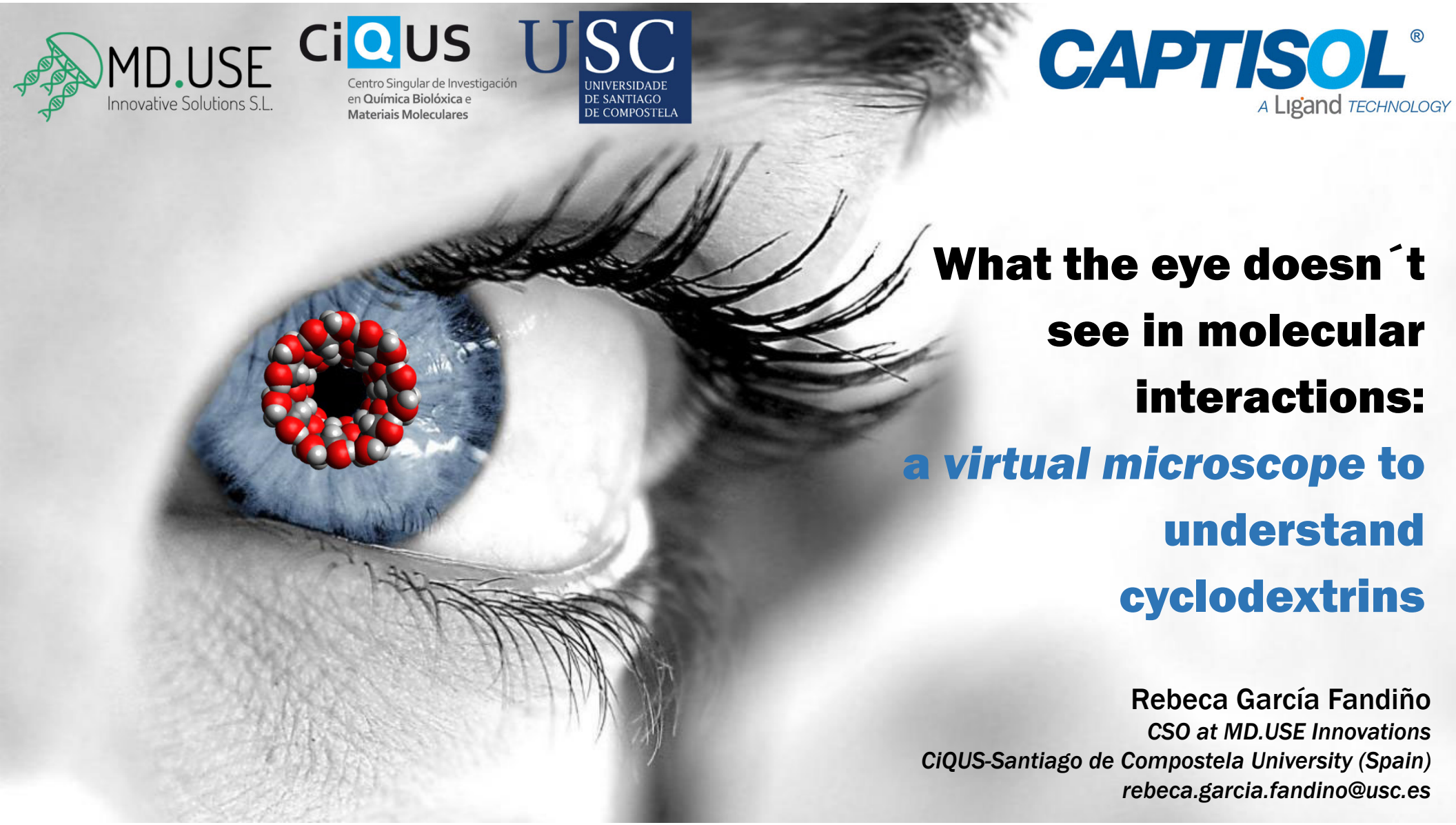

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USC Universidade de Santiago de Compostela

CAPTISOL® A Ligand TECHNOLOGY

What the eye doesn´t see in molecular interactions: a *virtual microscope* to understand cyclodextrins

Rebeca García Fandiño

CSO at MD.USE Innovations

CiQUS-Santiago de Compostela University (Spain)

rebeca.garcia.fandino@usc.es

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Characterization of molecular interactions: Molecular Dynamics & ITC experiments
3D, VR, AR & 3D-printing for Research and Dissemination

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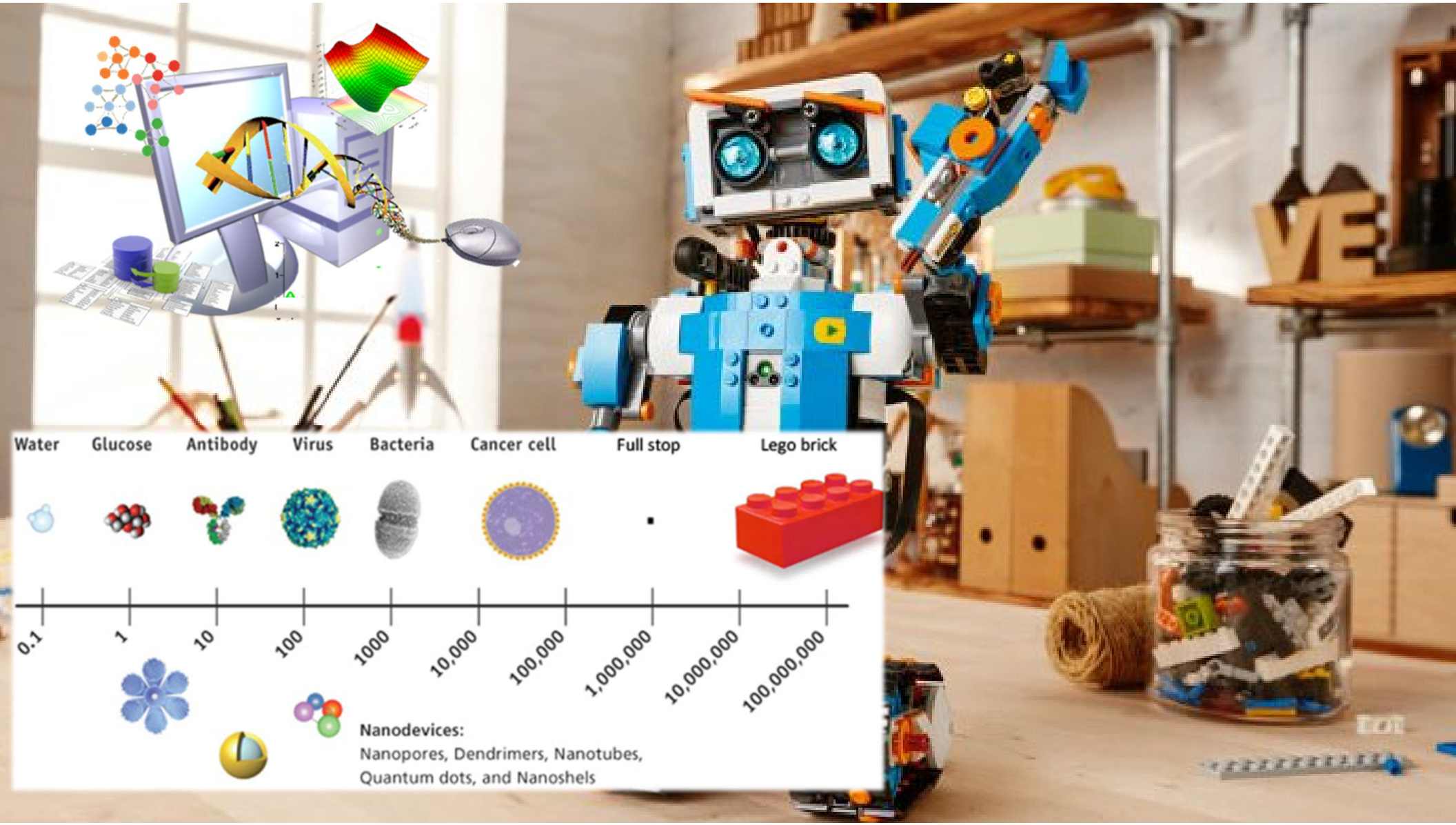
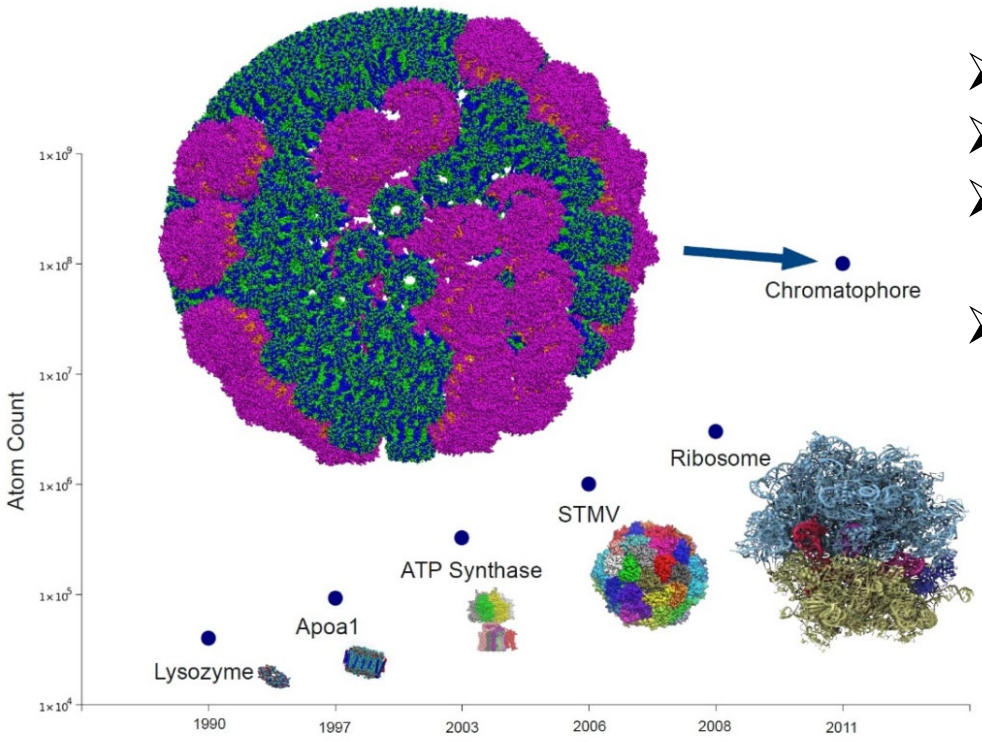
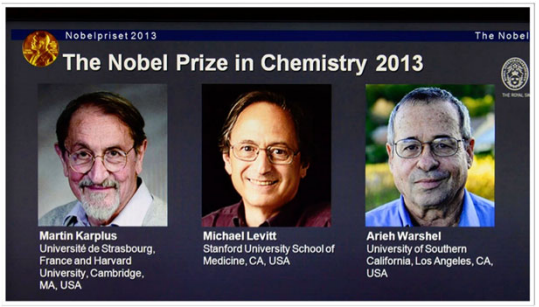
- Molecular Dynamics simulations studies, executed at supercomputer centers
- Isothermal Titration Calorimetry (ITC): experiments and analyses
- Software development for immersive visualization of molecules in Augmented and Virtual reality

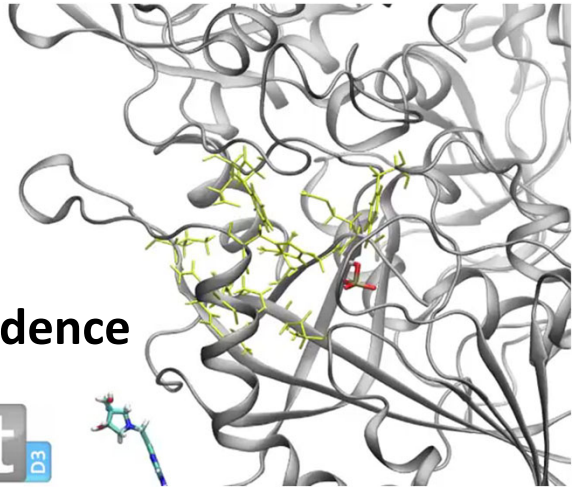

Water
Glucose
Antibody
Virus
Bacteria
Cancer cell
Full stop
Lego brick
0.1
1
10
100
1000
10,000
100,000
1,000,000
10,000,000
100,000,000
Nanodevices:
Nanopores, Dendrimers, Nanotubes,
Quantum dots, and Nanoshels

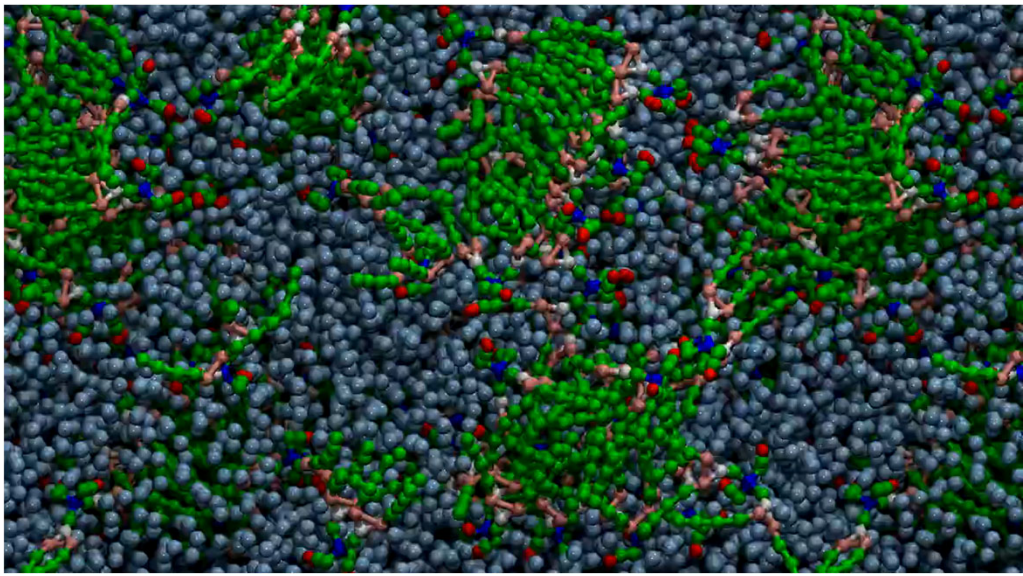
WHAT THE EYES DOESN´T SEE…THE COMPUTER DOES!



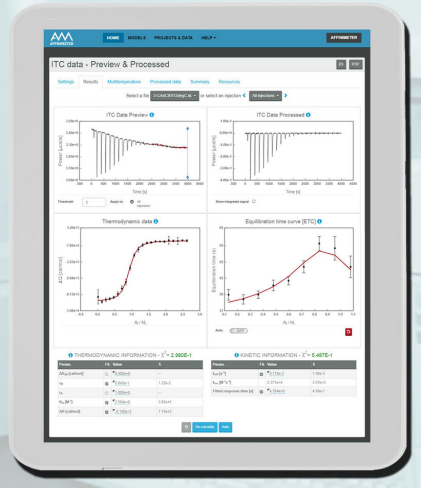


- **Atomic resolution**
- **Explicit solvent**
- **Structural-dynamic information**
- **Supercomputer dependence**





WHAT THE EYES DOESN´T SEE...ITC CAN MEASURE!



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- Generate tailored binding models.
- Perform global analysis of multiple ITC isotherms.

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AFFINIMETER FOR SPECTROSCOPIC TECHNIQUES

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- Perform a global analysis of multiple data generated from different frequencies of the spectra in a titration experiment or from different techniques.
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Learn more

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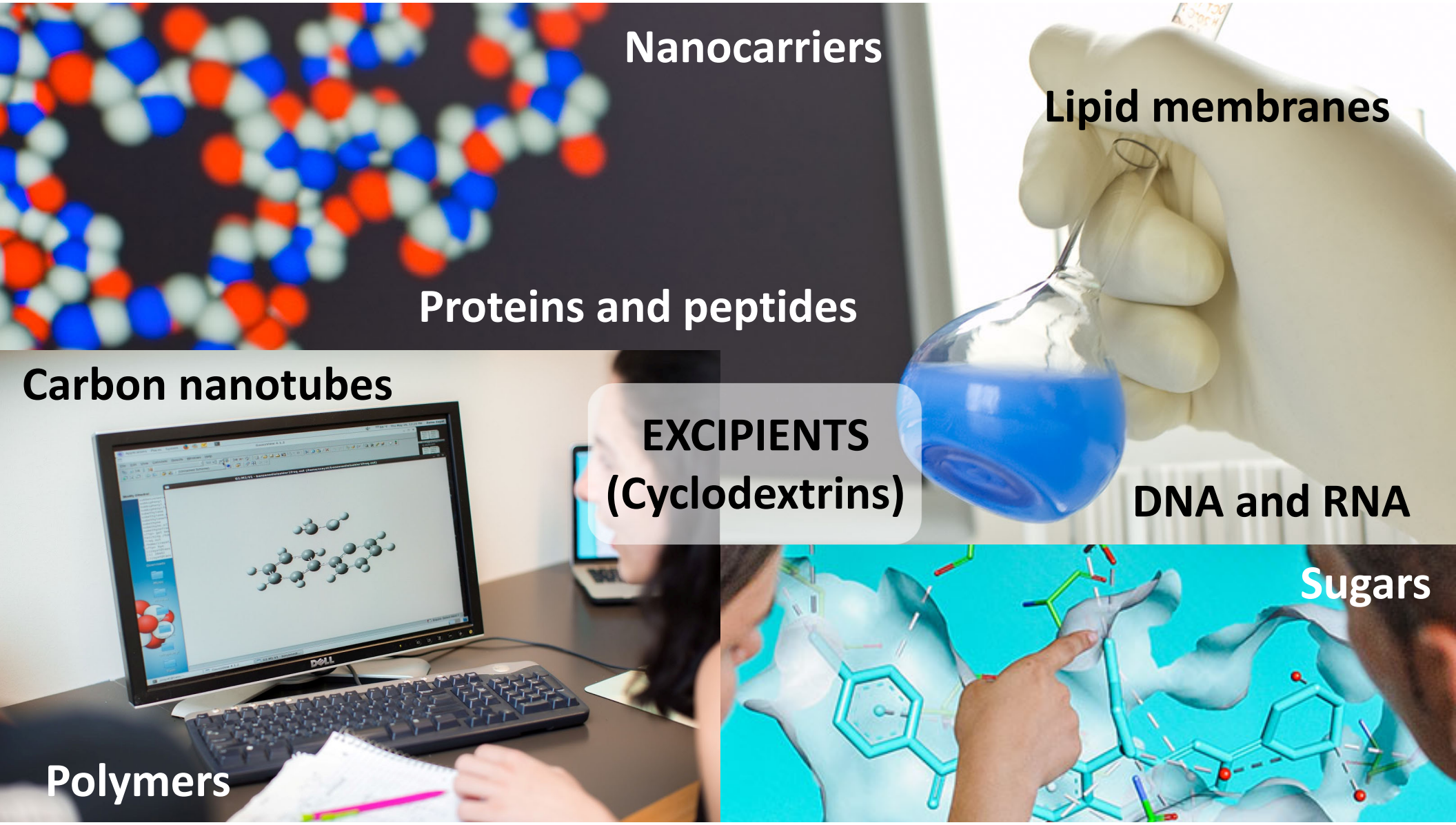
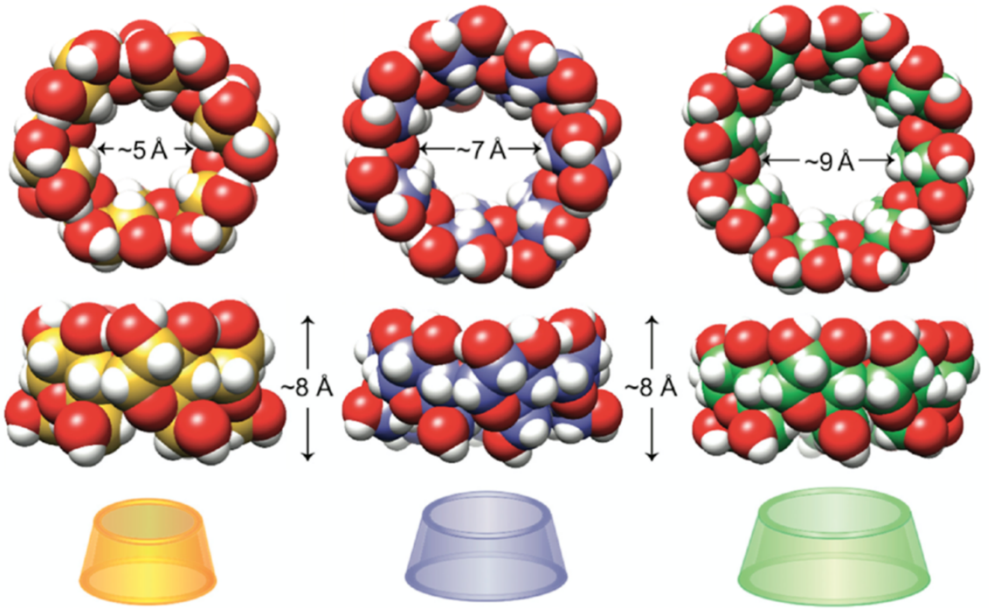
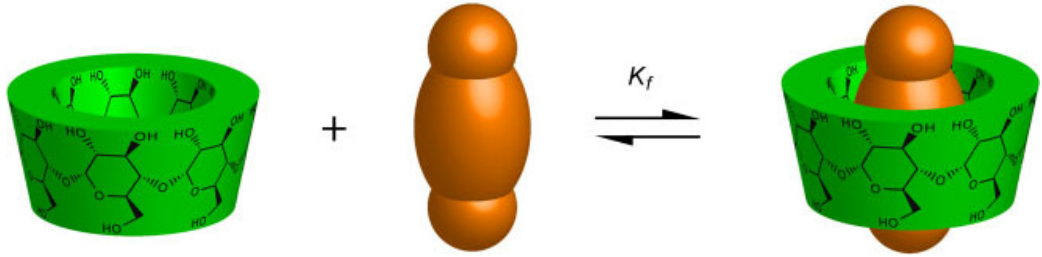

Nanocarriers
Lipid membranes
Proteins and peptides
Carbon nanotubes
EXCIPIENTS
(Cyclodextrins)
DNA and RNA
Sugars
Polymers

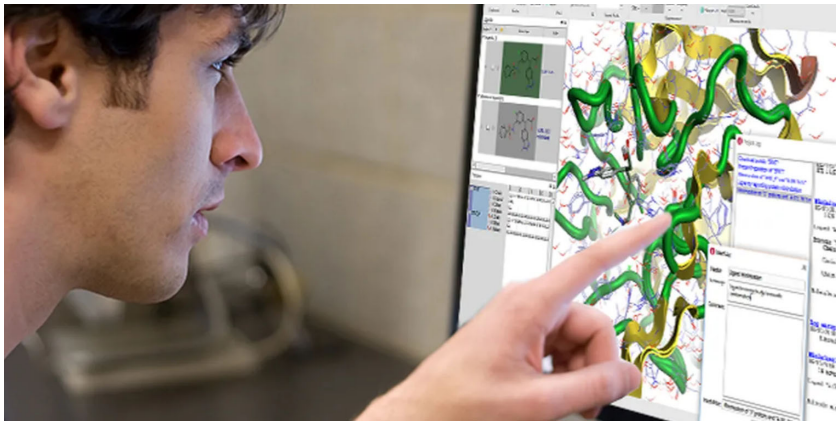
WHAT ARE CYCLODEXTRINS?



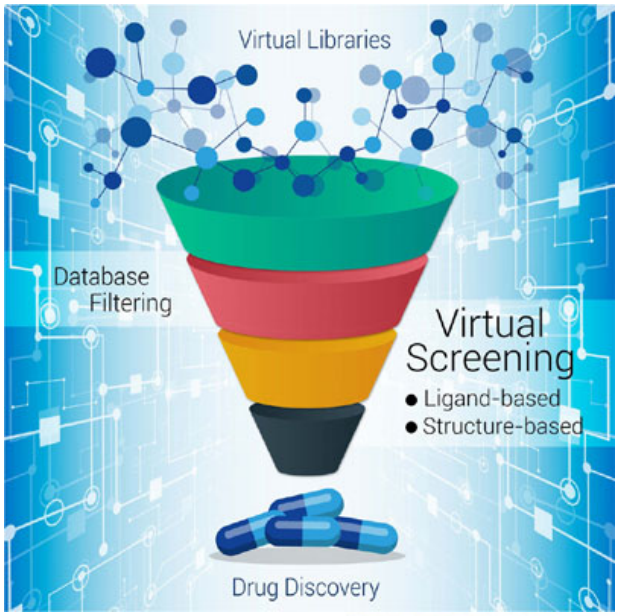
Cyclodextrins (CDs) are **excipients** which can influence the properties (such as toxicity, stability, solubility or skin penetration) of the active substance and other medicines.

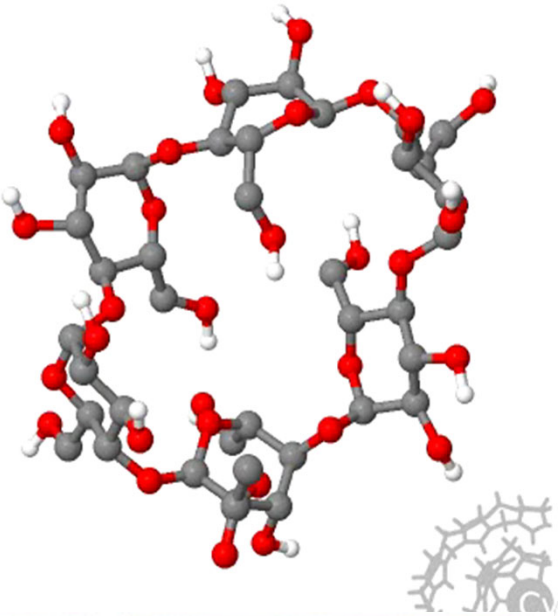


THE “CYCLODEXTRIN PARADOX”



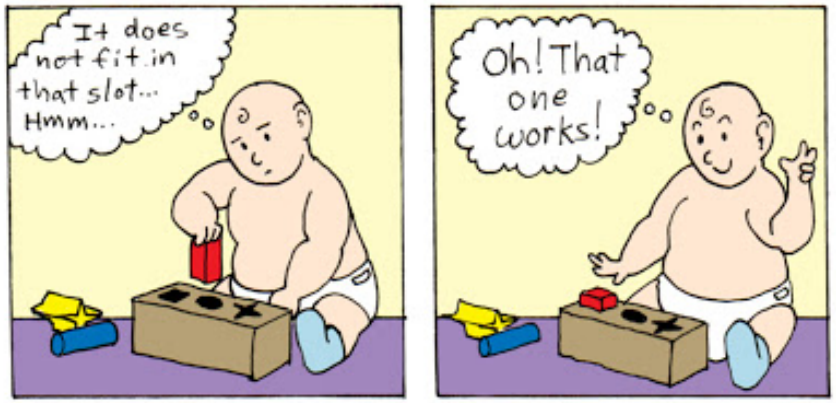
Almost any drug in the market has gone, at least in any step of its development, through a **computational modelling process**, saving to this sector a lot of money and time in their R&D process.





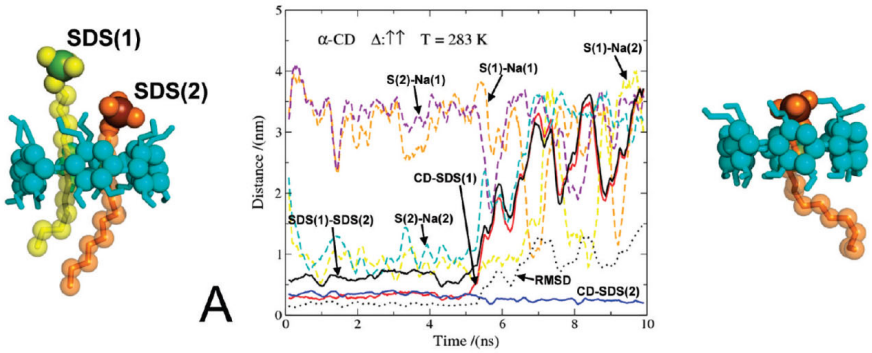
Typical for **protein + drug**... but what happens to **cyclodextrins**?

Computational tools are **scarcely used** in **cyclodextrin** industry…! …despite the elements implied in the process (receptor + ligand = CD + guest), are analogous to those typically implicated in the pharmaceutical industry.



MOLECULAR DYNAMICS SIMULATIONS WITH CYCLODEXTRINS

Starting Conformation **Final Conformation**



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Cyclo-lib: A database of computational molecular dynamics simulations of cyclodextrins

Cyclo-lib

http://cyclo-lib.mduse.com/

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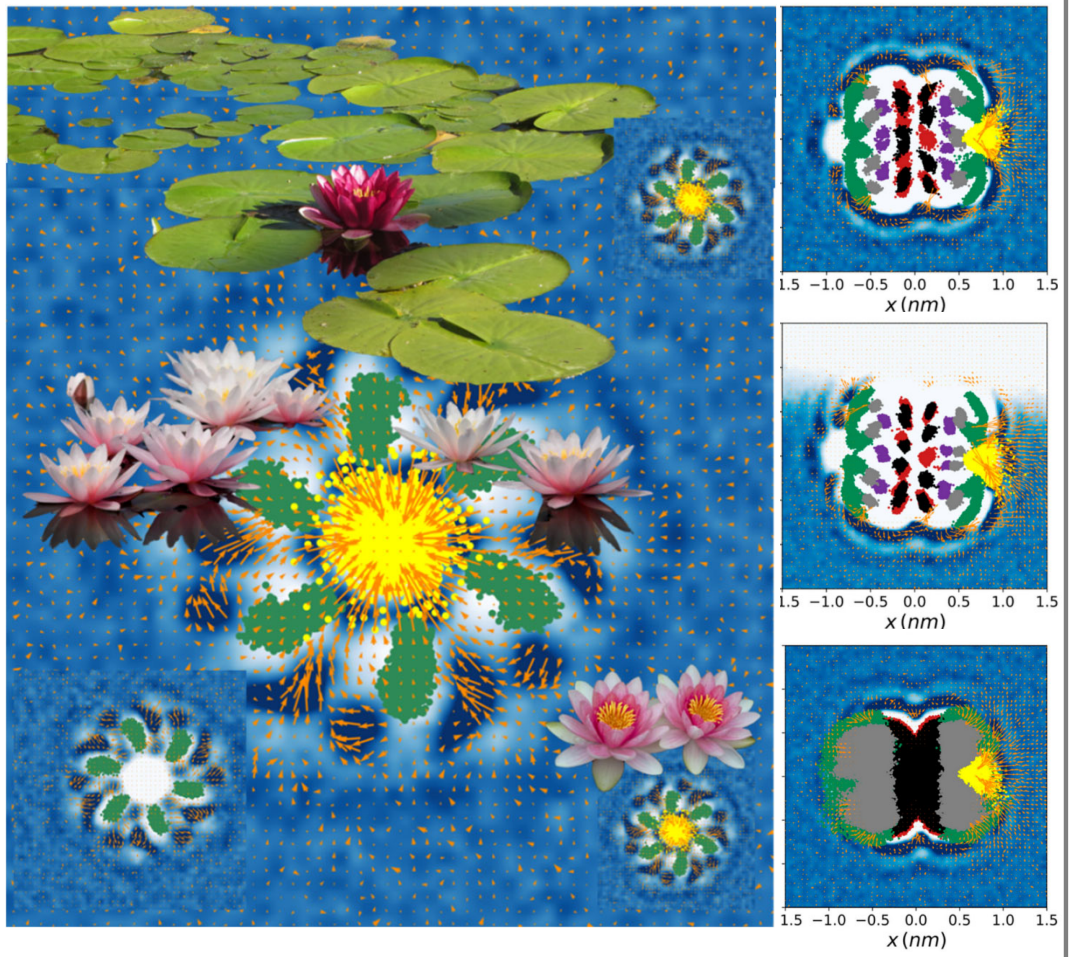
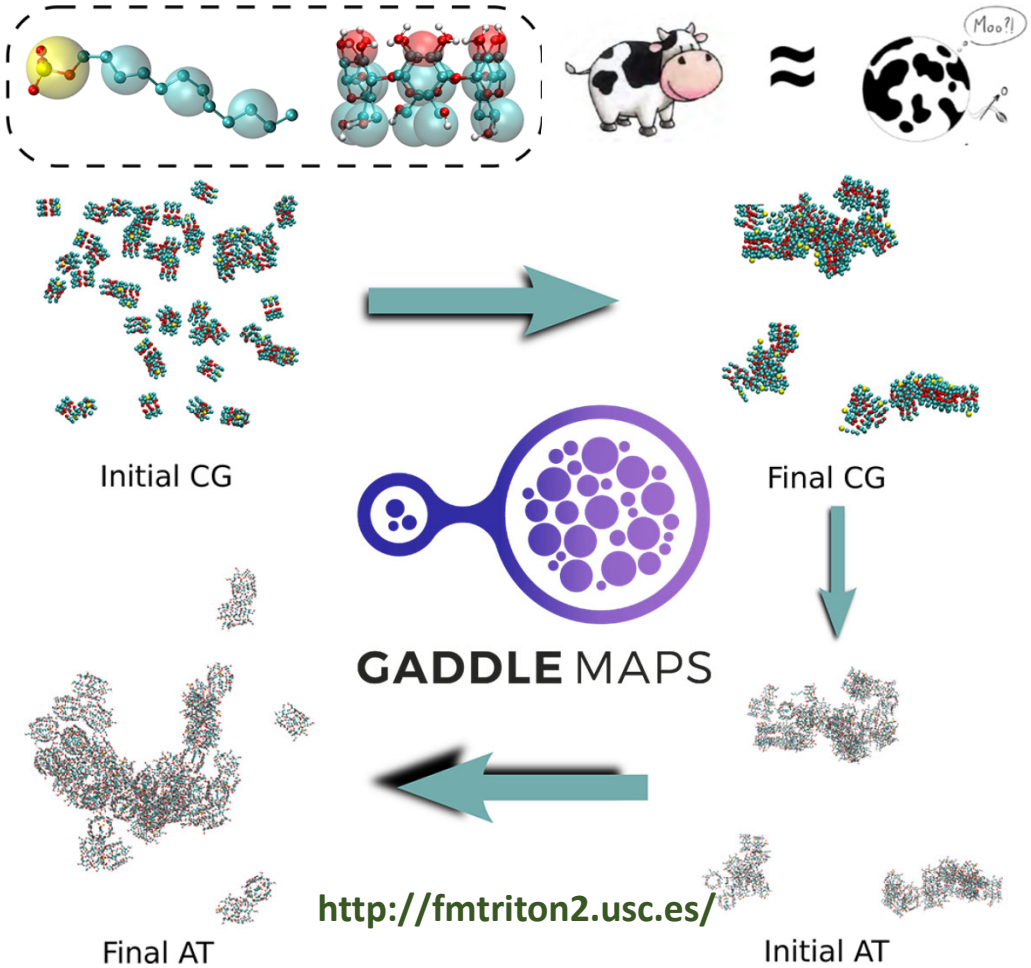
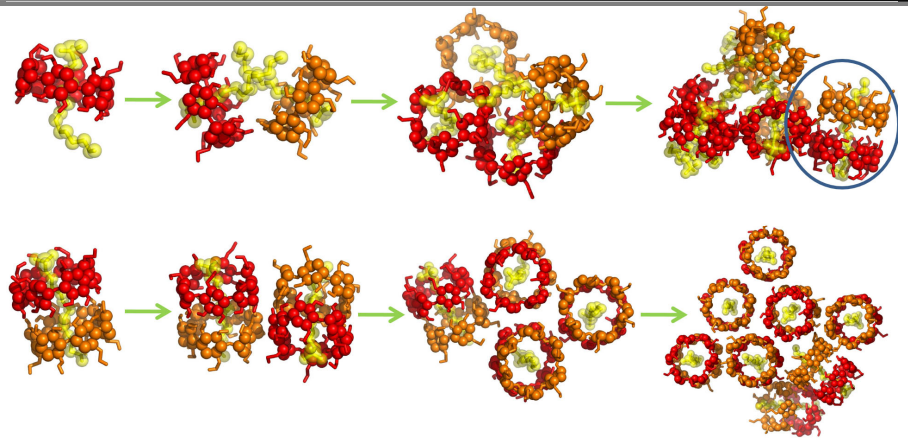


P. F. Garrido, M. Calvelo, R. Garcia-Fandiño, Á. Piñeiro, *Biomolecules* **2020**, *10* (3), 431.

MOLECULAR DYNAMICS SIMULATIONS WITH CYCLODEXTRINS



T. Otero, H. Montes, M. Calvelo, R. Garcia-Fandino, L. Gallego, Á. Piñeiro, L. M. Varela. *J. Chem. Theory Comput*. **2018**, 14(2), 466.



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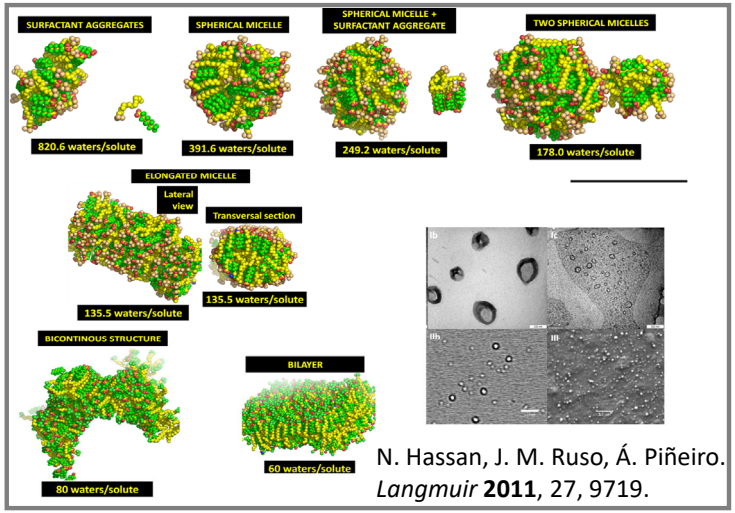

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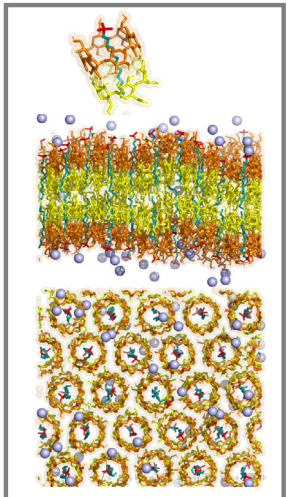


I. The encapsulating Army
Excipients for antiviral drugs

II. Collaborative weapons
Stabilizers or co-drugs

III. Using the ring as a direct weapon
Modified CDs as antiviral drugs

IV. Sentinels to prevent invasions
CDs in antiviral vaccines

V. Trying to break the enemy's borders
Cholesterol trappers to damage the viral capsid membrane

VI. Intercepting messages of the enemy
CD in RNA therapies

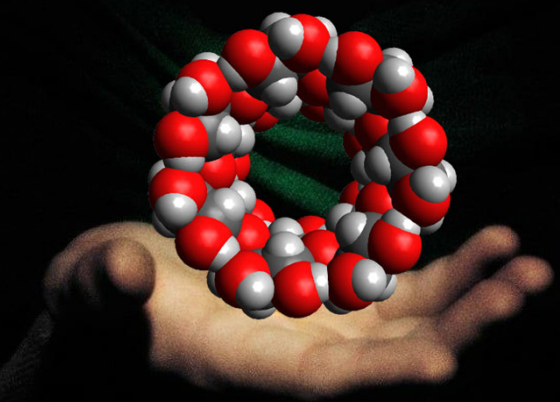
VII. Blood on the battlefield
CDs as anticoagulant agents

ELSEVIER
International Journal of Pharmaceutics
Volume 588, 15 October 2020, 119689

The Lord of the NanoRings: Cyclodextrins and the battle against SARS-CoV-2

Dedicated to Prof. Thorsteinn Loftsson, one of the greatest Nanoring Lords, in his 70th birthday.

Pablo F. Garrido [a], Martín Calvelo [b], Alexandre Blanco-González [b], Uxía Veleiro [a], Fabián Suárez [a], Daniel Conde [b], Alfonso Cabezón [b], Ángel Piñeiro [a] ✉, Rebeca Garcia-Fandino [b] ✉



THE LORD OF THE NANORINGS:
cyclodextrins and the battle against SARS-CoV-2

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CICLODEXTRINAS EN LA FORMULACIÓN DEL REMDESIVIR

Ligand's Captisol Technology Plays Key Role in the Manufacture of Gilead's Veklury, the First FDA-Approved COVID-19 Treatment

Ligand

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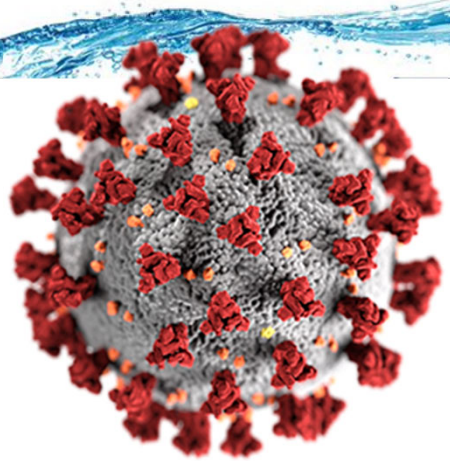

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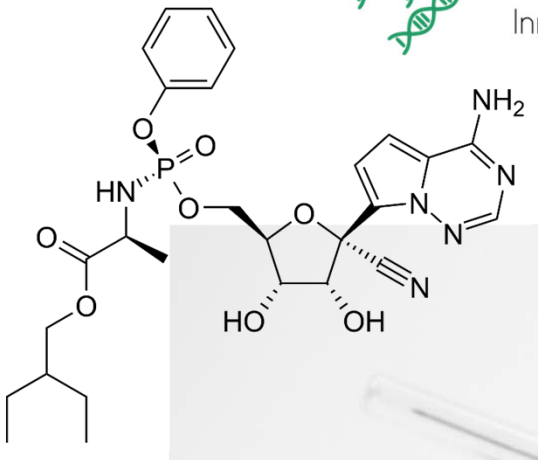

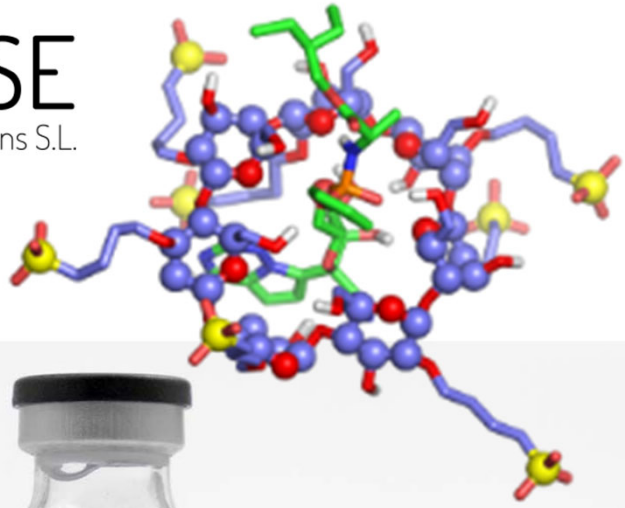

Piñeiro, A.; Pipkin, J.; Antle, V.; Garcia-Fandino, R. "Do the substitution pattern of modified cyclodextrins affect the encapsulation of drugs? A case study using sulphobutylether-b-cyclodextrin and remdesivir" sent to International Journal of Pharmaceutics **2020**

CAPTISOL

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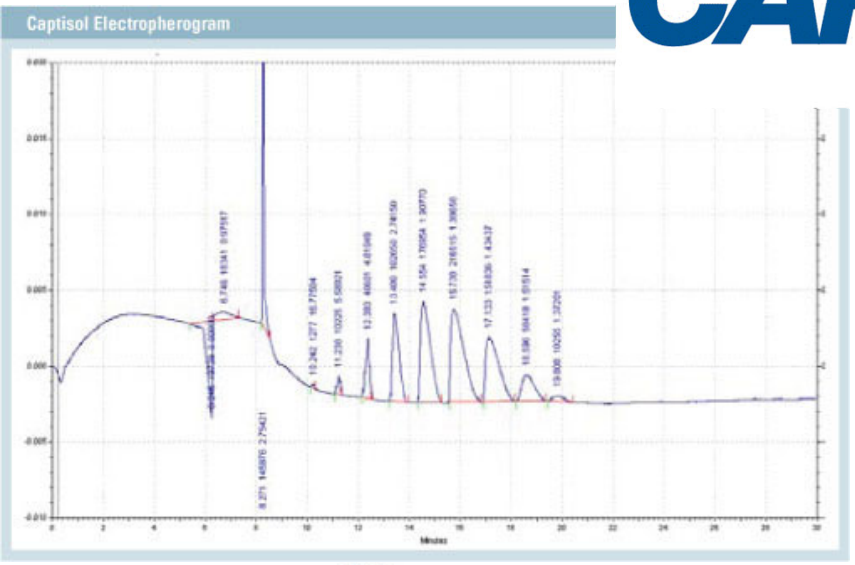
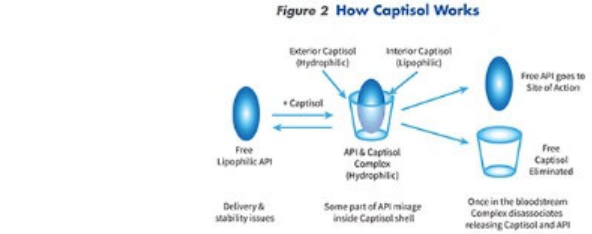
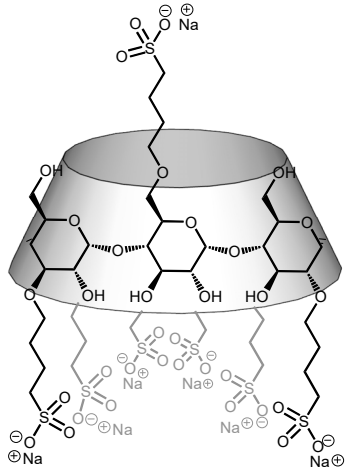






Nexterone (amiodarone HCl)
Baxter International

VFEND (voriconazole)
Pfizer

GEODON (ziprasidone HCl)
Pfizer

Cerenia (maropitant citrate)
Pfizer

Kyprolis (carfilzomib)
Amgen

EVOMELA (melphalan) for Injection
Acrotech

NOXAFIL posaconazole
Merck

Carnexiv (carbamazepine) injection
Continuity counts.
Lundbeck

Baxdela (delafloxacin)
Baxdela

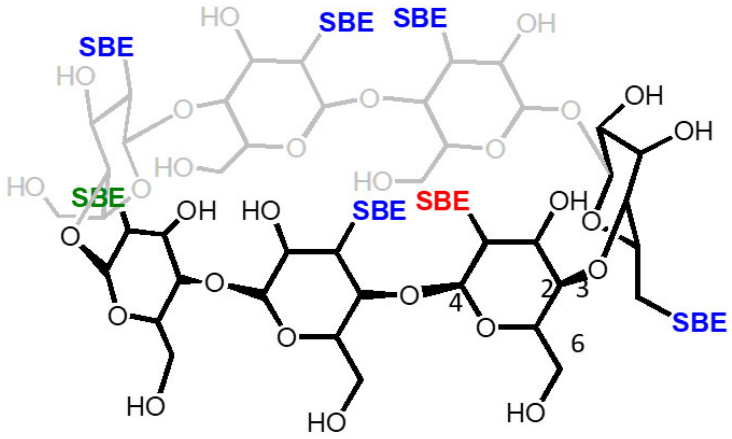
Veklury remdesivir
Gilead

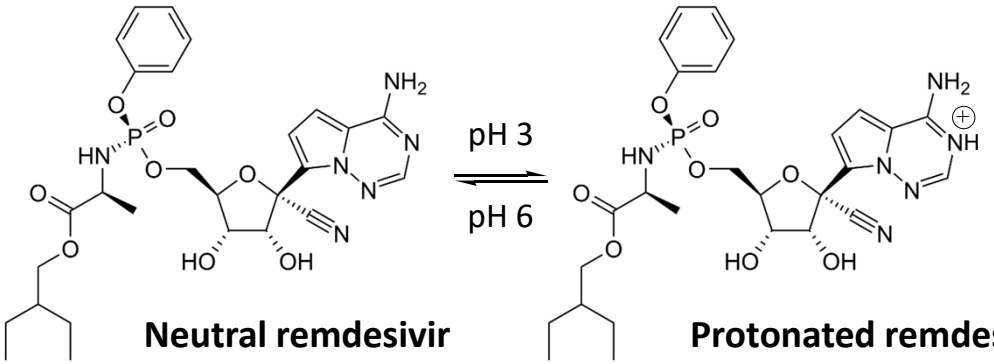
FDA-Approved Captisol-enabled® Drugs

CAPTISOL + REMDESIVIR: AN ORTHOGONAL STUDY

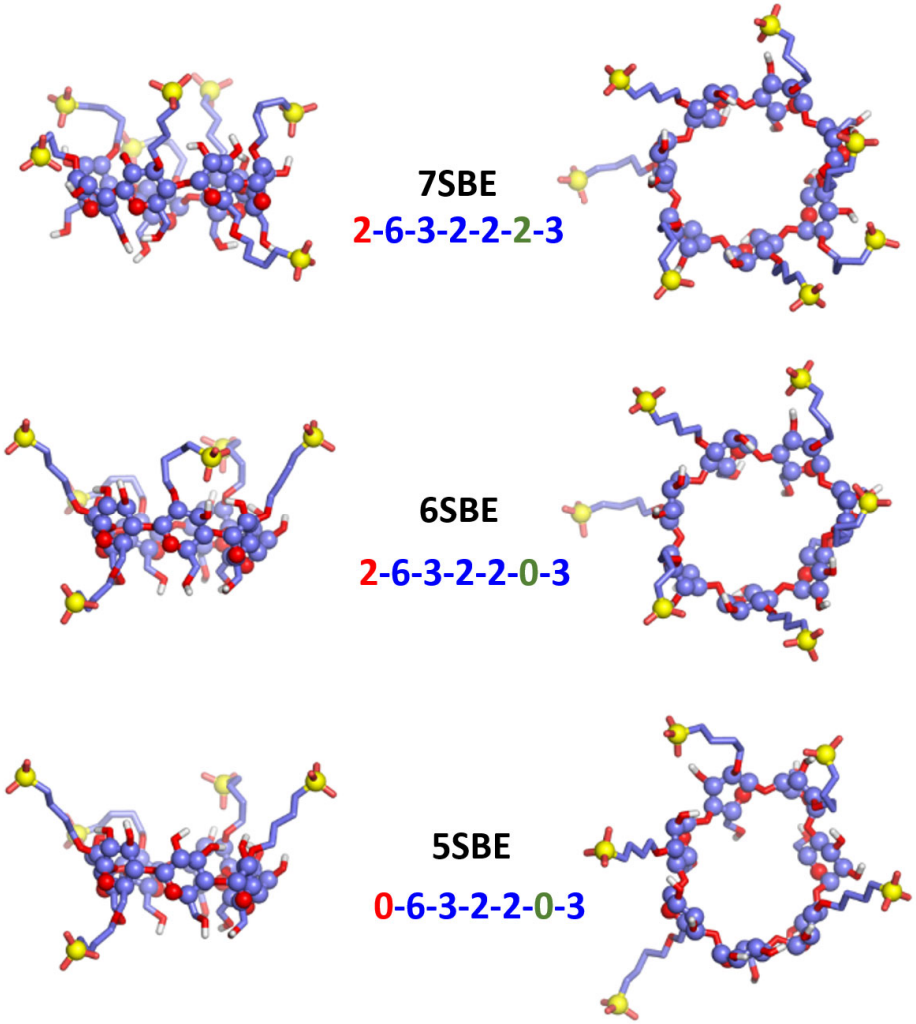
Molecular Dynamics simulations

Captisol:Remdesivir (10:1 to 30:1)





Neutral remdesivir **Protonated remdesivir**



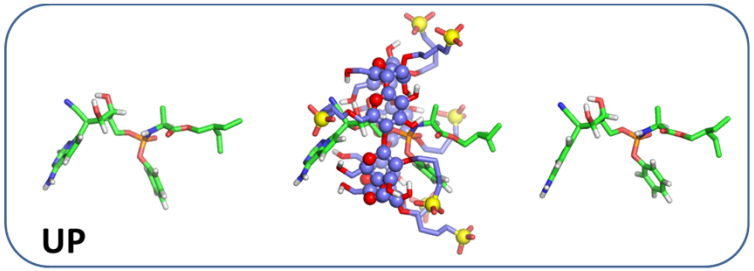
7SBE
2-6-3-2-2-2-3

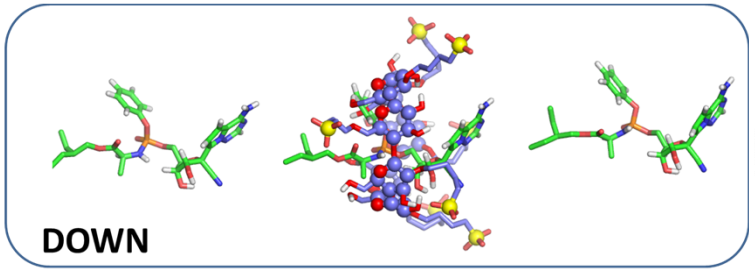
6SBE
2-6-3-2-2-0-3

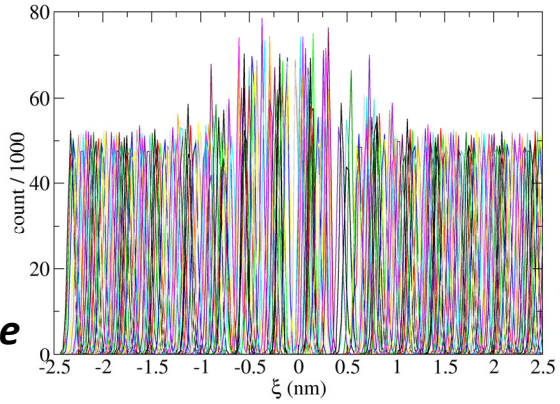
5SBE
0-6-3-2-2-0-3

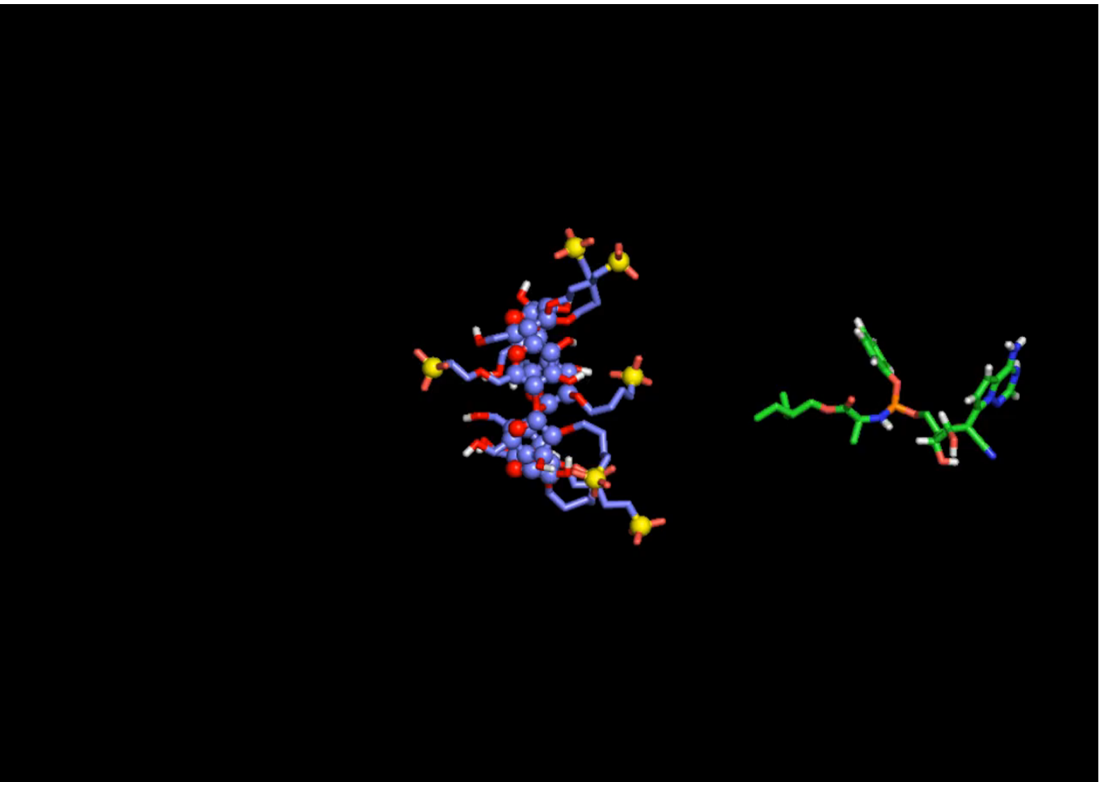
CAPTISOL + REMDESIVIR: AN ORTHOGONAL STUDY

Molecular Dynamics simulations



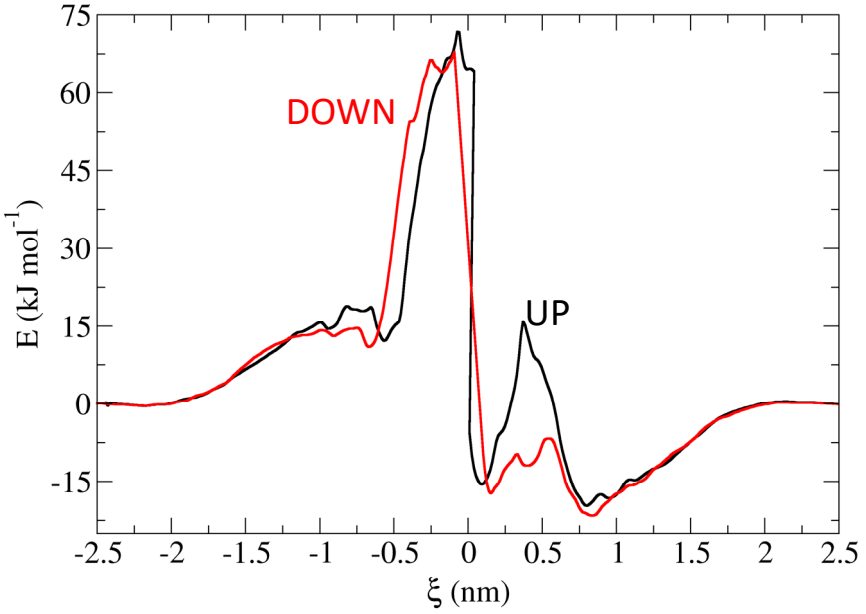






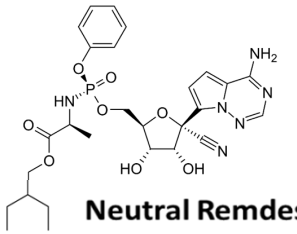
Potential of Mean Force

calculations

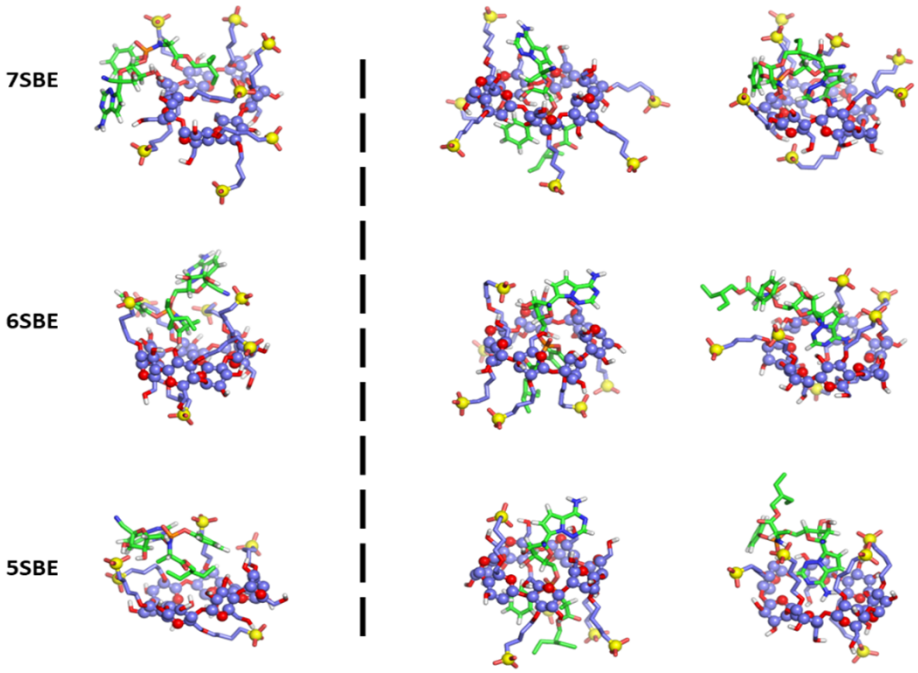


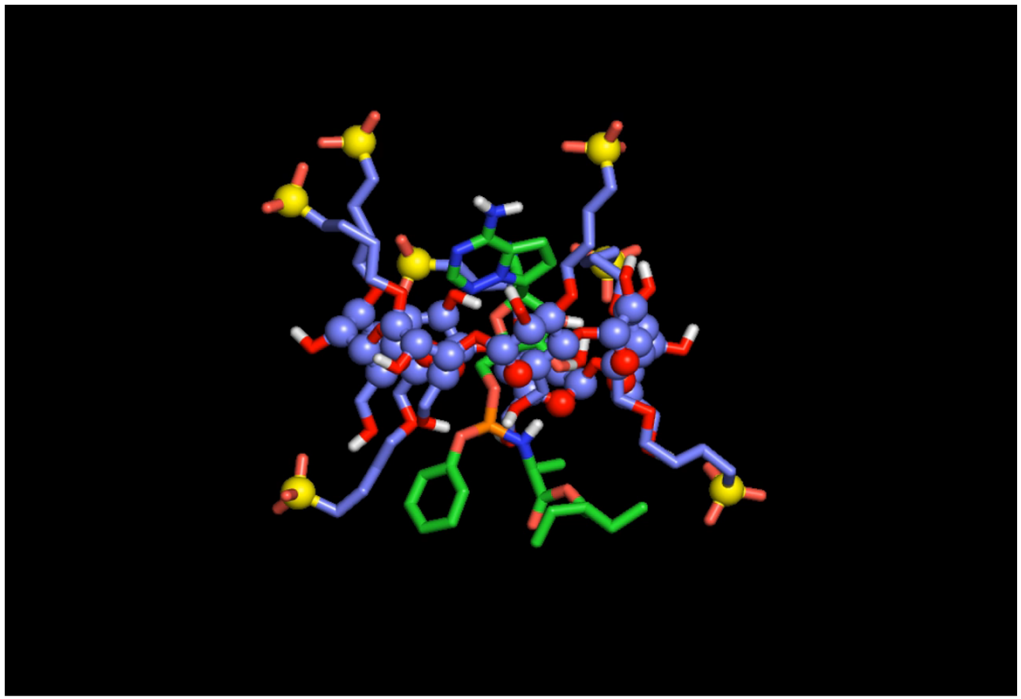
CAPTISOL + REMDESIVIR: AN ORTHOGONAL STUDY

Molecular Dynamics simulations



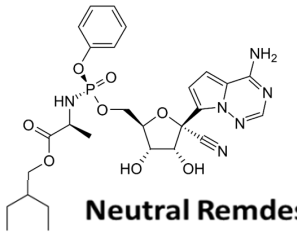
Neutral Remdesivir



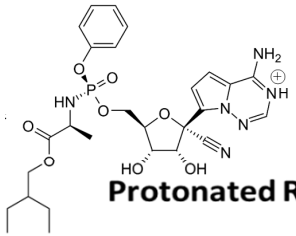


CAPTISOL + REMDESIVIR: AN ORTHOGONAL STUDY

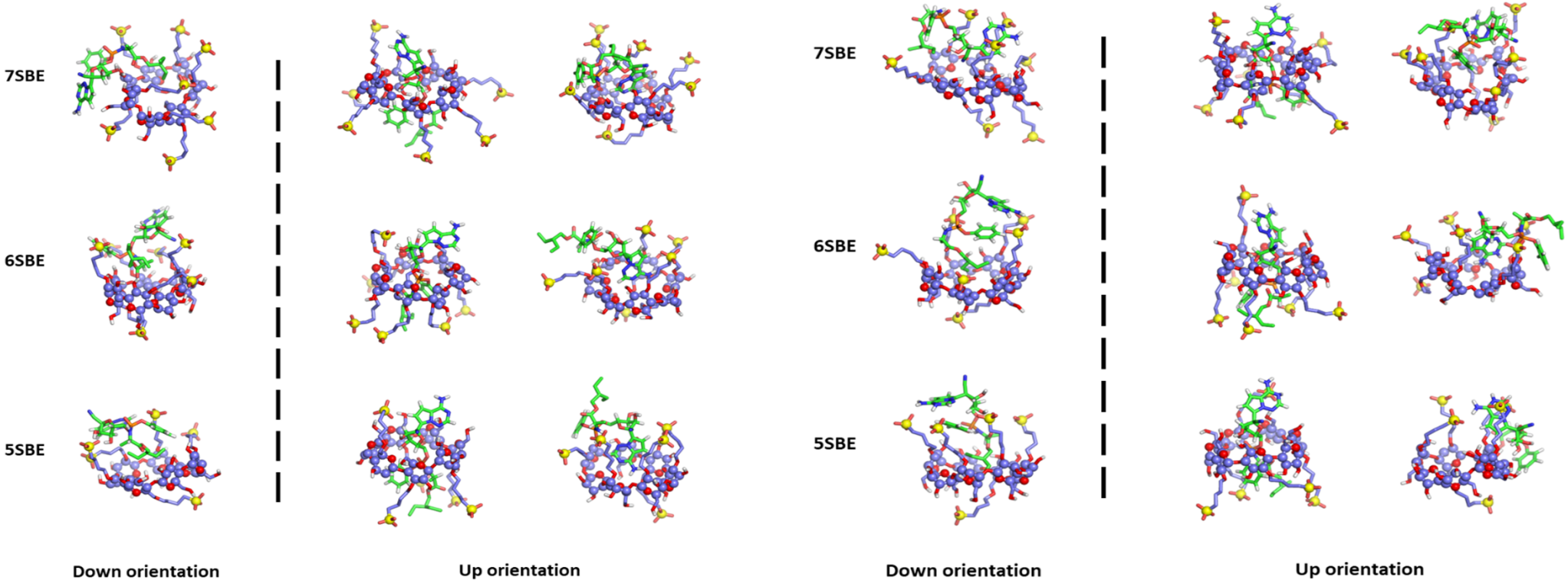
Molecular Dynamics simulations



Neutral Remdesivir



Protonated Remdesivir



CAPTISOL + REMDESIVIR: AN ORTHOGONAL STUDY

Molecular Dynamics simulations

Equilibrium constant: $A + B \rightleftharpoons C$: $K_{eq} = \frac{q_C/V}{q_A/V\, q_B/V}$ (V is the volume of the system)

No internal degrees of freedom for A and B

$$H_A = \sum_{i=1}^{3} \frac{p_i^2}{2m_A}; \qquad H_B = \sum_{i=1}^{3} \frac{p_i^2}{2m_B}$$

$$q_A = V\left(2\pi m_A k_b T/h^2\right)^{3/2}$$

$$q_B = V\left(2\pi m_B k_b T/h^2\right)^{3/2}$$

Si U=U(r) => spherical symmetry
Reference state=> 1 M concentration
(since U only depends on r, the two angles in the volume element are integrated)

$$K_{eq} = 4\pi N_a \int_0^{\infty} r^2\, e^{-U(r)/k_b T} dr$$

$U(\xi)$ ->potential describing the interaction between A and B

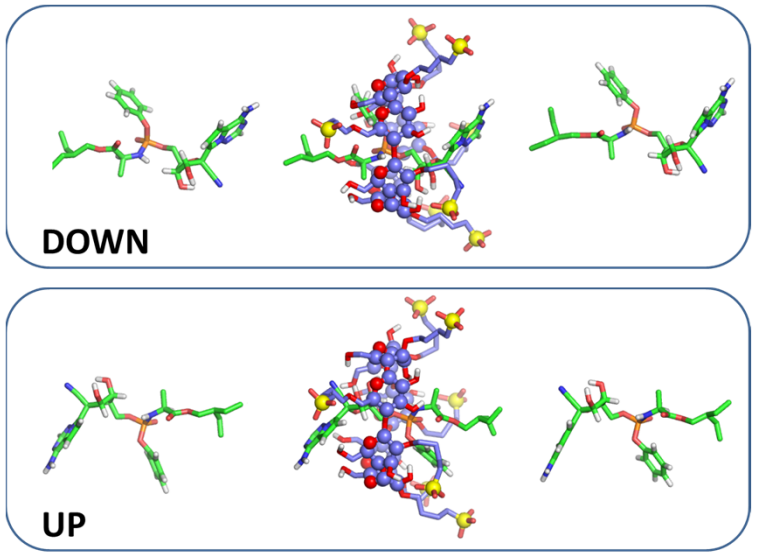
$$H_{AB} = \sum_{i=1}^{3} \frac{\left(p_i^{com}\right)^2}{2(m_A + m_B)} + \sum_{i=1}^{3} \frac{\left(p_i^R\right)^2}{2\mu} + U(\xi) \qquad \mu = \frac{m_A \cdot m_B}{(m_A + m_B)}$$

$$q_{AB} = V\left[2\pi(m_A + m_B)k_b T/h^2\right]^{3/2} \cdot \left(2\pi\mu k_b T/h^2\right)^{3/2} \cdot \int e^{-U(\xi)/k_b T} d\xi$$

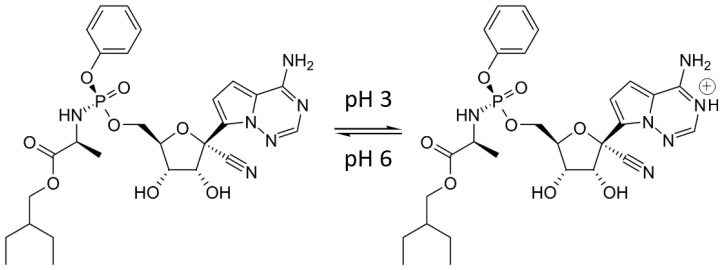
Substituting the partition functions in the expression for K_{eq}:

$$K_{eq} = \int e^{-U(r)/k_b T} dx dy dz$$

Mathematical development to obtain affinity constants from PMFs



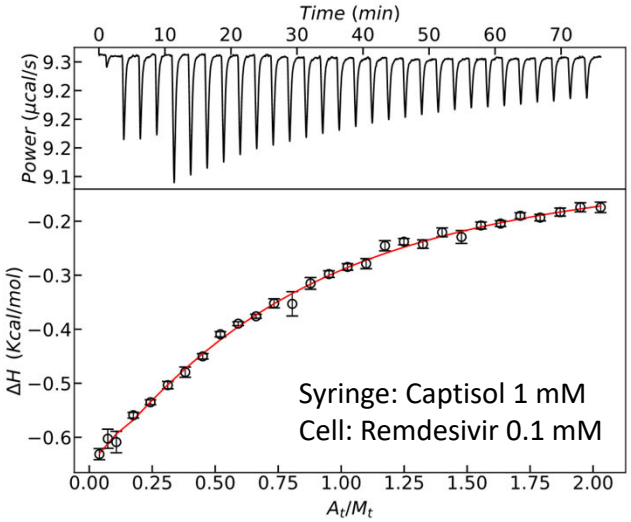
Cyclodextrin	Neutral		Protonated	
	UP	DOWN	UP	DOWN
SBE7	30	40	$2.0 \cdot 10^4$	$8.2 \cdot 10^3$
SBE6	24	13	$2.3 \cdot 10^4$	$4.0 \cdot 10^3$
SBE5	13	11	$2.3 \cdot 10^3$	$2.1 \cdot 10^3$

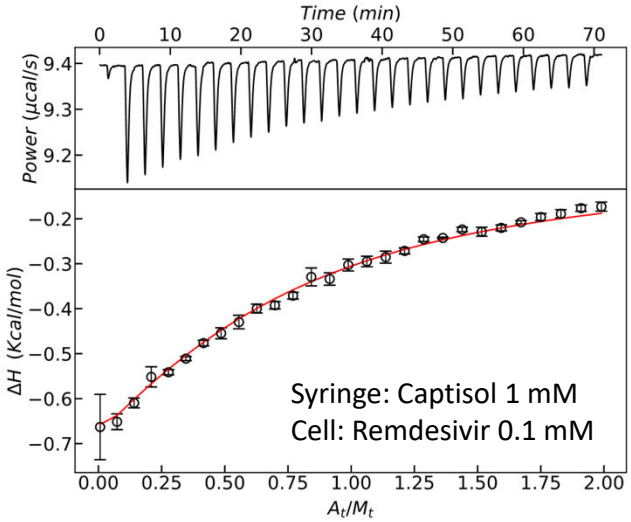


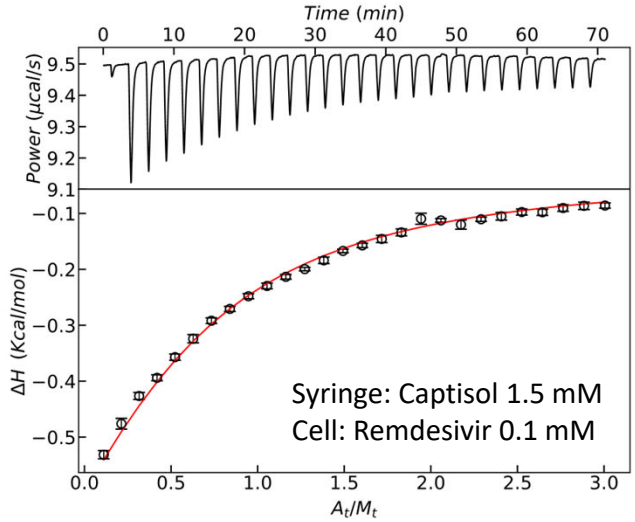
Neutral remdesivir **Protonated remdesivir**

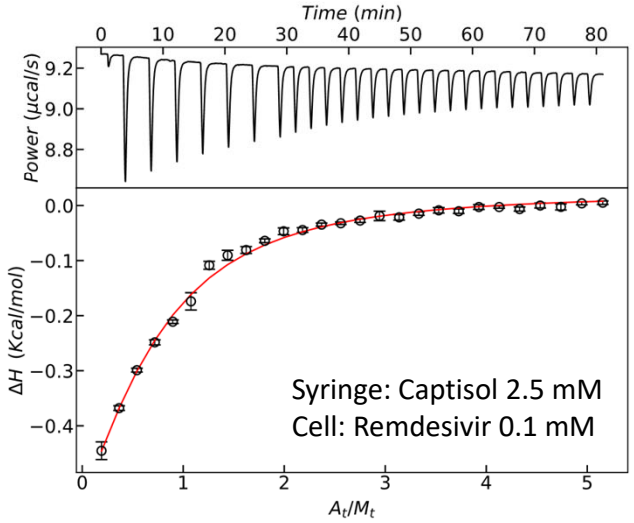
CAPTISOL + REMDESIVIR: AN ORTHOGONAL STUDY

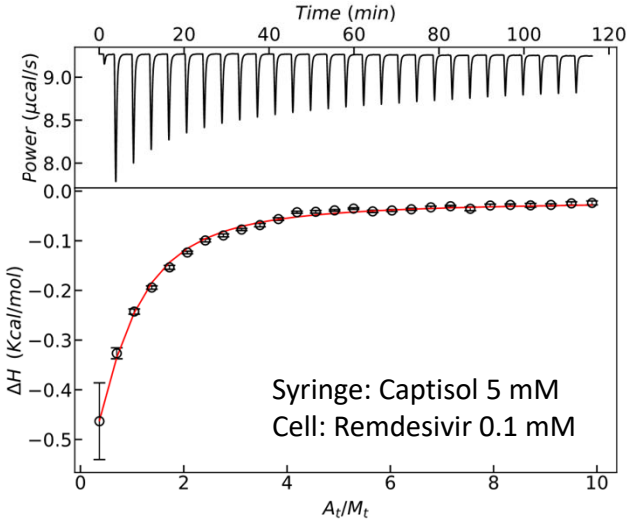
ITC experiments





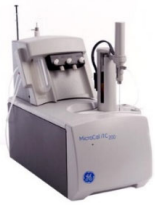






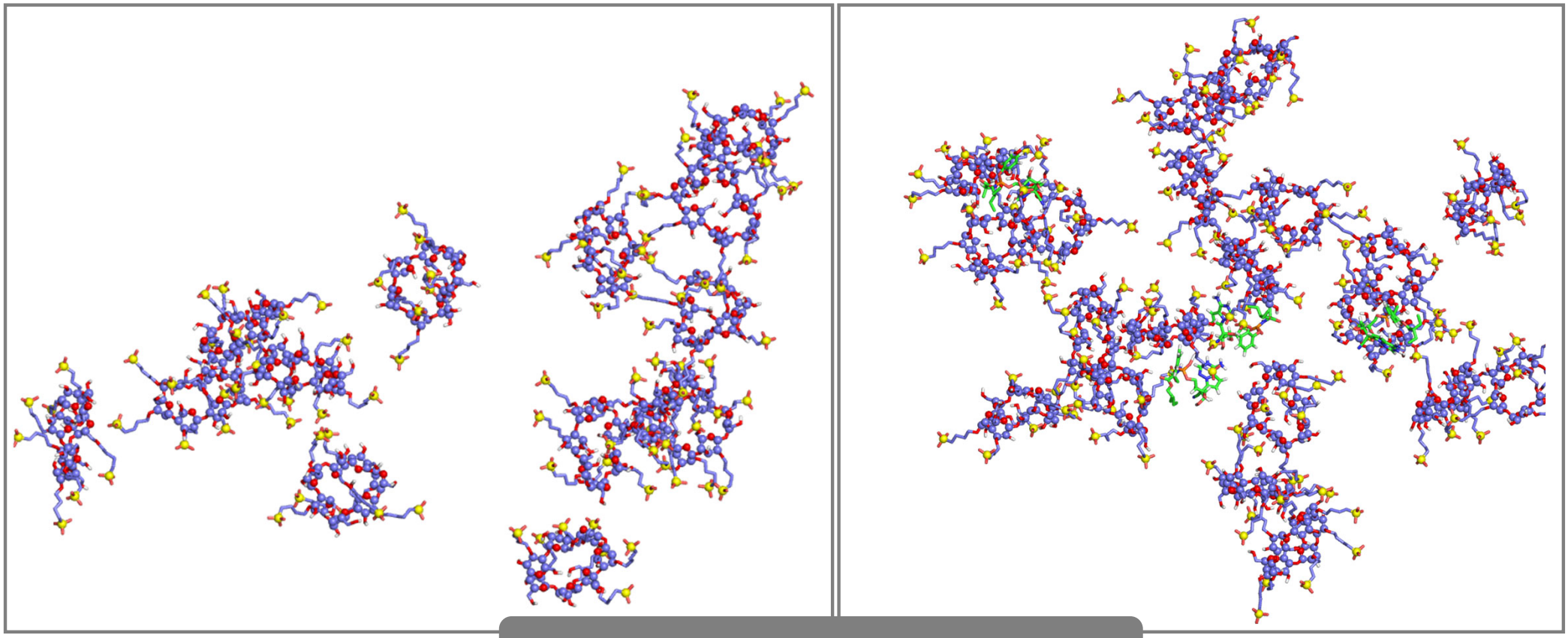
Parameter	Value	std dev
K_A (M^{-1})	6562	72
DH (cal/mol)	-678	2
r_C	1.905	0.009

AFFINIMETER



CAPTISOL + REMDESIVIR: AN ORTHOGONAL STUDY

Molecular Dynamics simulations



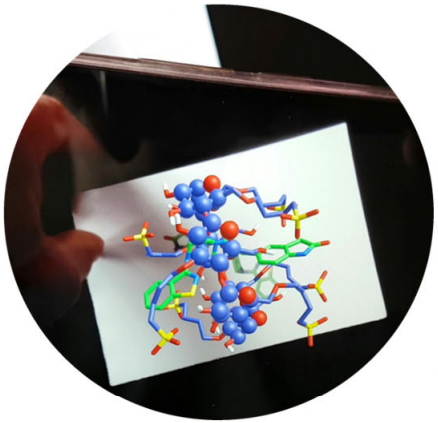
Aggregation studies

A NEW WAY TO SEE...WHAT THE EYES CANNOT SEE

Augmented Reality

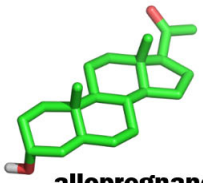
OLLOMOL AR MOLECULAR VIEWER for Captisol

Ollomol AR for Captisol is an Augmented Reality (AR) molecular viewer developed to visualize 3D-AR images of complexes formed by Captisol with the following 12 drugs: allopregnanolone, amiodarone, carbamazepine, aripiprazole, busulfan, delafloxacin, carfilzomib, melphalan, posaconazole, maropitant, voriconazole and ziprasidone mesylate. The 3D-movies were generated by Molecular Dynamics simulations.

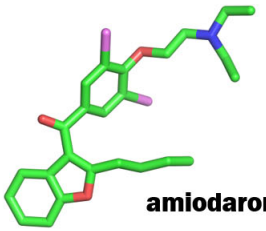


ANDROID APP ON Google play

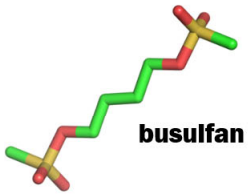
Available on the App Store



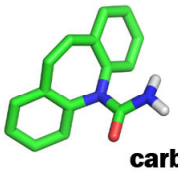
allopregnanolone



amiodarone

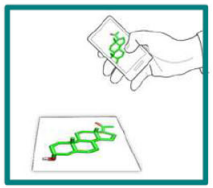


busulfan

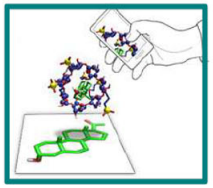


carbamazepine

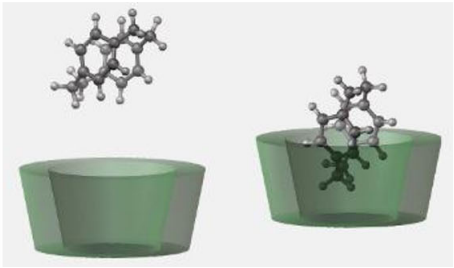
Download



Scan



Have fun!



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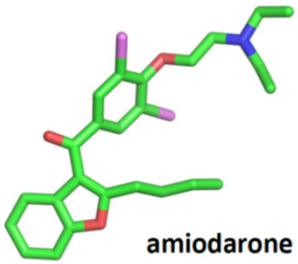
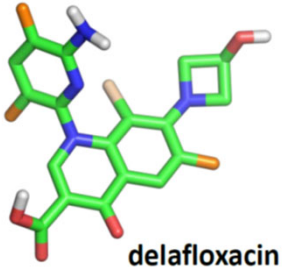
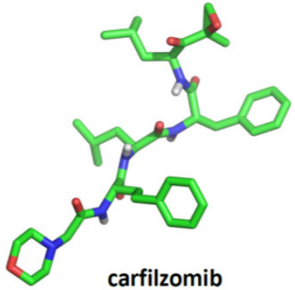
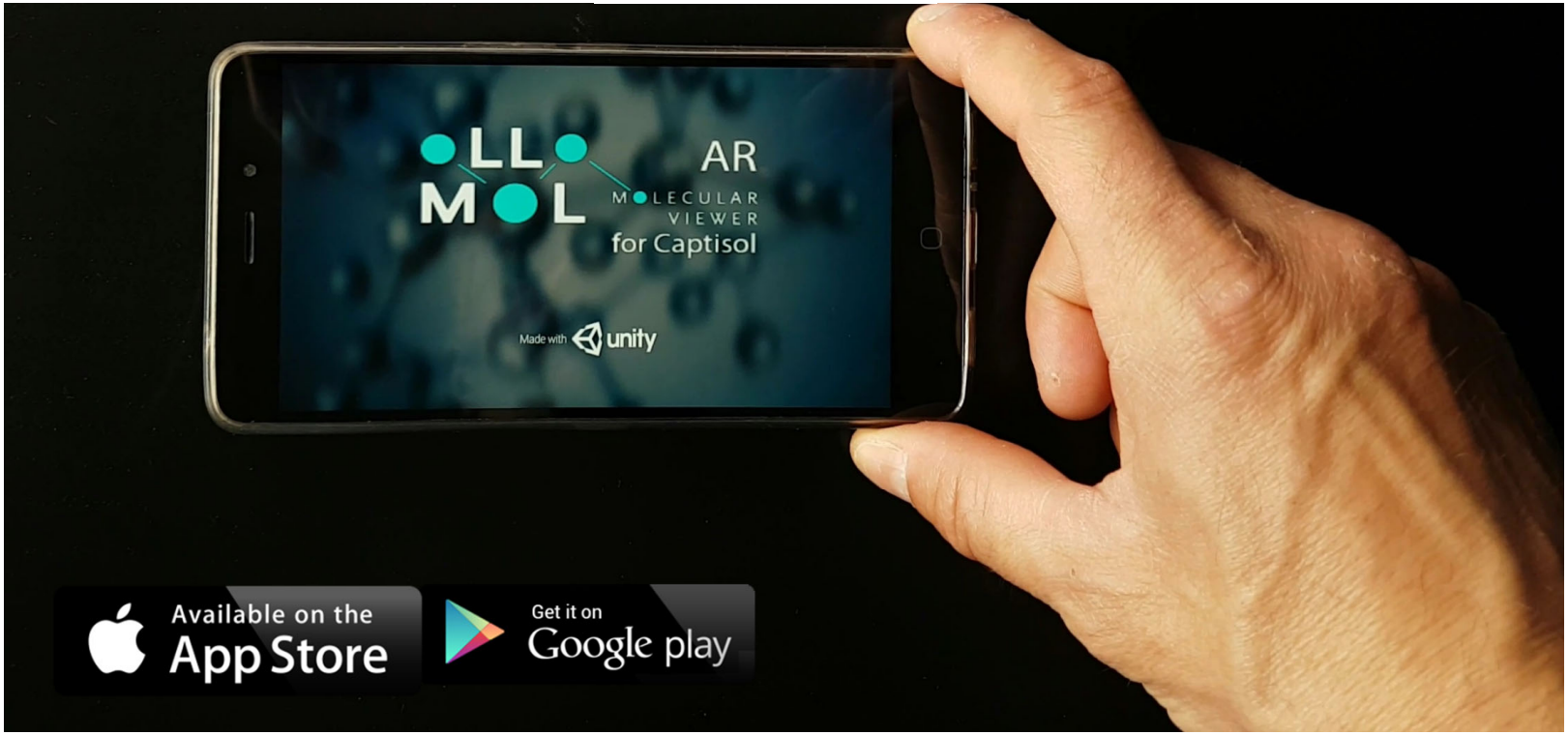
Augmented Reality









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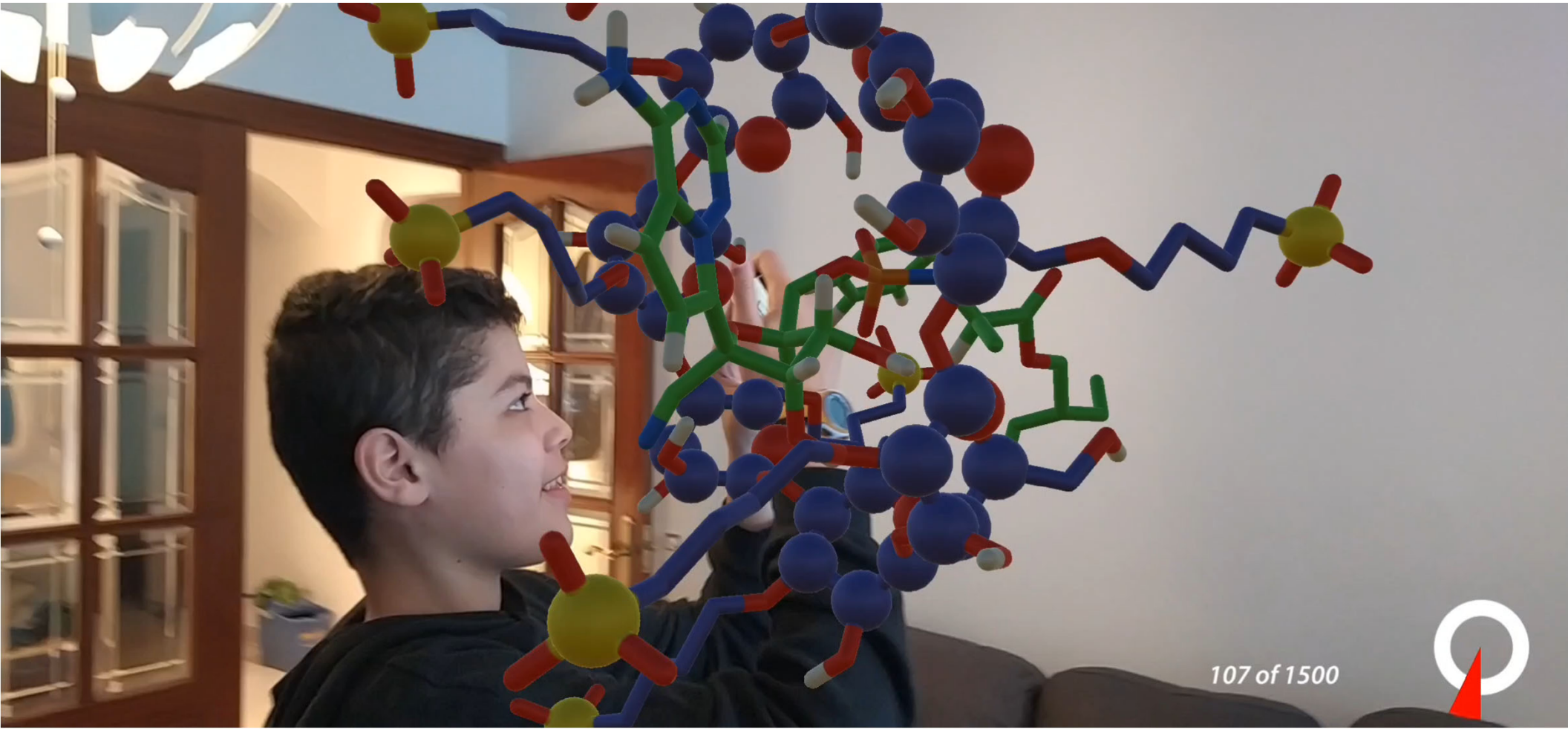

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Augmented Reality

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Virtual Reality

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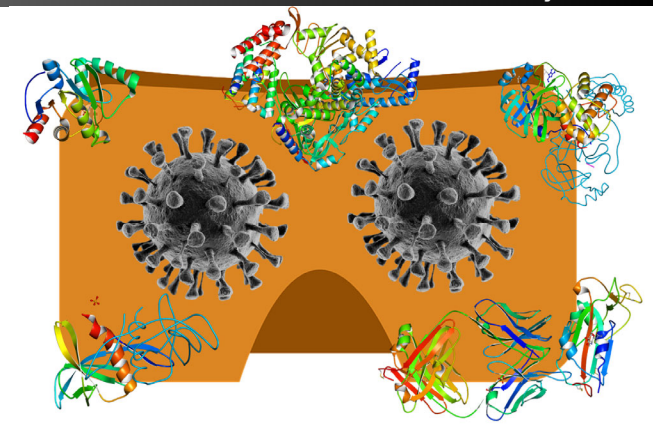
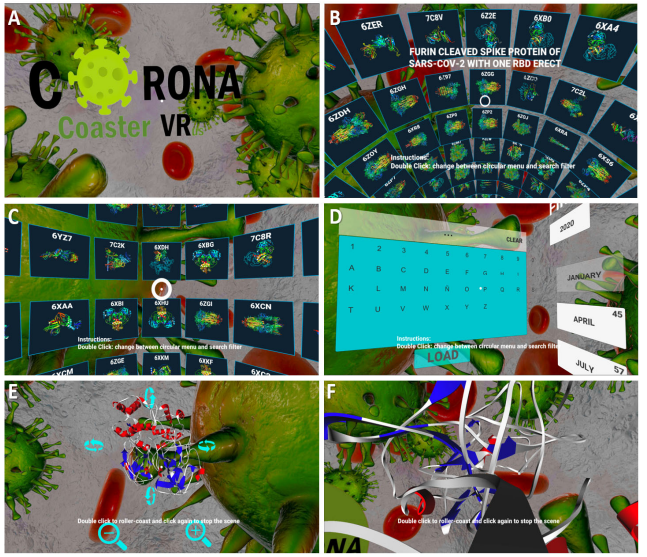
MOLLO VR

MOLECULAR VIEWER for Captisol





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