A Biological Application of the Calculus of Variations

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Abstract: In this paper, we introduce the calculus of variations and derive the general Euler-Lagrange equations for functionals that depend on functions of one variable. Although the calculus of variations has traditionally been applied to problems in mechanics, we apply the variational approach to a problem in biology by means of minimal surfaces. We introduce the idea of using space curves to model protein structure and lastly, we analyze the free energy associated with these space curves by deriving two Euler-Lagrange equations dependent on curvature.

1 Introduction to the Calculus of Variations

Problems of the calculus of variations came about long before the method. The first problems can be traced back to isoperimetric problems tackled by the Greeks. One such problem is that of Queen Dido, who desired that a given length of oxhide strips enclose a maximum area. This problem, as with many other isoperimetric problems, was solved using geometric methods and reasoning [AB]. However, the first problem solved using some form of the calculus of variations was the problem of the passage of light from one medium to another, and was resolved by Fermat.

In simplest terms, the calculus of variations can be compared to one-dimensional, standard calculus; that is, the study of a function $y = f(x)$ in one variable, for $x \in \mathbb{R}$. Suppose $y = f(x)$ is of class C^1, meaning continuous and differentiable in its domain, which we take to be $x \in \mathbb{R}$. We can seek the local and global extrema of the function, which potentially occur at some $x_i \in \mathbb{R}$, by studying the first and second derivatives. Similarly, the calculus of variations is the study of a functional of the form

$$E[y] = \int_a^b F(t, y(t), y'(t))\, dt, \tag{1.1}$$

where the integrand $F(t, y(t), y'(t))$ is a function of the independent variable t, a function $y(t)$ and the first derivative $y'(t)$, with prime notation denoting the derivative with respect to t. The function $y(t)$ is in D, the space of all C^1 functions defined on the interval $[a, b]$ with $y(a) = A$ and $y(b) = B$ for any $y(t) \in D$. We can seek the local and global extrema of this functional, which occur potentially at some $y(t) \in D$, by studying the first and second variations. This method is the typical application of the calculus of variations—seeking an unknown optimizer of a property by means of a known functional describing this property. What is interesting in our application to modeling protein structure is that we have known solutions and an unknown energy functional. We apply the calculus of variations to understand this unknown energy functional.

1.1 The First Variation

Consider a known local extrema $y(t)$ of the functional in Equation 1.1. We can perturb this extrema by considering

$$\tilde{y}(t) = y(t) + \epsilon\varphi(t),$$

where ϵ is a small real parameter and $\varphi(t)$ is in $\tilde{D}$, which is the space of all C^1 functions defined on $[a, b]$, with the condition

$$\varphi(a) = \varphi(b) = 0 \tag{1.2}$$

to ensure that the function $\tilde{y}(t)$ remains in the domain space D by preserving the boundary conditions. Suppose $y(t)$ is not only a known local extrema, but a known local minimum. Then,

$$E[y] \leq E[\tilde{y}]$$

for a "close" $\tilde{y}(t)$, meaning $\tilde{y}(t)$ that does not perturb $y(t)$ too much, or $\tilde{y}(t)$ with small $|\epsilon|$. This minimality condition can also be expressed as

$$E[y] \leq E[y + \epsilon\varphi].$$

We note that in the above condition, equality, and therefore a minimum, occurs when $\epsilon = 0$. Consider the first variation, defined as

$$\delta E[\tilde{y}] = \frac{d}{d\epsilon} E[y + \epsilon\varphi] \bigg|_{\epsilon=0}.$$

Recall that in the case of one-dimensional, standard calculus, if $y = f(x)$ is minimized at $x = x_0$, then $\frac{d}{dx} y(x)\big|_{x=x_0} = 0$. So if we think of $E[y + \epsilon\varphi]$ as a function of ϵ, that is a function of one variable, it is minimized at $\epsilon = 0$ and

$$\delta E[\tilde{y}] := \frac{d}{d\epsilon} E[y + \epsilon\varphi] \bigg|_{\epsilon=0} = 0. \tag{1.3}$$

Remark 1.1: In fact, $\delta E[\tilde{y}] = 0$ for all perturbed extrema $\tilde{y}$ in the domain space D. However, it is important to note that, although an extrema implies a vanishing first variation, a vanishing first variation does not imply an extrema; it could simply indicate the analogue of a point of inflection from one-dimensional calculus, in D. Whether or not a function $y(t) \in D$ is a true extrema lies in the study of the second variation, which is again very similar to one-dimensional, standard calculus, where we appeal to the second derivative to discriminate between true extrema and points of inflection. It is very important to be able to distinguish between the two cases, as applications of the calculus of variations often call for an extrema $y(t)$ of the functional in question, under the assumption that $\delta E[\tilde{y}] = 0$, allowing for potential solutions to be derived. These are only potential solutions and not true extrema until the second variation is studied. For a detailed and rigorous discussion of the second variation, see the book by Giaquinta and Hildebrandt [GH96]. For our purposes we will simplify and disregard the second variation.

1.2 Euler-Lagrange Equation

Keeping in mind that y, φ, y' and φ' are functions of t, we can rewrite Equation 1.3 as

$$\delta E[\tilde{y}] = \frac{d}{d\epsilon} \int_a^b F(t, y + \epsilon\varphi, y' + \epsilon\varphi')\, dt \bigg|_{\epsilon=0} = 0.$$

By Leibniz's Rule, the above simplifies to

$$\int_a^b \frac{\partial}{\partial\epsilon} F(t, y + \epsilon\varphi, y' + \epsilon\varphi')\, dt \bigg|_{\epsilon=0} = 0.$$

Applying the chain rule, simplifying and subsequently evaluating at $\epsilon = 0$, we get

$$\int_a^b \frac{\partial F}{\partial t}\frac{dt}{d\epsilon} + \frac{\partial F}{\partial [y+\epsilon\varphi]}\frac{d[y+\epsilon\varphi]}{d\epsilon} + \frac{\partial F}{\partial [y'+\epsilon\varphi']}\frac{d[y'+\epsilon\varphi']}{d\epsilon}\, dt \Bigg|_{\epsilon=0} = 0$$

$$\int_a^b \frac{\partial F}{\partial [y+\epsilon\varphi]}\varphi + \frac{\partial F}{\partial [y'+\epsilon\varphi']}\varphi'\, dt \Bigg|_{\epsilon=0} = 0$$

$$\int_a^b \frac{\partial F}{\partial y}\varphi + \frac{\partial F}{\partial y'}\varphi'\, dt = 0.$$

Next, we integrate the second term in the above by parts to get

$$\int_a^b \frac{\partial F}{\partial y}\varphi + \frac{\partial F}{\partial y'}\varphi \Bigg|_a^b - \int_a^b \frac{d}{dt}\frac{\partial F}{\partial y'}\varphi\, dt = 0,$$

but by Condition 1.2, the middle term vanishes and we are left with

$$\int_a^b \frac{\partial F}{\partial y}\varphi - \frac{d}{dt}\frac{\partial F}{\partial y'}\varphi\, dt = 0,$$

which can be written as

$$\int_a^b \left[\frac{\partial F}{\partial y} - \frac{d}{dt}\frac{\partial F}{\partial y'}\right]\varphi\, dt = 0. \tag{1.4}$$

Next, we apply the Fundamental Lemma of the Calculus of Variations.

Lemma 1.1 (Fundamental Lemma of the Calculus of Variations). Let $f(x)$ be a function of class C^n, that is, n-times continuously differentiable, on the interval $[a, b]$. Assume

$$\int_a^b f(x)g(x)\, dx = 0 \tag{1.5}$$

holds for any C^n function $g(x)$ on $[a, b]$ with $g(a) = g(b) = 0$. Then $f(x)$ is identically zero on $[a, b]$.

Proof. (by contradiction) Assume $f(x)$ is a C^n function on $[a, b]$ and Equation 1.5 holds for any C^n function $g(x)$ on $[a, b]$ with $g(a) = g(b) = 0$. In particular, choose a function $g(x)$ such that $g(x) = f(x) \quad \forall\, x \in (a, b)$. Then, Equation 1.5 reduces to

$$\int_a^b f^2\, dx = 0. \tag{1.6}$$

Assume that $f(x)$ is not identically zero. Without loss of generality, there exists an $x_0 \in [a, b]$ such that $f(x_0) > 0$. Since f(x) is continuous, then there must be some subinterval $[a_i, b_i]$ of $[a, b]$ such that all $x_i \in [a_i, b_i]$ have the property that $f(x_i) > 0$, including $x_i = x_0$. Now we take Equation 1.6 and rewrite it as

$$\int_a^b f^2\, dx = \int_a^{a_i} f^2\, dx + \int_{a_i}^{b_i} f^2\, dx + \int_{b_i}^b f^2\, dx. \tag{1.7}$$

We note that the first and the third terms above are either greater than or equal to zero, due to the fact that their integrands are greater than or equal to zero on their respective intervals. However, the second term is strictly greater than zero since its integrand is strictly greater than zero on the interval (a_i, b_i). Thus, the sum of these three integrals is strictly greater than zero, which contradicts our assumption, Equation 1.6. Therefore, f(x) must be identically zero.

□

Applying the Fundamental Lemma to Equation 1.4, with $f(t) = \frac{\partial F}{\partial y} - \frac{d}{dt}\frac{\partial F}{\partial y'}$ and $g(t) = \varphi$, we conclude that

$$\frac{\partial F}{\partial y} - \frac{d}{dt}\frac{\partial F}{\partial y'} = 0, \tag{1.8}$$

which is the Euler-Lagrange equation associated with the first variation of Equation 1.1.

2 Minimal Surfaces

The intuitive definition of a minimal surface is a surface which minimizes surface area. This definition translates nicely to a problem of the calculus of variations, in which a minimal surface is a surface $S = \{(x, y, z) \in \mathbb{R}^3 \mid z = g(x, y)\}$ that minimizes the surface area functional

$$S[g] = \iint F(x, y, g, g_x, g_y)\, dxdy = \iint \sqrt{1 + g_x^2 + g_y^2}\, dxdy \tag{2.1}$$

among admissible surfaces $z = g(x, y)$. Note that the subscript notation g_x denotes the partial derivative of g with respect to x. The associated Euler-Lagrange equation is

$$\frac{\partial F}{\partial g} - \frac{d}{dx}\frac{\partial F}{\partial g_x} - \frac{d}{dy}\frac{\partial F}{\partial g_y} = 0.$$

Notice that F does not depend explicitly on g, so the above simplifies to

$$\frac{d}{dx}\frac{\partial F}{\partial g_x} + \frac{d}{dy}\frac{\partial F}{\partial g_y} = 0. \tag{2.2}$$

Computing the appropriate partial derivatives, plugging them into Equation 2.2 and simplifying, we get

$$\begin{aligned}
\frac{d}{dx}\left[\frac{g_x}{\sqrt{1 + g_x^2 + g_y^2}}\right] + \frac{d}{dy}\left[\frac{g_y}{\sqrt{1 + g_x^2 + g_y^2}}\right] &= 0 \\
\frac{g_{xx}\sqrt{1 + g_x^2 + g_y^2} - g_x\left[\frac{g_x g_{xx} + g_y g_{xy}}{\sqrt{1+g_x^2+g_y^2}}\right] + g_{yy}\sqrt{1 + g_x^2 + g_y^2} - g_y\left[\frac{g_x g_{xy} + g_y g_{yy}}{\sqrt{1+g_x^2+g_y^2}}\right]}{1 + g_x^2 + g_y^2} &= 0 \\
\frac{g_{xx}(1 + g_x^2 + g_y^2) - g_x^2 g_{xx} - g_x g_y g_{xy} + g_{yy}(1 + g_x^2 + g_y^2) - g_x g_y g_{xy} - g_y^2 g_{yy}}{\sqrt{1 + g_x^2 + g_y^2}} &= 0 \\
(1 + g_y^2)g_{xx} - 2g_x g_y g_{xy} + (1 + g_x^2)g_{yy} &= 0,
\end{aligned}$$

which is the Minimal Surface Equation for the graph g.

3 Regular Secondary Structures in Proteins

It turns out that there is a rather neat application of minimal surfaces to modeling protein structure.

3.1 An Introduction to Basic Protein Structure

A protein is a chain of amino acids, also called a polypeptide chain, that has some biological function related to its structure. Protein structure can be described on four levels: primary, secondary, tertiary and quaternary structure. The primary structure describes the sequence of amino acids, while the secondary structure describes the way in which small portions of the chain are shaped, or in other words describes the

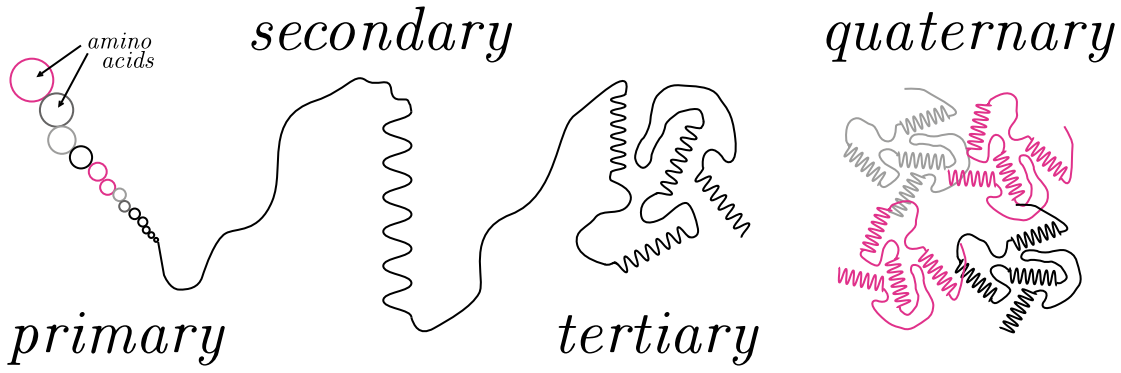

Figure 3.1: A good way to think about protein structure is to imagine zooming out at each step as you move from primary to quaternary.

local structure. The tertiary structure describes how the entire protein chain embeds itself in space and the quaternary structure describes the configuration of multiple polypeptide chains that combine to form one, larger, protein.

We will think of a protein mathematically as a smooth space curve that connects the α-carbons, which is a good approximation of the protein's overall structure as α-carbons form the main backbone. In terms of the application of minimal surfaces, we are interested in one of the most common regular secondary structures: namely, the α-helix, which can be modeled mathematically by a regular helix. Helices are special curves that lie on the surface of a helicoid, a minimal surface.

3.2 The Helicoid

To understand the helicoid, let us consider one parametrization, namely

$$\vec{x}(u,v) = (-b\,\sinh v\,\sin u\,, b\,\sinh v\,\cos u\,, bu) \qquad \left\{ \begin{array}{l} -\infty < u < \infty \\ -\infty < v < \infty \end{array} \right\},$$

where $b \in \mathbb{R}$ is an arbitrary constant. The tangent vectors associated with this parametrization of the helicoid are

$$\vec{x}_u = (-b\,\sinh v\,\cos u\,, -b\,\sinh v\,\sin u\,, b)$$
$$\vec{x}_v = (-b\,\cosh v\,\sin u\,, b\,\cosh v\,\cos u\,, 0).$$

Remark 3.1: The helicoid is the only ruled minimal surface: that is, a surface generated by a family of straight lines. In our parametrization, the generators are $u = c_i$ $(i = 1, ..., n)$, where the c_i are constant.

Notice that our above definition of a minimal surface is not suitable for the helicoid, since we restrict our admissible surfaces to graphs. Instead, to prove that the helicoid is in fact a minimal surface without restricting our domain in the uv-plane to make the helicoid a graph, we will introduce an alternate definition of a minimal surface. However, to understand this definition, we will need to introduce and compute certain quantities that reveal properties of the surfaces' intrinsic geometries. The quantities in question are the coefficients of the first fundamental form.

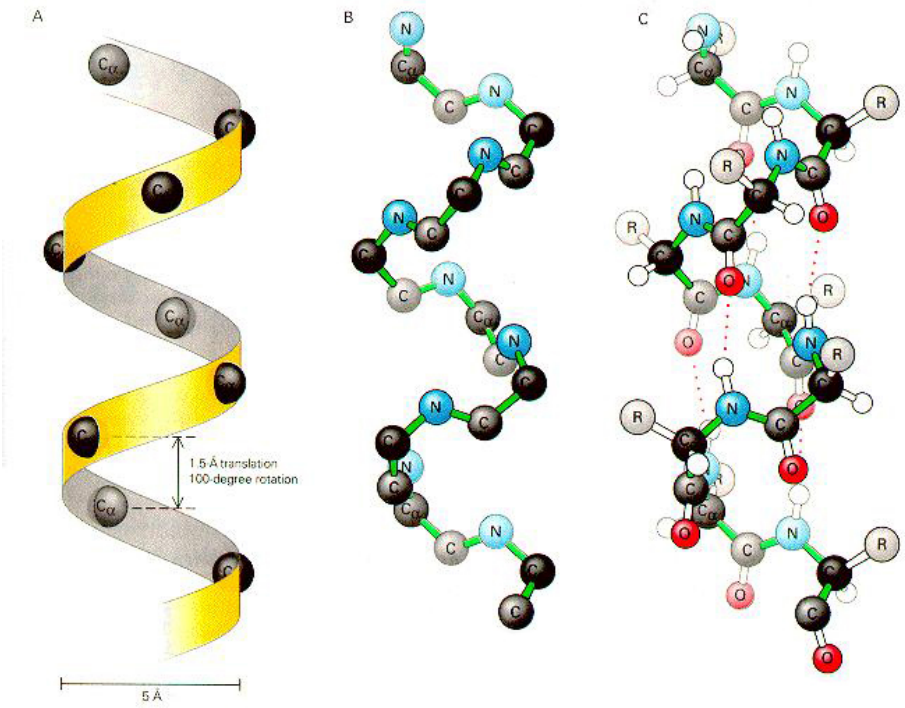

Figure 3.2: The α-helix. Image courtesy of `cmgm.stanford.edu`

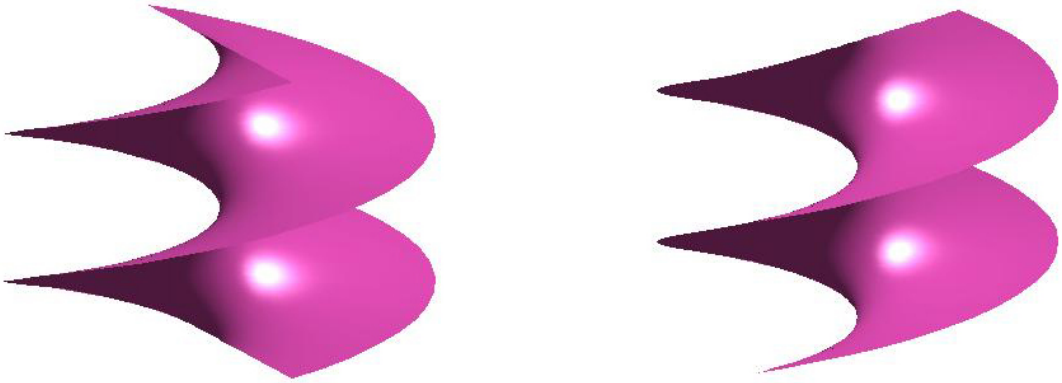

Figure 3.3: The helicoid.

Definition 3.1 (The First Fundamental Form). Let $\vec{x}(u,v) = (x_1(u,v), x_2(u,v), x_3(u,v))$ be a regular parametrized surface in $\mathbb{R}^3$ with tangent vectors

$$\vec{x}_u = \left(\frac{\partial x_1}{\partial u}, \frac{\partial x_2}{\partial u}, \frac{\partial x_3}{\partial u}\right) \qquad \vec{x}_v = \left(\frac{\partial x_1}{\partial v}, \frac{\partial x_2}{\partial v}, \frac{\partial x_3}{\partial v}\right)$$

The *first fundamental form* I of $\vec{x}(u,v)$ is the quadratic form defined by

$$I(du,dv) = \begin{pmatrix} du & dv \end{pmatrix} \begin{pmatrix} E & F \\ F & G \end{pmatrix} \begin{pmatrix} du \\ dv \end{pmatrix},$$

where

$$\begin{aligned} E &= <\vec{x}_u\,,\vec{x}_u> \\ F &= <\vec{x}_u\,,\vec{x}_v> \\ G &= <\vec{x}_v\,,\vec{x}_v> \end{aligned}$$

are the coefficients of the first fundamental form. Note that $<\vec{a}\,,\vec{b}>$ is the Euclidean inner product of $\vec{a}$ and $\vec{b}$.

3.2.1 An Interesting Property of the First Fundamental Form

The *surface area* of a region $\vec{x}(R)$ on $\vec{x}$ is given by

$$A = \iint_R |I|^{\frac{1}{2}}\, dudv.$$

Remark 3.2: Note this property would yield a surface area functional for us to analyze using the calculus of variations. However, computing $|I|^{\frac{1}{2}}$ is fairly involved on its own in this case, and the analysis of the resultant functional would be even more challenging. Instead, we will opt for another, more specific, definition that happens to suit our parametrization of the helicoid quite nicely.

3.2.2 An alternate definition of a minimal surface

The alternate definition of a minimal surface, given in by Louie and Somorjai [LS82], and useful for our purpose, is

Theorem 3.3. Given an isothermally parametrized regular surface $\vec{x}(u,v)$, that is a parametrization with

$$\begin{aligned} E &= G \\ F &= 0 \end{aligned}$$

then $\vec{x}$ is a minimal surface if and only if its coordinate functions are harmonic, that is

$$\vec{x}_{uu} + \vec{x}_{vv} = \vec{0}$$

The coefficients of the first fundamental form associated with our parametrization of the helicoid are

$$\begin{aligned} E = <\vec{x}_u\,,\vec{x}_u> &= b^2\,\sinh^2 v\,\cos^2 u + b^2\,\sinh^2 v\,\sin^2 u + b^2 \\ &= b^2\,\sinh^2 v + b^2 \\ &= b^2(\sinh^2 v + 1) \\ &= b^2\,\cosh^2 v \\ F = <\vec{x}_u\,,\vec{x}_v> &= b^2\,\sinh v\,\cosh v\,\sin u\,\cos u - b^2\,\sinh v\,\cosh v\,\sin u\,cosu \\ &= 0 \\ G = <\vec{x}_v\,,\vec{x}_v> &= b^2\,\cosh^2 v\,\sin^2 u + b^2\,\cosh^2 v\,\cos^2 u \\ &= b^2\,\cosh^2 v. \end{aligned}$$

Note that $E = G$ and $F = 0$.

Now let us show that the isothermally parametrized helicoid has harmonic coordinate functions. Recall the coordinate functions of the helicoid are

$$\vec{x}_{uu} = (b \sinh v \sin u\,, -b \sinh v \cos u\,, 0)\vec{x}_{vv} \qquad = (-b \sinh v \sin u\,, b \sinh v \cos u\,, 0)$$

which by inspection will sum to zero. Thus, we conclude that the helicoid is a minimal surface.

3.3 Minimal Surfaces and Protein Structure

Why is it significant that the α-helix, a common regular secondary structure, can be modeled as lying on minimal surfaces? Many minimal surfaces, including the helicoid, occur naturally as a soap films when a wire frame of their boundary is dipped in soap solution.

Figure 3.4: A soap film of a helicoid. Image courtesy of `http://www.math.cornell.edu/~mec/Summer2009/Fok/index.html`

Physically, this phenomenon makes sense as surface area being minimized also minimizes surface tension which is related to potential energy. Equilibrium states, such as that of soap films, often minimize potential energy, and this case is no exception.

In terms of proteins, structure is determined by the non-covalent (non-bonding) forces among and between the amino acids of the polypeptide chain. There are two theories as to why our regular secondary structure of interest should be thought of as lying on a minimal surface. The first theory is that non-polar groups on the polypeptide chain tend to configure themselves in a way that reduces the interface area between themselves and the polar solvent, which is often water in biological systems. Non-polar and polar groups repel each other, so a minimization of the interface surface area is fitting. The other theory is that the minimality could be due to molecular forces that are trying to reduce stress in the regular structures [LS82].

In either case, it makes sense to consider at least the α-helix as lying on the helicoid. Moreover, the native, or equilibrium, conformation of the entire protein can be thought of as lying on a collection of minimal surfaces connected by turns and random coils that are thought to provide the necessary flexibility for the best energetic configuration of this collection of minimal surfaces.

3.4 Geodesics on Helicoids

Let us take a closer look at helices by considering the parametrization

$$\vec{c}(u) = (-b\sin u, b\cos u, u) \qquad \{-\infty < u < \infty\}$$

It turns out that helices are actually geodesics, or length minimizing curves, on helicoids. According to Louie and Somorjai, the geodesics for the helicoid are given by the differential equations

$$\frac{d^2u}{ds^2} = 0$$

$$\frac{d^2v}{ds^2} + \tanh\left(\frac{dv}{ds}^2 - \frac{du}{ds}^2\right) = 0$$

and solutions to this set of differential equations are

$$\sinh\, v(s) = A\,\sinh\left(u(s) + B\right)$$

$$u(s) = Cs + D,$$

where A, B, C and D are constants of integration [LS82]. However, for sufficiently small $|u|$ and $|v|$, the geodesic is approximated by

$$v(s) = A(u(s) + B).$$

So, geodesics on the helicoid are images of straight line segments in the uv-plane. Ignoring any shifting or scaling of this linear function, and taking $v = u$, we see that the parametrization of the helicoid simplifies to

$$\vec{x}(u) = (-b\,\sinh u\,\sin u\,, b\,\sinh u\,\cos u\,, bu).$$

With sufficiently small $|u|$ and $|v|$, this parametrization is approximated by

$$\vec{x}(u) = (-b\sin u, b\cos u\,, bu),$$

which is a helix. This result makes sense if we consider the fact that geodesics in Euclidean space are linear functions. It is also significant that helices are geodesics on helicoids, and not just arbitrary curves that lie on this surface. They are length minimizing, which could be related to further minimization of energy in the context of protein structure.

4 Euler-Lagrange Equations and Energy Functionals Associated with Helices

4.1 The Setup

As we have seen, variational problems involve a known functional and unknown solutions, which we seek by deriving the Euler-Lagrange equation. However, when we think of regular secondary protein structures, we have known minimizing solutions in the form of helices, and an unknown energy functional. This energy functional would describe the total free energy of the system, the system being the segment of the protein containing the α-helix in solution. This free energy could involve the intra- and inter-molecular forces among and between the amino acids of the protein, as well as the interaction of the protein with the solution.

We seek the Euler-Lagrange equations associated with an unknown energy functional which represents the free energy of the protein segment, in order to better understand this unknown energy functional. We will assume that this energy functional depends only on the curvature of the space curve. This assumption is reasonable since, according to Feoli et al. [FNS05], the infinitesimal twisting associated with torsion in a protein chain does not require much effort and thus only yields small energy differences.

Let γ be a curve $[a,b] \to \mathbb{R}^3$ that is continuous and minimizes the energy functional

$$E(\gamma) = \int_\gamma F(\kappa)\, dL = \int_a^b F(\kappa(s))\, |\, \gamma'(s)\, |\, ds,$$

where $\kappa(s)$ is the curvature of γ, parametrized by the arc length parameter s and given by

$$\kappa(s) = \frac{|\, \gamma' \times \gamma''\, |}{|\, \gamma'\, |^3}.$$

Note that in this section, the prime notation indicated differentiation with respect to s. Now let

$$\tilde{\gamma}(s) = \gamma(s) + \epsilon_1\psi_1(s)\vec{T}(s) + \epsilon_2\psi_2(s)\vec{N}(s) + \epsilon_3\psi_3(s)\vec{B}(s)$$

be the total perturbation of the minimizing curve given by three component perturbations in the tangential $\vec{T}(s)$, normal $\vec{N}(s)$ and binormal $\vec{B}(s)$ directions. Note that $\vec{T}(s)$, $\vec{N}(s)$ and $\vec{B}(s)$ are all unit vectors and together are known as the Frenet frame. Also, ϵ_i are small parameters and $\psi_i(s)$ are smooth, arbitrary functions such that

$$\psi_i(a) = \psi_i(b) = 0 \qquad i = 1,2,3. \tag{4.1}$$

We want to consider the variations

$$\frac{\partial}{\partial \epsilon_i} E(\tilde{\gamma}) \,\Big|_{\epsilon_1=\epsilon_2=\epsilon_3=0} = 0$$

for each $i = 1,2,3$, which correspond to variations in the tangential, normal and binormal directions respectively. This method should yield a system of three Euler-Lagrange equations. We will disregard the case of

$$\frac{\partial}{\partial \epsilon_1} E(\tilde{\gamma}) \,\Big|_{\epsilon_i=0} = 0$$

since this variation simply corresponds to a reparametrization of the curve $\tilde{\gamma}$, as noted by Hill et al. [HMT08]. Let us consider the variations

$$\frac{\partial}{\partial \epsilon_2} E(\tilde{\gamma}) \,\Big|_{\epsilon_2=0} = 0 \qquad \text{and} \qquad \frac{\partial}{\partial \epsilon_3} E(\tilde{\gamma}) \,\Big|_{\epsilon_3=0} = 0$$

by first looking at the general case of

$$\frac{\partial}{\partial \epsilon_i} E(\tilde{\gamma}) \,\Big|_{\epsilon_1=\epsilon_2=\epsilon_3=0} = 0 \qquad i = 2,3.$$

We abbreviate $\epsilon_1 = \epsilon_2 = \epsilon_3 = 0$ as $\epsilon_i = 0$ and simplify to get

$$\begin{aligned}
\frac{\partial}{\partial \epsilon_i} E(\tilde{\gamma}) \,\Big|_{\epsilon_i=0} &= \frac{\partial}{\partial \epsilon_i} \int_{\tilde{\gamma}} F(\kappa)\, dL \,\Big|_{\epsilon_i=0} \\
&= \frac{\partial}{\partial \epsilon_i} \int_a^b F(\kappa(s))\, |\, \gamma'(s)\, |\, ds \,\Big|_{\epsilon_i=0} \\
&= \int_a^b \frac{\partial F}{\partial \kappa} \frac{\partial \kappa}{\partial \epsilon_i}\, |\, \tilde{\gamma}'\, |\, ds \,\Big|_{\epsilon_i=0} + \int_a^b F\, \frac{\partial |\, \tilde{\gamma}'\, |}{\partial \epsilon_i}\, ds \Big|_{\epsilon_i=0},
\end{aligned}$$

but since $|\, \tilde{\gamma}'\, |_{\epsilon_i=0} = |\, \gamma\, | = 1$, the above simplifies to

$$\frac{\partial}{\partial \epsilon_i} E(\tilde{\gamma}) \,\Big|_{\epsilon_i=0} = \int_a^b \frac{\partial F}{\partial \kappa} \frac{\partial \kappa}{\partial \epsilon_i}\, ds \,\Big|_{\epsilon_i=0} + \int_a^b F\, \frac{\partial |\, \tilde{\gamma}'\, |}{\partial \epsilon_i}\, ds \,\Big|_{\epsilon_i=0}. \tag{4.2}$$

In order to simplify Equation 4.2, let us isolate and simplify a few quantities before proceeding.

4.1.1 The integrand $\frac{\partial \kappa}{\partial \epsilon_i}$

Since

$$\kappa = \frac{|\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{|\,\tilde{\gamma}'\,|^3}$$

then

$$\begin{aligned}
\frac{\partial \kappa}{\partial \epsilon_i} &= \frac{\frac{\partial |\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{\partial \epsilon_i}\,|\,\tilde{\gamma}'\,|^3 - 3\,|\,\tilde{\gamma}'\,|^2\,\frac{\partial |\,\tilde{\gamma}'\,|}{\partial \epsilon_i}\,|\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{|\,\tilde{\gamma}'\,|^6} \\
&= \frac{1}{|\,\tilde{\gamma}'\,|^3}\,\frac{\partial |\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{\partial \epsilon_i} - 3\,\frac{\partial |\,\tilde{\gamma}'\,|}{\partial \epsilon_i}\,\frac{|\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{|\,\tilde{\gamma}'\,|^4} \\
\left.\frac{\partial \kappa}{\partial \epsilon_i}\right|_{\epsilon_i=0} &= \frac{1}{|\,\tilde{\gamma}'\,|^3}\,\left.\frac{\partial |\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{\partial \epsilon_i}\right|_{\epsilon_i=0} - 3\,\frac{\partial |\,\tilde{\gamma}'\,|}{\partial \epsilon_i}\,\left.\frac{|\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{|\,\tilde{\gamma}'\,|^4}\right|_{\epsilon_i=0}, \qquad (4.3)
\end{aligned}$$

but since $|\,\tilde{\gamma}'\,|_{\epsilon_i=0} = |\,\gamma\,| = 1$, Equation 4.3 simplifies to

$$\left.\frac{\partial \kappa}{\partial \epsilon_i}\right|_{\epsilon_i=0} = \left.\frac{\partial |\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{\partial \epsilon_i}\right|_{\epsilon_i=0} - 3\,|\,\tilde{\gamma}' \times \tilde{\gamma}''\,|\,\left.\frac{\partial |\,\tilde{\gamma}'\,|}{\partial \epsilon_i}\right|_{\epsilon_i=0}, \qquad (4.4)$$

but

$$|\,\tilde{\gamma}' \times \tilde{\gamma}''\,|^2\big|_{\epsilon_i=0} = \kappa^2,$$

as computed by Hill et al. [HMT08]. Equation 4.4 then simplifies further to

$$\left.\frac{\partial \kappa}{\partial \epsilon_i}\right|_{\epsilon_i=0} = \left.\frac{\partial |\,\tilde{\gamma}' \times \tilde{\gamma}''\,|}{\partial \epsilon_i}\right|_{\epsilon_i=0} - 3\,\kappa\,\left.\frac{\partial |\,\tilde{\gamma}'\,|}{\partial \epsilon_i}\right|_{\epsilon_i=0}.$$

Omitting the rest of the computations, we note that

$$\left.\frac{\partial \kappa}{\partial \epsilon_2}\right|_{\epsilon_i=0} = \psi_2'' + (\kappa^2 - \tau^2)\psi_2 \qquad \text{and} \qquad \left.\frac{\partial \kappa}{\partial \epsilon_3}\right|_{\epsilon_i=0} = 2\tau\psi_3' - \tau'\psi_3, \qquad (4.5)$$

which is the same as the result of Hill et al. [HMT08].

4.1.2 The integrand $\frac{\partial |\,\tilde{\gamma}'\,|}{\partial \epsilon_i}$

We begin with our perturbed space curve

$$\tilde{\gamma} = \gamma + \epsilon_1\psi_1\vec{T} + \epsilon_2\psi_2\vec{N} + \epsilon_3\psi_3\vec{B}.$$

Using the Frenet equations,

$$\vec{T}' = \kappa\vec{N} \qquad \vec{N}' = -\kappa\vec{T} + \tau\vec{B} \qquad \vec{B}' = -\tau\vec{N},$$

we get

$$\tilde{\gamma}' = [1 + \epsilon_1\psi_1' - \epsilon_2\kappa\psi_2]\,\vec{T} + [\epsilon_1\kappa\psi_1 + \epsilon_2\psi_2' - \epsilon_3\tau\psi_3]\,\vec{N} + [\epsilon_2\psi_2\tau + \epsilon_3\psi_3']\,\vec{B}.$$

Noting that $\vec{T}$, $\vec{N}$ and $\vec{B}$ are unit vectors, we are left with

$$|\,\tilde{\gamma}'\,|^2 = [1 + \epsilon_1\psi_1' - \epsilon_2\kappa\psi_2]^2 + [\epsilon_1\kappa\psi_1 + \epsilon_2\psi_2' - \epsilon_3\tau\psi_3]^2 + [\epsilon_2\psi_2\tau + \epsilon_3\psi_3']^2$$

so

$$\left.\frac{\partial |\,\tilde{\gamma}'\,|^2}{\partial \epsilon_2}\right|_{\epsilon_i=0} = -2\kappa\psi_2 \qquad \text{and} \qquad \left.\frac{\partial |\,\tilde{\gamma}'\,|^2}{\partial \epsilon_3}\right|_{\epsilon_i=0} = 0, \qquad (4.6)$$

and since

$$\frac{\partial|\,\tilde{\gamma}'\,|}{\partial\epsilon_i} = \frac{1}{2|\,\tilde{\gamma}'\,|}\frac{\partial|\,\tilde{\gamma}'\,|^2}{\partial\epsilon_i}$$

$$\left.\frac{\partial|\,\tilde{\gamma}'\,|}{\partial\epsilon_i}\right|_{\epsilon_i=0} = \frac{1}{2}\left.\frac{\partial|\,\tilde{\gamma}'\,|^2}{\partial\epsilon_i}\right|_{\epsilon_i=0}.$$

Then Equation 4.6 reduces to

$$\left.\frac{\partial|\,\tilde{\gamma}'\,|}{\partial\epsilon_2}\right|_{\epsilon_i=0} = -\kappa\psi_2 \qquad \text{and} \qquad \left.\frac{\partial|\,\tilde{\gamma}'\,|}{\partial\epsilon_3}\right|_{\epsilon_i=0} = 0. \tag{4.7}$$

4.2 Variation in the Normal Direction

With the above quantities calculated, let us return to Equation 4.2 and first consider the variation in the normal direction, which is given by

$$\left.\frac{\partial}{\partial\epsilon_2}E(\tilde{\gamma})\right|_{\epsilon_i=0} = 0$$

$$\int_a^b \frac{\partial F}{\partial\kappa}\frac{\partial\kappa}{\partial\epsilon_2}\,ds\,\Bigg|_{\epsilon_i=0} + \int_a^b F\,\frac{\partial|\,\tilde{\gamma}'\,|}{\partial\epsilon_2}\,ds\,\Bigg|_{\epsilon_i=0} = 0 \tag{4.8}$$

Substituting Equations 4.5 and 4.7 into Equation 4.8 and then simplifying, we get

$$\int_a^b \frac{\partial F}{\partial\kappa}\,[\psi_2'' + (\kappa^2-\tau^2)\psi_2]\,ds - \int_a^b F\kappa\,\psi_2\,ds = 0$$

$$\int_a^b \frac{\partial F}{\partial\kappa}\,\psi_2''\,ds + \int_a^b \left[(\kappa^2-\tau^2)\frac{\partial F}{\partial\kappa}\,F\kappa\right]\psi_2\,ds = 0.$$

Now we integrate the first term by parts, recalling the boundary condition Equation 4.1, and simplify to get

$$\frac{\partial F}{\partial\kappa}\,\psi_2'\,\Bigg|_a^b - \int_a^b \frac{d}{ds}\frac{\partial F}{\partial\kappa}\,\psi_2'\,ds + \int_a^b \left[(\kappa^2-\tau^2)\frac{\partial F}{\partial\kappa}\,-F\kappa\right]\psi_2\,ds = 0$$

$$-\int_a^b \frac{d}{ds}\frac{\partial F}{\partial\kappa}\,\psi_2'\,ds + \int_a^b \left[(\kappa^2-\tau^2)\frac{\partial F}{\partial\kappa}\,-F\kappa\right]\psi_2\,ds = 0.$$

Again we integrate the first term by parts and simplify to get

$$-\frac{d}{ds}\frac{\partial F}{\partial\kappa}\,\psi_2\,\Bigg|_a^b + \int_a^b \frac{d^2}{ds^2}\frac{\partial F}{\partial\kappa}\,\psi_2\,ds + \int_a^b \left[(\kappa^2-\tau^2)\frac{\partial F}{\partial\kappa}\,-F\kappa\right]\psi_2\,ds = 0$$

$$\int_a^b \frac{d^2}{ds^2}\frac{\partial F}{\partial\kappa}\,\psi_2\,ds + \int_a^b \left[(\kappa^2-\tau^2)\frac{\partial F}{\partial\kappa}\,-F\kappa\right]\psi_2\,ds = 0$$

$$\int_a^b \left[\frac{d^2}{ds^2}\frac{\partial F}{\partial\kappa} + (\kappa^2-\tau^2)\frac{\partial F}{\partial\kappa}\,-F\kappa\right]\psi_2\,ds = 0.$$

Now we apply the Fundamental Lemma of the Calculus of Variations and get

$$\frac{d^2}{ds^2}\frac{\partial F}{\partial\kappa} + (\kappa^2-\tau^2)\frac{\partial F}{\partial\kappa}\,-F\kappa = 0, \tag{4.9}$$

which is the Euler-Lagrange equation associated with the component of the total variation in the normal direction.

4.3 Variation in the Binormal Direction

Next, let us consider the variation in the binormal direction, which is given by

$$\frac{\partial}{\partial \epsilon_3} E(\tilde{\gamma})\bigg|_{\epsilon_i=0} = 0$$

$$\int_a^b \frac{\partial F}{\partial \kappa}\frac{\partial \kappa}{\partial \epsilon_3}\, ds\,\bigg|_{\epsilon_i=0} + \int_a^b F\,\frac{\partial |\,\tilde{\gamma}'\,|}{\partial \epsilon_3}\, ds\,\bigg|_{\epsilon_i=0} = 0. \tag{4.10}$$

Substituting (4.5) and (4.7) into (4.10) and then simplifying, we get

$$\int_a^b \frac{\partial F}{\partial \kappa}[-2\tau\psi_3' - \tau'\psi_3]\, ds = 0$$

$$2\int_a^b \frac{\partial F}{\partial \kappa}\tau\psi_3'\, ds + \int_a^b \frac{\partial F}{\partial \kappa}\tau'\psi_3\, ds = 0.$$

Integrate the first term by parts, keeping in mind the boundary condition Equation 4.1, and simplify to get

$$2\tau\frac{\partial F}{\partial \kappa}\psi_3\bigg|_a^b - 2\int_a^b \frac{d}{ds}\left(\frac{\partial F}{\partial \kappa}\tau\right)\psi_3\, ds + \int_a^b \frac{\partial F}{\partial \kappa}\tau'\psi_3\, ds = 0$$

$$\int_a^b \left[\frac{\partial F}{\partial \kappa}\tau' - 2\frac{d}{ds}\left(\frac{\partial F}{\partial \kappa}\tau\right)\right]\psi_3\, ds = 0.$$

Finally, by the Fundamental Lemma of the Calculus of Variations, we get

$$\frac{\partial F}{\partial \kappa}\tau' - 2\frac{d}{ds}\left(\frac{\partial F}{\partial \kappa}\tau\right) = 0,$$

which we simplify to get

$$\frac{\partial F}{\partial \kappa}\tau' - 2\left[\frac{d}{ds}\frac{\partial F}{\partial \kappa}\tau + \frac{\partial F}{\partial \kappa}\tau'\right] = 0$$

$$2\frac{d}{ds}\frac{\partial F}{\partial \kappa}\tau + \frac{\partial F}{\partial \kappa}\tau' = 0, \tag{4.11}$$

which is the Euler-Lagrange equation association with the component of the total variation in the binormal direction.

5 Conclusion

We have looked at the basic results of the calculus of variations, namely the simplest Euler-Lagrange equation (Equation 1.8), and have examined the connection to minimal surfaces. In considering minimal surfaces, we saw the link between the helicoid and the α-helix, one of the most common repeating units of protein structure, and then extended this connection to derive two Euler-Lagrange equations (Equation 4.9) and (Equation 4.11) which are related to the potential free energy functionals $E[\gamma] = \int F(\kappa)\, dL$ of protein structure.

We can use these two Euler-Lagrange equations to derive different solutions $F(\kappa)$. For a detailed discussion of some possible solutions, see the article by McCoy [McC08]. Naturally, we would want to restrict ourselves to $F(\kappa)$ that admit helices as minimizing solutions to the energy functional $E[\gamma]$. It would be even more interesting if we were to look at $F(\kappa)$ that admit helices as unique minimizing solutions to $E[\gamma]$. These solutions could shed some light on protein structure from a different angle, which are current avenues of research [BF09, FNS05, HMT08, McC08].

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