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

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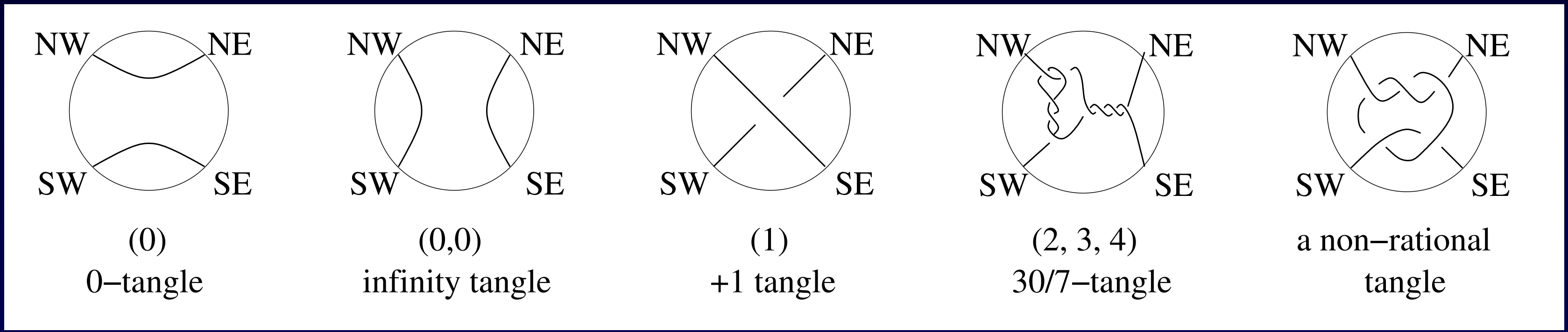
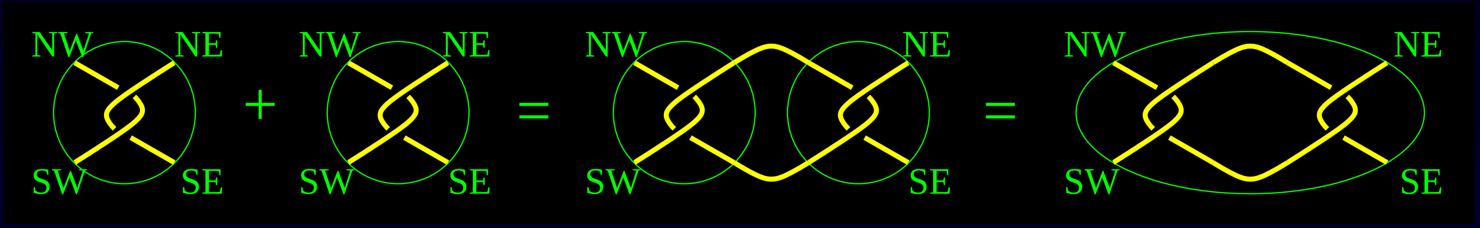
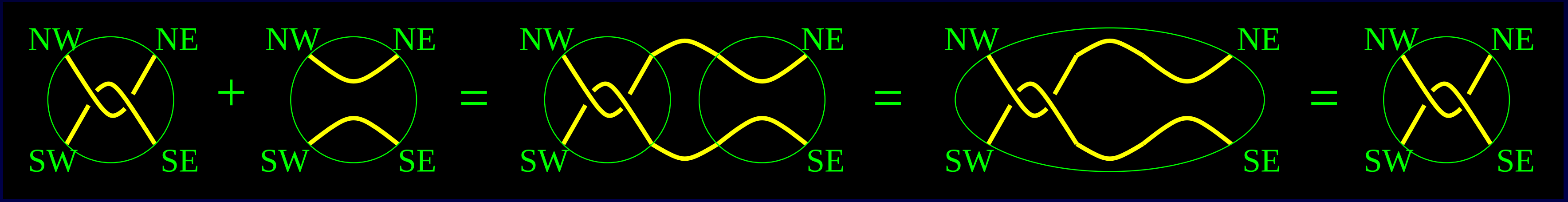
Some notation:

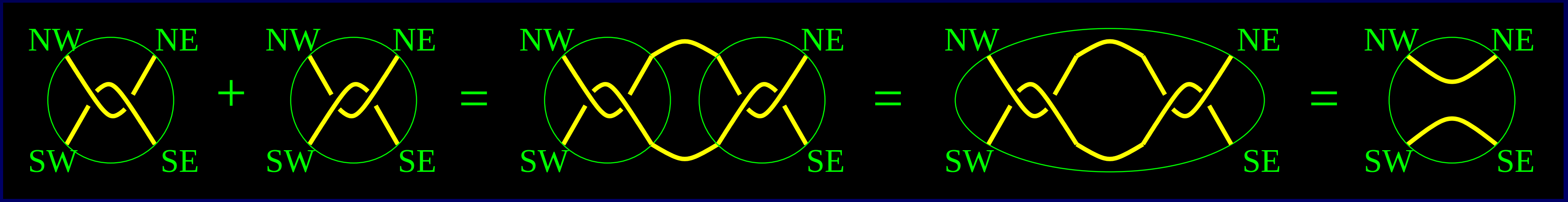
A 2-string tangle is a 3-dimensional ball containing two strings. Some examples:



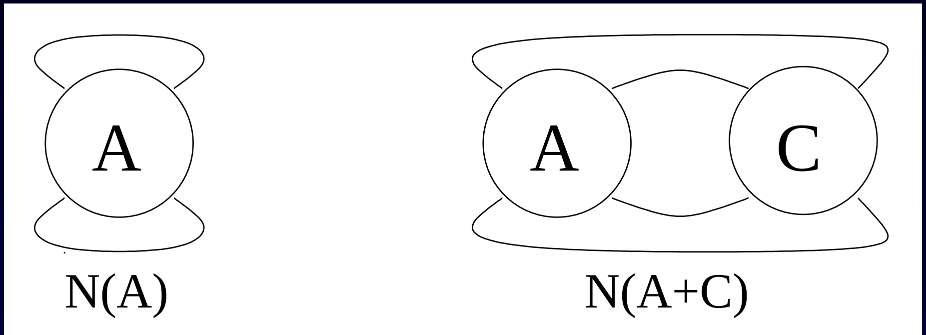
Tangles can be added:







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



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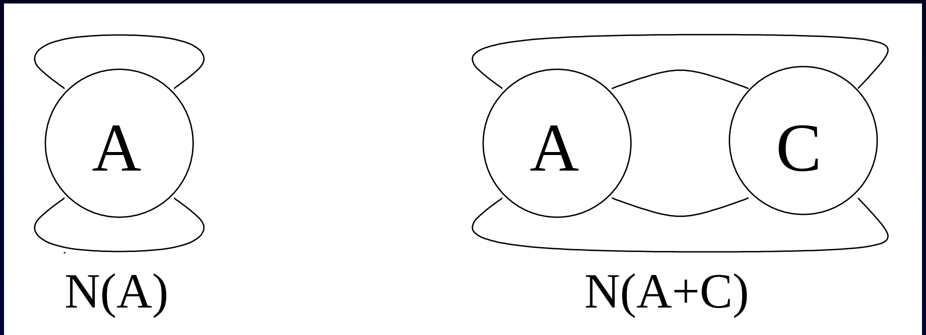

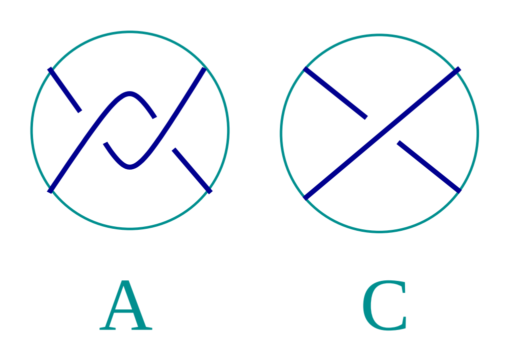

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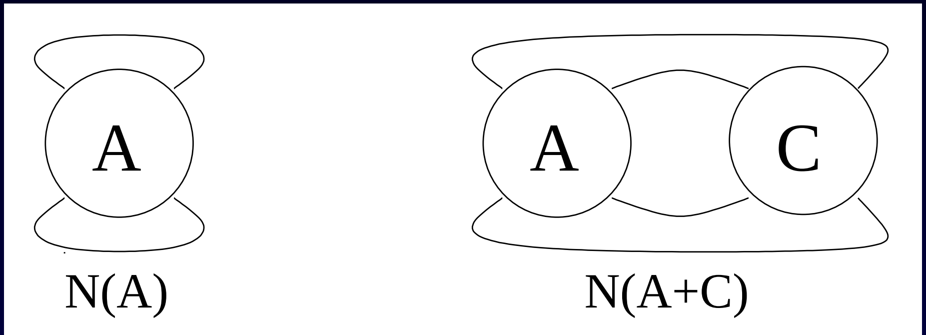

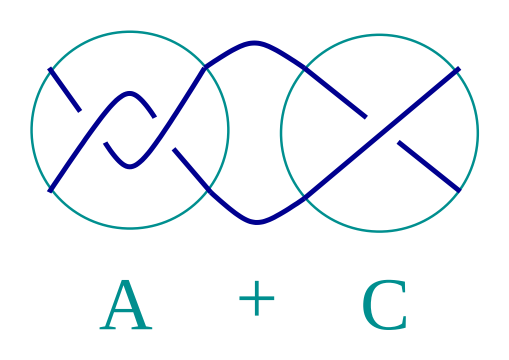

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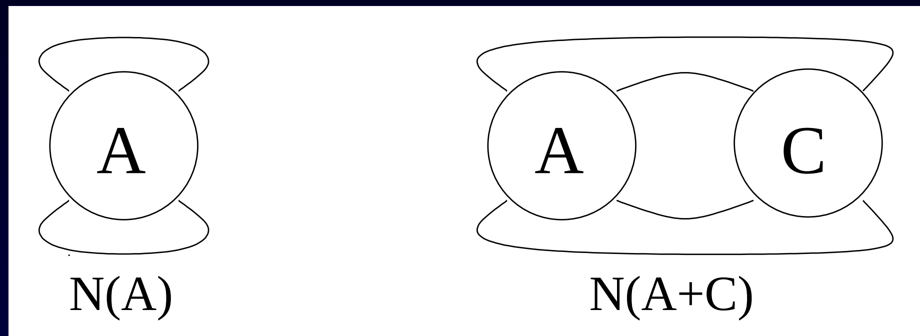
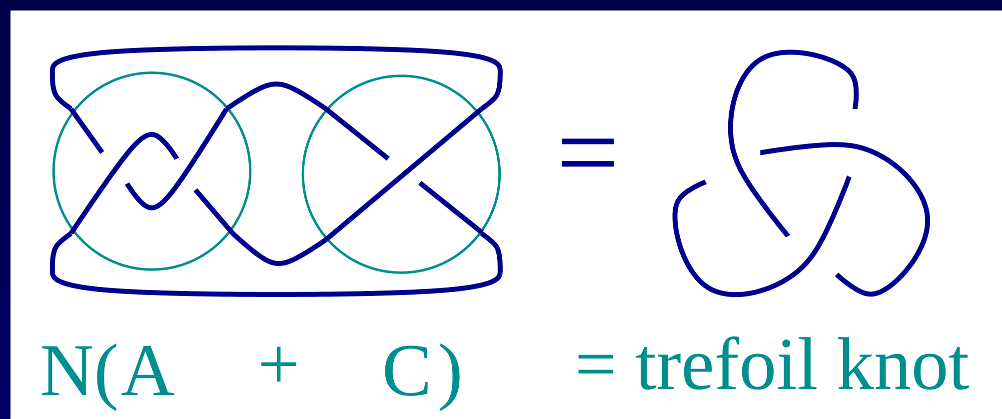




Solve $U_f + B = 2$

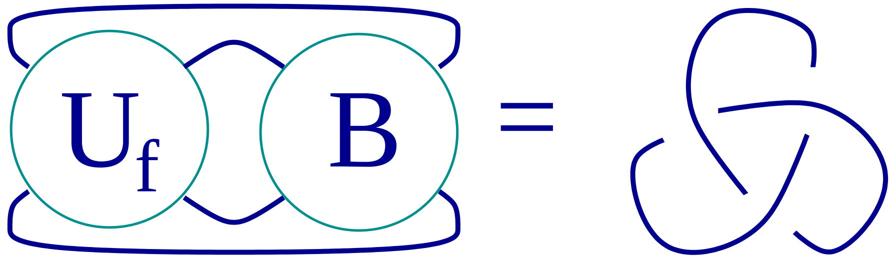
Solve $U_f + B = 2$

$$2 + 0 = 2$$

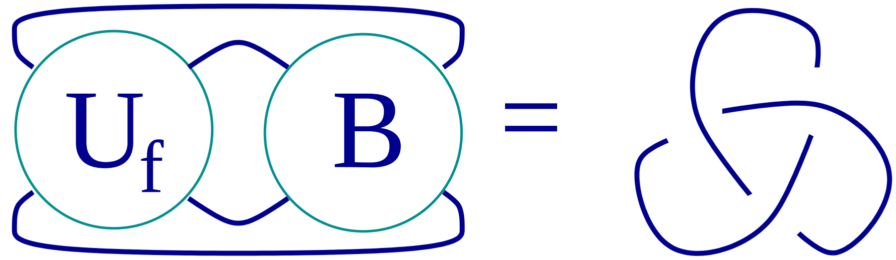
$$1 + 1 = 2$$

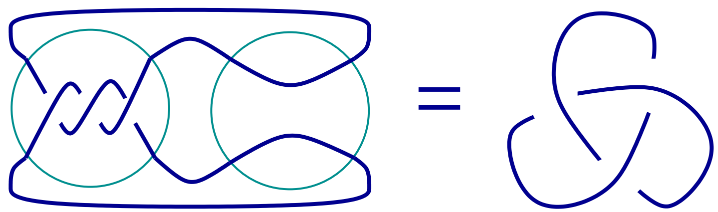
$$2 + (-1) \neq 2$$

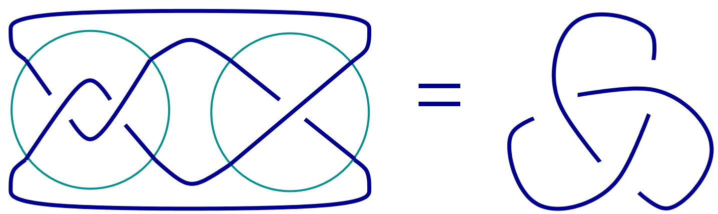
Solve

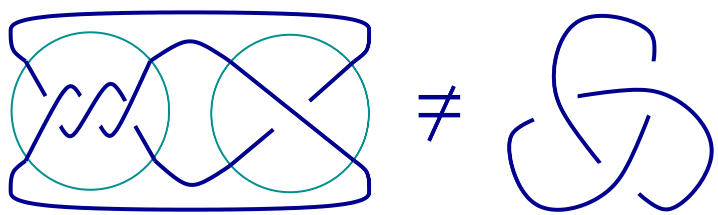


Solve



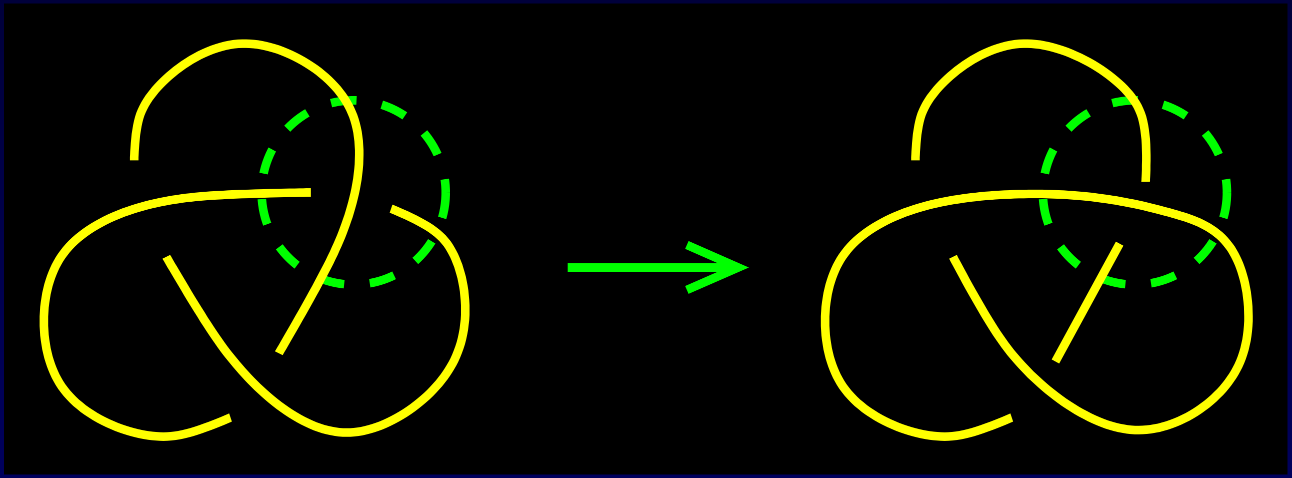






Why are we interested in solving these equations?

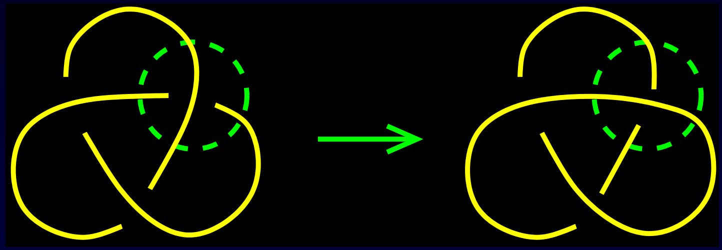
Topoisomerases are proteins which cut one segment of DNA allowing a second DNA segment to pass through before resealing the break.



Topoisomerases are involved in

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

Thus topoisomerase action can be modeled using tangles:



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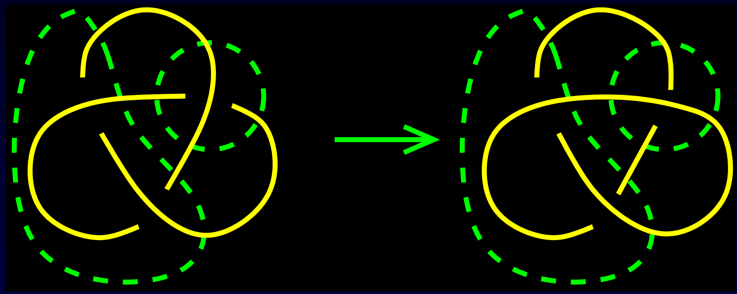
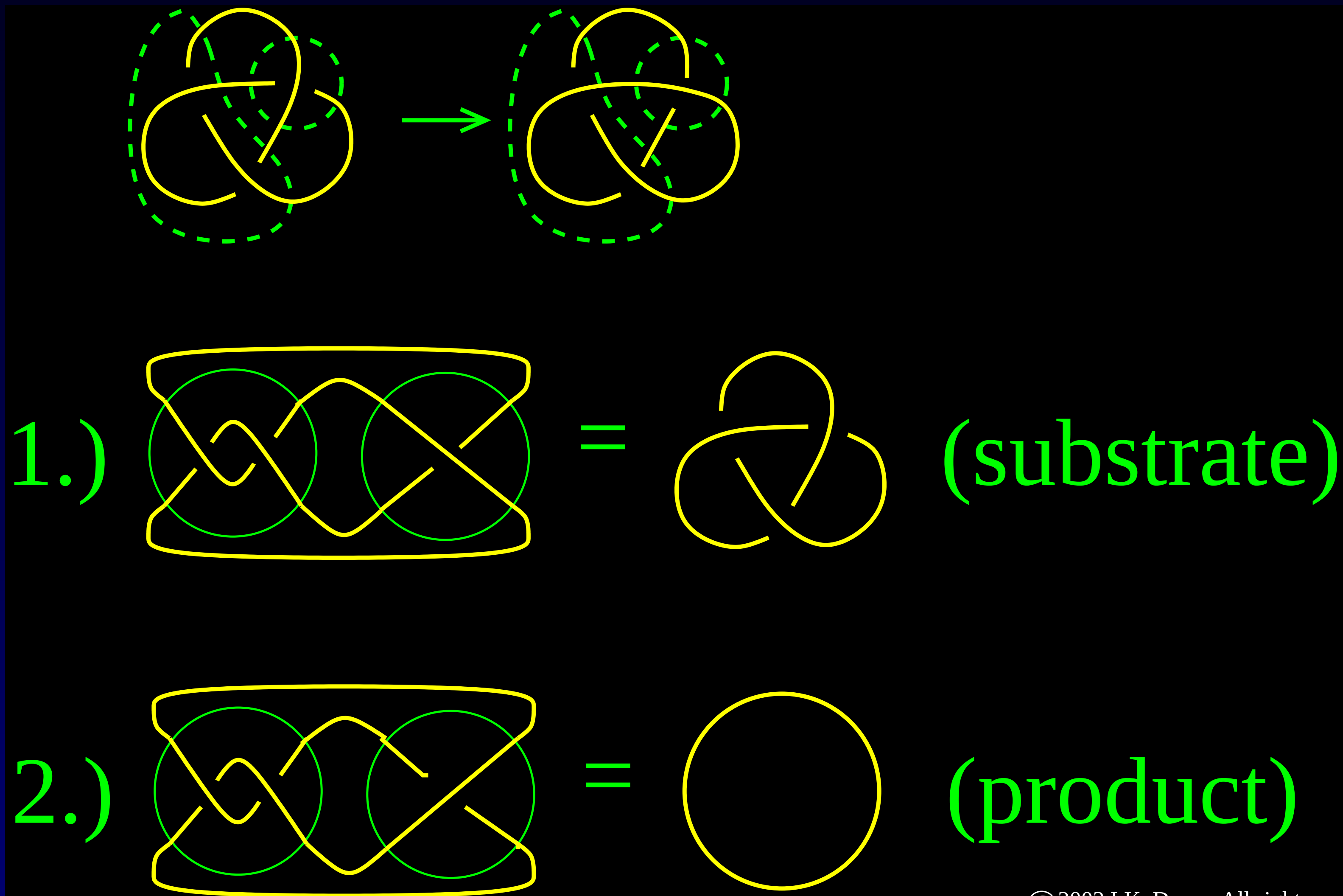
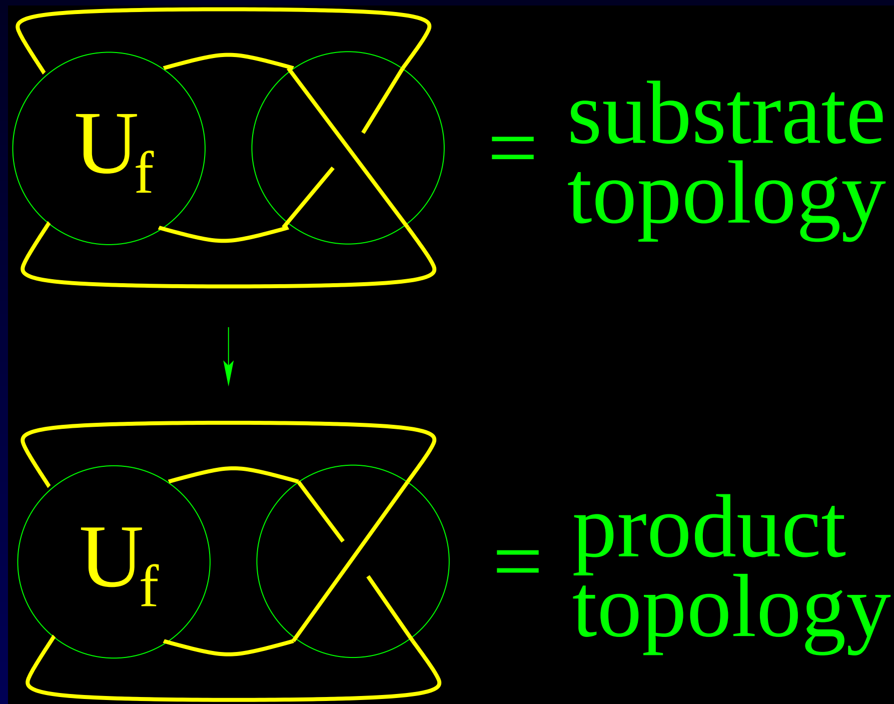


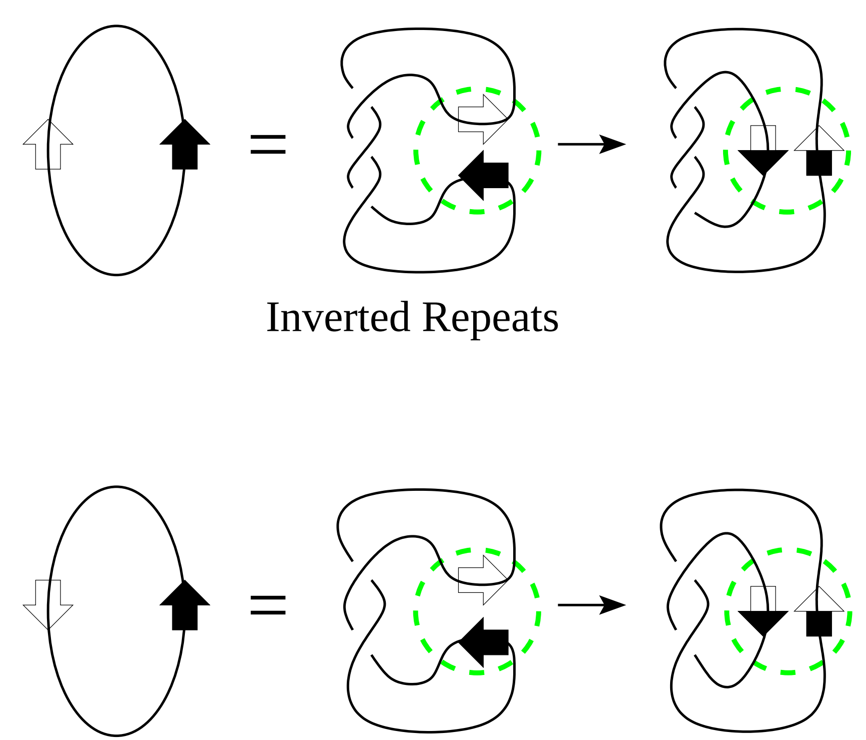
Thus topoisomerase action can be modeled using tangles:



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



Inverted Repeats

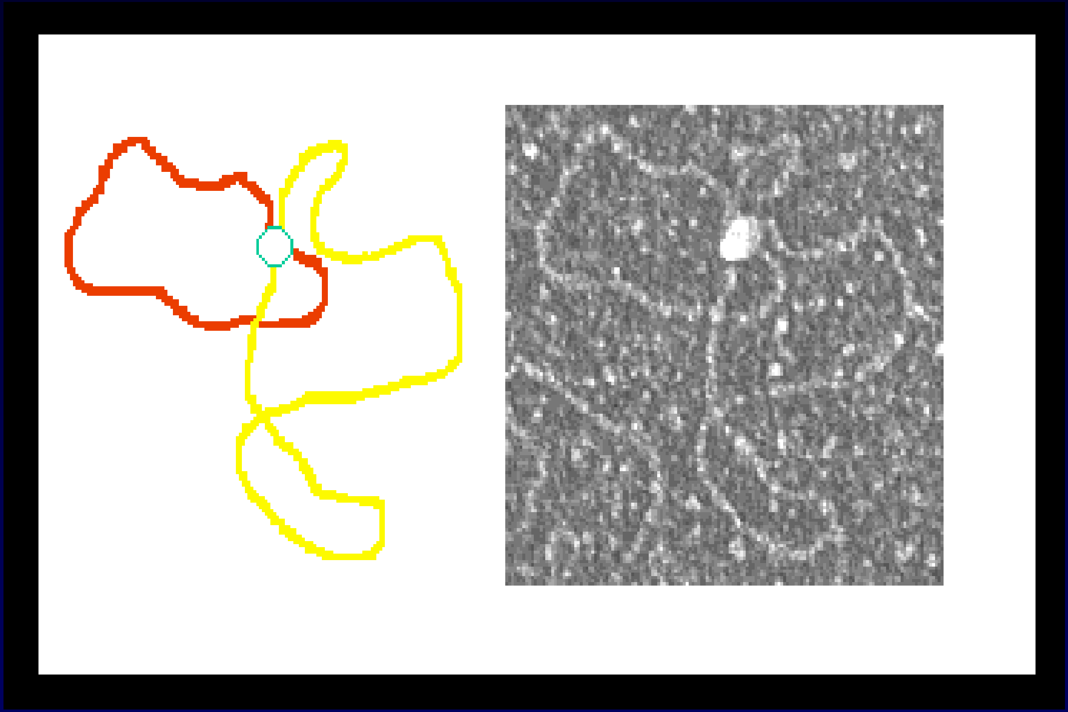
Direct Repeats

Recombinases are involved in

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

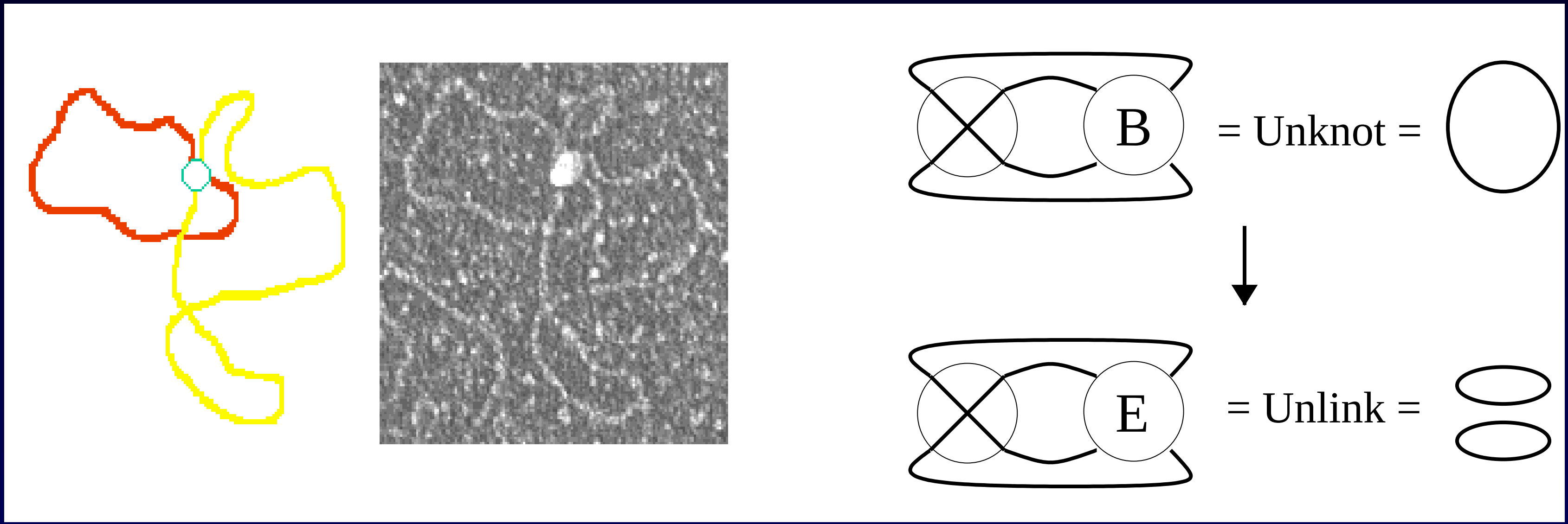
and in many more processes

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



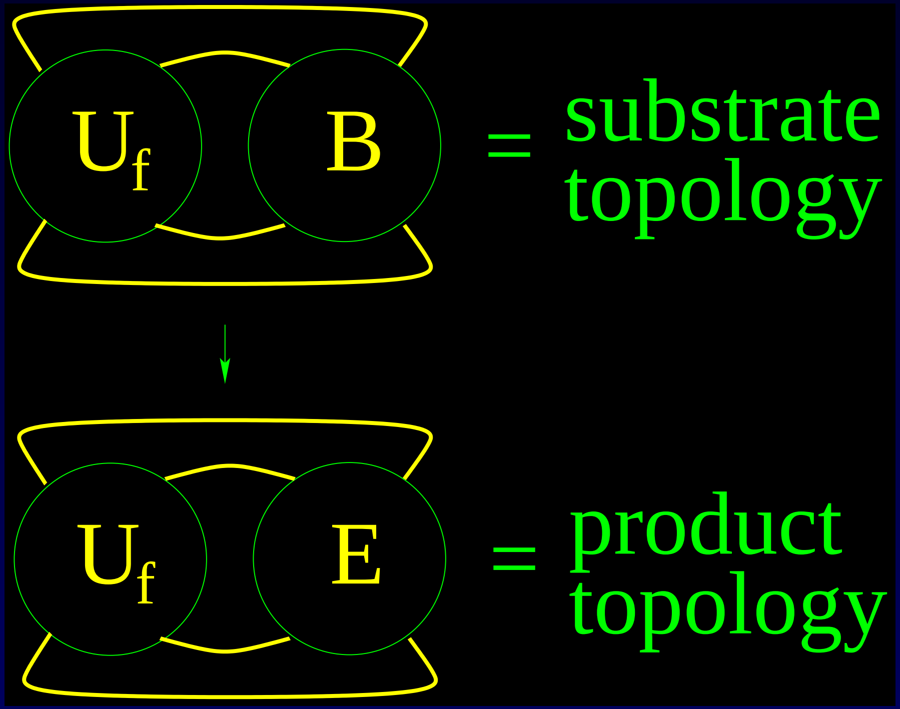
Electron micrograph courtesy of Kenneth Huffman and Steve Levene

The tangle equations corresponding to the electron micrograph:



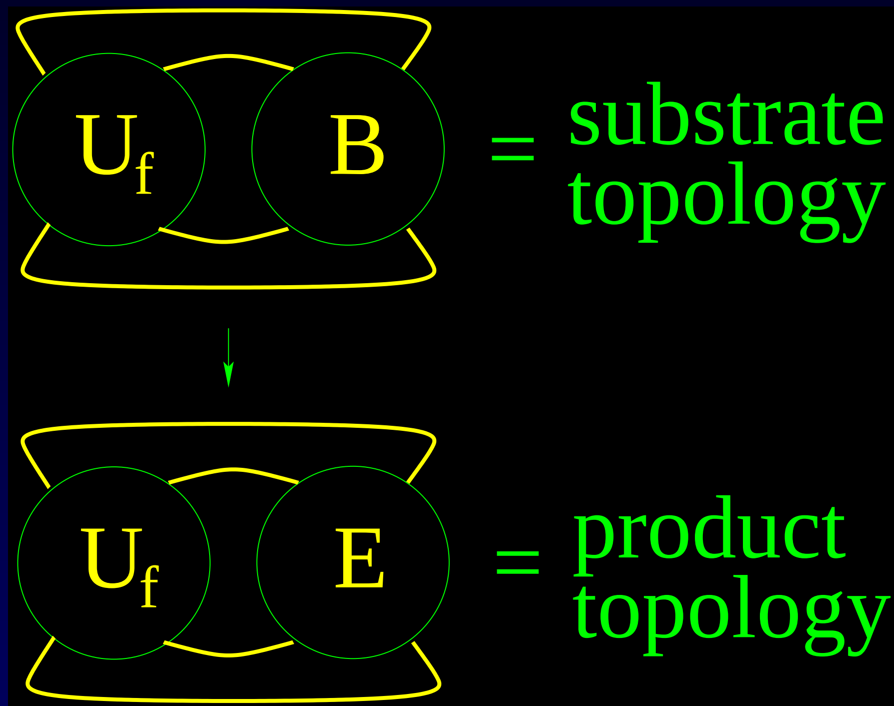
Electron micrograph courtesy of Kenneth Huffman and Steve Levene

In general, we are solving the tangle equations:

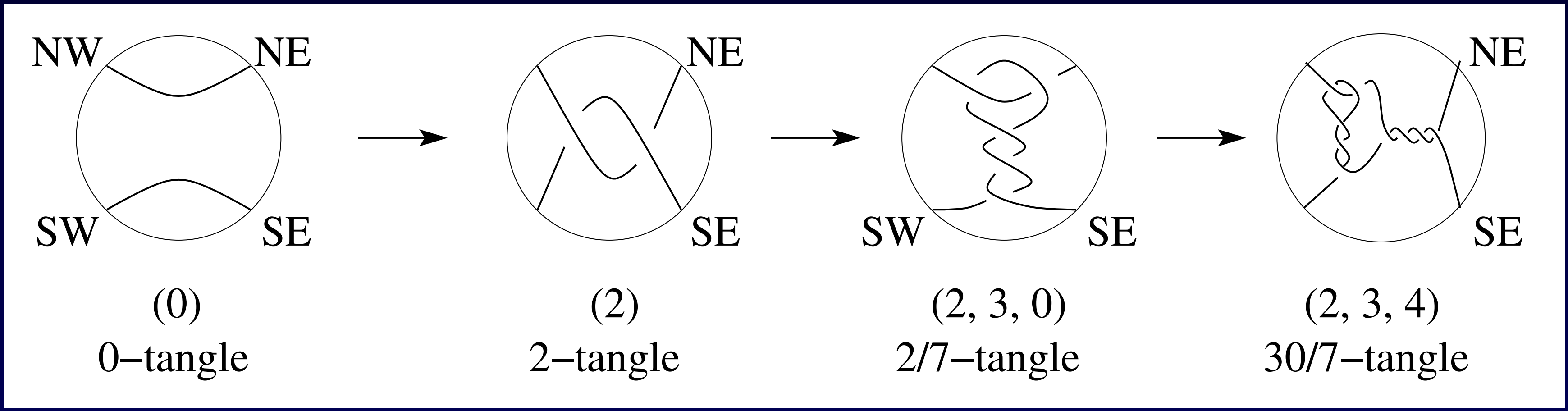


Solving Tangle Equations

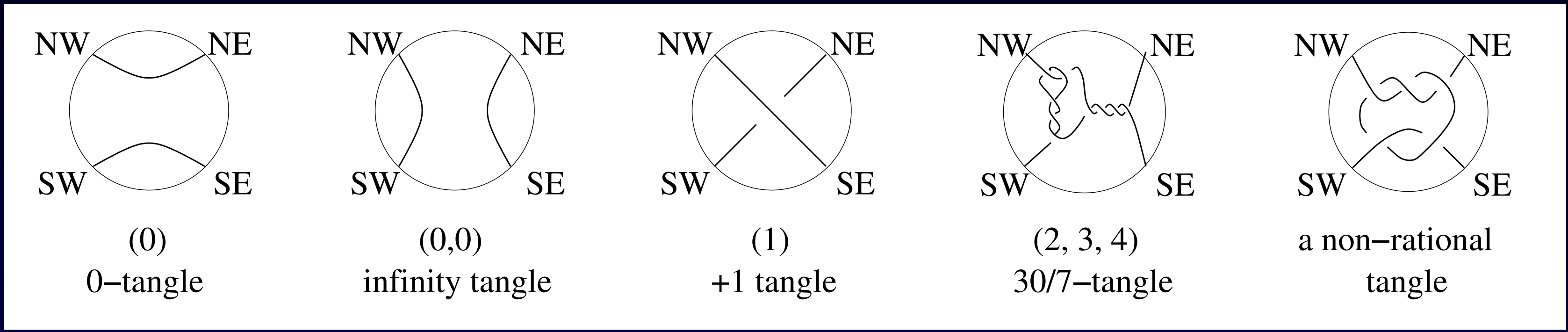
Step 1: Try to show that the tangles B and E are rational



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

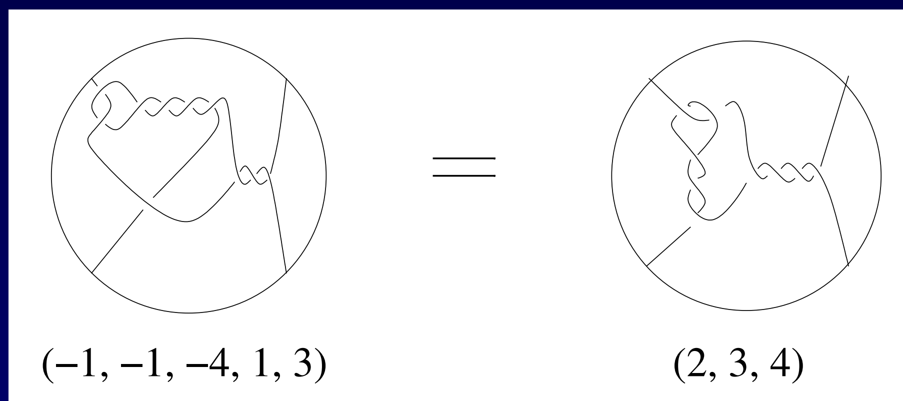


Tangle Examples

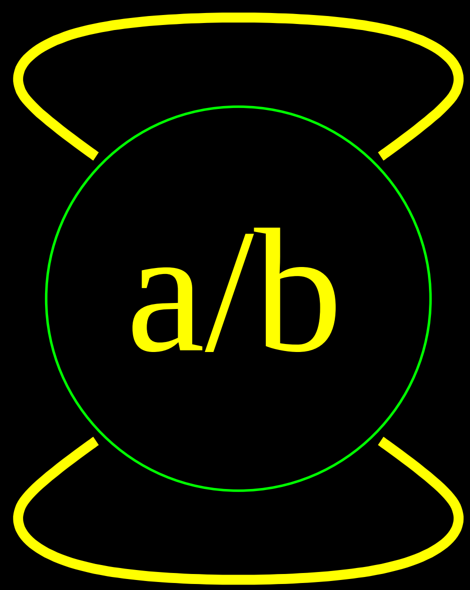


Rational tangles are uniquely identified by their corresponding continued fractions. For example the two tangles drawn below are equivalent since

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



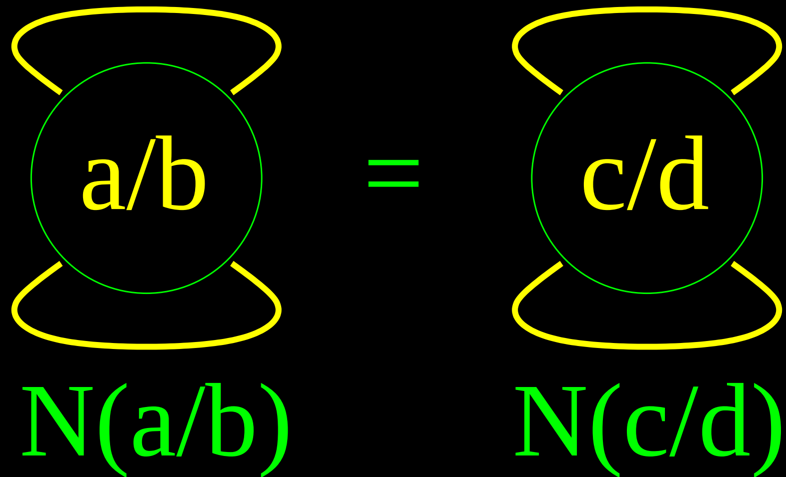
Definition: The numerator closure of a rational tangle is a rational knot or link (also called 4-plat or 2-bridge knot/link).



N(a/b)

Rational knot/link equivalence

Take a, c $\geq$ 0.



if and only if

$a = c$

and

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

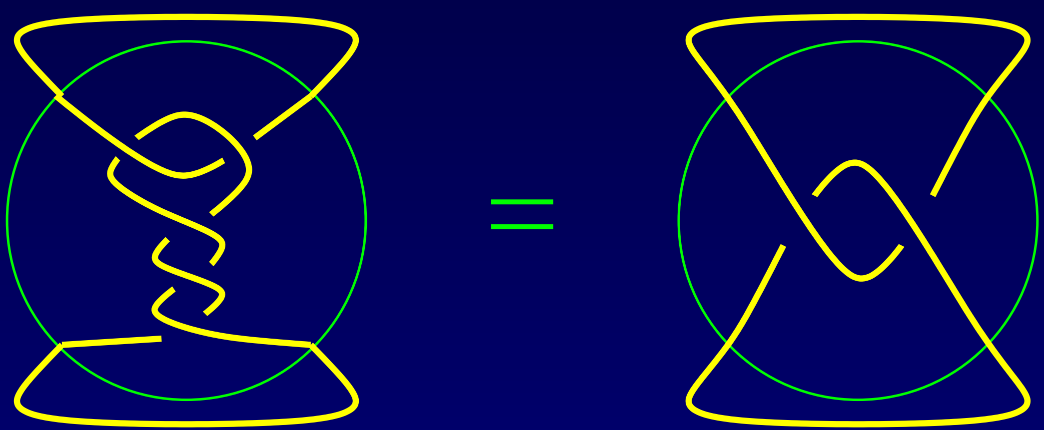
For example,

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

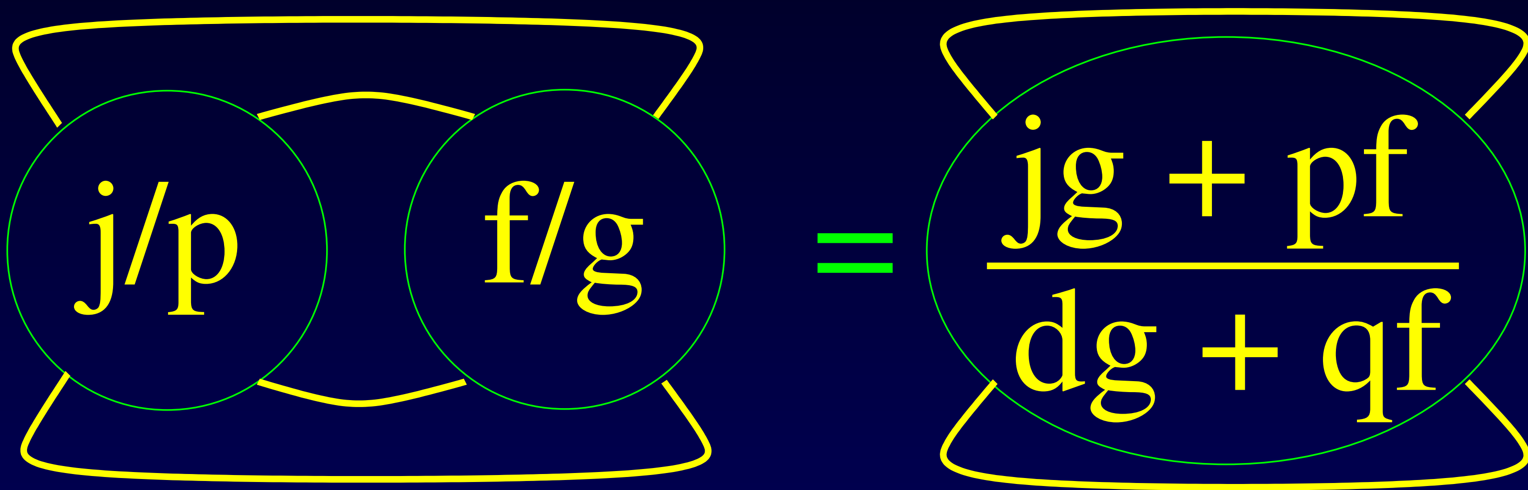
and $N((2)) = N\left(\frac{2}{1}\right) = N((2))$

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

since $7 = 1 + 2(3)$

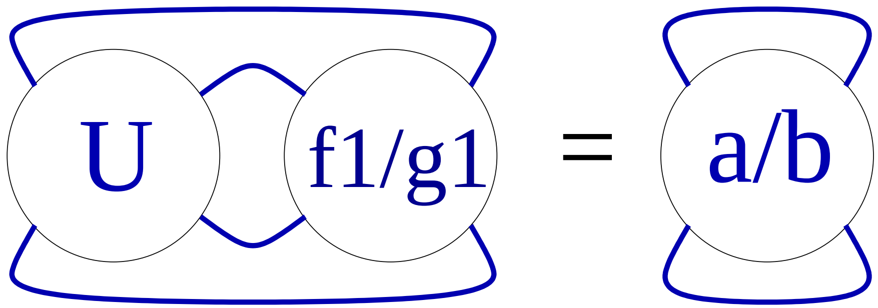


The numerator closure of the sum of two rational tangles is a rational knot or link

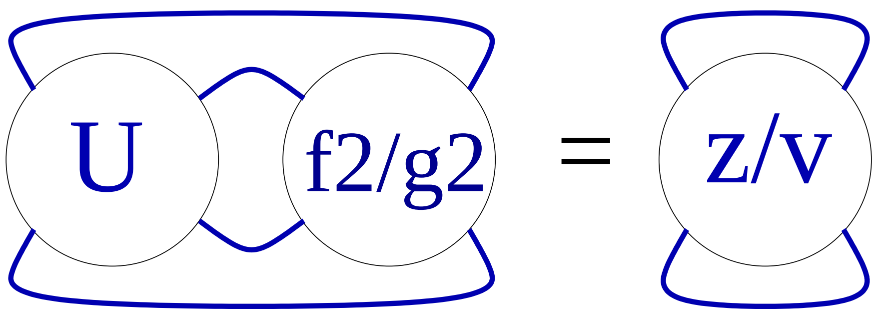


where dp - qj = 1

Goal: Given a, b, z, v, solve the following system of tangle equations for the tangles U and f2/g2 in terms of f1/g1.



and

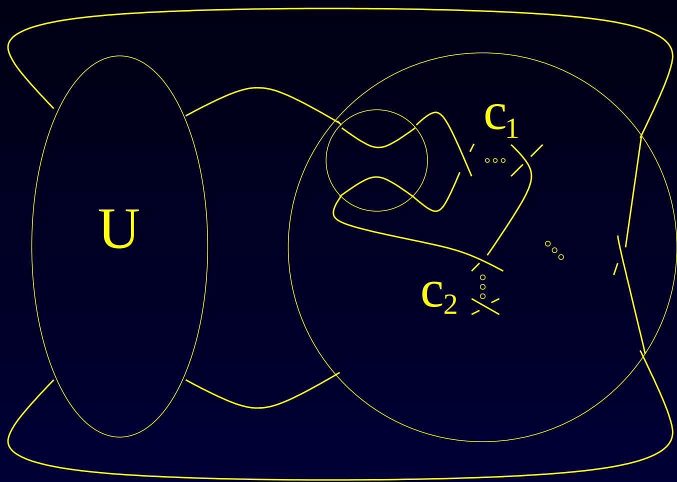


Solving

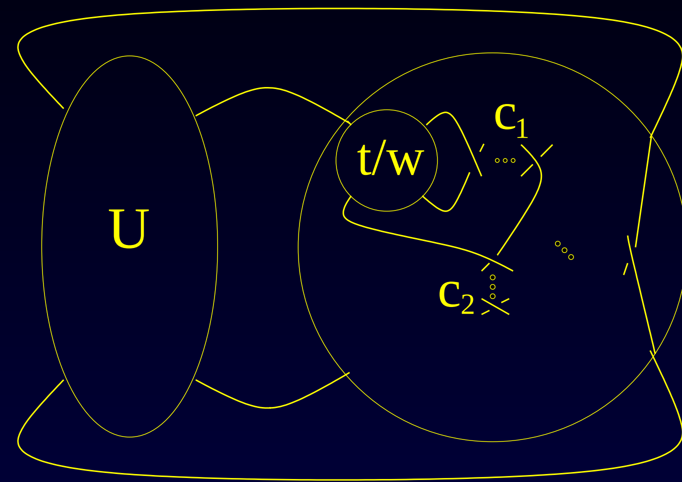
$$x + y = 2$$

is equivalent to solving

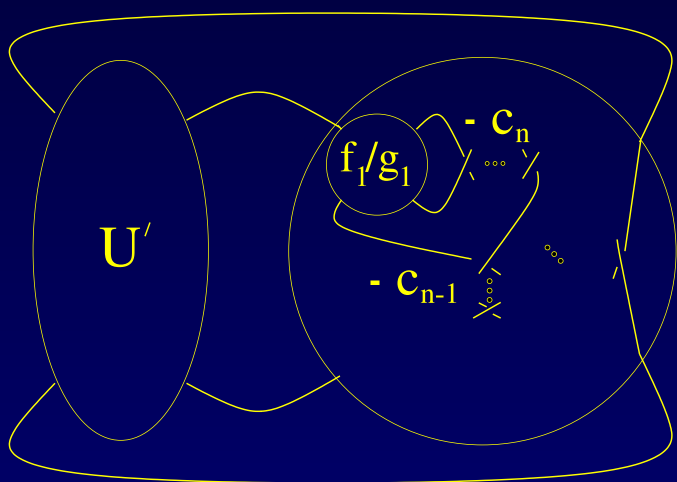
$$(x + y) + 0 = 2$$



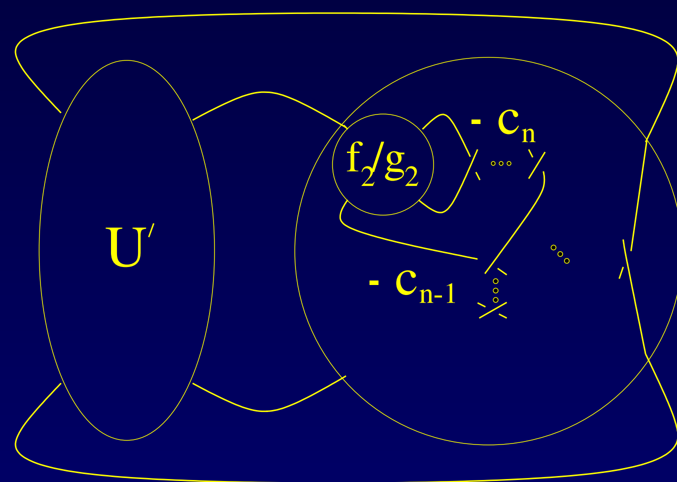
$= K_1,$



$= K_2$

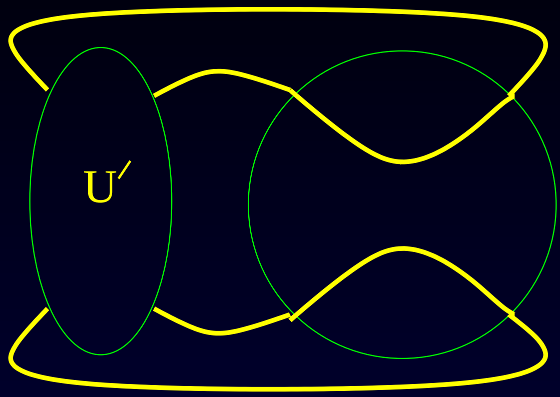


$= K_1,$

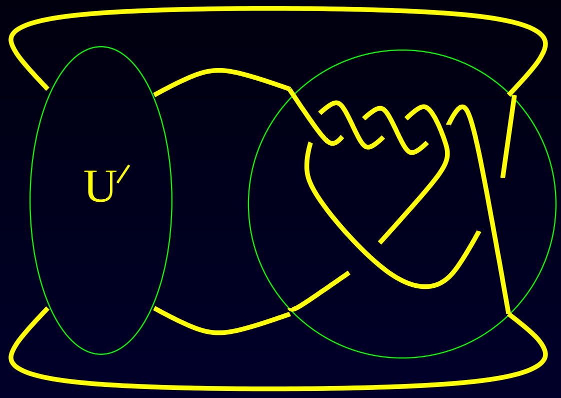


$= K_2$

Example

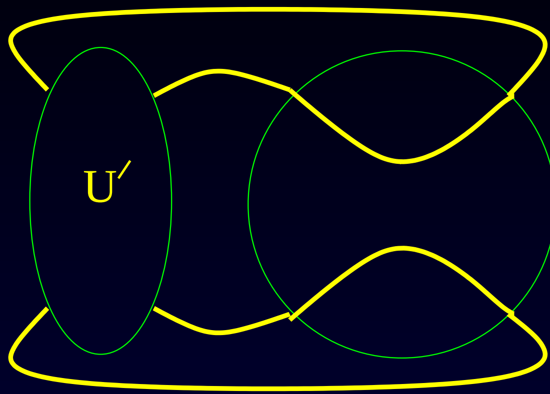


$= N(a/b)$,



$= N(z/v)$

Example



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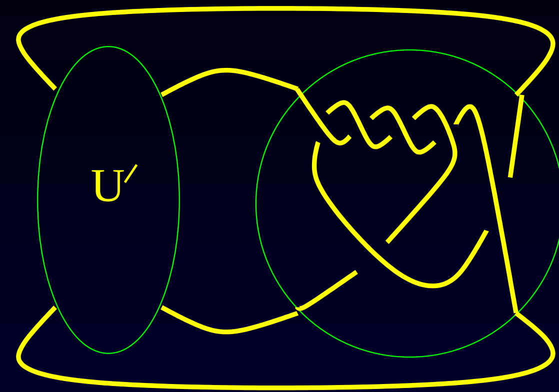
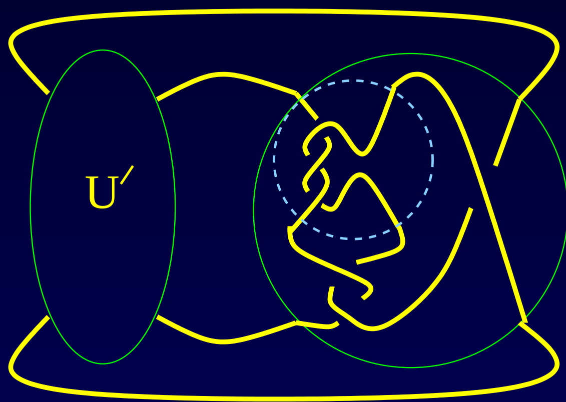


= N(z/v)



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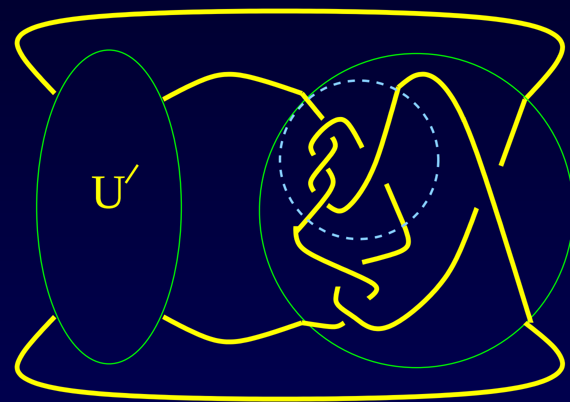
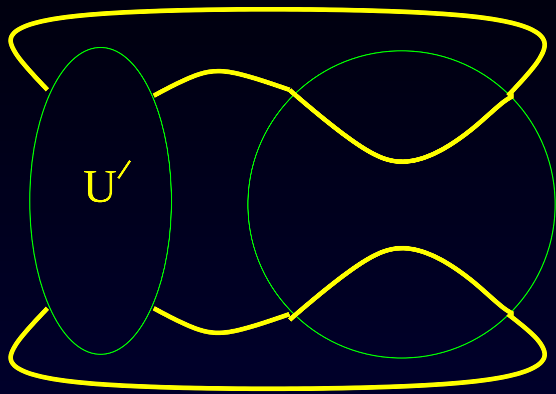


= N(z/v),

Example



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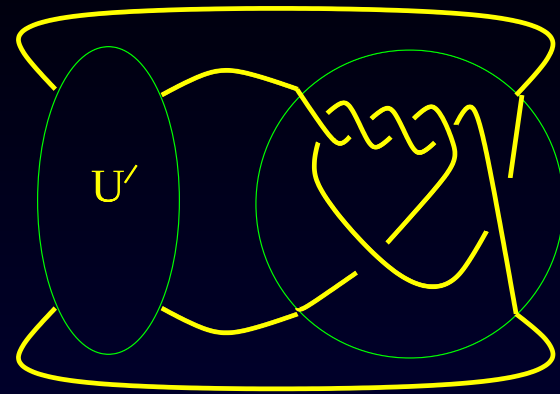
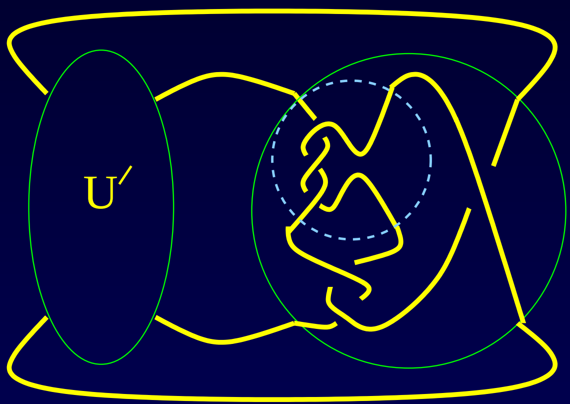


= N(z/v)



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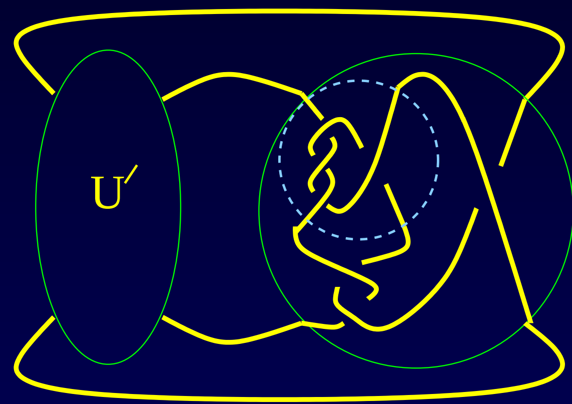
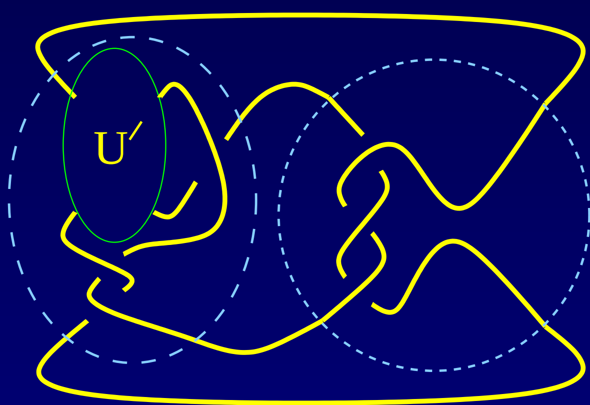


= N(z/v),



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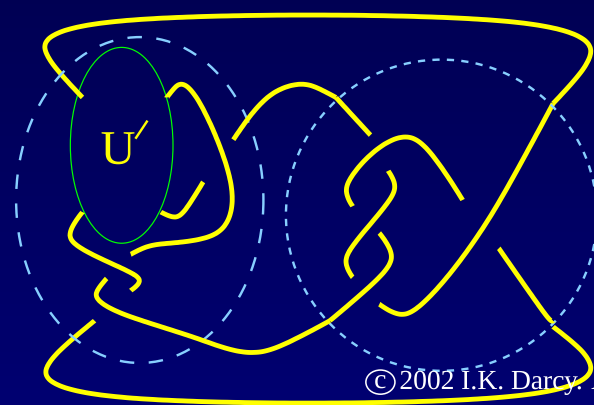
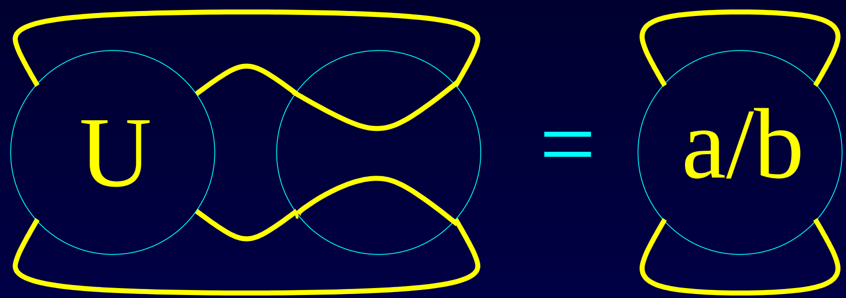
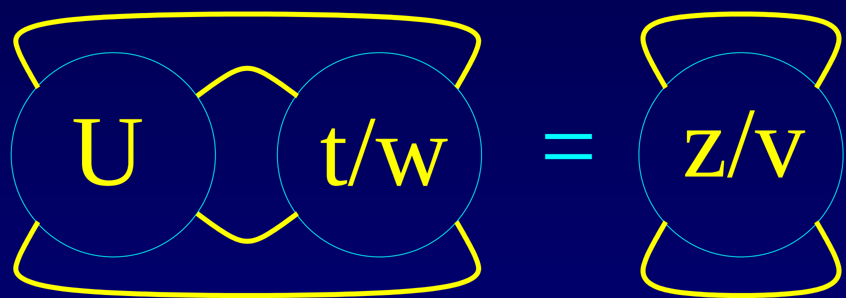


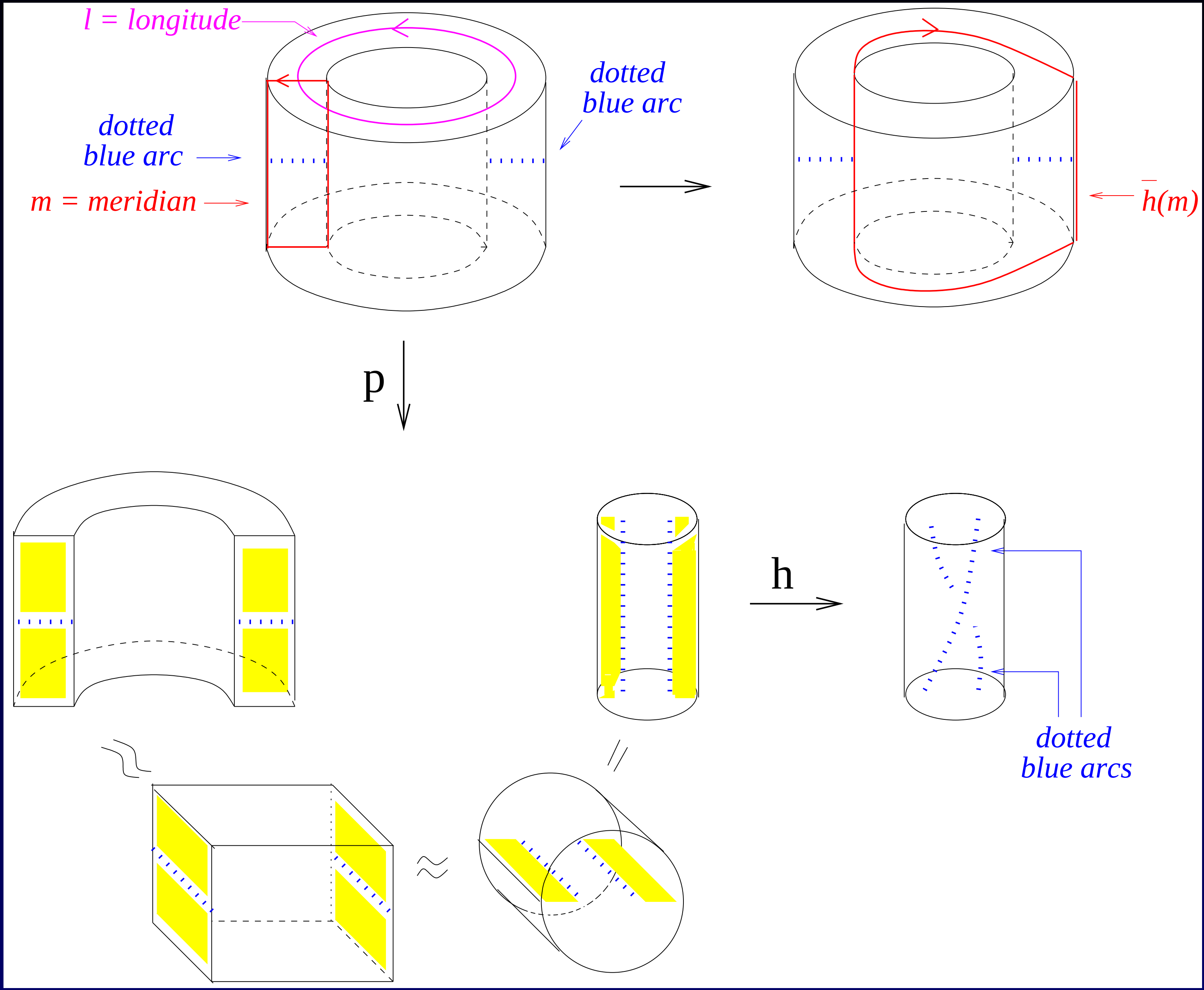
= N(z/v)

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



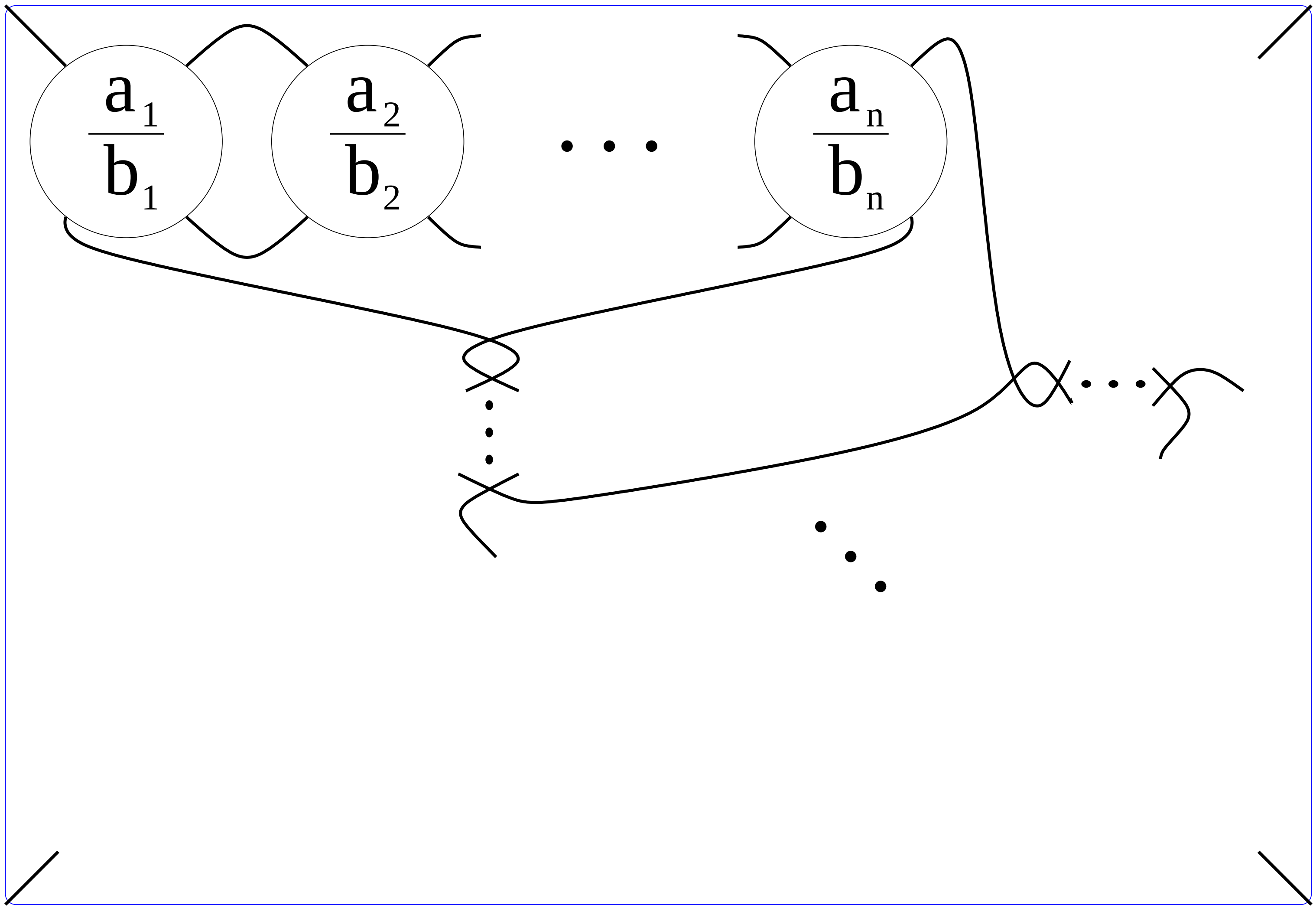
and

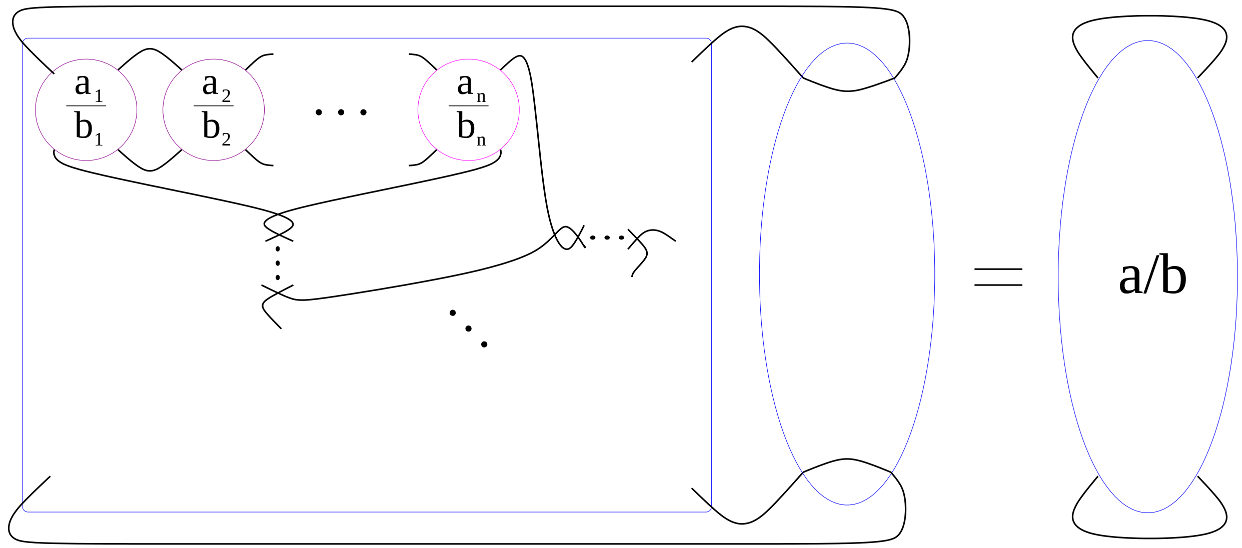



l = longitude
dotted
blue arc
dotted
blue arc
m = meridian
h(m)
p
h
dotted
blue arcs

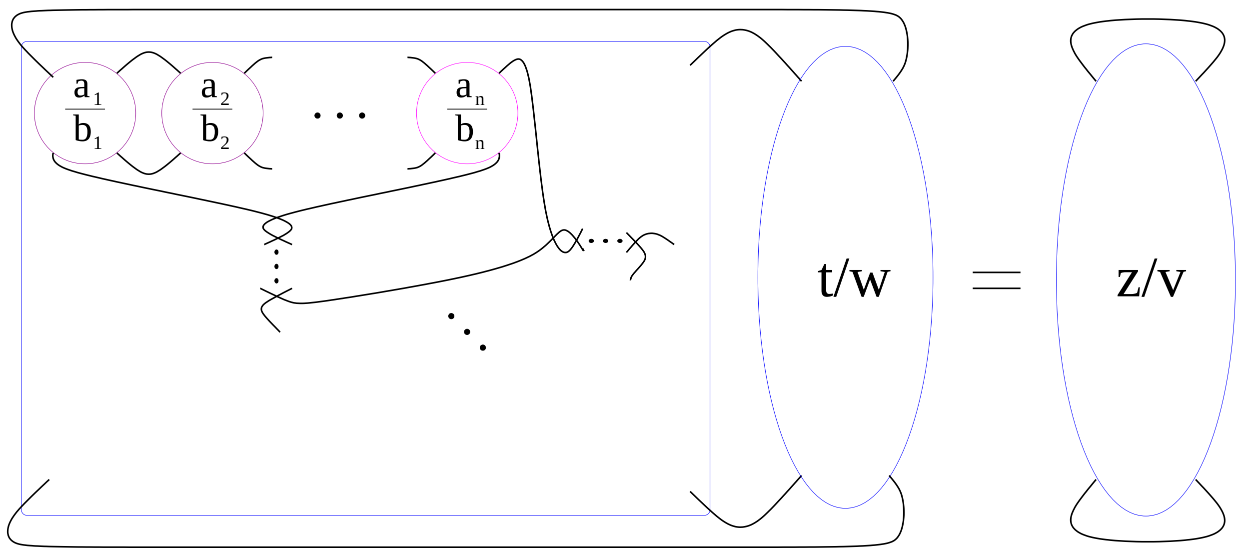
Cyclic Surgery Thm + Ernst implies

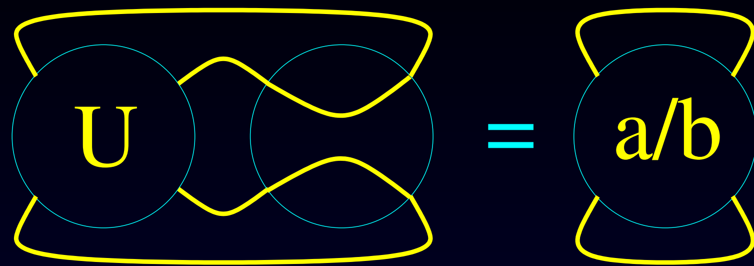
$U =$

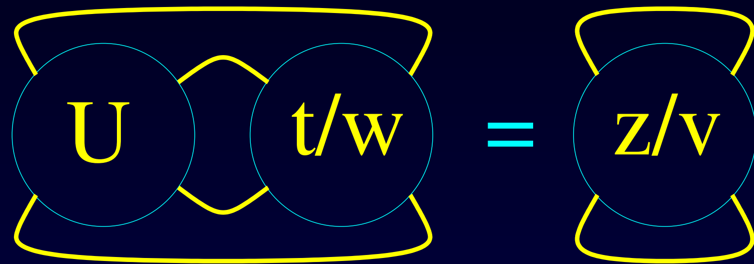



$\frac{a_1}{b_1}$
$\frac{a_2}{b_2}$
$\frac{a_n}{b_n}$
=
a/b

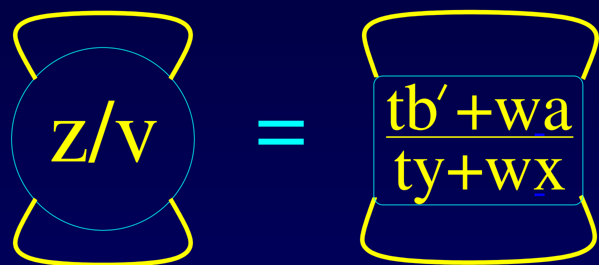
and


$\frac{a_1}{b_1}$
$\frac{a_2}{b_2}$
$\frac{a_n}{b_n}$
t/w
=
z/v

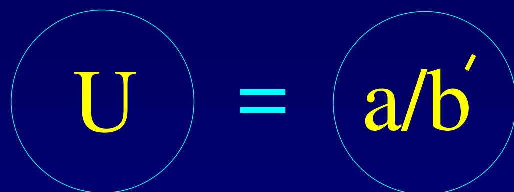
If 

and 

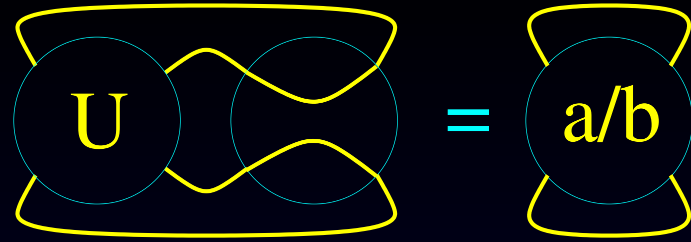
then if $w \neq \pm 1 \bmod t$,



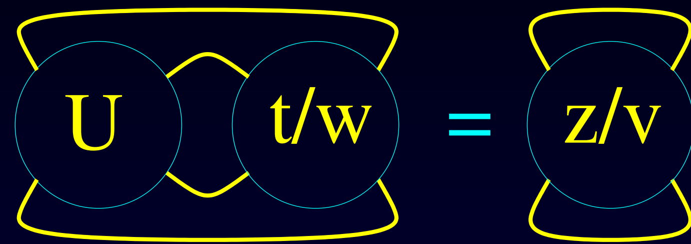
where $b' b^{\pm 1} = 1 \bmod a$, $b' x - ay = 1$,

and 

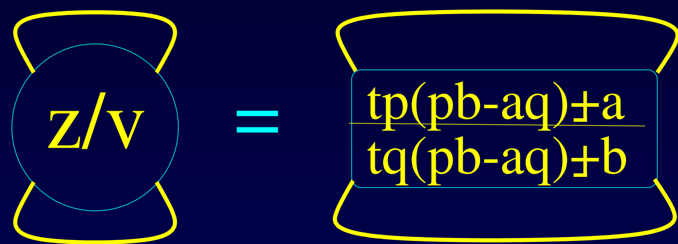
If



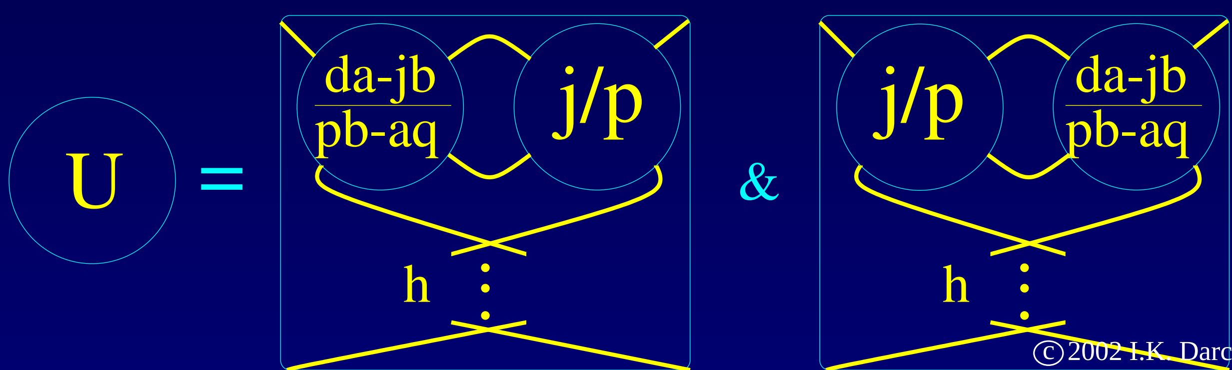
and



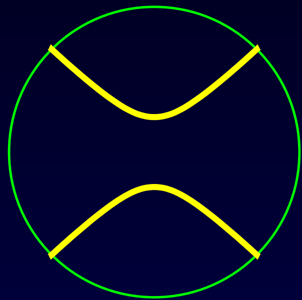
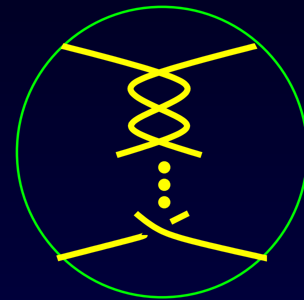
then if $w = \pm 1 \mod t$,



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

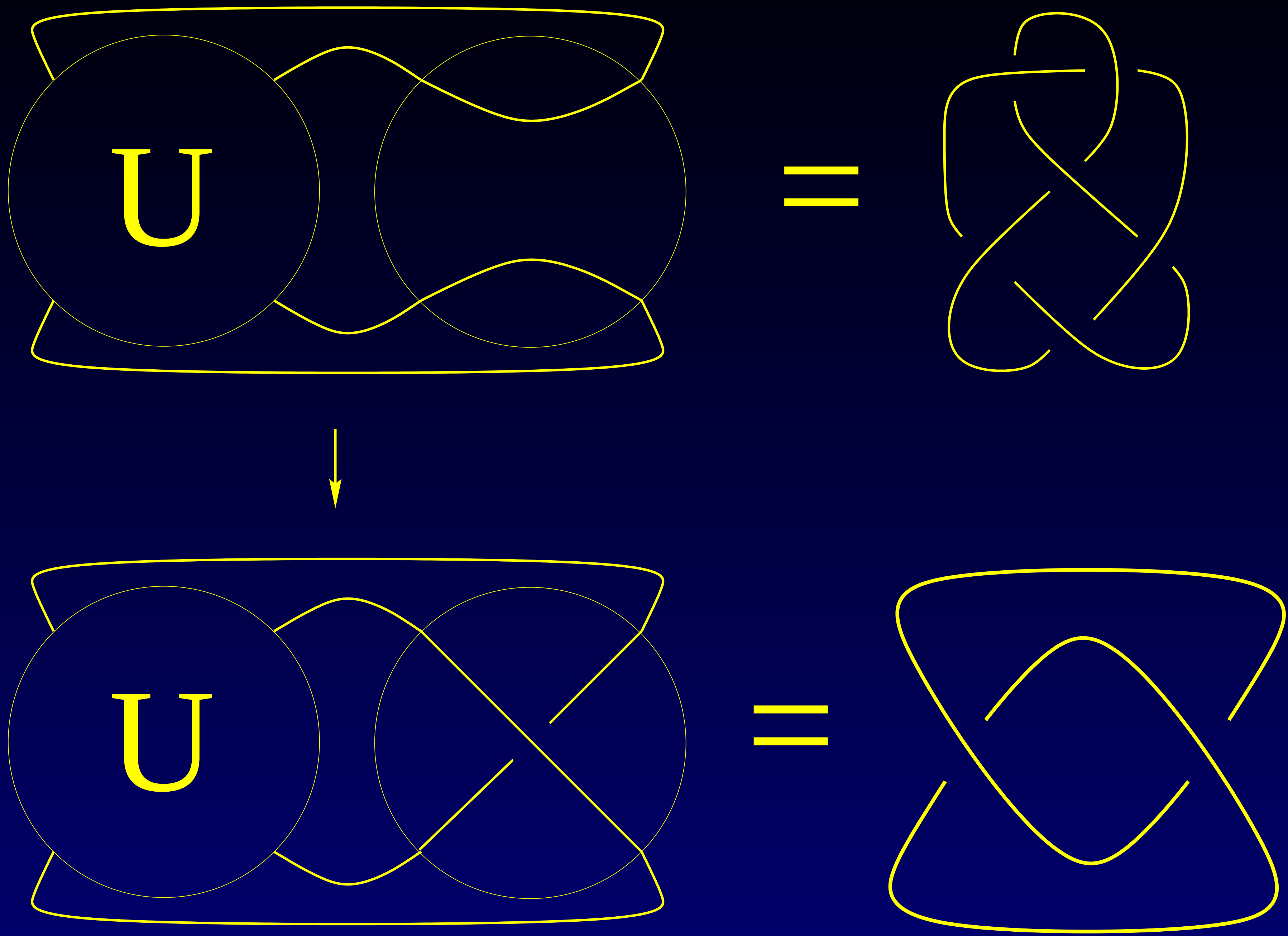


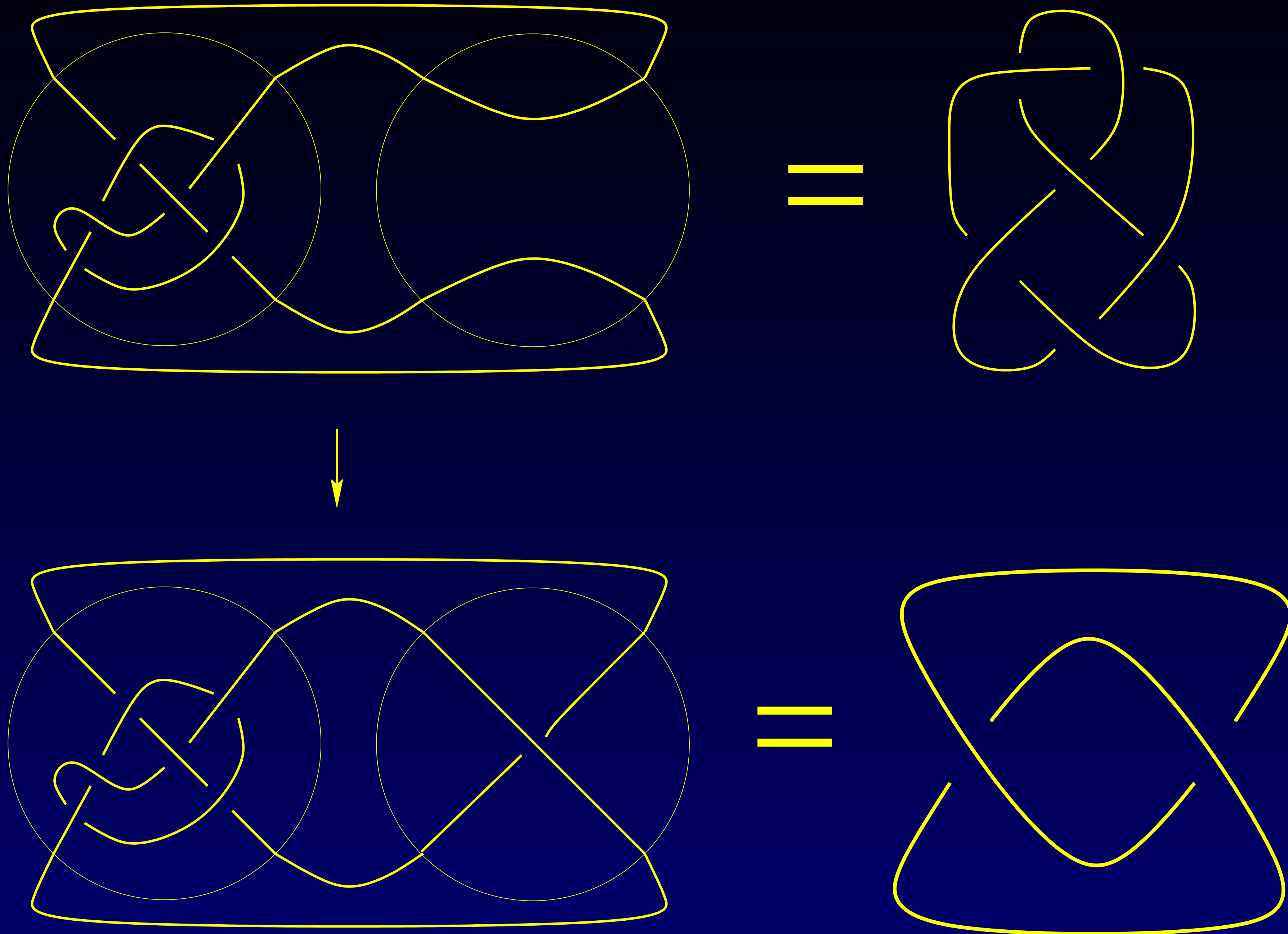
Unfortunately, when

B =  and E = 

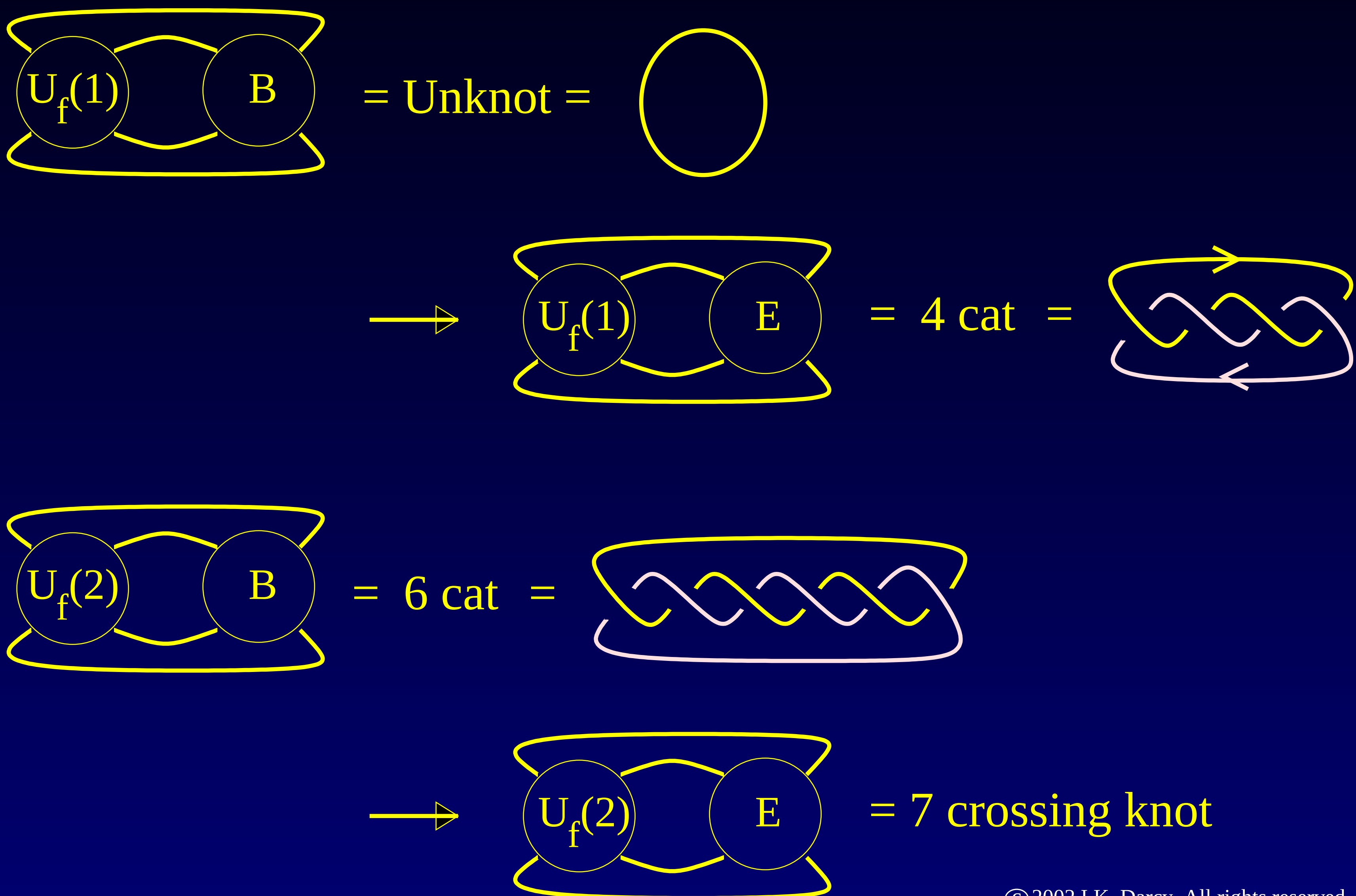
not all solutions are found.

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)

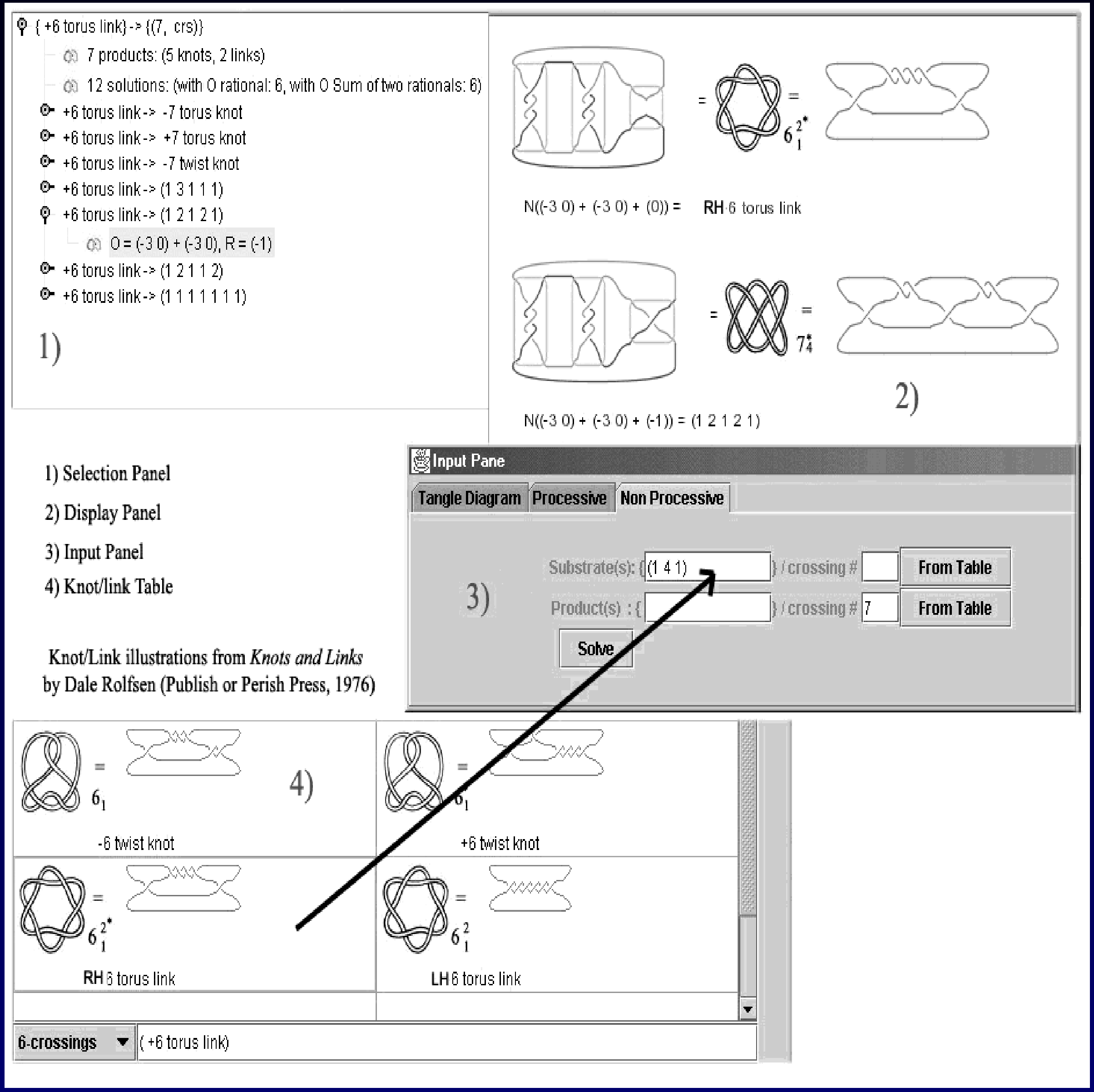
0/1 is similarly oriented if k even, and oppositely oriented if k odd

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

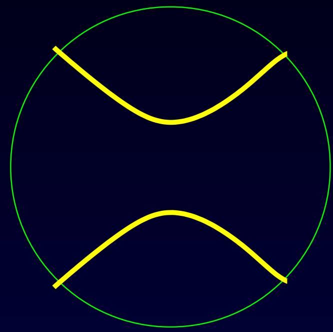
t = 1, (p,q) = (1, -2)

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

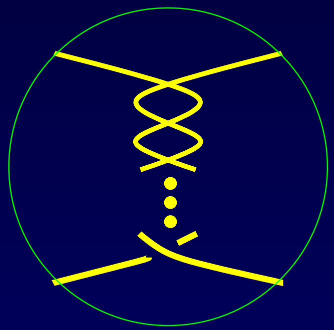
Yuki Saka and Mariel Vazquez (5 July)
http://bio.math.berkeley.edu/TangleSolve/



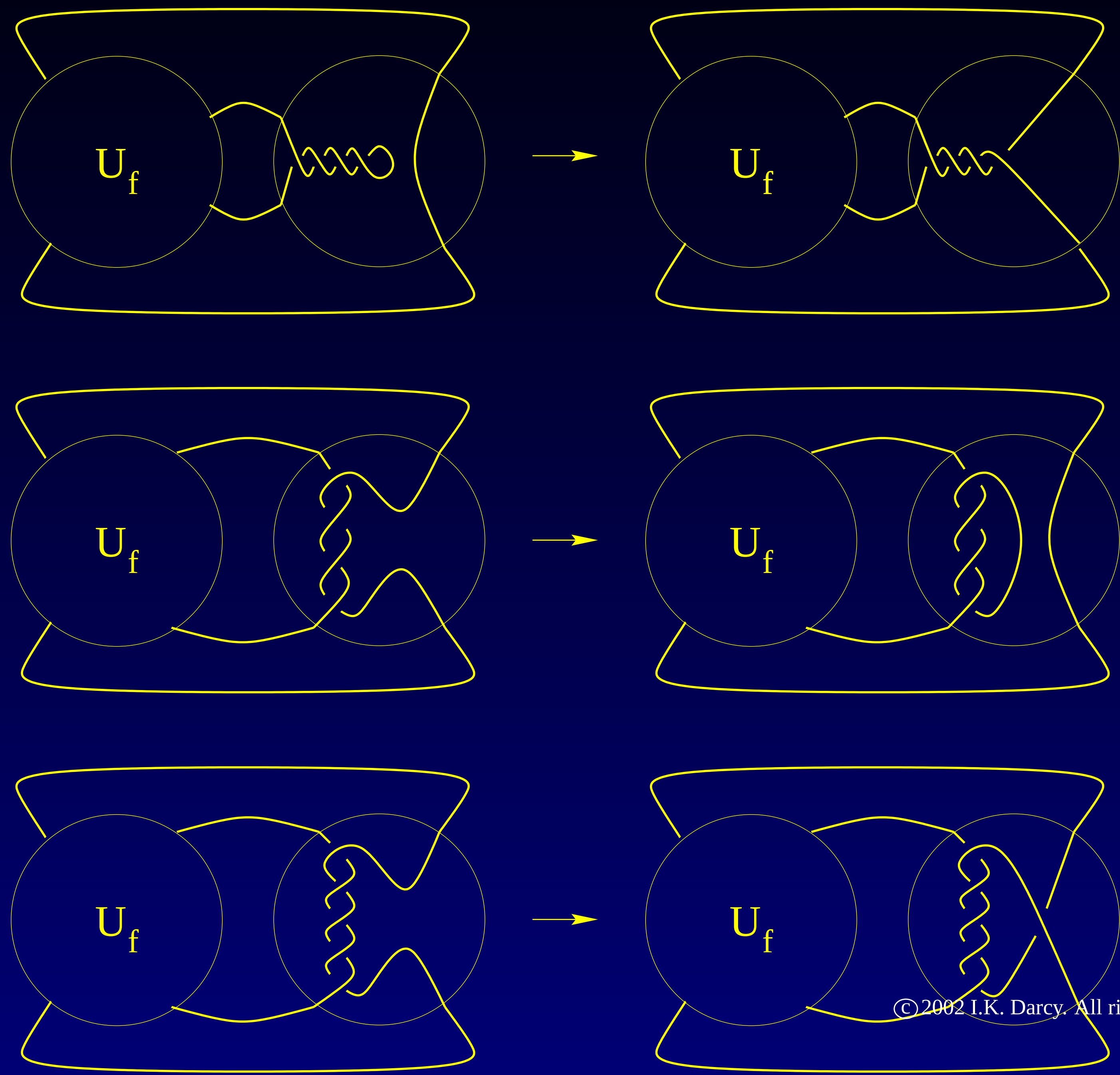
Solutions:

B is rational and if B = 

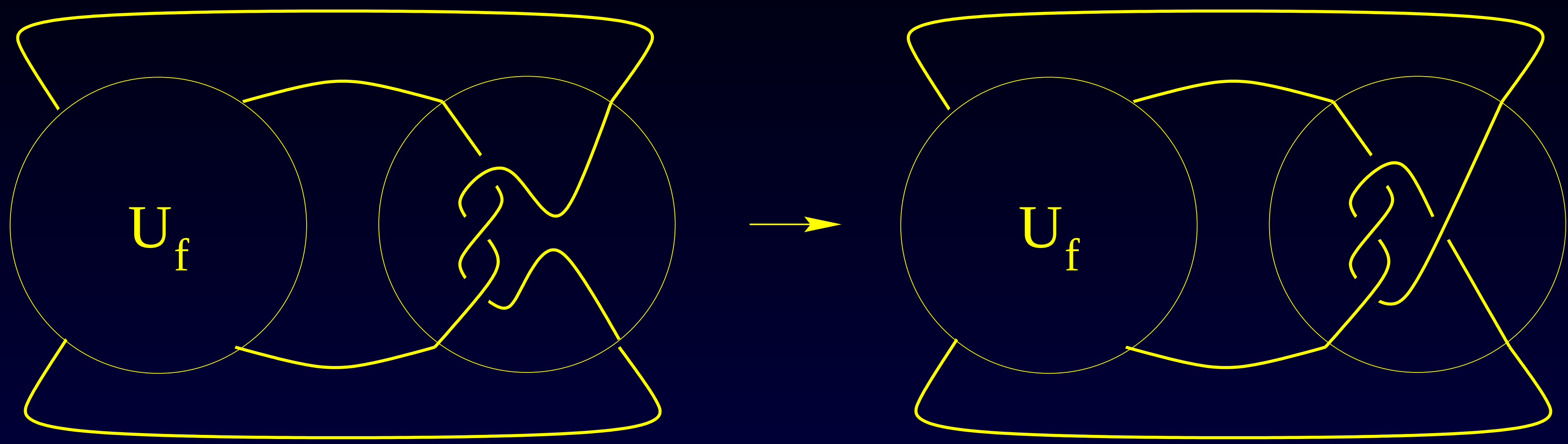
and if E is rational,

E =  or 

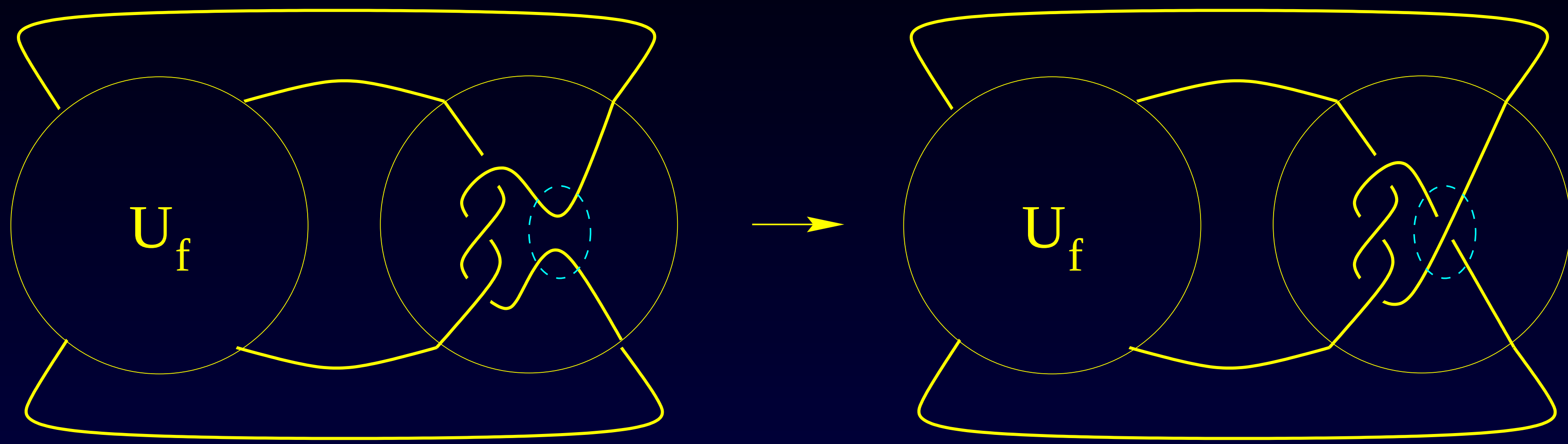
The following are NOT possible models for XER recombination:



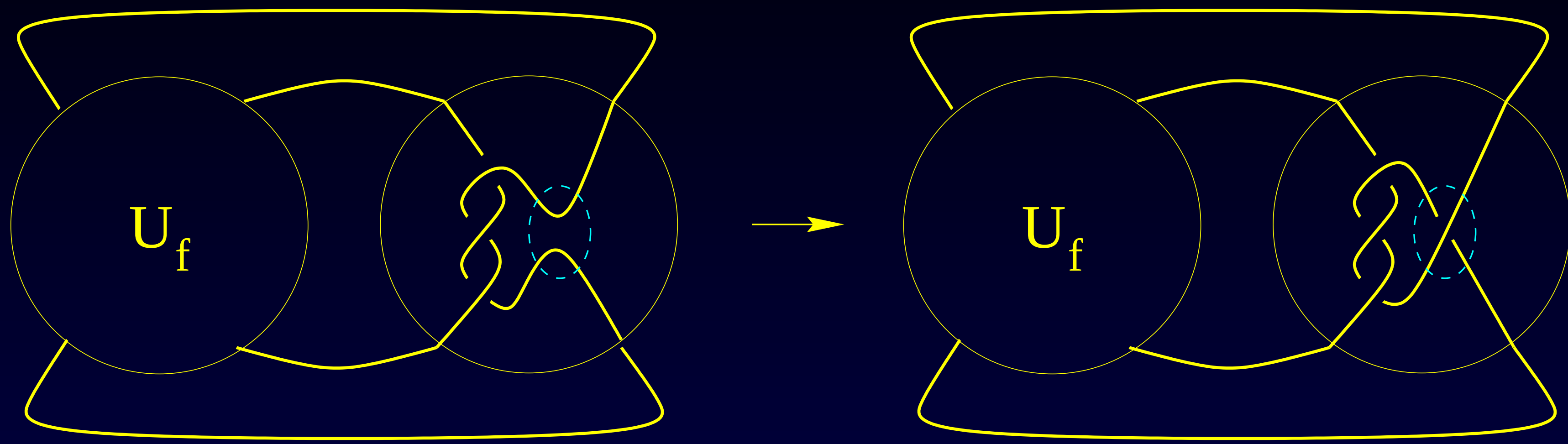
The following is a possible model for XER recombination:



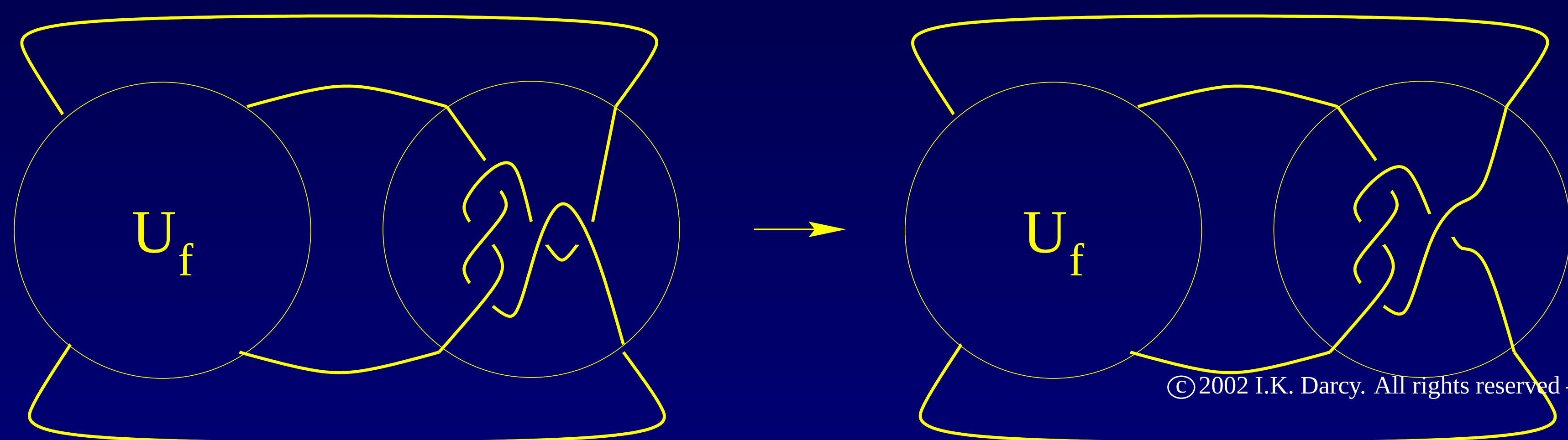
The following is a possible model for XER recombination:



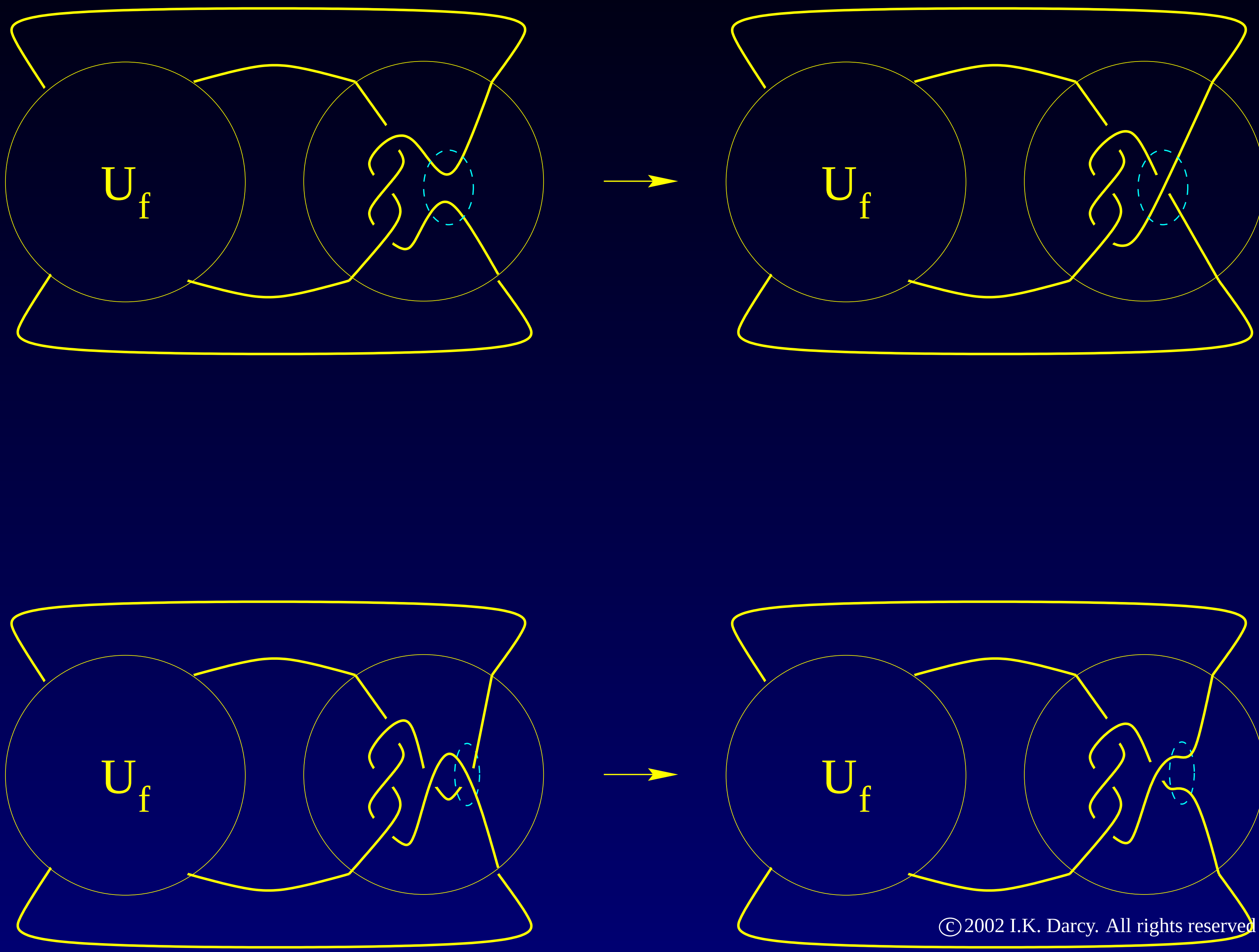
The following is a possible model for XER recombination:



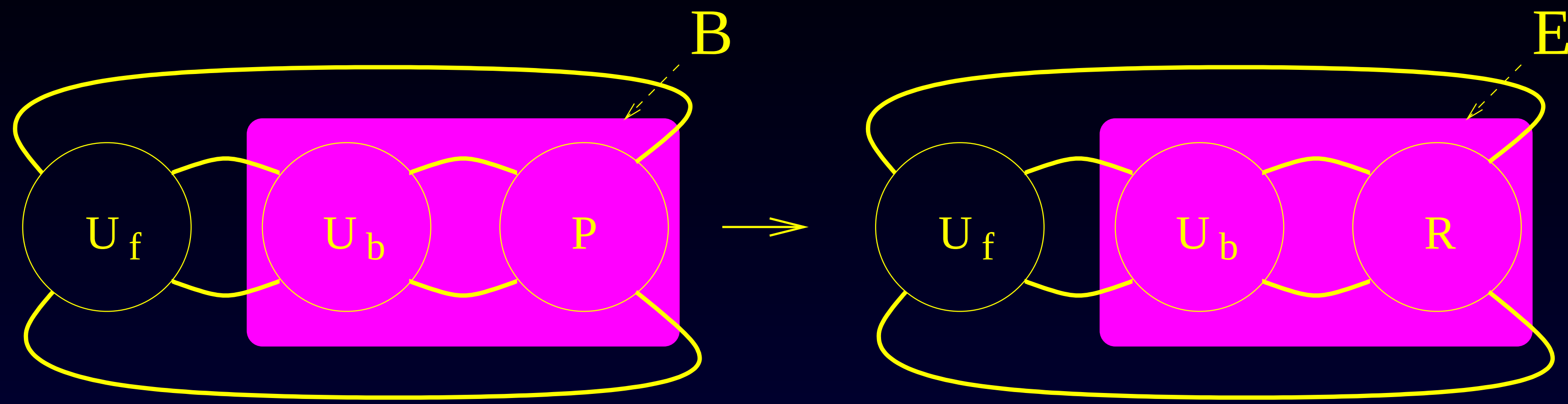
Thus, any model topologically equivalent to the above model would also be a possible model. For example:



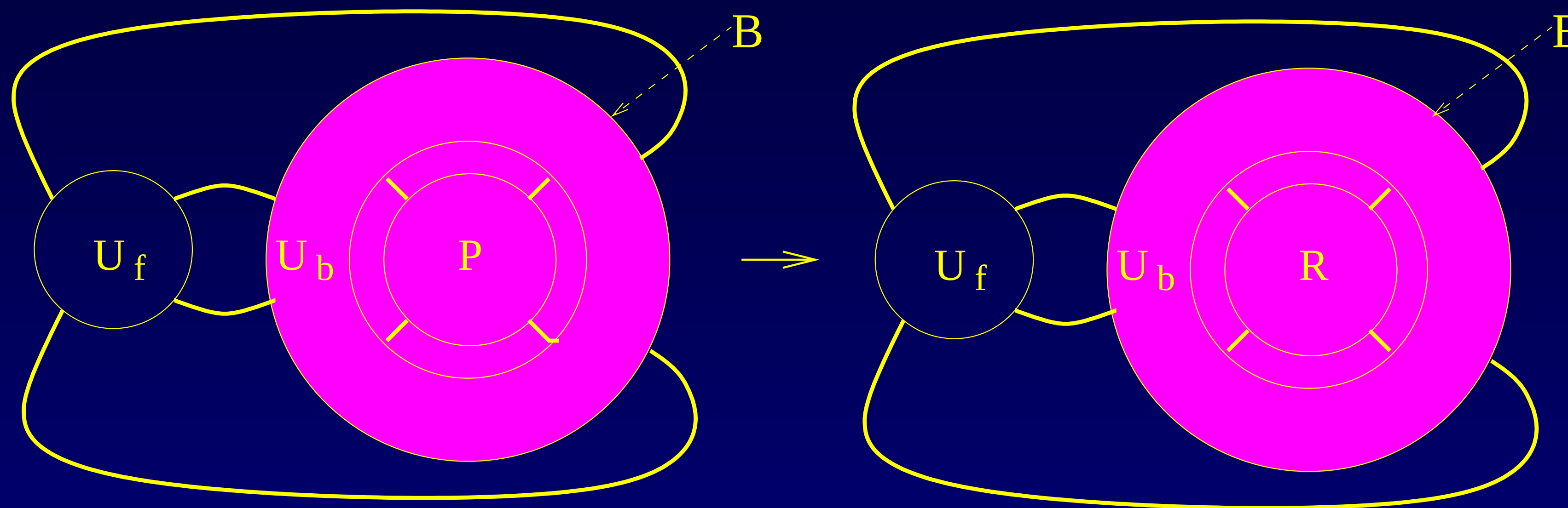
The following is a possible model for XER recombination:



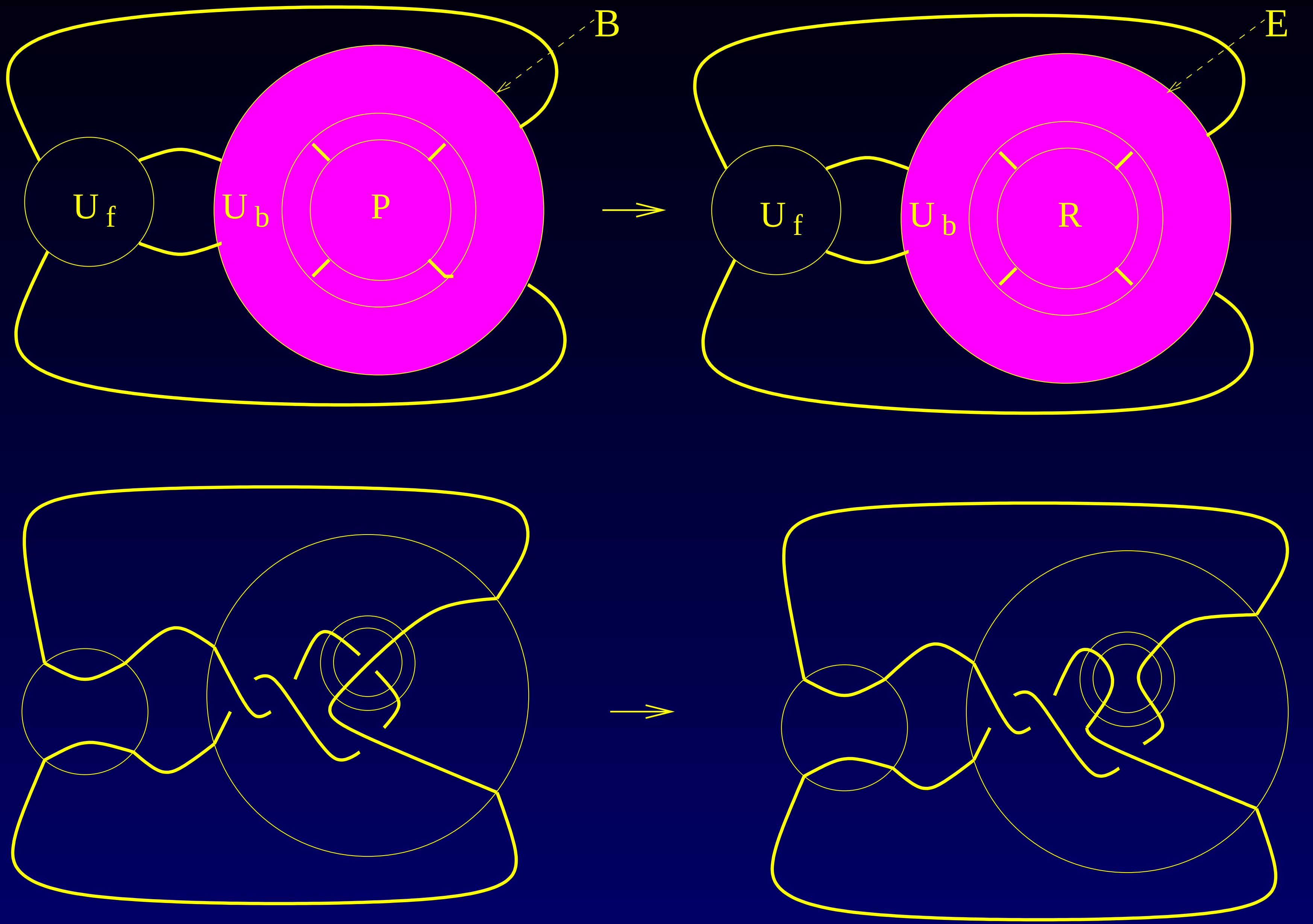
Sumners tangle model:



More general model



More general model



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

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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 availlable at

http://www.utdallas.edu/∼darcy/

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