

# COVID.SI - A Crowdsourced Drug Discovery Project

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Črtomir Podlipnik, Sebastian Pleško, Gašper Tomšič,  
Lennart Dreisewerd, Boštjan Laba, Marko Jukić



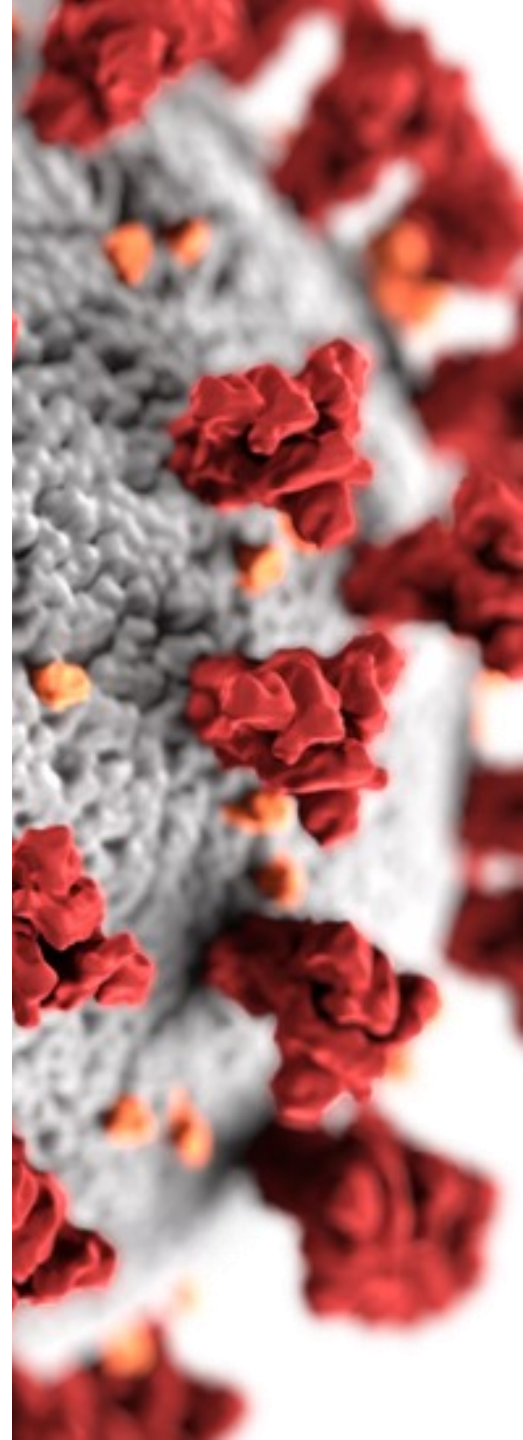
**“If you know the enemy and know yourself you need not fear the results of a hundred battles.”**

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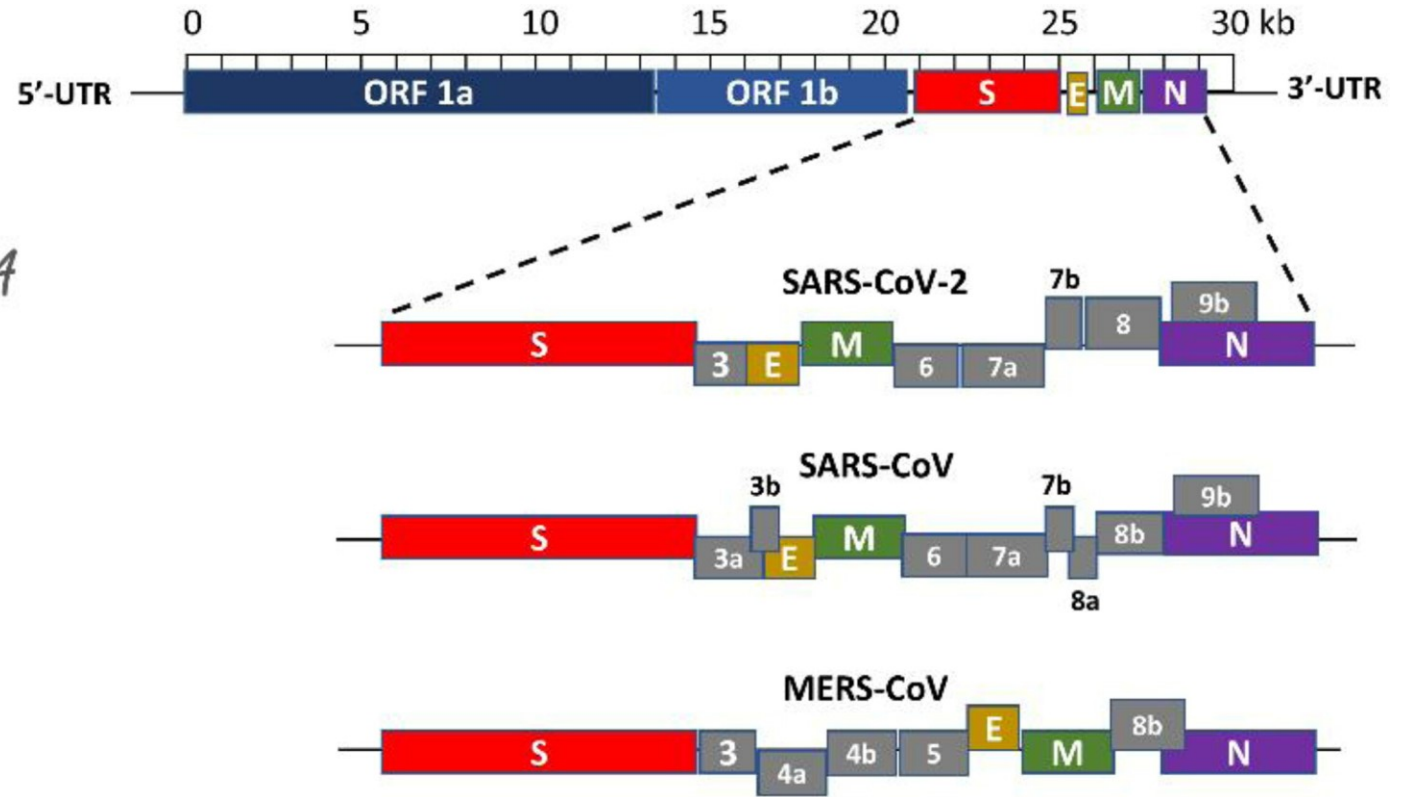
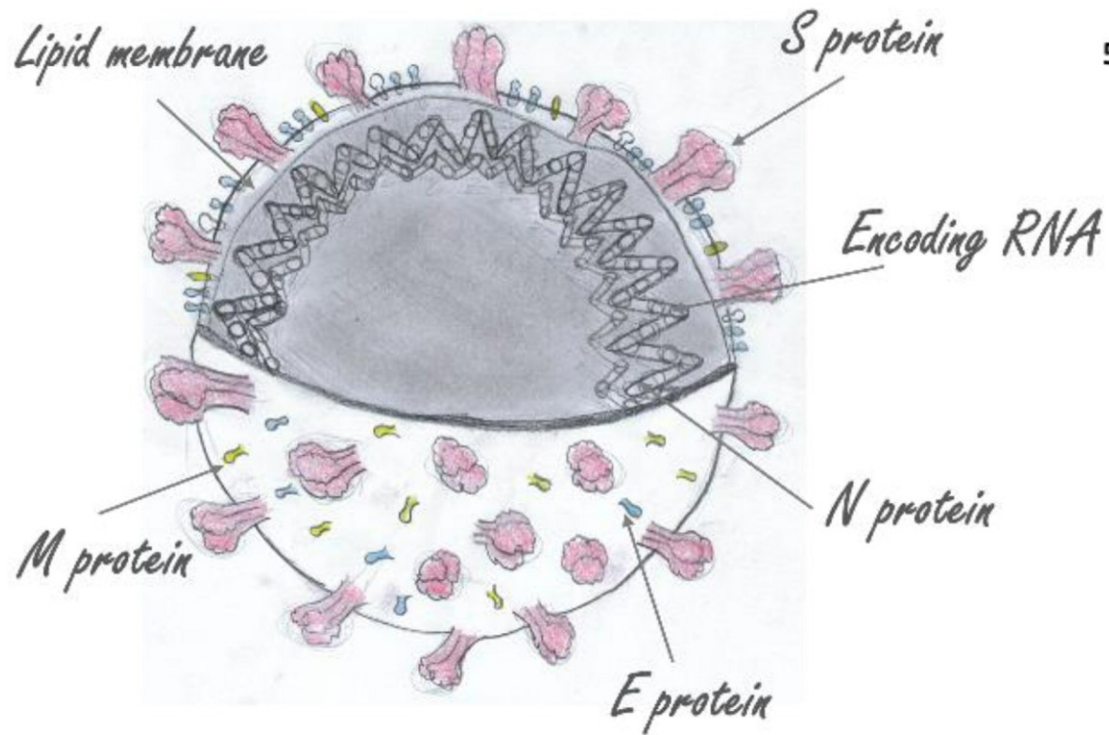
Sun Tzu

**SARS-CoV-2 is an invisible enemy we want to know as much as possible**

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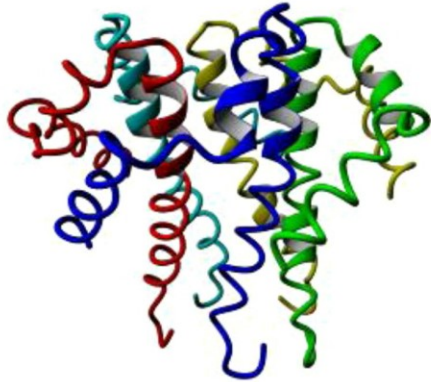
# STRUCTURE OF SARS-COV-2



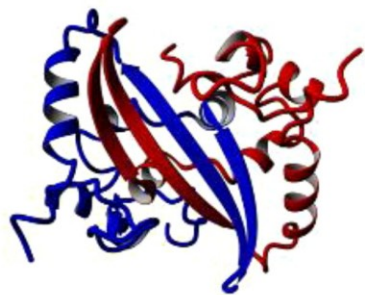
SARS-CoV-2 is (+) RNA Virus with a length of approximately 30 kb. The genome encodes **4 structural** proteins and **15 non-structural** proteins

# STRUCTURE OF SARS-COV-2

structural proteins

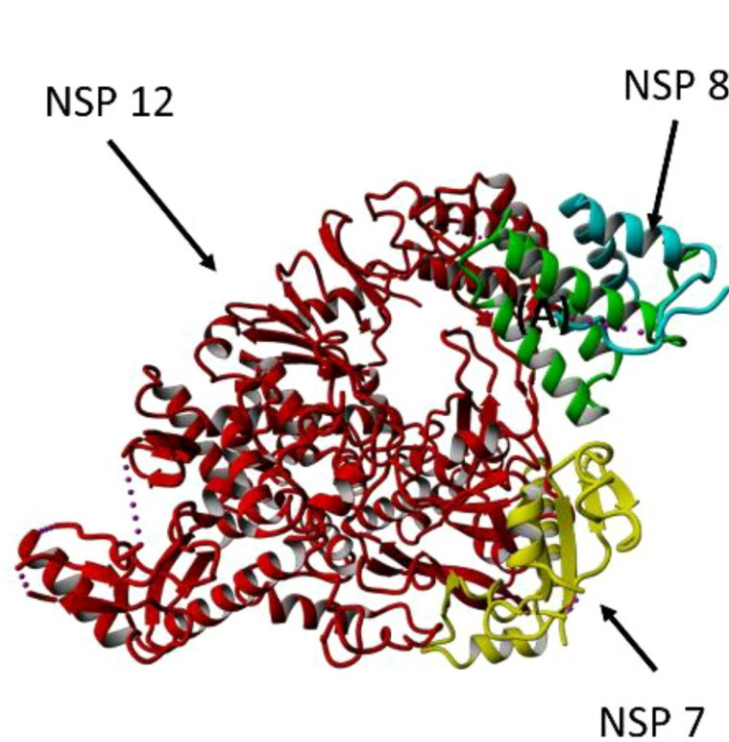


E-protein (pentamer)

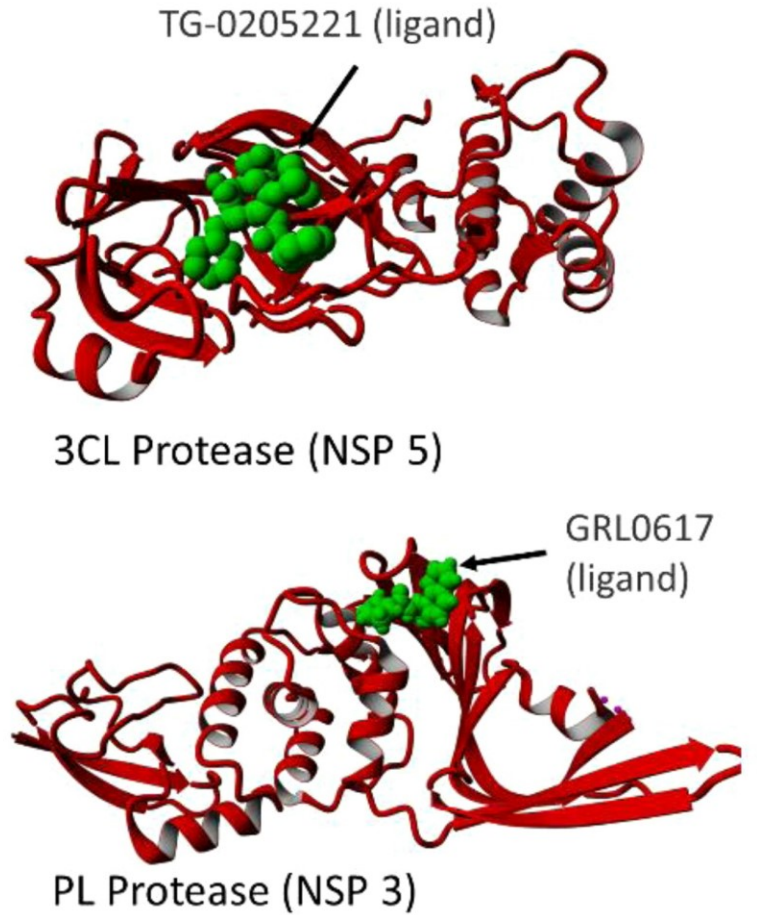


N-protein (dimer)

non – structural proteins



RNA-dependent RNA polymerase  
with cofactors



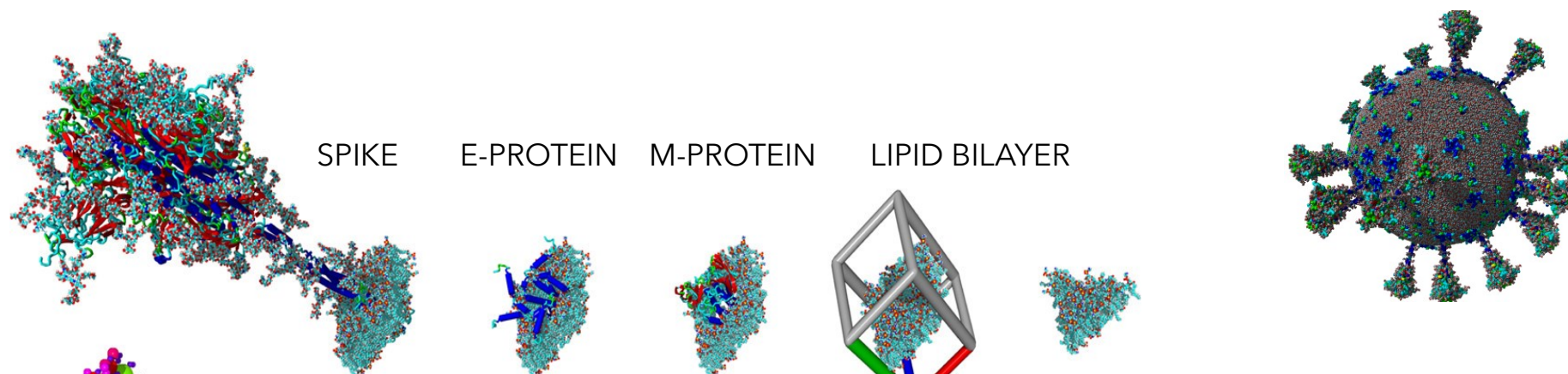
3CL Protease (NSP 5)

PL Protease (NSP 3)

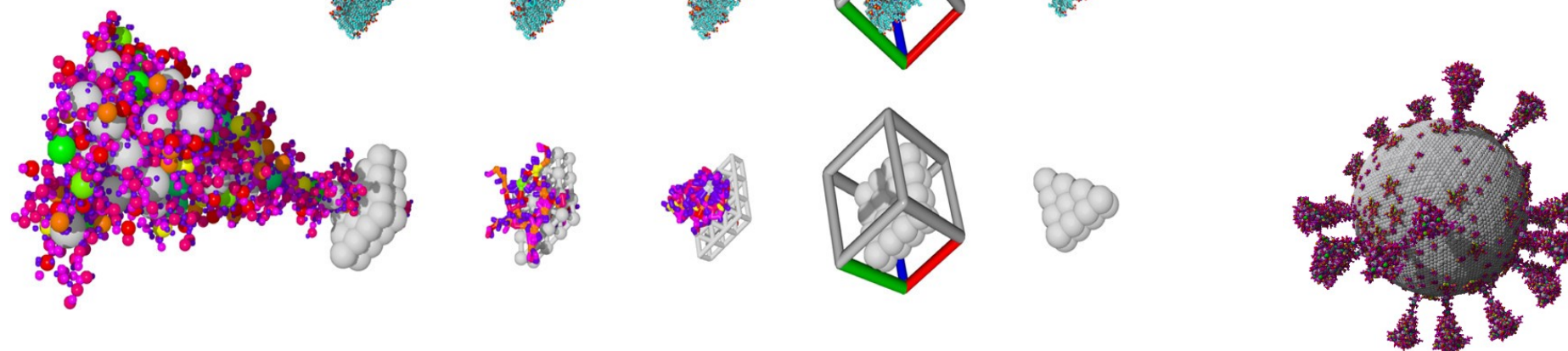


# 3D-MODEL OF SARS-CoV-2 VIRUS - BUILDING BLOCKS

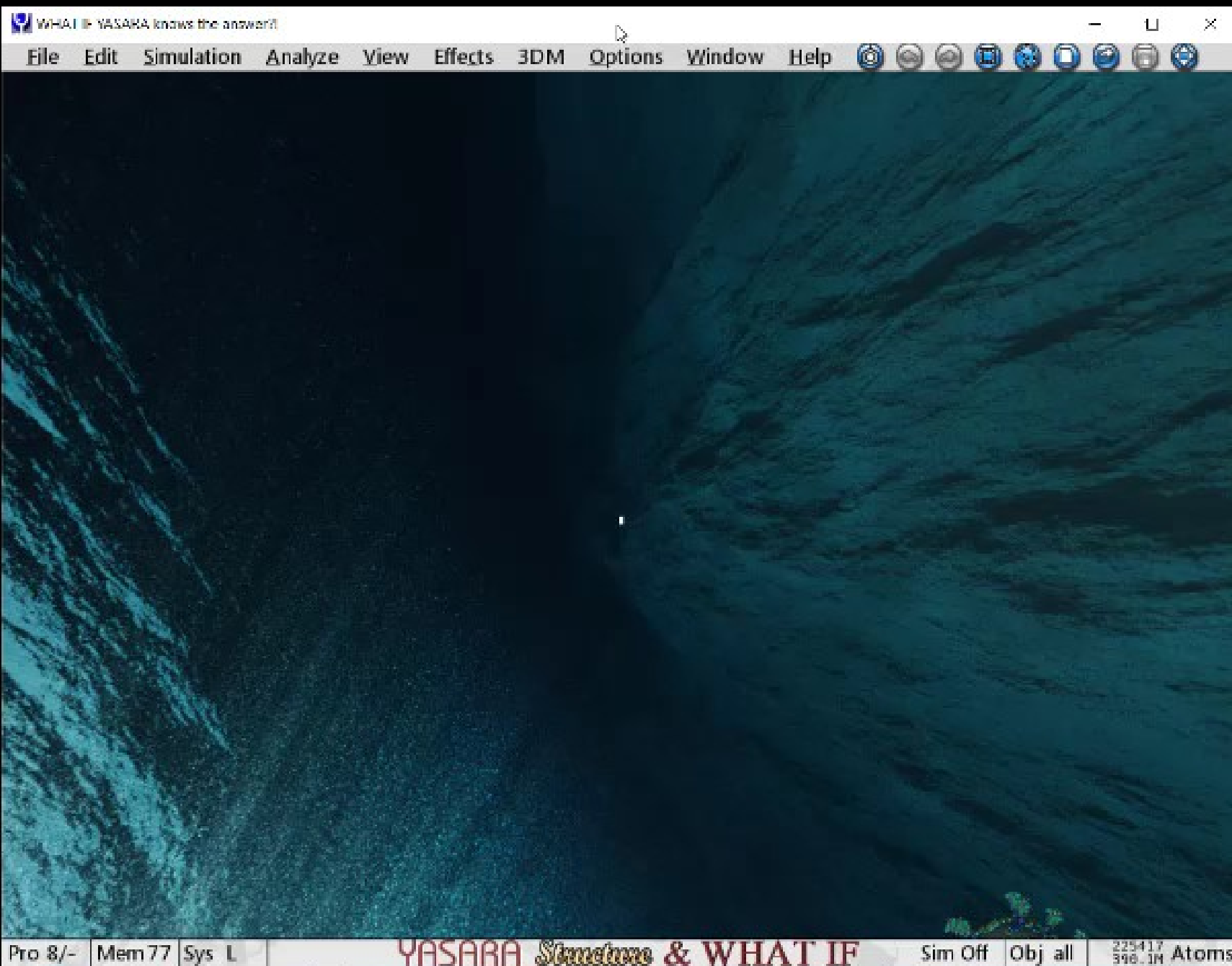
ALL  
ATOM



COARSE  
GRAINED



Five building blocks needed to construct a model of the SARS-CoV-2 envelope.



A 3D model of SARS-CoV-2 for interactive exploration, with components explained and built using Cryo-EM results from Yao et al. (2020) Cell 183,730-738.

Written by: Kornel Ozvoldik

License: GNU GPL Last modified: 2021/02/01

Download: sarscov2.zip

Modified by Črtomir Podlipnik

### **Assembly of Biomolecular Giga-structures and Visualization with the Vulkan Graphics API**

Kornel Ozvoldik, Thomas Stockner, Burkhard Rammner, and Elmar Krieger

*Journal of Chemical Information and Modeling* **2021** 61 (10), 5293-5303

DOI: 10.1021/acs.jcim.1c00743

# COVID-19 IS STILL THE GLOBAL HEALTH PROBLEM



Search by Country, Territory, or Area



Covid-19 Response Fund

Donate

WHO Coronavirus (COVID-19) Dashboard

[Overview](#)

[Measures](#)

[Table View](#)

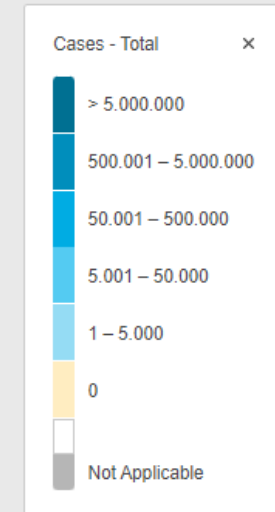
[Data](#)

[More Resources](#)

**MORE THAN HALF A BILLION CONFIRMED CASES**

**MORE THAN 6.3 MILLION OF DEATHS**

**MORE THAN 11.4 BILLION VACCINE DOSES  
ADMINISTRED**



Download Map Data

Globally, as of 5:47pm CEST, 29 April 2022, there have been 510.270.667 confirmed cases of COVID-19, including 6.233.526 deaths, reported to WHO. As of 27 April 2022, a total of 11.477.767.378 vaccine doses have been administered.



# Slovenian Citizen Science projects to rundown SARS-CoV-2

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The "**COVID.SI**" - the project that allows the general public to participate in the fight against the corona virus by sharing their knowledge and computer resources. The project aims to study libraries of molecular compounds and help find a cure for the coronavirus using high-throughput virtual screening.

**DISTRIBUTED COMPUTING  
SEARCH OF DRUG FOR COVID**

<https://covid.si>



The "**Covid-19 Tracker Slovenia**" project collects, analyses and publishes data on the spread of the SARS-CoV-2 coronavirus, the cause of COVID-19, in Slovenia. We wish to give the public a better overview of the magnitude of the issue and a proper assessment of the risk.

**COLLECTING AND ANALYZING  
EPIDEMIOLOGICAL DATA**

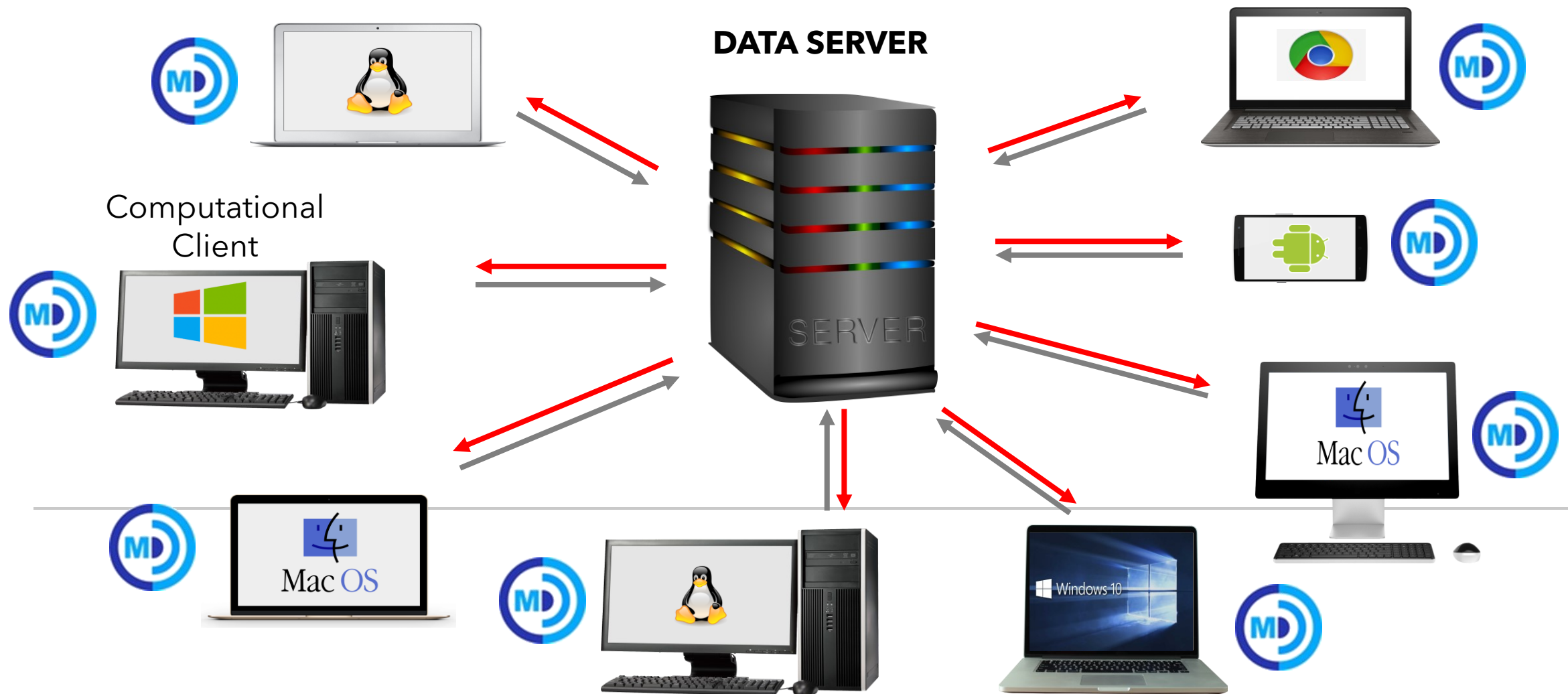
<https://covid-19.sledilnik.org>

# Activities of the COVID.SI project



- **Aggregation of Information about COVID-19**
- **Community-based 3D printing and distribution of Wuhan mask holders**
- **Tracking Mutations of SARS-CoV-2**
- **Developing and maintaining software for community-based distributed computing**
- **Developing and maintaining of CMDock software and SDFTools**
- **Gamification of Scientific problems**
- **Virtual Screening of COVID-19 related targets**

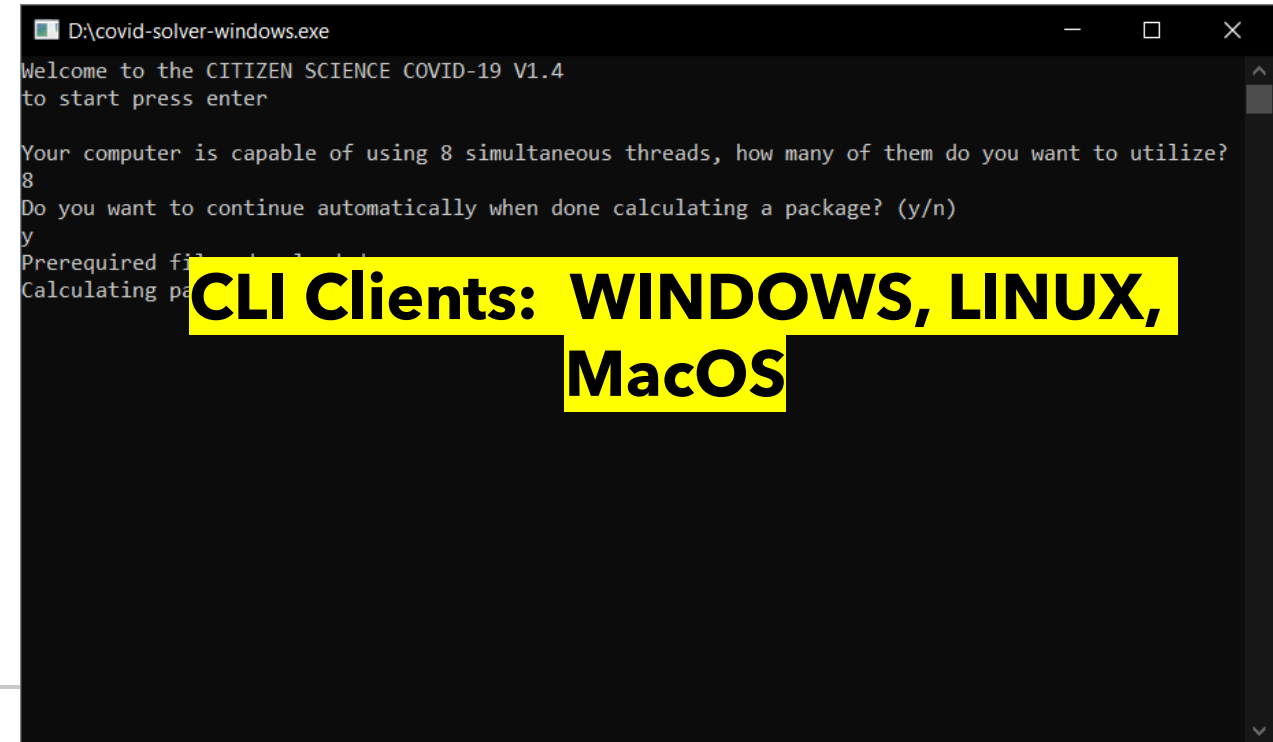
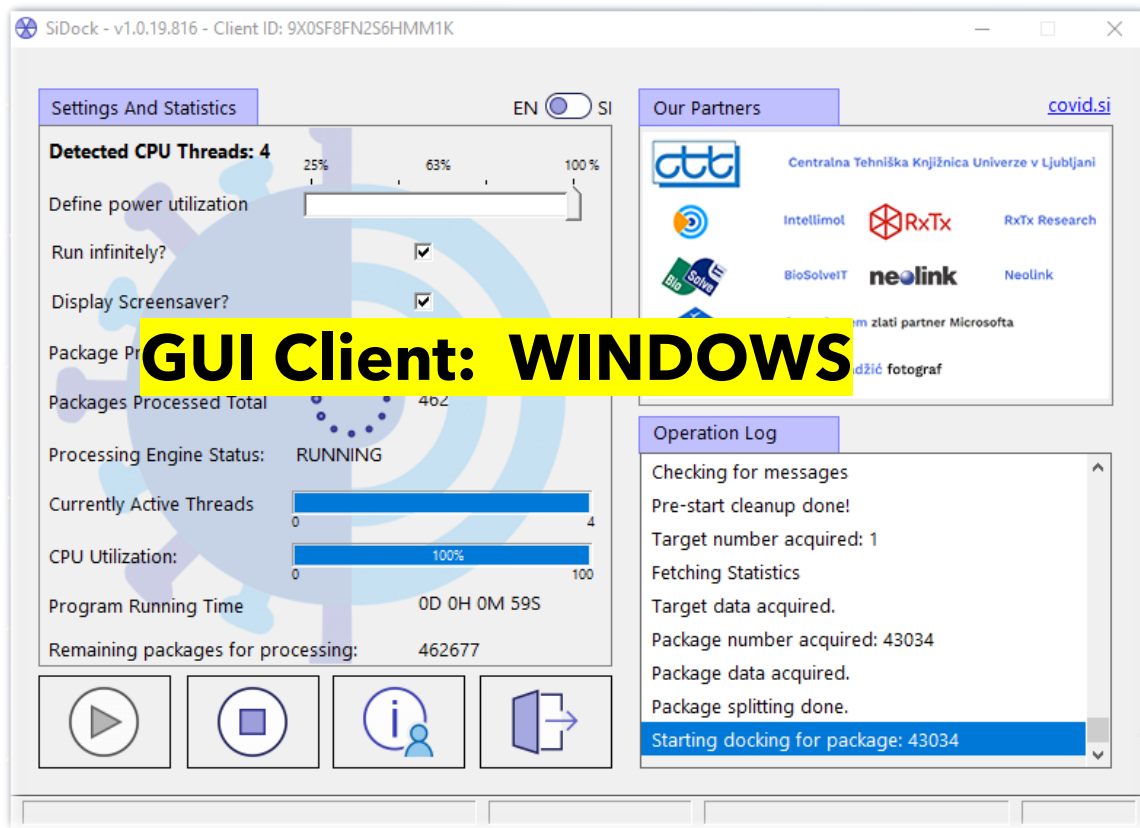
# Scheme of community computing



**From data server to client**  
Targets & Ligands' packages

**From client to dataserver:**  
poses & docking scores

# Clients for distributing computing

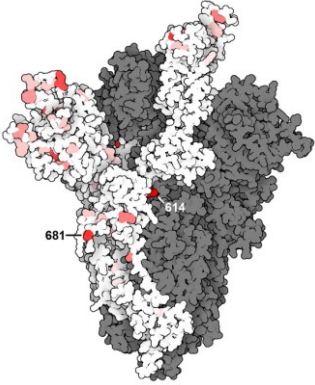
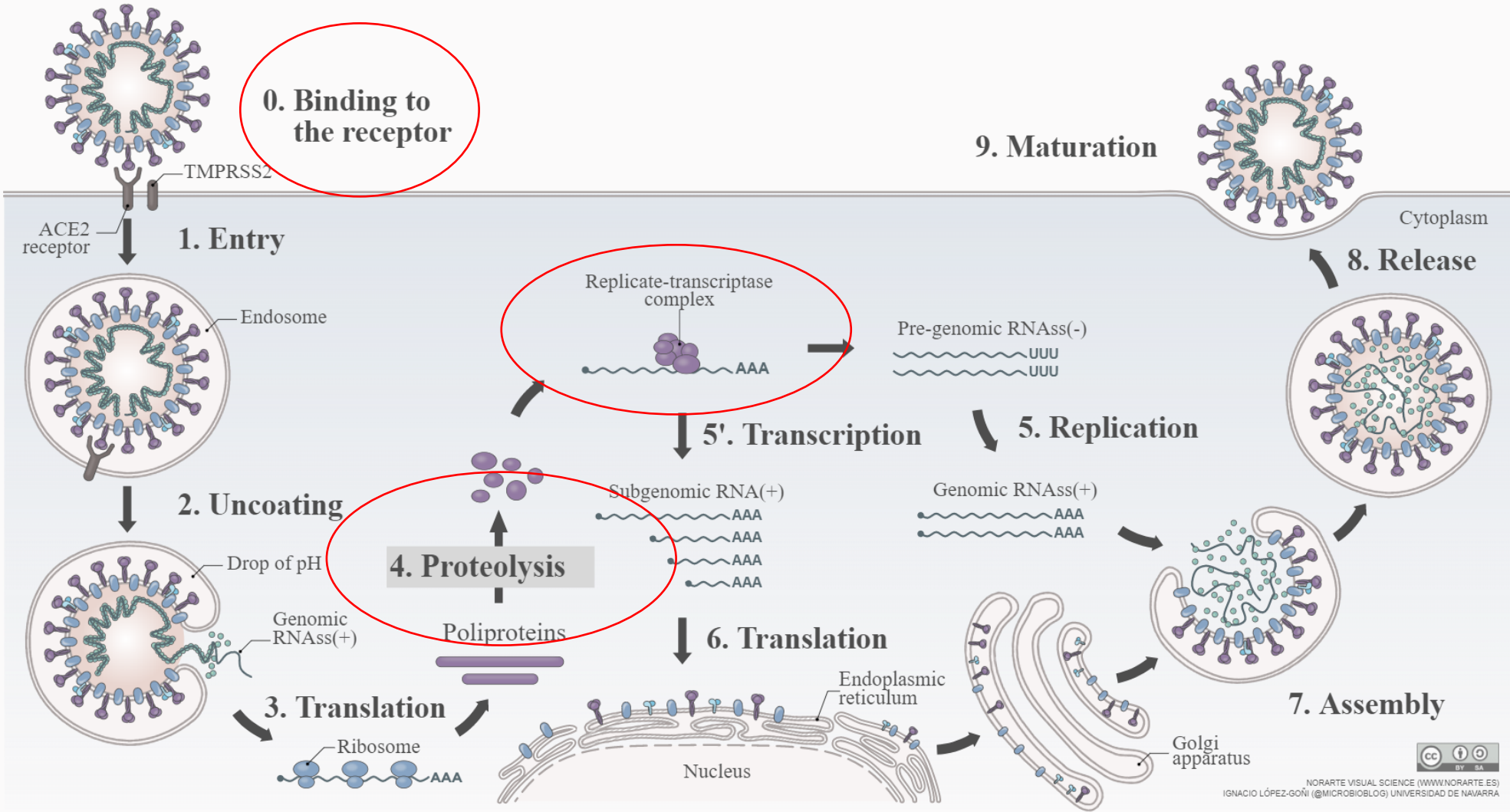


We developed the GUI Client for Windows and CLI Clients for Windows, MacOS and Linux. In all clients users can set the number of threads he wants to allocate to the project. The GUI Client has also option to switch on Screensaver which can be use for promotion of Slovenian touristic attractions.

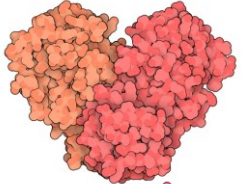
<https://covid.si/en/quick-start/>



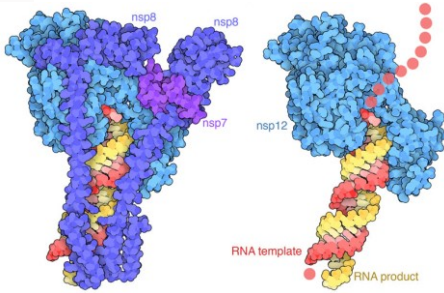
# The Live Cycle of SARS-CoV-2



**SPIKE PROTEIN**



**PROTEASES**



**RNA dependant RNA polymerase**

# Targets related to COVID-19 used for docking

Target ID	The protein	Organism	Source of structure	PDB Code
<b>1-21</b>	3CL Pro	SARS-2	Snapshots from MD trajectory	
<b>26-34</b>	Spike Protein	SARS/MERS/SARS-2	Crystallographic structures	2AJF,2DD8, 3SCL, 5X58,6ACK,6LZG, 6M0J,6M17,6VW1
<b>35-37</b>	DHODH	Human	Crystallographic structures	4IGH,4JTU,4OQV
<b>41-48</b>	PL Pro	SARS/MERS/SARS-2	Crystallographic structures	2FE8,3MP2,4OW0, 6W9C,6WRH,6WUU, 6WX4,6WZU
<b>49-50</b>	FURIN	Human	Crystallographic structures	5JXH, 5MIM
<b>51-54</b>	Methyl Transferase	SARS2	Crystallographic structures	6W4H,6W61,7C2I,7C2J
<b>55-56</b>	E Protein	SARS / SARS2	NMR/Homology model	5X29 (SARS) 5X29 - Homology (SARS2)
<b>58-59</b>	PL Pro	SARS2	Homology models	based on 3E9S based on 5E6J based on 6W9C

# Statistics of COVID.SI - distributed computing project

## DOCKING STATISTICS

(Updated: 2022-06-29 @ 20:50:02)

**EACH PACKAGE HAS 1000 CMPDS**

**510**

in last 60 minutes

Number of successfully docked packages

**5.413**

in last 24 hours

**47.020**

in last month

**2.199.634**

since May 13th 2020

These numbers mean number of successfully uploaded results to server. Each time a client returns results, it had had to dock 1000 molecules beforehand, some of them 50 times.

Number of computers docking

**4**

in last 60 minutes

**6**

in last 24 hours

**14**

in last month

**533**

since May 13th 2020

Only successful communications with the server are included. Last hour number can deviate due to some clients needing more than an hour to finish docking the package and to return the results.

The PHP/MySQL application is designed to monitor the activity on our platform.

# SiDock@home the extension of the COVID.SI project

SiDock@home Projekt ▾ Računanje ▾ Skupnost ▾ Spletna stran ▾ CrtomIP Log out

## Novice

**SPECIAL THANKS TO NATALIA NIKITINA AND MAXIM MANZYUK FOR GREAT CONTRIBUTIONS TO THE PROJECT**

**Project maintenance**  
Dear participants, n  
Thank you for participation!  
26 Feb 2022, 9:02:37 UTC · [Discuss](#)


**The project is online!**  
Dear participants!  
The work by upgrade is completed. Project database, website and request processing migrated on pair of mirrored SSD, workunit files (as previously) and uploaded results placed on mirrored HDD.  
Thank you for attention and participation!  
17 Feb 2022, 13:54:21 UTC · [Discuss](#)

## Welcome, CrtomIP

Želite pomagati več?

- Če BOINC v tem računalniku ni nameščen, [ga prenesite](#).
- Namestite BOINC na druge računalnike, tablične računalnike in telefone.
- Povejte svojim prijateljem o BOINC-u in jim pokažite, kako se pridružijo SiDock@home.

## Uporabnik dneva

 **ArsenEverlast**  
Software engineer from Lviv, Ukraine!

**SiDock@HOME** is extension of the COVID.SI, here the library of the compound is significantly bigger. The system of distributed computing is here based on BOINC server/client system. SiDock@HOME is now the biggest project not founded from the institutions (**Almost ZERO budget science**).



# Statistics of SiDock@home

## Server status

## Computing status

Program	Host	Status	Tasks ready to send	Tasks in progress	Tasks waiting for assimilation	Workunits waiting for file deletion	Tasks waiting for file deletion	Users (hours)
Download server	www.sidock.si	Running	23145					
Upload server	www.sidock.si	Running		46065				
Scheduler					0			
feeder					0			
transitioner	humpback	Running				18958		
transitioner	humpback	Running				0		
file_deleter								0.00
cmdock-boinc-zcp_assimilator (cmdock-boinc-zcp)	humpback	Running						
cmdock-boinc-zcp_assimilator (cmdock-boinc-zcp)	humpback	Running						
cmdock-boinc-zcp_script_validator (cmdock-boinc-zcp)	humpback	Running						
cmdock-boinc-zcp_script_validator (cmdock-boinc-zcp)	humpback	Running						
cmdock-boinc-zcp_script_validator (cmdock-boinc-zcp)	humpback	Running						
cmdock-boinc-zcp_script_validator (cmdock-boinc-zcp)	humpback	Running						

**ONLINE SINCE DEC 2020**

**MORE THAN 6600 USERS OF THEM  
2455 WITH RECENT CREDIT**

**MORE THAN 28 000 COMPUTERS**

**CURRENT CPU POWER: 65 000 GFLOPS**

**SCREENED 1 BILLION COMPOUNDS TO 15 TARGETS**

## Research progress

Target 16: corona_NSP16_v1 (%)	66.714	With recent credit	6395
Completed targets: corona_RdRp_v1, corona_E		Registered in past 24 hours	31
corona_3CLpro_v6, corona_3CLpro_v7, corona_3CLpro_v8, corona_Sprot_delta_v1, corona_NSP14_MTase, corona_PLpro_v3, corona_PLpro_v4, corona_NSP14_7n0d_7n0b			

**126.8 MILLIONS HOURS (14.465 YEARS) OF CPU**

# Action of Wuhobran mask holders 3D printing



A screenshot of a 3D printing project page. It features a blue background with a red thumbs-up icon at the top left. Below the icon, the number '13,890' is displayed in large white font. Underneath the number, the text 'Printed Wuhobran mask holders' is visible. At the bottom of the screenshot, the word 'CONTACT' is written in all caps, followed by the text 'For any questions, ideas or comments we are available at [info@covid.si](mailto:info@covid.si)'.



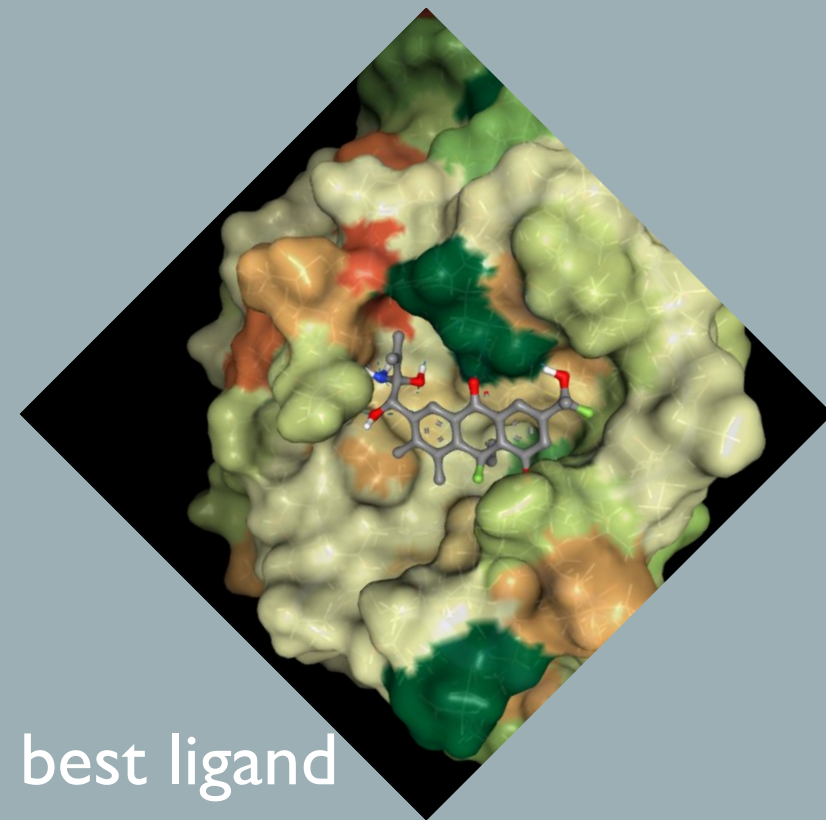
**WUHOBTRAN WAS SELECTED AS NEOLOGISM OF THE  
YEAR 2021 BY FRAN RAMOVŠ INSTITUTE OF THE  
SLOVENIAN ACADEMY OF SCIENCE**

We have organized volunteers to 3D print Wuhobran mask holders. Wuhobrans were distributed free of charge to Slovenian medicinal workers.

# DOCKIT

An interface for a synergistical human – computer cooperation via:

- Crowdsourcing
- Citizen's science
- Gamification
- Evolutionary algorithm



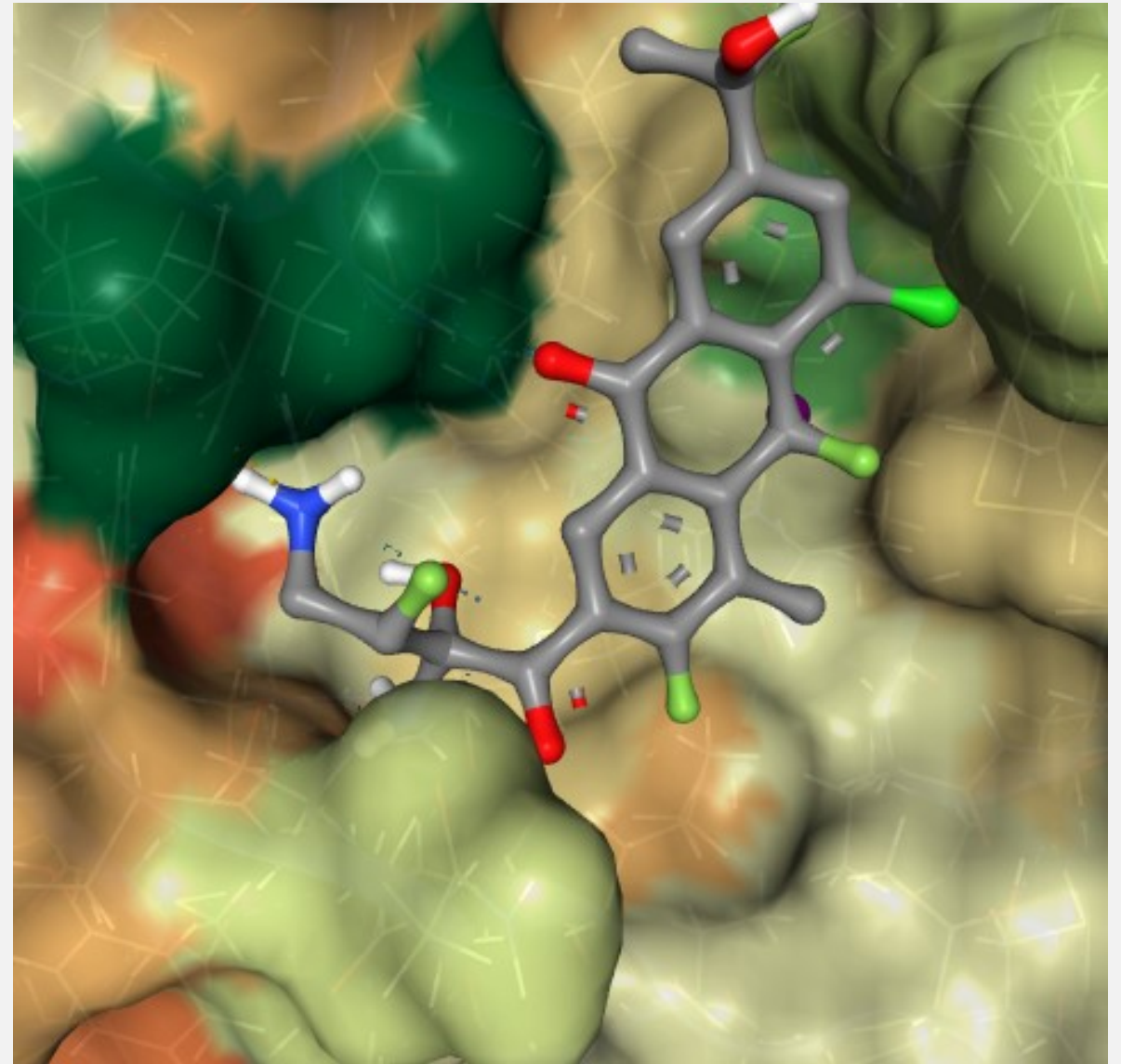
To solve the optimization problem of finding the best ligand for the receptor.

# DOCKIT

Humans are great at pattern recognition;

We (humans) see how we could easily fill the receptor cavity.

Computers are good to enhance the result of that, to find variations of it, that are better.





# DOCKIT

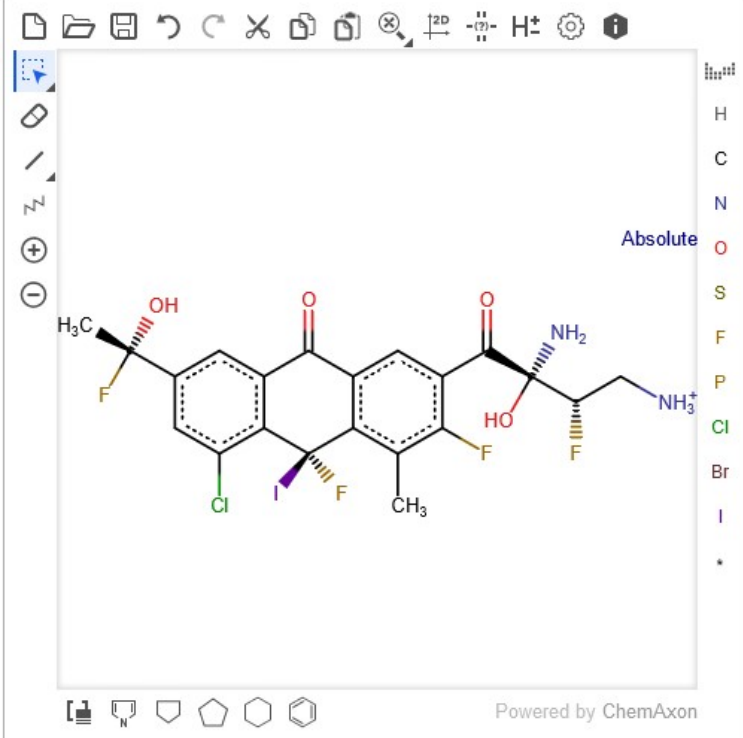
Score

Best / last ligands switch

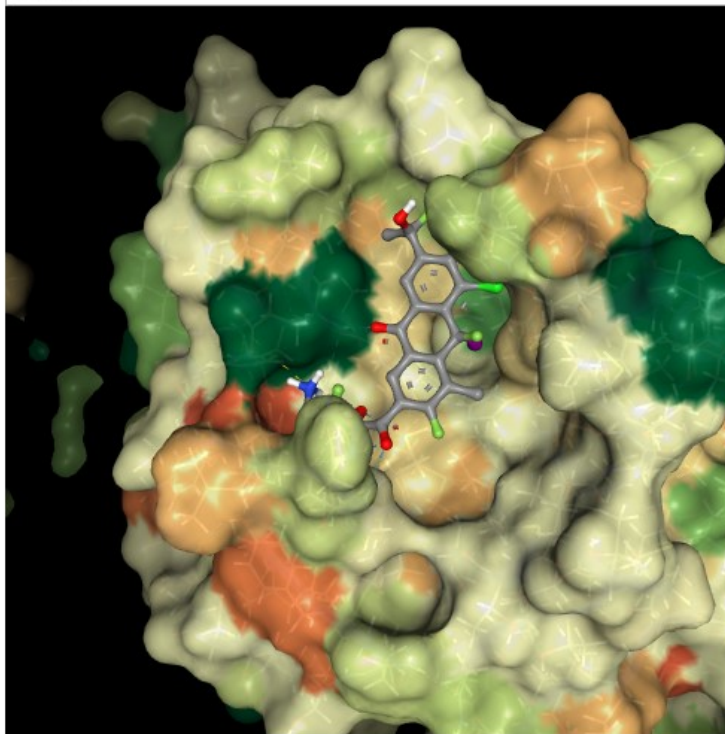
Prijavljen kot seba ([odjavi se](#)).

Cc1c(F)c(cc2C(=O)c3cc(cc(Cl)c3[C@](F)(I)c12)[C@@](C)(O)F)C(=O)[C@](N)(O)[C@@H](F

-44.5403



Sidraj molekulo v SARS-CoV-2 3CL Pro



Najboljši ligandi ▾ Prikaži samo moje ligande:

-40.4335	-40.3253	-40.0197	-39.9781
-39.637	-39.3634	-38.9909	-38.9407
-38.908	-38.7325	-38.4458	-38.2848

Ligandi dobljeni z algoritmom so oranžni.

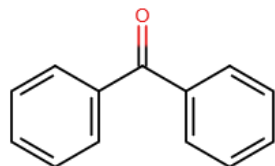
Molecule editor

Docking viewer

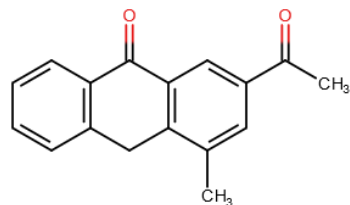
Best ligands list

# DOCKIT

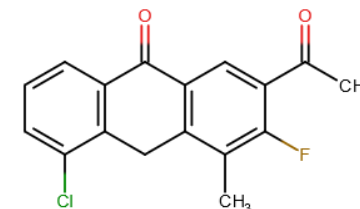
1st person has an idea:



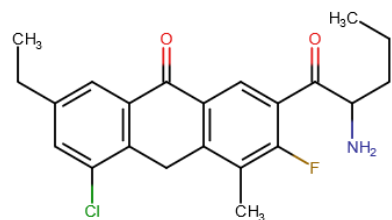
2nd person sees it and improves it:



Computer tries various combinations, if they are better, they get to the top

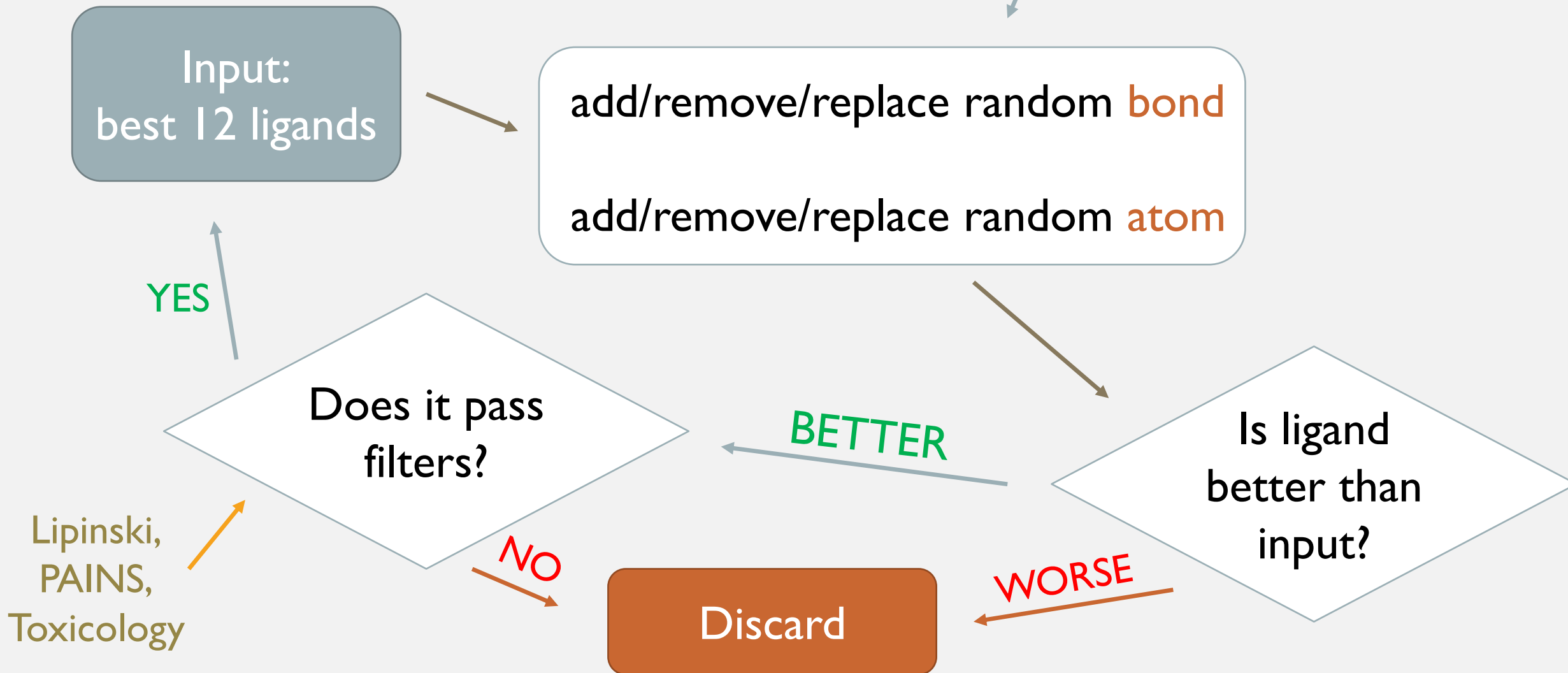


3rd person sees it and improves it:



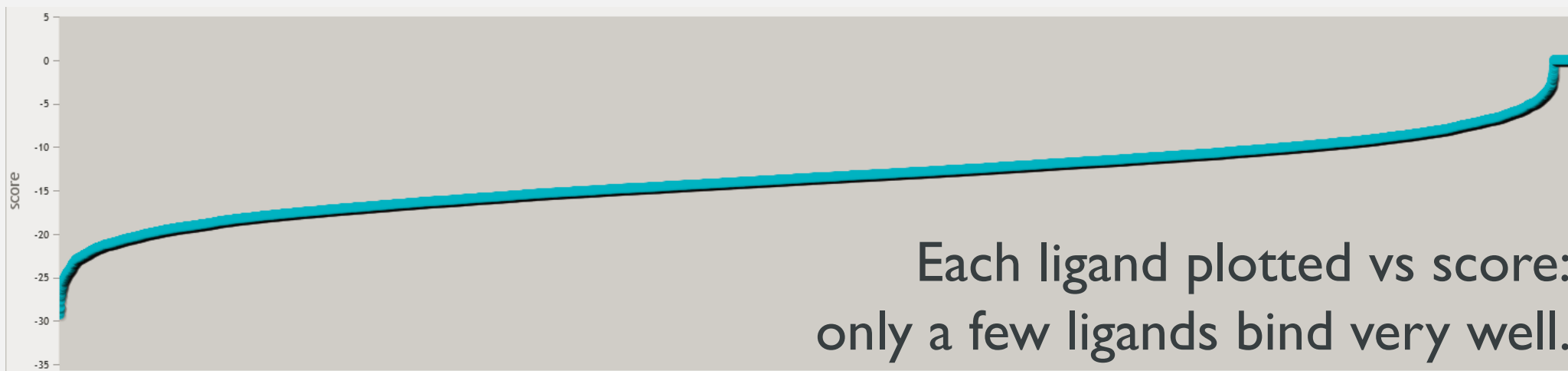
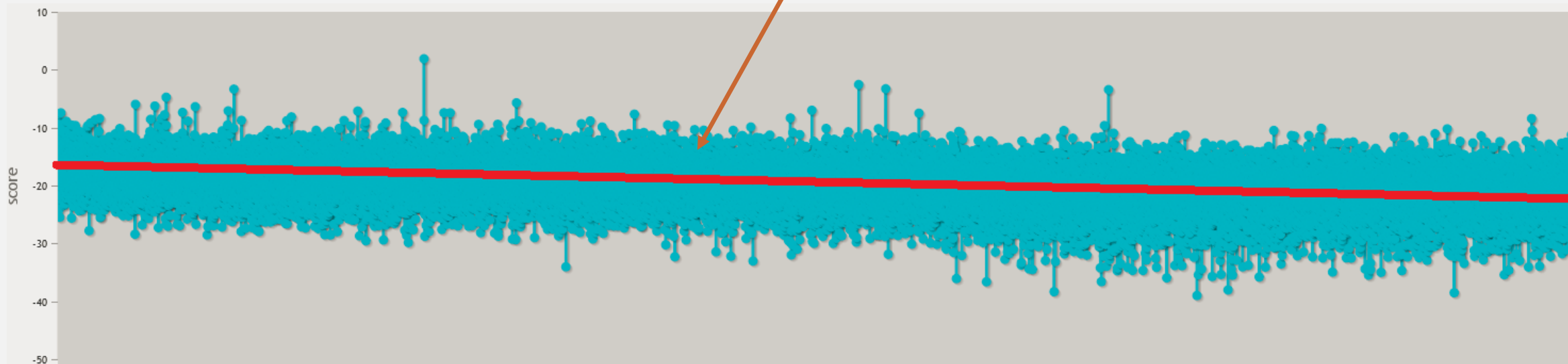
# DOCKIT

Loop this a few times,  
each action having a certain probability



# DOCKIT

Trendline of score improvement over time.



Each ligand plotted vs score:  
only a few ligands bind very well.

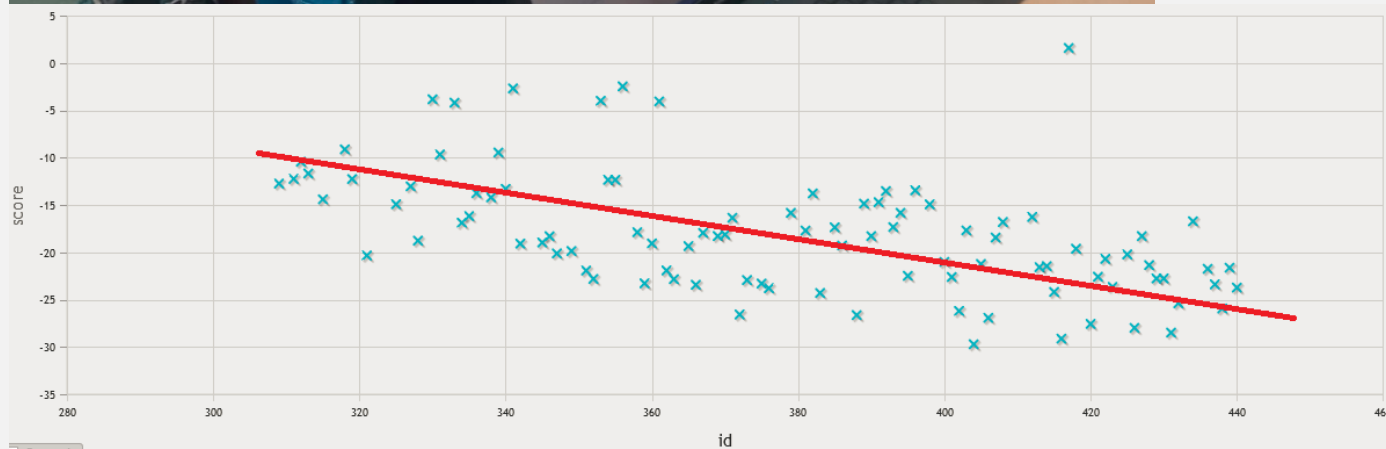
# DOCKIT

Easy to use.



Highschoolers competing between each other after just a few hours of introductory organic chemistry.

They have a very good trendline after just one hour.





# **Some results of the project**





## The virus that shook the world: questions and answers about SARS-CoV-2 and COVID-19

Radostina Alexandrova<sup>a</sup>, Pencho Beykov<sup>a, b</sup>, Dobrin Vassilev<sup>c</sup>, Marko Jukić<sup>d, e</sup>, and Črtomir Podlipnik<sup>f</sup>

<sup>a</sup> Department of Pathology Institute of Experimental Morphology, Pathology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia, Bulgaria <sup>b</sup> Faculty of Chemistry and Pharmacy, Sofia University “St. Kliment Ohridski”, Sofia, Bulgaria <sup>c</sup> “Alexandrovska” University Hospital, Medical University of Sofia, Sofia, Bulgaria <sup>d</sup> Laboratory of Physical Chemistry and Chemical Thermodynamics, Faculty of Chemistry and Chemical Technology, University of Maribor, Maribor, Slovenia <sup>e</sup> Natural Sciences and Information Technologies, Faculty of Mathematics, University of Primorska, Koper, Slovenia <sup>f</sup> Department of Physical Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia

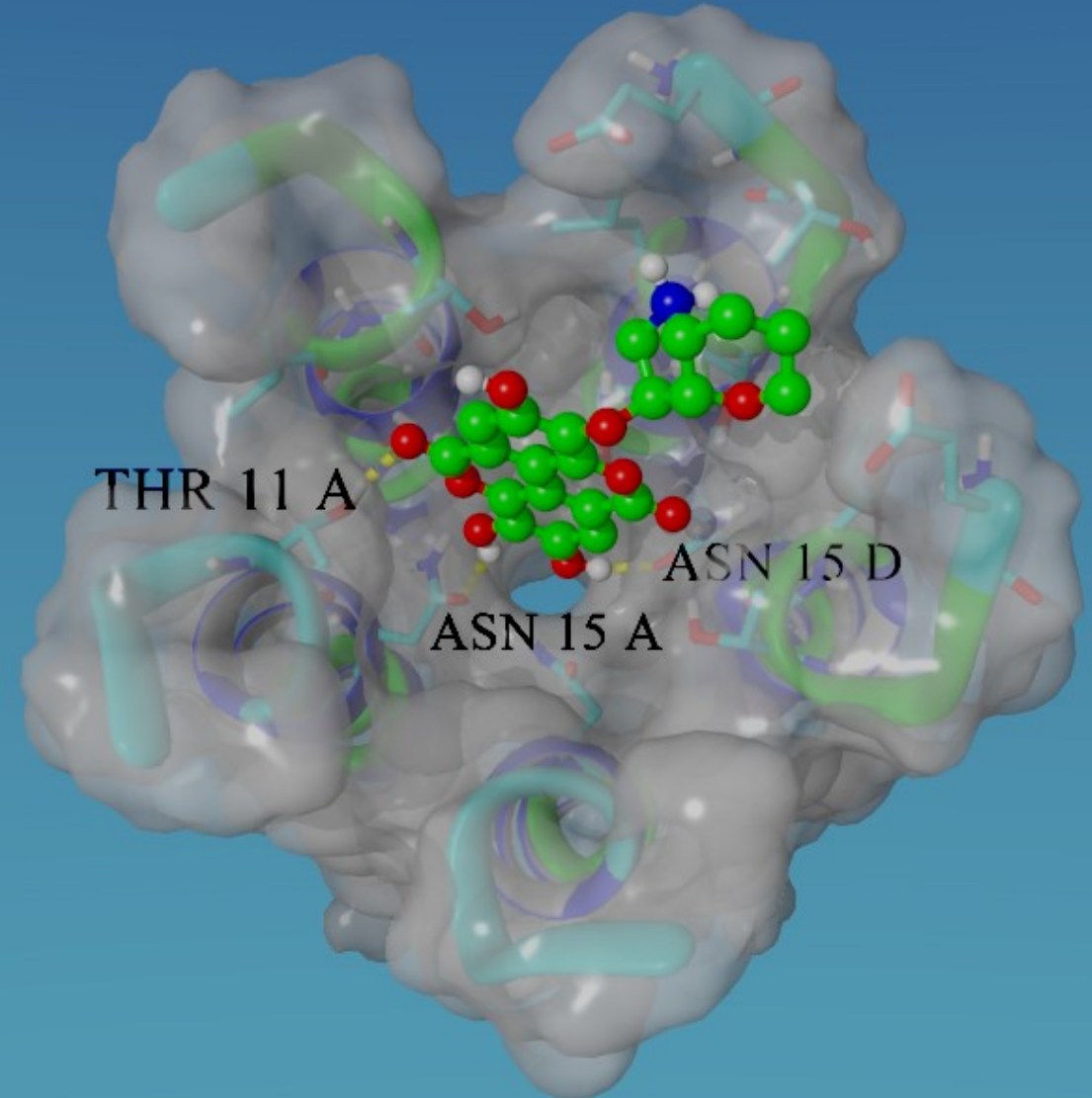
### ABSTRACT

SARS-CoV-2 is an emerging human beta-coronavirus that caused the COVID-19 (Coronavirus Disease – 19) pandemic, the most significant health and social crisis in the last 100 years. SARS-CoV-2 is not only a respiratory virus; the symptoms of COVID-19 can include gastrointestinal, neurological, renal, cardiovascular and other complications. A large part of SARS-CoV-2 infected individuals are asymptomatic or have mild symptoms, around 20% of COVID-19 cases require hospitalization, and 5% can become critically ill. This review summarizes data on the biology of the virus and its pathological manifestations, antiviral immune response, information on the experimental models used in the related studies, treatment approaches and vaccine strategies.

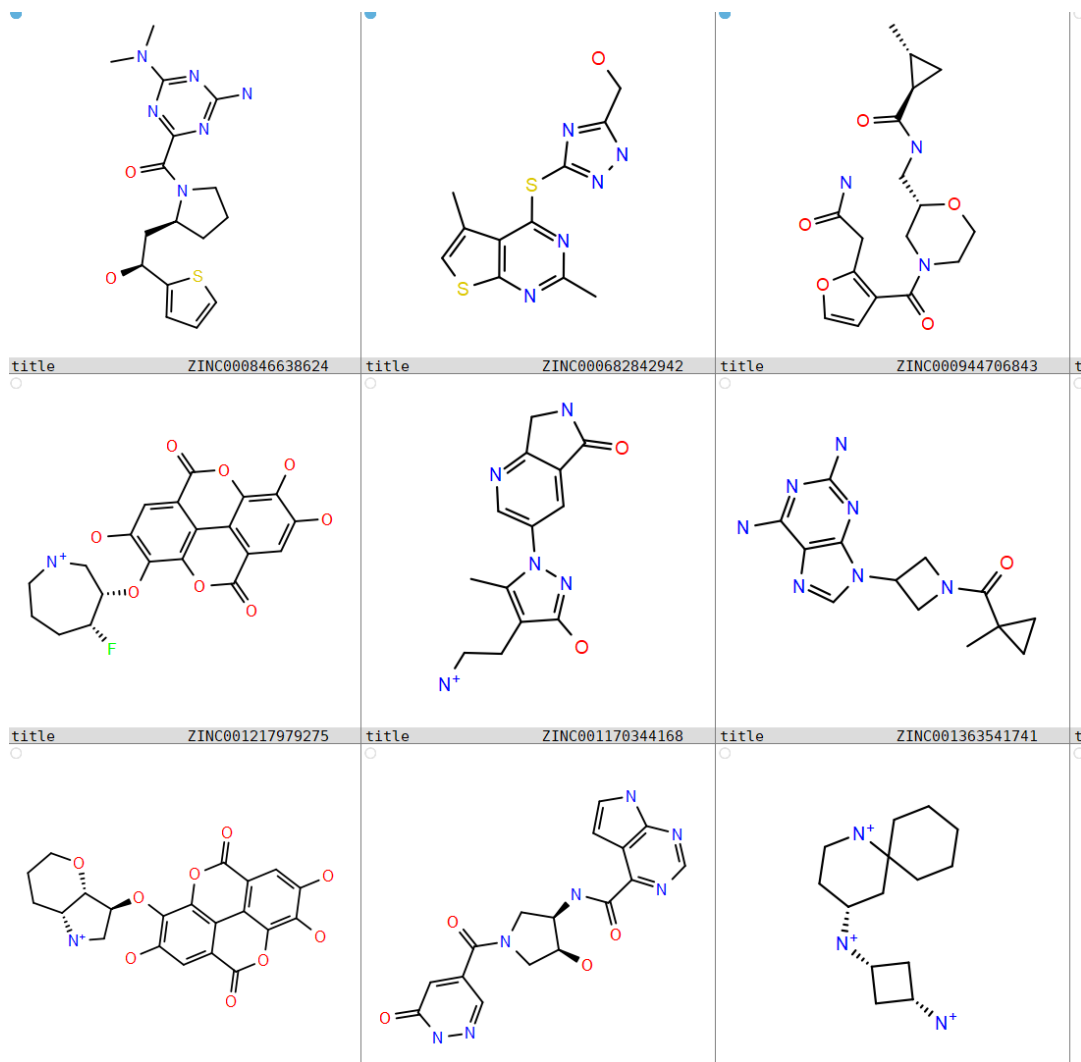
## Inhibition of the ion channel of SARS-CoV-2 E-Protein

- The SARS-CoV-2 envelope (E) protein is a small structural protein involved in many aspects of the viral life cycle. The E protein promotes the packaging and reproduction of the virus, and deletion of this protein weakens or even abolishes virulence.
- Here, we studied the inhibition of the ion channel of SARS-CoV-2 by small molecule inhibitors.
- Support of ERASMUS+ MSc student

**Lennart Dreisewerd**



# The workflow of the Screening (Epro - inhibitors)



HTVS

HTVS screening of **1B compounds** with CMDock using Boinc - Grid computing platform (output 35k compounds)

FILTER

Additional filtering of approx. **35k compounds** from HTVS with PAINS/REOS/Toxicity (output 3.3 k compounds)

MMGBSA

VSW of Schrodinger (Glide HTVS -> Glide SP -> Glide XP -> MMGBSA): input **3.3k compounds** output **22 compounds**




**MD - IN PROGRESS**

**IN VITRO TESTS? (SOFIA -)**



Article

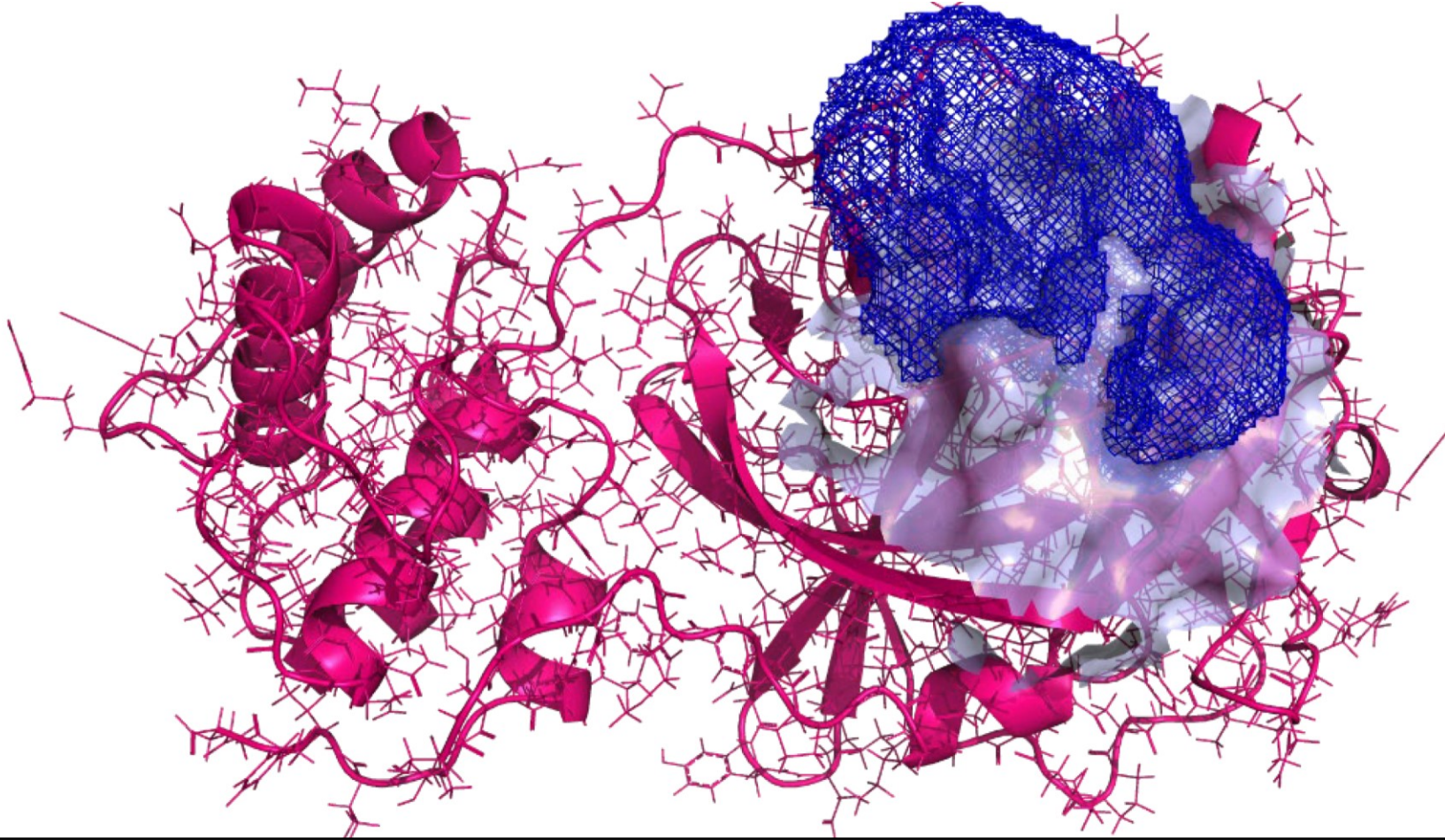
# Prioritisation of Compounds for 3CL<sup>Pro</sup> Inhibitor Development on SARS-CoV-2 Variants

Marko Jukič <sup>1,2</sup> , Blaž Škrlj <sup>3</sup> , Gašper Tomšič <sup>4</sup>, Sebastian Pleško <sup>5</sup>, Črtomir Podlipnik <sup>6,\*</sup>  and Urban Bren <sup>1,2,\*</sup>

- <sup>1</sup> Laboratory of Physical Chemistry and Chemical Thermodynamics, Faculty of Chemistry and Chemical Engineering, University of Maribor, Smetanova ulica 17, SI-2000 Maribor, Slovenia; marko.jukic@um.si
  - <sup>2</sup> Faculty of Mathematics, Natural Sciences and Information Technologies, University of Primorska, Glagoljaška 8, SI-6000 Koper, Slovenia
  - <sup>3</sup> Institute Jožef Stefan, Jamova cesta 39, SI-1000 Ljubljana, Slovenia; blaz.skrlj@ijs.si
  - <sup>4</sup> Independent Researcher, Cesta Cirila Kosmača 66, SI-1000 Ljubljana, Slovenia; gasper.tomsic@icloud.com
  - <sup>5</sup> Erudio, Litostrojska Cesta 40, SI-1000 Ljubljana, Slovenia; sebastian.plesko@erudio.si
  - <sup>6</sup> Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia
- \* Correspondence: crtomir.podlipnik@fkkt.uni-lj.si (Č.P.); urban.bren@um.si (U.B.); Tel.: +386-41-440-198 (Č.P.); +386-2-22-94-421 (U.B.)

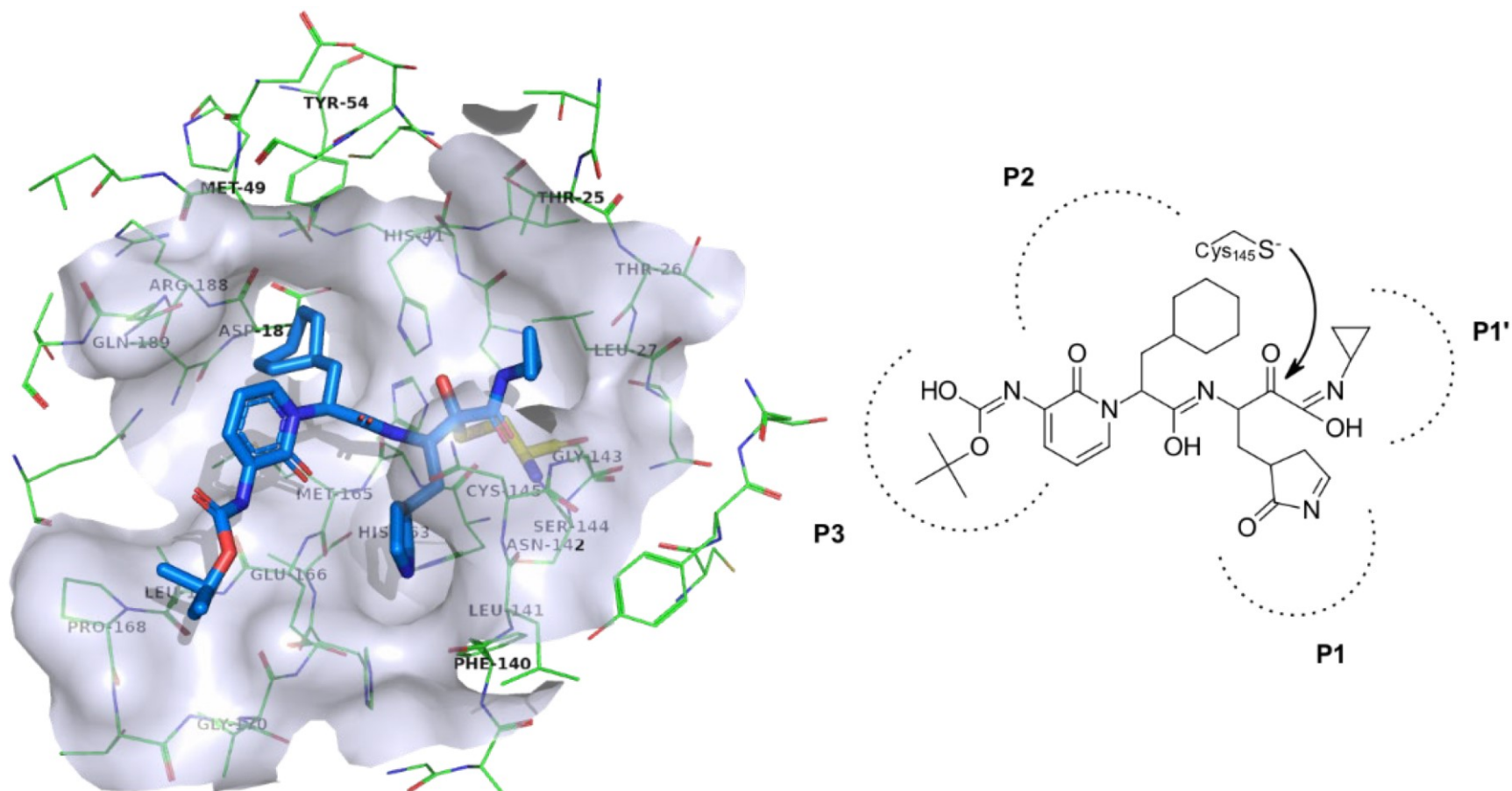


# Selecting and preparing biomolecular target



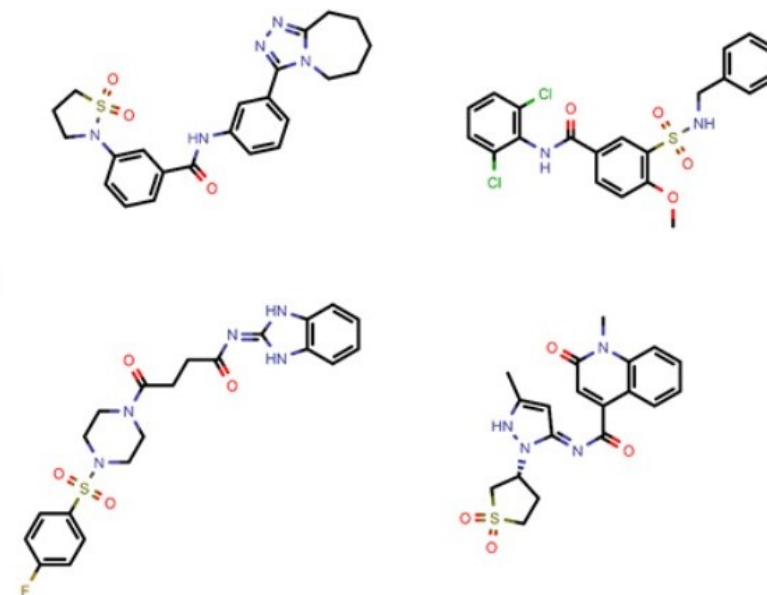
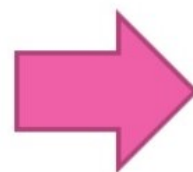
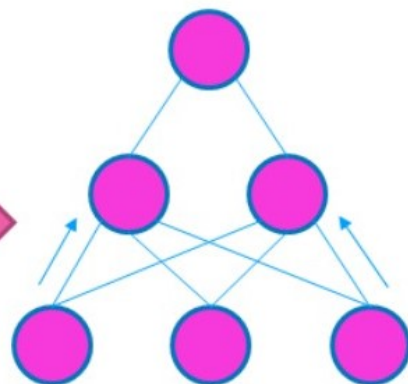
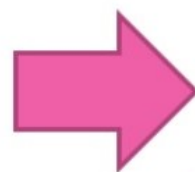
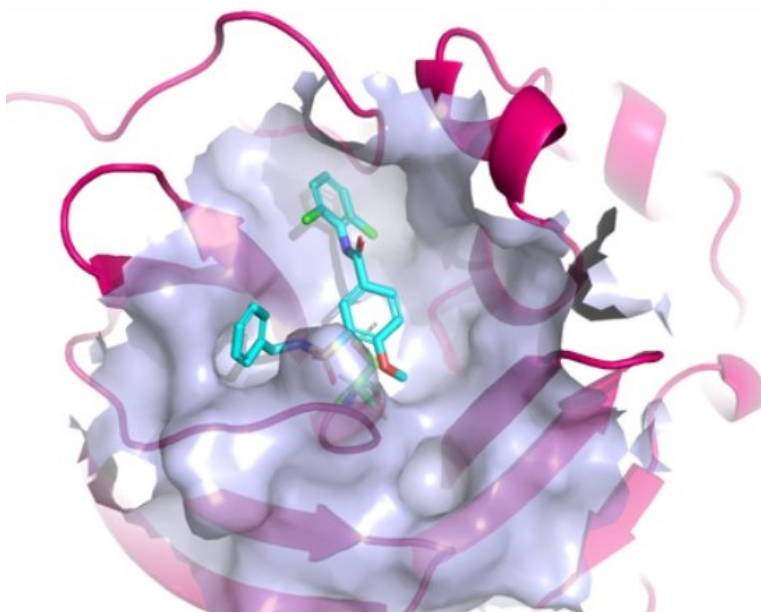
Schrodinger Protein Preparation Wizard has been used for preparing the structure of SARS-CoV-2 Main protease. CMCavity has been used for grid generation and Pymol has been used for visualization.

# Structure based HTVS and analysing results



With molecular docking we get information on what extent the ligand is complementary to the receptor; the higher is complementarity higher the score we may expect. Docking results **can only be used for filtering for the prioritisation** of further actions (**in vitro experiments are needed**).

# Compound prioritisation



Molecular docking is **not** almighty. It can be used for initial filtering; other methods and additional filtering must be taken to eliminate toxic and reactive compounds, to check favourable interactions, etc. Such prioritisation results in a list of compounds interesting for further ***in vitro*** or ***in vivo*** studies.

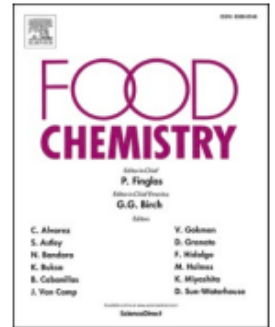




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# Food Chemistry

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## Inhibition of the SARS-CoV-2 3CL<sup>pro</sup> main protease by plant polyphenols

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<sup>e</sup> Department of Biology, Biotechnical Faculty, University of Ljubljana, SI-1000 Ljubljana, Slovenia

<sup>f</sup> Department of Pharmaceutical Biology, Faculty of Pharmacy, University of Ljubljana, SI-1000 Ljubljana, Slovenia

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We studied the binding of set polyphenols to the main protease of SARS-CoV-2, using "In Silico" methodology (molecular docking, molecular dynamics) and "In Vitro" experiments (enzyme assay, SPR).

# Set of polyphenols used in the study

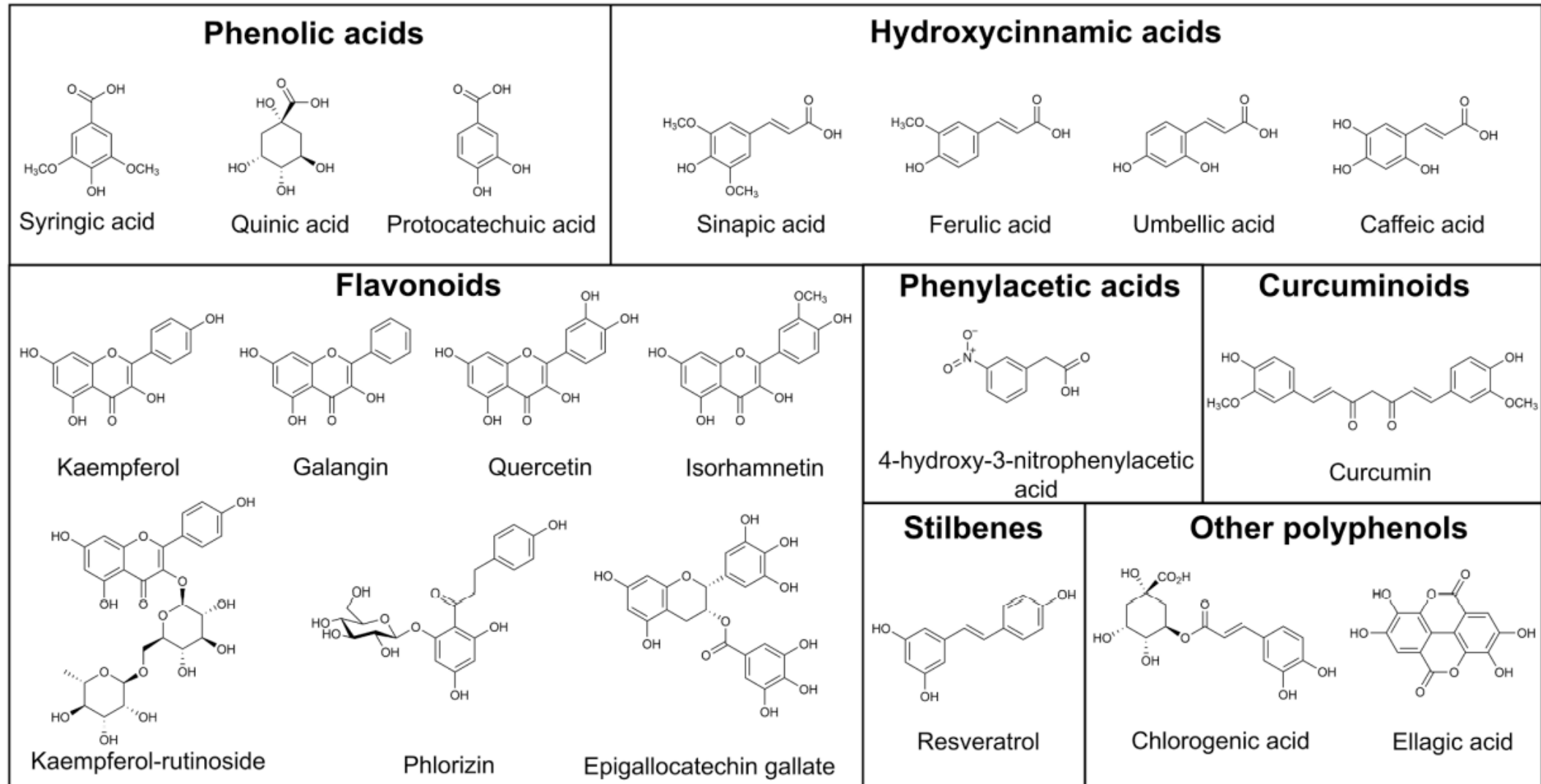
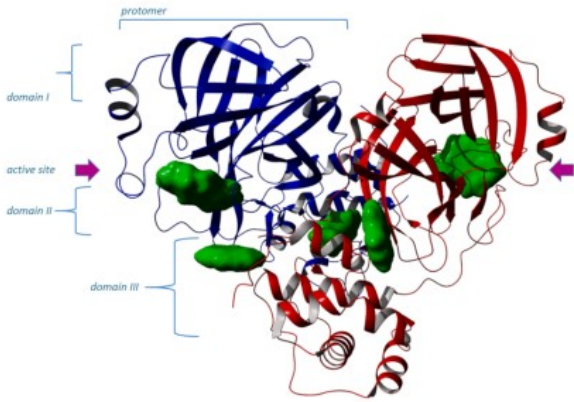


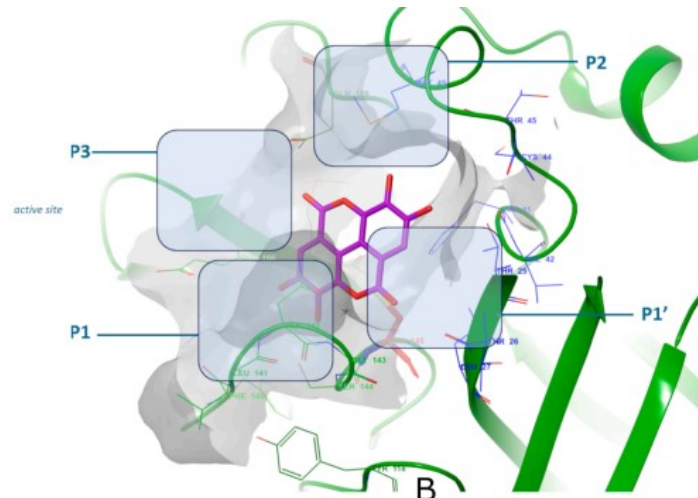
Fig. 1. Structures of the polyphenols used in this study. The polyphenols are divided into seven groups, according to their structures: phenolic acids, hydrox-



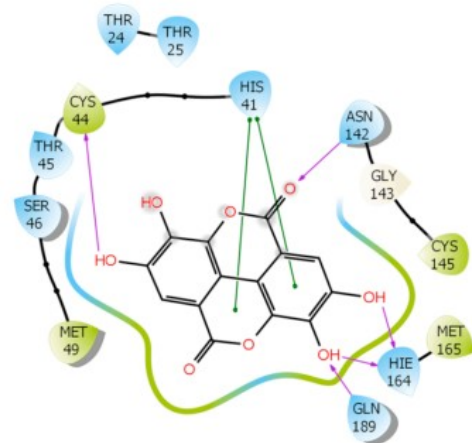
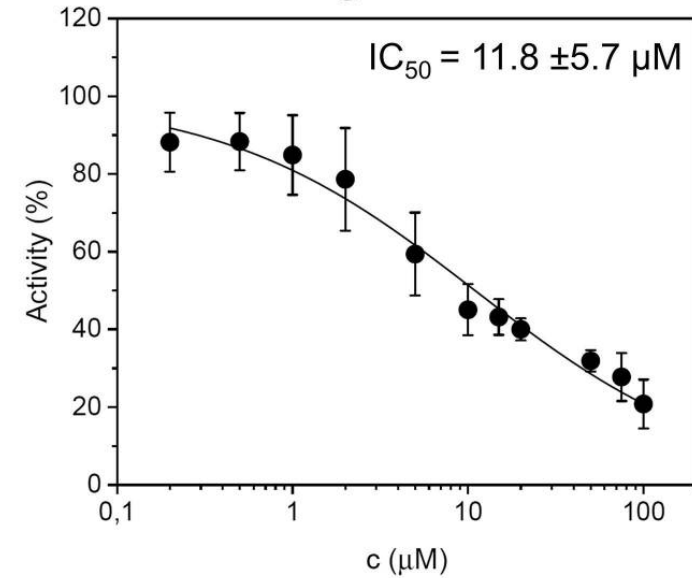
# The analysis of Ellagic acid binding to SARS-CoV-2 Main Protease



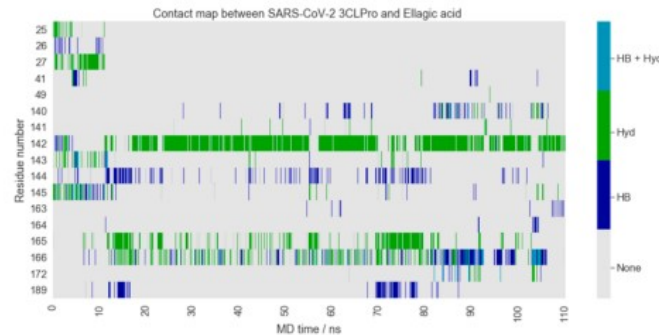
A



B



C



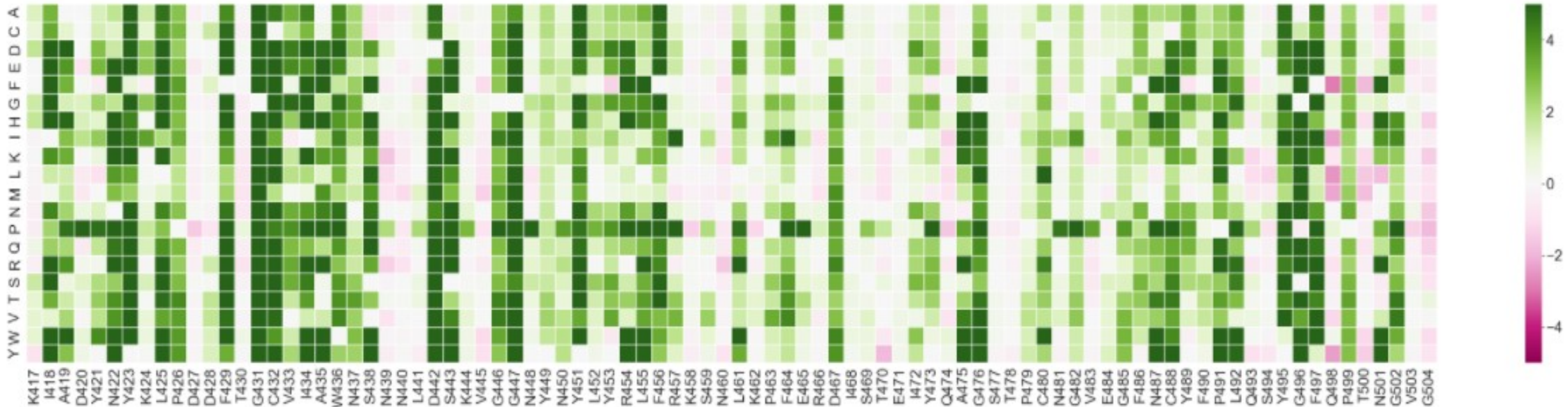
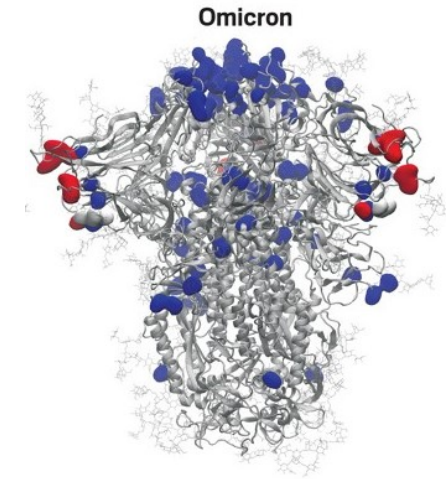
D

Of all the polyphenols included in the study, ellagic acid inhibited the major protease most strongly in the enzyme assay. Analysis of the docking interactions shows that the compound binds well to the binding site.



# Bioinformatics Study of the Evolution of SARS-CoV-2 Spike Protein

Črtomir Podlipnik<sup>1\*</sup>, Radostina Alexandrova<sup>2</sup>, Sebastian Pleško<sup>3</sup>, Urban Bren<sup>4,5</sup> and Marko Jukič<sup>4,5\*</sup>



We conducted a full RBD 417-505 mutagenesis study using **FoldX** in order to assess the key mutations and their effects on the stability of the ACE2:RBD complex; in total 1780-point mutations.

**Thank you  
for your  
attention !!!**

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