Gauge Fields, Strings, Solitons, Anomalies, and the Speed of Life

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Joel Cohen proposed that “mathematics is biology’s next microscope, only better; biology is mathematics’ next physics, only better.” Here, we aim for something even better. We try to combine mathematical physics and biology into a picoscope of life. For this, we merge techniques that were introduced and developed in modern mathematical physics, largely by Ludvig Faddeev, to describe objects such as solitons and Higgs and to explain phenomena such as anomalies in gauge fields. We propose a synthesis that can help to resolve the protein folding problem, one of the most important conundrums in all of science. We apply the concept of gauge invariance to scrutinize the extrinsic geometry of strings in three-dimensional space. We evoke general principles of symmetry in combination with Wilsonian universality and derive an essentially unique Landau–Ginzburg energy that describes the dynamics of a generic stringlike configuration in the far infrared. We observe that the energy supports topological solitons that relate to an anomaly similarly to how a string is framed around its inflection points. We explain how the solitons operate as modular building blocks from which folded proteins are composed. We describe crystallographic protein structures by multisolitons with experimental precision and investigate the nonequilibrium dynamics of proteins under temperature variations. We simulate the folding process of a protein at in vivo speed and with close to picoscale accuracy using a standard laptop computer. With picobiology as next pursuit of mathematical physics, things can only get better.

Keywords: physics of proteins, soliton, nonlinear Schrödinger equation, extrinsic string geometry

1. Introduction

Recently, Joel Cohen proposed that “mathematics is biology’s next microscope, only better; biology is mathematics’ next physics, only better” [1]. Long before that, Ludvig Faddeev first drew my attention to a sentence in the introduction of Dirac’s stunning 1931 article [2], “There are at present fundamental problems in theoretical physics awaiting solution, e.g. the relativistic formulation of quantum mechanics and the nature of atomic nuclei (to be followed by more difficult ones such as the problem of life).” This epitomizes what could be proclaimed as the three Dirac problems in theoretical physics. The first Dirac problem was solved de facto at the time of writing. Dirac introduced his equation in 1928. Maybe he already had quantum gravity in his mind; it has been stated in exalted circles that this is a problem settled by string theory. A resolution to the second Dirac problem, the nature of atomic nuclei, took almost half a century of collective efforts to develop. We now trust that LHC experiments at CERN demonstrate how all four known fundamental interactions are governed by the Weinberg–Salam standard...
model and quantum chromodynamics plus Einstein’s gravity. But there remain important conundrums awaiting solution, including quark (color) confinement.

The third Dirac problem, life, endures. Its inclusion demonstrates Dirac’s very high level of ambition and trust in the mastery of theoretical physics. How could Dirac envisage that the notion of life could be defined as a theoretical physics problem? Did he presume that eventually life can be described with a conceptual clarity that compares with quantum mechanics?

Today, we are reaching a point where a precise definition of the problem of life can be attempted. We understand that proteins are the workhorses of all living cells. They participate in all the metabolic activities that constitute life as we know it. We have learned that the biological function of a protein is intimately related to its shape. It might hence be argued that the protein folding problem is the way to address the problem of life à la Dirac. The quest is to describe the folding and dynamics of proteins with the eloquence of the equations in Dirac’s 1931 article.

2. Abelian Higgs model

The Abelian Higgs model (AHM) and its generalizations [3] comprise the paradigmatic theoretical framework for describing physical scenarios from cosmic strings to vortices in superconductors. The Weinberg–Salam model of electroweak interactions is a non-Abelian epitome of the AHM, and so are the various versions of the grand unified theory that aim to unify all subatomic forces. In what follows, we argue that a discretized version of the AHM might even describe the dynamics and folding of proteins with subatomic precision and at the speed of life.

The elemental AHM comprises a single complex scalar field $\phi$ and a vector field $A_i$. These fields are subjected to the $U(1)$ gauge transformation

$$\phi \rightarrow e^{ie\vartheta} \phi, \quad A_i \rightarrow A_i + \partial_i \vartheta, \quad (1)$$

where $\vartheta$ is a function and $e$ is a parameter. We can also introduce another set of variables $(J_i, \rho, \theta)$ related to $(A_i, \phi)$ by the change of variables

$$\rho = \rho e^{i\theta}, \quad J_i = \frac{i}{2\rho |\phi|^2} [\phi^* (\partial_i - ieA_i) \phi - c.c.] \quad (2)$$

These new variables can be introduced whenever $\rho \neq 0$. The $\rho$ and $J_i$ are both gauge invariant; they remain intact under transformation (1). But $\theta \rightarrow \theta + \vartheta$.

The standard AHM Hamiltonian is

$$\mathcal{H} = \frac{1}{4} F_{ij}^2 + |(\partial_i - ieA_i)\phi|^2 + \lambda (|\phi|^2 - v^2)^2, \quad (3)$$

where $F_{ij} = \partial_i A_j - \partial_j A_i$. This is the unique Landau–Ginzburg Hamiltonian of the AHM multiplet in the framework of Wilsonian universality [4], [5] and invariance under $U(1)$ gauge transformation (1) except that a Chern–Simons term (ChS) could be added in odd dimensions $D$ to break parity:

$$D = 1: \quad \text{ChS} \sim A, \quad \text{ChS} \sim A dA, \quad (4)$$

and so on.
The gauge invariance of (3) becomes manifest when we write it in terms of new variables (2),

\[ \mathcal{H} = \frac{1}{4} \left( J_{ij} + \frac{2\pi}{e} \sigma_{ij} \right)^2 + (\partial_i \rho)^2 + \rho^2 J_i^2 + \lambda (\rho^2 - \eta^2)^2 + \text{ChS}, \tag{5} \]

where \( J_{ij} = \partial_i J_j - \partial_j J_i \) and

\[ \sigma_{ij} = \frac{1}{2\pi} [\partial_i, \partial_j] \theta. \tag{6} \]

The \( \sigma_{ij} \) is a string current; its support coincides with the worldsheet of the cores of Abrikosov vortices. If (5) describes a vortex, then (6) subtracts a singular string contribution that appears in \( J_{ij} \). An irregular contribution then appears in the third term in the right-hand side of (5) but is removed by the density \( \rho \), which vanishes on the worldsheet of the vortex core. We note that Hamiltonian (5) involves only variables that are manifestly \( U(1) \) gauge invariant except along a vortex line. In particular, unlike in the case of (3), the local gauge invariance in (5) is entirely removed, not by fixing a gauge but by changing the variables [6].

3. Strings and the Frenet equation

Proteins are stringlike objects. To describe their physical properties, we must therefore develop the string formalism. We start with the continuous (differentiable) case.

The geometry of a class-\( C^3 \) differentiable string \( x(z) \) in \( \mathbb{R}^3 \) is governed by the Frenet equation [7]. Here, \( z \in [0, L] \), and \( L \) is the length of the string in \( \mathbb{R}^3 \) computed by

\[ L = \int_0^L dz \| x_z \| = \int_0^L dz \sqrt{x_z \cdot x_z} \equiv \int_0^L dz \sqrt{g}. \tag{7} \]

In this equation, we recognize the (static) Nambu–Goto action; the parameter \( z \in [0, L] \) is generic. We can always reparameterize the string and express it in terms of the arc length \( s \in [0, L] \) in the ambient \( \mathbb{R}^3 \). This is achieved by the change of variables

\[ s(z) = \int_0^z dz' \| x_z(z') \|. \]

In what follows, we use the arc-length parameterization. We also consider a single open string and assume that the string is not self-crossing, i.e., it is self-avoiding.

At a generic point along the string, we introduce the unit-length tangent vector

\[ t = \frac{dx(s)}{ds} \equiv x_s, \tag{8} \]

the unit-length binormal vector

\[ b = \frac{x_s \times x_{ss}}{\| x_s \times x_{ss} \|}, \tag{9} \]

and the unit-length normal vector

\[ n = b \times t. \tag{10} \]

These three vectors \( (n, b, t) \) form the right-handed orthonormal Frenet frame. This framing can be introduced at each point where

\[ x_s \times x_{ss} \neq 0. \tag{11} \]

We proceed by assuming that this is the case for now.
The Frenet equation \([7]\) transports the frames along the string,

\[
\frac{d}{ds} \begin{pmatrix} \mathbf{n} \\ \mathbf{b} \\ \mathbf{t} \end{pmatrix} = \begin{pmatrix} 0 & \tau & -\kappa \\ -\tau & 0 & 0 \\ \kappa & 0 & 0 \end{pmatrix} \begin{pmatrix} \mathbf{n} \\ \mathbf{b} \\ \mathbf{t} \end{pmatrix},
\]

(12)

where

\[\kappa(s) = \frac{||\mathbf{x}_s \times \mathbf{x}_{ss}||}{||\mathbf{x}_s||^3}\]

(13)

is the curvature of the string on the osculating plane spanned by \(\mathbf{t}\) and \(\mathbf{n}\) and

\[\tau(s) = \frac{(\mathbf{x}_s \times \mathbf{x}_{ss}) \cdot \mathbf{x}_{sss}}{||\mathbf{x}_s \times \mathbf{x}_{ss}||^2}\]

(14)

is the torsion that measures how the string deviates from its osculating plane. Both \(\kappa(s)\) and \(\tau(s)\) are preordained solely by the extrinsic geometry, i.e., the shape of the string. According to (12), the curvature and torsion also determine the string: if the two are known, then we construct \(\mathbf{t}(s)\) by solving the Frenet equation and then solve for the string by integrating (8). The solution is unique up to rigid translations and rotations of the string.

We note that curvature (13) and torsion (14) are scalars under reparameterizations. Under an infinitesimal local diffeomorphism along the string obtained by deforming \(s\) according to

\[s \rightarrow s + \epsilon(s),\]

(15)

where \(\epsilon(s)\) is an arbitrary infinitesimally small function such that

\[\epsilon(0) = \epsilon(L) = 0, \quad \epsilon_s(0) = \epsilon_s(L) = 0,
\]

we have

\[\delta\kappa(s) = -\epsilon(s)\kappa_s, \quad \delta\tau(s) = -\epsilon(s)\tau_s.\]

(16)

The Lie algebra of diffeomorphisms (15) is the classical Virasoro (Witt) algebra.

4. Abelian gauge fields

We can construct an example Abelian Higgs multiplet \([8]\)–\([10]\) from the extrinsic string geometry. For this, we observe that (8) does not involve the normal and binormal vectors. Therefore, an \(SO(2)\) rotation around \(\mathbf{t}(s)\) that sends the zweibein \((\mathbf{n}, \mathbf{b})\) into another zweibein \((\mathbf{e}_1, \mathbf{e}_2)\), as shown in Fig. 1, leaves the string intact.

The generic zweibein is obtained from the Frenet zweibein by

\[
\begin{pmatrix} \mathbf{n} \\ \mathbf{b} \end{pmatrix} \rightarrow \begin{pmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \end{pmatrix} = \begin{pmatrix} \cos \eta(s) & \sin \eta(s) \\ -\sin \eta(s) & \cos \eta(s) \end{pmatrix} \begin{pmatrix} \mathbf{n} \\ \mathbf{b} \end{pmatrix}.
\]

(17)

For the Frenet equation, this yields

\[
\frac{d}{ds} \begin{pmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \\ \mathbf{t} \end{pmatrix} = \begin{pmatrix} 0 & \tau + \eta_s & -\kappa \cos \eta \\ -(\tau + \eta_s) & 0 & \kappa \sin \eta \\ \kappa \cos \eta & -\kappa \sin \eta & 0 \end{pmatrix} \begin{pmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \\ \mathbf{t} \end{pmatrix}.
\]

(18)
Remarkably, by interpreting $\kappa(s)$ as the modulus of a complex quantity

$$\kappa \rightarrow \kappa e^{i\eta},$$

we can consider the transition of $\kappa$ and $\tau$ in (17) as a one-dimensional example of $U(1)$ gauge transformation (1) with the curvature identified as the Higgs field and the torsion identified as the gauge field,

$$\kappa \sim \phi \rightarrow \kappa e^{i\eta} \equiv \phi e^{i\eta},$$

$$\tau \sim A_i \rightarrow \tau + \eta_s \equiv A_i + \eta_s.$$  

(20)

We note that the choice

$$\eta(s) = -\int_0^s d\tilde{s} \tau(\tilde{s})$$

leads to the unitary gauge, which corresponds to the parallel transport framing [11]. Unlike the Frenet framing, which cannot be defined at points (or segments) where (11) vanishes, the parallel transport framing can still be defined continuously [12]. But there is a lurking anomaly, which we soon reveal.

5. Spinor Frenet equation

It is occasionally profitable to recognize that the Frenet equation admits a spinor representation [10]. For this, we introduce a two-component complex spinor

$$\psi = \begin{pmatrix} z_1 \\ z_2 \end{pmatrix}.$$  

(22)

We also introduce the conjugate spinor $\bar{\psi}$; the two are related by the charge conjugation operation $C$,

$$\bar{\psi} = C\psi = -i\sigma^2 \psi^* = \begin{pmatrix} -z_2^* \\ z_1^* \end{pmatrix}.$$  

(23)

We note that $C^2 = -I$. We impose the normalization condition

$$\psi^\dagger \psi \equiv \langle \psi, \psi \rangle = 1, \quad \bar{\psi}^\dagger \bar{\psi} = \langle \bar{\psi}, \bar{\psi} \rangle = 1, \quad \langle \psi, \bar{\psi} \rangle = 0.$$  

(24)
We define the spin polarization vector $t$ such that
\[ t \cdot \hat{\sigma} \psi = \psi \quad \iff \quad t \cdot \hat{\sigma} \bar{\psi} = -\bar{\psi}. \quad (25) \]

We obtain $t = \psi^\dagger \hat{\sigma} \psi = \langle \psi, \hat{\sigma} \psi \rangle$. We also define the complex vector
\[ e_+ = e_1 + ie_2 = \langle \bar{\psi}, \hat{\sigma} \psi \rangle \equiv \bar{\psi}^\dagger \hat{\sigma} \psi, \]
where $e_1$ and $e_2$ are real. We can verify that $e_i \cdot e_j = \delta_{ij}$ and $e_i \cdot t = 0$, and we conclude that $(e_1, e_2, t)$ is a right-handed orthonormal system. It can be identified with a Frenet framing of a string defined by $t(s)$ as the tangent vector, possibly modulo a global $SO(2)$ frame rotation.

We consider the local $U(1)$ rotation
\[ \psi \rightarrow e^{i\eta} \psi, \quad \bar{\psi} \rightarrow e^{i\eta} \bar{\psi}. \quad (26) \]
Then
\[ \langle \psi, \partial_s \psi \rangle = \bar{\psi}^\dagger \partial_s \psi \rightarrow \langle \psi, \partial_s \psi \rangle + i \partial_s \eta. \]
This suggests introducing the putative torsion
\[ \tau \sim -i\langle \psi, \partial_s \psi \rangle. \quad (27) \]
Furthermore, because
\[ \langle \bar{\psi}, \partial_s \psi \rangle = \bar{\psi}^\dagger \partial_s \psi \rightarrow e^{2i\theta} \langle \bar{\psi}, \partial_s \psi \rangle, \]
we identify
\[ \kappa \sim \langle \bar{\psi}, \partial_s \psi \rangle \]
as the putative (complex) curvature. Hence, we have the spinor Frenet equation
\[ \partial_s \psi = i\tau \psi + \kappa \bar{\psi}. \quad (29) \]
If the curvature and torsion in this equation are known, then we can solve for $\psi$ and compute $t = \langle \psi, \hat{\sigma} \psi \rangle$.

The string in the arc-length parameterization is then, as before, determined from
\[ \frac{dx}{ds} = t. \]

6. Non-Abelian gauge fields

The geometric interpretation of curvature and torsion in terms of the AHM multiplet extends to a non-Abelian framework. This leads to a relation between the extrinsic string geometry and the structure of non-Abelian gauge theories (in a decomposed format of the latter [13]–[16]). These relations are valuable for a wider perspective beyond the immediate scope of this paper.

We start by introducing the three matrices
\[ T_1 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{pmatrix}, \quad T_2 = \begin{pmatrix} 0 & 0 & 1 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \end{pmatrix}, \quad T_3 = \begin{pmatrix} 0 & -1 & 0 \\ -1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad (30) \]
which determine the canonical adjoint representation of the $so(3)$ Lie algebra,

$$[T_a, T_b] = \epsilon_{abc} T_c.$$  

The action of the $SO(2) \sim U(1)$ frame rotation on $\kappa$ and $\tau$ can be realized as

$$\kappa T_2 \rightarrow e^{-\eta T_3} (\kappa T_2) e^{\eta T_3} = \kappa (\cos \eta T^2 - \sin \eta T^1),$$

$$\tau T_3 \rightarrow (\tau + \eta') T_3.$$  

This suggests combining the (general frame) curvature and torsion into a non-Abelian $SO(3)$ gauge field,

$$A^a T^a = A^1 T^1 + A^2 T^2 + A^3 T^3 = \kappa \sin \eta T^2 + \kappa \cos \eta T^2 + \tau \eta T^3.$$  

The $SO(3)$ gauge transformation $A^a T^a \rightarrow g^{-1} (A^a T^a + i \partial_s) g$ corresponds to a general frame rotation, and (31) and (32) determine the subset of $SO(2)$ gauge transformations in the Cartan direction $g = e^{\eta T_3}$.

The spinor Frenet equation can be interpreted as follows. We combine the two spinors (22) and (23) into a four-component Majorana spinor

$$\Psi = \frac{1}{\sqrt{2}} \begin{pmatrix} \psi \\ \bar{\psi} \end{pmatrix}.$$  

Using (27) and (28), we recover connection (33), now in the $SU(2)$ basis,

$$A^a T^a \sim A_{\alpha \beta} = \Psi^\dagger \sigma_{\alpha} \partial_s \Psi_{\beta} = \begin{pmatrix} \tau & -i\kappa \\ i\kappa^* & -\tau \end{pmatrix} = A \cdot \hat{\sigma} =$$

$$= \tau \sigma^3 + \kappa_1 \sigma^1 + \kappa_2 \sigma^2 \equiv \tau \sigma^3 + \kappa \sigma^+ + \kappa^* \sigma^-,$$

where $\kappa_1 = \text{Re} \kappa$ and $\kappa_2 = \text{Im} \kappa$. From (29) for the Frenet equation, we then obtain

$$(i \partial_s + A \cdot \hat{\sigma}) \Psi = 0,$$

which remains covariant under the $SU(2)$ gauge transformation,

$$\Psi \rightarrow g \Psi \equiv \Psi_g \implies A \rightarrow g (A + i \partial_s) g^{-1} \equiv A_g,$$

corresponding to a general $SO(3) \simeq SU(2)$ rotation of frames along the string. The gauge transformation defined by $g \in SU(2)$ such that

$$g \sigma^3 g^{-1} = \mathbf{t} \cdot \hat{\sigma} \equiv \hat{\mathbf{t}},$$

$$g (\sigma^1 + i \sigma^2) g^{-1} = (\mathbf{n} + i \mathbf{b}) \cdot \hat{\sigma} \equiv e_+ \cdot \hat{\sigma} \equiv \hat{e}_+$$

is particularly interesting. It identifies the Frenet framing and sends (34) to

$$A \cdot \hat{\sigma} \rightarrow (\tau \hat{\mathbf{t}} + \kappa \hat{\mathbf{e}}_+ + \kappa^* \hat{\mathbf{e}}_-) + \alpha \hat{\mathbf{t}} + \frac{1}{2i} [\partial_s \hat{\mathbf{t}}, \hat{\mathbf{t}}],$$

where $\alpha = 2i(e^+, \partial_s e^-)$. The $SU(2)$ connection given by (36) has the functional form of the decomposed connection introduced in [13] including the "monopole" contribution. In particular, the $U(1) \in SU(2)$ gauge rotation around the Cartan direction $\hat{\mathbf{t}}$ [13] $g = e^{i\eta/2} \hat{\mathbf{t}}$ sends

$$\kappa \rightarrow e^{i\eta} \kappa, \quad \tau \rightarrow \tau + \partial_s \eta, \quad \alpha \rightarrow \alpha + \partial_s \eta.$$

This is the same as (17), (18). The present construction shows that there is an intrinsic string design hiding in non-Abelian gauge theories.
7. String energy

To describe the dynamics of strings and, eventually, proteins, we desire an energy function in terms of the curvature and torsion. For this, we recall that Landau–Ginzburg energy (3) of the elemental AHM is unique in the Wilsonian sense of universality. It emerges from only general arguments and symmetry principles. We also recall that the shape of a string is independent of the way it is framed. Accordingly, the string energy can only involve manifestly frame-independent combinations of curvature and torsion (20).

Because (3) is the universal $SO(2) \sim U(1)$ invariant energy function that involves a complex Higgs field $\phi \sim \kappa$ and gauge field $A \sim \tau$, it must serve as the Hamiltonian that describes strings and their dynamics in the far infrared. Therefore, we introduce

$$H = \int_0^L ds \left\{ |(\partial_s + i e \tau)\kappa|^2 + \lambda(|\kappa|^2 - m^2)^2 \right\} + a \int_0^L ds \tau. \quad (37)$$

We include the one-dimensional version of Chern–Simons term (4), which introduces chirality into the string; there is no $F_{ij}$ in one dimension.

In (37), the curvature $\kappa$ and torsion $\tau$ are expressed in a generic, arbitrary framing of the string. The resulting gauge-invariant variables (2) coincide with Frenet frame curvature (13) and torsion (14) characterizing the extrinsic string geometry. In terms of these gauge-invariant variables (hereafter denoted by $(\kappa, \tau)$), Hamiltonian (37) becomes

$$H = \int_0^L ds \left\{ (\partial_s \kappa)^2 + e^2 \kappa^2 \tau^2 + \lambda(\kappa^2 - m^2)^2 \right\} + a \int_0^L ds \tau. \quad (38)$$

This is our manifestly gauge-invariant Landau–Ginzburg Hamiltonian of strings (see (5)).

Finally, we indicate a non-Abelian variant of the energy. A solution of Eq. (35) minimizes the functional

$$S = \int ds |(i \partial_s + A)\Psi|^2.$$ 

This is an example of the gauged $SU(2)$ nonlinear $\sigma$-model; we recall that the Majorana spinor is subject to the normalization condition following from (24). We could introduce additional $SU(2)$ gauge-invariant functionals of $\Psi$ and $A$. This would lead to gauged nonlinear $\sigma$-models as string energy functions.

8. Integrable hierarchy

There is a relation between (38), the integrable hierarchy of the nonlinear Schrödinger (NLS) equation, and the Heisenberg spin chain. To show this, we follow Hasimoto [17] and combine the curvature and torsion into the complex variable

$$\psi(s) = \kappa(s) \exp \left\{ ie \int_0^s ds' \tau(s') \right\}. \quad (39)$$

This yields the standard NLS Hamiltonian density [18], [19]

$$\mathcal{H}_3 = \kappa_s^2 + e^2 \kappa^2 \tau^2 + \lambda \kappa^4 = \bar{\psi}_s \psi_s + \lambda (\bar{\psi} \psi)^2. \quad (40)$$

The lower-level conserved densities in the integrable NLS hierarchy are the helicity, length (i.e., the Nambu–Goto action), number operator, and momentum:

$$\mathcal{H}_{-2} = \tau, \quad \mathcal{H}_{-1} = L, \quad \mathcal{H}_1 = \kappa^2, \quad \mathcal{H}_2 = \kappa^2 \tau. \quad (41)$$
Energy (38) is a combination of \( \mathcal{H}_{-2}, \mathcal{H}_1, \) and \( \mathcal{H}_3 \). From the perspective of the NLS hierarchy, the momentum \( \mathcal{H}_2 \) could also be included. If higher-order corrections are desired, then the natural candidate is the modified Korteweg–de Vries density

\[
\mathcal{H}_4 = \kappa \kappa_{ss} \tau + 4 \kappa^2 \tau^3 - 4 e^2 \kappa_s^2 \tau + 3 \lambda \kappa^4 \tau,
\]

which appears as the conserved density at the next level in the NLS hierarchy.

The Heisenberg spin chain is obtained directly from \( \mathcal{H}_1 \) in terms of the Frenet equation:

\[
\int_0^L ds \mathcal{H}_1 = \int_0^L ds \kappa^2 = \int_0^L ds |t_s|^2.
\]

The combination of \( \mathcal{H}_{-1} \) and \( \mathcal{H}_1 \) leads to a rigid string action [20] and also relates to the Kratky–Porod model in polymer physics [21]. The perturbative-level Wilsonian universality was used in [20] to argue that no additional terms should emerge in the infrared. But a perturbative approach does not reach into the nonperturbative domain, and NLS Hamiltonian (40) is known to support solitons that are pivotal in the description of numerous far infrared physical phenomena.

9. Solitons

Solitons are the paradigmatic structural self-organizers in the physical world. They materialize in numerous scenarios [18], [19], [22], [23]. Solitons transmit data in transoceanic cables. Solitons conduct electricity in organic polymers and transport chemical energy in proteins. Solitons explain the Meissner effect in superconductivity and dislocations in liquid crystals. Solitons model hadronic particles, cosmic strings, and magnetic monopoles in high-energy physics. In what follows, we argue that solitons might even describe life. There are about \( 10^{20} \) or so solitons in a human body. They participate in all the metabolic processes that make you kick, spark, and live.

The NLS equation following from (40) is the paradigmatic equation supporting solitons [18], [19], [22], [23]. Depending on the sign of \( \lambda \), these solitons are either dark (\( \lambda > 0 \)) or bright (\( \lambda < 0 \)). Furthermore, on the real line \( \mathbb{R} \), the torsion independent contribution to (38)

\[
H = \int_{-\infty}^{\infty} ds \left\{ \kappa_s^2 + \lambda (\kappa^2 - m^2)^2 \right\}
\]

(42)

describes the double-well kink also called the paradigmatic topological soliton. For positive \( m^2 \) and when \( \kappa \) can take both positive and negative values, the resulting equation of motion

\[
\kappa_{ss} = 2 \lambda (\kappa \kappa^2 - m^2)
\]

is solved by

\[
\kappa(s) = m \tanh[m \sqrt{\lambda} (s - s_0)].
\]

(43)

The energy function

\[
\mathcal{E} = \int ds \left\{ \kappa_s^2 + \lambda (\kappa^2 - m^2)^2 + \frac{d}{2} \kappa^2 \tau^2 - b \kappa^2 \tau - a \tau + \frac{e}{2} \tau^2 \right\}
\]

(44)

is the most general linear combination of all densities (40) and (41). In addition, we include the Proca mass term (the last term) [9], [10]. Although the Proca mass does not appear in the integrable NLS hierarchy, it
does have a claim of gauge invariance and as such it is often taken into account. Because (44) is quadratic in the torsion, we can eliminate \( \tau \) using the resulting equation of motion,

\[
\frac{\delta \mathcal{E}}{\delta \tau} = d\kappa^2 \tau - b\kappa^2 - a + c \tau = 0. \tag{45}
\]

This gives

\[
\tau[\kappa] = \frac{a + b\kappa^2}{c + d\kappa^2}. \tag{46}
\]

We thus obtain the effective energy for the curvature,

\[
\mathcal{E}_\kappa = \int ds \left\{ \frac{1}{2}\kappa^2 + V[\kappa] \right\} \tag{47}
\]

with the equation of motion

\[
\frac{\delta \mathcal{E}_\kappa}{\delta \kappa} = -\kappa_{ss} + V_\kappa = 0, \tag{48}
\]

where

\[
V[\kappa] = -\left( \frac{bc - ad}{d} \right) \frac{1}{c + d\kappa^2} - \left( \frac{b^2 + 8\lambda m^2}{2b} \right) \kappa^2 + \lambda \kappa^4. \tag{49}
\]

This is a deformation of the potential in (42); the two share the same large-\( \kappa \) asymptotic behavior.

For a suitable choice of parameters, we expect that (45), (48), and (49) continue to support topological solitons. But we do not know their explicit profile in terms of elementary functions. In what follows, we construct the solitons numerically.

10. Frame anomaly

We now introduce the frame anomaly. It is the edifice of a topological soliton along the string. Up to now, we have tacitly assumed that (11) holds. It ensures that Frenet curvature (13) does not vanish. But we already noted that we have \( \rho = 0 \) at the core of a vortex line in the AHM. Moreover, explicit profile (43) is both positive and negative and vanishes at \( s = s_0 \). The consequences of \( \kappa = 0 \) for a string hence deserve an investigation. For this, it can be fruitful to extend the Frenet curvature \( \kappa(s) \) such that it takes both positive and negative values. From (19), we conclude that negative values of \( \kappa \) are related to the positive values by an \( \eta = \pm \pi \) frame rotation,

\[
\kappa^{\eta = \pm \pi} e^{\pm i\pi} \kappa = -\kappa. \tag{50}
\]

Hence, we compensate the extension of \( \kappa \) to negative values by involving a discrete \( \mathbb{Z}_2 \) symmetry [24].

An (isolated) point where the curvature \( \kappa(s) \) vanishes is an inflection point. We show an example of an inflection point in Fig. 2. It can be seen how the Frenet framing experiences a sudden change: the zweibein \((n, b)\) is reflected according to

\[
(n + ib) \rightarrow -(n + ib) = e^{\pm i\pi}(n + ib) \tag{51}
\]

as it passes through the inflection point. The Frenet frame is not defined at the inflection point itself. We therefore cannot directly determine whether there has been a jump by \( \eta = +\pi \) or by \( \eta = -\pi \) in Fig. 2, i.e., whether the frame turns left or right by \( \pi \) at the inflection point. We have a frame anomaly. To examine this anomaly, we consider a string \( x(s) \) that has a simple inflection point when \( s = s_0 \) such that \( \kappa(s_0) = 0 \) but \( \kappa_s(s_0) \neq 0 \). For notational simplicity, we here redefine the parameter \( s \) such that \( s_0 = 0 \). Because a
Fig. 2. A string with inflection point (shown by the ball): at each point, the normal vector of the Frenet frame points towards the center of the osculating circle. At the inflection point, there is a discontinuity in the direction of the normal vectors: the radius of the osculating circle diverges, and the normal vector is reflected in the osculating plane from one side to the other side of the string.

generic string in \( \mathbb{R}^3 \) has no inflection point, we can also remove it from \( x(s) \) by a generic deformation. We introduce two such deformations,

\[
x(s) \rightarrow x(s) + \delta x_{1,2}(s) = x_{1,2}(s). \tag{52}
\]

In Fig. 2, these deformations would amount to a move of the string either slightly up from the plane or slightly down from the plane to remove the inflection point; a move restricted to the plane only slides the inflection point. We assume the deformations are tiny and compactly supported such that

\[
\delta x_{1,2}(\pm \varepsilon) = 0.
\]

Here, the \( \varepsilon_{\pm} > 0 \) are small and determine the parameter values where the deformations \( x_{1,2}(s) \) bifurcate.

We consider a closed string \( \Gamma \) that starts from \( x(-\varepsilon_-) \), follows along \( x_1 \) to \( x(+\varepsilon_+) \), and then returns along \( x_2 \) back to \( x(-\varepsilon_-) \). We introduce the normal vectors of the Frenet frame of \( \Gamma \) to define a second closed string \( \tilde{\Gamma} \). It is obtained by shifting \( \Gamma \) slightly in the direction of its Frenet frame normals. Let \( \mathbf{t} \) and \( \tilde{\mathbf{t}} \) be the resulting tangent vectors. We compute the Gauss linking number

\[
\text{Lk} = \frac{1}{4\pi} \oint_{\Gamma} \oint_{\tilde{\Gamma}} ds \, d\tilde{s} \frac{x - \tilde{x}}{|x - \tilde{x}|^3} \cdot (\mathbf{t} \times \tilde{\mathbf{t}}).
\]

As we proceed along \( x_{1,2}(s) \), the respective Frenet frames are continuously rotated by \( \eta_{1,2} \approx \pm \pi \); in the limit as \( \delta x_{1,2} \to 0 \), we obtain discontinuous jump (51). By the continuity of Frenet framing in the complement of the inflection points, the linking number has values \( \text{Lk} = \pm 1 \) when the \( \eta_{1,2} \) change in the same direction; we recall that \( \Gamma \) proceeds “backwards” along \( x_2 \). But \( \text{Lk} = 0 \) if the framing along \( x_1(s) \) and \( x_2(s) \) rotate in the opposite directions. Crucially, the relative sign of \( \eta_{1,2} \) appears to depend on how the inflection point is circumvented. Hence, there is a frame anomaly as \( \delta x_{1,2} \to 0 \). The value of \( \text{Lk} \) depends on how we define \( \delta x_{1,2}(s) \).

11. Perestroikas

When an inflection point and a frame anomaly occur, we have a string-specific bifurcation, called an inflection point perestroika [25]–[29]. It renders futile our attempts to uniquely frame a string \( x(s) \) across the inflection point. But there is also another kind of perestroika occurring at the inflection point, which we now explain.
We start with a long flat string segment such that the torsion $\tau(s)$ of the segment vanishes. This is synonymous for the segment to be constrained on a plane, as shown in Fig. 2 for example. For a string on the plane, a simple isolated inflection is generically present somewhere along the string. Moreover, if we deform the string but strictly in a manner that keeps it on the plane, a simple inflection point cannot disappear. It only moves around unless it escapes through the ends of the string, which we assume is not the case. For a string on the plane, a single inflection point is a topological invariant.

We now consider the string in $\mathbb{R}^3$. Generically, it does not have any inflection points. But if the string moves freely, an isolated simple inflection point generically appears at some isolated value of the flow parameter. Furthermore, when the resulting inflection point perestroika occurs along the moving string, it leaves a trail behind. The momentary inflection point perestroika permanently changes the number of flattening points, which are the points along the string where its torsion $\tau(s)$ vanishes [28], [29].

At a simple flattening point, the curvature $\kappa(s)$ is generically nonzero, while the torsion $\tau(s)$ changes its sign. The inflection point perestroika can therefore only change the number of simple flattening points by two. Apparently, it always does so [28], [29].

Unlike the inflection point, a flattening point is generic in a static space string. Furthermore, unlike a simple inflection point, a single simple flattening point that occurs in a one-parameter family of strings in $\mathbb{R}^3$ is a topological invariant. It cannot disappear on its own under local deformations that do not touch the ends of the string. But a pair of flattening points can become combined into a single biflattening point, which can dissolve. When this happens, a second string-specific bifurcation called a biflattening perestroika occurs.

Apparently, the inflection point perestroika and the biflattening perestroika are the only two bifurcations with a change in the number of flattening points [29]. The number of simple flattening points is a local invariant of the string. In addition to the flattening number, and the self-linking number in the case of a framed string, a generic smooth string does not have any other essential local invariants [28]. The two invariants are also mutually independent, although they often conspire. For example, the self-linking number of the string increases by one if the torsion is positive as the string approaches its simple inflection point and if two simple flattening points disappear after the passage through the inflection point. Moreover, if the torsion is negative, the self-linking number decreases by one when two flattening points disappear after the passage [28]. But when two simple flattening points dissolve in a biflattening perestroika, the self-linking number does not change generally speaking.

We conclude this section with the following statement. Bifurcations are the paradigmatic causes for restructuring transitions in any dynamical system. Perestroikas are the only known stringy versions of bifurcations. Therefore, perestroikas have a potentially profound influence on the physical behavior of stringlike structures. Moreover, perestroikas relate to the frame anomaly, which is a structural attribute of a string. This identifies perestroikas as those bifurcations that drive string-specific phase transitions involving structural reorganizations. In particular, perestroikas prompt topological solitons such as (43) to appear and disappear along a string. Such processes are commonplace whenever we have an energy function of form (44). It seems that for strings that model proteins, this is always the case. We find solitons and perestroikas everywhere in proteins.

12. Discrete Frenet frames

Proteins are linear macromolecules with a highly complex chemical composition. Proteins are made of twenty different covalently bonded amino acid molecules (residues) that are joined together in a row one after another. But despite the diversity of amino acids, most proteins share many conformational similarities, to an extent that their structure and dynamics can be described using a single theoretical model that concurs with a distinct universality class in the sense of Kadanoff and Wilson [4], [5].
Fig. 3. All proteins are composed similarly with an identical and very rigid peptide-plane structure that makes Wilsonian universality operable: the central Cα carbons to which the twenty different amino acids (residues $R$) are attached form the vertices that connect the peptide planes into a one-dimensional discrete string. The distance between two consecutive Cα atoms is 3.8 Å except in the rare case of cis-proline where the distance 2.8 Å should be used.

But proteins are not really continuous, differentiable strings. We must therefore extend our considerations accordingly. We start with the Frenet equations. In the “scaling limit” where the concepts of Wilsonian universality become applicable, a protein is like a piecewise-linear polygonal string. Its vertices coincide with the positions of the central Cα carbons (see Fig. 3). This reduction of the entire protein chain to a skeletal Cα backbone is an a priori enormous simplification. But as we show, it is nevertheless sufficient for describing the structure and dynamics of a protein with a subatomic precision. The approach that we propose matches the accuracy obtained in ultrahigh-resolution x-ray crystallography experiments.

Accordingly, we proceed to generalize the Frenet frame formalism to the case of polygonal strings that are piecewise linear. Let $r_i$ be the vertices, $i = 1, \ldots, N$. At each vertex, we introduce the unit tangent vector

$$t_i = \frac{r_{i+1} - r_i}{|r_{i+1} - r_i|},$$

the unit binormal vector

$$b_i = \frac{t_{i-1} - t_i}{|t_{i-1} - t_i|},$$

and the unit normal vector

$$n_i = b_i \times t_i.$$  

The orthonormal triplet $((n_i, b_i, t_i))$ defines a discrete version of Frenet frames (8)–(10) at each position $r_i$ along the string.

In lieu of the curvature and torsion, we have the bond and torsion angles (see Fig. 4). The bond angles are

$$\kappa_i \equiv \kappa_{i+1,i} = \arccos(t_{i+1} \cdot t_i),$$

and the torsion angles are

$$\tau_i \equiv \tau_{i+1,i} = \text{sgn}(b_{i-1} \times b_i \cdot t_i) \arccos(b_{i+1} \cdot b_i).$$
When all these angles are known, we have the discrete Frenet equation

$$
\begin{pmatrix}
\mathbf{n}_{i+1} \\
\mathbf{b}_{i+1} \\
\mathbf{t}_{i+1}
\end{pmatrix}
\begin{pmatrix}
\cos \kappa \cos \tau & \cos \kappa \sin \tau & -\sin \kappa \\
-\sin \tau & \cos \tau & 0 \\
\sin \kappa \cos \tau & \sin \kappa \sin \tau & \cos \kappa
\end{pmatrix}
\begin{pmatrix}
\mathbf{n}_i \\
\mathbf{b}_i \\
\mathbf{t}_i
\end{pmatrix}.
$$

(58)

Using this, we obtain the frame at position $i+1$ from the frame at position $i$. After constructing all the frames, we obtain the entire string from

$$
\mathbf{r}_k = \sum_{i=0}^{k-1} |\mathbf{r}_{i+1} - \mathbf{r}_i| \cdot \mathbf{t}_i.
$$

(59)

Without loss of generality, we can set $\mathbf{r}_0 = 0$, choose $\mathbf{t}_0$ to point along the positive $z$ axis, and orient $\mathbf{t}_1$ to be in the $yz$ plane.

Relation (59) does not involve the vectors $\mathbf{n}_i$ and $\mathbf{b}_i$. In parallel with a continuous string, our discrete string remains intact under rotations of the zweibein $(\mathbf{n}_i, \mathbf{b}_i)$ around $\mathbf{t}_i$. Such a local $SO(2)$ rotation acts on the frames as

$$
\begin{pmatrix}
\mathbf{n}_i \\
\mathbf{b}_i \\
\mathbf{t}_i
\end{pmatrix}
\rightarrow
\begin{pmatrix}
\mathbf{n}_i \\
\mathbf{b}_i \\
\mathbf{t}_i
\end{pmatrix}
\begin{pmatrix}
\cos \Delta_i & \sin \Delta_i & 0 \\
-\sin \Delta_i & \cos \Delta_i & 0 \\
0 & 0 & 1
\end{pmatrix}
\begin{pmatrix}
\mathbf{n}_i \\
\mathbf{b}_i \\
\mathbf{t}_i
\end{pmatrix}.
$$

(60)

Here, $\Delta_i$ is the rotation angle at the vertex $i$, and we introduce $SO(3)$ generators (30). This yields the transformation of the bond and torsion angles (cf. (31), (32))

$$
\kappa_i T^2 \rightarrow e^{\Delta_i T^3} (\kappa_i T^2) e^{-\Delta_i T^3},
$$

$$
\tau_i \rightarrow \tau_i + \Delta_{i-1} - \Delta_i.
$$

(61)

(62)

Because the $\mathbf{t}_i$ remain intact under (60), this transformation of $(\kappa_i, \tau_i)$ has no effect on the discrete string geometry.

The a priori fundamental range of the bond angle is $\kappa_i \in [0, \pi]$, and the range for the torsion angle is $\tau_i \in [-\pi, \pi)$. We therefore identify $((\kappa_i, \tau_i))$ as the canonical latitude and longitude angles of a two-sphere.
In parallel with the continuous case, we find it useful to extend the range of \( \kappa_i \) into negative values \( \kappa_i \in [-\pi, \pi] \) (mod 2\( \pi \)). As in (50), we compensate for this twofold covering of \( \mathbb{S}^2 \) with the discrete \( \mathbb{Z}_2 \) symmetry,

\[
\tau_i \mapsto \tau_i - \pi, \quad \kappa_k \mapsto -\kappa_k \quad \text{for all } k \geq i. \tag{63}
\]

We note that this is a special case of (61) and (62) with

\[
\Delta_k = \begin{cases} 
\pi, & k \geq i + 1, \\
0, & k < i + 1.
\end{cases}
\]

### 13. Discretized energy

According to (58), the bond and torsion angles are the natural variables for constructing energy functions for discrete piecewise-linear strings. In analogy with the continuous case, the energy must be invariant under local \( \text{SO}(2) \) frame rotation (61), (62). We consider a generic energy function \( H(\kappa, \tau) \) that is \( \text{SO}(2) \) invariant. We assume \( H(\kappa, \tau) \) has an extremum with bond and torsion angle values \( \kappa_i = \kappa_{i0} \) and \( \tau_i = \tau_{i0} \). We introduce a (small) deformation

\[
\Delta \kappa_i = \kappa_i - \kappa_{i0}, \quad \Delta \tau_i = \tau_i - \tau_{i0}
\]

and expand the energy around the extremum,

\[
H(\kappa, \tau) = H(\kappa_{i0}, \tau_{i0}) + \sum_k \left\{ \frac{\partial H}{\partial \kappa_k} \Delta \kappa_k + \frac{\partial H}{\partial \tau_k} \Delta \tau_k \right\} + \
\sum_{k,l} \left\{ \frac{1}{2} \frac{\partial^2 H}{\partial \kappa_k \partial \kappa_l} \Delta \kappa_k \Delta \kappa_l + \frac{\partial^2 H}{\partial \kappa_k \partial \tau_l} \Delta \kappa_k \Delta \tau_l + \frac{1}{2} \frac{\partial^2 H}{\partial \tau_k \partial \tau_l} \Delta \tau_k \Delta \tau_l \right\} + O(\Delta^3). \tag{64}
\]

The first term evaluates the energy at the extremum. Because \((\kappa_{i0}, \tau_{i0})\) is an extremum, each term in the first sum vanishes. To proceed, we recall that the energy and hence its expansion (64) only depends on \( \kappa_i \) and \( \tau_i \) in an \( \text{SO}(2) \) gauge-invariant way. Accordingly, in the leading nontrivial order, the expansion should coincide with the discretized version of energy function (44). We rename \( \Delta \kappa \) and \( \Delta \tau \) as \( \kappa \) and \( \tau \), which we identify with the geometrically determined bond and torsion angles defined in Fig. 4. Following the steps from (3) to (5), we obtain

\[
H(\kappa, \tau) = \sum_{i=1}^{N-1} (\kappa_{i+1} - \kappa_i)^2 + \sum_{i=1}^{N} \left\{ \lambda (\kappa_i^2 - m^2)^2 + \frac{d}{2} \kappa_i^2 \tau_i^2 - bn \kappa_i \tau_i - a \tau_i + \frac{c}{2} \tau_i^2 \right\} \tag{65}
\]

up to an overall normalization factor (see [9], [10] for a detailed discussion of this equation). Because the arguments that lead to (65) are based entirely on general symmetry principles that are universally valid, result (65) is unique for small fluctuations around a given background. Energy (65) involves the complete set of gauge-invariant quantities in terms of the bond and torsion angles that arise in the leading order in a systematic Taylor expansion of the full energy around its local extremum.

The derivation of (65) utilizes only universal principles. It describes the structure and dynamics of any piecewise-linear polygonal string in the leading order of the fluctuations around a fixed background as an extremum of the free energy. In particular, in the case of proteins, any energy function that describes the dynamics at either the all-atom or the coarse-grained level must reproduce (65) in the appropriate small-fluctuation limit.

For a complete treatment of the Hamiltonian dynamics, the Poisson brackets of the variables \((\kappa_i, \tau_i)\) must be determined. The brackets that appear in the integrable discrete NLS (dNLS) hierarchy [18], [19] can be used.
14. Discretized solitons

Energy (65) is a variant of the energy that yields the dNLS equation [18], [19], [23]. The first term in (65) together with the \( \lambda \)- and \( d \)-dependent terms constitute the (naively) discretized Hamiltonian of the NLS model in the Hasimoto variables. The conventional dNLS equation is known to support solitons. We can try to find soliton solutions of (65).

As in (46), we first eliminate the torsion angle,

\[
\tau_i[\kappa] = \frac{a + b\kappa_i^2}{c + d\kappa_i^2} = \frac{1 + \hat{b}\kappa_i^2}{\hat{c} + d\kappa_i^2} \equiv a\hat{\tau}_i[\kappa].
\]  (66)

For the bond angles, we then have

\[
\kappa_{i+1} = 2\kappa_i - \kappa_{i-1} + \frac{dV[\kappa]}{d\kappa_i}\kappa_i, \quad i = 1, \ldots, N,
\]  (67)

where we set \( \kappa_0 = \kappa_{N+1} = 0 \) and \( V[\kappa] \) is given by (49). This equation is a deformation of the conventional dNLS equation; it is not a priori integrable. For a numerical solution, we convert (67) into the iterative equation [30], [31]

\[
\kappa_i^{(n+1)} = \kappa_i^{(n)} - \epsilon\{\kappa_i^{(n)}V'[\kappa_i^{(n)}] - (\kappa_{i+1}^{(n)} - 2\kappa_i^{(n)} + \kappa_{i-1}^{(n)})\}.
\]  (68)

Here, \( \{\kappa_i^{(n)}\}_{i\in\mathbb{N}} \) denotes the \( n \)th iteration of an initial configuration \( \{\kappa_i^{(0)}\}_{i\in\mathbb{N}} \), and \( \epsilon \) is some sufficiently small but otherwise arbitrary numerical constant; we often choose \( \epsilon = 0.01 \). The fixed point of (68) is clearly a solution of (67). Once the numerically constructed fixed point is available, we calculate the corresponding torsion angles from (66). We then obtain the frames from (58) and proceed to construct the discrete string by (59).

At the moment, we do not know an analytic expression for the soliton solution of Eq. (67). But we found [32]–[34] that an excellent approximate solution can be obtained by discretizing topological soliton (43):

\[
\kappa_i \approx \frac{m_1 e^{c_1(i-s)} - m_2 e^{-c_2(i-s)}}{e^{c_1(i-s)} + e^{-c_2(i-s)}},
\]  (69)

where \( c_1, c_2, m_1, m_2, \) and \( s \) are parameters. The \( m_1 \) and \( m_2 \) specify the asymptotic \( \kappa_i \)-values of the soliton. Hence, these parameters are entirely determined by the character of the regular, constant bond and torsion angle structures that are adjacent to the soliton; these parameters are specific not to the soliton itself but to the adjoining regular structures. The parameter \( s \) defines the location of the soliton along the string. This leaves only two loop-specific parameters, \( c_1 \) and \( c_2 \). These parameters quantify the length of the bond angle profile that describes the soliton.

For the torsion angle, Eq. (66) involves the single parameter \( a \), factored out as the overall relative scale between the bond angle and torsion angle contributions to the energy. There are then the three additional parameters \( b/a, c/a, \) and \( d/a \) in the remainder \( \hat{\tau}_i[\kappa] \). Two of these are again determined by the character of the regular structures that are adjacent to the soliton. As such, these parameters are not specific to the soliton. The remaining single parameter specifies the size of the regime where the torsion angle fluctuates.

Profile (69) is translation invariant. But translation invariance on a lattice is commonly broken by the Peierls–Nabarro barrier [35]. When the soliton moves along the backbone lattice, quasiparticle waves are emitted in its wake. These waves drain the kinetic energy of the soliton and cause a deceleration. Eventually, the soliton becomes pinned to a particular backbone site and is unable to translate.
After the soliton profile \((\kappa_i, \tau_i)\) is known, we construct the resulting discrete space string from (58) and (59). In the case of a protein backbone as shown in Figs. 3 and 4, where the vertices \(r_i\) coincide with the positions of the skeletal \(C_\alpha\) atoms, we use a fixed value in (59), \(|r_{i+1} - r_i| = 3.8 \text{ Å}\) for the distance between neighboring vertices. The only exception is \(\text{cis}\)-proline, in which case the distance \(2.8 \text{ Å}\) should be used; these are very rare. In our computations, we also impose the steric constraint, which prevents backbone self-crossing, in terms of the self-avoidance condition [36]

\[
|r_i - r_k| > 3.8 \text{ Å} \quad \text{for} \quad |i - k| \geq 2.
\]

On the regions adjacent to a soliton, we have constant values of \(\kappa_i\) and \(\tau_i\). In the case of a protein, these are the regions corresponding to the standard regular secondary structures. For example, the standard \(\alpha\)-helix is

\[
\kappa \approx \frac{\pi}{2}, \quad \tau \approx 1,
\]

and the standard \(\beta\)-strand is

\[
\kappa \approx 1, \quad \tau \approx \pi.
\]

Similarly, all the other familiar regular secondary structures such as 3/10 helices, left-handed helices, etc., are described by definite constant values of \(\kappa_i\) and \(\tau_i\). Protein loops are regions described by the soliton proper. The solitons interpolate between the regular structures; the values of \((\kappa_i, \tau_i)\) are variable along a protein loop.

Finally, in the case of a supersecondary structure, Eq. (65) should be properly interpreted as the internal Landau free energy above the background of a regular secondary structure with constant values of \(\kappa_i\) and \(\tau_i\).

15. Proteins and the Dirac problem of life

Proteins are delicate nanoscale machines. Like other high-precision machines, the way proteins function can be very sensitive to their conformation. The protein folding problem was originally posed some 50 years ago and has assumed various incarnations since then [37]–[39]. The problem endures as one of the most important unresolved problems in science; it aims to explain what life is. The Sampo\(^1\) would be a theoretical and computational framework that predicts the shape and describes the dynamics of a protein in its biological environment. The scale, complexity, and trophy of the endeavor are enormous. There are some 25 million protein sequences that have been identified through DNA sequencing, but only around 100 thousand structures have been experimentally determined so far [40]. Apparently, the average cost of a structure determination by x-ray crystallography is around $100,000, and crystallization of a protein can sometimes take years, if possible at all. We can hardly expect that the structures of a much larger percentage of sequences can ever be determined using the currently available experimental techniques. Therefore, the development of an accurate and reliable theoretical and computational approach is pivotal for our ability to understand proteins and to resolve the problem of life.

Moreover, a wrong fold is recognized as a common cause for a protein to loose its function. Misfolded proteins can be dangerous or even fatal to a biological organism. For example, neurodegenerative diseases (like Alzheimer’s and Parkinson’s), diabetes-II, and many forms of cancer are all caused by wrong folds in certain proteins. At the same time, the ability to elicit controlled protein misfolding might allow combatting viral diseases like HIV and coronaviruses (SARS) where no effective treatment presently exists. Controlled protein misfolding might eventually open the door for the development of a new generation

\(^1\)Sampo in Karelo-Finnish mythology is a unique miracle-object having magical powers and being a source of happiness, good luck, and abundance.
of molecular-level antibacterials to offset the emergence of resistance through evolutionary processes, which are rapidly rendering many existing antibiotics ineffective.

Clearly, there are very many, very good reasons to address the third Dirac problem.

16. Yearning for the speed of life

One goal of all-atom molecular dynamics (MD) is to provide an a priori description of protein folding and dynamics based on finely tuned force fields (like CHARMM [41] and AMBER [42]) that aspire to model all known (semi)classical interactions between all the atoms, both in the protein and in the surrounding solvent (water). The Newtonian equations of motion are introduced for each and every atom including solvent atoms. The equations are numerically integrated with a time step around a femtosecond, which is the characteristic time scale of peptide bond vibrations. Using purpose-built supercomputers like Anton [43], [44] and distributed computing projects as described in [45], the speediest MD simulations can reach a few microseconds of in vivo folding time in a day of numerical simulation [44]. This allows modeling relatively short, very fast-folding proteins such as the villin headpiece (HP35) and the λ-repressor protein 1LMB in the Protein Data Bank (PDB) [40] up to time scales that it takes for these proteins to fold.

But most proteins are considerably longer and fold during much longer times. For example, myoglobin, a protein described in all biochemistry textbooks, has 154 residues and folds in about 2.5 seconds [46]. Running at a top speed of a few microseconds per day, Anton should take more than 1,000 years to fold a myoglobin [44]. And Anton is by far the fastest special-purpose MD machine ever built. Accordingly, we need some $10^{11}$ orders of magnitude more in computer speed before MD simulations of proteins like myoglobin can occur at the speed of life, and this is if there is no compelling need to increase the number of involved atoms substantially. The development of processors with constantly increasing clock speeds has apparently stalled. Consequently, modeling protein dynamics over long time periods using all-atom MD at the speed of life seems unrealistic in the foreseeable future.

Moreover, it also seems that the presently available computers are incapable of handling sufficiently many individual atoms. Consequently, several essential all-atom ingredients still remain to be tackled by implicit and effective methods in lieu of all-atom MD. An important example is acidity in the case of explicit water. The proper level of acidity is pivotal to numerous biological processes. Even a slight shift in acidity sometimes leads to a major change in protein structure and function. A good example is amylin [47], a short polypeptide hormone that has been implicated in the onset of type-II diabetes. Much remains to be done to understand how amylin functions. Comprehensively mimicking its properties by computation requires performing simulations that model amylin both inside the β-cell granules of the pancreas, where pH ≈ 5.5, and in the extra-cellular domain, where pH ≈ 7.4 and where the disease-causing amyloidosis occurs, as well as in the passage through the cell membrane. The structure of amylin seems very different in the two different pH environments. For an all-atom simulation to tackle the difference, we suppose that $10^9$ explicit water molecules are introduced, which is four to five orders of magnitude more than what is currently possible, even with Anton. But this only allows a few tens of explicit hydronium ions to model the physiological pH ≈ 7.4 at the all-atom level. This hardly suffices. When it comes to acidity, today’s all-atom MD remains far from all atoms.

Summarizing, we dare to propose that some 15 orders of magnitude increase, or even more, in the speed of computer simulations is needed in all before a copious and accurate all-atom description of protein folding dynamics at the speed of life becomes a reality. This is an enormous number, obviously comparable to or even greater than the combined national debt of both the USA and the EU countries in rubles. From this standpoint, the protein folding problem seems doomed to endure among the preeminent unresolved conundrums in science for a long time to come. But this enormous gap between the speed of life and the available speed of computer modeling is also an excellent opportunity. There is a vast Every Man’s
available for the development of alternative computationally effective approaches. For this, various coarse-grained models are being developed. Contributions to the all-atom force fields that are presumed to be less relevant are systematically eliminated. A simplified geometry can also be used. For example, the UNRES [48] force field provides a very detailed and finely tuned coarse-grained potential energy with some 15 different terms in combination with a simplified geometry. Present coarse-graining can extend all-atom MD simulations by some four to five orders of magnitude. This considerable success of coarse-graining raises the question of what the truly relevant contributions to the free energy function are.

We note that there are also highly simplified approaches such as the model in [49] and its variants. In this model, the energy function is constructed from the knowledge of all atomic positions and native contacts in the studied protein. There are as many or even more parameters than there are atomic positions. These approaches consequently lack any predictive power for the native fold. But they can still be used, for example, to study how the folding might proceed.

In addition, there are several highly successful non-physics-based approaches to the protein folding problem. Structural classification schemes [50], [51] reveal that despite enormous diversity in the amino acid sequences, the number of different folds observed in PDB structures is quite small. This empirical observation forms the conceptual basis for new methods for predicting structure [52]. The basic idea is to use properly chosen fragments found among the protein conformations already deposited in the PDB database as modular building blocks very much like Lego bricks to construct a folded protein. These comparative methods currently have the best predictive power [53] for crystallographic folded protein structure. But the lack of a well-grounded energy function impedes their utility in investigating dynamical aspects such as the way in which folding occurs.

Finally, as what might seem a sign of desperation to some, we mention and recommend the online game Foldit (http://fold.it). The players help scientists discover and determine how a given protein might fold. The best players display an impressive ability and sometimes even beat scientific approaches.

17. Thermostats

The development of thermostats is among the theoretical issues where we believe important progress remains to be made [54]. The all-atom Newtonian equations of motion are integrated into MD, and the total energy is hence a conserved quantity. Consequently, MD describes a protein in a microcanonical ensemble. But this does not correspond to the situation in vivo. The biological environment of a protein is characterized by a constant temperature; the natural habitat of life in balance is in a canonical ensemble. The native state of a protein in (local) thermodynamic equilibrium with its environment corresponds to a local minimum of the Helmholtz free energy

\[ H = E - TS, \]

where \( E \) is the appropriate internal energy, \( T \) is temperature, and \( S \) is the entropy (we neglect the volume effect). We note that the entropic forces following from \( S \) are pivotal for protein collapse. To describe this in vivo environment, the Newtonian equations of the all-atom Hamiltonian must be modified to mimic a constant temperature setting. Diverse thermostats have been developed for this. They facilitate the MD simulation of protein folding, mostly under stationary nonequilibrium conditions. It remains a delicate challenge to construct a purely Hamiltonian thermostat that both models the canonical ensemble of the original system and allows a computationally effective discretizing for speedy and reliable simulations.

Realizing a thermostat often involves deforming the all-atom Newtonian equation into a Langevin equation. But such an equation is both nondeterministic and non-time-irreversible, and the original reason for considering a Hamiltonian framework is lost. Unfortunately, it appears impossible to construct a canonical
thermostat Hamiltonian that has both a finite number of thermostat variables and a nonsingular potential. The most widely used canonical thermostat in MD simulations of protein folding is perhaps the one by Nosé and Hoover [55, 56]. In its simplest variant, this thermostat has a Hamiltonian character, although it has a singularity. The all-atom phase space is extended by a single ghost particle with a logarithmically divergent potential; its role is to provide a temperature for all the other particles.

We consider the thermostatic extension of Hamiltonian (42)

\[ S = \int_{-\infty}^{\infty} dt \left\{ \frac{1}{2} q^2 \kappa_t^2 + V[\kappa] + \frac{1}{2} \dot{q}^2 + T \log q \right\}. \quad (74) \]

We assume that \( V[\kappa] \) has a double-well profile. If \( q(t) = 1 \), then \( S \) can be understood as the \( \kappa \)-dependent Euclidean action. The variable \( q \) is related to the Nosé–Hoover thermostat, and \( \kappa \) is the only common coordinate of the system with the thermostat.

Quantity (74) must be bounded, and the semiclassical amplitude of the coordinate \( \kappa \), necessary for passing through the potential barrier between two separate minimums of the potential \( V[\kappa] \), is therefore also bounded. It is interesting to learn how the thermostat \( q \) influences the amplitude of passing through the barrier. The equations of motion are

\[ q^2 \kappa_{tt} = V_\kappa - 2qq_t \kappa_t \simeq V_\kappa - \gamma \kappa_t, \quad (75) \]
\[ q\kappa_t = q^2 \kappa_t^2 + T. \quad (76) \]

We note how the coupling between \( \kappa \) and the thermostat variable \( q(t) \) yields an effective coefficient \( \gamma(t) \) similar to friction. In the absence of \( q \), we assume that (75) has a solution in the form of an instanton with a finite action, i.e., with a profile similar to (43). It is interesting to learn whether there exists an instanton with a finite action in the presence of a thermostat for Hamiltonian (74). Let

\[ \kappa(t) \xrightarrow{t \rightarrow \pm \infty} \kappa_\pm, \]

where \( \kappa_\pm \) are the values of \( \kappa \) on opposite sides of the potential barrier. For a finite action, we then obtain the Gibbs structure

\[ q(t) \xrightarrow{t \rightarrow \pm \infty} q_\pm = e^{-V[\kappa_\pm]/T}. \quad (77) \]

This indicates that \( T \) is like a temperature if it takes positive values. We integrate (76),

\[ \int_{-\infty}^{\infty} dt \left( q_t^2 + q^2 \kappa_t^2 \right) = - \int_{-\infty}^{\infty} dt \cdot T. \quad (78) \]

For finite (74), the integral in the left-hand side is finite. Because it is also nonnegative, the temperature \( T \), if it is indeed positive, must tend to zero. For a bounded value of \( S \), it is established that \( q(t) \) cannot be viewed as a variable that yields an equation of motion; it is merely a fixed background field with fixed profile and no dynamics. For an instanton to persist, any dynamical thermostat field \( q(t) \) must become entirely decoupled.

We conclude that realizing a thermostat must be done carefully. A hasty introduction of a thermostat can distort the unperturbed structure even to such an extent that a soliton-like configuration completely disappears. This would be a tragedy. We proceed to argue that topological solitons are the modular building blocks of folded proteins.
18. Solitons and proteins

Various taxonomy schemes such as CATH and SCOP [50], [51] reveal that folded proteins have a modular build. Novel topologies are rare, to the extent that some authors think most modular building blocks are already known [57], [58]. This convergence in protein architecture is a tangible indication that protein folding is driven by a universal structural self-organization principle.

We argue that a dNLS soliton is the principal driver. Indeed, it was shown that over 92% of all Cα traces of PDB proteins can be described by 200 different parameterizations of the discretized NLS kink (69) with better than 0.5 Å root-mean-square-distance (RMSD) precision [34]. Accordingly, we prepare to describe the modular building blocks of proteins in terms of various parameterizations of the dNLS soliton profile, which is described by Eqs. (68), (66), (58), and (59).

From the Cα coordinates of a given protein (available in the PDB), we compute the backbone bond and torsion angles. For this, we initially fix the \( \mathbb{Z}_2 \) gauge in (63) such that all the bond angles take positive values. A generic profile consists of a set of \( \kappa_i \), typically \( 1 \lesssim \kappa_i \lesssim \pi/2 \), and the upper bound is due to steric constraints. The torsion angle values \( \tau_i \) vary much more widely; they jump over the entire range from \( [-\pi,+\pi] \). As an example, we show the \((\kappa_i, \tau_i)\) spectrum in the case of the \( \lambda \)-repressor protein with the PDB code 1LMB in Fig. 5. The spectrum is fairly typical for a PDB configuration.

The Cα backbone of a protein is piecewise linear, and the spectrum of \((\kappa_i, \tau_i)\) is discrete. The general bifurcation analysis in Secs. 10 and 11 relates to a continuous string with a differentiable curvature and torsion. We therefore need an extension of the general results to the specific case of a piecewise-linear string. We continue to interpret a change in the sign of \( \tau_i \) in terms of a flattening point. This suggests that an inflection point perestroika has occurred. Accordingly, we implement a series of \( \mathbb{Z}_2 \) gauge transformations (63) in the vicinity of putative flattening points, where \( \tau_i \) changes sign or is otherwise unsettled, to identify the putative multisoliton profile in \( \kappa_i \). For example, in the 1LMB case, there are four regions with
The $Z_2$ gauge transformations of the bond angle $\kappa$ and torsion angle $\tau$ spectrum of the $\lambda$-repressor 1LMB; the indexing follows the PDB.

an irregular $\tau_i$ profile. By a judicious choice of $Z_2$ gauge transformations (see Fig. 6), we identify seven different solitons (69) in $\kappa_i$. Each soliton profile is clearly accompanied by a putative flattening points we note the multivaluedness of $\tau_i$. The general considerations in Secs. 10 and 11, although developed for continuous strings, are very much applicable for analyzing a generic discrete C$\alpha$ protein profile. We conclude that protein folding is due to inflection and flattening point perestroikas. These bifurcations deform the C$\alpha$ backbone and create dNLS solitons along it.

In the case of our example 1LMB, the seven $Z_2$ gauge-transformed soliton profiles define the background around which we perform expansion (64), (65). For this, we first tune the energy function to describe the background. In practice, we do the tuning by requiring that the fixed point of iterative equation (68) model the C$\alpha$ backbone as a dNLS multisoliton solution with a prescribed precision. We developed a program GaugeIT that implements the $Z_2$ gauge transformations to identify the background, and we developed a program PropoUI to tune the energy such that its extremum models the background as a multisoliton. These programs are described at http://www.folding-protein.org.

In the case of a protein for which the PDB structure is determined with an ultrahigh resolution, typically below 1.0 Å, PropoUI routinely constructs a multisoliton that describes the C$\alpha$ backbone with the experimental precision. The accuracy of a given experimental PDB structure can be estimated from the B-factors using the Debye–Waller formula, which relates the experimental B-factor to the one standard deviation fluctuation distance in the C$\alpha$ position,

$$\sqrt{\langle x^2 \rangle} \approx \sqrt{\frac{B}{8\pi^2}}.$$  (79)

The B-factors are available in the PDB. In Fig. 7, we compare the distance between the C$\alpha$ backbone, the dNLS soliton solution, and the B-factor fluctuation distance in the experimental structure for 1LMB. As shown in Fig. 7, the dNLS soliton describes the backbone with a precision that is fully comparable to the experimental uncertainties. The gray zone around the soliton profile denotes our best estimate for the extent
Fig. 7. The distance between the PDB backbone of the first 1LMB chain and its approximation by the seven-soliton solution: the black line denotes the distance between the soliton and the corresponding PDB configuration. The gray area around the black line describes our estimate of 15 picometer (essentially quantum mechanical) zero-point fluctuation distance around each soliton. The gray line denotes Debye–Waller fluctuation distance (79).

of quantum mechanical zero-point fluctuations. Analyzing available crystallographic PDB structures, we concluded that the quantum mechanical fluctuations in the positions of the C\textsubscript{α} atoms should not exceed 15 picometers. This estimate coincides with the historically used value for the wavelength boundary between x-rays and \(\gamma\)-rays.

Simulations performed using the UNRES force field so far support the idea that folded proteins display a soliton-driven structural self-organization. Furthermore, the cause of protein folding can be traced to a combination of inflection point and biflattening perestroikas, at least in the case of protein-A [59].
19. Folding at the speed of life

By construction, expression (65) for the energy is universal. It is the leading infrared contribution to expansion (64) of the full Helmholtz free energy (73) around a generic but predetermined extremum. Hence, (65) describes the energy landscape of a protein not only at the extremum but also in its vicinity. Expansion (65) can be used to explore the near-equilibrium dynamics, such as how the protein responds to temperature fluctuations and variations in other environmental parameters, acidity, and so on.

In particular, the present approach is designed to facilitate describing protein dynamics over biologically relevant time scales. It averages over all very rapid atomic-level oscillations, vibrations, and those tiny fluctuations and deformations in the positions of the individual atoms that are more or less irrelevant to how the folding progresses over time scales that are biologically important.

To describe the nonequilibrium dynamics, we adopt a Markovian Monte Carlo (MC) time evolution with the universal heat-bath probability distribution (Glauber dynamics) [60], [61]

$$\mathcal{P} = \frac{1}{1 + x}, \quad x = e^{\Delta E/kT}. \quad (80)$$

Here, $\Delta E$ is the energy difference between consecutive MC time steps, which we compute from (65). It can be proved [62], [63] that MC simulation with (80) approaches the Gibbsian distribution exponentially. The method should therefore provide a statistically meaningful description of near-equilibrium protein folding dynamics, at least during adiabatic temperature variations.

In our simulations of near-equilibrium proteins, we renormalize the numerical value of the temperature factor $kT$ such that it coincides with the experimentally observed $\theta$-point temperature [64]. We proceed as follows. We start by tuning (64) and (65) to describe a given, typically very low-temperature crystallographic protein configuration form the PDB as a multisoliton. For this, we use the program Propro (described in http://www.folding-protein.org). After the multisoliton is constructed, we subject it to extensive heating and cooling simulations. We start from a vanishingly low temperature value with no apparent thermal fluctuations in the $C_\alpha$ positions. We slowly increase the temperature until we observe a structural transition similar to a phase transition above which the configuration resembles a random walker. The transition identifies the renormalization point of the temperature factor; it occurs at the $\theta$-point temperature. A convenient order parameter for detecting the $\theta$-point is the $C_\alpha$-trace gyration radius [65], [66]

$$R_g^2 = \frac{1}{2N^2} \sum_{i,j} (r_i - r_j)^2 \sim \frac{N \to \infty}{R_0^2 N^{2\nu}}. \quad (81)$$

Here, $\nu$ is the compactness index, which governs the large-$N$ asymptotic form of Eq. (81), and $R_0$ is a form factor that characterizes the effective distance between the $C_\alpha$ atoms in the large-$N$ limit. The compactness index $\nu$ is a universal quantity, but the form factor $R_0$ is not. The form factor is in principle calculable from the atomic-level structure of the protein and the surrounding solvent.

As an example, in Fig. 8, we show how the $C_\alpha$ RMSD between the crystallographic X-ray myoglobin structure with PDB entry code 1ABS and its multisoliton description constructed using (64) and (65) evolves as we vary the temperature. In this simulation, we first heat the multisoliton. We thermalize it in the $\theta$-regime. We then cool it back to low temperatures where only a very small thermal motion persists.

Generally, in the case of proteins with a well-defined native state such as myoglobin and the $\lambda$-repressor (both previously used as examples), we recover the initial configuration with a very high RMSD precision as shown in Fig. 8. But this is not the case for a protein that is intrinsically disordered (amylin is an example described in Sec. 16). For an intrinsically disordered protein, we commonly find a complex conformational landscape in the low-temperature limit.
Fig. 8. The evolution of the RMSD between the myoglobin 1ABS backbone from the PDB entry and the simulated multisoliton configuration: the gray line is the average of 1000 simulations, and the surrounding shaded area describes fluctuations within one standard deviation. Along the top axis, we convert the temperature to the Kelvin scale using the renormalization procedure described in [67].

In the case of myoglobin, when we start from a random configuration above the $\theta$-point temperature, for example, 380K in Fig. 8, we reach the native state in over 99% of cooling simulations within 3.5 seconds using a single processor in MacBook Air. This can be contrasted with the experimentally measured in vivo folding time of 2.5 seconds [46]. It is quite possible to reach the speed of life with a currently available standard laptop (or even exceed it with a good workstation) by describing proteins as multisolitons.

20. Concluding remark

The formation of a protein is a complex physical phenomenon that involves a multitude of disparate temporal and spatial scales. In particular, there are many high-energy barriers that the protein must be able to overcome as it progresses from a random string towards the native fold. This obligates thousands of atoms to cooperate over quite long time periods such that complex collective multimolecular motions can occur and enable the conformation to cross the various steep hurdles and hindrances. These obstacles that come with varying scales and diverse structures pose major computational bottlenecks in any all-atom approach to the protein folding problem. A detailed MD simulation of the entire folding process therefore remains a formidable task. Nevertheless, in a seemingly paradoxical manner [68], proteins succeed in folding in the congestion of our cells very reliably and at quite a high speed.

Similar kinds of apparent paradoxes are encountered all over the physical world. Water quickly finds a way to self-organize into a wave, and a typhoon commonly emerges in the atmosphere. Each involves the collective cooperation of an enormous number of atomic-level constituents, far more than in a protein. Any attempt at an all-atom description would be preposterous. But in each case (as in numerous others), we have an exceedingly solid theoretical framework: the Korteweg–de Vries equation with its solitons in the...
first case and the vortices of the Navier–Stokes equation in the second. Why not try also using a similar approach to structural self-organization in the case of proteins?

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