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KNOWLEDGE IN ACTION

Relational Database Representation and Manipulation in DNA

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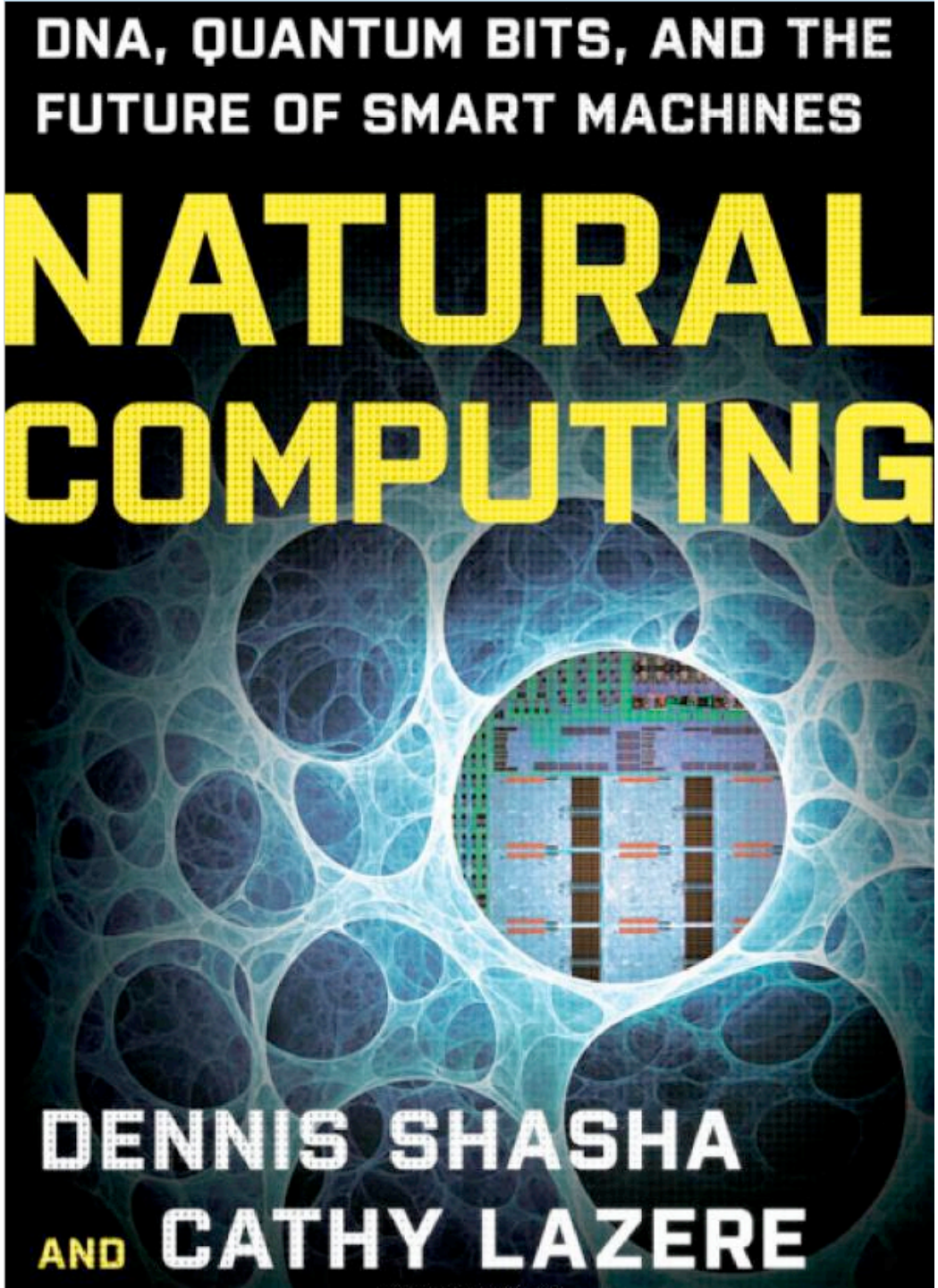
Natural Computing

1. Conventional computing, inspired by nature
   - Evolutionary systems, algorithms, programs
   - Parallel systems, swarm computing
2. Physics as a computation model
   - Analog computers
   - Quantum computing
3. "Wet" computing: use hardware from nature
   - ☞ DNA computing
   - Reprogrammed bacteria & viruses

DNA, QUANTUM BITS, AND THE FUTURE OF SMART MACHINES

NATURAL COMPUTING



DENNIS SHASHA
AND CATHY LAZERE

DNA Computing: What it is NOT

- Solving NP-complete problems
  - First DNA computing experiment solved a small instance of the Hamiltonian Path problem
  - [Adleman, Science 1994]
- Genetic engineering
  - DNA computing works with dead material
  - Synthetic DNA
- Bioinformatics
  - Conventional databases, algorithms to store, analyse genetic information

DNA Computing: What it IS

- Use synthetic DNA molecules as data carrier
- Programmed nanotechnology
- Computation on the DNA carried out by:
  - Biotechnology laboratory protocols
  - Enzymes
  - DNA itself: self-assembly
- Computation goes on in:
  - *In vitro:* Test tube (watery solution)
  - DNA chips, diamond surfaces
  - *In vivo* (smart medicine)

DNA Computing a vibrant field

- Two annual international meetings
  - International Conference on DNA Computing and Molecular Programming
  - Conference on Foundations of Nanoscience
- Diverse community
  - Experimental chemists, physicists
  - Theoretical computer scientists
  - Computer simulations
- Papers in Nature, Science
- Large gap between theory and practice

Use synthetic DNA molecules as data carrier

- In digital computers, all data is in strings of bits
  - 0 and 1
- Single-stranded DNA molecule:
  = string over the 4-letter alphabet {A,C,G,T}

Data storage in DNA

- Enormous capacity
  - Theoretical capacity ~ 455 EB per gram
  - ~ 2.2 PB per gram with reliable encode & decode
  - [Goldman et al., Nature 2013]
- Very robust
- Long term
  - 1000nds of years
  - Can be copied
- Archiving

Databases in DNA?

- We need much more than mere archival write/read
- Structured data
- Efficient and flexible access
- Logical data model
- Query language

☞ DNA computing

Talk Outline

1. Primer on databases
2. Representing tuples, relations in DNA
3. Doing relational algebra by DNA computing
4. DNAQL, the language
5. DNA complexes: the DNAQL data model
6. Typechecking
7. Expressive power of DNAQL

Relational database

- A collection of tables called relations
- Column headings are called attributes
- Rows are called tuples

Database schema

- Consists of:
  - Names of the relations
  - Attributes of each relation
- Example:
  - Likes(drinker,beer)
  - Visits(drinker,bar)
  - Serves(bar,beer)

Database instance

- Actual content (tuples) of the relations

Likes	
drinker	**beer**
John	Hoegaerden
John	Westmalle
Mary	Hoegaerden
Mary	Chouffe

Visits	
drinker	**bar**
John	Zur Laube
John	Albrecht
Mary	Albrecht

Serves	
bar	**beer**
Zur Laube	Duvel
Zur Laube	Westmalle
Zur Laube	Hoegaerden
Albrecht	Hoegaerden
Albrecht	Chouffe
Kugel	Westmalle

Relational algebra

- Operations applied to relations
- Compute new relations from given ones
- Answer queries to the database

  - selection (**σ**)
  - projection (**π**)
  - renaming (**ρ**)
  - union (∪)
  - set difference (**–**)
  - join (⋈)

Selection (σ)

- $\sigma_{drinker='John'}$: select tuples with specified value for given attribute

Likes	
drinker	**beer**
John	Hoegaerden
John	Westmalle
Mary	Hoegaerden
Mary	Chouffe

$\sigma_{drinker='John'}$ (Likes)	
drinker	**beer**
John	Hoegaerden
John	Westmalle

Projection (π)

- π_{beer} : select specified attribute(s)

$\sigma_{drinker='John'}$ (Likes)	
drinker	**beer**
John	Hoegaerden
John	Westmalle

$\pi_{beer}(\sigma_{drinker='John'}$ (Likes))
beer
Hoegaerden
Westmalle

Set difference (−)

- $R_1 - R_2$: all tuples from R_1 that are **not** in R_2
- "List all beers served by Albrecht that John does not like"

$\pi_{beer}(\sigma_{bar='Albrecht'}(Serves)) - \pi_{beer}(\sigma_{drinker='John'}(Likes))$

Join (⋈)

- Pairs up compatible tuples from two relations
- "List bars that serve a beer that John likes"

$$\sigma_{drinker='John'}(Likes) \bowtie Serves$$

$\sigma_{drinker='John'}$ (Likes)	
drinker	**beer**
John	Hoegaerden
John	Westmalle

⋈

Serves	
bar	**beer**
Zur Laube	Duvel
Zur Laube	Westmalle
Zur Laube	Hoegaerden
Albrecht	Hoegaerden
Albrecht	Chouffe
Kugel	Westmalle

➔

$\sigma_{drinker='John'}$ (Likes) ⋈ Serves		
drinker	**bar**	**beer**
John	Zur Laube	Hoegaerden
John	Albrecht	Hoegaerden
John	Kugel	Westmalle

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Use of DNA codewords

- 4-letter alphabet is a bit limiting
- Can use larger alphabet
  - Encode different letters by noninteracting DNA strands
  - library of DNA codewords

The alphabet we use

- Bits 0 and 1
  - Data entries in tuples: strings of ℓ bits
- Position markers: ϕ_1, …, ϕ_ℓ
- Attributes
- Tags: $\#_1$, $\#_2$, …, $\#_9$
  - Used for punctuation, marking, splitting

Tuples as DNA strands

- Tuple:

A	B
0101	1000

$$\#_2 A \#_3 \phi_1 0 \phi_2 1 \phi_3 0 \phi_4 1 \#_4 \#_2 B \#_3 \phi_1 1 \phi_2 0 \phi_3 0 \phi_4 0 \#_4$$

5’ → 3’

- Relation: set of DNA strings
- Content of a test tube

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Selection by affinity purification

- “Retrieve all tuples from test tube where some bit is 0”
- Perform affinity purification
- Probe: complementary codeword for 0

Abstract DNA operations

- Abstract protocol voor affinity purification:

1. Insert probe
2. Hybridize
3. Flush: wash away tuples that did not stick
4. Cleanup: recover remaining tuples

$\sigma_{\text{some bit is 0}}(R) =$

$\text{cleanup}(\text{flush}(\text{hybridize}(R \cup \text{immob}(0'))))$

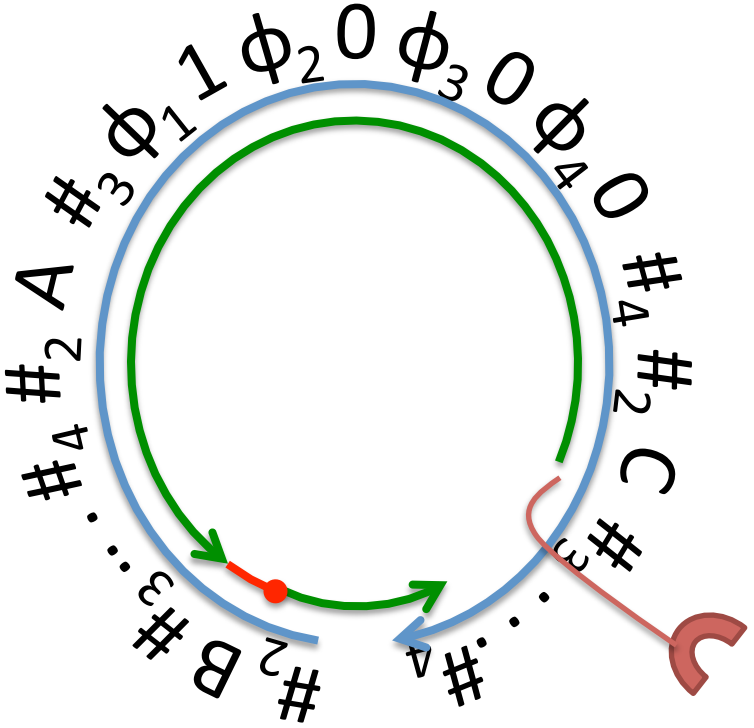
More selection

- So far we have done $\sigma_{\text{some bit is 0}}(R)$
- More interesting is $\sigma_{\text{drinker='John'}}(\text{Likes})$
- Let's do $\sigma_{\text{3rd bit of A=0}}(R)$
- Assume R has attributes B, A, C

$$\#_2\, B\, \#_3 \ldots \#_4\, \#_2\, A\, \#_3\, \phi_1\, 1\, \phi_2\, 0\, \phi_3\, 0\, \phi_4\, 0\, \#_4\, \#_2\, C\, \#_3 \ldots \#_4$$

Circularize

1. block B (use ddB’)
2. polymerase (primer C’)
3. immobilize (probe $\#_3$’)
4. use bridge $\#_2$’$\#_4$’
5. ligate



Circularize

1. block B (use ddB’)
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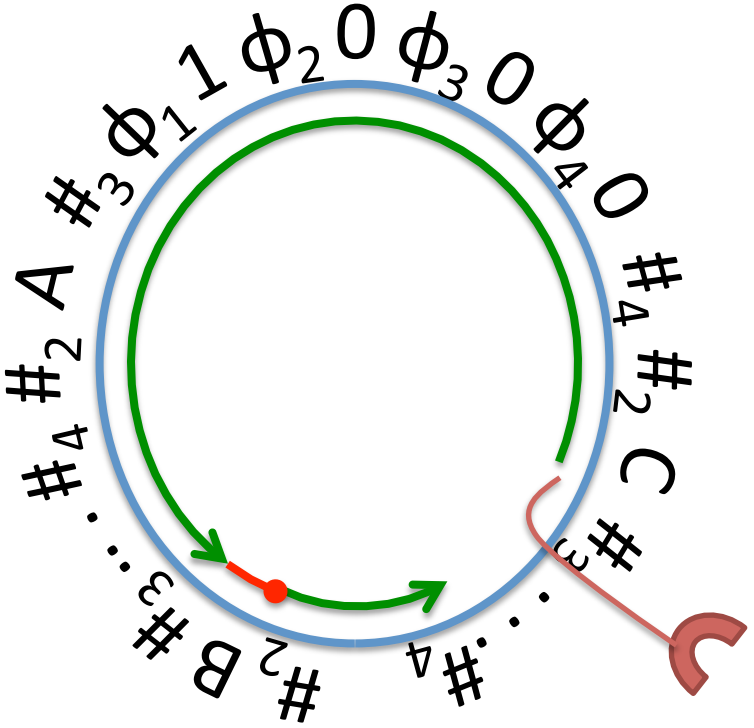
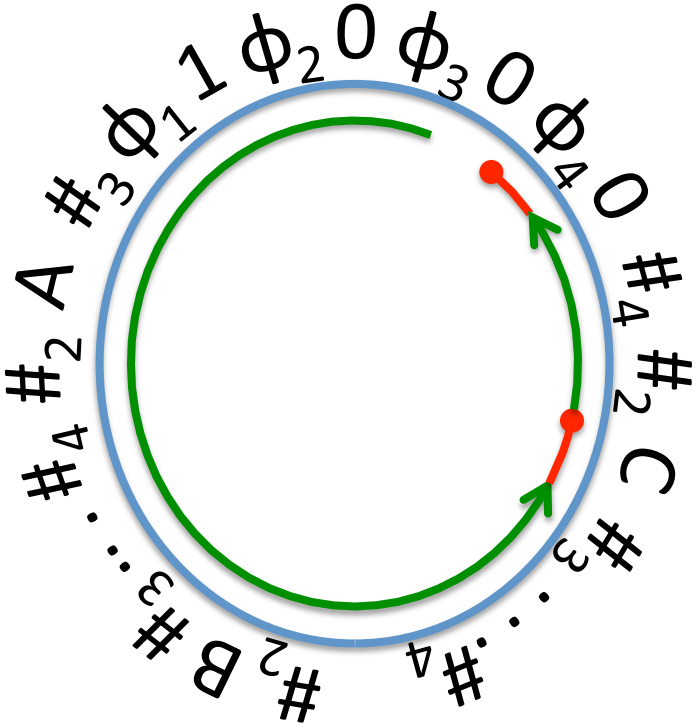


$\sigma_{\text{3rd bit of A=0}}(R)$

1. block C
2. polymerase (primer ϕ_3')
3. block ϕ_4
4. polymerase with $\#_2$'
5. probe for 0'



Join (⋈), Cartesian product (×)

- R × S combines each tuple from R with each tuple from S

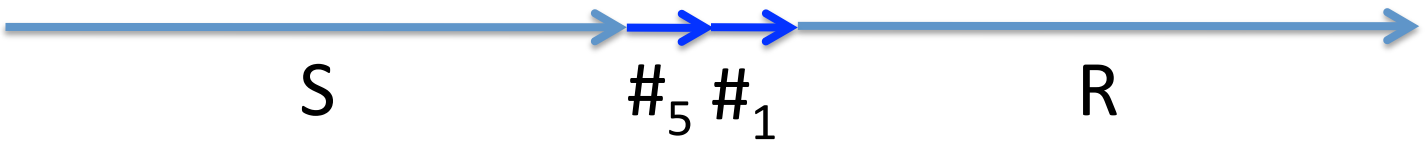
$$R \times S = \{ t_1 t_2 : t_1 \text{ in } R \text{ and } t_2 \text{ in } S \}$$

Algorithm for R × S

1. append $\#_5$ to every tuple of S (use bridge $\#_5$'$\#_4$' and ligate)
2. prepend $\#_1$ to every tuple of R (use bridge $\#_2$'$\#_1$' and ligate)

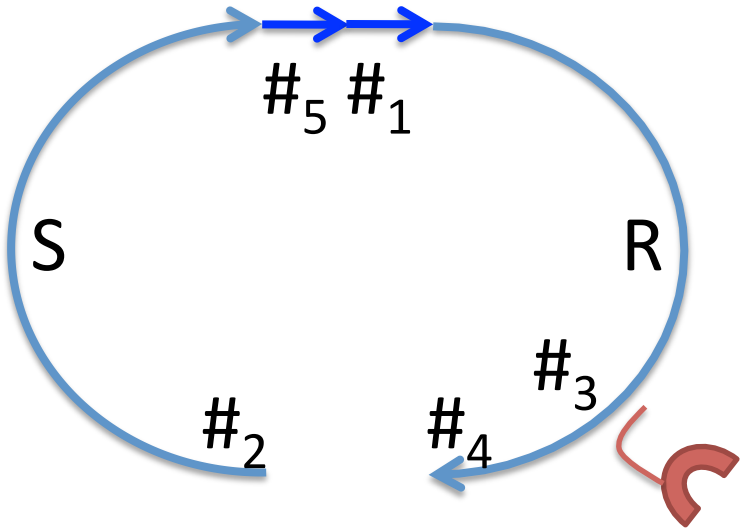
Algorithm for R × S

1. append $\#_5$ to every tuple of S
2. prepend $\#_1$ to every tuple of R
3. concatenate (use bridge $\#_1$'$\#_5$')



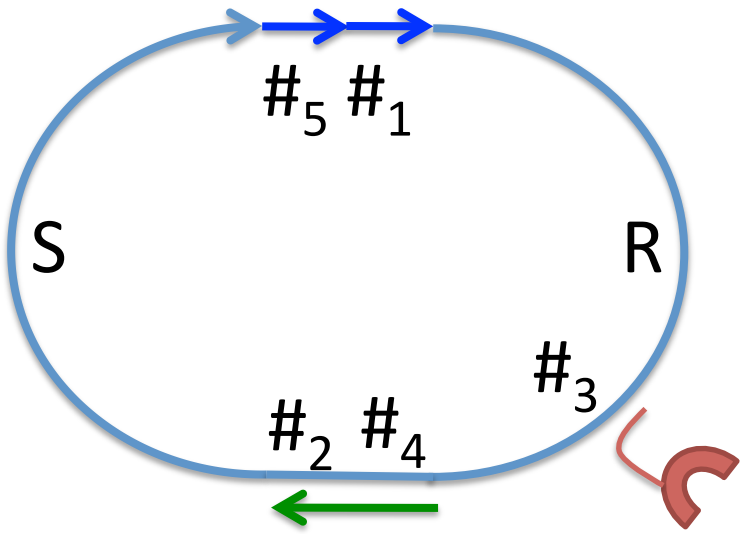
Algorithm for R × S

1. append $\#_5$ to every tuple of S
2. prepend $\#_1$ to every tuple of R
3. concatenate
4. immobilize



Algorithm for R × S

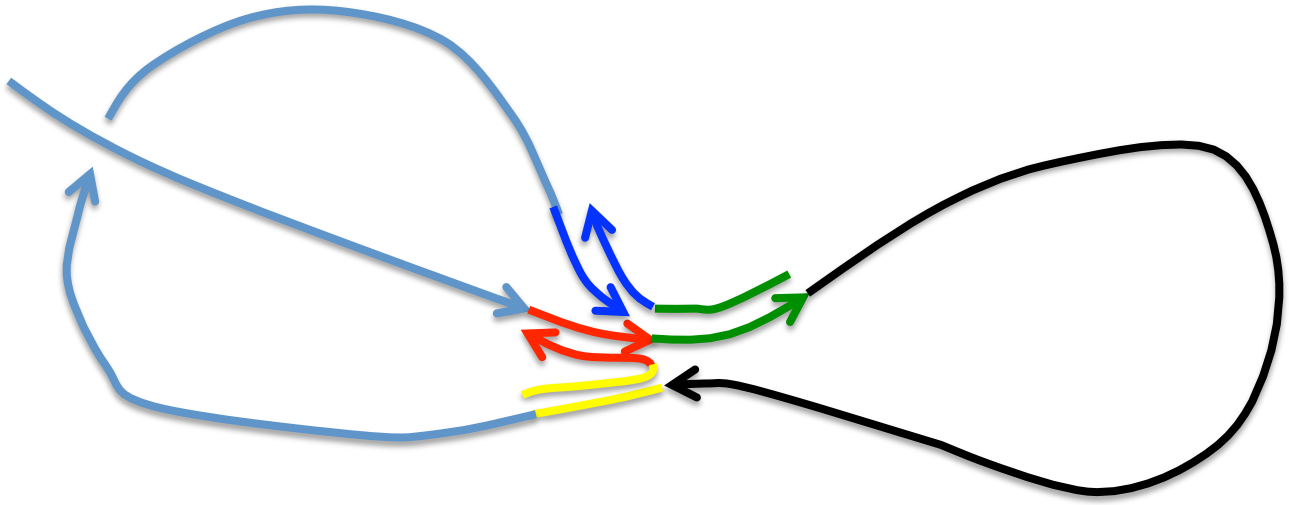
1. append $\#_5$ to every tuple of S
2. prepend $\#_1$ to every tuple of R
3. concatenate
4. immobilize
5. circularize
6. cleave at $\#_5$ and $\#_1$



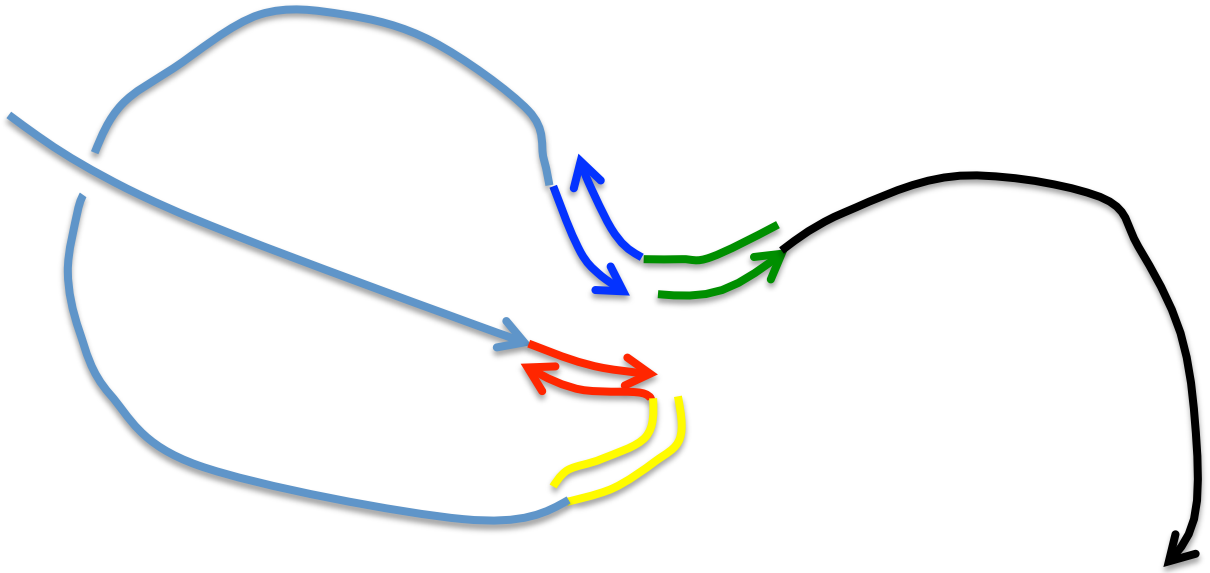
Other relational algebra operations

- Projection, renaming
  - similar methods
- Set difference R − S
  - subtractive hybridization
  - tuples in R and S have same length

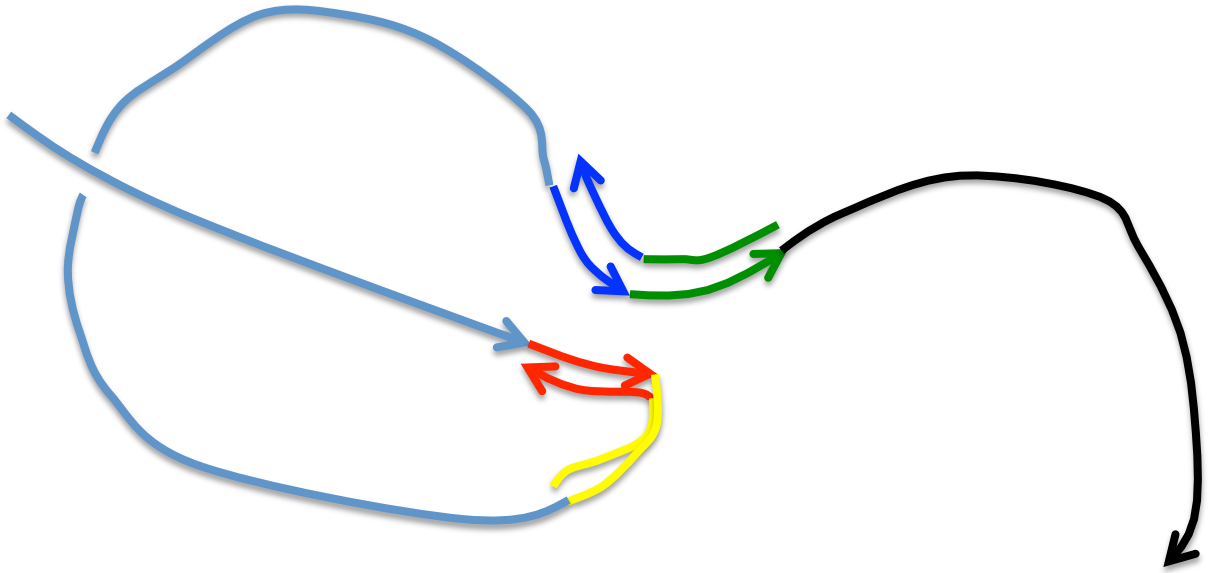
Shuffling attributes by double bridging



Shuffling attributes by double bridging



Shuffling attributes by double bridging



Abstract DNA operations

- Test-tube variables
- Probes
- Length-two bridges
- Union
- Difference
- For-loop
- Hybridize
- Ligate
- Flush
- Cleanup
- Cleave
- Block
- Polymerase, primer

For-loop

- DNAQL program for $\boldsymbol{\sigma}_{A=B}(R)$:

$$\texttt{for } s := r \texttt{ iter } i \texttt{ do}$$

$$\boldsymbol{\sigma}_{B=_i 0}\, \boldsymbol{\sigma}_{A=_i 0}(s) \cup \boldsymbol{\sigma}_{B=_i 1}\, \boldsymbol{\sigma}_{A=_i 1}(s)$$

DNA Query Language

$$
\begin{array}{rcl}
\langle expression \rangle & ::= & \langle complexvar \rangle \mid \langle foreach \rangle \mid \langle if \rangle \mid \langle let \rangle \mid \langle operator \rangle \mid \langle constant \rangle \\
\langle foreach \rangle & ::= & \texttt{for}\ \langle complexvar \rangle := \langle expression \rangle\ \texttt{iter}\ \langle counter \rangle\ \texttt{do}\ \langle expression \rangle \\
\langle if \rangle & ::= & \texttt{if empty}(\langle complexvar \rangle)\ \texttt{then}\ \langle expression \rangle\ \texttt{else}\ \langle expression \rangle \\
\langle let \rangle & ::= & \texttt{let}\ x := \langle expression \rangle\ \texttt{in}\ \langle expression \rangle \\
\langle operator \rangle & ::= & ((\langle expression \rangle) \cup (\langle expression \rangle)) \mid ((\langle expression \rangle) - (\langle expression \rangle)) \\
& \mid & \texttt{hybridize}(\langle expression \rangle) \mid \texttt{ligate}(\langle expression \rangle) \\
& \mid & \texttt{flush}(\langle expression \rangle) \mid \texttt{split}(\langle expression \rangle, \langle splitpoint \rangle) \\
& \mid & \texttt{block}(\langle expression \rangle, \Sigma - \Lambda) \mid \texttt{blockfrom}(\langle expression \rangle, \Sigma - \Lambda) \\
& \mid & \texttt{blockexcept}(\langle expression \rangle, \langle counter \rangle) \mid \texttt{cleanup}(\langle expression \rangle) \\
\langle constant \rangle & ::= & \Sigma^+ \mid \left(\overline{\Sigma} - \overline{\Lambda}\right)\left(\overline{\Sigma} - \overline{\Lambda}\right) \mid \texttt{immob}(\overline{\Sigma}) \mid \texttt{empty} \\
\langle splitpoint \rangle & ::= & \#_2 \mid \#_3 \mid \#_4 \mid \#_6 \mid \#_8
\end{array}
$$

Fig. 5. Syntax of DNAQL.

"the relational algebra for DNA"

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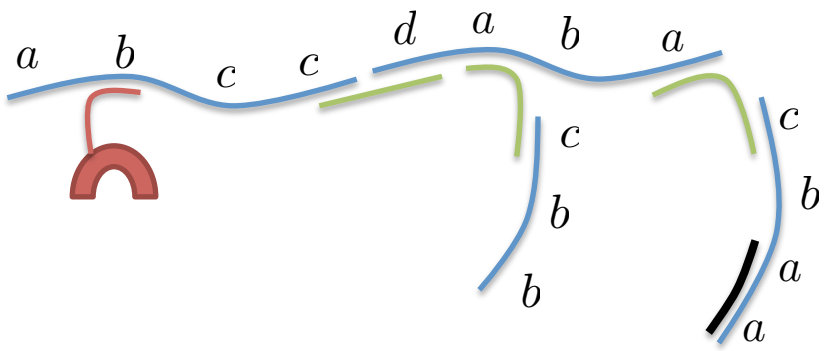
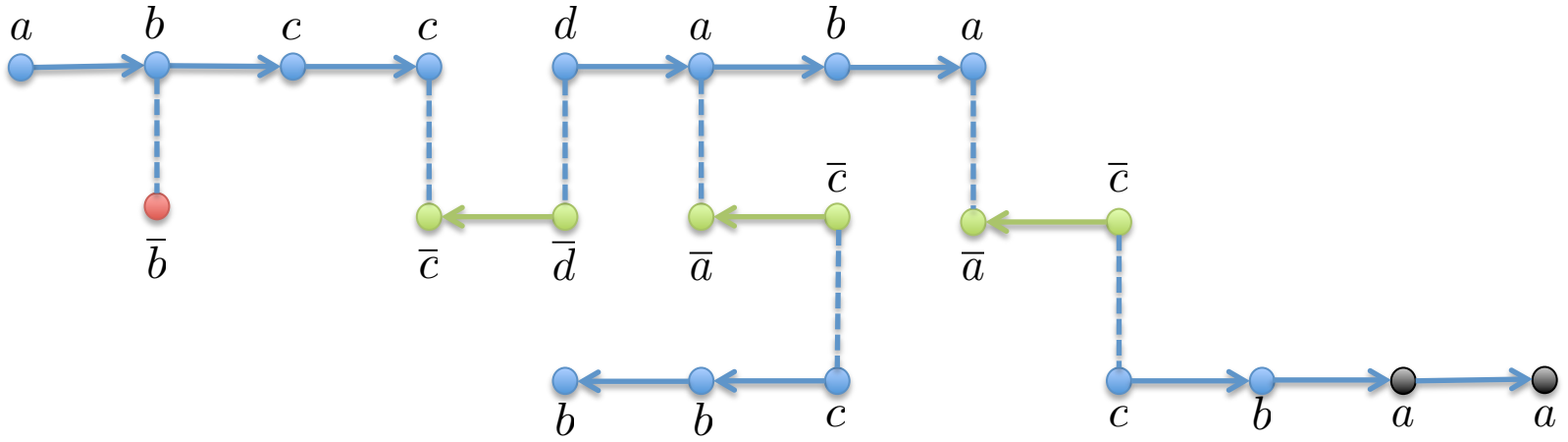
Complexes

- Relation in DNA: set of DNA strings
- During execution of DNAQL program, more complex structures are formed
- Complexes formalized as directed graph
- Data model for DNAQL

DNA complex as a graph structure





Types

- If complexes are the “instances” in our data model, what are the “schemes”?
- Approach:
  - All data values are carried by strings of value bits
  - All other nodes are for structuring

➔ Type of a complex:

  - Replace all value strings by wildcard ‘*’

Type of a relation

relation	type
$\#_2A\#_3\underline{0011}\#_4\#_2B\#_3\underline{1100}\#_4$	
$\#_2A\#_3\underline{0001}\#_4\#_2B\#_3\underline{1101}\#_4$	
$\#_2A\#_3\underline{1011}\#_4\#_2B\#_3\underline{1100}\#_4$	$\#_2A\#_3{*}\#_4\#_2B\#_3{*}\#_4$
$\#_2A\#_3\underline{0011}\#_4\#_2B\#_3\underline{1111}\#_4$	
$\#_2A\#_3\underline{0000}\#_4\#_2B\#_3\underline{1111}\#_4$	

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Well-definedness of DNAQL operations

- Implementability by biotechnological operations imposes some preconditions
- Always well-defined:
  - Union
  - Ligate
  - Split
  - Cleanup

Well-definedness conditions

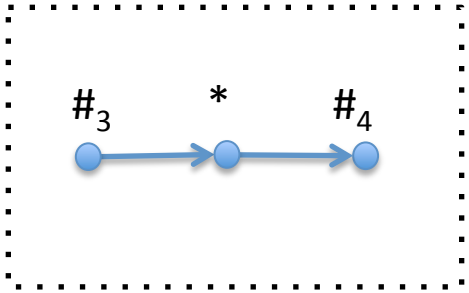
- Difference:
  - single strands only, all same length
- Blocking:
  - complex must be hybridized
- Hybridize:
  - termination (no chain reactions)
  - can be statically characterized in terms of absence of certain alternating cycles

Typechecking and inference

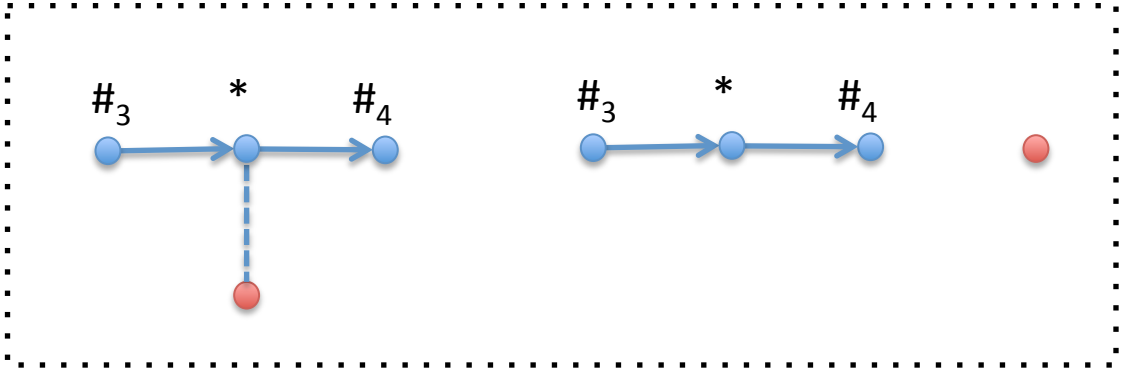
- Check well-definedness condition for operation statically, based on given input types
- Infer type for output, so that next operation can be typechecked

Type inference example

- e(x) = hybridize(x ∪ immob(ā))
- If x : S then e(x) : T



type S



type T

Typechecking Cleanup

- Input: any complex (always well-defined)
- Output: denature, remove all stickers, probes, keep only longest strands
- Gel electrophoresis

Typechecking Cleanup

- Consider type S = A*A*A ∪ AA*AA
- "Dimension" of a complex:
  - Number of value bits used for data values
  - Like word length in a digital computer
- Suppose dimension = d
  - Strands of type A*A*A have length 2d+3
  - Strands of type AA*AA length 4+d
  - 4+d < 2d+3 for all d

➔ If x : S then Cleanup(x) : A*A*A

Type inference algorithm

- Given input types for program:
  - Decides if “well-typed”
  - If so, computes result type
- Soundness: Well-typed programs always succeed on inputs of given type
  - Output guaranteed to be of computed result type
- Maximality: Converse to soundness
  - Only for individual operations
- Tightness

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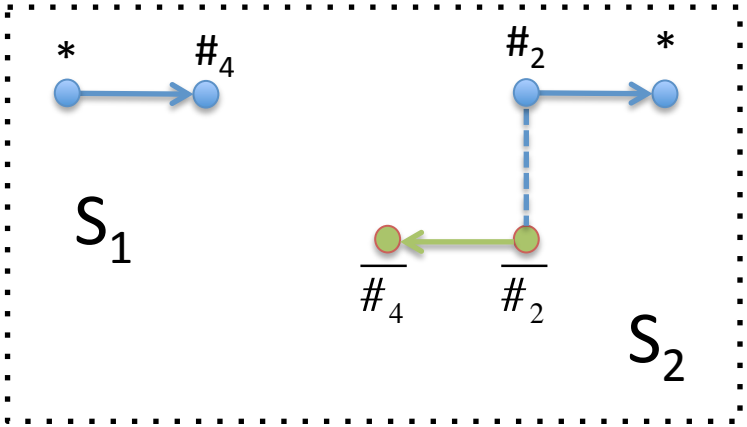
Expressive power

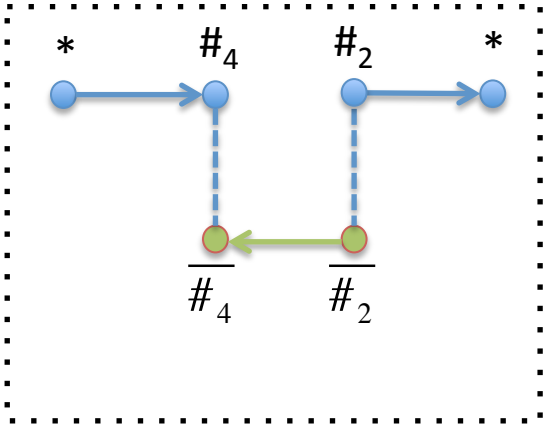
- We have seen that every relational algebra computation can be expressed by a DNAQL program
- Converse Theorem: DNA complexes can be simulated by relational databases, and DNAQL programs by relational algebra computations.

DNAQL to relational algebra

Type S



Type T



- If x : S then Hybridize(x) : T
- Store values in components of type S_1 in a relation R_1, similar for S_2
- Then pairs of values in components of Hybridize(x) can be computed R_1 x R_2
- Hybridization = Cartesian product!

Summary

- DNA computing develops algorithms for data represented in DNA
- Novel application area for biotechnology
- We have tried to find the equivalent of relational data model, relational algebra in the world of DNA computing
- Resulting DNAQL data model can stand on itself

Outlook

- Experiments?
- Simulation?
- Reliability?
- Self-assembly models of DNA computing
  - strand displacement

- References:
  - alpha.uhasselt.be/jan.vandenbussche