

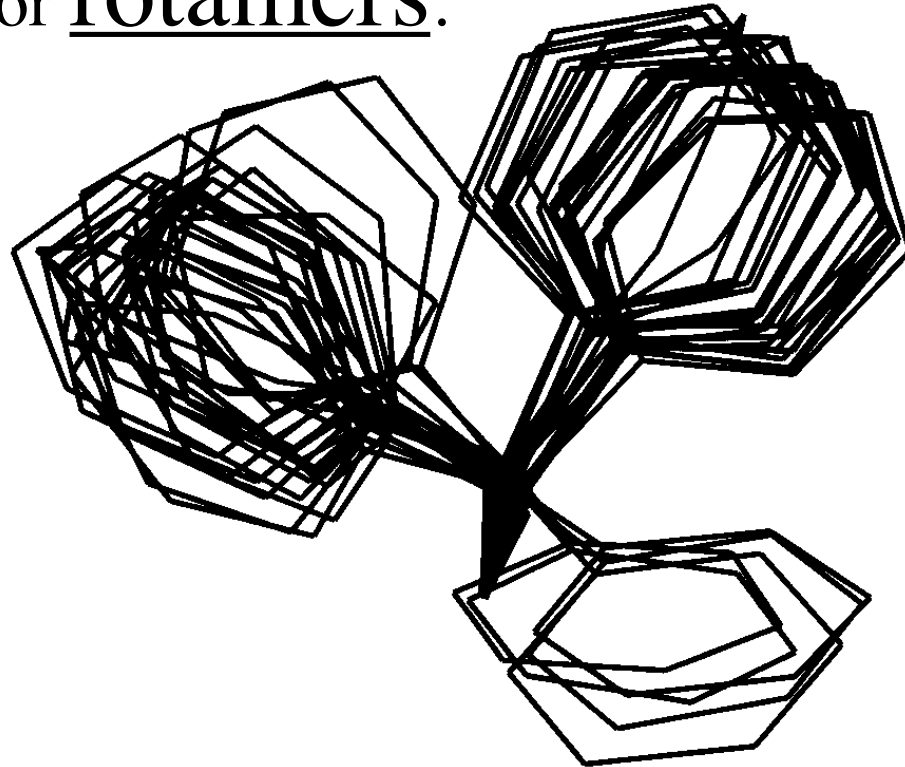
Molecular Modeling 2018

Lecture 11
side chain modeling
rotamers
rotamer explorer
buried cavities.

Sidechain Rotamers

Discrete approximation of the continuous space of backbone angles.

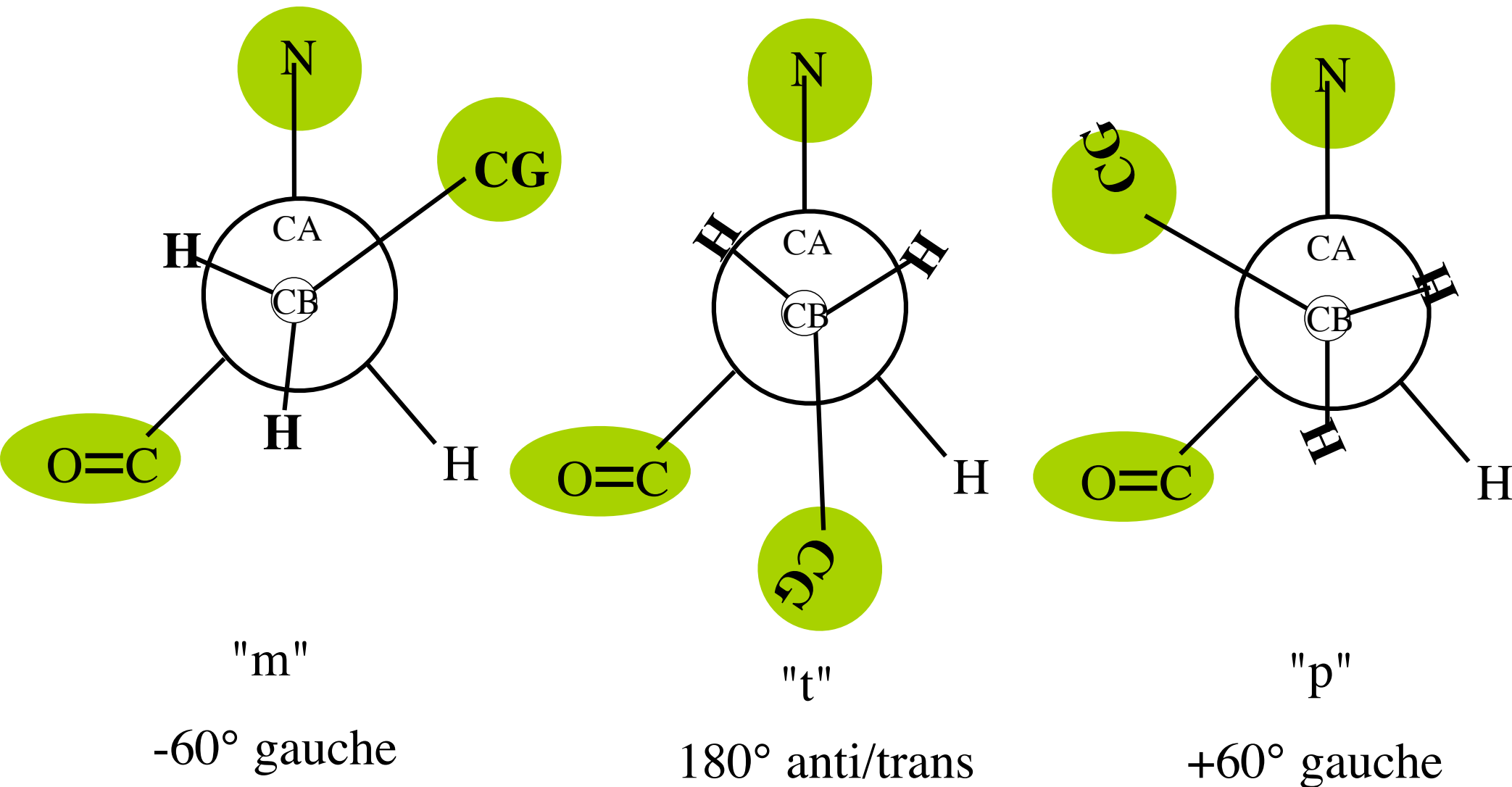
Sidechain conformations fall into discrete classes called rotational isomers, or rotamers.



A random sampling of Phenylalanine sidechains, w/
backbone superimposed

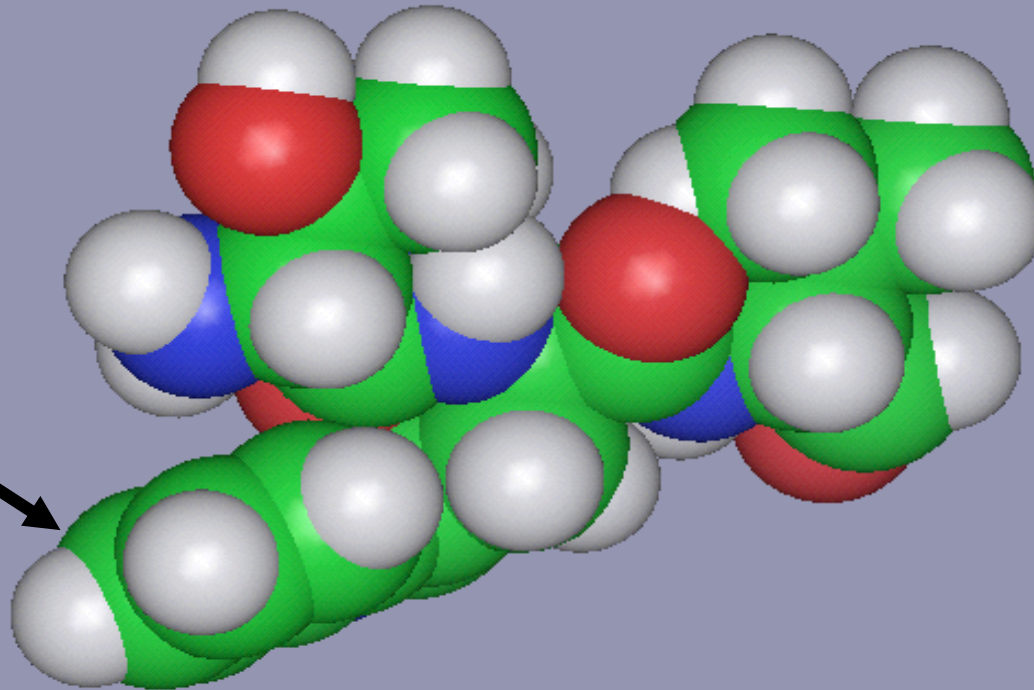
Sidechain rotamers, naming

1-4 interactions differ greatly in energy depending on the moieties involved.



Rotamer stability is dependent on the backbone $\phi\psi$ angles

W sidechain is shown here lying over Thr backbone



<u>Rotamers of W*:</u>	<u>ϕ</u>	<u>ψ</u>	<u>$P \phi=-140,\psi=160$</u>	<u>$P \phi=-60,\psi=-40$</u>
p-90	+60	-90	0.372	0.079
p90	+60	+90	0.238	0.005
t-105	180	-105	0.033	0.251
t90	180	90	0.021	0.268
m0	-65	5	0.038	0.124
m95	-65	95	0.183	0.203

Rotamer Libraries

Rotamer libraries have been compiled by clustering the sidechains of each amino acid over the whole database. Each cluster is a representative conformation (or rotamer), and is represented in the library by the best sidechain angles (chi angles), the "centroid" angles, for that cluster.

Two commonly used rotamer libraries:

*Jane & David Richardson: <http://kinemage.biochem.duke.edu/databases/rotamer.php>

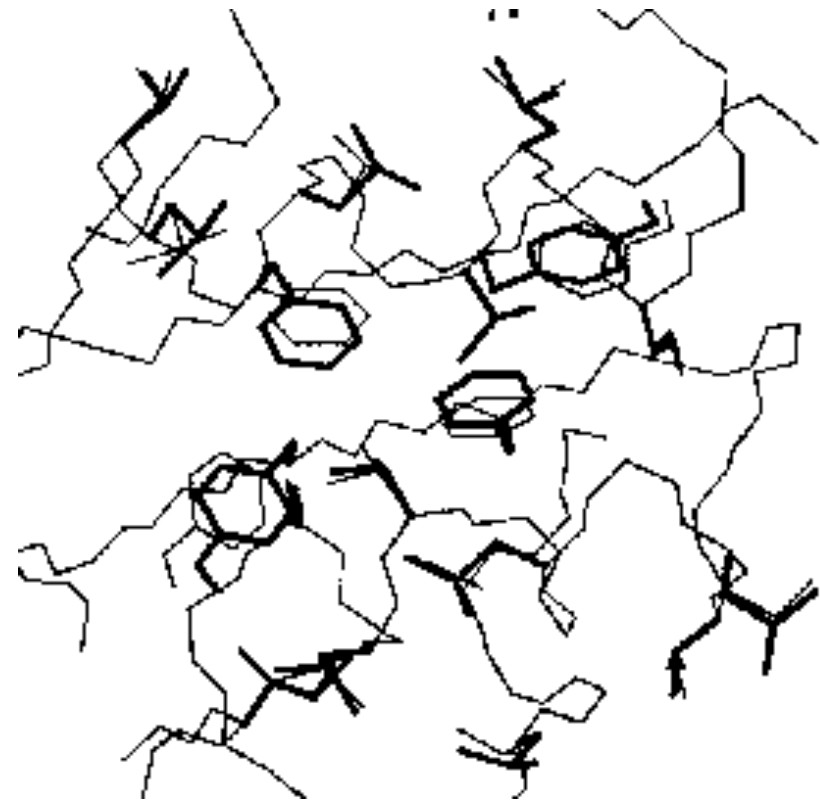
Roland Dunbrack: <http://dunbrack.fccc.edu/bbdep/index.php>

*rotamers of W on the previous page are from the Richardson library.

sidechain prediction

Given the sequence and only the backbone atom coordinates, accurately model the *positions of the sidechains*.

fine lines = true structure
thick lines = sidechain predictions using the method of Desmet et al.



Dead end elimination theorem

- Each residue is numbered (i or j) and each residue has a set of rotamers (r , s or t). So, the notation i_r means "choose rotamer r for position i ".
- The total energy is the sum of the three components:

$$E_{\text{global}} = E_{\text{template}} + \sum_i \overset{\text{fixed-fixed}}{E(i_r)} + \sum_i \sum_j \overset{\text{fixed-movable}}{\underset{\text{movable-movable}}{E(i_r, j_s)}}$$

where r and s are any choice of rotamers.

NOTE: $E_{\text{global}} \geq E_{\text{GMEC}}$ for any choice of rotamers.

Dead end elimination theorem

- If i_g is in the GMEC and i_t is not, then we can separate the terms that contain i_g or i_t and re-write the inequality.

$$E_{\text{GMEC}} = E_{\text{template}} + E(i_g) + \sum_j E(i_g, j_g) + \sum_j E(j_g) + \sum_j \sum_k E(j_g, k_g)$$

...is less than...

$$E_{\text{notGMEC}} = E_{\text{template}} + E(i_t) + \sum_j E(i_t, j_g) + \sum_j E(j_g) + \sum_j \sum_k E(j_g, k_g)$$

Canceling all terms in black, we get:

$$E(i_r) + \sum_j E(i_r, j_s) > E(i_g) + \sum_j E(i_g, j_s)$$

So, if we find two rotamers i_r and i_t , and:

$$E(i_r) + \sum_j \min_s E(i_r, j_s) > E(i_t) + \sum_j \max_s E(i_t, j_s)$$

Then i_r cannot possibly be in the GMEC.

Dead end elimination theorem

$$E(i_r) + \sum_j \min_s E(i_r j_s) > E(i_t) + \sum_j \max_s E(i_t j_s)$$

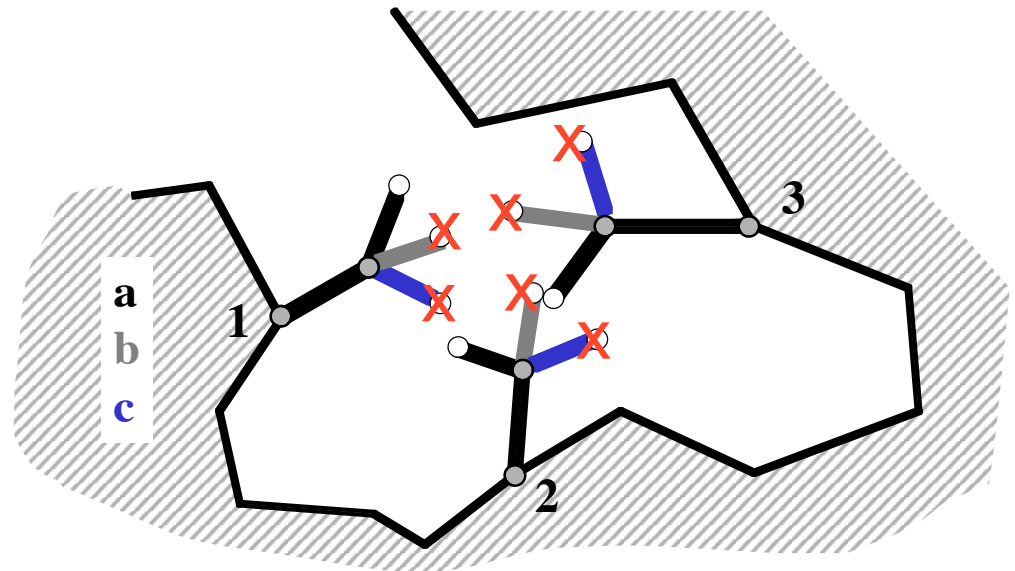
DEE theorem can be translated into plain English as follows:

If the "worst case scenario" for t is better than the "best case scenario" for r , then you always choose t .

DEE algorithm

$$E_{\text{global}} = E_{\text{template}} + \sum_i E(i_r) + \sum_i \sum_j E(i_r, j_s)$$

		1			2			3			
		a	b	c	a	b	c	a	b	c	
1	a	-1	3	5	-1	1	1	-2	2	5	0
	b	3	5	0	3	5	0	0	0	0	0
	c	5	0	0	5	0	0	0	0	0	5
2	a	-1	3	5	-1	3	5	0	0	1	0
	b	1	5	0	E(r ₁ , r ₂)	5	0	12	5	0	0
	c	1	0	1	0	0	4	0	0	0	0
3	a	-2	0	0	0	12	4	0	0	0	0
	b	2	0	0	0	5	0	0	0	0	0
	c	5	0	0	1	0	0	0	0	0	12
E(r ₁)		0	0	5	0	0	0	0	0	0	12

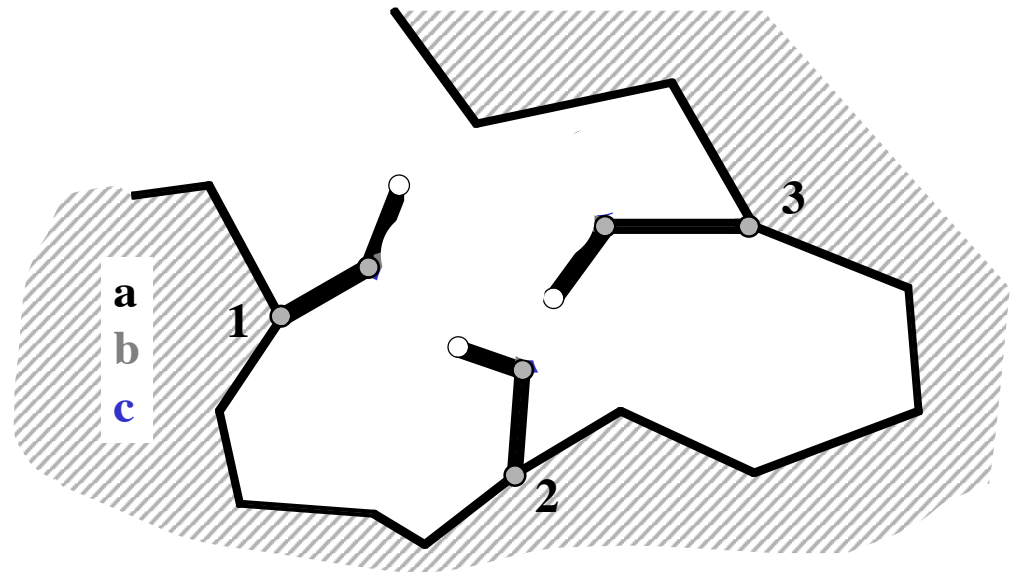
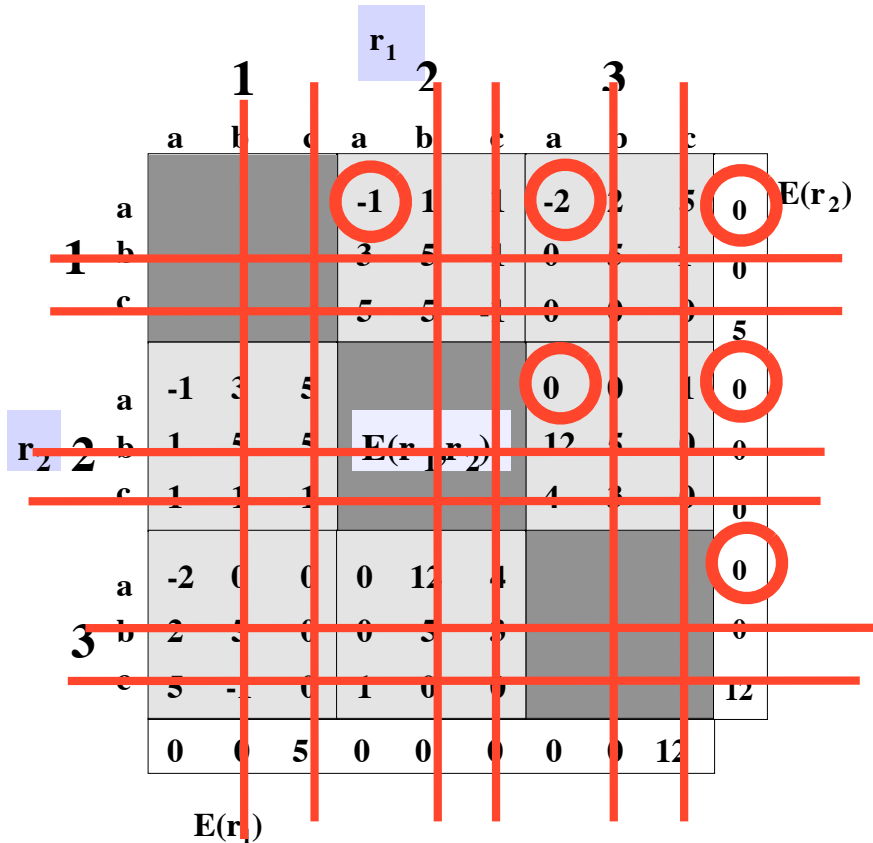


Find two columns (rotamers) within the same residue, where one is always better than the other. Eliminate the rotamer that can always be beat. (repeat until only 1 rotamer per residue)

		1			r_1 2			3				
		a	b	c	a	b	c	a	b	c		
1	a				-1	1	1	-2	2	5	0	$E(r_2)$
	b				3	5	1	0	5	-1	0	
	c				5	5	-1	0	0	0	5	
r_2 2	a	-1	3	5	$E(r_1, r_2)$			0	0	1	0	
	b	1	5	5				12	5	0	0	
	c	1	1	-1				4	3	0	0	
3	a	-2	0	0	0	12	4				0	
	b	2	5	0	0	5	3				0	
	c	5	-1	0	1	0	0				12	
		0	0	5	0	0	0	0	0	12		
												$E(r_1)$

DEE algorithm

$$E_{\text{global}} = E_{\text{template}} + \sum_i E(i_r) + \sum_i \sum_j E(i_r, j_s)$$



Find two columns (rotamers) within the same residue, where one is always better than the other. Eliminate the rotamer that can always be beat. (repeat until only 1 rotamer per residue)

Rotamer explorer

- Pulls side chain rotamers from a rotamer library. Superposes on the backbone.
- Note difference in chi angles (side chain torsion angles)
- Only displays rotamers that have a good energy.
- Energy is calculated relative to the best rotamer.
- *Not shown in Rotamer Explorer:* Rotamers have intrinsic energies. Some are intrinsically better than others.

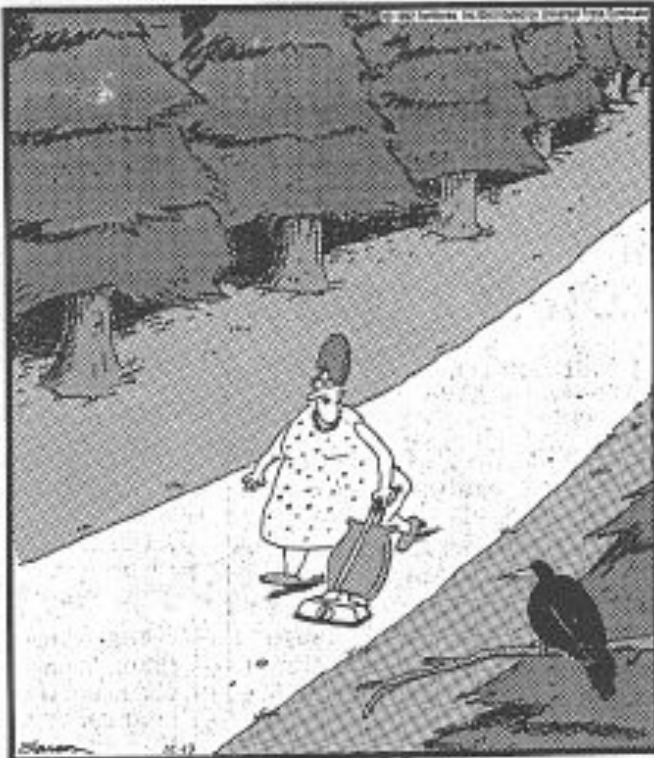
Try Rotamer explorer

- Study your structure. Find a side chain that is not "happy". Select it.
- **Protein | Rotamer explorer**
- **Get from MOE**
- **Explore**
 - click through results
 - inspect.
- **Mutate.**
- Repeat.

Nature abhors a vacuum

no, not this kind...

THE FAR SIDE • Gary Larson



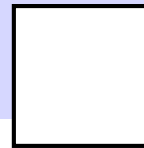
The woods were dark and foreboding, and Alice sensed that sinister eyes were watching her every step. Worst of all, she knew that Nature abhorred a vacuum.

There is only **one way** to make space empty, but **many ways** to fill it.

$S = p \log p$, where p is the number of states.

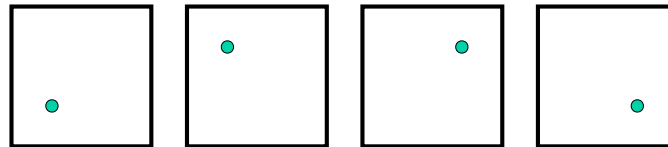
Higher entropy means more probable.

$S=0$

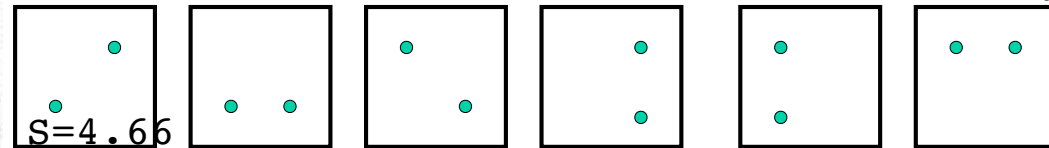


zero particles, 4 possible locations, one state

$S=2.44$

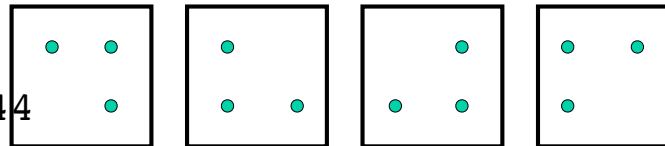


$S=4.66$

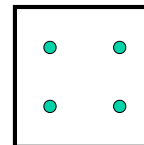


two particles, 4 possible locations, 6 states

$S=2.44$

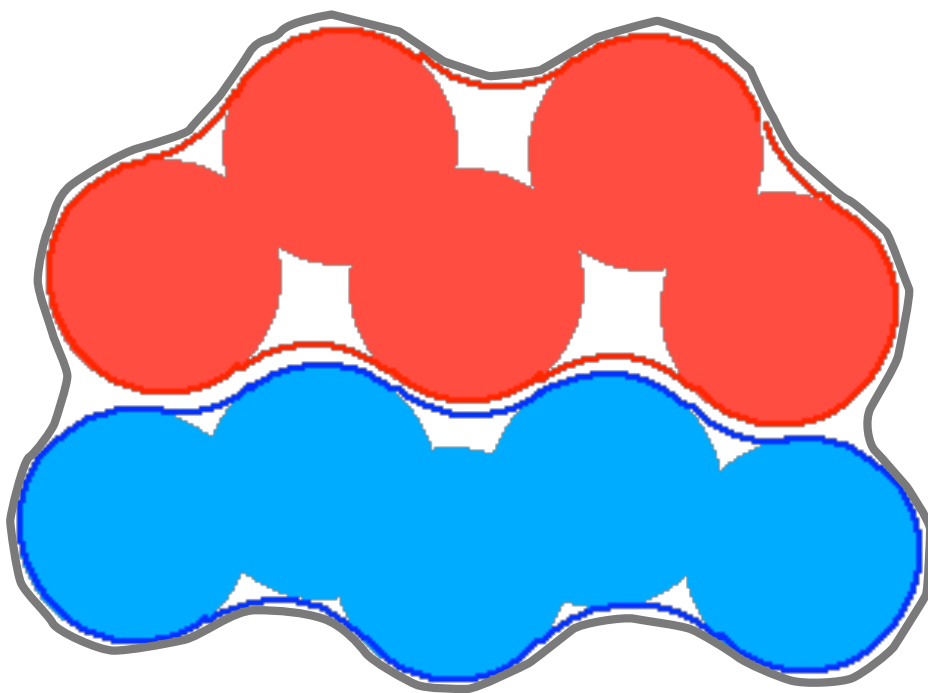


$S=0$



4 particles, 4 possible locations, one state

Solvent excluded surface complementarity.



Complementary surfaces leave relatively little unfilled (void) space.

White space within colored outlines are **solvent excluded** spaces in the *monomer*.

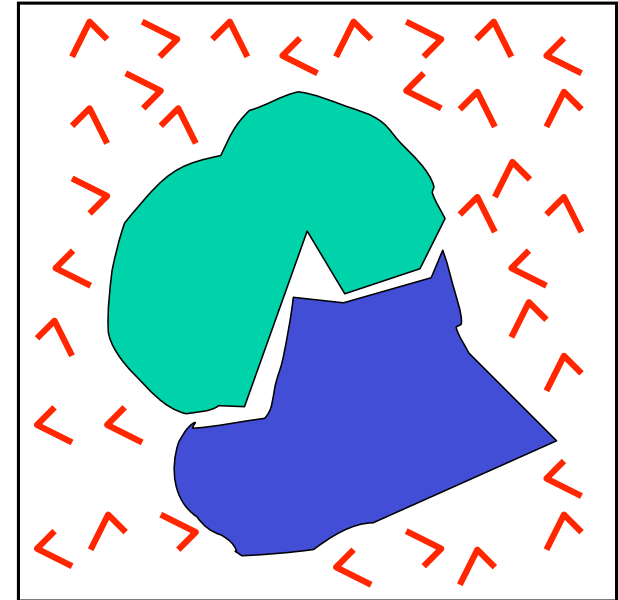
White space in grey outline is solvent excluded in the *dimer*.

No addition solvent excluded space means tight binding.

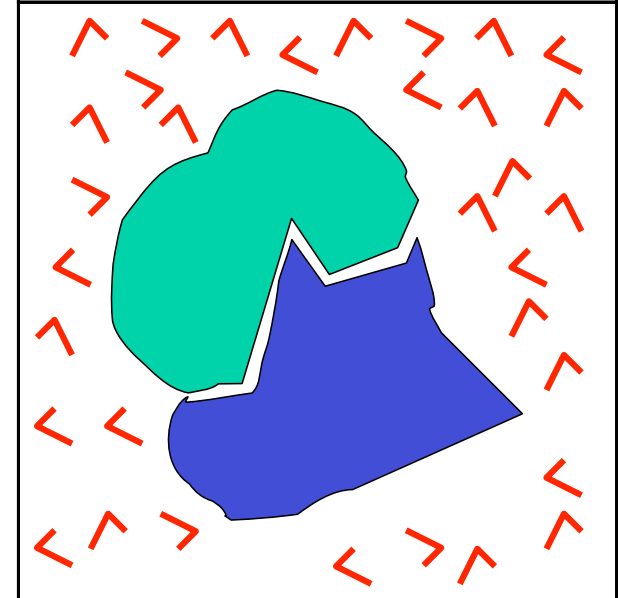
Better fit, less wasted space, lower energy.

If we compare two surface-surface interactions, all else being equal, the one with more void spaces has a higher free energy, and is therefore less favorable. The one that fills space has a lower energy.

higher E

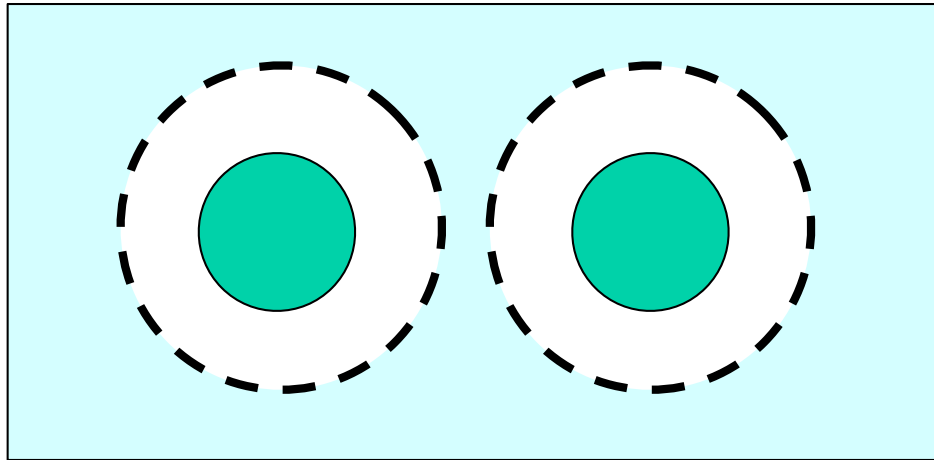


lower E

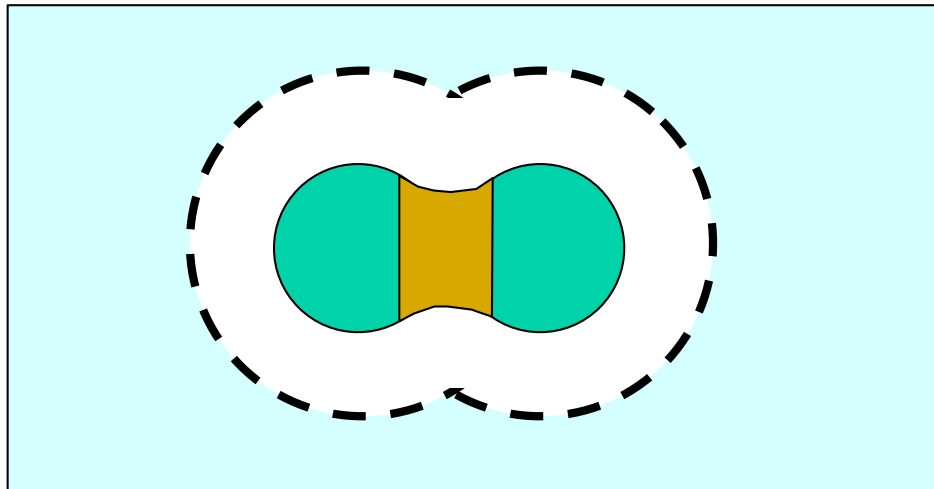


The Hydrophobic Effect

Solvent accessible surface (dashed line) around non-polar atoms contains "high energy waters" because those waters lose H-bonds.



Non-polar atoms come together because it decreases the number of high energy waters. (Even at the cost of creating void space (brown)).



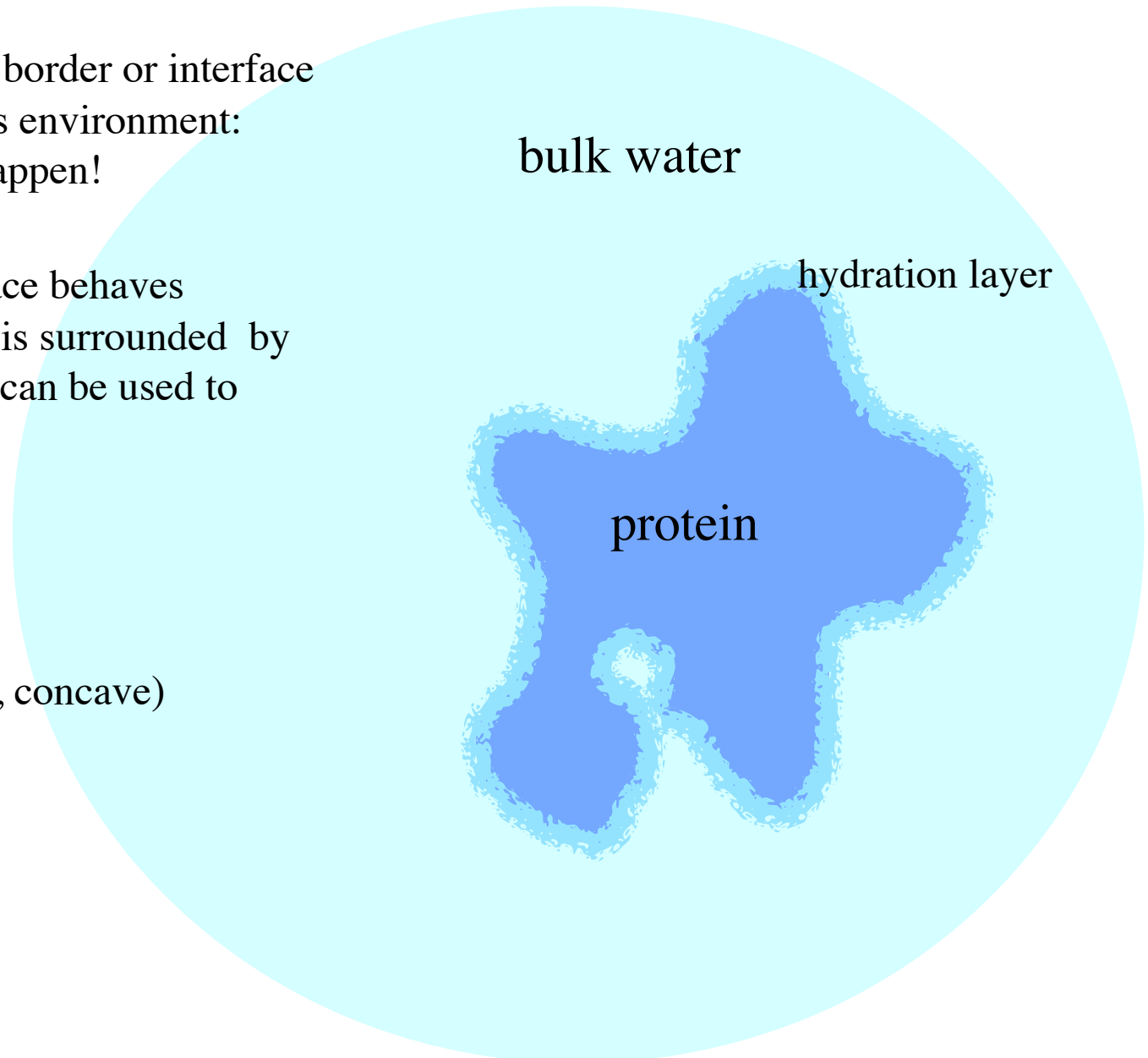
Solvation

A molecular surface is the border or interface between a molecule and its environment: where interesting things happen!

Water that sits on the surface behaves differently than water that is surrounded by water. Therefore, surfaces can be used to model *solvation*.

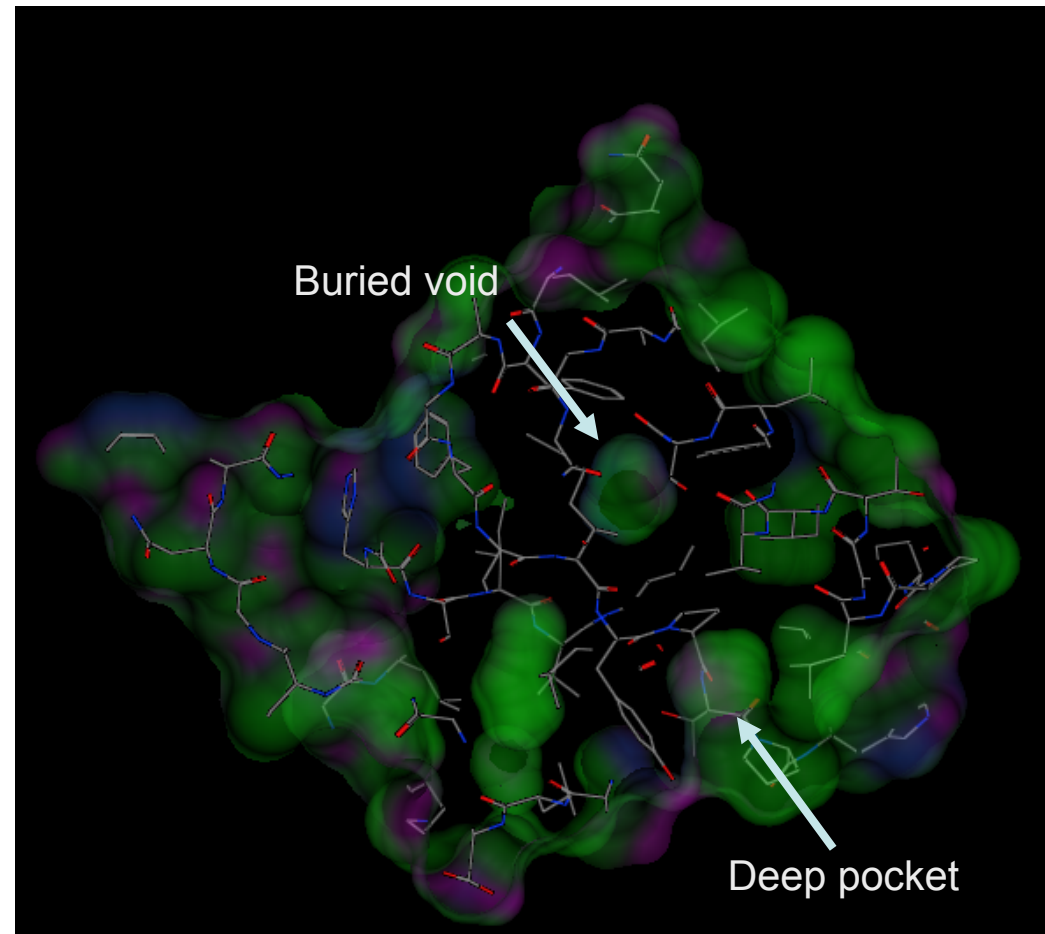
Surfaces properties:

- size/area
- electrostatic properties
- shape properties (convex, concave)



Exercise 11.1 Finding voids

- Select an atom near the center of the model.
- **Compute | Surfaces & Maps | Molecular surface**
 - Set *transparency* to allow you to see the atoms through the front surface



Exercise 11.2 Filling void by Rotamer Explorer

Find a side chain that could potentially rotate into the buried cavity.

Protein | Rotamer explorer

Get from MOE

Explore.

Click on each rotamer and look at where it goes.

“Mutate” to the rotamer that best fills the void.

Select the side chain and minimize around it.

Select | Extend , Edit | potential | unfix , Select | invert , Edit | potential | fix

Minimize

Recalculate the surface. Name it something different.

Toggle between before and after surfaces.

Did the void disappear? Did another one appear?

Review questions

- What variables define side chain rotamers?
- What makes some rotamers intrinsically lower energy than others?
- What kinds of positions tend to have many allowed rotameric states?
- What kind of positions tend to have few allowed rotameric states?
- Which amino acids have only 1 rotamer?
- Which amino acids have the most rotamers? Why does “nature abhor a vacuum” ?
- What is the solvent excluded surface?
- What is the energetic significance of the solvent interface?
- Where do you tend to find ordered waters?
- How can we fill voids?