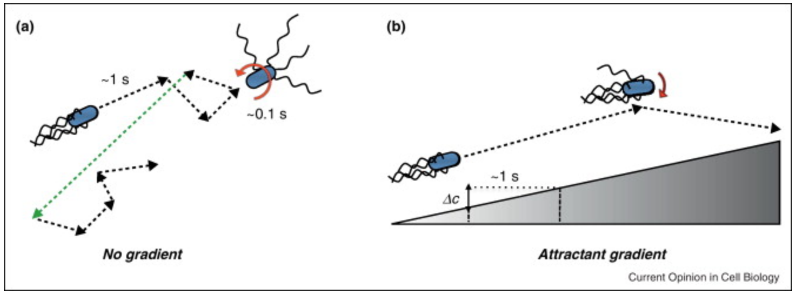
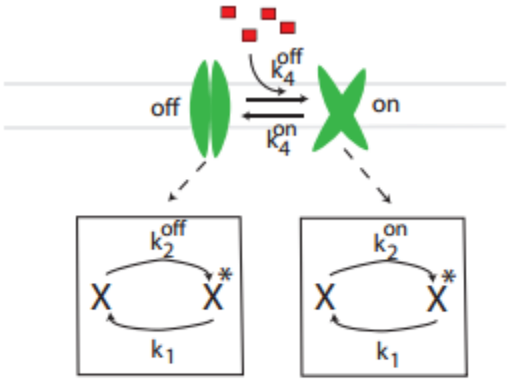
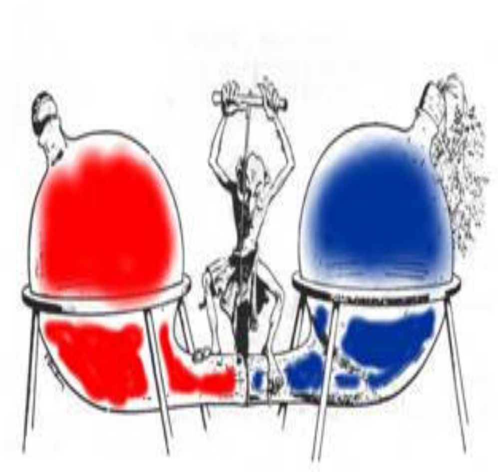
The thermodynamics of cellular computation



Sourjik and Wingreen (2012) Cur. Opinions in Cell Bio.

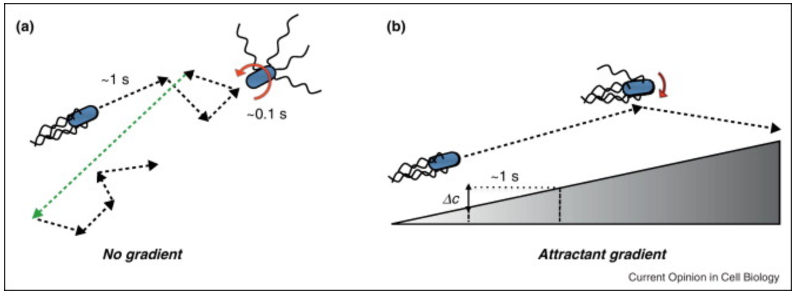




Pankaj Mehta

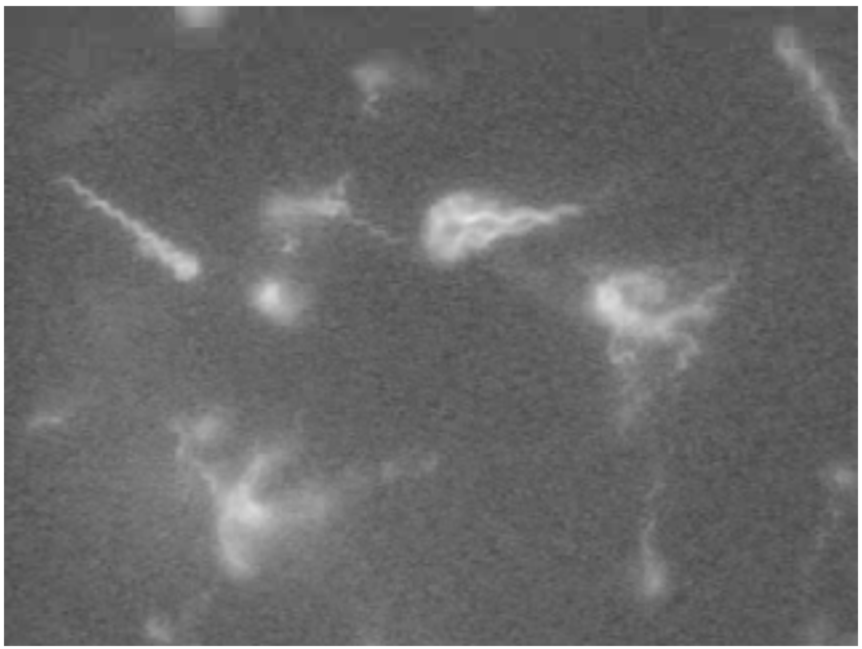
Collaborators: David Schwab, Charles Fisher, Mo Khalil

Cells perform complex computations

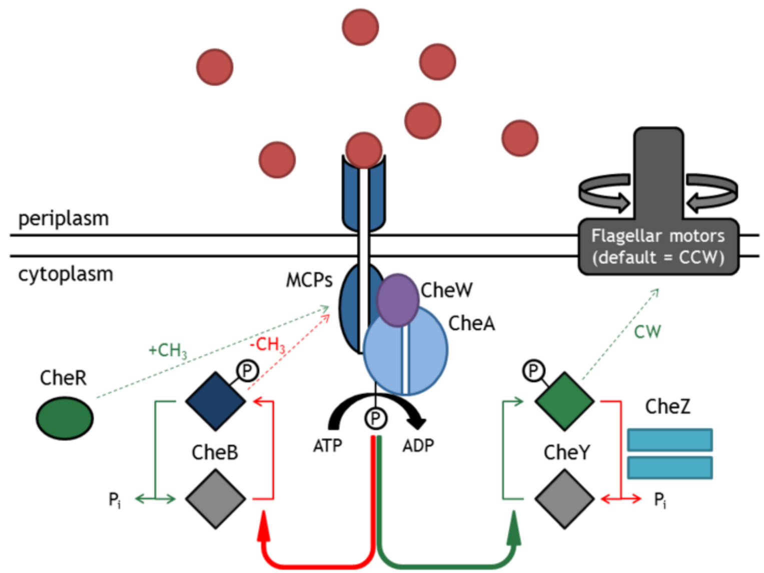


Sourjik and Wingreen (2012) Cur. Opinions in Cell Bio.

Compute gradients of external concentrations



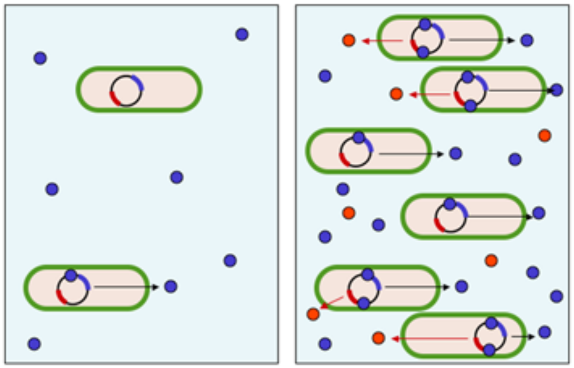
Howard Berg

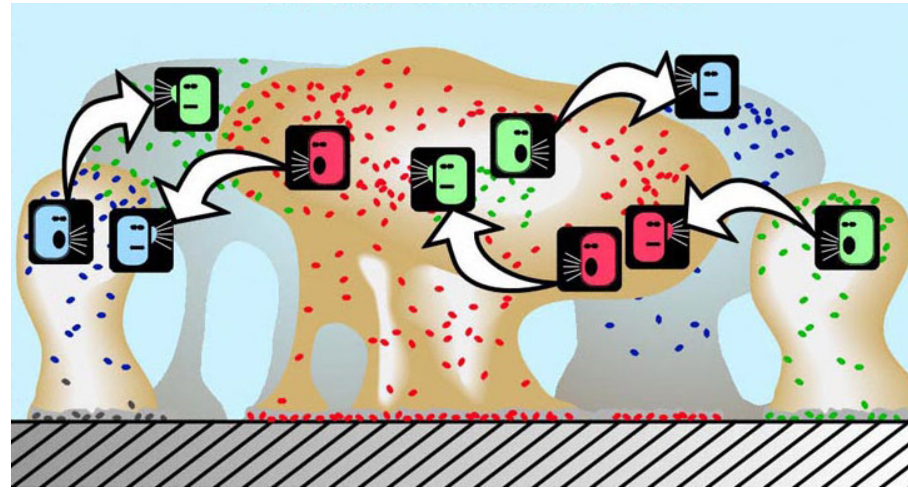


IGEM website

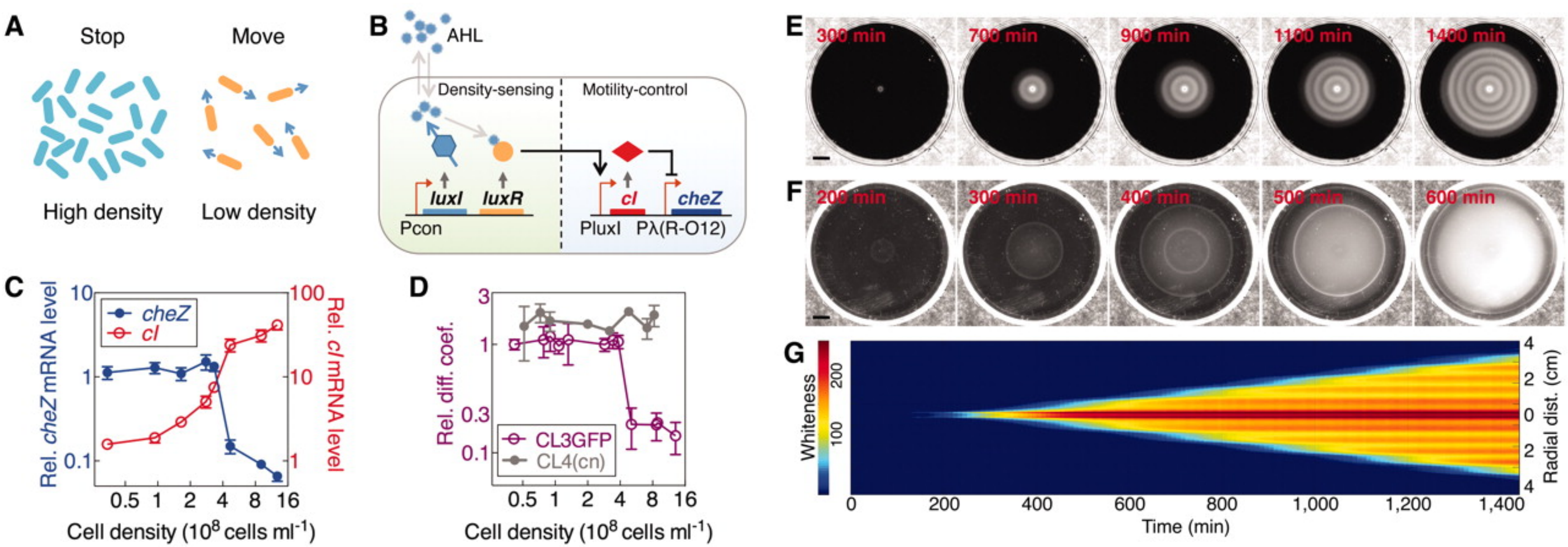
Cells perform complex computations

Quorum Sensing





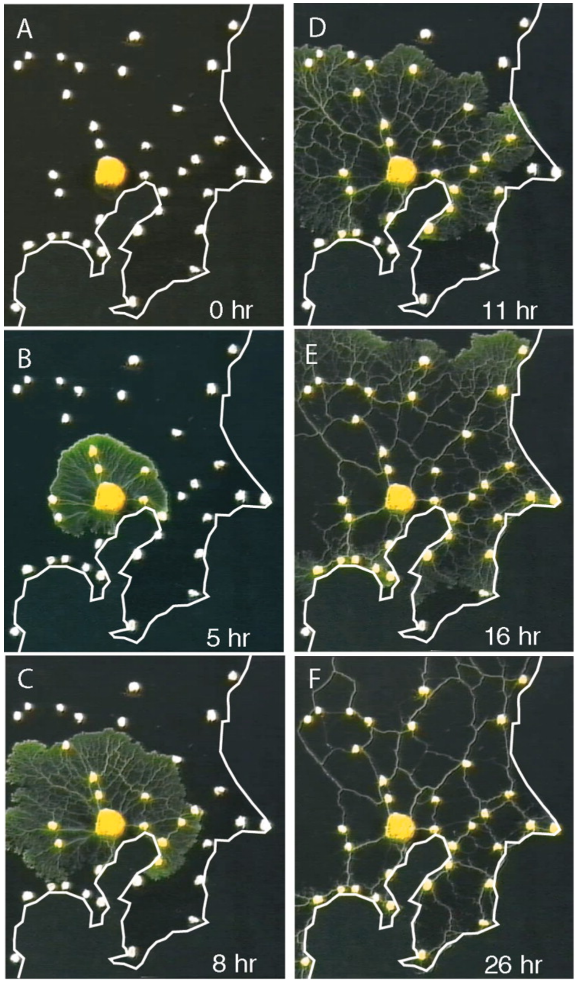
Quorum Sensing + Synthetic Biology= Stripes

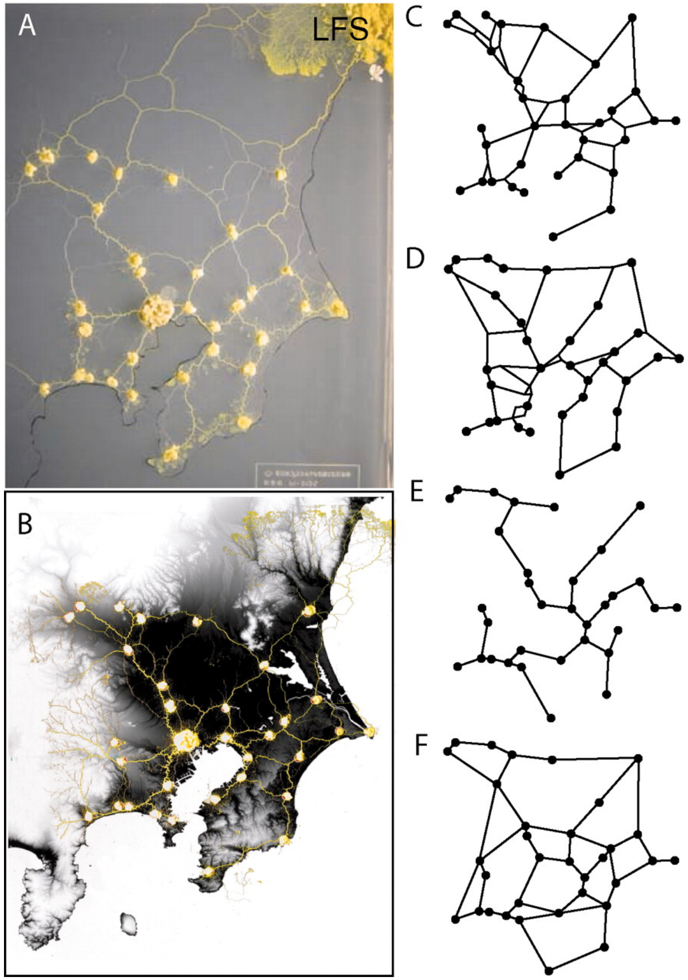


Science 334 (6053): 238-241

Cells perform complex computations

Slime mold (*Physarum polycephalum*) can design transportation networks!

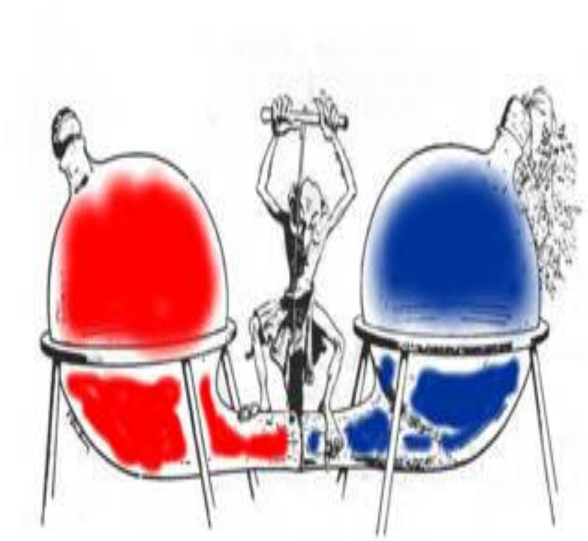


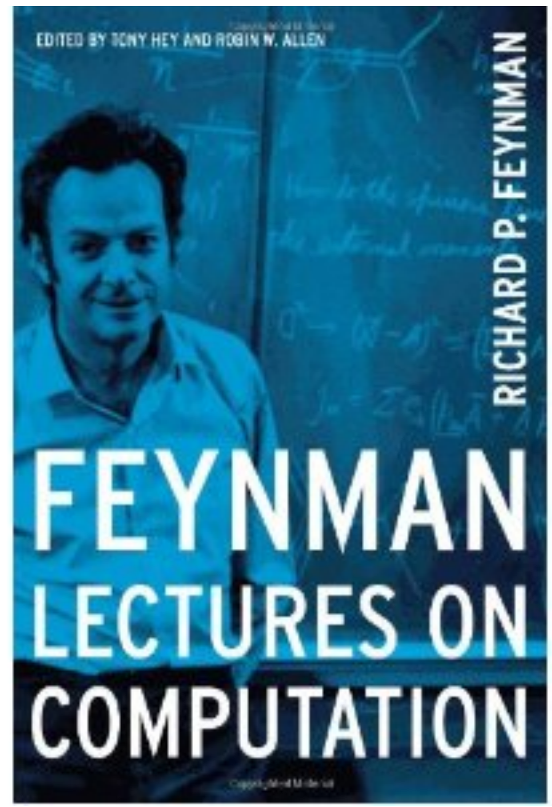


Tero *et al* Science 327 (5964): 439-442 (2010)

Thermodynamics of Computation

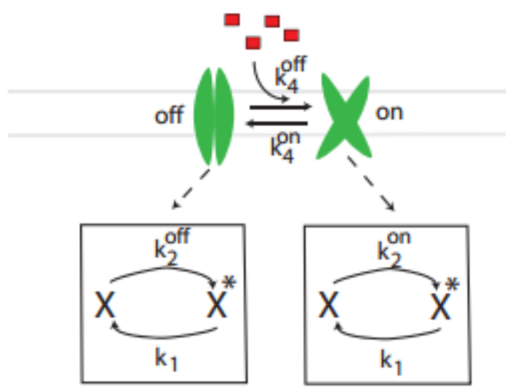
Information is physical! (Maxwell, Landauer, Charles Bennett, many others)

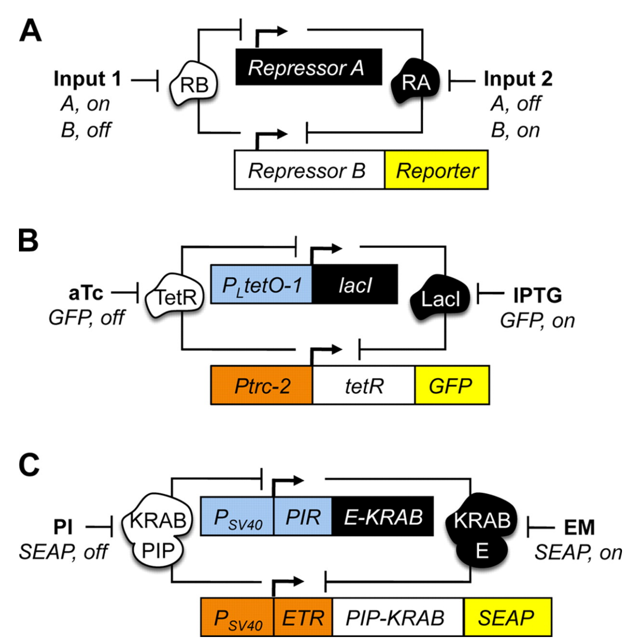




Outline

- Part I: Crash Course in Thermodynamics of Computation
- Part II: Energetics of the simplest cellular computation (Berg-Purcell)
- Part III: Landauer's principle and the design of synthetic biological memory





Haynes K A, Silver P A J Cell Biol 2009;187:589-596

Part I: Thermodynamics of computation

R. Landauer

Irreversibility and Heat Generation in the Computing Process

Abstract: It is argued that computing machines inevitably involve devices which perform logical functions that do not have a single-valued inverse. This logical irreversibility is associated with physical irreversibility and requires a minimal heat generation, per machine cycle, typically of the order of *kT* for each irreversible function. This dissipation serves the purpose of standardizing signals and making them independent of their exact logical history. Two simple, but representative, models of bistable devices are subjected to a more detailed analysis of switching kinetics to yield the relationship between speed and energy dissipation, and to estimate the effects of errors induced by thermal fluctuations.

IBM JOURNAL • JULY 1961

Information is physical

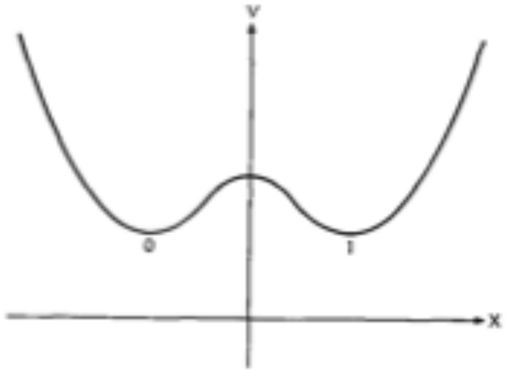


Figure 1 **Bistable potential well.**
x is a generalized coordinate representing quantity which is switched.

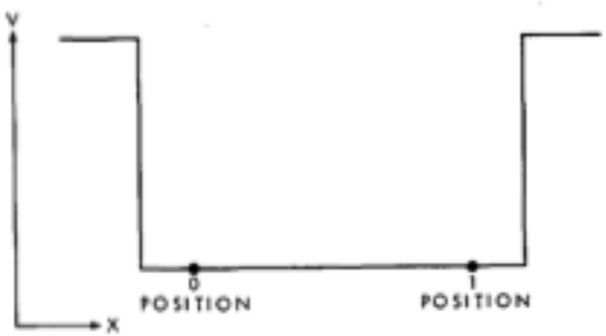
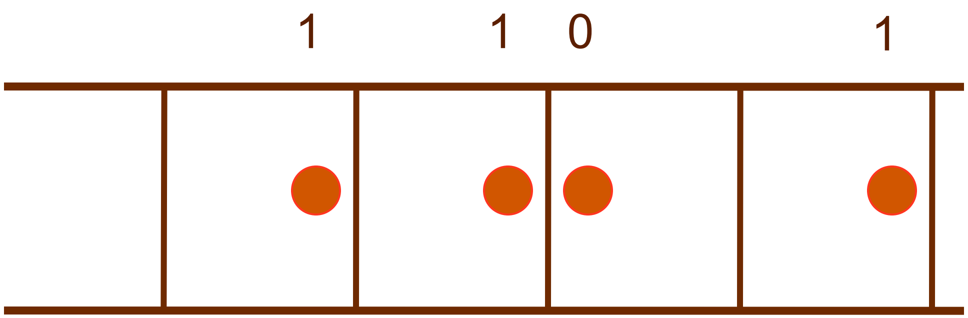


Figure 2 **Potential well in which ZERO and ONE state are not separated by barrier.**
Information is preserved because random motion is slow.

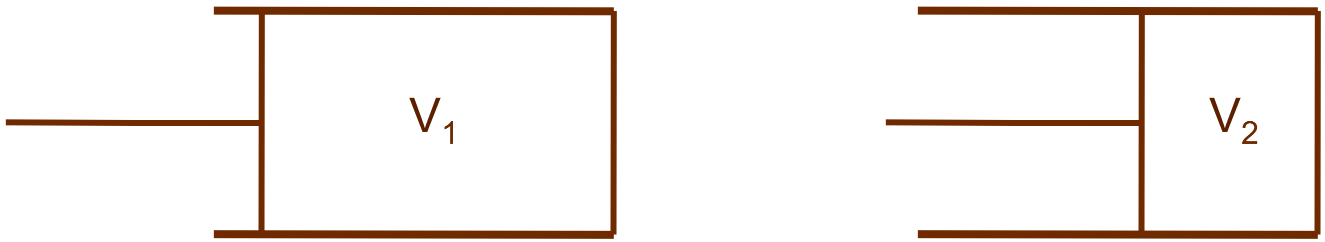


Basic Atomic Message

Left side of box: 1
Right side of box: 0

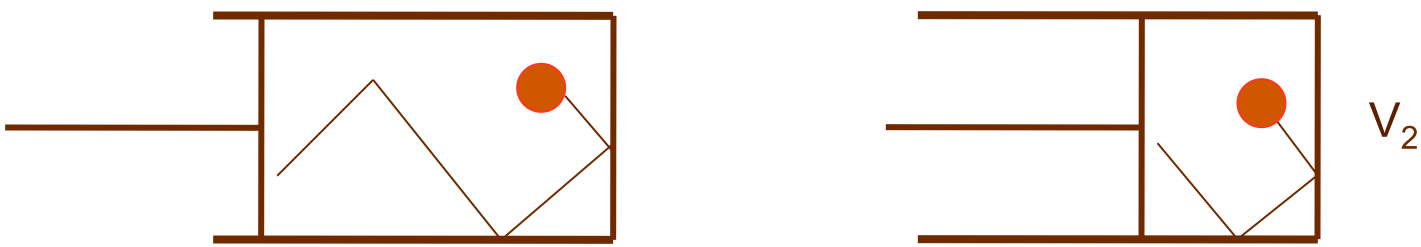
Entropy of a compressed gas

- Compress ideal gas **isothermally**



$$W = \int_{V_1}^{V_2} \frac{NkT}{V} dV = NKT \log \frac{V_2}{V_1} = T\Delta S$$

- Now consider single particle

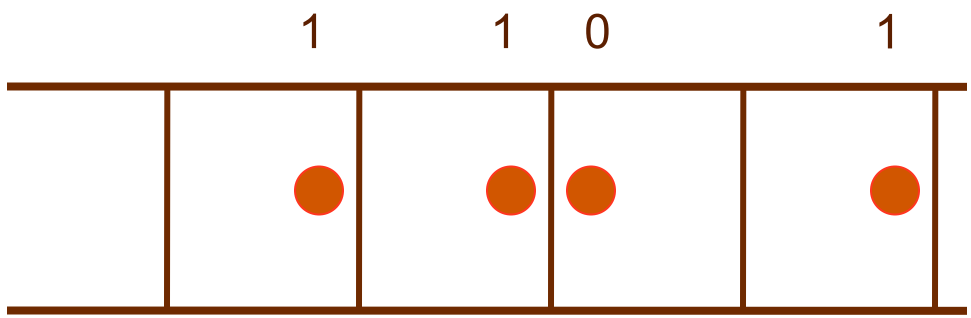


$$\Delta S \approx k \log \frac{\Omega_2}{\Omega_1} = k \log \frac{V_2}{V_1}$$

$$\Omega = \text{Number of accesible configurations}$$

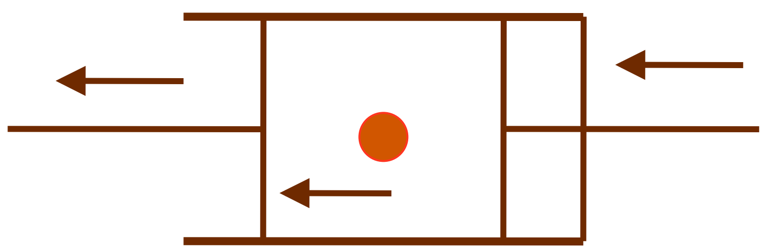
The less information we have about state, the higher the entropy!

Thermodynamic definitions of information



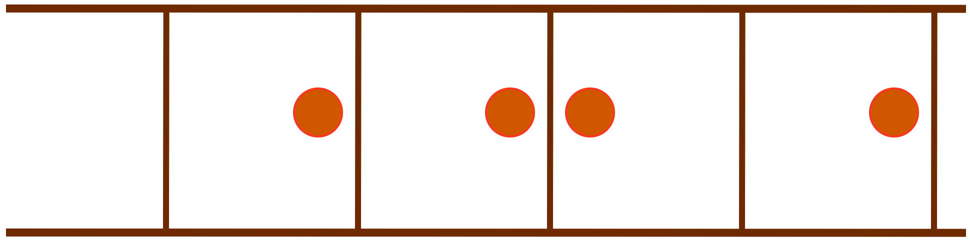
• **Define** information theoretic (Shannon) entropy *H* to be proportional to **amount of free energy required to reset the tape to zero**!

• If we know position of particle we can reset to zero with no energy costs!



(two pistons push to the left to reset 1 state)

Thermodynamic definitions of information



• **Define** information theoretic (Shannon) entropy *H* to be proportional to **amount of free energy required to reset the tape to zero**!

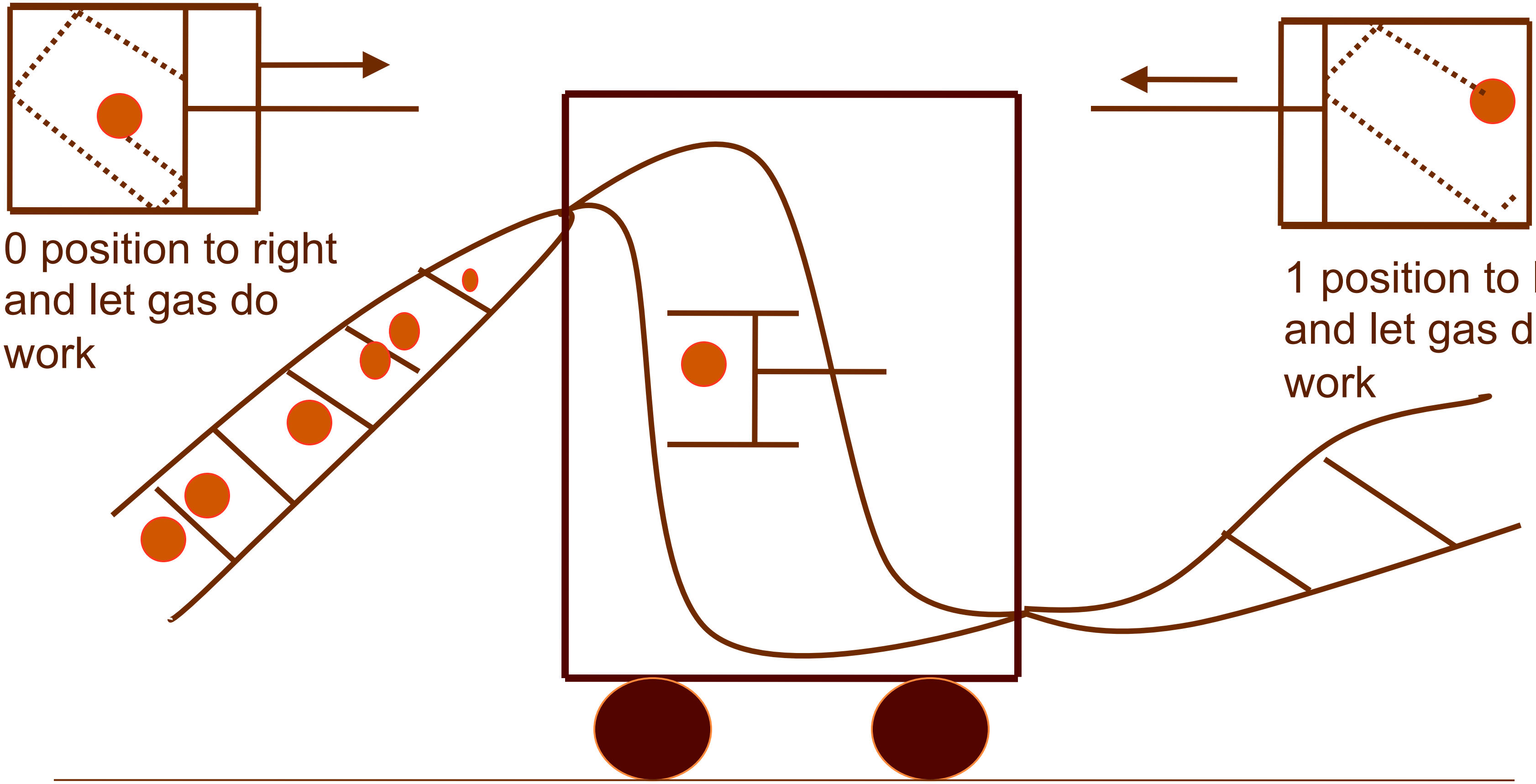
• Example: Uniform message 00000000000 11111111111 $H = 0$

• Random message 100100110101 $H \propto N \log 2$

(Compress N squares- each one half configuration space)

Erasing/resetting memory if we don't know state requires energy!

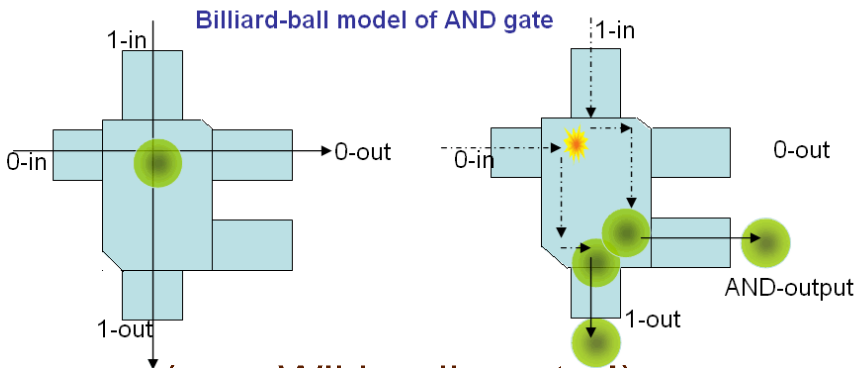
Information as fuel



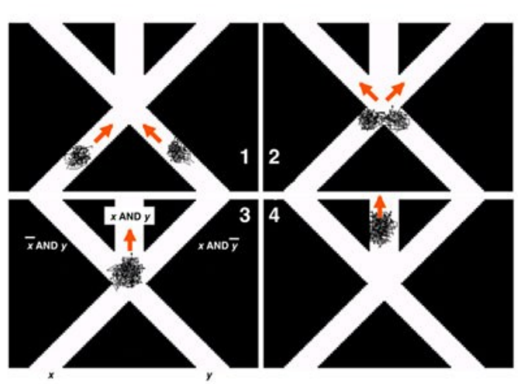
Use knowledge of message to power engine

What causes energy dissipation?

Reversible computation- computation in principle can be done without energy dissipation at expense of speed/efficiency/resources

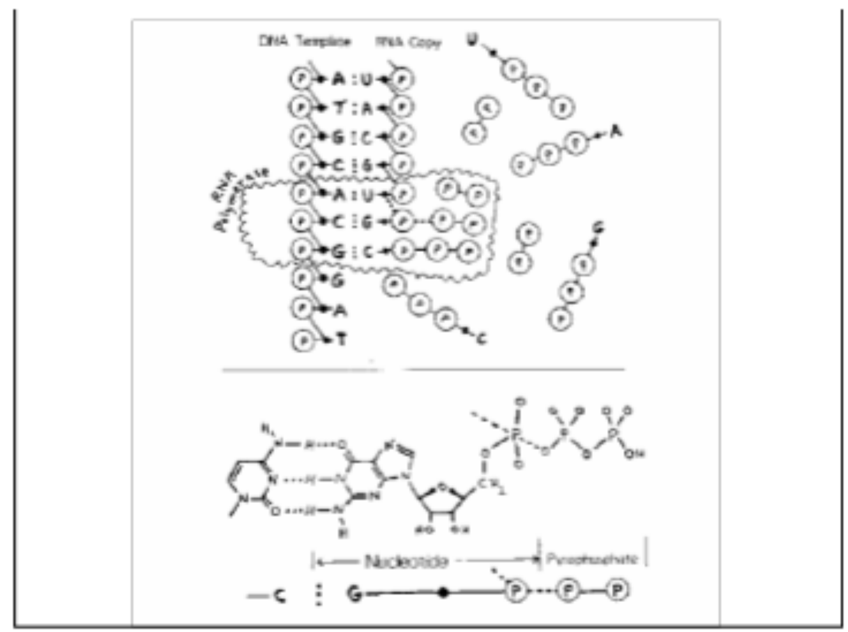


(own Wikipedia entry!)



Gunji *et al* Complex Systems 2010

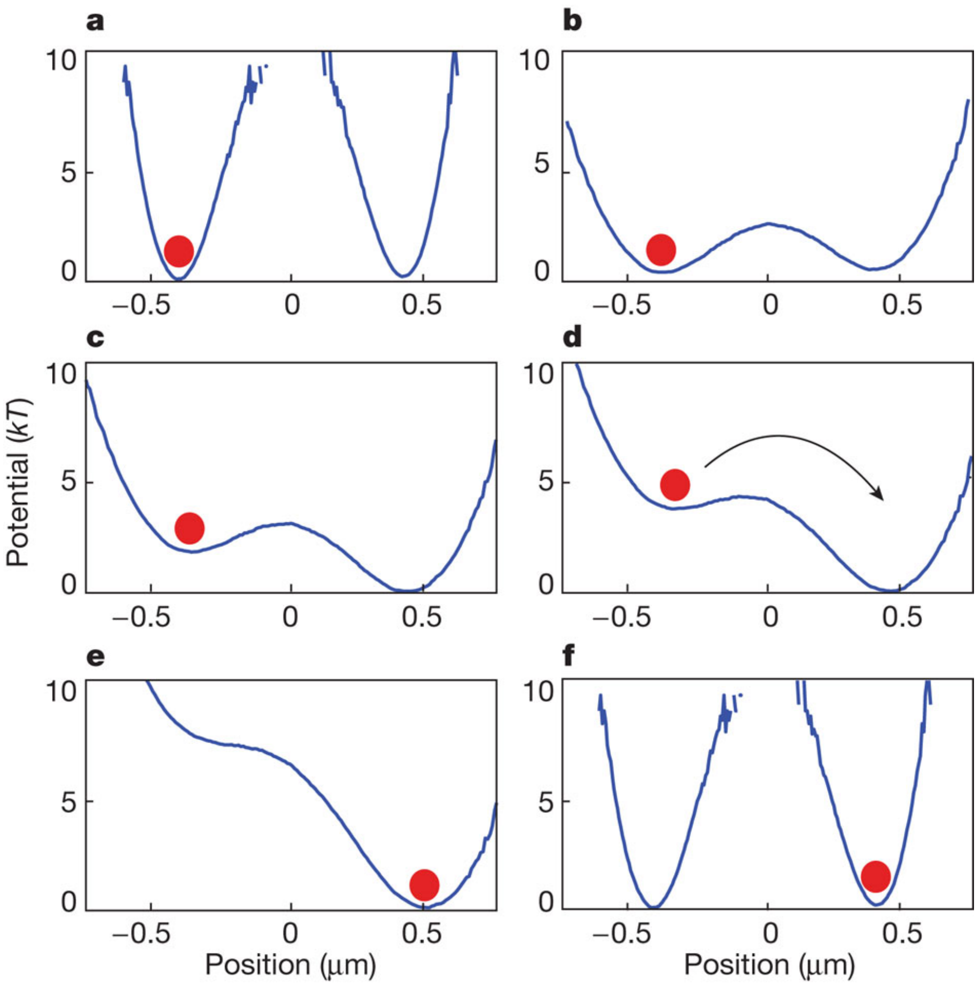
Crab computing



Resetting always requires dissipation!

Landauer's Principle

Erasing memory cost energy (1bit = $1K_bT$ of entropy)



Berut *et al* Nature 483, 187–189 (2012)

Experimental verification!

Current devices 1000 times limit

Validity in quantum regime
active area of research!
(many papers in last 3 years)

Part I: Conclusions

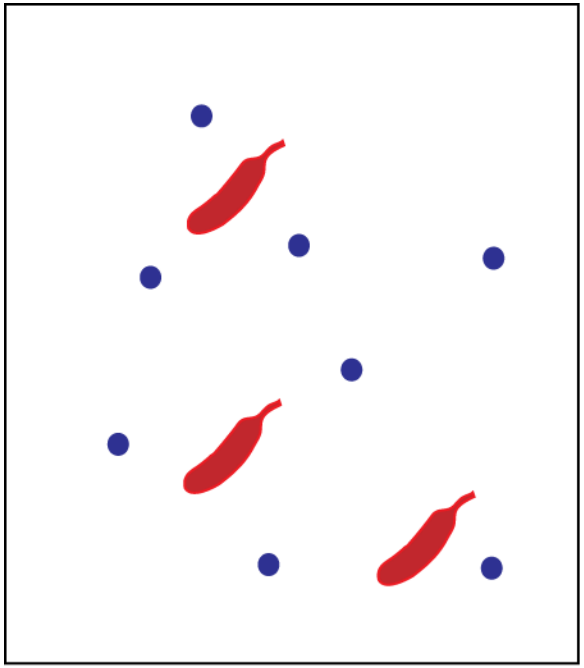
- Information is physical!

- Direct relationship between information and dissipation

- Erasing memory causes dissipation and entropy production in environment

- More info: see many reviews by Bennett, Landauer, and Feynman’s book

Part II: Thermodynamics of the simplest cellular computation

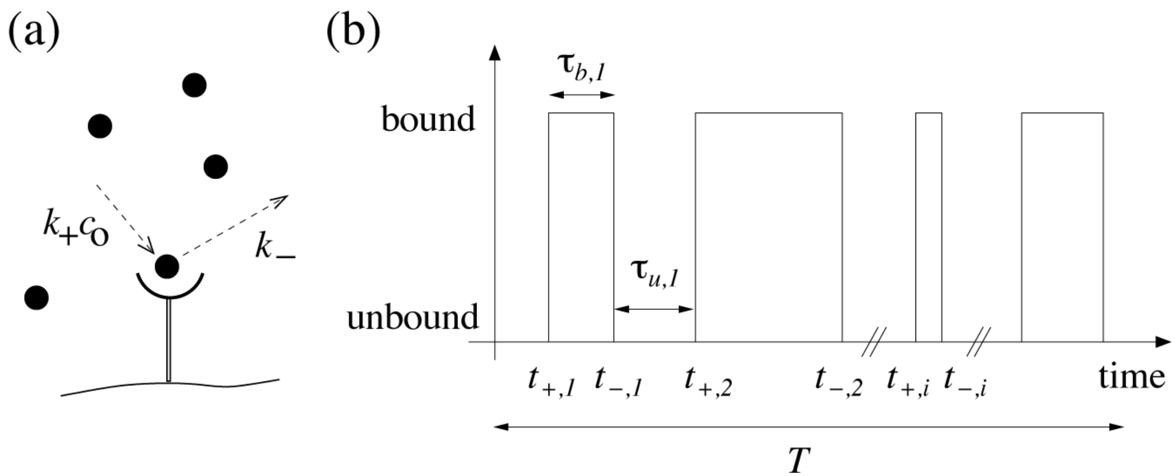


Compute (sense) concentration of external chemical or ligand

Sensing external concentrations

Classic paper: Berg and Purcell, Biophysics Journal (1977)

Endres and Wingreen PRL (2009)



Use receptor time series to estimate concentration of external ligand

Stochasticity leads to uncertainty!

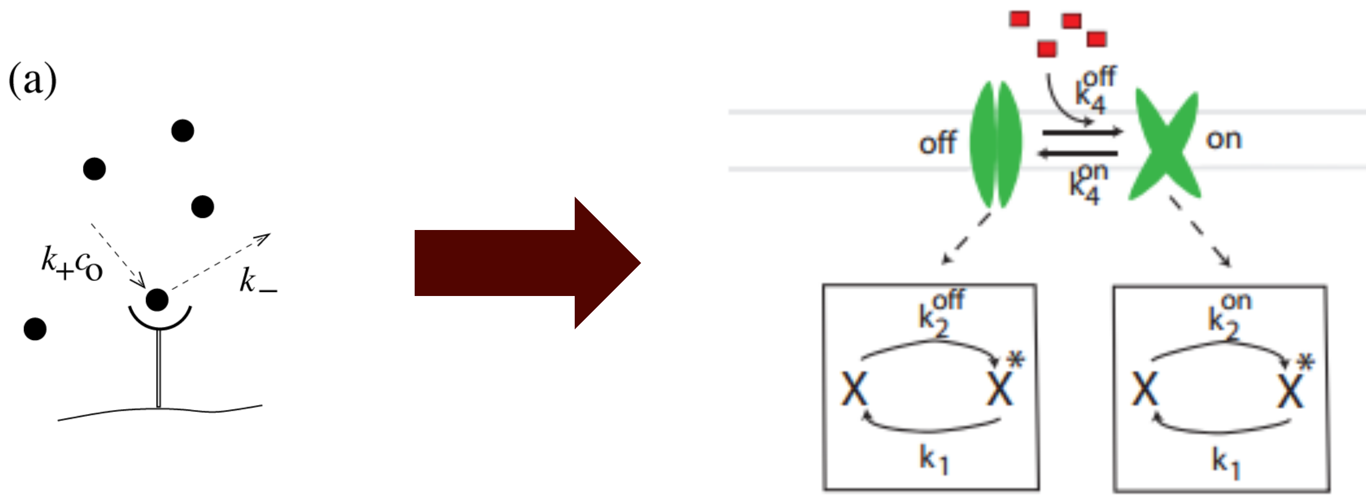
What computation should cell do? How much does it learn?

Recent work: Setayeshagar and Bialek PNAS (2005), Endres and Wingreen (2009), Mora Wingreen (2011)

Cellular information is physical

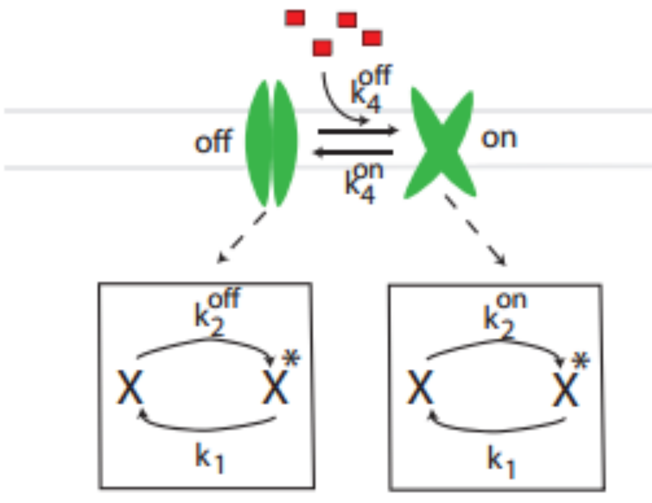
• To relate to thermodynamics must think about physical/biological implementation of calculation

• Can show Berg-Purcell calculation can be carried out by simple network shown below



See: Mehta Schwab (2012)

Cellular information is physical

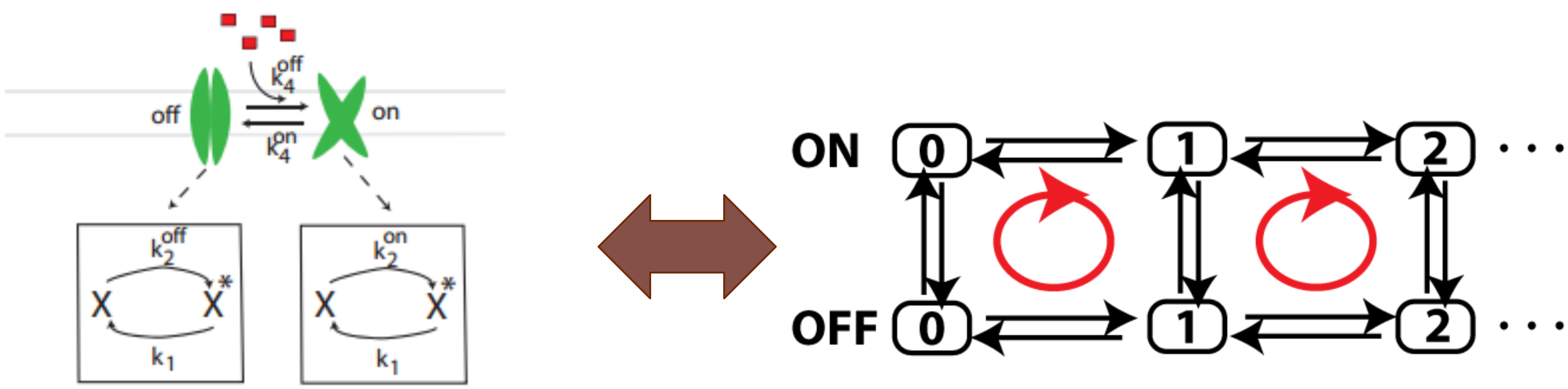


- Receptor exists in two states: an unbound "off" state and bound "on" state.
- Receptor modifies (i.e. phosphorylates) downstream protein from inactive form X to anactive form X* in a state-dependent manner
- X^* is read out of average receptor occupancy
- Process depends on kinetic parameters shown above

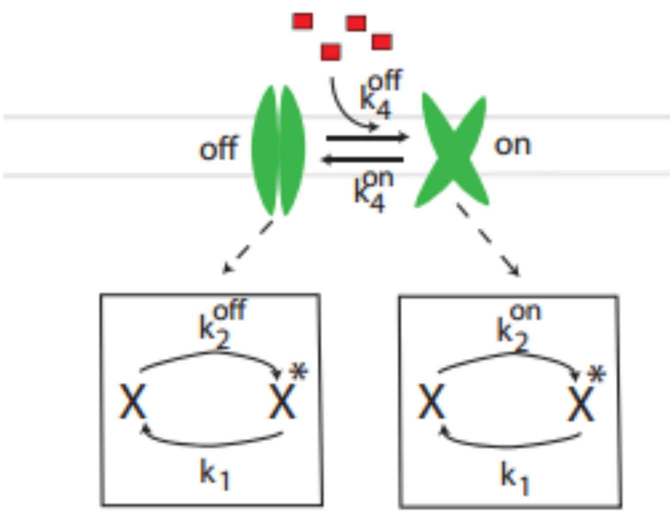
See: Mehta Schwab (2012)

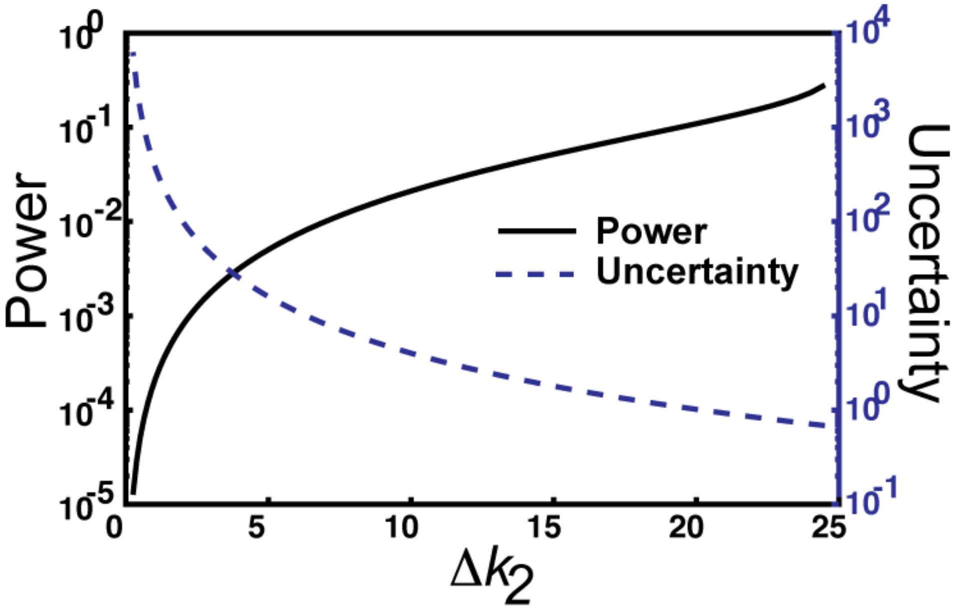
From information to thermodynamics

- Need to relate this circuits computation to thermodynamics
- Thermodynamics hidden in the relationship of the kinetic parameters
- Key insight: can think of circuit dynamics as non-equilibrium Markov process



Energy consumption versus uncertainty



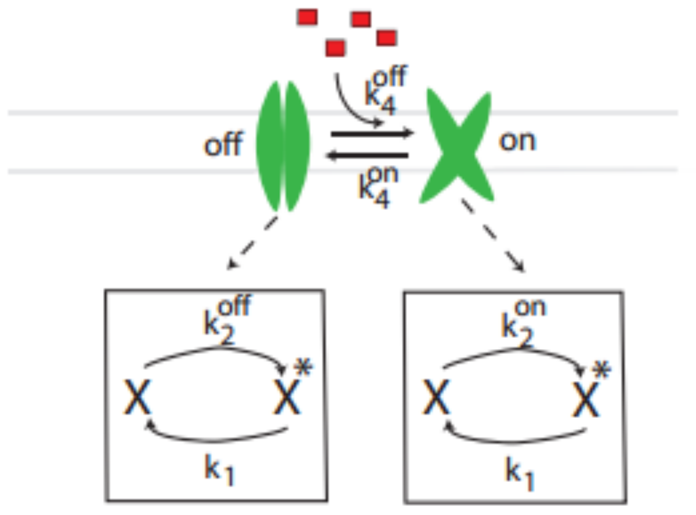


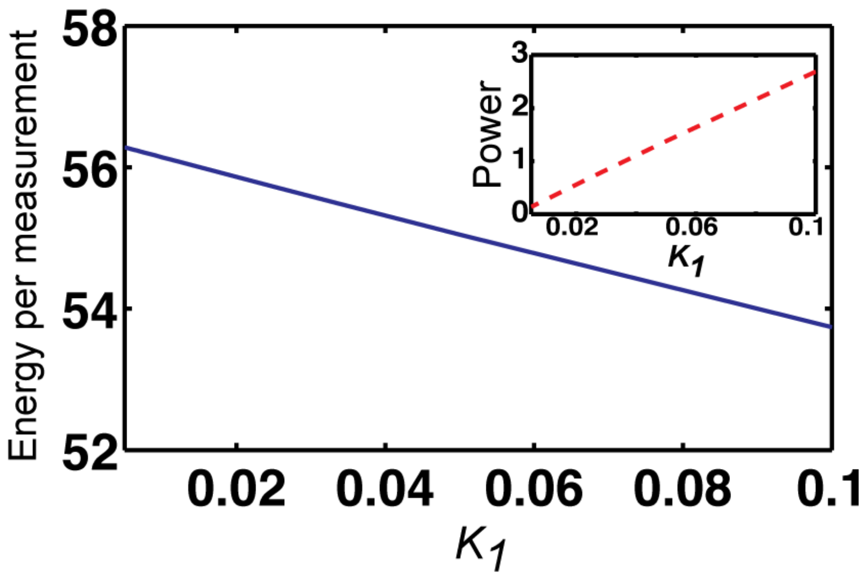
- Can show that detailed balanced implies infinite uncertainty

- Learning requires consumption of energy!!

- Biological manifestation of Landauer's principle!

"Erasing Memory" costs energy



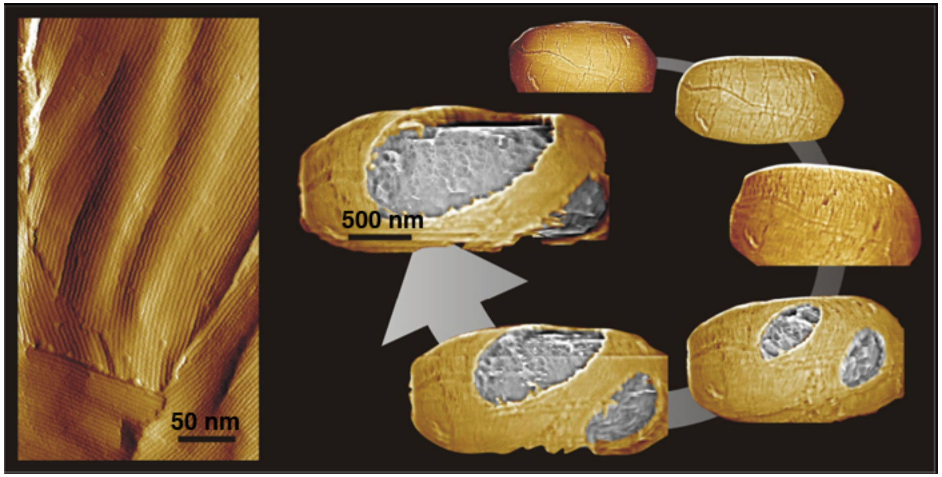


- Notice power consumption tends to zero as k_1 tends to zero
- This is the rate at which we erase memory stored in X^* (reversible computing limit)
- Total energy per measurement still goes up

Is this biologically important?

- This energy is a miniscule part of total energy consumed by cells.

- Still can imagine scenario where this is important: bacterial spore germination



Proc. Natl. Acad. Sci. 104: 9644-9649 (2007)

- Spores can be dormant for thousands of years- germinate in response to improved environment

- Experiments suggest work in “reversible” limit where a store of chemical be degraded

Part II: Conclusions

- Biological information is also physical!

- Showed Berg-Purcell task of computing external concentration could be implemented by a simple network

- Learning about the environment required consuming energy

- Energy consumption is small but may be relevant to extreme environments such as spore germination.

Part III: Landauer in the age of synthetic biology

R. Landauer

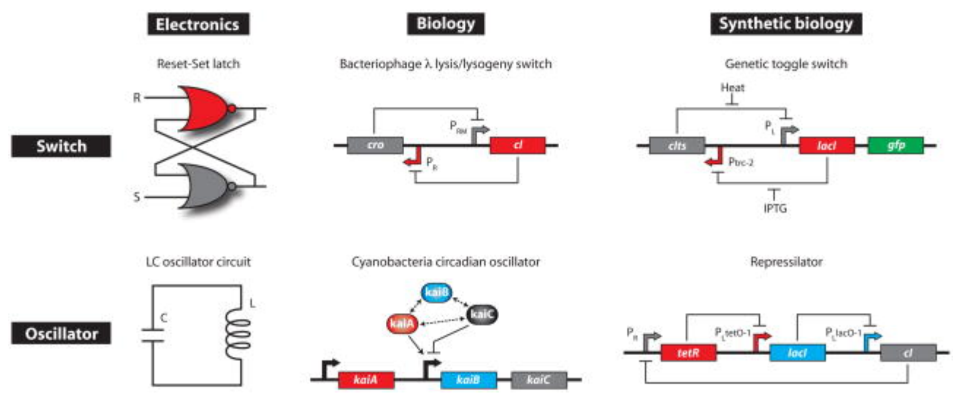
Irreversibility and Heat Generation in the Computing Process

Abstract: It is argued that computing machines inevitably involve devices which perform logical functions that do not have a single-valued inverse. This logical irreversibility is associated with physical irreversibility and requires a minimal heat generation, per machine cycle, typically of the order of kT for each irreversible function. This dissipation serves the purpose of standardizing signals and making them independent of their exact logical history. Two simple, but representative, models of bistable devices are subjected to a more detailed analysis of switching kinetics to yield the relationship between speed and energy dissipation, and to estimate the effects of errors induced by thermal fluctuations.

- Concerned with thermodynamic
- and kinetic constraints on memory devices

- Trade offs between energy consumption, reliability, and speed

IBM JOURNAL • JULY 1961



Khalil and Collins, Nat Rev Genet. 2010 May; 11(5): 367–379.

Landauer's memory classification

- Distinguished two kinds of memory in physical computers:

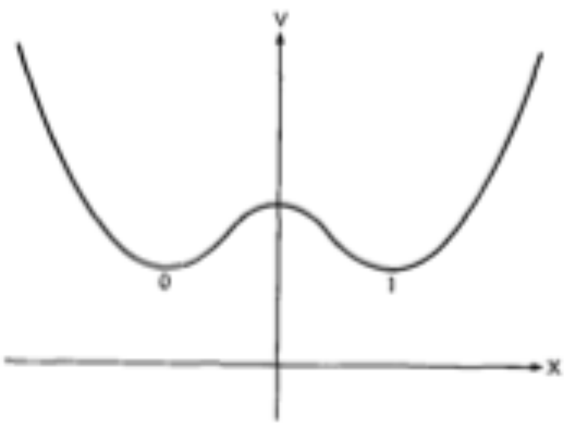


Figure 1 **Bistable potential well.**
x is a generalized coordinate representing quantity which is switched.

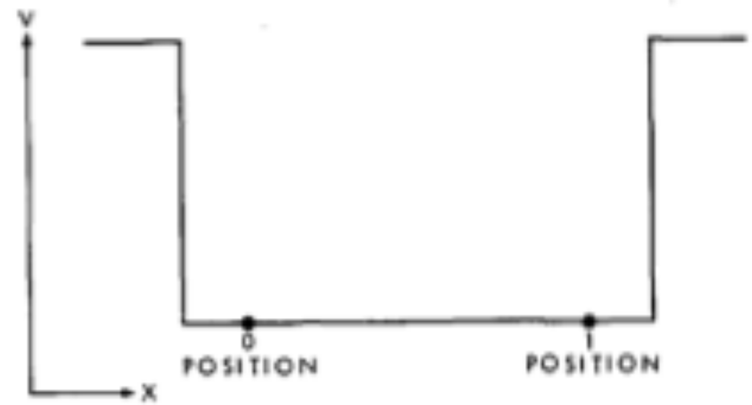


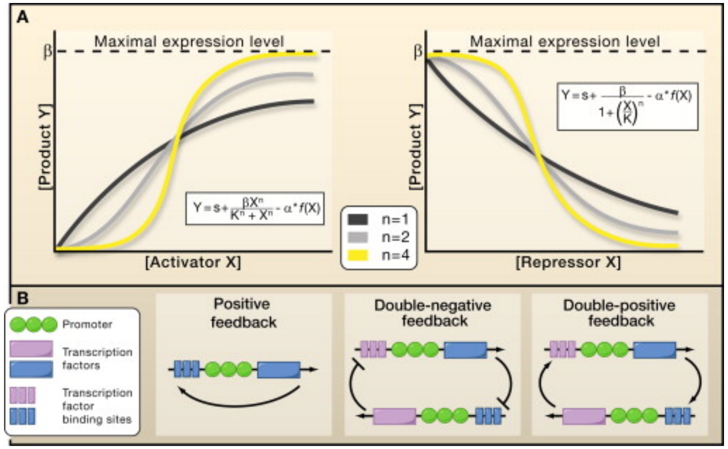
Figure 2 **Potential well in which ZERO and ONE state are not separated by barrier.**
Information is preserved because random motion is slow.

Barrier-based memories

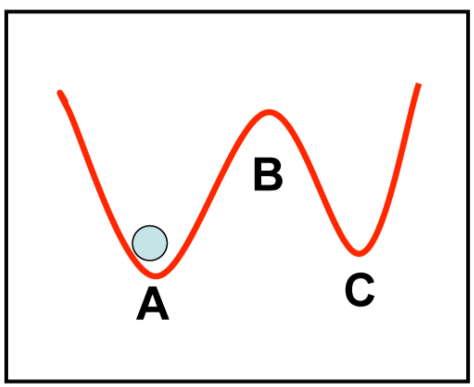
Kinetic memories

Landauer memory- synthetic biology version

Barrier-based memories



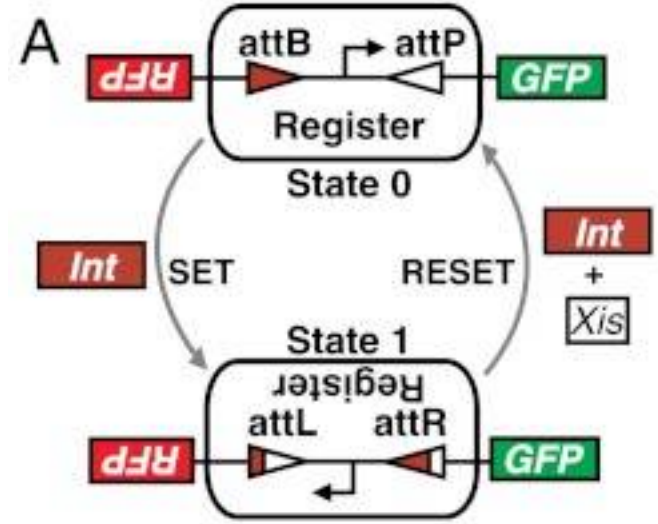
Burill et al *Cell* **140** 113 (2010)



Mehta et al Physical Biology 2007

Memory stored in # of proteins

Kinetic memories



Proc Natl Acad Sci U S A. 2012 June 5; 109(23): 8884-8889.

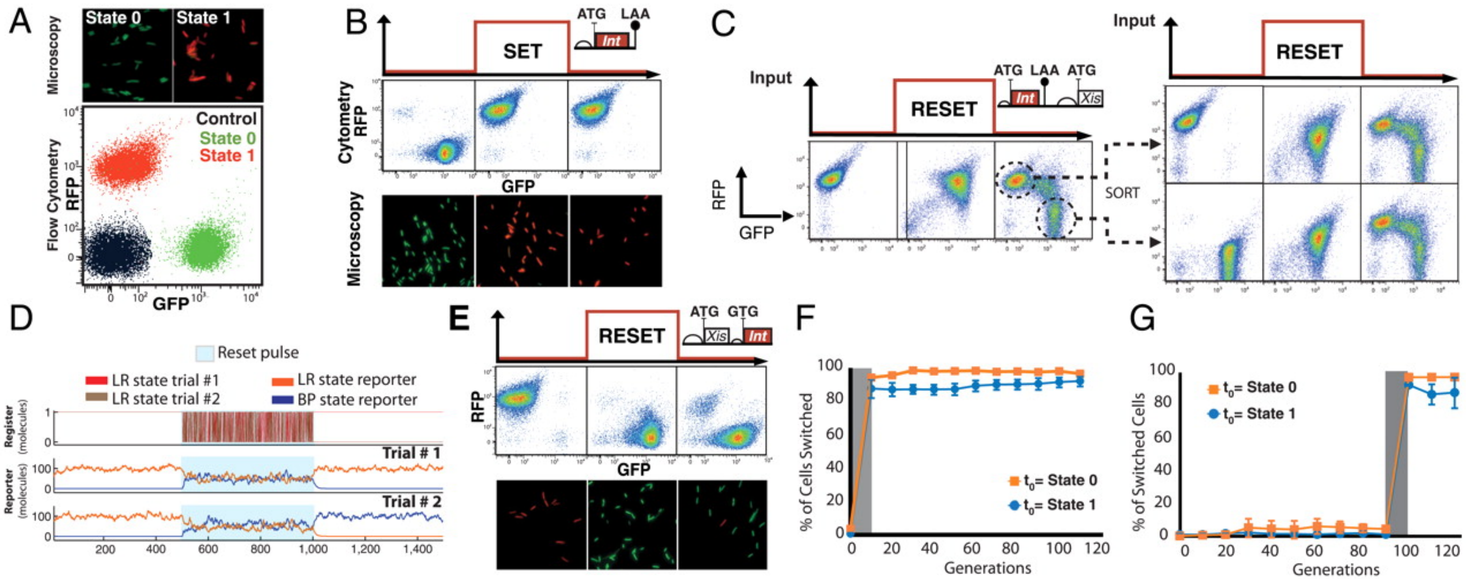
Endy Group

Memory stored in orientation of DNA strand

Resetting memory

Want to make memory that can be reset -> Landauer's principle says must break detailed balance and consume energy

Proc Natl Acad Sci U S A. 2012 June 5; 109(23): 8884-8889.



Resetting memory

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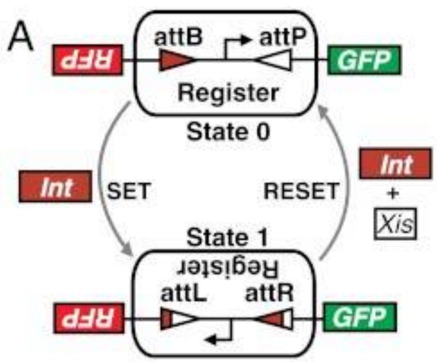
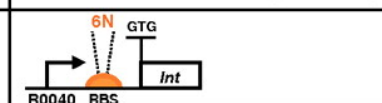
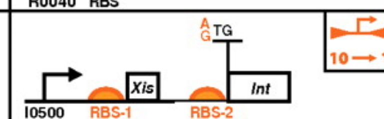
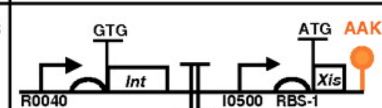
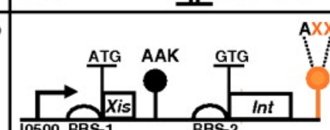


• Landauer outlines general thermodynamic tradeoffs between energy consumption, stability, and ability to reset!

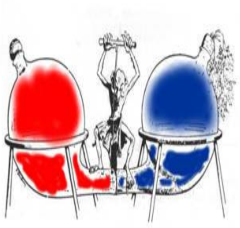
• Can interpret the circuit it terms of these basic principles Landauer outlined

Proc Natl Acad Sci U S A. 2012 June 5; 109(23): 8884-8889.

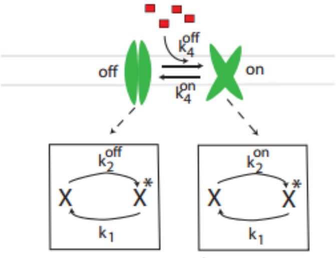
Device		Failure Mode	Engineering Solution		# constructs tested / Figure #
Set Generator		**"Spontaneous flipping":** Basal integrase expression above flipping threshold level.		Decrease Int translation.	~300 / 2B; S4
Reset Generator		**"Stoichiometry mismatch":** Low Xis to Int ratio leading to bidirectional DNA inversion.		Increase Xis translation. Decrease Int translation. Reduce register copy number.	~40 / 2C, 2D, 2E, S2, S3.
Set/Reset RAD	SET	**"Interference":** Spontaneous Xis basal expression corrupts directionality of the Set Integrase.		Increase Xis degradation.	5 / S5
Set/Reset RAD	RESET	**"Stoichiometry mismatch":** Levels of destabilized Xis are too low to reach the correct Xis:Int ratio. Also, following an otherwise successful reset pulse, "back flipping" can occur if Xis is degraded faster than Int.		Increase Int degradation.	~400 / 3B, 3C, S5, S11.

Conclusions

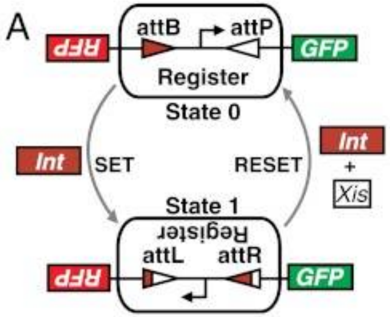
• Part I: Thinking about information physically highlights relationship between information and thermodynamics



• Part II: The simplest cellular computation



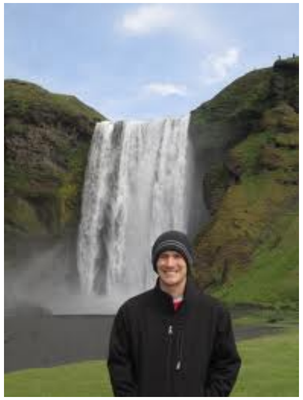
• Part III: Landauer's analysis also applicable to memory in synthetic biology



Acknowledgements

THE GROUP:

Charles Fisher



Alex Lang

JavadNoorbakhsh

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