Algebras and Languages for Molecular Programming

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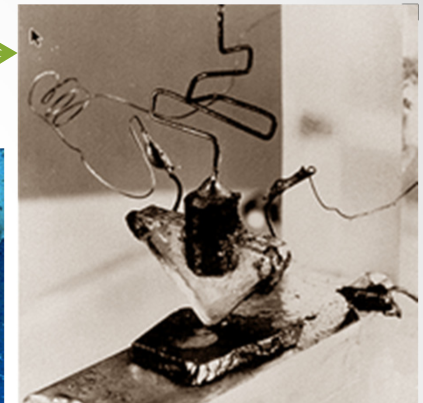
MSRC Summer School, 2010-06-30

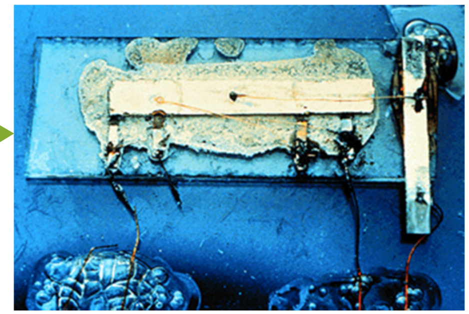
http://lucacardelli.name

Smaller and Smaller

Dec. 23, 1947. John Bardeen and Walter Brattain show the first working transistor.

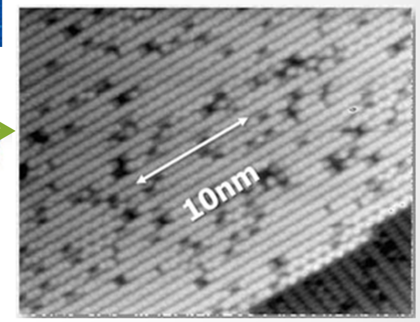


Sep. 1958. Jack Kilby builds the first integrated circuit.



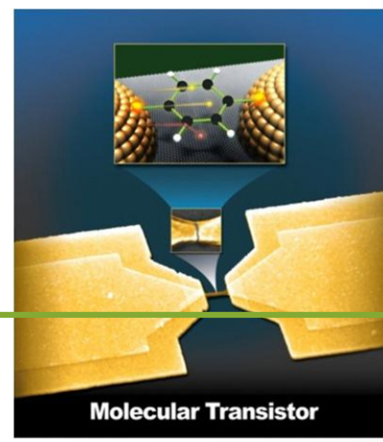
50 years later

Jan. 2010. Intel and Micron announce 25nm NAND flash.



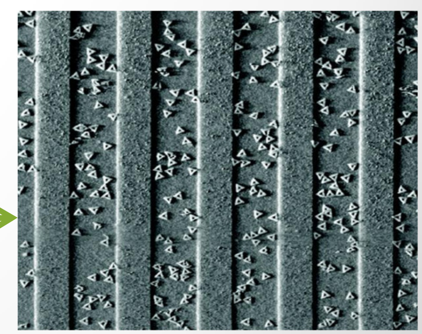
Scanning tunneling microscope image of a silicon surface showing 10nm is ~20 atoms across

Dec. 24, 2009. Working transistor made of a single molecule.



Observation of molecular orbital gating. *Nature*, 2009; 462 (7276): 1039

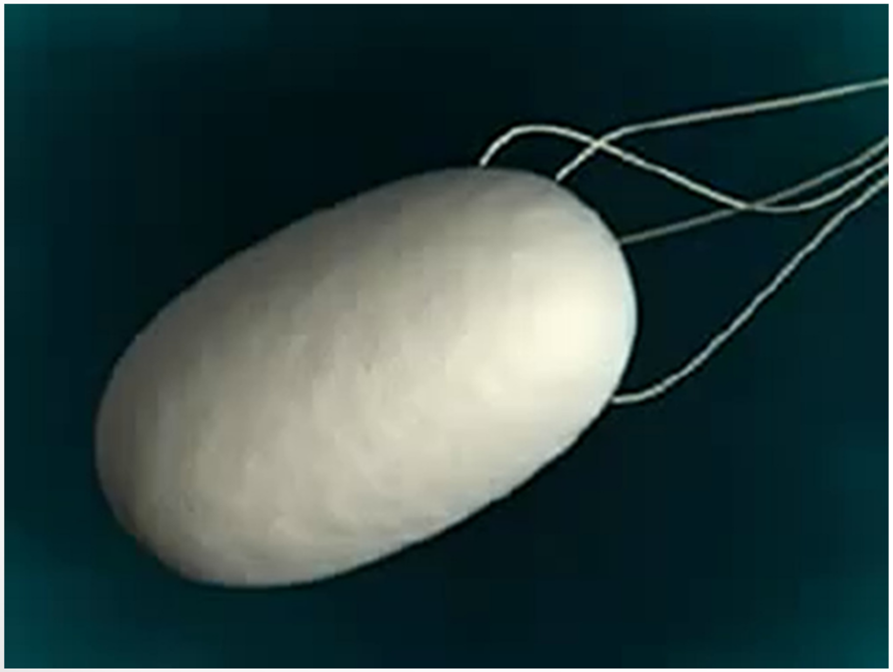
<10 iterations of Moore's Law left!
The race is on for *molecular scale integrated circuits*.



Placement and orientation of individual DNA shapes on lithographically patterned surfaces. Nature Nanotechnology 4, 557 – 561 (2009).

Building The Small*est* Things

- How do we build structures that are by definition smaller than your tools?
- Basic answer: you can't. Structures (and tools) should build themselves!
- By *programmed self-assembly*.



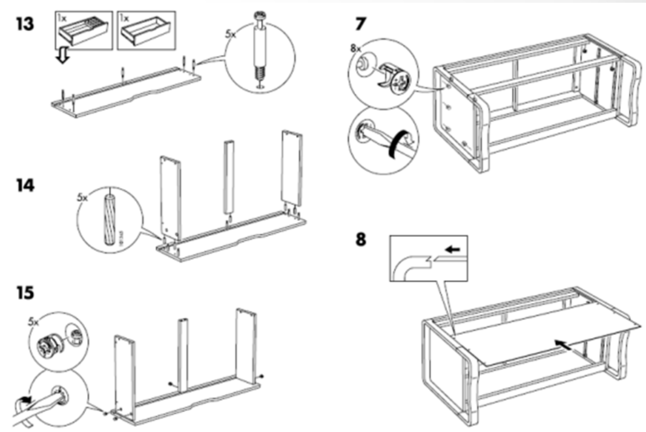
Molecular IKEA

- Nature can self-assemble.
  Can we?

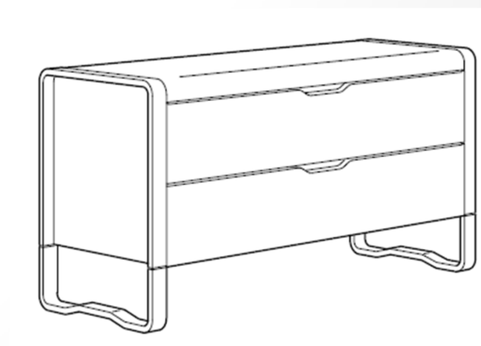
- *"Dear IKEA, please send me a chest of drawers that assembles itself."*

- We need a magical material where the pieces are pre-programmed to fit into to each other.

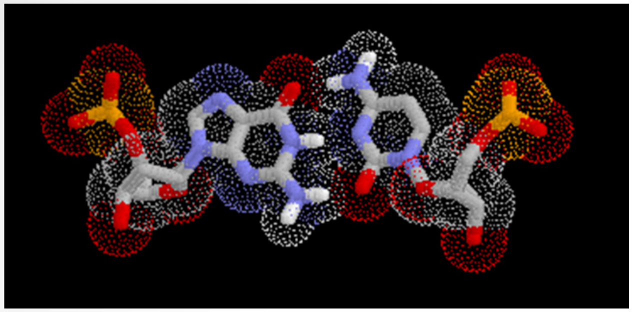
- At the molecular scale many such materials exist; let's pick one…



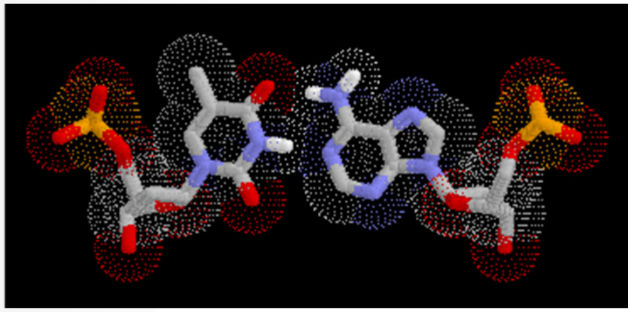
Add water



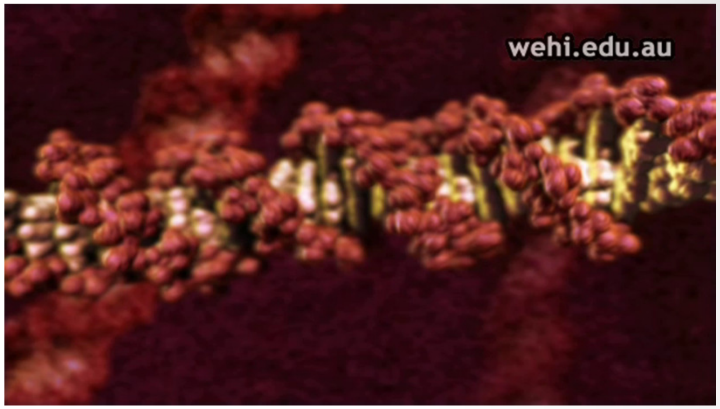
DNA



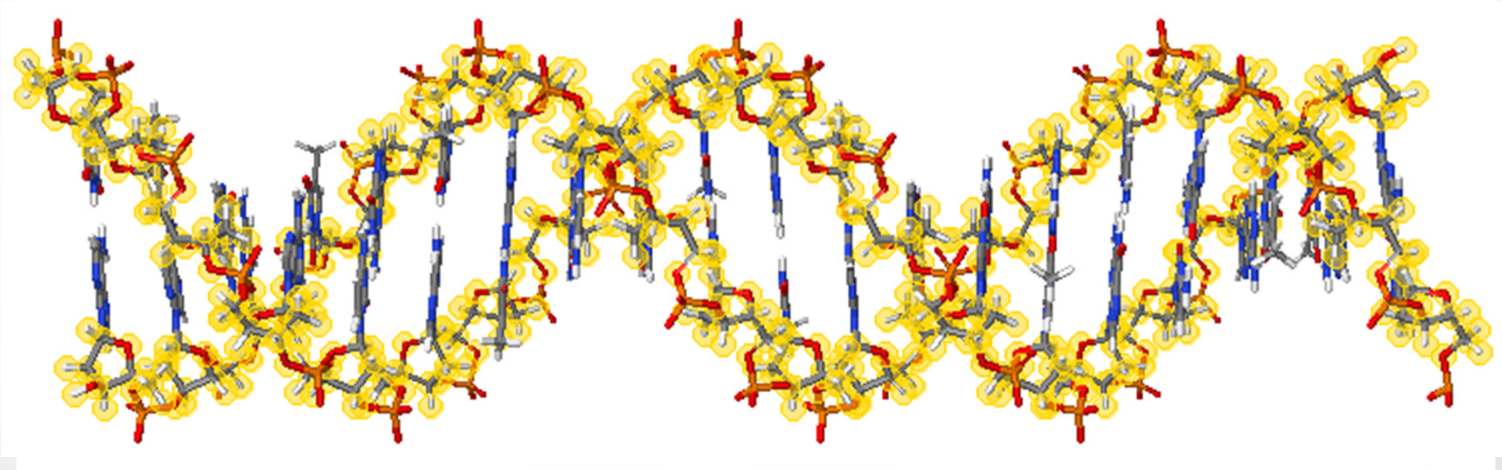
GC Base Pair
Guanine-Cytosine



TA Base Pair
Thymine-Adenine



[Interactive DNA Tutorial](http://www.biosciences.bham.ac.uk/labs/minchin/tutorials/dna.html)
(http://www.biosciences.bham.ac.uk/labs/minchin/tutorials/dna.html)



Sequence of Base Pairs (GACT alphabet)

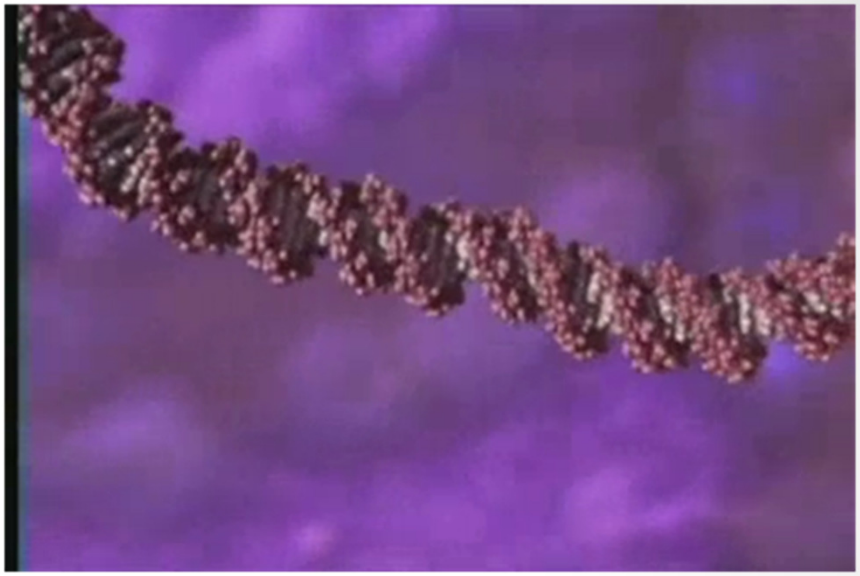
Robust, and *Long*

- DNA in each human cell:
  - 3 billion base pairs
  - 2 meters long, 2nm thick
  - folded into a 6μm ball
  - 750 MegaBytes

- A huge amount for a cell
  - Every time a cell replicates it has to copy *2 meters of DNA* reliably.
  - To get a feeling for the scale disparity, compute:

- DNA in human body
  - 10 trillion cells
  - 133 Astronomical Units long
  - 7.5 OctaBytes

- DNA in human population
  - 20 million light years long

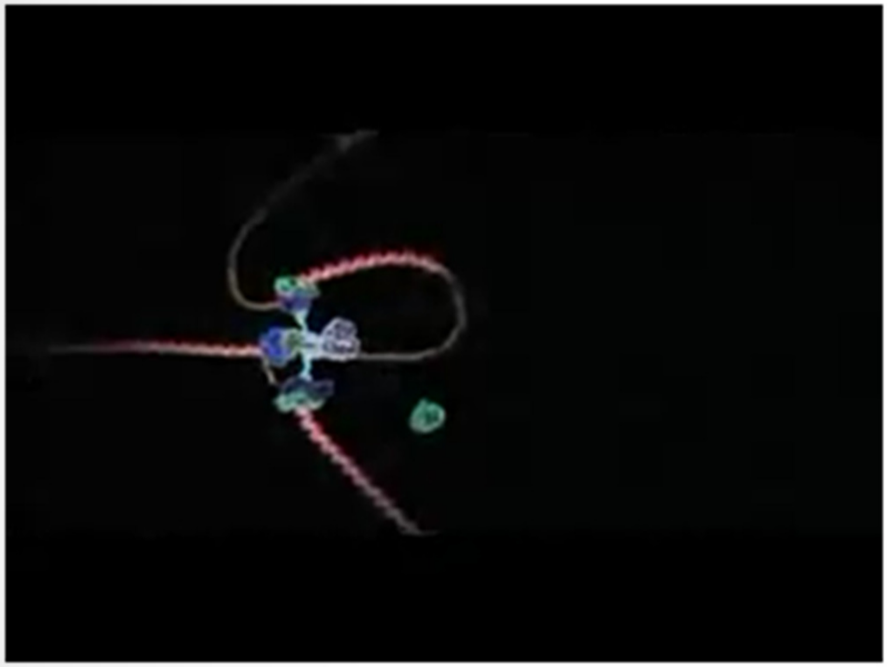


DNA wrapping into chromosomes

Andromeda Galaxy
2.5 million light years

Zipping Along

- DNA can support structural and computational complexity.



DNA replication in *real time*

In Humans: 50 nucleotides/second
Whole genome in a few hours (with parallel processing)

In Bacteria: 1000 nucleotides/second
(higher error rate)

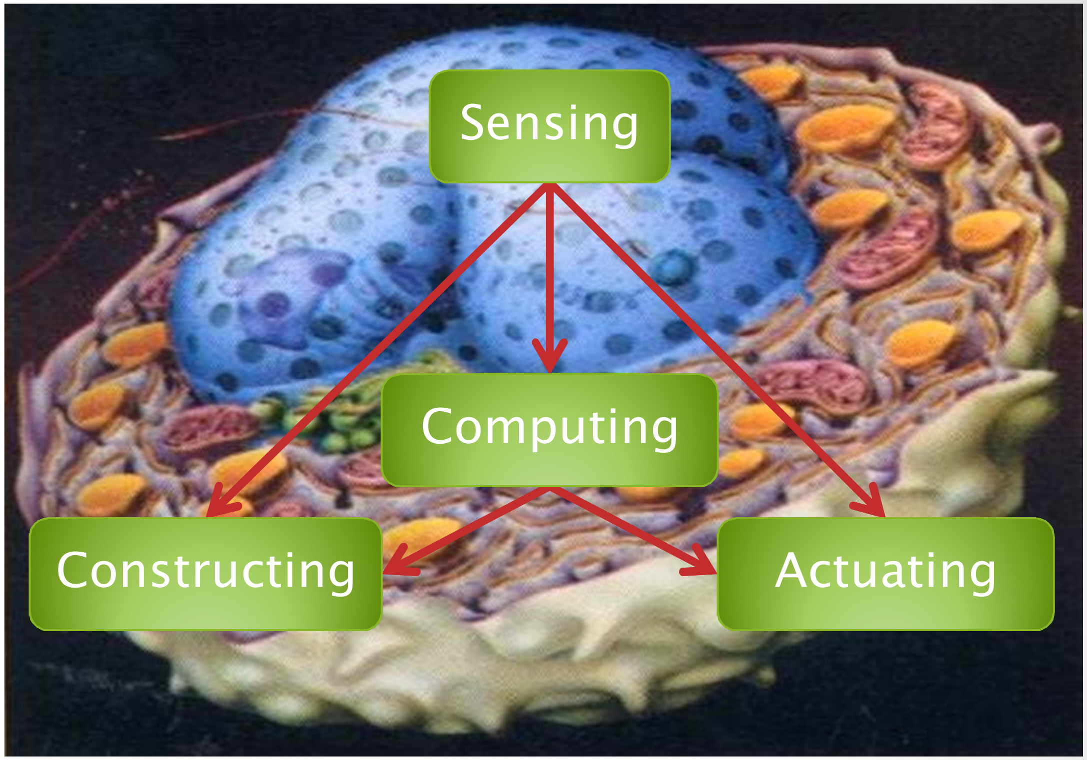
DNA transcription in *real time*

RNA polymerase II: 15-30 base/second

Drew Berry
http://www.wehi.edu.au/wehi-tv

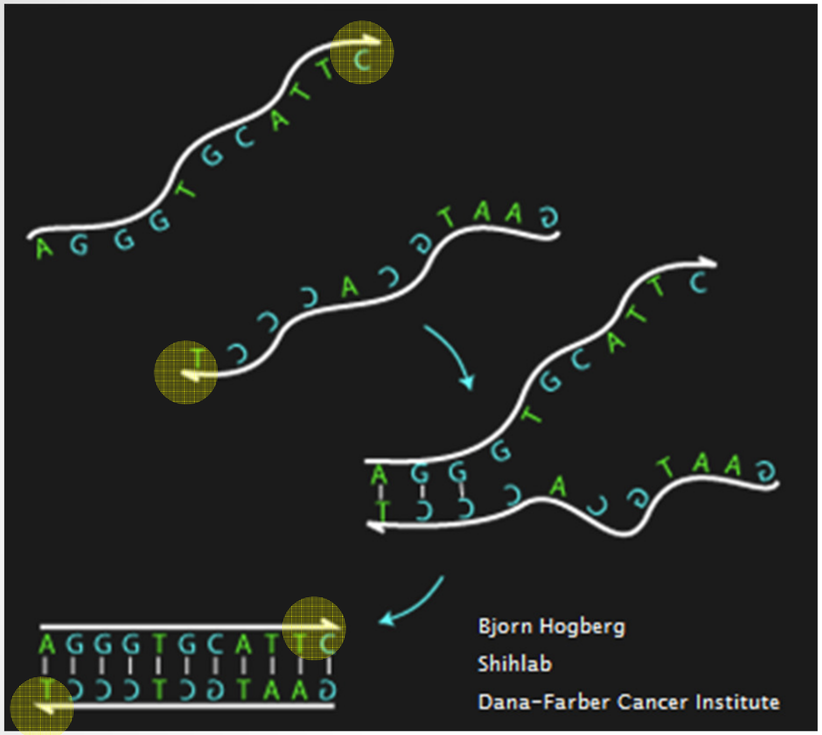
Nanoscale Engineering

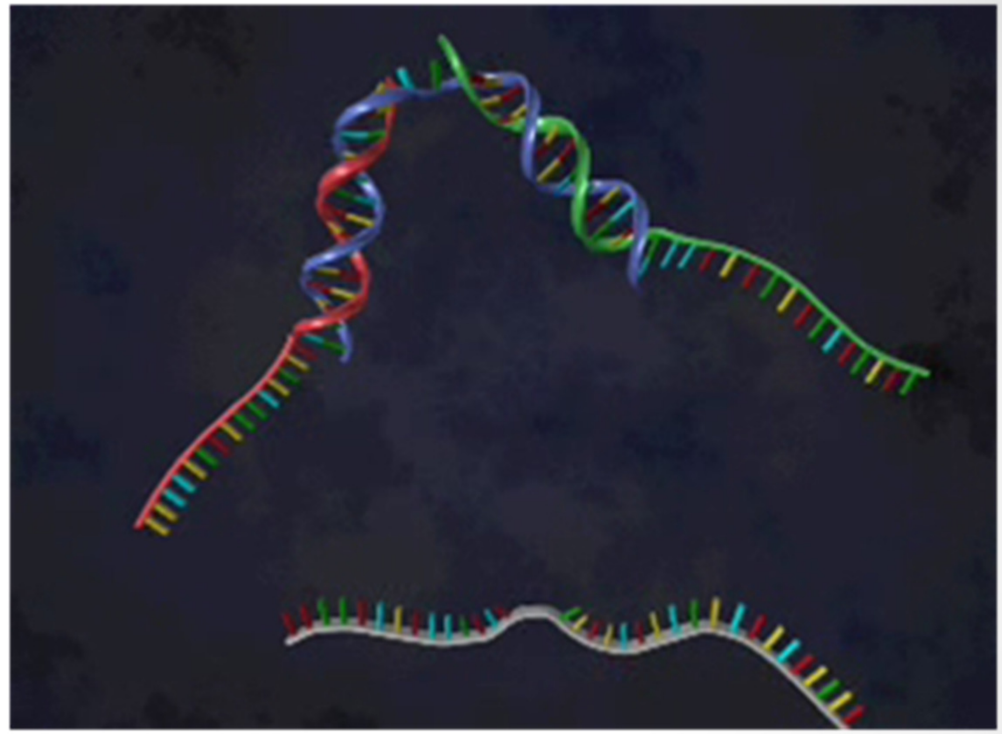
- Sensing
  - Reacting to forces
  - Binding to molecules
- Actuating
  - Releasing molecules
  - Producing forces
- Constructing
  - Chassis
  - Growth
- Computing
  - Signal Processing
  - Decision Making



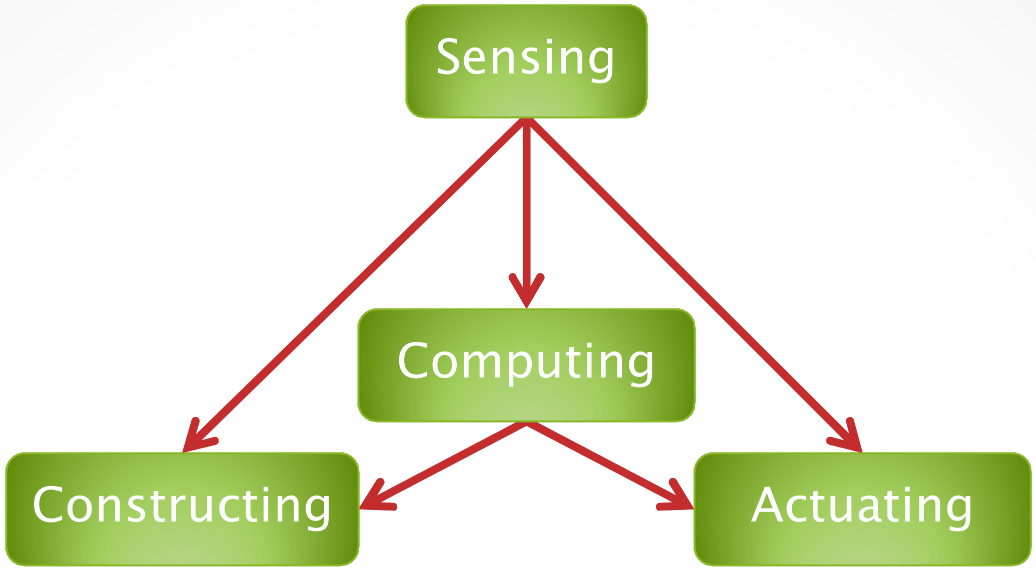
Nucleic Acids can do all this.
And interface to biology.

Hybridization

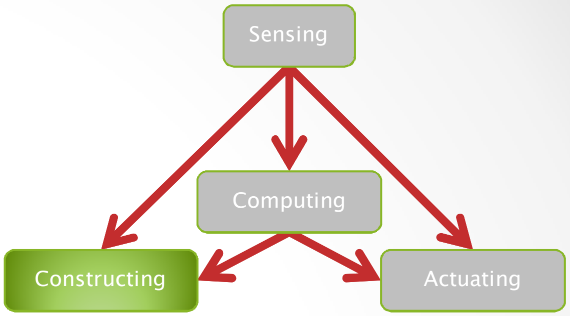




- Strands with **opposite orientation** and **complementary base pairs** stick to each other (Watson-Crick duality).
- This is all we are going to use
  - We are not going to exploit DNA replication, transcription, translation, **restriction and ligation enzymes**, etc., which enable other classes of tricks.



Hybridization Tricks



Constructing

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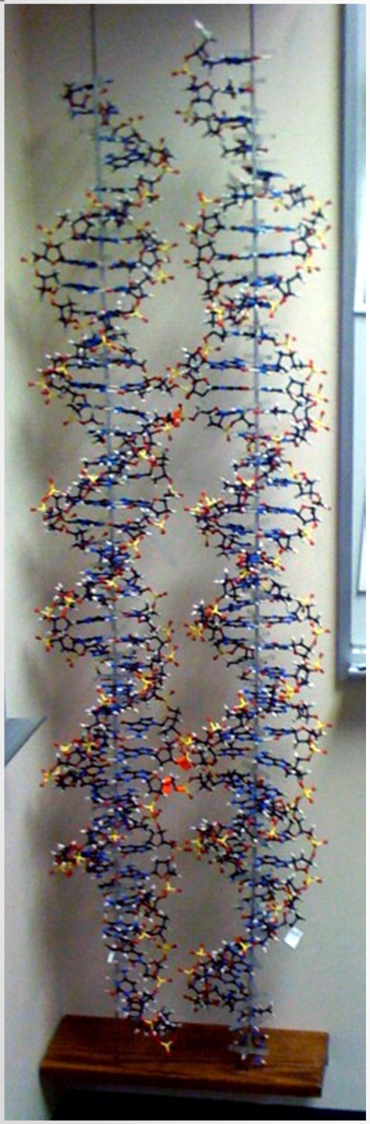
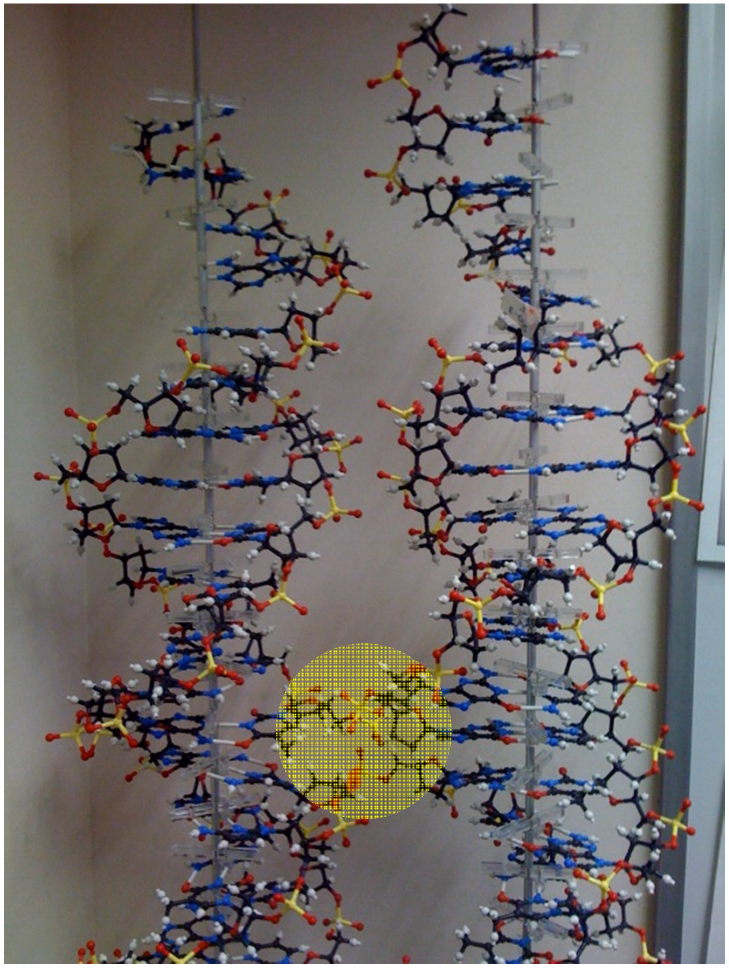
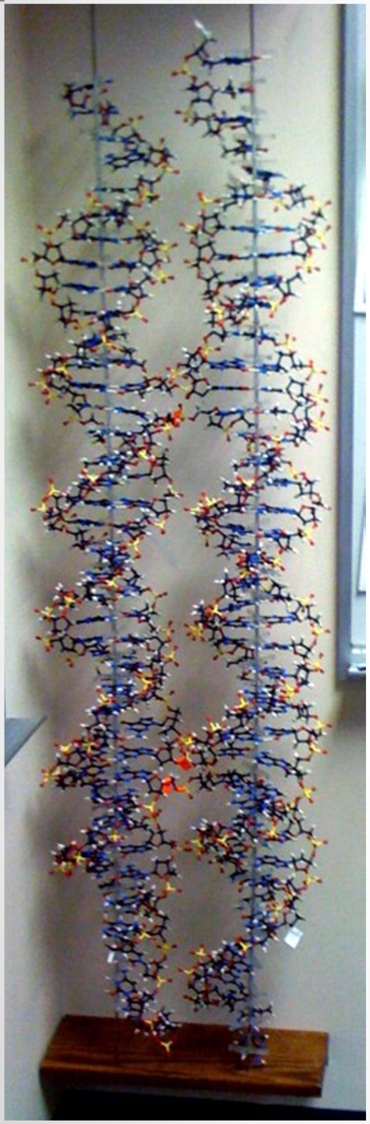
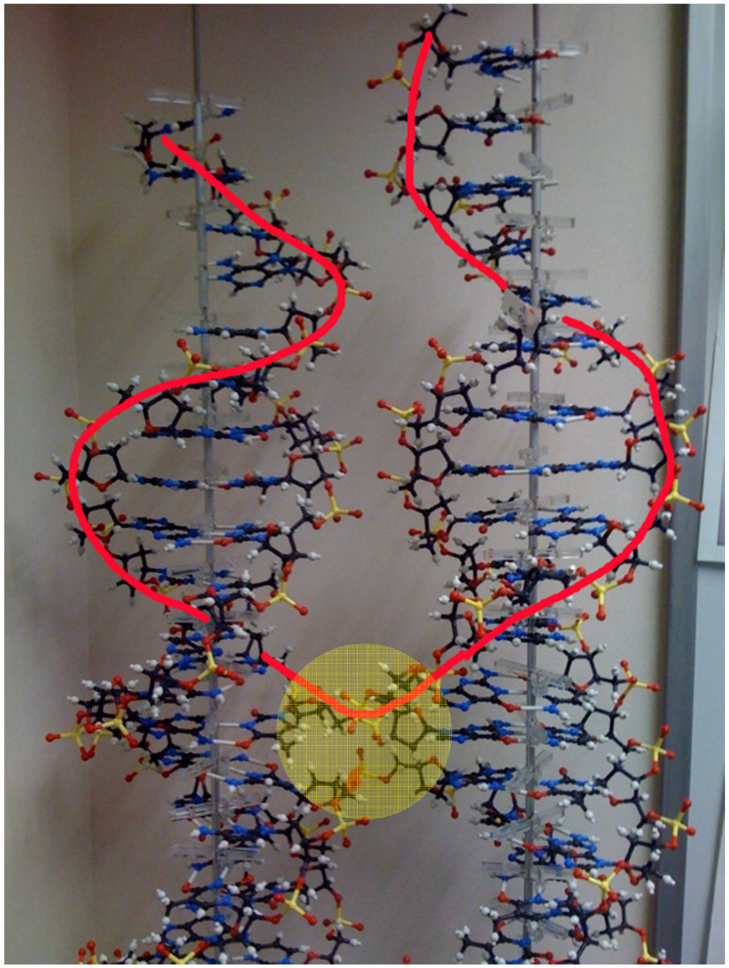
Crosslinking



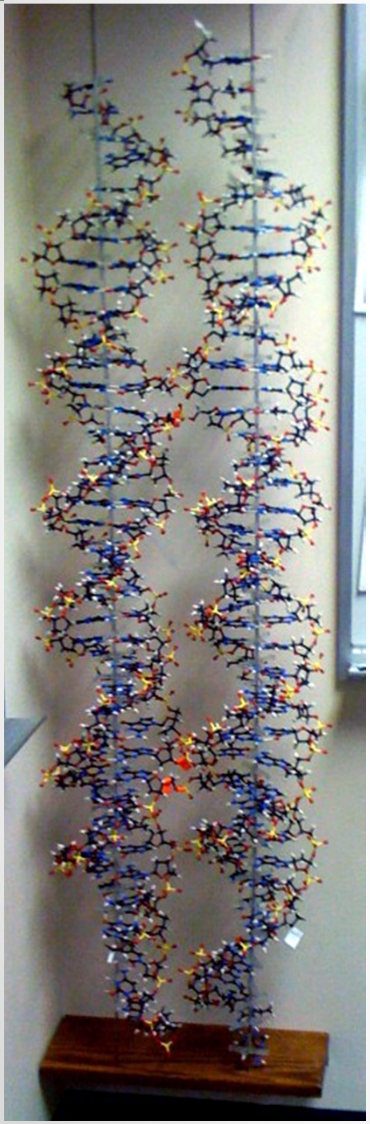


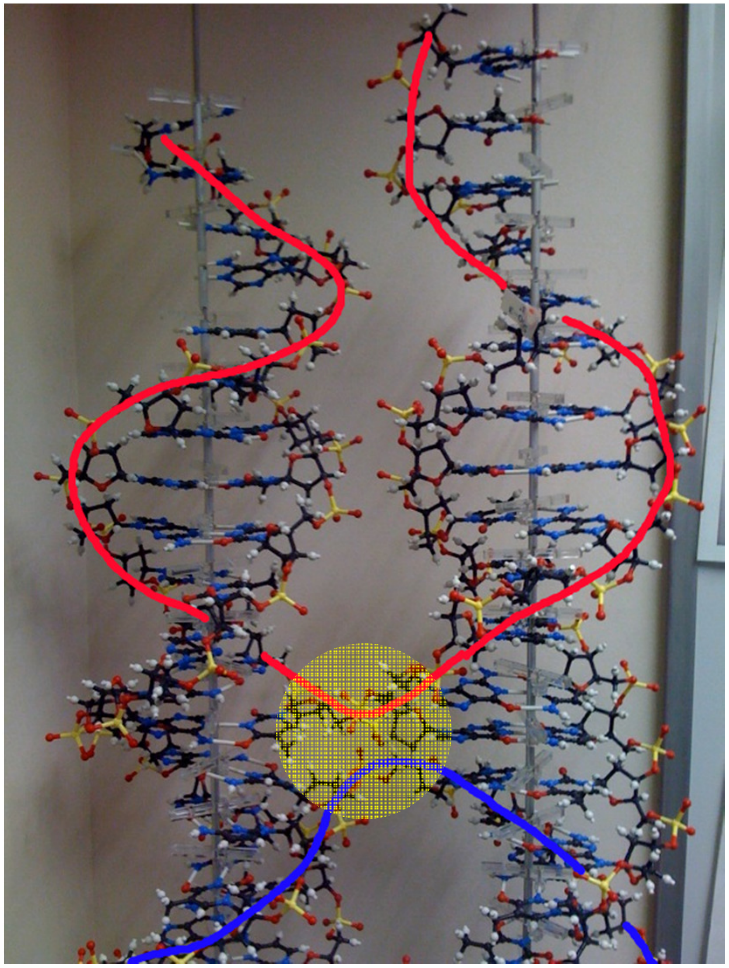
Crosslinking



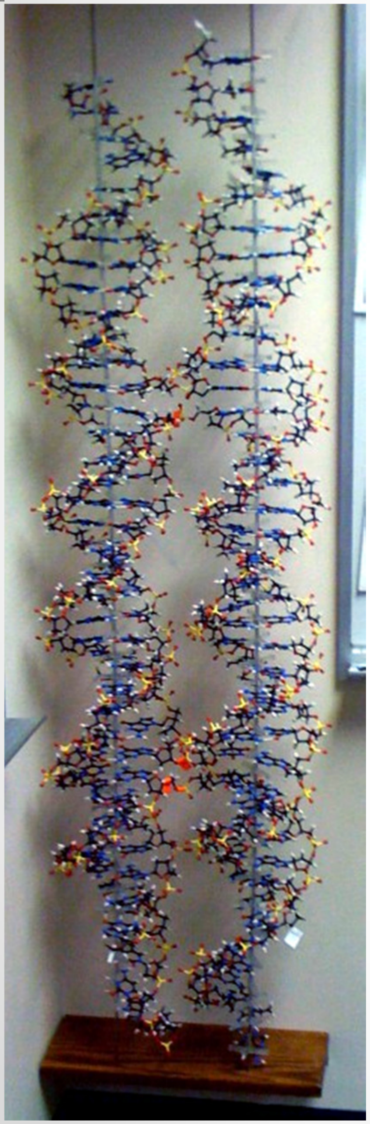


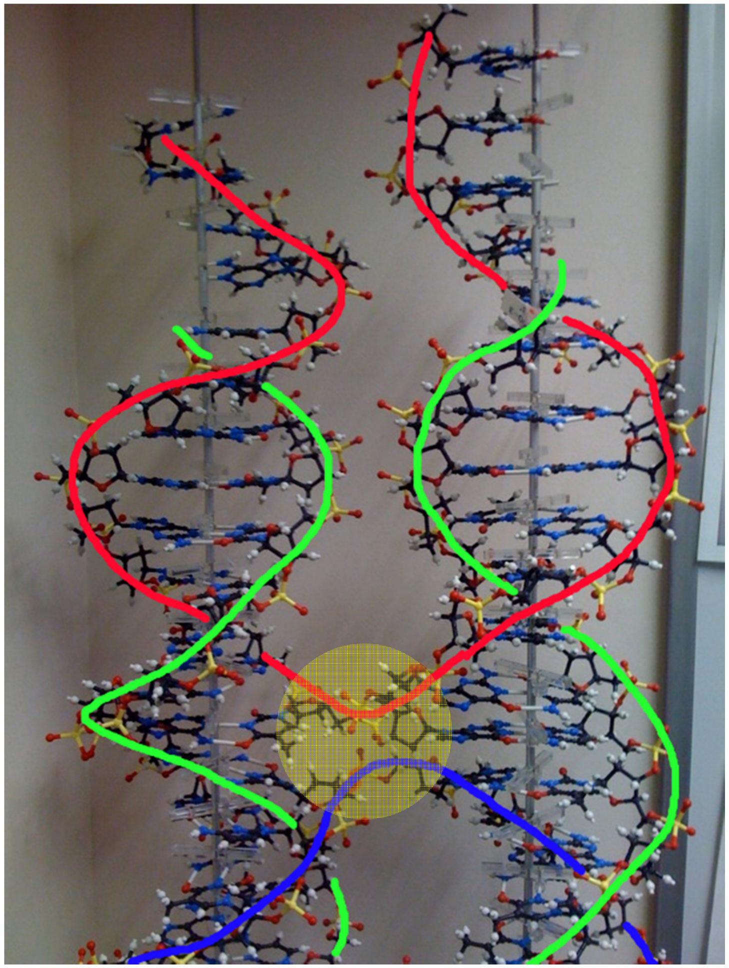
Crosslinking



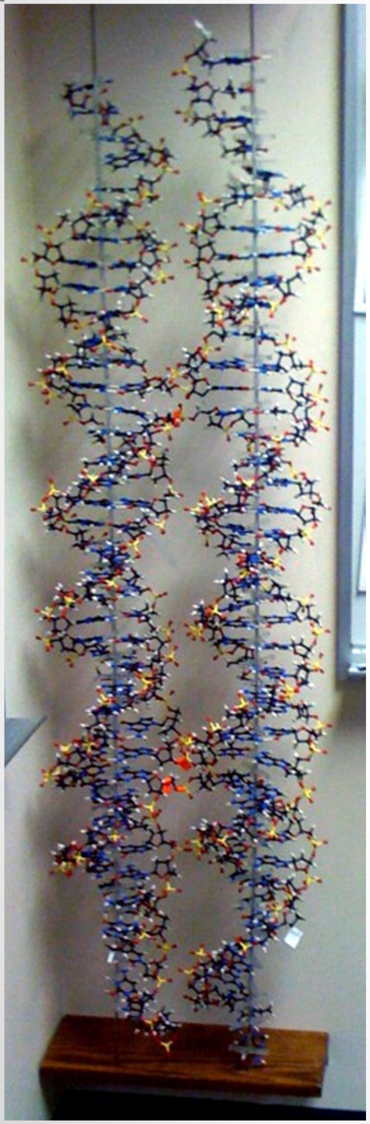


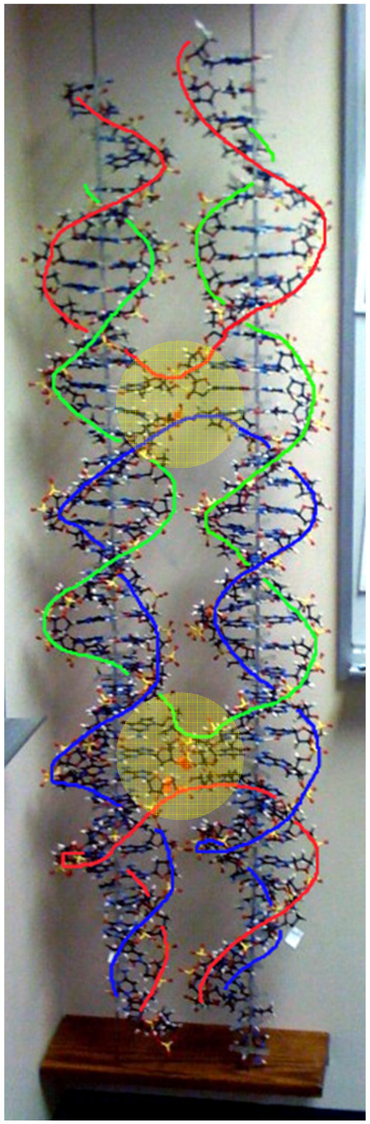
Crosslinking



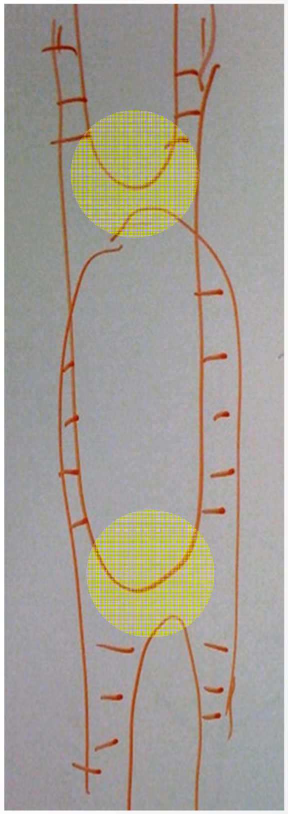


Crosslinking



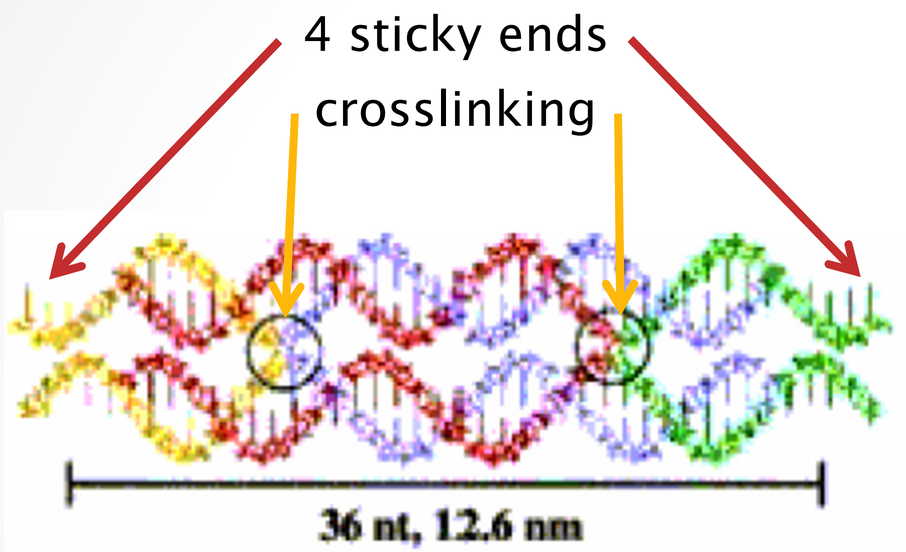


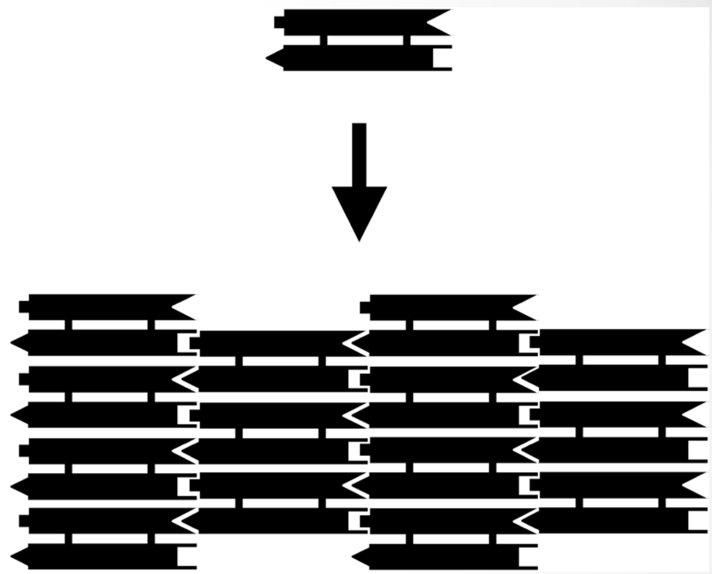
In nature, crosslinking is deadly (blocks DNA replication).

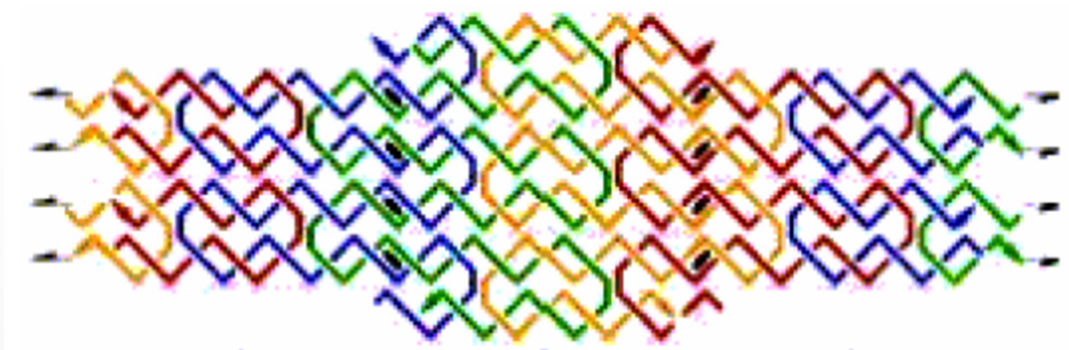


In engineering, crosslinking is the key to using DNA as a construction material.

DNA Tiling



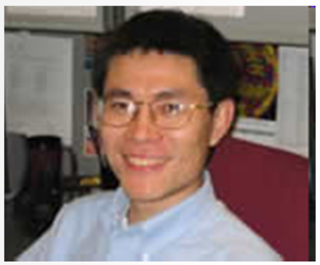




Construction and manipulation of DNA tiles in free space

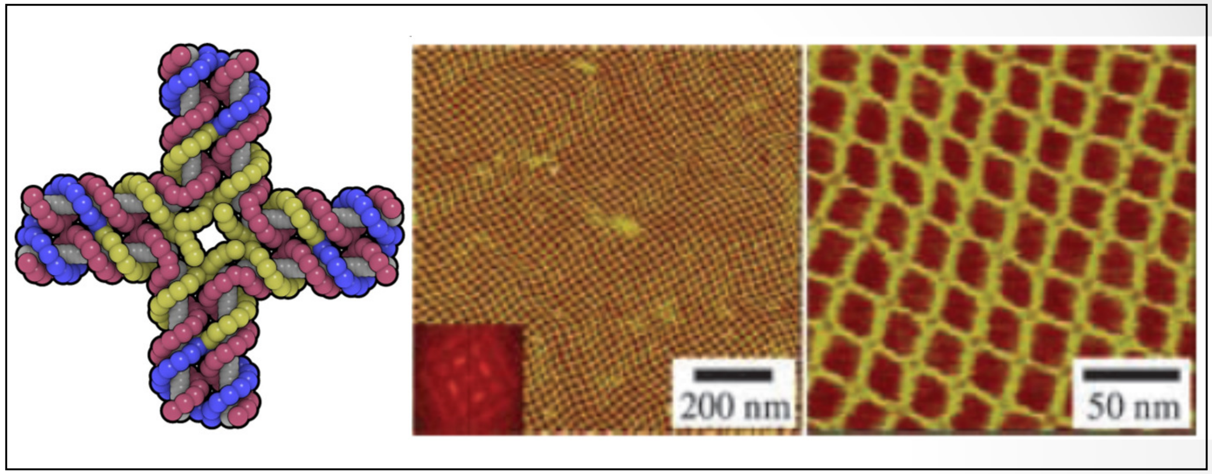
Pankhudi

2D DNA Lattices

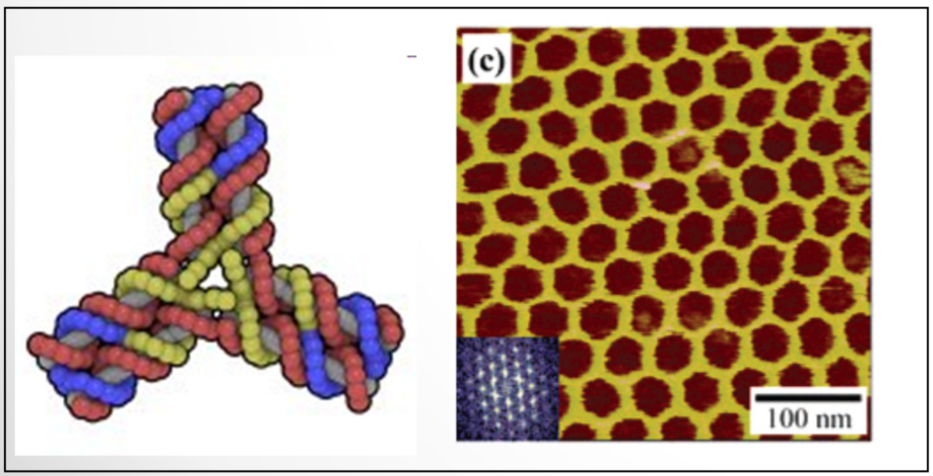


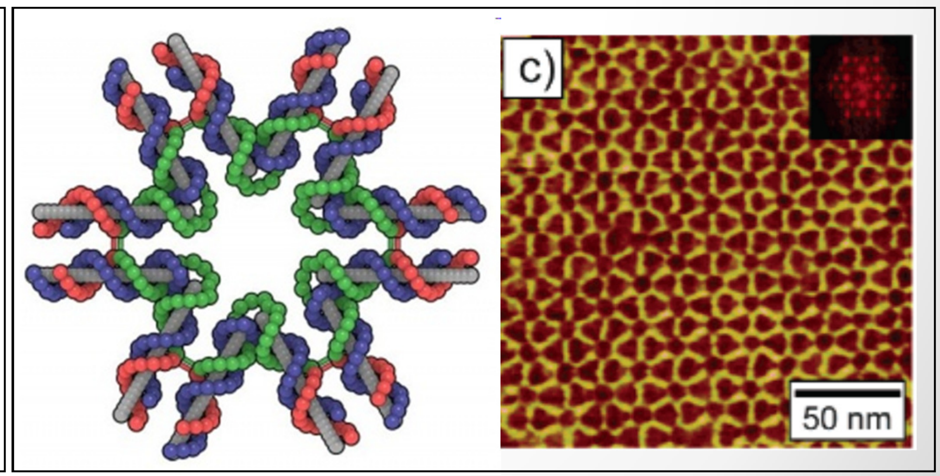
Chengde Mao

Purdue University, USA



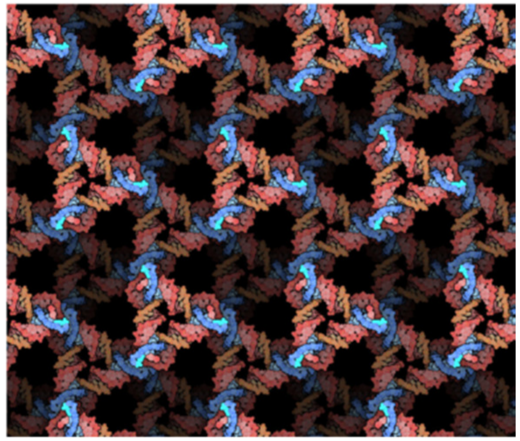
N-point Stars

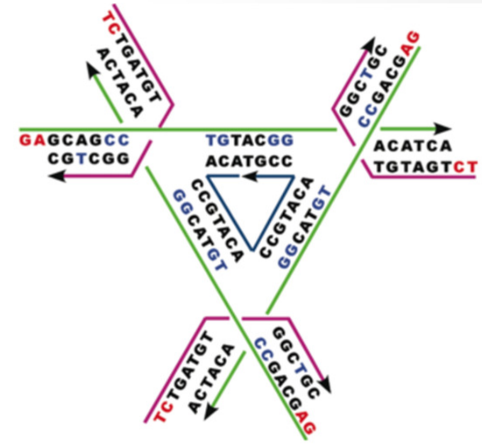




3D DNA Structures

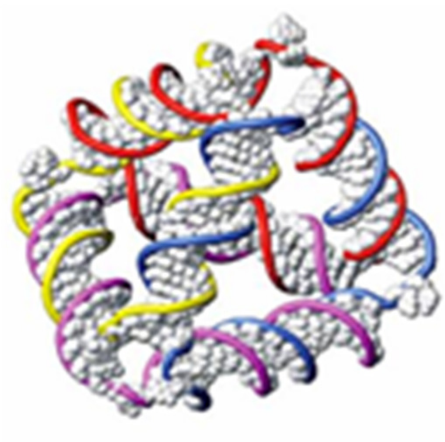
Ned Seeman
NYU

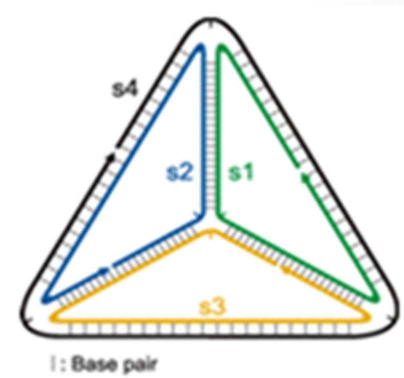




3D Cyrstal

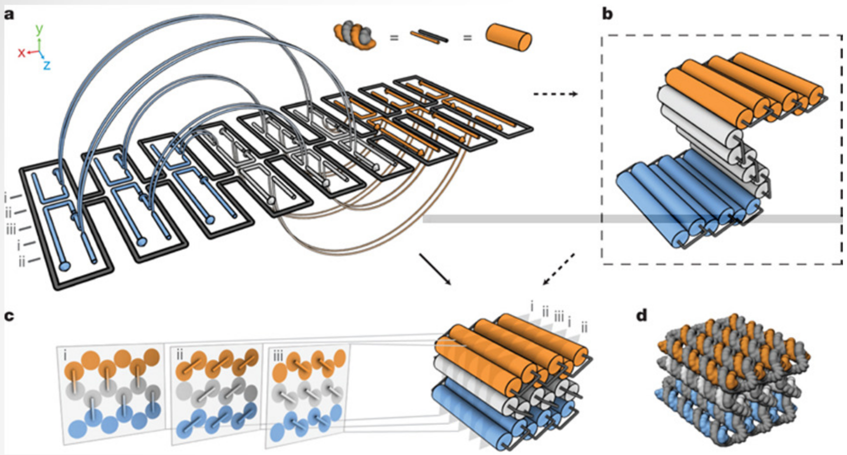
AndrewTuberfield
Oxford





Tetrahedron

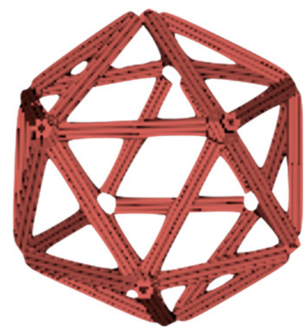
CADnano

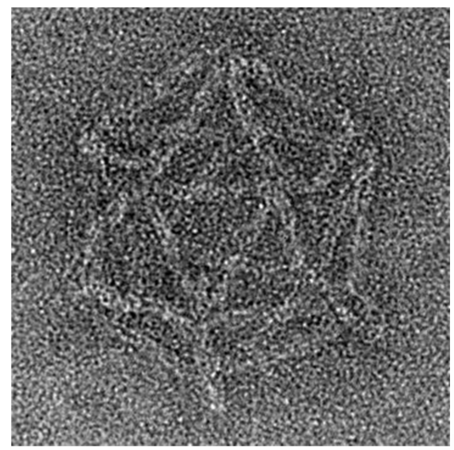


Folding DNA into Twisted and Curved Nanoscale Shapes

Hendrik Dietz, Shawn M. Douglas, & William M. Shih

Science, 325:725–730, 7 August 2009.



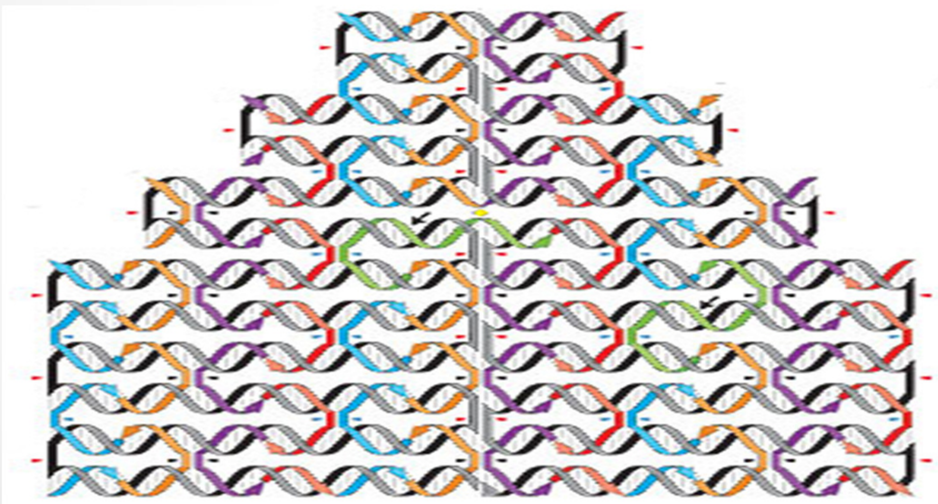


William Shih
Harvard

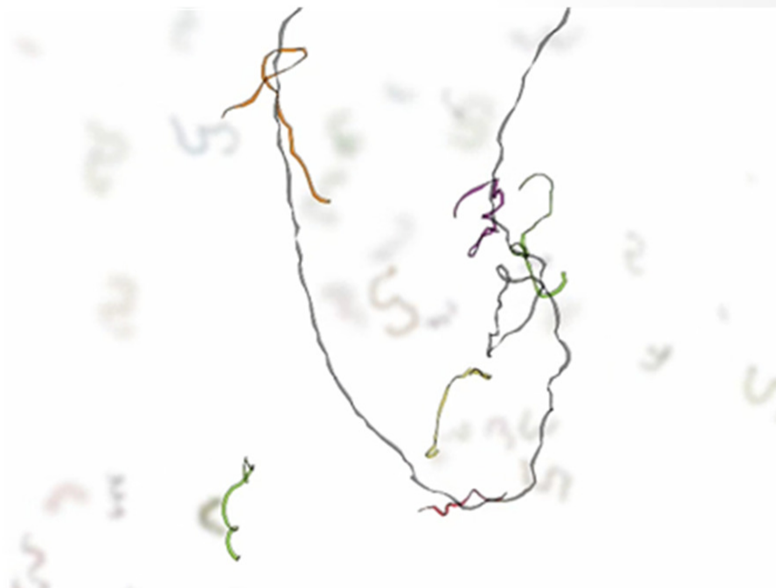
S.M. Douglas, H. Dietz, T. Liedl, B. Högberg, F. Graf and W. M. Shih
Self-assembly of DNA into nanoscale three-dimensional shapes, Nature (2009)

DNA Origami

- *Folding* long (7000bp) naturally occurring (viral) ssDNA
- By lots of short ‘staple’ strands that constrain it

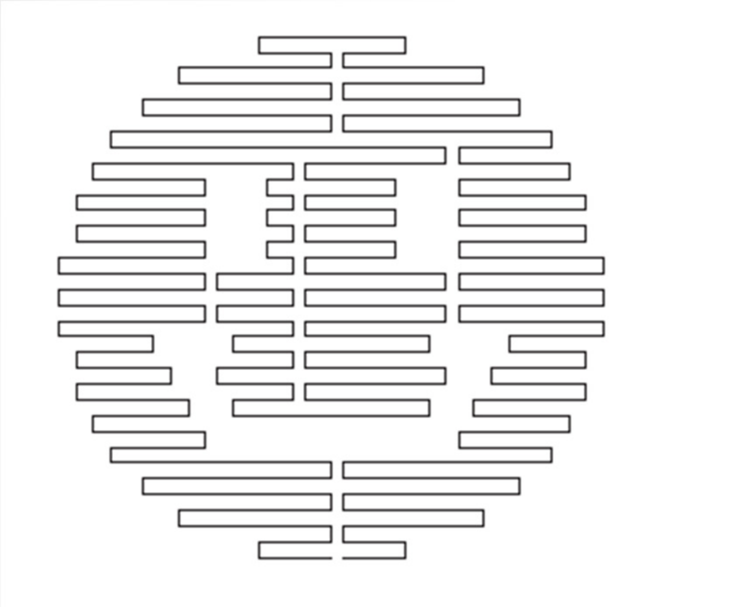


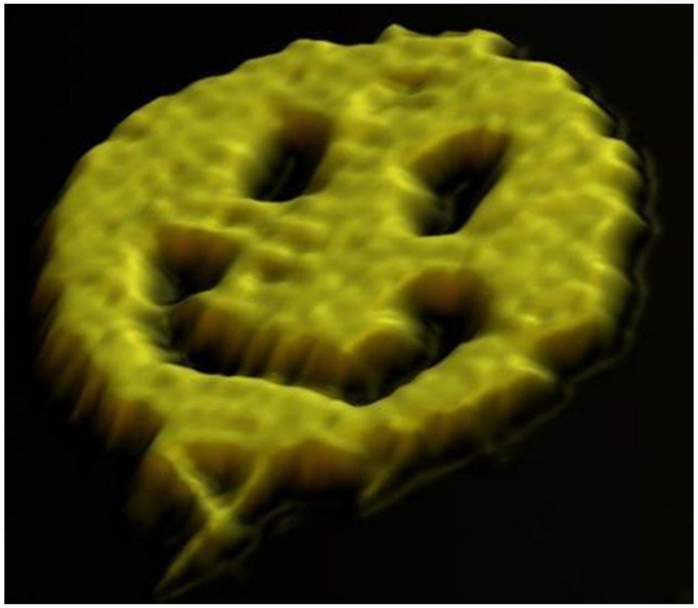
PWK Rothemund, *Nature* 440, 297 (2006)



Black: long viral strand
Color: short staple strands

DNA Origami





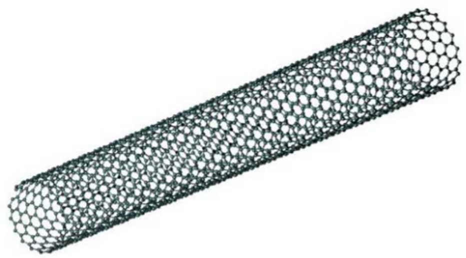
Paul Rothemund's "Disc with three holes" (2006)

Paul W K Rothemund
California Institute of Technology

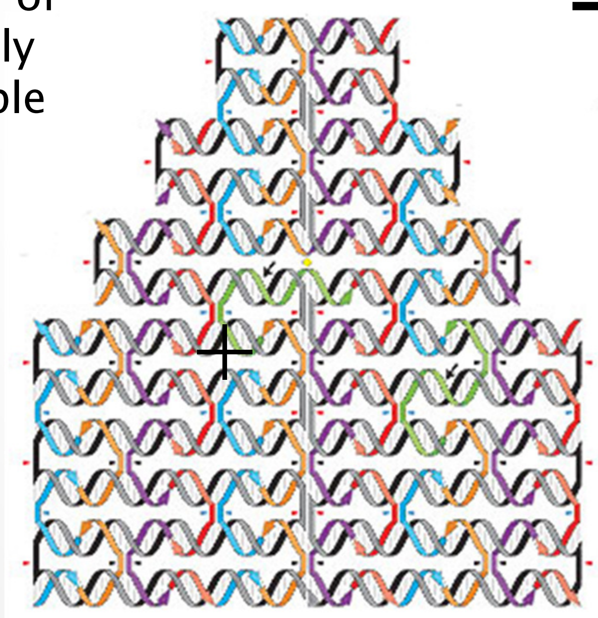
This means we can already self-assemble meso-scale structures.

DNA Circuit Boards

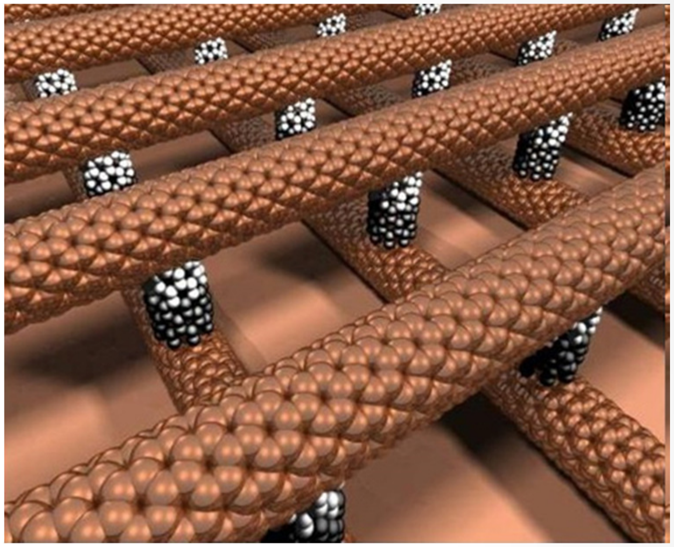
DNA-wrapped nanotubes



6 nm grid of individually addressable pixels



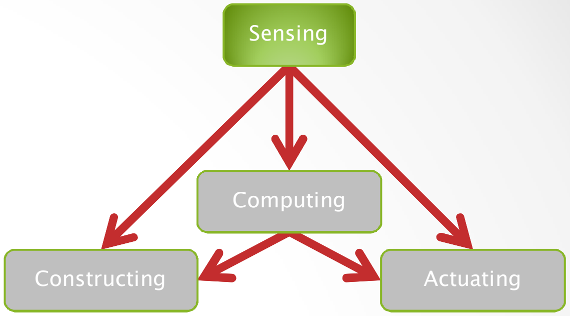
PWK Rothemund, *Nature* 440, 297 (2006)



European Nanoelectronics Initiative Advisory Council

"What we are really making are tiny DNA circuit boards that will be used to assemble other components."

Greg Wallraff, IBM



Sensing

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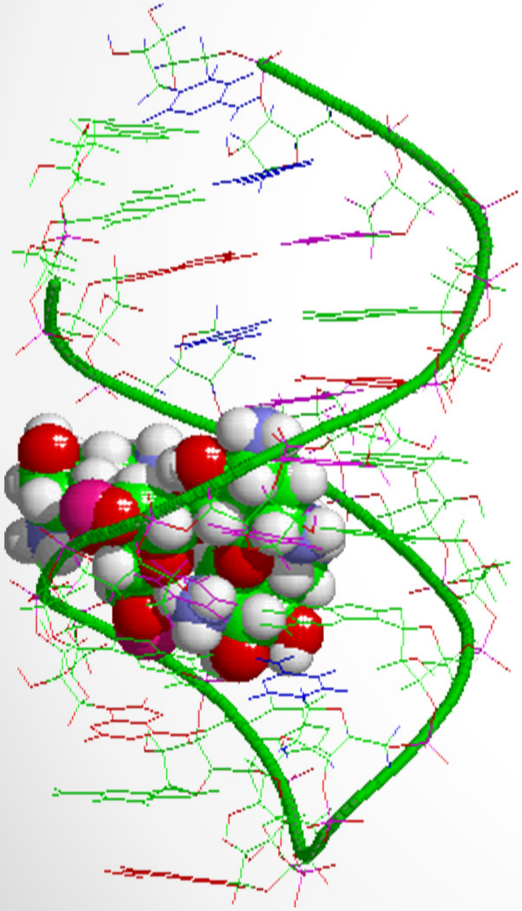
Aptamers

- Artificially eveloved DNA molecules that stick to anything you like (highly selectively).



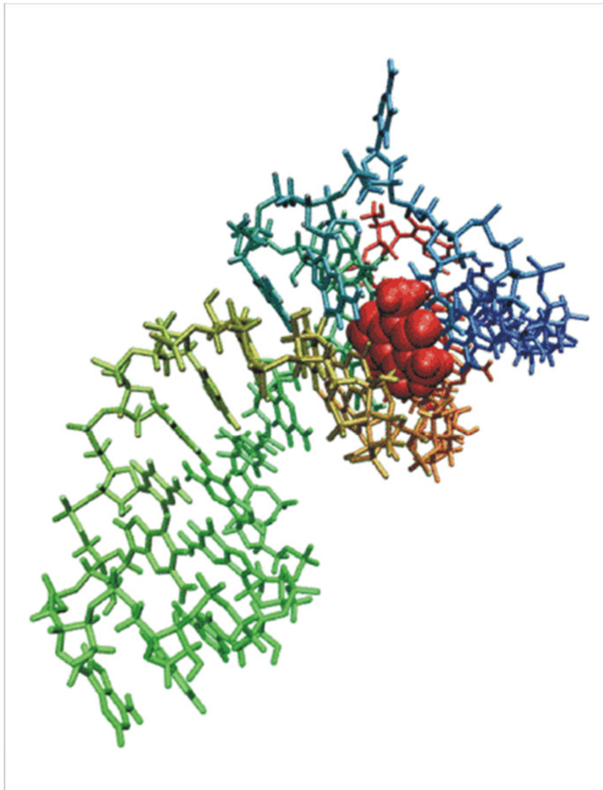
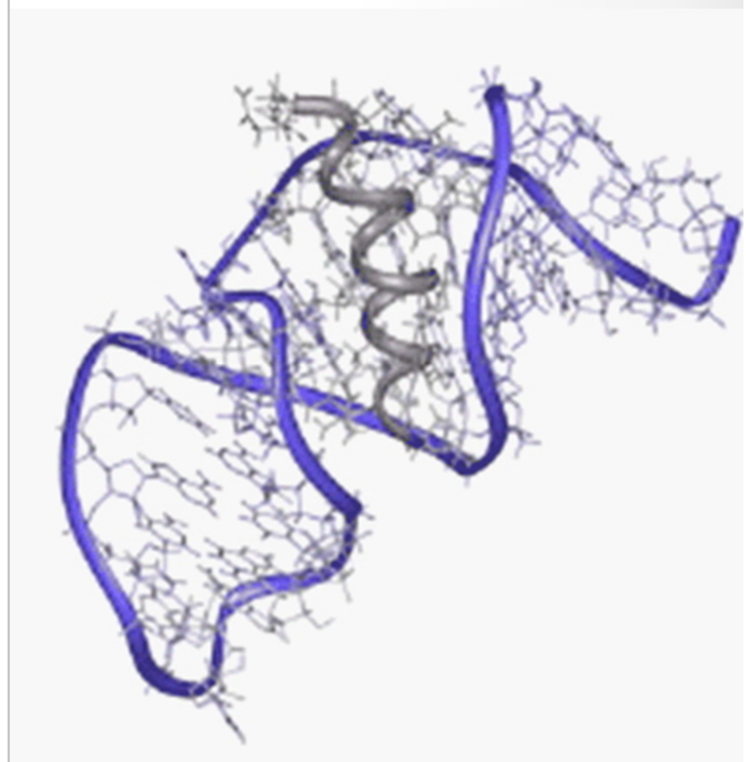
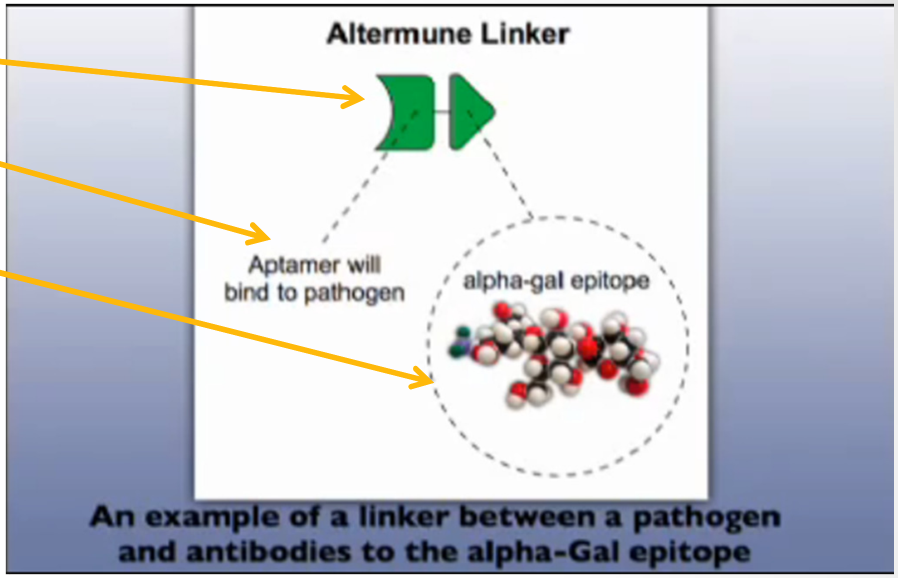


Fig.: RNA-aptamer - purine complex

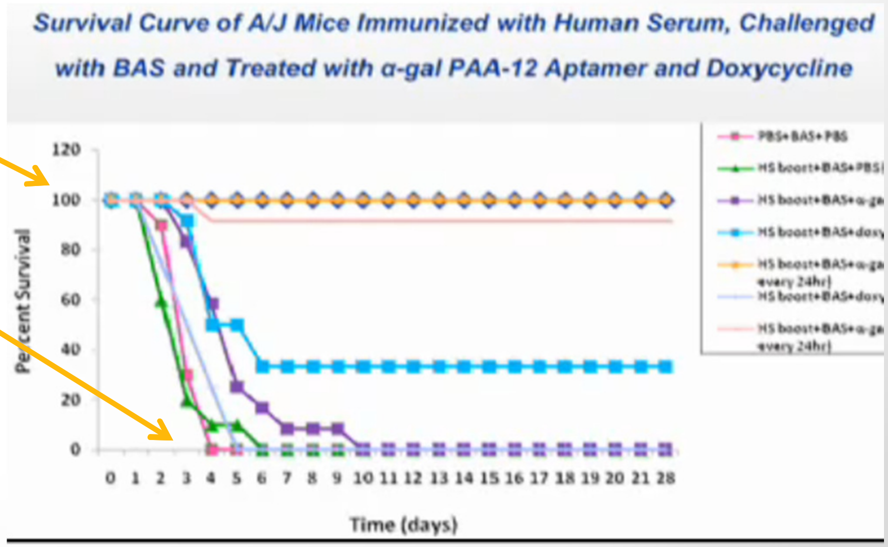


Pathogen Spotlights

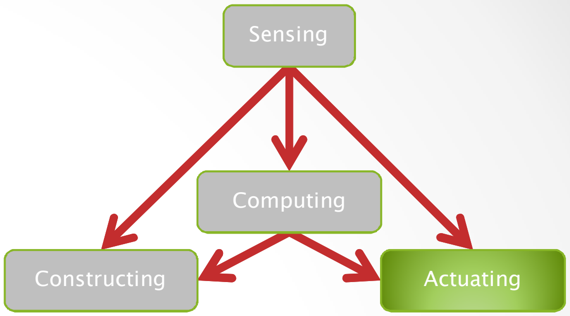
- DNA aptamer binds to:
  - A) a pathogen
  - B) a molecule our immune system already hates and immediately removes (eats) along with anything attached to it



- Result: instant immunity
  - Mice poisoned with Anthrax plus aptamer (100% survival)
  - Mice poinsoned with Anthrax (not so good)



Kary Mullis (incidentally, also Nobel prize for inventing the Polymerase Chain Reaction)



Actuating

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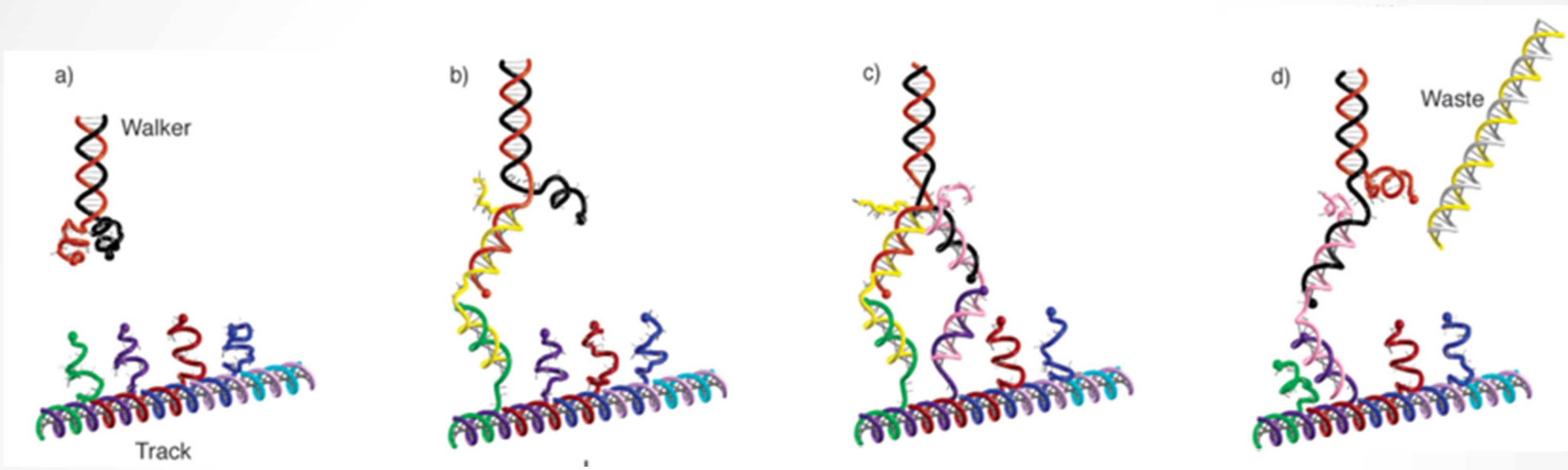
DNA Walkers

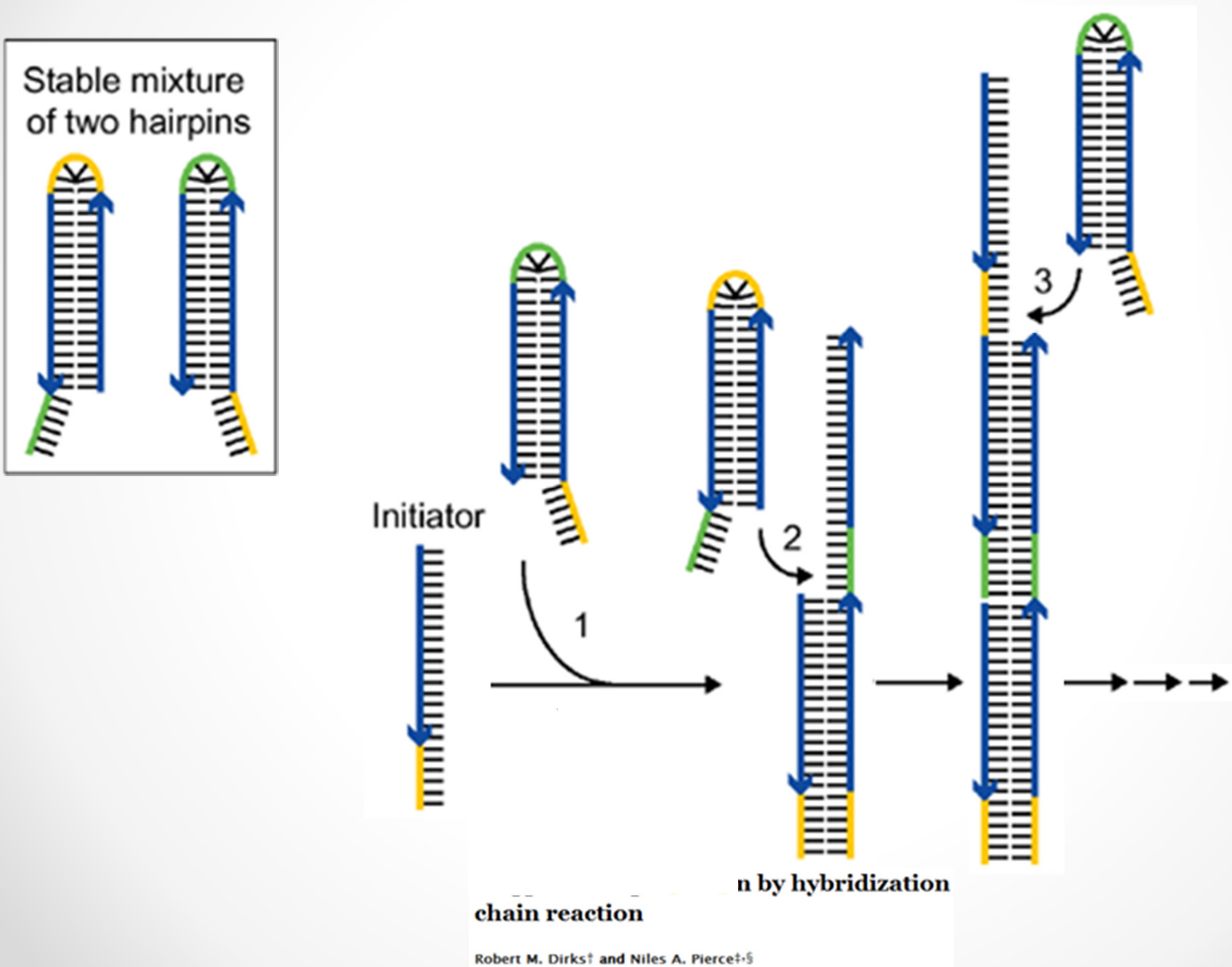


J|A|C|S
COMMUNICATIONS
Published on Web 08/17/2004

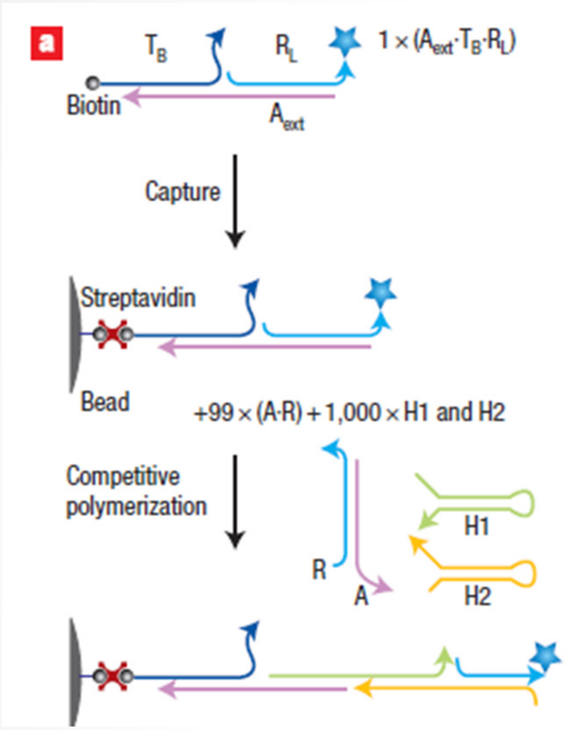
A Synthetic DNA Walker for Molecular Transport

Jong-Shik Shin[†] and Niles A. Pierce[*,†,‡]
Departments of Bioengineering and Applied & Computational Mathematics, California Institute of Technology, Pasadena, California 91125

Hybridization Chain Reaction



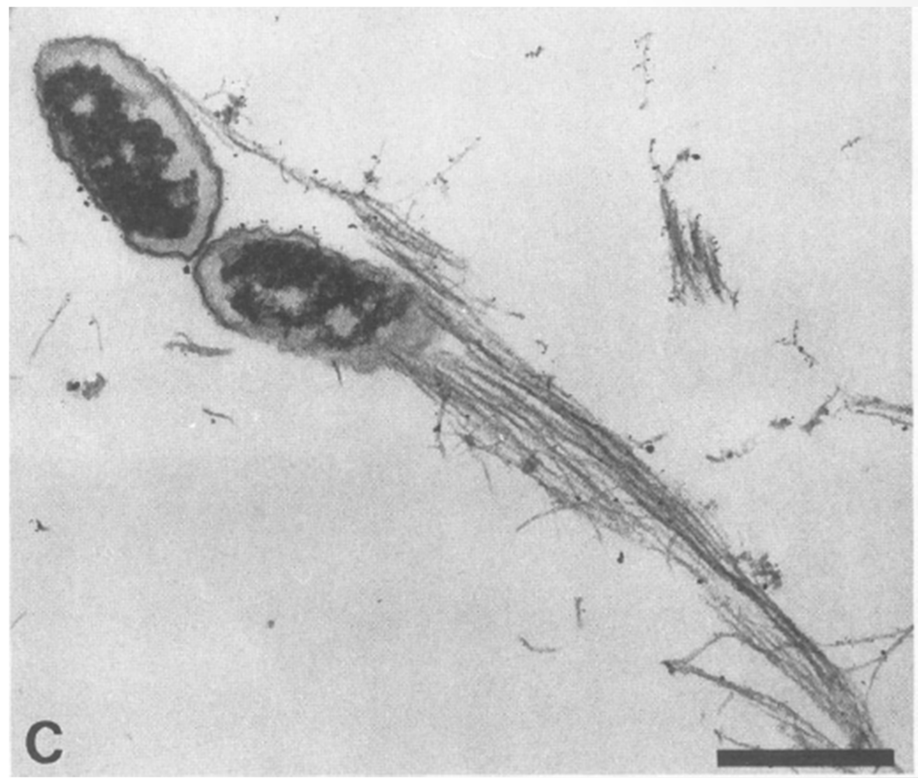
Polymerization Motor



An autonomous polymerization motor powered by DNA hybridization

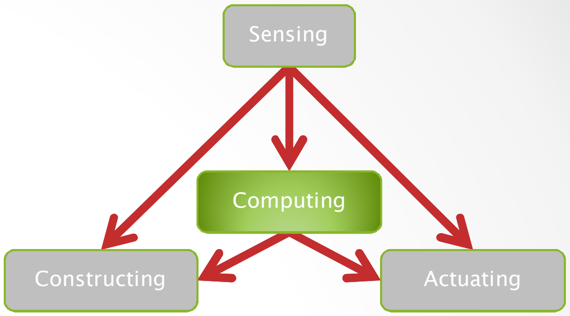
SUVIR VENKATARAMAN[1], ROBERT M. DIRKS[1], PAUL W. K. ROTHEMUND[2,3], ERIK WINFREE[2,3] AND NILES A. PIERCE[1,4]*

Rickettsia (spotted fever)



Directional Actin Polymerization Associated with Spotted Fever Group Rickettsia Infection of Vero Cells

ROBERT A. HEINZEN, STANLEY F. HAYES, MARIUS G. PEACOCK, AND TED HACKSTADT*



Computing

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Basic Notions

Compositionality

- Sensors and Actuators at the 'edge' of the system
  - They can use disparate kinds of inputs (sensors) and outputs (actuators)

- The 'kernel' of the system computes
  - Must use uniform inputs and outputs

- Compositionality in the kernel
  - Supporting 'arbitrary' computing complexity
  - The **output** of each computing components must be the **same kind of 'signal'** as the **input**
- sdf
  - If the inputs are voltages, the outputs must be voltages
  - If the inputs are DNA, the outputs must be DNA

- Central design question
  - What should our **signals** (not components!) be?
  - Then design components that manipulate those signals.

What does DNA Compute?

- Electronics has *electrons*
  - All electrons are the same: you can only count them
  - *Few* electrons = False; *lots* of electrons = True
  - But Boolean Logic is only a necessary evil to build symbolic computation
- DNA computing has *symbols* (DNA words)
  - DNA words are not all the same
  - Symbolic computation on abstract signals can be done *directly*
  - Signals are presented concurrently (in a soup)
  - No requirement to do Boolean Logic
- Then, what are our 'gates' (if not Boolean?)
  - Theory of Concurrency
  - Process Algebra as the "Boolean Algebra" of DNA Computing

Why Compute with DNA?

- Not to solve NP-complete problems.
- Not to put Intel out of business.
- Not to orchestrate protein production.
- To precisely control the organization and dynamics of matter and information at the molecular level.
  - The use of DNA is “accidental”.
  - No genes involved.
  - In fact, no material of biological origin.

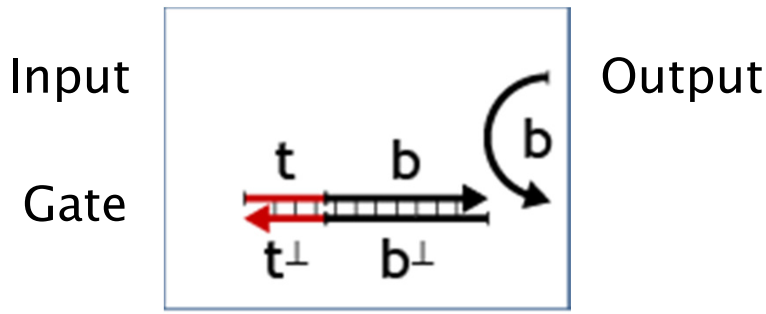
Rules of the Game

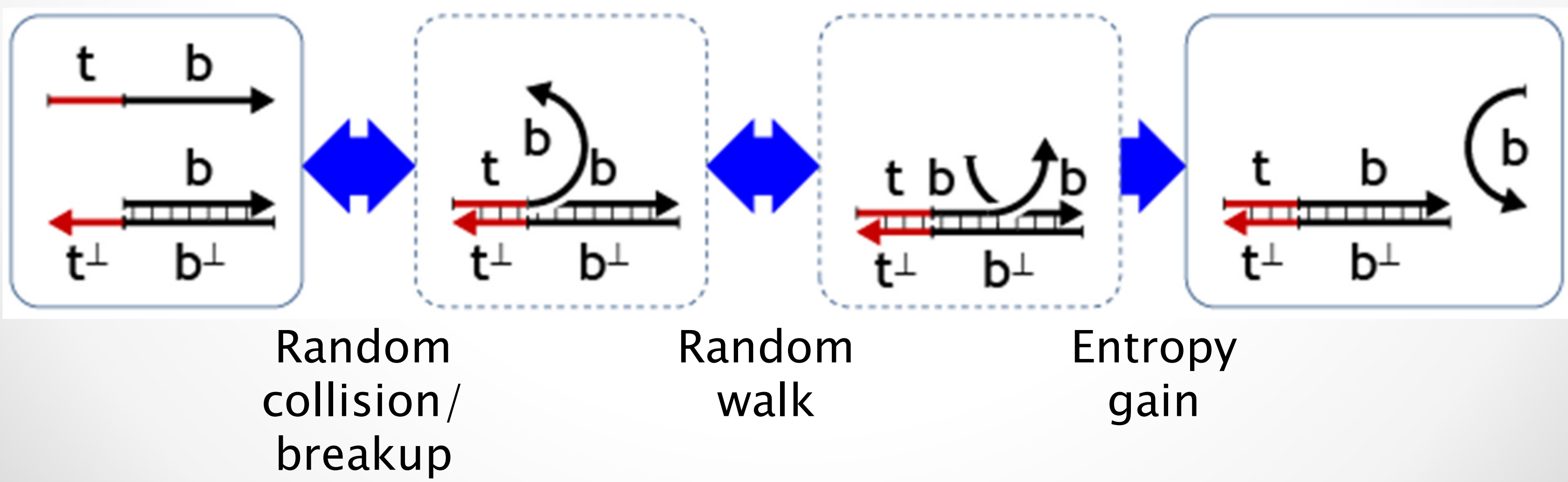
- Short complementary segments hybridize **reversibly**

- Long complementary segments hybridize **irreversibly**

DNA Strand Displacement

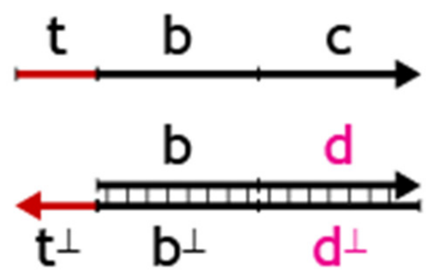
- Short strand (**toehold**): reversible binding
- Long strand (**body**): irreversible binding



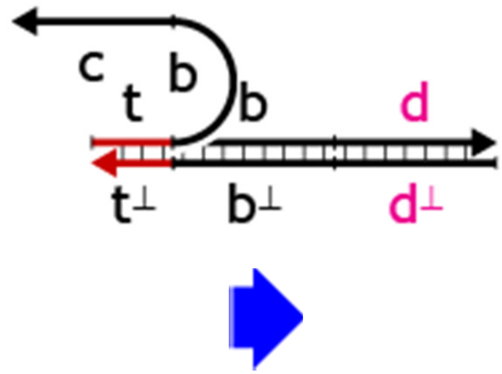


Failed Strand Displacement

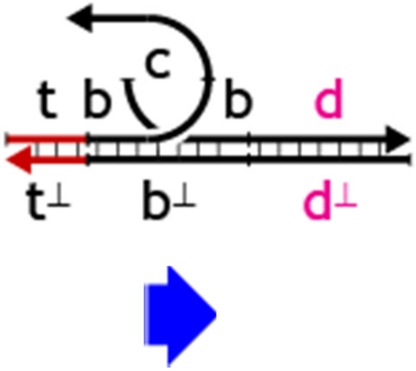
- What if the input does not match the gate?



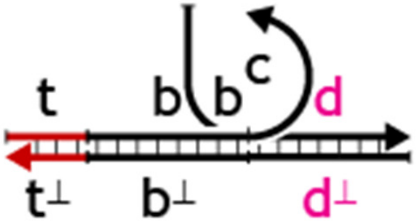
Failed Strand Displacement



Failed Strand Displacement



Failed Strand Displacement



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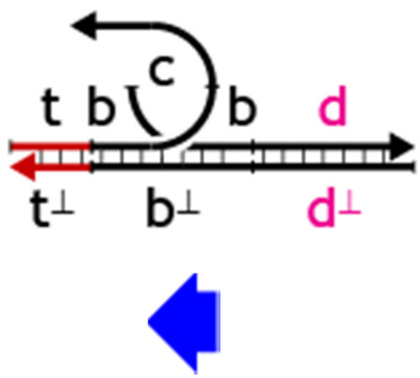
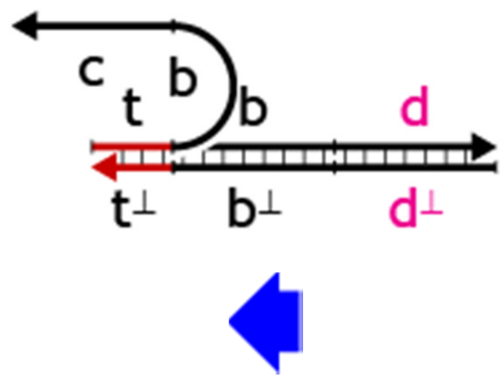
Failed Strand Displacement

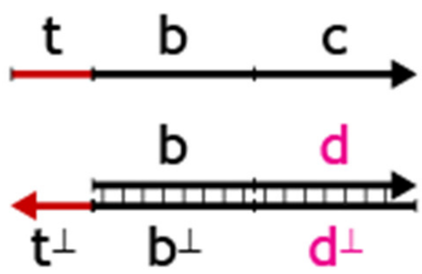


Failed Strand Displacement

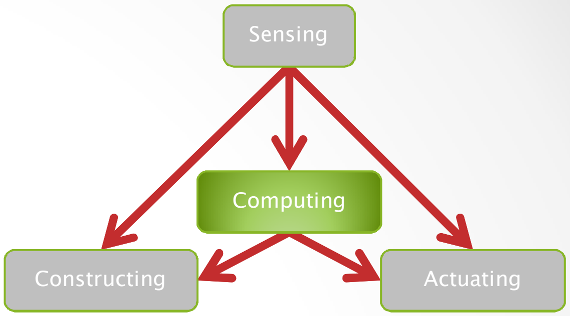


Failed Strand Displacement

- Hence an incorrect binding will undo
  - That's why toeholds must bind reversibly



- Matching depends on the long segment only
  - Strand displacement succeeds iff the whole long segment matches
  - The address space is determined by the size of the long segment, which is unbounded (not by the size of the toehold)
  - The toehold is just a 'cache' of the address



Computing

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Implementing "Arbitrary" Computing Functions

Signals

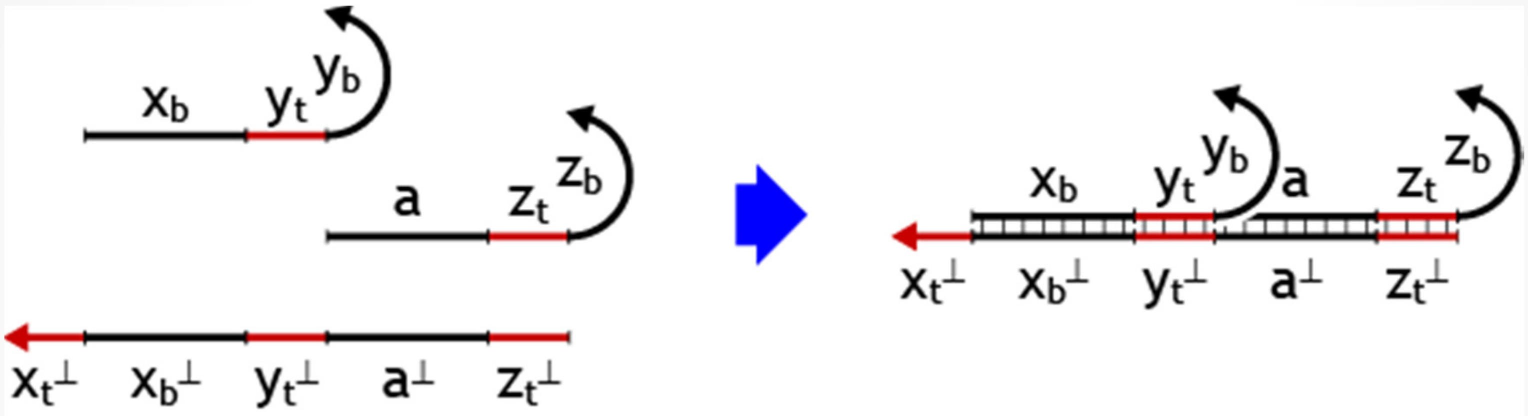
- A signal is the representation of an abstract event
  - E.g. generated by a sensor
  - E.g. accepted by an effector
  - We are not limited to true/false

- 3-domain signals
  - x_h: hystory (ignore)
  - x_t: toehold (binding)
  - x_b: body (recognition)

- Signals (single stranded DNA) are prepared by (artificial) DNA synthesis

Gates

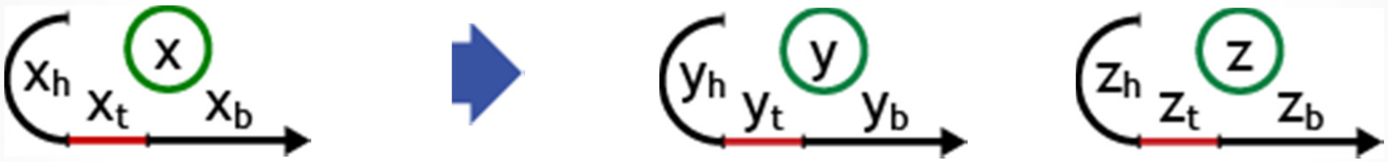
- Double-stranded structures with free toeholds



- Gates are prepared by **self-assembly** from single-stranded DNA that is synthesized

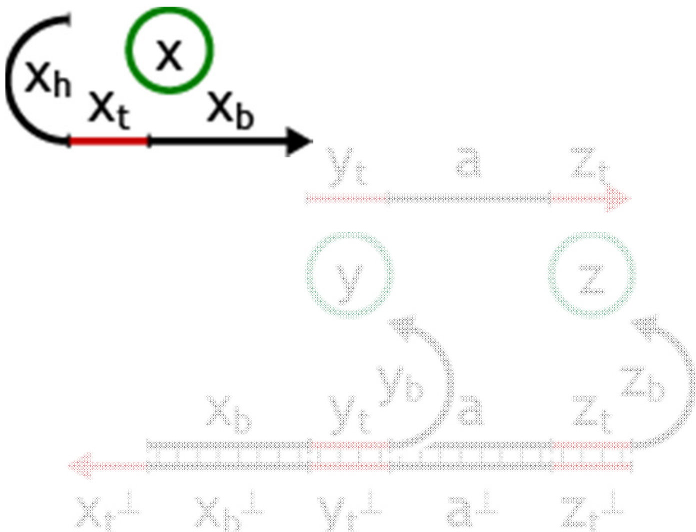
Fork Gate

- $x \rightarrow y + z$



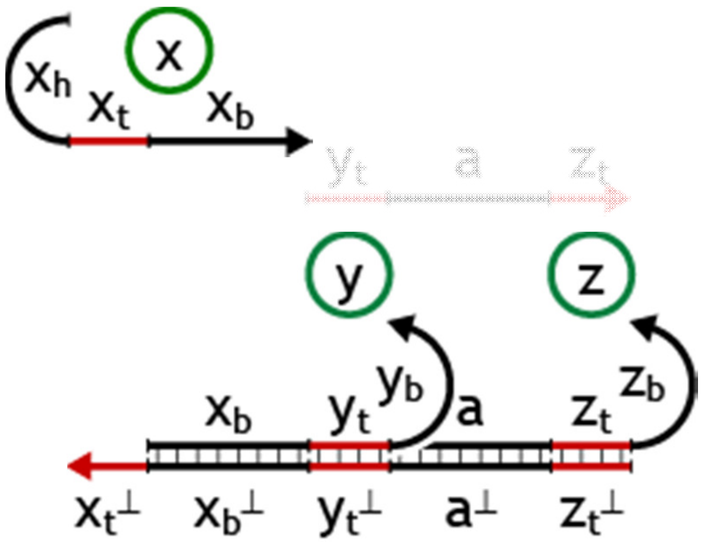
- $x \rightarrow y + 0$ transform x to y (transducer)
- $x \rightarrow x + y$ linear production of y (catalyst)
- $x \rightarrow x + x$ exponential production of x (amplifier)

Fork Gate



This is the Fork Gate structure

Fork Gate



x
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x_t
x_b
y_t
a
z_t
y
z
y_b
z_b
x_b
y_t
a
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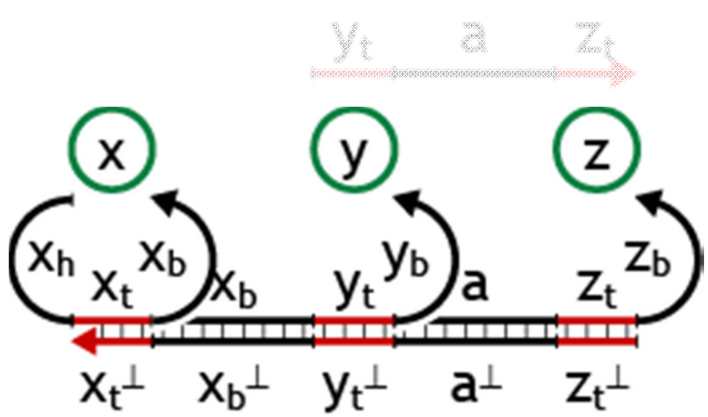
$x_t^{\perp}$
$x_b^{\perp}$
$y_t^{\perp}$
$a^{\perp}$
$z_t^{\perp}$

Fork Gate



y_t
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$x_t^\perp$
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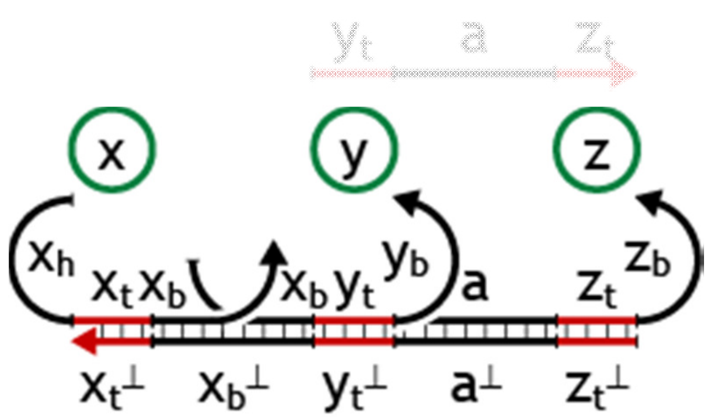
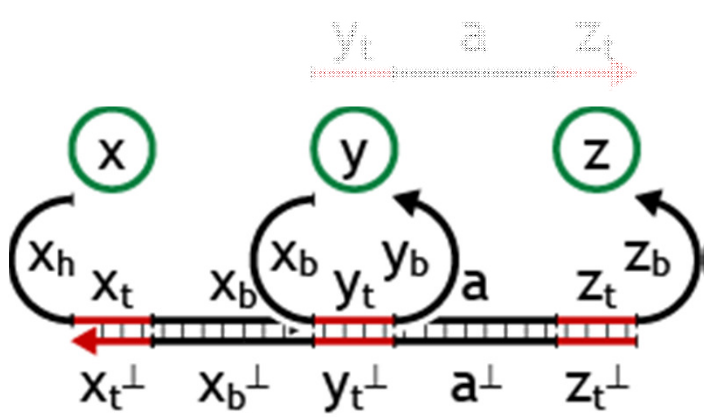
Fork Gate

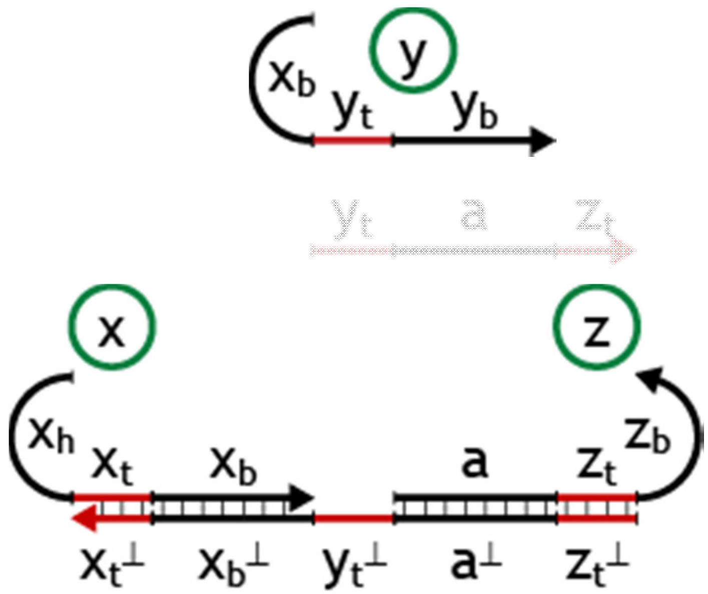


Fork Gate



y$_t$ a z$_t$
x
y
z
x$_h$ x$_t$ x$_b$ x$_b$ y$_t$ y$_b$ a z$_t$ z$_b$
x$_t$$^\perp$ x$_b$$^\perp$ y$_t$$^\perp$ a$^\perp$ z$_t$$^\perp$

Fork Gate



y
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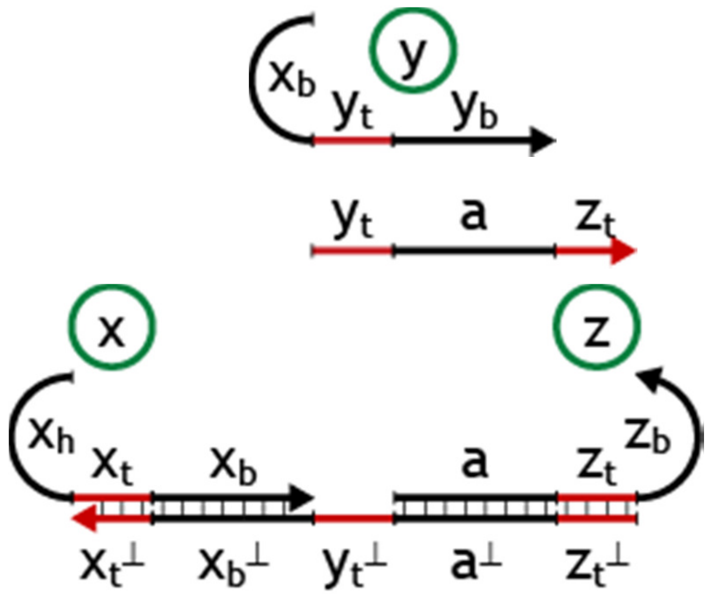
$z_t^\perp$

Fork Gate



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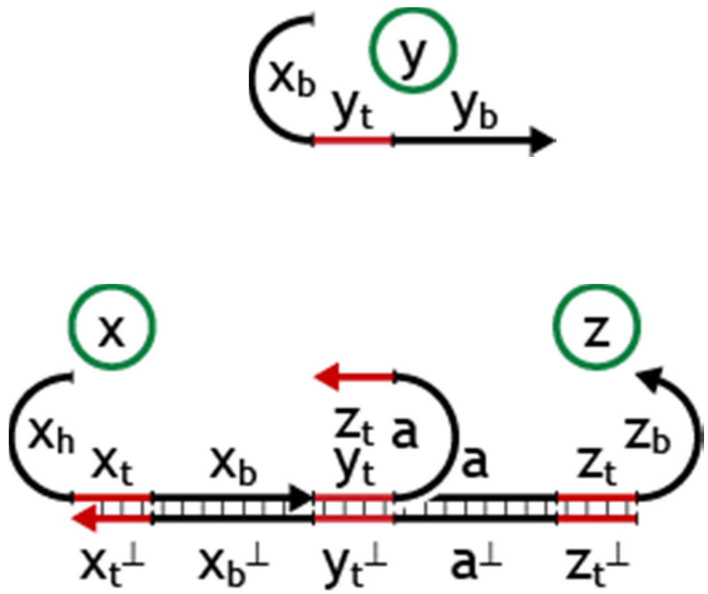
Fork Gate


y
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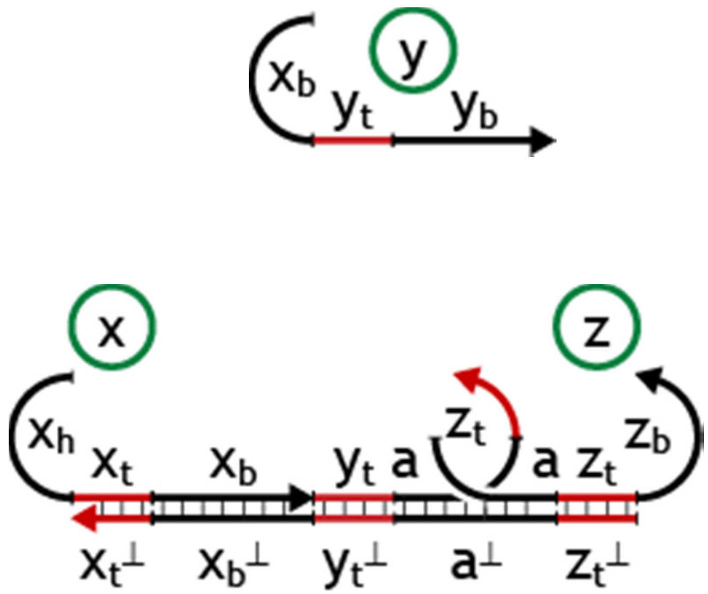
z_t a
x_h x_t x_b y_t a z_t z_b
$x_t^\perp$ $x_b^\perp$ $y_t^\perp$ $a^\perp$ $z_t^\perp$

Fork Gate



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x_b
y_t
a
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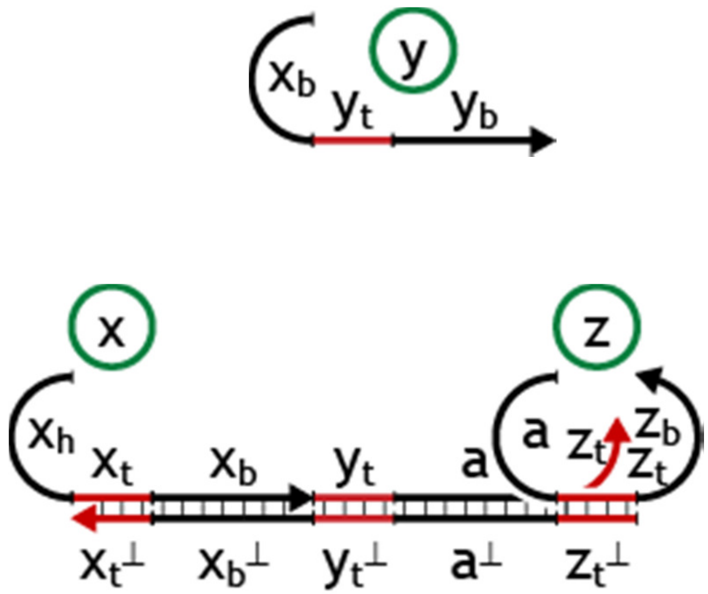
z_b
$x_t^\perp$
$x_b^\perp$
$y_t^\perp$
$a^\perp$
$z_t^\perp$

Fork Gate



y
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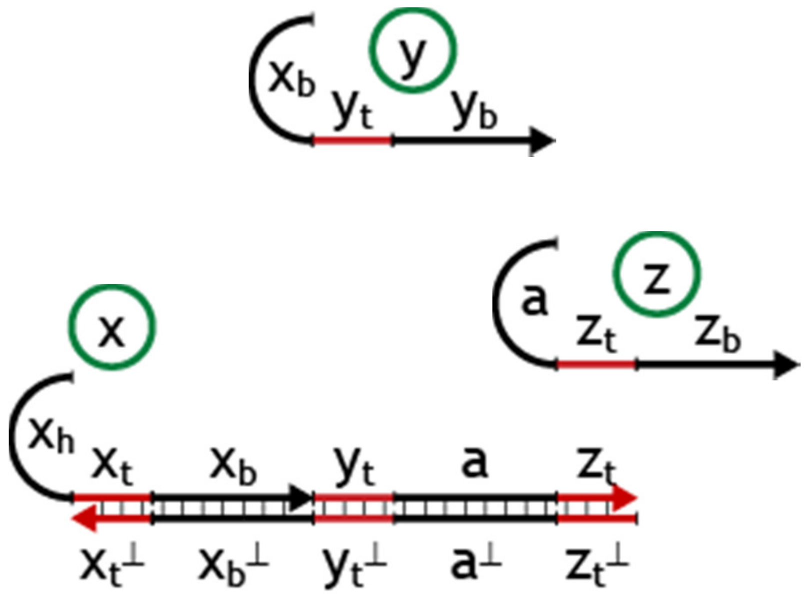
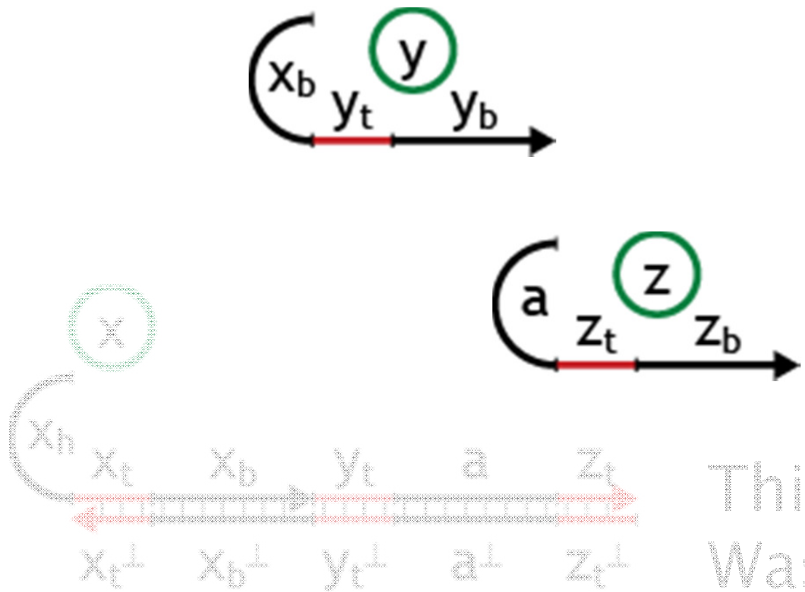
$x_t^\perp$
$x_b^\perp$
$y_t^\perp$
$a^\perp$
$z_t^\perp$

Fork Gate



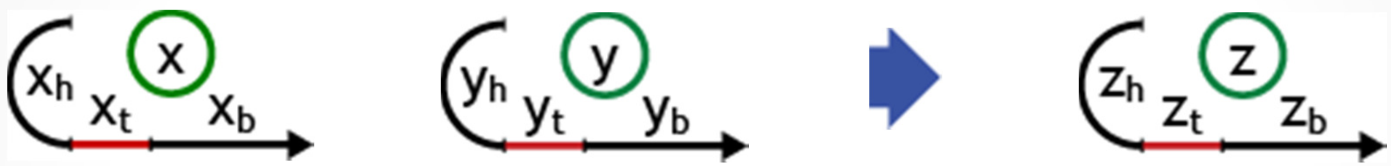
Fork Gate



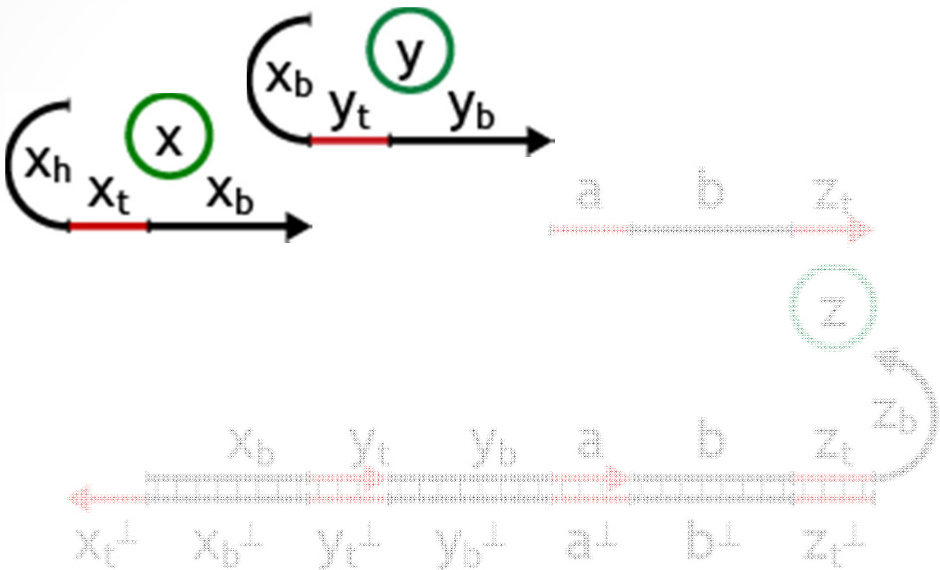
This is Waste

Join Gate

- $x + y \rightarrow z$

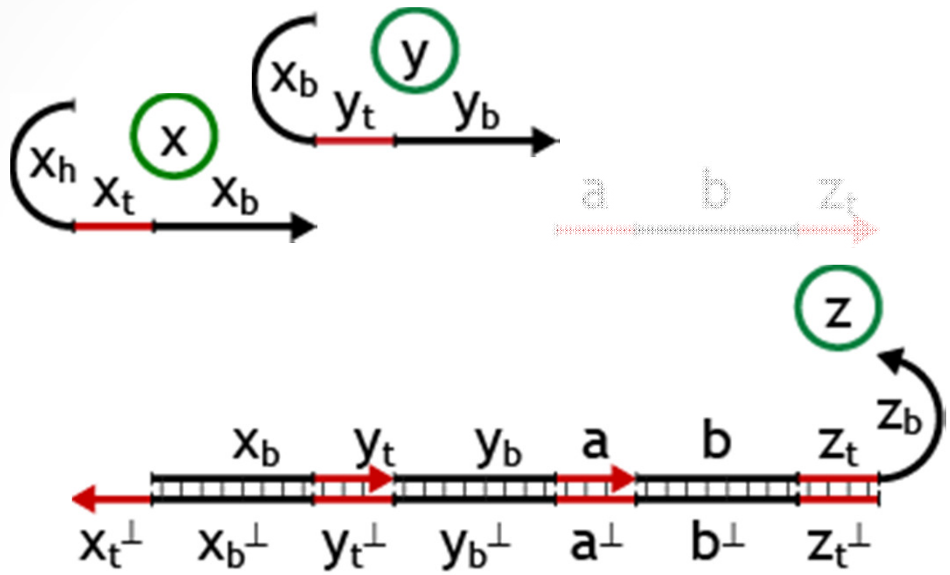


Join Gate



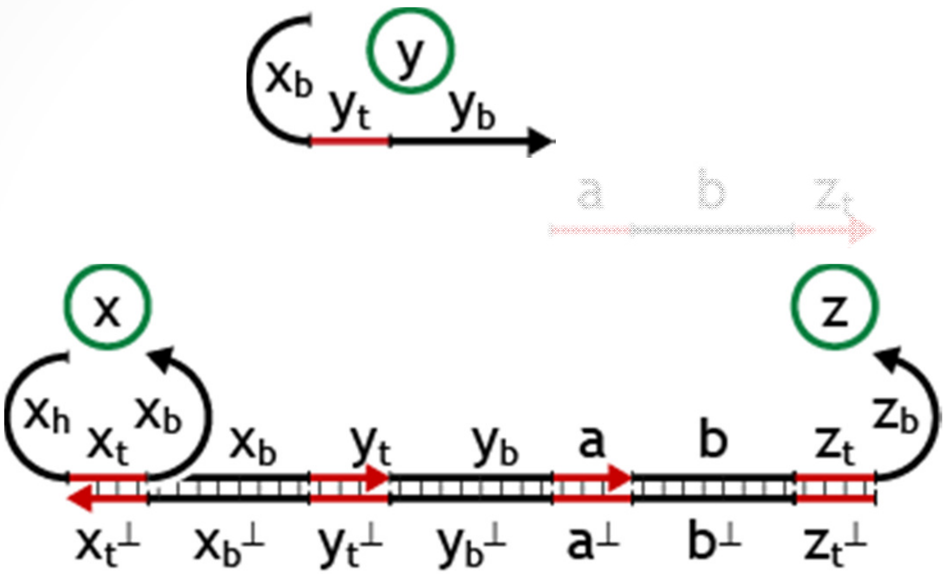
This is the Join Gate structure

Join Gate



x
y
z
x_h x_t x_b
x_b y_t y_b
a b z_t
z_b
x_b y_t y_b a b z_t
$x_t^\perp$ $x_b^\perp$ $y_t^\perp$ $y_b^\perp$ $a^\perp$ $b^\perp$ $z_t^\perp$

Join Gate



y
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y_t
y_b
a
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z_t
x
z
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x_b
y_t
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a
b
z_t
z_b
$x_t^\perp$
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$y_b^\perp$
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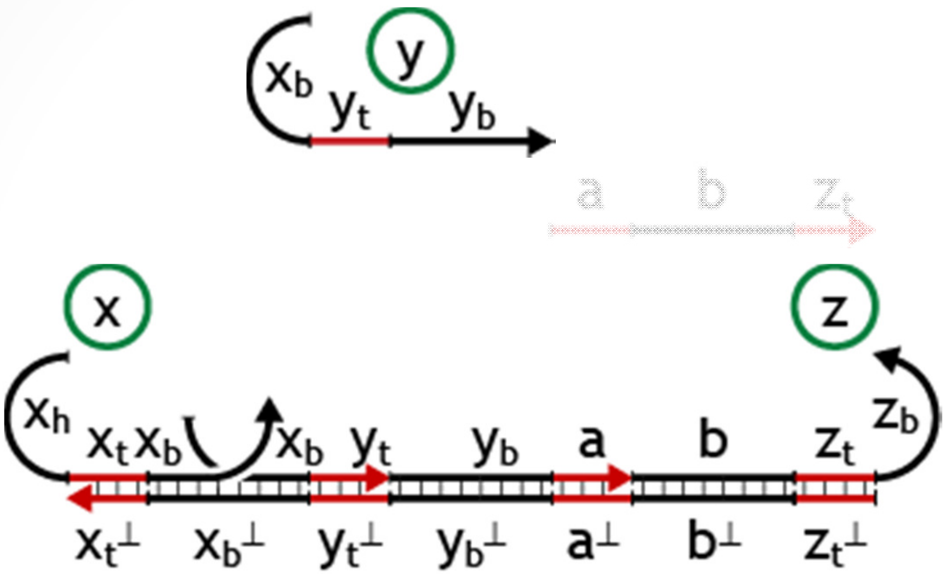
$b^\perp$
$z_t^\perp$

Join Gate



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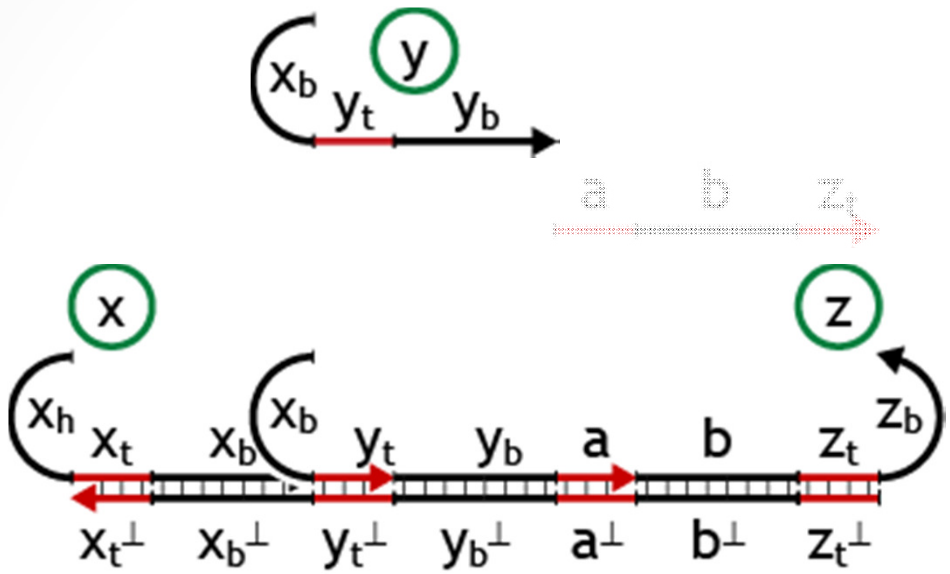
Join Gate



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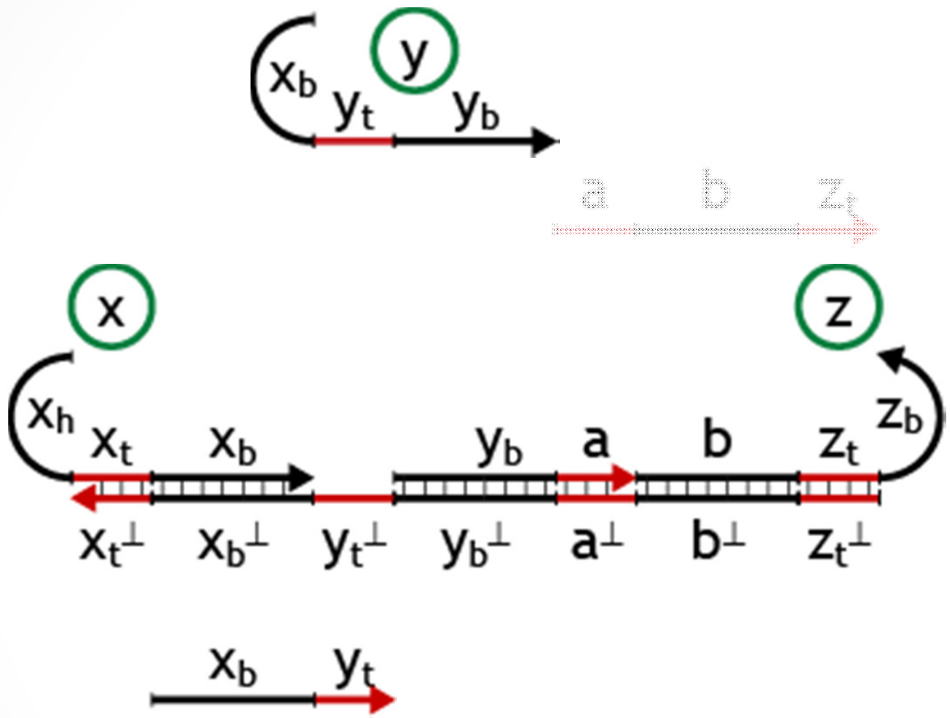

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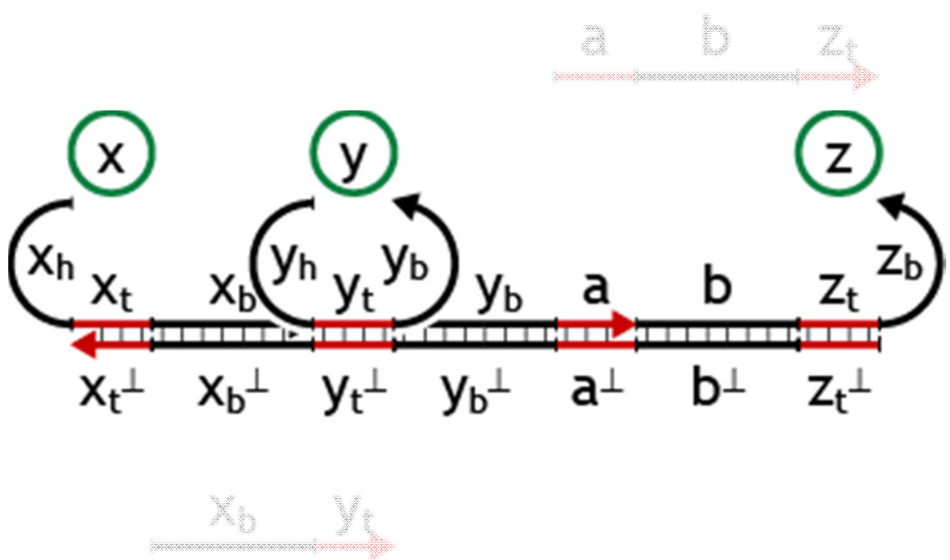

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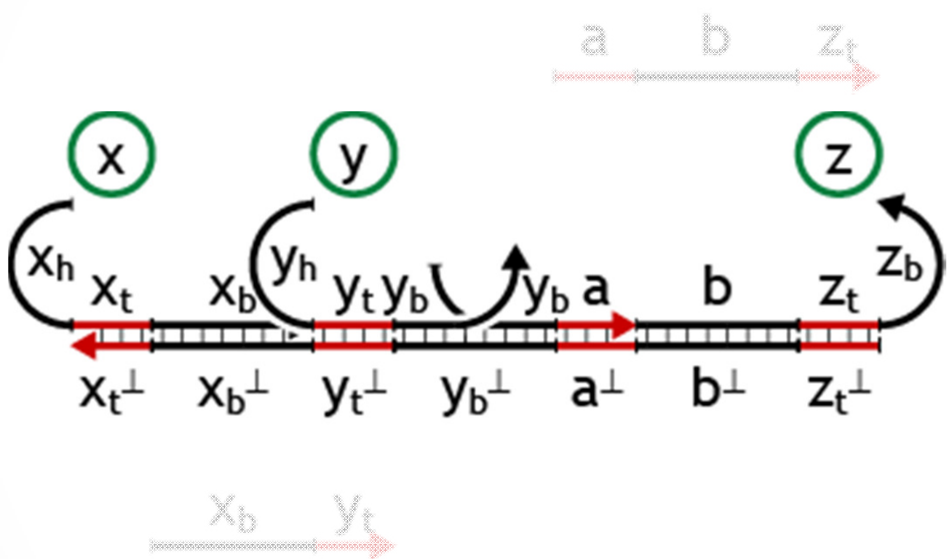
Join Gate



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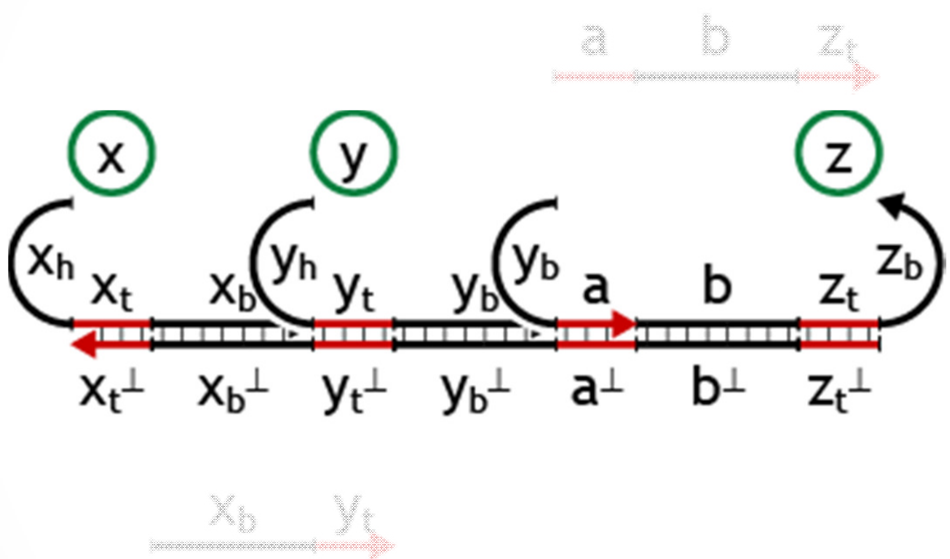
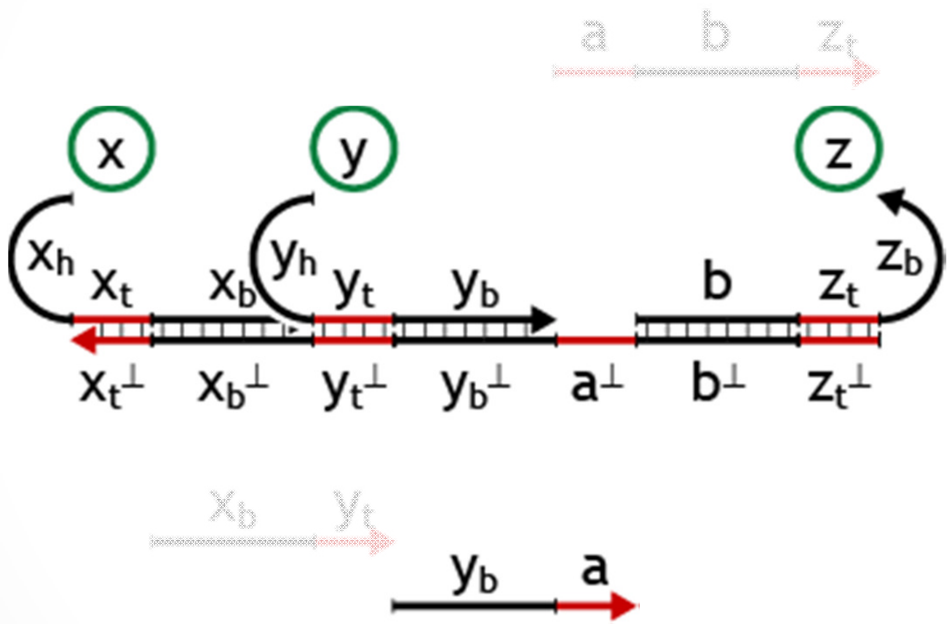
Join Gate



a b z_t
x y z
x_h x_t x_b y_h y_t y_b y_b a b z_t z_b
$x_t^\perp$ $x_b^\perp$ $y_t^\perp$ $y_b^\perp$ $a^\perp$ $b^\perp$ $z_t^\perp$
x_b y_t

Join Gate



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$x_b^\perp$
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y_t
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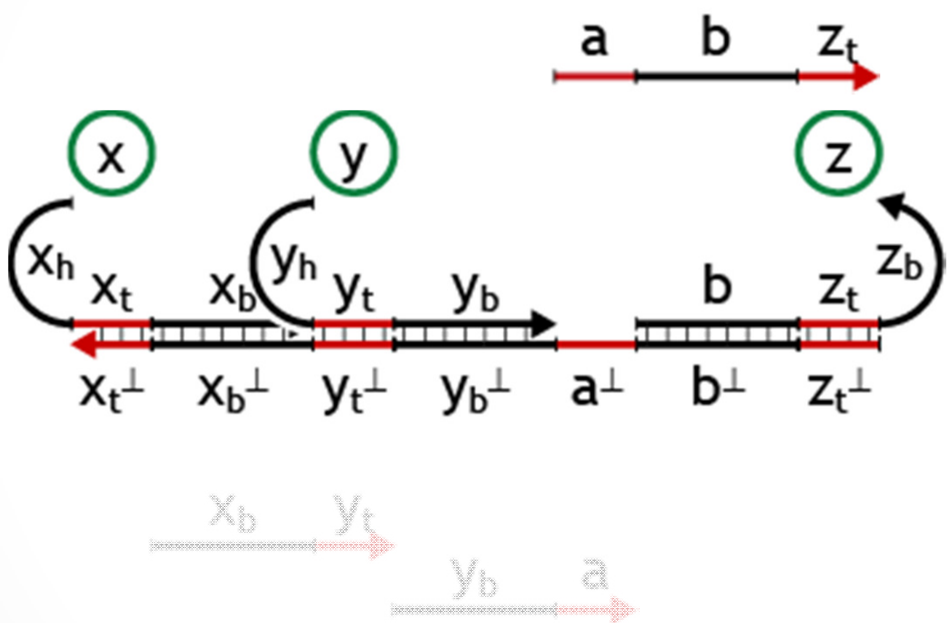
Join Gate



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y_b
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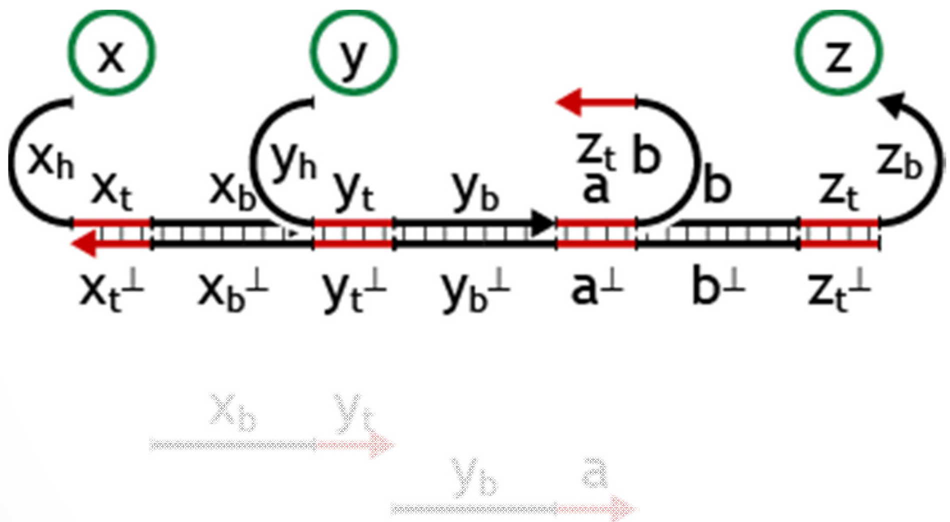
Join Gate



x
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y_h y_t y_b
z_t b
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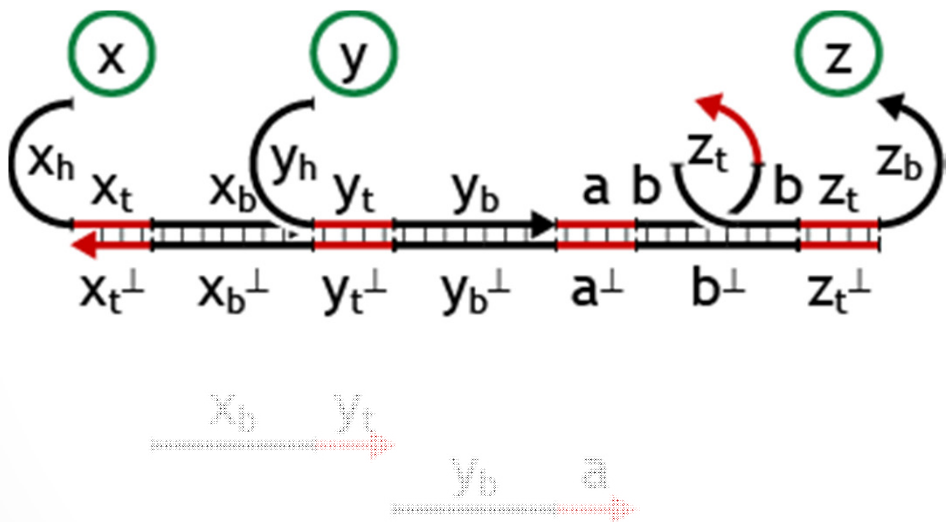
b
z_t z_b
$x_t^\perp$ $x_b^\perp$ $y_t^\perp$ $y_b^\perp$ $a^\perp$ $b^\perp$ $z_t^\perp$
x_b y_t
y_b a

Join Gate



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$x_b^\perp$
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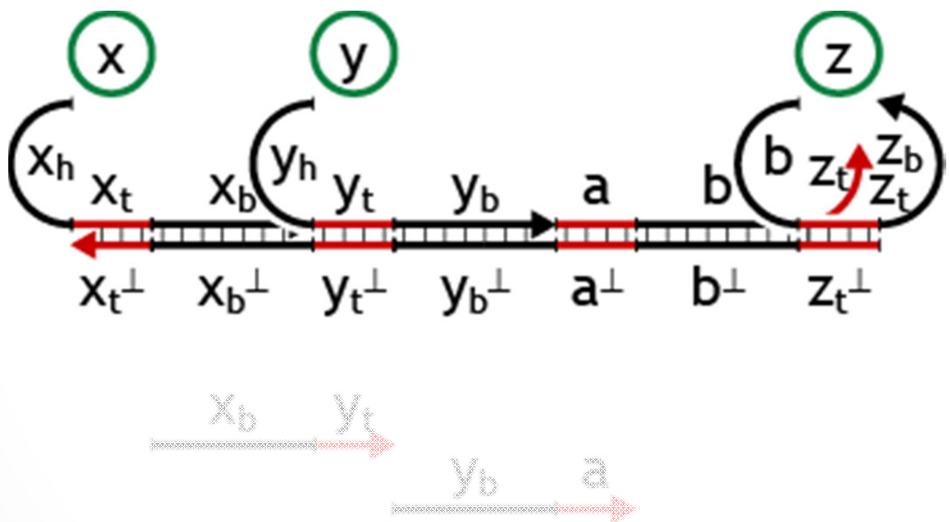
Join Gate



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y_t
y_b
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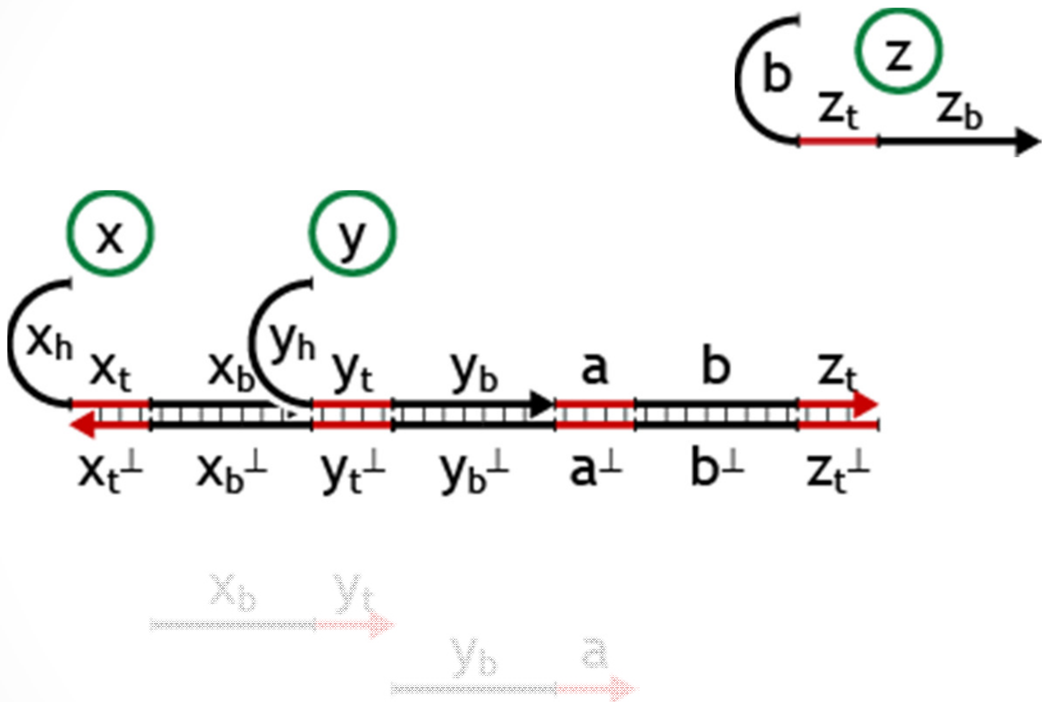
Join Gate



b
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$x_b^\perp$
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y_t
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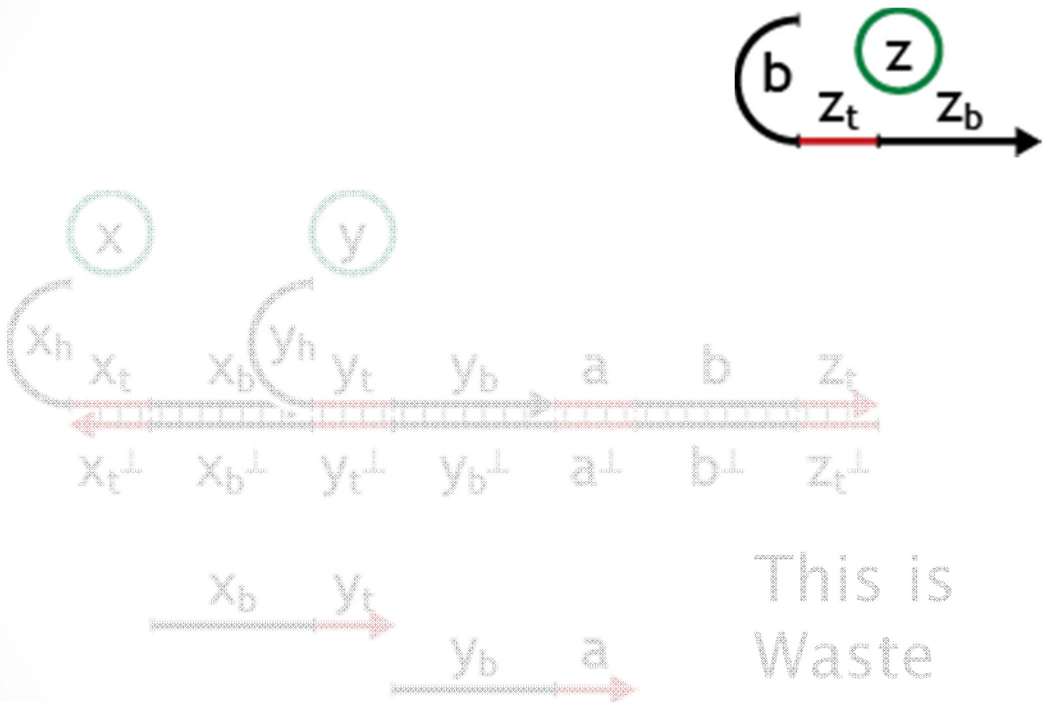
Join Gate



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$x_b^\perp$
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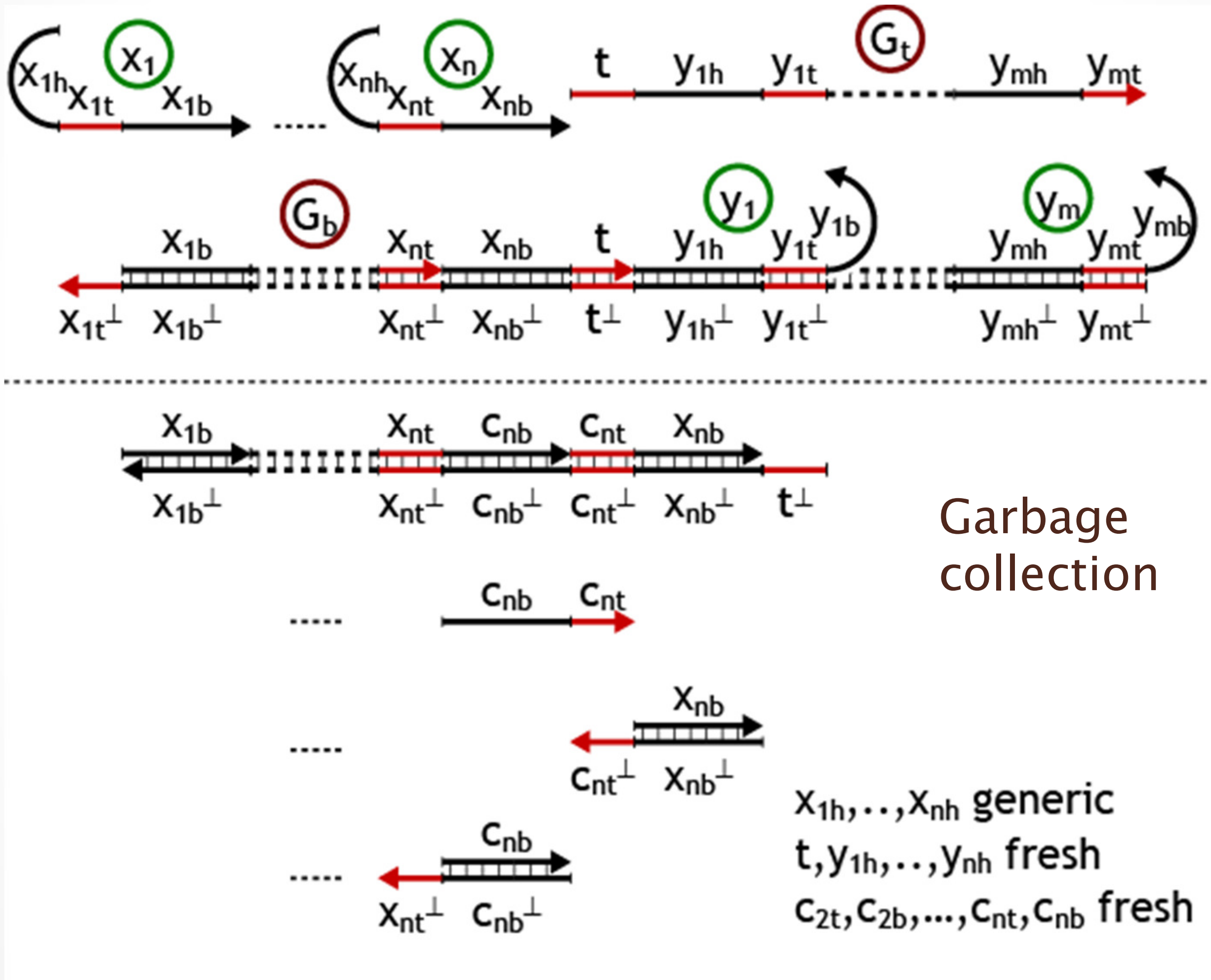
$a^\perp$
$b^\perp$
$z_t^\perp$
x_b
y_t
y_b
a
This is Waste

General n-Join/m-Fork Gate



Gate Design Verification

- Active garbage
  - The active join residuals slow down the performance of following joins.
  - → Add a garbage collector to remove the active residuals.

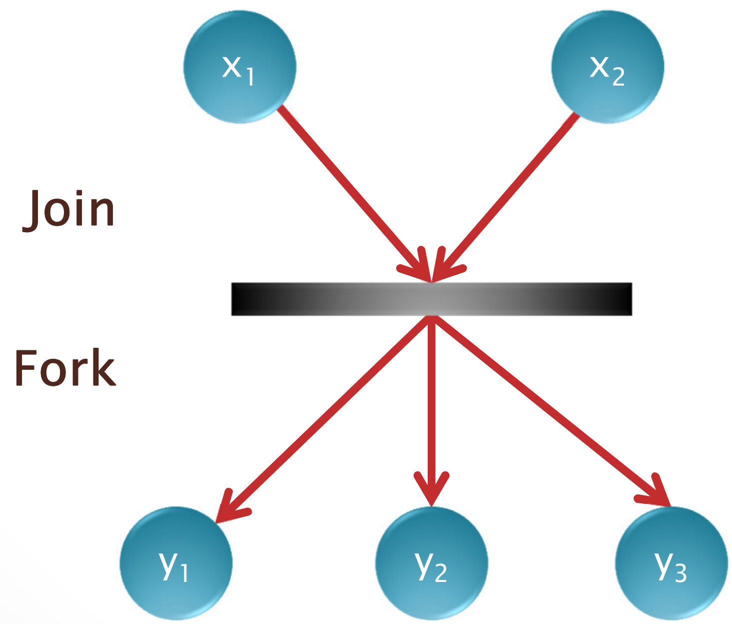
- Interference between gates
  - The join garbage collector interferes with the fork gate.
  - → Modify the fork gate to remove the interference.

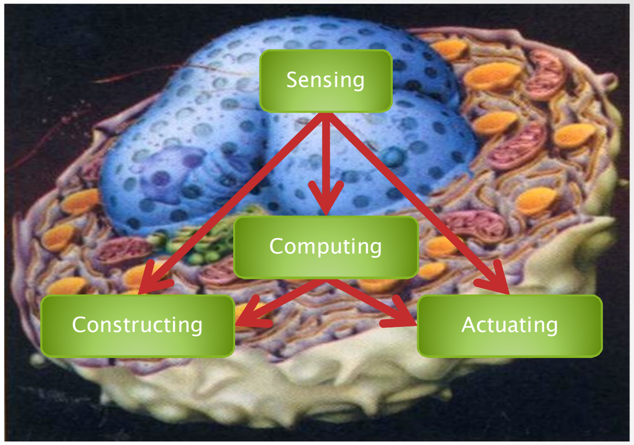
- What else could go wrong?
  - Endless possibilities.
  - → Prove that the fork/join gate structures correctly implement fork/join in all larger circuits.

Strand Algebra

$$x_1 \mid .. \mid x_n \mid [x_1,..,x_n].[y_1,..,y_m] \to y_1 \mid .. \mid y_m$$

- Join + Fork + Populations = (Stochastic) Petri Nets





Curing

...

A Doctor in Each Cell

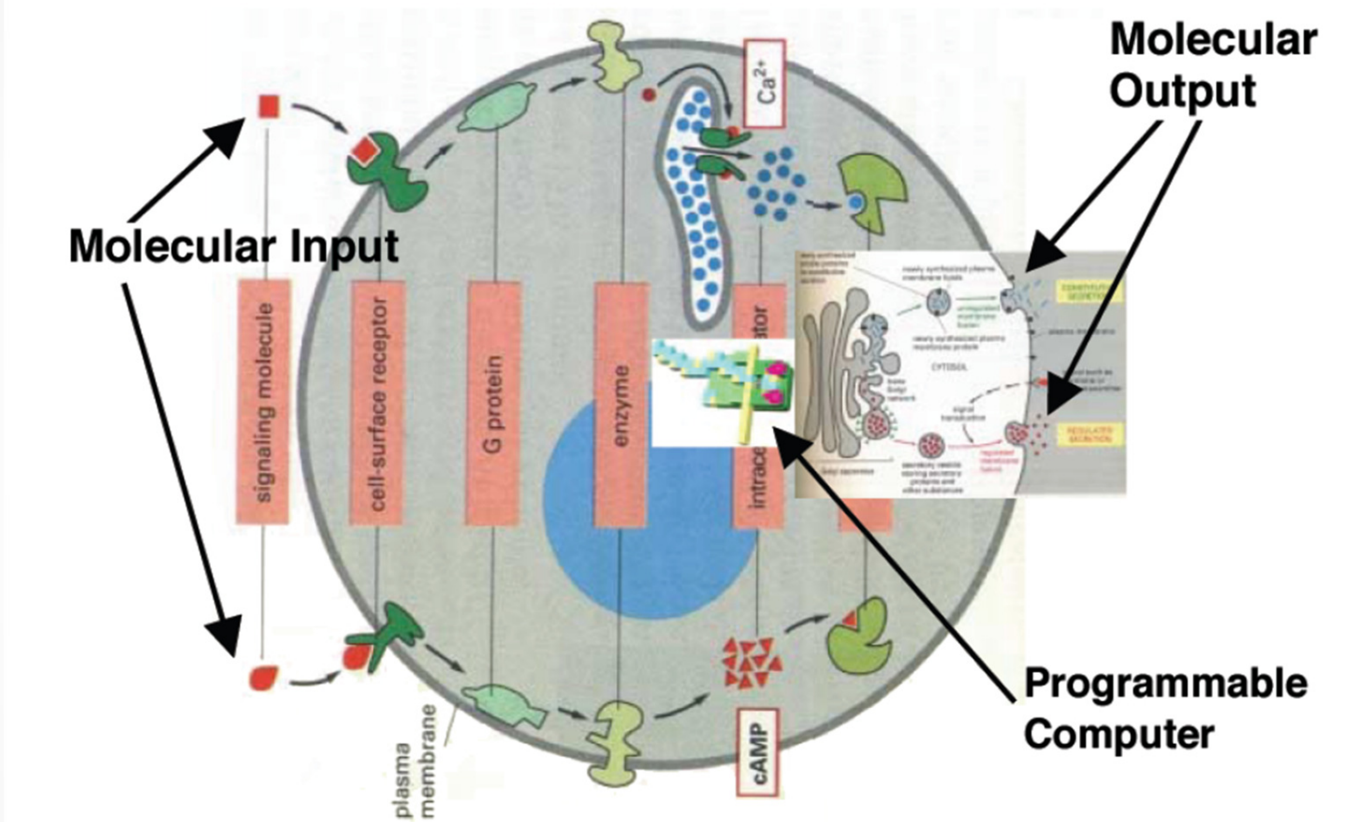


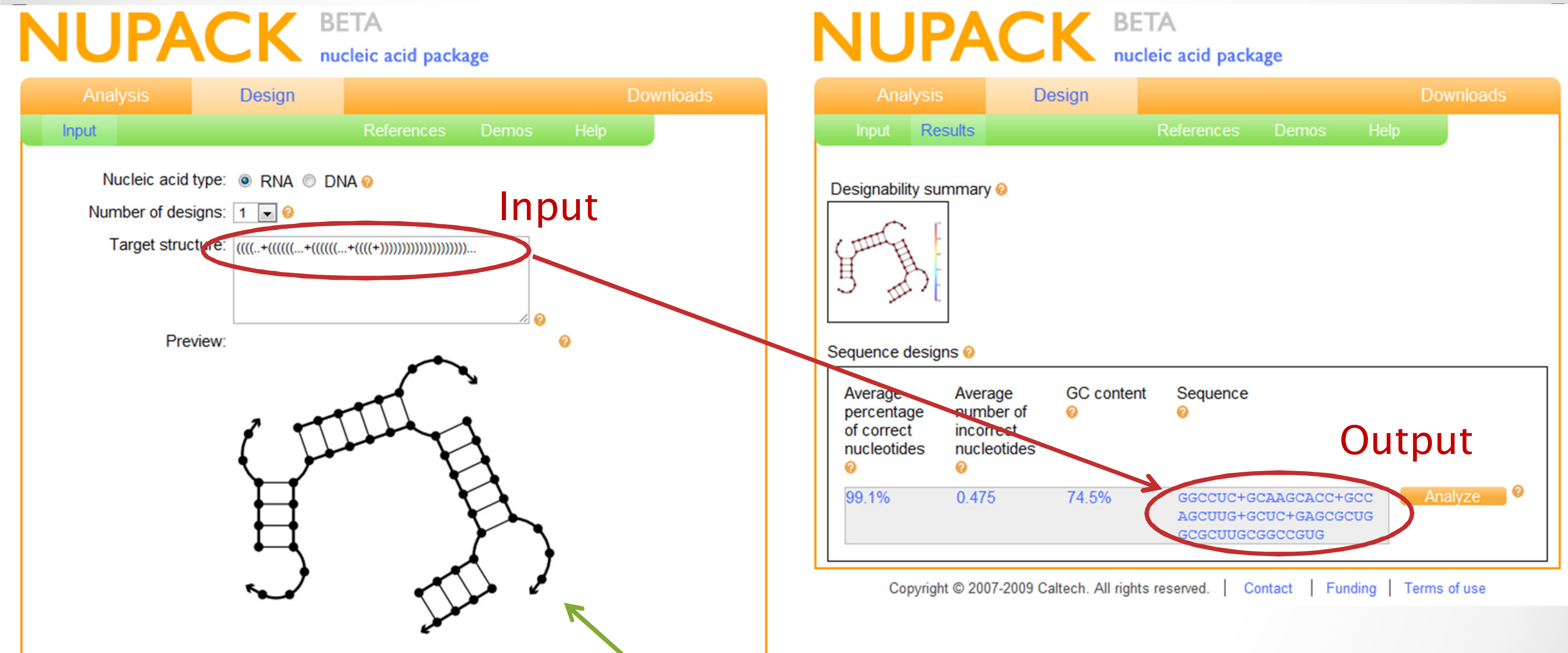
Fig. 1 Medicine in 2050: "Doctor in a Cell"

Ehud Shapiro
Rivka Adar
Kobi Benenson
Gregory Linshitz
Aviv Regev
William Silverman

Molecules and computation

Tools

Sequence Design



So we can in principle work at this level.

Visual DSD
A Strand Displacement Simulator

Matthew Lakin, Simon Youssef, Andrew Phillips

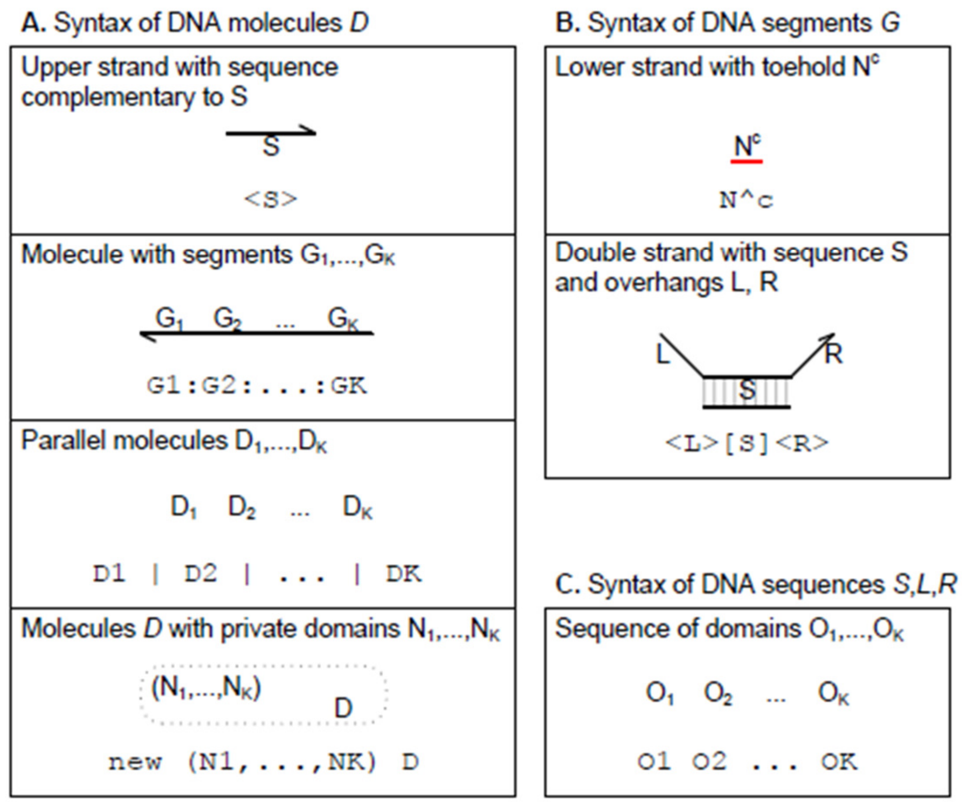
http://lepton.research.microsoft.com/webdna/

Syntax

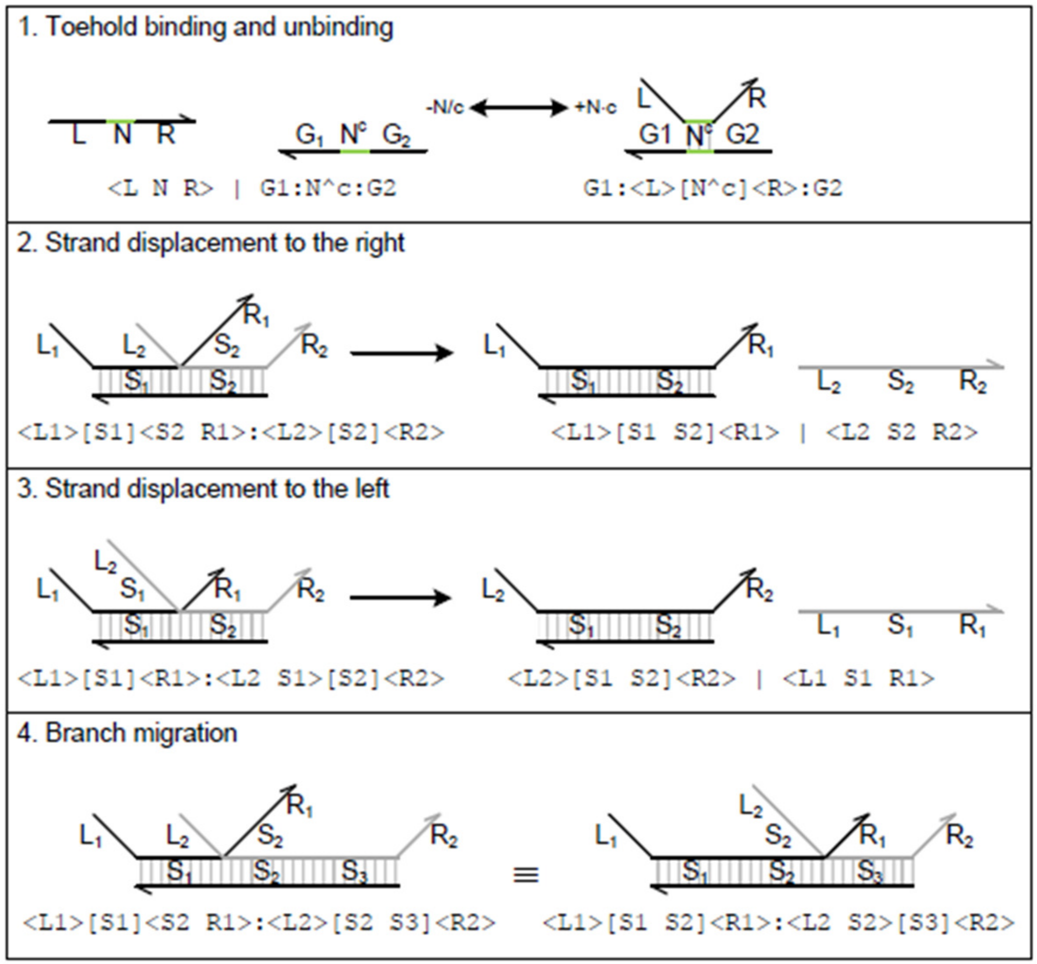
J. R. Soc. Interface
doi:10.1098/rsif.2009.0072.focus
Published online

A programming language for composable DNA circuits

Andrew Phillips* and Luca Cardelli

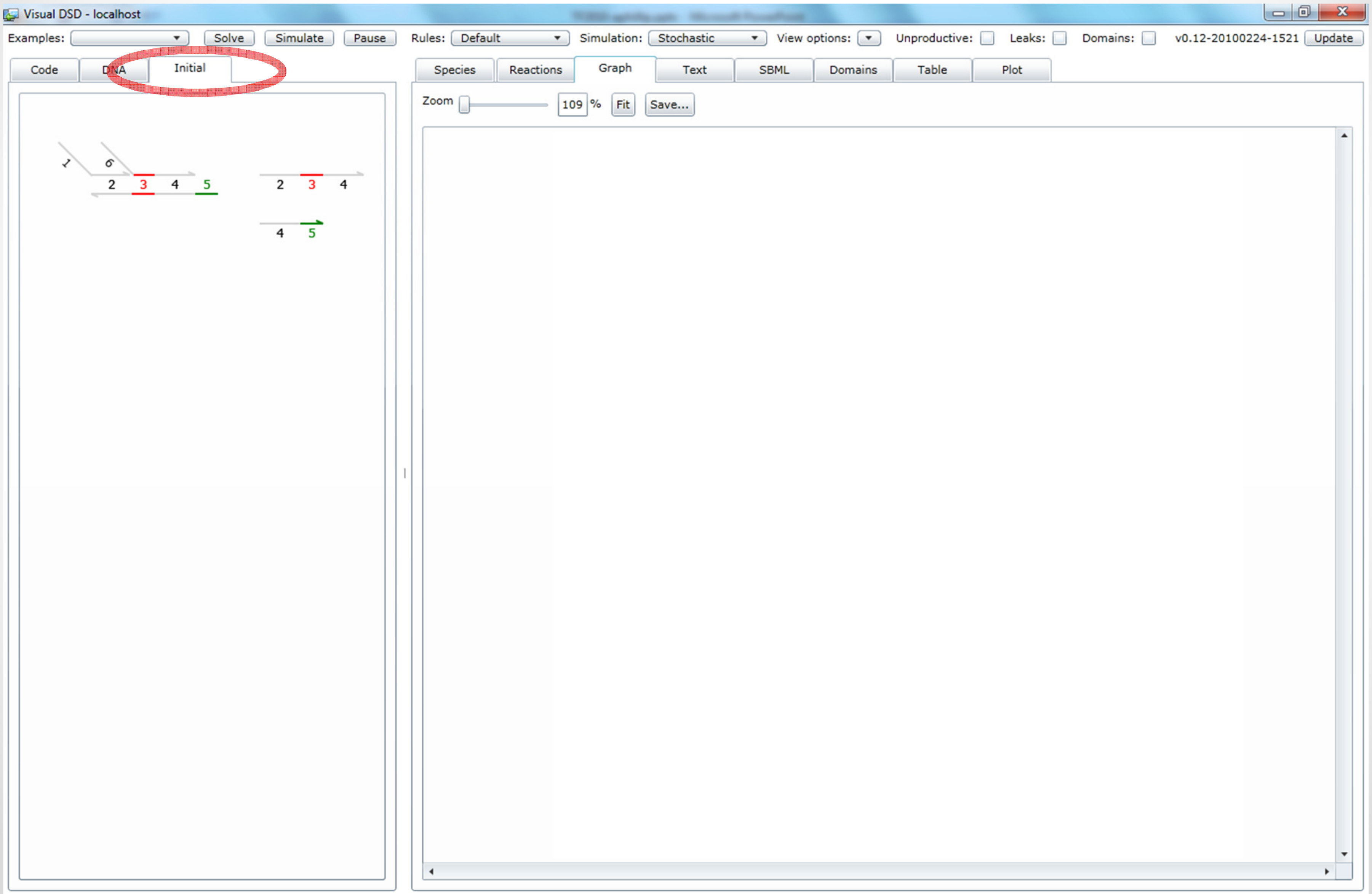


Dynamics

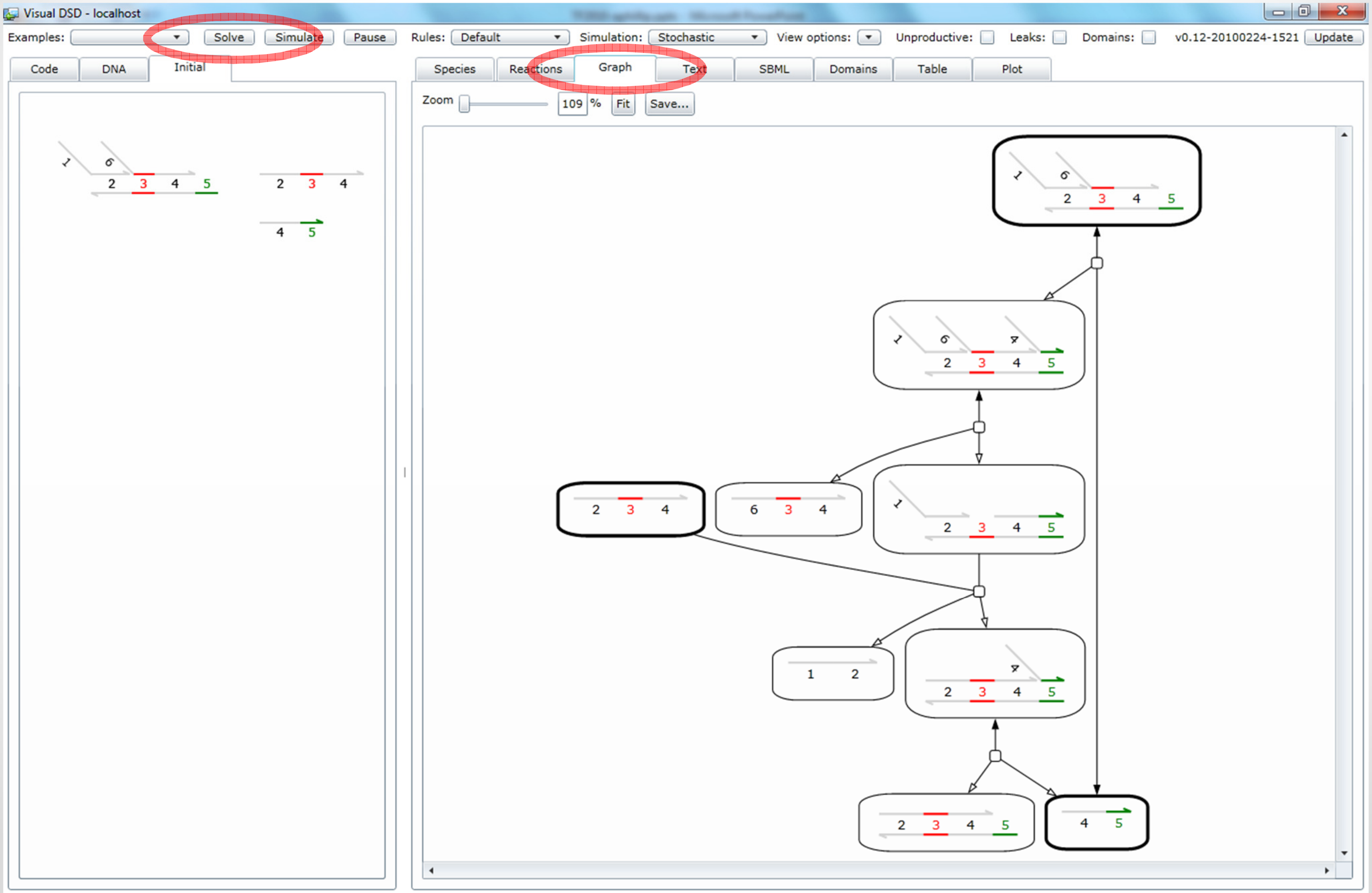


1. Toehold binding and unbinding
L N R
G_1 N^c G_2
-N/c
+N·c
L R
G1 N^c G2
<L N R> | G1:N^c:G2
G1:<L>[N^c]<R>:G2
2. Strand displacement to the right
L_1 L_2 R_1 S_2 R_2 S_1 S_2
L_1 R_1 S_1 S_2
L_2 S_2 R_2
<L1>[S1]<S2 R1>:<L2>[S2]<R2>
<L1>[S1 S2]<R1> | <L2 S2 R2>
3. Strand displacement to the left
L_2 L_1 S_1 R_1 R_2 S_1 S_2
L_2 R_2 S_1 S_2
L_1 S_1 R_1
<L1>[S1]<R1>:<L2 S1>[S2]<R2>
<L2>[S1 S2]<R2> | <L1 S1 R1>
4. Branch migration
L_1 L_2 R_1 S_2 R_2 S_1 S_2 S_3
≡
L_2 L_1 S_2 R_1 R_2 S_1 S_2 S_3
<L1>[S1]<S2 R1>:<L2>[S2 S3]<R2>
<L1>[S1 S2]<R1>:<L2 S2>[S3]<R2>

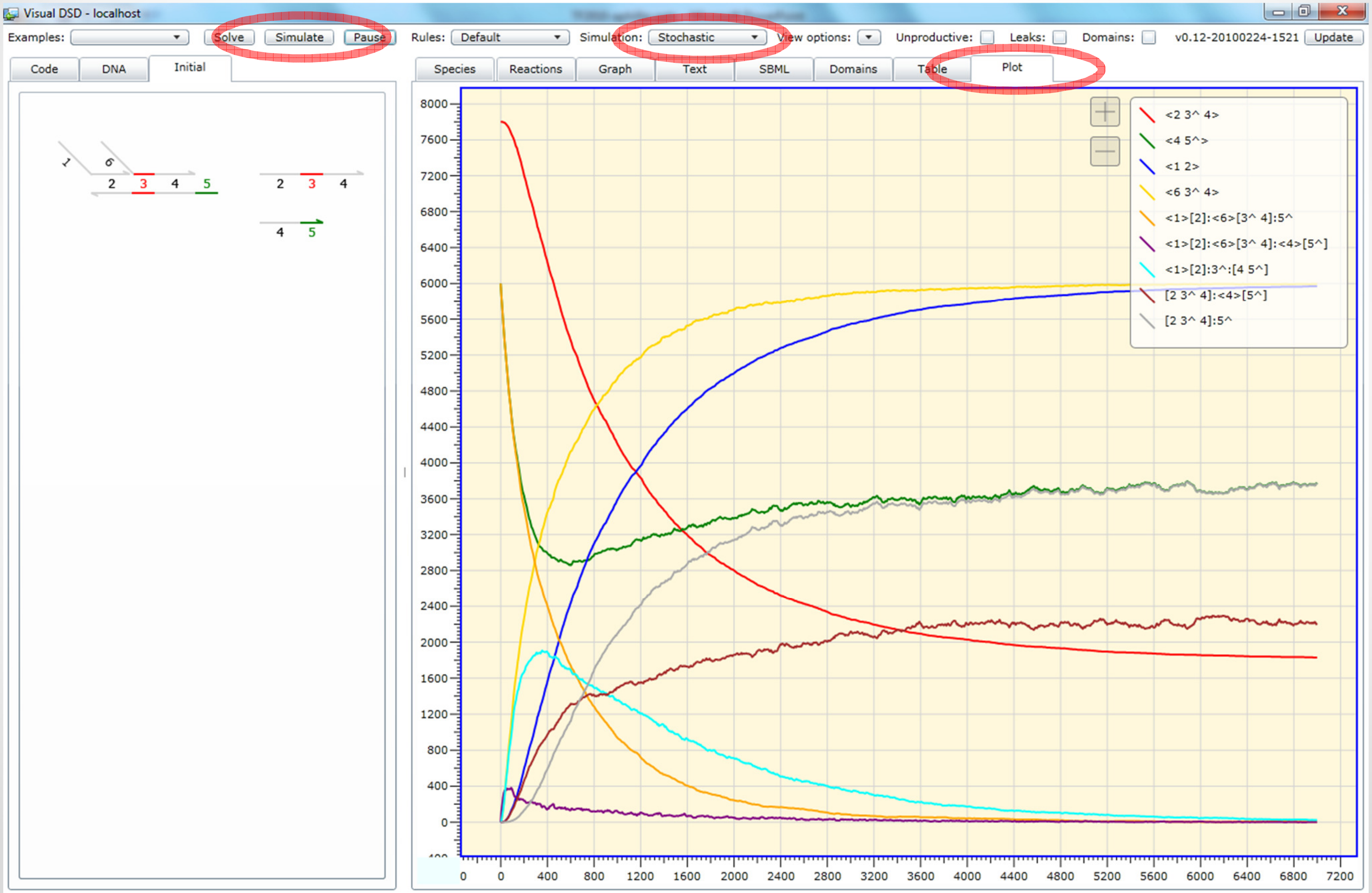
Initial Species



Reaction Graph

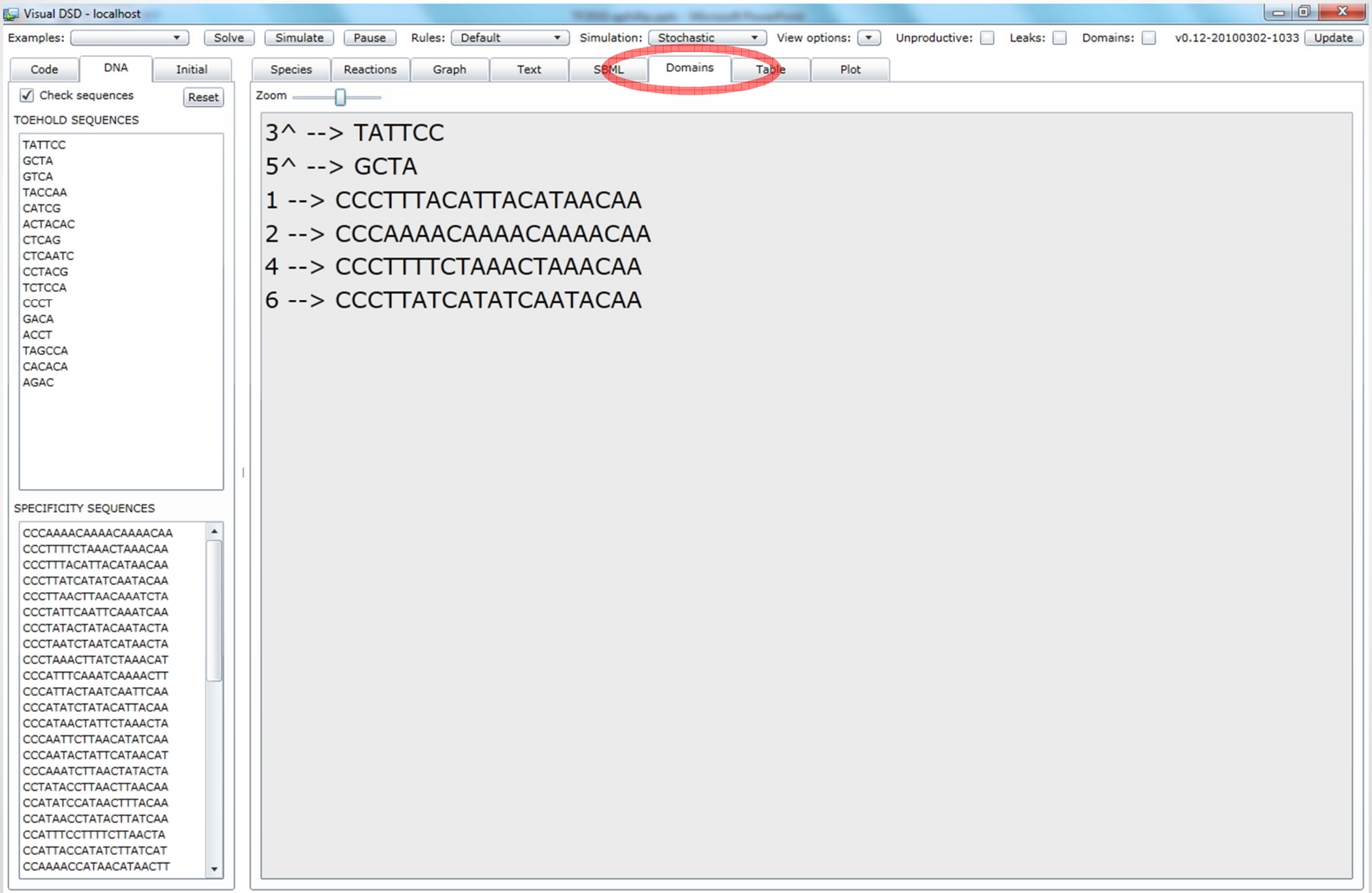


Simulation

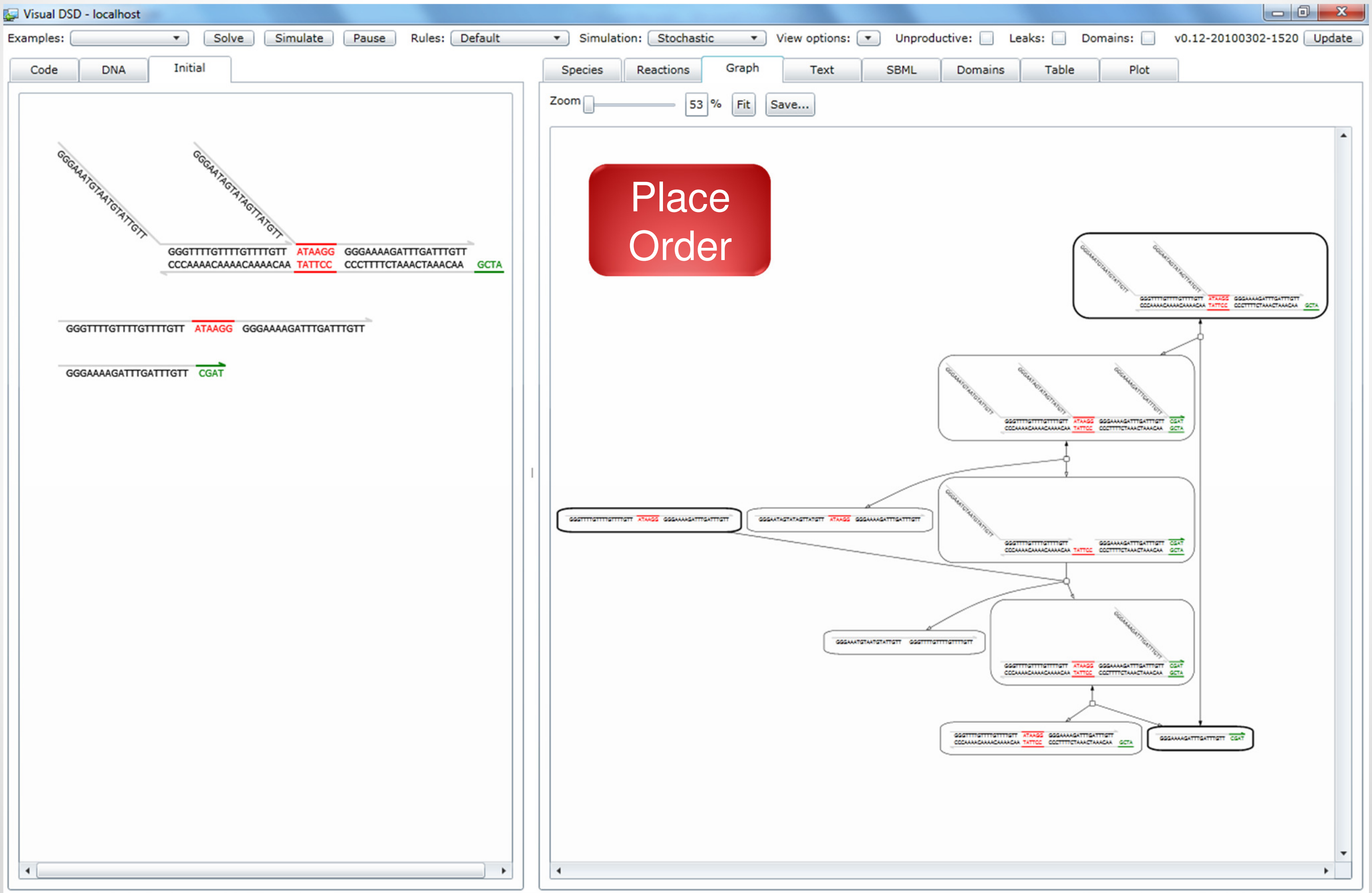


Visual DSD - localhost
Examples:
Solve
Simulate
Pause
Rules:
Default
Simulation:
Stochastic
View options:
Unproductive:
Leaks:
Domains:
v0.12-20100224-1521
Update
Code
DNA
Initial
Species
Reactions
Graph
Text
SBML
Domains
Table
Plot
<2 3^ 4>
<4 5^>
<1 2>
<6 3^ 4>
<1>[2]:<6>[3^ 4]:5^
<1>[2]:<6>[3^ 4]:<4>[5^]
<1>[2]:3^:[4 5^]
[2 3^ 4]:<4>[5^]
[2 3^ 4]:5^

DNA Sequences



Final DNA Circuit

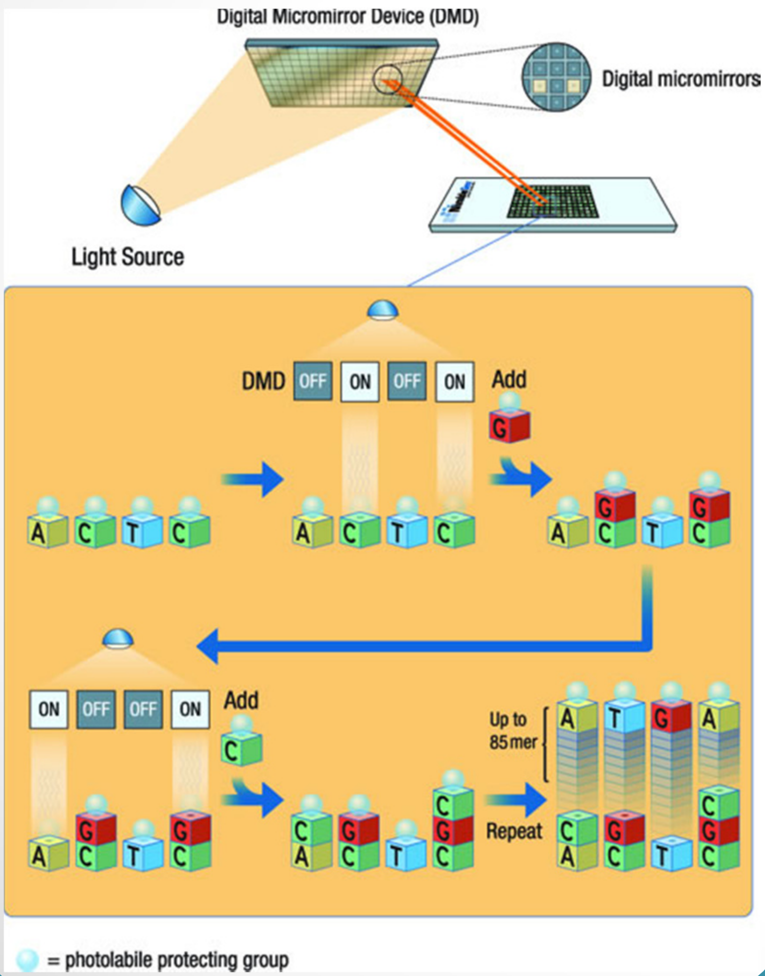


Experiments

How are they Actually Done?

Sequences to DNA

Oligonucleotide Synthesis



Gene Synthesis

- Synthesize gene at $0.39/bp (till 3/31/2010)
- Guaranteed 100% sequence fidelity
- CloneEZ® seamless cloning technology

Struggling with cloning?
Try Gene-on-Demand® Service!

Fastest tunaround time for less money!

Standard gene synthesis from 0.36 €/bp in just 8 days

Your Chance to Win a Nintendo Wii

Find Out G-Reward
Earn rewards for every purchase!

SameDay® Oligo Service

Only £0.57 GBP / Base!

Base Pricing		
Synthesis Scale	Price	
25 nmole DNA Oligo	£0.25 GBP / Base	Order
100 nmole DNA oligo	£0.45 GBP / Base	Order
250 nmole DNA oligo	£0.80 GBP / Base	Order
1 µmole DNA oligo	£1.60 GBP / Base	Order
5 µmole DNA oligo	£7.50 GBP / Base	Order
10 µmole DNA oligo	£14.50 GBP / Base	Order

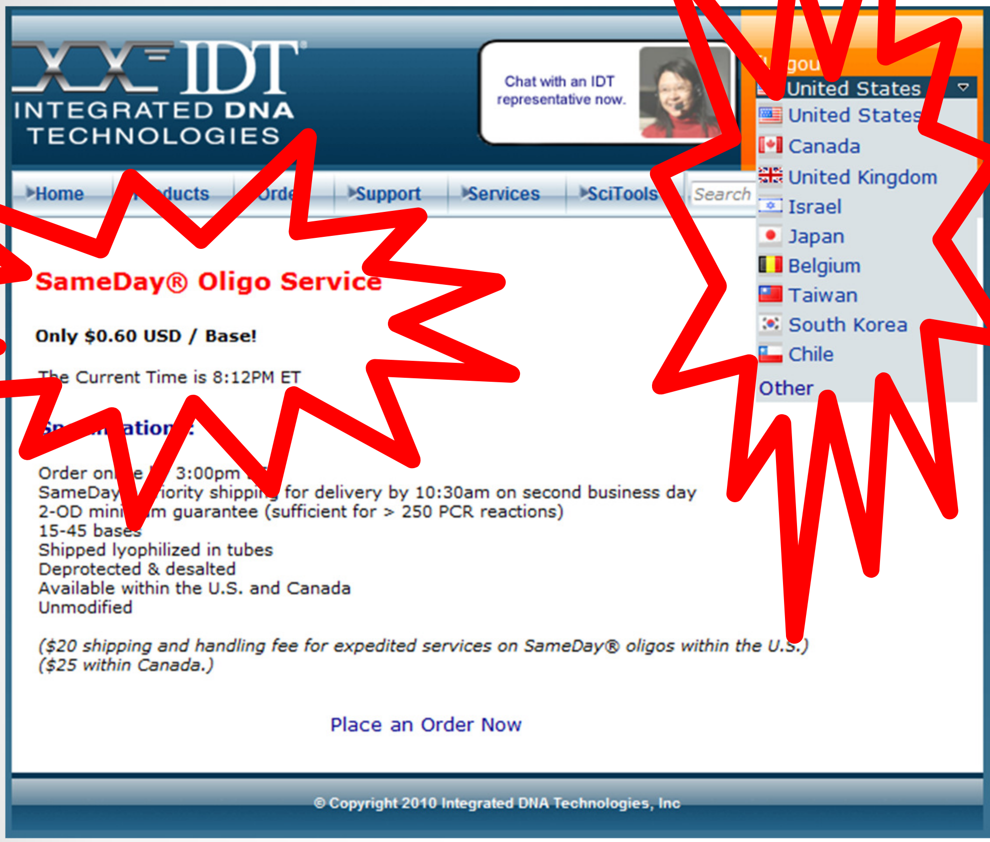
Custom DNA/RNA
Pricing (USD)

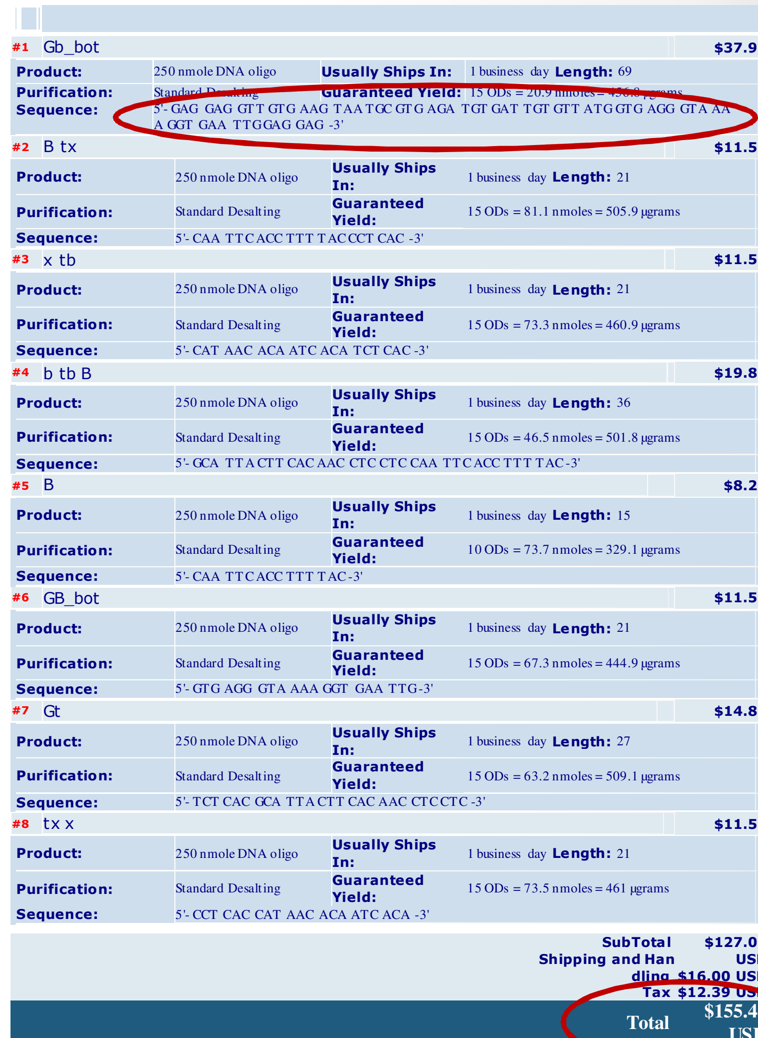
DNA(mg)	Desalted	Purified
15	$700	$1,050
50	$1,200	$1,450
100	$1,500	$1,800
250	$2,000	$2,400
500	$2,900	$3,400
1000	$4,550	$5,400
5000	$9,000	$10,700

RNA(mg)	Desalted	Purified
5	$1,500	$1,925
15	$1,950	$2,490
50	$2,050	$2,625
100	$2,575	$3,575
250	$4,575	$5,725
500	$7,900	$9,190
1000	$13,900	$15,900
5000		$37,125

Please inquire for larger quantities

Next-Day Oligos!





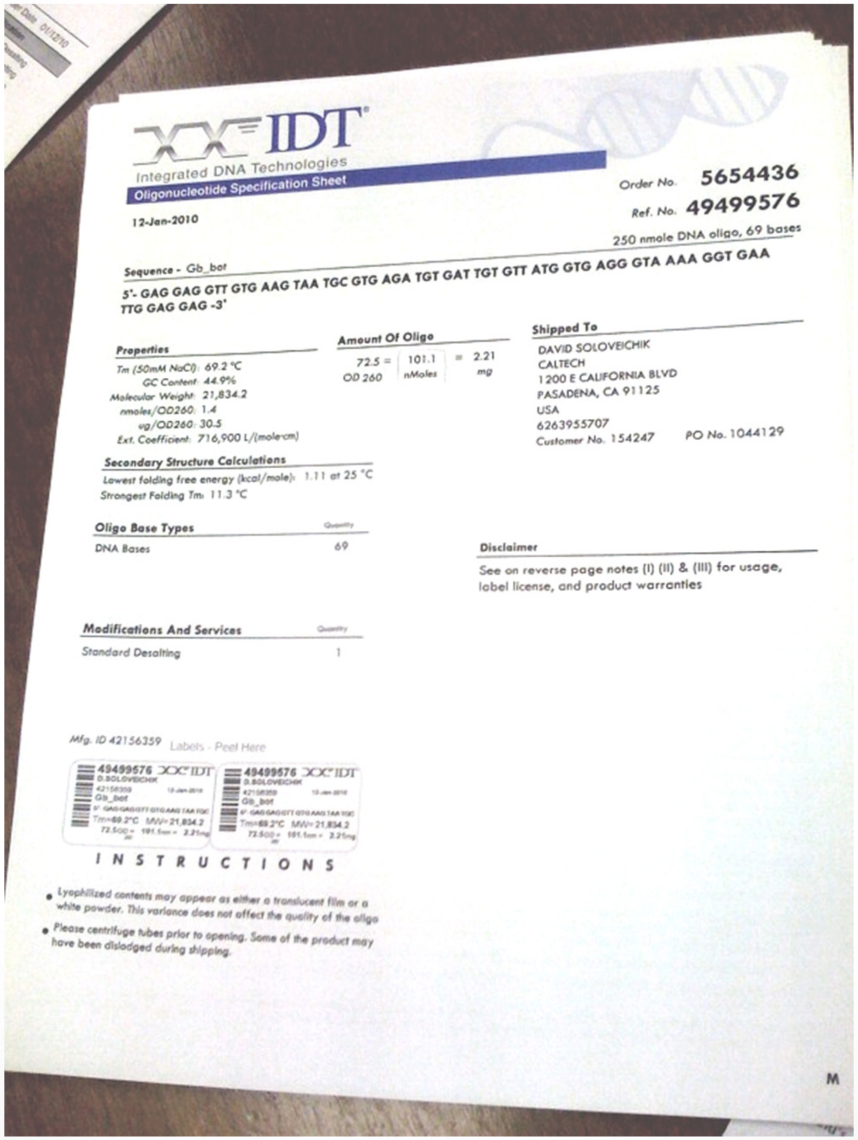
#1 Gb_bot				$37.95
Product:	250 nmole DNA oligo	Usually Ships In:	1 business day **Length:** 69	
Purification:	Standard Desalting	Guaranteed Yield:	15 ODs = 20.9 nmoles = 456.8 µgrams	
Sequence:	5'- GAG GAG GTT GTG AAG TAA TGC GTG AGA TGT GAT TGT GTT ATG GTG AGG GTA AA A GGT GAA TTG GAG GAG -3'			
#2 B tx				$11.55
Product:	250 nmole DNA oligo	Usually Ships In:	1 business day **Length:** 21	
Purification:	Standard Desalting	Guaranteed Yield:	15 ODs = 81.1 nmoles = 505.9 µgrams	
Sequence:	5'- CAA TTC ACC TTT TAC CCT CAC -3'			
#3 x tb				$11.55
Product:	250 nmole DNA oligo	Usually Ships In:	1 business day **Length:** 21	
Purification:	Standard Desalting	Guaranteed Yield:	15 ODs = 73.3 nmoles = 460.9 µgrams	
Sequence:	5'- CAT AAC ACA ATC ACA TCT CAC -3'			
#4 b tb B				$19.80
Product:	250 nmole DNA oligo	Usually Ships In:	1 business day **Length:** 36	
Purification:	Standard Desalting	Guaranteed Yield:	15 ODs = 46.5 nmoles = 501.8 µgrams	
Sequence:	5'- GCA TTA CTT CAC AAC CTC CTC CAA TTC ACC TTT TAC -3'			
#5 B				$8.25
Product:	250 nmole DNA oligo	Usually Ships In:	1 business day **Length:** 15	
Purification:	Standard Desalting	Guaranteed Yield:	10 ODs = 73.7 nmoles = 329.1 µgrams	
Sequence:	5'- CAA TTC ACC TTT TAC -3'			
#6 GB_bot				$11.55
Product:	250 nmole DNA oligo	Usually Ships In:	1 business day **Length:** 21	
Purification:	Standard Desalting	Guaranteed Yield:	15 ODs = 67.3 nmoles = 444.9 µgrams	
Sequence:	5'- GTG AGG GTA AAA GGT GAA TTG -3'			
#7 Gt				$14.85
Product:	250 nmole DNA oligo	Usually Ships In:	1 business day **Length:** 27	
Purification:	Standard Desalting	Guaranteed Yield:	15 ODs = 63.2 nmoles = 509.1 µgrams	
Sequence:	5'- TCT CAC GCA TTA CTT CAC AAC CTC CTC -3'			
#8 tx x				$11.55
Product:	250 nmole DNA oligo	Usually Ships In:	1 business day **Length:** 21	
Purification:	Standard Desalting	Guaranteed Yield:	15 ODs = 73.5 nmoles = 461 µgrams	
Sequence:	5'- CCT CAC CAT AAC ACA ATC ACA -3'			
			SubTotal	$127.05 USD
			Shipping and Handling	$16.00 USD
			Tax	$12.39 USD
			Total	$155.44 USD

Wait 24 Hours

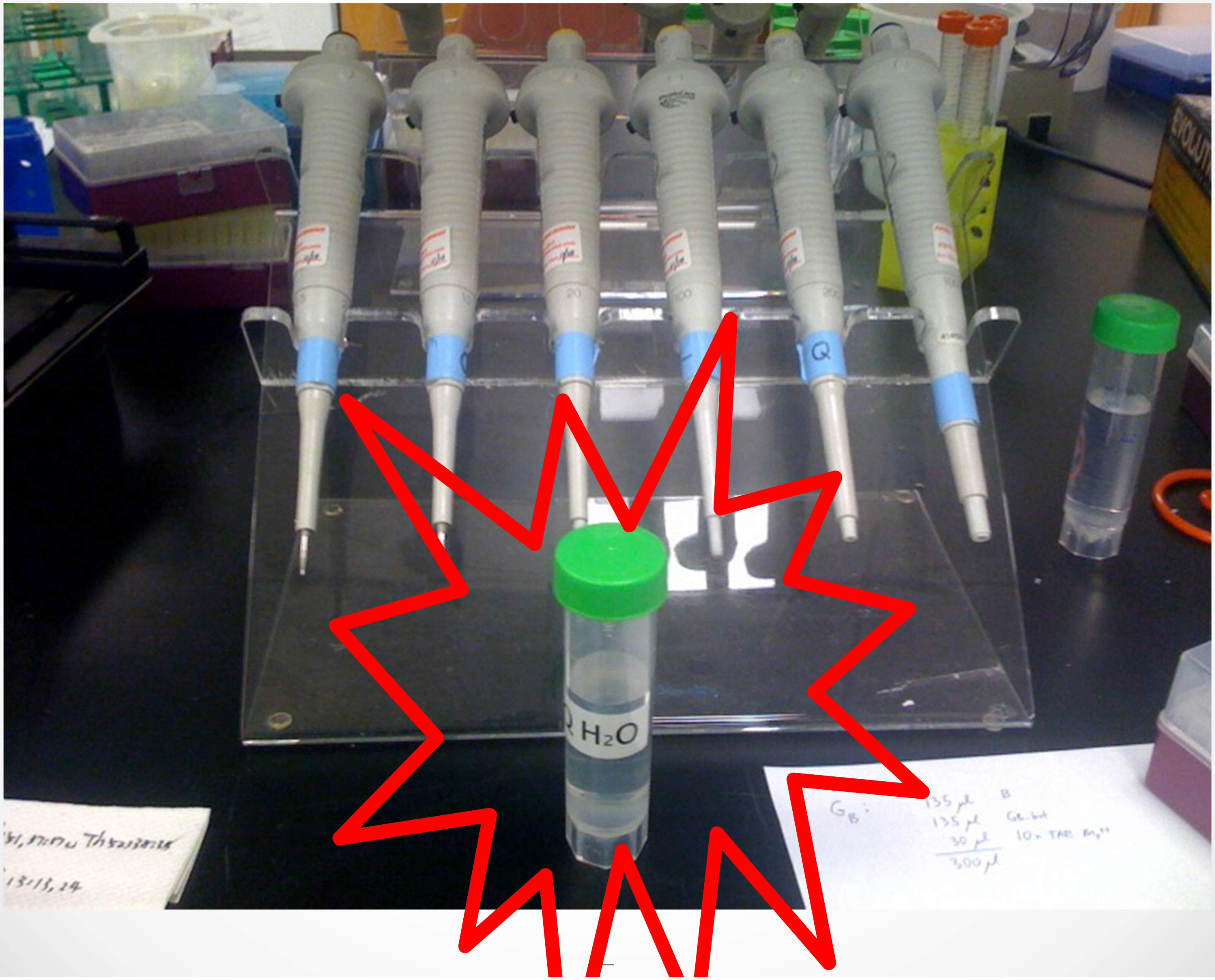
DNA by Mail


IDT
INTEGRATED DNA
TECHNOLOGIES, INC.
Custom
Oligonucleotide
Synthesis
Innovation and
Precision in
Nucleic Acid
Synthesis

Spec Sheet

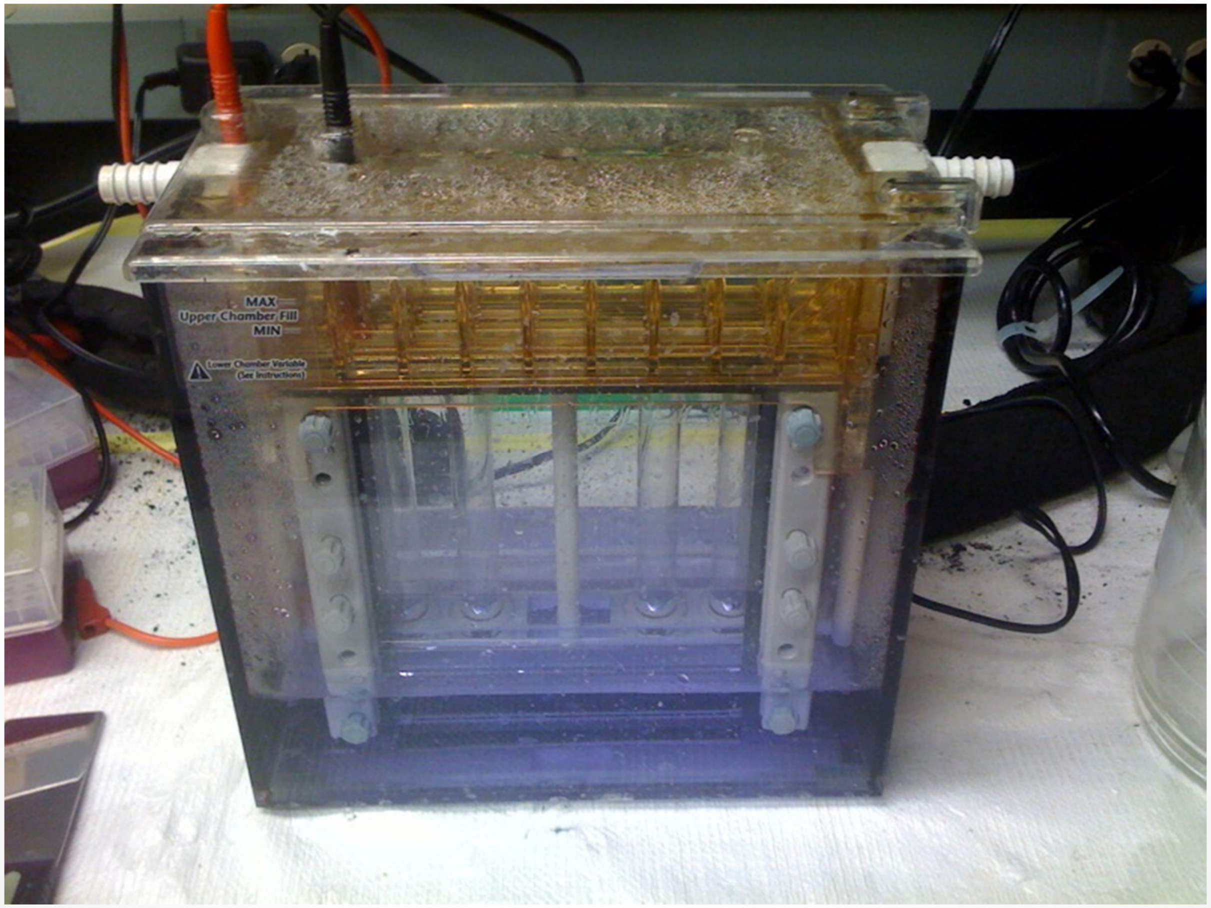

IDT
Integrated DNA Technologies
Oligonucleotide Specification Sheet
12-Jan-2010
Order No. 5654436
Ref. No. 49499576
250 nmole DNA oligo, 69 bases
Sequence - Gb_bot
5'- GAG GAG GTT GTG AAG TAA TGC GTG AGA TGT GAT TGT GTT ATG GTG AGG GTA AAA GGT GAA TTG GAG GAG -3'
Properties
Tm (50mM NaCl): 69.2 °C
GC Content: 44.9%
Molecular Weight: 21,834.2
nmoles/OD260: 1.4
ug/OD260: 30.5
Ext. Coefficient: 716,900 L/(mole·cm)
Amount Of Oligo
72.5 = 101.1 = 2.21
OD 260 nMoles mg
Shipped To
DAVID SOLOVEICHIK
CALTECH
1200 E CALIFORNIA BLVD
PASADENA, CA 91125
USA
6263955707
Customer No. 154247
PO No. 1044129
Secondary Structure Calculations
Lowest folding free energy (kcal/mole): 1.11 at 25 °C
Strongest Folding Tm: 11.3 °C
Oligo Base Types
DNA Bases 69
Disclaimer
See on reverse page notes (I) (II) & (III) for usage, label license, and product warranties
Modifications And Services
Standard Desalting 1
Mfg. ID 42156359 Labels - Peel Here
INSTRUCTIONS
Lyophilized contents may appear as either a translucent film or a white powder. This variance does not affect the quality of the oligo
Please centrifuge tubes prior to opening. Some of the product may have been dislodged during shipping.
M

Add Water



Put DNA into Gel

- Polyacrylamide gel electrophoresis (PAGE)
- Sorts DNA strands by length

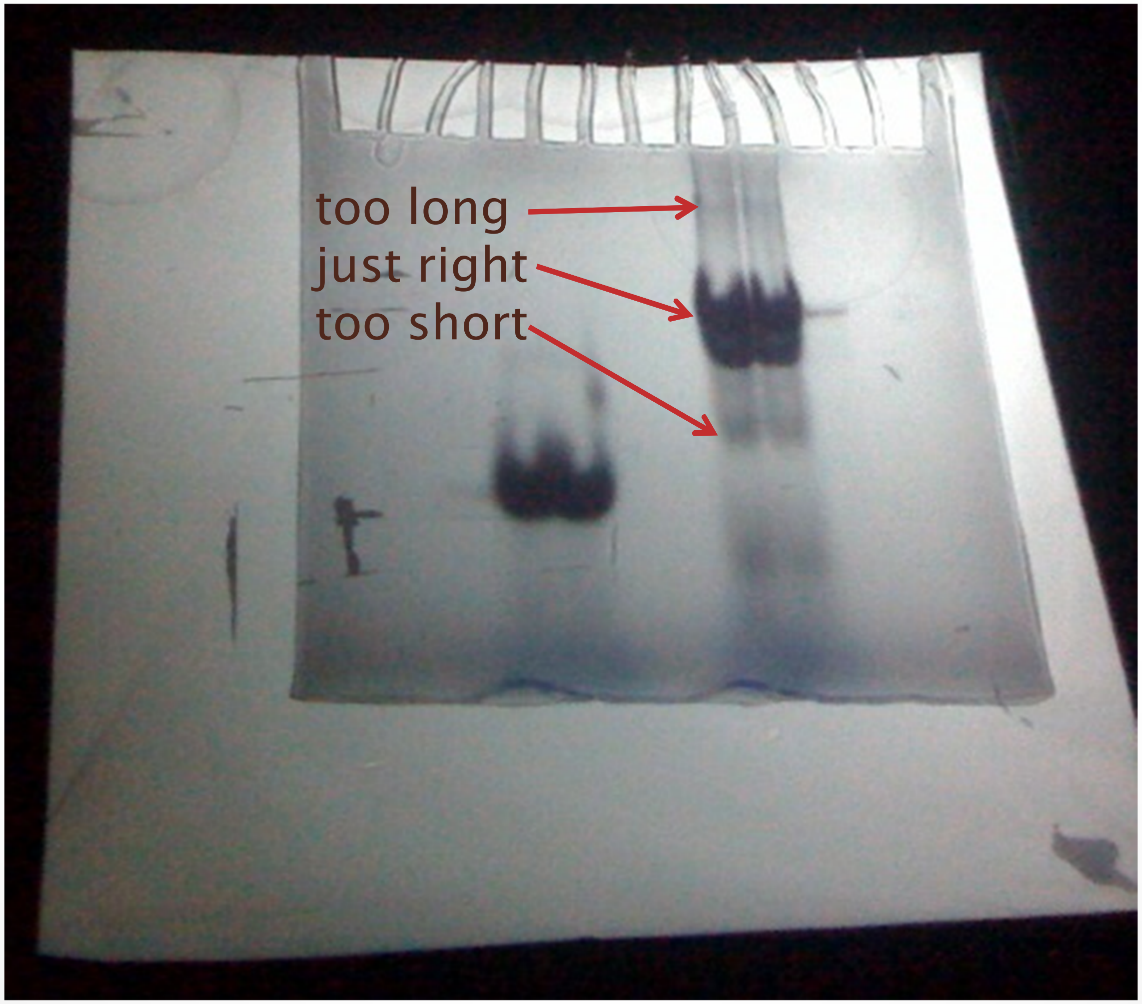


Wait 6 Hours

• • •

Get DNA out of Gel

- Find DNA with ultraviolet light. Cut it out.



Wait 12 Hours

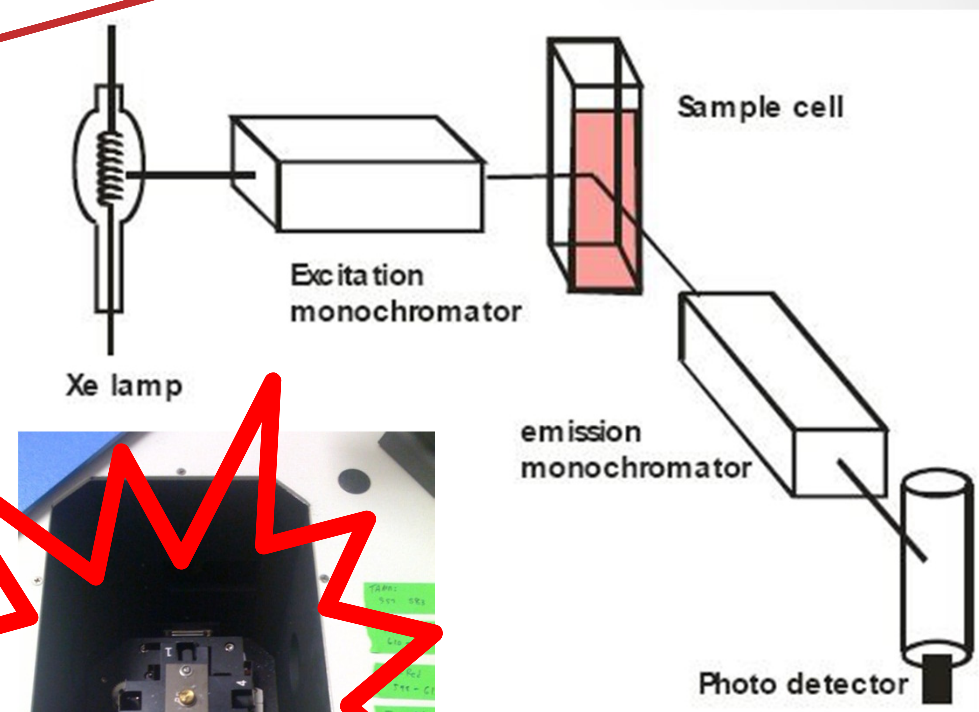
…

Mix DNA Up

- Screaming for robotic automation

Spectrofluorometer

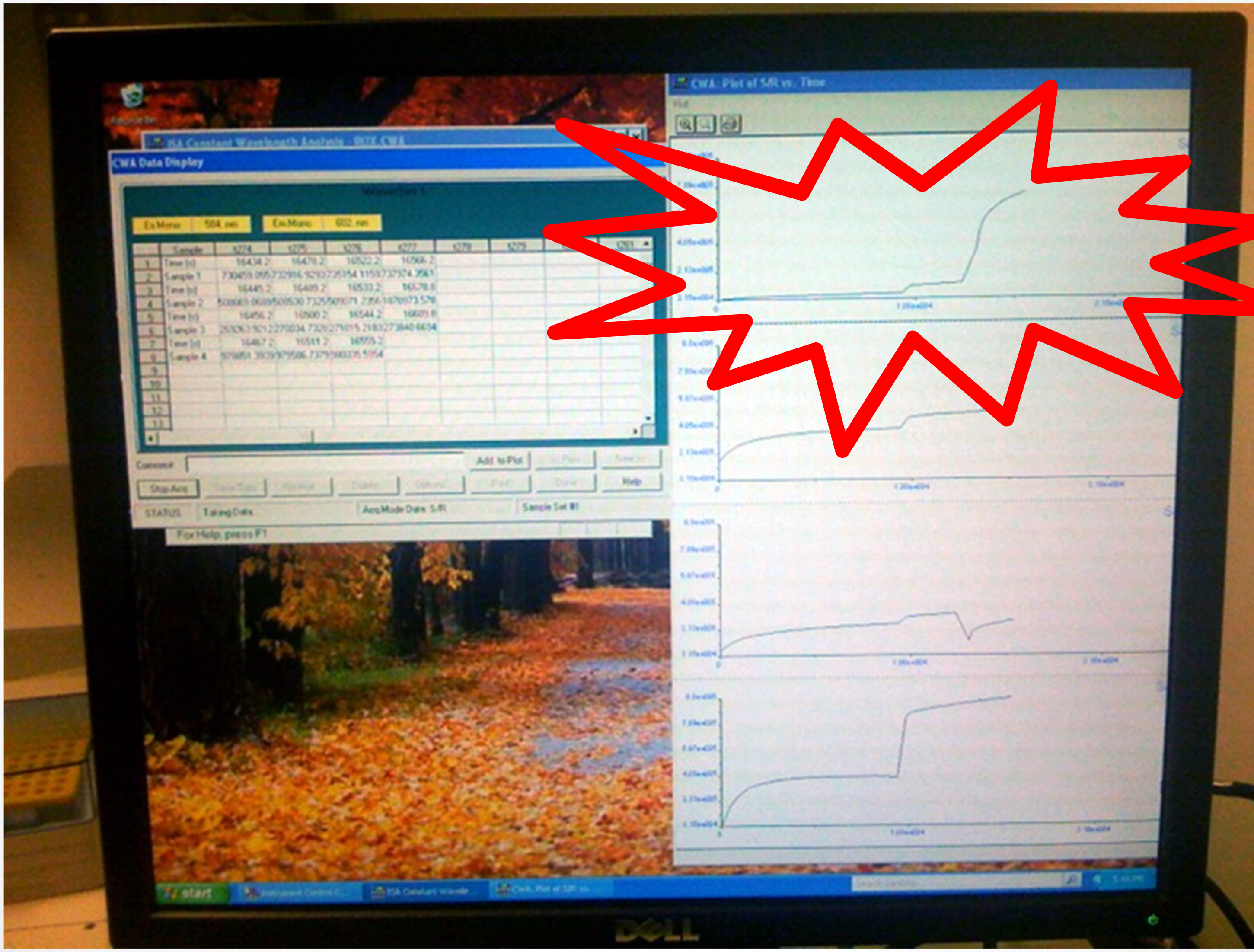
- Fluorescence is your ‘print’ statement



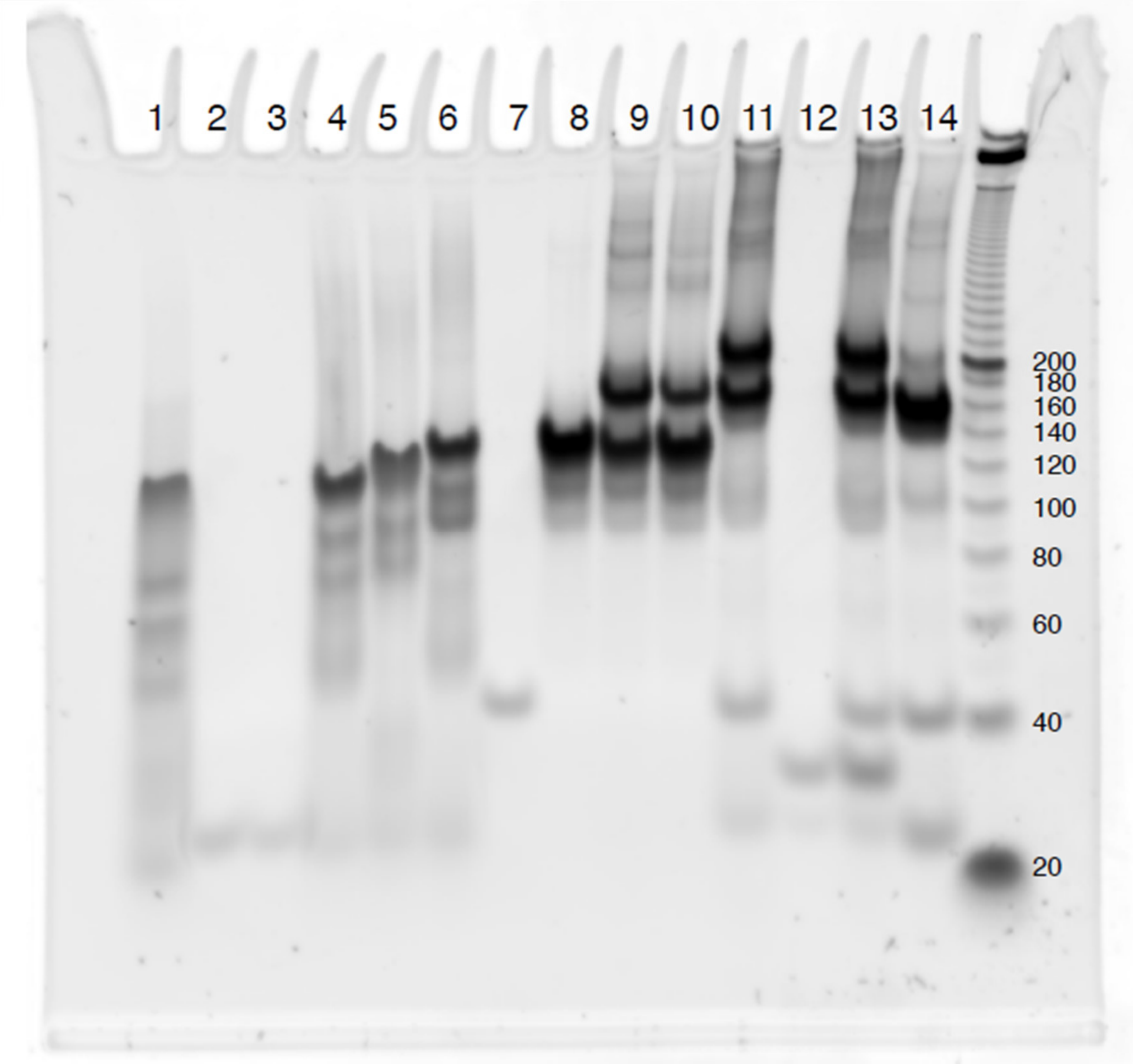
Go To Lunch

• • •

Execution Trace



Core Dump



RINSE

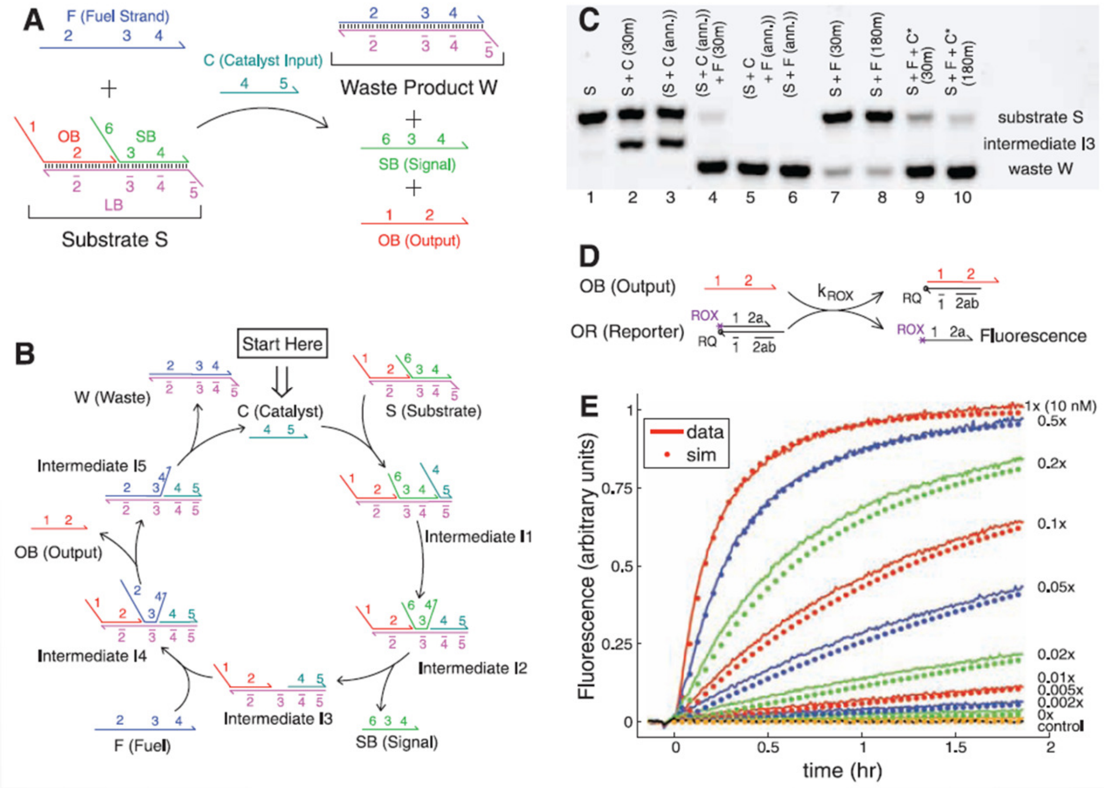
&

Repeat

• • •

Publish!

Engineering Entropy-Driven Reactions and Networks Catalyzed by DNA
David Yu Zhang, *et al.*
Science **318**, 1121 (2007);
DOI: 10.1126/science.1148532

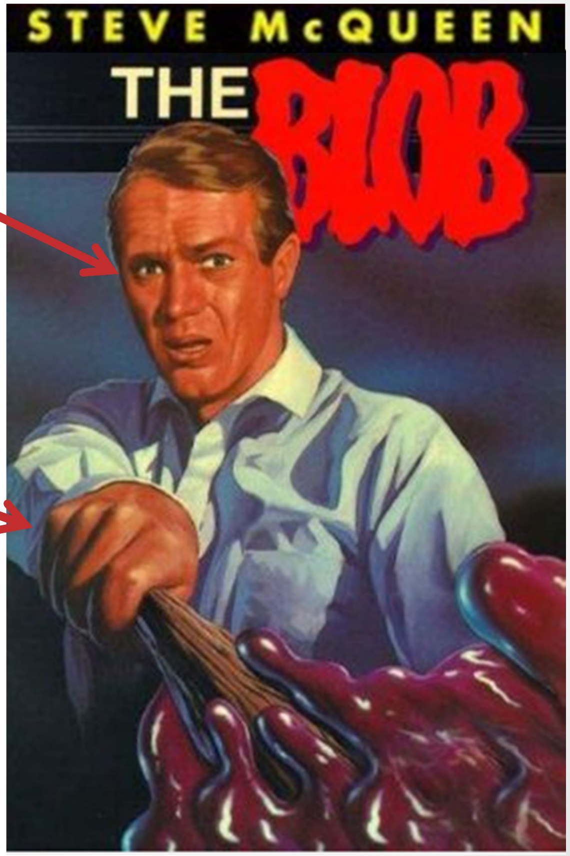


Health and Safety

- Don't try this at home
  - (Although you could)
- Latex gloves, UV glasses
  - Fear the Gel (acrylamide)
  - Fear the Light (UV)
- Otherwise safe
  - No smells
  - No fires
  - No biohazards
  - No life forms
- Most complex machines:
  - Gel machine
  - Fluorometer
  - Atomic force microscope
- Most dangerous activity:
  - Replacing the light bulb in the fluorometer (hot; may explode)

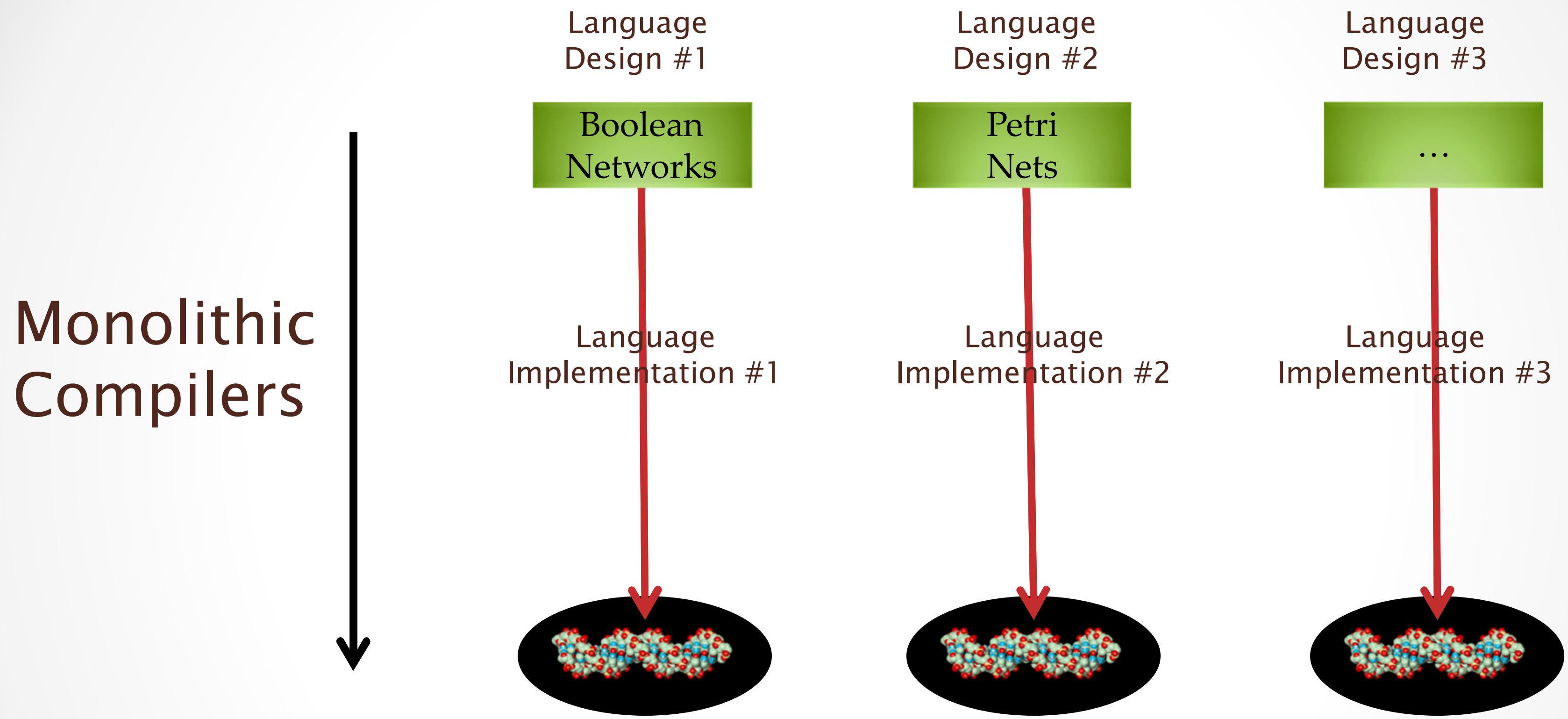
Not wearing glasses

Not wearing gloves



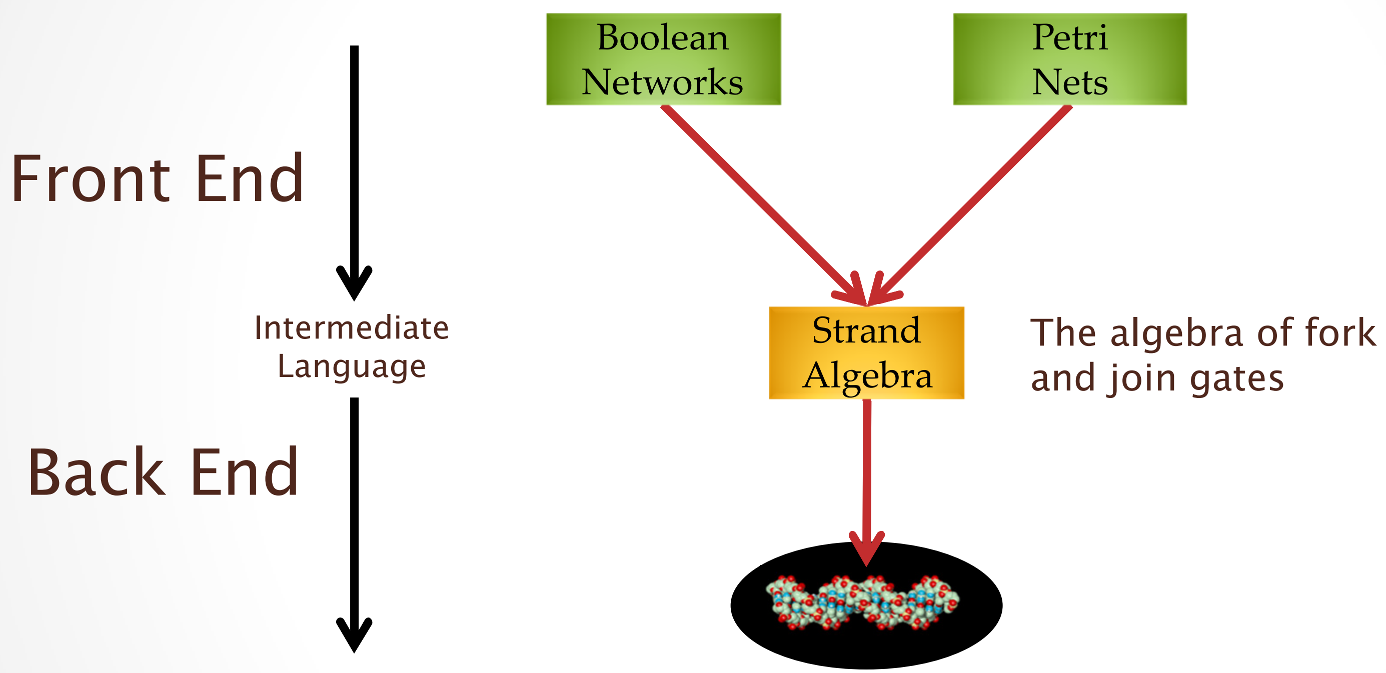
DNA Compilation

Compilers

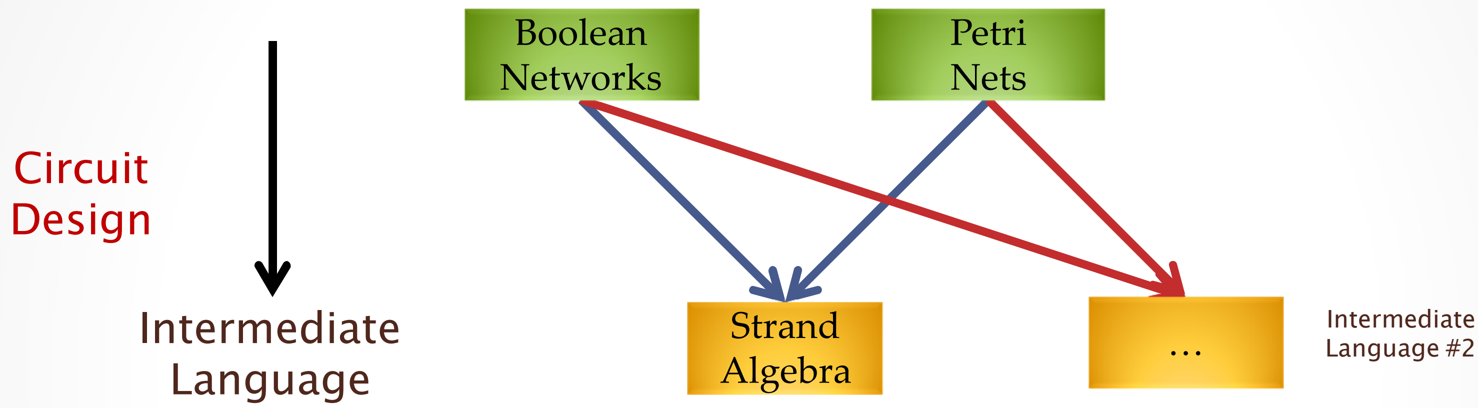


Monolithic Compilers
Language Design #1
Language Design #2
Language Design #3
Boolean Networks
Petri Nets
...
Language Implementation #1
Language Implementation #2
Language Implementation #3

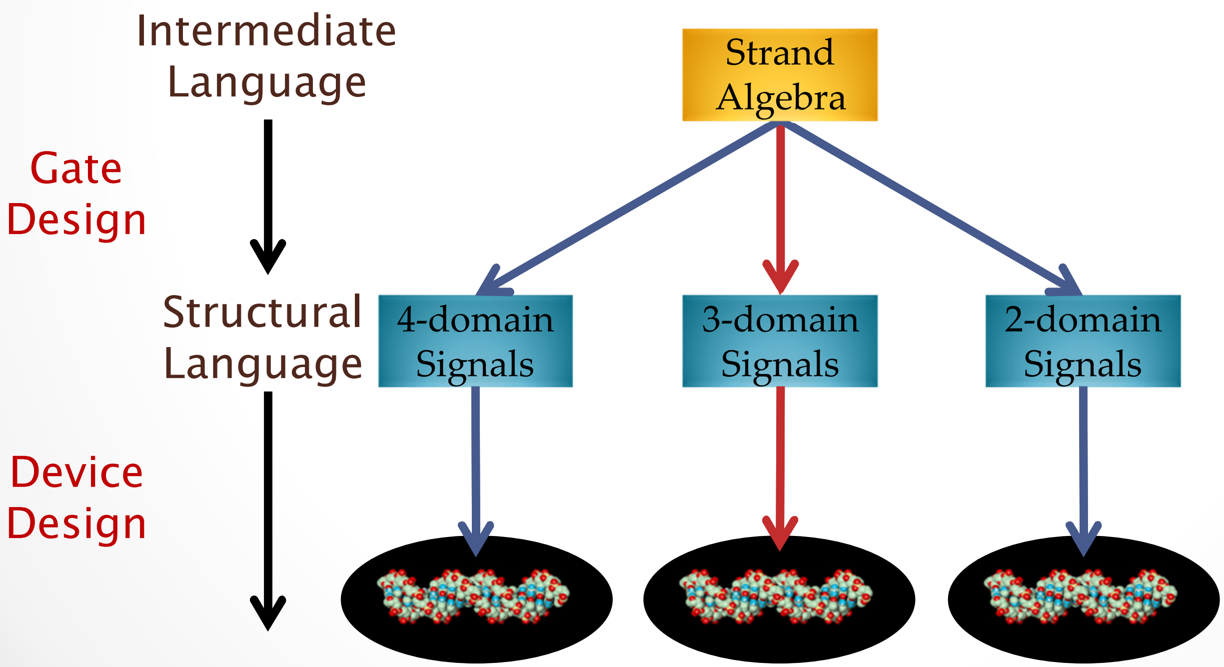
Intermediate Languages



Front Ends


Circuit
Design
Intermediate
Language
Boolean
Networks
Petri
Nets
Strand
Algebra
...
Intermediate
Language #2

Back Ends

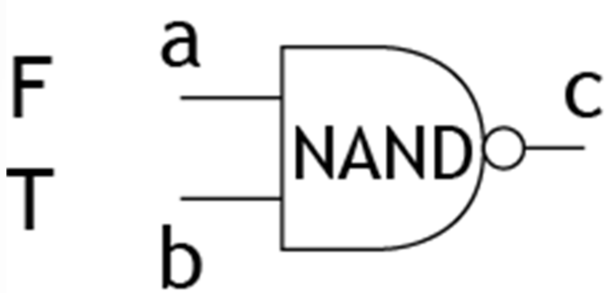

Intermediate Language
Gate Design
Structural Language
Device Design
Strand Algebra
4-domain Signals
3-domain Signals
2-domain Signals

Compiling Abstract Machines

• • •

Boolean Networks

Boolean Networks to Strand Algebra



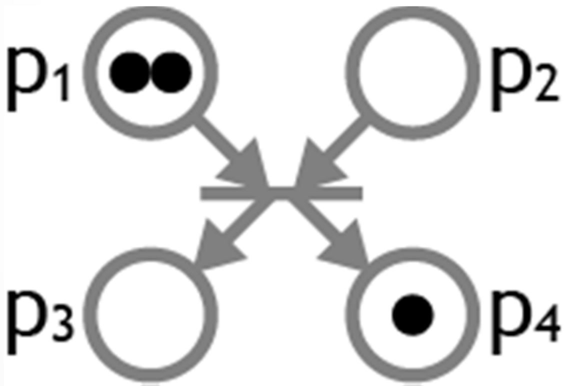
$$([a_F, b_F].c_T)^* \mid$$
$$([a_F, b_T].c_T)^* \mid$$
$$([a_T, b_F].c_T)^* \mid$$
$$([a_T, b_T].c_F)^* \mid$$
$$a_F \mid b_T$$

This encoding is *compositional*, and can encode *any* Boolean network:
- multi-stage networks can be assembled (combinatorial logic)
- network loops are allowed (sequential logic)

Petri Nets

Petri Nets to Strand Algebra

Transitions as Gates
Place markings as Signals



$$([p_1,p_2].[p_3,p_4])^* \mid p_1 \mid p_1 \mid p_4$$

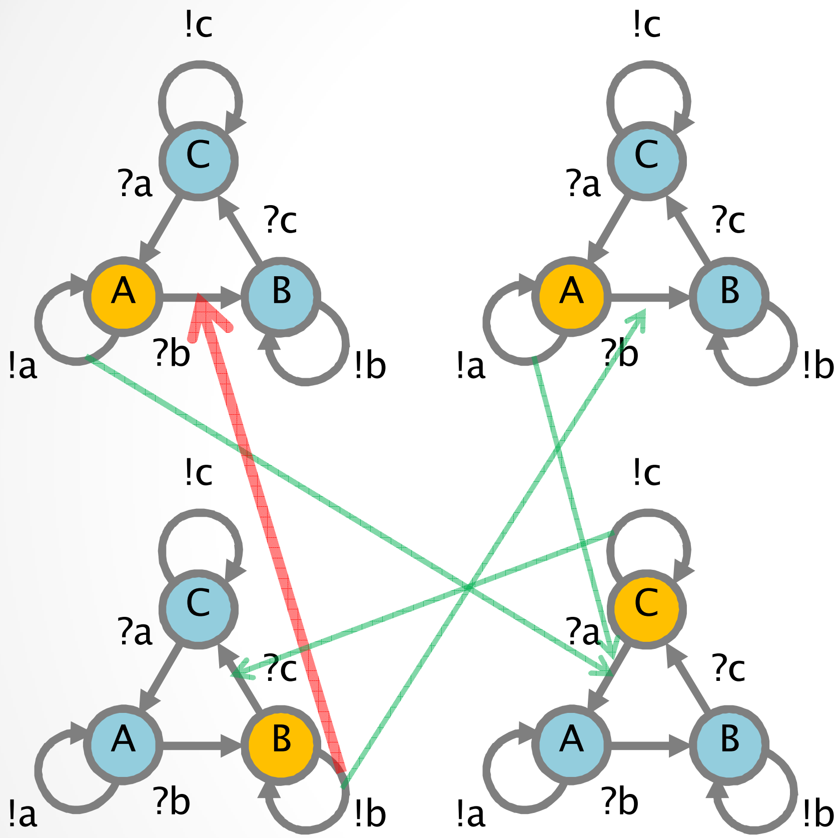
Chemical Reaction Networks

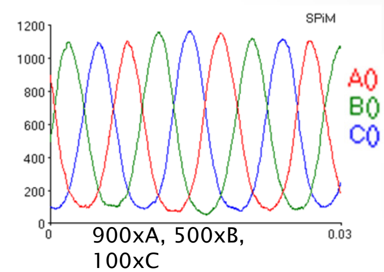
Implementing an arbitrary finite chemical system in DNA with asymptotically correct kinetics
Soloveichick & al. DNA 15

Species become signals
Reactions become gates

$$A + B \rightarrow C + D \qquad \Rightarrow \qquad [A,B].[C,D]$$

Interacting Automata

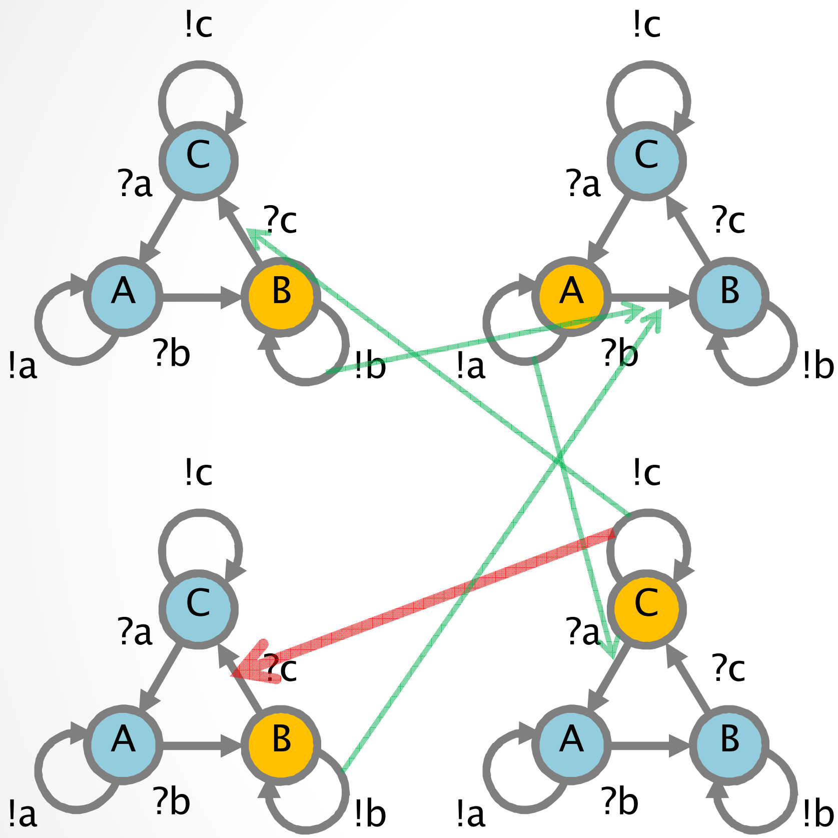


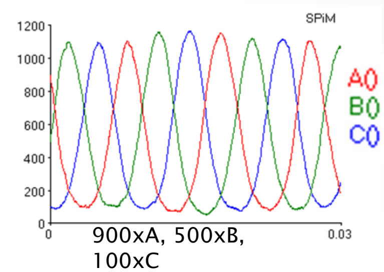


([A,B].[B,B])* |
([B,C].[C,C])* |
([C,A].[A,A])* |
A | A | B | C

This is a uniform population of identical automata,
but heterogeneous populations of interacting automata can be similarly handled.

Interacting Automata

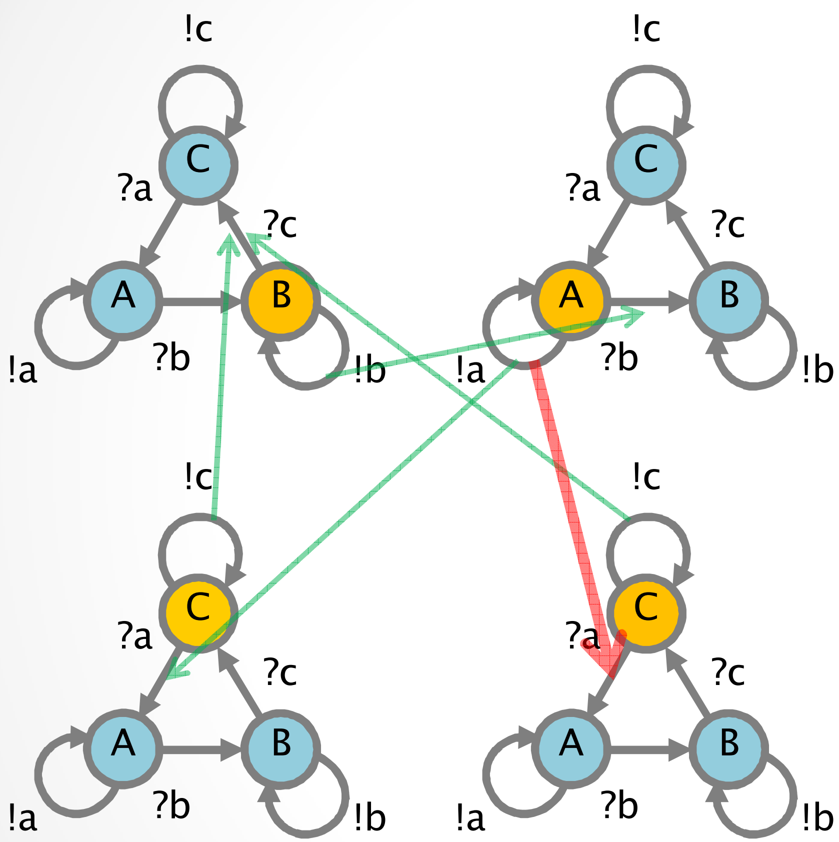


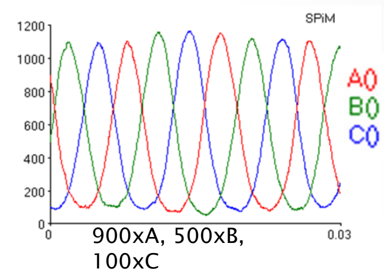


([A,B].[B,B])* |
([B,C].[C,C])* |
([C,A].[A,A])* |
A | B | B | C

This is a uniform population of identical automata,
but heterogeneous populations of interacting automata can be similarly handled.

Interacting Automata

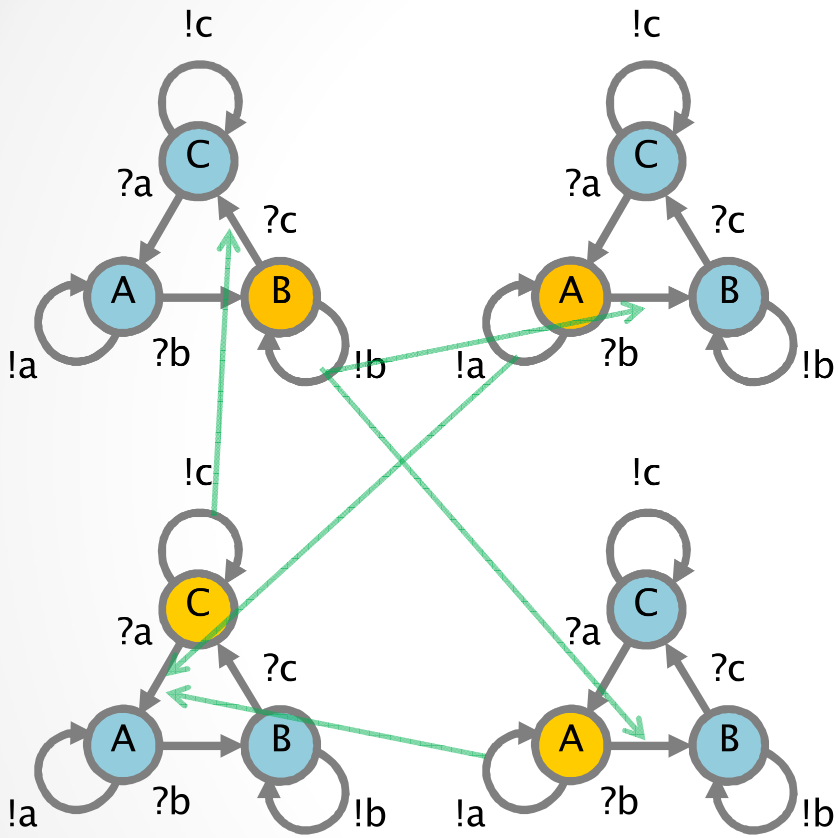


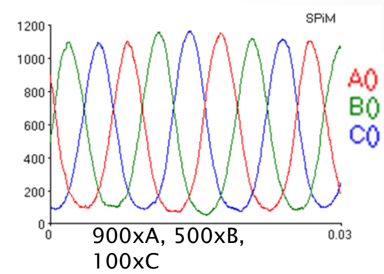


([A,B].[B,B])* |
([B,C].[C,C])* |
([C,A].[A,A])* |
A | B | C | C

This is a uniform population of identical automata,
but heterogeneous populations of interacting automata can be similarly handled.

Interacting Automata





([A,B].[B,B])* |
([B,C].[C,C])* |
([C,A].[A,A])* |
A | A | B | C

This is a uniform population of identical automata,
but heterogeneous populations of interacting automata can be similarly handled.

And finally...

• • •

Summary

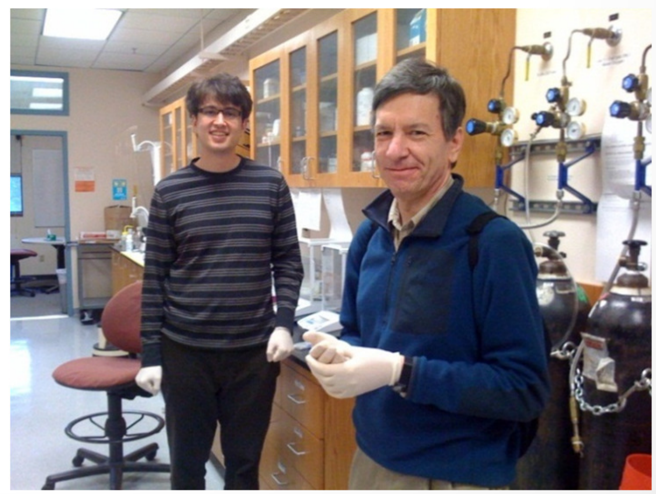
- Abstract Machines to Strand Algebra
  - Or other intermediate language
- Strand Algebra to DSD
  - Or other structural language
- Simulation, analysis, etc.
  - Design iteration
- DSD to Sequences
  - E.g. NuPack, or pre-build strand libraries
- Sequences to DNA
  - Web order
- DNA experiments
  - Fairly basic wet lab
- Deployable Nanotech

Conclusions

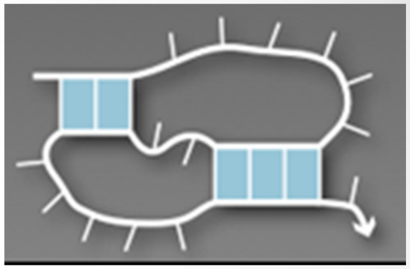
- Programmable Matter
  - Nucleic acids
- Molecular Computation
  - DNA strand displacement
- Molecular Compilation
  - From programming abstractions (Petri Nets, Process Algebra, etc.),
    through intermediate language (Strand Algebra)
    to molecule synthesis (DNA).
- Correctness
  - Ensuring molecular programs work as intended
  - Through thermodynamic analysis, simulation, formal verification.

Acknowledgments

- Illustrations
  - John Reif, Duke
  - Ned Seeman, NYU
  - Erik Winfree, Caltech
  - Bernard Yurke, Boise State
  - Molecular movies by Drew Berry
  - Wikipedia, YouTube
- David Soloveichik



The Molecular Programming Project



- Caltech & U.Washington
  - National Science Foundation's Expeditions in Computing
  - Shuki Brooks, Erik Klavins, Richard Murray, Niles Pierce, Paul Rothemund, Erik Winfree.

- Goals
  - Create a functional abstraction hierarchy and use this hierarchy to construct programming languages and compilers.
  - Create a theoretical framework for the analysis and design of molecular programs, one that serves as the underpinning for an actual practice of molecular programming.
  - Validate our compilers and theoretical framework with experimental systems utilizing molecular programs with 10 to 100 times the number of components currently used.
  - Test our molecular programming technologies on real-world applications.
  - Recruit and train a generation of molecular programmers with the insight and skills necessary to conceive, design, and implement complex molecular systems.