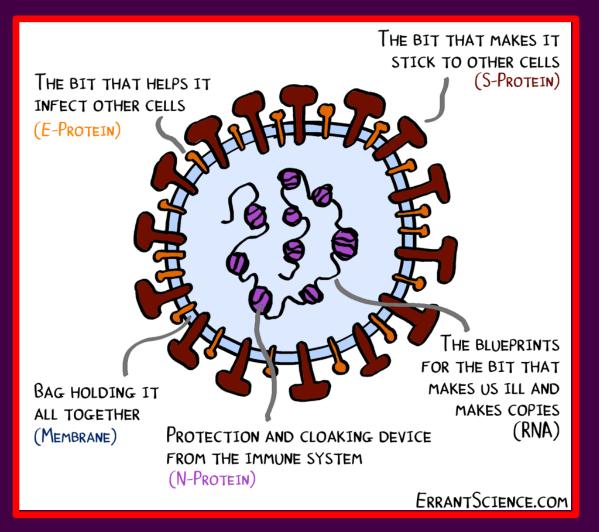
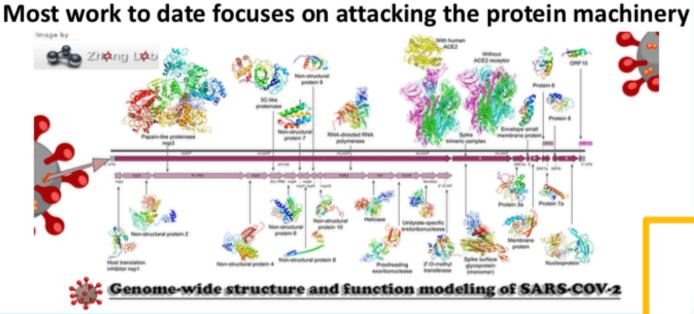
Tamar Schlick's Research Team New York University (Courant/Chemistry) COVID-19 (bad news wrapped inside proteins)

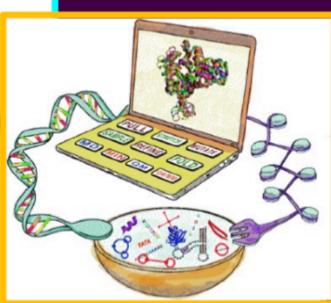


Infectious agent is a single 30,000 nucleotide-long RNA molecule that uses host cell machinery to copy itself and make all the proteins essential to its life cycle and thus rapidly multiply and overtake host organs

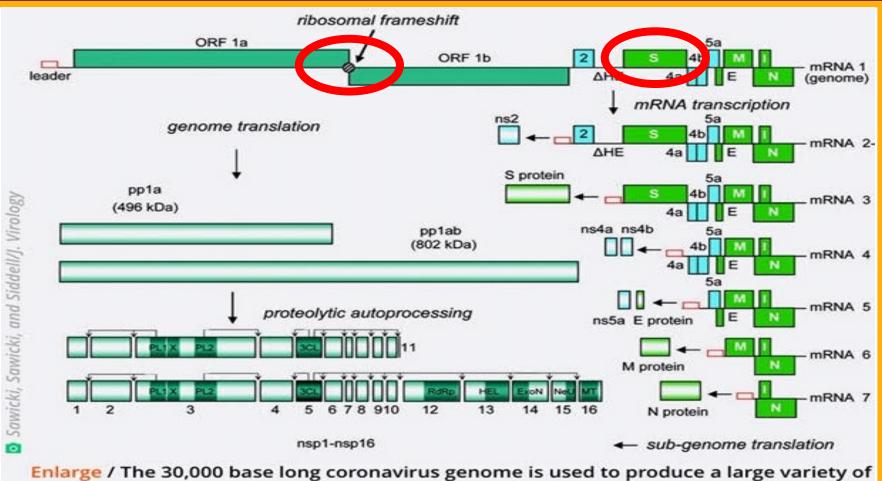
# Exploring COVID-19 RNA Viral Genome Targets by Graph-Theory Based Modeling



- 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



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

**S1** 

(a), (b) 2D+3D Modeling

(homology, various programs,

literature and consensus)

C in SARS

Stem 2

**PKNOTS** Prediction

13454

Stem 3

Stem 1

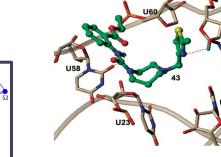
AUUU

(c) Destroy Pseudoknot/Stem 2

52

RAG.IF





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

(d) Drug Binding

**Studies** 

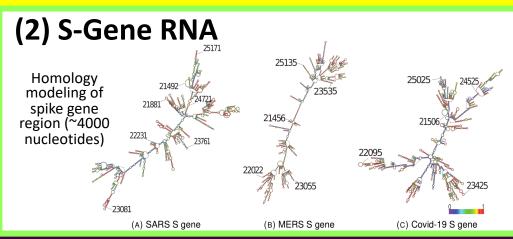
June-July (Steps a,b)

Aug-Sep (Step c)

graph

araph

**Oct-Nov** (Step d)

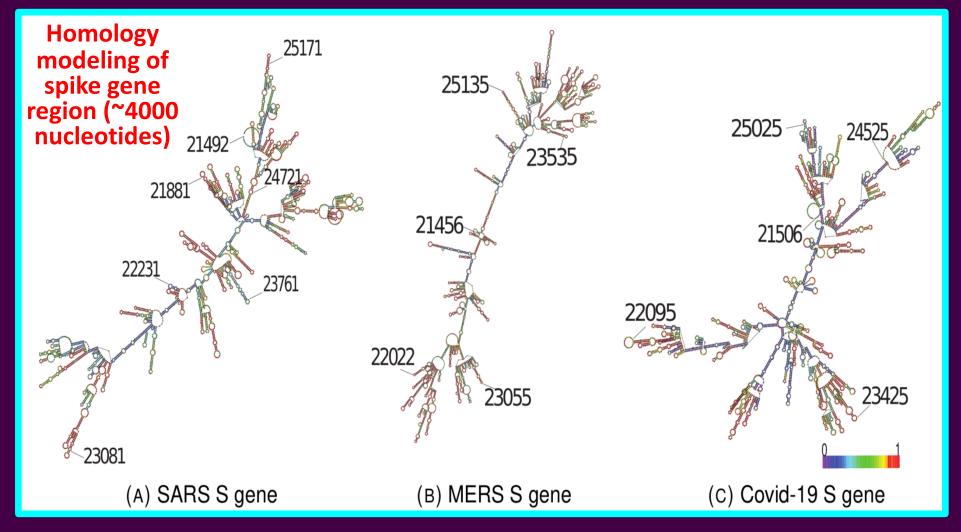


#### Shuting Yan & Lucille Tsao

Qiyao Zhu & Swati Jain

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

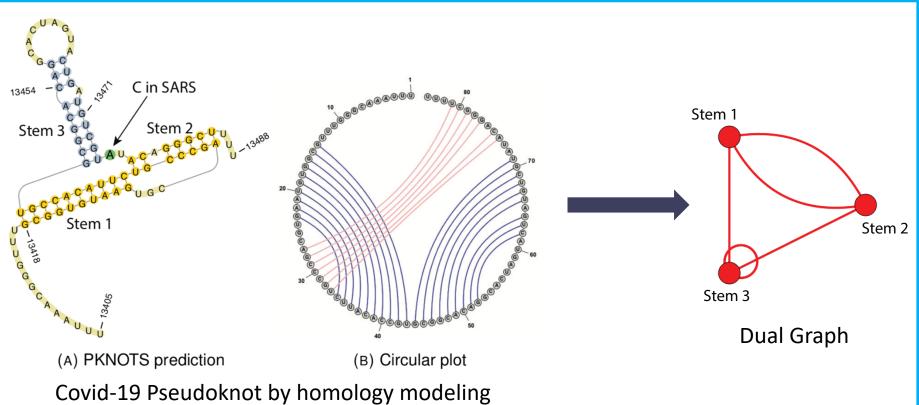
## Preliminary RNA Model of Spike Protein Gene



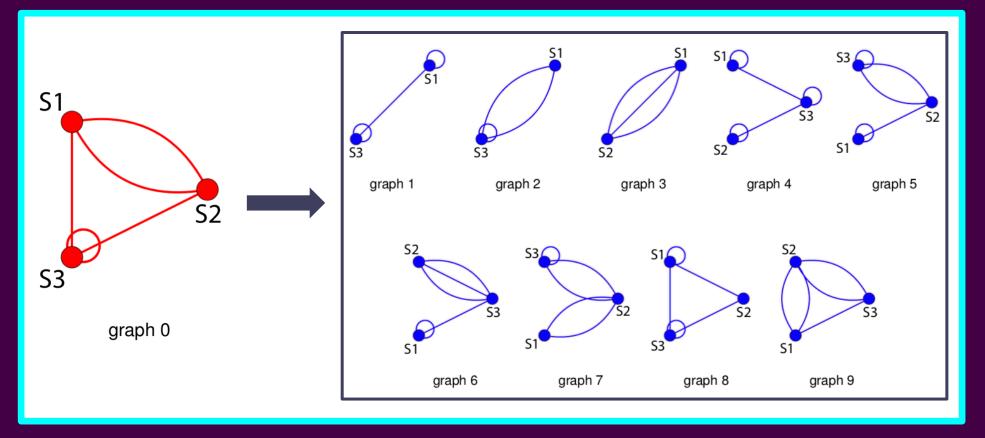
COVID-19 RNA is 89% similar to SARS-Cov and 50% similar to MERS-Cov

# **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



### 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

| 2-1           | 3-1          | 4-1 4-2           | / 5-1  | 5-2       | $\sim$   | 6-1      | 6-2      | 6-3           | 10-1     | 10-2 1    | 0-3 10-4            | 10-5     | 10-6           | 10-7  | 10-8          | 10-9 1        | 10-10   |                | 11-3                          | $\frac{1}{\sqrt{1}}$    | 1-5 11-4           |                     | 11-8          |               | / 7                | $\sim$    | 3                |            |             |           |                         |
|---------------|--------------|-------------------|--------|-----------|----------|----------|----------|---------------|----------|-----------|---------------------|----------|----------------|-------|---------------|---------------|---------|----------------|-------------------------------|-------------------------|--------------------|---------------------|---------------|---------------|--------------------|-----------|------------------|------------|-------------|-----------|-------------------------|
|               | 1            | : -               | V 1    | ×.        | $\sim$   | 1        | $\sim$   | ~             | 10.11    |           |                     |          |                | 10.17 | 10.10         | Y- 1          | N. 10   | 11-11 11-      | 12 11-13                      | 11-14 11                | 1-15 11-1          | 6 11-17             | 11-18         | 11-19 11      | -20 11-13          | 31 11-132 | 11-1             | EXI        | stir        | <b>Ig</b> |                         |
| 6-4           | 6-5          | 6-6 7-1           | 7-2    | 7-3       | 7-4      | 7-5      | 7-6      | 7.7           | 10-11    | 10-12 10  | 10-13               | 4 10-15  | 10-16          |       | 10-18         | 10-19         | 10-20   | TI             | ~~/                           | 6/1                     | 1 4                | $\sim T$            | Y             | 1-1-          | <b>Г</b> +         | . +-      | 4                |            |             |           |                         |
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| 7-8           | 7-9          | 7-10 7-1          | 8-1    | 8-2       | 8-3      | 8-4      | 8-5      | 8-6           | 10-21    | 10-22 10  | 0-23 10-24          | 4 10-25  | 10-26          | 10-27 | 10-28         | 10-29 1       | 10-30   | $T \checkmark$ |                               | Ka                      | エル                 | 1 12                | $\mathcal{X}$ | 木い            | とーシ                | KK.       | ネ                |            |             |           |                         |
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| 0.7           |              | 8.0 8.1           |        | 0.12      | 0.13     | 0.14     | 0.15     | 0.16          | 10-31    | 10-32 10  | -33 10-3            | 4 10-35  | 10-36          | 10-37 | 10-38         | 10-39         | 10-40   | イン             | ィン                            | $\langle \cdot \rangle$ | $\Upsilon \lambda$ | $\cdot \mathcal{X}$ | 士             | とい            | < 7. A             | 4         | ×                | ועיי       | 500         | ICU       | Cai                     |
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| 1             | Y.           | <u>}</u>          | <      | J.        | 4        | $\times$ | ж        | J.            | 10.91    | 10-92 10  | 0-93 10-94          | 4 10-95  | 10-96          | 10-97 | 10-98         | 10-99 1       | 0-100   | 11-101 11-1    | 02 11-103                     | 11-104 11               | -105 11-1          | 06 11-107           | 11-108        | 11-109 11     | 110 11-22          | 21 11-222 | 11-223 11-       | 224 11-225 | 11-226 11-2 | 27 11-228 | 11-229 11-23            |
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#### 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 SARSpseudoknot
- 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**

