

Introduction to Molecular Modelling

Concepts and Methods

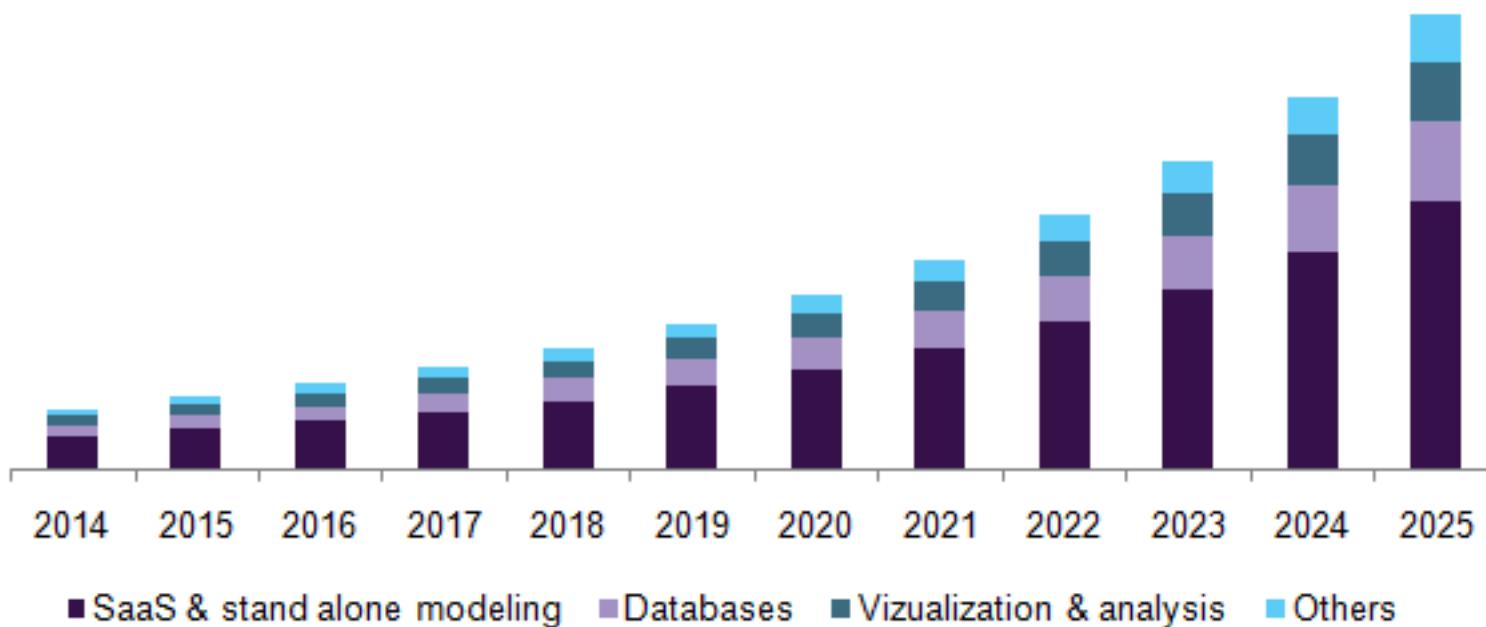
Industry Insights

From : <https://www.grandviewresearch.com/industry-analysis/structural-biology-and-molecular-modeling-technique-market>

“ The global structural biology & molecular modeling techniques market accounted for USD 2.52 billion in 2015 and is expected to grow at a CAGR of 18.2% over the coming years. The market is predominantly driven by rise in the prevalence of chronic diseases with acquired drug resistance that exemplifies the need for new and advanced therapeutics. This has resulted in the high clinical urgency to incorporate structural biology & molecular modeling techniques to develop a new generation of drugs. For instance, in 2011, researchers from the University of Natural Resources and Life Sciences in Austria carried out molecular dynamics simulations to study the activity of humanized antibodies (Ab2/3H6), which is believed to neutralize HIV-1. The results generated through this simulation successfully identified back mutation sites in antibodies to enable antibody immunization without the loss of specificity and binding affinity in them.”

U.S. structural biology & molecular modeling techniques market, by tools, 2014 - 2025 (USD Million)

From : <https://www.grandviewresearch.com/industry-analysis/structural-biology-and-molecular-modeling-technique-market>



Molecular Modelling and Integrative Structural Biology

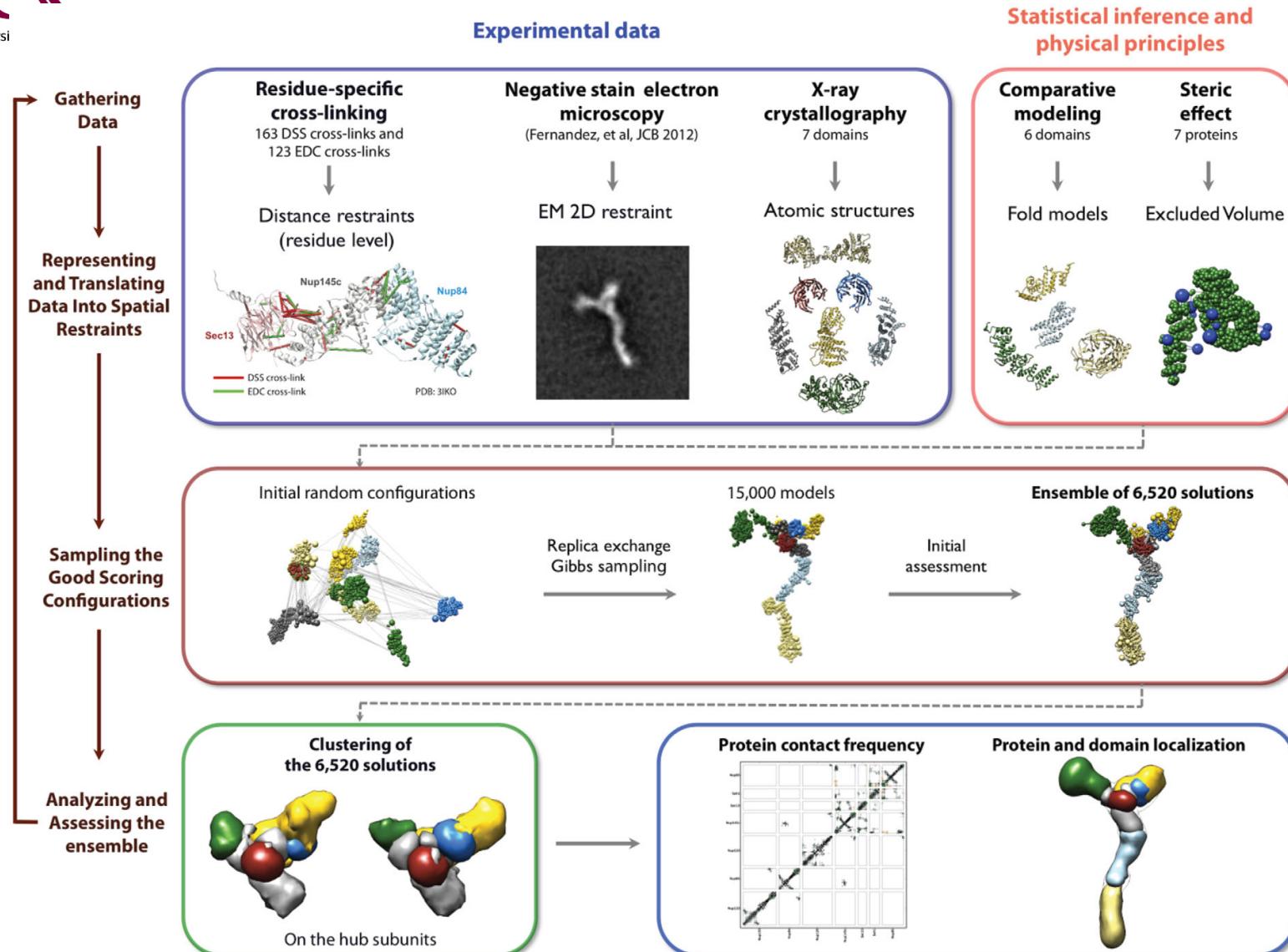


Figure 1. The four stages of integrative structure modeling (see text). These are illustrated by the determination of the Nup84 subcomplex of the yeast NPC.¹⁰

Why and How?

- Hypotheses: (Bio)chemistry
 - Biological functions are related to **interactions** between molecules: proteins, RNA, DNA, lipids, sugars, ligands, ions, solvent.... etc
 - Studying **small parts** of a system help in understanding/predicting the behaviour of the whole system.

Definition

- Molecules => Ensemble of **atoms** interacting through **covalent bonds** or **not**
- Modelling : Not reality but a **model** of “reality”=> *Approximations* !

A field at the interface of Chemistry, Physics, Statistics (Thermodynamics), Computer Science and ... Biology

Recently

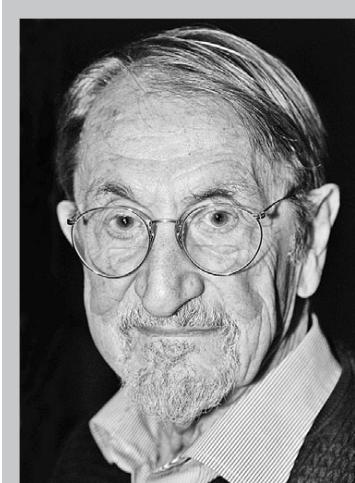
Nobel Prize in Chemistry 2013



© Linda Cicero
Michael Levitt was born in Pretoria in 1947. He studied Physics at King's College London, and got his Ph.D. in Biophysics from the MRC Laboratory of Molecular Biology and Cambridge University. After having worked at the Weizmann Institute, the MRC Laboratory of Molecular Biology, and the Salk Institute, he became Professor of Structural Biology at the Department of Structural Biology, Stanford University School of Medicine in 1987. Today he is the Robert W. and Vivian K. Cahill Professor of Cancer Research. To the honors he had received before being awarded the Nobel prize belong the Federation of European Biochemical Societies Anniversary Prize, being elected as a Fellow of the Royal Society and becoming a member of the US National Academy of Science.



Arieh Warshel was born in 1940 in Kibbutz Sde-Nahum, Israel. He received his Ph.D. in 1969 from the Weizmann Institute of Science, Rehovot, and is currently Distinguished Professor and the Dana and David Dornsife Chair in Chemistry at the University of Southern California, Los Angeles. Photo: Max S. Gerber.



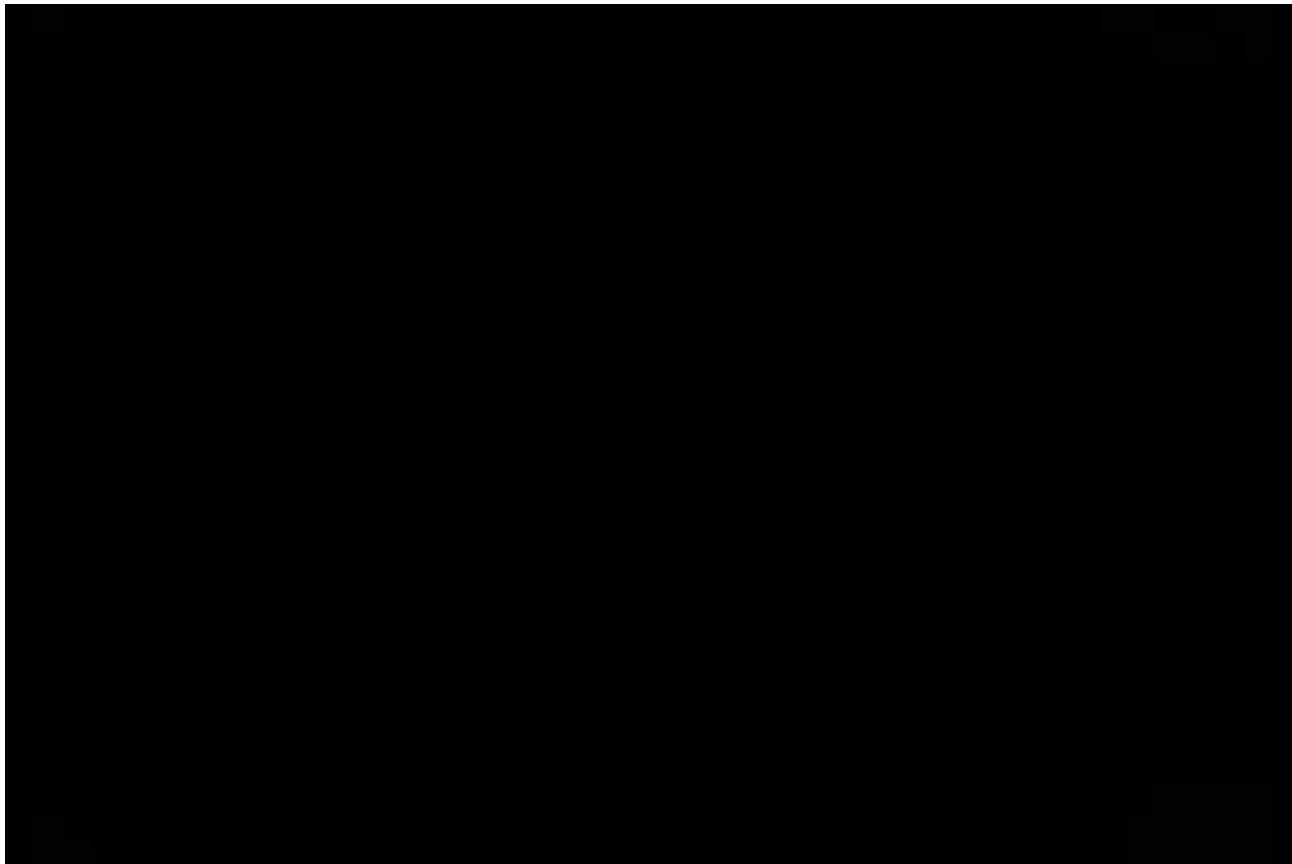
Martin Karplus was born 1930 in Vienna, Austria, and received his Ph.D. 1953 from the California Institute of Technology. He is currently Professeur Conventionné at the Université de Strasbourg, France, and Theodore William Richards Professor of Chemistry, Emeritus, at Harvard University in Cambridge, Massachusetts, USA. Photo: P. Badge.

For the development
of multiscale models
for complex chemical
systems

A few key points

- Expérimentalement
 - Début cinquante:
 - Séquence primaire d'une protéine : l'insuline par Sanger
 - Début soixante:
 - Structure 3D d'une protéine: hemoglobine (Kendrew et al) et myoglobine Perutz et al.
 - 1965 :le lysozyme.
- Théoriquement
 - Pauling et Corey:
 - Structure secondaire
 - 1965: Ramachandran
 - Carte [■■■] acides aminés modèle de sphères dures.

- https://www.youtube.com/watch?v=_hMa6G0ZoPQ



- Expérimentalement
 - Depuis :
 - > 140000 structures de macromolécules biologiques : protéines, fragments d'ADN, complexes ADN-protéine, complexes membranaires, Ribosome

Simulations meet Experiment

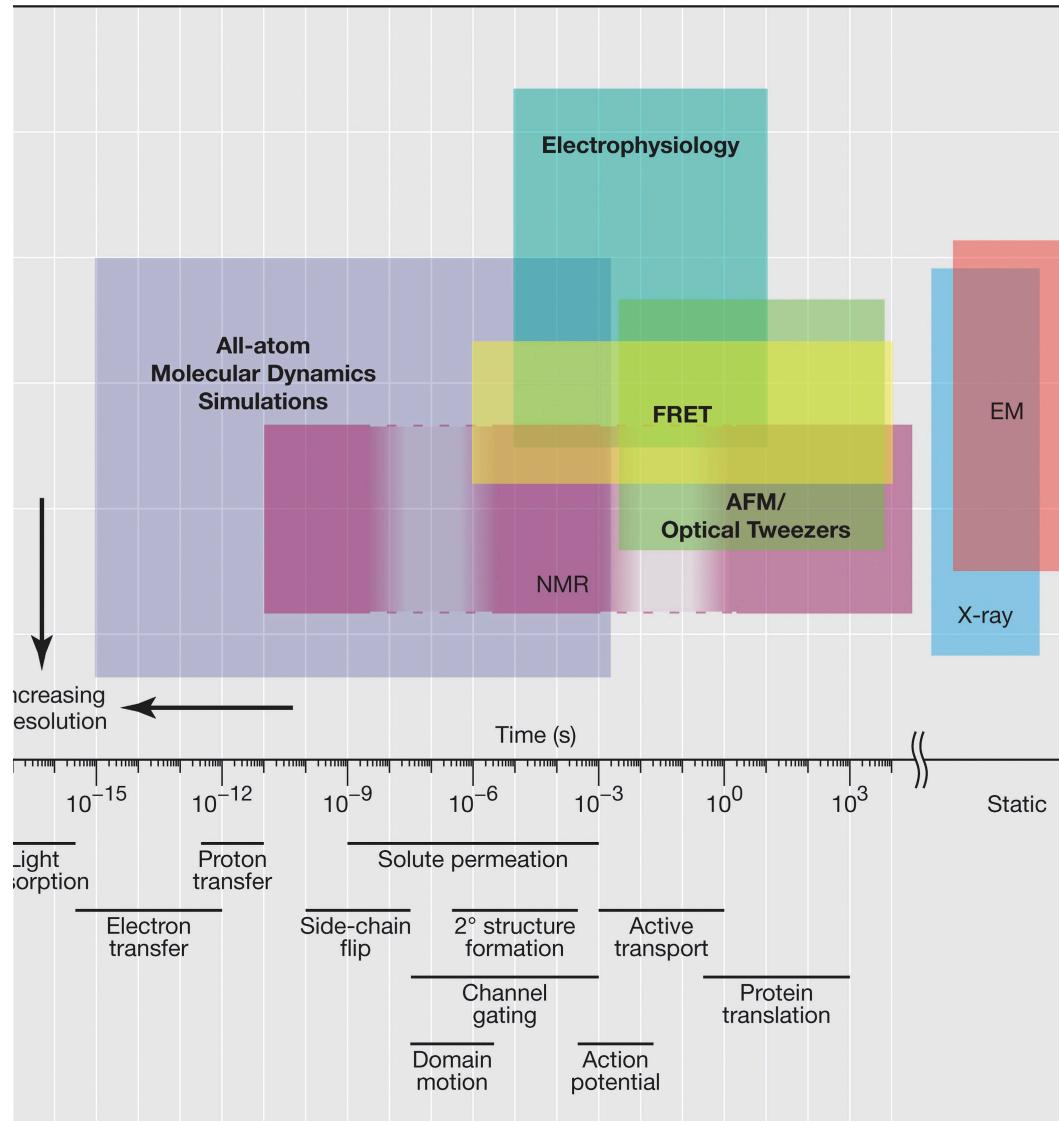


Figure 1. Spatiotemporal resolution of various biophysical techniques. The temporal (abscissa) and spatial (ordinate) resolutions of each technique are indicated by colored boxes.

- Théoriquement:
 - Depuis: Etude de macromolécules: repliement de protéines sur des échelles de temps ~micro voire milliseconde



Available online at www.sciencedirect.com



Current Opinion in
Structural Biology

Long-timescale molecular dynamics simulations of protein structure and function

John L Klepeis¹, Kresten Lindorff-Larsen¹, Ron O Dror¹ and David E Shaw^{1,2}

Published May 31, 2010

228

Biophysical Journal Volume 108 January 2015 228–229

Perspective

New and Notable

Beating the Millisecond Barrier in Molecular Dynamics Simulations

Frank Noé^{1,*}

In such a model, the rate constant that is measurable by ensemble kinetics experiments is given by the sum of folding and unfolding rate constants, $k = k_{\text{fold}} + k_{\text{unfold}}$. In protein folding under

Perspectives on: Molecular dynamics and computational methods

Exploring atomic resolution physiology on a femtosecond to millisecond timescale using molecular dynamics simulations

Ron O. Dror,¹ Morten Ø. Jensen,¹ David W. Borhani,¹ and David E. Shaw^{1,2}

¹D.E. Shaw Research, New York, NY 10036

²Center for Computational Biology and Bioinformatics, Columbia University, New York, NY 10032

OBJECTIF:

**Comprendre et éventuellement prédire
les propriétés conformationnelles,
énergétiques, dynamiques des molécules**

Domaines d'application de la modélisation moléculaire

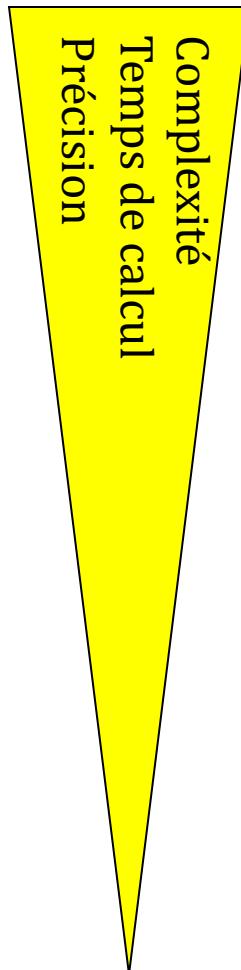
- Détermination de la structure des protéines
- Prédiction de la structure des protéines
- Ingénierie des protéines
- Repliement / Mérepliement des protéines
- Hydratation, dynamique et mouvements macromoléculaires
- Conception de médicaments (drug design)
- Etudes des lipides et des membranes
- ...

Besoins de base en modélisation moléculaire

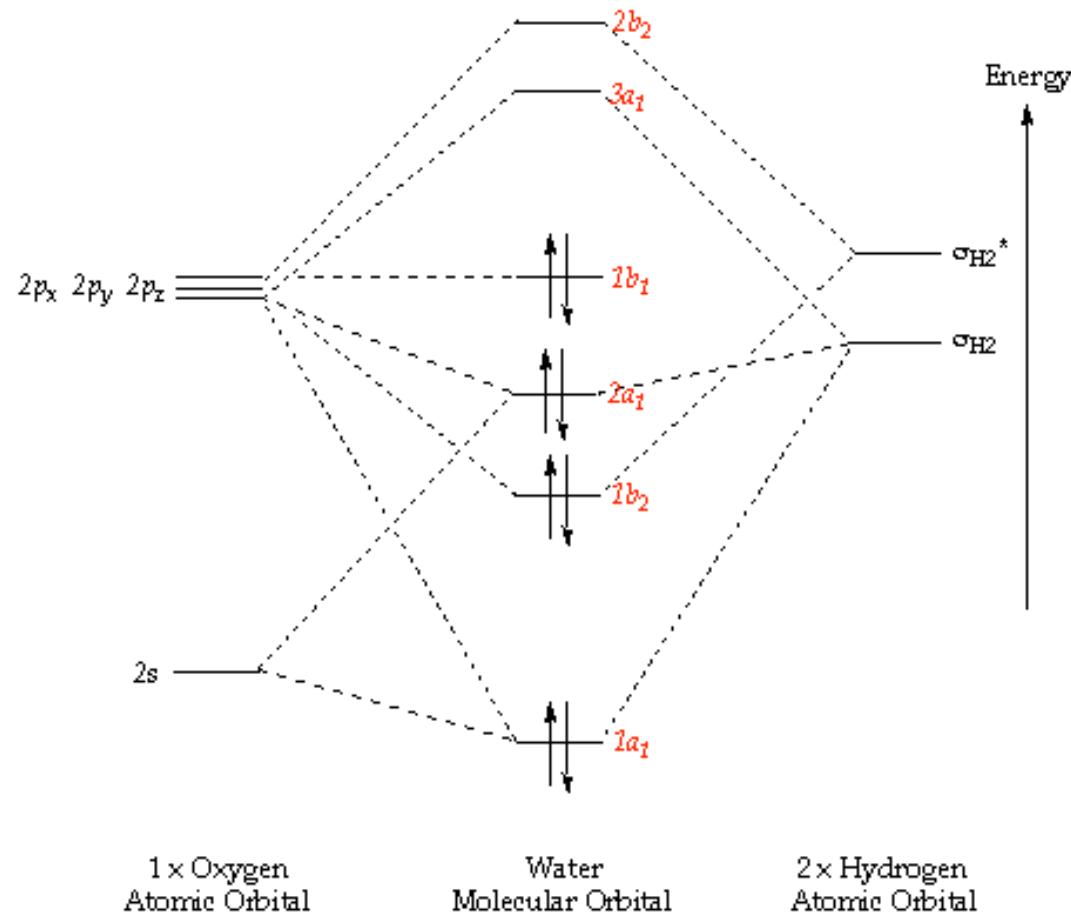
- Evaluation de l' **énergie potentielle**
 - Permet de prédire certaines propriétés des molécules
 - Basée sur le postulat: plus l' énergie potentielle d' une molécule est basse, plus sa conformation est stable
 - Choix du modèle pour la calculer
- Utilisation des ordinateurs
 - Modèles mathématiques permettant le calcul de l' énergie potentielle à partir des coordonnées
 - Algorithmes et procédures informatiques

Choix d' un modèle

- Mécanique quantique
 - prise en compte de toutes les particules de la molécule (électrons (orbitales), noyaux)
- Mécanique moléculaire: modèles empiriques (seulement les noyaux, approximation de Born-Oppenheimer)
 - tout-atome
 - atomes unifiés (seulement les hydrogènes polaires)
 - basés sur les atomes lourds (pas d'hydrogènes)
 - simplifiés :
 - gros grain : résidus représentés par 1,2... particule(s)
 - “In lattice” : modèles basés sur des grilles
 - ...

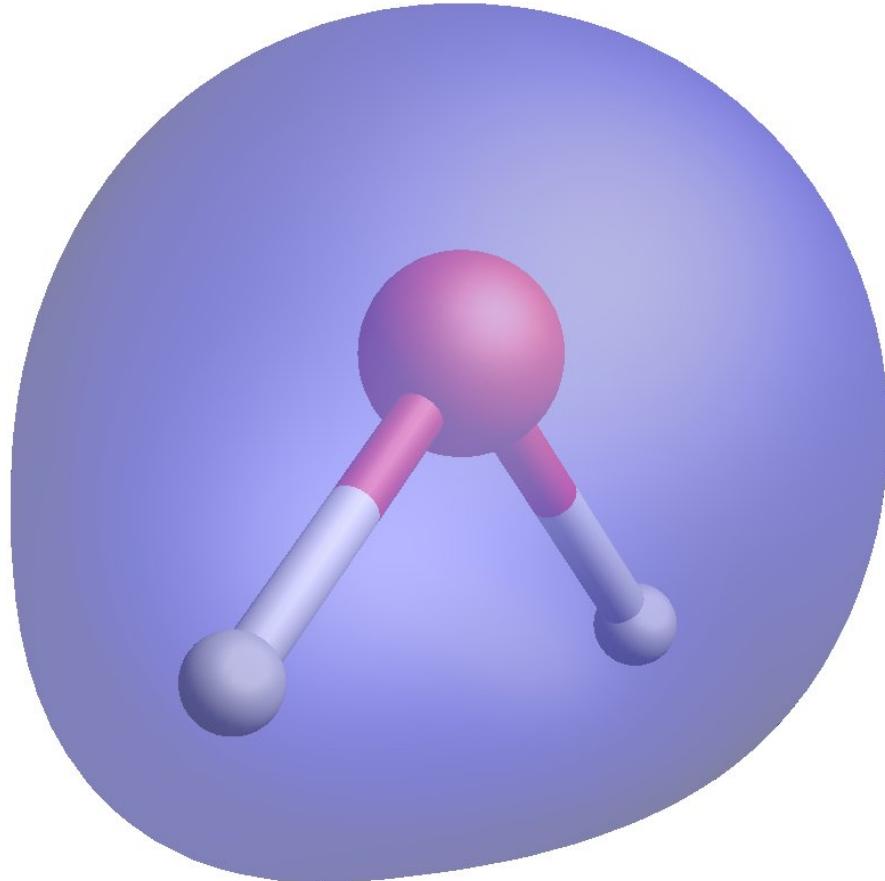


Exemples d'orbitales moléculaires



Exemple d' orbitale

première orbitale
moléculaire d'une
molécule d'eau

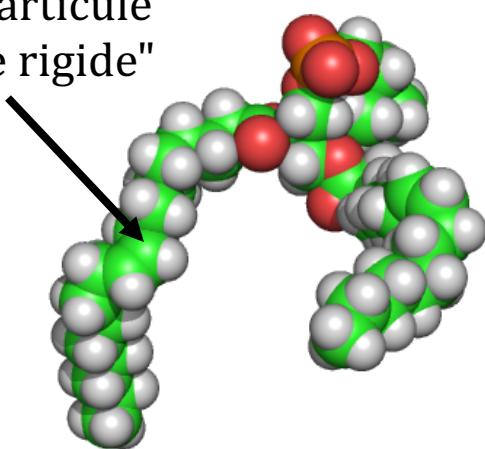


<http://www.staff.ncl.ac.uk/j.p.goss/symmetry/Water/water1.html>

Exemple de modèles de DOPC

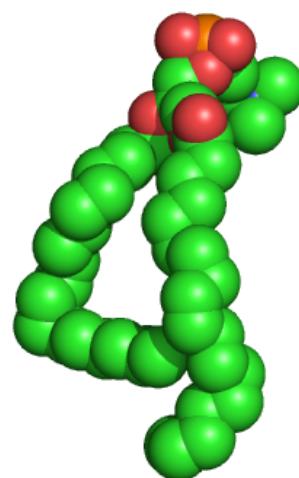
(DOPC = dioleoylphosphatidylcholine)

chaque particule
= "sphère rigide"



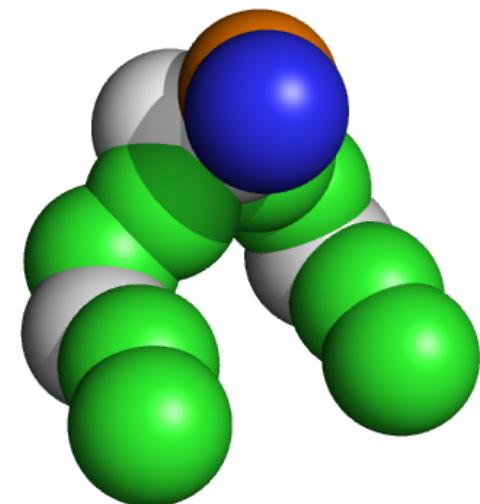
all-atom

138 particules
(CHARMM)



united-atom

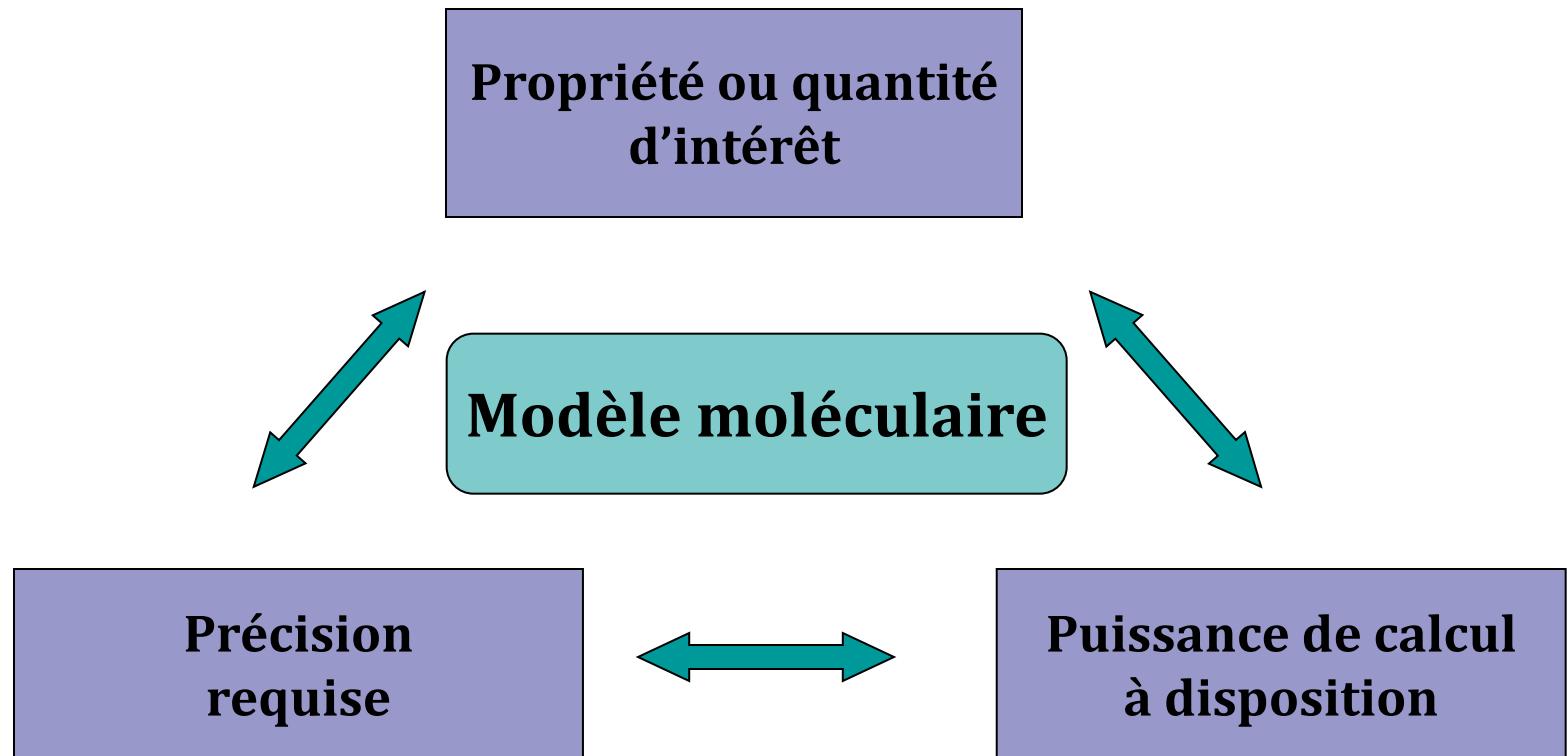
54 particules
(Berger)



coarse-grained

14 particules
(MARTINI)

Choix d'un modèle (2)



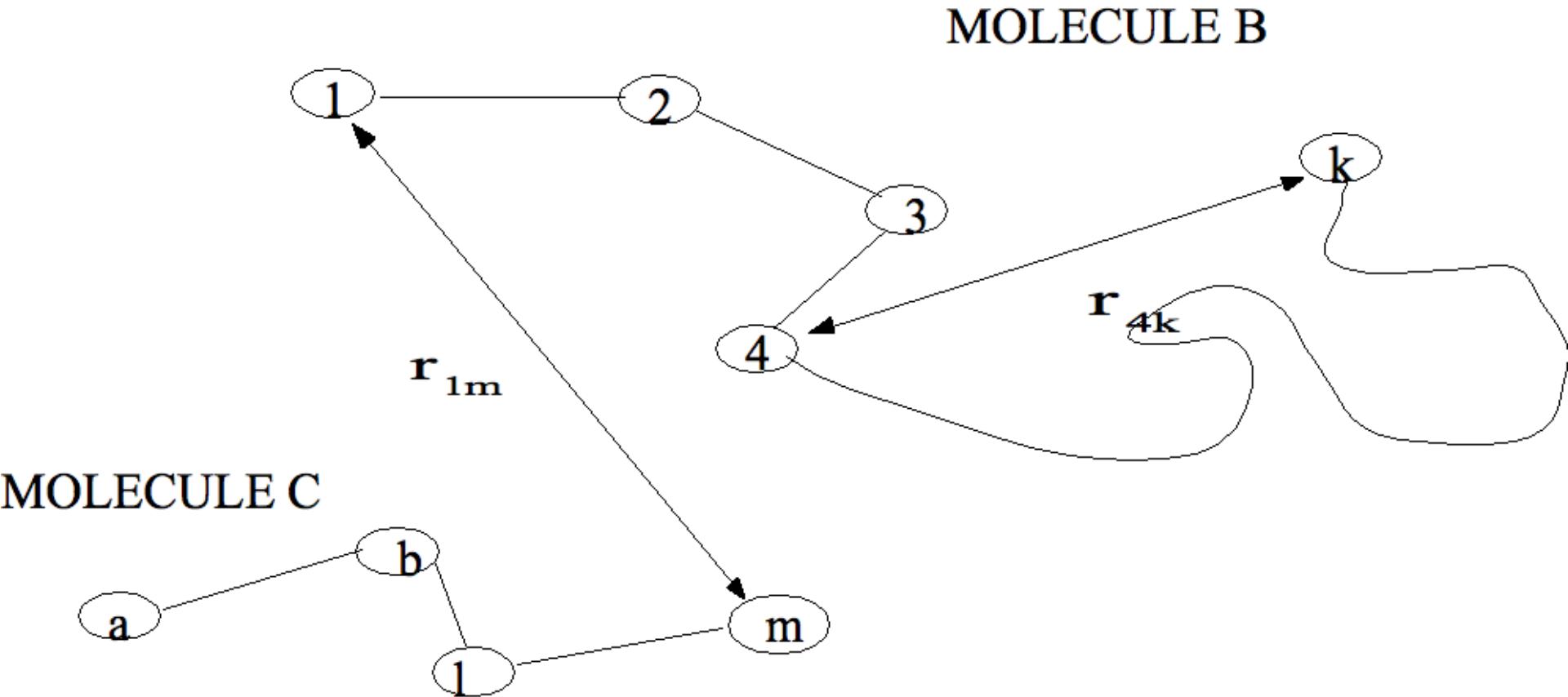
Choix du modèle (3)

- Macromolécules biologiques
 - plusieurs milliers d' atomes (e.g. protéine de 100 résidus ~ 1500 à 2000 atomes)
 - nécessité de simuler un environnement "naturel" (milieu aqueux, bicouches phospholipidiques...)
- ➔ Obligation d' utiliser les champs de forces empiriques (mécanique moléculaire)

Modélisation moléculaire

- Champs de forces empiriques
- Méthodes d'exploration de la surface d'énergie potentielle
 - Minimisation
 - Monte-Carlo
 - Dynamique moléculaire

Molécules : Description



Interactions atomiques

Distinction entre



COVALENTE:
énergie « interne »

NON COVALENTE:
énergie externe

$$E(\vec{R}) = E(\vec{R})_{\text{interne}} + E(\vec{R})_{\text{externe}}$$

Champs de forces empiriques

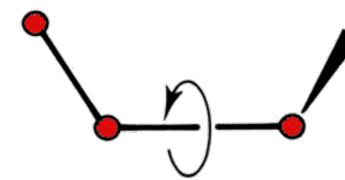
- Définition:
 - jeu de paramètres décrivant les interactions entre atomes dans un système moléculaire
- But :
 - calculer l'énergie potentielle d'un système moléculaire à partir de ses coordonnées
 - énergie potentielle permet la reproduction des propriétés structurales, thermodynamiques ou dynamiques des molécules
- Basé sur:
 - Divers types d'atomes, e.g. O_{hydroxyl}, O_{carbonyl}, C_{planar}, C_{tetra}, ...
 - Divers types de liaisons, angles..., e.g. C=C, C=O, C-N, ...
- 2 propriétés importantes
 - Additivité : les différents termes sont séparables et additifs
 - Transférabilité : à d'autres molécules (petites ou grandes !)

Termes du champ de forces

$$V_{\text{potential}} = V_{\text{bonds}} + V_{\text{angles}}$$

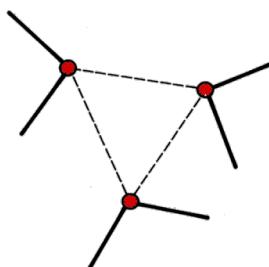


$$+ V_{\text{torsion}}$$

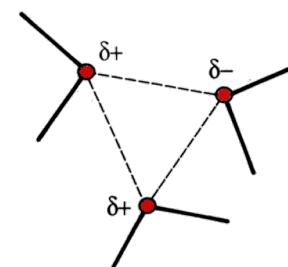


$$+ V_{\text{non-bonded}}$$

termes non liés



Van der Waals



electrostatic

Bond stretching

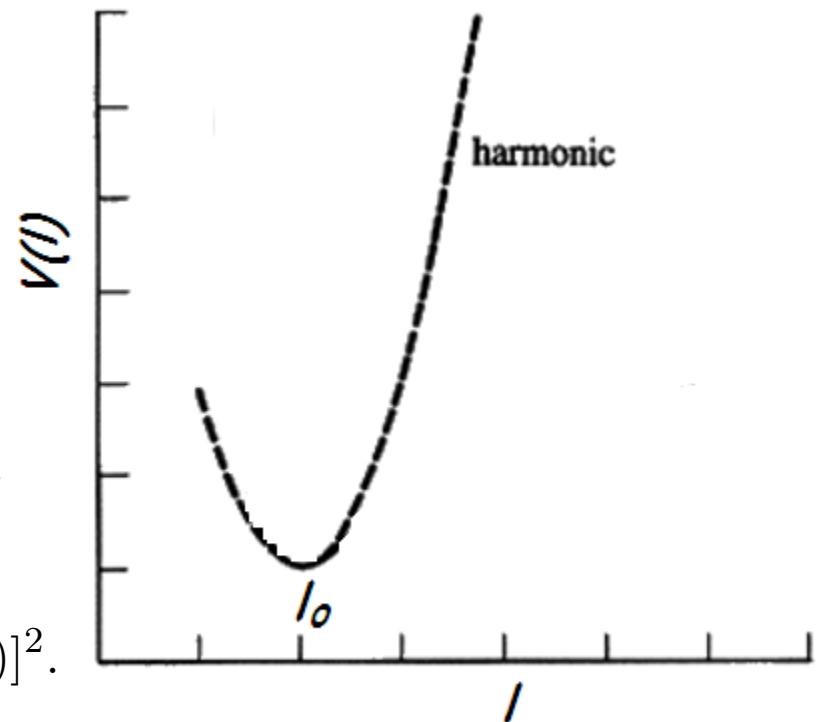


- Harmonic Potential

$$V(l) = \frac{k}{2} (l - l_0)^2$$

The harmonic potential may be replaced by the more realistic Morse potential:

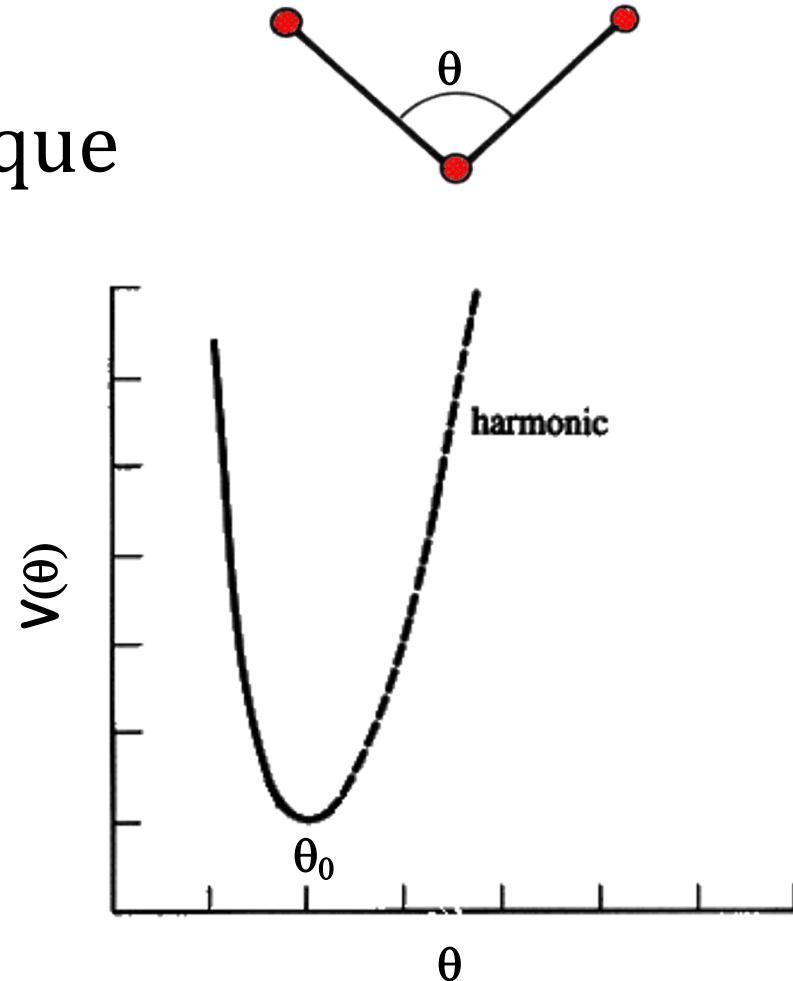
$$V_{\text{morse}}(\mathbf{r}_i, \mathbf{r}_j) = D_{ij} [1 - \exp(-\beta_{ij}(r_{ij} - b))]^2.$$



Déformation des angles

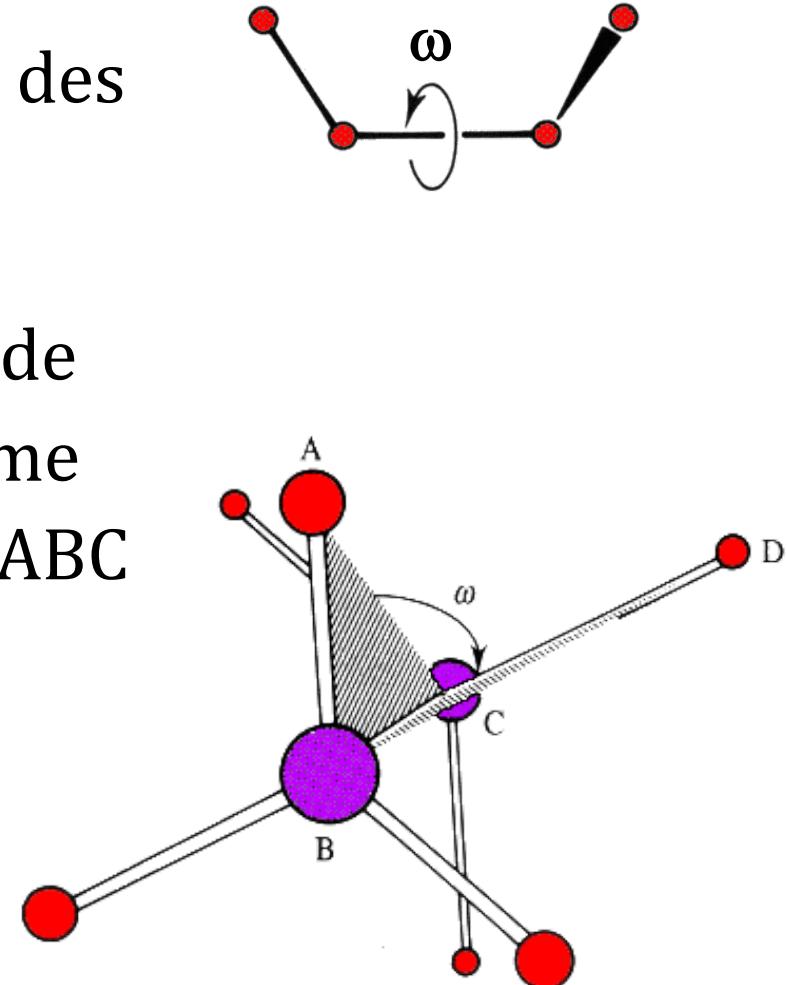
- potentiel harmonique

$$V(\theta) = \frac{k}{2}(\theta - \theta_0)^2$$



Termes de torsion

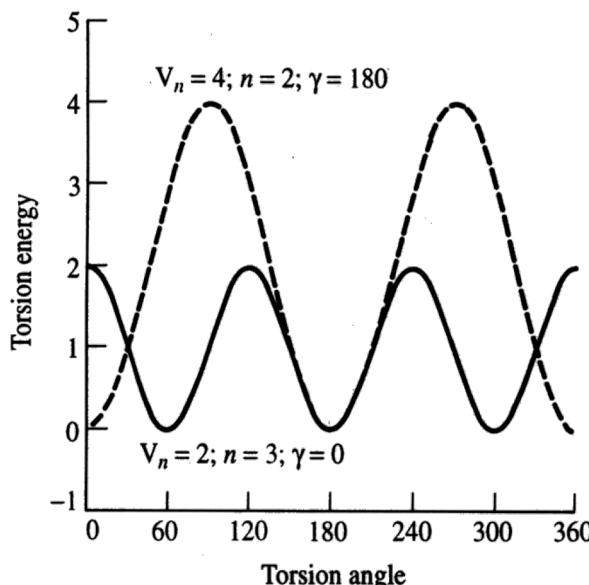
- Décrivent la rotation autour des liaisons
- L'angle de torsion ω autour de la liaison B-C est défini comme étant l'angle entre les plans ABC et BCD
- V_{torsion} doit présenter des minima multiples



Termes de torsion (2)

- Généralement exprimés avec un développement limité en cosinus :

$$V(\omega) = \sum_{n=0}^N \frac{V_n}{2} [1 + \cos(n\omega - \gamma)]$$

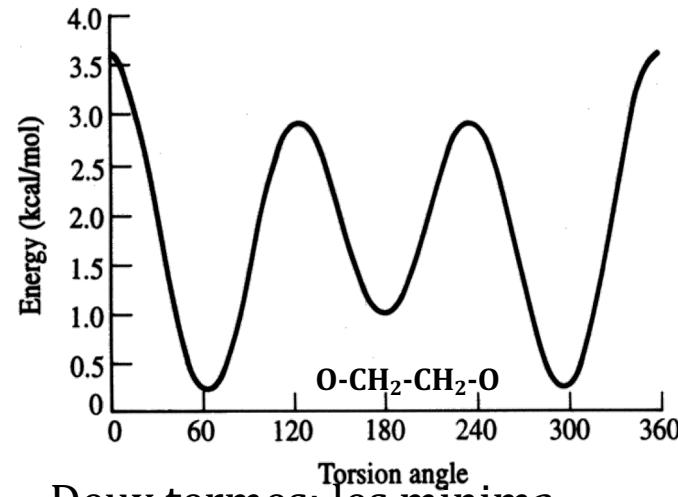


Terme unique : tous les minima sont égaux

12/14/20

avec V_n = "hauteur de la barrière",
 n = multiplicité, γ = phase

Introduction of an extra interaction between atoms i and j , called the 1-4 interaction.



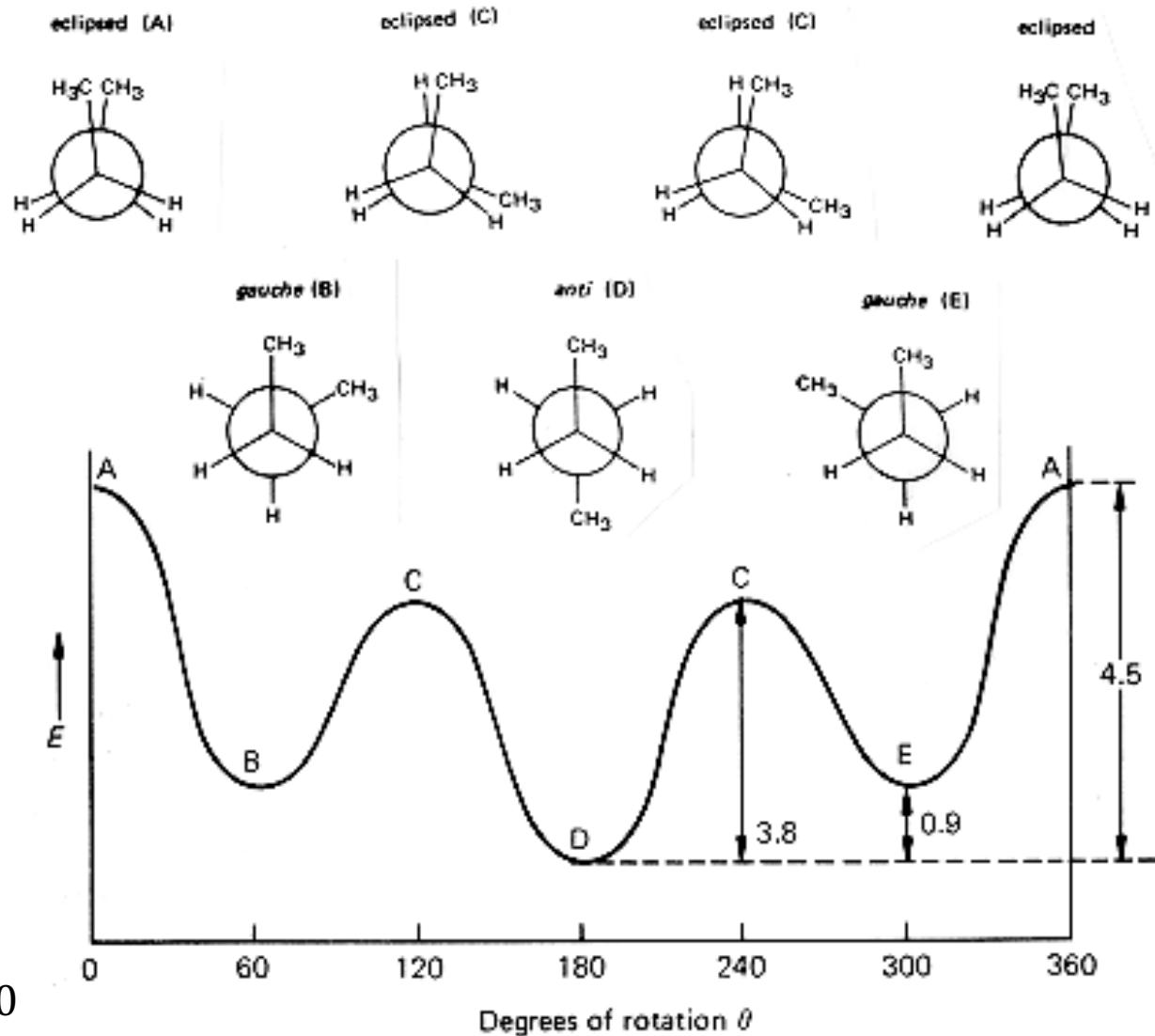
Deux termes: les minima ne sont plus égaux

Instead of 1-4 extra term

- Ryckaert–Bellemans function: a set of periodic functions with different periodicity, or a set of powers of cosine functions,

$$\begin{aligned} U_{proper} &= U_{RB}(\psi) = \sum_{n=0}^5 C_n (\cos(\psi))^n \\ &= C_0 + C_1 \cos \psi + C_2 \cos^2 \psi + C_3 \cos^3 \psi + C_4 \cos^4 \psi + C_5 \cos^5 \psi \end{aligned}$$

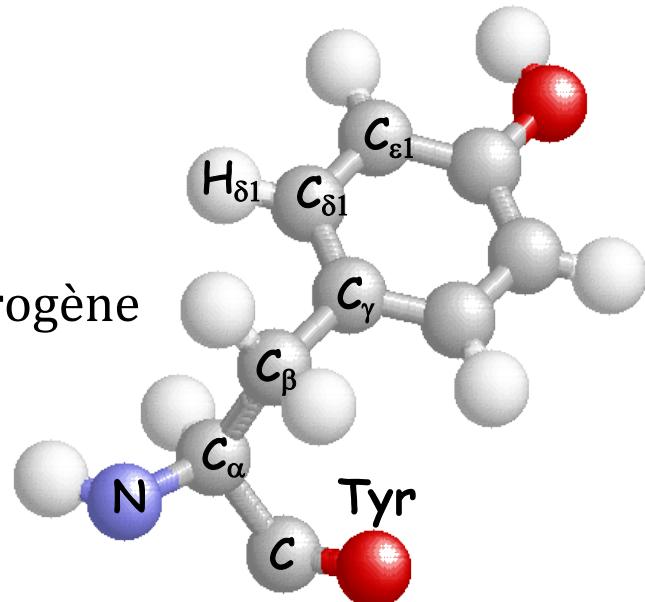
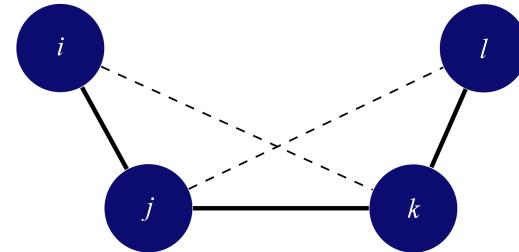
Butane Torsion



Torsions improches

- Mouvements de courbure hors du plan
- Maintient la planarité des cycles aromatiques ou la chiralité des atomes e.g.:
 - Torsion C_α -N-C-C $_\beta$ pour maintenir la conformation tétrahédrique du C_α
 - 35° pour les acides aminés L
 - -35° pour les acides aminés D
 - Torsion $C_{\delta 1}$ -C $_\gamma$ -C $_{\varepsilon 1}$ -H $_{\delta 1}$ pour garder l'hydrogène aromatique H $_{\delta 1}$ dans le plan du cycle
- Souvent sous la forme de potentiels harmoniques:

$$V_{\text{improper}}(\xi) = \frac{1}{2} k_\xi (\xi - \xi_0)^2.$$



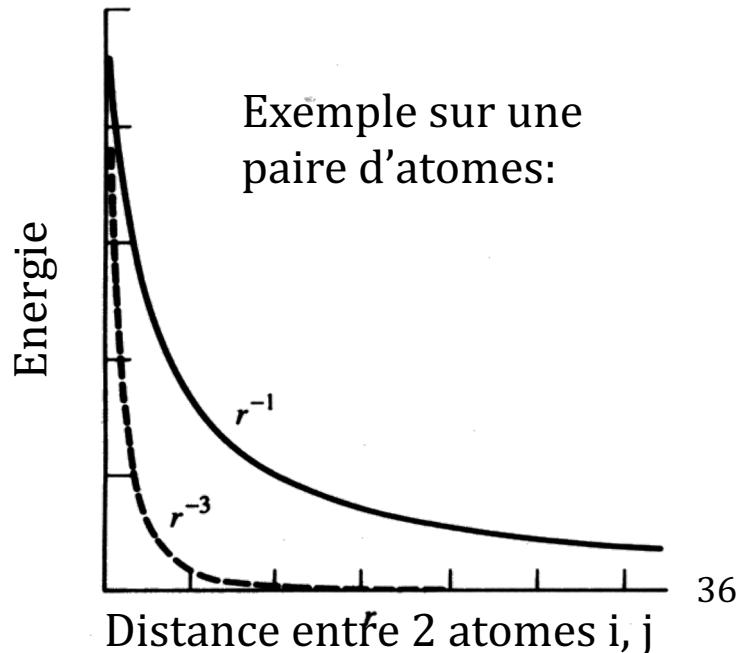
Interactions électrostatiques

- Chaque atome porte une charge partielle (q_i)
- somme des interactions entre paires de “point chargés” (loi de Coulomb)
- Lent déclin en fonction de la distance entre atomes ($\sim 1/r$)
- Contributions à longue portée

$$V_{elec} = \sum_{i=1}^{N-1} \sum_{j=i+1}^N \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

q : charges partielles

ϵ_0 : constante diélectrique du vide

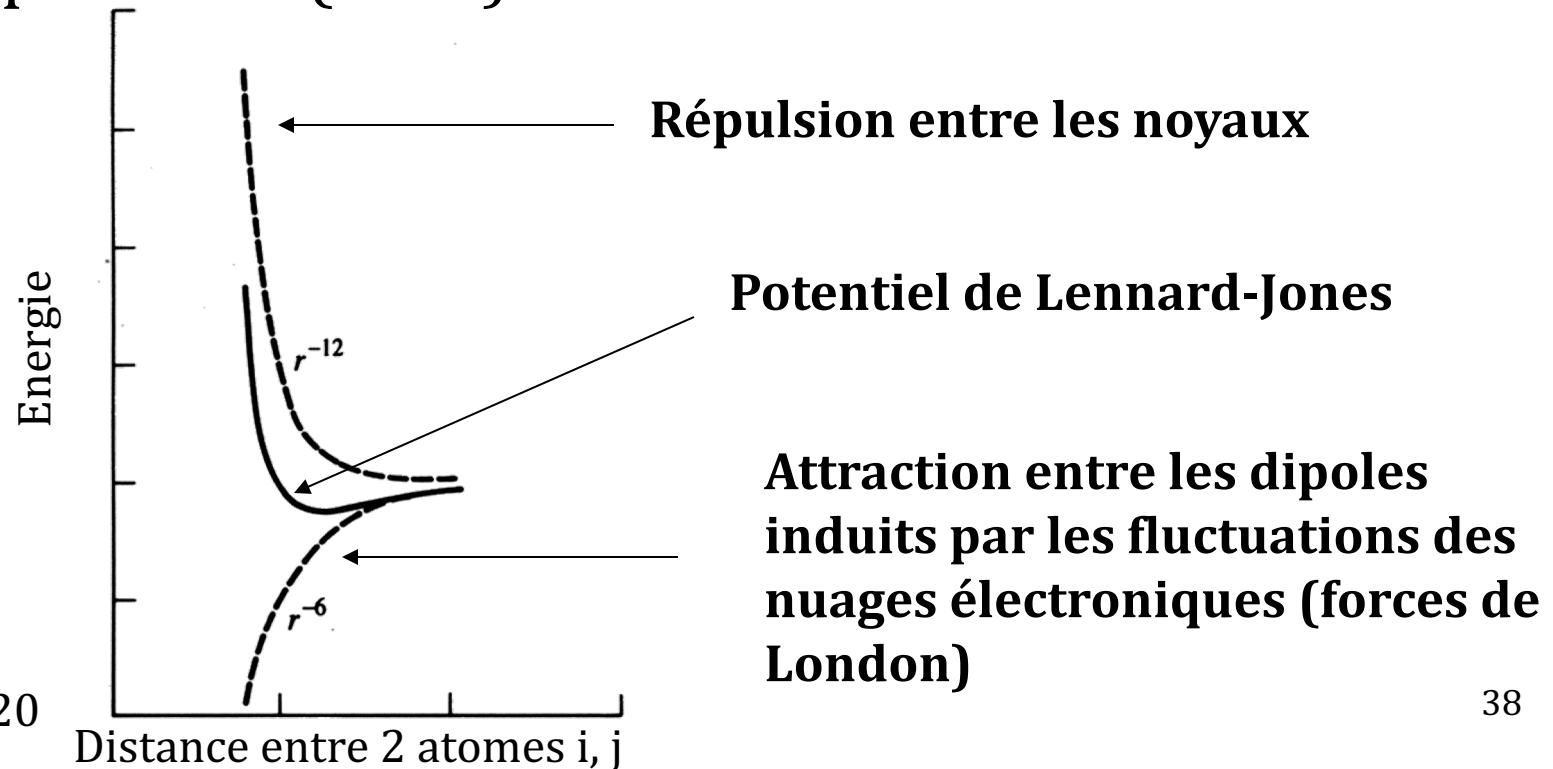


Partial Charges

- Derived from empirical dipole, quadrupole moments of small molecules or QM calculations
- Mulliken Analysis or resulting from the occupation of atomic orbitals: not sufficient
- Better: potential-derived charges.

van der Waals Interactions

- Long-range attractive forces and short-range repulsive forces.
- Frequently modelled by Lennard-Jones potential (6-12)



Lennard-Jones Potential

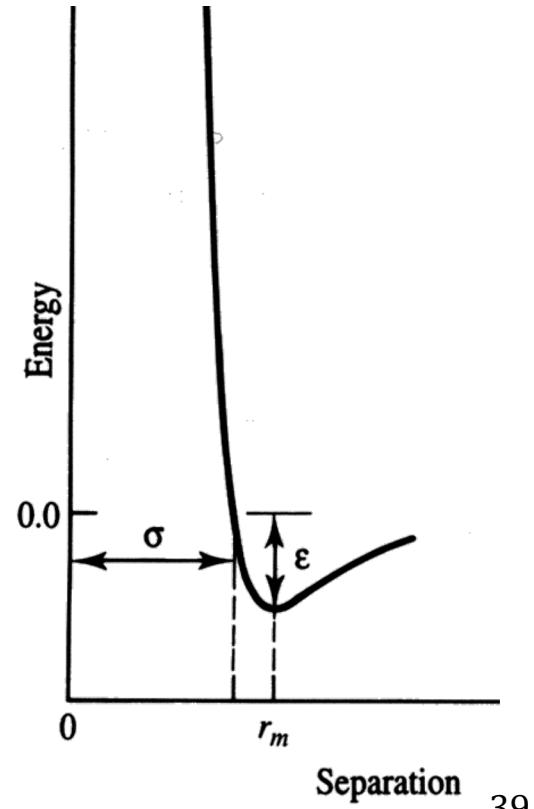
$$V_{L-J} = \sum_{i=1}^{N-1} \sum_{j=i+1}^N 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]$$

σ_{ij} : distance où $V_{LJ}=0$

ϵ_{ij} : profondeur du puits

- Autre écriture fonctionnelle

$$V_{L-J} = \sum_{i=1}^{N-1} \sum_{j=i+1}^N \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} \right]$$



Buckingham Potential

- The repulsive term is replaced by

$$v_{\text{rep}} = A \exp(-Br),$$

Interactions de van der Waals

- Sigma et epsilon *a priori* évalués sur des atomes seuls (e.g. pour un atome A: σ_{AA} et ε_{AA})
- Règle de Lorentz-Berthelot
 - e.g. pour 2 atomes A et B:

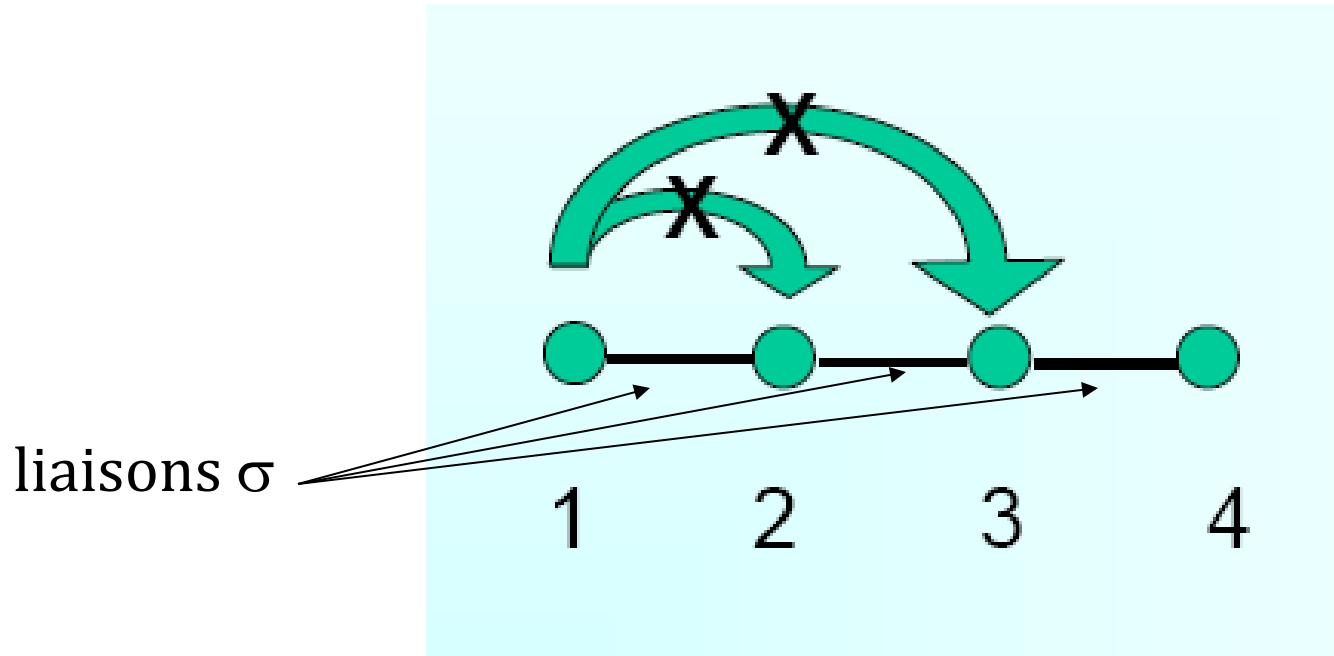
$$\sigma_{AB} = \frac{1}{2}(\sigma_{AA} + \sigma_{BB})$$

- Geometrical average

$$\sigma_{AB} = \sqrt{(\sigma_{AA} * \sigma_{BB})}$$

$$\varepsilon_{AB} = \sqrt{(\varepsilon_{AA} \varepsilon_{BB})}$$

Termes non liés



- Ne pas calculer d' interactions non liées entre les atomes pour les partenaires 1-2 et 1-3
- Eventuellement, atténuer les interactions non liées entre les partenaires 1-4

Récapitulatif

$$V_{potential} =$$

termes liés

$$\begin{aligned}
 & \sum_{\text{toutes les liaisons}} \frac{k}{2} (\boxed{l} - \boxed{l_0})^2 + \sum_{\substack{\text{tous les angles} \\ \text{de valence}}} \frac{k}{2} (\boxed{\theta} - \boxed{\theta_0})^2 \\
 & + \sum_{\text{tous les dièdres}} \sum_{m=1}^M \frac{\boxed{V_m}}{2} [1 + \cos(\boxed{m} \boxed{\omega} - \boxed{\gamma})]
 \end{aligned}$$

termes

non liés

$$+ \sum_{i=1}^N \sum_{j=i}^N 4 \boxed{\epsilon_{ij}} \left[\left(\frac{\boxed{\sigma_{ij}}}{\boxed{r_{ij}}} \right)^{12} - \left(\frac{\boxed{\sigma_{ij}}}{\boxed{r_{ij}}} \right)^6 \right]$$

constantes du
champ de forces

$$+ \sum_{i=1}^N \sum_{j=i}^N \frac{\boxed{q_i q_j}}{4 \pi \epsilon_0 \boxed{r_{ij}}}$$

$$+ V_{user}$$

variables : géométrie
de la molécule

Popular molecular mechanics force fields:

Classical

[AMBER](#) (Assisted Model Building and Energy Refinement) - widely used for proteins and DNA

[CHARMM](#) - originally developed at Harvard, widely used for both small molecules and macromolecules

[CHARMm](#) - commercial version of CHARMM, available through [Accelrys](#)

[CVFF](#) - also broadly used for small molecules and macromolecules

[GROMACS](#) - The force field optimized for the package of the same name

[GROMOS](#) - A force field that comes as part of the [GROMOS](#) (GROningen MOlecular Simulation package), a general-purpose molecular dynamics computer simulation package for the study of biomolecular systems. GROMOS force field (A-version) has been developed for application to aqueous or apolar solutions of proteins, nucleotides and sugars. However, a gas phase version (B-version) for simulation of isolated molecules is also available

OPLS-aa, OPLS-ua, OPLS-2001, OPLS-2005 - Members of the [OPLS](#) family of force fields developed by [William L. Jorgensen](#) at Yale Department of Chemistry.

[ECEPP/2](#) - free energy force field

Champs de forces classiques pour les biomolécules

- **GROMOS** (*J. Comp. Chem.*, 2004)
 - <http://www.igc.ethz.ch/gromos-docs/index.html>
 - <http://www.gromacs.org>
- **AMBER** (*J. Am. Chem. Soc.*, 1995)
 - <http://www.amber.ucsf.edu/amber/amber.html>
- **OPLS** (*J. Phys. Chem B*, 2001)
 - <http://zarbi.chem.yale.edu>
- **CHARMM** (*J. Phys. Chem. B.*, 1998)
 - <http://www.scripps.edu/brooks>

Popular molecular mechanics force fields:

Second-generation

[CFF](#) - a family of forcefields adapted to a broad variety of organic compounds,
includes forcefields for polymers, metals, etc.

[MMFF](#) - developed at Merck, for a broad range of chemicals

[MM2](#), [MM3](#), [MM4](#) - developed by Norman L. Allinger, for a broad range of chemicals

Reactive force fields

[ReaxFF](#) - reactive force field developed by William Goddard and coworkers. It is fast, transferable and is the computational method of choice for atomistic-scale dynamical simulations of chemical reactions.

Table 2. Standardized Parameters for Scaling Algorithms

atom	type	description	bond	r_{eq}^a	K_r^b
hydrogen	H	H attached to N	pure C—C	1.507 ^c	317 ^d
	HW	H in TIP3P water		1.336 ^e	570 ^f
	HO	H in alcohols and acids		1.449 ^g	337 ^h
	HS	H attached to sulfur		1.273 ⁱ	570 ^j
	HA	H attached to aromatic carbon	torsion	r_{eq}^a	V_2^k
	HC	H attached to aliphatic carbon with no electron-withdrawing substituents		1.507 ^c	0.0 ^l
	H1	H attached to aliphatic carbon with one electron-withdrawing substituent		1.397 ^m	14.5 ⁿ
	H2	H attached to aliphatic carbon with two electron-withdrawing substituents		1.336 ^e	30.0 ^o
	H3	H attached to aliphatic carbon with three electron-withdrawing substituents		1.449 ^g	0.0 ^p
	HP	H attached to carbon directly bonded to formally positive atoms (e.g. C next to NH ₃ ⁺ of lysine)		1.335 ^q	10.0 ^r
	H4	H attached to aromatic carbon with one electronegative neighbor (e.g. hydrogen on C5 of Trp, C6 of Thy)	pure X—C=N—X	1.273 ⁱ	30.0 ^s
	H5	H attached to aromatic carbon with two electronegative neighbors (e.g. H8 of Ade ar Gua and H2 of Ade)			

^a In Å. ^b In kcal/(mol Å²). ^c Microwave data from acetone (ref 32).

^d Value taken from MM2, ref 2. ^e Microwave data from propene (ref 32). ^f Default from NMA normal mode analysis for carbonyl force constant. ^g Benedetti structural data (ref 33). ^h Value derived from normal mode analysis on NMA. ⁱ Microwave data from methylenimine (ref 32). ^j Default value, see footnote f. ^k In kcal/mol. ^l Assumed free rotation about pure C—C single bond. ^m Structural data from benzene (ref 32). ⁿ From normal modes analysis of benzene. ^o Approximate rotational barrier of ethylene is ~60 kcal/mol (see ref 34). ^p Assume free rotation about a pure single C—N bond. ^q Benedetti structural data (ref 33). ^r Reference 35. ^s Calculated rotational barrier in methylenimine is 57.5 kcal/mol (see ref 36).

Exemple: CHARMM

BONDS

```
!atom type Kb          b0
!
C   C      600.000     1.3350 ! ALLOW ARO HEM
      ! Heme vinyl substituent (KK, from propene
(JCS))
CA   CA      305.000     1.3750 ! ALLOW     ARO
      ! benzene, JES 8/25/89
```

...

ANGLES

```
!atom types      Ktheta    Theta0    Kub      S0
!
CA   CA   CA      40.000     120.00   35.00    2.41620 ! ALLOW
ARO
      ! JES 8/25/89
```

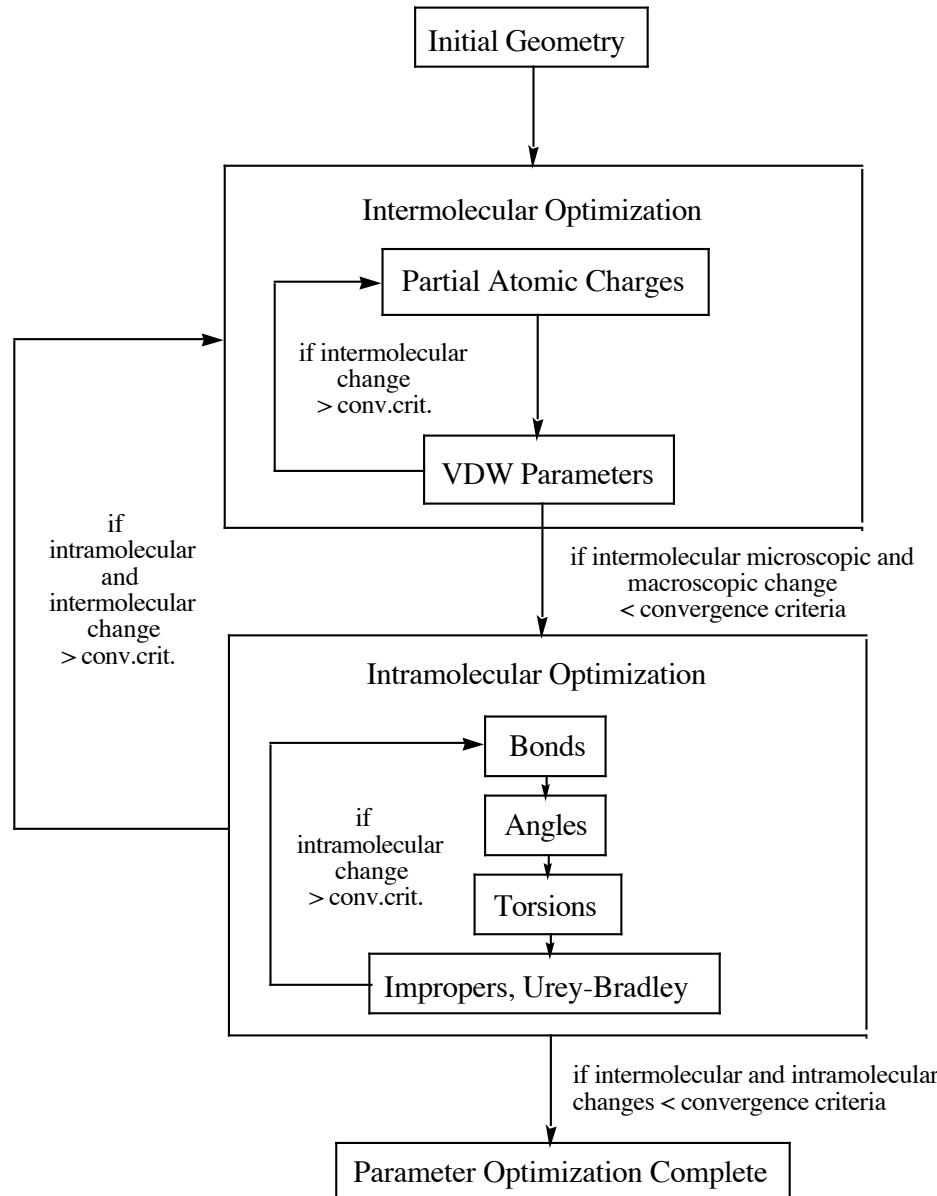
Exemple: GROMOS

```
;           GROMOS bond-stretching parameters
; Bond type code
; Force constant
; Ideal bond length
;
; ICB(H) [N]      CB[N]  B0[N]
#define gb_1          0.1000  1.5700e+07
; H - OA          750
#define gb_2          0.1000  1.8700e+07
; H - N (all)    895
...
; Bond-angle type code
; Force constant
; Ideal bond angle
;
; ICT(H) [N]    CT[N]   (T0[N])
#define ga_1          90.00    420.00
; NR(heme) - FE - NR(heme) 100
```

Force Field parametrisation

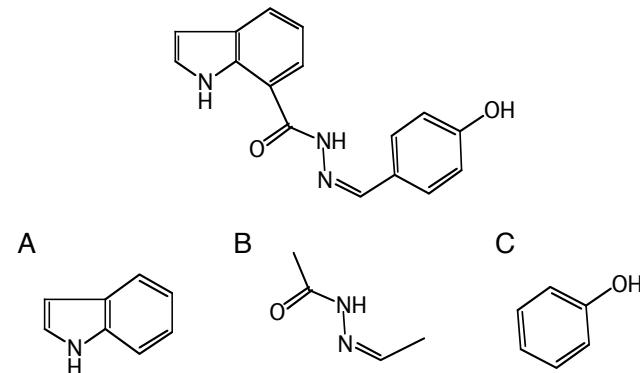
Table 1 Types and Sources of Target Data Used in the Optimization of Empirical Force Field Parameters

Term	Target data	Source
Internal		
Equilibrium terms, multiplicity, and phase (b_0 , θ_0 , n , δ)	Geometries	QM, electron diffraction, microwave, crystal survey
Force constants (K_b , K_θ , K_χ)	Vibrational spectra, Conformational properties	QM, IR, Raman QM, IR, NMR, crystal survey
External		
VDW terms (ϵ_i , $R_{\min,i}$)	Pure solvent properties [56] ($\Delta H_{\text{vaporization}}$, molecular volume) Crystal properties ($\Delta H_{\text{sublimation}}$ [56] lattice parameters, non-bond distances)	Vapor pressure, calorimetry, densities X-ray and neutron diffraction, vapor pressure, calorimetry
	Interaction energies (dimers, rare gas–model compound, water–model compound)	QM, microwave, mass spectrometry
Atomic charges (q_i)	Dipole moments [57]	QM, dielectric permittivity, Stark effect, microwave
	Electrostatic potentials	QM
	Interaction energies (dimers, water–model compound)	QM, microwave, mass spectrometry
	Aqueous solution ($\Delta G_{\text{solvation}}$, $\Delta H_{\text{solvation}}$, partial molar volume [58])	Calorimetry, volume variations



Reproduced from
McKerell

Deconstruct target molecule into molecular fragments for parameter assignment and optimization



- A) Indole
- B) Hydrazine (model compound 1)
- C) Phenol

Linking model compounds: When creating a covalent link between model compounds move the charge on deleted H into the carbon to maintain integer charge
(i.e. methyl ($q_C=-0.27$, $q_H=0.09$) to methylene ($q_C=-0.18$, $q_H=0.09$)

- 1) Identify previously parameterized model compounds in the CHARMM FF
- 2) Access topology information
 - i) Assign atom types
 - ii) Connectivity (bonds)
 - iii) Charges

In CHARMM toppar and stream subdirectory search for compounds representative of the molecular fragments

Phenol: stream/toppar_all22_prot_model.str (RESI PHEN)

Indole: stream/toppar_all22_prot_model.str (RESI INDO)

Model B not available: create RTF

Identify appropriate parent toppar files that contain the necessary residues and parameters (protein and lipid, as the lipid includes C=C moieties).

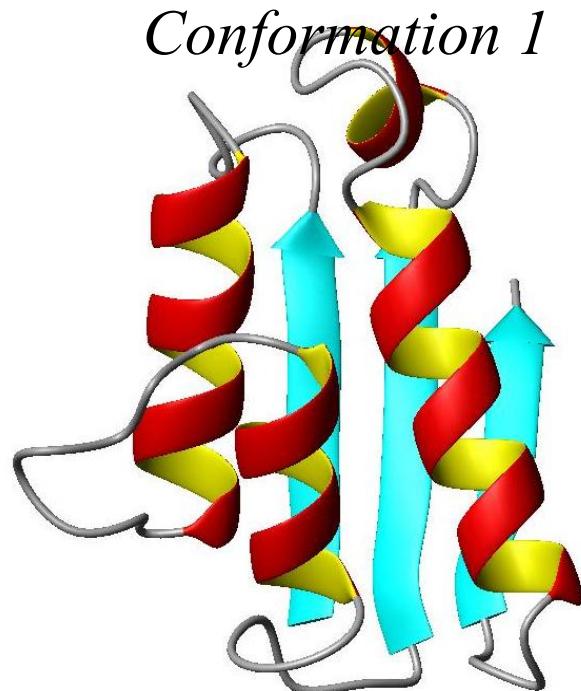
top_all27_prot_lipid.rtf

par_all27_prot_lipid.prm

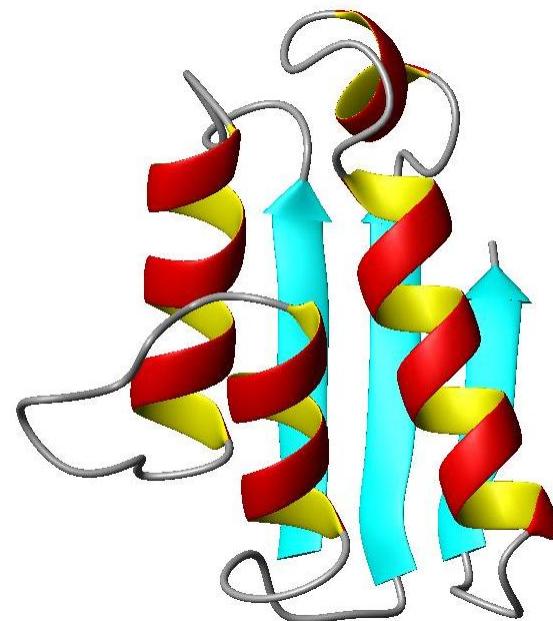
Finesse du champ de forces

- Exemple d' une protéine dans le vide :
 - 1BTA (inhibiteur de ribonucléase) : 89 résidus
 - Champ de forces : GROMOS 96

Conformation 1



Conformation 2



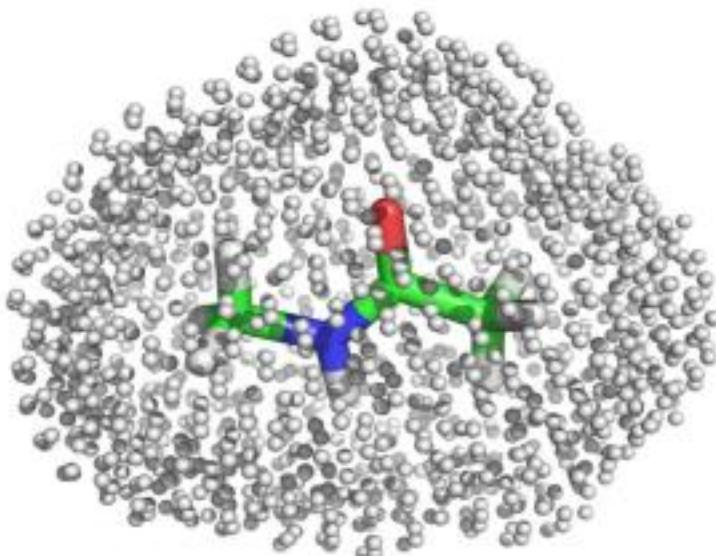
12/14/20 $V_{conf1} = 4068.7 \text{ kJ.mol}^{-1}$

$V_{conf2} = -373.4 \text{ kJ.mol}^{-1}_{54}$

Remarques importantes

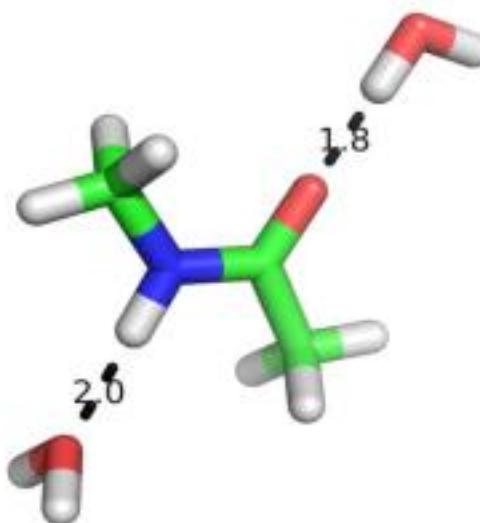
- Mise en garde sur les énergies évaluées
 - Les valeurs n'ont pas de signification en soi
 - On peut seulement comparer 2 conformations d'un système moléculaire identique
 - INTERDIT de comparer l'énergie potentielle entre 2 systèmes constitués de molécules différentes
- Paramètres *a priori* non transférables d'un champ de force à l'autre
- Unités
 - CHARMM : kcal.mol⁻¹, Å...
 - GROMOS : kJ.mol⁻¹, nm...

Charges Fit.



QM Electrostatic
potential (ESP)

+

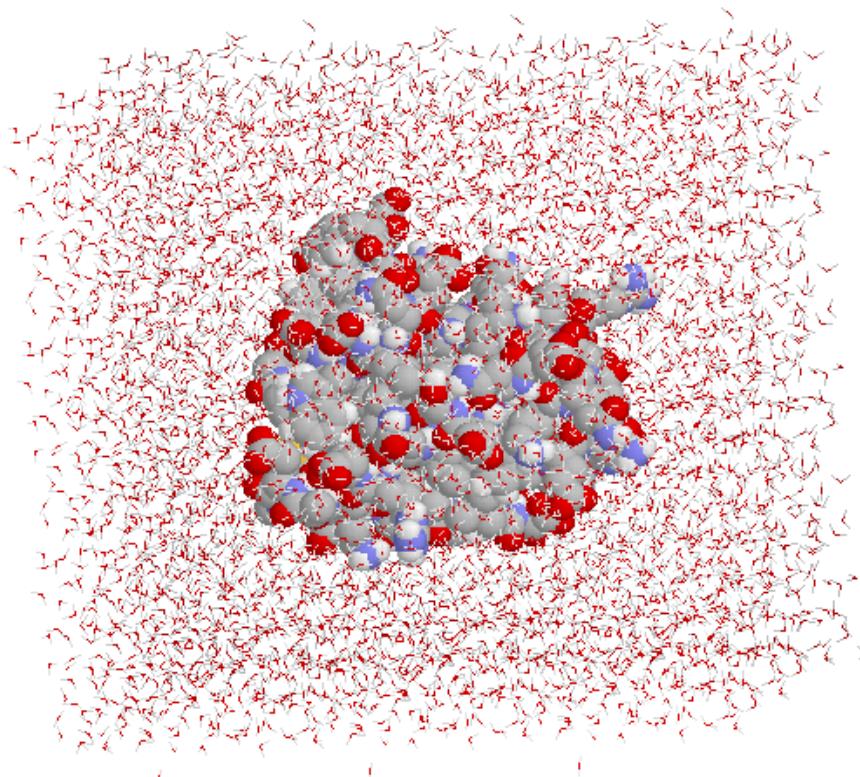


QM interactions with
water, E_{int} and R_{int}

Solvatation

Exemple sur 1BTA (inhibiteur de ribonucléase)

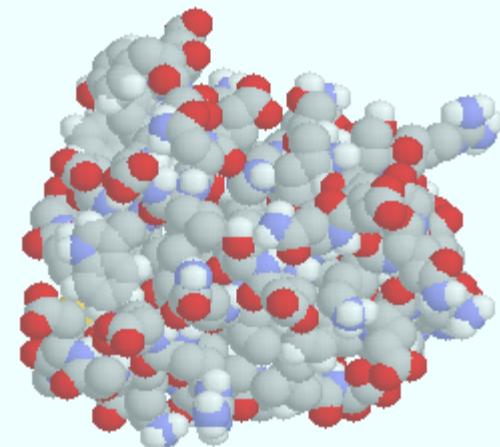
Explicite



12/14/2018 18114 atomes

Implicite

$$\epsilon = 80$$



915 atomes

Solvatation (2)

- 1BTA (89 résidus) dans le vide (915 atomes):

- 928 liaisons
- 1,354 angles de valence
- 483 dièdres
- 415,390 interactions → plus de 800 mille interactions !
- 415,390 interactions électrostatiques

- 1BTA dans une boîte d' eau (18114 atomes) :

- facteur 400

- 12,394 liaisons

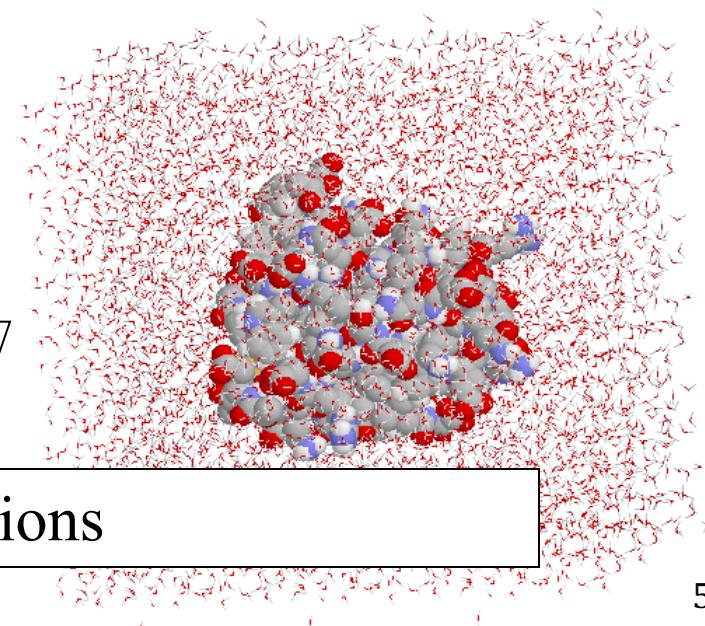
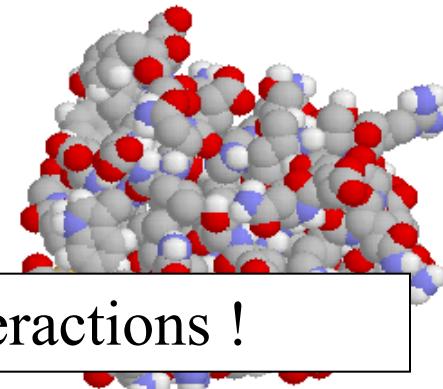
- 7,087 angles de valence

- 483 dièdres

- 164,029,477 interactions vdw

- 164,029,477 → plus de 328 millions

12/14/26
électrostatiques interactions !



Solvatation implicite

- Modification de la constante diélectrique dans le terme électrostatique

$$V_{elec} = \sum_{i=1}^{N-1} \sum_{j=i+1}^N \frac{q_i q_j}{4\pi\epsilon_0 \epsilon_r r_{ij}}$$

constante
diélectrique
du milieu

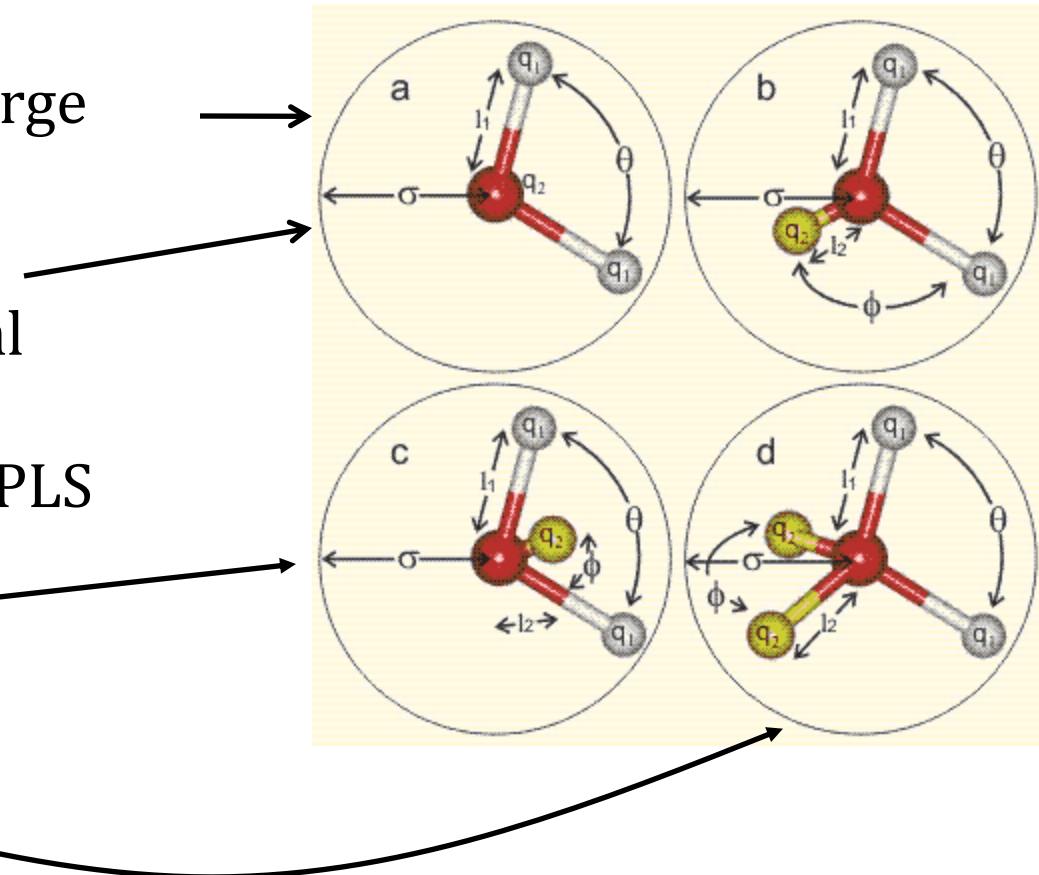
- Avantage : moins coûteux en temps de calcul
- Inconvénients:
 - approximation très grossière
 - problèmes avec les résidus chargés (Asp, Glu, Arg, Lys...)

Autres solvations implicites

- Constante diélectrique dépendant de la distance
 - Avantage : meilleur traitement des interactions dans le cœur de la protéine
 - Inconvénient : même problème avec les charges
- Ajout d' un terme spécifique dans le potentiel mimant l' effet du solvant
 - Born généralisé basé sur la surface accessible (GBSA)
 - Avantage : meilleur traitement des charges
 - Inconvénients :
 - dérivée du terme de solvatation : coûteuse en temps de calcul
 - surface accessible : coûteuse en temps de calcul
- *etc...*

Modèles d'eau

- SPC = Single Point Charge
→ GROMOS
- TIP3P = Transferable Intermolecular Potential (3 points)
→ CHARMM, AMBER, OPLS
- TIP4P
- TIP5P
- etc



Probablement la molécule la plus difficile à modéliser !

Introduction de termes supplémentaires

- Termes dits de torsion impropres (distorsion hors du plan et maintien de la chiralité)
- Urey-Bradley pour les angles pour reproduire les spectres vibrationnels
- Termes de contraintes pour tenir compte de données expérimentales.

-APPROXIMATIONS :

- Potentiel dit additif par paire
- Notion de transférabilité

Au delà de l'énergie potentielle: les champs de force pour l'énergie libre

- Energie libre : NECESSITE D'OBTENIR DES ENSEMBLES STATISTIQUES
- Alternative : Champs de force calibrés sur des énergies libres.
 - Energie potentielle : Reproduction de la surface d'énergie potentielle de torsion déterminée par MQ pour un composé donné
 - Energie libre: Reproduction de la distribution de probabilité observée expérimentalement de ce dièdre en solution. EXEMPLES: ECEPP Empirical conformational Energy Program for Peptides . Calibrés sur des structures cristallines. MAIS pb du rôle du solvant

REMARQUES

- Les énergies potentielles ainsi définies mettent en évidence les **variations énergétiques** liées à des changements de conformation ou à des interactions intermoléculaires.



- Notion d'énergie de référence
- Les valeurs calculées n'ont pas de signification en soi



Université de Paris