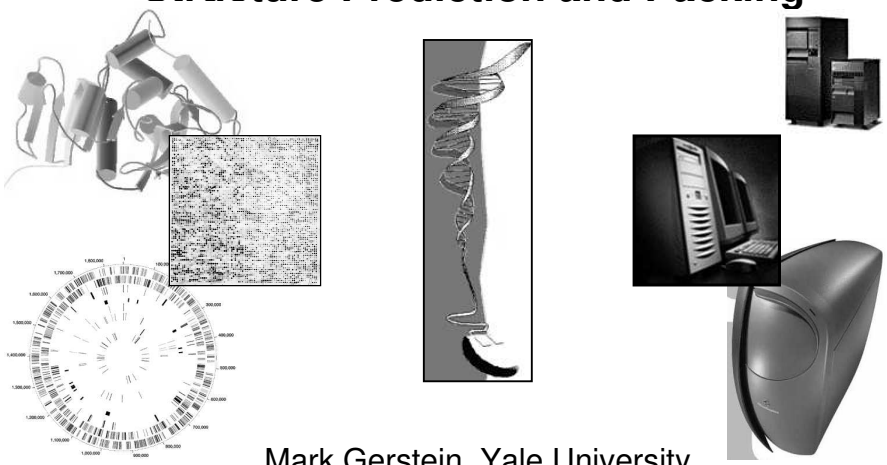
Macromolecules
Computational Aspects of Secondary Structure Prediction and Packing



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Overview

- Why interesting?
  - ◊ Not tremendous success, but many methods brought to bear.
  - ◊ What does difficulty tell about protein structure?
- Start with TM Prediction (Simpler)
- Basic GOR Sec. Struc. Prediction
- Better GOR
  - ◊ GOR III, IV, semi-parametric improvements, DSC
- Other Methods
  - ◊ NN, nearest nbr.

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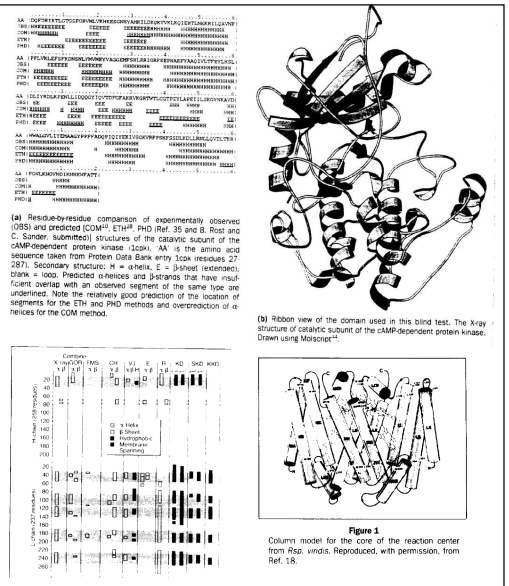
What secondary structure prediction tries to accomplish?

Credits: Rost et al. 1993;
Fasman & Gilbert, 1990

- Not Same as Tertiary Structure Prediction -- no coordinates
- Need torsion angles of terms + slight diff. in torsions of sec. str.



Sequence RPDFCLEPPYTGPCKARIIRYFYNAKAGLVQTFVYGGCRAKRNNFKSAEDAMRTCGGA
Structure CCGGGGCCCCCCCCCCCCEEEEEEETTTTEEEEEEECCCCCTTTTBTTHHHHHHHHHCC

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Some TM scales: GES KD

Goldman, Engelman, Steitz
KD – Kyte Dolittle

	GES		KD
F	−3.7	I	4.5
M	−3.4	V	4.2
I	−3.1	L	3.8
L	−2.8	F	2.8
V	−2.6	C	2.5
C	−2.0	M	1.9
W	−1.9	A	1.8
A	−1.6	G	−0.4
T	−1.2	T	−0.7
G	−1.0	W	−0.9
S	−0.6	S	−0.8
P	+0.2	Y	−1.3
Y	+0.7	P	−1.6
H	+3.0	H	−3.2
Q	+4.1	E	−3.5
N	+4.8	Q	−3.5
E	+8.2	D	−3.5
K	+8.8	N	−3.5
D	+9.2	K	−3.9
R	+12.3	R	−4.5

For instance, ΔG from transfer of a Phe amino acid from water to hexane

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How to use GES to predict proteins

- Transmembrane segments can be identified by using the GES hydrophobicity scale (Engelman et al., 1986). The values from the scale for amino acids in a window of size 20 (the typical size of a transmembrane helix) were averaged and then compared against a cutoff of -1 kcal/mole. A value under this cutoff was taken to indicate the existence of a transmembrane helix.
- H-19(i) = [H(i-9)+H(i-8)+...+H(i) + H(i+1) + H(i+2) + . . . + H(i+9)] / 19

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Graph showing Peaks in scales

Illustrations Adapted From: von Heijne, 1992; Smith notes, 1997

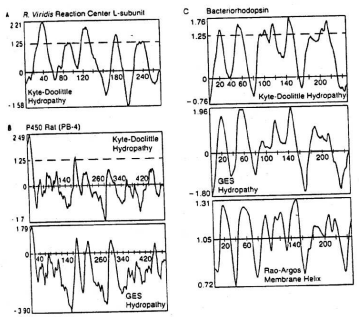
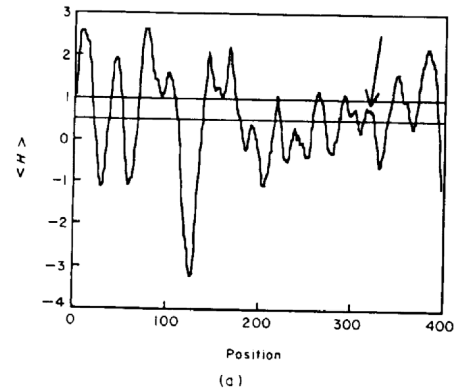
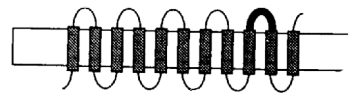


Figure 3.12. Representative profiles of three membrane proteins used to predict membrane-spanning helices. The amino acid scales of Kyte-Doolittle (804), Goldman–Engelman–Steitz (GES) (389), and Rao–Argos (1194) were used. A computer software package (SEQANAL) provided by Dr. A. Crofts (Univ. of Illinois) was used to generate these profiles. For comparative purposes, the Kyte–Doolittle and GES plots were obtained using a window of 19 residues and then smoothed using a second pass with a window of 7. The average value at each residue position is plotted as a function of residue number starting with the amino terminus on the left in each case. The values plotted for the Kyte–Doolittle and GES scales represent average hydropathy and transfer free energy per residue (kcal/mol). The Rao–Argos plot used a span of 7 residues and was smoothed used two additional passes with the same span of 7, as recommended by the authors. The scale values reflect the relative preference for being in a membrane-spanning helix. Note that the version of the GES algorithm which was used does not take into account possible ion pair formation. See text for details.





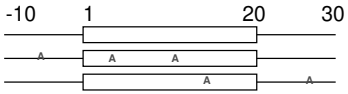
Ex. P(i,α) probability that residue i has secondary structure α

- Problem of DB Bias
- f(A) = frequency of residue A to have a TM-helical conf. in db
- f(A,i) = f(A) at position i in a particular sequence
- E(α)=statistical energy of helix over a window
- p(i, α) = probability that residue i is in a TM-helix

$$E_\alpha = \sum_i^N \ln f_\alpha^i$$

$$p_\alpha^i = \frac{e^{-Ea/RT}}{\sum_j^N e^{-E_j/RT}}$$

$F_{in\text{-}DB}(A) = 5/120$



$F_{in\text{-}TM}(A) = 3/60$

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Statistics Based Methods: Persson & Argos

- Propensity P(A) for amino acid A to be in the middle of a TM helix or near the edge of a TM helix

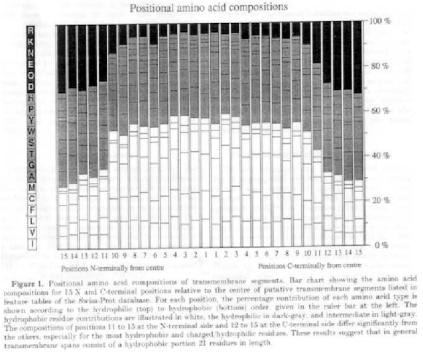

Figure 1. Positional amino acid compositions of transmembrane segments. Bar chart showing the amino acid compositions for 15 N and C-terminal positions relative to the centre of putative transmembrane segments listed in feature tables of the Swiss-Prot database. For each position, the percentage contribution of each amino acid type is shown according to the hydrophilic (top) to hydrophobic (bottom) order given in the ruler bar at the left. The hydrophobic residue contributions are illustrated in white, the hydrophilic in dark-gray, and intermediate in light-gray. The compositions of positions 11 to 15 at the N-terminal side and 12 to 15 at the C-terminal side differ significantly from the others, especially for the most hydrophobic and charged/hydrophilic residues. These results suggest that in general transmembrane spans consist of a hydrophobic portion 21 residues in length.

$$P(A) = \frac{\frac{n(A,\mathrm{TM})}{\sum_A n(A,\mathrm{TM})}}{\frac{n(A,\mathrm{everywhere})}{\sum_A n(A,\mathrm{everywhere})}}$$

Illustration Credits: Persson & Argos, 1994

$P(A) = f_{TM}(A)/f_{SwissProt}(A)$

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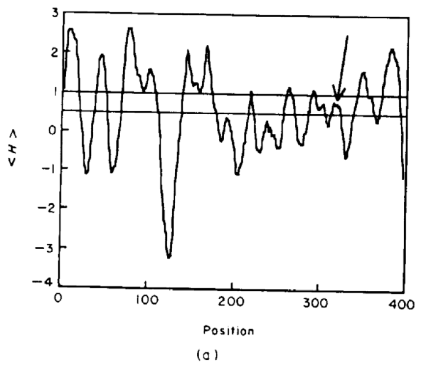
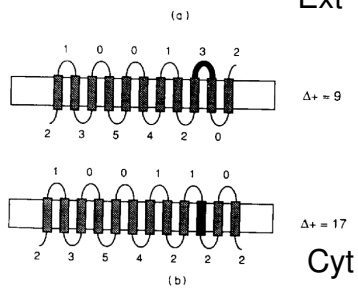
Refinements: Charge on the Outside, Positive Inside Rule

- for marginal helices, decide on basis of R+K inside (cytoplasmic)



Credits: von Heijne, 1992

Ext



Cyt

Figure 4. (a) Hydrophobicity plot for the SecY protein. The upper and lower cutoffs are marked. A tentative transmembrane segment with a mean hydrophobicity falling between the 2 cutoffs is marked by an arrow. (b) Two possible topologies for the SecY protein based on the hydrophobicity plot. The putative transmembrane segment is shown in black. The number of Arg+Lys residues is shown next to each polar segment. Note that the correct alternative (bottom, including the putative transmembrane segment) has a much higher charge-bias than the incorrect one.

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GOR: Simplifications

- For independent events just add up the information
- $I(S_j ; R_1, R_2, R_3, ...R_{last})$ = Information that first through last residue of protein has on the conformation of residue j (S_j)
  - ◊ Could get this just from sequence sim. or if same struc. in DB (homology best way to predict sec. struc.!)
- Simplify using a 17 residue window: $I(S_j$=H ; R[j-8], R[j-7], ..., R[j], ... R[j+8])
- Difference of information for residue to be in helix relative to not: I(dSj;y) = I(Sj=H;y)-I(Sj=~H;y)
  - ◊ odds ratio: I(dSj;y)= ln P(Sj;y)/P(~Sj;y)
  - ◊ I determined by observing counts in the DB, essentially a lod value

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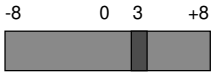
Basic GOR

- Pain & Robson, 1971; Garnier, Osguthorpe, Robson, 1978
- I ~ sum of I(Sj,R[j+m]) over 17 residue window centered on j and indexed by m
  - ◊ I(Sj,R[j+m]) = information that residue at position m in window has about conformation of protein at position j
  - ◊ 1020 bins=17*20*3
- In Words
  - ◊ Secondary structure prediction can be done using the GOR program (Garnier et al., 1996; Garnier et al., 1978; Gibrat et al., 1987). This is a well-established and commonly used method. It is statistically based so that the prediction for a particular residue (say Ala) to be in a given state (i.e. helix) is directly based on the frequency that this residue (and taking into account neighbors at +/- 1, +/- 2, and so forth) occurs in this state in a database of solved structures. Specifically, for version II of the GOR program (Garnier et al., 1978), the prediction for residue i is based on a window from i-8 to i+8 around i, and within this window, the 17 individual residue frequencies (singlets),



f(H,+3)/f(~H,+3)

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Directional Information

$$LOD = \ln \frac{OBS}{EXP}$$

helix

strand

coil

	i-8	i-7	i-6	i-5	i-4	i-3	i-2	i-1	i	i+1	i+2	i+3	i+4	i+5	i+6	i+7	i+8
a	-12	-15	-13	-12	-17	-13	-25	-24	-32	-35	-32	-29	-24	-20	-12	-5	-6
c	36	26	41	50	45	31	29	19	7	5	27	29	38	48	41	45	59
d	-8	-16	-13	-8	-13	-10	13	25	50	63	33	27	7	-7	-4	-9	-5
e	-3	-11	-10	-11	-10	-7	-5	-23	-26	-23	-2	5	-1	-3	1	-5	-9
f	22	25	20	25	21	9	-23	-34	-49	-40	-29	-12	9	20	13	18	13
g	-3	-8	-10	-17	-7	2	26	68	97	58	19	-2	-18	-14	-16	-11	-11
h	15	9	-4	-7	8	-2	12	8	8	5	-4	1	-3	-5	-5	-10	-9
i	7	12	19	14	7	1	-21	-42	-66	-55	-26	-14	14	18	4	2	1
k	-12	-7	-10	-9	-1	5	11	5	0	9	5	-8	-20	-15	-7	-10	-12
l	2	8	11	11	11	2	-21	-42	-65	-63	-52	-39	-15	-11	-10	-6	0
m	11	14	4	3	-9	-16	-33	-52	-62	-77	-71	-54	-32	-7	3	9	9
n	-2	-8	-11	-1	9	13	33	91	61	31	9	6	-6	-4	1	2	2
p	4	8	4	-1	0	15	39	76	120	159	98	59	32	17	11	3	0
q	-1	-11	-12	-15	-17	-4	8	-5	-13	1	1	2	-2	-5	-1	-9	-20
r	-4	-9	-8	-10	-10	-13	-18	-16	-14	-9	-14	-16	-14	-11	-5	-3	-2
s	-3	-4	-4	-4	4	11	22	26	41	31	20	13	3	5	4	8	11
t	-5	-5	-5	-4	-7	-5	6	2	15	21	29	30	19	7	3	-4	-5
v	3	17	20	20	8	-2	-26	-46	-68	-51	-20	3	25	24	23	15	11
w	5	9	20	26	12	-16	-32	-46	-53	-38	-20	5	13	30	9	2	-16
y	10	7	12	7	6	3	7	-1	-31	-14	-11	11	13	1	3	12	15

Credits: King & Sternberg, 1996

Table 3. *Directional informational parameters: I(Sj = x:x'; Rj + m) for residue position versus residue type for α-helices*[a]

	i-8	i-7	i-6	i-5	i-4	i-3	i-2	i-1	i	i+1	i+2	i+3	i+4	i+5	i+6	i+7	i+8
a	19	21	22	24	34	36	44	47	60	60	53	50	44	40	31	23	24
c	-47	-45	-44	-47	-44	-36	-44	-55	-56	-58	-54	-55	-58	-58	-59	-53	-66
d	14	15	14	15	17	21	15	17	-7	-11	-31	-42	-28	-12	-8	1	-5
e	14	16	15	20	26	27	34	52	62	57	32	15	19	12	6	7	9
f	-19	-14	-10	-4	-2	-1	6	-1	10	10	12	12	-4	-5	2	0	2
g	5	2	1	-5	-22	-30	-50	-70	-92	-52	-28	-21	-13	-17	-8	-6	-6
h	-22	-20	-9	-10	-19	-10	-14	-7	-11	-4	0	-3	-2	2	6	11	12
i	7	7	0	0	1	1	2	-5	1	2	1	7	-6	-3	10	8	6
k	-2	-1	-1	-1	-6	-9	-6	5	17	17	21	27	35	33	21	22	23
l	0	-1	0	6	9	16	30	33	45	47	51	53	37	32	30	25	18
m	4	3	15	23	30	30	39	36	45	54	57	53	44	29	30	14	1
n	2	3	2	-5	-9	-10	-16	-17	-31	-16	-17	-16	-9	-8	-9	-10	-5
p	-12	-15	-14	-19	-23	-25	-30	-48	-82	-195	-145	-104	-67	-49	-43	-33	-17
q	-4	3	7	4	13	8	10	24	35	32	31	21	18	18	9	8	6
r	5	3	6	13	7	13	19	27	34	32	36	41	33	29	23	21	18
s	-10	-7	-10	-10	-16	-17	-25	-21	-39	-35	-39	-41	-32	-35	-34	-35	-33
t	1	-1	-6	-8	-6	-11	-16	-25	-48	-47	-48	-46	-34	-31	-34	-26	-24
v	-5	-12	-13	-14	-13	-19	-17	-20	-15	-22	-22	-20	-26	-19	-15	-10	-5
w	0	-4	-12	-19	-7	14	16	12	18	17	12	8	1	-6	1	3	-13
y	-22	-19	-17	-20	-16	-21	-30	-32	-8	-10	-4	-12	-17	-9	-10	-14	-15

[a]Note that the convention used is the reverse of that adopted by (Garnier et al., 1978), for example the first entry for alanine at position j-8 is the amount of information that an alanine residue eight positions toward the N terminus has for predicting an α-helix

Table 4. *Directional informational parameters for residue position versus residue type for β-strands*

	i-8	i-7	i-6	i-5	i-4	i-3	i-2	i-1	i	i+1	i+2	i+3	i+4	i+5	i+6	i+7	i+8
a	-8	-7	-13	-17	-23	-33	-26	-32	-43	-37	-30	-30	-26	-27	-26	-25	-25
c	3	13	-9	-20	-15	-3	9	33	47	51	21	19	9	-5	7	-5	-14
d	-7	-5	0	-9	-4	-14	-42	-73	-83	-59	-21	10	22	24	16	11	13
e	-14	-5	-5	-11	-21	-27	-45	-44	-57	-54	-46	-29	-25	-12	-12	-2	0
f	-9	-23	-32	-34	-30	-12	24	44	49	39	24	2	-9	-23	-24	-29	-23
g	-3	9	24	29	34	30	18	-23	-48	-27	6	27	39	38	33	23	23
h	6	11	17	22	12	16	0	-2	3	-2	5	3	8	4	-1	1	-3
i	-21	-30	-31	-21	-12	-3	26	58	76	64	33	11	-14	-24	-20	-14	-11
k	20	12	15	14	8	4	-8	-14	-25	-40	-39	-27	-20	-24	-20	-15	-15
l	-2	-10	-18	-27	-30	-27	-6	15	27	21	2	-19	-31	-29	-28	-26	-25
m	-22	-26	-29	-40	-31	-17	-7	23	24	28	17	2	-15	-31	-53	-36	-16
n	1	8	14	5	0	-6	-30	-65	-62	-28	-6	11	18	21	16	10	3
p	9	7	12	24	20	8	-22	-65	-108	-64	-8	17	25	30	32	31	21
q	6	12	8	16	8	-5	-22	-27	-30	-52	-49	-34	-22	-17	-9	2	20
r	0	8	3	-3	5	2	1	-14	-26	-32	-30	-35	-27	-26	-25	-25	-21
s	16	14	17	19	14	5	-3	-13	-15	-4	15	27	32	32	31	28	21
t	6	8	14	15	16	21	19	25	31	22	13	9	12	25	34	34	34
v	1	-11	-15	-11	4	25	51	75	91	81	49	19	-6	-12	-16	-11	-11
w	-8	-8	-28	-19	-9	5	23	44	45	30	13	-18	-22	-40	-15	-7	-9
y	13	13	4	14	12	20	24	37	48	31	20	-1	2	11	7	0	-4

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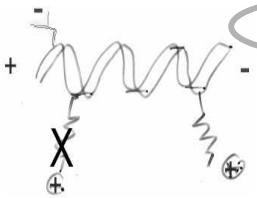
Types of Residues



Credits: King & Sternberg, 1996

Table 3. *Directional informational parameters: I(Sj = x:x': Rj + m) for residue position versus residue type for α-helices*[a]

	i-8	i-7	i-6	i-5	i-4	i-3	i-2	i-1	i	i+1	i+2	i+3	i+4	i+5	i+6	i+7	i+8
a	19	21	22	24	34	36	44	47	60	60	53	50	44	40	31	23	24
c	-47	-45	-44	-47	-44	-36	-44	-56	-56	-58	-54	-55	-58	-58	-59	-53	-66
d	14	15	14	15	17	21	15	1	-7	-11	-31	-42	-28	-12	-8	1	-5
e	14	16	15	20	26	27	34	52	62	57	32	15	19	12	6	7	9
f	-19	-14	-10	-4	-2	-1	6	-1	10	10	12	12	-4	-5	2	0	2
g	5	2	1	-5	-22	-30	-50	-70	-92	-52	-28	-21	-13	-17	-8	-6	-6
h	-22	-20	-9	10	-19	-10	-14	-7	-11	-4	0	-3	-2	2	6	11	12
i	7	7	0	0	1	1	2	-5	1	2	1	7	6	-3	10	8	6
k	-2	-1	-1	-1	-6	-9	-6	5	17	17	21	27	35	33	21	22	23
l	0	-1	0	6	9	16	30	33	45	47	51	53	37	32	30	25	18
m	4	3	15	23	30	30	39	36	45	54	57	53	44	29	30	14	1
n	2	3	2	-5	-9	-10	-16	-17	-31	-16	-17	-16	-9	-8	-9	-10	-5
p	-12	-15	-14	-19	-23	-25	-3	-48	-82	-195	-145	-104	-67	-49	-43	-33	-17
q	-4	3	7	4	13	8	10	24	35	32	31	21	18	18	9	8	6
r	5	3	6	13	7	13	19	27	34	32	36	41	33	29	23	21	18
s	-10	-7	-10	-10	-16	-17	-25	-21	-39	-35	-39	-41	-32	-35	-34	-35	-33
t	1	-1	-6	-8	-6	-11	-16	-25	-48	-47	-48	-46	-34	-31	-34	-26	-24
v	-5	-12	-13	-14	-13	-19	-17	-20	-15	-22	-22	-20	-26	-19	-15	-10	-5
w	0	-4	-12	-19	-7	14	16	12	18	17	12	8	1	-6	1	3	-13
y	-22	-19	-17	-20	-16	-21	-30	-32	-8	-10	-4	-12	-17	-9	-10	-14	-15

[a]Note that the convention used is the reverse of that adopted by (Garnier et al., 1978), for example the first entry for alanine at position j-8 is the amount of information that an alanine residue eight positions toward the N terminus has for predicting an α-helix at position j.

- Group I favorable residues and Group II unfavorable one:
- A, E, L -> H; V, I, Y, W, C -> E; G, N, D, S -> C
- P complex; largest effect on proceeding residue
- Some residues favorable at only one terminus (K)

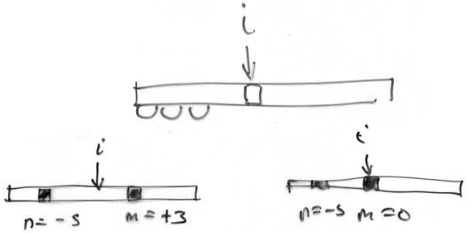
(c) M Gerstein (http://bioinfo.mbb.yale.edu)

GOR IV

- I(Sj; R[j+m], R[j+n]) = the frequencies of all 136 (=16*17/2) possible di-residue pairs (doublets) in the window.
  - ◊ 20*20*3*16*17/2=163200 pairs
- Parameter Explosion Problem: 1000 dom. struc. * 100 res./dom. = 100k counts, over how many bins
- Dummy counts for low values (Bayes)

All Singletons in 17 residue window

All Pairs



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Assessment

- Q3 + other assess, 3x3
- Q3 = total number of residues predicted correctly over total number of residues
- GOR gets 65%
  - ◊ sum of diagonal over total number of residue -- (14K+5K+21K)/ 64K
- Under predict strands & to a lesser degree, helices: 5.9 v 4.1, 10.9 v 10.6

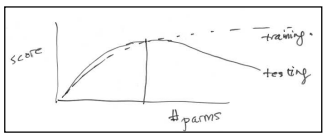
THE GOR METHOD

TABLE II
GLOBAL RESULTS FOR DATABASE PREDICTION

	Observed			
	H	E	C	Total
Predicted				
H	14,460	3094	4790	22,344
E	1124	4965	2089	8178
C	6002	5546	21,496	33,044
Total	21,586	13,605	28,375	63,566
Q_{pred} [a]	64.7	60.7	65.1	
Q_{obs} [b]	67.0	36.5	75.8	
Q_3 [c] = 64.4%				

[a] Number of correctly predicted residues/number of predicted residues.
[b] Number of correctly predicted residues/number of observed residues
[c] Total number of correctly predicted residues/total number of residues.

Credits: Garnier et al., 1996



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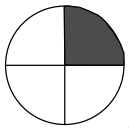
Training and Testing Set

- Cross Validation: Leave one out, seven-fold



4-fold

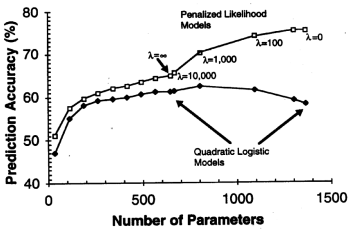


Figure 2. Comparison of prediction accuracy (correctly predicted residues as a proportion of total residues) versus effective number of parameters for linear-logistic models (number of parameters ≤640) and penalized likelihood models for crossvalidated (◆) and uncrossvalidated (❑) results. The values of the penalty parameter λ are shown.

Credits: Munson, 1995; Garnier et al., 1996

TABLE I
DATABASE PROTEINS[a]

1aaj.x	1aak.x	1aap.a	1aba.x	1abk.x	1abm.a	1add.x
1ads.x	1alk.a	1aoz.a	1apa.x	1apm.e	1arb.x	1atr.x
1avh.a	1ayh.x	1bab.a	1bbh.a	1bbp.a	1bet.x	1bge.a
1bll.e	1bmd.a	1bov.a	1bpb.x	1brs.d	1btc.x	1c2r.a
1caj.x	1cau.a	1cau.b	1cde.x	1cdt.a	1cew.i	1cgt.x
1chm.a	1cmb.a	1cob.a	1col.a	1cpc.a	1cpc.b	1cpt.x
1crl.x	1cse.i	1ctf.x	1ctm.x	1cus.x	1ddt.x	1dhr.x
1dog.x	1dsb.a	1eaf.x	1eco.x	1ede.x	1end.x	1epa.a
1fba.a	1fdd.x	1fha.x	1fia.a	1fkb.x	1fna.x	1fnr.x
1fxi.a	1gal.x	1gd1.o	1gdh.a	1gky.x	1glt.x	1gmf.a
1gof.x	1gox.x	1gp1.a	1gpb.x	1gpr.x	1gsr.a	1hbq.x
1hdx.a	1hiv.a	1hlb.x	1hle.a	1hmy.x	1hoe.x	1hpl.a
1hrh.a	1hsl.a	1huw.x	1ifc.x	1ipd.x	1isu.a	1ith.a
1l29.x	1le4.x	1len.a	1lga.a	1lis.x	1lla.x	1lmb.3
1lts.a	1lts.d	1mdc.x	1mgn.x	1min.a	1min.b	1mjc.x
1mpp.x	1mup.x	1nar.x	1nba.a	1ndk.x	1noa.x	1nsb.a
1nxb.x	1ofv.x	1olb.a	1omf.x	1omp.x	1onc.x	1osa.x
1pda.x	1pfk.a	1pgb.x	1pgd.x	1phh.x	1php.x	1pii.x
1plf.a	1poc.x	1poh.x	1pox.a	1ppa.x	1ppf.e	1ppf.i
1ppn.x	1prc.c	1prc.h	1prc.l	1prc.m	1pts.a	1pya.a
1pya.b	1pyd.a	1rcb.x	1rec.x	1rib.a	1rnd.x	1rop.a
1rve.a	1s01.x	1sac.a	1sbp.x	1ses.a	1sgt.x	1sha.a
1shf.a	1sim.x	1slt.b	1snc.x	1spa.x	1stf.i	1tbe.a
1tca.x	1tie.x	1tml.x	1tnd.a	1tpl.a	1trb.x	1trk.a
1tro.a	1ttb.a	1utg.x	1vaa.a	1vaa.b	1vmo.a	1wht.a
1wht.b	1wsy.a	1wsy.b	1ybh.x	1zaa.c	256b.a	2aai.b
2aza.a	2bop.a	2cey.a	2cdv.x	2chs.a	2cmd.x	2cp4.x
2cpl.x	2cro.x	2ctc.x	2cts.x	2cyp.x	2dnj.a	2er7.e
2hbg.x	2hhm.a	2hip.a	2hpd.a	2ihl.x	2lh2.x	2liv.x
2mhr.x	2mnr.x	2msb.a	2mta.c	2mta.h	2mta.l	2pf1.x
2pia.x	2pol.a	2por.x	2reb.x	2rn2.x	2rsl.a	2sar.a
2sas.x	2scp.a	2sga.x	2sn3.x	2spc.a	2tgi.x	2tmd.a
2tpr.a	2tsc.a	3aah.a	3aah.b	3adk.x	3b5c.x	3cd4.x
3chy.x	3cla.x	3cox.x	3dfr.x	3eca.a	3gap.a	3gbp.x
3ink.c	3rub.l	3rub.s	3sdh.a	3tgl.x	451c.x	4blm.a
4enl.x	4fgf.x	4gcr.x	4ts1.a	4xis.x	5fbp.a	5p21.x
5tim.a	6fab.h	6fab.l	6taa.x	8abp.x	8acn.x	8atc.a
8atc.b	8cat.a	8i1b.x	8rxn.a	8tln.e	9ldt.a	9rnt.x
9wga.a						

[a] The database was prepared by J. M. Levin and checked for homologous sequences with the help of V. Di Francesco. This database has been modified to restore the total length of the sequences as defined in the SEQRES field of the Protein Data Bank (PDB) file (the DSSP program omits residues whose coordinates are missing in the PDB file, and thus if this occurs in the middle of the polypeptide chain it is split into two or more chains). Residues having no coordinates were assigned the conformation X and were not taken into account for the prediction accuracy although the prediction was done with the whole sequence length. The PDB code is followed by the chain name a, b, c, d, h (heavy), l (light), x (one chain only), e (enzyme), or i (inhibitor).

(c) M Gerstein (http://bioinfo.mbb.yale.edu)

Types of Secondary Structure Prediction Methods

- Parametric Statistical
  - ◊ struc. = explicit numerical func. of the data (GOR)
- Non-parametric
  - ◊ struc. = NON- explicit numerical func. of the data
  - ◊ generalize Neural Net, seq patterns, nearest nbr, &c.
- Semi-parametric: combine both
- single sequence
- multi sequence
  - ◊ with or without multiple-alignment

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GOR Semi-parametric Improvements

- Filtering GOR to regularize

$[\neg a, \neg a, c, \mathbf{b}, *, \neg b] \rightarrow \mathbf{c}$

$[\neg a, *, *, \mathbf{a}, b] \rightarrow \mathbf{b}$

$[\neg a, *, *, \mathbf{a}, c] \rightarrow \mathbf{c}$

$[a, *, *, \mathbf{a}, c, *, \neg c] \rightarrow \mathbf{c}$

$[\neg a, \neg a, \mathbf{a}, a, c, \neg a] \rightarrow \mathbf{c}$

$[\neg a, c, \neg c, \mathbf{a}, a, c, \neg a] \rightarrow \mathbf{c}$

$[\neg a, c, c, a, a, \neg b, \neg a] \rightarrow \mathbf{c}$

$[a, c, *, \mathbf{a}, a, a, \neg a] \rightarrow \mathbf{c}$

$[*, c, *, \mathbf{a}, a, b, \neg a] \rightarrow \mathbf{c}$

$[c, b, b, \mathbf{a}, a, *, a] \rightarrow \mathbf{b}$

$[c, *, \mathbf{a}, a, \neg a, a] \rightarrow \mathbf{c}$

a = α-helix, b = β-strand, c = coil, * = wildcard (α-helix or β-strand or coil) ¬ = not.

If the pattern on the left is met in a prediction, then the secondary structure in bold on the left is rewritten as the secondary structure on the right of the rule. For example:

$[b, b, b, \mathbf{a}, c] \rightarrow [b, b, b, \mathbf{c}, c]$

$[b, b, c, \mathbf{a}, c] \rightarrow [b, b, c, \mathbf{c}, c]$

$[b, b, b, \mathbf{a}, b, b, b] \rightarrow [b, b, b, \mathbf{b}, b, b, b].$

Illustration Credits: King & Sternberg, 1996

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Subject II:

Packing

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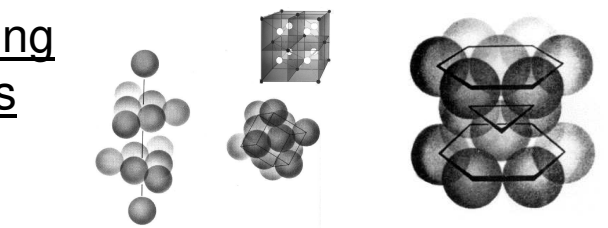
Close-Packing of Spheres

- Efficiency
  - ◊ Volume Spheres / Volume of space
- Close packed spheres
  - ◊ 74% volume filled
  - ◊ Coordination of 12
  - ◊ Two Ways of laying out
- Fcc
  - ◊ cubic close packing
  - ◊ ABC layers
- hcp
  - ◊ Hexagonally close packed
  - ◊ ABABAB



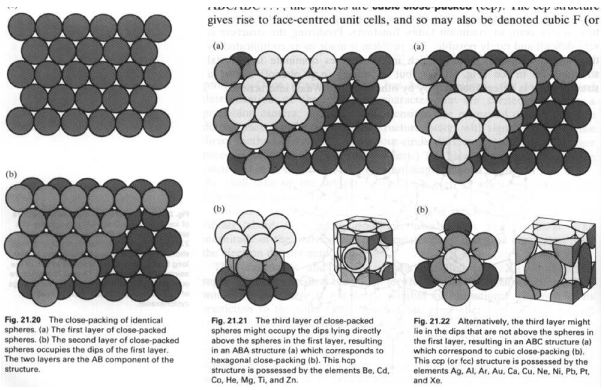


Fig. 21.20 The close-packing of identical spheres. (a) The first layer of close-packed spheres. (b) The second layer of close-packed spheres occupies the dips of the first layer. The two layers are the AB component of the structure.

Fig. 21.21 The third layer of close-packed spheres might occupy the dips lying directly above the spheres in the first layer, resulting in an ABA structure (a) which corresponds to hexagonal close-packing (b). This hcp structure is possessed by the elements Be, Cd, Co, He, Mg, Ti, and Zn.

Fig. 21.22 Alternatively, the third layer might lie in the dips that are not above the spheres in the first layer, resulting in an ABC structure (a) which correspond to cubic close-packing (b). This ccp (or fcc) structure is possessed by the elements Ag, Al, Ar, Au, Ca, Cu, Ne, Ni, Pb, Pt, and Xe.

Illustration Credits: Atkins, Pchem, 634

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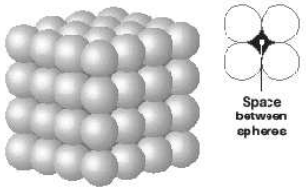
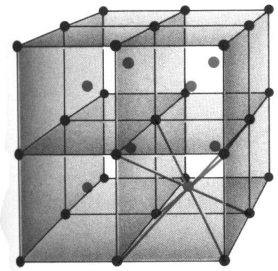
Other Well Known Sphere Arrangements



- Simple cubic packing
  - ◊ 8 nbrs
  - ◊ 52% efficiency
- bcc cubic packing
  - ◊ one sphere sits in middle of 8 others (body-centered)
  - ◊ 8 nbrs
  - ◊ 68% efficiency
- fcc -> bcc -> simple
  - ◊ apx 3/4, 2/3, 1/2



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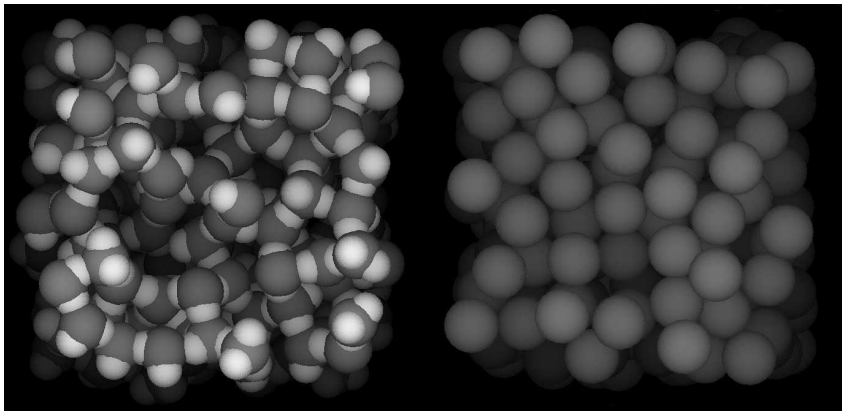
Water v. Argon



More Complex Systems -- what to do?

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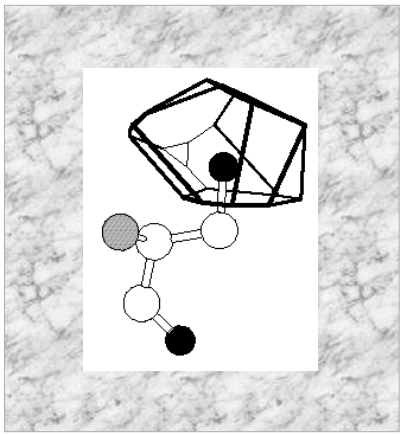
Finding Voronoi Volumes



- Draw Lines in Between Atoms
- Draw Equidistant Planes Between Atoms
- Intersect Planes for a Volume

Courtesy of N Voss

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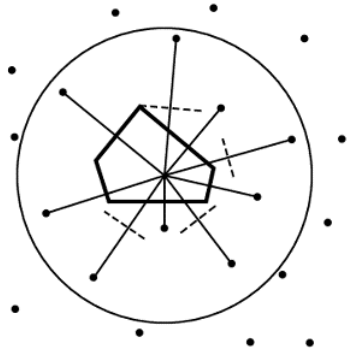
Voronoi Volumes

- Each atom surrounded by a single convex polyhedron and allocated space within it
  - ◊ Allocation of all space (large V implies cavities)
- 2 methods of determination
  - ◊ Find planes separating atoms, intersection of these is polyhedron
  - ◊ Locate vertices, which are equidistant from 4 atoms



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Classic Papers

- Lee, B. & Richards, F. M. (1971). "The Interpretation of Protein Structures: Estimation of Static Accessibility," *J. Mol. Biol.* **55**, 379-400.
- Richards, F. M. (1974). "The Interpretation of Protein Structures: Total Volume, Group Volume Distributions and Packing Density," *J. Mol. Biol.* **82**, 1-14.
- Richards, F. M. (1977). "Areas, Volumes, Packing, and Protein Structure," Ann. Rev. Biophys. Bioeng. 6, 151-76.

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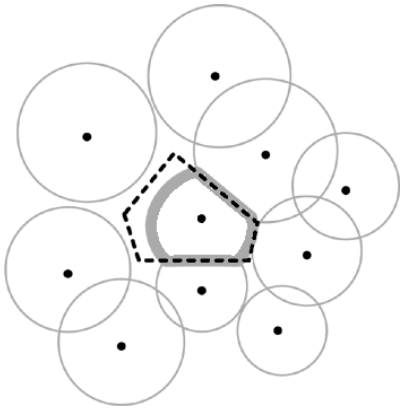
Voronoi Volumes, the Natural Way to Measure Packing

Packing Efficiency

```
= Volume-of-Object
  ----------------
  Space-it-occupies
```

= V(VDW) / V(Voronoi)

- Absolute v relative eff.
  V1 / V2
- Other methods
  - ◊ Measure Cavity Volume (grids, constructions, &c)



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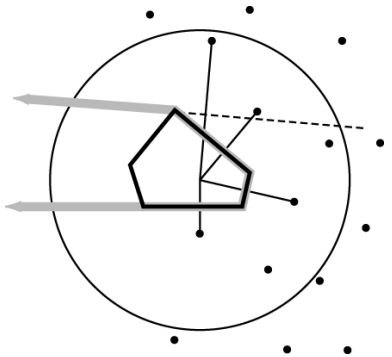
Problem of Protein Surface for Voronoi Construction



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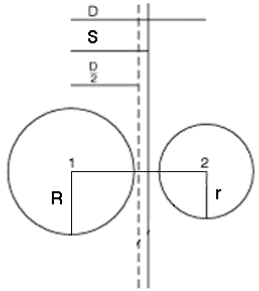
Atoms have different sizes

- Difficulty with Voronoi Meth. Not all atoms created equal
- Solutions
  - ◊ Bisection -- plane midway between atoms
  - ◊ Method B (Richards) Positions the dividing plane according to ratio
  - ◊ Radical Plane
- VDW Radii Set



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Set of VDW Radii

- Great differences in a sensitive parameter (Radii for carbon 1.87 vs 2.00)
- Complex calculation: minimizing SD, iterative procedure, from protein structures
- Look for common distances in CCD
- Preliminary Solution

Atom	Bondi	New
C4__	1.87	1.88
C3H1	1.76	1.76
C3H0	1.76	1.61
O1HO	1.40	1.42
O2H1	1.40	1.46
N___	1.65	1.64
S___	1.85	1.77

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Different Sets of Radii

Atom Type & Symbol		Bondi 1968	Lee & Richards 1971	Shrake & Rupley 1973	Richards 1974	Chothia 1975	Rich-mond & Richards 1978	Gelin & Karplus 1979	Dunfield et al. 1979	ENCAD derived 1995	CHARMM derived 1995	Tsai et al. 1998
$-CH_3$	Aliphatic, methyl	2.00	1.80	2.00	2.00	1.87	1.90	1.95	2.13	1.82	1.88	1.88
$-CH_2-$	Aliphatic, methyl	2.00	1.80	2.00	2.00	1.87	1.90	1.90	2.23	1.82	1.88	1.88
>CH−	Aliphatic, CH	−	1.70	2.00	2.00	1.87	1.90	1.85	2.38	1.82	1.88	1.88
=CH	Aromatic, CH	−	1.80	1.85	*	1.76	1.70	1.90	2.10	1.74	1.80	1.76
>C=	Trigonal, aromatic	1.74	1.80	*	1.70	1.76	1.70	1.80	1.85	1.74	1.80	1.61
$-NH_3+$	Amino, protonated	−	1.80	1.50	2.00	1.50	0.70	1.75		1.68	1.40	1.64
$-NH_2$	Amino or amide	1.75	1.80	1.50	−	1.65	1.70	1.70		1.68	1.40	1.64
>NH	Peptide, NH or N	1.65	1.52	1.40	1.70	1.65	1.70	1.65	1.75	1.68	1.40	1.64
=O	Carbonyl Oxygen	1.50	1.80	1.40	1.40	1.40	1.40	1.60	1.56	1.34	1.38	1.42
−OH	Alcoholic hydroxyl	−	1.80	1.40	1.60	1.40	1.40	1.70		1.54	1.53	1.46
−OM	Carboxyl Oxygen	−	1.80	1.89	1.50	1.40	1.40	1.60	1.62	1.34	1.41	1.42
−SH	Sulfhydryl	−	1.80	1.85	−	1.85	1.80	1.90		1.82	1.56	1.77
−S−	Thioether or −S-S-	1.80	−	−	1.80	1.85	1.80	1.90	2.08	1.82	1.56	1.77

(c) M Gerstein (http://bioinfo.mbb.yale.edu)

Standard Residue Volumes

- Database of many hi-res structures (~100, 2 Å)
- Volumes statistics for buried residues (various selections, resample, &c)
- Standard atomic volumes harder… parameter set development...

G 64	c 105	T 120	V 139	H 159	M 168	R 194
A 90	C 113	P 124	E 140	L 165	K 170	Y 198
S 94	D 117	N 128	N 150	I 165	F 193	W 233

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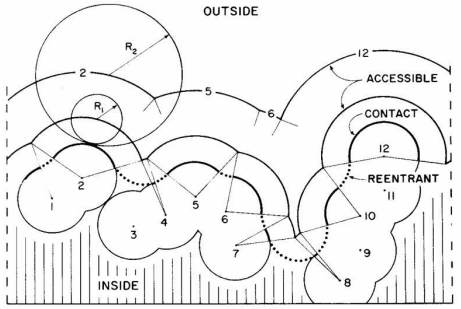
Richards' Molecular and Accessible Surfaces

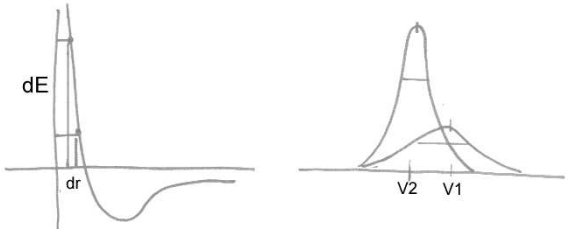


Probe Radius	Part of Probe Sphere	Type of Surface
0	Center (or Tangent)	Van der Waals Surface (vdWS)
1.4 Å	Center	Solvent Accessible Surface (SAS)
""	Tangent (1 atom)	Contact Surface (CS, from parts of atoms)
""	Tangent (2 or 3 atoms)	Reentrant Surface (RS, from parts of Probe)
""	Tangent (1,2, or 3 atoms)	Molecular Surface (MS = CS + RS)
10 Å	Center	A Ligand or Reagent Accessible Surface
∞	Tangent	Minimum limit of MS (related to convex hull)
""	Center	Undefined

(c) M Gerstein (http://bioinfo.mbb.yale.edu)

Small Packing Changes Significant

- Exponential dependence
- Bounded within a range of 0.5 (.8 and .3)
- Many observations in standard volumes gives small error about the mean (SD/sqrt(N))



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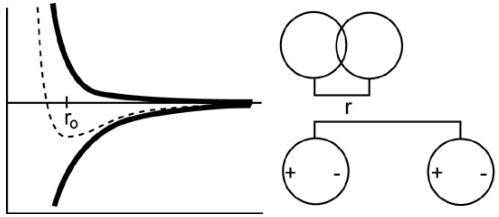
Packing ~ VDW force

- Longer-range isotropic attractive tail provides general cohesion
- Shorter-ranged repulsion determines detailed geometry of interaction
- Billiard Ball model, WCA Theory



Electron Overlap Replusion $U = \varepsilon \left(\frac{r_0}{r}\right)^{12}$

Dispersion Attraction $U = -4\varepsilon \left(\frac{r_0}{r}\right)^{6}$

(c) M Gerstein (http://bioinfo.mbb.yale.edu)