The RNA Folding Problem

AN INTEGER LINEAR PROGRAMMING APPROACH

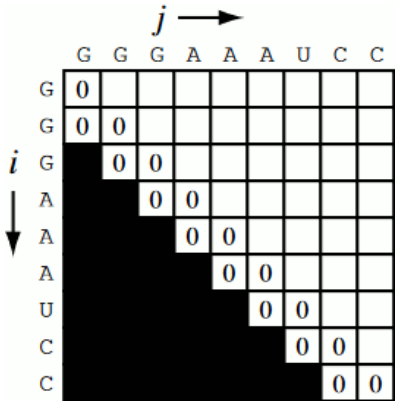
Problem Statement

The RNA Folding Problem is to predict the *secondary structure* of an RNA molecule, given its nucleotide sequence.

How?

$$\begin{aligned} \max\ & c^\top x \\ \text{s.t. } & Ax \leq b \\ & x \geq 0 \\ & x \in \mathbb{Z}^n \end{aligned}$$

Integer Linear Programming



Dynamic programming

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G = (V,E)
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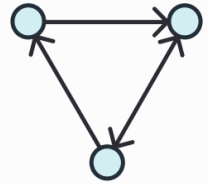
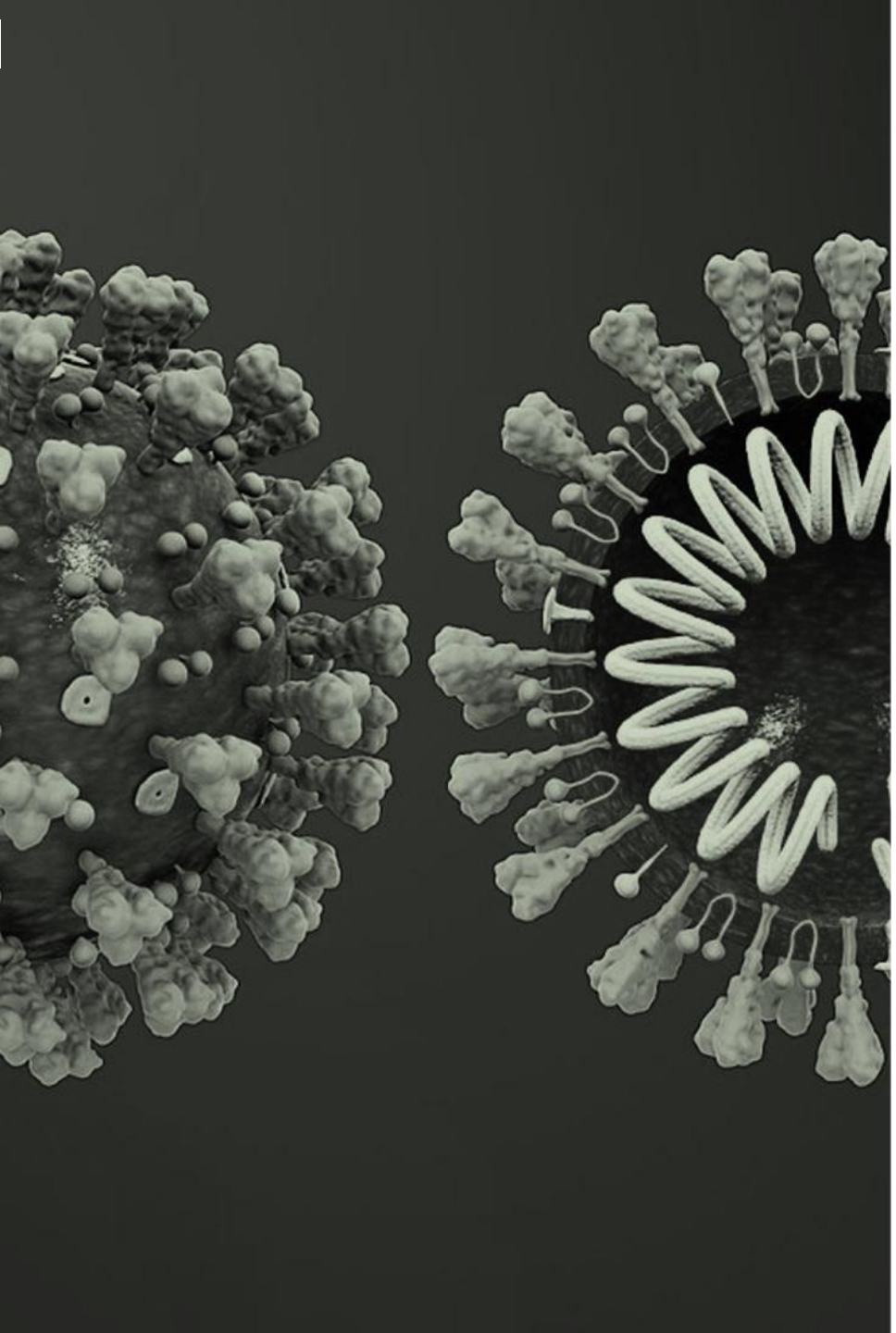


Graph theory



What about COVID-19?

- The Coronavirus genome is made up of a single strand of large positive polarity RNA
- RNA gives rise to 7 viral proteins and is associated with the N protein, which increases its stability
- To identify new antivirals it's necessary to know 3D structure of virus proteins that are responsible for cell infection and virus replication
- The enzyme forming the RNA chain of the virus is the ***RNA-dependent RNA polymerase***

What about COVID-19?

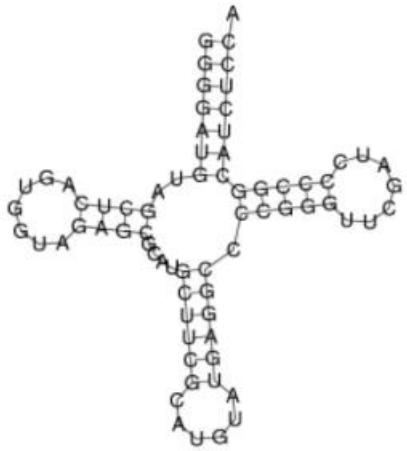
The Linearfold algorithm:

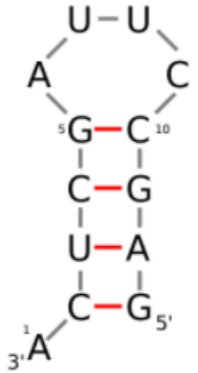
- It predicts the secondary structure for the Covid-19 RNA sequence, reducing overall analysis time from 55 minutes to 27 seconds with respect the classical dynamic programming approach
- It achives *linear runtime*: in dynamic programming algorithms runtime scales cubically with RNA length
- It doesn't impose constraints on the output structure
- *Less use of memory* and *more scalability* with respect dynamic programming algorithms

Paper: https://academic.oup.com/bioinformatics/article/35/14/i295/5529205

Code: https://github.com/LinearFold/LinearFold

RNA secondary structure representations





A crude first model

Given the nucleotide sequence, *s*, of a RNA molecule, find a nested pairing that pairs the *maximum* number of nucleotides, compared to any other nested pairing.

A crude first model

$$Maximize \sum_{i<j} P(i,j)$$

→ *Maximize the number of paired nucleotides*

$$s.t. \sum_{j<k} P(j,k) + \sum_{k>j} P(k,j) \leq 1$$

→ *Each nucleotide can be paired to at most one other nucleotide*

$$P(i,j) + P(i',j') \leq 1$$

→ *Disallow crossing pairs (i<i'<j<j')*

$$P \in [0,1]$$

→ *Decision variable*
0 : non complementary pair
1 : complementary pair

A more complex model

$$Maximize \sum_{i<j} P(i,j) + Q(i,j)$$

→ *Maximize the number of paired nucleotides*

$$s.t. \sum_{j<k} P(j,k) + \sum_{k>j} P(k,j) \leq 1$$

→ *Each nucleotide can be paired to at most one other nucleotide*

$$P(i,j) + P(i',j') \leq 1$$

→ *Disallow crossing pairs (i<i'<j<j')*

$$P(i,j) + P(i+1,j-1) - Q(i,j) \leq 1$$

$$2Q(i,j) - P(i,j) - P(i+1,j-1) \leq 0$$

Stacked quartet detection

$$P \in [0,1]$$

→ *Decision variable*
0 : non complementary pair
1 : complementary pair

DEMO

https://github.com/badcortex/opt4ds