AMS 2012 Spring Southeastern Section Meeting
University of South Florida, Tampa, FL
Special Session on Discrete Models in Molecular Biology
march 11, 2012

The Algebra of Ciliates

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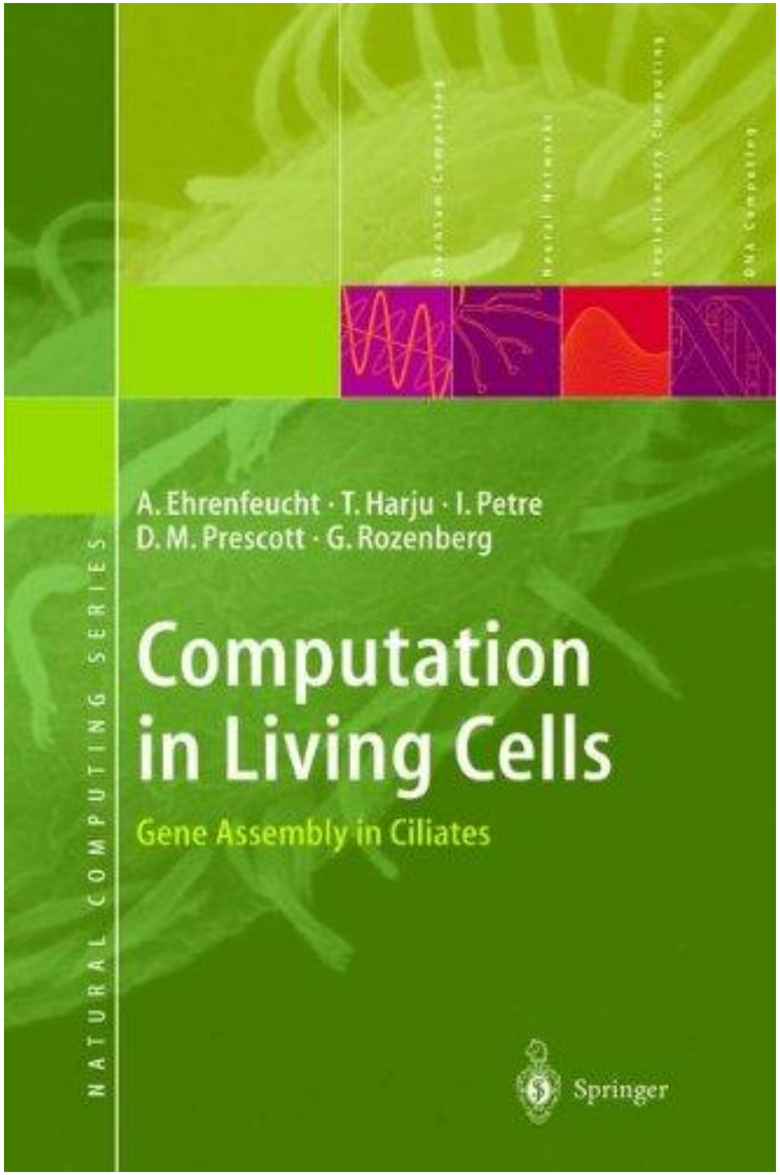
Leiden

with
Robert Brijder
Hasselt

image: http://www.depts.ttu.edu/hillcountry/research/protozoa.php

the book



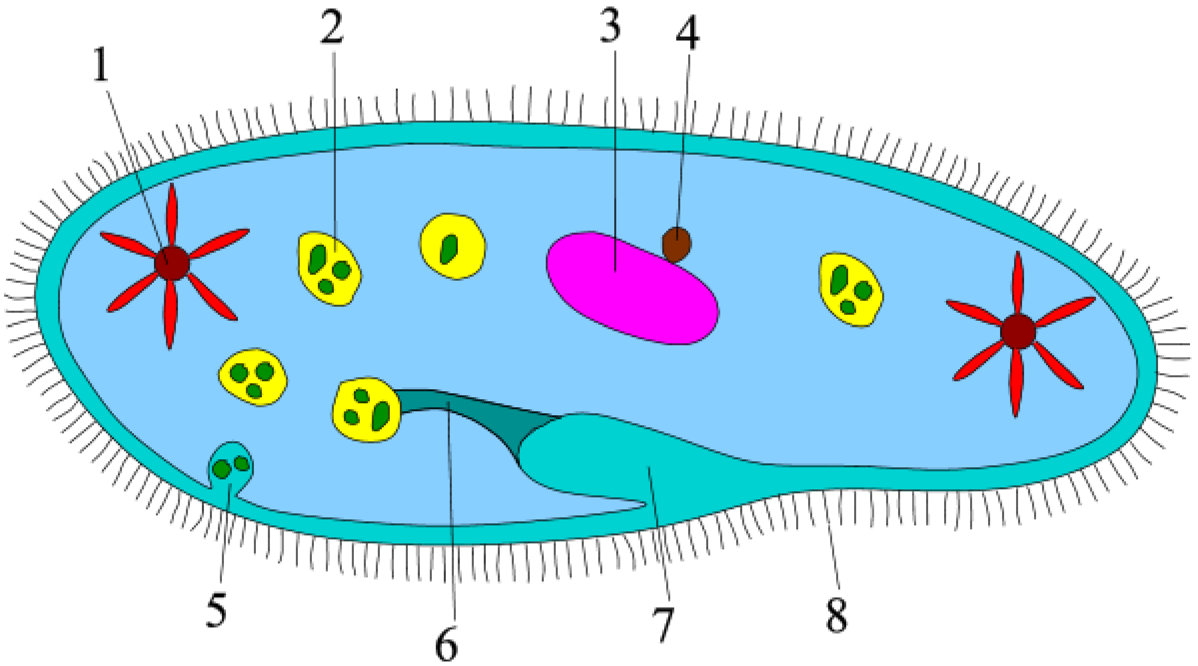
Computation in Living Cells
– Gene Assembly in Ciliates
A.Ehrenfeucht, T.Harju, I.Petre,
D.M.Prescott, G.Rozenberg
Springer, 2004

the overview

R.Brijder, M.Daley, T.Harju, N.Jonoska, I.Petre, G.Rozenberg: Computational nature of gene assembly in ciliates.

in: G. Rozenberg, T.H.W. Bäck, J.N. Kok, editors, *Handbook of Natural Computing,* Springer, 2012. Expected

ciliates: micro and macro



cell structure:

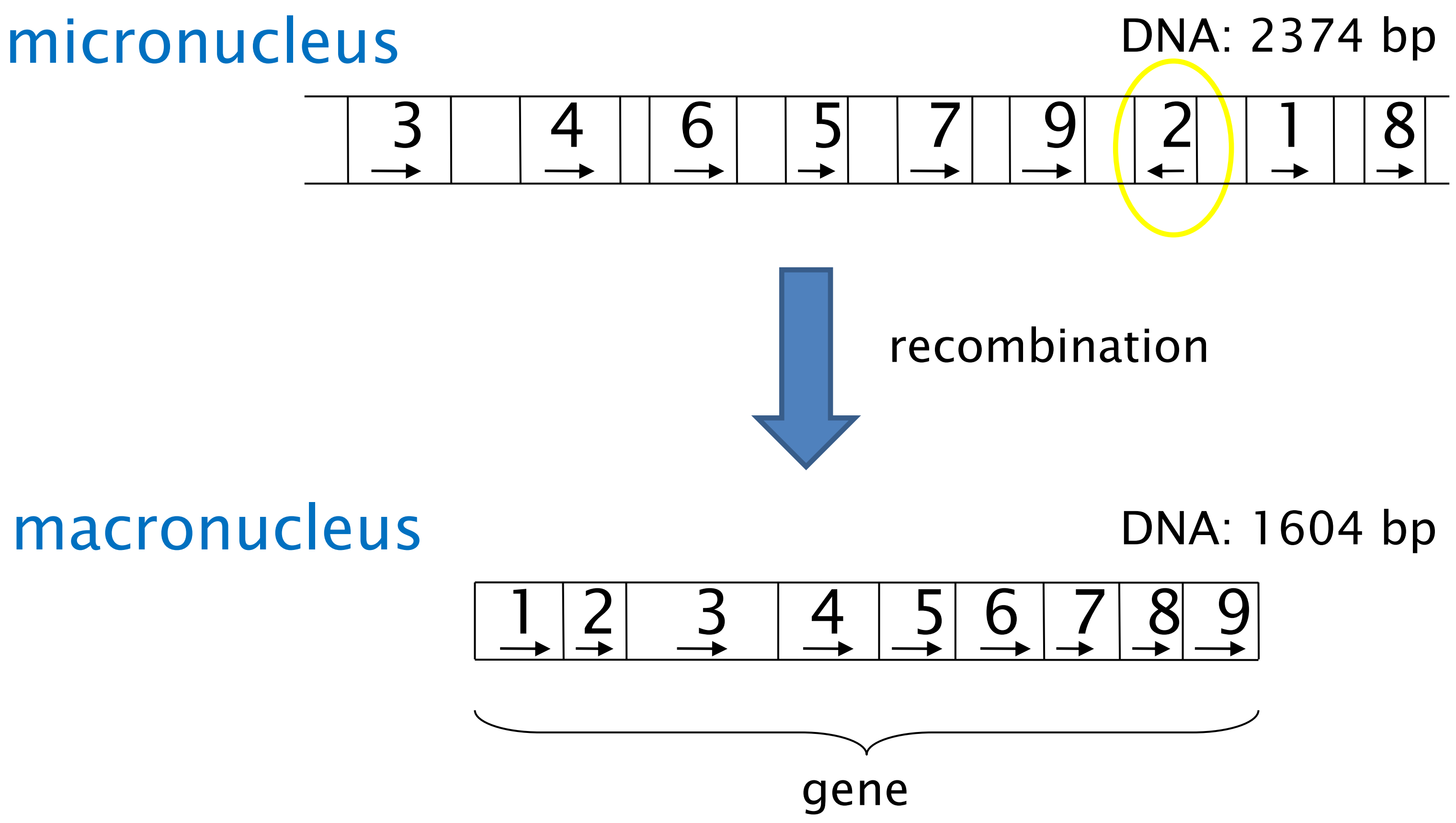
3. macronucleous
4. micronucleous
8. cilium

Unlike most other eukaryotes, ciliates have two different sorts of nuclei: a small, diploid **micronucleus** (reproduction), and a large, polyploid **macronucleus** (general cell regulation). The latter is generated from the micronucleus by amplification of the genome and heavy editing.

http://en.wikipedia.org/wiki/Ciliate

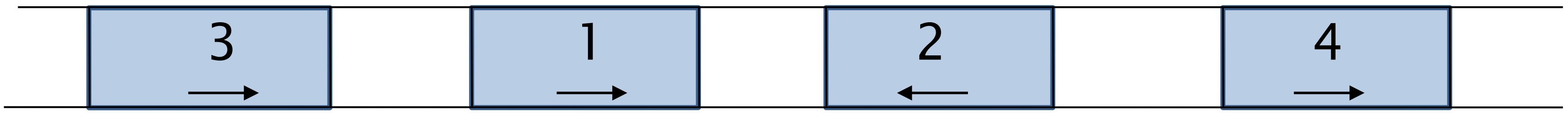
from micro to macro

http://oxytricha.princeton.edu/cgi-bin/get_MDS_IES_Info.cgi?num=38

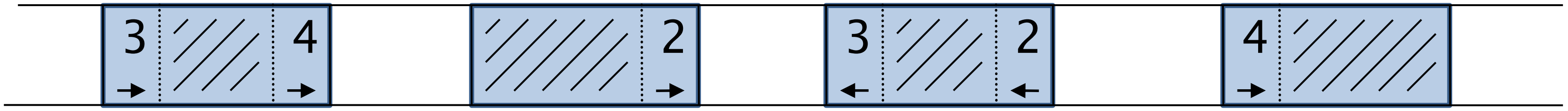


Greslin, Prescott etal. Reordering of nine exons is necessary to form a functional actin gene in Oxytricha nova. PNAS 86, 6264–6268, Aug 1989.

pointers

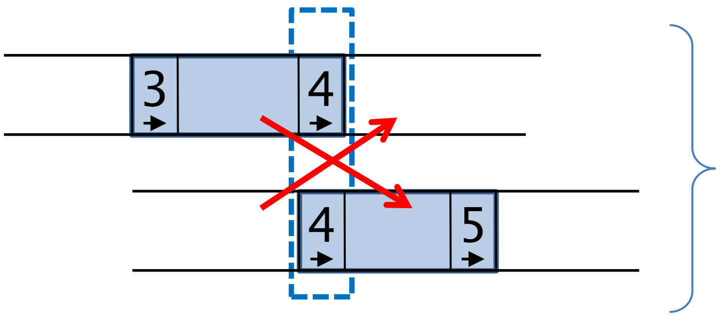


pointers – overlapping segments (for glueing)

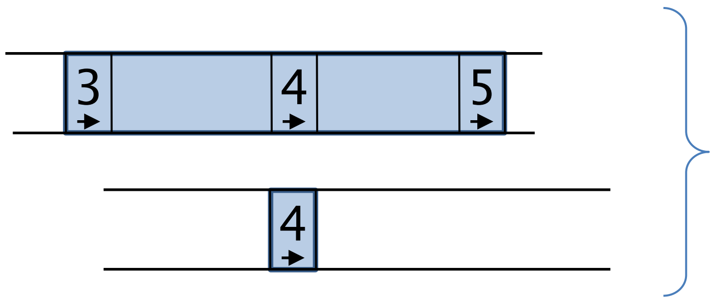


e.g., pointer 5 of actin gene: 13 bp

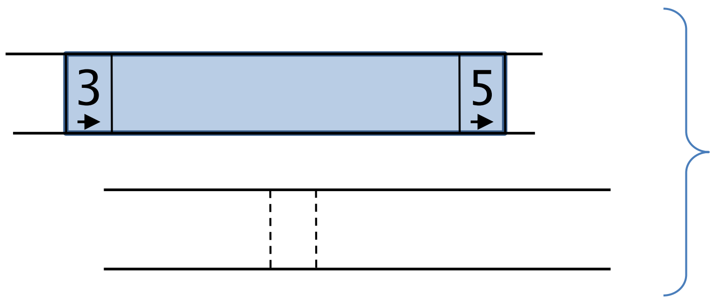
rc_4 recombination on pointer 4 'generic'



before



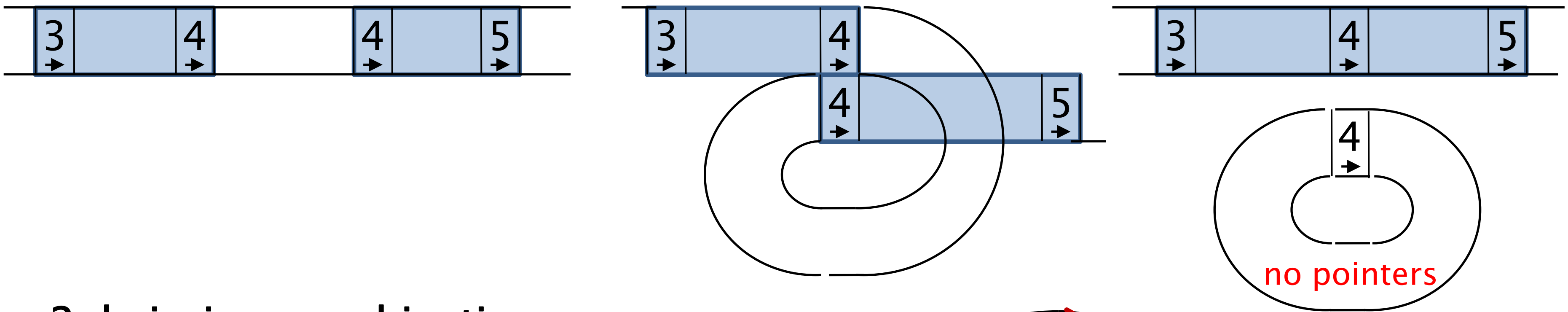
after 'math view'



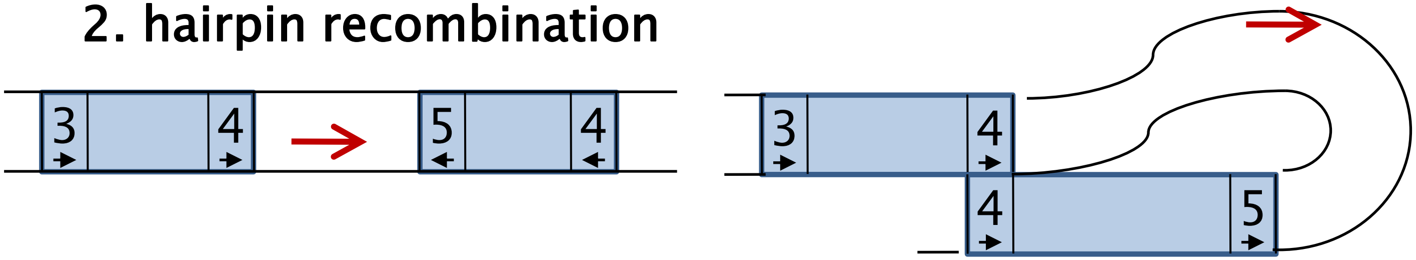
after 'ciliate view'

recombination on pointers

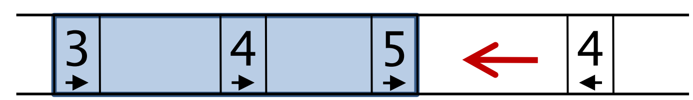
1. loop recombination

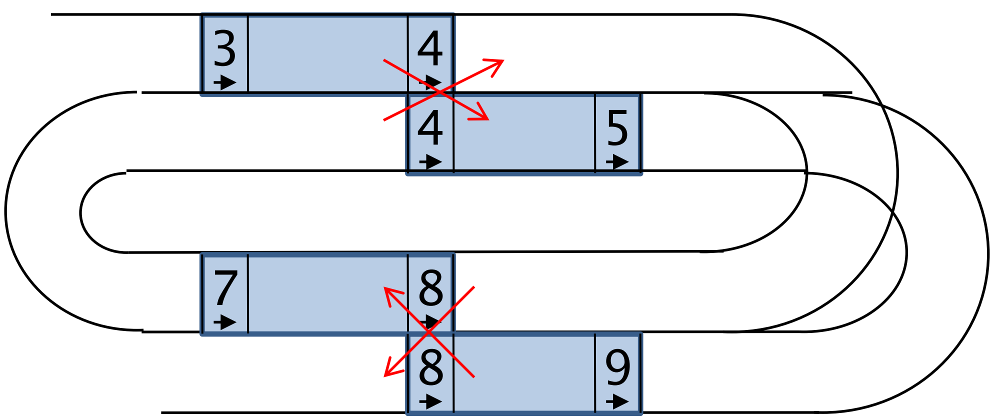


2. hairpin recombination



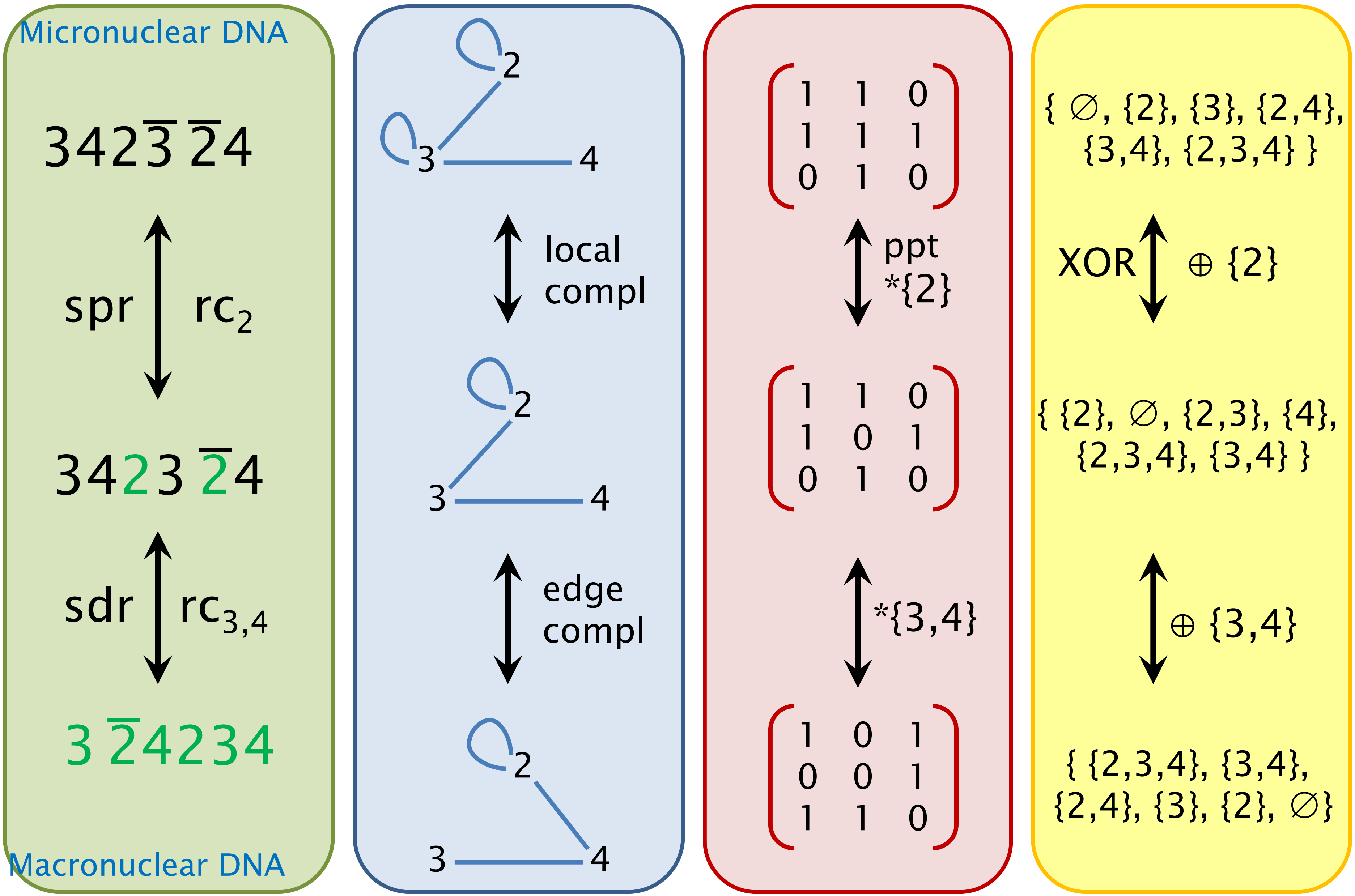
3. double-loop recombination





pointers between
two copies of 4

four worlds

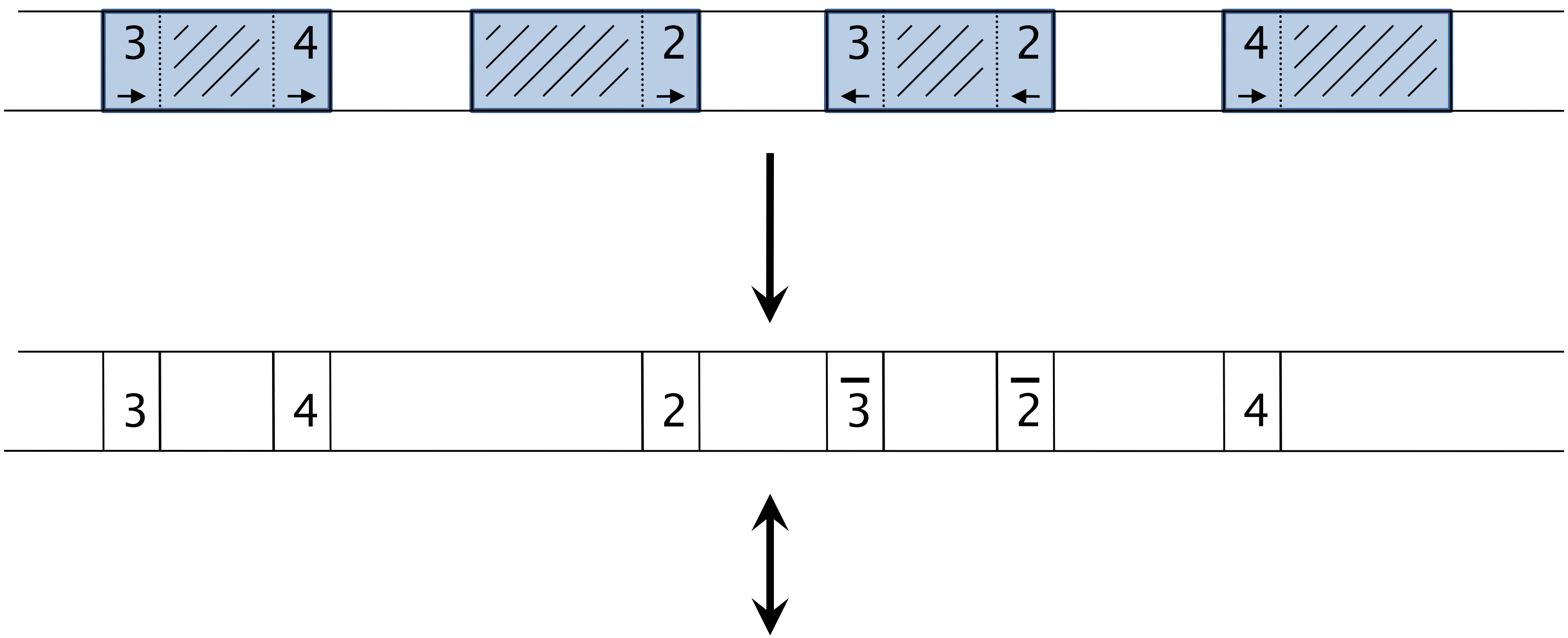


Micronuclear DNA
$342\overline{3}\,\overline{2}4$
spr
rc_2
$3423\,\overline{2}4$
sdr
$rc_{3,4}$
$3\,\overline{2}4234$
Macronuclear DNA
2
3
4
local compl
2
3
4
edge compl
2
3
4
$\begin{pmatrix} 1 & 1 & 0 \\ 1 & 1 & 1 \\ 0 & 1 & 0 \end{pmatrix}$
ppt
*{2}
$\begin{pmatrix} 1 & 1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 0 \end{pmatrix}$
*{3,4}
$\begin{pmatrix} 1 & 0 & 1 \\ 0 & 0 & 1 \\ 1 & 1 & 0 \end{pmatrix}$
{ ∅, {2}, {3}, {2,4}, {3,4}, {2,3,4} }
XOR
⊕ {2}
{ {2}, ∅, {2,3}, {4}, {2,3,4}, {3,4} }
⊕ {3,4}
{ {2,3,4}, {3,4}, {2,4}, {3}, {2}, ∅}

quest for the "right" model

- strings + graphs
- matrices
- set systems

abstraction: pointers



$3\,4\,2\,\bar{3}\,\bar{2}\,4$ ‘legal’ string

... 4774 ... realistic strings vs. generalizations

string pointer reduction systems

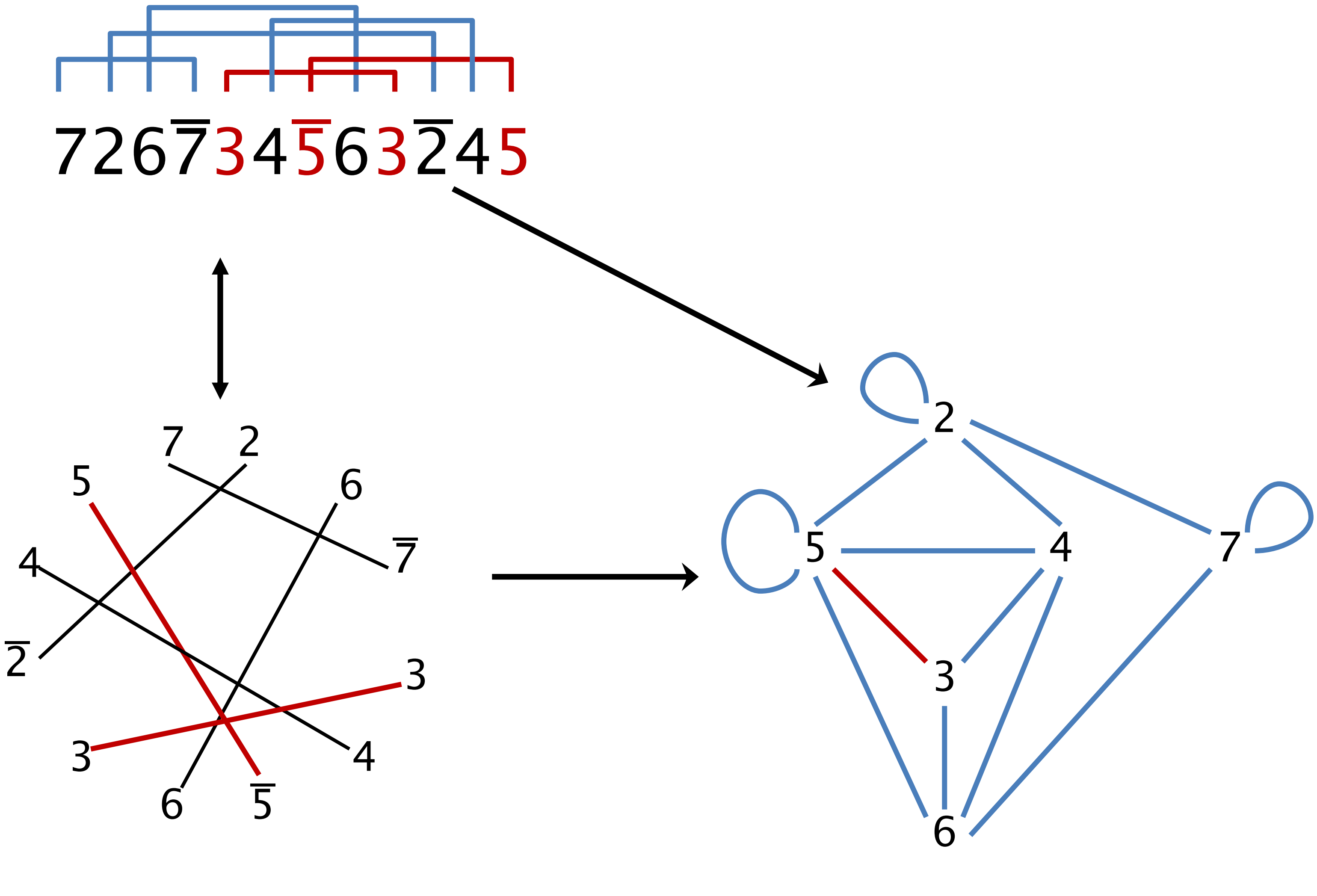
$$rc_p(\ u_1 p p u_2\ ) = u_1 p p u_2$$

no rearrangement
excision circular molecule

$$rc_p(\ u_1 p u_2 \bar{p} u_3\ ) = u_1 p \bar{u}_2 \bar{p} u_3$$

$$rc_{p,q}(\ u_1 p u_2 q u_3 p u_4 q u_5\ ) = u_1 p u_4 q u_3 p u_2 q u_5$$

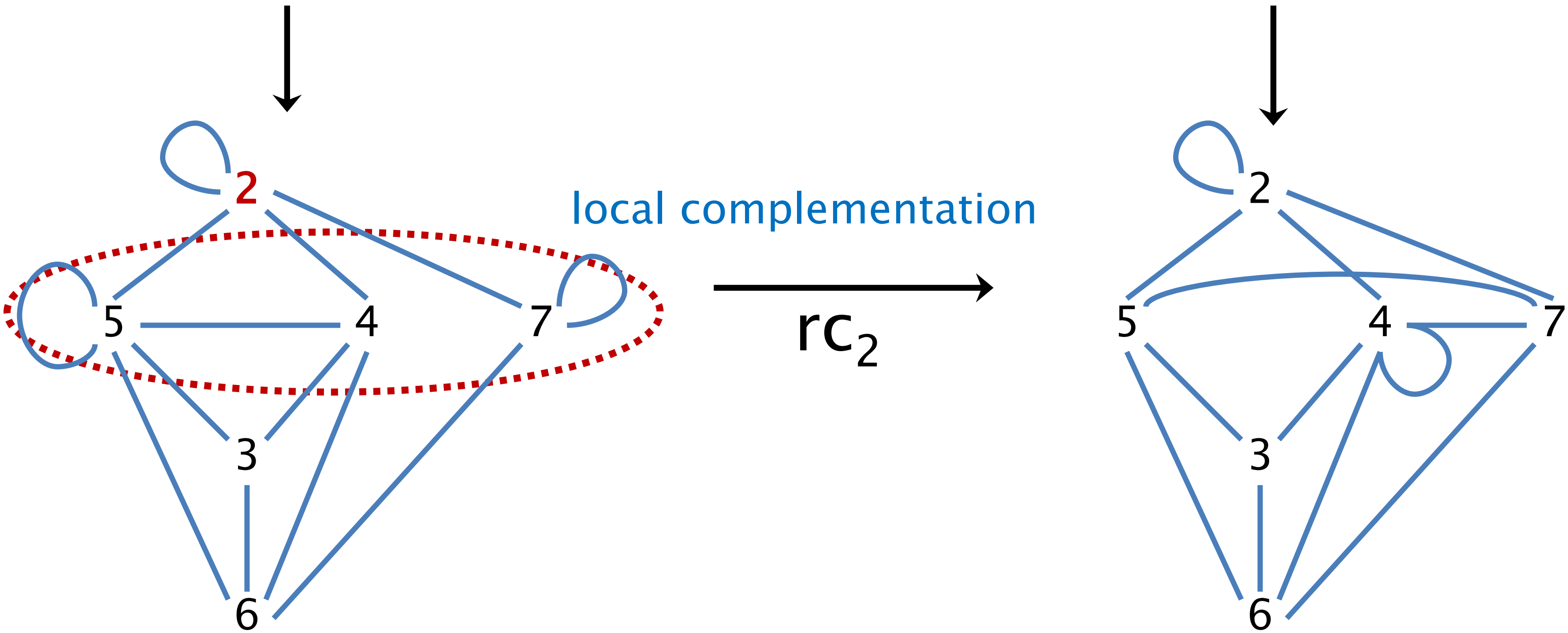
circle & interval / overlap graph



string to overlap graph

real generalization

$$7\,2\,6\,\overline{7}\,3\,4\,\overline{5}\,6\,3\,\overline{2}\,4\,5 \xrightarrow{\;rc_2\;} 7\,2\,\overline{3}\,\overline{6}\,5\,\overline{4}\,\overline{3}\,7\,\overline{6}\,\overline{2}\,4\,5$$

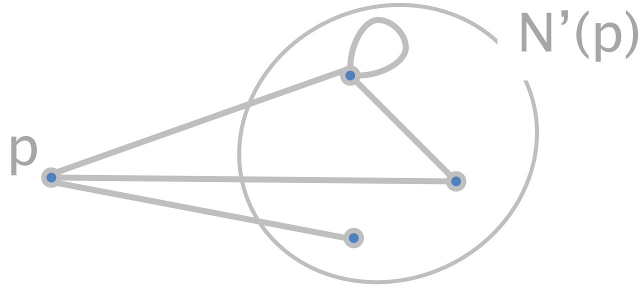


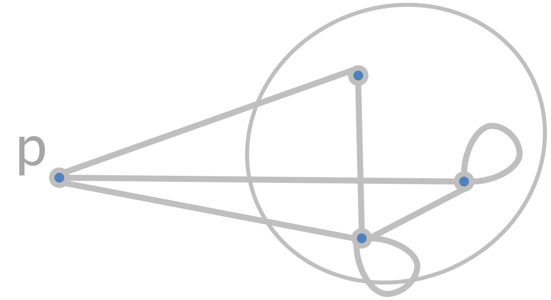
Ehrenfeucht etal, *Theor. Comp. Sci.*, 2003

(for signed graphs instead of looped graphs)

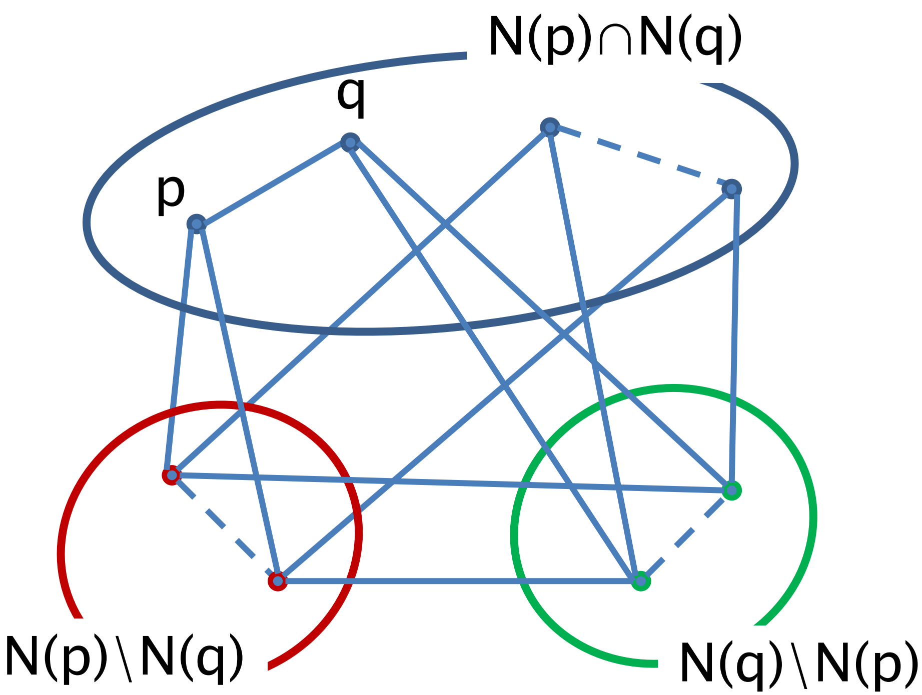
graph operations

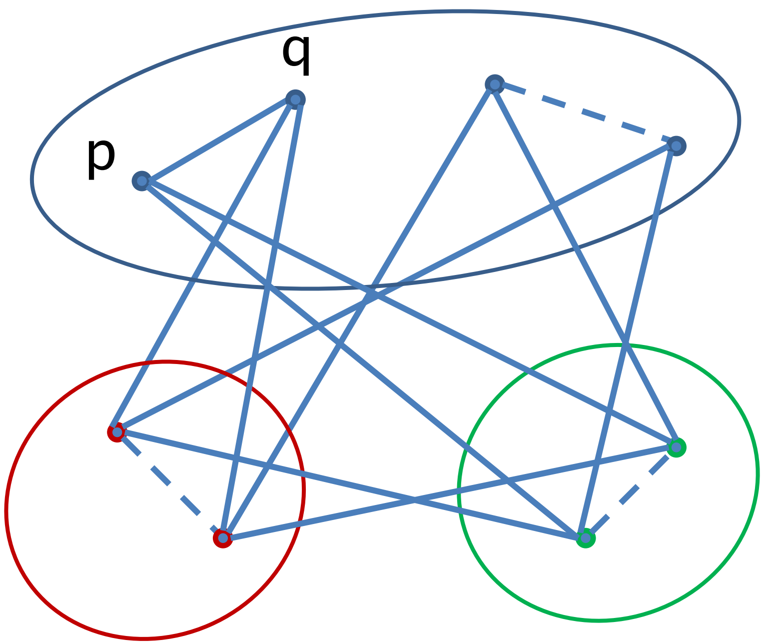
rc_p *local complementation* looped vertex p





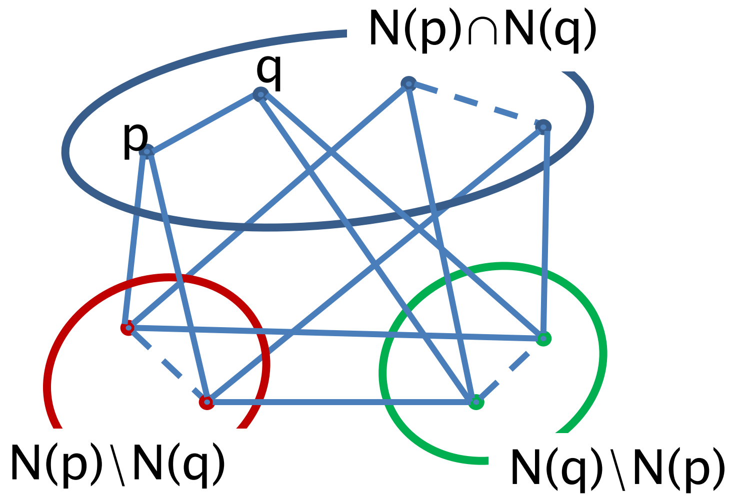
$rc_{p,q}$ *edge complementation* unlooped edge pq

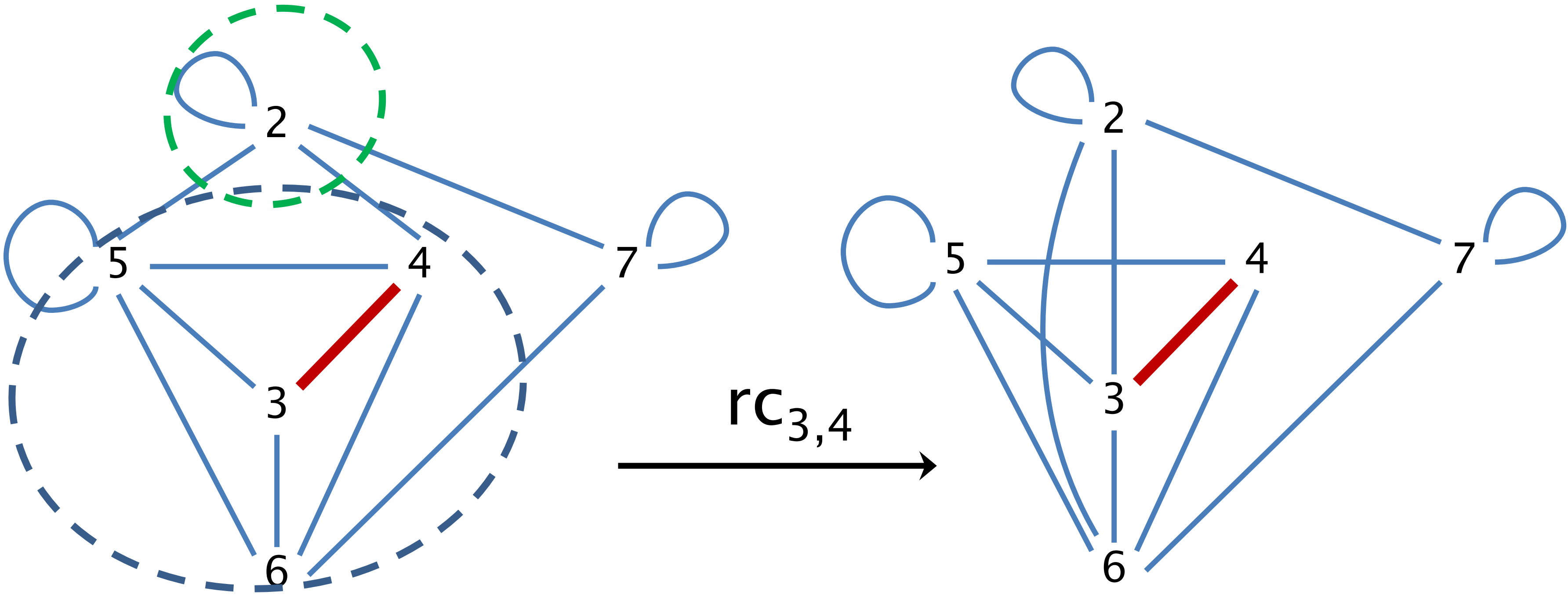


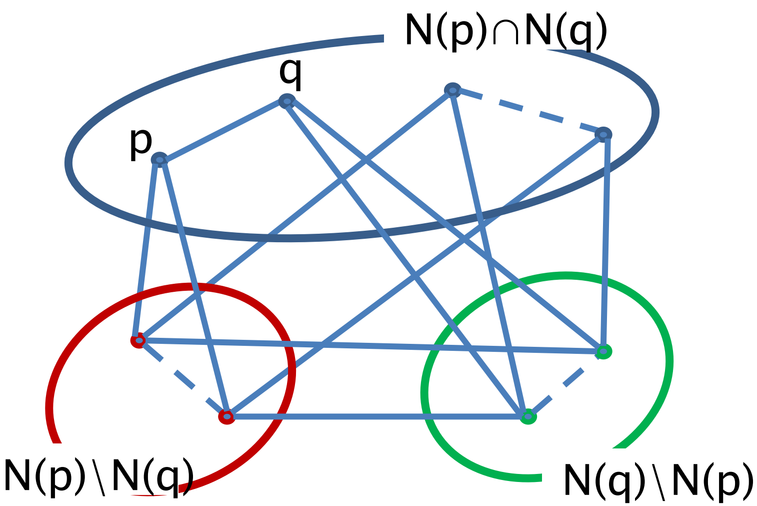


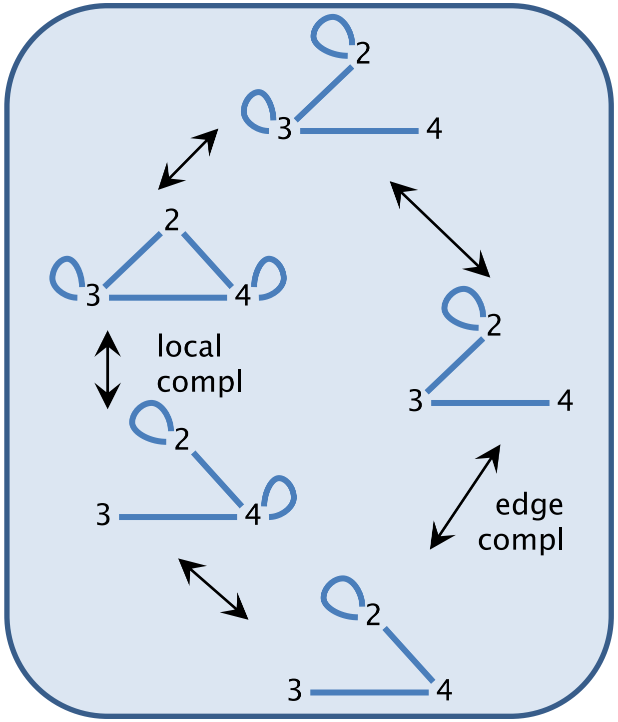
example edge complementation

$rc_{3,4}$ on edge 3,4









questions:

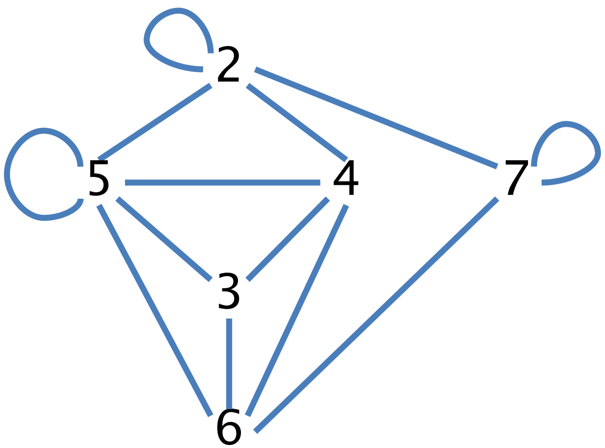
how do $rc_{p,q}$ and $rc_{p'}$ or $rc_{p',q'}$ interact ?

is the result of reductions dependent on (order) operations chosen?

quest for the “right” model

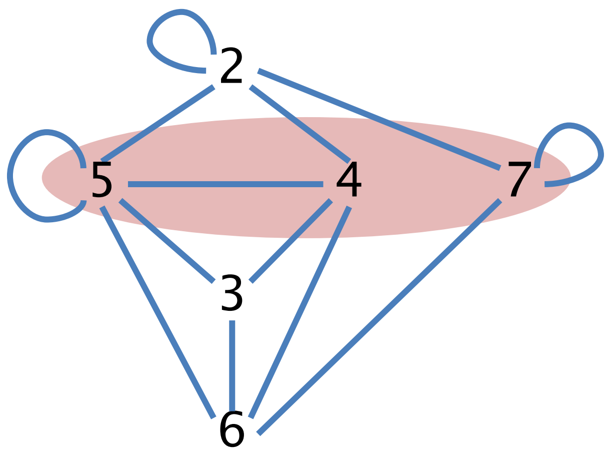
- strings
- graphs $\Leftrightarrow$ matrices
- set systems

graphs and matrices



$$
\begin{array}{c c}
 & \begin{array}{cccccc} 2 & 3 & 4 & 5 & 6 & 7 \end{array} \\
\begin{array}{c} 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \end{array} &
\begin{pmatrix}
1 & 0 & 1 & 1 & 0 & 1 \\
0 & 0 & 1 & 1 & 1 & 0 \\
1 & 1 & 0 & 1 & 1 & 0 \\
1 & 1 & 1 & 1 & 1 & 0 \\
0 & 1 & 1 & 1 & 0 & 1 \\
1 & 0 & 0 & 0 & 1 & 1
\end{pmatrix}
\end{array}
$$

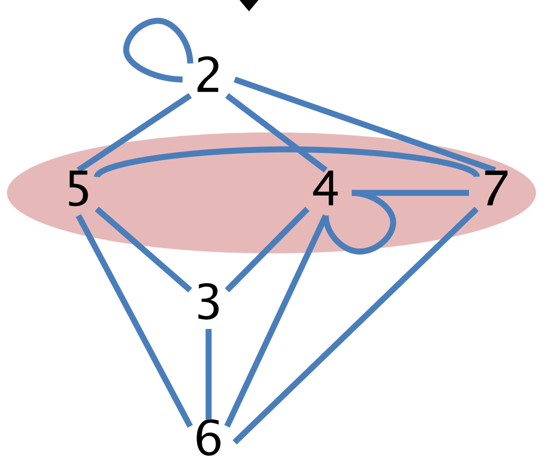
reconsider local/edge complementation



$\longleftrightarrow$

$$
\begin{array}{c|c}
 & \begin{matrix} 2 & 3 & 4 & 5 & 6 & 7 \end{matrix} \\
\begin{matrix} 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \end{matrix} &
\begin{pmatrix}
1 & 0 & 1 & 1 & 0 & 1 \\
0 & 0 & 1 & 1 & 1 & 0 \\
1 & 1 & 0 & 1 & 1 & 0 \\
1 & 1 & 1 & 1 & 1 & 0 \\
0 & 1 & 1 & 1 & 0 & 1 \\
1 & 0 & 0 & 0 & 1 & 1
\end{pmatrix}
\end{array}
$$

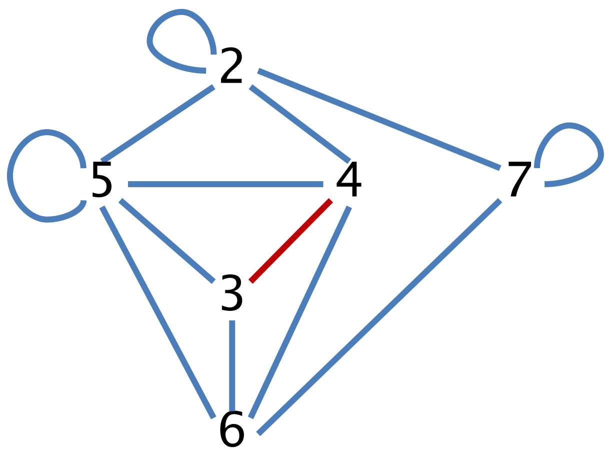
$\downarrow rc_2$ $\qquad$ $\downarrow rc_2$



$\longleftrightarrow$

$$
\begin{array}{c|c}
 & \begin{matrix} 2 & 3 & 4 & 5 & 6 & 7 \end{matrix} \\
\begin{matrix} 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \end{matrix} &
\begin{pmatrix}
1 & 0 & 1 & 1 & 0 & 1 \\
0 & 0 & 1 & 1 & 1 & 0 \\
1 & 1 & 1 & 0 & 1 & 1 \\
1 & 1 & 0 & 0 & 1 & 1 \\
0 & 1 & 1 & 1 & 0 & 1 \\
1 & 0 & 1 & 1 & 1 & 0
\end{pmatrix}
\end{array}
$$

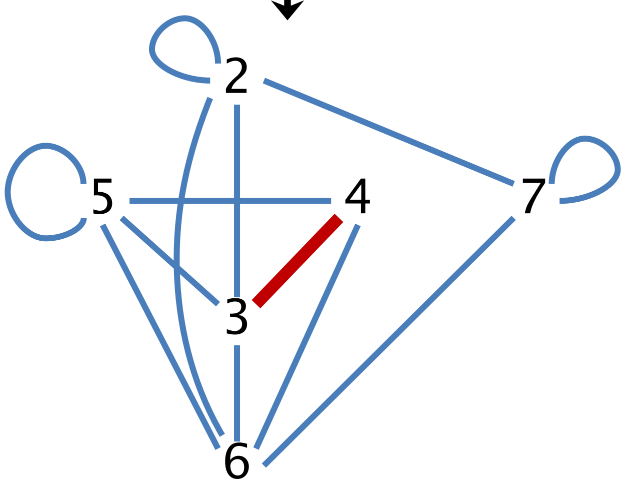
reconsider edge complementation



$$\longleftrightarrow$$

$$\begin{array}{c|cccccc} & 2 & 3 & 4 & 5 & 6 & 7 \\ \hline 2 & 1 & 0 & 1 & 1 & 0 & 1 \\ 3 & 0 & 0 & 1 & 1 & 1 & 0 \\ 4 & 1 & 1 & 0 & 1 & 1 & 0 \\ 5 & 1 & 1 & 1 & 1 & 1 & 0 \\ 6 & 0 & 1 & 1 & 1 & 0 & 1 \\ 7 & 1 & 0 & 0 & 0 & 1 & 1 \end{array}$$

$$\downarrow rc_{3,4} \qquad\qquad \downarrow rc_{3,4}$$



$$\longleftrightarrow$$

$$\begin{array}{c|cccccc} & 2 & 3 & 4 & 5 & 6 & 7 \\ \hline 2 & 1 & 1 & 0 & 0 & 1 & 1 \\ 3 & 1 & 0 & 1 & 1 & 1 & 0 \\ 4 & 0 & 1 & 0 & 0 & 1 & 1 \\ 5 & 0 & 1 & 0 & 1 & 1 & 0 \\ 6 & 1 & 1 & 1 & 1 & 0 & 1 \\ 7 & 1 & 0 & 1 & 0 & 1 & 1 \end{array}$$

principal pivot transform

$A * X$ is defined iff $A[X]$ is invertible/nonsingular/det $\neq 0$

$$A = \begin{array}{cc} & X \\ X & \left(\begin{array}{c|c} P & Q \\ \hline R & S \end{array}\right) \end{array}$$

$$A * X = \left(\begin{array}{c|c} P^{-1} & -P^{-1} Q \\ \hline R P^{-1} & S - R P^{-1} Q \end{array}\right)$$

partial inverse

$$A \begin{pmatrix} x_1 \\ y_1 \end{pmatrix} = \begin{pmatrix} x_2 \\ y_2 \end{pmatrix} \quad \text{iff} \quad A{*}X \begin{pmatrix} x_2 \\ y_1 \end{pmatrix} = \begin{pmatrix} x_1 \\ y_2 \end{pmatrix}$$

$\leftarrow$ X pointers

$\leftarrow$ other

M.J. Tsatsomeros. Principal pivot transforms: properties and applications.
Linear Algebra and its Applications, 307(1-3):151-165, 2000

principal pivot transform

$A * X$ is defined iff $A[X]$ is invertible/nonsingular/det $\neq 0$

$$A = \begin{array}{cc} & X \\ X & \left(\begin{array}{c|c} P & Q \\ \hline R & S \end{array}\right) \end{array} \qquad A * X = \left(\begin{array}{c|c} P^{-1} & -P^{-1} Q \\ \hline R P^{-1} & S - R P^{-1} Q \end{array}\right)$$

$$\begin{array}{c c} & \begin{array}{cccccc} 2 & 3 & 4 & 5 & 6 & 7 \end{array} \\ \begin{array}{c} 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \end{array} & \left(\begin{array}{cccccc} 1 & 0 & 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 1 & 1 & 0 \\ 1 & 1 & 0 & 1 & 1 & 0 \\ 1 & 1 & 1 & 1 & 1 & 0 \\ 0 & 1 & 1 & 1 & 0 & 1 \\ 1 & 0 & 0 & 0 & 1 & 1 \end{array}\right) \end{array} \xrightarrow{rc_{3,4}} \begin{array}{c c} & \begin{array}{cccccc} 2 & 3 & 4 & 5 & 6 & 7 \end{array} \\ \begin{array}{c} 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \end{array} & \left(\begin{array}{cccccc} 1 & 1 & 0 & 0 & 1 & 1 \\ 1 & 0 & 1 & 1 & 1 & 0 \\ 0 & 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 1 & 0 \\ 1 & 1 & 1 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 & 1 & 1 \end{array}\right) \end{array}$$

J.F. Geelen, A generalization of Tutte's characterization of totally unimodular matrices, Journal of Combinatorial Theory, Series B 70 (1997) 101–117.

principal pivot transform

$$A \begin{pmatrix} x_1 \\ y_1 \end{pmatrix} = \begin{pmatrix} x_2 \\ y_2 \end{pmatrix} \quad \text{iff} \quad A{*}X \begin{pmatrix} x_2 \\ y_1 \end{pmatrix} = \begin{pmatrix} x_1 \\ y_2 \end{pmatrix}$$

using partial inversion

$$\boxed{(A * X) * Y = A * (X \overset{\text{xor}}{\oplus} Y)}$$

(when defined)

$$\boxed{\underbrace{A * \{p_1, p_2\} \ldots * p_n}_{\text{any sequence involving all pointers}} = A * V = A^{-1}}$$

(all pointers)

this shows

- how the rc_p and $rc_{p,q}$ interact
- result does not depend on order of operations

what *is* happening?

$34 2 \bar{3} \bar{2} 4$ $\qquad\qquad$ $3 \bar{2} 4 2 3 4$

$$\begin{array}{c|ccc} & 2 & 3 & 4 \\ \hline 2 & 1 & 1 & 0 \\ 3 & 1 & 1 & 1 \\ 4 & 0 & 1 & 0 \end{array} \xrightarrow{rc_3\ rc_4\ rc_2} \begin{array}{c|ccc} & 2 & 3 & 4 \\ \hline 2 & 1 & 0 & 1 \\ 3 & 0 & 0 & 1 \\ 4 & 1 & 1 & 0 \end{array}$$

multiply (over the binary numbers)

$$\underbrace{\begin{pmatrix} 1 & 1 & 0 \\ 1 & 1 & 1 \\ 0 & 1 & 0 \end{pmatrix}}_{\text{micro}} \underbrace{\begin{pmatrix} 1 & 0 & 1 \\ 0 & 0 & 1 \\ 1 & 1 & 0 \end{pmatrix}}_{\text{macro}} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

$+$	xor $\oplus$	$1+1=0$
$*$	and $\wedge$	

sorting DNA = computing the inverse

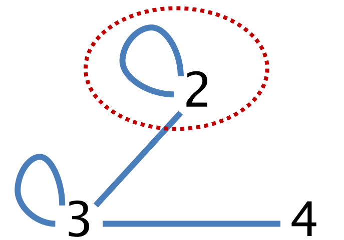
ppt is (partial) inverse

applicability

A * X is defined iff A[X] is invertible

rc_2

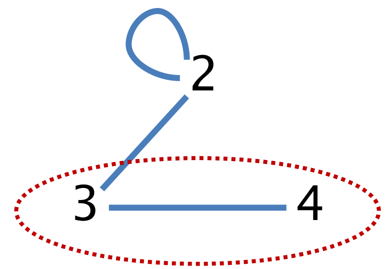
$3 4 2 \bar{3} \bar{2} 4$



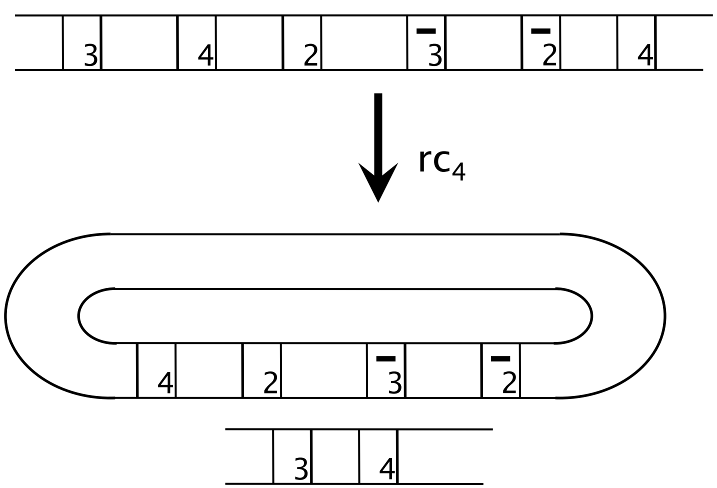
$$\begin{pmatrix} 1 & 1 & 0 \\ 1 & 1 & 1 \\ 0 & 1 & 0 \end{pmatrix}$$

$rc_{3,4}$

$3 4 2 3 \bar{2} 4$

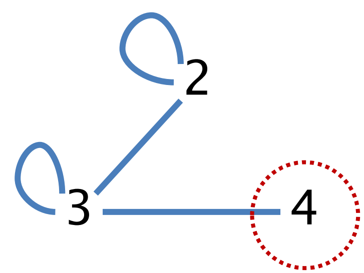


$$\begin{pmatrix} 1 & 1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 0 \end{pmatrix}$$



$3 4 2 \bar{3} \bar{2} 4$

undefined



$$\begin{array}{c|ccc} & 2 & 3 & 4 \\ \hline 2 & 1 & 1 & 0 \\ 3 & 1 & 1 & 1 \\ 4 & 0 & 1 & 0 \end{array}$$

conclusion (for now)

- by careful modeling we find that gene assembly is *actually* principal pivot transform (ppt)
- we can use results about ppt to know more about gene assembly
  - independent order operations
  - interaction operations

quest for the “right” model

- strings
- graphs
- matrices
- set systems

the most elegant model was hidden

4

applicable sets

A * X is defined iff A[X] is invertible

$$\begin{array}{c|ccc} & 2 & 3 & 4 \\ \hline 2 & \multicolumn{3}{c}{\multirow{3}{*}{$\begin{pmatrix} 1 & 1 & 0 \\ 1 & \boxed{1} & \boxed{1} \\ 0 & \boxed{1} & \boxed{0} \end{pmatrix}$}} \\ 3 & & & \\ 4 & & & \end{array} \longleftrightarrow$$

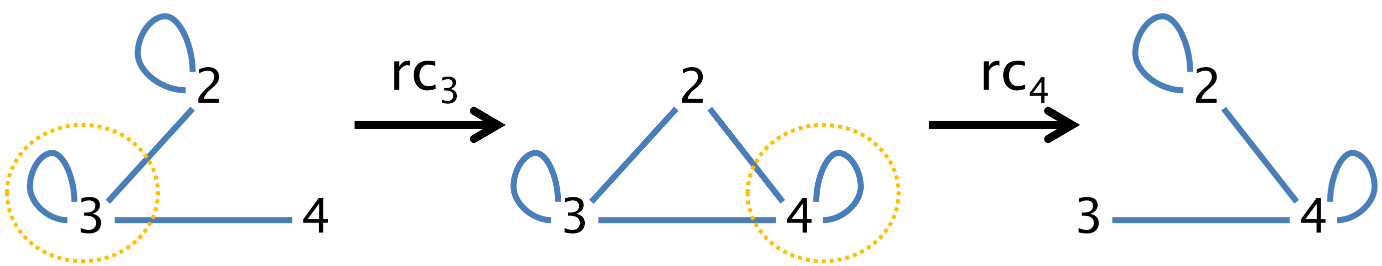
set system

$V = \{2,3,4\}$

$D = \{ \emptyset, \{2\}, \{3\}, \{2,4\}, \boxed{\{3,4\}}, \{2,3,4\} \}$

A[{3,4}]

*{3,4} is not $rc_{3,4}$



graphs $\subseteq$ set systems (strict)

$3\,4\,2\,\bar{3}\,\bar{2}\,4$

$$\begin{array}{c c} & \begin{array}{ccc} 2 & 3 & 4 \end{array} \\ \begin{array}{c} 2 \\ 3 \\ 4 \end{array} & \begin{pmatrix} 1 & 1 & 0 \\ 1 & 1 & 1 \\ 0 & 1 & 0 \end{pmatrix} \end{array}$$

$V = \{2,3,4\}$

$D = \{\ \emptyset, \{2\}, \{3\}, \{2,4\}, \{3,4\}, \{2,3,4\}\ \}$

rc_3

$\oplus 3$ xor 3

$3\,\bar{2}\,\bar{4}\,\bar{3}\,\bar{2}\,4$

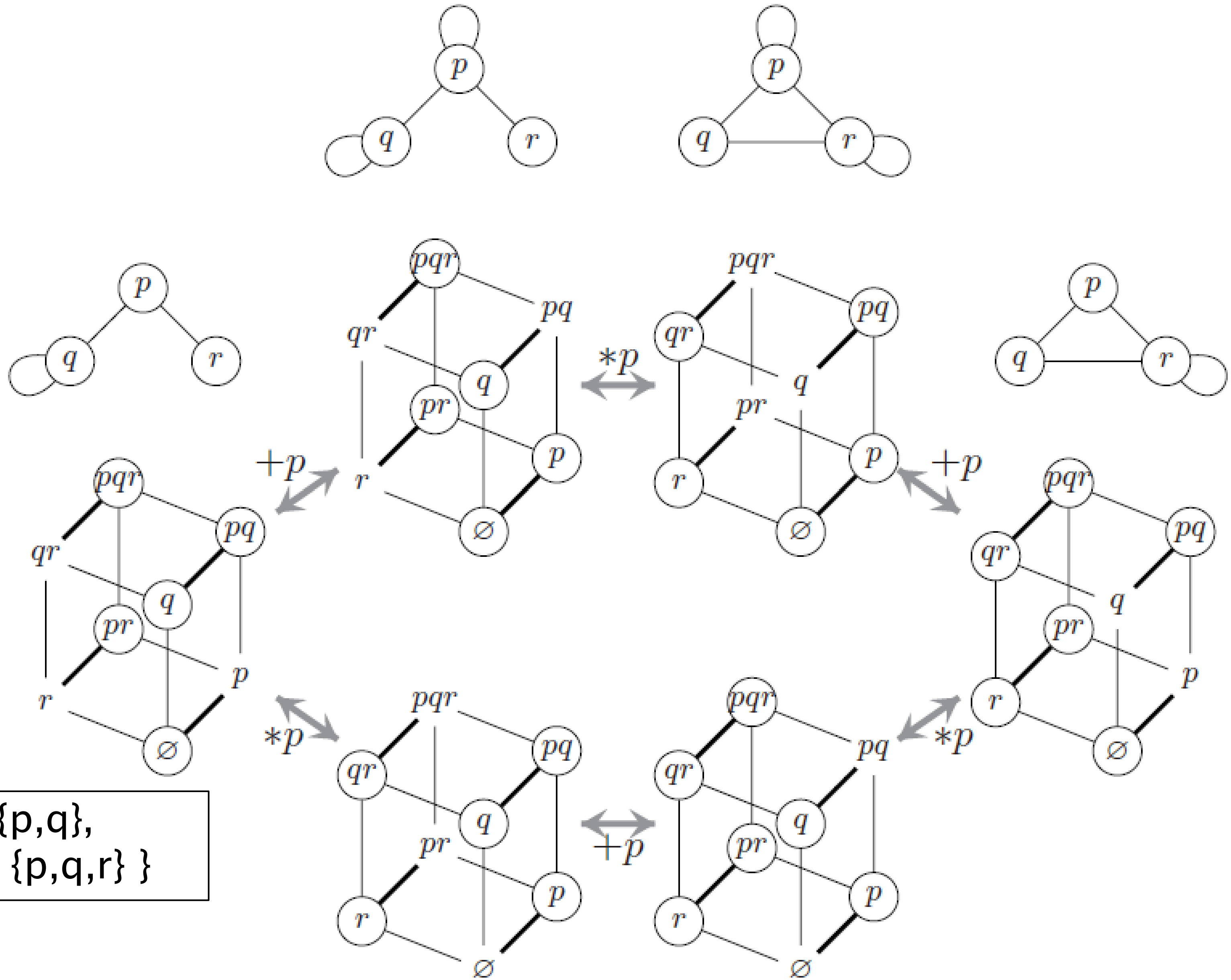
$$\begin{array}{c c} & \begin{array}{ccc} 2 & 3 & 4 \end{array} \\ \begin{array}{c} 2 \\ 3 \\ 4 \end{array} & \begin{pmatrix} 0 & 1 & 1 \\ 1 & 1 & 1 \\ 1 & 1 & 1 \end{pmatrix} \end{array}$$

$V = \{2,3,4\}$

$D' = \{\ \{3\}, \{2,3\}, \emptyset, \{2,3,4\}, \{4\}, \{2,4\}\ \}$

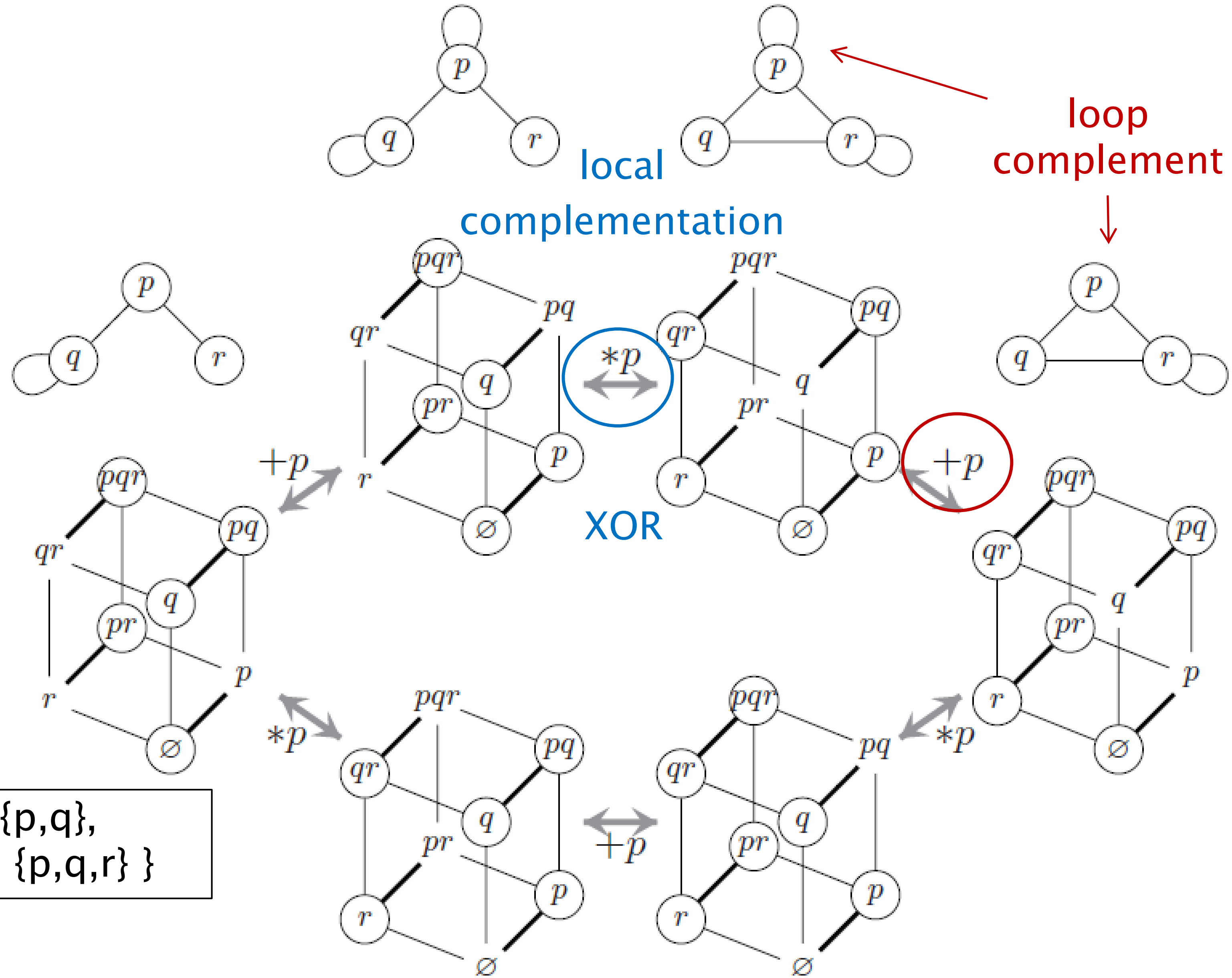
applicability (!) XOR {4} is defined,
while rc_4 is not, nb. {4} not in D

algebra of set systems



{ ∅, {q}, {p,q},
{p,r}, {p,q,r} }

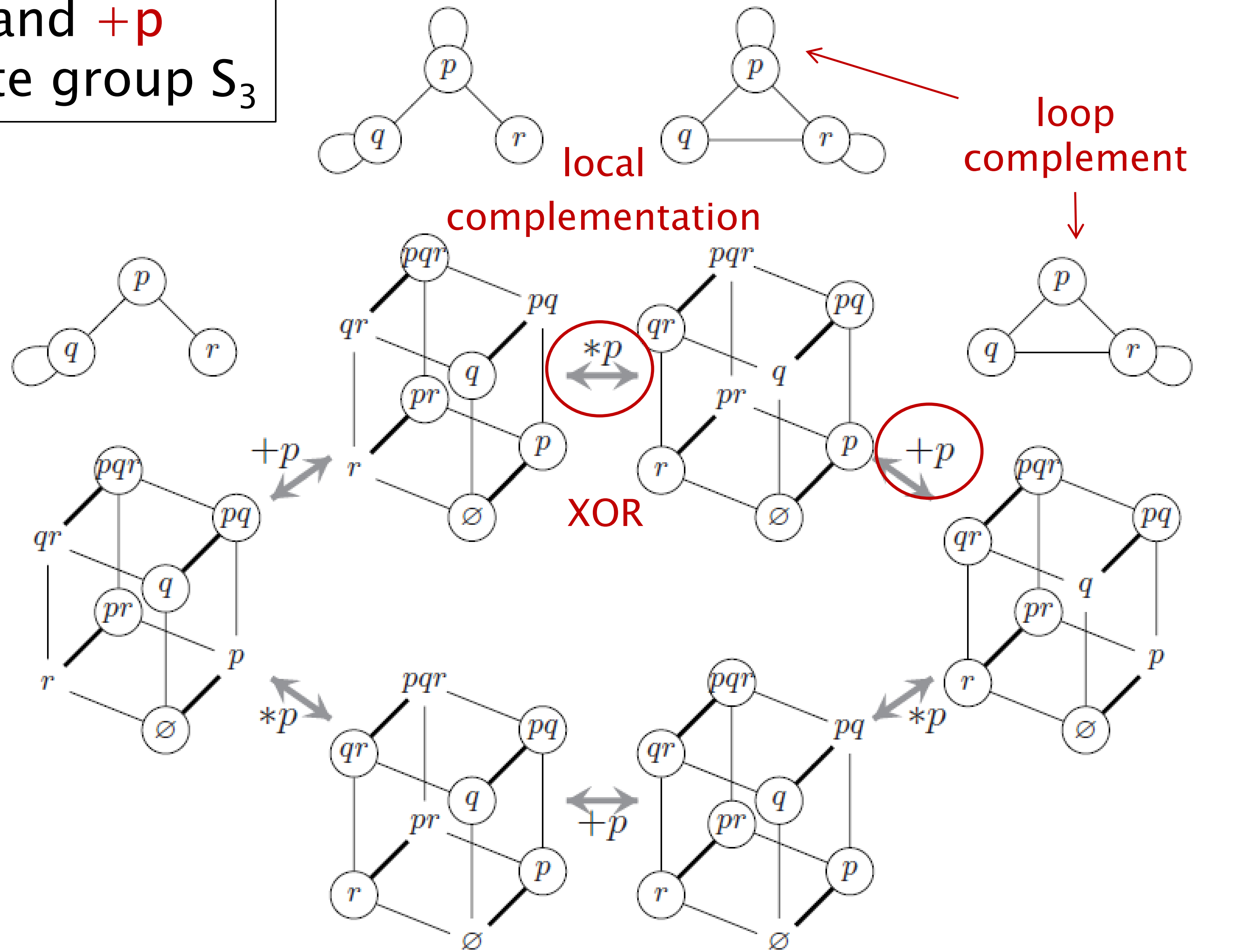
algebra of set systems



{ ∅, {q}, {p,q},
{p,r}, {p,q,r} }

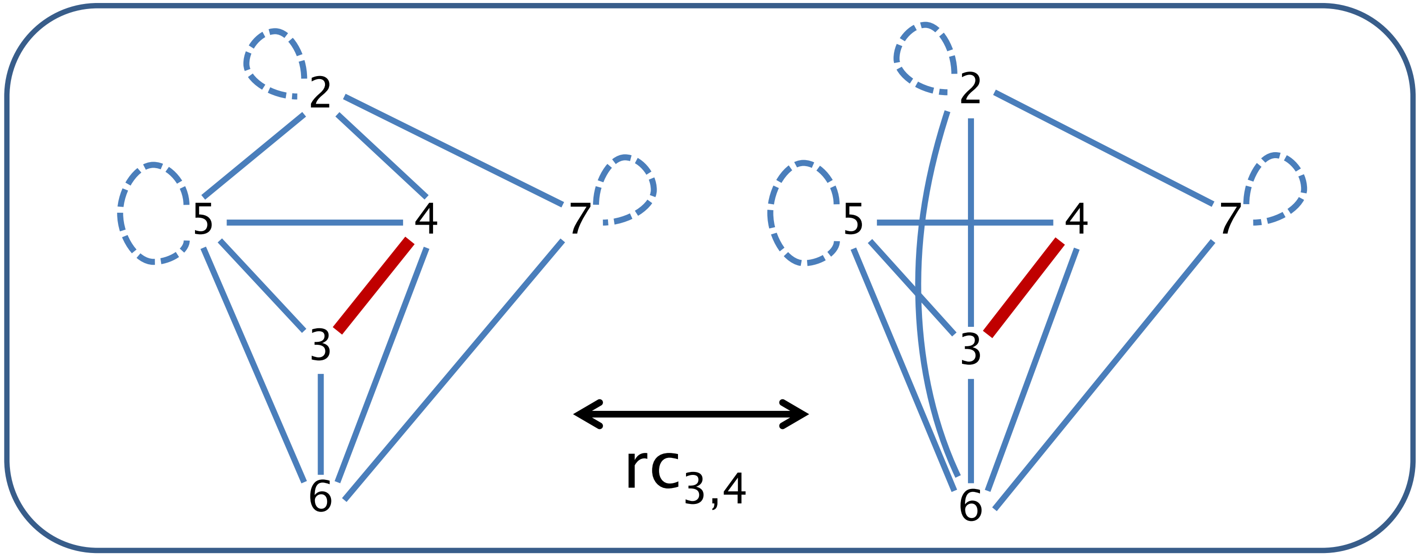
algebra of set systems

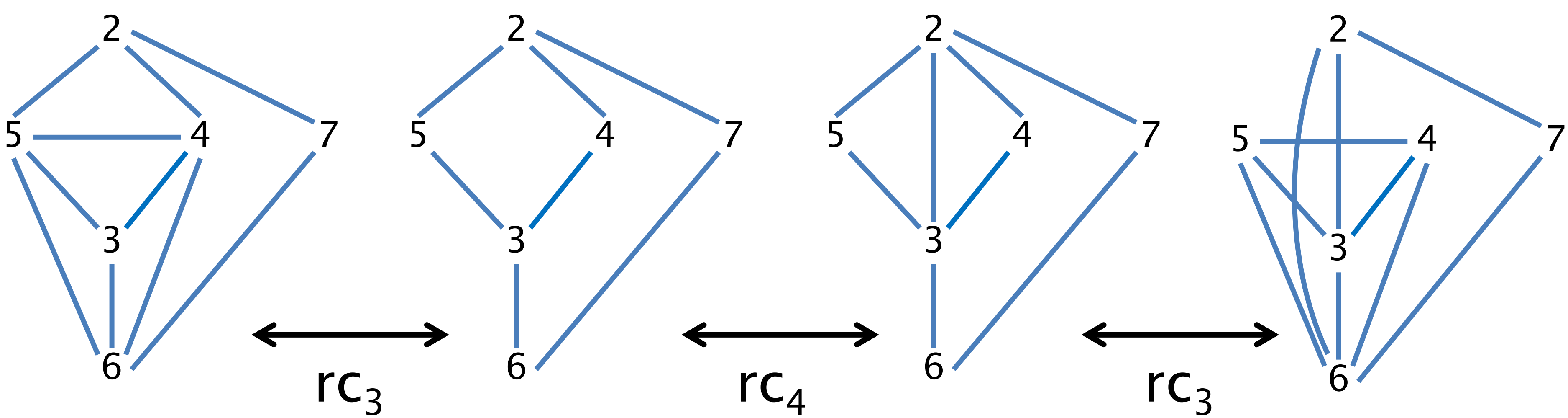
*p and +p
generate group S_3



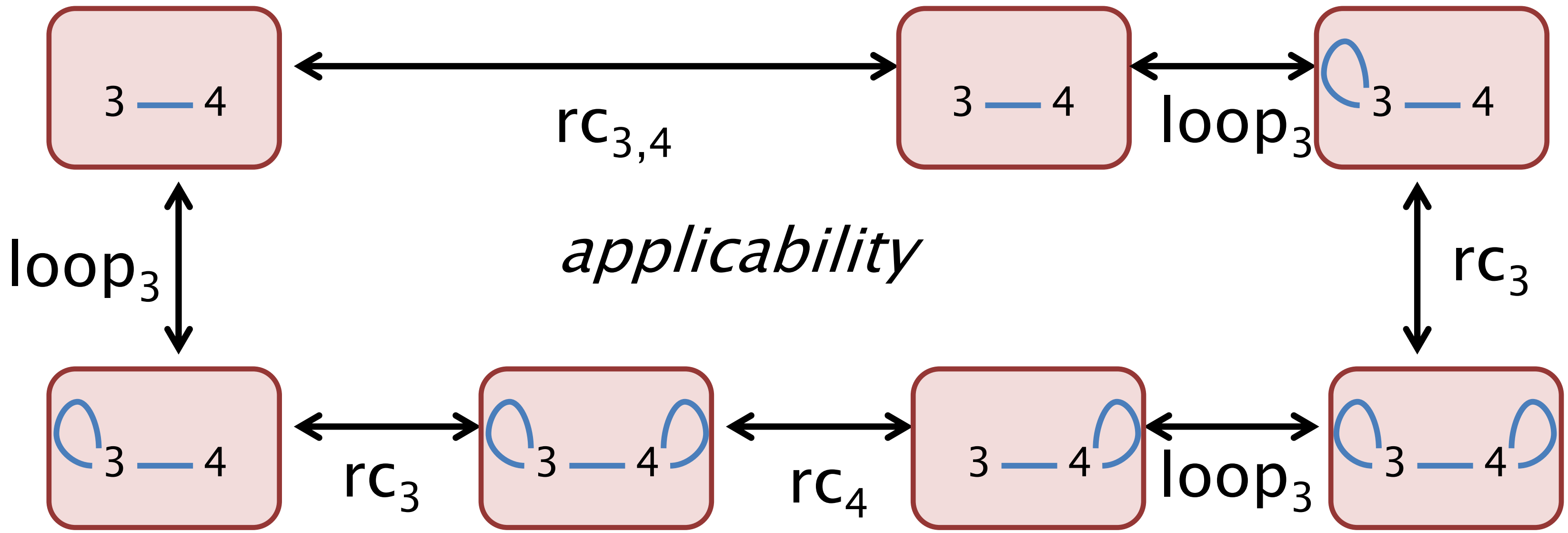
edge complement vs. local complement

ignoring loops





edge complement vs. local complement



basic algebra S_3

$*3 \; *4 = *4 \; *3$

$*3 \; *3 = \mathrm{id} = +3 \; +3$

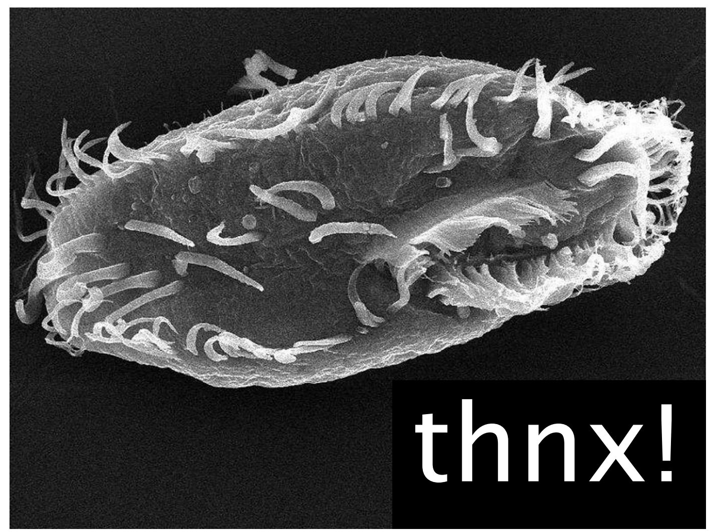
$+3 \; *3 \; +3 = *3 \; +3 \; *3$

$+3 \; *3 \; *4 \; +3 \; *3 \; +3 =$
$+3 \; *3 \; +3 \; *3 \; +3 \; *4 =$
$+3 \; *3 \; *3 {+} 3 \; *3 \; *4 =$
$+3 \; +3 \; *3 \; *4 =$
$*3 \; *4 =$
$*\{3,4\}$

- by careful modeling we find that gene assembly is *actually* principal pivot transform (ppt) and XOR
- we can use results about ppt (on matrices) and XOR (on set systems) to know more about gene assembly
- but also inspiration the other way around …

however …

- parallellism
- ‘simple’ operations



references (to self)

recombination is ppt

R. Brijder, T. Harju, H.J. Hoogeboom, Pivots, determinants, and perfect matchings of graphs (2008) [arXiv:0811.3500] finally to appear.

(independently) Nathan Pflueger: Graph reductions, binary rank, and pivots in gene assembly. DAM 159 (2011) 2117–2134.

*p +p algebra of operations

R. Brijder, H.J. Hoogeboom. The Group Structure of Pivot and Loop Complementation on Graphs and Set Systems. Eur.J.Comb. (2011).

general

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A. Ehrenfeucht, T. Harju, I. Petre, D. Prescott, G. Rozenberg, *Computation in Living Cells: Gene Assembly in Ciliates*, Natural Computing Series, Springer (2004).