

Water models / solvation

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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 $\frac{m\dot{x}^2}{2}$

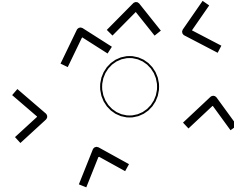
two particles ? interacting ?

- future velocity a bit more difficult
- easily bounded – cannot be more than $\frac{m_1\dot{x}_1^2 + m_2\dot{x}_2^2}{2}$

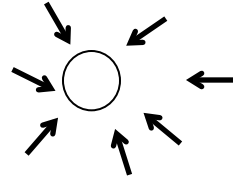
one particle in water...

Velocities of particles in water

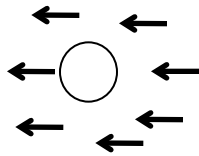
- lots of random interactions



- a small velocity ?



- a big velocity ?

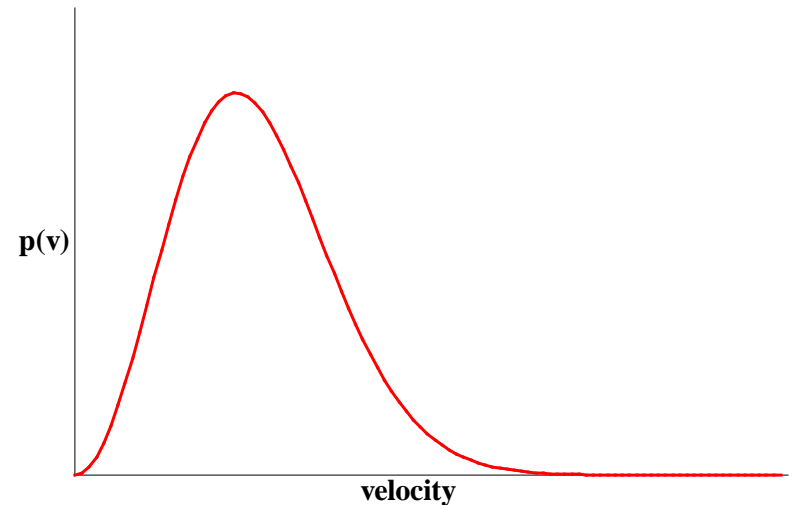


- a probability distribution

+

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

- much less



Modelling dynamic effects

Summary

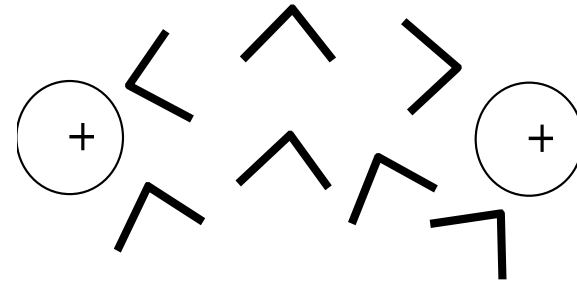
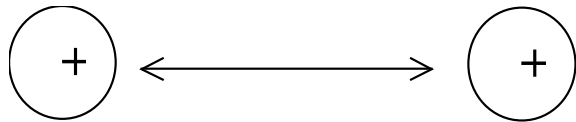
- solvent will add fluctuations
- makes us forget velocity faster

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

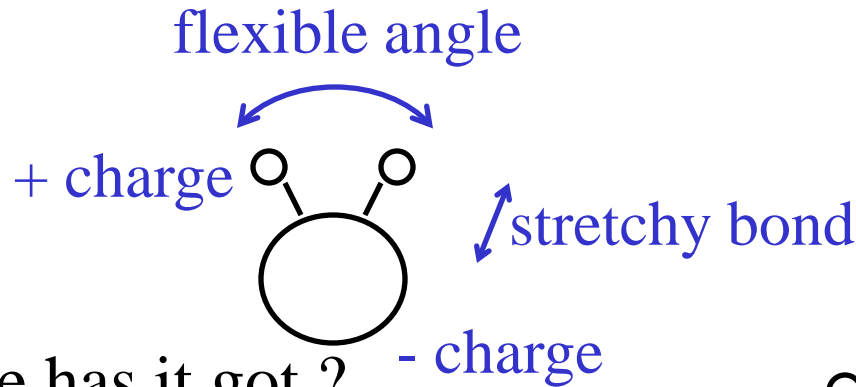
Electrostatic effects of water

- water molecules
 - not charged
 - polar
- interaction between charges very different if water in between
- details soon

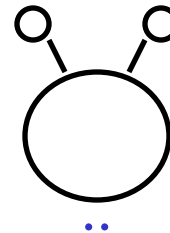


Explicit water

- earlier descriptions of proteins
 - a set of connected atoms
- extend to include water
- what does water look like ?



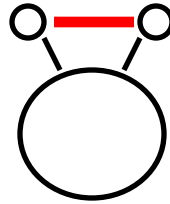
- what else has it got ?
 - think about electron pair on “O”
- what is really important ?



Important features of a water model

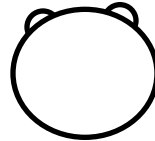
Do we care about water internal dynamics ?

- usually not
- make bonds rigid
- make angle rigid
 - treat as a bond



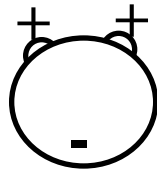
Dimensions

- protons are really small
- does water geometry matter ?
 - usually not



Charge

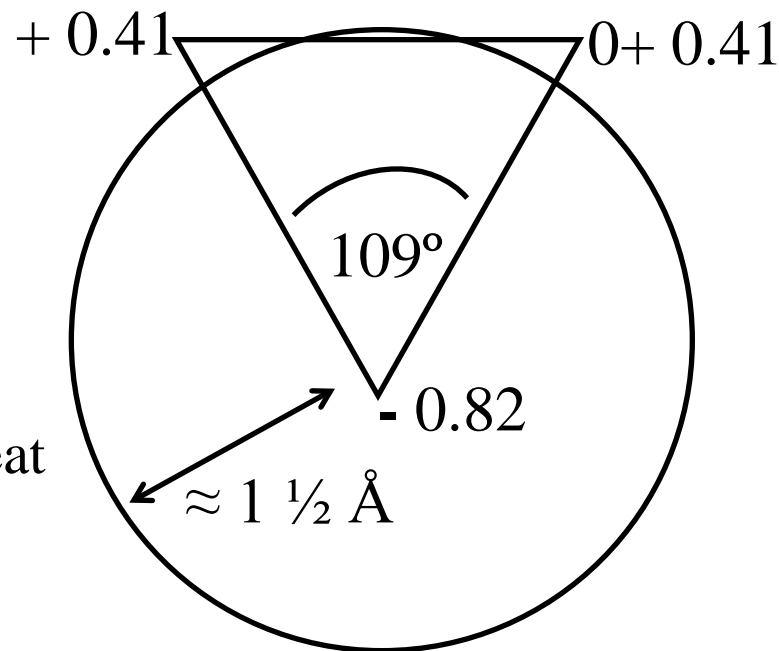
- most important



Final result..

A useful explicit water model

- 3 charges
- 1 Lennard-Jones radius
- 3 masses - why ?
 - only for molecular dynamics
- 3 bonds (completely rigid)
- has a 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

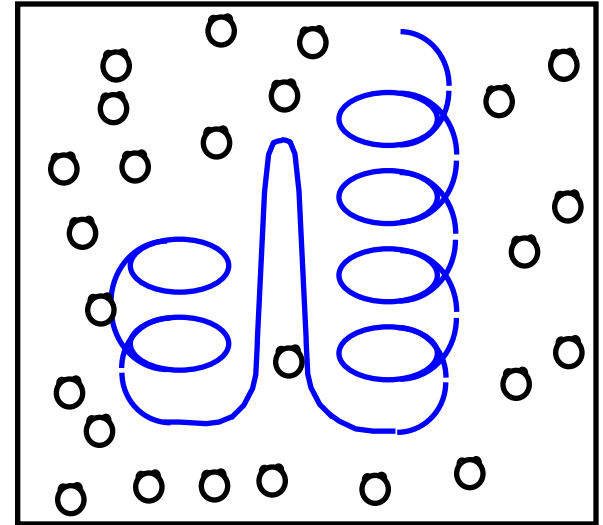
- useful only in simulations (MC, MD)

What is neat

- automatically incorporates
 - dynamic effects
 - electrostatics

Problems

- very 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 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)

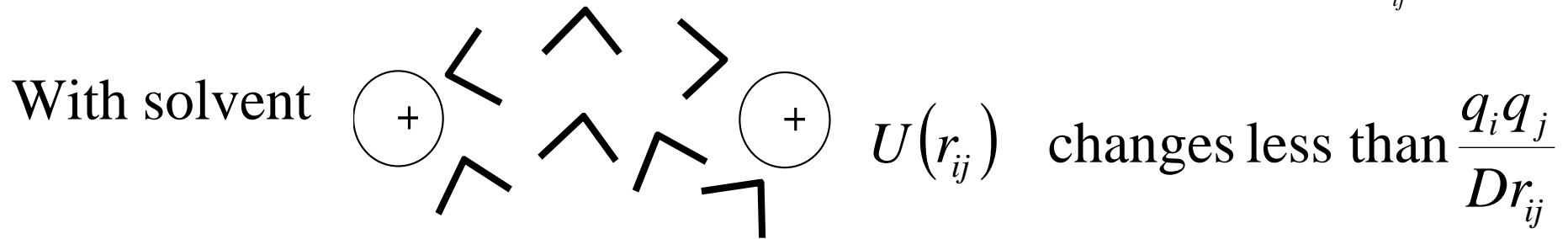
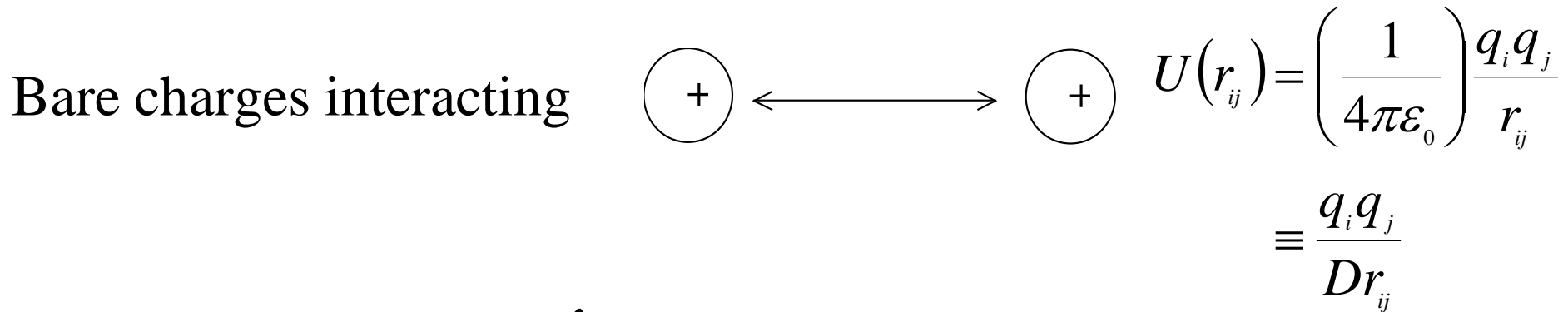
What to do ?

- 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



Net effect ?

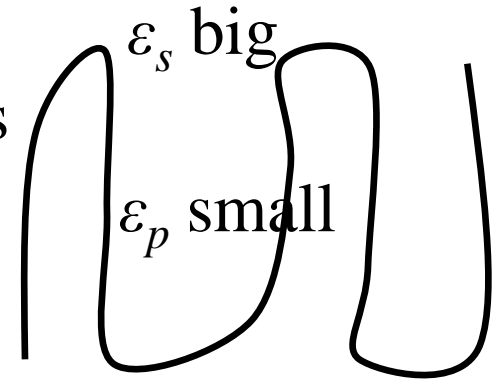
- water is very polar and tends to orient itself around charges
- as if the water "screened" the charges (makes them smaller)

Distance dependent dielectric implementation

- invent approximation $D_{eff}=r_{ij}$ then $U(r_{ij}) \approx \frac{q_i q_j}{D_{eff} r_{ij}} \approx \frac{q_i q_j}{r_{ij}^2}$
- is this physics ?
 - no
- does it work ?
 - a bit (ugly)
 - little real physical basis
- water does not behave so simply
- fundamental problem...

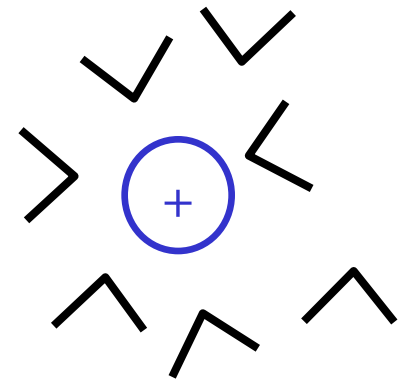
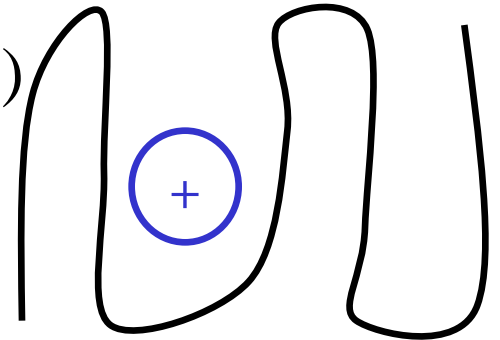
Fundamental problem with distance dependent D

- 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



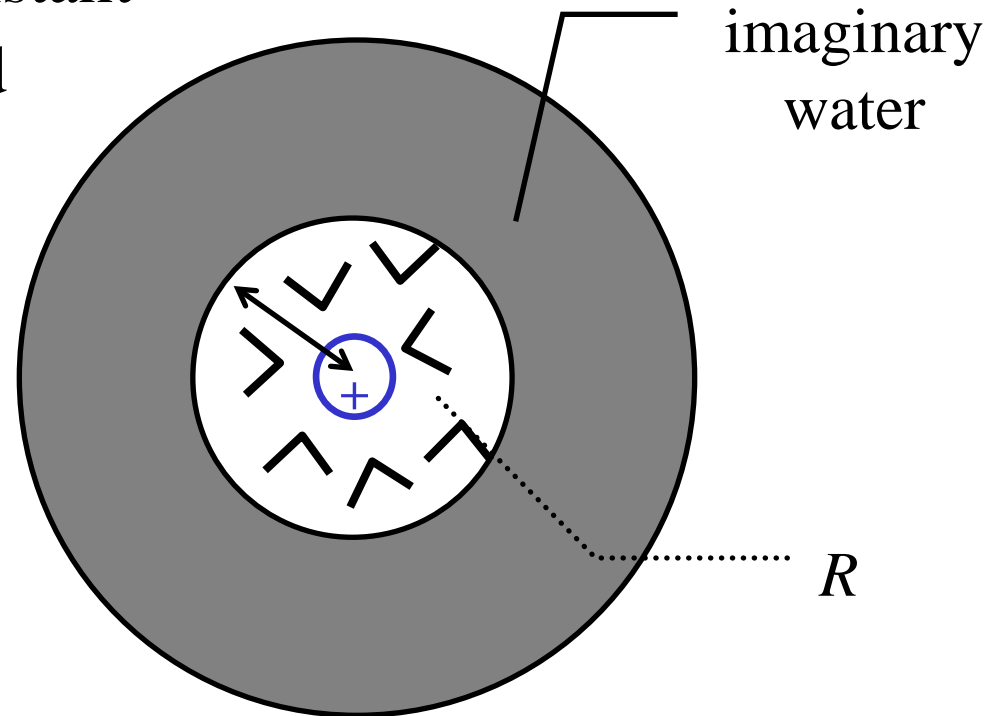
Reaction field idea

- 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 $-dU / dr$
 - can this be modelled ?

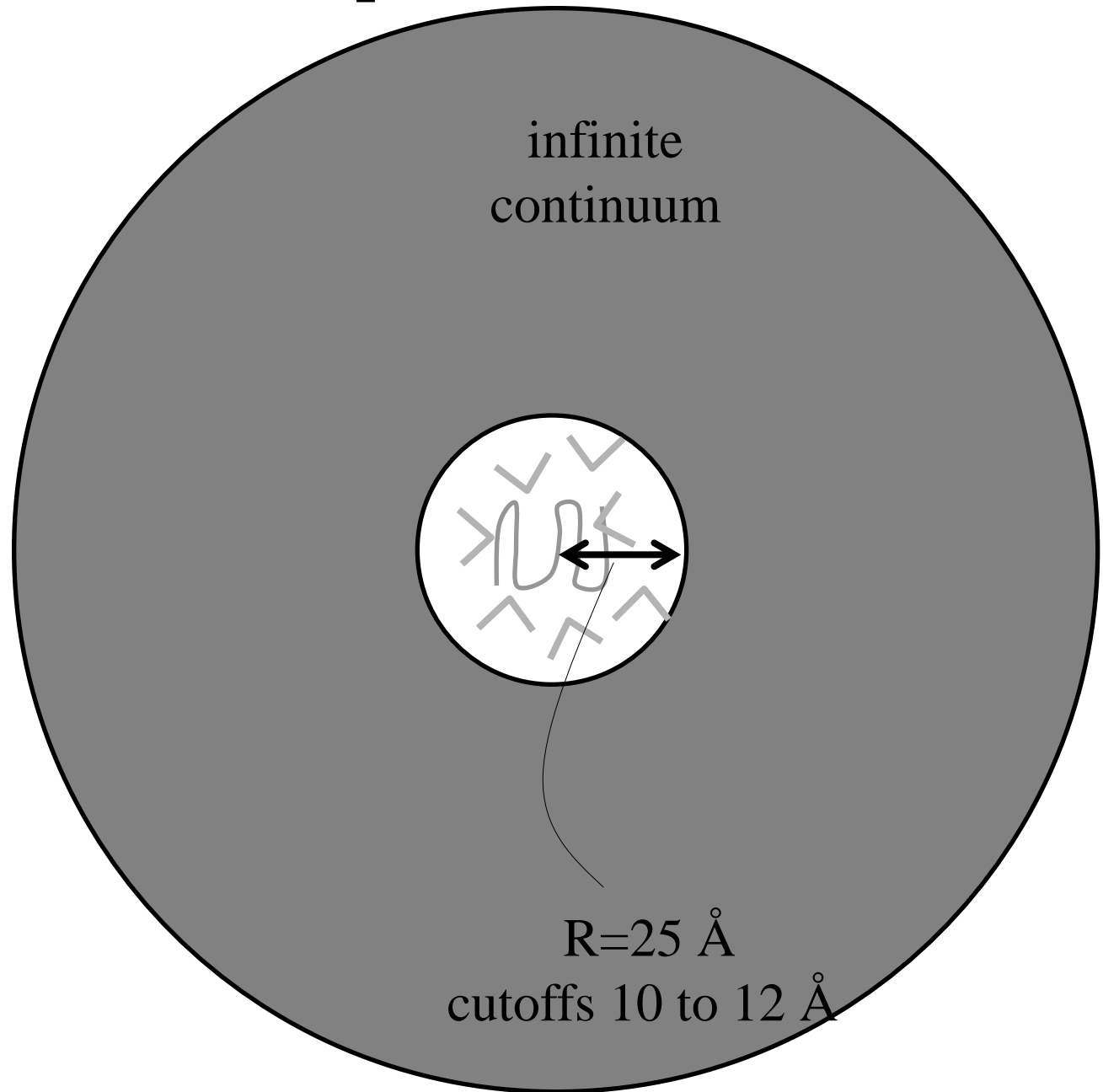


interaction with imaginary solvent

- 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 ϵ_r and
 - grey region ϵ_s
- within white region
 - treat atoms with a correction
- grey region
 - treat as continuum



Realistic picture



Reaction field / image charge formula

- as if we interact with an "image" charge

- size
$$q_{im} = -\frac{(\epsilon_s - \epsilon_r) q_i R}{(\epsilon_s + \epsilon_r) r_i}$$

- location $\left(\frac{R}{r_i}\right)^2 \vec{r}_i$

- near middle

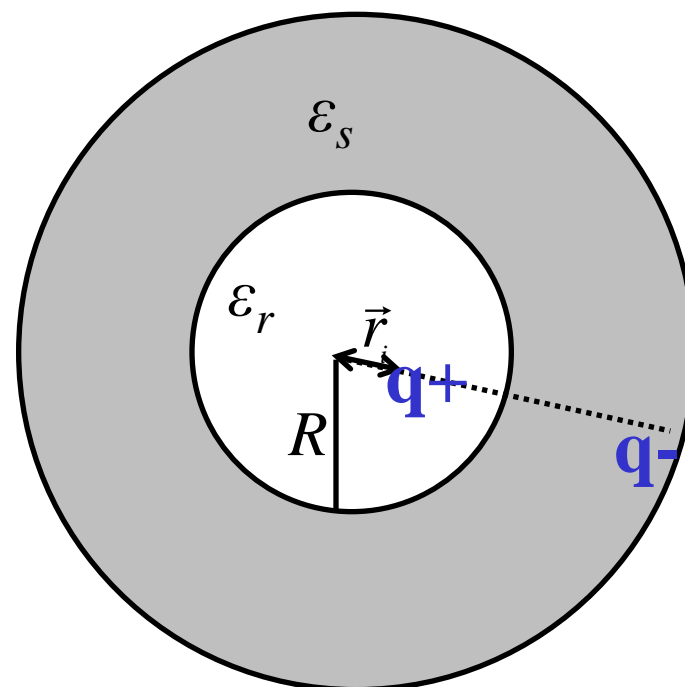
- $R \gg r_i$
- image far away

- 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,
$$U(r_{ij}) = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \cdot f(q_i, q_j, \text{distances to center, ...})$$

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

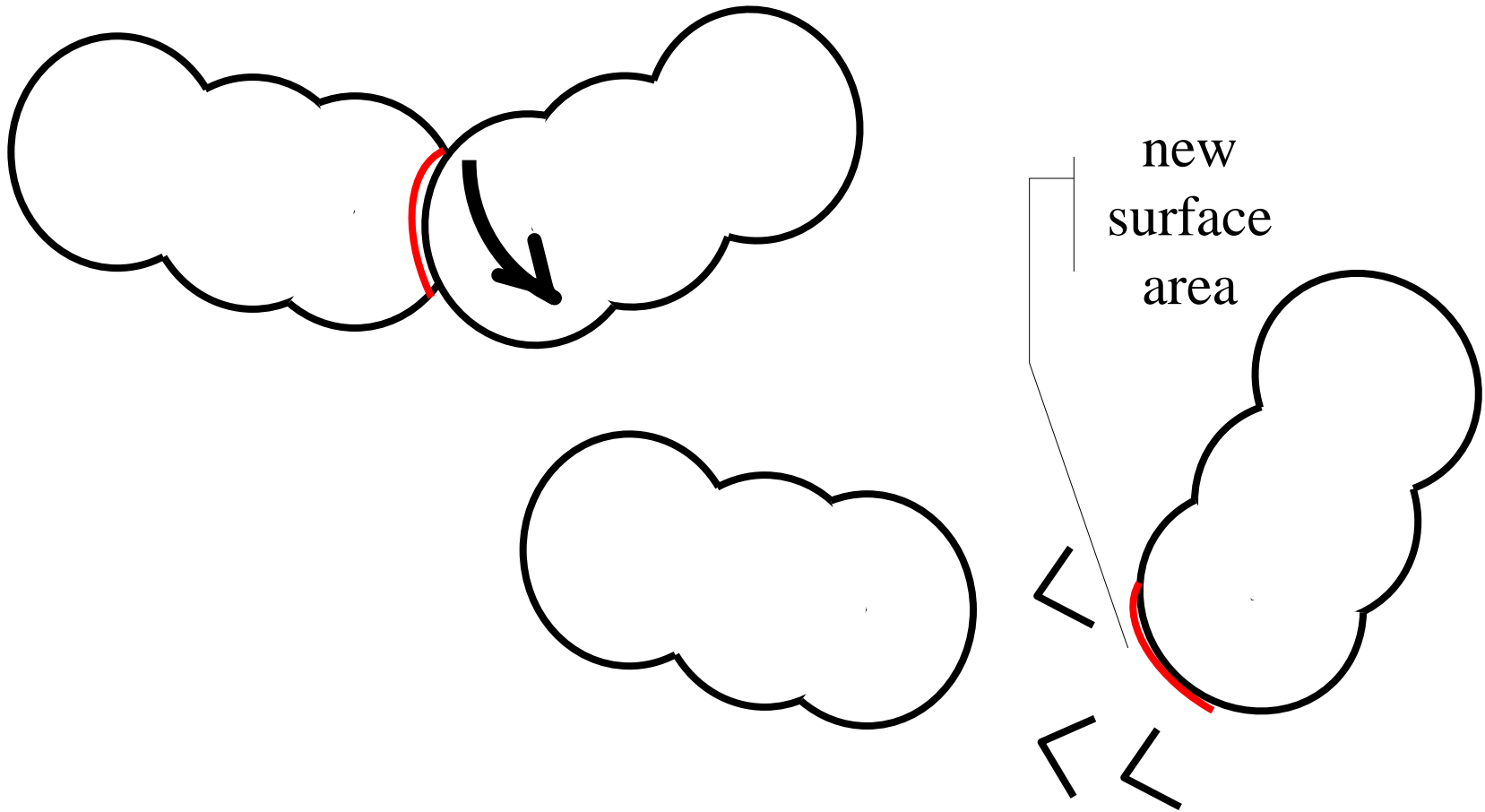
- less rigorous models

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 ?

Atom surface area



- 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
- γ_i is a specific parameter for each kind of atom
 - for O, N will be negative
 - for CH, CH₂, CH₃ will be positive or near zero
- area, A_i , has to be calculated

Problems

- A_i is difficult to calculate
 - use approximation
- γ_i not easy to estimate

Example SASA calculation¹

- classical atomistic force field
- distance dependent dielectric
- two γ_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 γ_i ?
 - not tested in detail
 - worst problems fixed

¹Ferrara, P, Apostolakis, J and Caflisch, A. 2002, Proteins, 46, 24-33

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 γ_i parameters
 - add in reaction field for better long range electrostatics
- changes and flaws in one parameter are hidden by others