DNA Reaction-Diffusion Systems

Dan Fu & John Reif

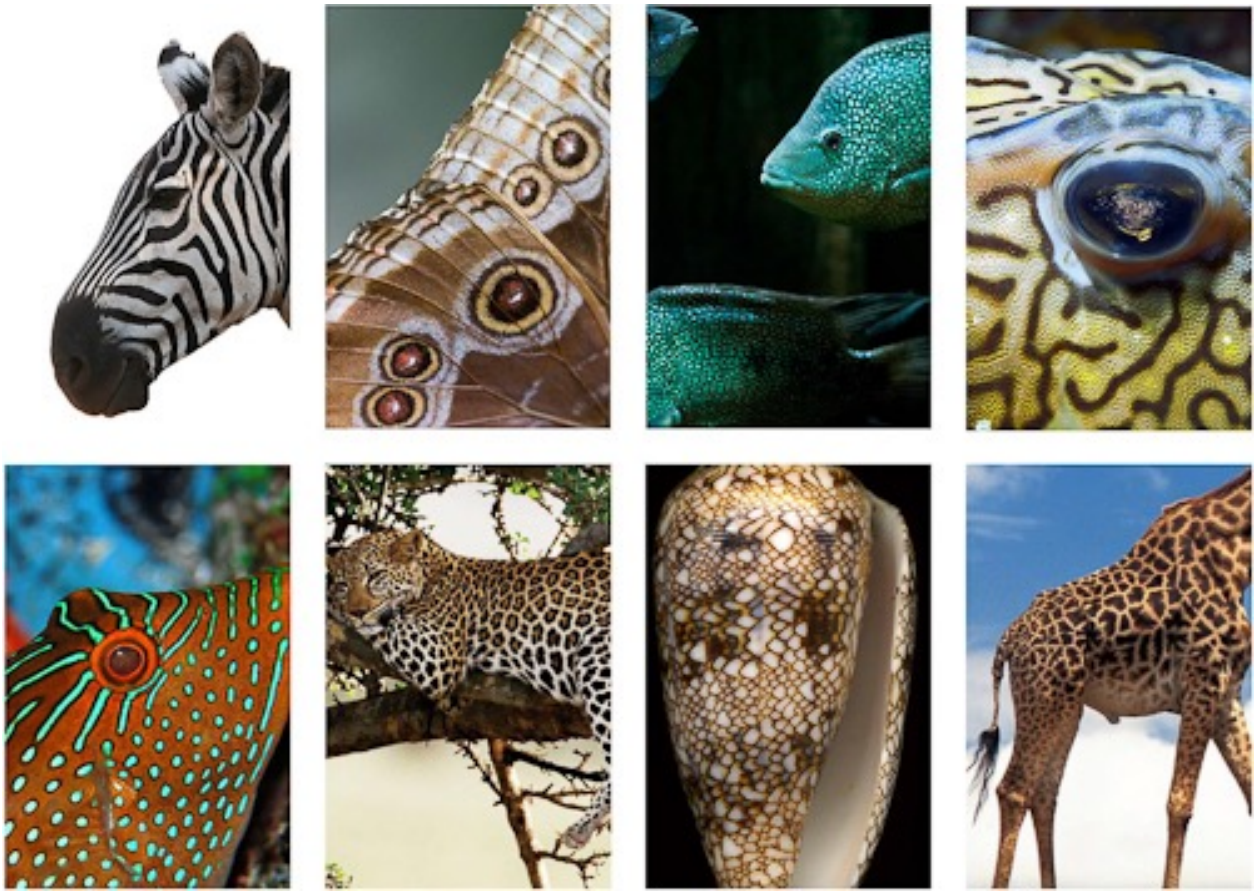
Adapted from PPT of:

- ***[Diogo Bolster, Notre Dame Univ]***
- ***[A.Sacan & S.Girgin, Drexel Univ]***

Reaction Diffusion (RD) Processes

- **A chemical mechanism for pattern formation.**
- **First described by Alan Turing (1952).**
- ***Two* chemicals diffusing across a *surface* and reacting with one another can form stable patterns of chemical concentration.**

Reaction Diffusion in Nature

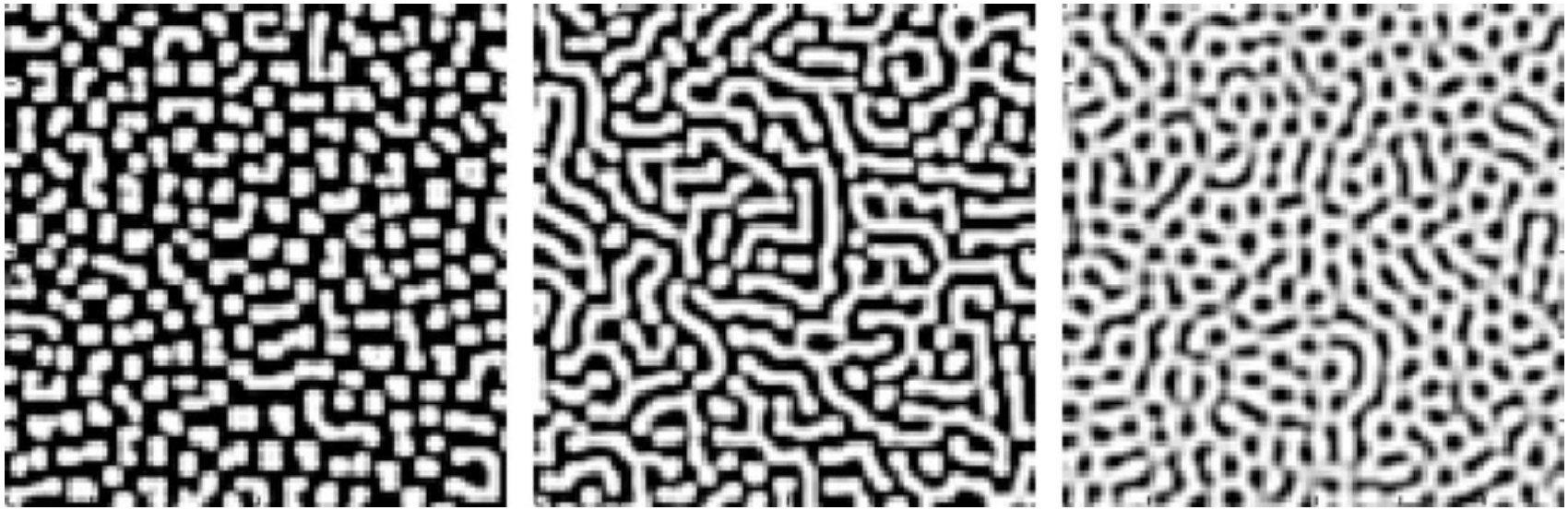


Animal Markings

Wikopedia

Turing's Pioneering Study of Reaction-Diffusion Systems

- **Turing (1952)**
  - *Turing, Alan (1952). "The Chemical Basis of Morphogenesis" (PDF). Philosophical Transactions of the Royal Society of London B. 237 (641): 37–72. Bibcode:1952RSPTB.237...37T . doi:10.1098/rstb.1952.0012*
  - **Proposed Mathematical Model for Morphogenesis:**
    - **the shaping of an organism by embryological processes of differentiation of cells, tissues, and organs and the development of organ systems according to the genetic "blueprint" of the potential organism and environmental conditions.**
  - **Also proposed natural examples: RD system on a sphere may be responsible for triggering gastrulation in the embryo.**



3 Examples of Turing Patterns

Further History of Reaction-Diffusion (RD) Systems

- Bard and Lauder (1974)
- **Computer simulations → Patterns generated by RD not regular enough to explain patterns in development.**
- **Explained less regular patterns: leaf organization, distribution of hair follicles.**

- Bard (1981), Murray (1981) independently
  - **RD can explain the patterns on coats of animals.**
- Bard (1981)
  - **Spot and stripe patterns.**
  - **Small, white spots on a deer.**
  - **Large, dark spots on a giraffe.**

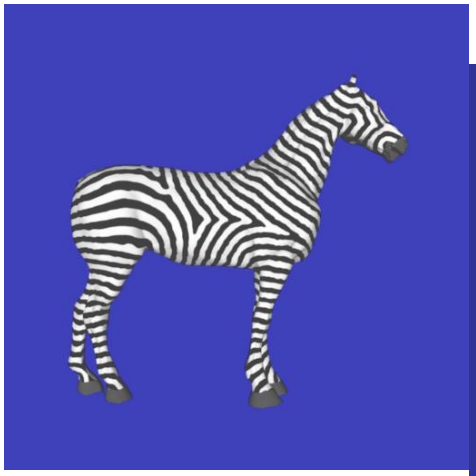
Further History of Reaction-Diffusion (RD) Systems

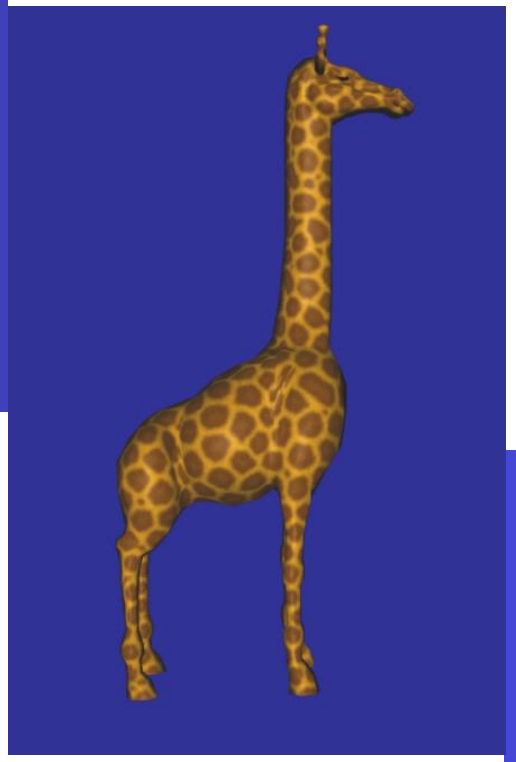
- Murray (1981)
  - **Spot-size dependent on size of animal.**
  - **Patterns found on butterfly wings.**
- Meinhardt (1982)
  - **Stripe patterns (by 5-morphogen RD)**
  - **Veins on a leaf.**
- Swindale (1980)
  - **Simulation by activation/inhibition between synapses.**
- Young (1984)
  - **Irregular striped patterns**
  - **Ocular dominance columns in mammalian visual system.**
- Meinhardt and Klinger (1987)
  - **Patterns of pigment found on mollusc shells**

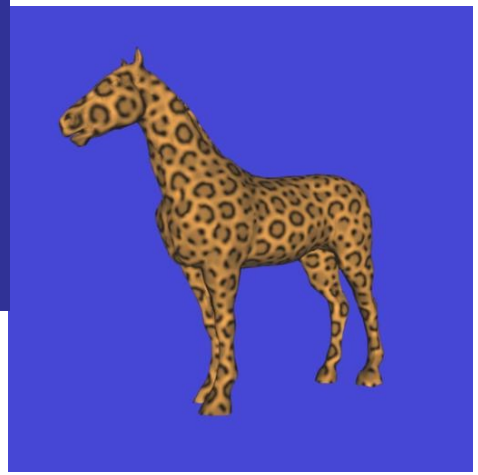
Further History of Reaction-Diffusion (RD) Systems

- Kauffman et al. (1978), Lacalli (1990), Hunding et al. (1990)
  - Segmentation of fruit fly (Drosophila) embryos
- Turk (1991)
  - Cascading
  - Clusters of spots on leopards and jaguars (rosettes)
  - Zebra's pajamas.
  - Mapping on arbitrary surfaces.

History of Reaction-Diffusion (RD) Systems, Cont





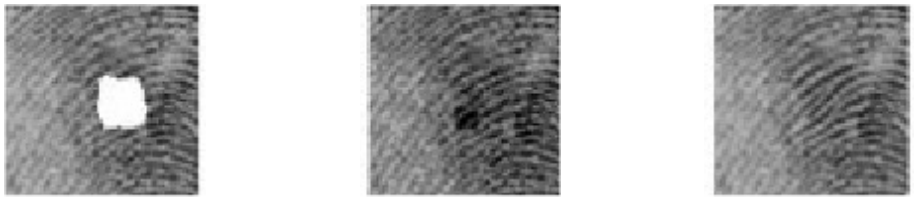


- **Turk (1991)**
  - **Cascading**
  - **Clusters of spots on leopard jaguars (rosettes)**
  - **Zebra's pajamas.**
  - **Mapping on arbitrary surfac**

Reaction-Diffusion by A.Sacan & S.Girgin

Reaction-Diffusion (RD) System used for Texture Completion

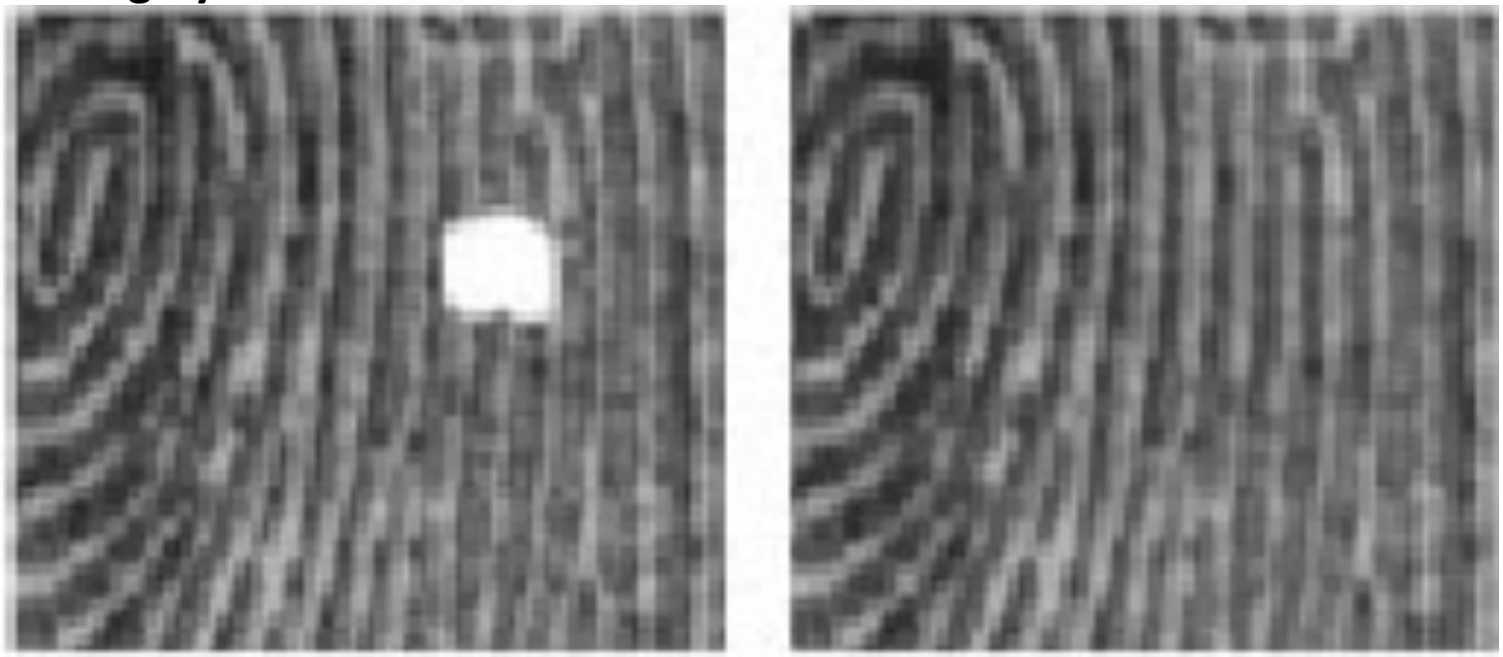
- **Acton, Mukherjee, Havlicek, Bovik (2001)**
  - **Reconstruction of large missing regions of homogeneous oriented textures.**
  - **RD seeded with noise identically distributed to surrounding region to match gray-level distribution.**



occluded **stripe formation** **AM-FM RD**

Reaction-Diffusion (RD) System used for Texture Completion

RD seeded with noise identically distributed to surrounding region to match gray-level distribution.



General Principles of Reaction Diffusion (RD)

Two **chemicals <u>diffusing</u> across a *surface* and <u>reacting</u> with one another can form stable patterns of chemical concentration.**

Let's Start Simple – Recall Chemistry 101:

Diogo Bolster@Notre Dame

Turing's Modelof Reaction-Diffusion Systems

- **Turing (1952)**
  - *Turing, Alan (1952). "The Chemical Basis of Morphogenesis" (PDF). Philosophical Transactions of the Royal Society of London B. 237 (641): 37–72. Bibcode:1952RSPTB.237...37T . doi:10.1098/rstb.1952.0012*
  - **Proposed Mathematical Model for Morphogenesis:**
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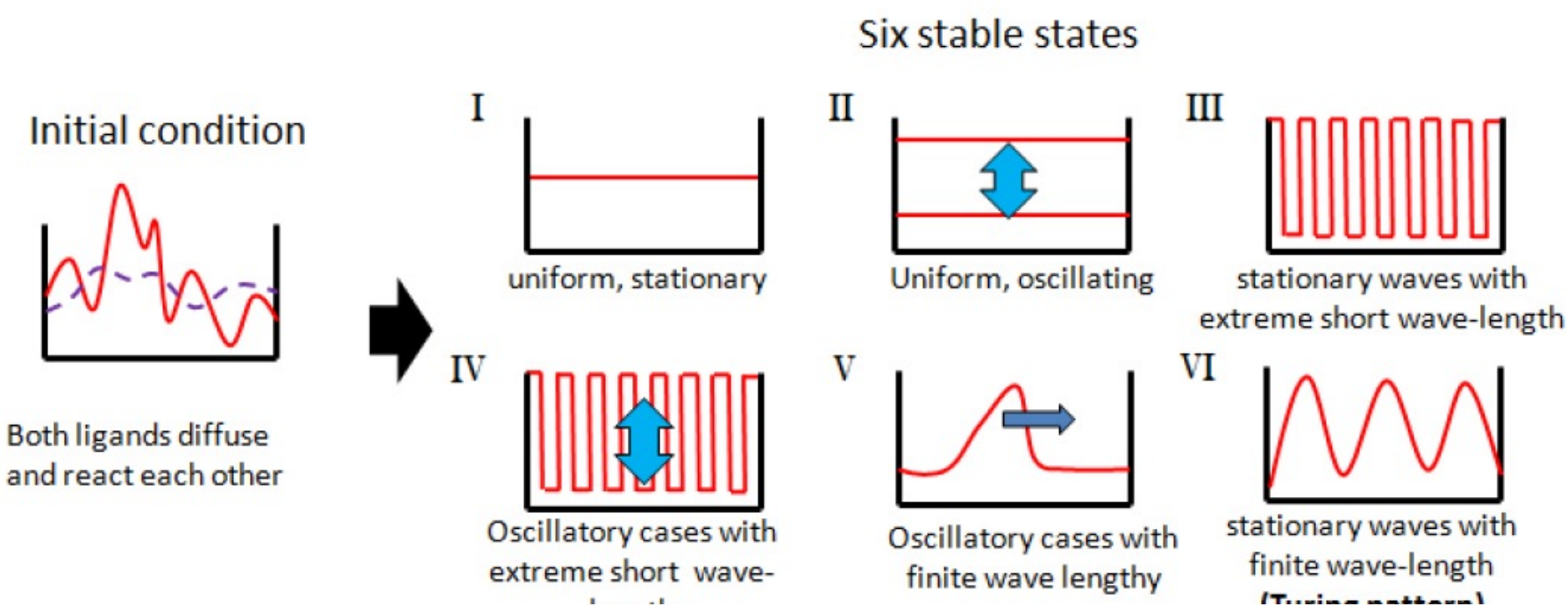
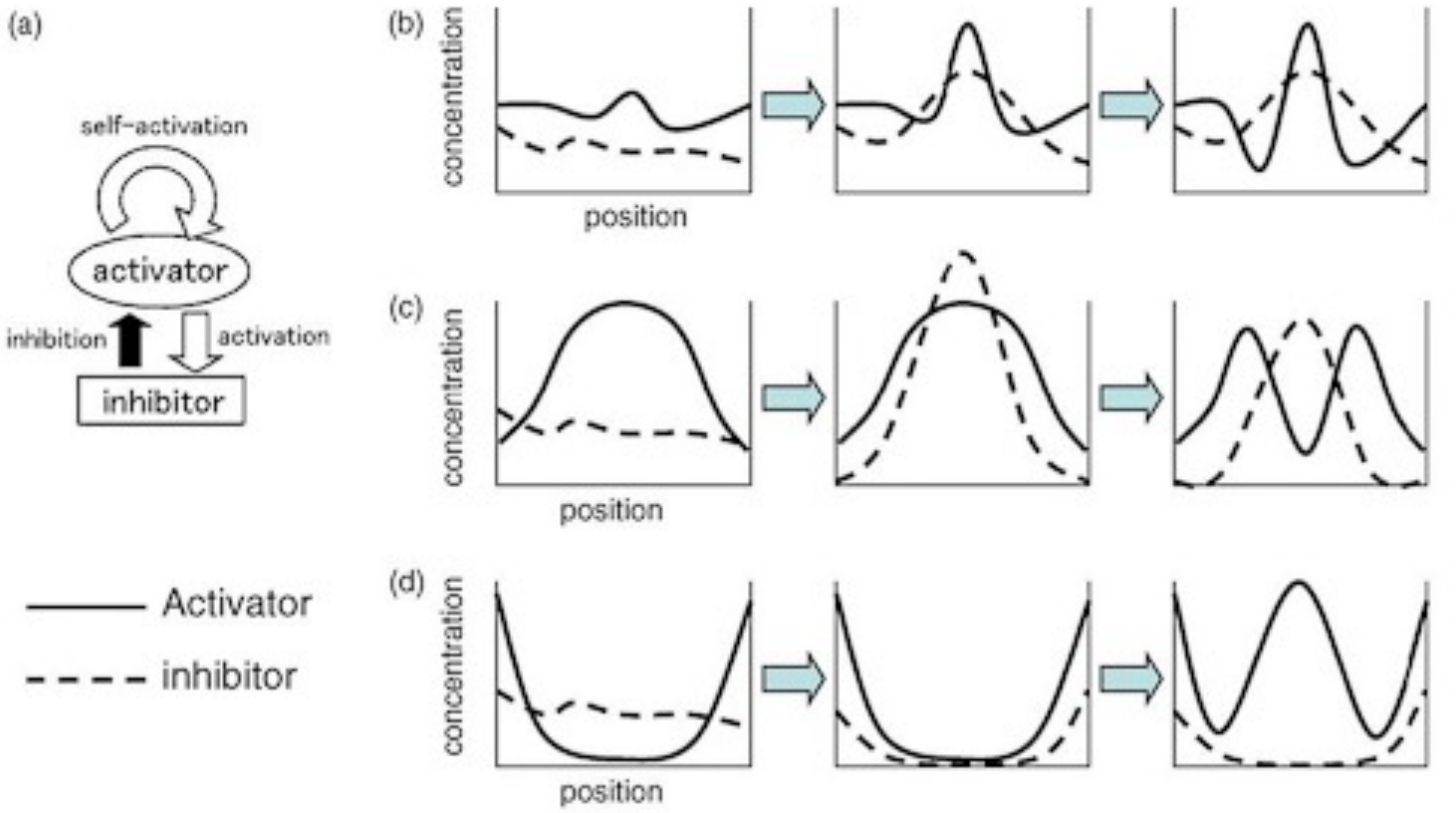
  -



Reaction Diffusion Surface Processes



Local Amplification, Lateral Inhibition

General Principles of Reaction Diffusion (RD)

- **Consider a reactive system made up of species A, B and C, where A and B can react to form C at some rate k_f and C can degrade back into A and B at some rate k_b** $A + B \underset{k_b}{\overset{k_f}{\longleftrightarrow}} C$

- **If the system is well-mixed (i.e. no spatial variability in concentration, reaction are governed by the law of mass action:**

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -k_f[A][B] + k_b[C]$$

$$\frac{d[C]}{dt} = k_f[A][B] - k_b[C]$$

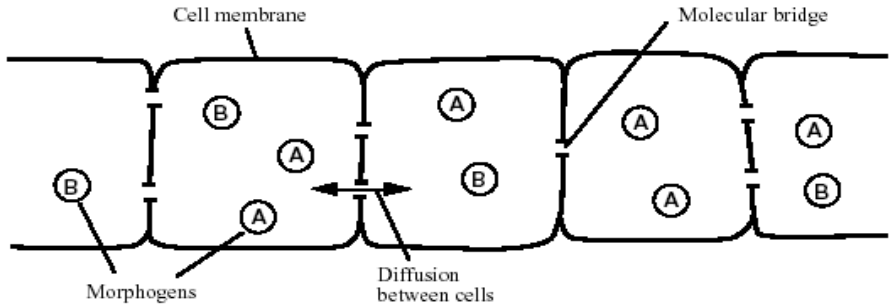
Diffusion-Reaction System

- **Now, rather than assuming that the system is well mixed, we allow A, B and C to move through space by diffusion, but they still react by the law of mass action**

$$\frac{\delta[C]}{dt} - D_A \frac{\delta^2[A]}{dx^2} = -k_f[A][B] + k_b[C]$$
$$\frac{\delta[B]}{dt} - D_B \frac{\delta^2[B]}{dx^2} = -k_f[A][B] + k_b[C]$$
$$\frac{\delta[C]}{dt} - D_C \frac{\delta^2[C]}{dx^2} = k_f[A][B] - k_b[C]$$

How can you solve these equations?

Diffusion-Reaction in a line of cells:



• The amount of chemical *a* in a cell changes based on the quantity of the chemicals *a* and *b* are already in the cell.

• If a particular cell has a higher concentration of chemical *b* than its neighbors, then that cell's concentration of *b* will decrease over time by diffusion to its neighbors.

•Likewise, if the concentration of *b* is at minimum at a particular place along the row of cells, then more of *b* will diffuse from adjacent cells to this cell to raise the concentration of *b* at that cell.

Mathematical Model for Diffusion-Reactions:

Fisher-Kolmogorov–Petrovsky–Piskunov equation

Diffusion term

Reaction term

$$\frac{\delta[A]}{\delta t} = D_A \nabla^2[A] + F([A],[B])$$

$$\frac{\delta[B]}{dt} = D_B \nabla^2[B] + G([A],[B])$$

Analytical Solution?

- **Closed-form solution: difficult/impossible (except when F,G very simple).**
- **Therefore,**
  - **Discretize and**
  - **Solve numerically.**

Turing's Approximate Solution:

$$\Delta a_i = D_a(a_{i+1} + a_{i-1} - 2a_i) + k(16 - a_i b_i)$$

$$\Delta b_i = D_b(b_{i+1} + b_{i-1} - 2b_i) + k(a_i b_i - b_i - 12 - \beta_i)$$

- **a_i : concentration of 1st morphogen at i^{th} cell. (inhibitor)**
- **b_i : concentration of 2nd morphogen at i^{th} cell. (activator)**
- **D_a : diffusion rate of a.**
- **D_b : diffusion rate of b.**
- **β : random substrate**
- **k : reaction rate**
- **Initial concentrations of a, b: 4**

Reaction-Diffusion by A.Sacan & S.Girgin

Simulating parameters and resultant patterns of Reaction-Diffusion

Case of No Diffusion:

n=1

n=1000

n=2000

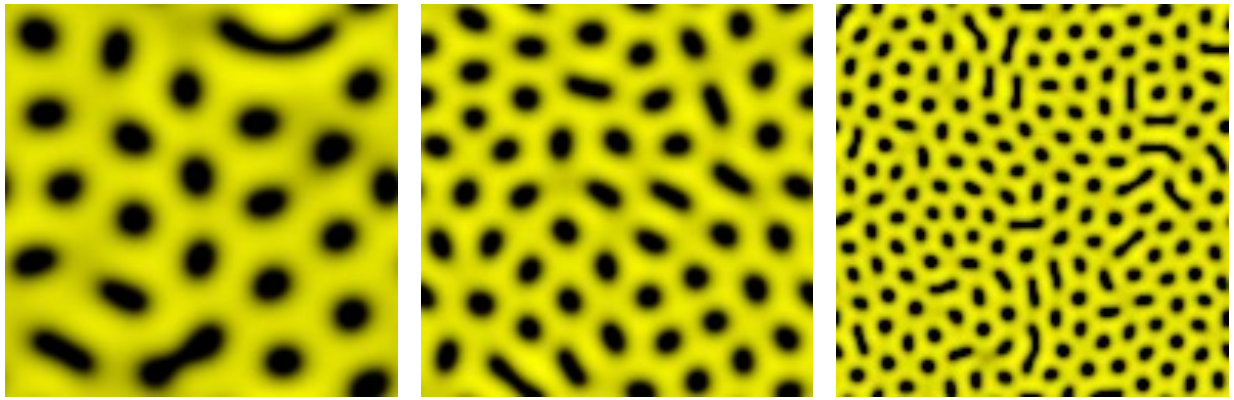
D_a : diffusion rate of a

D_b : diffusion rate of b

k : reaction rate

$$\mathbf{D_a=0.0\ D_b=0.0\ \beta=0.1\ k=0.01}$$

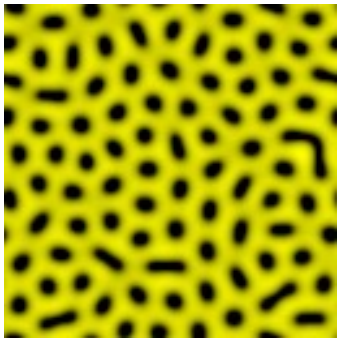
Parameter: reaction rate k



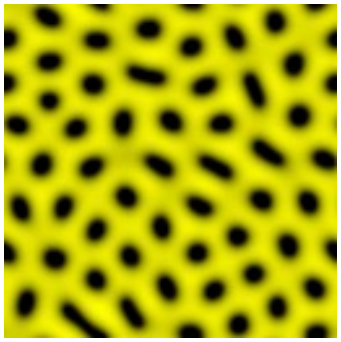
k=0.001 **k=0.005** **k=0.01**

D_a=0.1 D_b=0.02 β=0.1

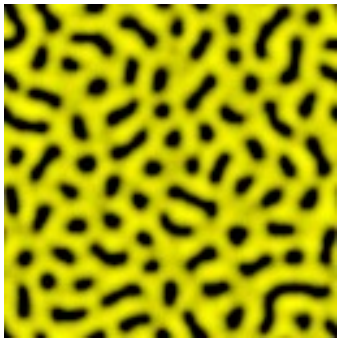
Parameter: random substrate β



β=0.05



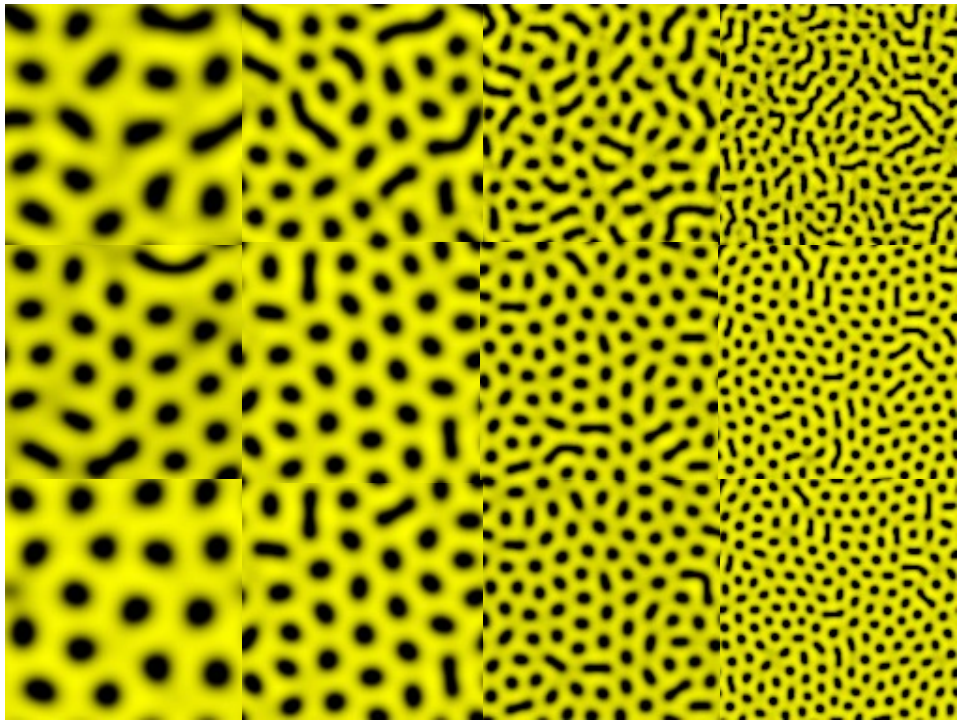
β=0.1



β=3

D_a=0.1 D_b=0.02 k=0.005

Parameter: random substrate β

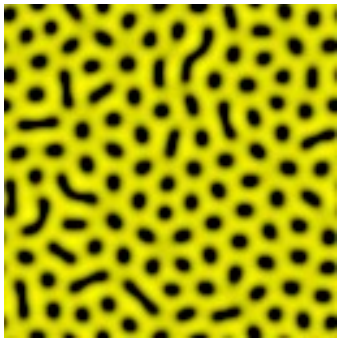


$D_a=0.1\ D_b=0.02$

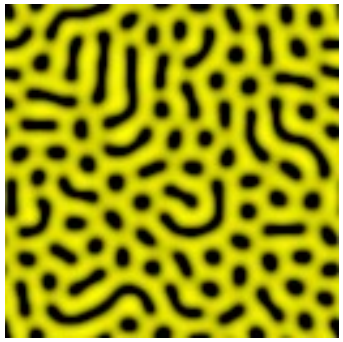
Parameter: D_a / D_b

D_a : diffusion rate of a.

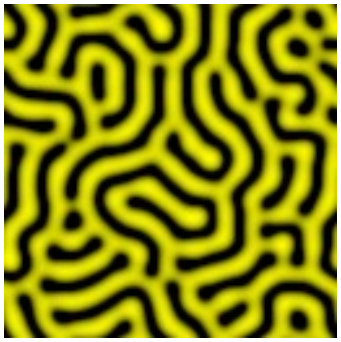
D_b : diffusion rate of b.



D_a=0.08



Da=0.1



Da=0.2

D_b=0.02 β=0.1 k=0.005

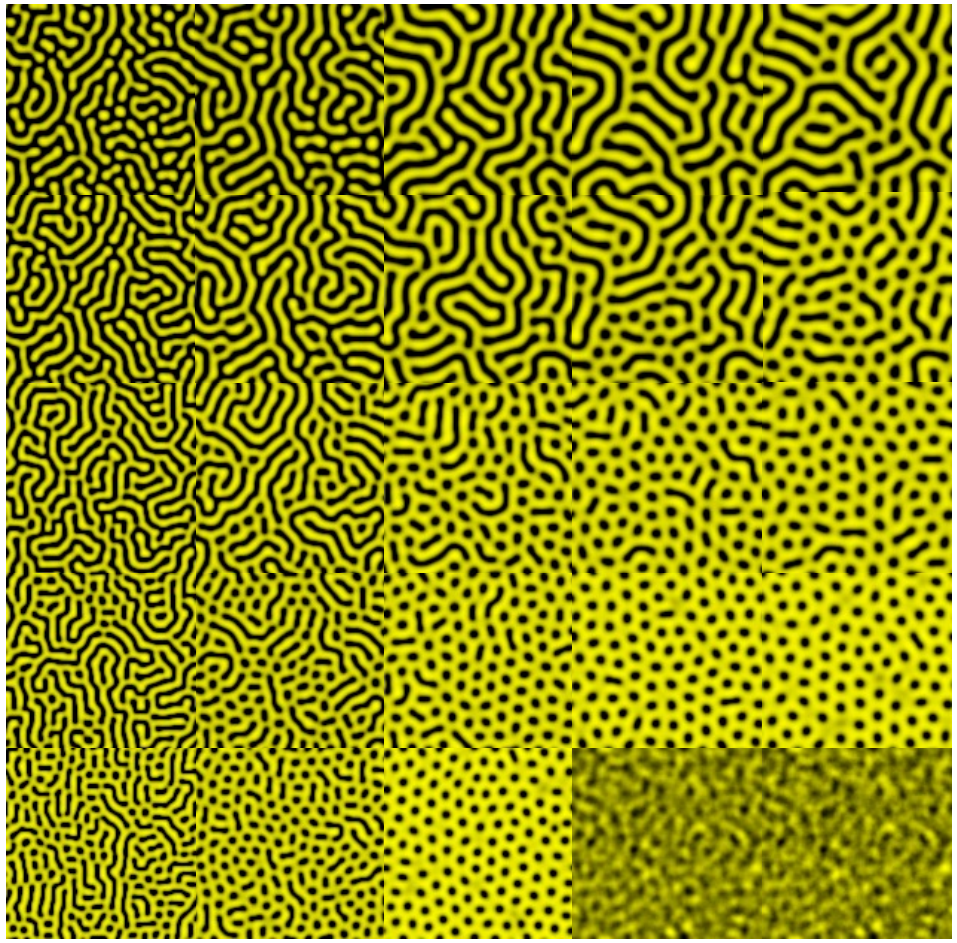
D_a vs D_b

D_a : diffusion rate of a.

D_b : diffusion rate of b.

β=0.1

k=0.005



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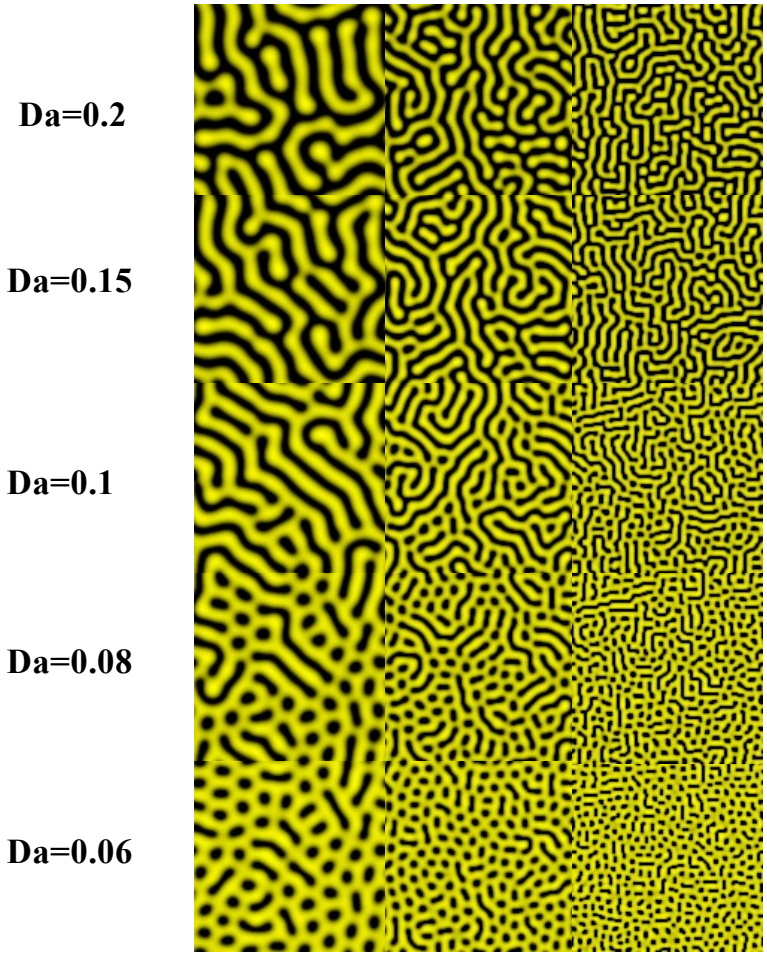
D_a vs k

D_a : diffusion rate of a

k : reaction rate



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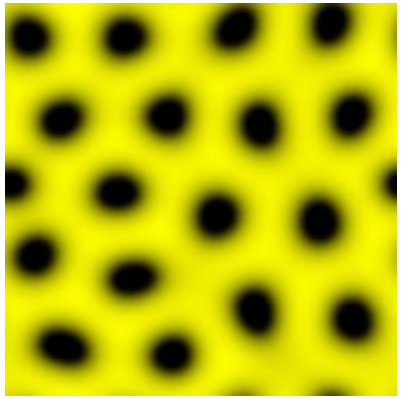
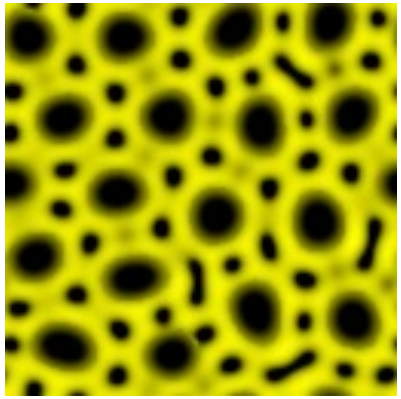
β=0.1

D_b=0.01

Cascading



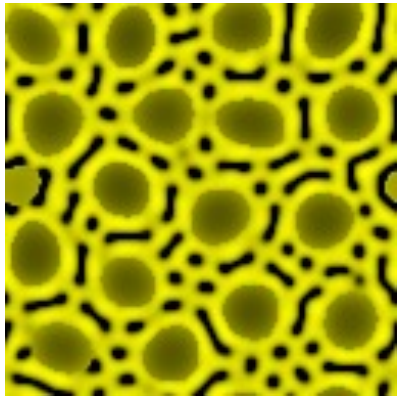
k=0.001, n=30000



Freeze b:[0-4]

k=0.01

Cheetah



Freeze b:[0-4]→4

k=0.01

Leopard

D_a : diffusion rate of a

D_b : diffusion rate of b

k : reaction rate

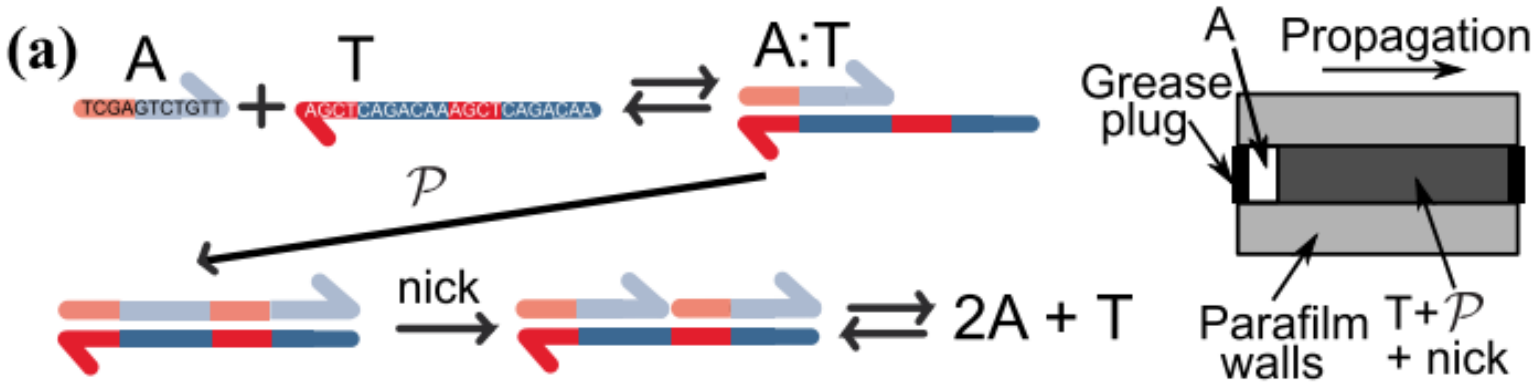
D_a=0.1 D_b=0.02 β=0.05

Reaction Diffusion using DNA

- **In nature: R-D systems:**
  - **Traditionally based on Belousov-Zhabotinsky (BZ) reaction with redox or acid-base reactions with small inorganic or organic molecules**
  - **Hard to predict/model**
  - **Difficult to program reaction and diffusion values. Depends on chemical.**
  - **Hard to experimentally demonstrate simulated results**
- **DNA-based CRNs:**
  - **Simple rules, base complementarity and hybridization**
  - **Predictable kinetics**
  - **Sequence programming can modify coefficients**

What is a DNA reaction equivalent to a Belousov-Zhabotinsky (BZ) reaction ?

- **An autocatalytic reaction that produces more [A]**



- **Inject T, Enzymes, single bases into single-channel reactor**

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Can Increase reaction speed:

Increase:
(1) autocatalyst template concentration &
(2) Polymerase Concentration

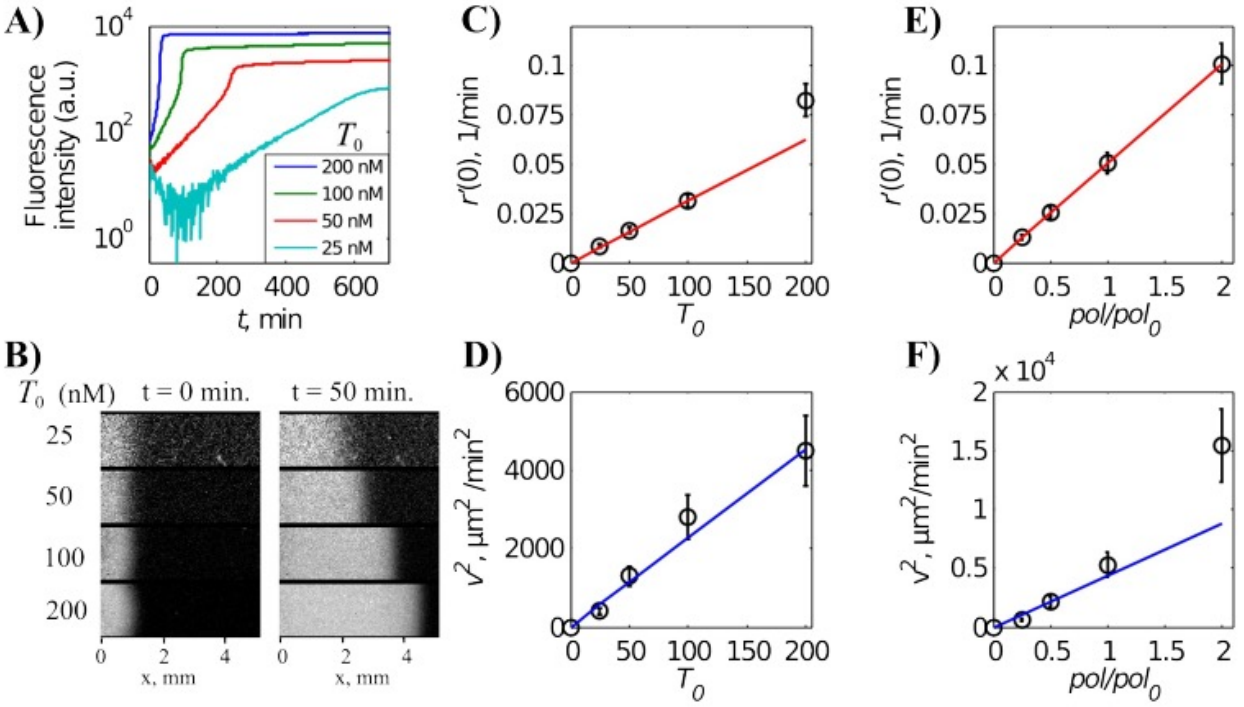

Figure 3: The growth rate of the autocatalyst and its propagation velocity can be tuned specifically with the template concentration and non-specifically with the polymerase concentration. A) Log-lin plots of the growth kinetics with different concentrations of the template, T_0. B) Fluorescent images of the front position at 0 min and 50 min for different T_0. For clarity, the brightness of the images with different T_0 has been normalized (SI video S2). C) First order rate constant $r'(0)$ *vs* T_0, the red line is a linear fit for T_0 = 0–100 nM. D) Square of the front velocity v *vs* T_0, the blue line is the prediction using Eqs. 3-5 with γ = 1.3. E) $r'(0)$ *vs* normalized polymerase concentration, pol/pol_0, the red line is a linear fit. F) v^2 *vs* pol/pol_0, the blue line is the prediction using Eqs. 3-5 with γ = 1.3 (SI video S3). Experimental conditions: A-D) 38°C, *pol* = 16 U/mL, *nick* = 300 U/mL, E-F) T_0 = 200 nM, pol_0 = 16 U/mL, *nick* = 500 U/mL, 44°C. Error bars were estimated from the 10% experimental precision (both on $r'(0)$ and v) measured for 4 independent experiments at T_0 = 200 nM (Table 1-2).

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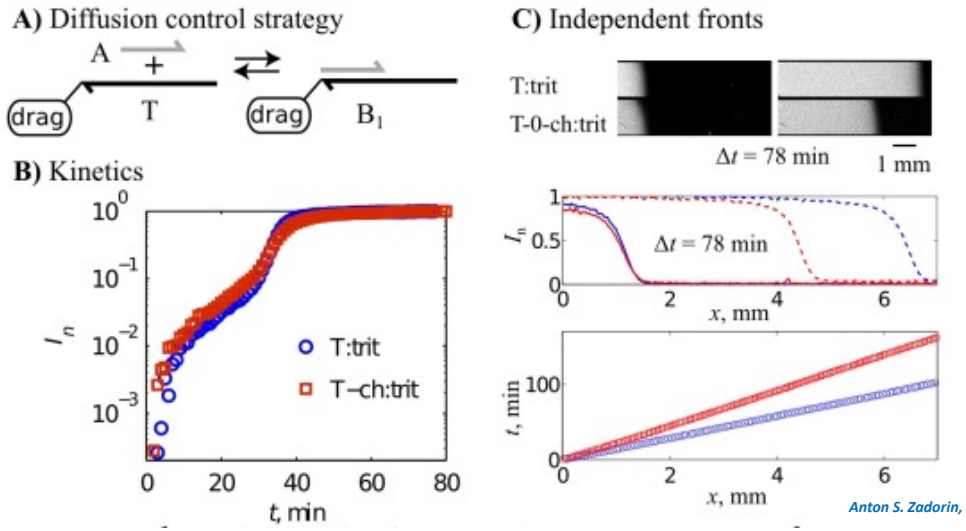
Diffusion equivalent System:

Add Diffusion Slowing Binding Molecule

- $\boldsymbol{R \sim M^{\frac{1}{2}}, D \sim R^{-1}}$
  $\boldsymbol{D}$ **= diffusion coefficient**
- $\boldsymbol{R}$ **=hydrodynamic radius of molecule**
- $\boldsymbol{M}$ **= molecular mass**
- **Molecular mass must increase a lot for this to work**
- **OR, attach another molecular that has low D and it will average out**



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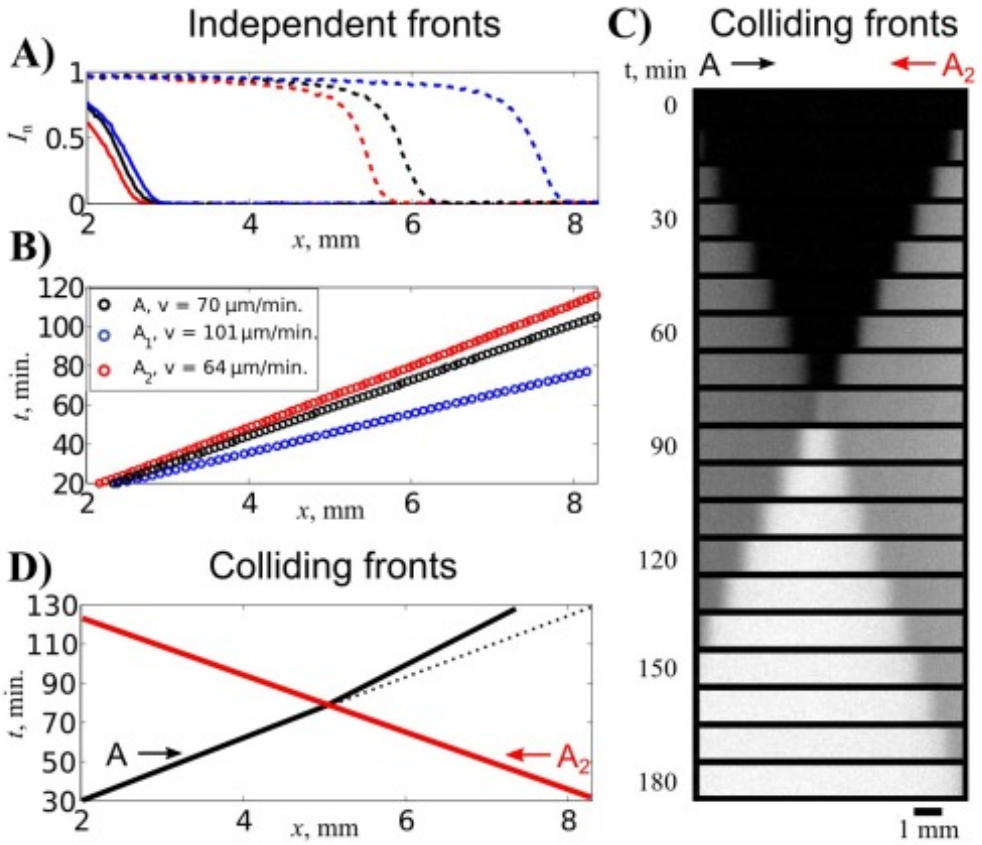
Basic pattern formation via Colliding Fronts

- **1x EvaGreen DNA binder fluorescence**



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Does the theoretical model hold up?

- **Has a known form: Fischer's Equation (or Fischer- KPP Equation)**

Fisher's equation

From Wikipedia, the free encyclopedia

Not to be confused with the Fisher equation in financial mathematics.

In mathematics, **Fisher's equation** (named after statistician and biologist Ronald Fisher; also known as **Kolmogorov–Petrovsky–Piskunov equation**—named after Andrey Kolmogorov, Ivan Petrovsky, and N. Piskunov—or **KPP equation** or **Fisher–KPP equation**) is the partial differential equation:

$$\frac{\partial u}{\partial t} - D\frac{\partial^2 u}{\partial x^2} = ru(1-u).$$

Contents [hide]

Details [edit]

Fisher's equation belongs to the class of reaction-diffusion equation: in fact, it is one of the simplest semilinear r.d.e. , the one which has the inhomogeneous term

$$f(u,x,t) = ru(1-u).$$

which can exhibit traveling wave solutions that switch between equilibrium states given by $f(u) = 0$. Such equations occur, e.g., in ecology, physiology, combustion, crystallization, plasma physics, and in general phase transition problems.

Fisher proposed this equation in his 1937 paper *The wave of advance of advantageous genes* in the context of population dynamics to describe the spatial spread of an advantageous allele and explored its travelling wave solutions.[1] For every wave speed $c \geq 2\sqrt{rD}$ ($c \geq 2$ in dimensionless form) it admits travelling wave solutions of the form

$$u(x,t) = v(x \pm ct) \equiv v(z),$$

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Does the theoretical model hold up?

- **Velocity of wave-front only depends on reaction-diffusion at leading wave front**

$$v_m = 2\sqrt{r'(0)D_{\text{eff}}(0)}. \qquad (3)$$

- **Diffusion constant D_{eff} depends on [A]**
- **$v_{observed}$ = 65 +/- 5 µm/min ; v_m = 59+/-7 µm/min**

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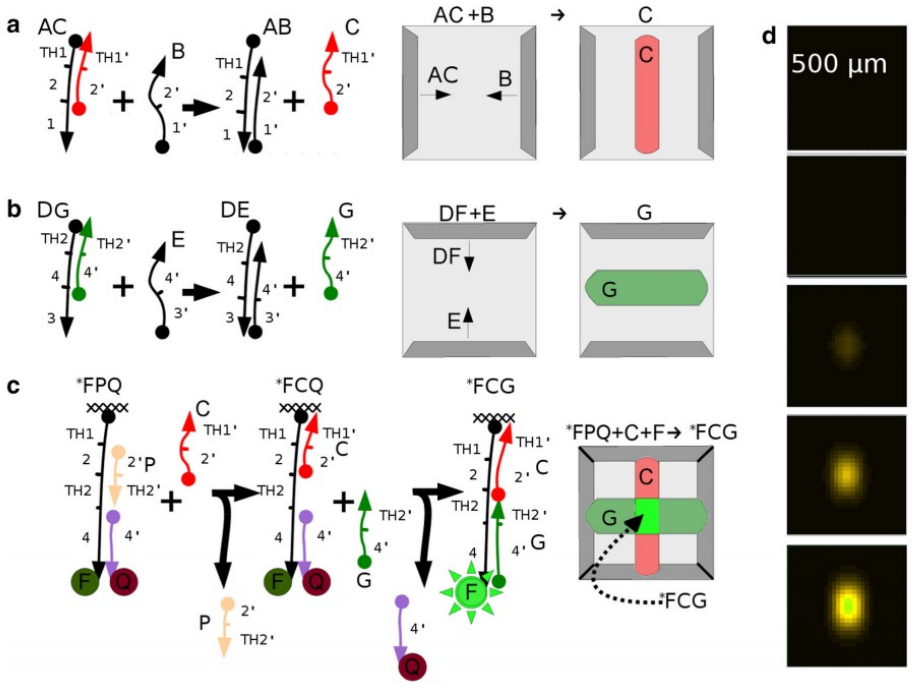
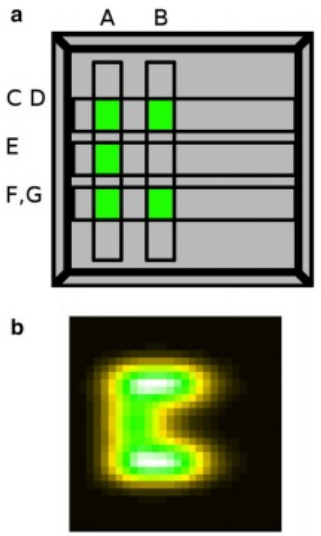
Modeling scalable pattern generation in DNA reaction networks:

Peter B. Allen, Xi Chen, Zack B. Simpson, Andrew D. Ellington, Modeling scalable pattern generation in DNA reaction networks, Nat Comput (2014) 13:583–595 DOI 10.1007/s11047-013-9392-7

Pattern Generation in DNA reaction networks operating in Agarose Gel

- **Embedded DNA at 2D positioned sites**





Peter B. Allen • Xi Chen • Zack B. Simpson • Andrew D. Ellington 2014

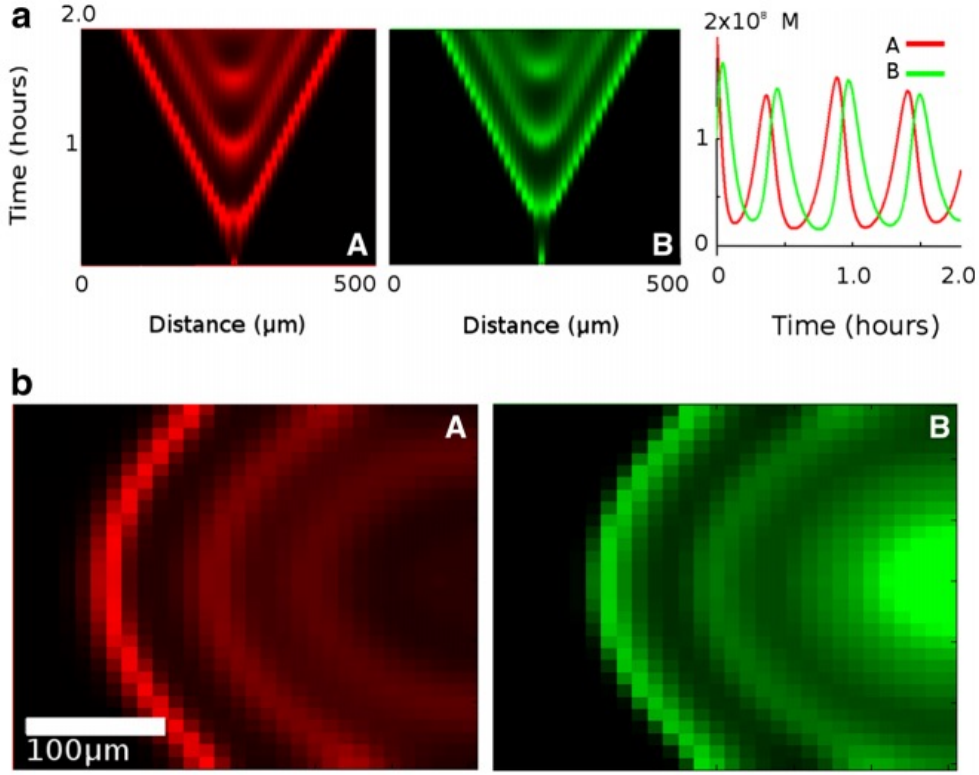
Periodic patterns of DNA in Agarose Gel

- **CRN Oscillator:**

$$A + B \rightarrow 2A \quad k = 1.5\ M^{-1}\,s^{-1}$$

$$B \rightarrow 2B \quad k = 1\,s^{-1}$$

$$B \rightarrow C \quad k = 1\,s^{-1}$$



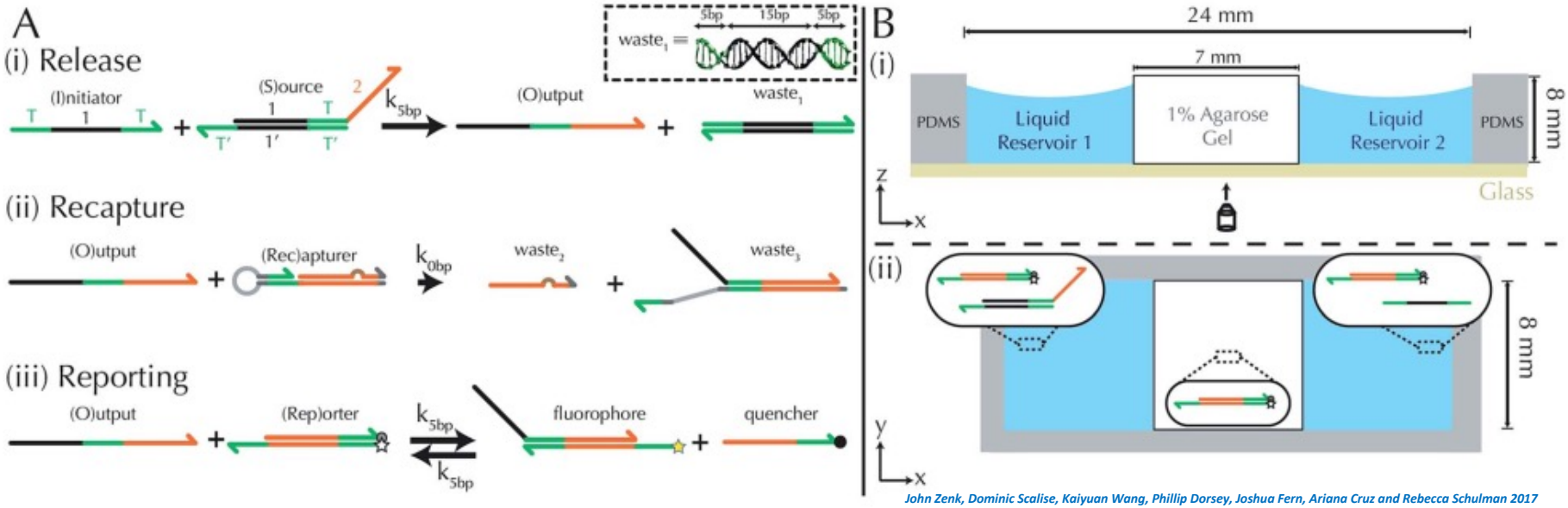
Peter B. Allen • Xi Chen • Zack B. Simpson • Andrew D. Ellington 2014

Stable DNA-based reaction–diffusion patterns

John Zenk, Dominic Scalise, Kaiyuan Wang, Phillip Dorsey, Joshua Fern, Ariana Cruza and Rebecca Schulman , Stable DNA-based reaction–diffusion patterns, RSC Advances, (2017), 7, 18032–18040

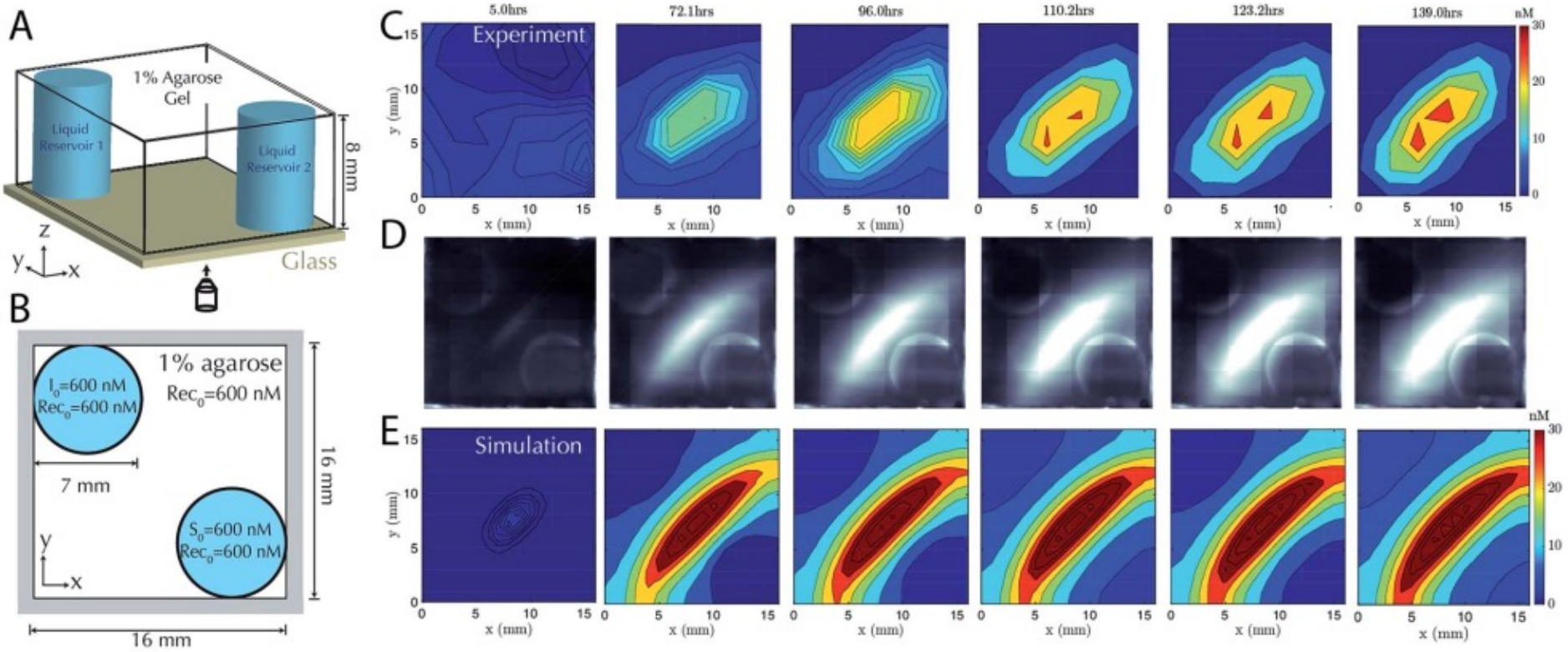
How to keep DNA patterns stable in Agarose Gel ?

- **Diffusion will keep happening until well-mixed**
- **Need to keep sufficient concentration**
- **Also need a process for degradation**



John Zenk, Dominic Scalise, Kaiyuan Wang, Phillip Dorsey, Joshua Fern, Ariana Cruz and Rebecca Schulman 2017

2D Patterns on Agarose Gel using DNA strand-displacement Circuits



John Zenk, Dominic Scalise, Kaiyuan Wang, Phillip Dorsey, Joshua Fern, Ariana Cruz and Rebecca Schulman 2017

Computing with Reaction Diffusion Systems:

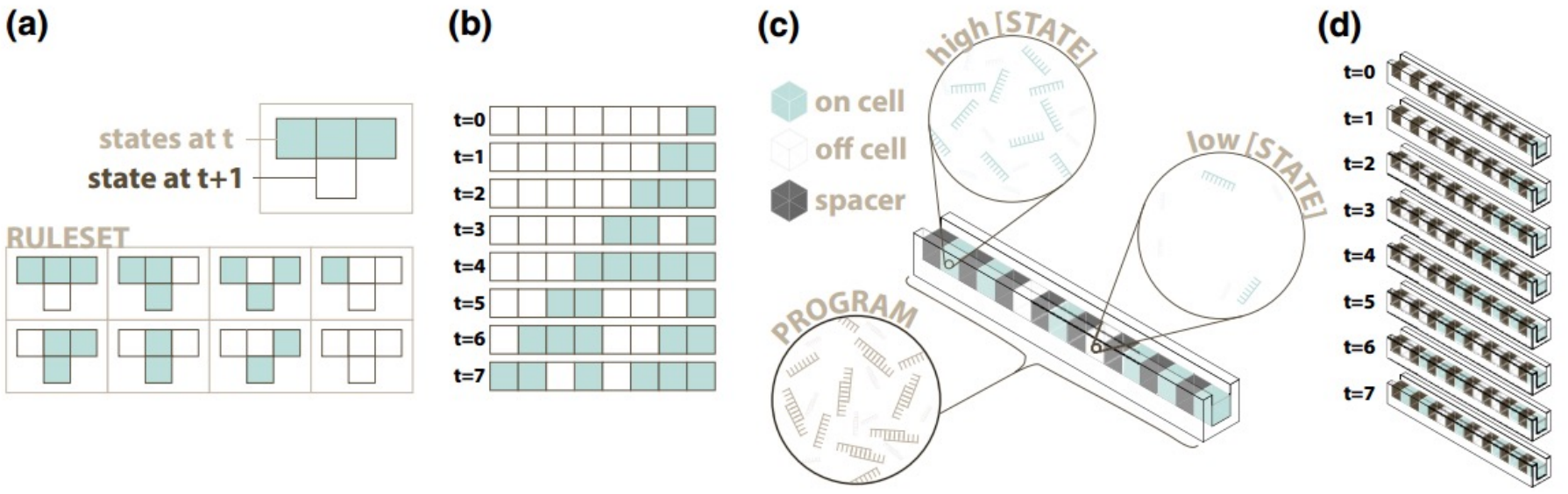
Emulating cellular automata in chemical reaction–diffusion networks

Dominic Scalise and Rebecca Schulman, Emulating cellular automata in chemical reaction–diffusion network, (2015) Nat Computing,

DOI 10.1007/s11047-015-9503-8

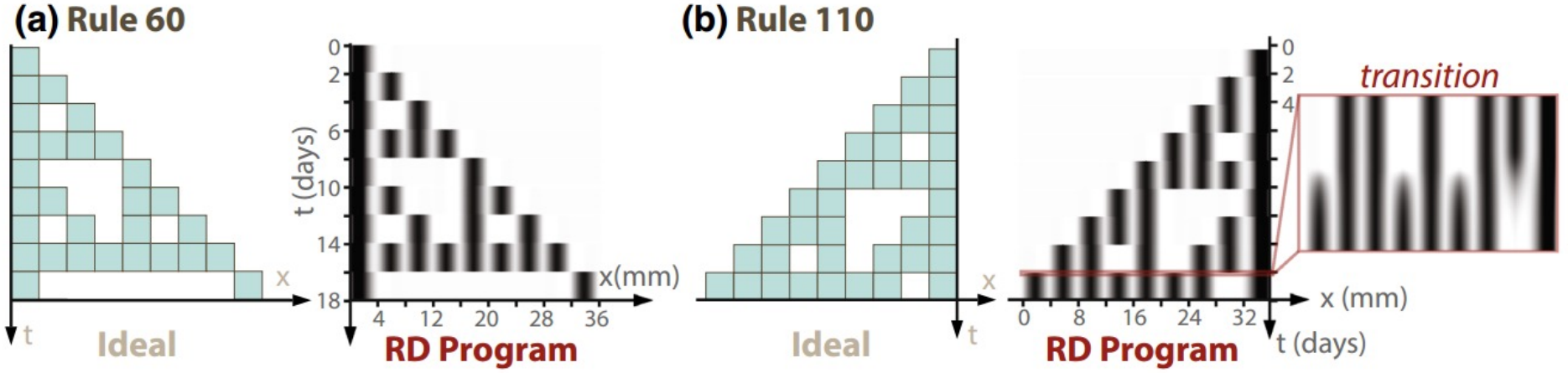
Rule Sets for Computing with Reaction Diffusion (RD) Systems

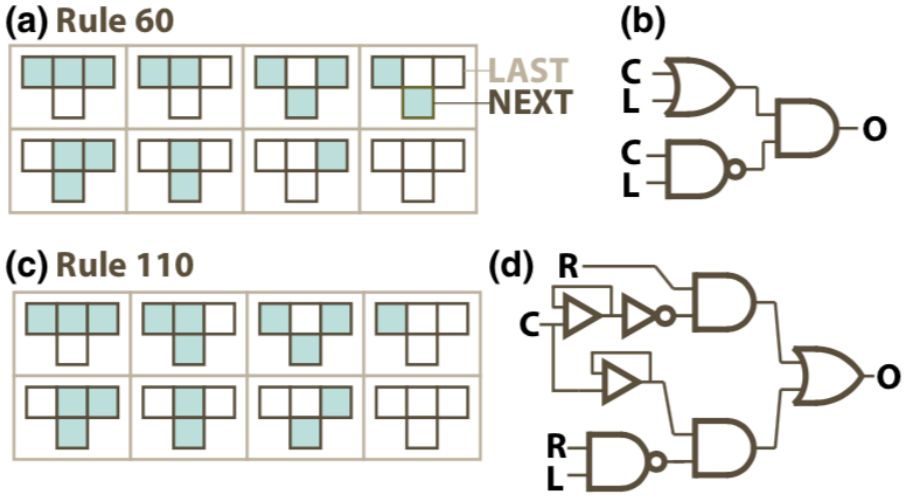
- **Rule sets for finite state automata defined by 2D patterning of DNA**



Dominic Scalise • Rebecca Schulman , 2015

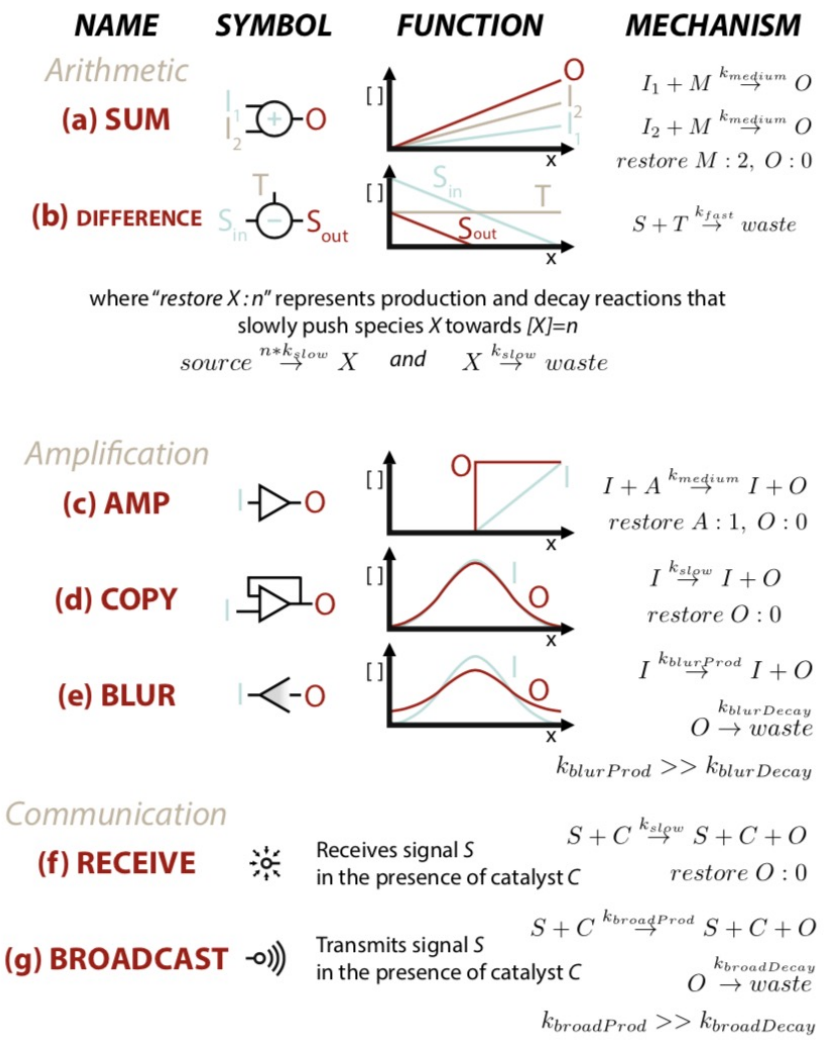
Rule Sets for Computing with Reaction Diffusion (RD) Systems

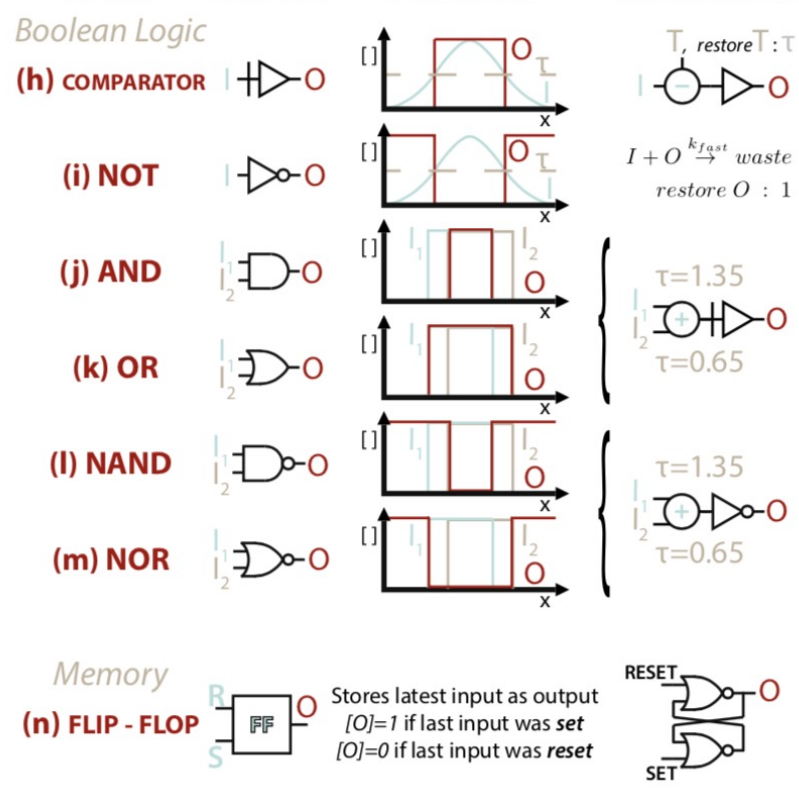




Dominic Scalise • Rebecca Schulman , 2015

Rule Sets for Computing with Reaction Diffusion (RD) Systems





Dominic Scalise • Rebecca Schulman , 2015

Rule Sets for Computing with Reaction Diffusion (RD) Systems

(a) Encoding Persistent Cell State

Repeating pattern of `key' concentrations defines cells.
Local `state' concentration encodes *on/off*.
Off cells have low [state], *on* cells have high [state].
Global `clock' is *off* until cells compute new state, then *on*.

[clock]=off

(b) Broadcasting Each Cell's Own State

On cells broadcast signal, *off* cells do not broadcast
(***e.g.*** *for keyA cells, keyA + S -> keyA + S + signal A).*
Broadcast species diffuse out, diluting with distance.

[clock]=off

(c) Receiving Neighbor States

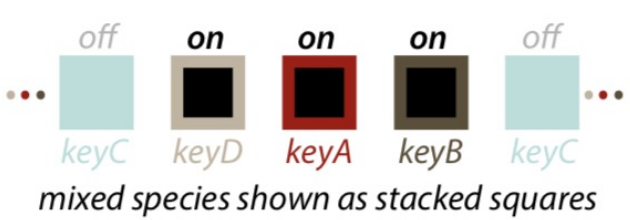
Cells interpret broadcasts locally based on keys
(***e.g.*** *for keyA cells, keyA + signal B -> keyA + signal B + R,*
and keyA + signal D -> keyA + signal D + L).

[clock]=off

(d) Calculating Next States

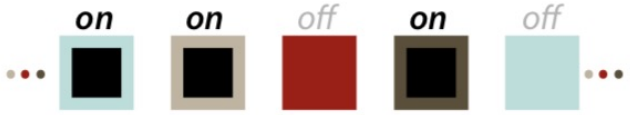
A composite Boolean function *f(L, S, R)*, executed by the global reaction network calculates next state.
When clock goes *high*, calculation is stored in *[state].*

[clock]=on



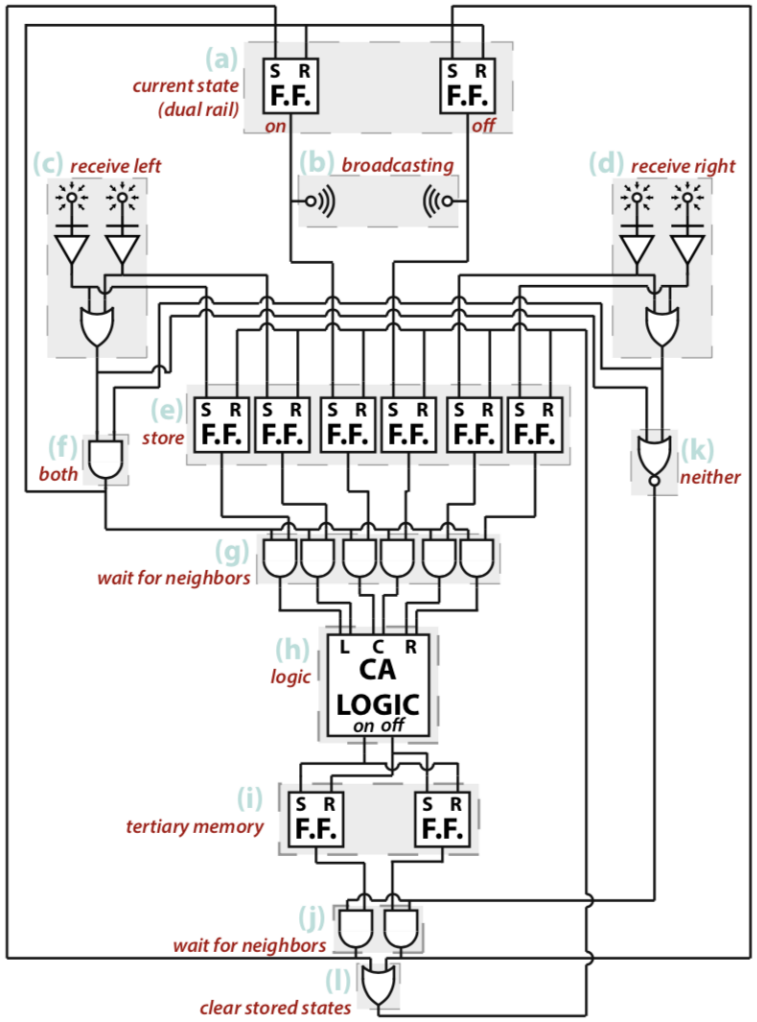
Legend:
State
KeyA
KeyB
KeyC
KeyD
SignalA
SignalB
SignalC
SignalD

Right neighbor ON
Left neighbor ON
Both neighbors ON



Dominic Scalise • Rebecca Schulman , 2015

Rule Set Program for Computing with Reaction Diffusion (RD) System

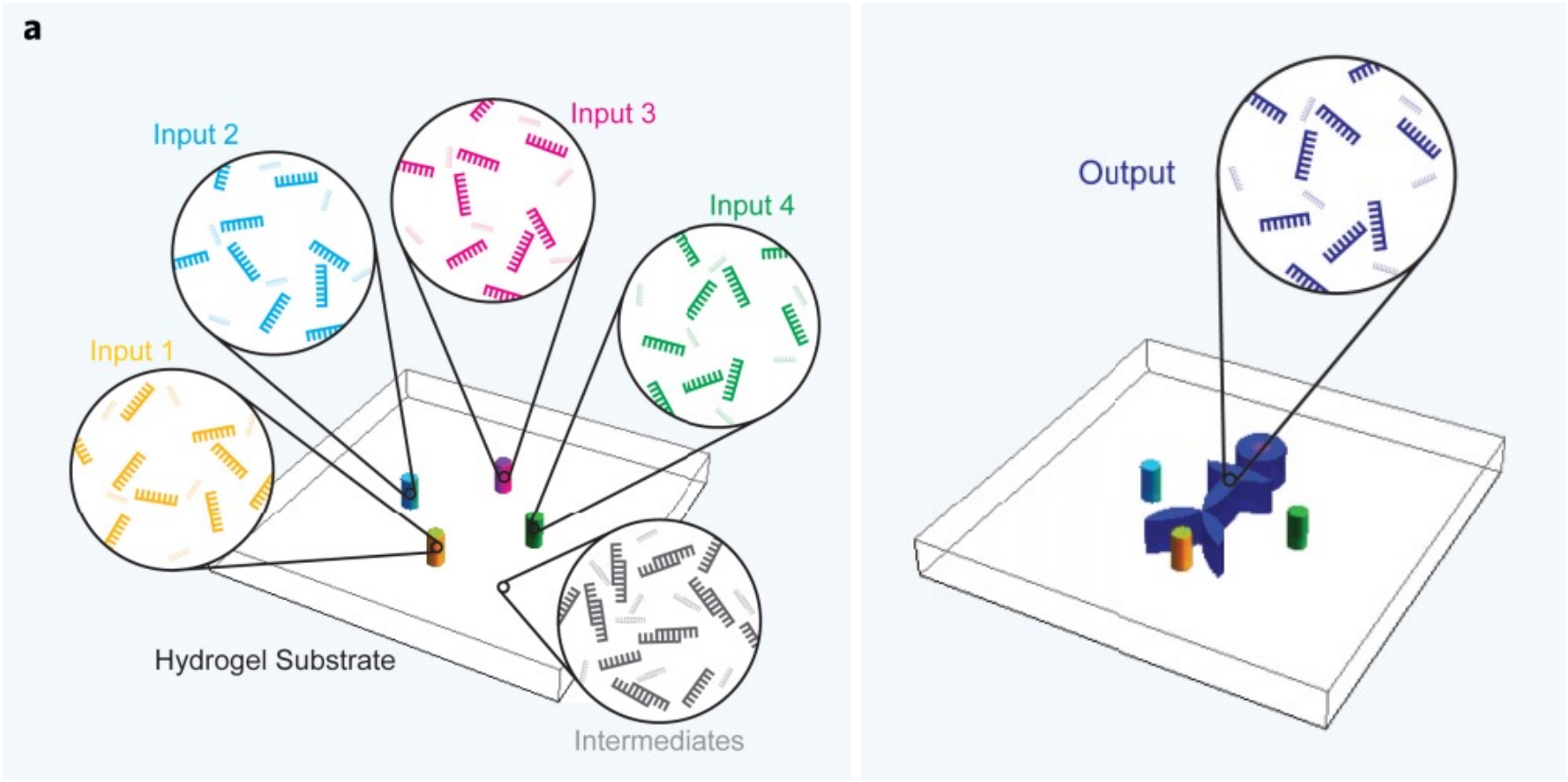


Dominic Scalise • Rebecca Schulman , 2015

Designing modular reaction-diffusion programs for complex pattern formation

Dominic Scalise and Rebecca Schulman, Designing modular reaction-diffusion programs for complex pattern formation, Technology, V. 2, Num 1, (2014)

Complex patterns in Agarose Gel

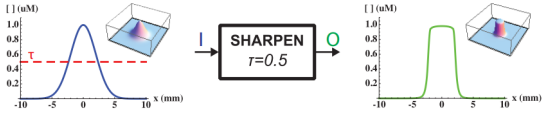


Dominic Scalise & Rebecca Schulman, 2014

2D Optical Modules

Agrawal et al. A self-regulating biomolecular comparator for processing oscillatory signals, (2015)

a *SHARPEN*



Converts *I* into a discrete output of *high/low* states. *High* regions are produced where *[I]* is greater than threshold τ, and *low* regions are produced elsewhere. First, a rapid thresholding reaction depletes *[I]* by τ, so *[I]* is zero except where *[I]*>τ initially. Any remaining *I* slowly catalyzes the conversion of inert amplifier A into output *O*, at *[O]*=α. At steady state, O is *high* only where *[I]*>τ initially.

thresholding:

$$I + T \xrightarrow{k_{react,T}} waste$$

amplification:

$$I + A \xrightarrow{k_{react,A}} I + O$$

species cycling:

$$O \xrightarrow{k_{degrade,O}} waste$$

$$\xrightarrow{k_{prod,T}} T, \text{ and } T \xrightarrow{k_{degrade,T}} waste$$

$$\xrightarrow{k_{prod,A}} A, \text{ and } A \xrightarrow{k_{degrade,A}} waste$$

reaction rate constants:

$$k_{react,T} >> k_{react,A}$$

$$k_{degrade,A}=k_{degrade,T}=k_{degrade,O}$$

$$k_{prod,T} = \tau * k_{degrade,T}$$

$$k_{prod,A} = \alpha * k_{degrade,A}$$

diffusion coefficients:

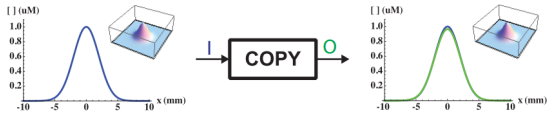
$$D_I = D_O = D_T = D_A$$

where:

$$\tau = [T]_{steadystate,noinput}$$

$$\alpha = [A]_{steadystate,noinput}$$

b *COPY*



Takes input pattern *I* and produces a copy of this pattern in *O*, without depleting *I*. If diffusion is much slower than the chemical reactions then $\frac{\partial [O]}{\partial t} = k([I] - [O])$, which is the equation for a proportional controller. Thus a COPY module continuously restores *[O]* to the set point *[I]* everywhere. Because *I* is a catalyst, it is not consumed regardless of what happens to *O*. The COPY module buffers *I* from downstream loading, allowing modules to deplete *[O]* without affecting *[I]*. This buffer is a crucial tool for adding and rearranging modules without affecting the upstream circuit.

catalytic copy:

$$I \xrightarrow{k_{prod,O}} I + O$$

species cycling:

$$O \xrightarrow{k_{degrade,O}} waste$$

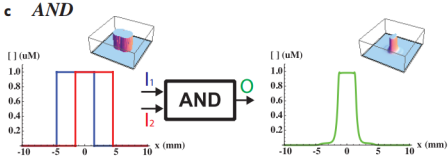
reaction rate constants:

$$k_{prod,O} = k_{degrade,O}$$

diffusion coefficients:

$$D_I = D_O$$

c *AND*



Takes Boolean input patterns *I1* and *I2*, and produces output pattern *O* that is *high* only where both inputs are *high*. First, *[I1]* and *[I2]* are summed into an intermediate pattern *N*. *[N]=2β* where both inputs are *high*, *[N]=β* where only one input is *high*, and *[N]=0* elsewhere. A SHARPEN module with τ=*1.3β* takes *N* as input, producing the described output pattern *O*.

summing of inputs:

$$I_1 + M \xrightarrow{k_{react,M}} N$$

$$I_2 + M \xrightarrow{k_{react,M}} N$$

thresholding of inputs:

$$N \rightarrow \boxed{sharpen(\tau{=}1.3\beta)} \rightarrow O$$

species cycling:

$$\xrightarrow{k_{prod,M}} M, \text{ and } M \xrightarrow{k_{degrade,M}} waste$$

$$N \xrightarrow{k_{degrade,N}} waste$$

reaction rate constants:

$$k_{degrade,N} = k_{degrade,M}$$

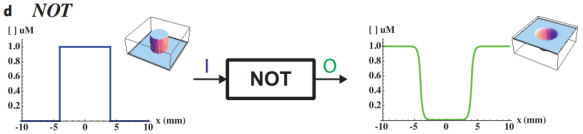
$$k_{react,M} >> k_{prod,M} = 2\beta k_{degrade,M}$$

where: $\beta = high$ concentration

diffusion coefficients:

$$D_{I_1} = D_{I_2} = D_N = D_O = D_M$$

d *NOT*



Takes a Boolean input pattern *I*, and produces an inverted Boolean output *O*. *[O]* is *high* where *[I]* is *low*, and *low* where *[I]* is *high*. Slow cycling reactions continuously push *[O] high*, so in the absence of *I*, *[O]* is *high*. *I* and *O* rapidly annihilate each other, so *[O]* is switched to *low* in the presence of *I*.

logical inversion:

$$I + O \xrightarrow{k_{react,O}} waste$$

species cycling:

$$source \xrightarrow{k_{prod,O}} O, \text{ and } O \xrightarrow{k_{degrade,O}} waste$$

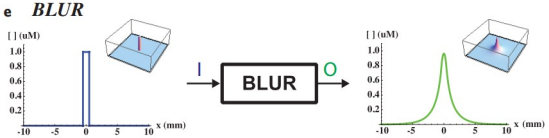
reaction rate constants/diffusion coefficients:

$$k_{react,O} >> k_{prod,O} = \alpha * k_{degrade,O}$$

$$D_I = D_O$$

where: $\alpha = [O]_{steadystate,noinput}$

e *BLUR*



Assembles a smooth gradient *O* centered around a fixed reference point *I*. This module uses the same reactions as the COPY module, but places different constraints on the constants. The distance from the reference to any point *p* can be calculated as a function of *[O]* at *p*, provided the reaction rate constants and diffusion coefficients are known. *I* catalyzes the local production of *O* at the reference. *O* diffuses away from this point and also degrades slowly. At steady state, *[O]* at a distance *r* from the reference is: $[O]_r = [O]_0 e^{-r/\sqrt{D_O/k_{prod,O}}}$

signal generation:

$$I \xrightarrow{k_{prod,O}} I + O$$

$$O \xrightarrow{k_{degrade,O}} waste$$

reaction rate constants:

$$k_{prod,O} > k_{degrade,O}$$

diffusion coefficients:

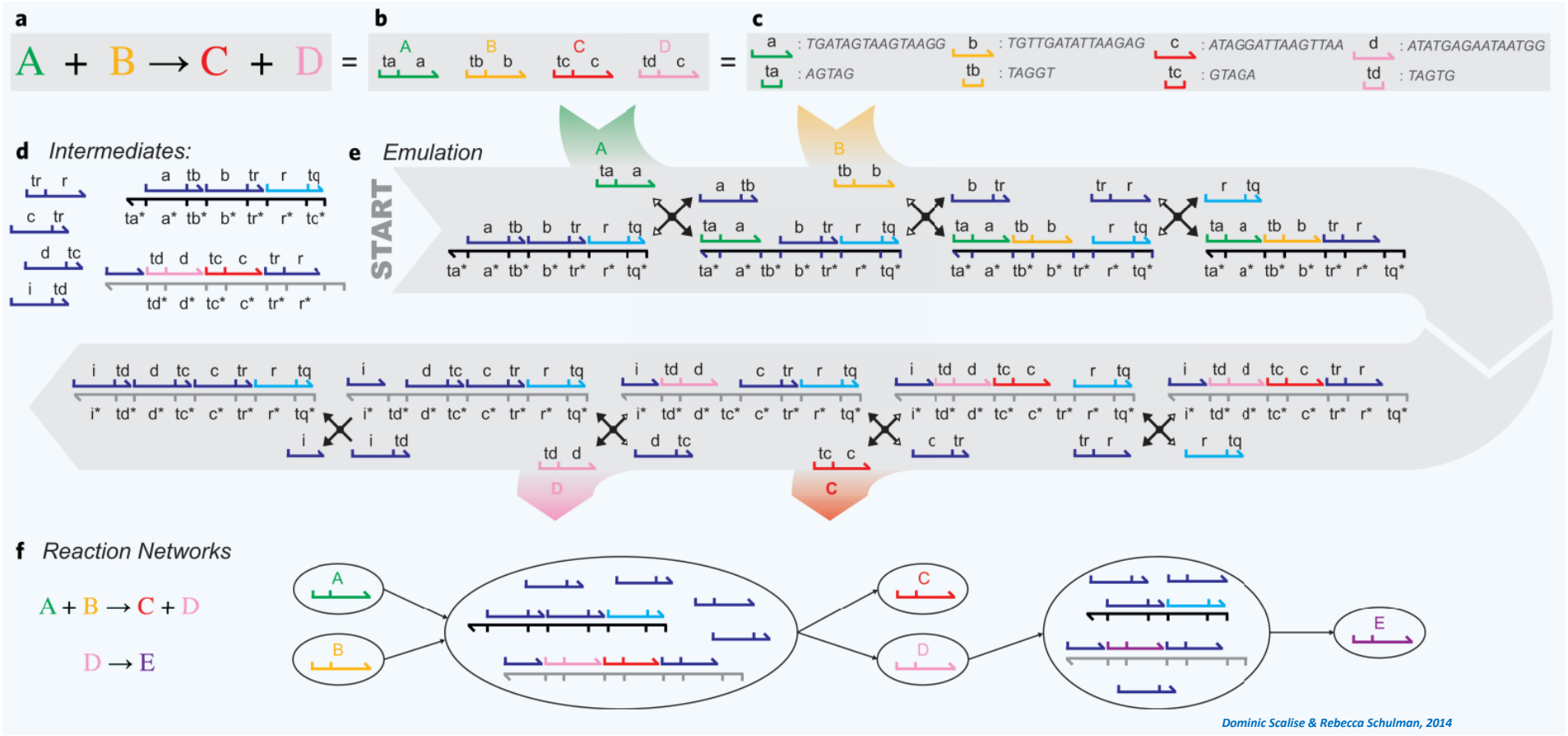
$$D_O > D_I = 0$$

initial conditions:

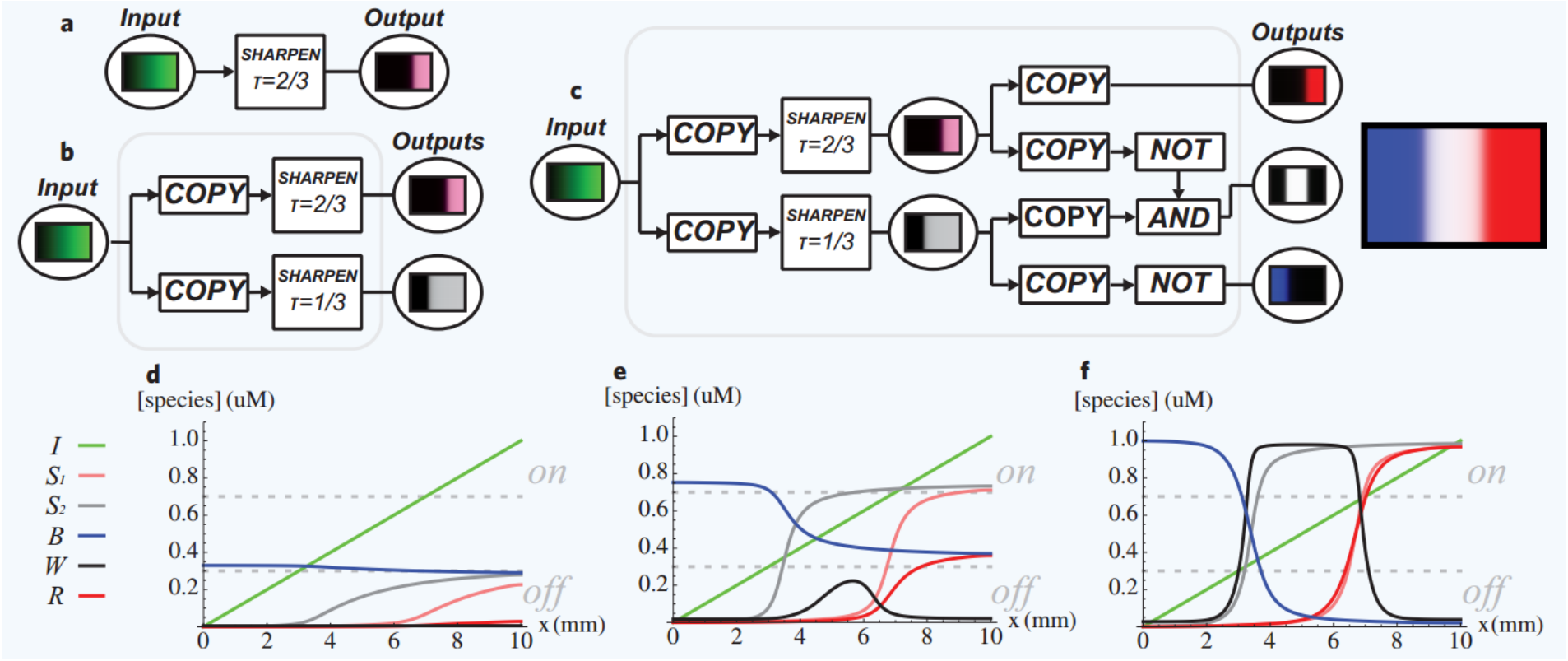
$$[I]_0 = \begin{cases} 1 & \text{if } r \le r_{max}, \\ 0 & \text{otherwise .} \end{cases}$$

Dominic Scalise & Rebecca Schulman, 2014

DNA reaction networks at 2D Sites

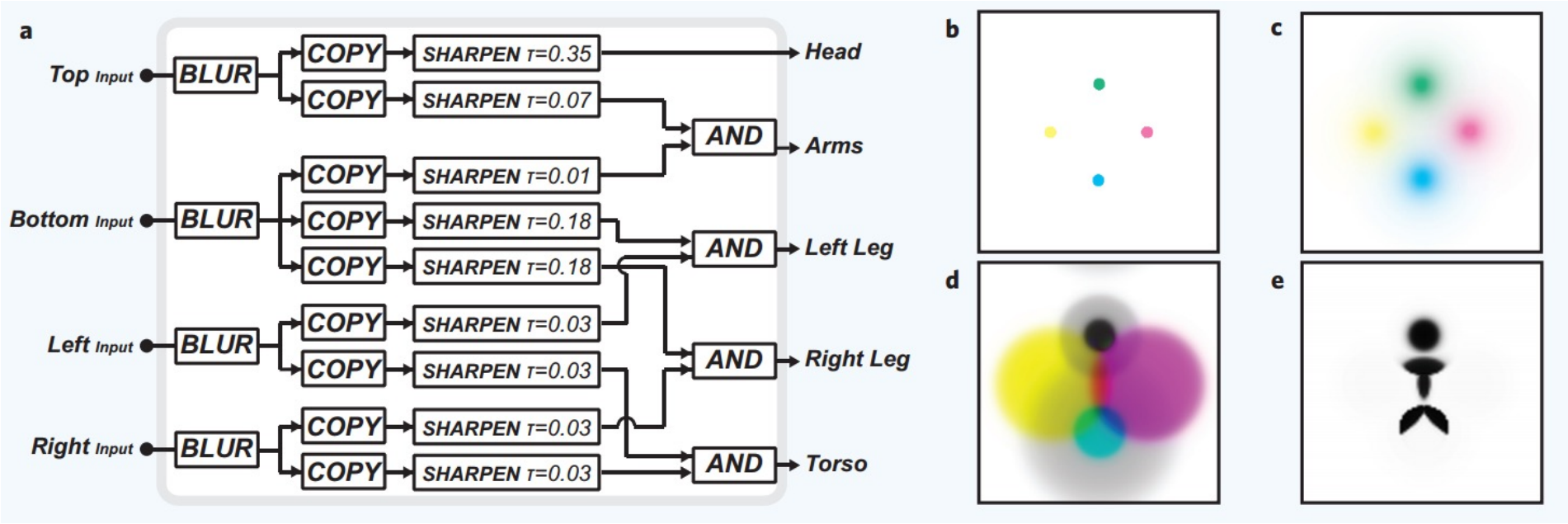


DNA reaction networks for 2D optical Modules



Dominic Scalise & Rebecca Schulman, 2014

2D Patterns Modification on Agarose Gel using DNA strand-displacement Circuits

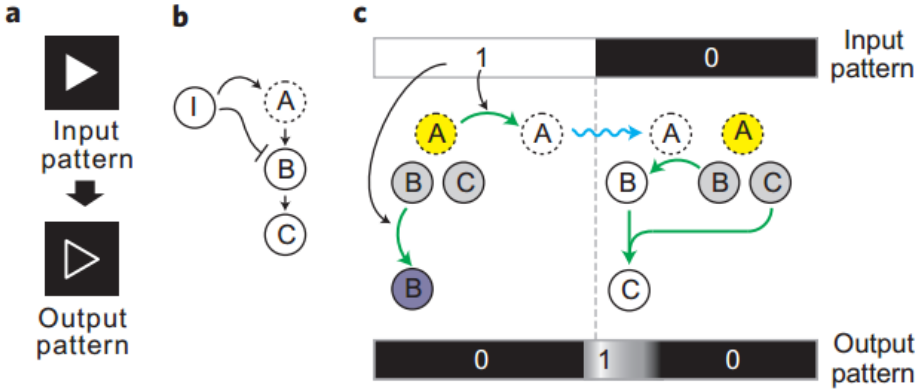


Dominic Scalise & Rebecca Schulman, 2014

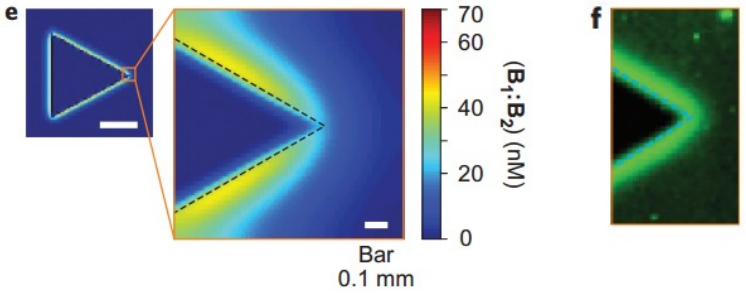
Pattern transformation with DNA circuits

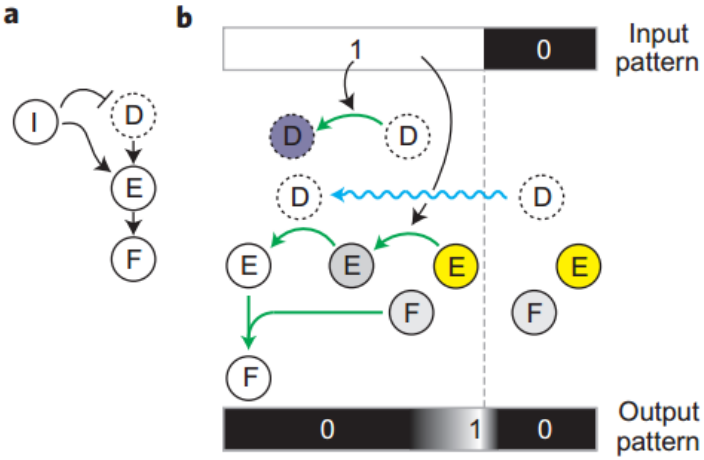
Steven Chirieleison, Peter Allen, Zack Simpson, Andrew Ellington and Xi Chen, Pattern transformation with DNA circuits, Nature Chemistry, 2013, DOI: 10.1038/NCHEM.1764

Edge detection



Negative edge



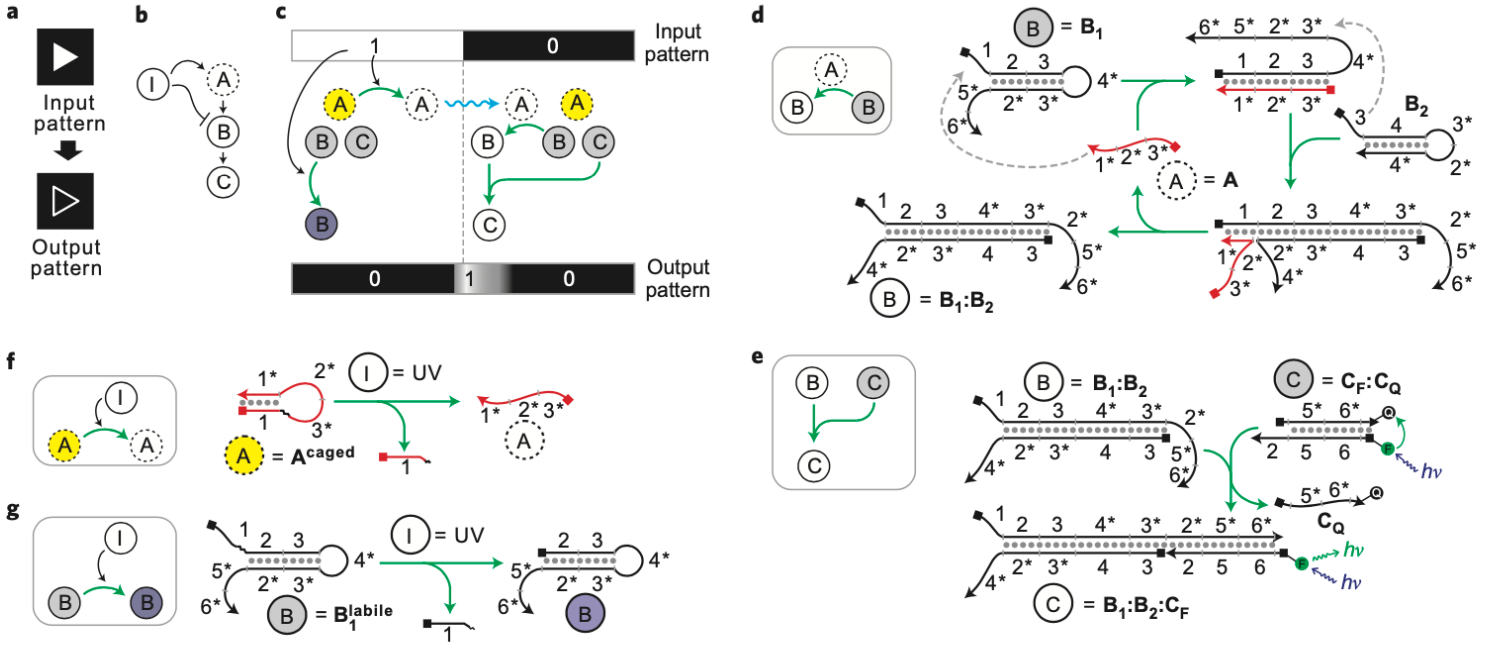


Positive edge

Steven M. Chirieleison, Peter B. Allen, Zack B. Simpson, Andrew D. Ellington and Xi Chen, 2013

Pattern transformation with DNA circuits

Negative edge case:



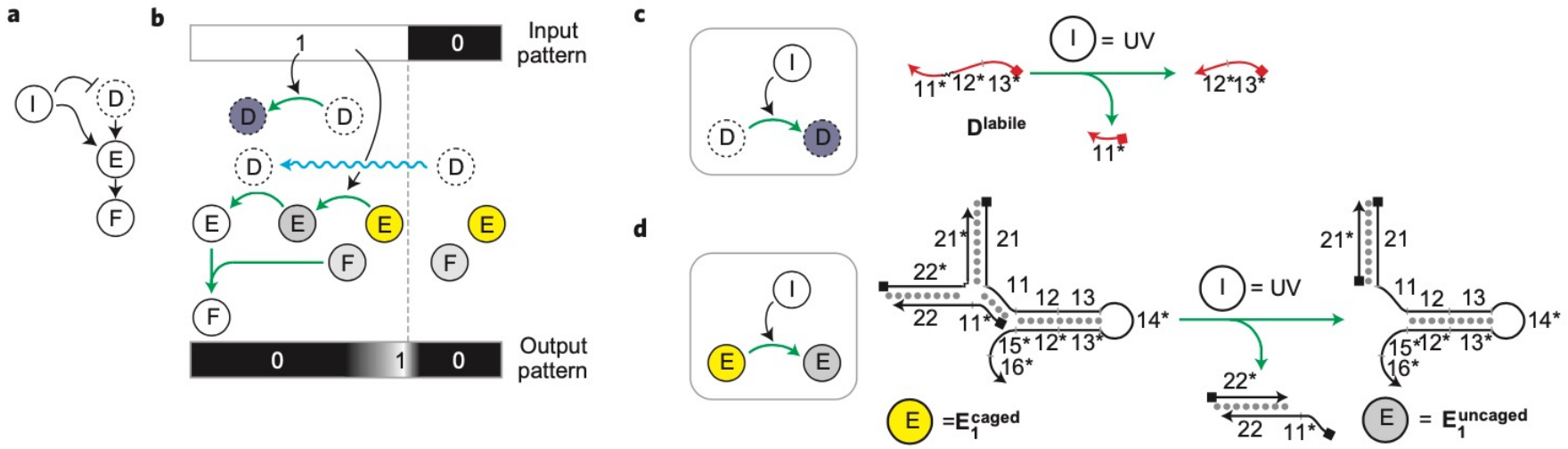
High-level description and molecular detail of an incoherent feed-forward loop that performs edge detection. a, Definition of edge detection wi a binary input. **b**, High-level description of the incoherent feed-forward loop. The input signal is denoted as I. The only fast-diffusing species (A) is denoted with a dashed circle. **c**, Detailed mechanism of the incoherent feed-forward loop. The input signal can turn caged A (yellow) into active A (white) and simultaneously turn inactive B (grey) into ablated B (purple), unable to be activated by A. Activated A can then diffuse (blue squiggle) to the area where th input signal is absent (0) and turn inactive B (grey) into active B (white). Active B can then combine with inactive C (grey) to form active C (white) near th I/0 boundary. **d**,**e**, Implementation of the circuit shown in **c** using a CHA circuit. Active A, inactive B and active B are represented by **A**, $\mathbf{B_1}$ and the $\mathbf{B_1{:}B_2}$ duplex, respectively. For simplicity $\mathbf{B_2}$ is not shown in **c**. **A** can catalyse the formation of the $\mathbf{B_1{:}B_2}$ duplex through the depicted pathway (**d**). Inactive C is represented by the $\mathbf{C_F{:}C_Q}$ duplex, where $\mathbf{C_F}$ and $\mathbf{C_Q}$ are labeled with a fluorophore and a quencher, respectively; thus in $\mathbf{C_F{:}C_Q}$ the fluorescence in quenched. Active C is represented by the $\mathbf{B_1{:}B_2{:}C_F}$ complex, in which the fluorescence is unquenched (**e**). Domains 1, 2, 3, 5 and 6 are eight nucleotides long; domain 4 is 11 nucleotides long (see Supplementary Table S1 and Fig. S8a for sequences). **f**, Mechanisms of the photoactivation of $\mathbf{A^{caged}}$. **g**, Mechanisms of the photoablation of $\mathbf{B_1^{labile}}$ (see Supplementary Fig. S1a for chemical structure of the photocleavable linker). UV, ultraviolet radiation.

Steven M. Chirieleison, Peter B. Allen, Zack B. Simpson, Andrew D. Ellington and Xi Chen, 2013

Peter B. Allen • Xi Chen • Zack B. Simpson • Andrew D. Ellington 2013

Pattern transformation with DNA circuits

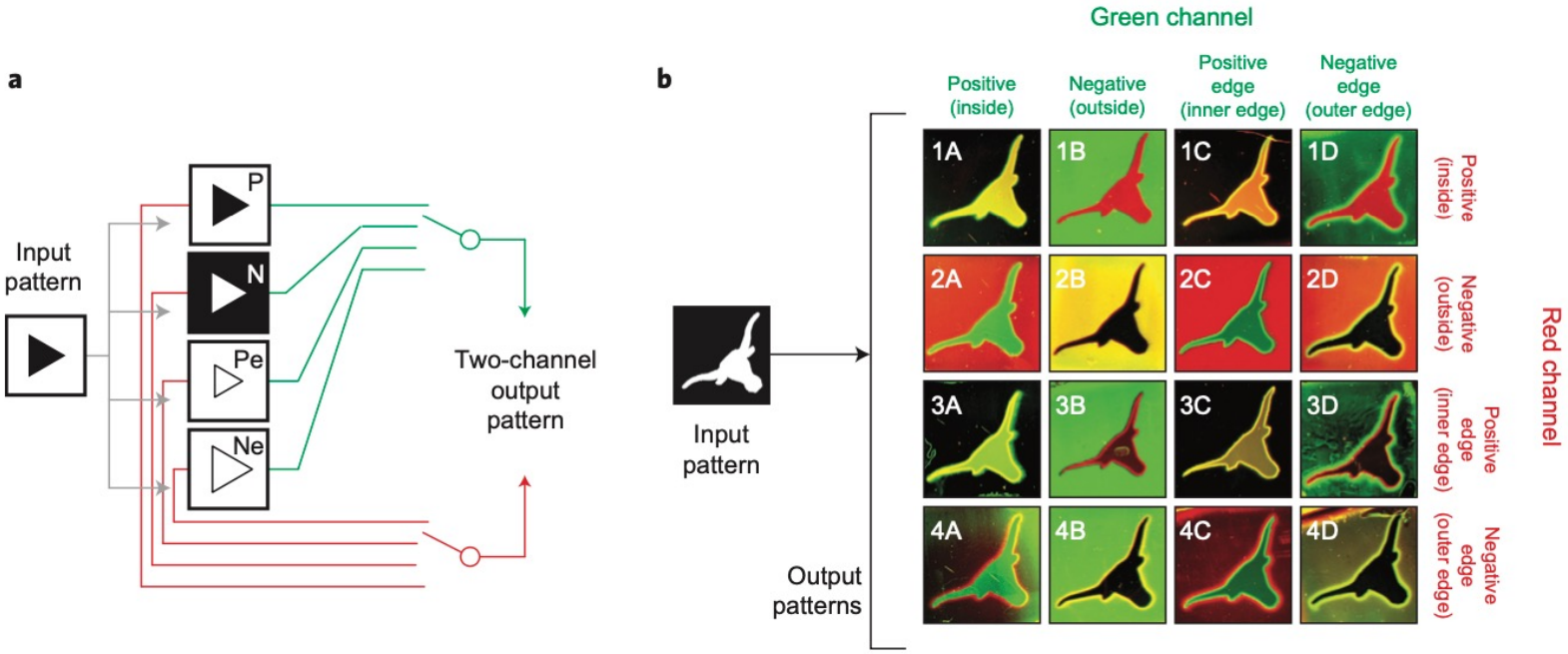
Positive edge Case



High-level description and molecular detail of the 'positive edge' circuit. a, An incoherent feed-forward loop with inversed logic. **b**, Detailed mecnanism of the incoherent feed-forward loop. Here D is ablated and E is uncaged by the input signal. Active, inactive, caged and ablated molecules are shown in white, grey, yellow and purple, respectively. **c**, Mechanisms of the photoablation of $\mathbf{D}^{\mathbf{labile}}$. **d**, Mechanisms of the photoactivation of $\mathbf{E}_1^{\mathbf{caged}}$. Domains 11, 13, 15 and 16 are eight nucleotides long; domain 12 is 11 nucleotides long; domain 14 is 15 nucleotides long; domains 21 and 22 are 20 nucleotides long

Steven M. Chirieleison, Peter B. Allen, Zack B. Simpson, Andrew D. Ellington and Xi Chen, 2013

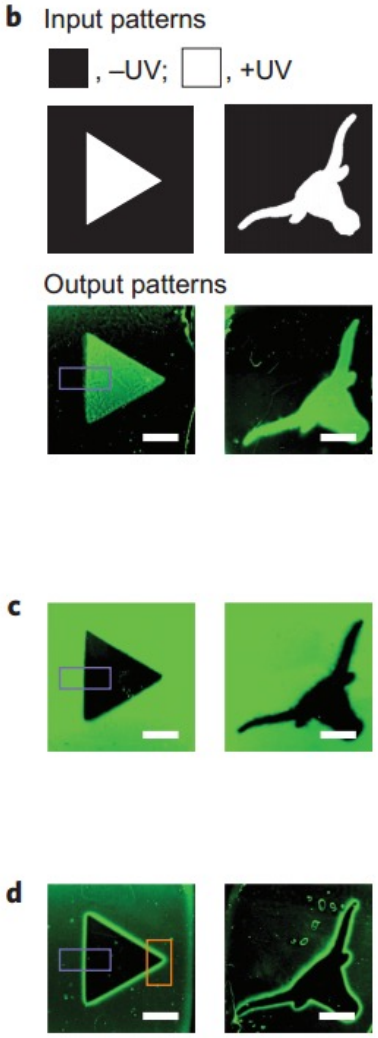
Pattern transformation with DNA circuits

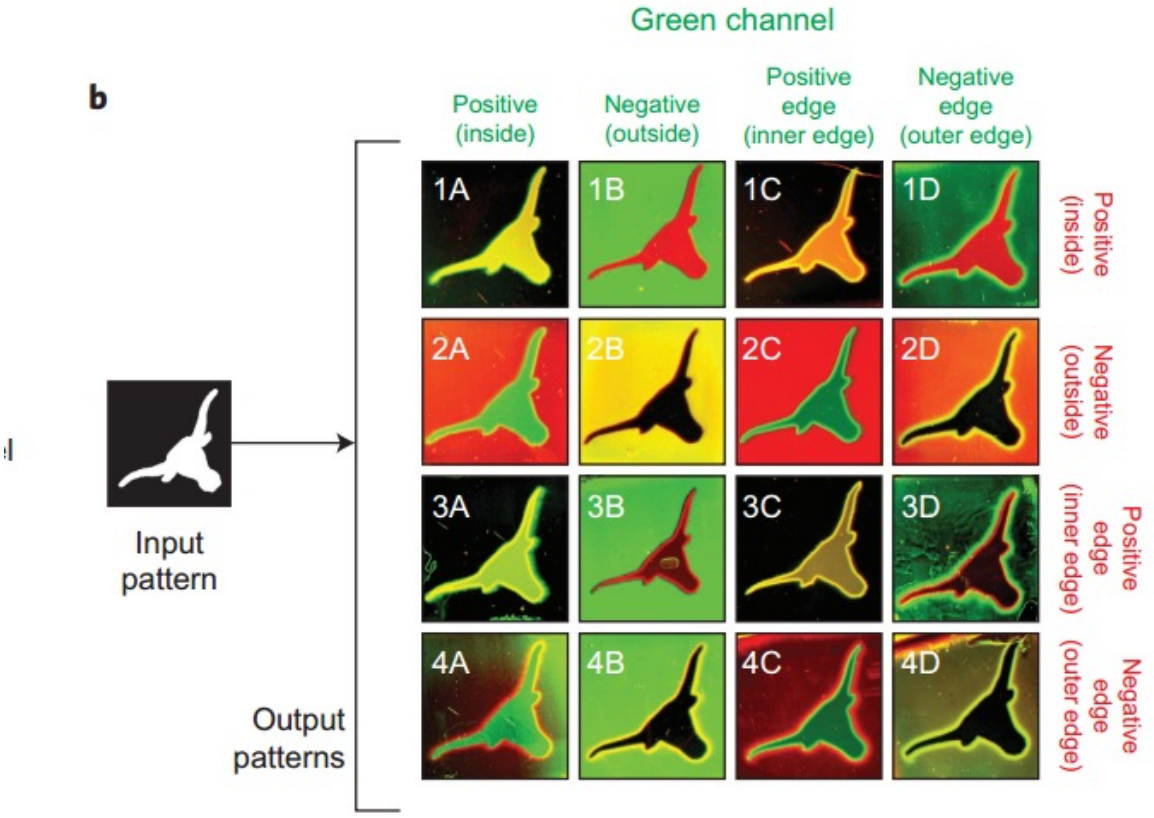


Combinatorial multiplexing of two-channel pattern-transformation programs. a, Scheme of the pattern-transformation programs. P, positive image; N, negative image; Pe, positive edge; Ne, negative edge. **b**, A total of 16 different two-channel output patterns generated from the same input pattern through 16 different pattern-transformation programs.

Peter B. Allen • Xi Chen • Zack B. Simpson • Andrew D. Ellington 2013

Pattern transformation with DNA circuits





Steven M. Chirieleison, Peter B. Allen, Zack B. Simpson, Andrew D. Ellington and Xi Chen, 2013