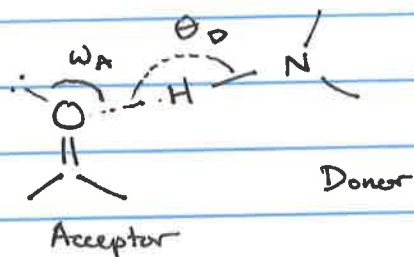


Hydrogen Bonding (not in all force fields)

(20)



← "YETI" form

$$V_{HB} = \left(\frac{A}{r_{H,A}^{12}} - \frac{C}{r_{H,A}^{10}} \right) \cos^2 \theta_D \cos^4 \omega_A$$

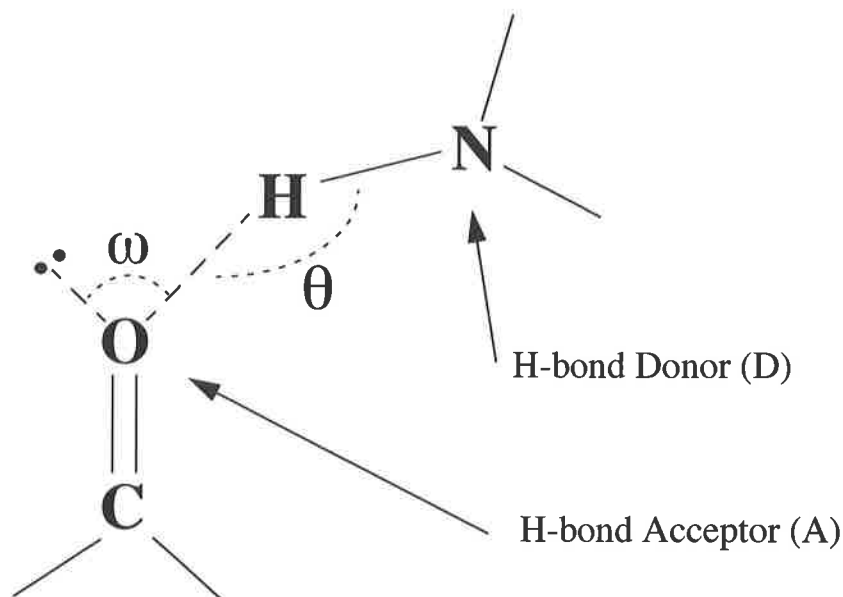
Distance-only: $V_{HB} = \left(\frac{A}{r_{H,A}^{12}} - \frac{C}{r_{H,A}^{10}} \right)$

CHARMM form: $V_{HB} = \left(\frac{A}{r_{H,A}^i} - \frac{C}{r_{H,A}^j} \right) \cos^m \theta \cos^n \omega$

↙ i, j, m, n depend on types of Donor & Acceptor atoms

In Most force fields, Hydrogen Bonding arises naturally out of electrostatic & vdw terms!

Hydrogen Bonding - Geometry



- Depending on the type of atom involved, there may be 1 or 2 preferred geometries for the hydrogen bond acceptor, and 1, 2, or 4 geometries preferred for the hydrogen bond donor.
- Hydrogen bonds are very short-ranged, and only certain angular ranges will give low-energy conformations

Functional Forms:

YETI form:
$$V_{HB} = \left(\frac{A}{r_{HA}^{12}} - \frac{C}{r_{HA}^{10}} \right) \cos^2 \theta \cos^4 \omega$$

Distance-only:
$$V_{HB} = \left(\frac{A}{r_{HA}^{12}} - \frac{C}{r_{HA}^{10}} \right)$$

GRID form:
$$V_{HB} = \left(\frac{C}{r_{HA}^6} - \frac{D}{r_{HA}^4} \right) \cos^4 \theta$$

CHARMM form:
$$V_{HB} = \left(\frac{A}{r_{HA}^i} - \frac{C}{r_{HA}^j} \right) \cos^m \theta \cos^n \omega$$

(i, j, n, m depend on the types of donor and acceptor atoms)

Constraints & Restraints

(21)

These are terms in the force field (or added separately to the intermolecular potential) that bias the calculation towards certain preferred geometries.

They can be used to focus on interestingly configurations or to drive a process.

- Constraint : an absolute restriction
- Restraint : an energetic bias

Some examples:

- Fixed atom constraints: fix certain atoms to particular positions
 - reduces number of degrees of freedom (faster calculation of dynamics)
 - forces between fixed atoms can be eliminated

Why would we do this?

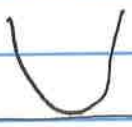
- fix a protein structure or backbone geometry to a known crystal structure and allow side-chains or solvent to relax around them
- fix most of a protein structure and allow motion only @ active site + ligand
- Bond constraints: fix 2 atoms to a relative distance but allow them to move under influence of other atoms

- Why impose bond constraints? ← These are very common - we don't need to specify force constants, or move atoms on 1fs timescales
- SHAKE & RATTLE are 2 common methods for satisfying bond constraints

Distance Restraints • force the distance between two atoms towards a preferred value

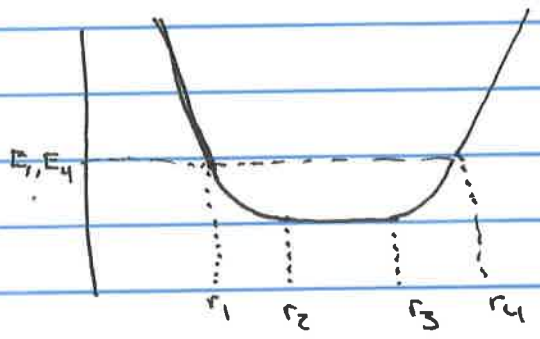
$$V_{\text{restraint}} = k (r_{ij} - r_{\text{target}})^2$$

↗ simple harmonic



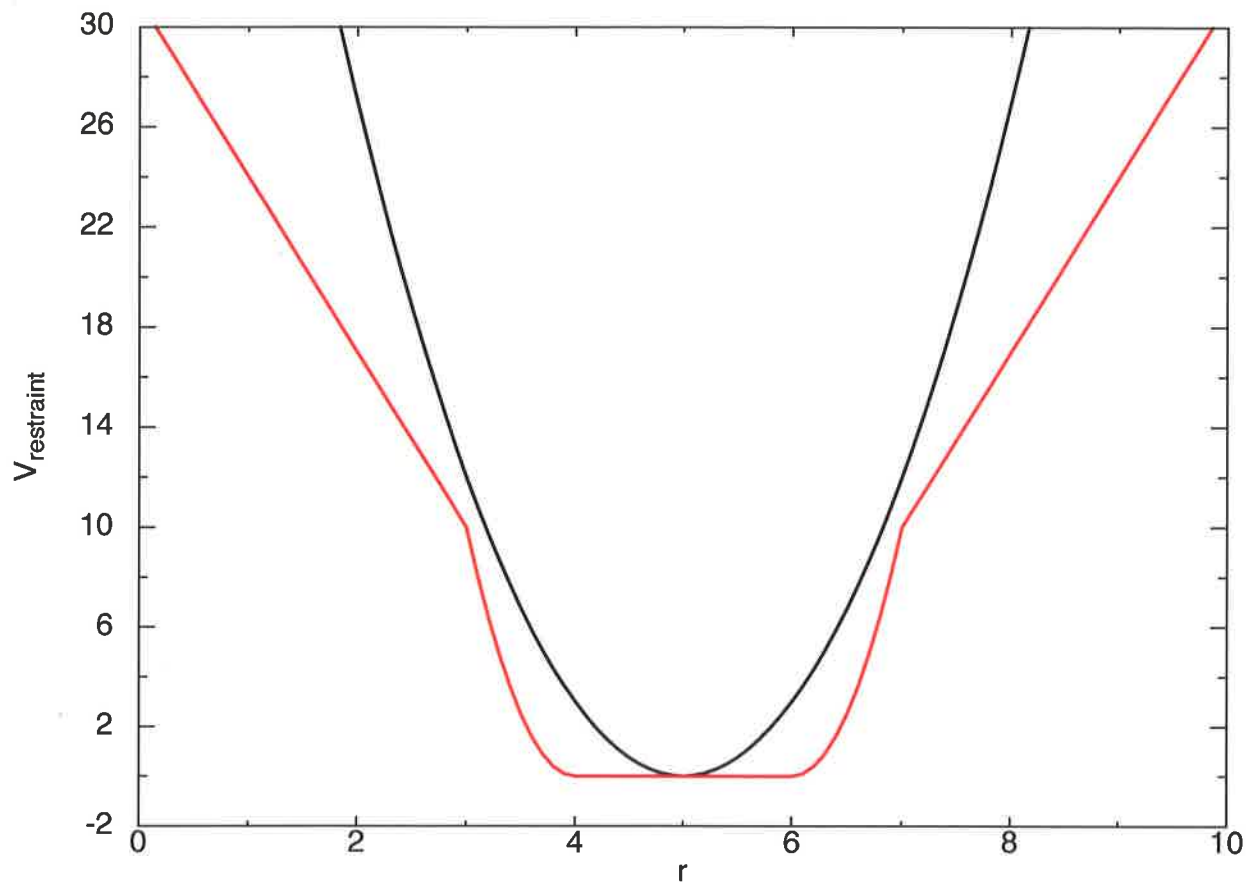
↗ Flat-bottomed restraint

$$V_{\text{restraint}} = \begin{cases} E_1 + (r_1 - r_{ij}) F_1 & r < r_1 \\ k_2 (r_{ij} - r_2)^2 & r_1 < r < r_2 \\ 0 & r_2 < r < r_3 \\ k_3 (r_{ij} - r_3)^2 & r_3 < r < r_4 \\ E_4 + (r_{ij} - r_4) F_4 & r > r_4 \end{cases}$$



Advantages: Does nothing if r is in an acceptable range; returns the coordinate to target range gently

Restraint Potentials



- Flat-bottomed restraint potential will not interfere if r is within acceptable limits
- Harmonic restraint potential can give unreasonably large restraint forces at large distances
- Flat-bottomed restraint potential allows asymmetry

Torsion Restraints: force a torsion angle to one of a few specific values

Harmonic: $V = k (\omega - \omega_{target})^2$

Periodic: $V = k (1 + \cos(n\omega - \gamma_{target}))$

↗ Looks exactly like a regular torsion potential!

Template Fixing: Drive a molecule to be similar to a reference configuration

$$V = k \left[\left(\sum_{atoms} (\vec{r}_i - \vec{r}_i^{ref})^2 \right) / N \right]^{1/2}$$

or

$$V = \sum_{atoms} k_i (\vec{r}_i - \vec{r}_i^{ref})^2$$

↖ gives best RMS fit

↖ gives ok RMS fit; but individual atoms won't deviate as much

(used to match fit of trial drug molecule to known ligand binding position)

This is sometimes called tethering if the reference configuration is a known configuration of a molecule (e.g. a crystal structure of a protein)

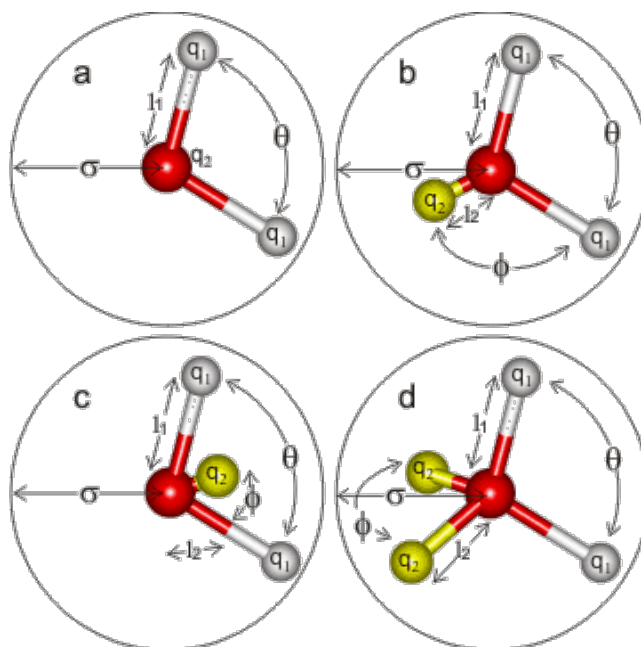
Water Models

Most force fields define a model for water. Many of these models are rigid or are constrained to have fixed internal geometries.

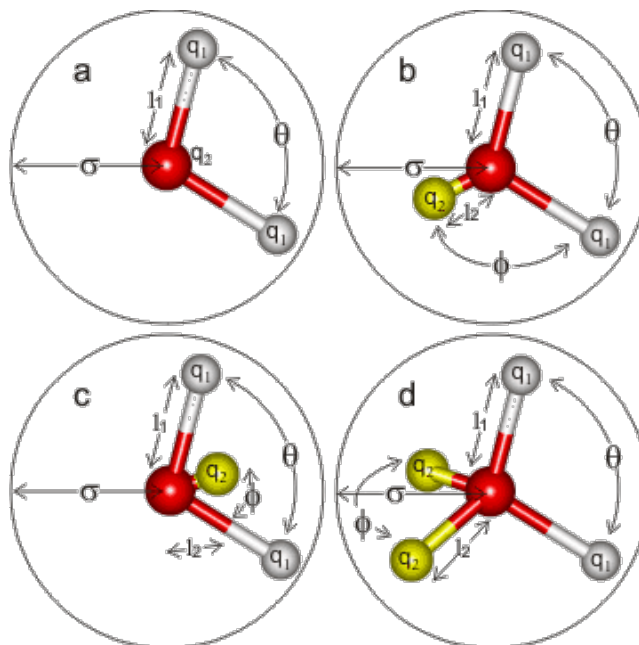
Water models are a complicated topic. Most of the models are parameterized around 273 - 298 K and perform poorly outside this range.

Water is difficult because it has a subtle set of behaviors:

- 1) Strong tetrahedral Hydrogen bonding
- 2) Dipoles that depend on local environment
- 3) "open" condensed phase structures
- 4) Physical properties with many anomalies compared to most materials
- 5) Strange behavior in low T & high T regimes



Model	Type	σ Å	ϵ kJ mol ⁻¹	l_1 Å	l_2 Å	q_1 (e)	q_2 (e)	θ°	ϕ°
SSD	1-site	3.016	15.319	-	-	-	-	109.47	109.47
SPC	a	3.166	0.650	1.0000	-	+0.410	-0.8200	109.47	-
SPC/E	a	3.166	0.650	1.0000	-	+0.4238	-0.8476	109.47	-
SPC/HW (D ₂ O)	a	3.166	0.650	1.0000	-	+0.4350	-0.8700	109.47	-
SPC/Fw	a+pol	3.166	0.650	1.0120	-	+0.410	-0.8200	113.24	-
TIP3P	a	3.15061	0.6364	0.9572	-	+0.4170	-0.8340	104.52	-
TIP3P/Fw	a+pol	3.1506	0.6368	0.9600	-	+0.4170	-0.8340	104.5	-
iAMOEBA	a+pol	3.6453	0.8235	0.9584	-	+0.2970 1	-0.59402	106.48	-
QCT	a	3.140	0.753	0.9614	-	+0.6064	-1.2128	104.067	-
PPC	b+pol	3.23400	0.6000	0.9430	0.06	+0.5170	-1.0340	106.00	127.00
TIP4P	c	3.15365	0.6480	0.9572	0.15	+0.5200	-1.0400	104.52	52.26
TIP4P-Ew	c	3.16435	0.680946	0.9572	0.125	+0.5242 2	-1.04844	104.52	52.26
TIP4P-FQ	c+pol	3.15365	0.6480	0.9572	0.15	+0.63	-1.26	104.52	52.26
TIP4P/lce	c	3.1668	0.8822	0.9572	0.1577	+0.5897	-1.1794	104.52	52.26
TIP4P/2005	c	3.1589	0.7749	0.9572	0.1546	+0.5564	-1.1128	104.52	52.26
TIP4P/2005f	c	3.1644	0.7749	0.9419	0.1546	+0.5564	-1.1128	107.4	53.7
OPC	c	3.1666	0.8903	0.8724	0.1594	+0.6791	-1.3582	103.6	51.8
SWFLEX-AI	c+pol	four terms used		0.968	0.14	+0.6213	-1.2459	102.7	51.35



Model	Type	σ Å	ϵ kJ mol ⁻¹	l_1 Å	l_2 Å	q_1 (e)	q_2 (e)	θ°	ϕ°
COS/G3	c+pol	3.17459	0.9445	1.0000	0.15	+0.4506 72	-0.901344	109.47	-
GCPM	c+pol	3.69	0.9146	0.9572	0.27	+0.6113	-1.2226	104.52	52.26
SWM4-NDP	c	3.18395	0.88257	0.9572	0.24034	0.55733	-1.11466	104.52	52.26
SWM6	c/ d+pol	3.19833	0.67781	0.9572	0.247 _M 0.315 _L	0.53070	-1.1334 _M -0.1080 _L	104.52	101.098
ST2	d	3.10000	0.31694	1.0000	0.80	+0.2435 7	-0.24357	109.47	109.47
TIP5P	d	3.12000	0.6694	0.9572	0.70	+0.2410	-0.2410	104.52	109.47
TIP5P-Ew	d	3.097	0.7448	0.9572	0.70	+0.2410	-0.2410	104.52	109.47
TTM2-F	c+pol	five parameters used		0.9572	0.70	+0.574	-1.148	104.52	52.26
POL5/TZ	d+pol	2.9837	Buckingham	0.9572	0.5	varies	-0.42188	104.52	109.47
Six-site	c/d	3.115 _{OO} 0.673 _{HH}	0.715 _{OO} 0.115 _{HH}	0.980	0.8892 _L 0.230 _M	+0.477	-0.044 _L -0.866 _M	108.00	111.00

This (and many more details) can be found at Martin Chaplin's wonderful "Water Structure and Science" site:

www1.lsbu.ac.uk/water/water_models.html

Model	Dipole moment	Dielectric constant	self-diffusion, $10^{-5} \text{ cm}^2/\text{s}$	Average configurational energy, kJ mol^{-1}	Density maximum, $^{\circ}\text{C}$	Expansion coefficient, $10^{-4} \text{ }^{\circ}\text{C}^{-1}$
SSD	2.35	72	2.13	-40.2	-13	-
SPC	2.27	65	3.85	-41.0	-45	7.3
SPC/E	2.35	71	2.49	-41.5	-38	5.14
SPC/Fw	2.39	79.63	2.32	-	-	4.98
PPC	2.52	77	2.6	-43.2	+4	-
TIP3P	2.35	82	5.19	-41.1	-91	9.2
TIP3P/Fw	2.57	193	3.53	-	-	7.81
iAMOEBA	2.78	80.7	2.54	-	4	2.5
QCT	1.85	-	1.5	-42.7	+10	3.5
TIP4P	2.18	53	3.29	-41.8	-25	4.4
TIP4P-Ew	2.32	62.9	2.4	-46.5	+1	3.1
TIP4P-FQ	2.64	79	1.93	-41.4	+7	-
TIP4P/2005	2.305	60	2.08	-	+5	2.8
TIP4P/2005f	2.319	55.3	1.93	-	+7	-
OPC	2.48	78.4	2.3	-	-1	2.7
SWFLEX-AI	2.69	116	3.66	-41.7	-	-
COS/G3	2.57	88	2.6	-41.1	-78	7.0
GCPM	2.723	84.3	2.26	-44.8	-13	-
SWM4-NDP	2.461	79	2.33	-41.5	<-53	-
SWM6	2.431	78.1	2.14	-41.5	-48	-
TIP5P	2.29	81.5	2.62	-41.3	+4	6.3
TIP5P-Ew	2.29	92	2.8	-	+8	4.9
TTM2-F	2.67	67.2	1.4	-45.1	-	-
POL5/TZ	2.712	98	1.81	-41.5	+25	-
Six-site	1.89	33	-	-	+14	2.4
Experimental	2.95	78.4	2.30	-41.5	+3.984	2.53