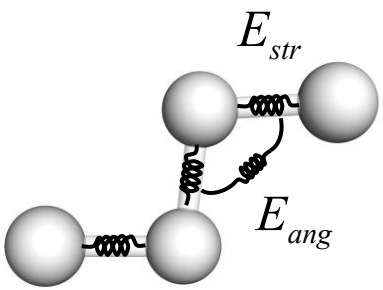
Molecular dynamics methods applied to food chemistry

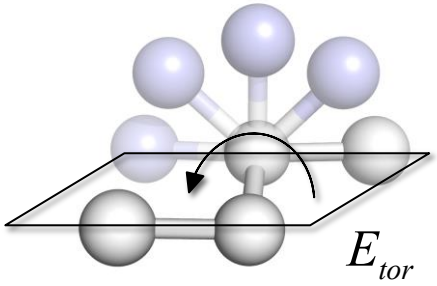
Axel Bidon-Chanal Badia

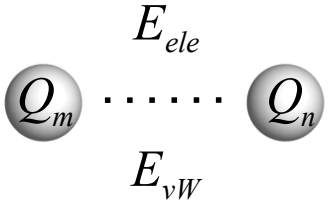
Department of Nutrition, food sciences and gastronomy

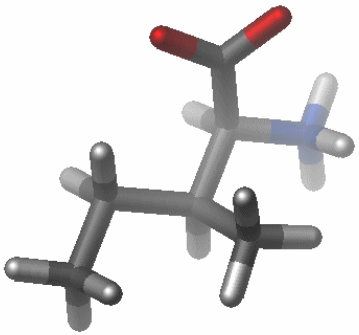
Faculty of Pharmacy and Food sciences, Food Science Campus, University of Barcelona

Molecular dynamics









Bonded-terms

Non bonded-terms

Other

Polarization

Restraints

$$E = E_{str} + E_{bnd} + E_{tor} + E_{nb} + E_{other}$$

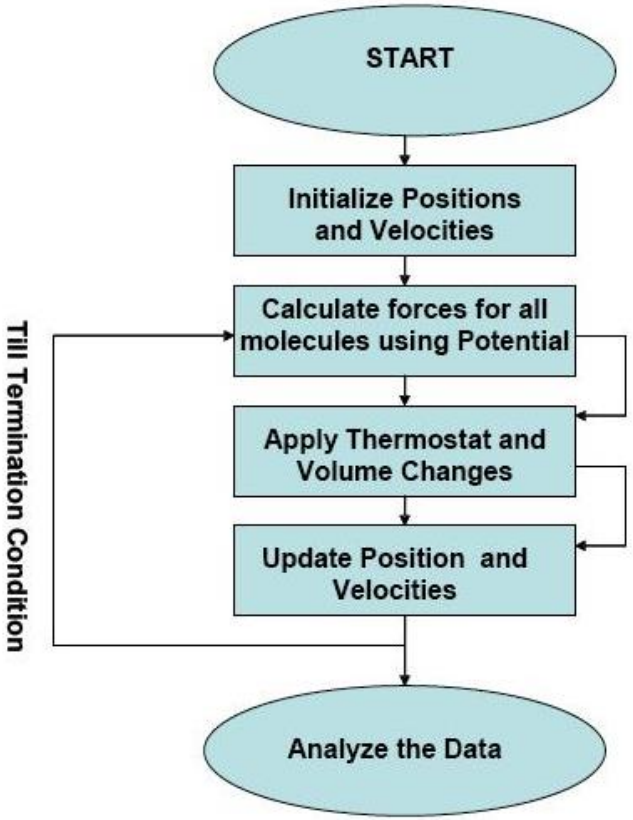
$$E_{str} = \sum_{bonds} K_{str}(l - l_o)^2$$

$$E_{bnd} = \sum_{angles} K_{ang}(\Theta - \Theta_o)^2$$

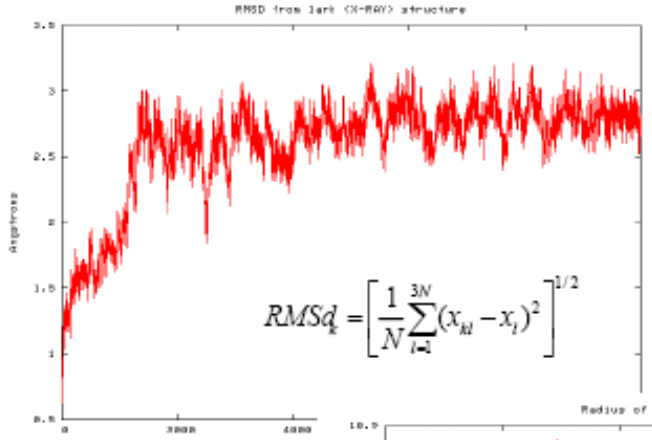
$$E_{tor} = \sum_{tor}\sum_{n=1}^{3} \frac{V_n}{2}(1 + \cos n\Phi - \gamma)$$

$$E_{ele} = \sum_{m,n} \frac{Q_m Q_n}{\varepsilon(R_{mn})R_{mn}}$$

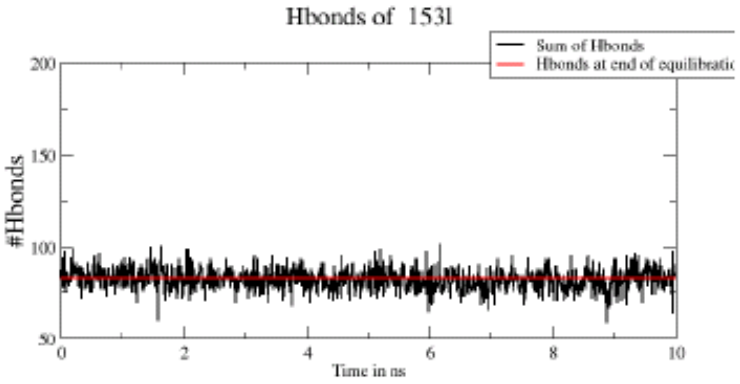
$$E_{vW} = \sum_{i,j} \left(\frac{A_{ij}}{R_{ij}^{12}} - \frac{C_{ij}}{R_{ij}^{6}} \right)$$



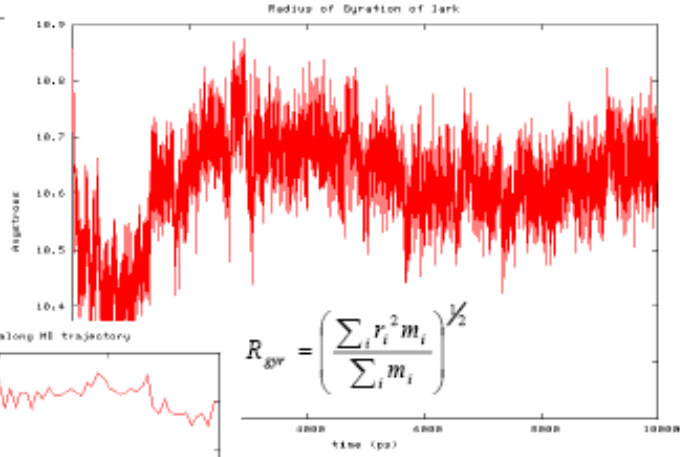
Root-mean
Square deviation



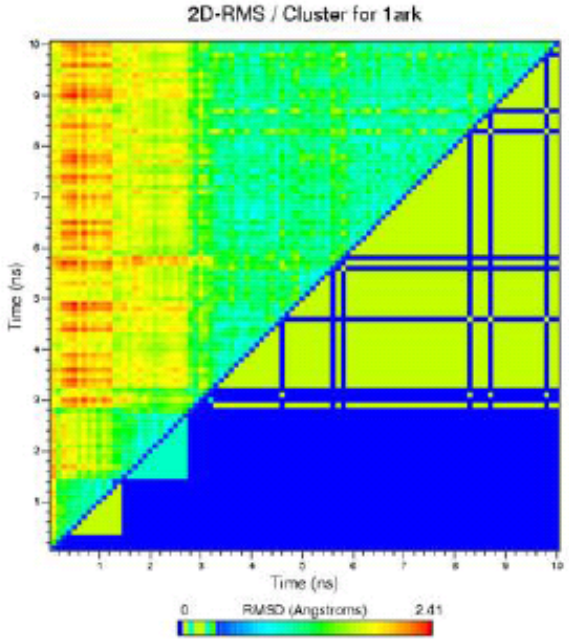
Specific interactions

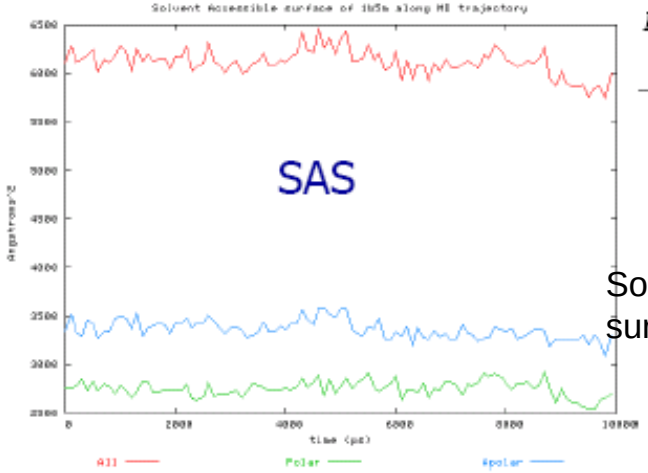


Radius of gyration



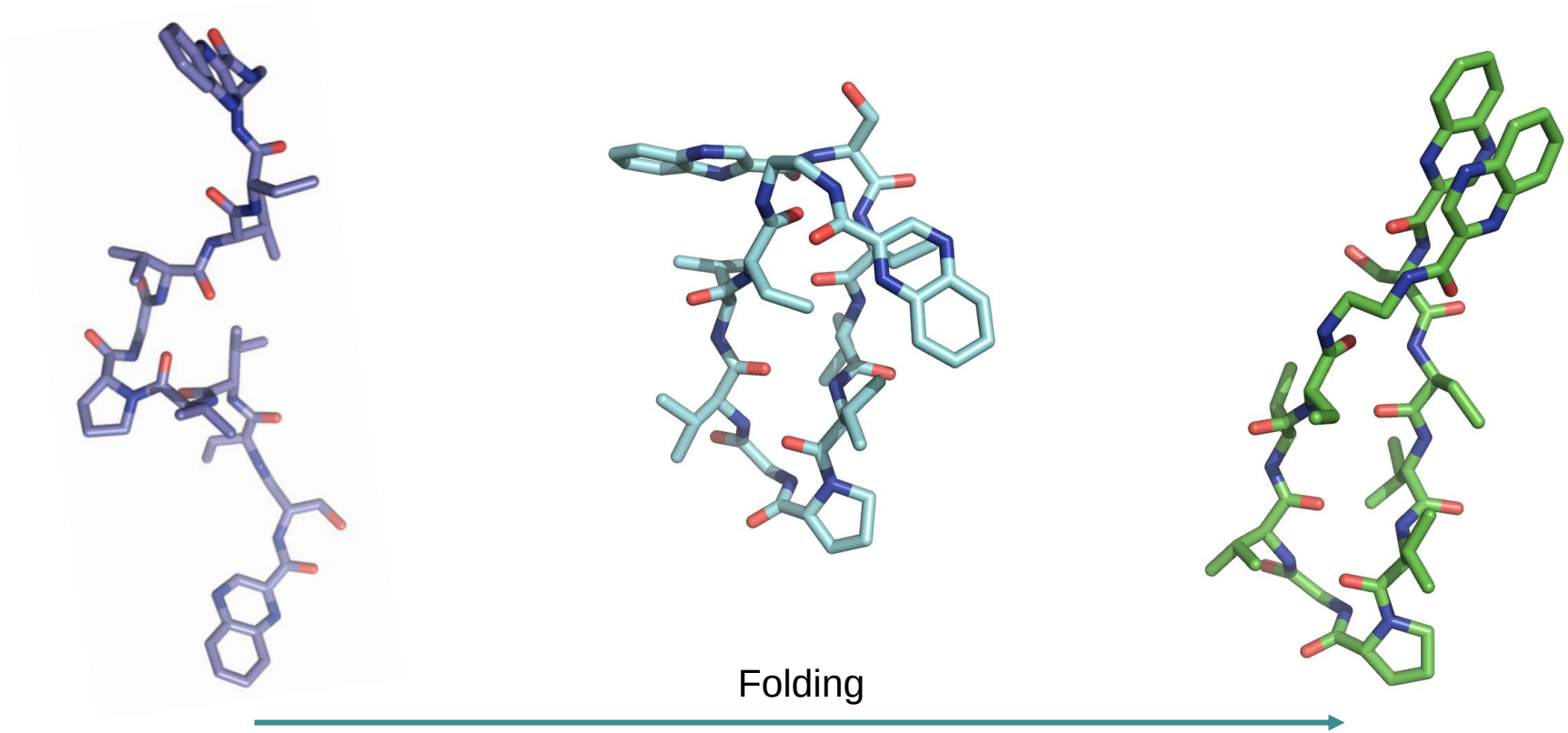
Conformational families (clustering)

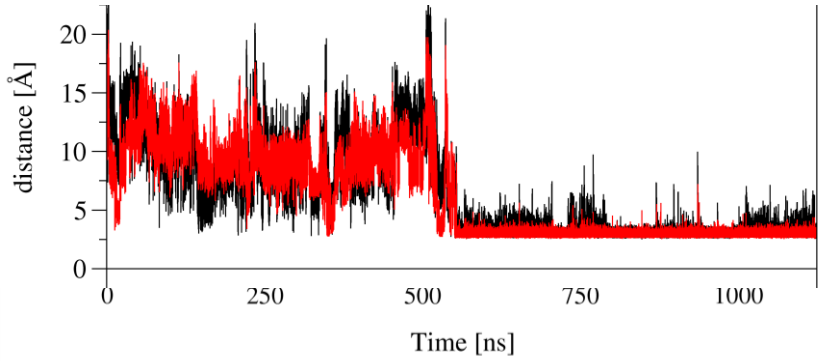


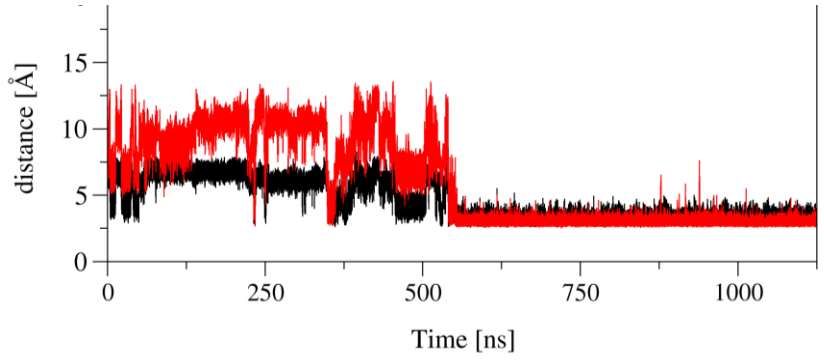


Solvent accessible
surface

Molecular Dynamics example

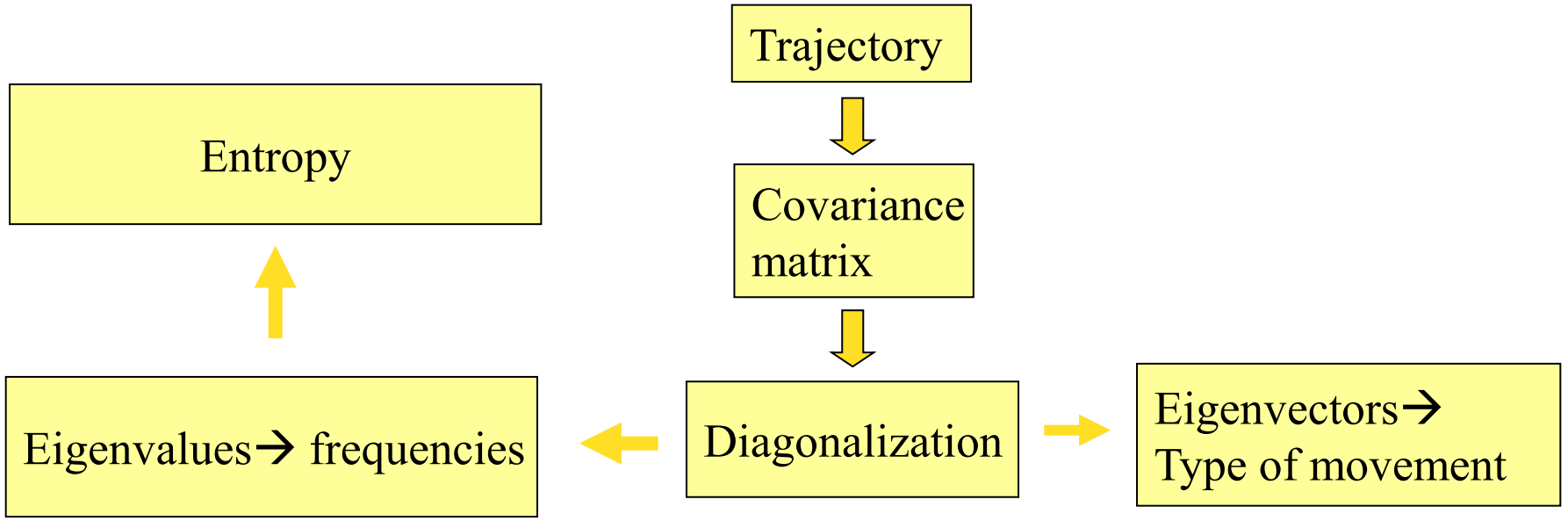






Time evolution of the hydrogen bond formation between the backbone NH··O=C groups of both ß-sheet strands

Structural Flexibility: Essential Dynamics



For a set of principal eigenvectors,

absolute similarity index

$$\gamma_{AB} = \frac{1}{n}\sum_{j=1}^{n}\sum_{i=1}^{n}(\nu_i^A \bullet \nu_j^B)^2$$

relative similarity index

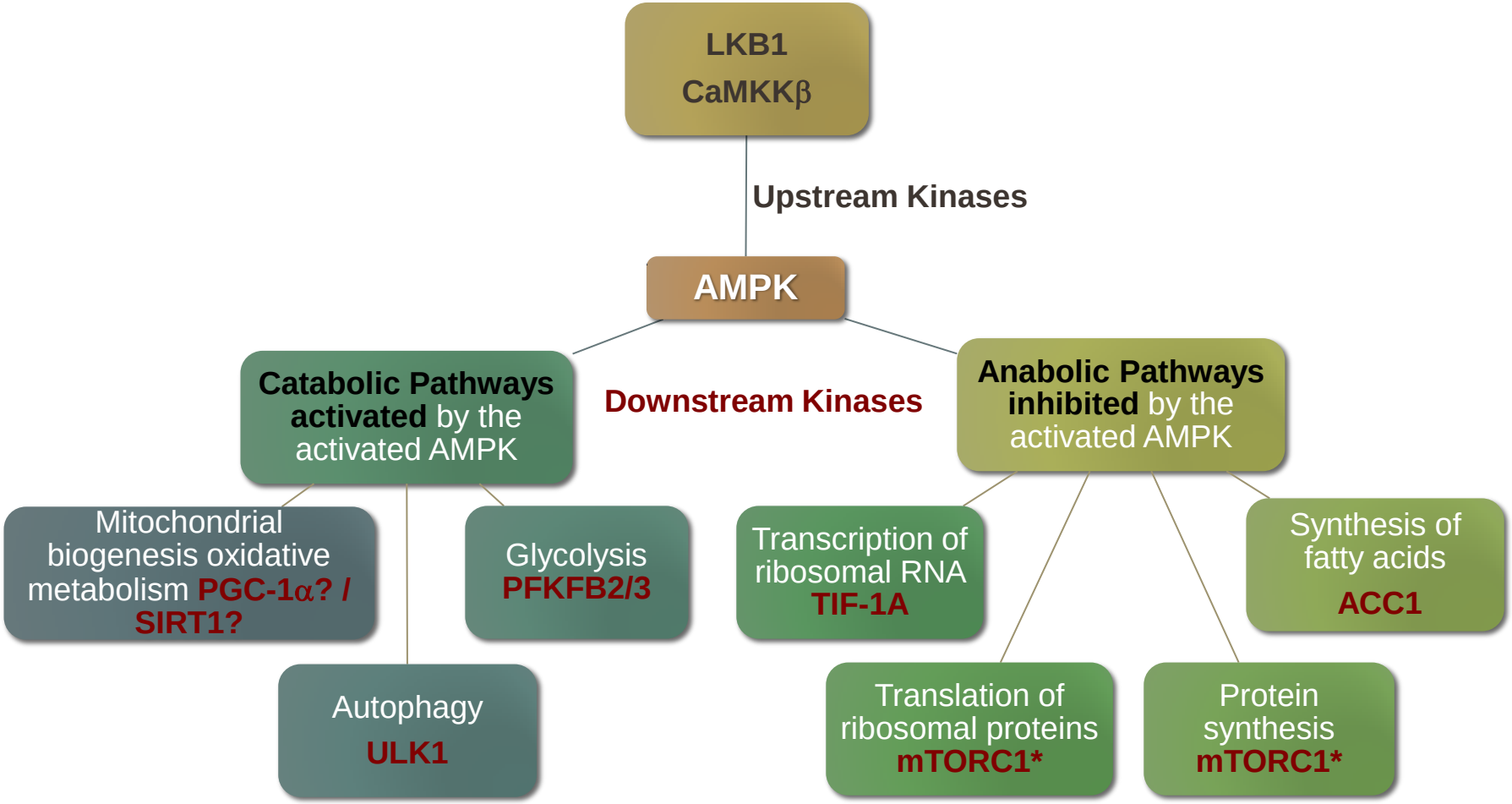
$$\kappa_{AB} = 2\frac{\gamma_{AB}}{\gamma_{AA} + \gamma_{BB}}$$

Mechanisms of ligand activity: enzyme activator

Haohao Fu; Yingzhe Liu; Ferran Adrià; Xueguang Shao; Wensheng Cai; Christophe Chipot; *J. Phys. Chem. B* **2014,** 118, 11747-11756.

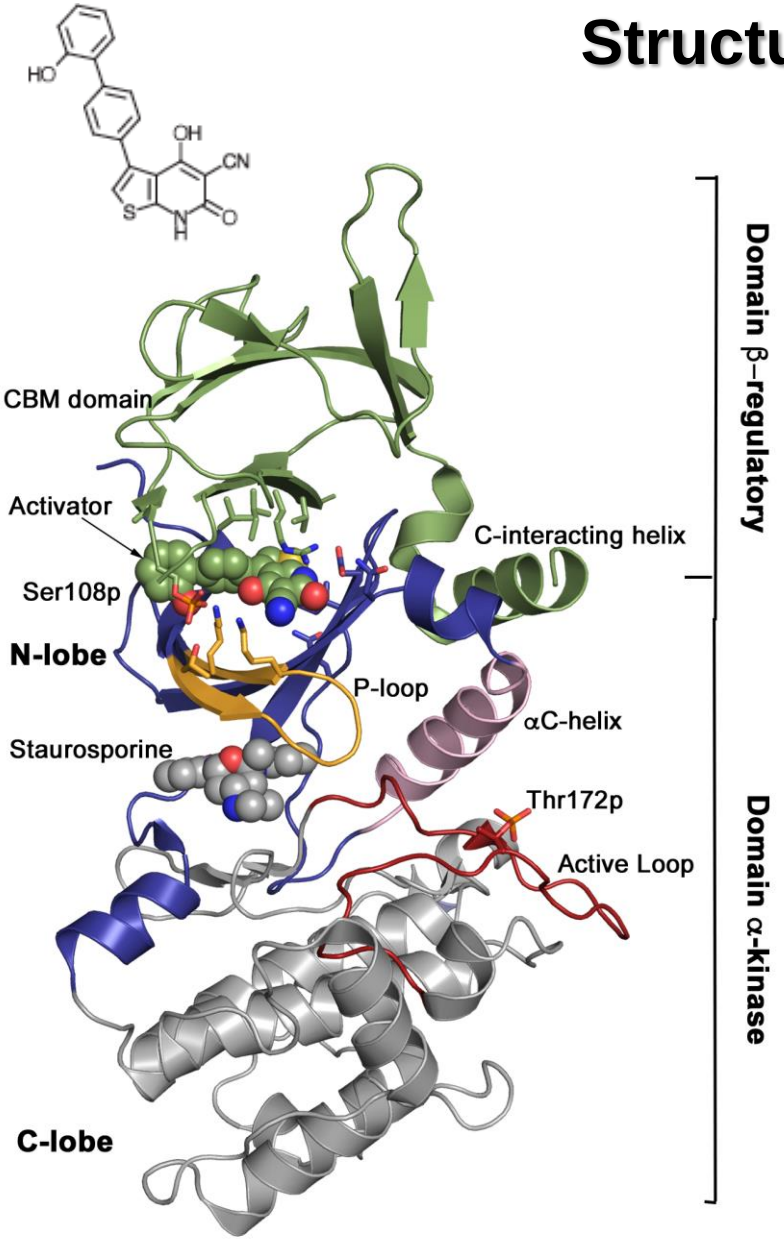
AMPK (AMP-activated protein kinase)

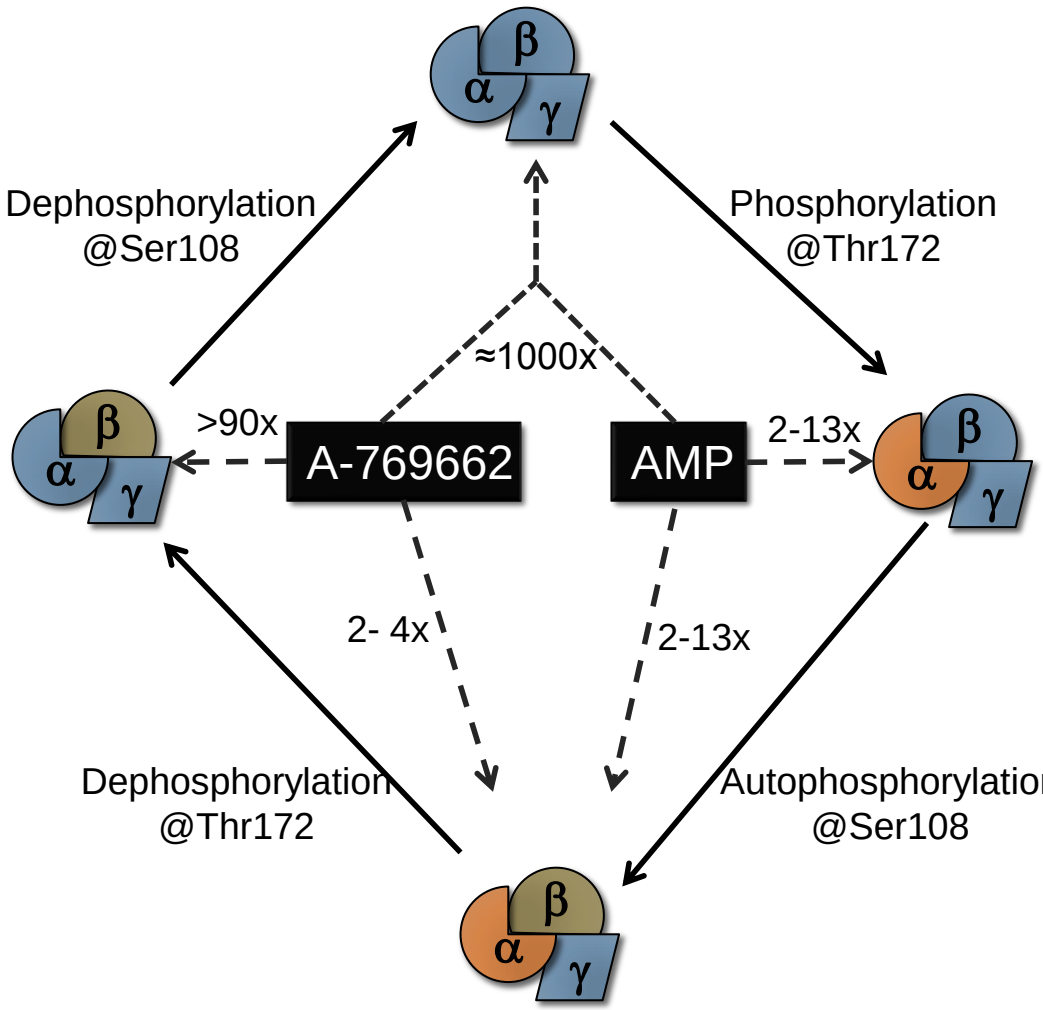
- Ser/Thr protein kinase
- Activated by low levels of ATP and high levels of AMP/ADP
- Sensor of energy homeostasis in the cell



Nat Cell Biol. **2012**, *13*, 1016. *BMC Biology* **2013**, *11*, 36.

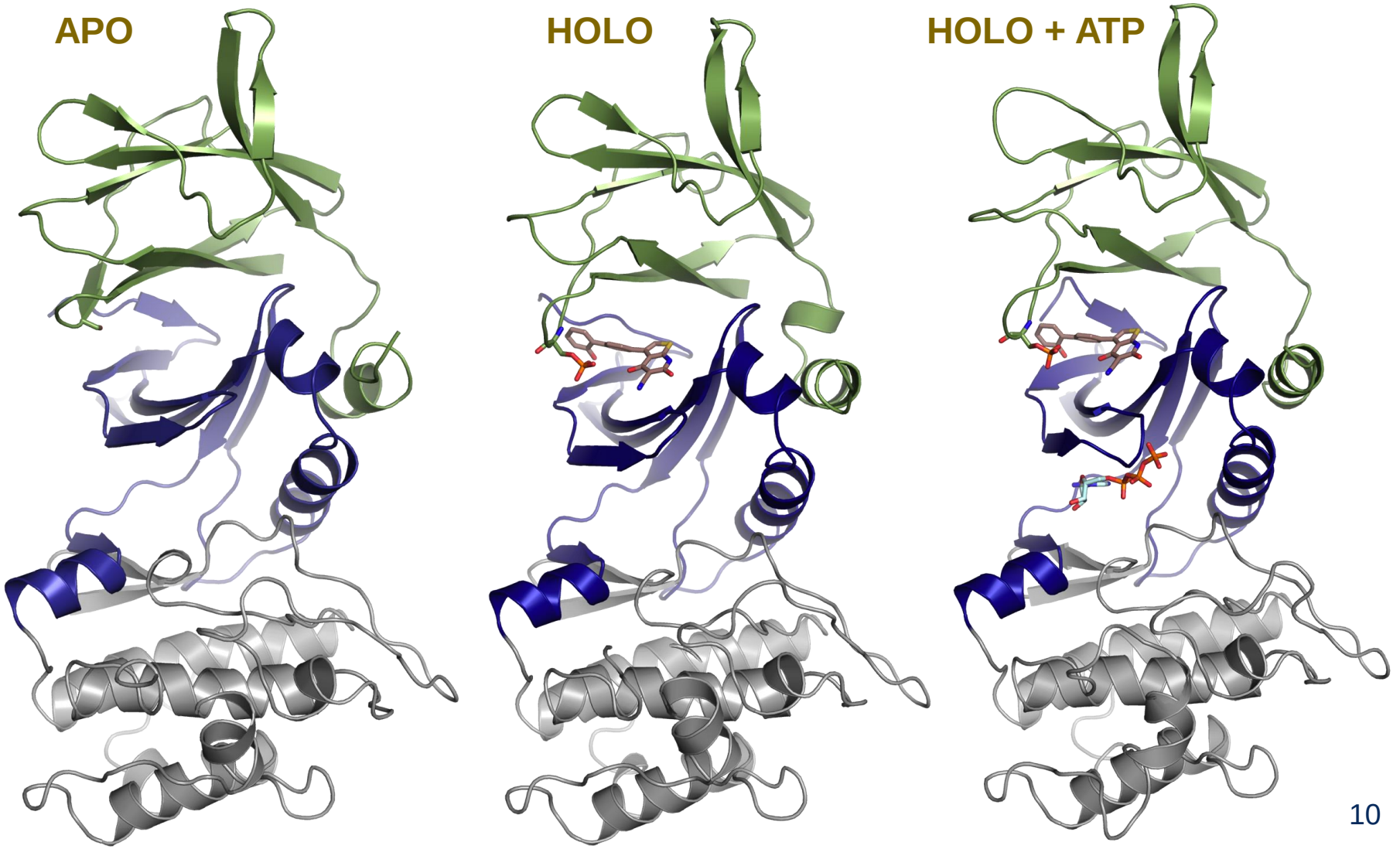
Structure vs. Function



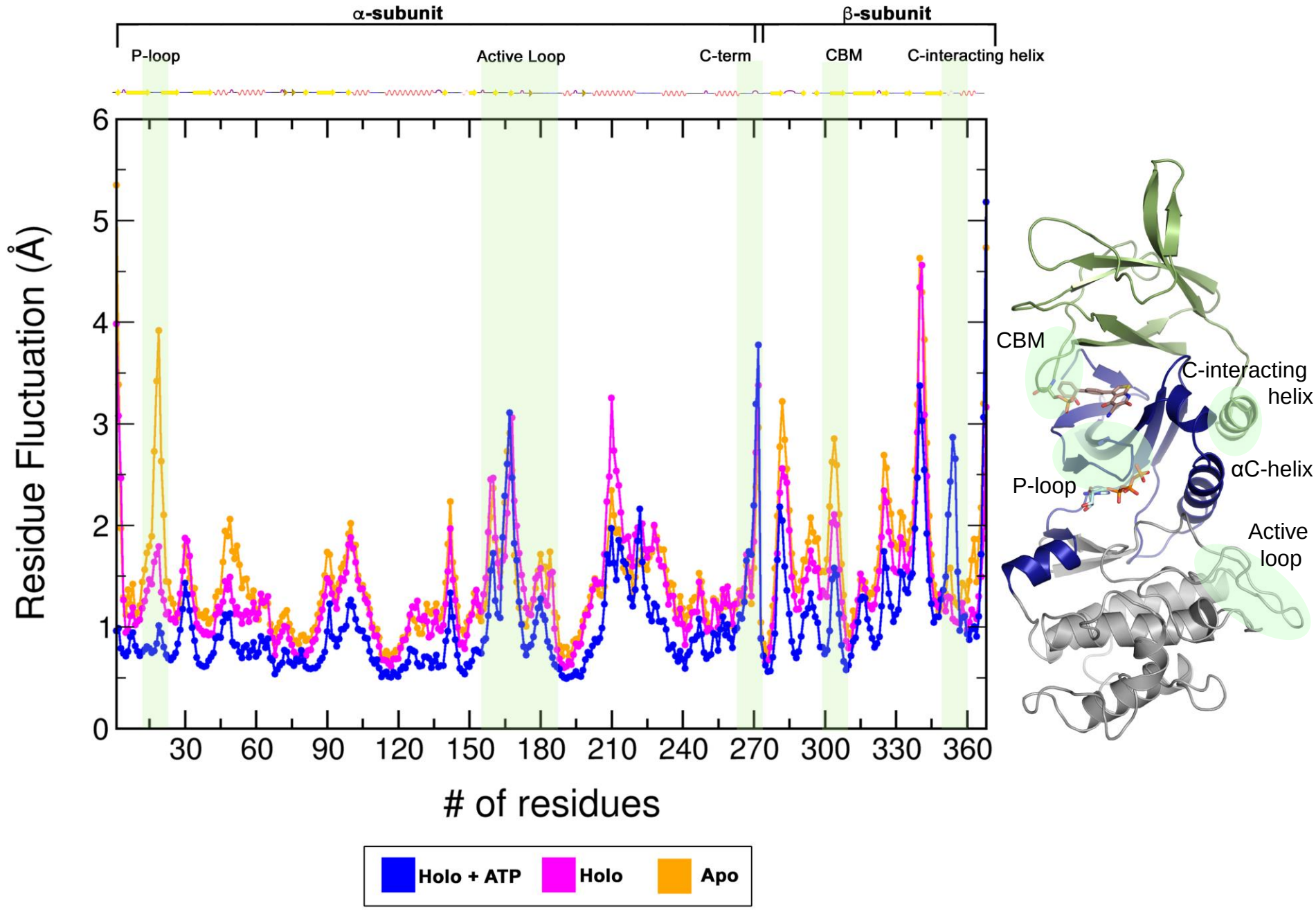


Chem. Biol., **2014**, *21*, 619.

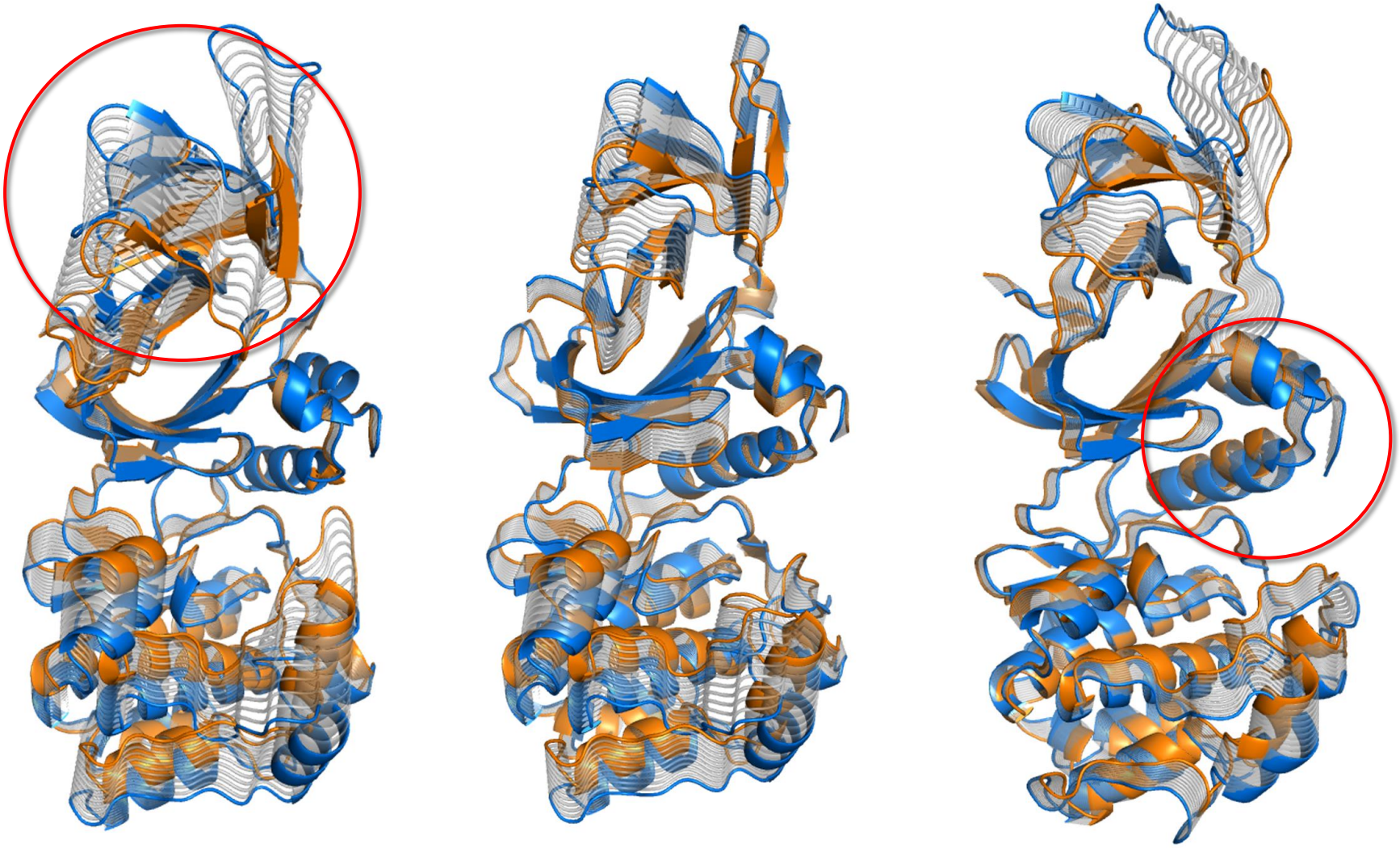
How does A-769662 trigger AMPK activation?

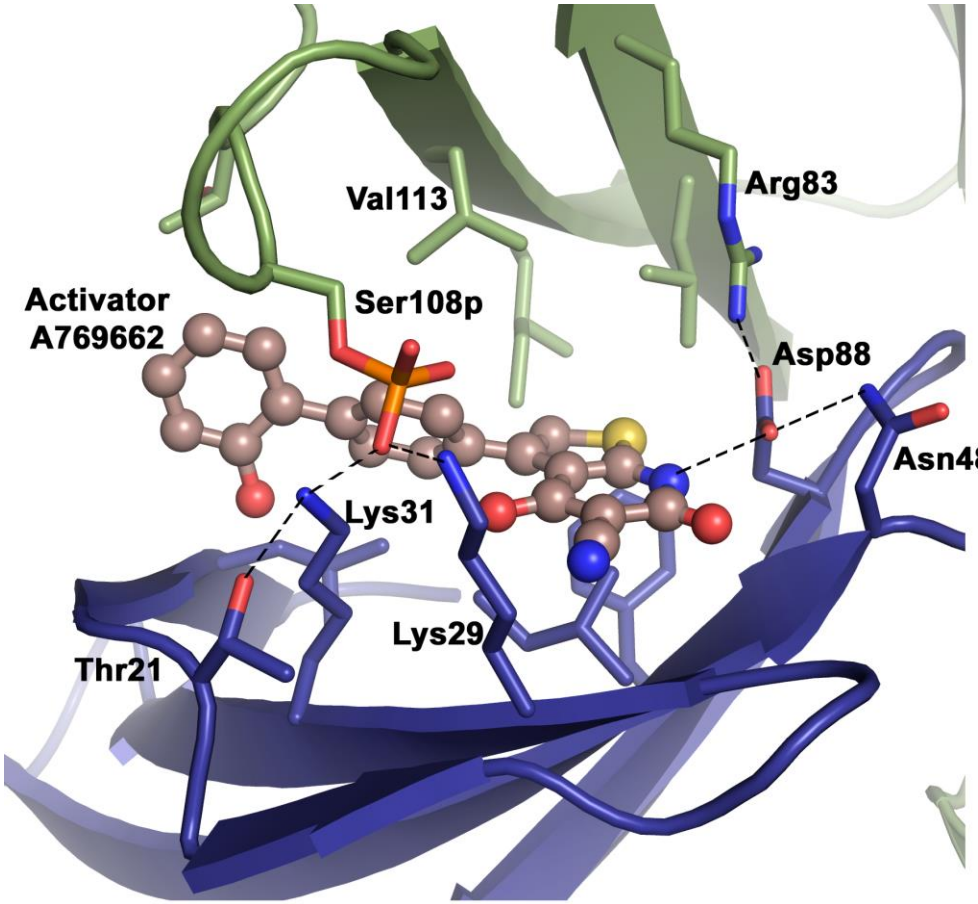


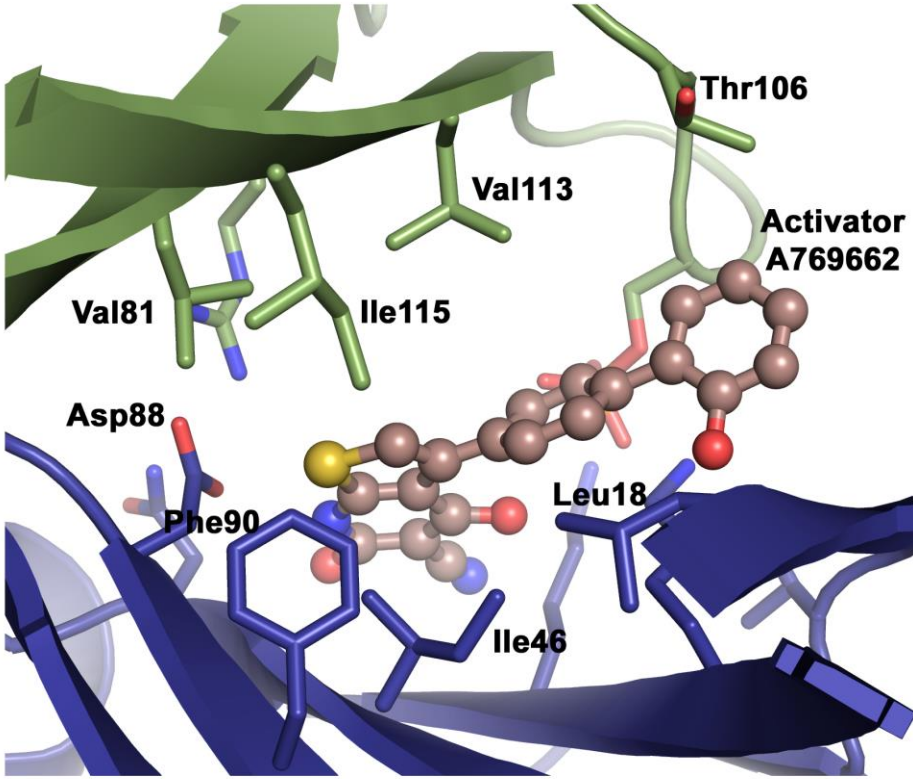
Mechanisms of ligand activity: enzyme activat



The effect of activator and ATP in the conformational and dynamic behaviour



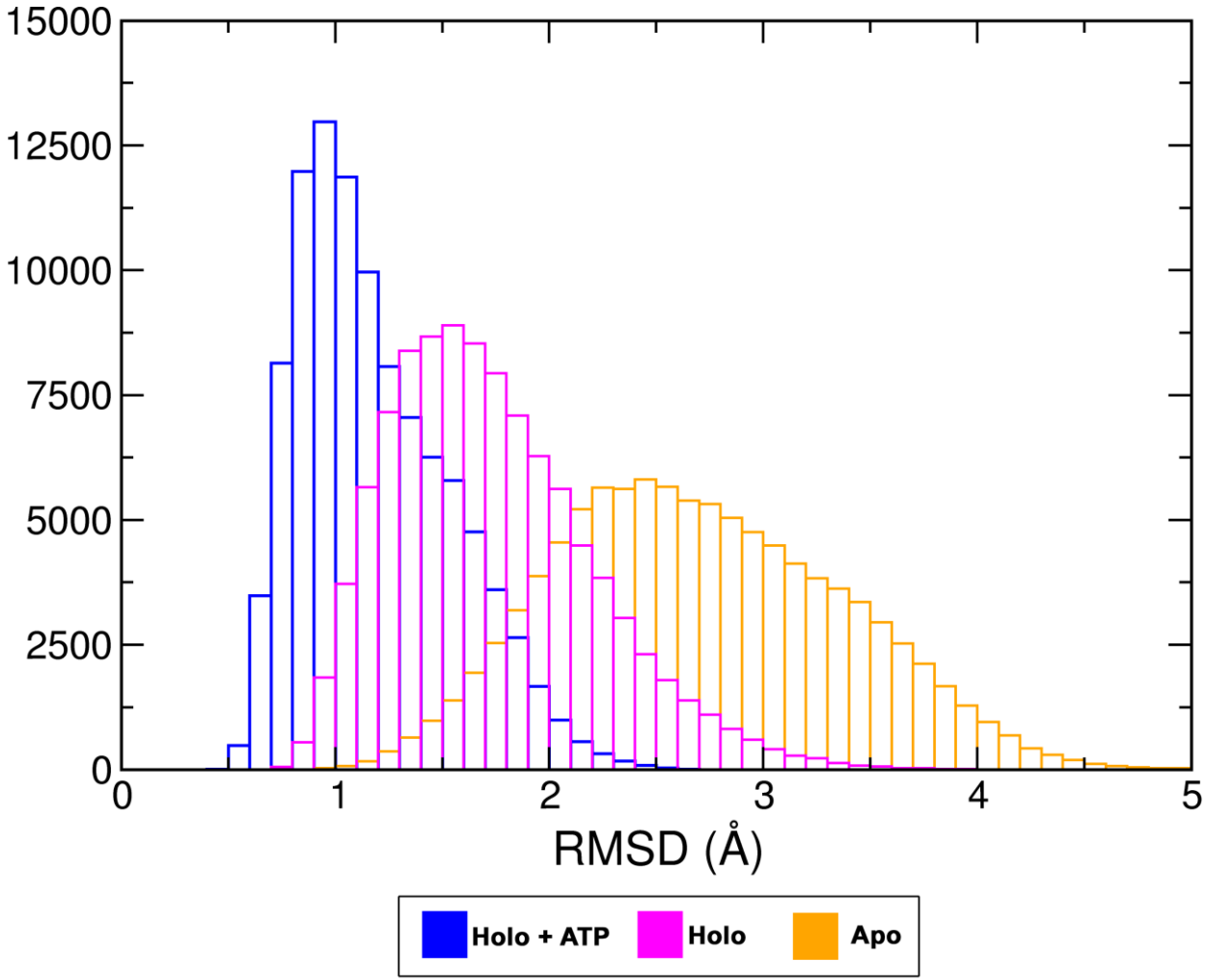


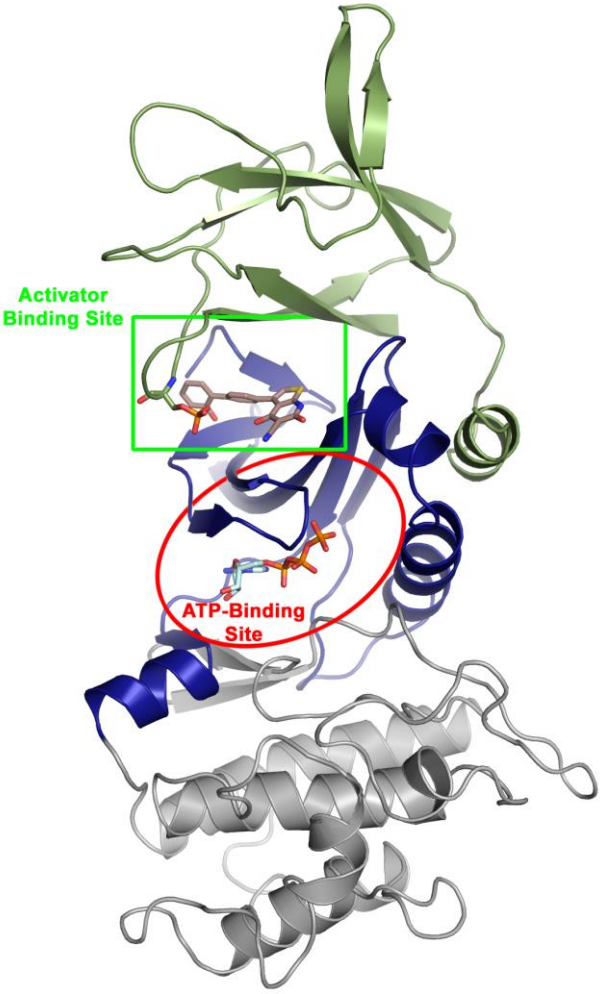


The activator acts like a glue between the α-kinase domain and the CBM domain of β-subunit

Allosteric Hypothesis

The activator pre-organizes the ATP-Binding Site

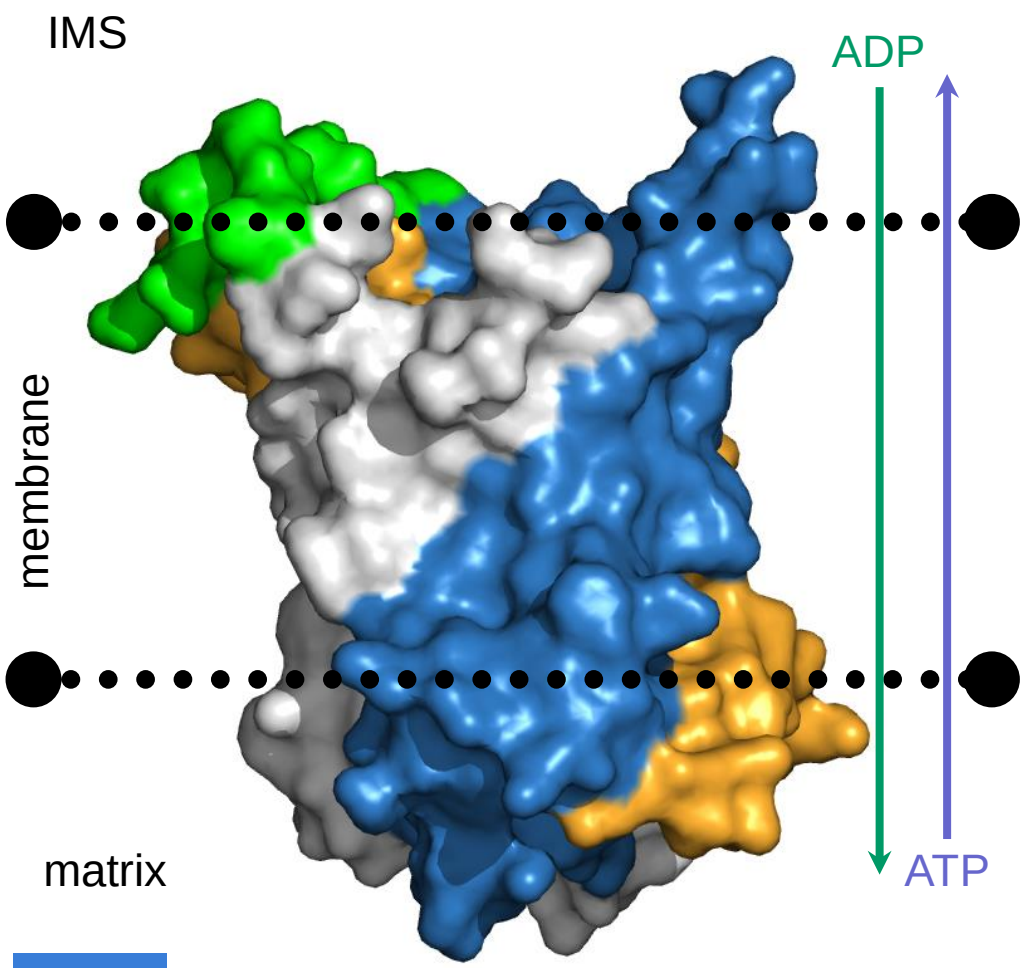




Mechanisms of ligand activity: enzyme mutations

Haohao Fu; Yingzhe Liu; Ferran Adrià; Xueguang Shao; Wensheng Cai; Christophe Chipot; *J. Phys. Chem. B* **2014,** 118, 11747-11756.

Mechanisms of ligand activity: enzyme mutatio



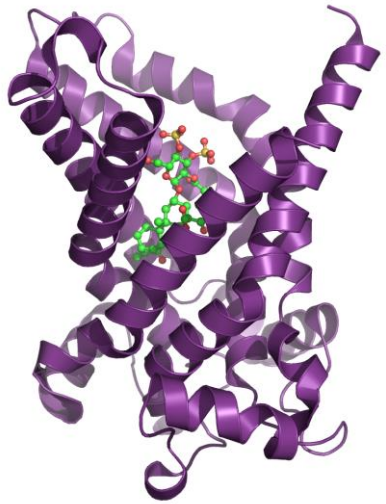
- Mitochondrial Carrier Family member.
- 6 TM helices
- Imports ADP to the matrix of the mitochondria and exports ATP to the Inter-membrane space (IMS)
- Two possible conformations, but only one has been crystalized

Capacity to interconvert between two different conformations to achieve proper nucleotide transport

AAC + CATR

↓

Fixed conformation



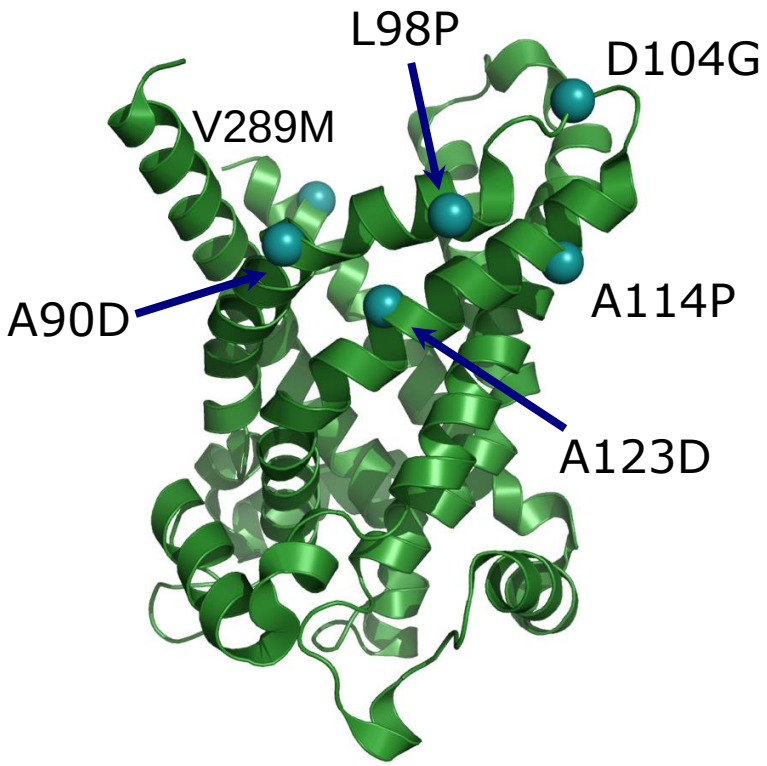
Pebay-Peyroula, E., *et al.*, Nature, 2003, 426, 39–44

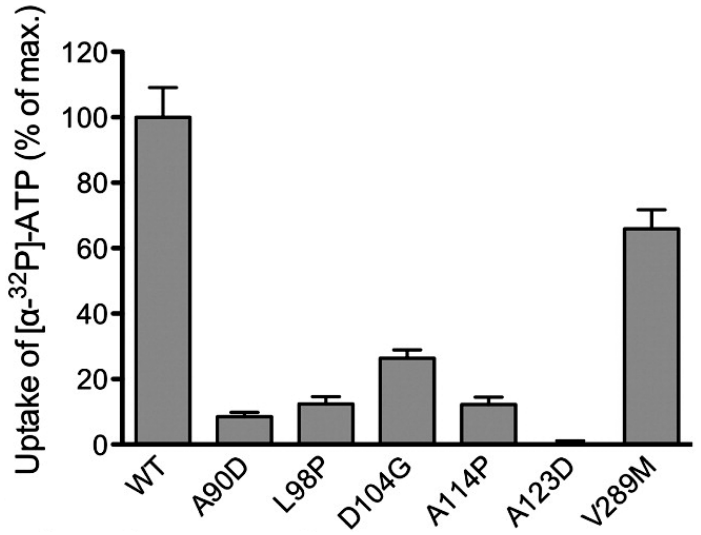
Falconi, M., *et al.*,Proteins, 2006, 65, 681-689

Measured Activity in *E. Coli* membrane

6 pathological mutations have been detected, all of them in the IMS

Localization in the protein structure



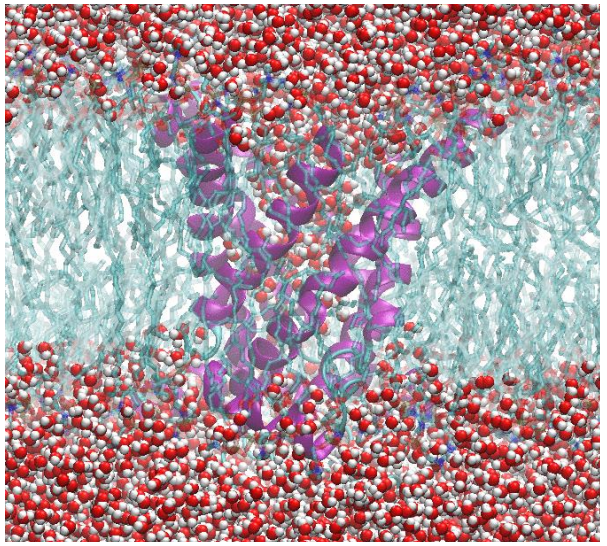


	K_M	V_{max}
Wild-Type	23.7 ± 5	14.6 ± 0.6
A90D	82.1 ± 7.8	7.8 ± 0.4
L98P	18.5 ± 9.8	1.7 ± 0.3
D104G	15.9 ± 6.4	4.1 ± 0.4
A114P	104.1 ± 47.9	4.5 ± 1.1
A123D	ND	ND
V289M	17.0 ± 2.4	10.3 ± 0.4

Ravaud, S., Bidon-Chanal, A., *et al*., ACS Chem. Biol., 2012

Simulated systems

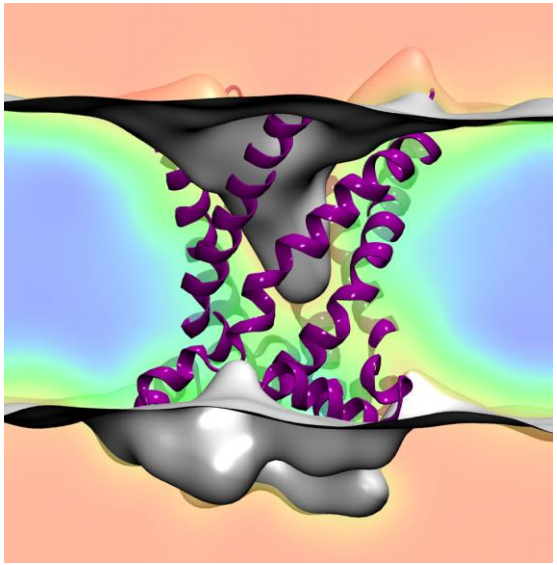
- Wild-type or mutant protein immersed in a lipid bilayer of united atom POPC lipids
- 114 lipids per leaflet
- System solvated with TIP3P waters
- 0.15 M NaCl concentration
- Total system box size of 90x81x81
- charmm27 forcefield with CMAP corrections.
- NPT ensemble. PBC and PME.
- 100 ns MD simulations for each system



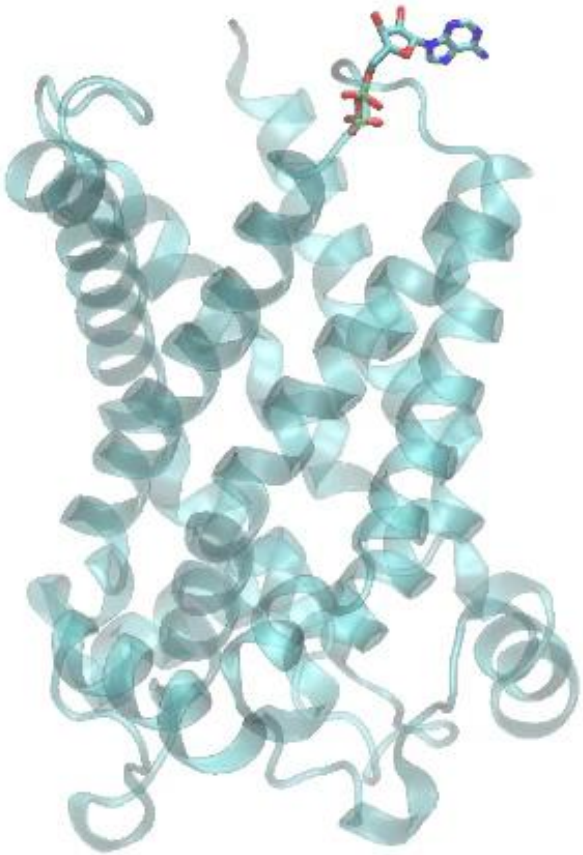
RMSD	Backbone Atoms	All Heavy Atoms
WT	1.9 ± 0.2	2.4 ± 0.2
A90D	1.6 ± 0.3	2.0 ± 0.3
A114P	1.5 ± 0.2	1.7 ± 0.2
L98P	1.5 ± 0.2	1.9 ± 0.2
D104G	1.7 ± 0.3	2.2 ± 0.5
A123D	1.5 ± 0.2	1.8 ± 0.2
V289M	1.5 ± 0.2	1.9 ± 0.2

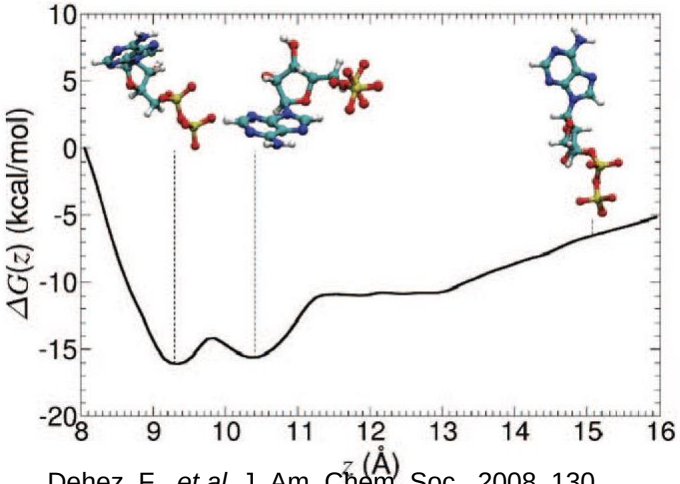
Mechanisms of ligand activity: enzyme mutatio

Electrostatic funnel



Binding of the ADP molecule is driven by an electrostatic funnel that attracts the phosphate moiety of ADP



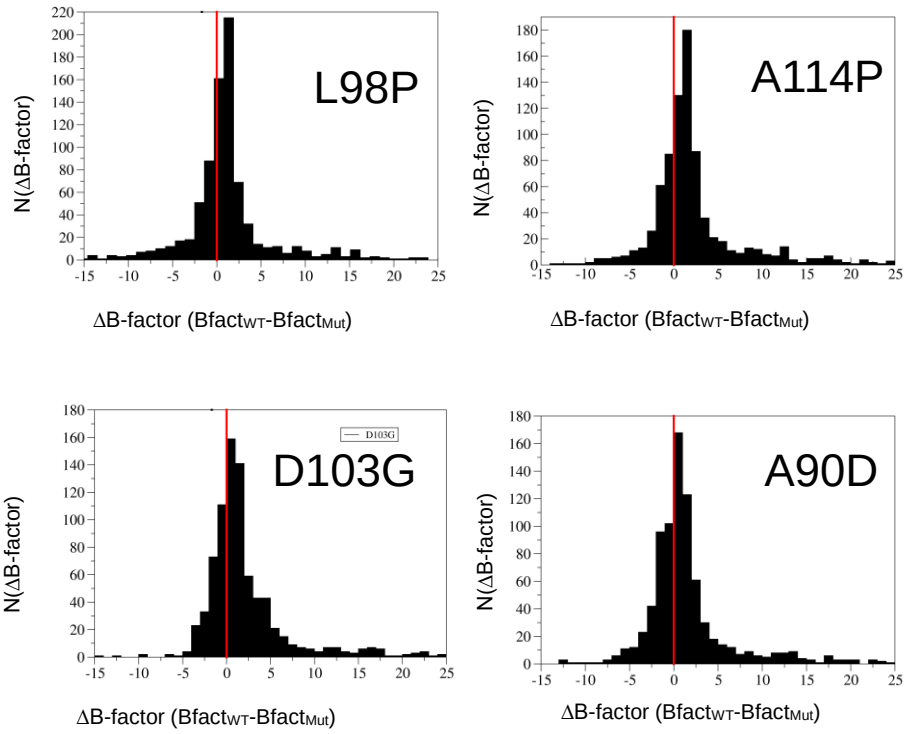


Dehez, F., *et al*.,J. Am. Chem. Soc., 2008, 130, 12725-12733

Path to the bottom of the cavity is nearly barrier less and is modulated by two basic patches

Mechanisms of ligand activity: enzyme mutatio

Atomic positional fluctuations

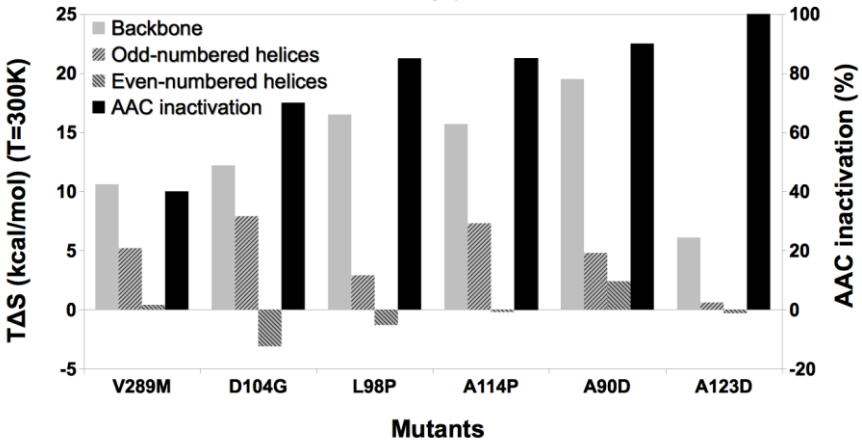


- B-factors were inferred from the atomic positional fluctuations computed for the backbone atoms along the molecular dynamics trajectory multiplied by $(8/3)\pi^2$.

- Configurational entropies were obtained using the Schlitter approximation with the eigenvalues that result from diagonalisation of the mass weighted covariance matrix, and differences were obtained as $Tx(S_{infWT}-S_{infMUT})$. S_{inf} was obtained by curve fitting of the configurational entropy computed at different times along the MD trajectory to the formula $S(t)=S_{inf}-at^b$

- Mutations A114P, L98P, A90D and D103G have a clear impact on the flexibility of the carrier which is reflected in a lower nucleotide uptake.

Entropy



Spherification: Role of calcium cations in alginate aggregation

Haohao Fu; Yingzhe Liu; Ferran Adrià; Xueguang Shao; Wensheng Cai; Christophe Chipot; *J. Phys. Chem. B* **2014,** 118, 11747-11756.

https://www.youtube.com/channel/UCxD2E-bVoUbaVFL0Q3PvJTg
http://www.chefsteps.com

https://www.youtube.com/watch?v=A7QFcP74zyg
http://www.chefsteps.com

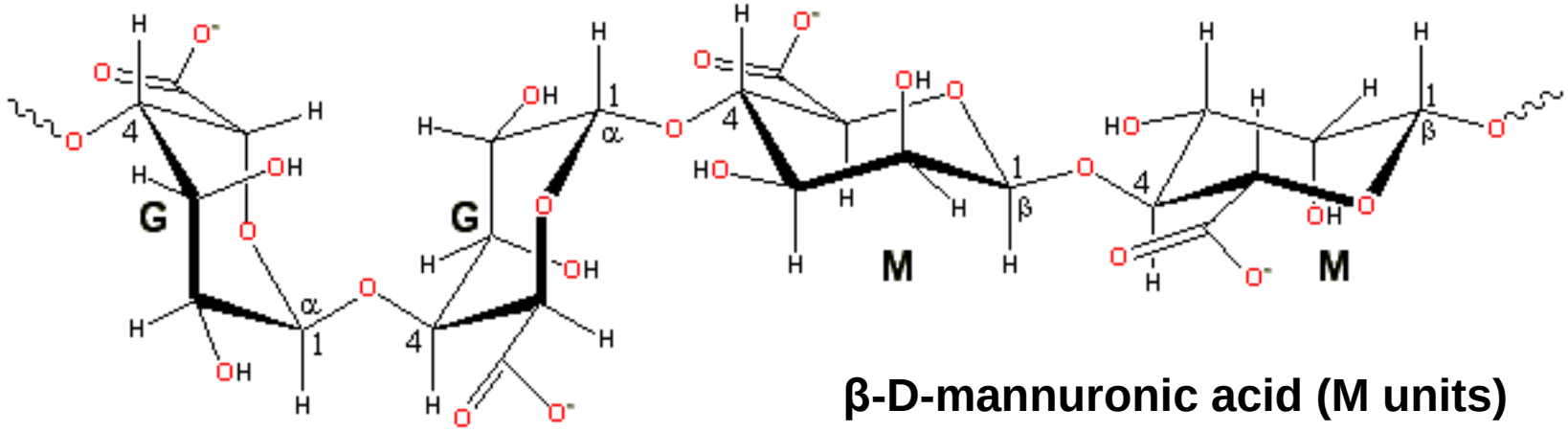
Origin

Obtained from brown algae of the *Phaeophyceae* class. Their celullar walls contain alginic acid and its different sodium, potassium or calcium salts in different proportions.

Comercial name

Alginate, Soduim Alginate, E-400.

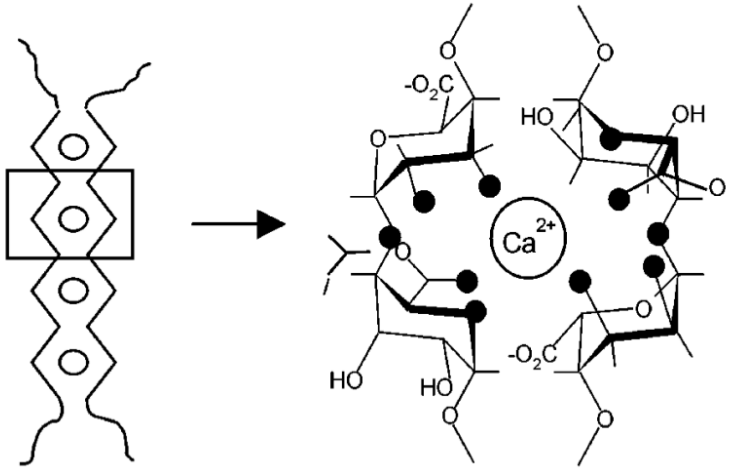
Chemical structure



α-L-guluronic acid (G units)

β-D-mannuronic acid (M units)

Preferential affinity for G compared to M: **‘egg-box’ model**

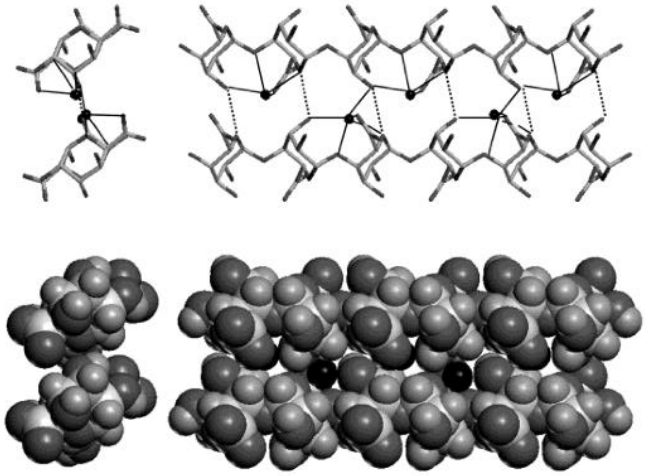


Grant, G. T. *et al. FEBS Lett.* 1973, 32, 195−198

10 oxygens from the guluronate molecules

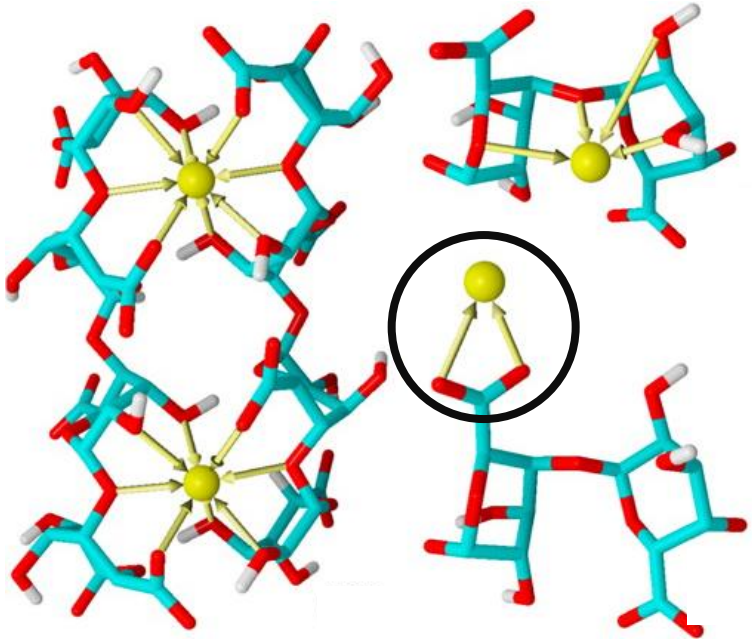
Hydroxyl groups coordinating Ca^{2+}.

Molecular Mechanics methods



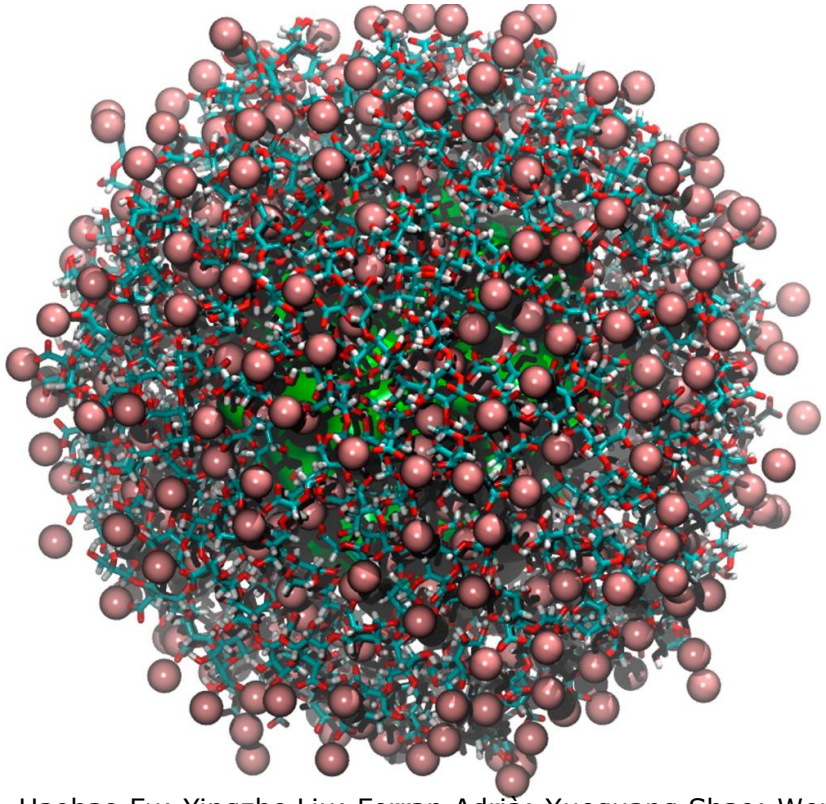
I. Braccini and S. Pérez. *Biomacromolecules* 2001, 2, 1089−1096

DFT-MD methods



Plazinski, W, *et al. J. Phys. Chem. B* 2013, 117, 12105−12112

spheroid	nanoparticle	interface nature	solute	C_{ion} [b] (mol/L)	no. of atoms	no. of water molecules	cell dimensions (Å^3)
OC	oleate	charged	$CaCl_2$	1	106 611	30 422	102 × 101 × 103
OAC	oleic acid	hydropilic	$CaCl_2$	1	114 282	32 905	102 × 105 × 107
DC	dodecane	hydrophobic	$CaCl_2$	1	113 370	32 795	104 × 104 × 104
OS	oleate	charged	NaCl	2	106 581	30 407	110 × 96 × 97

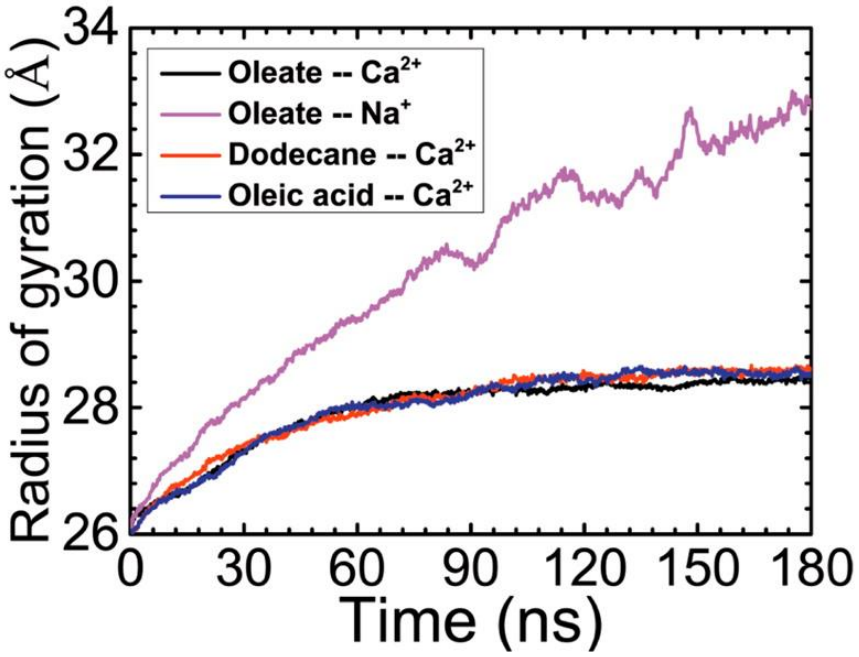


36 linear alginate chains

600 calcium ions randomly placed

TIP3P water molecules

Haohao Fu; Yingzhe Liu; Ferran Adrià; Xueguang Shao; Wensheng Cai; Christophe Chipot; *J. Phys. Chem. B* **2014,** 118, 11747-11756.



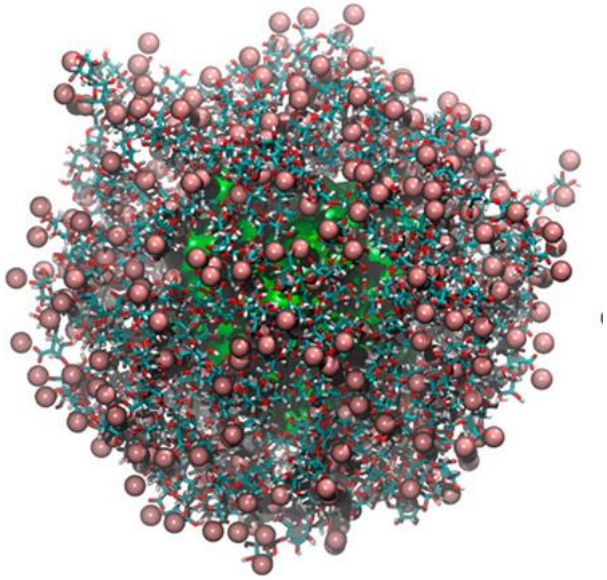
$$R_g^2 = \sum m_i (r_i - R_C)^2 / M$$

m_i = mass of atom *i*

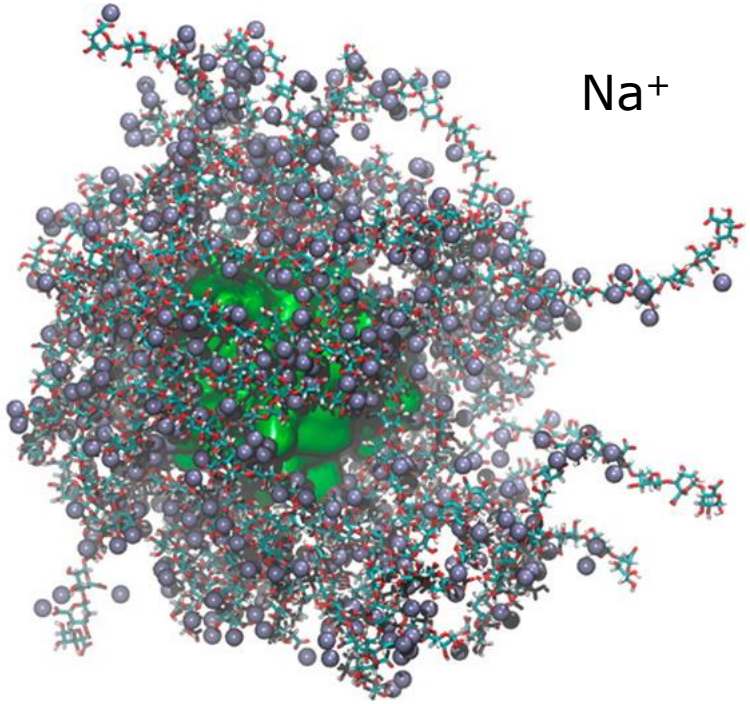
M = summed mass of the atoms

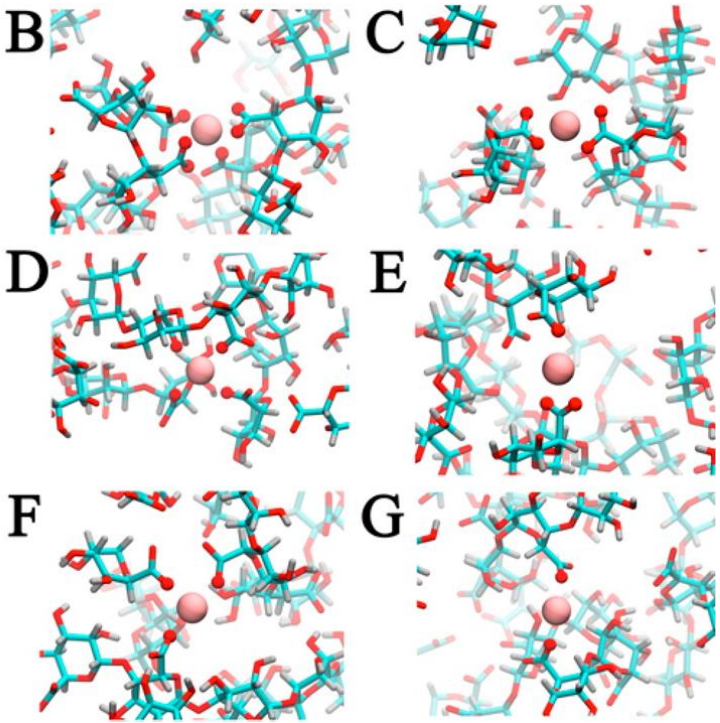
R_C = central reference point coords.

Ca^{+2}

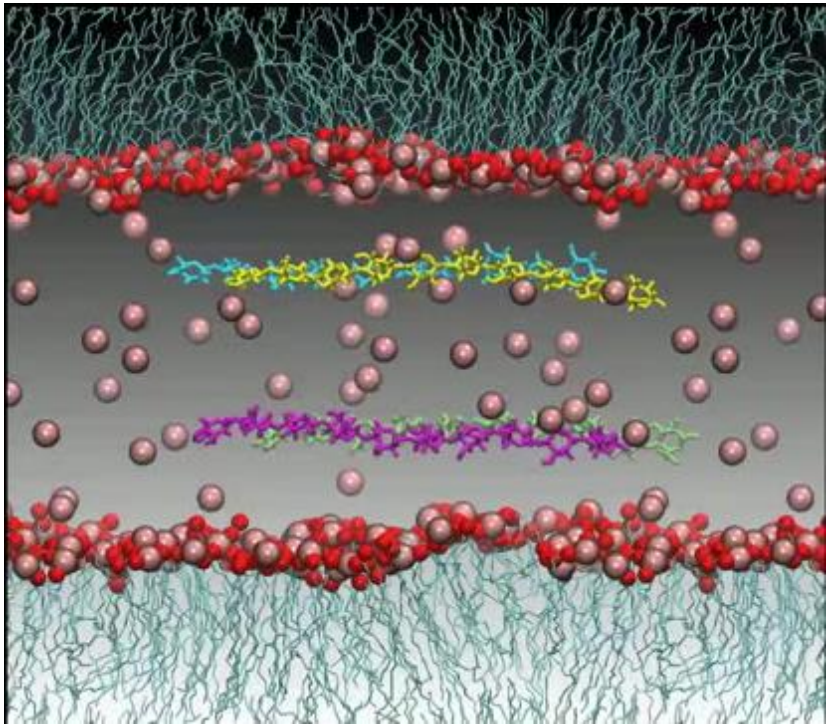


Na^{+}





Characteristic chain–chain interaction modes in the alginate membrane



Spontaneous association of alginate chains in non-restrained MD simulations of calcium alginate salts in solution.

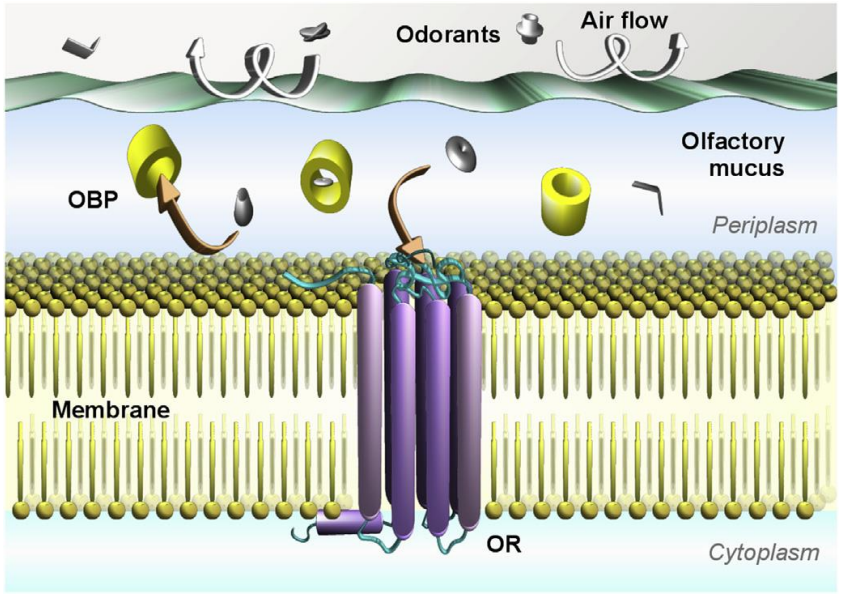
Olfactory receptors: the influence of food odor

Anselmi, C.; Buonocore, A.; Centini, M.; Facino, R. M.; Hatt, H. *Comp. Biol. Chem.* **2011**, 35, 159-168.

Lai, P. C.; Guida, B.; Shi, J.; Crasto, C. J. *Chem. Senses,* **2014**, 39, 107-123.

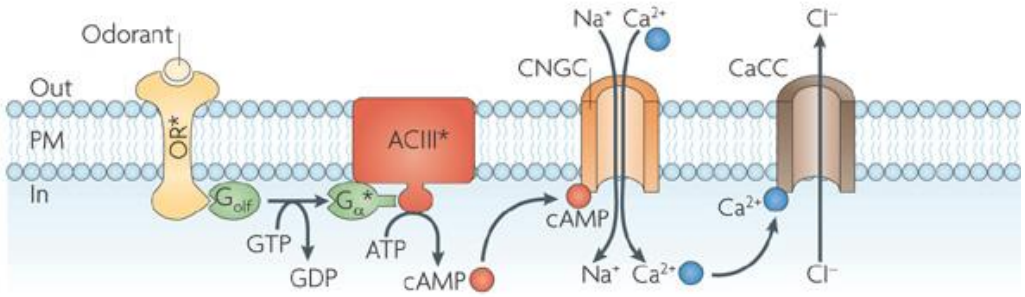
The actors

Olfactory Receptor Neuron surface

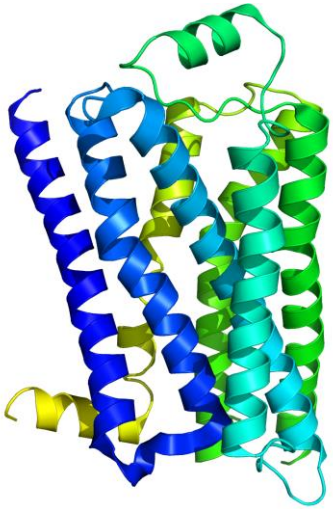


Olfactory receptors

- G-Protein Coupled Receptors
- Odorant binding activates signal cascade pathway
- Promiscuous
- Odours are fruit of the cooperativity

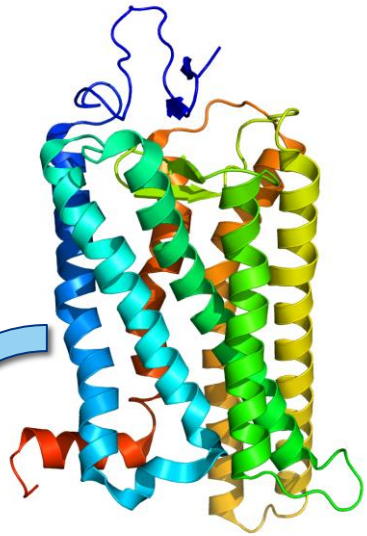


ß$_2$-adrenergic

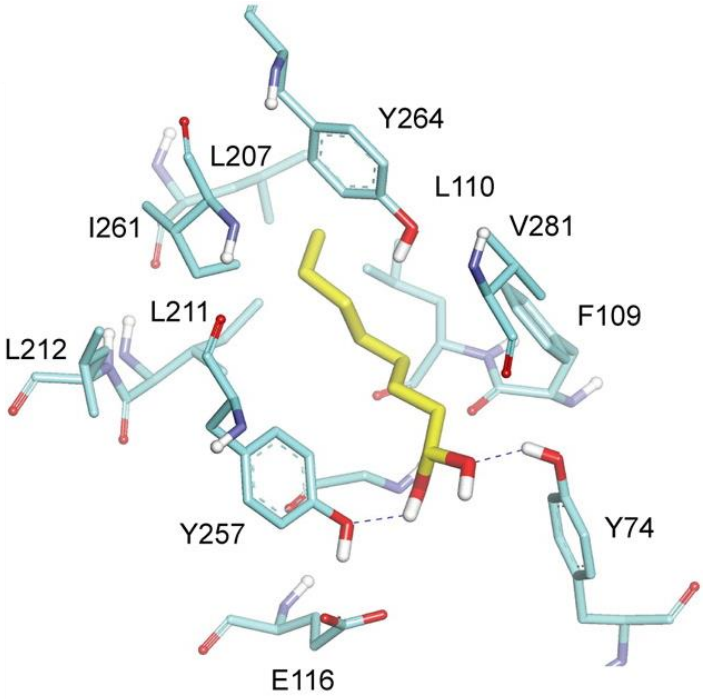


PDB ID: 5D6L

Rhodopsin



PDB ID: 5TE3



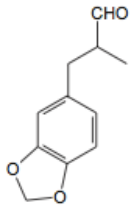
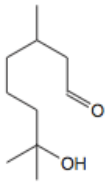
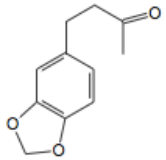
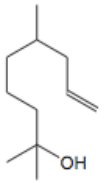
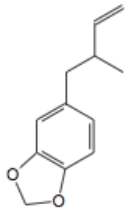
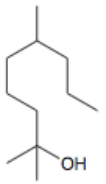
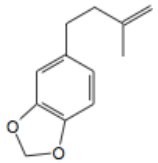
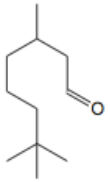
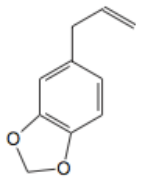
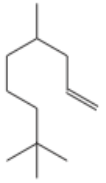
Homology modeling

Docking

Olfactory receptors: better binders

Anselmi, C.; Buonocore, A.; Centini, M.; Facino, R. M.; Hatt, H. *Comp. Biol. Chem.* **2011**, 35, 159-168.

Lai, P. C.; Guida, B.; Shi, J.; Crasto, C. J. *Chem. Senses,* **2014**, 39, 107-123.

Odorant	Structure	Odor properties	Odorant	Structure	Odor properties
Helional (**1**)		Floral[a] Green, aldehydic[b] S[c]	Hydroxycitronellal (**6**)		Muguet (lily of the valley) S[c]
Heliotropyl acetone (**2**)		Fruity[a] Sweet, blackberry[b] S[c]	2,6-Dimethyl-8-nonen-2-ol (**7**)		Floral (muguet)[a] Lime[b] M[c]
Helional analogue (**3**)		Pungent[a] S[c]	2,6-Dimethyl-nonan-2-ol (**8**)		Soapy, green[a] Floral[b] S[c]
Heliotropyl acetone analogue (**4**)		Fruity (peach, apricot)[a] S[c]	3,7,7-Trimethyloctanal (**9**)		Floral aldehydic[a] Green, fruity[b] VS[c]
Safrole (**5**)		Aniseed[a] Black pepper, nutmeg[b] S[c]	4,8,8-Trimethyl-1-nonene (**10**)		Floral (white floral)[a] W[c]

VS: very strong; S: strong; M: medium; W: weak.

[a] First note.

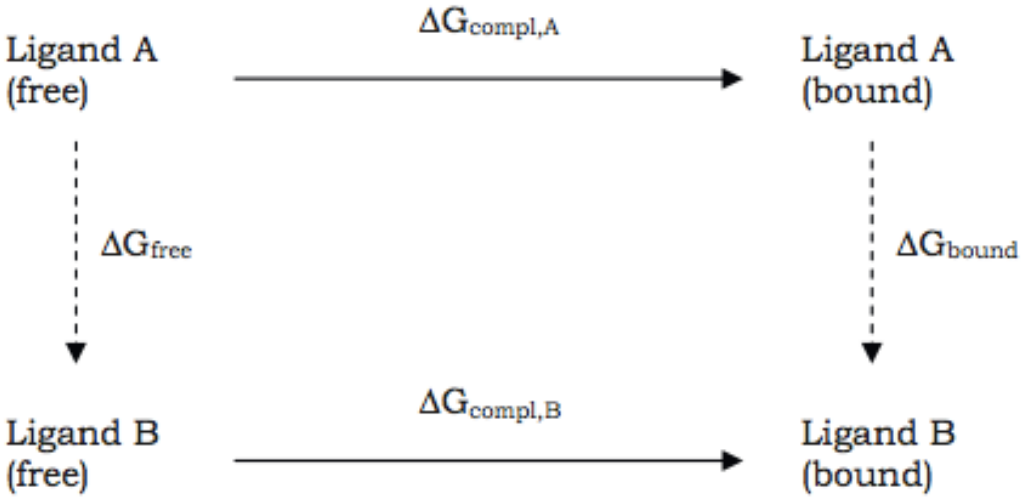
[b] Secondary note.

[c] Intensity.

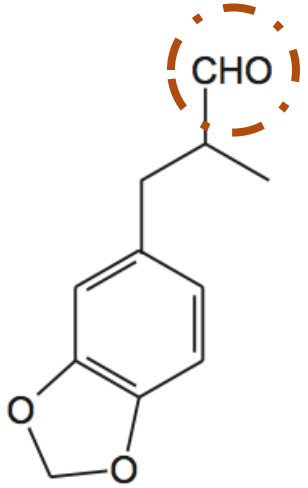
OR17-40

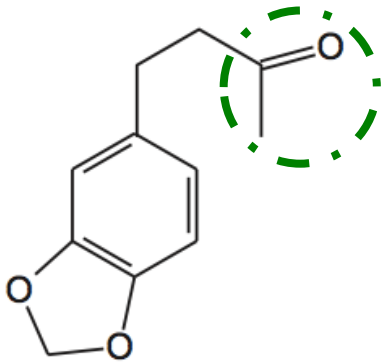
Anselmi, C.; Buonocore, A.; Centini, M.; Facino, R. M.; Hatt, H. *Comp. Biol. Chem.* **2011**, 35, 159-168.

Thermodynamic integration MD simulations



$$\Delta\Delta G_{free} = \Delta G_{compl,B} - \Delta G_{compl,A} = \Delta G_{bound} - \Delta G_{free}$$





ΔΔ*G* values (kJ/mol) for all the possible couples of ligands. A positive score means that the binding is favourable.

A	B	
	Helional (**1**)	Heliotropylacetone (**2**)
Helional (**1**)	–	21.7
Heliotropyl acetone (**2**)	−21.7	–
Helional analogue (**3**)	−41.3	−19.6
Heliotropyl acetone analogue (**4**)	−35.5	−13.8
Safrole (**5**)	−31.2	−9.6

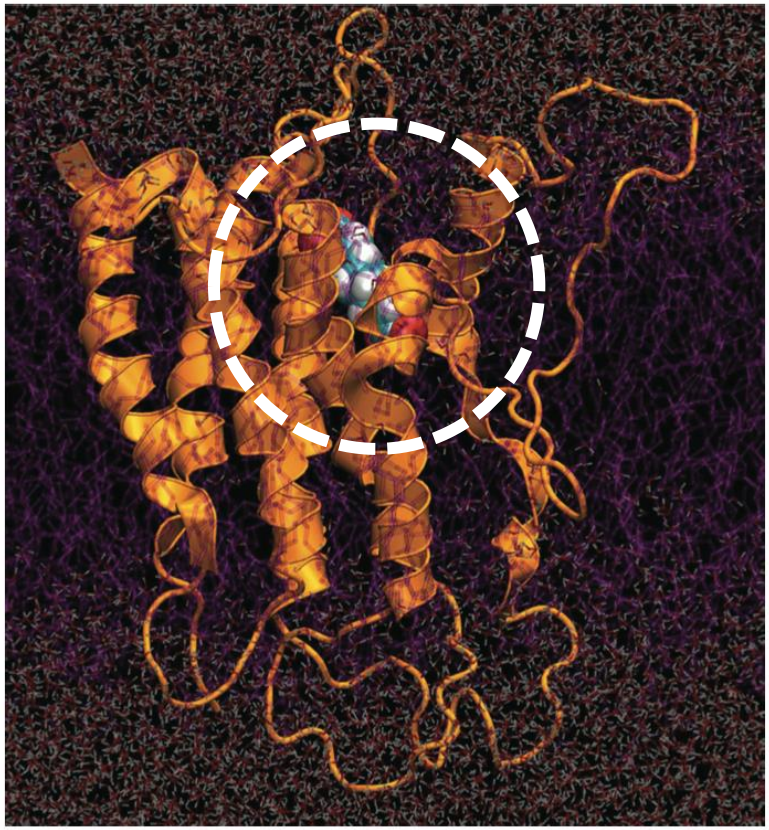
Anselmi, C.; Buonocore, A.; Centini, M.; Facino, R. M.; Hatt, H. *Comp. Biol. Chem.* **2011**, 35, 159-168.

Olfactory receptors: activators and inactivators

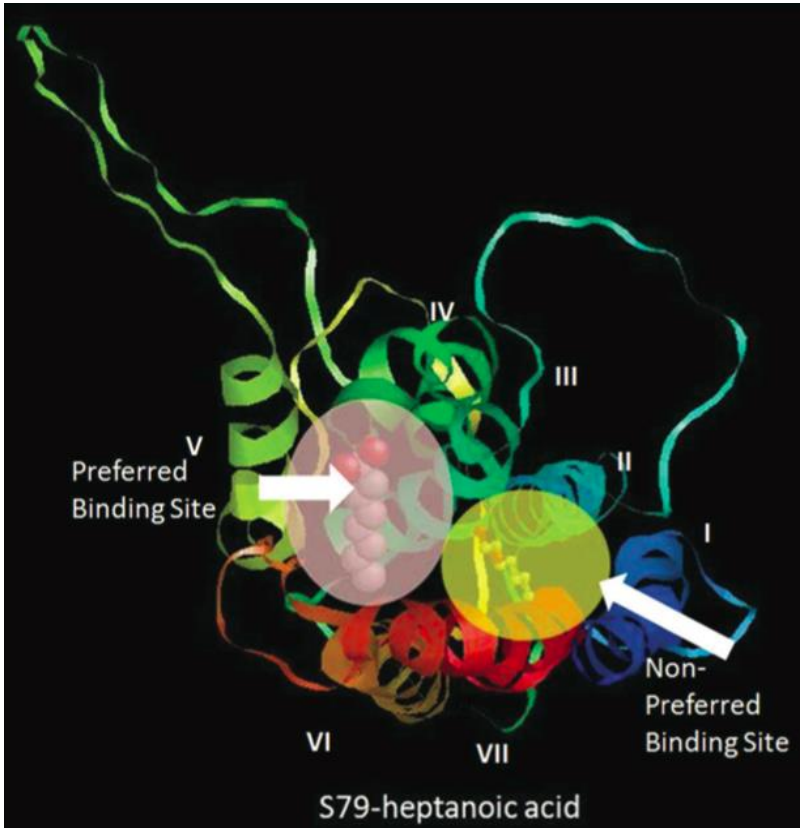
Anselmi, C.; Buonocore, A.; Centini, M.; Facino, R. M.; Hatt, H. *Comp. Biol. Chem.* **2011**, 35, 159-168.

Lai, P. C.; Guida, B.; Shi, J.; Crasto, C. J. *Chem. Senses,* **2014**, 39, 107-123.

		Acid					
		Heptanoic	Octanoic	Nonanedioic	Nonanoic	heptanol	heptanoic
OR	S79	+	+	+		–	
	S86				+		–



Docking
+
MD



Lai, P. C.; Guida, B.; Shi, J.; Crasto, C. J. *Chem. Senses,* **2014**, 39, 107-123.

Axel Bidon-Chanal Badia

Campus de l'Alimentació de Torribera
Verdaguer building, office 14.
Av. Prat de la Riba 171.
08921 Santa Coloma de Gramenet

abidonchanalb@ub.edu

THANK YOU FOR YOUR ATTENTION!