COVID-19 and SARS-COV-2 Research Update

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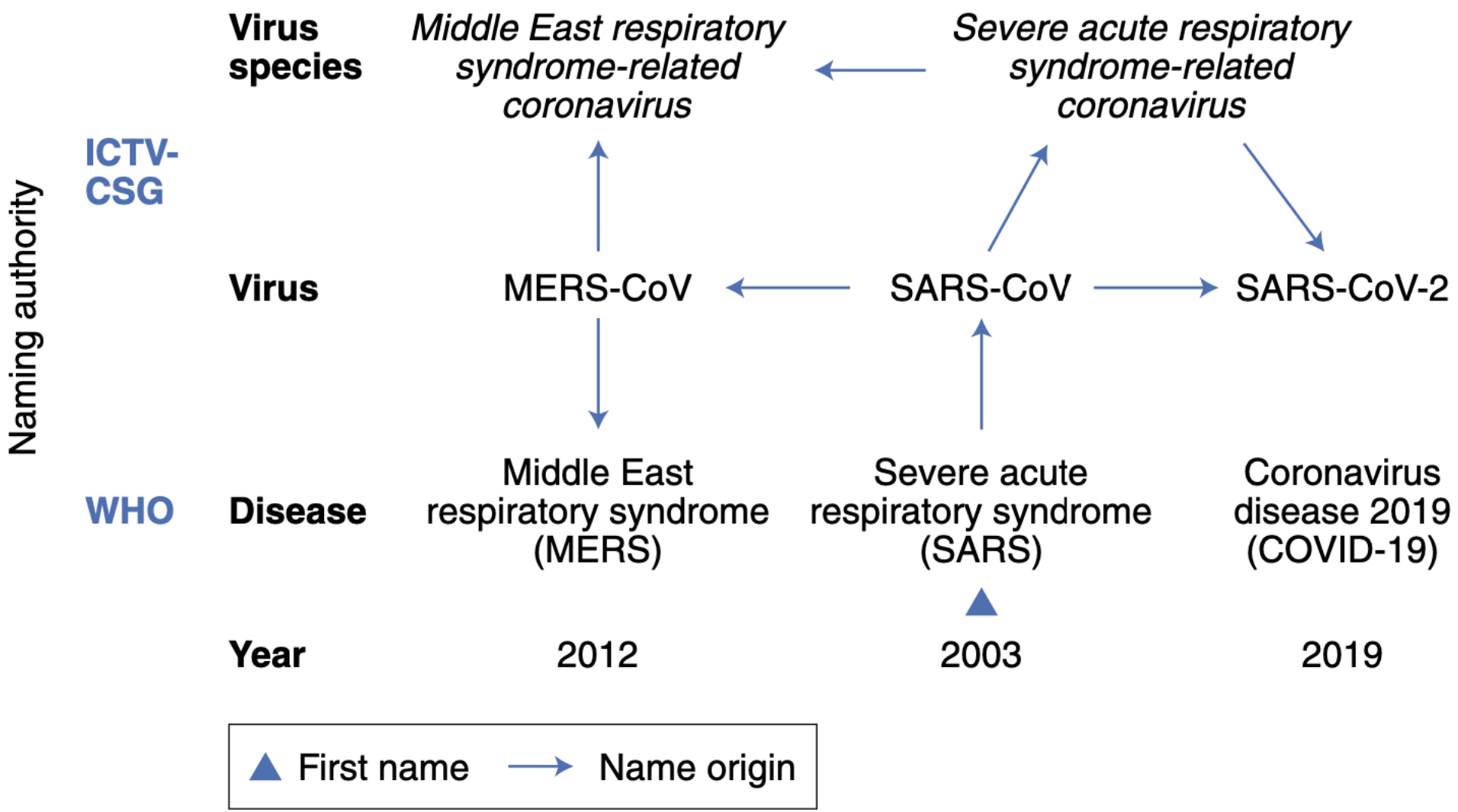
Logan Ward, Anna Woodward, Shantenu Jha, Kerstin Van Dam, Frank Alexander, Misha Salim,
Matteo Turilli, Andre Merzky, Mike Papka, Katherine Riley, Venkat Vishwanath, Carlos Simmerling,
Hubertus Van Dam, Gina Tourassi, Dan Stanzione, Mike Norman, and many others > 200

In 2003

The emergence of SARS and the identification of a coronavirus as the causative agent of the disease astounded the coronavirus community, as it was the first definitive association of a coronavirus with a severe disease in humans.


Naming authority
ICTV-CSG
WHO
Virus species
Virus
Disease
Year
Middle East respiratory syndrome-related coronavirus
Severe acute respiratory syndrome-related coronavirus
MERS-CoV
SARS-CoV
SARS-CoV-2
Middle East respiratory syndrome (MERS)
Severe acute respiratory syndrome (SARS)
Coronavirus disease 2019 (COVID-19)
2012
2003
2019
First name
Name origin

March 9th 2020

COVID-19 CORONAVIRUS OUTBREAK

Last updated: March 09, 2020, 15:01 GMT

https://www.worldometers.info/coronavirus/

Cases - Deaths - Countries - Death Rate - Incubation - Age - Symptoms - Opinions - News

Coronavirus Cases:

111,746

view by country

Deaths:

3,888

Recovered:

62,722

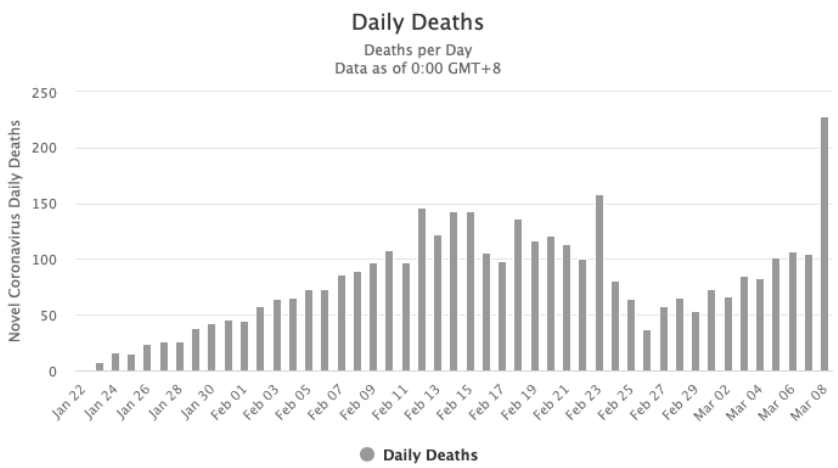
PRE-EXISTING CONDITION	DEATH RATE confirmed cases	DEATH RATE all cases
Cardiovascular disease	**13.2%**	**10.5%**
Diabetes	**9.2%**	**7.3%**
Chronic respiratory disease	**8.0%**	**6.3%**
Hypertension	**8.4%**	**6.0%**
Cancer	**7.6%**	**5.6%**
no pre-existing conditions		**0.9%**

COVID-19 Fatality Rate by AGE:

***Death Rate** = (number of deaths / number of cases) = **probability of dying if infected by the virus** (%). This probability differs depending on the age group. The percentages shown below **do not have to add up to 100%**, as they **do NOT represent share of deaths by age** group. Rather, it represents, for a person in a given age group, the **risk of dying** if infected with COVID-19.

AGE	DEATH RATE confirmed cases	DEATH RATE all cases
80+ years old	**21.9%**	**14.8%**
70-79 years old		**8.0%**
60-69 years old		**3.6%**
50-59 years old		**1.3%**
40-49 years old		**0.4%**
30-39 years old		**0.2%**
20-29 years old		**0.2%**
10-19 years old		**0.2%**
0-9 years old		**no fatalities**

Daily Deaths



April 24th, 2020

COVID-19 CORONAVIRUS PANDEMIC

Last updated: April 24, 2020, 10:32 GMT

Graphs - Countries - Death Rate - Symptoms - Incubation - Transmission - News

Coronavirus Cases:

2,744,606

view by country

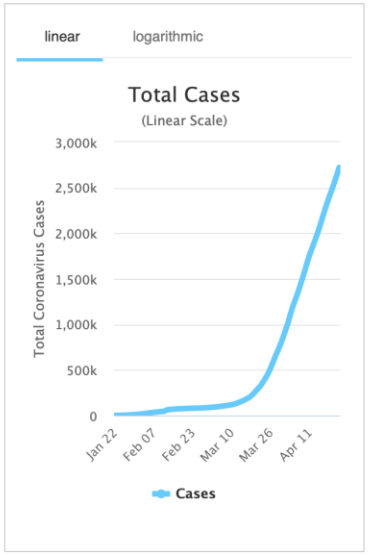
Deaths:

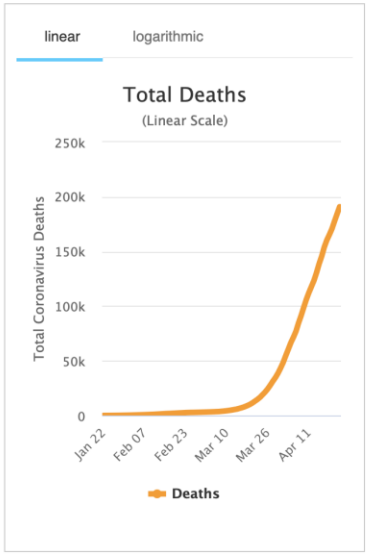
191,790

Recovered:

755,390

ACTIVE CASES	CLOSED CASES
1,797,426 Currently Infected Patients	**947,180** Cases which had an outcome:
1,738,733 (97%) in Mild Condition	755,390 (80%) Recovered / Discharged
58,693 (3%) Serious or Critical	191,790 (20%) Deaths
Show Graph	Show Graph





All | Europe | North America | Asia | South

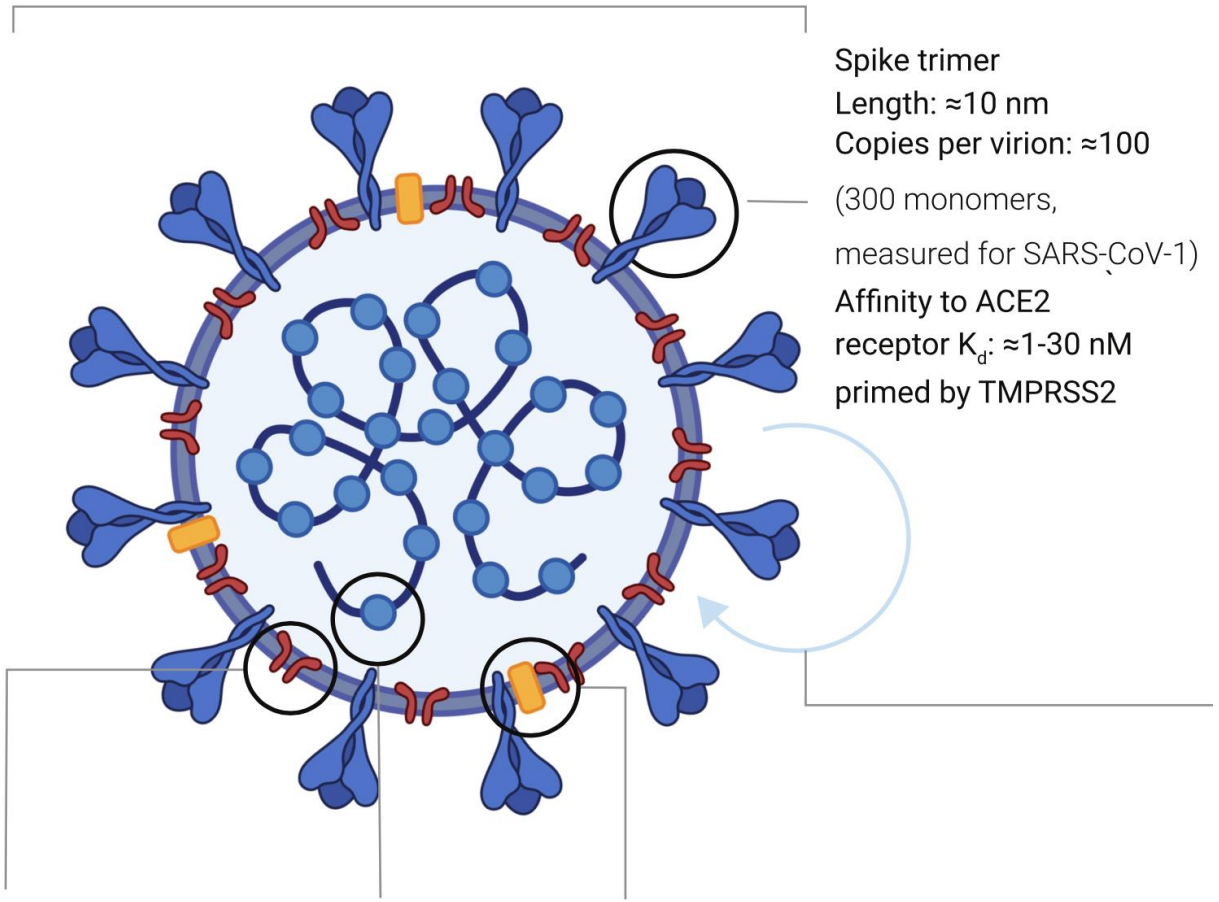
Country, Other	Total Cases	New Cases	Total Deaths
World	2,744,606	+21,562	191,790
USA	886,709	+267	50,243
Spain	219,764	+6,740	22,524
Italy	189,973		25,549
France	158,183		21,856
Germany	153,215	+86	5,575
UK	138,078		18,738
Turkey	101,790		2,491
Iran	87,026		5,481
China	82,804	+6	4,632
Russia	68,622	+5,849	615
Brazil	50,036	+544	3,331
Belgium	44,293	+1,496	6,679

Understanding the Enemy

eLife
published in eLife, March 31st, 2020
https://elifesciences.org/articles/57309

Size & Content

Diameter: ≈100 nm
Volume: ~10^6 nm^3 = 10^{-3} fL
Mass: ~10^3 MDa ≈ 1 fg



eLife
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Replication Timescales

in tissue-culture

Virion entry into cell: ~10 min (measured for SARS-CoV-1)

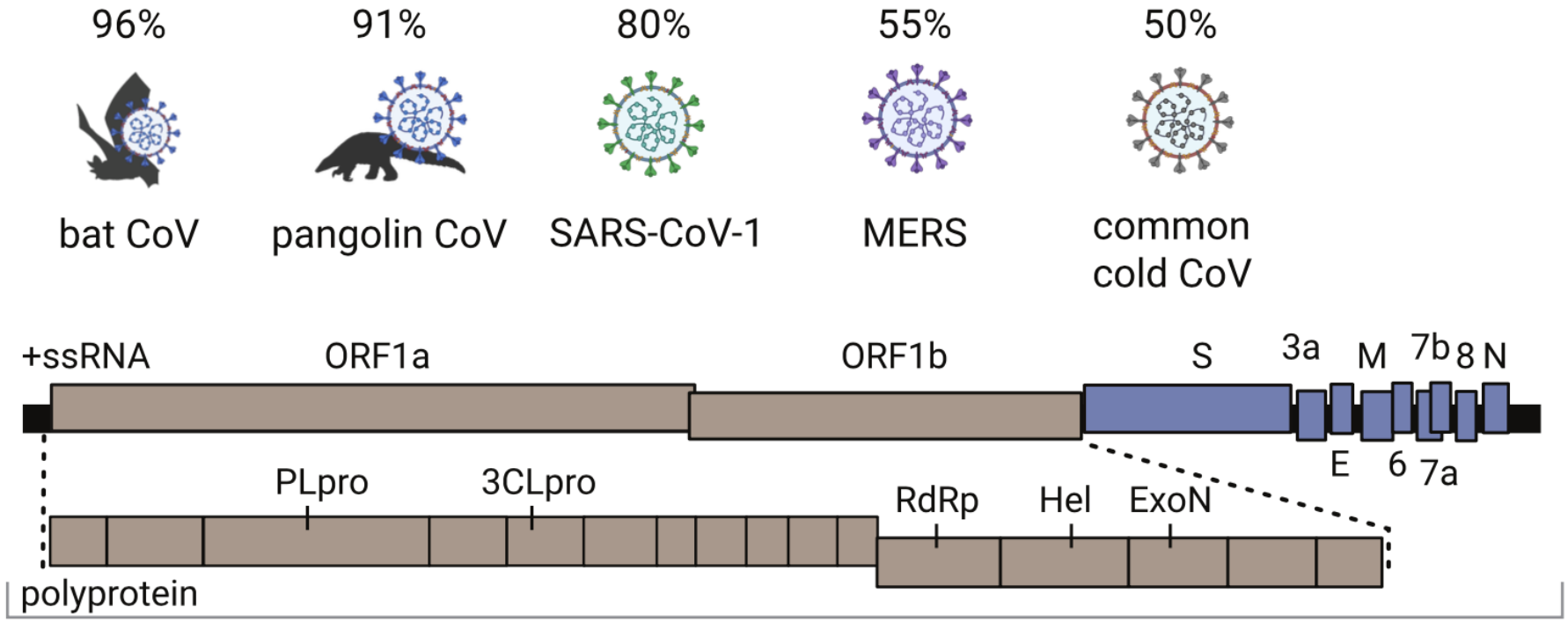
Eclipse period: ~10 hrs (time to make intracellular virions)

Burst size: ~10^3 virions (measured for MHV coronavirus)

Genome

published in eLife, March 31st, 2020
https://elifesciences.org/articles/57309

Nucleotide identity to SARS-CoV-2

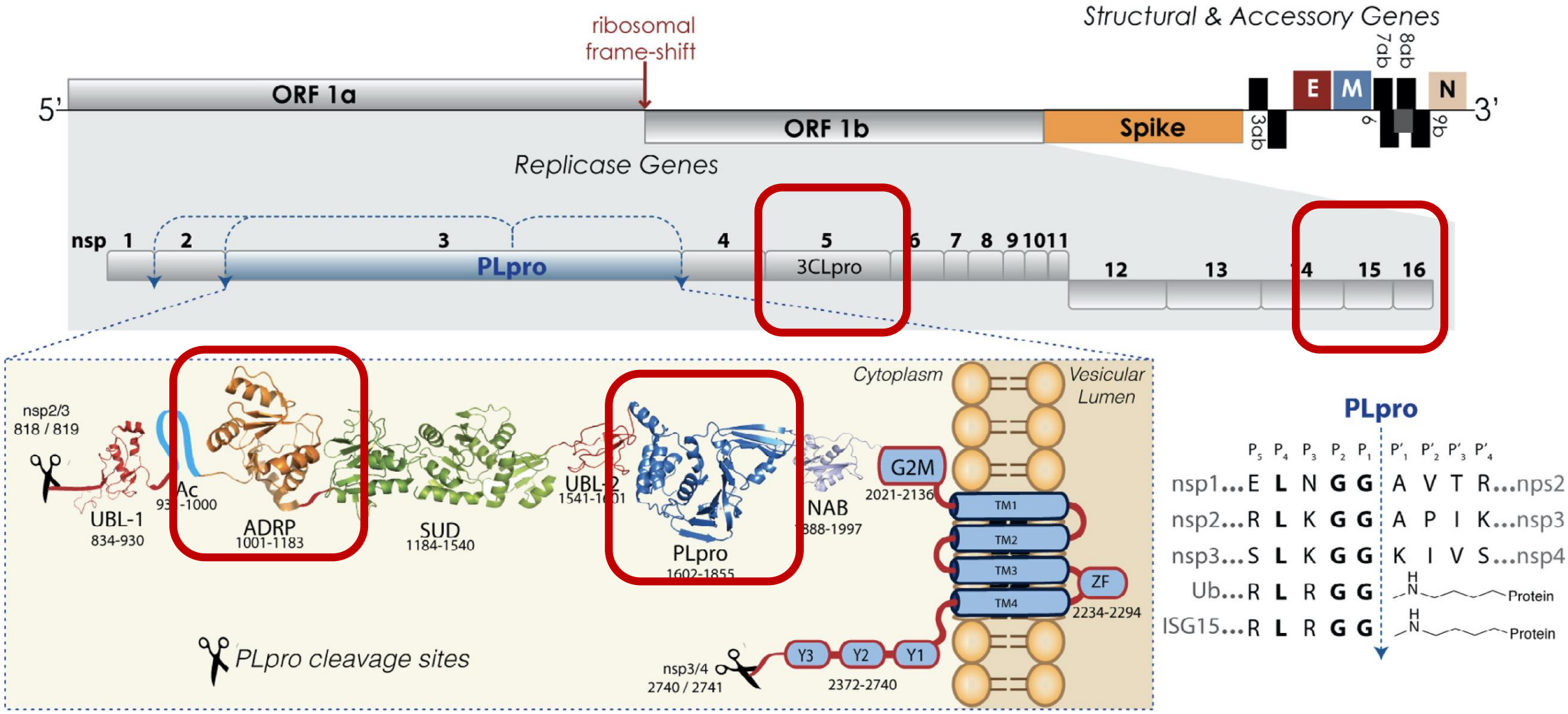


Length: ≈30kb; β-coronavirus with 10-14 ORFs (24-27 proteins)

Evolution rate: ~10^{-3} nt^{-1} yr^{-1} (measured for SARS-CoV-1)

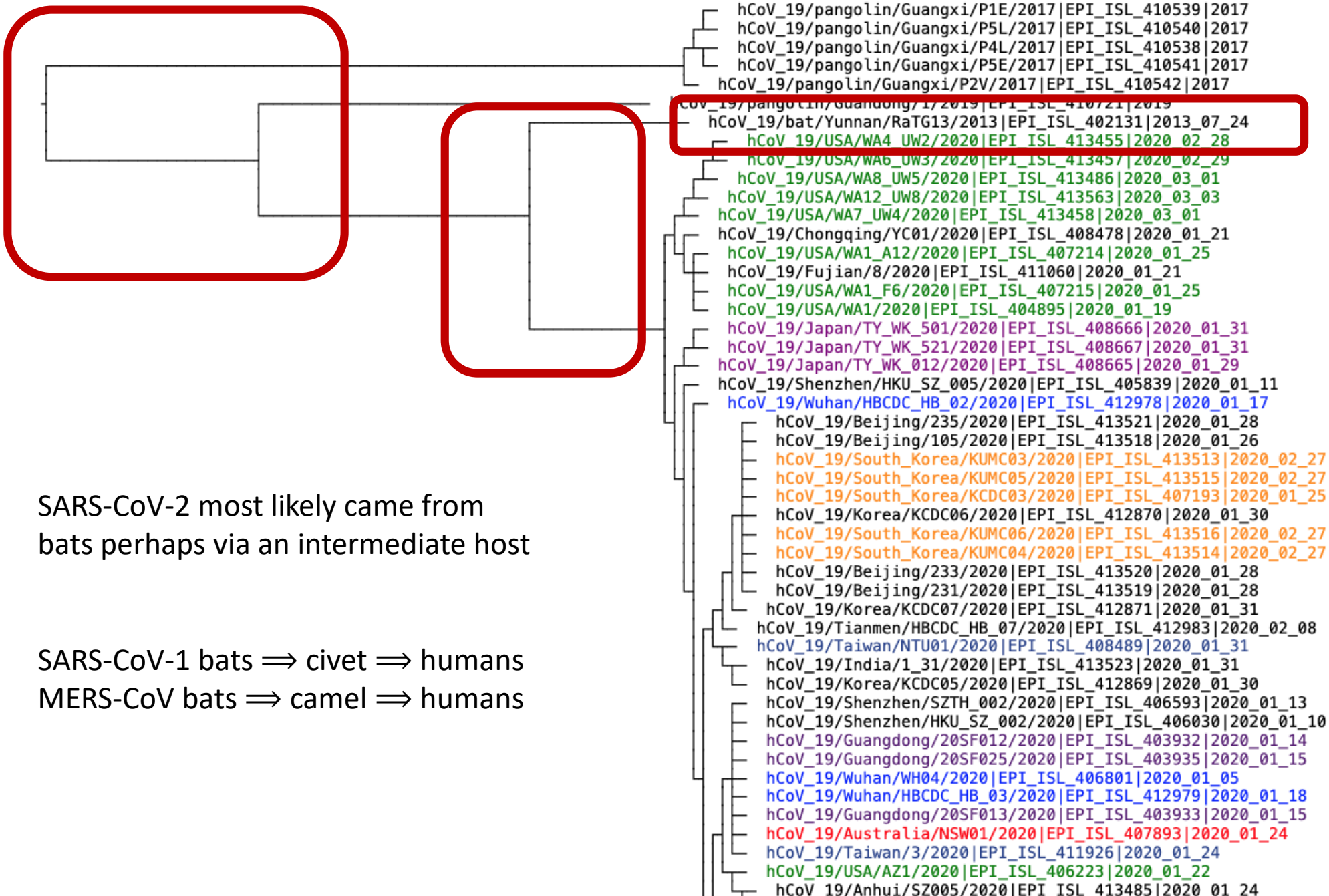
Mutation rate: ~10^{-6} nt^{-1} $cycle^{-1}$ (measured for MHV coronavirus)

Polyproteins encode many domains per gene



Antiviral Res. 2015 Mar; 115: 21–38.

Published online 2014 Dec 29. doi: 10.1016/j.antiviral.2014.12.015



SARS-CoV-2 most likely came from bats perhaps via an intermediate host

SARS-CoV-1 bats ⟹ civet ⟹ humans
MERS-CoV bats ⟹ camel ⟹ humans

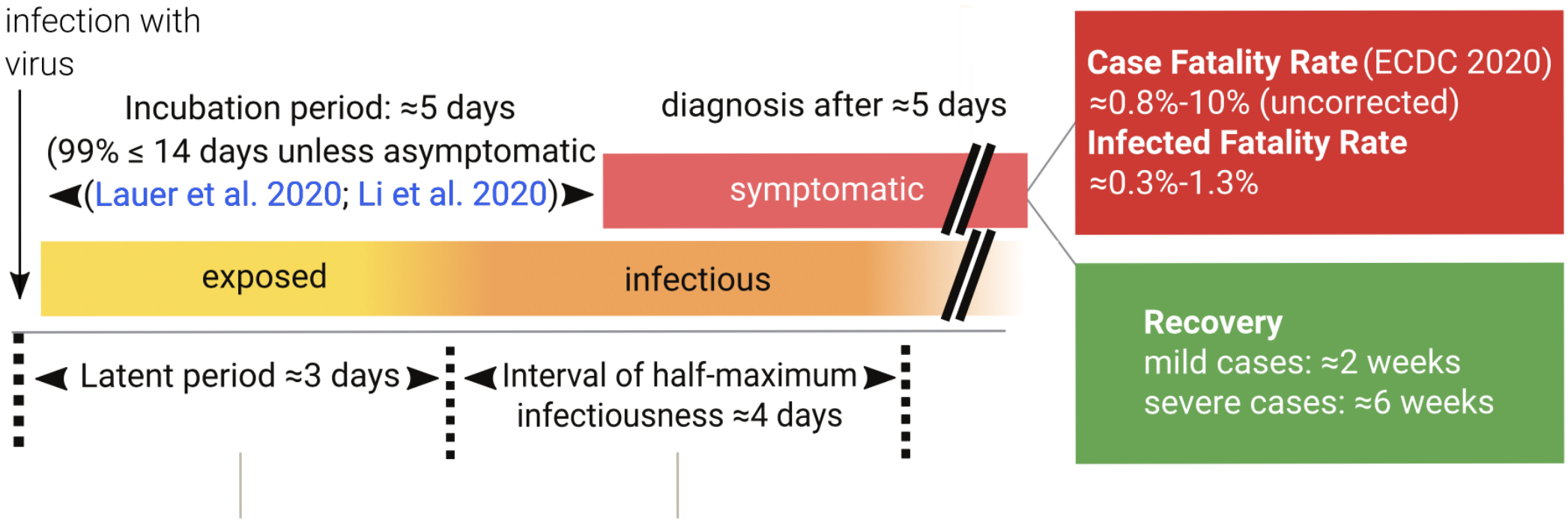
"Characteristic" Infection Progression in a Single Patient

published in eLife, March 31st, 2020
https://elifesciences.org/articles/57309

Basic reproductive number R_0: typically 2-4

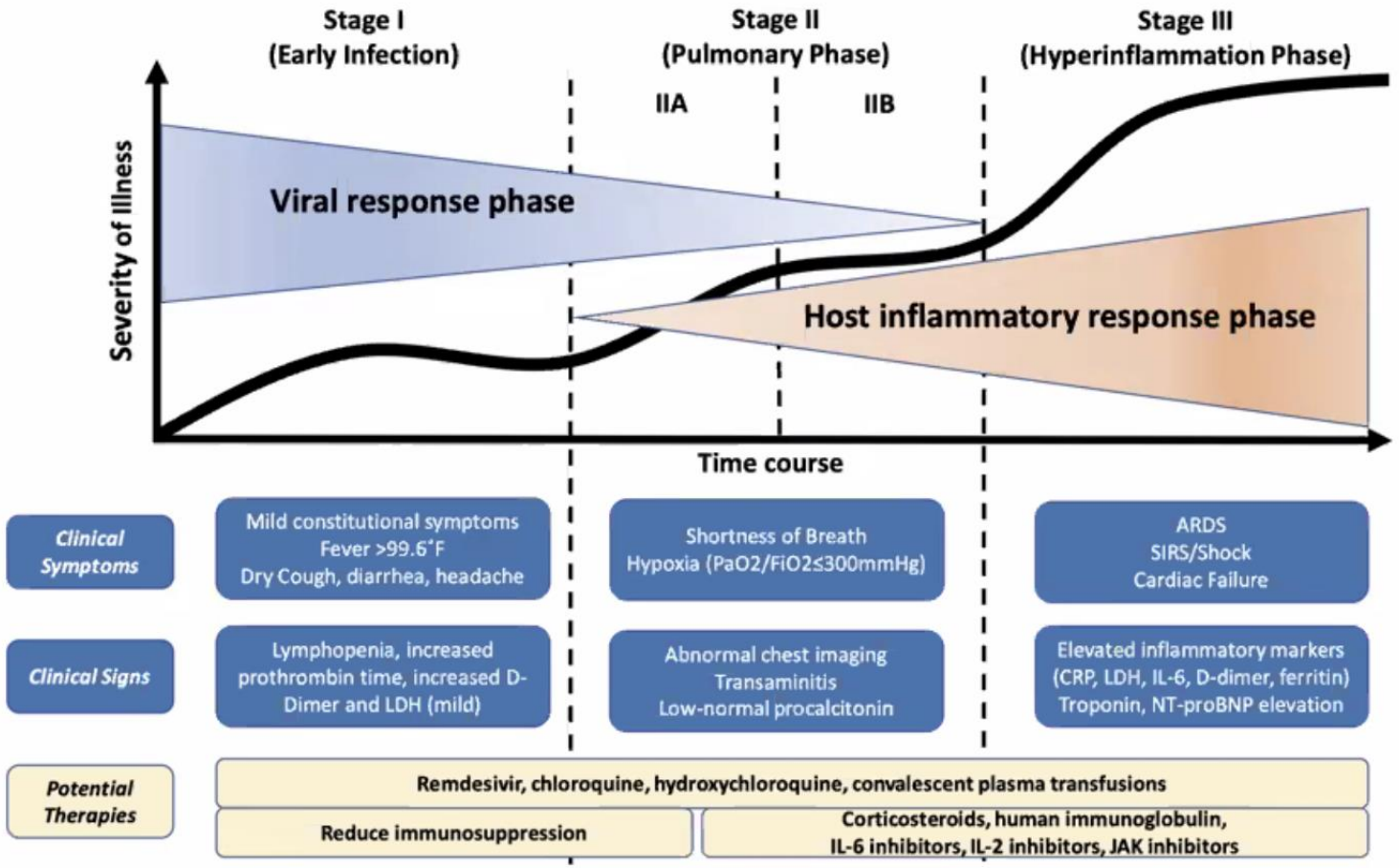
Varies further across space and time (Li et al. 2020; Park et al. 2020)

(number of new cases directly generated from a single case)



Inter-individual variability is substantial and not well characterized. The estimates are parameter fits for population median in China and do not describe this variability (Li et al. 2020; He et al. 2020).

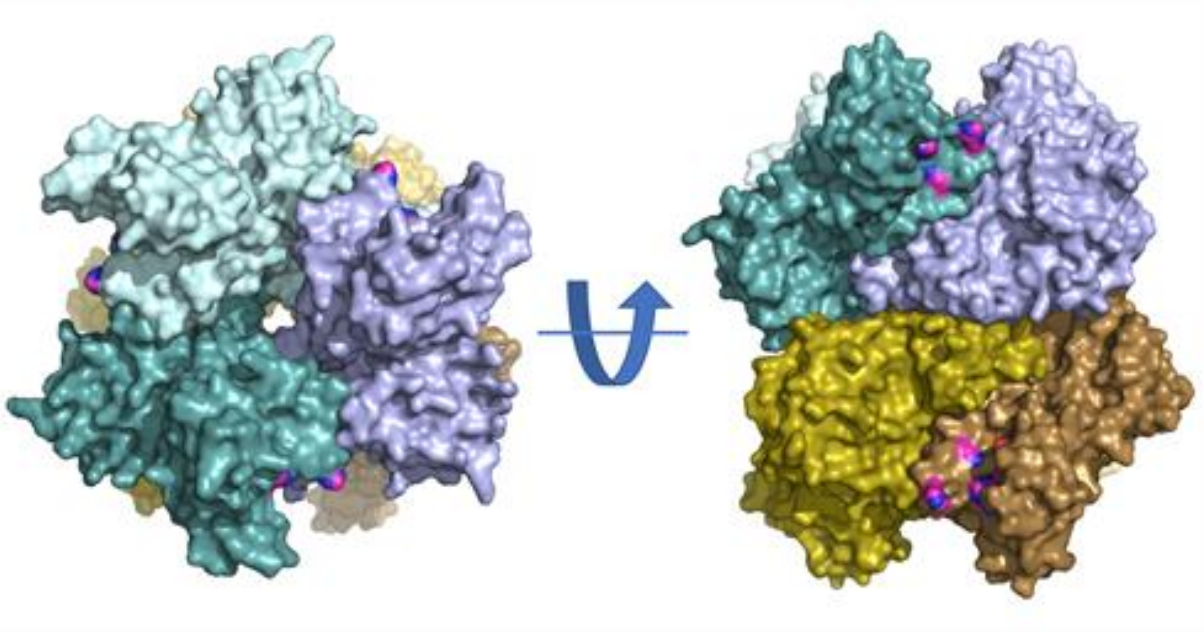
Kinetics of infection and clinical deterioration suggest that pathology is from immune over-stimulation



- Which immune parameters correlate with disease severity?
  - Serum cytokines (IL-6, IL-1β, others)
  - Antibody response
  - T cell response
- Why do some patients develop severe disease and some not?
  - Germline genetics
  - Airway microbiota
  - Pre-existing cross-reactive immunity

Research effort on COVID-19/SARS-COV-2

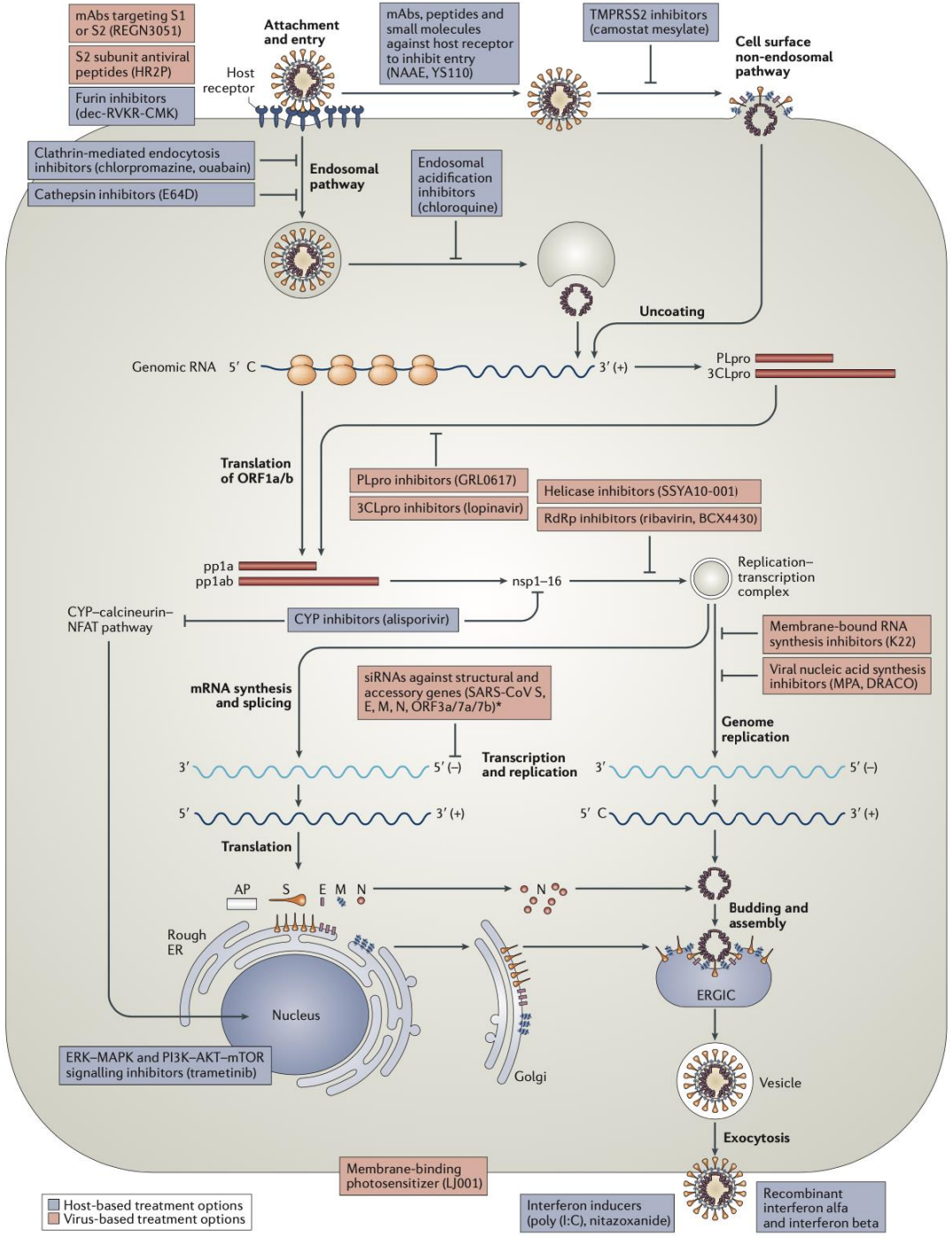
- Work at the APS and SBC to solve structures and screening small molecules (nsp15), 3CLpro, PLpro, etc.
- Participation in the NVBTL working groups (EPI, Testing, Manufacturing, Therapeutics)



- Computational work on five subproblems
  - **Antiviral drug screening ⟹ priority compounds for wet lab screening**
  - **Epidemiology ⟹ transmission and interventions**
  - **Evolution ⟹ origins, diversity and host-adaptation**
  - Vaccine ⟹ epitope analysis and antibody design
  - Host-pathogen interactions / host response ⟹ severity and drugs

Antiviral Drug Screening

Protein	Mol. weight (kDa)	Seq. similarity with SARS-CoV	Description
Nsp1	19.8	91.1%	Suppresses host antiviral response
Nsp2	70.5	82.9%	
Nsp3	217.3	86.5%	Nsp3-Nsp4-Nsp6 complex involved in viral replication
Nsp4	56.2	90.8%	Nsp3-Nsp4-Nsp6 complex involved in viral replication
Nsp5	33.8	98.7%	Main protease (3C-like)
Nsp6	33.0	94.8%	Nsp3-Nsp4-Nsp6 complex involved in viral replication
Nsp7	9.2	100.0%	Nsp7-Nsp8 complex is part of RNA polymerase
Nsp8	21.9	99.0%	Nsp7-Nsp8 complex is part of RNA polymerase
Nsp9	12.4	98.2%	ssRNA binding
Nsp10	14.8	99.3%	Essential for Nsp16 methyltransferase activity
Nsp11	1.3	92.3%	Short peptide
Nsp12	106.7	98.3%	RNA polymerase
Nsp13	66.9	100.0%	Helicase/triphosphatase
Nsp14	59.8	98.7%	3′–5′ exonuclease
Nsp15	38.8	95.7%	Uridine-specific endoribonuclease
Nsp16	33.3	98.0%	RNA-cap methyltransferase
S	141.2	87.0%	Spike protein, mediates binding to ACE2
Orf3a	31.1	85.1%	Activates the NLRP3 inflammasome
Orf3b	6.5	9.5%	
E	8.4	96.1%	Envelope protein, involved in virus morphogenesis and assembly
M	25.1	96.4%	Membrane glycoprotein, predominant component of the envelope
Orf6	7.3	85.7%	Type I IFN antagonist
Orf7a	13.7	90.2%	Virus-induced apoptosis
Orf7b	5.2	84.1%	
Orf8	13.8	45.3%	
N	45.6	94.3%	Nucleocapsid phosphoprotein, binds to RNA genome
Orf9b	10.8	84.7%	Type I IFN antagonist
Orf9c	8.0	78.1%	
Orf10	4.4	-	



Nature Reviews Drug Discovery **15**, 327–347(2016)

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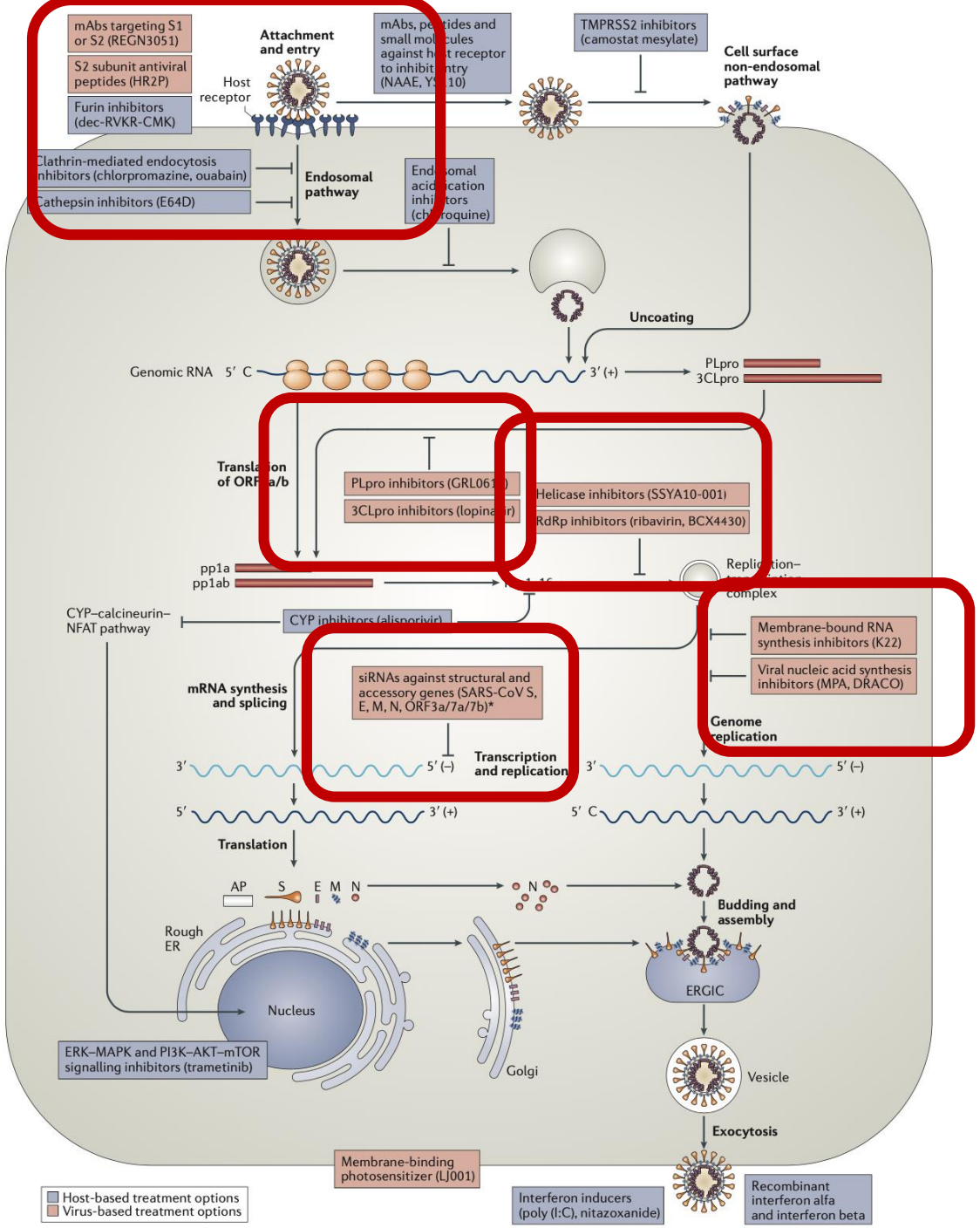
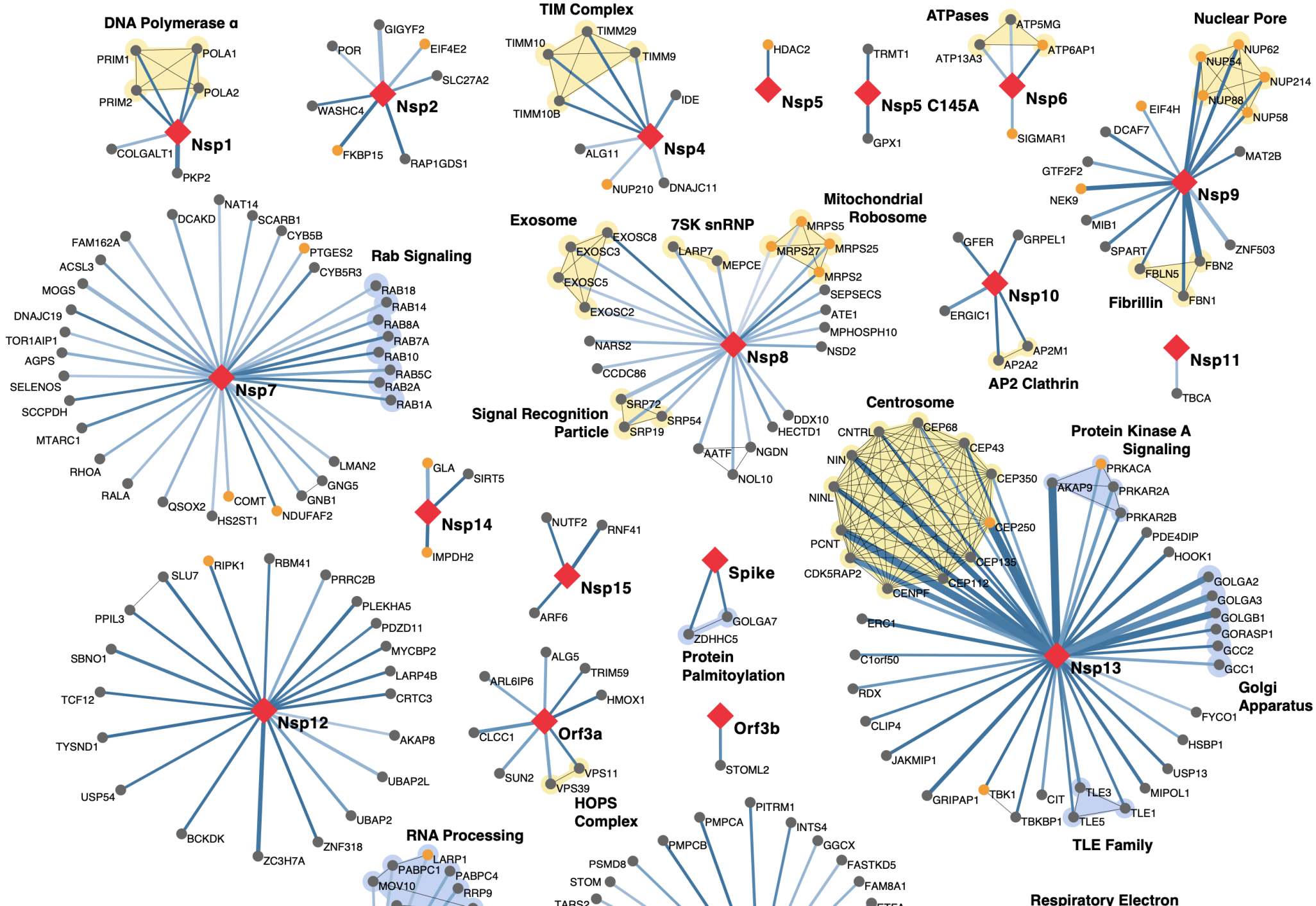


https://www.biorxiv.org/content/10.1101/2020.03.22.002386v1.full.pdf



Structures exist for most of the proteome

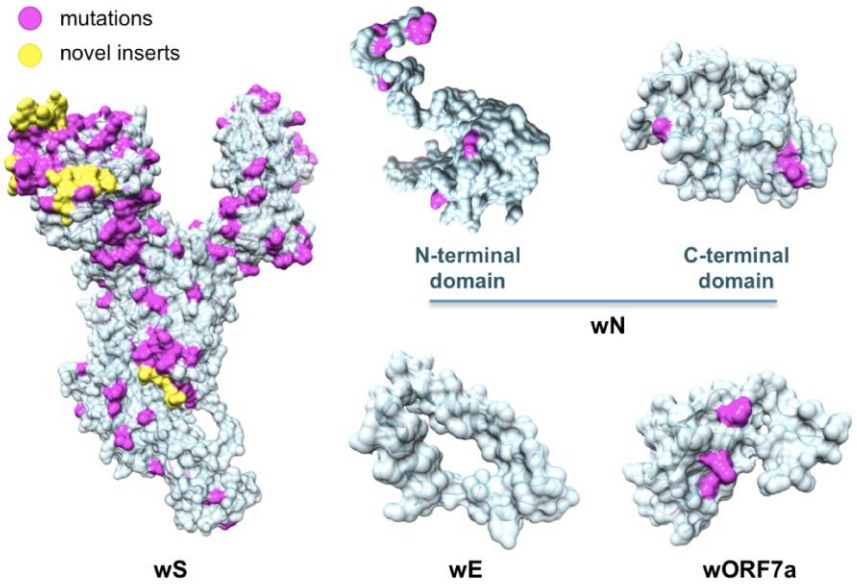


Figure 3. Structurally characterized structural proteins and an ORF of 2019-nCoV. Highlighted in pink are mutations found when aligning the proteins against their homologs from the closest related coronaviruses: 2019-nCoV and human SARS, bat coronavirus, and another bat betacoronavirus BtRf-BetaCoV. Highlighted in yellow are novel protein inserts found in wS.

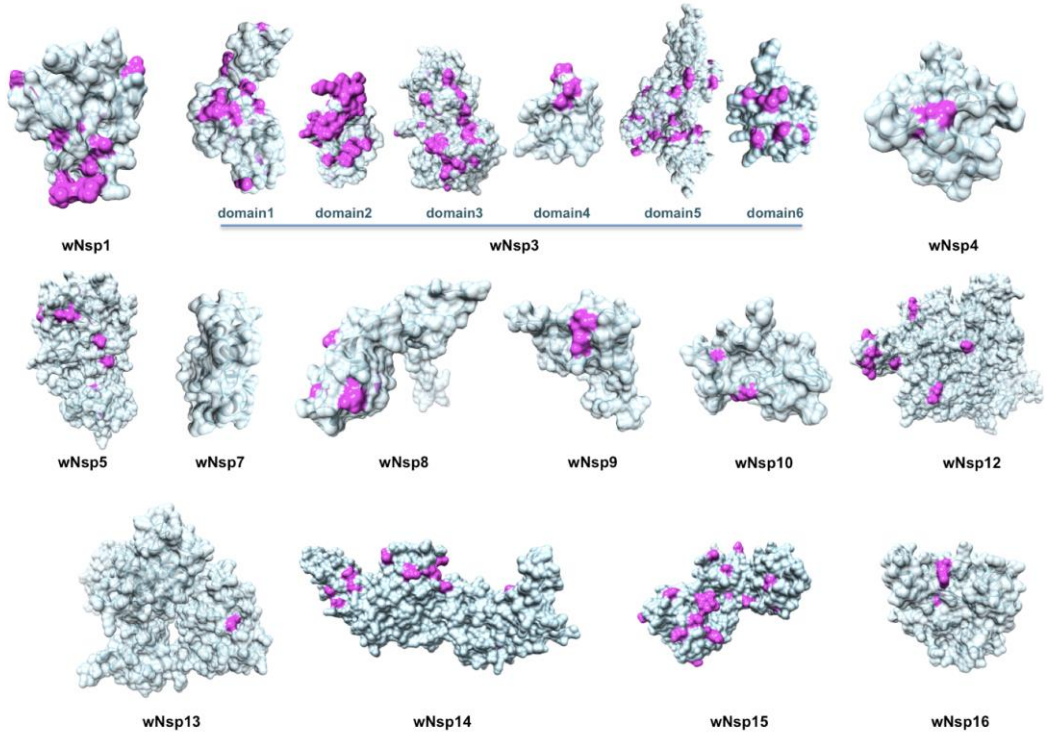
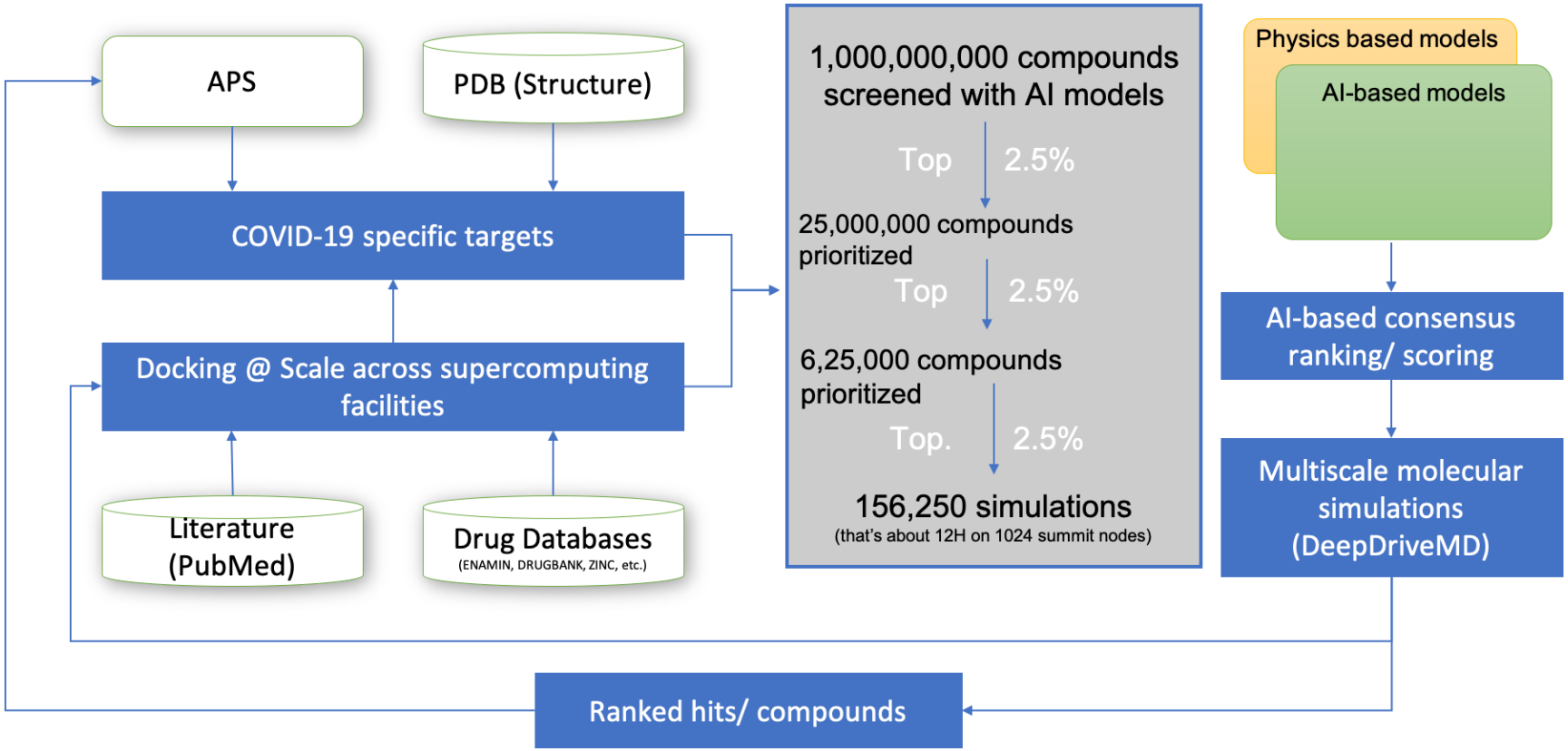


Figure 2. Structurally characterized non-structural proteins of 2019-nCoV. Highlighted in pink are mutations found when aligning the proteins against their homologs from the closest related coronaviruses: 2019-nCoV and human SARS, bat coronavirus, and another bat betacoronavirus BtRf-BetaCoV. The structurally resolved part of wNsp7 is sequentially identical to its homolog.

Viruses **2020**, *12*(4), 360; **https://doi.org/10.3390/v12040360**

HPC/AI is helping discover novel small molecules that can inhibit various virus proteins



- ML/AI approaches are enabling the identification of potential leads that can bind to 8 viral protein targets
- DeepDriveMD helps identify conformational states that bind to specific ligands
- Identified over 30 lead molecules that have been submitted to various open forums for experimental validation
- Collaborations with University of Chicago, Brookhaven National Lab, Frederick National Laboratory and the University of Michigan

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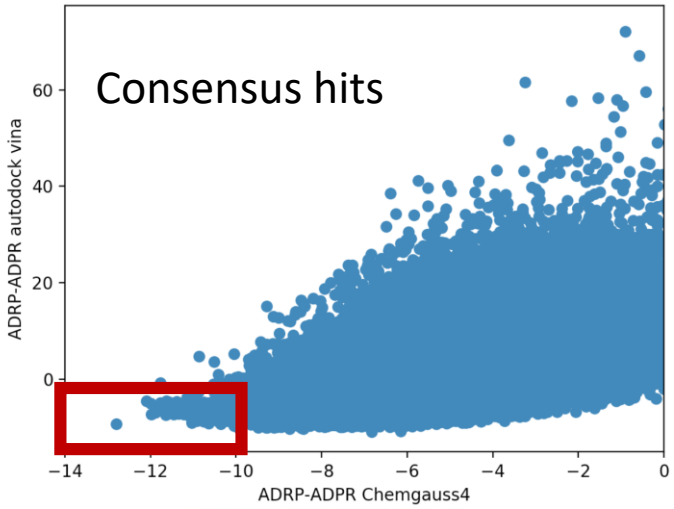
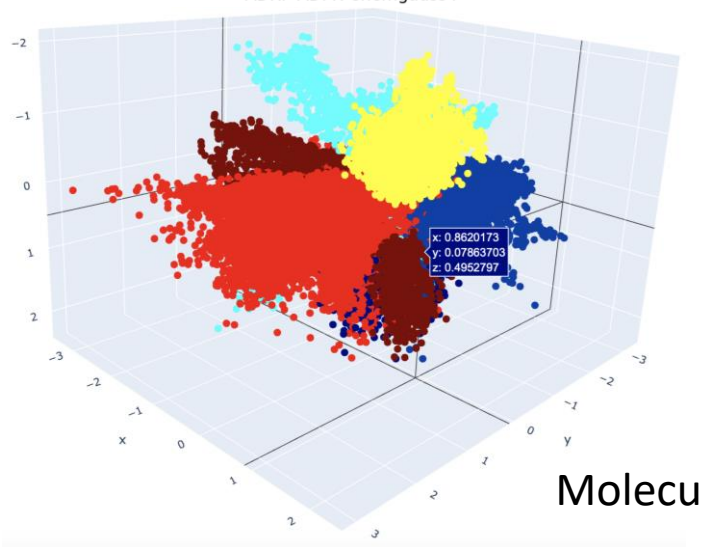
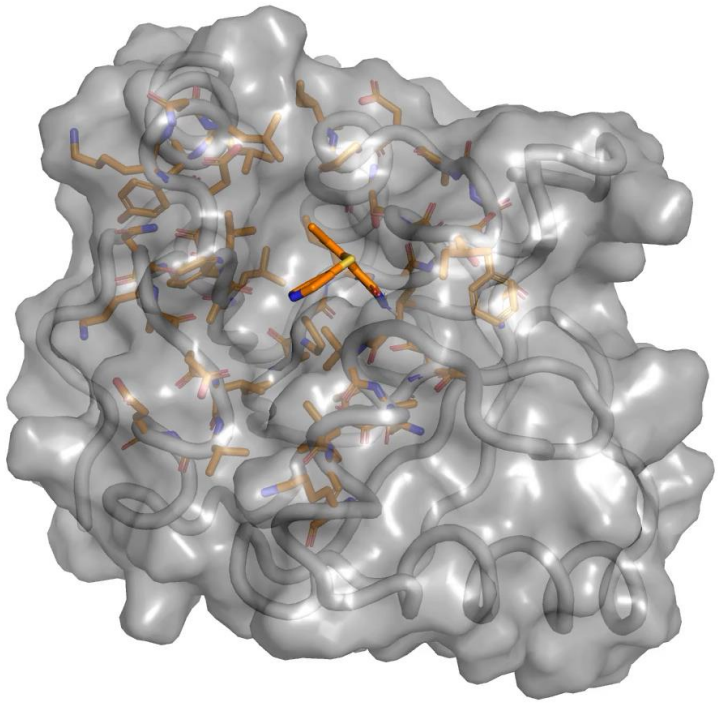
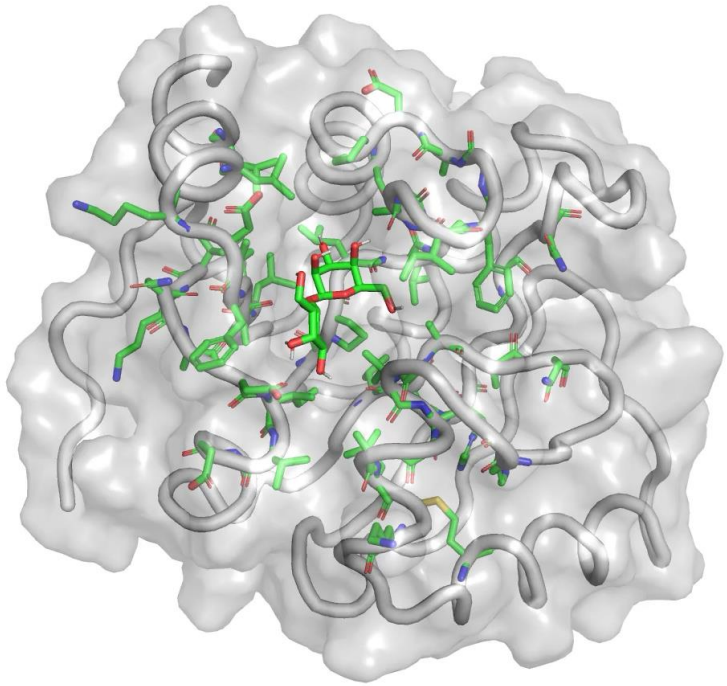




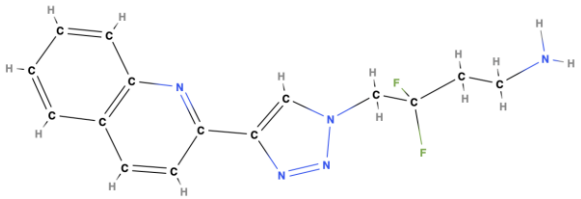
Molecular States Classified by ML



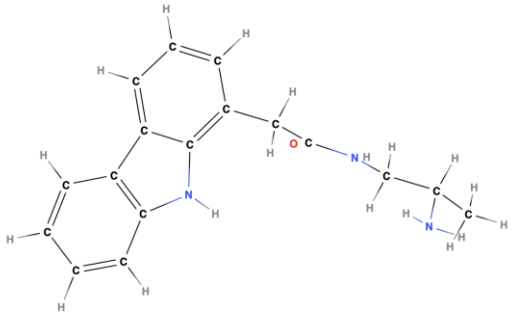


ADP-ribose-1"-monophosphatase (ADRP) (Nsp3)

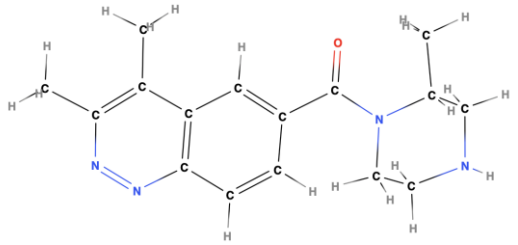
Sampling of Top Hits from ML (Enamine_REAL 1.2B) for ADRP-P1



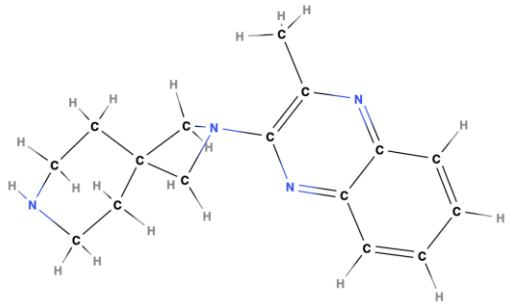
NCCC(Cn1nnc(c1)c1ccc2c(n1)cccc2)(F)F



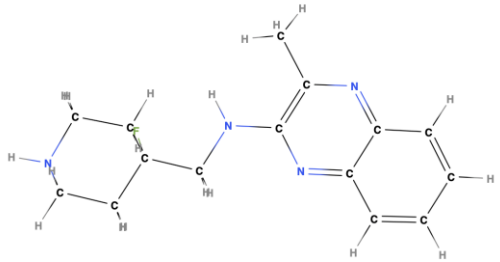
CC(CNC(=O)Cc1cccc2c1[nH]c1c2cccc1)N



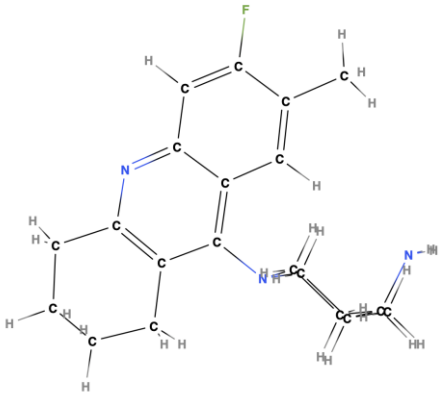
C[C@@H]1CNCCN1C(=O)c1ccc2c(c1)c(C)c(nn2)C



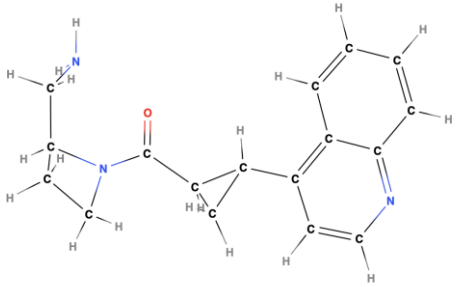
Cc1nc2ccccc2nc1N1CC2(C1)CCNCC2



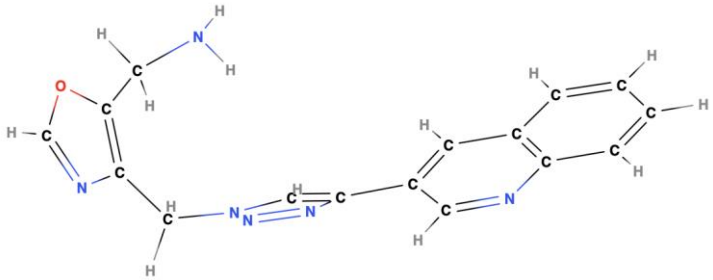
Cc1nc2ccccc2nc1NCC1(F)CCNCC1



NC1CCN(CC1C)c1c2CCCCc2nc2c1cc(C)c(c2)F



NCC1CCN1C(=O)[C@@H]1C[C@H]1c1ccnc2c1cccc2



NCc1ocnc1Cn1nnc(c1)c1cnc2c(c1)cccc2

2045 compounds with softmax = 1.0
Predicted docking score < -8.50

Left is BSL2 → BSL3

Vivarium is BSL3

LEGEND

- LAB
- LAB SUPPORT
- VIVARIUM
- LAB OFFICE
- ADMIN
- BLDG SUPPOR
- MECHANICAL
- UNASSIGNED

UNIVERSITY OF CHICAGO

Overall First Floor Plan

Flad & Associates

Our HPC- and AI-enabled small molecule filtering pipeline

Chemical Databases

Enamine

DRUGBANK

BindingDB GDB

eMolecules

cureFFI MOSES

ZINC15

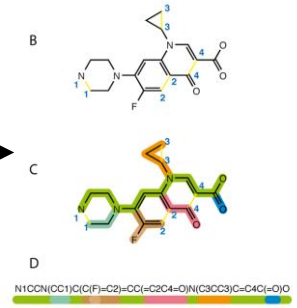
LINCS

SureChEMBL

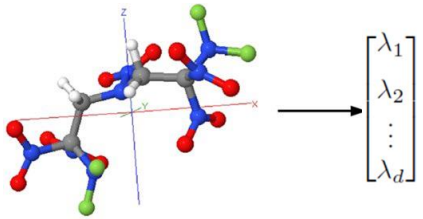
PubChem

And more…

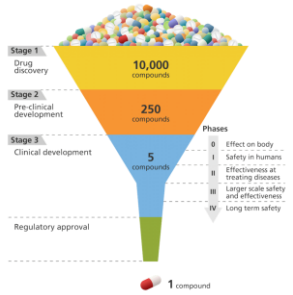
Canonicalization



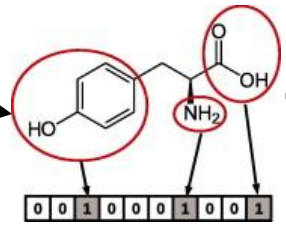
Compute Features



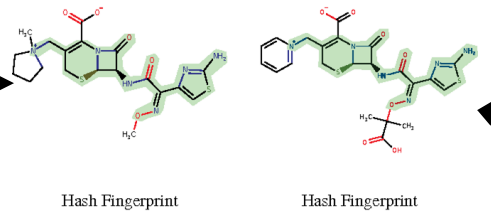
ML based filtering



Fingerprinting

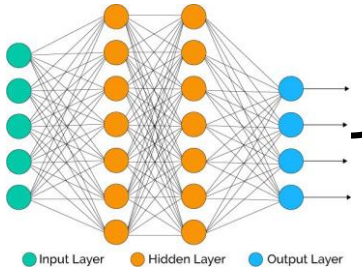


Similarity Search



Generate Images

DNN filtering

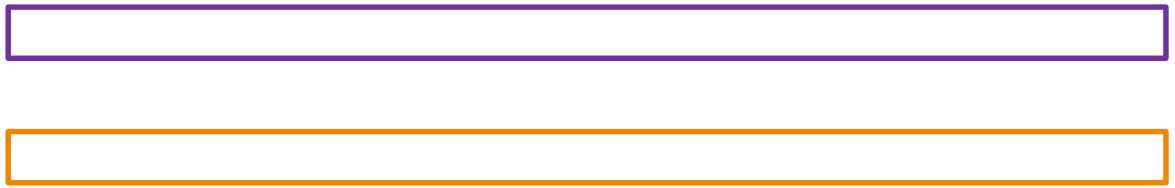


Computing Resources

https://2019-ncovgroup.github.io

First release: 21 sources, 3.9B molecules, 80 TB computed features

https://2019-ncovgroup.github.io



21 sources, 3.9B molecules, 80 TB computed features

ENAMINE REAL 1.2 billion molecules which comply with “rule of 5“ and Veber criteria: MW≤500, SlogP≤5, HBA≤10, HBD≤5, rotatable bonds≤10, TPSA≤140.

GDB-13 enumerates small organic molecules up to 13 atoms of C, N, O, S and Cl following simple chemical stability and synthetic feasibility rules.

https://2019-ncovgroup.github.io

Mining literature for drug discovery and repurposing

- Thousands of papers already published about COVID-19 and similar coronaviruses
- Developing human and machine pipelines to identify, extract drugs (current) and mechanisms (future)

- Identify key molecules for simulation team as starting points
- Build a list of known antiviral molecules and molecules active against SARS/MERS/HKU/SARS-CoV-2
- Use this list and “most-similar” molecules to build confidence in ML and simulation predictions

COVID-19 Open Research Dataset (CORD-19)

Access this dataset to help with the fight against COVID-19

A Free, Open Resource for the Global Research Community

In response to the COVID-19 pandemic, the Allen Institute for AI has partnered with leading research groups to prepare and distribute the COVID-19 Open Research Dataset (CORD-19), a free resource of over 45,000 scholarly articles, including over 33,000 with full text, about COVID-19 and the coronavirus family of viruses for use by the global research community.

This dataset is intended to mobilize researchers to apply recent advances in natural language processing to generate new insights in support of the fight against this infectious disease. The corpus will be updated weekly as new research is published in peer-reviewed publications and archival services like bioRxiv, medRxiv, and others.

CORD-19 Explorer is a quick and easy way to search the CORD-19 corpus, or you can download the complete data below.

Participate in the CORD-19 Challenge

Kaggle is hosting the COVID-19 Open Research Dataset Challenge, a series of important questions designed to inspire the community to use CORD-19 to find new insights about the COVID-19 pandemic including the natural history, transmission, and diagnostics for the virus, management measures at the human-animal interface, lessons from previous epidemiological studies, and more.

Download CORD-19

By downloading this dataset you are agreeing to the Dataset License. Specific licensing information for individual articles in the dataset is available in the metadata file.

Mining literature for drug discovery and repurposing

1. Manual Extraction

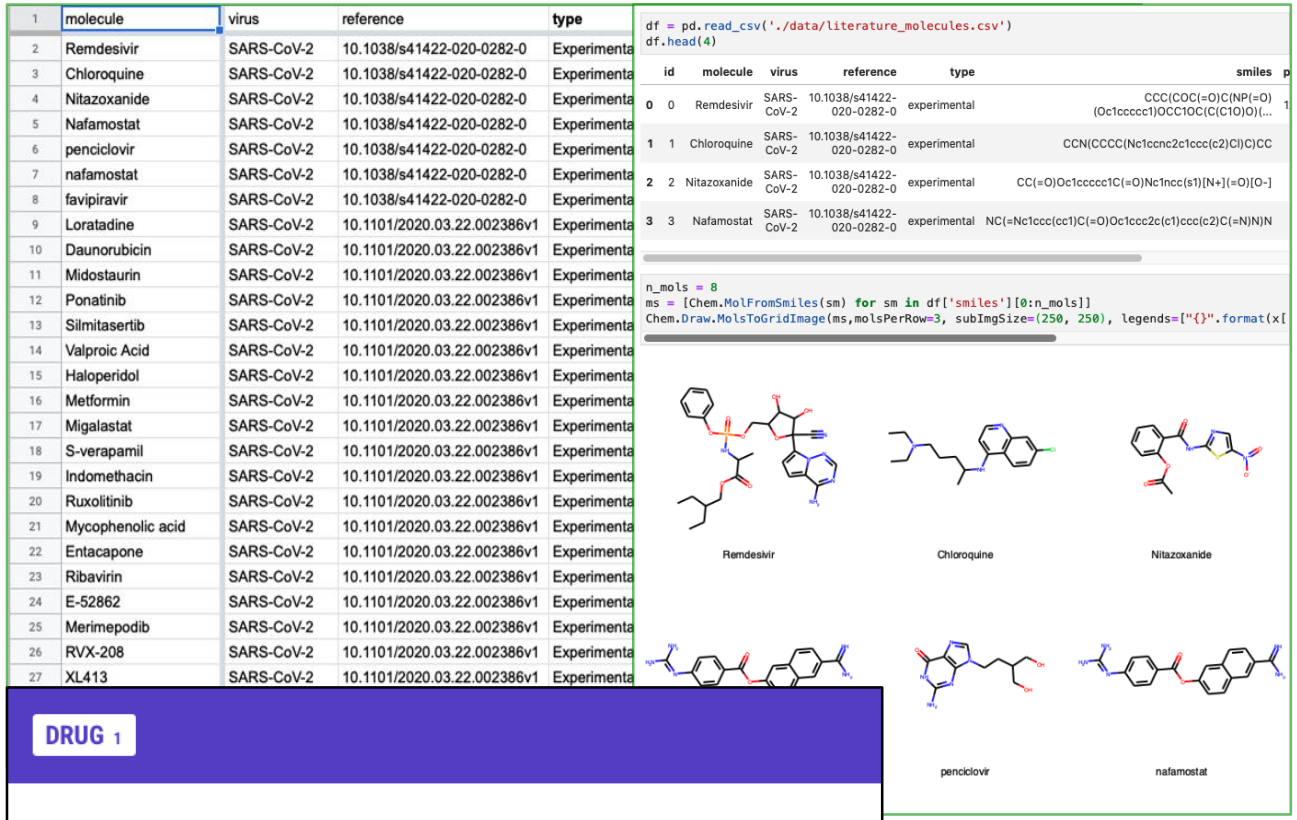
- Engaging CELS admin staff
- Currently have extracted 803 screened molecules and structures from 61 articles and reviews. (top figures)
- Capacity to extract from ~100 articles

2. Deep Learning (NLP)

- Team has labeled ~1500 abstracts with drugs in their natural language context in CORD-19 papers (bottom figure)
- Building named-entity models to enable automated extraction of drugs from entire corpus (~40k articles)

Current F1: 82.7 – more validation needed

Resulting data and models will be published openly



	molecule	virus	reference	type
2	Remdesivir	SARS-CoV-2	10.1038/s41422-020-0282-0	Experimenta
3	Chloroquine	SARS-CoV-2	10.1038/s41422-020-0282-0	Experimenta
4	Nitazoxanide	SARS-CoV-2	10.1038/s41422-020-0282-0	Experimenta
5	Nafamostat	SARS-CoV-2	10.1038/s41422-020-0282-0	Experimenta
6	penciclovir	SARS-CoV-2	10.1038/s41422-020-0282-0	Experimenta
7	nafamostat	SARS-CoV-2	10.1038/s41422-020-0282-0	Experimenta
8	favipiravir	SARS-CoV-2	10.1038/s41422-020-0282-0	Experimenta
9	Loratadine	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
10	Daunorubicin	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
11	Midostaurin	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
12	Ponatinib	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
13	Silmitasertib	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
14	Valproic Acid	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
15	Haloperidol	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
16	Metformin	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
17	Migalastat	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
18	S-verapamil	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
19	Indomethacin	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
20	Ruxolitinib	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
21	Mycophenolic acid	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
22	Entacapone	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
23	Ribavirin	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
24	E-52862	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
25	Merimepodib	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
26	RVX-208	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta
27	XL413	SARS-CoV-2	10.1101/2020.03.22.002386v1	Experimenta

```
df = pd.read_csv('./data/literature_molecules.csv')
df.head(4)
```

	id	molecule	virus	reference	type	smiles
0	0	Remdesivir	SARS-CoV-2	10.1038/s41422-020-0282-0	experimental	CCC(COC(=O)C(NP(=O)(Oc1ccccc1)OCC1OC(C(C1O)O)(...
1	1	Chloroquine	SARS-CoV-2	10.1038/s41422-020-0282-0	experimental	CCN(CCCC(Nc1ccnc2c1ccc(cc2)Cl)C)CC
2	2	Nitazoxanide	SARS-CoV-2	10.1038/s41422-020-0282-0	experimental	CC(=O)Oc1ccccc1C(=O)Nc1ncc(s1)[N+](=O)[O-]
3	3	Nafamostat	SARS-CoV-2	10.1038/s41422-020-0282-0	experimental	NC(=Nc1ccc(cc1)C(=O)Oc1ccc2c(c1)ccc(c2)C(=N)N)N

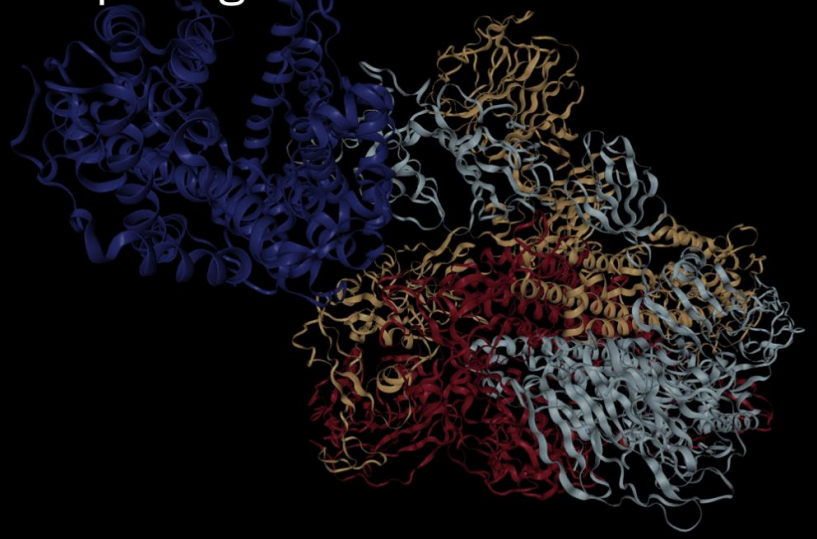
```
n_mols = 8
ms = [Chem.MolFromSmiles(sm) for sm in df['smiles'][0:n_mols]]
Chem.Draw.MolsToGridImage(ms,molsPerRow=3, subImgSize=(250, 250), legends=["{}".format(x[
```


DRUG 1

Science and Veterinary Medicine Academy of Shandong Province . Ethyl acetate , twain-80 , and span-80 were purchased from BASF (Berlin , Germany) . PPV (TCID 50 : 10 −5) and PK-15 cell were supplied by China Institute of Veterinary Drug Control . DMEM (GIBCO) with the supplement of 100 IU mL −1 **streptomycin** DRUG , 100 IU mL −1 **benzylpenicillin** DRUG , and 10 % fetal bovine serum was used for resuspending and washing cells , culturing the cells , and diluting mitogen . The

Computing at Argonne, Oak Ridge, TACC, SDSC, IU, LRZ, Brookhaven

The COVID-19 High Performance Computing Consortium



Bringing together the Federal government, industry, and academic leaders to provide access to the world's most powerful high-performance computing resources in support of COVID-19 research.

33

Consortium members

41k

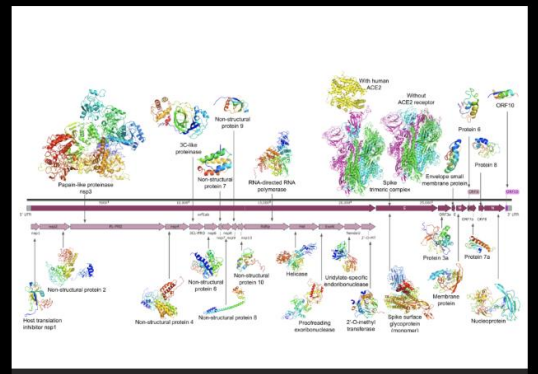
GPUs

Active projects

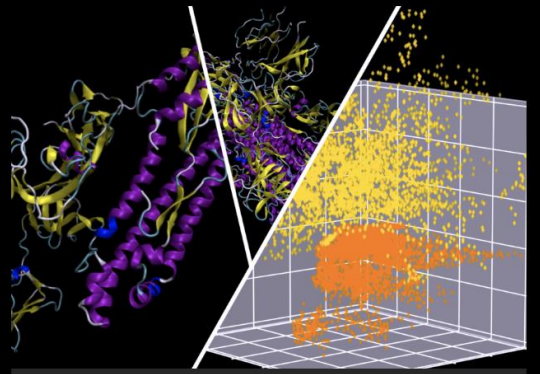
Fighting COVID-19 will require extensive research in areas like bioinformatics, epidemiology, and molecular modeling to understand the threat we're facing and to develop strategies to address it.

Here are some of our active projects.

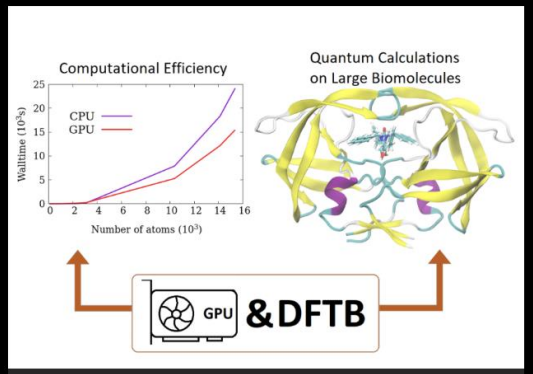
See all



Request computing resource for de novo protein therapeutics design simulations to treat the COVID-19...



Discovering molecular targets of the human coronavirus with HPC and AI



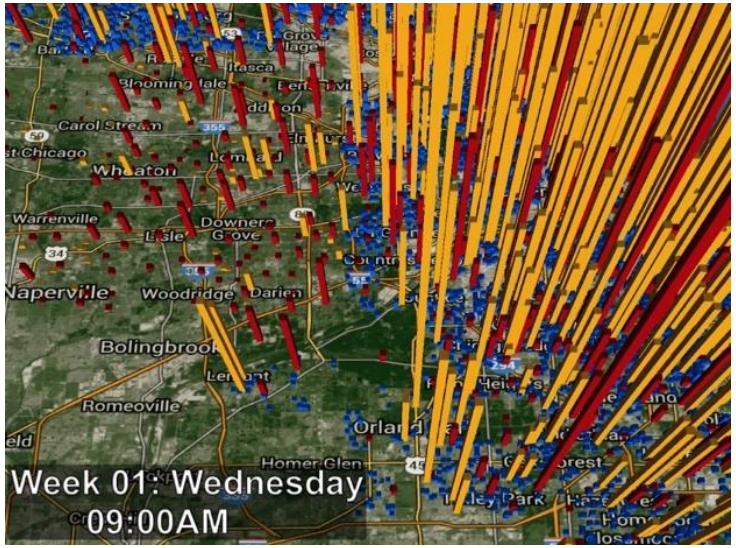
Harnessing Large-Scale Quantum-Based DFTB Calculations for a More Accurate Assessment of COVID-19...

Epidemiology

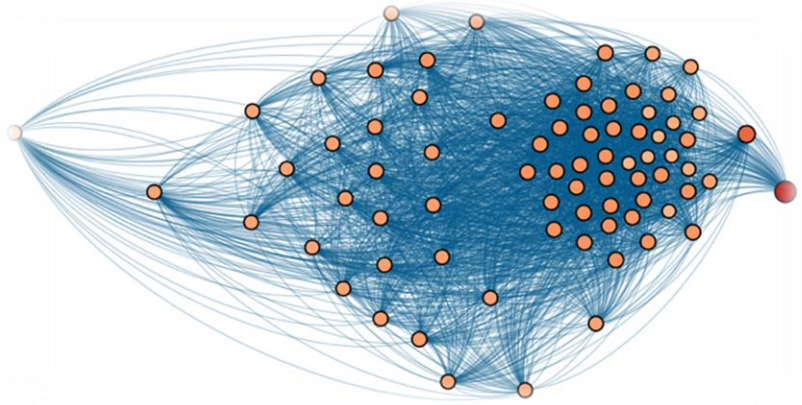
WE ARE MODELING COVID-19 SPREAD AMONG PEOPLE IN CHICAGO

Joint DOE Laboratory Plan for Pandemic Modeling and Analysis Capability

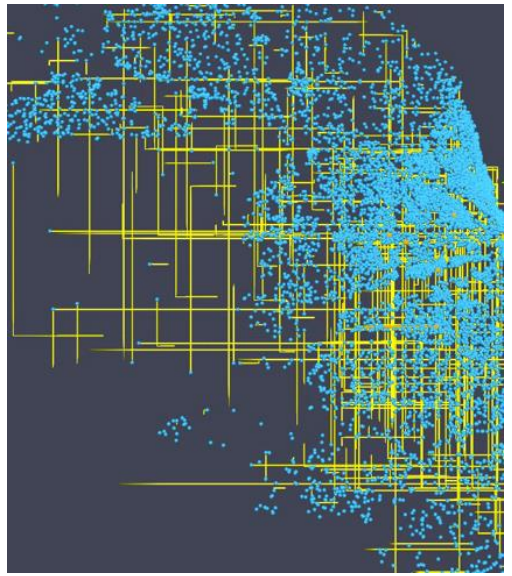
- Argonne, Oak Ridge, Los Alamos and Sandia will collaborate over a 3 month-period to develop an **integrated COVID-19 pandemic monitoring, modeling, and analysis capability** that ***will address the key questions about the pandemic***



Where are people located? With who?

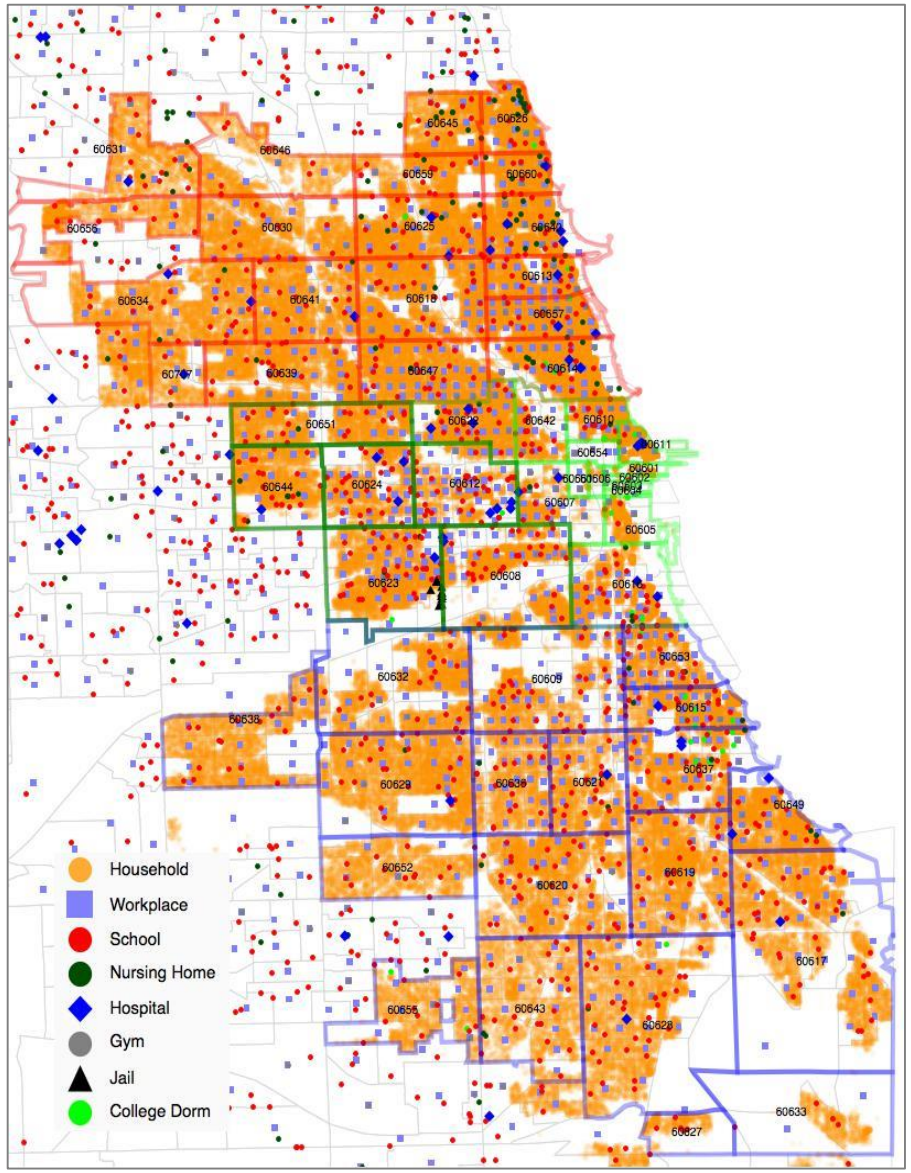


Who is infecting who? Who may be infected?



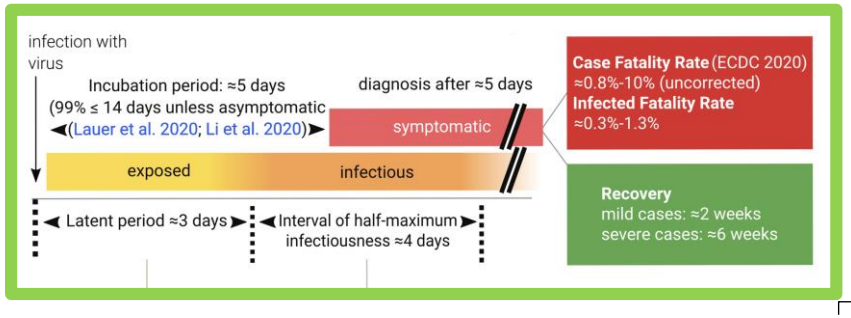
Where are people going, coming from?

Modeling PEOPLE WITH ARGONNE'S CityCOVID



- CityCOVID is a city-scale agent-based model
- 2.7M+ individual agents (people)
  - move to/from 1.2M spatially-located places
  - on an hourly basis
  - over a period of a year (8760 hours)
- Each agent has contact with other agents at each place (possible disease transmission)
  - agent has individual behaviors, engages in activities, and responds and adapts:
    - to the disease
    - to public health messaging
    - to public health interventions
- Up to 10^{12} (trillion) individual contacts during a yearly simulation

MODELING INDIVIDUAL AGENT DISEASE STATES WITH CITYCOVID



Beta(severe.infection.duration.alpha, severe.infection.duration.beta)

14 - 35 days

Severe Infected

At home

Hospitalization

13%
age dependent

0-3 days

per day probability
remain
at home
(si.start.home.isolation.prob)

age dependent

Deceased

Beta(incubation.duration.alpha,
incubation.duration.beta)

2-6 days

Susceptible

Exposed

susceptible.to.exposed.probability
seasonality.multiplier
seasonality.peak
age dependent
shielding.scaling

Beta(infection.duration.alpha, infection.duration.beta)

7-17 days

87%

Infected

Symptomatic
(at home)

Asymptomatic
(business as usual)

Asymptomatic
(business as
usual)

Recovered

0-14 days

per day probability
remain
asymptomatic
(start.home.isolation.prob)

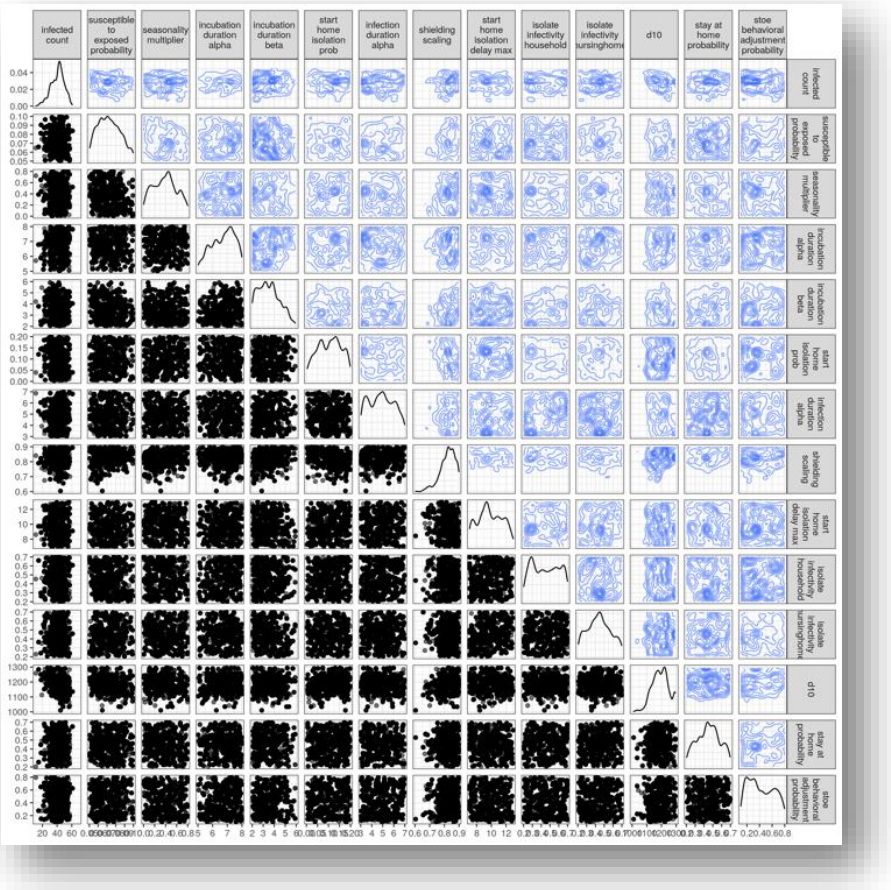
0-3 days

per day probability
remain
symptomatic
(end.home.isolation.prob)

Jonathan Ozik jozik@anl.gov
Chick Macal macal@anl.gov
Argonne National Laboratory
April 20, 2020

CityCOVID PARAMETER ESTIMATION ON THETA

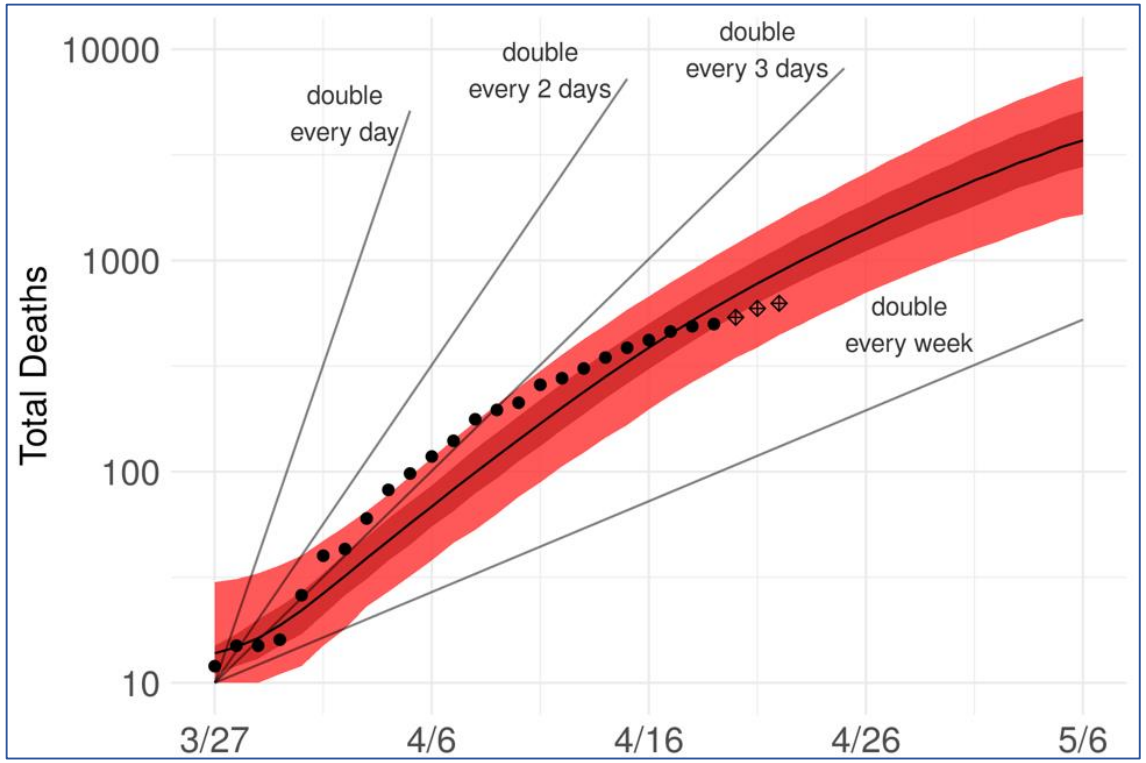
- CityCOVID is implemented as an MPI application using the Repast HPC ABM toolkit and the Chicago Social Interaction Model (ChiSIM) framework
- Each model is distributed across 256 ranks for efficient execution (each simulated year, at an hourly time step, takes approximately 8-12 minutes to complete for a full city-scale run)
- We are using our large-scale model exploration framework (EMEWS) to implement sequential approximate Bayesian computation (ABC) parameter estimation/calibration workflows, coordinating large ensemble runs (30k+ models) on Theta



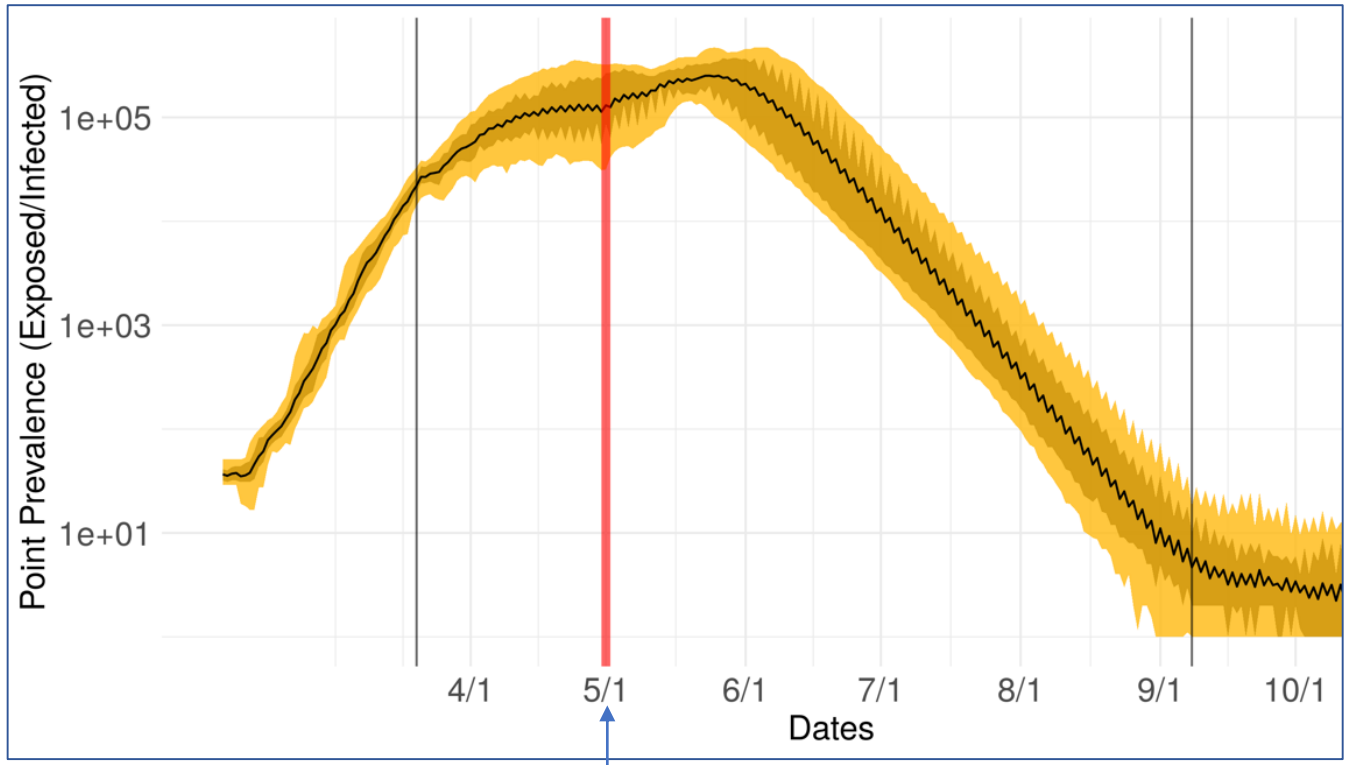
CityCOVID MODEL OUTPUTS

- CityCOVID generates projections of epidemiological variables, including COVID-19 exposures and deaths

- CityCOVID enables running policy scenarios, such as those examining the consequences of easing current in-place restrictions



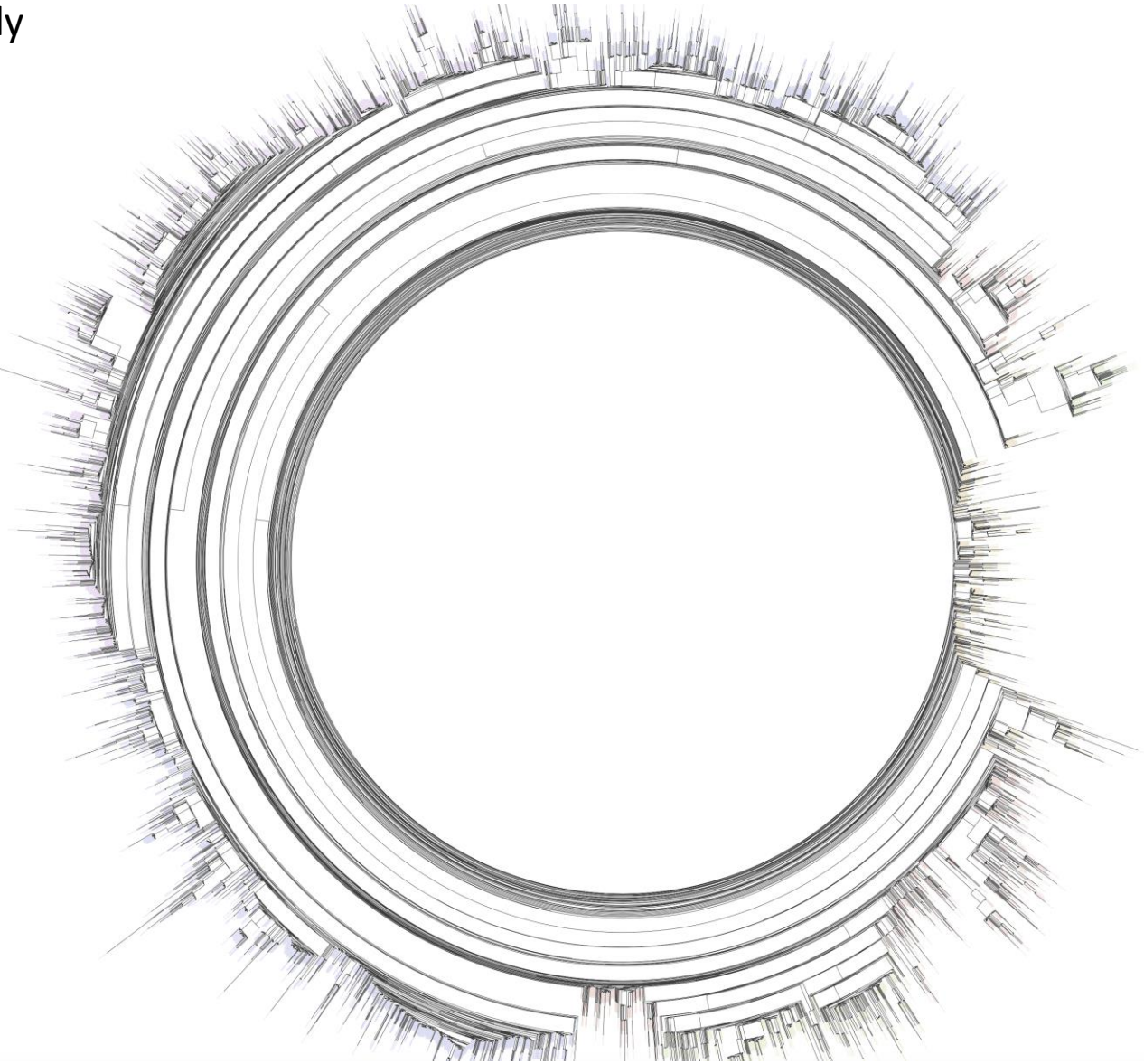
Model Output Uncertainty Bands Calibrated on Empirical Data

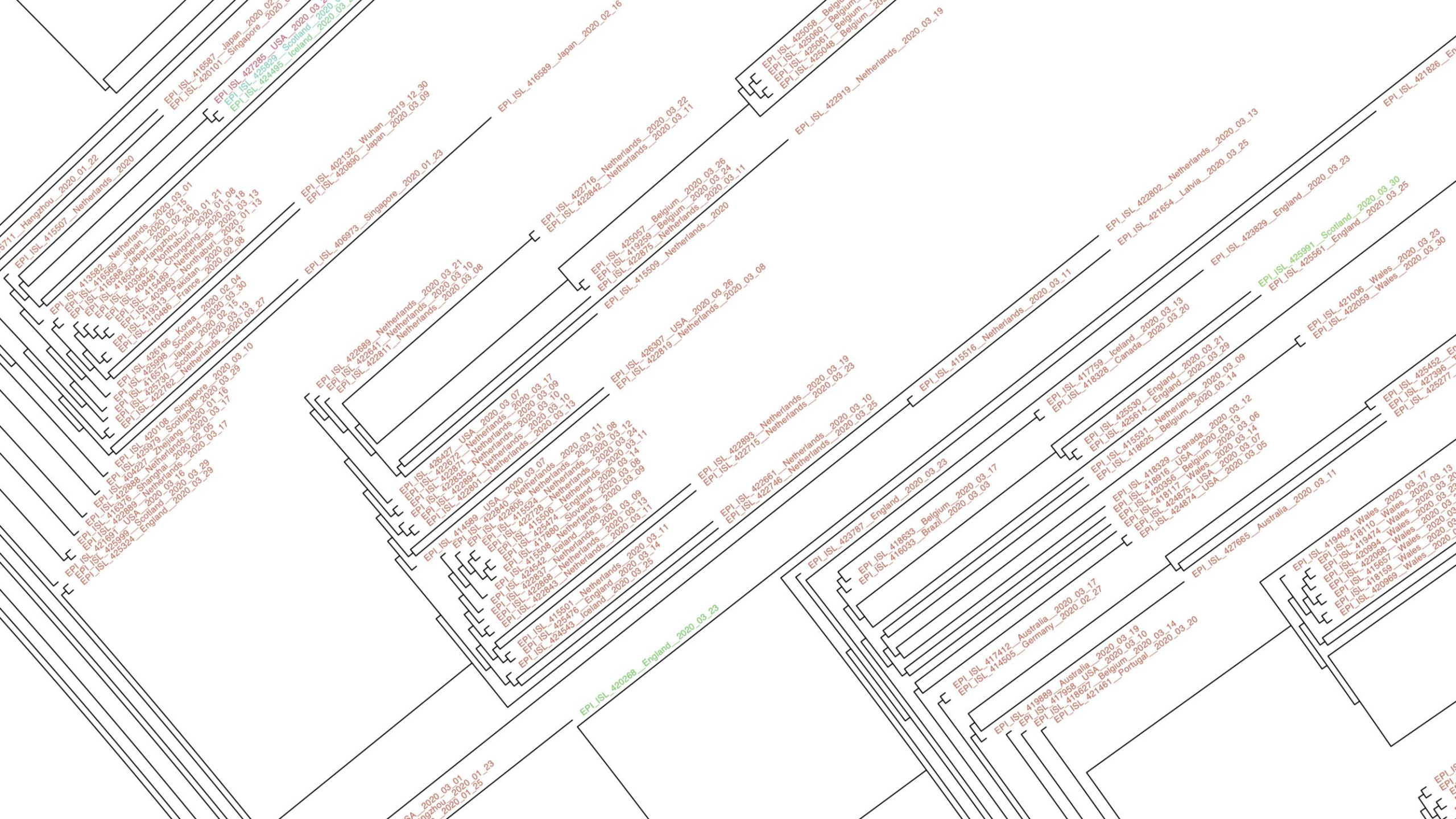


Simulated Restriction Easing Begins

Evolution

- >10,000 viral sequences
- Phylogenetic trees updated daily
- DOE ⟹ FEMA, BARDA etc.
- Place, Date
- Trees from WGS, SNPs
- Tracking new mutations
- Capturing significant variants

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EPI_ISL_422919__Netherlands__2020_03_19
EPI_ISL_426427__USA__2020_03_07
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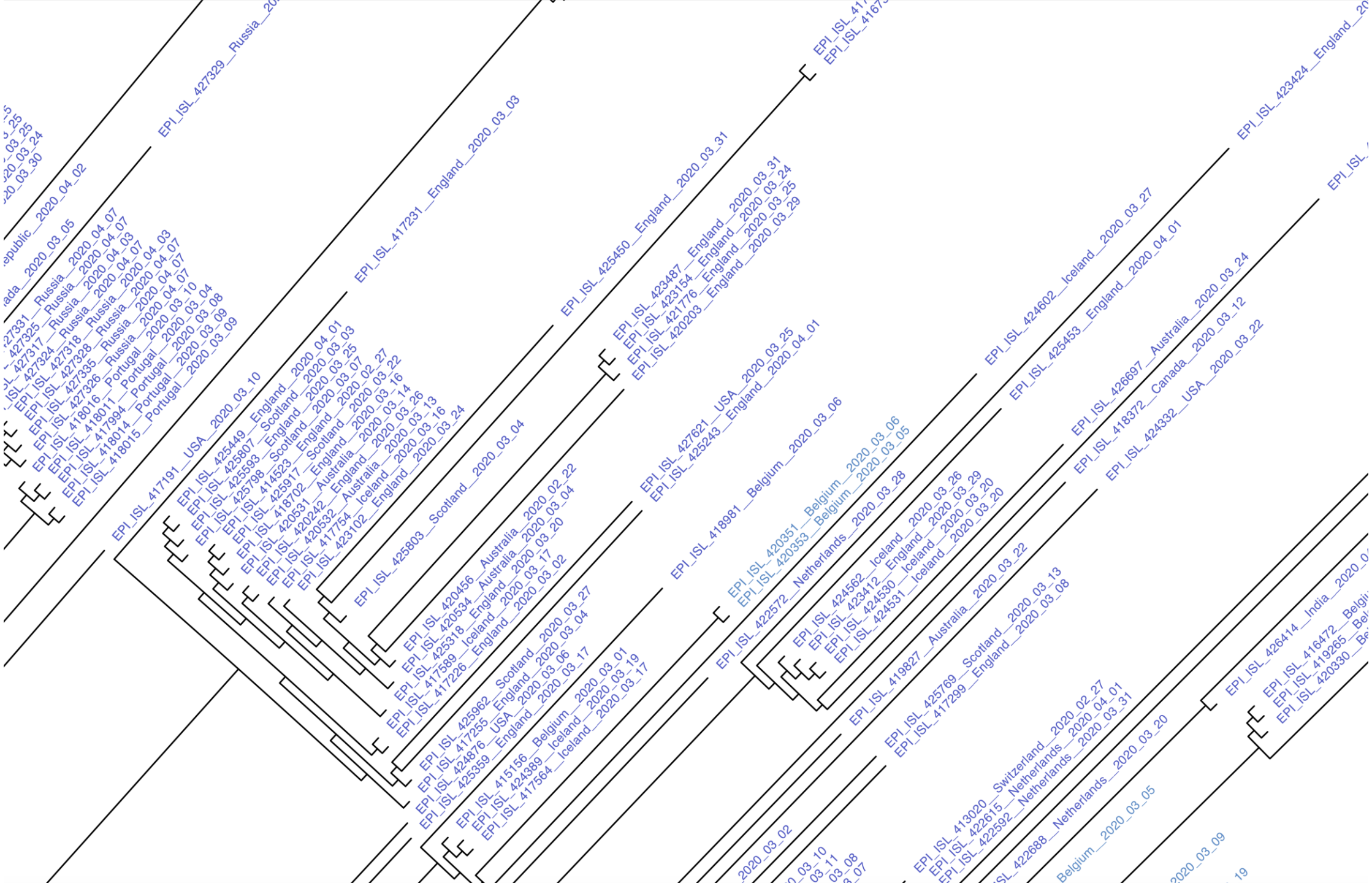
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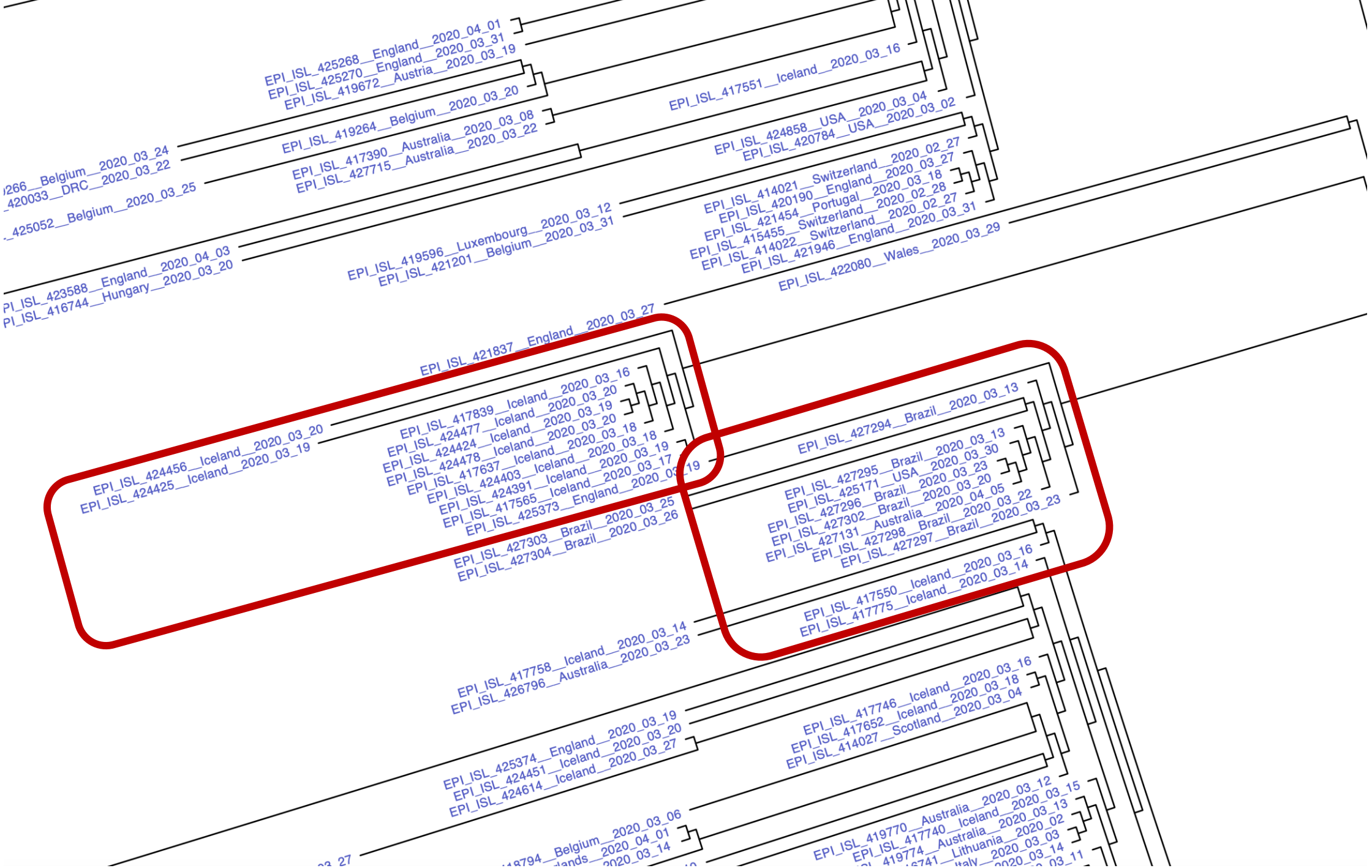
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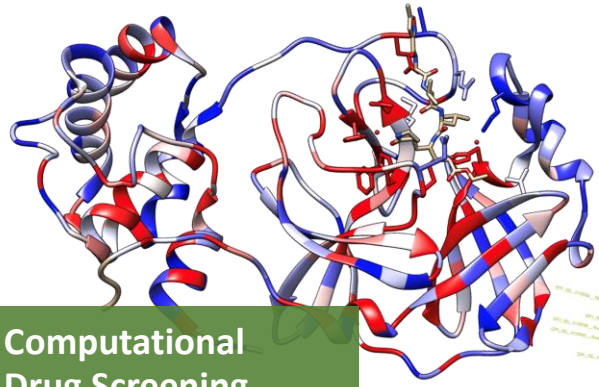
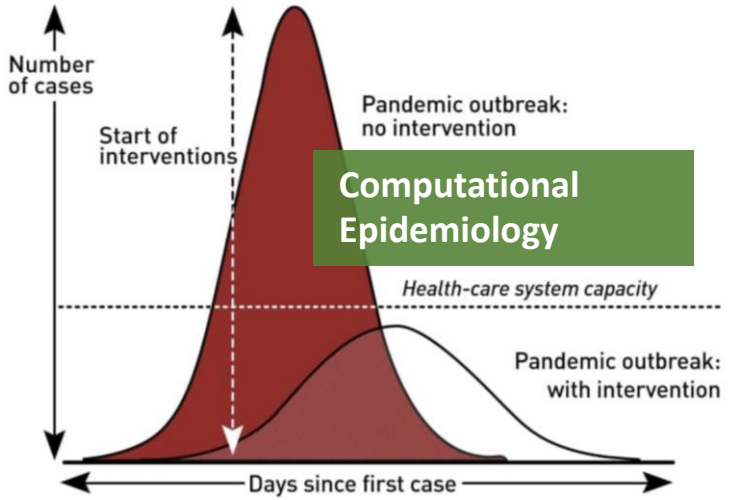
Supercomputing Focus Areas

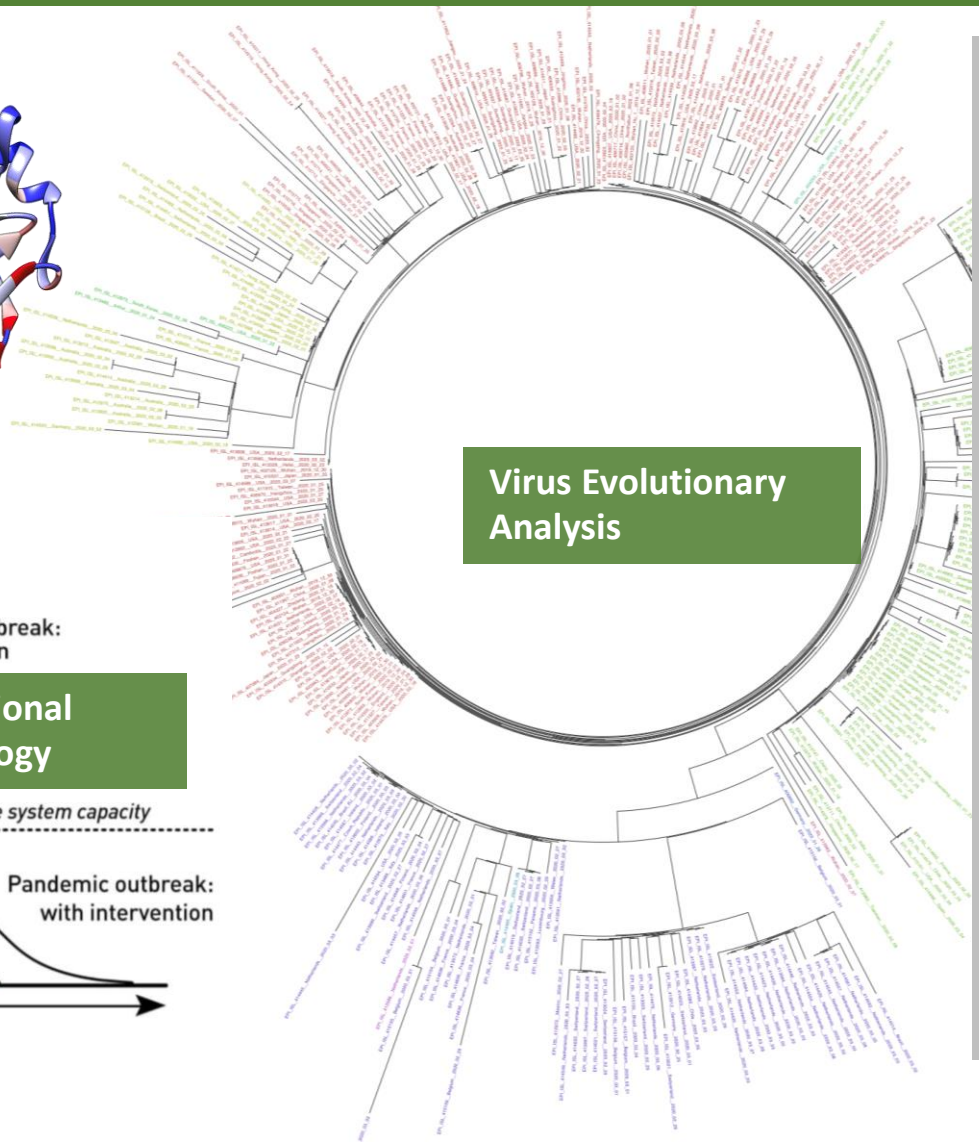
- Accelerating development of treatment options
- Learning how epidemics impact critical social services
- Improving understanding of human virus interactions



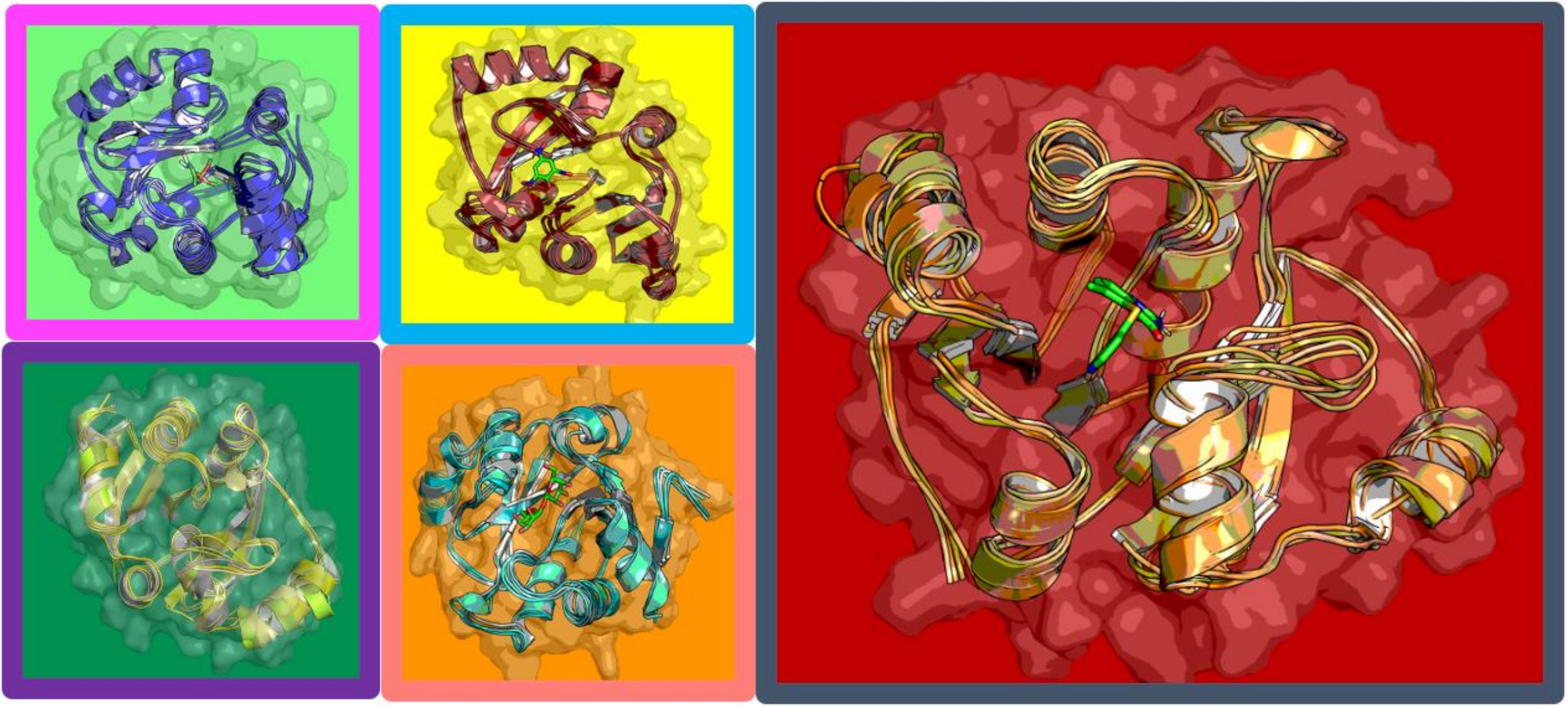
Computational Drug Screening



Computational Epidemiology



Virus Evolutionary Analysis



Questions