SIMULACIONES DE DINÁMICA MOLECULAR

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v 2.0

Temario

- Mecánicas Estadística.
  - Microestados y Macroestados.
  - Ensambles Termodinámicos.
  - Ensamble Termodinámico Promedio.
- Dinámica Molecular.
  - Campos de Fuerza.
- Modelamiento Comparativo
  - Suite Modeller.
  - Suite Rossetta.
  - Análisis de Modelos.
  - Validación otras técnicas experimentales.

Introducción a Simulaciones de Dinámica Molecular

¿Qué son las Dinámicas Moleculares?

Rangos de movimiento en moléculas.

Tiempos de simulación.

Aplicaciones

Idea Central de las MDS

- La actividad biológica es el resultados de interacciones dependientes del tiempo entre las interfaces de moléculas (proteínas-proteínas, proteínas-AD/RN, proteínas-ligando).
- Observaciones macroscópicas (otros experimentos de laboratorio) son relacionadas a comportamientos microscópicos (nivel atómico).
- Comportamiento microscópico dependiente del tiempo (e idendependiente) puede ser calculado por MDS.

MDS

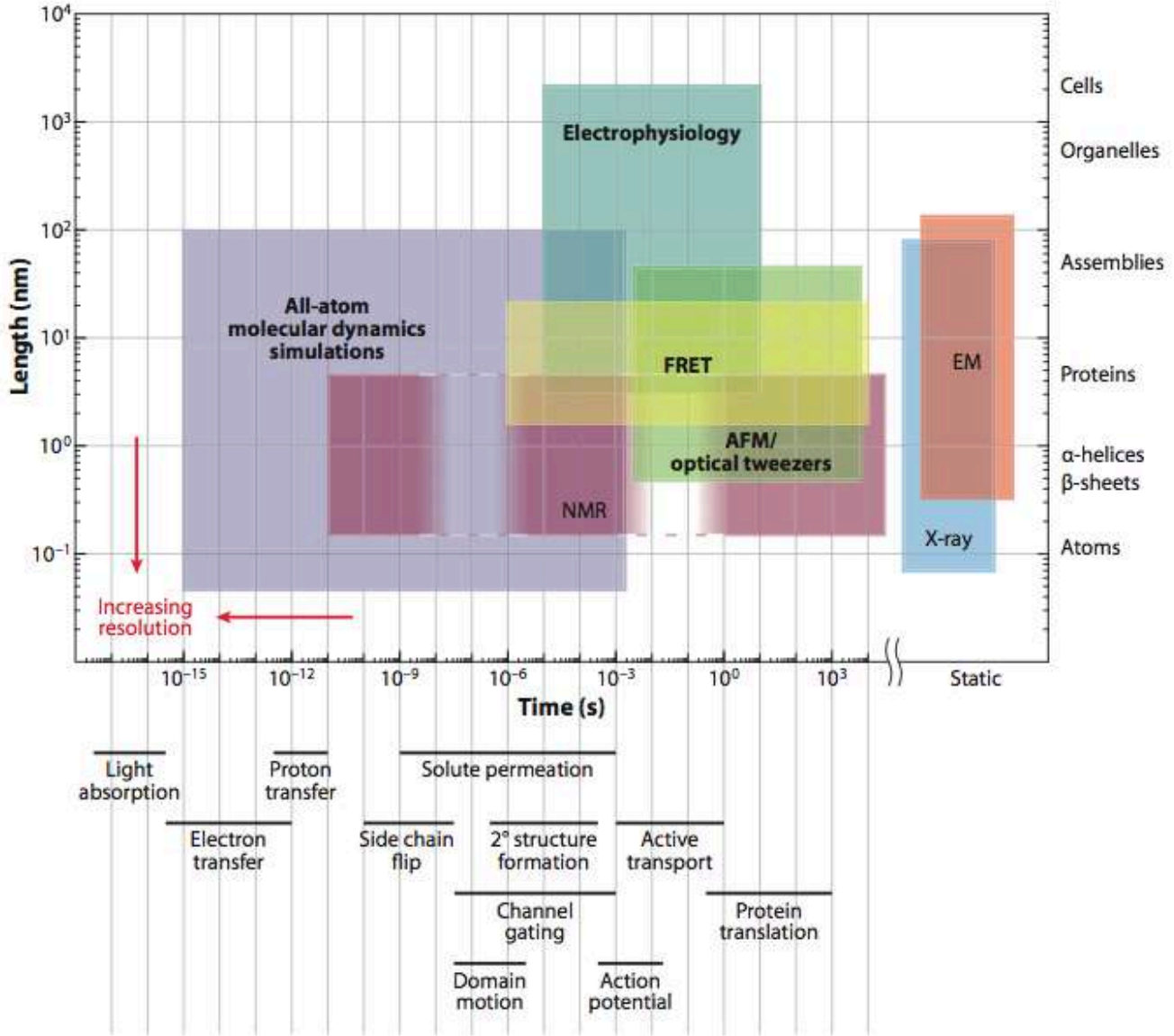
- Aproxima las interacciones del sistema utilizando modelos simplificados (cálculos más rápidos). Incluye rasgos del modelo que son necesarios para describir el sistema.
- En el caso de MDS, esta es una función de la energía potencial de las interacciones del modelo.
- Permite realizar observaciones a escalas de tiempo de fs y a resoluciones de 1Å.
- Permite simular varias condiciones en forma rápida y eficiente.
- El método permite la predicción de propiedades estáticas y dinámicas de moléculas directamente desde la interacción entre moléculas.

Macromoléculas en movimiento

- Movimientos Locales (0,01 a 5 A, 10^{-15} a 10^{-1})
  - Fluctuaciones atómicas.
  - Movimientos de cadenas laterales.
  - Movimientos de lazos.
- Movimientos de cuerpo rígido (1 a 10 A, 10^{-9} a 1s)
  - Movimientos de hélices.
  - Movimientos de dominios.
  - Movimientos de subunidades.
- Movimientos de gran escala (>5ª, 10^{-7} a 10^{4} s).
  - Transiciones hélice/vueltas.
  - Disociación/Asociación.
  - Plegamiento y desplegamiento.

- Flexibilidad es Requerida para las Funciones Biológicas (Dinámica).

Resolución Espacio-Temporal de Varias Técnicas Biológicas y Químicas



¿Cuánto tiempo se pueden simular?

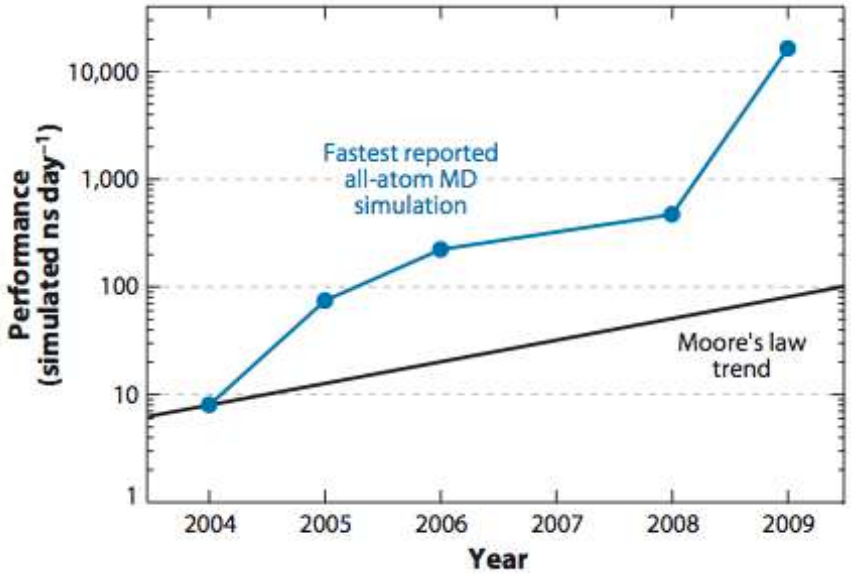


Table 1 Longest reported all-atom molecular dynamics simulations from 2006 to 2009

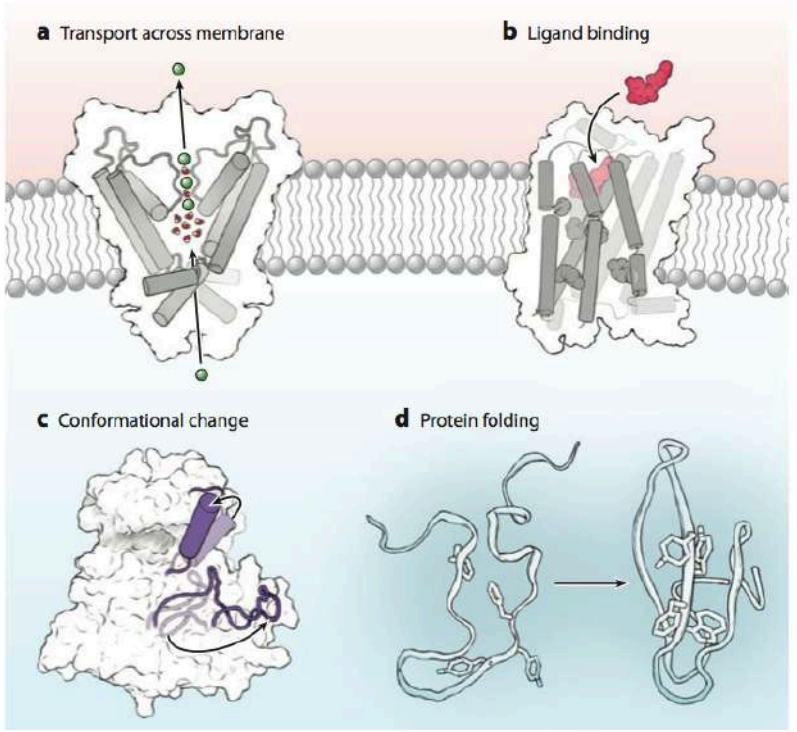
Year	Length (μs)	Protein	Platform	Reference
2006	2	Rhodopsin	Blue Gene/L[a]	54
2007	2	Villin HP-35	GROMACS[b]	22
2008	10	WW domain	NAMD[b]	27
2009	1,031	BPTI	Anton	82

[a]This simulation used IBM's Blue Matter software.

[b]These simulations were performed on a commodity computer cluster with the specified software.

Aplicaciones MDS

- Una de las herramientas principales para modelar proteínas, ácidos nucleicos y sus componentes.
- Estabilidad de proteínas.
- Plegamiento de proteínas.
- Reconocimiento molecular.
- Reacciones enzimáticas.
- Diseño racional de moléculas bioactivas (diseño de drogas).
- Cambios conformacionales pequeños y de gran escala.
- Determinación y construcción de estructuras 3D.
- Estudio de procesos dinámicos así como transporte de iones o moléculas.



Exploración espacio conformacional

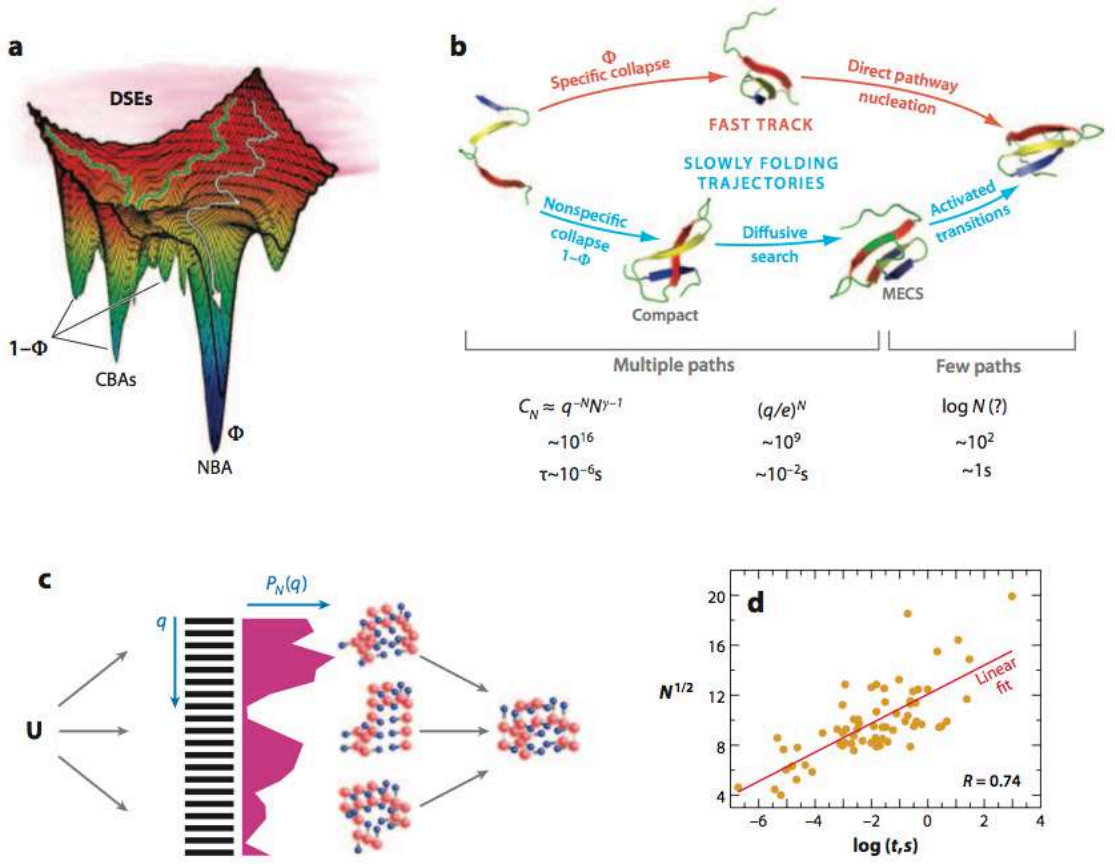
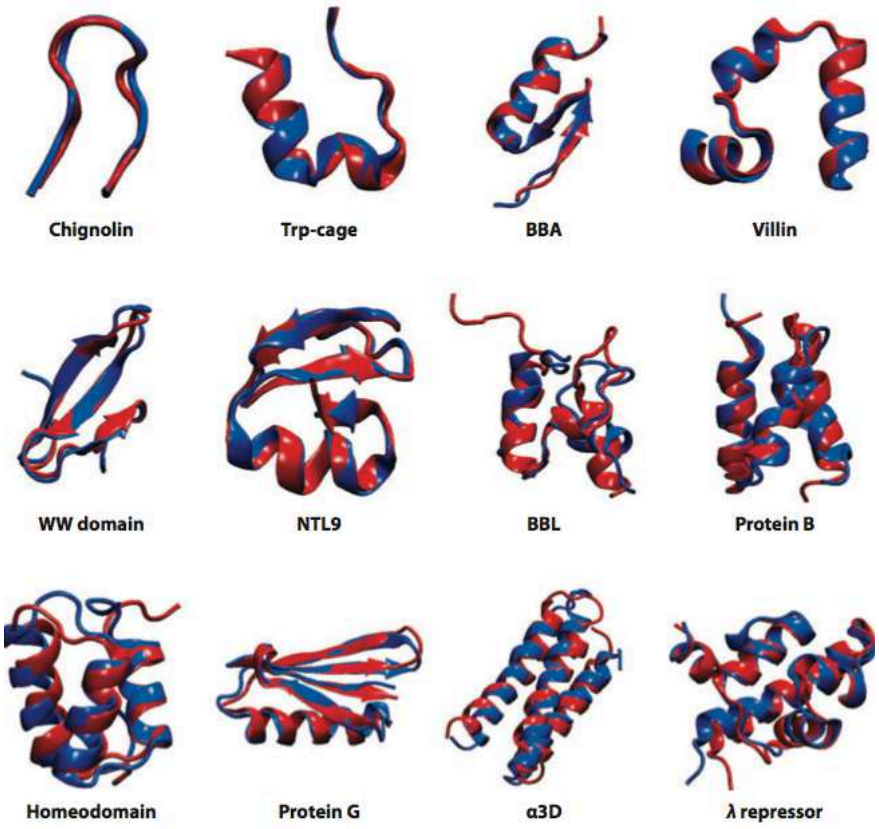


Figure 3

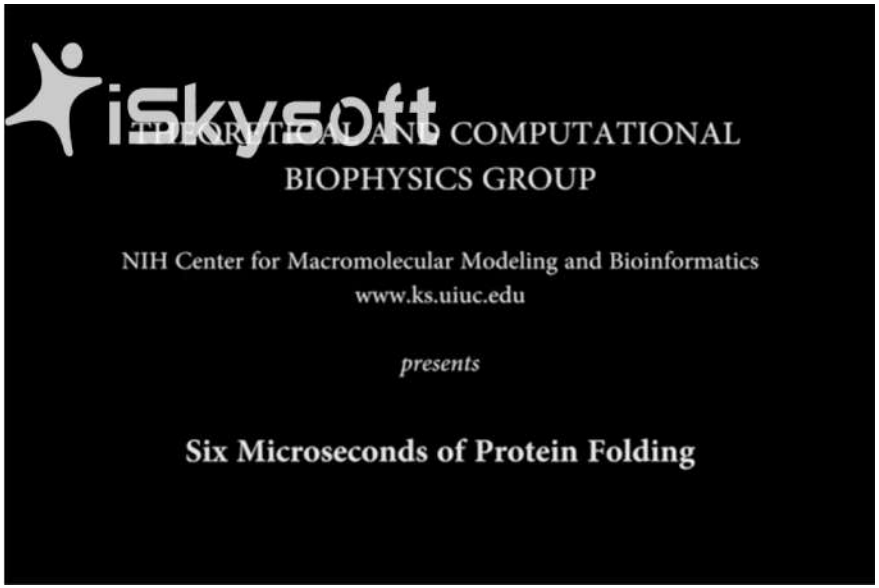
(*a*) Schematic of the rugged folding landscape of proteins with energetic and topological frustration. A fraction Φ of unfolded molecules follow the fast track (*white*) to the native basin of attraction (NBA), whereas the remaining fraction $(1 - \Phi)$ of slow trajectories (*green*) are trapped in one of the competing basins of attraction (CBAs). DSE, denatured state ensemble. (*b*) Summary of the mechanisms by which proteins reach their native state. The upper path is for fast track molecules. $\Phi \approx 1$ implies the folding landscape is funnel-like. The lower routes are for slowly folding trajectories (*green* in panel *a*). The number of conformations explored in the three stages as a function of N is given below, with numerical estimates for $N = 27$. The last line gives the timescale for the three processes for $N = 100$ using the estimates described in the text. (*c*) Multiple folding nuclei model for folding of a lattice model with side chains with $N = 15$ (77). The probability of forming the native contacts (20 in the native state shown as *black bars*) in the transition state ensemble (TSE) is highlighted in magenta. The average structures in the three major clusters in the TSE are shown. There is a nonnative contact in the most probable cluster (*shown in the middle*). The native state is on the right. (*d*) Dependence of the folding times versus $\sqrt{N}$ for 69 residues (adapted from Reference 98). The solid red line is a linear fit (correlation coefficient is 0.74) and the orange circles are data.

Plegamiento de Proteínas

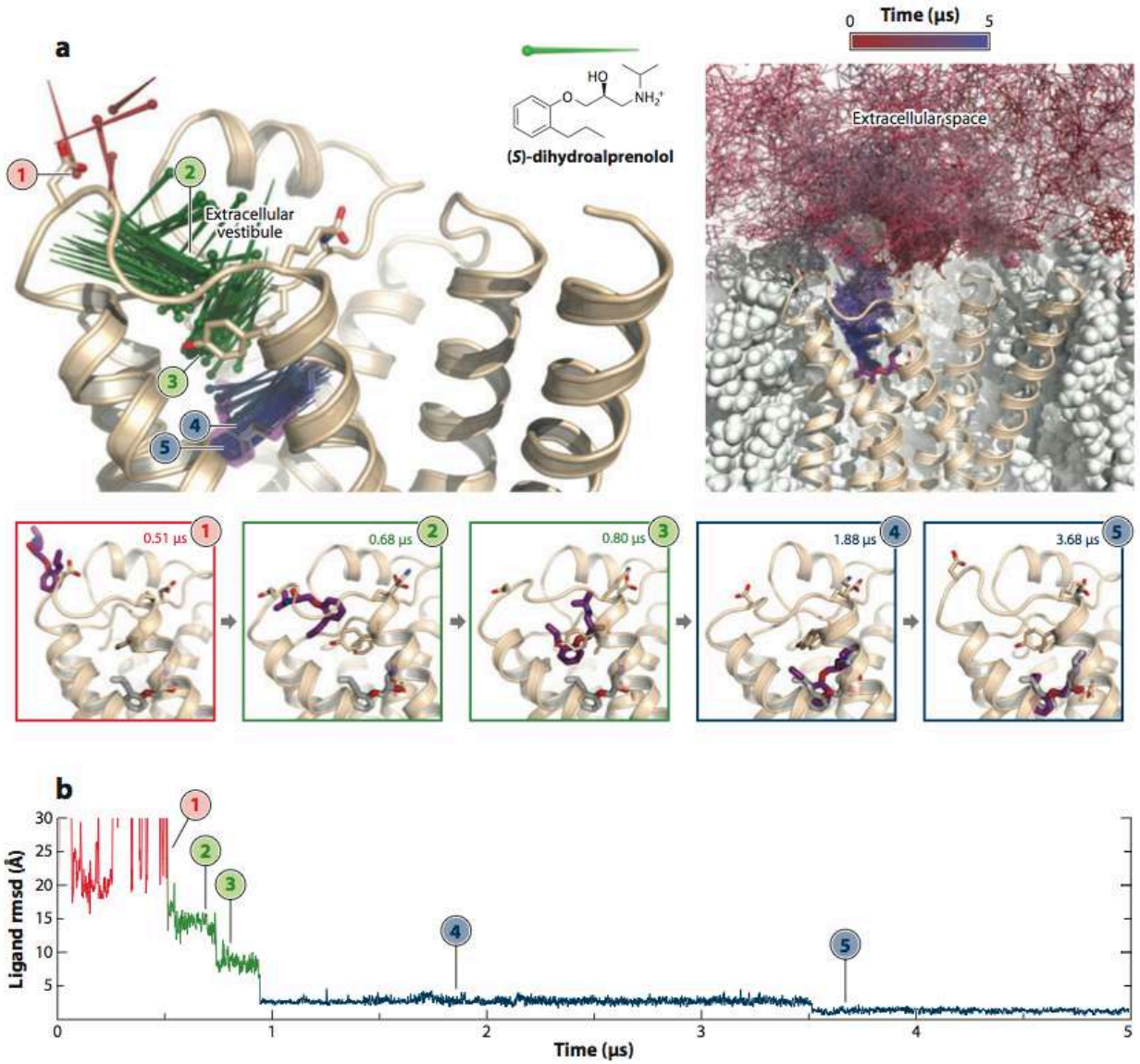


igure 6

ı simulations with a single force field, 12 structurally diverse proteins fold spontaneously to a structure *lue*) closely resembling that determined experimentally (*red*). The simulation snapshots were chosen ıtomatically based on a clustering analysis that did not exploit knowledge of the experimental structure. he total simulation time per protein ranged from 104 to 2,936 μs, allowing observation of at least 10 ılding and 10 unfolding events for each protein. Figure adapted from Reference 50.



Cambios Conformacionales



Transporte Molecular

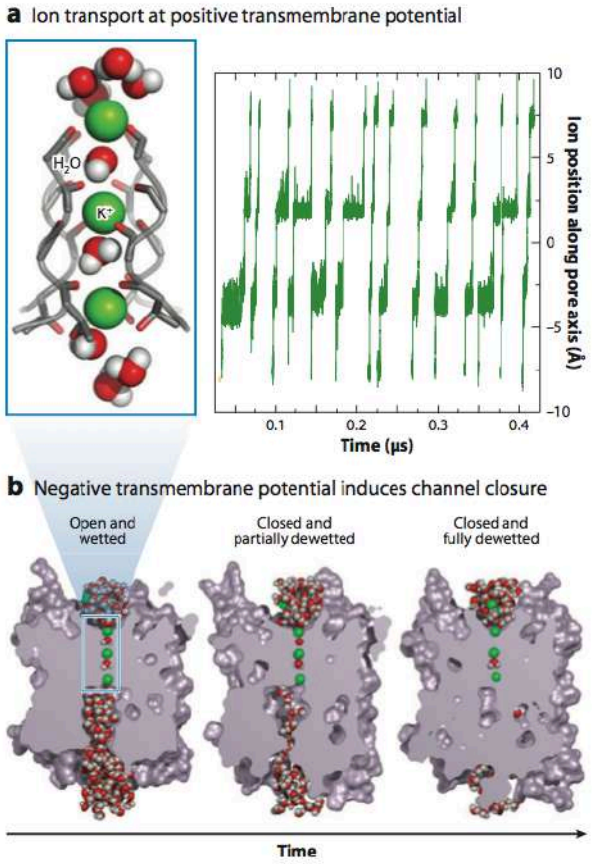


Figure 5

Simulation of ion permeation and gating in a potassium channel. (*a*) Potassium ions permeated outward (in the figure, upward) through the selectivity filter when the transmembrane potential was positive. Individual ions paused at well-defined sites within the filter, as shown by the representative traces in green. (*b*) When the transmembrane voltage was reversed, the hydrophobic cavity dehydrated, causing it to collapse and thus close the channel to conduction. Figure adapted from Reference 34.

Diseño de proteínas

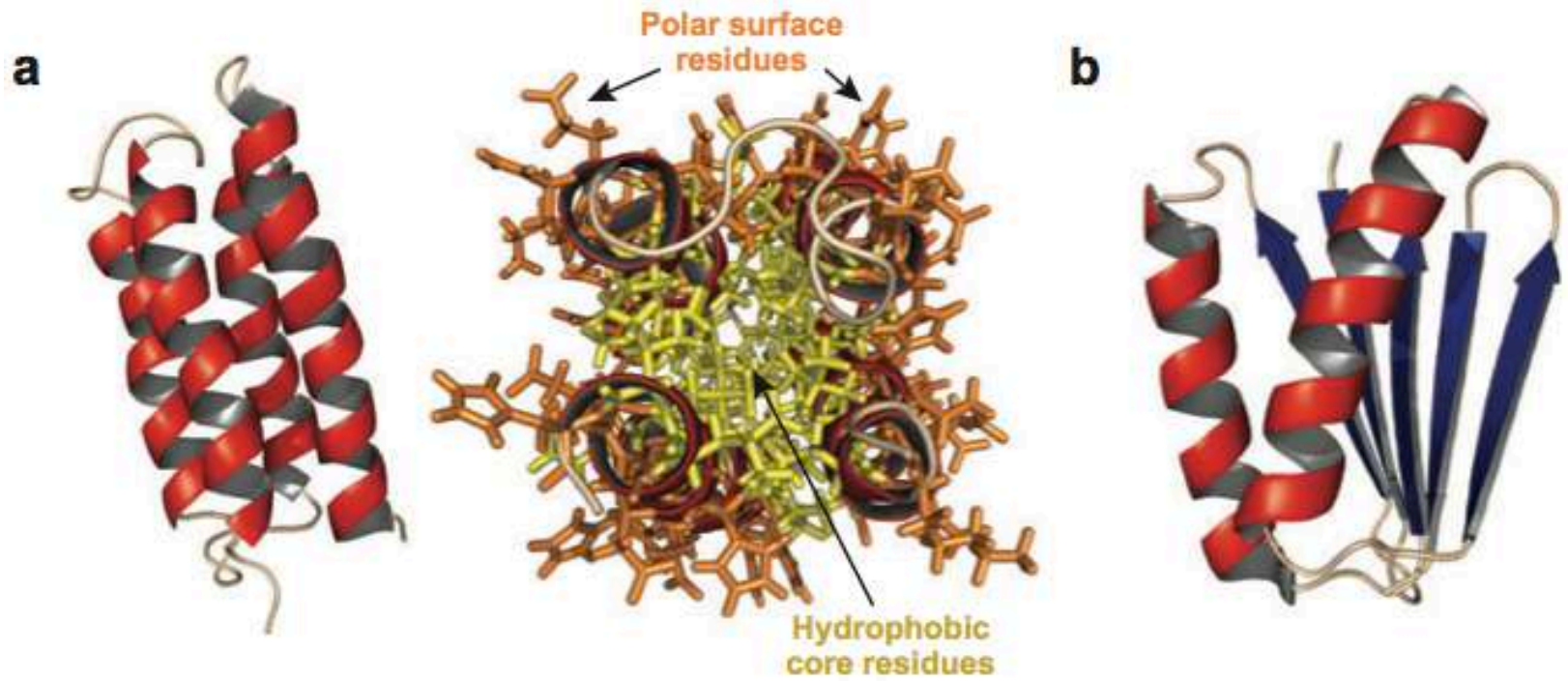


Figure 3

De novo protein design. (*a*) Four-helix-bundle protein designed by binary patterning (PDB code: 1P68; *left*, side view; *center*, view along the helix axis). Well-packed side chains in the hydrophobic core of the protein are shown in yellow, and polar surface residues are depicted in orange. (*b*) Computationally designed α/β-fold of Top7 (PDB code: 1QYS).

Premio Nobel Química 2013

Martin Karplus - Facts

© Harvard University

Martin Karplus

Born: 15 March 1930, Vienna, Austria

Affiliation at the time of the award: Université de Strasbourg, Strasbourg, France, Harvard University, Cambridge, MA, USA

Prize motivation: "for the development of multiscale models for complex chemical systems"

Michael Levitt - Facts

Photo: © S. Fisch

Michael Levitt

Born: 9 May 1947, Pretoria, South Africa

Affiliation at the time of the award: Stanford University School of Medicine, Stanford, CA, USA

Prize motivation: "for the development of multiscale models for complex chemical systems"

Arieh Warshel - Facts

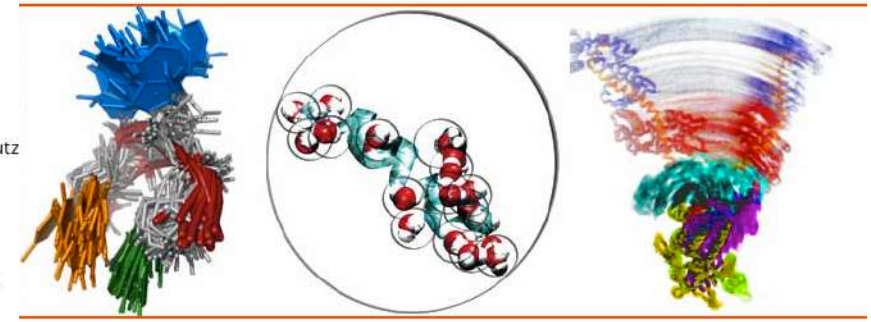
Photo: Wikimedia Commons

Arieh Warshel

Born: 20 November 1940, Kibbutz Sde-Nahum, Israel

Affiliation at the time of the award: University of Southern California, Los Angeles, CA, USA

Prize motivation: "for the development of multiscale models for complex chemical systems"



CHARMM

Q-CHEM

http://csb.stanford.edu/index.html

Mecánica Estadística

Mecánica Estadística: Microestados y Macroestados

- La relación entre propiedades microscópicas y macroscópicas de un sistema.
- Microestado: posiciones y momento de todas las partículas de un sistema.

$$\mathbf{r} = (\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_N),$$

$$\mathbf{p} = (\mathbf{p}_1, \mathbf{p}_2, ..., \mathbf{p}_N),$$

$$H(\mathbf{r}, \mathbf{p}) = K(\mathbf{p}) + V(\mathbf{r}).$$

$$K = \sum_{i=1}^{N} \frac{1}{2m_i}(p_{ix}^2 + p_{iy}^2 + p_{iz}^2),$$

Mecánica Estadística: Ensambles termodinámicos

- Ensambles Termodinámicos:
  - Canonico (NVT).
  - Microcanonico (NVE).
  - Isotermal-Isobárico (NPT).
  - Gran canonico (uVT).

$$A_{\text{obs}} = \langle A \rangle_{\text{ens}},$$

Mecánica Estadística: Ensamble Termodinámico Promedio

- Función de partición:

Factor Boltzmann

$$\beta = 1/k_{\mathrm{B}}T$$

$$Q_{\mathrm{NVT}} = \sum_{\mathbf{r},\mathbf{p}} \exp(-\beta\, H(\mathbf{r},\mathbf{p})),$$

Microestado
Se relaciona a una probabilidad

Eª Cinética

Eª Potencial

$$\mathrm{P}(\mathbf{r},\mathbf{p}) = \frac{\exp(-\beta\, H(\mathbf{r},\mathbf{p}))}{Q_{\mathrm{NVT}}}.$$

$$\langle A \rangle_{\mathrm{NVT}} = \sum_{\mathbf{r}} A(\mathbf{r})\,\mathrm{P}(\mathbf{r}) = \sum_{\mathbf{r}} \frac{A(\mathbf{r})\,\exp(-\beta\, V(\mathbf{r}))}{Z_{\mathrm{NVT}}}.$$

Campo de Fuerza (FF)

- La energía potencial de un ensamble termodinámico se puede calcular desde las aproximaciones entregadas por un campo de fuerza.
- Los FF más usados son:
  - AMBER
  - CHARMM
  - GROMOS
  - OPLS

Campo de Fuerza (FF)

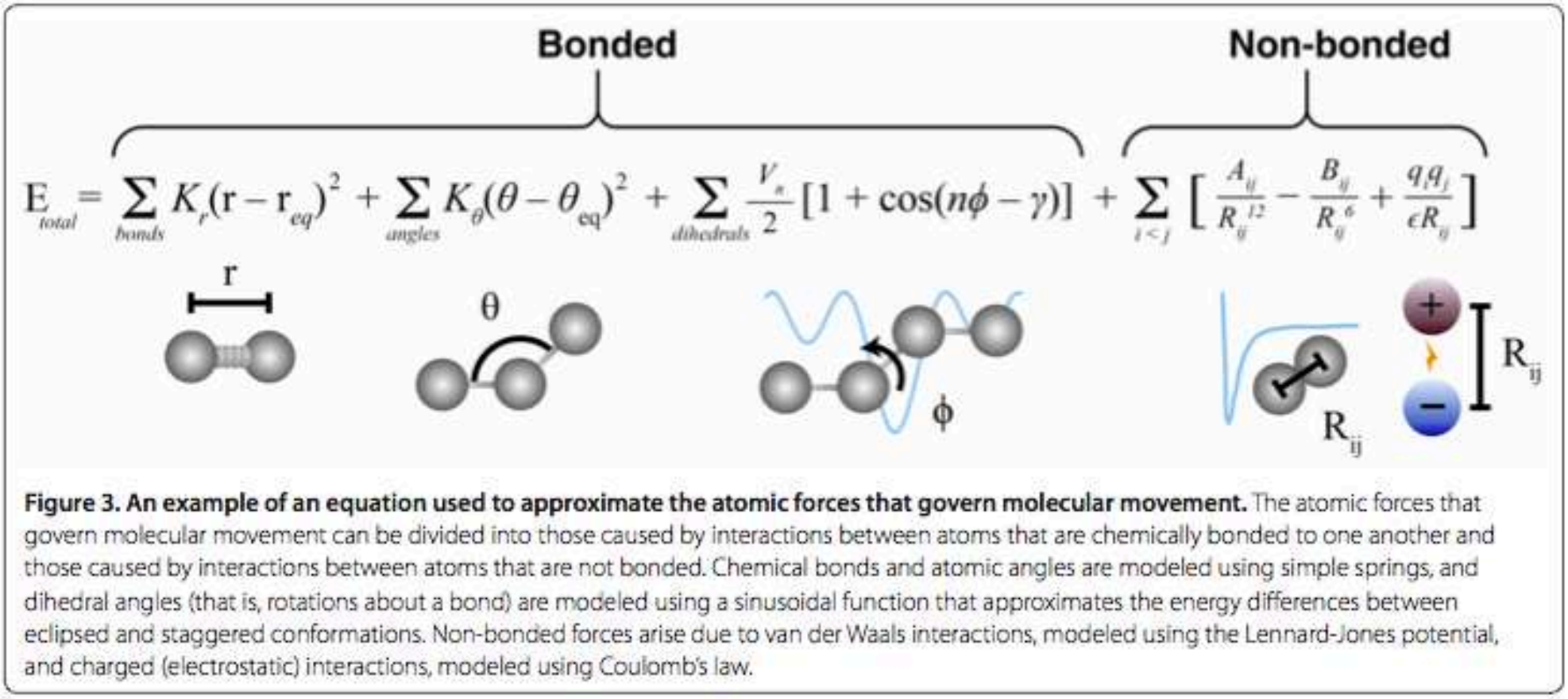


Figure 3. An example of an equation used to approximate the atomic forces that govern molecular movement. The atomic forces that govern molecular movement can be divided into those caused by interactions between atoms that are chemically bonded to one another and those caused by interactions between atoms that are not bonded. Chemical bonds and atomic angles are modeled using simple springs, and dihedral angles (that is, rotations about a bond) are modeled using a sinusoidal function that approximates the energy differences between eclipsed and staggered conformations. Non-bonded forces arise due to van der Waals interactions, modeled using the Lennard-Jones potential, and charged (electrostatic) interactions, modeled using Coulomb's law.

Campo de Fuerza (FF)

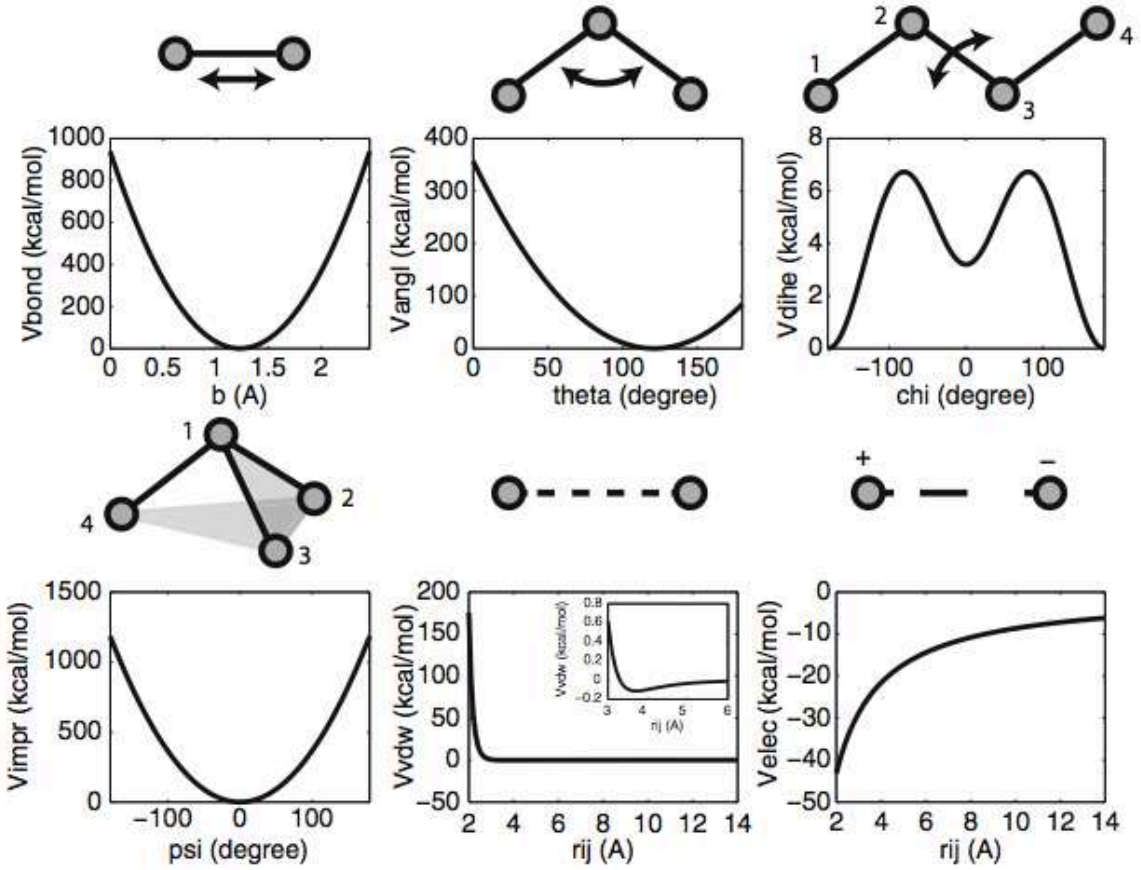


Fig. 2 Potential energy terms in a force field. Schematic representations are shown for the bond, angle, dihedral, improper, vdW and electrostatic interactions. The corresponding energy values for selected atom types in the CHARMM force field are plotted, including the C–O bond, the CA–C–O angle, the CA–C–N–CA (Φ) dihedral and the C–CA–N–O (peptide bond) improper. To demonstrate the nonbonded interactions, we also plotted the vdW and electrostatic energy values for a pair of C–O atoms. The atom names used here are consistent with the naming convention of protein data bank, where CA represents the Cα atom of the protein backbone

Tipos de Campo de Fuerza

- CHARMM
- AMBER
- OPLS
- GROMOS

Tipos de Campo de Fuerza

Agua Implícita y Explicita

- Dinámicas con constantes dieléctricas:
  - Agua: 70-80
  - Vacío: 0
  - Membrana: 30
  - Proteína: 20
- Explicita con moléculas de agua en la simulación.
  - Solvate.
  - Solvate VMD.
  - PSFGen

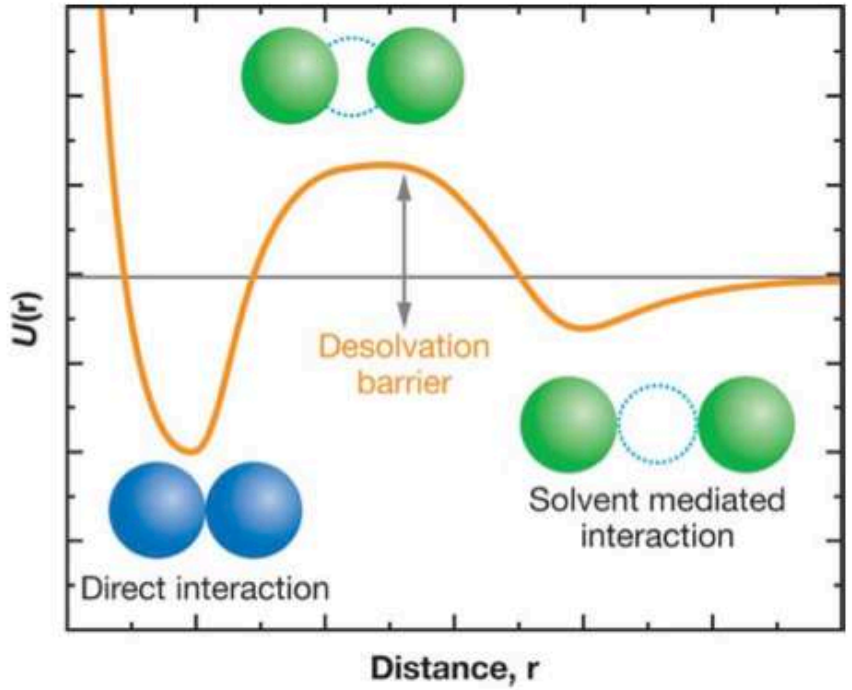
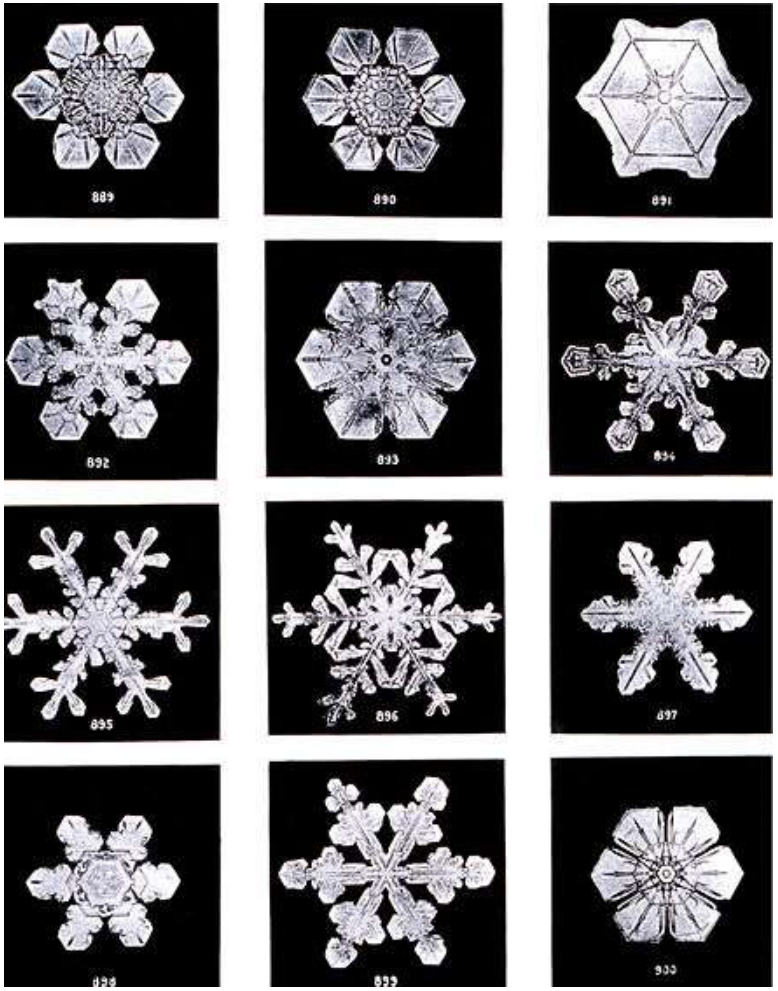
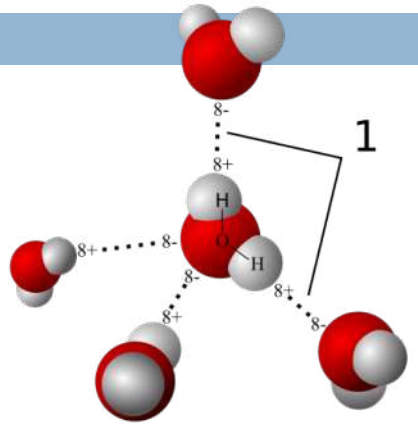


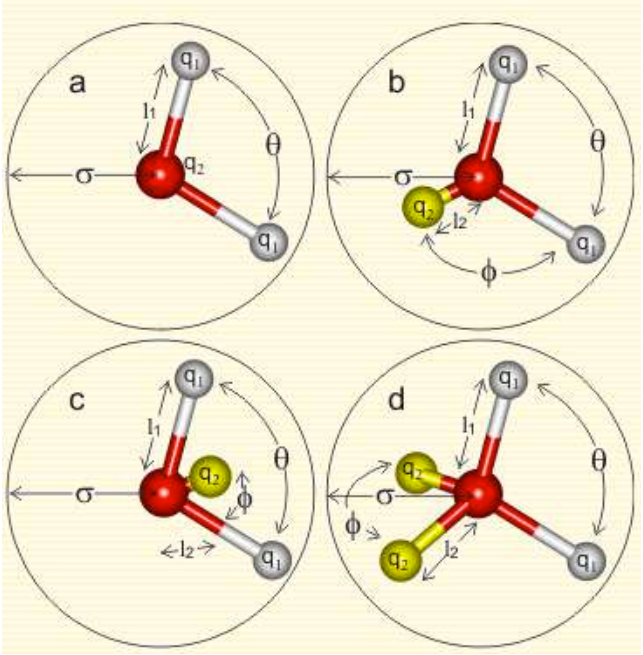
Figure 3

Schematic representation of the potential energy function, $U(r)$, in the desolvation model. In this model, any native interaction between two residues (*spheres*) can either be direct or separated by a water molecule (*light blue dashed circle*). The Cα-Cα distance of two residues that directly interact is defined by the native structure, and when a water molecule separates them the optimal distance increases by the diameter of the water molecule. At the desolvation barrier the water overlaps with the two residues.

Modelos de Agua







http://www.lsbu.ac.uk/water/models.html

Modelos de Agua

Parameters for some water molecular models

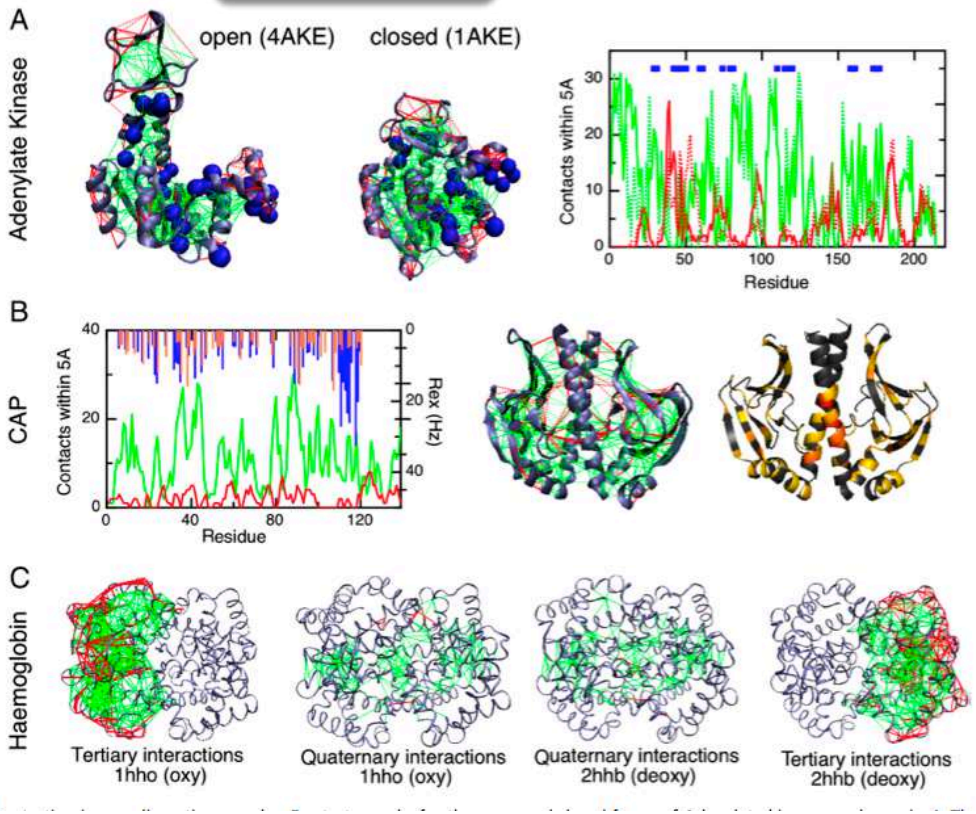
Model	Type	σ Å [6]	ε kJ mol^{-1} [6]	l_1 Å	l_2 Å	q_1 (e)	q_2 (e)	θ°	φ°
SSD [511]	-[8]	3.016	15.319	-	-	-	-	109.47	109.47
SPC [94]	a	3.166	0.650	1.0000	-	+0.410	-0.8200	109.47	-
SPC/E [3]	a	3.166	0.650	1.0000	-	+0.4238	-0.8476	109.47	-
SPC/HW (D_2O) [220]	a	3.166	0.650	1.0000	-	+0.4350	-0.8700	109.47	-
SPC/Fw [2] [994]	a	3.166	0.650	1.0120	-	+0.410	-0.8200	113.24	-
TIP3P [180]	a	3.15061	0.6364	0.9572	-	+0.4170	-0.8340	104.52	-
TIP3P/Fw [2] [994]	a	3.1506	0.6368	0.9600	-	+0.4170	-0.8340	104.5	-
PPC [1, 2] [3]	b	3.23400	0.6000	0.9430	0.06	+0.5170	-1.0340	106.00	127.00
TIP4P [180]	c	3.15365	0.6480	0.9572	0.15	+0.5200	-1.0400	104.52	52.26
TIP4P-Ew [649]	c	3.16435	0.680946	0.9572	0.125	+0.52422	-1.04844	104.52	52.26
TIP4P-FQ [197]	c	3.15365	0.6480	0.9572	0.15	+0.63[1]	-1.26[1]	104.52	52.26
TIP4P/Ice [838]	c	3.1668	0.8822	0.9572	0.1577	+0.5897	-1.1794	104.52	52.26
TIP4P/2005 [984]	c	3.1589	0.7749	0.9572	0.1546	+0.5564	-1.1128	104.52	52.26
TIP4P/2005f [1765]	c	3.1644	0.7749	0.9664	0.15555	+0.5564	-1.1128	104.75	52.375
SWFLEX-AI [2] [201]	c	four terms used		0.968[1]	0.14[1,3]	+0.6213	-1.2459	102.7[1]	51.35[1]
COS/G3 [704] [9]	c	3.17459	0.9445	1.0000	0.15	+0.450672	-0.901344	109.47	-
COS/D [1617] [9] [16]	c	3.4365	0.5119	0.9572	0.257	+0.5863	-1.1726	104.52	-
GCPM [2] [859] [10]	c	3.69 [4,11]	0.9146 [4]	0.9572	0.27	+0.6113	-1.2226	104.52	52.26
SWM4-NDP [2] [13] [933]	c	3.18395	0.88257	0.9572	0.24034	0.55733	-1.11466	104.52	52.26
ST2 [872] [12]	d	3.10000	0.31694	1.0000	0.80	+0.24357	-0.24357	109.47	109.47
TIP5P [180]	d	3.12000	0.6694	0.9572	0.70	+0.2410	-0.2410	104.52	109.47
TIP5P-Ew [619]	d	3.097	0.7448	0.9572	0.70	+0.2410	-0.2410	104.52	109.47
TTM2-F [1027] [14]	c	five parameters used		0.9572	0.70	+0.574	-1.148	104.52	52.26
POL5/TZ [2] [256]	d	2.9837 [4]	[4]	0.9572	0.5	varies[5]	-0.42188	104.52	109.47
Six-site [491]	c/d[7]	3.115_{OO} 0.673_{HH}	0.715_{OO} 0.115_{HH}	0.980	0.8892_{L} 0.230_{M}	+0.477	-0.044_{L} -0.866_{M}	108.00	111.00
QCT [1251]	a[15]	3.140	0.753	0.9614	-	+0.6064	-1.2128	104.057	-

Calculated physical properties of the water models

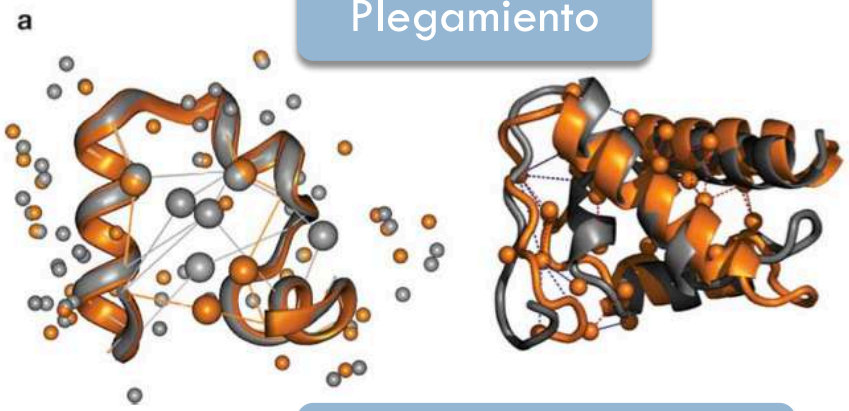
Model	Dipole moment[e]	Dielectric constant	self-diffusion, 10^{-5} cm^2/s	Average configurational energy, kJ mol^{-1}	Density maximum, °C	Expansion coefficient, 10^{-4} °C^{-1}
SSD	2.35 [511]	72 [511]	2.13 [511]	-40.2 [511]	-13 [511]	-
SPC	2.27 [181]	65 [185]	3.85 [182]	-41.0 [185]	-45 [983]	7.3 [704] **
SPC/E	2.35 [3]	71 [3]	2.49 [182]	-41.5 [3]	-38 [183]	5.14 [994]
SPC/Fw	2.39 [994]	79.63 [994]	2.32 [994]	-	-	4.98 [994]
PPC	2.52 [3]	77 [3]	2.6 [3]	-43.2 [3]	+4 [184]	-
TIP3P	2.35 [180]	82 [3]	5.19 [182]	-41.1 [180]	-91 [983]	9.2 [180]
TIP3P/Fw	2.57 [994]	193 [994]	3.53 [994]	-	-	7.81 [994]
TIP4P	2.18 [3,180]	53[a] [3]	3.29 [182]	-41.8 [180]	-25 [180]	4.4 [180]
TIP4P-Ew	2.32 [649]	62.9 [649]	2.4 [649]	-46.5 [649]	+1[649]	3.1[649]
TIP4P-FQ	2.64[197]	79 [197]	1.93 [197]	-41.4 [201]	+7 [197]	-
TIP4P/2005	2.305 [984]	60 [984]	2.08 [984]	-	+5 [984]	2.8 [984]
TIP4P/2005f	2.319 [1765]	55.3 [1765]	1.93 [1765]	-	+7 [1765]]	-
SWFLEX-AI	2.69 [201]	116 [201]	3.66 [201]	-41.7 [201]	-	-
COS/G3 **	2.57 [704]	88 [704]	2.6 [704]	-41.1 [704]	-	7.0 [704]
COS/D	2.43 [1617]	69.8 [1617]	2.5 [1617]	-41.8 [1617]	-	-
GCPM	2.723 [859]	84.3 [859]	2.26 [859]	-44.8 [859]	-13 [859]	-
SWM4-NDP	2.461 [933]	79 [933]	2.33 [933]	-41.5 [933]	-	-
TIP5P	2.29 [180]	81.5 [180]	2.62 [182]	-41.3 [180]	+4 [180]	6.3 [180]
TIP5P-Ew	2.29 [619]	92 [619]	2.8 [619]	-	+8 [619]	4.9[619]
TTM2-F	2.67 [1027]	67.2 [1027]	1.4 [1027]	-45.1 [1027]	-	-
POL5/TZ	2.712 [256]	98 [256]	1.81 [256]	-41.5 [256]	+25 [256]	-
Six-site *	1.89 [491]	33 [491]	-	-	+14 [491]	2.4 [491]
QCT **	1.85 [1251]	-	1.5 [1251]	-42.7 [1251]	+10 [1251]	3.5 [1251]
Experimental	2.95	78.4	2.30	-41.5 [180]	+3.984	2.53

Importancia del Agua

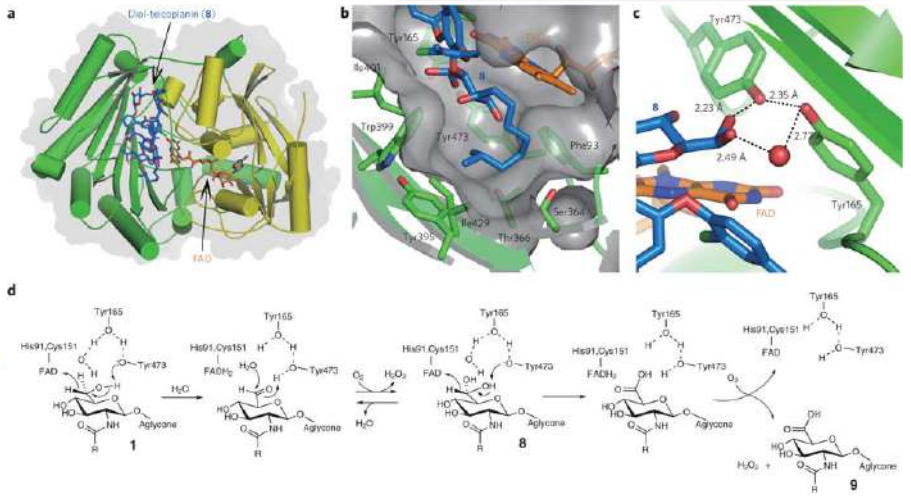
Frustración



Plegamiento

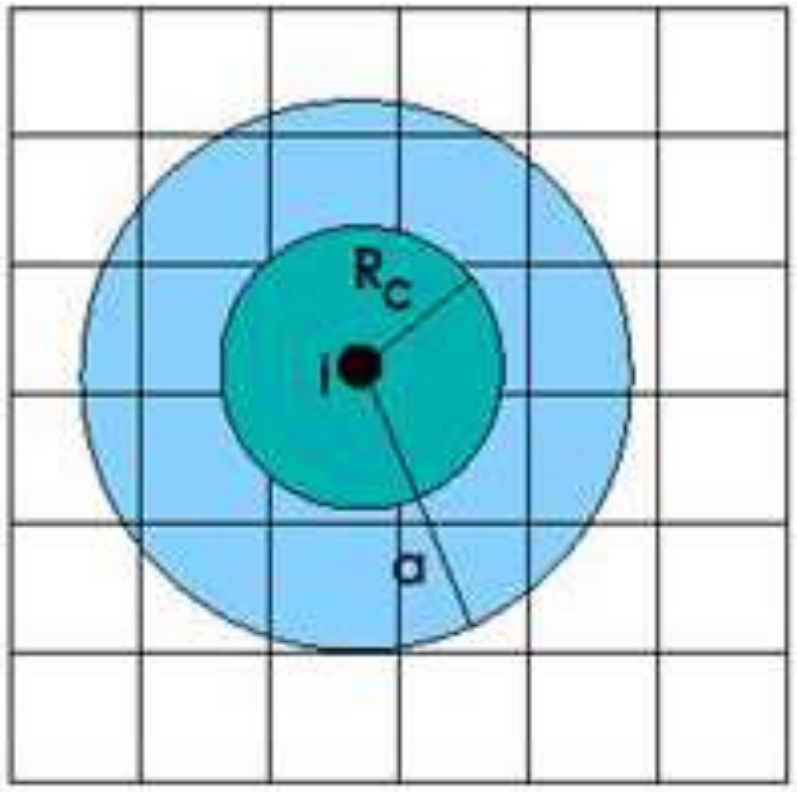


Reacción Enzimática



Interacciones de Largo Alcance

PME



Condiciones Periódicas de Borde

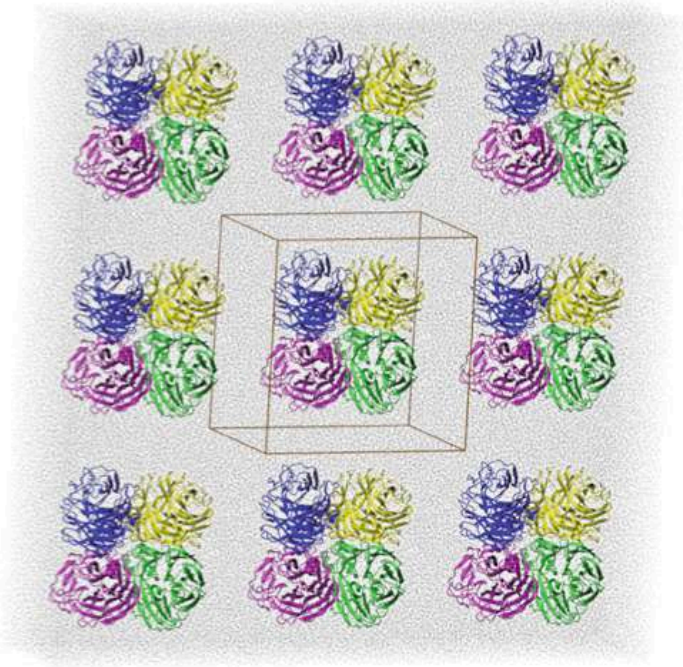


Fig. 3 The periodic boundary conditions. The original simulation box in the center is replicated throughout space to form an infinite lattice. For clarity, only eight replicas are shown in the figure

https://courses.physics.illinois.edu/phys466/sp2013/projects/2002/team1/Ewald3.htm

Ecuaciones de Movimiento: Algoritmo de Verlet.

Velocidad

Delta tiempo

Fuerza

Masa

Coordenadas

$$V_{n+\frac{1}{2}} = V_n + \frac{\Delta t}{2} M^{-1} F_n,$$

$$X_{n+1} = X_n + \Delta t V_{n+\frac{1}{2}},$$

$$F_{n+1} = F(X_{n+1}),$$

$$V_{n+1} = V_{n+\frac{1}{2}} + \frac{\Delta t}{2} M^{-1} F_{n+1}.$$

Delta tiempo: Este es valor de paso de integración de la secuencia, y debe ser de 10^{-15}s (1 fs) Para lograr la evaluación de los movimientos más rápidos de vibración de enlaces.

Trayectoria de una molécula

- Posiciones iniciales (x_0), PDB
  - Rayos X
  - NMR
  - Model
- Velocidades iniciales (v_0)
  - Acople a temperatura

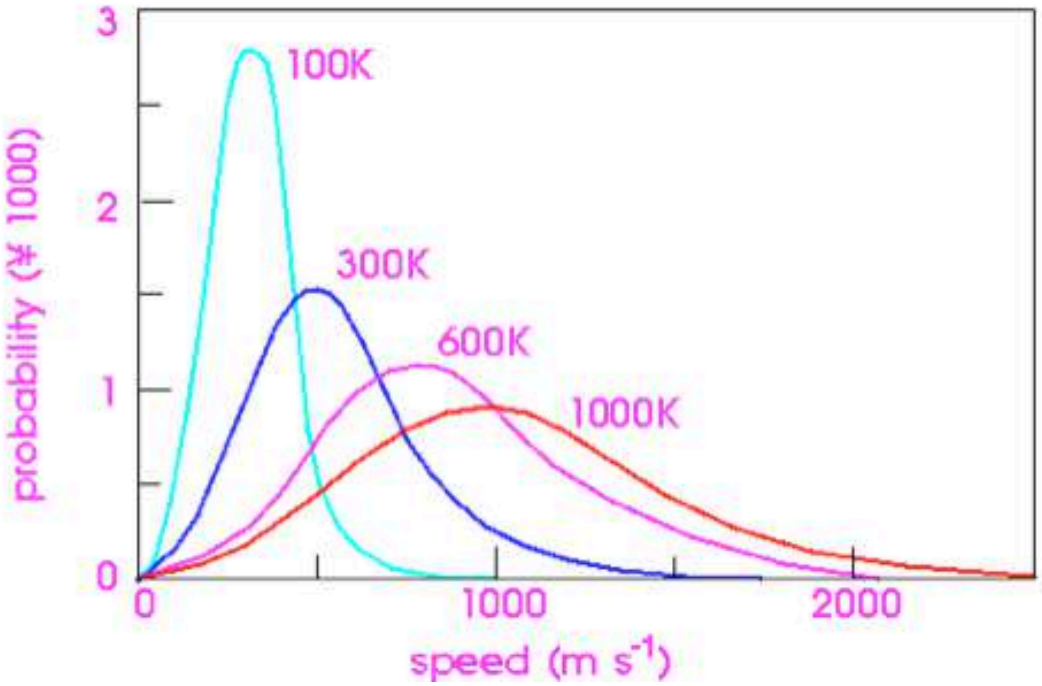
$$\frac{3}{2}NkT = \sum_i \frac{m_i v_i^2}{2}$$

- Acceleración
  - Calculada desde la fuerza, que es derivada desde la energía potencial.

$$a = -\frac{1}{m}\frac{dE}{dr}$$

Relación entre velocidad y temperatura

- La temperatura específica el estado termodinámico del sistema.
- La temperatura esta relacionada a la descripción microscópica de la simulación a través de la energía cinética.
- La energía cinética es calculada desde las velocidades atómicas.



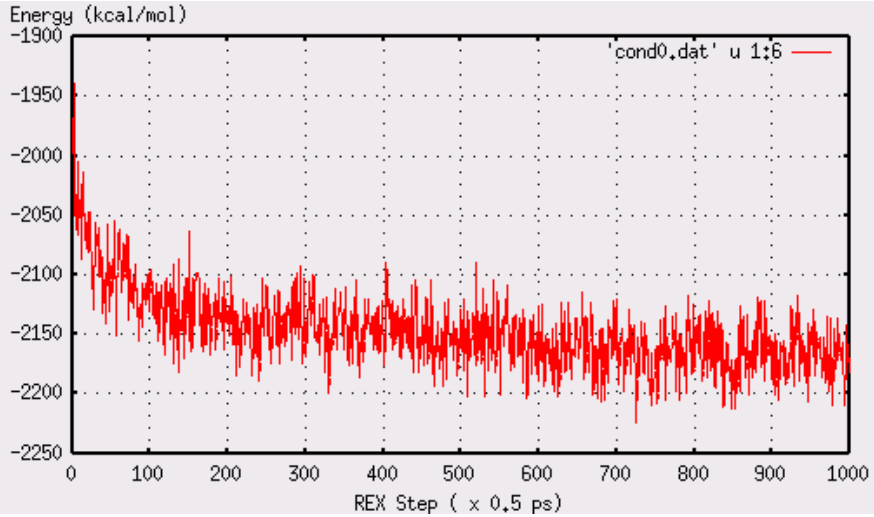
$$\frac{3}{2}NkT = \sum_i \frac{m_i v_i^2}{2}$$

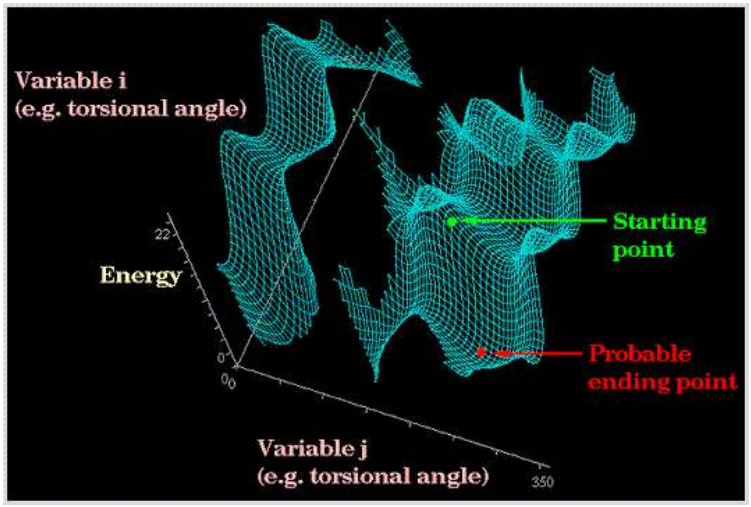
$$f(v)\,dv = \left(\frac{m}{2\pi kt}\right)^{3/2} e^{-\frac{mv^2}{2kT}} 4\pi v^2 dv$$

Minimización de Energía

Optimización geométrica

- Gradiente de Descenso.
- Gradiente Conjugado.
- Broyden-Fletcher-Goldfarb-Shanno (BFGS)



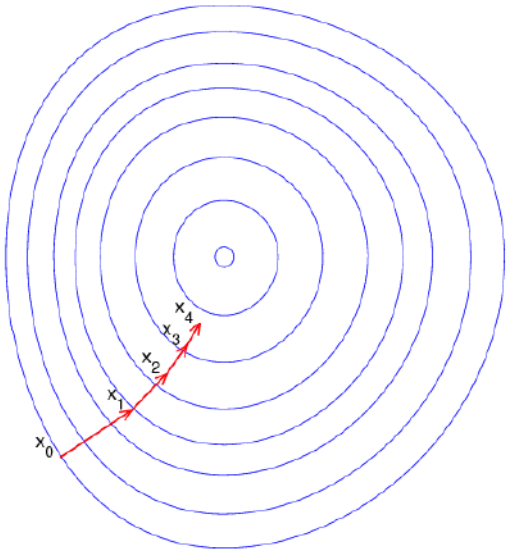


Python http://docs.scipy.org/doc/scipy/reference/tutorial/optimize.html
R stat http://stat.ethz.ch/R-manual/R-devel/library/stats/html/optim.html
SAGE http://www.sagemath.org/doc/reference/sage/numerical/optimize.html

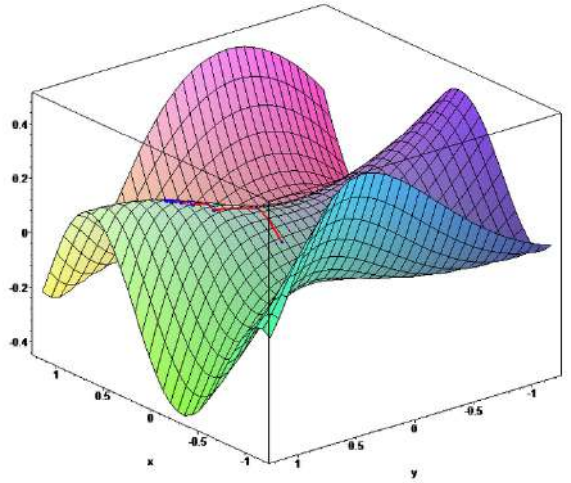
Optimización geométrica: Gradiente de descenso

$$\nabla E\big|_a \Rightarrow b \Rightarrow \nabla E\big|_b \Rightarrow c \Rightarrow \nabla E\big|_c \Rightarrow\Rightarrow\Rightarrow \nabla E\big|_{MIN} \cong 0 \Rightarrow fin$$

- *Ejemplo:*
  - $f(x)=x^4-3x^3+2$
  - $f'(x)=4x^3-9x^2$.

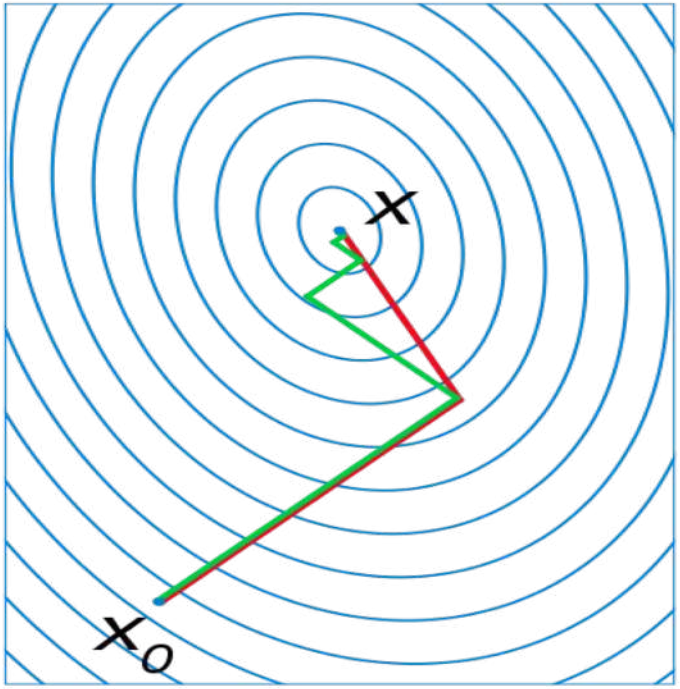



```
# From calculation, we expect that the local minimum occurs at x=9/4

x_old = 0
x_new = 6 # The algorithm starts at x=6
eps = 0.01 # step size
precision = 0.00001

def f_prime(x):
    return 4 * x**3 - 9 * x**2

while abs(x_new - x_old) > precision:
    x_old = x_new
    x_new = x_old - eps * f_prime(x_old)
print "Local minimum occurs at ", x_new
```



Optimización geométrica: Newton Gradiente Conjugado.

$$f(\mathbf{x}) = \frac{1}{2}\mathbf{x}^{\mathrm{T}}\mathbf{A}\mathbf{x} - \mathbf{x}^{\mathrm{T}}\mathbf{b}, \quad \mathbf{x} \in \mathbf{R}^n.$$

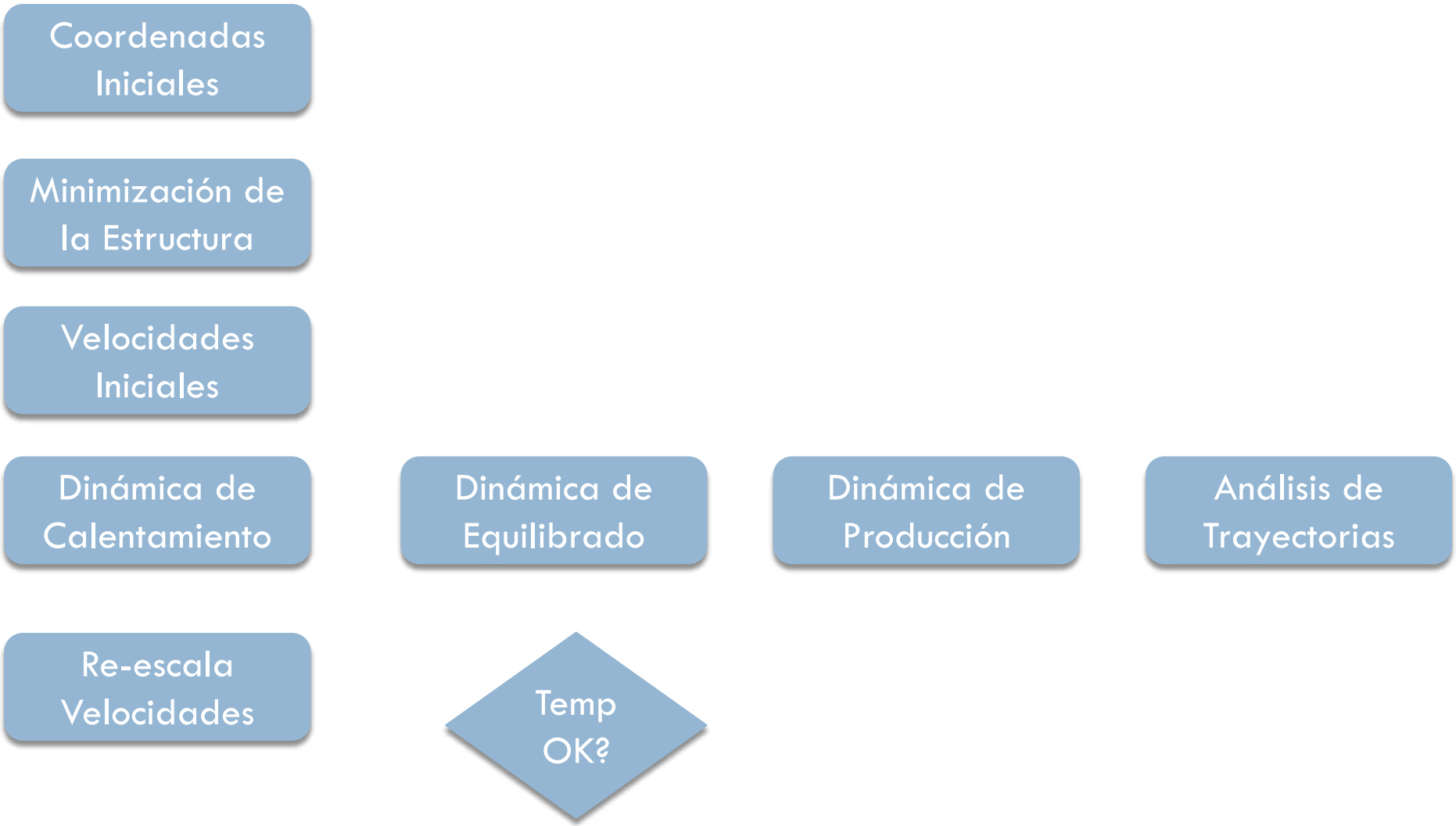



```
''' x, numIter = conjGrad(Av,x,b,tol=1.0e-9)
    Conjugate gradient method for solving [A]{x} = {b}.
    The matrix [A] should be sparse. User must supply
    the function Av(v) that returns the vector [A]{v}.
'''
from numpy import dot
from math import sqrt

def conjGrad(Av,x,b,tol=1.0e-9):
    n = len(b)
    r = b - Av(x)
    s = r.copy()
    for i in range(n):
        u = Av(s)
        alpha = dot(s,r)/dot(s,u)
        x = x + alpha*s
        r = b - Av(x)
        if(sqrt(dot(r,r))) < tol:
            break
        else:
            beta = -dot(r,u)/dot(s,u)
            s = r + beta*s
    return x,i
```

Protocolo MDS

- Coordenadas Iniciales
  - Coordenadas desde el PDB, obtenidas desde difracción de rayos X o NMR.
  - Coordenadas Construidas por modelamiento.
- Tratamiento de las interacciones no enlazantes.
  - Elección del método de truncado.
- Tratamiento del solvente.
  - Implícito. Elección de la constante dieléctrica.
  - Implícito. Born Generalizado, ACE, EFF1
  - Explicito. Protocolo de solvatación.
- Sí se usa tratamiento explicito del solvente > condiciones periódicas de borde.
  - PBC
  - Esfera de solvatación
  - Dinámica de sitio activo.
  - Selección del paso de integración para las ecuaciones de movimiento.

Pasos de una DM



Software Para Análisis de Trayectorias

- Scripts VMD. http://www.ks.uiuc.edu/Research/vmd/script_library
- Otras herramientas de Urbana. http://www.ks.uiuc.edu/Development/MDTools
- CATCDC. http://www.ks.uiuc.edu/Development/MDTools/catdcd
- **Bio3D**.
  Bio3D: An R package for the comparative analysis of protein structures.
  Grant, Rodrigues, ElSawy, McCammon, Caves, (2006) Bioinformatics 22, 2695-2696. Wiki http://bio3d.pbworks.com
- **ProDy**.
  ProDy: Protein Dynamics Inferred from Theory and Experiments
  Bakan A, Meireles LM, Bahar I. 2011 Bioinformatics 27(11):1575-1577.
- **Wordom**.
  Michele Seeber, Marco Cecchini, Francesco Rao, Giovanni Settanni and Amedeo Caflisch. Wordom: a program for efficient analysis of molecular dynamics simulations; Bioinformatics, 2007, 23(19):2625-2627
- mdAnalysis- Googlecode http://code.google.com/p/mdanalysis
- Gromacs Tools.
  http://sbcb.bioch.ox.ac.uk/users/oliver/software/GromacsWrapper/html/gromacs/core/tools.html

Propiedades que pueden ser calculadas desde una MDS

- Energía Promedio

$$\langle E \rangle = \frac{1}{N}\sum_{i=1}^{N} E_i$$

- RMSD

$$RMS = \left\langle \left(r_i^{\alpha} - r_i^{\beta} \right)^2 \right\rangle^{\frac{1}{2}} = \sqrt{\frac{1}{N_i}\sum_i \left(r_i^{\alpha} - r_i^{\beta} \right)^2}$$

- Fluctuaciones

$$RMS_i^{fluct} = \sqrt{\frac{1}{N_f}\sum_f \left(r_i^f - r_i^{ave} \right)^2}$$

- Factores de temperatura

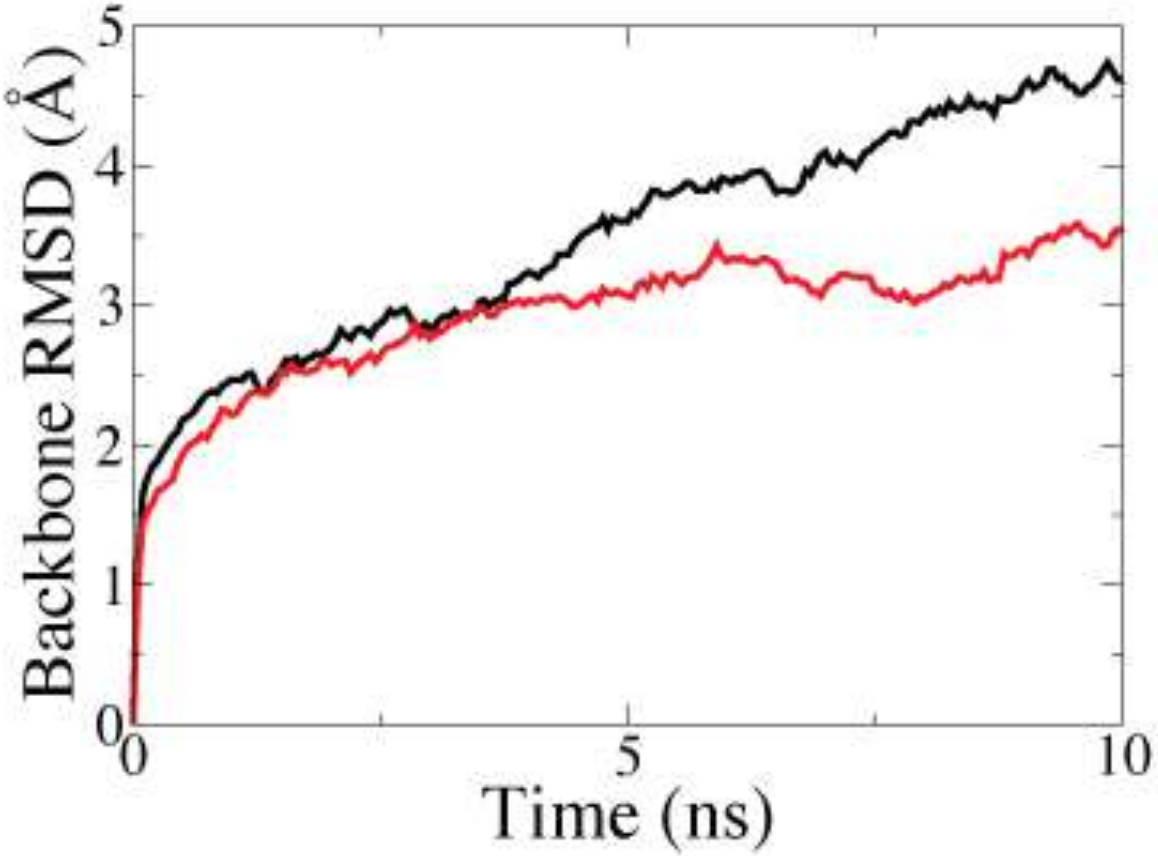
$$B_i = \frac{8}{3}\pi^2 \left(RMS_i^{fluct} \right)^2$$

- Radio de giro

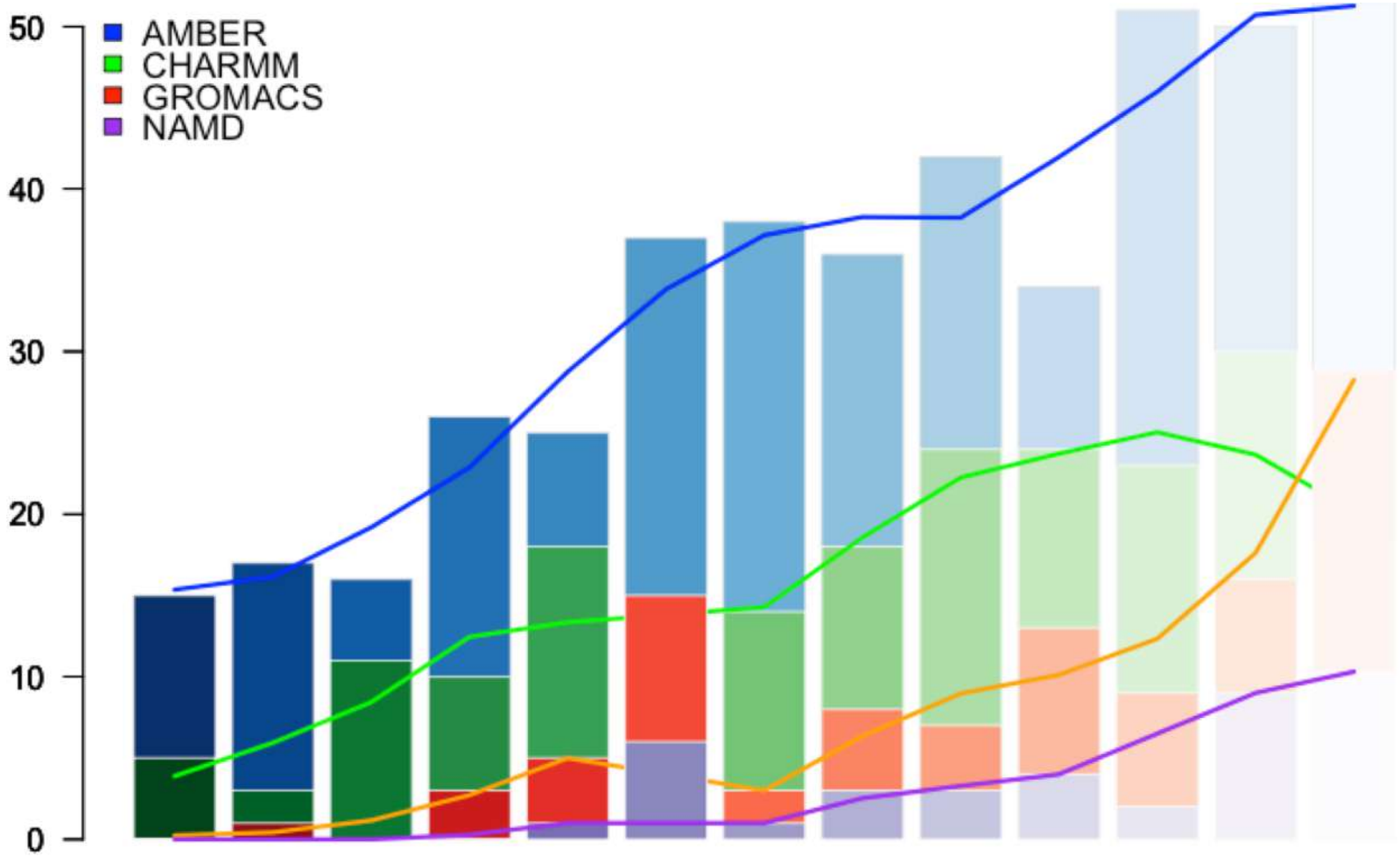
$$RadiusGyration = \sqrt{\frac{1}{Ni}\sum_i \left(r_i - r_{cm} \right)^2}$$

- Largos de Enlace (H-bond)
- Estructuras Secundarias.

RMSD



Programas Para Calcular Simulaciones de Dinámica Molecular



Software para realizar SMD.

- AMBER http://ambermd.org
- CHARMM http://www.charmm.org
- GROMACS http://www.gromacs.org
- NAMD http://www.ks.uiuc.edu/Research/namd

Cursos de MDS

- VMD/NAMD
  http://www.ks.uiuc.edu/Training/Tutorials
- GROMACS http://md.chem.rug.nl/~mdcourse

NAMD

- **Software Setup**
  - Libre de bajar y utilizar.
  - Binarios precompilados para 12 plataformas.
  - Instalado en los principales supercomputadores.
  - Portable a cualquier plataforma vía red o MPI.
  - Acceso al código fuente C++ y CVS para modificación.

- **Molecule Building**
  - Uso de VMD para preparar los ensambles para las simulaciones.
  - También lee archivos X-PLOR, CHARMM, AMBER y GROMACS.
  - La herramienta Psfgen genera archivos de estructura y coordenadas para el campo de fuerza CHARMM.
  - Eficiente Minimización con gradiente conjugado.
  - Permite fijar átomos o restringir sus movimientos.
  - Equilibrado termal vía re-escalamiento periodico, reiniciación o dinámica de Langevin.

- **Basic Simulation**
  - Mantención de la temperatura meiante re-escalado, acople o dinámica de Langevin.
  - Presión constante vía métodos de Berendsen o Langevin Nose-Hoover.
  - Cálculo de la electrostática con *Particle mesh Ewald* para sistemas periodicos.
  - Pasos de integración múltiple.
  - Rígidez de aguas y enlaces a átomos hidrógeno.

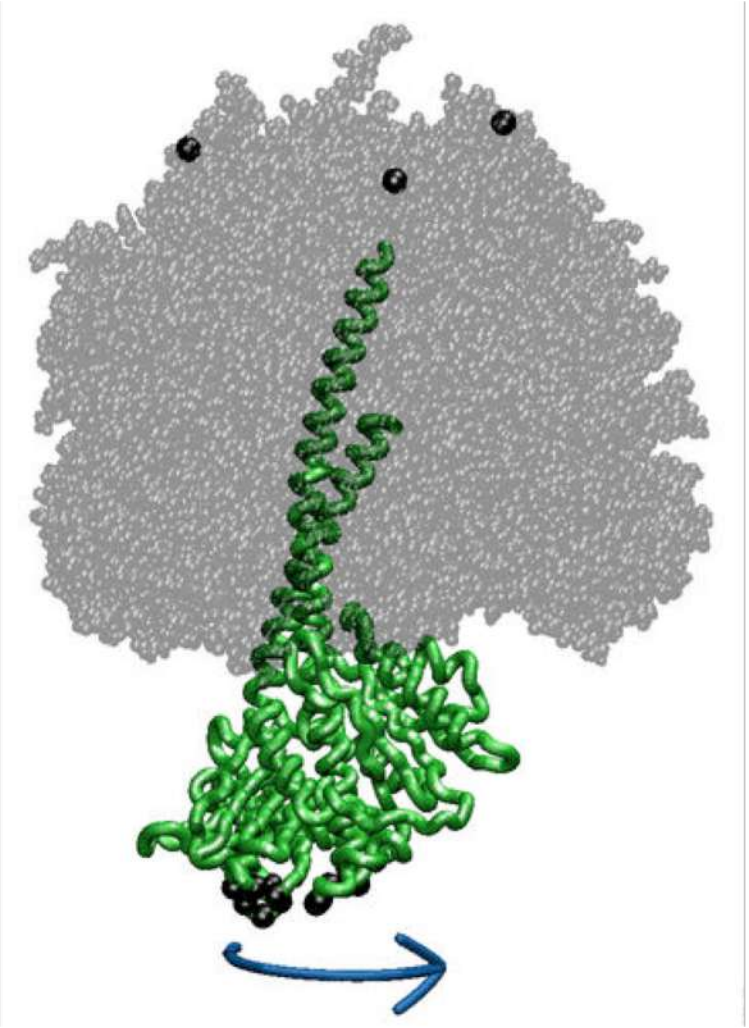
- **Advanced Simulation**
  - Cálculos de energía libre conformacional y química.
  - Muestreo lacal aumentado vía múltiples imágenes.
  - Aplicación de fuerzas vía scripts en Tcl.
  - Análisis implementado en scripts en Tcl en VMD.
  - Visualización interactiva con VMD.

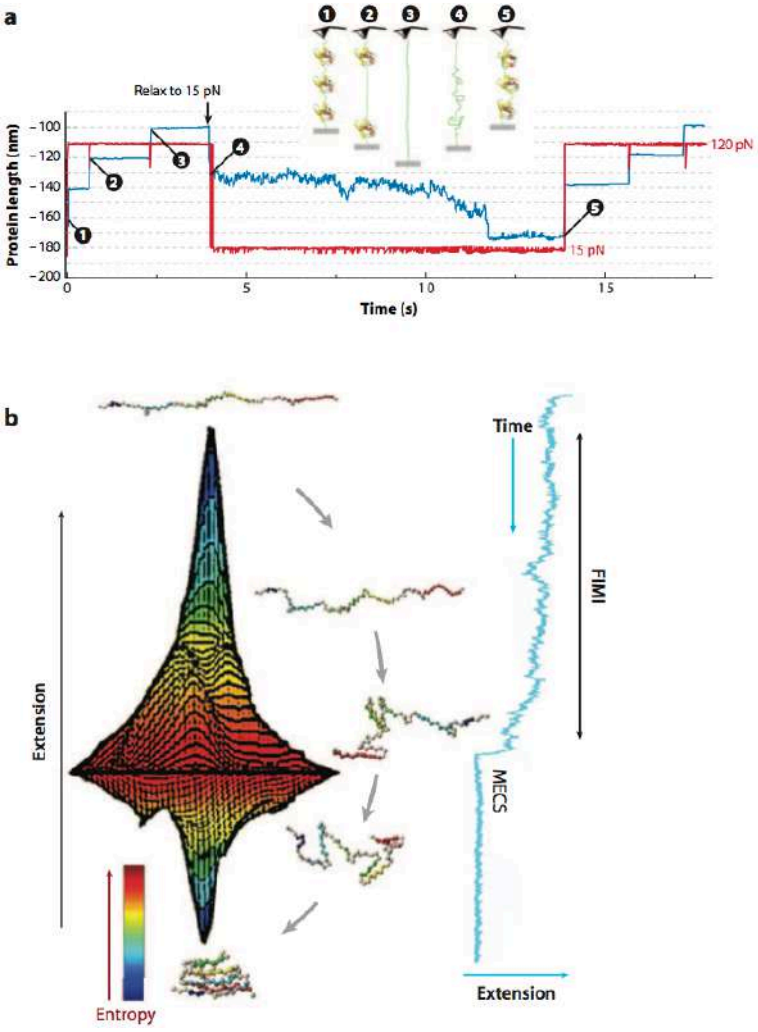
- **Scalable Performance**
  - Basado en un sistema de corrida en paralelo Charm++/Converse.
  - Permite realizar simulaciones largas de sobre 300,000 átomos en 1000 procesadores.

Dinámicas Avanzadas (DA)

- Steered MD
- Adaptative Biasing Force (ABF)
- Free Energy Perturbations (FEP)
- Target Molecular Dynamics.
- REM
- Coarse Grained MD

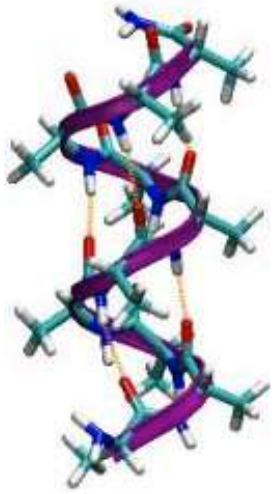
Steered MD




a
Relax to 15 pN
120 pN
15 pN
Protein length (nm)
Time (s)
b
Time
FIMI
MECS
Extension
Extension
Entropy

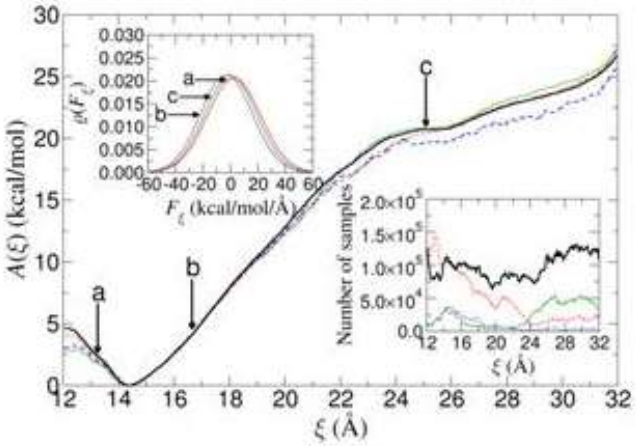
Adaptative Biasing Force (ABF)

- Se utilizan pequeñas ventana donde se calcula la energía con la aplicación de una fuerza que pasa las barreras energéticas conformacionales.



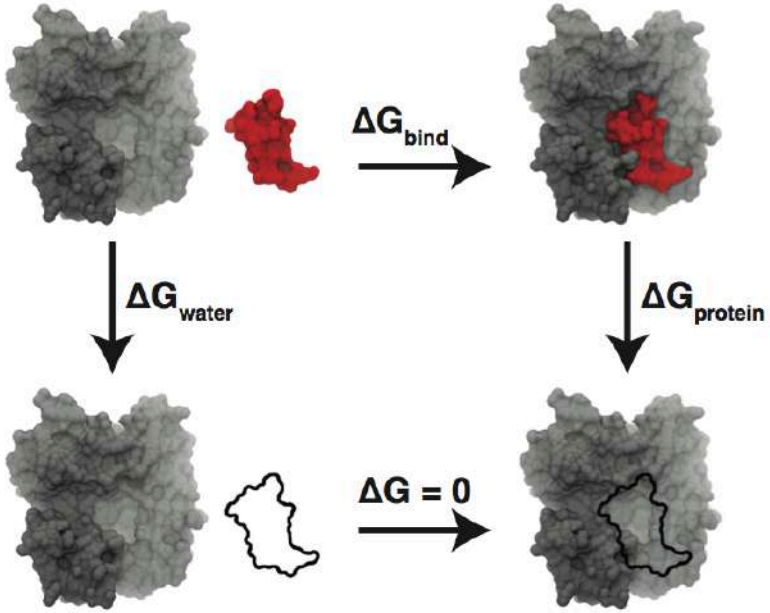
$$dA(\xi)/d\xi = \langle \partial V(\mathbf{x}) / \partial \xi \rangle_{\xi} - 1/\beta \langle \partial \ln |J| / \partial \xi \rangle_{\xi} = -\langle F_{\xi} \rangle_{\xi}$$

$$\mathbf{F}^{ABF} = -\langle F_{\xi} \rangle_{\xi} \nabla_{\xi} \xi$$



http://www.edam.uhp-nancy.fr/ABF

Free Energy Perturbations: FEP

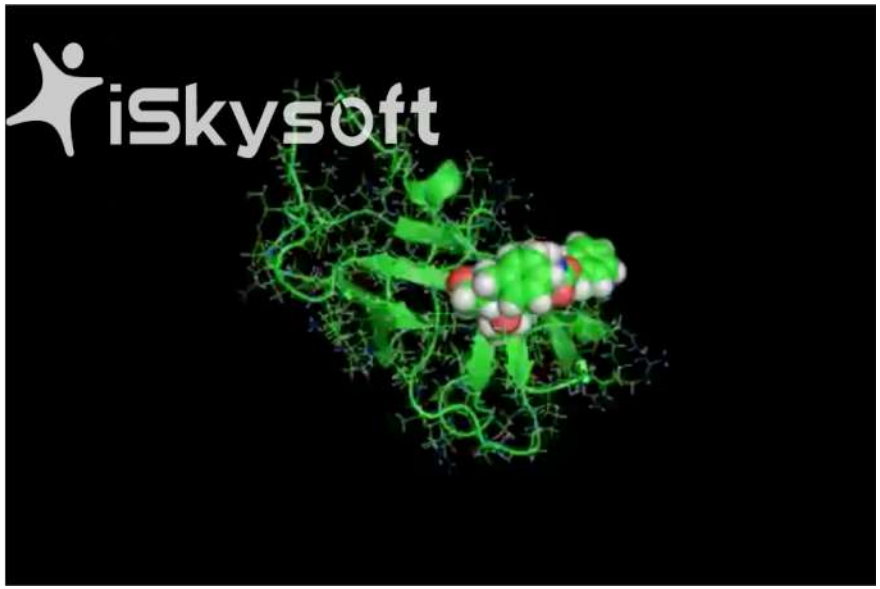


$$\Delta G_{bind} + \Delta G_{protein} - \Delta G - \Delta G_{water} = 0$$

$$\Delta G_{bind} + \Delta G_{protein} - \Delta G_{water} = 0$$

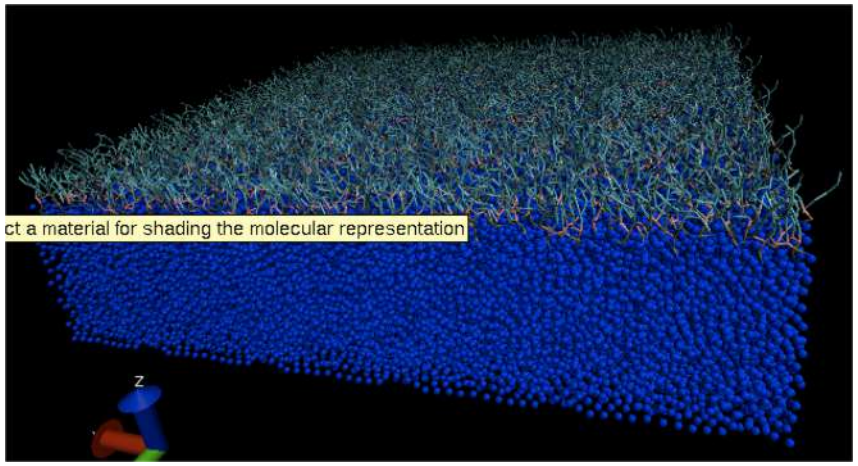
$$\Delta G_{bind} = \Delta G_{water} - \Delta G_{protein}$$

Figure 4. The thermodynamic cycle used for selecting alchemical transformations. Typically, one wishes to calculate the free energy of binding, ΔG_{bind}, shown across the top. However, it is generally impractical to run a molecular dynamics simulation long enough to capture an entire binding event. Instead, a series of alchemical transformations are performed using molecular dynamics simulations. $\Delta G_{protein}$ is the change in free energy that occurs when a bound ligand is 'annihilated'. ΔG is the change in free energy that occurs when an unbound 'ghost' ligand binds to the receptor; however, since a ghost ligand is not able to interact with any solvent or receptor atoms, this energy is always zero. Finally, ΔG_{water} is the change in free energy that occurs when an unbound ligand in solution is 'annihilated'. A system that proceeds from one state around this free-energy cycle only to return to the same initial state should have no change in total free energy; consequently, $\Delta G_{bind} = \Delta G_{water} - \Delta G_{protein}$.



The first results were a performance study between the constructed CG and FG monolayer systems.

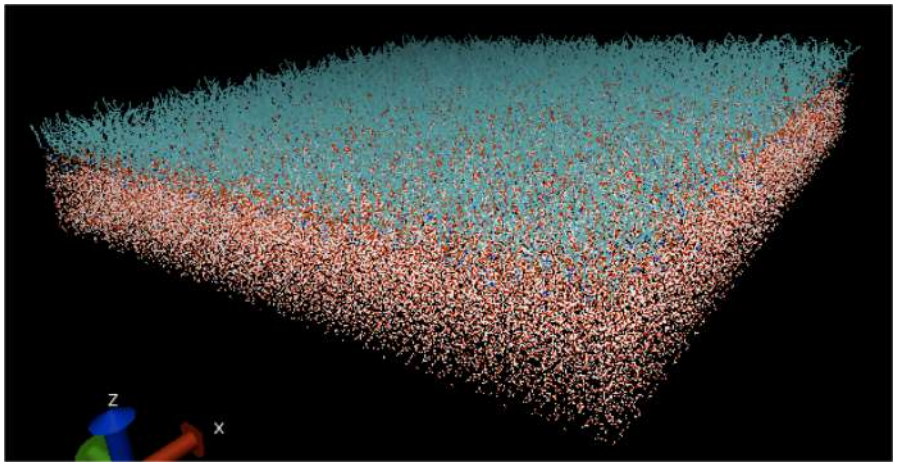
CG model



dt = 40fs

96,650 atoms

FG model



dt = 2fs

431,900 atoms

Performance at 120 processors

~ 1200 ns/day

~9 ns/day

Dinámicas de Grano Grueso

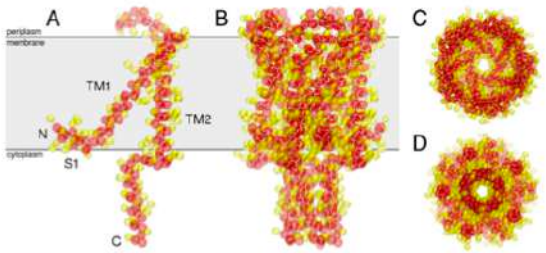


Fig. 1. Mechano-sensitive channel of large conductance. X-ray crystal structure (white licorice) overlaid with a coarse-grained protein mc in red; side chains in yellow). (A) Single subunit showing transmembrane helices TM1 and TM2, N-terminal helix S1, and the C-terminal he with all five subunits, (C) periplasmic view inside the channel, and (D) cytoplasmic view at the C-terminal helix bundle.

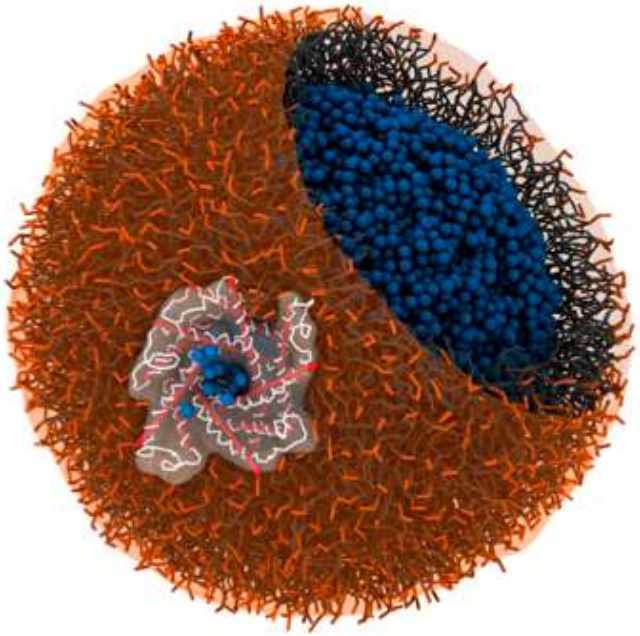


Fig. 3. A MscL in a liposome, right at the point of channel activation. Excess solvent (blue) is released from the pressurized liposome interior through the protein that acts as a nano-valve. For clarity, external water is not shown, the protein is shown as a backbone trace on a transparent surface representation (white) with transmembrane helices depicted as cylinders (red), and some of the lipids are cut away to reveal the inside of the liposome.

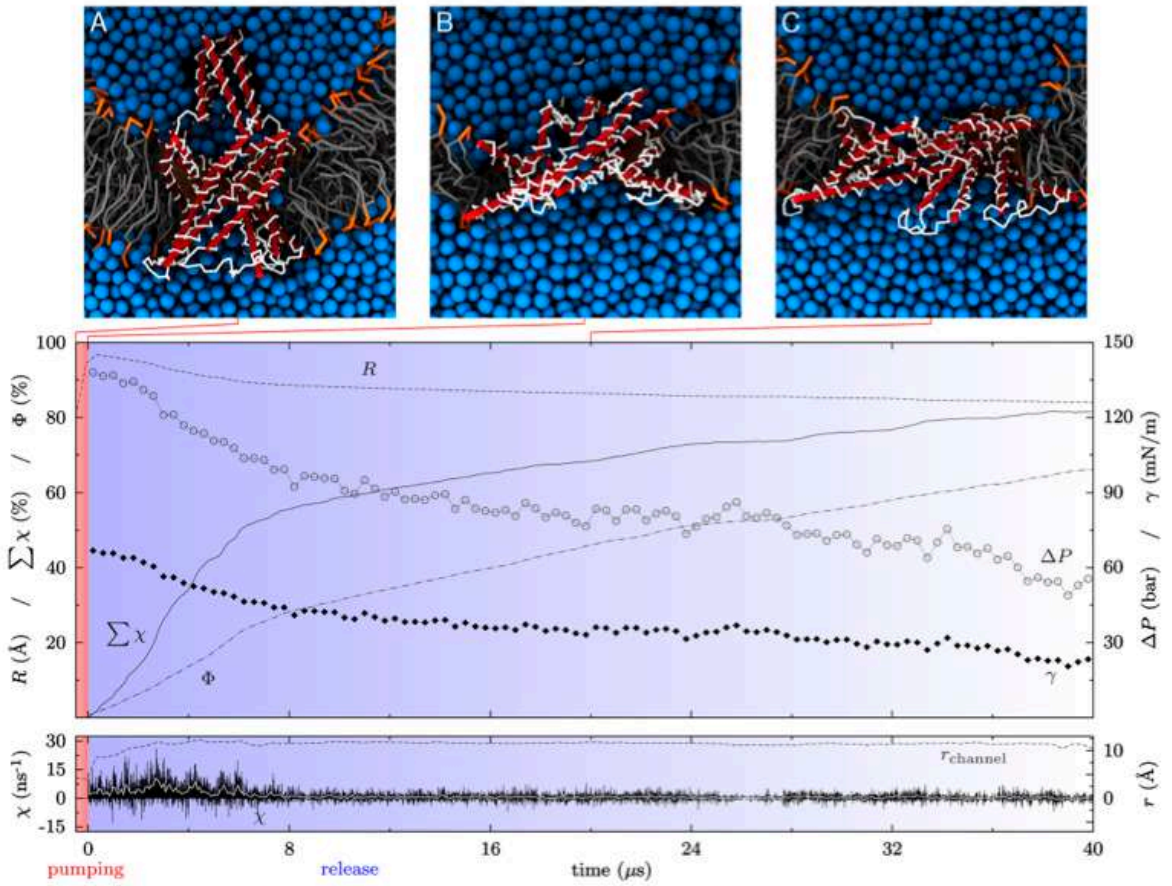
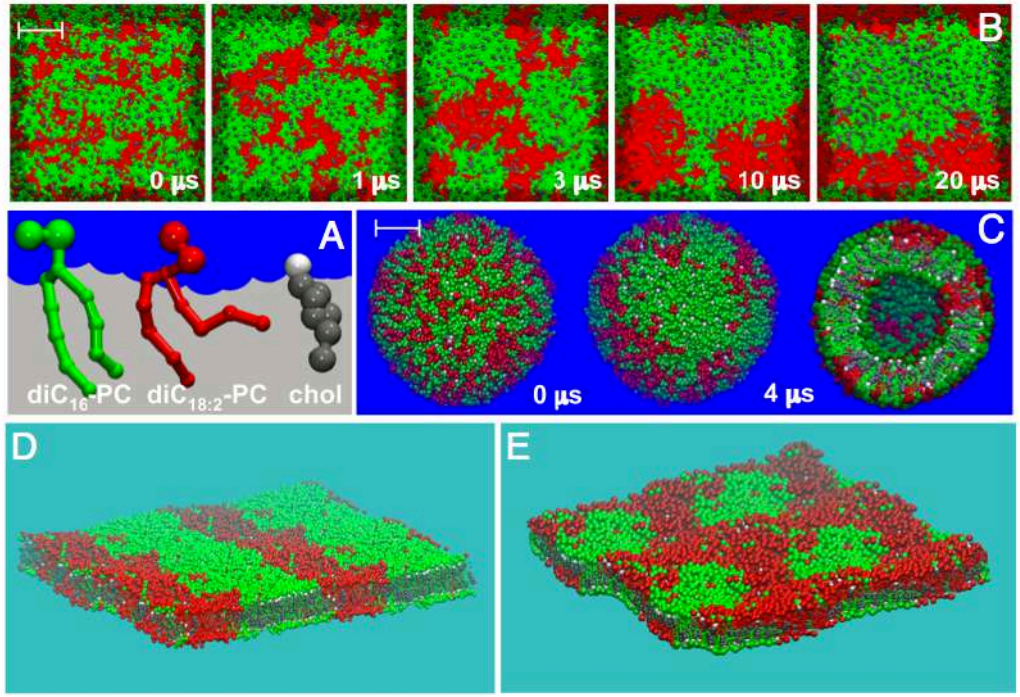
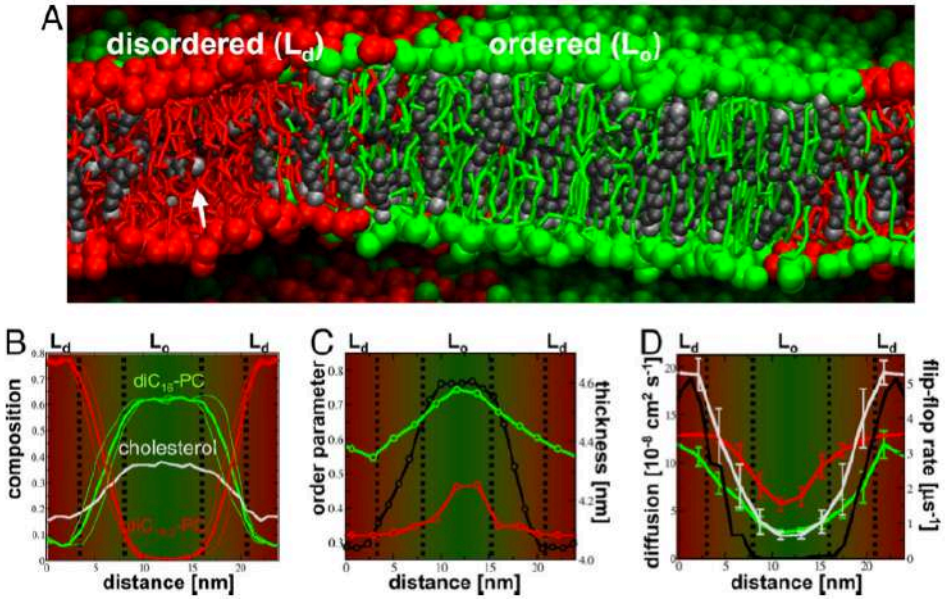


Fig. 4. Relaxation of a stressed liposome after channel activation by MscL-mediated solvent flux. Radius of the liposome (R), the pressure difference (ΔP) between the inside and the outside of the liposome, the surface tension (γ) in the membrane, the net amount of internal solvent transported outside the liposome ($\sum \chi$), and the normalized molar fraction (Φ) of internal solvent initially located outside the liposome are shown in the upper plot. The radius of the channel (r) and the momentary flux events (χ) are shown in the lower plot with the white line showing the net flux over 80-ns intervals. Above, snapshots of the protein and the surrounding lipids and water are shown (A) for the initial, closed channel; (B) for the activated, open channel; and (C) for the channel with a partially dissociated cytoplasmic helix bundle.

Louhivuori, M.; Risselada, H. J.; van der Giessen, E. & Marrink, S. J. (2010) 'Release of content through mechano-sensitive gates in pressurized liposomes.' *Proc Natl Acad Sci U S A* ***107(46), 19856—19860.***

Dinámicas de Grano Grueso





Risselada, H. J. & Marrink, S. J. (2008)
'The molecular face of lipid rafts in model membranes.'
Proc Natl Acad Sci U S A ***105(45), 17367—17372.***

Dinámicas de Grano Grueso

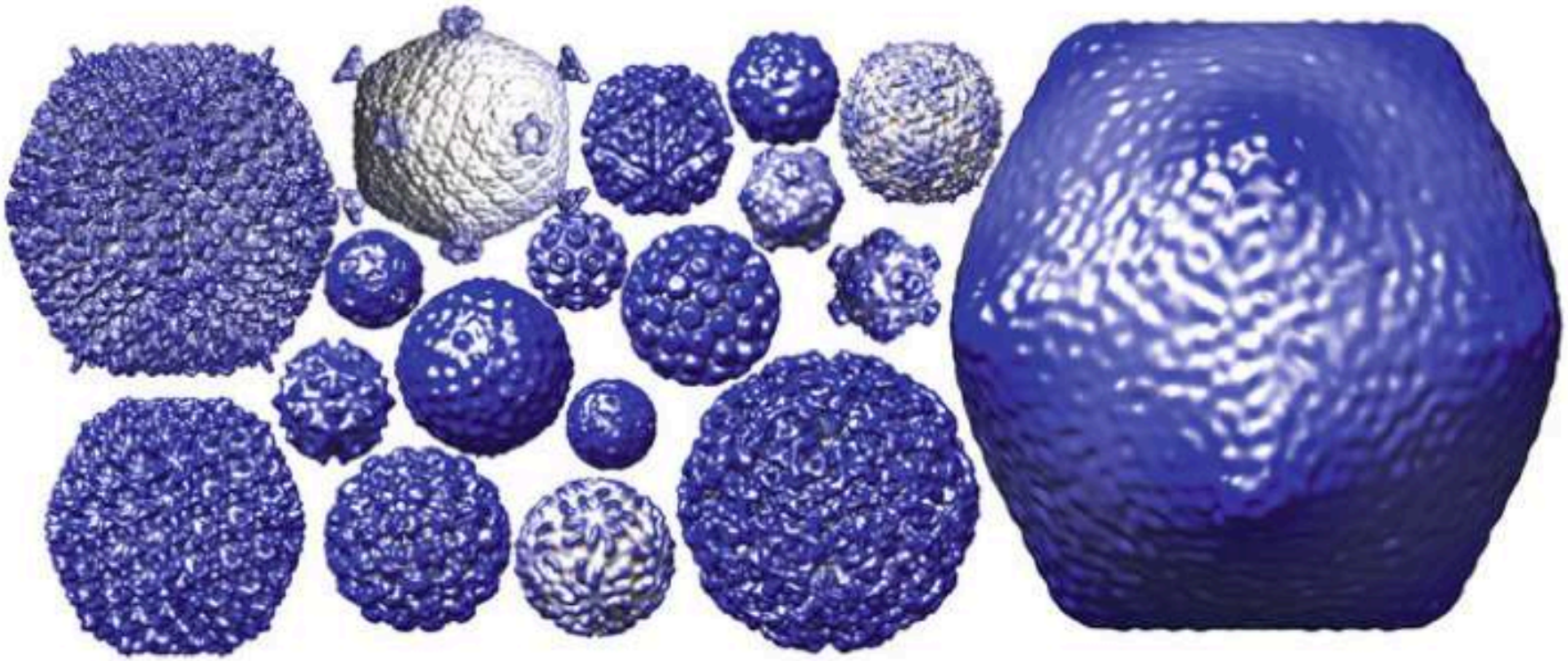


Fig. 1 As evident in the collage above, capsids come in a range of sizes (images represent electron microscopy reconstructions deposited into the virus particle explorer web site: viperdb.scripps.edu)

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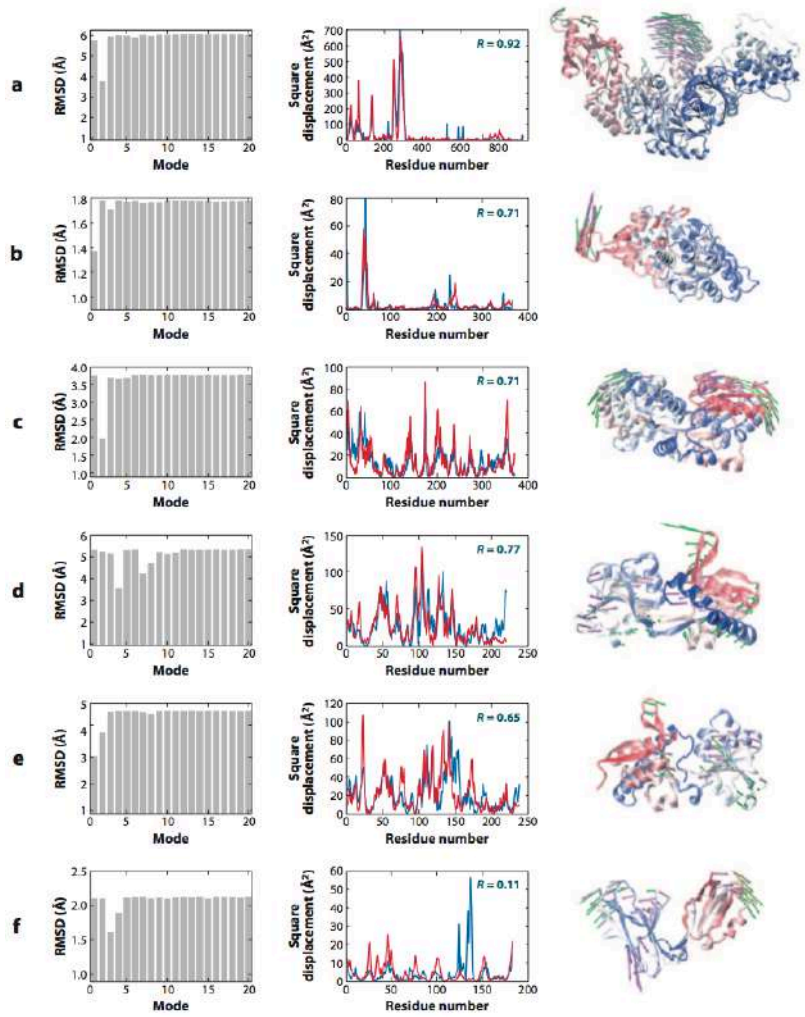
Modelos Elásticos


a
RMSD (Å)
Mode
Square displacement (Å²)
Residue number
R = 0.92
b
R = 0.71
c
R = 0.71
d
R = 0.77
e
R = 0.65
f
R = 0.11

Dinámicas con ligando

Energías de Unión