Topology of prion proteins

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Abstract

A conformal structure of a prion protein is thought to cause a prion disease by S. B. Prusiner's theory. Knot theory in mathematics is useful in studying a topological difference of topological objects. In this article, concerning this conjecture, a topological model of prion proteins (PrP^C, PrP^{SC}) called a prion-tangle is introduced to discuss a question of whether or not the prion proteins are easily entangled by an approach from the mathematical knot theory. It is noted that any prion-string with trivial loop which is a topological model of a prion protein cannot be entangled topologically unless a certain restriction such as " Rotaxsane Property " is imposed on it. Nevertheless, it is shown that any two split prion-tangles can be changed by a one-crossing change into a non-split prion-tangle with the given prion-tangles contained while some attentions are paid to the loop systems. The proof is made by a mathematical argument on knot theory of spatial graphs. This means that the question above is answered affirmatively in this topological model of prion-tangles. Next, a question of what is the simplest topological situation of the non-split prion-tangles is considered. By a mathematical argument, it is determined for every $n > 1$ that the minimal crossing number of n-string non-split prion-tangles is $2n$ or $2n - 2$, respectively, according to whether or not the assumption that the loop system is a trivial link is counted.

Keywords: Topological model, Prion protein, Prion-string, Prion-tangle, Spatial graph, Prion-bouquet, Unknotting number

1. Introduction

A conformal structure of a prion protein is thought to cause a prion disease by S. B. Prusiner's theory (see for example, [1, 8, 27]). An illustration of a precursor prion protein is in Figure 1 (see [25]). As previously known experimental facts, a

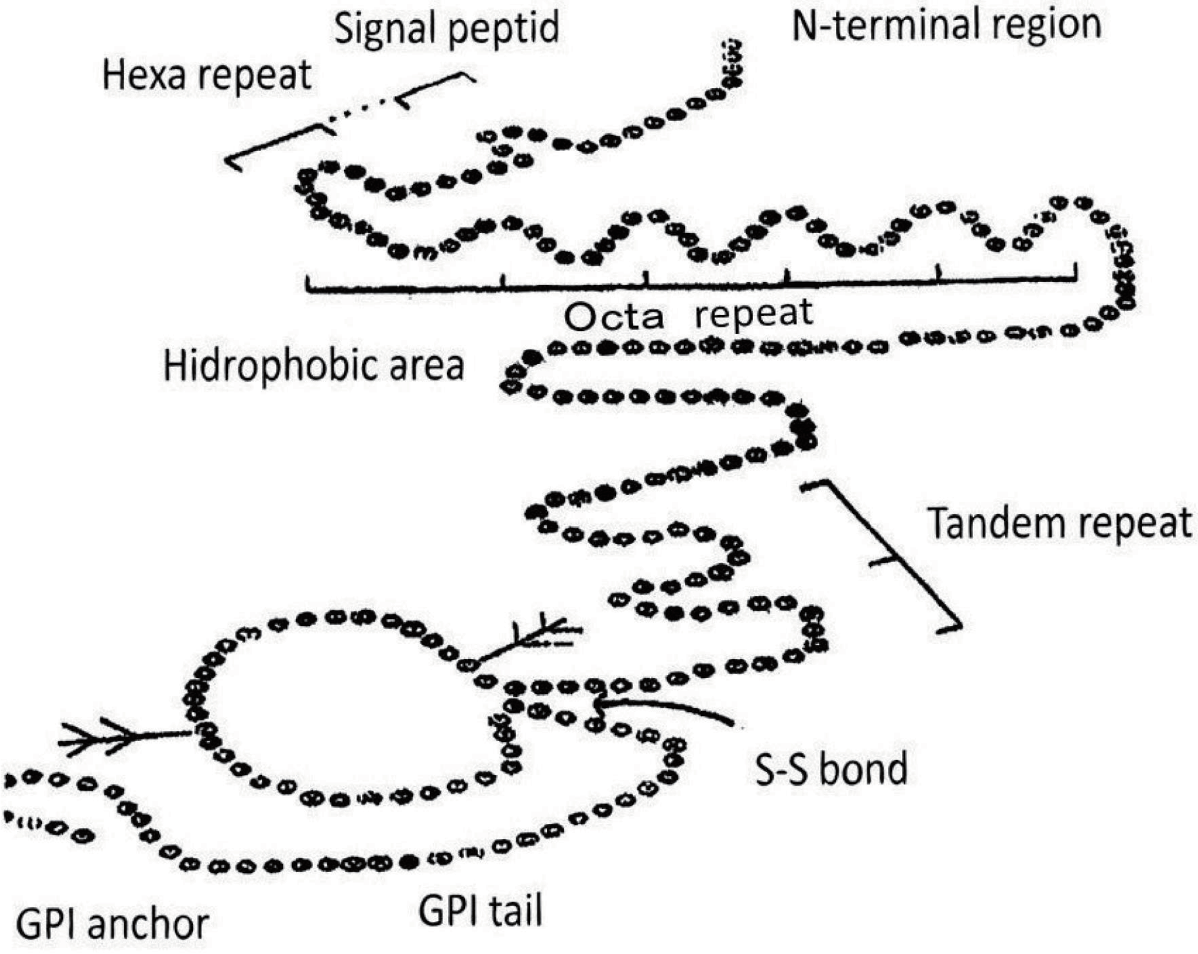

Figure 1: A precursor prion protein

prion precursor protein PrP which is regularly folded with the both ends fixed turns into a cellular prion protein, denoted by PrP^C, or a scrapie prion protein, denoted by PrP^{SC} by losing an N-terminal region. The GPI-anchor of PrP still remains in PrP^C and PrP^{SC} although PrP^C can be considered to leave from and re-attach to the cell surface at the GPI-anchor(cf. [2]). A set of p elements of PrP^C and a set of q elements of PrP^{SC} form a set of $p+q$ elements of PrP^{SC}. The linear structures of PrP^C and PrP^{SC} are considered as the same one, although an α-helix of PrP^C is changed into a β-sheet in PrP^{SC}. There is one S-S bond in PrP. There is a problem asking how cellular prion proteins PrP^C and scrapie prion proteins PrP^{SC} are changed into all the scrapie prion proteins PrP^{SC}. By counting these experimental facts, a topological model of prion proteins (PrP^C, PrP^{SC}) is proposed as follows: namely, a *prion-string* K is a graph consisting of a trivial loop $\ell(K)$ and an arc $\alpha(K)$ in the upper-half 3-space $H^3_+ = \{(x,y,z) \in \mathbb{R}^3 \,|\, y \geqq 0\}$ such that the arc $\alpha(K)$ joins a point in the loop

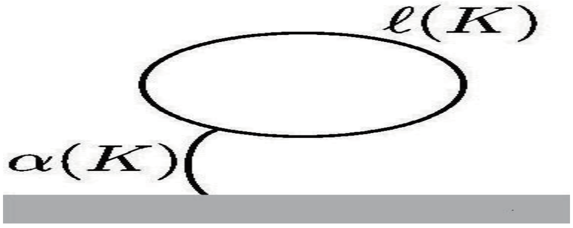

Figure 2: A prion-string

$\ell(K)$ with a point in the boundary plane $\partial H^3_+ = \{(x,0,z) \in \mathbb{R}^3\}$ (see Figure 2). The loop $\ell(K)$ and the arc $\alpha(K)$ are called the *SS-loop* and the *GPI-tail* of the prion-string K, respectively. The *SS-vertex* is the endpoint of the GPI-tail $\alpha(K)$ attaching to the SS-loop $\ell(K)$ and the *GPI-anchor* is the endpoint of the GPI-tail $\alpha(K)$ attaching to the boundary plane ∂H^3_+. If PrP^C's and PrP^{SC}'s are topologically distinct, then the topological difference between PrP^C's and PrP^{SC}'s are theoretically supposed to be constructed by crossing changes (see Figure 3) through the S-S bond or the GPI-anchor although any biological evidence is unknown except that $PrP\ SC$'s finally change into Amyloid fibrils (cf. [5, 6]).

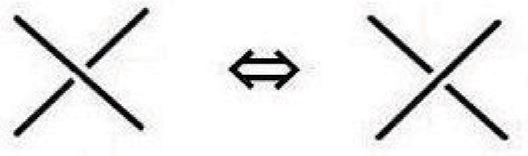

Figure 3: A crossing change

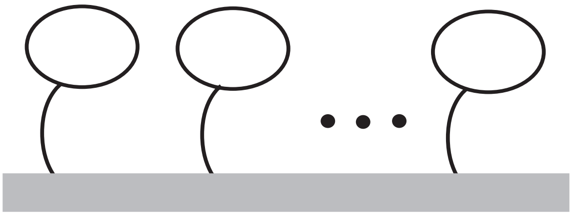

Figure 4: Prion-tangles in a standard position

The purpose of this article is to study how a system of prion strings is entangled by a knot theoretical approach and to study whether or not the prion proteins can be easily entangled. Because the one-crossing change is the most complexity-minimizing operation in the crossing changes, it is particularly interesting to ask how a system of prion strings K_i with $i = 1, 2, \ldots, n (n > 1)$ which is in a standard position as in Figure 4 is entangled by a one-crossing change. A possibility of the GPI-tail

$\alpha(K_i)$ or the SS-loop $\ell(K_i)$ passing through the SS-vertex of an SS-loop $\ell(K_j)$ or a possibility of the GPI-tail $\alpha(K_i)$ or the SS-loop $\ell(K_i)$ passing through the GPI-anchor of a GPI-tail $\alpha(K_j)$ (where $i = j$ is granted) is considered (see Figure 5). The crossing change is said to be *of type I, II or III*, respectively, if it is made on a pair $(\alpha(K_i), \alpha(K_j))$, $(\ell(K_i), \alpha(K_j))$ or $(\ell(K_i), \ell(K_j))$ for some i and j granting $i = j$. The SS-loop system $\cup_{i=1}^{n} \ell(K_i)$ is still a trivial link[1] after any one-crossing change of Type I or II. A one-crossing change of type III happens to make the SS-loop system a non-trivial link. In fact, any one-crossing change on $(\ell(K_i), \ell(K_j))$ $(i \neq j)$ always produces a non-trivial link such that the pair $(\ell(K_i), \ell(K_j))$ comes to have the linking number ± 1 but the linking numbers of the other distinct pairs are still zero in any orientations. In this case, all the knot components $\ell(K_i)$ $(i = 1, 2, \ldots, n)$ are still trivial. On the other hand, some one-crossing change on $(\ell(K_i), \ell(K_i))$ happens to produce a non-trivial link such that the knot component $\ell(K_i)$ comes to be a non-trivial knot, but the linking numbers of all distinct pairs are still zero in any orientations. An *n-string prion-tangle* is defined to be the union T of mutually disjoint n prion-strings K_i $(i = 1, 2, \ldots, n)$ in the upper-half 3-space H^3_+, but it is imposed (unless otherwise mentioned) that the *SS-loop system $\ell(T) = \cup_{i=1}^{n} \ell(K_i)$ is a trivial link*. An example of a 3-string prion-tangle is illustrated in Figure 6. It is a standard technique in knot theory to make various non-trivial links from the SS-loops $\ell(K_i)$ $(i = 1, 2, \ldots, n)$ by one-crossing changes of type III (see Figure 7). Two n-string prion-tangles T and T' are defined to be *equivalent* if there is an orientation-preserving homeomorphism $h : H^3_+ \to H^3_+$ sending T to T', whose meaning is also explained from now by a diagram-like approach. A *diagram* D_T of an n-string prion-tangle T is the projection image of T to the upper-half plane $H^2_+ = \{(x, y) \in \mathbb{R}^2 \mid y \geqq 0\}$ with, as the singularities, only *crossing points* (that is, transversely intersected double points apart from the vertices together with upper-lower information around the double points) under the projection $H^3_+ \to H^2_+$ sending (x, y, z) to (x, y). Every n-string prion-tange T has a diagram D_T after a slight isotopic deformation of T. Then, as it is seen from Lemma 3.1, two n-string prion-tangles T and T' are equivalent if and only if their diagrams D_T and $D_{T'}$ are transformed into each other by a finite number of generalized Reidemeister moves I-V(see Figure 8) in the interior of H^3_+ after making a position change of the GPI-anchors of T and T' in the boundary plane ∂H^3_+. An n-string prion-tangle T is defined to be *trivial* if it is equivalent to a prion-tangle with a diagram without crossing points (see Figure 4). It is noted in §3 that every prion-string K with $\ell(K)$ a trivial knot is trivial, but a non-trivial prion-string can occur under a certain non-topological assumption. An $n(\geqq 2)$-string prion-tangle T is *split* if it is equivalent to the union T' of two $n_i(\geqq 1)$-string prion-tangles T_i $(i = 1, 2)$ with $n_1 + n_2 = n$ such that the diagrams D_{T_i} of T_i $(i = 1, 2)$ in a diagram $D_{T'}$ of T' do not meet. The split n-string prion-tangle T is also called a *split sum* of the n_i-string prion-tangles T_i $(i = 1, 2)$. The existence of non-split n-string prion-tangles is explained in

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[1] See §2 for the definition of a trivial link.

§3 so that for every split $n(\geqq 2)$-string prion-tangle T, there are infinitely many (up to equivalences) non-split n-string prion-tangles T^* which are "almost identical" to T. Further, this family contains infinitely many non-split n-string prion-tangles T^* obtained from T by one-crossing changes of types I, II, III. As a result,the following non-split addition property on prion-tangles can be observed (see Corollary 3.6 later):

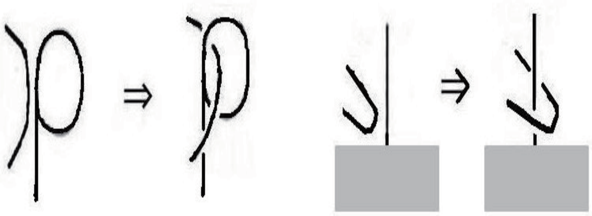

Figure 5: Creating crossing types

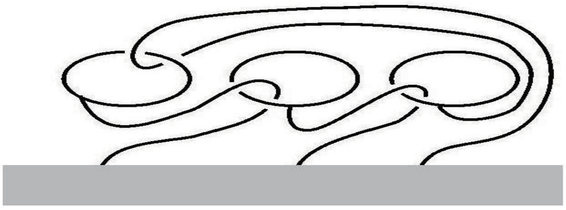

Figure 6: A prion-tangle

Addition property. Let T_1 and T_2 be any p-string and q-string prion-tangles such that T_1 and T_2 are separated by an upper-half plane in H^3_+. Then the split $(p+q)$-string prion-tangle $T = T_1 \cup T_2$ can be changed into a non-split prion-tangle T^* which is a union of two prion-tangles equivalent to T_1 and T_2, respectively, by a one-crossing change of any type I, II or III.

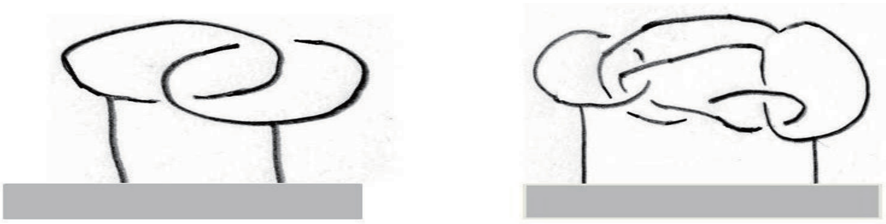

Figure 7: 2-string prion-tangles with non-trivial links by one-crossing changes of type III

It can be observed that the SS-loop system $\ell(T^*)$ is equivalent to the SS-loop system $\ell(T)$ except the case of any one-crossing change of type III on any pair of distinct SS-loops in $\ell(T)$ making always $\ell(T^*)$ a distinct llink from $\ell(T)$. In the present topological models of PrP^C and PrP^{SC}, it is regarded that a set of cellular prion proteins, PrP^C's forms a trivial prion-tangle and a set of scrapie prion proteins, PrP^{SC}'s forms a non-split prion-tangle. Then one can ask as mathematical problems in knot theory, for example, how a conformal difference of the cellular PrP and the scrapie PrP is explained and how the fact that a set of m scrapie PrP's and a set of n cellular PrP's can produce a set of $(m+n)$ scrapie PrP's, namely how

$$mPrP^{SC} + nPrP^C \longrightarrow (m+n)PrP^{SC}$$

is explained, which are imposed in S. B. Prusiner's theory. The addition property of prion-tangles may answer this problem theoretically. As another result of this paper, the minimal crossing number among the non-split prion-tangles with n strings for every $n > 1$ is determined in either case of assuming or not assuming that the loop system is a trivial link. This result is shown in §4. In fact, it will be shown that every diagram D_T of any non-split n-string prion-tangle T with $\ell(T)$ a trivial link has $c(D_T) \geqq 2n$ and there is a non-split n-string prion-tangle T such that $\ell(T)$ is a trivial link and a diagram D_T of T has $c(D_T) = 2n$, for every integer $n \geqq 2$. Likewise, it will be shown that every diagram D_T of any non-split n-string prion-tangle T granting that $\ell(T)$ is a non-trivial link has $c(D_T) \geqq 2n-2$ and there is a non-split n-string prion-tangle T such that $\ell(T)$ is a non-trivial link and a diagram D_T of T has $c(D_T) = 2n-2$, for every integer $n \geqq 2$. In §2, some basics on a spatial graph needed for our study are explained. In particular, a special spatial graph which is called a bouqet is introduced there as an object useful in studying a prion-bouquet in mathematical knot theory. In §3, prion-tangles are studied in terms of prion-bouquets. In §4, the minimal crossing numbers of prion-tangles are discussed. In the final section (§5), a concluding remark and a further question are stated.

2. Some basics on a spatial graph

A *spatial graph* of a finite graph Γ is the image $G = G_\Gamma$ of a topological embedding $\Gamma \to \mathbf{R}^3$ such that there is a homeomorphism $h : \mathbf{R}^3 \to \mathbf{R}^3$ sending G to a polygonal graph in $\mathbf{R}^3$. The spatial graph G is called a *link* if Γ is the disjoint union of finitely many loops, and it is *trivial* if it is the boundary of mutually disjoint disks in $\mathbf{R}^3$. A *knot* is a link with one component. For a general reference of knots, links and spatial graphs, refer to [14], and for a particular explanation on this section, refer to [16, 17]. A *diagram* D_G of a spatial graph G is the projection image of G to the plane $\mathbb{R}^2$ with, as the singularities, only *crossing points* (that is, transversely intersected double points apart from the vertices together with upper-lower information around the double points) under the projection $\mathbb{R}^3 \to \mathbb{R}^2$ sending (x,y,z) to (x,y). Every spatial graph G has a diagram D_G after a slight isotopic deformation of G. Let $c(D_G)$

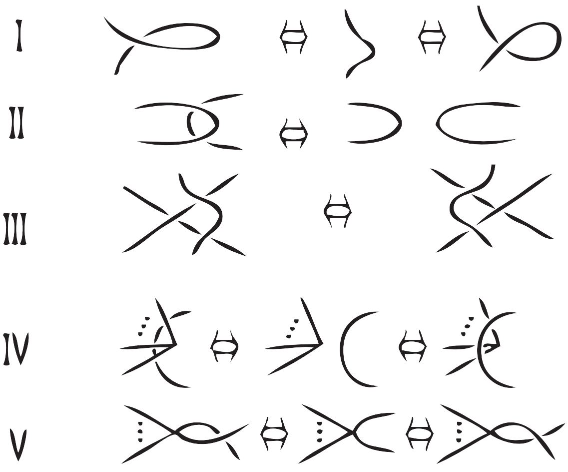

Figure 8: Generalized Reidemeister moves

be the number of crossing points of D_G. A spatial graph G is *equivalent* to a spatial graph G' if there is an orientation-preserving homeomorphism $h : \mathbf{R}^3 \to \mathbf{R}^3$ such that $h(G) = G'$. To consider the equivalence of a spatial graph, it is sufficient to consider a spatial graph G without degrees zero and one vertices. Also, the degree two vertices are ignored since they are useless in the present topological argument. Let $[G]$ be the class of spatial graphs G' equivalent to the spatial graph G. It is known that two spatial graphs G and G' are equivalent if and only if any diagram D_G of G is deformed into any diagram $D_{G'}$ of G' by a finite sequence of the generalized Reidemeister moves (see Figure 8), where only the moves I-III are needed for knots and links which are called the *Reidemeister moves* in this case (see [10], [11], [14]). Let $[D_G]$ be the class of diagrams obtained from a diagram D_G of G by the generalized Reidemeister moves I-V, which can be identified with the class $[G]$. This induces a topological invariant, the *crossing number* of G denoted by $c(G)$ which is the minimal crossing number of all diagrams in $[D_G]$.

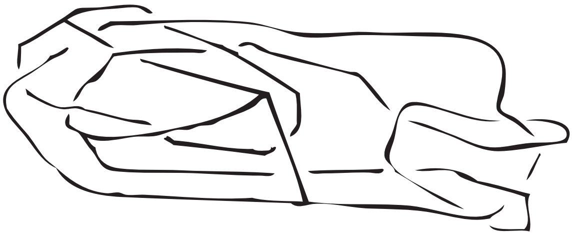

Figure 9: A bouquet

Our main concern here is a certain spatial graph called an n-string bouquet. To state it, some terminologies are needed. Let a graph α in $\mathbf{R}^3$ be the union of simple arcs α_i $(i = 1, 2, \cdots, n)$ such that the intersection $\alpha_i \cap \alpha_j$ is a fixed point v for every distinct i and j. This spatial graph α is called an *$n(\geqq 2)$-string total tail* with *base point* v and *tails* α_i. An *n-string bouquet* Λ is the union of a link ℓ of n components ℓ_i $(i = 1, 2, \ldots, n)$ in $\mathbf{R}^3$ and an $n(\geqq 2)$-string total tail α with the base point v and the tails α_i $(i = 1, 2, \ldots, n)$ such that $\ell \cap \alpha_i = v_i$ is the endpoint of α_i except v. Some 2-string bouquets are classified by Moriuchi [24] and Ishii, Kishimoto, Moriuchi, and Suzuki [9]. See Figure 9 for an example of a 3-string bouquet. The link ℓ, the knots ℓ_i $(i = 1, 2, \ldots, n)$, and the points v_i $((i = 1, 2, \ldots, n))$ are called the *loop system*, the *loops*, and the *vertices* of Λ, respectively. An n-string bouquet Λ^* is said to be *almost identical* to an n-string bouquet Λ if Λ^* is not equivalent to Λ and there is a homeomorphism[2] $q : \Lambda^* \to \Lambda$ such that $q(\alpha_i^*) = \alpha_i$ for all i after re-indexing the tails α_i^* $(i = 1, 2, \ldots, m)$ and the spatial graph $\mathrm{cl}(\Lambda^* \backslash \alpha_i^*)$ deleting the tail α_i^* is equivalent to the spatial graph $\mathrm{cl}(\Lambda \backslash \alpha_i)$ deleting the tail α_i for every i. An n-string bouquet Λ is said to be *split* if there is an n-string bouquet Λ' equivalent to Λ such that a 2-sphere in $\mathbb{R}^3$ meets Λ' at the base point v and separates Λ' into two $n_i(> 0)$-string bouquets Λ_i $(i = 1, 2)$ with $n_1 + n_2 = n$ (see Figure 10). This notion of a split graph is generalized to every spatial graph without degrees zero and one vertices as follows: A spatial graph G (without degrees zero and one vertices) is *split* if there is an essential 2-sphere S in $\mathbf{R}^3$ which does not meet G or meeting G only at a vertex of G, where the 2-sphere S is *essential* if every connected component of $\mathbf{R}^3 \backslash S$ meets G. For example, every connected spatial graph G without any cutting vertex is non-split. The following theorem is a basic theorem in this article.

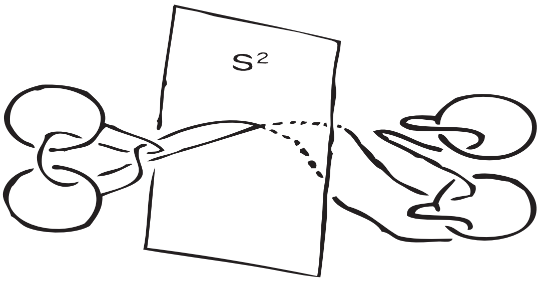

Figure 10: A split bouquet

Theorem 2.1. Let Λ be an $n(\geqq 2)$-string bouquet obtained from an n-string bouquet Λ' by a one-crossing change on any pair of tails or loops. Then there are infinitely

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[2] This map q is usually assumed to be extendable to a smooth map $q^+ : S^3 \to S^3$ so that$(q^+)^{-1}(\Lambda) = \Lambda^*$ (see [12, 13]), but we do not use the property in this paper.

many (up to equivalences) non-split n-string bouquets Λ^* which are almost identical to Λ and obtained from Λ' by certain one-crossing changes on the same pair of tails or loops.

Proof of Theorem 2.1. Theorem 2.1 is a combination result of [12] and [13] (see [20] for an explanation) where infinitely many n-string bouquets Λ^* are constructed with an important property that the compact 3-manifold E^* obtained from S^3 by removing an open regular neighborhood of Λ^* is a hyperbolic 3-manifold with totally geodesic boundary. This hyperbolicity of E^* is sufficient to see that the n-string bouquet Λ^* is non-split. This completes the proof of Theorem 2.1.

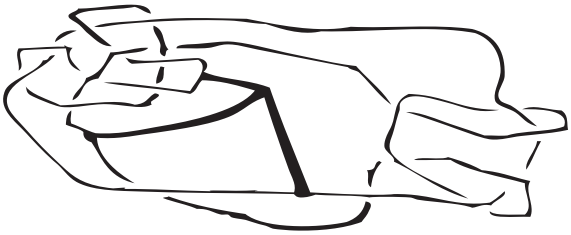

Figure 11: A based bouquet diagram

Concerning a crossing change, the unknotting number of a bouquet is discussed from now. A diagram D_Λ of an n-string bouquet Λ is *based* and written as (D_Λ, α) if the diagram D_α of of the total tail α in D_Λ does not contain any crossing point of D_Λ. Every n-string bouquet Λ is equivalent to a bouquet with a based diagram by first deforming α to a planar tree isotopically and then deforming the loop system ℓ of Λ to be disjoint from $\alpha\backslash\{v_1, v_2, \ldots, v_n\}$. For example, see Figure 11 for a based diagram of a 3-string bouquet obtained by deforming the 3-string bouquet of Figure 9 isotopically. A knot diagram D_{ℓ_k} which is the diagram of ℓ_k in D_Λ is *monotone* if there is an orientation on ℓ_k such that a point going along the oriented diagram D_{ℓ_k} from the vertex v_k always meets first the upper crossing point at every crossing point (see Figure 12). Similar notions are discussed in Lickorish and Millett [22], Ozawa [26], Shimizu [28, 29], the author [15], Fujimura [3], Fung [4], Okuda [23]. A based diagram (D_Λ, α) of an n-string bouquet Λ is *monotone* if there is an ordered sequence of the components ℓ_k $(k = 1, 2, \cdots, n)$ of the loop system ℓ of (Λ, α) such that the knot diagram D_{ℓ_k} is monotone for all k and the knot diagram D_{ℓ_k} is upper than the knot diagram D_{ℓ_s} for every $k < s$. The notion of a monotone diagram is generalized to every spatial graph and leads to the complexity and its related numerical invariants of every spatial graph (see [16, 17]). The unknotting number $u(\Lambda)$ of an n-string bouquet Λ is defined as follows. An n-string bouquet Λ is said to be *unknotted* if Λ is equivalent to an n-string bouquet Λ' with a monotone diagram, which is seen to be equivalent to a graph on a plane in the case of n-sptring bouquets. Thus, an unknotted n-string bouquet Λ exists uniquely up to equivalences for every n and has the crossing number $c(\Lambda) = 0$. The unknotting number $u(D_\Lambda)$ of a diagram D_Λ of an n-string bouquet Λ is the minimal number of crossing changes needed to obtain a diagram of an unknotted n-string bouquet. The *unknotting number* $u(\Lambda)$ of an n-string bouquet Λ is the minimum of the unknotting numbers of all diagrams in $[D_\Lambda]$. Since a monotone diagram can be obtained from any based diagram (D_Λ, α) by a finite number of crossing changes, the inequality $u(\Lambda) \leqq u(D_\Lambda) < +\infty$ always holds. Taniyama's method in [30] is used to determine that a given bouquet is non-split. To explain it, a disk D in $\mathbf{R}^3$ is said to be *essential* for G if the boundary ∂D of D is either in G with at least two vertices of G contained or in G with at most one vertex and the interior int$D$ of D meets G with at least one point transversely. Then a spatial graph G' is called an *essential quotient* of a spatial graph G if there is a finite sequence of spatial graphs G_i $(i = 0, 1, 2, \ldots, m)$ with $G_0 = G$ and $G' = G_m$ such that G_i is obtained from G_{i-1} by the contraction along an essential disk D_i for G_i for every $i = 1, 2, \ldots, m$. Then the main theorem of [30] says that if an essential quotient G' of a spatial graph G is non-split, then the spatial graph G is non-split. Some calculations are done in SS3-4 on the prion-tangles of Figures 18, 23 and 24.

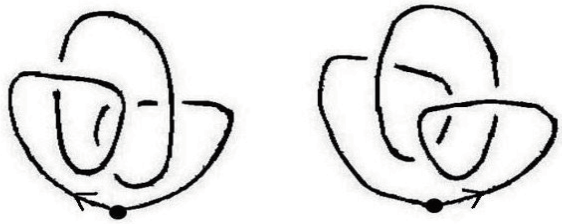

Figure 12: Monotone diagrams

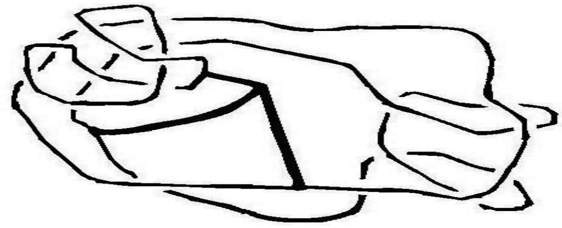

Figure 13: A monotone bouquet diagram

3. From a prion-tangle to a prion-bouquet

First, it is explained how an n-string prion-tangle is regarded as an n-string bouquet. For the lower-half 3-space $H^3_- := \{(x, y, z) \in \mathbb{R}^3 \,|\, y \leqq 0\}$, the one point compactification $(\mathbb{R}^3 \cup \{\infty\}, H^- \cup \{\infty\})$ is homeomorphic to a pair (S^3, B^3) of the 3-sphere

S^3 and a 3-ball B^3 in it. For an n-string prion-tangle T in H^3_+, a unique n-string bouquet Λ_T in S^3 can be constructed by shrinking the 3-ball B^3 to a point in S^3, which may be considered as a graph in $\mathbb{R}^3$ so that every diagram D_T of T induces a diagram D_{Λ_T} of Λ_T uniquely. In particular, the crossing number $c(D_T)$ is seen to be equal to the crossing number $c(D_{\Lambda_T})$ for every diagram D_T of every n-string prion-tangle T and the induced diagram D_{Λ_T}. This spatial graph Λ_T is called the *n-string prion-bouquet* of the n-string prion-tangle T. An n-string prion-bouquet Λ_T is nothing but an n-string bouquet with a trivial link as the loop system. The *crossing number $c(T)$* of an n-string prion-tangle T is defined to be the crossing number $c(\Lambda_T)$ of the n-string prion-bouquet Λ_T. Then the crossing number $c(T)$ of T is an invariant of T up to equivalences. For example, the 3-string prion-tangle T in Figure 6 induces a 3-string prion-bouquet Λ_T of Figure 14 which is a trivial 3-string bouquet, so that $c(T) = 0$. The following lemma is obtained by reminding the definition of equivalence of n-string prion-tangles and the definition of equivalence of n-string bouquets.

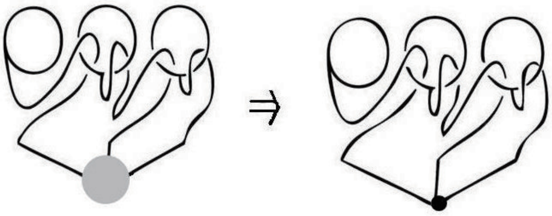

Figure 14: From a prion-tangle to a prion-bouquet

Lemma 3.1. Two n-string prion-tangles T and T' are equivalent if and only if the n-string prion-bouquets Λ_T and $\Lambda_{T'}$ are equivalent as spatial graphs. Equivalently, a diagram D_T is transformed into a diagram $D_{T'}$ by a finite number of the generalized Reidemeister moves I-V in the interior of the upper-half 3-space H^3_+ after making a position change of the GPI-anchors of T and T' in the boundary plane ∂H^3_+ if and only if a diagram D_{Λ_T} is transformed into a diagram $D_{\Lambda_{T'}}$ by a finite number of the generalized Reidemeister moves I-V.

The following two corollaries are direct from Lemma 3.1.

Corollary 3.2. An $n(\geqq 2)$-string prion-tangle T is split if and only if the n-string prion-bouquet Λ_T is split.

Corollary 3.3. An n-string prion-tangle T is trivial if and only if the n-string prion-bouquet Λ_T is unknotted. Thus, every prion-string K with $\ell(K)$ a trivial knot is always trivial.

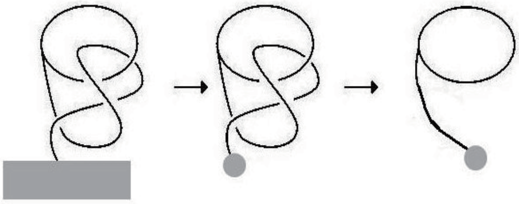

Figure 15: Triviality of a prion-string

By Corollary 3.3, the *unknotting number* $u(T)$ of an n-string prion-tangle T is defined by $u(T) = u(\Lambda_T)$. The latter-half of Corollary 3.3 is seen from the observation that for every prion-string K with $\ell(K)$ a trivial knot, the 1-string prion-bouquet Λ_K is always equivalent to a plane graph without crossing point (see Figure 15). On the other hand, in molecular chemistry there is a known concept called "Rotaxsane Property"(see[7]) meaning that ring molecules around a stick molecule cannot be excluded from the stick molecule by the stoppers of the stick molecule (see Figure 16). Analogously, under the assumption that a string of a non-trivial knot and the cell surface cannot pass through the SS-loop, a non-trivial prion-string can occur (cf. Figure 17). One of the main theorems is the following theorem which is obtained from Theorem 2.1 by interpreting an n-string prion-tangle as an n-string prion-bouquet.

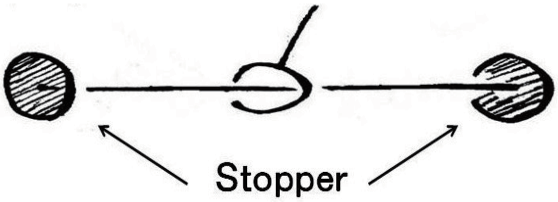

Figure 16: Rotaxsane Property

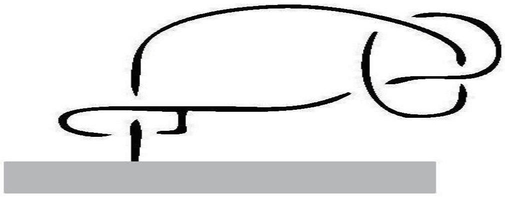

Figure 17: Non-triviality of a prion-string

Theorem 3.4. Let T be an $n(\geqq 2)$-string prion-tangle obtained from an n-string prion-tangle T' by a one-crossing change on a pair on GPI-tails and SS-loops of T'.

Then there are infinitely many (up to equivalences) non-split n-string prion-tangles T^* which are almost identical to T and obtained from T' by certain one-crossing changes on the same pair on GPI-tails and SS-loops of T'.

A *non-effective pair* among the GPI-tails and the SS-loops of a prion-tangle T is a pair on the tails and the loops of T such that there is a crossing change of a diagram D_T of T on the pair making an n-string prion-tangle equivalent to T. It is seen that any pair of the GPI-tails of T and the pairs $(\ell(K), \alpha(K))$, $(\ell(K), \ell(K))$ for any string K of T are non-effective. The following corollary is obtained from Theorem 3.4 by taking $T = T'$:

Corollary 3.5. For every $n(\geqq 2)$-string prion-tangle T, there are infinitely many (up to equivalences) non-split n-string prion-tangles T^* which are almost identical to T and obtained from T by certain one-crossing changes on any non-effective pair of type I, II or III (see Figure 5).

As a remark, any one-crossing change on the pair $(\alpha(K_i), \alpha(K_j))$ $(i \neq j)$ can be realized as an operation of the GPI-tail $\alpha(K_i)$ passing through the GPI-anchor of the GPI-tail $\alpha(K_j)$ once and any one-crossing change on the pair $(\alpha(K_i), \ell(K_i))$ or $(\ell(K_i), \ell(K_i))$ can be realized as an operation of the GPI-tail $\alpha(K_i)$ or the SS-loop $\ell(K_i)$ passing through the SS-vertex of the SS-loop $\ell(K_i)$ once, respectively . The following addition property of prion-tangles is a direct consequence of Theorem 3.4.

Corollary 3.6 (Addition Property). Let T_1 and T_2 be any p-string and q-string prion-tangles such that T_1 and T_2 are separated by an upper-half plane in H^3_+. Then the split $(p+q)$-string prion-tangle $T = T_1 \cup T_2$ can be changed into a non-split prion-tangle T^* which is a union of two prion-tangles equivalent to T_1 and T_2 by a one-crossing change of any type I, II or III.

It can be observed that the SS-loop system $\ell(T^*)$ is equivalent to the SS-loop system $\ell(T)$ except the case of any one-crossing change of type III on any pair of distinct SS-loops in $\ell(T)$ making $\ell(T^*)$ a distinct link from $\ell(T)$. In Figure 18, some examples of non-split 2-string prion-tangles are given so that they are almost identical to a trivial 2-string prion-tangle and obtained from a trivial 2-string prion-tangle by one-crossing changes of types I, II and III, respectively. The 2-string prion-bouquet Λ_T of the type I example T is listed as 6_{10} in [9]. The 2-string prion-bouquet $\Lambda_{T'}$ of the example T' of type II is introduced as Figure 2(c) of [24] and listed as 4_1 in [9]. The non-splitness of these 2-string prion-tangles can be shown by algebraic methods (cf. [9], [24]), but here the method of Taniyama [30] is used as follows. In the example T of type I, a 2-string bouquet with the Hopf link loop system (which is a non-trivial link) is obtained from Λ_T by the contractions along essential disks spanning the loops appearing in the diagram, which is non-split. In the example T' of type II, a plane graph without any cutting vertex is obtained from $\Lambda_{T'}$ by the contractions along essential disks bounded by the SS-loops appearing in the diagrams, which is non-split. In the example T'' of type III, a 2-string bouquet with the Whitehead link loop system, which is a non-trivial link, is obtained from $\Lambda_{T''}$ by the contraction along an essential disk spanning the loop appearing as a loop without self-crossing in the diagram, which is non-split. In conclusion, by the method of [30], it is shown that the 2-string prion-bouquets Λ_T, $\Lambda_{T'}$, $\Lambda_{T''}$ and hence the 2-string prion-tangles T, T', T'' are non-split.

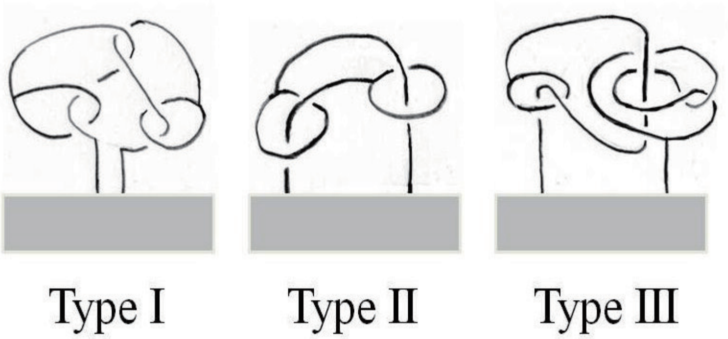

Figure 18: Non-split 2-string prion-tangles

4. Minimal non-split prion-tangles

The other one of our main theorems is the following theorem which determines the minimal crossing number of n-string non-split prion-tangle diagrams in two cases of that the loop system is assumed to be a trivial link and that the loop system may have a non-trivial link, for every $n \geqq 2$.

Theorem 4.1. The following statements (1) and (2) hold for every $n \geqq 2$.
(1) The minimal crossing number of the diagrams of non-split n-string prion-tangles with the trivial loop system is $2n$. Further, there is a non-split n-string prion-tangle T with $\ell(T)$ a trivial link which has a diagram D with the crossing number $c(D) = c(T) = 2n$ and the unknotting number $u(D) = u(T) = 1$.

(2) The minimal crossing number of the diagrams of non-split n-string prion-tangles granting non-trivial loop systems is $2n - 2$. Further, there is a non-split n-string prion-tangle T with $\ell(T)$ a non-trivial link which has a diagram D with the crossing number $c(D) = c(T) = 2n - 2$ and the unknotting number $u(D) = u(T) = 1$.

Proof of Theorem 4.1(1). Suppose that a non-split n-string prion-tangle T with $\ell(T)$ a trivial link has a diagram D with crossing number $c(D) \leqq 2n - 1$. Let Λ_T

be the n-string prion-bouquet of the n-string prion-tangle T. The n-string prion-bouquet Λ_T is non-split and has a diagram D' with $c(D') = c(D) \leqq 2n-1$. Let $\ell_i\,(i=1,2,\ldots,n)$ be the loops in Λ_T. The following lemma will be used.

Lemma 4.2. The n-string prion-bouquet Λ_T is split if there is a disk Δ bounding ℓ_i such that the interior of Δ does not intersect the $(n-1)$-string prion-bouquet $\Lambda_T\backslash\ell_i$, for some i.

To see this lemma, the loop ℓ_i is regarded as one point by shrinking the disk Δ. Then the string K_i is served like an edge with degree one vertex in the graph Λ_T. Let e_j $(j=1,2,\ldots,p)$ be the collection of the diagrams of the loops $\ell_i\,(i=1,2,\ldots,n)$ in D' such that e_j has a zero or one self-crossing, and f_k $(k=1,2,\ldots,s)$ the collection of the diagrams of the loops $\ell_i\,(i=1,2,\ldots,n)$ in D' such that f_k has more than one self-crossings. By regarding the loop system $\ell=\cup_{i=1}^{n}\ell_i$ of the n-string prion-bouquet Λ_T as the diagram in D', let

$$\ell = (\cup_{j=1}^{p} e_j) \cup (\cup_{k=1}^{s} f_k).$$

For two diagrams D_{G_i} $(i=1,2)$ of spatial graphs G_i $(i=1,2)$, let $c(D_{G_1}\cap D_{G_2})$ denote the crossing numbers between D_{G_1} and D_{G_2}. The following lemma proved later is used.

Lemma 4.3. If the n-string prion-bouquet Λ_T is non-split, then the following inequality holds.

$$c(\cup_{j=1}^{p} e_j) + c((\cup_{j=1}^{p} e_j)\cap(D'\backslash\ell)) \geqq 2p.$$

Assuming Lemmas 4.2 and 4.3, the proof of Theorem 4.1 will be completed as follows: Since Λ_T is non-split and $c(\cup_{j=1}^{s} f_j) \geqq 2s$, the following inequalities are obtained from Lemma 4.3.

$$c(D') \geqq c(\cup_{j=1}^{p} e_j) + c(((\cup_{j=1}^{p} e_j)\cap(D'\backslash\ell)) + c(\cup_{j=1}^{s} f_j) \geqq 2p + 2s = 2n$$

which contradicts that $c(D') \leqq 2n-1$. This completes the proof of Theorem 4.1 except the proof of Lemma 4.3.

The following two lemmas are key steps to the proof of Lemma 4.3.

Lemma 4.4. The n-string prion-bouquet Λ_T is split if $c(e_j\cap(\ell\backslash e_j)) = 2$ and $c(e_j\cap(D'\backslash\ell)) = 0$ for some j.

Lemma 4.5. The n-string prion-bouquet Λ_T is split if $c(e_j\cap(\ell\backslash e_j)) = 0$ and $c(e_j\cap(D'\backslash\ell)) \leqq 1$ for some j.

These lemmas are shown as follows.

Proof of Lemma 4.4. The proof is divided into the following two cases (i) and (ii).

Case (i). The case that e_j has no self-crossings. In this case, the gray part in the left-hand side of Figure 19 can be deformed into that in the right-hand side of Figure 19. Then there is a 2-disk bounded by the loop e_j. By Lemma 4.2, Λ_T is split.
Case (ii). The case that e_j has one self-crossing,. In this case, the arising situations are given in Figure 20. In every case, the self-crossing is canceled. By the case (i), Λ_T is split. This completes the proof of Lemma 4.4.

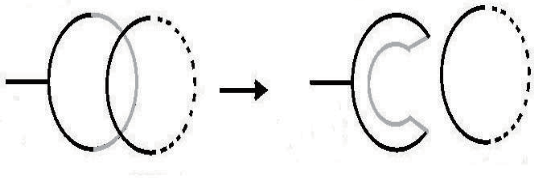

Figure 19: A deformation in the case (i)

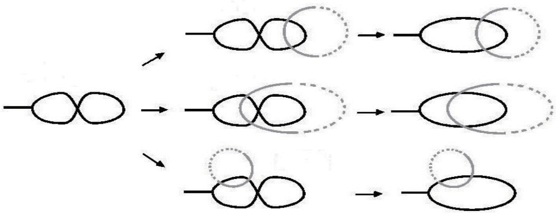

Figure 20: The situations arising in the case (ii)

Proof of the Lemma 4.5. Assume that $c(e_j \cap (D'\backslash\ell)) = 1$. Then the proof is divided into the following two cases (iii) and (iv).

Case (iii). The case that e_j has no self-crossing. In this case, the gray string in the left-hand side of Figure 21 can be deformed into that in the right-hand side of Figure 21. Then there is a 2-disk bounded by the loop e_j. By Lemma 4.2, Λ_T is split.
Case (iv). The case that e_j has one self-crossing. In this case, the arising situations are given in Figure 22. In every case, the self-crossing is canceled. By the case (i), Λ_T is split. By the same way, it can be shown that Λ_T is split in the case

$$c(e_j \cap (D'\backslash\ell(D'))) = 0.$$

This completes the proof of Lemma 4.5.

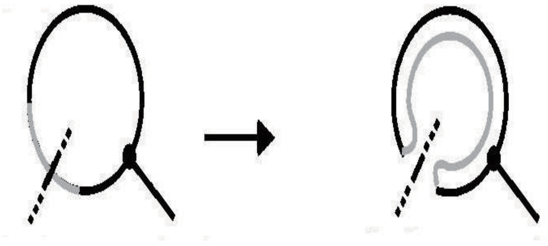

Figure 21: A deformation in the case (iii)

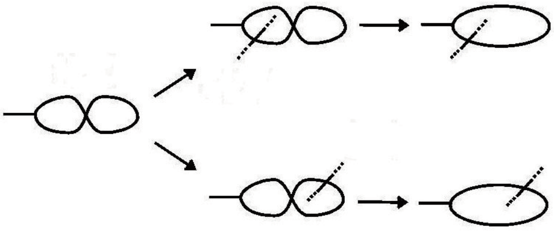

Figure 22: The situations arising in the case (iv)

By using Lemmas 4.4 and 4.5, Lemma 4.3 can be shown as follows:

Proof of Lemma 4.3. A non-negative integer m is defined to be the minimum of

$$\frac{1}{2}c(e_j \cap (\ell \backslash e_j)) + c(e_j \cap (D' \backslash \ell))$$

for all j. Suppose that $m = 0$. Since

$$c(e_j \cap (\ell \backslash e_j)) = c(e_j \cap (D' \backslash \ell)) = 0$$

for some j, it is seen from Lemma 4.5 that Λ_T is split. Suppose that $m = 1$. If $c(e_j \cap (\ell \backslash e_j)) = 2$ and $c(e_j \cap (D' \backslash \ell)) = 0$ for some j, then Λ_T is split by Lemma 4.4. If $c(e_j \cap (\ell \backslash e_j)) = 0$ and $c(e_j \cap (D' \backslash \ell)) = 1$ for some j, then Λ_T is split by Lemma 4.5. Hence we have $m \geqq 2$. Then

$$\begin{aligned} & c(\cup_{j=1}^{p} e_j) + c((\cup_{j=1}^{p} e_j) \cap (D' \backslash \ell)) \\ & \geqq \sum_{j=1}^{p} (\frac{1}{2}c(e_j \cap (\ell \backslash e_j)) + c(e_j \cap (D' \backslash \ell))) \\ & \geqq mp \geqq 2p, \end{aligned}$$

completing the proof of Lemma 4.3. This completes the proof of the first half of Theorem 4.1(1).

Figure 23: A minimal non-split prion-tangle with the trivial loop system

To show the second half of the proof of Theorem 4.1(1), the n-string prion-tangle T in Figure 23[3] is taken, which has a diagram D with $c(D) = 2n$. The inequality $u(D) \leqq 1$ holds by a one-crossing change of Type II. It suffices to show that the n-string prion-bouquet Λ_T is non-split. From the diagram D_T of Λ_T, mutually disjoint essential n disks Δ_i $(i = 1, 2, \ldots, n)$ can be found so that the boundary of Δ_i is the loop ℓ_i of Λ_T and the interior of Δ_i intersects Λ_T transversely only at one point. Then the plane graph G obtained from Λ_T by the contractions along the essential disks Δ_i $(i = 1, 2, \ldots, n)$ does not have any cut vertex. Hence Λ_T and hence T are non-split by the result of Taniyama [30]. Hence $c(D) = c(T) = 2n$ and $u(D) = u(T) = 1$. The n-string prion-tangle T' illustrated in Figure 24 is another example of a non-split n-string prion-tangle T with $c(D) = c(T) = 2n$ and $u(D) = u(T) = 1$ shown by the same method, which has has the additional property that it is almost identical to a trivial n-string prion-tangle. This completes the proof of Theorem 4.1(1).

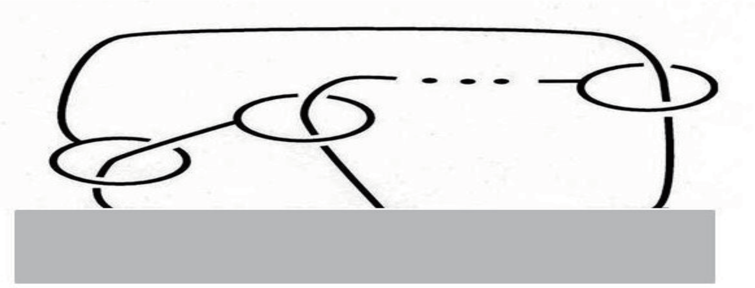

Figure 24: Another minimal non-split prion-tangle with the trivial loop system

Theorem 4.1 (2) is shown as follows.

Proof of Theorem 4.1(2). Suppose that a non-split n-string prion-tangle T with $\ell(T)$ a non-trivial link has a diagram D with crossing number $c(D) \leqq 2n - 3$. Then the n-string prion-bouquet Λ_T is non-split and has a diagram D' with $c(D') = c(D) \leqq$

---

[3] The example with $n = 2$ is equivalent to the example of type II in Figure 18.

$2n-3$. Let $\ell = \cup_{i=1}^{n} \ell_i$ be the loop system of Λ_T. Introduce the equivalence relation $\sim$ in the loops ℓ_i $(i = 1, 2, \ldots, n)$ generated by the elementary relation $\ell_i \sim_e \ell_j$ if and only if $c(\ell_i \cap \ell_j) \geqq 1$ (meaning necessarily $c(\ell_i \cap \ell_j) \geqq 2$). Let $\mathbf{e}_k$ $(k = 1, 2, \ldots, r)$ be the equivalence classes of the loops ℓ_i $(i = 1, 2, \ldots, n)$, and $\mathbf{a}_k$ $(k = 1, 2, \ldots, r)$ the corresponding classes of the tails α_i attaching to ℓ_i of Λ_T. If $r = 1$, then the inequality $c(D') \geqq 2n-2$ holds, a contradiction. Assume that $r \geqq 2$. Then, since Λ_T is non-split, for each k there is an index h with $h \neq k$ such that $c(\mathbf{a}_h \cap \ell_i) \geqq 2$ for some loop ℓ_i in $\mathbf{e}_k$. This observation is used to make a graph Γ with the vertices $\mathbf{e}_k$ $(k = 1, 2, \ldots, r)$ and the edges consisting of the pairs $\mathbf{e}_k\mathbf{e}_h$ for all such pairs (h, k) with $h \neq k$. Since Λ_T is non-split, this graph Γ is connected. Since the maximal tree of Γ has $r-1$ edges, the following inequality holds:

$$c(D') \geqq \sum_{k=1}^{r} 2(|\mathbf{e}_k| - 1) + 2(r-1) \geqq 2n-2,$$

which contradicts $c(D') = c(D) \leqq 2n-3$, completing the first half of Theorem 4.2(2). To show the second half, the n-string prion-tangle T in Figure 25 is taken, which has a diagram D with $c(D) = 2n-2$. The inequality $u(D) \leqq 1$ holds by a one-crossing change of Type III. The SS-loop system $\ell(T)$ is non-trivial since the Hopf link is contained in it. It suffices to show that the n-string prion-bouquet Λ_T is non-split. By the contractions along a series of essential disks bounding the loop system, a plane graph G which does not have any cut vertex is obtained from Λ_T. Therefore, Λ_T and hence T are non-split by [30]. Hence $c(D) = c(T) = 2n-2$ and $u(D) = u(T) = 1$, completing the proof of Theorem 4.1 (2).

Figure 25: A minimal non-split prion-tangle with a non-trivial loop system

5. Conclusion and a further question

Our question was to ask whether the prion proteins are easily entangled. A prion-string is a spatial graph $K = \ell(K) \cup \alpha(K)$ in the upper half space H^3_+ consisting of the SS-loop $\ell(K)$ and the GPI-tail $\alpha(K)$ joining the SS-vertex with the GPI-anchor in the cell surface. In the present topological model, the following identifications are made:

A set of cellular prion proteins PrP^C's = a trivial prion-tangle,
A set of scrapie prion proteins PrP^{SC}'s = a non-split prion-tangle.

The addition property of prion-tangles may explain a conformal difference of PrP^C and PrP^{SC} relating to the fact:

$$sPrP^{SC} + tPrP^C \longrightarrow (s+t)PrP^{SC}.$$

S. B. Prusiner et al. report that the PrP^{SC}'s form Amyloid fibrils in [6]. The following properties (1) and (2) of Amyloid fibrils are known (see [5]):
(1) Amyloid fibrils are related to more than 20 serious human diseases such as Alzheimer's disease.
(2) Amyloid formation is a generic property of polypeptides.

Thus, it would be interesting to ask how a knotting model of Amyloid fibrils is constructed.

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