

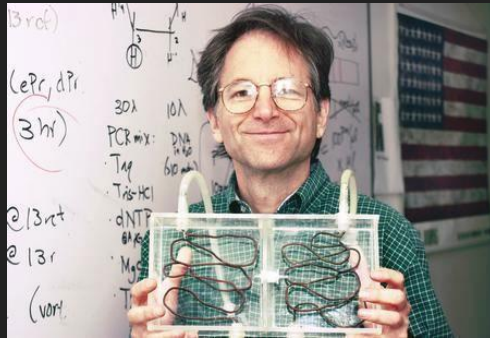
Engineering Molecular Computers

Konstantinos Samaras-Tsakiris

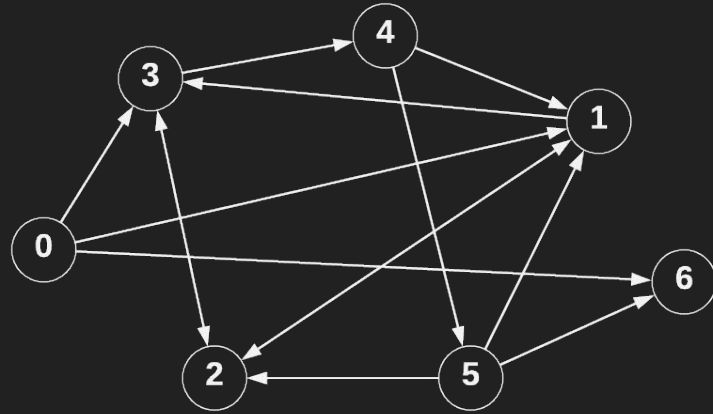
ksamtsak@gmail.com

20 April 2018

RSAdleman

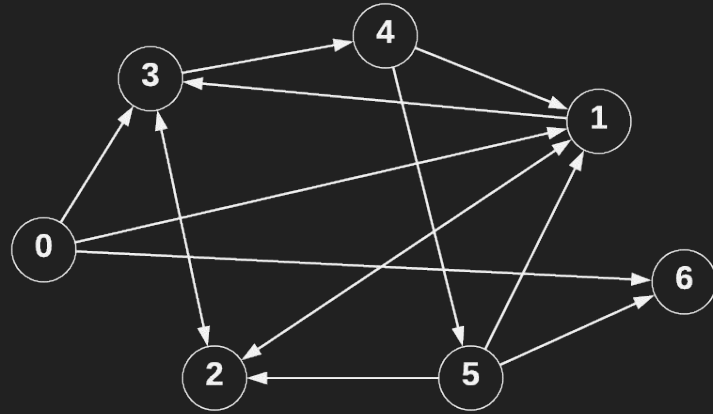


travelling salesman



Hamiltonian paths with DNA

1. random paths (lots)
2. begins at 0, ends at 6
3. length == 7
4. visits every node
5. any path left ?



O₂ TATCGGATCGGTATATCCGA

O₃ GCTATTCGAGCTTAAAGCTA

O_{2→3} GTATATCCGA | GCTATTCGAG

O_{3→4} CTTAAAGCTA | GGCTAGGTAC

O₄ GGCTAGGTACCAGCATGCTT

lots of random paths

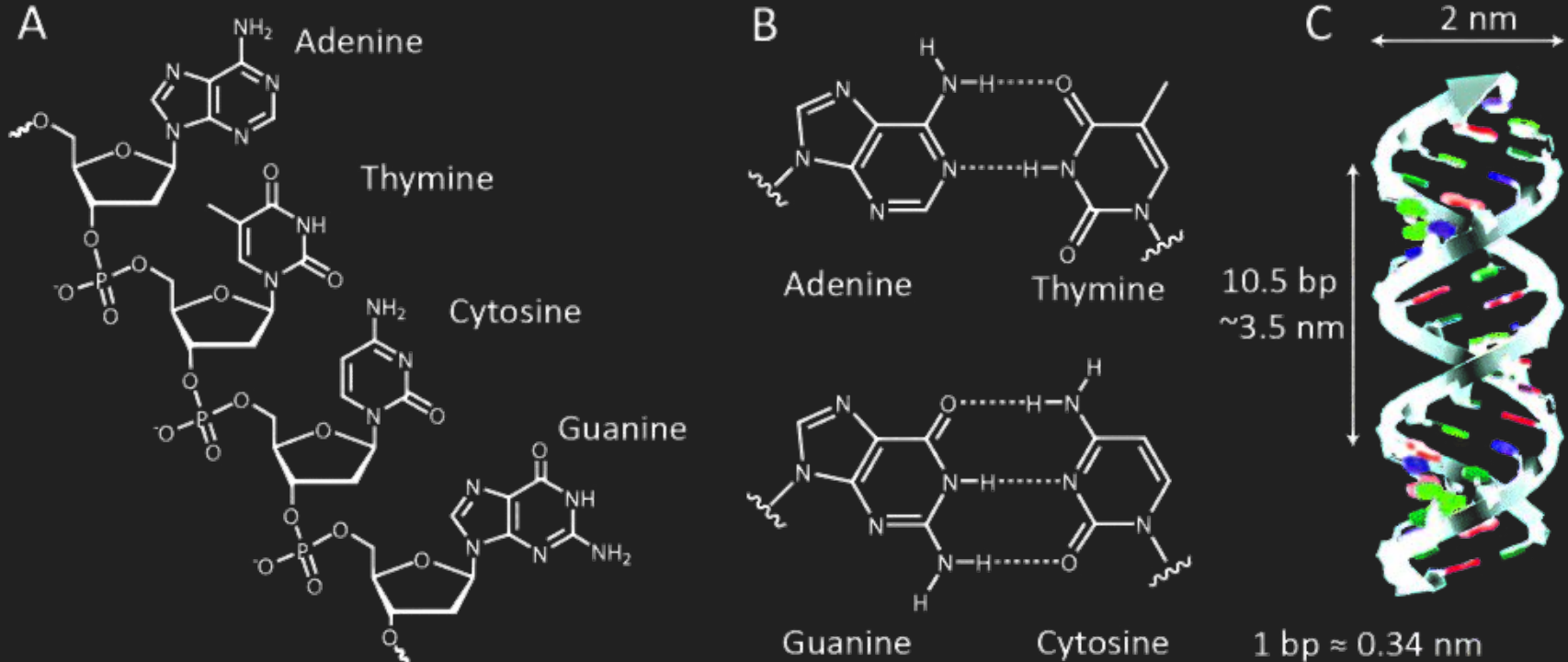
O_{2→3}

O_{3→4}

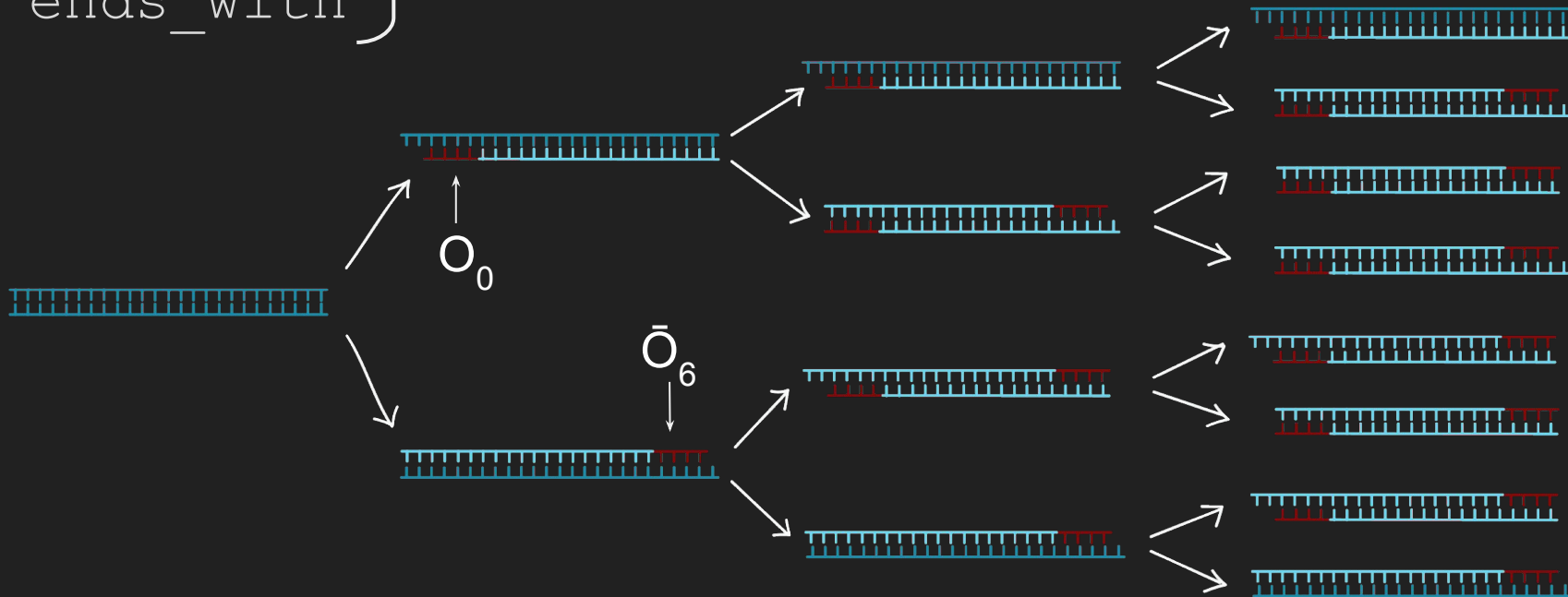
GTATATCCGA GCTATTCGAG CTTAAAGCTA GGCTAGGTAC
CGATAAGCTC GAATTCGAT

O₂

Nucleotides, a DNA alphabet



starts_with
ends_with } PCR



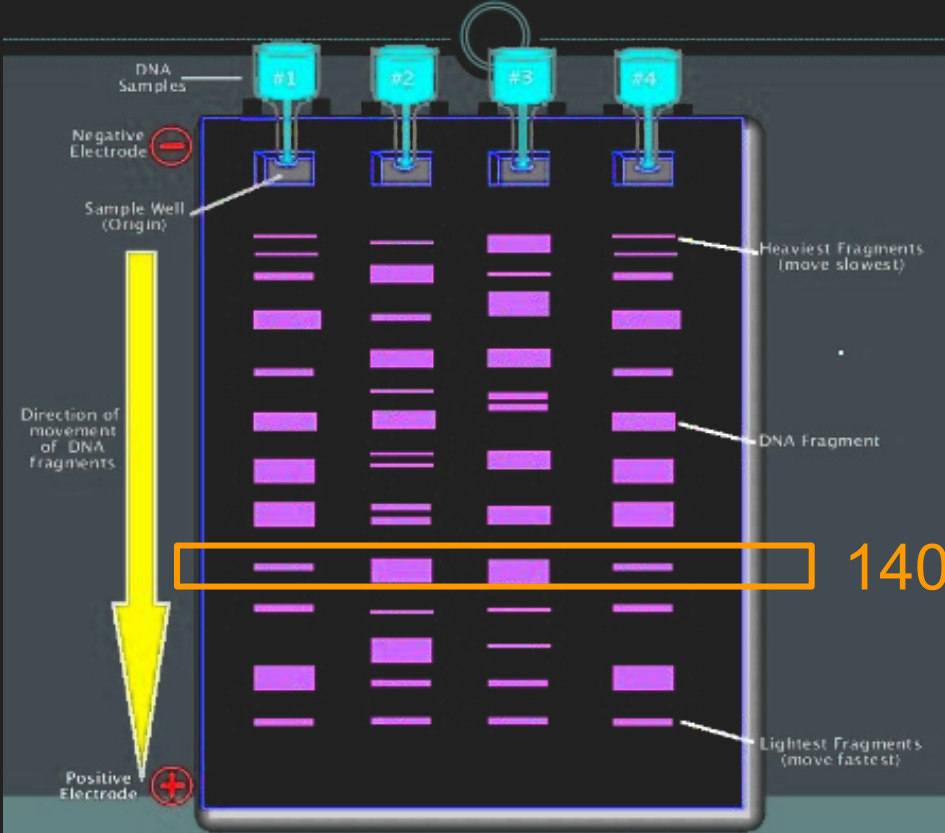
cycle:

1

2

3

select_length: Electrophoresis

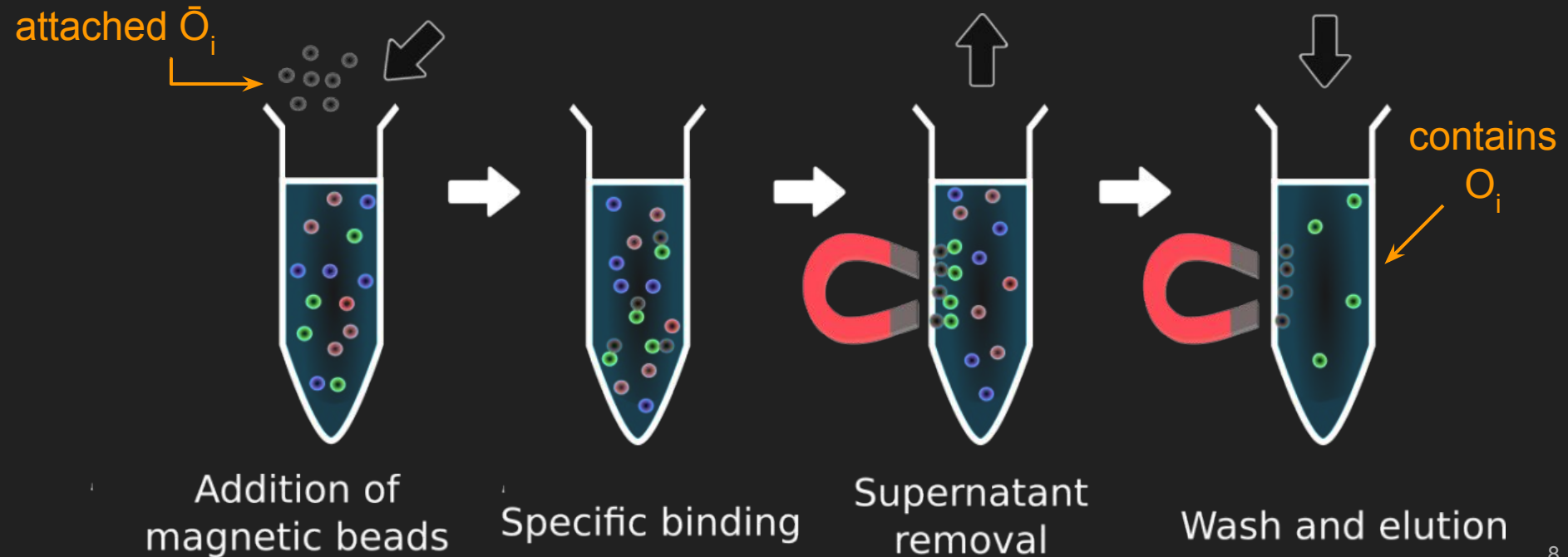


140bp
7 nodes
20bp/node

visit every node

\Rightarrow visit O_i for all i

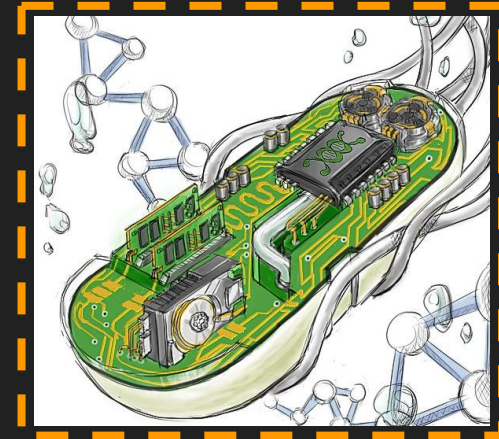
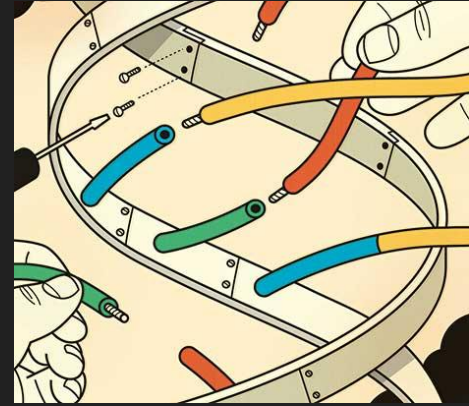
Magnetic bead
filtering

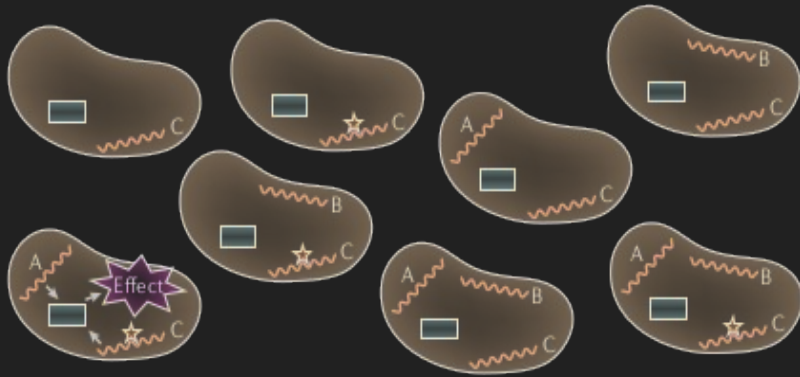


Hamiltonian paths with DNA

- Massively parallel searches!
 - DNA quantities: $O(2^V)$
- 7 days labwork (1994)
- Imprecise processes
 - error stability?

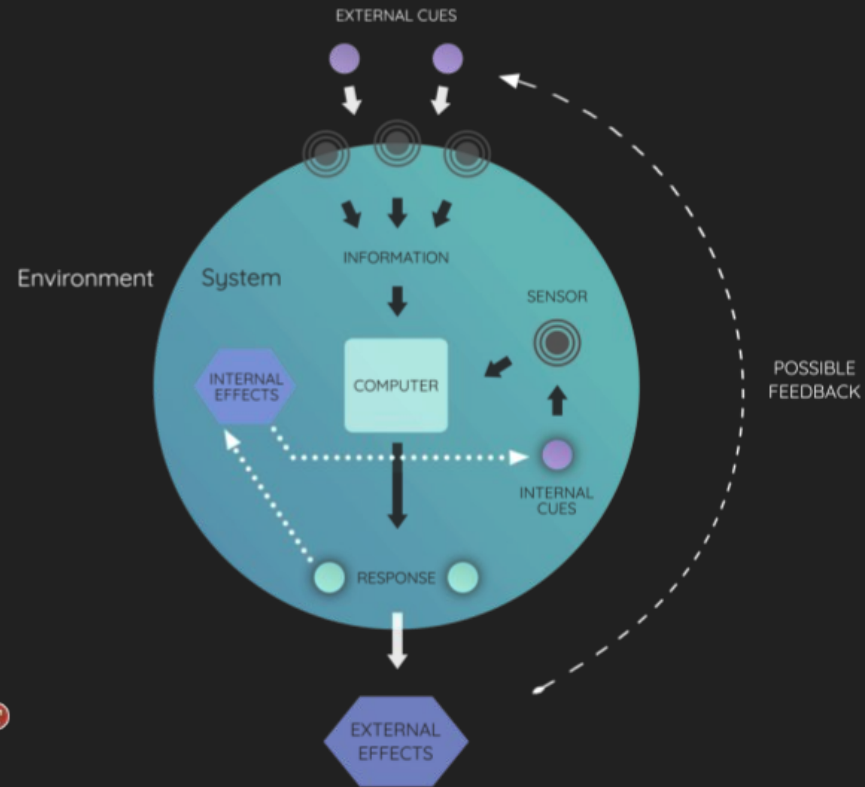
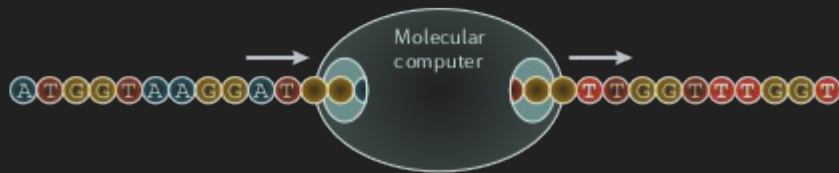
Synthetic Biology

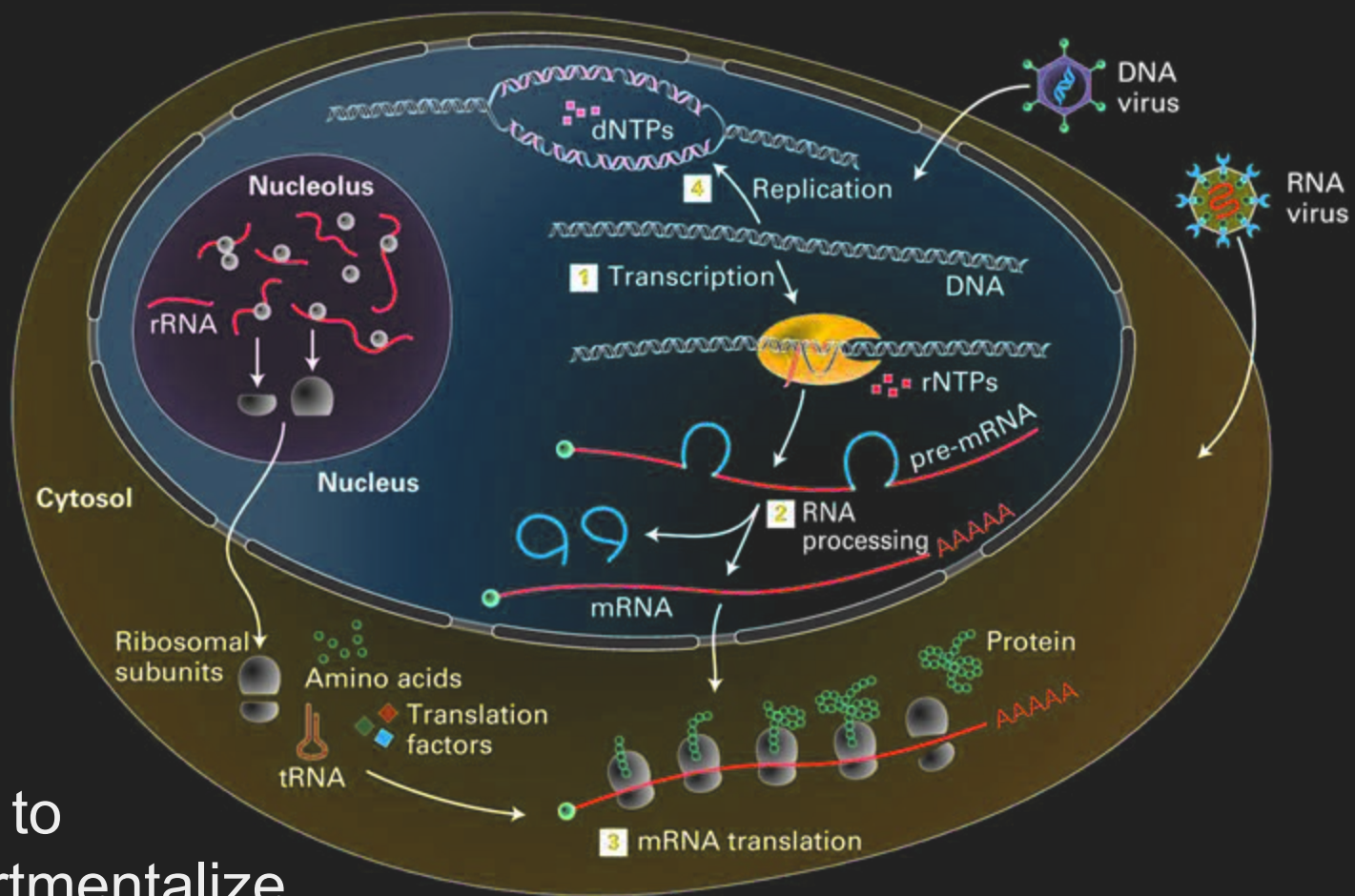




molecular computing

controlling cells

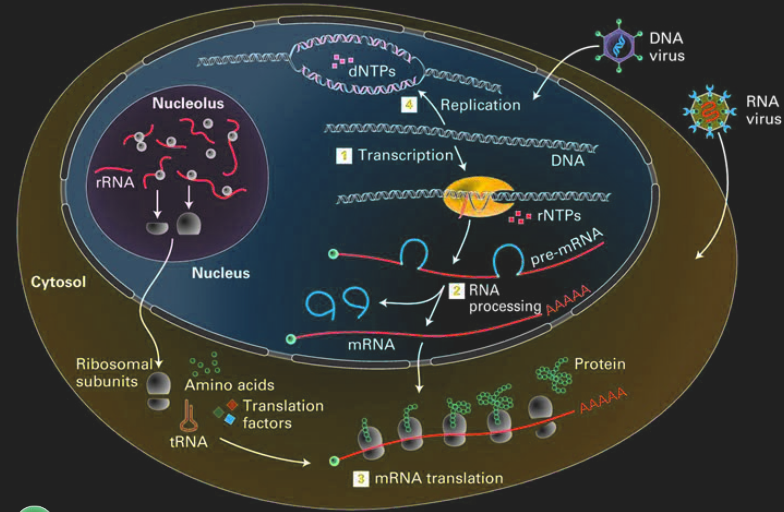
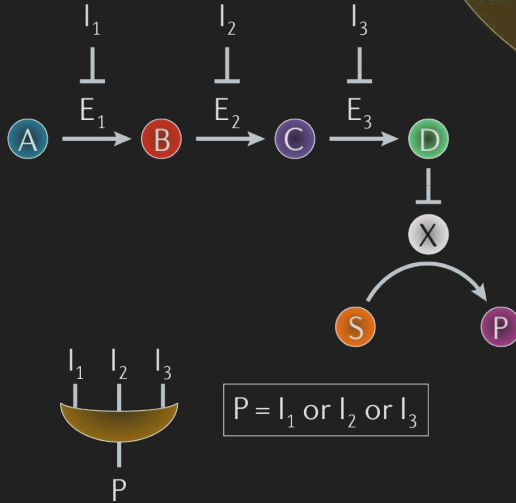
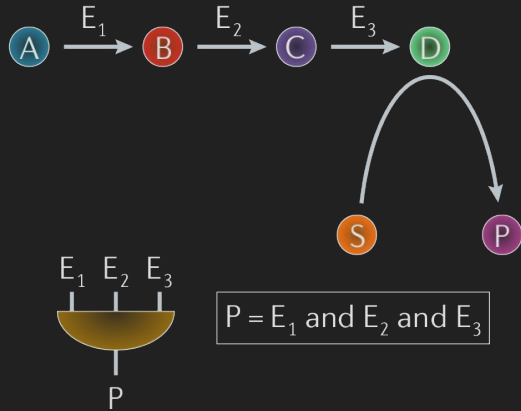




“soup”

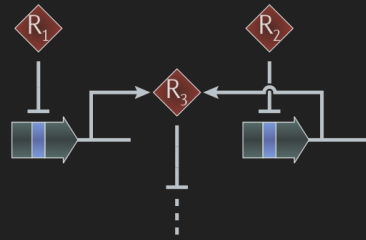
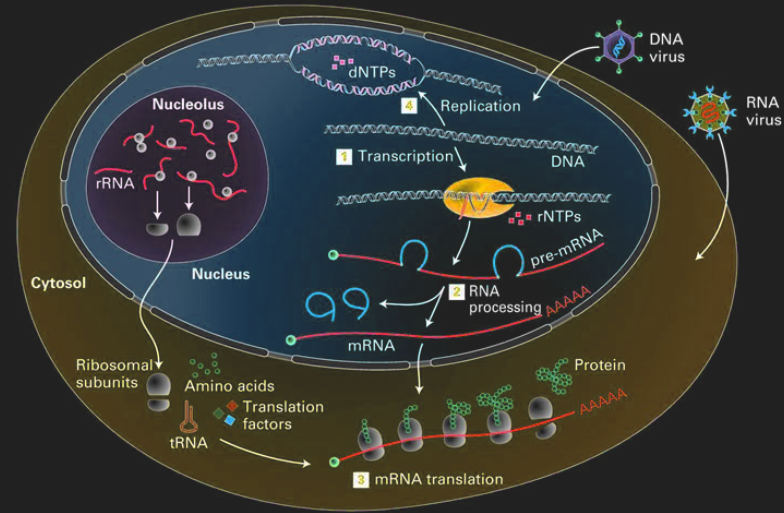
difficult to compartmentalize

hacking cells



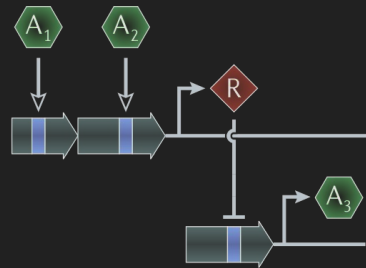
logic function
 ➤ proteins

hacking cells



$$R_3 = \text{NAND}(R_1, R_2)$$

R_1	R_2	R_3
-	-	+
-	+	+
+	-	+
+	+	-



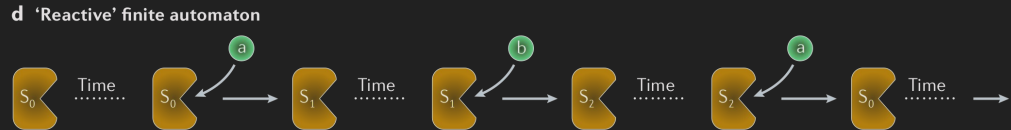
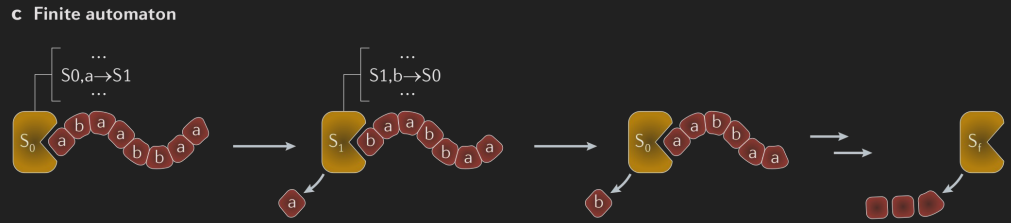
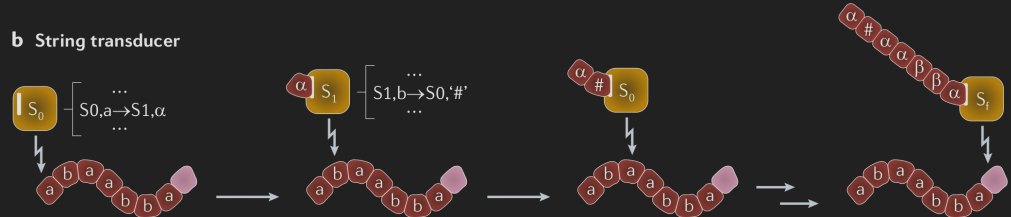
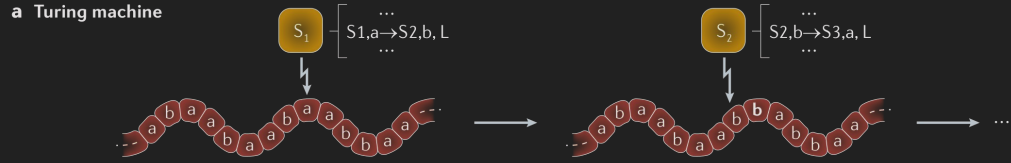
$$A_3 = \text{NOR}(A_1, A_2)$$

A_1	A_2	A_3
-	-	+
-	+	-
+	-	-
+	+	-



logic function
 ➤ transcription factors

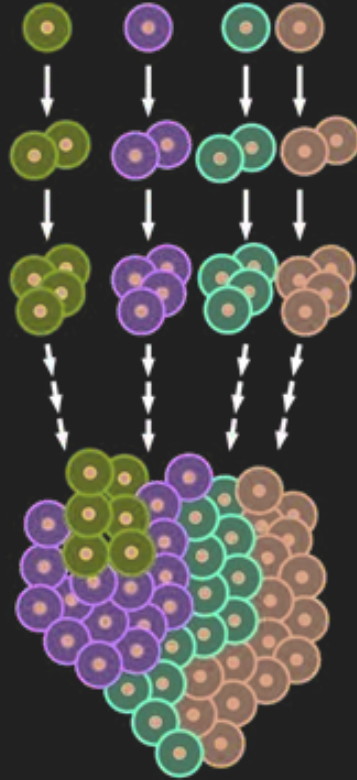
hacking cells



state machines
➤ theoretical mostly

Problem

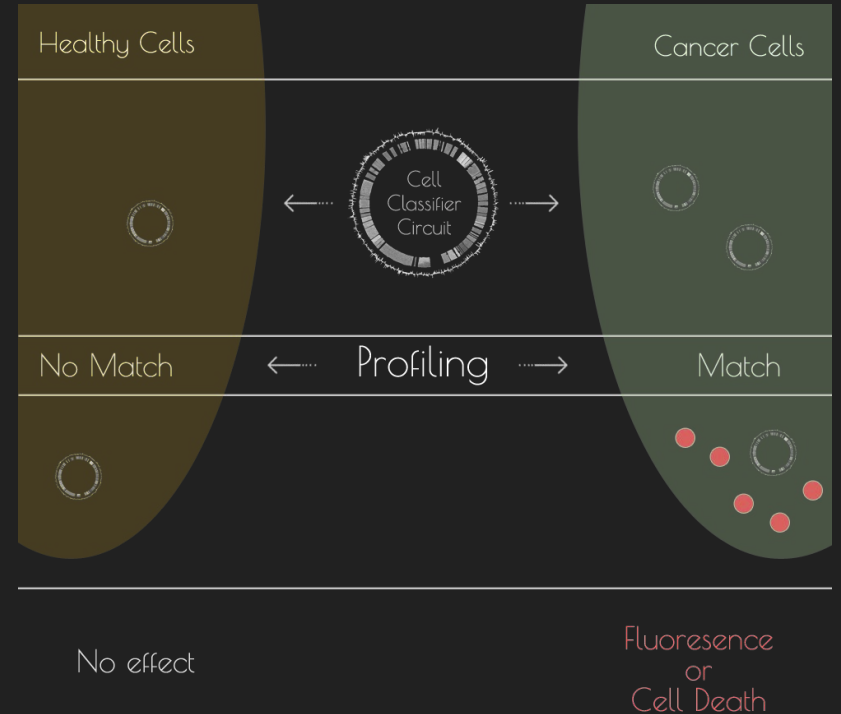
➤ Healthy or Cancerous?



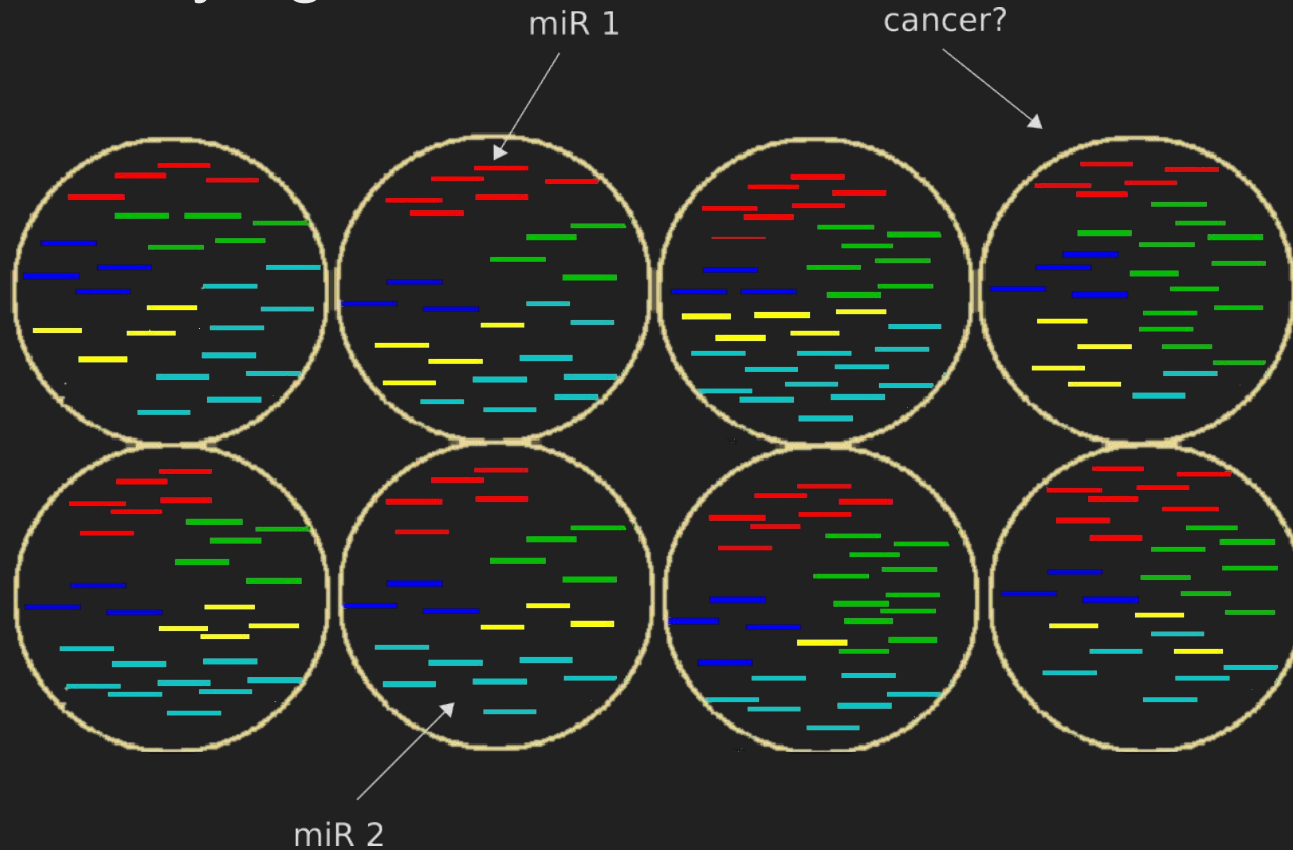
Problem

➤ Healthy or Cancerous?

- Kill cancerous
- Do nothing to healthy

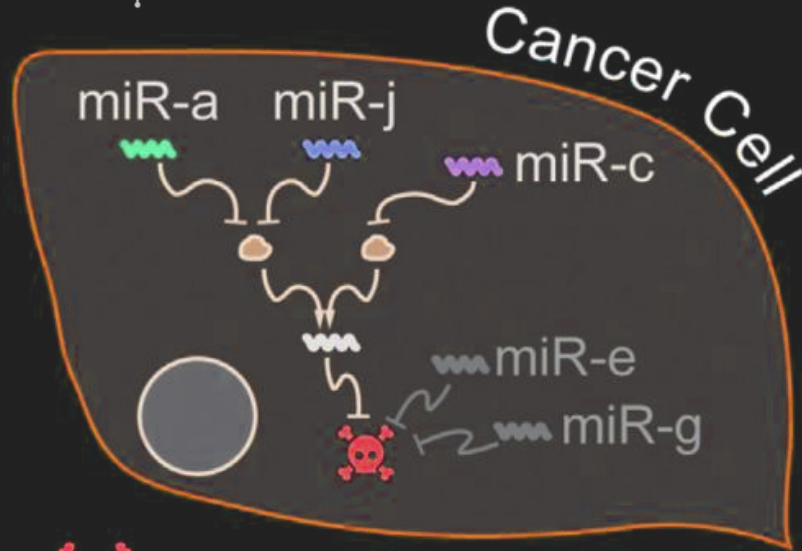
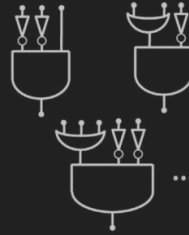



classifying cells



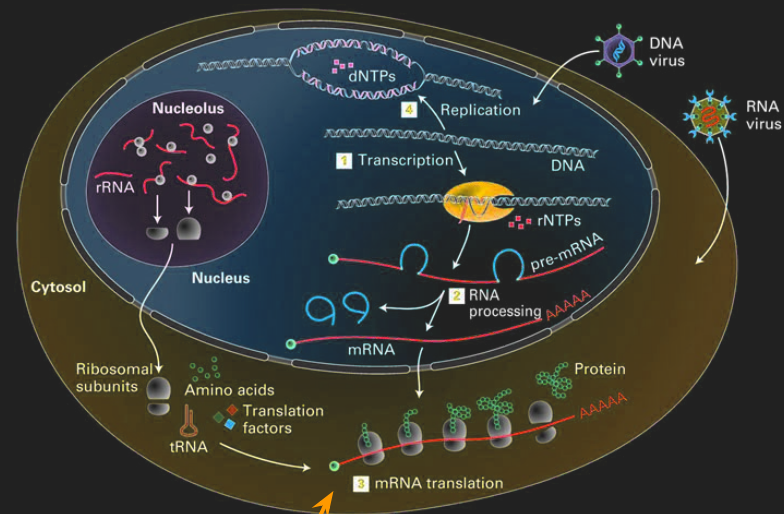
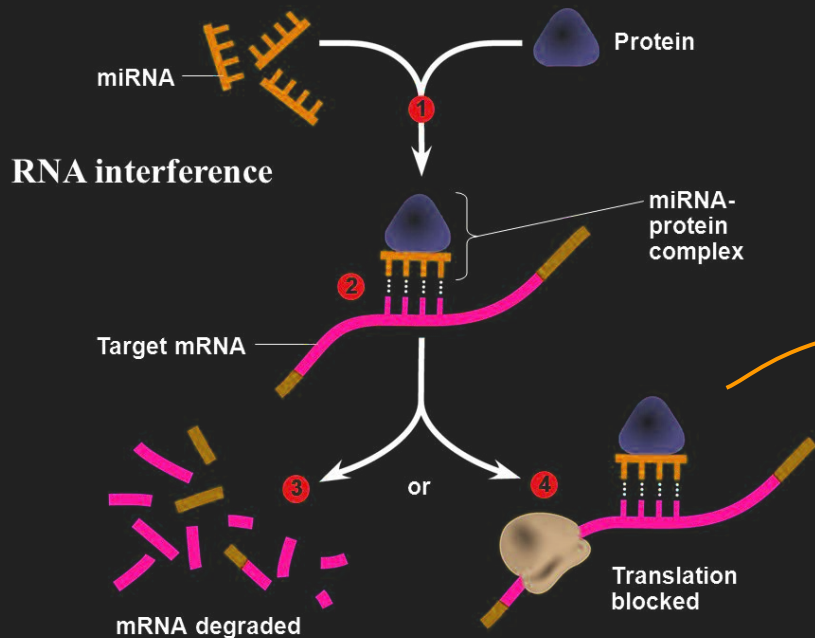
miRNA
vocabulary

classifying cells



 = (miR-a | miR-j) & miR-c
& not(miR-e) & not(miR-g)

RNA interference



miRNA suppresses protein synthesis

© 2012 Pearson Education, Inc.

1995

1996: RNAi silencing demonstrated in animals

1998: Discovered that RNAi done by dsRNA

2001: Targeted RNAi silencing occurs

2002: First therapeutic use of RNAi

2004: First Phase I and II clinical trials involving RNAi begin

2006: Fire and Mello share the Nobel Prize in Physiology or Medicine

2010: First in-human Phase I clinical trials begin

2015: Phase I and II clinical trials demonstrate RNAi's therapeutic applications

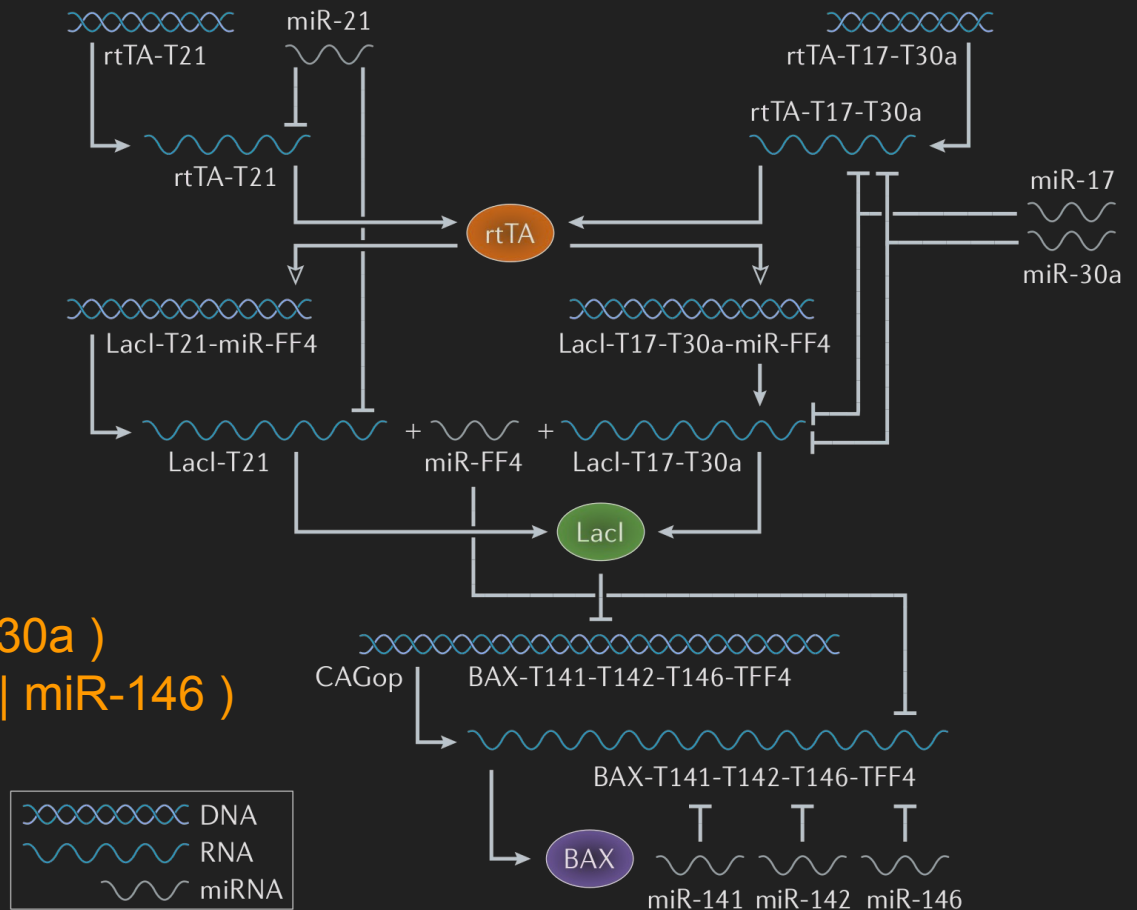
2017: First in-human Phase III clinical trials begin

2020

RNAi classifier

Output=

miR-21 & (miR-17 | miR-30a)
 & \neg (miR-141 | miR-142 | miR-146)



RNAi classifier

- **Inputs:** <https://portal.gdc.cancer.gov/>

Healthy

	case1	case2	case3	...
miR-20	52	85	120	
miR-37a	25851	42701	1115	
...				

RNAi classifier

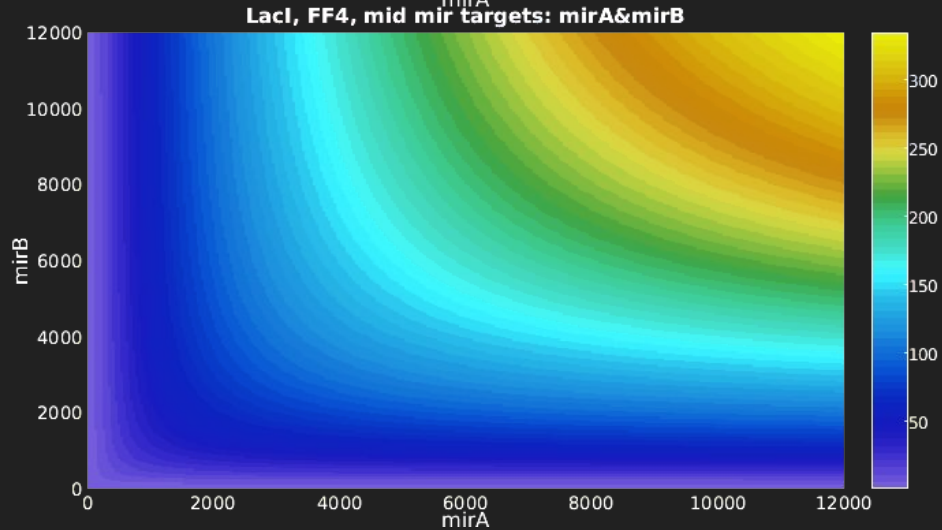
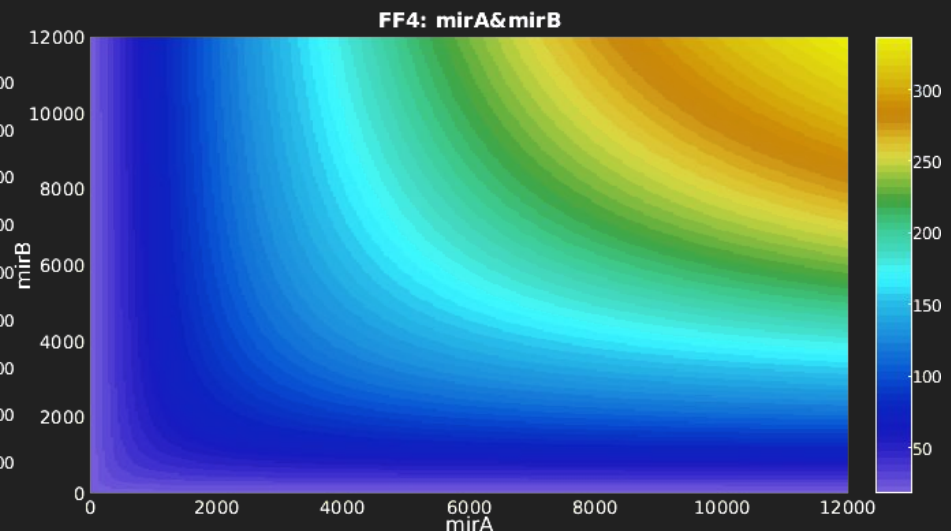
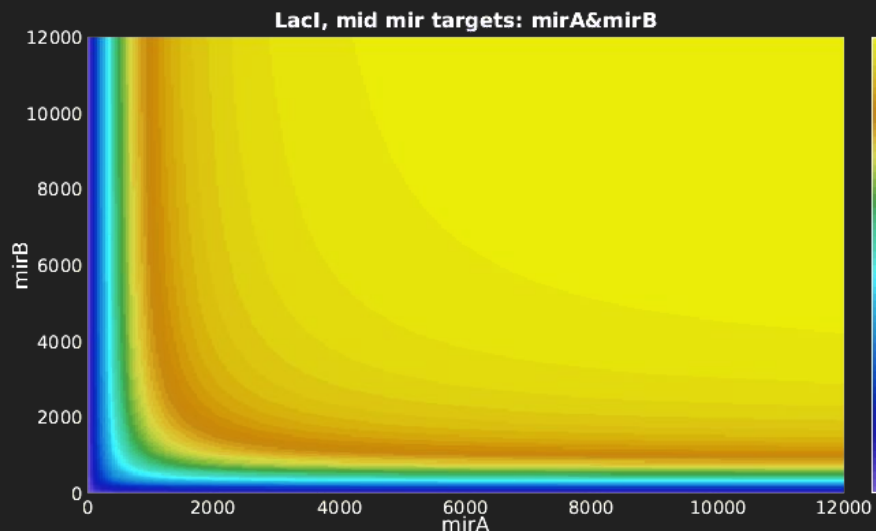
- Datasets
miRNA expression

Cancer

	case1	case2	case3	...
miR-20	631	520	584	
miR-37a	1400	980	1261	
...				

Modeling classifiers

- http://2017.igem.org/Team:Greece/RNAi_Classifier_Design#



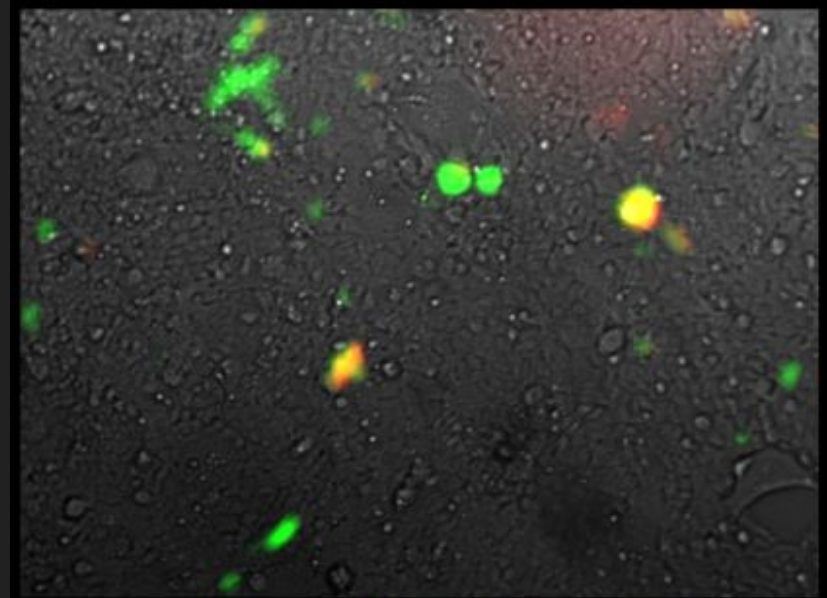
Model vs Reality

Non-native building blocks?

➤ Xeno nucleic acids?

Lab results

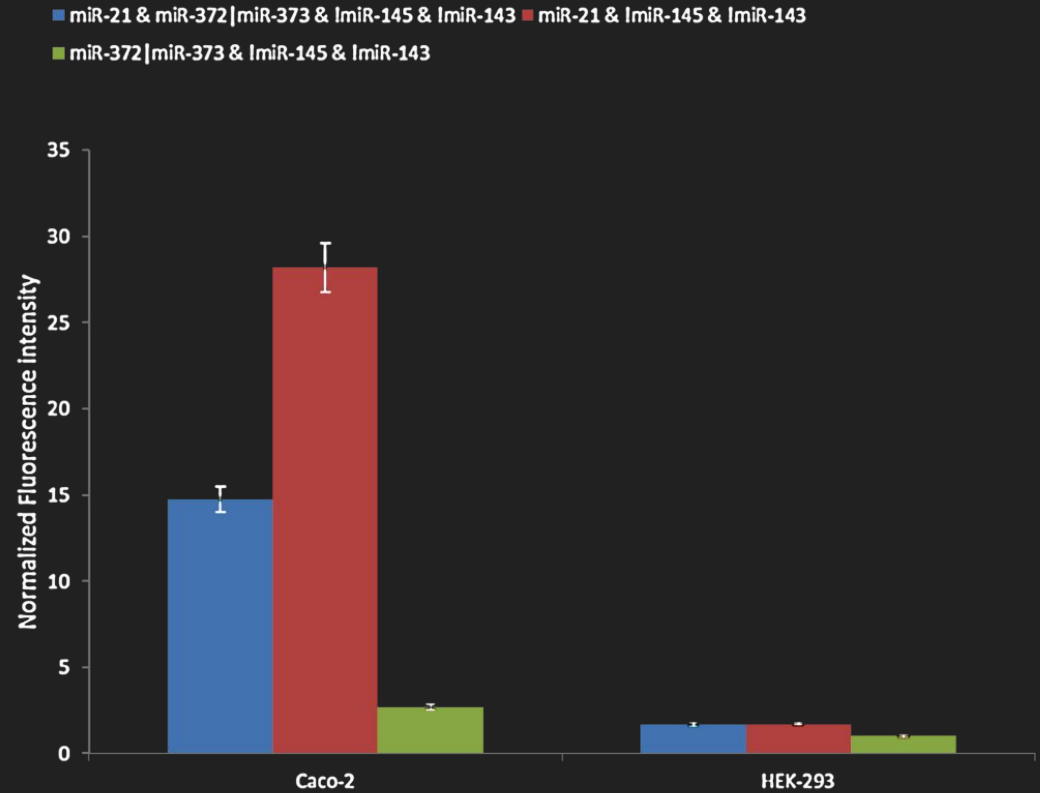
- Cancer fluoresces



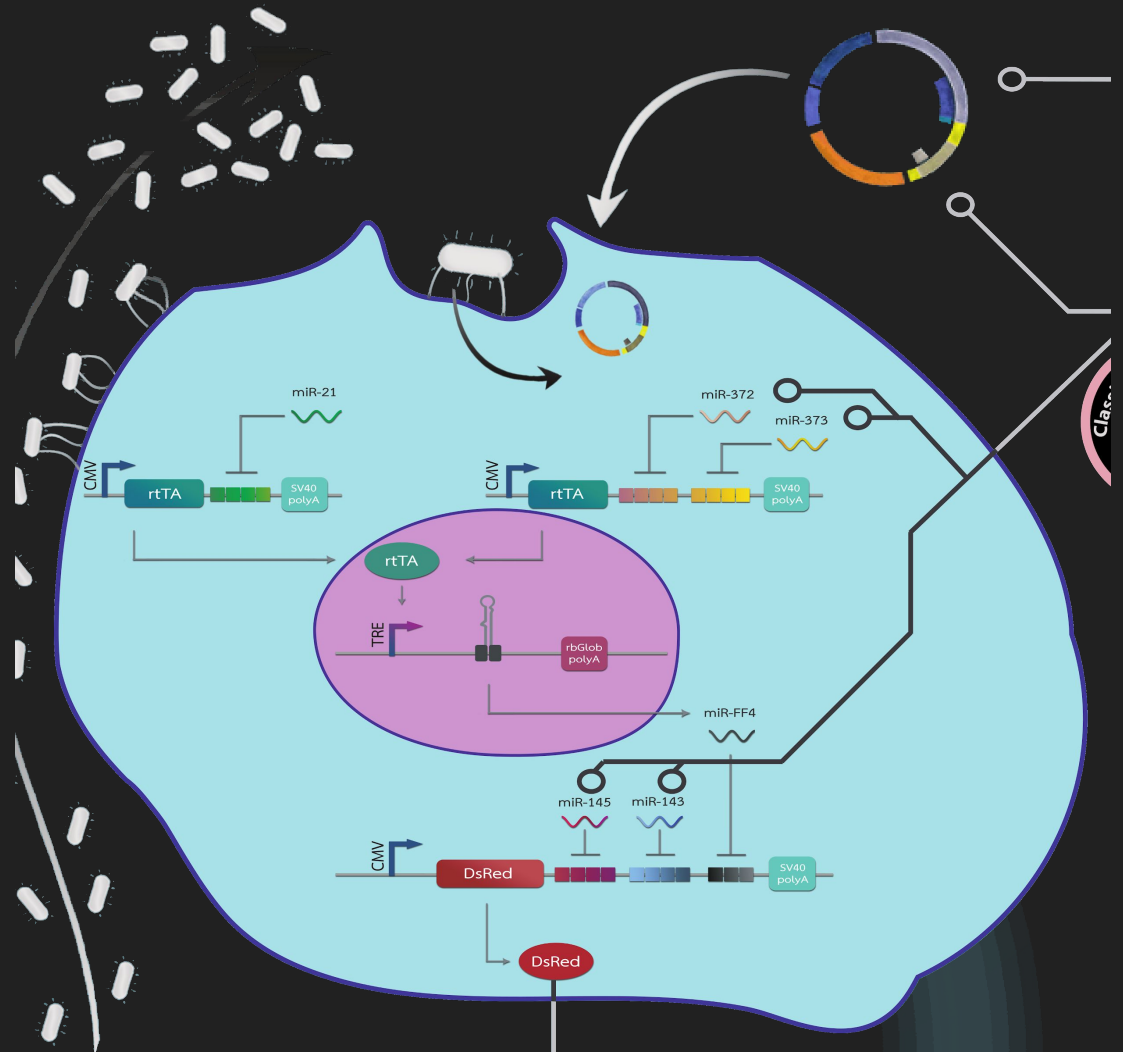
pCMV-DsRed-T145-143-TFF4-SV40
GFP marker

Lab results

➤ Selective expression in cancer



iGEM design



Working with doctors and biologists

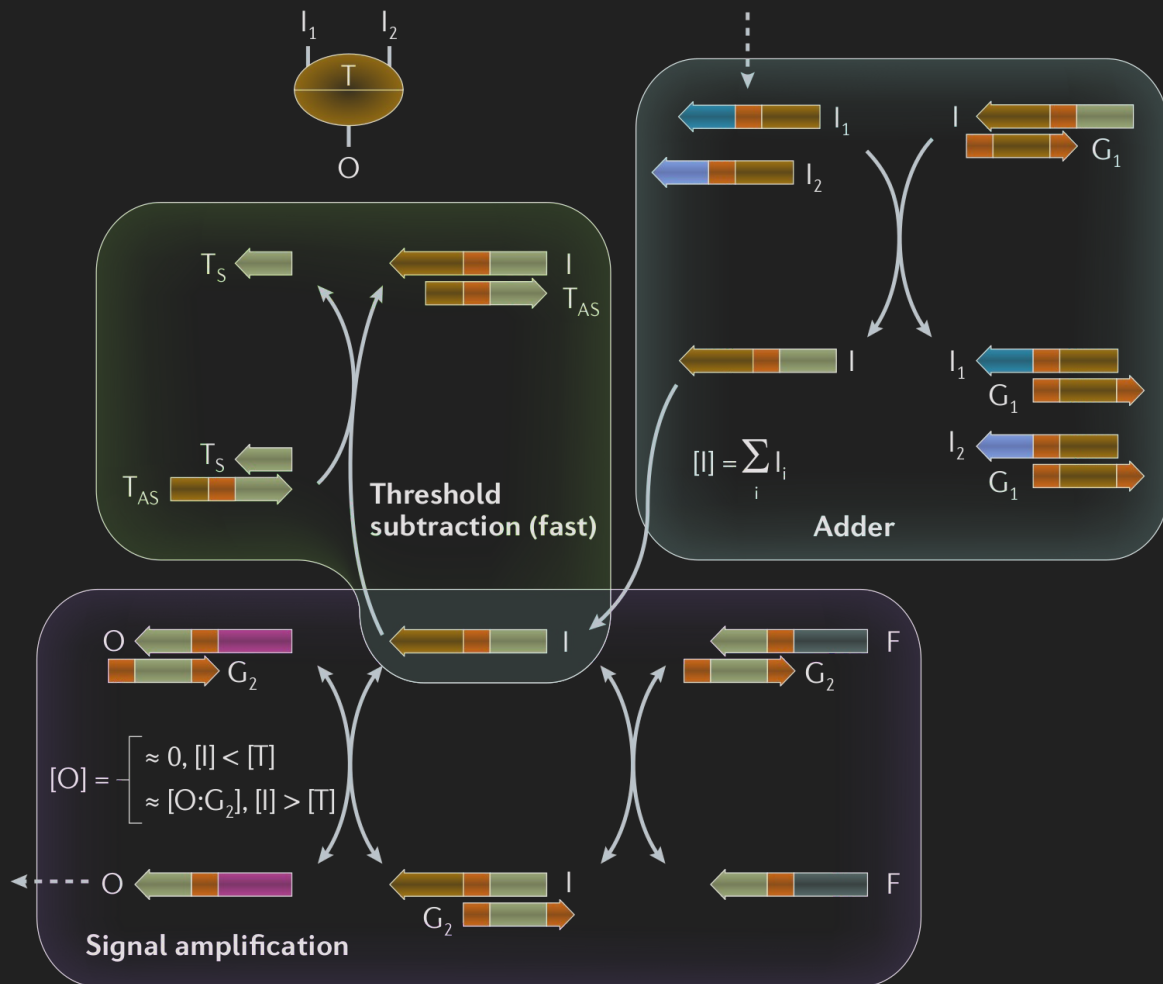


Thanks!

EXTRA

DNA strand displacement

➤ ANN^[5]



References

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5. L. Qian, E. Winfree & J. Bruck, *Neural network computation with DNA strand displacement cascades*, Nature 2011

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