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SMR.961 - 6

WORKSHOP ON:
PROTEINS, MEMBRANES and their INTERACTIONS

22 JULY - 2 AUGUST 1996

"Empirical energy functions: applications to structure and dynamics"

PART I

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Lecture 1

Empirical energy functions: applications to structure and dynamics

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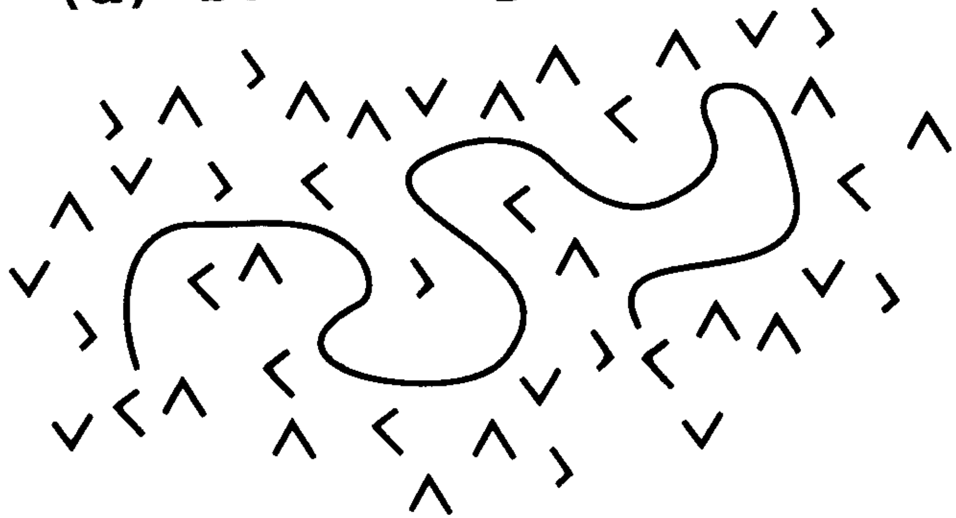
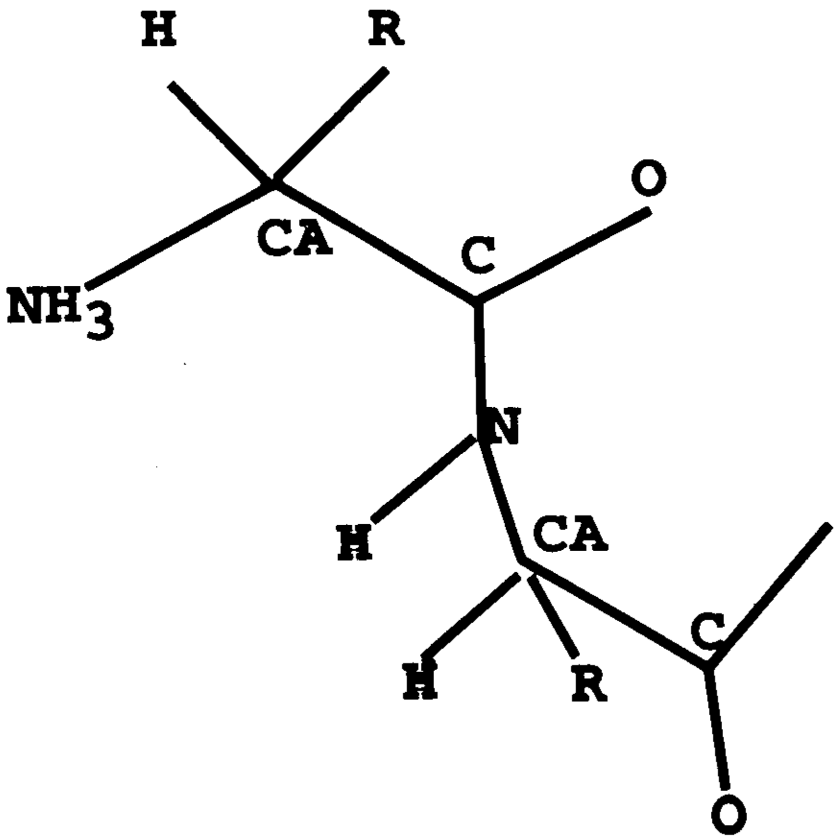
Hebrew U

Empirical energy function describe molecular interactions in atomic detail and help to correlate between different experimements

(a) ligand binding
(b) structure refinement
(c) activation
(d) stability



How to describe a molecule that looks like?



The empirical energy:

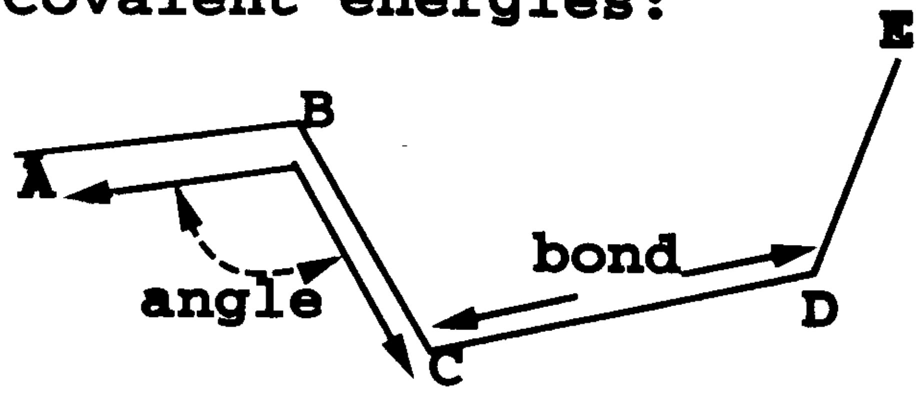
$$U = U_{covalent} + U_{nonbond}$$

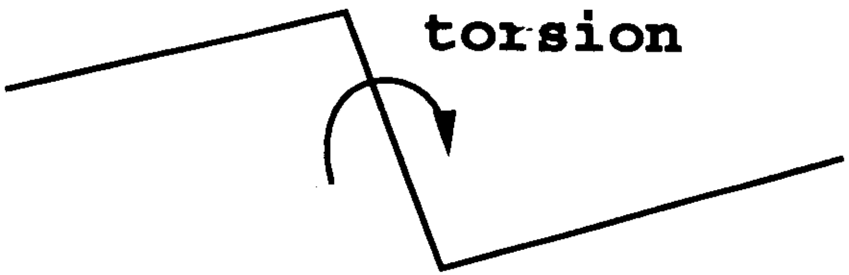
$$U_{covalent} = \Sigma U_b + \Sigma U_\theta + \Sigma U_\phi + \Sigma U_{i\phi}$$

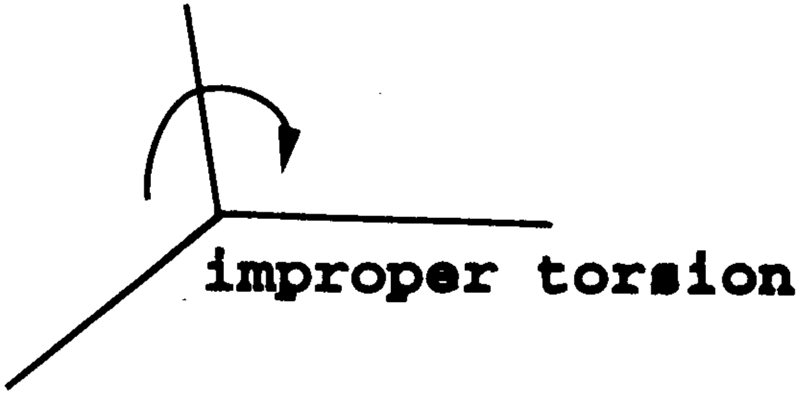
$$U_{nonbond} = \Sigma U_{elec} + \Sigma U_{vdw}$$

(*) hydrogen bonds?
(*) polarisability?
(*) hydrophobicity
(*) coupling between covalent terms

Covalent energies:







Covalent energies:

$U_{bond} = 1/2 K_b x^2 \quad (x = b - b_o)$

or

$U_{bond} = D[\exp(-2ax) - 2\exp(-ax)]$

$U_{angle} = 1/2 K_\theta (\theta - \theta_0)^2$

$U_{torsion} = \Sigma a_n \cos(n\phi + \delta_n)$

$U_{imp.tors.} = 1/2 K_{\phi i} (\phi_i - \phi_{eq})^2$

coupling internal coordinates?!

e.g. $K_{b\theta}(b - b_o)(\theta - \theta_0)$

Non-bonded interactions:

$U_{elec.} = q_1 q_2 / \varepsilon R_{12}$

ε – dielectric constant (should be one)

$U_{vdw.} = 4\varepsilon[(\sigma/R)^{12} - (\sigma/R)^{6}]$

or

$U_{vdw} = (A/R)^{12} - (B/R)^{6}$

Different combination rules

$A_{ij} = a_i a_j \quad B_{ij} = b_i b_j$

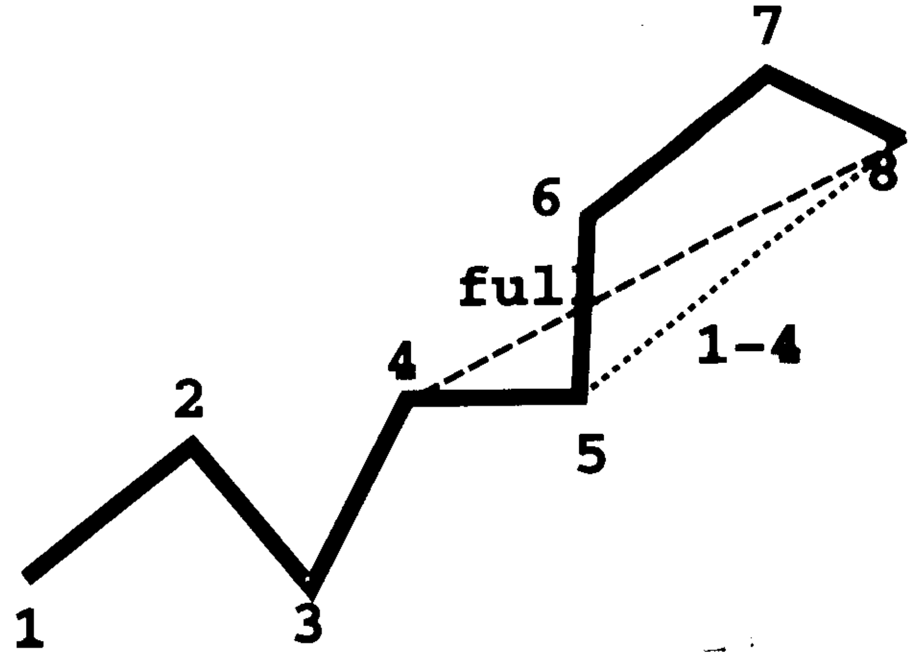
or

$\varepsilon_{ij} = e_i e_j \quad \sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j)$

1-4 interactions

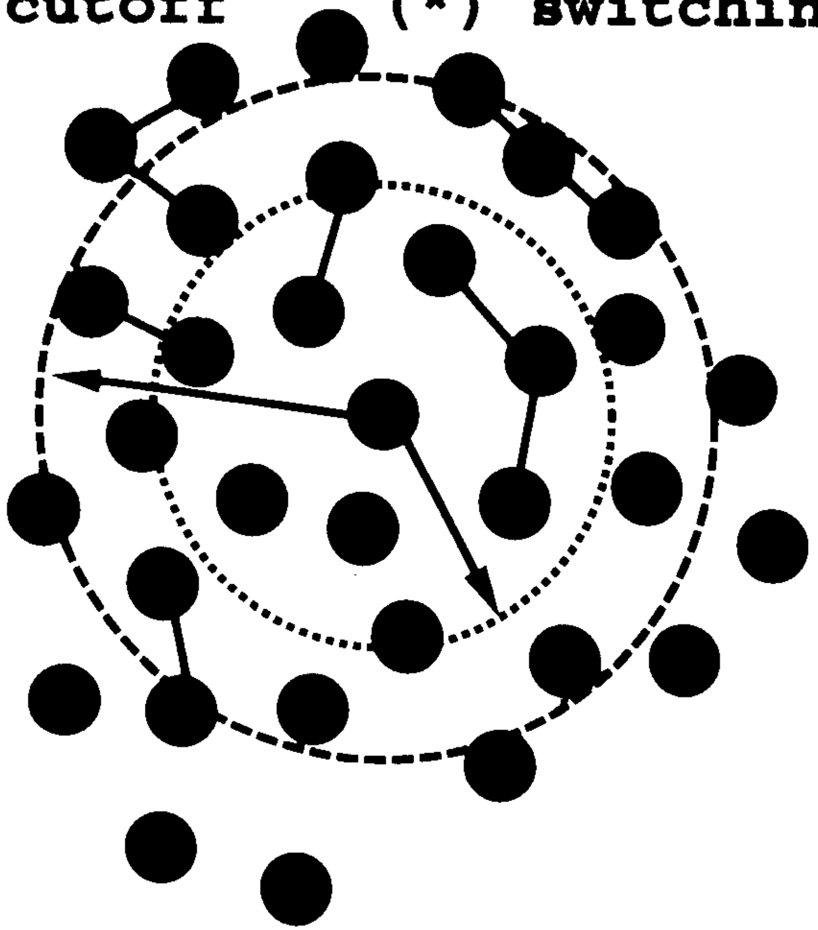
or

when covalent interactions end and nonbonded interactions start?



Use of cutoff distances

(*) buffer (*) residue cutoff (*) switching



Non-bonded inter.

An empirical correction to get 1-4 interactions to reproduce torsion barriers:

$$U_{el1-4}=el14*q_1q_4/R_{14}$$

$$U_{vdw1-4}=evdw14*[(A/R)^{12}-(B/R)^6]$$

For OPLS
el14=0.5 ; evdw14=0.125

For CHARMm
el14=0.4 ; evdw14=1.

Minimization of energy

* steepest descent
$\Delta \propto -dU/dR$

* conjugate gradient

* Netwon-Raphson
$\Delta \propto H^{-1} dU/dR$

*Molecular dynamics with simulated annealing

$$G(t) = -dU(t)/dR + \gamma V(t) + Y(t)$$

$$X(t+\Delta t) = X(t) + V(t)\Delta t + \Delta t^2 G(t)/2m$$

$$V(t+\Delta t) = V(t) + \Delta t/2m(G(t)+G(t+\Delta t))$$

Monte Carlo is rarely used in inhomogeneous systems.

Solution of X-ray diffraction to determine structures of biomol.

Addition of experimental constraints:

Scattering amplitude :

$$F(k) = \int \rho(r) \exp(ikr) dr$$

$\rho(r)$ - electron density - sum of Gaussians

measured = F^2

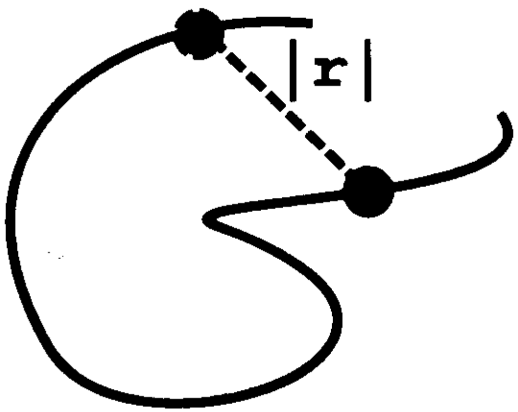
Optimize:

$$U' = U + c(F_{comp} - F_{exp})^2$$

Similar penalty function can be added to NMR NOE constraints (provide estimates of distances:

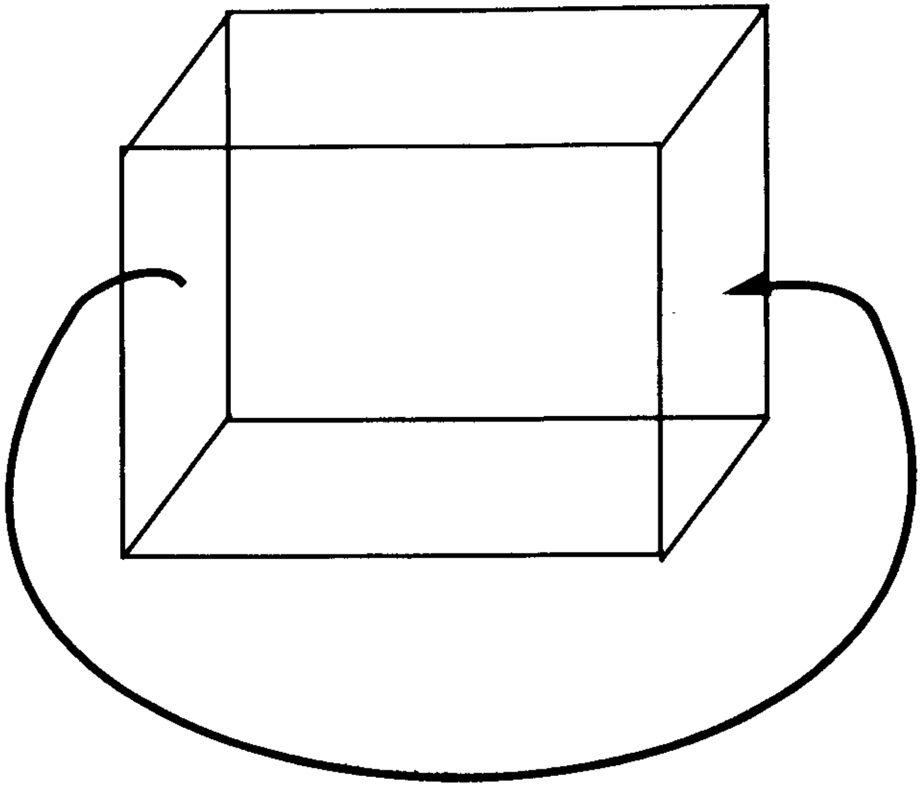
$$P = c(|r| - r_{exp})^2$$

$$U' = U + P$$

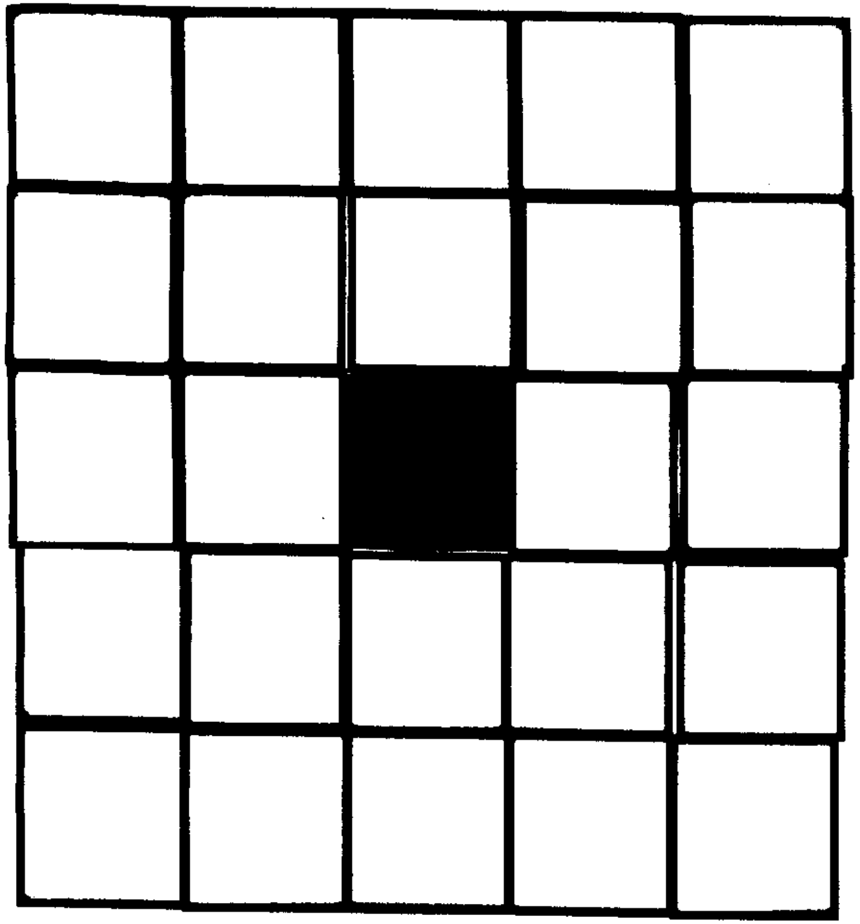


Boundary conditions:

(*) Periodic boundary conditions with cutoffs:



Ewald summation:summing electrostatic and ionic images (P. Ewald, Ann. Phys.64,253(21)



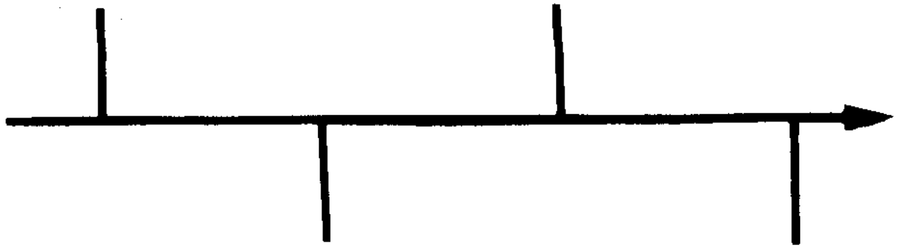
Brief outline of Ewald summation:

The total electrostatic energy

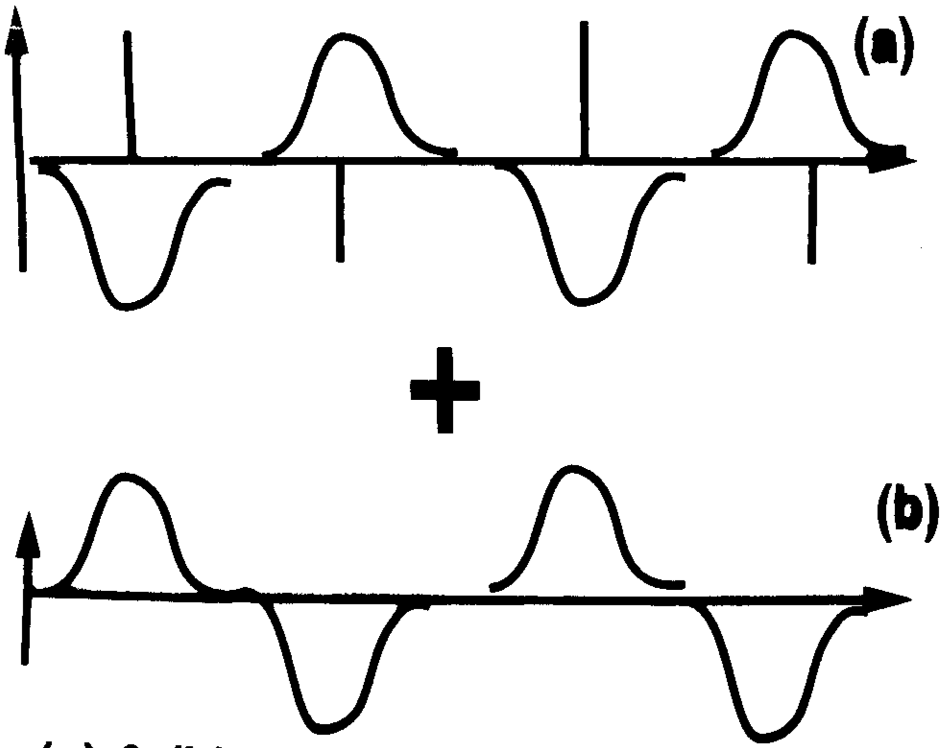
$$U = 1/2\Sigma_n \Sigma_i \Sigma_j q_i q_j |r_{ij}+na|^{-1}$$

where "a" stands for the vector of the cubic lattice and "n" is a vector of integers.
The convergence of the sum is conditional.
The idea in Ewald summation is to replace the original distribution of charges with a distribution that converges faster

Normal distribution of charges:



EWALD SUM



(a) & (b) summed separately

where the cancelling distribution for the i–th charge is:

$$\rho(r) = (-q_i\, k^3/\pi^{3/2})\exp(-k^2 r^2)$$

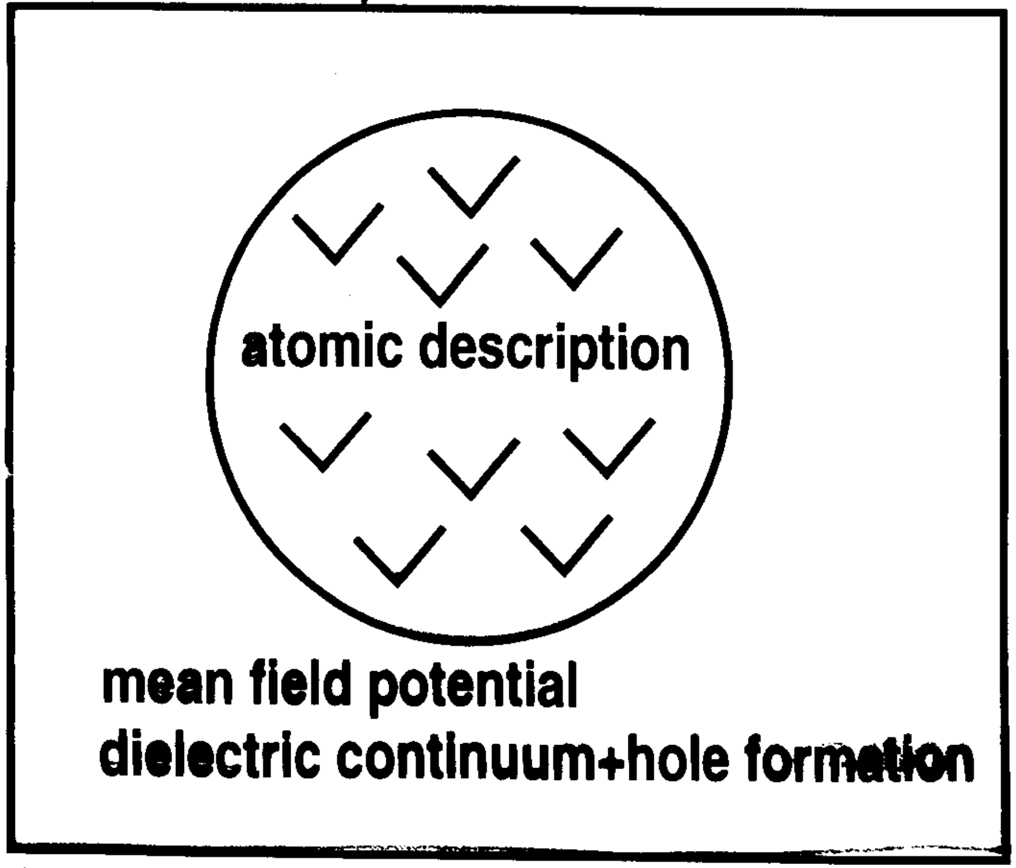
k is an arbitrary parameter. Adding and substracting the charge distribution does not change (in principle) the result. However, as the series is only conditionally converged summing up (a) and (b) separately ((b) is summed in reciprocal space) converges.

The result includes the summation of (a), (b), a surface term, and a self energy term. Fast rearrangments of the sums are also available

Other approaches:

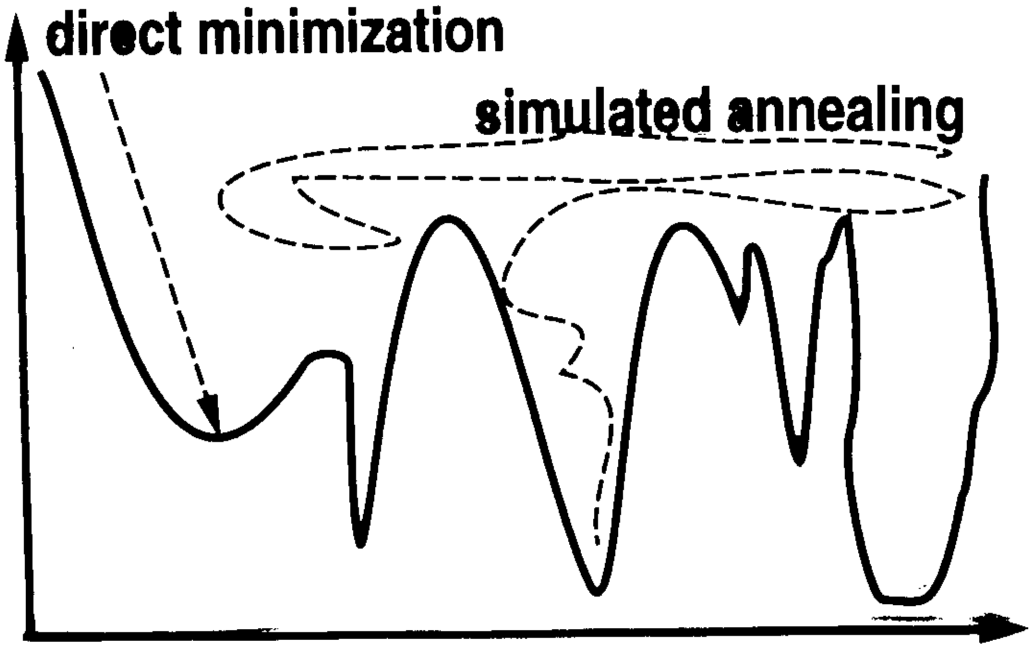
(*) fast multipoles expansion.

(*) stochastic boundaries (Adelman, Berkovitch & McCammon, Warshel, Roux)



Optimization of the energy function is a global optimization problem

The larger the number of experimental constraints is the smaller is the number of the minima. However, the problem is not necessarily easier to solve.



Recent global optimizers

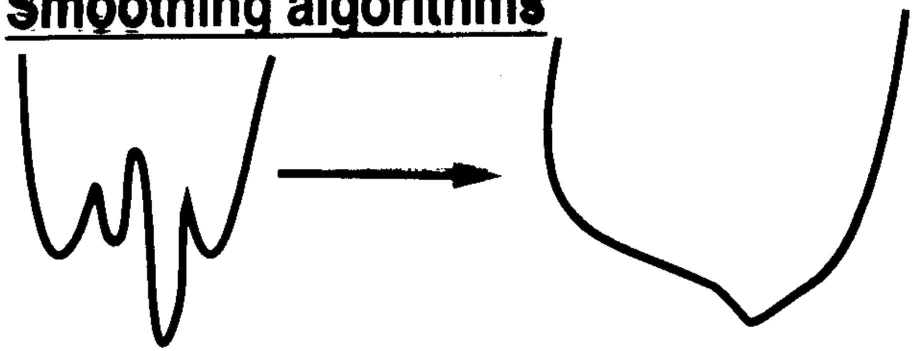
(*) Somorjai, Scheodinger eq.

(*) Piella, Kostrowicki & Scheraga, Diffusion Eq.

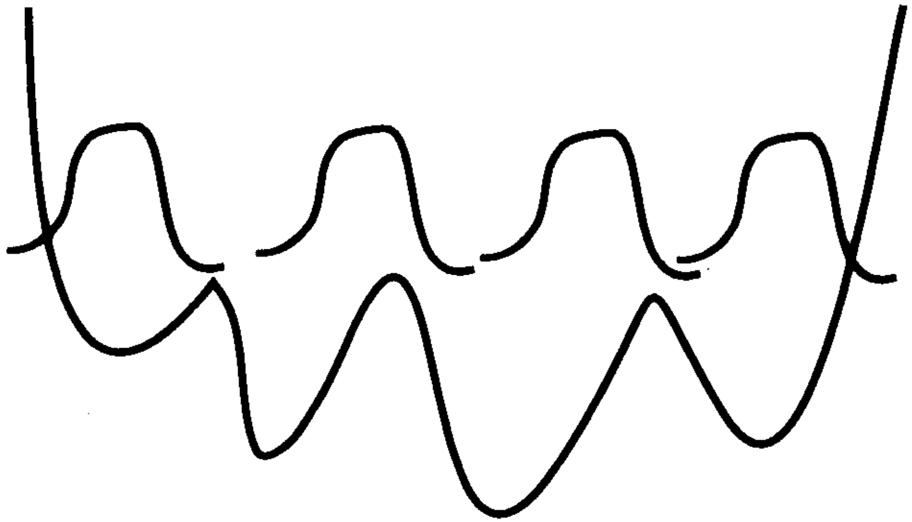
(*) Roitberg and Elber, Locally Enhanced Sampling

(*) Straub et al., Liouville eq.

Smoothing algorithms



(*) Somorjai: Distributed Fixed Gaussian over the energy surface and compute the ground QM state



The hopefully localized ground state is at the neighborhood of the global minimum.

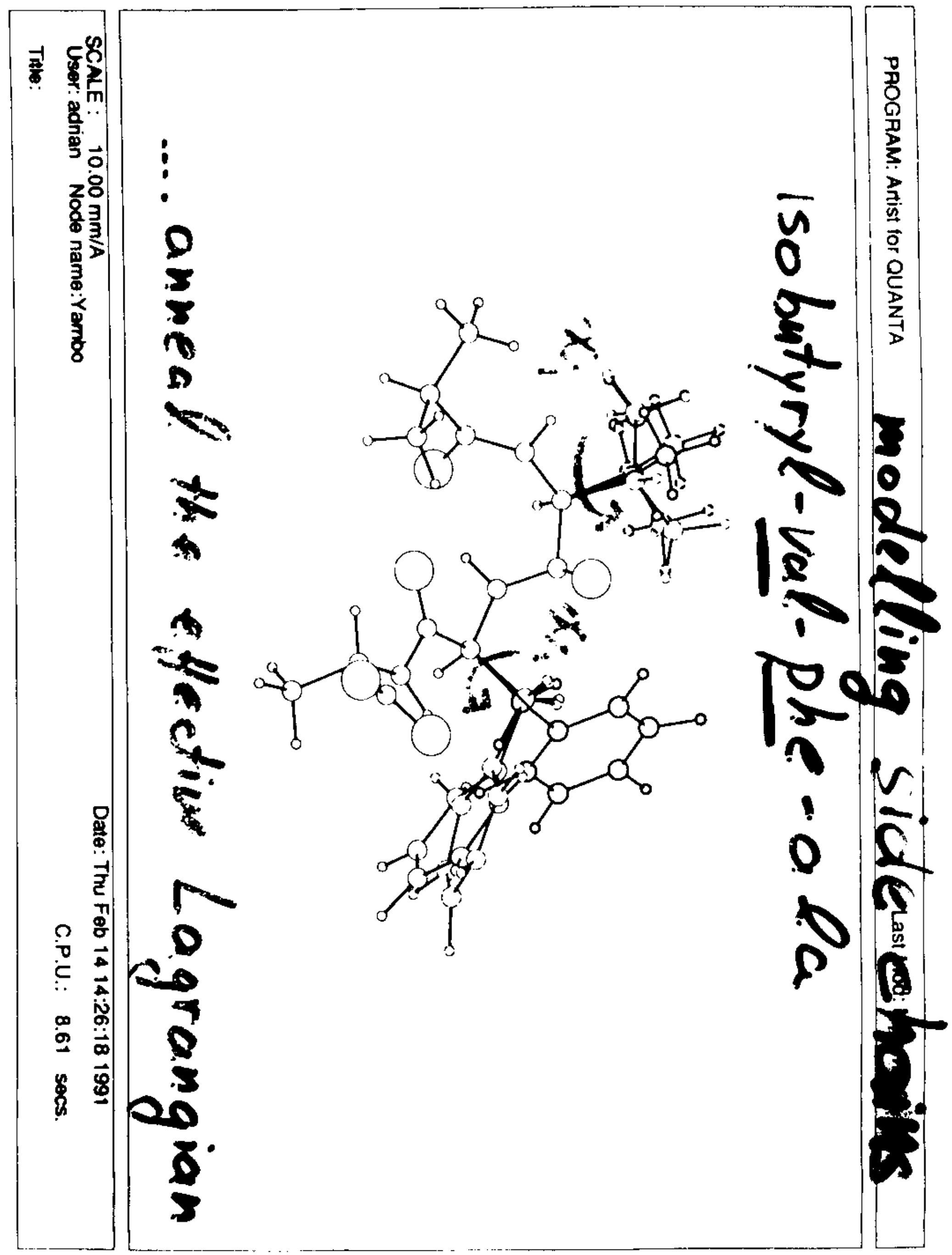
(*) Piela. Kostrowicki & Scheraga: diffusion equation

Solve the diffsuion equation for the potential. In an integral representation, a Gaussian transform of the potential is computed

$$V_{eff}(r_o) = \int V(r) \exp[-a(r-r_o)^2]\,dr$$

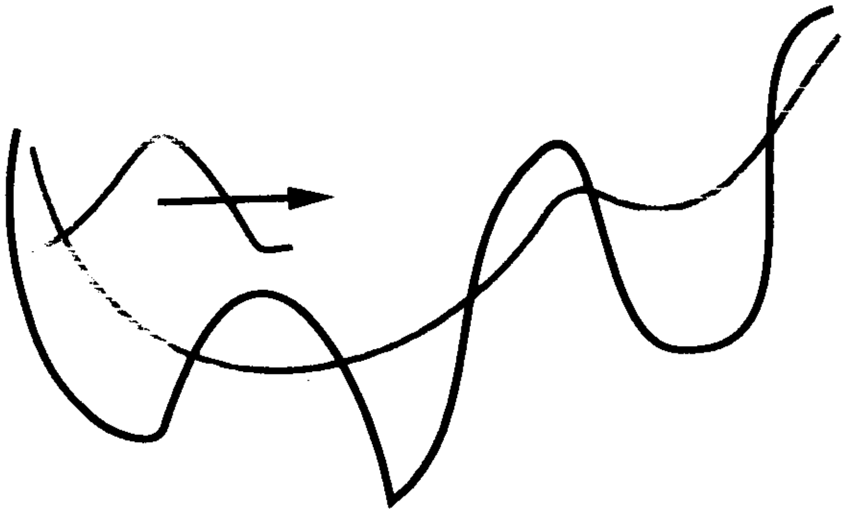
Solve the minimum of the potential in the smoothed potential.

Perform a seqence of minimizations with different a–s (a1>a2>a3>a4) starting from the previous coordinate to initiate a new calculation.



Straub et al.

Solve the Liouville equation for the density represented by a Gaussian with a fixed width



Other ideas:

Shalloway: Different potential transform

$$V_{eff}(r_o) = -\log \int \exp[-aV(r)-b(r-r_o)^2]$$

On lattices (or torsion space):

(*) genetic algorithms
(*) Monte Carlo annealing