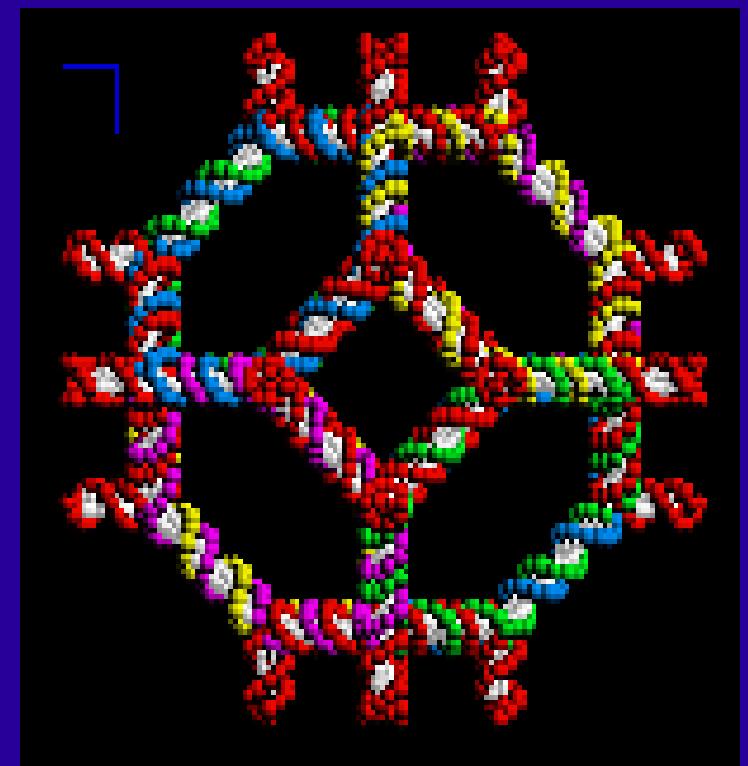


# Molekularne obliczenia na DNA

Piotr Wąsiewicz



Biologia

Chemia

Techniki informacyjne,  
sztuczna inteligencja,  
informatyka

# Komputery - zastosowania

## Komputery ogólnego zastosowania

- automaty
- maszyna Turinga
- maszyna von Neumanna

## Komputery dedykowane

- maszyny wnioskujące
- systemy logiczne
- smart sensors
- transducers

# Komputery – medium obliczeniowe

- elektroniczne – elektryny
- nieelektroniczne
  - mechaniczne
  - kwantowe
  - chemiczne
    - DNA
    - białkowe
    - specjalne związki

# Komputery – rodzaj realizacji

- w ciele stałym – półprzewodniki
- przepływowe – płyny
- przepływowe - gazy

# Komputer biomolekularny - Shapiro

Jest autonomiczną programowalną maszyną liczącą, której sygnał wejściowy, sygnał wyjściowy, “software” oraz “hardware” są implementowane na molekułach

# Dla komputerów na DNA (automaty)

- sygnał wejściowy, wyjściowy – cząsteczki DNA
- software: reguły zmiany stanu – zakodowane na cząsteczkach DNA
- hardware: cięcie cząsteczek DNA odpowiednimi enzymami

# Rodzaje komputerów przepływowych na DNA

- DNA jest tylko medium obliczeniowym
  - hardware: odpowiednie reaktory przepływowe
  - software: sterowanie przepływami i reakcjami
- DNA odgrywa rolę medium obliczeniowego oraz może pełnić rolę procesora
  - hardware: w postaci różnych cząsteczek
  - software: odpowiedni algorytm sterujący

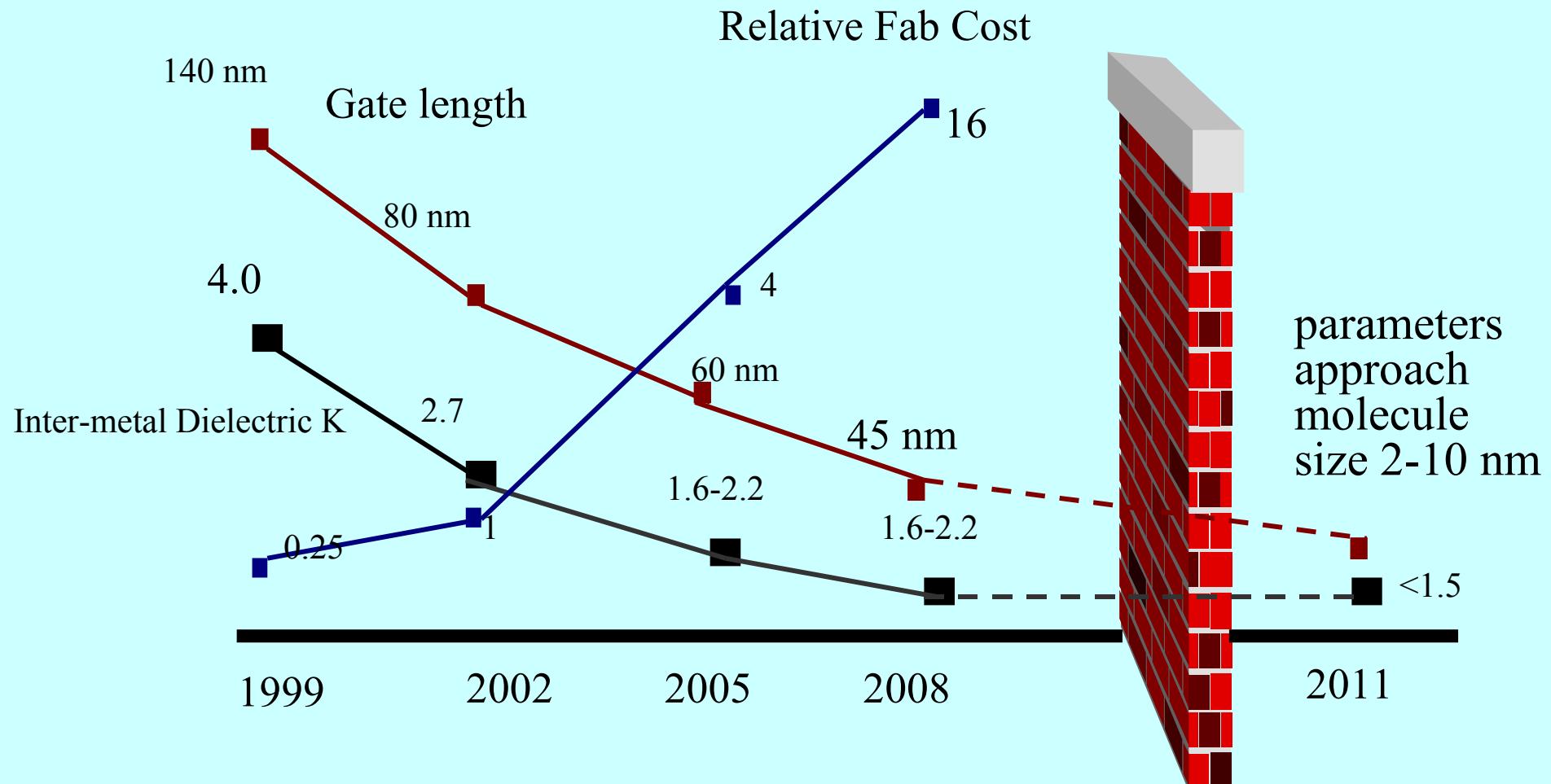
# Hybrydowy komputer przepływowy na DNA

- Obliczenia molekularne na DNA realizowane w lab-on-a-chip
- Sterowanie pneumatyczne zaworami w lab-on-a-chip

# Zalety komputerów molekularnych

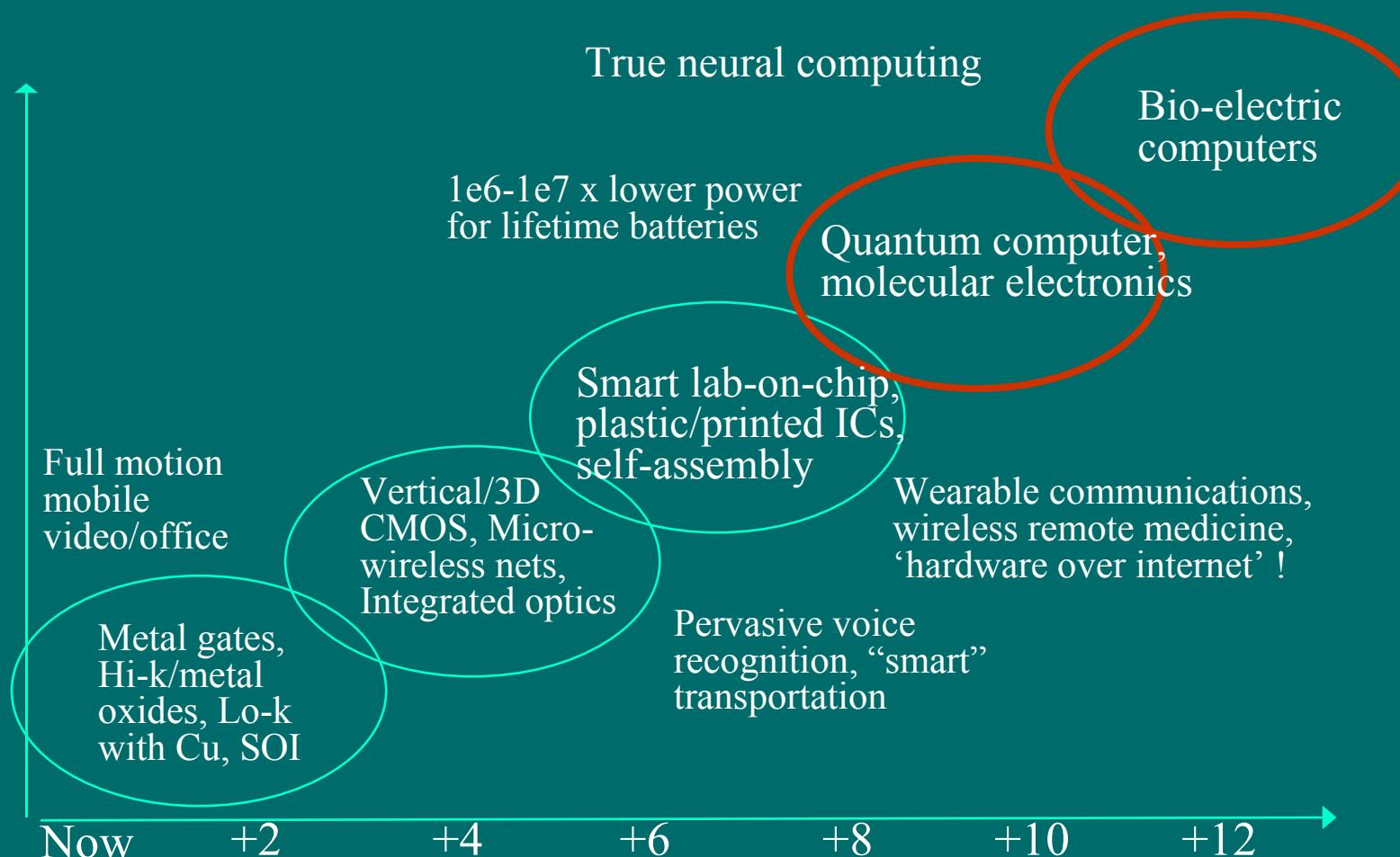
- Implementacja w nanotechnologii
- Możliwość obliczeń równoległych i wieloprocesorowych
- Obliczenia są stochastyczne
- Są one dostosowane do środowiska badawczego inżynierii genetycznej, biologii, chemii i medycyny

# Granica możliwości technologii krzemu - CMOS



Source: Texas Instruments and  
ITRS IC Design Technology Working  
Group

# Przyszłość nanotechnologii



Source: Motorola, Inc, 2000

# Transistor Nanotechnology

90nm Node

P1262

2003



65nm Node

P1264

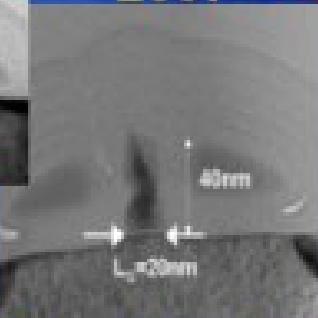
2005



45nm Node

P1266

2007



Improving performance through innovative materials, processes and structures.

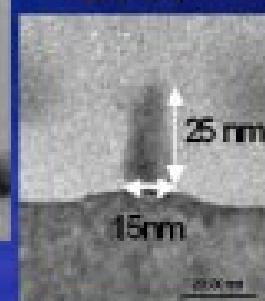
50nm Length  
(Production)

30nm Length  
(Development)

32nm Node

P1268

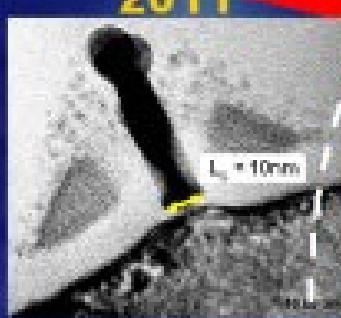
2009



22nm Node

P1270

2011



III-V Device  
Prototype  
(Research)

Uniaxial  
Strain

20nm Length  
(Development)

15nm Length  
(Research)

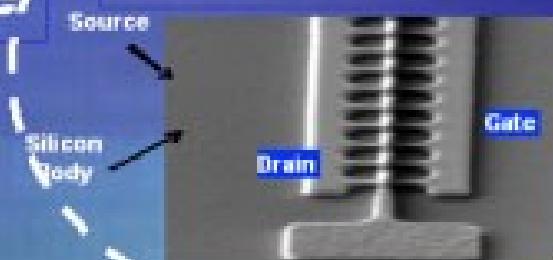
10nm Length  
(Research)

C-nanotube  
Prototype  
(Research)

Nanowire  
Prototype  
(Research)

High-K  
Metal Gate/

Non-planar  
Tri-Gate



2013-2019

intel.

Other names and brands may be trademarks or the property of others.

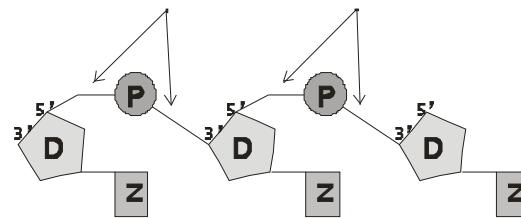
Copyright © Intel Corporation 2012

# Molekularne obliczenia

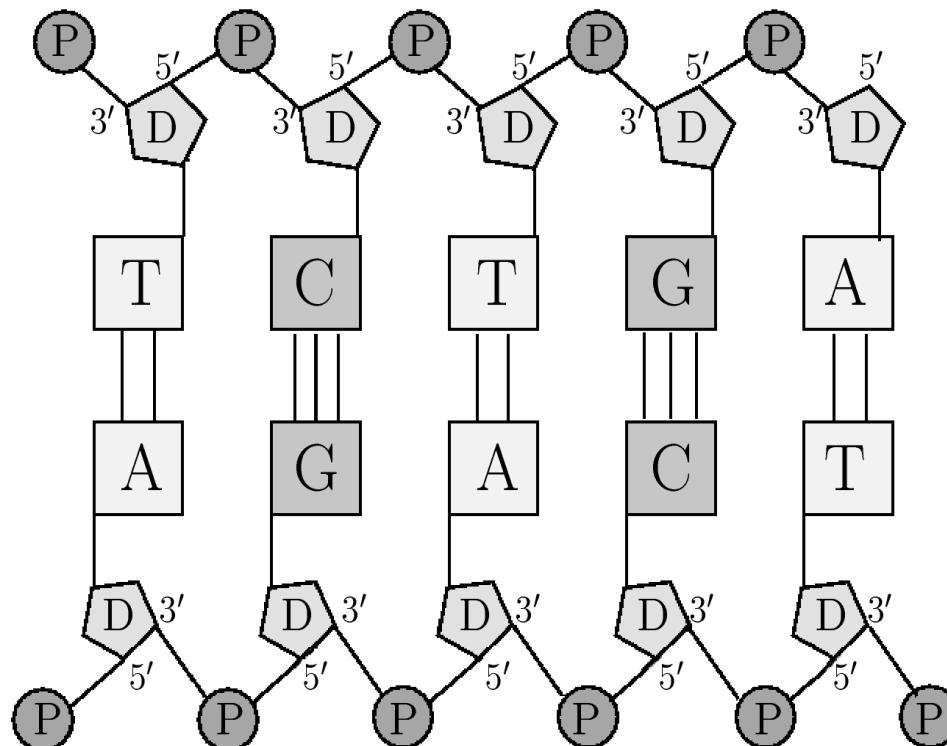
- Obliczenia molekularne to algorytmy technik informacyjnych implementowane w czasie reakcji chemicznych lub w warstwach cienkich złożonych molekuł.
- Molekuły przenoszą информацию, reakcje chemiczne ją przetwarzają.
- Badania nad obliczeniami molekularnymi są sponsorowane przez uniwersytety (Princeton, MIT, USC, Rutgers, etc) oraz firmy takie jak NEC, Lucent Bell Labs, Telcordia, IBM.

# DNA struktura molekularna

- Pojedyncza nić DNA zwana też oligonukleotydem, odcinkiem DNA

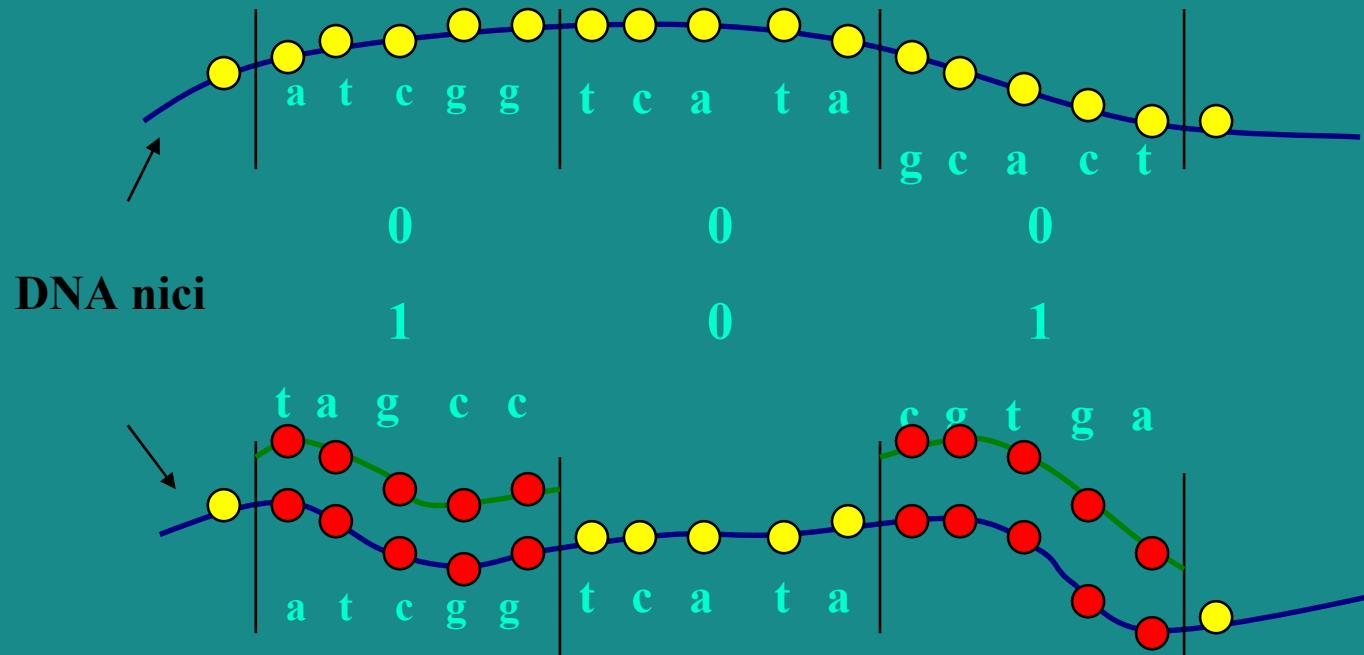


- Podwójny odcinek DNA



# Zapis informacji na DNA

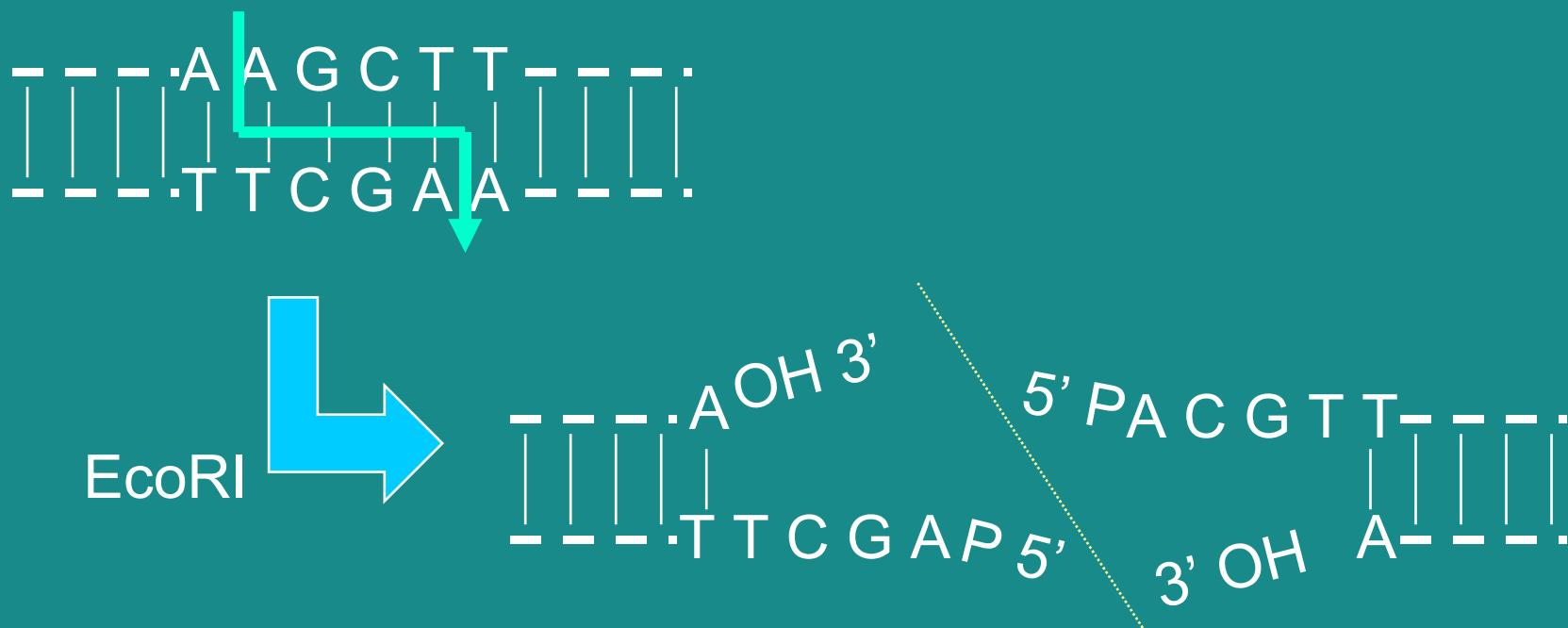
Tworzenie nici DNA



Czytanie nici DNA

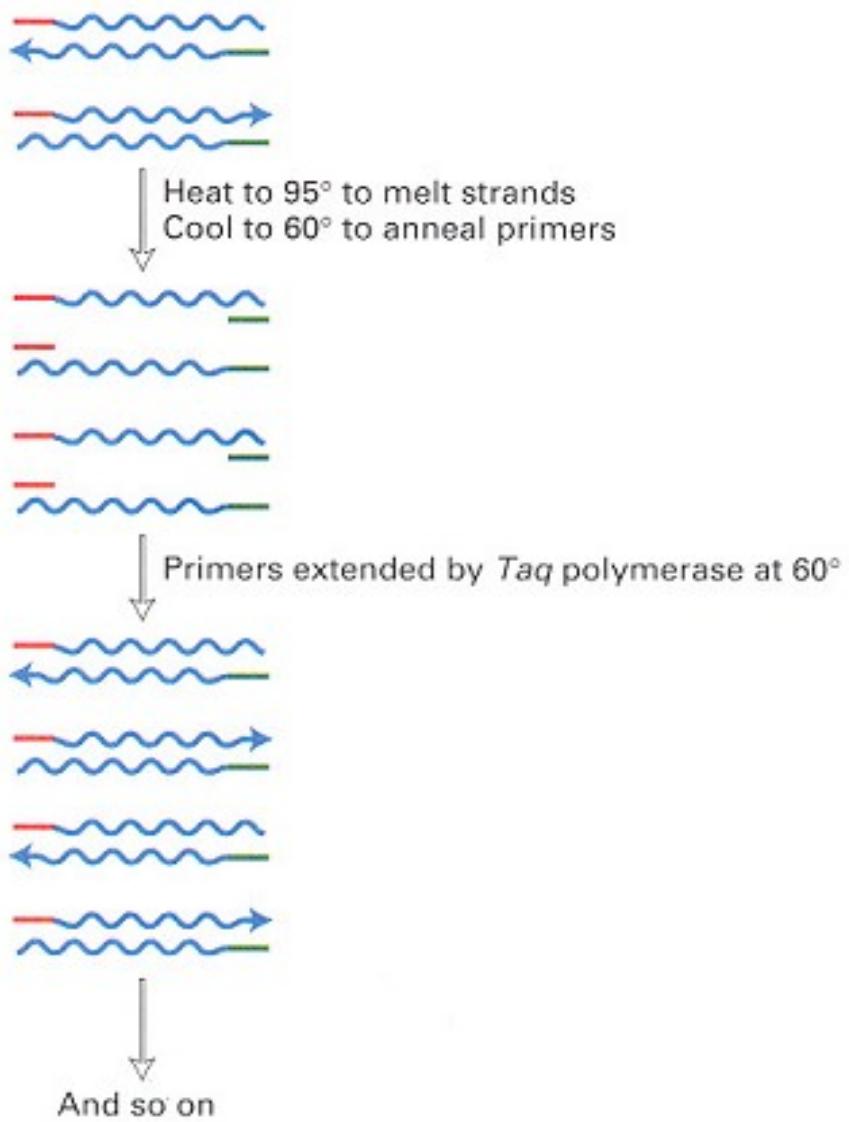
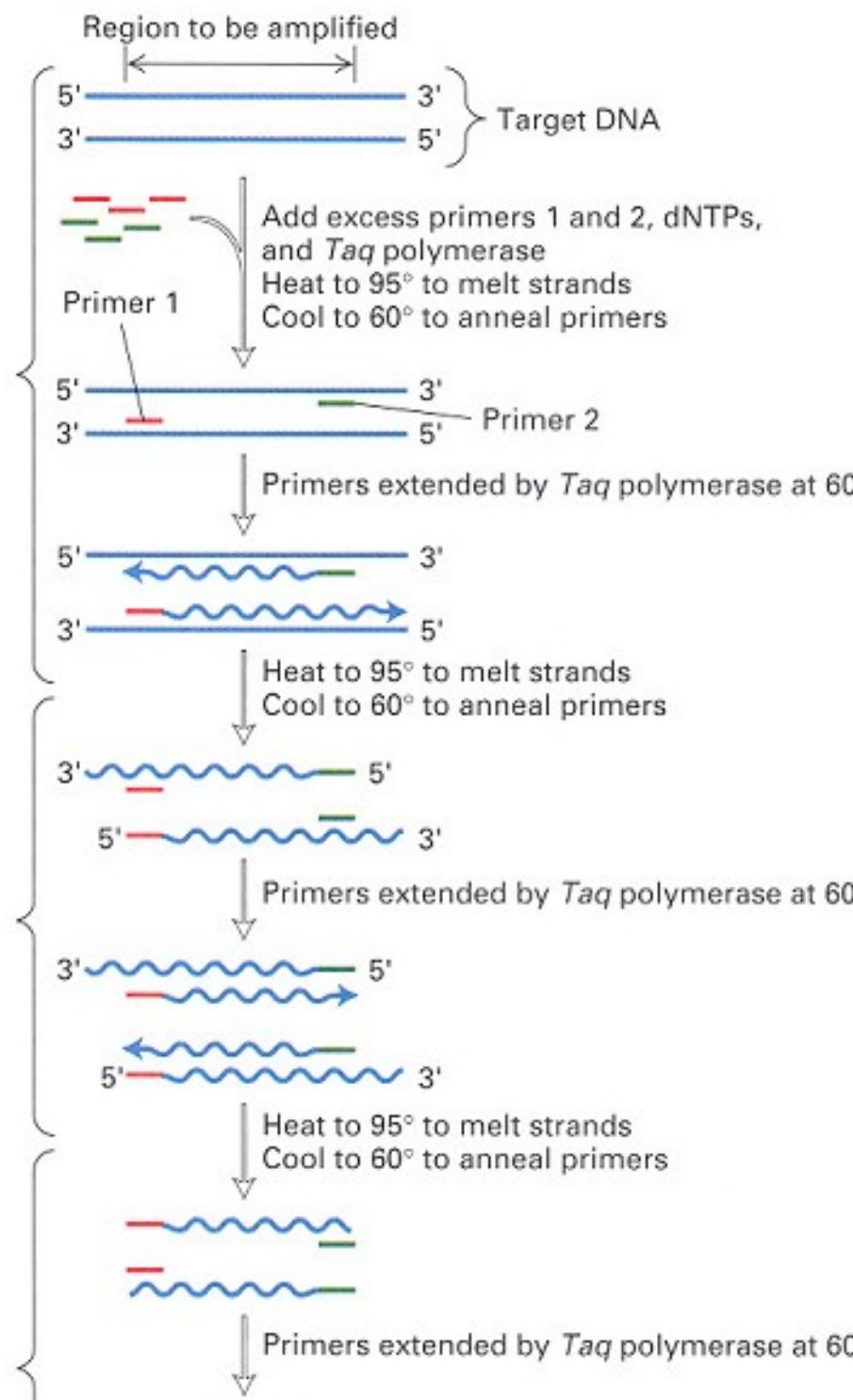
# Enzymy tnące

- Enzymy restryktazy przecinają DNA



# PCR

## (Polymerase Chain Reaction)



# Moc obliczeniowa molekuł

- $6.022 \times 10^{23}$  molekuł na mol
- Masywnie równoległa metoda Monte Carlo
  - Desktop:  $10^9$  operacji na sekundę
  - Superkomputer:  $10^{12}$  operacji na sekundę
  - $1 \mu\text{mol DNA}$ :  $10^{26}$  reakcji
- Energooszczędność
  - $1 \text{ J}$  na  $2 \times 10^{19}$  operacji
- Pojemność nanopamięci: 1 bit na  $\text{nm}^3$

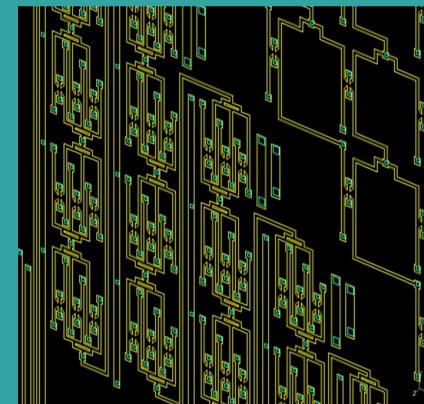
# Moc obliczeniowa molekuł cd.

- Superkomputer || Obliczenia na DNA
  - $10^{12}$  op/sec ||  $10^{14}$  op/sec
  - $10^9$  op/J ||  $10^{19}$  op/J (in ligation step)
  - 1 bit per  $10^{12}$  nm<sup>3</sup> || 1 bit per 1 nm<sup>3</sup> (video taśma || molekuły)

# Molecular Computer on a Chip



+

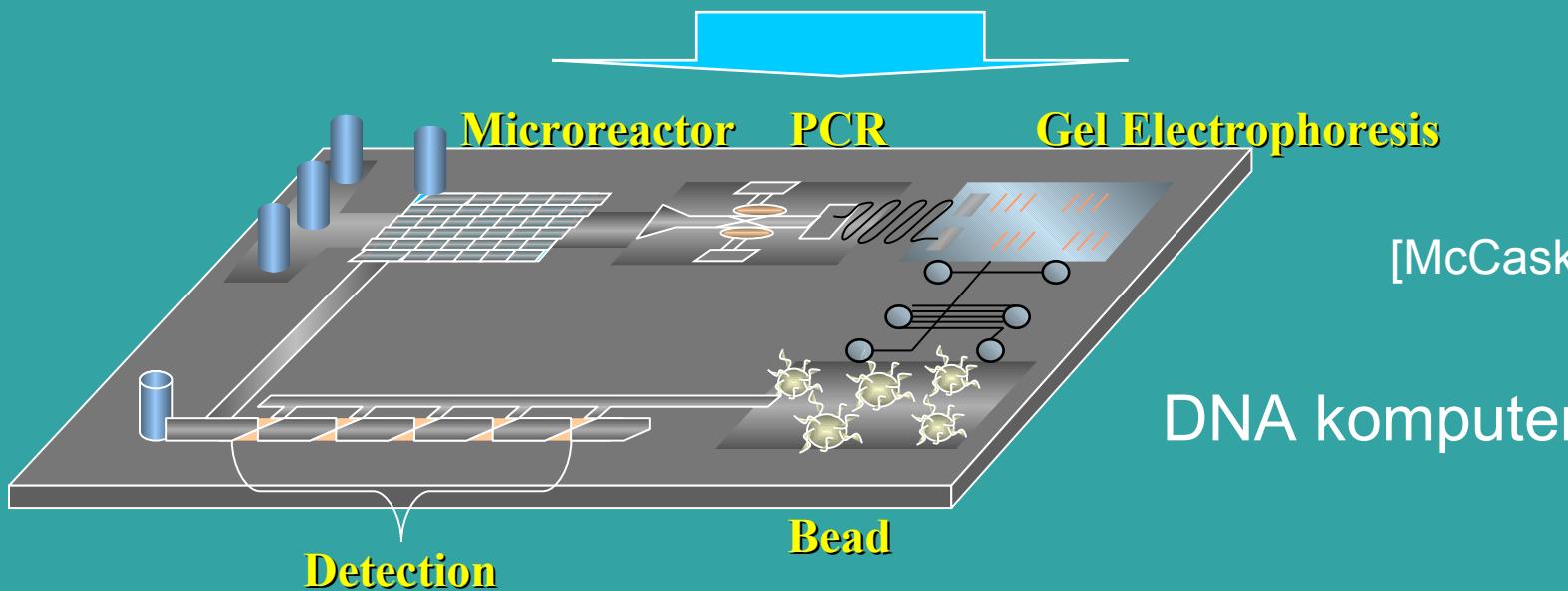


=



Algorytm  
obliczeń na DNA

MEMS (Microfluidics)



[McCaskill, Zhang]

# Mikroprzepływowe systemy lab-on-a-chip

Są to płytki krzemowe na których wykonane są technikami jak dla scalonych układów elektronicznych – różne urządzenia do przesyłania roztworów oraz przeprowadzania reakcji, a więc: reaktory, kanały przewodzące, miejsce do przechowywania próbek, zawory, pompki, miksery, grzejniki, czujniki pomiarowe etc.

Technologia ta pozwala przeprowadzać eksperymenty chemiczne w objętościach pikolitrów.

# Zalety lab-on-a-chip

- znaczna oszczędność zużycia reagentów
- mniejsze zanieczyszczenie środowiska
- duża przepustowość
- redukcja czasu
- nieosiągalny dotychczas stopień automatyzacji
- redukcja kosztów
- możliwość miniaturyzacji całego laboratorium i uczynienie go przenośnym
- możliwość prowadzenia skomplikowanych analiz chemicznych przez osoby o małych kwalifikacjach

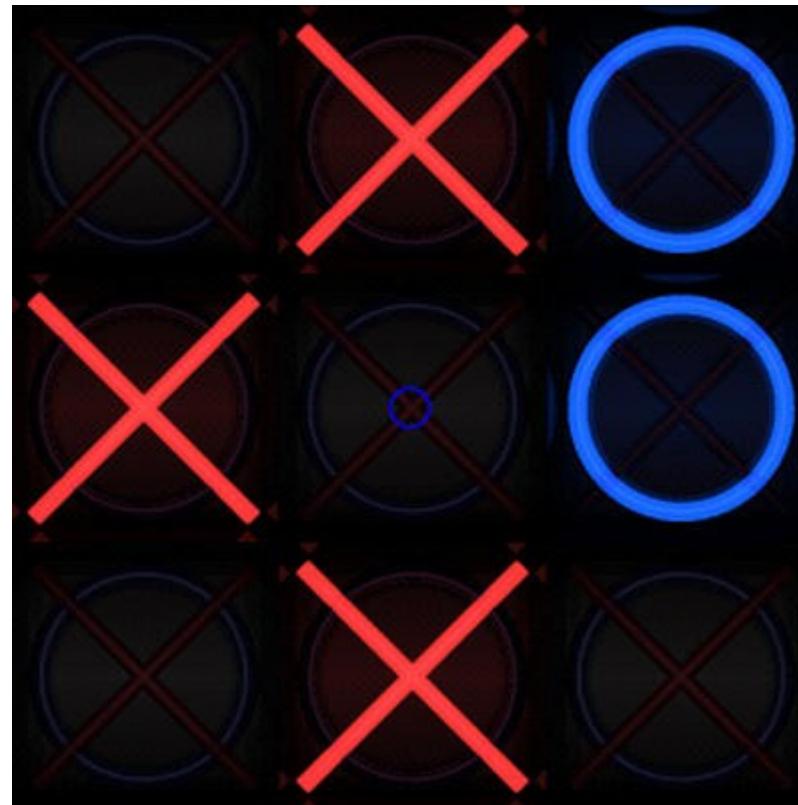
# Szybki rozwój lab-on-a-chipsów

Największe obecnie realizowane systemy zawierają na chipie około 3,5 tys zaworów oraz 1 tys niezależnie adresowanych komór przechowujących próbki

# Prawo Moore'a dla lab-on-a-chipsów

Liczba zaworów na chipsie na jednostkę powierzchni podwaja się co 4,5 miesiąca

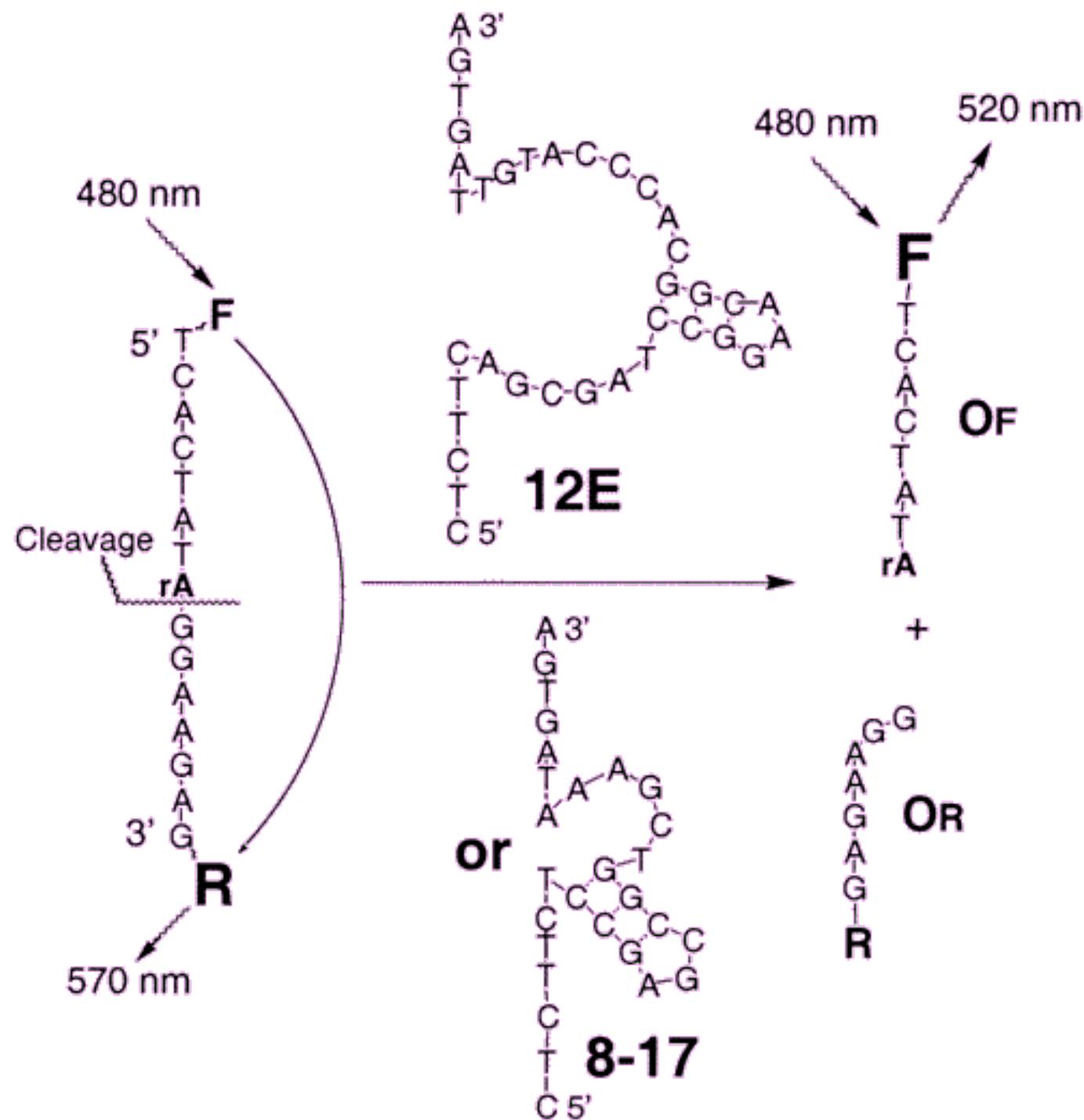
# Gra w kółko i krzyżyk

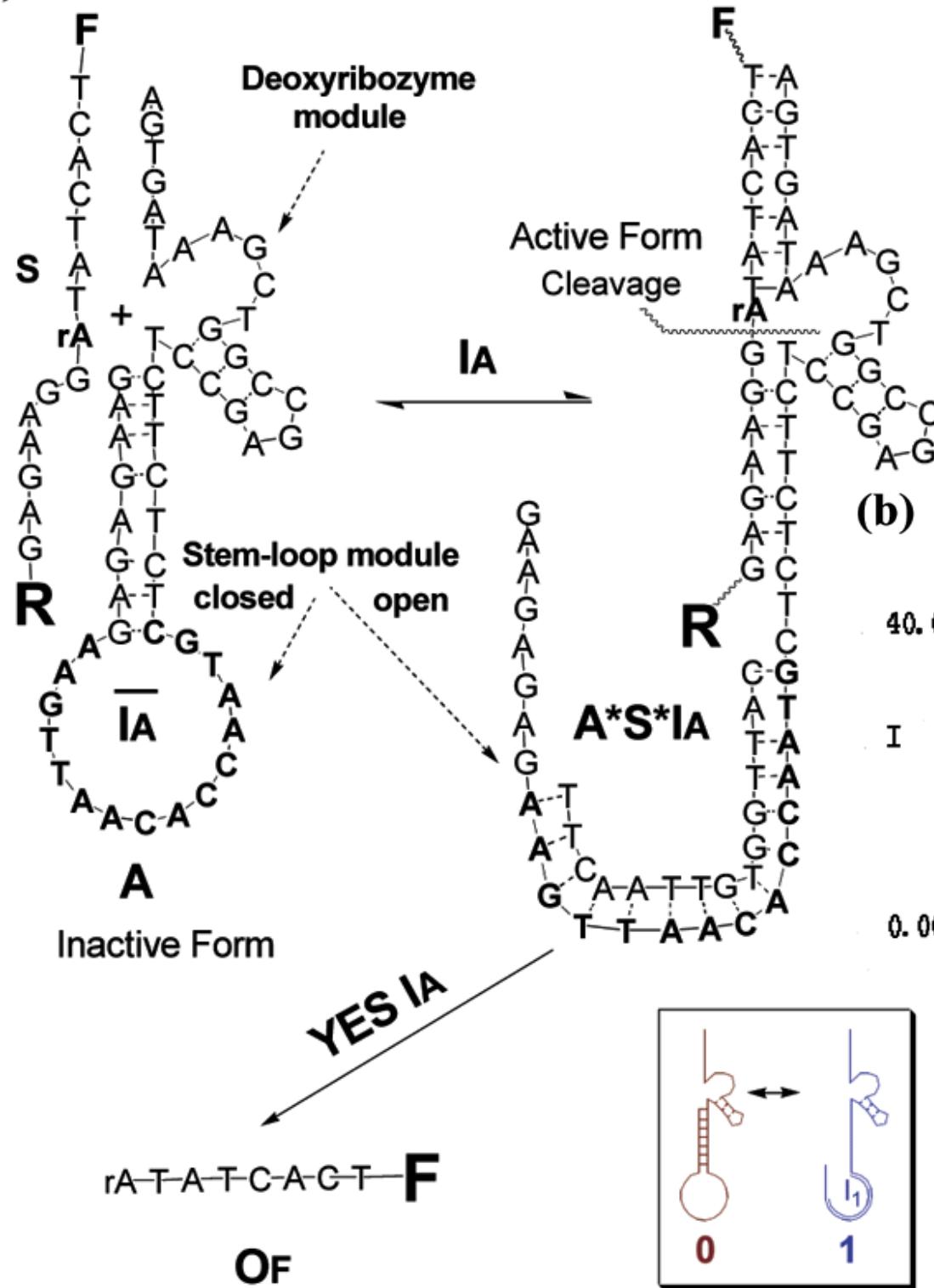


M.Stojanovic, D.Stefanovic, A deoxyribozyme-based molecular automaton, *Nature Biotechnology*, 21 (9) 2003: 1069-1074.

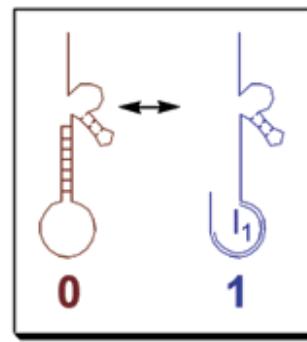
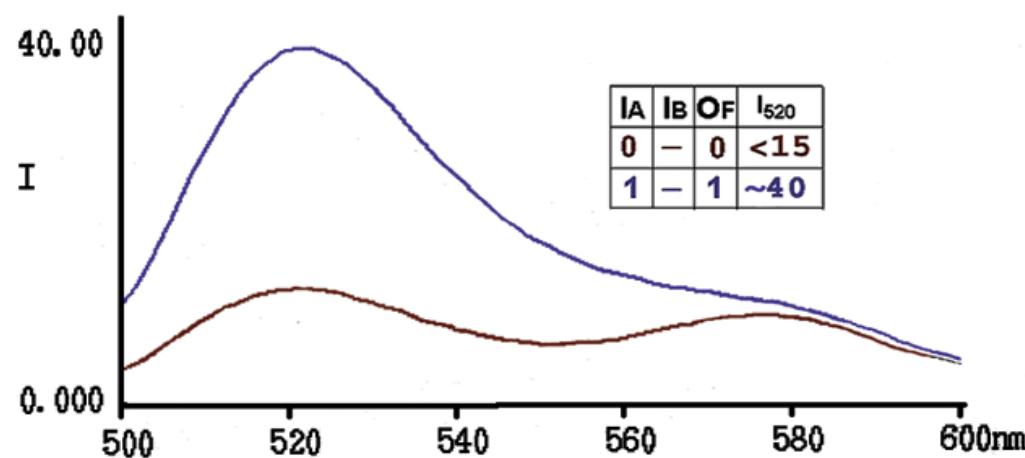
## Struktura RNA tnąca odcinek FR

Po przecięciu fluorescencja się zwiększa.

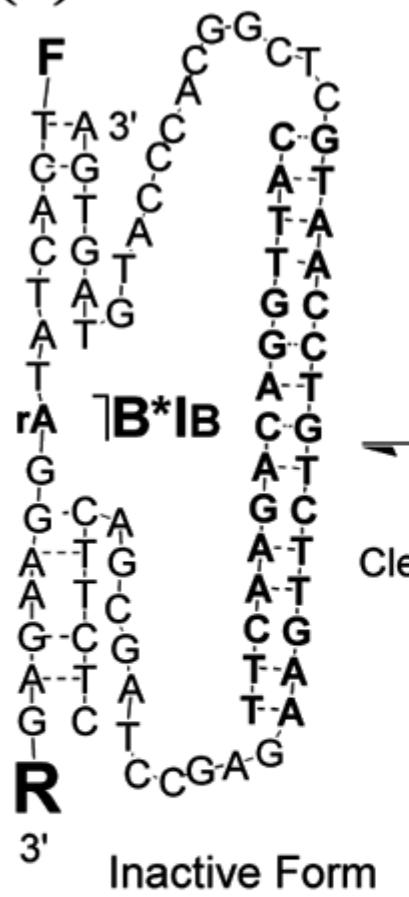


**(a)**

## Detektor sygnału IA

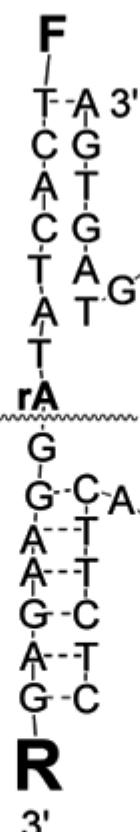
**(b)**

**(a)**

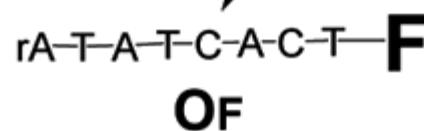


**IB**

Cleavage

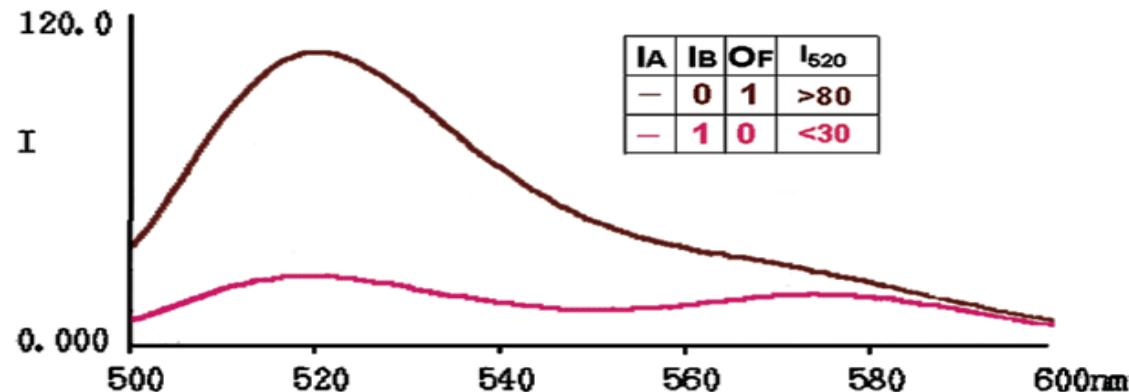


**NOT IB**

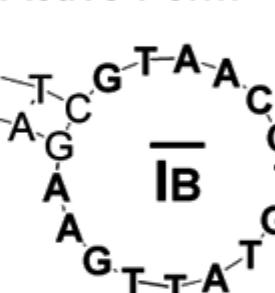


**OF**

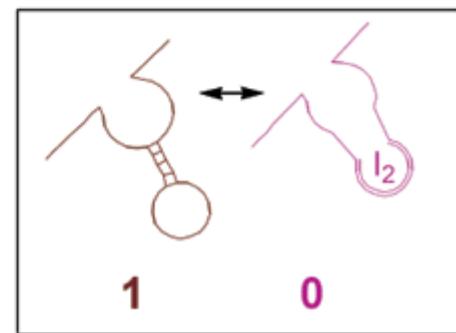
**(b)**



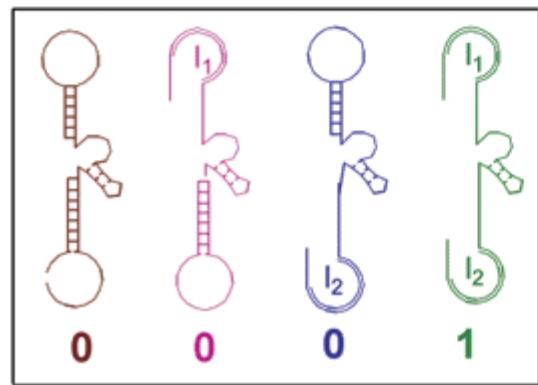
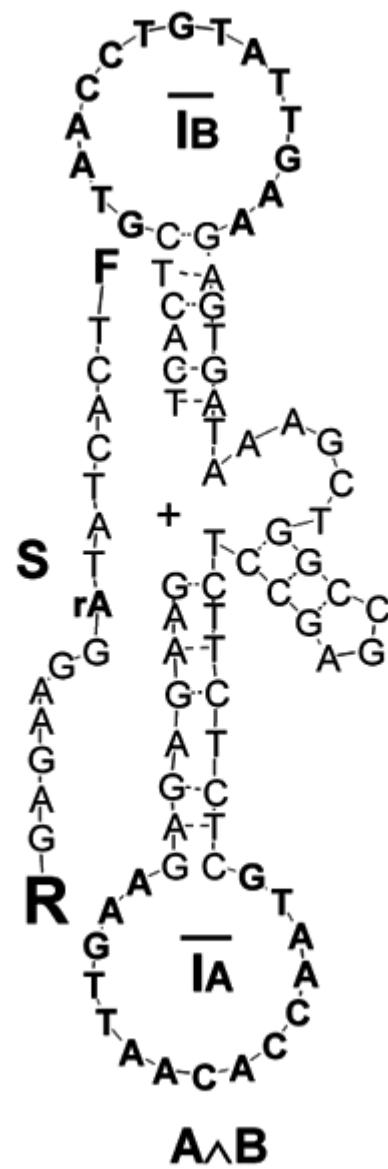
Active Form



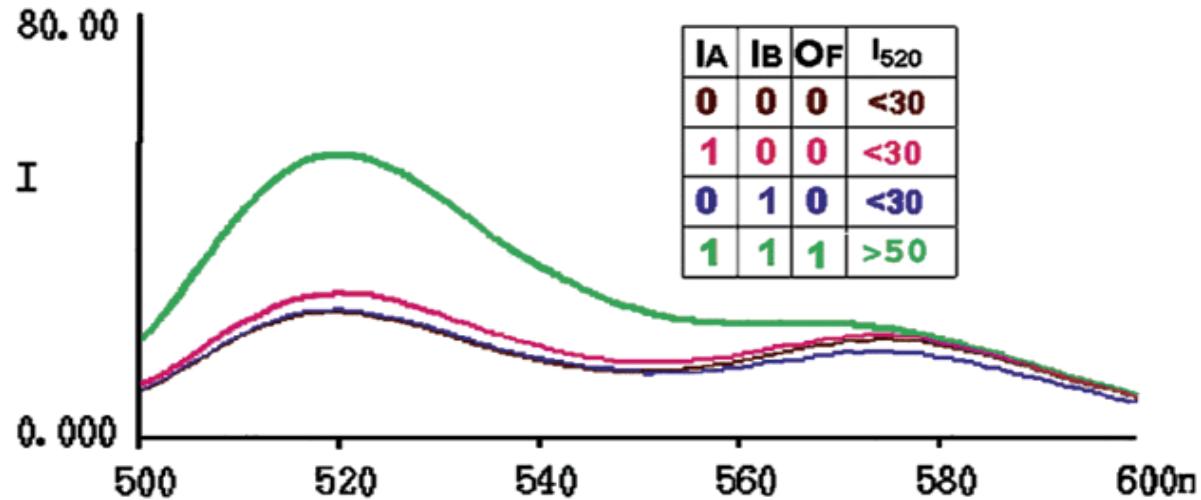
**Negator molekularny  
NOT IB**



(a)



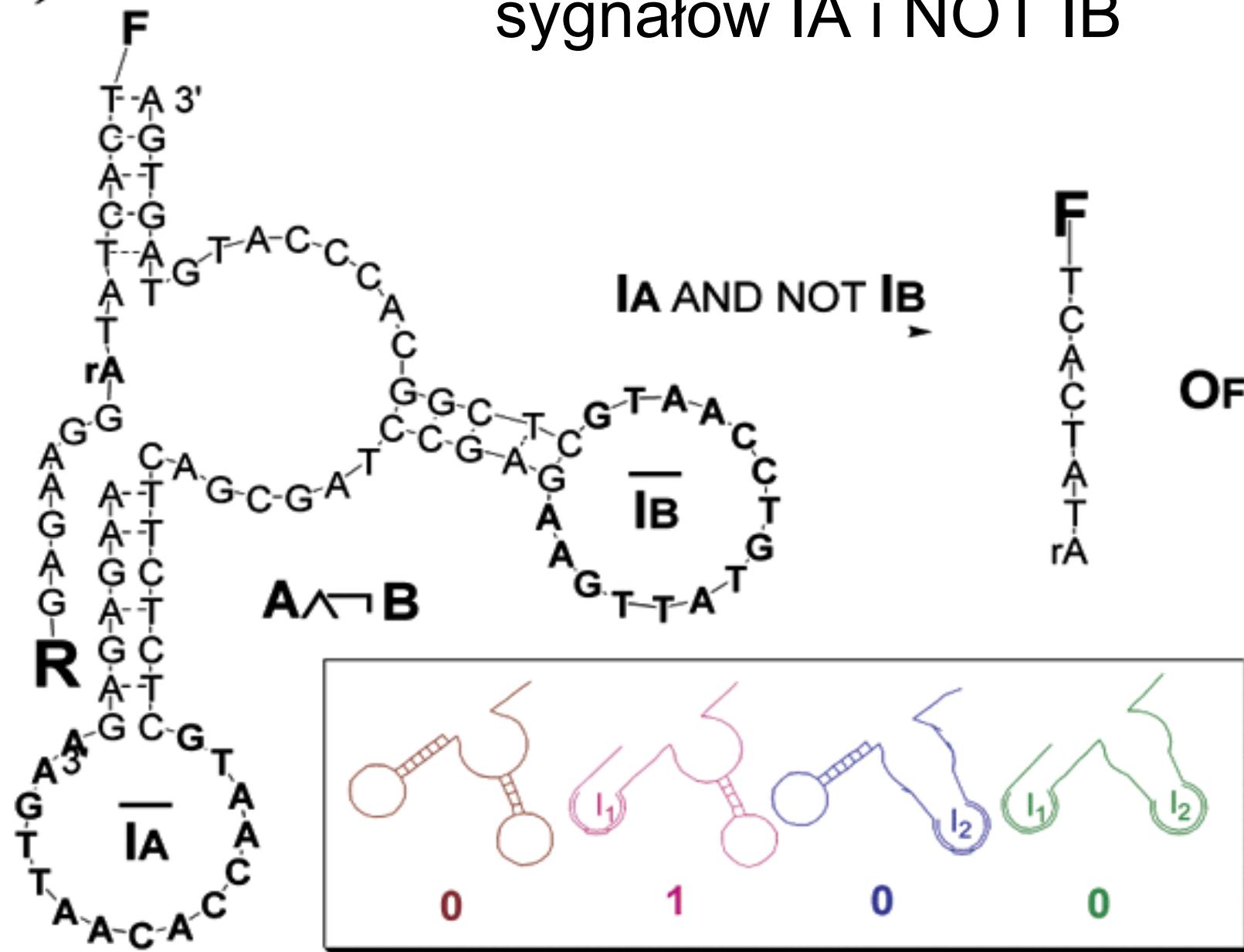
(b)



Bramka AND  
sygnalów IA i IB

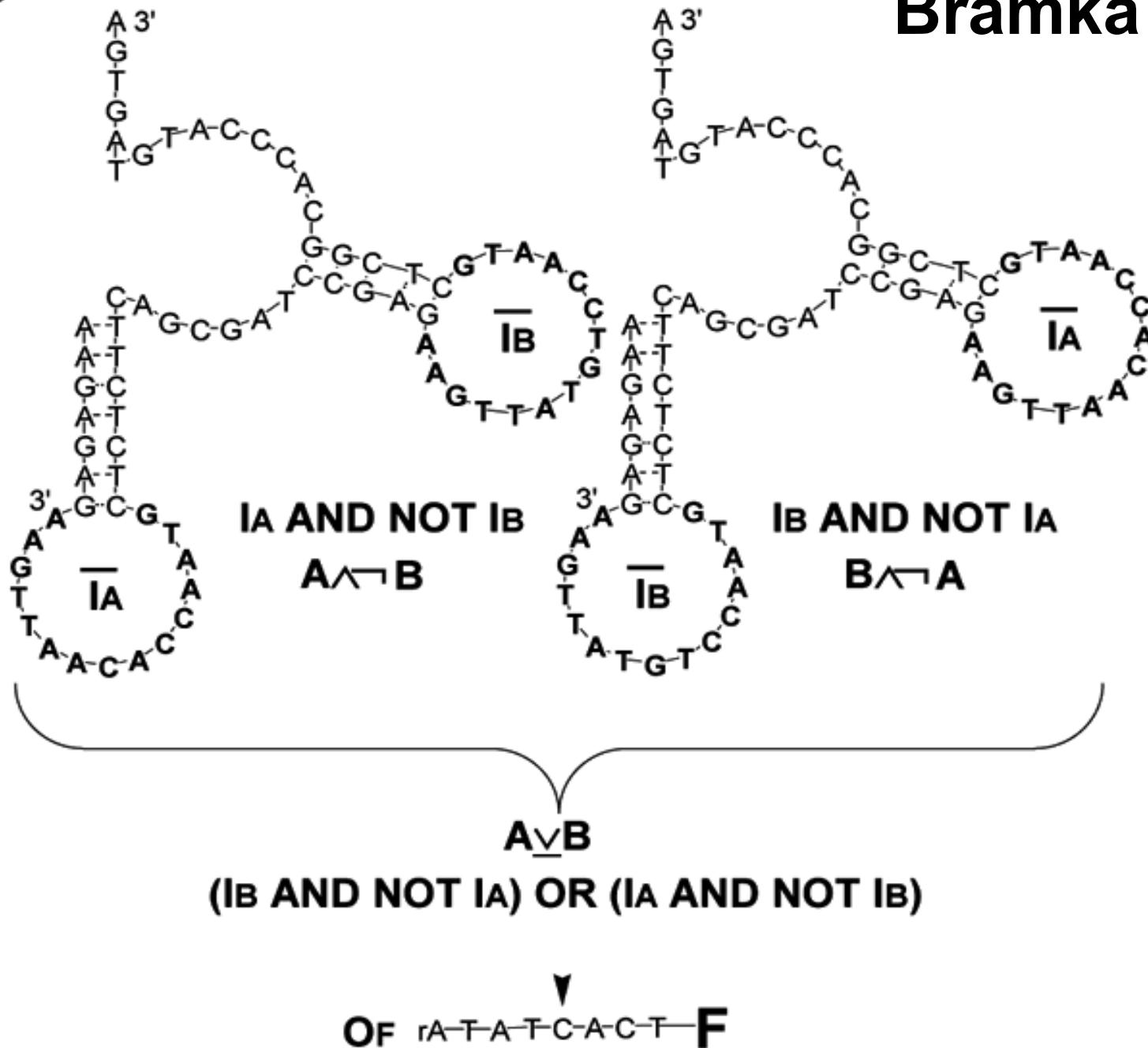
# Bramka AND sygnalów IA i NOT IB

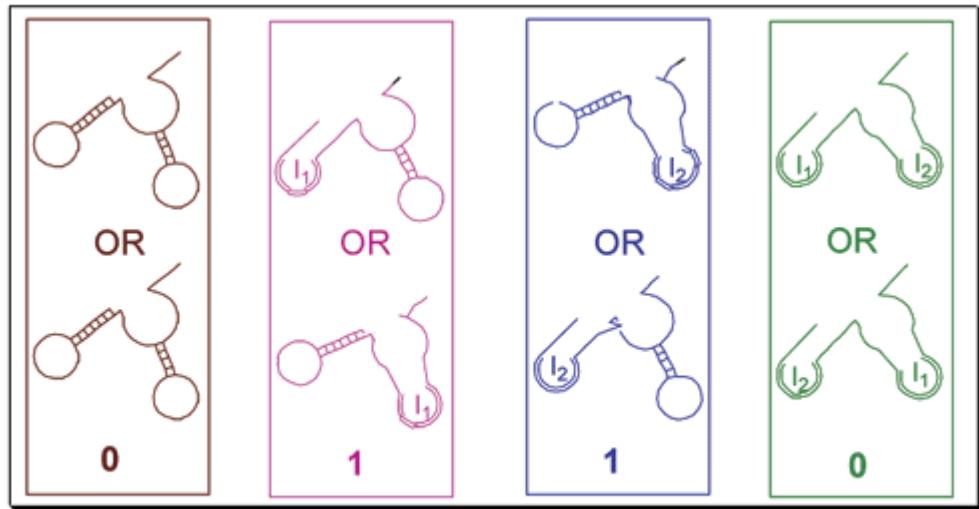
(a)



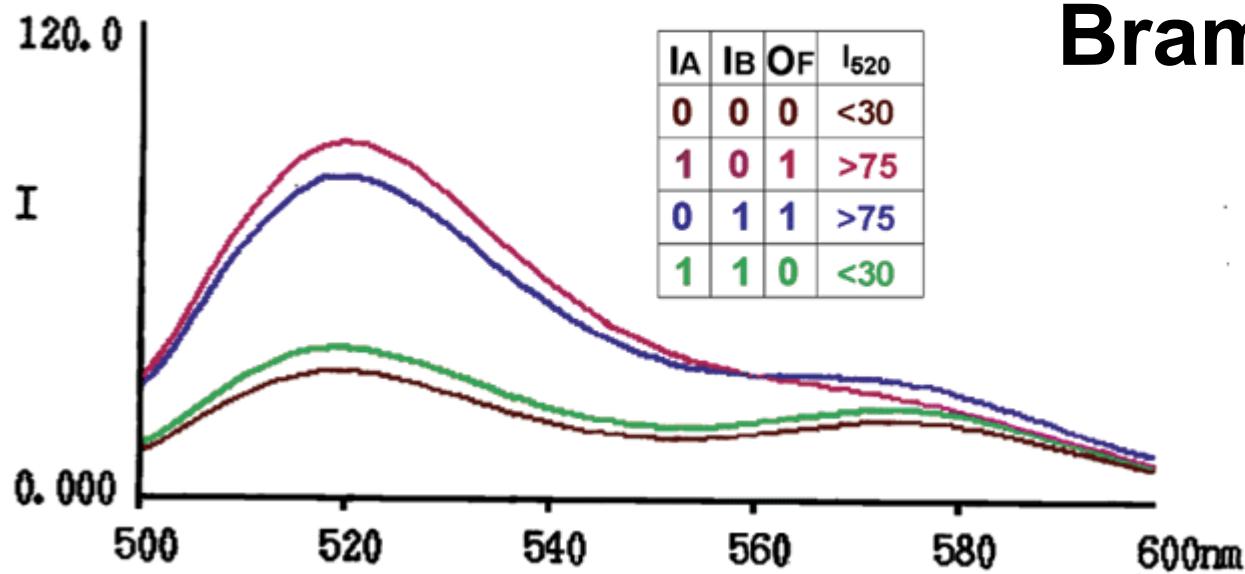
# Bramka XOR

(a)



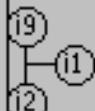


(b)



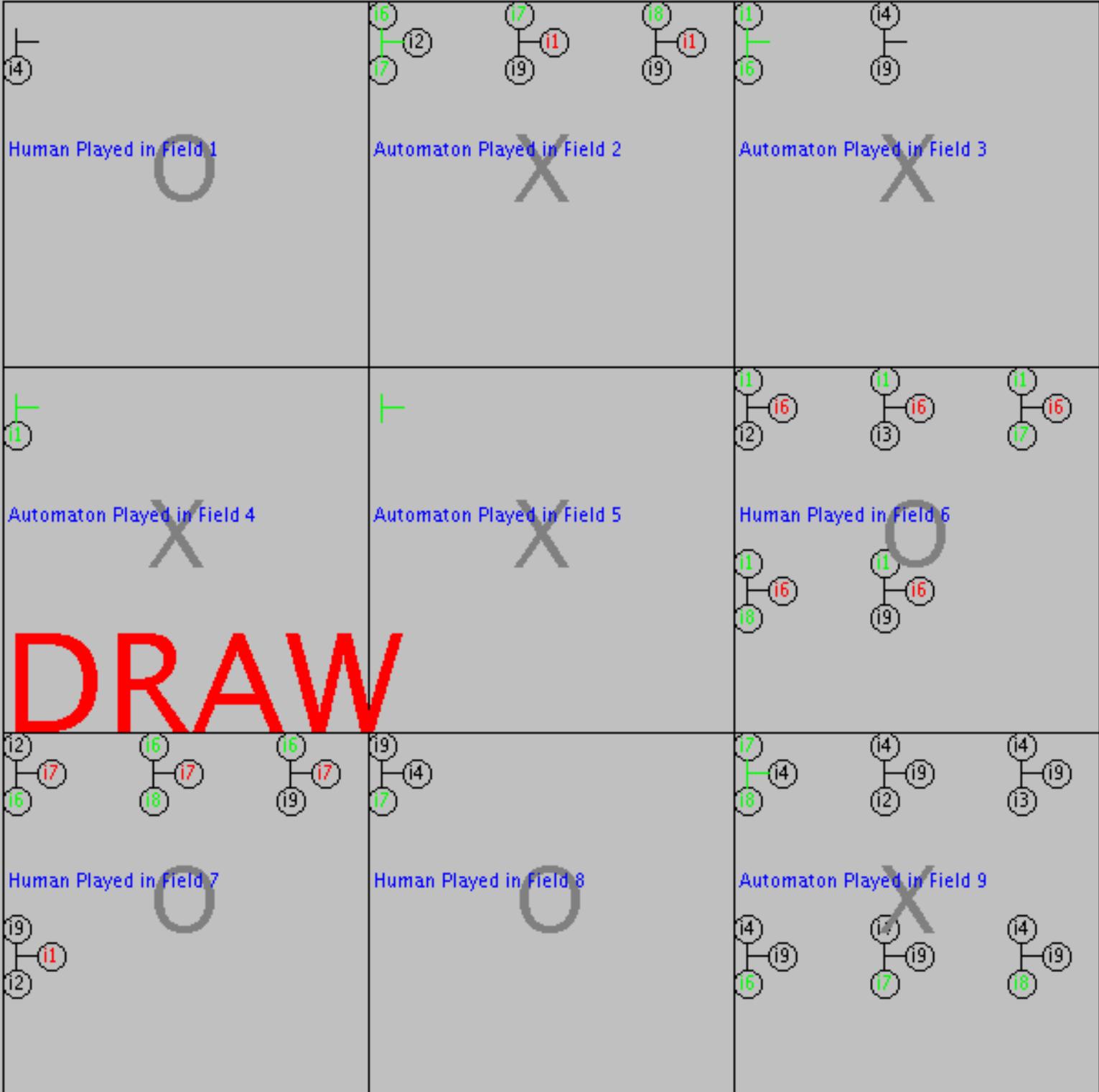
**Bramka XOR c.d.**

<p>Field 1 Open</p>	<p>Field 2 Open</p>	<p>Field 3 Open</p>
<p>Field 4 Open</p>	<p>Automaton Played in Field 5</p>	<p>Field 6 Open</p>
<p>Field 7 Open</p>	<p>Field 8 Open</p>	<p>Field 9 Open</p>

 Automaton Played in Field 1 	 Field 2 Open 	 Field 3 Open 
 Human Played in Field 4 	 Automaton Played in Field 5 	 Field 6 Open 
 Field 7 Open 	 Field 8 Open 	 Field 9 Open 

 Automaton Played in Field 1 	 Field 2 Open 	 Automaton Played in Field 3 
 Human Played in Field 4 	 Automaton Played in Field 5 	 Field 6 Open 
 Field 7 Open 	 Field 8 Open 	 Human Played in Field 9 

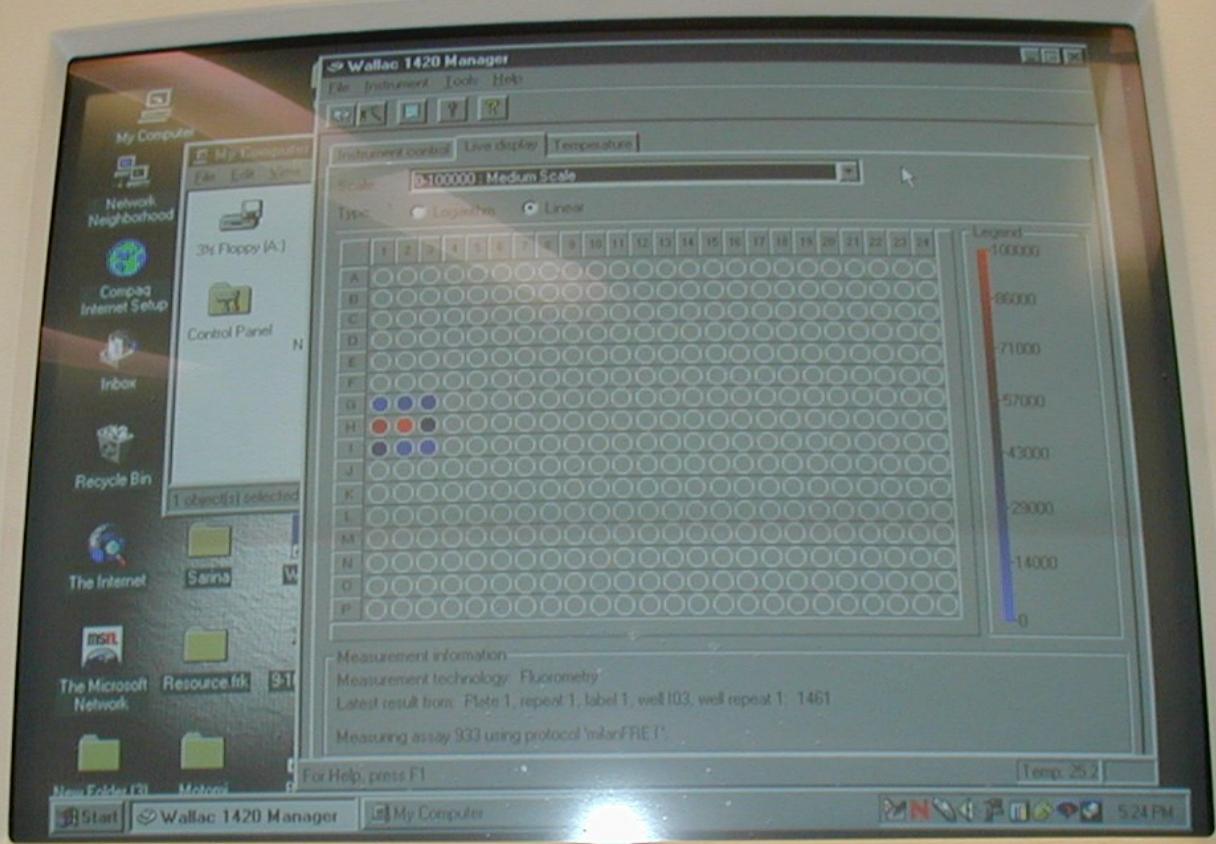




**DRAW**



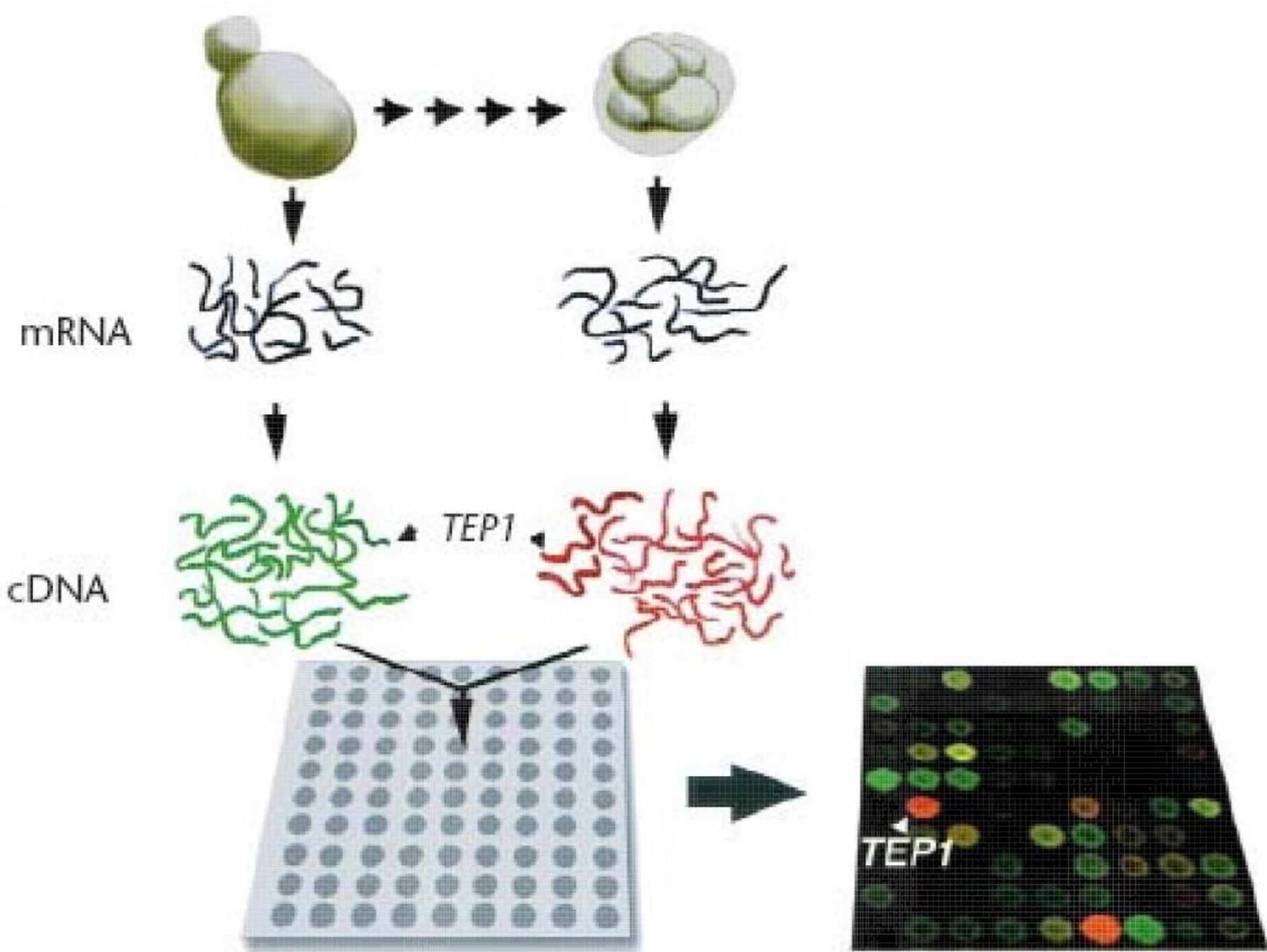


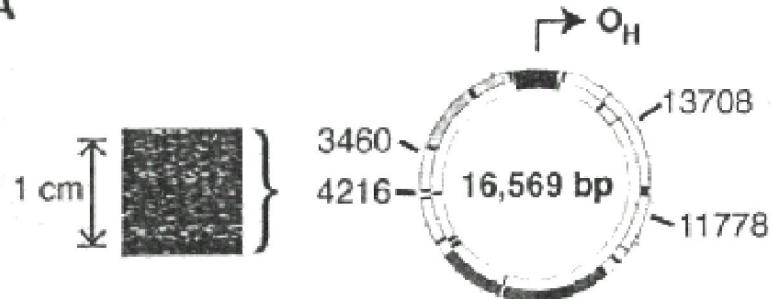
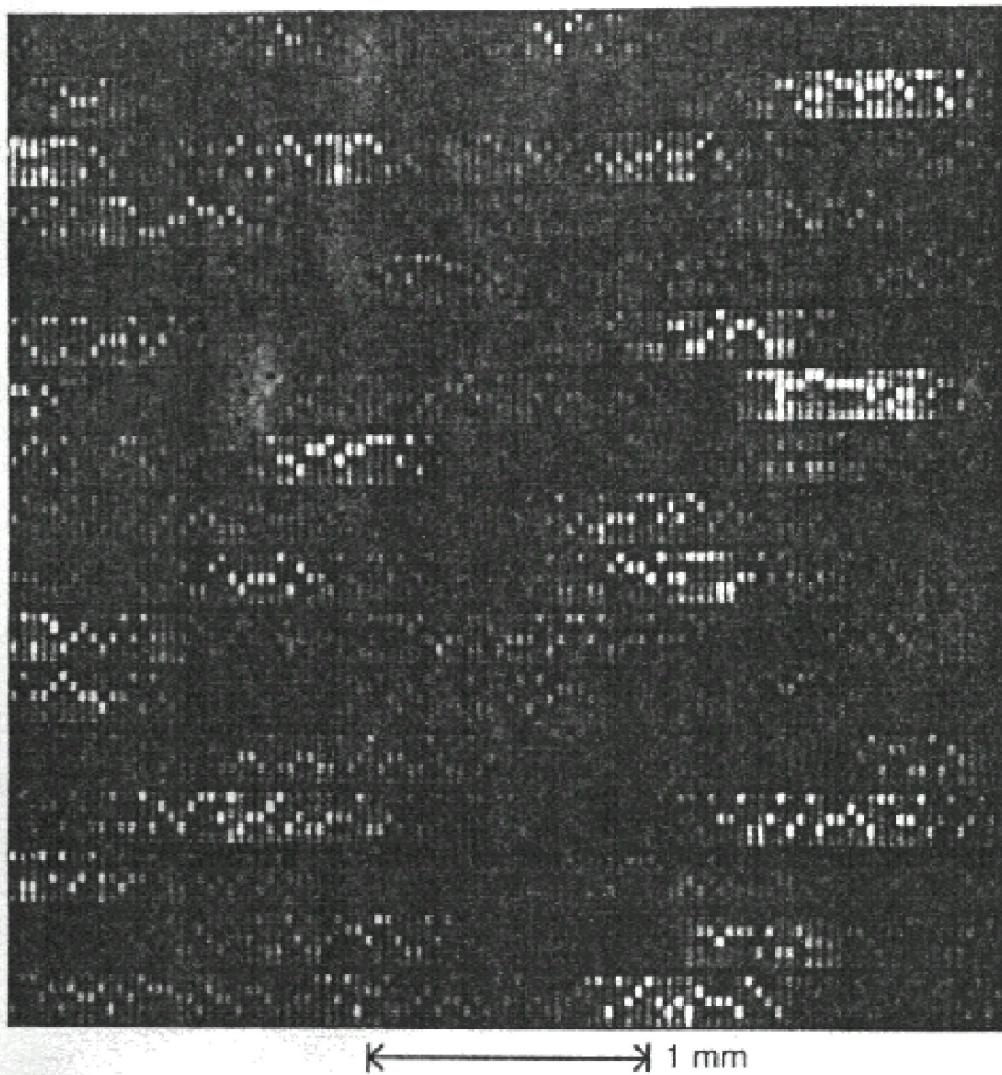
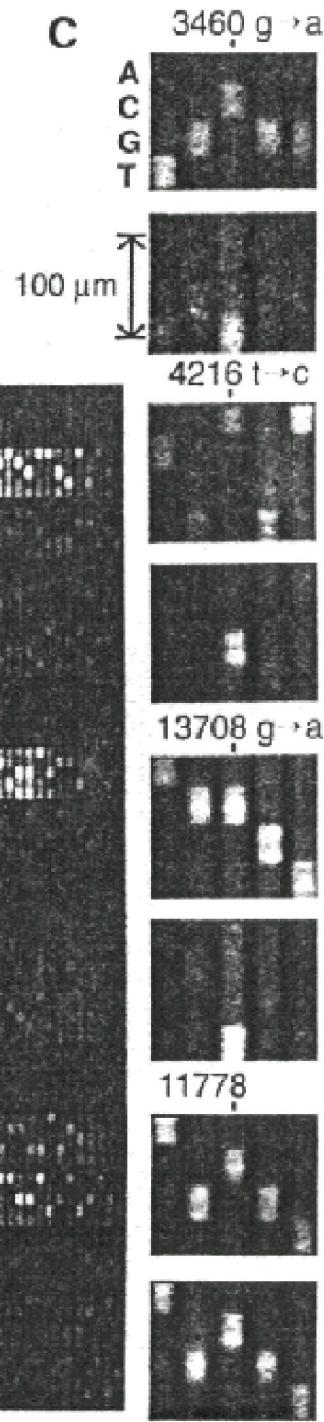


NEC

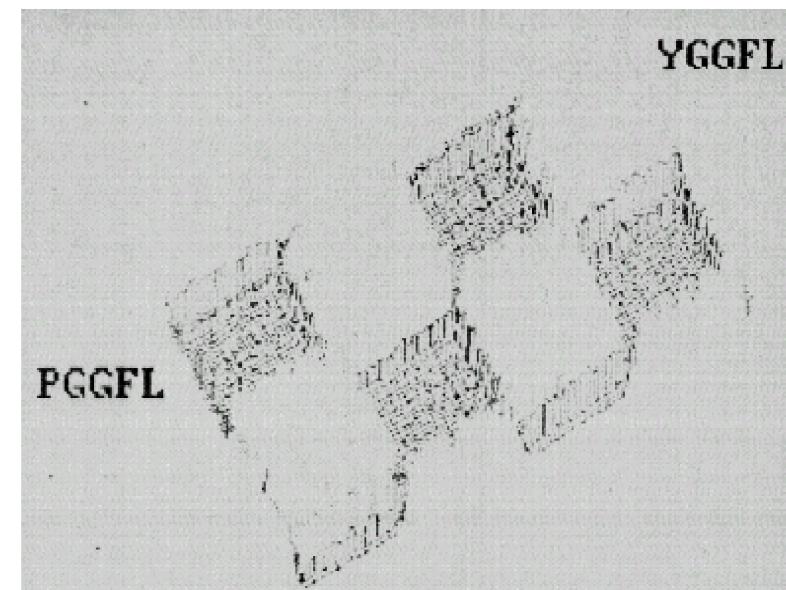
MultiSync A500

# DNA Matryca



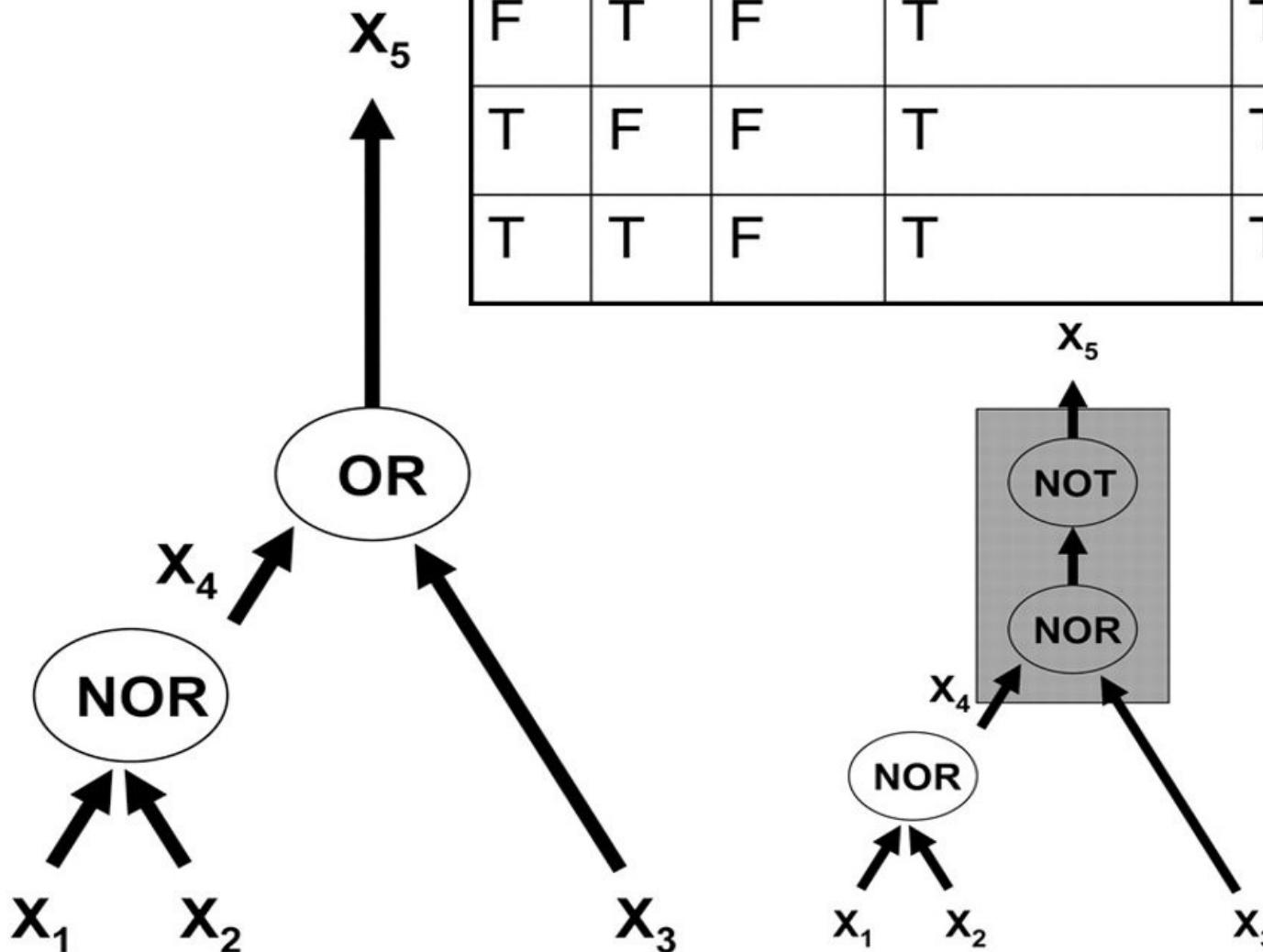
**A****B****C**

# DNA Chip

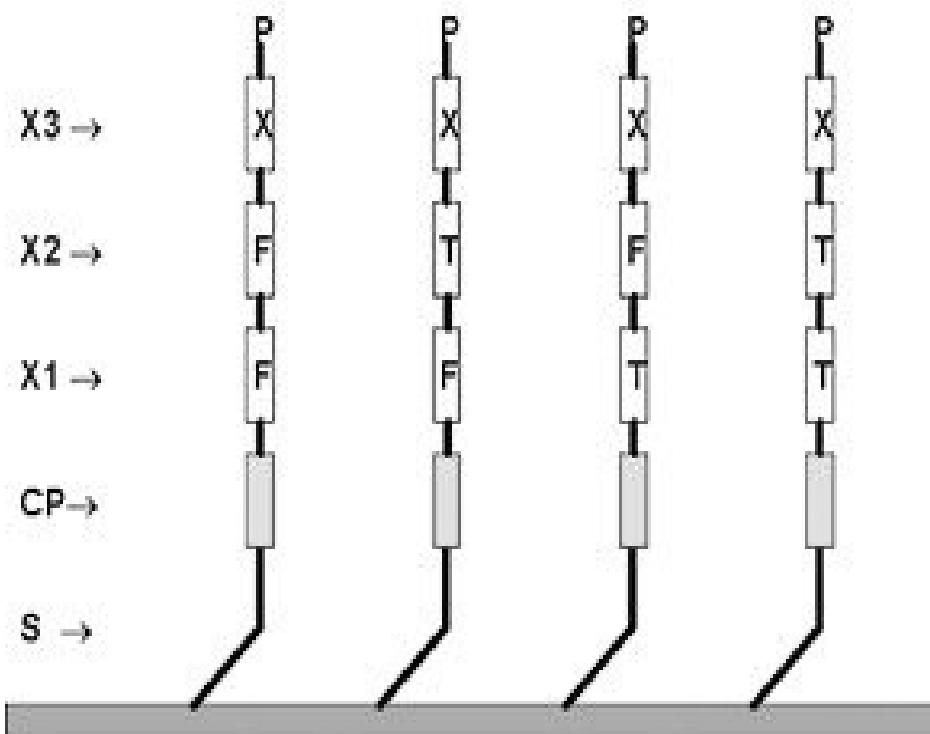


# Bramki logiczne na DNA chipie Su i Smitha

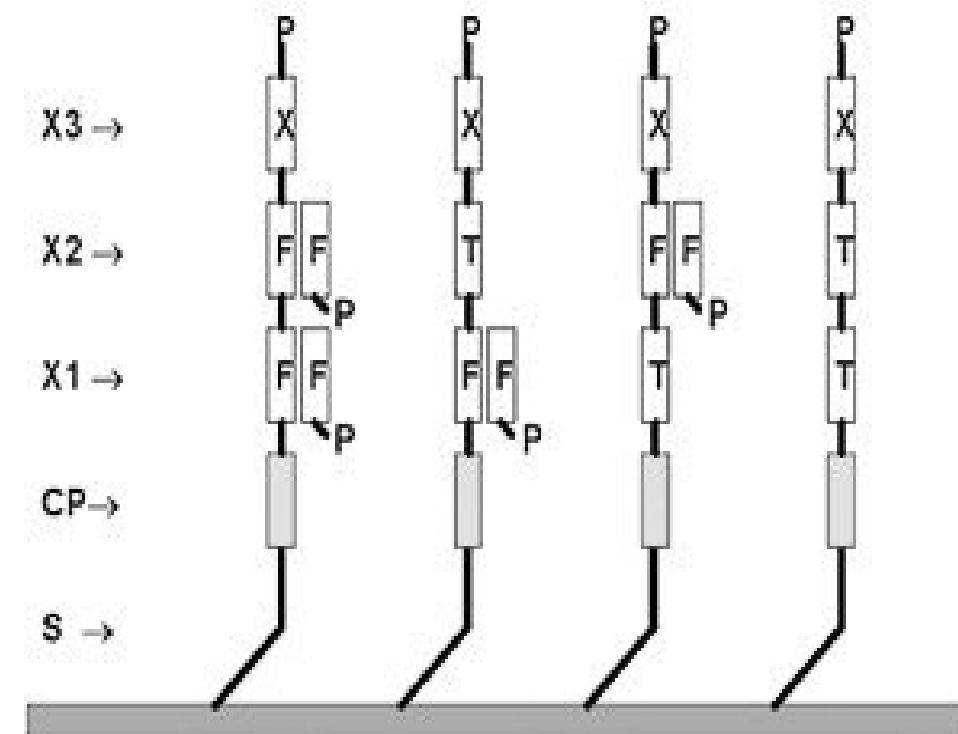
INPUT		OUTPUT		
1	2	NOR	NOR+NOT	OR
F	F	T	F	F
F	T	F	T	T
T	F	F	T	T
T	T	F	T	T



# Bramki logiczne na DNA chipie Su i Smitha



a

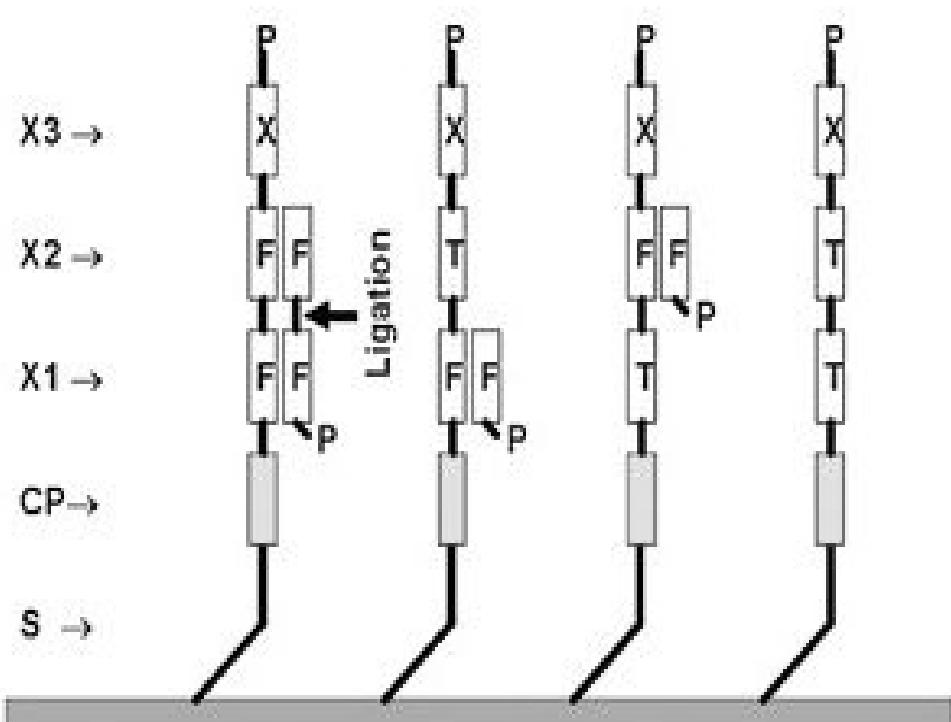


b

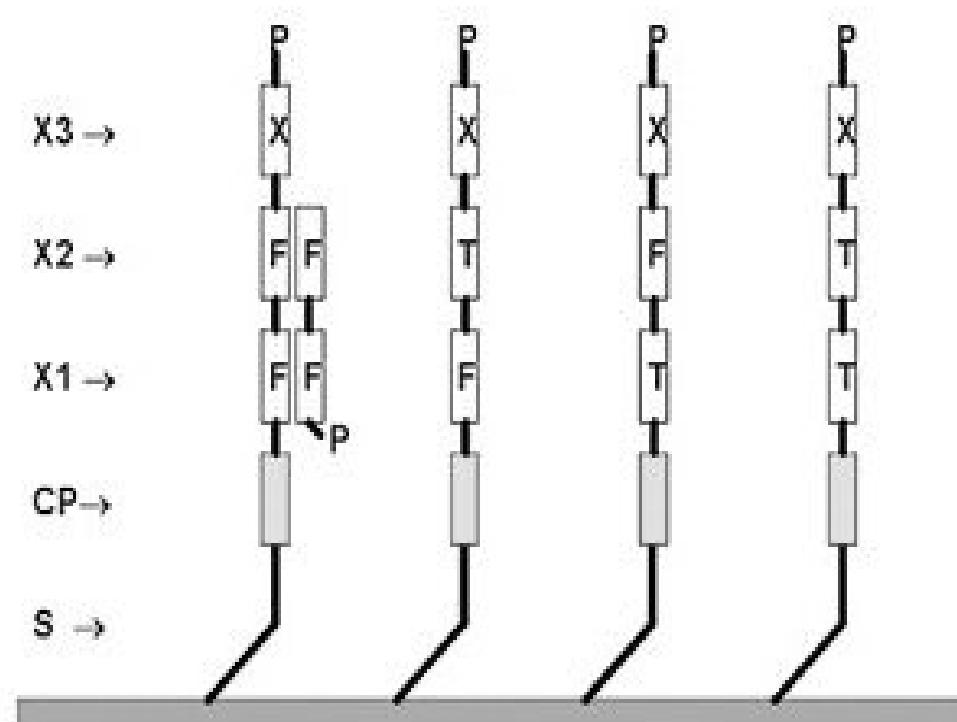
X.Su, L.M. Smith, Demonstration of a universal surface DNA computer, *Nucleic Acids Research*, 32 (10) 2004: 3115-3123.

# Bramki logiczne na DNA chipie c.d.

Usuwanie krótkich odcinków



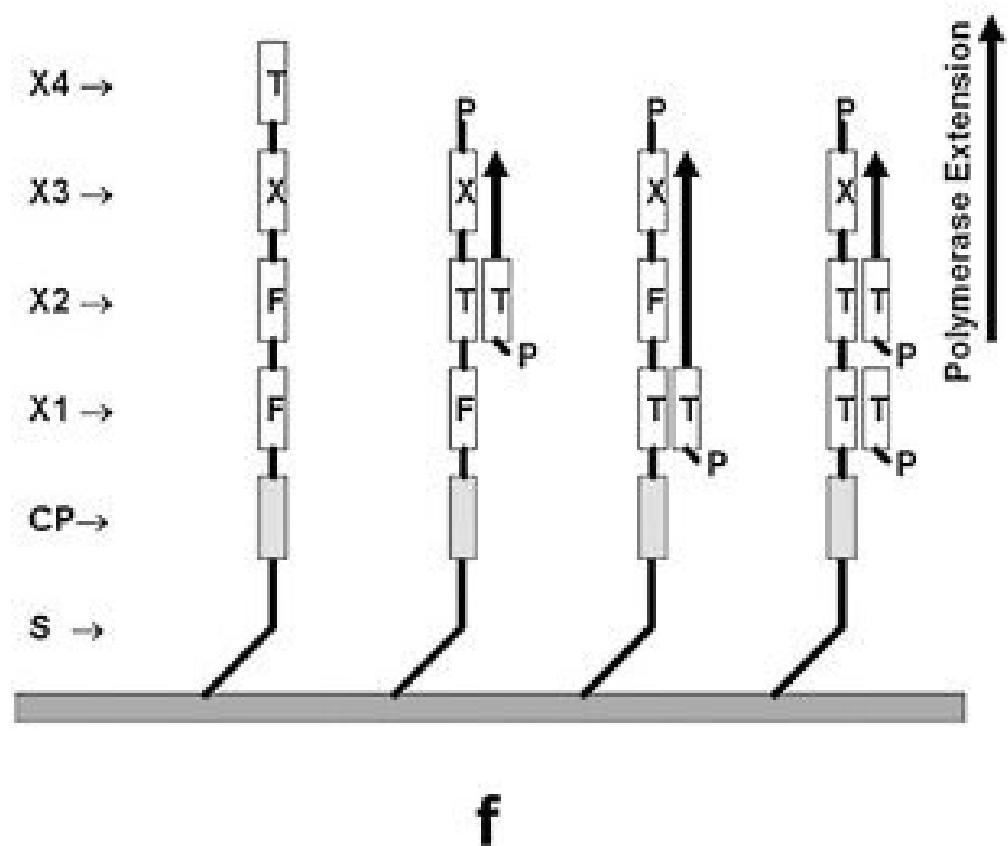
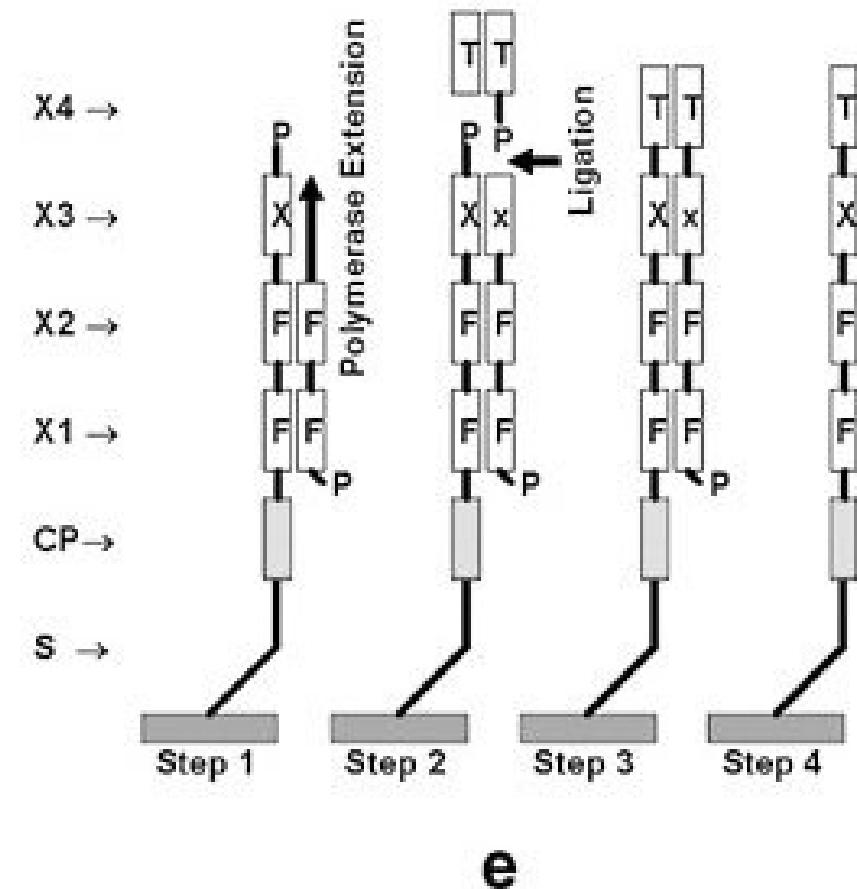
c



d

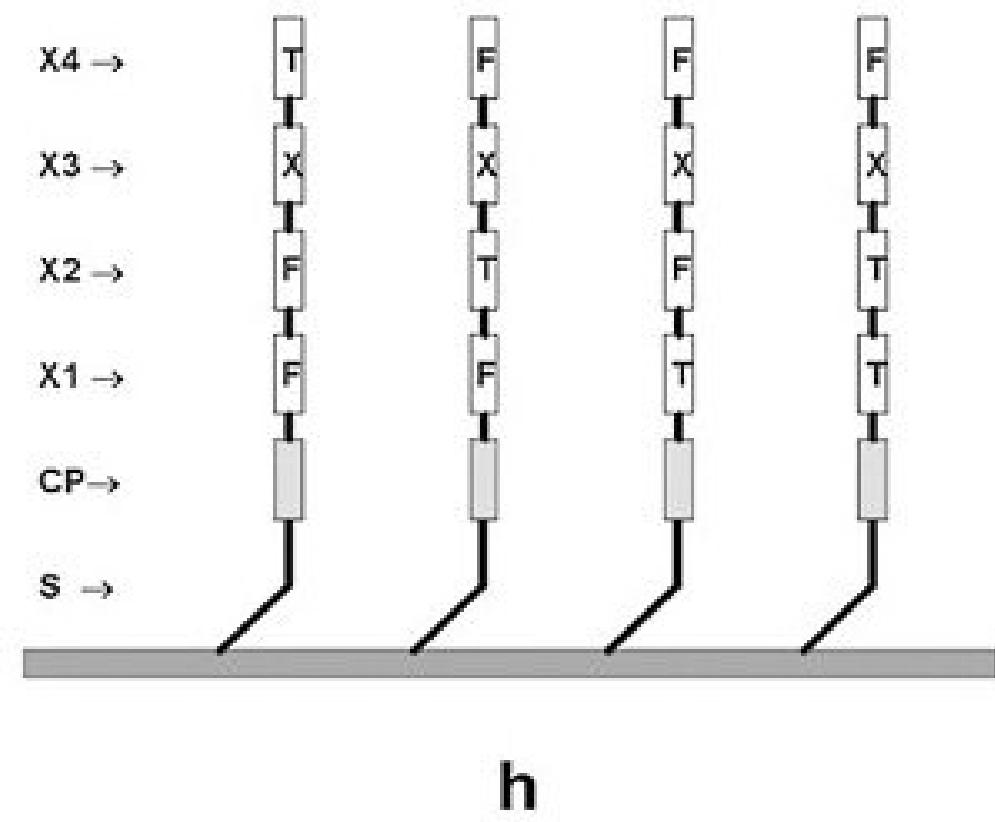
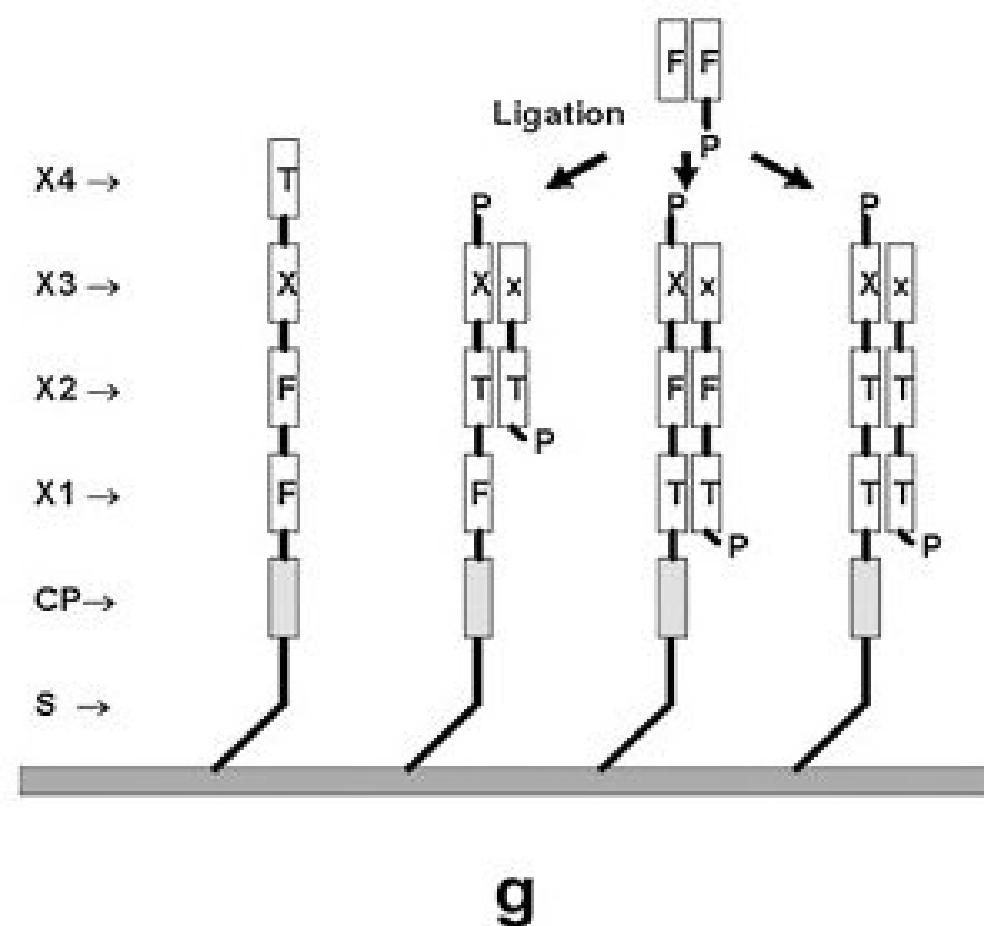
# Bramki logiczne na DNA chipie c.d.

Generacja sygnału wyjściowego bramki NOR

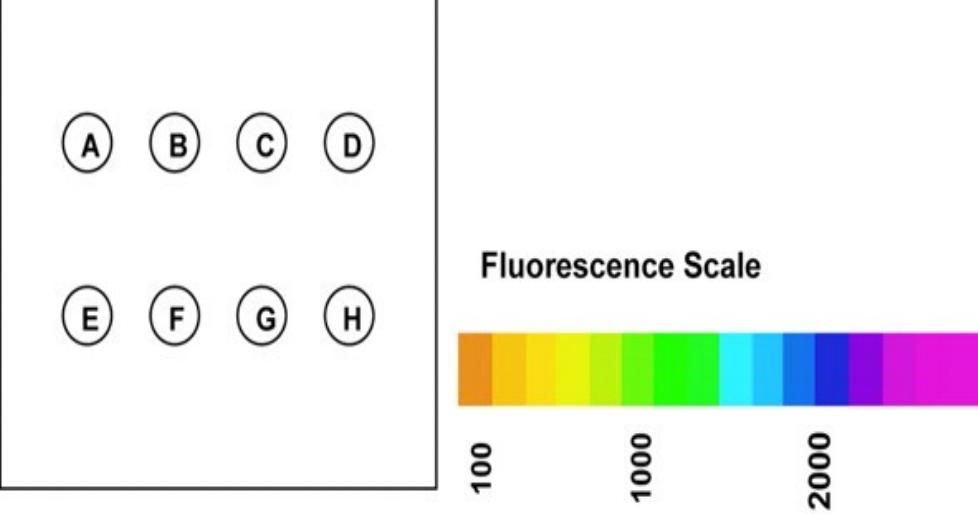


# Bramki logiczne na DNA chipie c.d.

Generacja sygnału wyjściowego NOR i końcowa postać

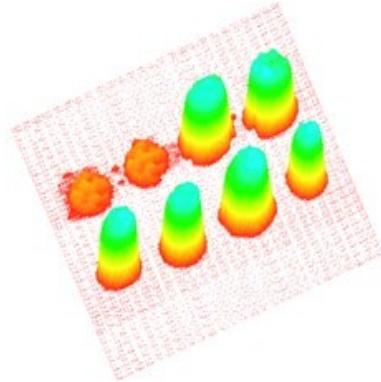
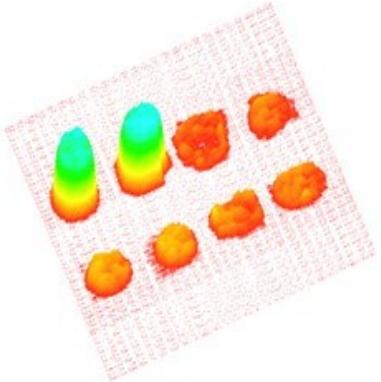


A	F	F	F	T	T	T	T
B	F	F	T	T	T	F	F
C	F	T	F	F	F	T	T
D	F	T	T	F	T	F	T
E	T	F	F	F	F	F	F
F	T	F	T	F	T	F	F
G	T	T	F	F	F	F	T
H	T	T	T	F	T	F	T

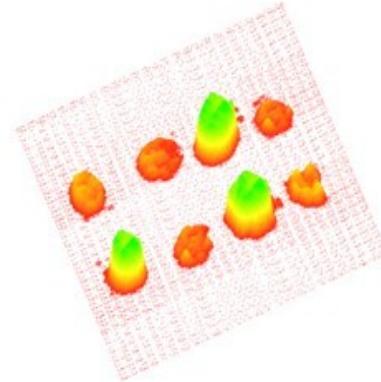
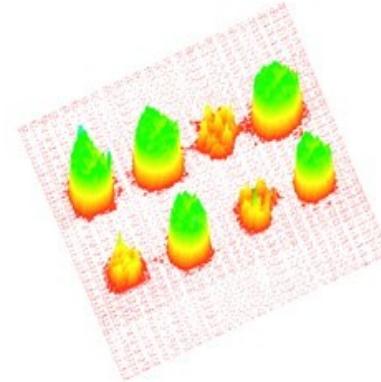


a

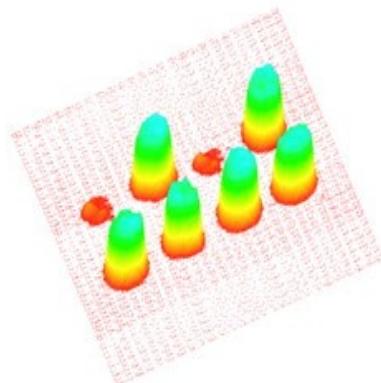
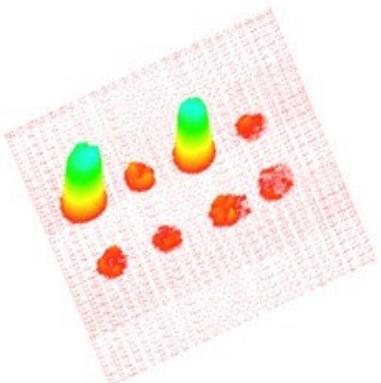
Contiguous



b



Noncontiguous

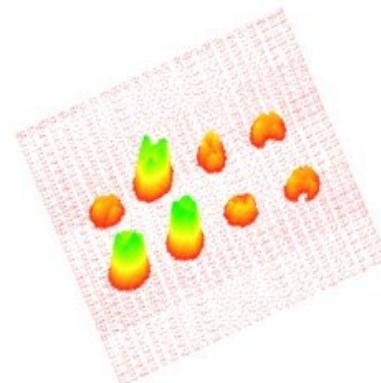
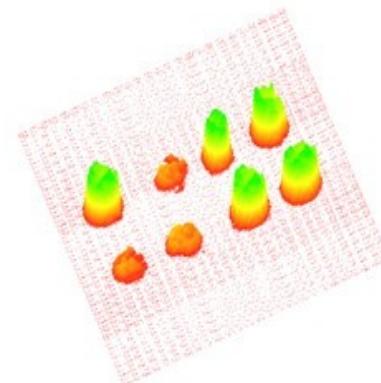


c

d

e

f



# Koncepcja Mulawki systemów inferencyjnych

$H'$

5'

Hipoteza H

A

5'

Reprezentacja faktu A

B

5'

Reprezentacja faktu B

C

5'

Reprezentacja faktu C

K'

B'

A'

5'

Reguła I: Jeżeli A i B to K

H

C'

K

Reguła II: Jeżeli K i C to H

H

C'

K

B

A

H'

C

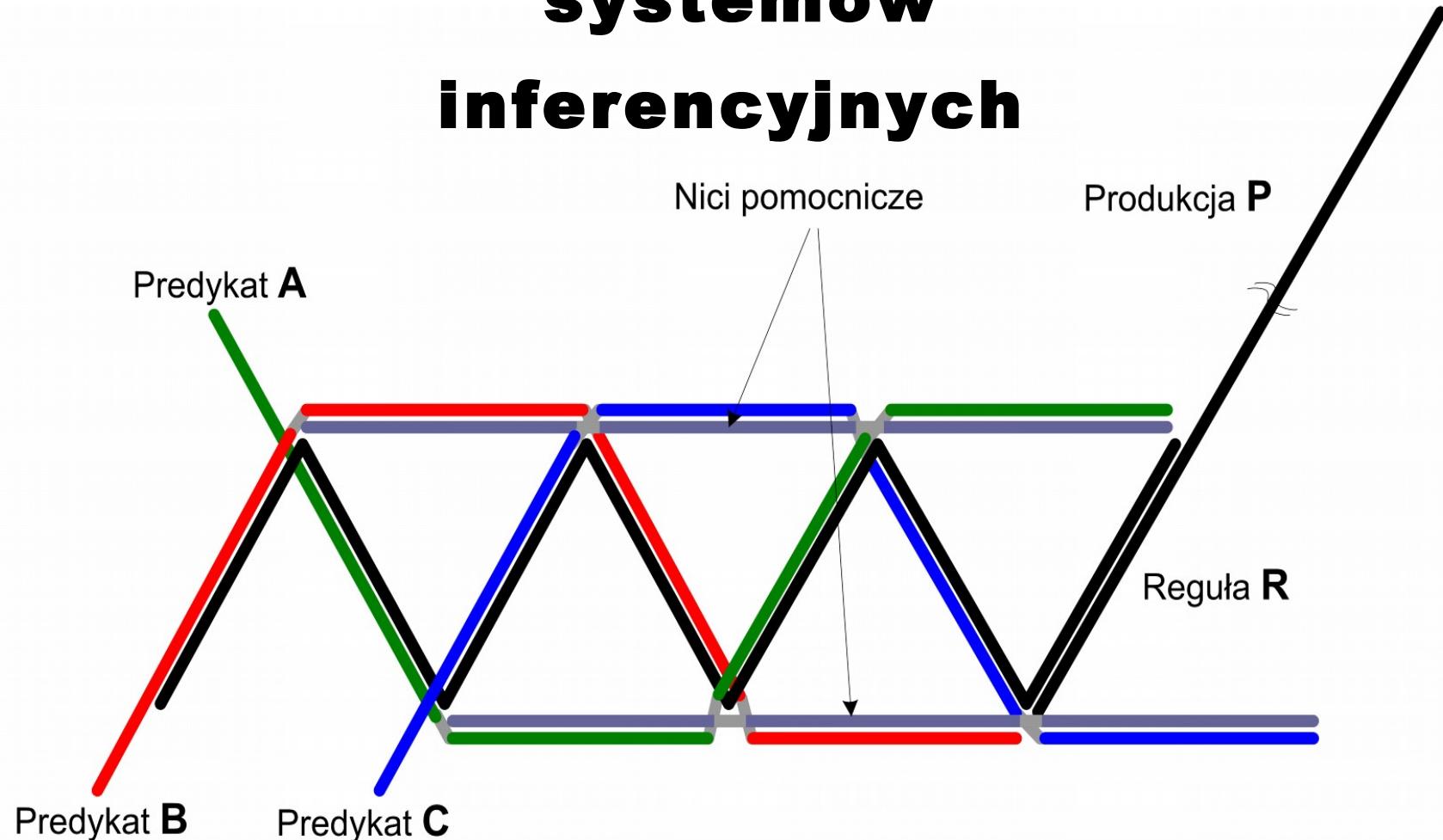
K'

B'

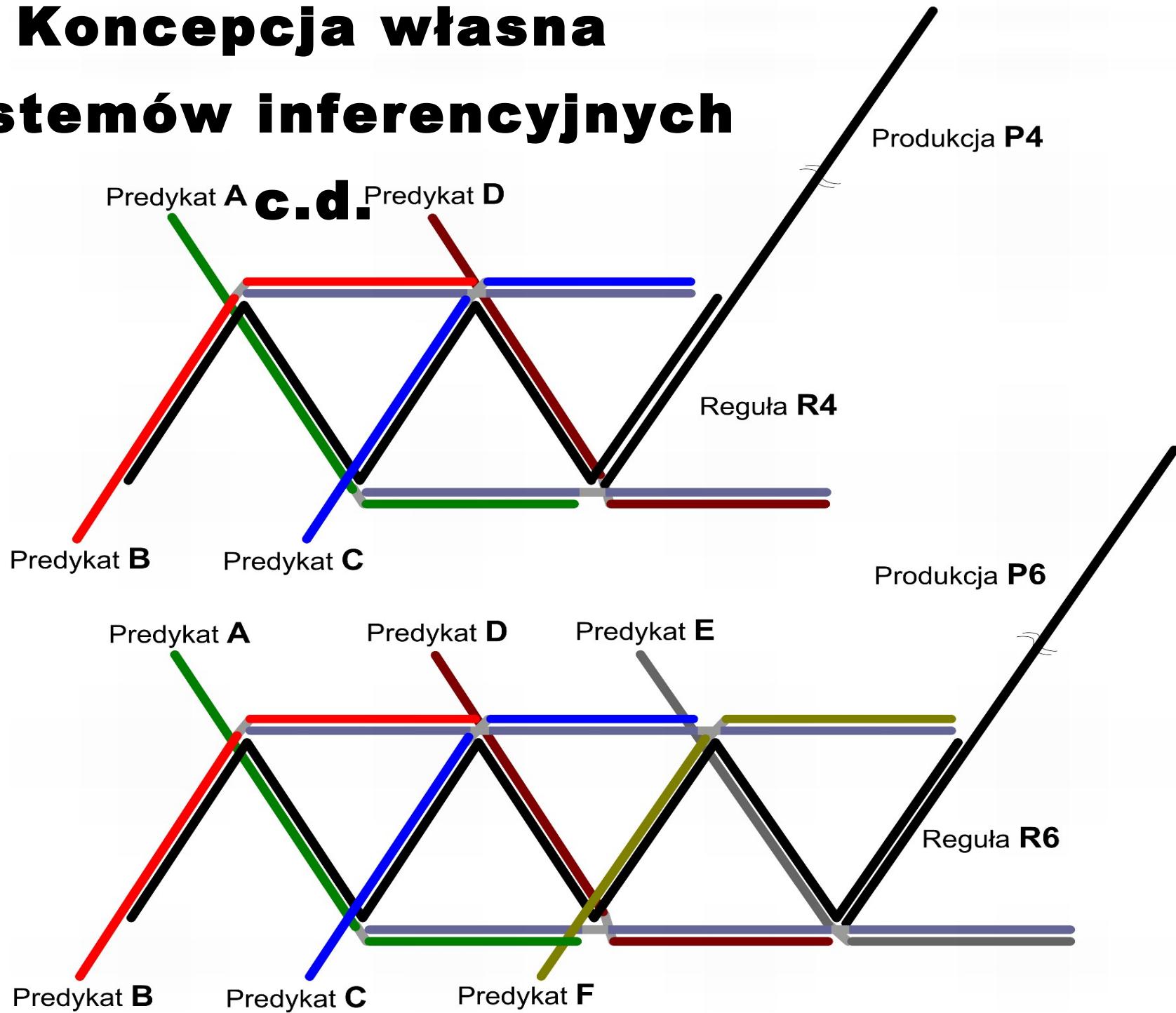
A'

Ciąg wnioskowania - Zastosowana reguła I i II

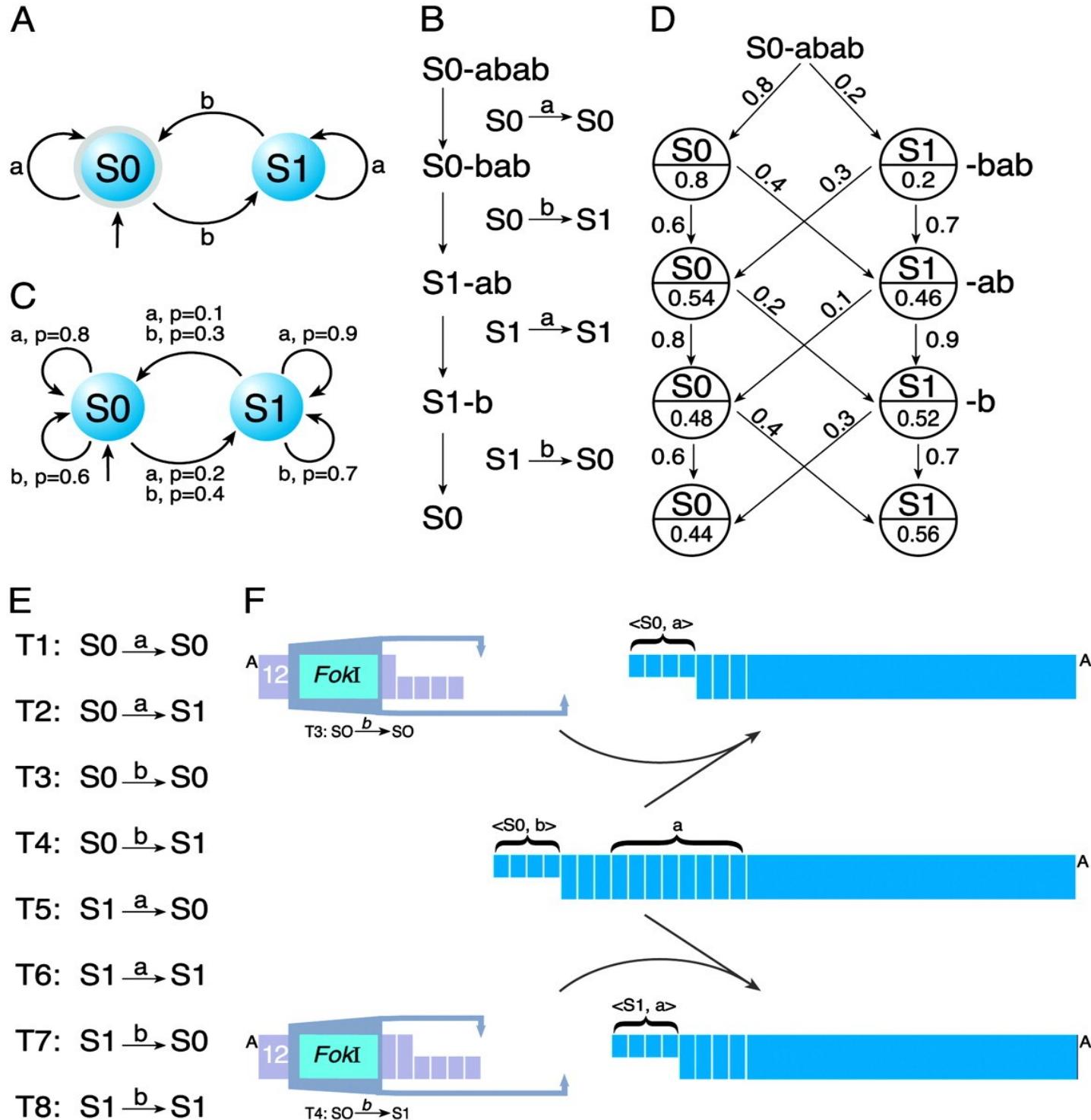
# Koncepcja własna systemów inferencyjnych



# Koncepcja własna systemów inferencyjnych



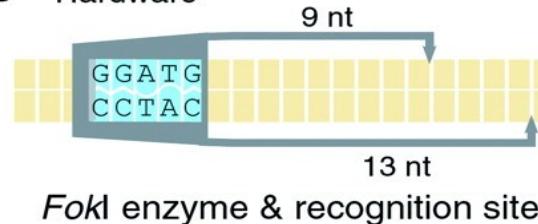
# Automat Shapiro, An autonomous molecular computer..., Nature 2004



### A Explanation of state and symbol encoding

Symbol	a	b	terminator (t)
encodings & sticky ends	$\langle S1, a \rangle$ 	$\langle S1, b \rangle$ 	$\langle S1, t \rangle$ 
	$\langle S0, a \rangle$	$\langle S0, b \rangle$	$\langle S0, t \rangle$

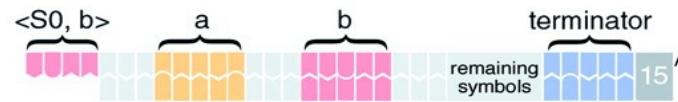
### B Hardware



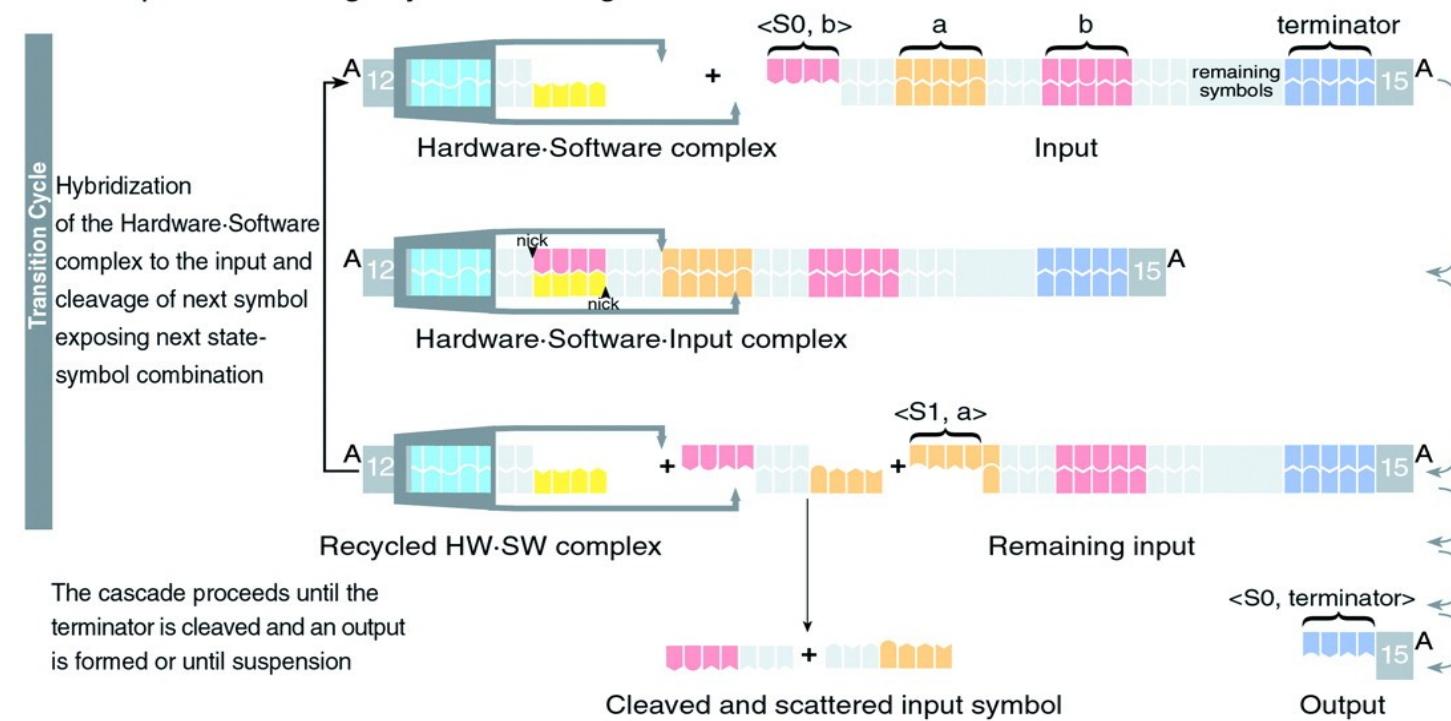
### C Software



### D Input

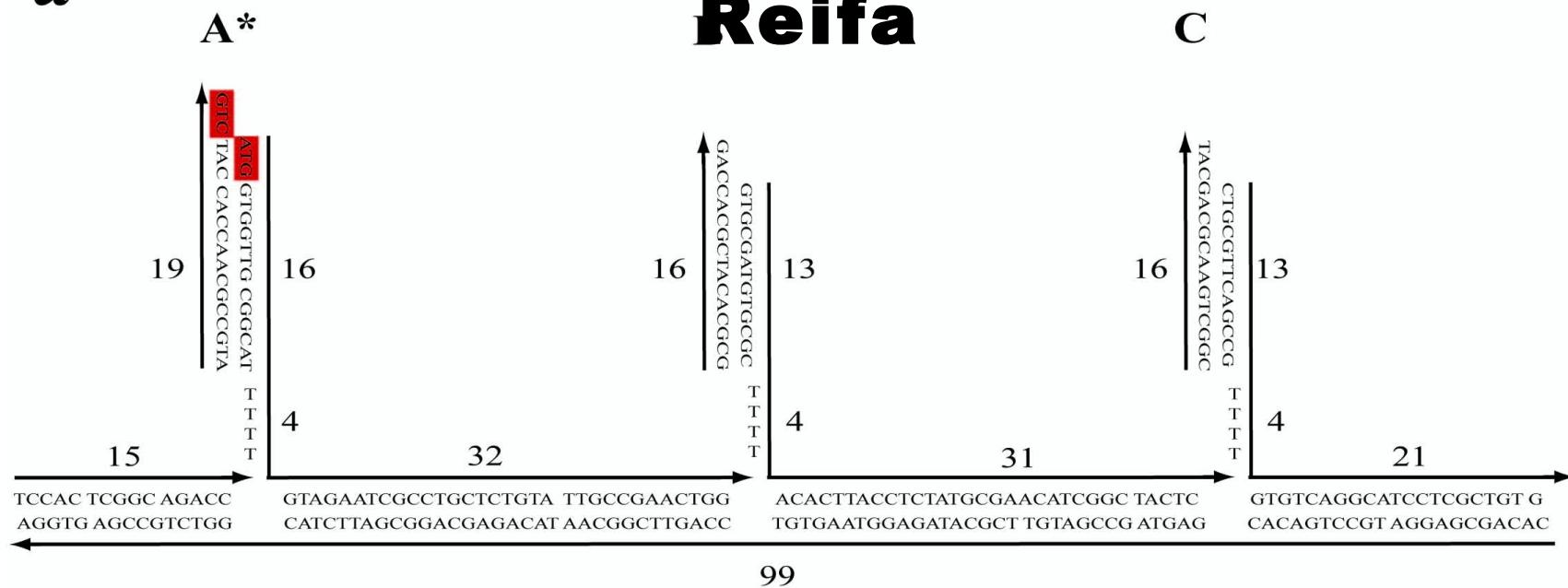


### E Computation through symbol cleavage and scatter

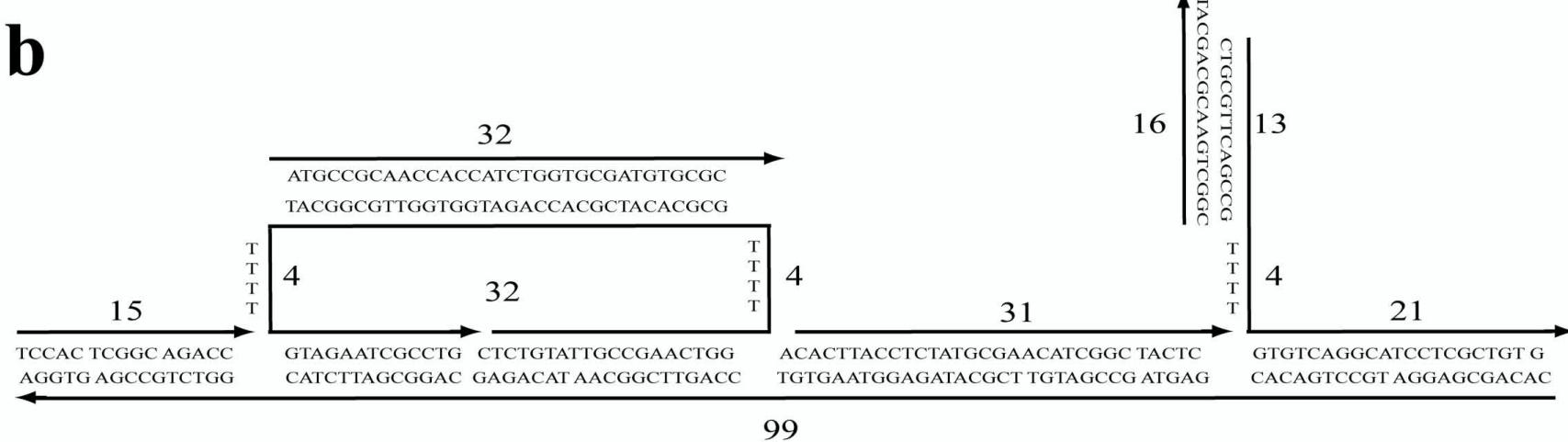


# Koncepcja nanorobota Turberfielda,

a

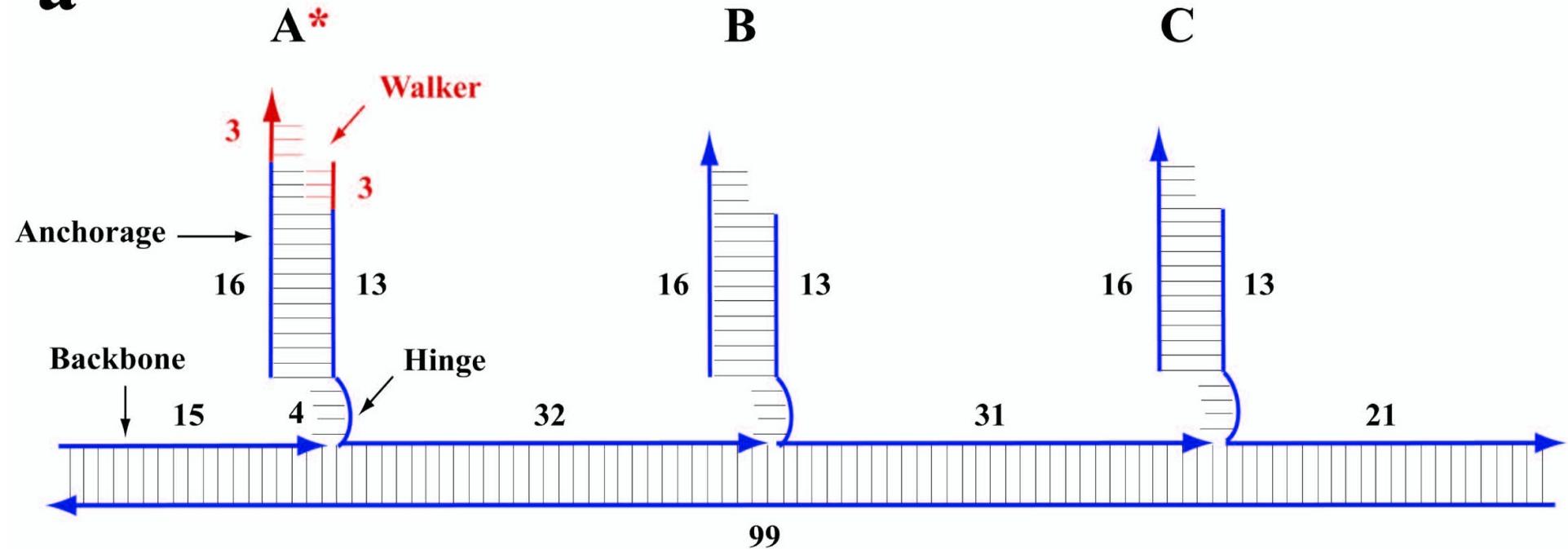


b



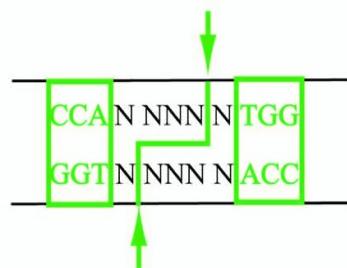
# Koncepcja nanorobota

a

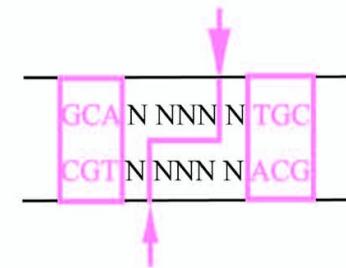


b

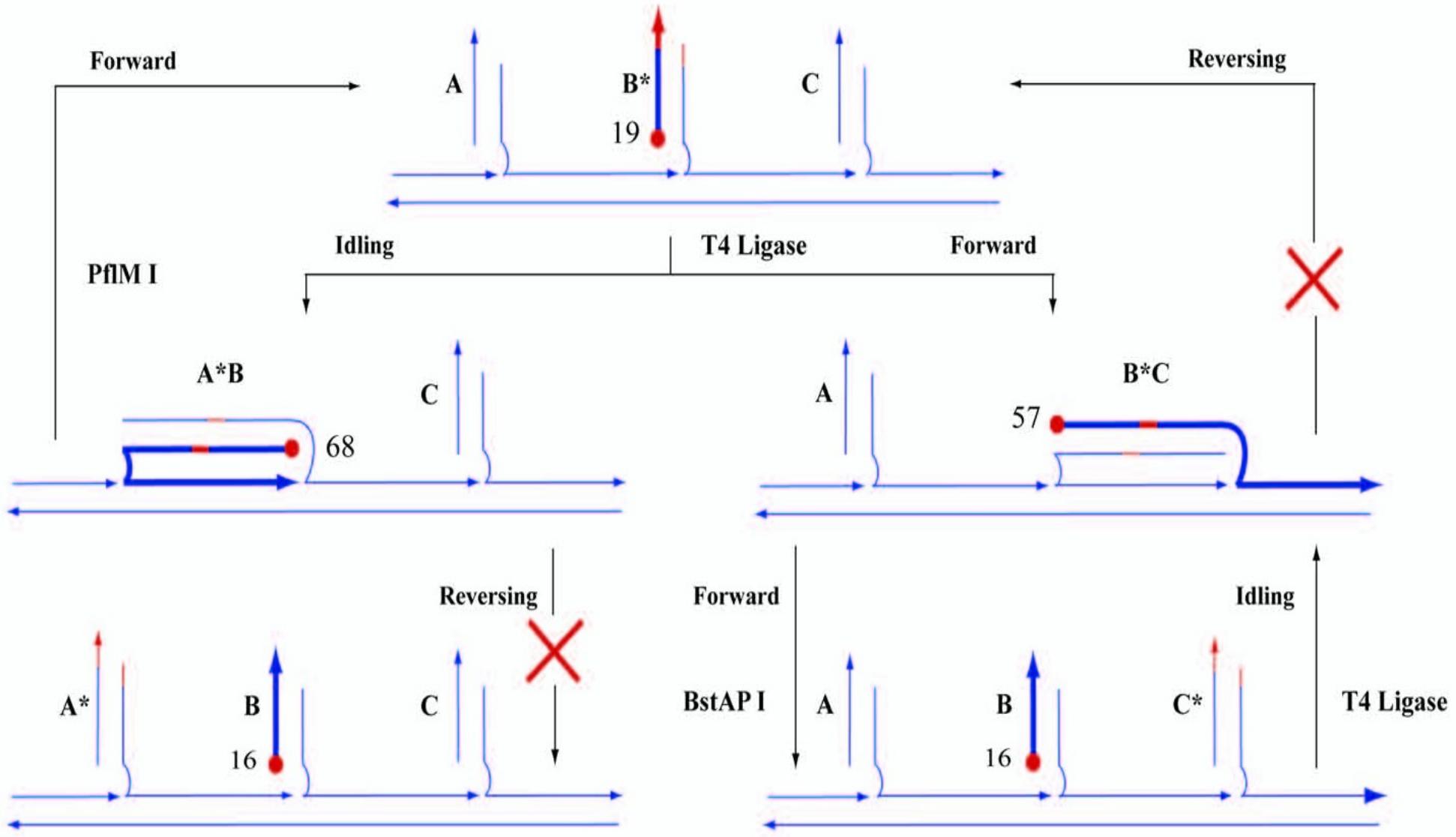
PflM I

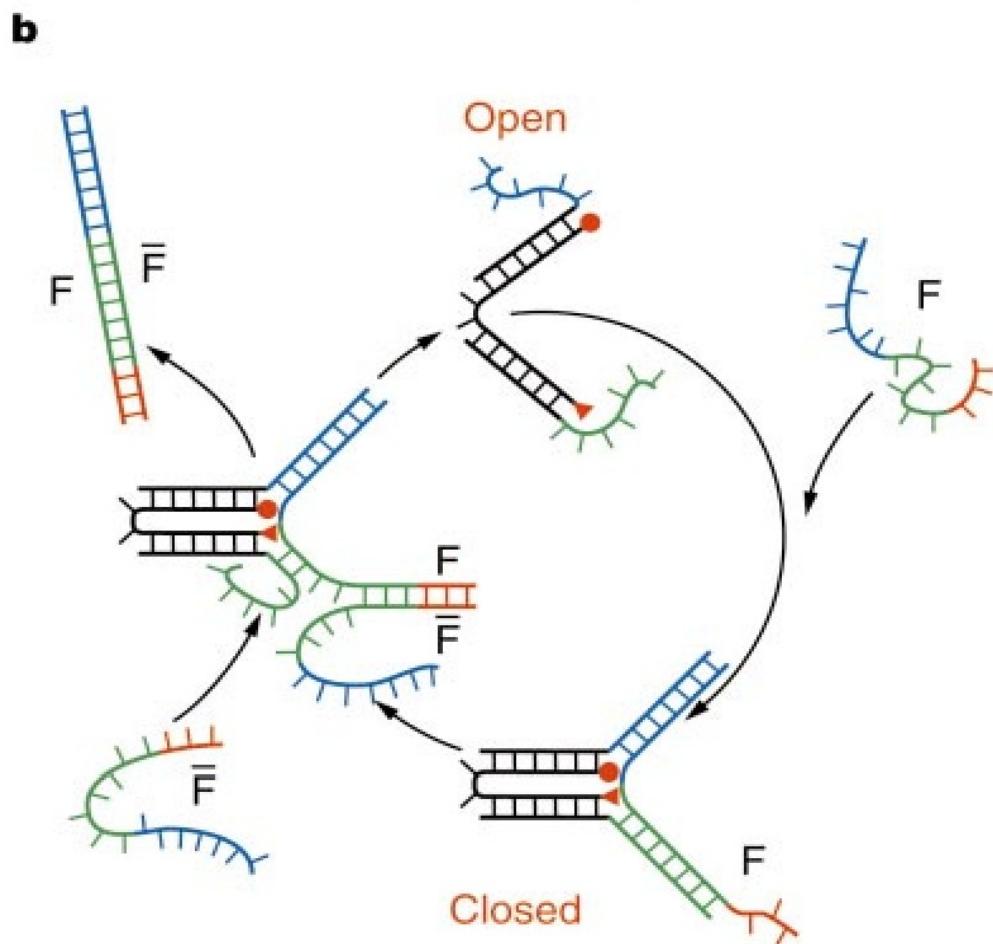
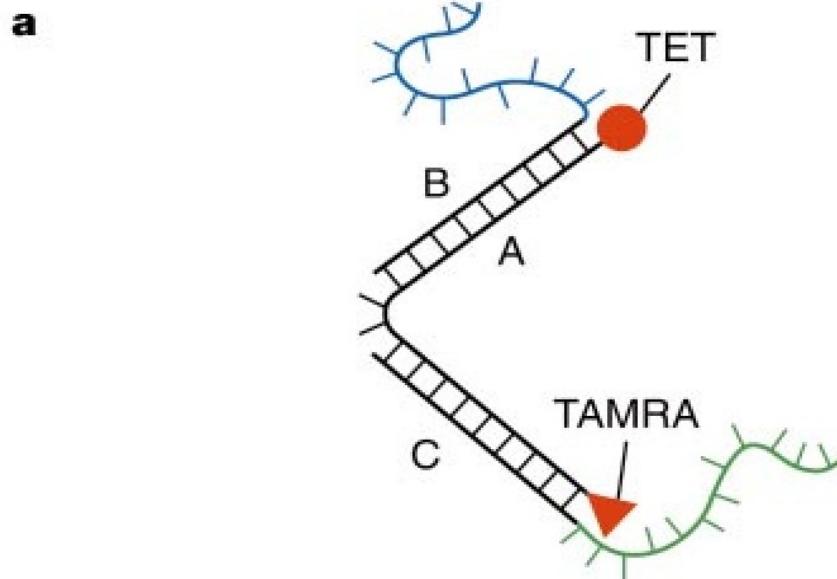


BstAP I



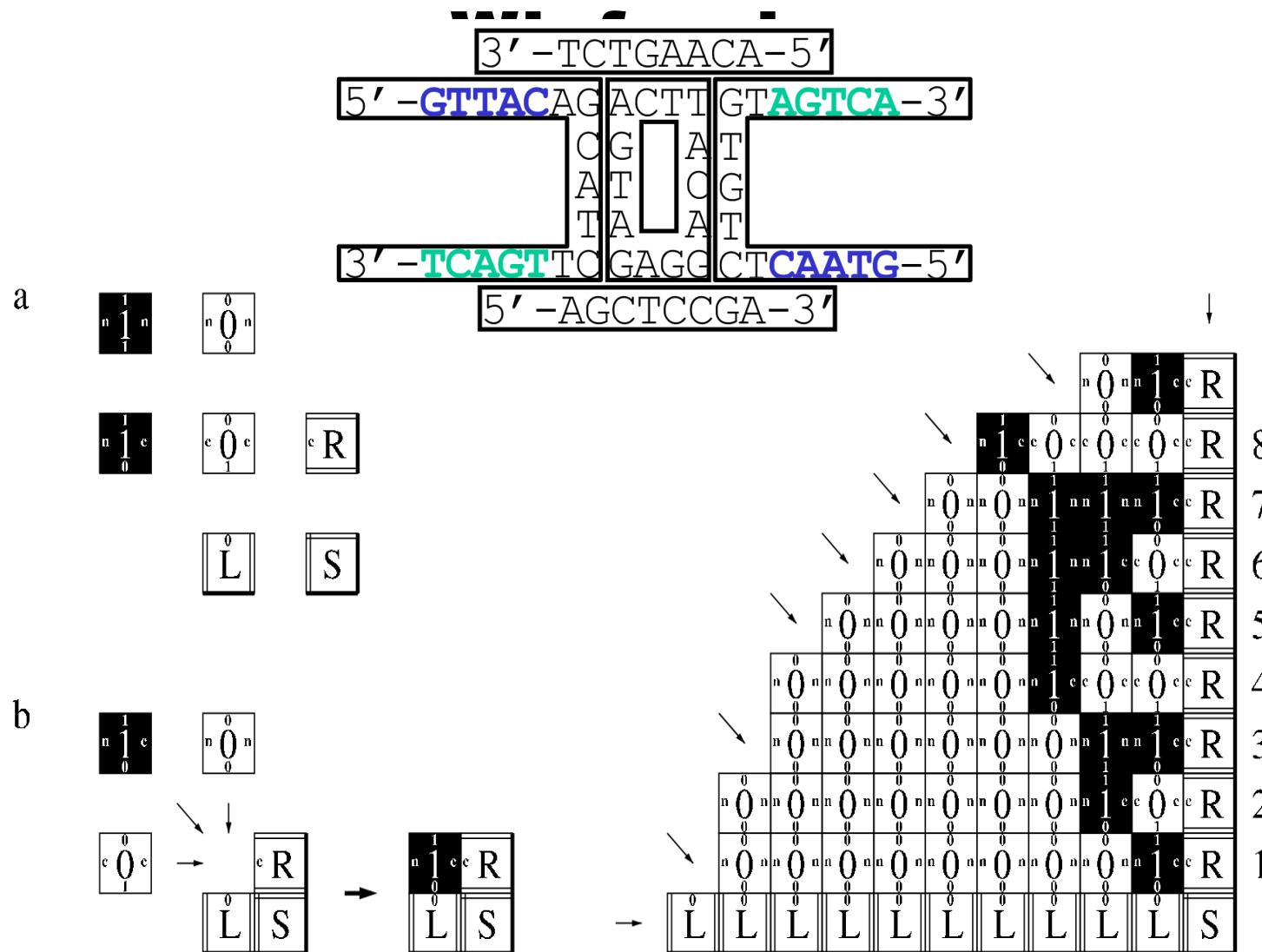
# Koncepcja nanorobota



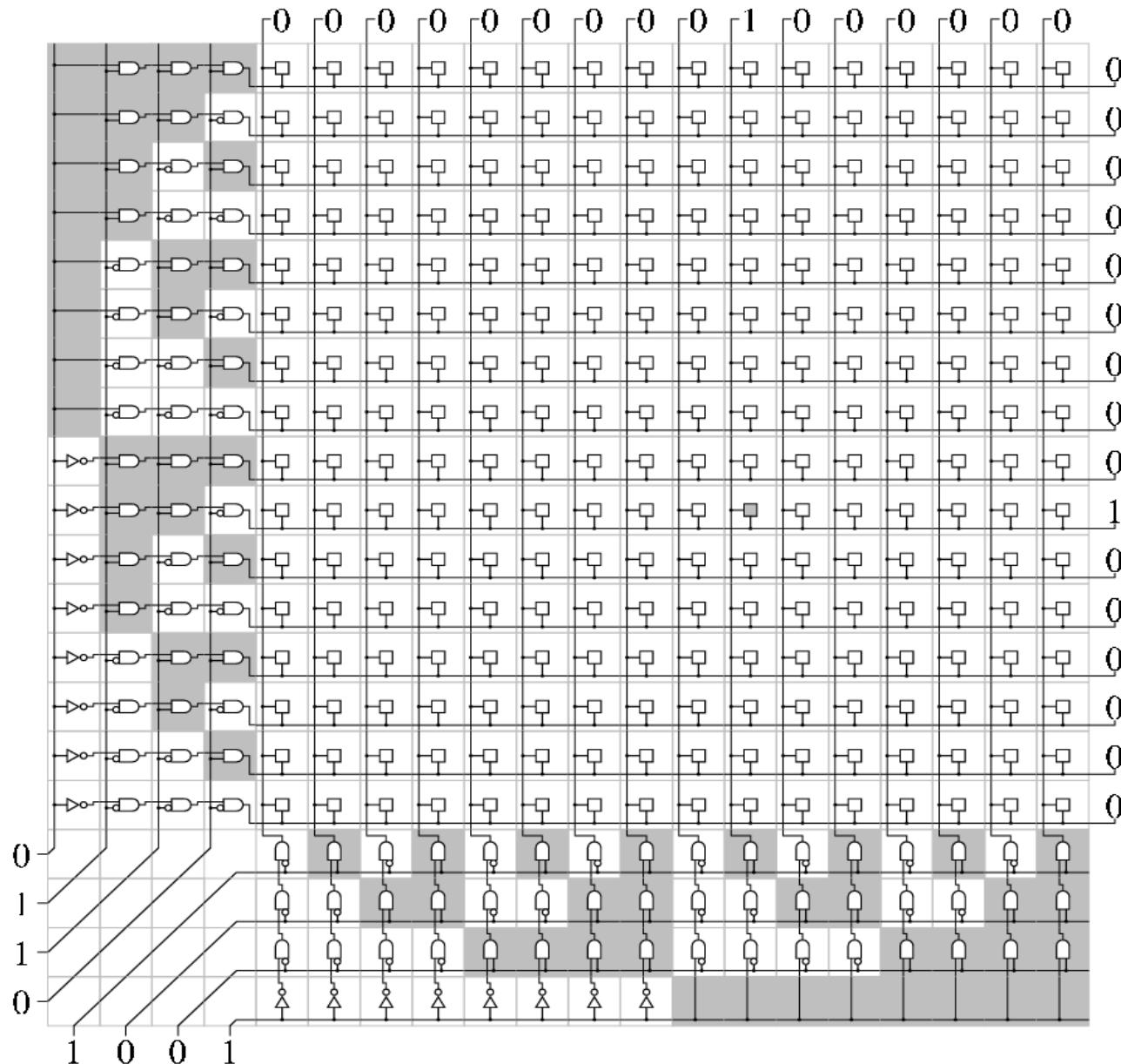


**Koncepcja  
“nożyczek”  
DNA  
Millsa,  
Turberfielda  
i innych  
*Nature 2000*  
DNA-fuelled molecular  
machine**

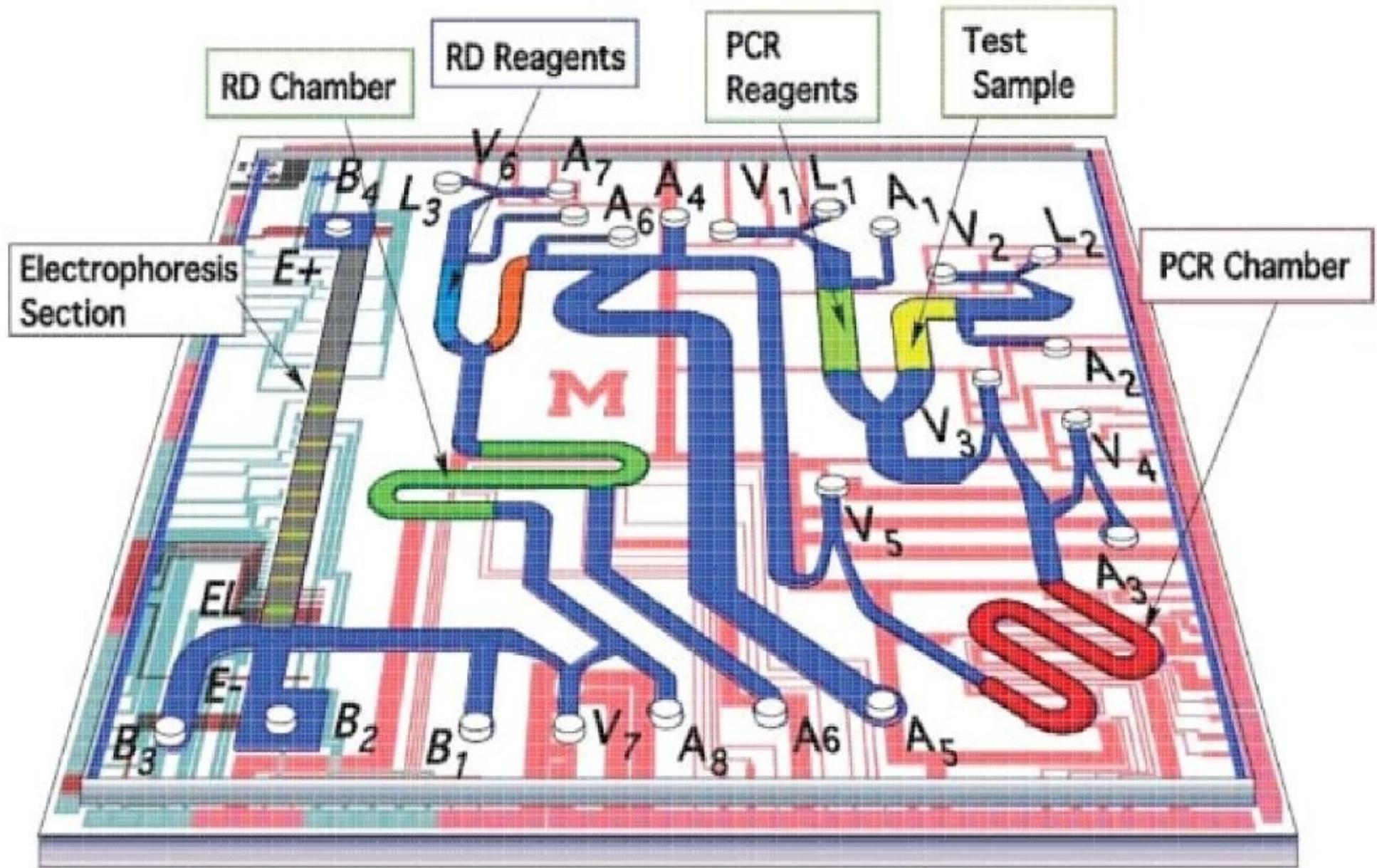
# Koncepcja składania



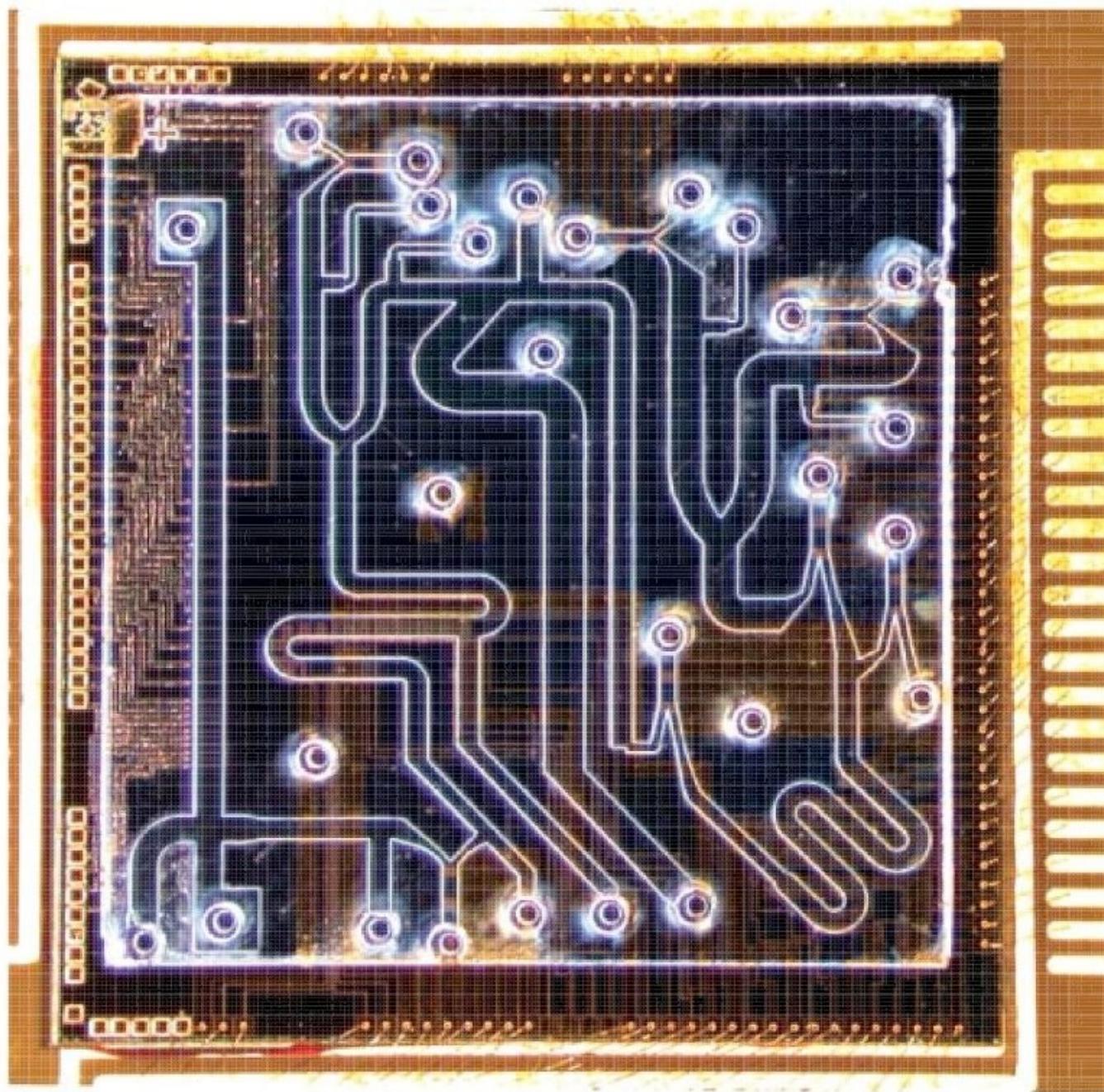
# Koncepcja multiplekserów z



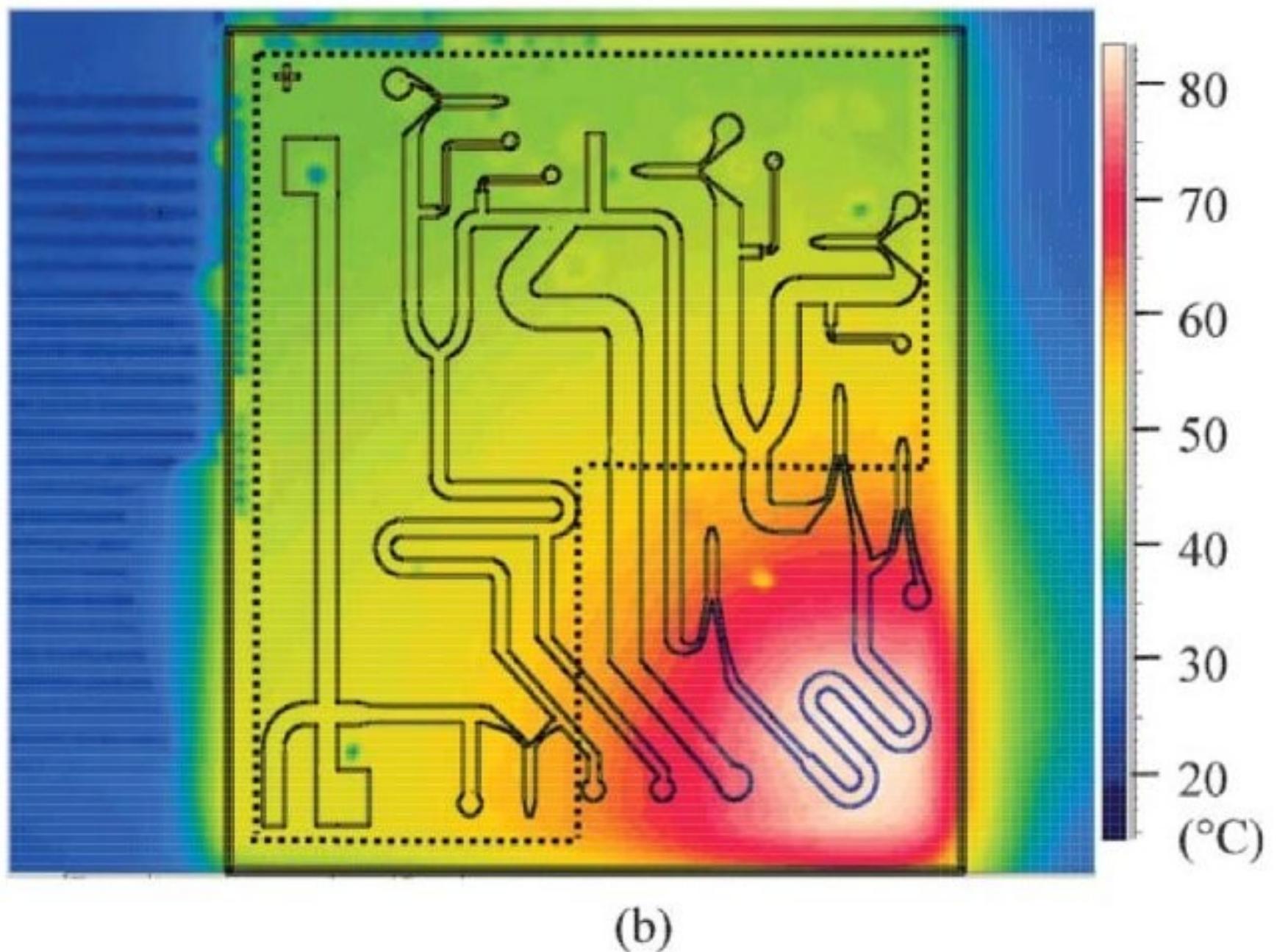
# Lab-on-a-Chip (LOC) – Pal, Burns et al, 2005

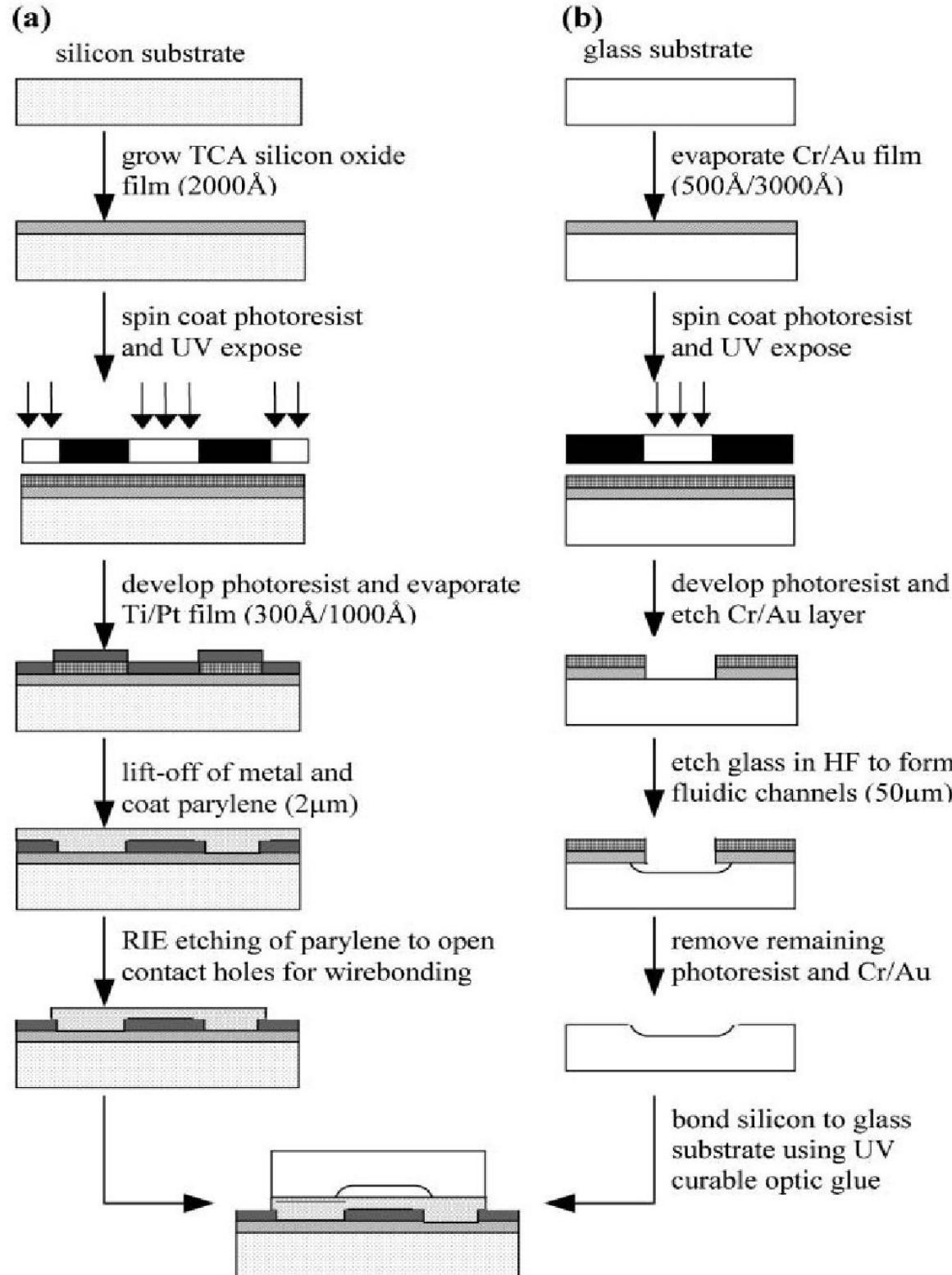


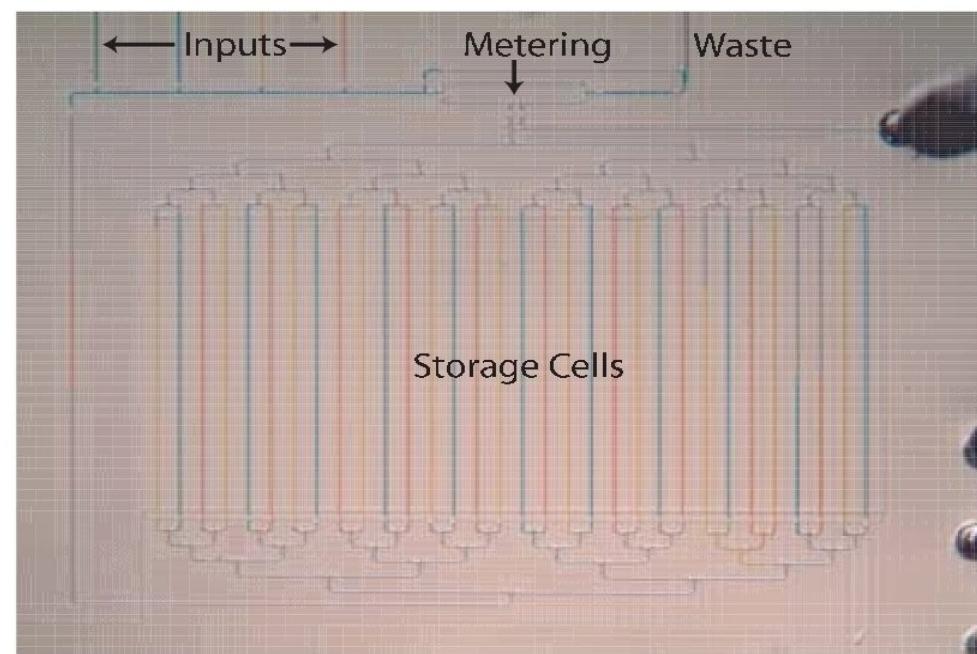
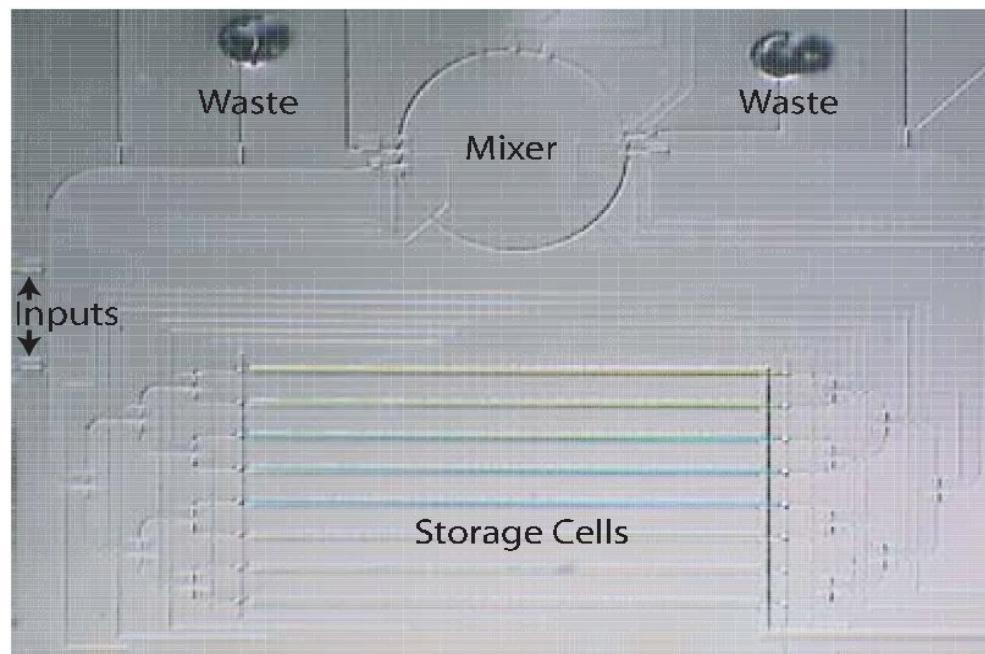
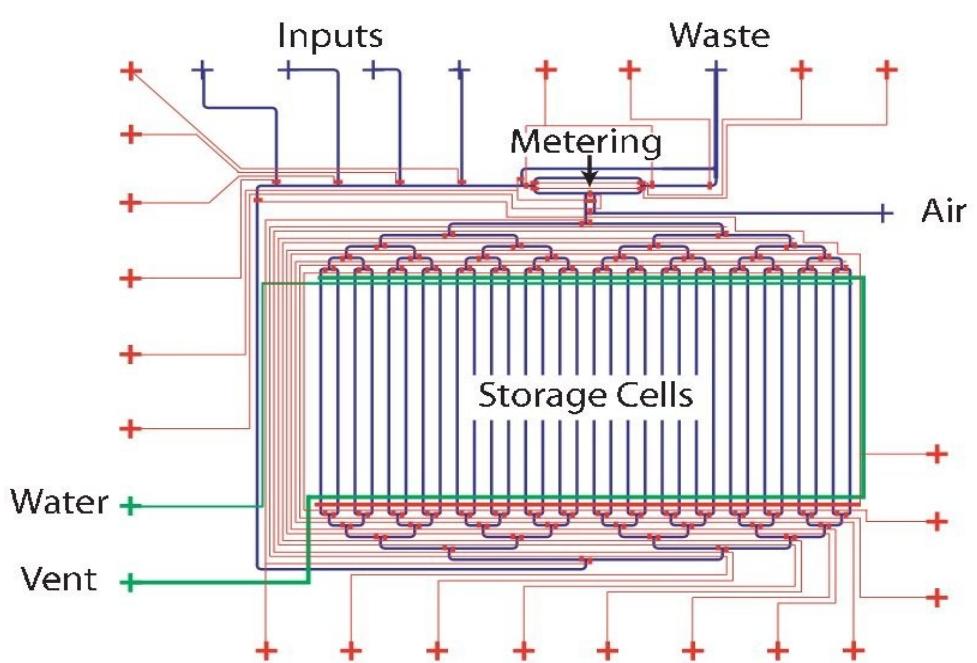
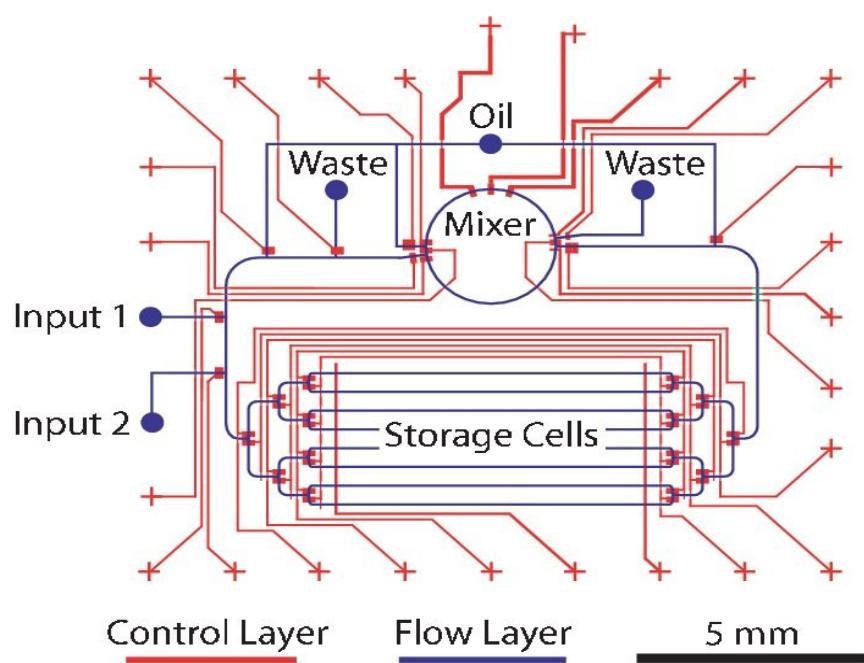
# Lab-on-a-Chip (LOC) – photograph of the assembled device



# Lab-on-a-Chip (LOC) – thermal control

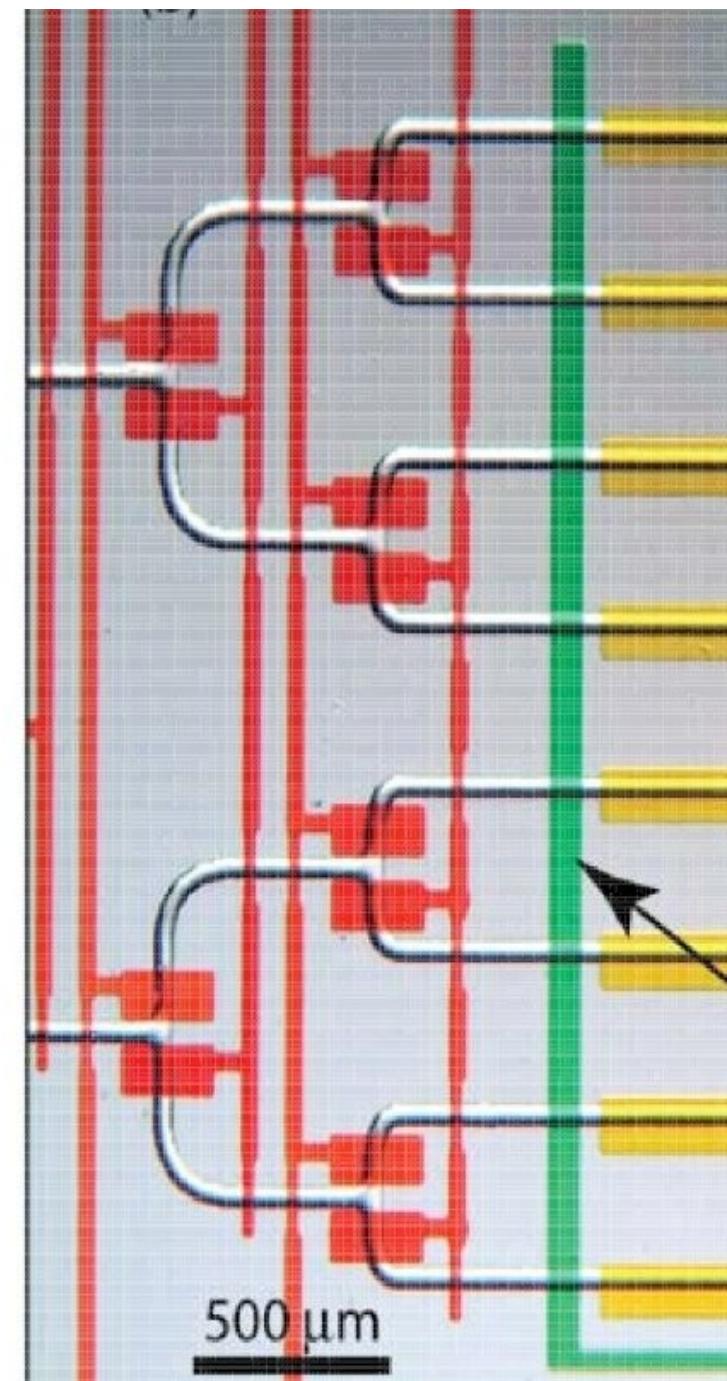
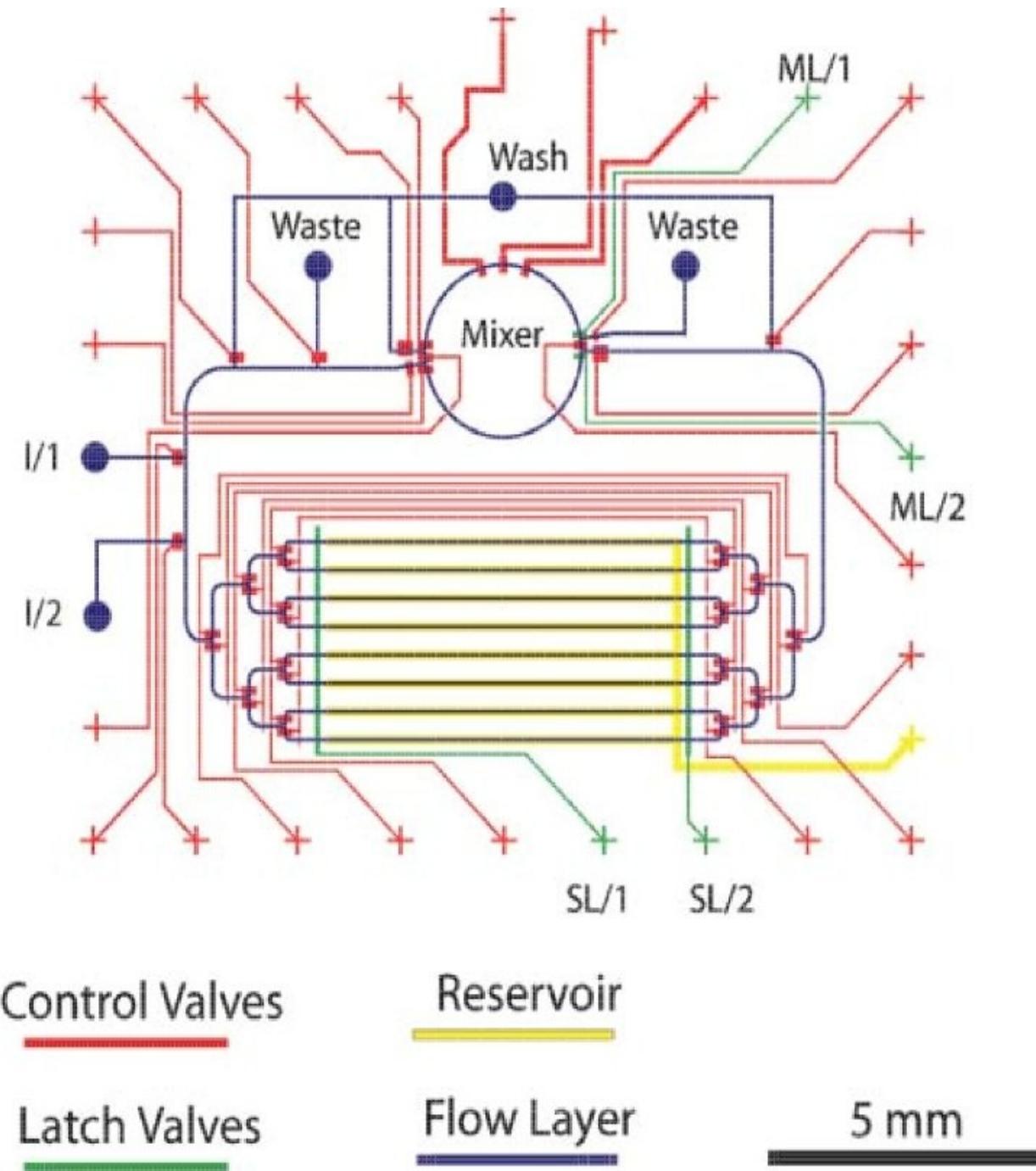




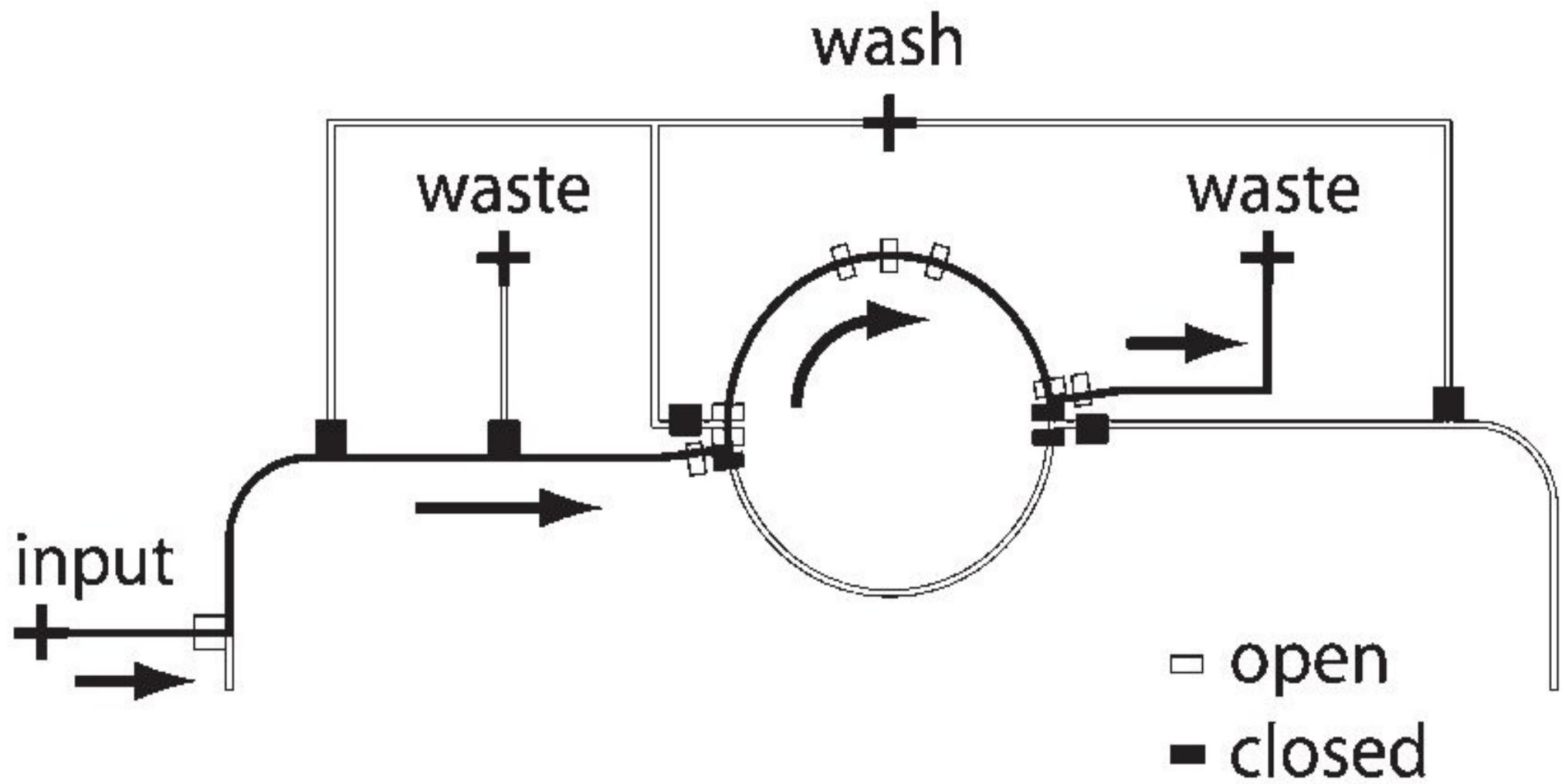


	Driving fluid	Wash fluid	Mixing	Sample size	Inputs	Storage cells	Valves	Control lines	Advantages
Chip 1	oil	N/A	rotary mixer	half of mixer	2	8	46	26	better sample isolation and retention
Chip 2	air	water	during transport	full mixer	4	32	140	21	faster and simpler chip operation

# Digital microfluidics – Urbanski, Thies, Thorsen 2006

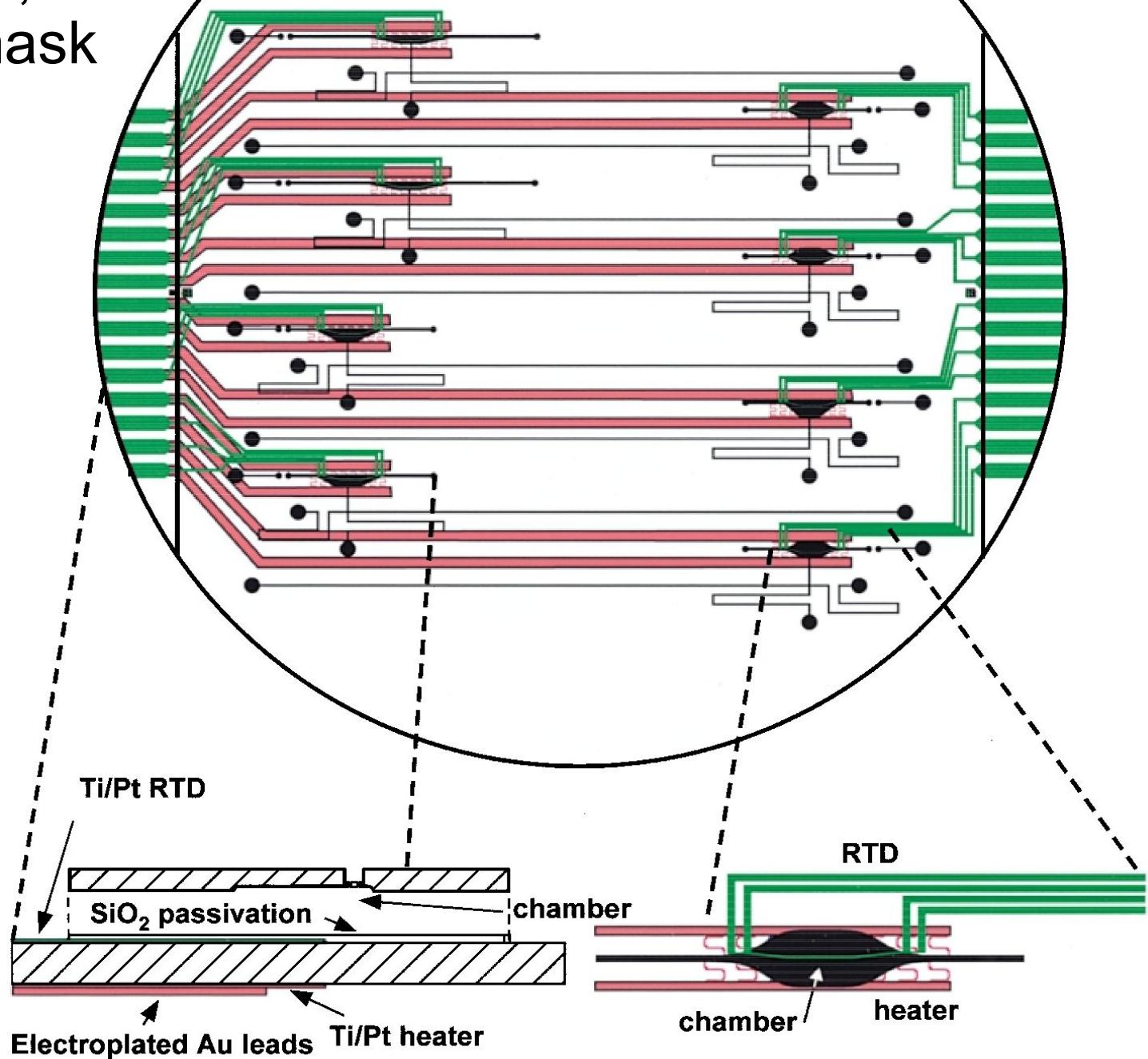


# Microfluidic flow process

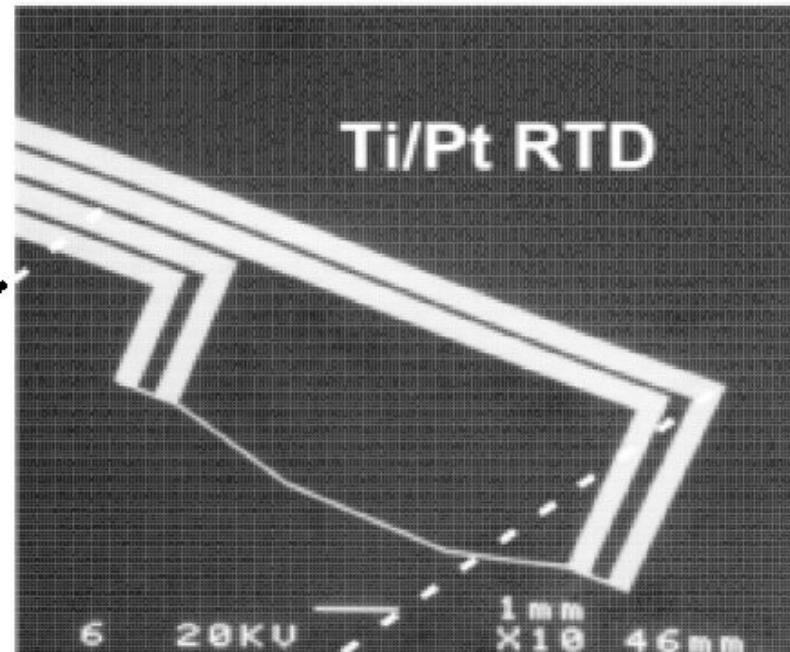
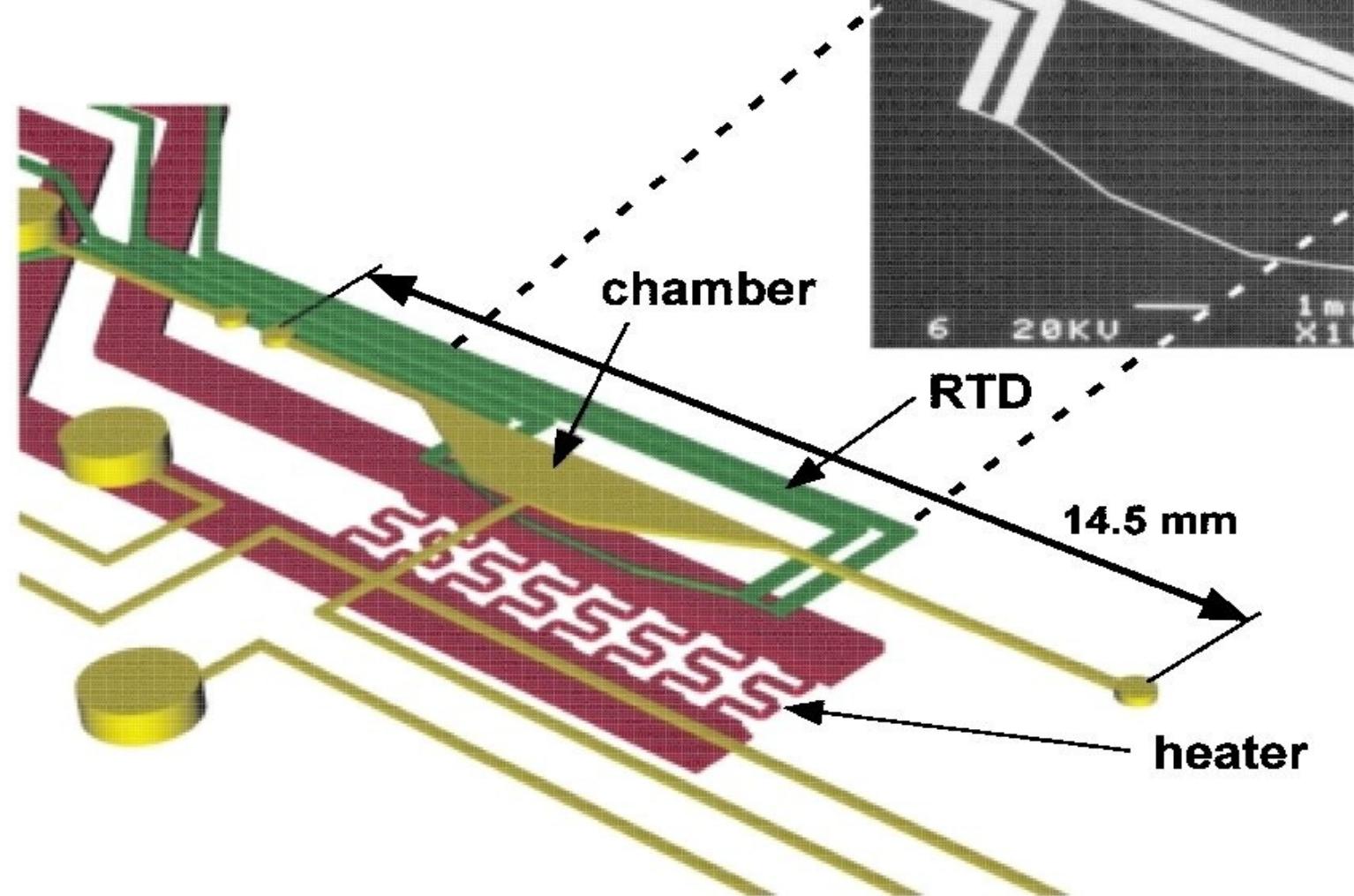


# Fully integrated PCR – Lagally, Emrich, Mathies 2001 - mask design

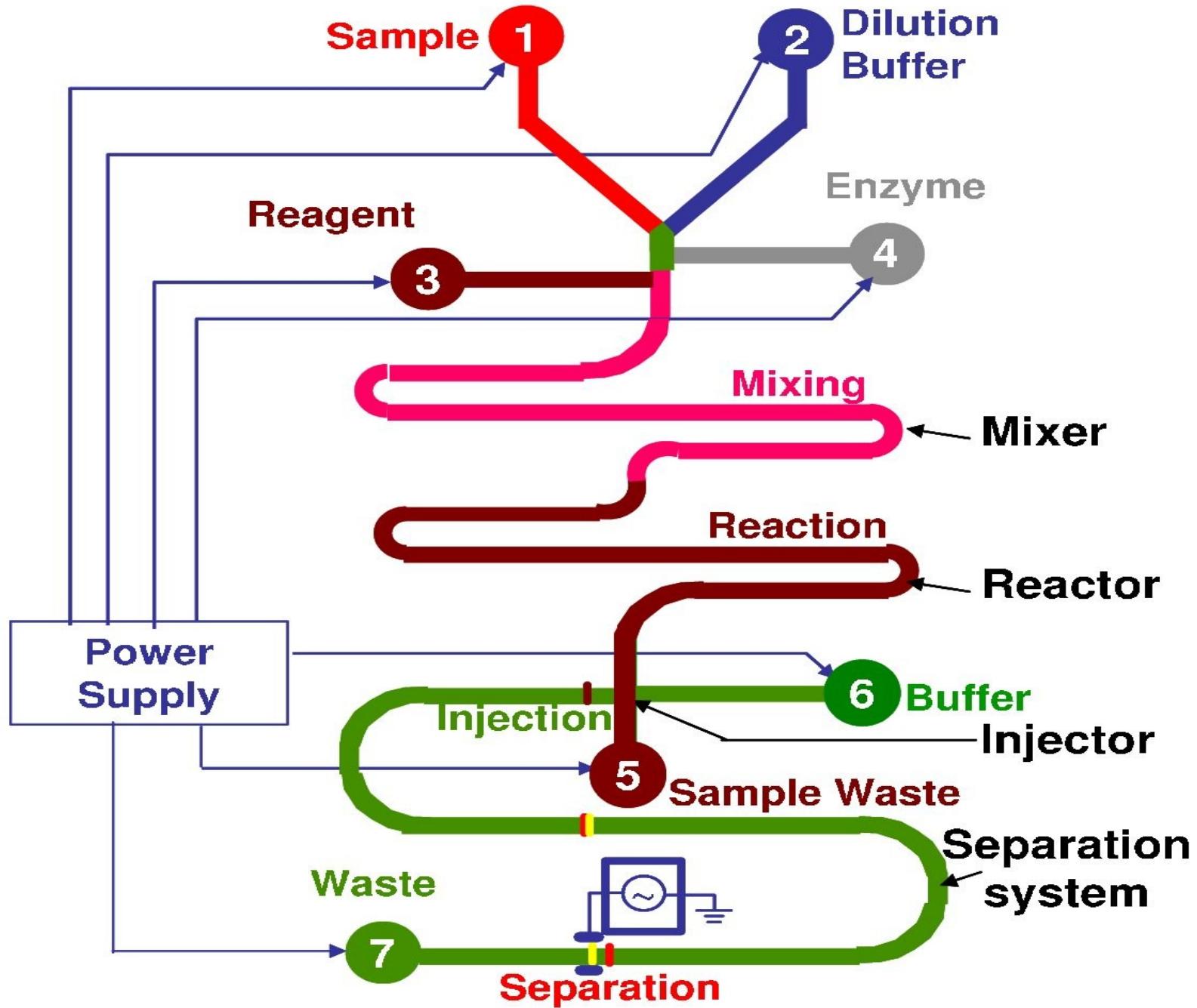
MATHIES LAB  
UC BERKELEY  
00-16



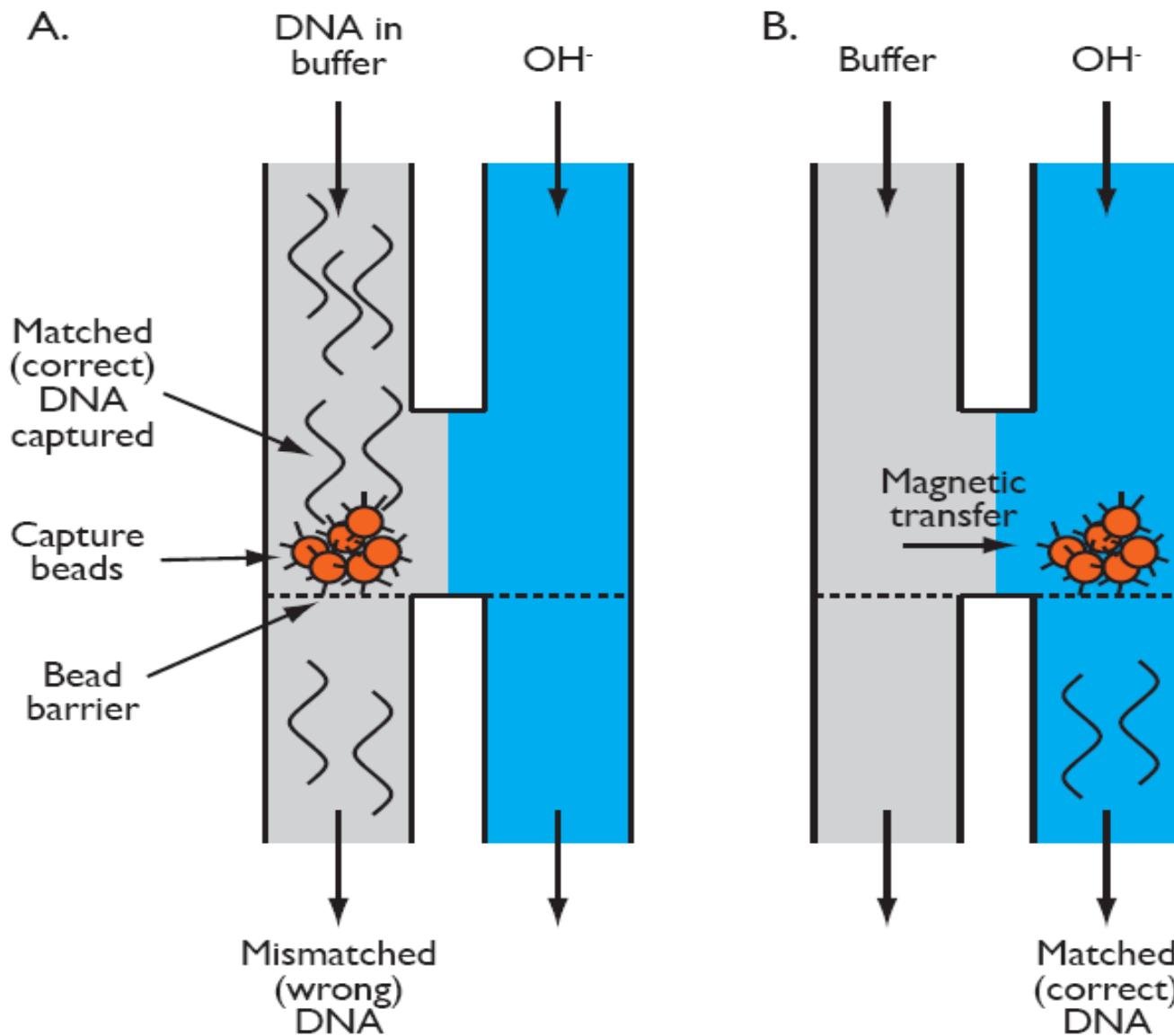
# Perspective view of PCR reaction chamber



# Molecular-System-on-a-Chip (MsoC)

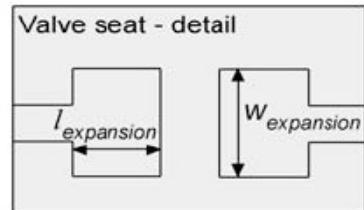
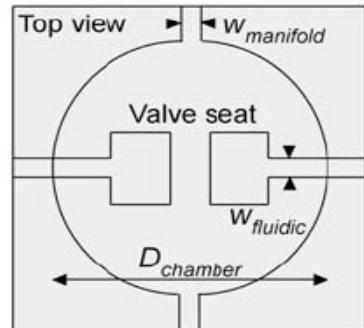
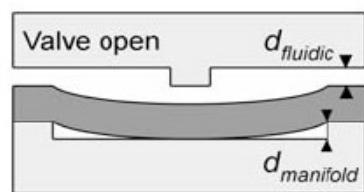
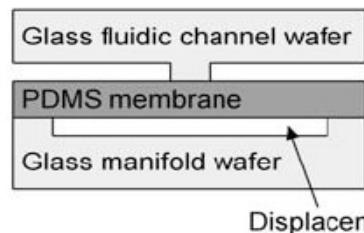


# Molecular-System-on-a-Chip (MsoC) - McCaskill

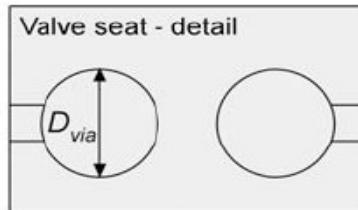
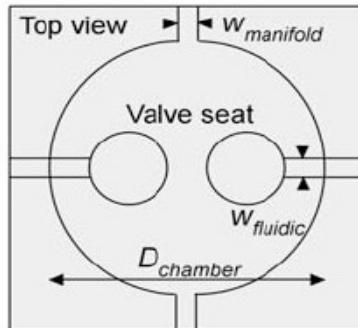
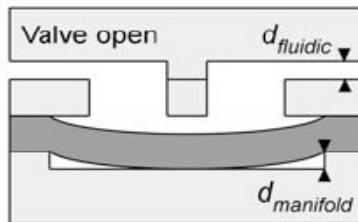
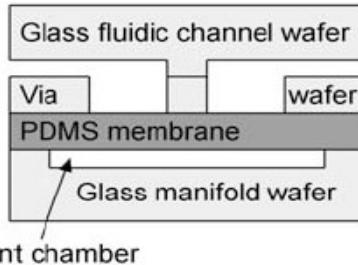


# Molecular-System-on-a-Chip (MsoC) - Grover

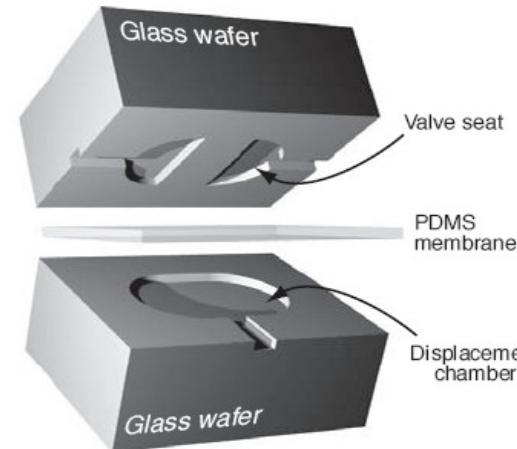
A) 3-layer valve



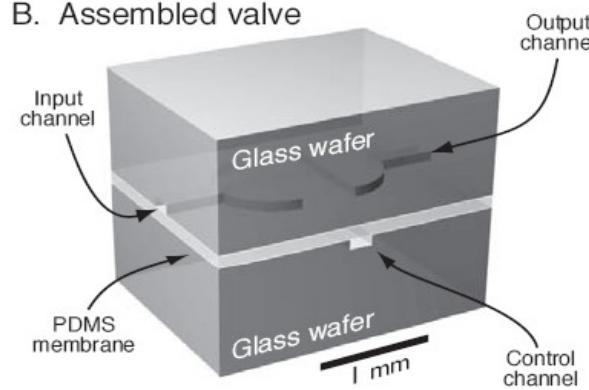
B) 4-layer valve



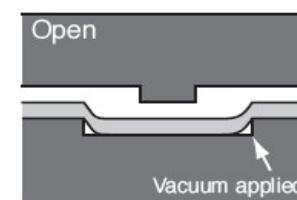
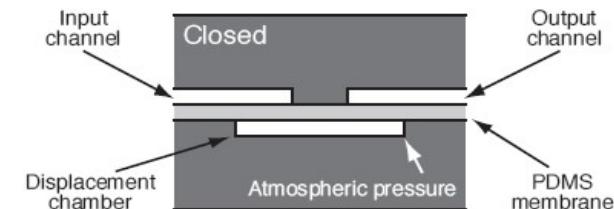
A. Exploded view of single valve



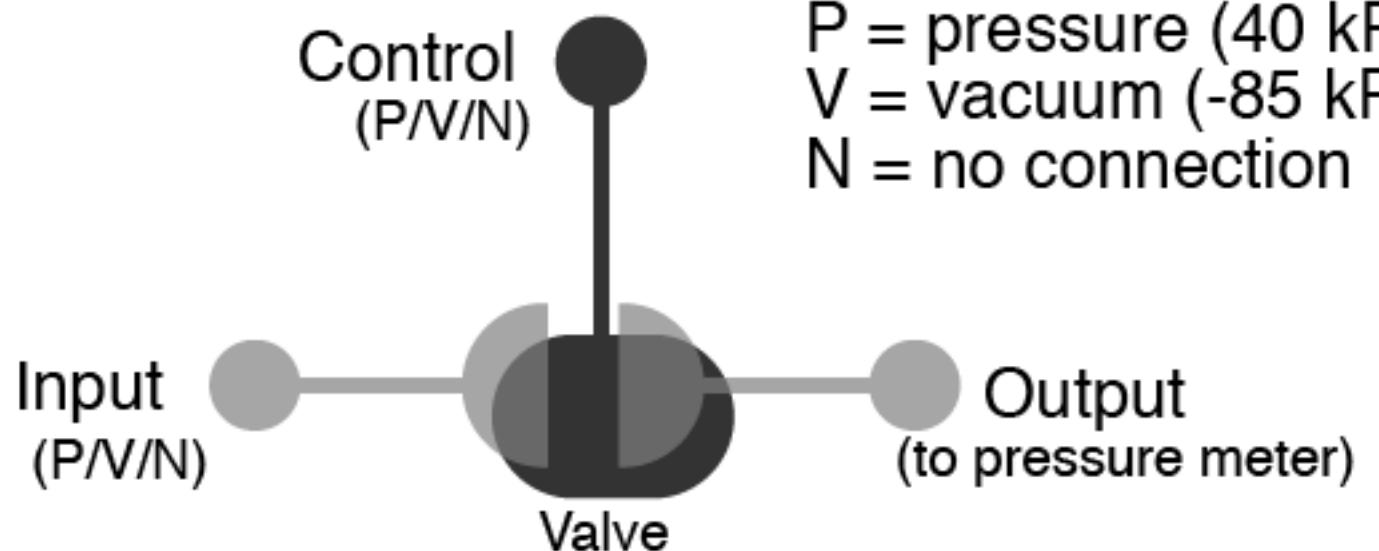
B. Assembled valve



C. Cross-section



# Molecular-System-on-a-Chip (MsoC) - Grover



Rule	Maintained at Input (kPa)	Maintained at Control (kPa)	Measured at Output (kPa)
$PP$	40	40	0
$PV$	40	-85	40
$PN$	40	0	40
$VP$	-85	40	0
$VV$	-85	-85	-83
$VN$	-85	0	0

# Spełnianie funkcji logicznej

$$y = (x_1 \vee \neg x_2) \wedge (\neg x_1 \vee x_2)$$

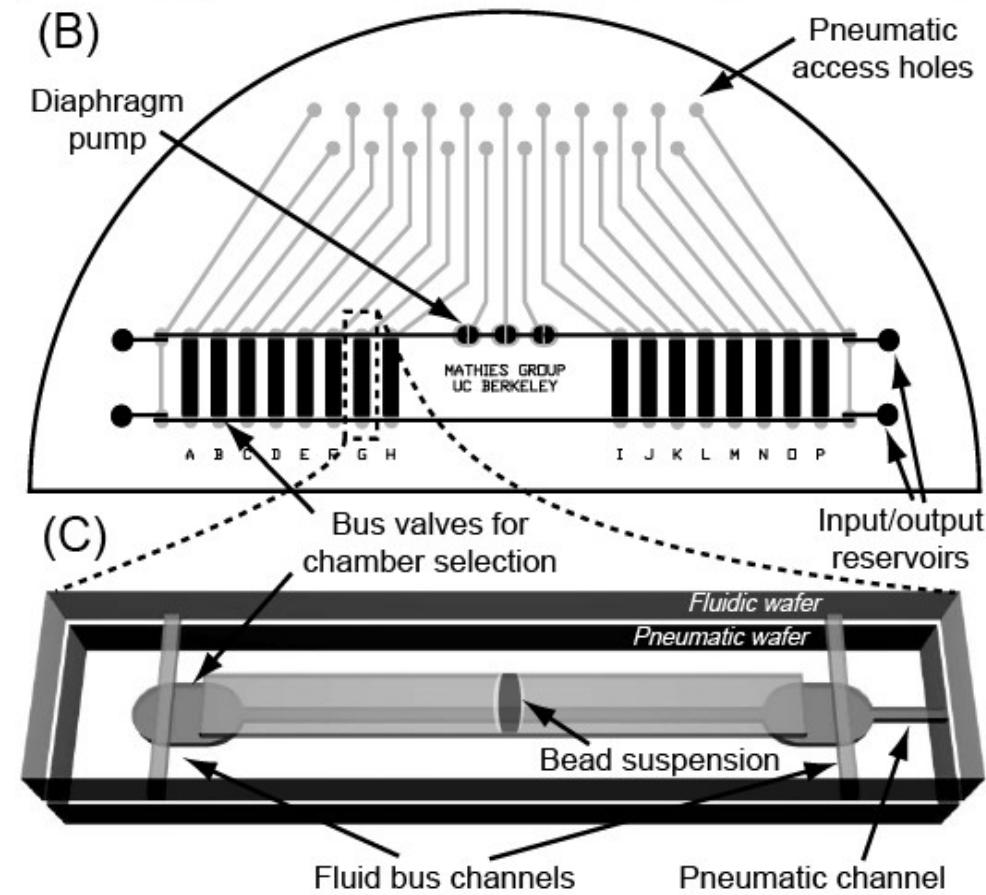
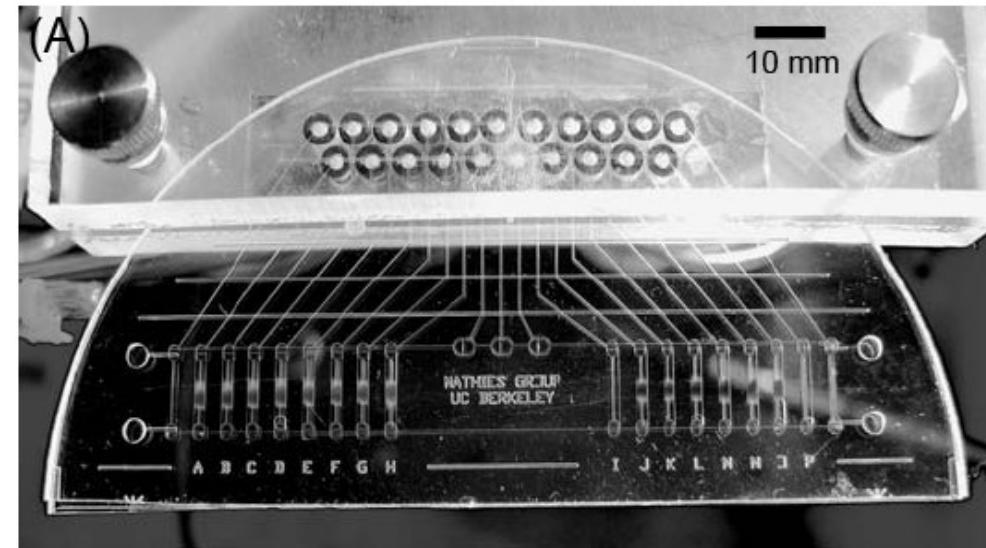
10	10	10	00	11	11
11	00	00			00
		11			

$$y = (\neg x_0 \vee x_2) \wedge (x_0 \vee x_1) \wedge (\neg x_1 \vee \neg x_2) \wedge (\neg x_0 \vee \neg x_1)$$

# Molecular-System-on-a-Chip (MsoC) - Grover

Synthesis ( $5' \rightarrow 3'$ )	Population members ( $5' \rightarrow 3'$ )	Computational role
Bio-agTtcWcaWgt ( $B_0 = \text{TRUE}$ )	Bio-agTtcTcaTgt Bio-agTtcTcaAgt Bio-agTtcAcaTgt Bio-agTtcAcaAgt	captures $B_0 = \text{TRUE}$ (FAM-acWtgWgaAct)
Bio-agWtcTcaWgt ( $B_1 = \text{TRUE}$ )	Bio-agTtcTcaTgt Bio-agTtcTcaAgt Bio-agAtcTcaTgt Bio-agAtcTcaAgt	captures $B_1 = \text{TRUE}$ (FAM-acWtgAgaWct)
Bio-agWtcWcaTgt ( $B_2 = \text{TRUE}$ )	Bio-agTtcTcaTgt Bio-agTtcAcaTgt Bio-agAtcTcaTgt Bio-agAtcAcaTgt	captures $B_2 = \text{TRUE}$ (FAM-acAtgWgaWct)
Bio-agAtcWcaWgt ( $B_0 = \text{FALSE}$ )	Bio-agAtcTcaTgt Bio-agAtcTcaAgt Bio-agAtcAcaTgt Bio-agAtcAcaAgt	captures $B_0 = \text{FALSE}$ (FAM-acWtgWgaTct)
Bio-agWtcAcaWgt ( $B_1 = \text{FALSE}$ )	Bio-agTtcAcaTgt Bio-agTtcAcaAgt Bio-agAtcAcaTgt Bio-agAtcAcaAgt	captures $B_1 = \text{FALSE}$ (FAM-acWtgTgaWct)
Bio-agWtcWcaAgt ( $B_2 = \text{FALSE}$ )	Bio-agTtcTcaAgt Bio-agTtcAcaAgt Bio-agAtcTcaAgt Bio-agAtcAcaAgt	captures $B_2 = \text{FALSE}$ (FAM-acTtgWgaWct)
FAM-tcWagWgtWca (all 8 possible values for $B_2$ , $B_1$ , and $B_0$ )	FAM-acTtgTgaTct FAM-acTtgTgaAct FAM-acTtgAgaTct FAM-acTtgAgaAct FAM-acAtgTgaTct FAM-acAtgTgaAct FAM-acAtgAgaTct FAM-acAtgAgaAct	input population (FAM-acWtgWgaAct)

# Molecular-System-on-a-Chip (MsoC) - Grover



(A) Load capture beads into chambers



(B) Load input DNA into fluidic loop and chamber



(C) Circulate input DNA through selected beads



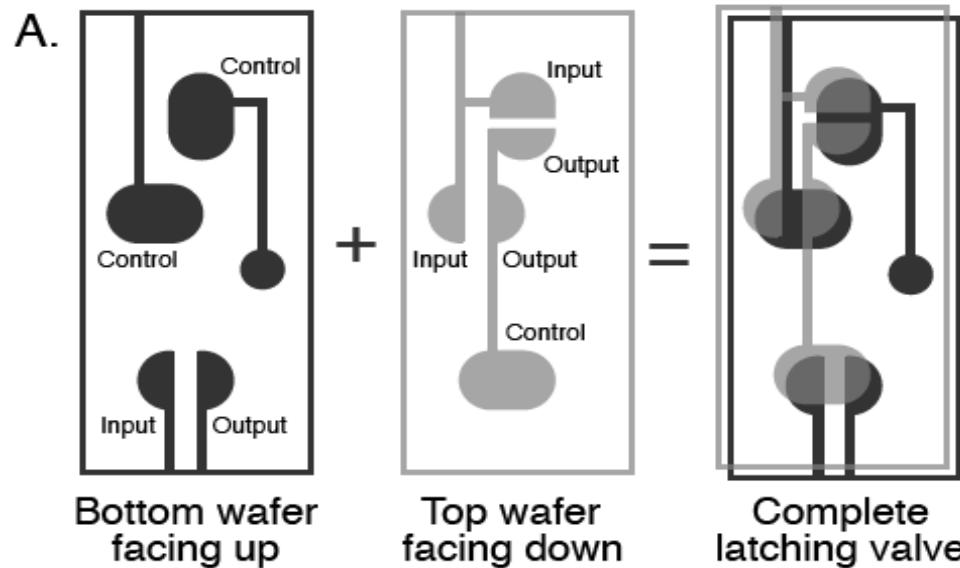
(D) Release and transfer DNA to next capture step



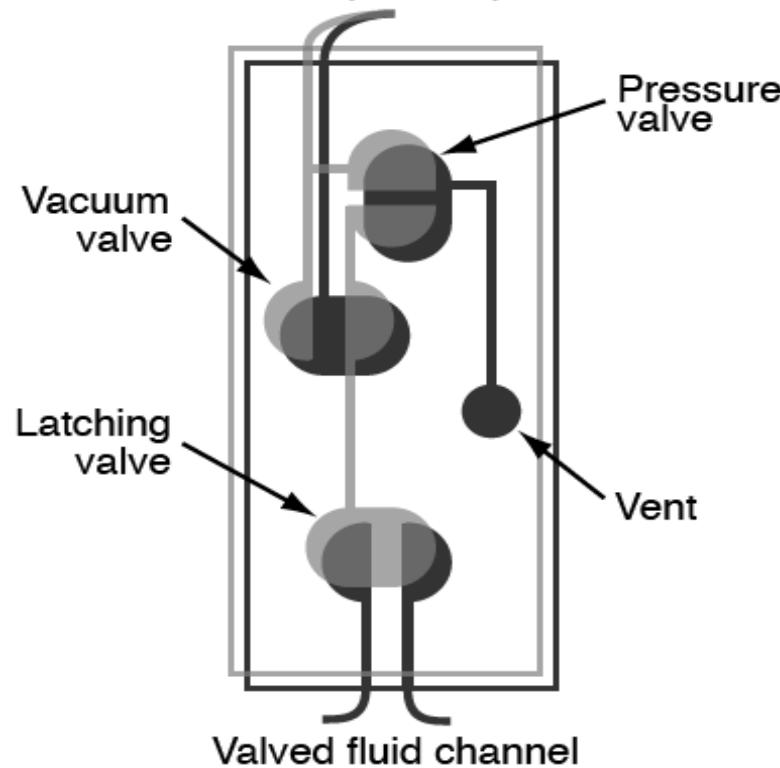
(E) Release and transfer DNA to first readout step



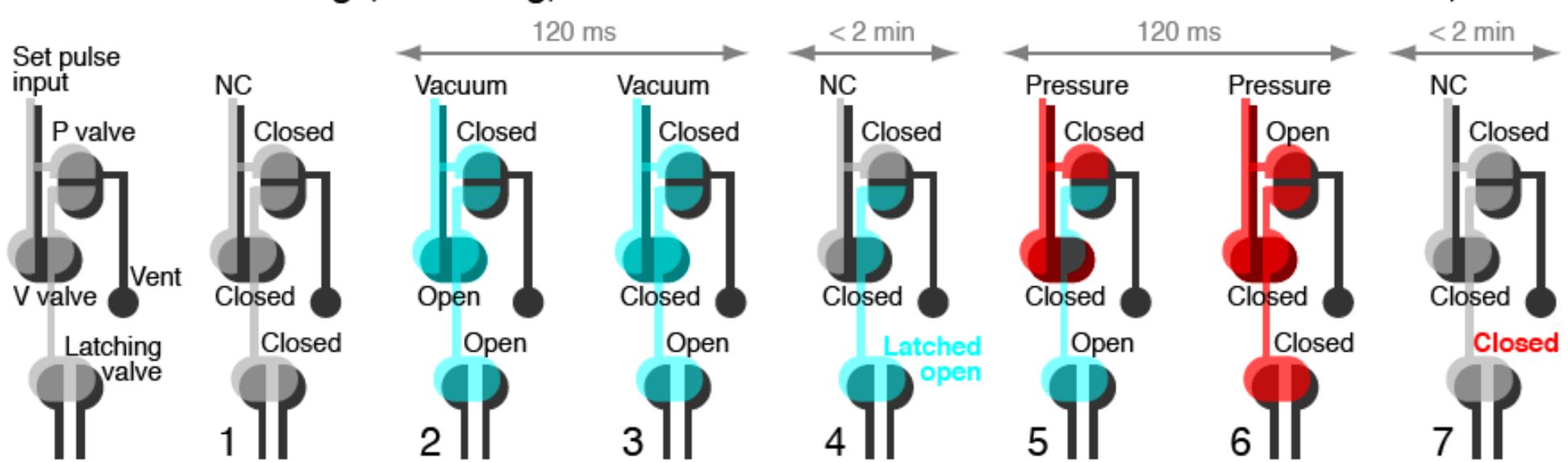
# Molecular-System-on-a-Chip (MsoC) - Grover



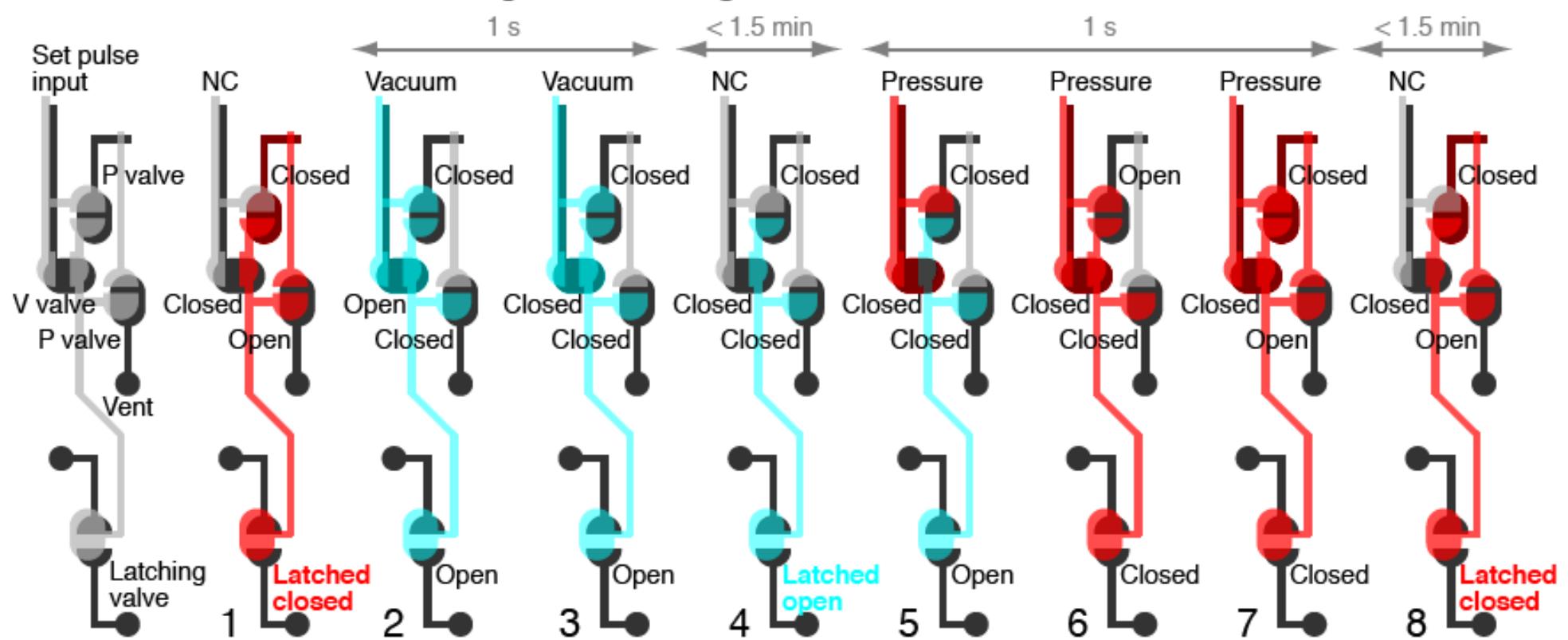
B. Set pulse input

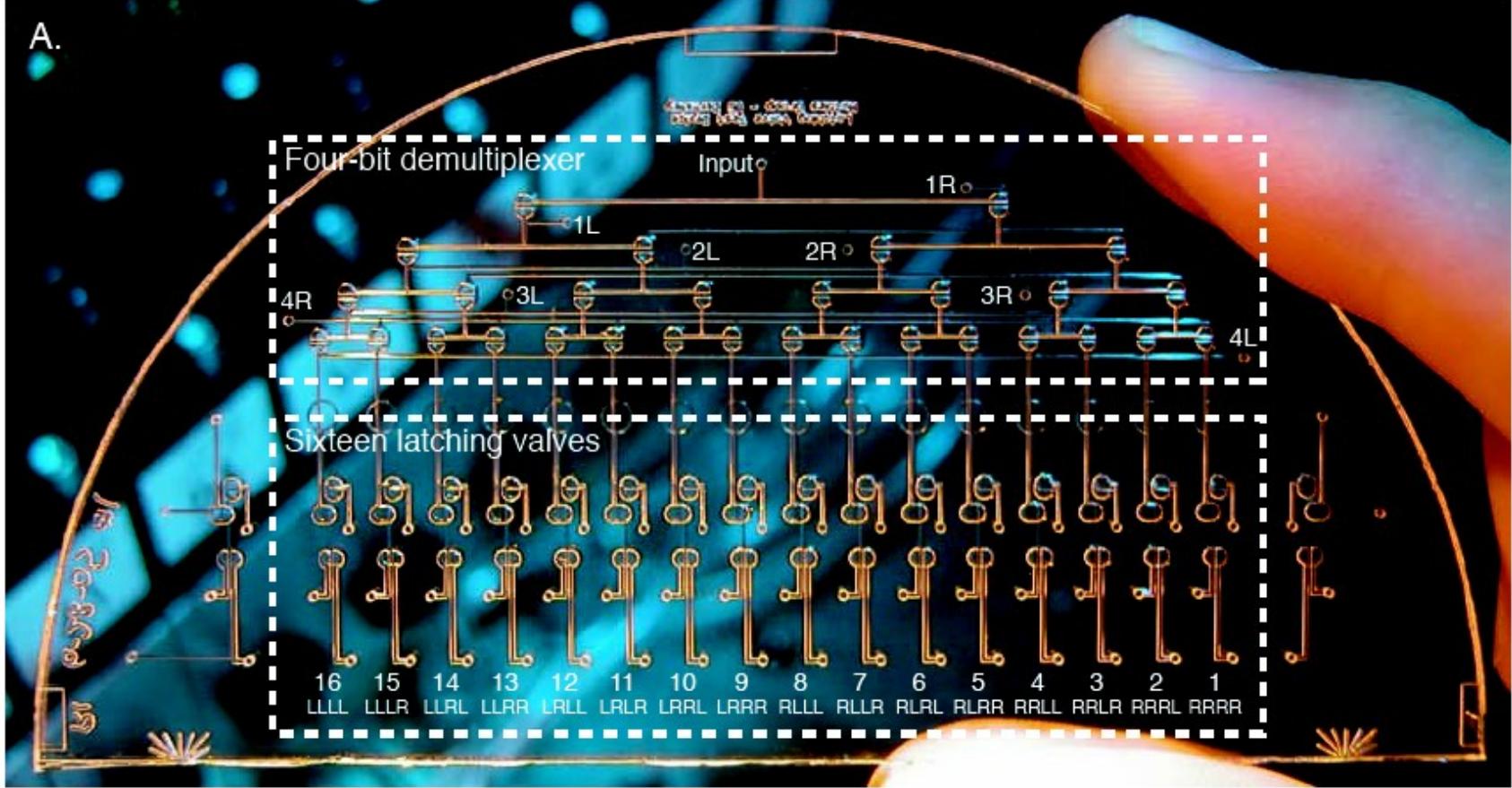


### A. Vacuum-latching (V-latching) valve



### B. Pressure/vacuum-latching (PV-latching) valve

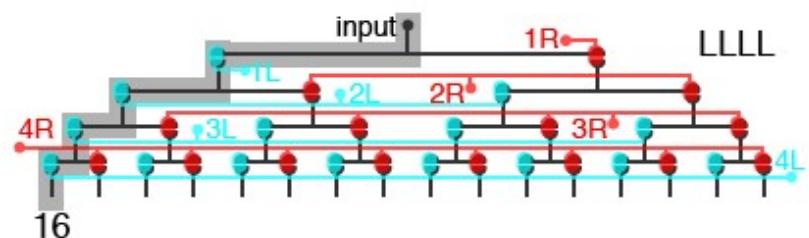
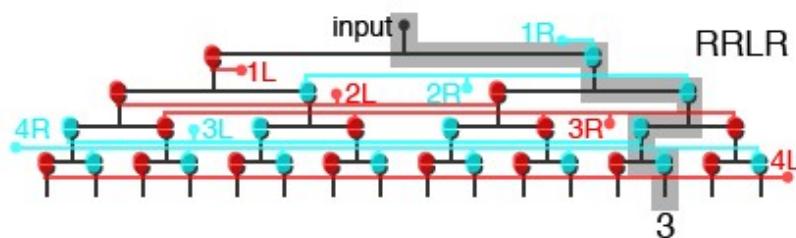
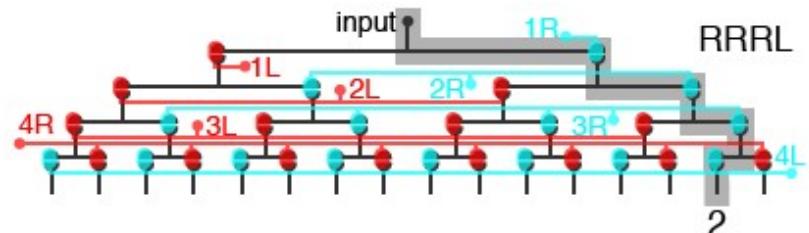
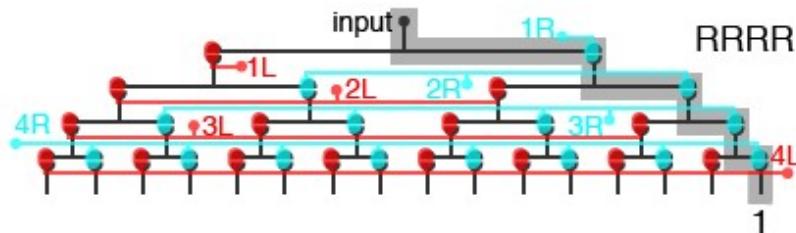




### B. Sample demultiplexer operations

Channel under vacuum

Channel under pressure



# Podsumowanie

- Dzięki technologii lab-on-a-chip możliwość przeprowadzania reakcji chemicznych w formie zminiaturyzowanej o dużym stopniu automatyzacji przy jednocześnie niższych kosztach
- Dynamiczny rozwój inżynierii genetycznej i molekularnej diagnostyki medycznej
- Potrzeba opracowania nowych sposobów przetwarzania informacji: przełamywanie barier wynikających z technologii scalonych układów elektronicznych
- Otwiera się nowy interdyscyplinarny obszar badań naukowych – komputery biomolekularne