Permutation Patterns and RNA Secondary Structure Prediction

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Permutation Patterns 2017
27 June, 2017

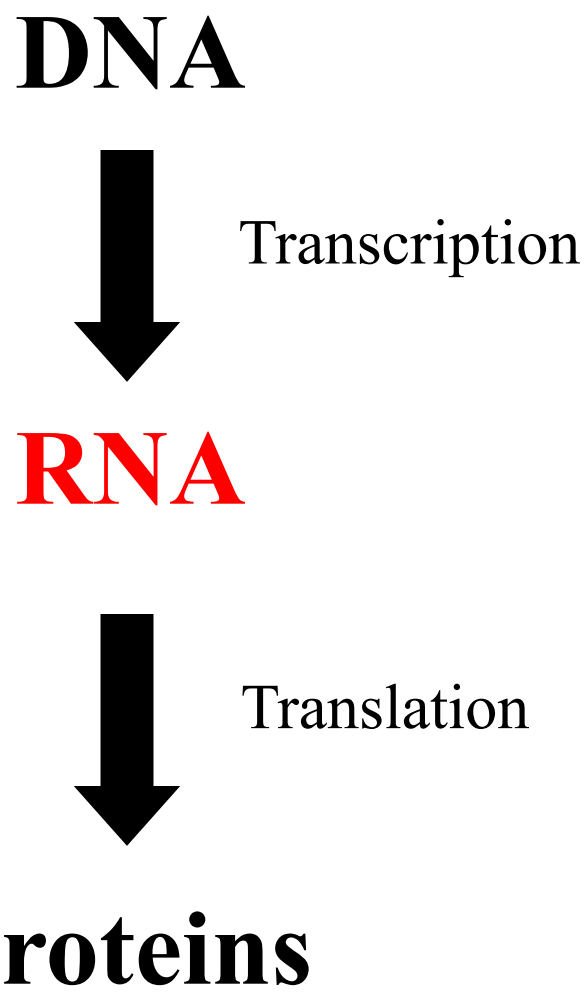
Acknowledgments

Robert S. Willenbring
(SJU ’05)
Heather Akerson and Cam Christensen
(CSB ’09 and SJU ‘09)

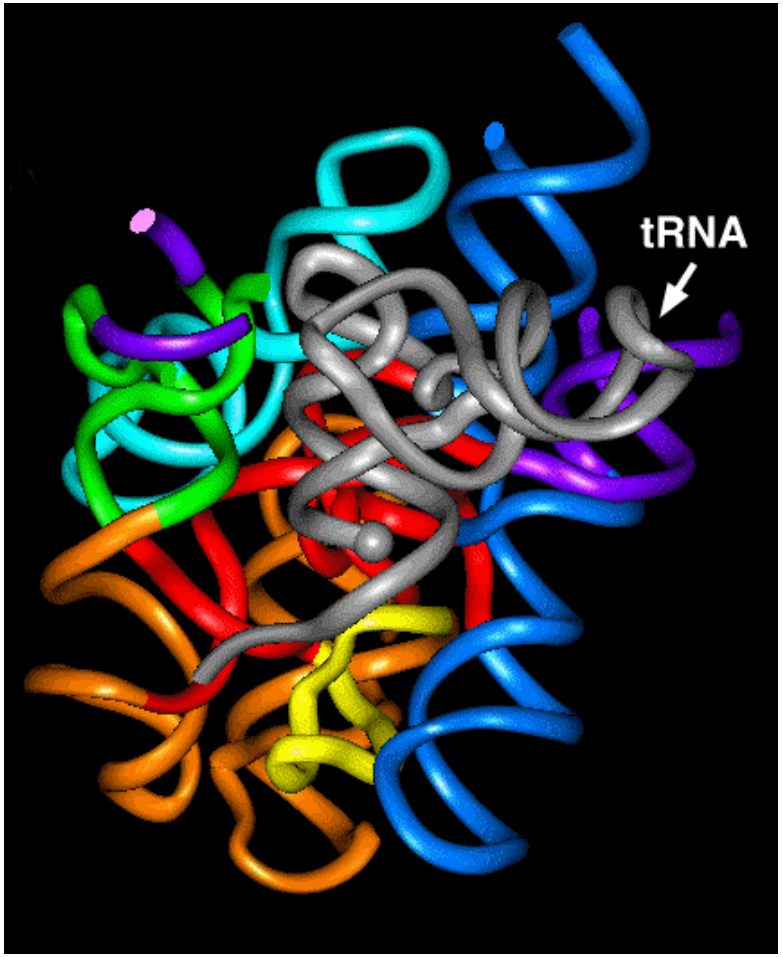
Overview

- What is RNA secondary structure? (from a biologist's point of view…)
- What is RNA secondary structure? (from a mathematician's point of view…)
- A permutation model for RNA secondary structures;
  A bijection and some statistics
- Biological insight (?)
- Future directions

Crick's Central Dogma



B. Subtilis RNase P RNA

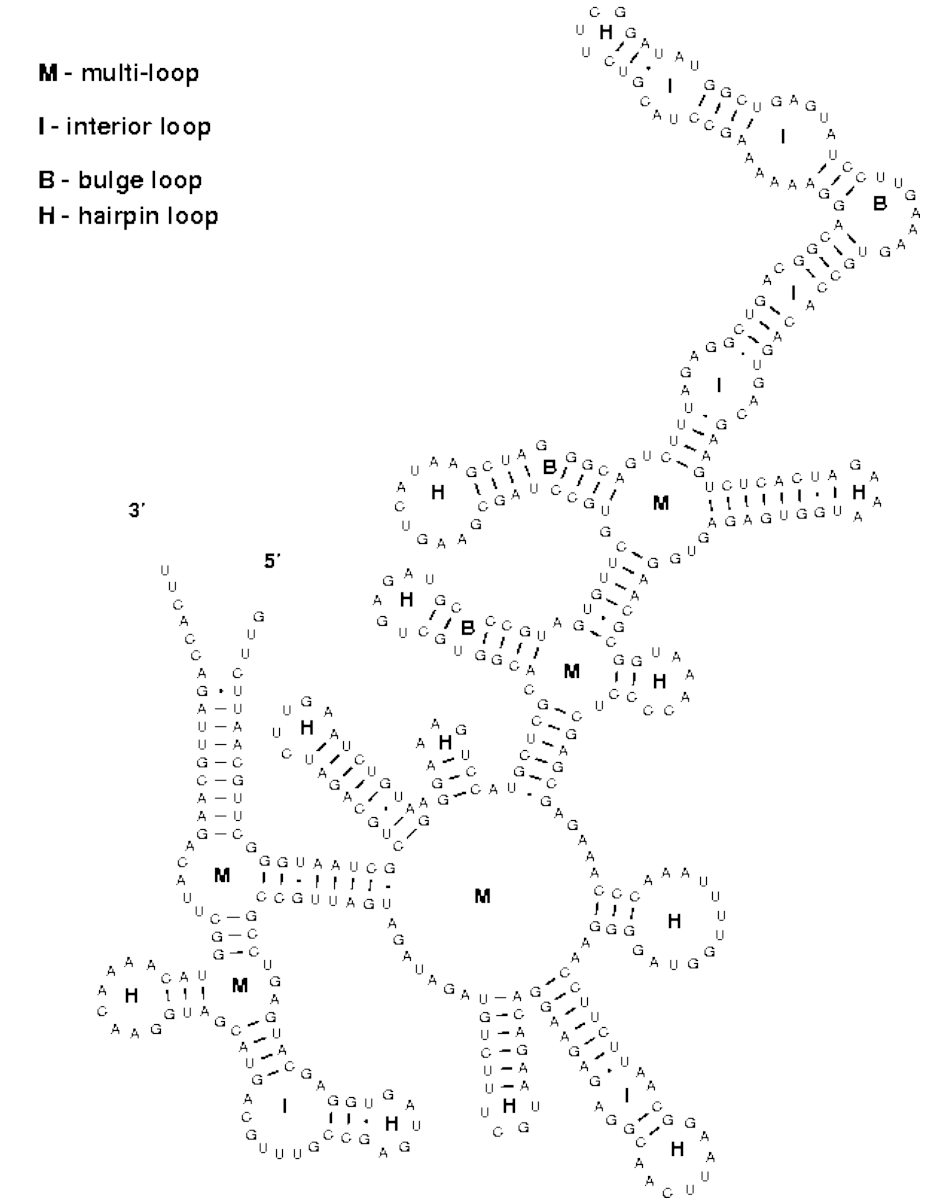


http://www.pharmazie.uni-marburg.de/pharmchem/akhartmann/bilder/rnase_p_bsubtilis.gif

B. Subtilis RNase P RNA (Primary Structure)

GUUCUUAACGUUCGGGUAAUCGCUGCAGAUCUUGA
AUCUGUAGAGGAAAGUCCAUGCUCGCACGGUGCUG
AGAUGCCCGUAGUGUUCGUGCCUAGCGAAGUCAUA
AGCUAGGGCAGUCUUUAGAGGCUGACGGCAGGAAA
AAAGCCUACGUCUUCGGAUAUGGCUGAGUAUCCUU
GAAAGUGCCACAGUGACGAAGUCUCACUAGAAAUG
GUGAGAGUGGAACGCGGUAAACCCCUCGAGCGAGA
AACCCAAAUUUUGGUAGGGGAACCUUCUUAACGGA
AUUCAACGGAGAGAAGGACAGAAUGCUUUCUGUAG
AUAGAUGAUUGCCGCCUGAGUACGAGGUGAUGAGC
CGUUUGCAGUACGAUGGAACAAAACAUGGCUUACA
GAACG UUAGACCACU

Bacillus subtilis RNase P RNA



http://www.bioinfo.rpi.edu/~zukerm/lectures/RNAfold-html/img24.gif

Combinatorial approaches

Idea: Ignore biochemical properties and focus on the possible topologies.

Several models have been proposed:

Non-crossing set partitions

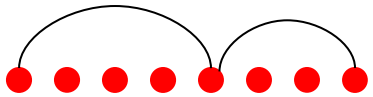
(Unlabelled) linear trees (Schmitt and Waterman 1994

Trees and their duals (Schlick et al. 2002)

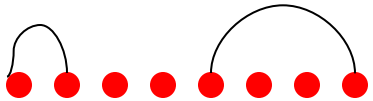
Permutations

Definition: A *secondary structure* on $\{1, 2, ..., n\}$ is a non-crossing set partition such that

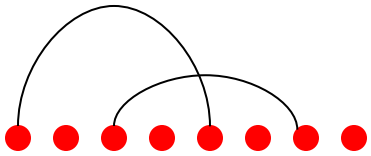
(i) the degree of every vertex is at most 1
(ii) if (i, j) is an edge, then $|i - j| > 1$



NO…



NO…



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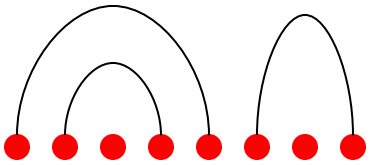
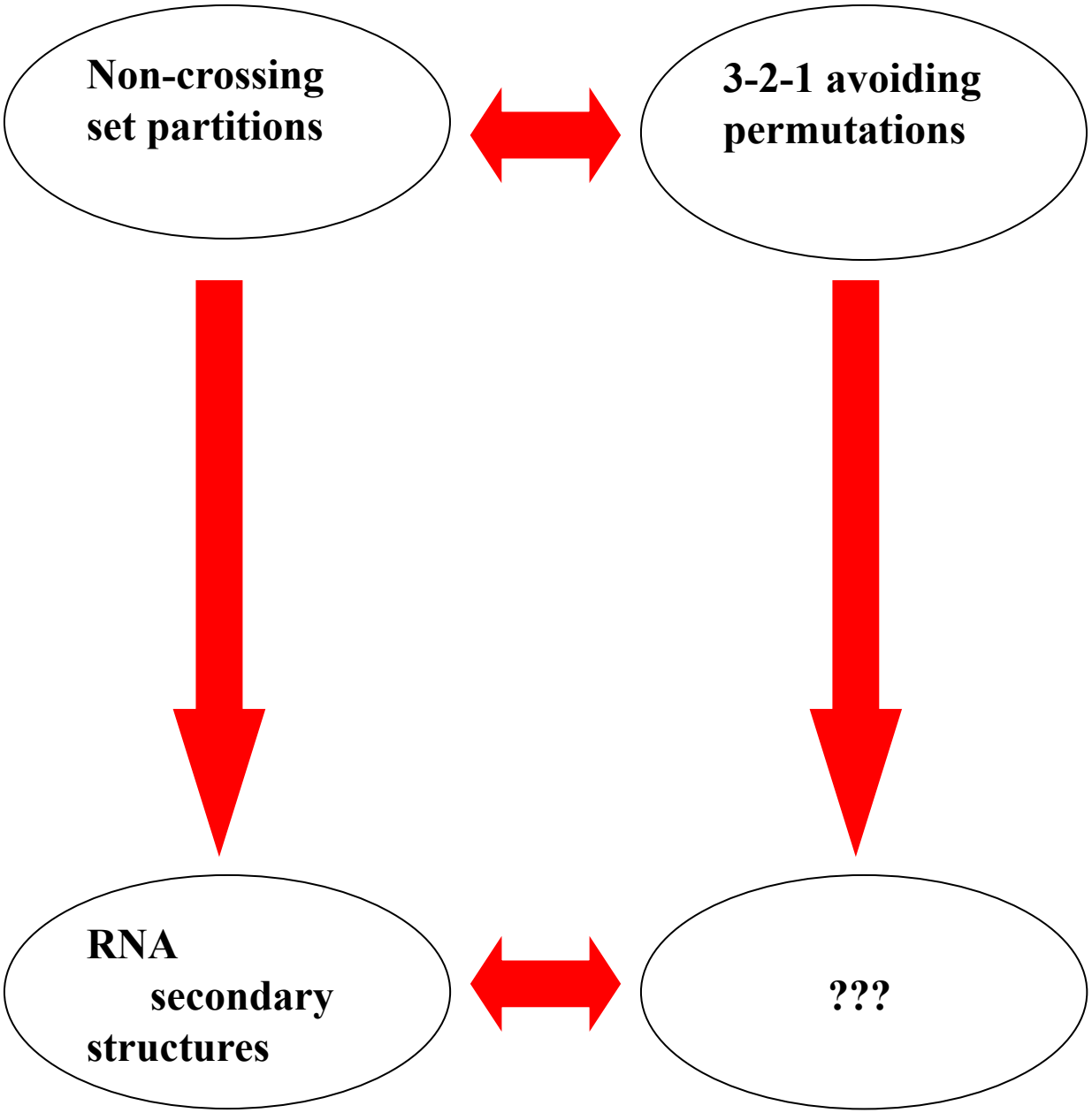


YES


Non-crossing
set partitions
3-2-1 avoiding
permutations
RNA
secondary
structures
???

Let Π_n be the set of all 3-2-1 avoiding permutations such that:

(i) If position i has a fall, position $i+1$ does not.
(ii) If c is a fall, then c+1 is not.
(iii) Every fall is the second element of at least two inversion pairs.

Let $\Pi_{n,k}$ be the set of all permutations in Π_n which have exactly k falls.

Example: $n = 13; k = 4$

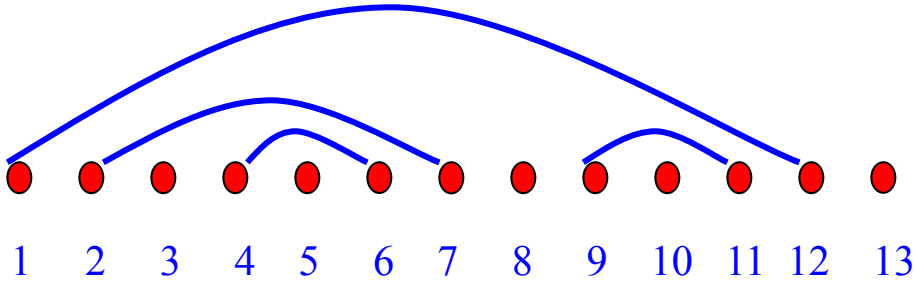
k:	1	2	3	4	5	6	7	8	9	10	11	12	13
π_k :	2	4	5	1	7	3	8	9	11	6	12	10	13

Main Theorem

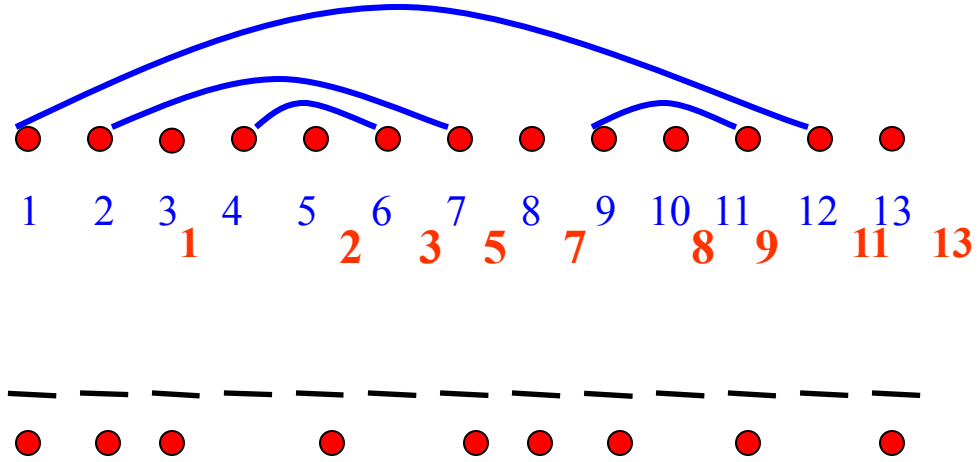
Let $SS_{n,k}$ be the set of all RNA secondary structures with k bonds.

Then there is a bijection from $SS_{n,k}$ to $\Pi_{n,k}$.

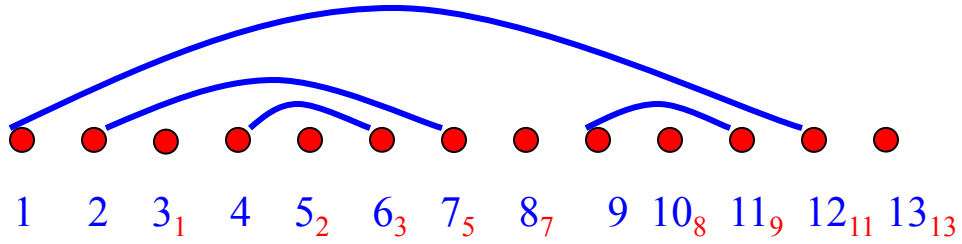
How does the bijection work?

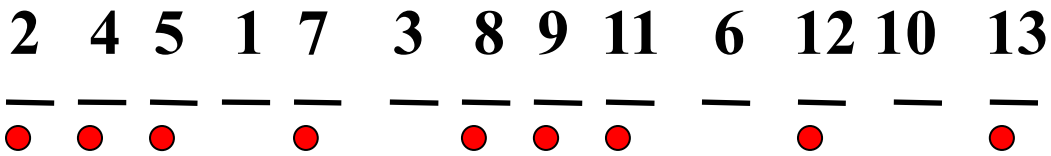


Labelling: Ignoring left bonds, number the unpaired bases and right bonds in order, skipping one after each right bond. Mark the numbered positions with ●



Insertion: Ignoring right bonds, and working left to right, insert pairs of the form *(i+1, i)* in (marked, unmarked) positions for each left bond and singleton values in marked positions for unpaired bases.

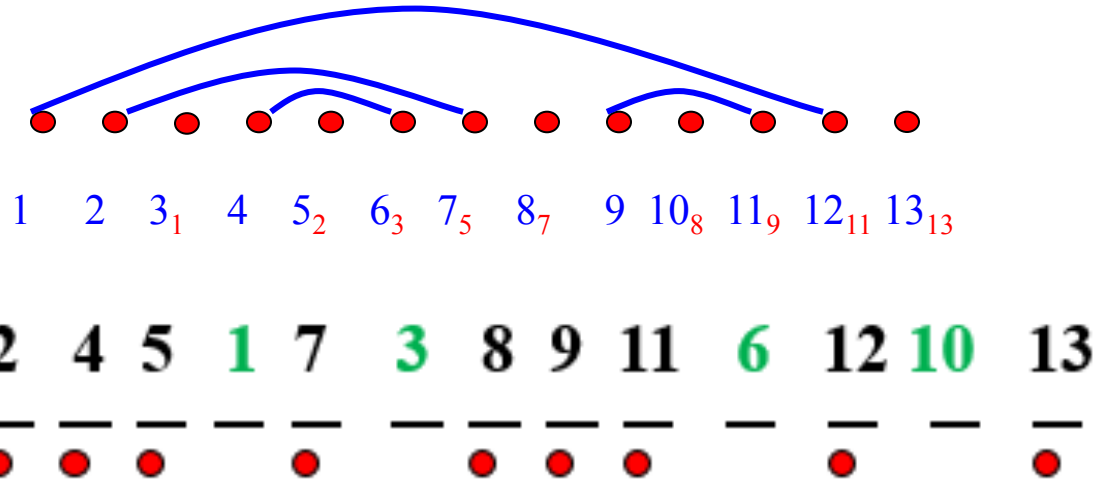




Why does this work?

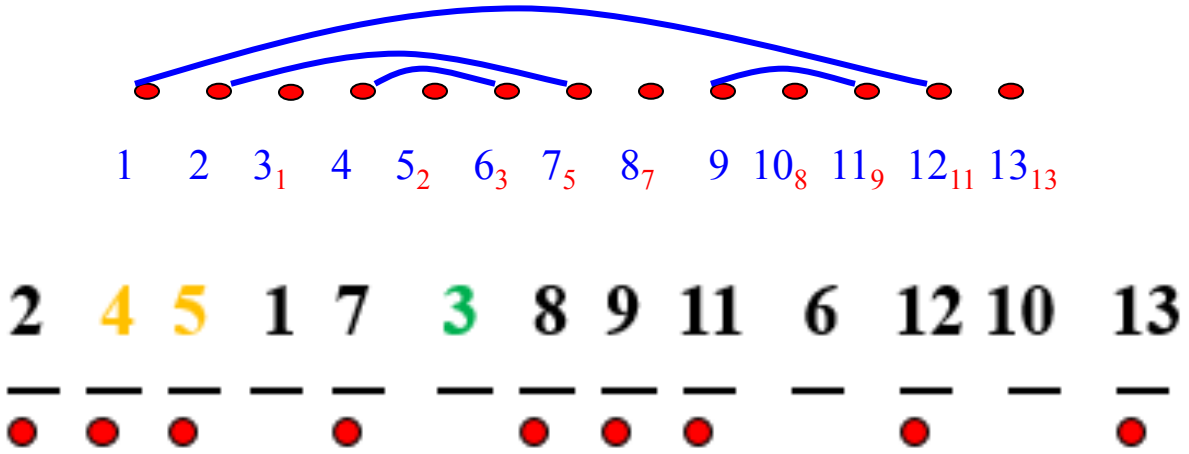
- The unmarked positions are exactly the positions of the falls, and each corresponds to a bond.
- The marked positions form an increasing sequence, as do the unmarked positions. This guarantees that the permutation is

  3-2-1 avoiding.



Why does this work?

- Consecutive unmarked positions cannot occur so if there is a fall in position j then there is NOT a fall in position *j+1* (condition i)
- Unmarked positions are always filled in pairs with *i* in the unmarked position and *i+1* in the marked position. Therefore *i+1* can never be a fall when *i* is (condition ii).
- Each fall will correspond to at least two inversions, for if *i* is a fall, then *i+1* precedes it, as does the value corresponding to the unpaired bas(es) enclosed by the bond (condition iii).



Permutation Statistics

$\mathrm{exc}(\pi)$ = number of excedances in π

$\mathrm{inv}(\pi)$ = number of inversions in π

$\mathrm{maj}(\pi)$ = sum of the descent positions in π

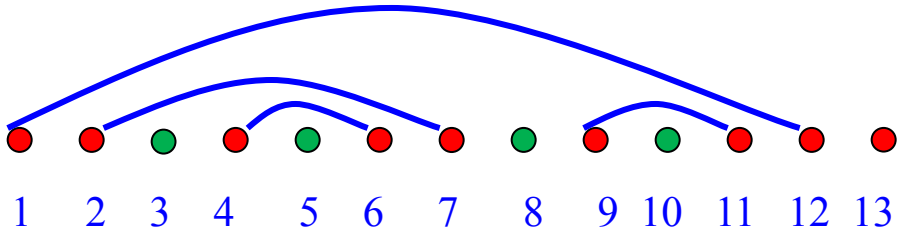
Two RNA SS Statistics

Tau: Let v_i be the number of unpaired bases internal to bond i. Then we define

$$\tau(s) = \sum_i v_i$$

Bond Index : B(s) = sum of the positions corresponding to left or right bonds.

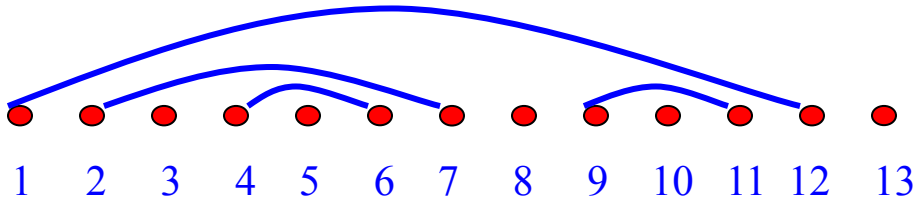
$\tau(s)$ = (4 + 2 + 1 + 1) = 8



B(s) = (1+2+4+6+7+9+11 +12) = 52

Our Example: $n = 13, k = 4$

s:



π: *2 4 5 1 7 3 8 9 11 6 12 10 13*

$\text{exc}(\pi) = 7$
$\text{inv}(\pi) = 12$
$\text{maj}(\pi) = 28$

$\tau(s) = 8$
$B(s) = 52$

Theorem:

(1) $\text{inv} = \tau + k$

(2) $B = 2\,(\text{maj} + k) - \text{inv}$

Distribution Properties for B and τ

Fact: B is symmetric on $SS_{n,k}$

Conjectures: B is unimodal for any value of k.
τ is unimodal, but not symmetric.

Compare to actual RNA data…

Assume that B is unimodal, and see what the values are for RNA from various (prokaryotic) organisms

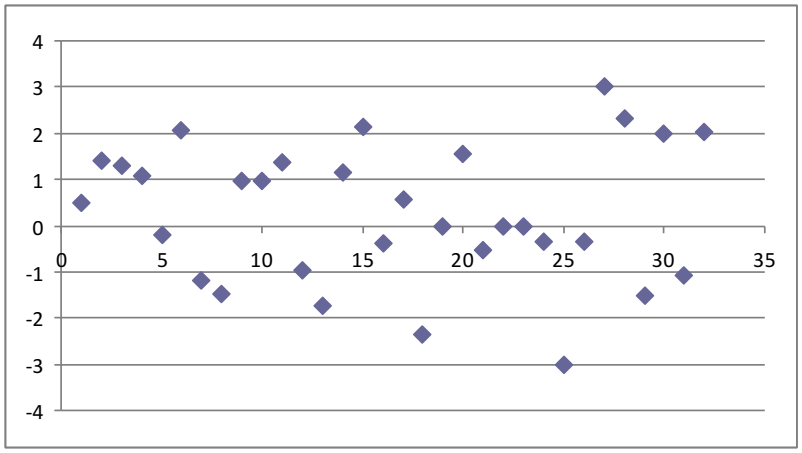
- Minimum value of B is $2k^2 + 2k$
- Maximum value of B is $2kn - 2k^2$

So if we assume B is unimodal, then the mode is

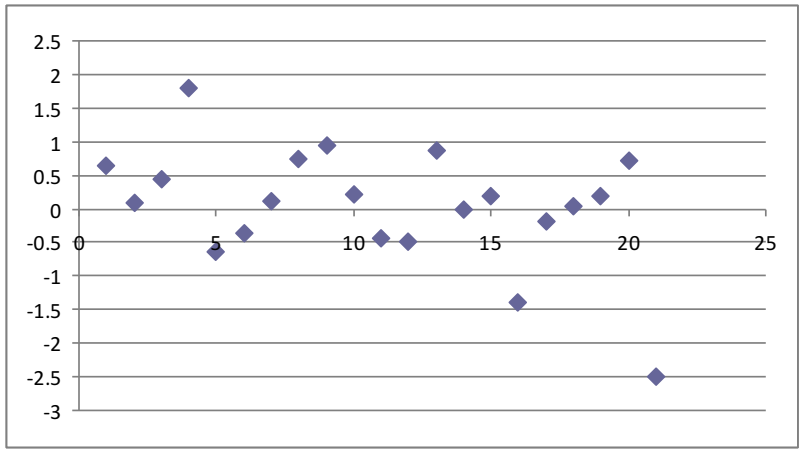
$$(n+1)\,k$$

Standard Deviation

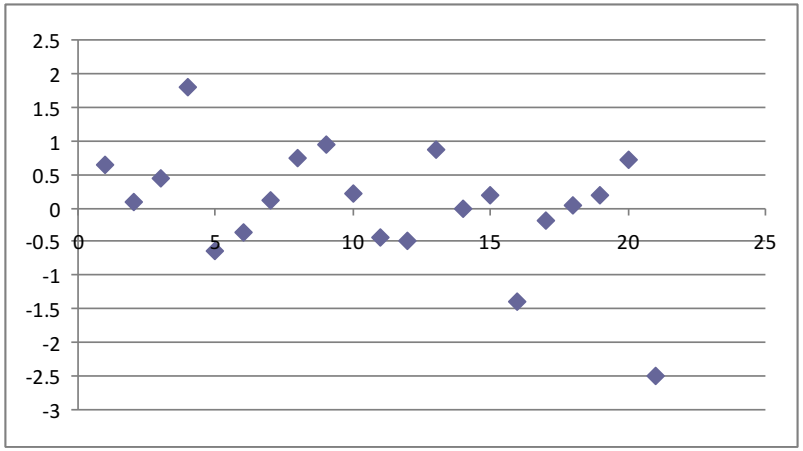
- Calculate for $n \leq 30$.
- Extrapolate the pattern.



Si RNA

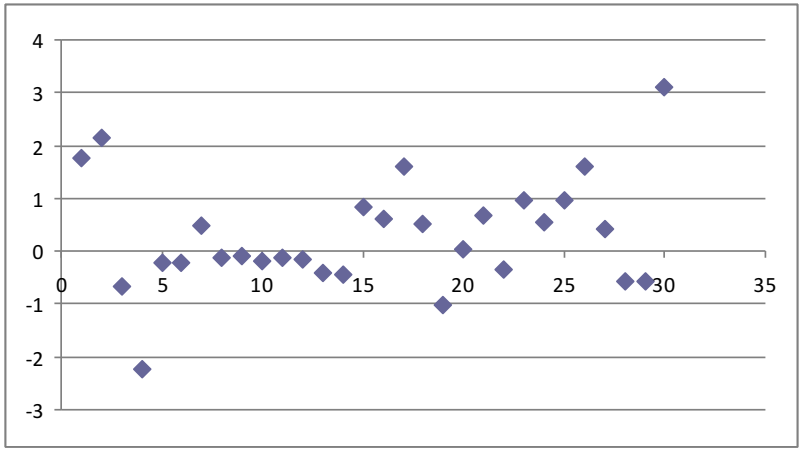


5s rRNA



RNase P

Group I



Other nc RNA

Group II

Conclusions

- Group II RNA appear to have a B statistic that runs above average
- Group I RNA appear to have a B statistic that is symmetrically distributed
- The sample sizes are way too small to draw any real conclusions.

Some Questions…

- Is there some biologically appropriate way of distinguishing Group I and Group II?
- Does either of these statistics (B or τ) have biological meaning? Is there a biological aspect of RNA that could be better captured by a different statistic?
- Could either the B or τ statistic be used to evaluate folding algorithms or find potential novel RNA structures?

To Do List….

- Prove the unimodality conjectures for B (known through n = 20 or so) and τ
- Use permutation statistics to describe/identify RNA motifs
- Look at B stat on experimentally verified structures
- Make the model more biological realistic by increasing the minimum number of unbonded bases (hairpins and bulges)

Thank you