MultiScale Simulations for the Design and Testing of SARS-CoV-2 3CL Protease Inhibitors

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VNIVERSITAT DE VALÈNCIA

16th Users Conference

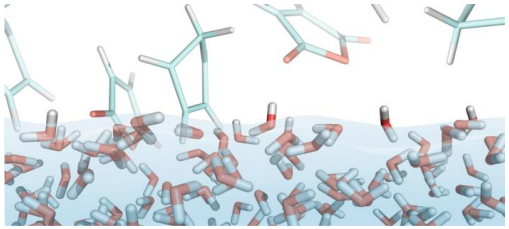
CÁCERES

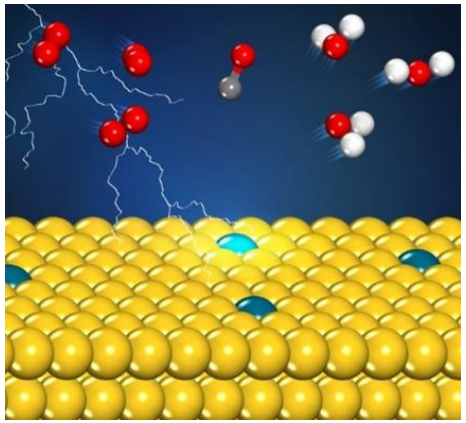
14th - 15th September 2022

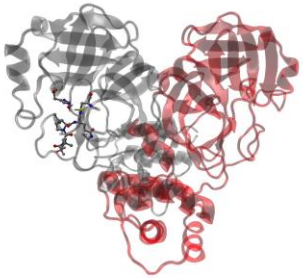
RES

RED ESPAÑOLA DE SUPERCOMPUTACIÓN

Simulating Chemical Processes in Complex Environments





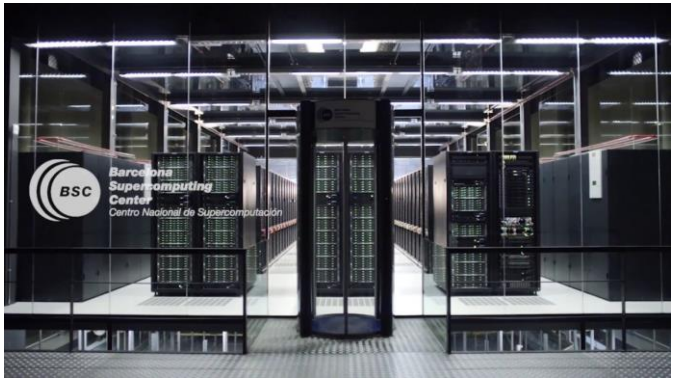


Paxlovid action in 3CL protease of SARS-CoV-2 Virus

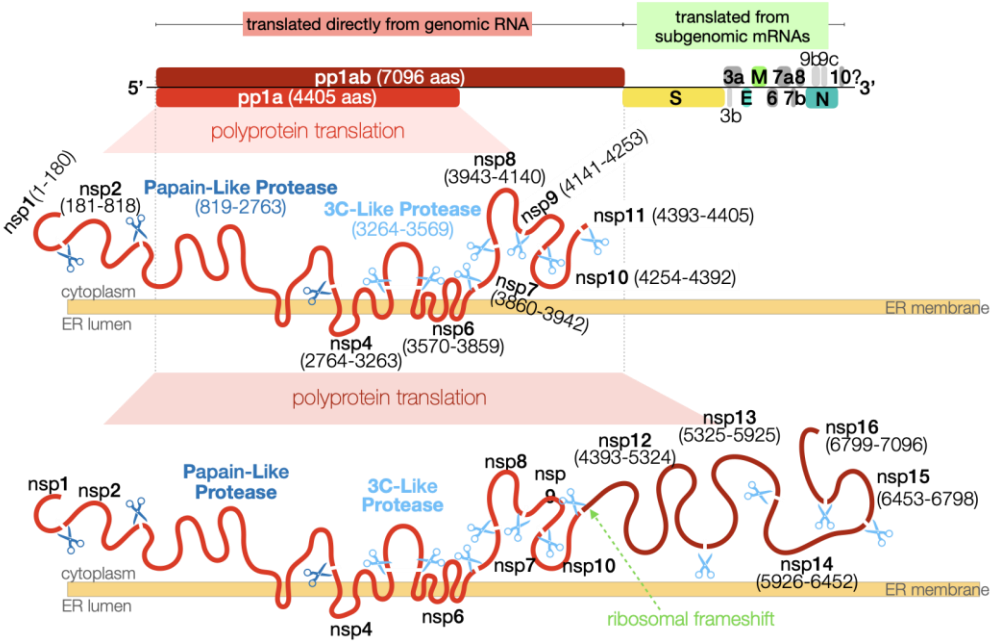
- **Energy Function** able to describe bond breaking/forming processes (**electrons**) in very large systems

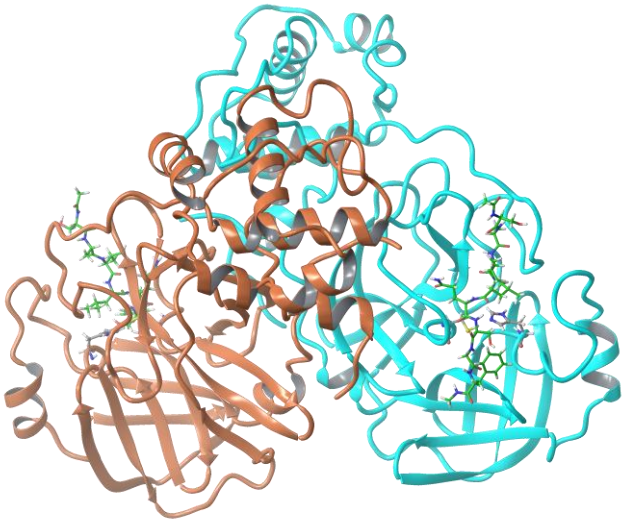
- **Sampling of configurations**
  (Exploring the **Free Energy Landscape**)

- **Supercomputers**



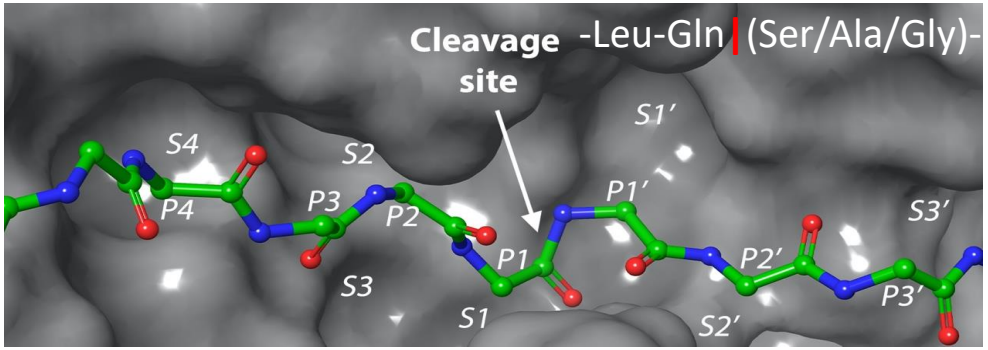
3CL (or Main) Protease of SARS-CoV-2





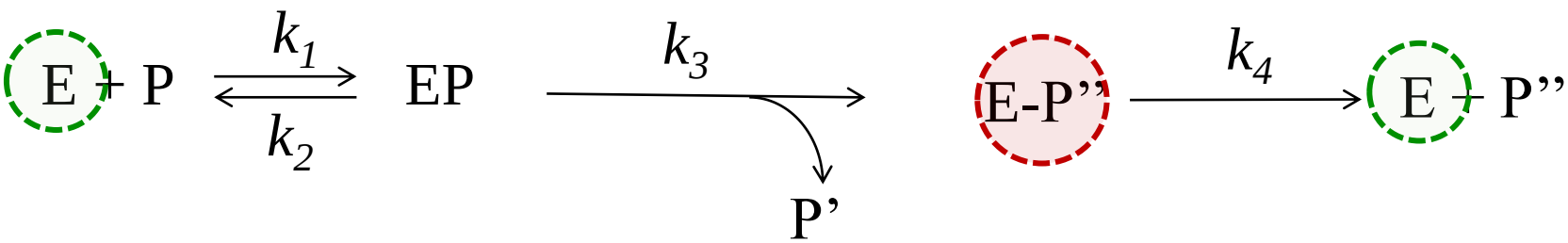
Good target for drug design:

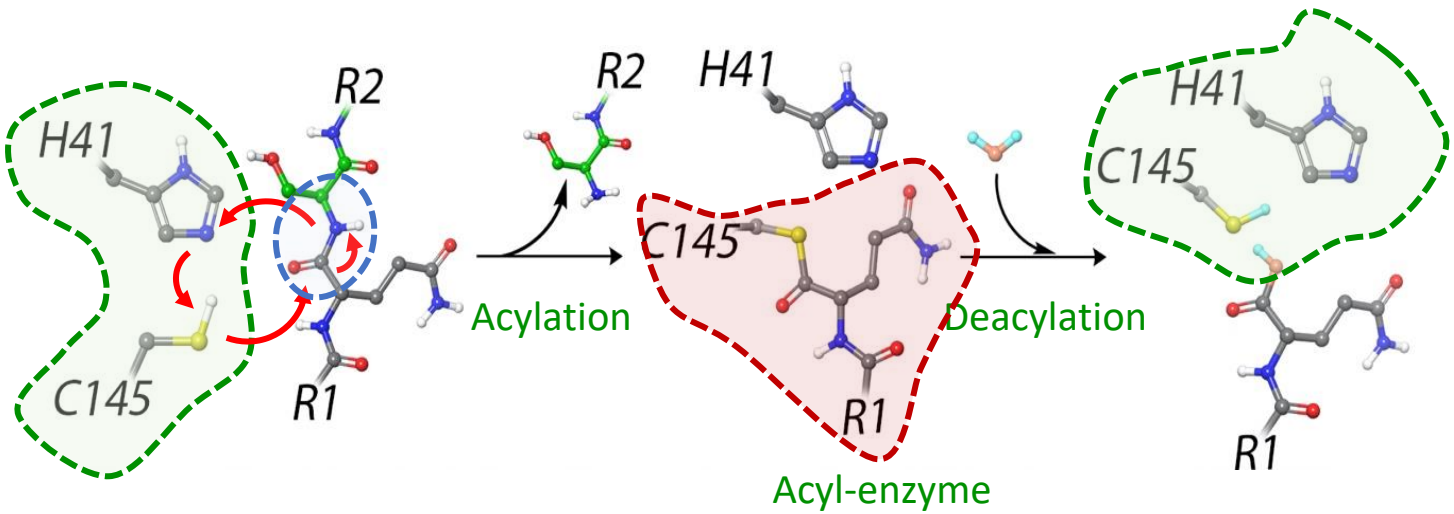
- Essential in the replication cycle of the virus
- Conserved among variants and different Cvs
- Sequence specificity not used by other human proteases



3CL Catalytic reaction

Proposed Mechanism:

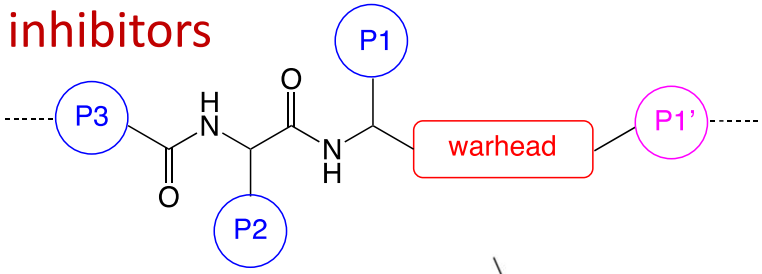




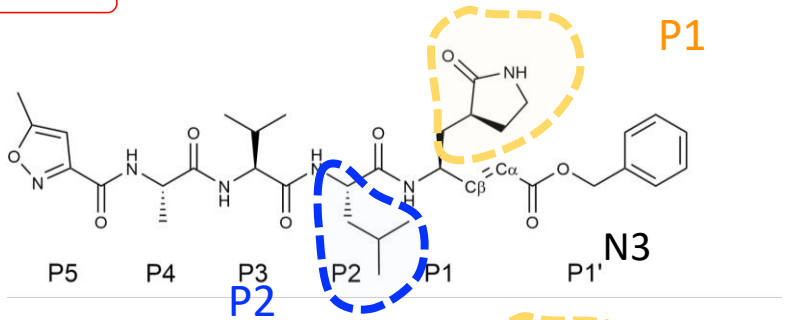
Covalent Inhibition Mechanism

$$E + I \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EI \xrightarrow{k_3} E\text{-}I \not\longrightarrow E + I'$$

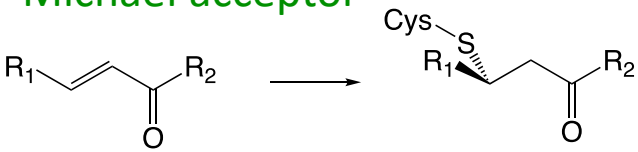
Peptidomimetic covalent inhibitors



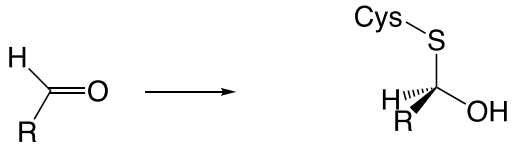
-Leu-Gln|(Ser/Ala/Gly)-



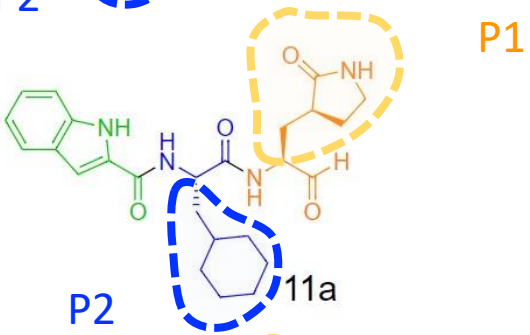
Michael acceptor



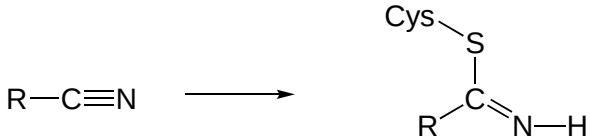
Aldehydes/Ketones



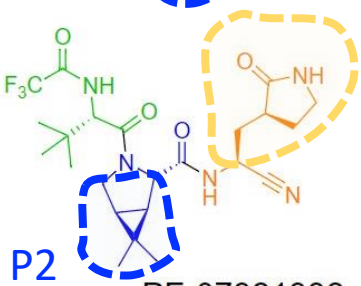
hemithioacetal



Nitriles



thioimidiate



PF-07321332 / Paxlovid

MultiScale Methods

The Nobel Prize in Chemistry 2013
Martin Karplus, Michael Levitt, Arieh Warshel

The Nobel Prize in Chemistry 2013

© Nobel Media AB
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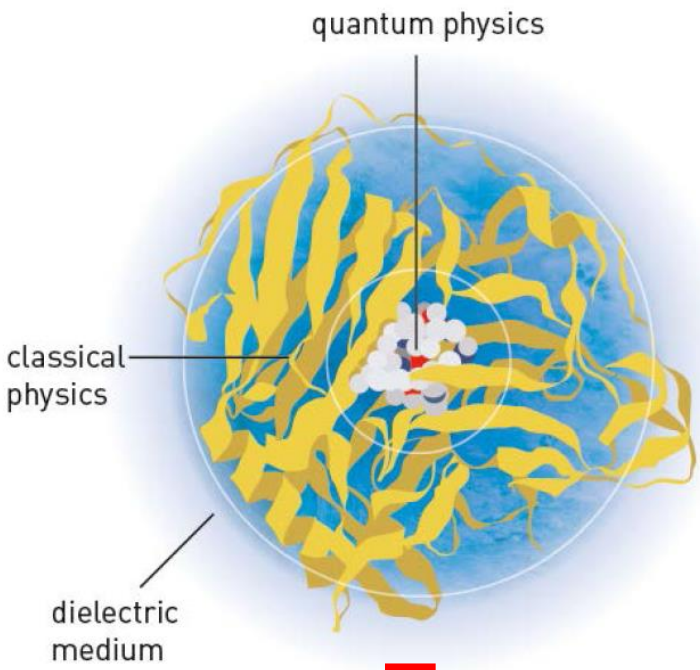
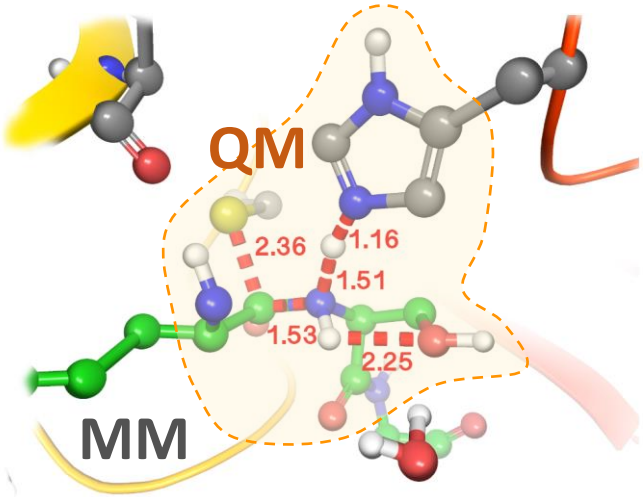
Photo: Keilana via Wikimedia Commons
Michael Levitt

Photo: Wikimedia Commons
Arieh Warshel



MM MD: Amber ff14SB + TP3P + Antechamber

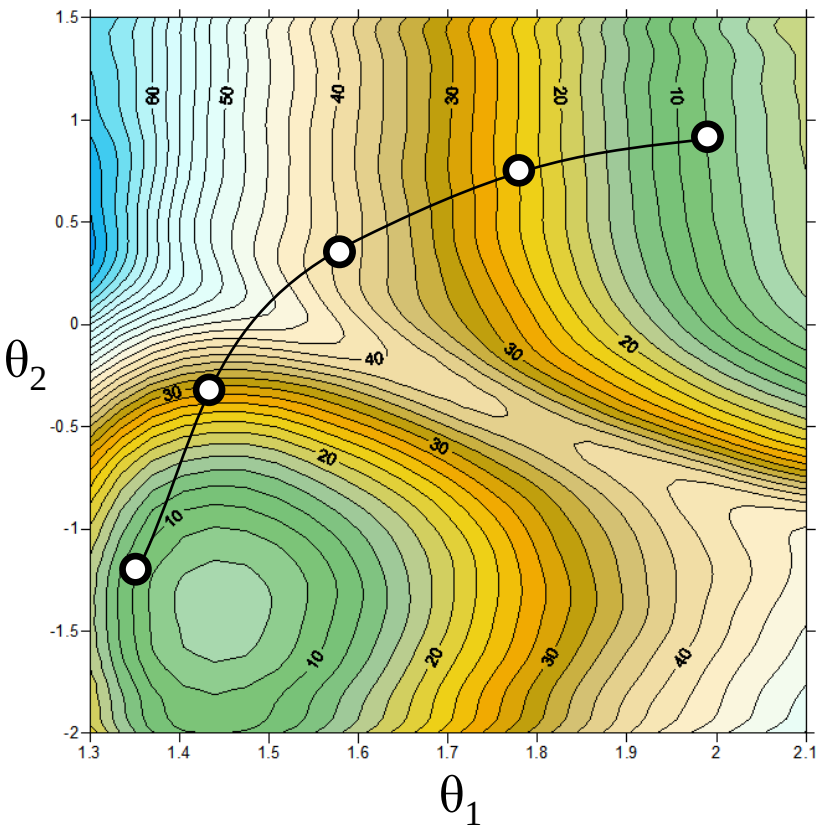
QM/MM: B3LYPD3/6-31+G* (validated against exp. and other functionals)



Free Energy Calculations with the Adaptive String Method:

- Multidimensional problem
- Several mechanistic possibilities:
  - Which is the timing of the different events?
  - Concerted/Stepwise ?

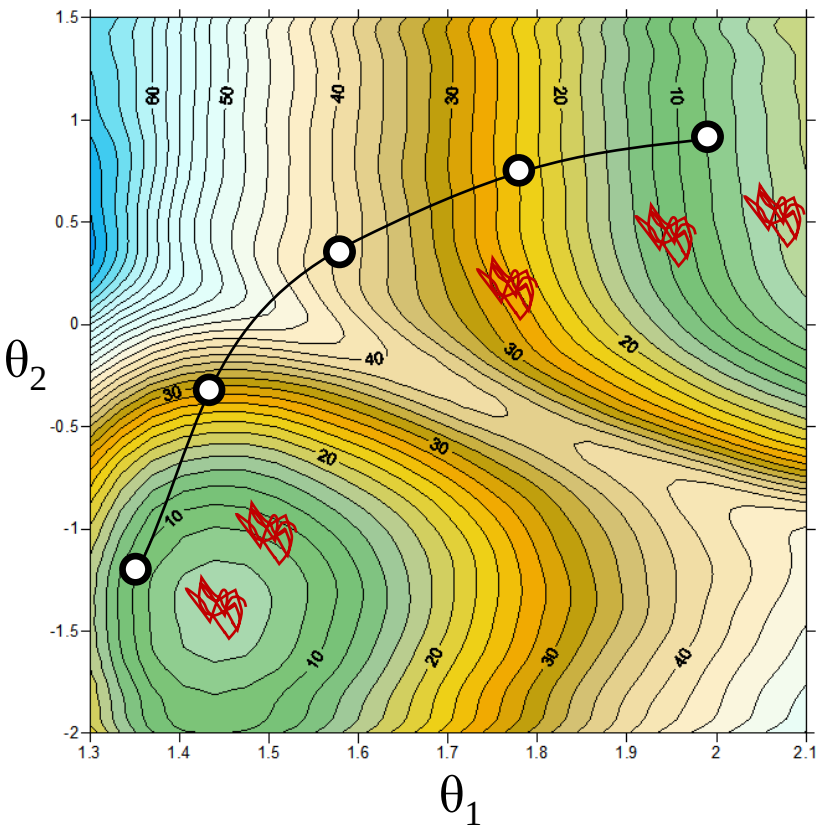
String method



- Select a set of **Collective Variables** CVs (e.g. valence coordinates)
- Build **N** replicas of the system with a biased potential centered at different values of the CVs (**string nodes**)

L. Maragliano and E. Vanden-Eijnden. *Chem. Phys. Lett.*, 446, 182-190, 2007.
K.Zinovjev and I. Tuñón. *J. Phys. Chem. A*, 2017, 121, 9764–9772

String method



- Select a set of **Collective Variables** CVs (e.g. valence coordinates)
- Build **N** replicas of the system with a biased potential centered at different values of the CVs (**string nodes**)
- Evolve the position of the nodes according the average force

L. Maragliano and E. Vanden-Eijnden. *Chem. Phys. Lett.*, 446, 182-190, 2007.
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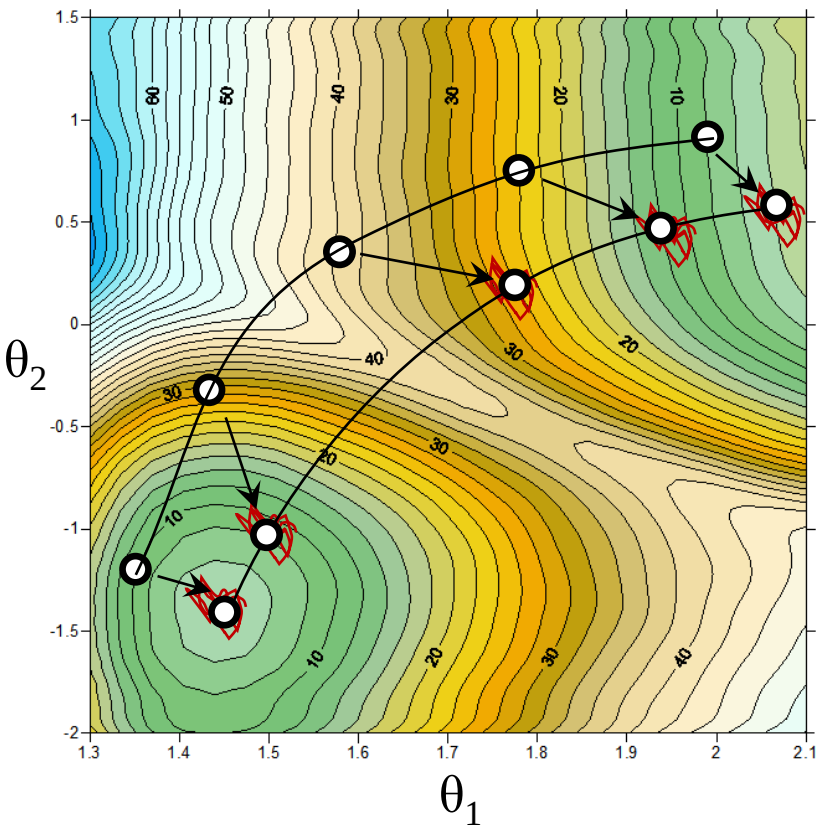
String method



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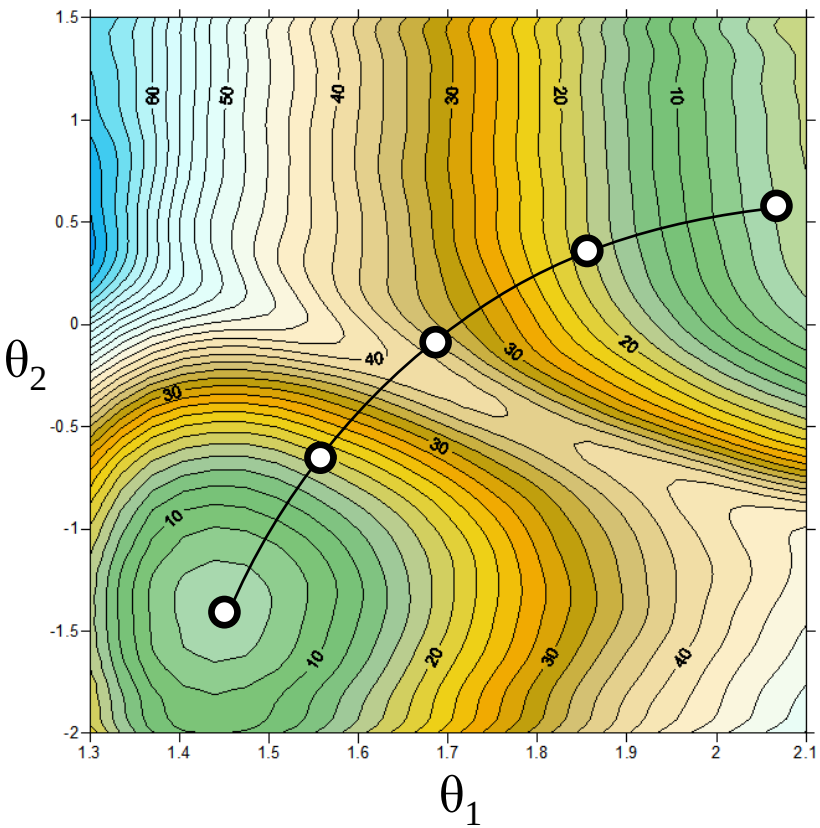
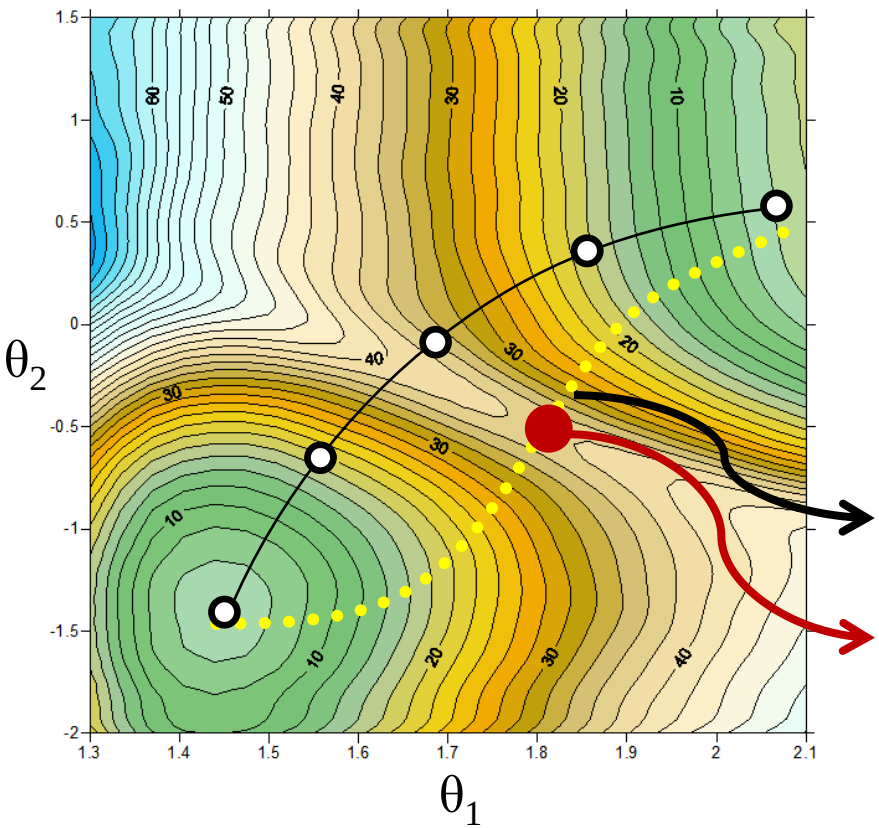


- Select a set of **Collective Variables** CVs (e.g. valence coordinates)
- Build **N** replicas of the system with a biased potential centered at different values of the CVs (**string nodes**)
- Evolve the position of the nodes according the average force
- Evolve nodes keeping them **equidistant** along the string

L. Maragliano and E. Vanden-Eijnden. *Chem. Phys. Lett.*, 446, 182-190, 2007.
K.Zinovjev and I. Tuñón. *J. Phys. Chem. A*, 2017, 121, 9764–9772

String method

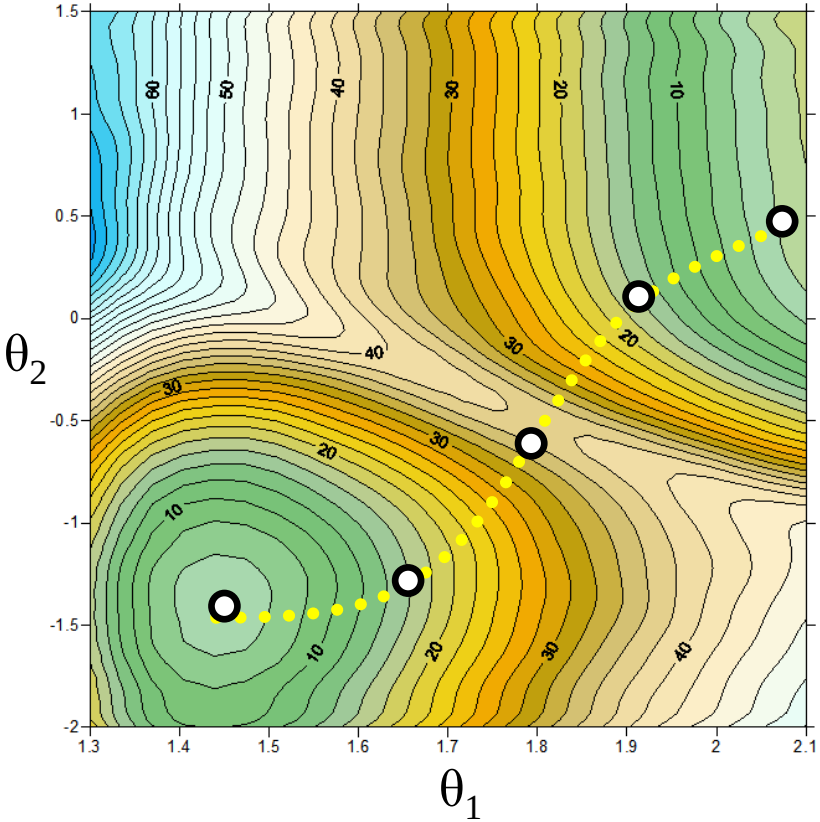


Minimum Free Energy Path

Transition State (kinetic properties)

L. Maragliano and E. Vanden-Eijnden. *Chem. Phys. Lett.*, 446, 182-190, 2007.
K.Zinovjev and I. Tuñón. *J. Phys. Chem. A*, 2017, 121, 9764–9772

String method



On-the-fly version:

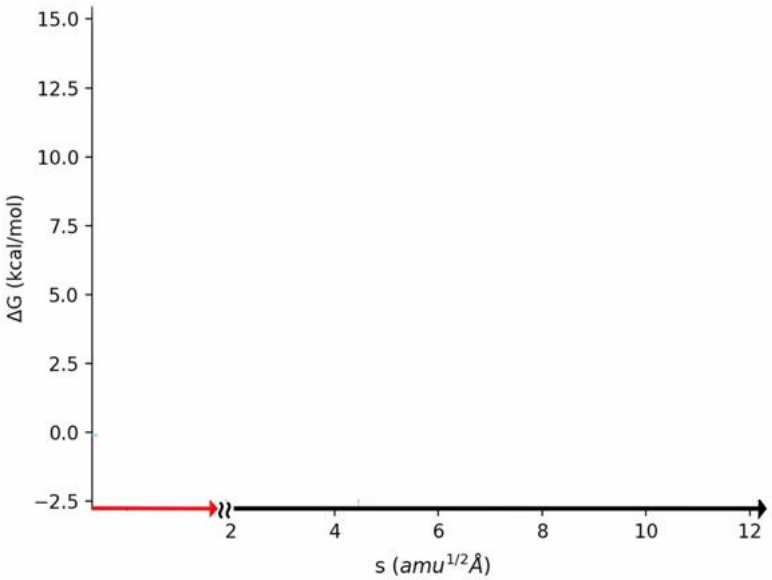
N string nodes run as N *loosely coupled* processes (N ~ 10^2)

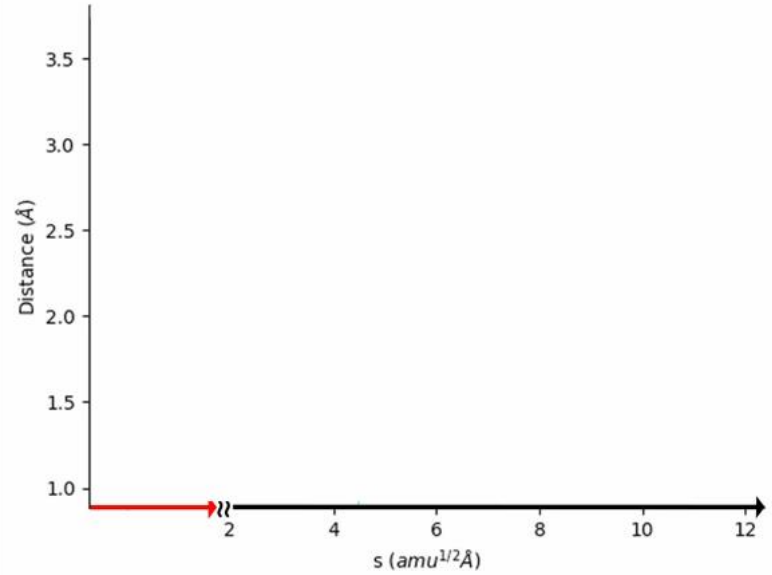
Each of the N processes may be parallelized in **M** cores (M~ 10^1)

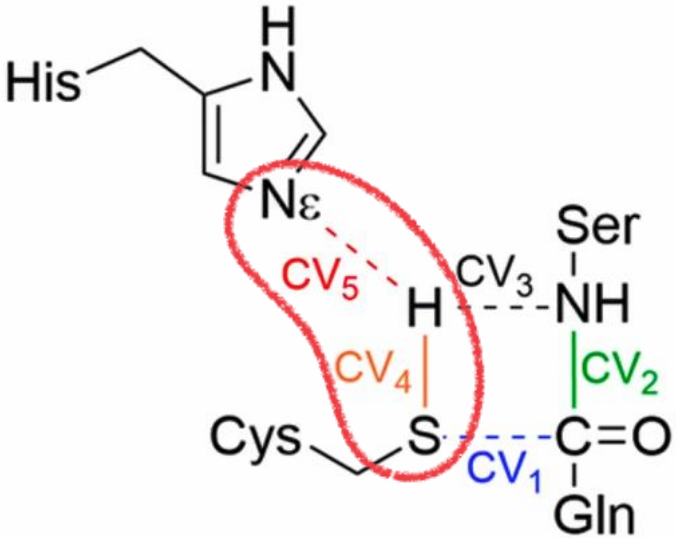
N x M ~ 10^3 cores

L. Maragliano and E. Vanden-Eijnden. *Chem. Phys. Lett.*, 446, 182-190, 2007.
K.Zinovjev and I. Tuñón. *J. Phys. Chem. A*, 2017, 121, 9764–9772

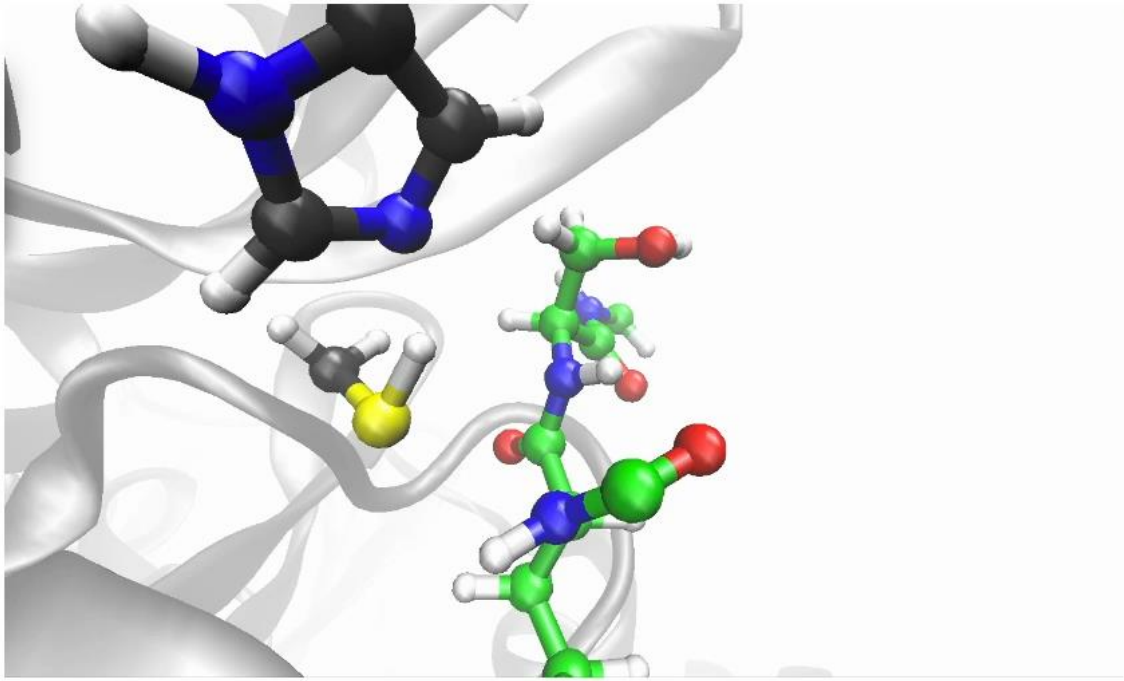
ACYLATION





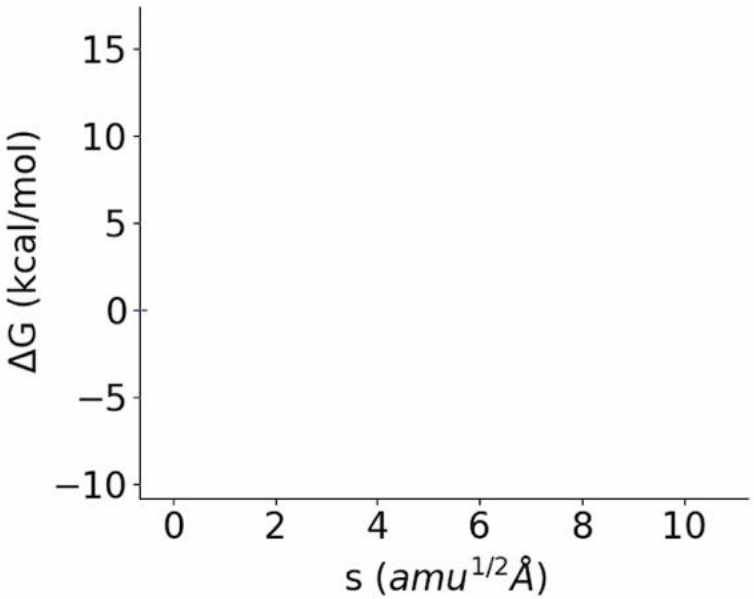


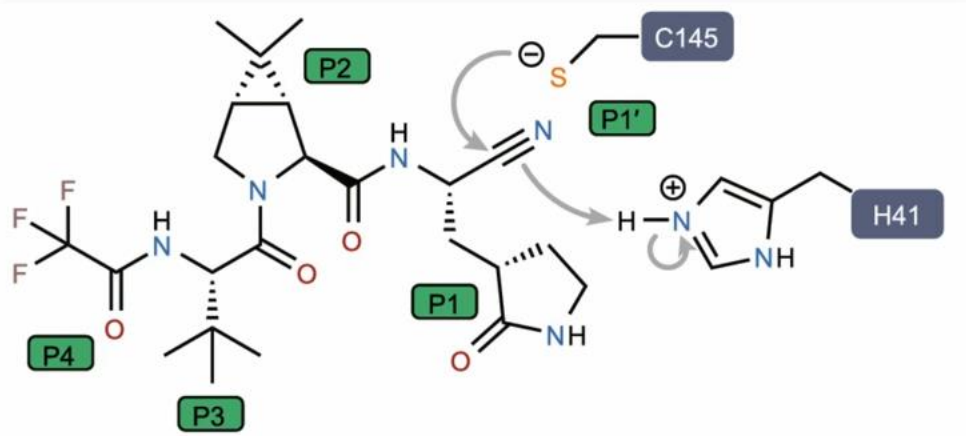
Carlos A. Ramos-Guzmán, J. Javier Ruiz-Pernía, Iñaki Tuñón. ACS Catal. 2020, 10,12544–12554

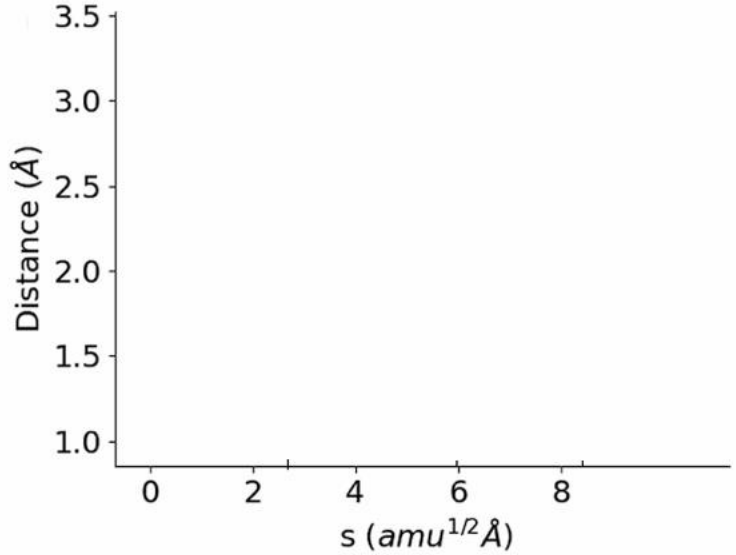


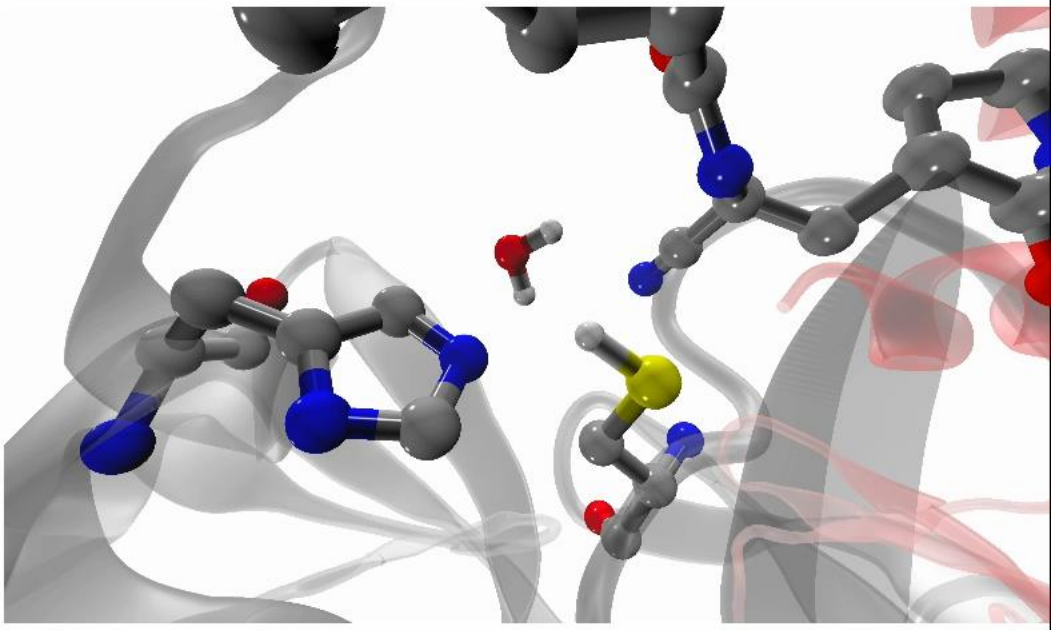
3CL^{pro} of SARS-CoV-2

PAXLOVID



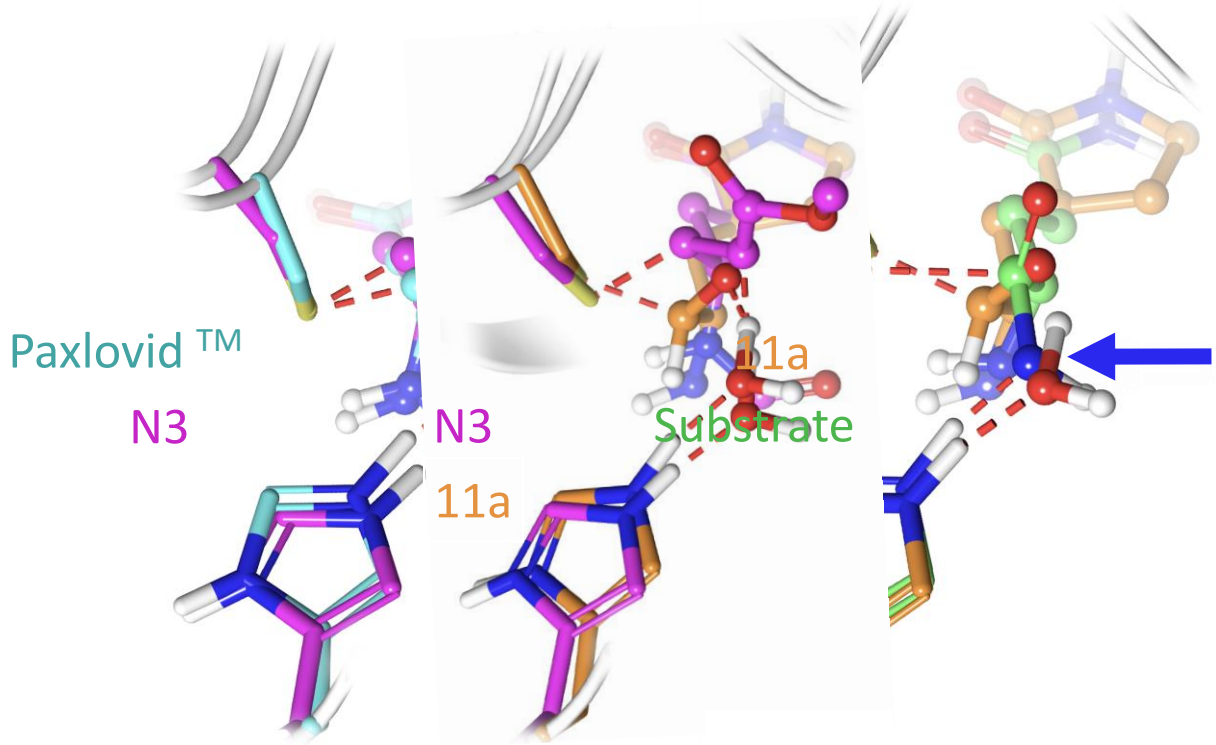




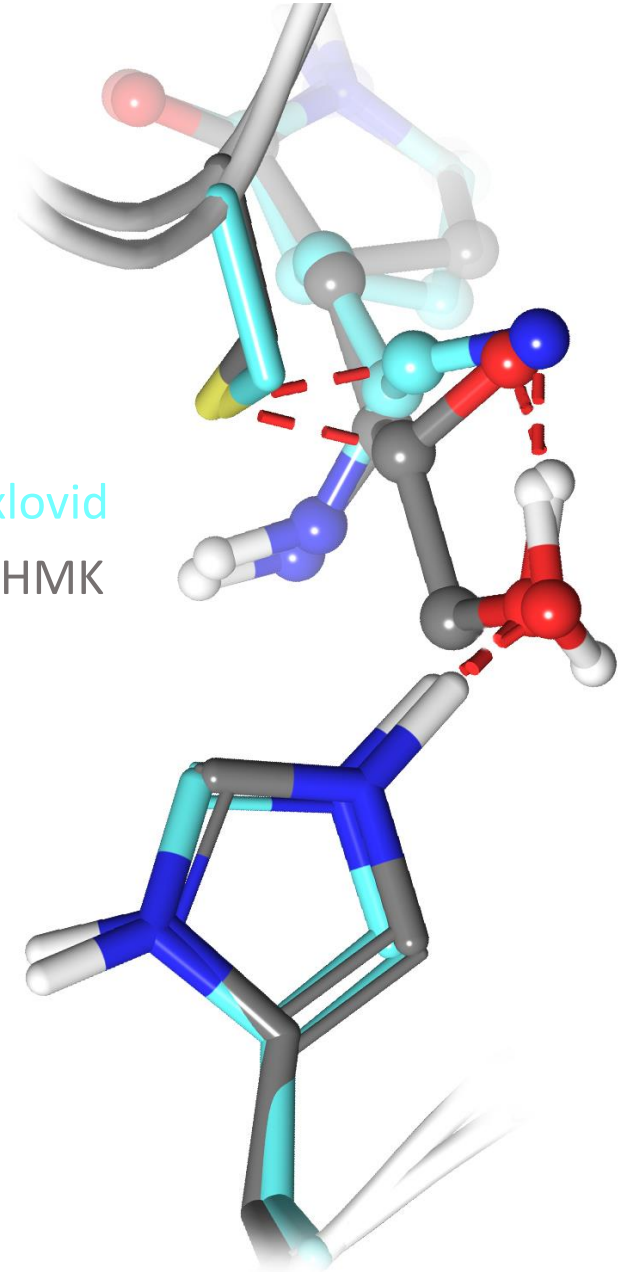


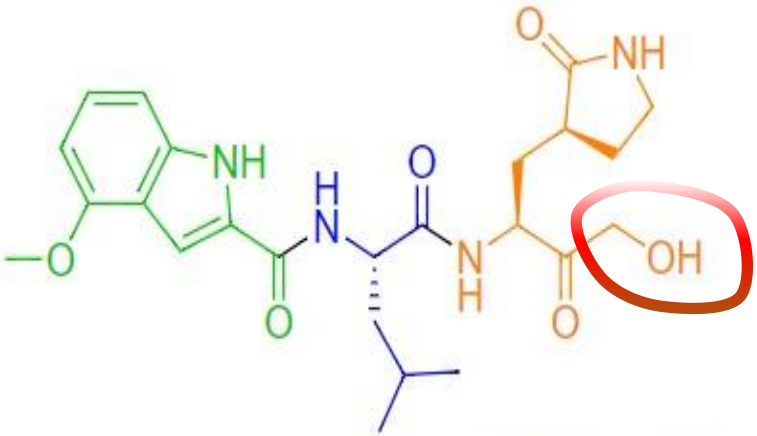
Zhao, Y., Fang, C., Zhang, Q. *et al.* Crystal structure of SARS-CoV-2 main protease in complex with protease inhibitor PF-07321332. *Protein Cell* (2021).
Carlos A. Ramos-Guzmán, J. Javier Ruiz-Pernía, Iñaki Tuñón. Chem. Commun. 2021, 2-5.

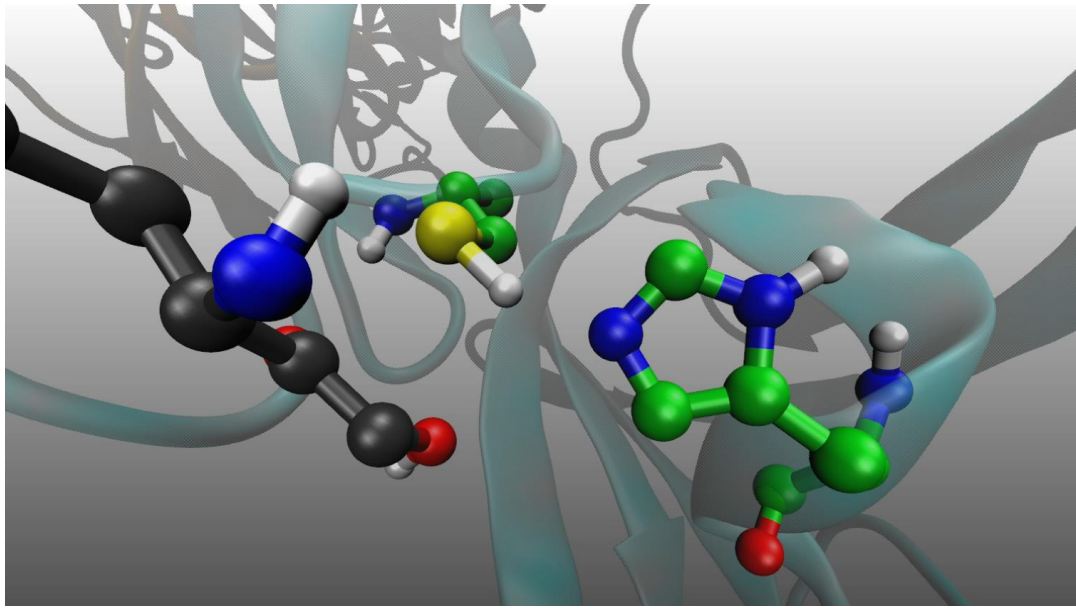
3CL inhibitors



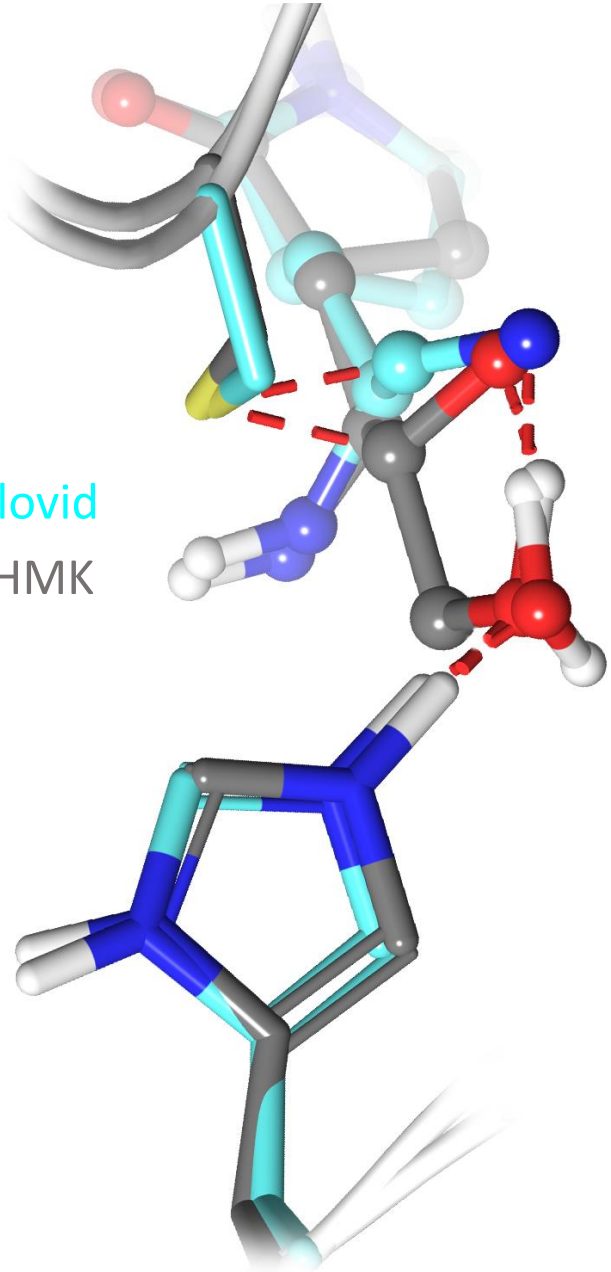
HYDROXYMETHYL KETONE

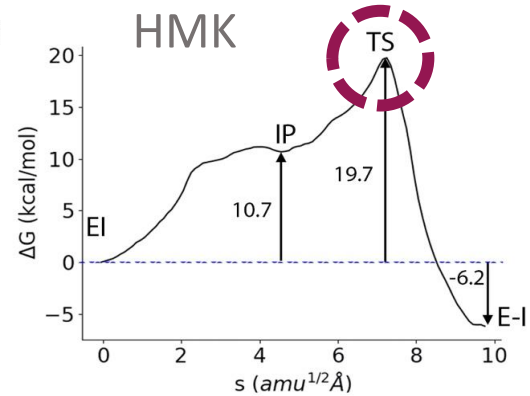




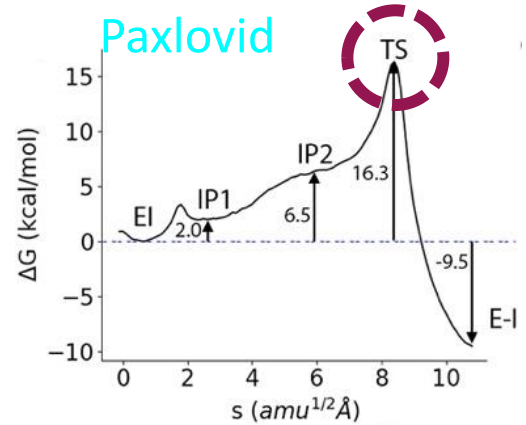


HYDROXYMETHYL KETONE



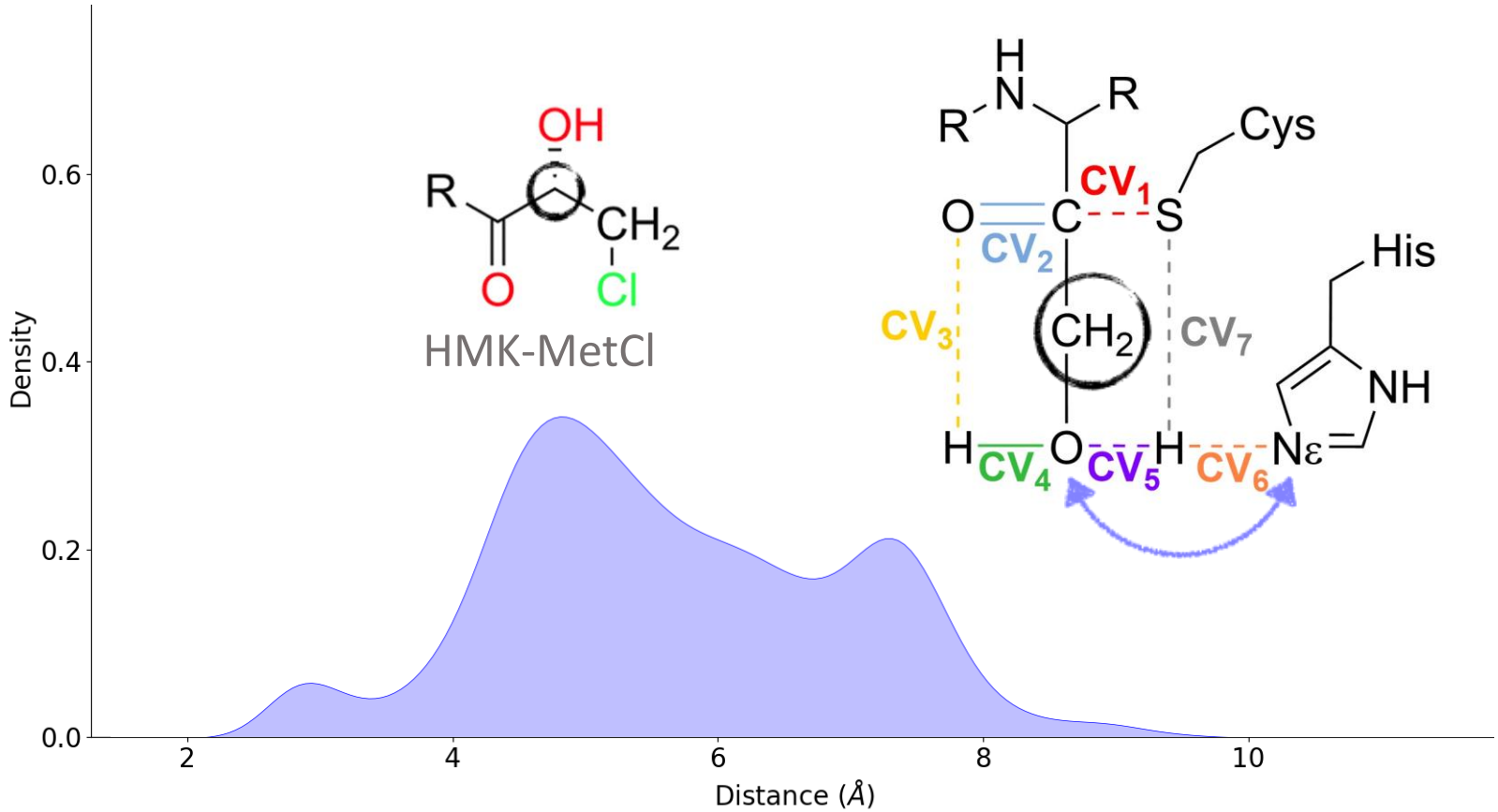


$\Delta G^{\ddagger}$ **19.7** kcal·mol^{-1}

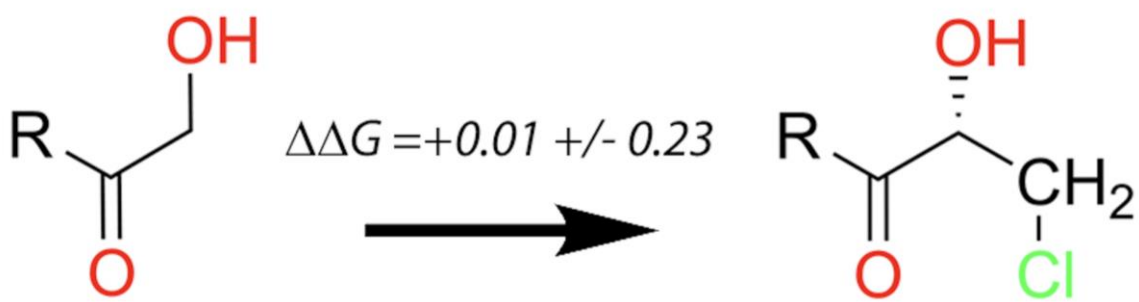


$\Delta G^{\ddagger}$ **16.3** kcal·mol^{-1}

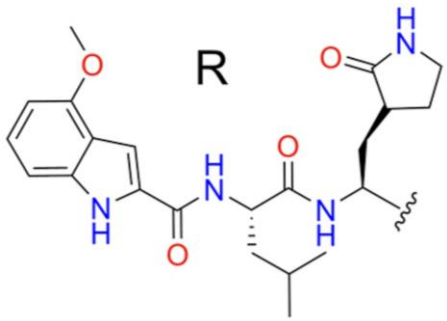
Improving the design

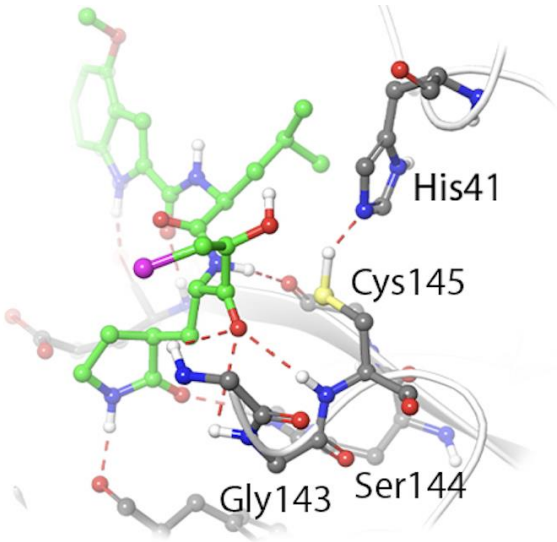


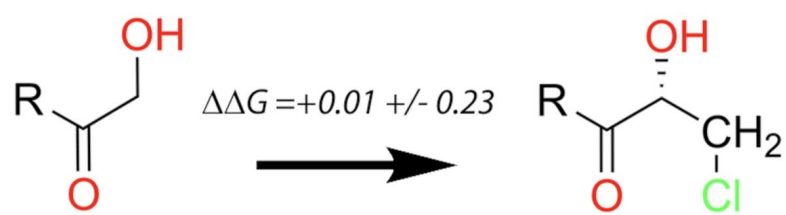
Alchemical transformations & TI: Binding free energy contributions

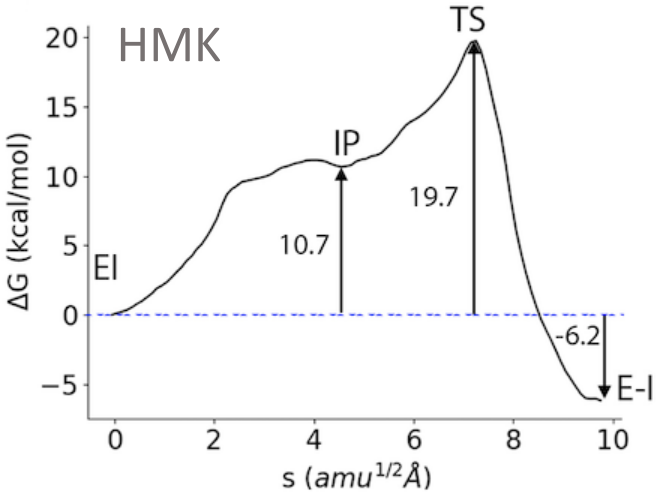


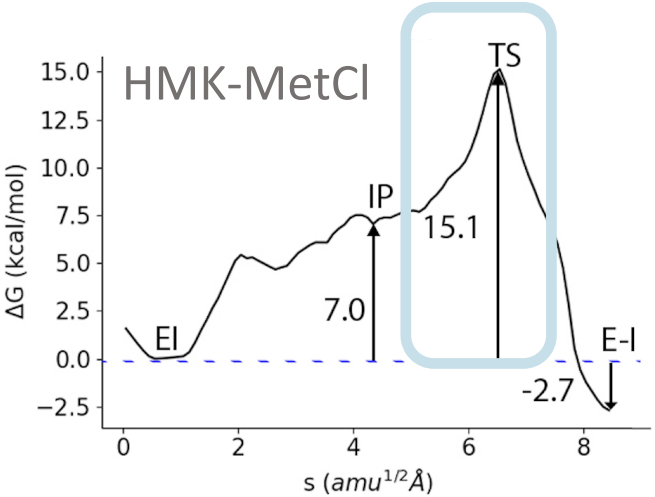
Improving the design











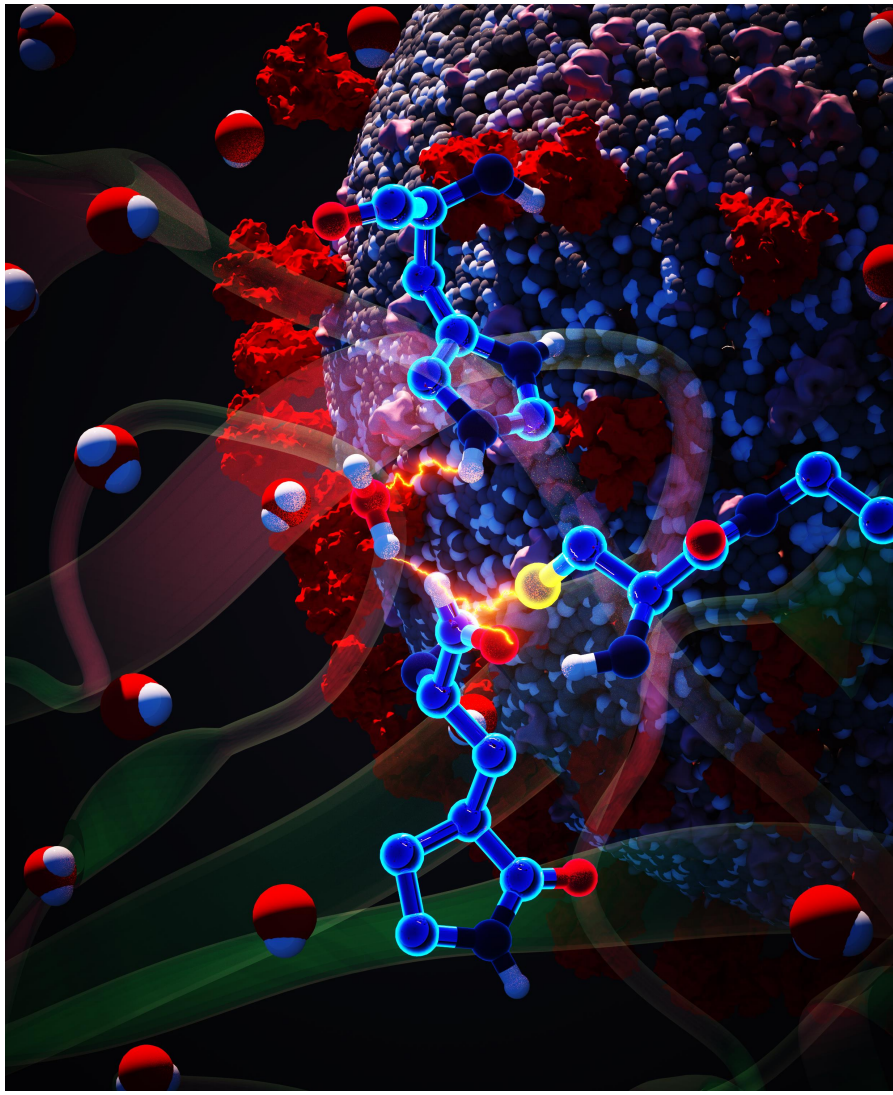
Carlos A. Ramos-Guzmán, J. Javier Ruiz-Pernía, Iñaki Tuñón. Angew. Chemie Int. Ed. 2021, 2-11.

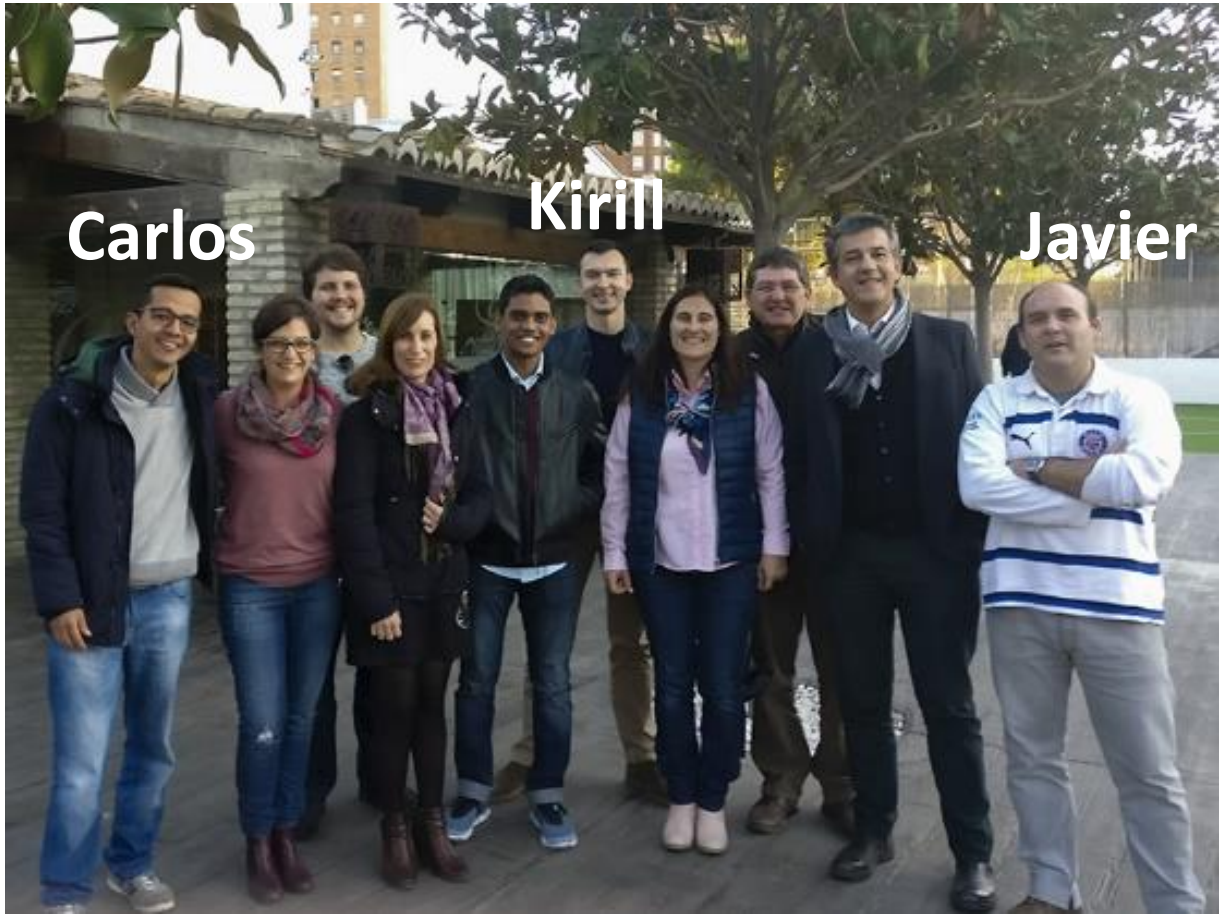
Conclusions

The Adaptive String method is a useful tool to explore complex chemical reactions, adapted for the use of HPC facilities.

The reaction mechanism of SARS-CoV-2 3CL protease has been explored using the string method. The proposed catalytic cycle explains experimental observations.

Inhibition mechanisms of 3CL protease involves Ion Pair formation and Proton Shuttle steps. This knowledge can be used to guide rational design.





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CETA Ciemat

Barcelona Supercomputing Center

Centro Nacional de Supercomputación

Colabora:

Centro de Cirugía de Mínima Invasión

Minimally Invasive Surgery Centre

Jesús Usón

Thank you for your attention !

Gracias !