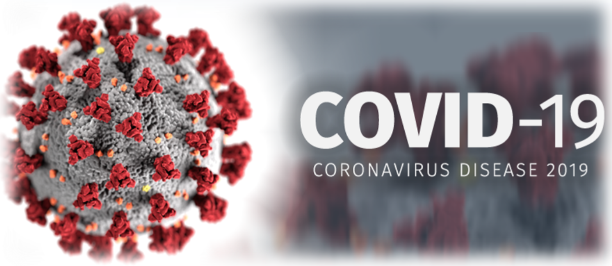
Rol del Diseño de Fármacos y la Biología Computacional en Respuesta a la Pandemia del Covid-19

William J. Zamora R, Ph. D
Universidad de Costa Rica

Introducción



Dec. 31, 2019

China alerts World Health Organization (WHO) to several cases of pneumonia with no known cause in Wuhan. The disease goes on to be named COVID-19.

Jan. 7

WHO officials announce they have identified a new virus named SARS-CoV-2 that causes COVID-19. It belongs to the coronavirus family, which includes viruses that cause SARS, MERS and the common cold.

Jan. 11

China announces the first death linked to COVID-19.

Jan. 13

WHO reports the first case outside of China in Thailand.

Feb. 26

National Institutes of Health (NIH) begin the first clinical trial in the U.S. for a potential COVID-19 treatment, remdesivir, an antiviral drug originally developed to treat Ebola.

Feb. 29

The FDA took steps to expand novel coronavirus testing to hospital clinical microbiology laboratories.

Mar. 11

WHO declares COVID-19 a pandemic, with more than 100,000 cases and 4,000 deaths in 114 countries.

Apr. 2

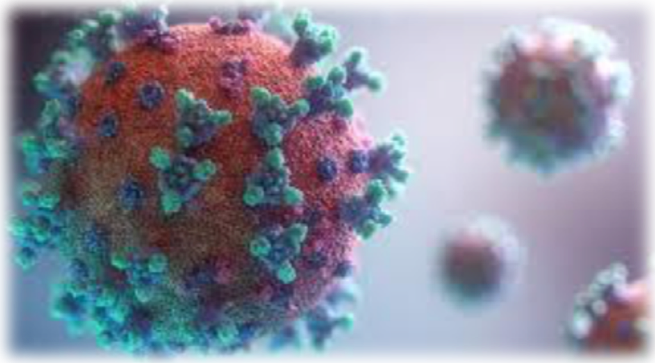
Confirmed cases of COVID-19 top 1 million worldwide.

Apr. 10

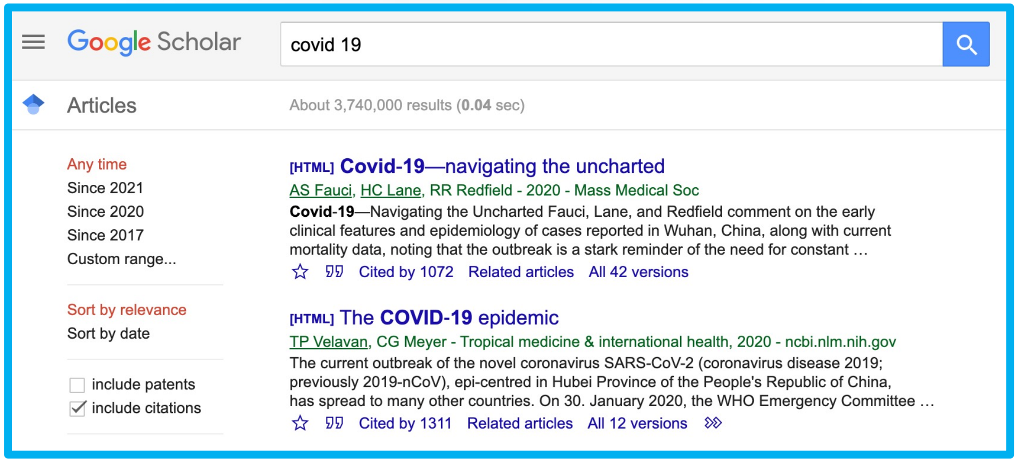
Global deaths due to COVID-19 top 100,000.

Introducción

- ✓ Creciente Recolección de Información
- ✓ Colaboracion Interdisciplinaria
- ✓ Métodos Computacionales:
  - -Visualización y Simulación
  - -Secuenciación e Identificación de Mutaciones
  - -Identificación de Drogas
  - -Desarrollo de Códigos



Recoleccion de Información



covid 19

About 3,740,000 results (**0.04** sec)

[HTML] **Covid-19**—navigating the uncharted

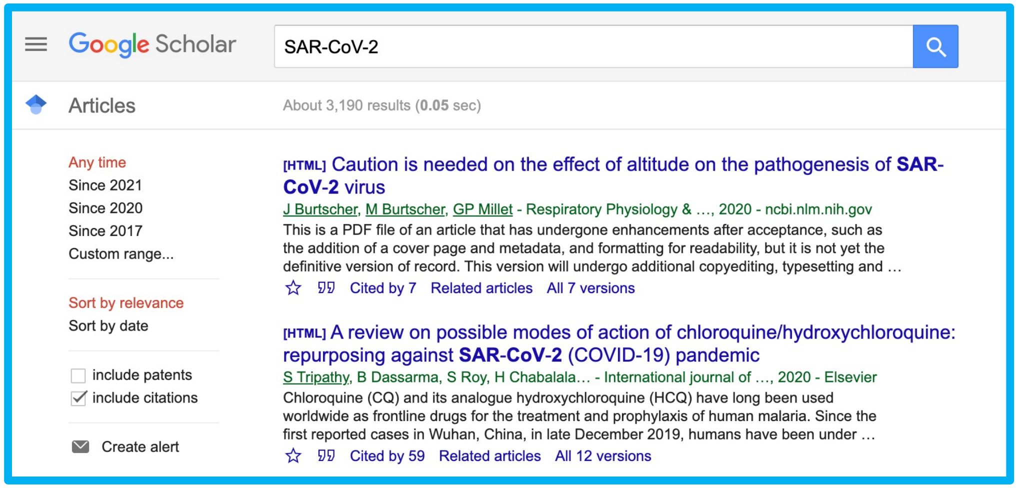
AS Fauci, HC Lane, RR Redfield - 2020 - Mass Medical Soc

Covid-19—Navigating the Uncharted Fauci, Lane, and Redfield comment on the early clinical features and epidemiology of cases reported in Wuhan, China, along with current mortality data, noting that the outbreak is a stark reminder of the need for constant …

[HTML] The **COVID-19** epidemic

TP Velavan, CG Meyer - Tropical medicine & international health, 2020 - ncbi.nlm.nih.gov

The current outbreak of the novel coronavirus SARS-CoV-2 (coronavirus disease 2019; previously 2019-nCoV), epi-centred in Hubei Province of the People's Republic of China, has spread to many other countries. On 30. January 2020, the WHO Emergency Committee …



SAR-CoV-2

About 3,190 results (**0.05** sec)

[HTML] Caution is needed on the effect of altitude on the pathogenesis of **SAR-CoV-2** virus

J Burtscher, M Burtscher, GP Millet - Respiratory Physiology & …, 2020 - ncbi.nlm.nih.gov

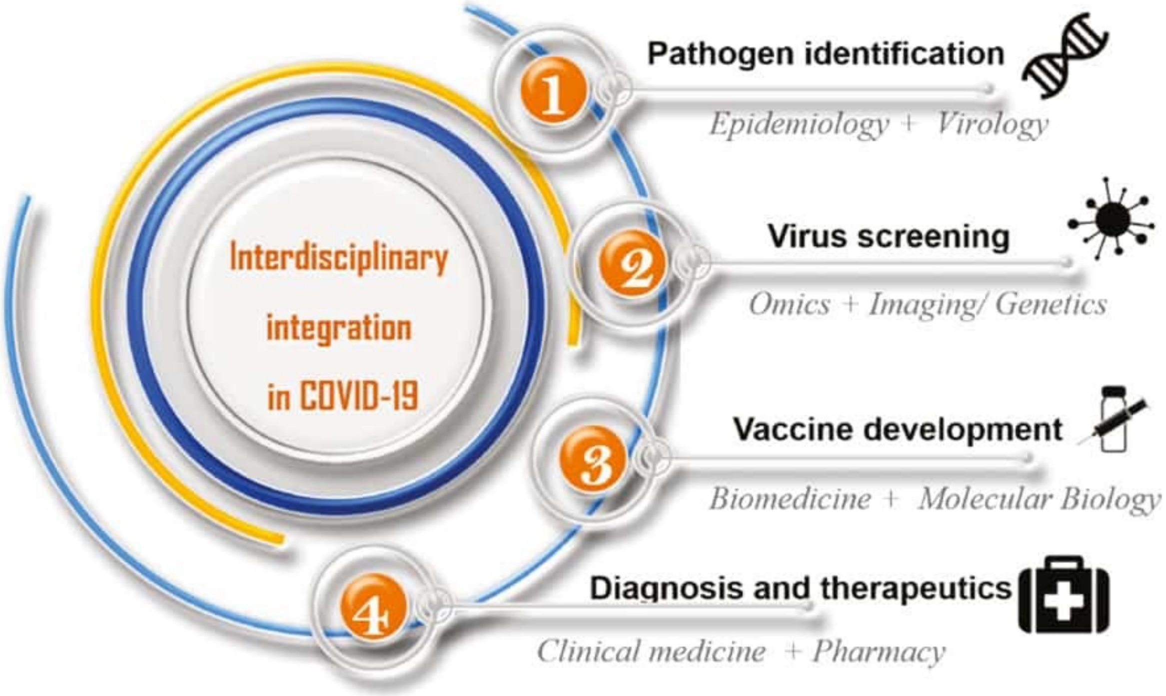
This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and …

[HTML] A review on possible modes of action of chloroquine/hydroxychloroquine: repurposing against **SAR-CoV-2** (COVID-19) pandemic

S Tripathy, B Dassarma, S Roy, H Chabalala… - International journal of …, 2020 - Elsevier

Chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) have long been used worldwide as frontline drugs for the treatment and prophylaxis of human malaria. Since the first reported cases in Wuhan, China, in late December 2019, humans have been under …

Colaboracion Interdisciplinaria

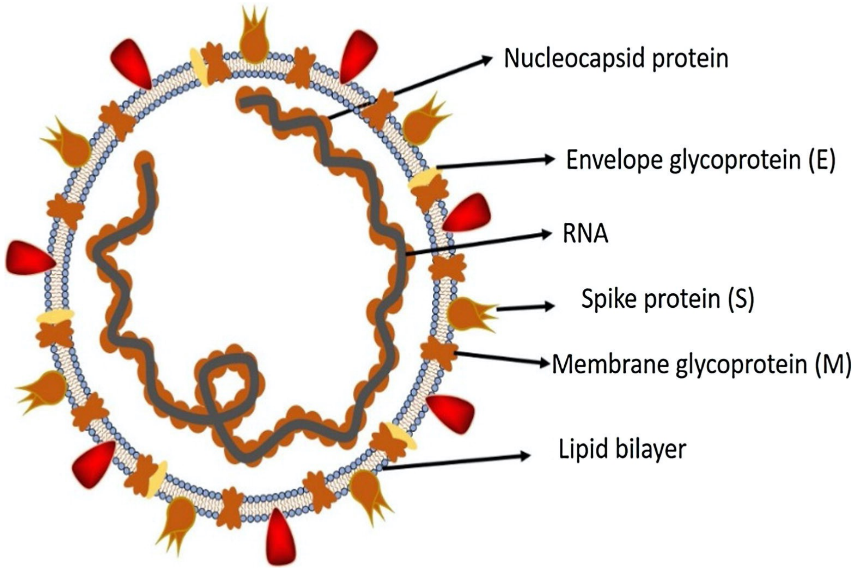


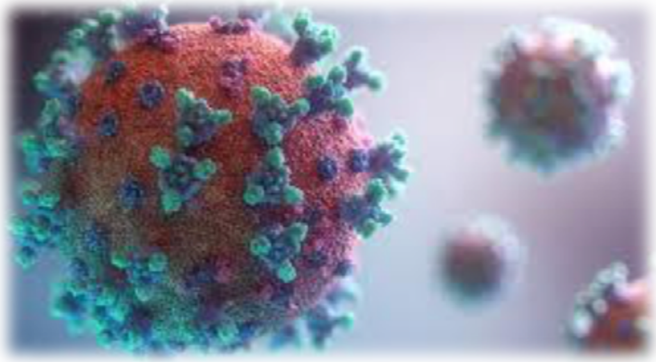
Interdisciplinary integration in COVID-19

1. **Pathogen identification**
   Epidemiology + Virology
2. **Virus screening**
   Omics + Imaging/ Genetics
3. **Vaccine development**
   Biomedicine + Molecular Biology
4. **Diagnosis and therapeutics**
   Clinical medicine + Pharmacy

Métodos computacionales

Visualización y Simulación





The Protein Journal (2020) 39:600–618
https://doi.org/10.1007/s10930-020-09933-w

An Overview of the Crystallized Structures of the SARS-CoV-2

Mihaela Ileana Ionescu[1,2]

Métodos computacionales

Visualización y Simulación

RCSB PROTEIN DATA BANK

177655 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education

SARS-CoV-2

Advanced Search | Browse Annotations

Help

Displaying 1 to 25 of 1298 **Structures**

Page 1 of 52

Display 25 per page

6LU7

The crystal structure of COVID-19 main protease in complex with an inhibitor N3

Liu, X., Zhang, B., Jin, Z., Yang, H., Rao, Z.

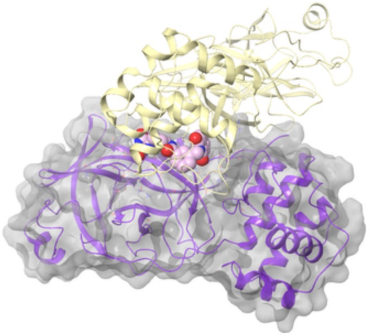
(2020) Nature **582**: 289-293

Released	2020-02-05
Method	X-RAY DIFFRACTION 2.16 Å
Organisms	Severe acute respiratory syndrome coronavirus 2 synthetic construct
Macromolecule	3C-like proteinase (protein) N-[(5-METHYLISOXAZOL-3-YL)CARBONYL]ALANYL-L-VALYL-N~1~-((1R,2Z)-4-(BENZYLOXY)-4-OXO-1-{[(3R)-2-OXOPYRROLIDIN-3-YL]METHYL}BUT-2-ENYL)-L-LEUCINAMIDE (protein)

Métodos computacionales

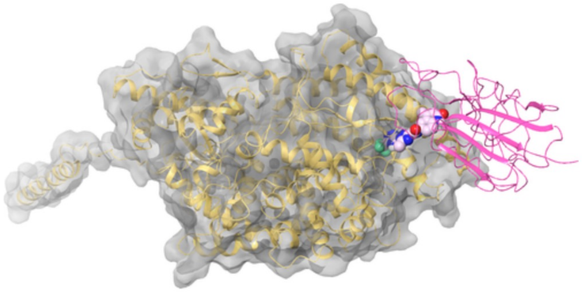
Visualización y Simulación

40 different sites among
17 critical proteins related to SARS-CoV-2



nsp5 (Mpro) - Dimerization Site

Mpro, the main protease of coronavirus, cleaves PP1a and PP1ab into many of their constituent nsps (11 cleavage sites in PP1ab). Mpro is a functional dimer, meaning it does not have any significant activity when it is not in dimer form. We have targeted the dimerization interface of Mpro (Screen ID 18).



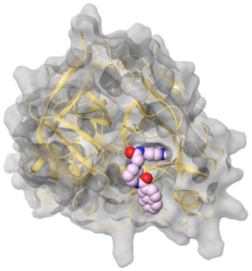
ACE2 - Site 1 - Spike Binding Interface

The angiotensin-converting enzyme 2 (ACE2) receptor plays a keyrole in the entry process of the virus into human cells. We have targeted a site (around residue Glu37) with two virtual screens (Screen IDs 1 and 2).

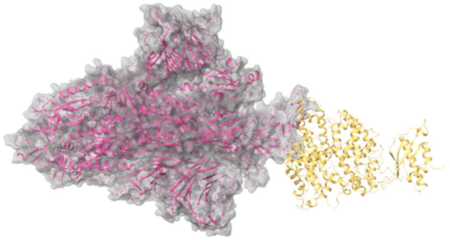
https://vf4covid19.hms.harvard.edu

Métodos computacionales

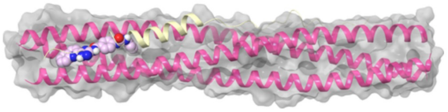
Visualización y Simulación



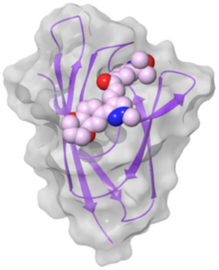
TMPRSS2 - Active Site
The essential priming of S during entry can be executed by the host serine protease TMPRSS2 in the case of SARS-CoV-2, making it a potential therapeutic target. In addition, recent research has shown that the TMPRSS2 inhibtor, camostat mesylate, can block viral entry in cell-based assays. We have targeted the active site of TMPRSS2 (Screen ID 6).



Spike Protein - ACE2 Binding Site
The spike protein forms the highly glycosylated trimeric receptor-binding protein that decorates the virion surface and facilitates entry into the host cell through interaction with its receptor ACE2. We have targeted the ACE2 binding interface on the RBD of the spike protein via an ultra-large virtual screen (Screen ID 7).



Spike Protein - HR1 Domain - HR2 Binding Interface
The HR domains of the spike protein and their mode of interaction are known to be of critical importance, and are highly conserved across corona viruses, making them an attractive target for the development of pan-coronavirus fusion inhibitors. We have targeted the HR2 binding interface of the HR1 domain.

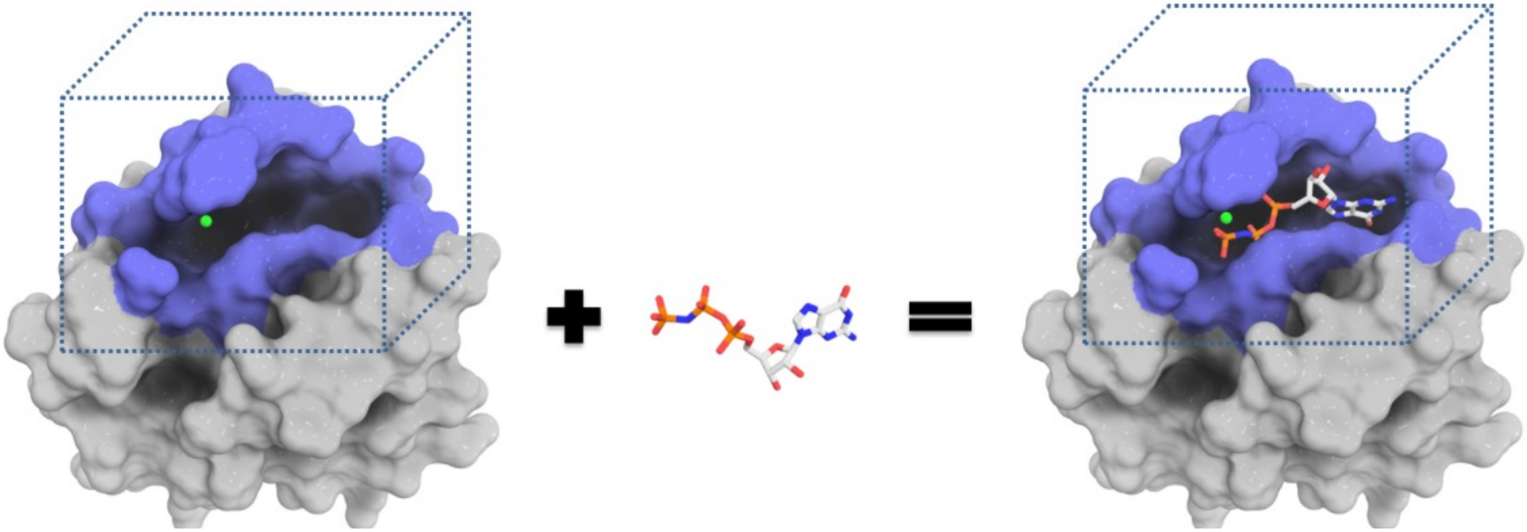


ORF7a - Entire Surface (Blind Docking)
ORF7a is an accessory protein with a transmembrane helix at the C-terminus that is known to localize to the ER, Golgi, and cell surface. The assembly of ORF7a into viral particles suggests that the protein is important in the viral replication cycle, and that it might have a function early on in the infection. We have carried out a blind docking against the entire surface (Screen ID 8).

Métodos computacionales

Visualización y Simulación

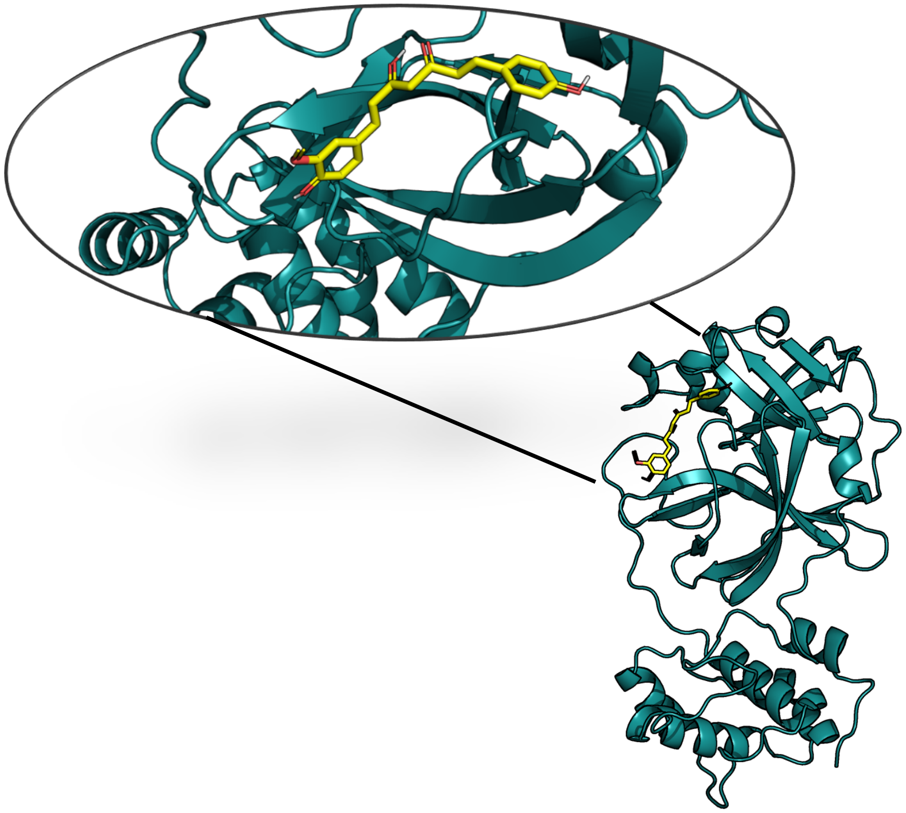
Anclaje Molecular



Métodos computacionales

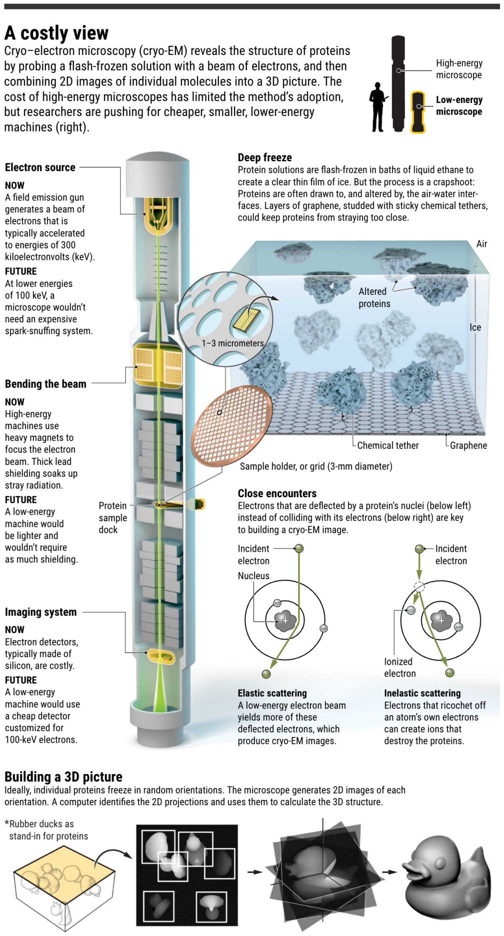
Visualización y Simulación

Proteasa principal (Mpro/3CLpro) PDB 6lu7				
Ligands	**Vina (DINC)**	**Vinardo (DINC)**	**AD4 (DINC)**	**SwissDock**
Curcumin	-7.67	**-8.39**	**-8.32**	-8.22
Demetoxi curcumin	**-7**.75	**-8.27**	-**8.56**	**-8.40**
Bisdemetoxi curcumin	-7.64	-7.54	-8.03	**-**8.00
Ellagic Acid	**-8.54**	-7.45	-7.01	-7.52
Gallic Acid	-6.29	-6.33	-5.15	-6.35
Gallate	-6.29	-6.30	-4.61	-6.04
Piperine	-6.58	-5.96	-5.99	-7.94
Quercetin	**-8.49**	-6.76	-6.52	-8.00



Métodos computacionales

Visualización y Simulación



A costly view

Cryo–electron microscopy (cryo-EM) reveals the structure of proteins by probing a flash-frozen solution with a beam of electrons, and then combining 2D images of individual molecules into a 3D picture. The cost of high-energy microscopes has limited the method's adoption, but researchers are pushing for cheaper, smaller, lower-energy machines (right).

Electron source

NOW
A field emission gun generates a beam of electrons that is typically accelerated to energies of 300 kiloelectronvolts (keV).

FUTURE
At lower energies of 100 keV, a microscope wouldn't need an expensive spark-snuffing system.

Bending the beam

NOW
High-energy machines use heavy magnets to focus the electron beam. Thick lead shielding soaks up stray radiation.

FUTURE
A low-energy machine would be lighter and wouldn't require as much shielding.

Imaging system

NOW
Electron detectors, typically made of silicon, are costly.

FUTURE
A low-energy machine would use a cheap detector customized for 100-keV electrons.

Deep freeze
Protein solutions are flash-frozen in baths of liquid ethane to create a clear thin film of ice. But the process is a crapshoot: Proteins are often drawn to, and altered by, the air-water interfaces. Layers of graphene, studded with sticky chemical tethers, could keep proteins from straying too close.

Close encounters
Electrons that are deflected by a protein's nuclei (below left) instead of colliding with its electrons (below right) are key to building a cryo-EM image.

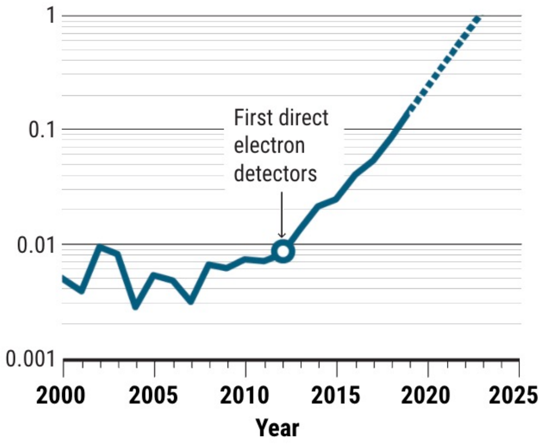
Elastic scattering
A low-energy electron beam yields more of these deflected electrons, which produce cryo-EM images.

Inelastic scattering
Electrons that ricochet off an atom's own electrons can create ions that destroy the proteins.

Building a 3D picture
Ideally, individual proteins freeze in random orientations. The microscope generates 2D images of each orientation. A computer identifies the 2D projections and uses them to calculate the 3D structure.

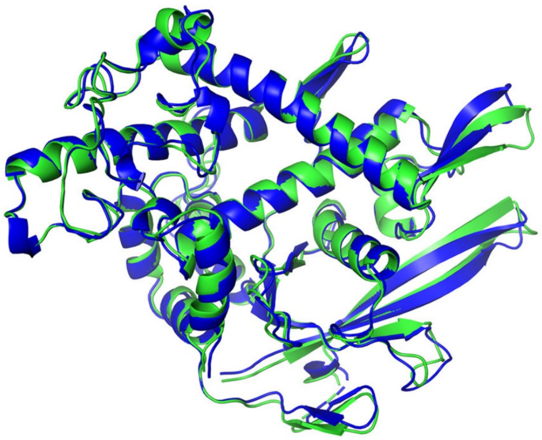
*Rubber ducks as stand-in for proteins

Ratio of proteins solved by cryo-EM to proteins solved by crystallography



Métodos computacionales

Secuenciación e Identificación de Mutaciones



Structures of a protein that were predicted by artificial intelligence (blue) and experimentally determined (green) match almost perfectly. DEEPMIND

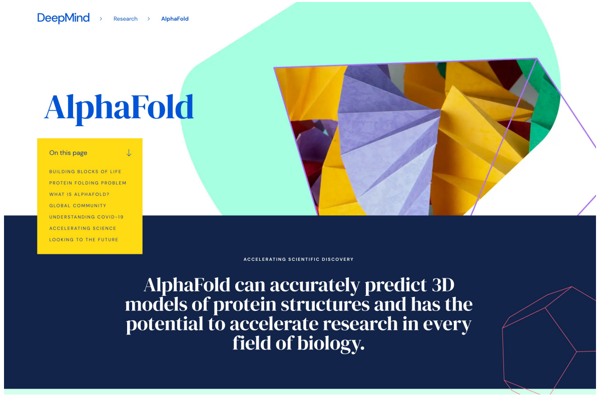
‘The game has changed.’ AI triumphs at solving protein structures

Science

'The game has changed.' AI triumphs at protein folding

Robert F. Service

Science **370** (6521), 1144-1145.
DOI: 10.1126/science.370.6521.1144



DeepMind › Research › AlphaFold

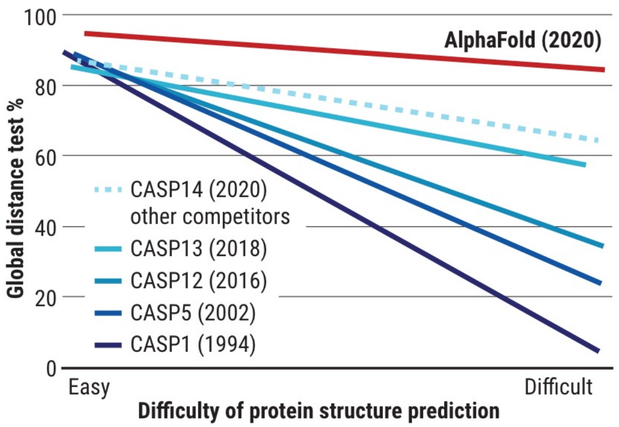
AlphaFold

On this page ↓

- BUILDING BLOCKS OF LIFE
- PROTEIN FOLDING PROBLEM
- WHAT IS ALPHAFOLD?
- GLOBAL COMMUNITY
- UNDERSTANDING COVID-19
- ACCELERATING SCIENCE
- LOOKING TO THE FUTURE

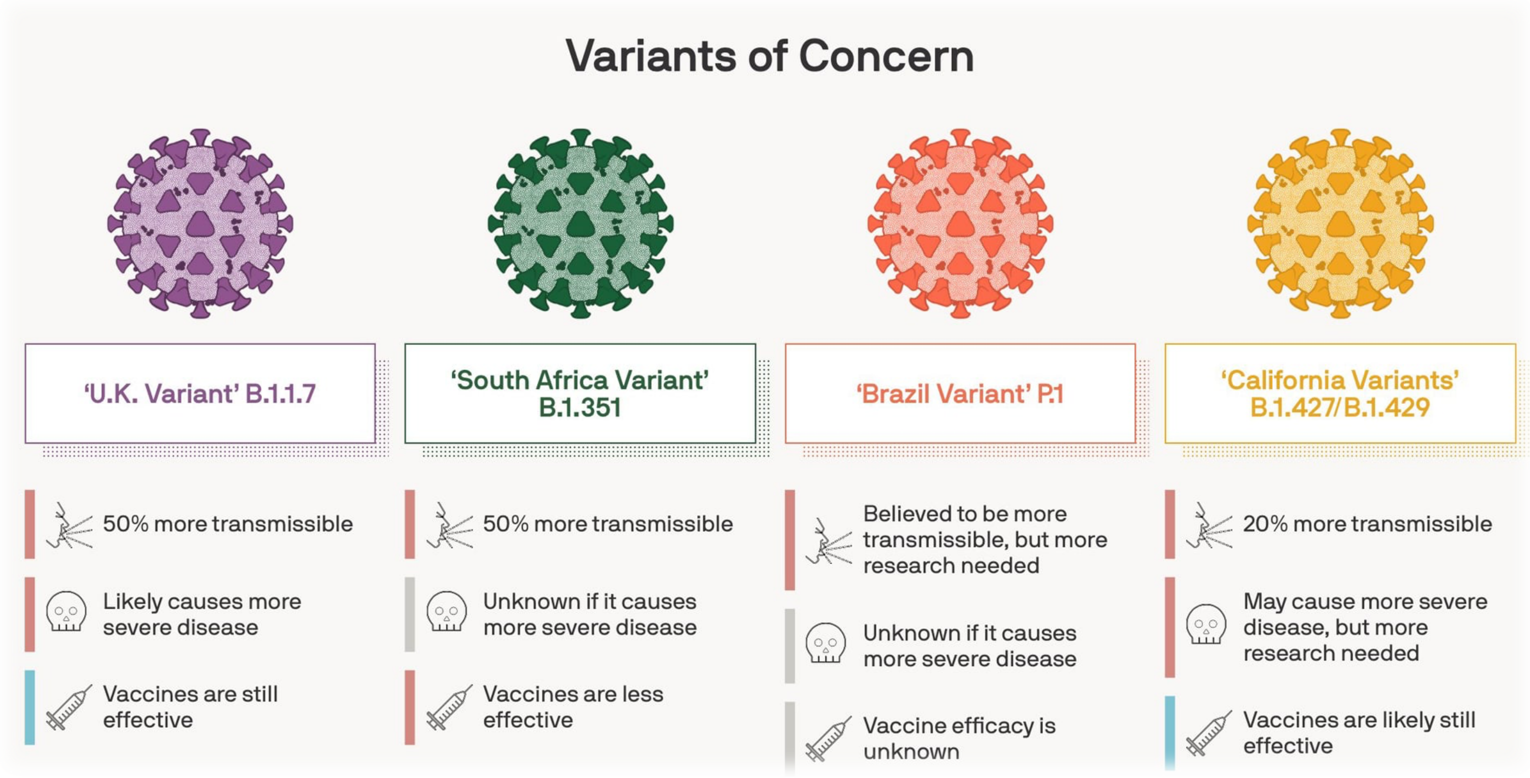
ACCELERATING SCIENTIFIC DISCOVERY

AlphaFold can accurately predict 3D models of protein structures and has the potential to accelerate research in every field of biology.



Métodos computacionales

Secuenciación e Identificación de Mutaciones



Variants of Concern

'U.K. Variant' B.1.1.7	'South Africa Variant' B.1.351	'Brazil Variant' P.1	'California Variants' B.1.427/B.1.429
50% more transmissible	50% more transmissible	Believed to be more transmissible, but more research needed	20% more transmissible
Likely causes more severe disease	Unknown if it causes more severe disease	Unknown if it causes more severe disease	May cause more severe disease, but more research needed
Vaccines are still effective	Vaccines are less effective	Vaccine efficacy is unknown	Vaccines are likely still effective

Métodos computacionales

Identificación de Drogas

JOC

The Journal of Organic Chemistry

AUGUST 21, 2020 VOLUME 85, NUMBER 16 pubs.acs.org/joc

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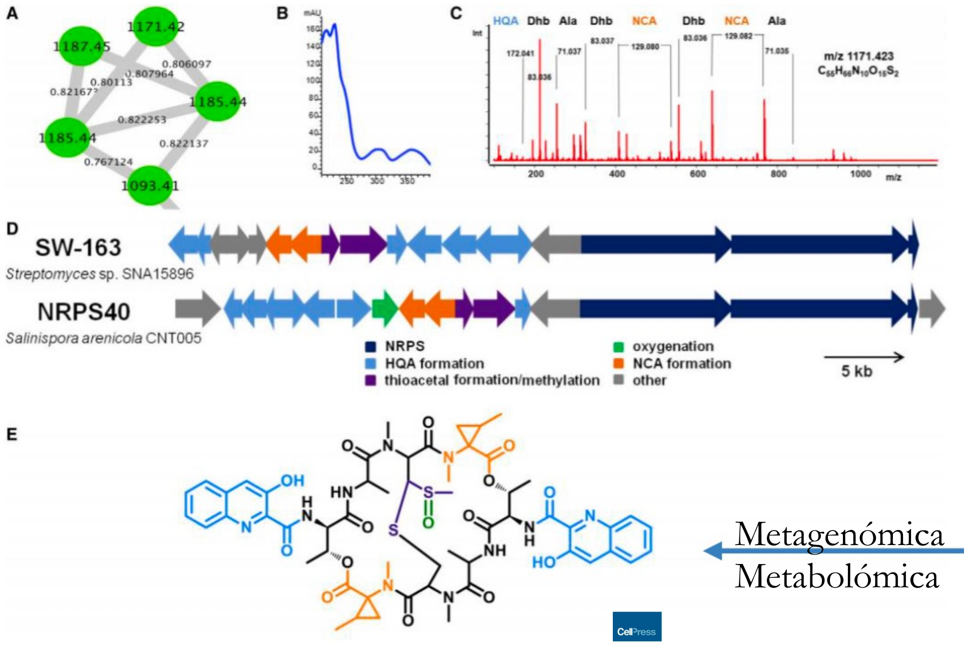

← Metagenómica
Metabolómica

Chemistry & Biology
Article

Molecular Networking and Pattern-Based Genome Mining Improves Discovery of Biosynthetic Gene Clusters and their Products from *Salinispora* Species

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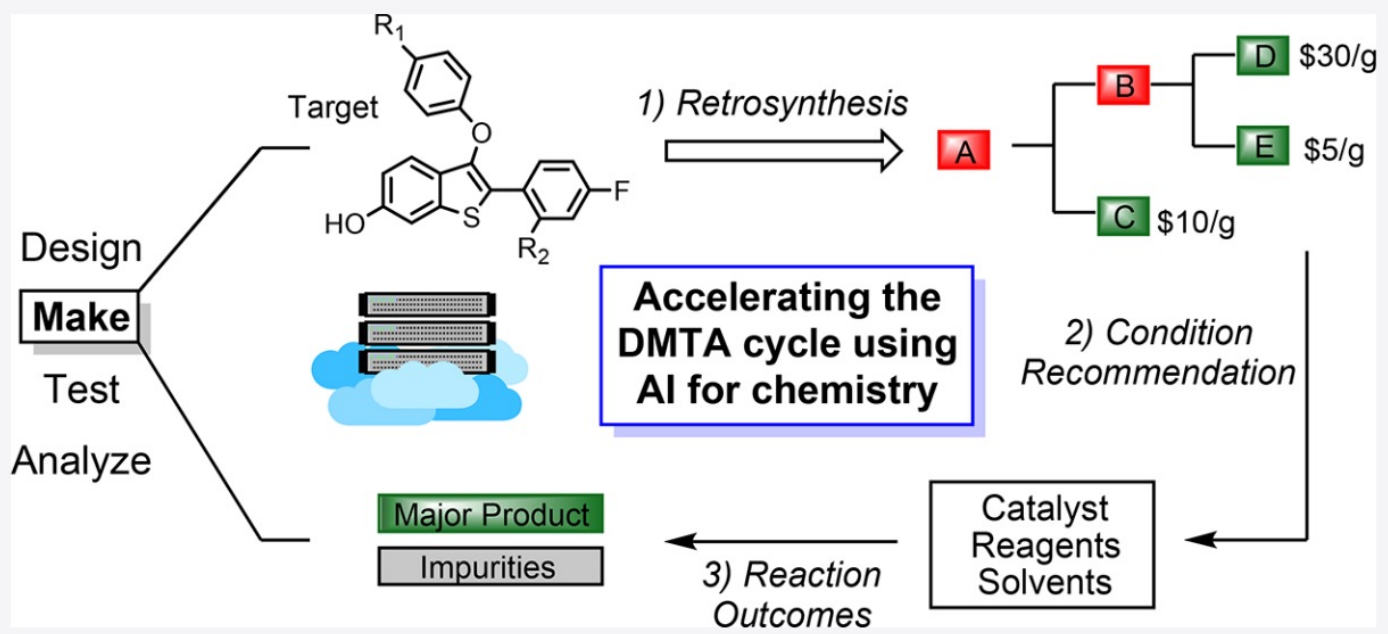
Diseño de Drogas



Accelerating the DMTA cycle using AI for chemistry

Journal of
Medicinal
Chemistry

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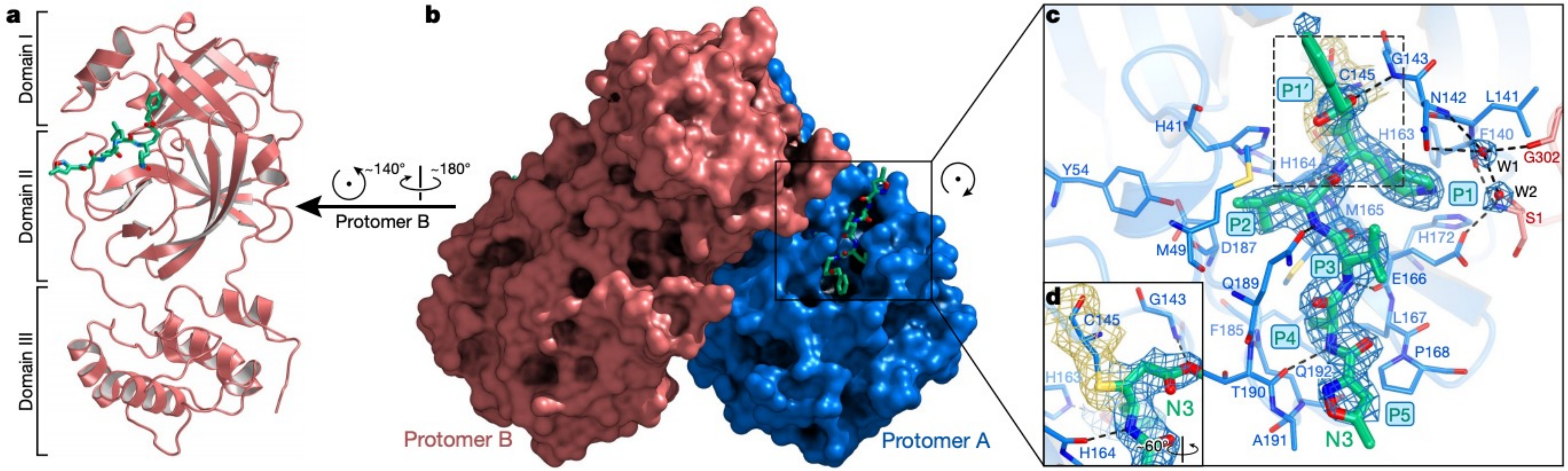
Perspective

Current and Future Roles of Artificial Intelligence in Medicinal Chemistry Synthesis

Métodos computacionales

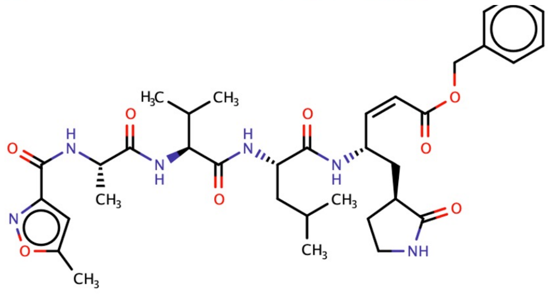
Identificación de Drogas



Article

Structure of M^{pro} from SARS-CoV-2 and discovery of its inhibitors

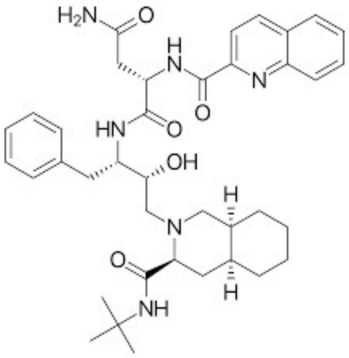
Nature | Vol 582 | 11 June 2020 | **289**

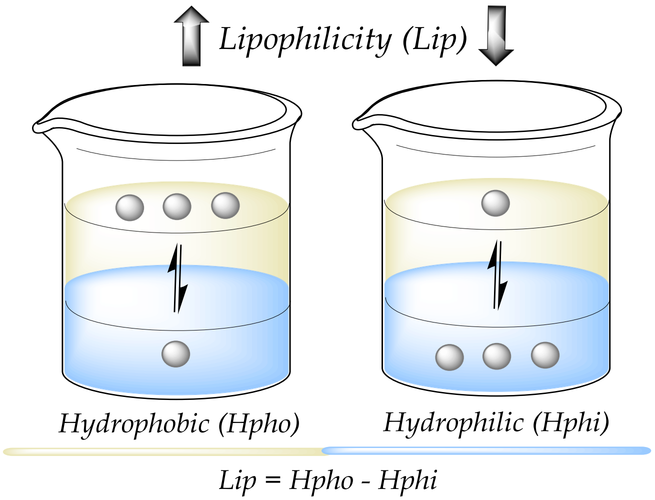


Métodos computacionales

Propiedades de Drogas

SMILES	NC(=O)CC(C(=O)NC(C(CN1CC2CCCCC2CC1C(=O)NC(C)(C)C)O)Cc1ccccc1)NC(=O)c1ccc2c(n1)cccc2
Physicochemical Properties	
Formula	C38H50N6O5
Molecular weight	670.84 g/mol
Num. heavy atoms	49
Num. arom. heavy atoms	16
Fraction Csp3	0.50
Num. rotatable bonds	16
Num. H-bond acceptors	7
Num. H-bond donors	5
Molar Refractivity	192.87
TPSA	166.75 Å^2
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.66
Log $P_{o/w}$ (XLOGP3)	4.24
Log $P_{o/w}$ (WLOGP)	2.71
Log $P_{o/w}$ (MLOGP)	1.40
Log $P_{o/w}$ (SILICOS-IT)	3.84
Consensus Log $P_{o/w}$	3.17





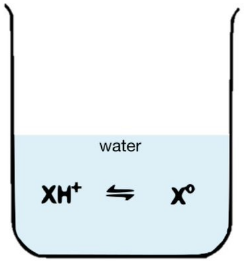
Métodos computacionales

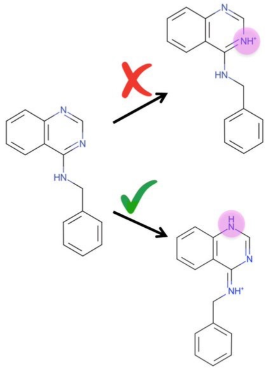
Propiedades de Drogas

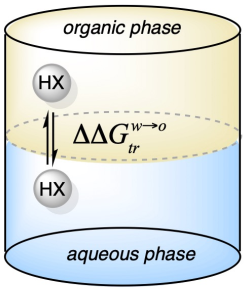
SAMPL
challenges

Drug Design Data Resource

SAMPL6 pK_a Challenge







$$\log P = -\frac{\Delta\Delta G_{tr}^{w\to o}}{RT\ln 10} = -\frac{\Delta G^{o} - \Delta G^{w}}{RT\ln 10}$$

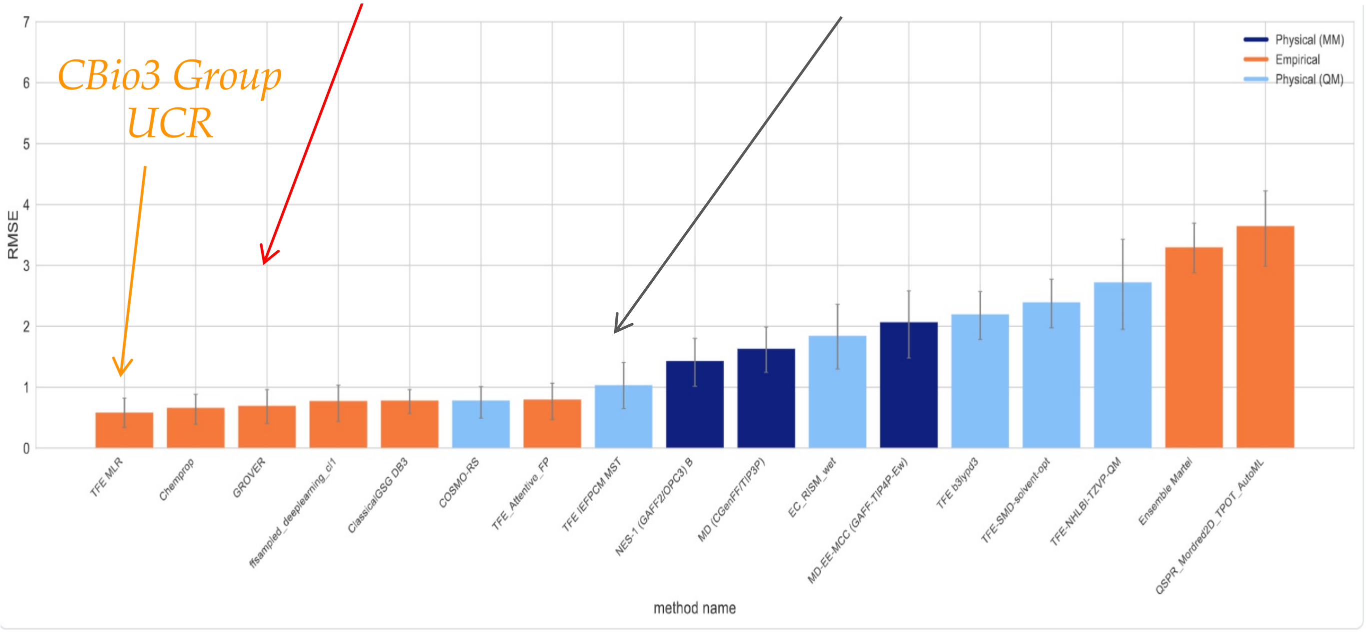
Métodos computacionales

Propiedades de Drogas

MIT Chemprop

Galápagos

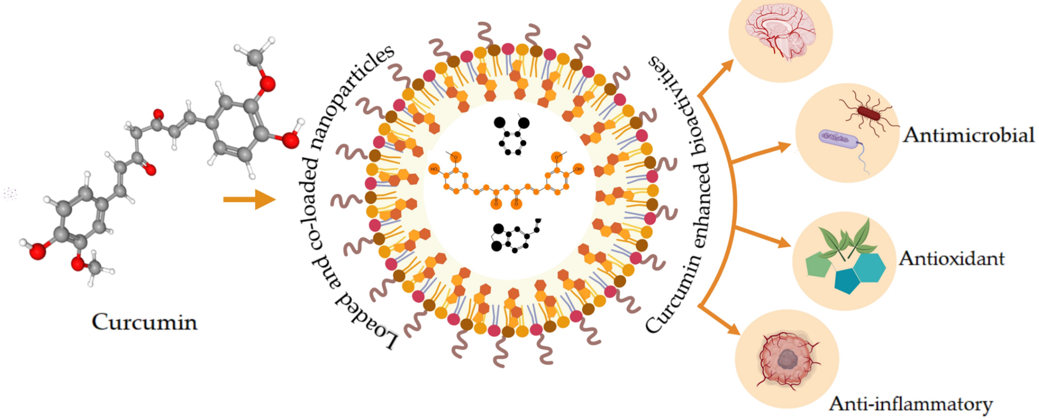
IEFPCM/MST
CBDD Group
Barcelona



CBio3 Group
UCR

Métodos computacionales

Mejoramiento de Propiedades



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Conclusiones