Tohoku Knot Seminar(Oct. 15, 2011)

Topology of prion proteins

A joint work with Kayo Yoshida

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Preprint is available from
http://www.sci.osakacu.ac.jp/~kawauchi/TopologyofPrionProteins.pdf

Abstract

A topological model of prion proteins (PrP^C, PrP^{SC}) which we call a *prion-tangle* is proposed to explain some tangle properties of prion proteins. We show that **two splitted prion-tangles can be changed into a non-split prion-tangle with the given prion-tangles contained by a one-crossing change.**

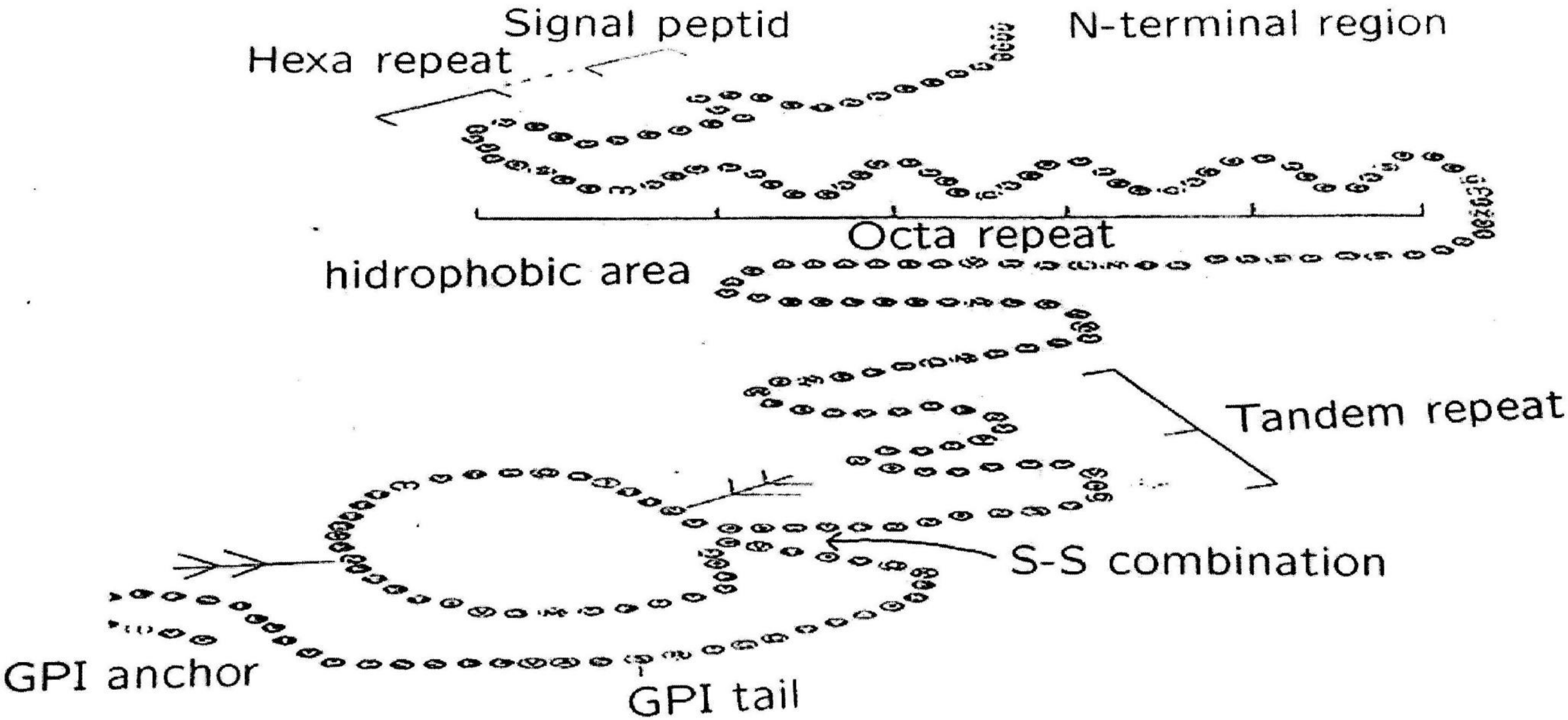
We also determine for every n>1 that **the minimal crossing number of n-string non-split prion-tangles is 2n or 2n-2, respectively, according to whether or not we count the assumption that the loop system is a trivial link.**

Talk contents

1. Introduction
2. Some basics on a spatial graph
3. Changing a prion-tangle into a prion-bouquet
4. Minimal non-split prion-tangles
5. Conclusion and a further question

1. Introduction

Prion Precursor Protein



From:

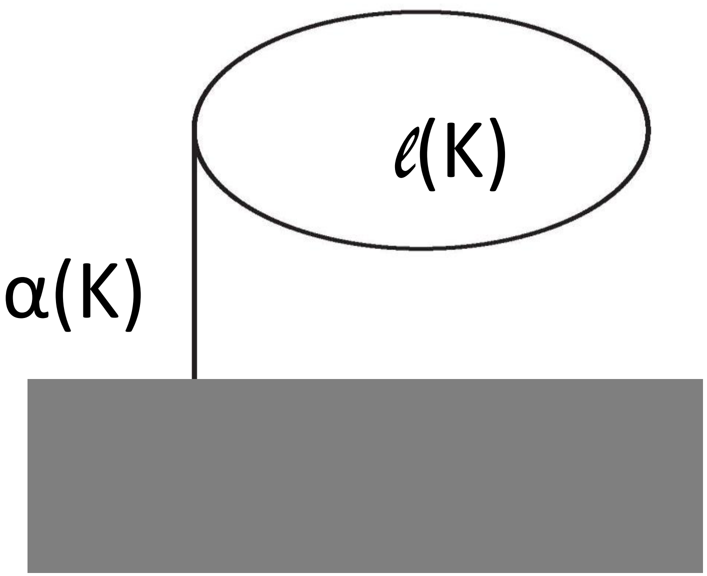
K. Yamanouchi & J. Tateishi Editors, Slow Virus Infection and Prion (in Japanese), Kindaishuppan Co. Ltd. (1995)

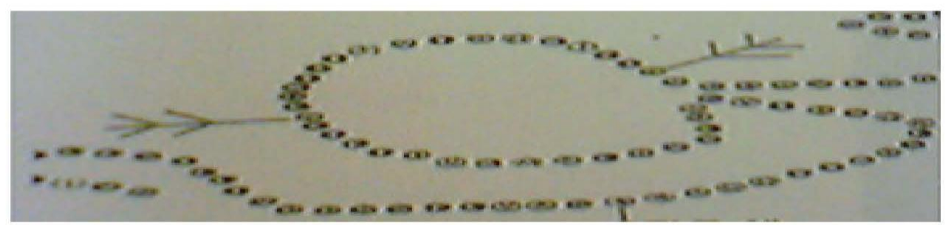
Some points of S. B. Prusiner's theory are:

(1) By losing the N-terminal region, Prion precursor protein changes into Cellular PrP (PrP^c) or Scrapie PrP (PrP^{SC}), and α-helices change into β-sheets.
(2) The linear structures of PrP^c and PrP^{SC} are the same, so that *the conformations of PrP^c and PrP^{SC} may differ.*
(3) There is one S-S combination.

- **Z. Huang et al., Proposed three-dimensional Structure for the cellular prion protein, Proc. Natl. Acad. Sci. USA, 91(1994), 7139-7143.**
- **K. Basler et al., Scrapie and cellular PrP isoforms are encoded by the same chromosomal gene, Cell 46(1986), 417-428.**

Definition. A prion-string is a spatial graph $K = \ell(K) \cup \alpha(K)$ in the upper half space $\mathbb{H}^3$ consisting of SS-loop $\ell(K)$ and GPI-tail $\alpha(K)$ joining the SS-vertex in $\ell(K)$ with the GPI-anchor in $\partial\mathbb{H}^3$.



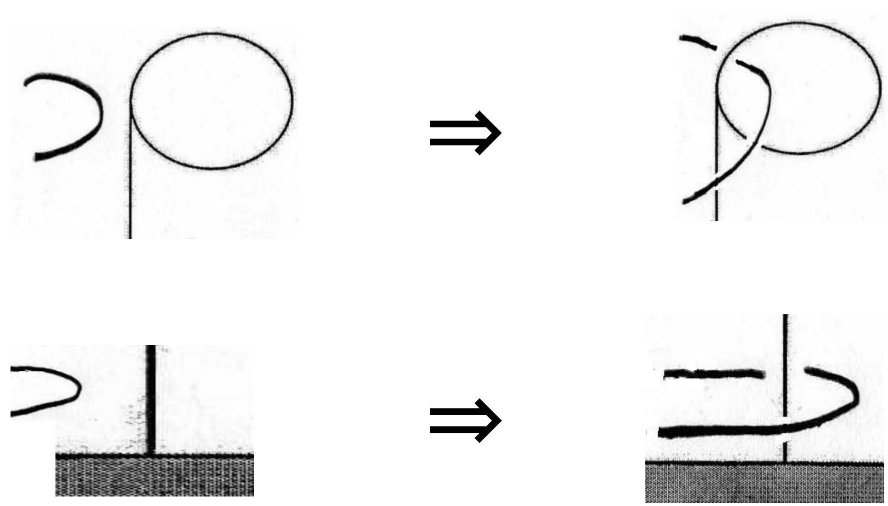


Definition.

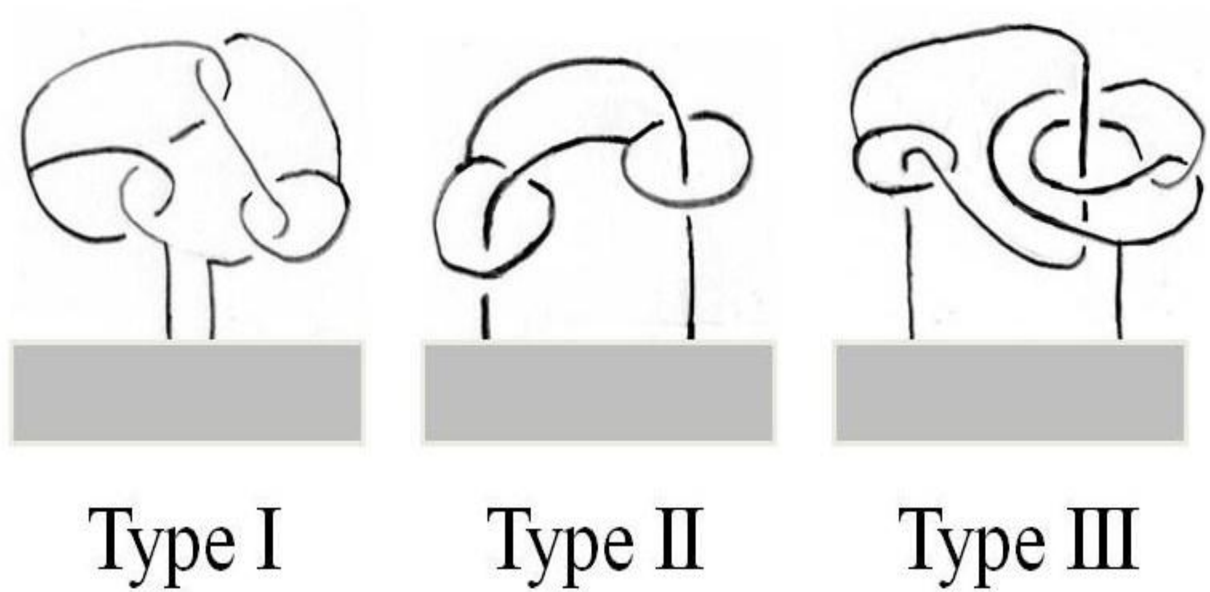
A **prion-tangle** is the union $T = K_1 \cup K_2 \cup \ldots \cup K_r$ of finitely many, mutually disjoint prion-strings K_i $(i=1,2,\ldots,r)$.

Our problem is to explain by a knot theoretical approach *how a prion-tangle is entangled?*

In this topological model, we suppose in PrP^{SC} that the GPI-tails of some prion-strings happened to pass through S-S combination parts of some prion-strings or pass through some GPI-anchor's of some prion-strings.

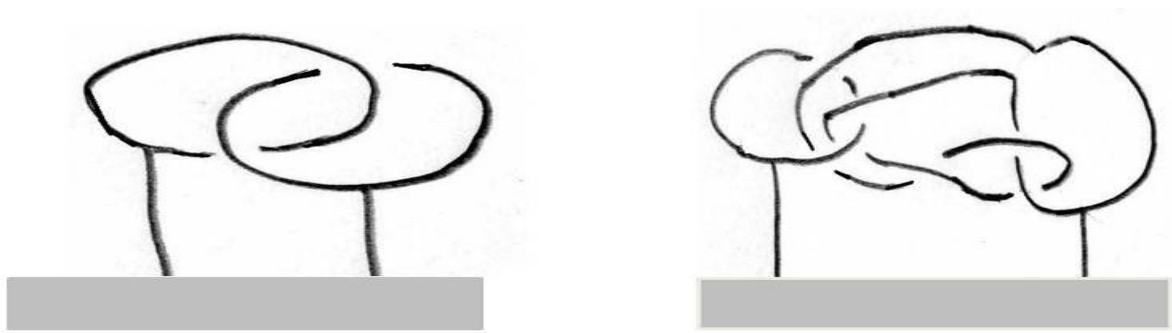


We are interested in a one-crossing change, where there are three types of entanglements.



Non-split prion-tangles obtained by a one-crossing change

By a one-crossing change of type III, we can easily change the SS-loop system ℓ(T) into a non-split link.



We assume (unless otherwise mentioned) that the SS-loop system ℓ(T) forms a trivial link because this assumption is always satisfied except* one-crossing changes of *type III .

Addition Property on Prion-tangles.

Any n-string prion-tangle T separated into two prion-tangles T_1,T_2 by $\mathbb{H}^2$ in $\mathbb{H}^3$ is changed into a non-split prion-tangle T^* by a certain one-crossing change of type I, II or III on any pair in $\ell(K_i)$, $\alpha(K_i)$ (i=1,2,…,n) of T, where we can have that $T^* \supset T_1$,T_2 and $\ell(T^*)$ is a trivial link except any one-crossing change on any pair of distinct SS-loops making always $\ell(T^*)$ a non-trivial link.

In our topological model, we regard

Cellular PrP's = trivial prion-tangles,
Scrapie PrP's = non-split prion-tangles.

The addition property of prion-tangles supports :

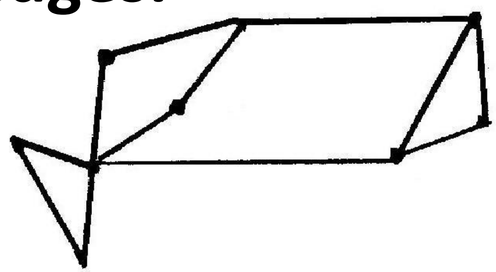
a conformal difference of PrP^{C} and PrP^{SC}

and also explains a mysterious fact:

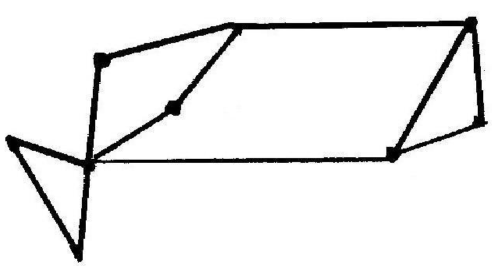
$$s\, PrP^{SC} + t\, PrP^{C} \rightarrow (s+t)\, PrP^{SC}.$$

2. Some basics on a spatial graph

A <u>finite graph</u> Γ is a collection of a finite number of vertices and edges.



A <u>spatial graph</u> of Γ is the image $G=G_\Gamma$ of Γ by a topological embedding into $\mathbb{R}^3$, where we disregard the vertices of degree 2.



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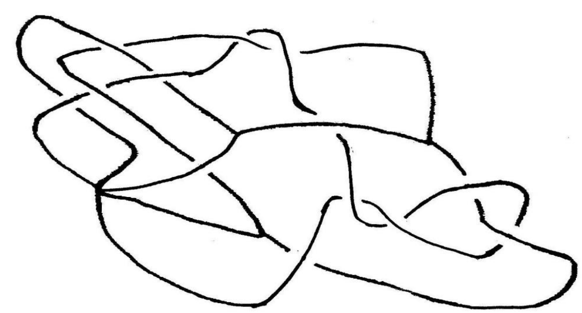
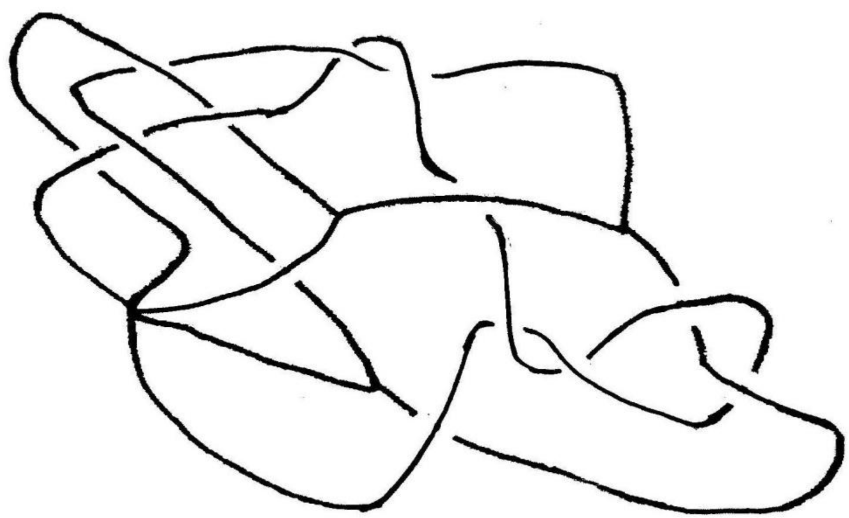
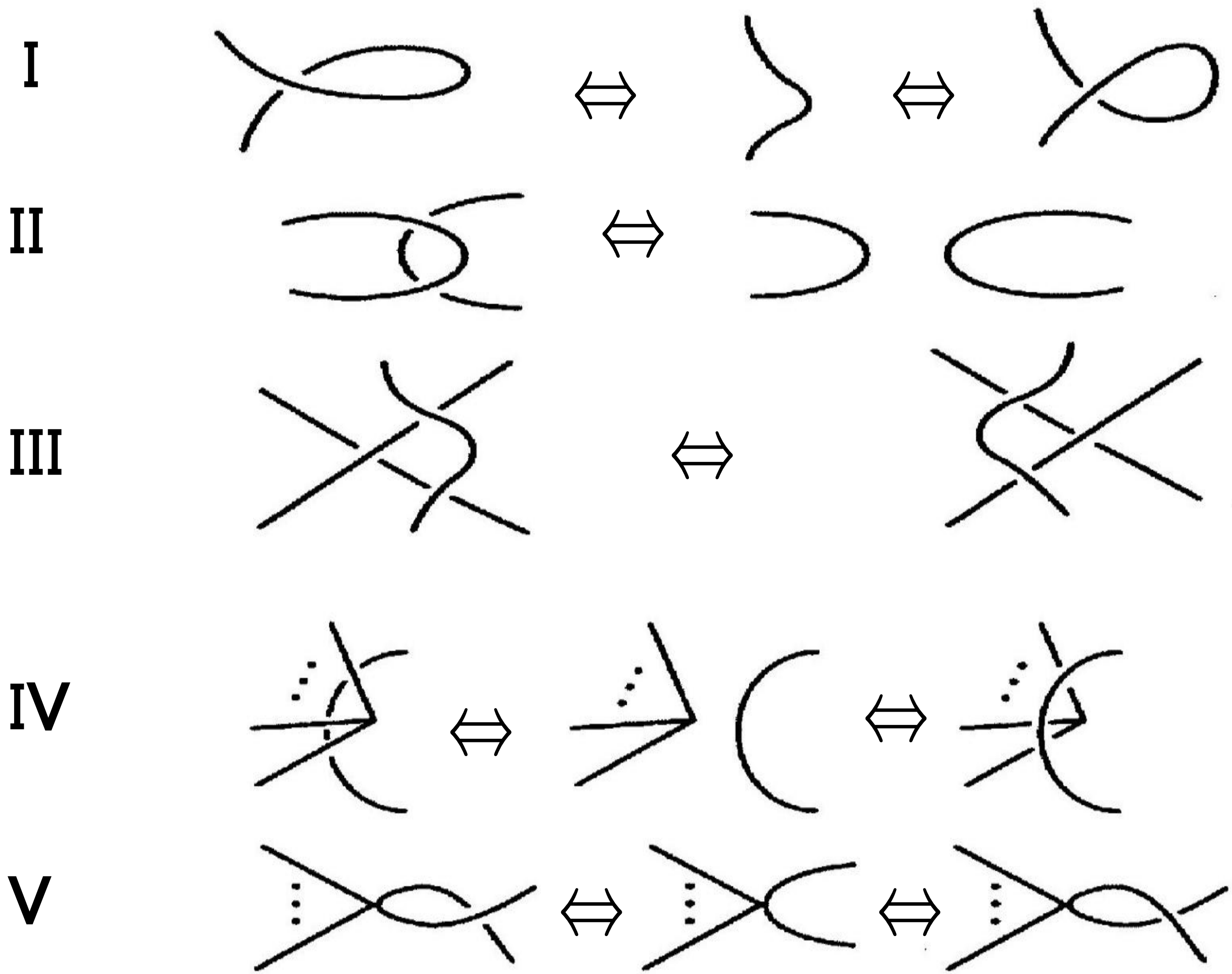


A <u>diagram</u> D of a spatial graph G is the image of G by the projection of $\mathbb{R}^3$ to a plane together with the upper-lower crossing information on every double point.



Definition.

Spatial graphs G and G' are equivalent if any diagram D of G is deformed into any diagram D’ of G’ by a finite sequence of the generalized Reidemeister moves:

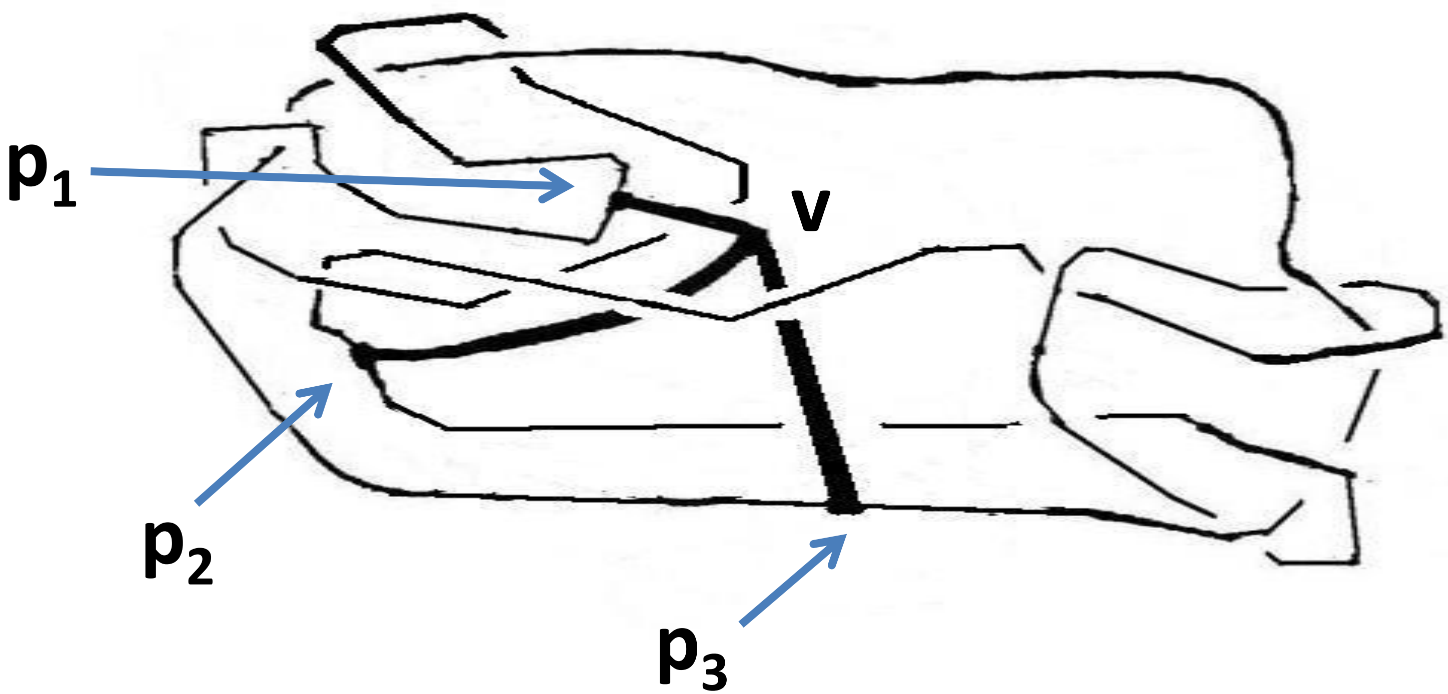

I
II
III
IV
V

For a finite graph G and an open edge α of it, let G-α be the spatial graph obtained from G by removing α.

Definition. **A spatial graph G^* is almost identical to a spatial graph G if $G^* \neq G$ and ∃ a graph-isomorphism $f : G^* \to G$ such that $G^*-\alpha^* = G-\alpha$ for any open edges α^*, α with $f(\alpha^*) = \alpha$.**

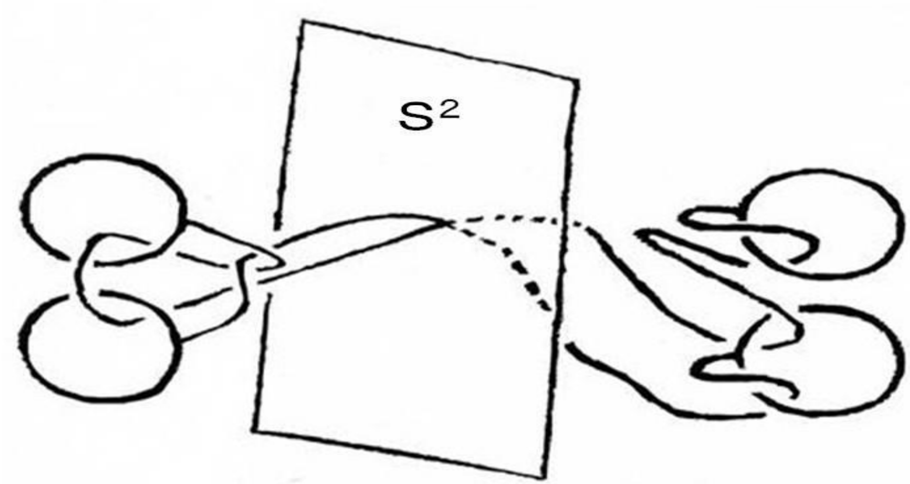
<u>Definition</u>.

A spatial graph Λ is an n-<u>string bouquet</u> if Λ is the union of an n-component link ℓ with components ℓ_i (i=1,2,…,n) and n simple arcs α_i joining a point v and a point p_i of ℓ_i (i=1,2,…,n).



Definition.

A spatial graph G is split if G is equivalent to a vertex sum of two spatial graphs as in the following picture:



K. Taniyama's creterion to non-splitting

●Every connected spatial graph G without any cutting vertex is non-split.

Definition. A disk D in R^3 is essential for G if either $\partial D \cap G = \partial D \supset \{$at least two vertices of G$\}$ or $\partial D \cap G = \partial D \supset \{$at most one vertex of G $\}$ and int(D) meets G transversely in at least one point.

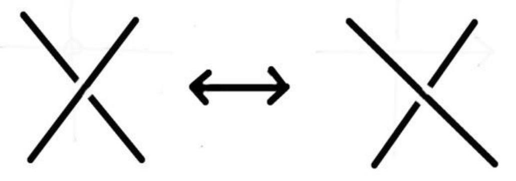
Definition. A spatial graph G' is an essential quotient of a spatial graph G if ∃ a sequence of spatial graphs G_i (i=0,1,2,..., m) such that G_0=G, G'=G_m and G_i is obtained from G_{i-1} by contraction along an essential disk D_i for G_i for ∀ i.

Theorem(Taniyama). If an essential quotient G' of a spatial graph G is non-split, then the spatial graph G is non-split.

● K.Taniyama, Irreducibility of spatial graphs, JKTR 11(2002), 121--124.

BASIC THEOREM.

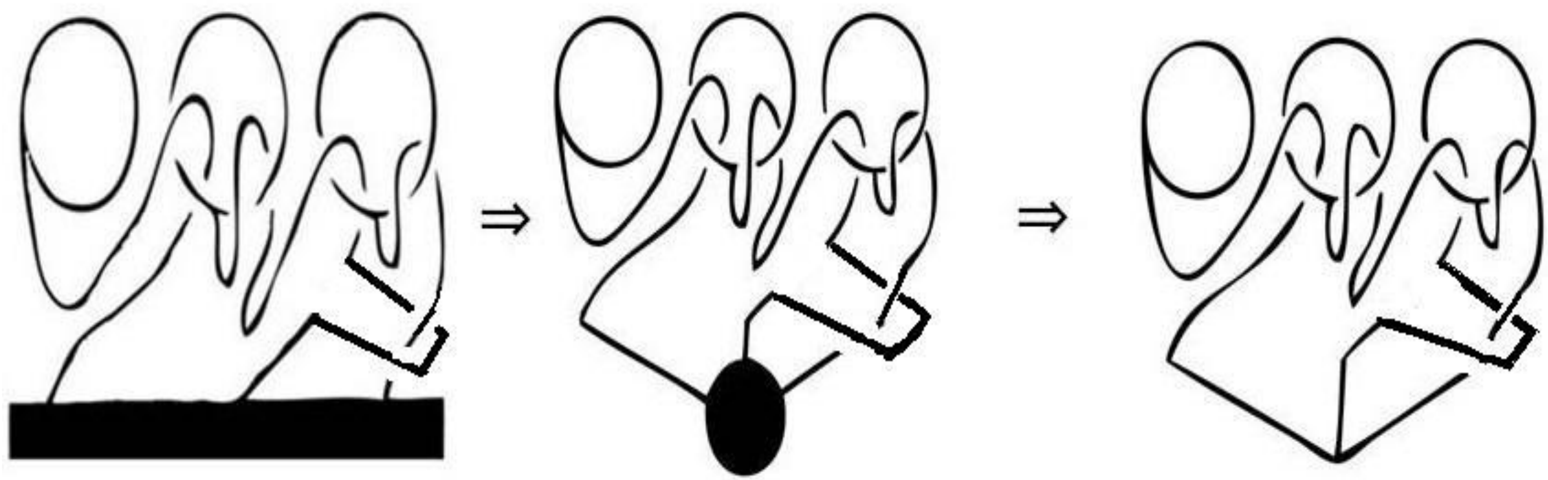
Let Λ be an n-string bouquet obtained from an n-string bouquet Λ’ by a one-crossing change on any pair of arcs or loops. Then ∃ ∞-many non-split n-string bouquets $Λ^*$ which are almost identical to Λ and obtained from Λ’ by a certain one-crossing change on the same pair of arcs or loops.

Here, a crossing change: 

- **A. Kawauchi, Osaka J. Math. 26(1989),743-758.**
- **A. Kawauchi, Knots 90,Walter de Gruyter, 1992, 465-476.**

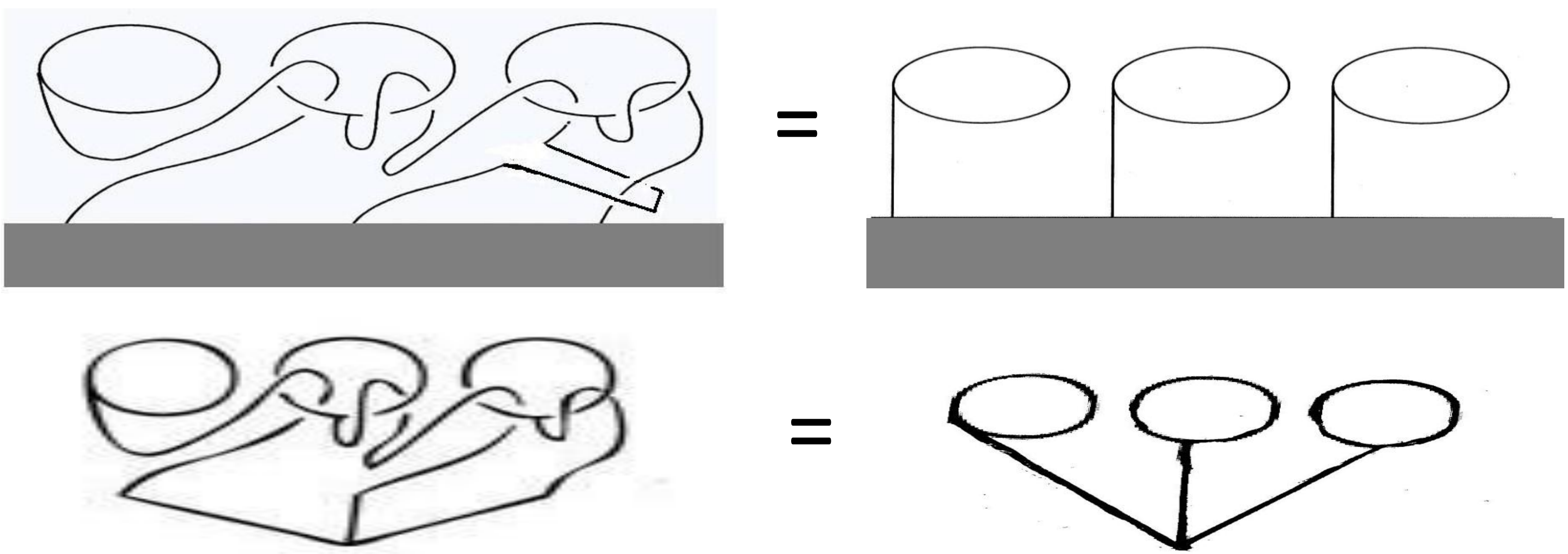
3. Changing a prion-tangle into a prion-bouquet

A prion-tangle T ⇒ The prion-bouquet Λ_T induced from T

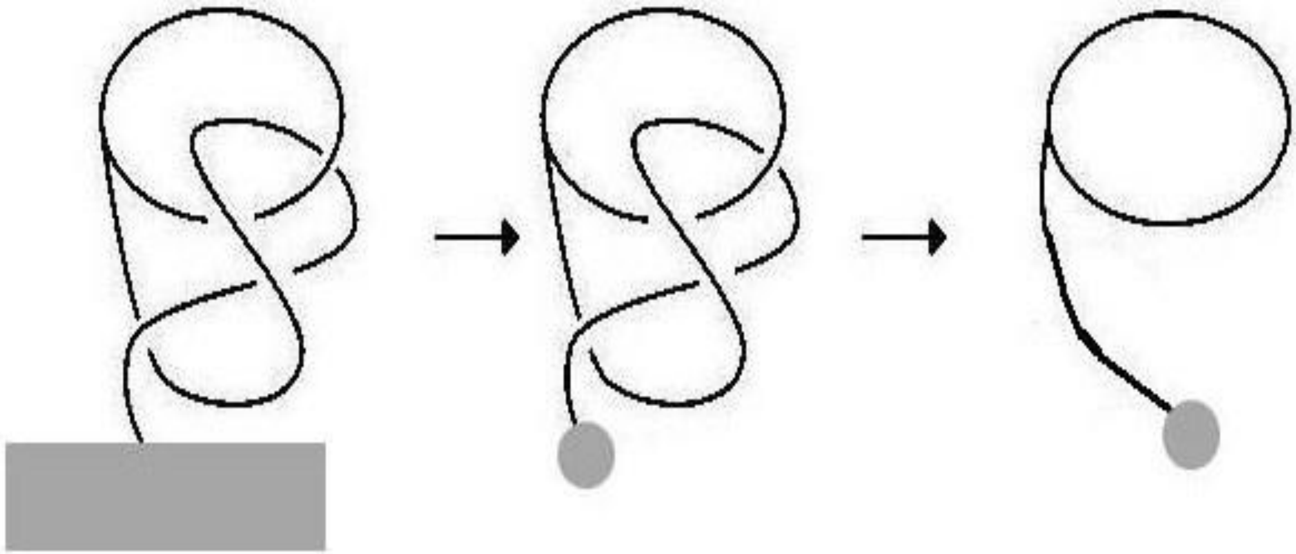


<u>Definition.</u> **Prion-tangles T and T' are <u>equivalent</u> if the prion-graphs Λ_T and $\Lambda_{T'}$ induced from T and T' are equivalent.**

For example,



- Every prion-string with $\ell(K)$ a trivial knot is equivalent to a trivial prion-string.



Rotaxsane Property

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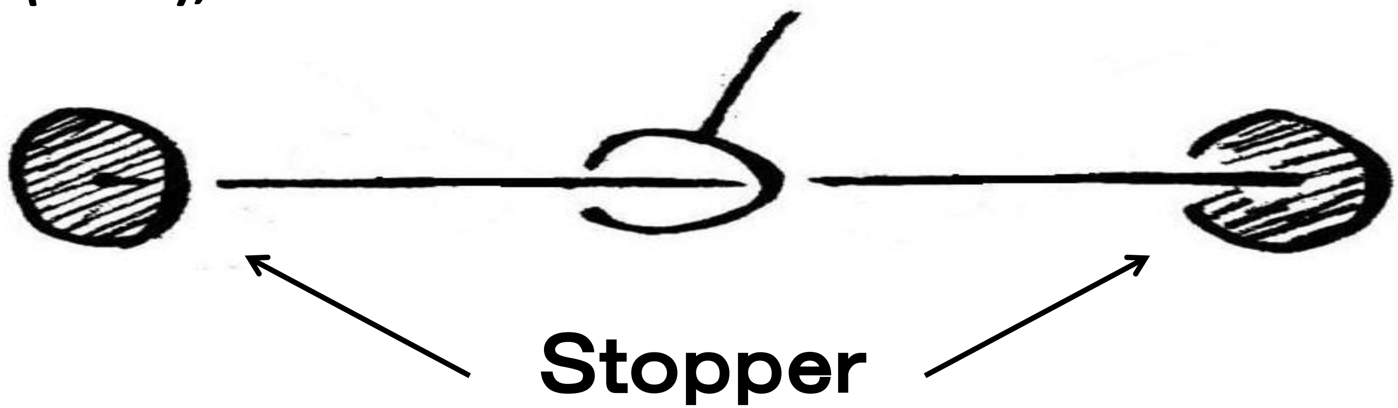
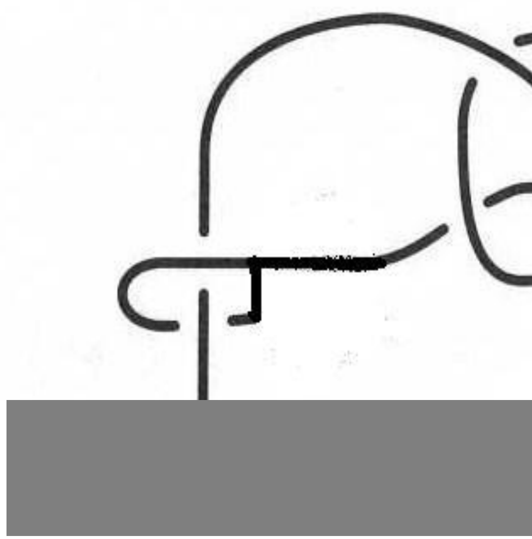
- A. Harada; J. Li; M. Kamachi, The molecular necklace: a rotaxane containing many threaded α-cyclodextrins, *Nature 356(*1992), 325-327



- **If we assume a "rotaxane property", then a "knotted" prion-string can arise.**

In fact, if we assume that the SS-loop cannot pass through a "knotted tangle part" and the cell surface, then we have a "knotted prion-string" with a trivial SS-loop:



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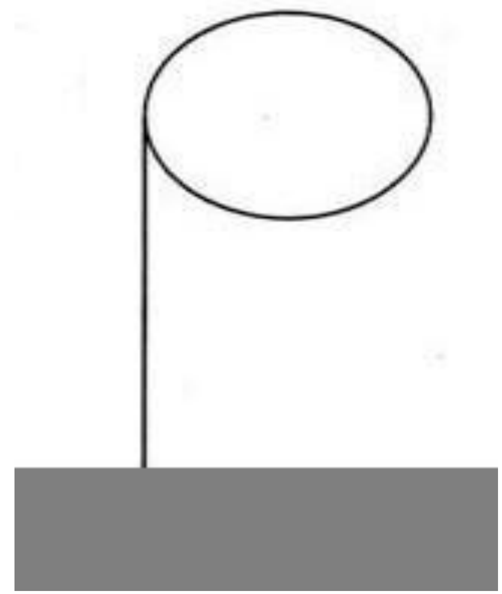


Definition. A prion-tangle T is split if the induced prion-bouquet Λ_T is split.

Definition.

A prion-tangle T* is almost identical to a prion-tangle T if the induced prion-graph Λ_{T^*} is almost identical to the induced prion-graph Λ_T .

BASIC THEOREM implies:

<u>THEOREM A.</u>

Let T be an n(>1)-string prion-tangle obtained from an n-string prion-tangle T' by a one-crossing change on a pair of GPI-tails or SS-loops.

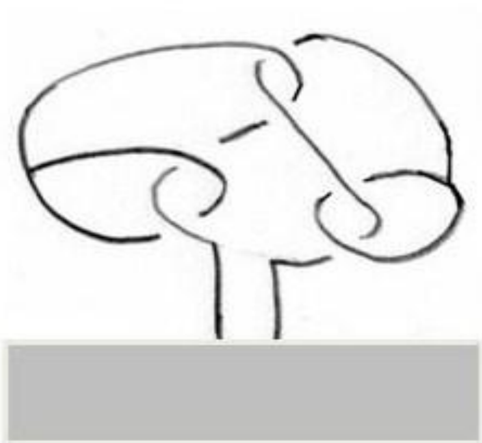
Then ∃ ∞-many non-split n-string prion-tangles T^* which are almost identical to T and obtained from T' by a certain one-crossing change on the same pair of GPI-tails or SS-loops.

The case T'=T implies:

<u>Addition Property on Prion-tangles.</u>

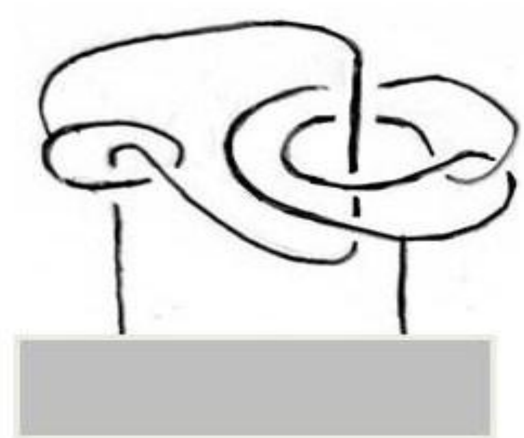
Any prion-tangle T separated into two prion-subtangles by an upper-half plane in $\mathbb{H}^3$ is changed into a non-split prion-tangle T* by a certain one-crossing change of type I, II or III on any pair in the GPI-tails or SS-loops of T. The loop system ℓ(T*) is taken a trivial link except the case of a one-crossing change on any pair of distinct SS-loops making necessarily ℓ(T*) a non-trivial link.

The following pictures are non-split prion-tangles with the loop system a trivial link obtained from a trivial 2-string prion-tangle by one-crossing changes.



Type I

Type II



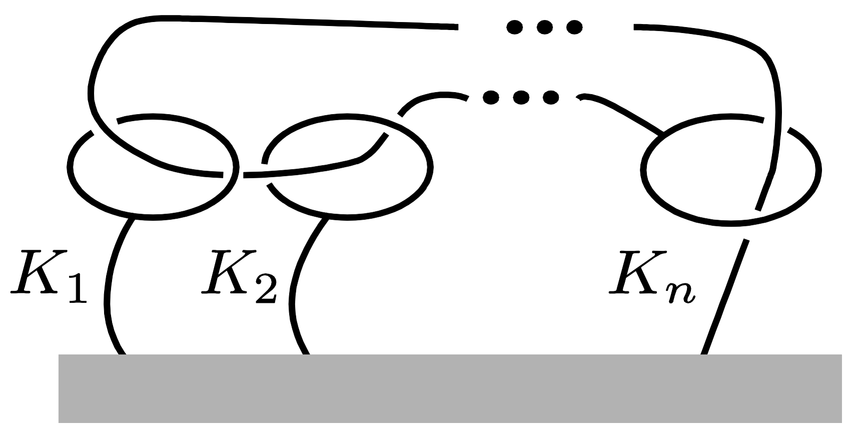
Type III

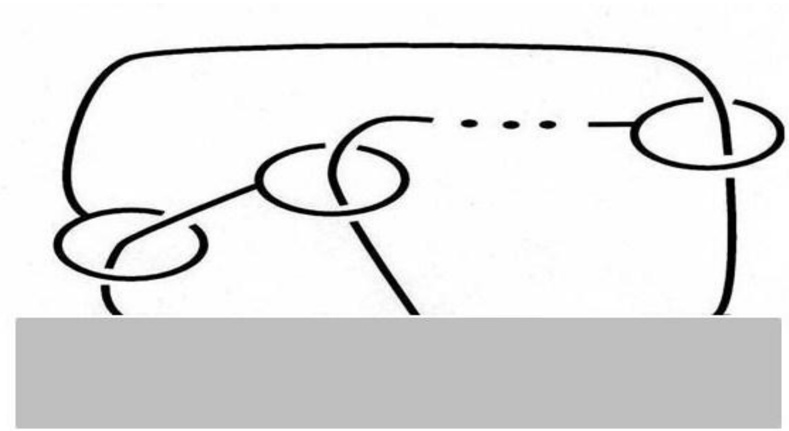
__Theorem B.__ **For every n> 1, we have the following (1) and (2).**

(1) The minimum of the crossing numbers of diagrams of non-split n-string prion-tangles with the trivial loop system is 2n.

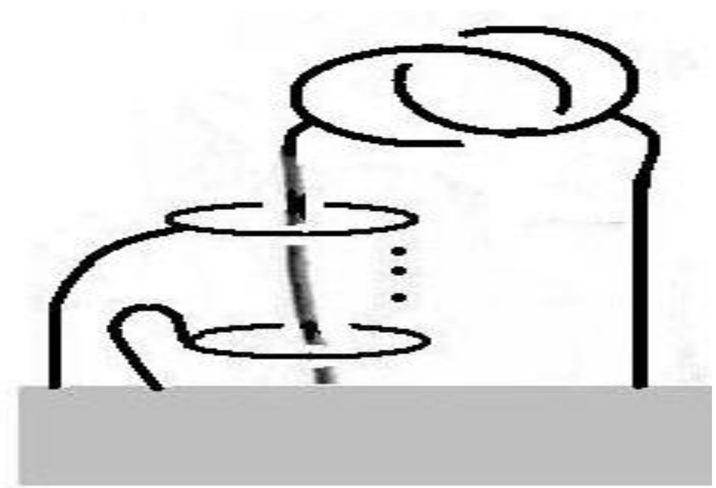
(2) The minimum of the crossing numbers of diagrams of non-split n-string prion-tangles granting non-trivial loop systems is 2n-2.

The following pictures give non-split n-string prion-tangles T with ℓ(T) a trivial link such that T is obtained from a trivial n-string prion-tangle by a one-crossing change and has a diagram D with c(D)=2n.





The following picture gives a non-split n-string prion-tangle T with ℓ(T) a non-trivial link such that T is obtained from a trivial n-string prion-tangle by a one-crossing change and has a diagram D with c(D)=2n-2.

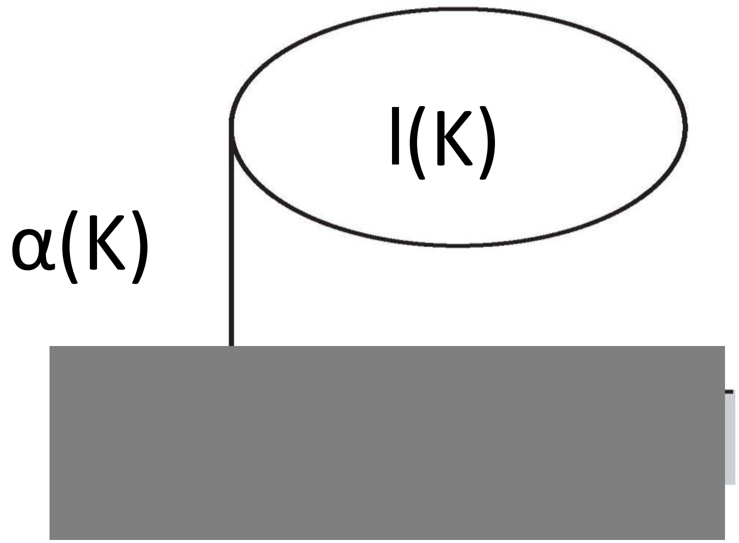


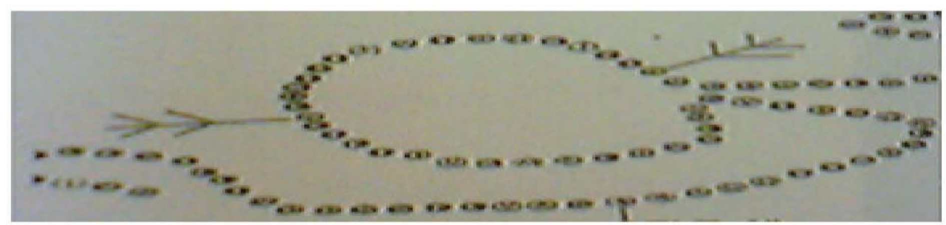
5. Conclusion and a further question

Our question on prions is:

Prion proteins are easily entangled ?

A prion-string is a spatial graph $K = \ell(K) \cup \alpha(K)$ in the upper half space $\mathbb{H}^3$ consisting of SS-loop $\ell(K)$ and GPI-tail $\alpha(K)$ joining the SS-vertex with the GPI-anchor.





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$$s\, PrP^{SC} + t\, PrP^{C} \rightarrow (s+t)\, PrP^{SC}.$$

S. B. Prusiner et al report

PrP^{SC}'s form Amyloid fibrils.

- S. B. Prusiner et al., Molecular properties, partial purification, and assay by incubation period measurements of the hamster scrapie agent, Biochemistry 19(1980), 4883-4891.

The following (1) and (2) on Amyloid fibrils are known:

(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.

- Y. Goto ,Amyloid Fibril Formation and Protein Science (in Japanese),POLYMERS,58,No.2(2009),92-96.

It would be interesting to consider:

Question. ***How is a knotting model of Amyloid fibrils constructed ?***