DESIGN OF COTRANSCRIPTIONAL FOLDING PATHS

tbi

Laurenz Miksch

Ivo Hofacker

BLED 2025

Stefan Badelt
Theoretical Biochemistry Group (tbi),
University of Vienna

40th TBI Winterseminar

COTRANSCRIPTIONAL DYNAMICS

- Interesting examples from literature exist
- Simulation software exists
- Intuition on what is possible is really fuzzy

COTRANSCRIPTIONAL DYNAMICS

- Interesting examples from literature exist
- Simulation software exists
- Intuition on what is possible is really fuzzy
  - **How many rearrangements are possible?**
  - When does transcription rate/pausing matter?
  - When do point mutations alter folding paths?

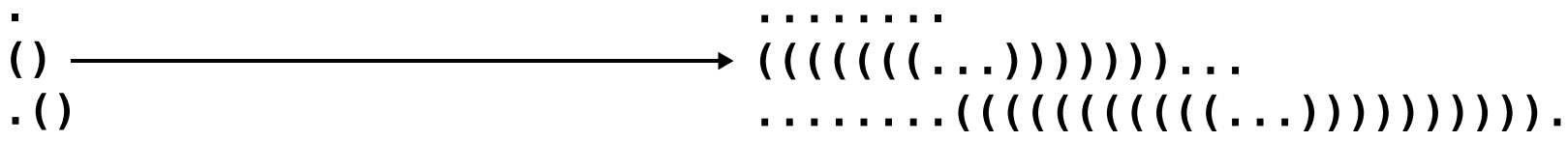
COTRANSCRIPTIONAL DYNAMICS

- Interesting examples from literature exist
- Simulation software exists
- Intuition on what is possible is really fuzzy
  - **How many rearrangements are possible?**
  - When does transcription rate/pausing matter?
  - When do point mutations alter folding paths?

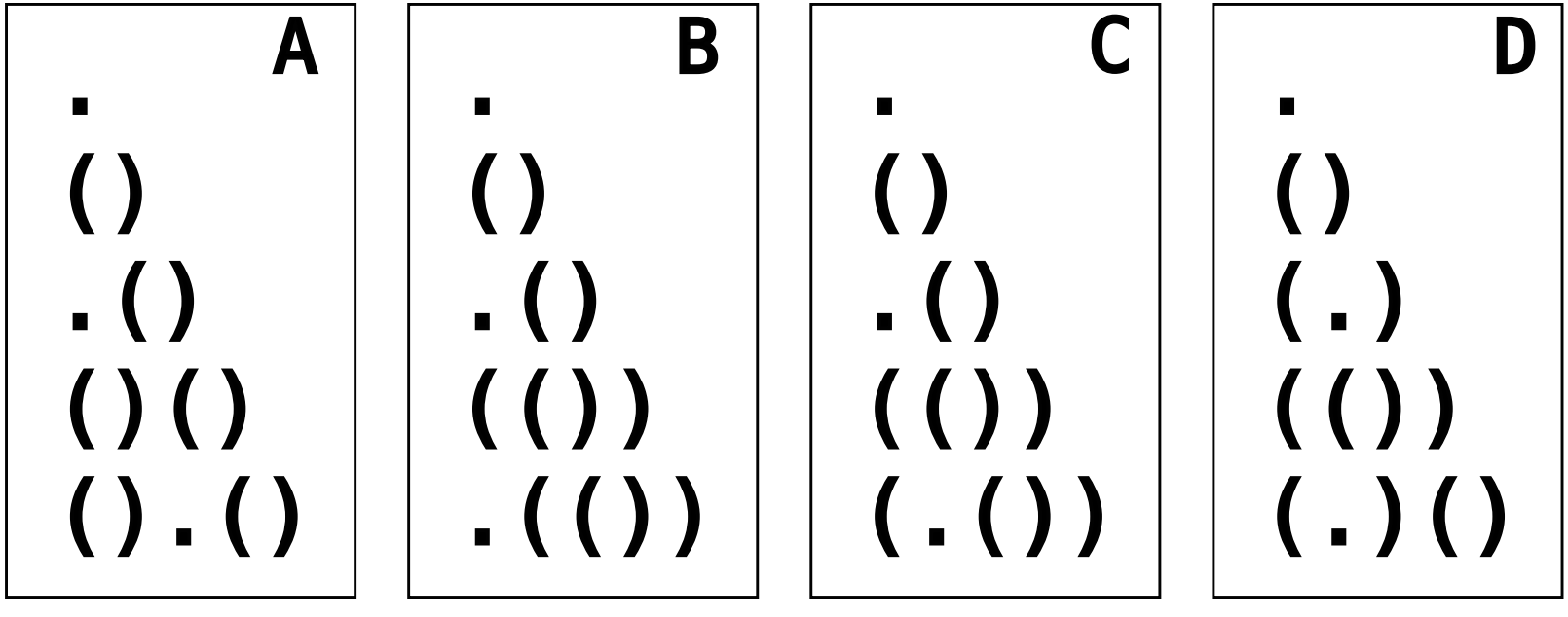
A formal framework to formulate these questions is necessary.

WHICH PATHWAYS CAN BE DESIGNED?

Given *“abstract cotranscriptional folding paths”*:



Can the following four paths be designed?

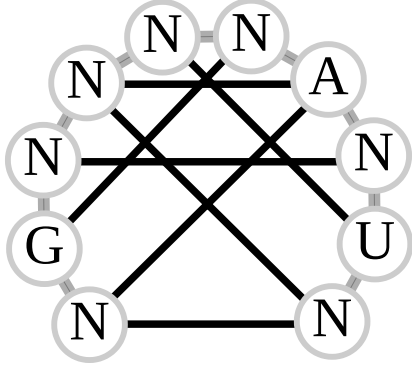


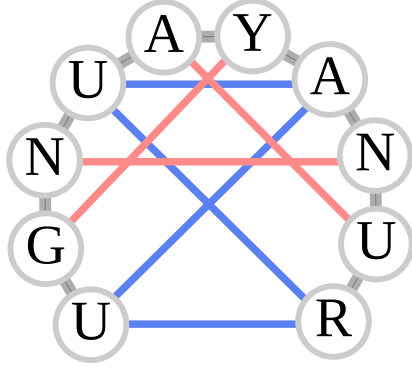
MULTI-STABLE SEQUENCE DESIGN

Given multiple structures of interest:

1. Sample candidates among compatible sequences

```
((...))...
...((...))
(.((..)).)
NGNNNNANUN
```

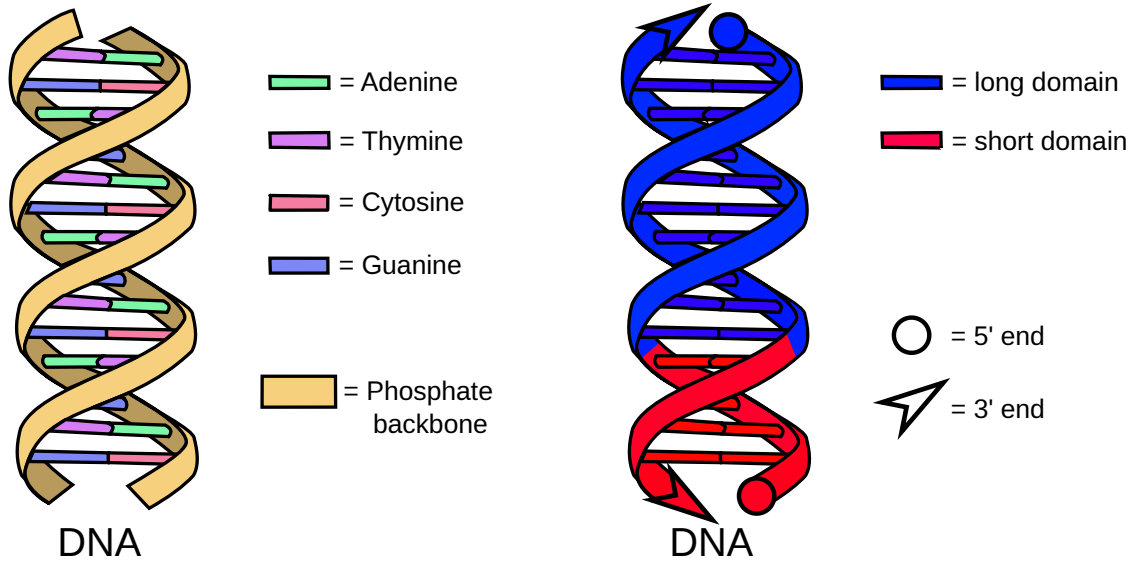




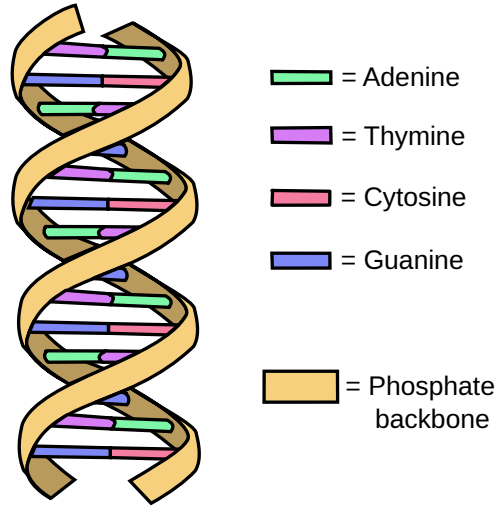
UAUR	2
GY	2
NN	6
AU	1
total	24

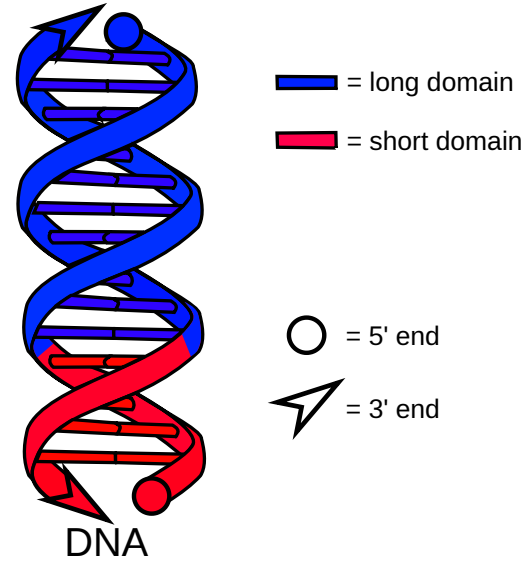
2. Pick best candidate based on an objective function

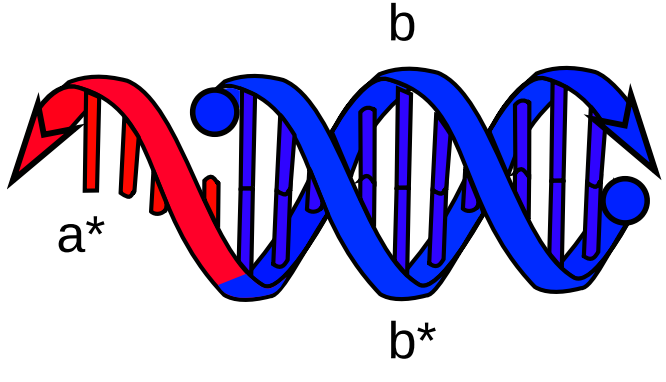
DOMAIN-LEVEL STRAND DISPLACEMENT

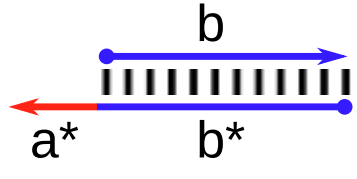


DOMAIN-LEVEL STRAND DISPLACEMENT

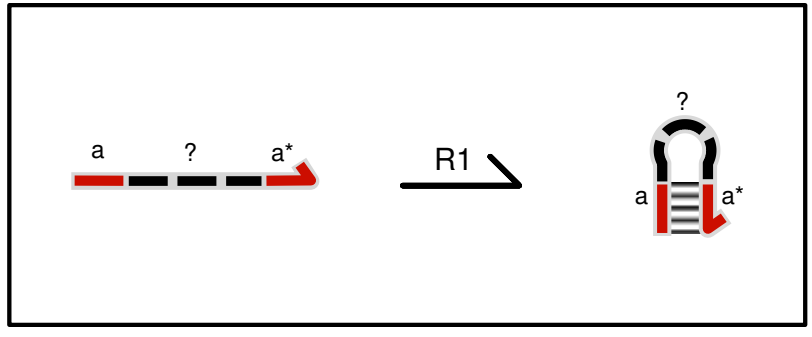




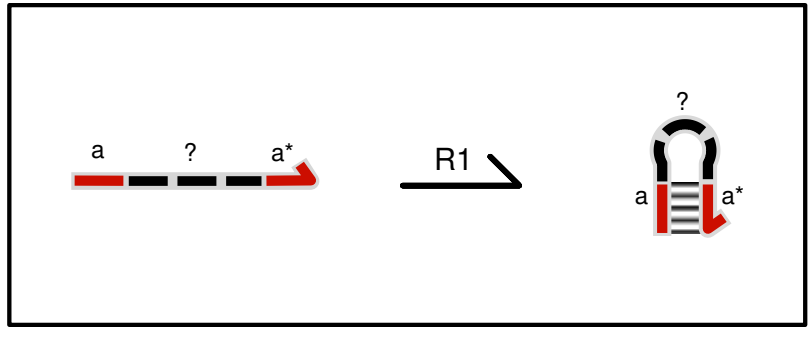


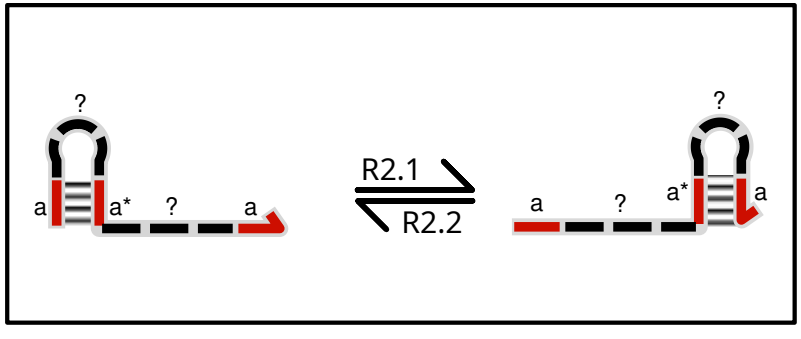


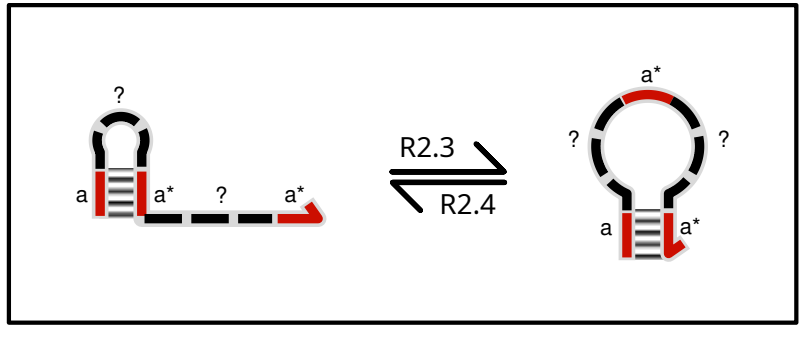
THE DOMAIN-LEVEL MOVE SET

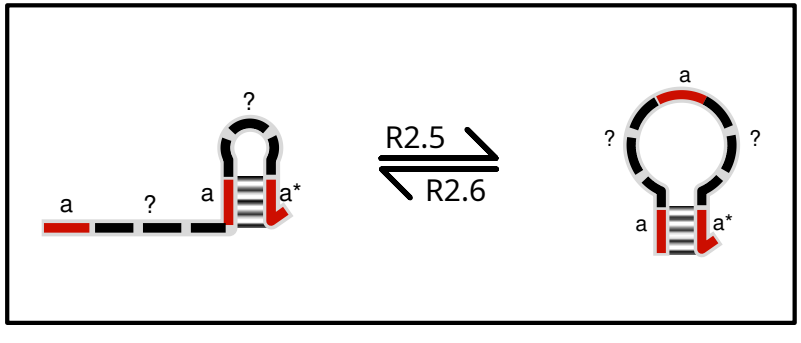


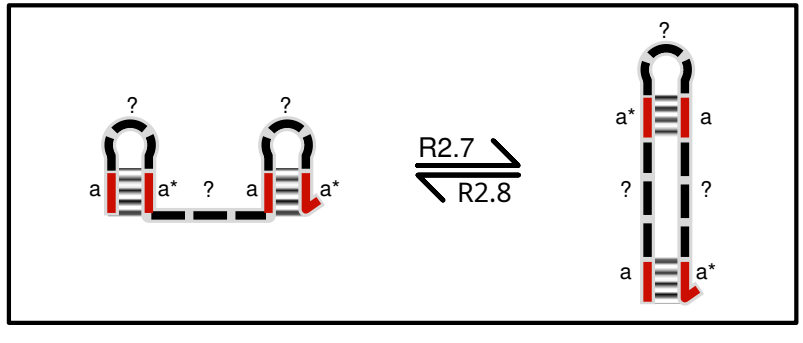
THE DOMAIN-LEVEL MOVE SET



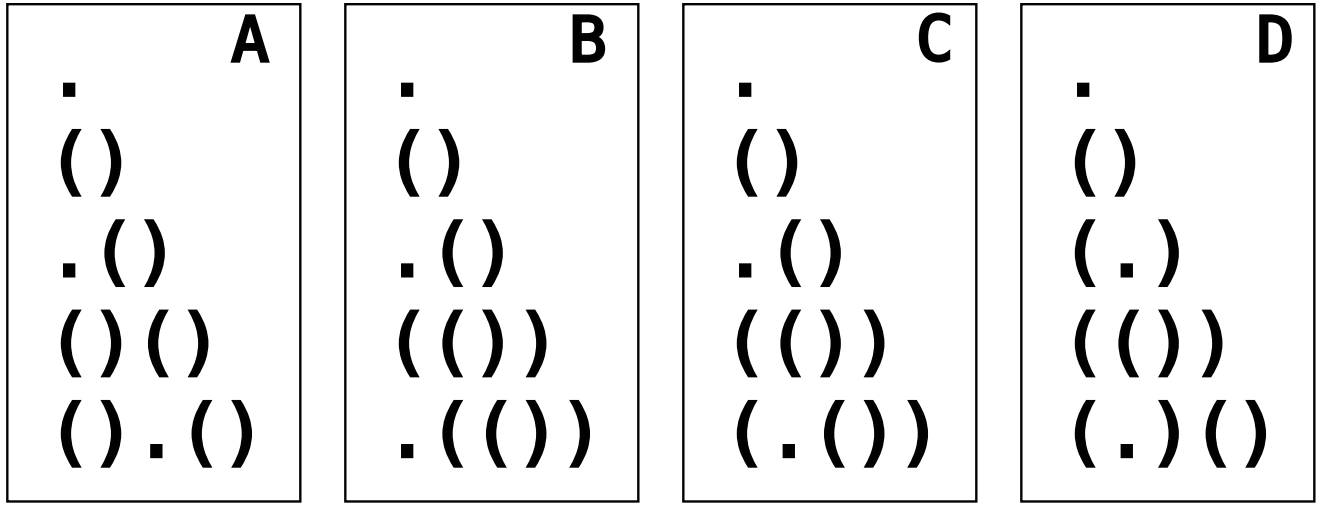








WHICH PATHWAYS CAN BE DESIGNED?

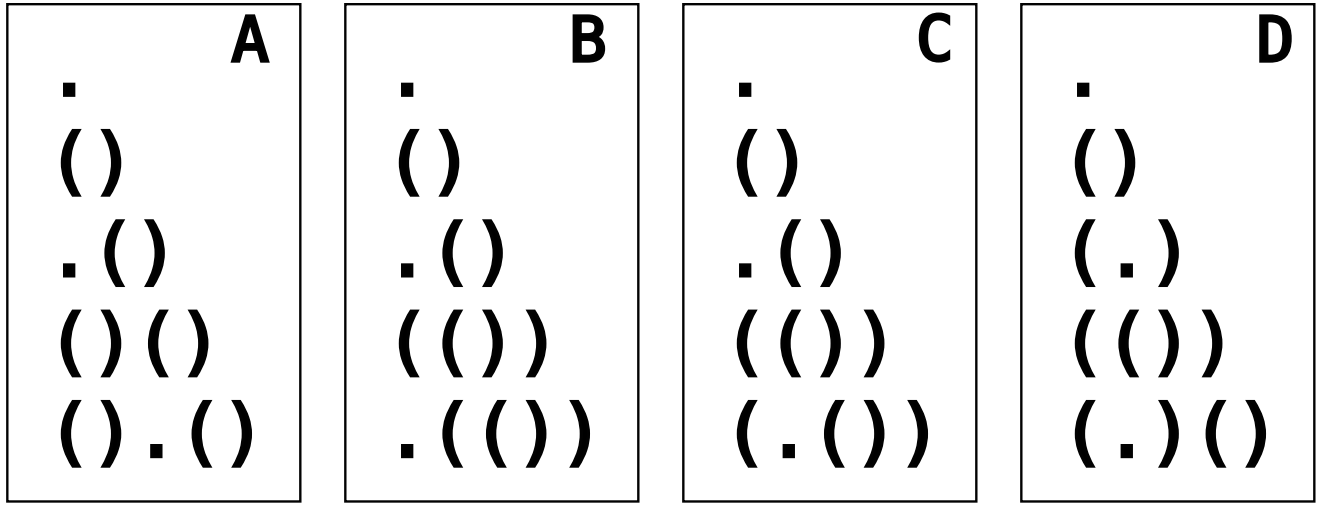


assignability

consistency

traversability

WHICH PATHWAYS CAN BE DESIGNED?

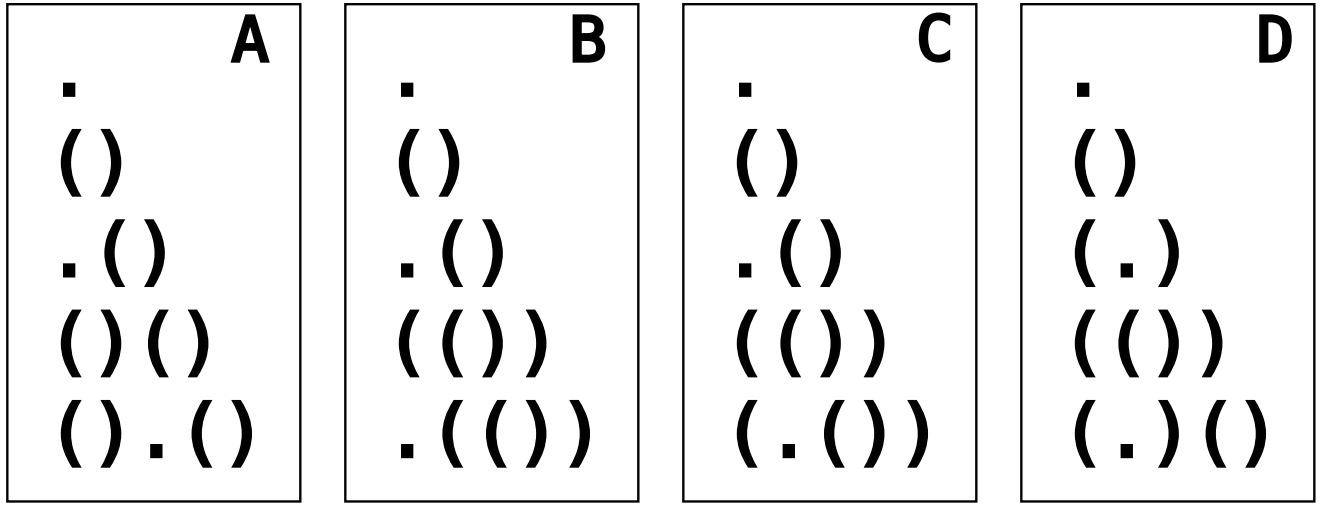


assignability ✓ ✓ ✓ ✗

consistency

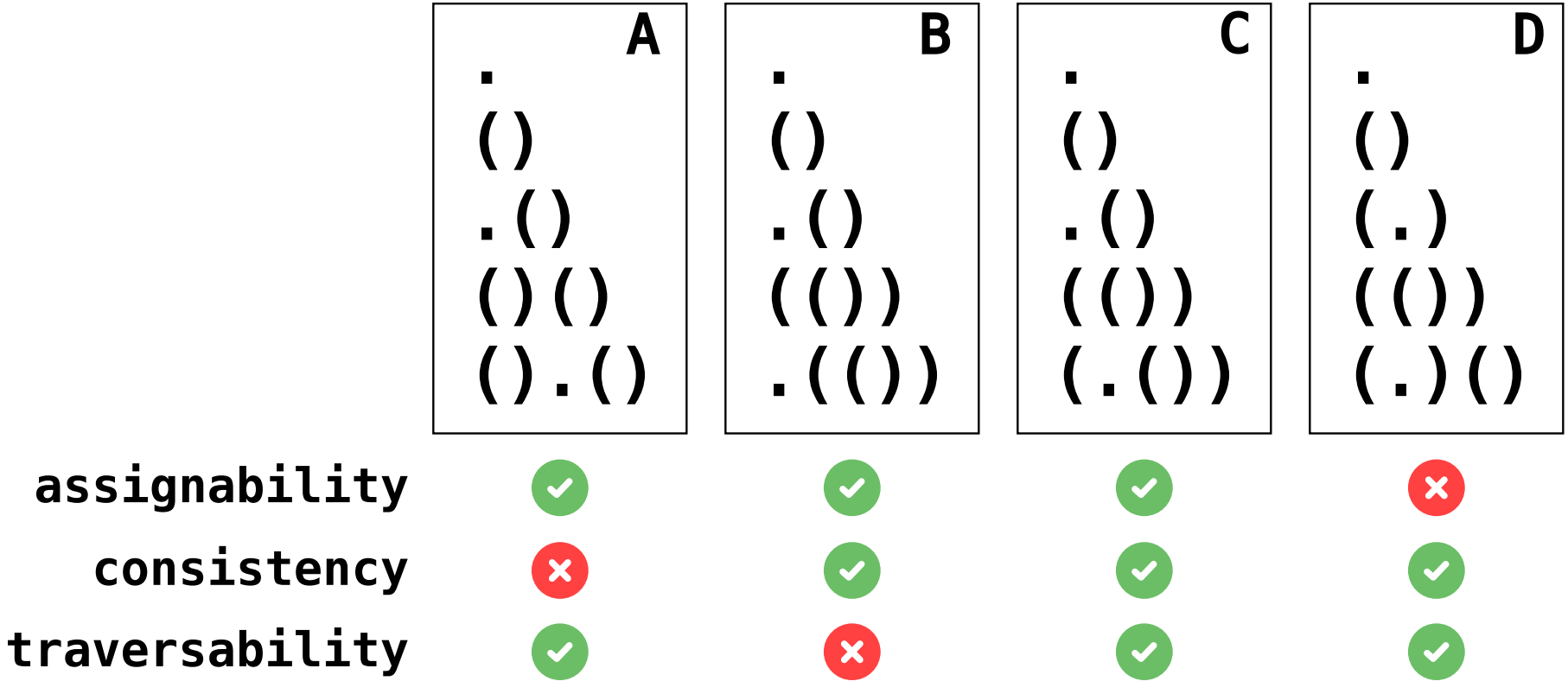
traversability

WHICH PATHWAYS CAN BE DESIGNED?



	A	B	C	D
assignability	✓	✓	✓	✗
consistency	✗	✓	✓	✓
traversability				

WHICH PATHWAYS CAN BE DESIGNED?



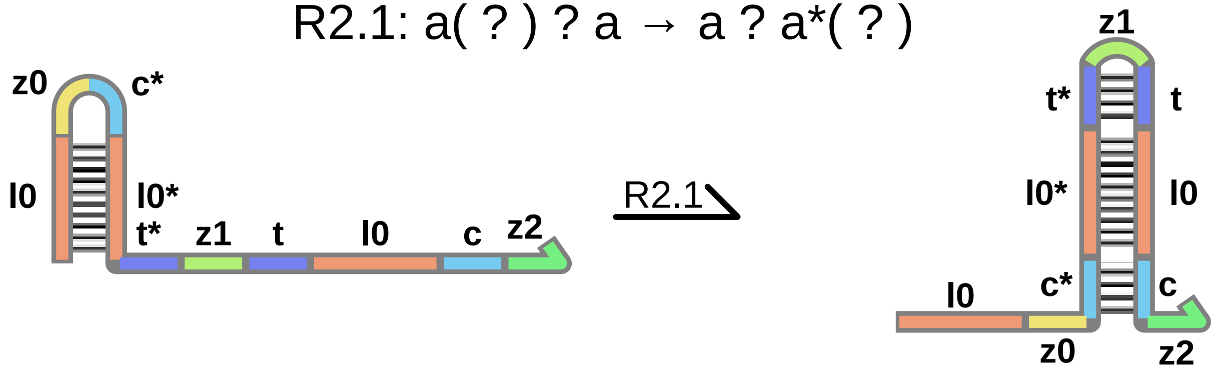
→ path C is **sls-translatable**

SLS-TRANSLATION

```
.         . .                         ........
() ---->  ( . . ) . .        ---->    (((((((...)))))))...
.()       . . ( ( ( . ) ) ) .         ........(((((((((((...)))))))))).
          L S a* L* b* S b L a S
```

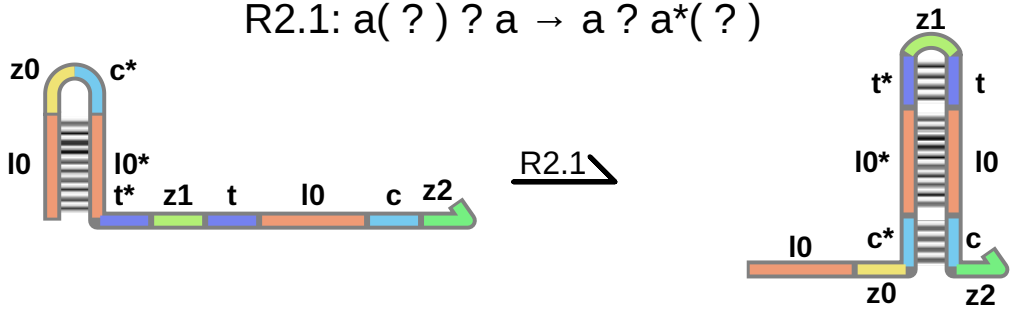
... this works for all types of domain-level rearrangements!

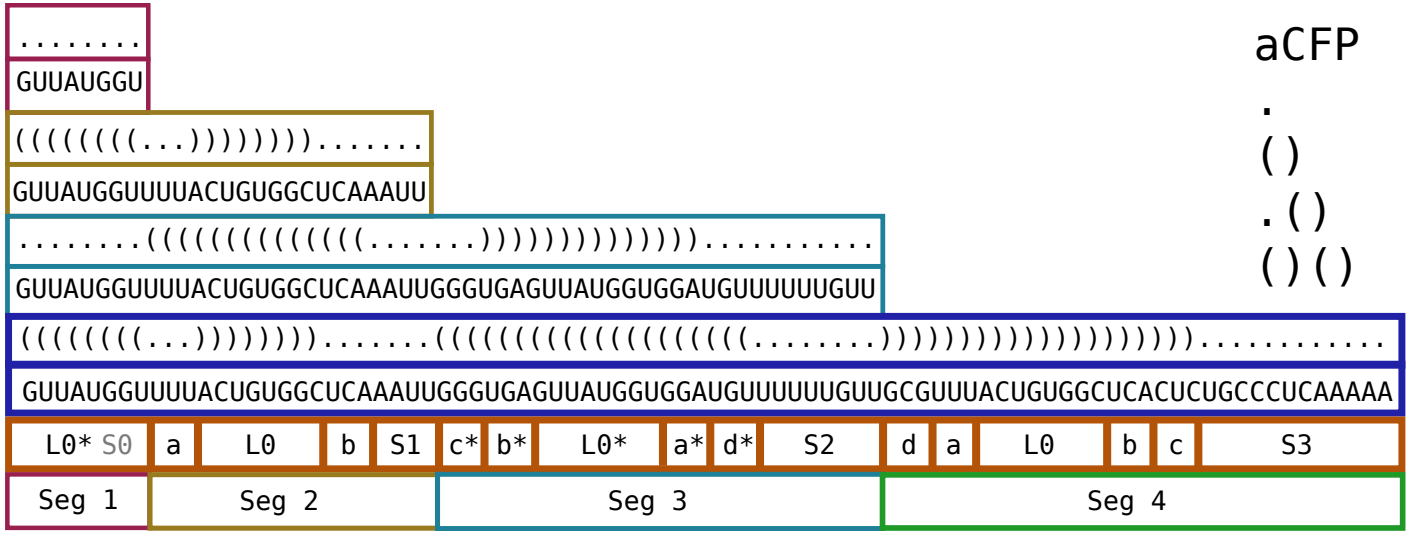
R2.1: a(?) ? a → a ? a*(?)



COCOPATHS

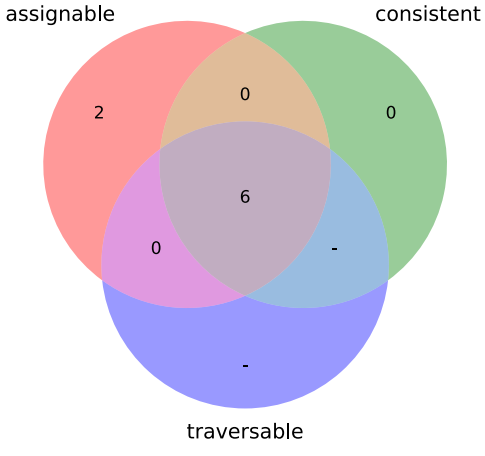
DESIGN OF "SLS-TRANSLATABLE" PATHS



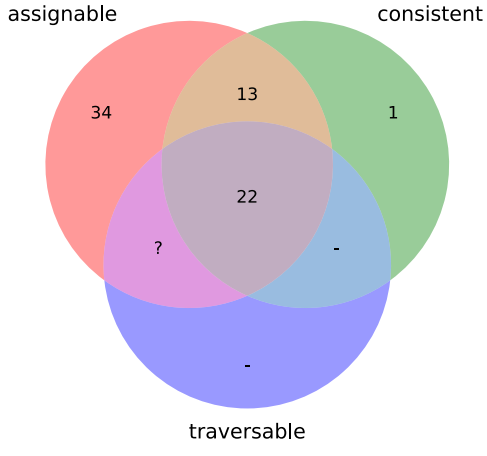


HOW MANY PATHS ARE THERE?

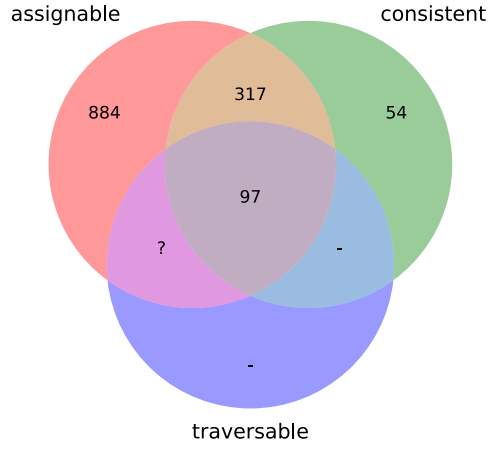
Length 3: 6 of 8 sls-translatable



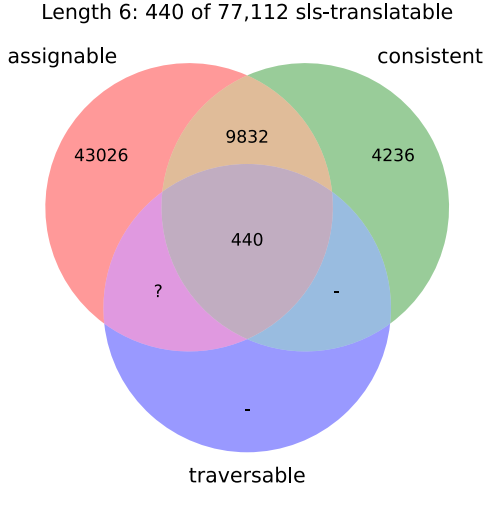
Length 4: 22 of 72 sls-translatable



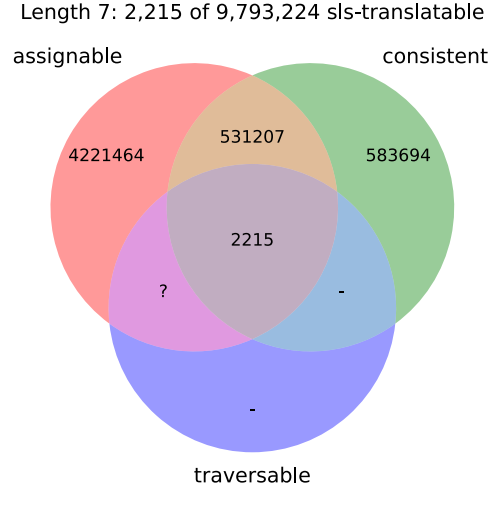
Length 5: 97 of 1,512 sls-translatable



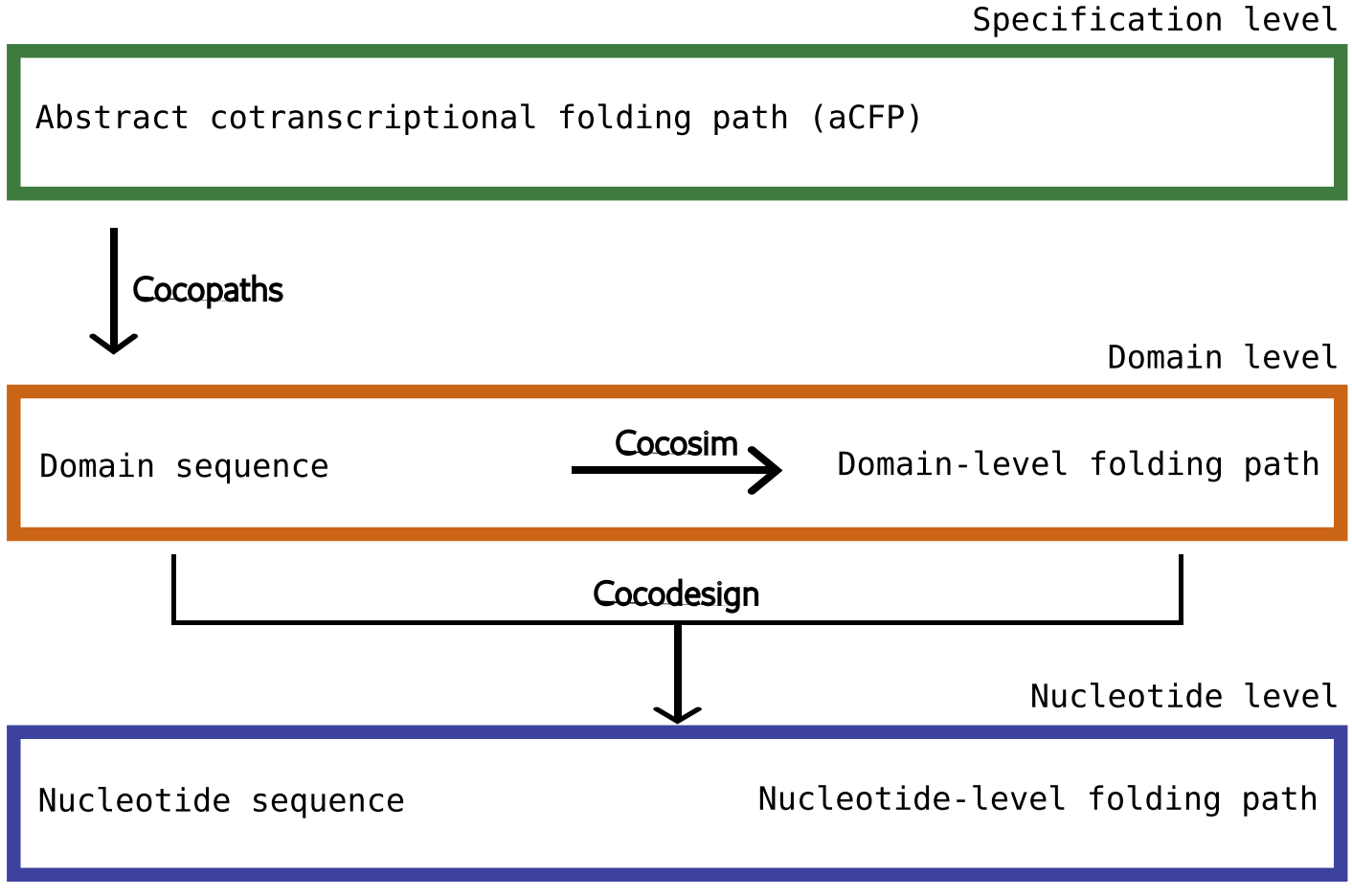
Length 6: 440 of 77,112 sls-translatable



Length 7: 2,215 of 9,793,224 sls-translatable

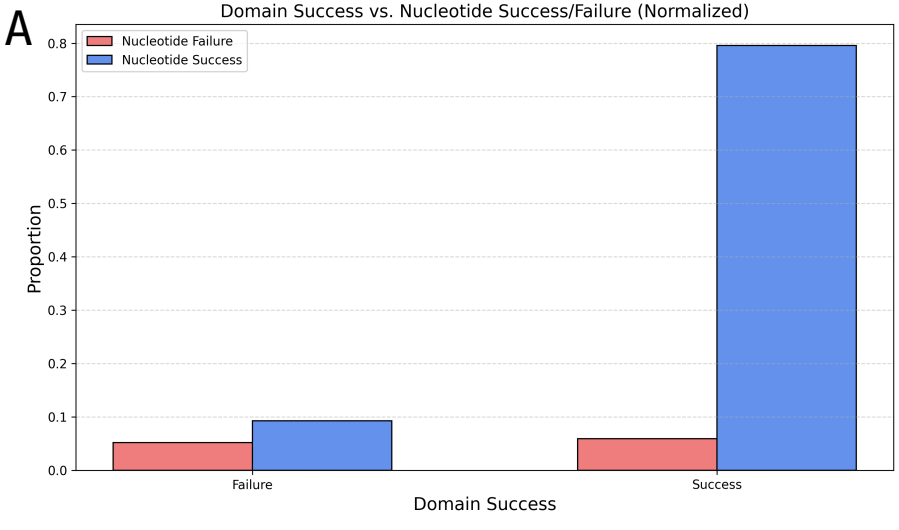


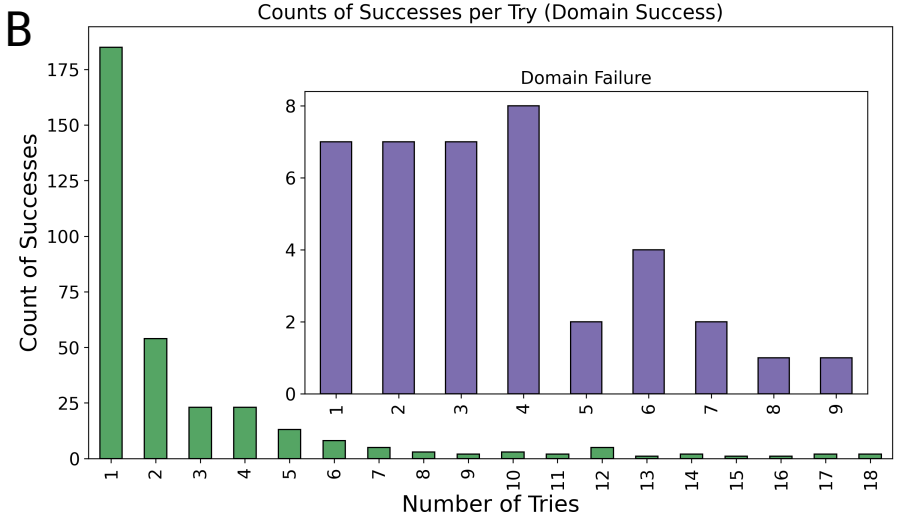
COCOPATHS FRAMEWORK



SEQUENCE DESIGN

$$O = \min\left(\max_{i=1}^{C}\left(G(\chi_i) - G_c(\chi_i, C_i) + 0.1 \cdot b(\chi_i, C_{i-1}, C_i)\right)\right)$$

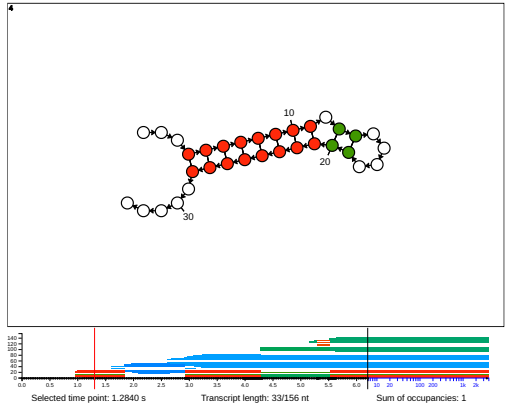


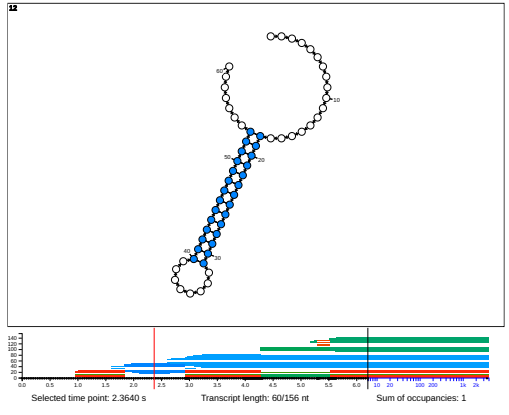


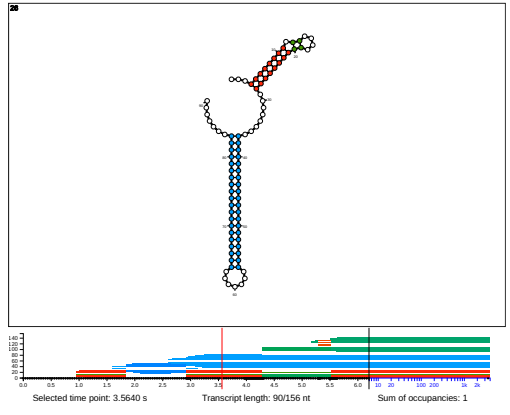
Success means that the target structure occupies more than 50% of the population at each transcription step.

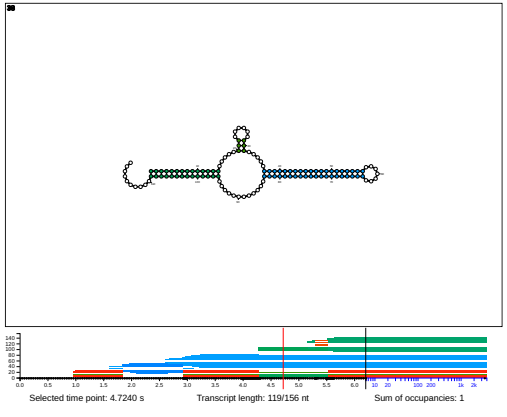
AN EXAMPLE SEQUENCE

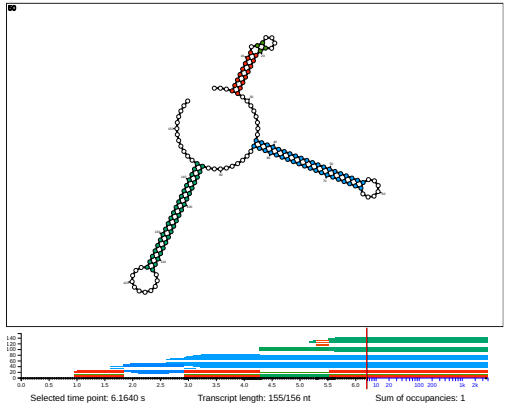
```
.
()
.()
()()
(.())
()()()
```





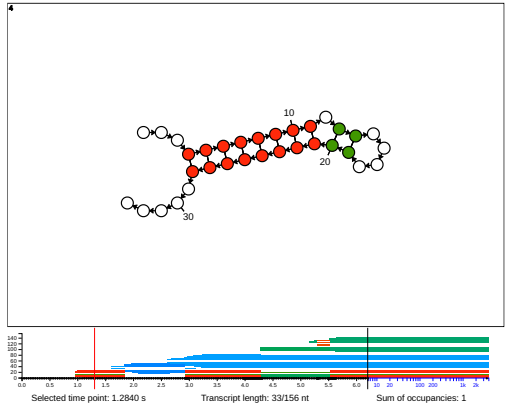


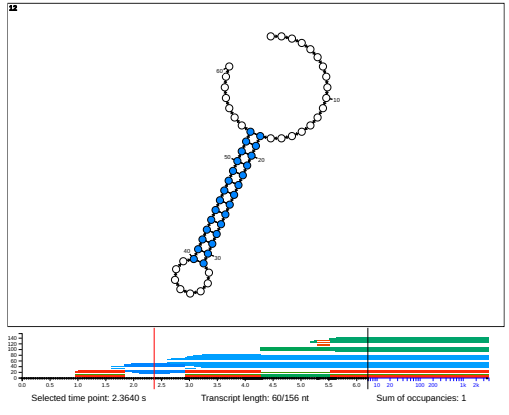


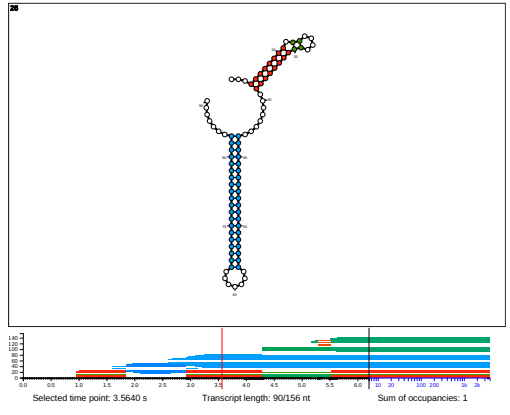


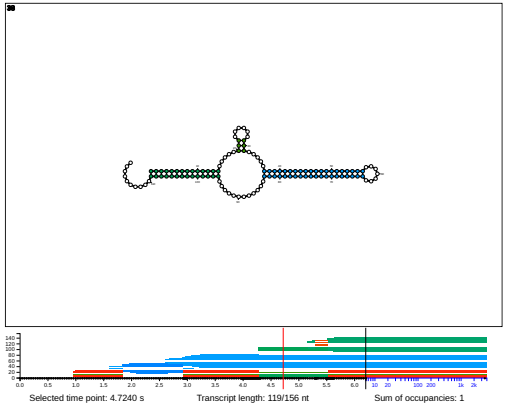
AN EXAMPLE SEQUENCE

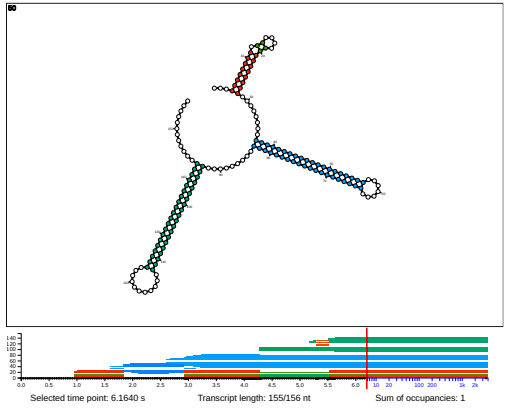
```
.
()
.()
()()
(.())
()()()
```











Thank you for your attention.

COCOSIM

Domain-level cotranscriptional folding