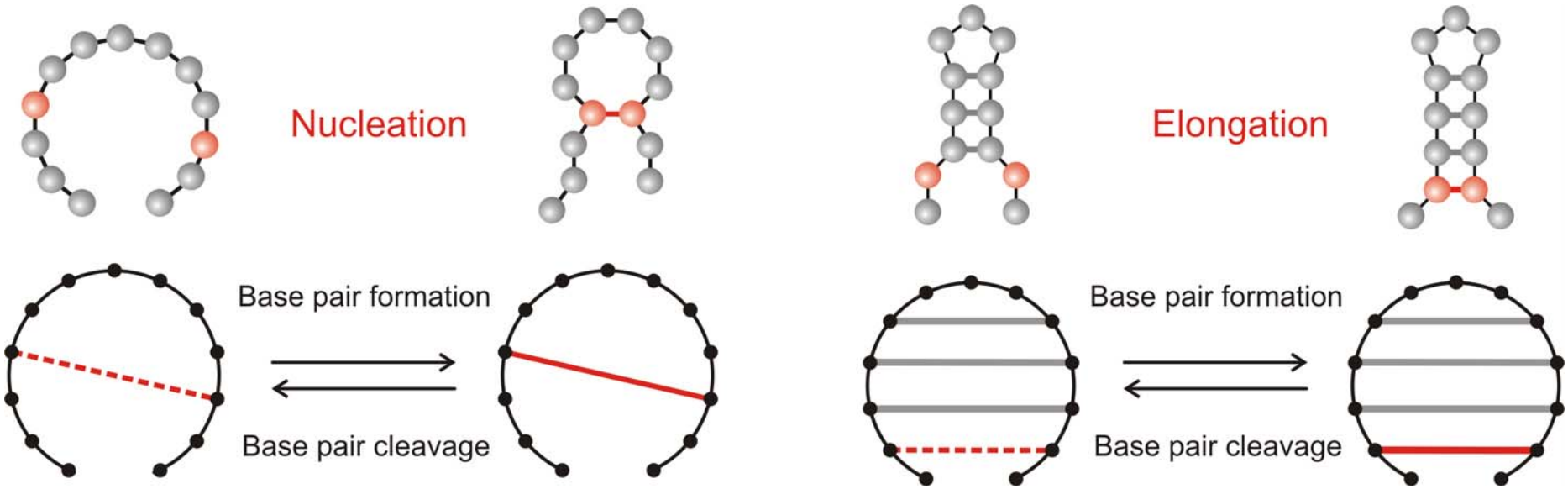
Kinetic folding of RNA as a Markow process

Kinetic folding of RNA secondary structures

Christoph Flamm, Walter Fontana, Ivo L. Hofacker, Peter Schuster. *RNA folding kinetics at elementary step resolution.* RNA **6**:325-338, 2000

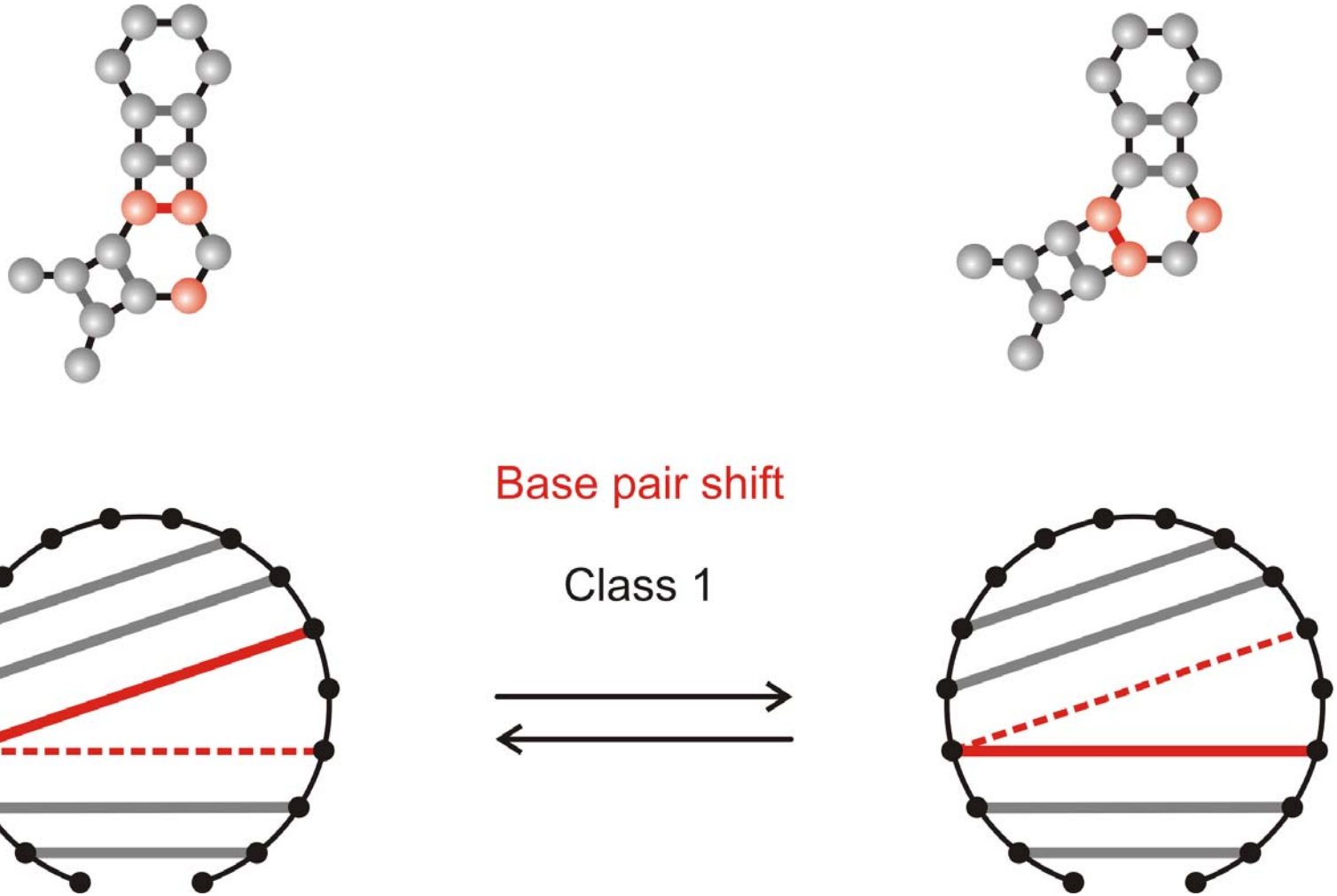
Christoph Flamm, Ivo L. Hofacker, Sebastian Maurer-Stroh, Peter F. Stadler, Martin Zehl. *Design of multistable RNA molecules.* RNA **7**:325-338, 2001

Michael T. Wolfinger, W.Andreas Svrcek-Seiler, Christoph Flamm, Ivo L. Hofacker, Peter F. Stadler. *Efficient computation of RNA folding dynamics*. J.Phys.A: Math.Gen. **37**:4731-4741, 2004



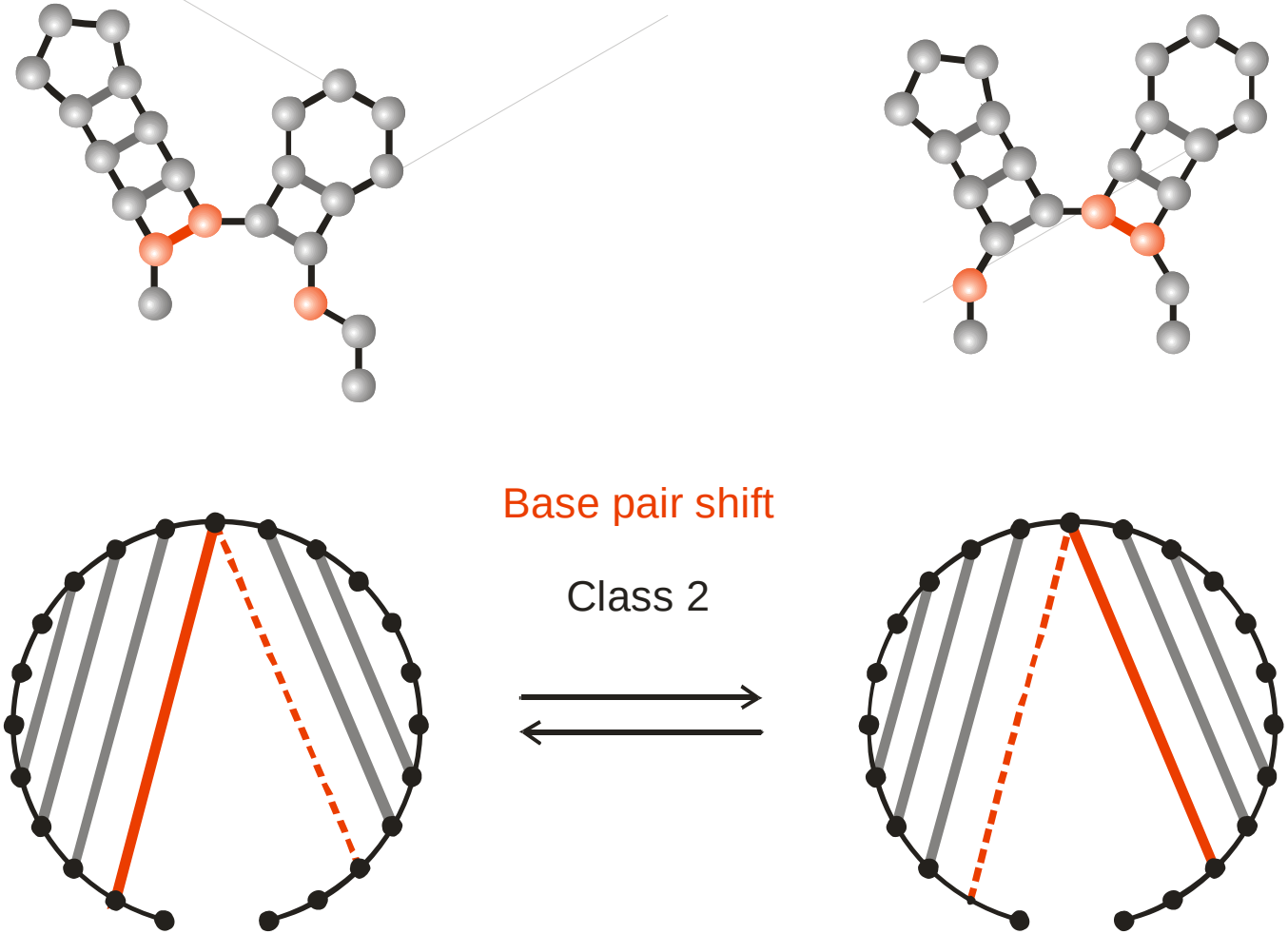
Corresponds to base pair distance: $d_p(S_1,S_2)$

Base pair formation and base pair cleavage moves for nucleation and elongation of stacks



Base pair closure, opening and shift corresponds to Hamming distance: $d_H(S_1,S_2)$

Base pair shift move of class 1: Shift inside internal loops or bulges



Base pair closure, opening and shift corresponds to Hamming distance: $d_H(S_1,S_2)$

Base pair shift move of class 2: Shift involves free ends

Formulation of kinetic RNA folding as a stochastic process

The kinetic folding algorithm

A sequence **X** specifies an energy ordered set of compatible structures $\mathfrak{S}(\mathbf{X})$:

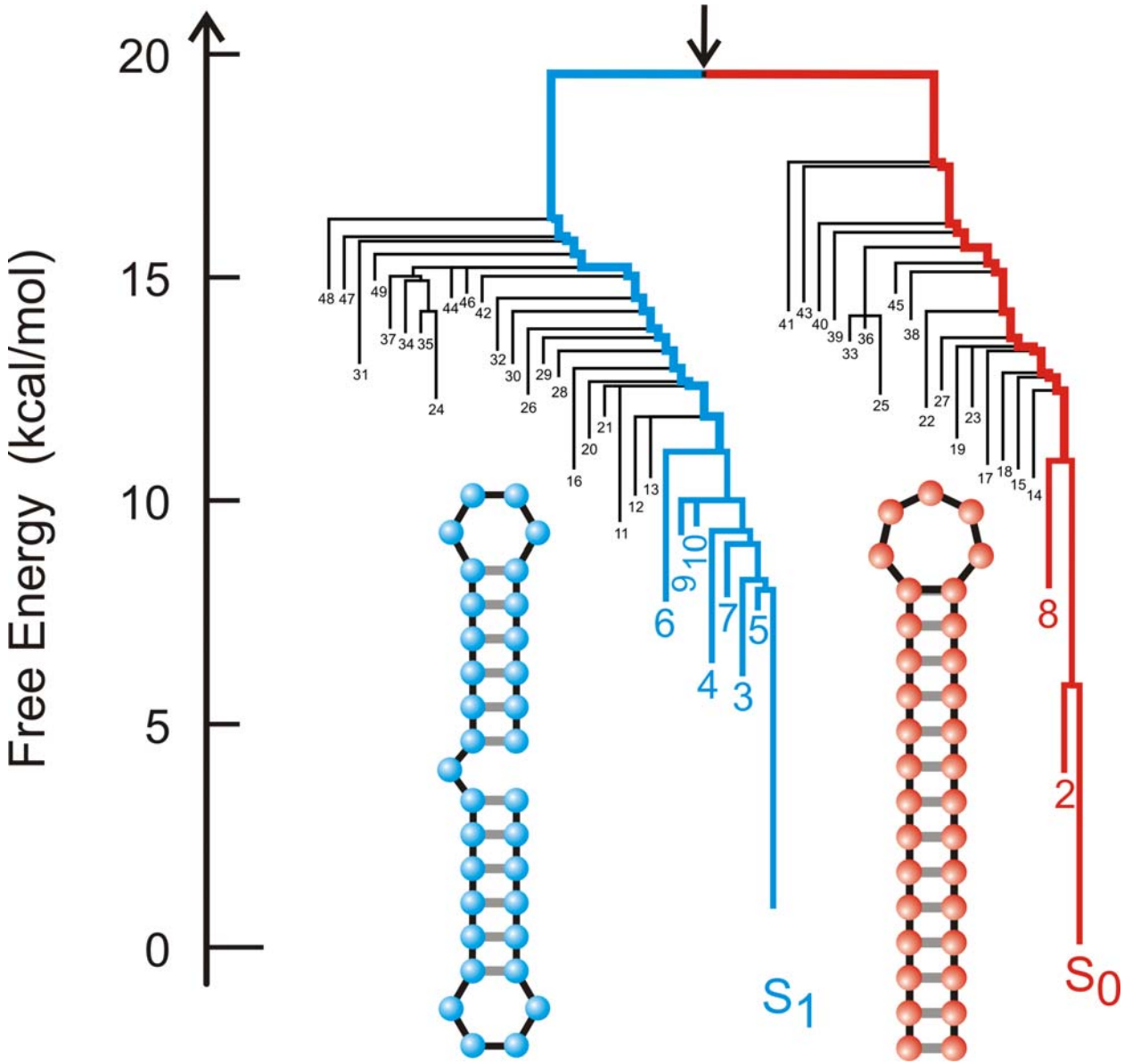
$$\mathfrak{S}(\mathbf{X}) = \{S_0, S_1, \ldots, S_{m-1}, \mathbf{O}\}$$

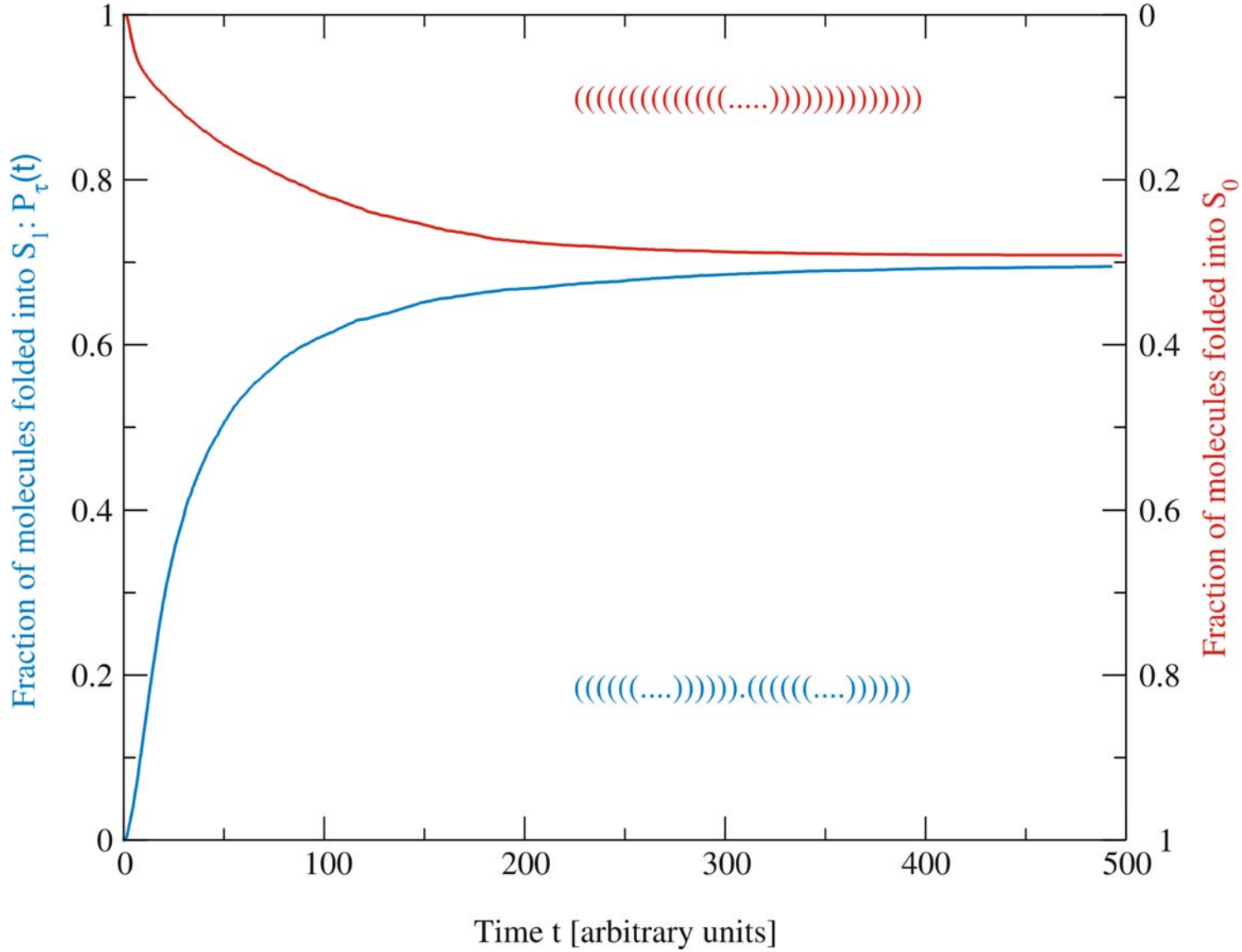
A trajectory $\mathbf{T}_k(\mathbf{X})$ is a time ordered series of structures in $\mathfrak{S}(\mathbf{X})$. A folding trajectory is defined by starting with the open chain **O** and ending with the global minimum free energy structure, $\mathbf{S_0}$ or a metastable structure $\mathbf{S_k}$, which represents a local energy minimum:

$$\mathbf{T}_0(\mathbf{X}) = \{\mathbf{O}, S(1), \ldots, S(t-1), S(t), S(t+1), \ldots, \mathbf{S_0}\}$$
$$\mathbf{T}_k(\mathbf{X}) = \{\mathbf{O}, S(1), \ldots, S(t-1), S(t), S(t+1), \ldots, \mathbf{S_k}\}$$

A description of the folding process is obtained through sampling a large number of trjectories.

When no stopping structure, $\mathbf{S_0}$ or $\mathbf{S_k}$, is defined, the long time distribution of conformations is the Boltzmann ensemble.


Free Energy (kcal/mol)
20
15
10
5
0
48 47 49 37 34 35 31 44 46 42 24 32 30 29 28 26 21 20 16 13 12 11 6 9 10 7 5 4 3
41 43 40 39 36 33 45 38 25 27 22 23 19 17 18 15 14 8 2
S1
S0



Folding dynamics of the sequence **GGCCCCUUUGGGGGCCAGACCCCUAAAAAGGGUC**

Stochastic variables: $\mathcal{X}_j(t)$ ⋯ number of molecules with conformation S_j

Probabilities: $P_n^{(j)}(t) = \mathcal{P}rob\{\mathcal{X}_j(t) = n^{(j)}\}$ with $\sum_j \mathcal{X}_j(t) = N$

Expectation values: $N_j(t) = < n^{(j)} > = \sum_{n=0}^{N} n\, P_n^{(j)}(t) = p_j(t)$

$$\frac{dP_n^{(j)}(t)}{dt} = \sum_{\ell=0,\ell\neq j}^{m} \left\{ P_{\ell j}(t)\, P_{n-1}^{(j)}(t) + k_{jl}\,(n+1)\, P_{n+1}^{(j)}(t) - \left(k_{j\ell}\, n + P_{\ell j}(t)\right) P_n^{(j)}(t) \right\} =$$

$$= \sum_{\ell=0,\ell\neq j}^{m} \left\{ k_{\ell j} \left(\sum_{i=0}^{N} i P_i^{(\ell,n-1)} \right) P_{n-1}^{(j)} + k_{j\ell}\,(n+1)\, P_{n+1}^{(j)} \right\} - P_n^{(j)} \sum_{\ell=0,\ell\neq j}^{m} \left\{ k_{j\ell}\, n + k_{\ell j} \left(\sum_{i=0}^{N} i P_i^{(\ell,n)} \right) \right\}$$

$n, i = 0,1,2,\ldots,N$ and

$j, \ell = 0,1,\ldots,m$; single step: $n \to n \pm 1(,n)$ or $\Delta n = \pm 1(,0)$

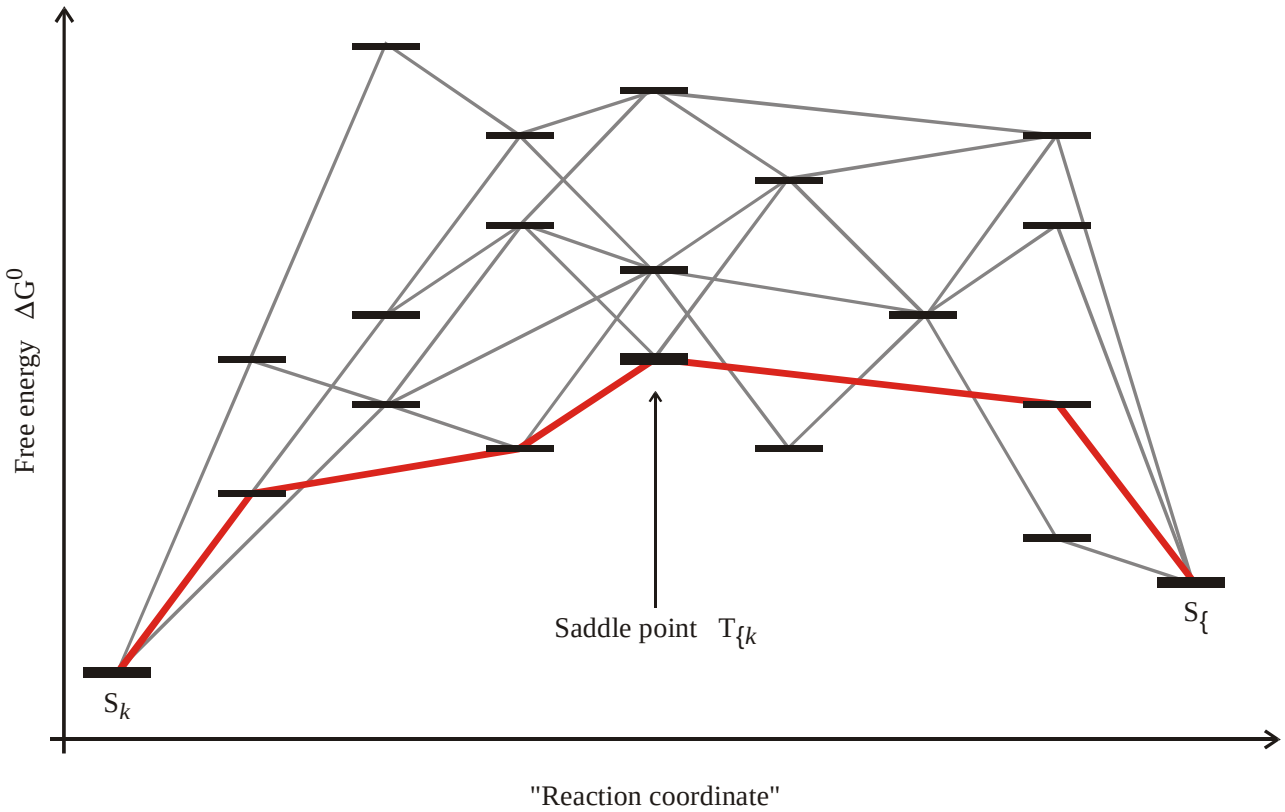
Transition probabilities: $P_{\ell j}(t)\, dt = \mathcal{P}rob\{S_\ell \to S_j \,|\, t \leq \tau \leq t+dt\}$

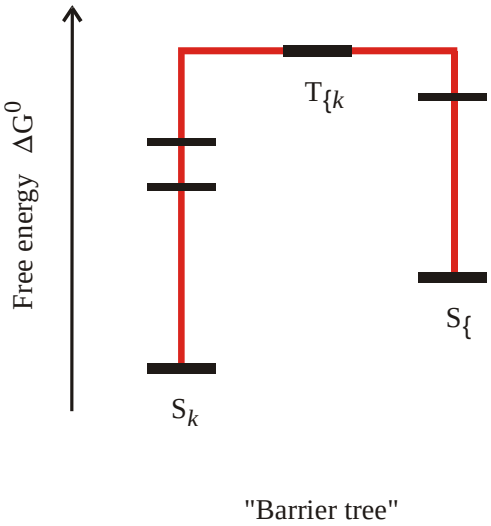
$$P_{\ell j}(t) = k_{\ell j} \sum_{i=0}^{N} i P_i^{(\ell,n-1)}(t) = k_{\ell j} < n^{(\ell)} > = k_{\ell j}\; p_\ell^{(n-1)}(t)$$

with $k_{\ell j} = k_0 \exp\left(-\Delta G_{\ell j}/RT\right) \Big/ \sum_{k=0,k\neq\ell}^{m} \exp\left(-\Delta G_{\ell k}/RT\right)$ and $\Delta G_{\ell j} = \Delta G_j^0 - \Delta G_\ell^0$

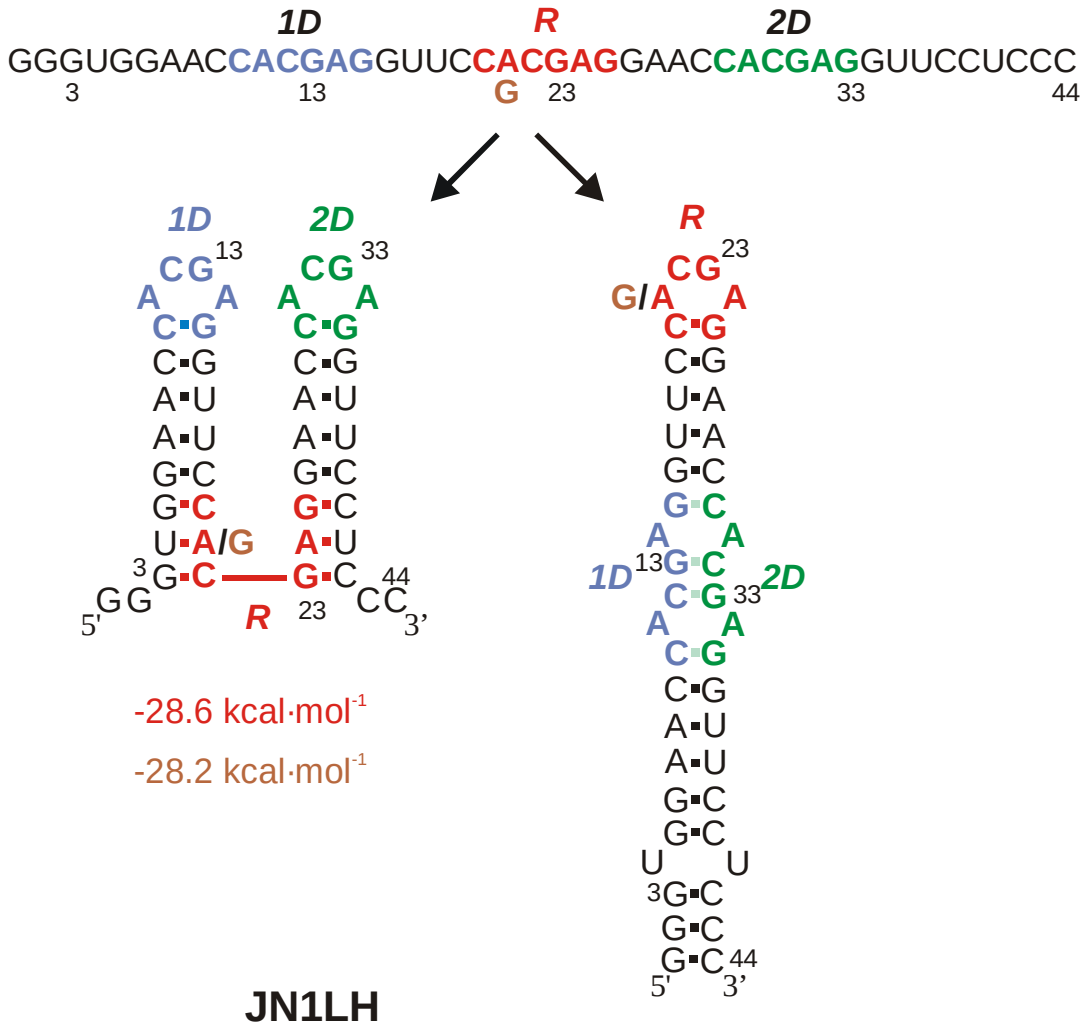
$$\sum_{n=0}^{N} n \frac{dP_n^{(j)}}{dt} = \frac{dp_j}{dt} = \sum_{n=0}^{N} \sum_{\ell=0,\ell\neq j}^{m} \left\{ k_{\ell j}\ p_\ell^{(n-1)}\ P_{n-1}^{(j)} + k_{j\ell}\,(n+1)\,P_{n+1}^{(j)} - \left(k_{j\ell}\,n + k_{\ell j}\,p_\ell^{(n)} \right) P_n^{(j)} \right\}$$

$$\frac{dp_j}{dt} = \sum\nolimits_{\ell=0,\ell\neq j}^{m} k_{\ell j}\ p_\ell - p_j \sum\nolimits_{\ell=0,\ell\neq j}^{m} k_{j\ell}\,; \quad j = 0,1,2,\ldots,m$$





Definition of a ‚barrier tree‘

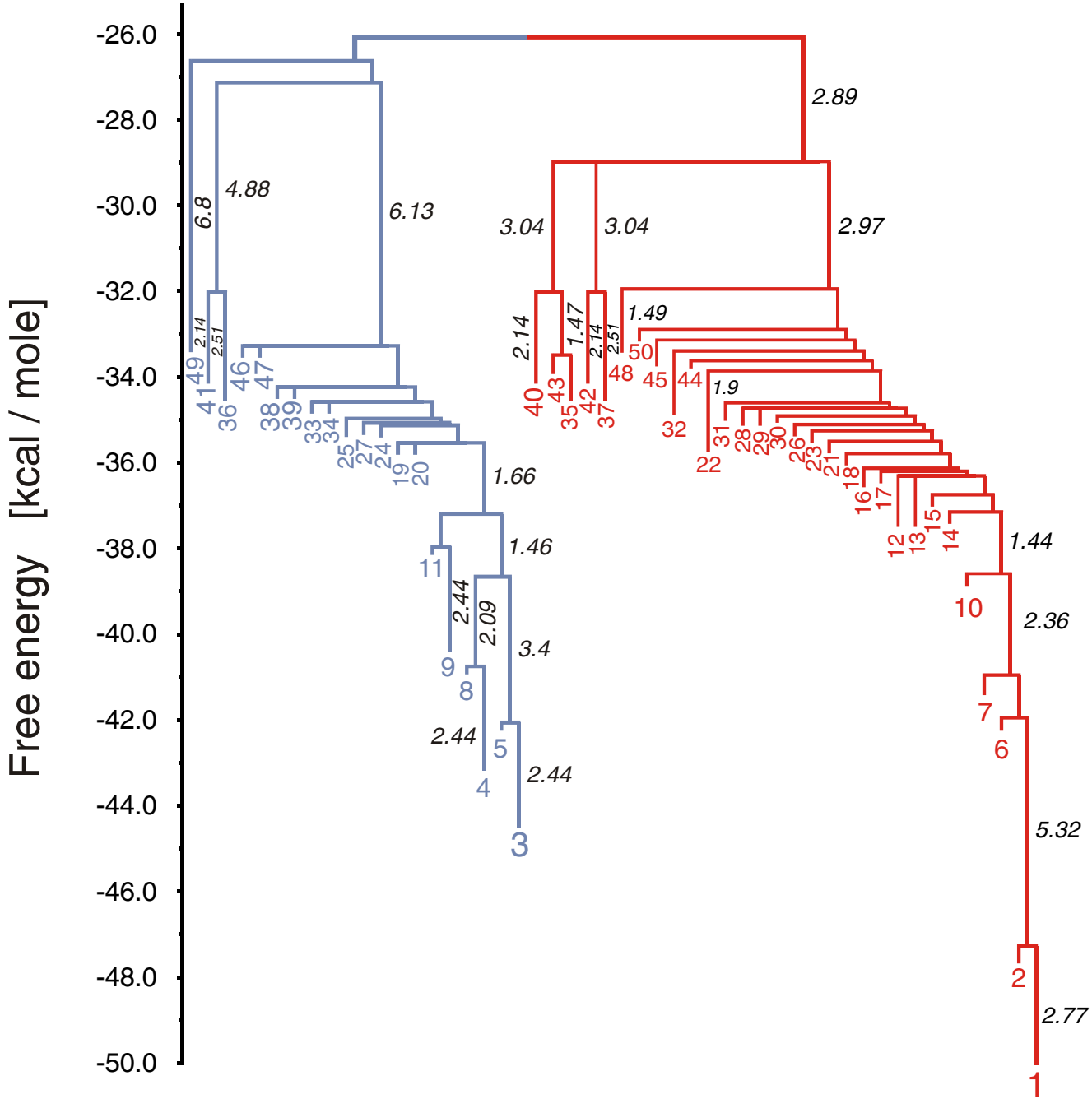


An RNA switch

JN1LH

J.H.A. Nagel, C. Flamm, I.L. Hofacker, K. Franke,
M.H. de Smit, P. Schuster, and C.W.A. Pleij.

Structural parameters affecting the kinetic competition of RNA hairpin formation, *Nucleic Acids Res.* **34**:3568-3576, 2006.



J1LH barrier tree

A ribozyme switch

E.A.Schultes, D.B.Bartel, Science **289** (2000), 448-452

minus the background levels observed in the HSP in the control (Sar1-GDP–containing) incubation that prevents COPII vesicle formation. In the microsome control, the level of p115-SNARE associations was less than 0.1%.
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50. GST-SNARE proteins were expressed in bacteria and purified on glutathione-Sepharose beads using standard methods. Immobilized GST-SNARE protein (0.5 μM) was incubated with rat liver cytosol (20 mg) or purified recombinant p115 (0.5 μM) in 1 ml of NS buffer containing 1% BSA for 2 hours at 4°C with rotation. Beads were briefly spun (3000 rpm for 10 s) and sequentially washed three times with NS buffer and three times with NS buffer supplemented with 150 mM NaCl. Bound proteins were eluted three times in 50 μl of 50 mM tris-HCl (pH 8.5), 50 mM reduced glutathione, 150 mM NaCl, and 0.1% Triton X-100 for 15 min at 4°C with intermittent mixing, and elutes were pooled. Proteins were precipitated by MeOH/CH_3Cl and separated by SDS–polyacrylamide gel electrophoresis (PAGE) followed by immunoblotting using p115 mAb 13F12.
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69. We thank G. Waters for p115 cDNA and p115 mAbs; G. Warren for p97 and p47 antibodies; R. Scheller for rbet1, membrin, and sec22 cDNAs; H. Plutner for excellent technical assistance; and P. Tan for help during the initial phase of this work. Supported by NIH grants GM 33301 and GM42336 and National Cancer Institute grant CA58689 (W.E.B.), a NIH National Research Service Award (B.D.M.), and a Wellcome Trust International Traveling Fellowship (B.B.A.).

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One Sequence, Two Ribozymes: Implications for the Emergence of New Ribozyme Folds

Erik A. Schultes and David P. Bartel*

We describe a single RNA sequence that can assume either of two ribozyme folds and catalyze the two respective reactions. The two ribozyme folds share no evolutionary history and are completely different, with no base pairs (and probably no hydrogen bonds) in common. Minor variants of this sequence are highly active for one or the other reaction, and can be accessed from prototype ribozymes through a series of neutral mutations. Thus, in the course of evolution, new RNA folds could arise from preexisting folds, without the need to carry inactive intermediate sequences. This raises the possibility that biological RNAs having no structural or functional similarity might share a common ancestry. Furthermore, functional and structural divergence might, in some cases, precede rather than follow gene duplication.

Related protein or RNA sequences with the same folded conformation can often perform very different biochemical functions, indicating that new biochemical functions can arise from preexisting folds. But what evolutionary mechanisms give rise to sequences with new macromolecular folds? When considering the origin of new folds, it is useful to picture, among all sequence possibilities, the distribution of sequences with a particular fold and function. This distribution can range very far in sequence space (*1*). For example, only seven nucleotides are strictly conserved among the group I self-splicing introns, yet secondary (and presumably tertiary) structure within the core of the ribozyme is preserved (*2*). Because these disparate isolates have the same fold and function, it is thought that they descended from a common ancestor through a series of mutational variants that were each functional. Hence, sequence heterogeneity among divergent isolates implies the existence of paths through sequence space that have allowed neutral drift from the ancestral sequence to each isolate. The set of all possible neutral paths composes a "neutral network," connecting in sequence space those widely dispersed sequences sharing a particular fold and activity, such that any sequence on the network can potentially access very distant sequences by neutral mutations (*3–5*).

Theoretical analyses using algorithms for predicting RNA secondary structure have suggested that different neutral networks are interwoven and can approach each other very closely (*3*, *5–8*). Of particular interest is whether ribozyme neutral networks approach each other so closely that they intersect. If so, a single sequence would be capable of folding into two different conformations, would have two different catalytic activities, and could access by neutral drift every sequence on both networks. With intersecting networks, RNAs with novel structures and activities could arise from previously existing ribozymes, without the need to carry nonfunctional sequences as evolutionary intermediates. Here, we explore the proximity of neutral networks experimentally, at the level of RNA function. We describe a close apposition of the neutral networks for the hepatitis delta virus (HDV) self-cleaving ribozyme and the class III self-ligating ribozyme.

In choosing the two ribozymes for this investigation, an important criterion was that they share no evolutionary history that might confound the evolutionary interpretations of our results. Choosing at least one artificial ribozyme ensured independent evolutionary histories. The class III ligase is a synthetic ribozyme isolated previously from a pool of random RNA sequences (*9*). It joins an oligonucleotide substrate to its 5′ terminus. The prototype ligase sequence (Fig. 1A) is a shortened version of the most active class III variant isolated after 10 cycles of in vitro selection and evolution. This minimal construct retains the activity of the full-length isolate (*10*). The HDV ribozyme carries out the site-specific self-cleavage reactions needed during the life cycle of HDV, a satellite virus of hepatitis B with a circular, single-stranded RNA genome (*11*). The prototype HDV construct for our study (Fig. 1B) is a shortened version of the antigenomic HDV ribozyme (*12*), which undergoes self-cleavage at a rate similar to that reported for other antigenomic constructs (*13*, *14*).

The prototype class III and HDV ribozymes have no more than the 25% sequence identity expected by chance and no fortuitous structural similarities that might favor an intersection of their two neutral networks. Nevertheless, sequences can be designed that simultaneously satisfy the base-pairing requirements

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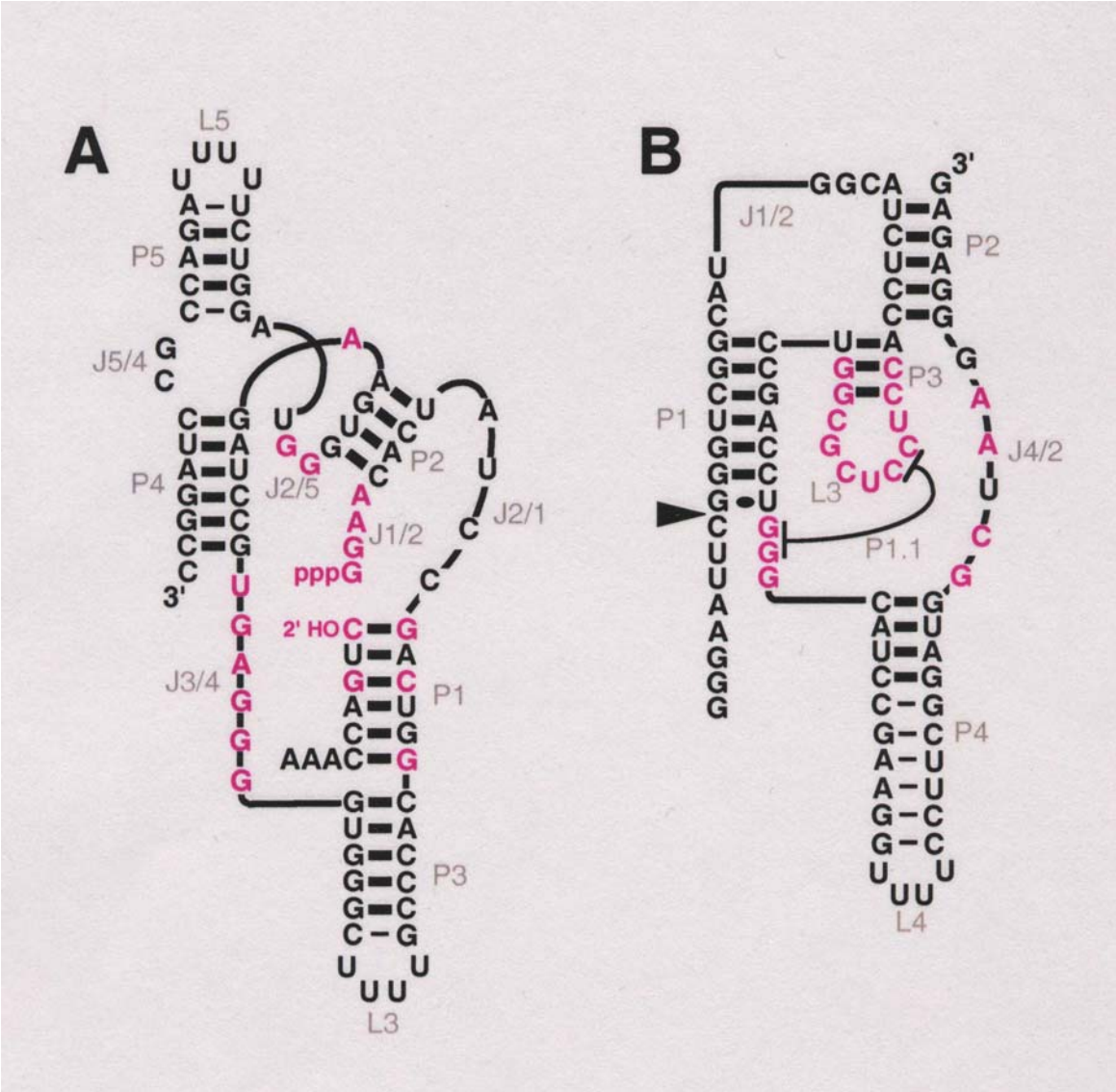
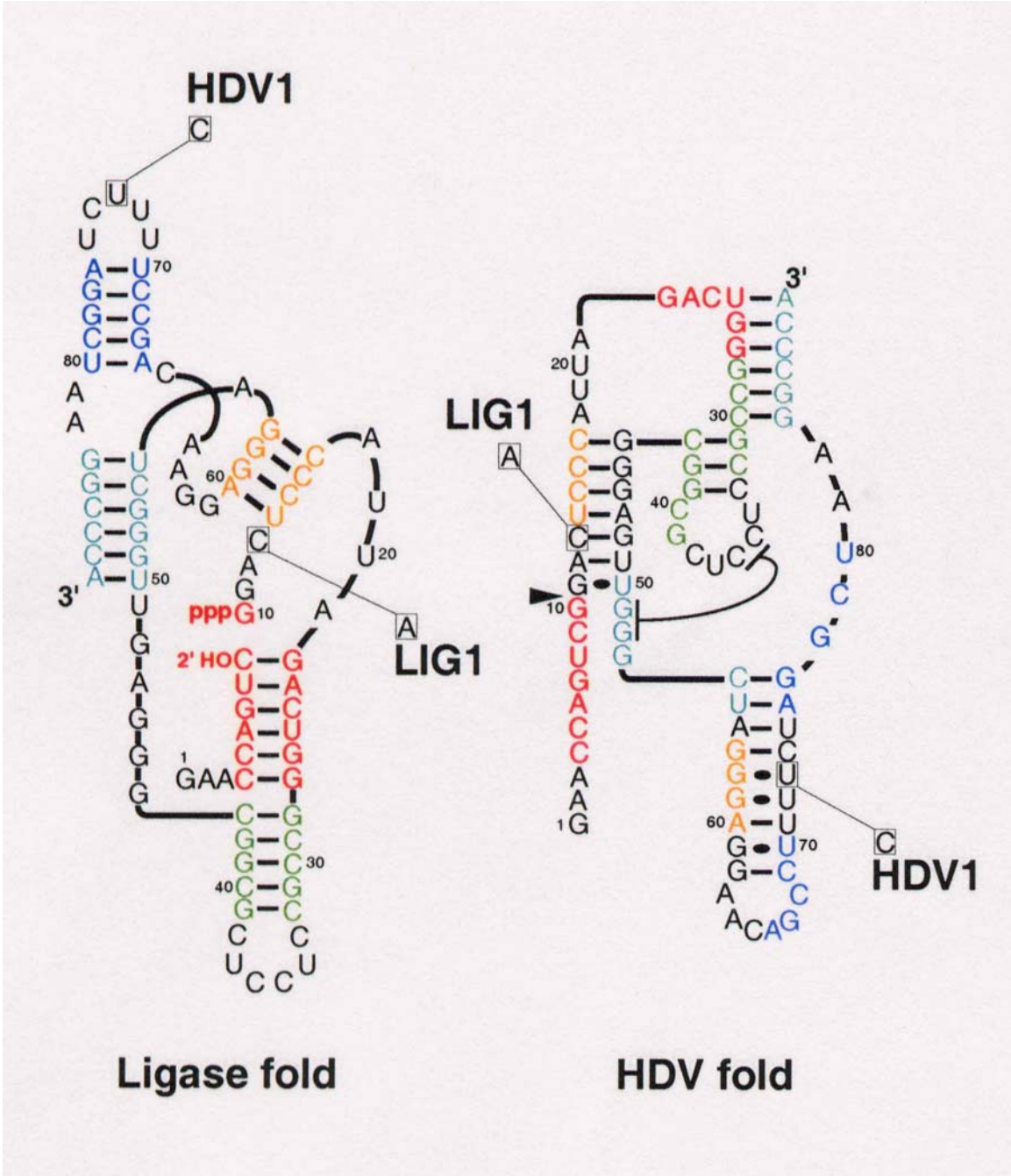
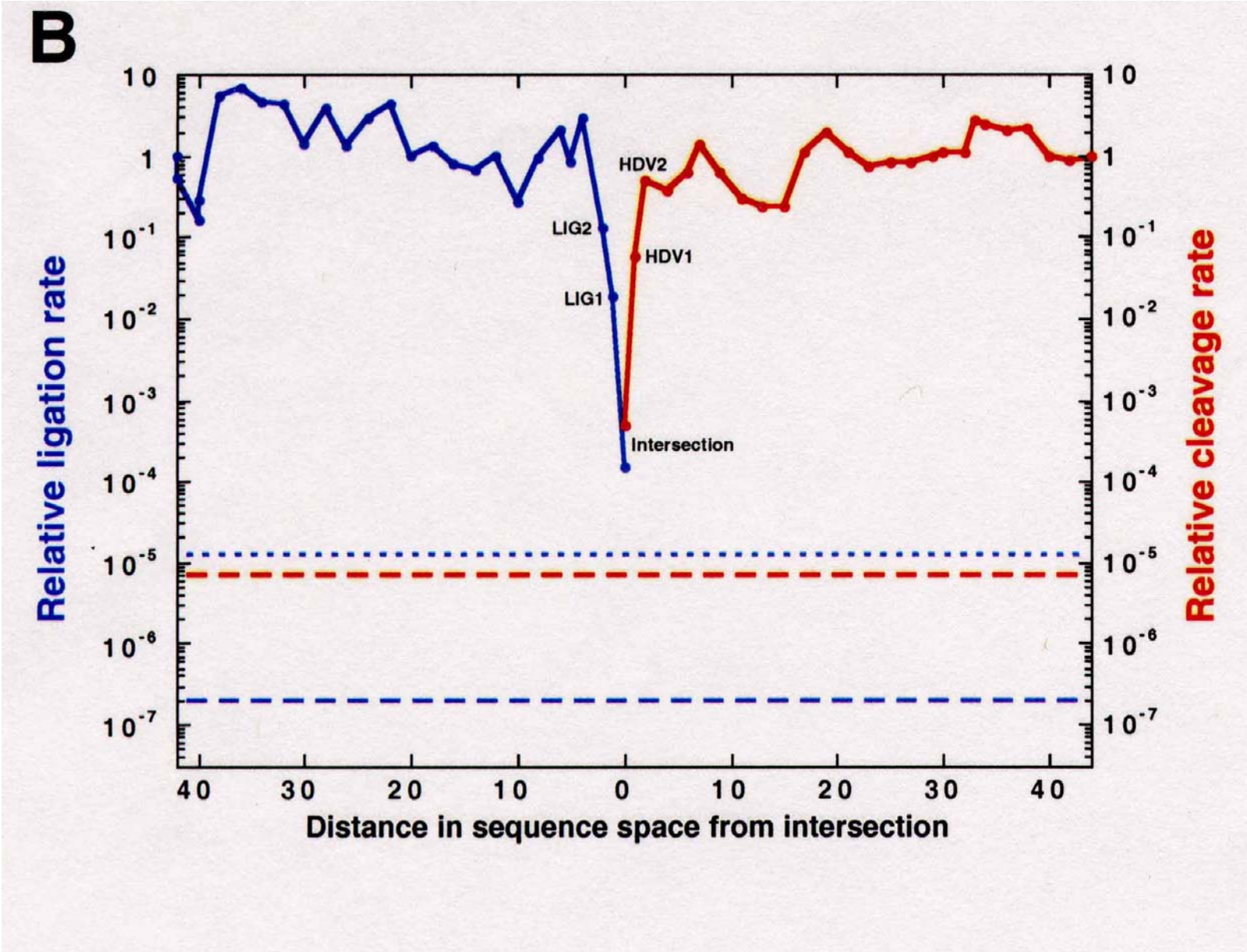


Two ribozymes of chain lengths n = 88 nucleotides: An artificial ligase (**A**) and a natural cleavage ribozyme of hepatitis-δ-virus (**B**)

The sequence at the ***intersection***:

An RNA molecules which is 88 nucleotides long and can form both structures





Two neutral walks through sequence space with conservation of structure and catalytic activity

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