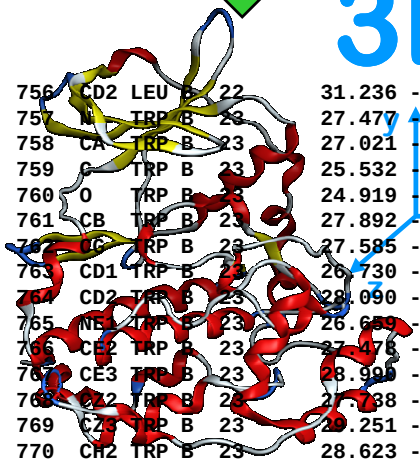
We love Silvio but, pragmatically, we prefer…

NMR
Spectroscopy

3D

X-Ray
Crystallography



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…
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ATOM    757  N   TRP B  23      27.477 -25.871  -8.251
ATOM    758  CA  TRP B  23      27.021 -24.553  -7.803
ATOM    759  C   TRP B  23      25.532 -24.284  -8.011
ATOM    760  O   TRP B  23      24.919 -23.498  -7.297
ATOM    761  CB  TRP B  23      27.892 -23.448  -8.451
ATOM    762  CG  TRP B  23      27.585 -22.055  -8.009
ATOM    763  CD1 TRP B  23      26.730 -21.178  -8.613
ATOM    764  CD2 TRP B  23      28.090 -21.382  -6.842
ATOM    765  NE1 TRP B  23      26.659 -20.002  -7.892
ATOM    766  CE2 TRP B  23      27.476 -20.101  -6.799
ATOM    767  CE3 TRP B  23      28.999 -21.731  -5.830
ATOM    768  CZ2 TRP B  23      27.738 -19.177  -5.784
ATOM    769  CZ3 TRP B  23      29.251 -20.809  -4.825
ATOM    770  CH2 TRP B  23      28.623 -19.548  -4.812
ATOM    771  N   LYS B  24      24.939 -24.930  -8.991
…
```

Comparative/Homology
Modeling

Cryo-
Electron Microscopy
(Cryo-EM)

Cryo-EM: the future of structural biochemistry is today!

A 3 minute introduction to CryoEM

credits: https://www.youtube.com/watch?v=BJKkC0W-6Qk

We are coordinates hunters!

… and this is our favorite hunting place!

www.rcsb.org

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RCSB PDB PROTEIN DATA BANK

An Information Portal to 107436 Biological Macromolecular Structures

Search by PDB ID, author, macromolecule, sequence, or ligands

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PDB-101 wwPDB EMDataBank NDB Nucleic Acid Database StructuralBiology Knowledgebase

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A Structural View of Biology

This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.

As a member of the wwPDB, the RCSB PDB curates and annotates PDB data.

The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

Structure and Health Focus: Ebola Virus Proteins

Video Tour

Molecule of the Month Article

March Molecule of the Month

Phototropin

PDB… in numbers:

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Other Statistics

PDB Data Distribution by Experimental Method and Molecular Type

Copy CSV

Experimental Method	Proteins	Nucleic Acids	Protein/NA Complex	Other	Total
X-Ray	126880	2012	6547	8	135447
NMR	11062	1279	259	8	12608
Electron Microscopy	2277	31	800	0	3108
Other	256	4	6	13	279
Multi Method	129	5	2	1	137
Total	140604	3331	7614	30	151579

125334 structures in the PDB have a structure factor file.
9949 structures in the PDB have an NMR restraint file.
3701 structures in the PDB have a chemical shifts file.
3167 structures in the PDB have a 3DEM map file.

Data cellected: May 2019

PDB… in numbers:

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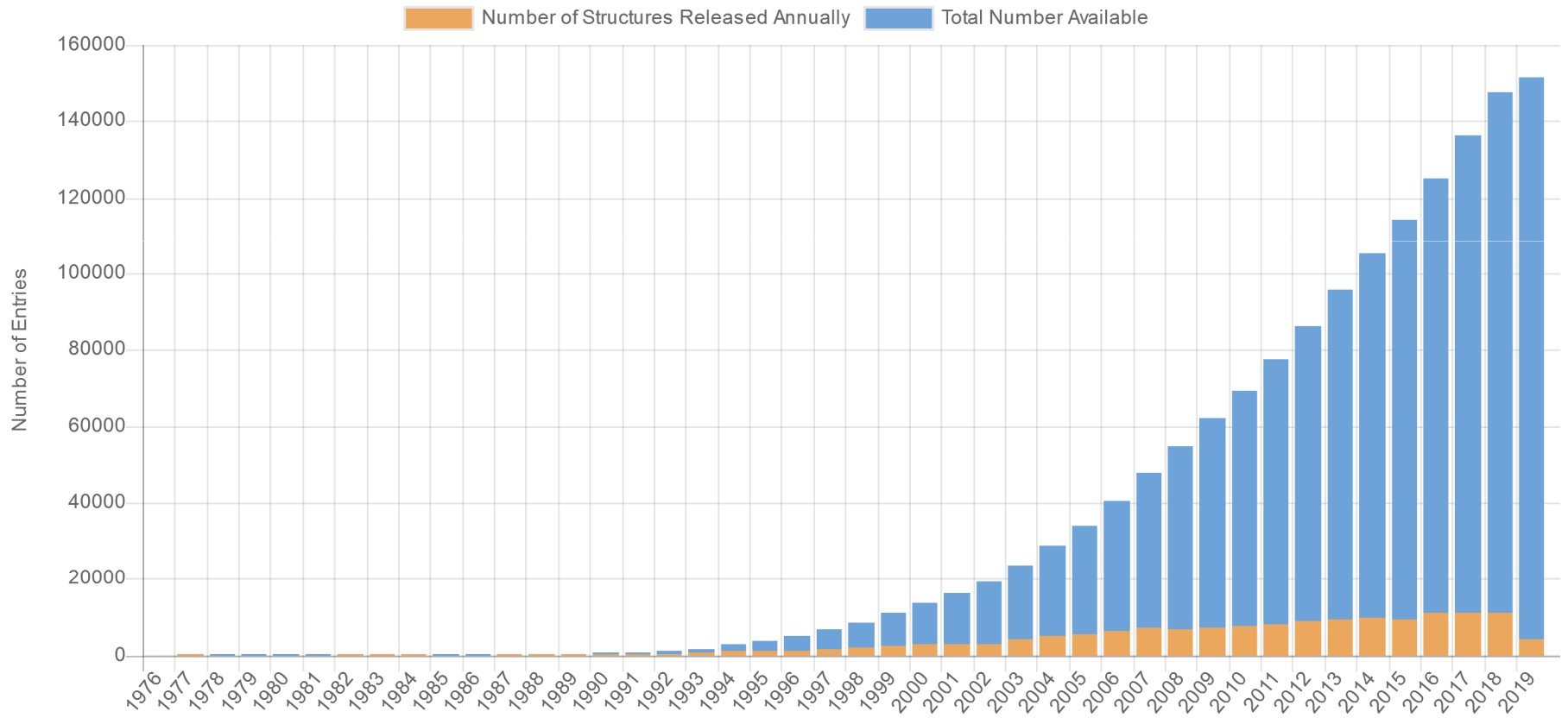
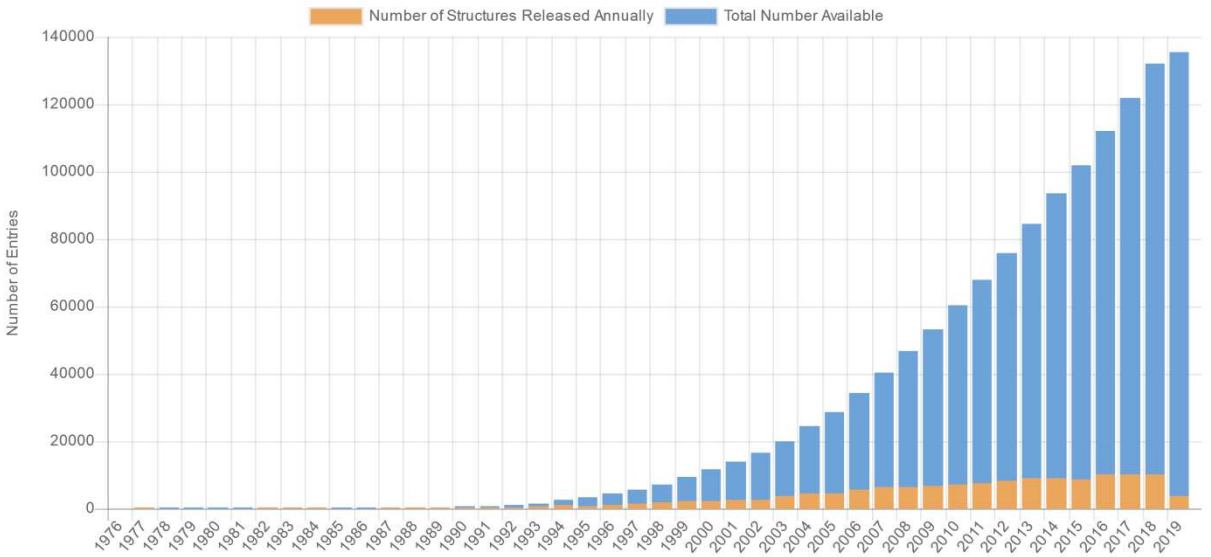


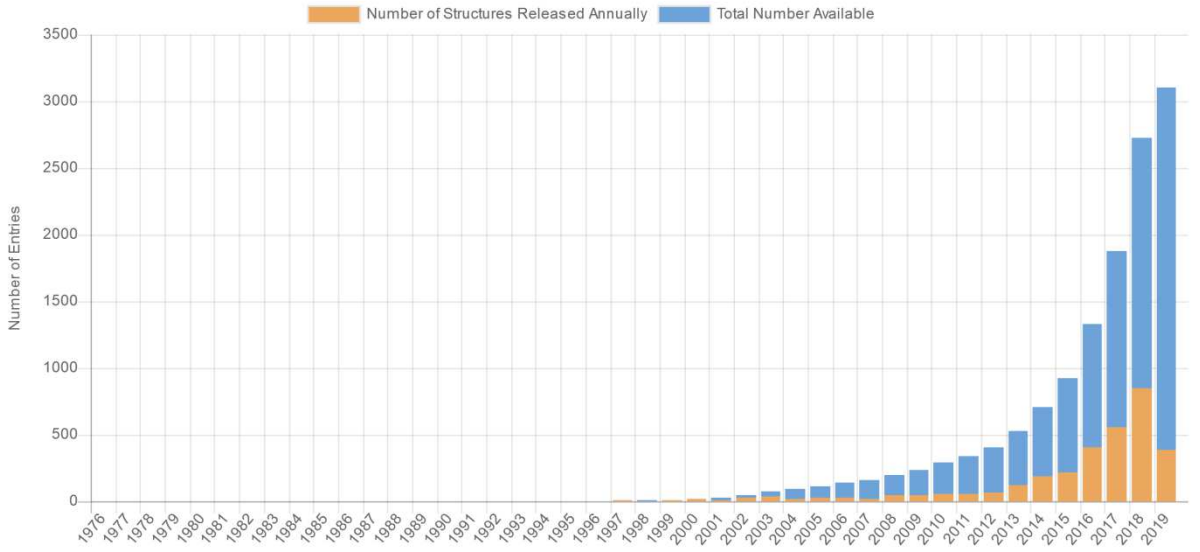
Data cellected: May 2019

PDB… in numbers:

X-Ray Crystallography



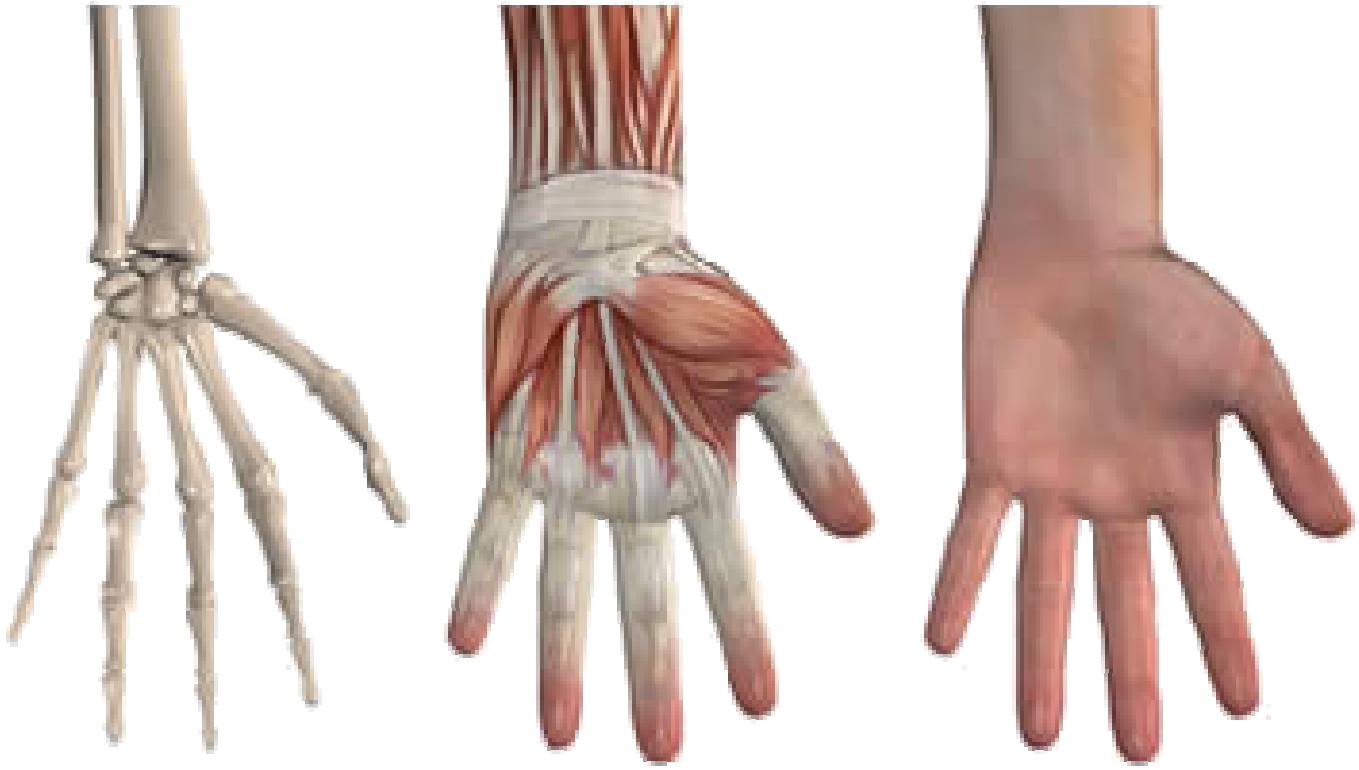
Cryo-Electron Microscopy (Cryo-EM)



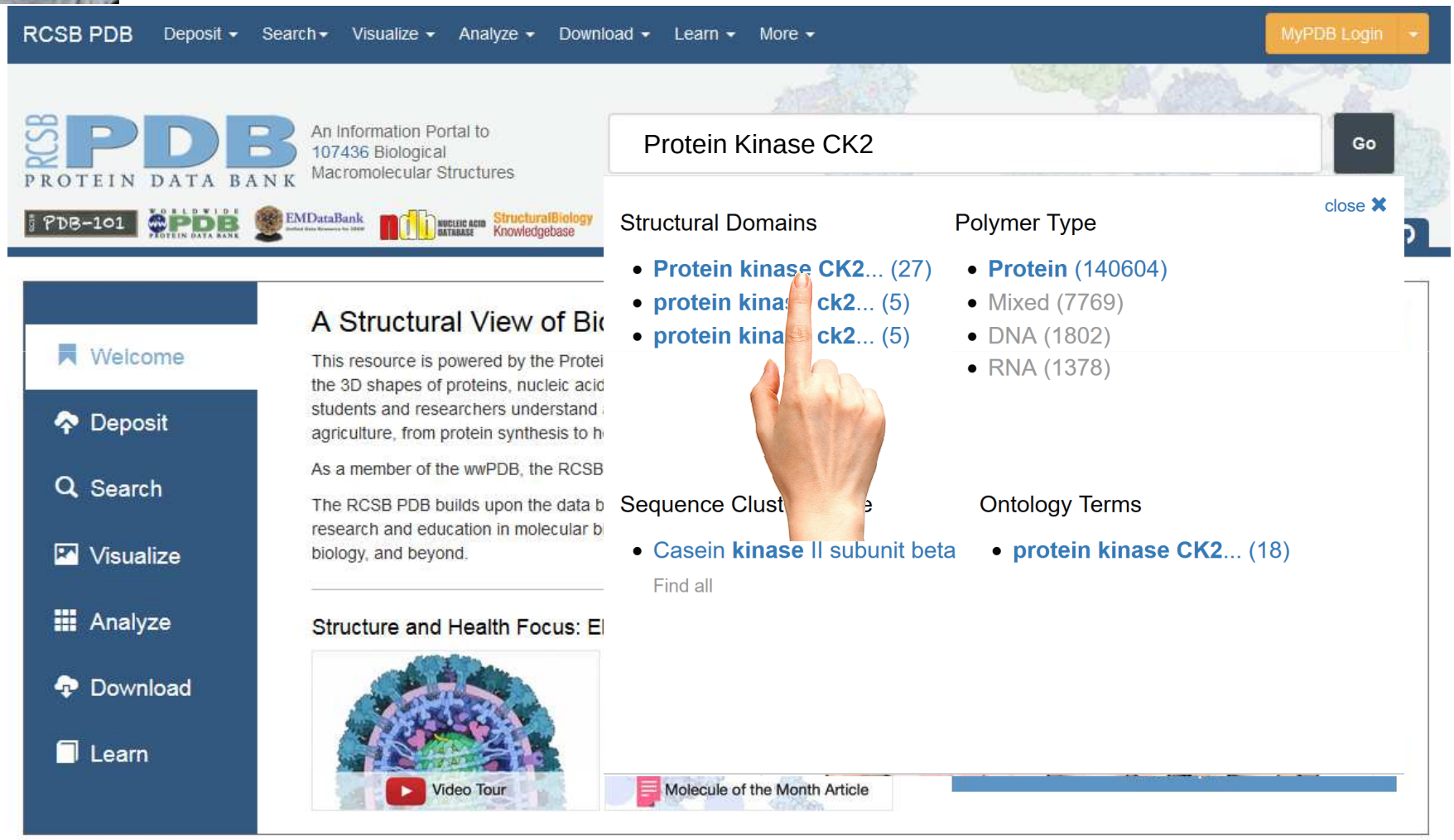
Data cellected: May 2019

Can you understand why pharma companies are very interested to structural biology/biochemistry?

From 3D coordinates to molecular surface



How we can start?



The magic word of PDBland..

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Refinements

ORGANISM

Homo sapiens (93)
Zea mays (40)
Saccharomyces cerevisiae (13)
Rattus norvegicus (3)
Xenopus laevis
synthetic construct
Plasmodium falciparum

UNIPROT MOLECULE NAME

Casein kinase II subunit ... (116)
Casein kinase II subunit ... (11)
Casein kinase II subunit ... (11)
60S ribosomal protein L19-A (9)
60S ribosomal protein L10 (9)
60S ribosomal protein L15-A (9)
60S ribosomal protein L9-A (9)
Refine Query

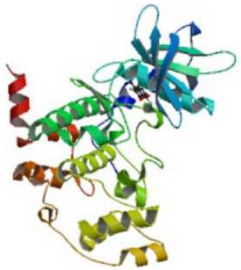
Currently showing 1 - 25 of 150 Page: 1 of 6 ← Previous Next → Displaying 25 Results

View: Detailed Download

Reports: Select

Sort: ↓ Match score: Higher to Lower

- ↓ Match score: Higher to Lower
- ↑ Match score: Lower to Higher
- ↓ Release Date: Newest to Oldest
- ↑ Release Date: Oldest to Newest
- ↓ PDB ID: A to Z
- ↑ PDB ID: Z to A
- ↓ Residue Count: Largest to Smallest
- ↑ Residue Count: Smallest to Largest
- ↓ Resolution: Best to Worst
- ↑ Resolution: Worst to Best



3D View

2QC6

Protein kinase CK2

Chilin A, Battistutta R, ... Zagotto ... A., Meggio F., ...

(20 ... Chem 51 7

Rele ... /26/2008
Method: X-ray Diffraction
Resolution: 1.85 Å
Residue Count: 332

Macromolecule:
Casein kinase II subunit alpha (protein)
Unique Ligands: CSO, G12
Search term match score: 548.51

Matched fields in ...

The magic word of PDBland..

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Structure Summary | 3D View | Annotations | Sequence | Sequence Similarity | Structure Similarity | Experiment

Apertura di 2qc6.pdb

È stato scelto di aprire:

2qc6.pdb

tipo: pdb File (64,5 kB)

da: https://files.rcsb.org

Che cosa deve fare Firefox con questo file?

Aprirlo con UCSF Chimera molecular visualization application

Salva file

Da ora in avanti esegui questa azione per tutti i file di questo tipo.

OK Annulla

Scegliere un'applicazione

pdb File

2qc6.pdb

Invia questo elemento a:

moe.exe

Blocco note

Microsoft Office Picture Manager

Windows Media Player

Applicazione WordPad di Windows

Sfoglia... OK Annulla

Download Files

Quality Automatic

Water Ions

Hydrogens Clashes

2fo-fc Map (DSN6)

fo-fc Map (DSN6)

What is 2QC6 (PDB) file?

```
HEADER          JRNL
2QC6            JRNL
TITLE           JRNL
COMPND          REMARK
COMPND          REMARK
COMPND          REMARK
COMPND          REMARK
COMPND          REMARK
COMPND          REMARK
SOURCE          REMARK
SOURCE          REMARK
SOURCE          REMARK
SOURCE          REMARK
SOURCE          REMARK
SOURCE          REMARK
KEYWDS          REMARK
EXPDTA          REMARK
AUTHOR          REMARK
REVDAT          REMARK
REVDAT          REMARK
REVDAT          REMARK
JRNL            REMARK
JRNL            REMARK
JRNL            REMARK
JRNL            REMARK
JRNL            REMARK
JRNL            REMARK
EXPLAIN         REMARK
JRNL            REMARK
JRNL            REMARK
2008            REMARK
```

```
REMARK 6 HELIX    1   1 ASP A   14  ARG A   19  1                                   6
REMARK 6 HELIX    2   2 PRO A   20  ASP A   25  1                                   6
REMARK 6 HELIX    3   3 TYR A   26  LEU A   29  5                                   4
REMARK 6 HELIX    4   4 GLU A   35  ASP A   37  5                                   3
REMARK 6 HELIX    5   5 LYS A   74  CSO A   89  1                                  16
DBREF  2 HELIX    6   6 ASP A  120  TYR A  125  1                                   6
SEQADV 2 HELIX    7   7 PRO A  126  LEU A  128  5                                   3
SEQRES   HELIX    8   8 THR A  129  GLN A  150  1                                  22
SEQRES   HELIX    9   9 LYS A  158  HIS A  160  5                                   3
SEQRES   HELIX   10  10 ASP A  175  ALA A  179  5                                   5
SEQRES   HELIX   11  11 SER A  194  LYS A  198  5                                   5
SEQRES   HELIX   12  12 GLY A  199  VAL A  204  1                                   6
SEQRES   HELIX   13  13 TYR A  211  ARG A  228  1                                  18
SEQRES   HELIX   14  14 ASP A  237  GLY A  250  1                                  14
SEQRES   HELIX   15  15 GLY A  250  TYR A  261  1                                  12
SEQRES   HELIX   16  16 ASP A  266  GLY A  274  1                                   9
SEQRES   HELIX   17  17 PRO A  280  MET A  285  5                                   6
SEQRES   HELIX   18  18 ASN A  289  VAL A  293  5                                   5
SEQRES   HELIX   19  19 SER A  294  LEU A  305  1                                  12
SEQRES   HELIX   20  20 THR A  314  THR A  320  1                                   7
SEQRES   HELIX   21  21 HIS A  321  TYR A  323  5                                   3
SEQRES   HELIX   22  22 PHE A  324  ASN A  332  1                                   9
SEQRES   SHEET    1   A 5 TYR A  39  ARG A  47  0
SEQRES   SHEET    2   A 5 SER A  51  ASN A  58 -1  O  GLU A  55   N  ARG A  43
SEQRES   SHEET    3   A 5 LYS A  64  LEU A  70 -1  O  ILE A  69   N  GLU A  52
SEQRES   SHEET    4   A 5 PRO A 109  PHE A 113 -1  O  LEU A 111   N  LYS A  68
SEQRES   SHEET    5   A 5 LEU A  97  ARG A 102 -1  N  LEU A  98   O  ILE A 112
SEQRES   SHEET    1   B 2 ILE A 152  MET A 153  0
SEQRES   SHEET    2   B 2 GLU A 180  PHE A 181 -1  O  GLU A 180   N  MET A 153
SEQRES   SHEET    1   C 2 VAL A 162  ASP A 165  0
SEQRES   SHEET    2   C 2 LYS A 170  LEU A 173 -1  O  LYS A 170   N  ASP A 165
SEQRES   LINK         C   LEU A  88                 N   CSO A  89     1555   1555  1.33
SEQRES   LINK         C   CSO A  89                 N   GLY A  90     1555   1555  1.34
SEQRES   CISPEP   1 GLU A  230    PRO A  231          0        -5.99
         SITE     1 AC1  7 ILE A  66  LYS A  68  PHE A 113  MET A 163
```

What is 2QC6 (PDB) file?

Protein Section

		Atom type				x	y	z		B-factor	Atom nature
ATOM	1	N	SER	A	7	18.809	-11.548	-9.537	1.00	30.22	N
ATOM	2	CA	SER	A	7	17.758	-10.860	-8.731	1.00	29.23	C
ATOM	3	C	SER	A	7	17.891	-9.329	-8.850	1.00	29.40	C
ATOM	4	O	SER	A	7	18.997	-8.794	-8.756	1.00	29.43	O
ATOM	5	CB	SER	A	7	17.853	-11.306	-7.257	1.00	29.91	C
ATOM	6	OG	SER	A	7	16.761	-10.832	-6.474	1.00	28.29	O
ATOM	7	N	LYS	A	8	16.765	-8.642	-9.075	1.00	29.05	N
ATOM	8	CA	LYS	A	8	16.661	-7.201	-8.846	1.00	28.10	C
ATOM	9	C	LYS	A	8	15.546	-6.888	-7.842	1.00	26.83	C
ATOM	10	O	LYS	A	8	14.668	-7.713	-7.590	1.00	26.71	O
ATOM	11	CB	LYS	A	8	16.479	-6.409	-10.156	1.00	28.45	C
ATOM	12	CG	LYS	A	8	15.230	-6.746	-10.960	1.00	31.04	C
ATOM	13	CD	LYS	A	8	15.113	-5.946	-12.280	1.00	29.28	C
ATOM	14	CE	LYS	A	8	13.733	-6.182	-12.904	1.00	32.90	C
ATOM	15	NZ	LYS	A	8	13.412	-5.378	-14.148	1.00	34.62	N
ATOM	16	N	ALA	A	9	15.607	-5.689	-7.270	1.00	25.59	N
ATOM	17	CA	ALA	A	9	14.514	-5.118	-6.483	1.00	24.63	C
ATOM	18	C	ALA	A	9	13.282	-4.941	-7.363	1.00	23.75	C
ATOM	19	O	ALA	A	9	13.376	-4.516	-8.526	1.00	23.15	O
ATOM	20	CB	ALA	A	9	14.934	-3.766	-5.885	1.00	24.47	C
ATOM	21	N	ARG	A	10	12.130	-5.234	-6.781	1.00	22.67	N
ATOM	22	CA	ARG	A	10	10.856	-5.139	-7.459	1.00	22.08	C
ATOM	23	C	ARG	A	10	10.371	-3.694	-7.515	1.00	21.33	C
ATOM	24	O	ARG	A	10	9.507	-3.357	-8.324	1.00	20.81	O
ATOM	25	CB	ARG	A	10	9.833	-6.045	-6.754	1.00	21.79	C
ATOM	26	CG	ARG	A	10	9.946	-7.504	-7.139	1.00	21.89	C
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ATOM	28	NE	ARG	A	10	7.573	-8.170	-6.669	1.00	23.88	N
ATOM	29	CZ	ARG	A	10	6.588	-8.289	-5.780	1.00	24.40	C
ATOM	30	NH1	ARG	A	10	6.863	-8.648	-4.532	1.00	23.52	N
ATOM	31	NH2	ARG	A	10	5.322	-8.034	-6.136	1.00	24.29	N
ATOM	32	N	VAL	A	11	10.931	-2.853	-6.635	1.00	21.41	N
ATOM	33	CA	VAL	A	11	10.640	-1.408	-6.579	1.00	21.07	C
ATOM	34	C	VAL	A	11	11.914	-0.562	-6.456	1.00	21.26	C
ATOM	35	O	VAL	A	11	12.946	-1.050	-5.997	1.00	22.06	O

What is 2QC6 (PDB) file?

Atom type

x y z

B-factor

Atom nature

Non Protein Section

Ligand

Water

```
ATOM   2727  CB  SER A 333      -8.342  13.167  11.706  1.00 51.40           C
ATOM   2728  OG  SER A 333      -7.797  12.662  12.919  1.00 52.01           O
TER    2729      SER A 333
HETATM 2730 BR2  G12 A   1      20.650   8.471  20.916  1.00 51.98          BR
HETATM 2731  C9  G12 A   1      21.692   7.938  19.427  1.00 45.05           C
HETATM 2732  C8  G12 A   1      22.621   6.774  19.465  1.00 44.74           C
HETATM 2733 O15  G12 A   1      22.787   6.088  20.498  1.00 44.64           O
HETATM 2734  O7  G12 A   1      23.314   6.442  18.337  1.00 45.00           O
HETATM 2735 C10  G12 A   1      21.551   8.693  18.173  1.00 44.20           C
HETATM 2736 C13  G12 A   1      20.618   9.867  18.082  1.00 44.59           C
HETATM 2737  C5  G12 A   1      22.354   8.248  17.019  1.00 45.13           C
HETATM 2738  C6  G12 A   1      23.193   7.145  17.166  1.00 45.44           C
HETATM 2739  C4  G12 A   1      23.939   6.712  16.090  1.00 45.37           C
HETATM 2740 BR1  G12 A   1      25.061   5.204  16.311  1.00 44.84          BR
HETATM 2741  C1  G12 A   1      22.267   8.913  15.806  1.00 45.05           C
HETATM 2742  C2  G12 A   1      23.018   8.470  14.731  1.00 45.33           C
HETATM 2743  C3  G12 A   1      23.853   7.371  14.882  1.00 44.73           C
HETATM 2744 O11  G12 A   1      24.583   6.936  13.845  1.00 44.40           O
HETATM 2745  O   HOH A 338      28.603  -4.301   0.274  1.00 13.90           O
HETATM 2746  O   HOH A 339      10.108  -7.819  -1.861  1.00 13.66           O
HETATM 2747  O   HOH A 340      29.059   0.775  16.008  1.00 19.28           O
HETATM 2748  O   HOH A 341      28.308  -2.821  17.106  1.00 19.02           O
HETATM 2749  O   HOH A 342       8.605   0.556  -0.492  1.00 18.64           O
HETATM 2750  O   HOH A 343       5.590  -1.502  -3.364  1.00 15.93           O
HETATM 2751  O   HOH A 344      27.589   3.375  18.794  1.00 14.60           O
HETATM 2752  O   HOH A 345       8.818 -18.316   2.986  1.00 20.07           O
HETATM 2753  O   HOH A 346      17.195 -13.534  11.106  1.00 20.47           O
HETATM 2754  O   HOH A 347      23.343   0.813   8.635  1.00 14.16           O
HETATM 2755  O   HOH A 348      15.283 -12.405  15.280  1.00 17.82           O
HETATM 2756  O   HOH A 349      10.663  -1.408   0.328  1.00 17.95           O
HETATM 2757  O   HOH A 350      10.339  -6.191   0.394  1.00 17.39           O
HETATM 2758  O   HOH A 351      22.933  -5.598  18.304  1.00 20.84           O
HETATM 2759  O   HOH A 352      23.709  -1.241  17.886  1.00 24.15           O
HETATM 2760  O   HOH A 353      12.658  -4.413  -3.116  1.00 23.02           O
HETATM 2761  O   HOH A 354       1.686   3.543   1.943  1.00 17.91           O
HETATM 2762  O   HOH A 355      12.045  -6.921  18.846  1.00 14.26           O
HETATM 2763  O   HOH A 356      20.687  12.874   8.027  1.00 21.36           O
```

Can we represent 2QC6 (PDB) data?

Protein Section

		Atom type				x	y	z		B-factor	Atom nature
ATOM	1	N	SER	A	7	18.809	-11.548	-9.537	1.00	30.22	N
ATOM	2	CA	SER	A	7	17.758	-10.860	-8.731	1.00	29.23	C
ATOM	3	C	SER	A	7	17.891	-9.329	-8.850	1.00	29.40	C
ATOM	4	O	SER	A	7	18.997	-8.794	-8.756	1.00	29.43	O
ATOM	5	CB	SER	A	7	17.853	-11.306	-7.257	1.00	29.91	C
ATOM	6	OG	SER	A	7	16.761	-10.832	-6.474	1.00	28.29	O
ATOM	7	N	LYS	A	8	16.765	-8.642	-9.075	1.00	29.05	N
ATOM	8	CA	LYS	A	8	16.661	-7.201	-8.846	1.00	28.10	C
ATOM	9	C	LYS	A	8	15.546	-6.888	-7.842	1.00	26.83	C
ATOM	10	O	LYS	A	8	14.668	-7.713	-7.590	1.00	26.71	O
ATOM	11	CB	LYS	A	8	16.479	-6.409	-10.156	1.00	28.45	C
ATOM	12	CG	LYS	A	8	15.230	-6.746	-10.960	1.00	31.04	C
ATOM	13	CD	LYS	A	8	15.113	-5.946	-12.280	1.00	29.28	C
ATOM	14	CE	LYS	A	8	13.733	-6.182	-12.904	1.00	32.90	C
ATOM	15	NZ	LYS	A	8	13.412	-5.378	-14.148	1.00	34.62	N
ATOM	16	N	ALA	A	9	15.607	-5.689	-7.270	1.00	25.59	N
ATOM	17	CA	ALA	A	9	14.514	-5.118	-6.483	1.00	24.63	C
ATOM	18	C	ALA	A	9	13.282	-4.941	-7.363	1.00	23.75	C
ATOM	19	O	ALA	A	9	13.376	-4.516	-8.526	1.00	23.15	O
ATOM	20	CB	ALA	A	9	14.934	-3.766	-5.885	1.00	24.47	C
ATOM	21	N	ARG	A	10	12.130	-5.234	-6.781	1.00	22.67	N
ATOM	22	CA	ARG	A	10	10.856	-5.139	-7.459	1.00	22.08	C
ATOM	23	C	ARG	A	10	10.371	-3.694	-7.515	1.00	21.33	C
ATOM	24	O	ARG	A	10	9.507	-3.357	-8.324	1.00	20.81	O
ATOM	25	CB	ARG	A	10	9.833	-6.045	-6.754	1.00	21.79	C
ATOM	26	CG	ARG	A	10	9.946	-7.504	-7.139	1.00	21.89	C
ATOM	27	CD	ARG	A	10	8.988	-8.414	-6.372	1.00	22.38	C
ATOM	28	NE	ARG	A	10	7.573	-8.170	-6.669	1.00	23.88	N
ATOM	29	CZ	ARG	A	10	6.588	-8.289	-5.780	1.00	24.40	C
ATOM	30	NH1	ARG	A	10	6.863	-8.648	-4.532	1.00	23.52	N
ATOM	31	NH2	ARG	A	10	5.322	-8.034	-6.136	1.00	24.29	N
ATOM	32	N	VAL	A	11	10.931	-2.853	-6.635	1.00	21.41	N
ATOM	33	CA	VAL	A	11	10.640	-1.408	-6.579	1.00	21.07	C
ATOM	34	C	VAL	A	11	11.914	-0.562	-6.456	1.00	21.26	C
ATOM	35	O	VAL	A	11	12.946	-1.050	-5.997	1.00	22.06	O

I would like to be very honest with you!

z

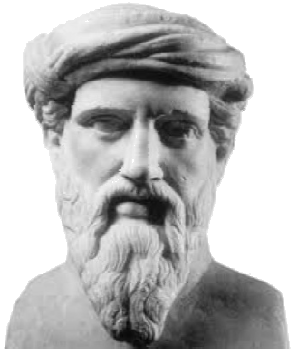
C (x, y, z)

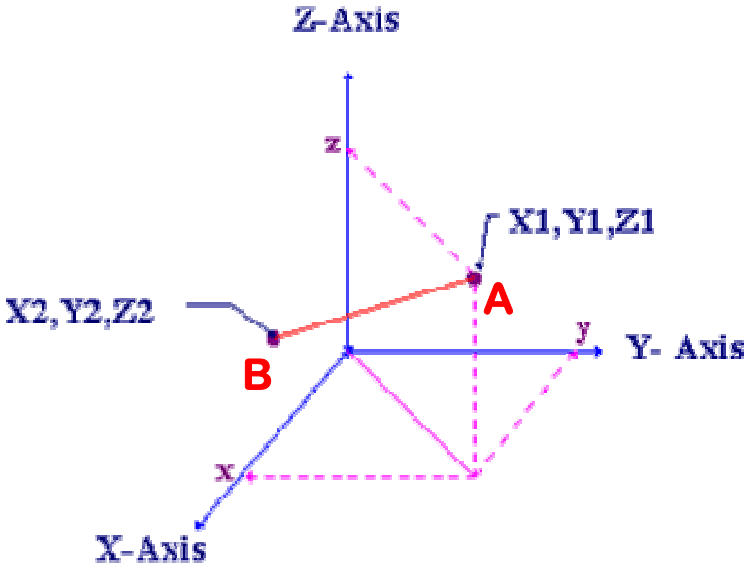
x

y

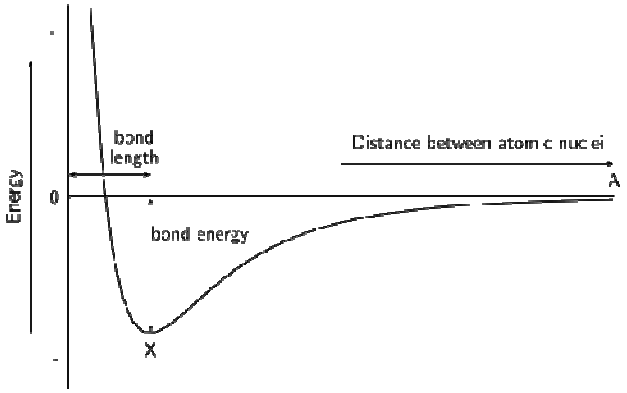
= C
= N
= O
= S

What can we easily measure in a 3D Cartesian space?

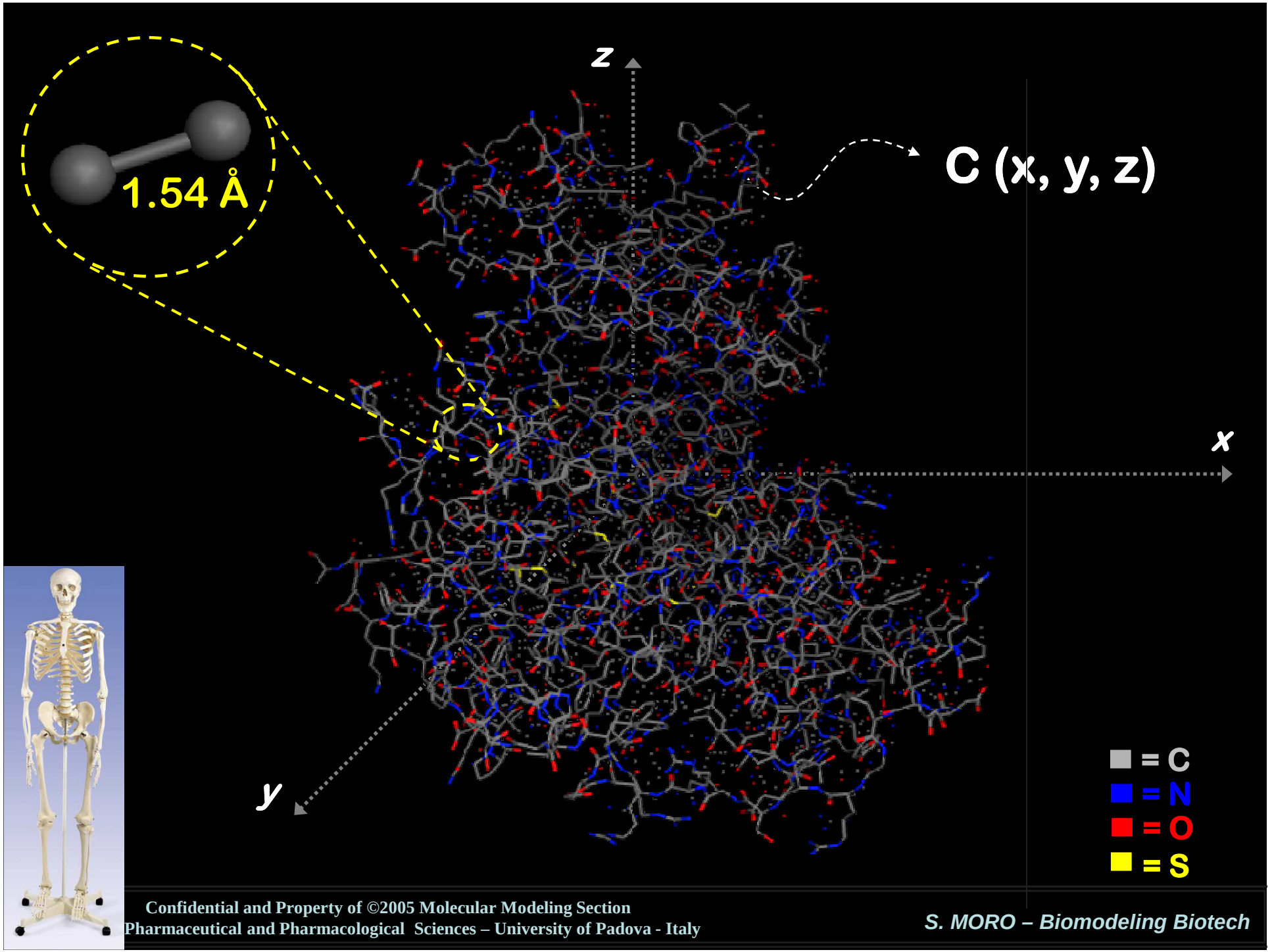




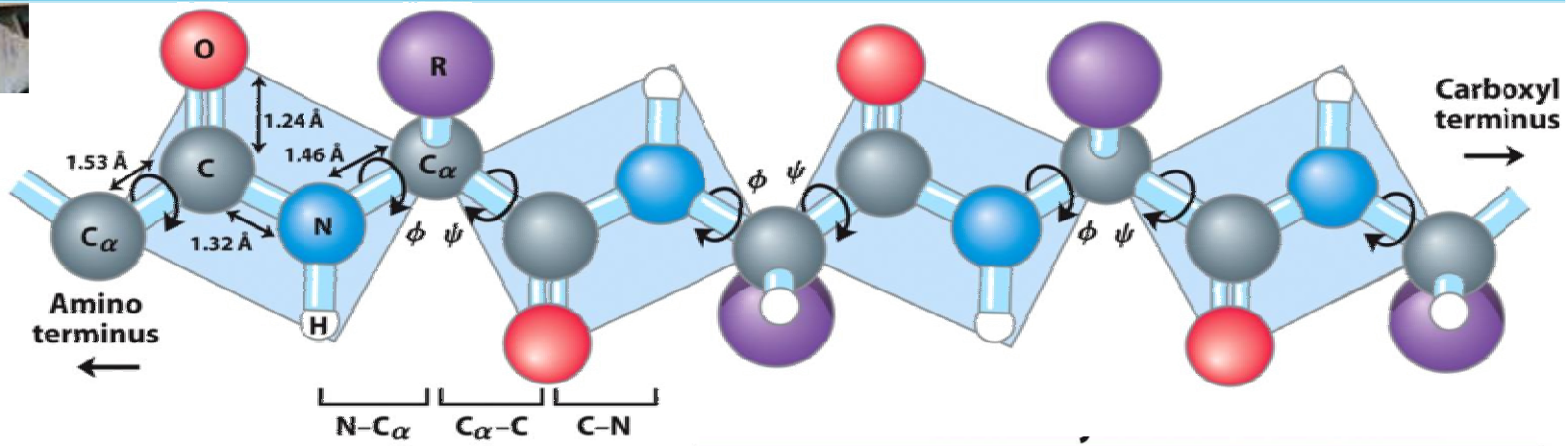
$$\overline{AB} = \sqrt{(X1 - X2)^2 + (Y1 - Y2)^2 + (Z1 - Z2)^2}$$

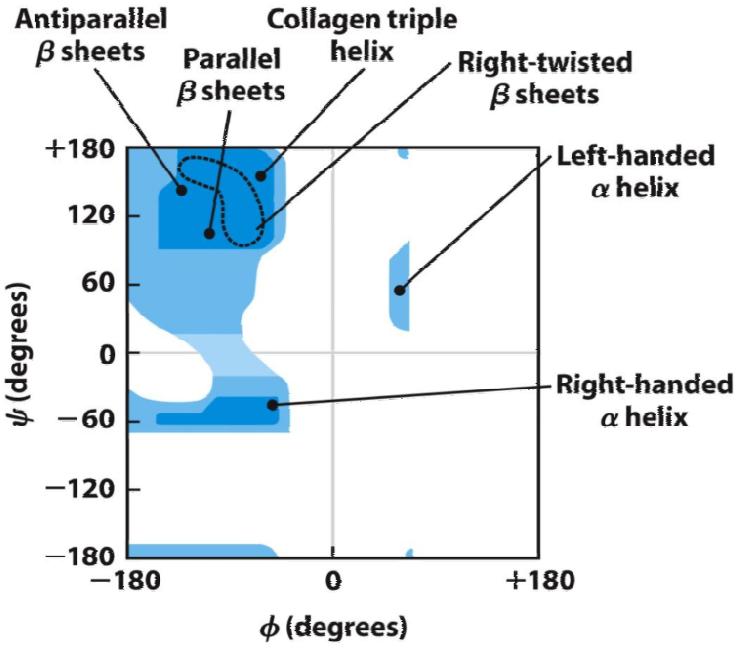


Bond	Bond Length (Å)	Bond	Bond Length (Å)
C—C	1.54	N—N	1.47
C═C	1.34	N═N	1.24
C≡C	1.20	N≡N	1.10
C—N	1.43	N—O	1.36
C═N	1.38	N═O	1.22
C≡N	1.16		
		O—O	1.48
C—O	1.43	O═O	1.21
C═O	1.23		
C≡O	1.13		



There are some interesting geometrical regularity inside our polimer:

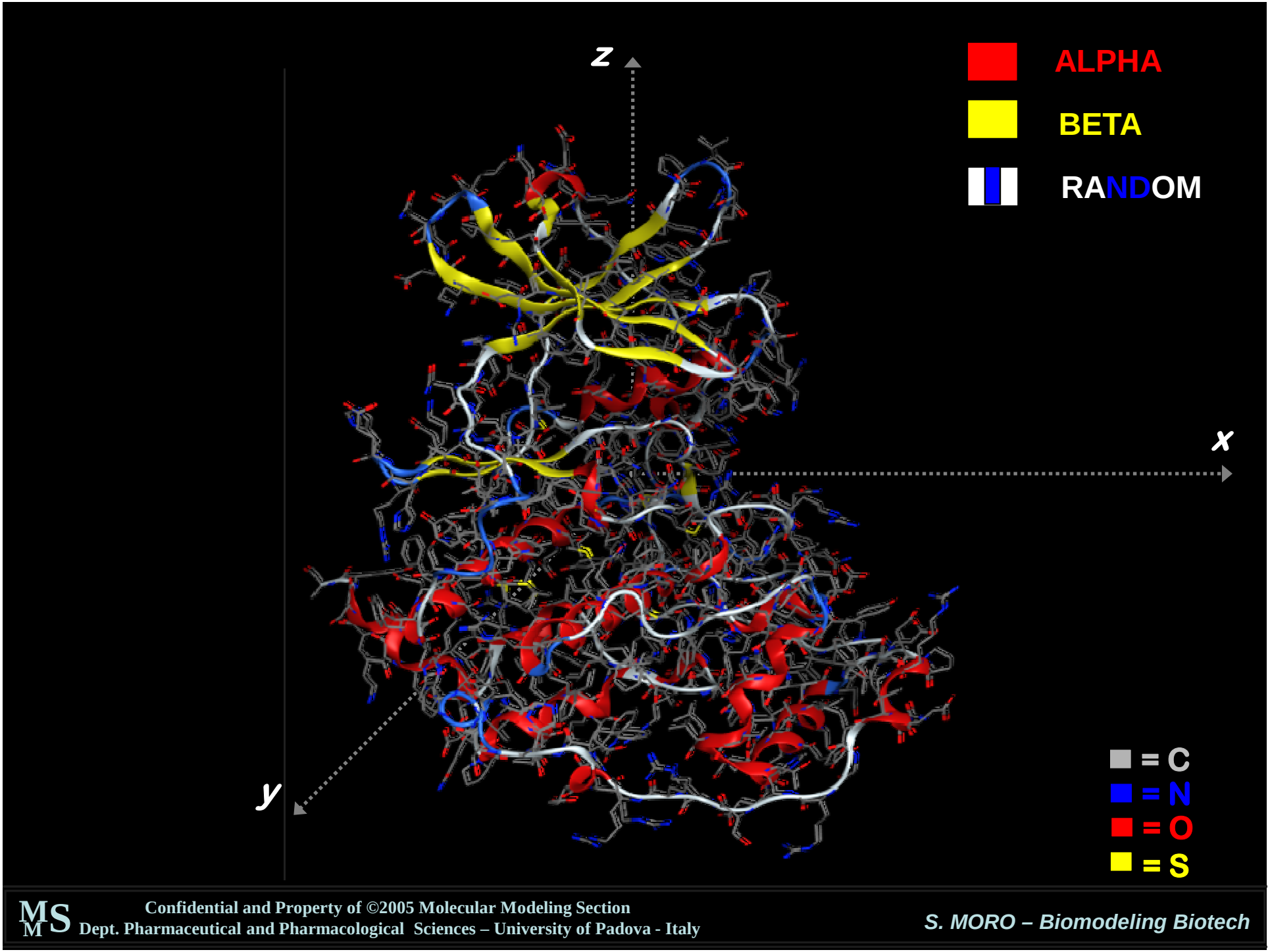




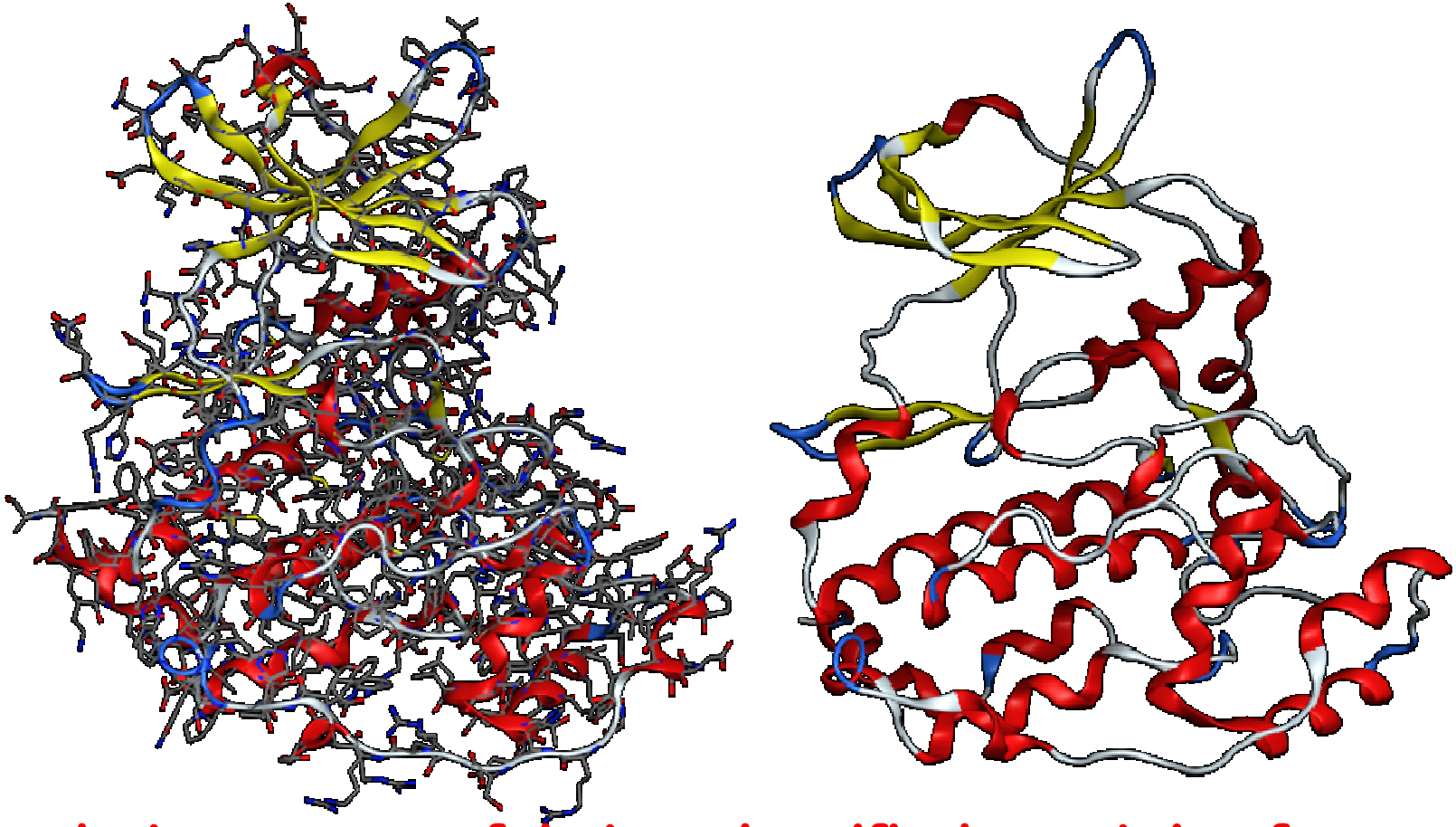
Structure	ϕ	ψ
α Helix	−57°	−47°
β Conformation		
Antiparallel	−139°	+135°
Parallel	−119°	+113°
Collagen triple helix	−51°	+153°
β Turn type I		
i + 1*	−60°	−30°
i + 2*	−90°	0°
β Turn type II		
i + 1	−60°	+120°
i + 2	+80°	0°

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!!!

Atomic radius… could be one?

The atomic radius of a chemical element is a measure of the size of its atoms, usually the mean or typical distance from the nucleus to the boundary of the surrounding cloud of electrons.

Since the boundary is not a well-defined physical entity, there are various non-equivalent definitions of atomic radius. Three widely used definitions of atomic radius are *van der Waals radius, ionic radius, and covalent radius.*

Johannes Diderik van der Waals (23 November 1837 – 8 March 1923) was a Dutch theoretical physicist and thermodynamicist famous for his work on an equation of state for gases and liquids.

His name is primarily associated with the van der Waals equation of state that describes the behavior of gases and their condensation to the liquid phase. His name is also associated with van der Waals forces (forces between stable molecules), with van der Waals molecules (small molecular clusters bound by van der Waals forces), and with van der Waals radii (sizes of molecules).

He became the first physics professor of the University of Amsterdam when it opened in 1877 and won the 1910 Nobel Prize in physics.

WIKIPEDIA
The Free Encyclopedia

van der Waals radius: **in principle, half the minimum distance between the nuclei of two atoms of the element that are not bound to the same molecule.**

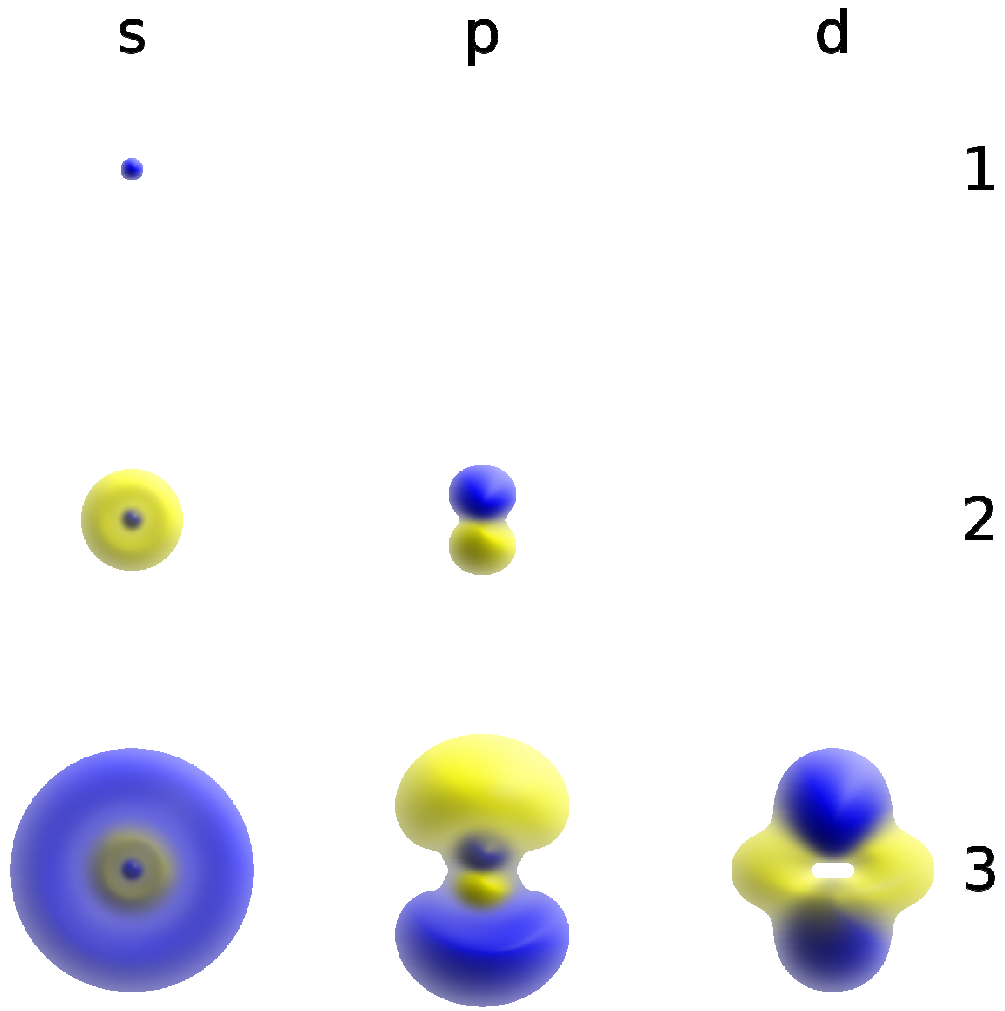
A quick refresh…

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

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

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

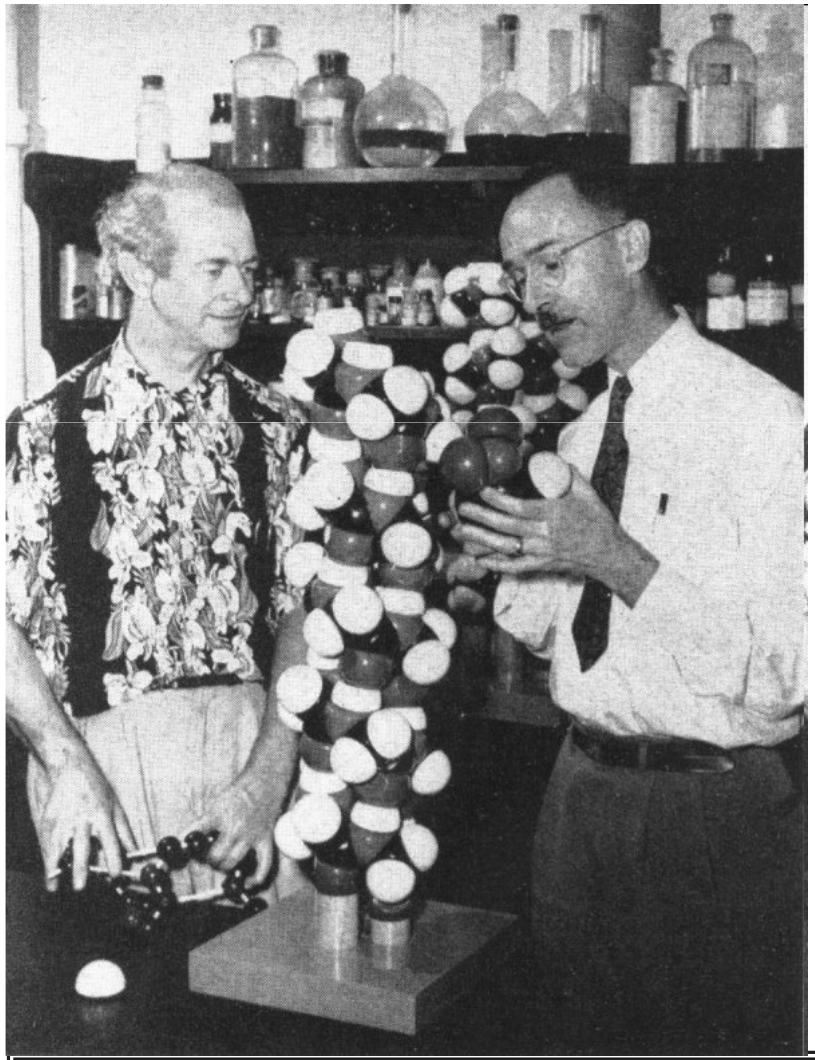
Why an atom has a spherical shape?



The images are 3D renderings of the spatial density distribution of $|\psi|^2$ with the color depicting the phase of ψ. The spatial distribution is smooth and vanishes for large radii. The cloud is a more realistic representation of an orbital than the more common solid-body approximations.

Credits: https://en.wikipedia.org/wiki/Electron#/media/File:Atomic-orbital-clouds_spd_m0.png

From Cartesian coordinates to van der Waals spheres:



Robert B. Corey and Linus Pauling "Molecular Models of Amino Acids, Peptides, and Proteins." Rev. Sci. Instrum. 24, 621 (1953).

Abstract: A set of accurate scale models has been developed for use in studies of the structures of amino acids, peptides, and proteins. Models representing atoms or groups of atoms built from hard wood to the scale 1 in. = 1Å are connected by a clamping device which maintains desired molecular configurations. These accurate models have been used as substitutes for calculation in investigations of the probable configuration of the polypeptide chain in proteins. Analogous models constructed of rubber-like plastic to the scale 1 in. = 2Å and connected by snap fasteners are designed for qualitative studies of protein structure.

From Cartesian coordinates to van der Waals spheres:

NOW AVAILABLE FOR THE FIRST TIME-THE LONG AWAITED, INEXPENSIVE

NEW COREY-PAULING SPACE FILLING ATOMIC MODELS WITH KOLTUN CONNECTORS

Note the strength of the individual linkages. Locking connectors are used to assure the planarity of the amide group.

These new CPK Models were designed by the Atomic Models Subcommittee of the Biophysics and Biophysical Chemistry Study Section of the National Institutes of Health, Washington, D.C. Over 40 scientists from more than two dozen research centers contributed to the work of this Committee.

The CPK designs which emerged have been implemented by the American Society of Biological Chemists with financial support from the United States National Science Foundation.

A definitive history and technical analysis of the CPK Models has appeared: W. L. Koltun, *Biopolymers*, 3, (1965), pp. 665-79. Reprints are available upon request.

These new CPK Models are offered by Ealing for immediate delivery from stock:
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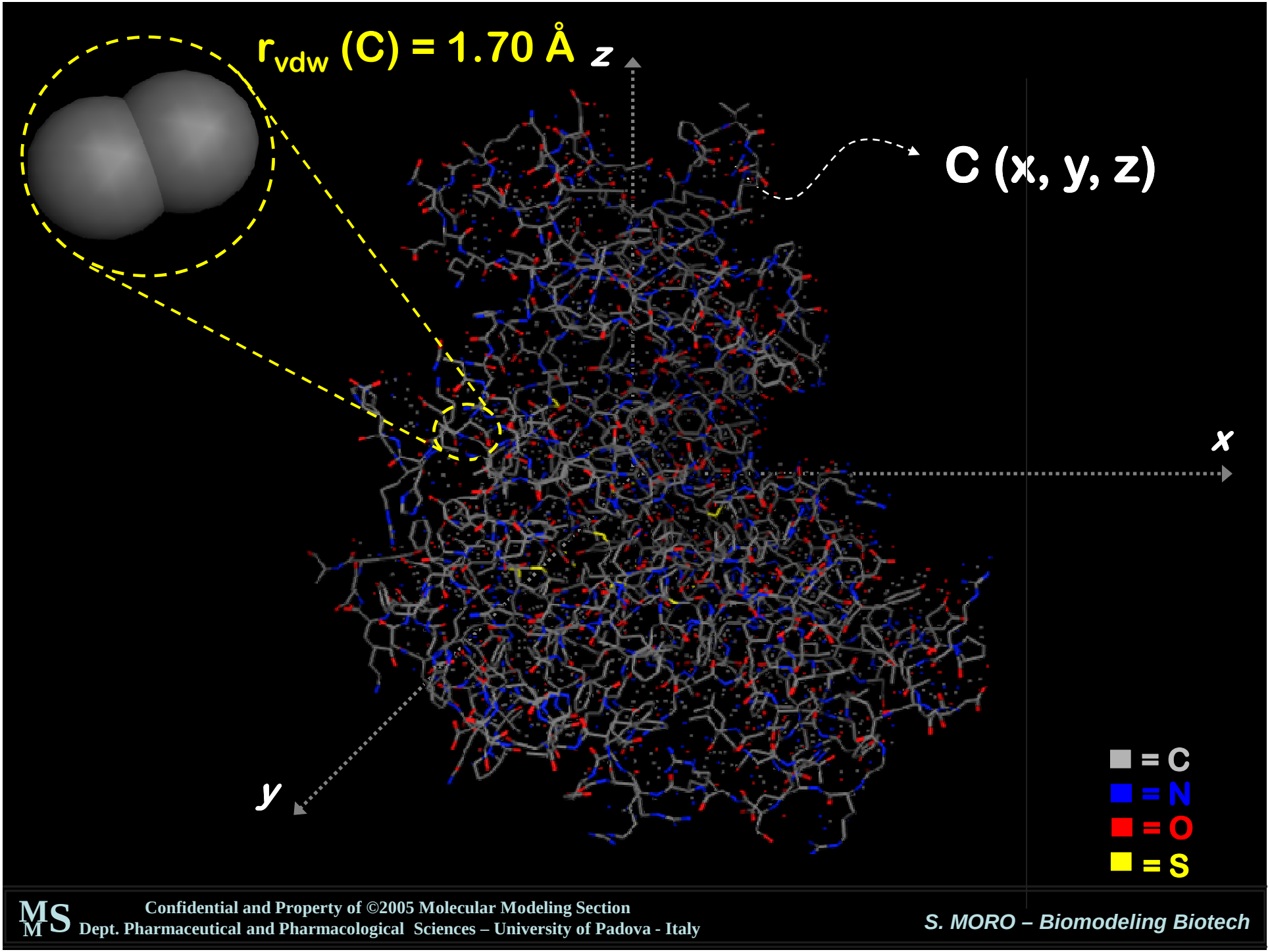
SCIENCE, VOL. 152

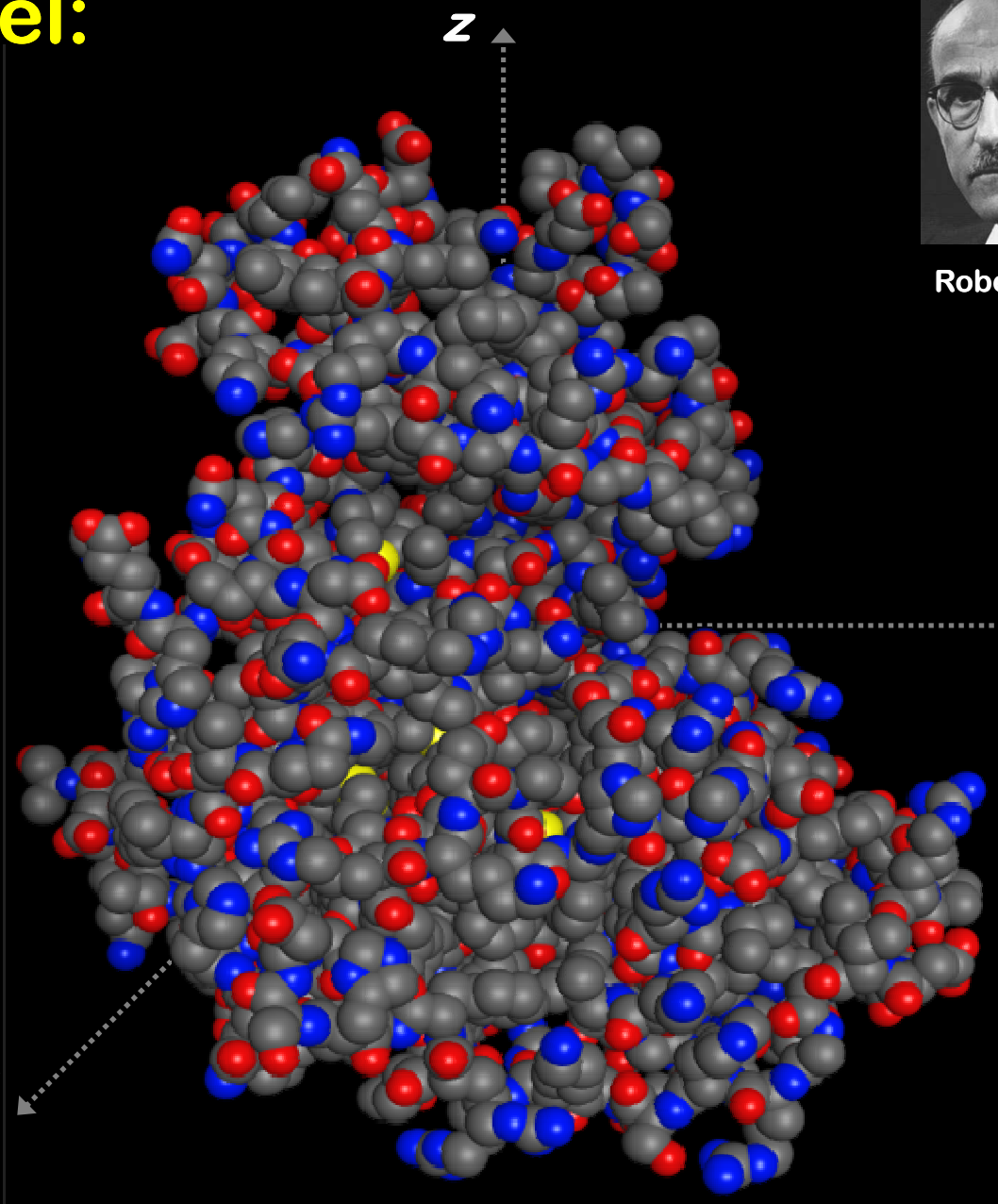
DR. WALTER LANG KOLTUN



CPK model:

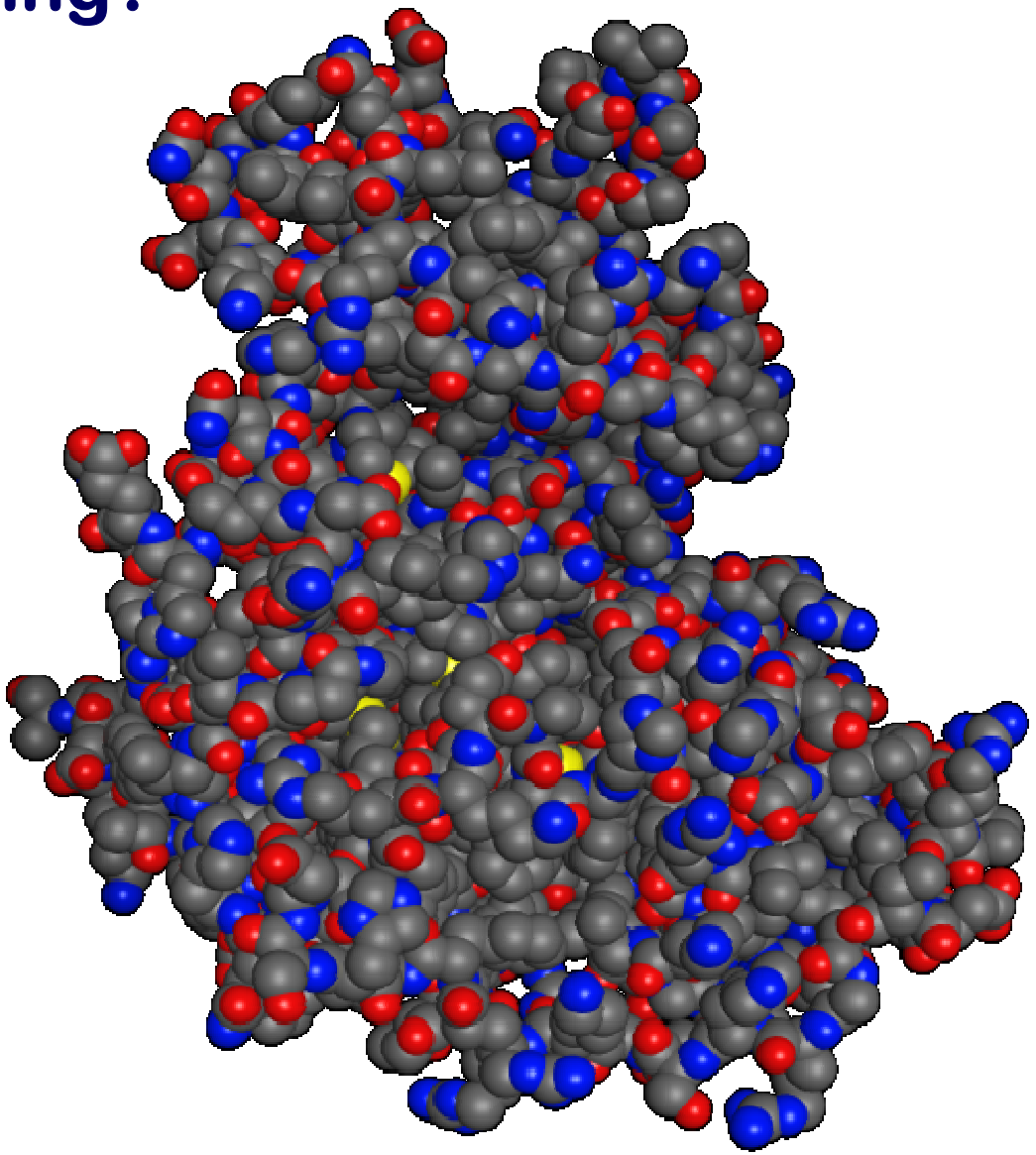
Robert Corey Linus Pauling

Walter Koltun



= C
= N
= O
= S

Before proceeding further… what is it missing?

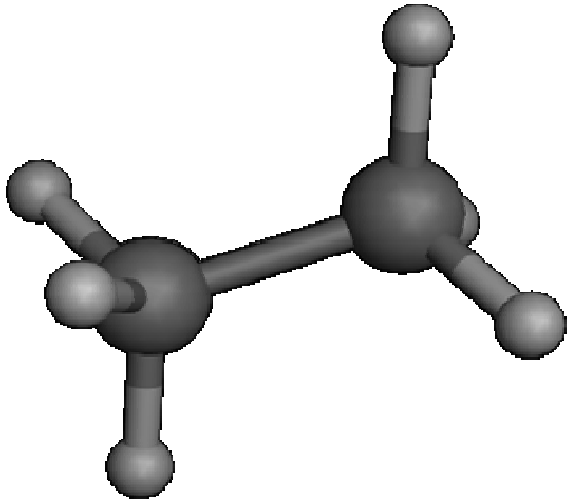


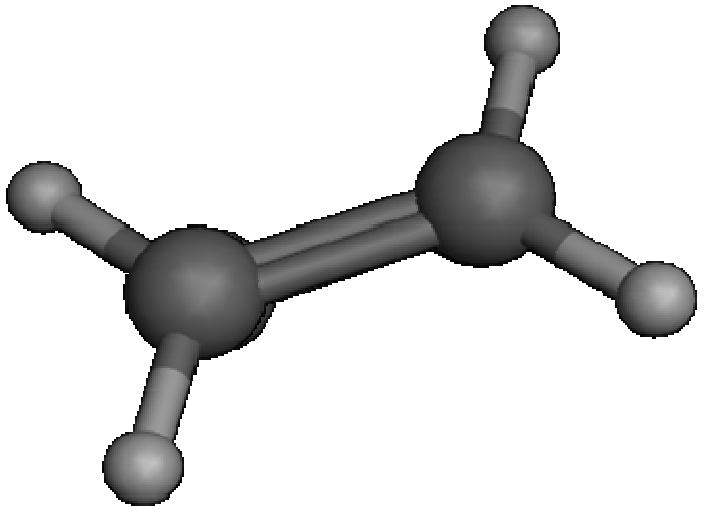
Yes, hydrogen atoms!

REMEMBER: X-ray crystallography and Cryo_EM cannot resolve *hydrogen atoms* in most protein crystals, so in most *PDB files*, *hydrogen atoms* are absent.

a. Several tools can be used to hydrogen atoms… respecting the valence properties of all heavy atoms and the geometrical characteristics (distances and angles) of all X-H bonds.

Yes, hydrogen atoms!





C_{sp3} angle 109 °

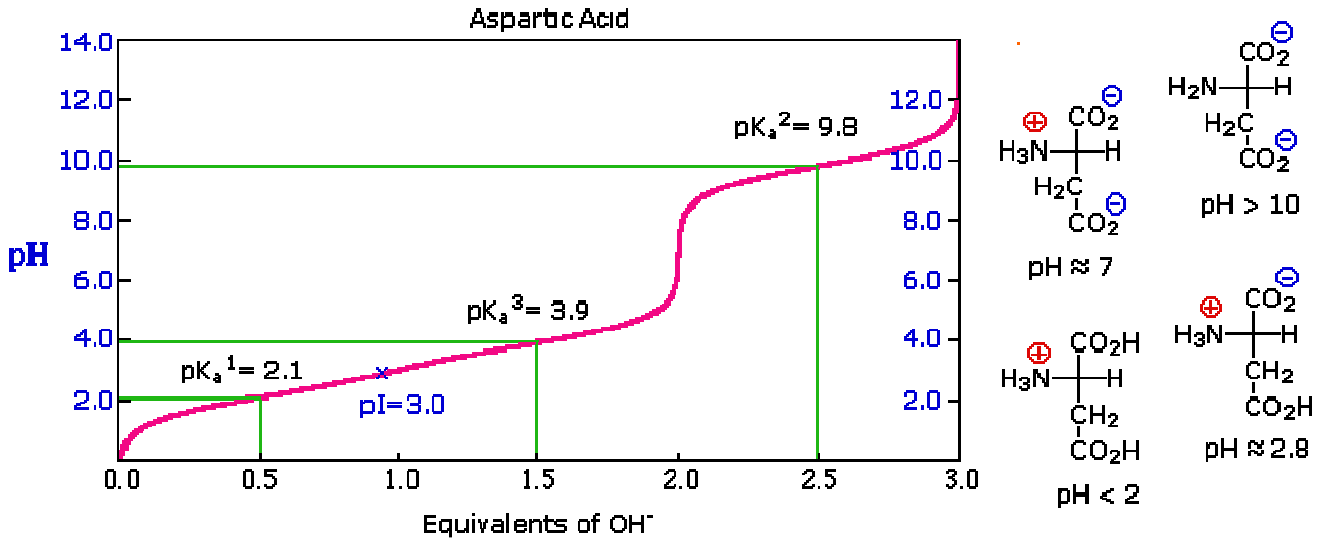
C_{sp2} angle 120 °

C_{sp3} – H length 1.09 Å

C_{sp3} – H length 1.08 Å

but we have hydrogens… and hydrogens!

b. Moreover, hydrogen atoms associated with ionizable groups are 'titrated' according to their value of pKa and pH value of medium solvent:



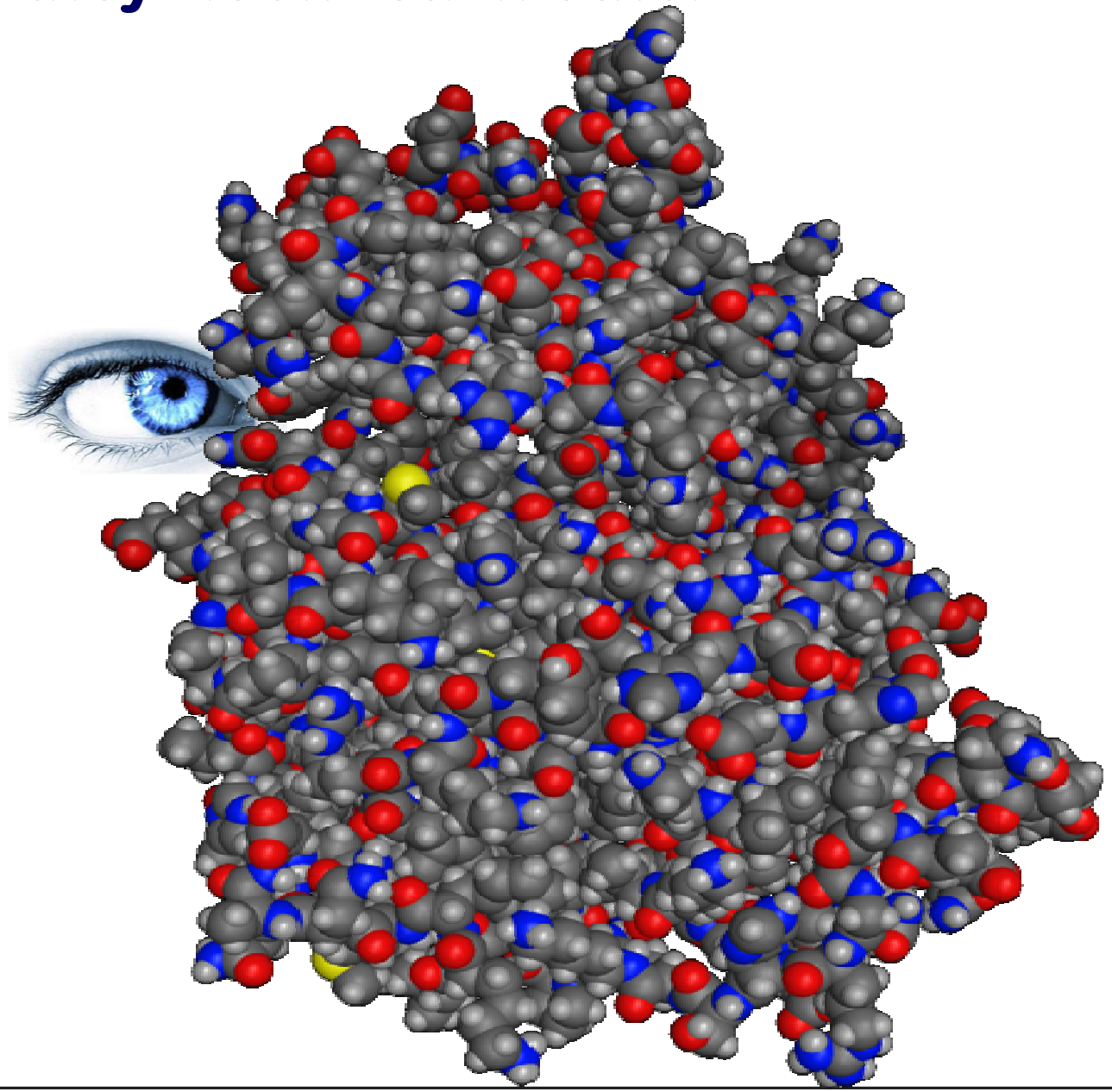
… here they are!

Lys

Glu

= C
= N
= O
= S
= H

But how they “look” each other?



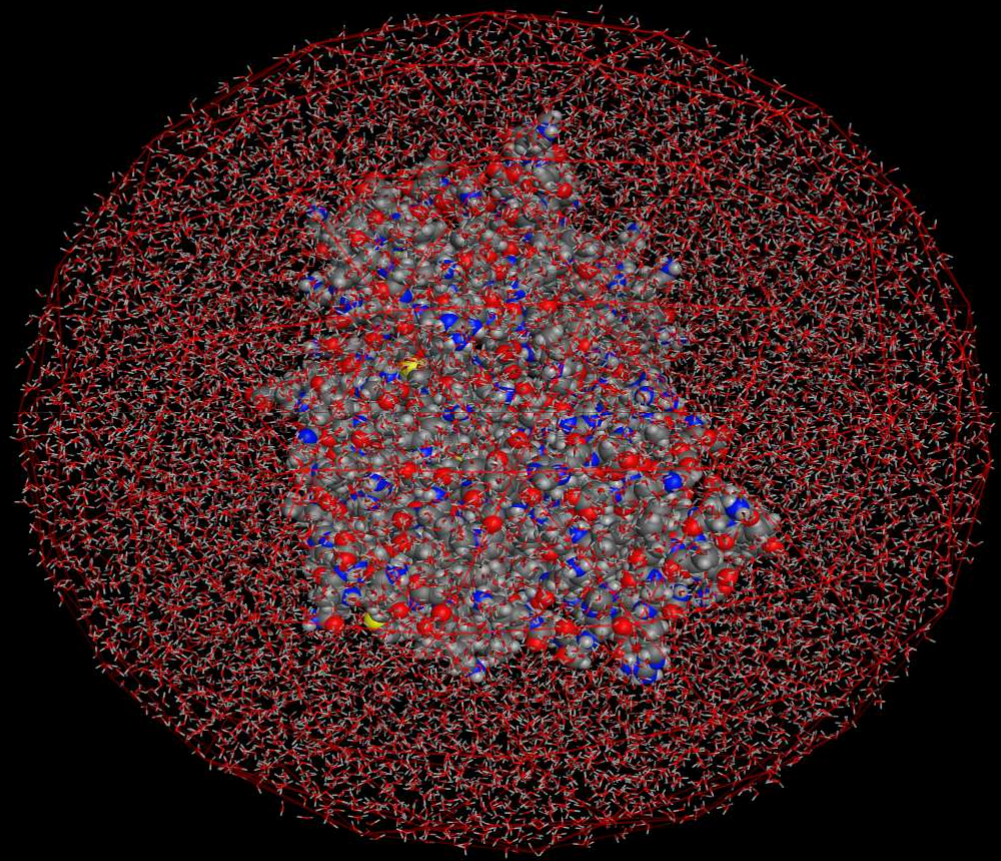
Back when I was a young PhD student.

"It is generally accepted that receptor and substrate molecules recognize each other at their molecular surfaces. Therefore, the binding strength of a receptor-drug complex depends on the shape of the substrate surface and on the distribution of certain properties on this surface. Any method attempting to model biological activity should take into account this information and try to correlate it to biological activity…"

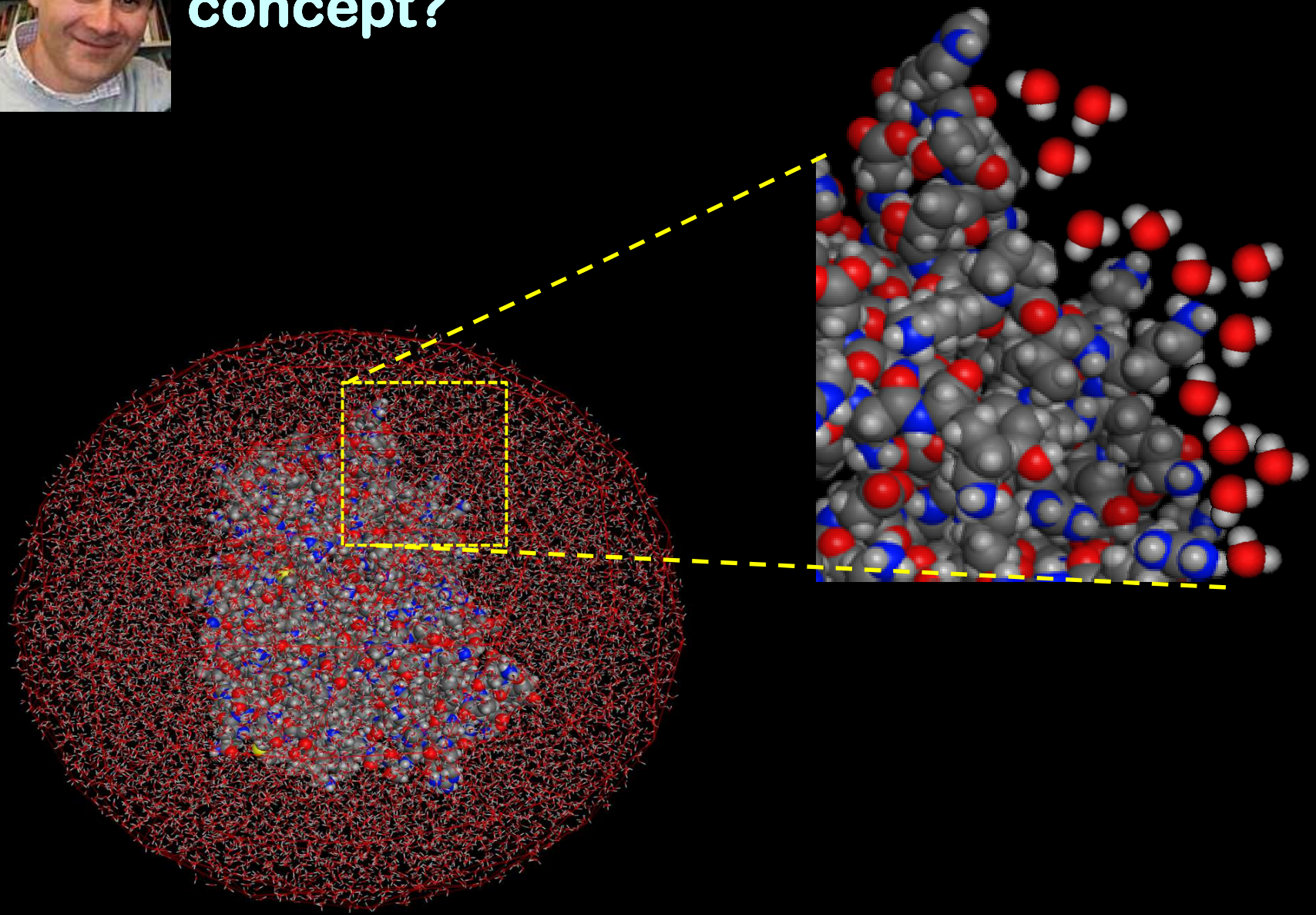
by Johann Gasteiger *et al J.A.C.S.* 1995, **117**, 7769-7775

The magic role of the solvent…

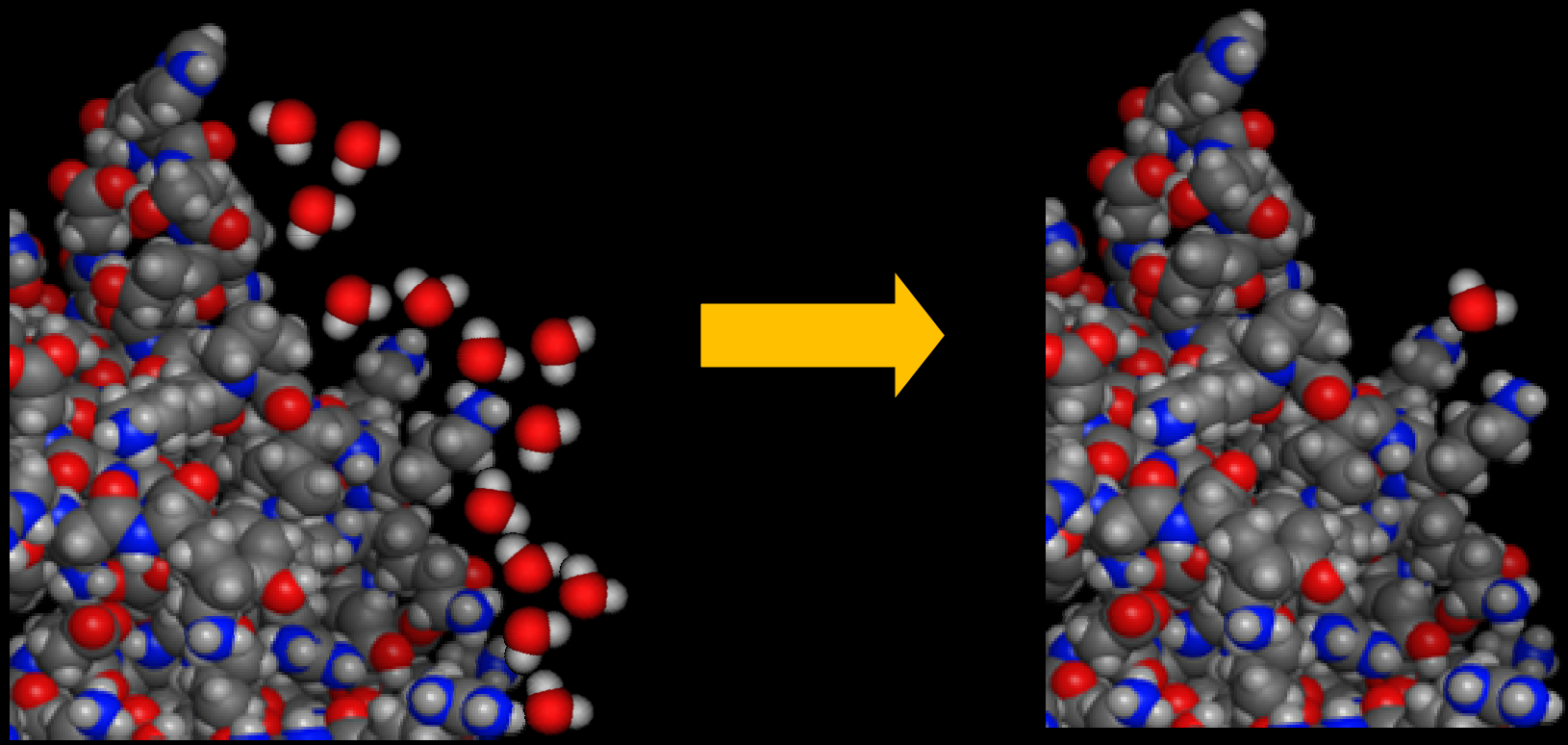
The magic role of the solvent…



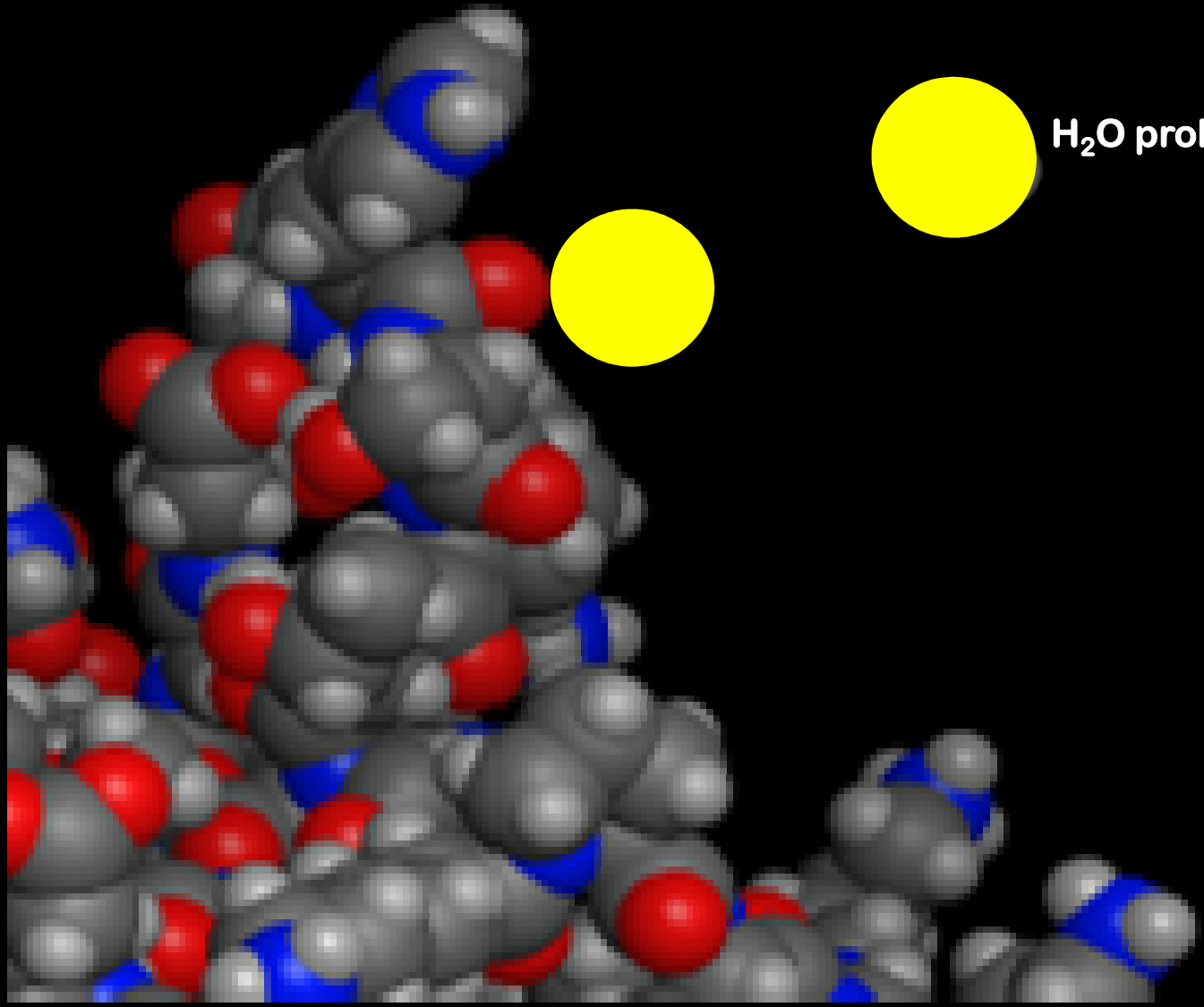
Do you remember the *hydration shell* concept?



Here is a nice experiment: how we can simulate the first shell of hydration using only ONE water molecule?



From CPK models to molecular surfaces:

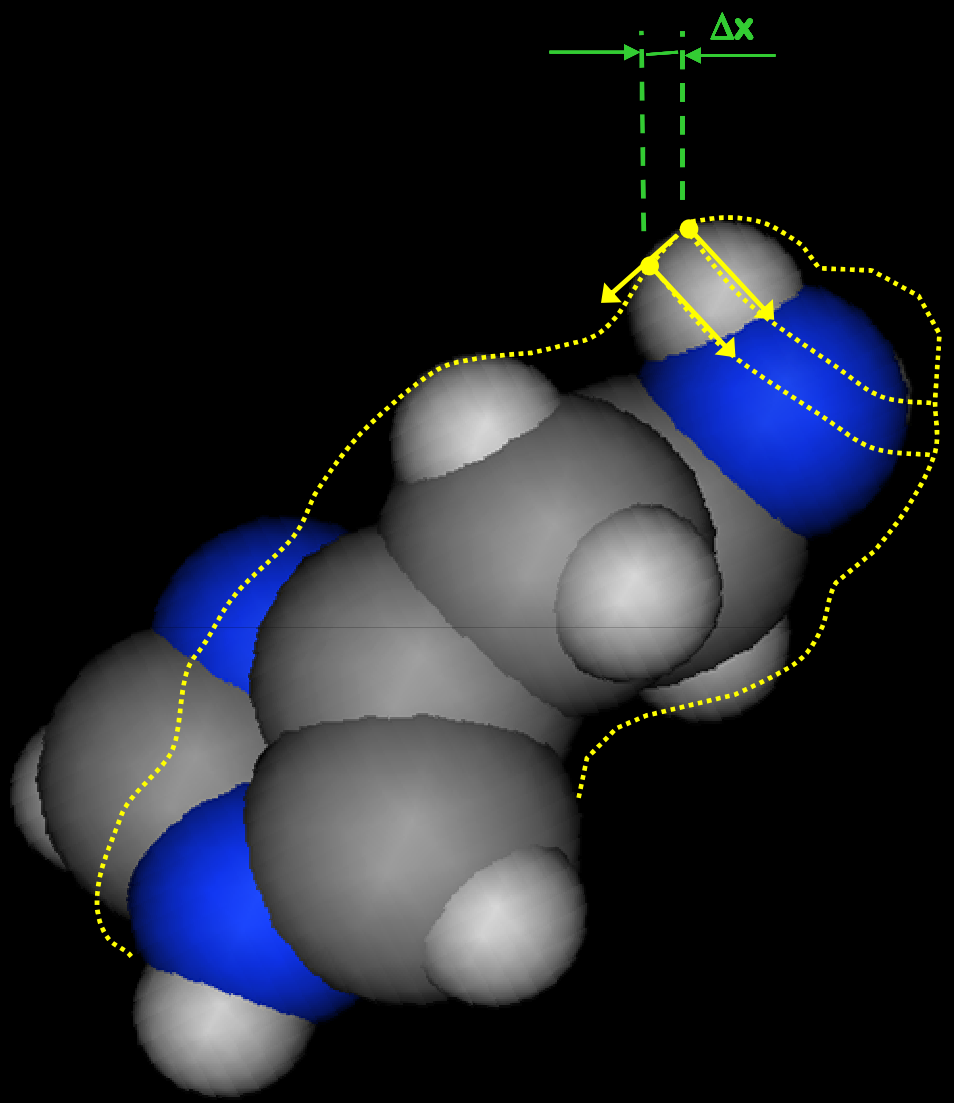


How can we SEE what has TOUCHED the probe?

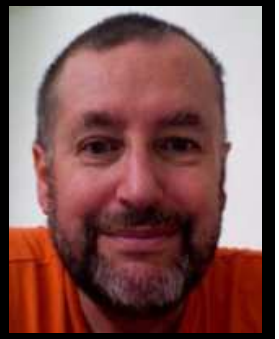
but, to transform this virtual experiment is an useful experiments we need TWO smart ideas:

1. Remember Pollicino's fairytale;
2. and…

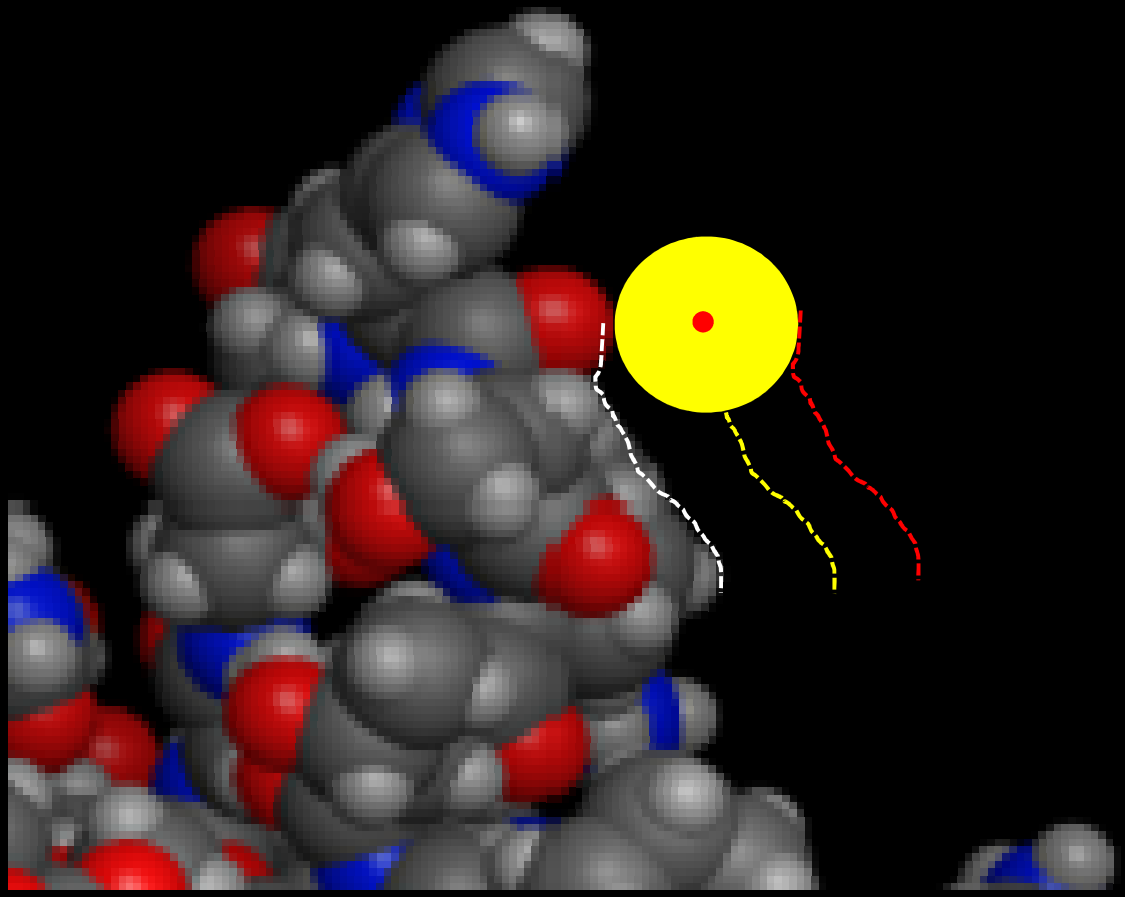
A bit of algorithm:



Molecular surface representations: Rolling Sphere method



Michael Connolly



The van der Waals Surface (vdWS) is the exterior boundary of the union of van der Waals spheres.

The Solvent Excluded Surface (SES, also known as *Connolly surface*) is the results of the SAS erosion by the same probe.

The Solvent Accessible Surface (SAS) is the result of the vdW Surface dilatation by a structuring element, or a probe, representing a solvent molecule, typically water.

Michael Connolly

z

x

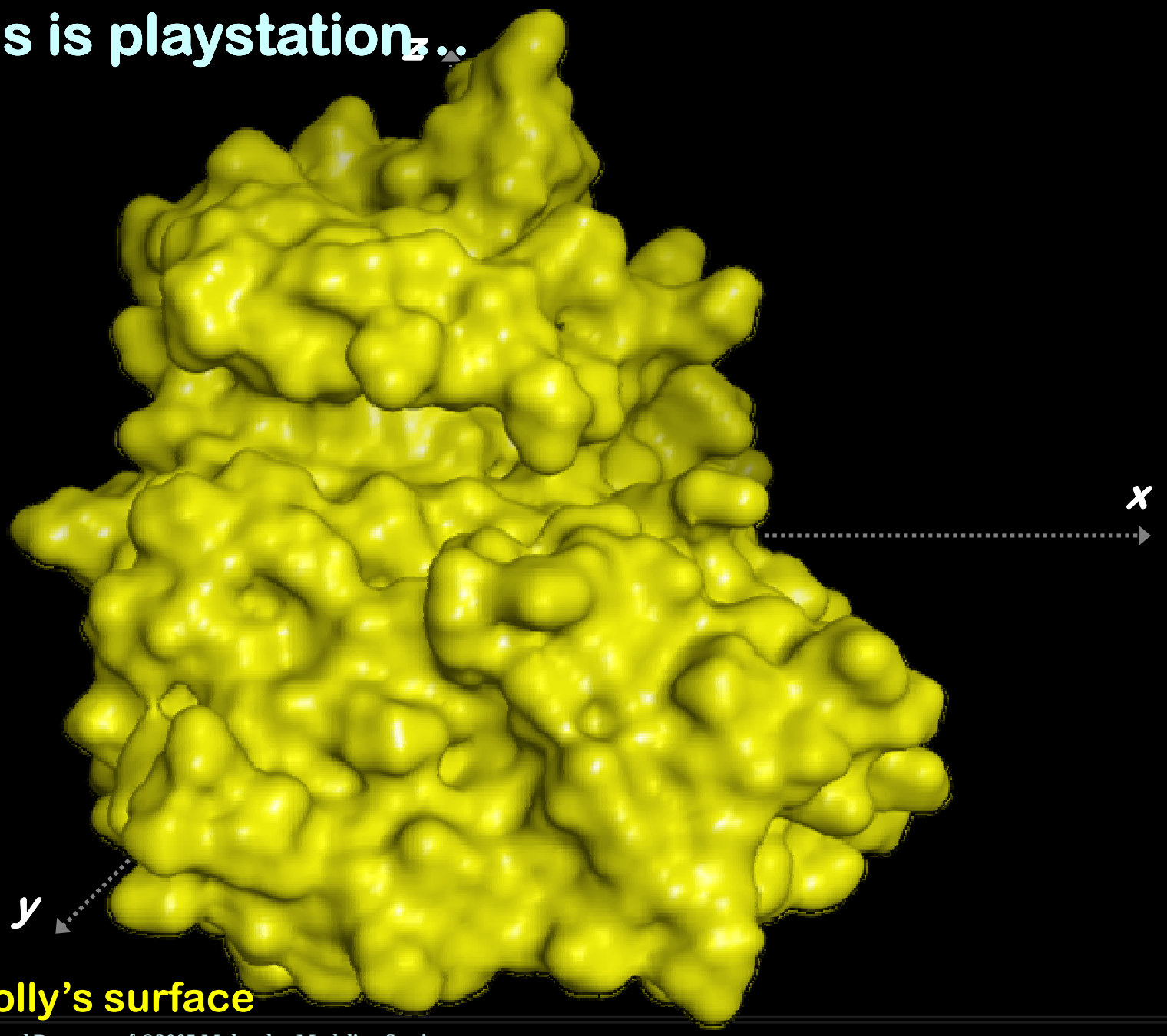
y

Connolly's surface

MS M Dept. Pharmaceutical and Pharmacological Sciences – University of Padova - Italy

S. MORO – Biomodeling Biotech

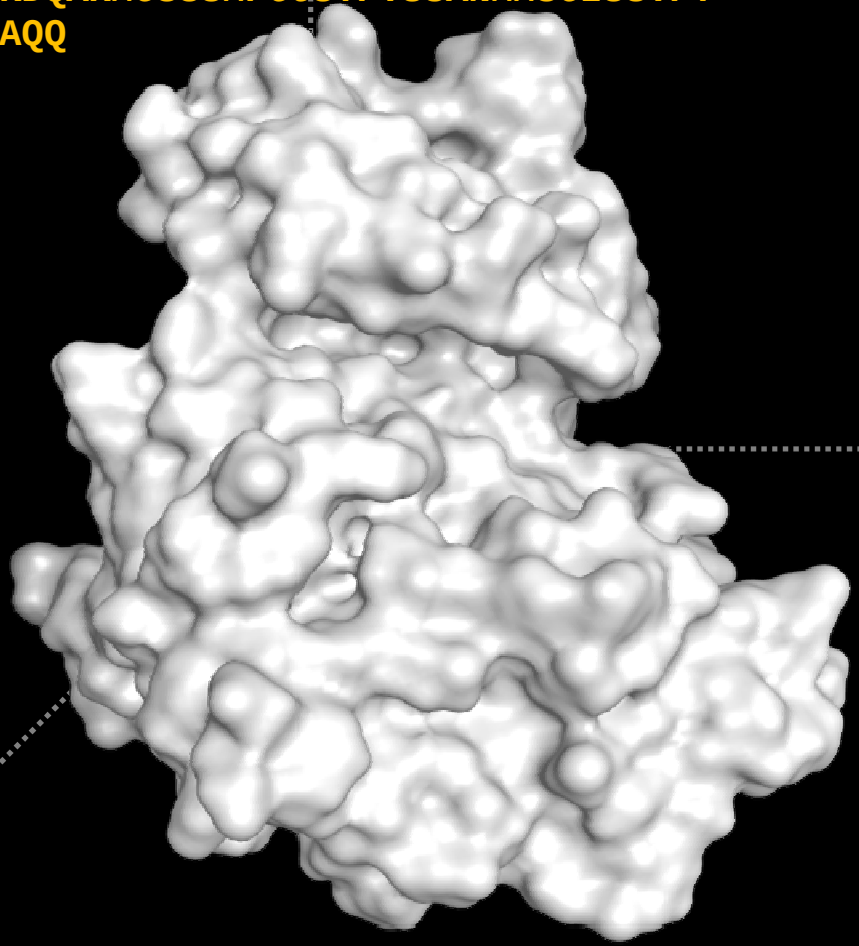
This is playstation..



Connolly's surface

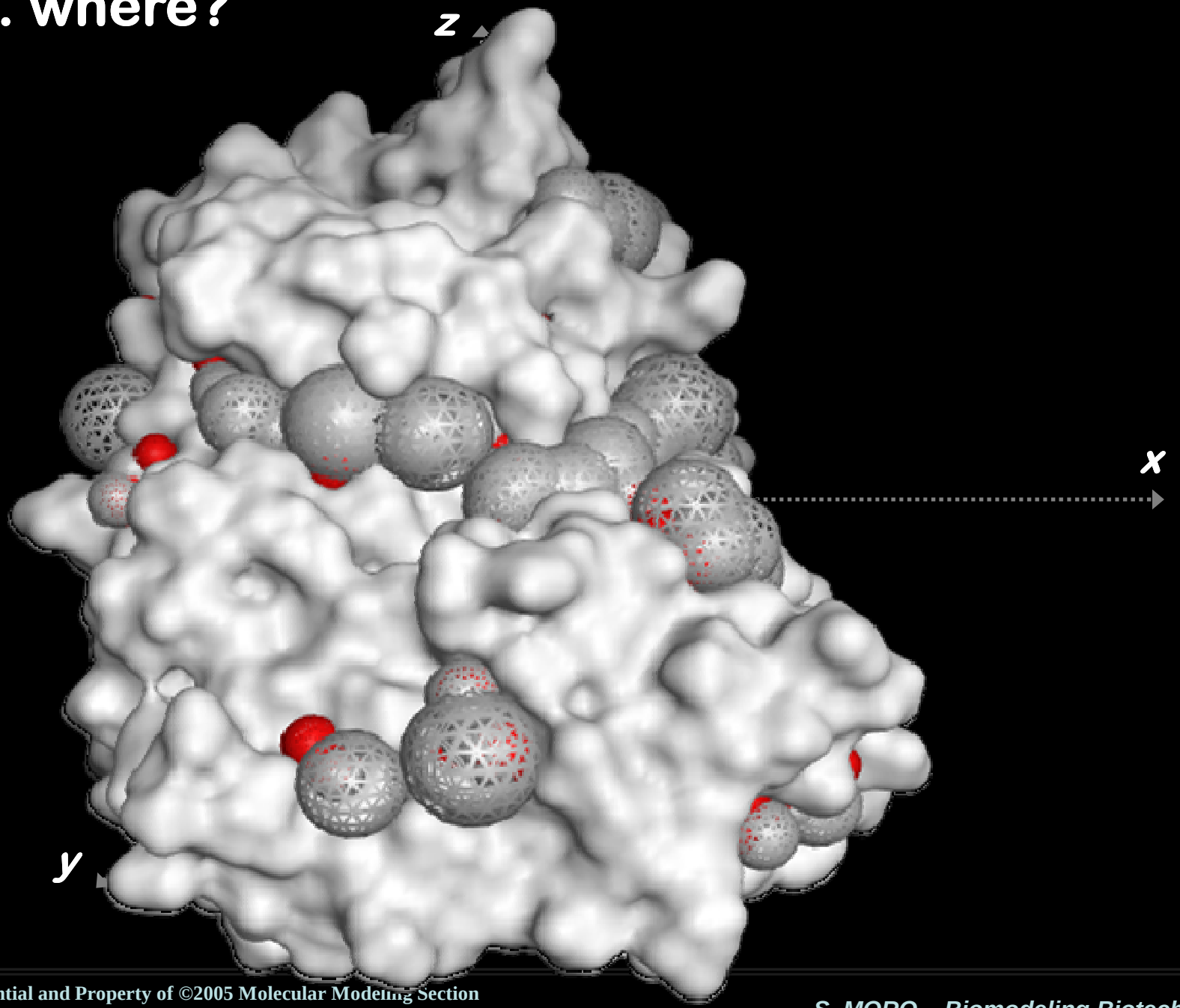
MSGPVPSRARVYTDVNTHRPREYWDYESHVVEWGNQDDYQLVRKLGRGKYSEVFEAINIT
NNEKVVVKILKPVKKKKIKREIKILENLRGGPNIITLADIVKDPVSRTPALVFEHVNNTD
FKQLYQTLTDYDIRFYMYEILKALDYCHSMGIMHRDVKPHNVMIDHEHRKLRLIDWGLAE
FYHPGQEYNVRVASRYFKGPELLVDYQMYDYSLDMWSLGCMLASMIFRKEPFFHGHDNYD
QLVRIAKVLGTEDLYDYIDKYNIELDPRFNDILGRHSRKRWERFVHSENQHLVSPEALDF
LDKLLRYDHQSRLTAREAMEHPYFYTVVKDQARMGSSSMPGGSTPVSSANMMSGISSVPT
PSPLGPLAGSPVIAAANPLGMPVPAAAGAQQ

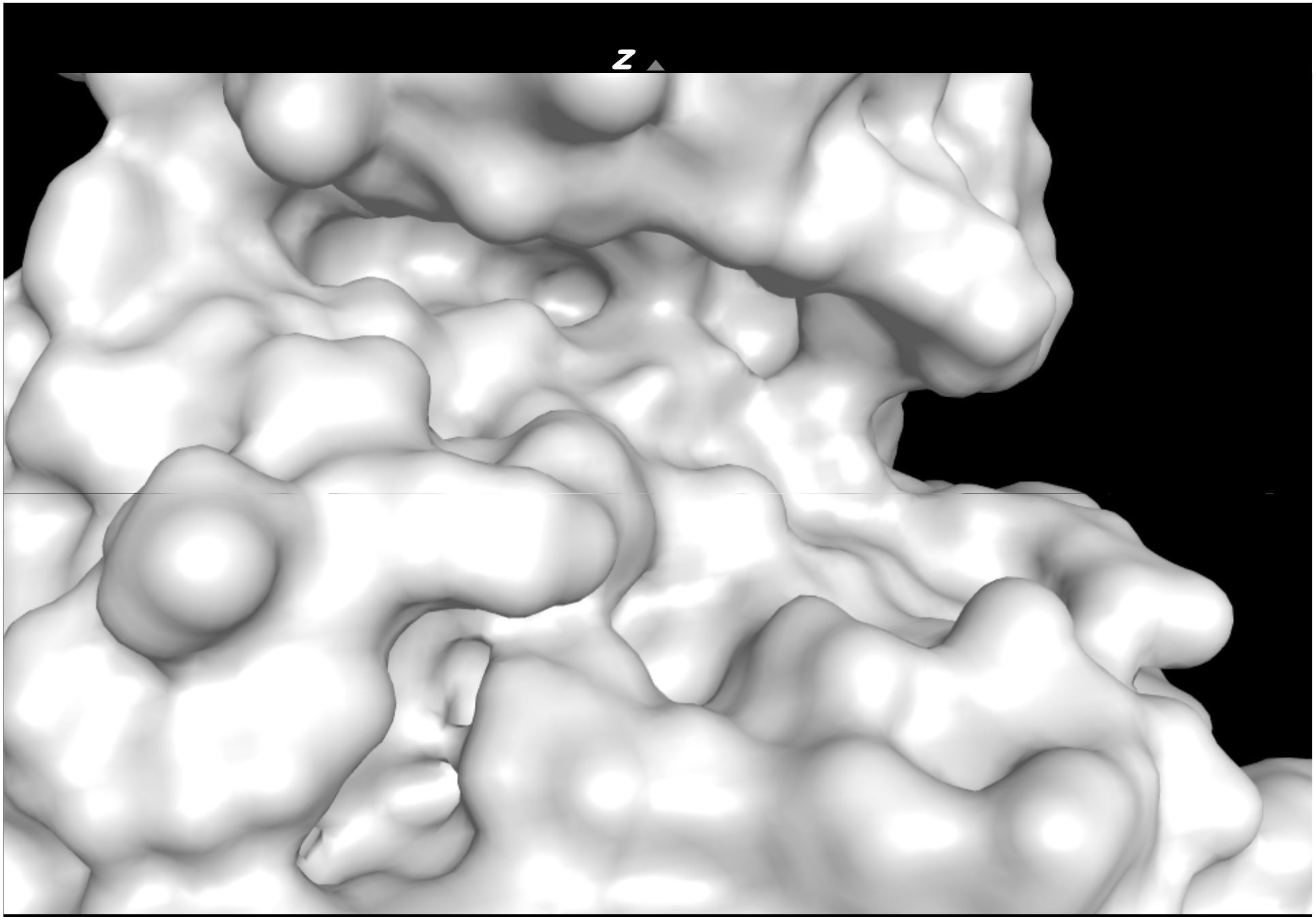
1. where?
2. how?
3. how long?

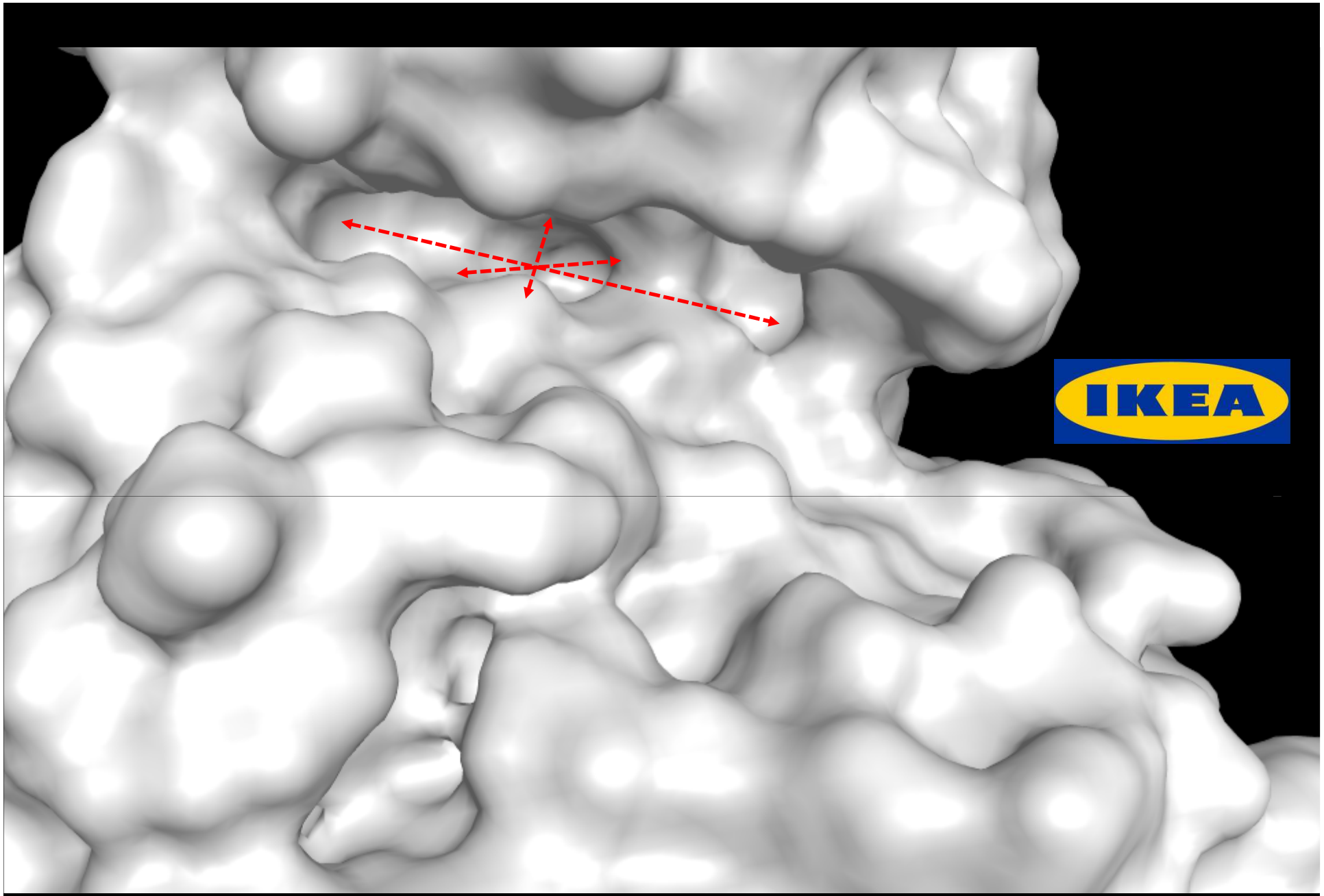


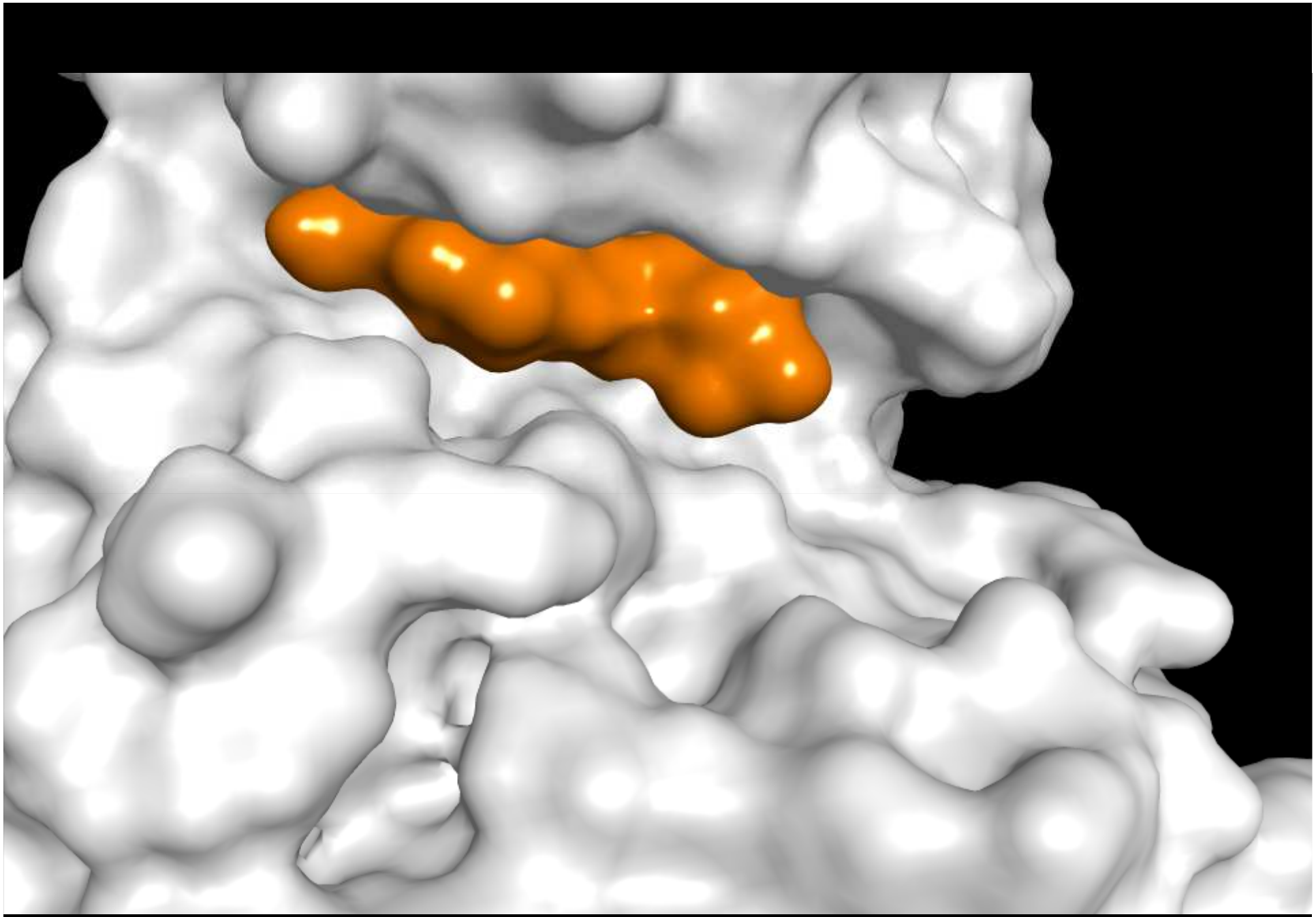
From sequence to topology… from topology to recognition

… where?

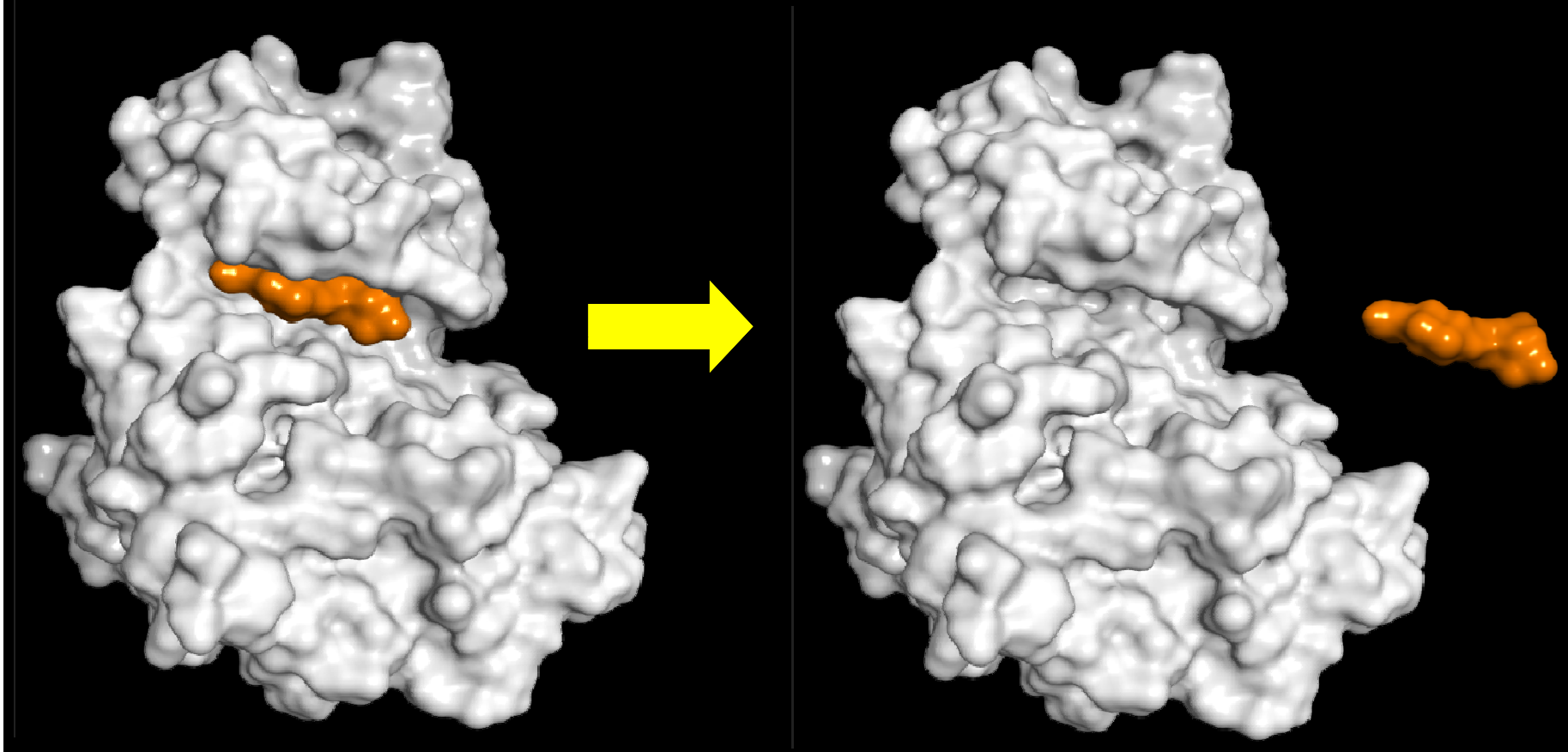




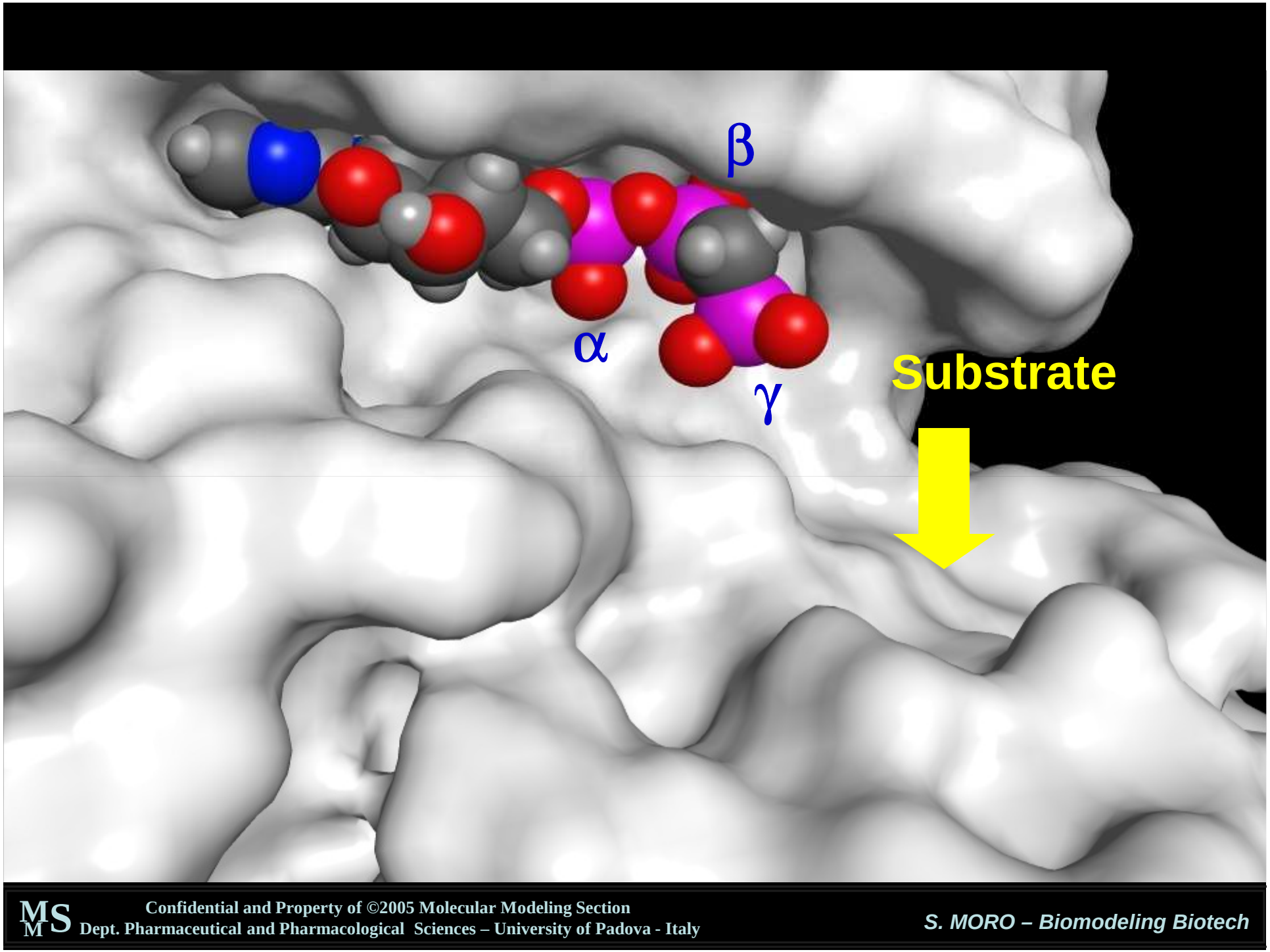


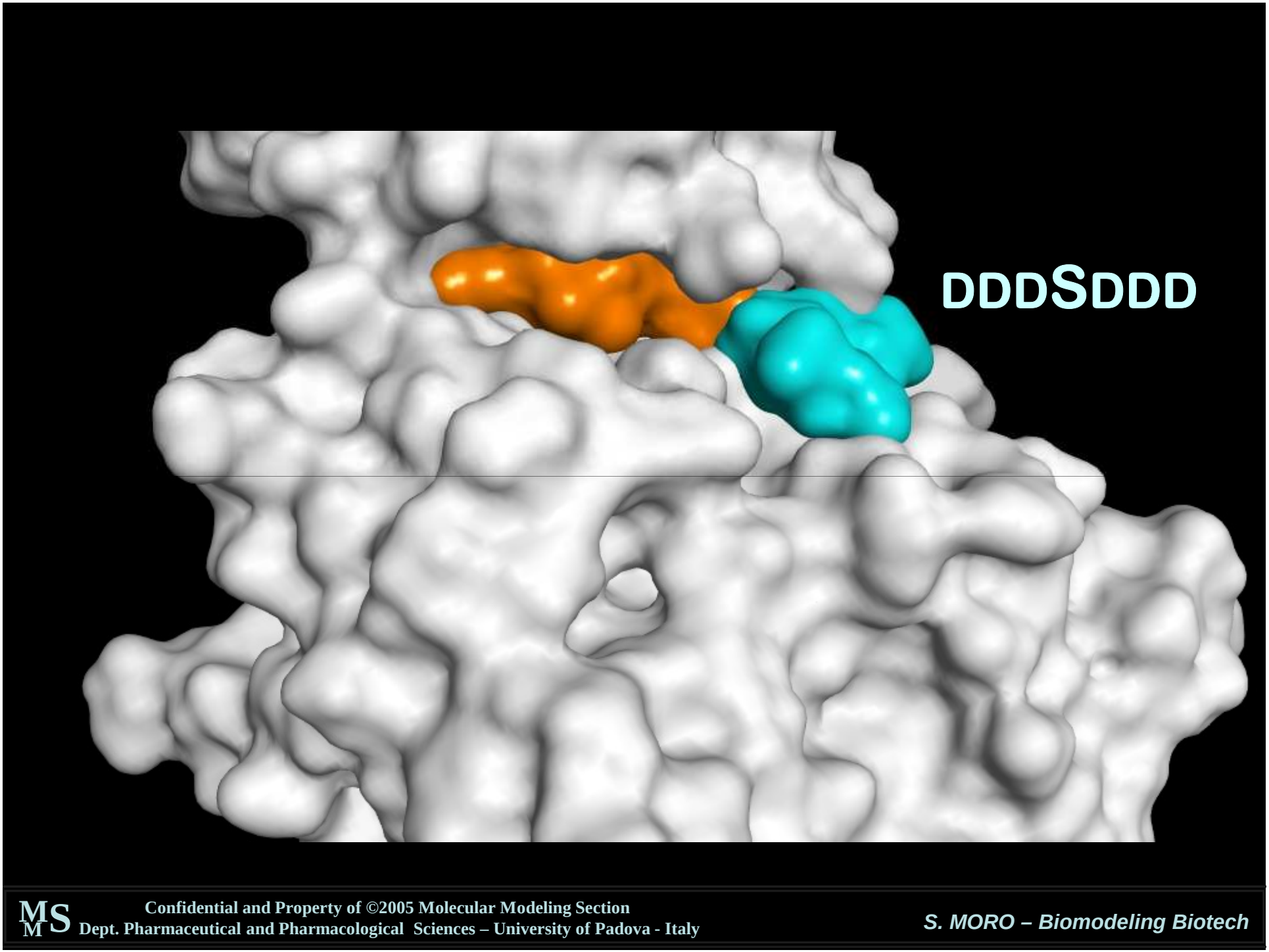


You have now a wonderful tool to estimate the topological complementarity between a cavity and its ligand:

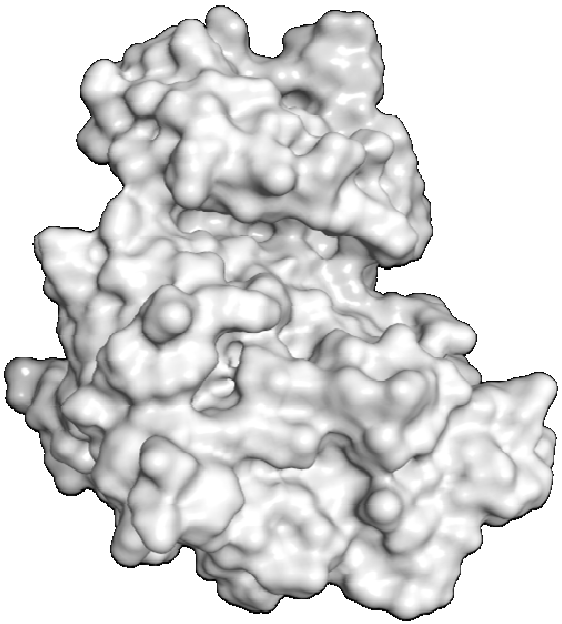


$$\text{Complementarity} \propto \text{Vol}_{\text{cavity}} - \text{Vol}_{\text{ligand}}$$

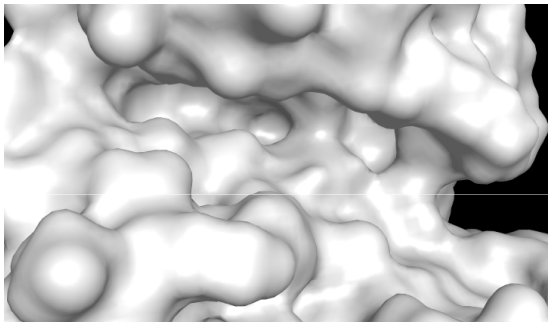




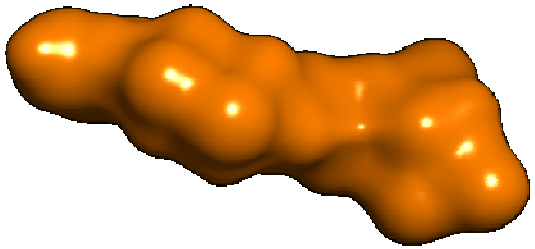
Are we able to measure these volumes?



Volume of
the protein (Å^3)



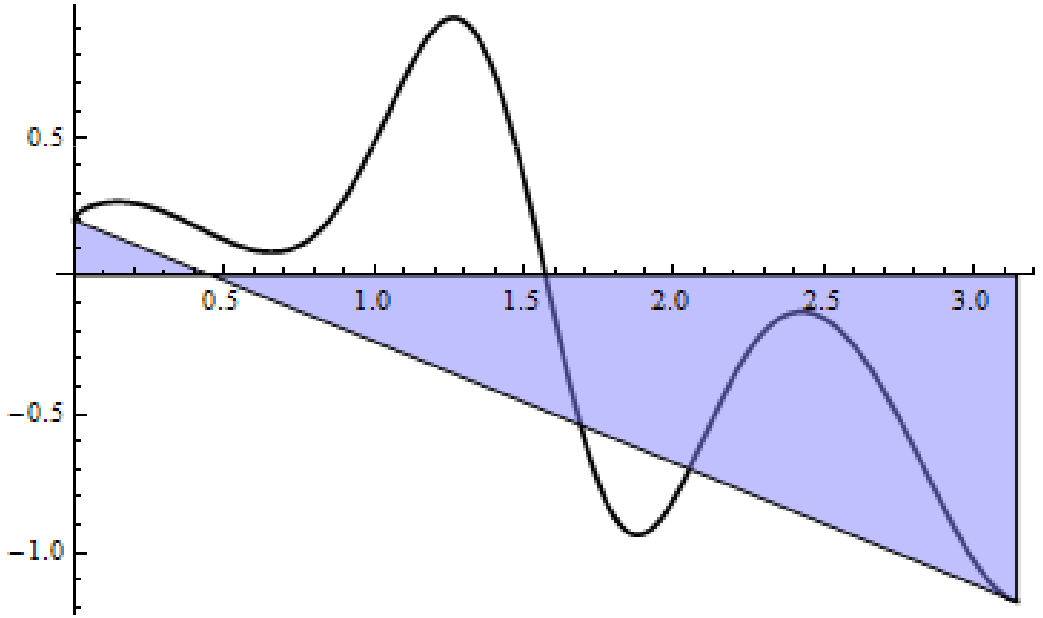
Volume of
the cavity (Å^3)



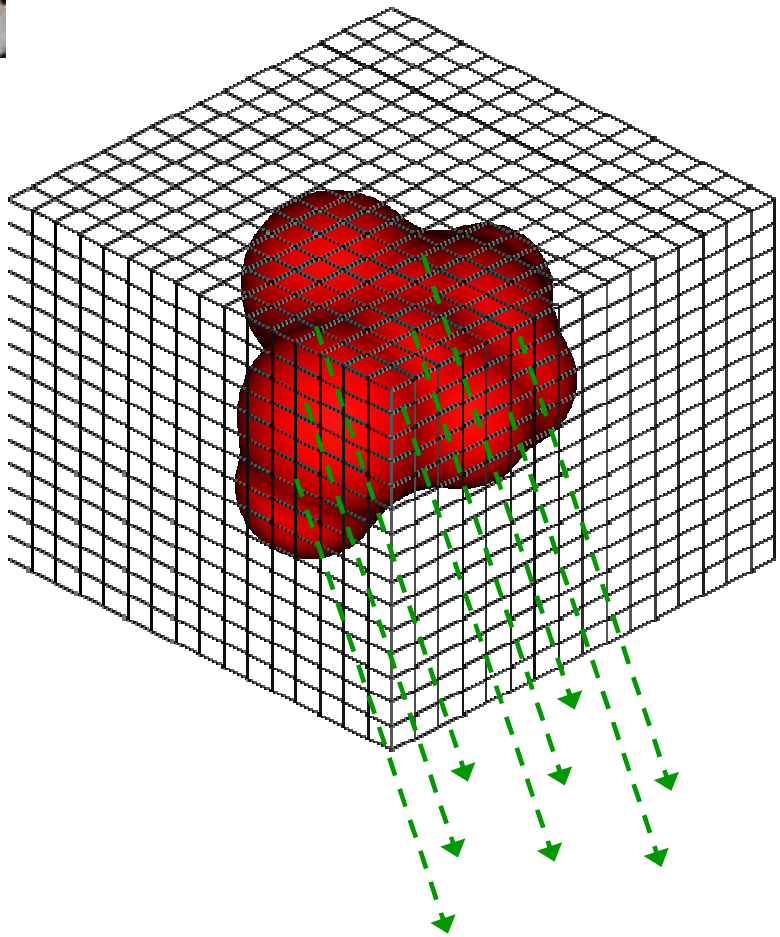
Volume of
the ligand (Å^3)

do you remember the *trapezoidal rule*?

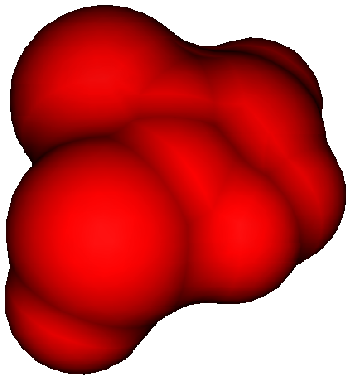
$$\int_a^b f(x)dx \approx (b-a)\frac{f(a)+f(b)}{2}$$



a 3D version of our *trapezoidal rule*

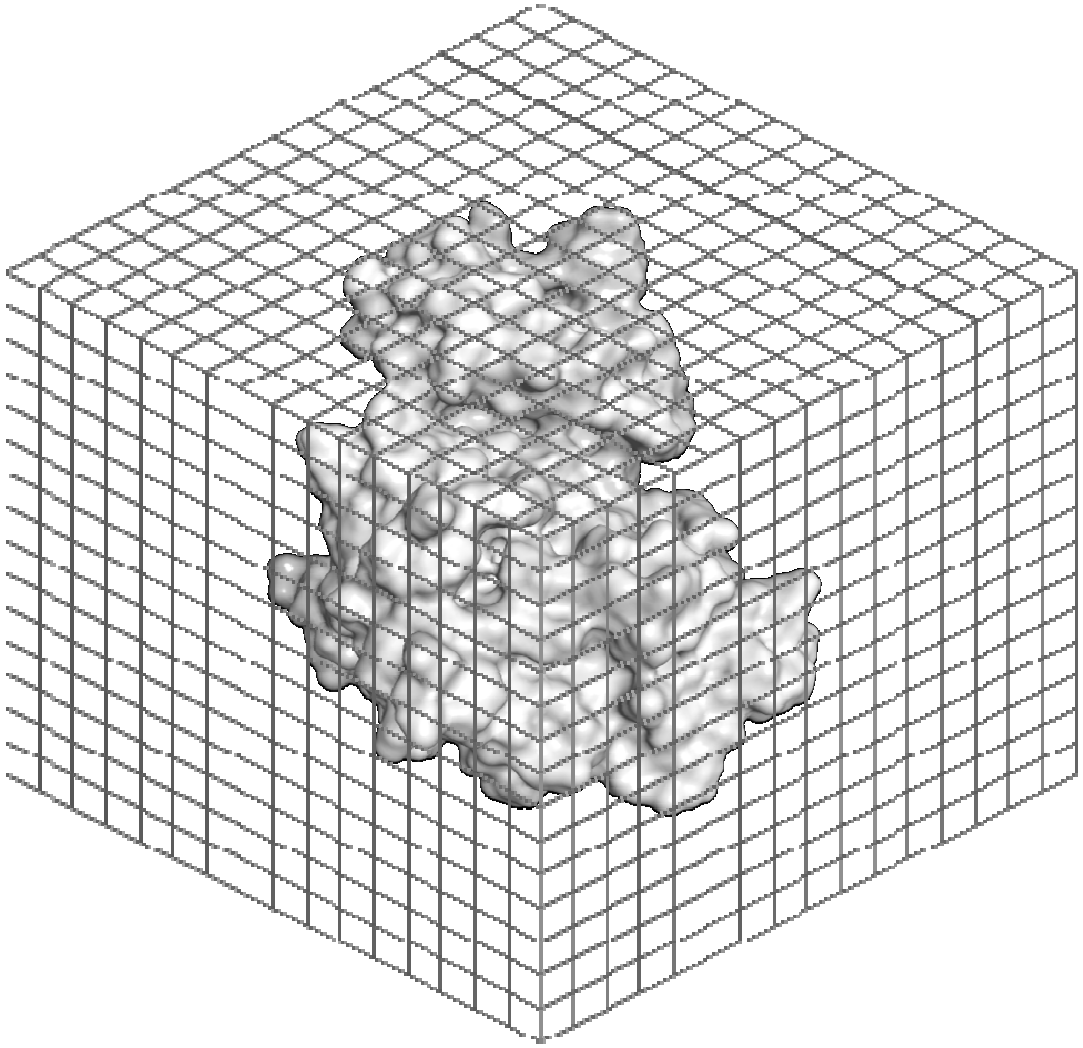


$= V_i$



$V_{mol} \cong n\ V_i$

a 3D version of our *trapezoidal rule*



Volume of the protein = 43450 Å^3

Now also *surface* extension is very easy to calculate… approximately!

$$ASA\ (Å^2) \cong \Sigma \blacktriangle$$

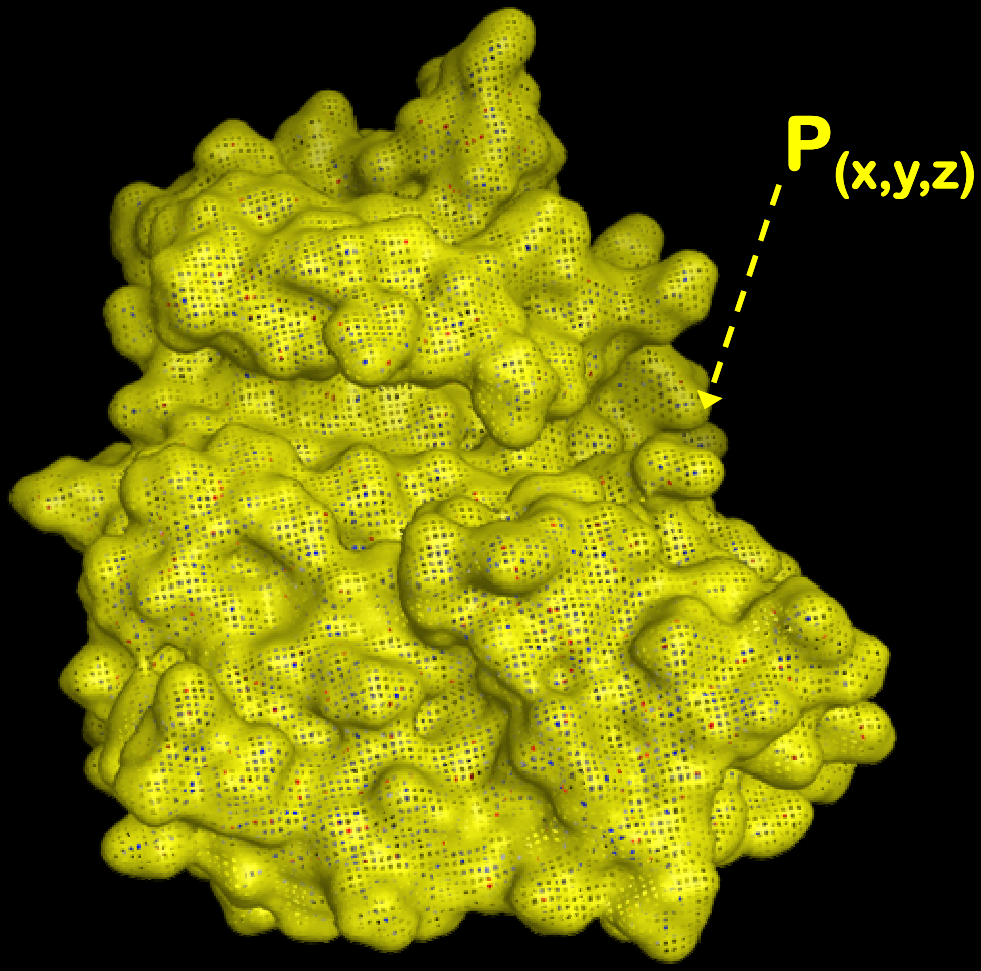
Accessible Surface Area = 15410 Å²

Remember?

"It is generally accepted that receptor and substrate molecules recognize each other at their molecular surfaces. Therefore, the binding strength of a receptor-drug complex depends on the shape of the substrate surface and on the **distribution of certain properties on this surface**. Any method attempting to model biological activity should take into account this information and try to correlate it to biological activity…"

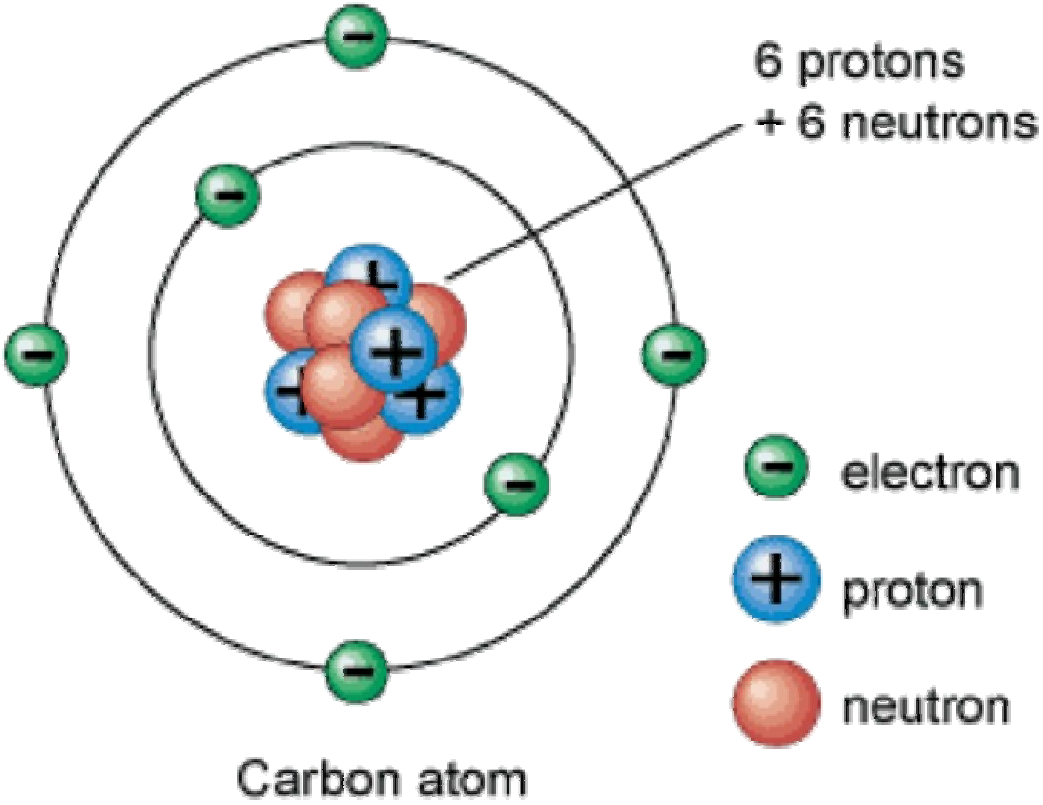
by Johann Gasteiger *et al J.A.C.S.* 1995, **117**, 7769-7775

Molecular surfaces as a locus for the projection of molecular properties:

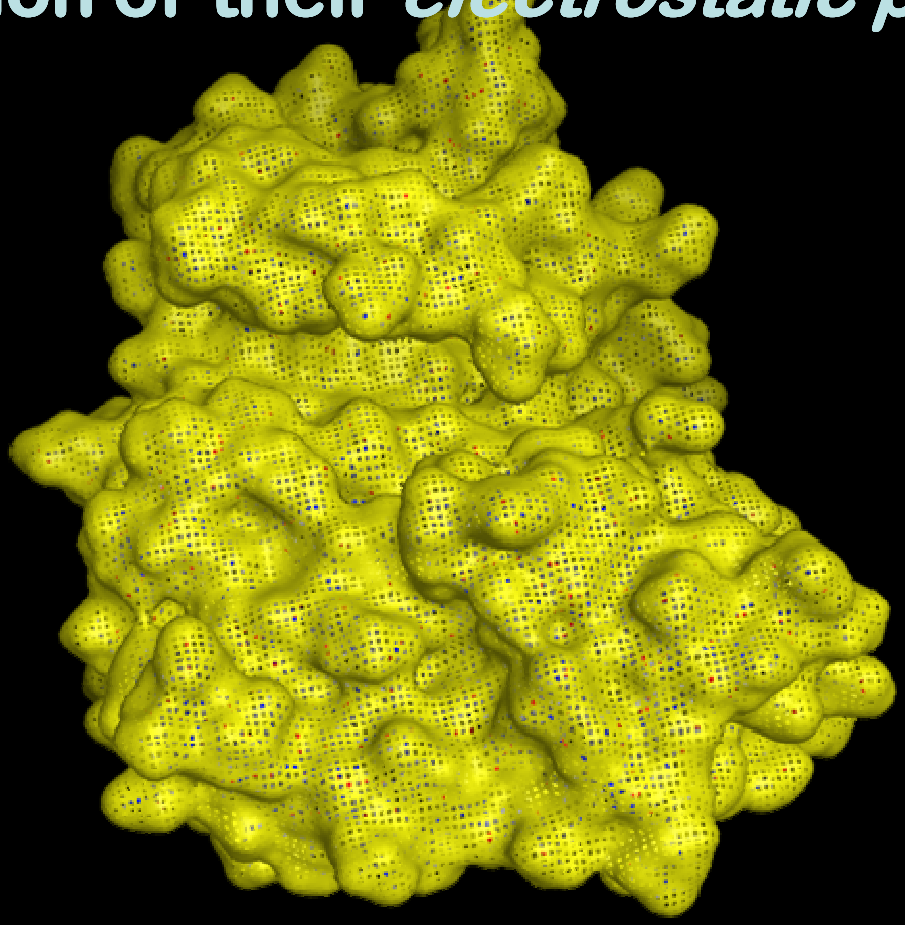


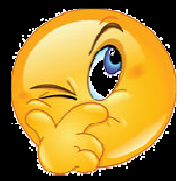
As chemists, what is the first property that you would like to see projected ?

We cannot forget that under the real surface we surely find… charges!



Considering that molecules are an ensemble of electric charges… probably the distribution of their *electrostatic potentials*?





How we can virtualize the projection of the electrostatic potential on a molecular surface?

We can surely start with him!

Charles Augustin de Coulomb (Angoulême, 14 giugno 1736 – Parigi, 23 agosto 1806).

$$F_{el} = k_0 \frac{q_1 q_2}{r^2}$$

$$\text{Coulomb's costant} : k_0 = 9 \times 10^9 \frac{Nm^2}{C^2}$$

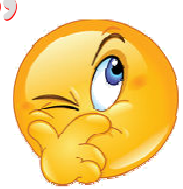
$$k_0 = \frac{1}{4\pi\varepsilon_0}$$

$$\text{where } \varepsilon_0 \text{ is the electric permittivity of free space}$$

$$\varepsilon_0 = 8{,}9 \times 10^{-12} \frac{C^2}{Nm^2}$$

I try to recite it:

"The magnitude of the electrostatic force of interaction between two **point charges** is directly proportional to the scalar multiplication of the magnitudes of charges and inversely proportional to the square of the distance between them."

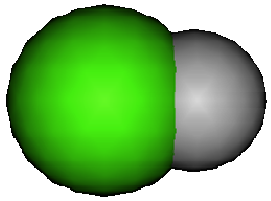


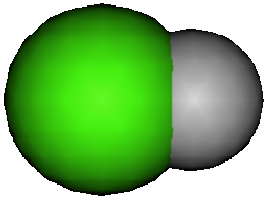
How we can deal with the *point charges* concept when, in the real world, we usually deal with charge distributions?

Probably, using a very interesting physical trick:

$\Delta\chi = 1.9$ $\mu = 1.82$ D

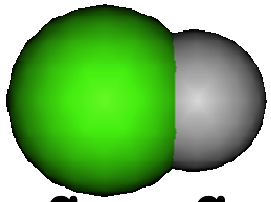
F - H





$\chi_F = 4.0$ $\chi_H = 2.1$ $-\delta$ $+\delta$

q, partial atomic charge



q_F q_H

$\mu\ f\ (q_F; q_H)$

Probably, using a very interesting physical trick:

H - H

$\Delta\chi = 0$ $\mu = 0$ D

$\chi_H = 2.1$ $\chi_H = 2.1$

F - H

$\Delta\chi = 1.9$ $\mu = 1.82$ D

$\chi_F = 4.0$ $\chi_H = 2.1$ $-\delta$ $+\delta$

Probably, using a very interesting physical trick:

F - H

$\Delta\chi = 1.9$

$\mu = 1.82$ D

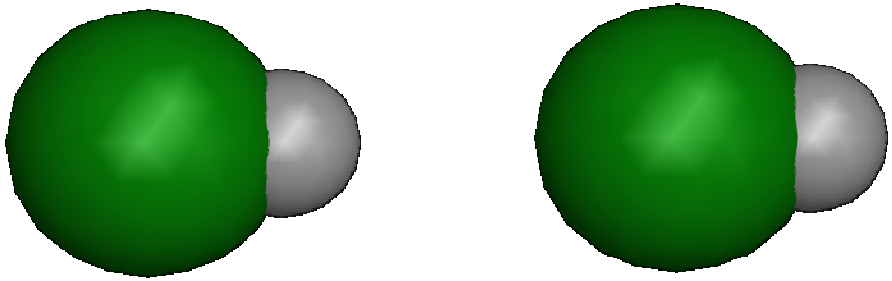
$\chi_F = 4.0$ $\chi_H = 2.1$

$-\delta$ $+\delta$

Cl - H

$\Delta\chi = 1.1$

$\mu = 1.08$ D



$\chi_{Cl} = 3.2$ $\chi_H = 2.1$

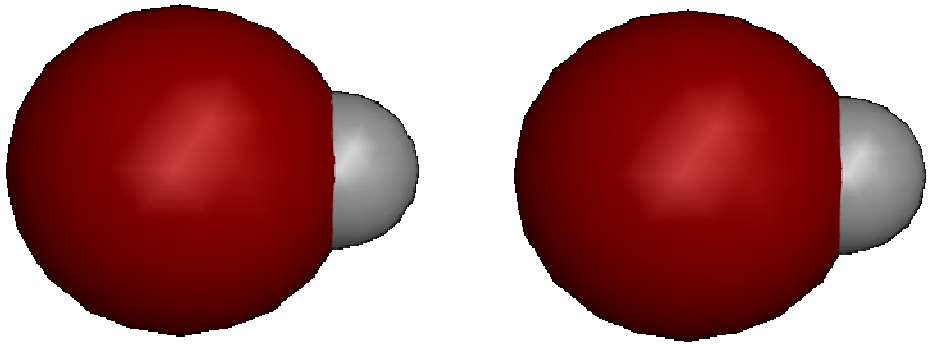
$-\delta$ $+\delta$

Probably, using a very interesting physical trick:

Br - H

$\Delta\chi = 0.8$

$\mu = 0.82$ D ←



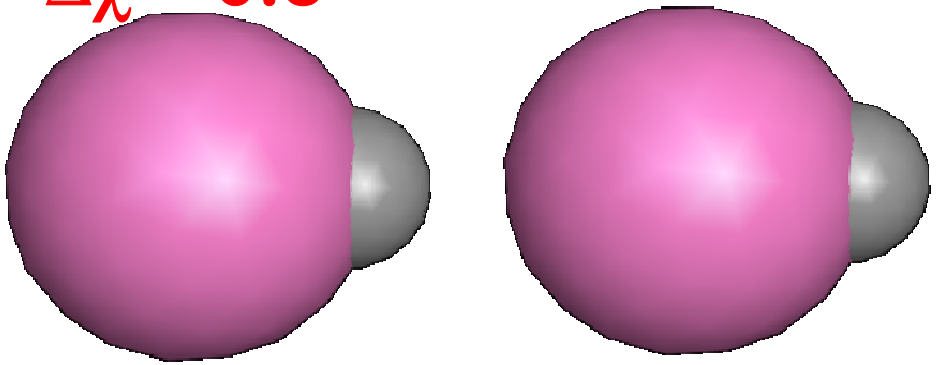
$\chi_{Br} = 2.9$ $\chi_{H} = 2.1$

$-\delta$ $+\delta$

I - H

$\Delta\chi = 0.5$

$\mu = 0.44$ D ←



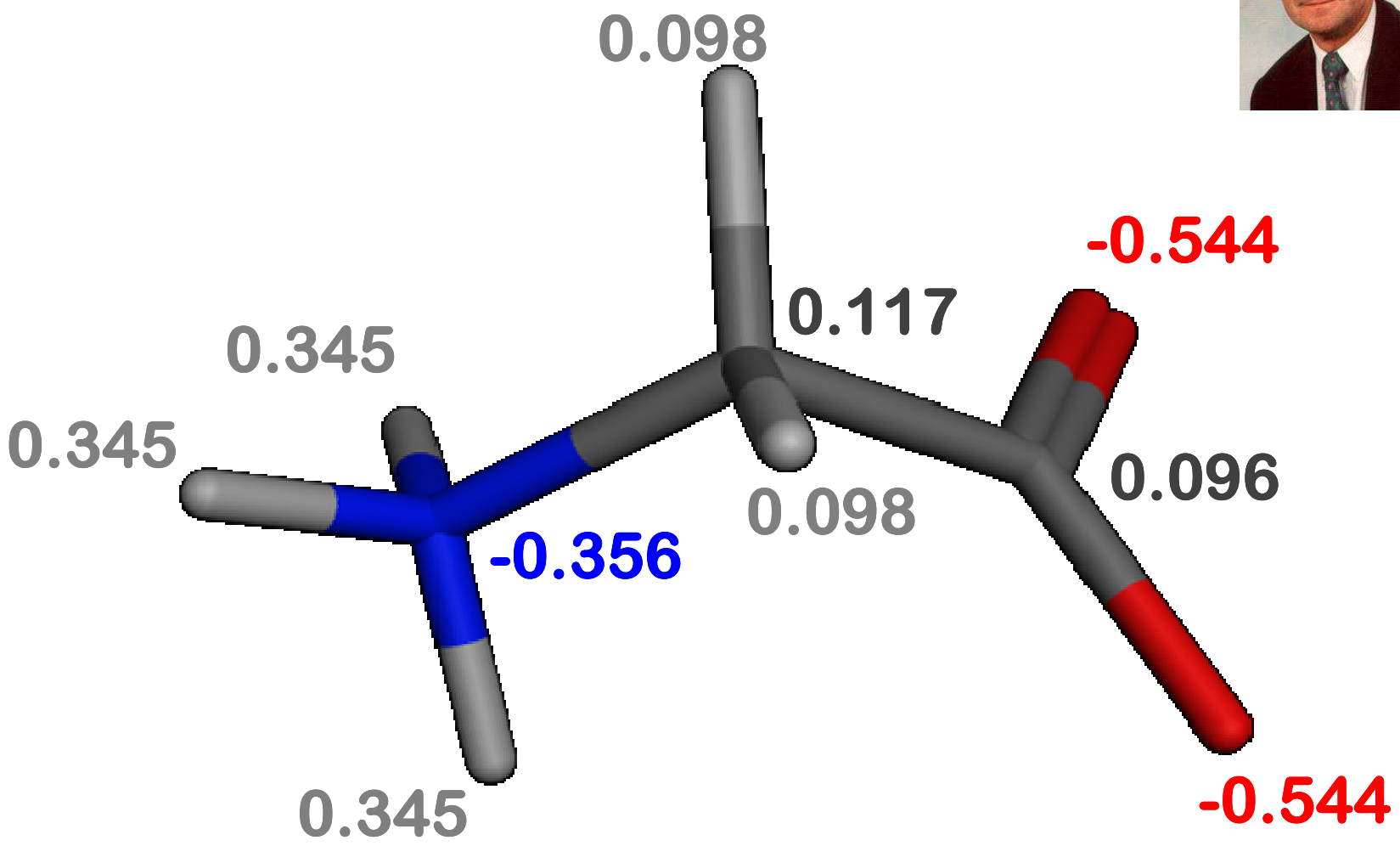
$\chi_{I} = 2.6$ $\chi_{H} = 2.1$

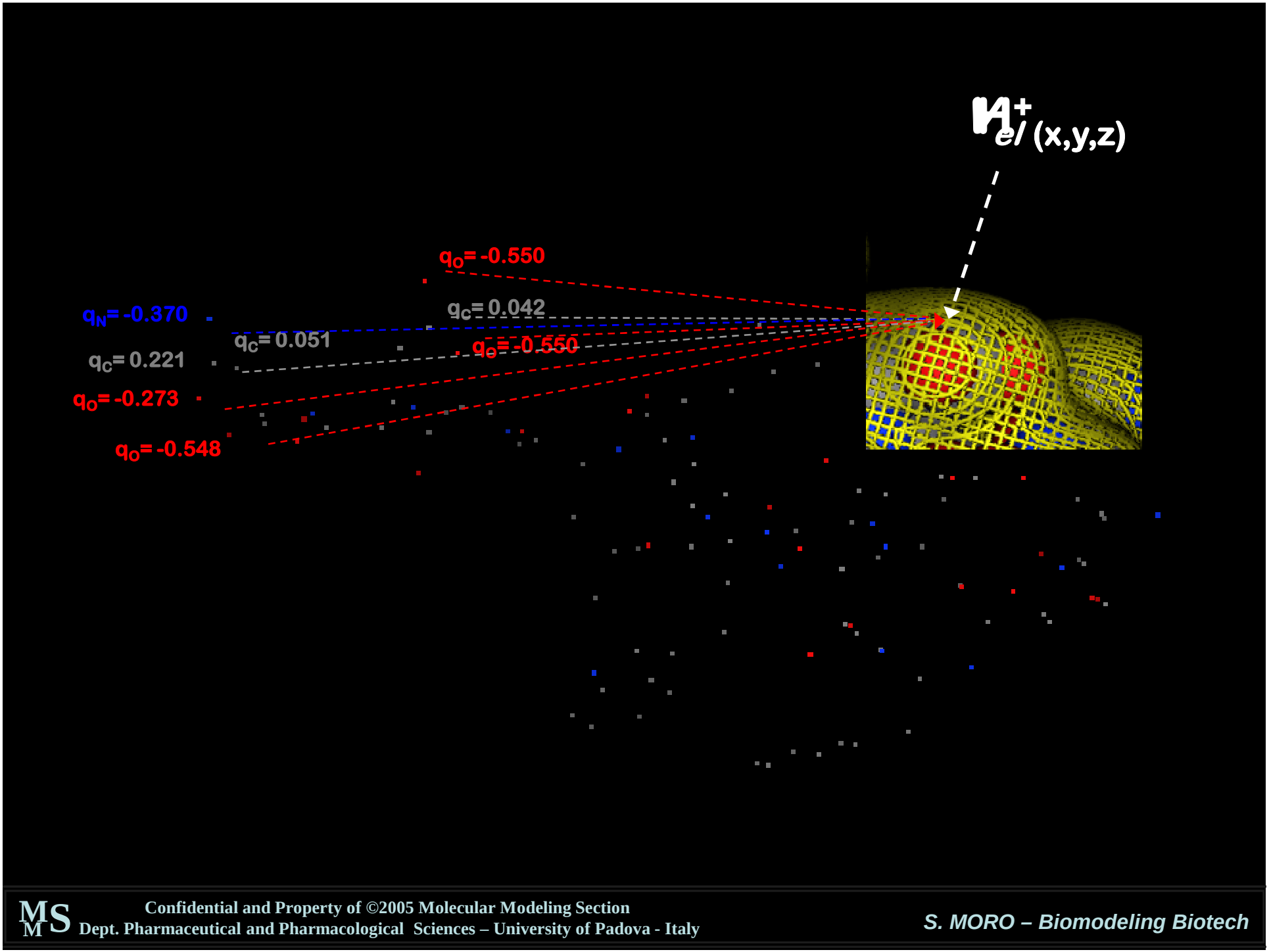
$-\delta$ $+\delta$

Probably, using a very interesting physical trick:

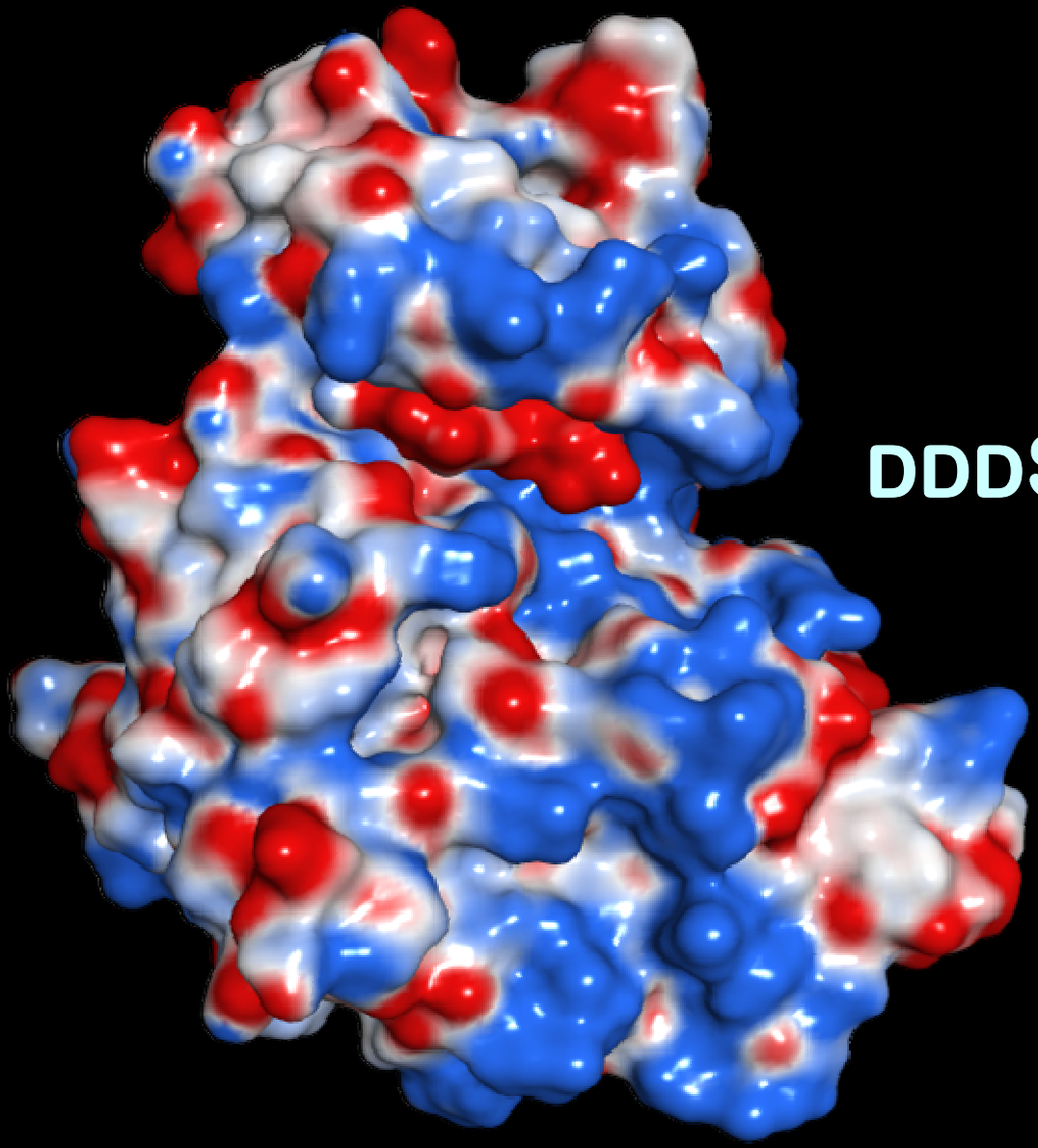
	$\Delta\chi$	μ (D)	q_X	q_H
F - H	1.9	1.82	-0.267	0.267
Cl - H	1.1	1.08	-0.145	0.145
Br - H	0.8	0.82	-0.113	0.113
I - H	0.5	0.44	-0.107	0.107
H - H	0	0	0	0

and now it is very simple to extend:





… very charming!



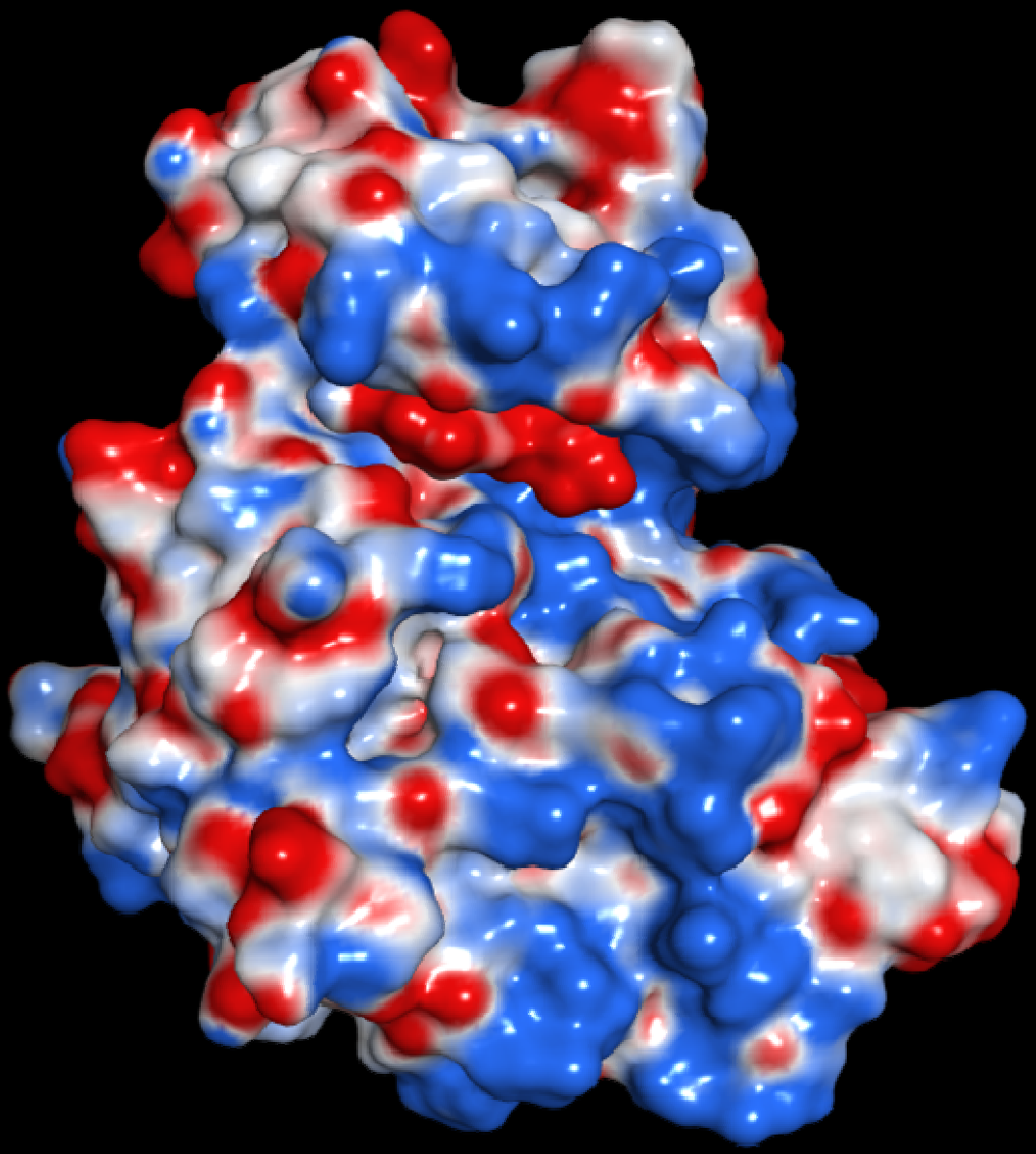
DDDSDDD

$V_{el} < 0$

$V_{el} = 0$

$V_{el} > 0$

we can reflect for a moment about $V_{el} = 0$

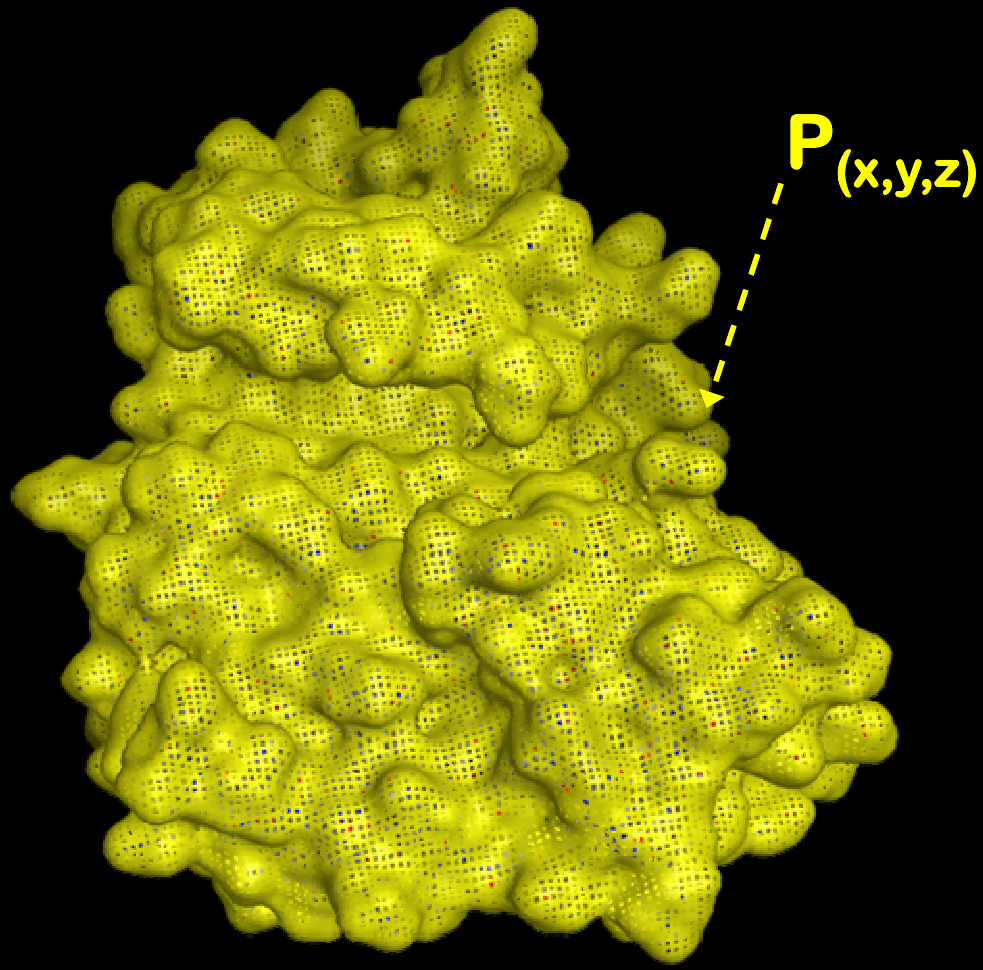


$V_{el} < 0$

$V_{el} = 0$

$V_{el} > 0$

Which other property could be interesting to project on this surface?



Do you remember the *hydrophobic effect*?

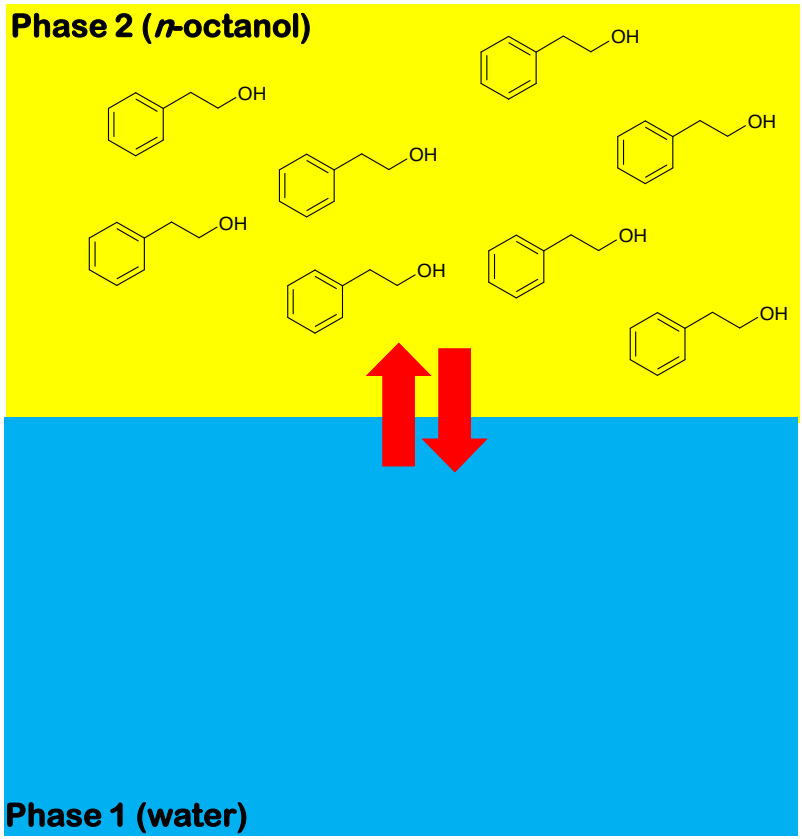
Folding

Aggregation

Recognition

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

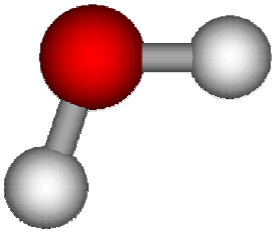
$$\left[\frac{C_{(phase1)}}{C_{(H_2O)}}\right] = P$$ **Partition coefficient**

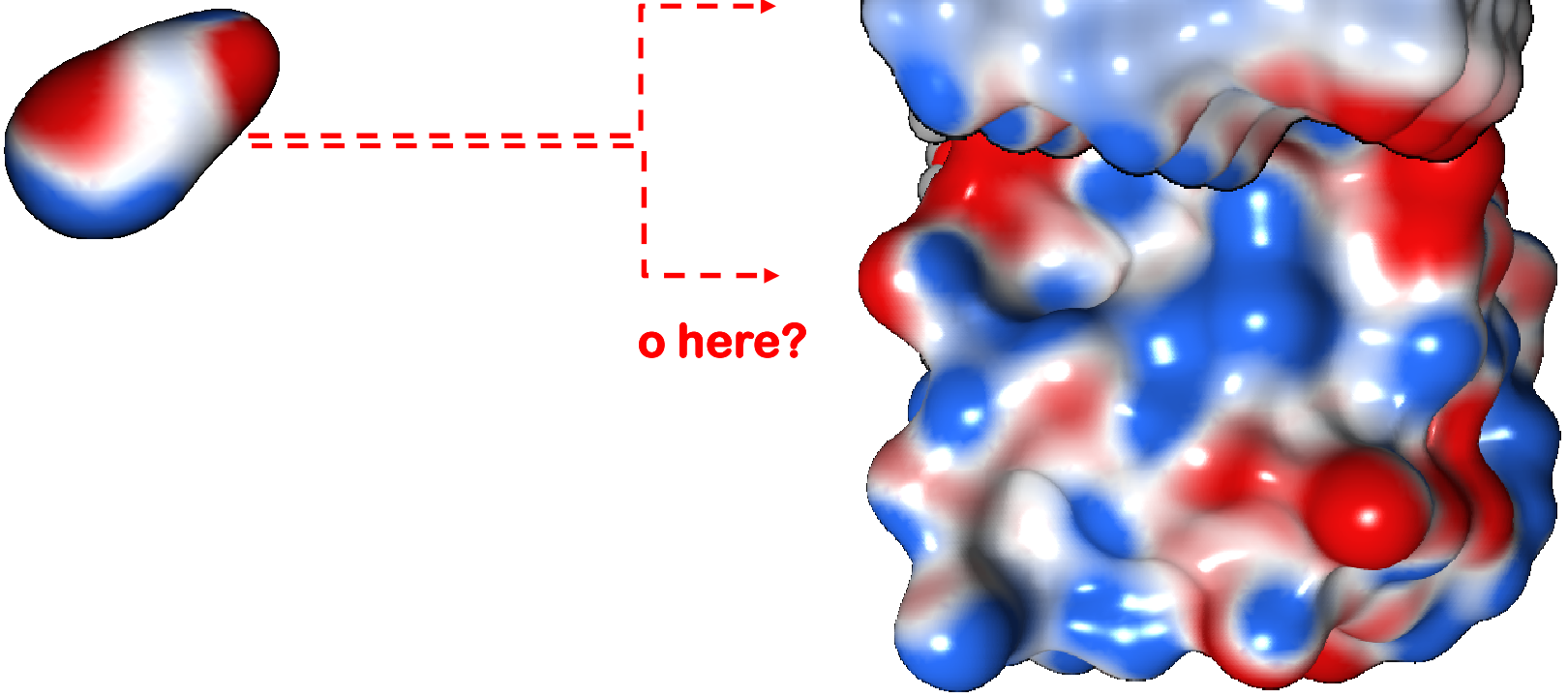
We can define: **"*hydrophobic*" a compound with P > 1;**
"*hydrophilic*" a compound with P < 1.

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

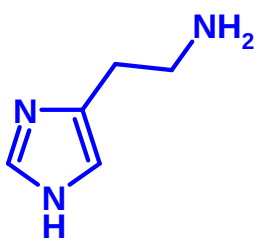
We can define: **"*hydrophobic*" a compound with logP > 0;**
"*hydrophilic*" a compound with logP < 0.

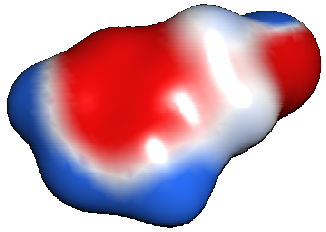
How we can address in the real world about phobicity ?



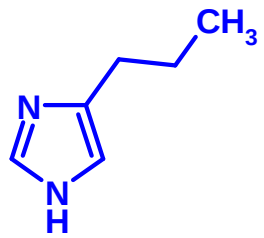


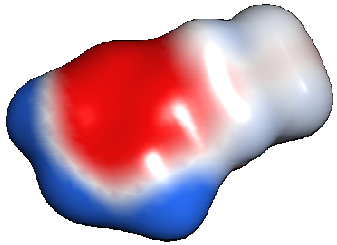
and this is understandable!



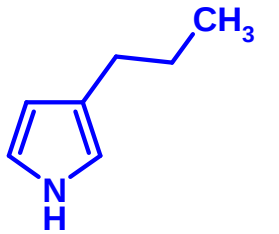


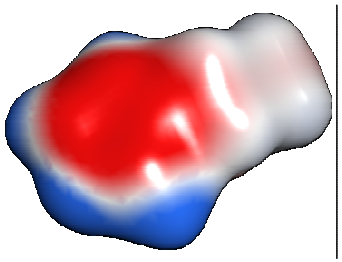
log P = -0.26



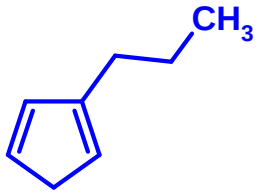


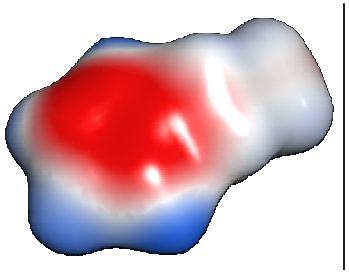
log P = 0.90



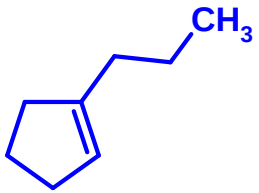


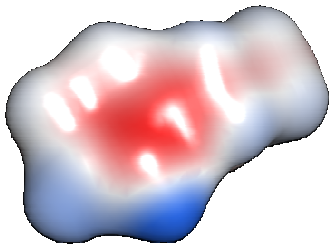
log P = 2.17



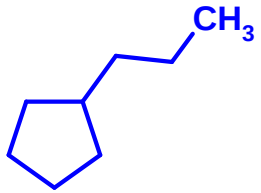


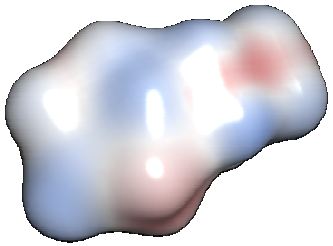
log P = 2.94





log P = 3.31



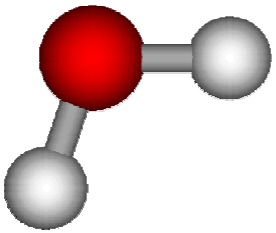


log P = 3.84

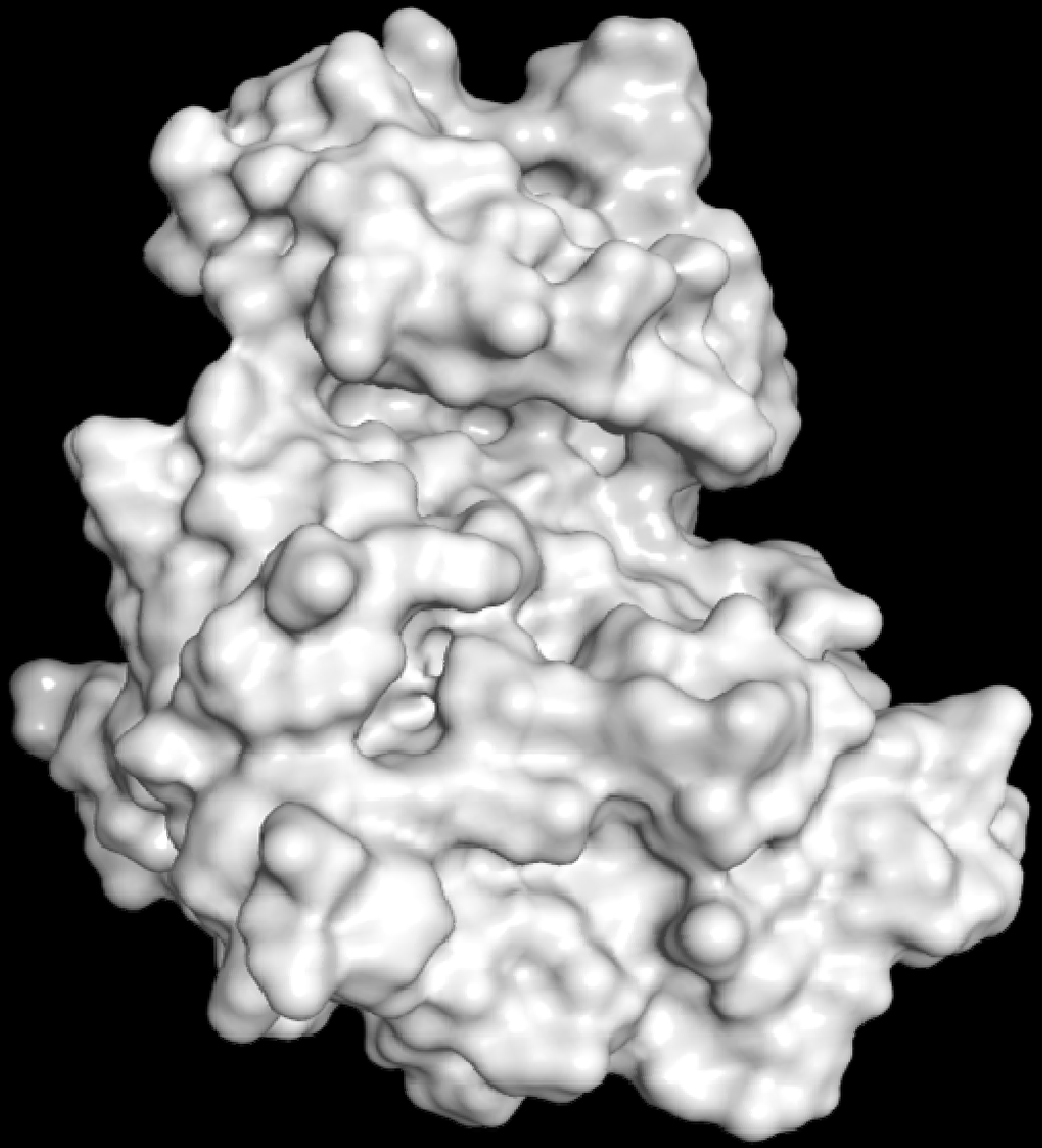
Back to our “white” potential surface:

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

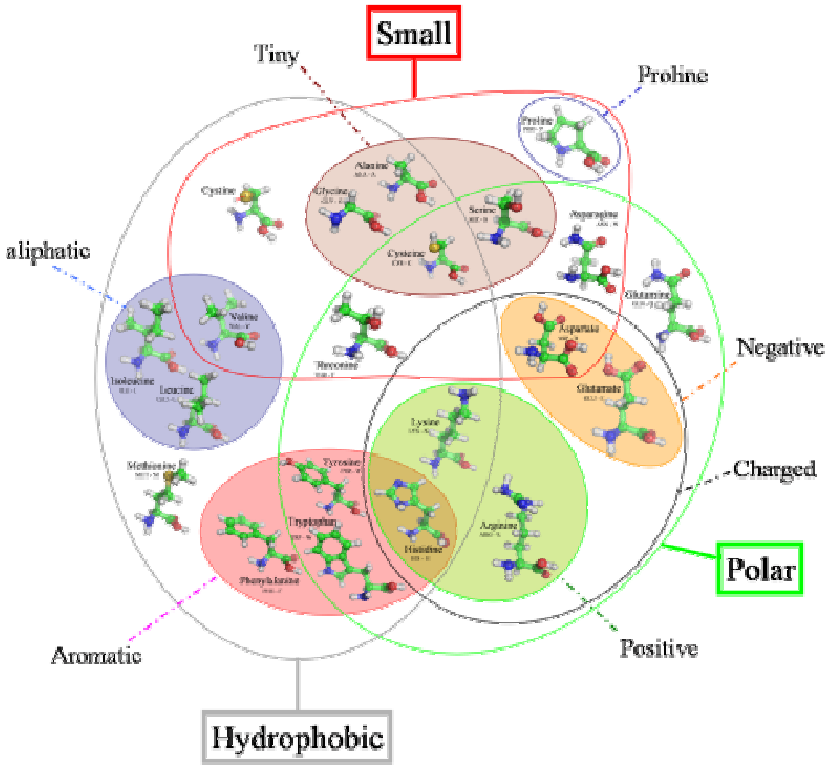
HYDROCARBONS

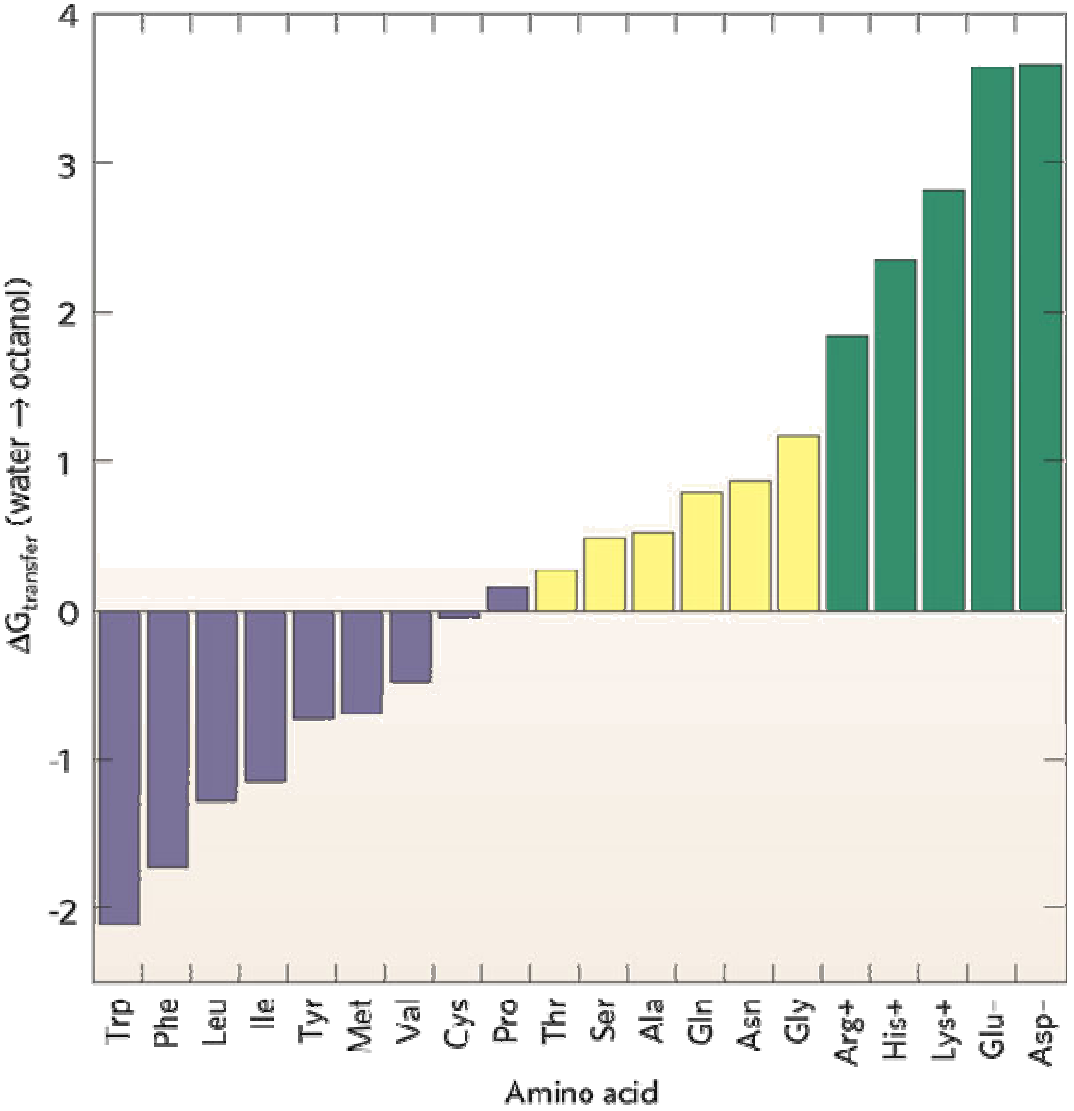
and they are surely  **phobics!!!**

Back to our molecular surface:



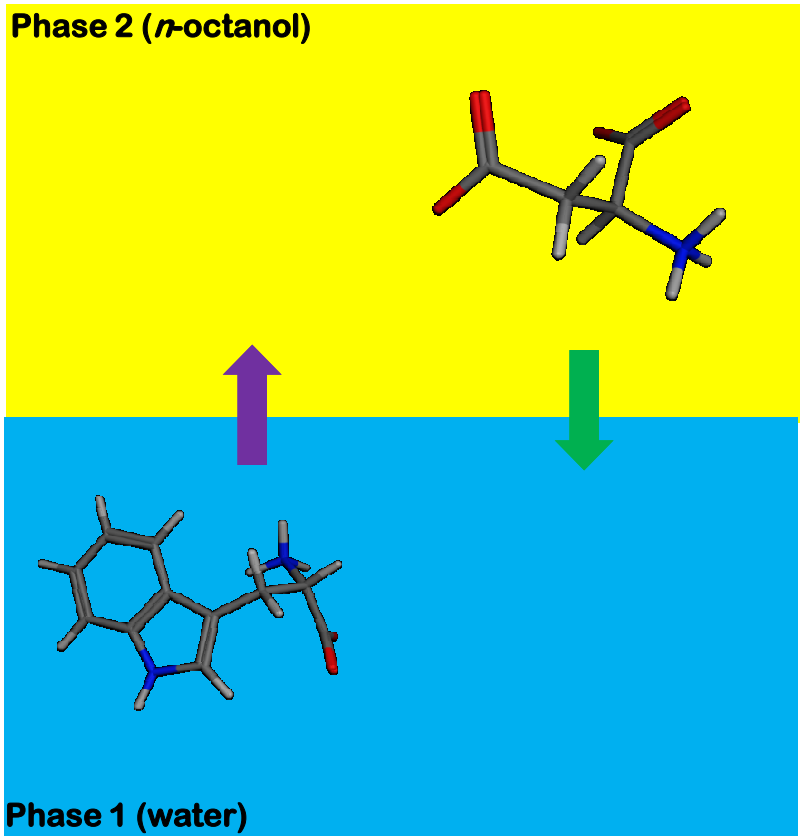
Amino acids and hydrophobicity:



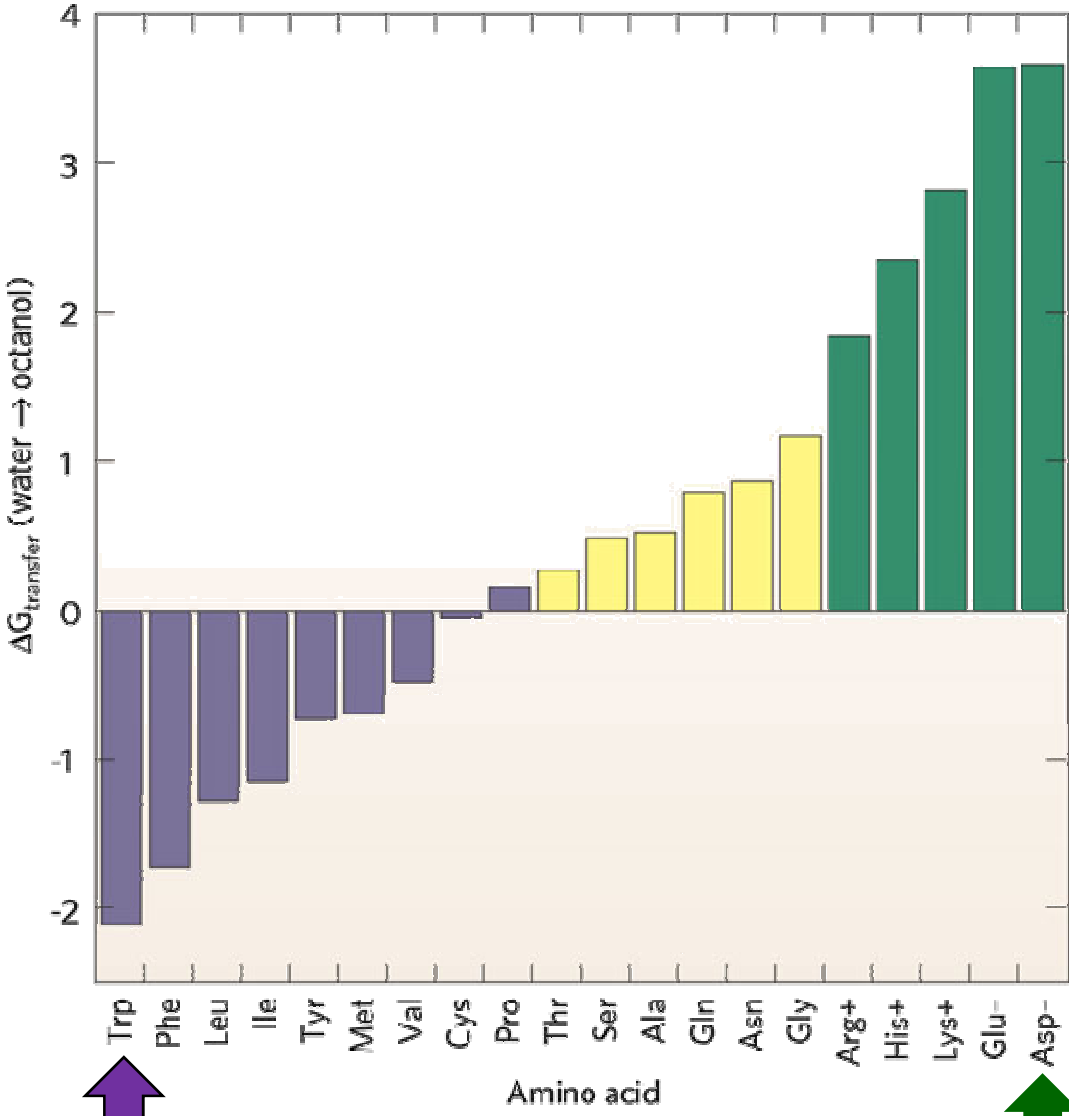


James U. Bowie Nature 438, 581-589 (1 December 2005)

Amino acids and hydrophobicity:

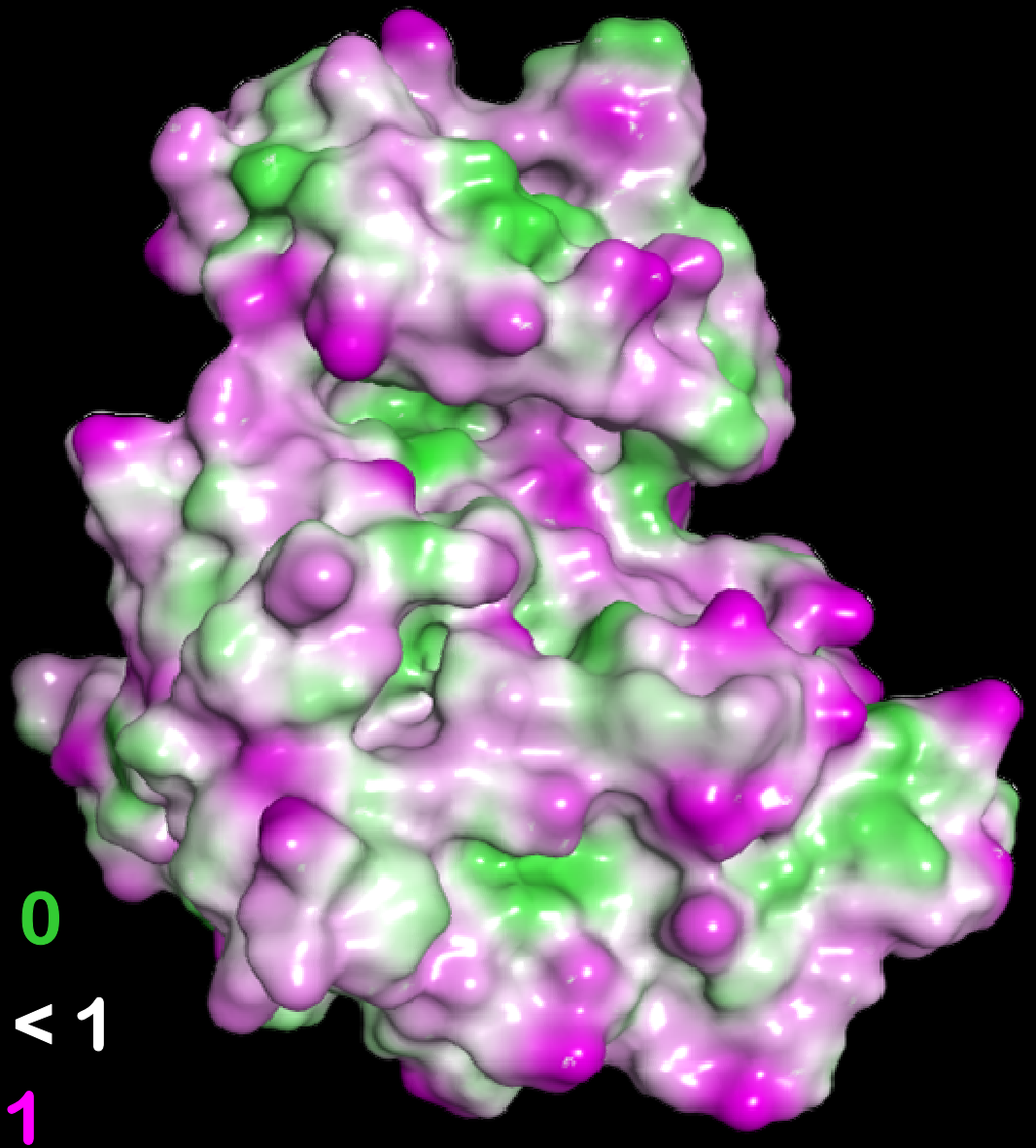


$\Delta G < 0$ $\Delta G > 0$



James U. Bowie Nature 438, 581-589 (1 December 2005)

Back to our molecular surface:

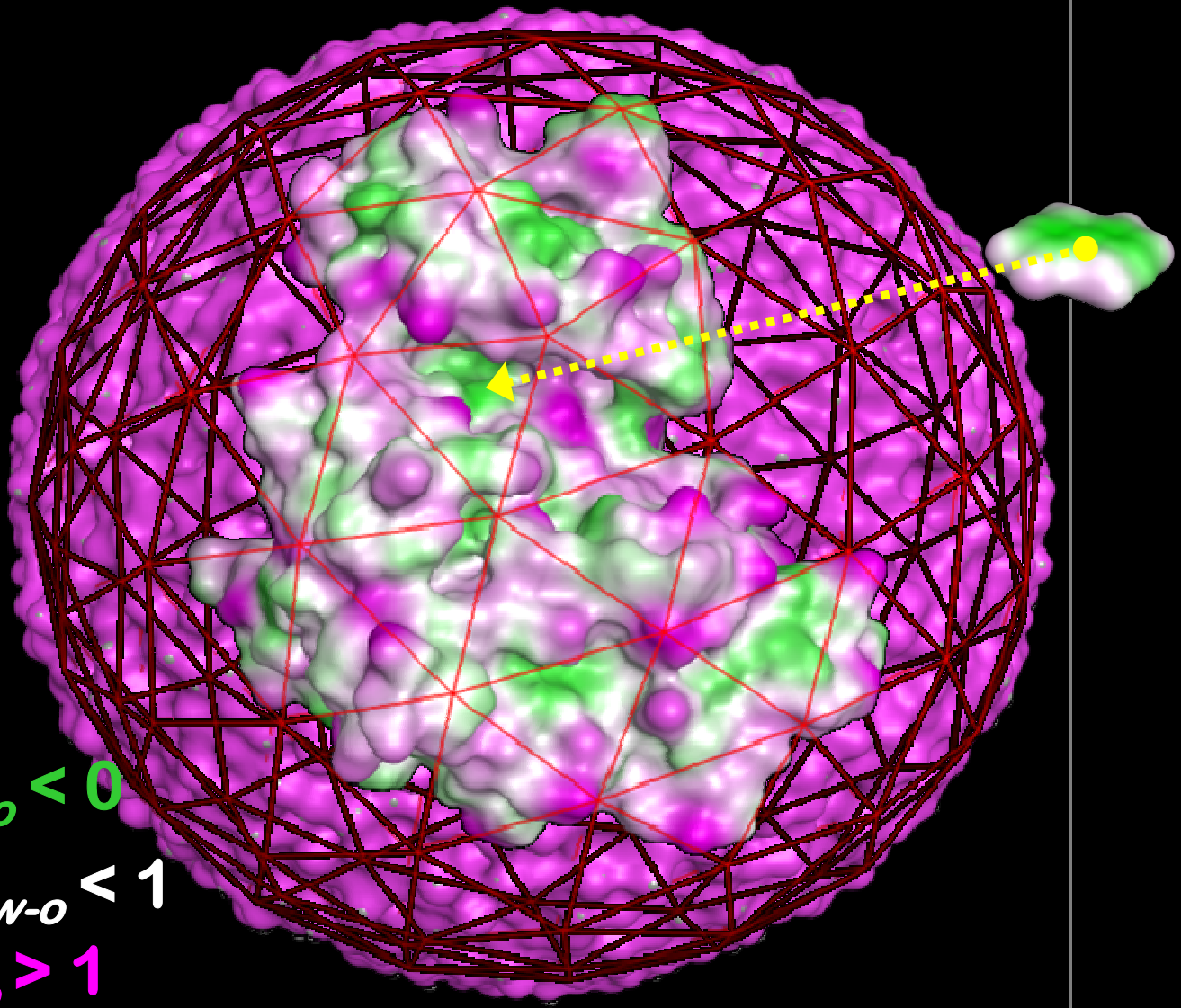


$\Delta G_{w\text{-}o} < 0$

$0 < \Delta G_{w\text{-}o} < 1$

$\Delta G_{w\text{-}o} > 1$

A wonderful strategy to tune the residence time of water molecules on the protein surface:

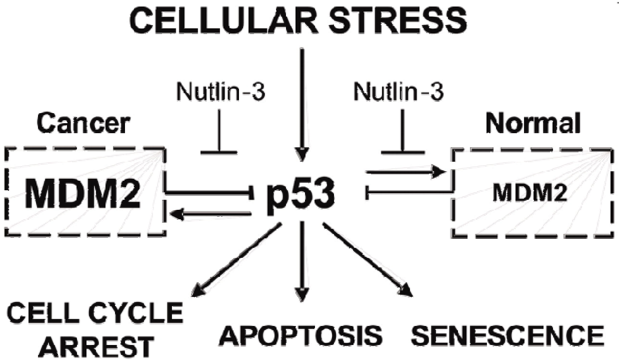


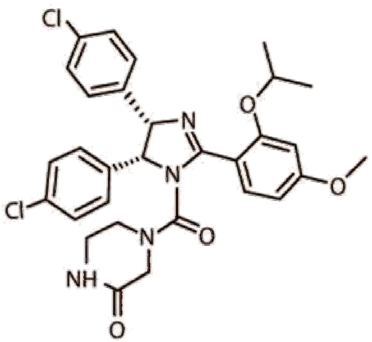
$\Delta G_{w\text{-}o} < 0$

$0 < \Delta G_{w\text{-}o} < 1$

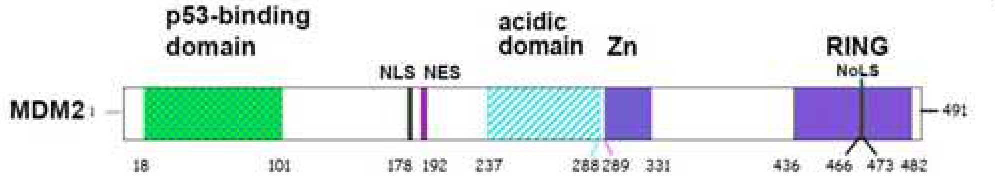
$\Delta G_{w\text{-}o} > 1$

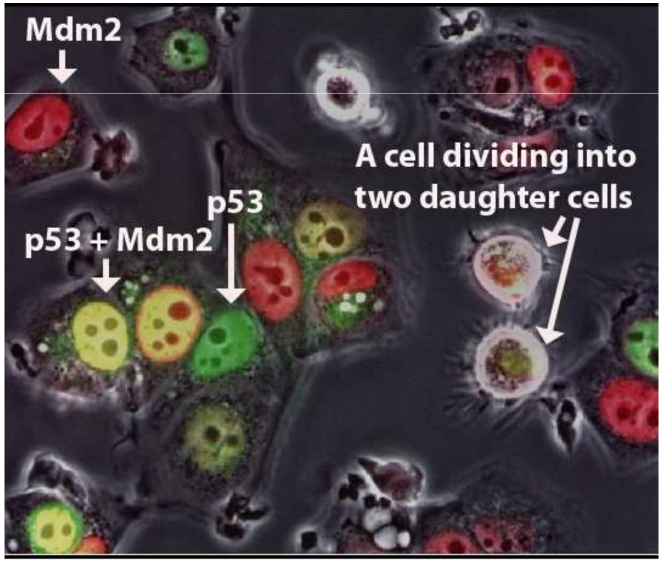
I.hopedt iswecleaanwitthoutt strructurre favoritteraxationpsleudy!

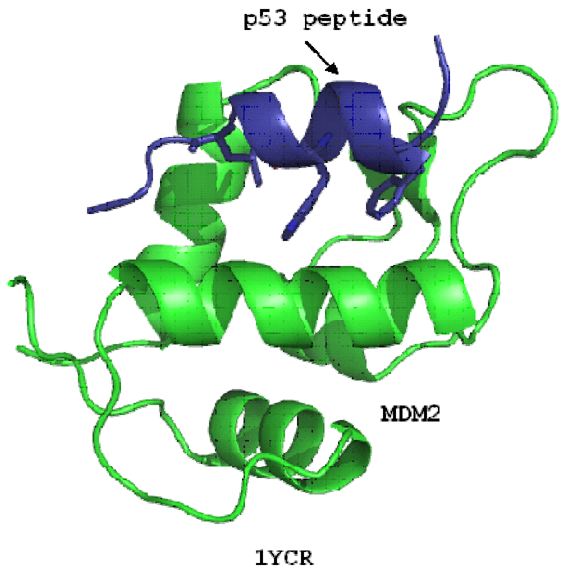




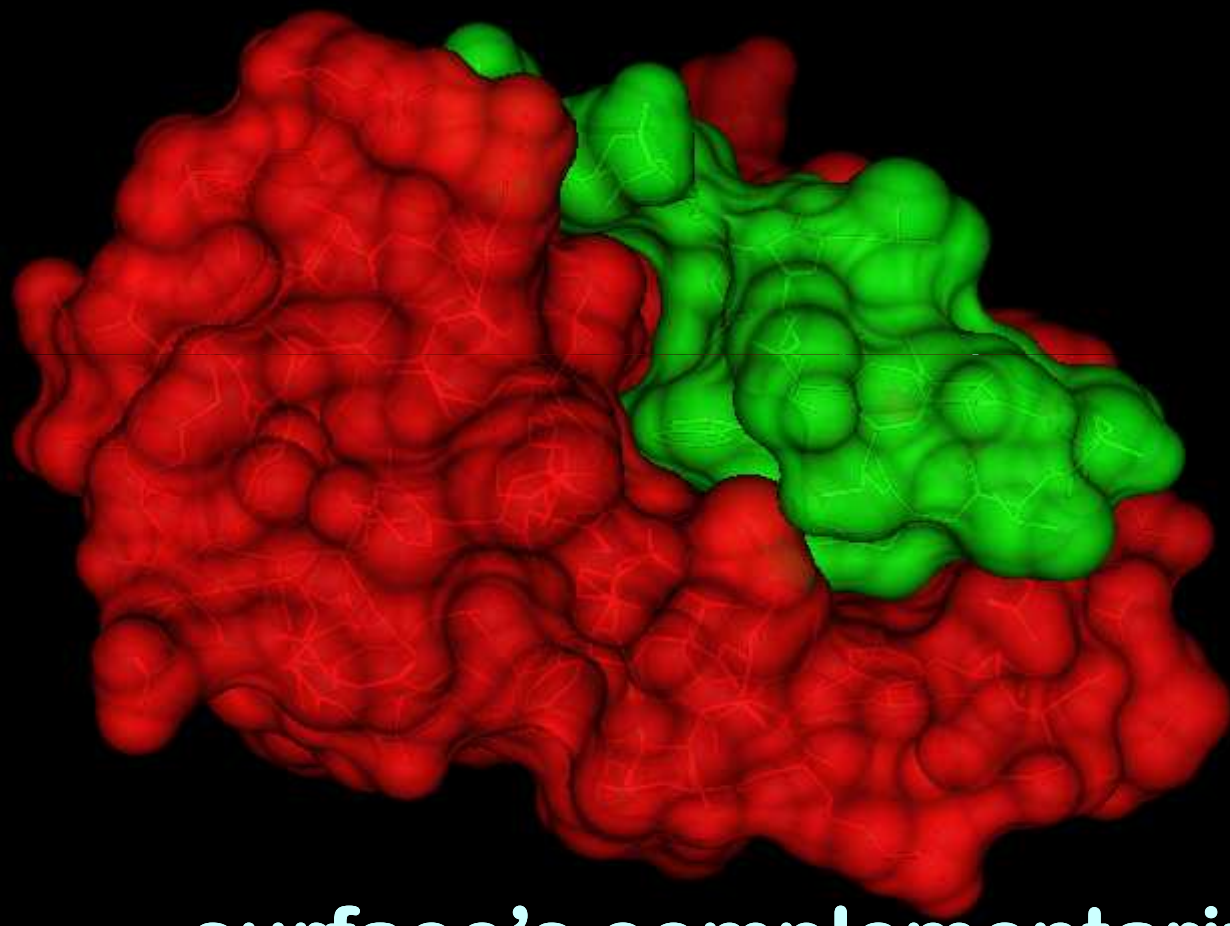
Nutlin-3a





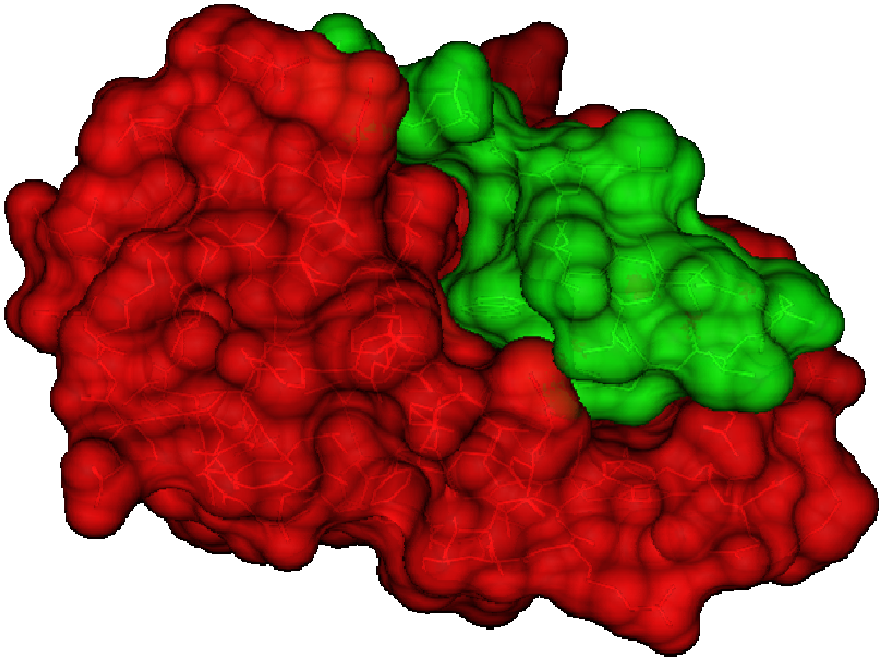


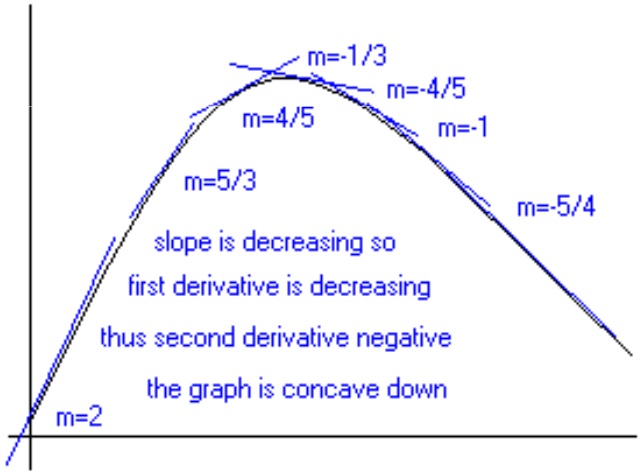
Now is more clear what Johnny wanted to say…



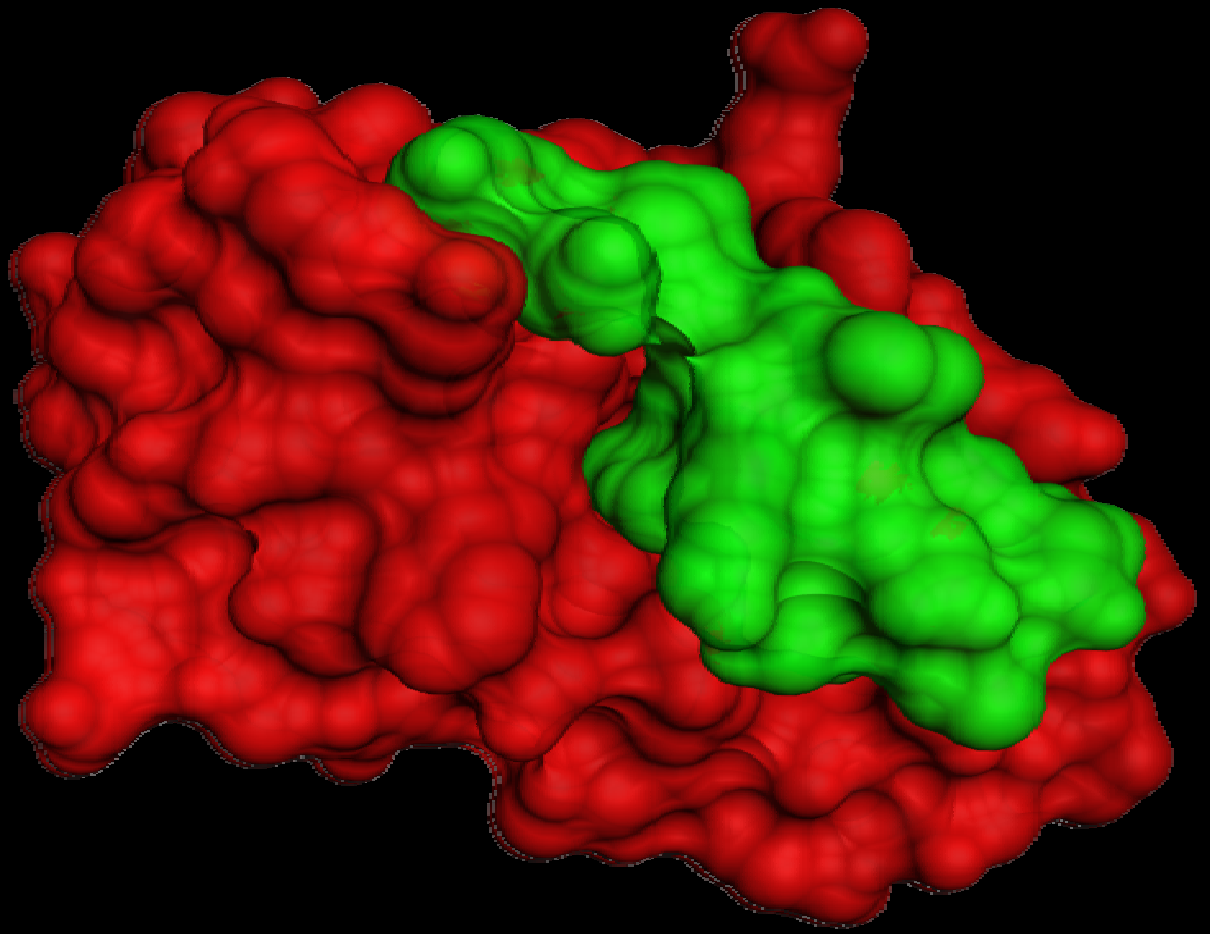
surface's complementarity

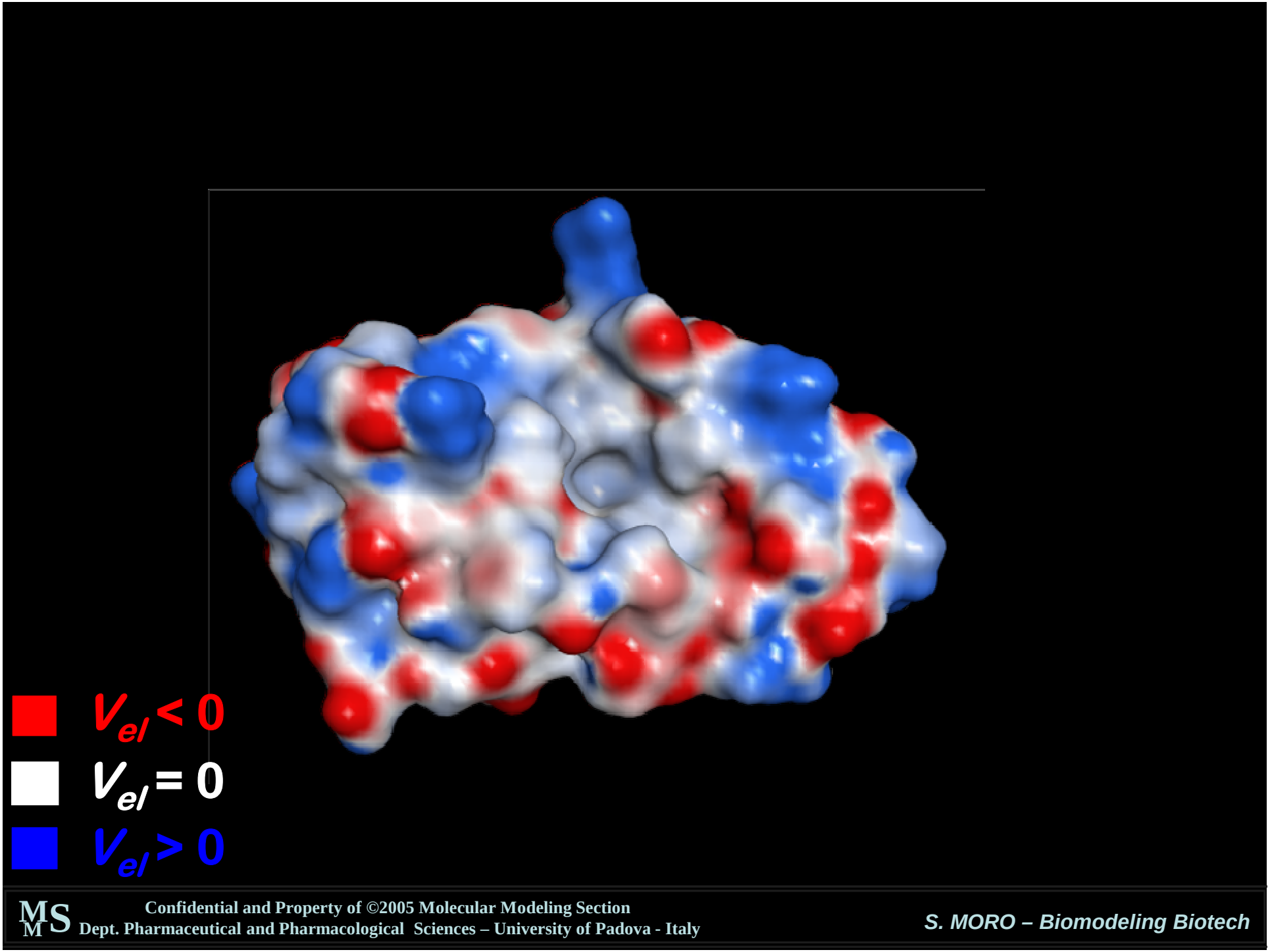
An alternative approach to evolutionary selection… optimizing shape complementarity using the analysis of derivatives first and second!





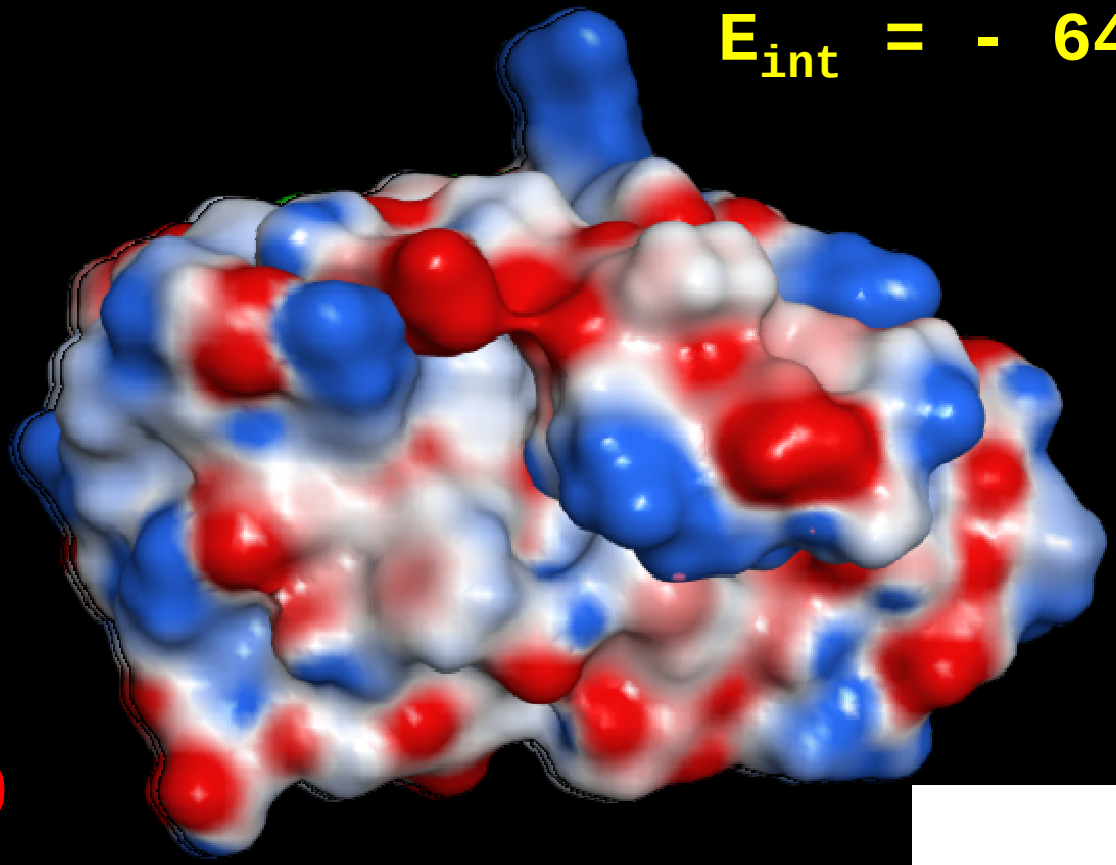
An alternative approach to evolutionary selection… optimizing shape complementarity using the analysis of derivatives first and second!





Now the complementarity described by Johnny is much much more clear!

E_{int} = - 64 kcal/mol



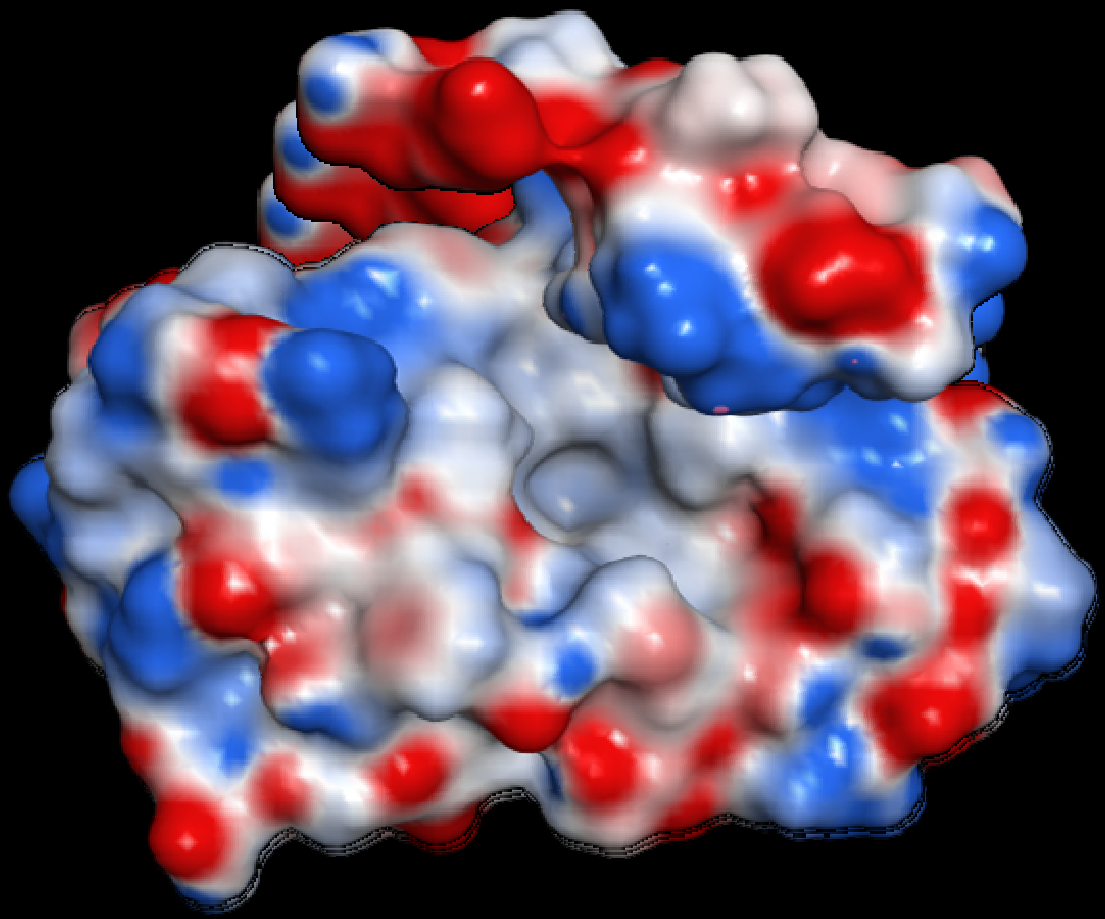
$V_{el} < 0$

$V_{el} = 0$

$V_{el} > 0$

$$Eint = \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

Molecular surfaces as superb *docking* platforms!



$V_{el} < 0$

$V_{el} = 0$

$V_{el} > 0$

SQETFSDLWKLLPDN E_{int} (wt)= - 64 kcal/mol

SQETFSDLWKLLPAN E_{int} (wt)= - 58 kcal/mol