Molecular dynamics simulations

Biophysical Chemistry II, Spring 2014

Basics of molecular mechanics and dynamics
  Statistical mechanics of liquids
  Basic ideas of continuum solvation
  The MM/PBSA model
  Mechanical properties (of DNA)
1901 (and earlier?) ball and stick models

Baird & Tatlock 1901
1950s: wire models of proteins
- separate nuclei and electrons
- polarisation, electron transfer and correlation
- can specify electronic state
- can calculate formation energies
- can do chemistry (bond breaking and making)
- variationally bound
- computationally expensive
- typically ~10-100 atoms
- dynamics ~1 ps

QM MOLECULE
Nuclei
Electrons
- no explicit electrons, net atomic charges
- no polarisation, electron transfer or correlation
- conformational energies for ground state
- no chemistry
- semi-empirical force fields
- not variationally bound
- solvent and counterion representations
- typically ~1000-100000 atoms
- dynamics up to ~100 ns

MM MOLECULE
Some force field assumptions

1. **Born-Oppenheimer approximation** (separate nuclear and electronic motion)
2. **Additivity** (separable energy terms)
3. **Transferability** (look at different conformations, different molecules)
4. **Empirical** (choose functional forms and parameters based on experiment)
What does a force field look like?

\[ U = \sum_{\text{bonds}} K_b (b - b_{eq})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{eq})^2 + \sum_{\text{improvers}} K_w w^2 + \sum_{\text{torsions}} K_\phi \cos(n\phi) + \sum_{\text{nonbonded pairs}} \left\{ 4\varepsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^{6} \right] + \frac{q_i q_j}{r} \right\} \]

Amber tradition for parameters:
- top line from X-ray structures, quantum calculations, vibrational spectroscopy
- partial charges from fits to electrostatic potential from HF/6-31G*
- van der Waals \( \varepsilon, \sigma \) from neat liquids (not water/solute simulations)
- torsional parameters from quantum calculations
Lennard-Jones energy curve
Distance dependence

Energy (kcal/mol)

Rij (angstroms)

Electrostatic

Lennard-Jones
<table>
<thead>
<tr>
<th>Atom Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H bonded to nitrogen atoms</td>
</tr>
<tr>
<td>HC</td>
<td>H aliph. bond. to C without electrwd. group</td>
</tr>
<tr>
<td>H1</td>
<td>H aliph. bond. to C with 1 electrwd. group</td>
</tr>
<tr>
<td>H2</td>
<td>H aliph. bond. to C with 2 electrwd. groups</td>
</tr>
<tr>
<td>H3</td>
<td>H aliph. bond. to C with 3 electrwd. groups</td>
</tr>
<tr>
<td>HA</td>
<td>H arom. bond. to C without electrwd. groups</td>
</tr>
<tr>
<td>H4</td>
<td>H arom. bond. to C with 1 electrwd. group</td>
</tr>
<tr>
<td>H5</td>
<td>H arom. bond. to C with 2 electrwd. groups</td>
</tr>
<tr>
<td>HO</td>
<td>Hydroxyl group</td>
</tr>
<tr>
<td>HS</td>
<td>Hydrogen bonded to sulphur</td>
</tr>
<tr>
<td>HW</td>
<td>H in TIP3P water</td>
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<tr>
<td>HP</td>
<td>H bonded to C next to positively charged gr</td>
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</tbody>
</table>

**AMBER parm94 H atom types**
<table>
<thead>
<tr>
<th>C</th>
<th>sp2 C carbonyl group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>sp2 C pure aromatic (benzene)</td>
</tr>
<tr>
<td>CB</td>
<td>sp2 aromatic C, 5&amp;6 membered ring junction</td>
</tr>
<tr>
<td>CC</td>
<td>sp2 aromatic C, 5 memb. ring HIS</td>
</tr>
<tr>
<td>CK</td>
<td>sp2 C 5 memb. ring in purines</td>
</tr>
<tr>
<td>CM</td>
<td>sp2 C pyrimidines in pos. 5 &amp; 6</td>
</tr>
<tr>
<td>CN</td>
<td>sp2 C aromatic 5&amp;6 memb. ring junct.(TRP)</td>
</tr>
<tr>
<td>CQ</td>
<td>sp2 C in 5 mem. ring of purines between 2 N</td>
</tr>
<tr>
<td>CR</td>
<td>sp2 arom as CQ but in HIS</td>
</tr>
<tr>
<td>CT</td>
<td>sp3 aliphatic C</td>
</tr>
<tr>
<td>CV</td>
<td>sp2 arom. 5 memb. ring w/1 N and 1 H (HIS)</td>
</tr>
<tr>
<td>CW</td>
<td>sp2 arom. 5 memb. ring w/1 N-H and 1 H (HIS)</td>
</tr>
<tr>
<td>C*</td>
<td>sp2 arom. 5 memb. ring w/1 subst. (TRP)</td>
</tr>
</tbody>
</table>

**AMBER parm94 C atom types**
Force fields in Amber

- **ff94**: widely used ("Cornell et al."), pretty good nucleic acid, too much $\alpha$-helix for proteins
- **ff99**: major recalibration by Junmei Wang and others; basis for most current Amber ff’s
- **ff99SB**: recalibration of backbone potentials for proteins by Carlos Simmerling ("SB")
- **ff02r1**: polarizable extension for ff99
- **ff03**: new charge model (Yong Duan) + backbone torsions for proteins
- **ff03ua**: united atom extension
Periodic boundary conditions
Basics of the Ewald approach

direct, short-ranged, smooth, use FFT
Minimization and simulated annealing
The Simplex algorithm

See Numerical Recipes, by Press, Teukolsky, Verretling and Flannery
Eq. (1) is the original Verlet propagation algorithm; Eqs. 2 and 3 are the “leap-frog” version of that. Remember that
\[ a = d^2x/dt^2 = F/m = -\left(\partial V/\partial x\right)/m. \]
Regulating temperature

“Temperature” is a measure of the mean kinetic energy. The instantaneous KE is

\[ T(t) = \frac{1}{k_B N_{dof}} \sum_{i} m_i v_i^2 \]

(cf. classical rule of thumb: “\( k_B T / 2 \) of energy for every squared degree of freedom in the Hamiltonian”)

Suppose the temperature is not what you want. At each step, you could scale the velocities by:

\[ \lambda = \left[ 1 + \frac{\hbar}{2\tau} \left( \frac{T_0}{T(t)} - 1 \right) \right]^{1/2} \]

This is the “Berendsen” or “weak-coupling” formula, that has a minimal disruption on Newton’s equations of motion. But it does not guarantee a canonical distribution of positions and velocities. See Morishita, J. Chem. Phys. 113:2976, 2000; and Mudi and Chakravarty, Mol. Phys. 102:681, 2004.
Langevin dynamics

Consider the stochastic, Langevin equation:

\[
\frac{dv}{dt} = -\zeta v + A(t)
\]

By Stokes’ law, the friction coefficient is related to the viscosity of the environment: \( \zeta = \frac{6\pi \alpha \eta}{m} \). At long times, we want this system to go to equilibrium at a temperature \( T \), which is a Maxwell-Boltzmann distribution:

\[
W(v, t; v_0) \sim \exp \left[ -\frac{mv^2}{2k_B T} \right]
\]

for every value of \( v_0 \). This places restraints on the properties of the stochastic force \( A(t) \). It can be shown that

\[
\zeta = (\beta / m) \langle A^2 \rangle
\]

where we have assumed that \( \langle A \rangle = 0 \) and \( \langle A(0)A(t) \rangle = \langle A^2 \rangle \delta(t) \).
More coarse-grained potentials

Remove non-polar hydrogens

United atom approximation
Go model for protein folding

- square-well potential
- native contacts "+1"
- non-native contacts "-1"
- cannot represent frustration during folding
Gaussian network model

\[ r_{ij}^n < R_{cut} \]

\[ E_{ij} = k (r_{ij} - r_{ij}^n)^2 \]
Conformational energy changes

\[ \frac{\rho_B}{\rho_A} = K_{eq} = \exp(-\Delta A/kT) \]

To create a potential of mean force:

\[ \rho_i = \exp(-W(\delta_i)/kT) \]
Knowledge-based potentials

- Start from set of known protein structures
- Assume energy can be decomposed into residue pair interactions
- Assume that frequency of interactions within the ensemble = frequency of interactions within the equilibrium ensemble of a single protein
- Derive potential of mean force for residue pairs from observed occurrence probabilities
- Knowledge-based potentials are used in both threading and folding

Reduced distribution functions

Now $\rho(\delta)$ is a reduced distribution function:

$$\rho(\delta) = \frac{\int \exp(-\beta V)d\Sigma}{\int \exp(-\beta V)d\delta d\Sigma}$$

In order to improve sampling in high-energy regions, add a biasing (umbrella) potential $U(\delta)$. Then the observed (simulated) reduced distribution will be:

$$\rho^*(\delta) = e^{-\beta U(\delta)} \frac{\int \exp(-\beta V)d\Sigma}{\int \exp(-\beta(U+V))d\delta d\Sigma}$$

$$= e^{-\beta U(\delta)} \frac{\int \exp(-\beta V)d\Sigma}{\int \exp(-\beta V)d\delta d\Sigma} \frac{\int \exp(-\beta(U+V))d\delta d\Sigma}{\int \exp(-\beta U)\exp(-\beta V)d\delta d\Sigma}$$

$$= e^{-\beta U(\delta)} \rho(\delta) / \left< e^{-\beta U} \right>$$
Taking logarithms:

$$W^*(\delta) = W(\delta) + U(\delta) + kT \ln \left< e^{-\beta U} \right>$$

Note that the final term is independent of $\delta$. These can be treated as adjustable parameters, determined so that the $W(\delta)$ values from adjacent windows agree in their overlap region. See J. Comput. Chem. 16, 1339 (1995).
Example of explicit solvation setup
Basic ideas of continuum solvent models


$$\Delta W = -\frac{1}{2}(1-1/\epsilon)q/\rho$$

Born Approximation: (1929)
Conductor-like Screening Model

\[ E = E_{\text{gas}} + \int \frac{\sigma_1}{r_{ij}} \, d \sigma + \frac{1}{2} \int \sigma \left( \frac{1}{r_{ij}} + \frac{1}{r_{il}} \right) \, d \sigma' \]

\[ = E_{\text{gas}} + e^2 B_0 + \frac{1}{2} \sigma A_0 \]

\[ \frac{dE}{d\sigma} = 0 \Rightarrow A_0 = -B_0 \quad \text{or} \quad B_0 = -A \cdot B_0 \]

molecule-solvent interaction:

\[ -\frac{1}{2} B \Theta B \Theta B = -\frac{1}{2} \Theta R F \]

solvent-solvent interaction:

\[ \frac{1}{2} \frac{\sigma_1}{r_{ij}} \, d \sigma + \frac{1}{2} \int \sigma \left( \frac{1}{r_{ij}} + \frac{1}{r_{il}} \right) \, d \sigma' \]

Klammt
JCP 99
2224 (1995)

Ponder + Case pp65-67
Defining the continuum solvent model

Simplest model has “high” $\varepsilon_{\text{ext}}$ outside (white) and “low” $\varepsilon_{\text{in}}$ where solvent is excluded:
Generalized Born model

The solvation energy can be computed by quadrature if one adopts the Coulomb field approximation:

\[ W = \frac{1}{8\pi} \int \mathbf{E} \cdot \mathbf{D} dV = \frac{1}{8\pi} \left[ \int_{in} \frac{q^2}{\varepsilon_{in} r^4} dV + \int_{ext} \frac{q^2}{\varepsilon_{ext} r^4} dV \right] \]

\[ \Delta G = W(\varepsilon_{ext} = 80) - W(\varepsilon_{ext} = 1) \]

\[ \Delta G_{GB} = -\frac{1}{2} \left( 1 - \frac{1}{\varepsilon_{ext}} \right) \frac{q^2}{R_{eff}} ; \quad \text{or} \quad -\frac{1}{2} \left( 1 - \frac{1}{\varepsilon_{ext}} \right) \frac{q_i q_j}{f^{GB}(R_{eff}^i, R_{eff}^j, r_{ij})} \]

\[ R_{eff}^{-1} = \frac{1}{4\pi} \int_{ext} r^{-4} dV \]

Effects of added salt

$\left(1 - \frac{1}{\varepsilon}\right) \rightarrow \left(1 - \frac{e^{-\kappa f^{GB}(d_{ij})}}{\varepsilon}\right)$

![Graph showing the salt contribution to $\Delta G(solv)$, kcal/mol](image)

B-A energy differences for r,d(CCAACGTTGG)₂

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<tr>
<th></th>
<th>DNA</th>
<th>RNA</th>
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<tbody>
<tr>
<td>Coulomb</td>
<td>-293.0</td>
<td>-266.9</td>
</tr>
<tr>
<td>PB</td>
<td>286.6</td>
<td>240.2</td>
</tr>
<tr>
<td>GB</td>
<td>288.1</td>
<td>242.2</td>
</tr>
<tr>
<td>vDW</td>
<td>-7.7</td>
<td>18.7</td>
</tr>
<tr>
<td>bad</td>
<td>-7.0</td>
<td>17.6</td>
</tr>
<tr>
<td>−TΔS</td>
<td>2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>total</td>
<td>-21.0</td>
<td>9.8</td>
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<tr>
<td>0.1M salt</td>
<td>5.2</td>
<td>3.4</td>
</tr>
<tr>
<td>1.0M salt</td>
<td>6.0</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Srinivasan, Cheatham, Kollman, Case, JACS 120, 9401 (1998)
Equilibrium Statistical Mechanics

(good reading: J.C. Slater, "Introduction to Chemical Physics"; Dover, pp. 3-51)

- First law of thermodynamics:
  \[ dU = dQ - dW \text{ or } \Delta U = \int dU = \int dQ - \int dW \]  

- Second law of thermodynamics:
  \[ dS \geq \frac{dQ}{T} \text{ or } TdS \geq dU + dW \]
Connections to microscopic properties

Let $p_i$ be the probability (fraction) of micro-state $i$. Then we can postulate a connection to the entropy:

\[
S = -k \sum_i p_i \ln p_i
\]  

(6)

This is large when the system is “random”. For example, if $p_i = 1/W$ (same for all $i$), then $S = k \ln W$. This entropy is also additive (or “extensive”). Consider two uncorrelated systems that have a total number of states $W_1$ and $W_2$. The total number of possibilities for the combined system is $W_1 W_2$. Then:

\[
S = k \ln(W_1 W_2) = k \ln W_1 + k \ln W_2 = S_1 + S_2
\]  

(7)
Now consider dividing an isolated system (whose total energy $U$ is therefore fixed) into a number of subsystems, each of which could have its own internal energy $E_i$, but where there is thermal contact between the subsystems, so that energy can be transferred among them. The fixed total energy is

$$U = \sum_i E_i p_i$$

where $p_i$ is the probability that subsystem $i$ will have energy $E_i$. Let us find the most probable configuration by maximizing the entropy, subject to the constraint of constant total energy and that $\sum p_i = 1$:

$$dS = 0 = -k \sum dp_i (\ln p_i) + k\beta \sum E_i dp_i - ka \sum dp_i$$

(8)

Here $a$ and $\beta$ are undetermined multipliers. The only general solution is when the coefficients of the $dp_i$ terms add to zero:

$$\ln p_i = a - \beta E_i$$

(9)

The Lagrange multiplier $a$ is just the denominator of Eq. 9. To figure out what $\beta$ is, we connect this back to thermodynamics:

$$dS = k\beta \sum_i dp_i E_i = k\beta dQ \Rightarrow \beta = 1/kT$$
Connections to classical thermodynamics

The denominator of Eq. 9 is called the partition function, and all thermodynamic quantities can be determined from it and its derivatives:

\[
Q \equiv \sum \exp(-\beta E_i)
\]

\[
U = Q^{-1} \sum E_i \exp(-\beta E_i)
\]

\[
TS = -\beta^{-1} \sum \left( \frac{\exp(-\beta E_i)}{Q} \right) \ln \left( \frac{\exp(-\beta E_i)}{Q} \right) = -(\beta Q)^{-1} \sum \exp(-\beta E_i) (-\beta E_i - \ln Q)
\]

\[
A = U - TS = -kT \ln Q
\]

\[
S = -(\partial A/\partial T)_V = k \ln Q + kT (\partial \ln Q / \partial T)_V
\]

\[
U = -(\partial \ln Q / \partial \beta); \quad C_V = T \left( \frac{\partial^2 (kT \ln Q)}{\partial T^2} \right)
\]
Now suppose that $V$ (and hence $Q$ and $A$) are parameterized by $\lambda$:

$$V \rightarrow V(\lambda).$$

Then, since $A = -kT\ln Q$:

$$\frac{\partial A(\lambda)}{\partial \lambda} = -kT \int \frac{\partial}{\partial \lambda} e^{-\beta V(\lambda)} \frac{dq}{Q} = \frac{1}{Q} \int \left( \frac{\partial V}{\partial \lambda} \right) e^{-\beta V(\lambda)} dq = \left( \frac{\partial V}{\partial \lambda} \right)_\lambda$$

The total change in $A$ on going from $\lambda = 0$ to $\lambda = 1$ is:

$$\Delta A = A(1) - A(0) = \int_0^1 \left( \frac{\partial V}{\partial \lambda} \right)_\lambda d\lambda \quad (10)$$

This is called thermodynamic integration, and is a fundamental connection between macroscopic free energies, and microscopic simulations. The integral over $\lambda$ can be done by quadrature, and the Boltzmann averages $\left( \frac{\partial V}{\partial \lambda} \right)_\lambda$ can be carried out by molecular dynamics or Monte Carlo procedures.
Consider the special case of linear mixing, where

$$V(\lambda) = (1 - \lambda)V_0 + \lambda V_1$$

Then $\partial V/\partial \lambda = V_1 - V_0 \equiv \Delta V$ (often called the energy gap), and

$$\Delta A = \int_0^1 \langle \Delta V \rangle_\lambda d\lambda$$  \hspace{1cm} (11)

The simplest numerical approximation to the $\lambda$ integral is just to evaluate the integrand at the midpoint, so that $\Delta A = \langle \Delta V \rangle_{1/2}$. This says that the free energy difference is approximately equal to the average potential energy difference, evaluated for a (hypothetical) state half-way between $\lambda = 0$ and $\lambda = 1$.

It is often convenient for other purposes to perform simulations only at the endpoints. In this case, a convenient formula would be:

$$\Delta A \simeq \frac{1}{2} \langle \Delta V \rangle_0 + \frac{1}{2} \langle \Delta V \rangle_1$$

And more elaborate formulas (e.g. from Gaussian integration) are feasible (and often used). See Hummer & Szabo, *J. Chem. Phys.* 105, 2004 (1996) for a fuller discussion.
Here is an (initially) completely different approach:

$$\Delta A = -kT \ln \left( \frac{Q_1}{Q_0} \right)$$

$$= -kT \ln \left( \frac{\int \exp(-\beta E_1) \exp(\beta E_0) \exp(-\beta E_0) dq}{\int \exp(-\beta E_0) dq} \right)$$

$$= -kT \ln \left( \frac{1}{Q_0} \int \exp(-\beta [E_1 - E_0]) \exp(-\beta E_0) dq \right)$$

$$= -kT \ln \left\langle \exp\left(-\frac{[E_1 - E_0]}{kT}\right) \right\rangle_0$$

$$= -kT \ln \left\langle \exp\left(-\frac{[E_0 - E_1]}{kT}\right) \right\rangle_1$$

This is generally called “perturbation theory”, and involves averaging the exponential of the energy gap, rather than the energy gap itself.
A simple model: “Marcus theory”

\[ V_A(q) = \frac{1}{2} k (q - q_A)^2 \]
\[ V_B(q) = \frac{1}{2} k (q - q_B)^2 \]
\[ \Delta V(q) = \sqrt{2\lambda} (q - q_A) + \frac{\lambda^2}{k} + \Delta E \]
\[ \langle V_B - V_A \rangle_A = Q_A^{-1} \int \left[ \sqrt{2} \lambda (q - q_A) + \frac{\lambda^2}{k} + \Delta E \right] e^{-\beta V_A(q)} dq = \frac{\lambda^2}{k} + \Delta E \]

\[ \langle V_B - V_A \rangle_B = -\frac{\lambda^2}{k} + \Delta E; \quad \Delta A \simeq \frac{1}{2} [\langle \Delta V \rangle_A + \langle \Delta V \rangle_B] = \Delta E \]

What is the distribution of \( \Delta V \) in the \( V_A \) state?

\[ \rho(\Delta V) = \rho(q) \left| \frac{dq}{d\Delta V} \right| \quad \text{where} \quad q(\Delta V) = \left( \frac{\lambda^2 + k \Delta E}{\sqrt{2k\lambda}} \right) - \frac{\Delta V}{\sqrt{2}\lambda} \]

\[ \rho(\Delta V) \sim \frac{1}{\sqrt{2\lambda}} \exp \left\{ -\beta V_A[q(\Delta V)] \right\} \sim \exp \left\{ -\frac{(\Delta V - \lambda^2/k - \Delta E)^2}{2\sigma^2} \right\} \quad \text{with} \quad \sigma^2 = \frac{2\lambda^2}{k\beta} \]

Hence, the mean of the distribution gives \( \lambda^2/k + \Delta E \), and the width of the distribution gives \( \lambda^2/k \) (the “relaxation”); knowing both allows you to get \( \Delta E \) and \( \lambda \) separately.

For perturbation theory:

\[ \Delta A = -kT \ln \left\langle e^{-\beta \Delta V} \right\rangle_A = \Delta E \]
Application: pKa behavior in proteins

\[ \Delta G_{\text{prot}} \]

\[ \text{Prot-AspH} \rightarrow \text{Prot-Asp} \]

\[ \Delta \Delta G = \Delta G_{\text{prot}} - \Delta G_{\text{model}} \]

\[ \Delta G_{\text{solv}} \]

\[ \text{AspH} \rightarrow \text{Asp}^- \]

\[ \Delta G_{\text{qm}} \]

\[ \text{AspH (vacuum)} \rightarrow \text{Asp}^- (\text{vacuum}) \]

\[ pK_a \]
Energy gap distributions

Lambda | DG/DL (kcal/mol)
---|---
0.11270 | -3.1
0.50000 | -64.5
0.88729 | -131.4

Not everything is linear!

Thermodynamics cycles in ligand binding

\[ \Delta G_B \uparrow \]

\[ \Delta G_1 \]

\[ \Delta G_A \downarrow \]

\[ \Delta G_2 \leftarrow \]
Bending rigidity: \( A = \frac{M(2\pi \nu_n)^2}{LP_n^4} \); \( a = A/(k_B T) \)

Twisting rigidity: \( C = \frac{l(2L \nu_n)^2}{n^2} \)

Stretching rigidity: \( Y = \frac{ML(2 \nu_n)^2}{n^2} \)

Lord Rayleigh, *The Theory of Sound*, 1894
Bending rigidity for linear duplex DNA

<table>
<thead>
<tr>
<th>n</th>
<th>GB frequencies</th>
<th>Analytical frequencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.114</td>
<td>0.116</td>
</tr>
<tr>
<td>2</td>
<td>0.294</td>
<td>0.295</td>
</tr>
<tr>
<td>3</td>
<td>0.522</td>
<td>0.532</td>
</tr>
</tbody>
</table>

Bending motions

GB frequencies

Analytical frequencies

1 0.114 0.116 0.100
2 0.294 0.295 0.275
3 0.522 0.532 0.539

d(GACT) 60 base pairs

$\lambda = 594 \text{ Å} \quad (550 \text{ Å})$

$A = 2.44 \times 10^{-19} \text{ erg.cm}$

$\approx 2.26 \times 10^{-19} \text{ erg.cm}$

Stretching rigidity for linear duplex DNA

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<thead>
<tr>
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<tr>
<td>1</td>
<td>0.664</td>
<td>0.619</td>
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<tr>
<td>2</td>
<td>1.289</td>
<td>1.237</td>
</tr>
<tr>
<td>3</td>
<td>1.807</td>
<td>1.846</td>
</tr>
</tbody>
</table>

\[ Y = 1502 \, \text{pN} \left(1000 - 1500 \, \text{pN}\right) \]
Salt dependence of bending

Baumann, Smith, Bloomfield, Bustamante, *PNAS* 94, 6185 (1997)
Salt dependence of stretching

Baumann, Smith, Bloomfield, Bustamante, *PNAS* 94, 6185 (1997)
Now consider circular DNA

\[ \nu_n = f(\Omega, R, \Delta Tw, n, \rho) \]

- \( R \) is the circle radius
- \( \Delta Tw \) is the excess twist
- \( \Omega = C/A \)
- \( \rho \) is the mass density

Matsumoto, Tobias, Olson, *JCTC* 1, 117 (2005)
In-plane and out-of-plane modes for circular DNA

**In plane bending motions**

<table>
<thead>
<tr>
<th>n</th>
<th>Relaxed minicircle with 94 base pairs</th>
<th>Overtwisted minicircle with 94 base pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GB frequencies</td>
<td>Analytical frequencies</td>
</tr>
<tr>
<td>2</td>
<td>0.165</td>
<td>0.172</td>
</tr>
<tr>
<td>3</td>
<td>0.394</td>
<td>0.452</td>
</tr>
<tr>
<td>4</td>
<td>0.672</td>
<td>0.724</td>
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**Out of plane bending motions**

<table>
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<th>n</th>
<th>Relaxed minicircle with 94 base pairs</th>
<th>Overtwisted minicircle with 94 base pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GB frequencies</td>
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DNA binding to the histone core proteins