Quasistatic stretching of the collagen triple helix

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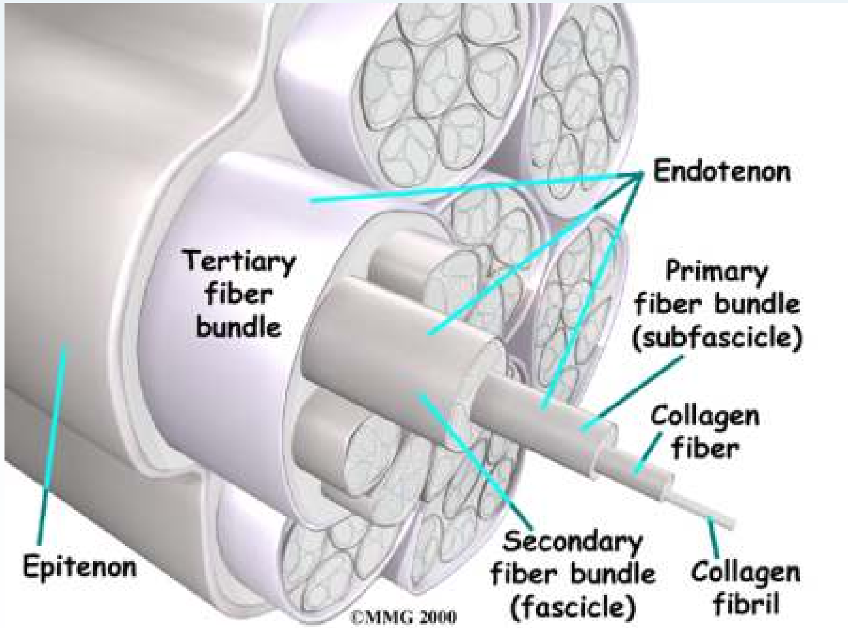
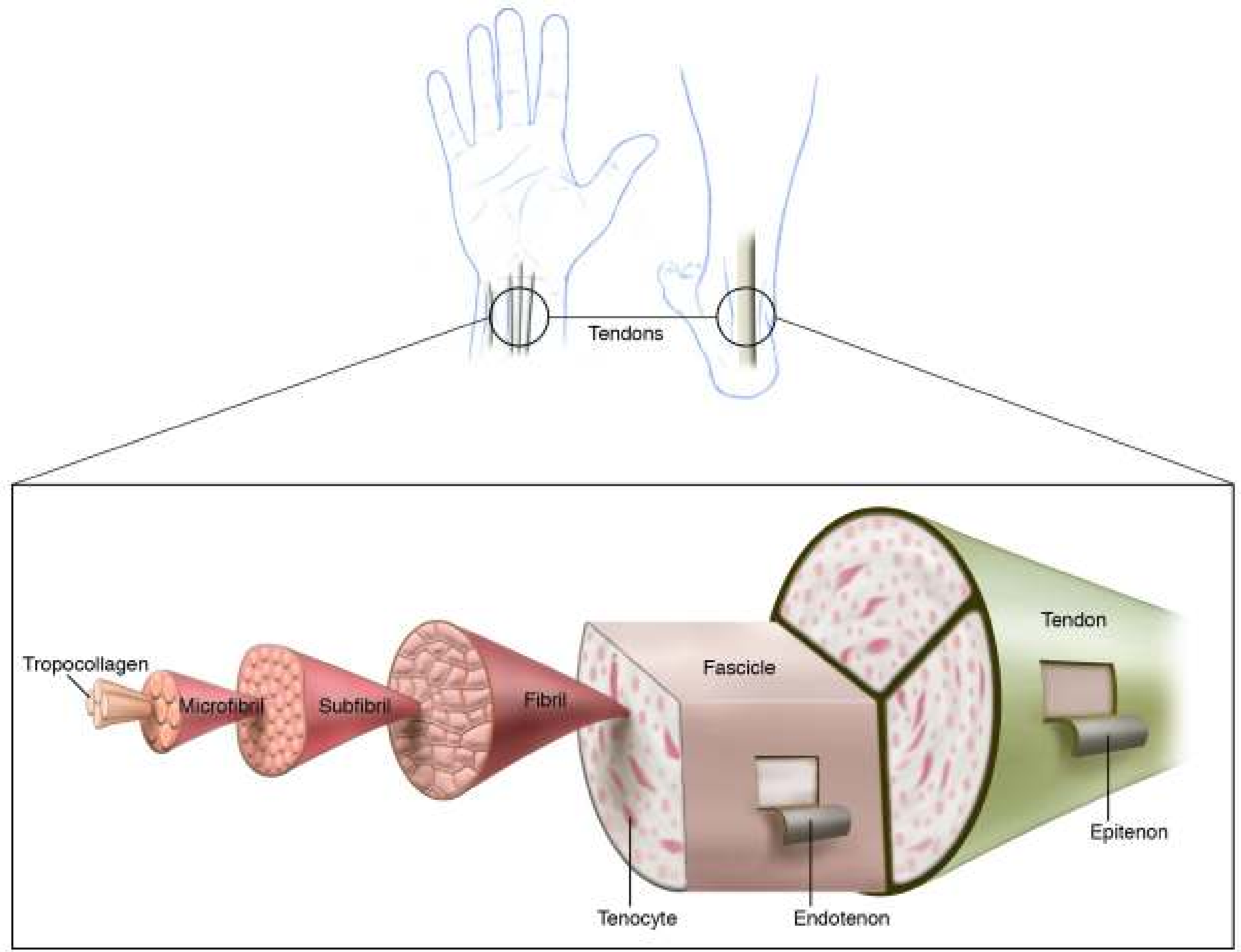
Introduction

- Use statistical mechanics to study the nucleation of tearing of multi-stranded biomolecules under external forces.
- Looking at a shearing problem where a single strand of the tropocollagen (TC) molecule is pulled out along its axis.

Collagen - biological tissues, including tendon, bone, teeth, Cartilage.

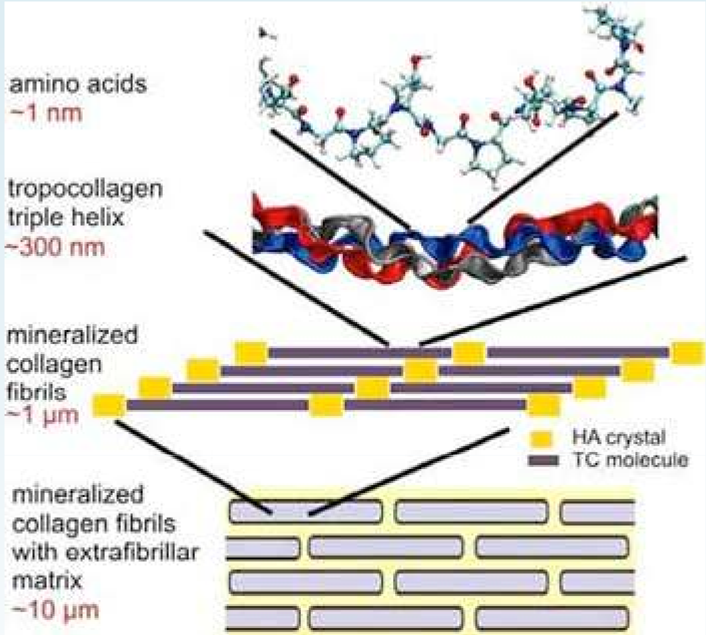
Elasticity of individual TC molecules, fibrils, and collagen fibres remains controversial.

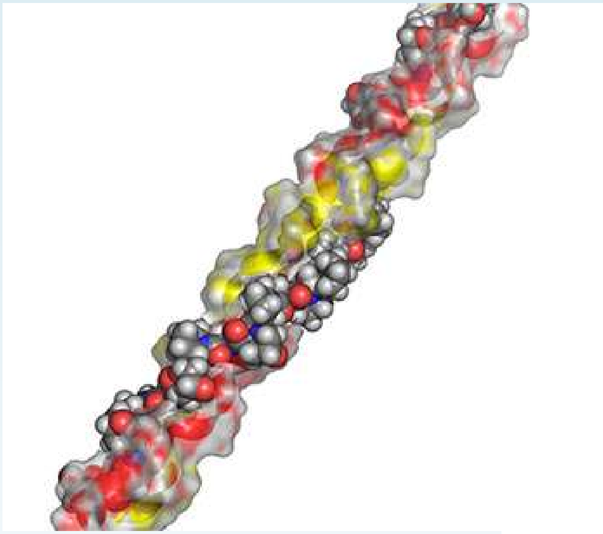


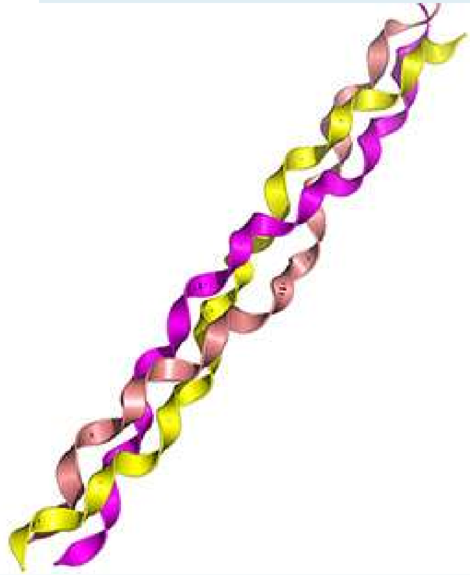

Tendons
Tropocollagen
Microfibril
Subfibril
Fibril
Fascicle
Tendon
Tenocyte
Endotenon
Epitenon

.....so I'm not talking about this!!!

What does Tropocollagen look like?



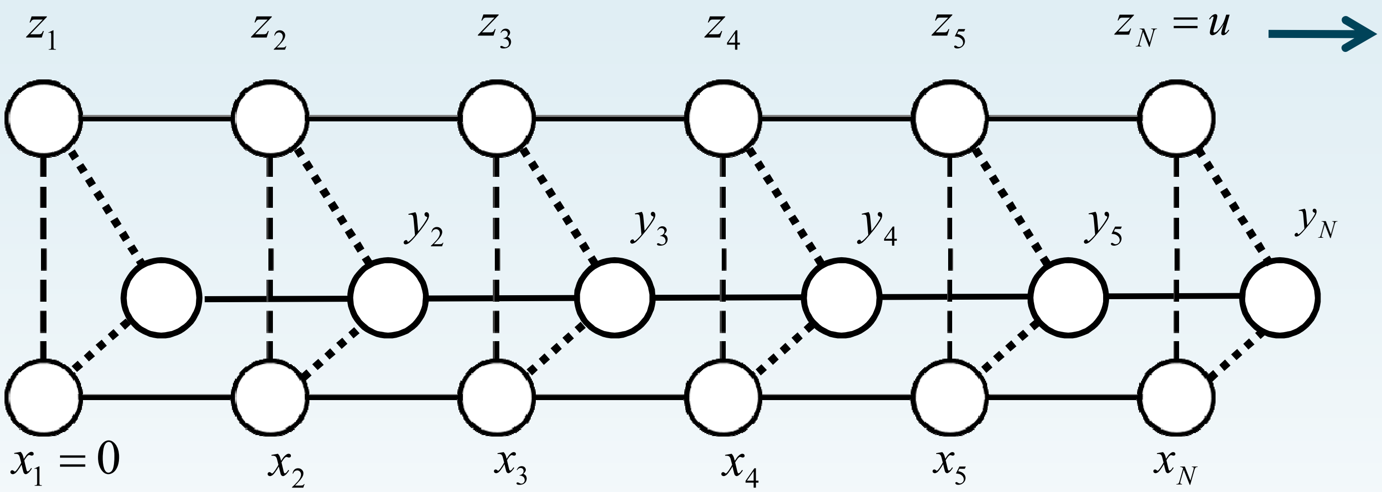




- Approximately 300 nm long and 1.5 nm in diameter.
- Three left-handed helices twisted together into a right-handed coiled coil; a triple helix.
- Tropocollagen structure is stabilised by hydrogen bonds

TC Toy Model – Geometric Representation

- Represent TC as a Toblerone (Trangular Prism)



- Interactions along the backbones are assumed to be harmonic.
- Each residue-pair interacts through a potential V which is dependent on the axial pair separation $x_i - y_i$, $x_i - z_i$, $y_i - z_i$.
- Case where V is harmonic, residue-pair spring constant = σ . Backbone spring constant = κ .
- N triplets of beads.

TC Toy Model - Hamiltonian

- Substitutions were used to decouple the variables.

$$R_i = \frac{1}{\sqrt{3}}(x_i + y_i + z_i) \qquad \rho_i = \frac{1}{\sqrt{2}}(x_i - y_i) \qquad \lambda_i = \frac{1}{\sqrt{6}}(x_i + y_i - 2z_i)$$

- Transformations to dimensionless coordinates:

$$R \rightarrow R\left(\frac{\kappa\beta}{\sqrt{2}}\right)^{-\frac{1}{2}} \qquad \rho \rightarrow \rho\left(\frac{\kappa\beta}{\sqrt{2}}\right)^{-\frac{1}{2}} \qquad \lambda \rightarrow \lambda\left(\frac{\kappa\beta}{\sqrt{2}}\right)^{-\frac{1}{2}}$$

- The Hamiltonian becomes:

$$\beta H = \sum_{i=1}^{N-1}(R_{i+1} - R_i)^2 + \sum_{i=1}^{N-1}(\rho_{i+1} - \rho_i)^2 + \sum_{i=1}^{N-1}(\lambda_{i+1} - \lambda_i)^2$$

$$+ \sum_{i=1}^{N} V(2\rho_i) + V(\rho_i + \sqrt{3}\lambda_i) + V(\sqrt{3}\lambda_i - \rho_i)$$

TC Toy Model – Harmonic Residue Potential

- If residue-pair interactions is approximated by a harmonic potential:

$$V(\eta) = \frac{1}{2}\sigma\eta^2$$

- Simplifies the Hamiltonian

$$\beta H = \sum_{i=1}^{N-1}(R_{i+1} - R_i)^2 + \sum_{i=1}^{N-1}(\rho_{i+1} - \rho_i)^2 + \sum_{i=1}^{N-1}(\lambda_{i+1} - \lambda_i)^2$$

$$+ 6\sum_{i=1}^{N} V(\rho_i) + V(\lambda_i)$$

Transfer Integral Method (I)

$$Z = \int \prod_{i=1}^{N} e^{-\beta H(R_i,\rho_i,\lambda_i)} dR d\rho d\lambda$$

$$= \int \prod_{i=1}^{N} dR_i \; T(R_1,R_2)\, T(R_2,R_3)\, T(R_3,R_4) \ldots T(R_{N-1},R_N)$$

$$\times \int \prod_{i=1}^{N} d\rho_i \; \hat{T}(\rho_1,\rho_2)\, \hat{T}(\rho_2,\rho_3)\, \hat{T}(\rho_3,\rho_4) \ldots \hat{T}(\rho_{N-1},\rho_N)$$

$$\times \int \prod_{i=1}^{N} d\lambda_i \; \hat{T}(\lambda_1,\lambda_2)\, \hat{T}(\lambda_2,\lambda_3)\, \hat{T}(\lambda_3,\lambda_4) \ldots \hat{T}(\lambda_{N-1},\lambda_N)$$

$$\times \exp\left(-\left(3V(\rho_1) + 3V(\rho_N)\right)\right)$$

$$\times \exp\left(-\left(3V(\lambda_1) + 3V(\lambda_N)\right)\right)$$

- With the Transfer Matrices:

$$\boxed{T(R,R') = \exp\left(-(R-R')^2\right)}$$

$$\hat{T}(\rho,\rho') = \exp\left(-(\rho-\rho')^2\right) \exp\left(-3\left(V(\rho)+V(\rho')\right)\right)$$

$$\hat{T}(\lambda,\lambda') = \exp\left(-(\lambda-\lambda')^2\right) \exp\left(-3\left(V(\lambda)+V(\lambda')\right)\right)$$

Transfer Integral Method (II)

- Introducing the boundary conditions,

$$\delta(x_1)\delta(z_N-u)=\delta(R_1+\frac{\sqrt{3}}{\sqrt{2}}\rho_1-\frac{\lambda_1}{\sqrt{2}})\delta(\frac{R_N}{\sqrt{3}}+\frac{\sqrt{2}}{\sqrt{3}}\lambda_N-u)$$

- Expand in the eigenfunctions of $T(R,R'),\hat{T}(\lambda,\lambda')$

$$\delta(R_1+\frac{\sqrt{3}}{\sqrt{2}}\rho_1+\frac{\lambda_1}{\sqrt{2}})=\sum_{R_\ell}\psi_{R_\ell}(R_1)\psi^*_{R_\ell}(-\frac{\sqrt{3}}{\sqrt{2}}\rho_1-\frac{\lambda_1}{\sqrt{2}})$$

$$\delta(\frac{R_N}{\sqrt{2}}+\lambda_N-\frac{\sqrt{3}}{\sqrt{2}}u)=\sum_{\lambda_\ell}\psi^*_{\lambda_\ell}(\lambda_N)\psi_{\lambda_\ell}(\frac{R_N}{\sqrt{2}}-\frac{\sqrt{3}}{\sqrt{2}}u)$$

- Need an additional condition for ρ ,

$$\int d\rho_N\delta(\rho_N-\rho_N^{'})=\int d\rho_N\sum_{\rho_\ell}\psi^*_{\rho_\ell}(\rho_N^{'})\psi_{\rho_\ell}(\rho_N)$$

Transfer Integral Method (III)

$$\int dR' T(R,R')\psi_{R_\ell}(R') = \lambda_R \psi_{R_\ell}(R)$$

$$\int d\rho' \hat{T}(\rho,\rho')\hat{\psi}_{\rho_\ell}(\rho') = \hat{\lambda}_\rho \hat{\psi}_{\rho_\ell}(\rho)$$

$$\int d\lambda' \hat{T}(\lambda,\lambda')\hat{\psi}_{\lambda_\ell}(\lambda') = \hat{\lambda}_\lambda \hat{\psi}_{\lambda_\ell}(\lambda)$$

- The partition functions now looks like

$$\begin{aligned} Z(u) = &\int \prod_{i=1}^{N} dR_i d\rho_i d\lambda_i \prod_{i=1}^{N-1} T(R_i, R_{i+1}) \prod_{i=1}^{N-1} \hat{T}(\rho_i, \rho_{i+1}) \prod_{i=1}^{N-1} \hat{T}(\lambda_i, \lambda_{i+1}) \\ &\times \exp\left(-\left(3V(\rho_1) + 3V(\rho_N) + 3V(\lambda_1) + 3V(\lambda_N)\right)\right) \\ &\times \sum_{R_\ell} \psi_{R_\ell}(R_1)\psi^*_{R_\ell}\left(-\frac{\sqrt{3}}{\sqrt{2}}\rho_1 - \frac{\lambda_1}{\sqrt{2}}\right) \sum_{\lambda_\ell} \psi^*_{\lambda_\ell}(\lambda_N)\psi_{\lambda_\ell}\left(\frac{R_N}{\sqrt{2}} - \frac{\sqrt{3}}{\sqrt{2}}u\right) \\ &\times \int d\rho_N \sum_{\rho_\ell} \psi^*_{\rho_\ell}(\rho'_N)\psi_{\rho_\ell}(\rho_N) \end{aligned}$$

Transfer Integral Method (III)

Contract all R, ρ, λ terms,

$$Z(u) = \frac{4}{(\kappa\beta)^{\frac{3}{2}}} \sum_{R_\ell} \sum_{\lambda_\ell} \sum_{\rho_\ell} \lambda_{R_\ell}^{N-1} \lambda_{\rho_\ell}^{N-1} \lambda_{\lambda_\ell}^{N-1} \times \int d\widetilde{R}_N \psi_{R_\ell}(\sqrt{2}\widetilde{R}_N + u\sqrt{3}) \exp(-\frac{3V(\widetilde{R}_N)}{\kappa}) \psi_{\lambda_l}(\widetilde{R}_N)$$

$$\times \int d\rho'_1 \psi_{\rho_\ell}(\rho'_1) \exp(-\frac{3V(\rho'_1)}{\kappa}) \psi_{R_\ell}(\frac{\sqrt{3}}{\sqrt{2}} \rho'_1)$$

$$\times \int d\lambda_1 \psi^*_{\lambda_\ell}(\lambda_1) \exp(-\frac{3V(\lambda'_1)}{\kappa}) \psi_{R_\ell}(\frac{\lambda_1}{\sqrt{2}}) \times \int d\rho_N \exp(-\frac{3V(\rho_N)}{\kappa}) \psi^*_{\rho_\ell}(\rho'_N)$$

- Substitutions

$$\frac{R_N - u\sqrt{3}}{\sqrt{2}} = \widetilde{R}_N$$

- Eigenfunctions for T(R,R') have an analytical form!!!

Eigenfunctions – Analytical Form

- Full form of the transfer integral for R

$$\int dR' \exp(-(R-R')^2)\psi_{R_\ell}(R') = \lambda_{R\ell}\psi_{R_\ell}(R)$$

- Assume a solution of the form

$$\psi_{R_\ell}(R') = A\exp(iR_\ell R' B)$$

$$\boxed{\psi_{R_\ell}(R') = \frac{1}{\sqrt{L}}\exp(\frac{iR_\ell R'\pi}{L})}$$

- L appears from the periodicity of the assumed solution

$$\psi_{R_\ell}(R'+2L) = \psi_{R_\ell}(R')$$

Eigenfunctions – Analytical Form(II)

- Full form of the transfer integral for ρ and λ

$$\int d\rho \exp\left(-(\rho-\rho')^2\right) \exp\left(-3\left(V(\rho)+V(\rho')\right)\right)\psi_{\rho_\ell}(\rho') = \lambda_{\rho_\ell}\psi_{\rho_\ell}(\rho)$$

- Can solve for $\psi_{\rho_\ell}(\rho)$ using Hermite Polynomials

$$\psi_{\rho_\ell}(\rho) = \left(\frac{\pi}{c}\right)^{-\frac{1}{4}} \frac{1}{\sqrt{2^{\rho_\ell}\rho_\ell!}} H_{\rho_\ell}(b\rho)\exp\left(-\frac{c\rho^2}{2}\right)$$

- Where

$$\beta = 4 \qquad \mu = \frac{6\sigma}{\kappa} \qquad c = \frac{(\mu^2 + 2\beta\mu)^{\frac{1}{2}}}{2}$$

$$b = \frac{1}{2}\left(\frac{\delta^2 - \beta^2}{\delta}\right)^{\frac{1}{2}} \qquad \delta = 2c + \mu + \beta$$

General Residue Pair Potential

- The residue pair potential in the Hamiltonian

$$\Gamma(\rho_i, \lambda_i) = V(2\rho_i) + V(\rho_i + \sqrt{3}\lambda_i) + V(\sqrt{3}\lambda_i - \rho_i)$$

- Transfer Matrix becomes

$$\hat{T}(\rho, \lambda, \rho', \lambda') = \exp\left(-(\rho - \rho')^2\right)\exp\left(-(\lambda - \lambda')^2\right)\ \exp\left(-3\left(\Gamma(\rho, \lambda) + \Gamma(\rho', \lambda')\right)\right)$$

$$\boxed{\iint d\rho' d\lambda' \hat{T}(\rho, \lambda, \rho', \lambda') \hat{\psi}_{\rho\lambda_\ell}(\rho', \lambda') = \hat{\lambda}_{\rho\lambda} \hat{\psi}_{\rho\lambda_\ell}(\rho, \lambda)}$$

- Construct a Hypermatrix for $\hat{T}$ and represent the matrix as a normal 2D matrix to get Eigenvalues and Eigenvectors.

General Residue Pair Potential (II)

- Amend Expansion of delta functions

$$\int d\rho_N \delta(\rho_N - \rho'_N)\delta(\frac{R_N}{\sqrt{2}} - \lambda_N - \frac{\sqrt{3}}{\sqrt{2}}u) = \int d\rho_N \sum_{\rho\lambda_\ell} \psi^*_{\rho\lambda_\ell}(\rho'_N, \lambda_N)\psi_{\rho\lambda_\ell}(\rho_N, \frac{R_N}{\sqrt{2}} - \frac{\sqrt{3}}{\sqrt{2}}u)$$

- Partition function for a general residue potential

$$Z(u) = \int \prod_{i=1}^{N} dR_i d\rho_i d\lambda_i \prod_{i=1}^{N-1} T(R_i, R_{i+1}) \prod_{i=1}^{N-1} \hat{T}(\rho_i, \lambda_i, \rho_{i+1}\lambda_{i+1})$$
$$\times \exp\left(-3\left(\Gamma(\rho_1, \lambda_1) + \Gamma(\rho_N, \lambda_N)\right)\right)$$
$$\times \sum_{R_\ell} \psi_{R_\ell}(R_1)\psi^*_{R_\ell}(-\frac{\sqrt{3}}{\sqrt{2}}\rho_1 - \frac{\lambda_1}{\sqrt{2}}) \times \int d\rho_N \sum_{\rho\lambda_\ell} \psi^*_{\rho\lambda_\ell}(\rho'_N, \lambda_N)\psi_{\rho\lambda_\ell}(\rho_N, \frac{R_N}{\sqrt{2}} - \frac{\sqrt{3}}{\sqrt{2}}u)$$

$$Z(u) = \frac{4}{(\kappa\beta)^{\frac{3}{2}}} \sum_{R_\ell} \sum_{\rho\lambda_\ell} \lambda_{R_\ell}^{N-1} \lambda_{\rho\lambda_\ell}^{N-1} \int d\tilde{R}_N d\rho_N \psi_{R_\ell}(\sqrt{2}\tilde{R}_N + u\sqrt{3}) \exp(-\frac{3\Gamma(\rho_N, \tilde{R}_N)}{\kappa})\psi_{\rho\lambda_l}(\rho_N, \tilde{R}_N)$$
$$\times \int d\lambda_1 d\rho'_1 \psi^*_{\rho\lambda_\ell}(\rho'_1, \lambda_1) \exp(-\frac{3\Gamma(\rho'_1, \lambda_1)}{\kappa})\psi^*_{R_\ell}(-\frac{\sqrt{3}}{\sqrt{2}}\rho'_1 + \frac{\lambda_1}{\sqrt{2}})$$

Transfer Integral Method Test

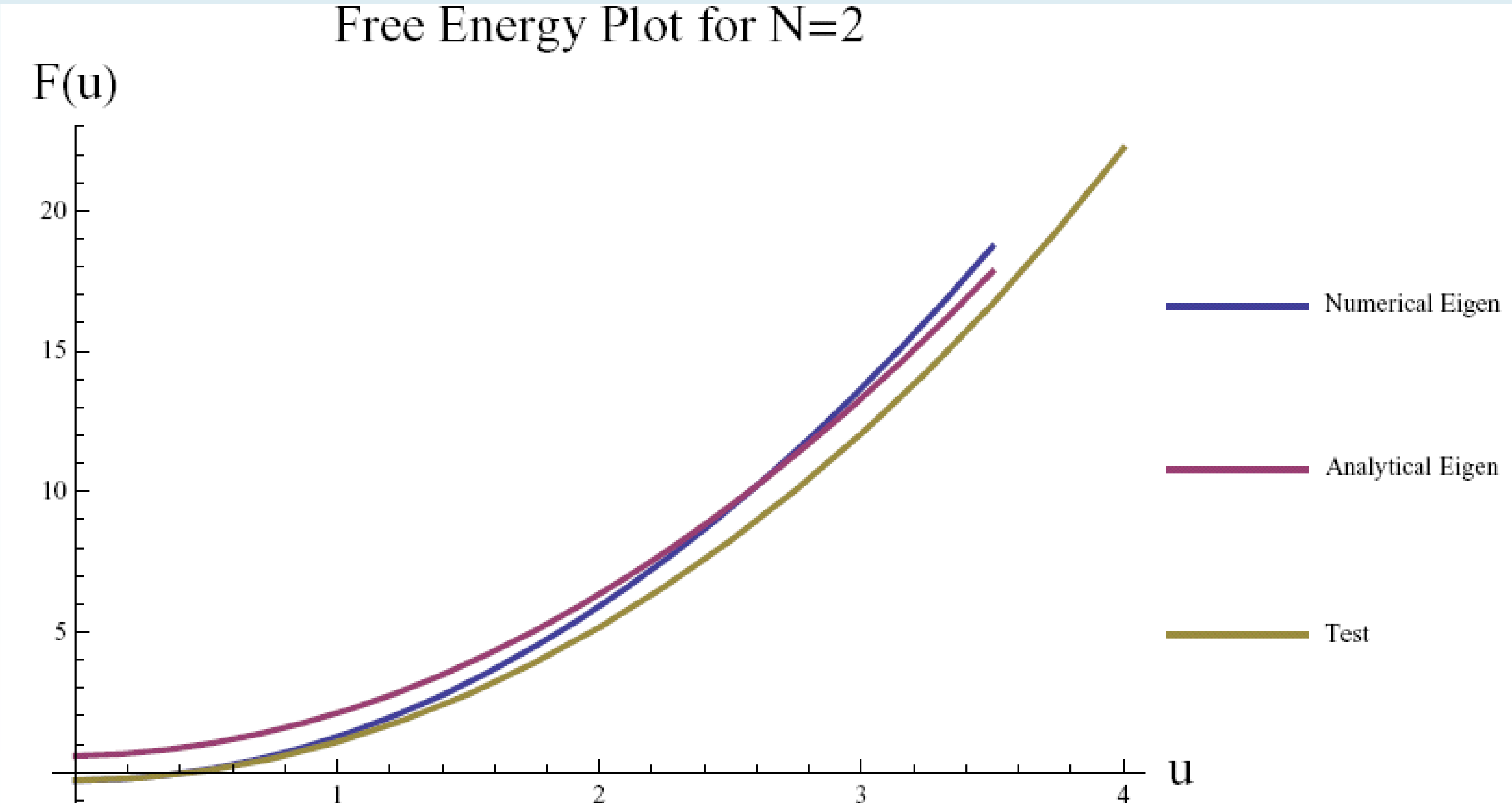
$$Z = \int \prod_{i=1}^{N} \exp(-\beta H(x_i, y_i, z_i)) dx_i dy_i dz_i$$

$$\beta H(x_i, y_i, z_i) = \sum_{i=1}^{N-1} \beta \frac{(x_{i+1} - x_i)^2}{2\kappa} + \sum_{i=1}^{N-1} \beta \frac{(y_{i+1} - y_i)^2}{2\kappa} + \sum_{i=1}^{N-1} \beta \frac{(z_{i+1} - z_i)^2}{2\kappa}$$
$$+ \beta \sum_{i=1}^{N} V(x_i - y_i) + V(x_i - z_i) + V(y_i - z_i)$$

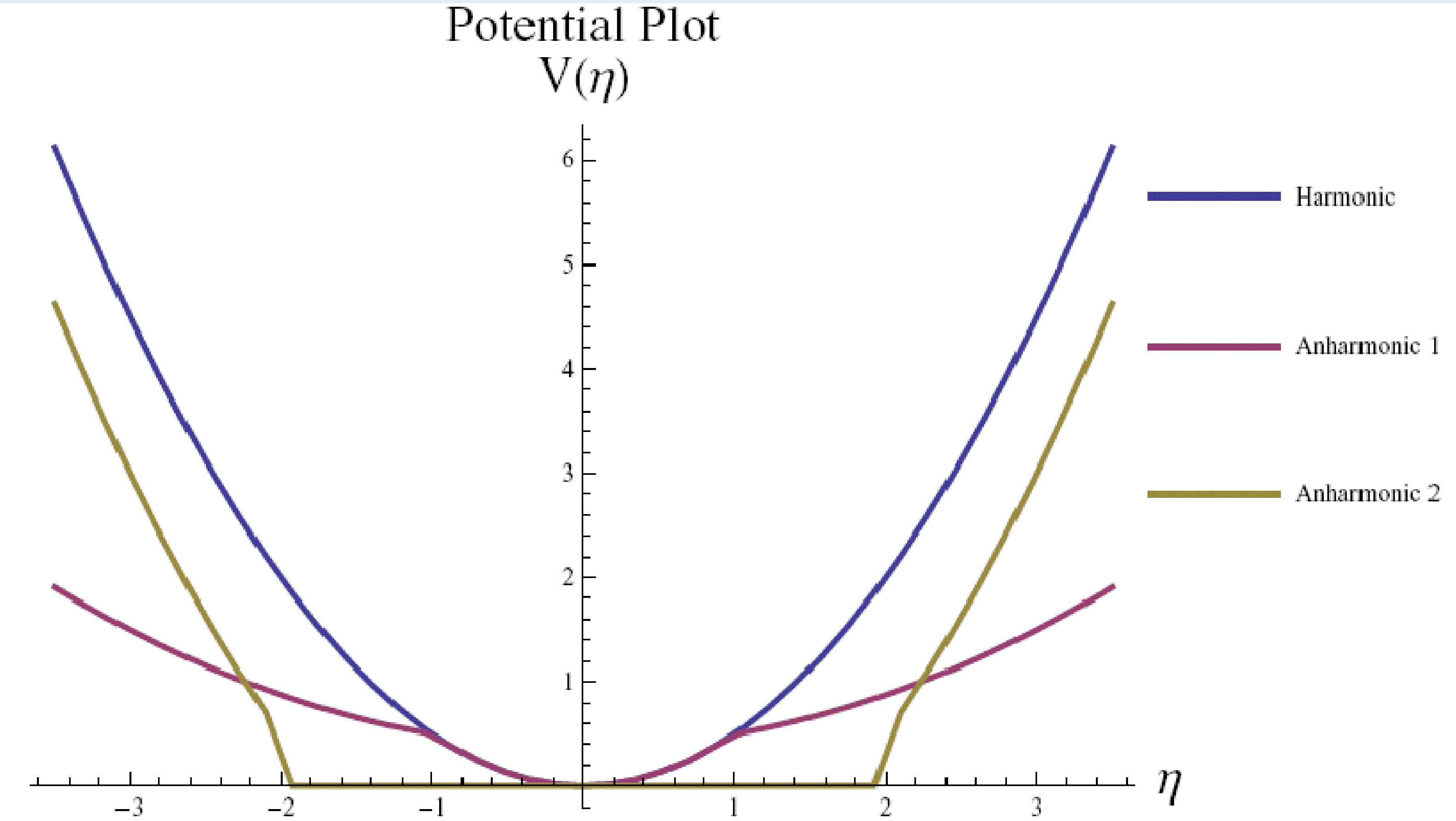
- Numerically calculate Z for N=2 with $\delta(x_1)\delta(z_2 - u)$

$$Z(u) = \int dx_2 \int dy_1 \int dy_2 \int dz_1 \exp\left(-\tfrac{\beta\kappa}{2}\left((-x_2)^2 + (y_1 - y_2)^2 + (z_1 - u)^2\right)\right)$$
$$\times \exp\left(-\beta\left(V(-z_1) + V(-y_1) + V(z_1 - y_1) + V(x_2 - u) + V(x_2 - y_2) + V(u - y_2)\right)\right)$$

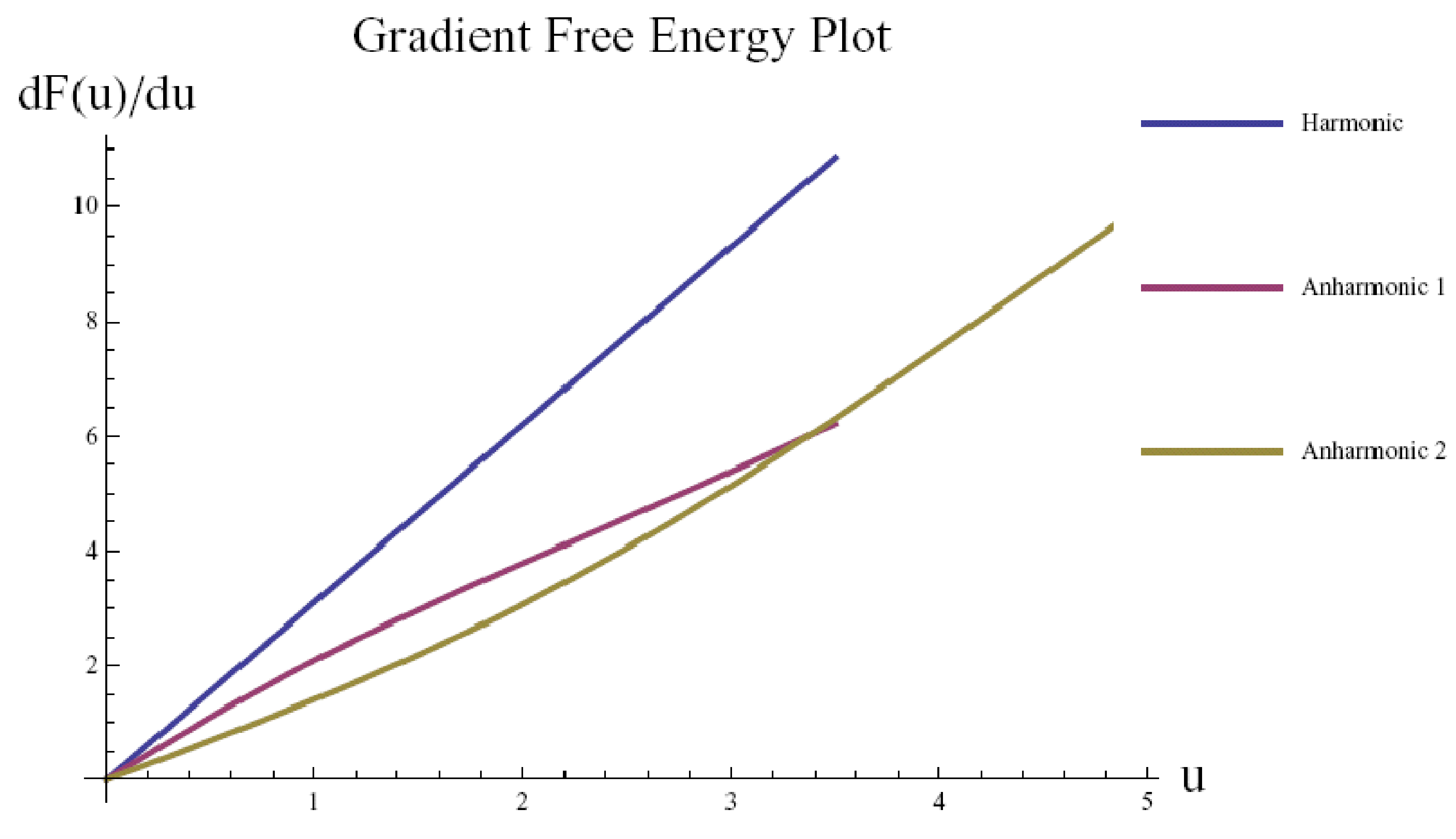
Comparison Plots for F(u) - Harmonic Potential



Various Potentials



dF(u)/du - Various Potentials



Final Notes

- Find suitable potentials to match residue base-pairs.
- Compare with real data, experimental pulling of TP molecules
- Calculation of Mean Axial Displacement
- Base-pair breakage
- Thankyou's: Prof Ian Ford (UCL)