

# Advanced Molecular Dynamics

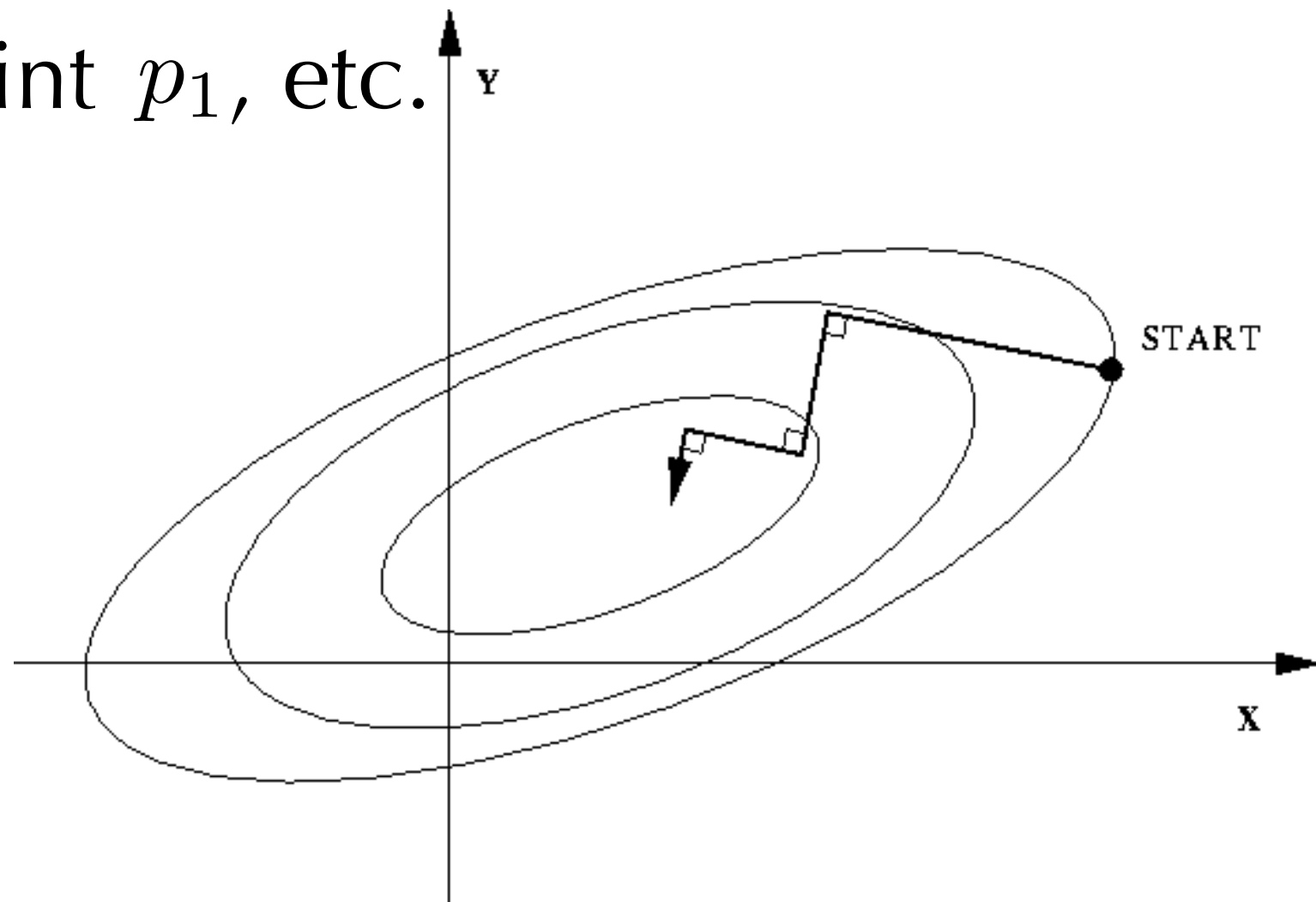
Tricks for more complex models

May 11, 2021

# Energy Minimization

# Steepest descent

- Calculate  $U(\vec{r})$ ,  $g(\vec{r}) = \nabla U(\vec{r})$  at starting point  $p_0$
- $g(\vec{r})$  is a vector: the search direction
- Find the lowest value of  $U(\vec{r})$  along this line (one dimensional minimization).
- Repeat with new point  $p_1$ , etc.
- How to do the line minimization?



# Line minimization

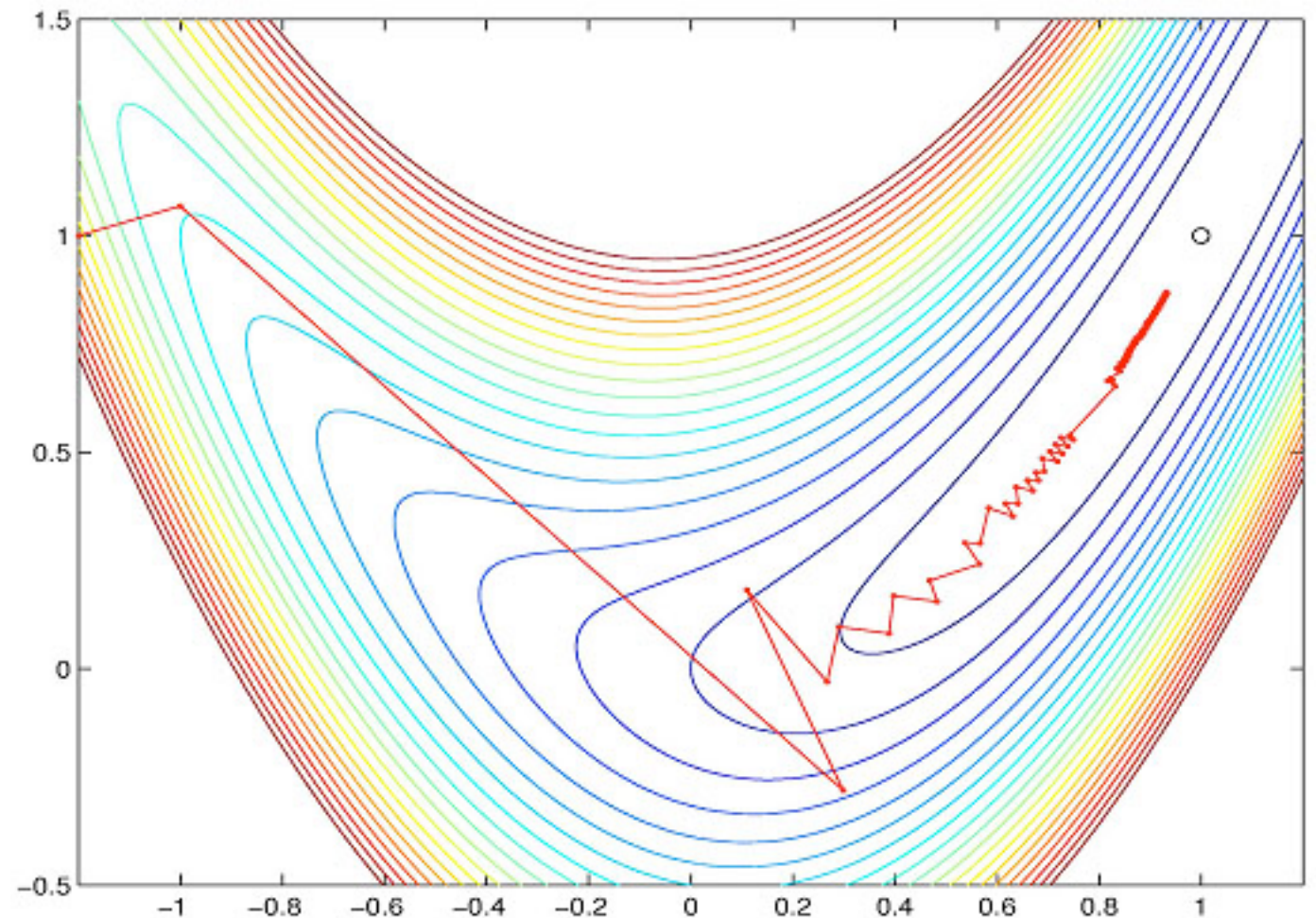
- It is possible to calculate the one-dimensional minimum
- However, our problem is special:
  - It is expensive to calculate  $U(\vec{r})$
  - We're not *that* interested in the best possible minimum. If we're close to it, it's better to choose a new search direction.

# Line minimization

- Take a step along  $g(\vec{r})$
- Is the value of  $U(\vec{r})$  lower? Accept it, and take a longer step next time.
- Is the value of  $U(\vec{r})$  higher? There must be a local minimum between this and the starting point, so take the next step halfway between them.
- Repeat until  $g(\vec{r})$ , or step size is sufficiently small.

# Steepest descent

- Stable and very fast initially (large gradient)
  - Good to get rid of bad contacts
- Quite slow at the final stage
  - Bad for finding exact minimum point
- Very slow convergence for some types of functions (narrow valleys)



# Conjugate gradient

- Try to fix the slow convergence problem
- Start with a first step of steepest descent
- Instead of using the gradient, select the next search direction  $v_k$  as

$$v_k = -g_k + \gamma_k v_{k-1}$$

Memory from previous step

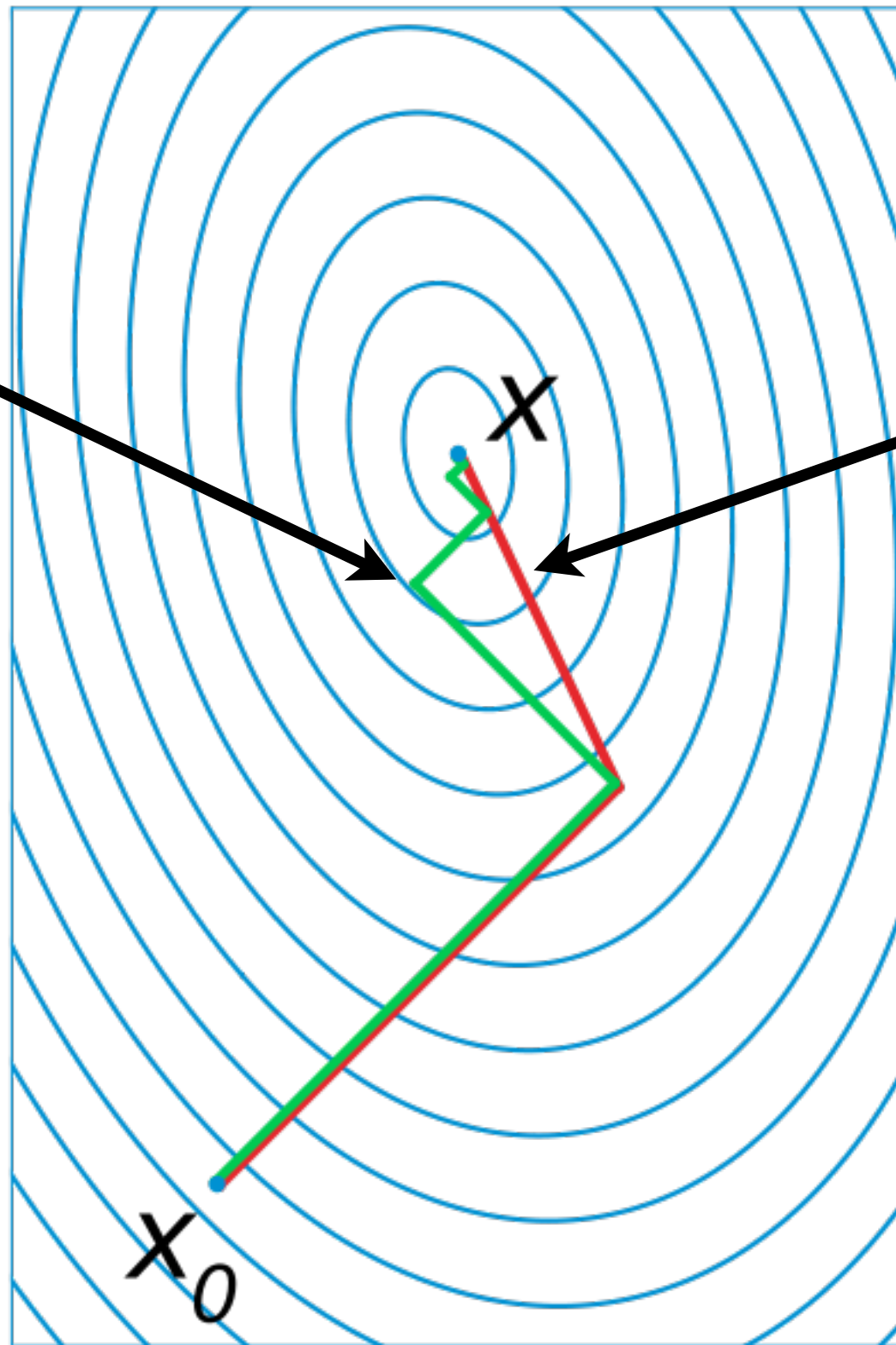
$$\gamma_k = \frac{g_k \cdot g_k}{g_{k-1} \cdot g_{k-1}}$$

The larger the previous gradient was, the smaller memory term

# Conjugate gradient

Steepest descent

Conjugate gradient

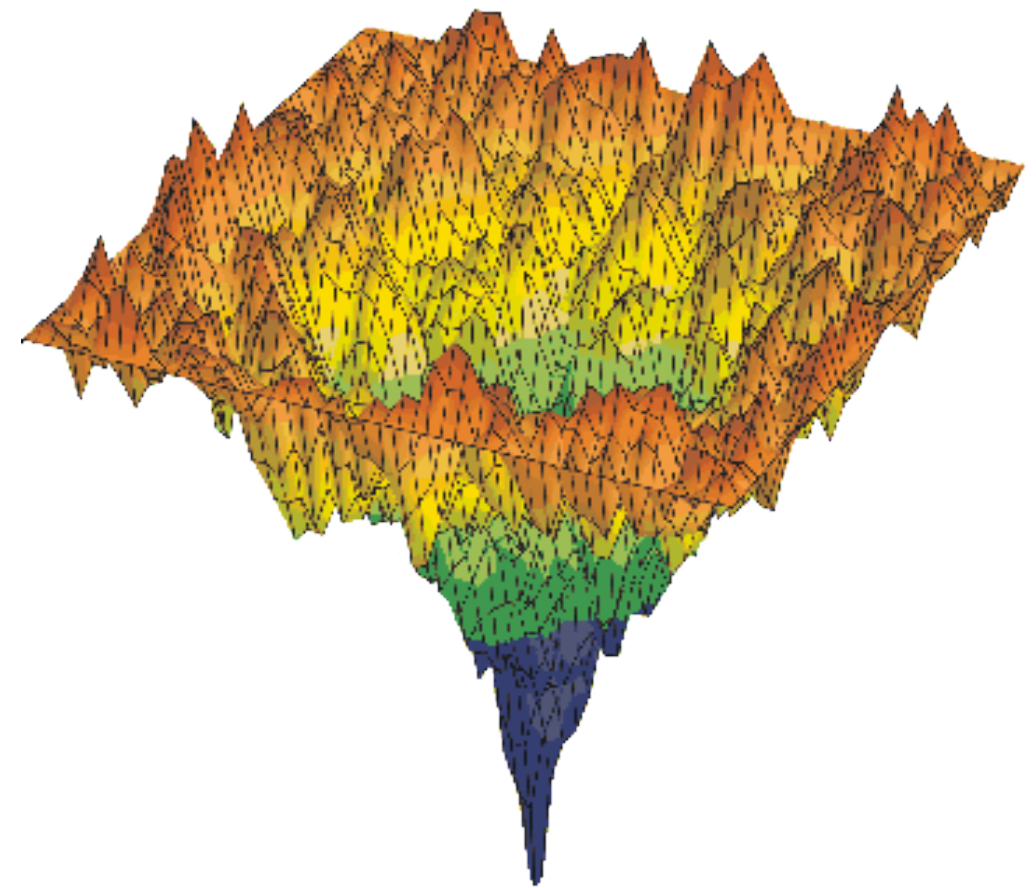


Minimum  
reached much  
faster!



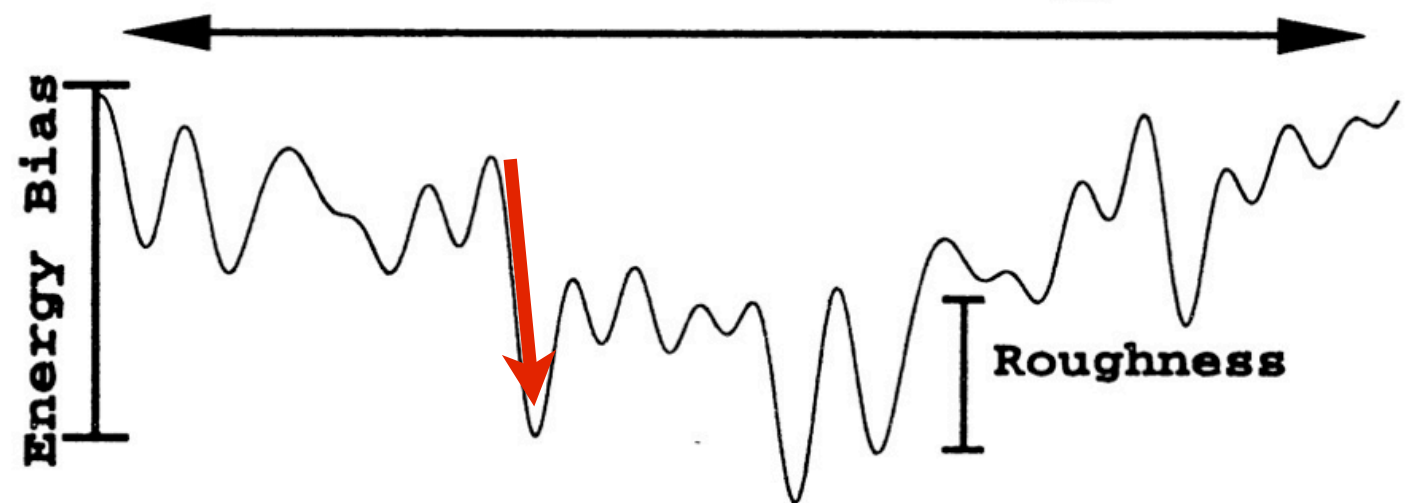
# Limitations of energy minimization

- Most energy landscapes of interest (polymers, proteins) are very complex and have very many local minima
- Energy minimization only brings you to a local minimum
- Energy minimization is good for fixing “bad” initial conformations, but not for much more!



A

**Random Heteropolymer  
Configurational Entropy**



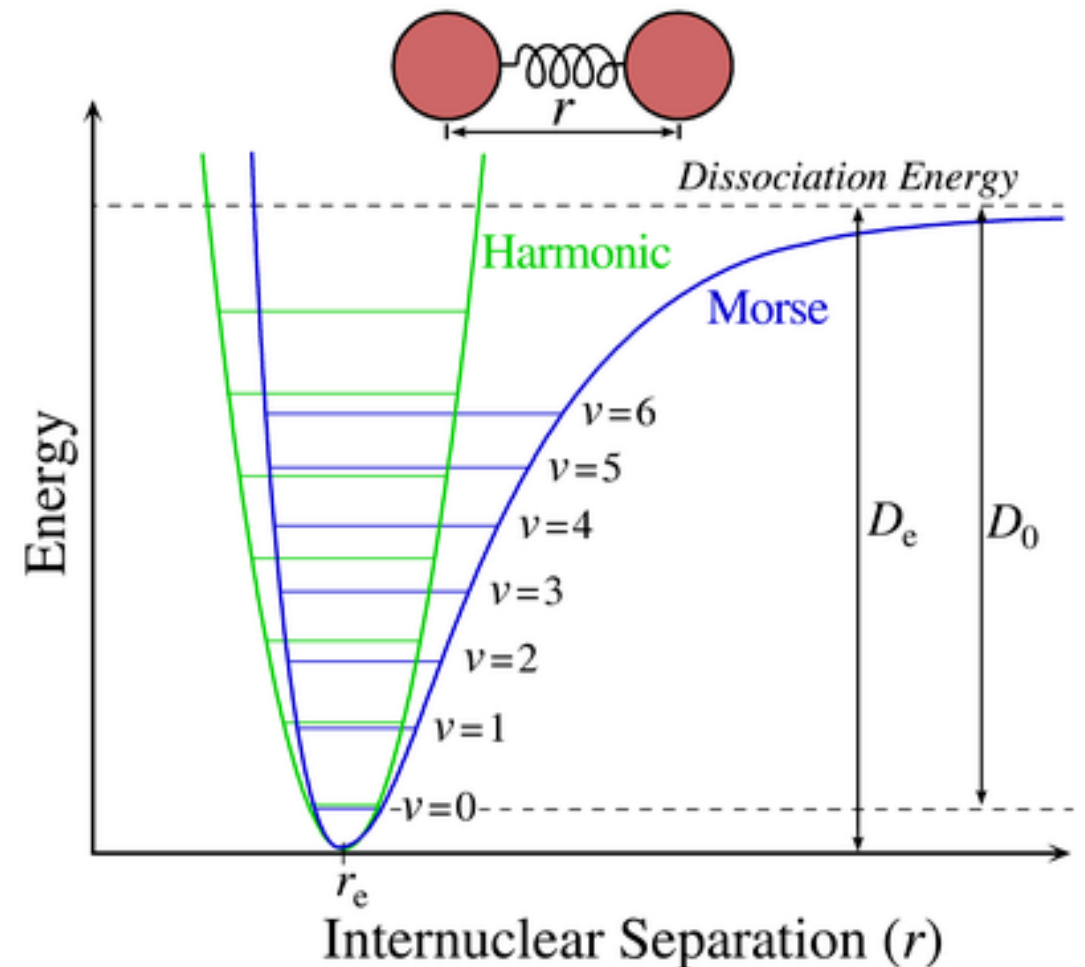
bias  $\sim$  roughness

# Constraints

and other tricks

# Modeling chemical bonds

- The potential of a chemical bonds is close to a Morse potential
- Usually approximated by a harmonic potential
- But:
  - for constant is large
  - masses are small (H)
    - quantum oscillator
      - mainly in the ground state
- Fixing the bond length is a better description



# Constraints

- Fixing bond length leads to constraints
  - holonomic constraints depend only on  $x$ , not on velocities or time
- Constraints remove degrees of freedom:
  - the equations of motions are modified
- Constraining bonds removes the fastest motions in the system  $\rightarrow$  larger time steps!

# Constraint equations

Constraint equations:

$$\sigma_k(\mathbf{r}_1 \dots \mathbf{r}_N) = 0; \quad k = 1 \dots K$$

$$\text{e.g. } (\mathbf{r}_1 - \mathbf{r}_2)^2 - b^2 = 0$$

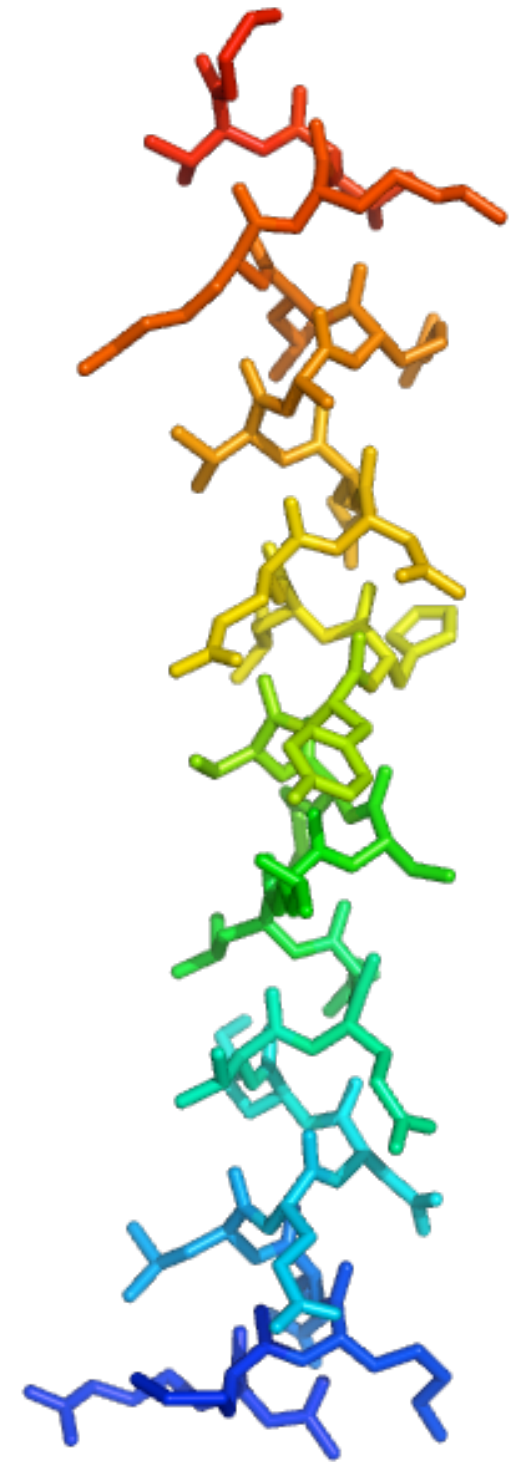
The constraint equations can be added to the potential (or better: Hamiltonian) multiplied by a Lagrange multiplier giving the force:

$$m_i \frac{d^2 \mathbf{r}_i}{dt^2} = - \frac{\partial}{\partial \mathbf{r}_i} \left( V + \sum_{k=1}^K \lambda_k \sigma_k \right)$$

thus there is a constraint force:  $\mathbf{G}_i = - \sum_{k=1}^K \lambda_k \frac{\partial \sigma_k}{\partial \mathbf{r}_i}$

# Set of non-linear equations

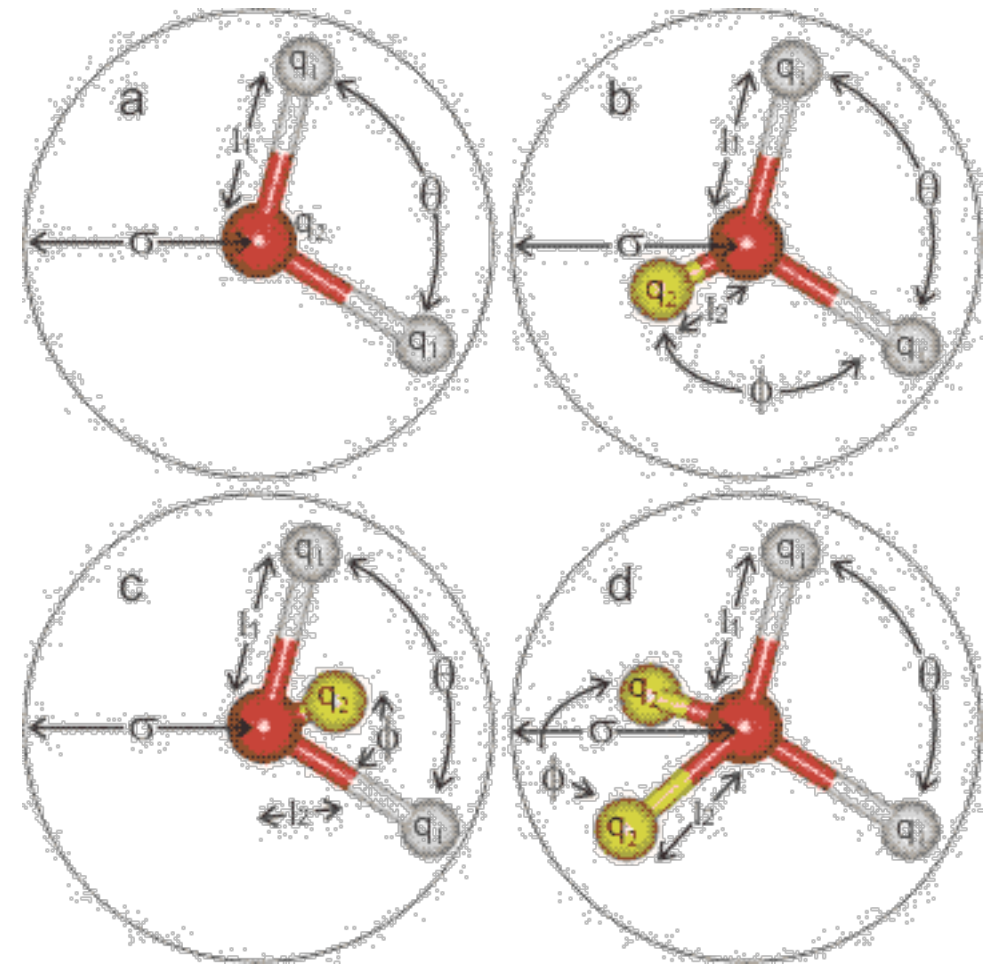
- Constrained bonds couple to create a set of coupled non-linear equations
- Solving these can be difficult
- Simple solution: SHAKE
  - loop over all bonds and reset the bond lengths to their target length by displacing atoms in the old bond direction
  - continue until converged
  - determine constraint F from  $dX$





# SETTLE for water

- The most used water models have rigid bonds and angle
- The non-linear equations can be solved analytically for 3 atoms coupled by 3 distance constraints
- This algorithm is called SETTLE
  - exact
  - faster than SHAKE



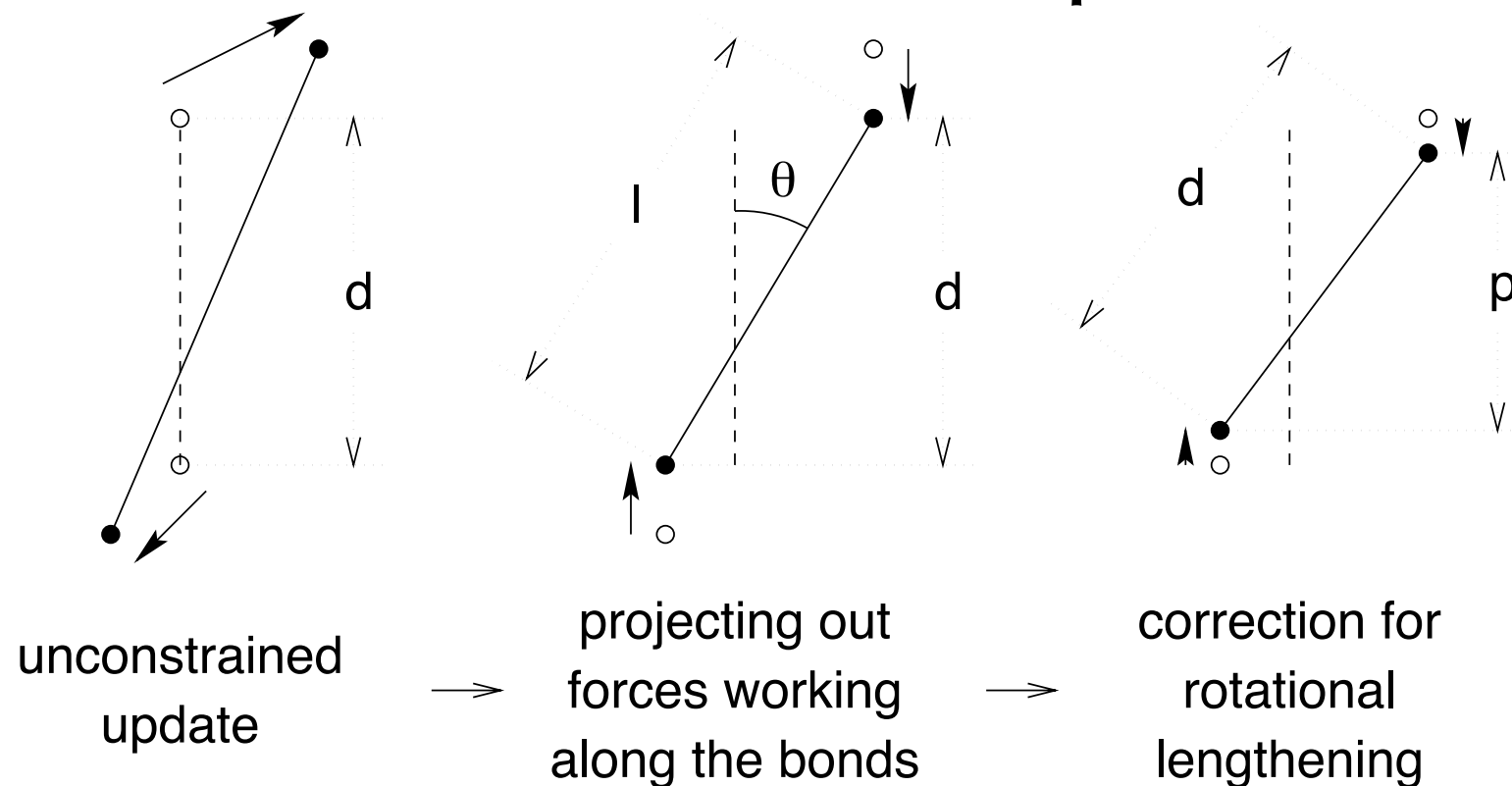
# Constraints and parallel simulations

- SHAKE needs 10 - 50 iterations
  - in parallel simulations this means adding 10 - 50 communication events
- In parallel a method with less communication is required
  - one such method: LINCS (LINear Constraint Solver)



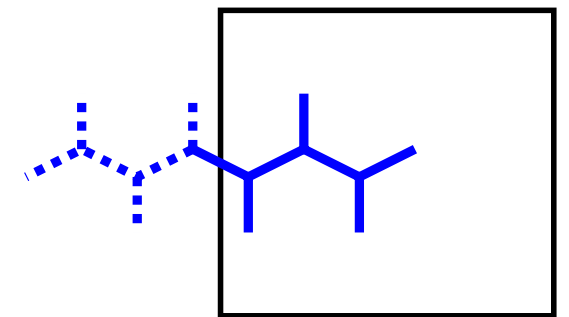
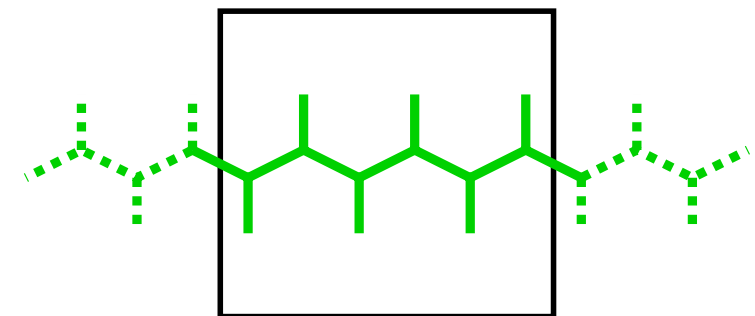
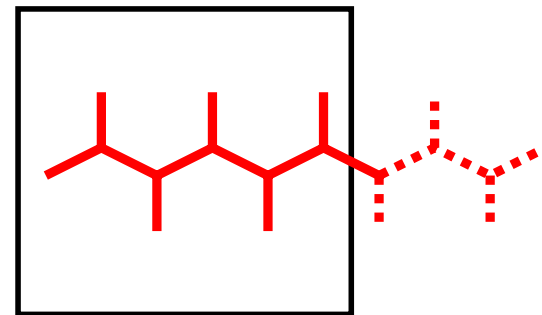
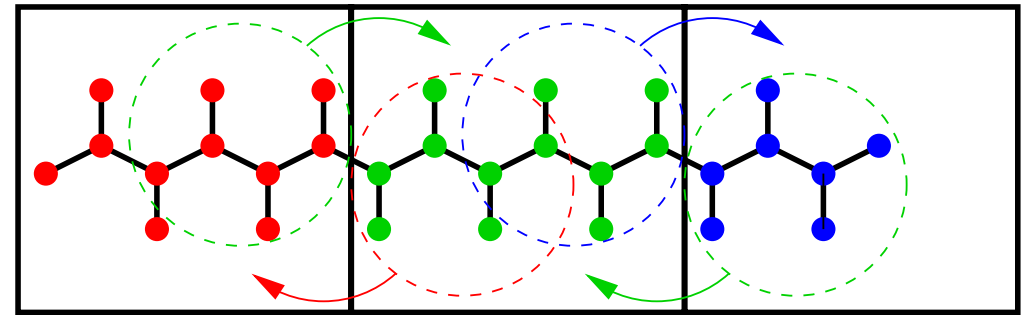
# LINCS

- Non-linear constraint equations can be written as an iterative set of linear matrix equations
  - solve using conjugate gradient (MSHAKE)
  - solve using a series expansion (LINCS)
- Only 1 or 2 iterations are required



# LINCS parallelization

- The order of matrix expansion corresponds to a bond connectivity count
- We only need to communicate atoms connected up to this count



example of parallelization  
over 3 processors/domains

# Virtual interaction sites

Mathematical trick:

define a new potential  $U'$  which is a function of  $\mathbf{s}$ :

$$U(\mathbf{r}) = U'(\mathbf{r}, \mathbf{s}(\mathbf{r}))$$

The force now has a contribution from the direct derivative and indirectly through  $\mathbf{s}$ :

$$\begin{aligned} F_i(\mathbf{r}) &= -\frac{\partial U(\mathbf{r})}{\partial \mathbf{r}_i} = -\frac{\partial U'(\mathbf{r}, \mathbf{s}(\mathbf{r}))}{\partial \mathbf{r}_i} \\ &= -\frac{\partial U'(\mathbf{r}, \mathbf{s})}{\partial \mathbf{r}_i} - \frac{\partial U'(\mathbf{r}, \mathbf{s})}{\partial \mathbf{s}} \frac{\partial \mathbf{s}}{\partial \mathbf{r}_i} \end{aligned}$$

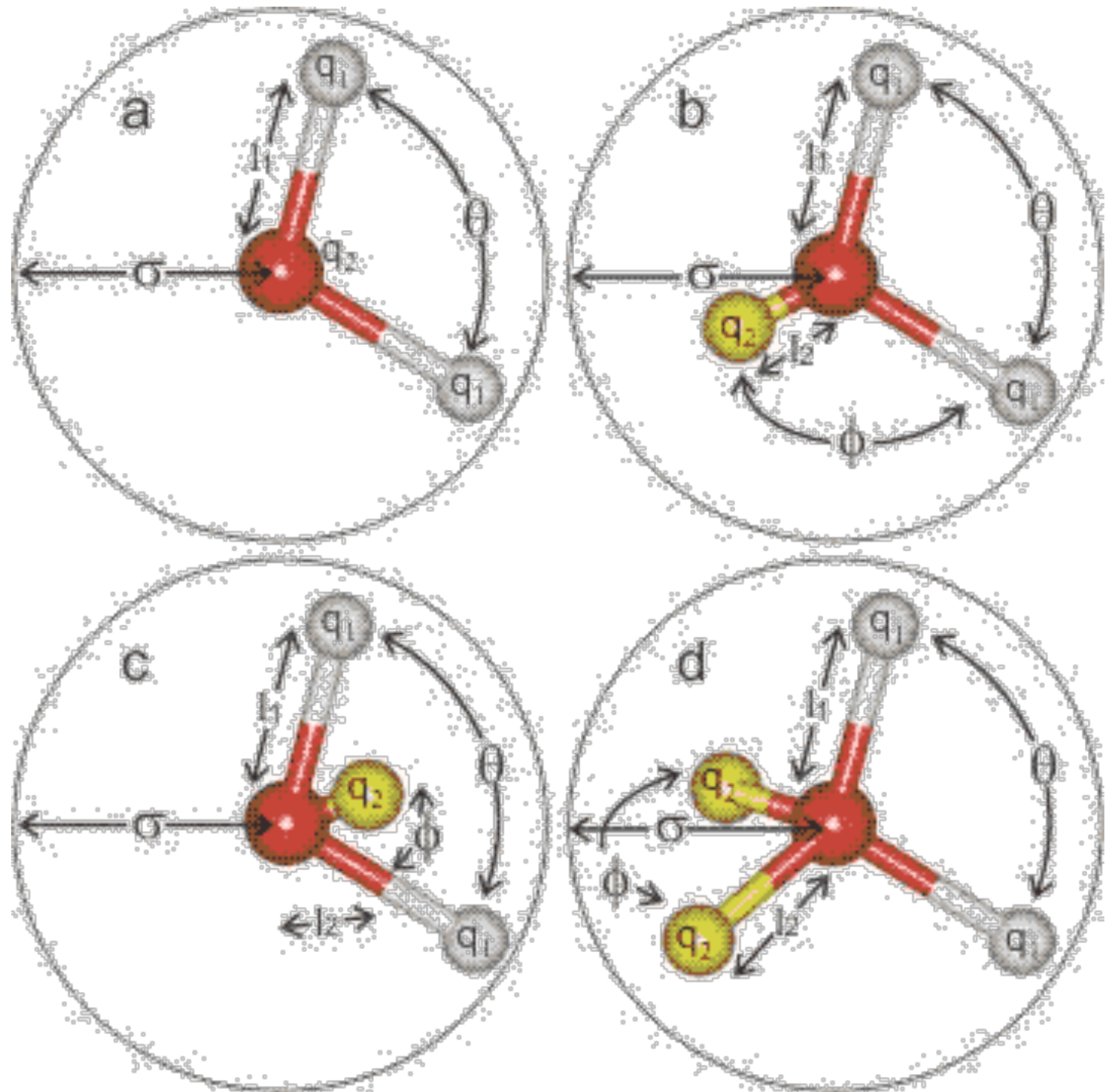
Why do this?

# Constraints on bonds with H only

- Most force fields have been parametrised with only bonds involving hydrogens constrained
- No performance gain of constraining all bonds when using a 2 fs time step
  - Better to constrain only bonds with hydrogens

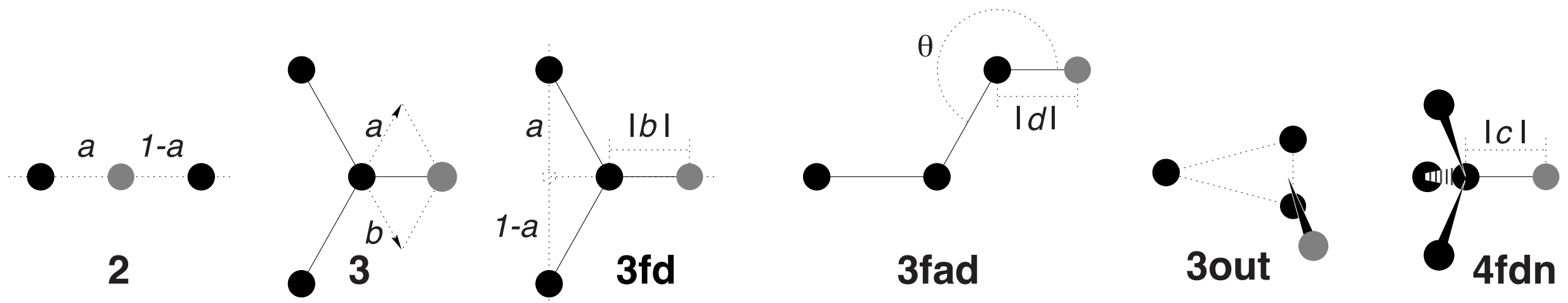
# Virtual interaction sites in water

- Charge centers often don't coincide with mass or LJ centers
- many water models use virtual sites
  - TIP4P (c)
  - TIP5P (d)



# Virtual sites can speed up MD

- After constraining all bonds the fastest motions are the angle vibrations involving H
- Replace H masses by virtual interaction sites:
  - time-step can be increased from 2 to 5 fs
  - you loose a few degrees of angular spread



# Multiple time stepping

- The force can be split into:
  - a fast varying and a slow varying part
  - or a short-range and long-range part:

$$\mathbf{F} = \mathbf{F}_{\text{SR}} + \mathbf{F}_{\text{LR}}$$

- Integrate using a reversible Trotter scheme using time steps  $\Delta t$  and  $n\Delta t$ :

$$\mathbf{v}(t + \frac{\Delta t}{2}) = \begin{cases} \mathbf{v}(t - \frac{\Delta t}{2}) + \frac{1}{m} [\mathbf{F}_{\text{SR}}(t) + n\mathbf{F}_{\text{LR}}(t)] \Delta t & , \text{ step \% } n = 0 \\ \mathbf{v}(t - \frac{\Delta t}{2}) + \frac{1}{m} \mathbf{F}_{\text{SR}}(t) \Delta t & , \text{ step \% } n \neq 0 \end{cases}$$

- Often used for the mesh part of PME

# Shell MD

Mathematical trick:

define a new potential  $U'$  which is a function of  $\mathbf{s}$ :

$$U(\mathbf{r}) = U'(\mathbf{r}, \mathbf{s}(\mathbf{r})) = \min_{\mathbf{s}} U'(\mathbf{r}, \mathbf{s})$$

The force now has a contribution from the direct derivative and **not** indirectly through  $\mathbf{s}$ :

$$\begin{aligned} F_i(\mathbf{r}) &= -\frac{\partial U(\mathbf{r})}{\partial \mathbf{r}_i} = -\frac{\partial U'(\mathbf{r}, \mathbf{s}(\mathbf{r}))}{\partial \mathbf{r}_i} \\ &= -\frac{\partial U'(\mathbf{r}, \mathbf{s})}{\partial \mathbf{r}_i} - \cancel{\frac{\partial U'(\mathbf{r}, \mathbf{s})}{\partial \mathbf{s}} \frac{\partial \mathbf{s}}{\partial \mathbf{r}_i}} \end{aligned}$$

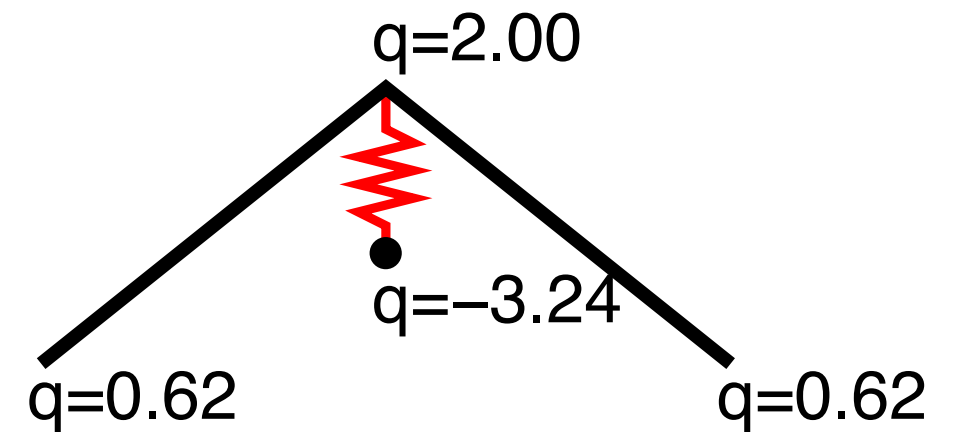
Why do this?



# Polarizable models

- Putting a charge on a shell “particle” lets the charge distribution adapt to the environment, this results in polarizable models:

- polarizable water
- polarizable ions
- polarizable ...



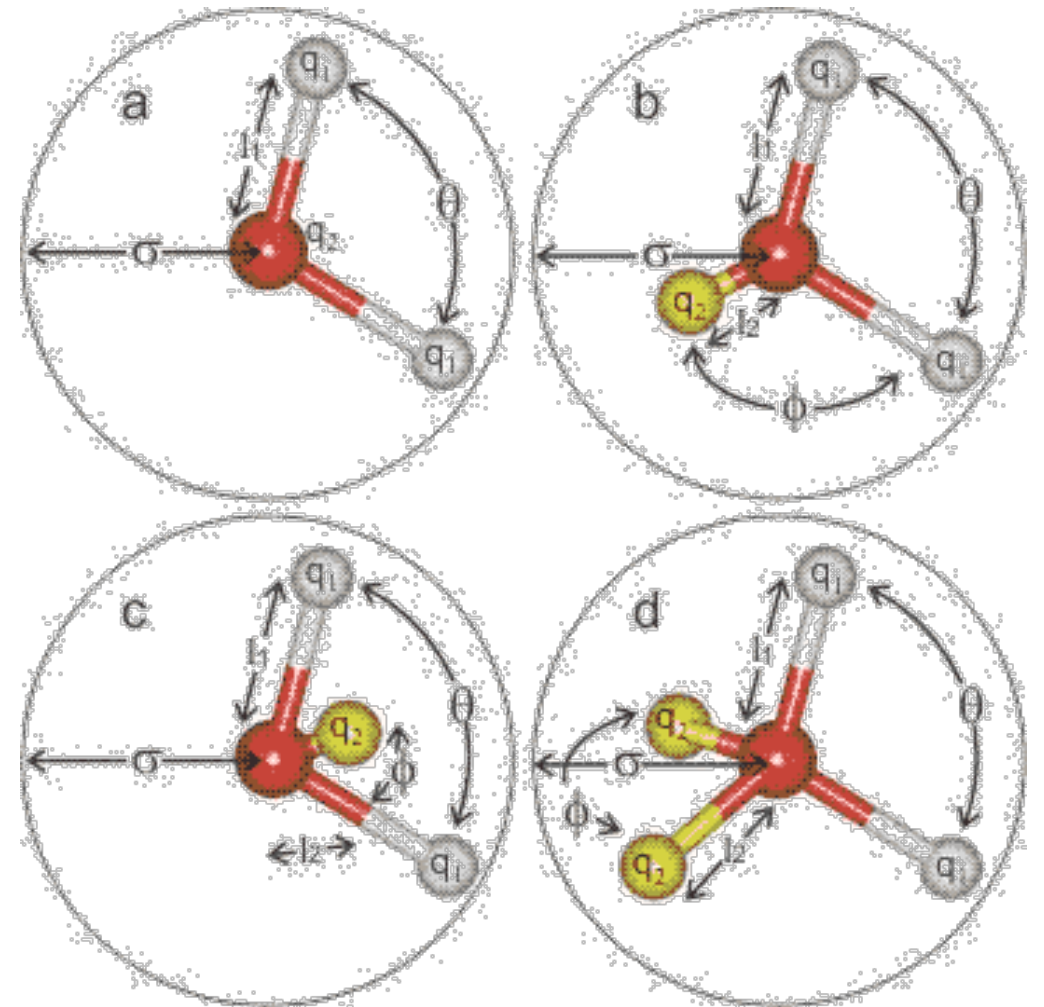
example of a “simple” polarizable water model, the polarizability can be tuned by the force constant of the red spring

# Cost of polarization

- Using shell particles requires minimization
  - 5-20 iterations required:
    - simulations 5-20 times slower!
- One solution: use Drude oscillators
  - give the additional charge a small mass
  - do MD with low temperature for these
  - advantage: cheap
  - disadvantage: no proper Hamiltonian
    - no proper ensemble, depends on  $m_q, T_q$

# Water models

- There are about 100 simple 3 and 4 site water models
  - most popular: TIP3P, SPC, SPC/E, TIP4P, used with force-fields
- There are dozens of more complex, polarizable and charge density models, area of active research



Short list: <http://www.lsbu.ac.uk/water/models.html>

# Some water models

Model	Type	$\sigma \text{ \AA}^6$	$\epsilon \text{ kJ mol}^{-1}^6$	$l_1 \text{ \AA}$	$l_2 \text{ \AA}$	$q_1 (e)$	$q_2 (e)$	$\theta^\circ$	$\varphi^\circ$
SSD <sup>[511]</sup>	<sup>8</sup>	3.016	15.319	-	-	-	-	109.47	109.47
SPC <sup>[94]</sup>	<b>a</b>	3.166	0.650	1.0000	-	+0.410	-0.8200	109.47	-
SPC/E <sup>[3]</sup>	<b>a</b>	3.166	0.650	1.0000	-	+0.4238	-0.8476	109.47	-
SPC/HW (D <sub>2</sub> O) <sup>[220]</sup>	<b>a</b>	3.166	0.650	1.0000	-	+0.4350	-0.8700	109.47	-
SPC/Fw <sup>2 [994]</sup>	<b>a</b>	3.166	0.650	1.0120	-	+0.410	-0.8200	113.24	-
TIP3P <sup>[180]</sup>	<b>a</b>	3.15061	0.6364	0.9572	-	+0.4170	-0.8340	104.52	-
TIP3P/Fw <sup>2 [994]</sup>	<b>a</b>	3.1506	0.6368	0.9600	-	+0.4170	-0.8340	104.5	-
PPC <sup>1, 2 [3]</sup>	<b>b</b>	3.23400	0.6000	0.9430	0.06	+0.5170	-1.0340	106.00	127.00
TIP4P <sup>[180]</sup>	<b>c</b>	3.15365	0.6480	0.9572	0.15	+0.5200	-1.0400	104.52	52.26
TIP4P-Ew <sup>[649]</sup>	<b>c</b>	3.16435	0.680946	0.9572	0.125	+0.52422	-1.04844	104.52	52.26
TIP4P-FQ <sup>[197]</sup>	<b>c</b>	3.15365	0.6480	0.9572	0.15	+0.63 <sup>1</sup>	-1.26 <sup>1</sup>	104.52	52.26
TIP4P/Ice <sup>[838]</sup>	<b>c</b>	3.1668	0.8822	0.9572	0.1577	+0.5897	-1.1794	104.52	52.26
TIP4P/2005 <sup>[984]</sup>	<b>c</b>	3.1589	0.7749	0.9572	0.1546	+0.5564	-1.1128	104.52	52.26
SWFLEX-AI <sup>2 [201]</sup>	<b>c</b>	four terms used		0.968 <sup>1</sup>	0.14 <sup>1,3</sup>	+0.6213	-1.2459	102.7 <sup>1</sup>	51.35 <sup>1</sup>
COS/G3 <sup>[704] 9</sup>	<b>c</b>	3.17459	0.9445	1.0000	0.15	+0.450672	-0.901344	109.47	-
COS/D <sup>[1617] 9 16</sup>	<b>c</b>	3.4365	0.5119	0.9572	0.257	+0.5863	-1.1726	104.52	-
GCPM <sup>2 [859] 10</sup>	<b>c</b>	3.69 <sup>4,11</sup>	0.9146 <sup>4</sup>	0.9572	0.27	+0.6113	-1.2226	104.52	52.26
SWM4-NDP <sup>2 13 [933]</sup>	<b>c</b>	3.18395	0.88257	0.9572	0.24034	0.55733	-1.11466	104.52	52.26
ST2 <sup>[872] 12</sup>	<b>d</b>	3.10000	0.31694	1.0000	0.80	+0.24357	-0.24357	109.47	109.47
TIP5P <sup>[180]</sup>	<b>d</b>	3.12000	0.6694	0.9572	0.70	+0.2410	-0.2410	104.52	109.47
TIP5P-Ew <sup>[619]</sup>	<b>d</b>	3.097	0.7448	0.9572	0.70	+0.2410	-0.2410	104.52	109.47
TTM2-F <sup>[1027] 14</sup>	<b>c</b>	five parameters used		0.9572	0.70	+0.574	-1.148	104.52	52.26
POL5/TZ <sup>2 [256]</sup>	<b>d</b>	2.9837 <sup>4</sup>	<sup>4</sup>	0.9572	0.5	varies <sup>5</sup>	-0.42188	104.52	109.47
Six-site <sup>[491]</sup>	<b>c/d</b> <sup>7</sup>	3.115 <sub>OO</sub> 0.673 <sub>HH</sub>	0.715 <sub>OO</sub> 0.115 <sub>HH</sub>	0.980	0.8892 <sub>L</sub> 0.230 <sub>M</sub>	+0.477	-0.044 <sub>L</sub> -0.866 <sub>M</sub>	108.00	111.00
QCT <sup>[1251]</sup>	<b>a</b> <sup>15</sup>	3.140	0.753	0.9614	-	+0.6064	-1.2128	104.067	-

<sup>1</sup> Average values; <sup>2</sup> Polarizable models; <sup>3</sup> charge = -2.48856; <sup>4</sup> Buckingham potential <sup>a</sup>. This exponential potential presents



# Some water model properties

Model	Dipole moment <sup>e</sup>	Dielectric constant	Self diffusion, $10^{-5} \text{ cm}^2/\text{s}$	Average configurational energy, $\text{kJ mol}^{-1}$	Density maximum, $^{\circ}\text{C}$	Expansion coefficient, $10^{-4} ^{\circ}\text{C}^{-1}$
SSD	2.35 [511]	72 [511]	2.13 [511]	-40.2 [511]	-13 [511]	-
SPC	2.27 [181]	65 [185]	3.85 [182]	-41.0 [185]	-45 [983]	7.3 [704] **
SPC/E	2.35 [3]	71 [3]	2.49 [182]	-41.5 [3]	-38 [183]	5.14 [994]
SPC/Fw	2.39 [994]	79.63 [994]	2.32 [994]	-	-	4.98 [994]
PPC	2.52 [3]	77 [3]	2.6 [3]	-43.2 [3]	+4 [184]	-
TIP3P	2.35 [180]	82 [3]	5.19 [182]	-41.1 [180]	-91 [983]	9.2 [180]
TIP3P/Fw	2.57 [994]	193 [994]	3.53 [994]	-	-	7.81 [994]
TIP4P	2.18 [3,180]	53 <sup>a</sup> [3]	3.29 [182]	-41.8 [180]	-25 [180]	4.4 [180]
TIP4P-Ew	2.32 [649]	62.9 [649]	2.4 [649]	-46.5 [649]	+1 [649]	3.1 [649]
TIP4P-FQ	2.64 [197]	79 [197]	1.93 [197]	-41.4 [201]	+7 [197]	-
TIP4P/2005	2.305 [984]	60 [984]	2.08 [984]	-	+5 [984]	2.8 [984]
SWFLEX-AI	2.69 [201]	116 [201]	3.66 [201]	-41.7 [201]	-	-
COS/G3 **	2.57 [704]	88 [704]	2.6 [704]	-41.1 [704]	-	7.0 [704]
COS/D	2.43 [1617]	69.8 [1617]	2.5 [1617]	-41.8 [1617]	-	-
GCPM	2.723 [859]	84.3 [859]	2.26 [859]	-44.8 [859]	-13 [859]	-
SWM4-NDP	2.461 [933]	79 [933]	2.33 [933]	-41.5 [933]	-	-
TIP5P	2.29 [180]	81.5 [180]	2.62 [182]	-41.3 [180]	+4 [180]	6.3 [180]
TIP5P-Ew	2.29 [619]	92 [619]	2.8 [619]	-	+8 [619]	4.9 [619]
TTM2-F	2.67 [1027]	67.2 [1027]	1.4 [1027]	-45.1 [1027]	-	-
POL5/TZ	2.712 [256]	98 [256]	1.81 [256]	-41.5 [256]	+25 [256]	-
Six-site *	1.89 [491]	33 [491]	-	-	+14 [491]	2.4 [491]
QCT **	1.85 [1251]	-	1.5 [1251]	-42.7 [1251]	+10 [1251]	3.5 [1251]
Experimental	2.95	78.4	2.30	-41.5 [180]	+3.984	2.53

All the data is at 25°C and 1 atm, except \* at 20°C and \*\* at 27°C.

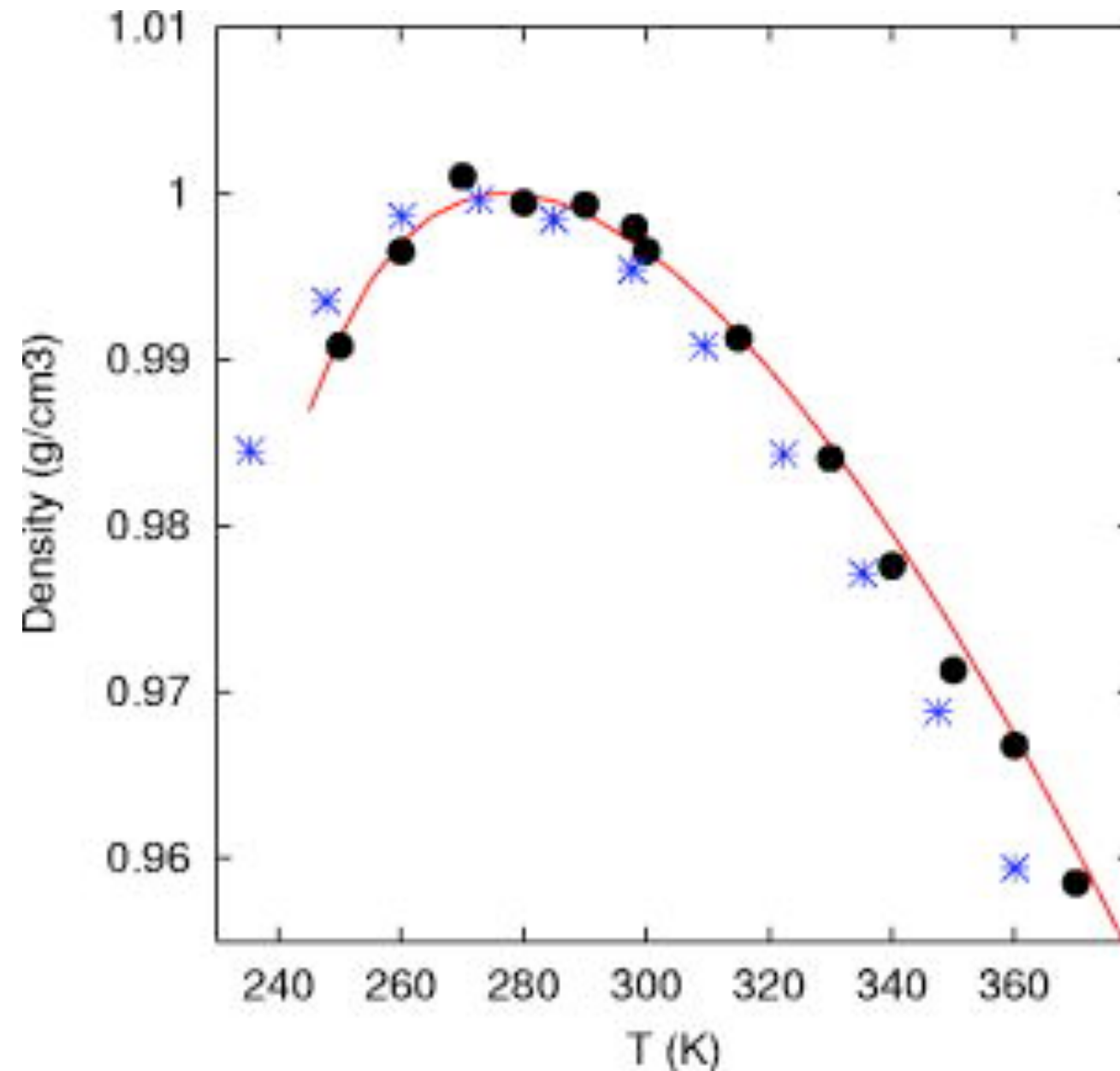
# Popular water models

- SPC and TIP3P often used for the parametrization of force fields
  - diel. const. off (SPC 65, TIP3P 100)
  - expans. coeff too high (too little structure)
    - leads to less accurate solvation
- SPC/E and TIP4P are better
  - SPC/E good dielectric constant (72)
  - TIP4P more expensive (4 sites)
- In practice all the details might not matter

# TIP4P/2005

- TIP4P 4-site model reparametrized in 2005
  - to reproduce as many properties as possible
  - parametrization including polarization correction for heat of vaporization (as for SPC/E and TIP4P/Ew)
  - parametrized with long-range electrostatics

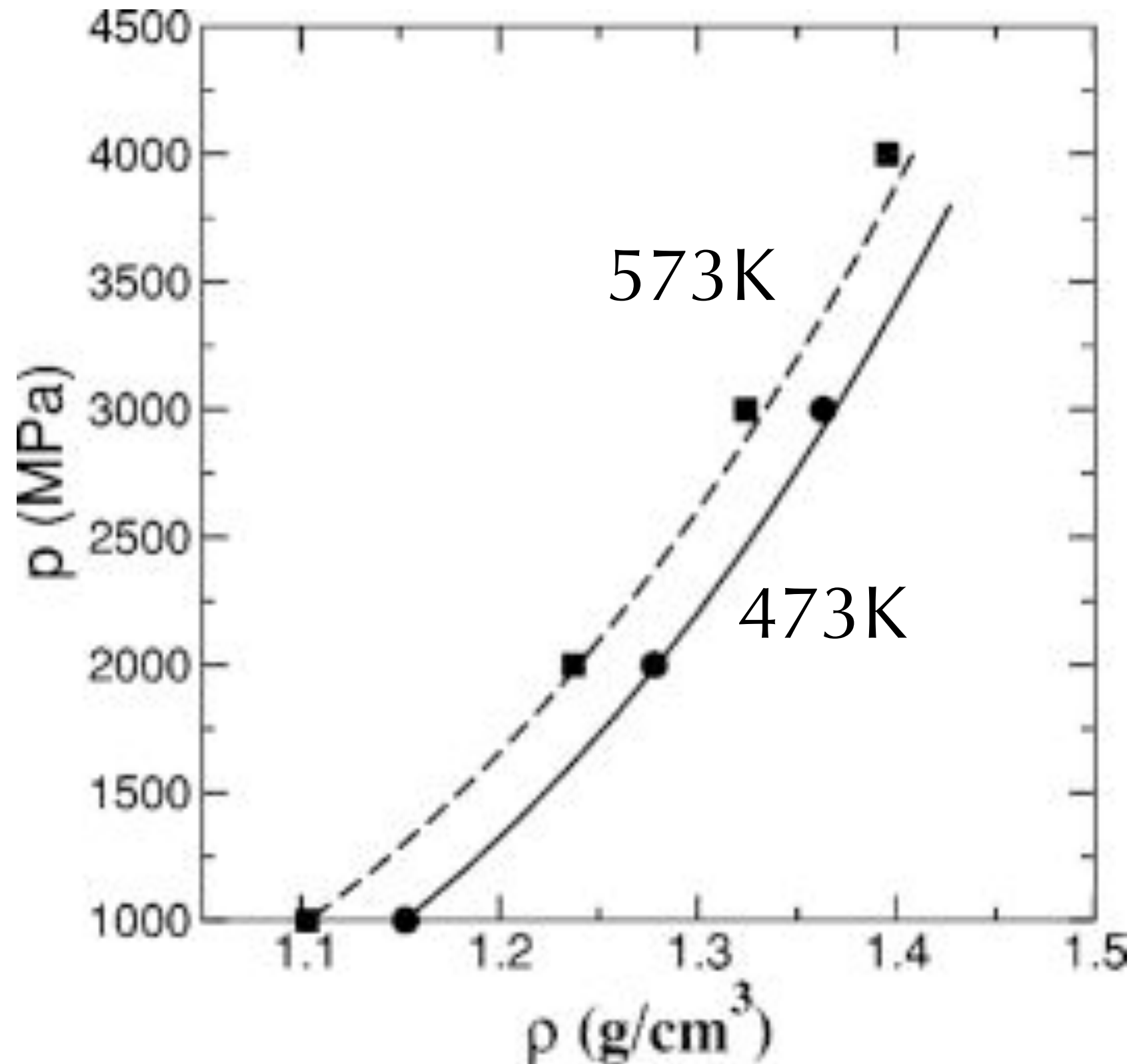
# TIP4P/2005 density maximum



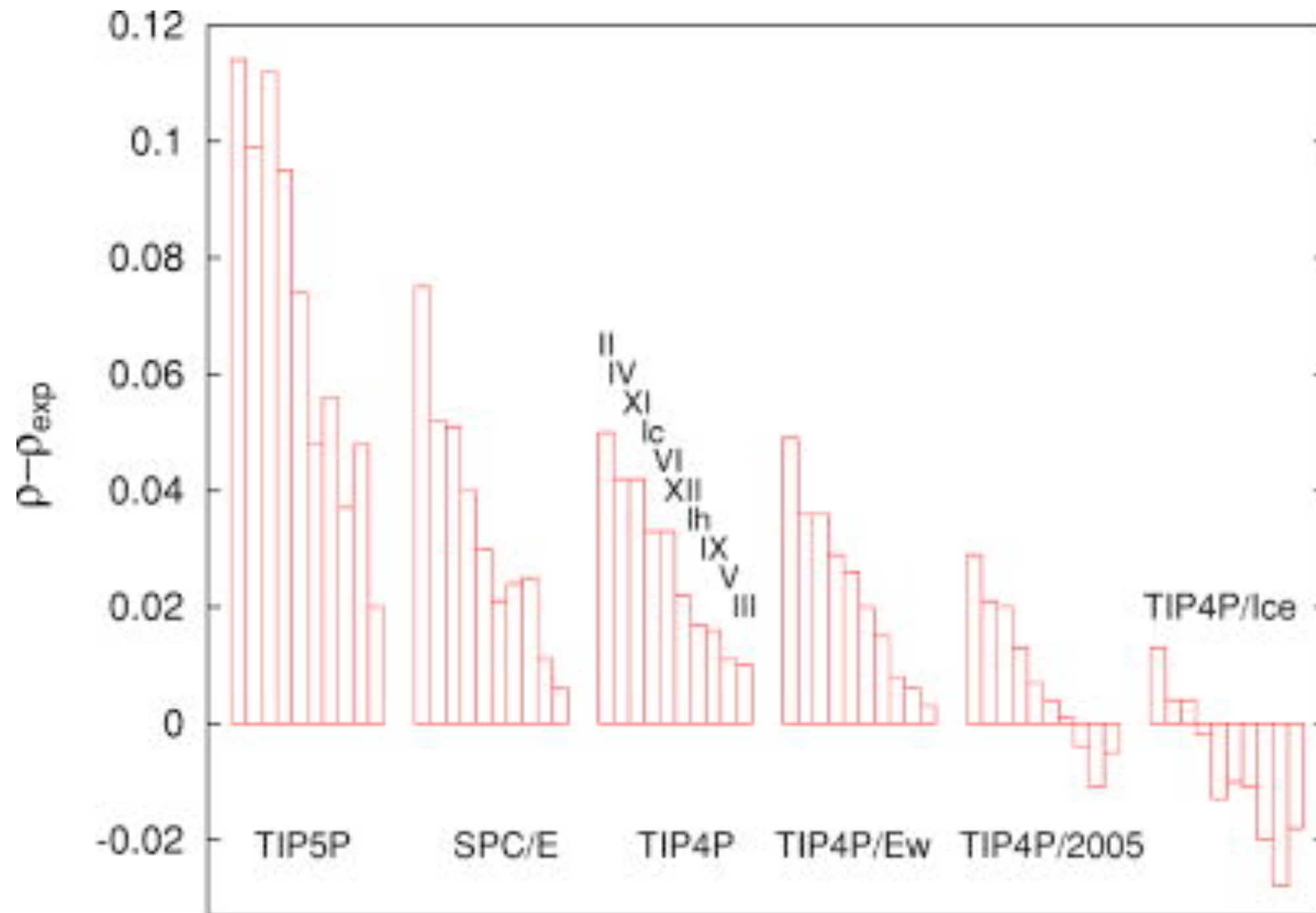
line: experiment  
circles TIP4P/2005  
crosses: TIP4P/Ew



# TIP4P/2005 at high pressure

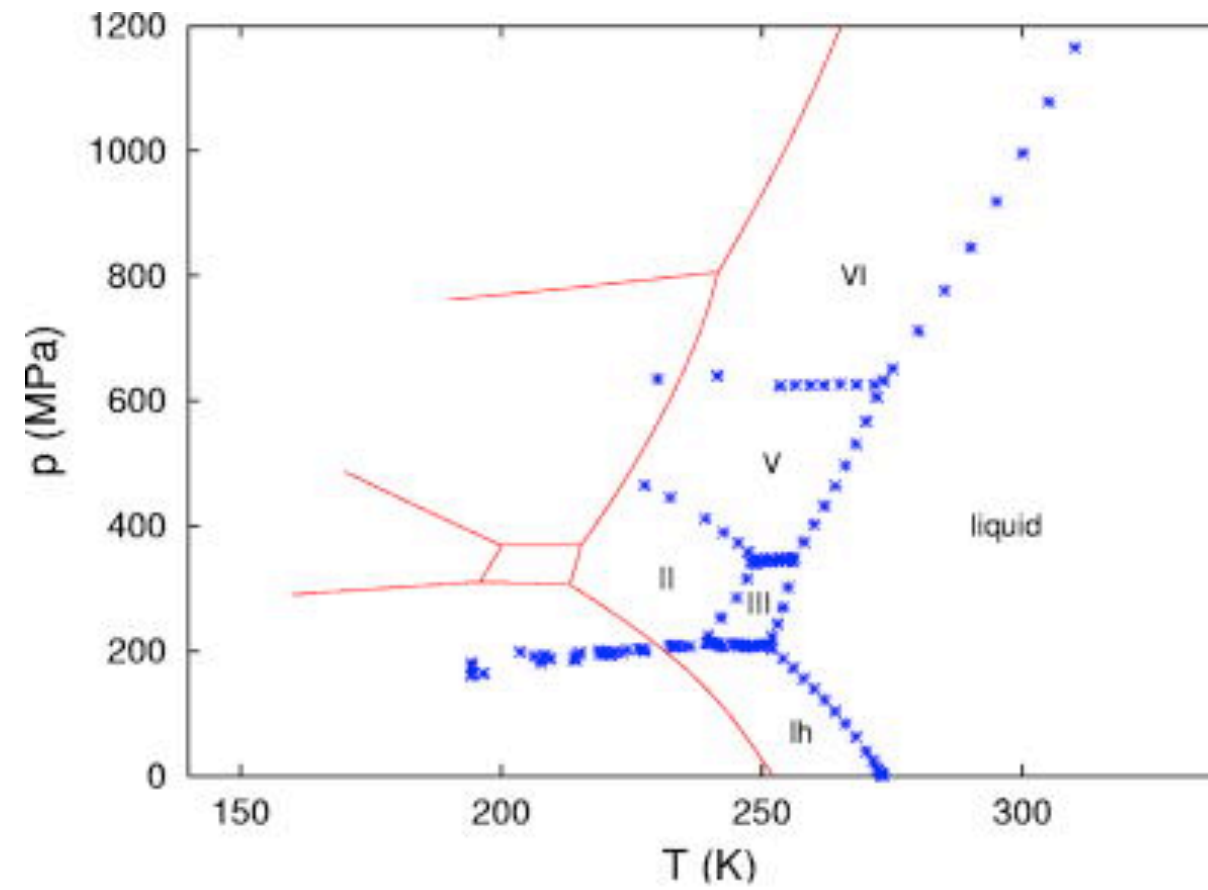


# Density of ice phases

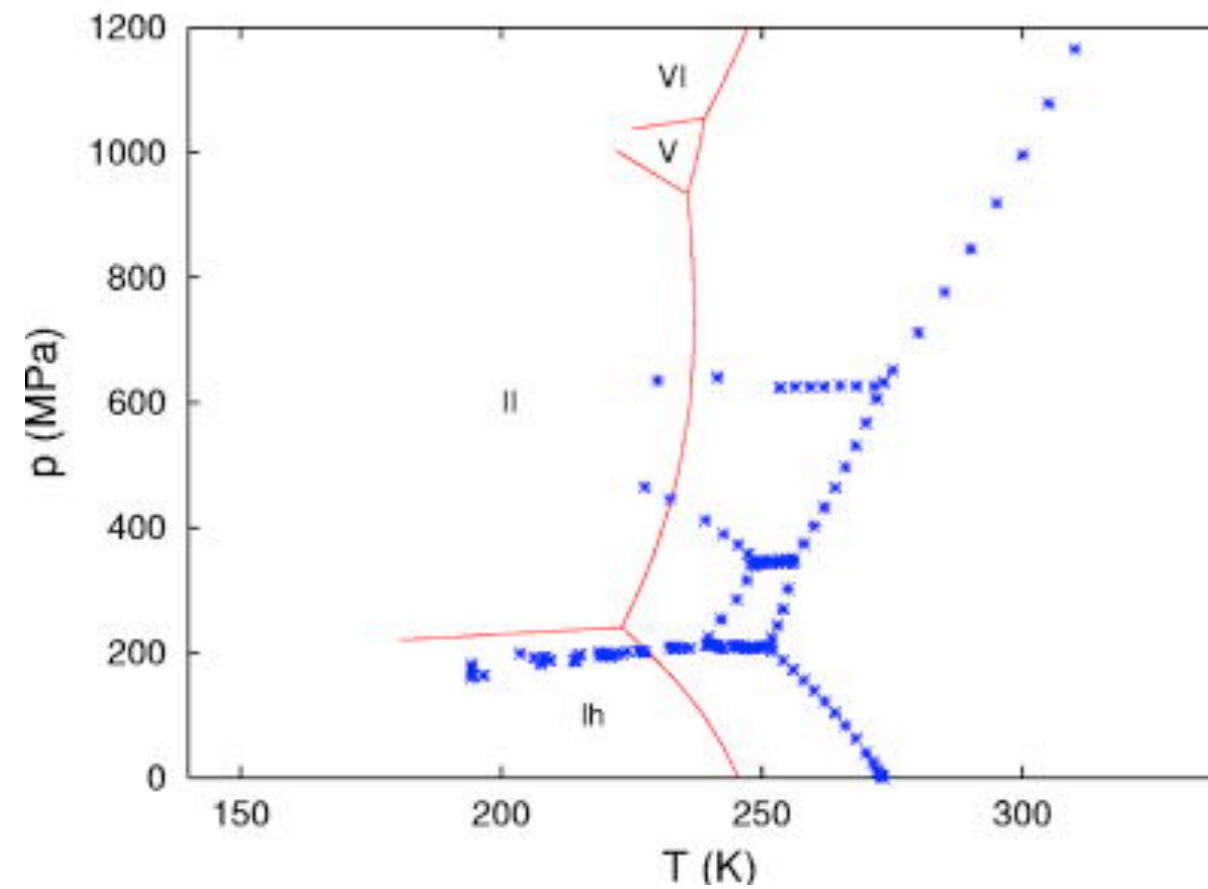


# Phase diagram

TIP4P/2005



TIP4P/Ew



# Water model conclusions

- TIP4P/2005 impressive reproduction of many properties (especially for a non-polarizable model)
  - but dielectric constant is off
- For pure water simulation: use TIP4P/2005
- For anything else: use a model compatible with your force-field
  - personal opinion: use SPC/E (compatible with most force-fields, good diel. const.)
- More (complex) water models will come