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Geometry and Mechanics of Condensed DNA: Toroids and Beyond

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Geometry and mechanics of condensed DNA: Toroids and beyond

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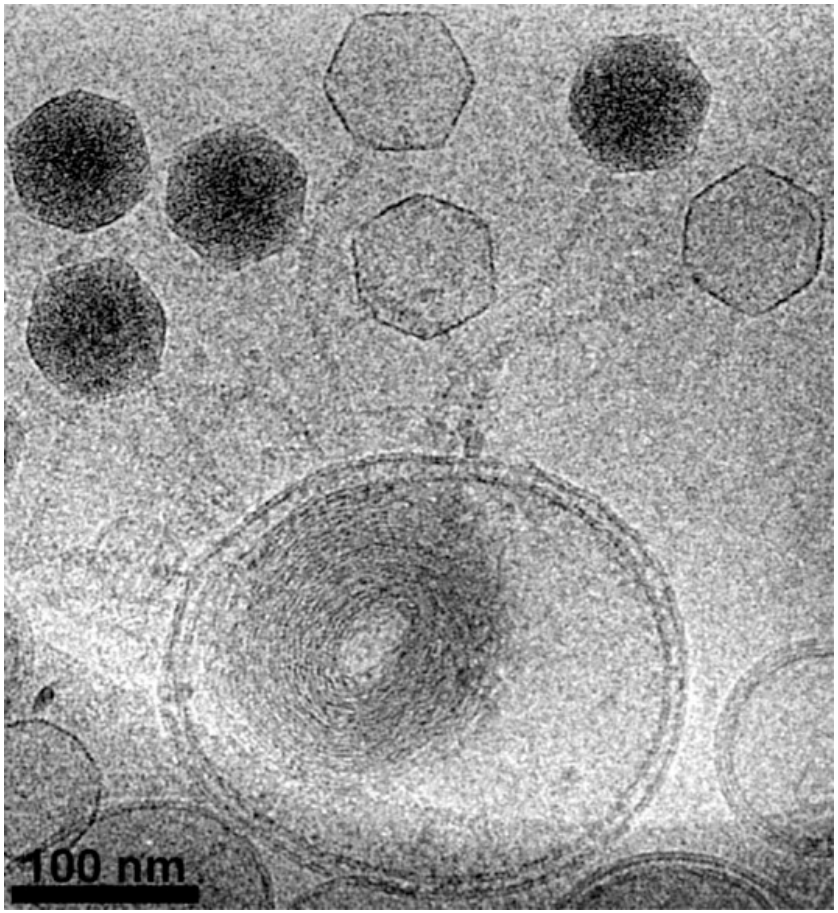
"From DNA-Inspired Physics to Physics-Inspired Biology"
ICTP, Trieste, Italy, 1–5 June 2009

Outline

- Closed parallel bundles
- Elastic and exposed surface energy
- Diagram of state
- Toroids vs. spheroids

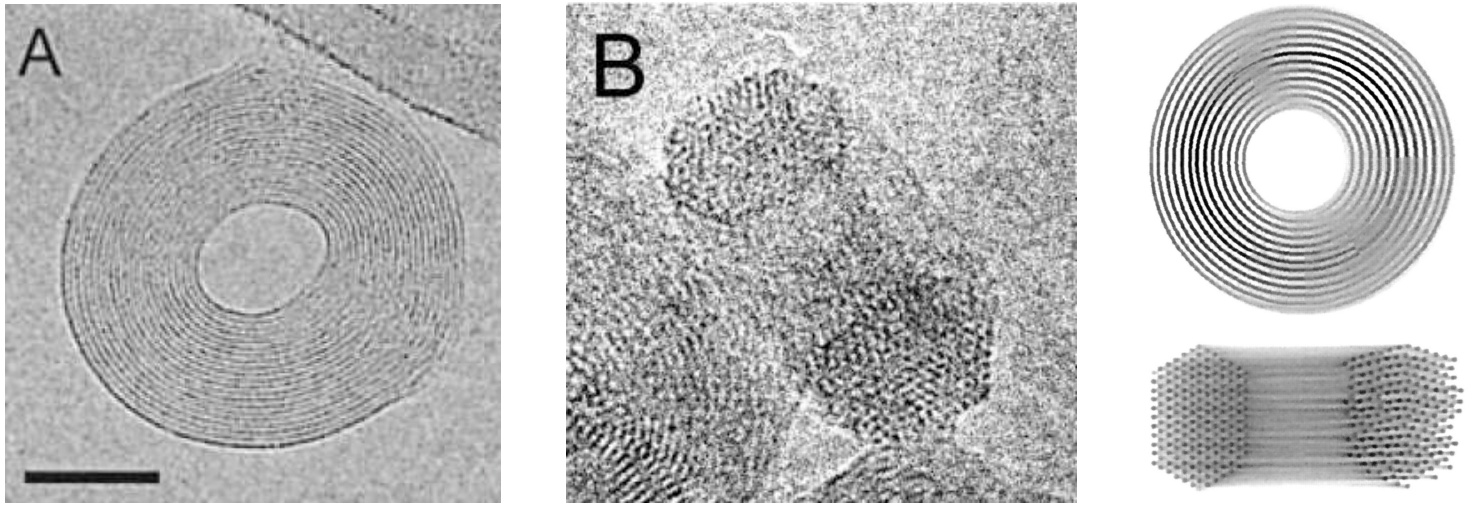
DNA condensation



Images of DNA ejected into a lipid bilayer vesicle. Empty capsids are distinguishable from their full counterparts because the full capsids are much darker.

J. Böhm et al. (2001) Curr. Biol. **11** *1168.*

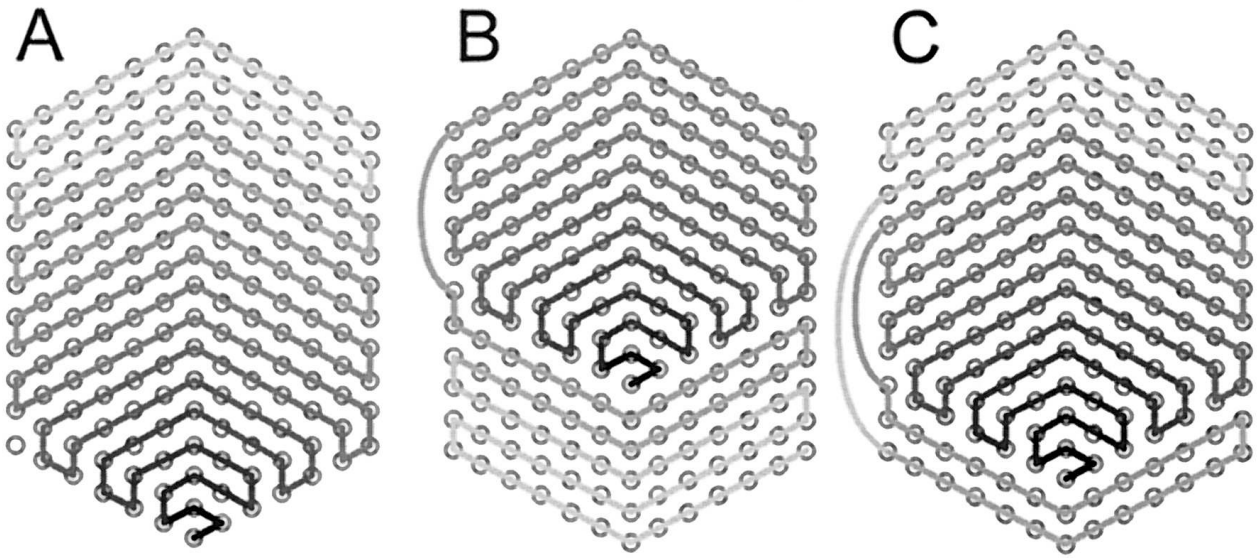
DNA toroids



Cryoelectron micrographs: (A) top-view (bar 50 nm), (B) edge-view. *Right:* Simulated TEM images of a model toroid constructed from a single continuous path.

N. V. Hud, K. H. Downing. (2001) Cryoelectron microscopy of lambda phage DNA condensates in vitreous ice: The fine structure of DNA toroids. PNAS **98** *(26) 14925.*

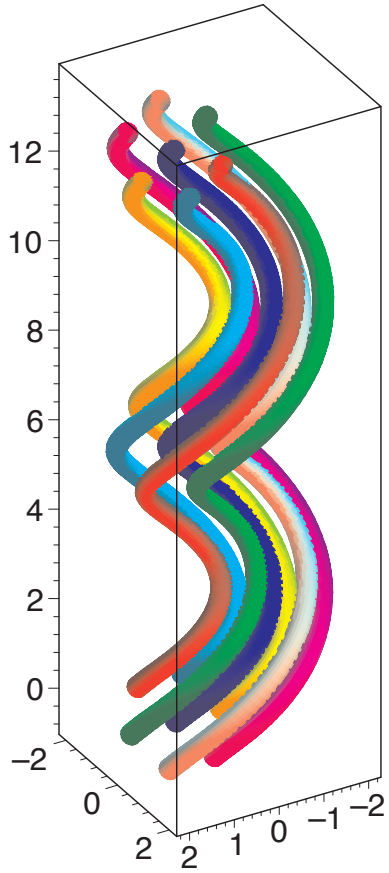
How are layers formed?



Schemes of three (im?)possible paths for the winding of a single DNA polymer into a toroid.

N. V. Hud, K. H. Downing. (2001) Cryoelectron microscopy of lambda phage DNA condensates in vitreous ice: The fine structure of DNA toroids. PNAS **98** *(26) 14925.*

How to pack curved tubes hexagonally?



Twistless bundle of parallel curved tubes.

The vector field $\mathbf{v}_{ij}(s) \equiv \mathbf{r}_i(s) - \mathbf{r}_j(s)$ connects the closest points on two curves and has to be relatively parallel, i.e. there is no twist of vectors $\mathbf{v}_{ij}(s)$ about $\mathbf{r}_i(s)$, $\mathbf{r}_j(s)$.

Take a curve $\mathbf{r}(s)$ and form a bundle with the orientation vector $\mathbf{v}$ which is governed by

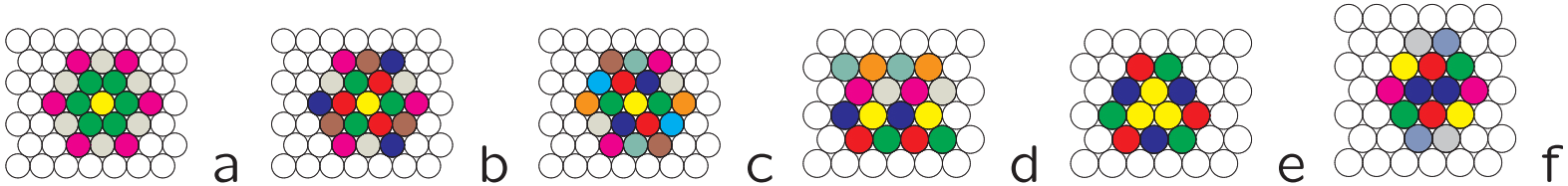
$$\frac{d\mathbf{v}}{ds} = -\varkappa(\mathbf{v}\cdot\mathbf{N})\mathbf{T},$$

where $\mathbf{T} = \frac{d\mathbf{r}}{ds}$ the tangent to the axis, $\frac{d\mathbf{T}}{ds} = \varkappa\mathbf{N}$, $\varkappa$ the curvature.

Closed bundles of parallel packed rods

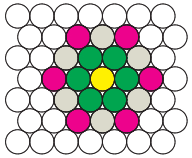
The 2D triangular lattice in an orthogonal cross-section maps onto itself. The automorphisms that preserve both the distances and the connectivity form a discrete infinite group which is finitely generated by the following set of transformations:

- *an identity map,*
- *translations along the lattice vectors* $\mathbf{e}_1$ *and* $\mathbf{e}_2$ *(fig. d),*
- *a rotation through* $\frac{1}{3}\pi$ *around the origin (figs. a,b,c),*
- *a rotation through* $\frac{2}{3}\pi$ *around* $\frac{1}{3}(\mathbf{e}_1 + \mathbf{e}_2)$ *(fig. e),*
- *a rotation through* π *around* $\frac{1}{2}\mathbf{e}_1$ *(fig. f).*



E. L. Starostin (2006) J. Phys.: Cond. Mat. **18** *S187-S204.*

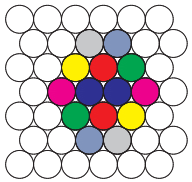
Parallel packed bundle. Case (a)

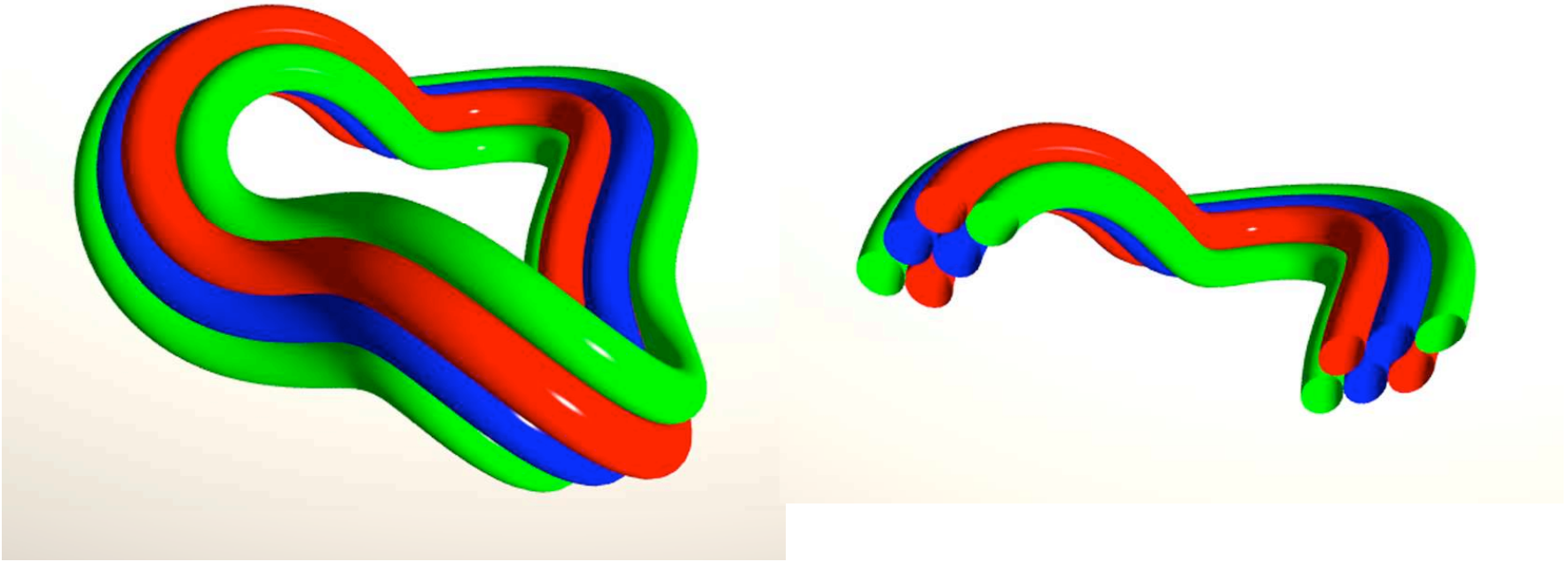


The bundle made up of two closed tubes. The core (dark) makes one turn and the second tube winds 6 times. The colour variation codes the arc length. The tubes are shown thinner to ease representation.

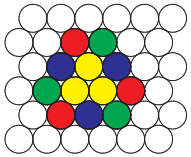
For all possible closed hexagonally packed bundles, *the writhing number* of each axis that realises the mapping should equal $n/6$, $n \in \mathbb{Z}$.

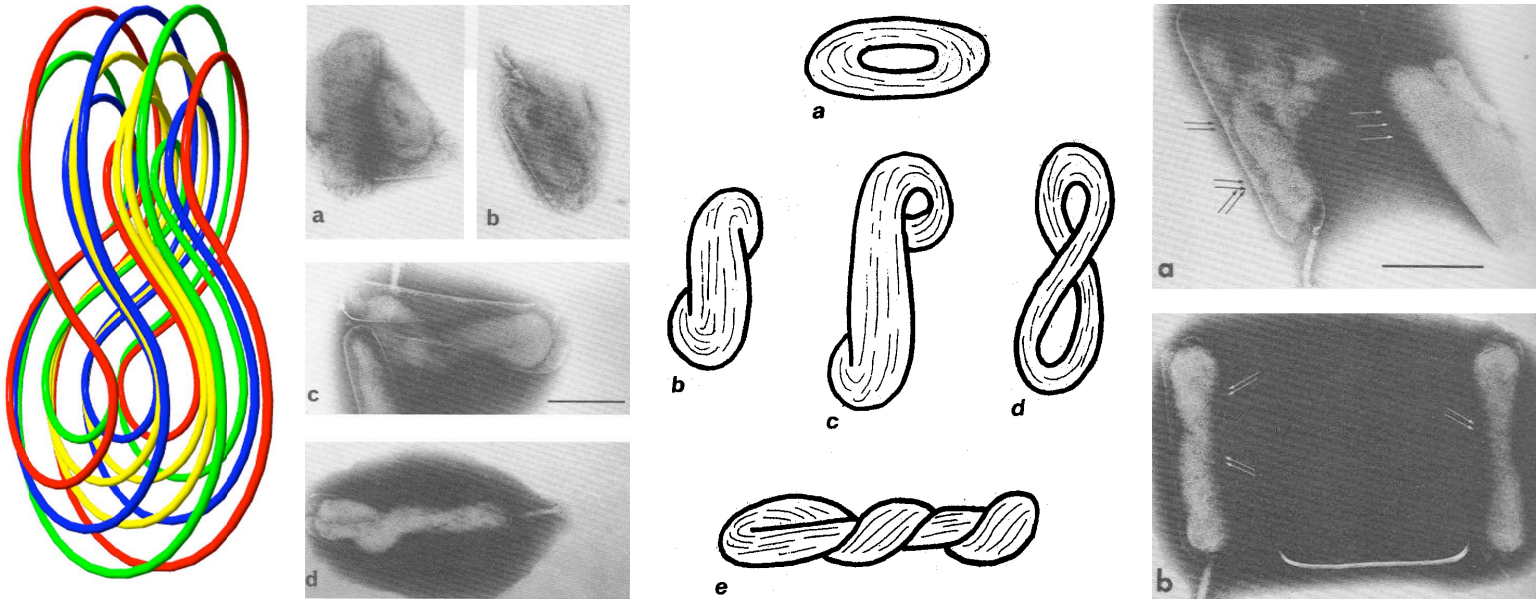
Parallel packed bundle. Case (f)





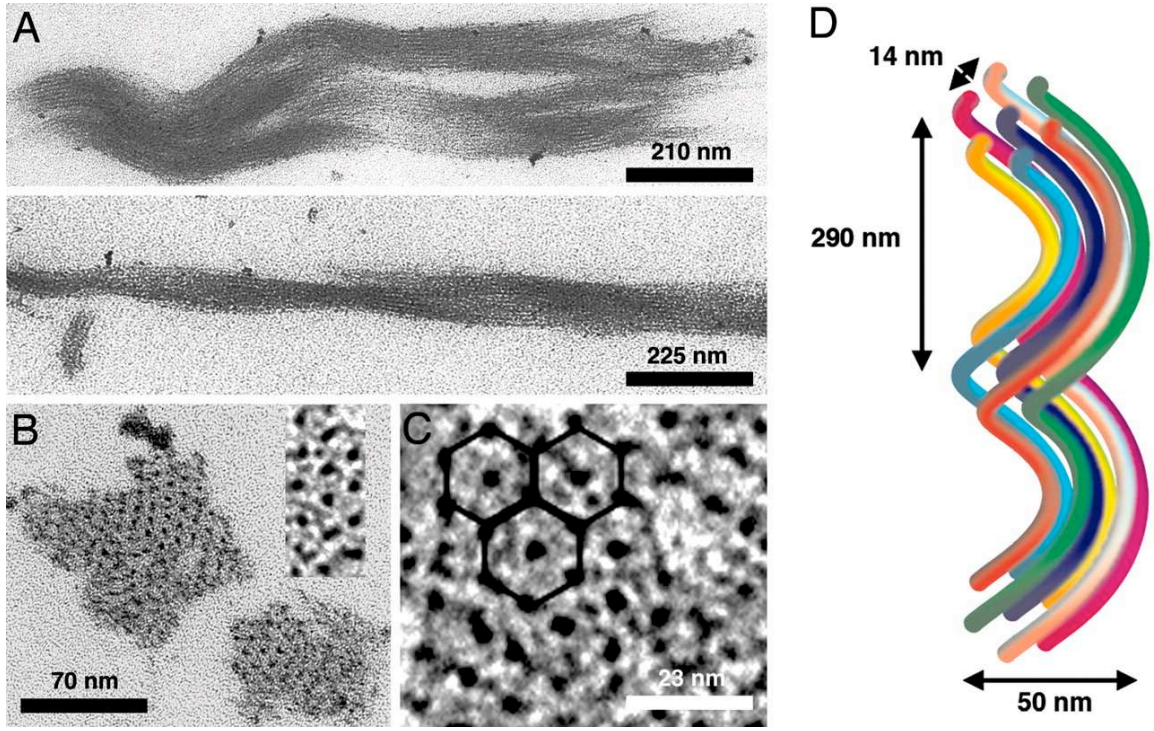
Parallel packed bundle made up of 4 closed tubes

Case (e) 



B&w: W. C. Earnshaw et al. (1978) The structural organization of DNA packaged within the heads of T4 wild-type, isometric and giant bacteriophages. Cell **14** *559.*

Ultrastructural analysis of bacteriophage-polymer bundles



B. Willis et al. (2008) Biologically templated organic polymers with nanoscale order. PNAS **105***(5) 1416.*

Bending energy of a parallel bundle of circular cross section

$$E_{bend} = \pi b \int_0^L \left(1 - \sqrt{1 - R^2 \varkappa^2(s)}\right) \, ds,$$

b bending stiffness, R radius of thickness, $\varkappa(s)$ curvature of the axis of length L.

Approximate expression for a *THIN* bundle.

If $R\varkappa << 1$, then

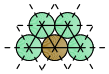
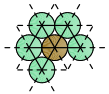
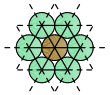
$$E_{bend} = \pi R^2 \, \frac{b}{2} \int_0^L \varkappa^2(s) \, ds.$$

$\Rightarrow$ *elastic equilibrium*

Tightest hexagonal bundle

Coordination number = 1/2 number of exposed binding sites.

Minimal coordination number is $\alpha_N = \left\lceil \sqrt{12N-3} \right\rceil$, where N is the number of rods in the bundle.

N	1	2	3	4	5	6	7
							
α_N	3	5	6	7	8	9	9

E. L. Starostin (2008) J. Chem. Phys. **129***(15) 154104.*

Conformational energy

1. The bending energy as that of a slender elastic rod

$$U_{bend} = \frac{B}{2} \int_0^L \varkappa^2(s)\, \mathrm{d}s,$$

B is the bending stiffness, $\varkappa(s)$ is the curvature of the centreline.

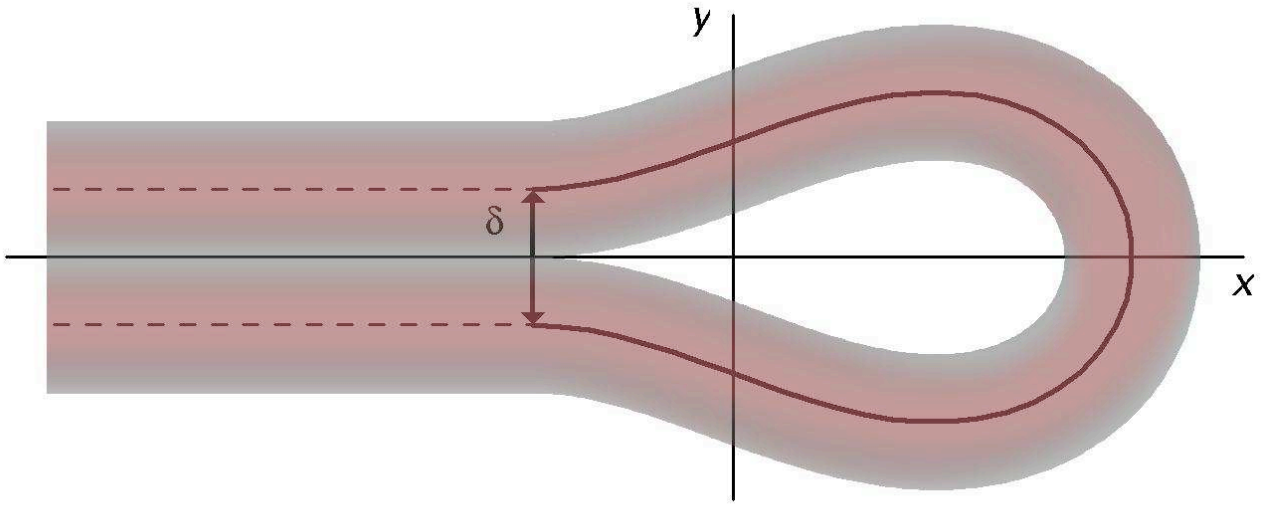
2. The surface energy of a N-fold parallel bundle of length L_N

$$U_N = \nu \alpha_N L_N,$$

ν is a surface tension parameter that represents the energy cost of polymer-solvent relative to polymer-polymer contact.
Normalisation on the *condensation length* $L_c = \sqrt{B/\nu}$ and the *condensation energy* $U_c = \sqrt{B\nu}$.

B. Schnurr et al. (2002) Phys. Rev. E **65** *061904.*

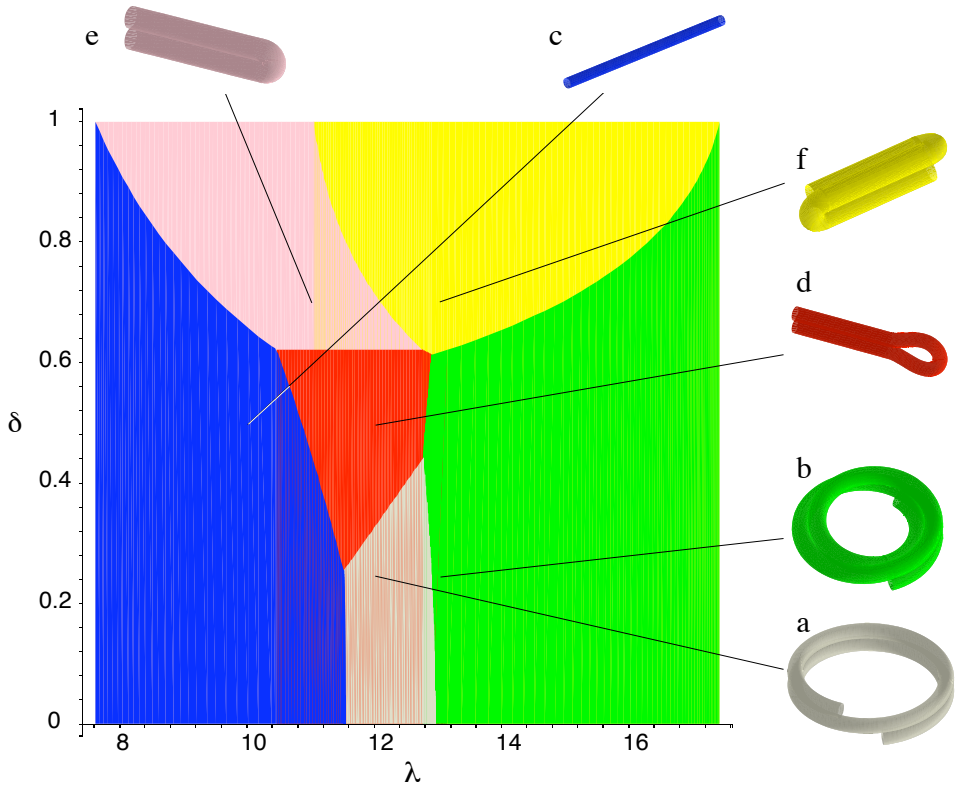
Racquet-like shape



The centreline of the racquet head is modeled as a thin elastic rod with its ends separated by δ.

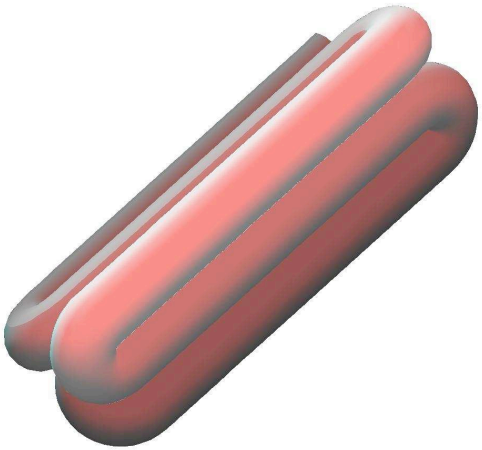
Diagram of state

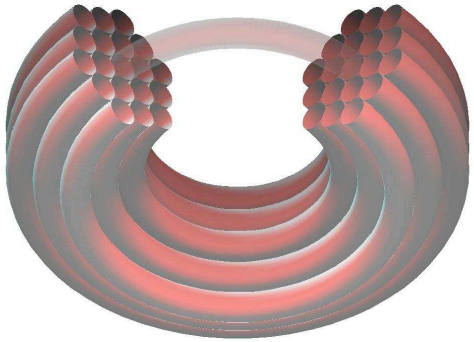
λ and δ are the normalised length and thickness diameter of the polymer, resp. The regions are shown where total energy is minimal for particular conformations.



E. L. Starostin, R. Everaers (2009) Submitted.

Stacked hairpins vs. toroids





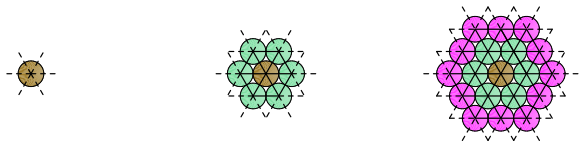
Conformational energy of N stacked hairpins

$$u_N^H(\lambda,\delta) = (N-1)u + \frac{1}{N}\left(\lambda - (N-1)\frac{\pi\delta}{2}\right)\left\lceil\sqrt{12N-3}\right\rceil,$$

u the energy cost of U-turn.

Bending energy of a toroid

A toroid made up with N closed circular rings which are tightly packed hexagonally. If N is a centred hexagonal number, i.e., if there exists a positive integer n such that $N = 3n^2 + 3n + 1$,



$n = 0$ $n = 1$ $n = 2$

then the bending energy

$$u_{bend}^{T} = \frac{2\pi}{\sqrt{3}\delta}[(n+1)(\beta+n)^{-1} - 2\beta\Psi(\beta) + \\ +(\beta+2n+1)\Psi(\beta+n) + (\beta-2n-1)\Psi(\beta-n)],$$

where Ψ is the digamma function and $\beta = \frac{\lambda}{\sqrt{3}\pi\delta N}$.

Conformational energy of a toroid

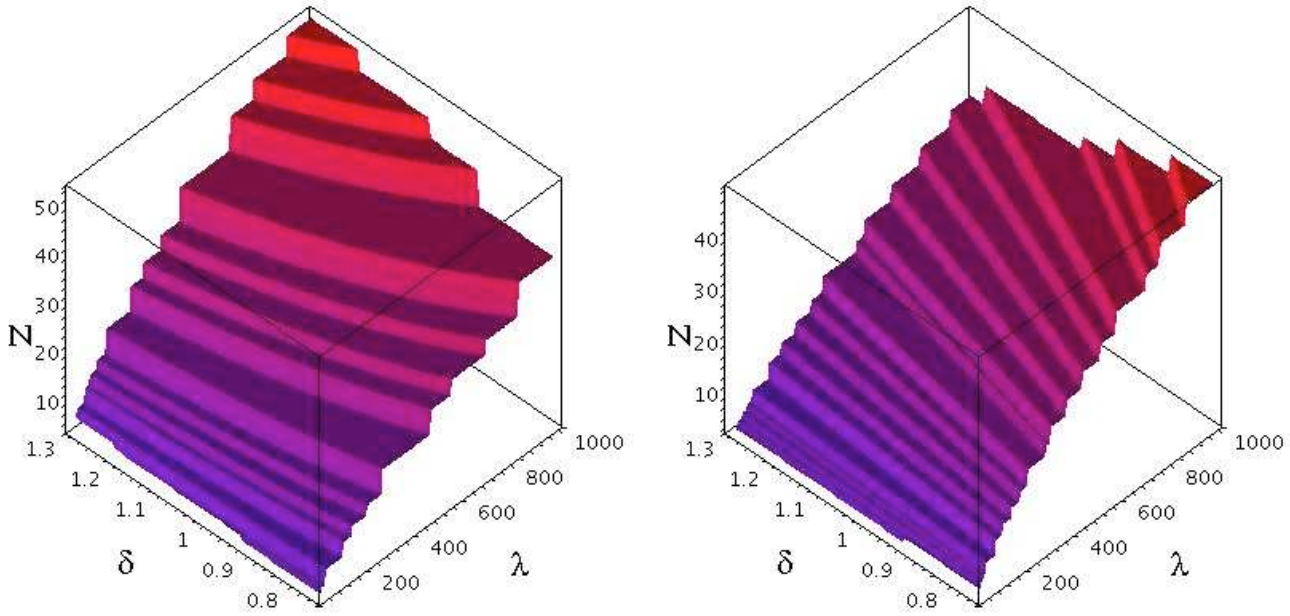
To describe the intermediate bundles we simply allow

$$n = \frac{1}{6}\sqrt{12N-3} - \frac{1}{2}, \quad n \in \mathbb{R}, \quad N \in \mathbb{N}^{+}.$$

The total energy

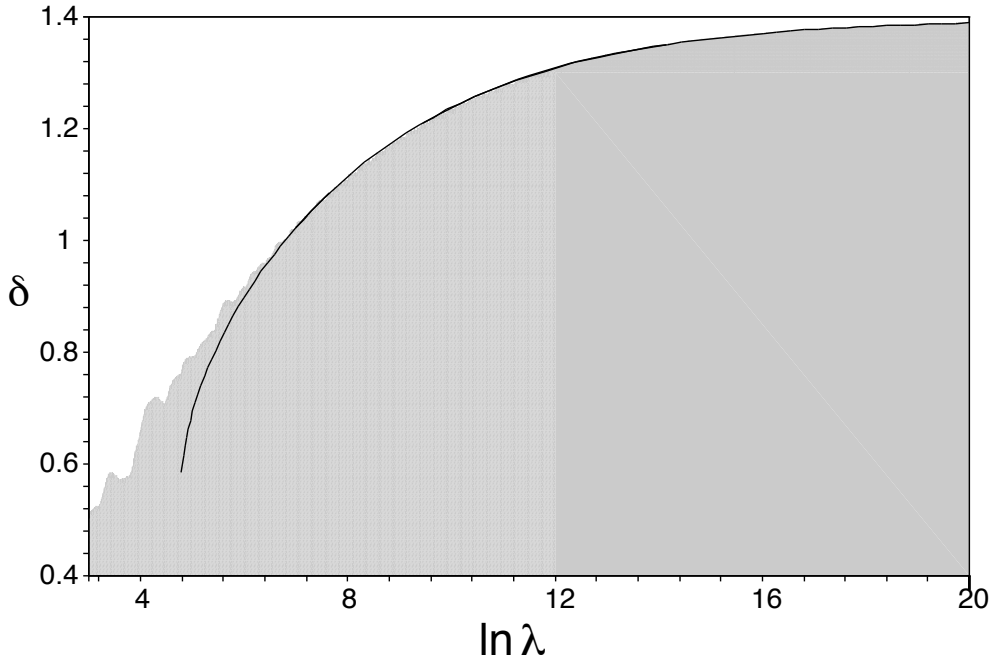
$$u_N^T(\lambda, \delta) = u_{bend}^T(N, \lambda, \delta) + \frac{\lambda}{N}\left\lceil \sqrt{12N-3} \right\rceil$$

Optimal number of filaments N



for the stacked hairpins (*left*) and tori (*right*)

Diagram of state



The toroids are energetically preferable in the shaded domain and the stacked hairpins have smaller conformational energy above. The approximate boundary curve is shown.

From toroids to hollow spheroids

- A hollow ball may provide a lower conformational energy than toroids.

- This globular shape may be potentially useful as a container for drug delivery.

- We study the morphological transformation of the toroid into the hollow spheroid.

I. C. B. Miller et al. (2005) Phys. Rev. E **71** *031802.*

Problem formulation

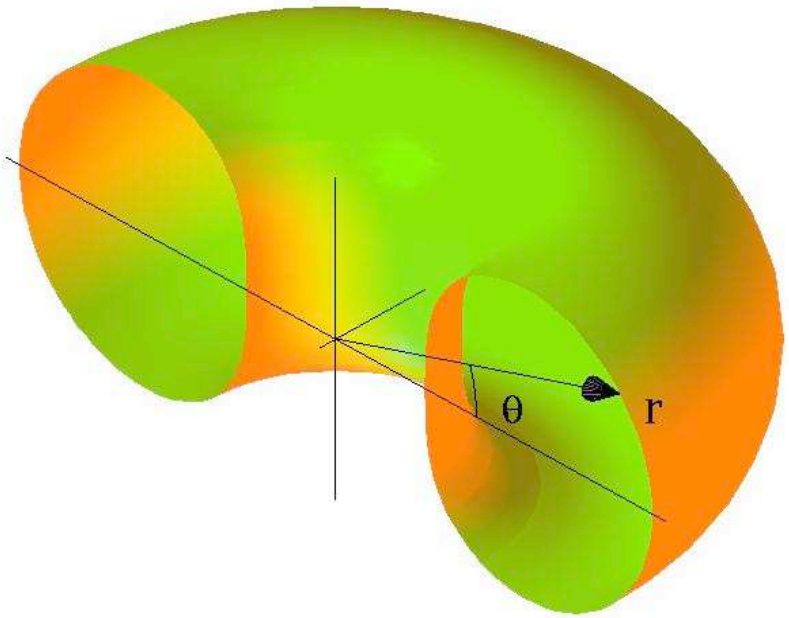
- A semiflexible polymer (e.g. DNA) chain of length L is immersed in a poor solvent.

- To find a shape that minimises the integral bending and surface energies under the constraint of constant volume.

- The globule is formed by a tightly packed strand which wraps around the centre (a concentric spool).

- The density is constant.

J. Ubbink, T. Odijk (1996) EPL **33** *353.*



Polar coordinates r, θ

$$\left(r \in [r_1, r_2], \theta \in \left[0, \frac{\pi}{2}\right]\right)$$

describe the contour curve of one quarter of the cross section.

To be physically meaningful, the cross section of a rotationally symmetric shape of the condensate must satisfy the following condition of connectivity of spherical layers:

if the point (r_0, θ_0) *belongs to the condensate, then the entire arc*

$$\{(r_0, \theta), \theta \in [-\theta_0, \theta_0]\}$$

must belong to it, too.

The surface area A and the volume V of the toroid are

$$A = 4\pi \int_{r_1}^{r_2} r \cos\theta \sqrt{1 + r^2(\theta_r)^2}\ dr \quad \text{and} \quad V = 4\pi \int_{r_1}^{r_2} r^2 \sin\theta\ dr.$$

The surface energy is modelled as $E_s = \gamma A$, where γ is the polymer-solvent surface tension.

Assuming that the polymer cross section is a square of side a, the elastic bending energy is computed as

$$E_b = \frac{b}{2a^2} \int_{r_1}^{r_2} \iint_{S_r} \frac{1}{r^2}\ d\sigma dr = 2\pi \frac{b}{a^2} \int_{r_1}^{r_2} \sin\theta\ dr,$$

where $d\sigma$ is a spherical area element of sphere S_r of radius r, b stands for the bending rigidity.

The variational problem:

Find $\theta(r)$ such that

$$\int_{r_1}^{r_2} \left(r\cos\theta\sqrt{1+r^2\theta_r^2} + B\sin\theta - pr^2\sin\theta \right) dr \to \min,$$

where B is the normalised bending coefficient and p is the Lagrange multiplier.

Then the Euler-Lagrange equation is

$$r^2(r\theta_{rr} + 3\theta_r + 2r^2\theta_r^3)\cos\theta + r(1+r^2\theta_r^2)\sin\theta - \\ -(B - pr^2)(1+r^2\theta_r^2)^{3/2}\cos\theta = 0.$$

Boundary conditions: the contour curve must meet each coordinate axis orthogonally.

Introduce a characteristic parameter

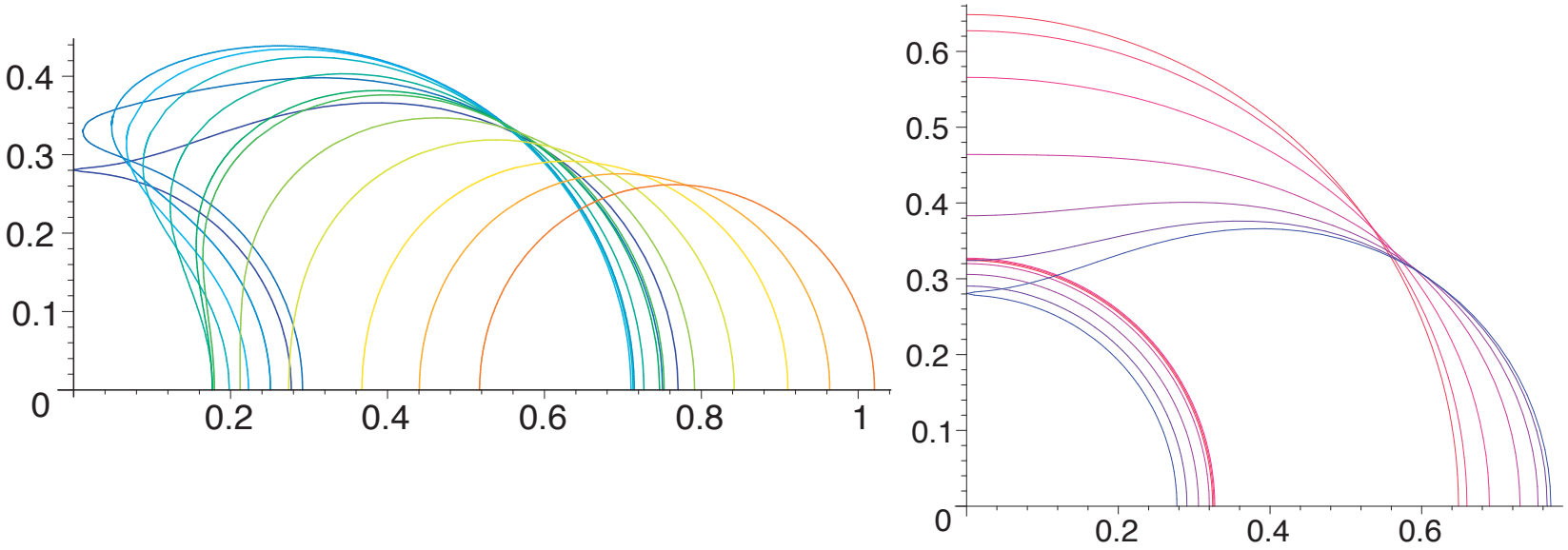
$$\eta = \frac{a^2 \gamma V^{1/3}}{b} = \frac{V^{1/3}}{2B}$$

and the dimensionless conformational energy

$$\mathcal{E} = \frac{E a^2}{b V^{1/3}} = \frac{E}{2B\gamma V^{1/3}}.$$

Numerical solution of the BVP reveals a one-parameter family of solutions.

Morphological variation of toroids and spheroids

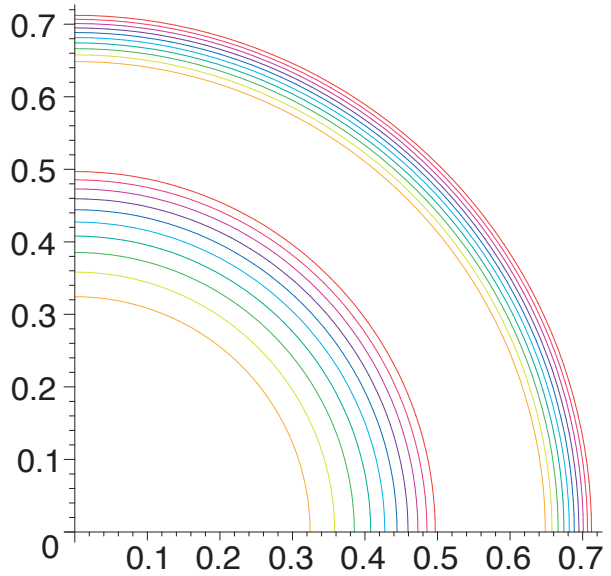


Hollow balls

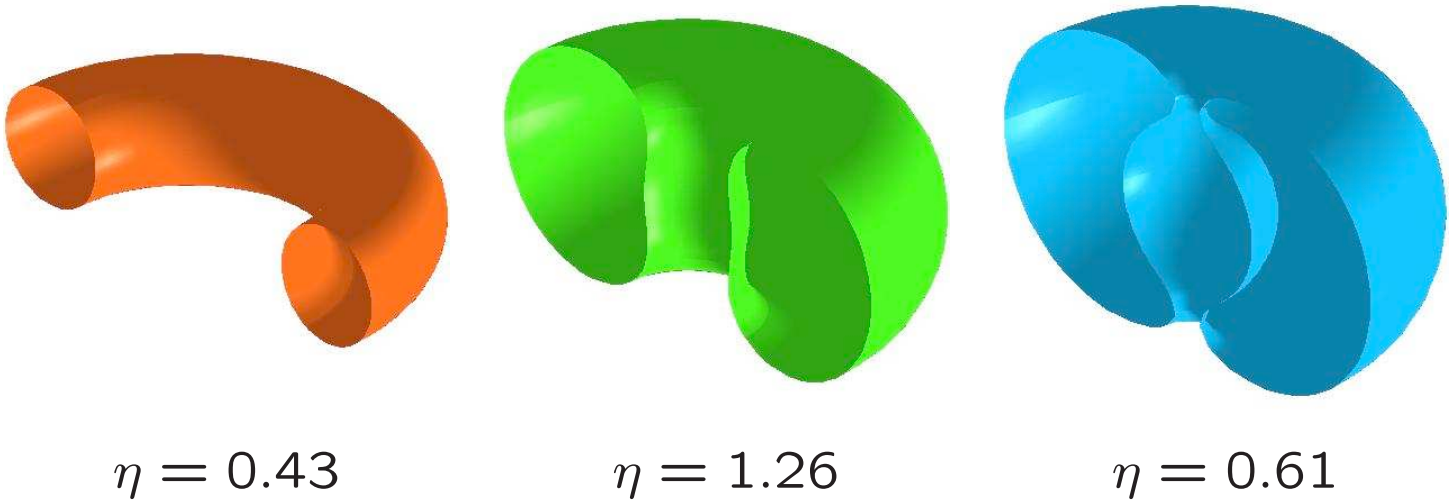
The concentric spool model allows for another solution: the exact hollow balls. Their inner and outer radii can be found as stationary solutions of the governing equation:

$$r_{\pm} = \frac{\sqrt{Bp+1} \pm 1}{p}$$

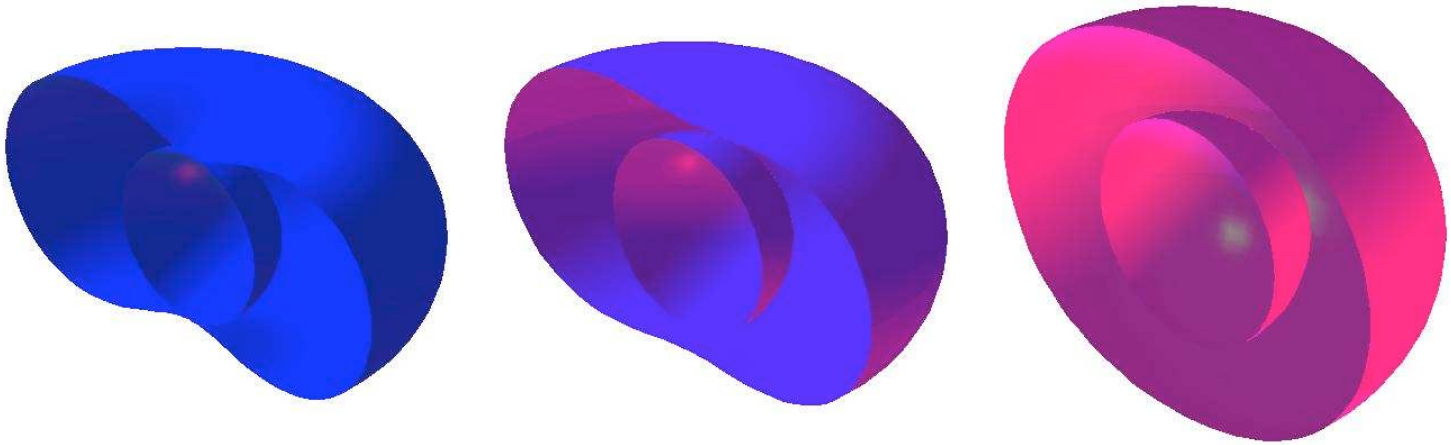
$\Rightarrow$ linearisation



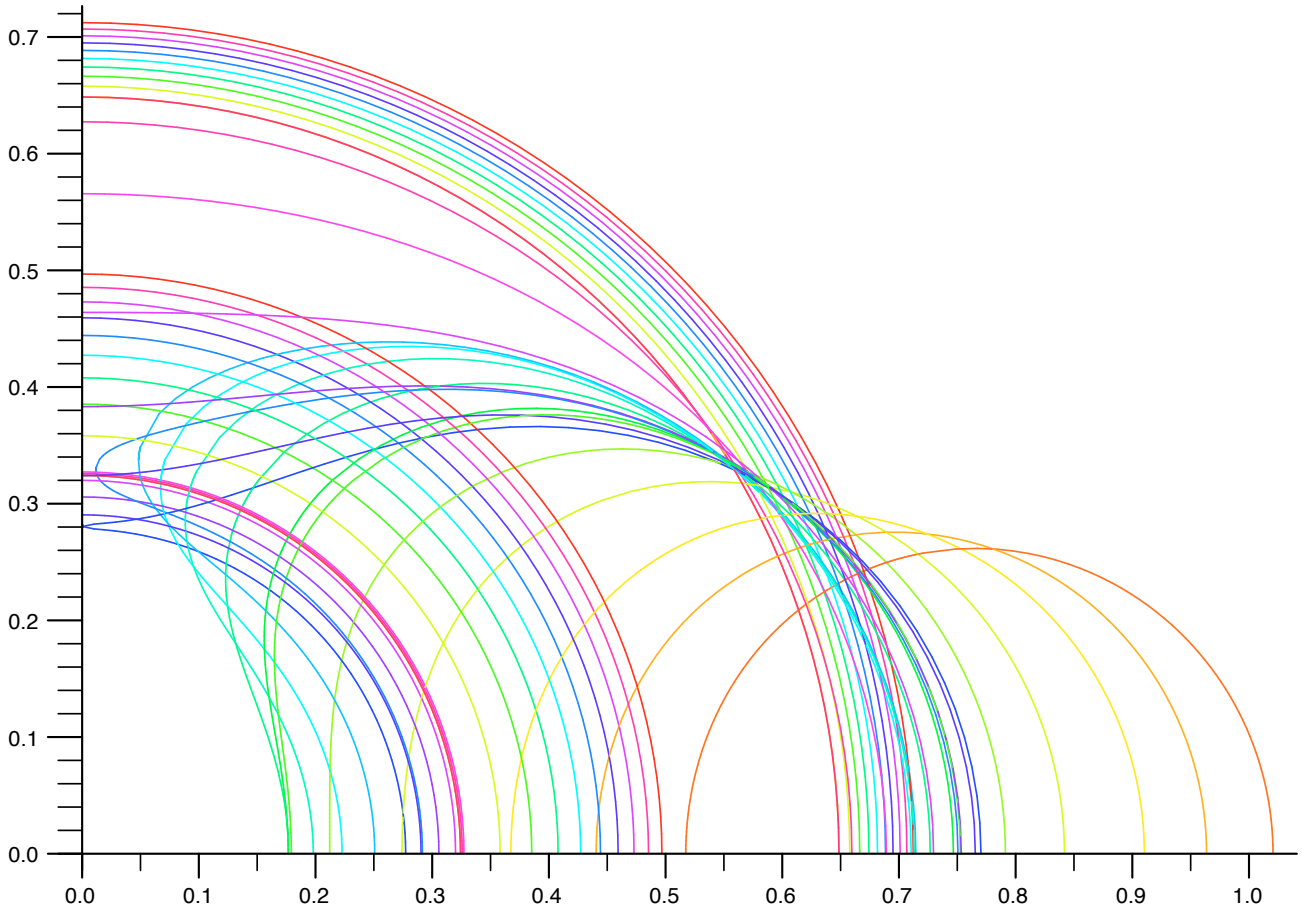
Cross-sections of hollow balls.



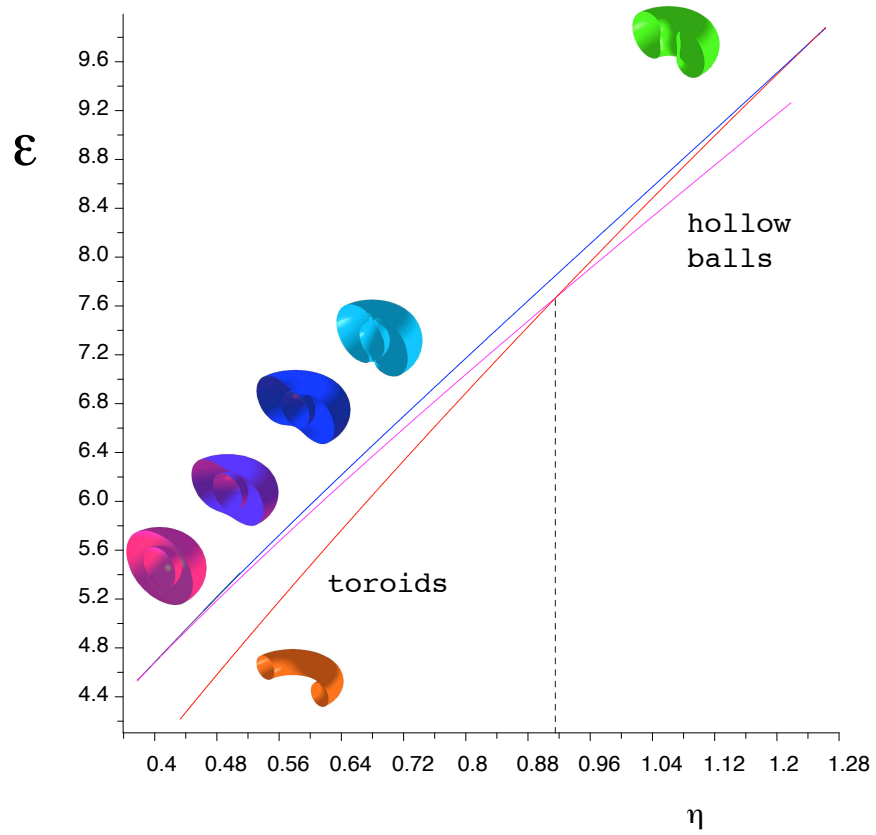
$\eta = 0.43$ $\eta = 1.26$ $\eta = 0.61$



$\eta = 0.50$ $\eta = 0.43$ $\eta = 0.38$

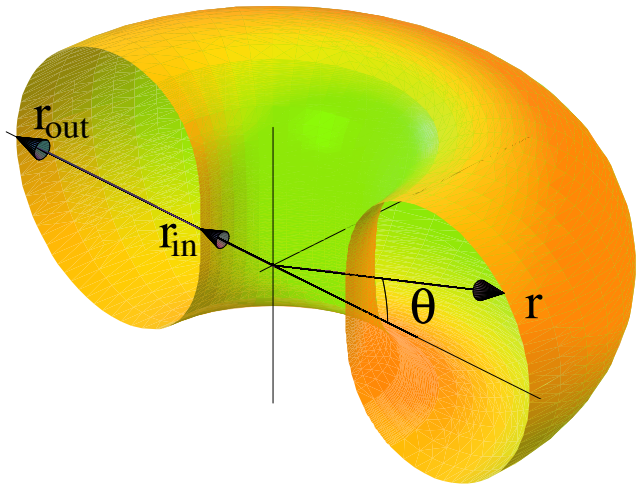


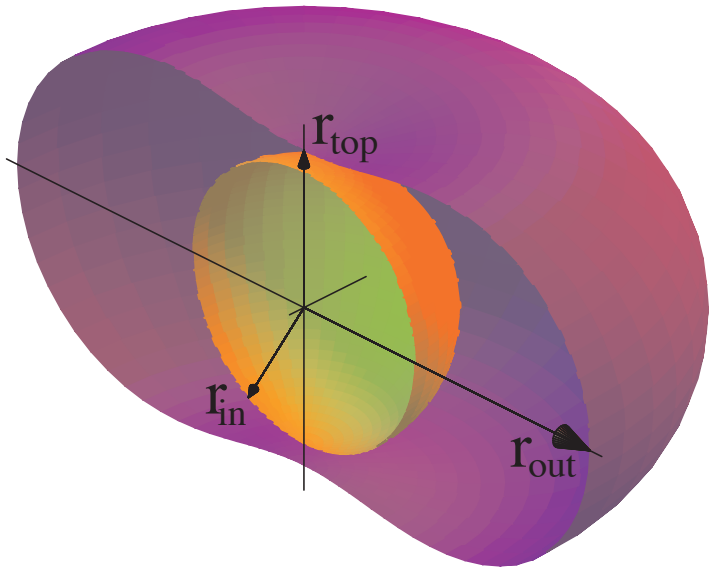
Morphological transformation.



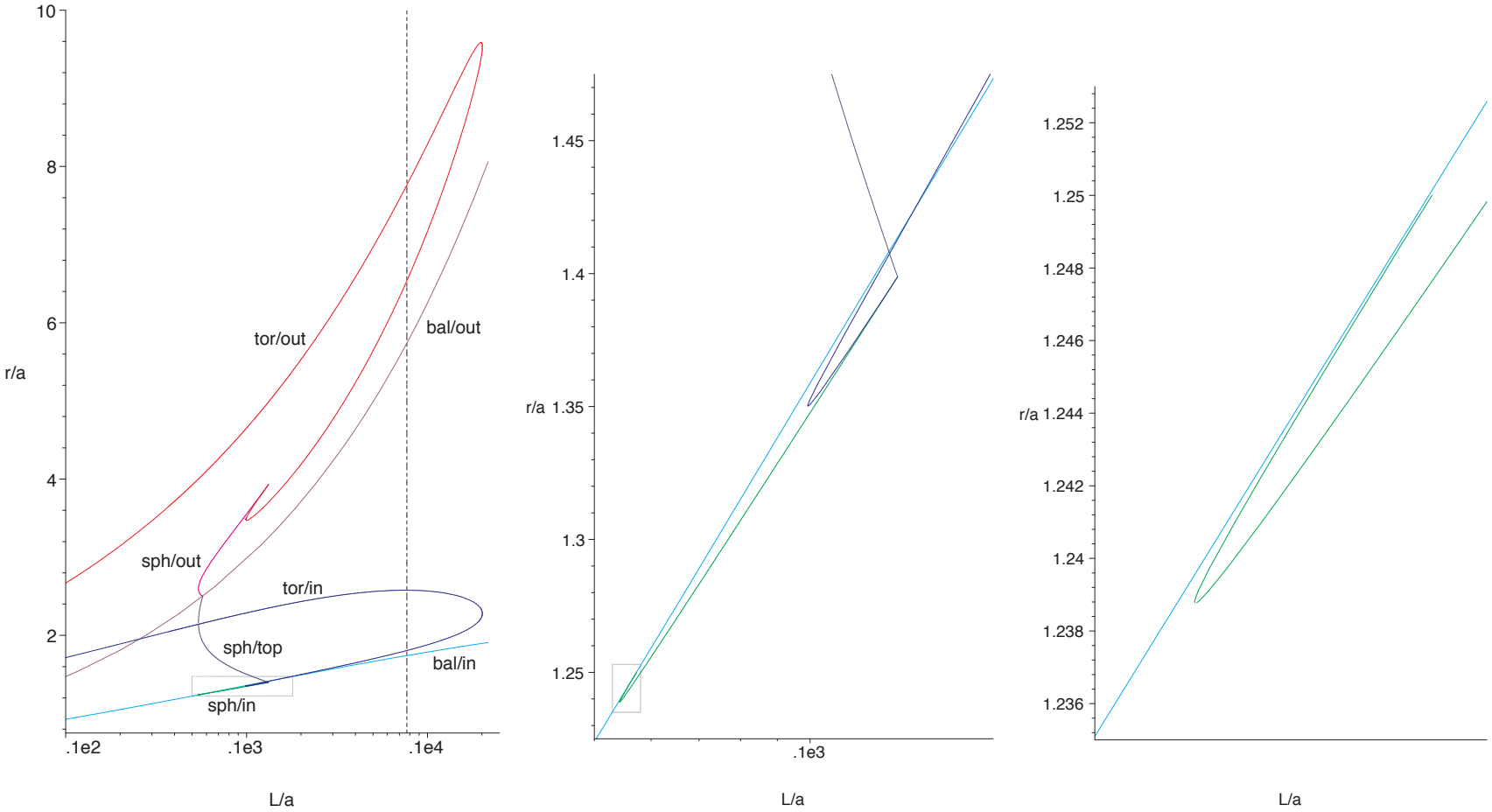
Conformational energy $\mathcal{E}$ vs. the characteristic parameter η. For $\eta < \eta_{cr} \approx 0.916$, the toroids have the smallest energy, while the hollow balls are the shapes with minimal energy for $\eta > \eta_{cr}$.

Characteristic sizes of the toroids and spheroids





Dependence of globule's sizes on the DNA length



Concluding remarks

- A one-parameter family connects the toroids (not simply-connected) and the hollow balls (simply-connected). Both shapes are non-contractible.

- The hollow balls become energetically preferable to the toroids above the critical value of the characteristic parameter.

- The intermediate conformations have olnly slightly higher energy and may be considered as metastable. The found pathway may help explain transition from toroids to hollow balls from the kinetics point of view.

Appendix 1

Elastic equilibrium of a parallel bundle

If a curve is the axis of a perfect bundle (made up with symmetric Kirchhoff elastic rods) in equilibrium, then the curve is an extremal for a linear combination of three integrals

$$\mathcal{F} = \lambda_1 \mathcal{L} + \lambda_2 \mathcal{T} + \lambda_3 \mathcal{K},$$

where $\mathcal{L} = \int ds$, $\mathcal{T} = \int \tau ds$, $\mathcal{K} = \int \frac{f(\varkappa^2)}{2} ds$.

For thin bundle, $f(\varkappa^2) = \varkappa^2$.

For thick bundle of circular cross section,
$f(\varkappa^2) = \frac{2}{R^2}\left(1 - \sqrt{1 - R^2\varkappa^2(s)}\right)$.

Variational problem in invariant form (1)

$$\int_0^L f(\kappa, \tau, \kappa', \tau', \kappa'', \tau'', \ldots, \kappa^{(n)}, \tau^{(n)})\, \mathrm{d}s \to \min$$

It is possible to write the Euler-Lagrange equation in invariant form [Anderson (1989)].

Example: the planar elastica with $\int \kappa^2\, \mathrm{d}s$.
Its Euler-Lagrange equation is $\kappa'' + \frac{1}{2}\kappa^3 = 0$.

Variational problem in invariant form (2)

The Euler-Lagrange equations of the problem

$$\int_0^L f(\kappa, \tau, \kappa', \tau', \kappa'', \tau'', \ldots, \kappa^{(n)}, \tau^{(n)})\, \mathrm{d}s \to \min$$

can be presented in the form of balance equations for force $\boldsymbol{F} = (F_t, F_n, F_b)^T$ and moment $\boldsymbol{M} = (M_t, M_n, M_b)^T$

$$\boldsymbol{F}' + \boldsymbol{\omega} \times \boldsymbol{F} = \boldsymbol{0}, \quad \boldsymbol{M}' + \boldsymbol{\omega} \times \boldsymbol{M} + \boldsymbol{t} \times \boldsymbol{F} = \boldsymbol{0},$$

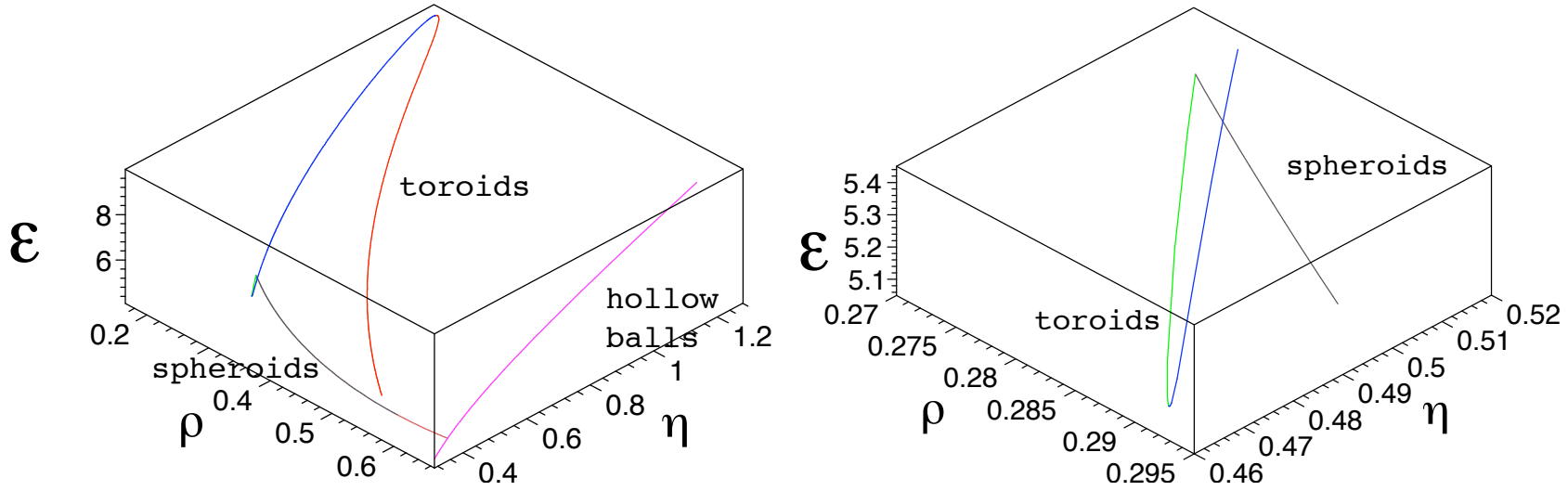
where $\boldsymbol{\omega} = (\tau, 0, \kappa)^T$ is the Darboux vector and

$$M_b = \partial_\kappa f - (\partial_{\kappa'} f)' + (\partial_{\kappa''} f)'' - \ldots, \quad M_t = \partial_\tau f - (\partial_{\tau'} f)' + (\partial_{\tau''} f)'' - \ldots.$$

E. L. Starostin, G. H. M. van der Heijden (2009) Phys. Rev. E, in press. arXiv:0905.1880

Tightest hexagonal bundle ⇐

Appendix 2



Conformational energy $\mathcal{E}$ vs. the characteristic parameter η and the characteristic size ρ; ρ is the normalised minimal radius of the inner free volume for toroids and of the outer surface for spheroids. *Right:* Zoomed neighbourhood of the point where the hole of the toroids disappears.

Characteristic sizes ⇐

Euler-Lagrange equation for $r(\theta)$

For some shapes the contour may be conveniently represented as a function $r(\theta)$, which should satisfy

$$r^2(-rr_{\theta\theta} + 3r_\theta^2 + 2r^2)\cos\theta + rr_\theta(r_\theta^2 + r^2)\sin\theta - \\ - \operatorname{sign} r_\theta(B - pr^2)(r_\theta^2 + r^2)^{3/2}\cos\theta = 0.$$

Introduce a characteristic parameter $\Leftarrow$

Linearisation

Consider a perturbation of a stationary solution $r = r_0$, where $r_0 = r_i$ or $r_0 = r_o$. Let $r = r_0 + \delta, |\delta| \ll 1$, then Eq. (2) implies

$$\delta_{\theta\theta} \cos\theta - \delta_\theta \sin\theta - K\delta \cos\theta = 0$$

with $K = \operatorname{sign} r_\theta \; 2\sqrt{Bp+1}$.

The solution of the last equation is

$$\delta = C_1 P_\nu(\sin\theta) + C_2 Q_\nu(\sin\theta),$$

where P_ν, Q_ν are the Legendre functions of the first and second kind, resp., $\nu = (\sqrt{1-4K} - 1)/2$ and C_1, C_2 are arbitrary constants.

The only solution of the linearised equation that satisfies the boundary conditions and makes physical sense, exists for $K = -6$ (hence, for $Bp = 8$):

$$\delta = C_1 P_2(\sin\theta) = \tilde{C}_1(1 - 3\sin\theta^2).$$

This gives us the value of the characteristic parameter η where the spheroid branch meets the hollow ball solutions:

$$\eta_\star = \frac{1}{8}\left(\frac{28\pi}{3}\right)^{1/3} \approx 0.385.$$

Hollow Balls $\Leftarrow$