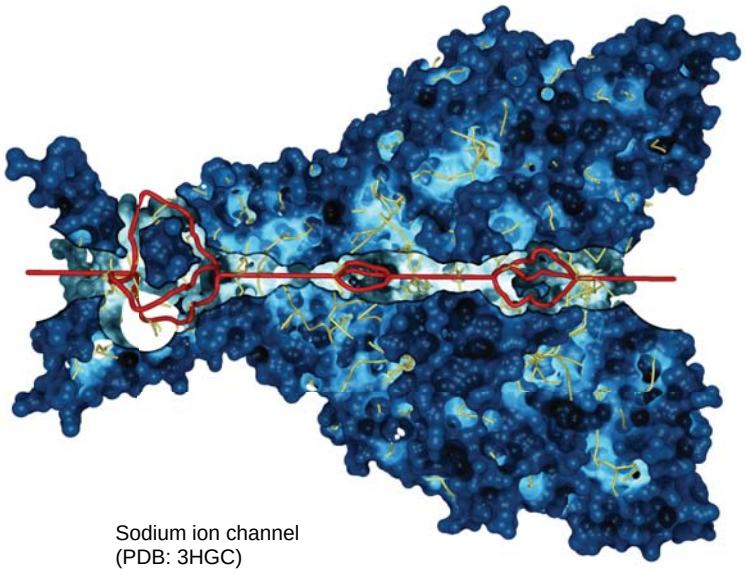
Are there better ways to depict molecules?



Sodium ion channel
(PDB: 3HGC)

Hans-Christian Hege

Overview

- Epistemological Perspective
- Atoms & Molecules as Physical Objects
- Standard Depictions & Problems
- Two Attempts for Improved Modeling
  - Atomic accessibility radii
  - Substrate accessible surfaces
- Summary

Preliminary, not yet published

Joint work with

Norbert Lindow

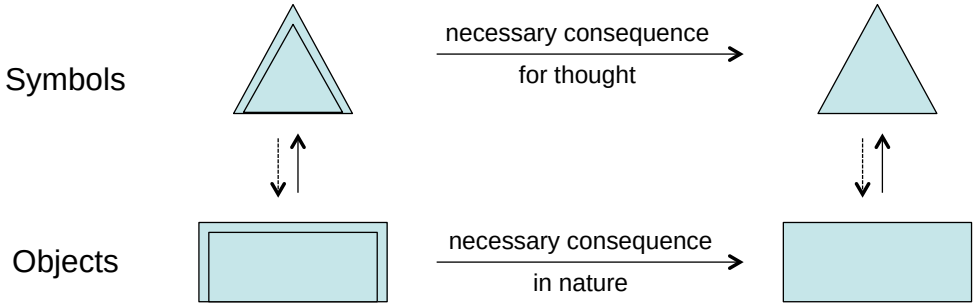
Daniel Baum

Epistemological Perspective

Do we need to depict molecules realistically?

- Not necessarily!
- Follow the advice that Heinrich Hertz gave (in 1894) to physics:

> We construct internal simulacra or symbols for external objects
> and we construct these in such a way that
> the consequences of the images necessary for thought are always
> images of the consequences in nature of the objects represented.



Visualizers are Utilitarians…

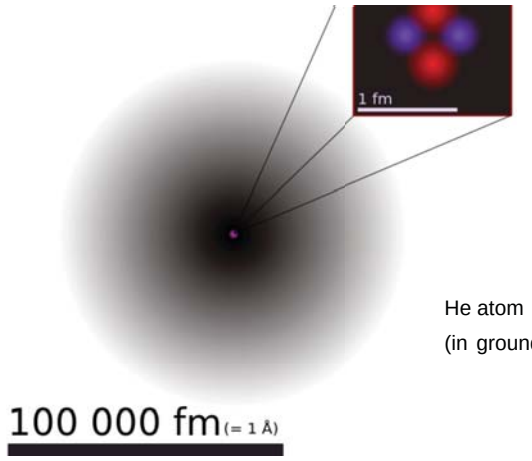
- All representations in Vis serve a purpose
- Abstracting representations are good,
  as long as one can draw the right conclusions
- When the latter is no longer the case,
  we should question the abstraction
  and construct a better one
- Doing this, it is helpful to know how a molecule really “looks” like

⇒ Let us start with this…

Atoms & Molecules as Physical Objects

Atoms

Each atom consists of a positively charged nucleus and electron orbitals.



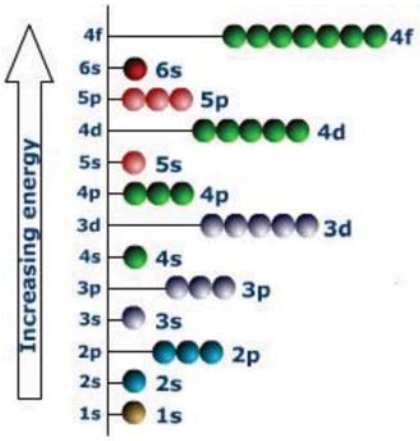
He atom
(in ground state)

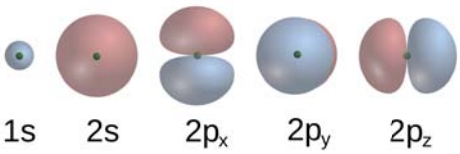
small size of nucleus

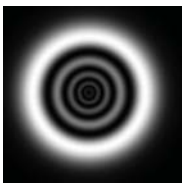
→ in atomistic / molecular visualization only electron “cloud” is considered

Single Electron Atom

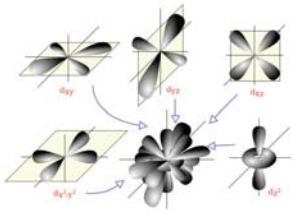
Different energy levels ⇒ different electron orbitals







6s orbital



d orbitals

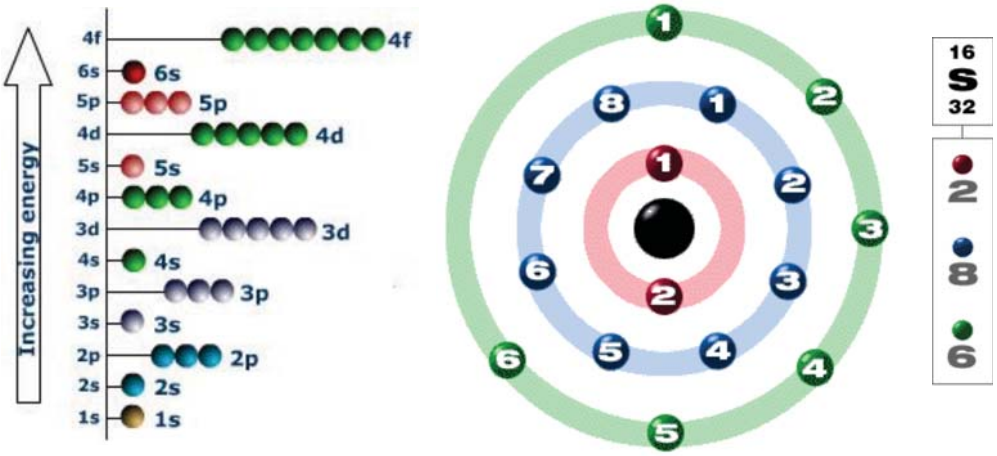
$|\Psi|^2$ function; iso-surfaces for some threshold

p, d, f, … orbitals: far from spherically symmetric

Multi-Electron Atoms

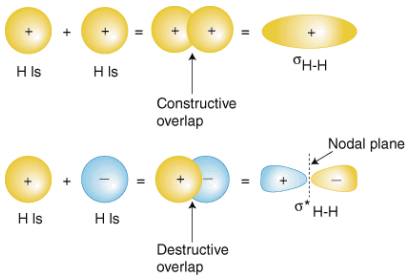
- Orbital — region of space occupied by an electron in a particular energy level
- Shell — set of all orbitals having the same n-value
- Subshell — set of orbitals of the same type

S: $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^4$

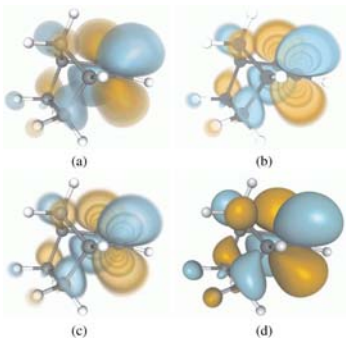


Atoms in Molecules

- Atoms retain their individuality
- Each atom: positively charged nucleus
  + cloud of core electrons (usually in closed shells)
  + valence electrons
- Molecular orbitals



- Complex superposition of molecular orbitals



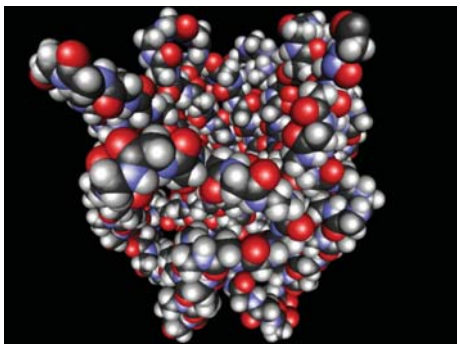
Y. Jang / U. Varetto. Interactive volume rendering of functional representations in quantum chemistry, TVCG 15:6 (2009): 1579-1586.

Atoms in Molecules

When the orbital structure is not of interest or is unknown:

Iconic "van-der-Waals" spheres can be used to represent atoms

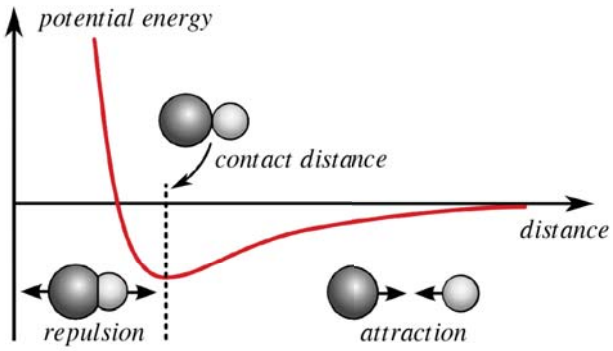
- Directions and lengths of bonds:
  represented by positions of the bonded close-by atoms
- Radii : determined by different experimental methods
  - Varying values, depending on experiment & on chemical situation
  - Typically consensus values are used
  - Range: H: 110 pm … Cs: 343 pm



- Computer graphically simple
- Mathematically nice

Backed up by van-der-Waals' Research

- Non-bonded atoms
  - For distances 3 - 4 Å: attract each other
  - At a certain distance: strong repulsive force (Pauli repulsion)
  - Modeled by Lennard-Jones potential



$$V(d) = 4\varepsilon\left(\left(\frac{\sigma}{d}\right)^{12} - \left(\frac{\sigma}{d}\right)^{6}\right)$$

repulsion (short range) attraction (long range)

⇒ non-bonded atoms behave like hard spheres

  - Introduction of hard-sphere model & vdW radii
- Bonded atoms: distance < $r_1 + r_2$
  atomic spheres overlap

Size and Shape of Molecules

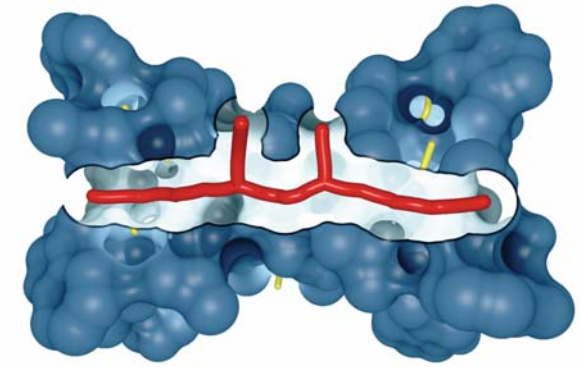
- How to determine the shape?
  - X-ray diffraction
    ⇒ limited to crystals
  - Via repulsive forces that prevent interpenetration of bodies
    ⇒ appropriate when mutual accessibility is of interest
- No fine tip for scanning the object available
  ⇒ use objects of similar size: atoms or molecules
- Carry own force fields
  ⇒ result depends on the 'probe', energy (= temperature), …

∃ no absolute sizes for molecules & atom radii !

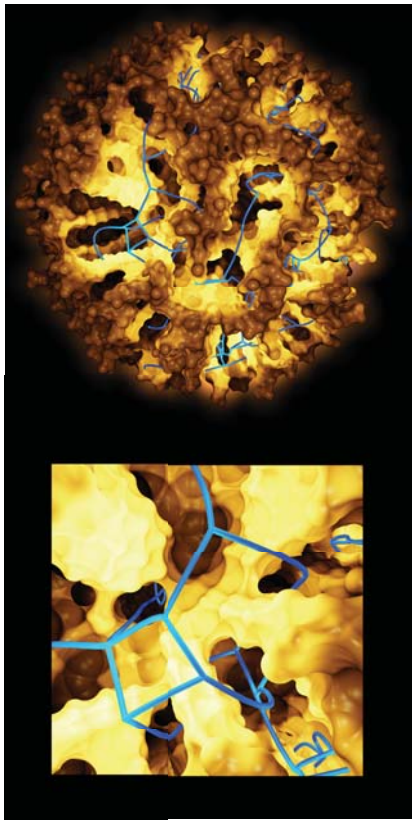
Nevertheless, when accessibility of molecules is analyzed, one gets exactly the required information

Importance of Accessibility

- Analysis of binding sites
  channels, tunnels
  internal cavities

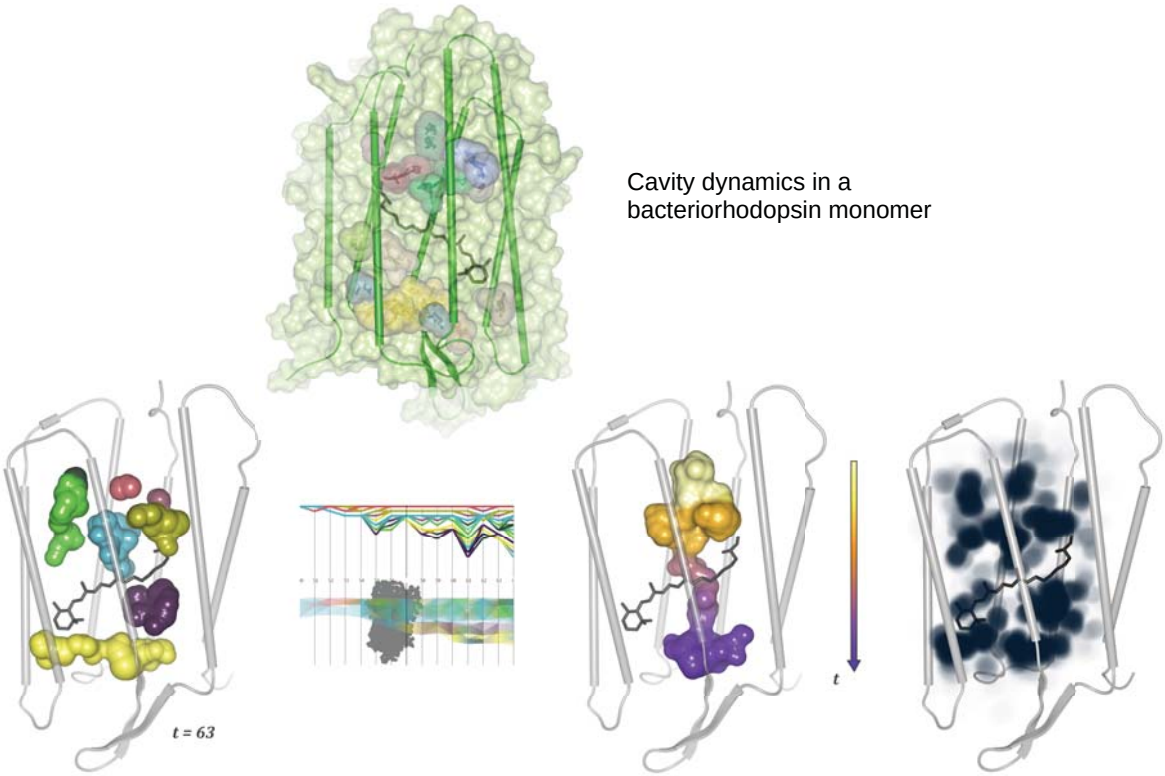


Ion-channel in Gramicidin A (PDB: 1GRM)



Molecular paths in nanotransporter

Importance of Accessibility



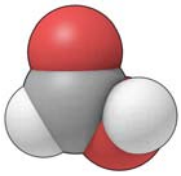
Cavity dynamics in a bacteriorhodopsin monomer

Two Problems with Standard Depictions

Standard Depictions

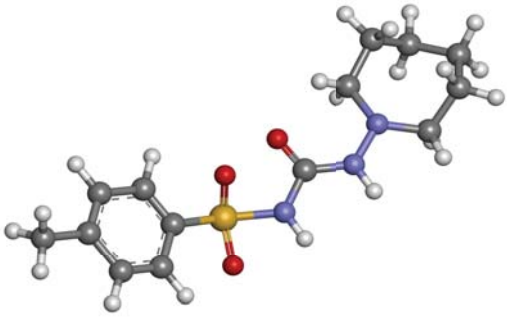
Space filling models

(vdW spheres)



formic acid

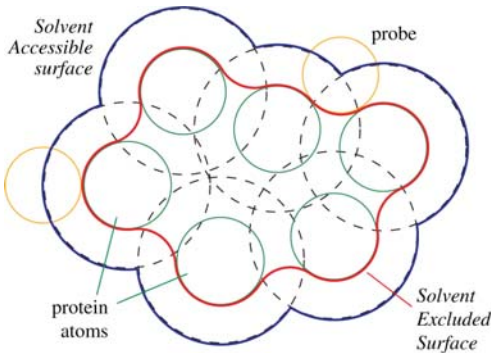
Ball and stick



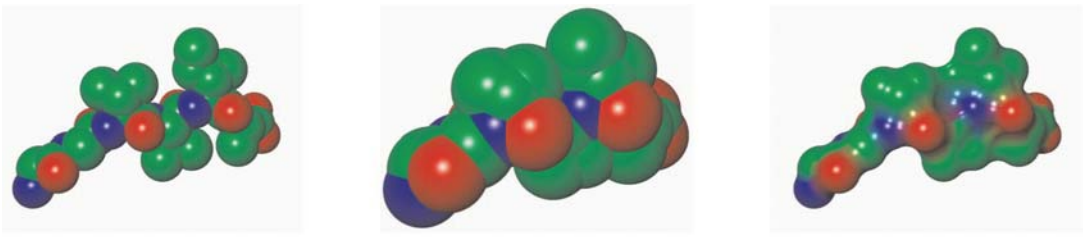
tolazamid

…

Accessibility ⇒ Molecular Surfaces: SAS, SES, …



From: Krone, Bidmon & Ertl, TVCG 15:6 (2009)



(a). *Van-der-Waals surface* (b). *Solvent Accessible Surface* (c). *Solvent Excluded Surface*

⇒ Many depictions, particularly those used for spatial analysis, depend on atomic sphere model & atomic radii

Problem 1 with vdW-based Depictions

- Various definitions of vdW radii exist

  ⇒ Molecular visualization & analysis tools use different radii
- In MD simulations vdW spheres of non-bonded atoms can intersect
- Fixed vdW radii per element ignore dependency on
  - number & type of covalently bonded atoms
  - thermodynamical state

All such visualizations are less objective than commonly believed !

Many visual & quantitative analyses rely on vdW representations:
e.g. extraction of internal cavities and channels

vdW-based analyses are less trustable than commonly believed !

Problem 2 with vdW-based Depictions

Accessibility of molecules by each other:

Standard tool: SAS, SES…

Not only definition depends on vdW radii,

but also solvent molecule is crudely approximated by sphere

- Even for water molecules: bad approximation!
- Instead: accessibility between arbitrarily shaped molecules is of interest

More realistic is modeling needed !

Two Attempts for Improved Modeling

Atom Accessiblity Radii

Atomic Accessibility Radii

- Data to be analyzed are typically MD trajectories
- An immense amount of work has been invested to make MD realistic (sophisticate force fields)
- MD trajectories reflect the thermodynamical situation

Idea:

- New type of atomic radius:

  ”atomic accessibility radius”

  based on the analysis of MD trajectories
- Maximal radii, such that the intersections of all pairs of non-bonded atoms are empty
- Reflects the accessibility of atoms for a given MD trajectory

Atomic Accessibility Radii

- Radii should be maximal such that the intersection of all pairs of non-bonded atoms is empty
- Optimization problem:
  - Objective function: sum of a set of atomic radii
  - Maximize under constraints:
    No pair of non-bonded atom spheres intersects

Three levels of abstraction: atomic radii for

- chemical elements
- atom types (more specific; also used in some MD simulation programs):
  - Depends on elements
  - Type and number of covalently bonded atoms
- individual atoms

Radii Computation

- r_i radius of atom class i

$$\begin{aligned} \textit{maximize} \quad & \sum_{i=1}^{m} w_i \cdot r_i \\ \textit{constraints} \quad & r_i + r_j \leq d_{i,j} \quad i \leq j | i, j \in \{1, \ldots, m\} \\ \textit{bounds} \quad & r_i \geq 0. \end{aligned}$$

- Weights w_i take care of …
- Suggested choice: $w_i = \sqrt[3]{m_e} \cdot c_i$

  c_i = # atoms in class i

  m_e = mass of the chemical element
- LP solution, e.g. with Gurobi

Results

- For element / atom type radii: up to 150 variables, O(1000) constraints
  few seconds
- For individual radii: 5 min – 50 min

Results

- For element / atom type radii: up to 150 variables, O(1000) constraints
  few seconds
- For individual radii: 5 min – 50 min
- Element-based radii:

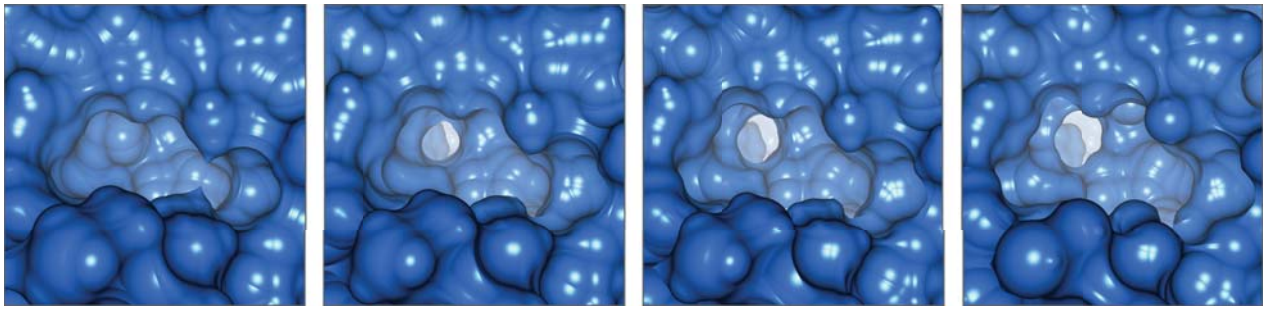
Radii Source	H	C	N	O	S
Protein-Ligand	0.23	1.42	1.21	1.16	1.58
Protein-RNA	0.22	1.41	1.25	1.15	1.64
Polymer-Solvent	0.46	1.36	1.37	1.01	-
Protein in Mem.	0.44	1.46	1.31	1.08	1.60
Protein in Mem.	0.34	1.40	1.33	1.03	1.70
Rowland [RT96]	1.10	1.77	1.64	1.58	1.81

⇐ vdW radii

- Nearly all computed atomic radii < van derWaals radii (as expected)
- Radii for the hydrogen atoms are much smaller
- Small differences between different trajectories

Results

Close-up of the solvent excluded surface showing a cavity in bacteriorhodopsin



vdW radii | r_i for individual atoms | r_i for atom type | r_i for elements

Substrate Accessible Surface

Substrate Accessible Surface

Preliminary

= Extension of the classical SAS & SES

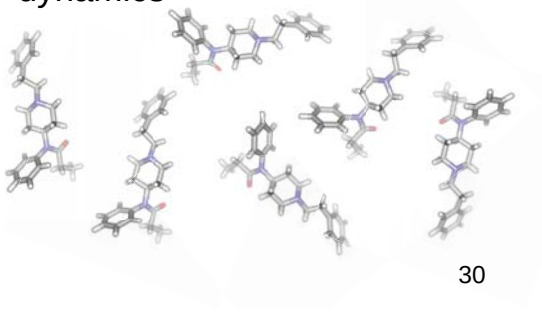
Classical Approach

- solvent is geometrically approximated by a probe sphere

- surface shows all boundaries of regions accessible / not accessible to the probe

Better approximation

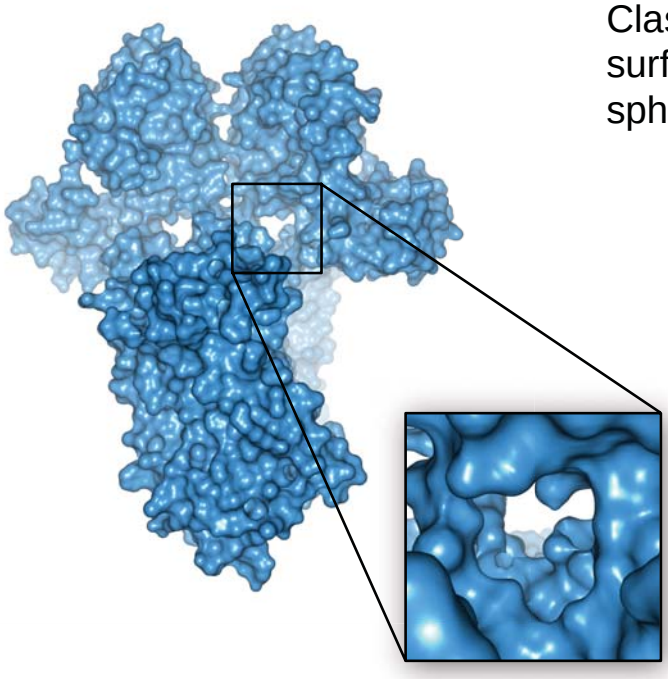
- directly use geometry of solvent/substrate
- test accessibility by discretizing substrate positions, rotations and dynamics



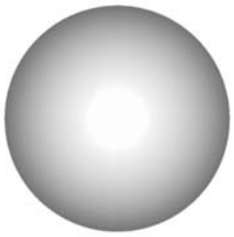
Substrate Accessible Surface

Preliminary

Example: μ-opioid receptor (PDB: 4DKL)



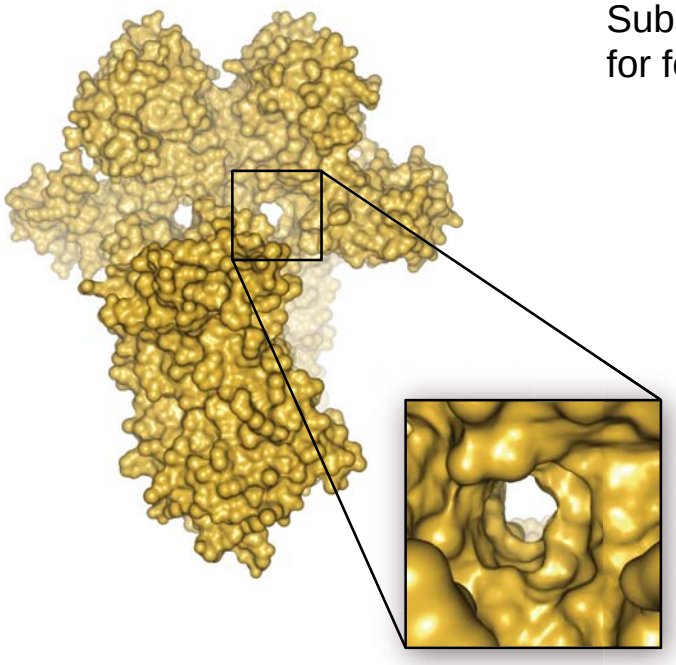
Classical smooth molecular surface (SES) with a probe sphere approximating water



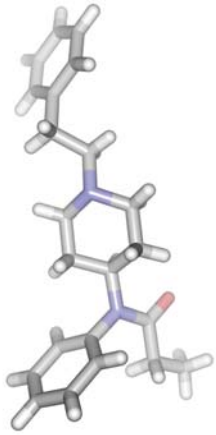
Substrate Accessible Surface

Preliminary

Example: μ-opioid receptor (PDB: 4DKL)



Substrate accessible surface for fentanyl

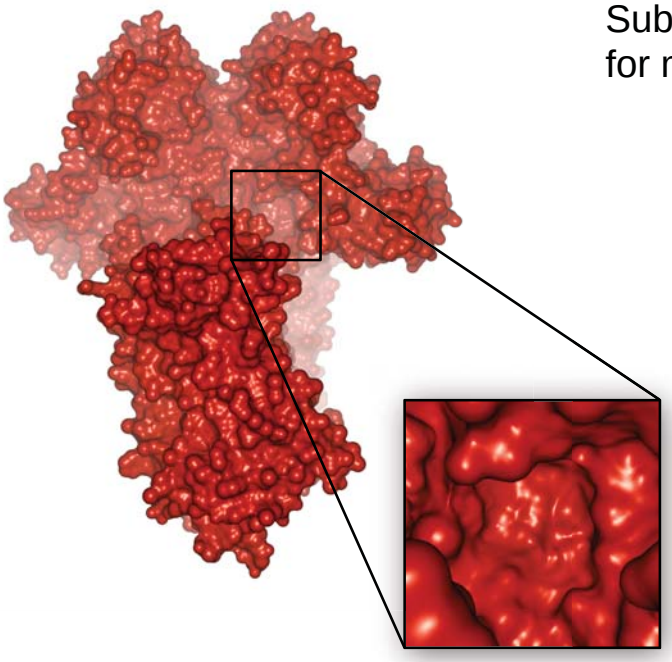


~ 30 min for 0.25 A resolution

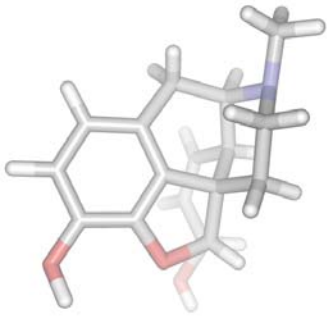
Substrate Accessible Surface

Preliminary

Example: μ-opioid receptor (PDB: 4DKL)



Substrate accessible surface for morphine



~ 15 min for 0.25 A resolution

Summary / Discussion