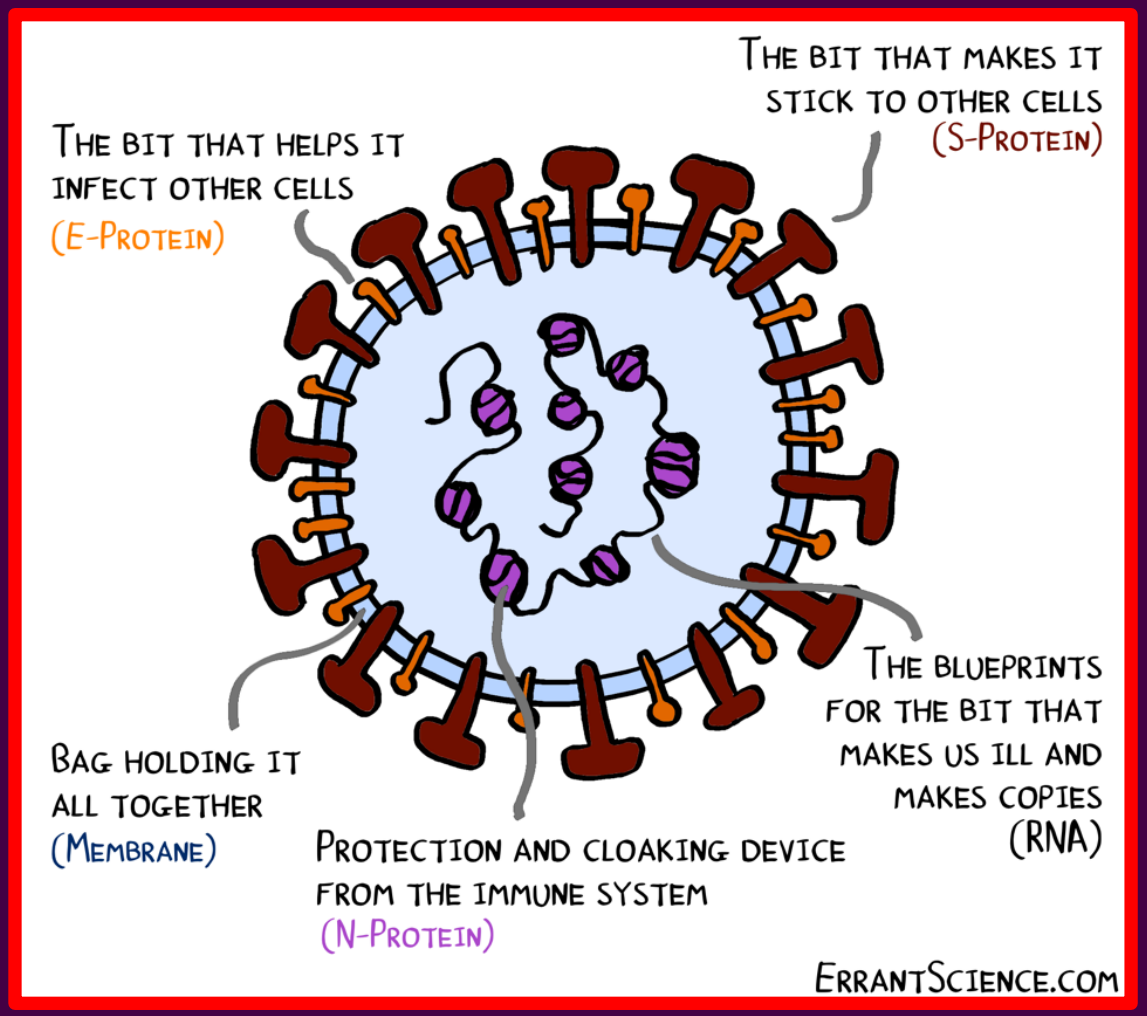
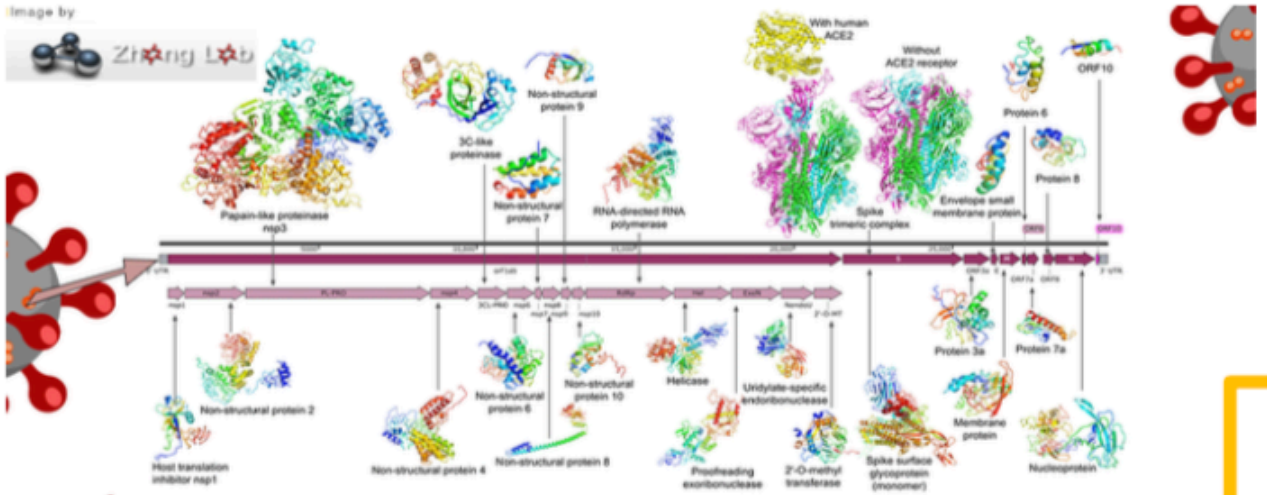
# COVID-19: Anatomy of the Killer
## (bad news wrapped inside proteins)



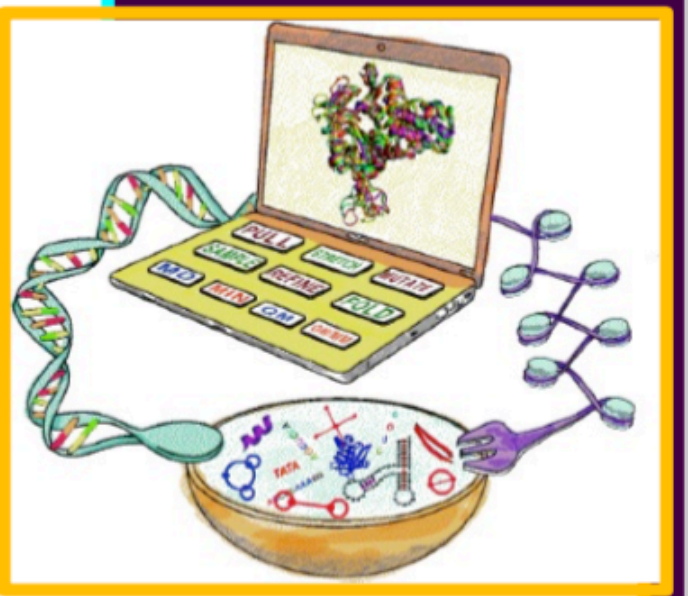

**Infectious agent is a single 30,000 nucleotide-long RNA molecule that uses host cell machinery to copy itself and make all the proteins essential to its life cycle and thus rapidly multiply and overtake host organs**

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

**Most work to date focuses on attacking the protein machinery**

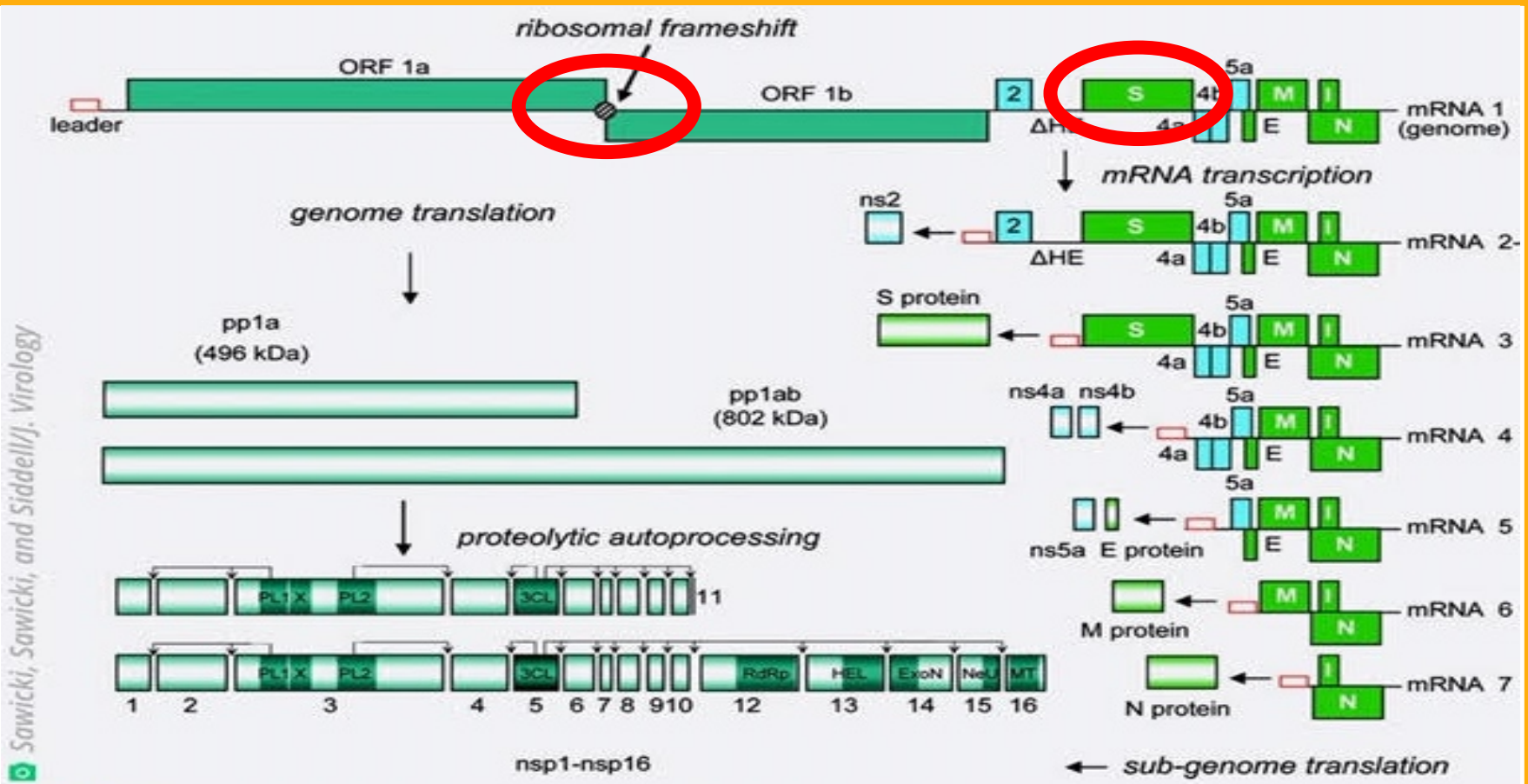



**Genome-wide structure and function modeling of SARS-COV-2**



- 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.

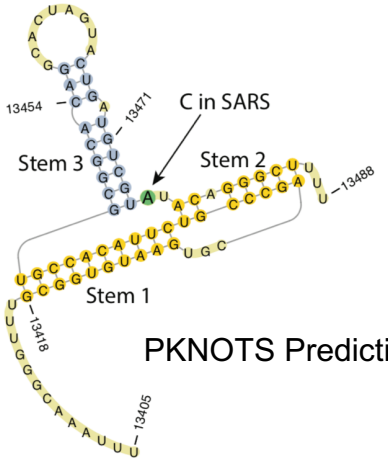
- **ORF1ab makes a chain of NSPs involved in replication**
  **NSP1 – has key role early in infection (suppresses cell's natural defenses)**
- **Spike protein – assembles and releases new virus copies**

# Project Outline

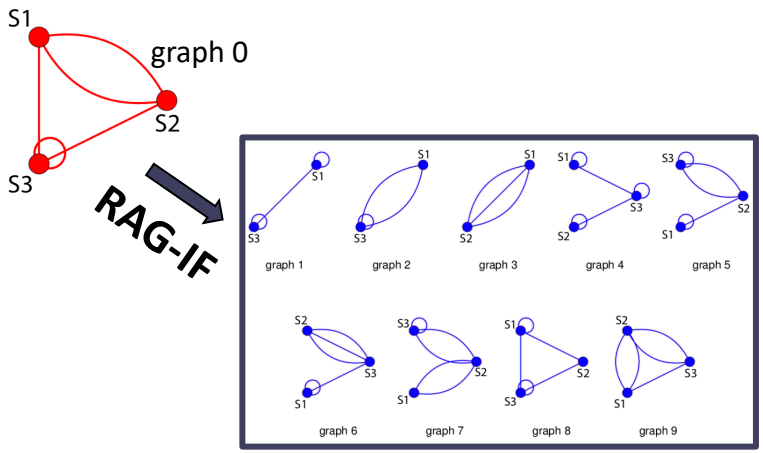
## (1) Frame-Shifting Pseudoknot

Qiyao Zhu & Swati Jain

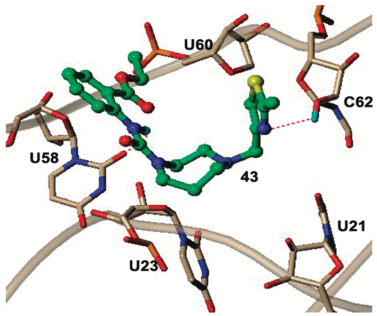
### (a), (b) 2D+3D Modeling (homology, various programs, literature and consensus)




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




### (d) Drug Binding Studies



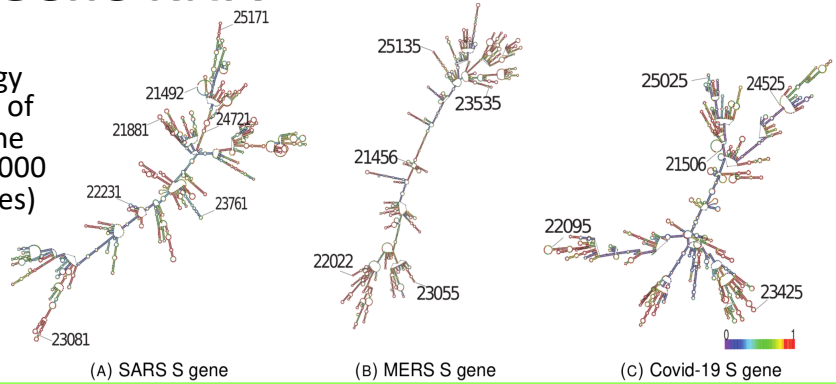

**Binding of *1,4-diazepam derivative 10* in the active site of SARS-pseudoknot**

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

## (2) S-Gene RNA

Shuting Yan & Lucille Tsao

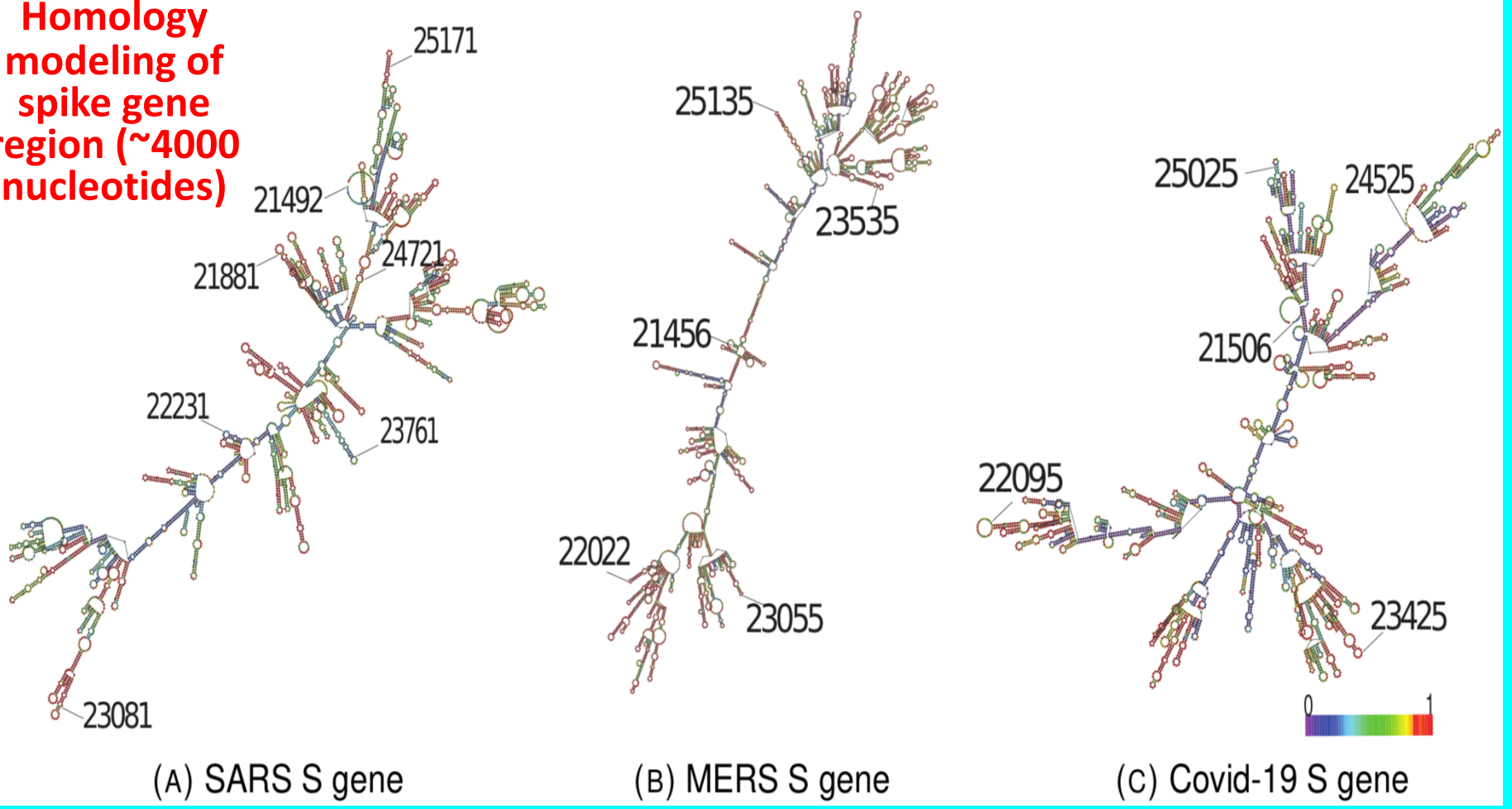
Homology modeling of spike gene region (~4000 nucleotides)




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

# Preliminary RNA Model of Spike Protein Gene

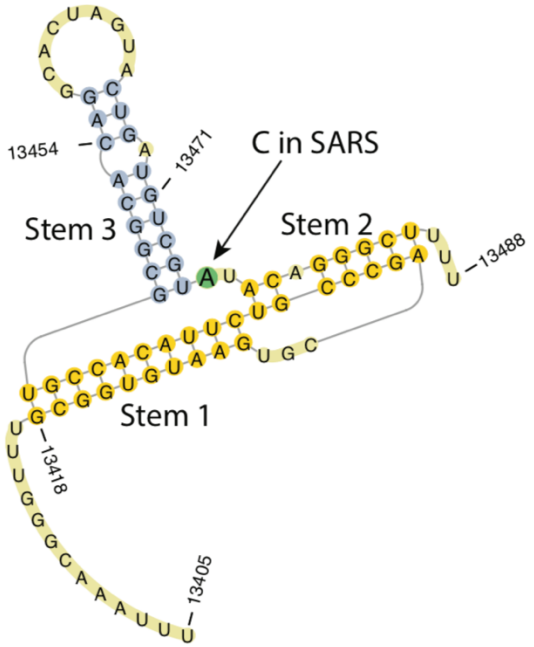
**Homology modeling of spike gene region (~4000 nucleotides)**



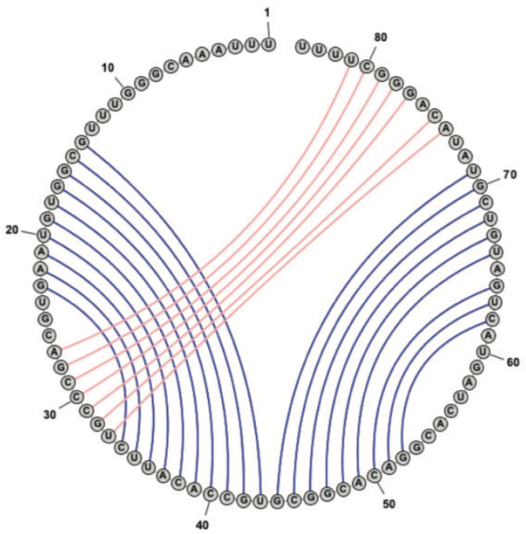

- **COVID-19 RNA is 89% similar to SARS-Cov and 50% similar to MERS-Cov**

# ORF1ab Frame Shifting Pseudoknot

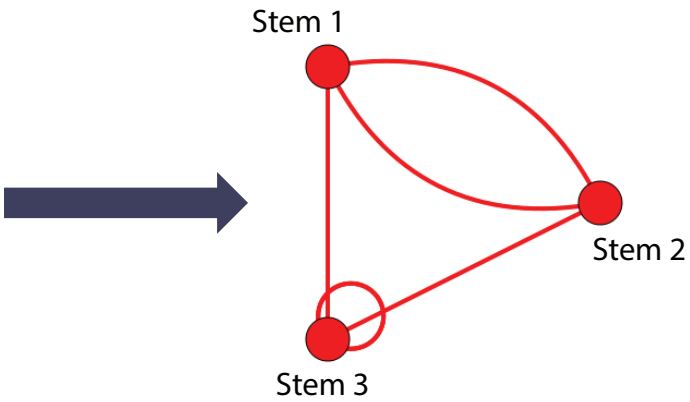
- **Ribosomal frame shifting is a strategy to translate overlapping reading frames—used in HIV, SARS, and others**
- **Frame shifting mechanisms rely on specific fold motifs and associated structural transitions**
- **These regions and/or transitions are potential anti-infective targets**
- **In SARS,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




(A) PKNOTS prediction



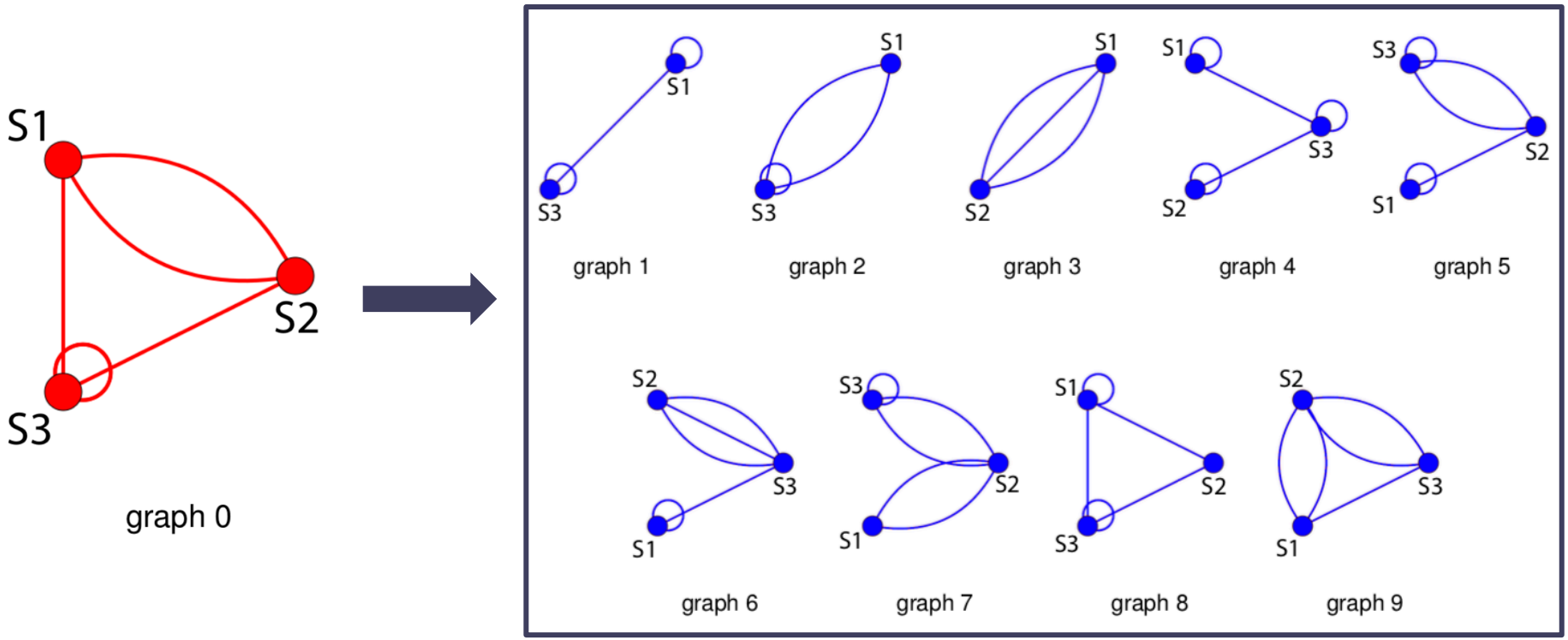
(B) Circular plot




Dual Graph

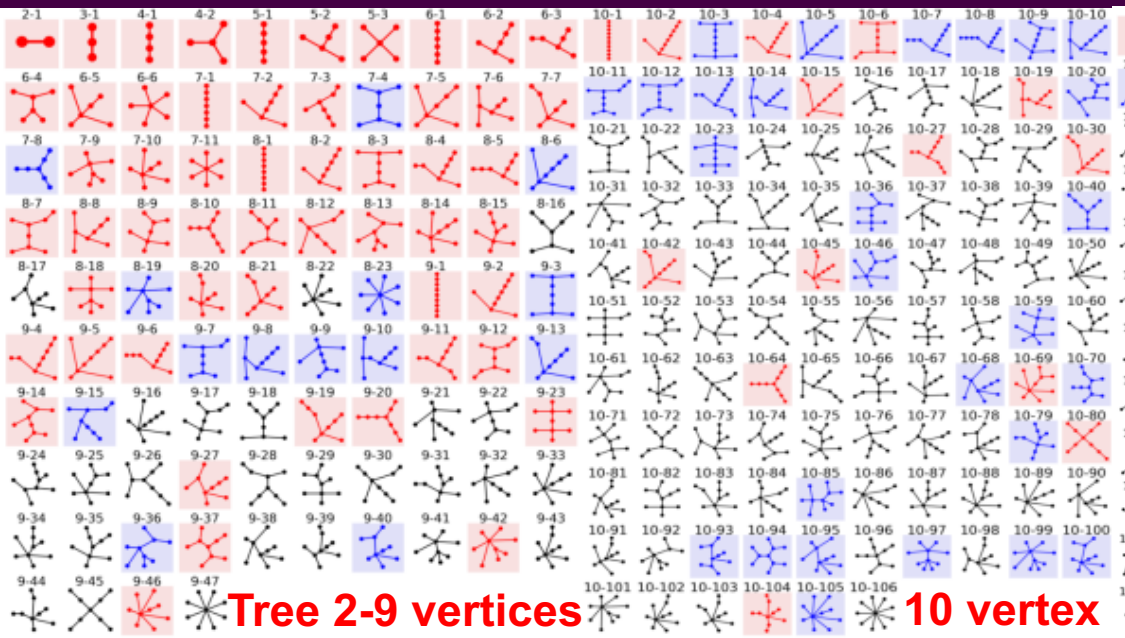
Covid-19 Pseudoknot by homology modeling

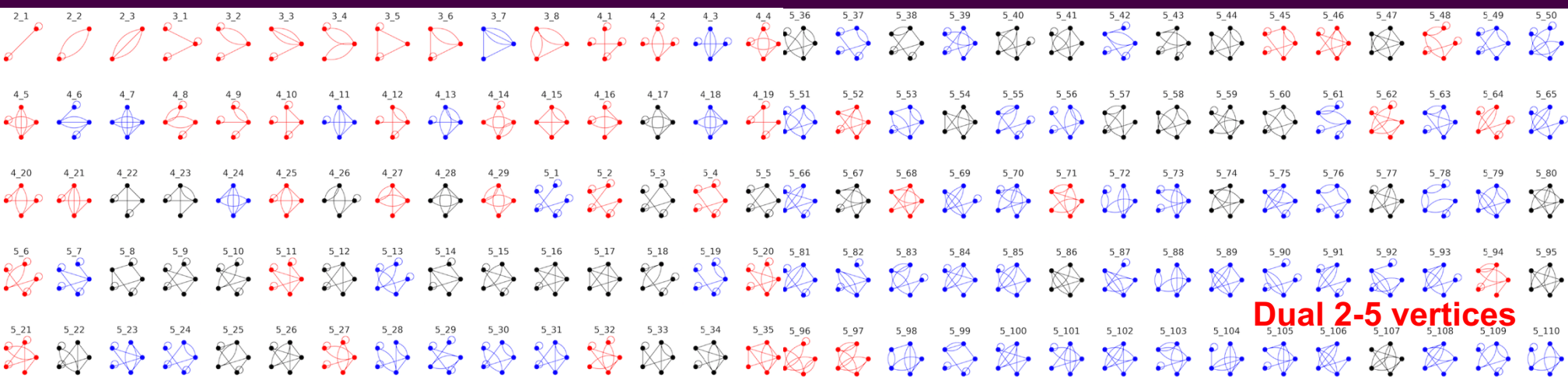
# Destroy This Pseudoknot by Mutations or Drugs

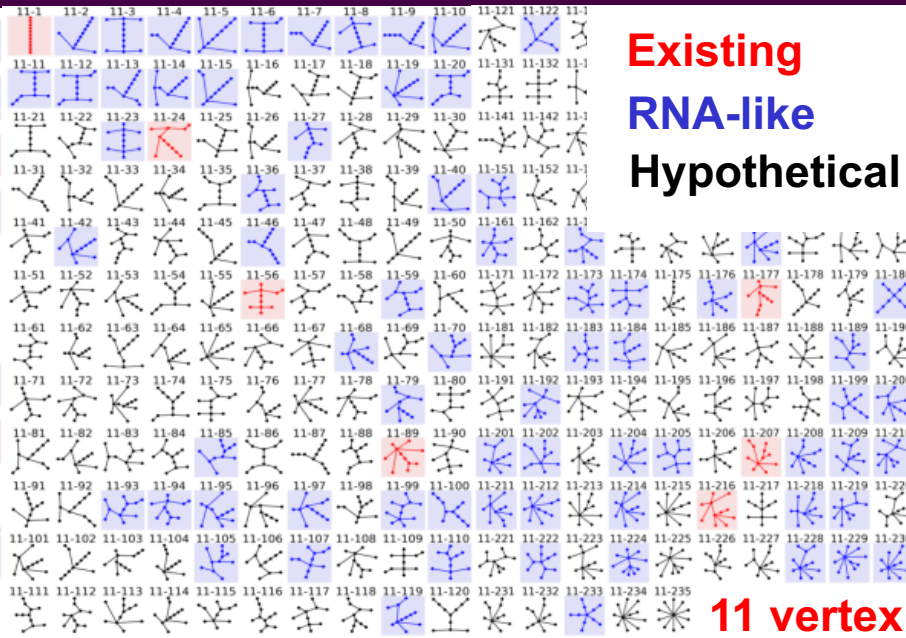



- Use our graph-based genetic algorithm (RAG-IF) to destroy stem and/or pseudoknot
- Identify fragile residues for mutations or drug binding

# Structural Repertoire Available from RAG Analysis



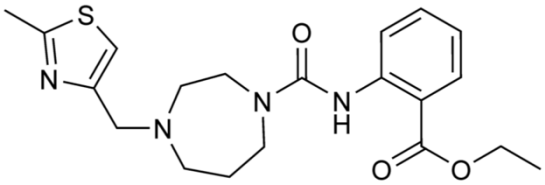



http://www.biomath.nyu.edu/rna

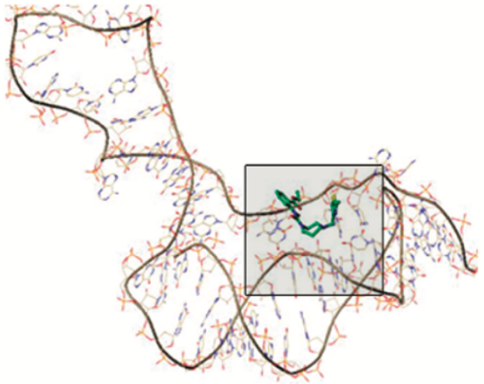
# Drug Exploration: Screen for Compounds to Bind Fragile Mutations

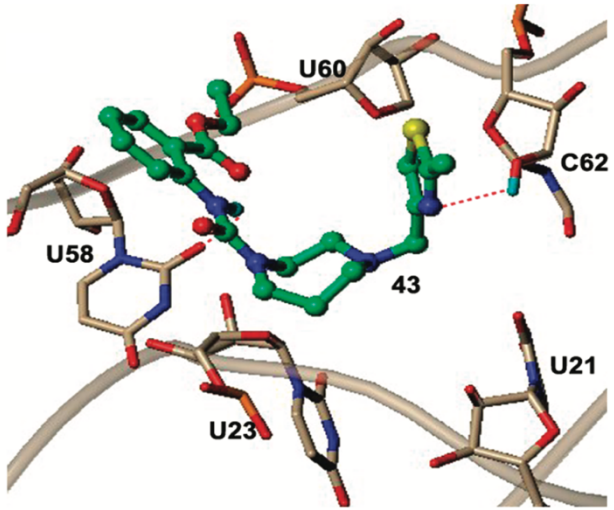
- **SARS drug … already known to inhibit pseudoknot: "1,4-diazepam derivative 10" inhibits translational frame shifting in cell models**

**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)

# Our Team

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