Nucleic Acid Secondary Structure Prediction and Design

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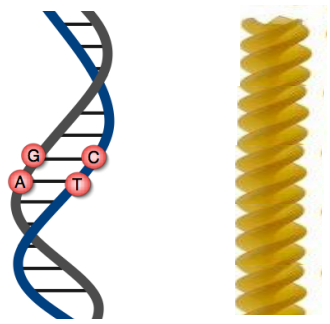
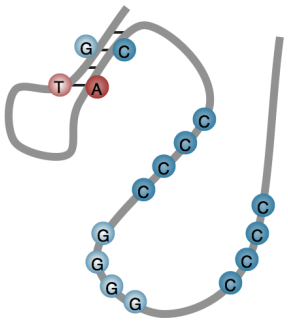
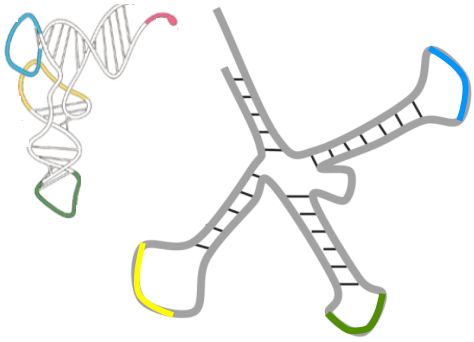
nucleic acid secondary structure



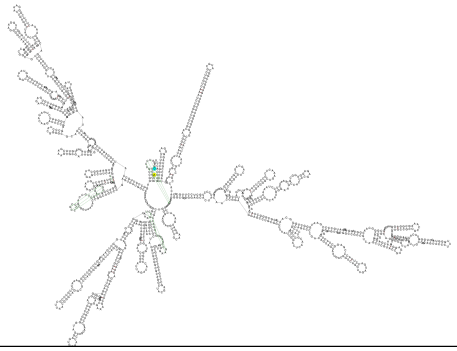
nucleic acid secondary structure



nucleic acid secondary structure

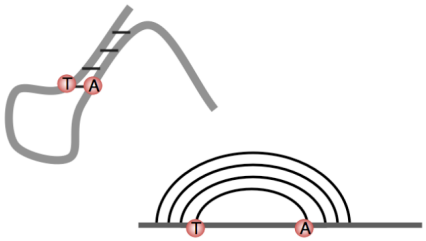


nucleic acid secondary structure



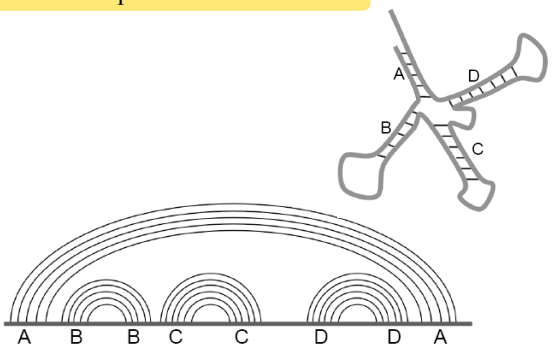
nucleic acid secondary structure

structure representation



nucleic acid secondary structure

structure representation: exercise



why predict secondary structure?

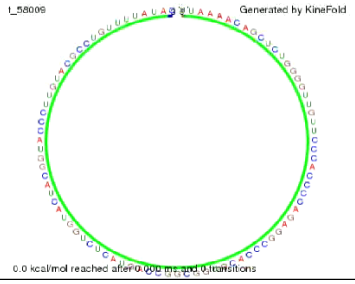
- to determine RNA 3D structure and ultimately function
- to establish phylogenetic relationships among organisms, via better RNA sequence alignment
- to understand gene regulation
- … and much more

research question

- given a sequence, *predict* its secondary structure

predicting structure

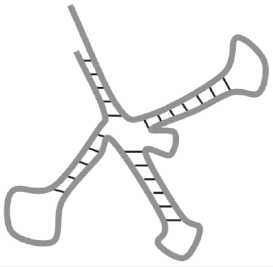
- structure formation is a (thermodynamically driven) process, whereby the strand seeks a minimum free energy configuration



predicting structure

simple energy model

- each *base pair* contributes a (negative) score
- sum the scores to get the total energy



predicting structure

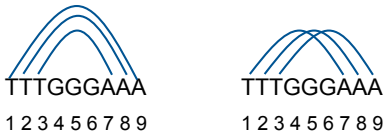
precise problem formulation

- given an RNA sequence, find the *minimum free energy (MFE)* structure, relative to the simple energy model

predicting structure

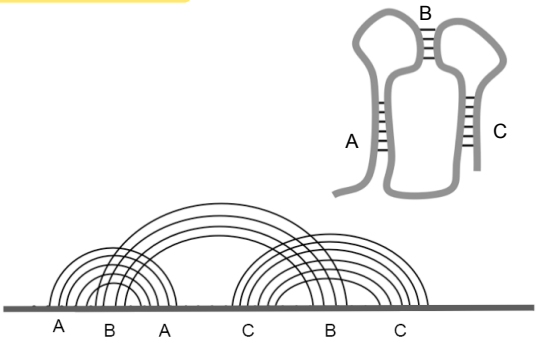
exercise

- draw two MFE secondary structures for the sequence



predicting structure

a pseudoknot



predicting structure

revised problem formulation

- given an RNA sequence, find the *minimum free energy (MFE)* ***pseudoknot free structure***, relative to the simple energy model
- pseudoknot free: no arcs cross in the arc diagram representation of the structure

predicting structure

a "brute force" algorithm

- enumerate all possible pseudoknot free secondary structures for the given input sequence
- for each, calculate its free energy
- keep track of structure with lowest free energy enumerated, so far, and output this at the end
- exercise: can you find a lower bound on the number of distinct pseudoknot free structures a sequence could have?

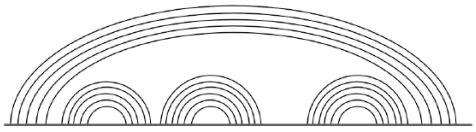
predicting structure

a "brute force" algorithm

- the number of pseudoknot free secondary structures consistent with an RNA or DNA sequence may be exponential in its length ☹

predicting structure

other ideas?



predicting structure

dynamic programming

- let W(*i*,*j*) be the energy of the MFE pseudoknot free structure from position *i* to position *j* of the sequence
- express W(*i*,*j*) in terms of "smaller" W()'s

predicting structure

dynamic programming

$$W(i,j) = \min \begin{cases} -1 + W(i+1,j-1), & \text{if i and j can pair} \\ \min_{i \le k < j} \{ W(i,k) + W(k+1,j) \}, & \text{otherwise} \end{cases}$$

predicting structure

dynamic programming

if i < j:

$$W(i,j) = \min \begin{cases} -1 + W(i+1,j-1), & \text{if i and j can pair} \\ \min_{i \le k < j} \{ W(i,k) + W(k+1,j) \}, & \text{otherwise} \end{cases}$$

$W(i,j) = 0$ if $i = j$

MFE approach: applying the recurrences

dynamic programming

- input: AGCUU

i \ j	1	2	3	4	5
1	0	0	1	2	2
2		0	1	1	1
3			0	0	0
4				0	0
5					0

W(*i,j*)

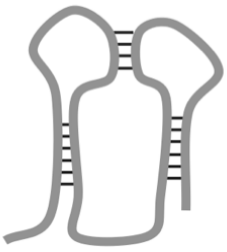
what RNA research do I do?

…in collaboration with many others at UBC, U. Rochester, Caltech, and elsewhere

what RNA research do I do?

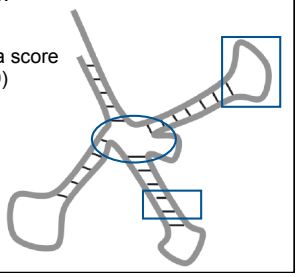
structure prediction

- design algorithms for prediction of certain types of pseudoknotted structures



what RNA research do I do?

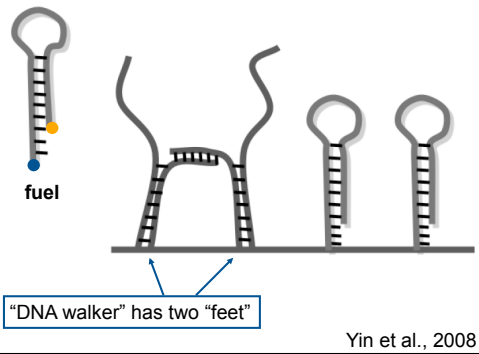
- apply machine learning to improve "loop based" energy models:
  - each *loop* contributes a score (Mathews et al., 1999)
  - sum the scores to get the total energy



what RNA research do I do?

- predict *folding pathways* and their properties and design folding pathways (or show that these problems are NP-hard)

what RNA research do I do?



Yin et al., 2008

the possibilities are endless…