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 \( \frac{m \dot{x}^2}{2} \)

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 velocity ?

• a big velocity ?

• a probability distribution

+ 

• how does $\dot{x}_t$ tell us about $\dot{x}_{t+\delta t}$ ?
  • much less
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?
• 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.
A useful explicit water model

- 3 charges
- 1 Lennard-Jones radius
- 3 masses - why?
  - only for molecular dynamics
- 3 bonds (completely rigid)
- Name – “SPC”

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

Perfect?
- no
  - add polarisation, bonds, bond angles, offset charge from mass
Explicit water + protein

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

Only average properties are interesting
- useful only in simulations (MC, MD)

Elegant / Simple
- automatically incorporates
  - dynamic effects
  - electrostatics

Problems
- very expensive
- typical simulation $10^3$ protein atoms
- $10^4$ solvent atoms
Imagine a world with no cutoffs for interactions
- scales as $O(n^2)$
- adding water takes 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
Distance dependent idea

\[ U(r_{ij}) = \left( \frac{1}{4\pi\varepsilon_0} \right) \frac{q_iq_j}{r_{ij}} \]

Bare charges

\[ \equiv \frac{q_iq_j}{Dr_{ij}} \]

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

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

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

Think of formula \( U(r_{ij}) = \frac{q_i q_j}{4 \pi \varepsilon_0 r_{ij}} \)

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

\( R = 25 \text{ Å} \)
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 $\left(\frac{R}{r_i}\right)^2 \vec{r}_i$
- 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 $U(r_{ij}) = \frac{q_i q_j}{4\pi \epsilon_0 r_{ij}}$

• instead, $U(r_{ij}) = \frac{q_i q_j}{4\pi \epsilon_0 r_{ij}} \cdot f(q_i, q_j, \text{distances to centre, ...})$
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, \( i \quad G_i^{\text{solv}}(\vec{r}_i) = \gamma_i A_i(\vec{r}_i) \)
- \( G \) because we no longer have a pure potential energy
- \( G_i^{\text{solv}}(\vec{r}_i) \) 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 $\gamma_{O,N} = -0.060 \text{ kcal mol}^{-1}$

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

Andrew Torda
08/06/2015

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