Discrete Nonlinear Schrödinger Equation, Solitons and Organizing Principles for Protein Folding

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We introduce a novel generalization of the discrete nonlinear Schrödinger equation. It supports solitons that describe how proteins fold. As an example we scrutinize the villin headpiece HP35, an archetypal protein for testing both experimental and theoretical approaches to protein folding. Using explicit soliton profiles we construct its carbon backbone with an unprecedented accuracy.

The discrete nonlinear Schrödinger equation \( \text{DNLSE} \) is a prime example of a universal nonlinear equation. The equation originally appeared in connection of a study of polarons in molecular crystals \( \text{DNLSE} \). It supports both stationary and time dependent soliton solutions that were first introduced to describe Davydov solitons in proteins \( \text{DNLSE} \), then found applications to the crystalline state of acetonilide \( \text{DNLSE} \), and subsequently emerged in the study of optical waveguides and Bose-Einstein condensates \( \text{DNLSE} \). Today the discrete nonlinear Schrödinger equation together with its generalizations (DGNLS) form a very actively studied family of nonlinear equations that are widely employed to describe a multitude of phenomena in disparate physical, chemical and biological scenarios \( \text{DNLSE} \) - \( \text{DNLSE} \).

Here we introduce a novel generalization of the discrete nonlinear Schrödinger equation that governs the organizing principle for protein folding \( \text{DNLSE} \), arguably among the most important unresolved phenomena in modern science. Our version of the GDNLS equation stems from a discrete lattice model introduced in \( \text{DNLSE} \) to describe the statistical properties of folded chiral homopolymers. A recent Monte Carlo investigation \( \text{DNLSE} \) has suggested that this model might support soliton-like solutions, and furthermore that these solitons might accurately model the folded protein structures that are stored in the Protein Data Bank (PDB) \( \text{DNLSE} \). The goal of the present article is to adapt and develop the powerful exact and numerical techniques of GDNLS equations to address and resolve the organizing principles that underlie protein folding, whereupon a folded protein becomes very accurately described by a set of heteroclinic structures that are stored in the Protein Data Bank (PDB) \( \text{DNLSE} \).

Our GDNLS equation for protein folding originates from the following energy functional \( \text{DNLSE} \).

\[
E = -\sum_{i=1}^{N-1} 2\kappa_{i+1}\kappa_i + \sum_{i=1}^{N} \left\{ 2\kappa_i^2 + c \cdot (\kappa_i^2 - m^2)^2 \right\} + \sum_{i=1}^{N} \left\{ b\kappa_i^2\tau_i^2 + d\tau_i + e\tau_i^2 + q\kappa_i^2\tau_i \right\}
\]

\( \text{DNLSE} \)

We take \( \kappa_i \) to be periodic, \( \kappa_i \in [-\pi, \pi] \mod(2\pi) \). It is our primary variable and subject to both local and nearest-neighbor interactions. In applications to protein folding we identify \( \kappa_i \) with the discrete signed Frenet curvature of the protein backbone, at the position of the \( i \text{th} \) \( C\alpha \) carbon. The variable \( \tau_i \in [-\pi, \pi] \mod(2\pi) \) is a periodic auxiliary variable and only subject to local interactions, it describes the discrete Frenet torsion at the site \( i \) of the protein backbone. Finally, \( (b, c, d, e, m, q) \) are global parameters, they are specific to a given secondary superstructure.

Our GDNLS equation emerges as follows: We first eliminate the auxiliary variable by varying the energy functional with respect to \( \tau_i \). This gives us an equation of motion to resolve for \( \tau_i \) in terms of \( \kappa_i \),

\[
\frac{\partial E}{\partial \tau_i} = 2b\kappa_i^2\tau_i + 2c\tau_i + d + q\kappa_i^2 = 0
\]

\( \Rightarrow \quad \tau_i[\kappa_i] = -\frac{1}{2}\frac{d + q\kappa_i^2}{c + b\kappa_i^2} \quad \text{DNLSE} \)

We then perform a variation of the energy functional with respect to \( \kappa_i \), and substitute \( \tau_i[\kappa_i] \) from \( \text{DNLSE} \) into the ensuing equation of motion to arrive at our GNLS equation

\[
\kappa_{i+1} - 2\kappa_i + \kappa_{i-1} = U'[\kappa_i][\kappa_i] \equiv \frac{dU[\kappa_i]}{d\kappa_i^2} \quad \kappa_i \quad (i = 1, \ldots, N)
\]

\( \text{DNLSE} \)
(with $\kappa_0 = \kappa_{N+1} = 0$.) This equation determines the stationary points of the following GDNLS Hamiltonian

$$H = -2 \sum_{i=1}^{N-1} \kappa_{i+1}\kappa_i + \sum_{i=1}^N \left\{ 2\kappa_i^2 + U[\kappa_i] \right\}$$

where the potential has the following functional form

$$U[\kappa] = -\left( \frac{bd-\epsilon q}{2b} \right)^2 - \frac{1}{e+br^2} - \left( \frac{q^2+8bcm^2}{4b} \right) \kappa^2 + c \cdot \kappa^4$$

Here the second and the third term are familiar in the context of the nonlinear Schrödinger equation \[1\]-\[6\]. But the first term appears to be novel in the present context, it resembles the potential term for the relative coordinate in the nonlinear Schrödinger equation \[1\]-\[6\].

As an example we here scrutinize the dark two-soliton that models the chicken villin headpiece subdomain HP35. We follow \[12\] to solve (3) iteratively by locating a fixed point of

$$\kappa_i^{(n+1)} = \kappa_i^{(n)} - \epsilon \left\{ \kappa_i^{(n)} U[\kappa_i^{(n)}] - (\kappa_{i+1}^{(n)} - 2\kappa_i^{(n)} + \kappa_{i-1}^{(n)}) \right\}$$

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. It is obvious that a fixed point of (4) satisfies the GDNLS equation (3).

In our simulations we start from an initial configuration $\{\kappa_i^{(0)}\}_{i\in\mathbb{N}}$ chosen to have the same overall topology as the desired dark multi-soliton solution. We take $\kappa_i^{(0)}$ to have the profile of a piecewise constant step-function, the constant values approximate the true potential minimum. They correspond to the $\alpha$-helices and $\beta$-strands in the protein backbone. There is a step with a change of sign in $\kappa_i^{(0)}$ at each lattice site $i = N_a$ where a backbone loop is centered. Notice that as it stands, the energy functional (1) has the $\kappa \leftrightarrow -\kappa$ reflection symmetry that may not be exactly realized by the desired dark soliton profiles - the $\alpha$ helices are not ideal, and there are proteins where a loop connects an $\alpha$-helix with a $\beta$-sheet. Thus we explicitly break this symmetry using the parameter $m$, and for this we set

$$m \to m_a \text{ for } N_{a-1} \leq i \leq N_a$$

along the chain. Typical values for $m_a$ are $m_a \approx \pm \pi/2$ for $\alpha$-helix, and $m_a \approx \pm 1$ for $\beta$-strand.

We have performed extensive numerical investigations of the dark soliton solutions to (1). We have found that for proper values of the parameters these solitons can be combined into multi-solitons that together with (2) give a very high accuracy approximation of various folded protein structures that are stored in the Protein Data Bank \[10\], with the $\alpha$-helices and $\beta$-strands as the ground states and interpolated by dark solitons that describe the protein loops.

As an example we here scrutinize the dark two-soliton that models the chicken villin headpiece subdomain HP35 (PDB code 1YRF), a naturally existing 35-residue protein that has three $\alpha$-helices separated from each other by two loops. The structure of HP35 is very robust and since the protein is also a very fast folder, the folding time is around 4ps, together with the engineered version (2F4K in PDB) and the very similar HP36 (1VII in PDB), the HP35 has become the subject to very extensive studies both experimentally \[13\]-\[16\] and theoretically \[17\]-\[20\]. Indeed, HP35 is now a paradigm platform for testing approaches to protein folding.

According to \[14\], the root mean square distance (RMSD) between the NMR spectroscopy and the x-ray crystallography structures of HP35 is around 1.3 Å for the $C_{\alpha}$ carbons. The overall resolution of the presumably more accurate x-ray data is 1.07 Å \[15\].

The authors of \[17\]-\[20\] report on the construction of native and near-native folds using various methods and with both explicit and implicit water. For example the proposed native fold in \[19\] deviates in average around 1.63 Å in $C_{\alpha}$ RMSD from the x-ray data \[15\] for the sites 2-34 (counting from the N-terminus). The article also describes a single
trajectory that reaches a value of 0.39 Å in RMSD i.e. a distance that is about half the radius of a single carbon atom [sic]. The authors of [20] report very similar results, with a proposed native fold average Cα RMSD around 1.54 - 1.65 Å for the sites 2-34. They also report on a single trajectory that reaches Cα RMSD value 0.55 Å.

We shall now explain how the dark solitons of (4) quite effortlessly enable us to construct a backbone with 0.74 Å RMSD accuracy for the Cα carbons, for the sites 3-33 (counting from the N-terminus); The reason we do not consider the entire chain is that in order to compute the local curvature from the three dimensional space coordinates we need to know the coordinates of three adjacent Cα carbons, and for the computation of local torsion we need four.

We convert the PDB data for the Cα carbons to the local curvature and torsion. The result is shown in Figure 1. From the κi profile we conclude that the Cα backbone of 1YRF consists of two dark solitons. These correspond to the two loops of 1YRF and are located around the sites 49-53 (PDB indexing) and 58-62 in Figure 1, respectively. These solitons interpolate between ground states that correspond to the three α-helices of 1YRF. The first helix is located between the sites 42-49, the second between the loops around sites 53-58 and the third occupies the remaining sites starting from 62 in Figure 1. While the two soliton profiles \{κi\} are clearly identifiable, the profile of \{τi\} is substantially less regular and a priori one may expect that the strong irregularity in \{τi\} reflects the amino acid differences in the side chains. However, we find that this is not the case. The \{τi\} profile can be computed very accurately from (2) in terms of the soliton profile κi, the apparent irregularity reflects solely the \text{mod}(2\pi) multivalued character of a periodic variable.

To construct the soliton profile we introduce for each of the two would-be solitons the parameters (b, c, d, e, m, q): There is one set of parameters for the sites i=3-13 (counting from N terminus) and another set of parameters for the remaining sites. We construct the ensuing soliton solution of (3) by iterating (4) to a fixed point, starting from the initial profile which is a step-function located at the solitons. We compute the RMSD between the fixed point and 1YRF. We then change the parameters randomly and compute the new soliton profile, always starting from the same piecewise constant initial profile for the κi(0). We compute its RMSD to 1YRF with that obtained for the first set of initial parameters using the standard Metropolis algorithm devised to minimize RMSD. By repeating these steps in combination with simulated annealing we eventually produce our final soliton solution. The construction of a folded structure takes about 10 hours using a single processor in a MacPro desktop computer.

Figure 2 compares our minimal RMSD two-soliton configuration with the 1YRF backbone constructed from the x-ray data, for the sites i=3-33. The RMSD between the two configurations is 0.74 Å, well below the overall resolution of the x-ray data (which is 1.07 Å). Consequently our dark soliton pair describes the native 1YRF backbone for all practical purposes, and with an accuracy comparable to that of the radius 0.70 Å of a carbon atom. In Table 1 we provide the parameter values for this configuration, together with the parameter values for the best individual solitons we have found for the two loops. It is visible from the data that for values of κ away from κ ≈ 0 the potential energy is indeed strongly dominated by the double well contribution i.e. second term in (1), as we have expected.

We have found that folded proteins can be described by dark soliton solutions of a generalized discrete nonlinear Schrödinger equation. This equation involves only global parameters specific to a secondary superstructure, and the final protein configuration is determined by a single function. In the particular case of 1YRF where there are several high precision results to compare with, we have constructed a two-soliton configuration that describes the native backbone with an atomary level accuracy which is around one Ångström less than the present consensus value.
FIG. 2: Comparison between 1YRF backbone (red) and a soliton solution of (1) (blue). The RMSD distance is 0.74 Å.

| parameter | $b$     | $c$     | $d$     | $e$     | $q$     | $m_1$   | $m_2$   |
|-----------|---------|---------|---------|---------|---------|---------|---------|
| 1$^{st}$ set | -0.000646646 | 0.227432 | 0.0141014 | 0.00162415 | -0.0051673 | 1.68028 | 1.68844 |
| 2$^{nd}$ set | -0.0001126726 | 0.418995 | 0.000670547 | 0.00025209 | -0.000318858 | 1.69553 | 1.53529 |
| soliton-1 | -0.000516175 | 0.662187 | 0.0081804 | 0.00110988 | -0.00356352 | 1.48643 | 1.48167 |
| soliton-2 | -0.0000443408 | 0.577717 | 0.000294502 | 0.0000936295 | -0.000132267 | 1.53816 | 1.54597 |

TABLE I: The parameter values for the two-soliton solution that describes the entire 1YRF protein with accuracy 0.74 Å, for its first (1$^{st}$) loop (sites 2-13) and second (2$^{nd}$) loop (sites 14-33). We also present the parameter values for a dark soliton (soliton-1) that describes the first loop with accuracy 0.76 Å, and the corresponding values for a dark soliton (soliton-2) that describes the second loop with accuracy 0.58 Å.

obtained in molecular dynamics simulations. Among our future challenges is the enumeration and modeling of the different secondary superstructures in PDB and to develop a soliton basis for protein structure prediction. Indeed, we find it remarkable that in our construction we assume nothing about the details of the amino acid sequence, we only describe a homogeneous $C_\alpha$ backbone. Thus it is very unlikely that the common point of view that folding is mainly driven by side-chain interactions can be the full explanation. Instead, our results suggest the presence of a strong contribution from backbone hydrogen bonding [21], [22]. The detailed amino acid structure then breaks the translation invariance along an otherwise homogeneous chain, and amino acids in particular structural disruptor proline determine the location and the size of the loops a.k.a. dark solitons. In this manner the folding geometry is dictated by genome.

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