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Synthesising topological links

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Abstract We discuss the chemical synthesis of topological links, in particular higher order links which have the Brunnian property (namely that removal of any one component unlinks the entire system). Furthermore, we suggest how to obtain both two dimensional and three dimensional objects (surfaces and solids, respectively) which also have this Brunnian property.

Keywords Synthetic DNA topology of links · Brunnian links · Carpets and solids · Hopf links · Synthesizing double stranded DNA nodes

Mathematics Subject Classification 57M25

1 Introduction

In this paper we will give a detailed discussion of some of the ideas developed by the first two authors in [1], which again was based on [2–4]. We will here single out specific links which seem suitable for synthesis and present their topological structure in a way that may be useful in planning and performing the process of synthesis.

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2 Topological structures

Links are less studied than knots and not classified to the same extent. Therefore it is of interest to single out specific families which may be natural from a topological point of view. Lots of choices exist, but in [2] two general and interesting families were introduced, examples of which can be seen in Figs. 1 and 2.

2.1 The generating links

The Hopf family is based on the Hopf link, Fig. 3, from which one forms chains and then loops, as in Fig. 4.

Before discussing the Brunnian family we will give a definition of a characterising property of certain links, given in [2].

Definition A $B(n, k)$ link is a link in three dimensional space of n circular components with the property that any subset of k or fewer components are unlinked.
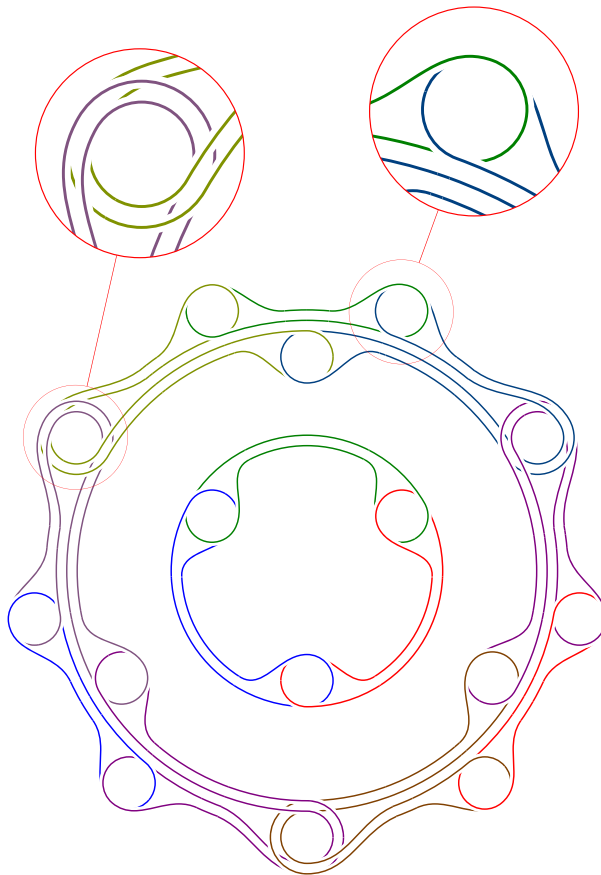

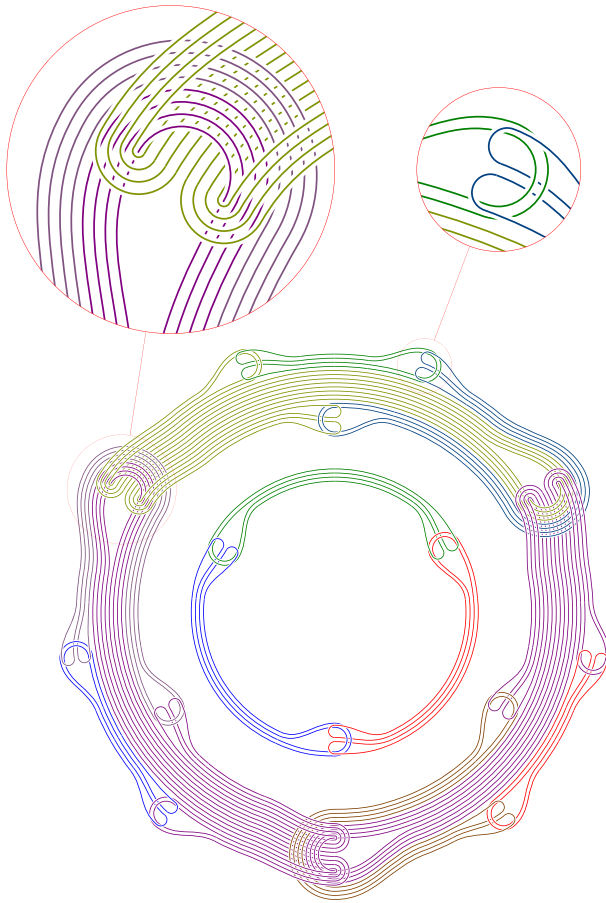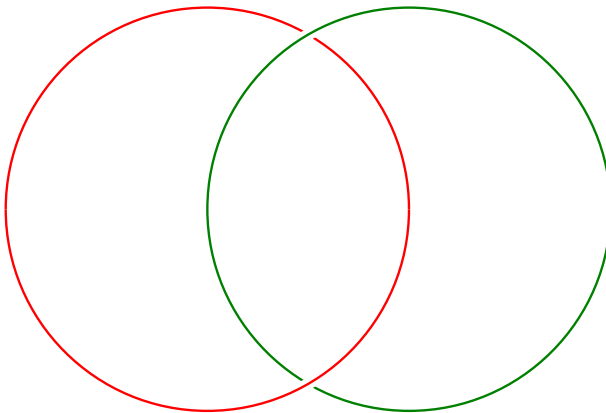**Fig. 1** The Hopf family

Fig. 2 The Brunnian family
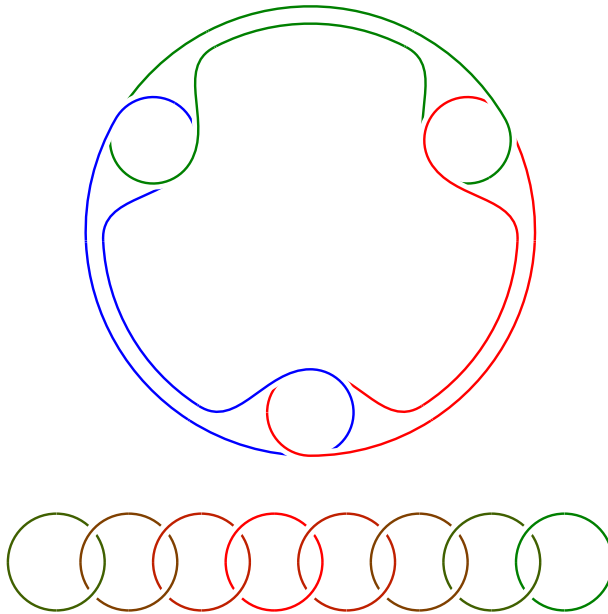

Fig. 3 The Hopf link

Fig. 4 Hopf links to Hopf chains

For clarity, let us state that for simplicity we consider our links to be unoriented.

Examples 1. Links of type $B(n, n-1)$ are classically known as *Brunnian* links as any proper subset of the components is unlinked but the link as a whole may be linked.
2. At the other end of the scale, any non-trivial link with n components is of type $B(n, 1)$.
3. We will refer to the next level up in the scale, namely $B(n, 2)$, as *Borromean* links. The Borromean rings are, of course, the primary example of this.

2.2 Higher order links

The idea of higher order links is straightforward. It consists in replacing the components of one link by a second link. These links are similar to satellite links for knots, in that they are componentwise satellites. For this work, the components of our links should be considered embedded in tori in such a way that they intersect any meridinal disc (often called framed). The two families identified in [2] are built in this way from particular sets of links.

In the Hopf family, the sets of links consist of the *Hopf rings*. A Hopf ring of length k consists of k components together with a cyclic order such that each component is Hopf linked to its neighbours, as in Fig. 5. In the Brunnian family, the linking method is the Brunnian linkage which is derived from a deformed version of the Borromean rings and is the core component of the so-called *Rubberband links* (see [5]). An example of a
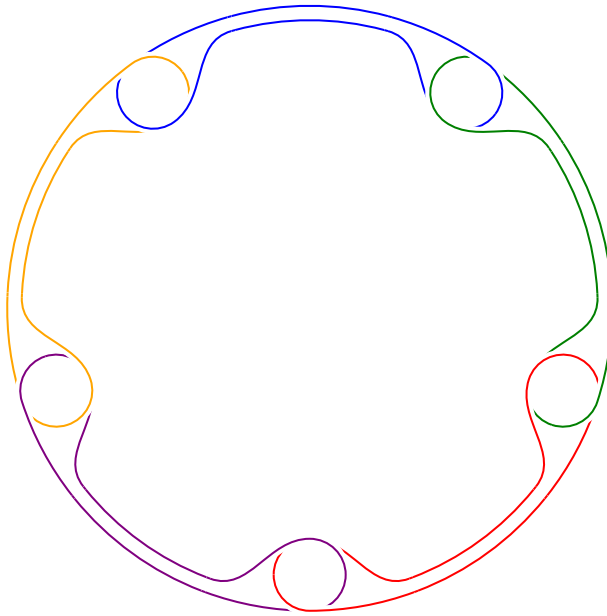
Fig. 5 A Hopf ring

Brunnian ring with four components is in Fig. 6. In Fig. 7 we show a three component Brunnian ring next to the Borromean rings which are related but not of this family (see [2] for commentary on the difference).

These two linkages, the Hopf and Brunnian, can also be used to form chains. In the Brunnian case, the chain needs additional components at the ends to prevent it unravelling. These are not of particular interest for higher order structures as they are not suitable for the iterative process.

Borromean rings also play a role in this article because they have been successfully synthesised, [6–8].

As pointed out in [1] we are especially interested in the synthesis of higher order links, and there are many alternatives. We propose to start with examples from the Hopf and Brunnian families.

3 Proposals

3.1 The Hopf-family

First make a chain of Hopf links of some length n, for example $n = 3$, and loop it up; see Fig. 8. Then take 3 such rings and form a second order Hopf ring, $2H(3, 3)$. Here we use the terminology of [2] wherein the outer number indicates the number of levels, the letter denotes the linking type (H for Hopf or B for Brunnian) and the numbers in the parentheses indicate the number of rings in each level in turn. This particular link is the outer link in Fig. 1. If this works well one may continue with $3H(3, 3, 3)$. When
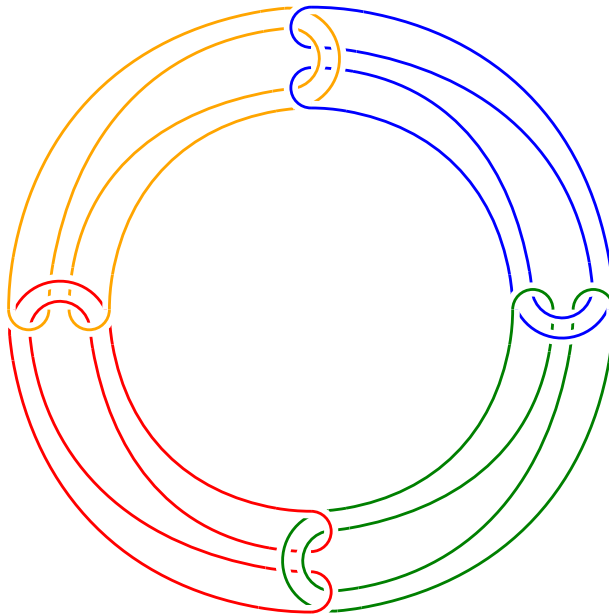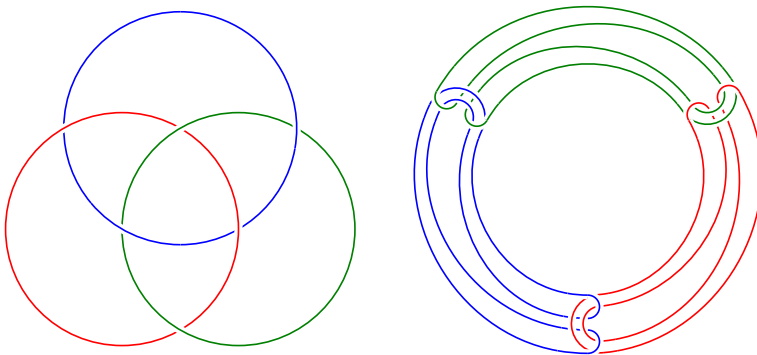
Fig. 6 A Brunnian ring

Fig. 7 The Borromean rings and the Brunnian ring of length 3

done, one may consider differences in chemical and physical properties, for example optical.

3.2 The Brunnian-family

The first report of Borromean ring synthesis used DNA as the component material, [6], but Brunnian rings have not so far been synthesised.

One should start with the synthesis of Brunnian chains, see Fig. 9, for example $n = 3$, and loop them up. This gives $1B(3)$ in our terminology. Take these
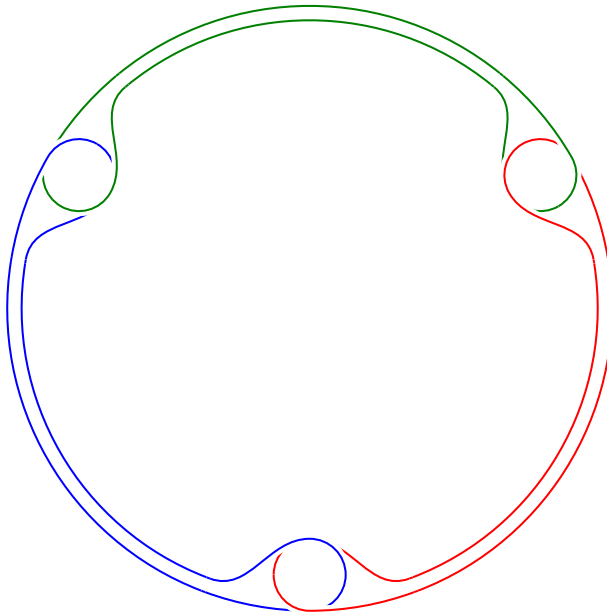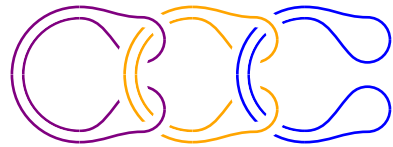
Fig. 8 First order Hopf ring of length 3

Fig. 9 Brunnian chain

$1B(3)$-rings and form a $2B(3, 3)$-ring as shown in the outer link in Fig. 2. Of course, one may also strive for $3B(3, 3, 3)$.

In the synthesising process one may have to consider more complicated versions of the chains with more crossings and twists, but still having the Brunnian property.

Finally, one should study material and topological properties, and look into possible relations. The topology is highly non-trivial. New physical and chemical properties would be of great interest like conductivity and optical properties. Conducting polymers may be used. The new materials constructed by using DNA and its derivatives may also be used as scaffolds for the construction of similar geometries of other polymers. Here the Brunnian property may come in when getting rid of the scaffold.

There are numerous properties that are likely to be a function of the topology of the molecules (e.g., H. K. Moffatt [9]) such as induced currents or magnetic fields. This is largely an unexplored area on the molecular scale. The work of Canary and Seeman [10] suggests ways to approach these phenomena on an experimental basis. Those authors have been approaching the control of polymer topology by means of ladder polymers based on DNA structures. They have focussed primarily on nylon and
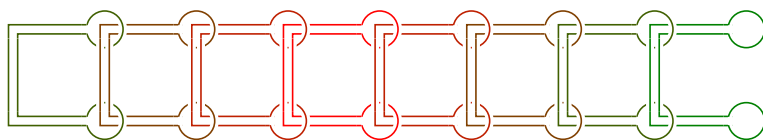
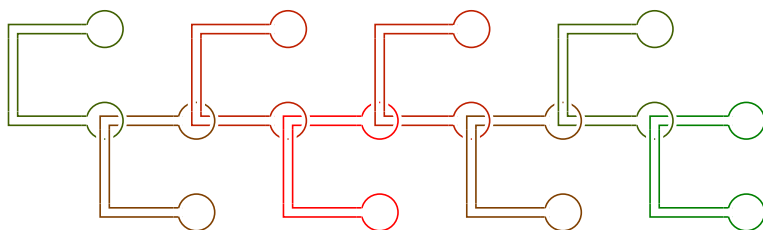**Fig. 10** Schematic Brunnian chain with eight components

Fig. 11 Schematic Brunnian chain with shifted components

polyethylene oxide, but conducting polymers are also likely to be amenable to their approach.

3.3 Brunnian surfaces

Consideration of the above families of links leads to some other structures that may be suitable for synthesis. These other structures that we would like to propose are not "higher order" links, but "higher dimensional" and were suggested by considering the Brunnian family.

Consider the (interior of the) Brunnian chain in Fig. 9. This particular rendering makes obvious how to extend the chain to an arbitrary number of components, and how to close it up into a ring as described in Sect. 3.2. We can render it more schematically by using straight lines in the components as in Fig. 10.

The basic shape in Fig. 10 is of a square. This redrawing brings to attention the "non-end" corners of the square. We can view these as the "opposite" corners of the corners that correspond to the doubling back loops. This suggests that we can consider moving the components providing that the basic rule is upheld: an "open end" must link round a "non-end". In particular, we can consider shifting alternate components vertically as in Fig. 11.

This now has a suggestion of 2-dimensionality to it. We can easily envision adding more vertical layers to produce a carpet effect as in Fig. 12.

As drawn, this is unlinked. We need a way to close off the link whilst keeping the exhibited structure. To do this, we impose the obvious rule. To state this rule, let us label the parts of a component: we have "open ends" (the circular parts) and "interior bends". The rule then is that every open end must go around an interior bend.

Closing the top and bottom edges of the segment in Fig. 12 is simple enough: we simply deform the edge components as in Fig. 13.
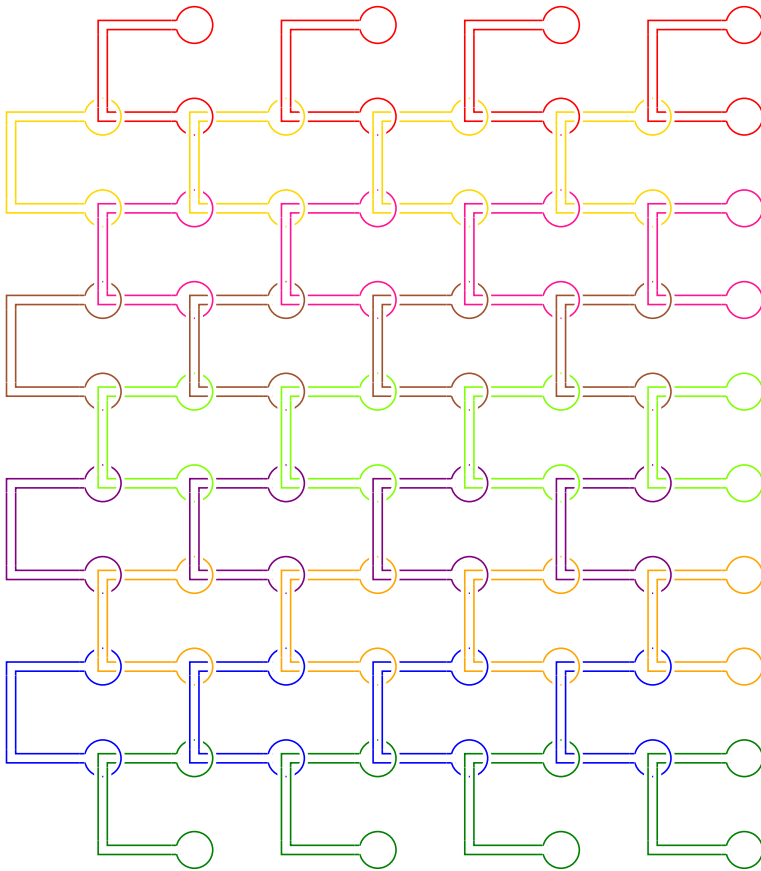
Fig. 12 Segment of a Brunnian carpet

The simplest method of closing the right and left edges is to realise the title of this section and make a *surface*. That is, we bring round the right edge and connect it to the left. This makes a tube.

We could have done this for the upper and lower edges as well to make a torus, however in so doing we would have had to make adjustments to take into account the curvature of a torus in 3-space. This echoes the standard construction of a torus from a square as shown in Fig. 14. Going further, we could build higher genus surfaces, or other surfaces such as a Möbius band or Klein bottle, using flexible links.

Rather than describe those adjustments for the case of a torus (which is somewhat tricky to draw), we prefer to describe them by showing a way to make a flat surface of finite extent that is closed. This we call the *Brunnian carpet* and it is shown in Fig. 15.

Figure 16 illustrates how Brunnian carpets can be fused together to create a more complex 3D topology which retains the Brunnian property, namely a Brunnian solid. Carpets are stacked and then, following [11], at some points where two strands are juxtaposed then a fused species is created. Application of this notion here entails fusing double strands, rather than single strands, but the result is the same. Care must be taken
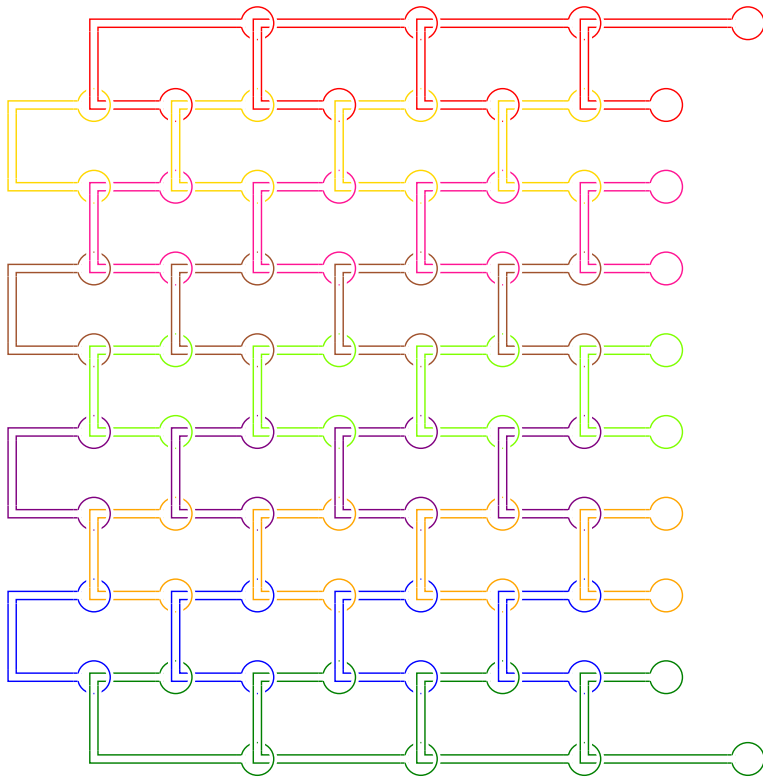
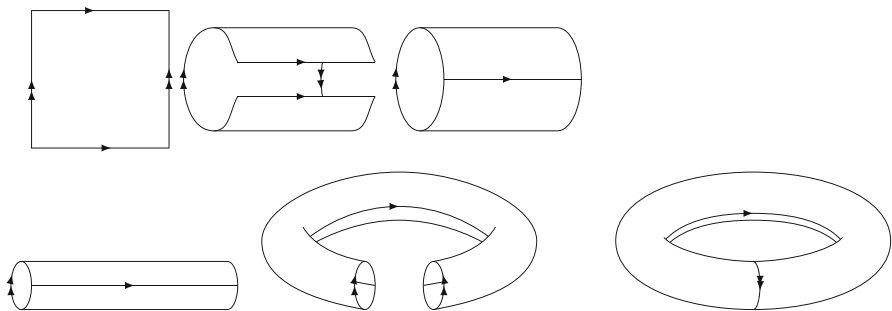**Fig. 13** Segment of a Brunnian carpet with closed running edges

Fig. 14 Building a torus from a square

to ensure that the resulting structure still retains the Brunnian property. In Fig. 16 the three layers are meant to form a stack of three carpets with certain components that are vertically aligned fused together.

Let us isolate the components used so far. We have the basic chain component, the left and right extensions, and the left and right corner pieces. These are shown in Fig. 17.
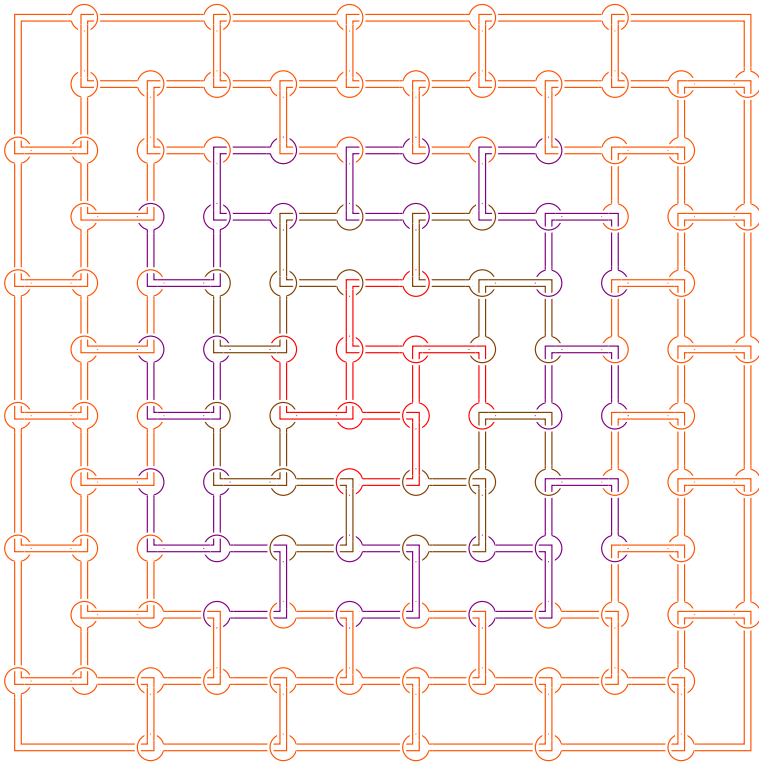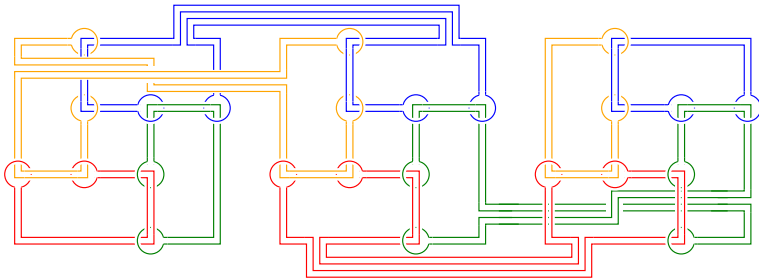
Fig. 15 A Brunnian carpet

Fig. 16 Layered carpets

There is another variant on these shapes which involves bending one or more of the legs into a third dimension. With four of these based on the basic chain type it is possible to make a cube as in Fig. 18 (with hopefully obvious condensation of complexity in the diagram). Clearly, we can further extend this to construct very general wireframe shapes where we build the shape out of zigzag wires subject to the constraint that the end points of each wire must connect to an interior kink on some wire (possibly the same wire). We could also impose the constraint that every wire must have a kink, and that every kink must be connected to the end point of some wire.
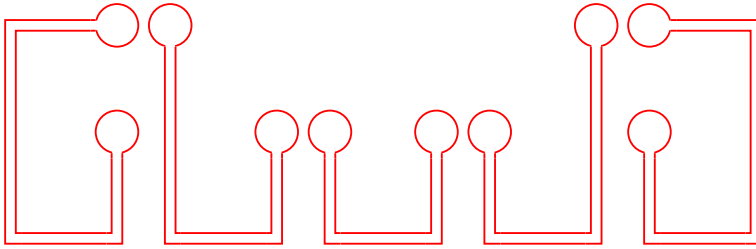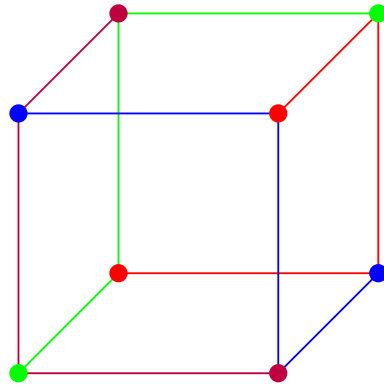
Fig. 17 The Brunnian surface components

Fig. 18 Brunnian cube of four components

However, at this stage we are introducing these shapes for possible synthesis and so introducing such complexity is further than we wish to go. Rather, let us focus on the key property that we want these shapes to have: that upon removing a single component the entire shape unlinks. For the Brunnian chain and ring this is evident as removing one component completely frees the neighbouring components and so the process continues until the entire structure is unlinked. For the surfaces this is no longer the case. What happens is illustrated in Fig. 19 where we begin by removing the upper-most light-green (online version) component (central along the top).

Removing this component releases the two components immediately below it. These are not unlinked, but one end of each is released. Once a component has at least one end released, the two components immediately below it also have an end released. Therefore the process continues.

This releasing spreads out, and on its edge then the components only have one end released and so are not unlinked. However, in the interior each component has both ends released and therefore becomes unlinked.

In Fig. 19 then components are marked corresponding to which end is released (starting with the removal of the initial component). The components marked with a single line only have one end released, but components marked with a cross have both.

It is important to note that there is a direction to this unlinking. The components *above* the original one are not affected by this process. Therefore for the entire structure to be unlinked the region that is falling apart must loop round in some fashion to bring all components under its sway. The tube described above accomplishes this in the
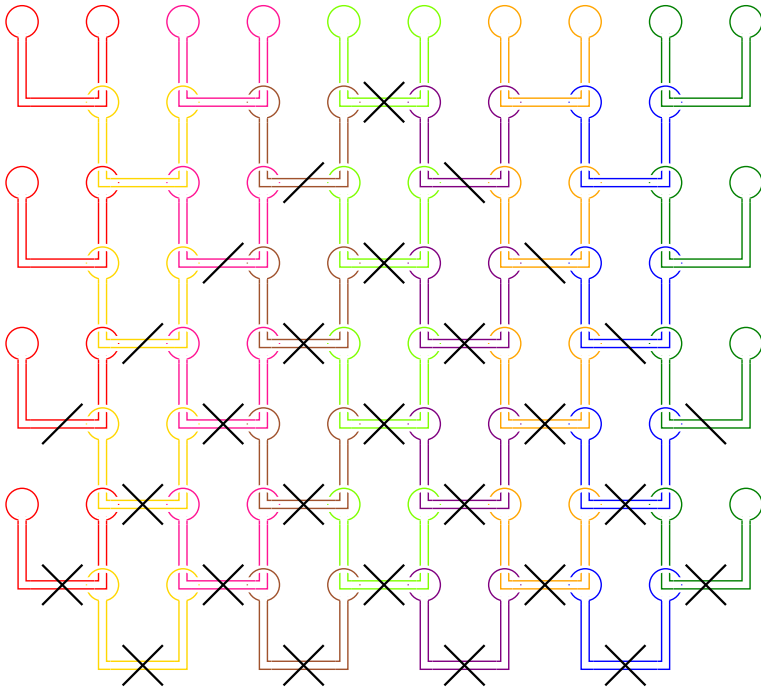
Fig. 19 Segment of a Brunnian carpet with unlinkings marked

obvious way. The carpet in Fig. 15 does so as the direction of unravelling rotates around the centre. However, an infinite carpet based on the layout in Fig. 12 would not have this Brunnian property. It is also possible to construct the tube (and thus the torus) in such a way that cutting one component does not fully unlink the structure. This is achieved by introducing a sufficiently large shift in the pattern when the tube is closed up so that the pattern spirals around the tube.

4 The design of double-stranded nucleic acid knots and links

A key feature of the systems that we have described here is that they can be reduced to practice in real systems containing polymers, so that they do not exist merely in the computer, or as pretty pictures. The possibility that polymers can form knots was pointed out by Frisch and Wasserman 50 years ago [12]. Designed molecular knots in polymers have been realized most successfully in DNA [13]. The reason for this is that a crossing in a single-stranded knot is easily constructed from a half-turn of double helical DNA [14], as illustrated in Fig. 20. The close relationship between knots and links [15] means that this notion can be extended readily to links, as well. Naturally occurring DNA contains chiral backbone elements [D-sugars], so that the well-known Watson–Crick B-DNA double helical structure [16] is right-handed, leading to negative nodes. A novel left-handed conformation of DNA, known as Z-DNA [17] leads to positive nodes, even though its sugars retain the same chirality. There is a limited
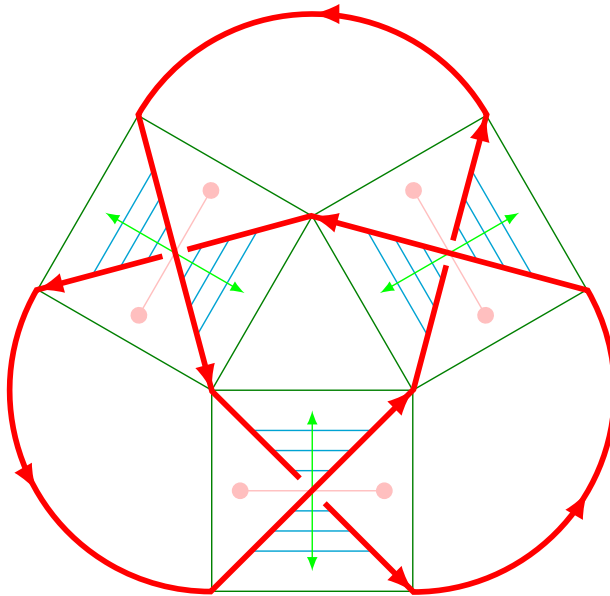
Fig. 20 The relationship between nodes and antiparallel B-DNA illustrated on a trefoil knot. A trefoil knot is drawn with negative nodes. The path is indicated by the *arrows* and the *very thick curved lines* connecting them. The nodes formed by the individual *arrows* are drawn at *right angles* to each other. Each pair of *arrows* forming a node defines a quadrilateral (a *square* in this figure), which is drawn in *dotted lines*. Each *square* is divided by the *arrows* into four of domains, two between *parallel arrows* and two between *antiparallel arrows*. The domains between *antiparallel arrows* contain lines that correspond to base pairing between antiparallel DNA (or RNA) strands. *Dotted double-arrowheaded* helix axes are shown perpendicular to these lines. The amount of DNA shown corresponds to about half a helical turn. It can be seen that three helical segments of this length could assemble to form a trefoil knot. The DNA shown could be in the form of a 3-arm DNA branched junction. A trefoil of the opposite sense would need to be made from Z-DNA, in order to generate positive nodes

set of sequences that are readily converted from B-DNA to Z-DNA. Nevertheless, the combination of B-DNA and Z-DNA components led to the construction of Borromean rings from conventional DNA molecules in 1997 [6].

Two recent developments have in principle enabled the extension of this sin-glestranded strategy to double stranded DNA. First, synthetic DNA components with chiralities opposite to those of natural DNA, i. e. components containing L-sugars, have become commercially available; consequently it has been simple to build a Solomon's knot and to prototype molecular weaving without the need to resort to the use of Z-DNA [18]. Secondly, a new four-stranded DNA motif has been discovered, known as PX-DNA [19]. It is shown in Fig. 21 to consist of two DNA duplexes that appear to wrap around each other. In fact, closer inspection shows that the duplexes actually exchange strands every other double-helical halfturn. Nevertheless, PX-DNA appears to provide a means for producing the same crossings in double helical DNA that double helices provide for single-stranded DNA. Note that the pitch of PX-DNA is roughly twice that of conventional DNA. The importance of the availability of DNA with the opposite chirality (containing L-sugars) is that no four-stranded equivalent of Z-DNA

Fig. 21 PX DNA. PX-DNA is drawn with strands of two colors, *red* and *dark blue*. The four strands form a structure with a central dyad axis (indicated by *green arrows*), and consisting of two double helical domains that are linked every half-turn. The double helical domains are indicated by *small black arrows* above and below them. Half-turns near the dyad axis corresponding to minor (narrow) groove spacings are indicated by '*N*' and half-turns corresponding to major (wide) groove spacings are indicated by '*W*'. The helical pitch consists of four of these half-turns. Each duplex contains a repeat of a *red–red* half turn above a *red–blue* half turn, below which is a *blue–blue* half-turn, and then a *blue–red* half turn, before the sequence repeats. Note that the central portion of the PX structure consists of a right-handed (negative) node. at each point (Color figure online)
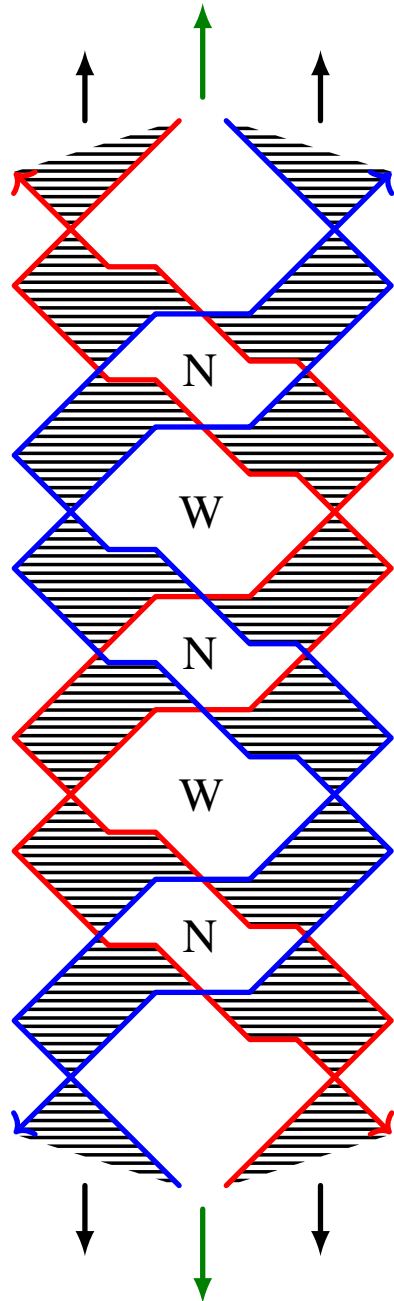
is known, so it is not otherwise obvious how to generate positive nodes from PX-like double crossings without using L-sugars.

In addition to synthetic issues that have impeded the application of DNA nanotechnology [20] to chemical topological construction in its most general senses, there have also been analytical problems, arguably more severe. The three DNA knots that have been most completely characterized have all been identified using biochemical techniques: Gel electrophoresis, ultracentrifugation and antibody binding [21,22]. Biochemical methods are adequate for differentiating the two enantiomers of trefoil (3_1) knots from each other, from the circle (0_1) and from the Fig. 8 (4_1) knot. However, biochemical techniques are insufficient for discriminating knot topoisomers (e. g., the three 6-noded knots) unambiguously, or for establishing various failure products or byproducts that may be encountered in the construction of complex links. Without doubt, the best way to characterize synthetic topological targets is to look at them.

Recent advances suggest that it may now be practical to apply imaging approaches to the characterization of topological targets. One of these is the advent of self-assembled DNA crystals containing large guest cavities [23]. These scaffold arrays may be used to organize guests for X-ray diffraction analysis [24], much as Fujita and his colleagues have done with MOFs [25]. Crystallization of topological targets is particularly chancy, unless they are as tight as possible, a tedious experimental determination [26]. The targets made from double helical DNA are likely to be much tighter than those made from single-strands. Current selfassembled crystals with cavities large enough to fit the targets do not diffract adequately to resolve single-strands, but are likely to diffract well enough to resolve double-stranded topological targets, where the 'strand' is 20 across. A second development, not yet completely tested, is high resolution holography using X-ray lasers [27,28]. One or the other of these techniques is likely soon to rescue synthetic DNA topology from the basin in which it has largely been stuck since the twentieth century.

5 Discussion

We have described exciting new topological systems above. One of their most exciting features is that it appears that they can be reduced to molecular reality. Small molecule knots and Borromean rings constituted chemical holy grails for much of the second half of the twentieth century, being synthesised only relatively recently [7,21]. By contrast, DNA and DNA-based polymers present a simplified set of synthons that can lead to the construction of complex topological targets [13], but on a somewhat larger size scale. The key impediment to implementing this approach lies not in the synthesis, but in the characterisation of the products. Nevertheless, the new developments noted above offer reasons for optimism in our ability to characterise the topological structures of these species within the coming decade.

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