

## Knotting and linking in macromolecules

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### ABSTRACT

In the 1980's, knotting in DNA became a fundamental research dimension in the study of the mechanisms by which enzymes act on it. Later, the first compelling identification of knotting in proteins, in 2000, launched the study of knotting in protein structures, and linear macromolecules more generally, following on theoretical efforts of the 1960's. The linking occurring in structures such as DNA, with the articulation of the relationship between linking, twisting, and writhe, and, more directly, linking in Olympic gels has been of interest to geometers, molecular biologists, and polymer physicists since the 1960's. More recently, a new mathematical analysis of both global and local facets of knotting and linking is providing promising discoveries. Following a discussion of the topological structures of knotting and linking, we will consider some of their applications, and close with a consideration of new questions that suggest attractive directions for future research.

### 1. Introduction

In the 1960's, Edwards [24] undertook a theoretical study of the effects of knotting on the properties of polymer gels, but it was not until 1981 that Liu and David [39] demonstrated the presence of a knot in DNA in the lab. This discovery launched an ongoing theoretical and experimental research effort to understand the occurrence and character of these DNA knots and to employ them to discover the mechanisms through which enzymes act on DNA in vivo [25, 36, 67, 75, 76]. Buck [7] gives a very helpful introduction to this direction of research. It was not until 2000 that Taylor [70] identified the first deep knots in protein structures, thereby launching another thread in the application of topology to biology. Assessing the presence of knotting and linking in proteins has provided an ongoing stream of theoretical and experimental research into the functional role such structures might play in living organisms. The objective of this report is to describe key facets of knotting and linking in polymeric systems and in protein structures. As these are usually linear macromolecules, we describe one approach to identifying knotting in such structures [51] as well as applications of refinements of this method [32, 48, 66, 65, 68].

Historically, the first published consideration of knots appears to be due to Vandermonde [62] but Gauss is recognized for initiating the mathematical study of knots in his notes, Fig. 1. In the 1870's [26], he gave an integral, Eq. 1, that captures the integer linking between two oriented rings. This integral can be employed to define a real number

quantifying the extent of linking between two oriented spatial arcs, such as those in Fig. 1, or the self-linking of a single arc, for example the open chains in models of proteins or of filamental systems that employ periodic boundary conditions (PBC) such as polymer melts [5, 54, 56, 58, 63]. These enable one to define periodic linking and periodic self-linking numbers that quantify the linking between pairs of filaments, either open or closed, and, thereby, define the periodic linking matrix. Here, we will describe an application to Olympic gels [4, 17, 31], see Fig. 2, an application to the local linking in mathematical knots, and its extension to proteins. Finally, we will also briefly discuss the analysis of linking in proteins when cysteine bridges are added to the structure.

In the next section we give an introduction to knots [1] and the study of knots and slipknots in open polymers, such as proteins, by employing the knotting fingerprint [30, 32, 66, 65, 68]. Next, we discuss the Gauss linking [26] and self-linking numbers, one-dimensional periodic boundary condition models, the extension to periodic linking and self-linking, and the definition of the periodic linking matrix whose eigenvalues quantify the extent of entanglement in the systems to which they are applied [56, 58]. These are applied to the analysis of Olympic gels [4, 17, 31]. In another direction, the local linking number and linking fingerprint is described and applied to classical knots, to illustrate its implications, and to proteins. In the third section, we will briefly describe the application of linking to lassos and their extensions occurring in proteins when cysteine bridges enrich the structural analysis.

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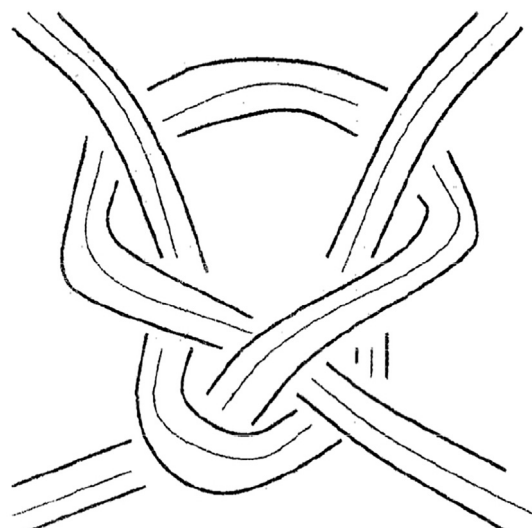


Fig. 1. One of Gauss' 1797 knot drawings [62].

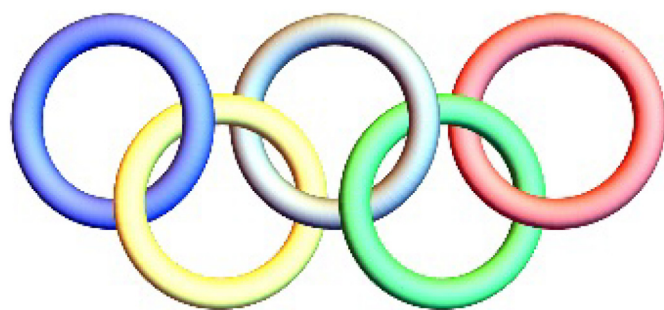


Fig. 2. Olympic gels are collections of simply linked ring polymers [17].

## 2. Knots, slipknots, and knotting fingerprints

### 2.1. Mathematical knots

While, for thousands of years, humans have employed knotting and entanglement of materials and, later, in their artistic representations, it is not until the time of Gauss and, later, Kelvin that the mathematical study of knots was systematically undertaken in the context of electromagnetism and as proposed models of atoms. Knots are closed rings in space with two knots being equivalent if one can be deformed to the other without breaks or singularities in the evolution. Although Gauss provided a method to symbolically codify knots, i.e. the Gauss code, it was the later purpose that gave rise to the first efforts by William Thomson (Lord Kelvin) to classify knots and links by formulating a study of indivisible, or prime, knots and links [71], see Fig. 3. The mathematical study of knots developed steadily as a subfield of topology with connections to geometry. The topology and geometry of knots are the areas most relevant to the mathematical analysis of polymer gels, DNA, proteins, and other macromolecules. Important features of this knot theory, for our purposes, are the decomposition of a knot into indecomposable subknots via the “connected sum,” as illustrated in Fig. 3 where the two upper left knots are prime, a right trefoil and a seven-crossing knot, while the upper right knot is the composition of two three-crossing knots, a left and a right trefoil. Note that, below them, is a two component link and a three component link, the latter being known as the Borromean rings. The indecomposable, i.e. prime, knots through sixteen crossings have been classified [29]: there are 1, 701, 936, only the simpler ones are most often encountered. They are currently identified using “knot polynomials” such as Alexander, Jones, or HOMFLYPT or their convenient evaluations [2, 33, 37]. We

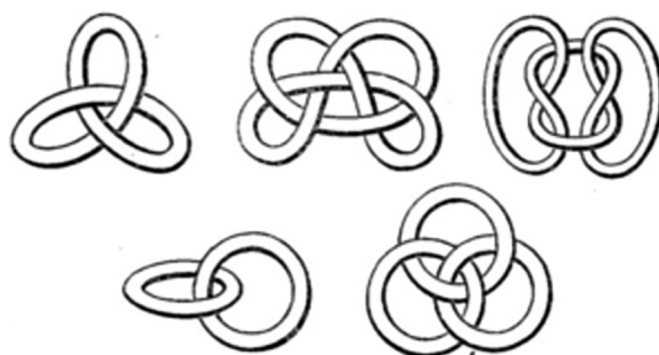


Fig. 3. Knots and links from Kelvin's “On vortex motion” [71].

note that there are more powerful and more complex methods now available.

### 2.2. Knots and slipknots in arcs

The fundamental challenge in defining the knot type associated to an open arc in 3-space is to translate the question into the case of an associated 3-space closed curve. One approach, see [23], is to define a closure using points on a very large sphere containing the finite chain and add segments from the two endpoints of the arc to the chosen point on the sphere. This defines a knot type for almost all points, the exceptions being a set of measure zero on the sphere. The designation is locally constant allowing to estimate the area of the regions on the sphere associated to each knot type using, for example, the HOMFLYPT polynomial. Since there are only finitely many possible types, one is able to determine the proportion of the sphere associated to each knot type, i.e. the knotting spectrum of the arc, and to associate the dominant knot type to arc, Fig. 4. This provides a powerful method in that it almost always successfully identifies a specific knot type, even for random walks, [53]. One may modify this method to improve the computational speed, for example see [72].

Empowered with the ability to determine the knot type of an open arc, one is now in position to identify slipknots and their associated ephemeral knots as follows: an unknotted segment in an arc containing a knotted segment, the associated *ephemeral knot*, is called a *slipknot*, Fig. 5. Mathematicians have proved that the probability that a random arc or ring is knotted or contains a slipknot goes to one as the length of the arc or ring goes to infinity, [18, 22, 48, 60, 69].

## 3. Gauss linking, periodic boundary condition (pbc) models, periodic linking, and the periodic linking matrix

### 3.1. Gauss linking and self-linking

The linking number between two oriented chains,  $l_1$  and  $l_2$ , is defined using parameterizations of the chains,  $\gamma_1(t)$  and  $\gamma_2(s)$ , via the Gauss linking integral:

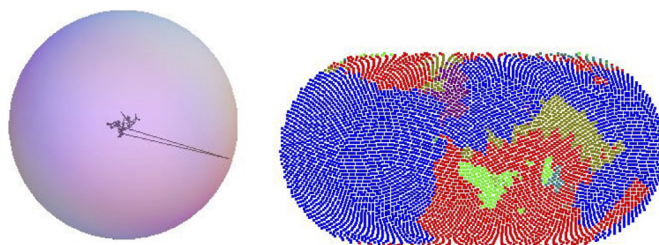


Fig. 4. Knotting in open arcs: one closure of an open arc and the distribution of knot types [23].

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