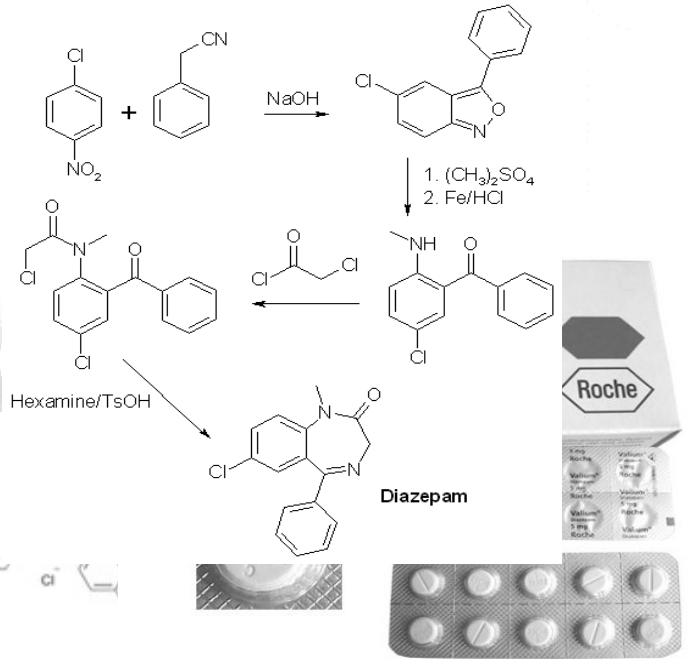
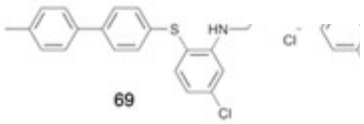
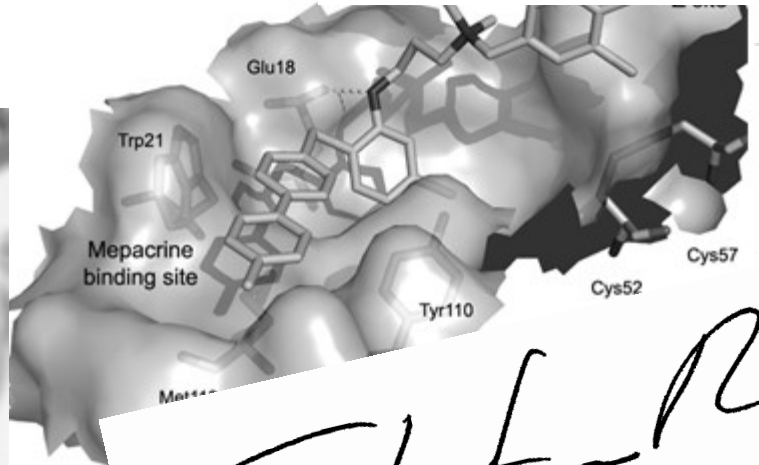
Chimica Farmaceutica e Tossicologica – Parte II







Ecco come organizzeremo il nostro viaggio…

http://mms.dsfarm.unipd.it

Cerca

UNIVERSITÀ DEGLI STUDI DI PADOVA

MMS Molecular Modeling Section

Department of Pharmaceutical and Pharmacological Sciences, University of Padova

Via Marzolo 5, 35131 Padova (Italy) - phone: +39 049 8275704, fax: +39 049 8275366

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News & Updates

01, 2023

MMS: Events

September, 2022
XXVII National Meeting in Medicinal Chemistry… *more*

MMS: Latest Hot Publication

Pavan M et al. "Qualitative Estimation of Protein–Ligand Complex Stability through Thermal Titration Molecular Dynamics Simulations" J. Chem If Mod (2022) ***more…***

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Cerca

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pdates

ation with Cresset. *more...*

hermal Titration Molecular
ol. *more...*

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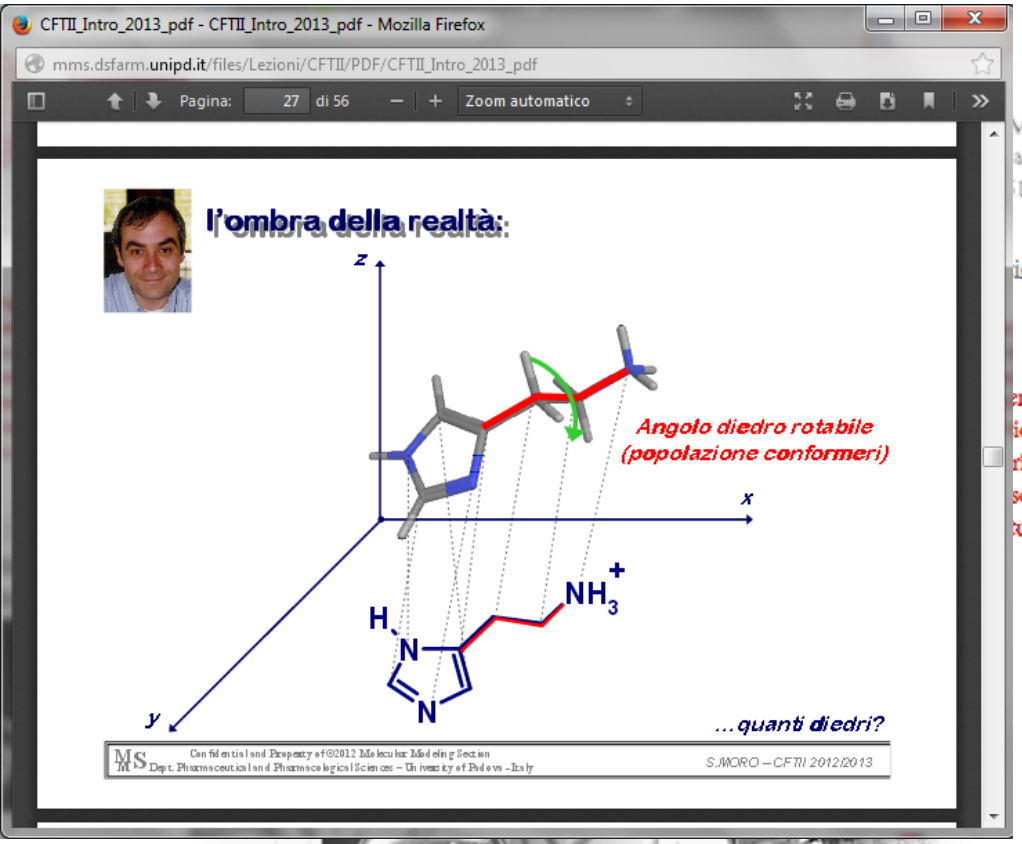

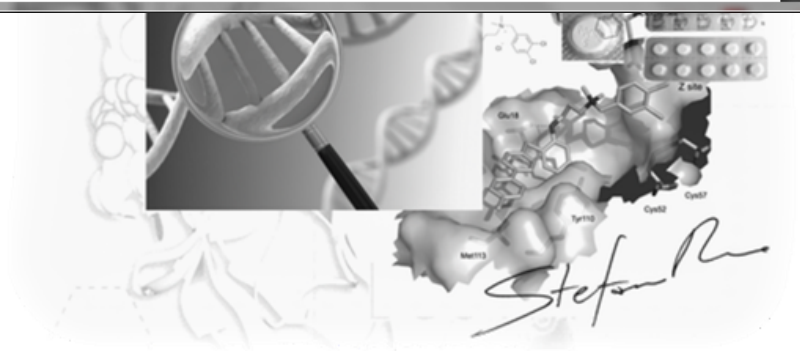

Cerca

Modeling Section

armaceutical and Pharmacological Sciences, University of Padova

131 Padova (Italy) - phone: +39 049 8275704, fax: +39 049 8275366

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ntali riguardanti le strategie generali di progettazione, la sintesi, lo studio dei
ioni fra struttura chimica e attività biologica di alcune classi di farmaci. In
riferici. Si prevede che lo studente acquisisca la conoscenza dei concetti
scutere i meccanismi d'azione e le relazioni struttura-attività di farmaci sulla
udente acquisisca gli elementi indispensabili per progettare farmaci su basi

1. Parte generale		
Basi termodinamiche del riconoscimento farmaco-recettore		
Sistemi di comunicazione cellulare		
	parte	
	parte	
2. Sistematica Farmaceutica		
Comunicazione colinergica		
	parte I	
	parte II	
	parte III	

http://mms.dsfarm.unipd.it

CFT2@podcast:

CFT2@zoomcas

CFT2@GoogleC

@sertiamoci: **ıi on-line da usare come "foraggio" celebrale)**

Principi attivi di farmaci che non possiamo non conoscere:

	Comunicazione adrenergica			
		parte I		
		parte II		
	Comunicazione gabaergica			
	Comunicazione serotoninergica			
	Comunicazione degli oppioidi endogeni			
	Comunicazione istaminergica			
	Comunicazione degli endocannabinoidi			

Chimica Farmaceutica e Tossicologica – Parte II

	riconoscimento farmaco-recettore (diapositiva 11-16)	
	PDF: Basi Temodinamiche del riconoscimento farmaco-recettore (diapositiva 17-32)	

http://mms.dsfarm.unipd.it

CFT2@podcast:

CFT2@zoomcast:

CFT2@GoogleGruppi:

@sertiamoci: **(esercitazioni on-line da usare come "foraggio" celebrale)**

Principi attivi di farmaci che non possiamo non conoscere

	Comunicazione adrenergica			
		parte I		
		parte II		
	Comunicazione gabaergica			
	Comunicazione serotoninergica			
	Comunicazione degli oppioidi endogeni			
	Comunicazione istaminergica			
	Comunicazione degli endocannabinoidi			

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…principi attivi di farmaci che non possiamo non conoscere.

Miei cari, a seguito la lista dei principi attivi che non possiamo non conoscere… almeno per il completamento del percorso fatto insieme. Volevo sottolineare che molti di questi principi attivi fanno parte di quella lista che l'WTO considera come la "List of Essential Medicines" compilata per la prima volta nel 1977… e giunta al suo XVIII aggiornamento (Aprile 2013).

Comunicazione colinergica:		
	Metacolina	
	Carbacolo	
	Betanecolo	
	Epibatedina	
	Pilocarpina	
	Arecolina	
	Atropina	
	Scopolamina	
	Butilscopolamina	
	Tiotropium	
	Amprotropina	
	Pirenzepina	
	Telenzepina	

http://mms.dsfarm.unipd.it

Welcome to the **Molecular Modeling Section (MMS)** of the Department of Pharmaceutical and Pharmacological Sciences, at the University of Padova in Italy. Our mission is to develop and apply new IT and computational methodologies to speed up the identification and development of new drug candidates through the creation of collaborative interfaces with synthetic chemistry, biochemistry and biology, pharmacology, and different medical disciplines.

In the spirit of the motto "interdisciplinarity is dialog" the aim of the MMS is to face computational medicinal chemistry and therapeutic needs in collaboration with all field experts... not mixing our expertise but summing them up.

L'aiuto grande che vi chiedo:

- Chimica Organica 1
- Chimica Farmaceutica 1
- Biochimica (Chimica Biologica)

che cosa ci manca enormemente:

- Farmacologia generale

I nostri compagni di viaggio:

… il mio personale suggerimento:

WIKIPEDIA
The Free Encyclopedia

ChatGPT

Menù (turistico) del *trimestre* di CFTII

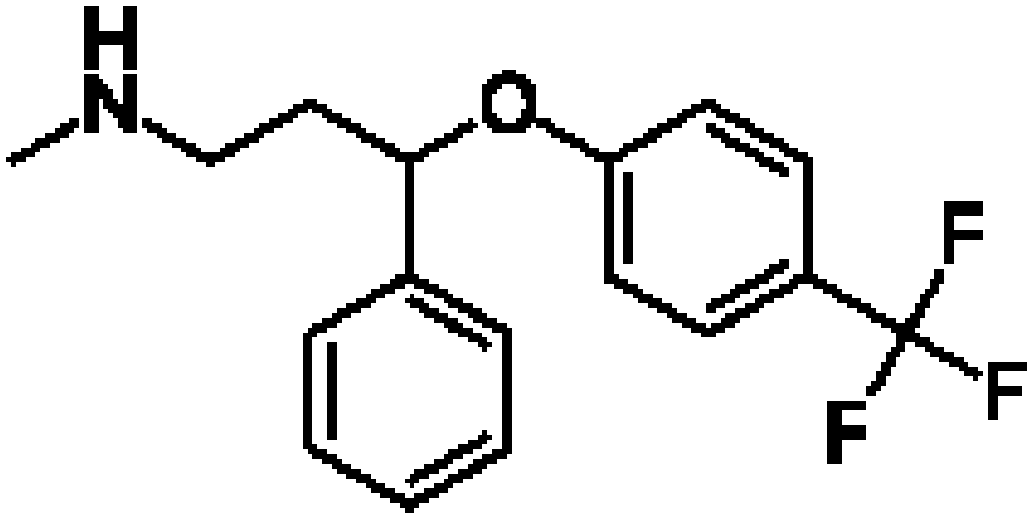
- **Parte prima: generale**

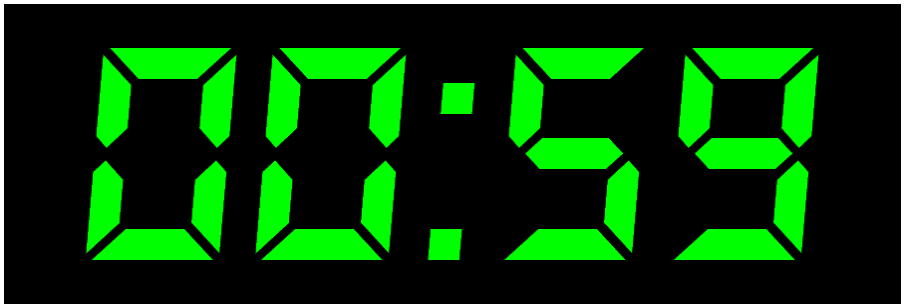
Le basi chimico-fisiche dell'interazione farmaco-bersaglio molecolare;
Sistemi di comunicazione cellulare

- **Parte seconda: sistematica**

Farmaci terapeuticamente rilevanti in patologie del SNC, dell'apparato cardiovascolare, del sistema immunitario e del sistema riproduttivo

To explain you our mission… a need a volunteer!



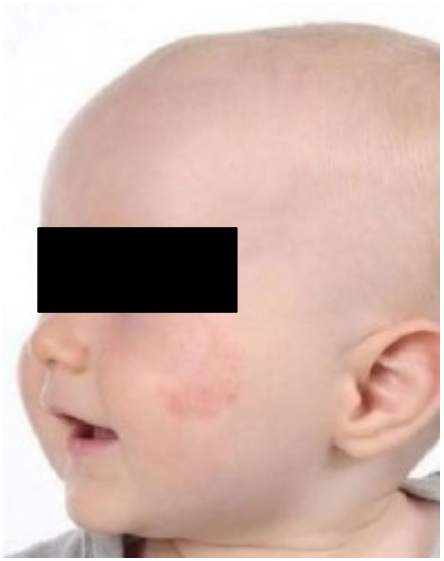


Are you ready to start?

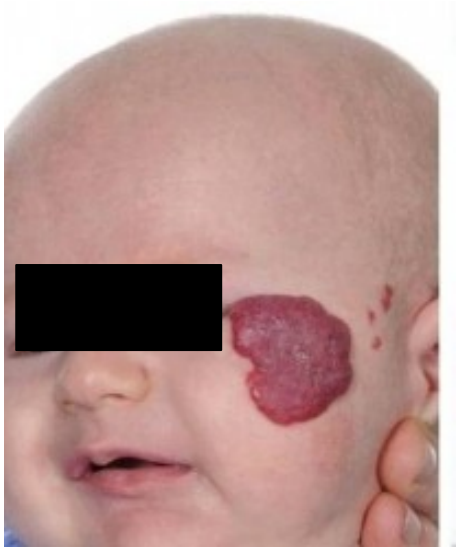
Lesson 0: drug definition…

how can we define a drug, very pragmatically?

Physiology State

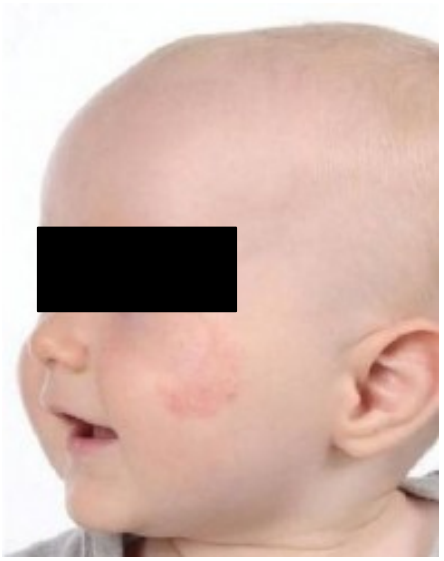


Pathology State



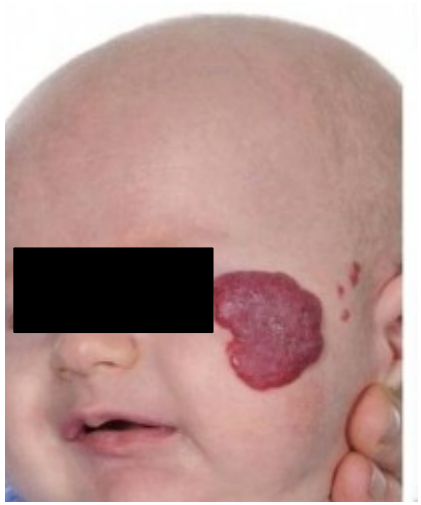
DRUG

Physiology State

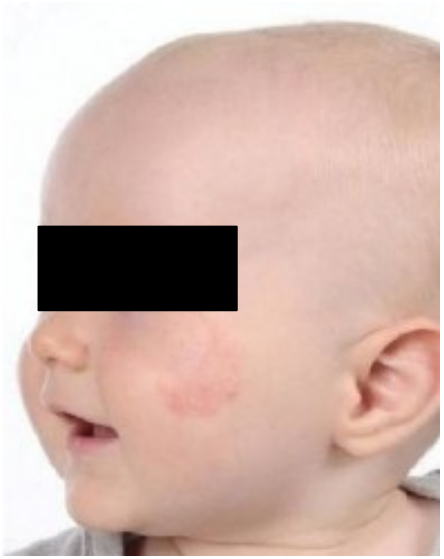


Infantile Hemangioma

how can we define a drug, very pragmatically?



DRUG

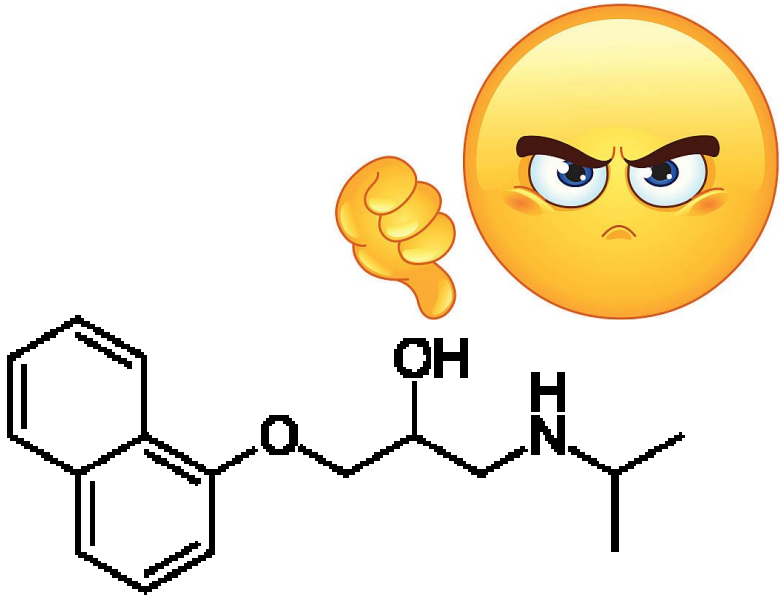


Infantile Hemangioma

Propranolol

THM Lesson 0: I pray you, never believe that

=



Propranolol

Drug discovery statistics:

https://www.nature.com/articles/d41573-025-00001-5

nature reviews drug discovery

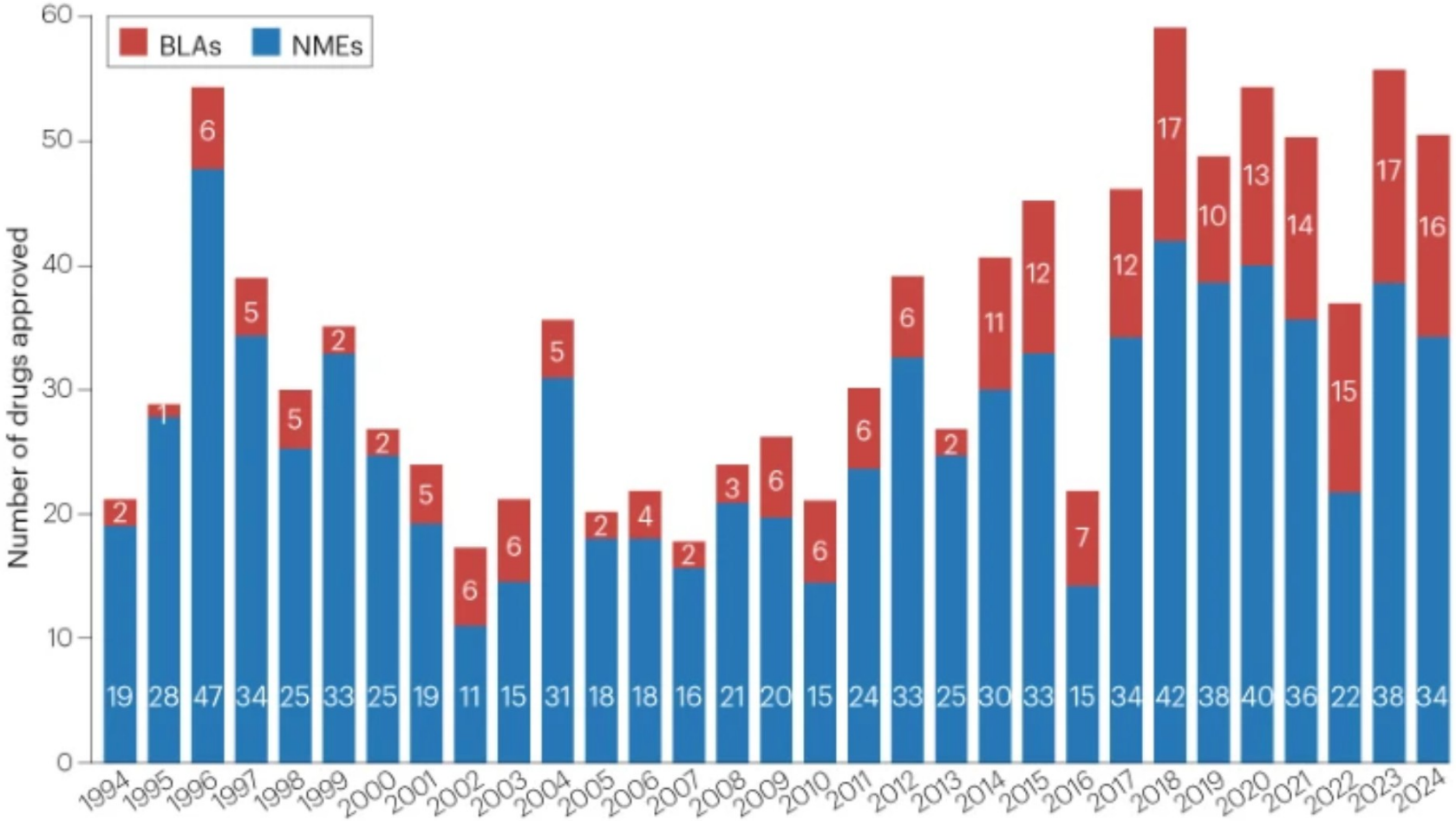
NEWS | 02 January 2025 | Update 20 January 2025

2024 FDA approvals

The FDA approved 50 new therapeutics in 2024, with green lights for a novel schizophrenia drug, a first NASH medicine and much more.

By Asher Mullard

Houston, we've had a problem here!



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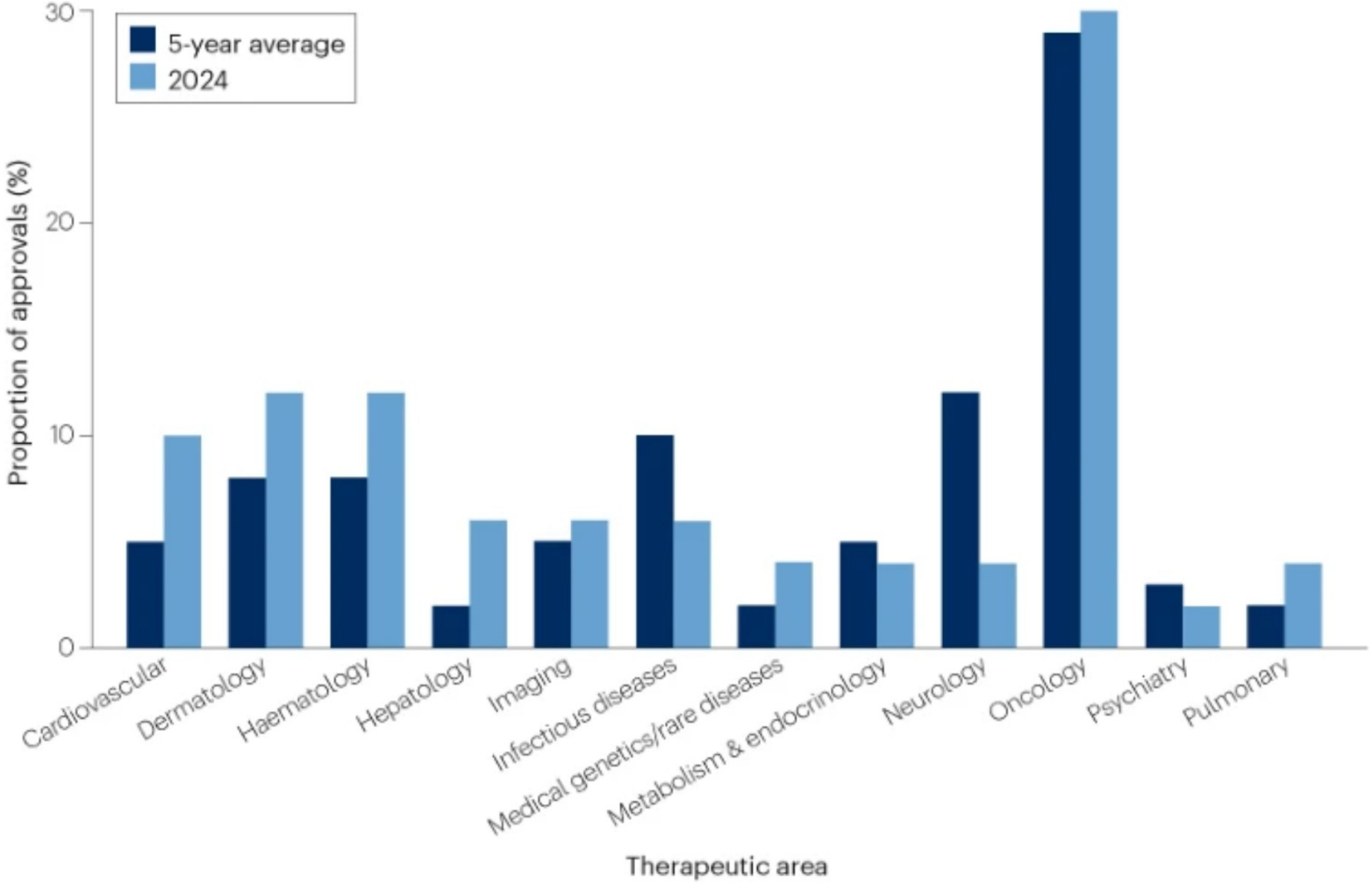
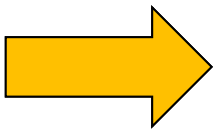
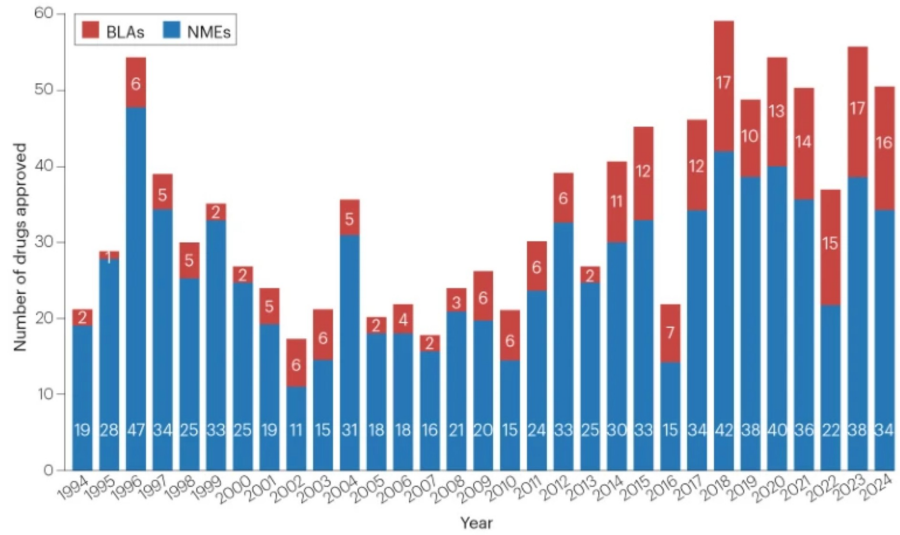
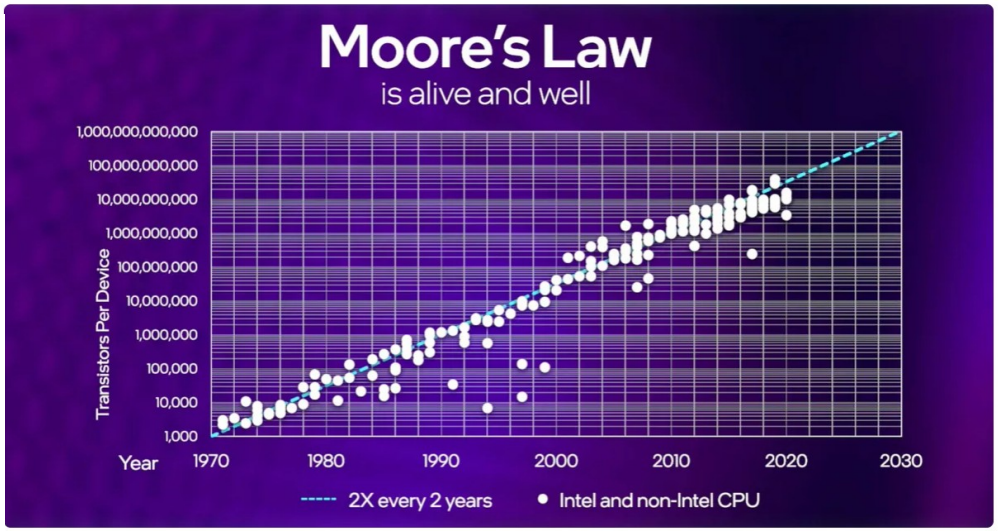


https://www.nature.com/articles/d41573-025-00001-5

we can stop for a second and reflect together?

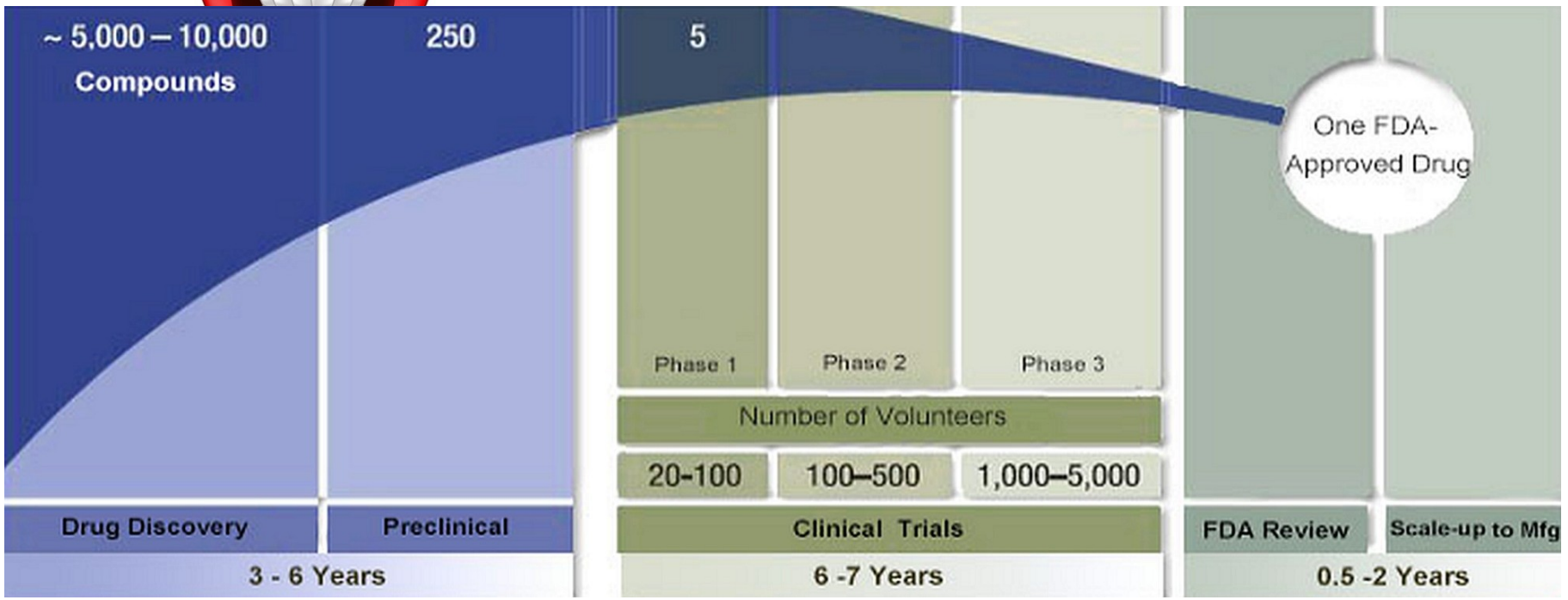






https://www.cnet.com/tech/computing/intel-will-outpace-moores-law-ceo-pat-gelsinger-says/

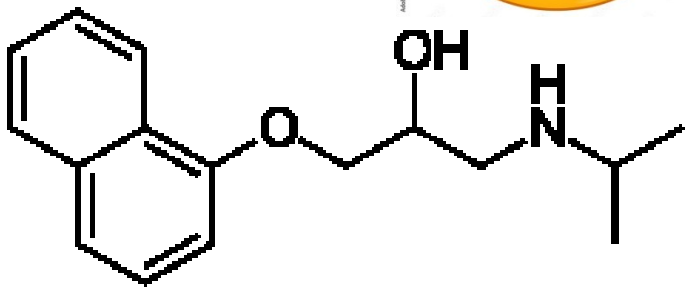
What you already know very very well: the long history of the birth of a drug…



Bringing a new drug to market can take 8-14 years and costs between $400 and $1000 million (even more!!!)

In fact, that's happen if you believe that:

=

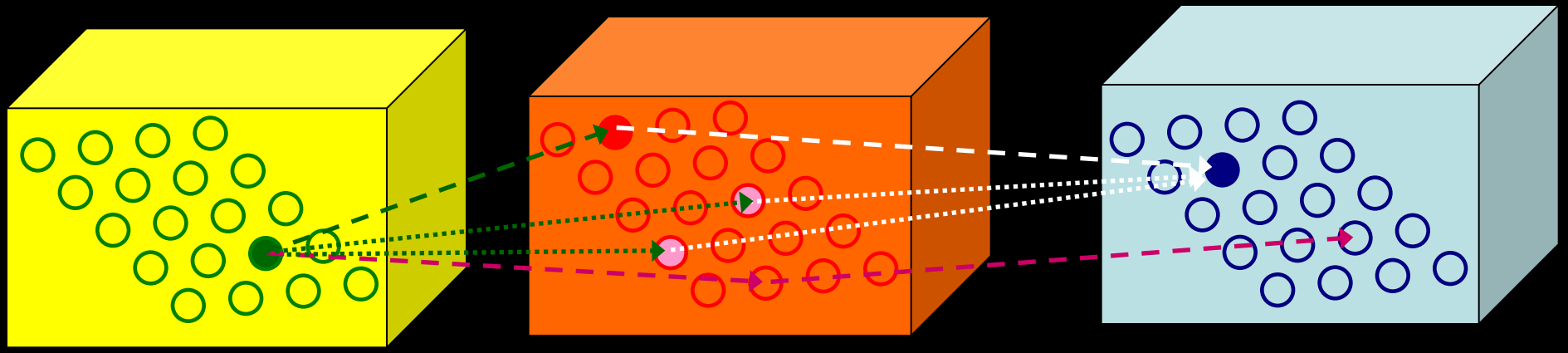


Propranolol

Lesson 1: change our drug discovery paradigm… let's try in this way!

How we can schematize our definition?

Drug
Therapeutic Interaction
Collateral Interaction
Biological or "On" Target
Secondary On Target
Anti or "Off" Target
Pathology



Chemical Space

Biological Space

Physio-Pathological Space

Summarizing:

Biological or “On” Target:

is a receptor, enzyme, or other cellular target that, when affected by a drug, causes the desired theraputical effect.

Anti or “Off” Target:

is a receptor, enzyme, or other cellular target that, when affected by a drug, causes undesirable side-effects.

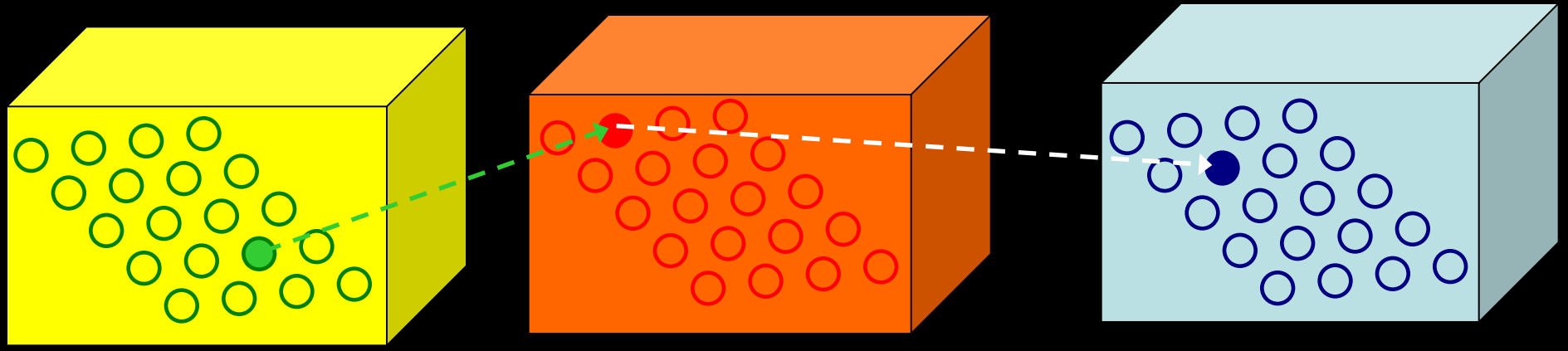
For a long long time we have considered as true this egoistic stoichiometry… 1 : 1 : 1

Biological or "On" Target

Drug

Therapeutic Interaction

Pathology

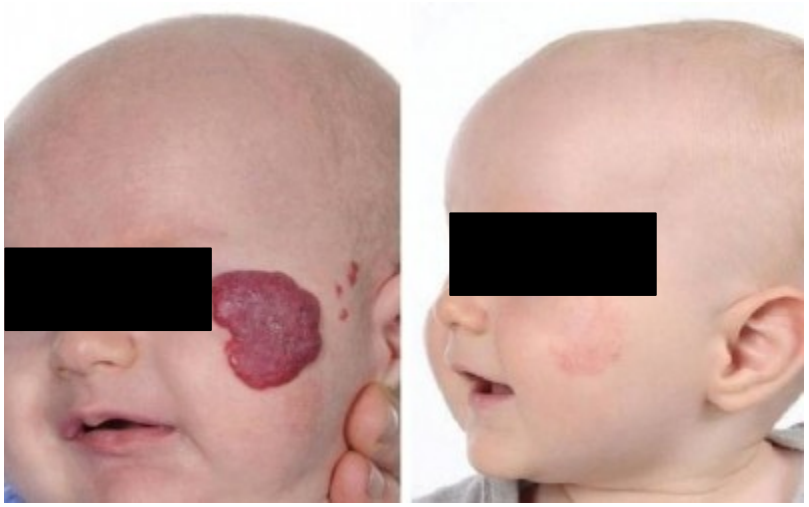


Chemical Space

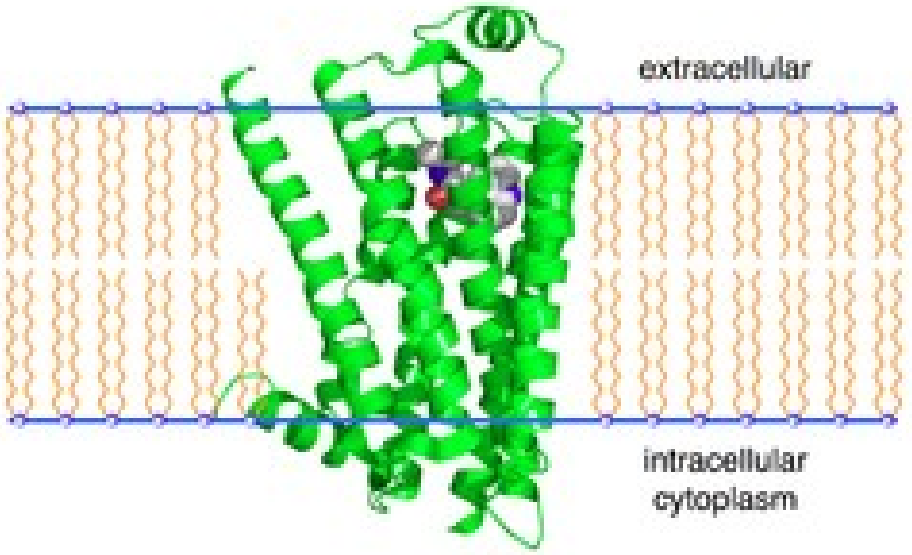
Biological Space

Physio-Pathological Space

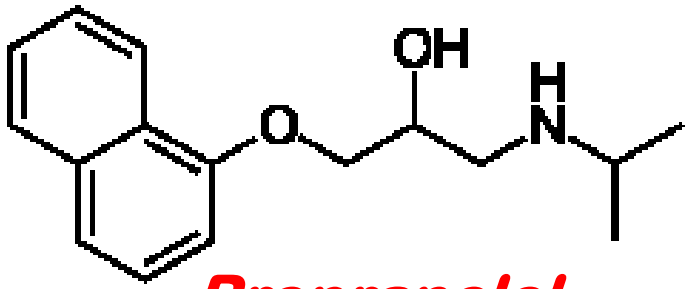
Choose the best solution:



Infantile Hemangioma



Beta adrenergic receptors



Propranolol

Now we have to change our mind: from *single-target* to *multi-targets* changing the stoichiometry to 1 : N : 1

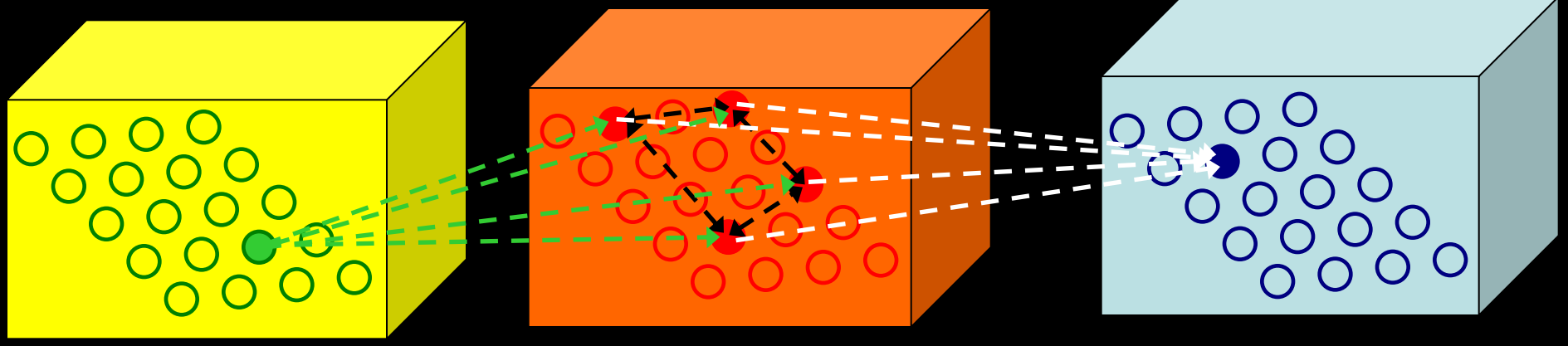
Biological or "On" Target

Secondary On Target

Drug

Therapeutic Interaction

Pathology



Chemical Space

Biological Space

Physio-Pathological Space

This is the era of *multi -target pharmacology*

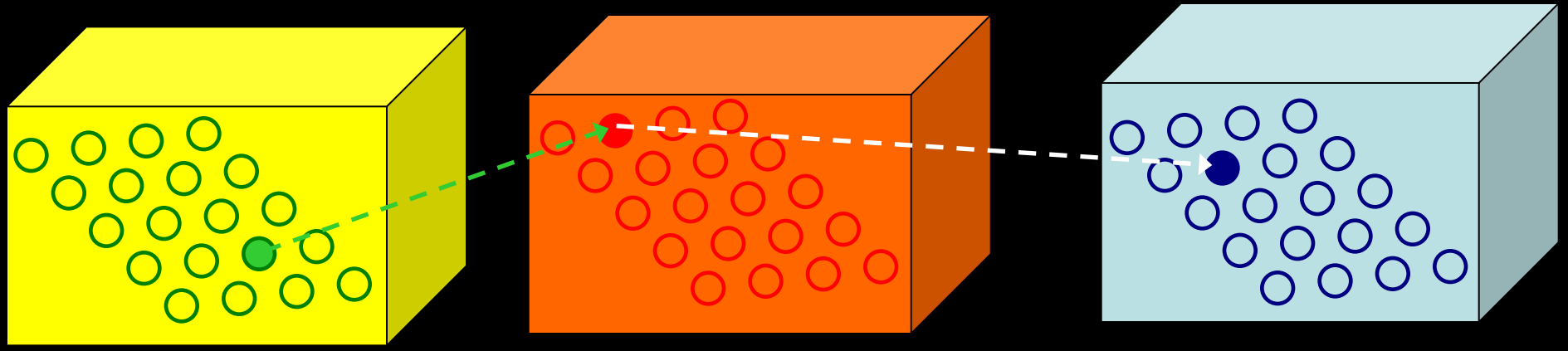
As medicinal chemists we often reduce the complexity of drug's concept in this way:

Biological or "On" Target

Drug

Therapeutic Interaction

Pathology



Chemical Space

Biological Space

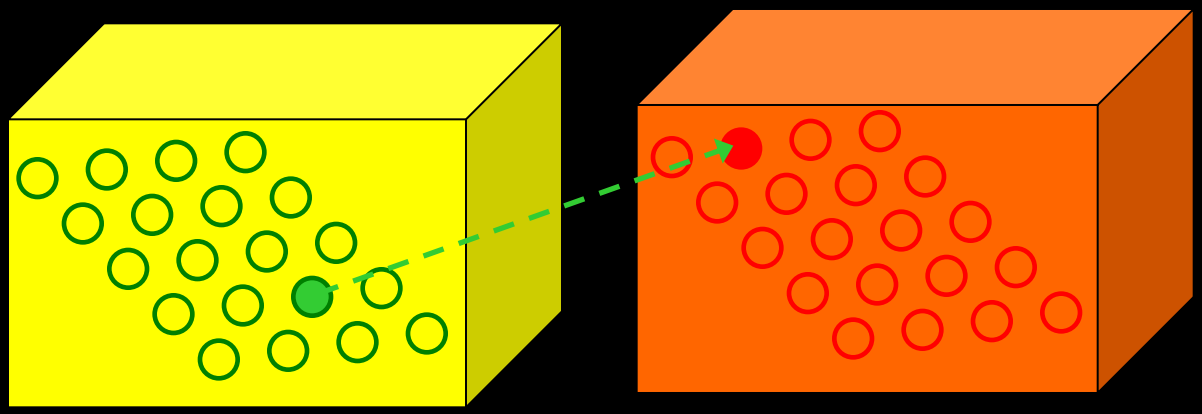
Physio-Pathological Space

And very very often as medicinal chemists we pretend to oversimplify the complexity of drug's concept in this way:

Biological or "On" Target

Drug

Therapeutic Interaction



Chemical Space

Biological Space

but we will never forget:

PHARMACODYNAMIC (PD) PROFILE

the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure.

PHARMACOKINETIC (PK)/TOX PROFILE

The study of the process by which a drug is absorbed (A), distributed (D), metabolized (M), and eliminated (E) by the body.

FORMULATION PROFILE

… and as in our life:

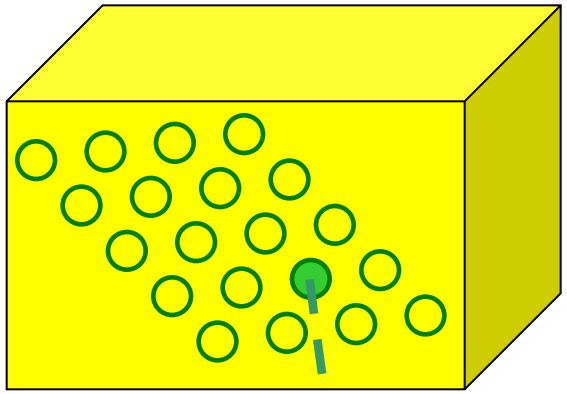
we must meet each other

recognize each other

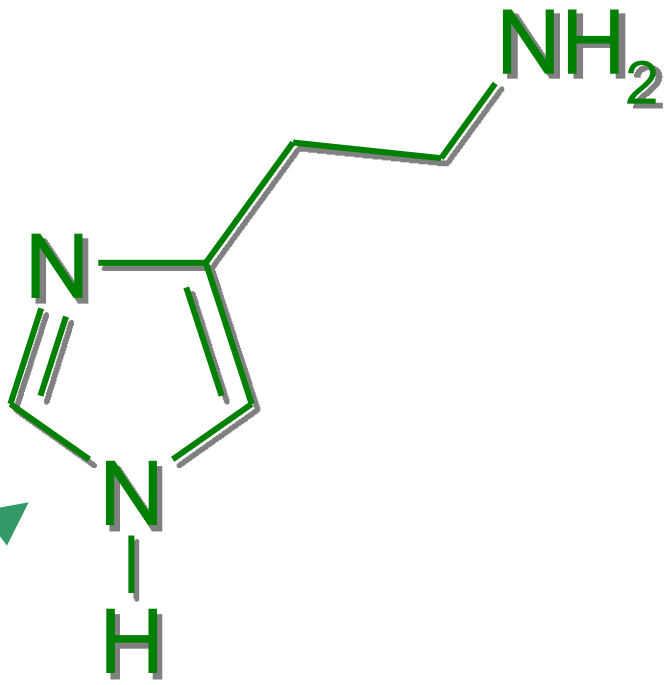
and in the end choose us!

where PD and PK profiles are stored in a drug?

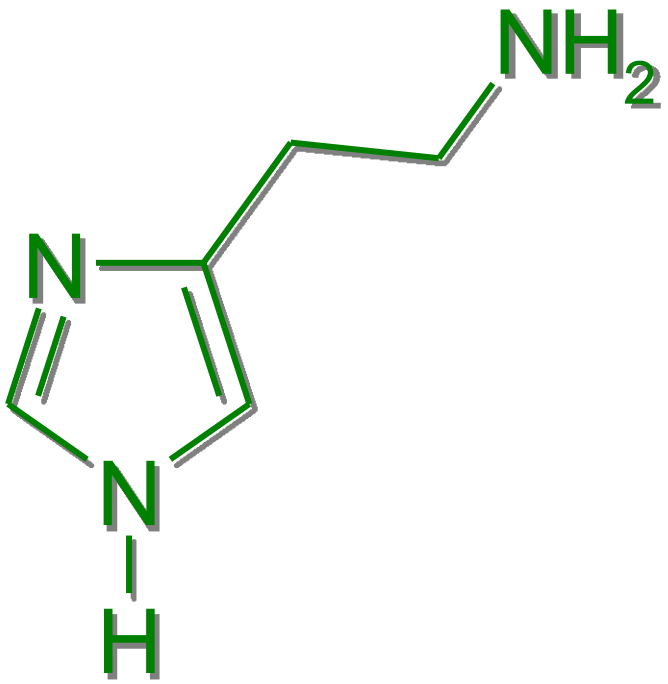
Chemical/Drug



Chemical Space

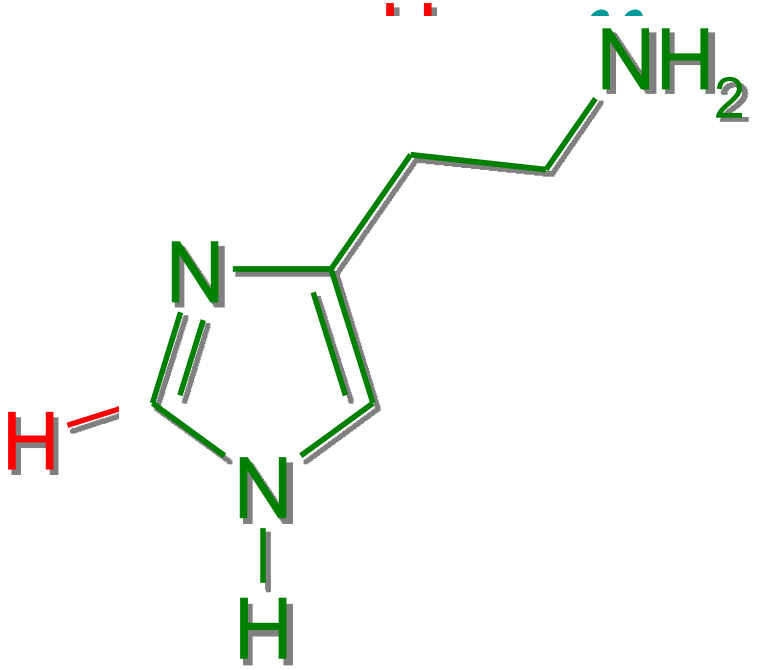


Please, we will never forget:



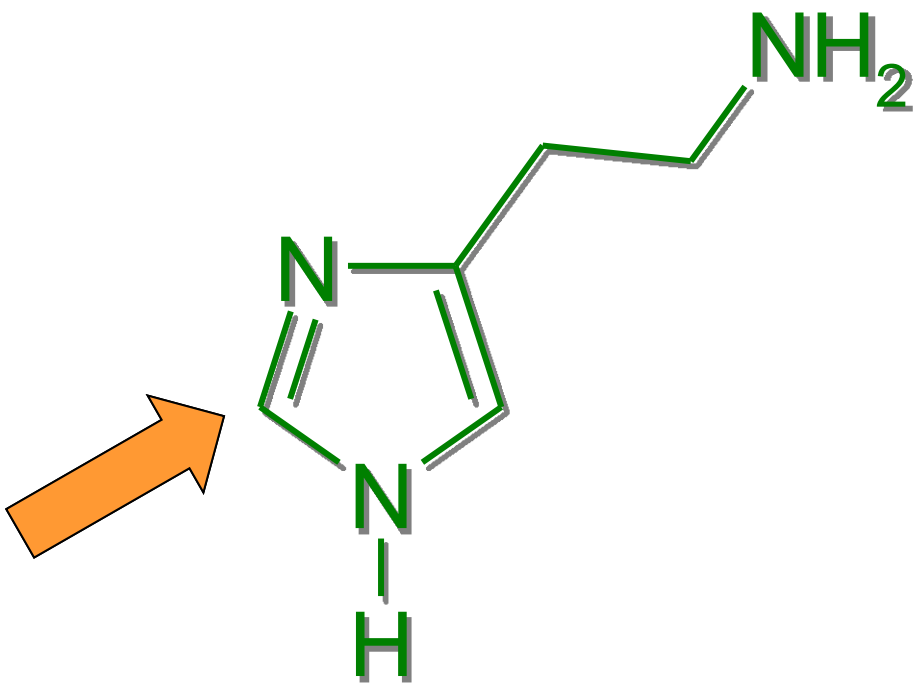
take the right distance from these representations!!!

First of all, please do not never forget the good orthography!



Of course this is our *slang!*

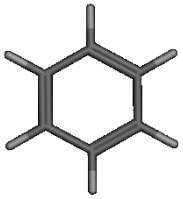
The first gold rule:

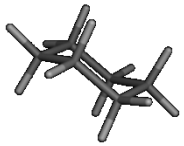


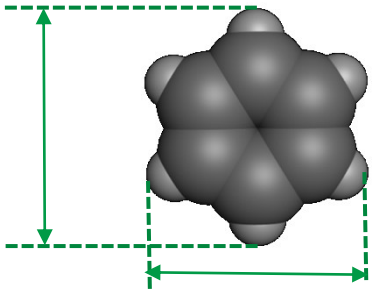
Identify the cyclic substructures, if any!!!

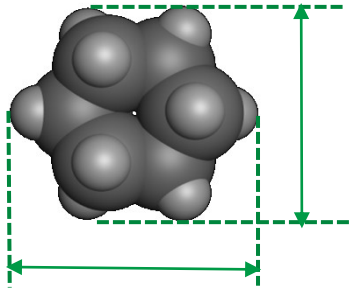
Why cycle: aromatic or not, few hints from 2D to 3D!

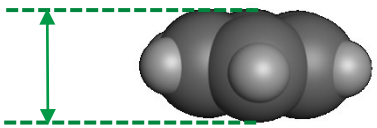
4n + 2

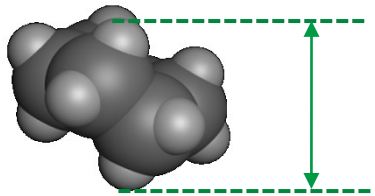










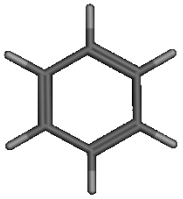


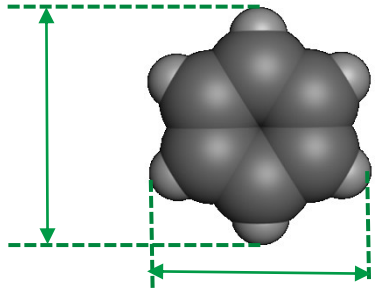
rigid and flat

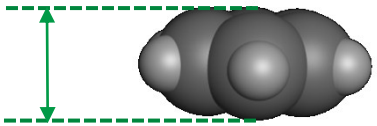
flexible and non flat

Why cycle: aromatic from carbocycle to heterocycle

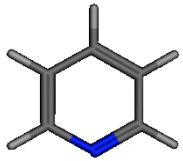
4n + 2



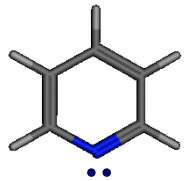


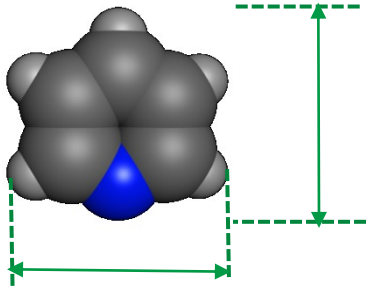


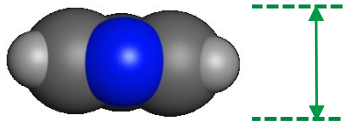
rigid and flat



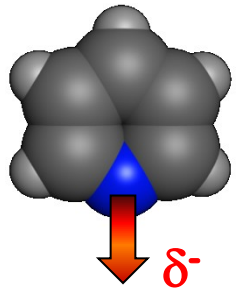
4n + 2





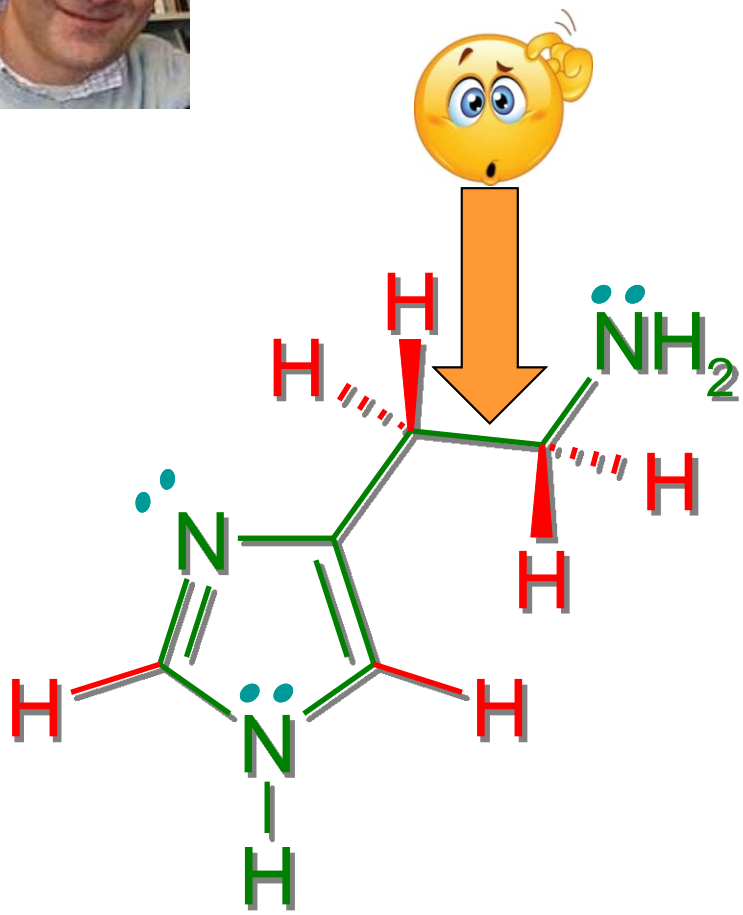


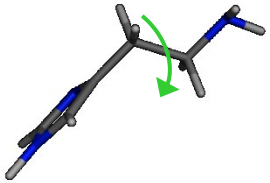
rigid and flat

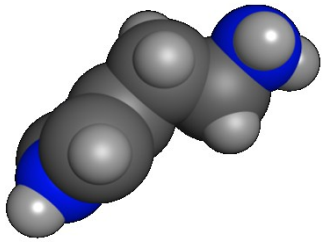


new interactor

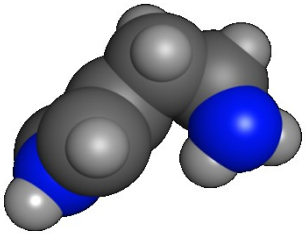
The second gold role:







IKEA

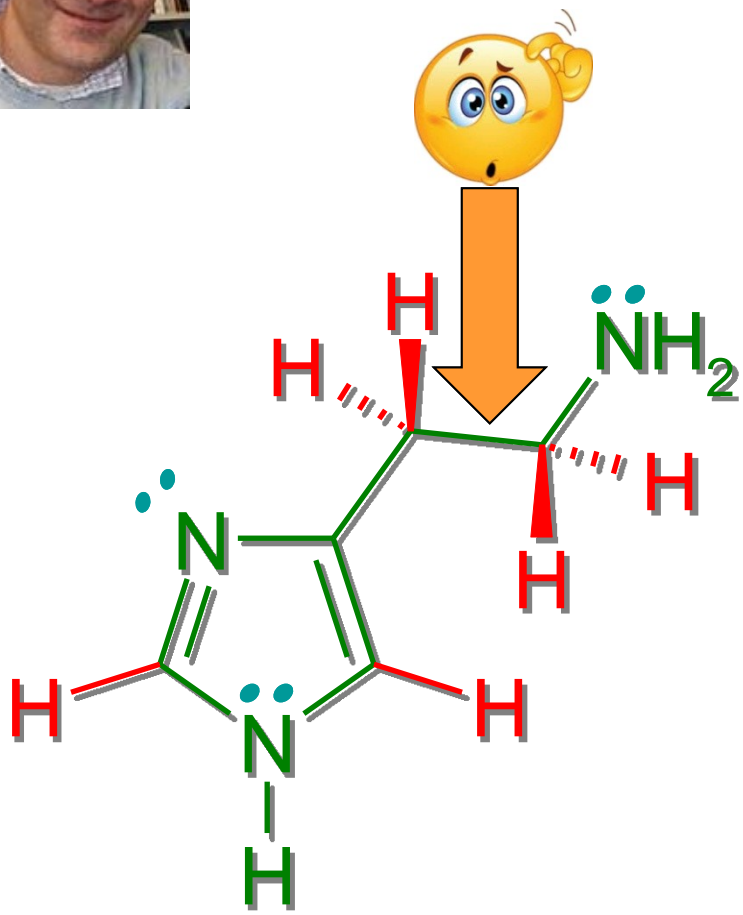


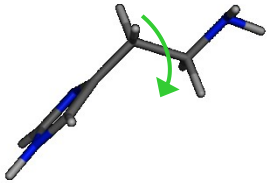
...

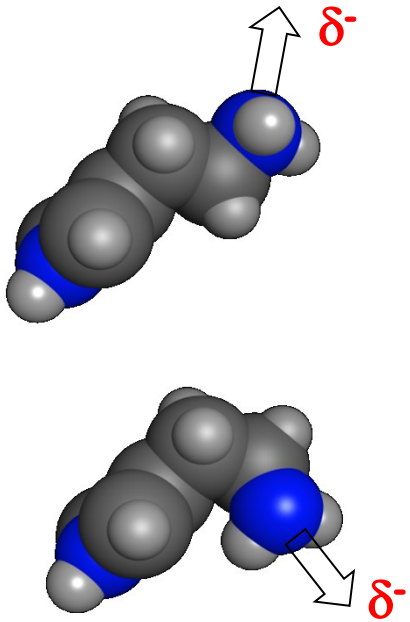
flexible and non flat

Identify the rotable bonds, if any!!!

The second gold role:



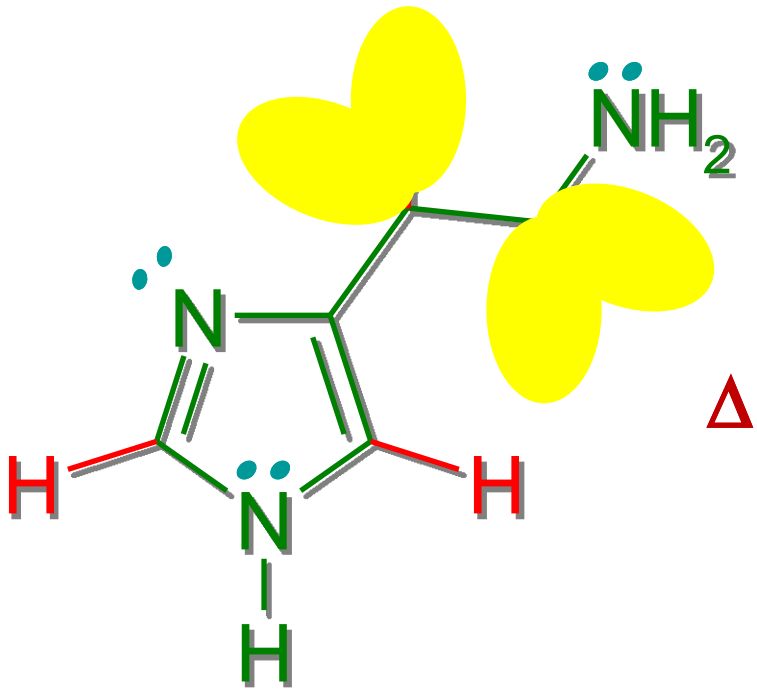




...

Change the interaction scheme

… and finally:



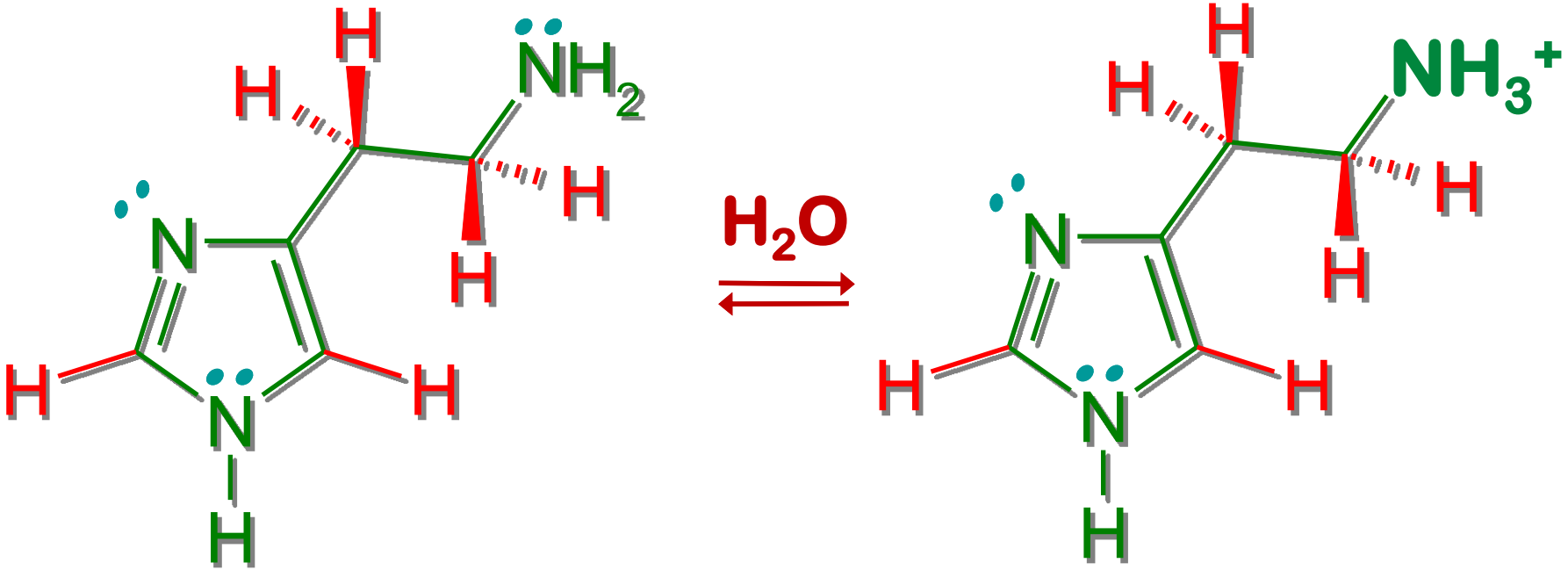
4 C-H bonds

$\Delta EN_{C-H} = 0.3$ (2.4-2.1)

Remember to count the C-H bonds, if any!!!

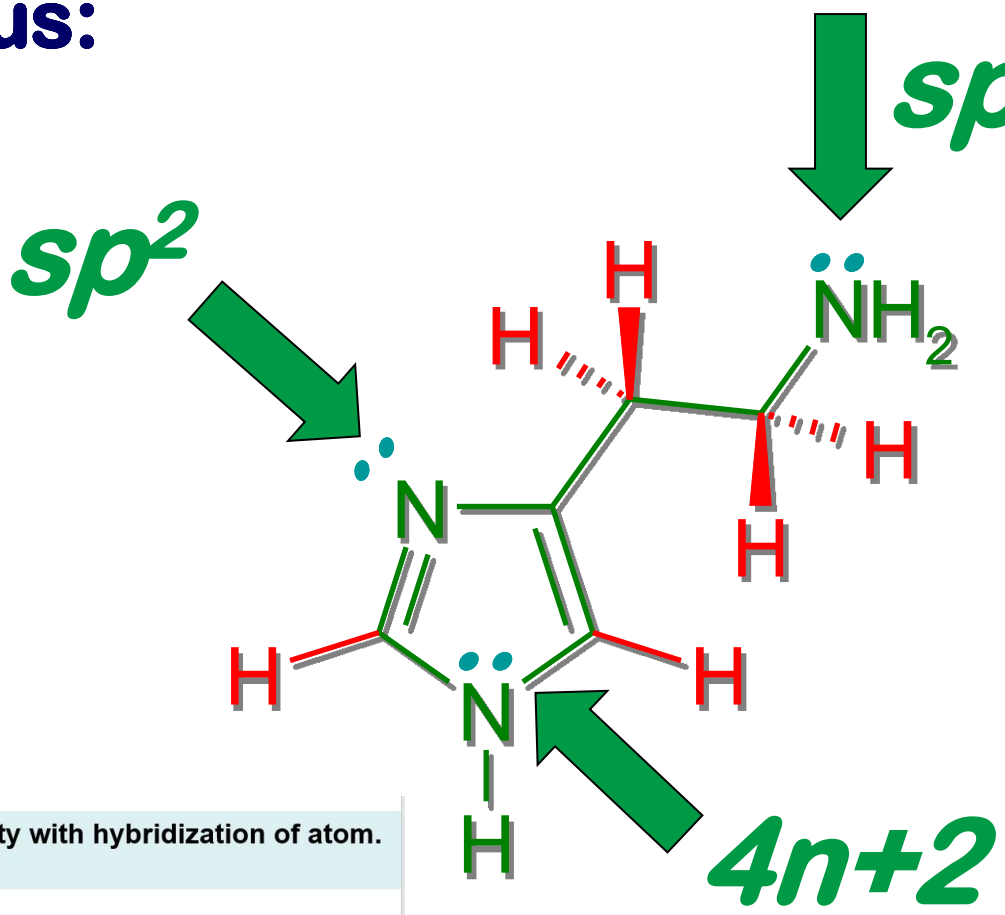
(we will see why in a couple of slides)

… and you can immediately associate:

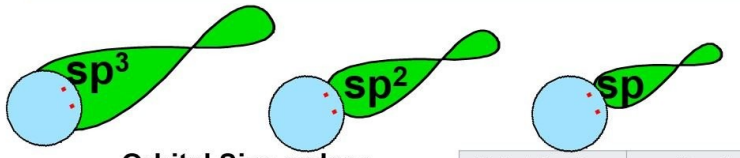


… two populations, as function of the intrinsic pKa and the local pH.

… and please check the hybridization status:



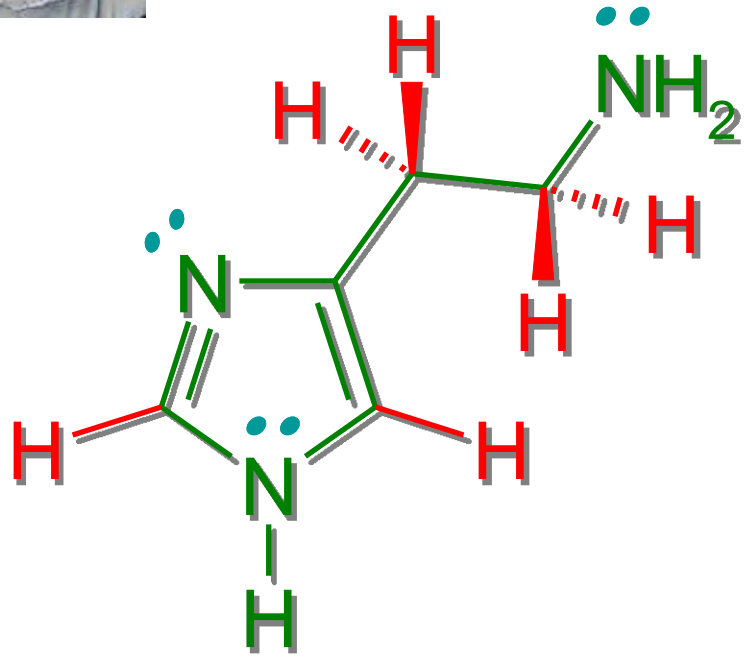
Variation of electronegativity with hybridization of atom.

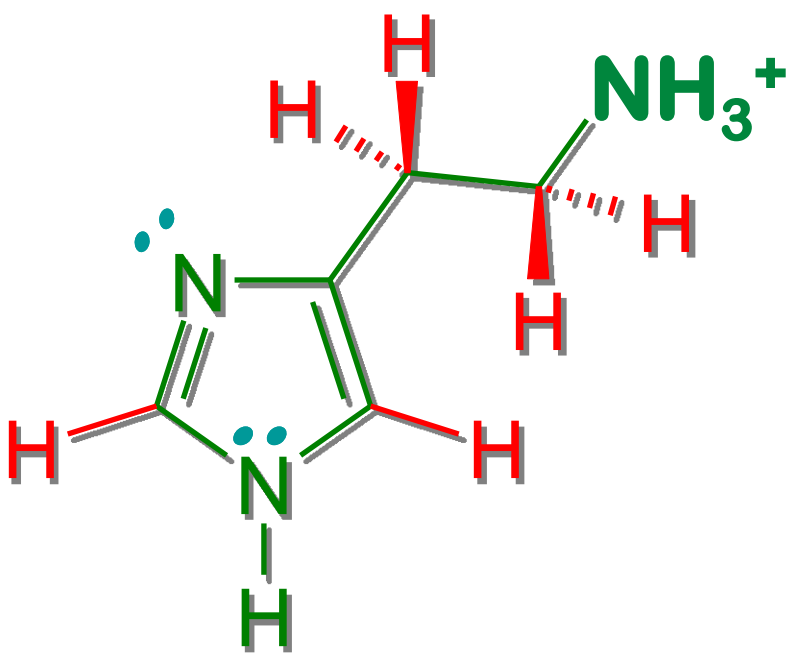


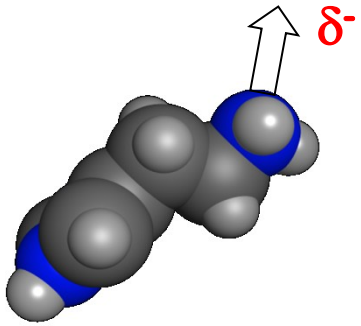
Orbital Size order :
$sp^3 > sp^2 > sp$
Electronegativity order:
$sp > sp^2 > sp^3$

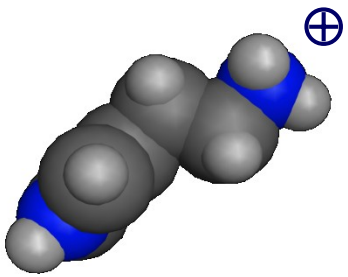
Hybridization	χ (Pauling)
C(sp^3)	2.3
C(sp^2)	2.6
C(sp)	3.1
'generic' C	2.5

The second gold role:



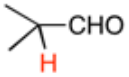
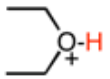
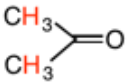
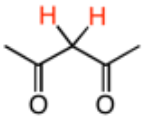
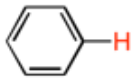
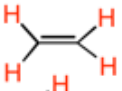
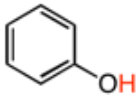
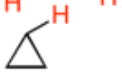






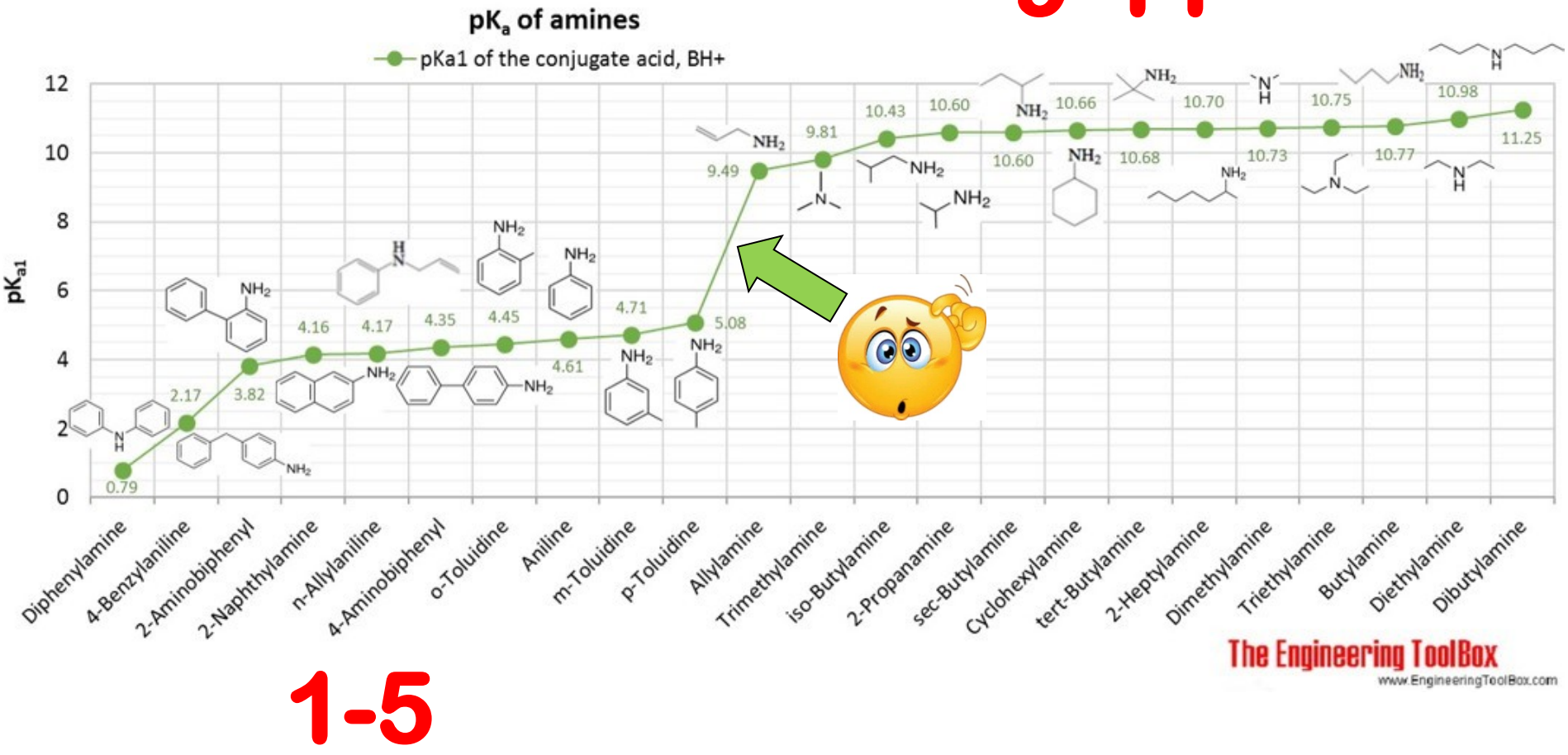
Change the interaction scheme

Just in case:

Brønsted Acids	pK_a	Brønsted Acids	pK_a
$CH_3C{\equiv}N^+\text{-}H$	-10	$CH_3COCH_2CO_2R$	11
HI	-10		15.5
HBr	-9	CH_3OH	15.5
$(CH_3)_2C{=}O^+\text{-}H$	-7.2	HOH	15.7
HCl	-7	C_2H_5OH	15.9
$(CH_3)_2\overset{+}{S}\text{-}H$	-5.4	$(CH_3)_3COH$	18
	-3.6		20
$C_2H_5\overset{+}{O}H_2$	-2.4	$(CH_3)_2SO_2$	23
H_3O^+	-1.7	$CH_3CO_2C_2H_5$	25
CF_3CO_2H	0.2	$CH_3C{\equiv}N$	25
HF	3.18	$HC{\equiv}CH$	25
CH_3CO_2H	4.76	NH_3	35
H_2S	7.0	$C_2H_5NH_2$	35
	9	$CH_3CH{=}CH_2$	38
NH_4^+	9.25		43
HCN	9.40		44
	10.0		46
CH_3NO_2	10.2		
C_2H_5SH	10.5	CH_4, C_2H_6	~50

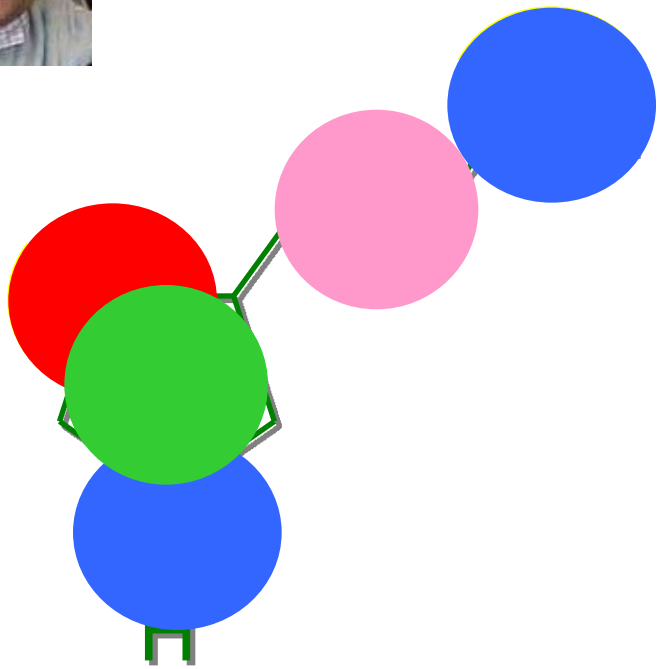
This will be crucial for us during all our course!!!

9-11



1-5

Good orthography means ability to recognize:



1. acid/base groups (*ionic bond*);

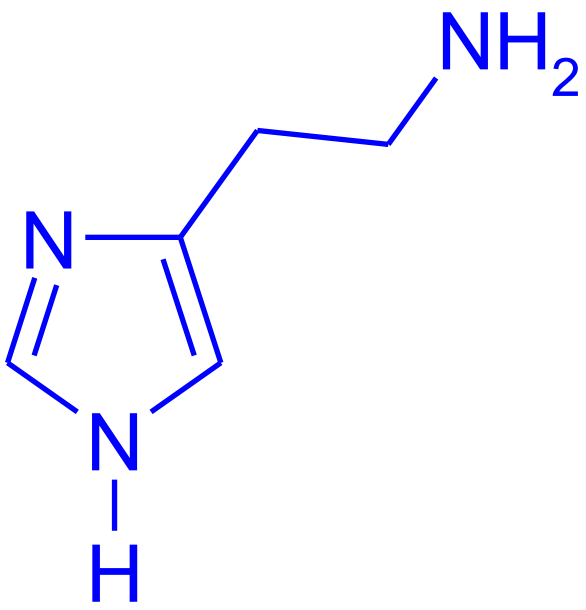
2. strong bond dipoles (*H-bond, dipole-dipole, charge-dipole…*);

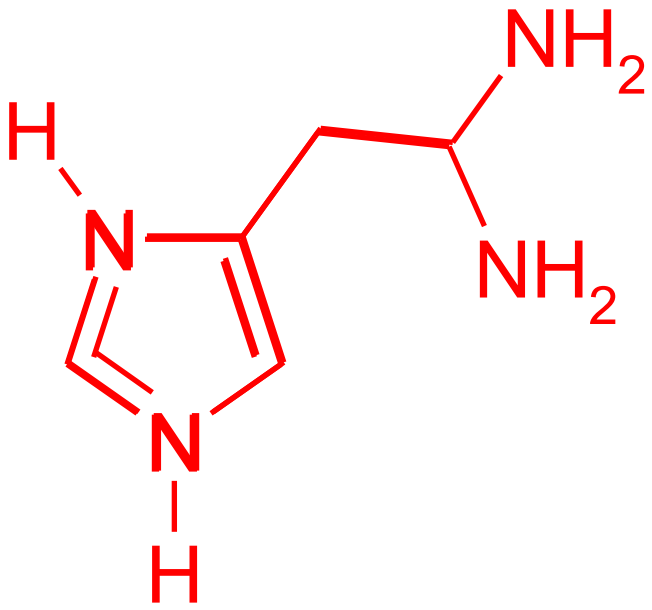
3. *π bonds (π-π interactions, charge-π, …)*;

4. weak bond dipoles (*dipole-dipole as van der Waals interactions*);

Do you remember:

1. pKa scale of acidity
2. hydrogen bond strength
3. aromaticity rule (4n+2)
4. bond dipole moment





1. acid/base groups (*ionic bond*);

2. Strong bond dipoles (*H-bond, dipole-dipole, charge-dipole…*);

3. π *bonds* (π-π *interactions, charge-*π*, ..)*;

4. Weak bond dipoles (*dipole-dipole as van der Waals*);

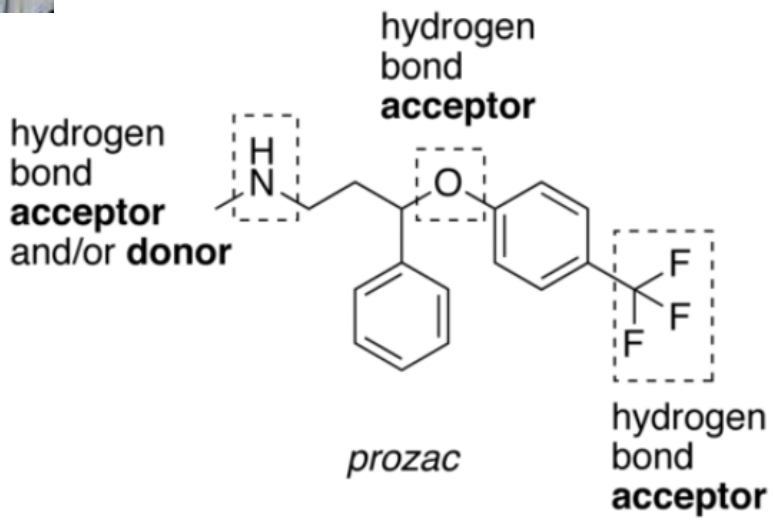
5. Tautomers (*tautomeric equilibrium and tautomer stability*);

6. Conformers (*conformational equilibrium and conformer stability*);

7. Stereochemistry (chiral centers)

8. Chemical reactivity;

Just in case:



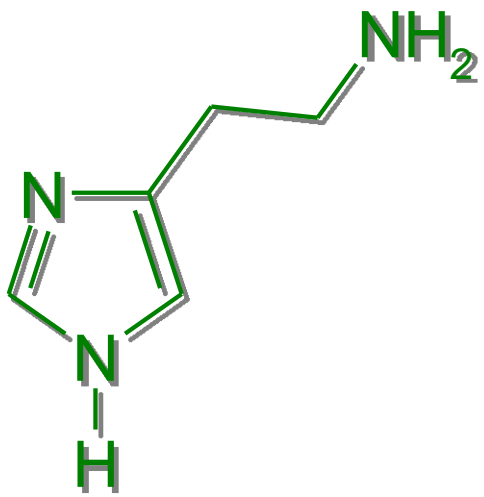
F−H ··· :F (38.6 kcal/mol)
O−H ··· :N (6.9 kcal/mol)
O−H ··· :O (5.0 kcal/mol)
N−H ··· :N (3.1 kcal/mol)
N−H ··· :O (1.9 kcal/mol)
HO−H ··· :OH_3^+ (4.3 kcal/mol)

Bond Dipole Moments

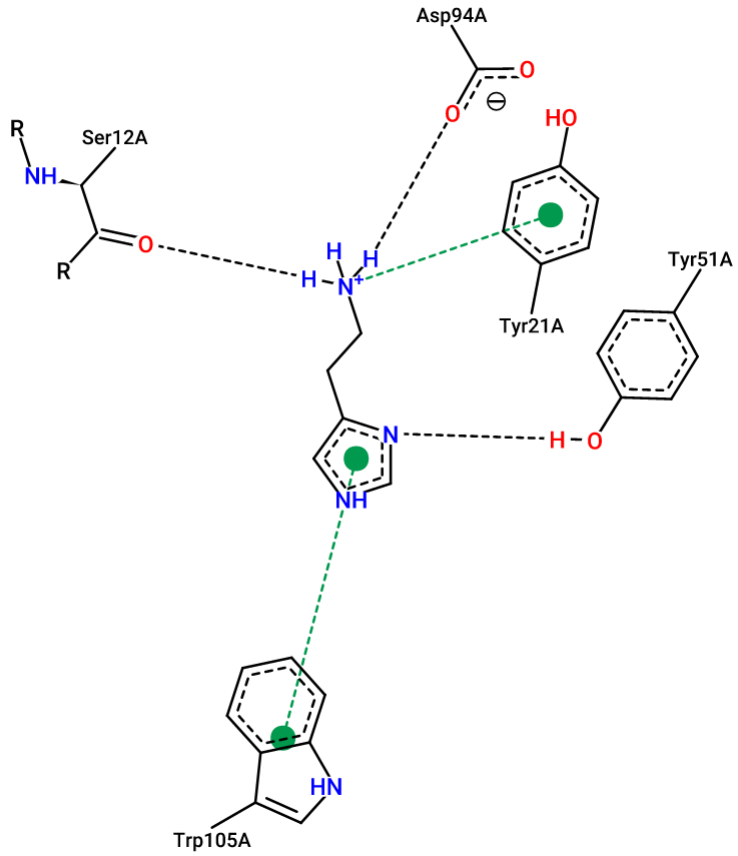
$\delta^+ \longrightarrow \delta^-$

Bond	Dipole Moment (D)
H-C	0.3
H-N	1.31
H-O	1.53
C-N	0.22
C-O	0.86
C-F	1.51
C-Cl	1.56
C-Br	1.48
C-I	1.29
C=O	2.4
CN (cyano)	3.6

THM Lesson 1: the first major difference between an organic chemist and a medicinal chemist:

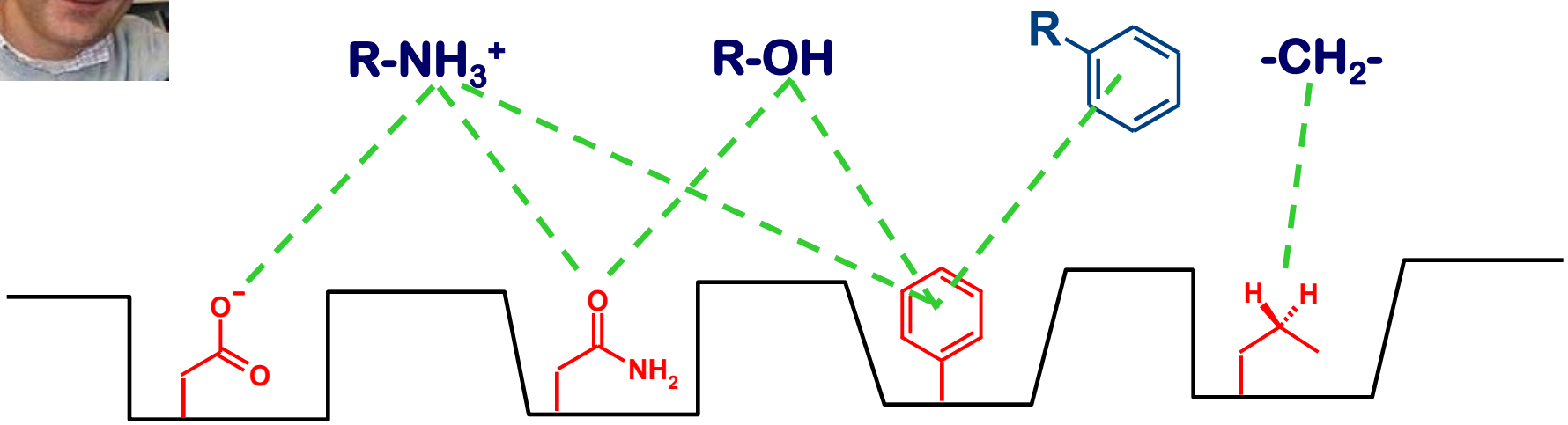


I'm like that and I have these properties



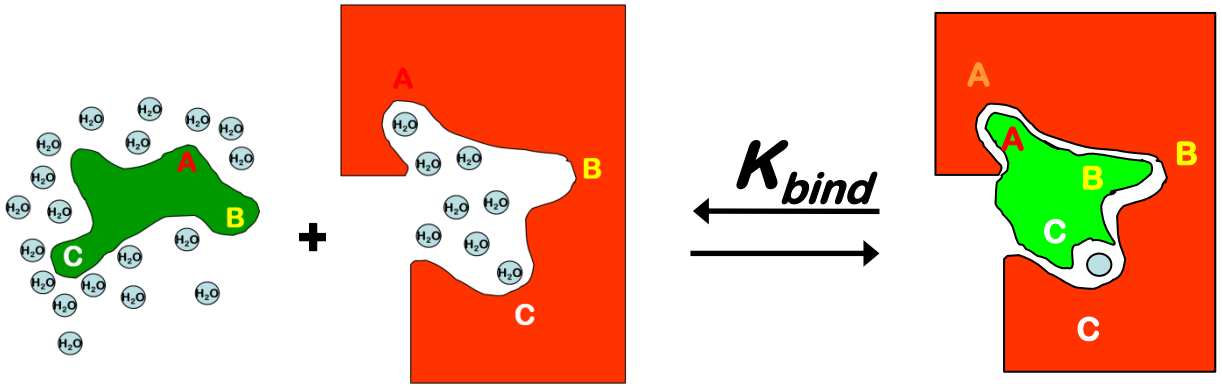
I'm like this and have these properties, and consequently I could recognize in this way …

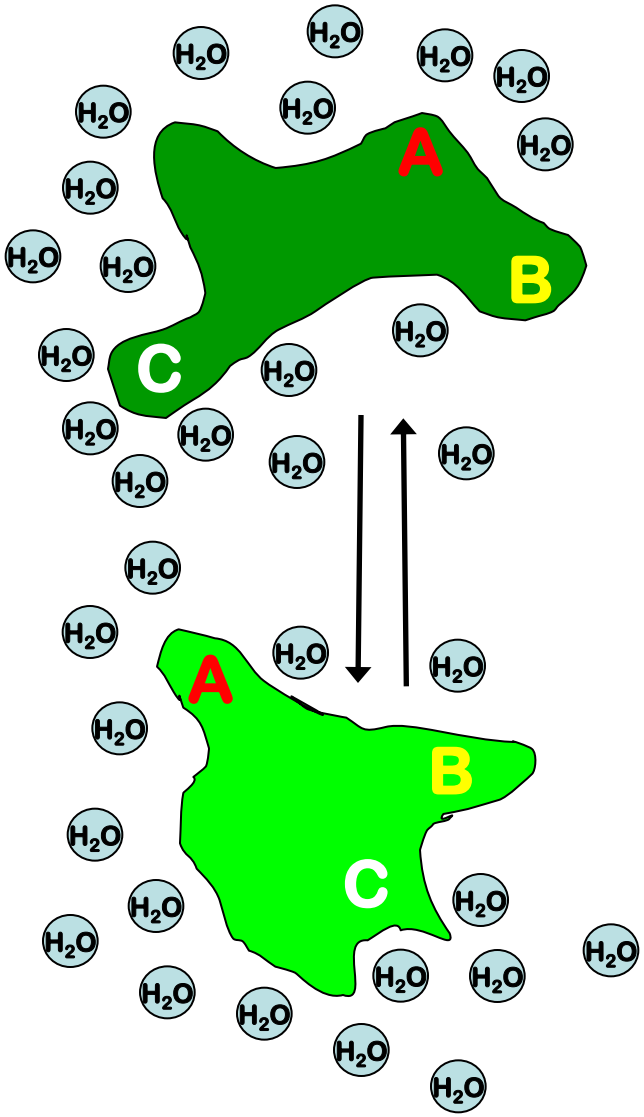
From structure to interaction:

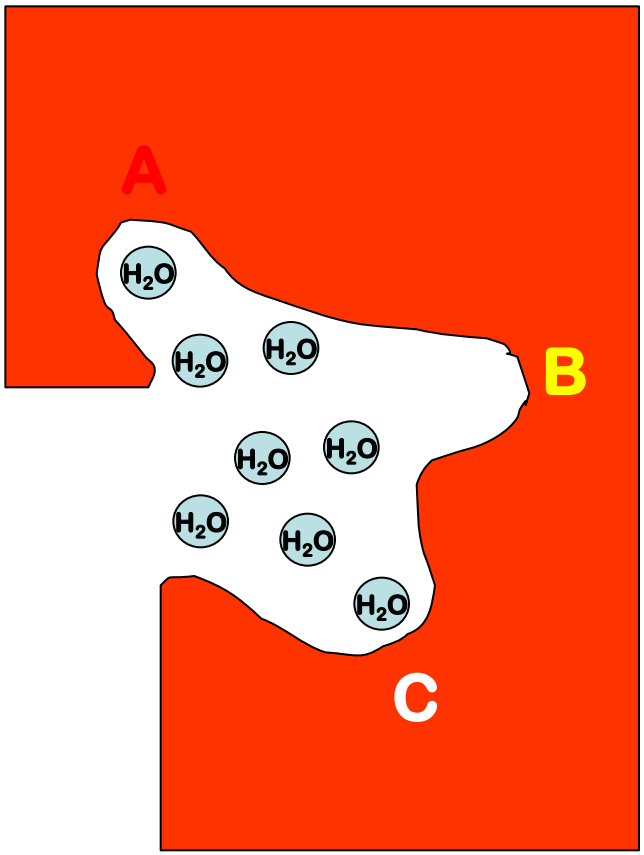


		(kcal/mol)
charge-charge interaction (*ionic bond*):	$-\Delta G^0 \cong$	5 ÷ 10
charge-dipole interaction:	$-\Delta G^0 \cong$	1 ÷ 7
charge-π interaction:	$-\Delta G^0 \cong$	8 ÷ 10
hydrogen bond:	$-\Delta G^0 \cong$	1 ÷ 7
charge transfer interaction:	$-\Delta G^0 \cong$	1 ÷ 6
π-π interaction:	$-\Delta G^0 \cong$	1 ÷ 2
dipole-dipole interaction (van der Waals):	$-\Delta G^0 \cong$	0.5 ÷ 1

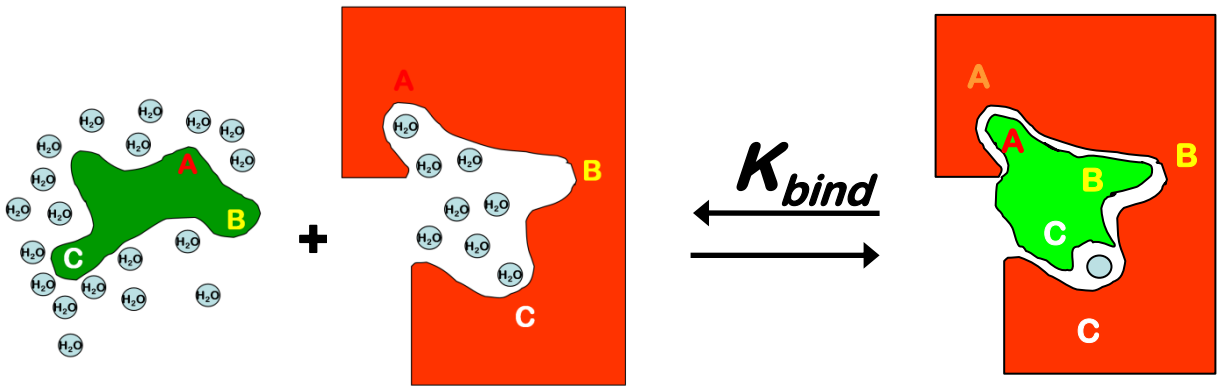
A wonderful lesson from mother nature:







A wonderful lesson from mother nature:

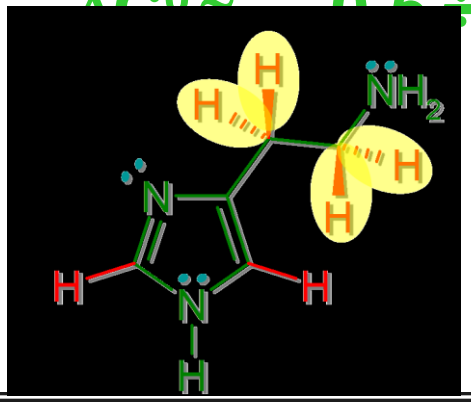


The only interaction that are always able to shift the equilibrium to the right are those vdW.

Even if:

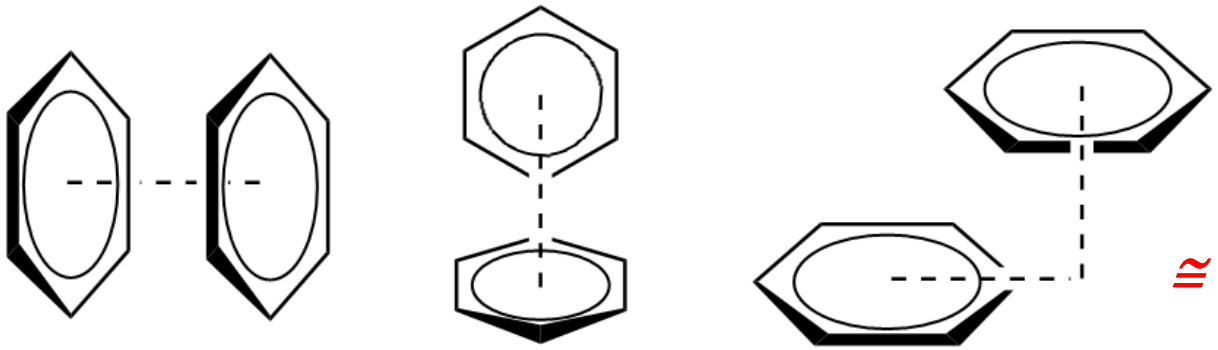
dipole-dipole interaction (van der Waals):

$\Delta G^0 \sim -0.5 \div 1$



<u>remember that the unity is strength!</u>

The mystery of π-π interactions:

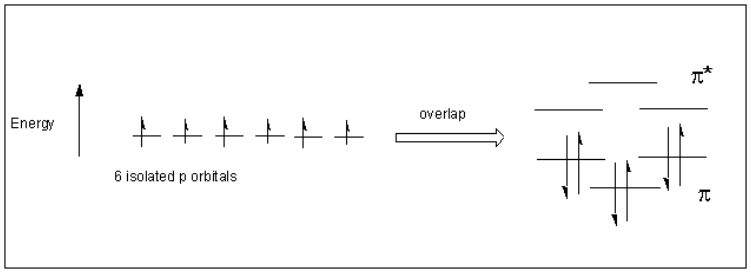


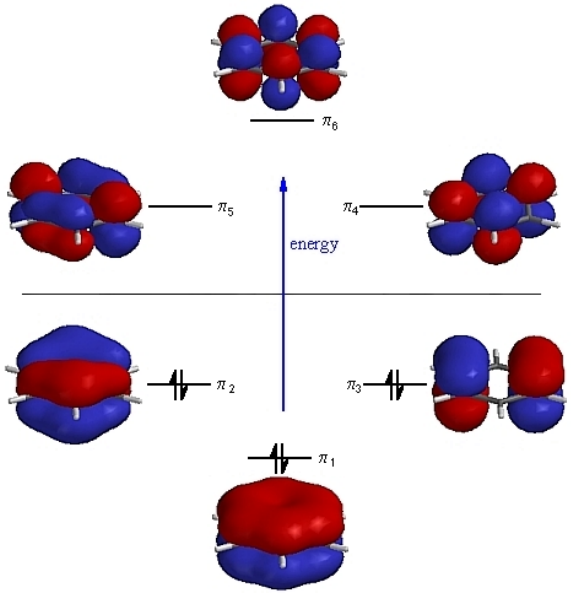
≅4.9 Å

≅-2.5 kcal/mol

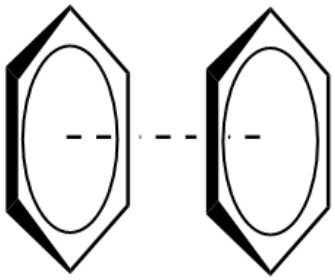
Sandwich | T-shaped | Parallel-dispaced

≅-1.5 kcal/mol



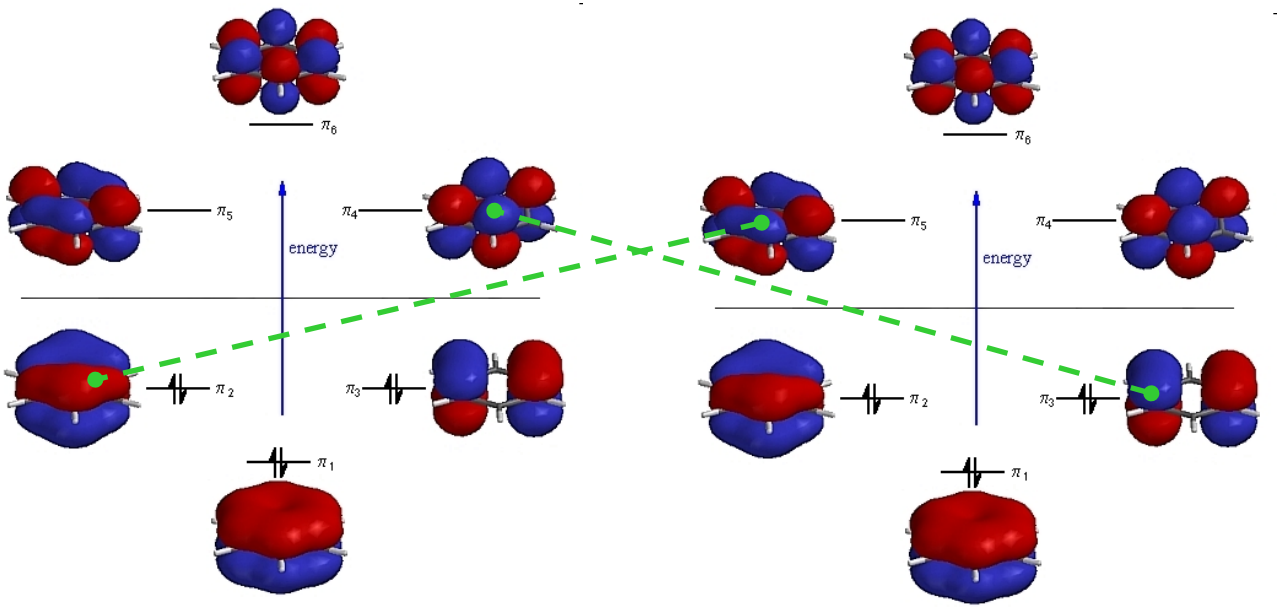


The mystery of π-π interactions:



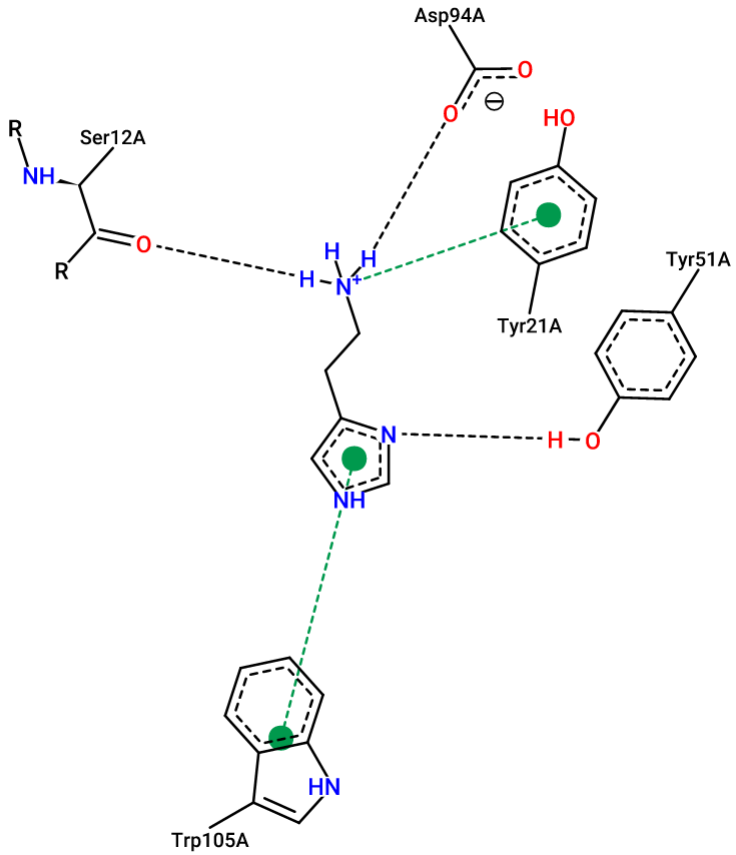
Sandwich

≅ -1.5 kcal/mol



Not only electrostatic moves the molecular world!!

from structure to interaction ..



Journal of
Medicinal
Chemistry
Perspective

d. Chem. **2010,** *53,* 5061–5084 **5061**
DOI: 10.1021/jm100112j

A Medicinal Chemist's Guide to Molecular Interactions

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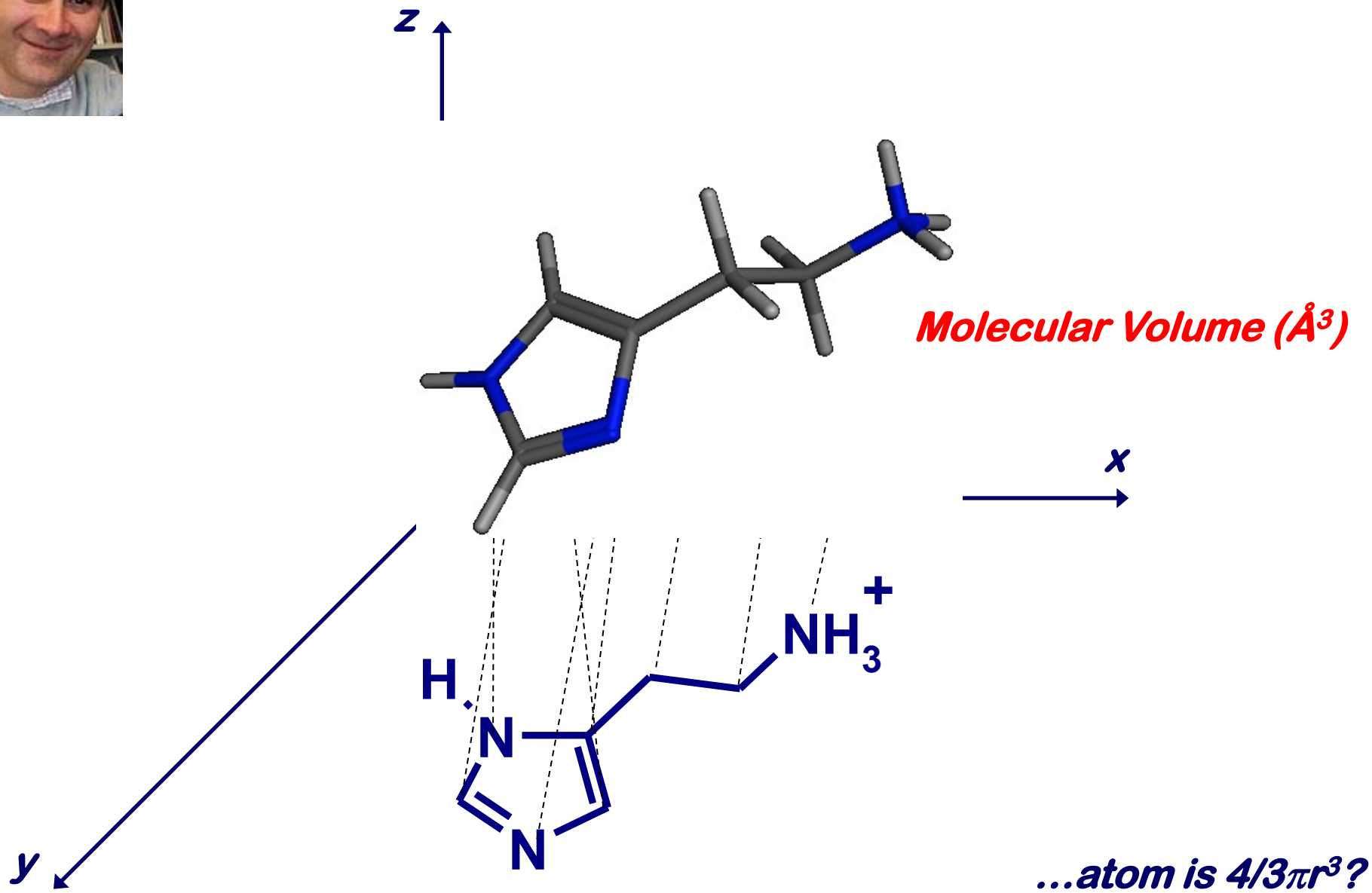
Discovery Chemistry, F. Hoffmann-La Roche AG, CH-4070 Basel, Switzerland

Received January 27, 2010

… a super paper!!!

the shadow of the reality:



Molecular Volume (Å³)

…atom is 4/3πr³?

A quick refresh… atoms present spherical shapes!

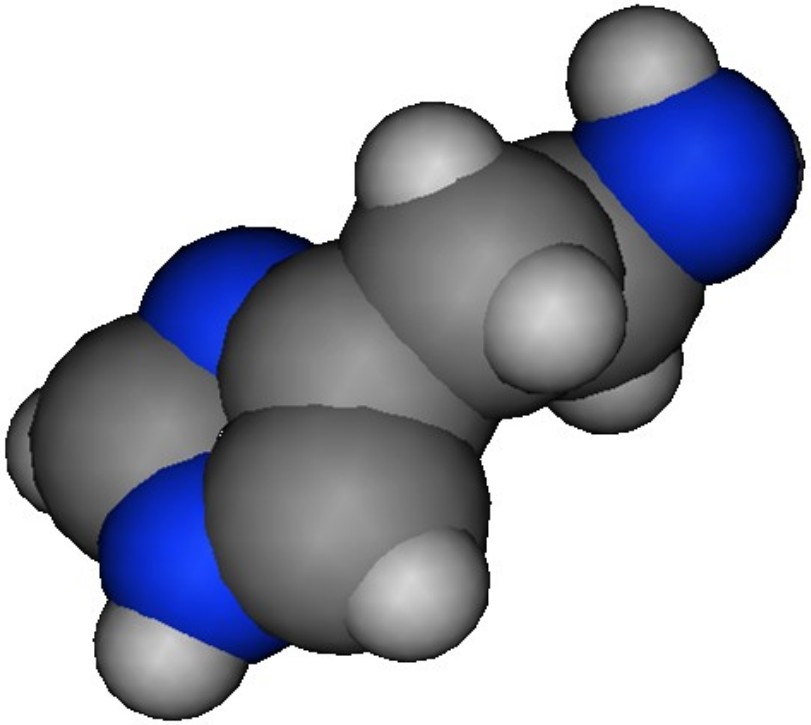
Element	radius (Å)
Hydrogen	1.20
Carbon	1.70
Nitrogen	1.55
Oxygen	1.52
Fluorine	1.47
Phosphorus	1.80
Sulfur	1.80
Chlorine	1.75
Copper	1.4

$$V_{vdW} = \frac{4}{3}\pi \; r_{vdW}^{3}$$

$$r_{vdW} = \sqrt[3]{V_{vdW} \frac{3}{4\pi}}$$

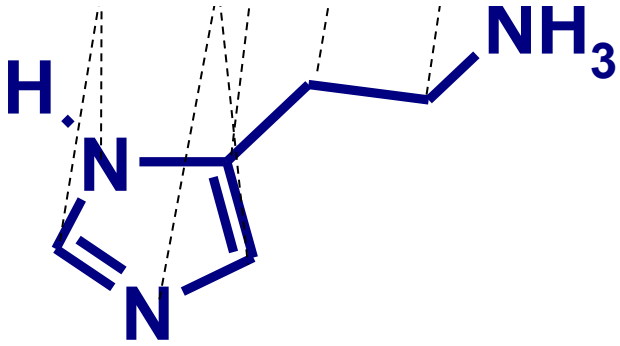
… e voilà!

z



ecular Volume (Å³)

x



y

…atom is 4/3πr³?

At this point measure the molecular size is easy…

Verloop A., Hoogenstraaten W., Tipker J. "Development and application of new steric substituent parameters in drug design." In Drug Design (Ed. Ariëns), vol.7, pp.165-207 (1976), New York: Academic Press.

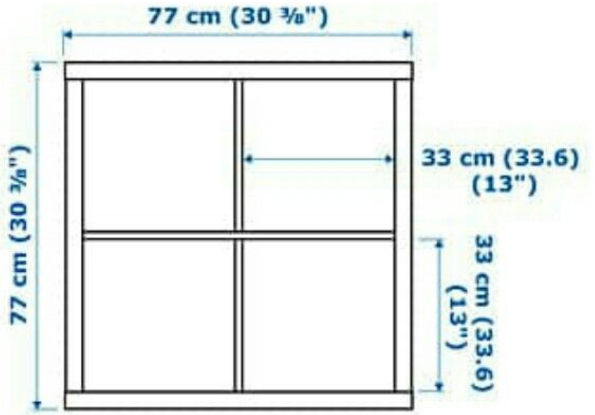
My favorite example:

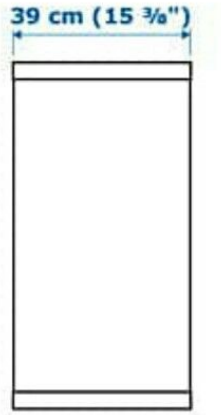
IKEA

CERCA UN PRODOTTO O UN SERVIZIO

NOVITÀ | OFFERTE | PRODOTTI | AMBIENTI | IDEE | RISTORANTE E BOTTEGA | DOVE SIAMO

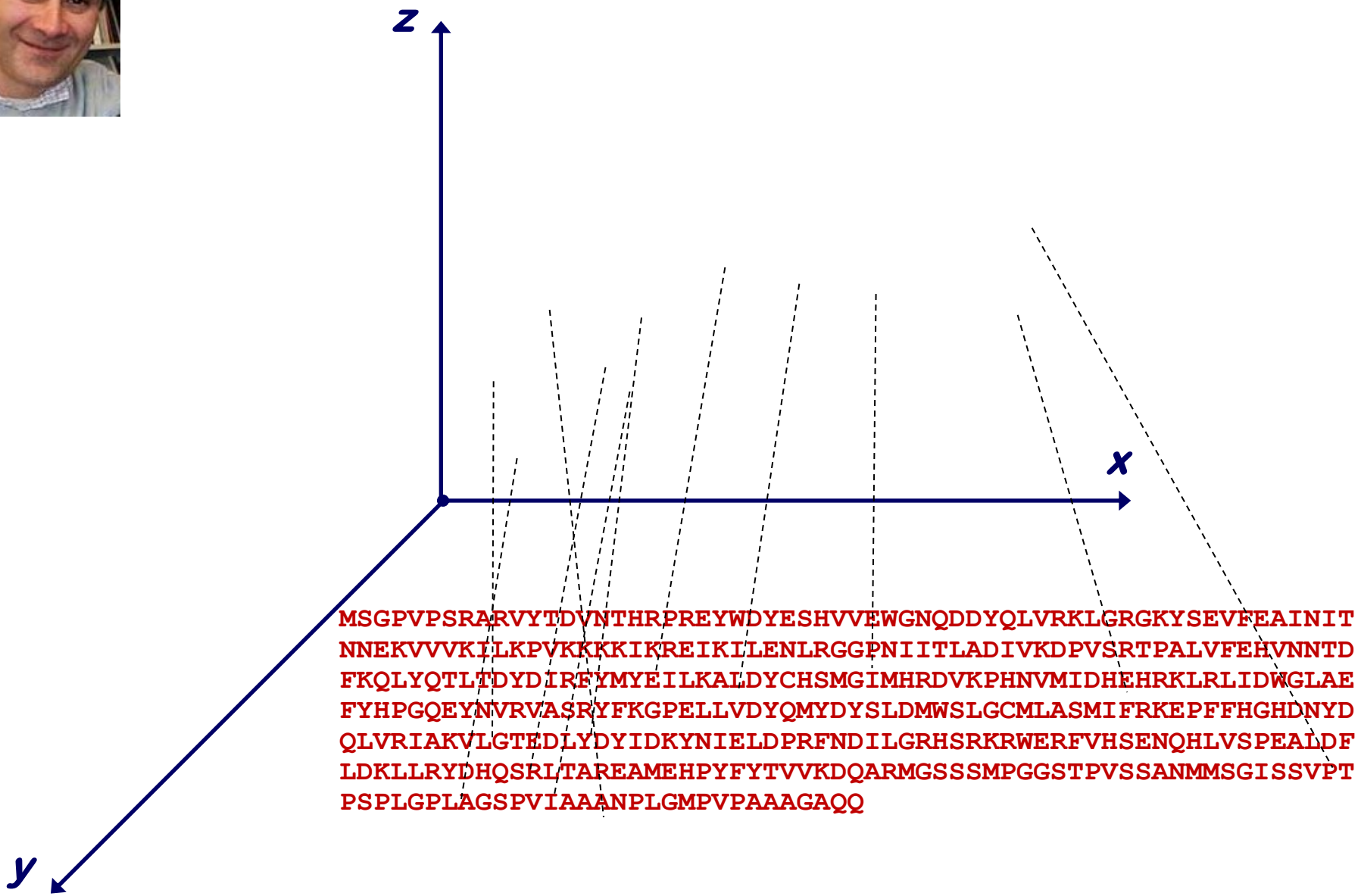
Home / Soggiorno / Scaffali

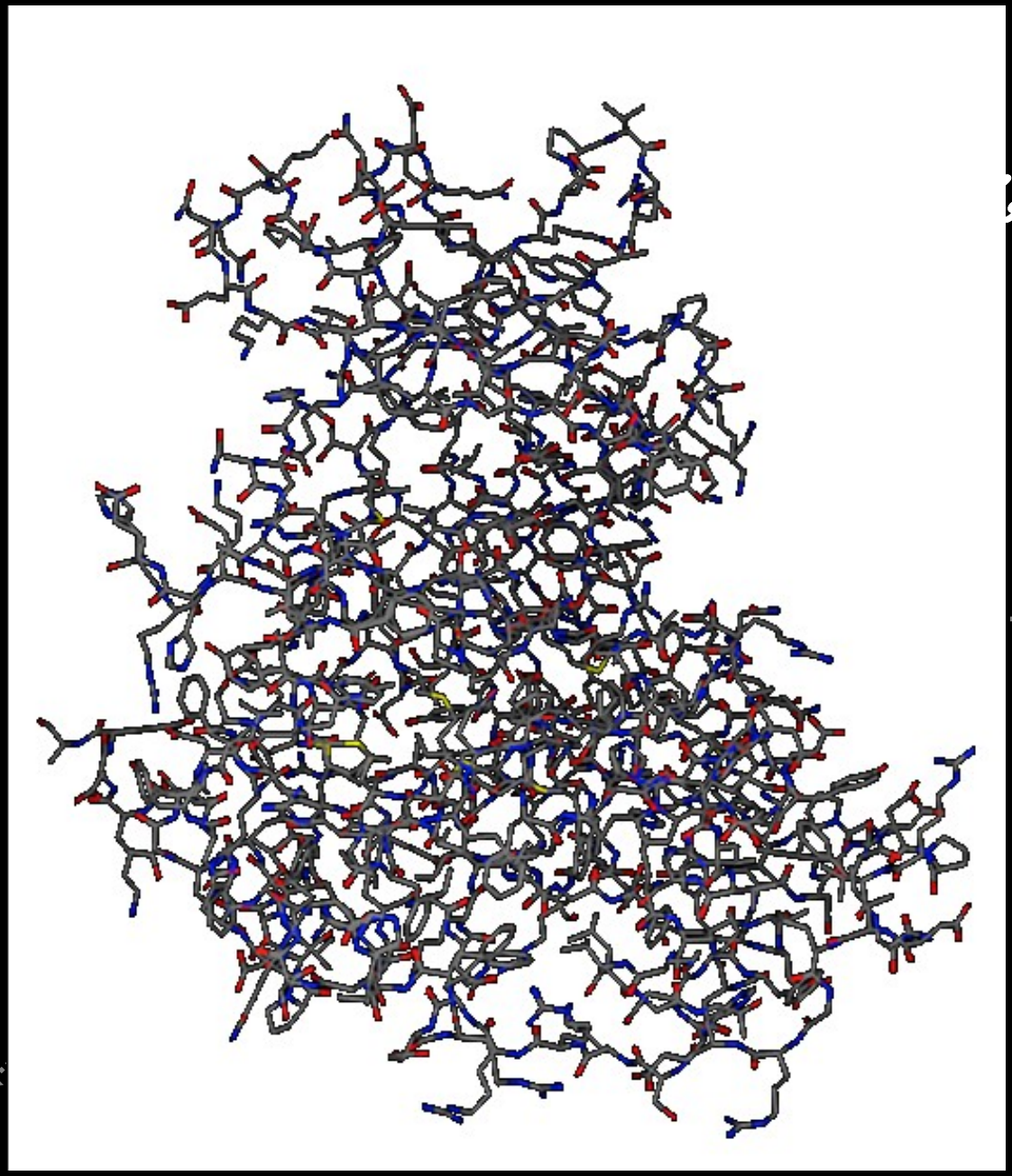


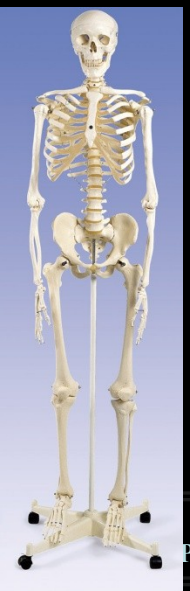


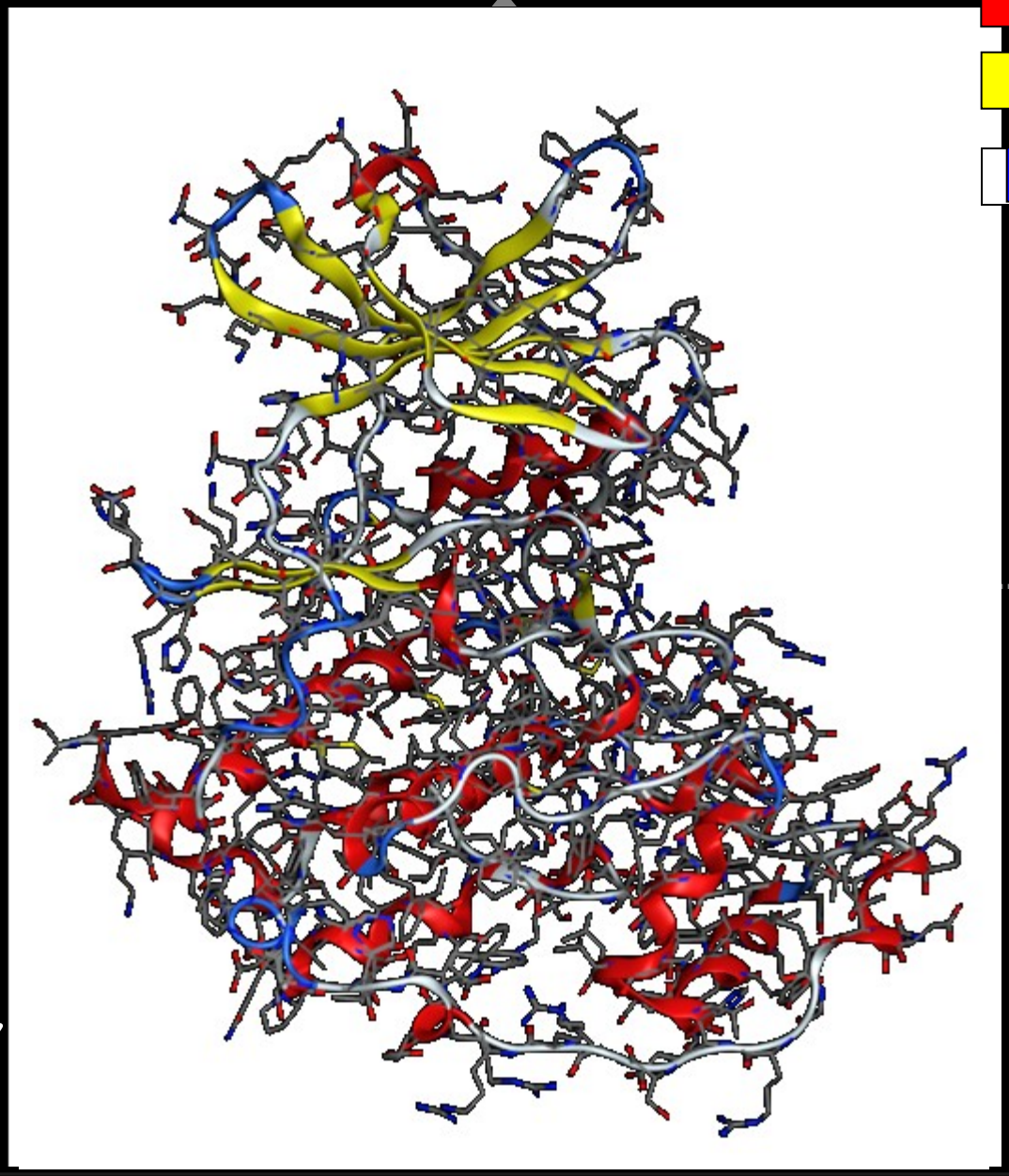
Credits: https://www.ikea.com/it/it/catalog/products/20275814/

… and what about a protein?

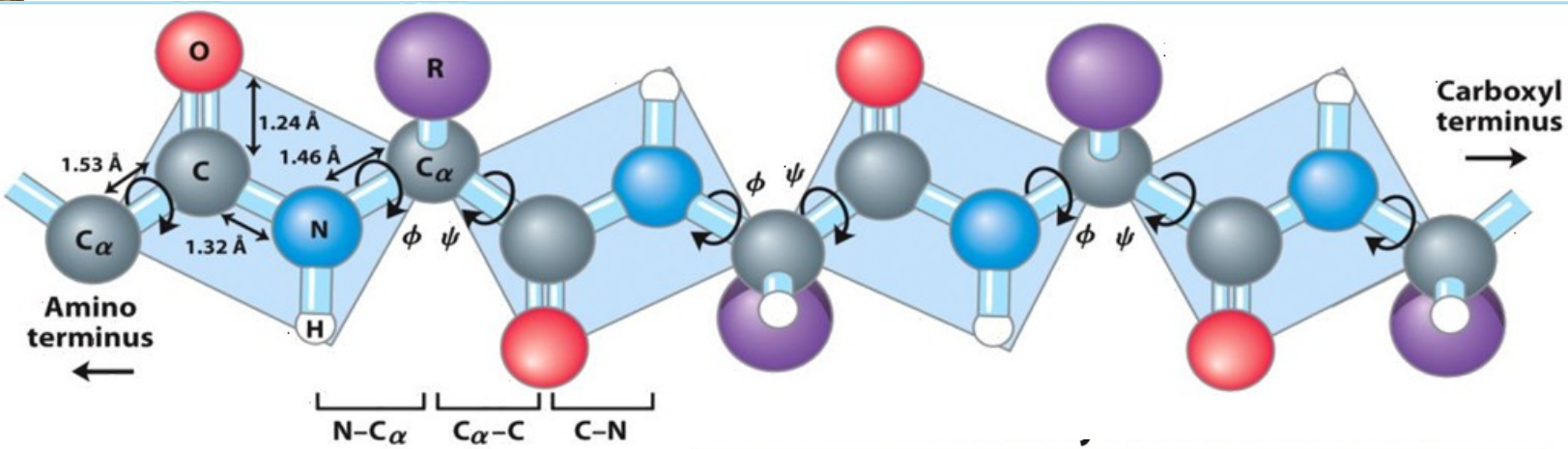


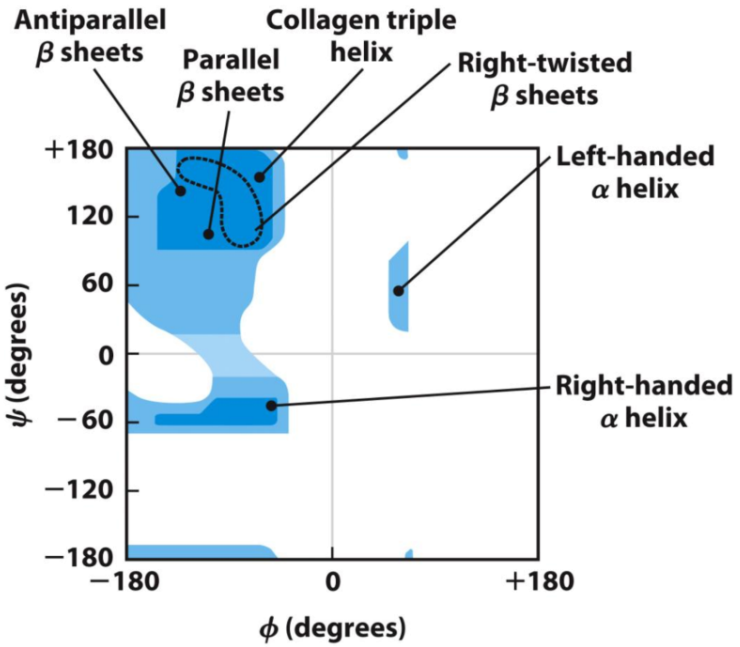






There are some interesting geometrical regularity inside our polymer:



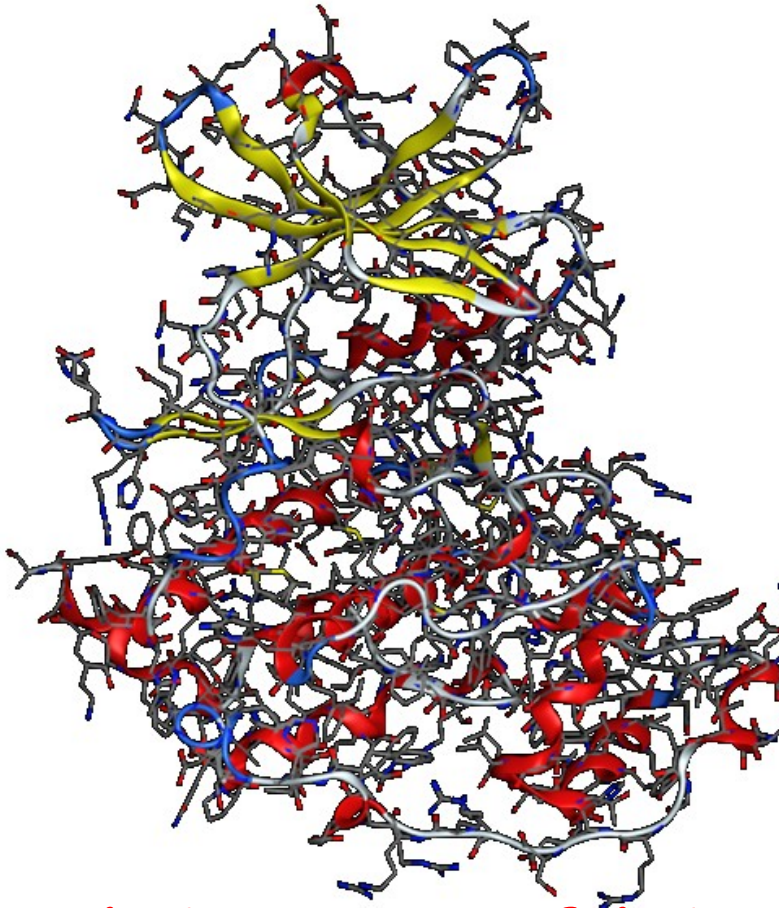


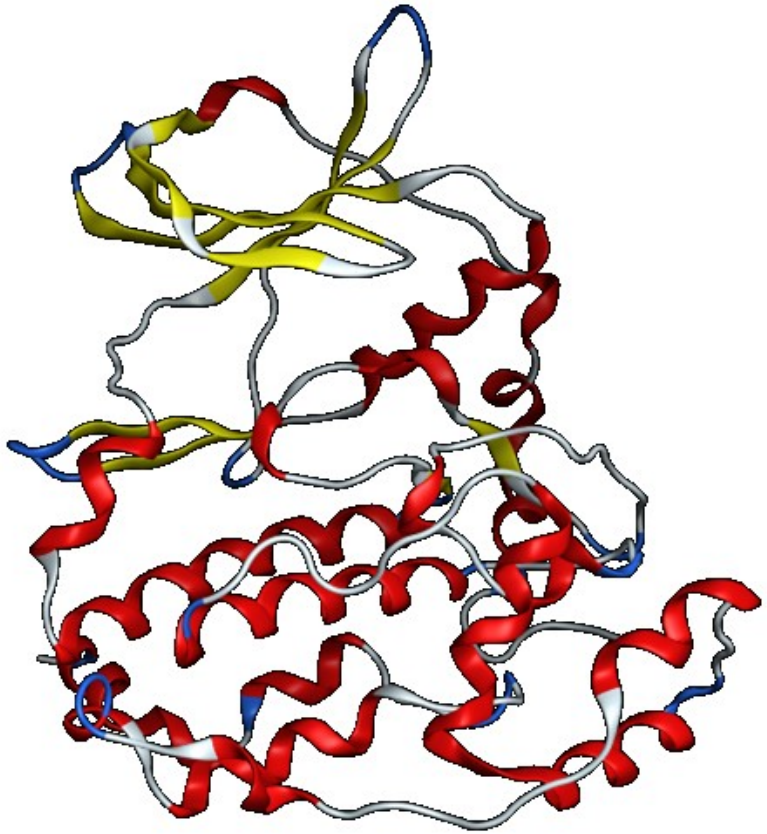
Structure	ϕ	ψ
α Helix	−57°	−47°
β Conformation		
Antiparallel	−139°	+135°
Parallel	−119°	+113°
Collagen triple helix	−51°	+153°
β Turn type I		
i + 1*	−60°	−30°
i + 2*	−90°	0°
β Turn type II		
i + 1	−60°	+120°
i + 2	+80°	0°

Note: In real proteins, the dihedral angles often vary somewhat from these idealized values.

*The i+1 and i+2 angles are those for the second and third amino acid residues in the β turn, respectively.

This is just a useful way to represent geometrical regularity of 3D coordinates and not the real shape of our protein!!!

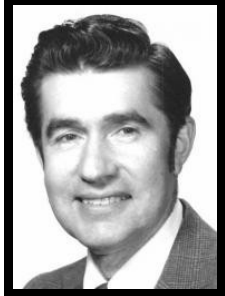




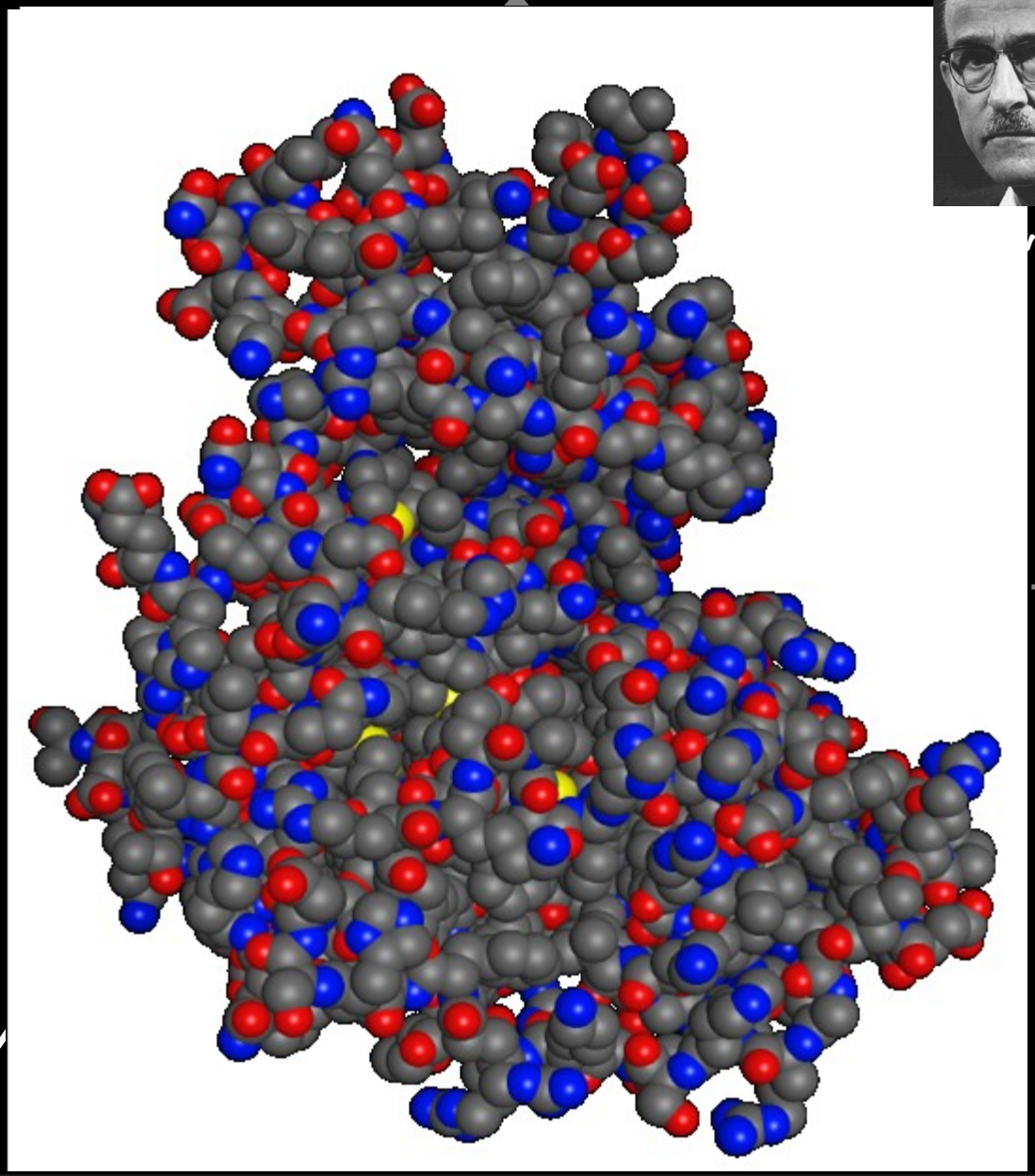
... but very useful to classified protein from a structural point of view!!!

CPK model:

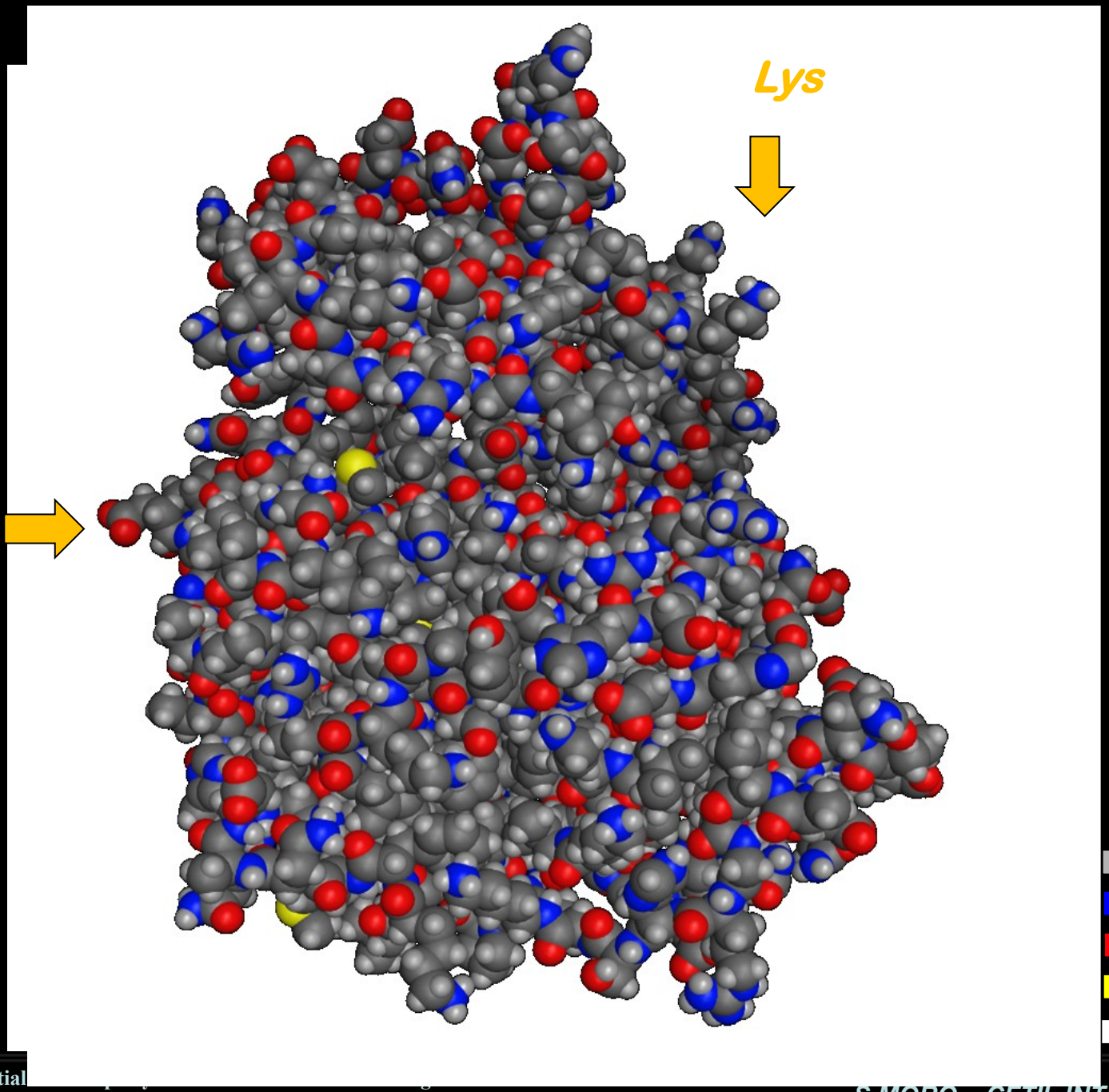
rt Corey Linus Pauling

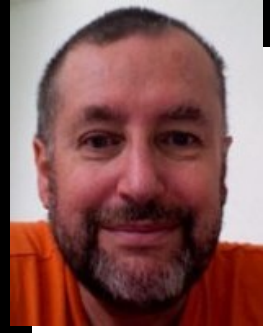


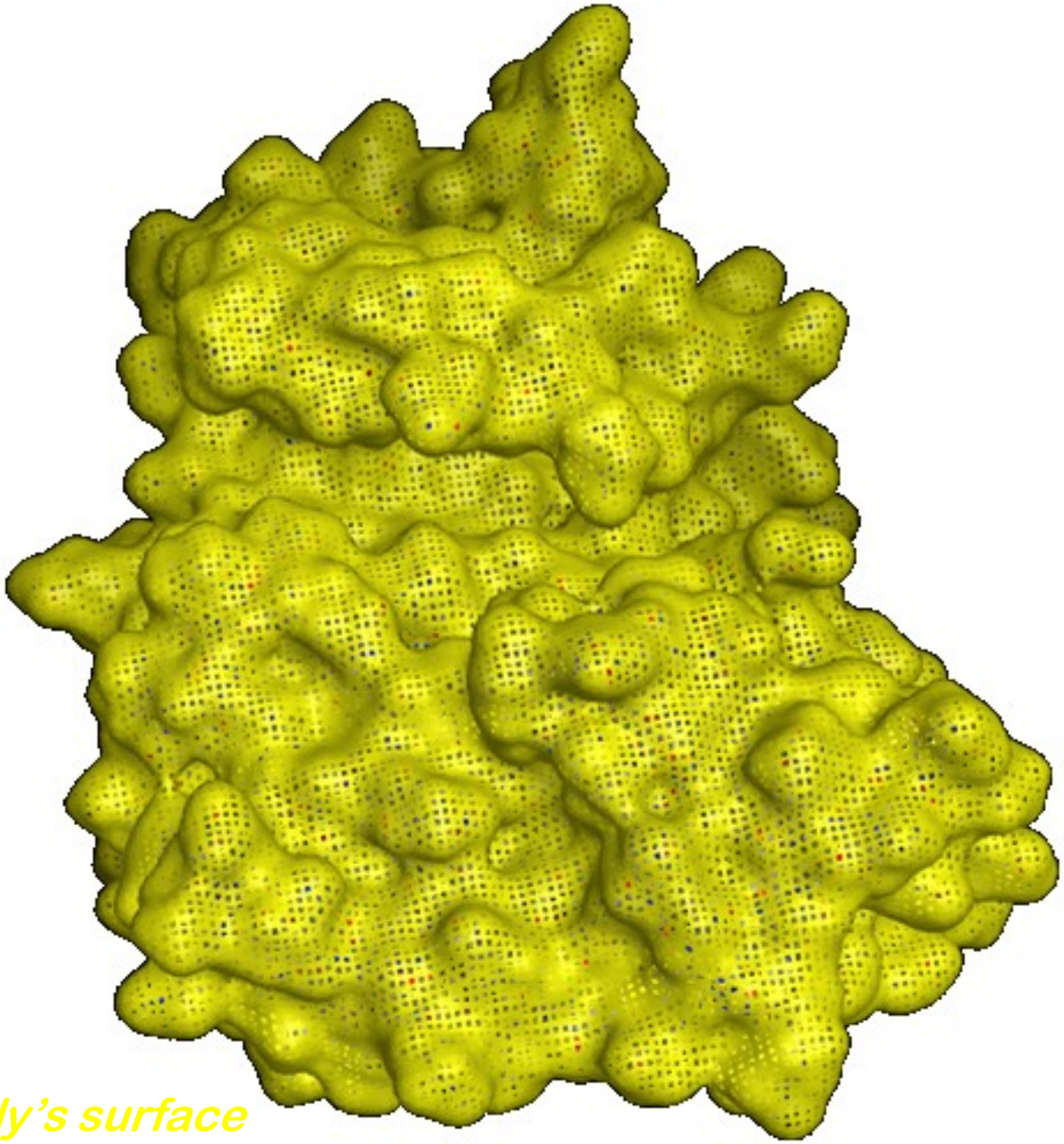
Walter Koltun



= C
= N
= O
= S

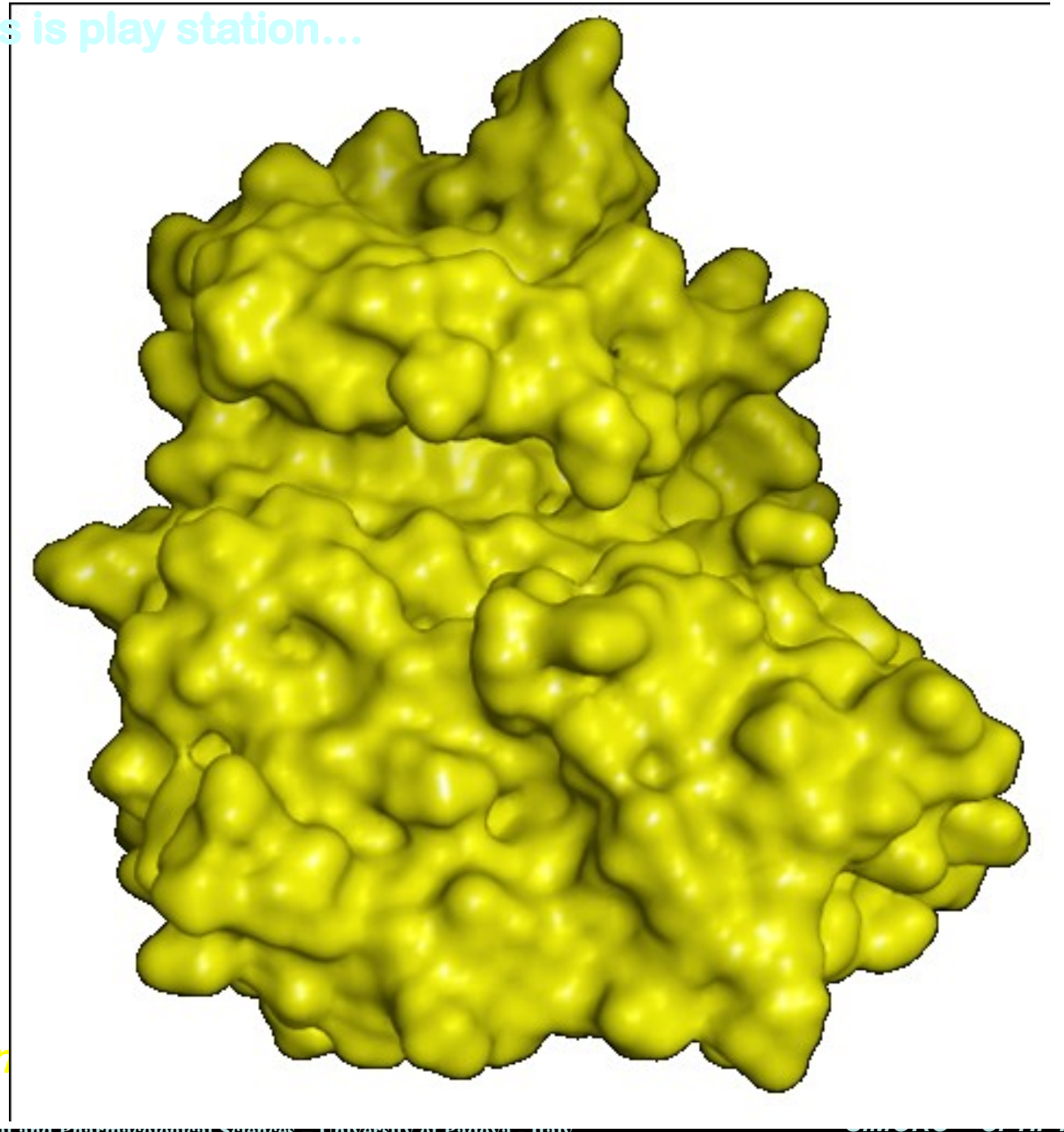

Lys
Glu
= C
= N
= O
= S
= H





Connolly's surface

This is play station…

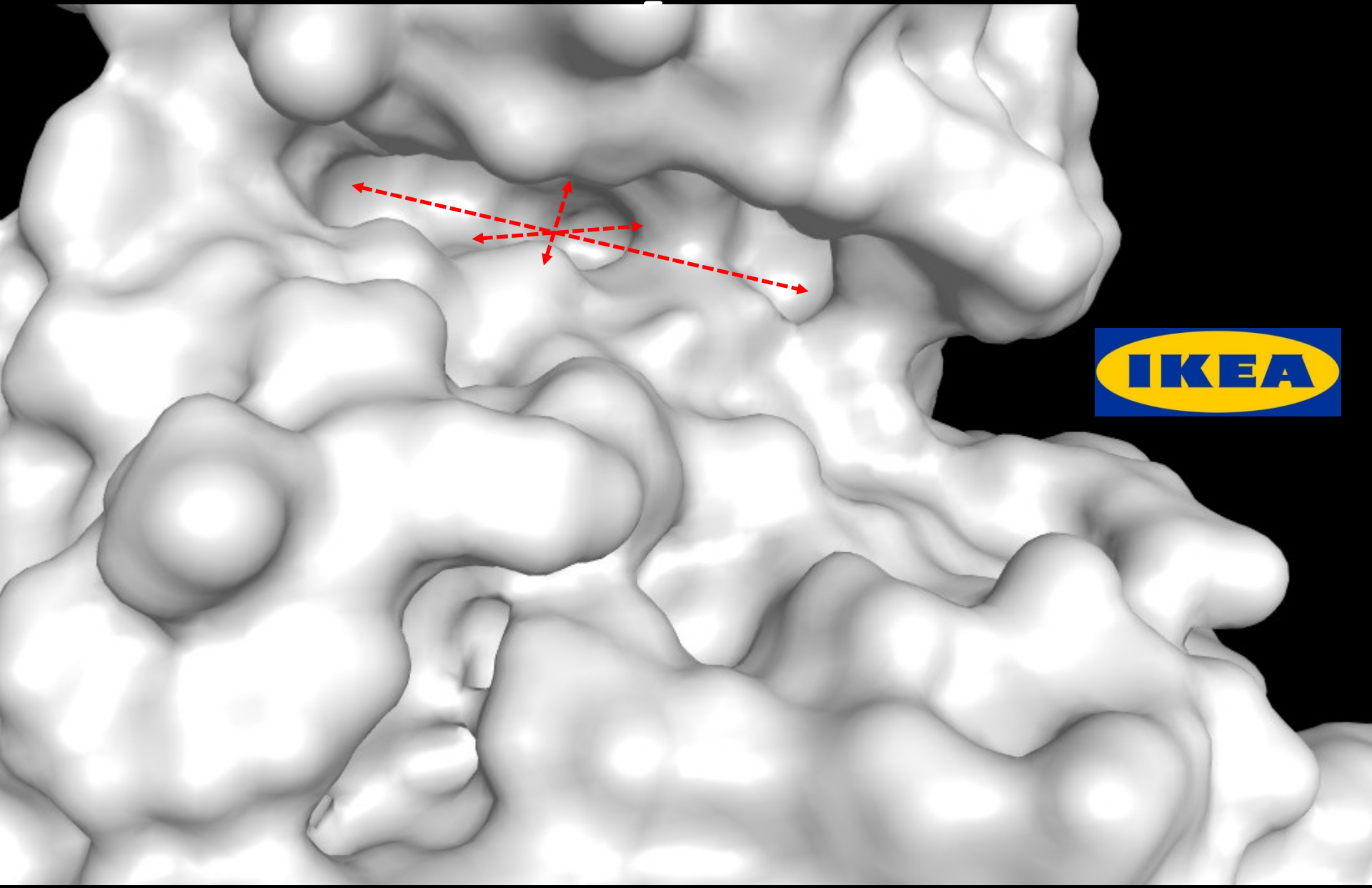


x

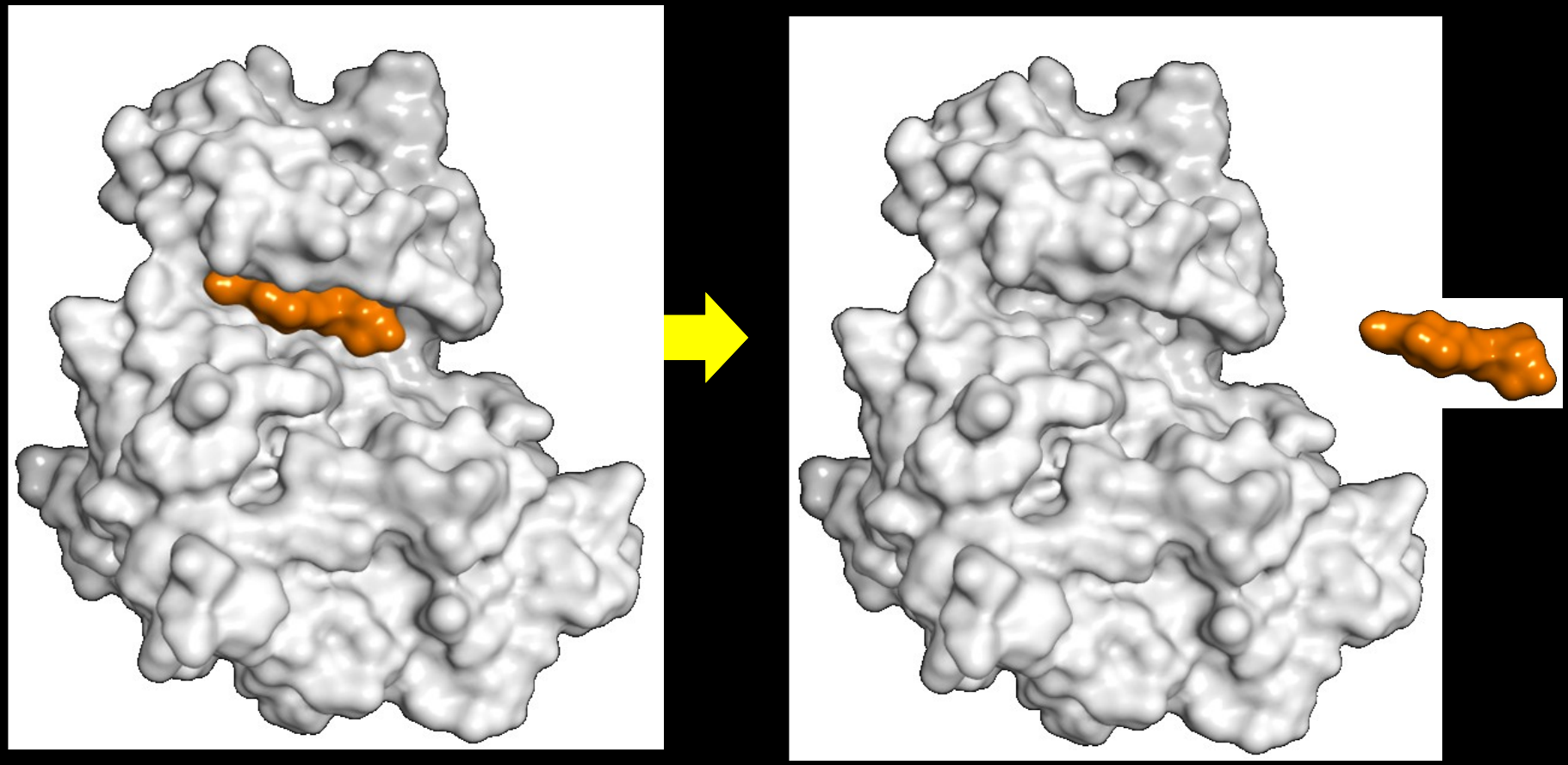
Conn

z

Michael Connolly

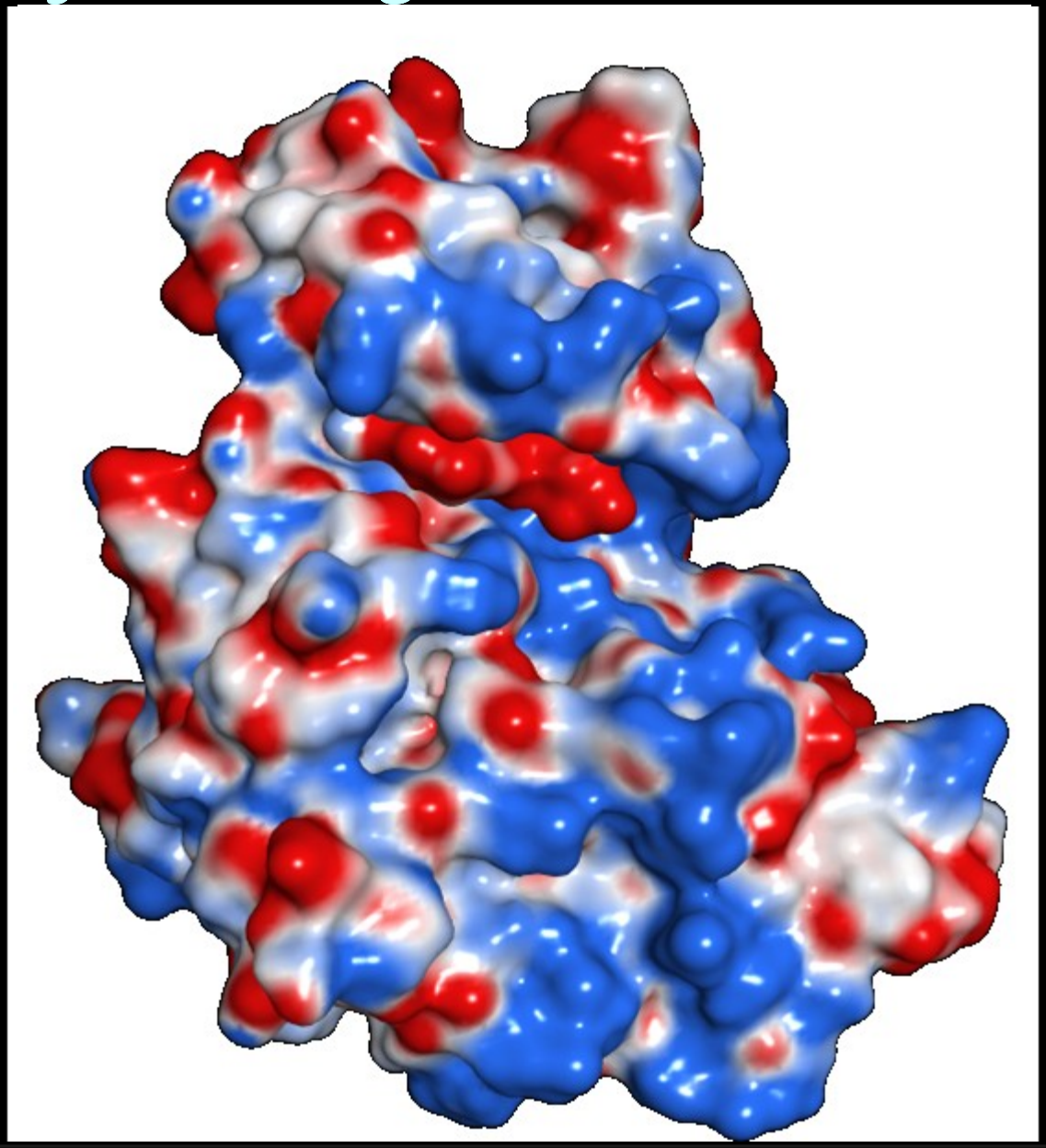


You have now a wonderful tool to estimate the topological complementarity between a cavity and its ligand:



$$Complementarity \propto Vol_{cavity} - Vol_{ligand}$$

… very charming!

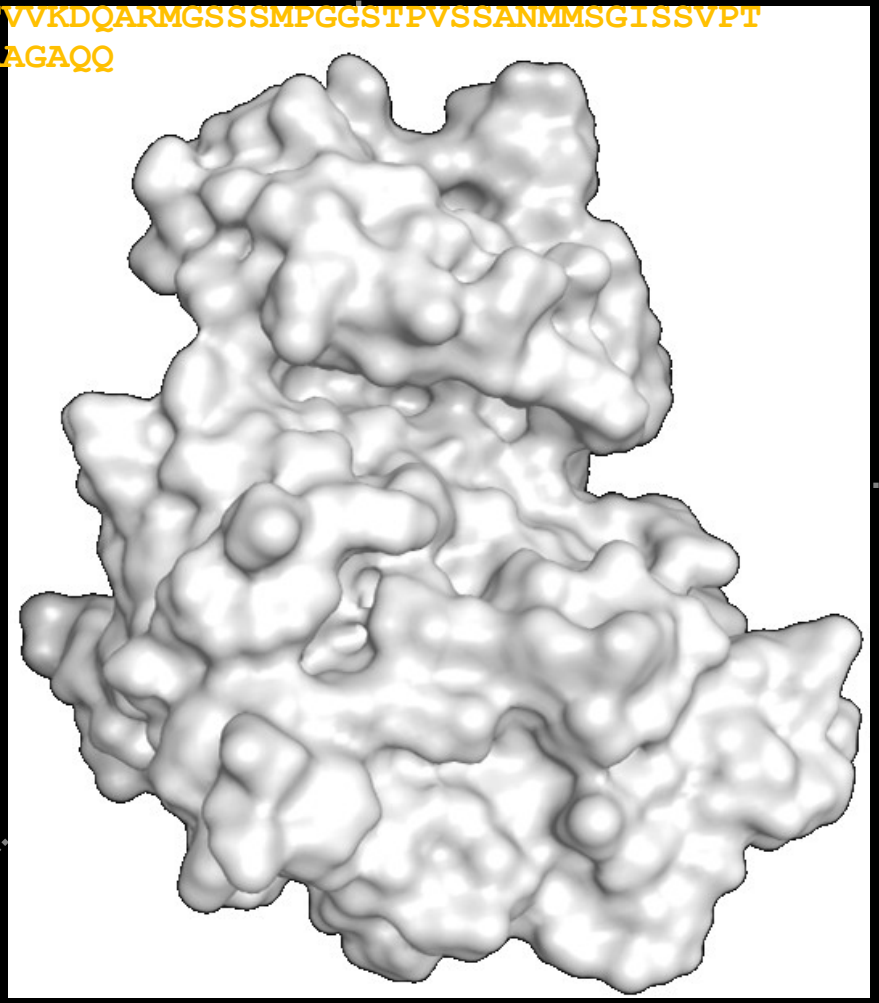


$V_{el} < 0$

$V_{el} = 0$

$V_{el} > 0$

MSGPVPSRARVYTDVNTHRPREYWDYESHVVEWGNQDDYQLVRKLGRGKYSEVFEAINIT
NNEKVVVKILKPVKKKKIKREIKILENLRGGPNIITLADIVKDPVSRTPALVFEHVNNTD
FKQLYQTLTDYDIRFYMYEILKALDYCHSMGIMHRDVKPHNVMIDHEHRKLRLIDWGLAE
FYHPGQEYNVRVASRYFKGPELLVDYQMYDYSLDMWSLGCMLASMIFRKEPFFHGHDNYD
QLVRIAKVLGTEDLYDYIDKYNIELDPRFNDILGRHSRKRWERFVHSENQHLVSPEALDF
LDKLLRYDHQSRLTAREAMEHPYFYTVVKDQARMGSSSMPGGSTPVSSANMMSGISSVPT
PSPLGPLAGSPVIAAANPLGMPVPAAAGAQQ



From sequence to topology… from topology to function

Here is my first favorite example of PD concept:

Nanor

Chimic

Chemo

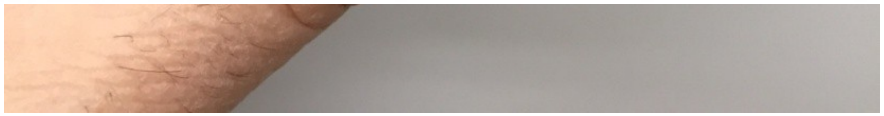
Tossico

(Maste

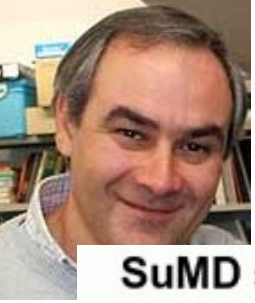
Master

MMS

oculus



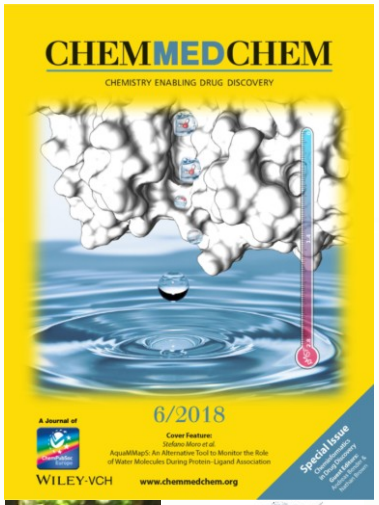
MMS Lab (2015): 3D printed model of the human A2A adenosine receptor co-crystallized its antagonist ZM 241385 (PDB entry: 4EIY)



… and with some of you in a couple of years:

SuMD simulation time: 0.01 ns

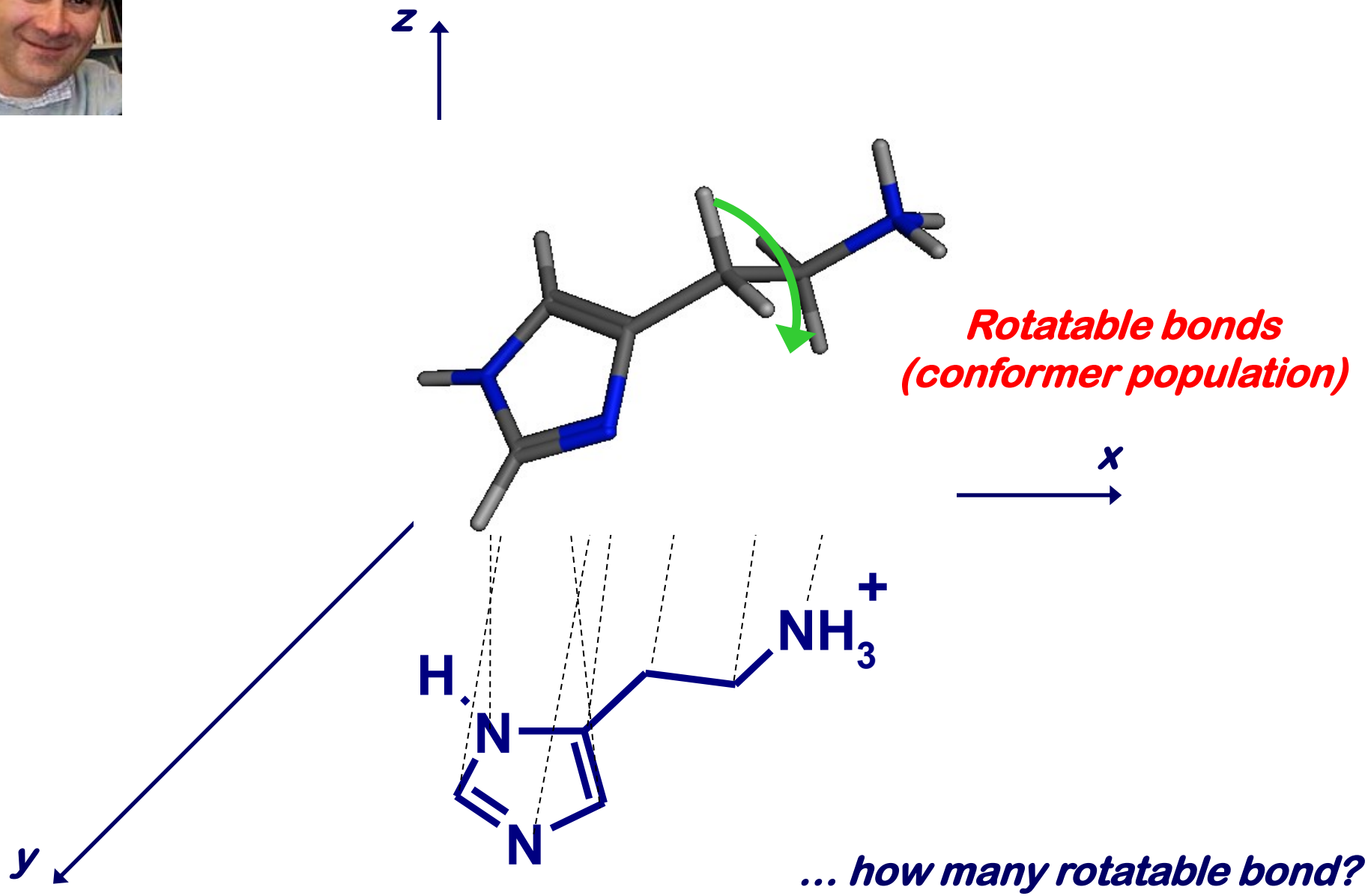
MMS
mms.dsfarm.unipd.it



Cuzzolin A, Deganutti G, Salmaso V, Sturlese M, Moro S. "AquaMMapS: an alternative tool to monitor the role of water molecules during protein-ligand association." ChemMedChem. 1, 1-13 (2018)

G. Deganutti *A. Cuzzolin*

the shadow of the reality:

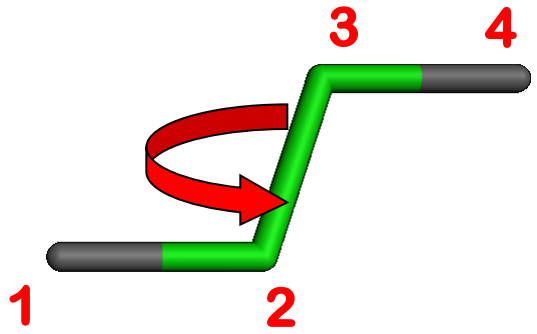


Rotatable bonds (conformer population)

… how many rotatable bond?

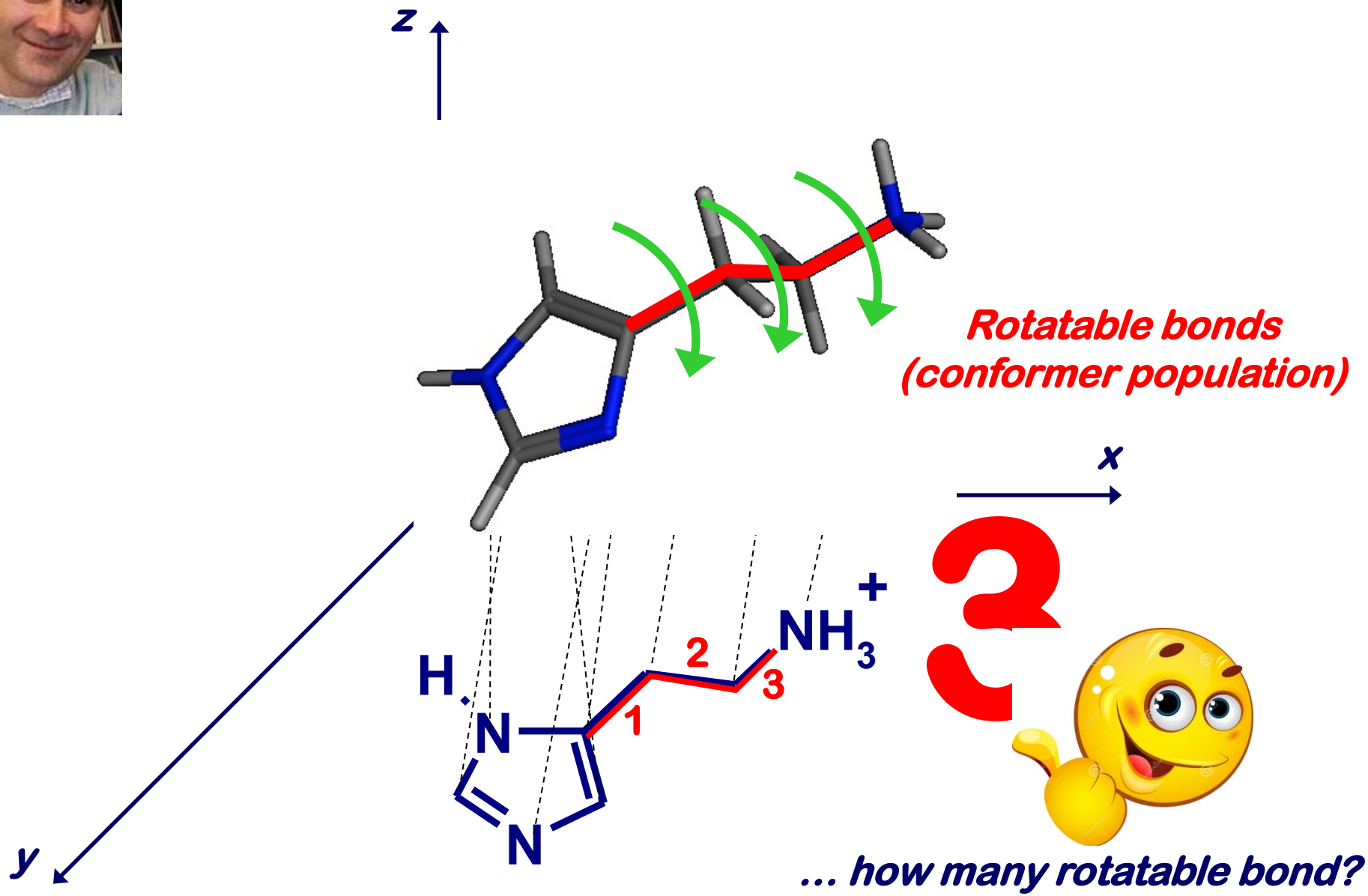
An easy way to determine *molecular rigidity*:

A ***rotatable bond*** is defined as any single non-ring bond, attached to a non-terminal, non-hydrogen atom. *Amide C-N bonds are not counted because of their high barrier to rotation.*



… and it is easily countable!!!

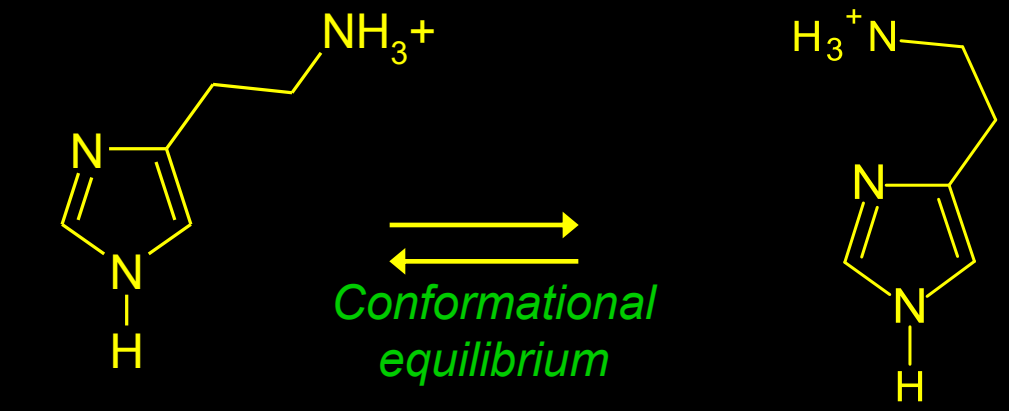
the shadow of the reality:

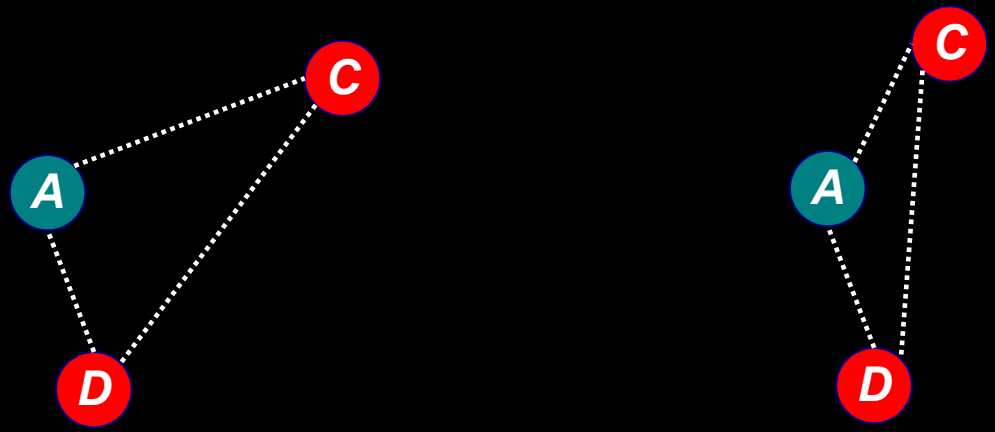


Rotatable bonds (conformer population)

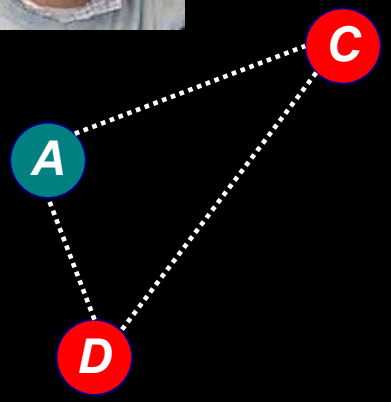
… how many rotatable bond?

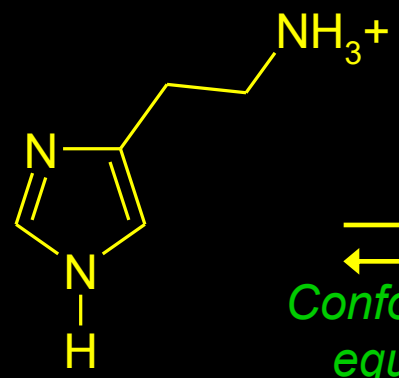
and this incredible consequence:



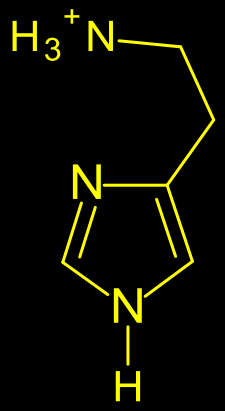


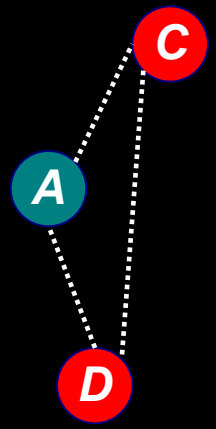
and the story is going on…



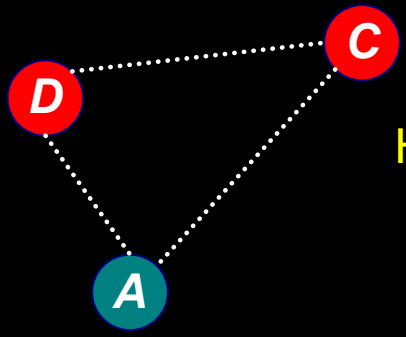


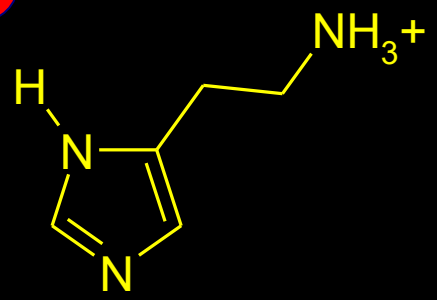
Conformational equilibrium





Tautomeric equilibrium



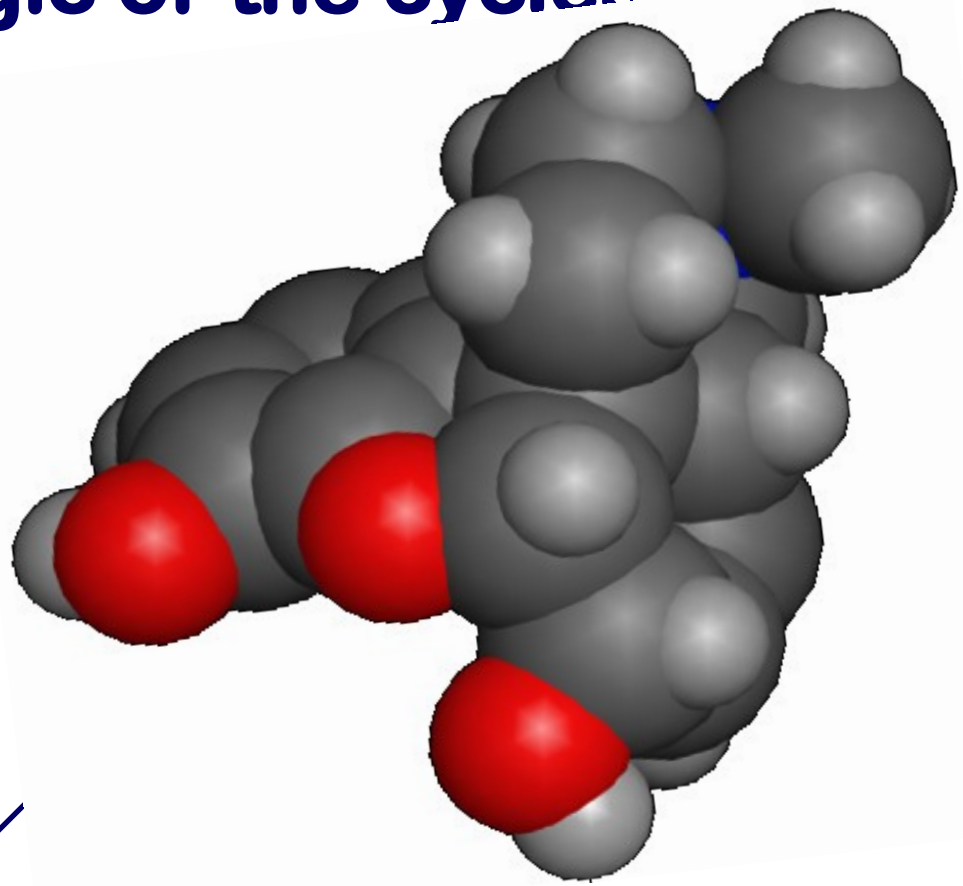


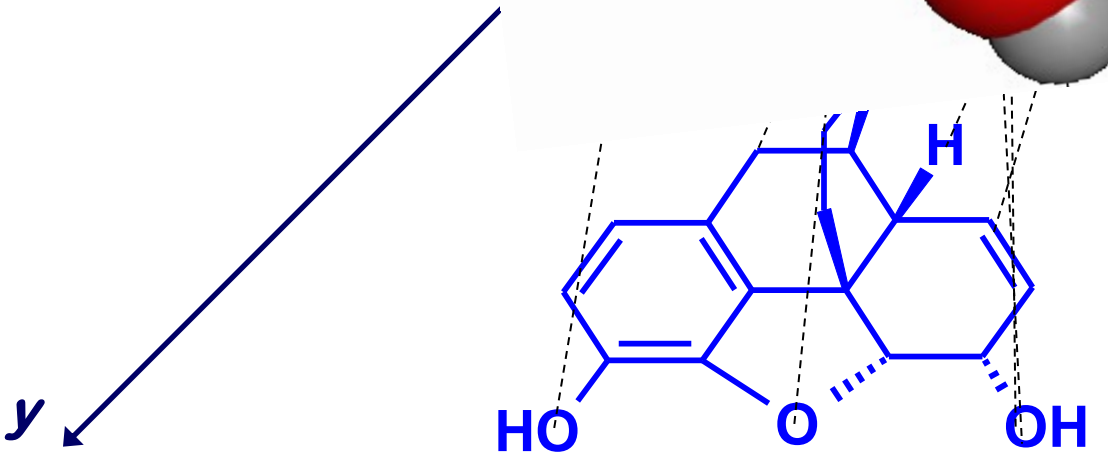
Do you remember these two concepts:

Stability *as a measure of the geometrical deformability of an object;*

Rigidity *as a measure of the reduction degree of the geometrical deformability of an object.*

the magic of the cycles!

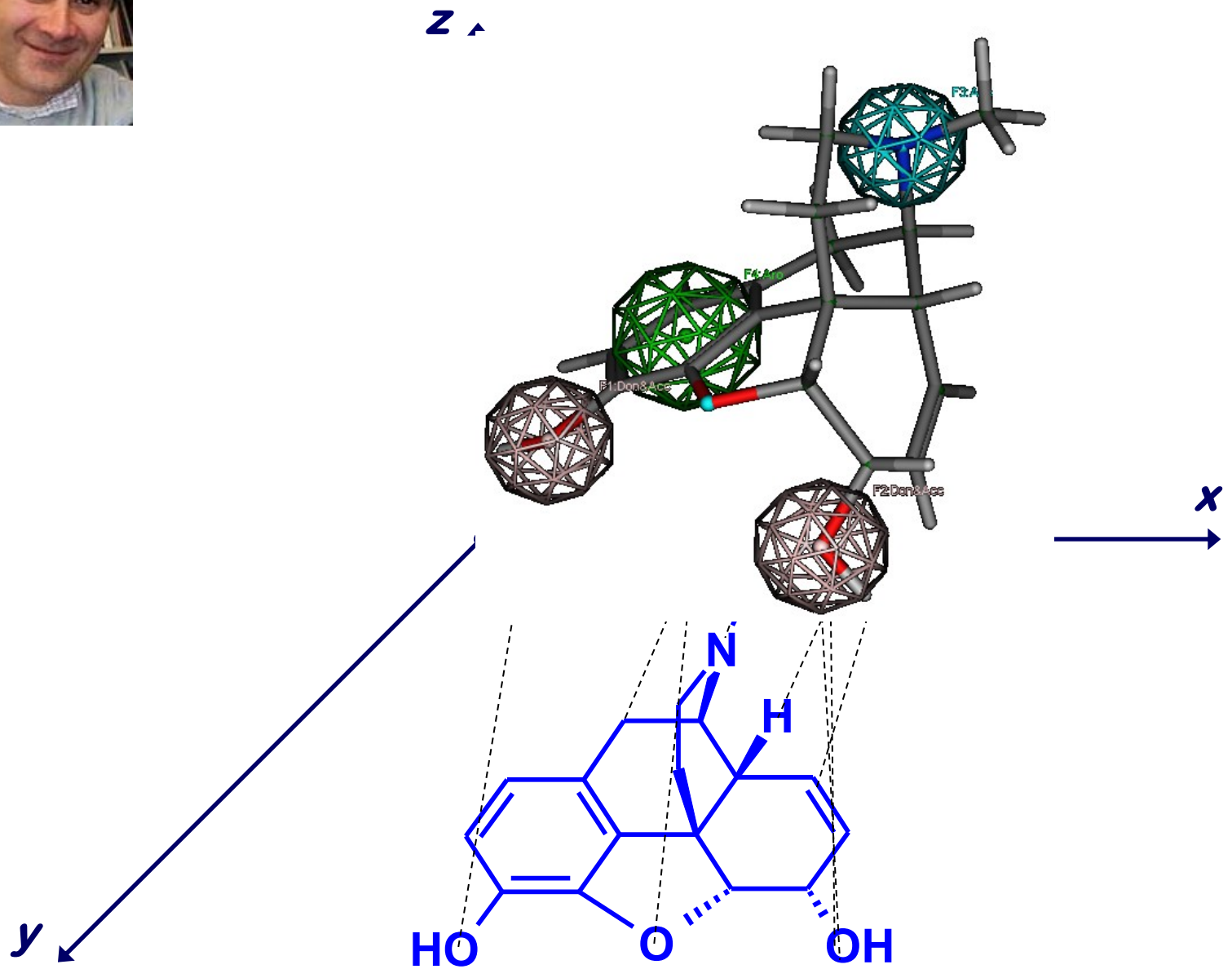




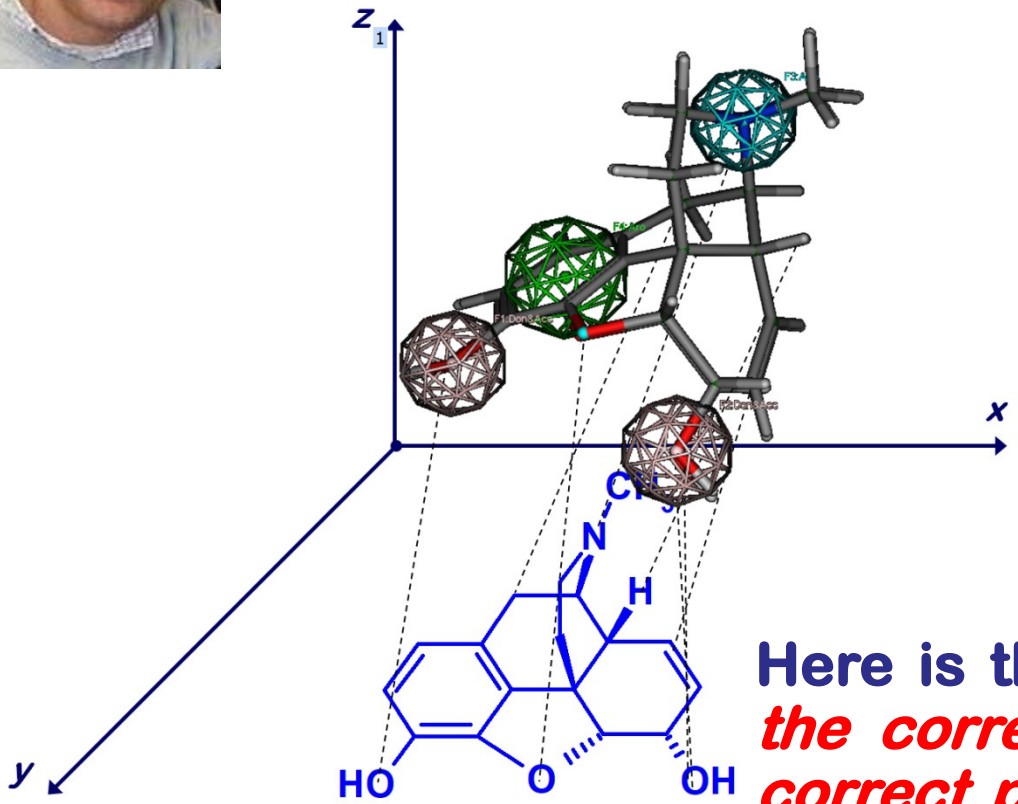
y

… how many rotatable bond?

the magic of the cycles!

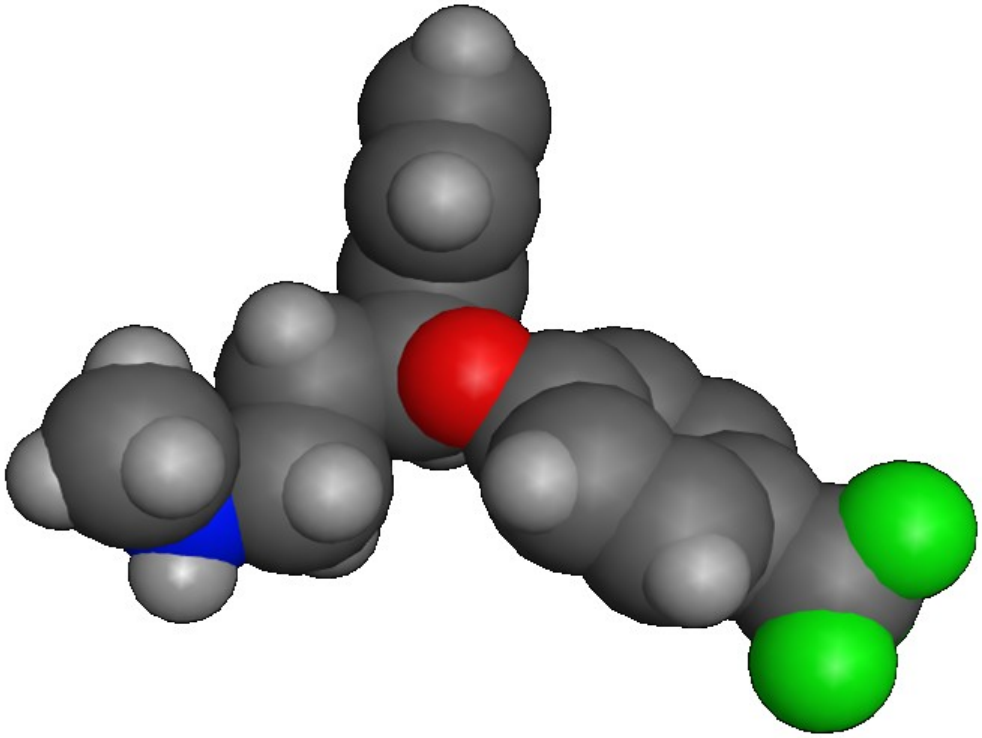


the magic of the cycles!



Here is the magic of cycles: ***to place the correct functional groups, in the correct position in space for the time necessary to maximize the effect of the complementarity between the ligand and its recognition cavity (activity)***

Can we try again our little experiment?



1. Chemical class;
2. Functional groups;
3. Possible interaction scheme;
4. Guess pKa value;
5. Number of rotatable bonds;
6. Tautomers;
7. Chiral centers;
8. Chemical/enzinatic reactivity;
9. …

1. Do you have 3D guess?

but we will never forget:

PHARMACODYNAMIC (PD) PROFILE

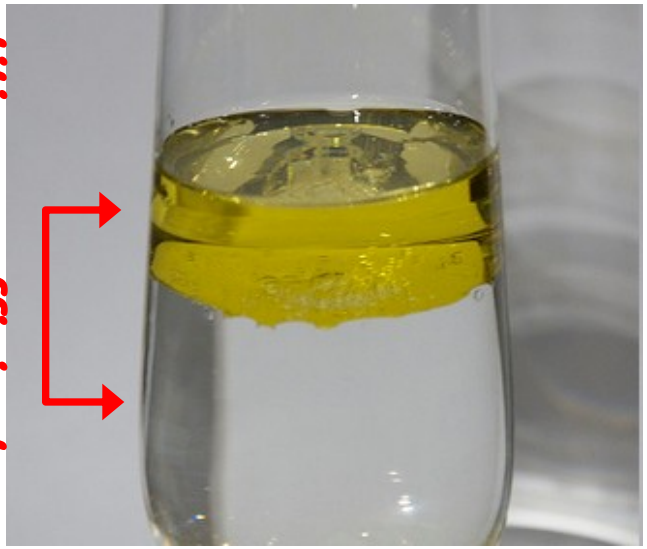
the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure.

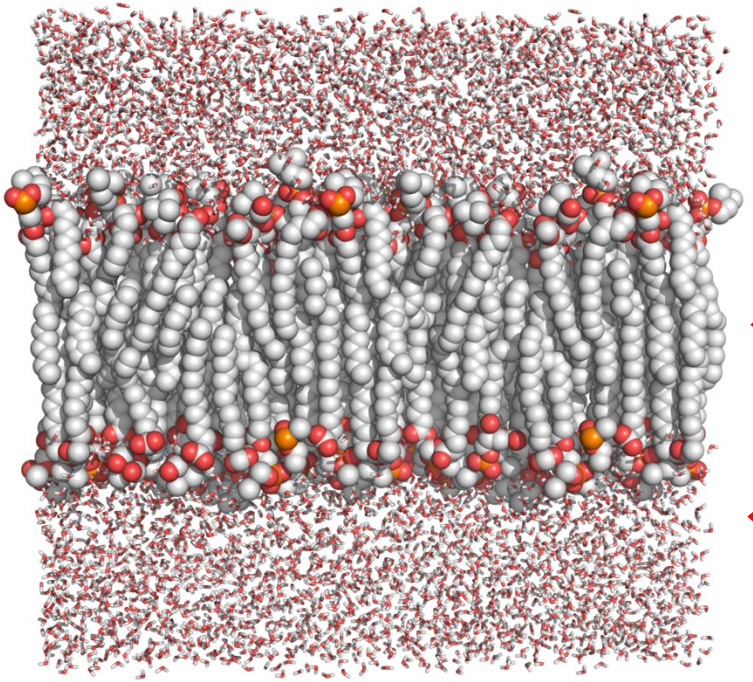
PHARMACOKINETIC (PK)/TOX PROFILE

The study of the process by which a drug is absorbed (A), distributed (D), metabolized (M), and eliminated (E) by the body.

FORMULATION PROFILE

But you don't find a wonderful analogy?

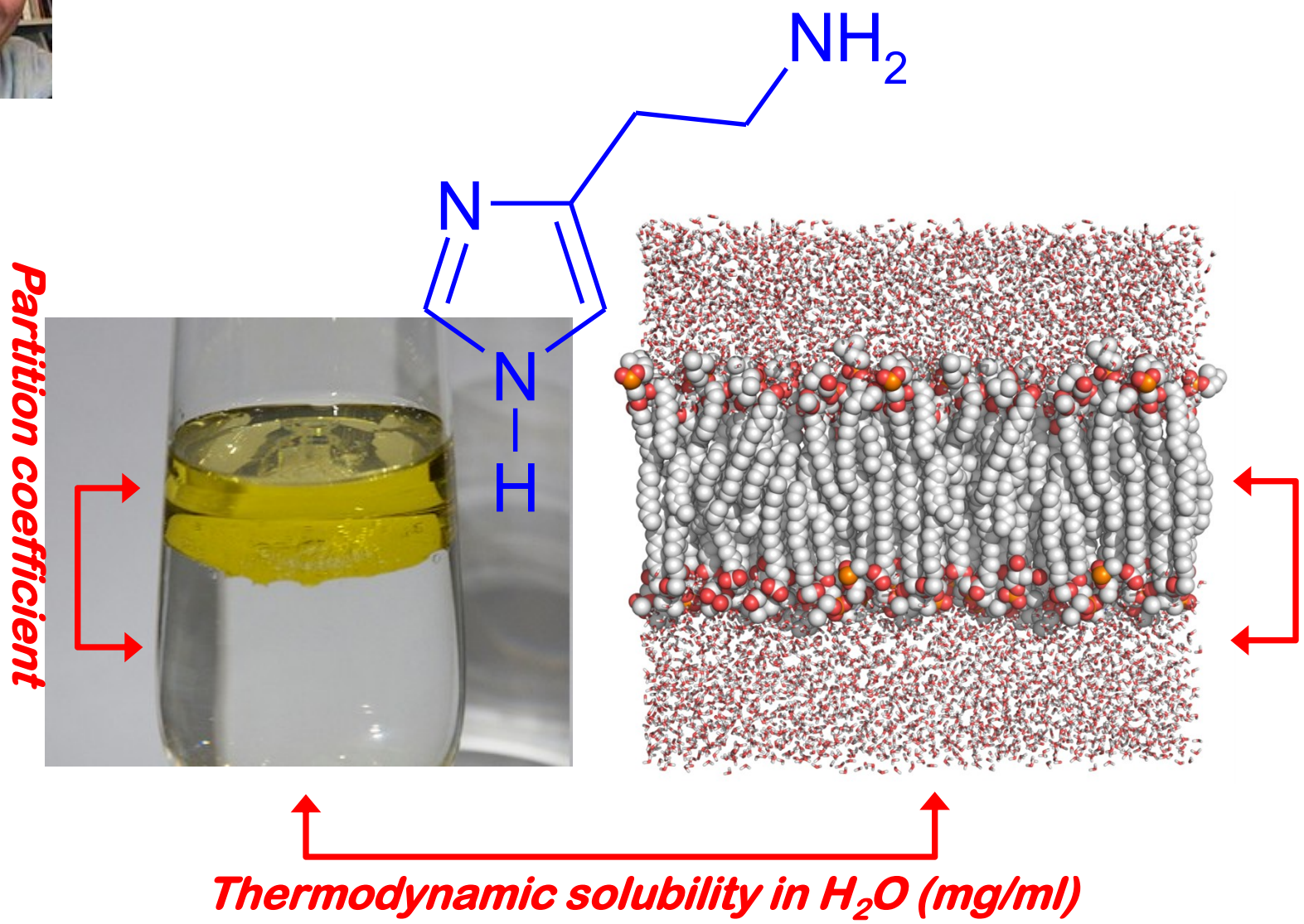




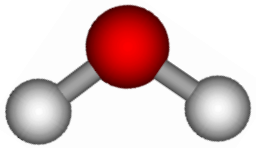
Partition coefficient

Thermodynamic solubility in H_2O (mg/ml)

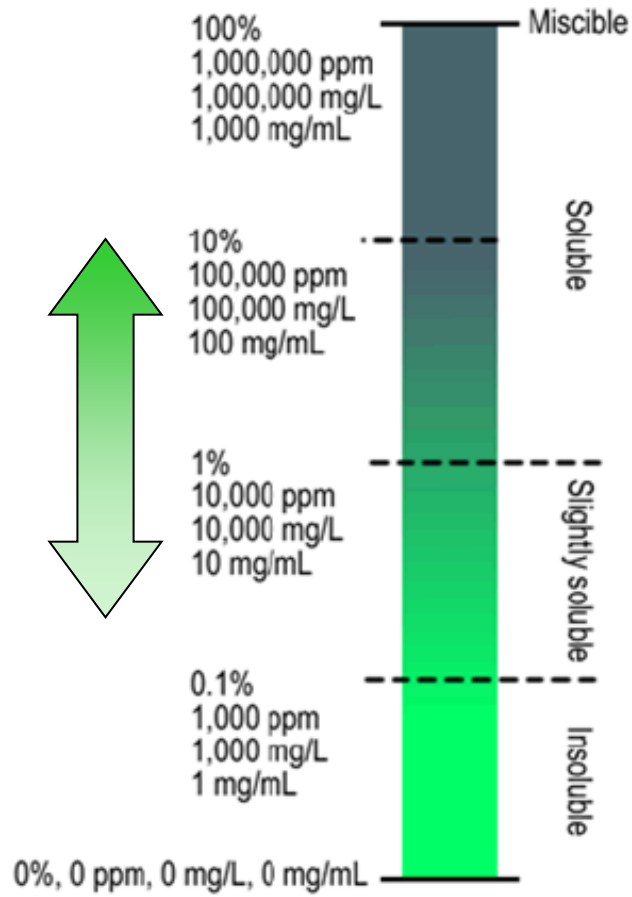
But where are written these properties?



Solubility in



" corpora non agunt nisi soluta "



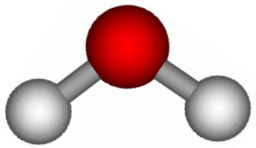
Chemical factors influencing solubility in H_2O:

***presence of ionisable groups** (depending upon pH)*

***hydrogen bonds** (donors/acceptors)*

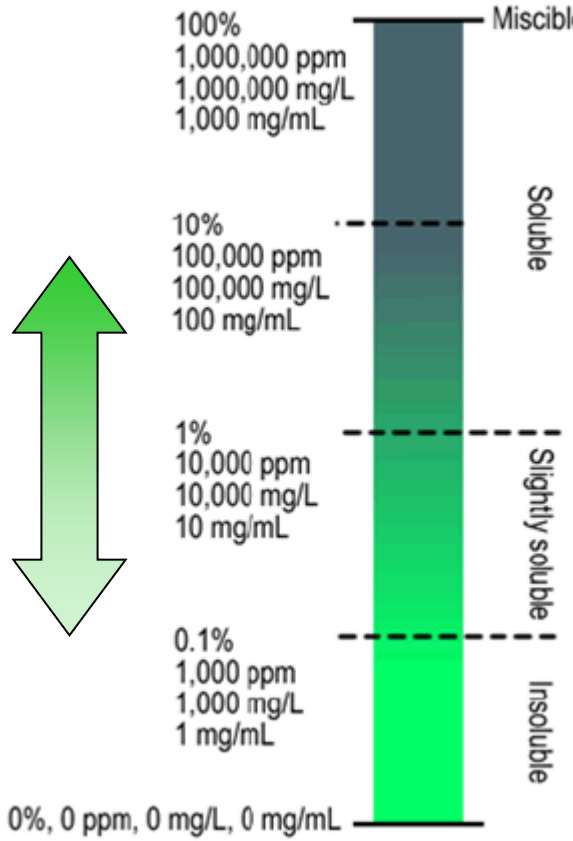
polarized functional groups

Solubility in



" corpora non agunt nisi soluta "

Dwayne Friesen



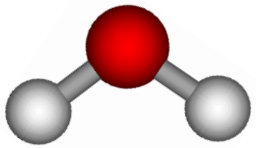
$$C/(N+O) \leq 3$$

$$3 < C/(N+O) < 5$$

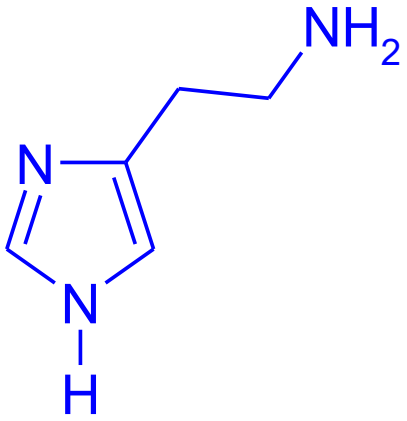
$$C/(N+O) \geq 5$$

Applies to only neutral molecular and represents only a qualitative and approximate indication of water solubility of an organic compound!!!

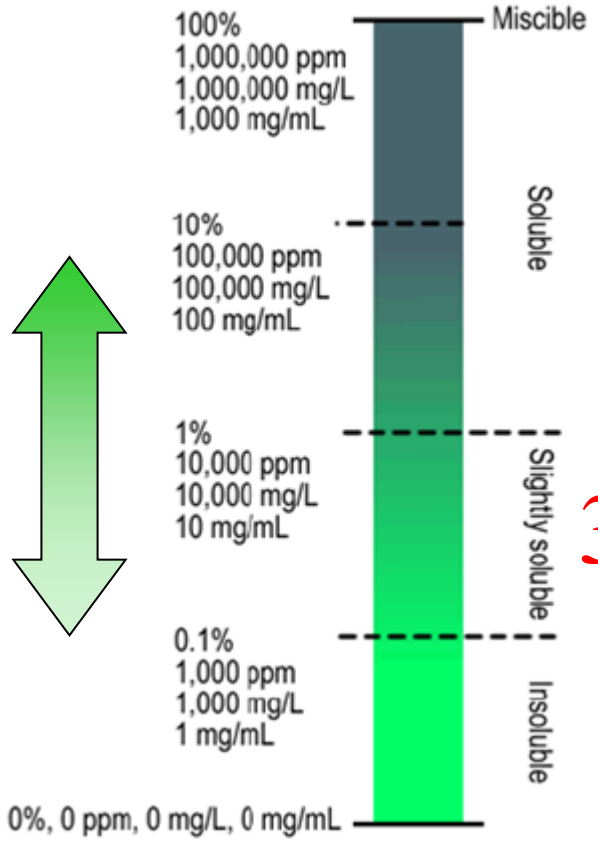
Solubility in



" corpora non agunt nisi soluta "



$C_5H_9N_3$



$$C/(N+O) \leq 3$$

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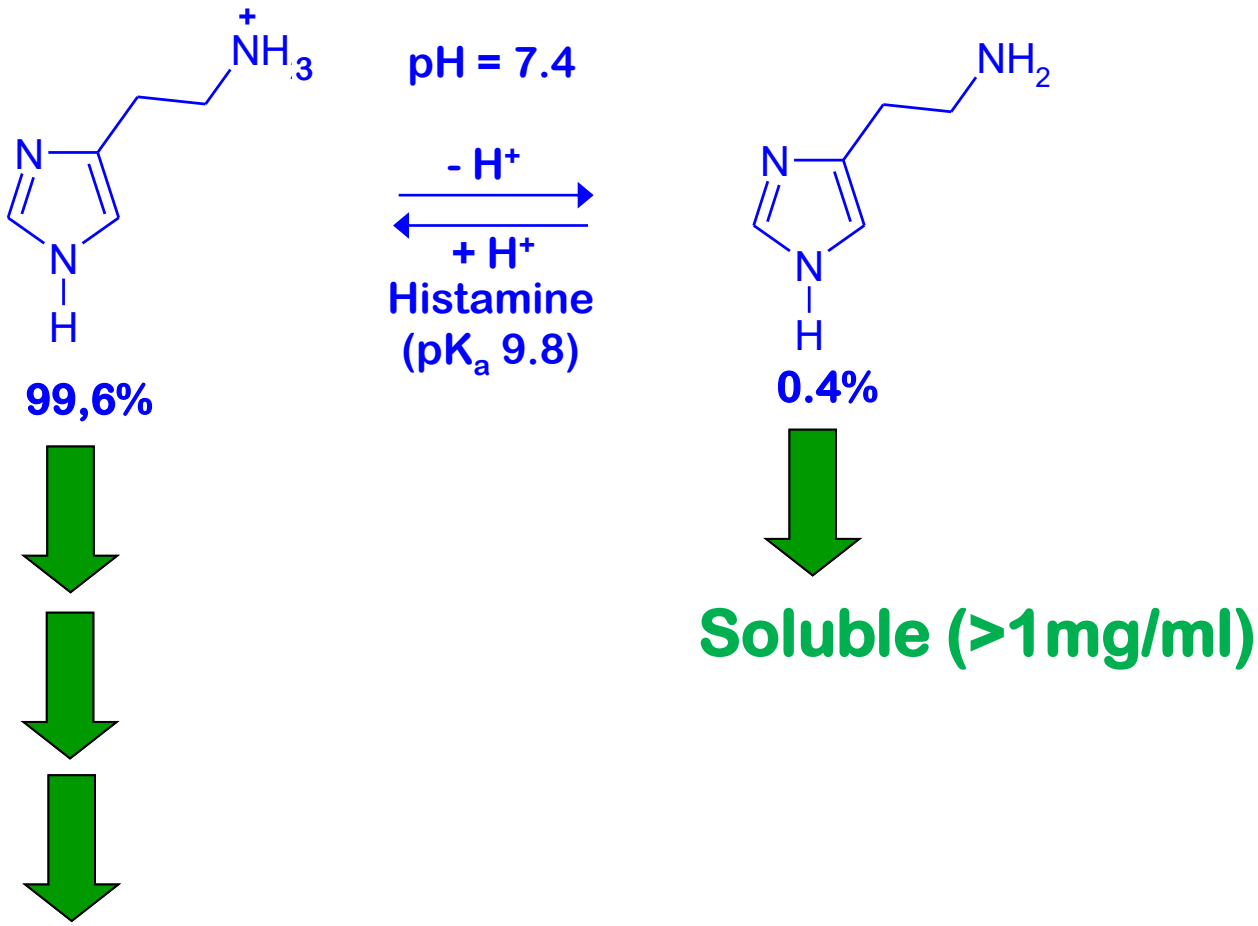
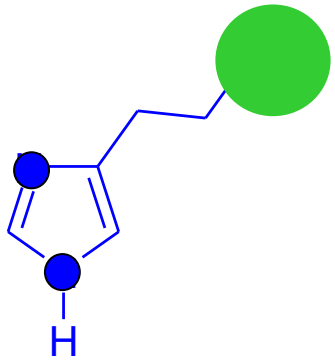
Applies to only <u>neutral molecular</u> and represents only a qualitative and approximate indication of water solubility of an organic compound!!!

The first crucial pharmaceutical difference!



but…

Solubility Prediction



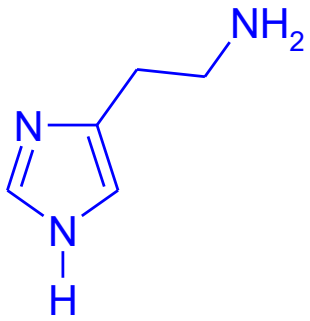
99,6%

pH = 7.4

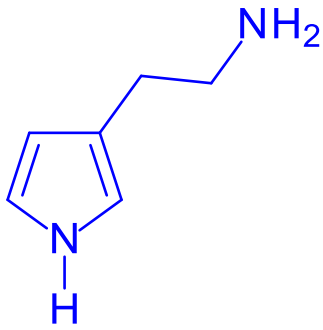
$- H^+$

$+ H^+$

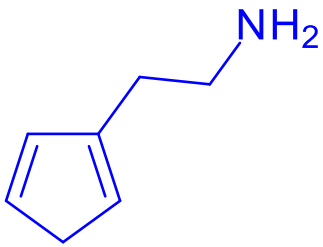
$(pK_a \approx 9.8)$



1.7



3

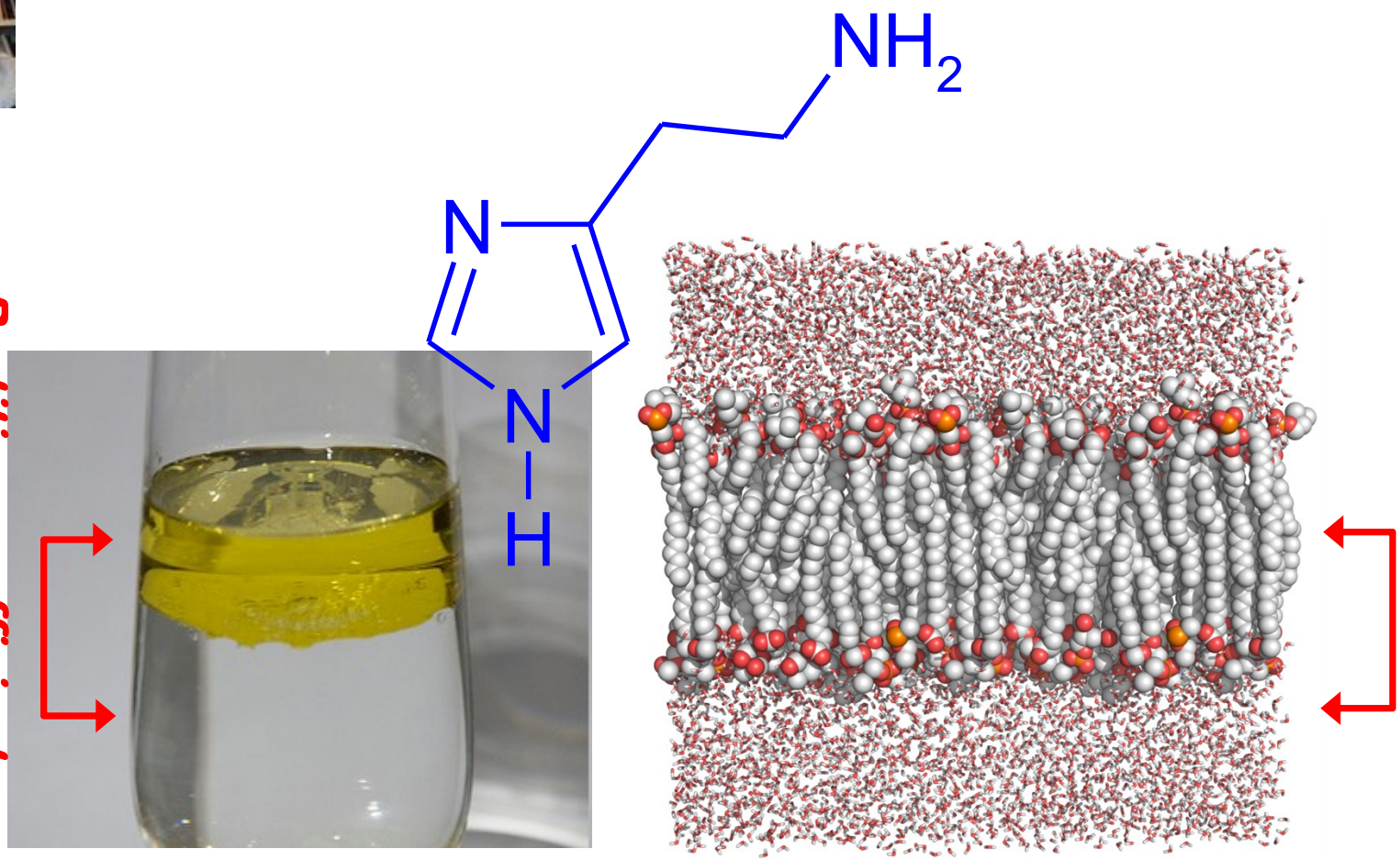


≈ 0.4%

7

Soluble

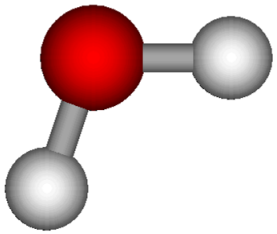
But where are written these properties?



A very simple definition:

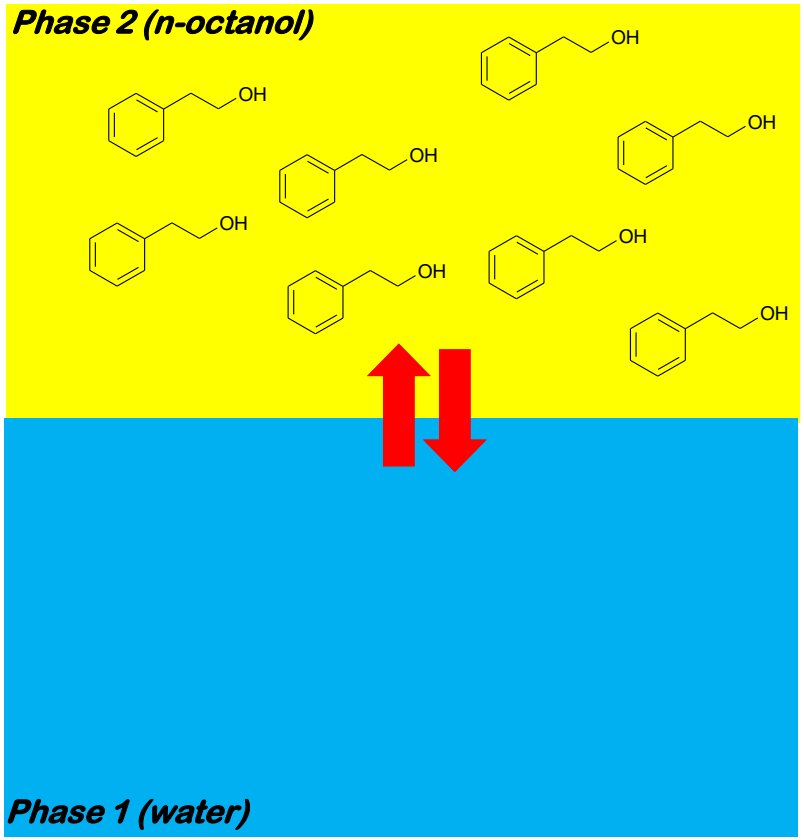
In organic chemistry, we have a family of compounds characterized by bonds with $\Delta EN \cong 0$

HYDROCARBONS

and they are surely  phobics!!!

Hydrophobicity and partition coefficient

$$\mu_{(phase2)} = \mu^{0}_{(phase2)} - RT \ln\left[C_{(phase2)}\right]$$



$$\mu_{(phase1)} = \mu^{0}_{(phase1)} - RT \ln\left[C_{(phase1)}\right]$$

At the equilibrium:

$$\mu_{(phase1)} = \mu_{(phase2)}$$

$$\mu^{0}_{(phase1)} - RT \ln\left[C_{(phase1)}\right] = \mu^{0}_{(phase2)} - RT \ln\left[C_{(phase2)}\right]$$

$$\mu^{0}_{(phase1)} - \mu^{0}_{(phase2)} = RT \ln\left[C_{(phase1)}\right] - RT \ln\left[C_{(phase2)}\right]$$

$$\mu^{0}_{(phase1)} - \mu^{0}_{(phase2)} = RT \ln\left[\frac{C_{(phase1)}}{C_{(phase2)}}\right]$$

$$\left[\frac{C_{(phase1)}}{C_{(phase2)}}\right] = P$$ **Partition coefficient**

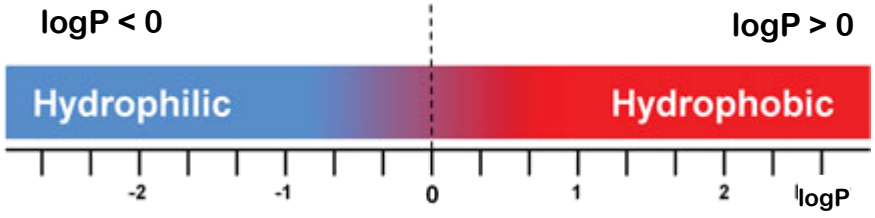
Hydrophobicity and partition coefficient

$$\left[\frac{C_{(phase1)}}{C_{(H_2O)}}\right] = P$$ **Partition coefficient**

We can define: **"*hydrophobic*" a compound with P > 1;**
"*hydrophilic*" a compound with P < 1.

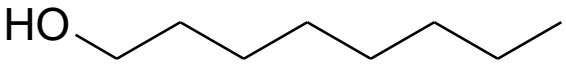
$$\log\left[\frac{C_{(phase1)}}{C_{(H_2O)}}\right] = \log P$$

We can define: **"*hydrophobic*" a compound with logP > 0;**
"*hydrophilic*" a compound with logP < 0.



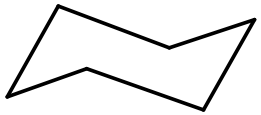
Hydrophobicity and partition coefficient

How we can choose the second phase:



***n*-octanol**

- immiscible in water even if 27% of water dissolves in it… so the first region of hydration of the solute is preserved;
- UV transparent;
- Low vapor pressure.



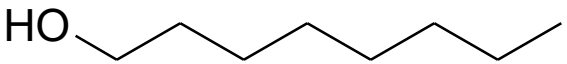
cyclohexane

Immiscible in water and very low amount of water dissolves in it… so also the first region of hydration of the solute is lost.
The differences between the logP values in *n*-octanol and cyclohexane is a measure of the de-hydration energy of a solute.

Do you see any similarity?

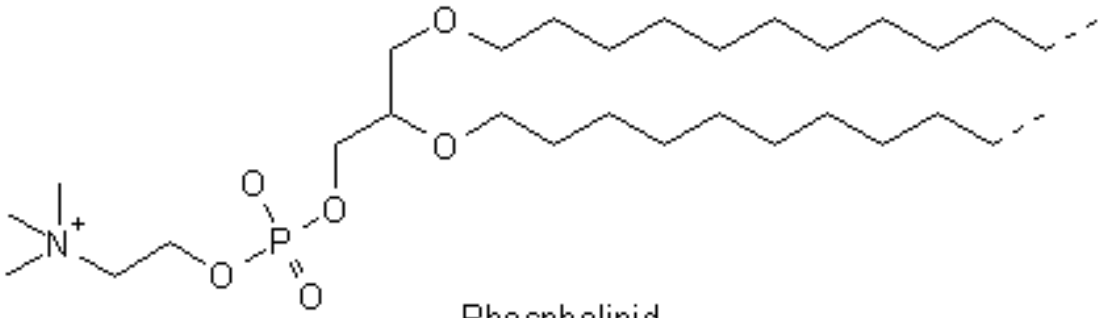
…in addition to this?

How we can choose the second phase:

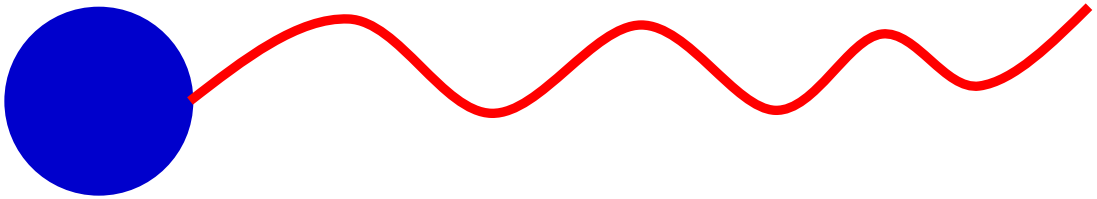


***n*-octanol**

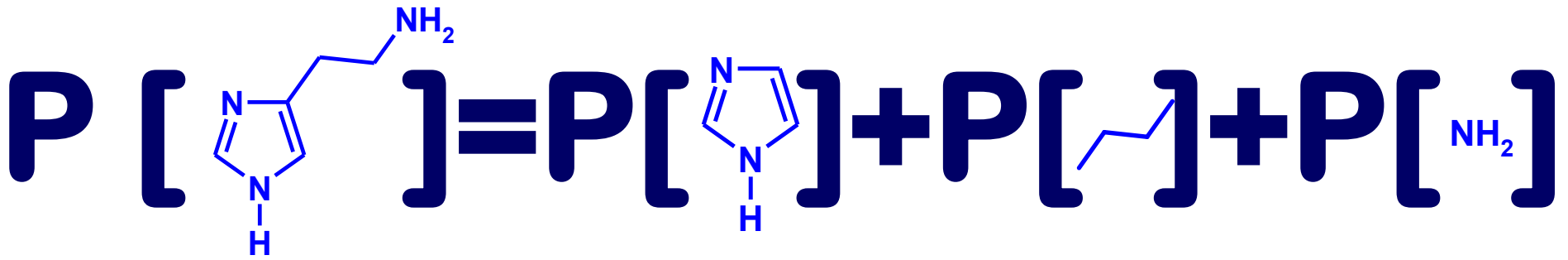
- **"Similarity" with biological membrane;**

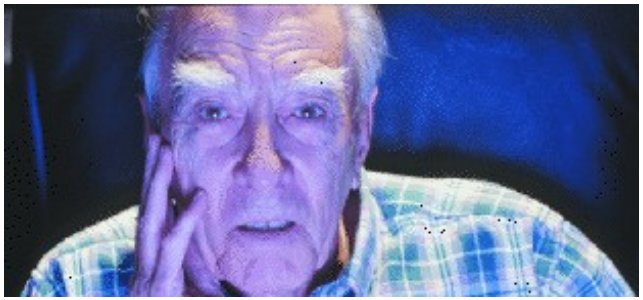


Phospholipid



Could it be that the partition coefficient (P) of a chemical compound is the sum of the coefficients of individual fragments that compose it?





Corwin Hansch

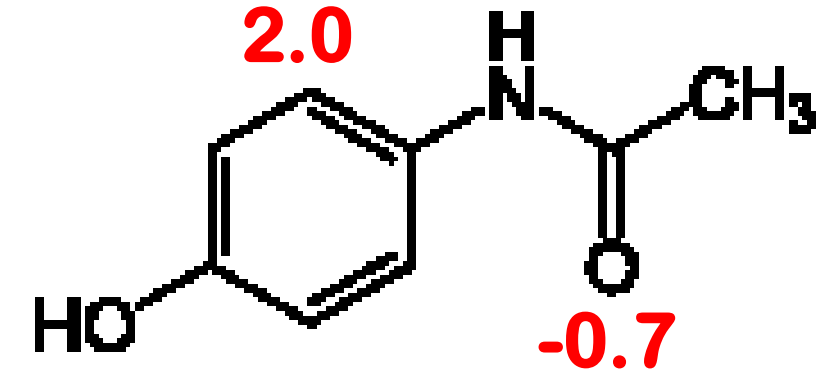
Fragments	Pi value*
C	+0.5
phenyl/benzene/aromatic ring	+2.0
Cl	+0.5
S	0.0
carboxylic acid or ester	-0.7
amide or imide	-0.7
O (hydroxyl, phenol, ether)	-1.0
N (amine)	-1.0

** in log scale*

Just a little example:

Fragments	Pi value
C	+0.5
phenyl/benzene/aromatic ring	+2.0
Cl	+0.5
S	0.0
carboxylic acid or ester	-0.7
amide or imide	-0.7
O (hydroxyl, phenol, ether)	-1.0
N (amine)	-1.0

clogP = 0.3



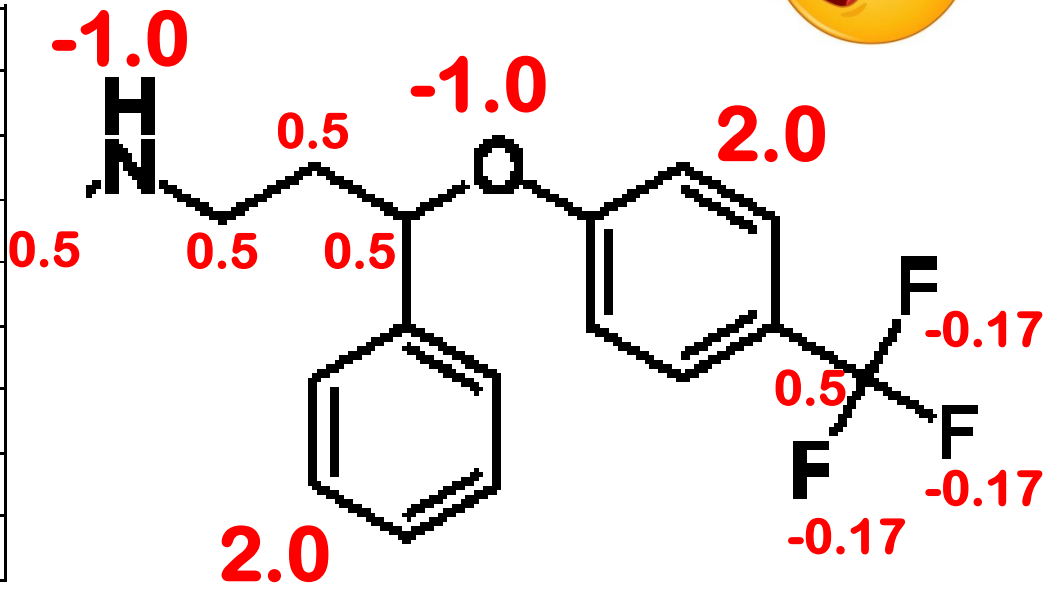
logP = 0.46

Now it's your turn!

clogP = 3.99

logP = 4.05

Fragments	Pi value
C	+0.5
phenyl/benzene/aromatic ring	+2.0
Cl	+0.5
S	0.0
carboxylic acid or ester	-0.7
amide or imide	-0.7
O (hydroxyl, phenol, ether)	-1.0
N (amine)	-1.0

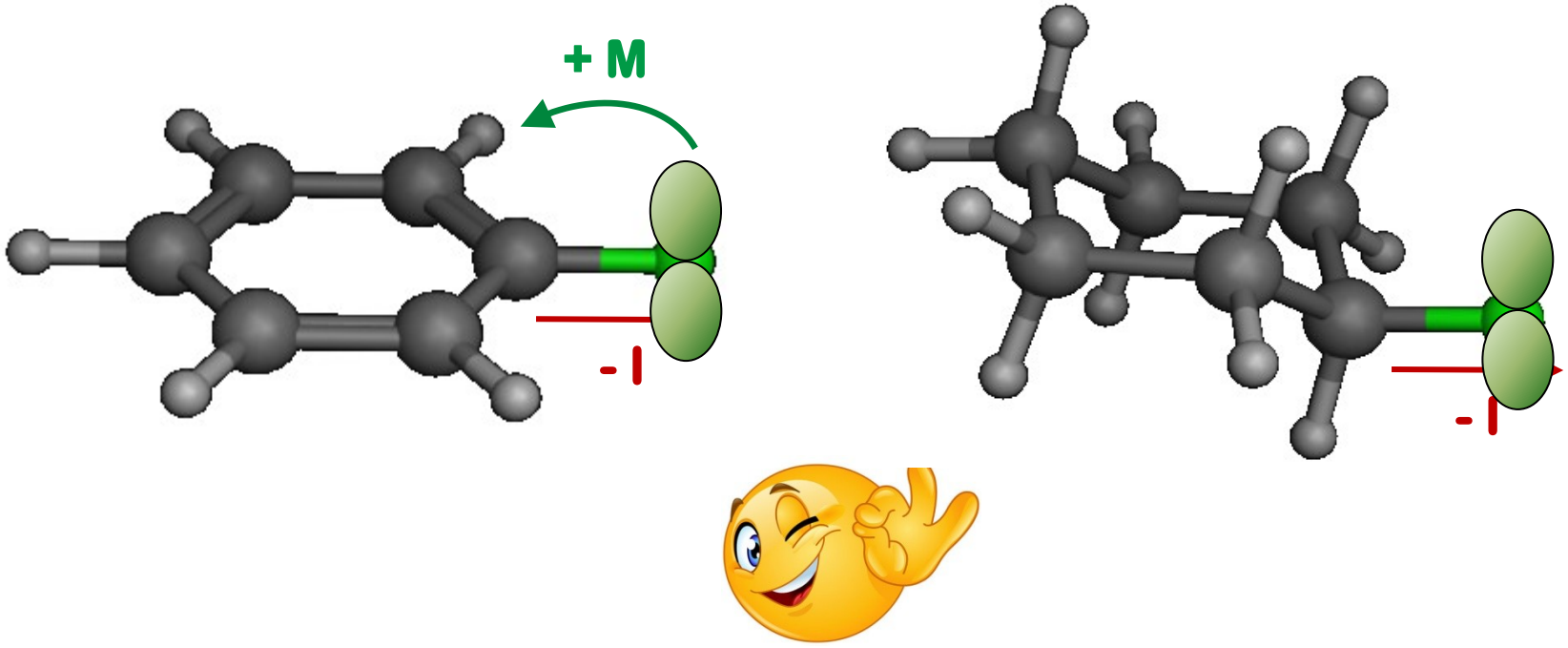


F (aliphatic) **-0.17**

F (aromatic) **0.14**

Fluorine… aliphatic is not aromatic!

F (aliphatic) -0.17
F (aromatic) 0.14



Lipinski's "Rule of Five"

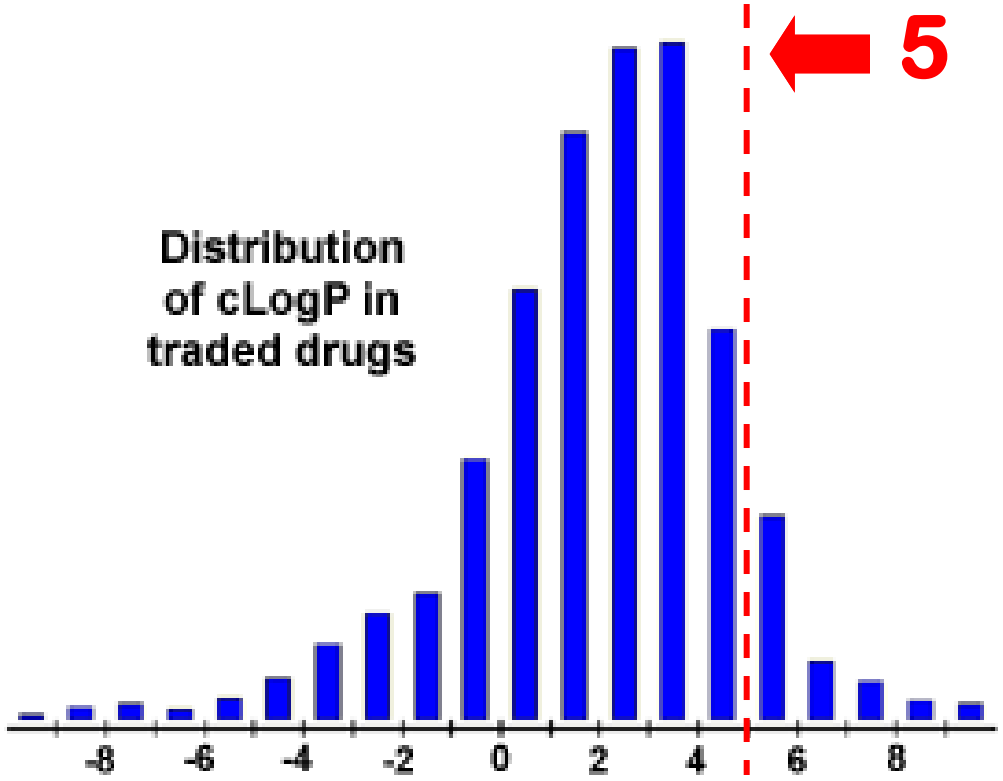
Poor *oral* absorption or permeation, if …

- **Number of H-bond donors > 5 (OH & NH)**
- **Number of H-bond acceptors > 10 (O & N)**
- **Molecular weight > 500**
- **log *P* > 5**

Lipinski et al., Adv. Drug Deliv. 23 (1997) 3.

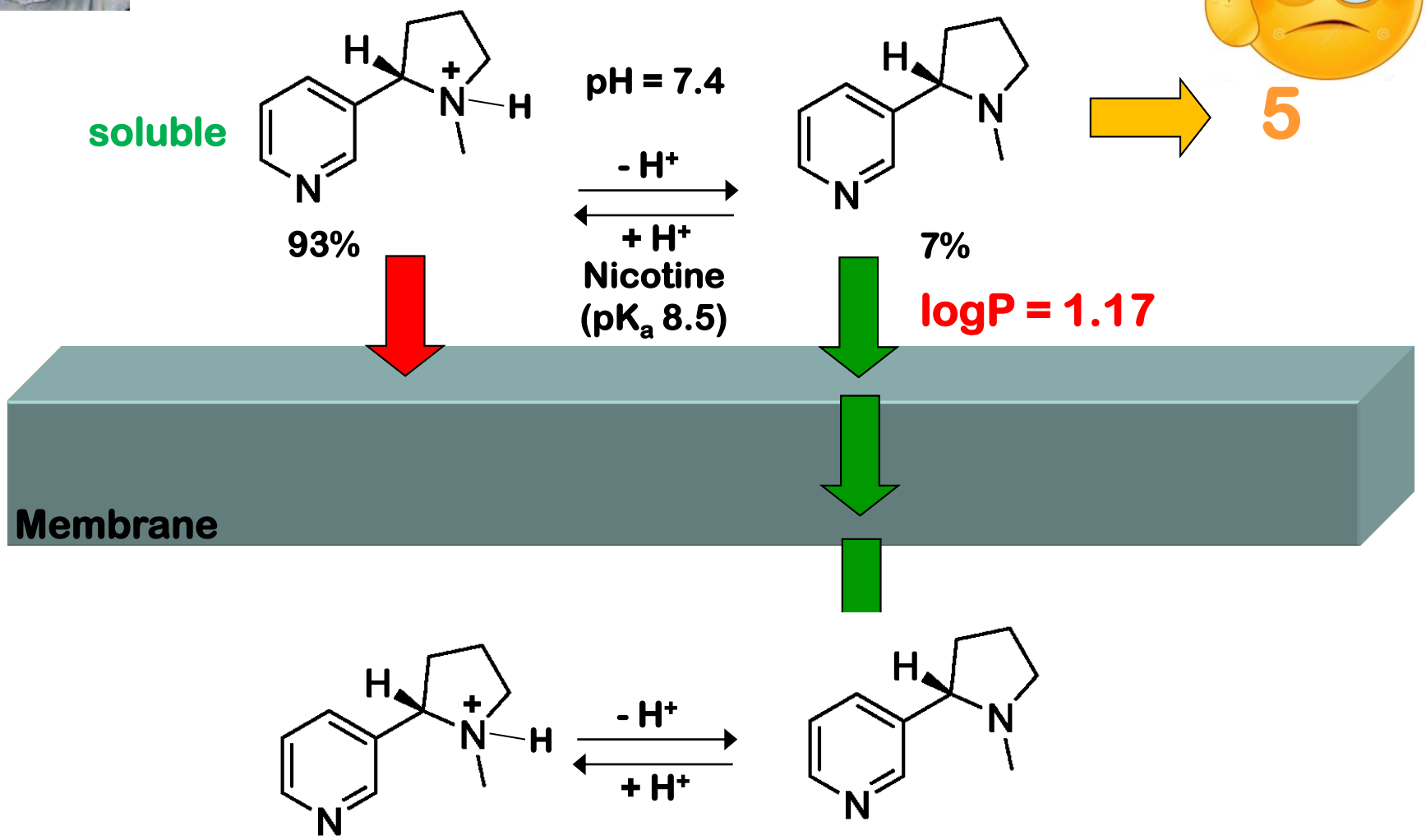
N.B. Like all rules they are there to be broken and a number of exceptions exist. I have personally worked on a couple of well-absorbed drugs which broke this rule but as a general guide it works well. Remember that you may have charge in your molecule so that LogD(7.4) or LogD(5.5) is really the important parameter rather than Log P. Keeping LogD(7.4) around 2 seem generally good advice. Manipulating the pKa can be a way of improving a molecule.

Hydrophobicity and partition coefficient

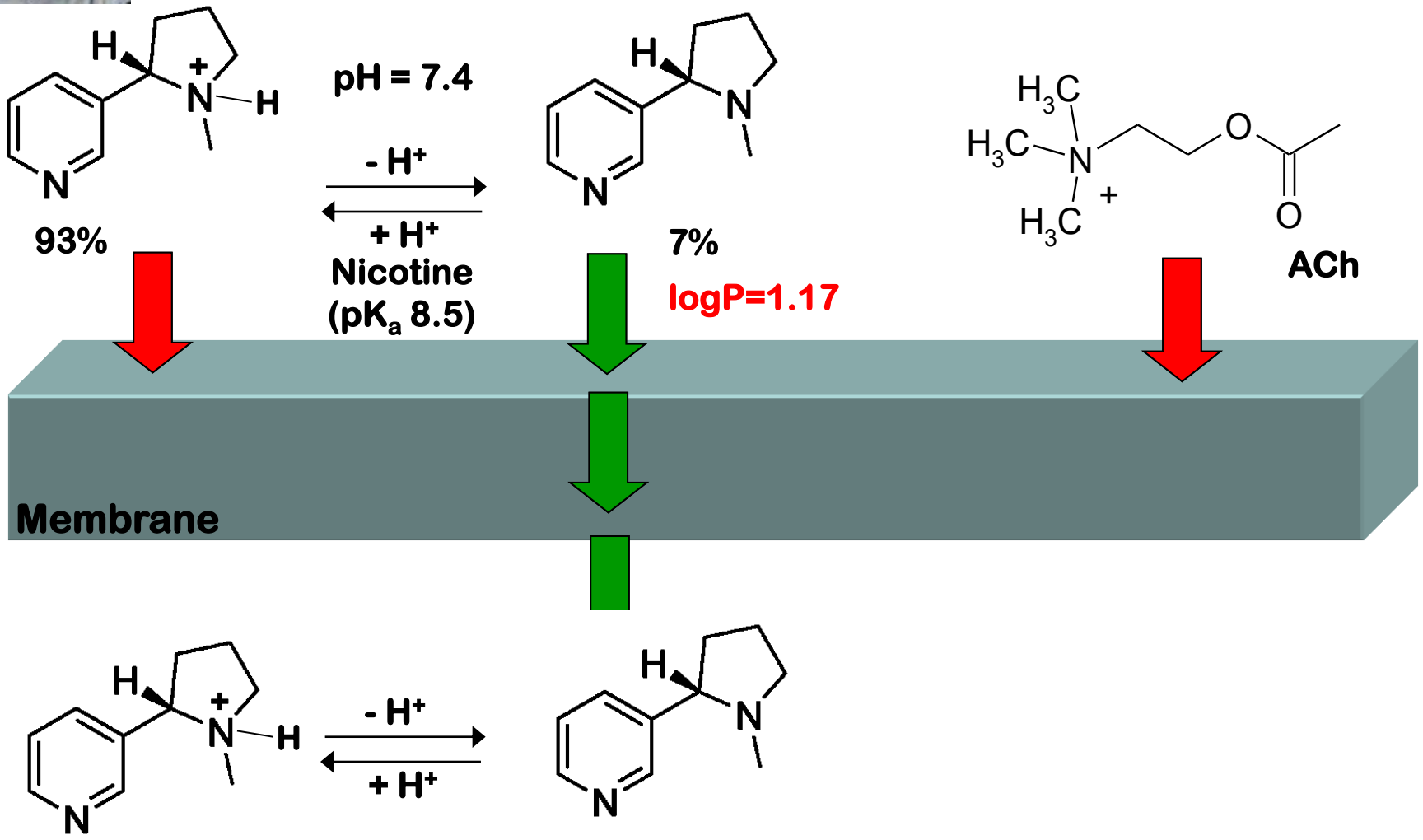


It has been shown for compounds to have a reasonable probability of being well *orally absorb* their logP value must not be greater than 5.0. The distribution of calculated logP values of more than 3000 drugs on the market underlines this fact (see diagram).

Another crucial pharmaceutical difference!

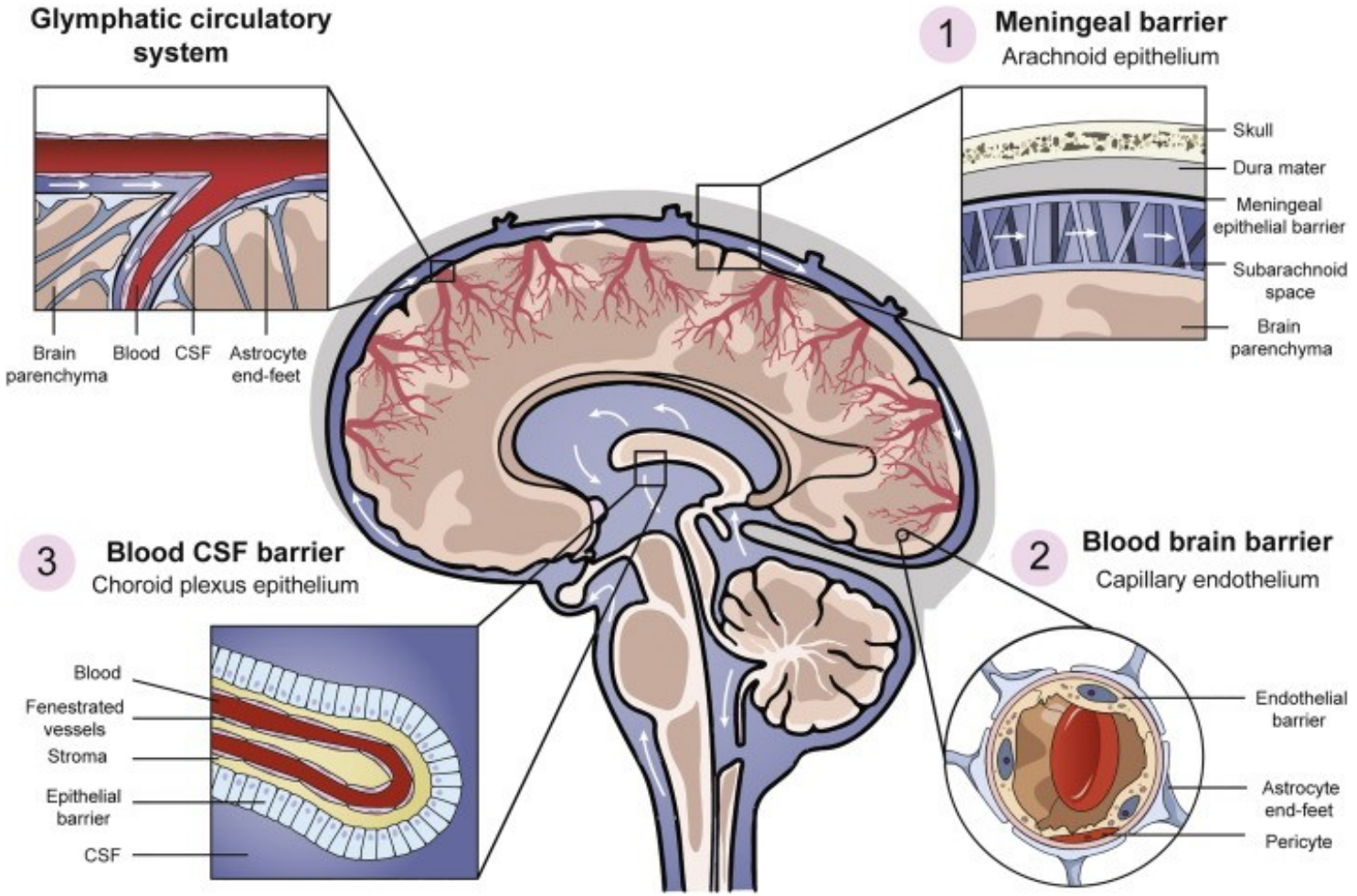


The first crucial pharmaceutical difference!



Beyond Lipinski's "Rule of Five"

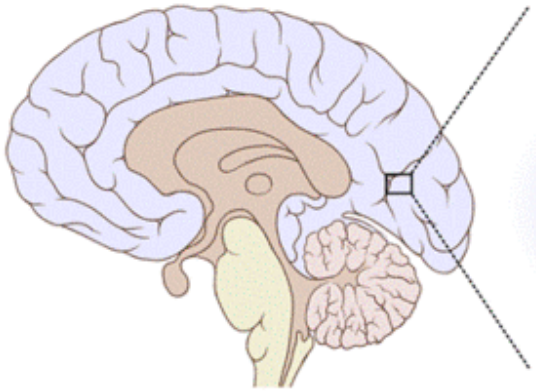
Organization of brain barriers:

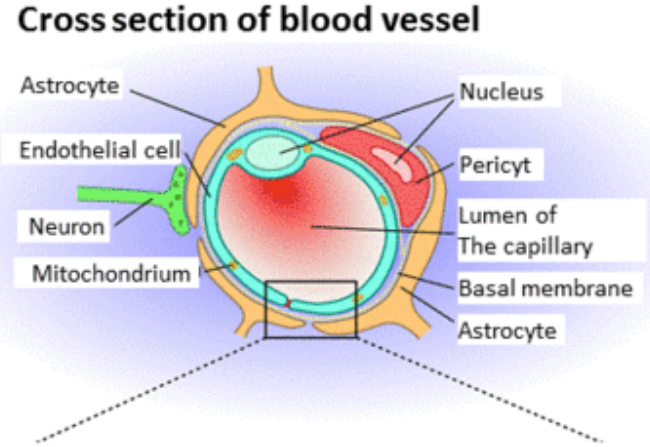


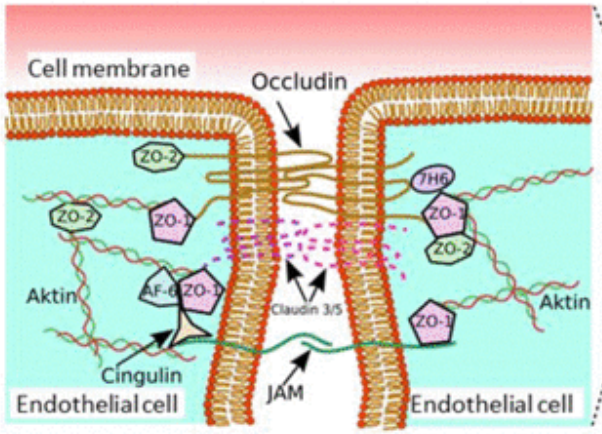
credits: https://www.sciencedirect.com/science/article/abs/pii/S1568997217301052/

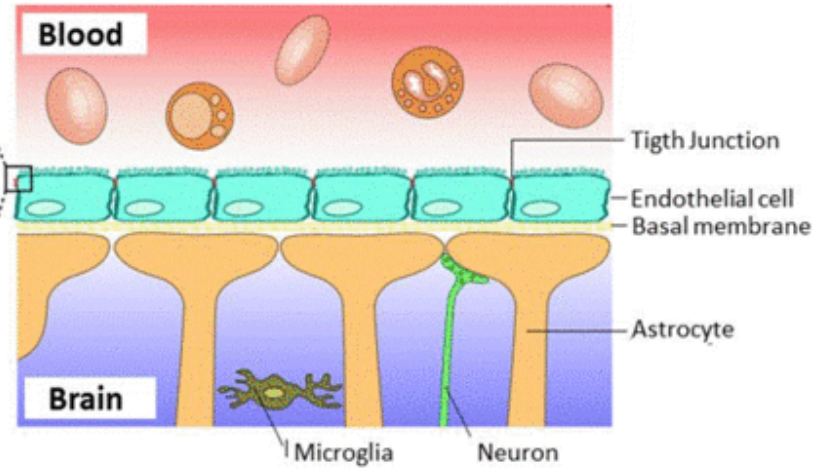
Beyond Lipinski's "Rule of Five"

Pathways across the blood–brain barrier









credits: https://www.emf.ethz.ch/en/knowledge/topics/health/blood-brain-barrier/

Beyond Lipinski's "Rule of Five"

Pathways across the blood–brain barrier

Lipophilicity: $0 \leq logP \leq 3$

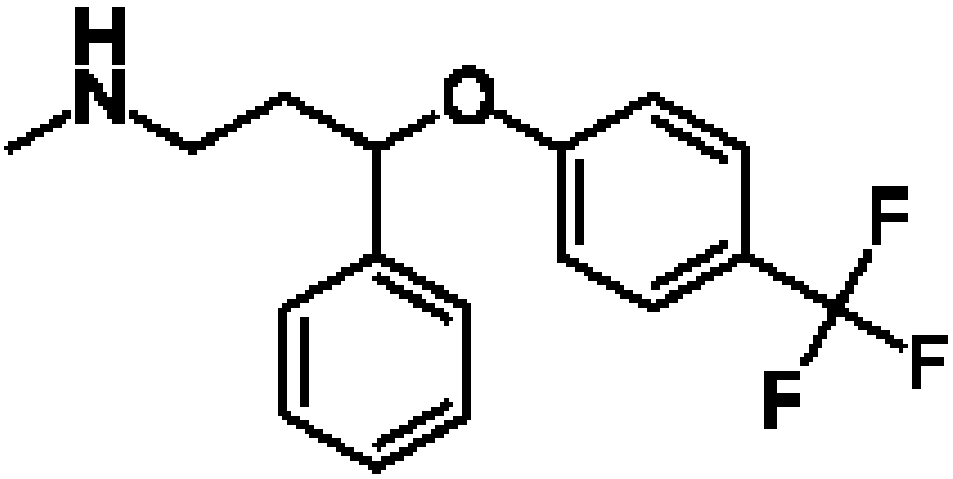
Molecular weight: < 450

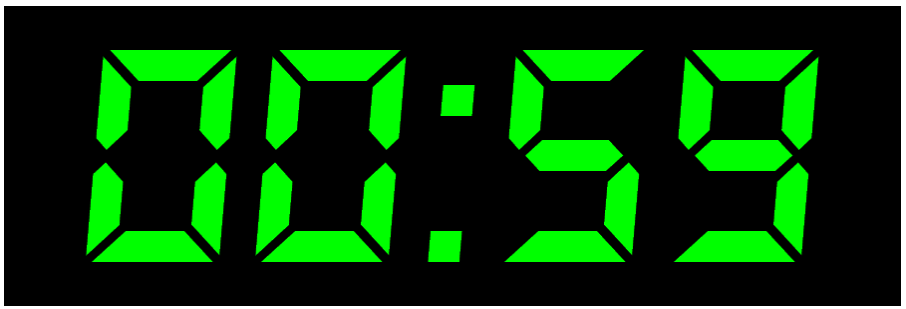
Polar surface area (PSA): $60 \div 90\ Å^2$

Hydrogen bonding (O + N): ≤ 5

Charge: $4 \leq pKa \leq 10$

Can we try again our little experiment?





1. Chemical class;
2. Functional groups;
3. Possible interaction scheme;
4. Guess pKa value;
5. Number of rotatable bonds;
6. Tautomers;
7. Chiral centers;
8. Chemical/enzimatic reactivity;
9. Guess 3D- shape
10. Guess water solubility;
11. Guess logP;
12. Guess BBB permeation;
13. …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DIRECTOR
Stefano Moro
CAMERA
Chimica e Tecnologia Farmaceutiche
DATE
SCENE
TAKE