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Molecular Programming

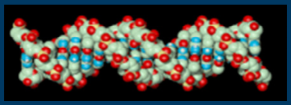
Luca Cardelli

2013-06-21 TCN Programming Languages Community Event, Redmond

Objectives

- The promises of Molecular Programming:
  - In Science & Medicine
  - In Engineering
  - In Computing

- The current practice of Molecular Programming
  - DNA technology
  - Molecular languages and tools
  - Example of a molecular algorithm

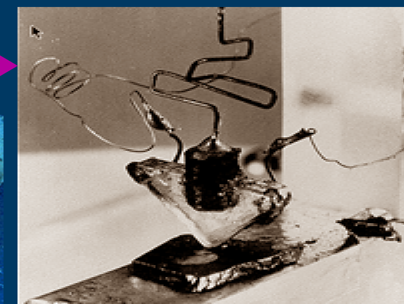


The Hardware Argument

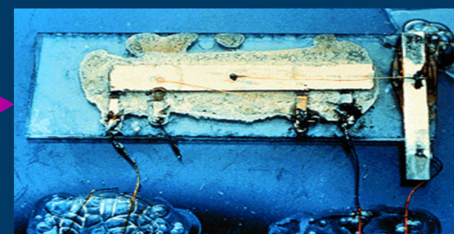
Smaller and smaller things can be built

Smaller and Smaller

First working transistor
John Bardeen and Walter Brattain , Dec. 23, 1947

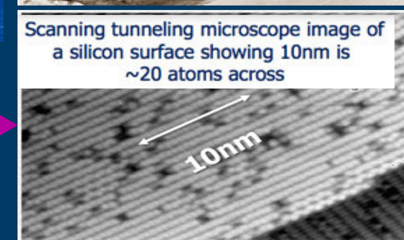


First integrated circuit
Jack Kilby, Sep. 1958.

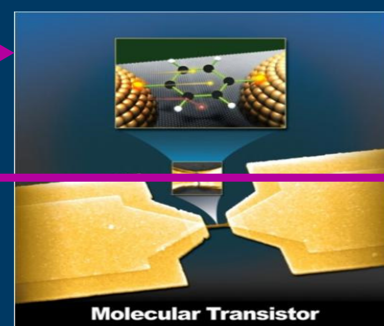


50 years later

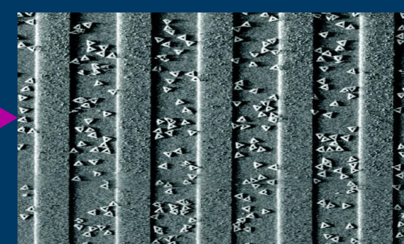
25nm NAND flash
Intel&Micron, Jan. 2010. ~50atoms



Single molecule transistor
Observation of molecular orbital gating
Nature, 2009; 462 (7276): 1039



Molecules on a chip

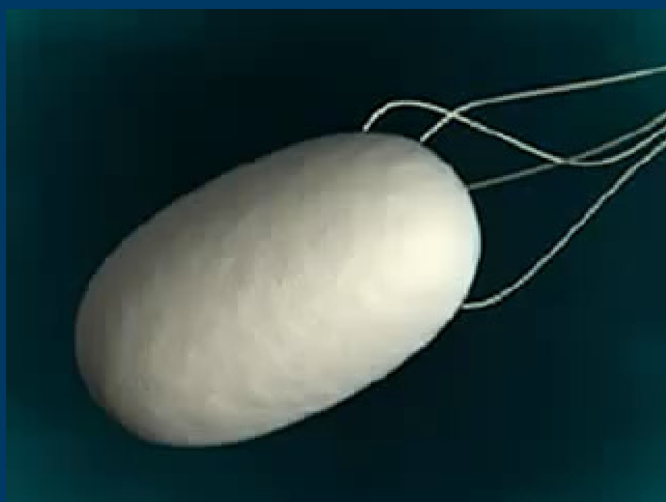


Placement and orientation of individual DNA shapes on lithographically patterned surfaces. Nature Nanotechnology 4, 557 - 561 (2009).

~10 Moore's Law cycles left!

Building the *Smallest* 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*



www.youtube.com/watch?v=Ey7Emmddf7Y

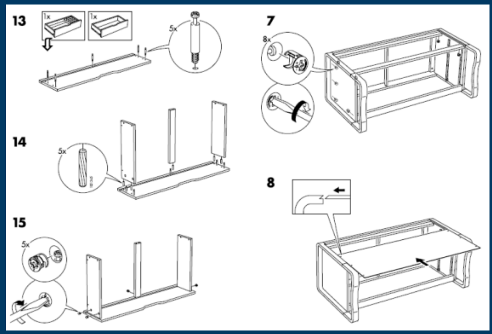
Molecular IKEA

- Nature can self-assemble.
  Can we?

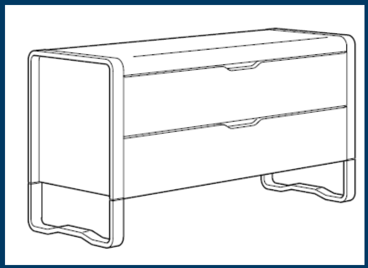
- *"Dear IKEA, please send me a chest of drawers that assembles itself."*

- 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…



Add water

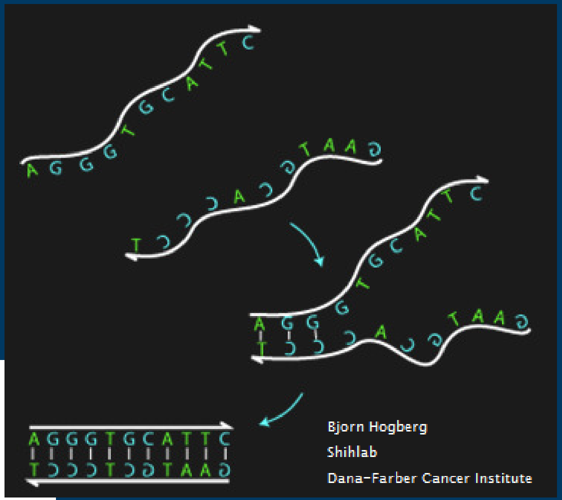


http://www.ikea.com/ms/en_US/customer_service/assembly_instructions.html

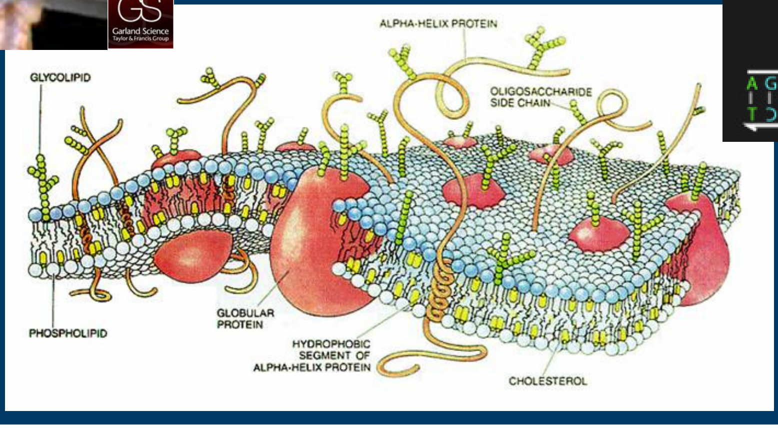
Programmed Self-Assembly

Proteins

DNA/RNA



Membranes

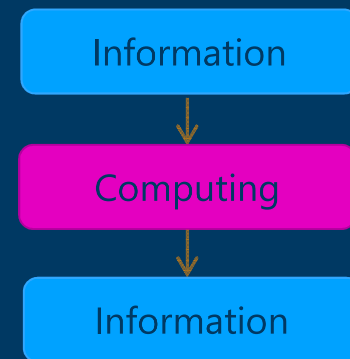


The Software Argument

Smaller and smaller things can be programmed

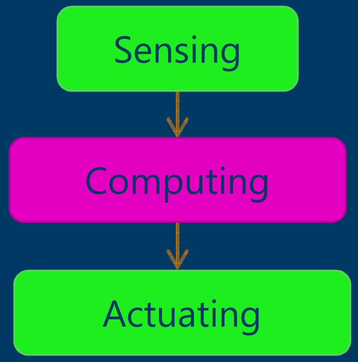
We can program…

- Computers.
  - Completely!



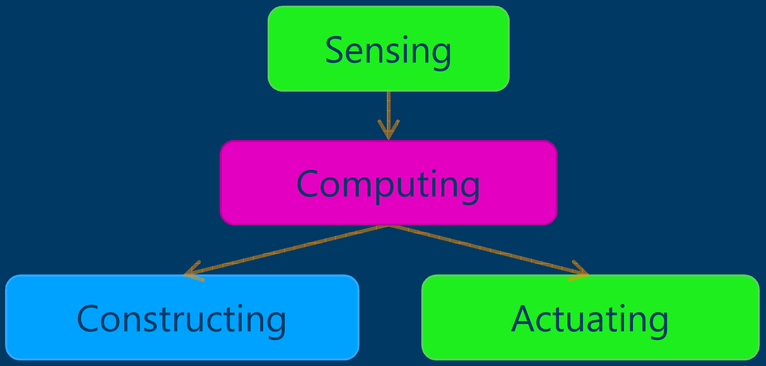
We can program…

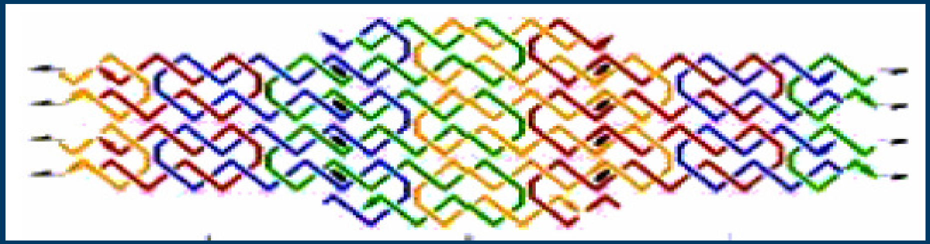
- Physical systems.
  - Completely!
    (Modulo sensors/actuators)



We can program...

- Matter
  - Completely and directly!
  - Currently: only DNA/RNA.

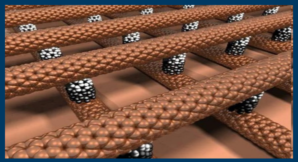




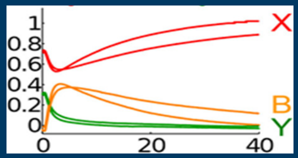
It's like a 3D printer without the printer!
[Andrew Hellington]

What can we do with "just" DNA?

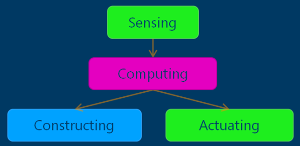
- Organize ANY matter [caveats apply]



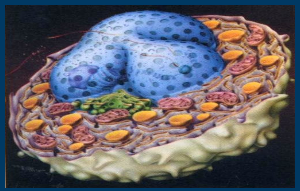
- Execute ANY kinetics [caveats: up to time scaling]



- Build Nano-Control Devices



- Interface to Biology

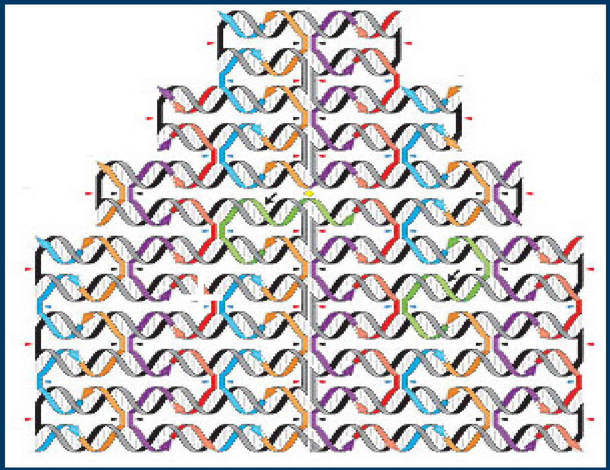


H.Lodish & al. Molecular Cell Biology 4th ed.

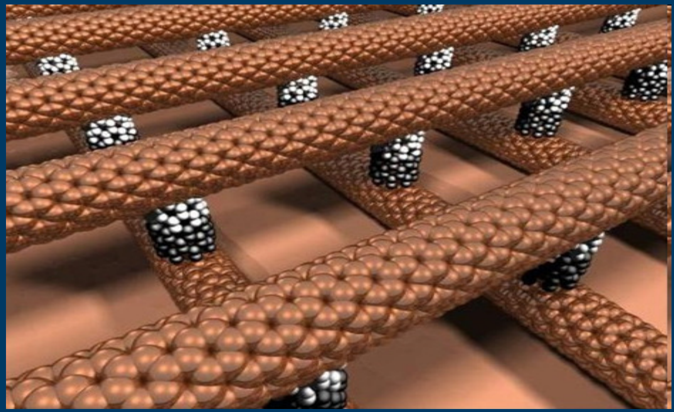
Organizing Any Matter

- Use one kind of programmable matter (e.g. DNA).
- To organize (almost) ANY matter through it.

6 nm grid of individually addressable DNA pixels



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



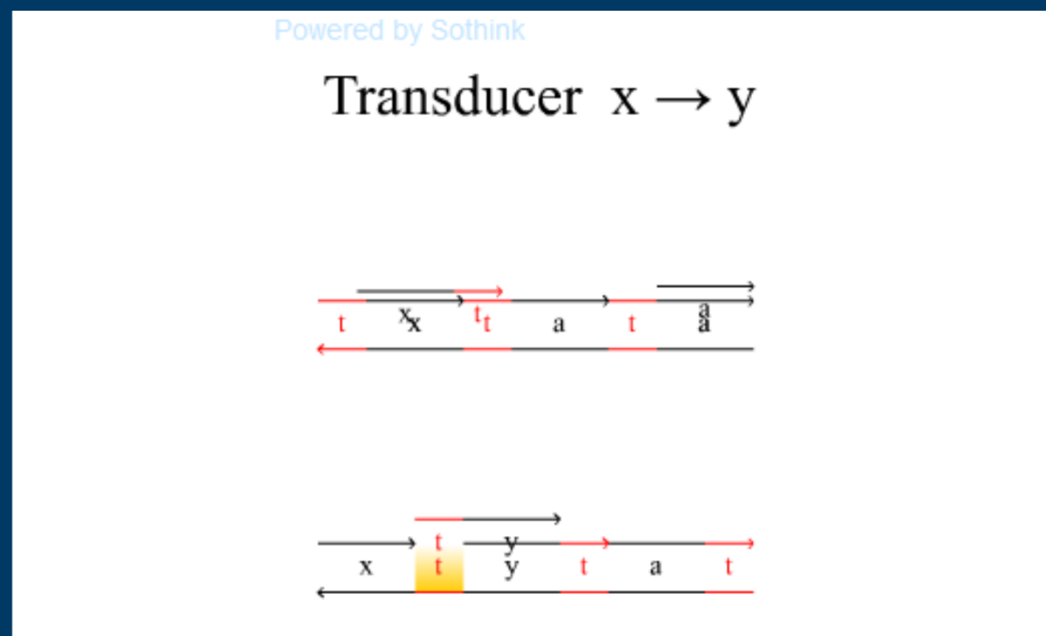
European Nanoelectronics Initiative Advisory Council

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

Executing Any Kinetics

- The kinetics of any finite network of chemical reactions, can be implemented (physically) with especially programmed DNA molecules.

- Chemical reactions as an executable programming language for dynamical systems!

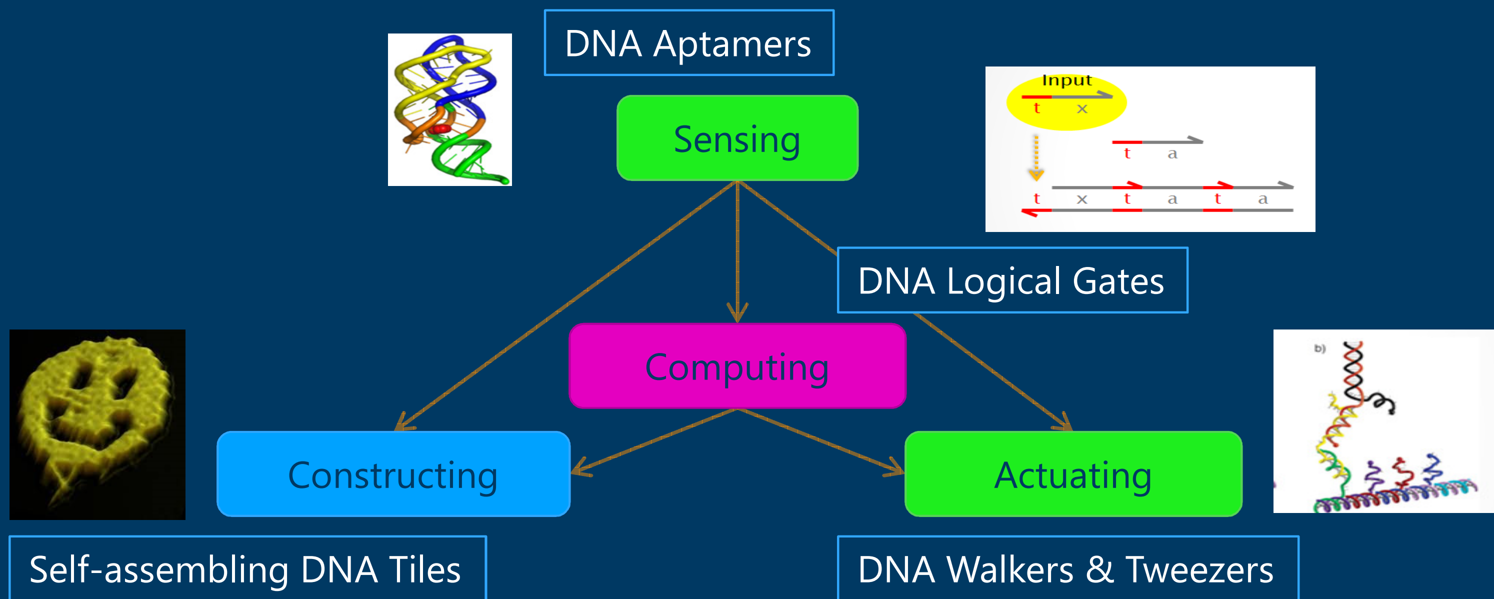


DNA as a universal substrate for chemical kinetics PNAS

David Soloveichik[a,1], Georg Seelig[a,b,1], and Erik Winfree[c,1]

Building Nano-Control Devices

- All the components of nanocontrollers can already be built entirerly and solely with DNA, and interfaced to the environment



Interfacing to Biology

- A doctor in each cell

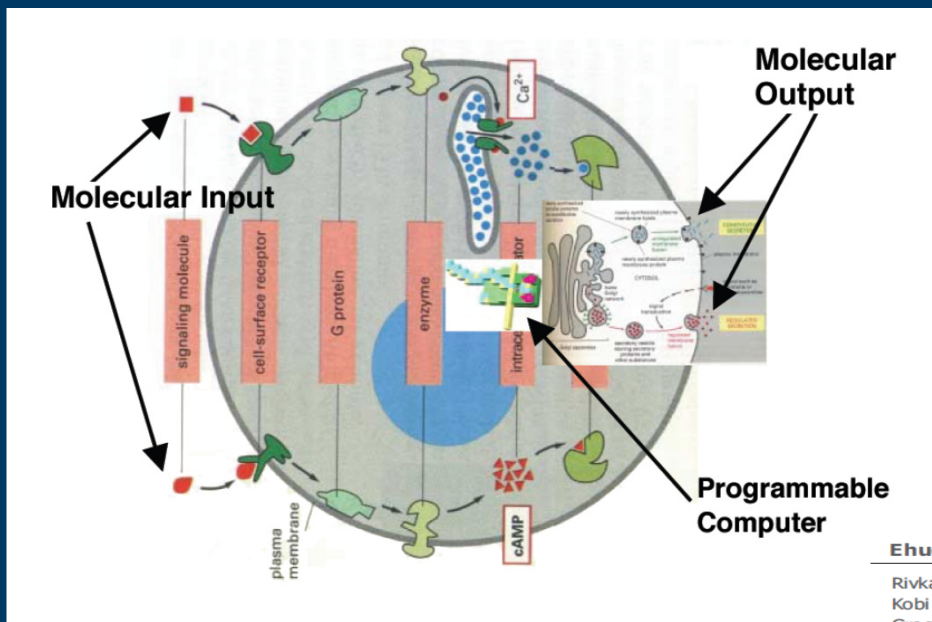


Fig. 1 Medicine in 2050: "Doctor in a Cell"

Ehud Shapiro

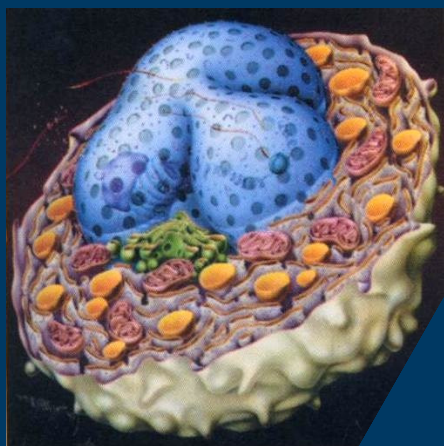
Rivka Adar
Kobi Benenson
Gregory Linshitz
Aviv Regev
William Silverman

Molecules and computation

The Biological Argument

Biological systems are already 'molecularly programmed'

Abstract Machines of Biology



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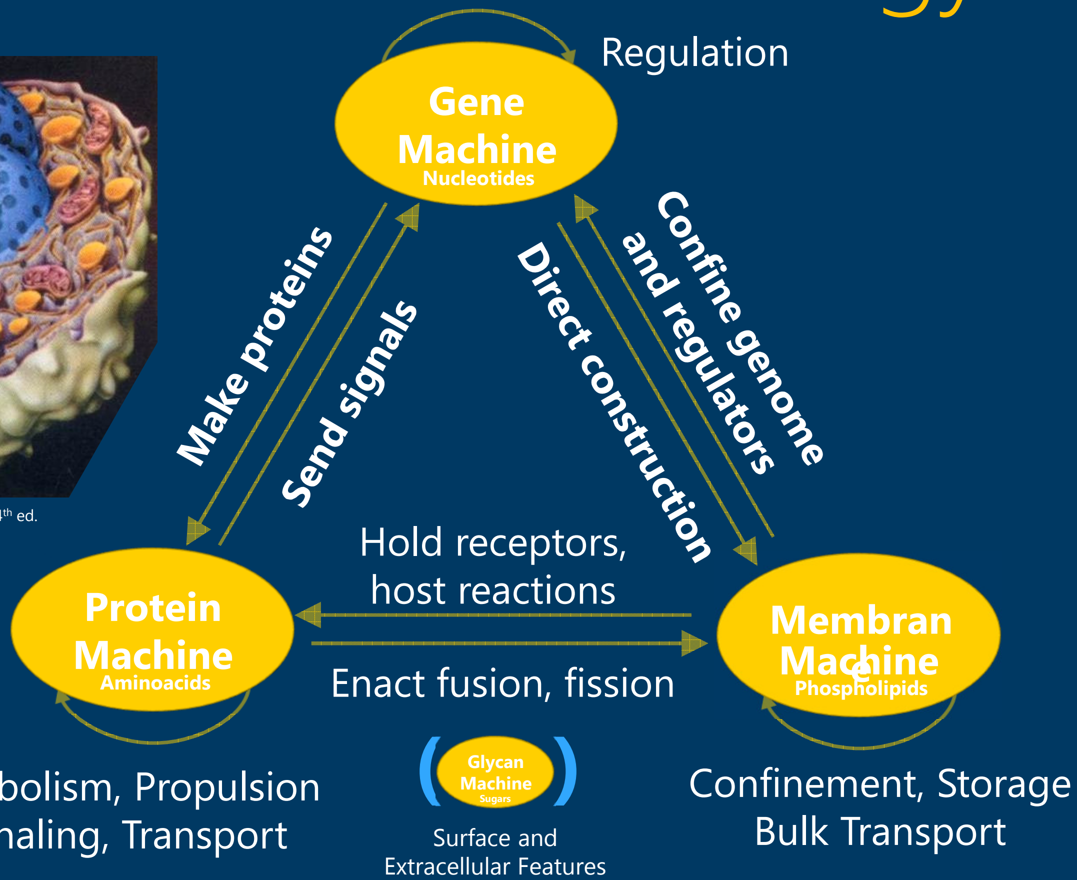
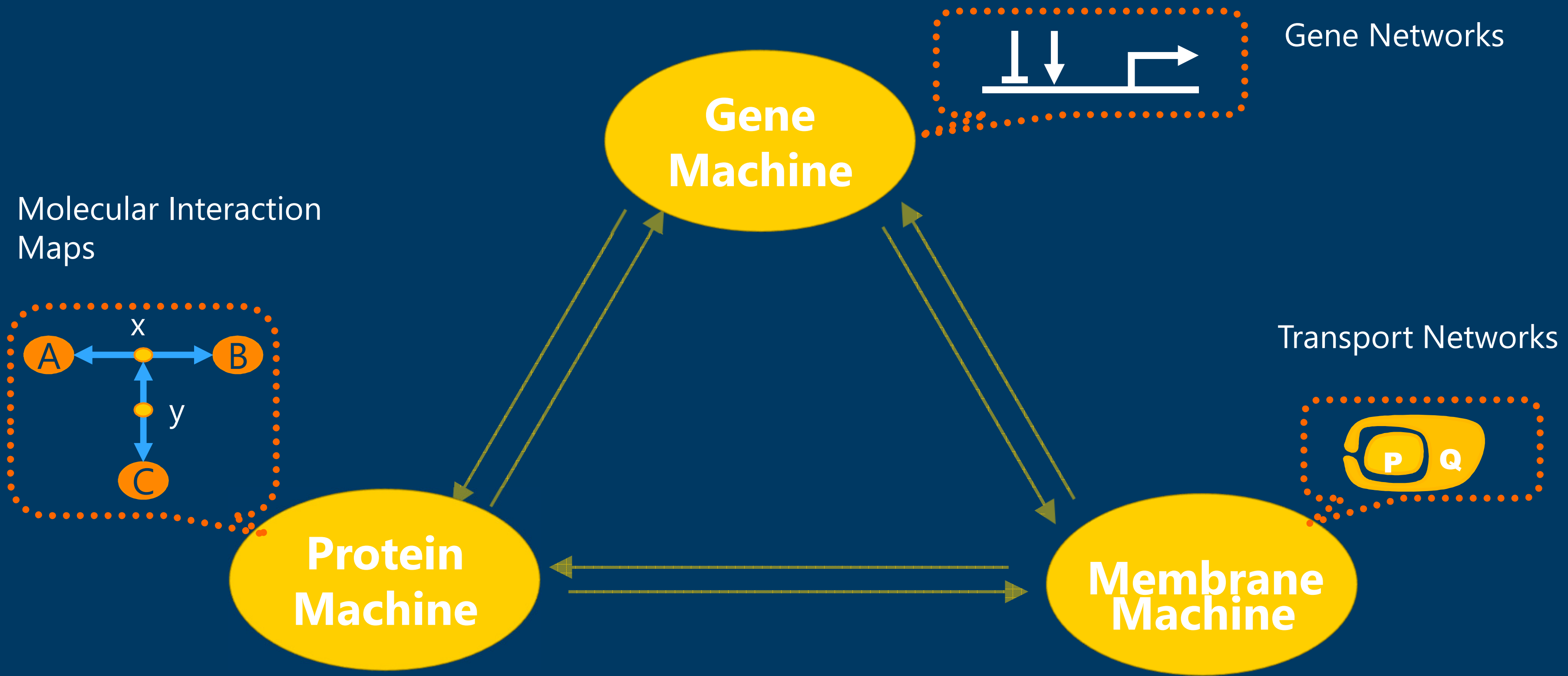


Biological Languages



But …

- Biology is programmable, but (mostly) not by us!

- Still work in progress:
  - Gene networks are being programmed in synthetic biology, but using existing ‘parts’
  - Protein networks are a good candidate, but we cannot yet effectively design proteins
  - Transport networks are being looked at for programming microfluidic devices manipulating vesicles

Molecular Languages

… that we can execute

Action Plan

- Building a full software/hardware pipeline for a new fundamental technology
  - Mathematical Foundations [~ concurrency theory in the 80's]
  - Programming Languages [~ software engineering in the 70's]
  - Analytical Methods and Tools [~ formal methods in the 90's]
  - Device Architecture and Manufacturing [~ electronics in the 60's]
- To realize the potential of Molecular Programming
- "With *no alien technology*" [David Soloveichik]
- This is largely a 'software problem' even when working on device design

Our Assembly Language: Chemistry

- A Lingua Franca between Biology, Dynamical Systems, and Concurrent Languages

- Chemical Reaction Networks
  - $A + B \rightarrow_r C + D$ (the program)

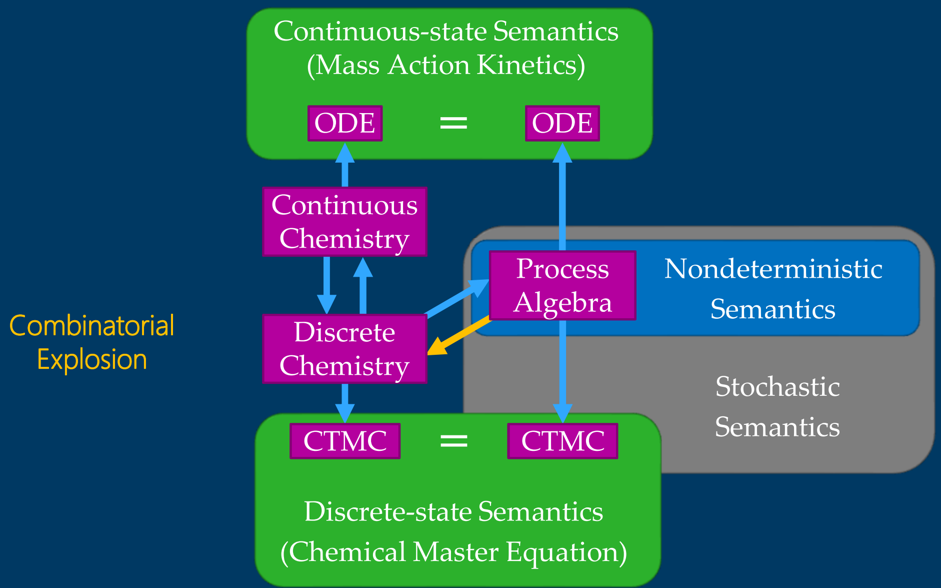
- Ordinary Differential Equations
  - $d[A]/dt = -r[A][B]$ ... (the behavior)

- Rich analytical techniques based on Calculus

- But prone to combinatorial explosion
  - E.g., due to the peculiarities of protein interactions

Chemistry as a Concurrent Language

- A connection with the theory of concurrency
  - Via Process Algebra and Petri Nets



How do we “run” Chemistry?

- Chemistry is not easily executable
  - “Please Mr Chemist, execute me this bunch of reactions that I just made up”
- Most molecular languages are not executable
  - They are descriptive (modeling) languages
- How can we execute molecular languages?
  - With real molecules?
  - That we can design ourselves?
  - And that we can buy on the web?

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Molecular Programming with DNA

Building the cores of programmable molecular controllers

The role of DNA Computing

- Non-goals
  - Not to solve NP-complete problems with large vats of DNA
  - Not to replace silicon

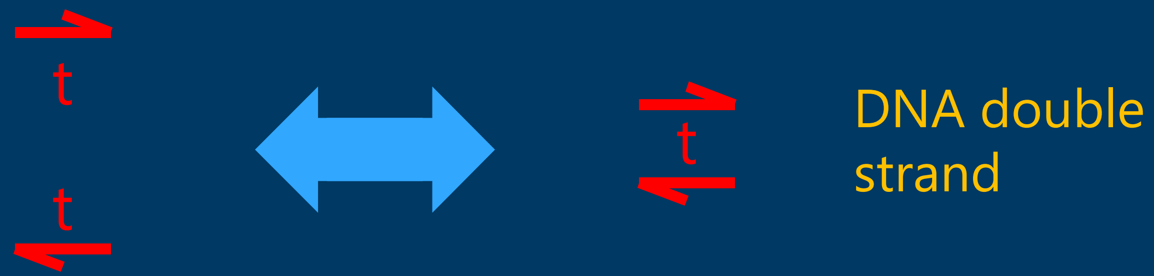
- Bootstrapping a carbon-based technology
  - To precisely control the organization and dynamics of matter and information at the molecular level
  - DNA is our engineering material
    - Its biological origin is “accidental” (but convenient)
    - It is an information-bearing programmable material
    - Other such materials will be (are being) developed

Domains

- Subsequences on a DNA strand are called domains
  - *provided* they are “independent” of each other

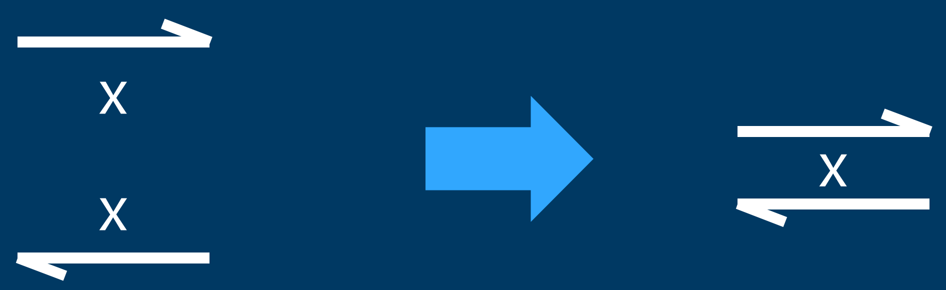
- Differently named domains must not hybridize
  - With each other, with each other’s complement, with subsequences of each other, with concatenations of other domains (or their complements), etc.

Short Domains



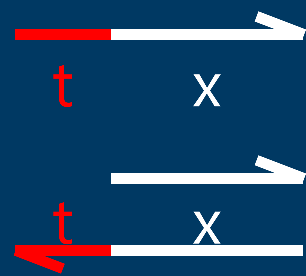
Reversible Hybridization

Long Domains



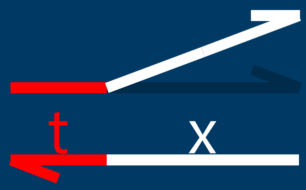
Irreversible Hybridization

Strand Displacement



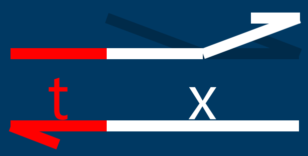
"Toehold Mediated"

Strand Displacement



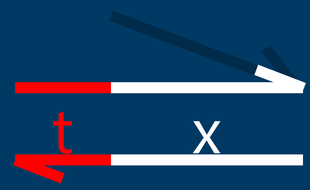
Toehold Binding

Strand Displacement



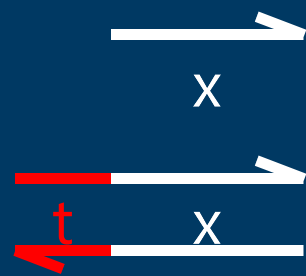
Branch Migration

Strand Displacement



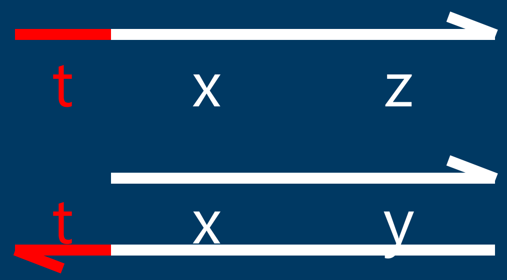
Displacement

Strand Displacement

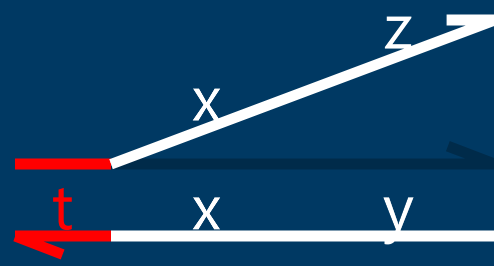


Irreversible release

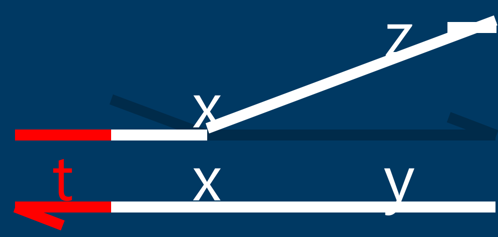
Bad Match



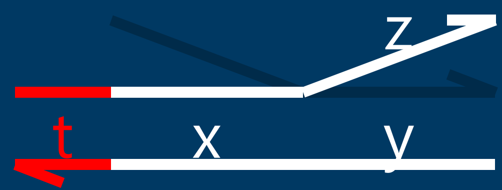
Bad Match



Bad Match



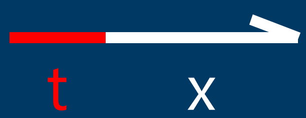
Bad Match



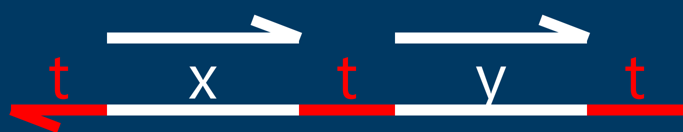
Cannot proceed
Hence will undo

Two-Domain Architecture

- Signals: 1 toehold + 1 recognition region



- Gates: “top-nicked double strands” with open toeholds



Garbage collection “built into” the gate operation

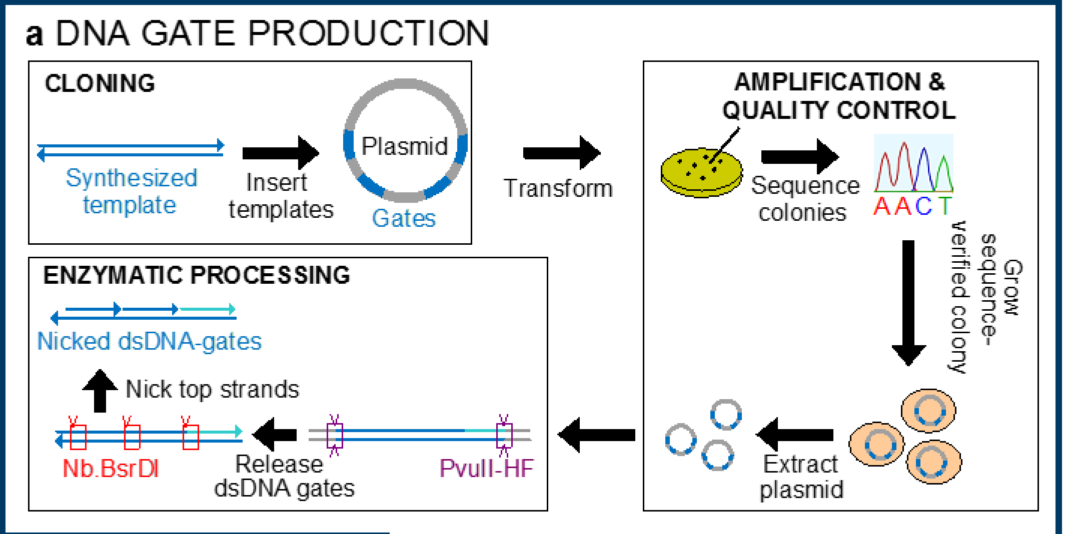
Two-Domain DNA Strand Displacement

Luca Cardelli

In S. B. Cooper, E. Kashefi, P. Panangaden (Eds.): Developments in Computational Models (DCM 2010). EPTCS 25, 2010, pp. 33-47. May 2010.

Plasmidic Gate Technology

- Synthetic DNA is length-limited
  - Finite error probability at each nucleotide addition, hence ~ 200nt max
- Bacteria can replicate plasmids for us
  - Loops of DNA 1000's nt, with extremely high fidelity
  - Practically no structural limitations on gate fan-in/fan-out



Programmable chemical controllers made from DNA

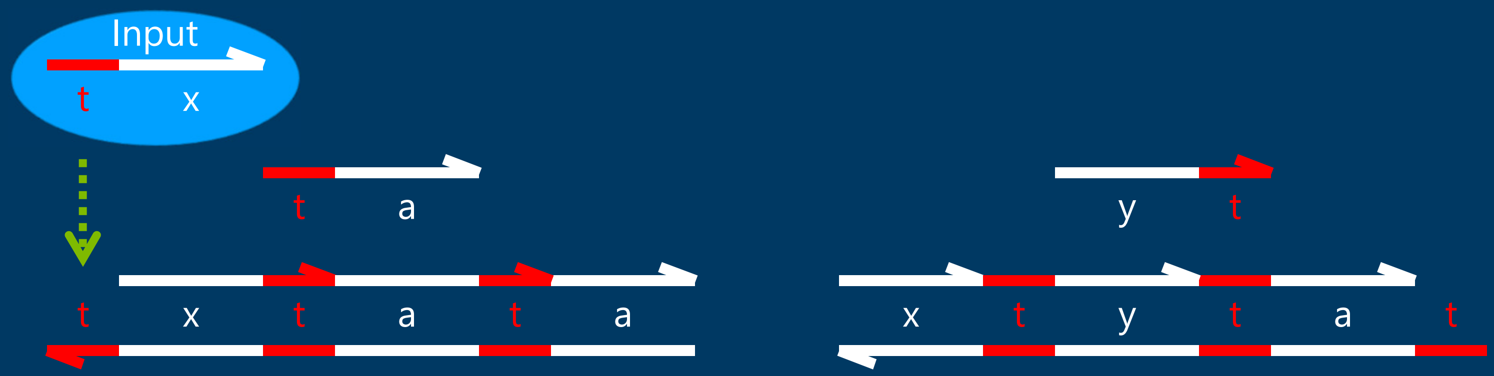
Yuan-Jyue Chen[1], Neil Dalchau[2], Niranjan Srinivas[3], Andrew Phillips[2], Luca Cardelli[2], David Soloveichik[4], and Georg Seelig[1,5]

Only possible with two-domain architecture

Transducer

Transducer x⟶y

Transducer x⟶y

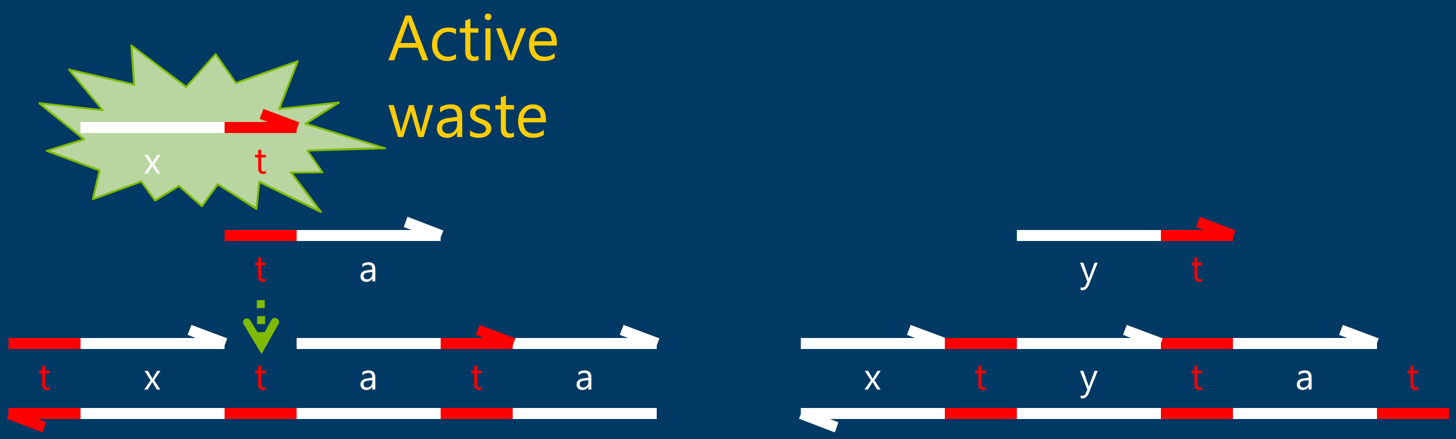


Built by self-assembly!

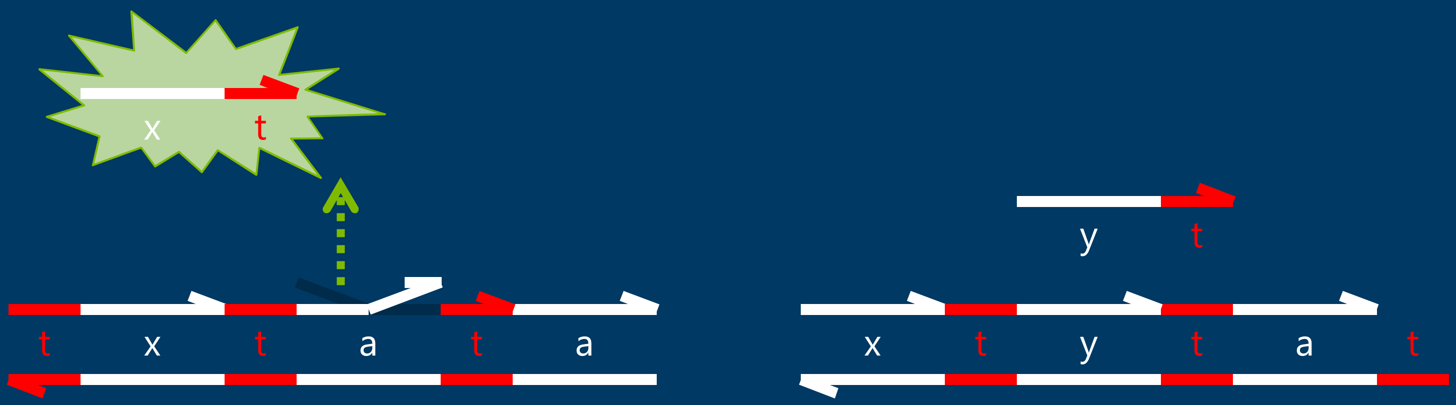
ta is a *private* signal (a different 'a' for each xy pair)

Transducer x⟶y

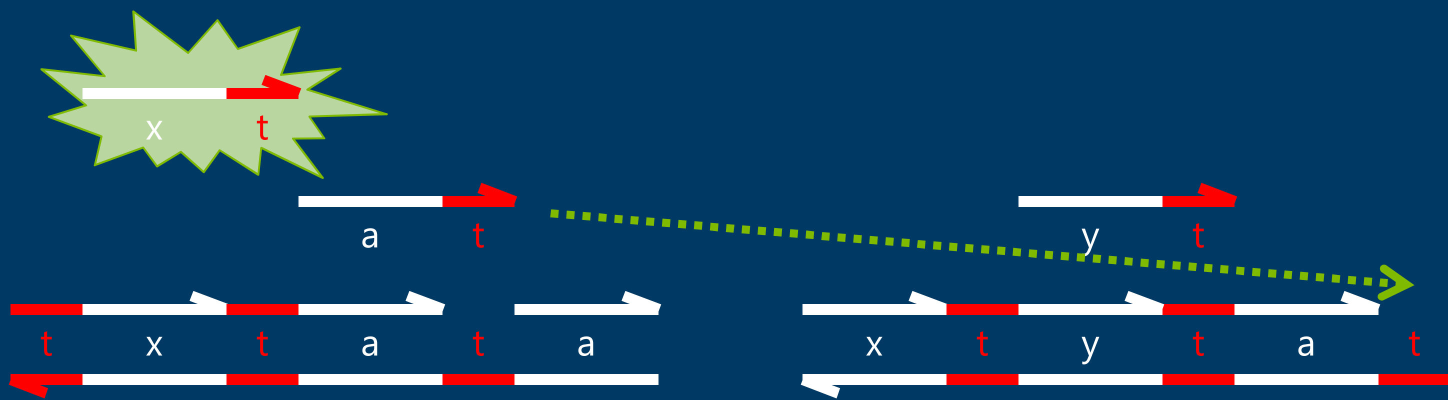
Transducer x⟶y



Transducer x⟶y

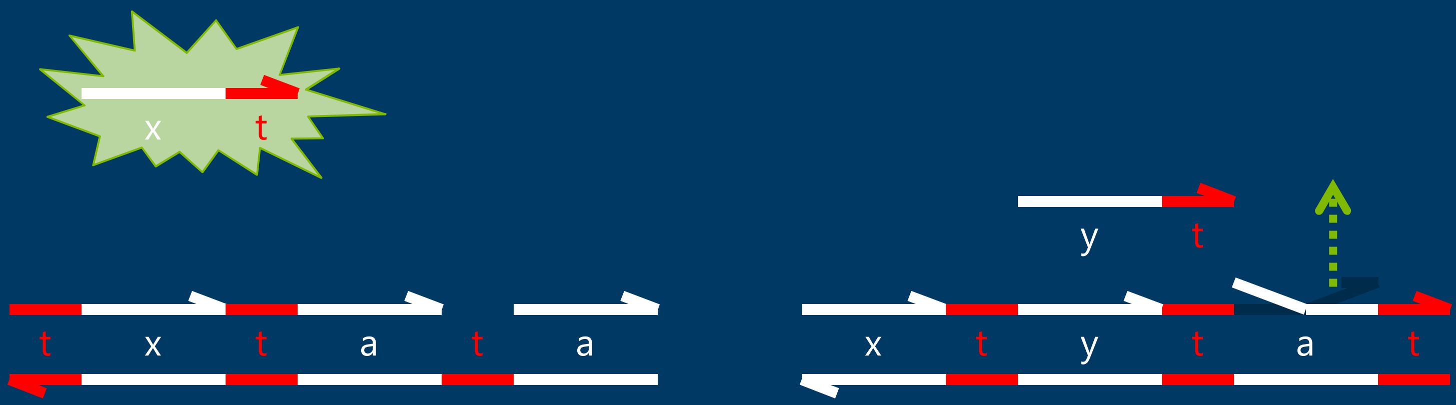


Transducer x⟶y

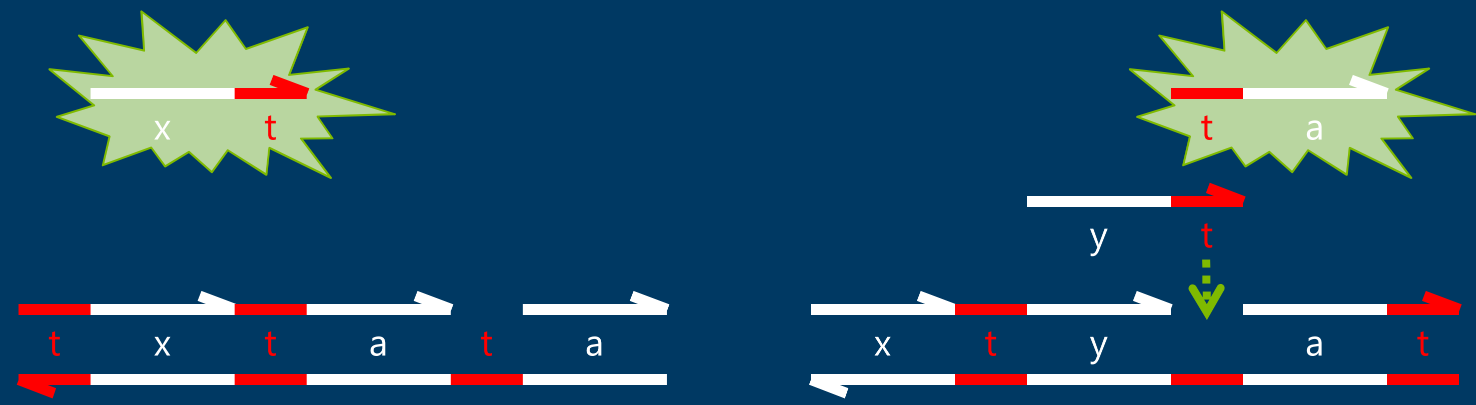


So far, a **tx** *signal* has produced an **at** *cosignal*.
But we want signals as output, not cosignals.

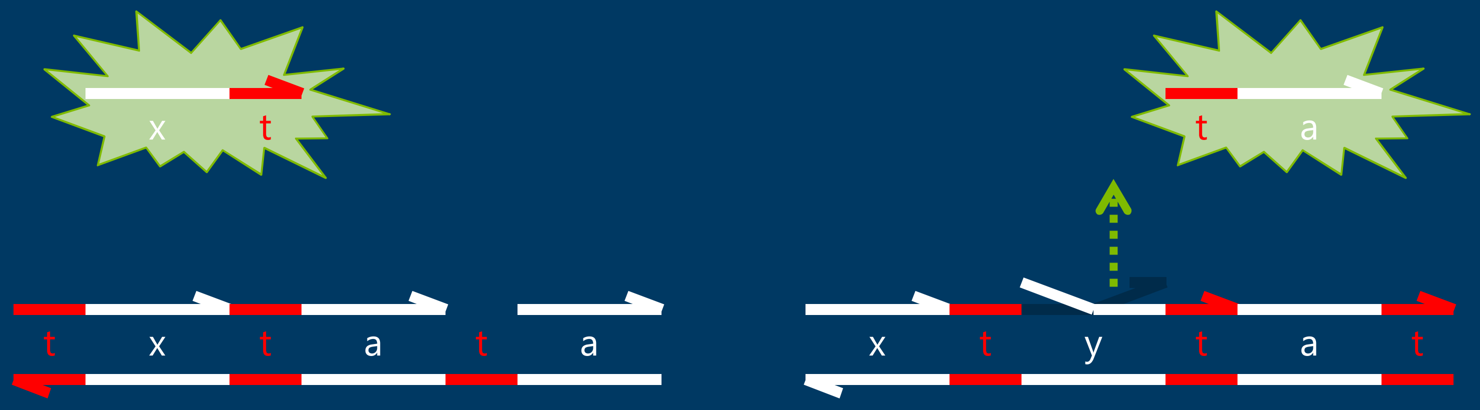
Transducer x⟶y



Transducer x⟶y



Transducer x→y



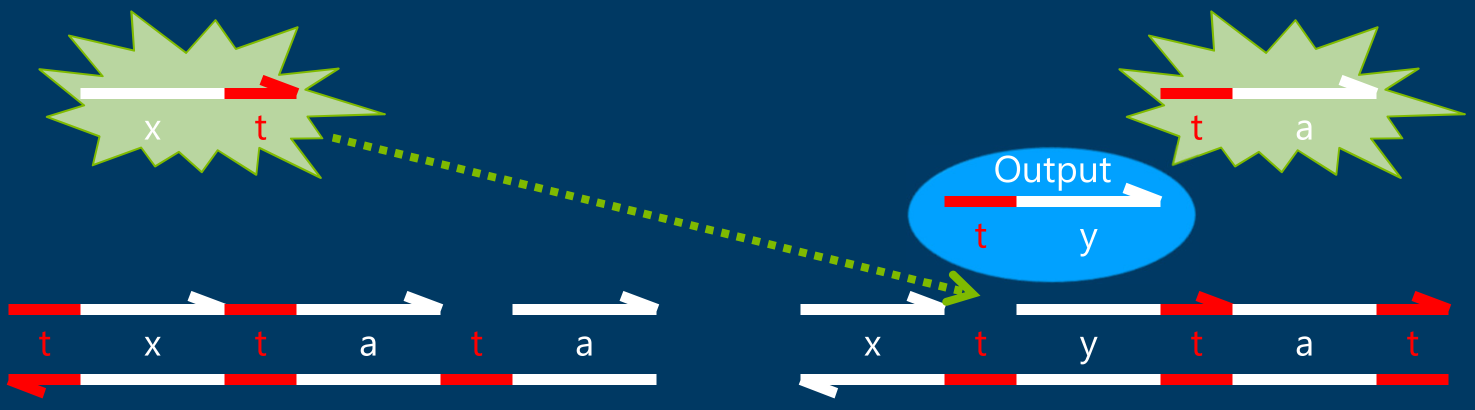
Transducer x⟶y

Here is our output **ty** *signal*.
But we are not done yet:

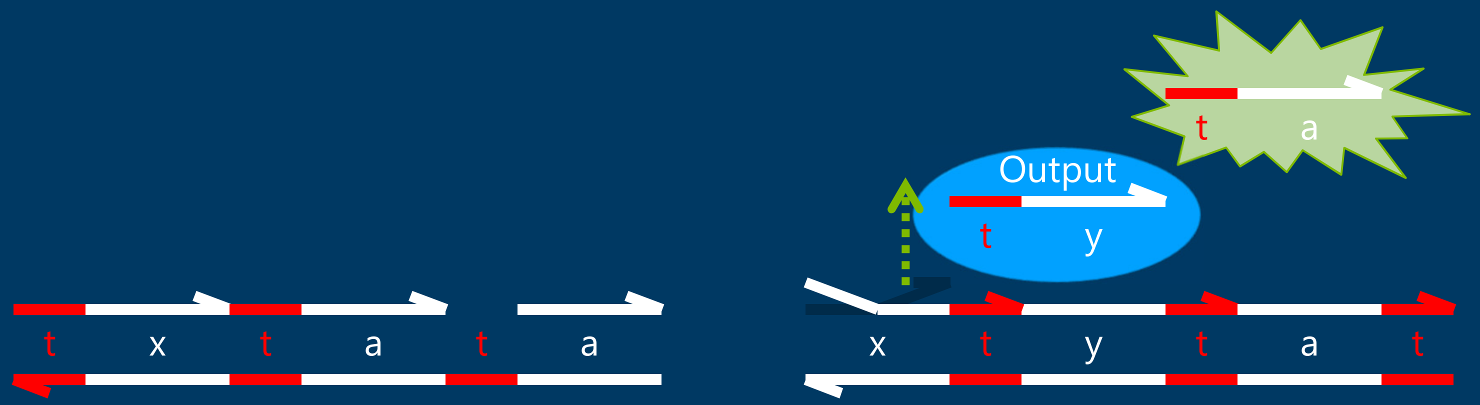
1) We need to make the output irreversible.
2) We need to remove the garbage.

We can use (2) to achieve (1).

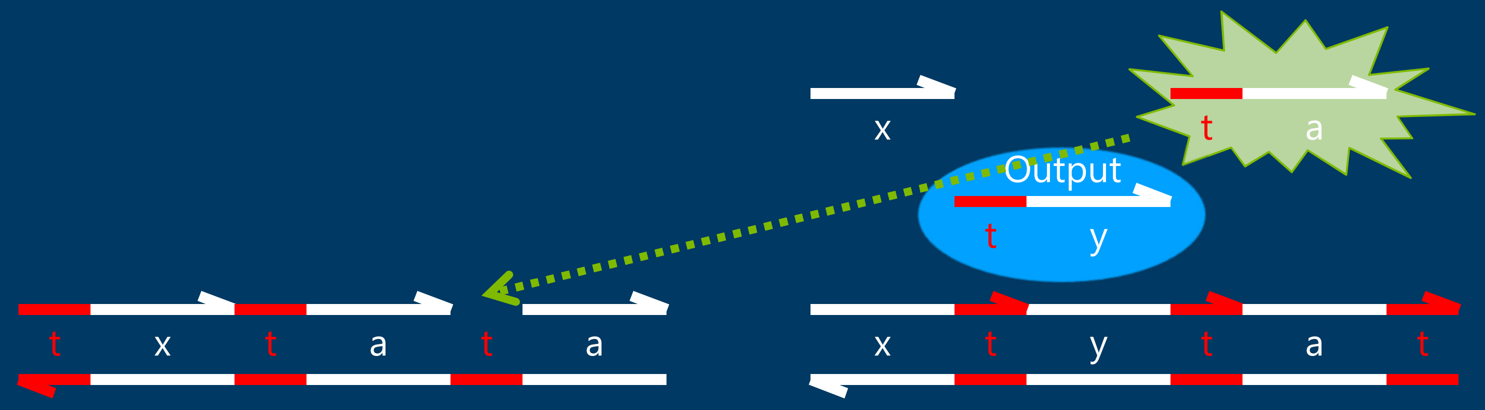
Transducer x→y



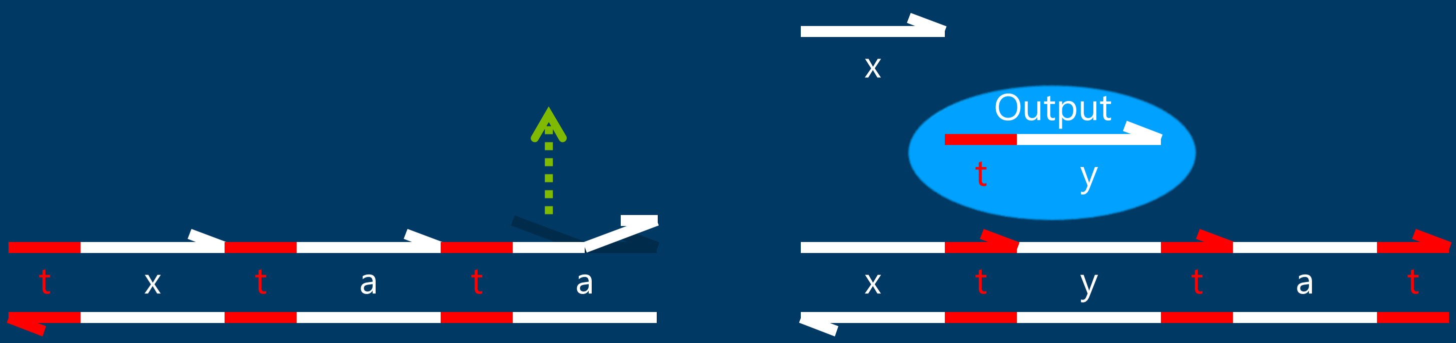
Transducer x⟶y



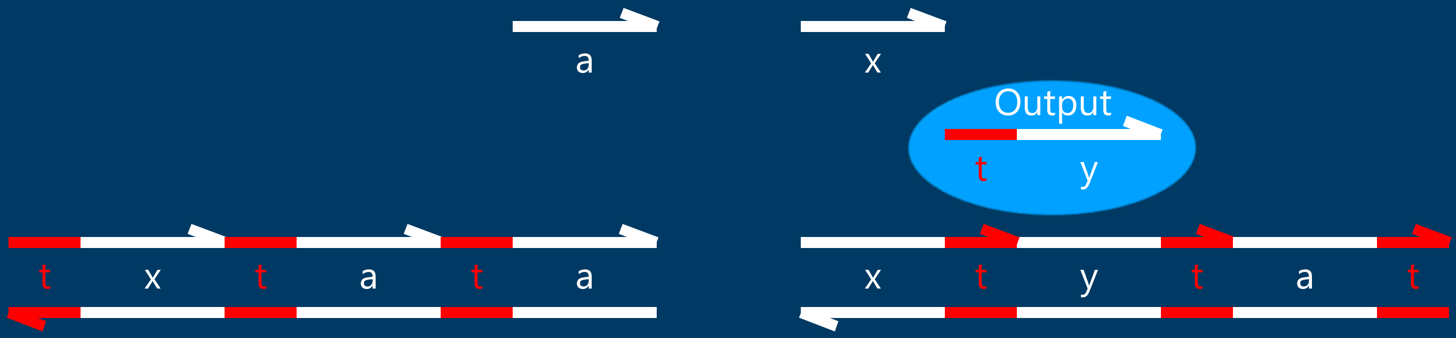
Transducer x→y



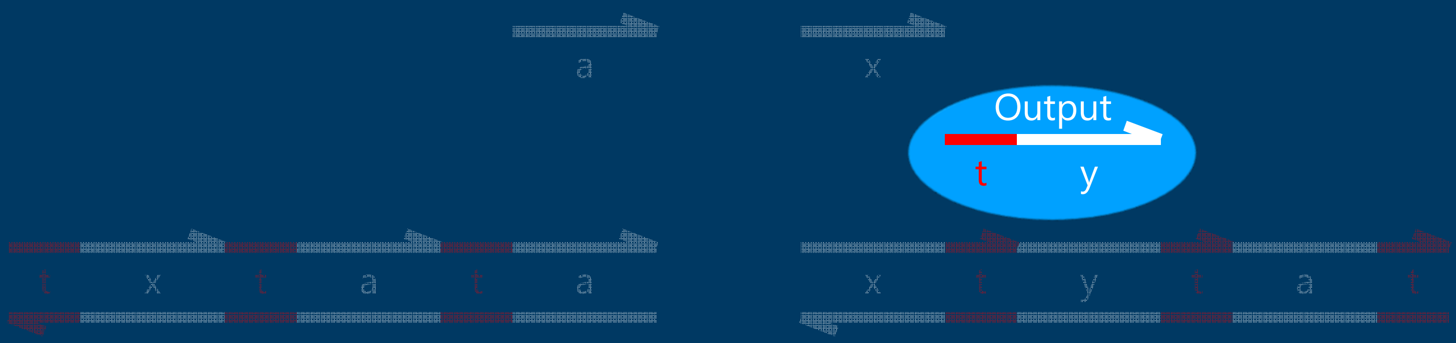
Transducer x⟶y



Transducer x⟶y



Transducer x⟶y

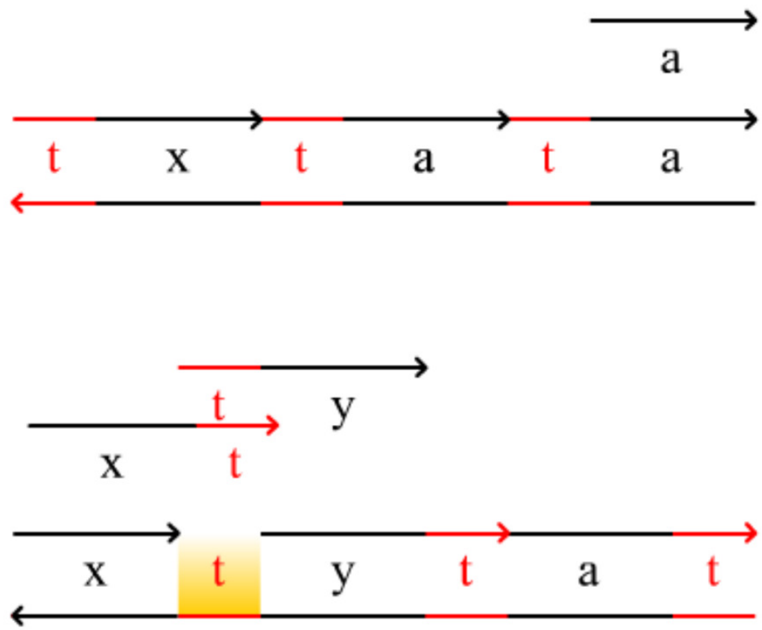


Done.

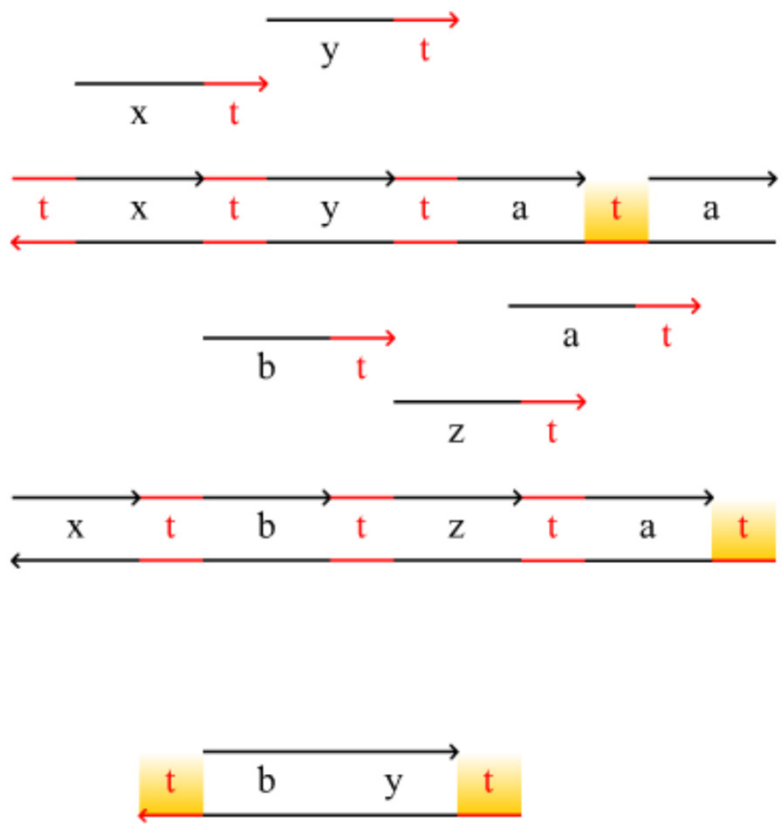
N.B. the gate is consumed: it is the energy source

(no proteins, no enzymes, no heat-cycling, etc.; just DNA in salty water)

Transducer $x \rightarrow y$



Join x+y → z



Microsoft Research

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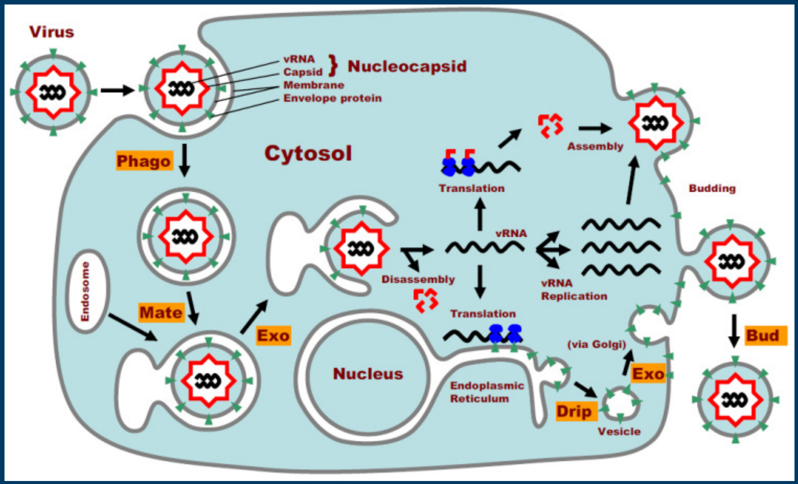
Tools and Techniques

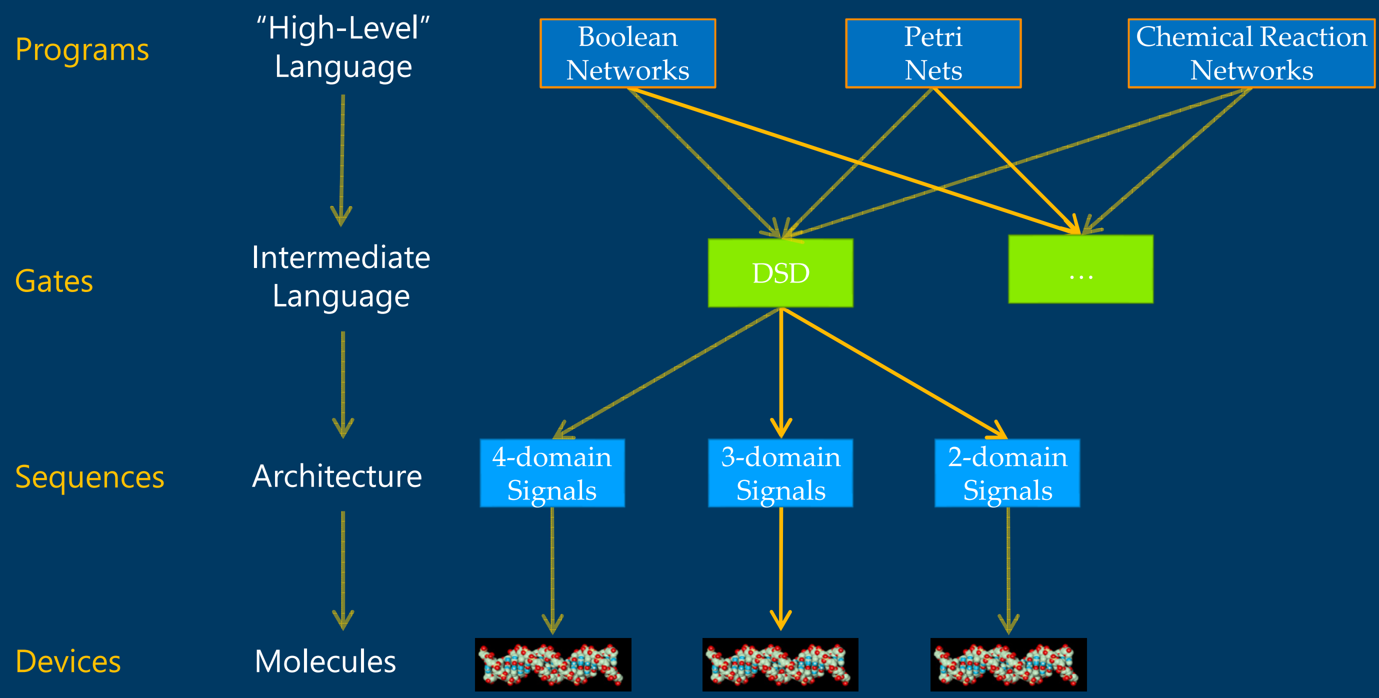
A software pipeline for Molecular Programming

High(er)-Level Languages

- Gene Networks
  - Synchronous Boolean networks
    - Stewart Kauffman, etc.
  - Asynchronous Boolean networks
    - René Thomas, etc.
- Protein Networks
  - Process Algebra (stochastic π-calculus etc.)
    - Priami, Regev-Shapiro, etc.
  - Graph Rewriting (kappa, BioNetGen etc.)
    - Danos-Laneve, Fontana & al., etc.
- Membrane Networks
  - Membrane Computing
    - Gheorghe Păun, etc.
  - Brane Calculi
    - Luca Cardelli, etc.
- Waiting for an architecture to run on…

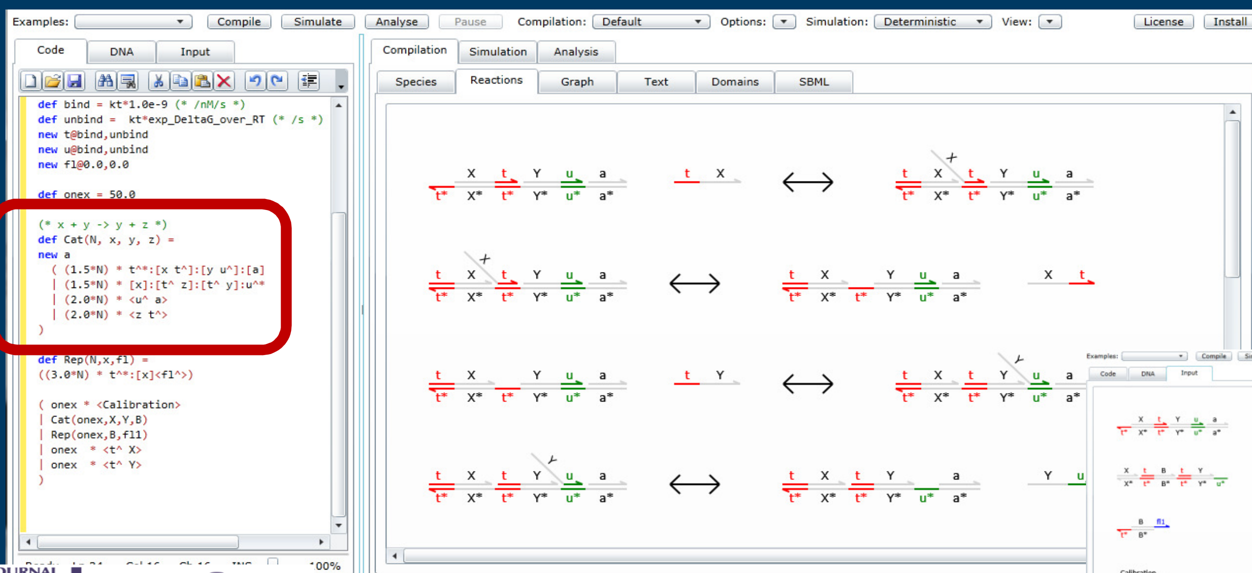


Molecular Compilation



Development Tools

MSRC Bio Computation Group



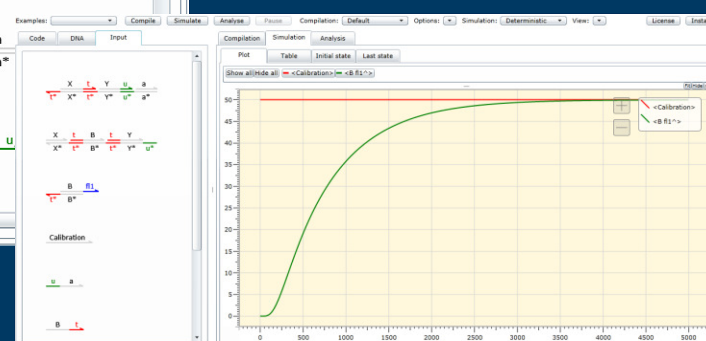
JOURNAL OF THE ROYAL SOCIETY Interface

A programming language for composable DNA circuits

Andrew Phillips and Luca Cardelli

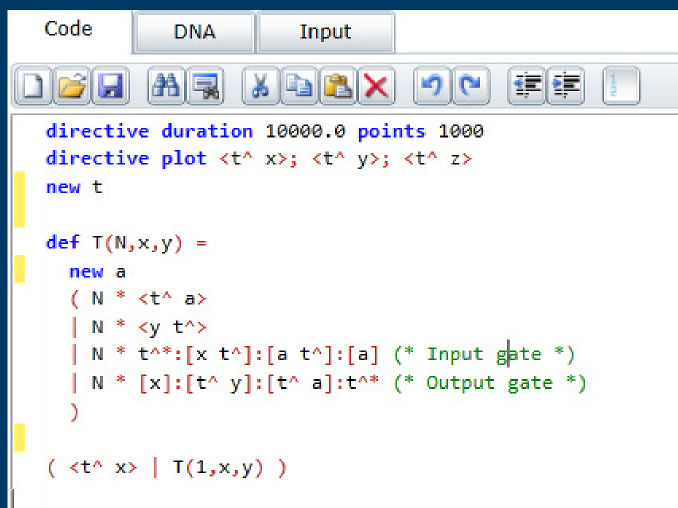
Visual DSD

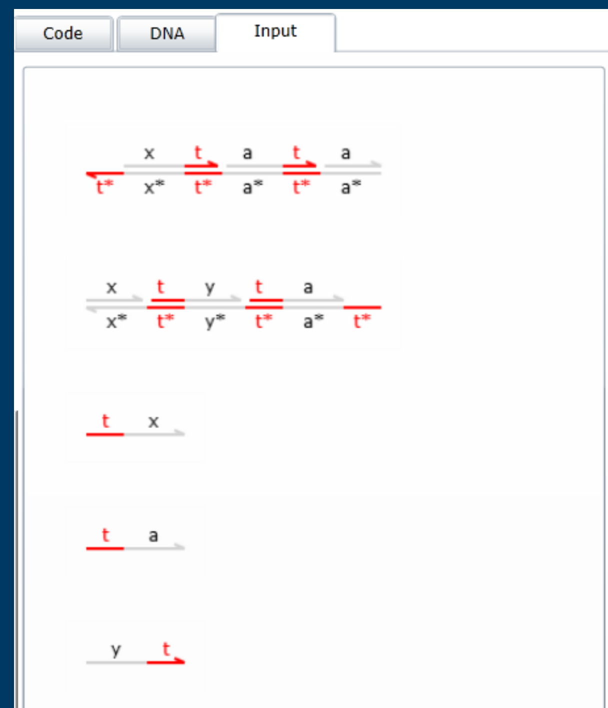
A Development Environment for DNA Strand Displacement



A Language for DNA Structures

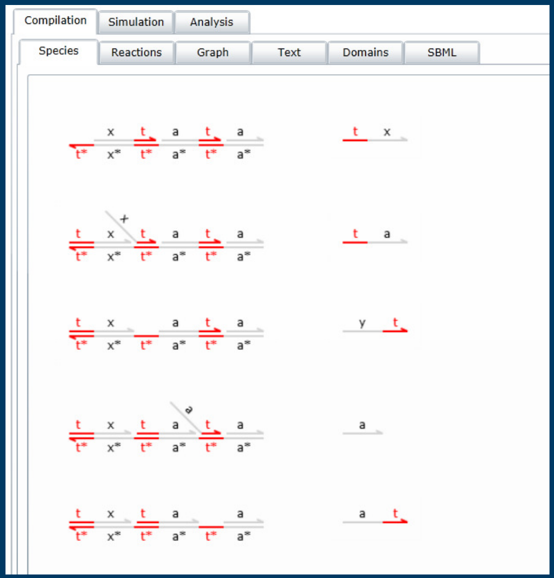
- Describe the initial structures

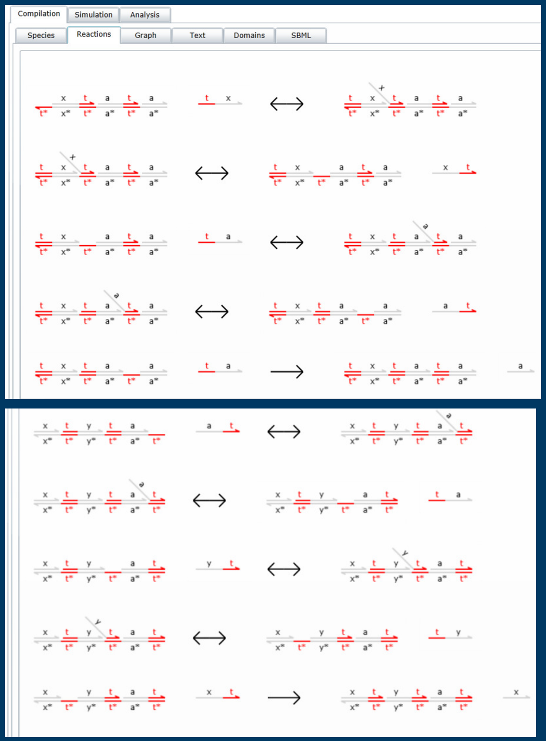




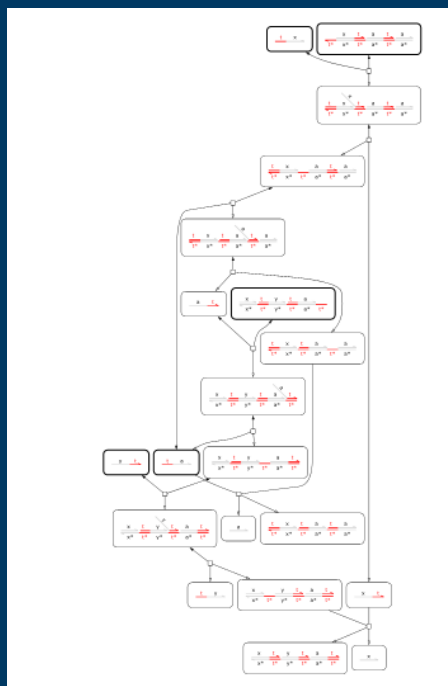
Compute Species and Reactions

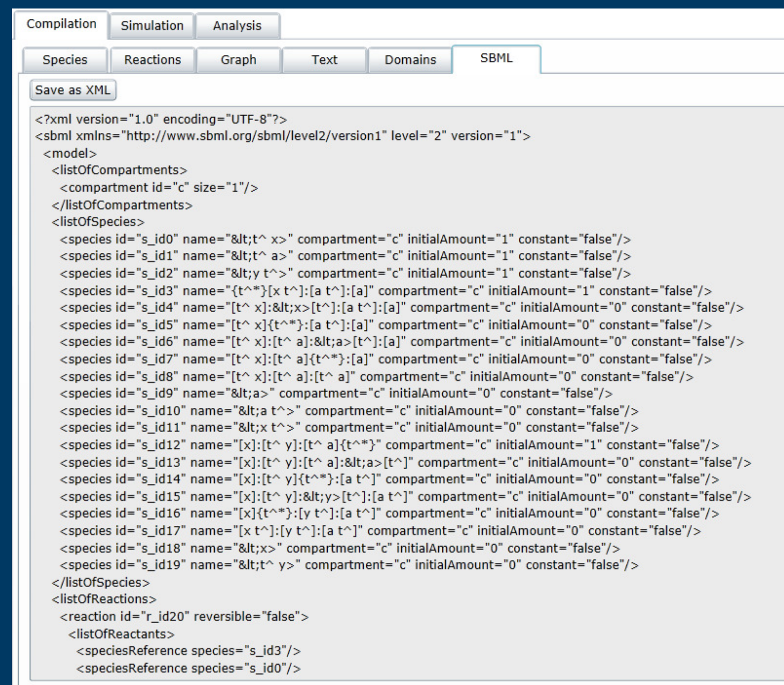
- Recursively computed from the initial structures





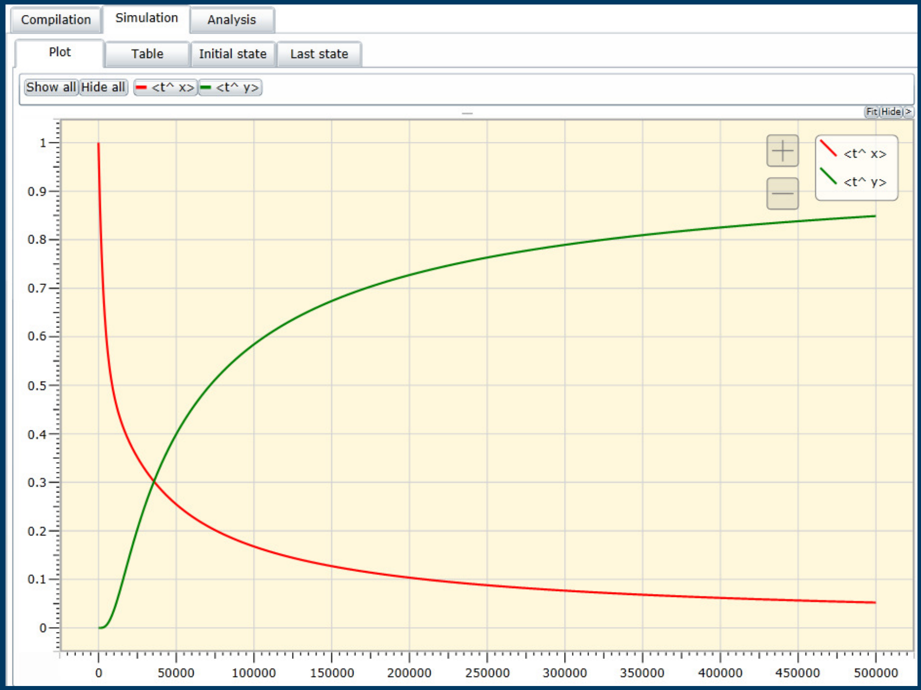
Reaction Graph and Export



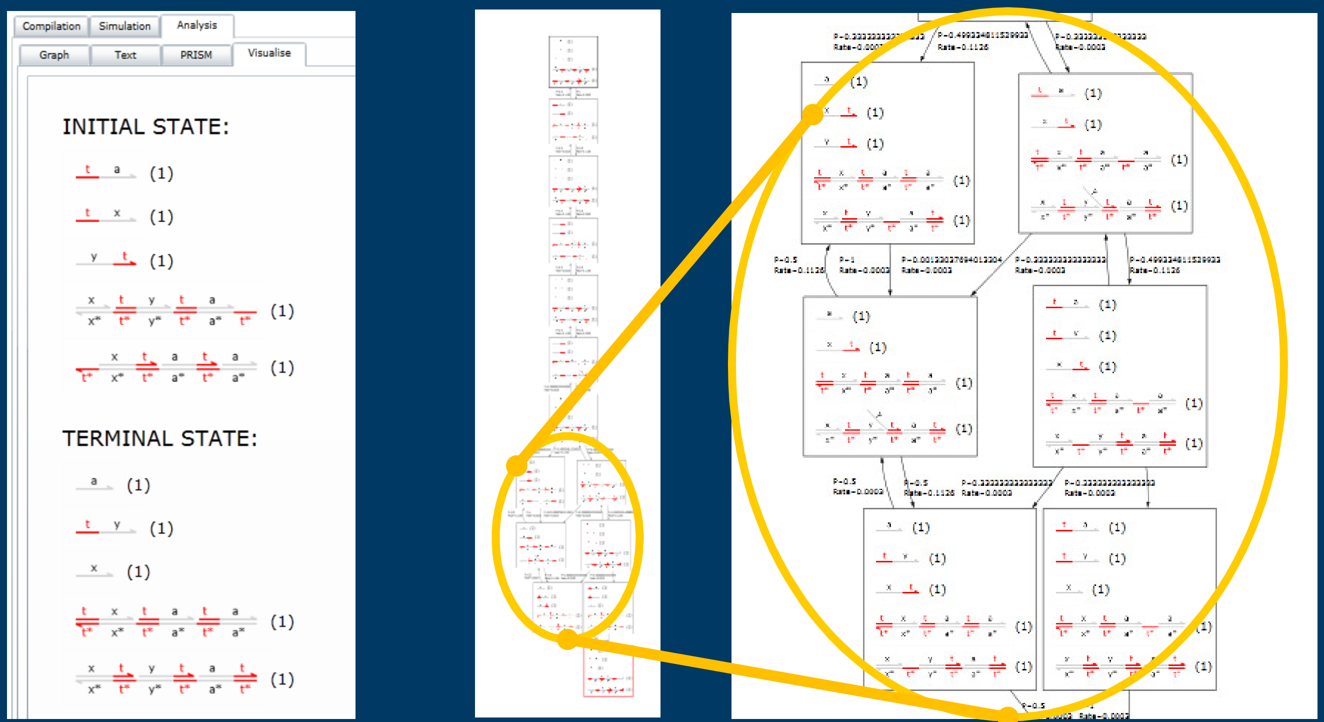


Simulation

- Stochastic
- Deterministic
- "JIT"

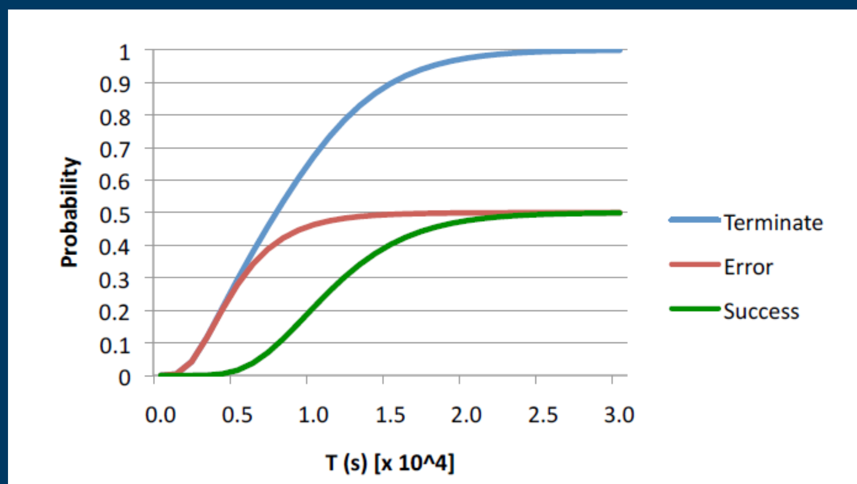


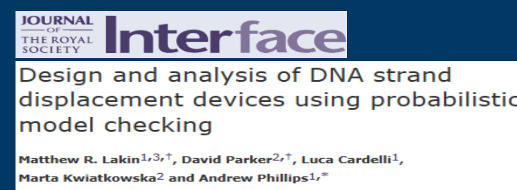
State Space Analysis



Modelchecking

- Export to PRISM probabilistic modelchecker




JOURNAL OF THE ROYAL SOCIETY Interface

Design and analysis of DNA strand displacement devices using probabilistic model checking

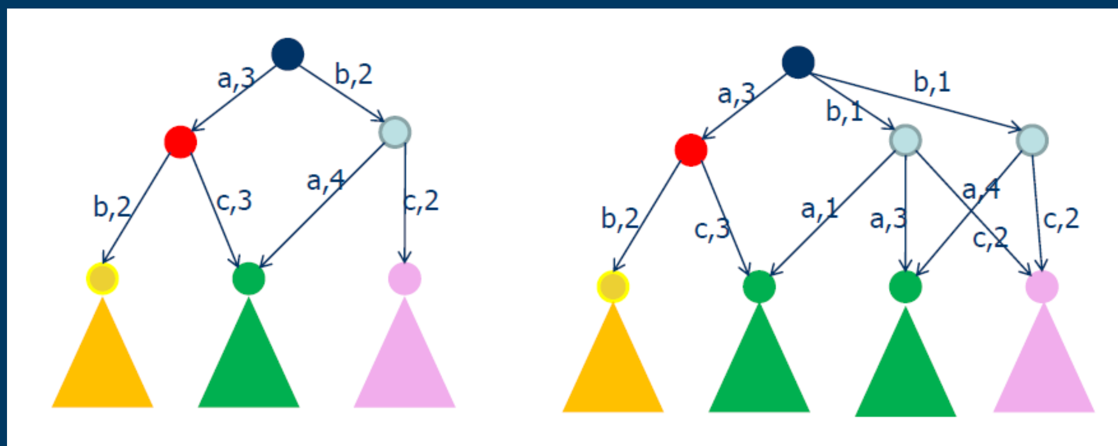
Matthew R. Lakin[1,3,†], David Parker[2,†], Luca Cardelli[1], Marta Kwiatkowska[2] and Andrew Phillips[1,*]

Verification

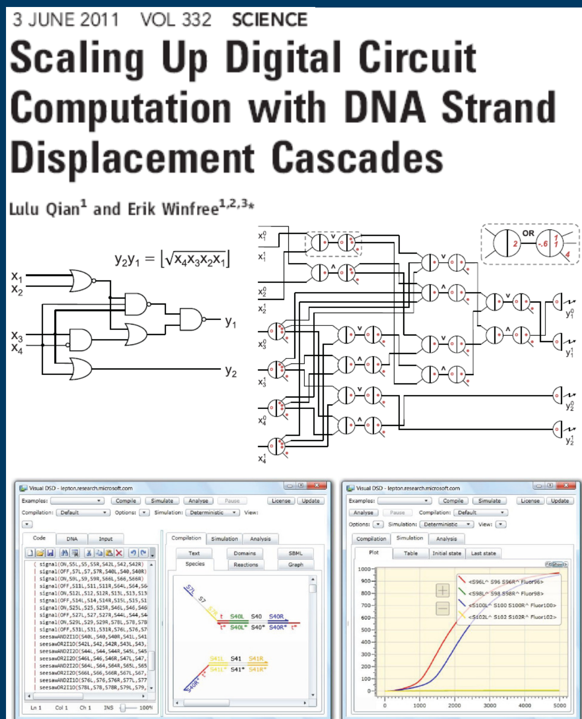
- Quantitative theories of system equivalence and approximation.

CONTINUOUS MARKOVIAN LOGICS
AXIOMATIZATION AND QUANTIFIED METATHEORY

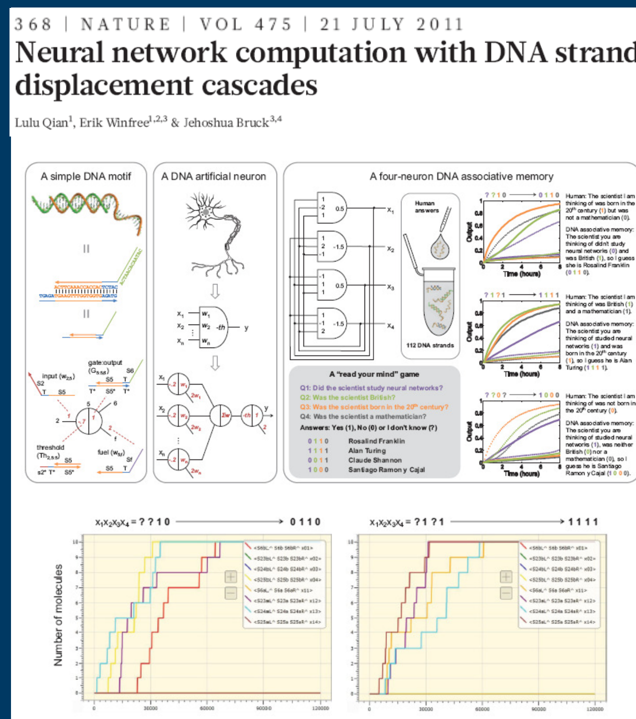
RADU MARDARE, LUCA CARDELLI, AND KIM G. LARSEN



Related Work Supporter by our Tools



Square root of a 4-bit number



Associative memory

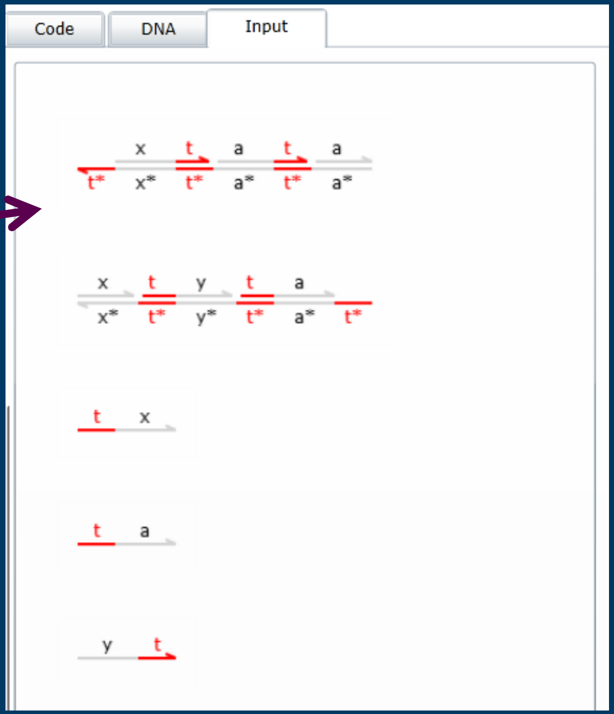
Execution

A software/wetware pipeline for Molecular Programming

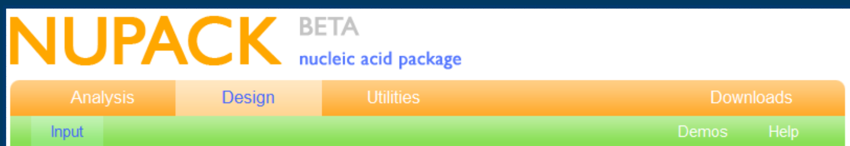
Output of Design Process

- Domain structures
  - (DNA sequences to be determined)

"Ok, how do I run this for real"

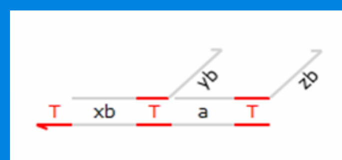


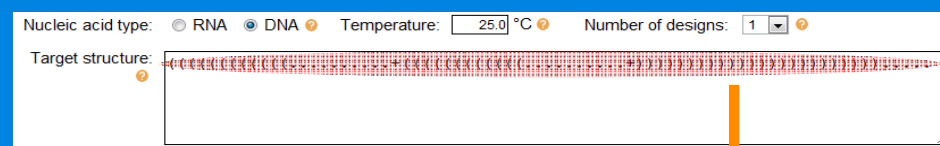
From Structures to Sequences



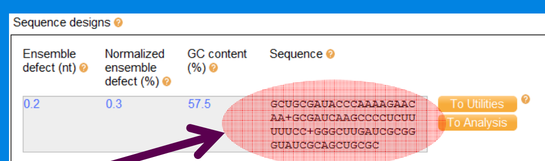
www.nupack.org

DSD Structure → "Dot-Paren" representation



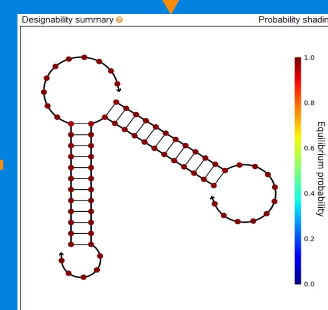


Output Sequences


Sequence designs

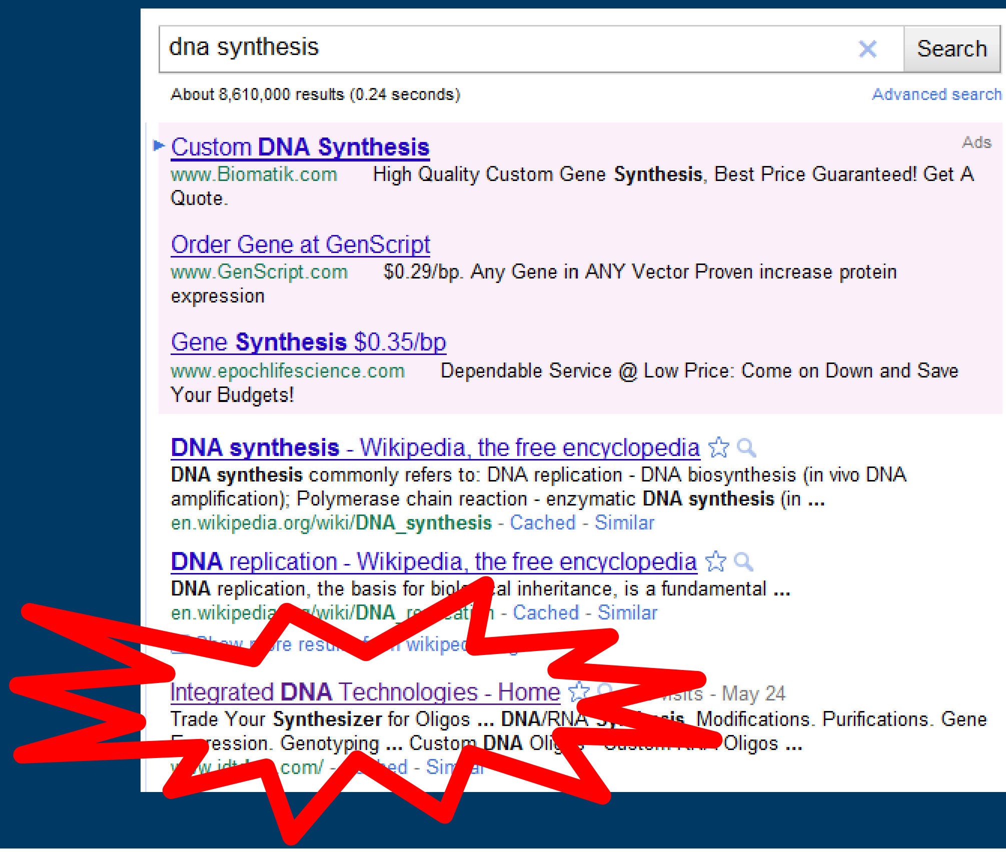
Ensemble defect (nt)	Normalized ensemble defect (%)	GC content (%)	Sequence
0.2	0.3	57.5	GCUGCGAUACCCAAAAGAAC AA+GCGAUCAAGCCCCUCUU UUUCC+GGGCUUGAUCGCGG GUAUCGCAGCUGCGC

Thermodynamic Synthesis



"Ok, where do I buy these?"

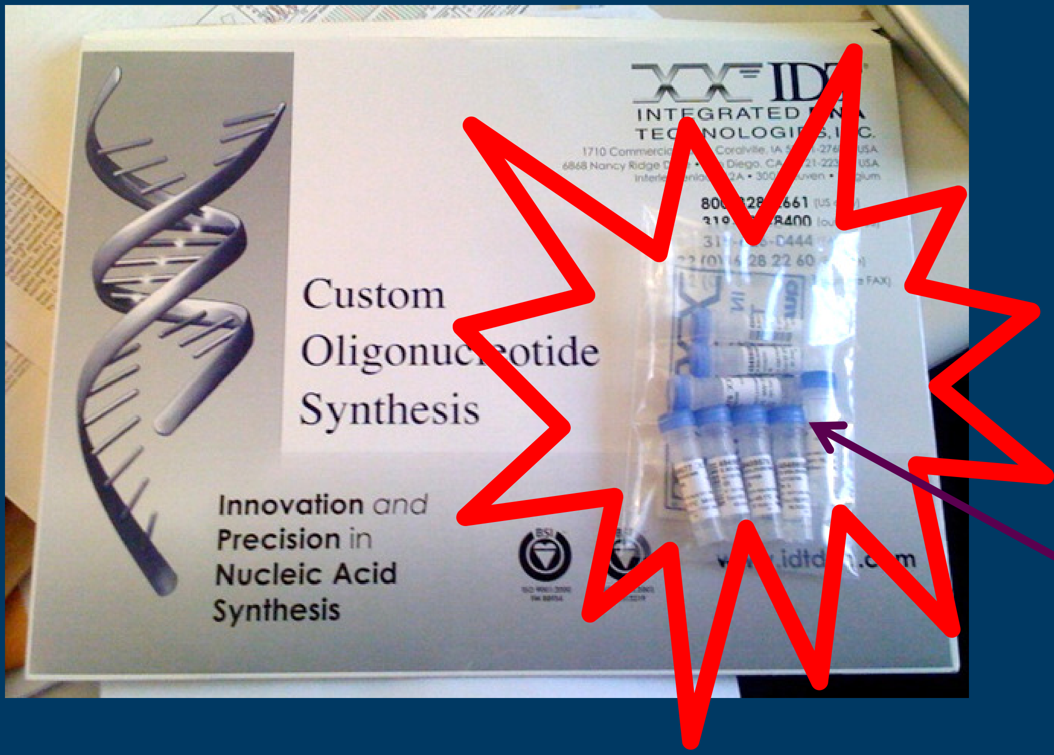
“DNA Synthesis”



From Sequences to Molecules

- Copy&Paste from nupack

Molecules by FedEx

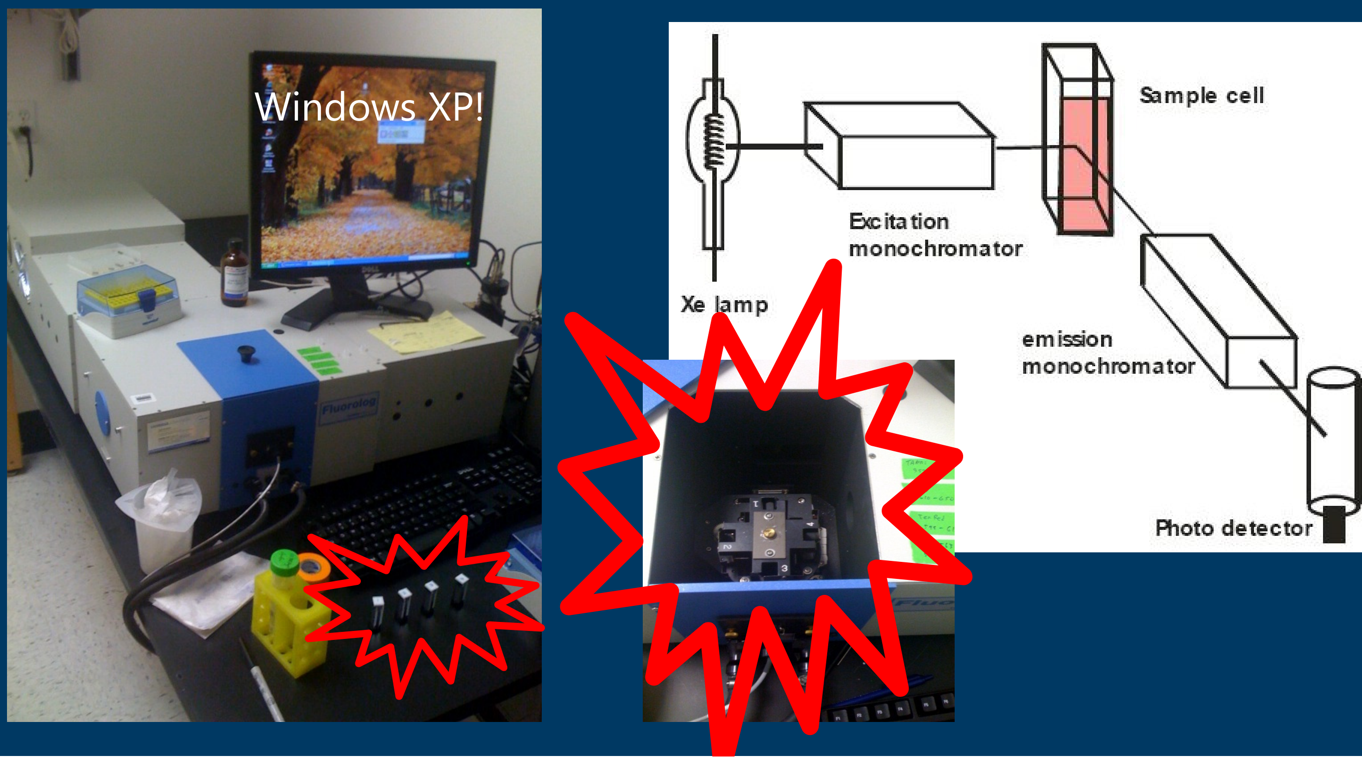


"Ok, how do I run these?"

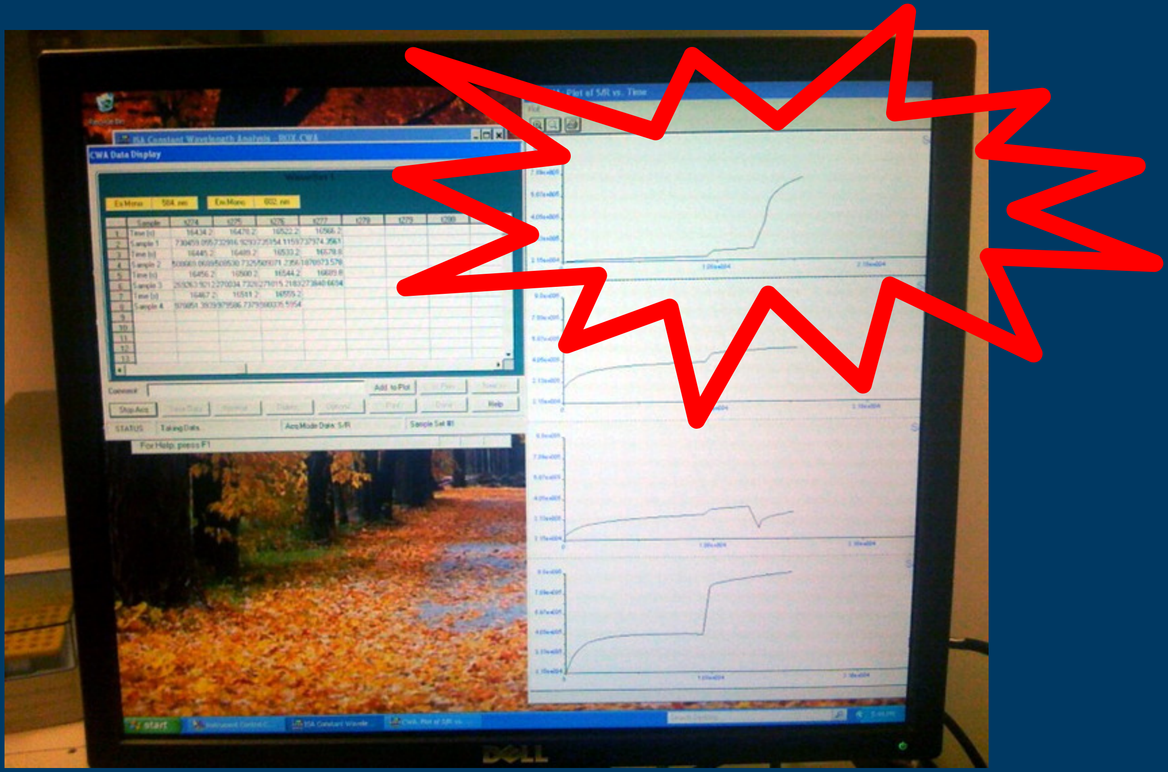
Add Water

Execute (finally!)

- Fluorescence is your one-bit ‘print’ statement



Output

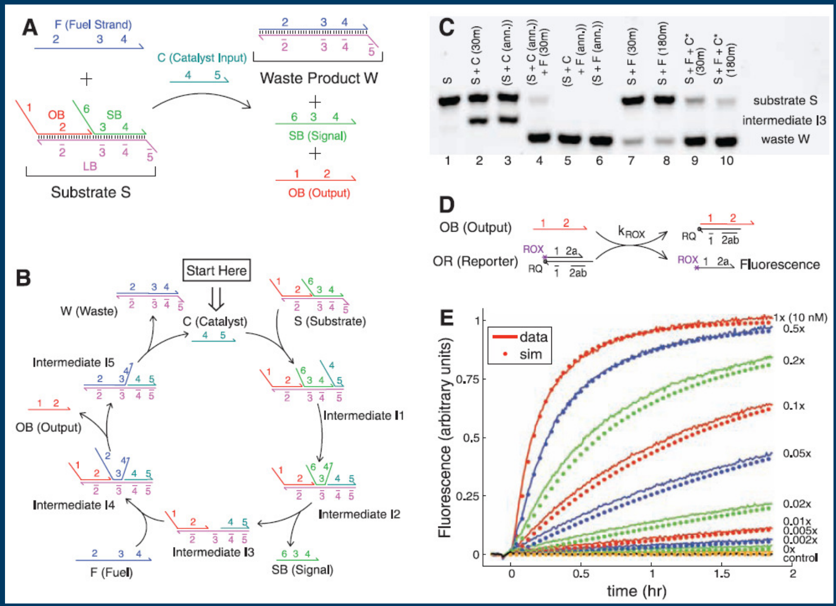


Debugging

- A core dump

Delivery!

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



Microsoft Research

Microsoft

A Molecular Algorithm

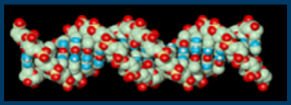
Running something interesting with DNA

Approximate Majority Algorithm

- Given two populations of agents (or molecules)
  - Randomly communicating by radio (or by collisions)
  - Reach an agreement about which population is in majority
  - By converting all the minority to the majority
    [Angluin et al., Distributed Computing, 2007]

- 3 rules of agent (or molecule) interaction
  - X + Y → B + B
  - B + X → X + X
  - B + Y → Y + Y

"our program" →

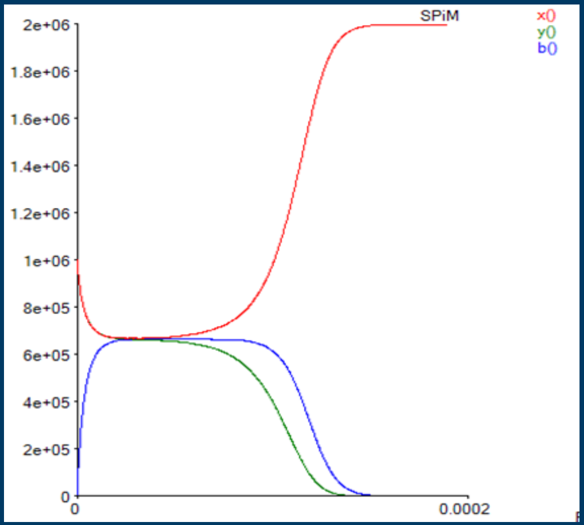


Surprisingly good (in fact, optimal)

- Fast: reaches agreement in O(log n) time w.h.p.
  - O(n log n) communications/collisions
  - Even when initially #X = #Y! (stochastic symmetry breaking)

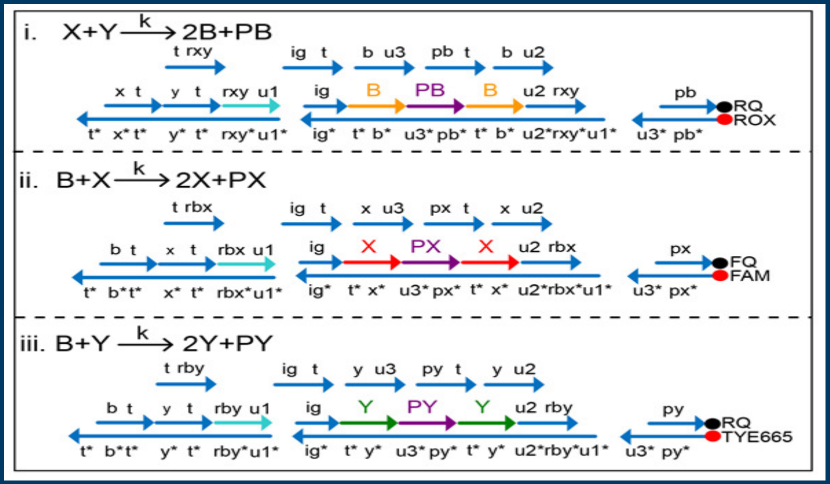
- Robust: true majority wins w.h.p.
  - If initial majority exceeds minority by ω(√n log n)
  - Hence the agreement state is stable

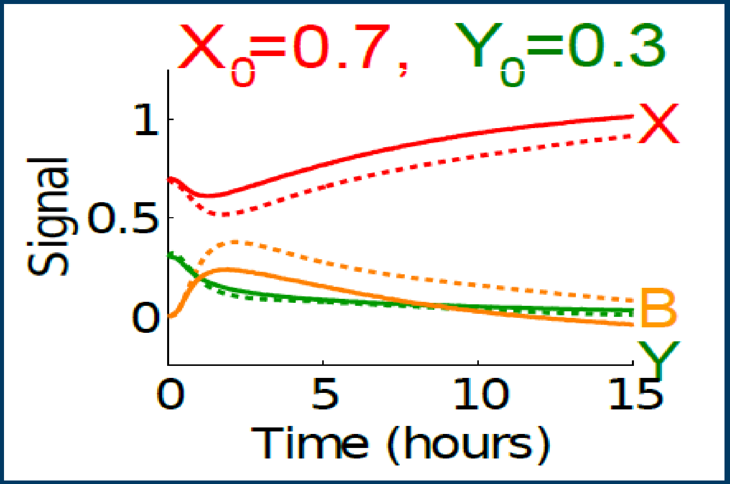
Stochastic simulation of worst-case scenario with initially #X = #Y



DNA Implementation, at U.W.

- Programmable chemical controllers made from DNA
  [Yuan-Jyue Chen, Neil Dalchau, Niranjan Srinivas, Andrew Phillips, Luca Cardelli, David Soloveichik and Georg Seelig]

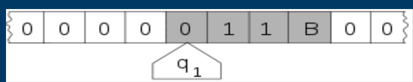




Final Remarks

A Brief History of DNA

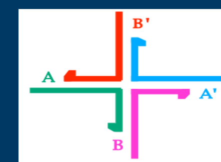
Turing Machine, 1936



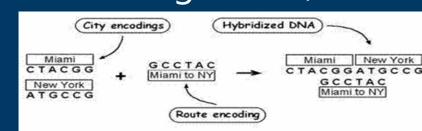
Transistor, 1947

DNA, -3,800,000,000

Structural DNA Nonotech, 1982



DNA Algorithm, 1994



~~Digital Computers~~

Computer programming

Software
systematic manipulation of information

20th century

<??>
systematic manipulation of matter

~~DNA Computers~~

Molecular programming

21th century

Acknowledgments

- Microsoft Research
  - Andrew Phillips, Biological Computation Group
- Caltech
  - Winfree Lab
- U.Washington
  - Seelig Lab

Microsoft Research

Microsoft

Questions?

Resources

- Visual DSD at MSR
  http://research.microsoft.com/en-us/projects/dna/
- Molecular Programming Project at Caltech
  http://molecular-programming.org/
- Georg Seelig's DNA Nanotech Lab at U.W. CS&E
  http://homes.cs.washington.edu/~seelig/

Microsoft