

Tied in Knots: Applications of knot theory to the study of protein mechanism.

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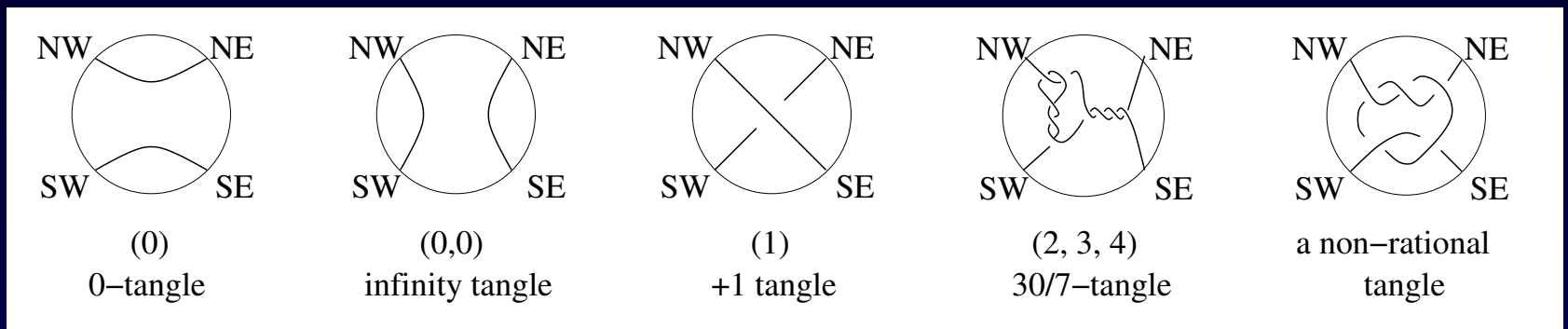
USA

darcy@utdallas.edu

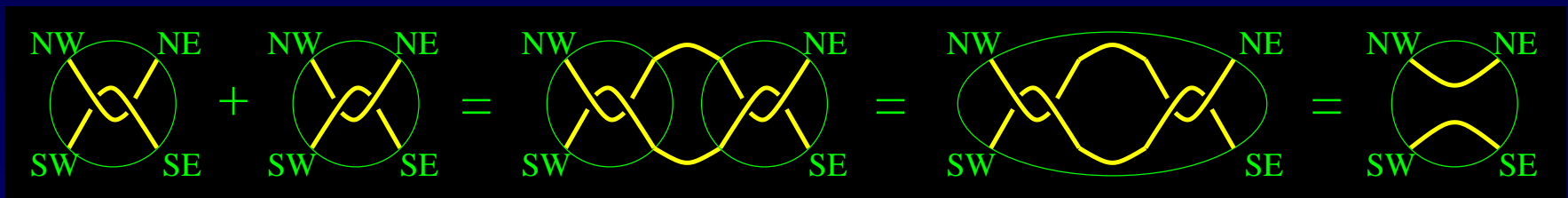
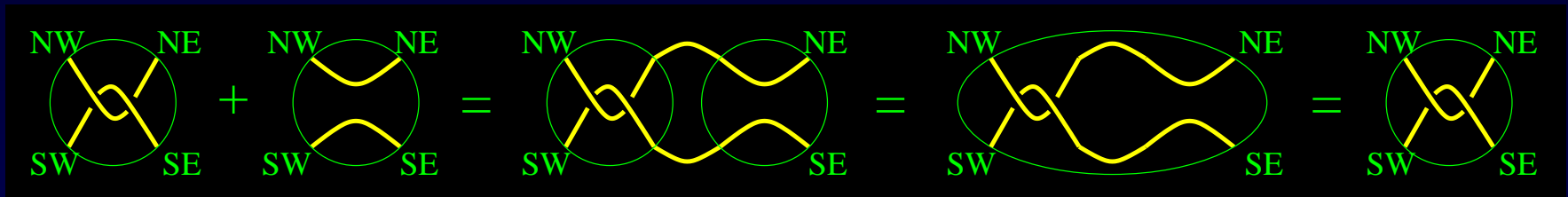
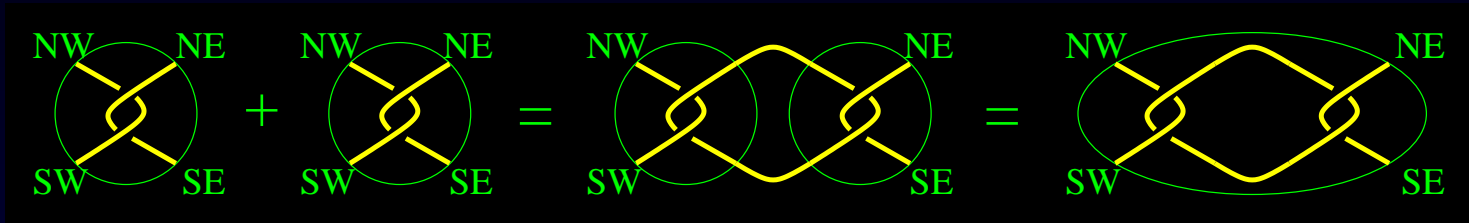
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Some notation:

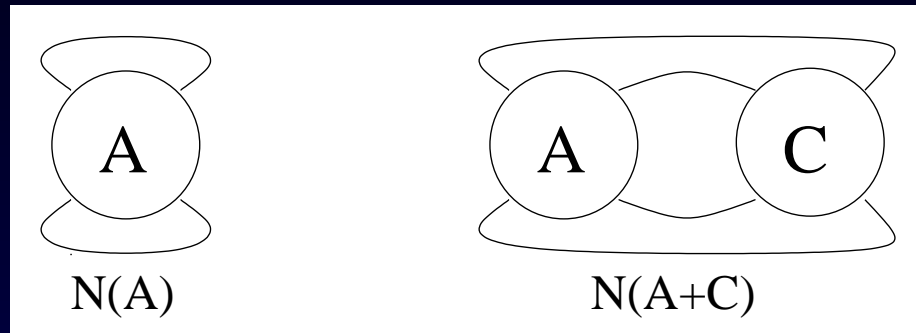
A 2-string tangle is a 3-dimensional ball containing two strings. Some examples:



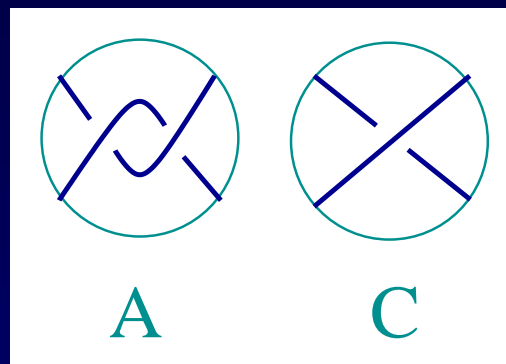
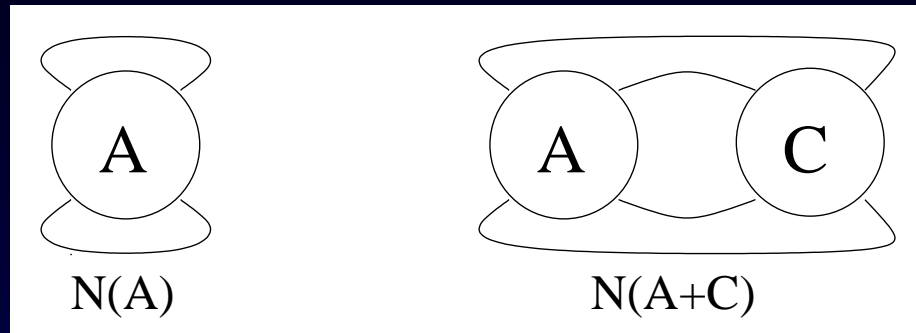
Tangles can be added:



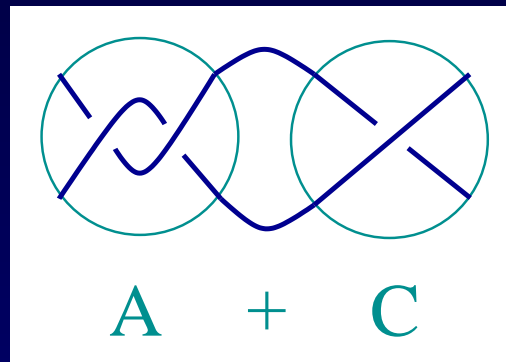
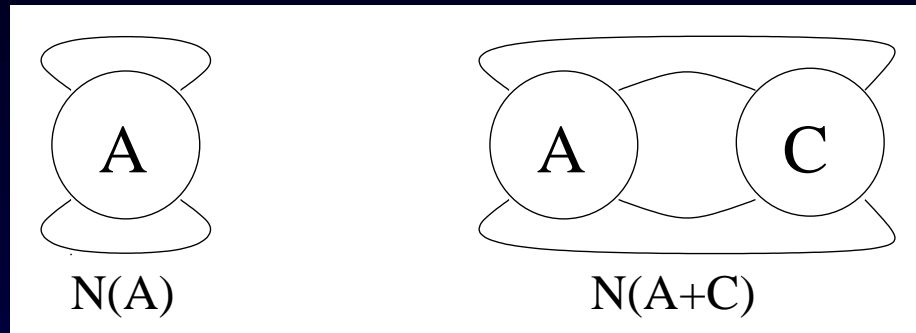
Knots and links can be formed by taking the numerator closure of a tangle or a sum of tangles



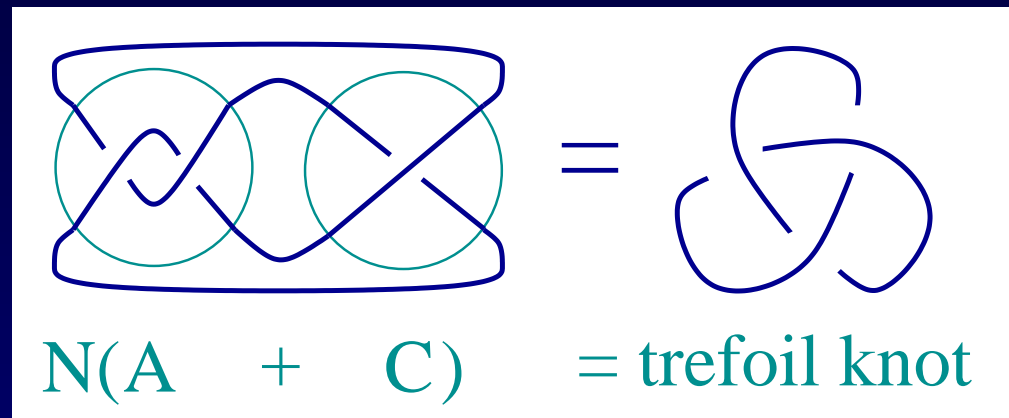
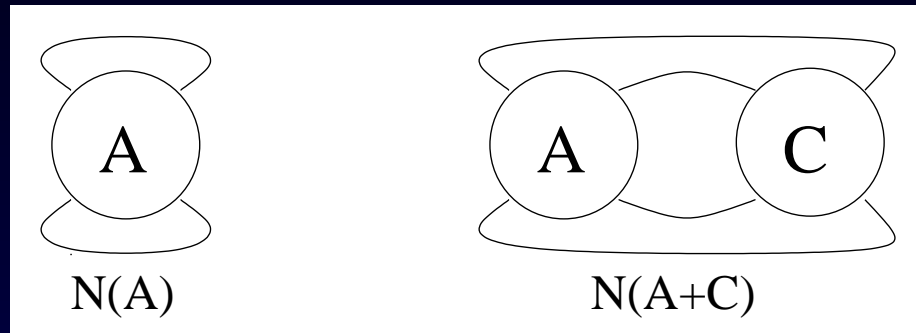
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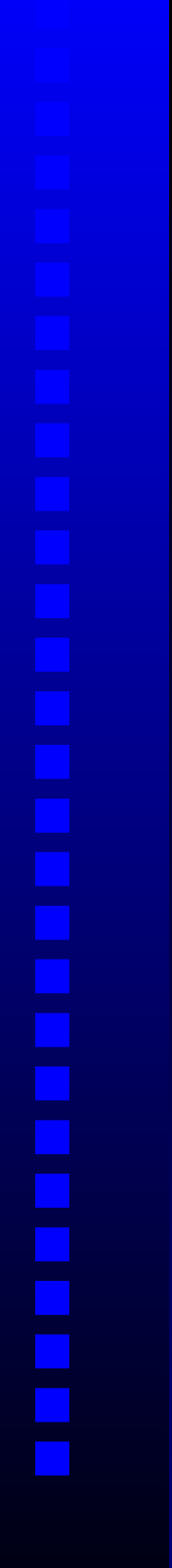


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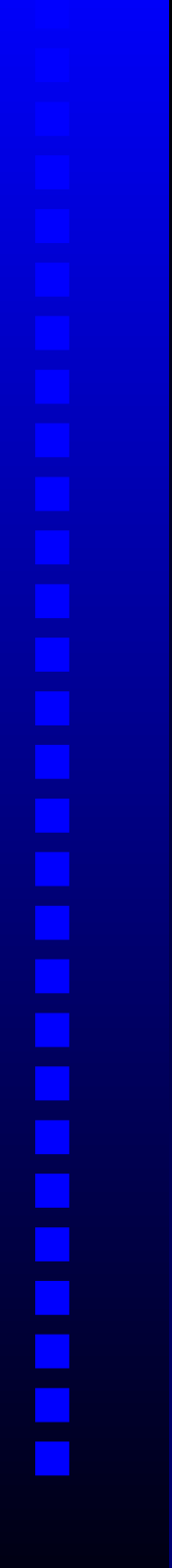


Knots and links can be formed by taking the numerator closure of a tangle or a sum of tangles





Solve $U_f + B = 2$



Solve $U_f + B = 2$

$$2 + 0 = 2$$

$$1 + 1 = 2$$

$$2 + (-1) \neq 2$$

Solve

$$\left(\begin{array}{c} \text{U}_f \\ \text{B} \end{array} \right) = \text{Knot}$$

Solve

$$\begin{array}{|c|c|} \hline U_f & B \\ \hline \end{array} = \text{Trefoil}$$

$$\begin{array}{|c|c|} \hline \text{Diagram 1} & \text{Trefoil} \\ \hline \end{array} = \text{Trefoil}$$

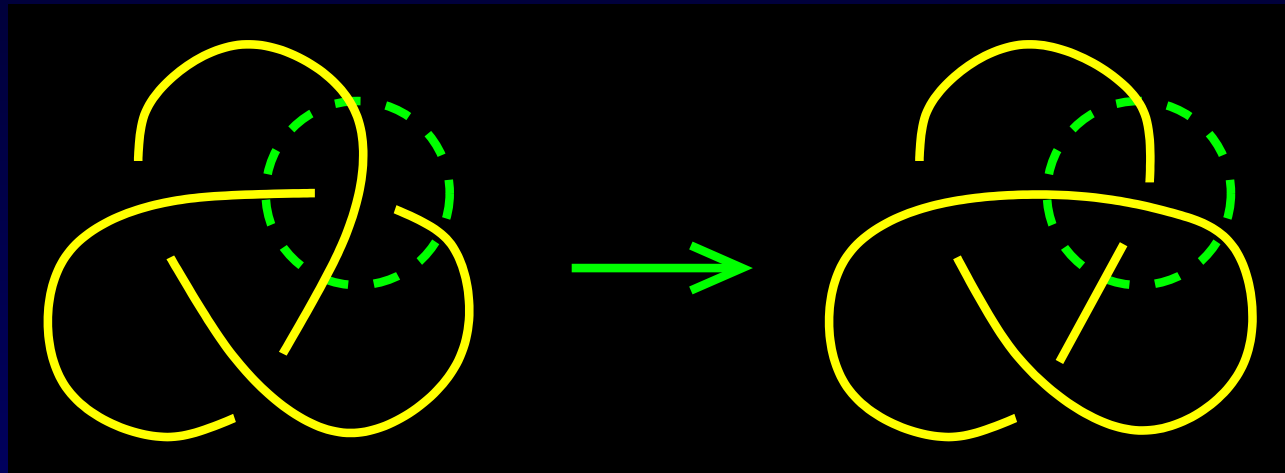
$$\begin{array}{|c|c|} \hline \text{Diagram 2} & \text{Trefoil} \\ \hline \end{array} = \text{Trefoil}$$

$$\begin{array}{|c|c|} \hline \text{Diagram 3} & \text{Trefoil} \\ \hline \end{array} \neq \text{Trefoil}$$



Why are we interested in solving these equations?

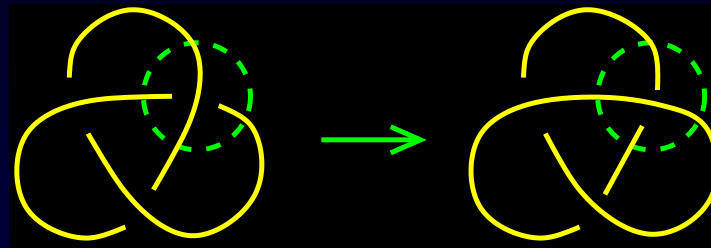
Topoisomerases are proteins which cut one segment of DNA allowing a second DNA segment to pass through before resealing the break.



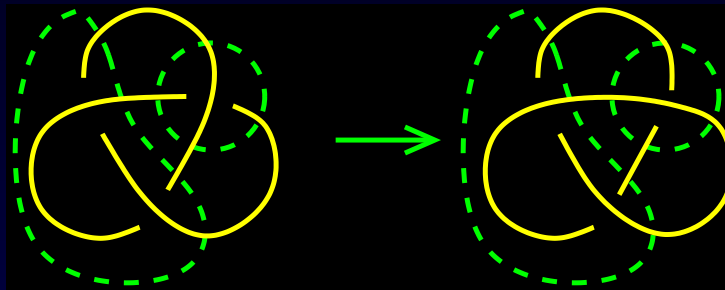
Topoisomerases are involved in

- Replication
- Transcription
- Unknotting, unlinking, supercoiling.
- Targets of many anti-cancer drugs.

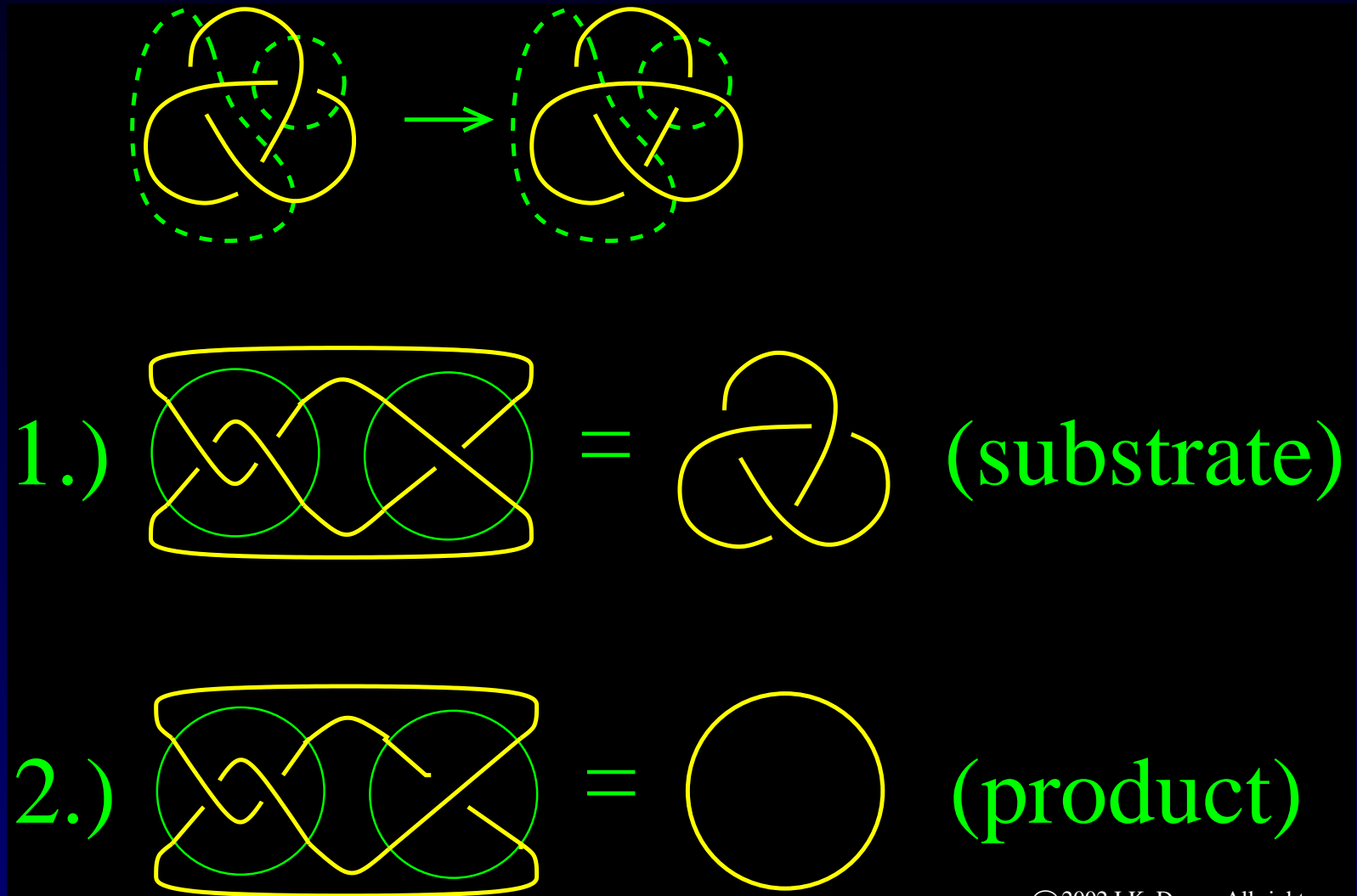
Thus topoisomerase action can be modeled using tangles:



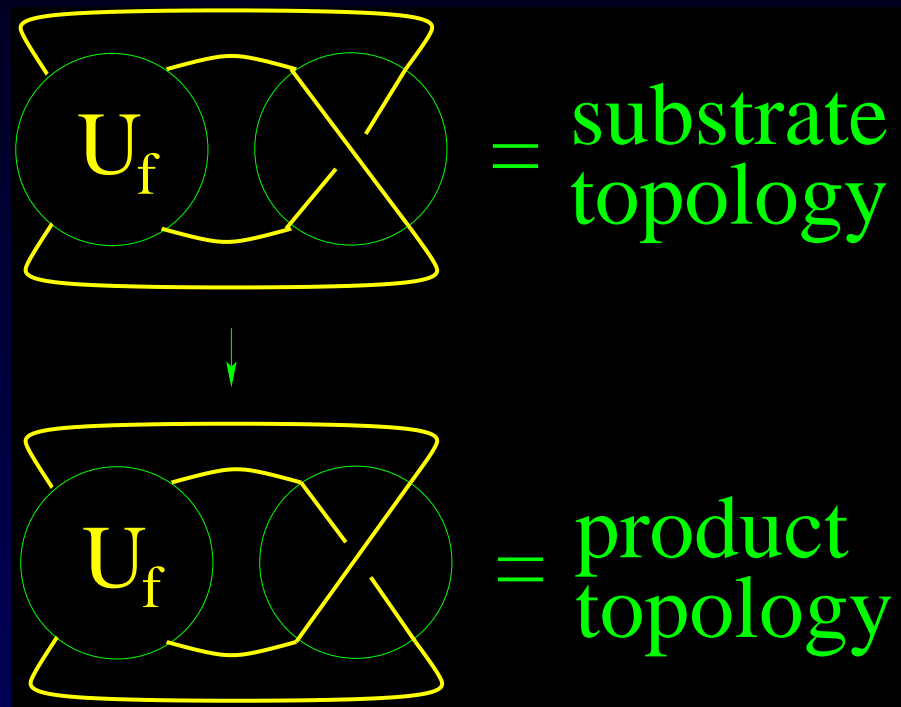
Thus topoisomerase action can be modeled using tangles:



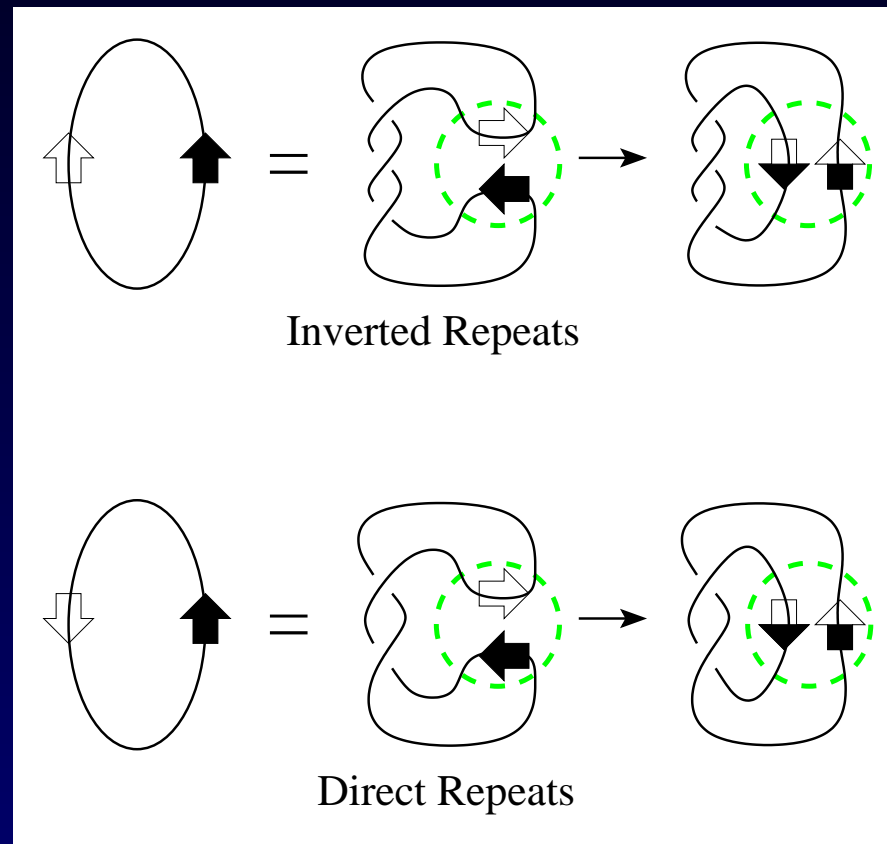
Thus topoisomerase action can be modeled using tangles:



Thus we are solving the tangle equations:



Recombinases are proteins which cut two segments of DNA and interchange the ends resulting in the inversion or the deletion or insertion of a DNA segment

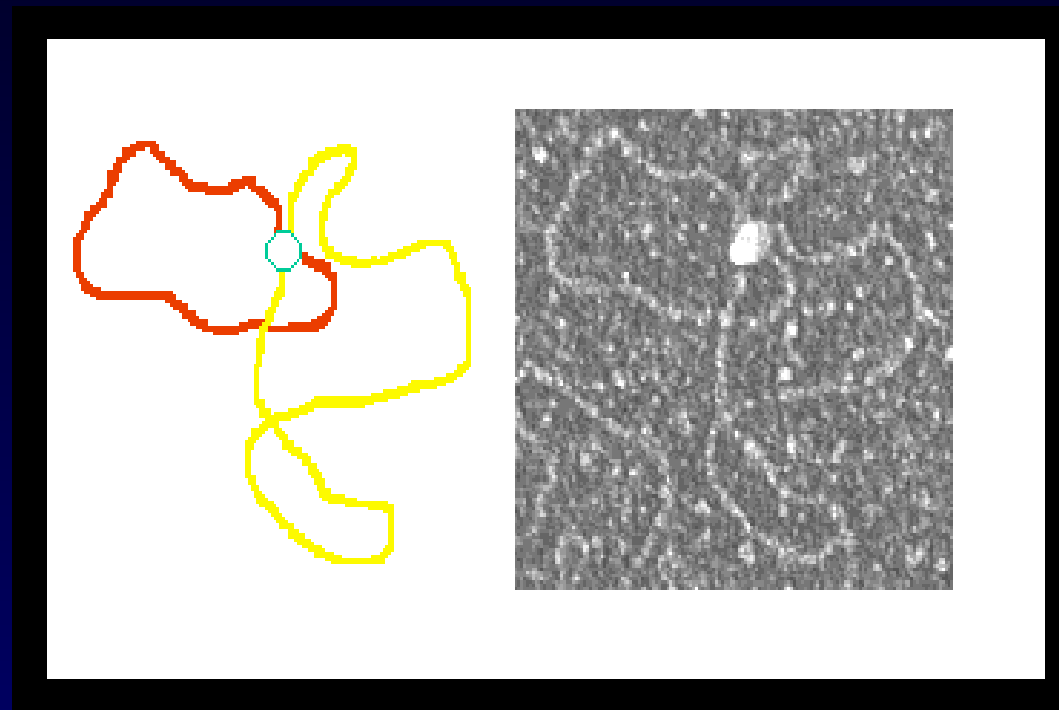


Recombinases are involved in

- gene rearrangement
- viral integration
- gene regulation
- copy number control
- gene therapy

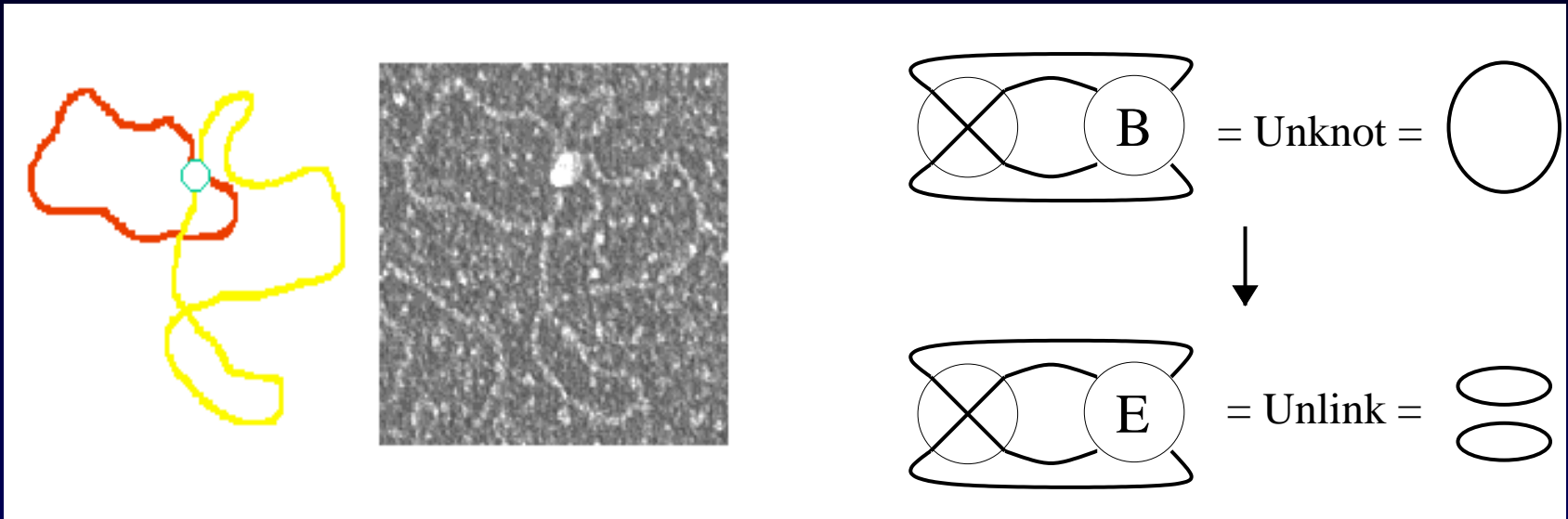
and in many more processes

A protein bound to two segments of DNA can be modeled by a tangle. An electron micrograph of the Flp DNA complex is shown below



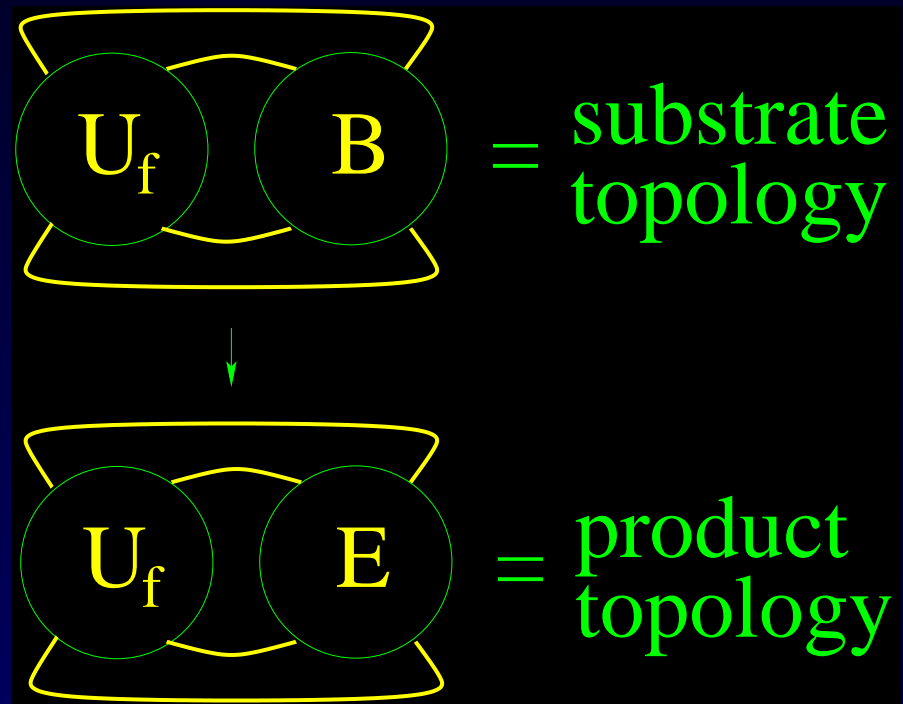
Electron micrograph courtesy of Kenneth Huffman and Steve Levene

The tangle equations corresponding to the electron micrograph:



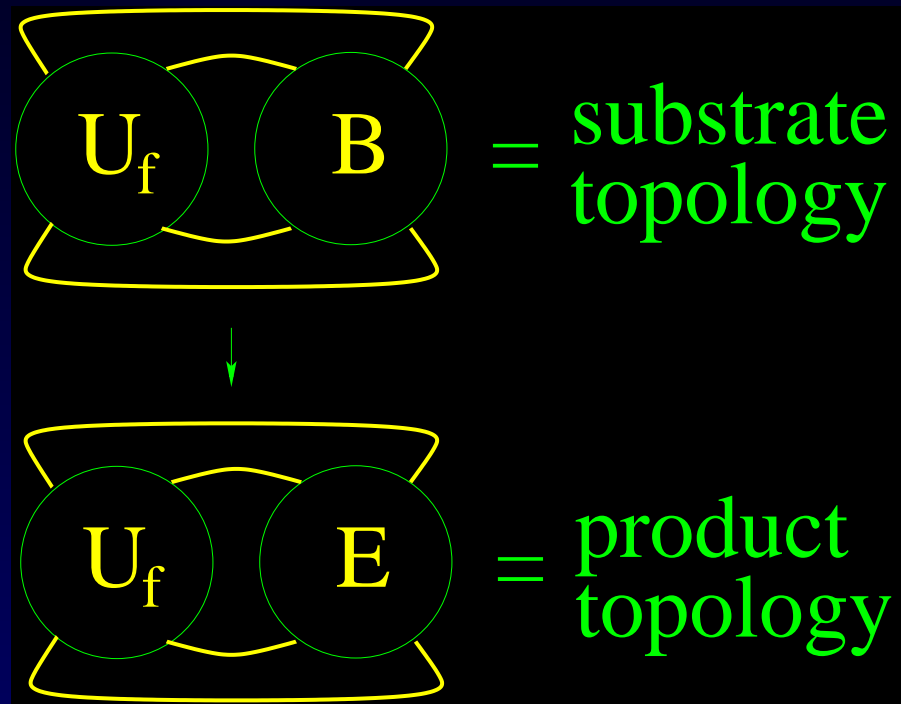
Electron micrograph courtesy of Kenneth Huffman and Steve Levene

In general, we are solving the tangle equations:

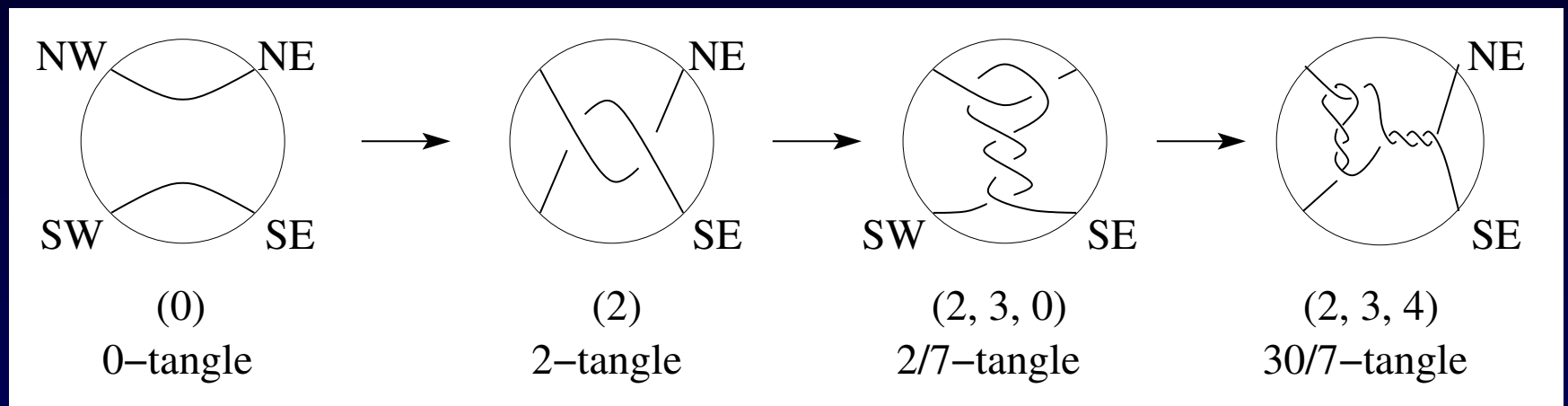


Solving Tangle Equations

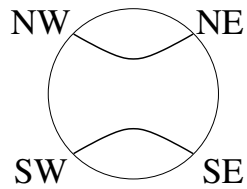
Step 1: Try to show that the tangles B and E are rational



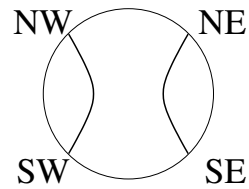
A tangle is rational if it is ambient isotopic to the zero tangle allowing the boundary of the 3-ball to move



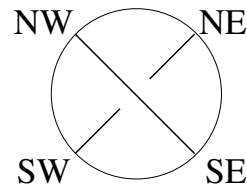
Tangle Examples



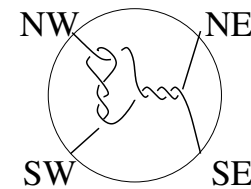
(0)
0-tangle



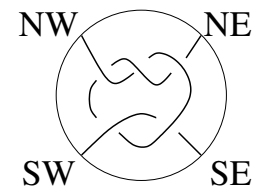
(0,0)
infinity tangle



(1)
+1 tangle



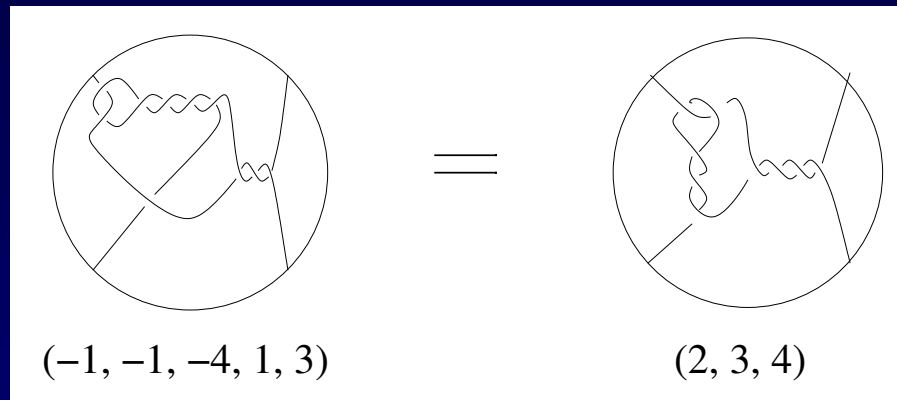
(2, 3, 4)
30/7-tangle



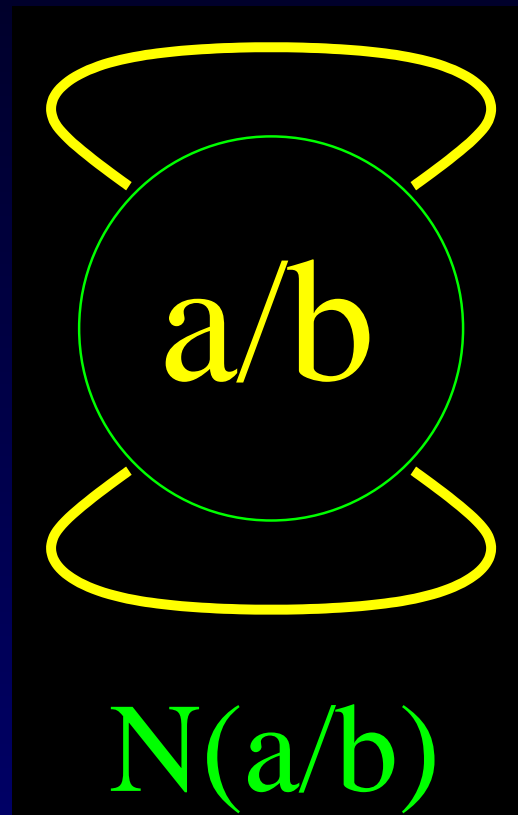
a non-rational
tangle

Rational tangles are uniquely identified by their corresponding continued fractions. For example the two tangles drawn below are equivalent since

$$4 + \frac{1}{3 + \frac{1}{2}} = \frac{30}{7} = 3 + \frac{1}{1 + \frac{1}{-4 + \frac{1}{-1 + \frac{1}{-1}}}}$$

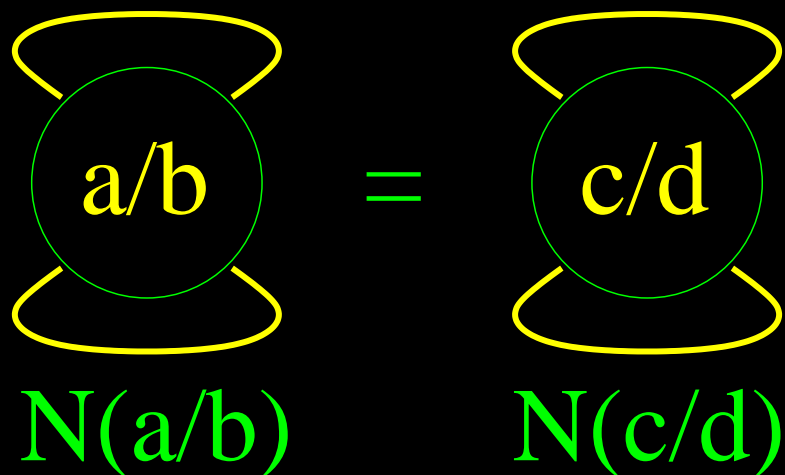


Definition: The numerator closure of a rational tangle is a rational knot or link (also called 4-plat or 2-bridge knot/link).



Rational knot/link equivalence

Take $a, c \geq 0$.


$$\begin{array}{ccc} \text{Diagram 1} & = & \text{Diagram 2} \\ \text{N}(a/b) & & \text{N}(c/d) \end{array}$$

if and only if

$$a = c$$

and

$$bd^{\pm 1} = 1 \pmod{a}$$

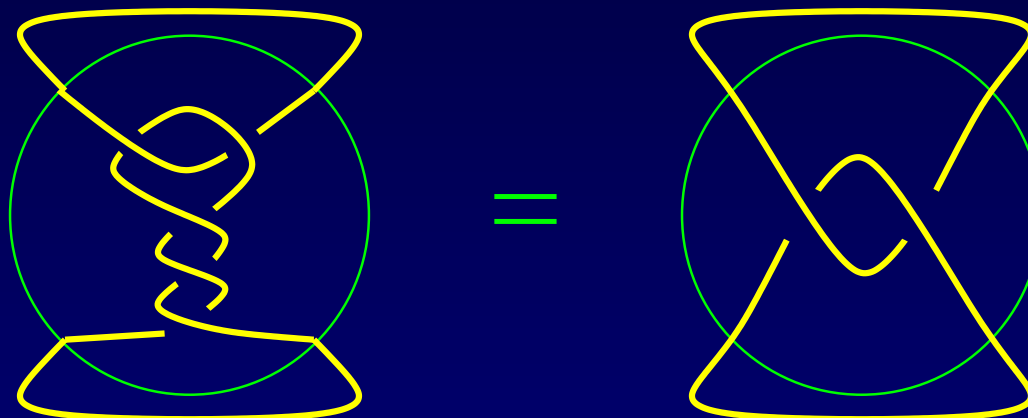
For example,

$$N((2, 3, 0)) = N(0 + \frac{1}{3+\frac{1}{2}}) = N(\frac{2}{7})$$

$$\text{and } N((2)) = N(\frac{2}{1}) = N((2))$$

$$\text{Thus, } N((2, 3, 0)) = N(\frac{2}{7}) = N(\frac{2}{1}) = N((2))$$

$$\text{since } 7 = 1 + 2(3)$$

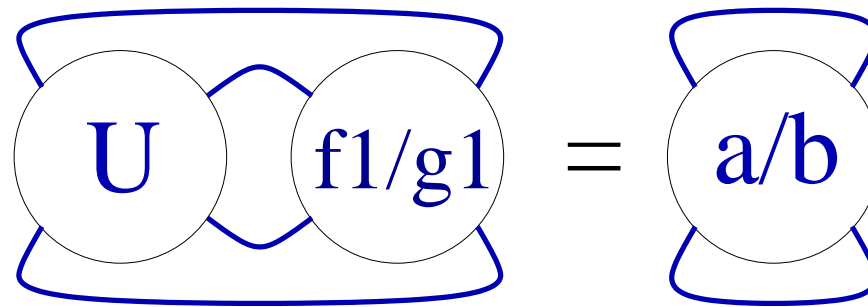


The numerator closure of the sum of two rational tangles is a rational knot or link

$$\left(\frac{j}{p} \right) \# \left(\frac{f}{g} \right) = \frac{jg + pf}{dg + qf}$$

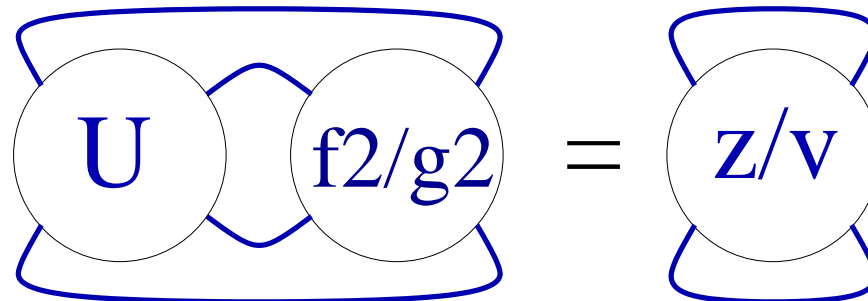
where $dp - qj = 1$

Goal: Given a, b, z, v , solve the following system of tangle equations for the tangles U and f_2/g_2 in terms of f_1/g_1 .



$$\text{Diagram 1: } U \text{ and } f_1/g_1 \text{ in a box} = a/b \text{ in a box}$$

and



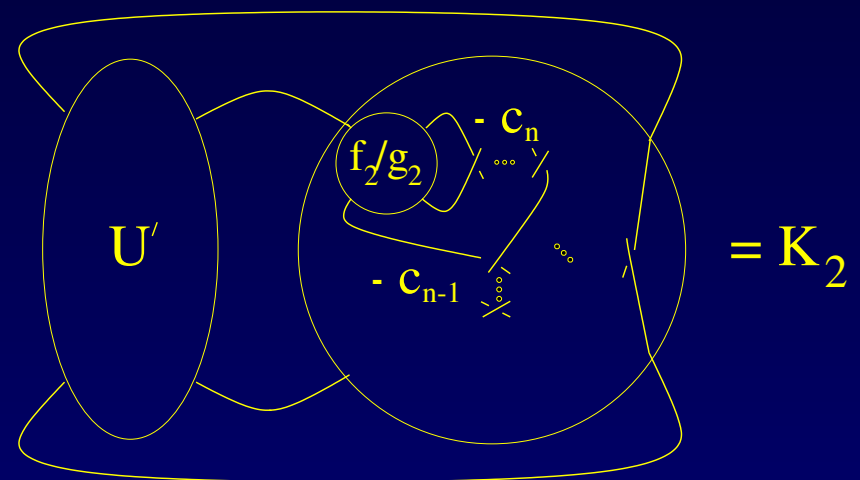
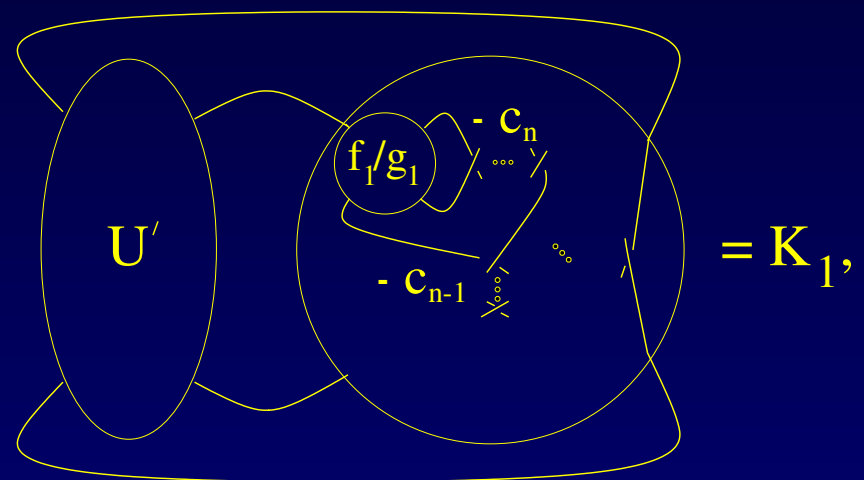
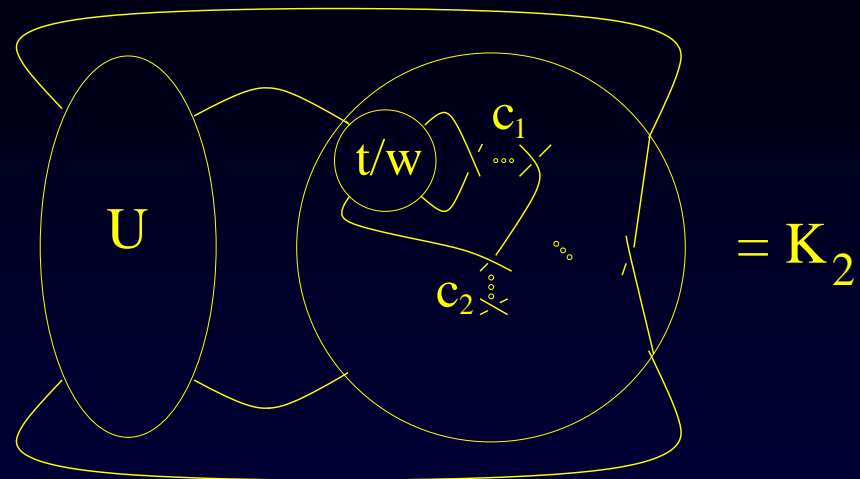
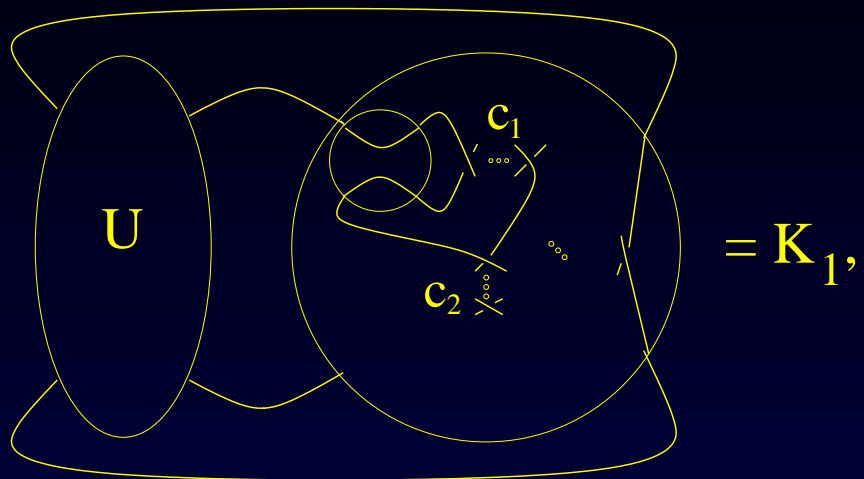
$$\text{Diagram 2: } U \text{ and } f_2/g_2 \text{ in a box} = z/v \text{ in a box}$$

Solving

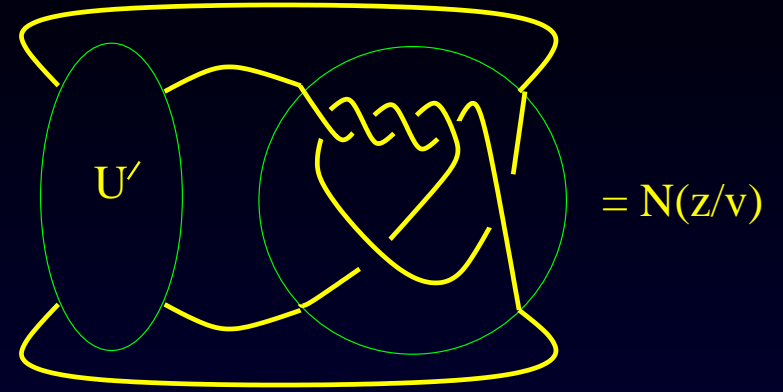
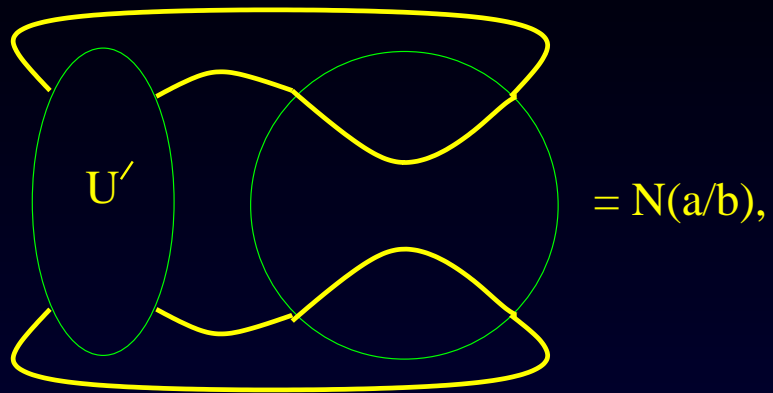
$$x + y = 2$$

is equivalent to solving

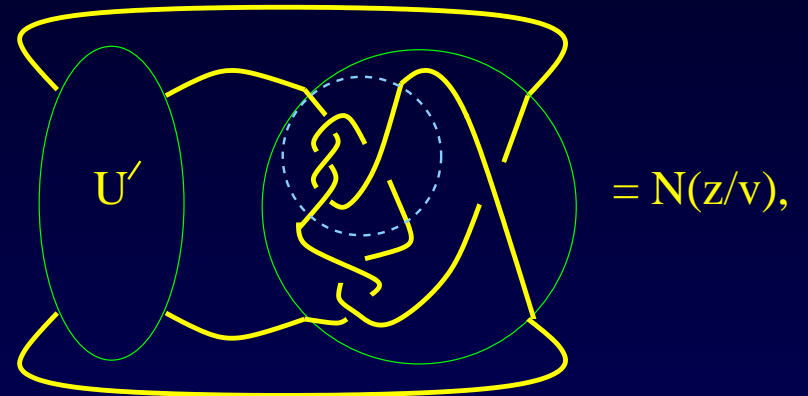
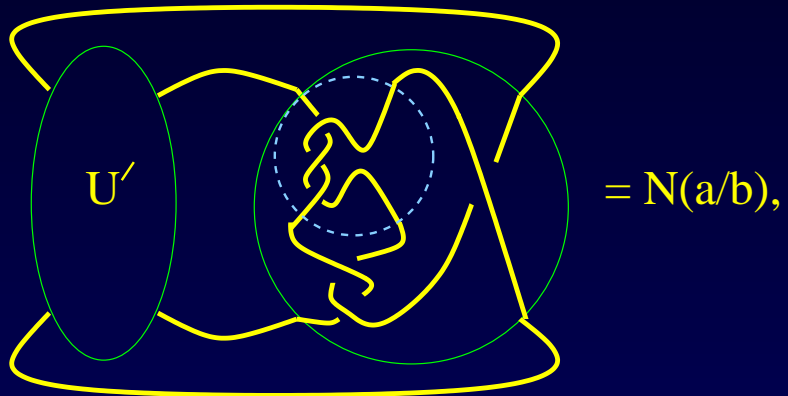
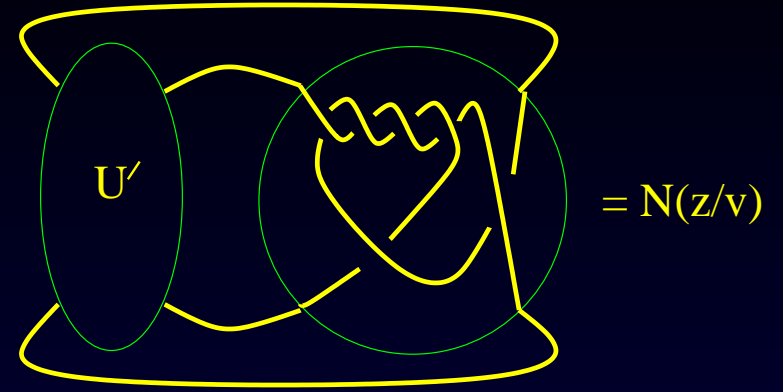
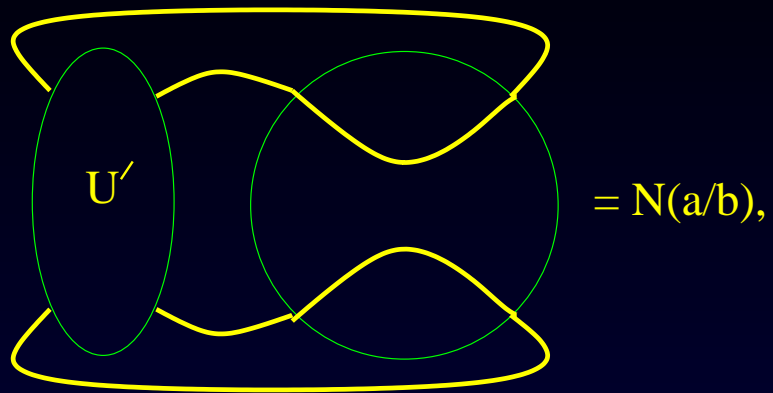
$$(x + y) + 0 = 2$$



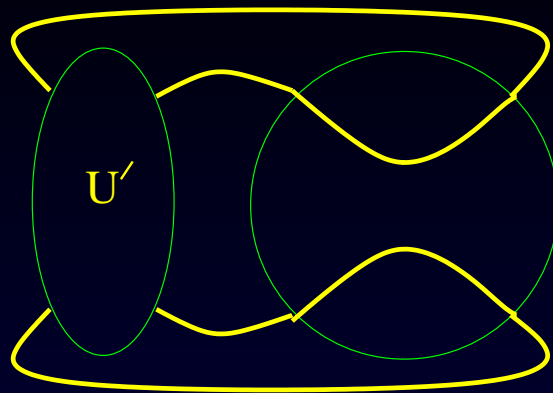
Example



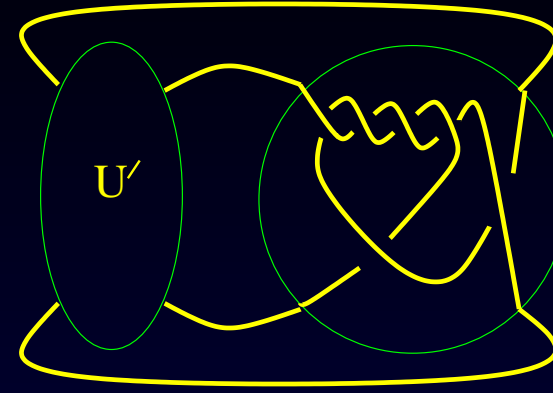
Example



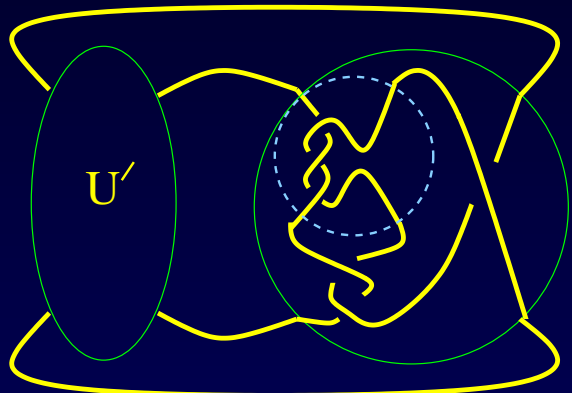
Example



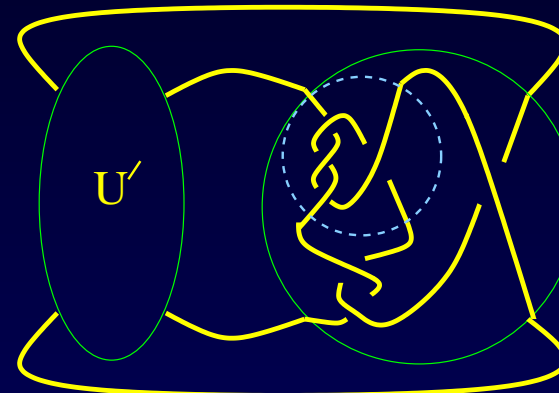
$$= N(a/b),$$



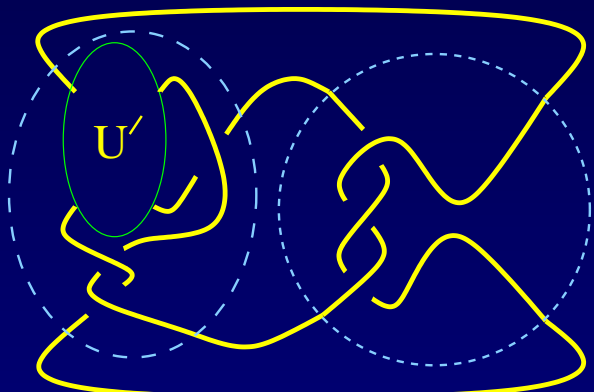
$$= N(z/v)$$



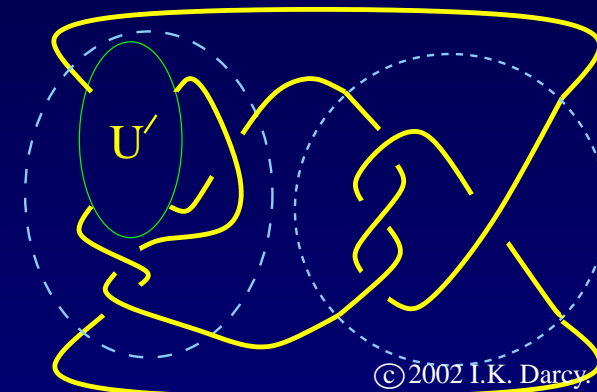
$$= N(a/b),$$



$$= N(z/v),$$



$$= N(a/b),$$



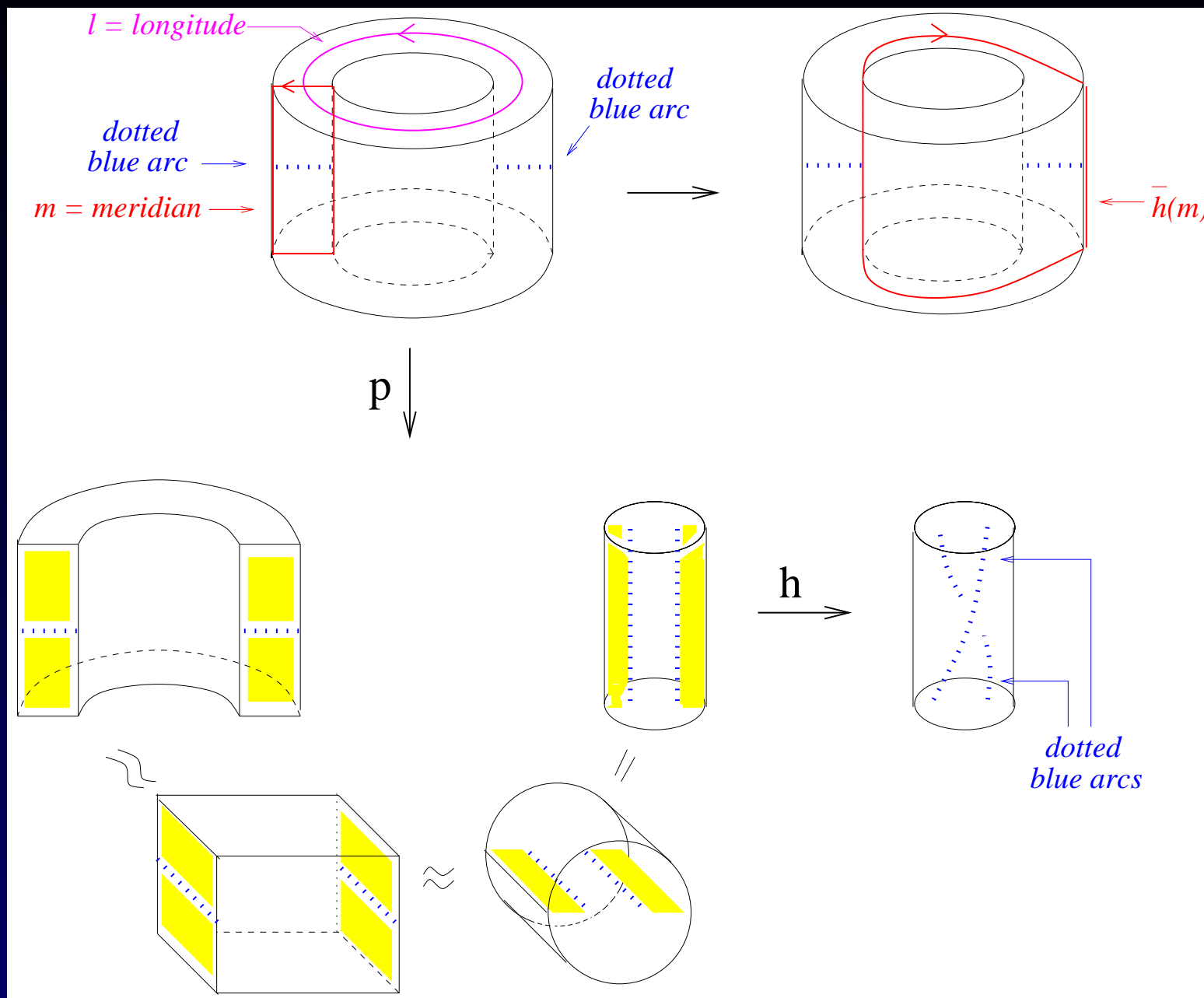
$$= N(z/v)$$

Step 2: Given a, b, z, v , solve the following system of tangle equations for the tangles U and t/w .

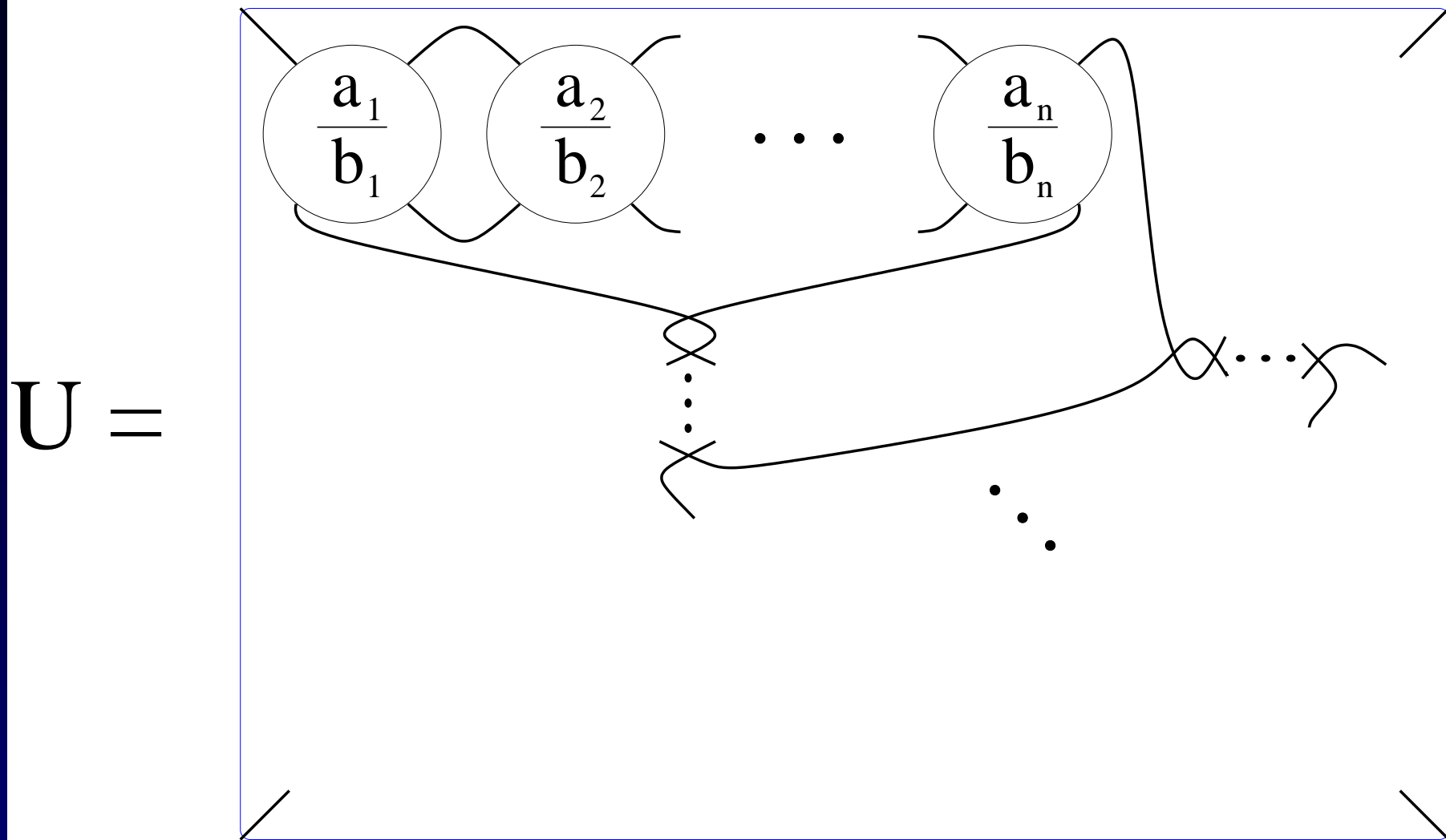
A diagram showing a tangle U (represented by a circle) connected to a tangle a/b (represented by a circle). The connection is made by two strands that enter from the left, pass through U , and then enter a/b from the left. The strands exit a/b from the right and loop back to enter U from the right. This is equal to a single tangle a/b where the strands enter from the top and exit from the bottom.

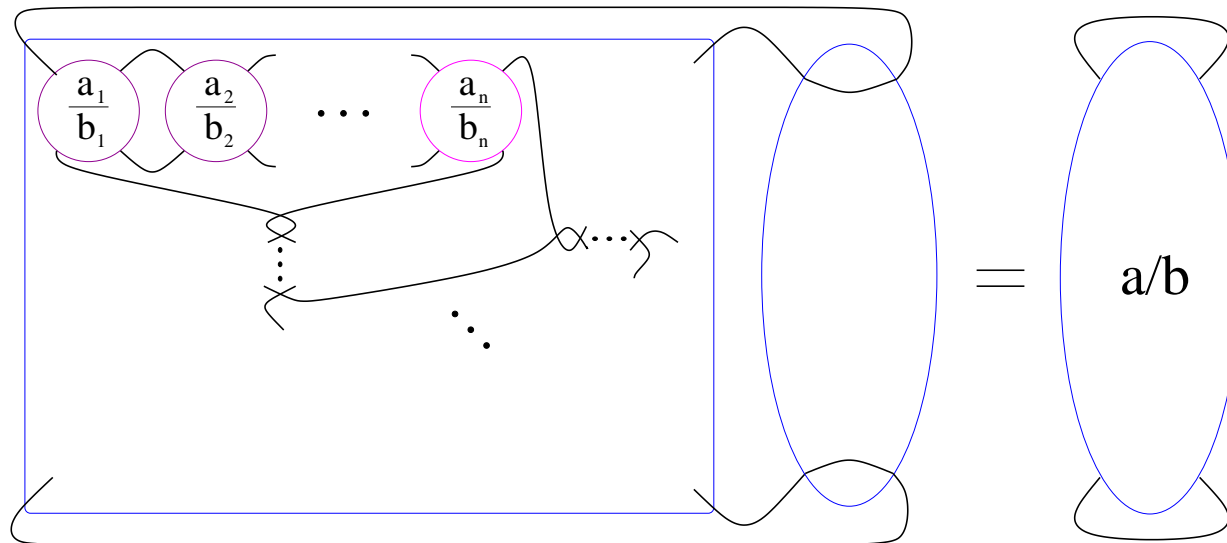
and

A diagram showing a tangle U (represented by a circle) connected to a tangle t/w (represented by a circle). The connection is made by two strands that enter from the left, pass through U , and then enter t/w from the left. The strands exit t/w from the right and loop back to enter U from the right. This is equal to a single tangle z/v where the strands enter from the top and exit from the bottom.

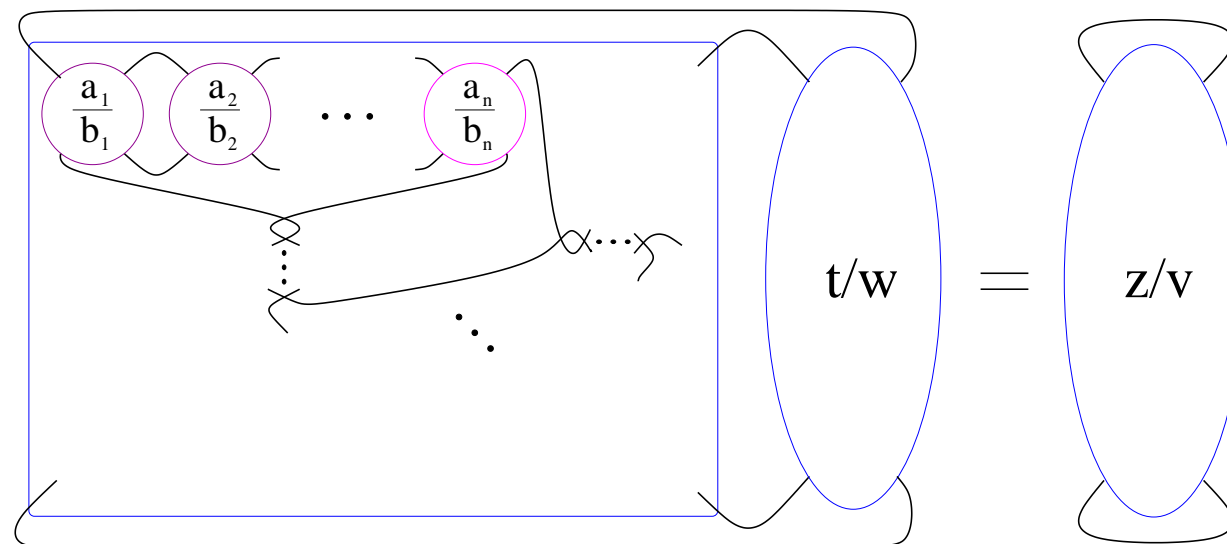


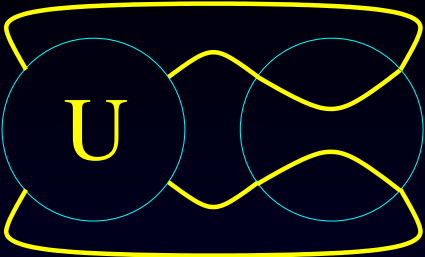

Cyclic Surgery Thm + Ernst implies

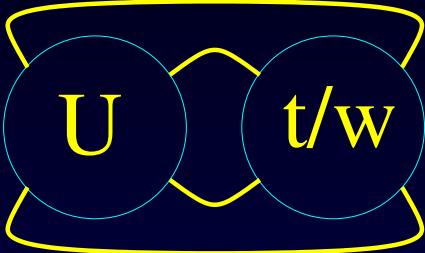






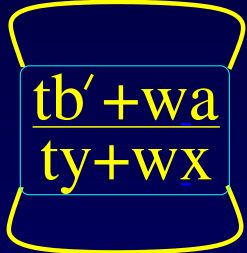
and



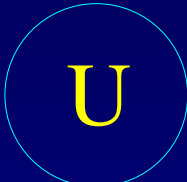
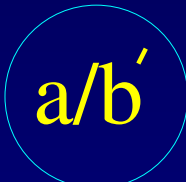
If  = 

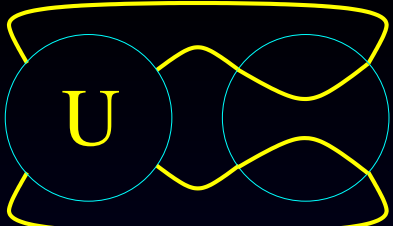
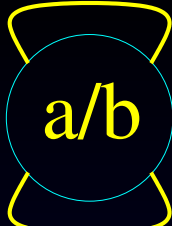
and  = 

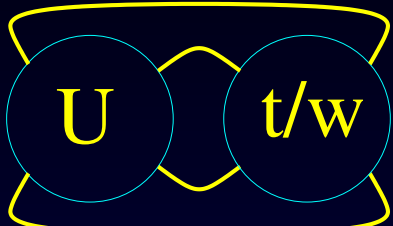

then if $w \not\equiv \pm 1 \pmod t$,

 = 


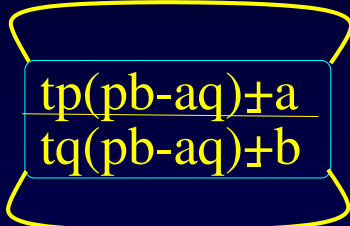
where $b' b^{\pm 1} \equiv 1 \pmod a$, $b' x - ay = 1$,

and  = 


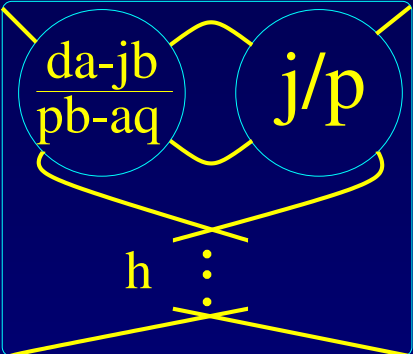
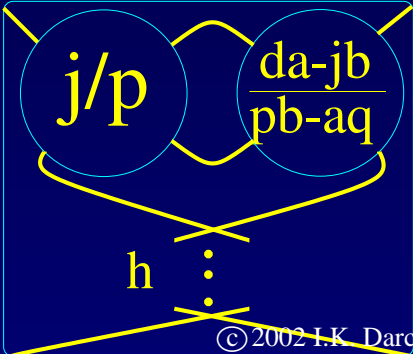
If  = 

and  = 

then if $w = \pm 1 \pmod t$,

 = 

where $(p,q) = 1$, $h = \frac{-w \pm 1}{2}$, and

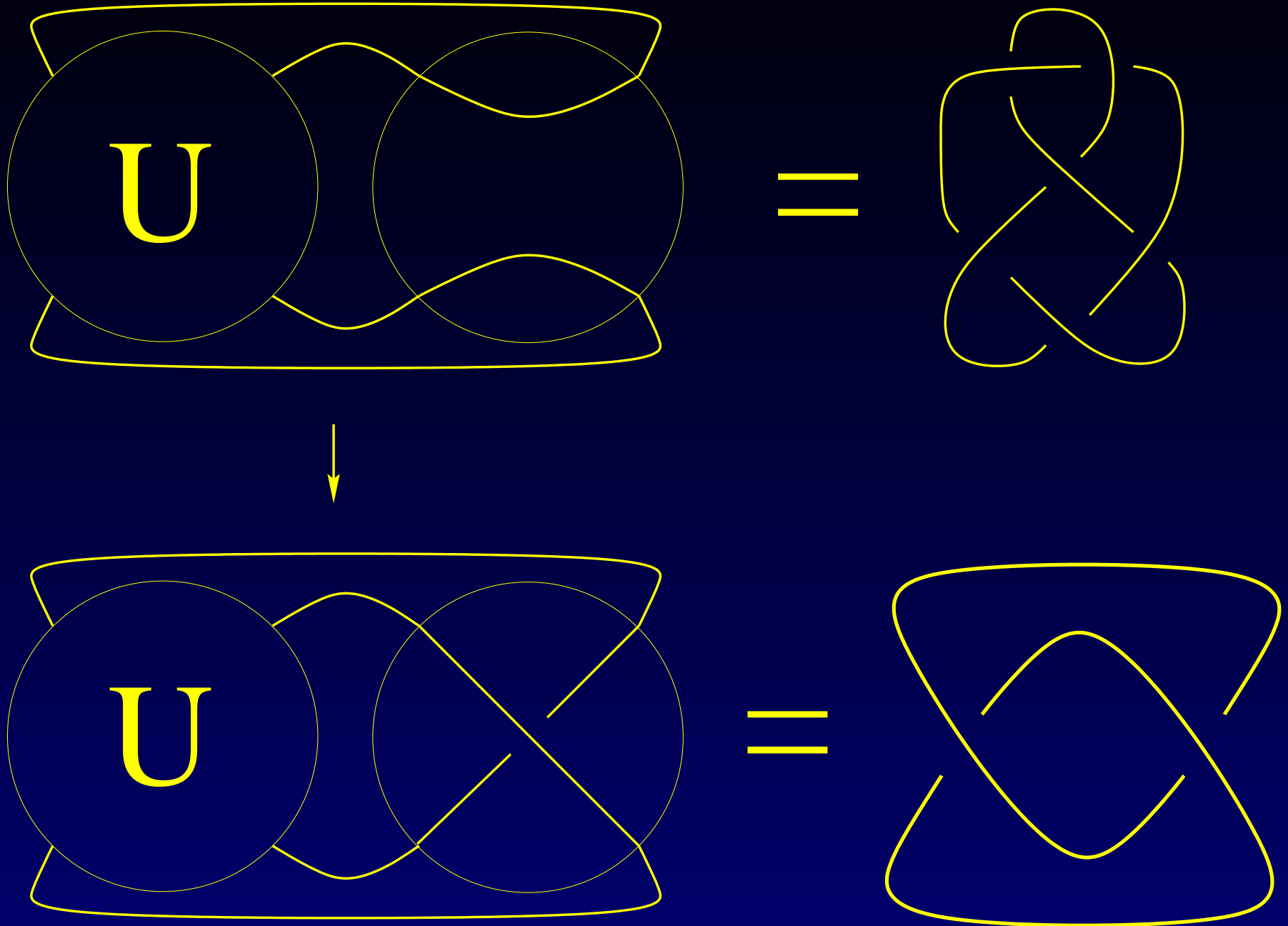
 =  & 

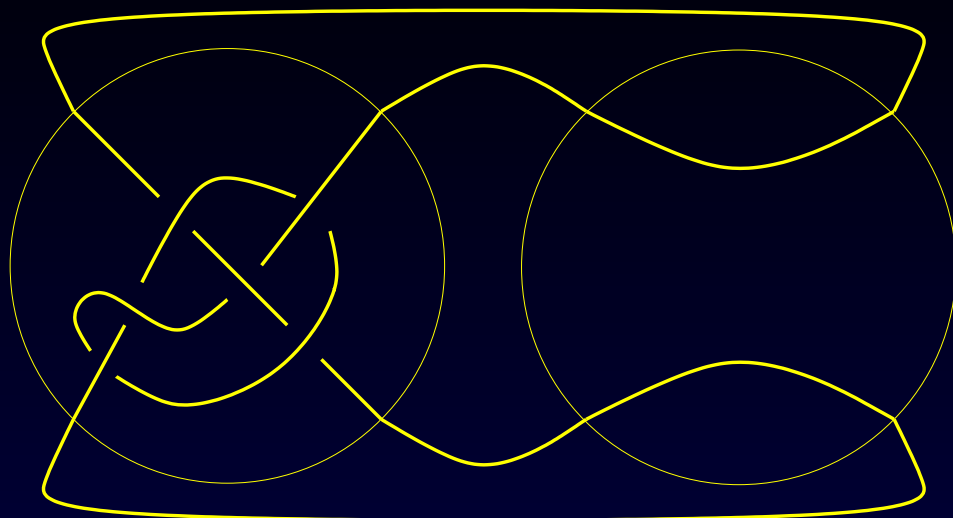
Unfortunately, when

$$B = \text{[diagram of a circle with two internal yellow arcs forming a lens shape]} \quad \text{and} \quad E = \text{[diagram of a circle with a yellow wavy line and a dashed line inside]}$$

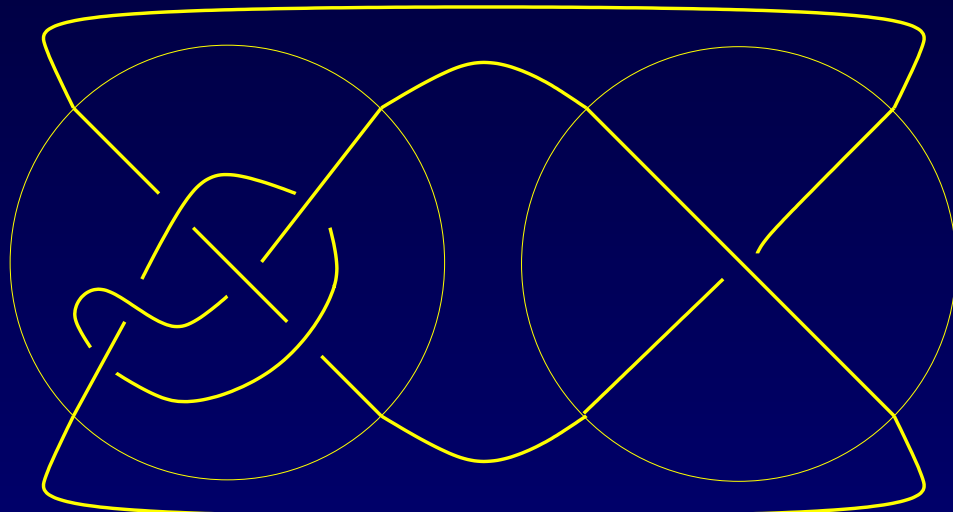
not all solutions are found.

For example,

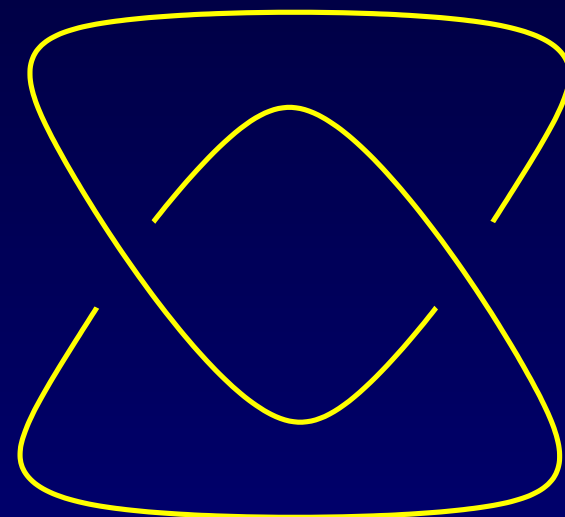




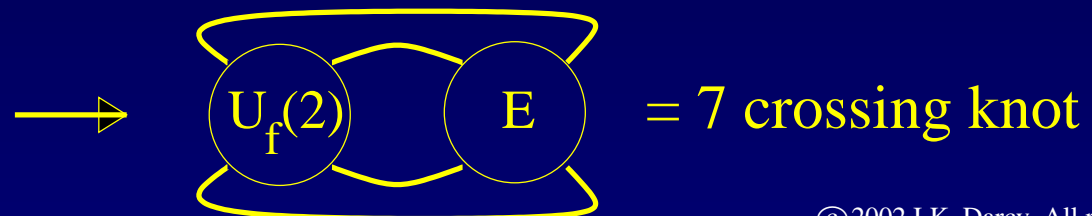
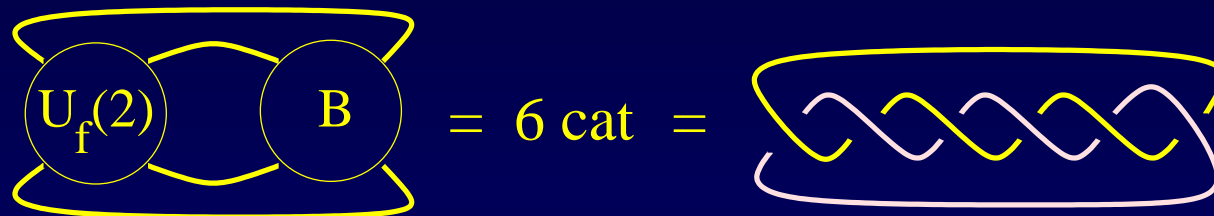
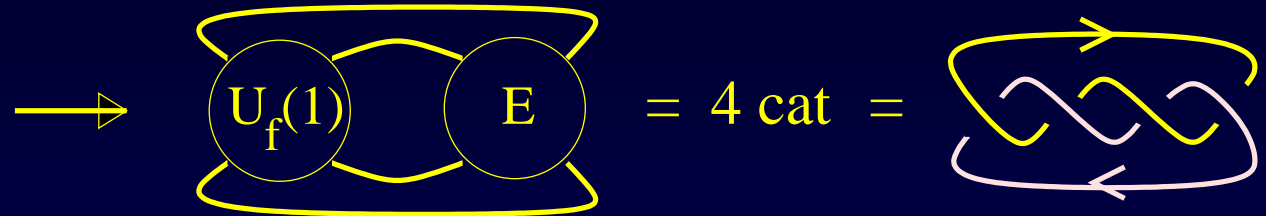
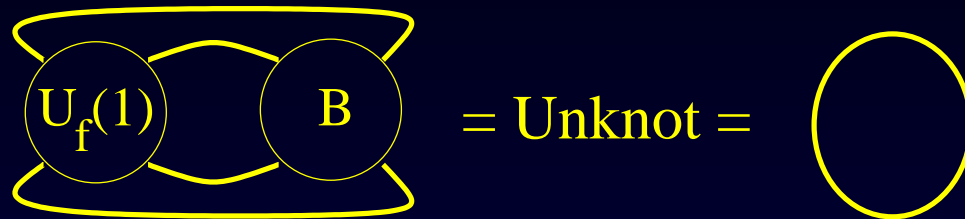
=



=



Xer recombination results in a unique product dependent on substrate (J. Bath, D.J. Sherratt, S.D. Colloms, JMB 1999):



input A or 99 to exit
1

input B
1

input Z
4

input V
-1

$$N(1/(1 + 1k) + 0/1) = N(1/1)$$

0/1 is similarly oriented if k even, and oppositely oriented if k odd

$$N(1/(1 + 1k) + (1 - 4i)/[3 + 4i - k(1 - 4i)]) = \\ N(4/3) = N(4/-1)$$

$$t = 1, (p,q) = (1, -2)$$

$$N(1/(1h + 3) + 0/1) = N(1/1)$$

Yuki Saka and Mariel Vazquez (5 July)

<http://bio.math.berkeley.edu/TangleSolve/>

Φ { +6 torus link } \rightarrow { (7, crs) }
 7 products: (5 knots, 2 links)
 12 solutions: (with 0 rational: 6, with 0 Sum of two rationals: 6)
 +6 torus link \rightarrow -7 torus knot
 +6 torus link \rightarrow +7 torus knot
 +6 torus link \rightarrow -7 twist knot
 +6 torus link \rightarrow (1 3 1 1 1)
 +6 torus link \rightarrow (1 2 1 2 1)
 +6 torus link \rightarrow (1 2 1 2 1)
 0 = (-3 0) + (-3 0), R = (-1)
 +6 torus link \rightarrow (1 2 1 1 2)
 +6 torus link \rightarrow (1 1 1 1 1 1)


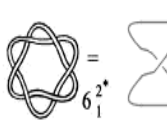

1)

2)


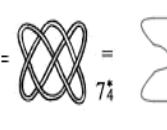
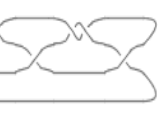
3)

4)

Knot/Link illustrations from *Knots and Links*
by Dale Rolfsen (Publish or Perish Press, 1976)


 $=$

 $=$


$N(-3\ 0) + (-3\ 0) + (0) =$ RH 6 torus link


 $=$

 $=$


$N(-3\ 0) + (-3\ 0) + (-1) = (1\ 2\ 1\ 2\ 1)$

2)

1) Selection Panel

2) Display Panel

3) Input Panel

4) Knot/link Table

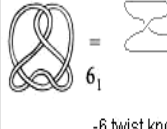
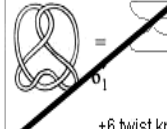
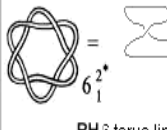
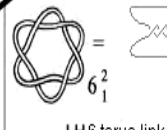
Input Pane

Tangle Diagram Processive Non Processive

Substrate(s): { (1 4 1) } / crossing # From Table

Product(s): { } / crossing # 7 From Table

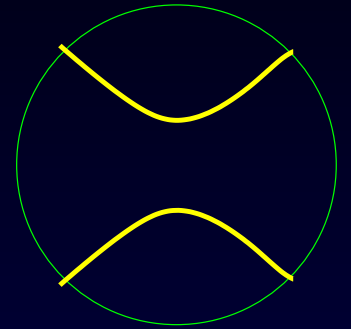
Solve

 $6_1^2^*$ -6 twist knot	 $6_1^2^*$ +6 twist knot
 $6_1^2^*$ RH 6 torus link	 $6_1^2^*$ LH 6 torus link

6-crossings (+6 torus link)

Solutions:

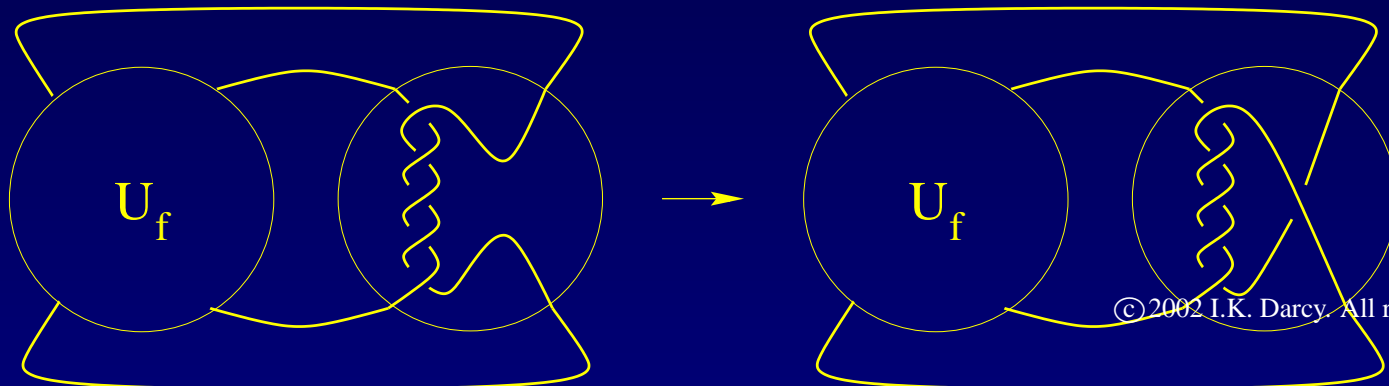
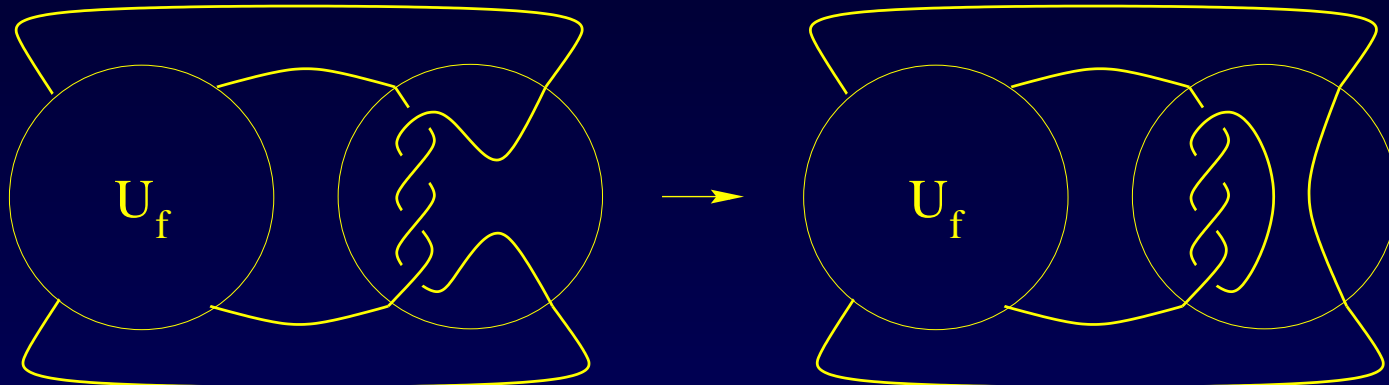
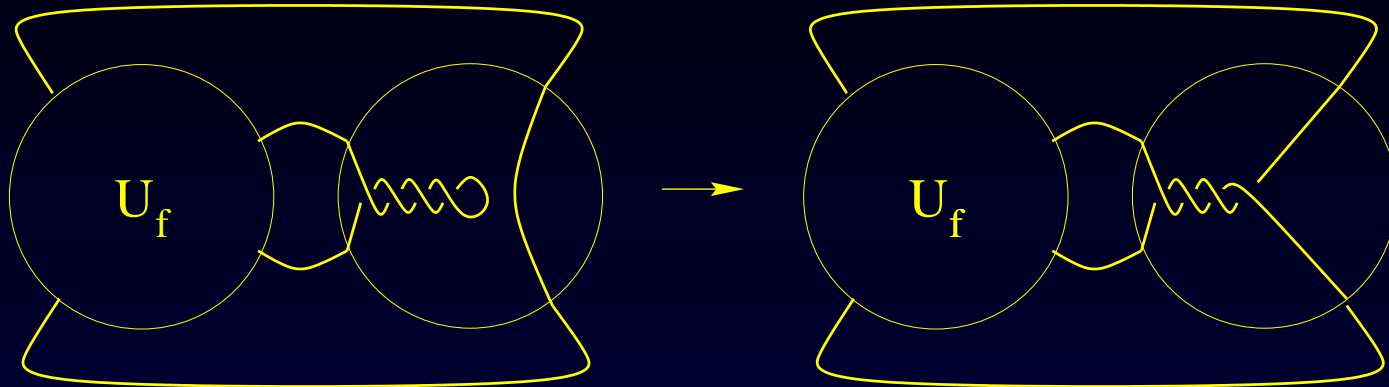
B is rational and if $B =$



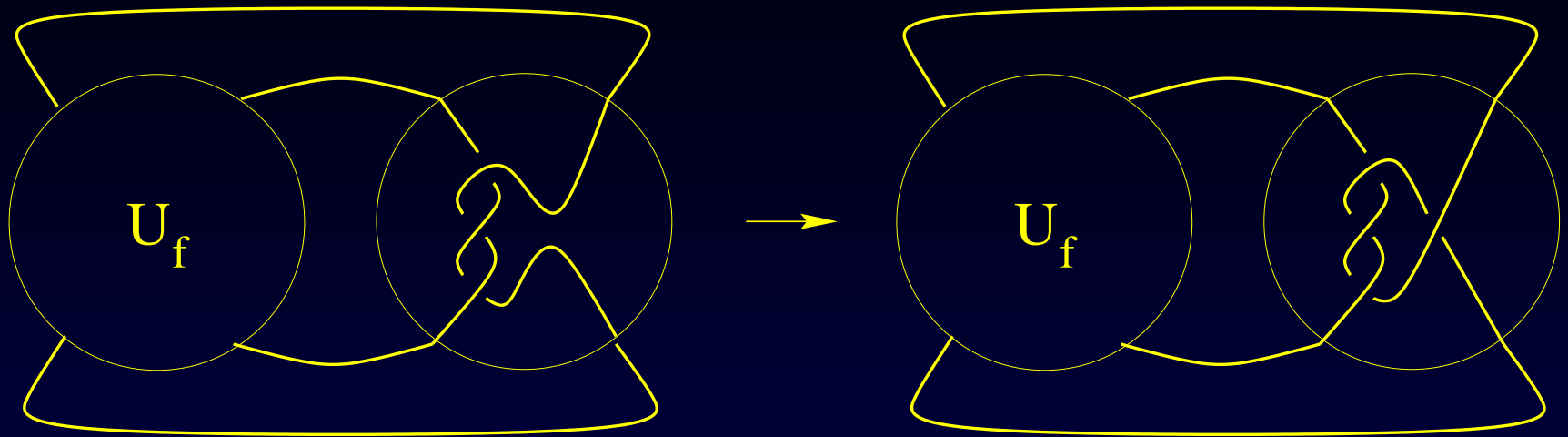
and if E is rational,



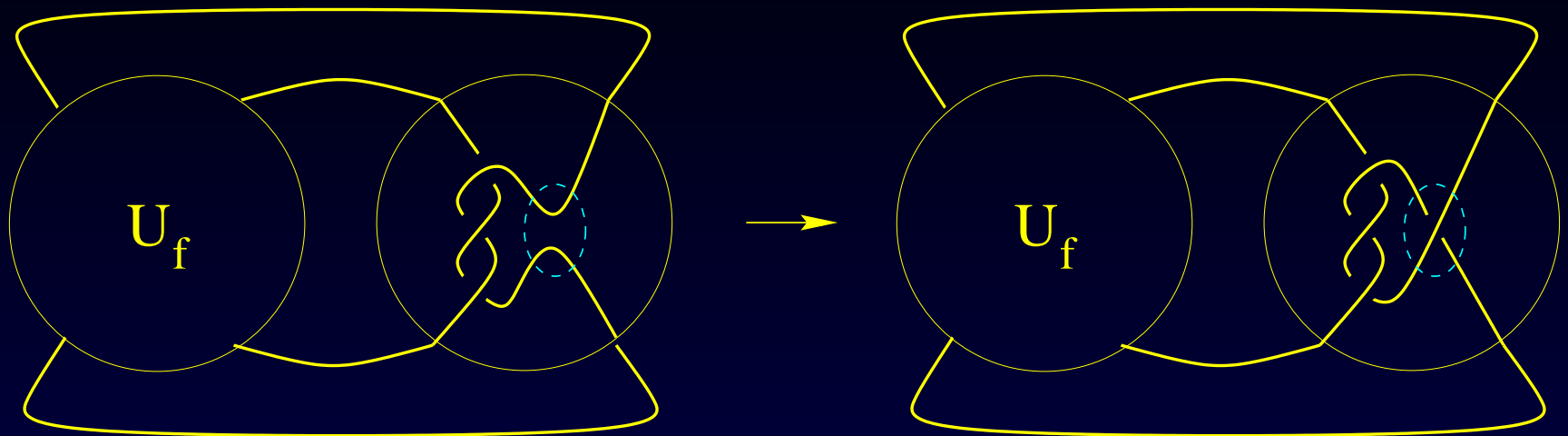
The following are NOT possible models for XER recombination:



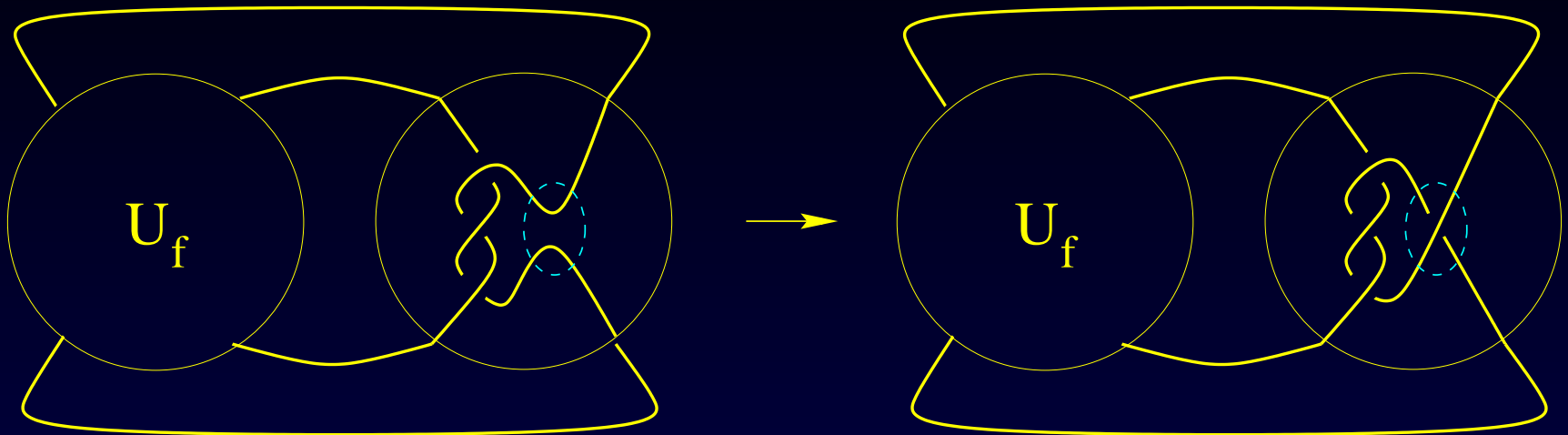
The following is a possible model for
XER recombination:



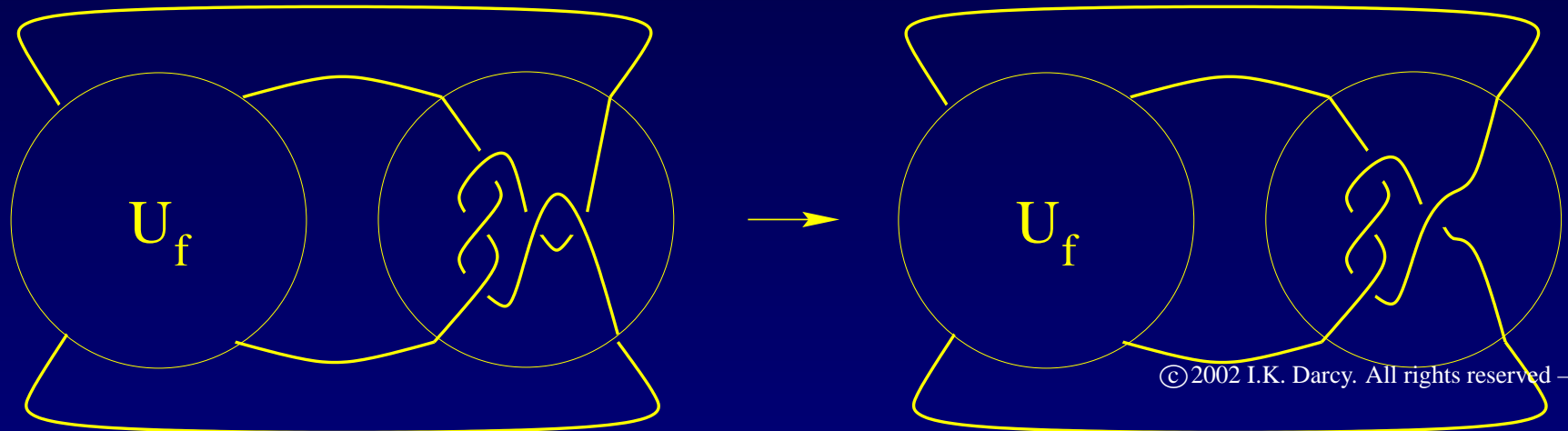
The following is a possible model for
XER recombination:



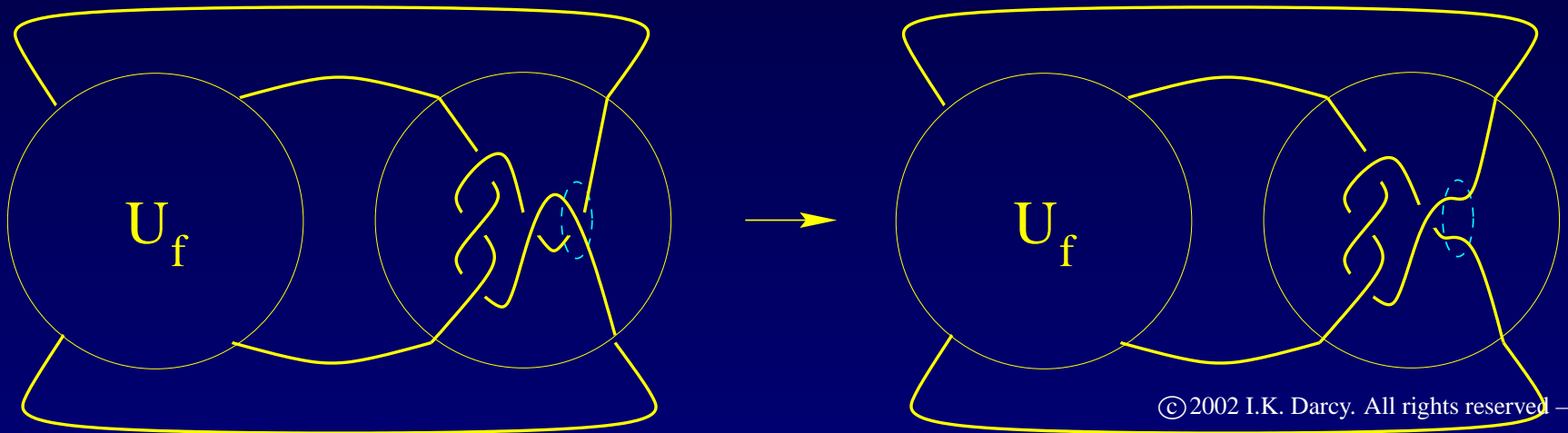
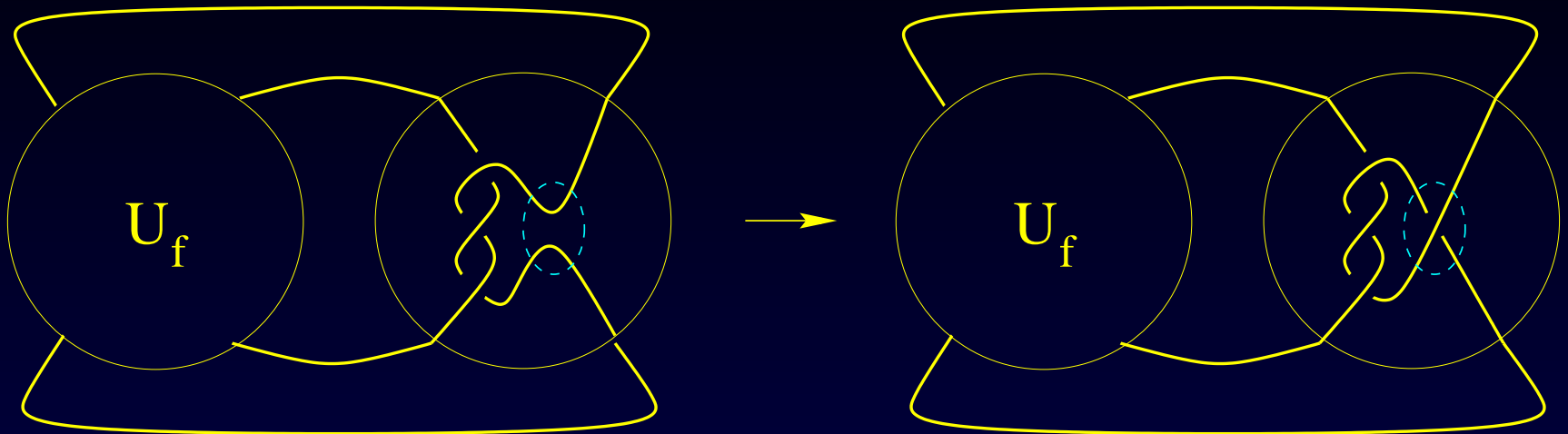
The following is a possible model for XER recombination:



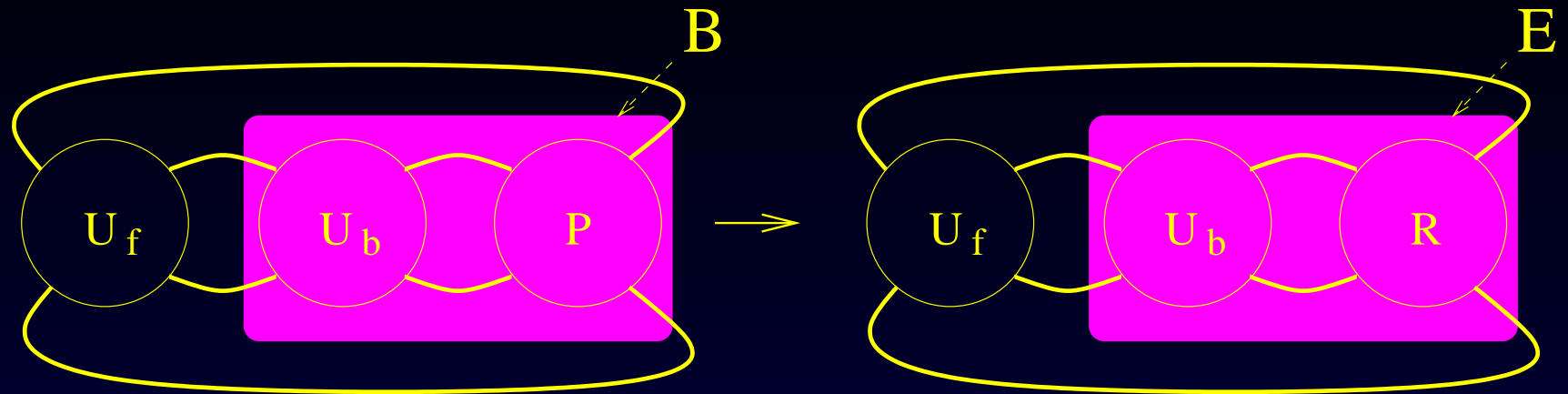
Thus, any model topologically equivalent to the above model would also be a possible model. For example:



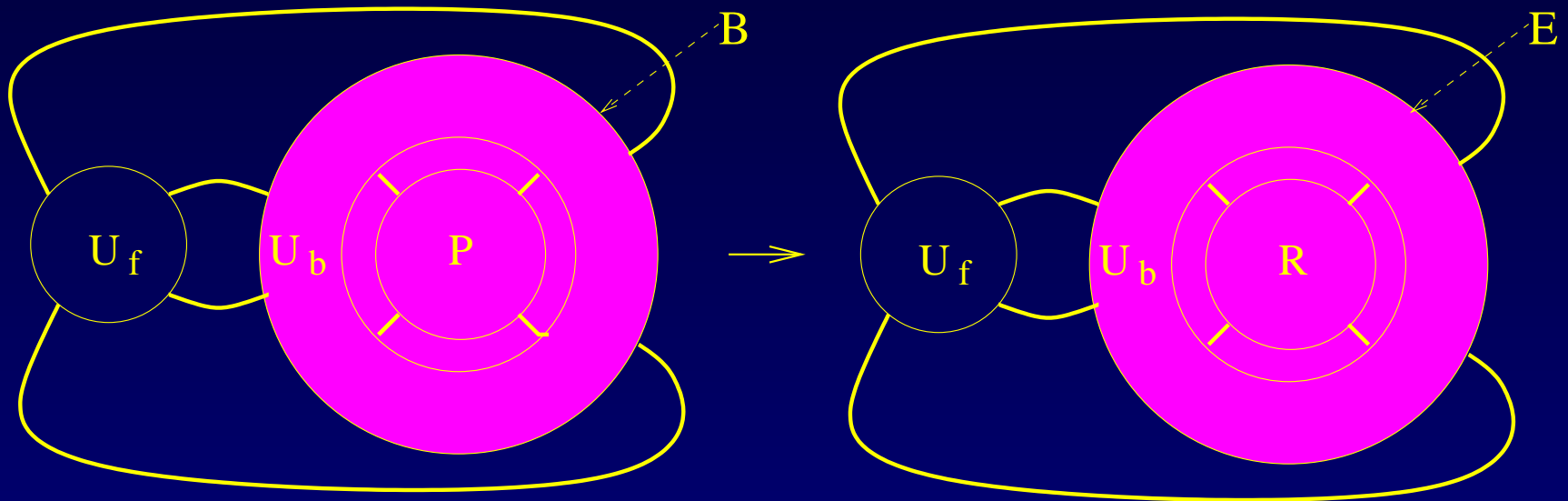
The following is a possible model for
XER recombination:



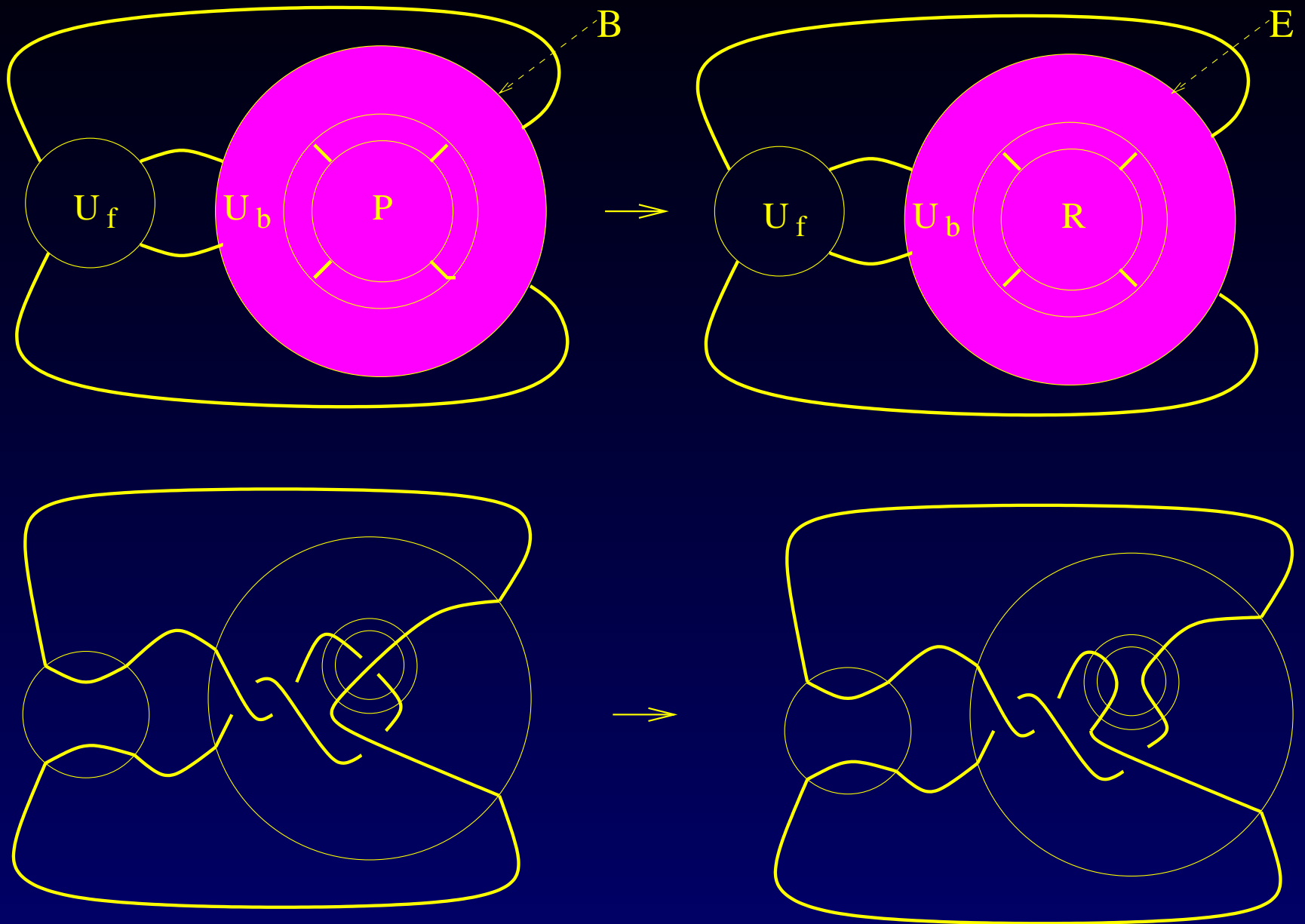
Sumners tangle model:



More general model



More general model



J. Bath, D. Sherratt, S. Colloms, Topology of Xer recombination on catenanes produced by Lambda Integrase, J. Mol. Biol. 289 (1999) 873-883.

S. Colloms, J. Bath, D. Sherratt, Topological selectivity in Xer site-specific recombination Cell 88 (1997), 855–864.

I. D. Biological Distances on DNA Knots and Links: Applications to XER recombination Knots in Hellas '98, Vol. 2 (Delphi). J. Knot Theory Ramifications, 10 (2001), no. 2, 269–294.

C. Ernst, D. W. Sumners, Solving tangles equations arising in a DNA recombination model, Math. Proc. Camb. Phil. Soc. 124 (1998).

Y. Saka, M. Vazquez, TangleSolve: topological analysis of site-specific recombination, Bioinformatics, to appear
and preprints, some of which are available at

<http://www.utdallas.edu/~darcy/>