Geometric Models for Secondary Structures in Proteins

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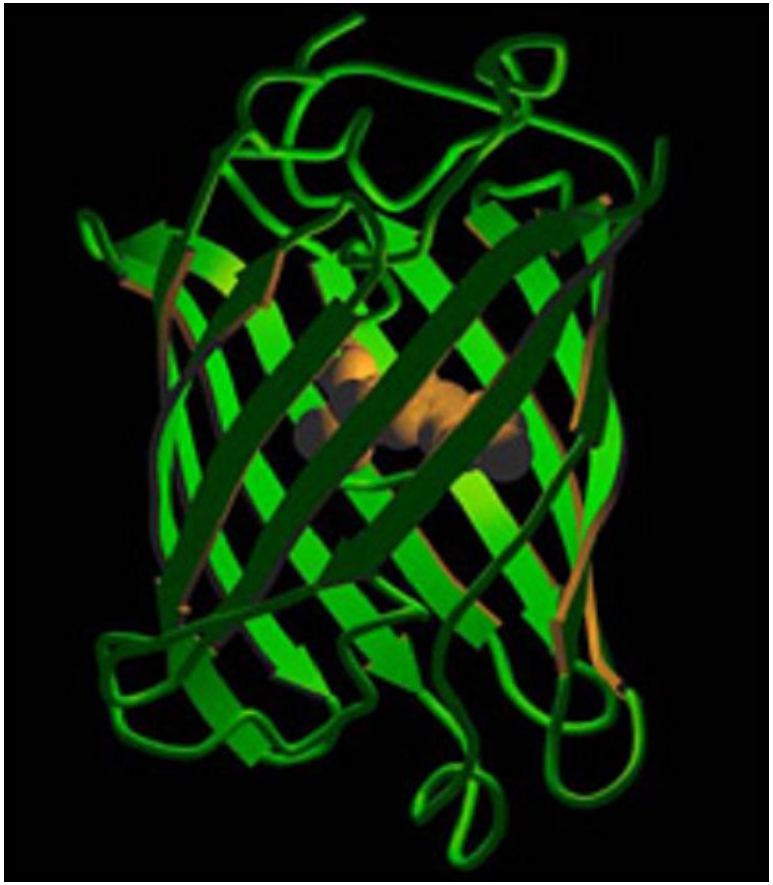
Abstract

ABSTRACT:
This report was motivated by a study of beta barrels as a secondary structure in proteins, using methods from differential geometry and variational calculus, namely Dirichlet and Willmore-type energies. We review some historical models of beta sheets and explain why those models are outdated. We provide an elastic membrane model for these structures, via a certain 'Generalized Willmore type energy'. We study the corresponding Euler-Lagrange, as well as a specific boundary value problem whose solutions are 'Generalized Willmore surfaces of revolution'. We study corresponding solutions both theoretically and numerically (using COMSOL).

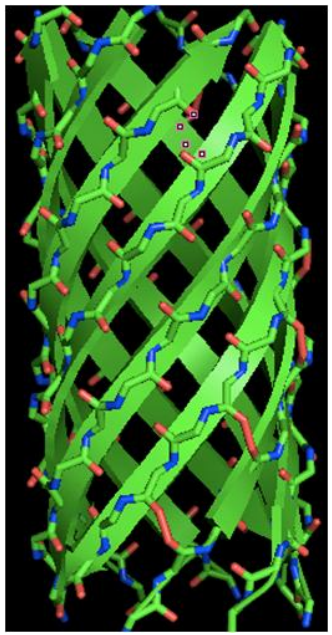
In biochemistry, biophysics and mathematical biology, secondary structures represent the main types of three-dimensional geometric shapes of local segments of biopolymers (e.g., proteins and nucleic acids (DNA/RNA)). On a finer level, the atomic positions in three-dimensional space are said to form the tertiary structure. Secondary structure can be formally defined by the hydrogen bonds of the biopolymer, as observed in an atomic-resolution structure. In proteins, the secondary structure is defined by the patterns of hydrogen bonds between backbone amino and carboxyl groups. In nucleic acids, the secondary structure is defined by the hydrogen bonding between the nitrogenous bases.

The sheet (also -pleated sheet) is the second form of regular secondary structure in proteins, only somewhat less common than the alpha helix. Beta sheets consist of beta strands connected laterally by at least two or three backbone hydrogen bonds, forming a generally twisted, pleated sheet. The higher-level association of sheets has been implicated in formation of the protein aggregates and fibrils observed in many human diseases, notably the amyloidoses involved in Alzheimer's disease. In contrast to the alpha helix, the beta pleated sheet, whose name derives from the corrugated appearance of the extended polypeptide chain, involves hydrogen bonds between backbone groups from residues distant from each other in the linear sequence. In beta sheets, two or more stands that may be widely separated in the protein sequence are arranged side by side, with hydrogen bonds between the strands. The strands can run into the same direction (parallel beta sheet) or antiparallel to one another; mixed sheets with both parallel and antiparallel strands are also possible.



http://www.aacc.org/resourcecenters/TestKnowledge/MOM/Pages/molecule2008.aspx GFP (green fluorescent protein) has a typical beta barrel structure. Martin Chalfie, Osamu Shimomura, and Roger Y. Tsien were awarded the 2008 Nobel Prize in Chemistry on 10 October 2008 for their discovery and development of the GFP.

About the GFP: Isolated from jellyfish; has amino-terminal and carboxyl-terminal beta-pleated sheet motifs that form a barrel. The alpha-helical middle portion of the protein, which runs through the barrel, is the chromophore. Cells genetically modified to express one of the many different forms of green fluorescent protein remain colored under ultraviolet light and this feature may be used to study them in an enormous variety of ways. Thanks to Dr. Binchen Mao and Dr. David Baker (University of Washington) for this pic. As best-fit math model, they currently use the one-sheeted hyperboloidal model as being convenient - in spite of the sheets not being straight lines.

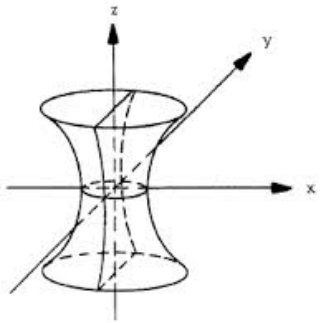


What is the 'real' shape of a beta barrel? Or: what is the best model?

Various existing models and their history

- **- one sheeted hyperboloid (Salemme, 1983; Laster and al, PNAS, 1988) - still used by chemists in 2014**
- **- twisted hyperboloid (Strophoid), (Novotny, 1984)**
- **- surface on which strands are viewed as helical sheets (Znamenskiy, 2000)**
- **-"almost-a-cylinder" (in encyclopedia of biochemistry and online materials)**
- **- catenoid (Kim and Koh, Bioinformatics, 2006)**

Advantages and disadvantages: while these models may be 'convenient', they are too far from the physical and geometric model of beta barrel. For example:
- the one-sheeted hyperboloidal model assumes the strands are straight-lines - and they are not!
- the catenoid model assumes $H = 0$ everywhere, while experiments show that H is small, but not very small!



Experimental data sustains our hypothesis that the mean curvature of beta-barrels (performed by Lasters) is far from being equal to zero for most or all aminoacids; also, it does not vary much from a point to another so it may be assumed to lie in an interval in an interval of type (h-c, h+c), for a sufficiently small constant c.
A = Protein type B = Average mean curvature H C = S.D. standard deviation of mean curvature Examples:
A). Glicolate-oxydase
B). H = 0.035
C). SD = 0.007
A). Taka-amylase
B). H = 0.035
C). SD = 0.007
A). Aldolase
B). H = 0.035
C). SD = 0.012

No guessing game: time to model beta barrels as elastic surfaces!

Different types of energies for different elastic surfaces :

- Poisson & Sophie German - $2k_c \int_M H^2 \, dS$
- Willmore - $\int_M (H^2 - K) \, dS$
- Helfrich for elastic biomembranes- lipid bilayers and cell membranes - $\int_M \frac{k}{2}(2H - c_0)^2 + \bar{k}K \, dS$

Note: c_0 is called spontaneous curvature for biomembranes and spontaneous splay for liquid crystal theory.... A c_0 for proteins, called spontaneaus curvature, will depend on the solvent used!

Question: can we assume $c_0 = 0$? Answer: As a pure mathematician: yes! As an applied scientist: no.
At first, we shall assume $c_0 = 0$ and also the strain tensor coming from the backbone structure to be negligible. We may reconsider later!

Therefore, we introduce.... the Generalized Willmore energy functional

Theorem

Assume M is a closed surface in $\mathbb{R}^3$. Let E_w be the Generalized Willmore energy functional

$$E_w = \int_M (kH^2 + \mu)\, dS, \tag{1}$$

where $k = 2k_c$, and k_c represents the bending rigidity, while μ is the surface tension coefficient. Then the Euler-Lagrange equation of (**??**) *is:*

$$\Delta H + 2H(H^2 - K - \epsilon) = 0 \tag{2}$$

with $\epsilon = \frac{\mu}{k}$.

The proof is a 7 page one (even with Einstein summation conventions). It is based on calculus of variations and classical differential geometry. It mimics the proof of Willmore equation as Euler-Lagrange equation for the usual Willmore energy functional. The additional term coming from surface tension complicates things but not too much!

Generalized Willmore (G-W.) surfaces of revolution

Consider the parametrization:

$$\mathbf{r}(x,\varphi) = (x, u(x)\cos\varphi, u(x)\sin\varphi)$$

- ⋆ L-B:

$$\Delta_g H = \frac{1}{u\sqrt{1+u'^2}}\frac{d}{dx}\left(\frac{u}{\sqrt{1+u'^2}}\frac{dH}{dx}\right)$$

- ⋆ H:

$$H = \frac{-u''}{2(1+u'^2)^{3/2}} + \frac{1}{2u\sqrt{1+u'^2}}$$

- ⋆ K:

$$K = \frac{-u''}{u(1+u'^2)^2}$$

For details on H and K formulas for surfaces of revolution, one can consult John Oprea's books (Differential Geometry and its Applications; and, Mathematics of Soap Films).

$$\frac{d}{dx}\left(\frac{u}{\sqrt{1+u'^2}}\frac{dH}{dx}\right)+2H\left((H^2-\epsilon)u\sqrt{1+u'^2}-2H+\frac{1}{u\sqrt{1+u'^2}}\right) \quad = \quad 0$$

Numerically compute the profile curve $u(x)$ with the boundary conditions:

$$u(\pm 1)=\alpha \qquad \text{and} \qquad H(\pm 1)=0$$

Case 1: Fixed α

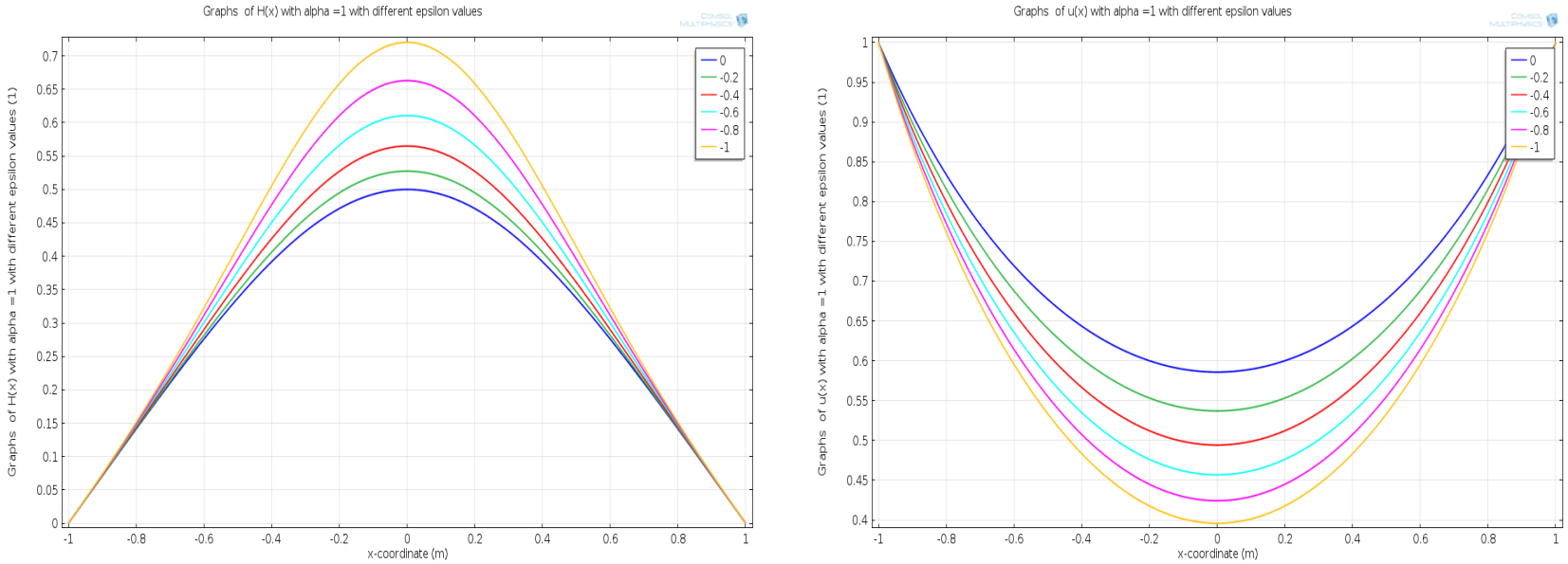


Figure: Mean curvature graphs (left), Profile curve $u(x)$ (right) $\alpha = 1.0$ and $\epsilon = 0 : 0.2 : 1$

Case 2: Fixed ϵ

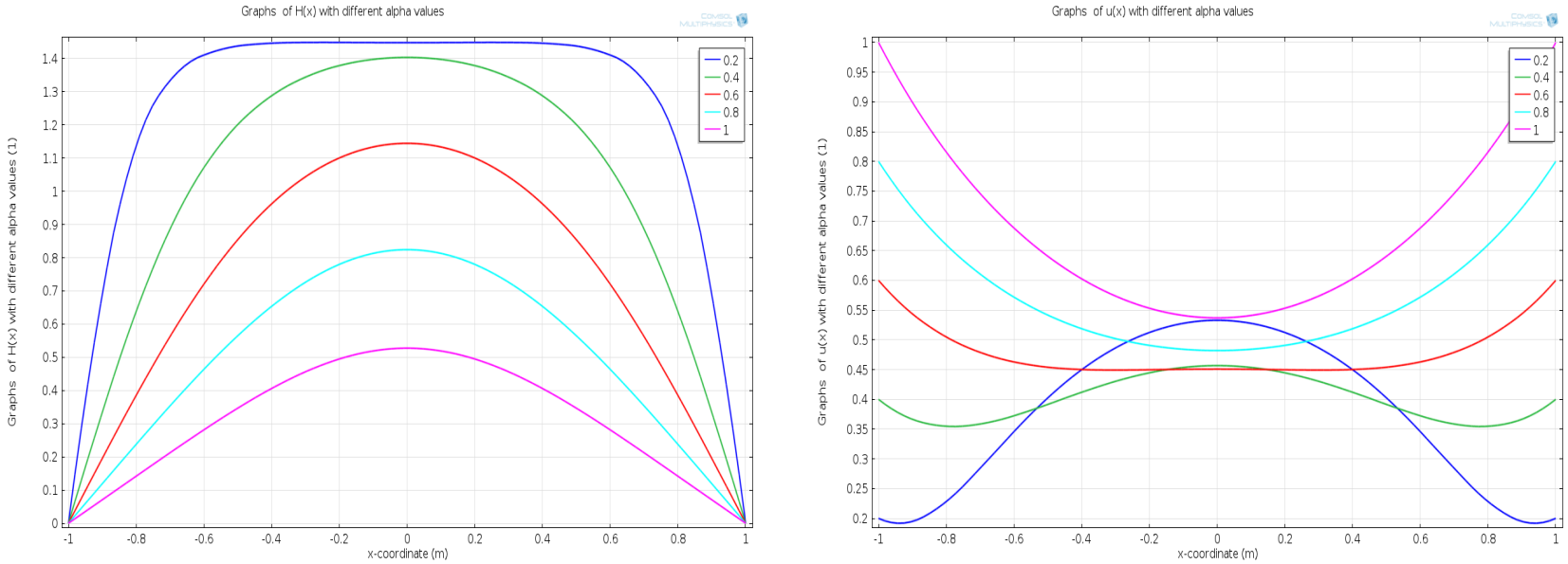


Figure: Mean curvature graphs (left), Profile curve $u(x)$ (right) $\epsilon = 0.2$ and $\alpha = 0.2 : 0.2 : 1$ and

Interesting cases

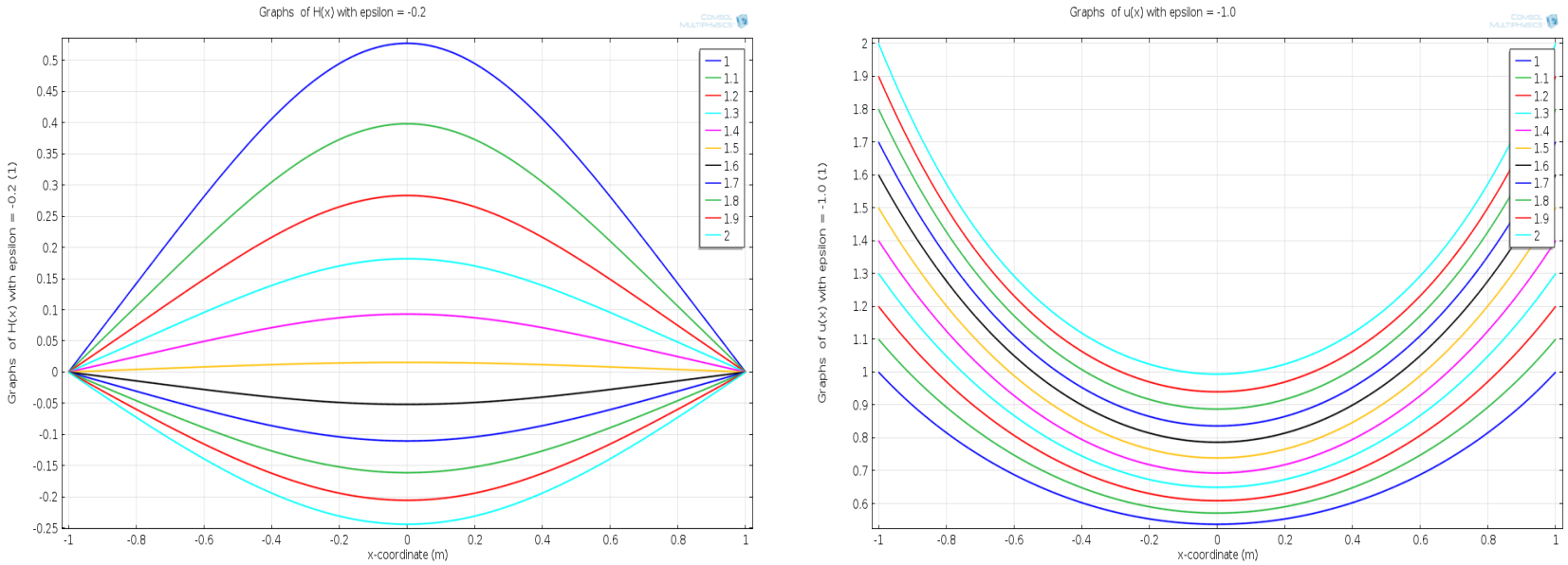


Figure: Variation of mean curvature for different α values with fixed $\epsilon = 0.2$ value.

Interesting cases

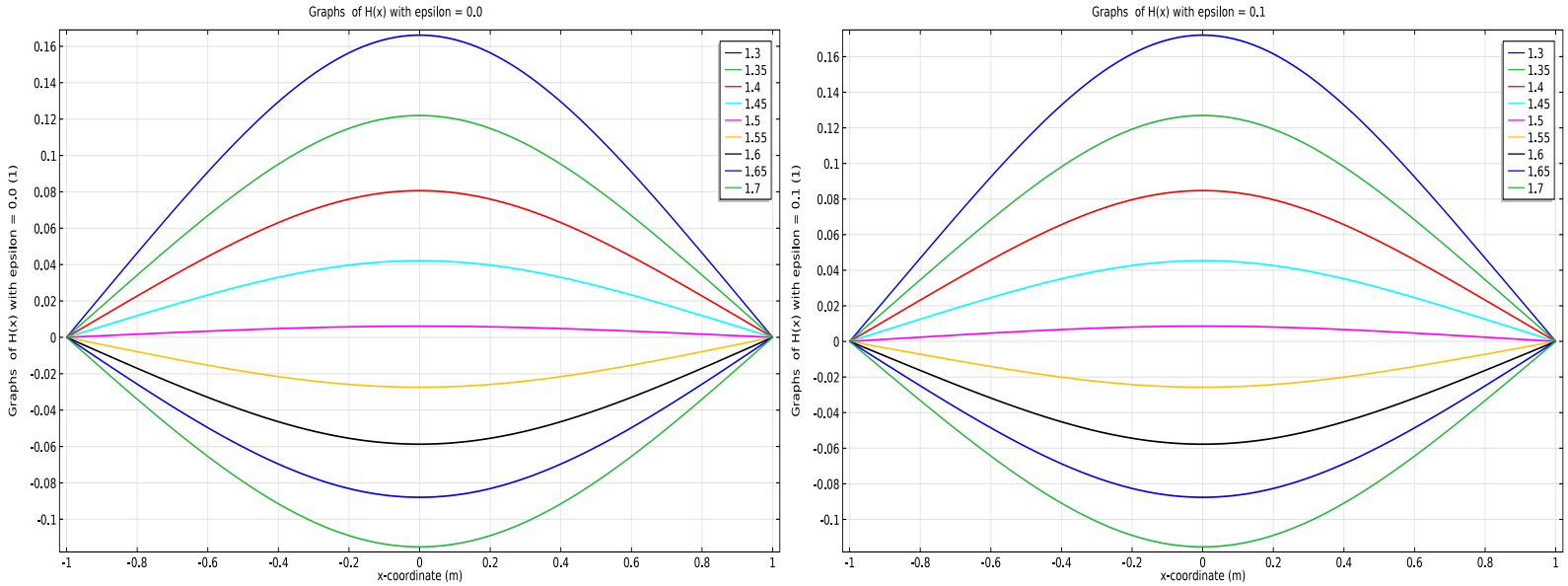


Figure: Variation of mean curvature for different α values (see values in the color code legend) with fixed $\epsilon = 0.0, 0.1$.

Interesting cases

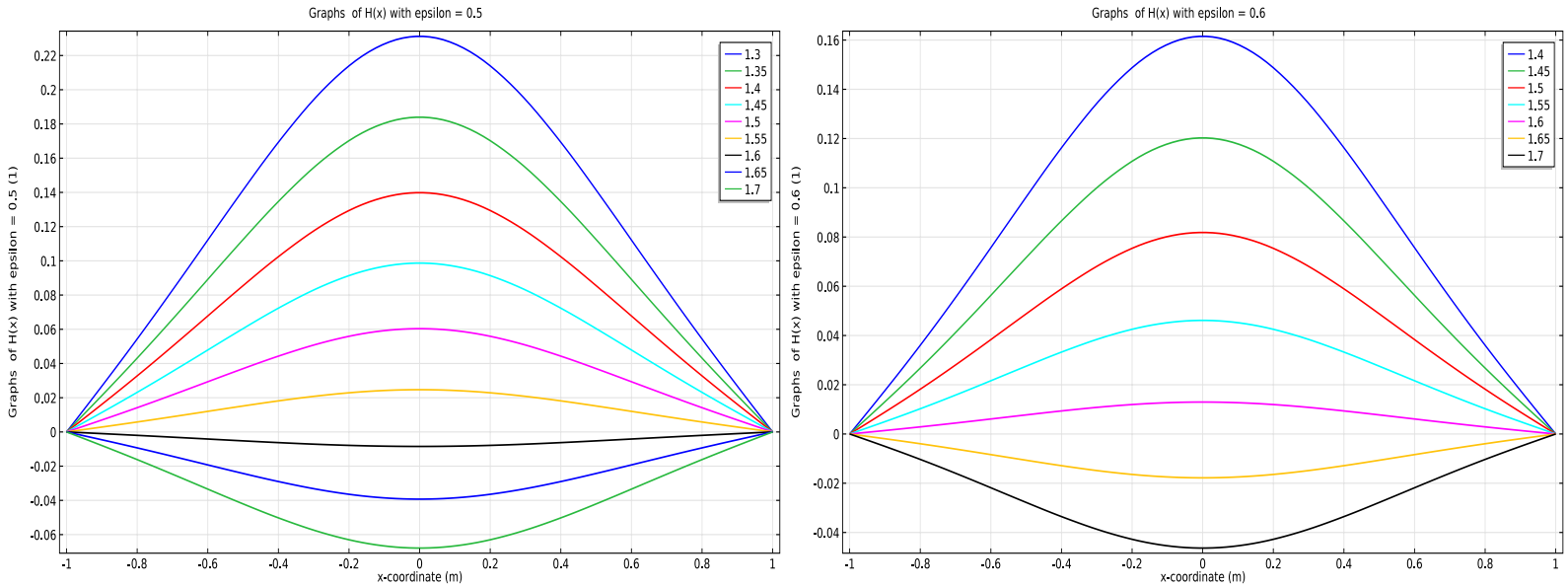


Figure: Variation of mean curvature for different α values with $\epsilon = 0.5, 0.6$ values.

Interesting cases

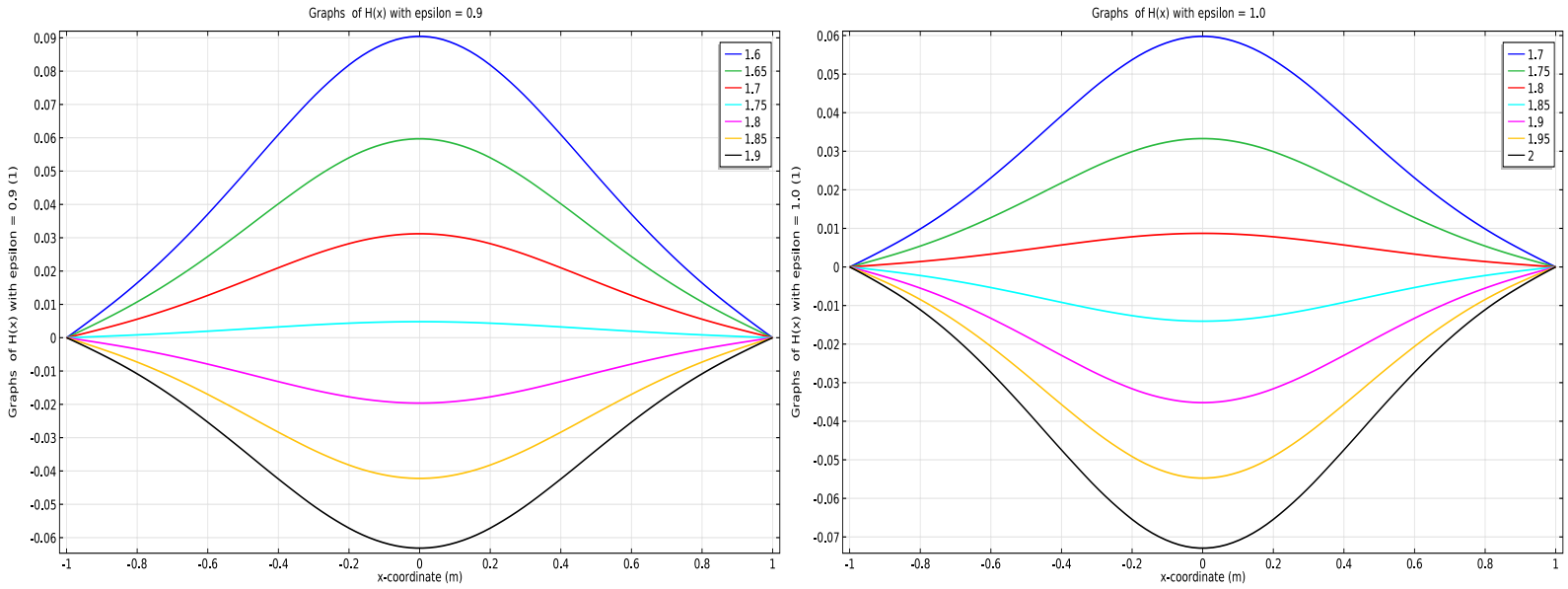
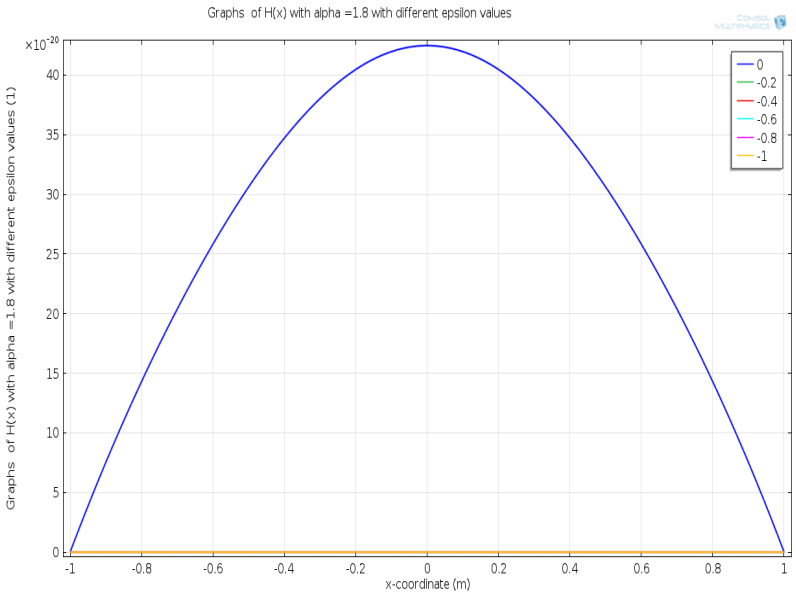


Figure: Variation of mean curvature for different α values with $\epsilon = 0.9, 1.0$ values.

ϵ	α^*	ϵ	α^*
0.0	$1.50 < \alpha^* < 1.55$	0.6	$1.60 < \alpha^* < 1.65$
0.1		0.7	$1.65 < \alpha^* < 1.70$
0.2		0.8	$1.70 < \alpha^* < 1.75$
0.3		0.9	$1.75 < \alpha^* < 1.80$
0.4	$1.55 < \alpha^* < 1.60$	1.0	$1.80 < \alpha^* < 1.85$
0.5			

Table: Experimentally looking for α^* values corresponding to minimal case $H = 0$... Interval of existence of α^* with variation of ϵ values.

Catenoid !



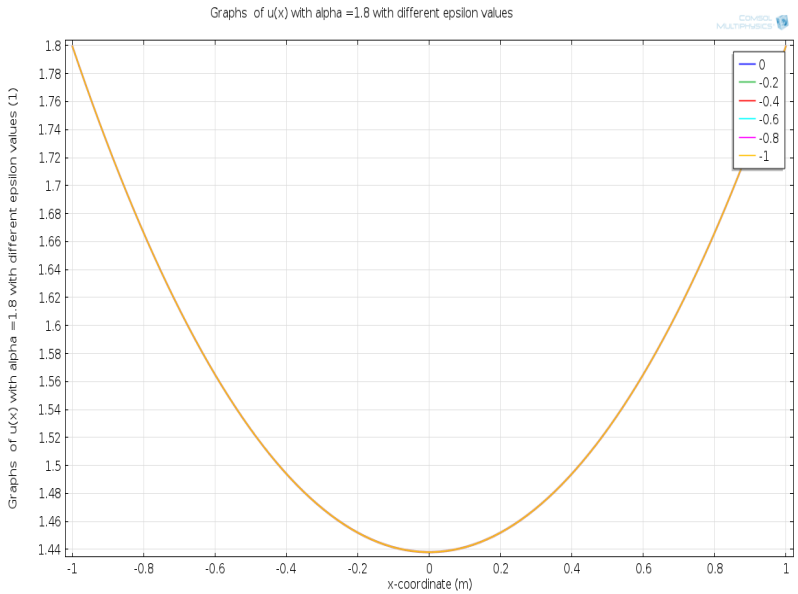


Figure: $\alpha = 1.8$ and $\epsilon = 0 : 0.2 : 1$

Generalized Willmore Surfaces of Revolution

Theorem

Consider a Cartesian system of axes of coordinates x, y, z *in* $\mathbb{R}^3$ *and the circles* C_1, C_2 *of the same radius* α*, centered at* $(-1, 0, 0)$ *and* $(1, 0, 0)$*, situated in planes orthogonal to the x-axis. Consider all regular surfaces of revolution of annular-type with boundary* $C_1 \cup C_2$*. Assume that among all these surfaces, there exists at least a surface* M *minimizing the generalized Willmore energy. This surface in assumed embedded in* $\mathbb{R}^3$ *and admitting the representation*

$$M := \{x, u(x)\cos\varphi, u(x)\sin\varphi\} : \ x \in [-1, 1], \ \varphi \in \mathbb{R}$$

with some function $u \in C^4([-1, 1], (0, \infty))$*.*

Theorem

(continuation) Then, the surface M is a solution of the following boundary value problem:

$$\Delta H + 2H(H^2 - K - \epsilon) = 0 \quad \text{on } M \text{ where } \epsilon = \frac{\mu}{k} \tag{3}$$

$$\partial M = C_1 \cup C_2,\ H = 0 \text{ on } \partial M,\ u(\pm 1) = \alpha \tag{4}$$

Moreover: there exists a positive value $\alpha^*(\epsilon)$ such that

(a) *If $0 < \alpha < \alpha^*$, then G.W.E. admits NO minimal solution, that is, any solution satisfies: $H = 0$ on ∂M and $H \neq 0$ on $M \setminus (\partial M)$.*

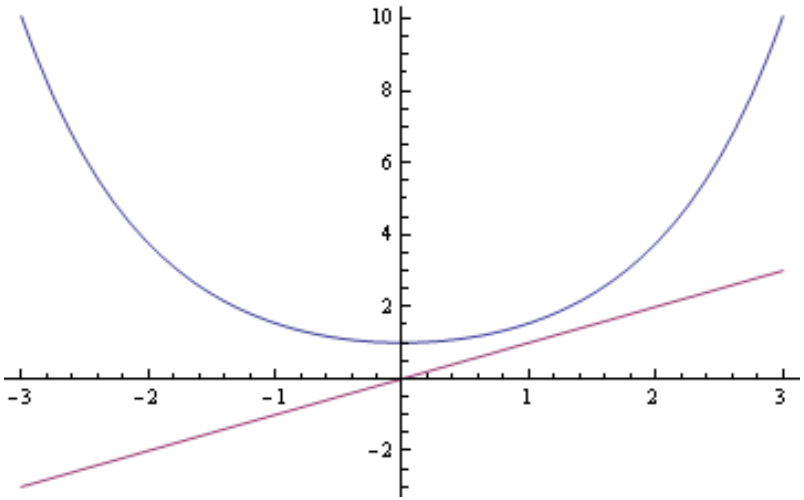
(b) *If $\alpha = \alpha^*$, then G.W.E. admits exactly one minimal solution (a unique catenoid that exclusively depends on α^*).*

(c) *If $\alpha > \alpha^*$, then G.W.E admits exactly two minimal solutions (two catenoids whose equations exclusively depend on α).*

Proof. We deduced the Euler-Lagrange equation based on the generalized Willmore energy, using standard methods of Calculus of Variations and Differential Geometry. The last part of the theorem follows immediately by studying the solutions of the equation $\cosh t/t = \alpha$. It is easy to prove that in the case a)., this equation has no solutions, in the case b)., this equation has a unique solutions, and for the case c)., here are two distinct solutions, corresponding to the two catenoids of type $y = (\cosh(tx))/t$.

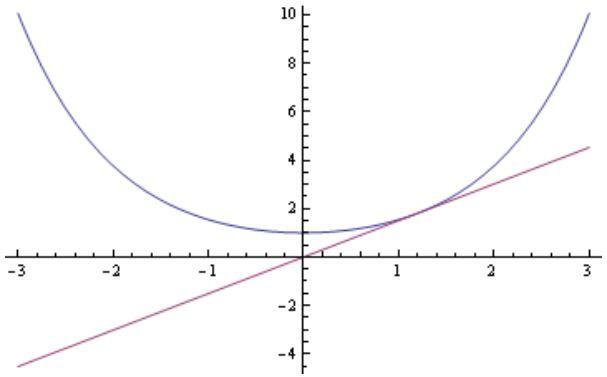
Solutions of $\frac{\cosh t}{t} = \alpha$

Case a: $\alpha = 1.0$

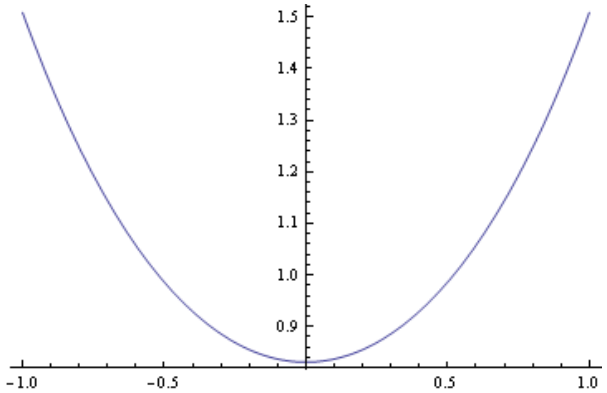


No solutions!

Case b: $\alpha \approx 1.5089$



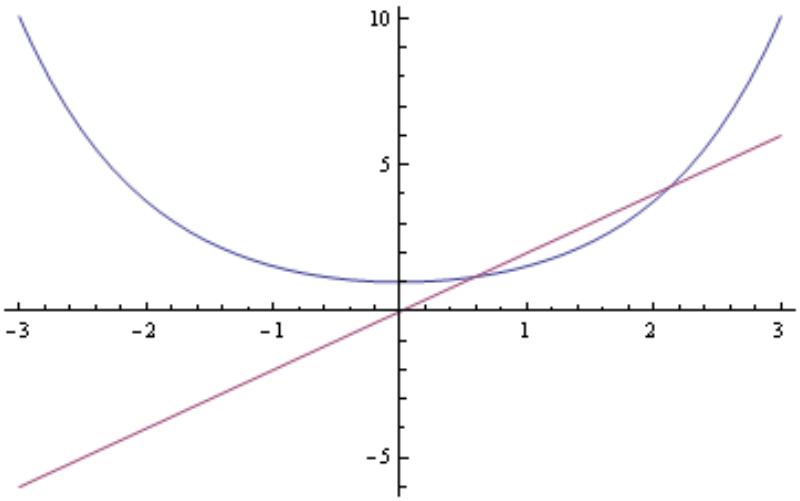
Exactly one solution! $t \approx 1.2$



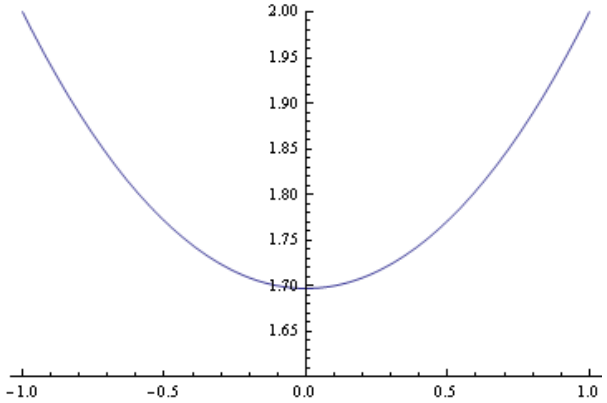
$y = (\cosh(tx))/t$

Solutions of $\frac{\cosh t}{t} = \alpha$

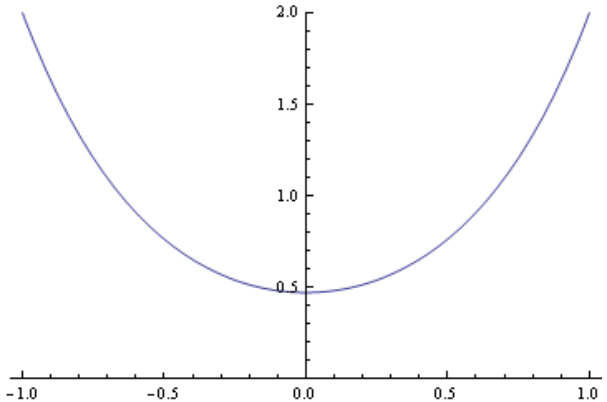
Case c: $\alpha = 2.0$



Two solutions!



$t \approx 0.5894$



$t \approx 2.1268$

Q: And what if we work with the generalized Willmore energy WHILE considering the spontaneous curvature c_0 as being non-negligible, and while the strain tensor due to a back-bone atomic structure (such as in beta barrels) is not zero?
A: Then we obtain a slightly modified generalized Willmore equation:

The constant c_0 highly depends on the solvent that is used for the protein molecule. On the other hand, the backbone (consisting of molecular chains of atoms) imposes an additional "backbone strain tensor" which can be represented by a 2×2 diagonal matrix A. Hence, the strain tensor changes the Willmore-type equation into an equation of a similar form (which we will call Willmore-Helfrich (W-H) equation for secondary structures in proteins). In isothermic coordinates, this equation becomes:

$$k\Delta_g(2H) - 2\lambda H + k(2H - c_0)(2H^2 - c_0 H - 2K) + l(a_{11}k_1 + a_{22}k_2) = 0, \tag{5}$$

If the strain tensor matrix is a constant multiple of the identity matrix, then we can rewrite our equation as:

$$\Delta_g(H) - (H - c_0)(2(H^2 - K) - c_0 H) + (aH - b) = 0, \qquad (6)$$

where the additional constants a, b depend on the magnitude of the strain tensor for the backbone structure, as well as two different bending rigidity constants. Remark again that if a, b are negligible, then $H = c_0$ is a trivial solution of the generalized Willmore equation. Also remark that CMC solutions are possible even if a, b constants are non-zero.

Until now, we saw cases when generalized Willmore surfaces of revolution (modeling beta barrels) were either catenoids, or generalized Willmore surfaces, non-minimal. This happened since we assumed $c_0 = 0$ and negligible backbone strain tensor.
New Case: As we observed before, rotationally symmetric solutions of the Generalized Willmore equation may be CMC surfaces for some choices of parameters. These choices may include some appropriately chosen a, b, or a, b negligible and c_0 non-negligible.

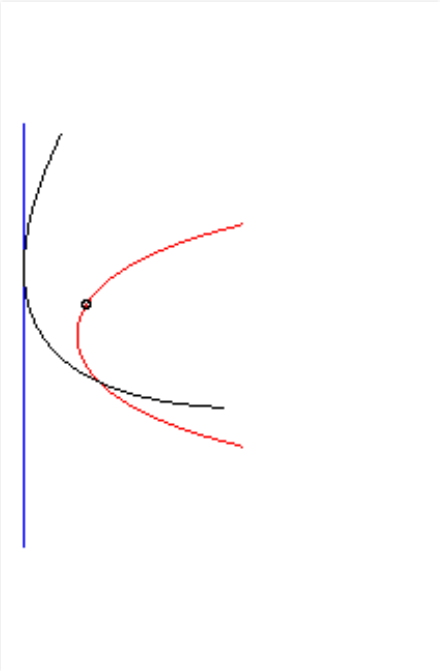
CMC surfaces of revolution (also called Delaunay surfaces)

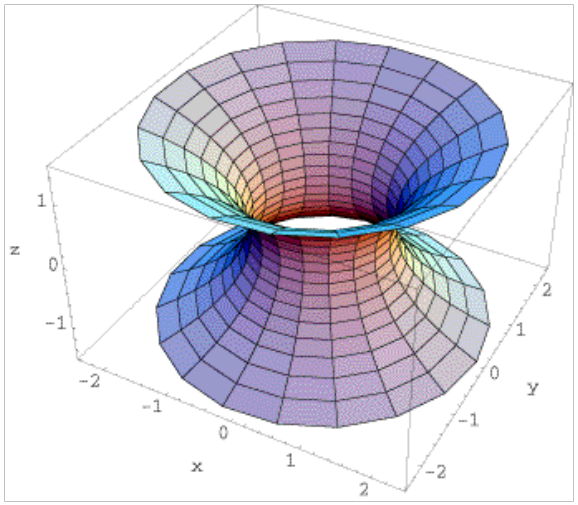
Constant mean curvature surfaces of revolution were obtained by rotating the roulettes of the conics

- **Parabola**
- **Ellipse**
- **Hyperbola**

Delaunay surfaces

Catenary $\rightarrow$ Catenoid ($H = 0$)





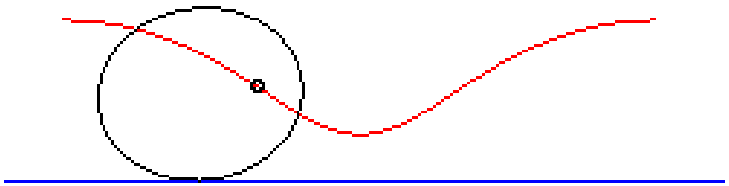
www.mathcurve.com/courbes2d/delaunay/delaunay.shtml

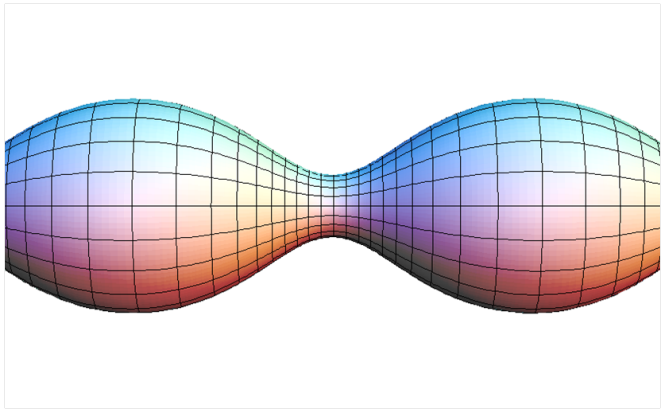
http://www.math.hmc.edu/~gu/curves_and_surfaces/surfaces/catenoid.html

Delaunay surfaces

Surfaces of revolution with CMC that are obtained by rotating the roulettes of the conics

Undulary $\rightarrow$ Unduloid ($H \neq 0$)





www.mathcurve.com/courbes2d/delaunay/delaunay.shtml

http://virtualmathmuseum.org/Surface/unduloid/unduloid.html

Delaunay surfaces

Parametrization of an undulary:

$$\begin{aligned} x(t) &= \frac{a^2-\epsilon^2}{a}\int_0^t \frac{du}{(1+\frac{\epsilon}{a}\cos u)\sqrt{1-\frac{\epsilon^2}{a^2}\cos^2 u}}, \\ y(t) &= \sqrt{a^2-\epsilon^2}\sqrt{\frac{a-\epsilon\cos t}{a+\epsilon\cos t}}. \end{aligned}$$

For an ellipse with arc length $2h$, we have

$$2h = \int_0^{2\pi} \sqrt{a^2-\epsilon^2\cos^2\theta}\, d\theta,$$

$$a(\epsilon,h) = \frac{h}{2\pi}\left(1+\sqrt{1+\frac{\epsilon^2\pi^2}{h^2}}\right) = \frac{h}{\pi}+\frac{\epsilon^2}{4}\frac{\pi}{h}+\mathcal{O}\left(\frac{\epsilon^3\pi^3}{h^3}\right)$$

Figure: Undulary profiles with their limiting cases: sphere, and right cylinder

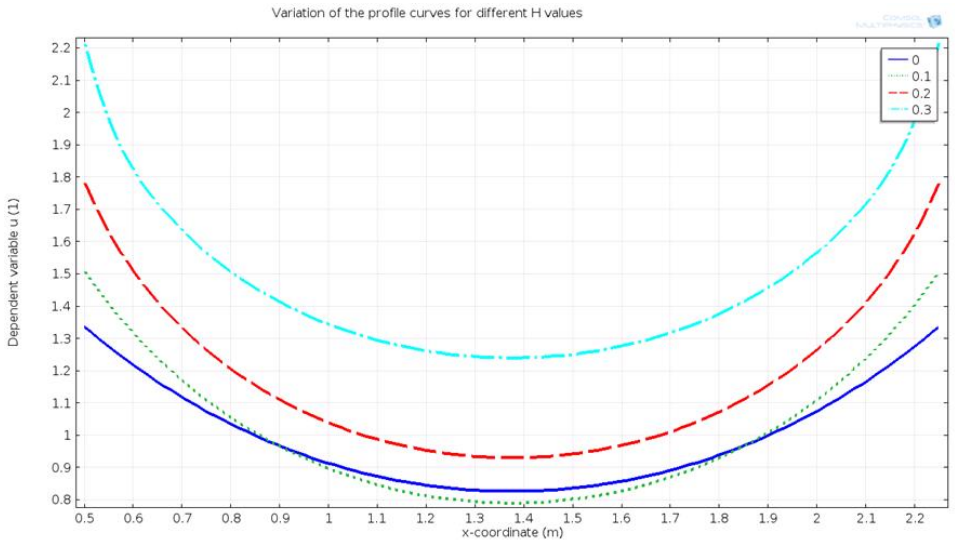


Figure: Profiles of an unduloidal beta barrel for different radii α

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