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**COLLEGE ON BIOPHYSICS:
FROM MOLECULAR GENETICS TO STRUCTURAL BIOLOGY**

1 - 12 OCTOBER 2001

MOLECULAR DYNAMICS AND MODELLING: AN INTRODUCTION

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These are preliminary lecture notes, intended only for distribution to participants.

Biomolecular modeling: an introduction

Molecular Modeling

- **Study function**: with different potentials
- Molecular dynamics F=MA
- simple/fast: scoring function (pharmaceutical applications), protein folding
- more accurate/expensive: $H\Psi=E\Psi$

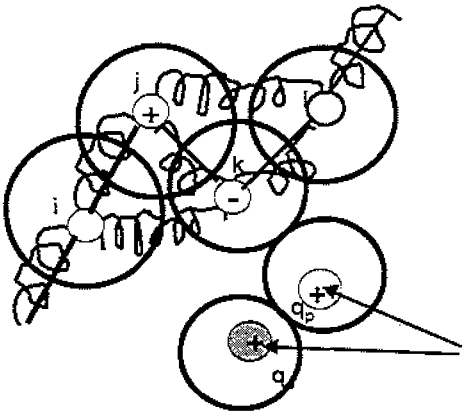
- **Construct molecular models:** Structural Bioinformatics

MD simulations

Atomic motion by integration of Newton eq:

$F_i = M_i A_i = -\nabla_i E$, I=1,...N

E empirically derived

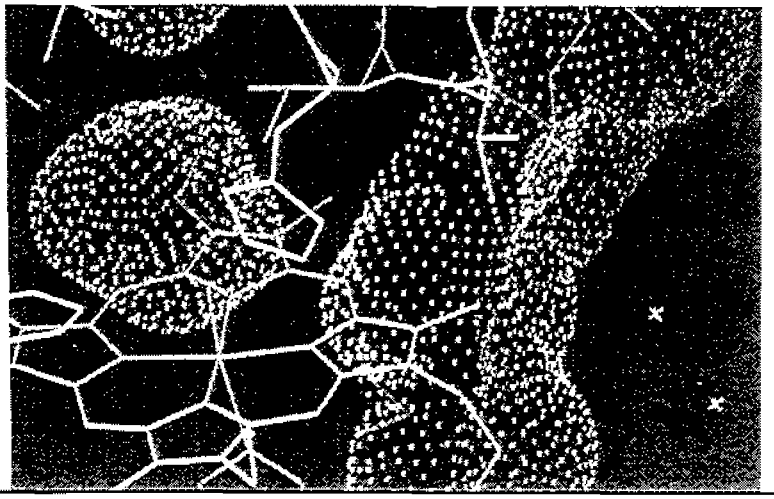


$$E = \sum_{b} \frac{1}{2} k_b (r_{ij} - b_0)^2 + \sum_{\theta} \frac{1}{2} k_\theta (\theta_{ijk} - \theta_0)^2 + \sum_{\phi} \sum_{n} k_n \left[1 + \cos(n\phi_{ijkl} - \phi_0)\right]$$

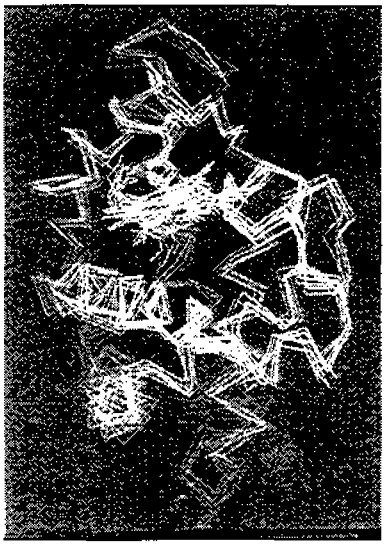
$$+ \sum_{lm} \frac{q_l q_m}{4\pi\varepsilon_0 r_{lm}} + \sum_{op} 4\varepsilon \left(\left(\frac{\sigma}{r_{op}} \right)^{12} - \left(\frac{\sigma}{r_{op}} \right)^{6} \right)$$

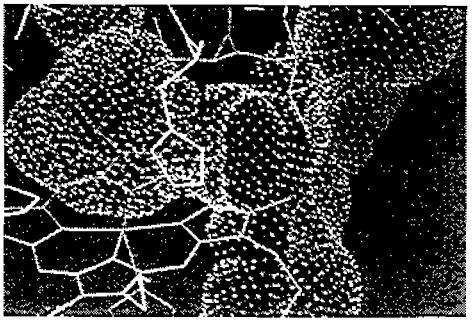
standard biomolecular force field

The beginning of MD in biological systems: Molecular oxygen in myoglobin

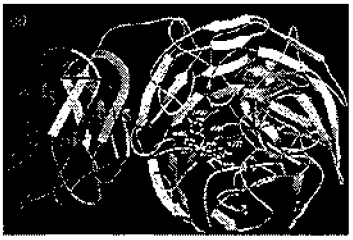


MD conformational fluctuations

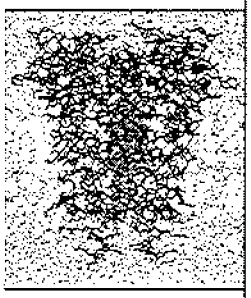




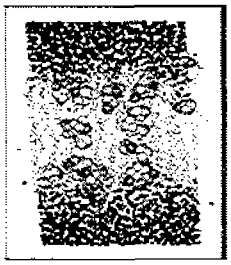
Dimensions of accessible systems



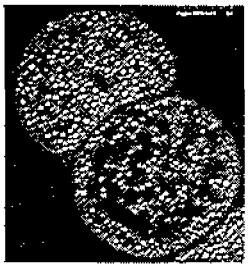
Proteins in water or embedded in membrane
(1000-100000 atoms)



DNA, RNA



membranes



Cells ??

Accessible Time-scale

fs 100 fs -ps µs

Vibrations Rotations

Conformational Changes

ps-s e-transfer reactions | Enzymatic reactions | µs-s

Peptide folding Protein Folding

ns 10µs-s

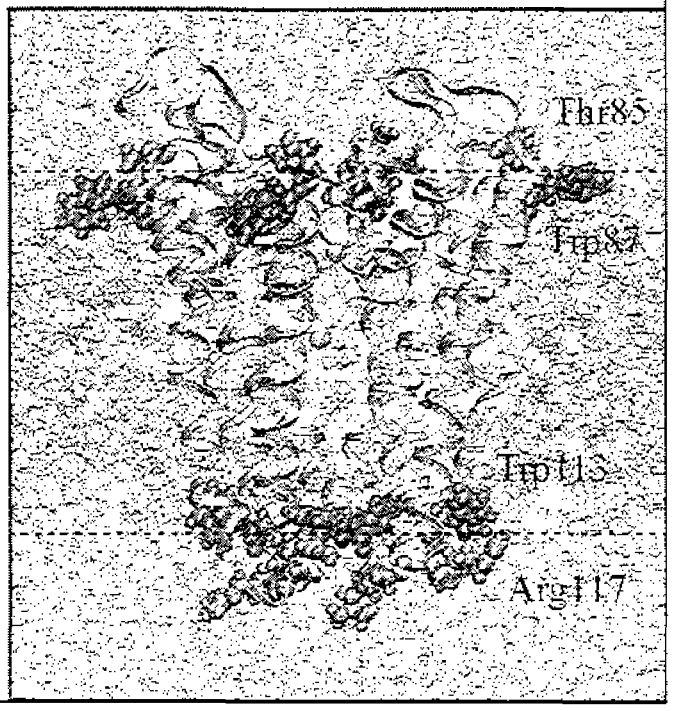
Watching a peptide fold:

•Kollman et al.:

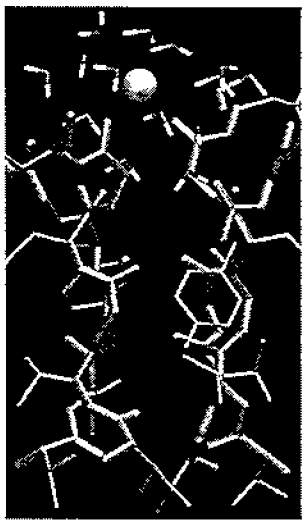
1 μs simulation of small protein:
36AS (12'000 atoms)
(256 nodes T3E ~ 3 months)

MD of the
Potassium Channel

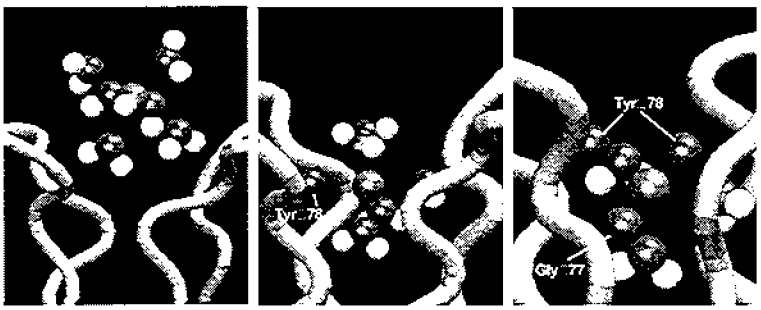
(Guidoni et al..
Biochemistry 1999)



K+ in the Outer Mouth



Na+



Hydration may play a role for selectivity —

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Techniques with simplified potentials

- **Drug/design**

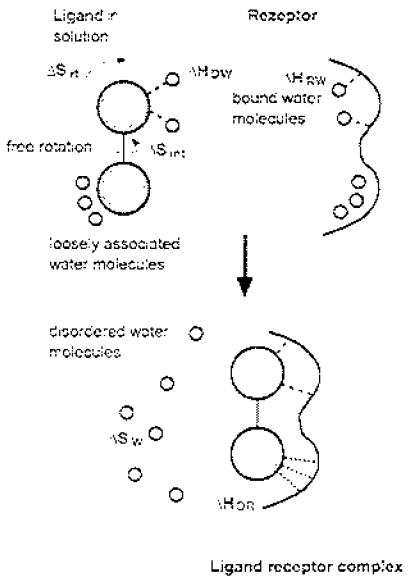
- **Protein Folding**

Drug design

Scoring Functions To estimate Ligand Affinity:

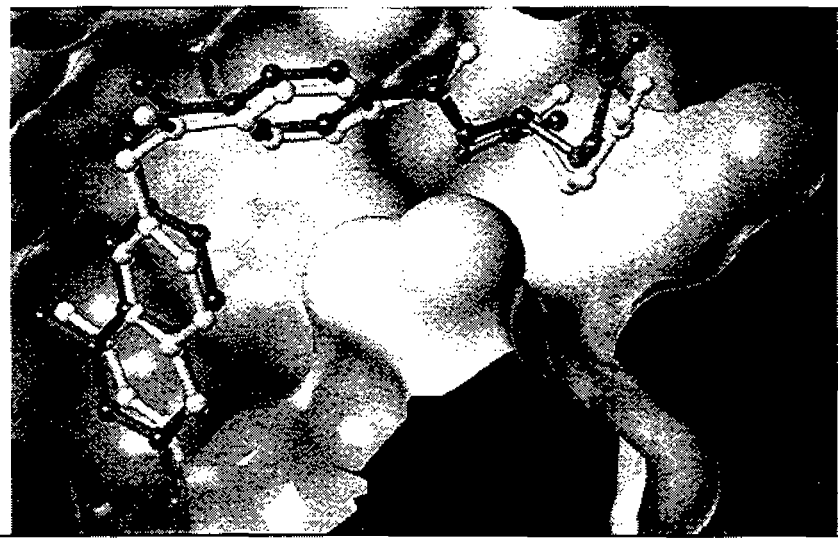
1- docking

2-screening



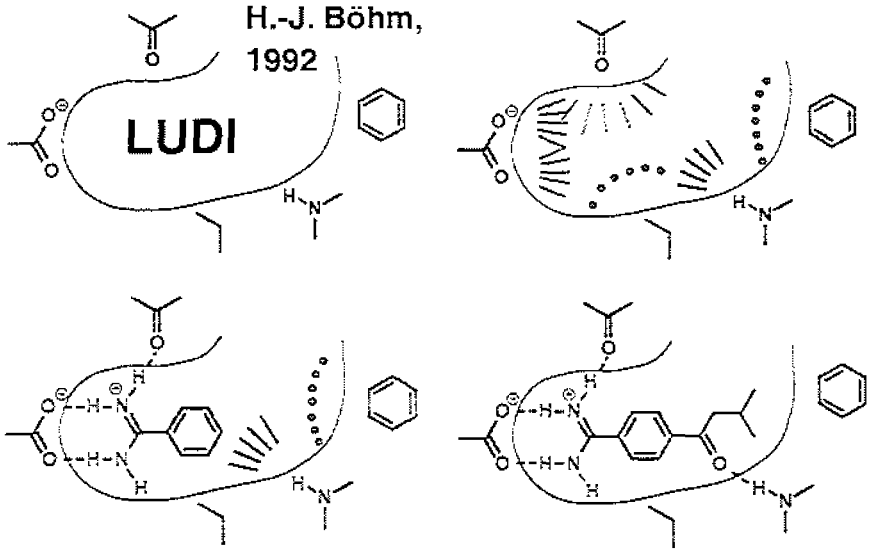
Ligand receptor complex

No physical description of ligand/receptor interactions, but accurate docking: Methotrexate/DHFR binding

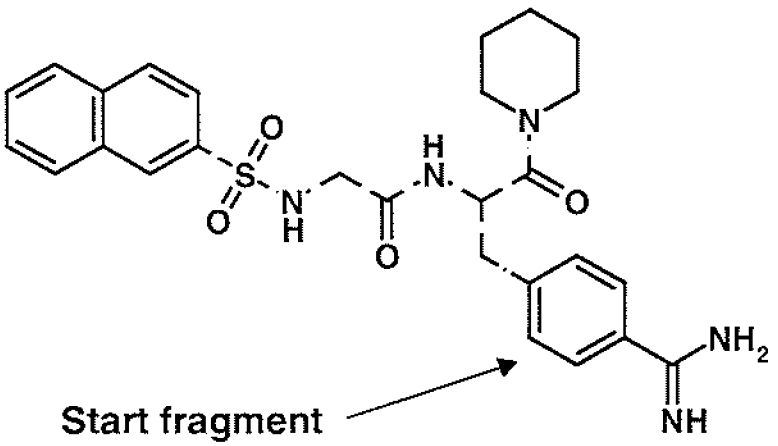


2. Drug-Screening: individuate pharmacophore

H.-J. Böhm, 1992



2. Screening: select molecules from database



Protein Folding

Ab initio Molecular Dynamics

$$F_i = -\nabla_i E, \quad i = 1, \ldots N$$

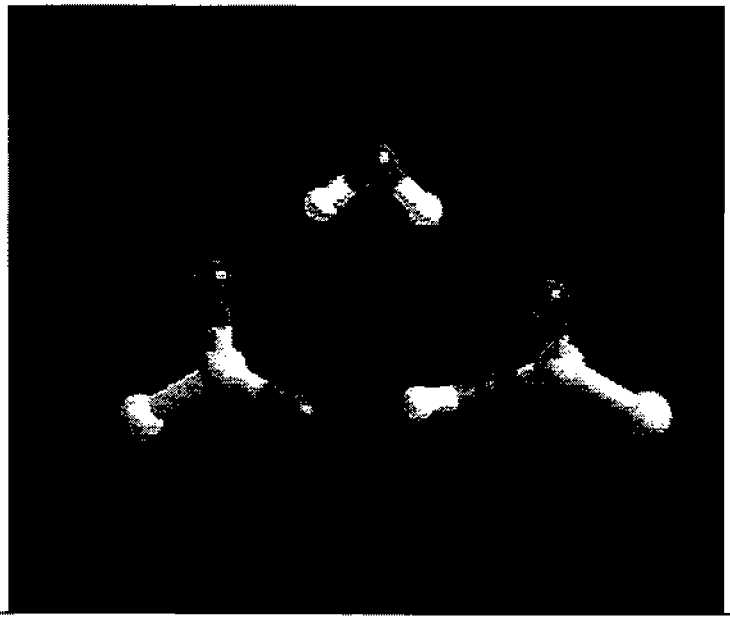
E from first principles:

$$H\Psi = E\Psi$$

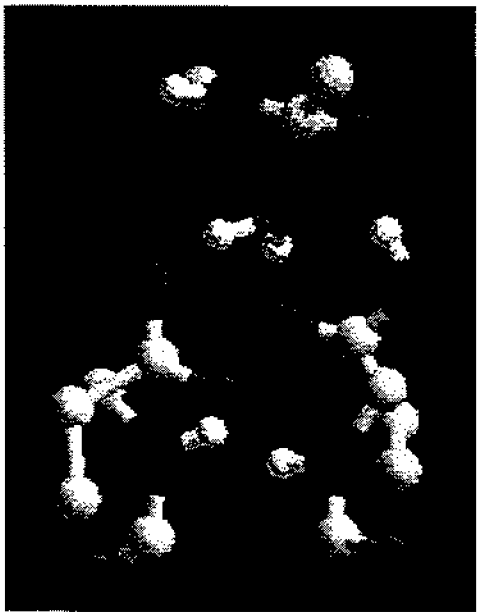
-Parameter Free, Transferability (Water, Meta ions)
-Description of phenomena which depend on electronic structure
-Computational Cost

- Charge Transfer (Xiao et al. J. Mol. Biol. 1998)
- Proton Transfer, Low barrier hydrogen bonds (Frey, Science 1994)
- Polarization effects
- Photoreceptors, Enzyme reaction mechanism
- Spectroscopic Properties (NMR, EPR..)

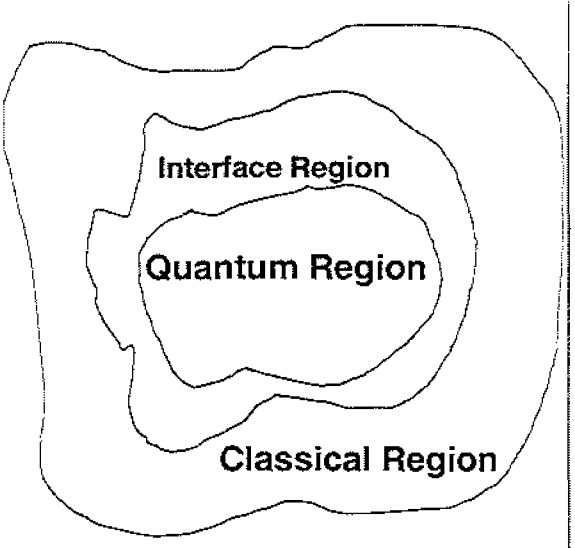
Proton Transfer Processes in HIV-1 protease

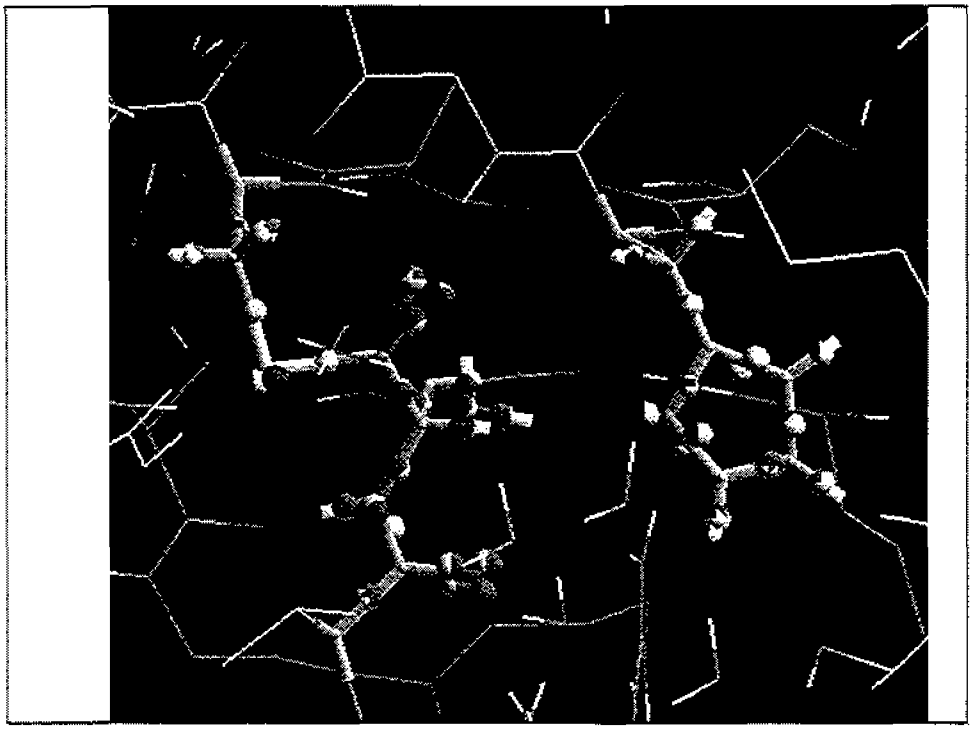


Enzymatic Reaction catalyzed by HIV-1 protease



Mixed Quantum-Classical QM/MM- Simulations



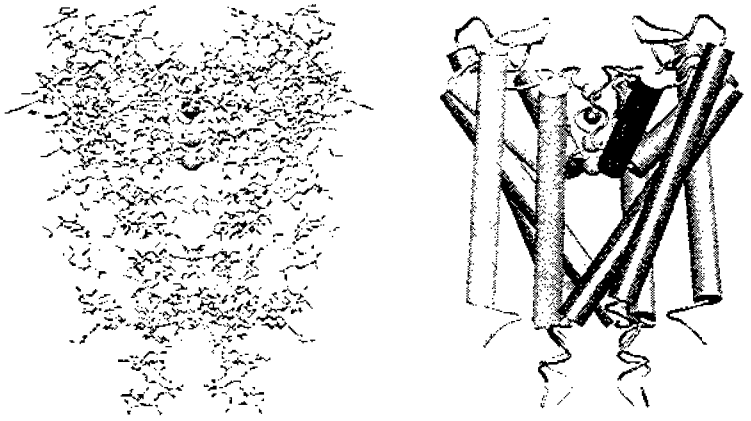


Structural Bioinformatics

- Striking similarities among protein 3D structures
- Construct 3D structures using other protein as template and exploiting structural similarities

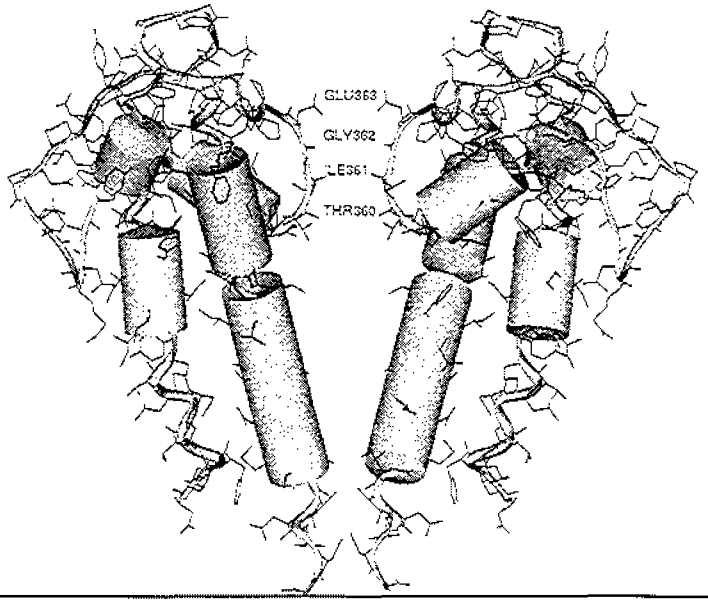
Example: ion channels

The Structure of the K Channel from *Streptomyces lividans*



Doyle *et al. Science* 1998

Homology modeling-based structure



Outline

- Folding of proteins: M. Cieplak, A. Maritan
- MD, electronic structure: K. Schulten
- MD of ion channels: M. Klein

- Structural Bioinformatics: A. Tramontano

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