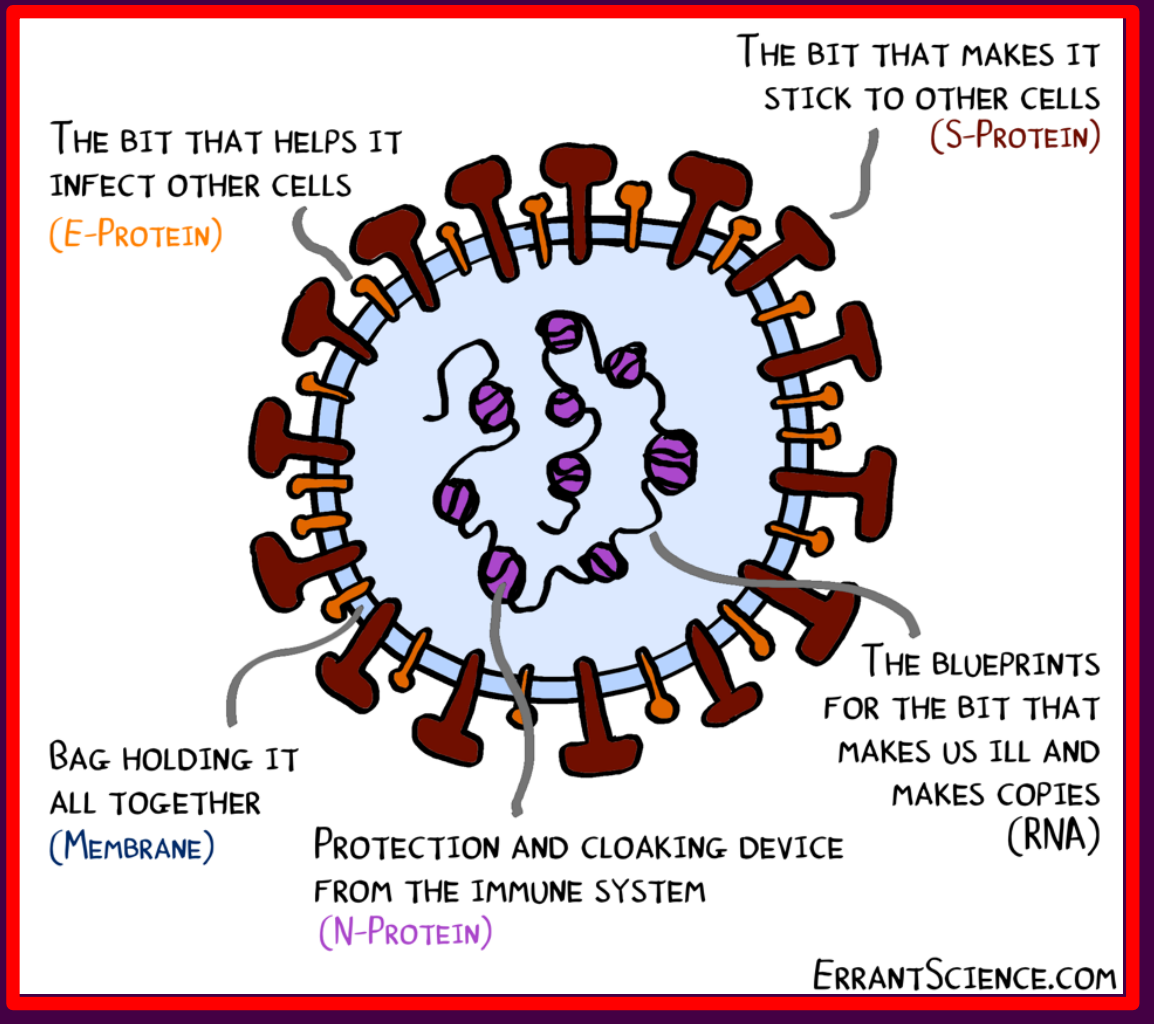
Tamar Schlick's Research Team
New York University (Courant/Chemistry)

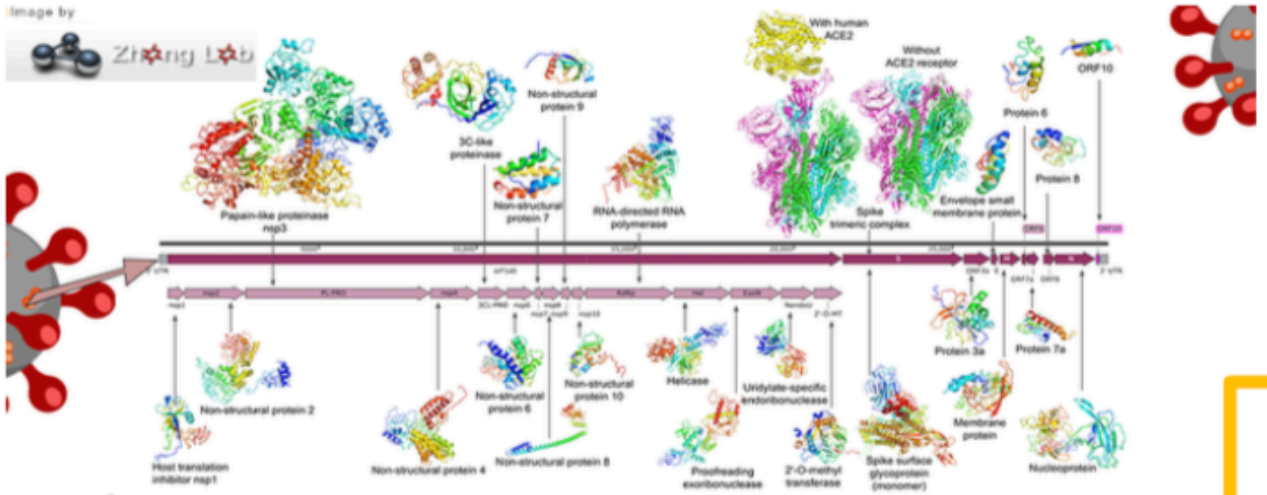
COVID-19 (bad news wrapped inside proteins)



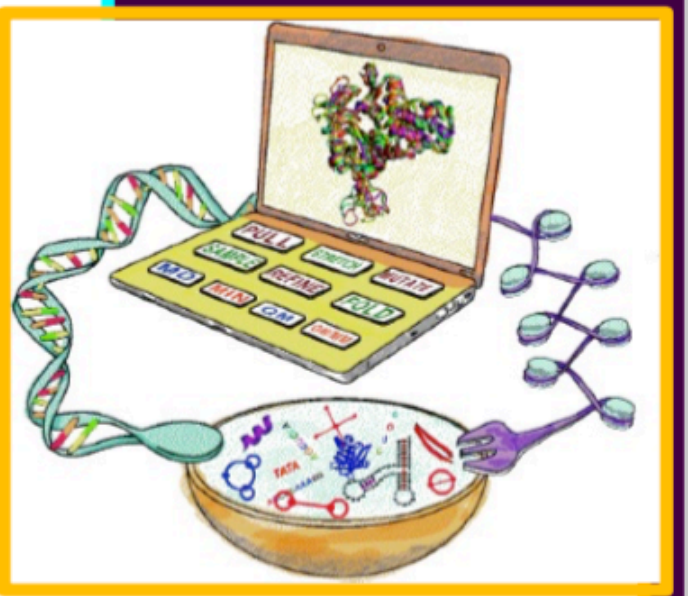
Infectious agent is a single 30,000 nucleotide-long RNA molecule that uses host cell machinery to copy itself and make all the proteins essential to its life cycle and thus rapidly multiply and overtake host organs

Exploring COVID-19 RNA Viral Genome Targets by Graph-Theory Based Modeling

Most work to date focuses on attacking the protein machinery

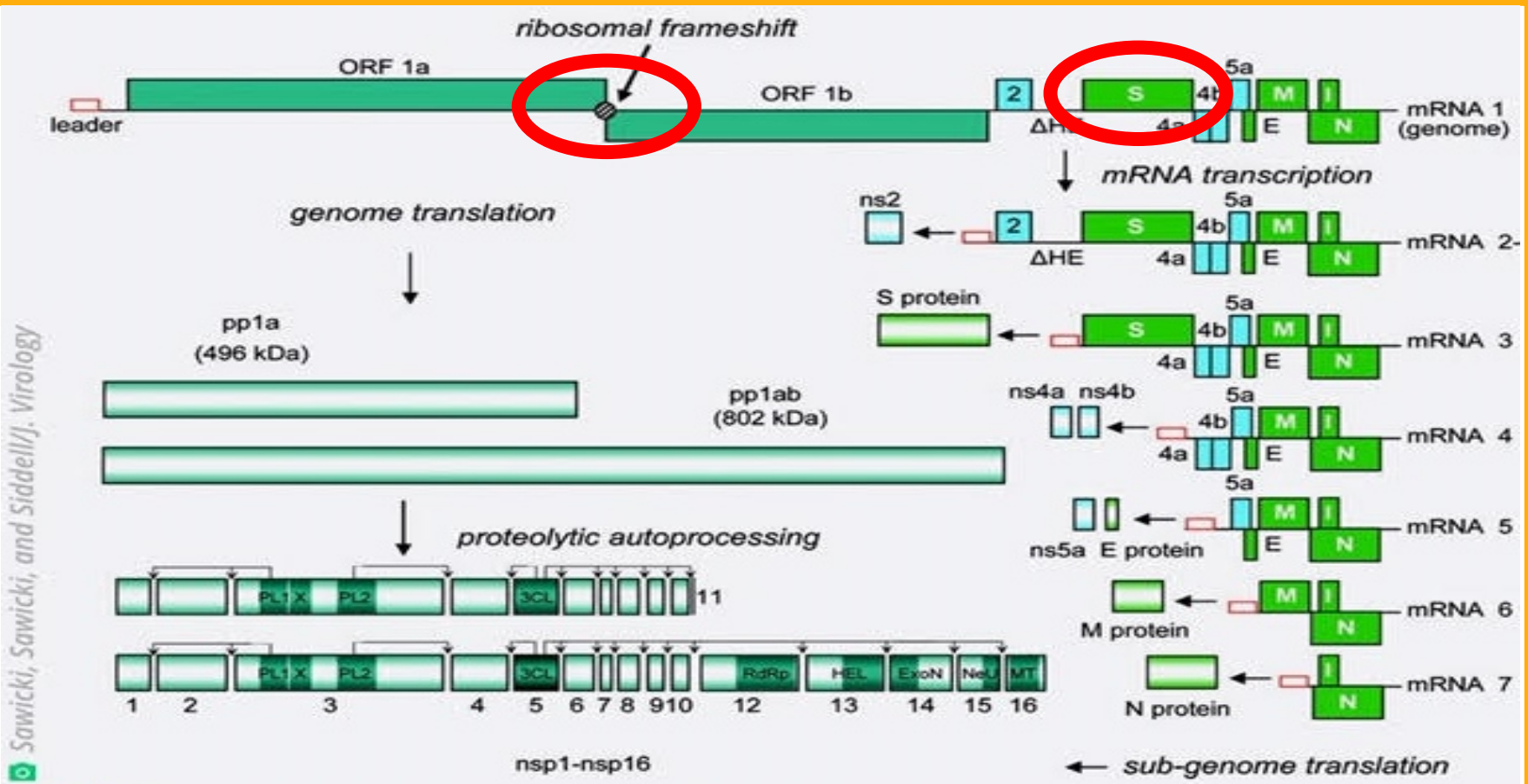


Genome-wide structure and function modeling of SARS-COV-2



- RNA itself may be able to replicate even when proteins are dismantled
- Highly conserved RNA genomes offer opportunities to block viral replication (HIV, HCV)
- CRISPR gene editing technology may be applicable
- Need long-term mechanistic understanding of entire virus (future waves, other coronavirus)
- We aim to determine structures and drug binding potential for 2 RNA regions

Build 2D and 3D Structures of Two RNA Gene Regions Using Graph-Theory Machinery



Enlarge / The 30,000 base long coronavirus genome is used to produce a large variety of proteins.

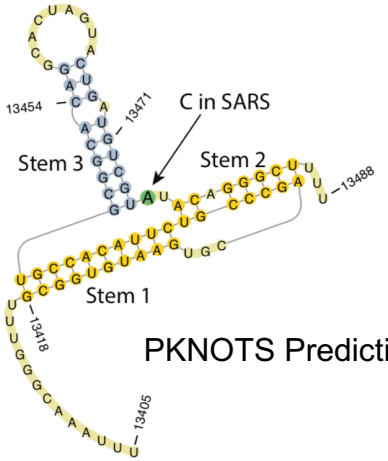
- **ORF1ab makes a chain of NSPs involved in replication**
  NSP1 – has key role early in infection (suppresses cell's natural defenses)
- **Spike protein – assembles and releases new virus copies**

Project Outline

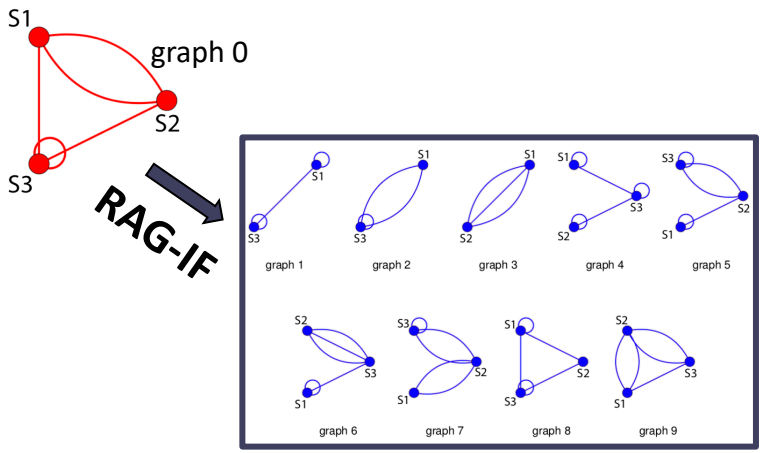
(1) Frame-Shifting Pseudoknot

Qiyao Zhu & Swati Jain

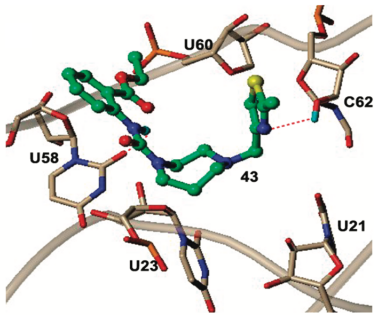
(a), (b) 2D+3D Modeling (homology, various programs, literature and consensus)



(c) Destroy Pseudoknot/Stem 2 (RAG-IF for dual graphs, computations & analysis)



(d) Drug Binding Studies



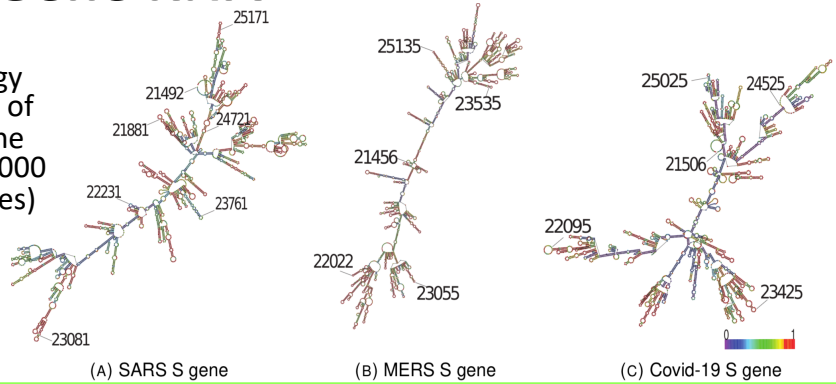
Binding of *1,4-diazepam derivative 10* in the active site of SARS-pseudoknot

June-July (Steps a,b) → **Aug-Sep (Step c)** → **Oct-Nov (Step d)**

(2) S-Gene RNA

Shuting Yan & Lucille Tsao

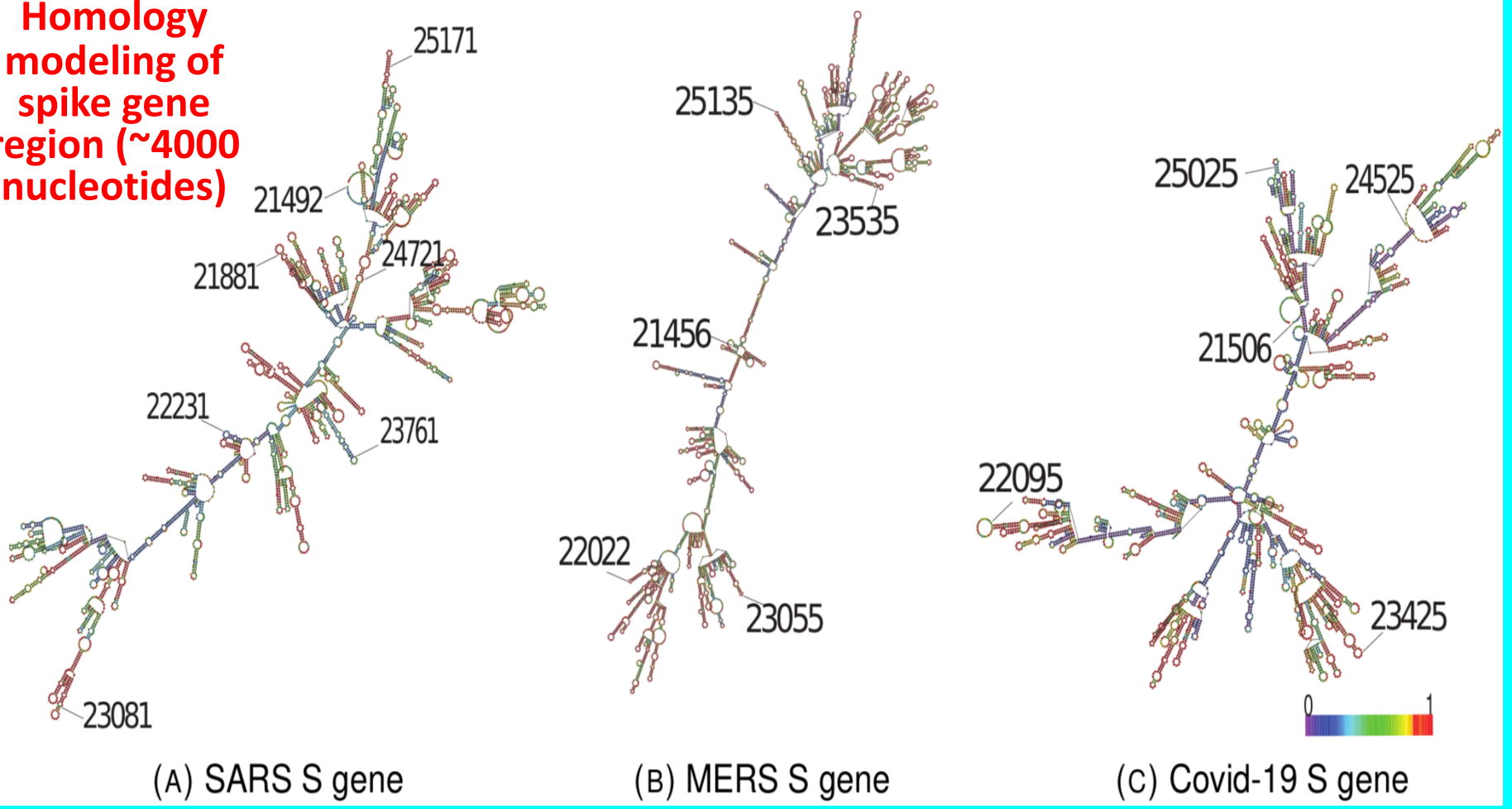
Homology modeling of spike gene region (~4000 nucleotides)



- (a) Identify self-folding subdomains
- (b) 2D + 3D modeling
- (c) Mutation Analysis (Eterna)
- (d) Drug Binding Studies

Preliminary RNA Model of Spike Protein Gene

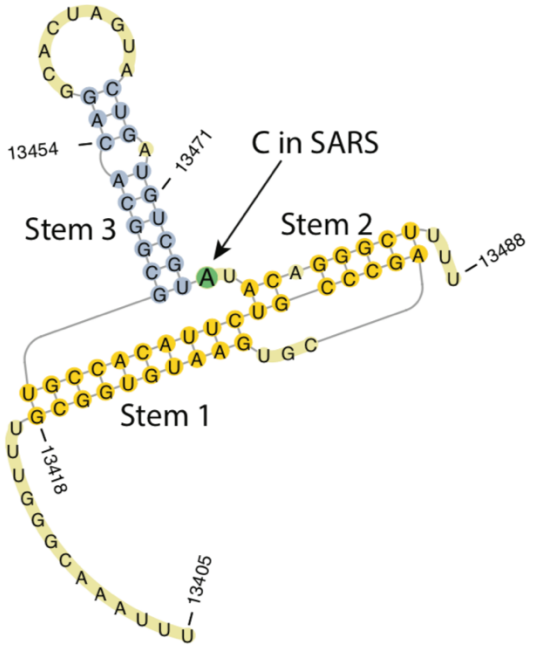
Homology modeling of spike gene region (~4000 nucleotides)



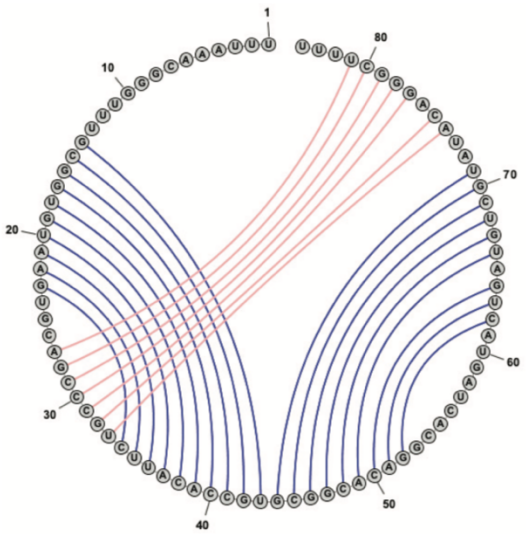
- **COVID-19 RNA is 89% similar to SARS-Cov and 50% similar to MERS-Cov**

ORF1ab Frame Shifting Pseudoknot

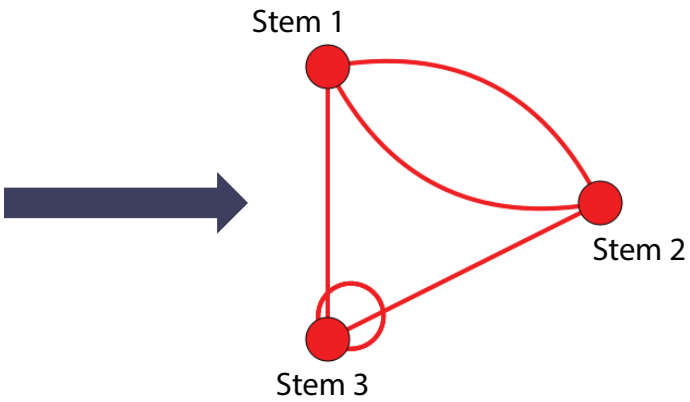
- **Ribosomal frame shifting is a strategy to translate overlapping reading frames—used in HIV, SARS, and others**
- **Frame shifting mechanisms rely on specific fold motifs and associated structural transitions**
- **These regions and/or transitions are potential anti-infective targets**
- **In SARS, the key fold motif is a 3-stem pseudoknot (intertwined base pairs) region**



(A) PKNOTS prediction



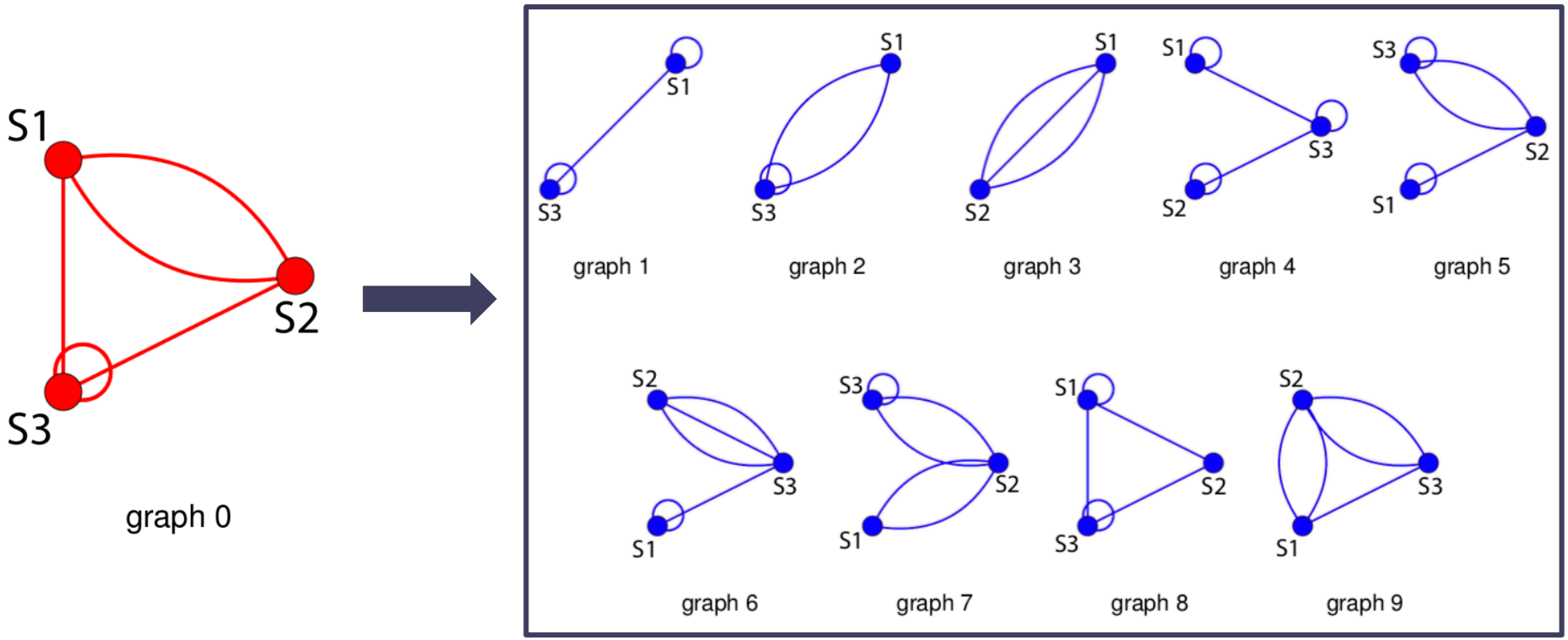
(B) Circular plot



Dual Graph

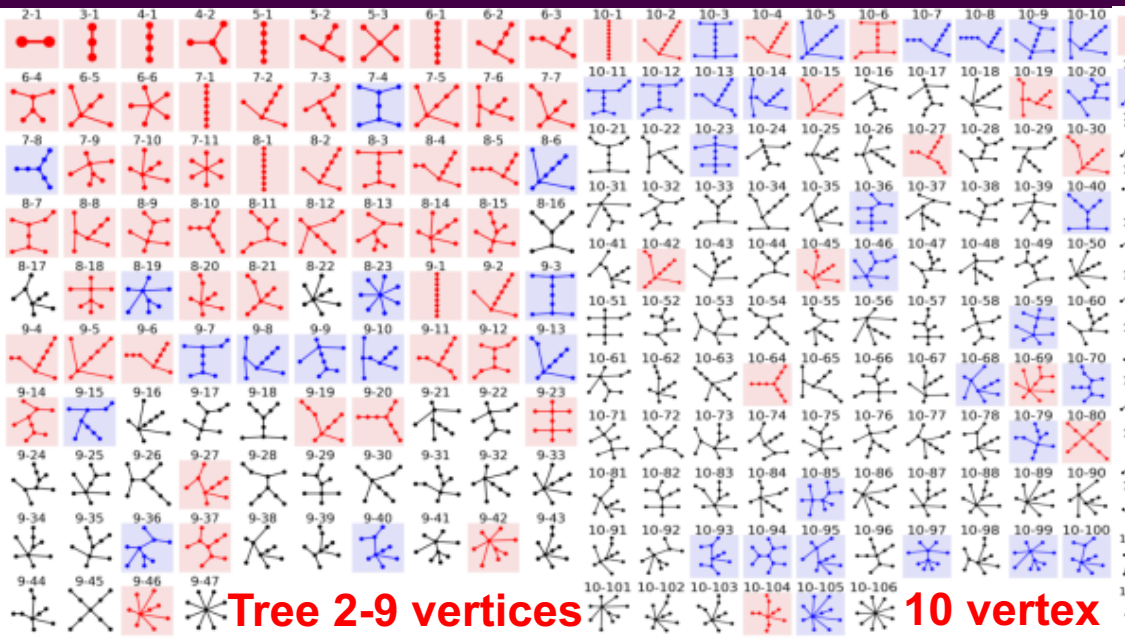
Covid-19 Pseudoknot by homology modeling

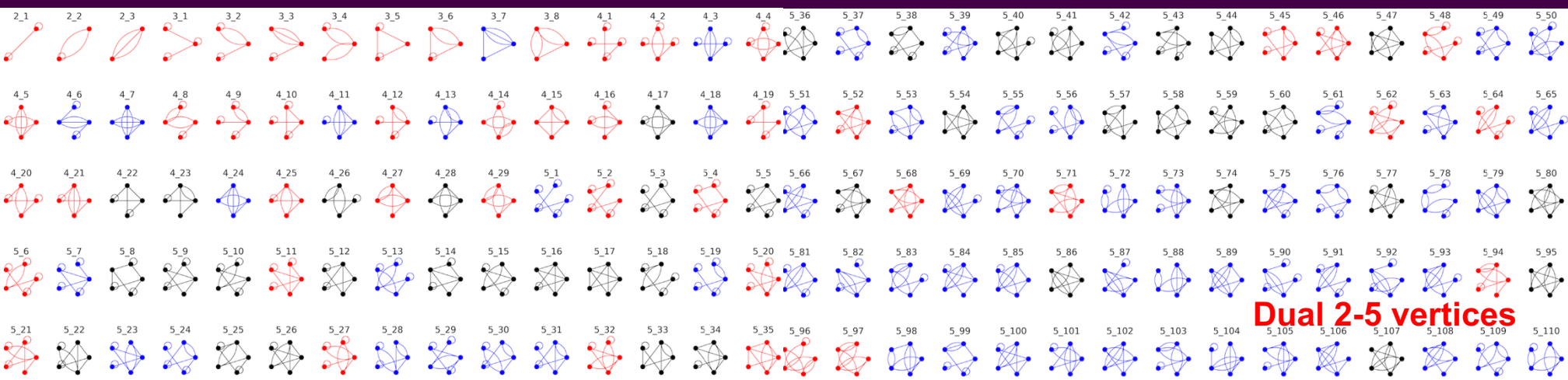
Destroy This Pseudoknot by Mutations or Drugs

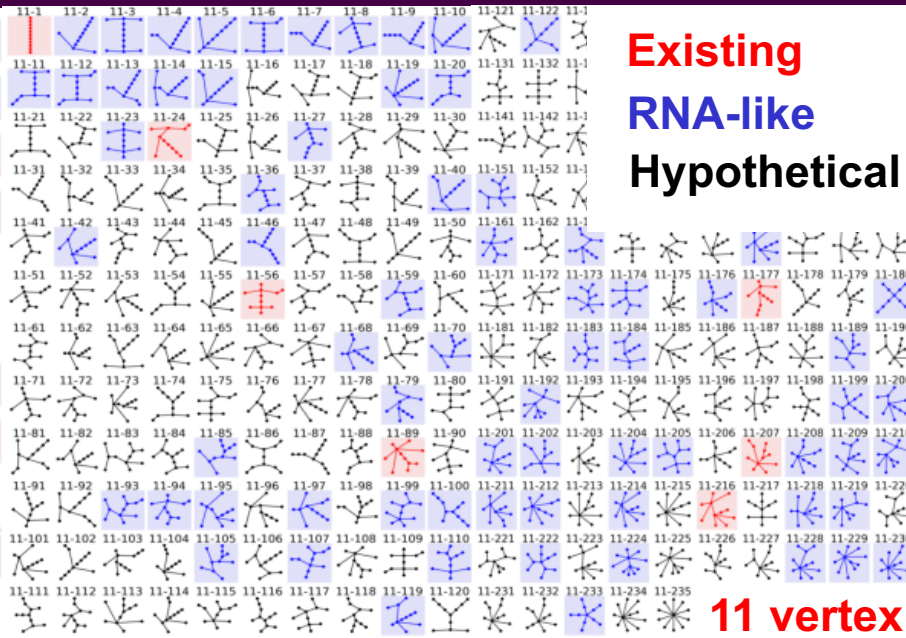


- Use our graph-based genetic algorithm (RAG-IF) to destroy stem and/or pseudoknot
- Identify fragile residues for mutations or drug binding

Structural Repertoire Available from RAG Analysis





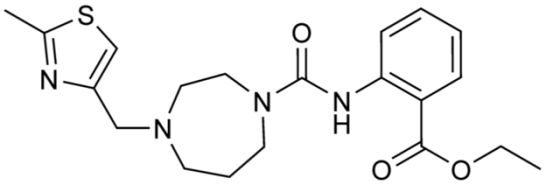


http://www.biomath.nyu.edu/rna

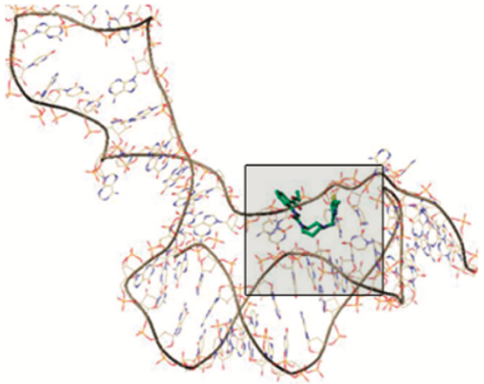
Drug Exploration: Screen for Compounds to Bind Fragile Mutations

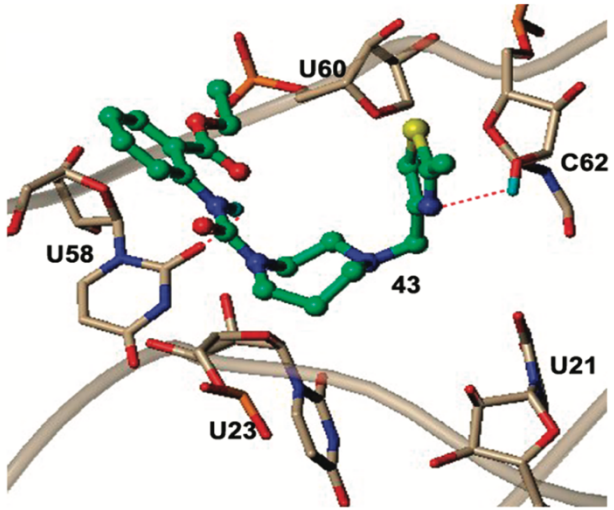
- **SARS drug … already known to inhibit pseudoknot: "1,4-diazepam derivative 10" inhibits translational frame shifting in cell models**

Chemical structures of 1,4-diazepam derivative 10



Binding in the active site of SARS-pseudoknot





Enlarged binding model

- **Virtual drug screening for related compounds that bind fragile regions will identify potential candidates**

Park, Kim, and Park, *JACS* 133(26):10094 (2011)

Tamar Schlick's NYU Team

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