Water models / solvation

Biggest effects of water
• electrostatic
• dynamic

Model types
• explicit
• implicit

Dynamic effects of water
Dynamic effects of water

one lonely moving particle
• initial velocity \( \dot{x}_t \)
• future velocity easy \( \dot{x}_{t+\delta t} = \dot{x}_t \)
• energy ? constant \( \frac{m x^2}{2} \)

two particles ? interacting ?
• future velocity a bit more difficult
• easily bounded – cannot be more than \( \frac{m_1 \dot{x}_1^2 + m_2 \dot{x}_2^2}{2} \)

one particle in water...
Velocities of particles in water

Lots of random interactions

A small acceleration?

A big acceleration?

A probability distribution

+ how does $\dot{x}_t$ tell us about $\dot{x}_{t+\delta t}$?

• much less

$p(v)$

velocity

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Modelling dynamic effects

Summary
- solvent will add fluctuations
- particles forget their velocity faster

Can this be modelled?
- yes (in molecular dynamics simulations)
- not really a force field / energy topic
- add random fluctuations to velocities
- can be made to look like water
Electrostatic effects of water

water molecules
• not charged
• polar

Interaction between charges very different if water in between

• details soon
Explicit water

Earlier descriptions of proteins
• a set of connected atoms
• extend to include water

What does water look like?

What else has it got?
• think about electron pairs on “O”
• what is really important?
Important features of a water model

Do we care about water internal dynamics? (bonds and angle)
• usually not
  • make bonds rigid
  • make angle rigid
    • treat as a bond

Dimensions
• protons are really small
• does water geometry matter?
  • usually not

Charge
• most important

Final result..
SPC - A useful explicit water model

- 3 charges
- 1 Lennard-Jones radius
- 3 masses - why?
  - only for molecular dynamics
- 3 bonds (completely rigid)
- Name – "SPC", simple point charge

What can it do?
- diffusion, density, compressibility, heat capacity
- dielectric constant
- solvation energies?

Perfect? No
- add polarisation, offset charge from mass, ...
Explicit water + protein

Protein-water interactions
• via charge
• via Lennard-Jones term ($r^{-12}$ and $r^{-6}$)

Elegant / Simple - automatically incorporates
• dynamic effects
• electrostatics

Problems
• very expensive
• typical simulation $10^3$ protein atoms
• $10^4$ solvent atoms
worst case for proteins + water

Imagine a world with no cutoffs for interactions
- scales as $O(n^2)$
- adding water gives 5 or 10 times as many atoms
- takes 25 or 100 times as much CPU time

Even worse
- proteins move more slowly in water (viscosity)

What to do?
- look for cheaper model
Cheaper water models

Do we really need dynamic effects of water?
• maybe not
  • only want energies
  • only care about structures
or
  • model with a random force

Then look for model which gets most essential aspects of water
• electrostatics
  • distance-dependent dielectric
  • reaction field
  • surface area methods
\[ U(r_{ij}) = \left( \frac{1}{4\pi\varepsilon_0} \right) \frac{q_i q_j}{r_{ij}} \]

Bare charges

\[ \equiv \frac{q_i q_j}{D r_{ij}} \]

With solvent, \( U(r_{ij}) \) changes less than \( \frac{q_i q_j}{D r_{ij}} \)

Net effect?

- water is very polar and tends to orient itself around charges
- as if the water "screened" the charges (makes them smaller)
Distance-dependent dielectric implementation

Invent approximation \( D_{\text{eff}} = r_{ij} \) then

\[
U(r_{ij}) \approx \frac{q_i q_j}{D_{\text{eff}} r_{ij}} \approx \frac{q_i q_j}{r_{ij}^2}
\]

Is this physics?
- no

Does it work?
- a bit (ugly)
- little real physical basis
- water does not behave so simply
- fundamental problem...
Fundamental problem with distance-dependent $D$

If we rely on distance-dependent dielectric constant
- assume one 'fix' works everywhere (not true)

Think of formula $U(r_{ij}) = \frac{q_i q_j}{4\pi \epsilon_0 r_{ij}}$

Model will differ on big and small proteins
Reaction field idea

Different problem to before

- charge in a protein (lots of neutral CH groups)
  - not much happens
- particle in water
  - what does the water do?
  - tends to orient
  - lots of $q^+q^-$ interactions
    - much better energy
- is this like a force?
  - yes, think $-\frac{dU}{dr}$

Can this be modelled?

Friedman, H.L., Mol. Phys. 29, 1533-1543 (1975) Image approximation to the reaction field
interaction with imaginary solvent

Think of particle interacting with distant water molecules

- Our charge interacts with them all but
  - if they are far away (big $R$) less important
  - depends on dielectric constant
  - inside white region $\varepsilon_r$ and
  - grey region $\varepsilon_s$
- Within white region
  - treat atoms with a correction
- Grey region
  - treat as continuum
Realistic picture

infinite continuum

R=25 Å
cutoffs 10 to 12 Å
Reaction field / image charge charge formula

- as if we interact with an "image" charge
- size $q_{im} = -\frac{\varepsilon_s - \varepsilon_r}{\varepsilon_s + \varepsilon_r} \frac{q_i R}{r_i}$

- location $\left(\frac{R}{r_i}\right)^2 \hat{r}_i$
  - near middle
    - $R \gg r_i$
    - image far away
  - near boundary
    - imaginary solvent important
    - strong (favourable) interaction

Important result
- we have modelled the happiness of a charge in solution
- charges happiest on outside of protein
Reaction fields and pairs

• charge \( q_i \) interacts with water
• water responds
• \( q_j \) feels effect of water

• no longer
  \[
  U(r_{ij}) = \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}
  \]

• instead,
  \[
  U(r_{ij}) = \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \cdot f(q_i, q_j, \text{distances to centre}, \ldots)
  \]
Simpler ways to model solvent

Problem with real physics
  • if you use this model, you are obliged to use
    • real charges, real coordinates...
  • parameters not perfect
  • hard to rationalise repairs

Many effects simultaneously
  • charges interacting with water dipoles
  • loss of water – water interactions
  • change of solvent entropy
  • change of solute entropy?

Different approach
  • less rigorous models
Basis of quick water model

Philosophy

- I can not model water properly
- find a very general way to incorporate effects
- Water makes some atoms happy
- Others do not care too much
- Find some very general way to include water effects
  - whether they are favourable / unfavourable
- what is easiest way to think about water influence?
Simple model
- for each atom, energy depends on surface area
Formalising SASA model

- Solvent accessible surface area (SASA)
  - for every atom, $i$ $G_i^{solv}(\vec{r}_i) = \gamma_i A_i(\vec{r}_i)$
- $G$ because we no longer have a pure potential energy
- $G_i^{solv}(\vec{r}_i)$ because the energy term depends on coordinates
- $\gamma_i$ is a specific parameter for each kind of atom
  - for O, N will be negative
  - for CH, CH$_2$, CH$_3$ will be positive or near zero
- area, $A_i$, has to be calculated

Problems

- $A_i$ is difficult to calculate
  - use approximation
- $\gamma_i$ not easy to estimate
Example SASA calculation

- classical atomistic force field
- distance-dependent dielectric
- two $\gamma_i$ parameters, $\gamma_{C,S} = 0.012$ and $\gamma_{O,N} = -0.060$ kcal mol$^{-1}$

Results

- better than *in vacuo*
  - deviation from known structure during simulation
  - not too many H-bonds formed
  - radius of gyration ? (how big is protein)
- why do they appear OK ? why only two $\gamma_i$ ?
  - not tested in detail
  - worst problems fixed
summary

• Explicit water is best, but expensive
• We have not discussed dynamic effects
• distance-dependent dielectric +
  • SASA style models
  • complementary
• many variations
  • surface accessible volume
  • more $\gamma_i$ parameters
  • add in reaction field for better long range electrostatics
• changes and flaws in one parameter are hidden by others