Computing with stochastic systems.

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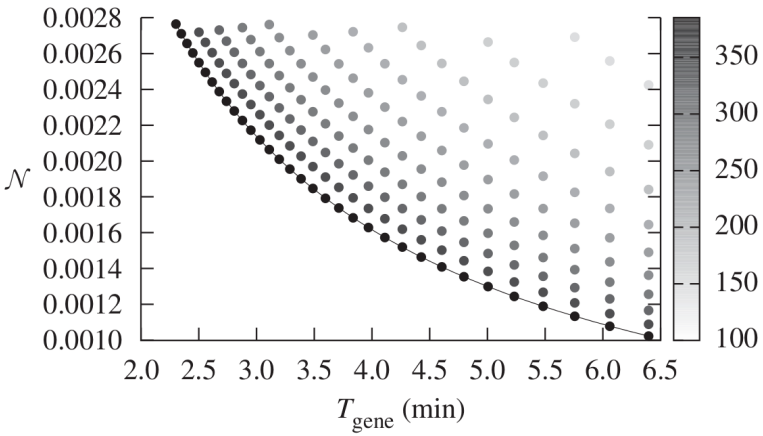
Outline

A word of warning before we start

- This talk is in large parts about how chemical and biochemical systems compute.
- These systems can be, in principle, used for universal computation.
- This is not the point here though.
- Relevant “algorithms” in biological systems are often simple, sometimes very sophisticated (Immune systems).
- The theme of this talk will be how much energy is necessary to perform a computation and how fast they can compute.
- I am not interested in:
  - Computational complexity
  - Pointer arithmetic
  - How to implement a database in biochemistry
  - etc...

Computing and cost

There is a general (?) trade-off in biochemical computers between the accuracy, the time taken for the computation and the energy usage/energy cost/dissipation rate.

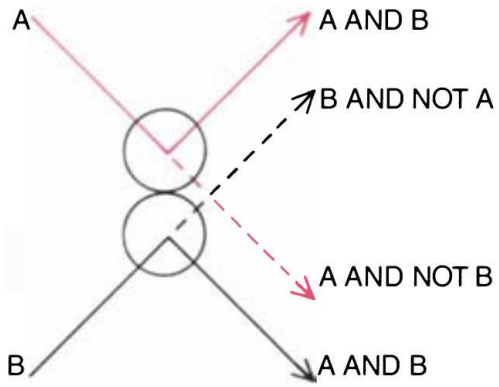


Where does the cost come from? Landauer Limit (informally)

- Information (as in information theory) is (almost) the same as (Shannon) entropy (as used in statistical mechanics).
- Closed systems maximise entropy.
- In order to lower entropy it is necessary to use work.
- Erasing bits (i.e. resetting memory) is destruction of information.
- In order to overwrite 1 bit of information, the minimal work is $W = k_B T \ln(2)$.

Otherwise...

- Otherwise there appears to be no minimal amount of work required to compute.
- Reversible computers (Fredkin gates)
- Billard ball computers

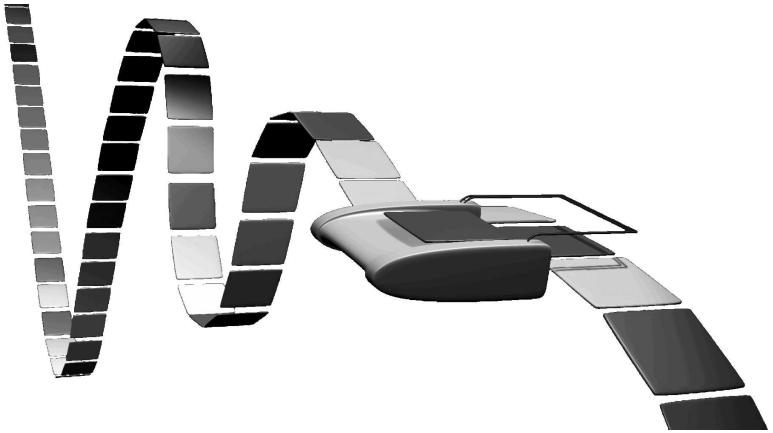


Taken from: Bennett and Landauer, Fundamental Limits on Computation, Scientific American, 1985

Turing machine

A standard model in computer science is the idea of a Turing machine. It is believed that for every *computable function* function there is a Turing machine that computes it.

- An input tape
- A reading head.
  - Is always in a particular state.
  - Reads a symbol from the input tape
  - Moves to the left or right depending on the internal state and the input it received.
  - Writes to the tape.
- When it is in the state `H` then it halts and the computation is finished.



Taken from: https://commons.wikimedia.org/w/index.php?curid=1505152

Turing machine II

- An important feature of the TM is that it can deterministically move from some location to the left or to the right.
- What is needed so that the the TM can do this?
- A battery!
- Directed motion is not possible without some sort of energy input.
- Yet, there is no minimal size of battery to drive the reading head.
- However: Absolute determinism would come at a cost of infinite entropy production.
- (Writing to tape is an additional cost of the machine.)

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Formal systems

Inference rules

$$\begin{aligned} \spadesuit\S &\mapsto \nabla \\ \nabla &\mapsto \spadesuit\sharp \\ \bigstar\square &\mapsto \lozenge\flat \\ \sharp\flat &\mapsto \S\bigstar \end{aligned}$$

Formal systems

Inference rules

$$\begin{array}{ccc} \spadesuit\S & \mapsto & \nabla \\ \nabla & \mapsto & \spadesuit\sharp \\ \bigstar\square & \mapsto & \Diamond\flat \\ \sharp\flat & \mapsto & \S\bigstar \end{array}$$

Theorems

$$\spadesuit\S\nabla\nabla\nabla\sharp\flat\cdots$$
$$\nabla\nabla\nabla\nabla\sharp\flat\cdots$$
$$\nabla\nabla\nabla\nabla\S\bigstar\cdots$$
$$\spadesuit\sharp\nabla\nabla\nabla\S\bigstar\cdots$$
$$\cdots$$

Formal systems

Formally this is similar to enzymatic reactions.

$$E + A \rightharpoonup C \rightharpoonup E + B$$

Only that the reactions should be reversible.

$$E + A \rightleftharpoons C \rightleftharpoons E + B$$

- When we specify the rules of the formal system, we do not need to worry about physical realism.
- If we want to implement this in matter, then we do need to worry about this.

Formal systems

Only that the reactions should be reversible.

$$E + A \rightleftharpoons C \rightleftharpoons E + B$$

- If we are in equilibrium, then there would be fixed mean abundances of E, A, C, B plus some stochastic fluctuations.
- Or: The system would constantly and **without direction** flip back and forth between EA, C and EB.
- Computation is not possible in equilibrium.
- if we are out of equilibrium, we have to expend energy to drive the system.
- The hypothesis is: The more energy we spend the more reliable the system is driven to a particular (output) state.

Entropy production of biochemical reactions

Assume the following system

$$\mathrm{A} \underset{k^-}{\overset{k^+}{\rightleftharpoons}} \mathrm{B}$$

Whenever the forward reaction happens, then the heat dissipated to the environment is given by

$$\Delta s \sim \ln\left(\frac{k^+}{k^-}\right)$$

This formula tells us two things:

1. The more biased a reaction, the higher the heat dissipation
2. Unidirectional reactions cannot exist!
3. This also relates to the Turing machine.
4. Based on this deterministic computation cannot exist.

Microscopic computing

- Does this means that microscopic computing has to be non-deterministic?
- There is a trade-off between accuracy and speed.
- Example: In biological computers this trade-off appears everywhere.
- This now begs the questions:
  - How can electronic computers achieve determinism at finite energy expense?
  - How can the brain compute deterministically?

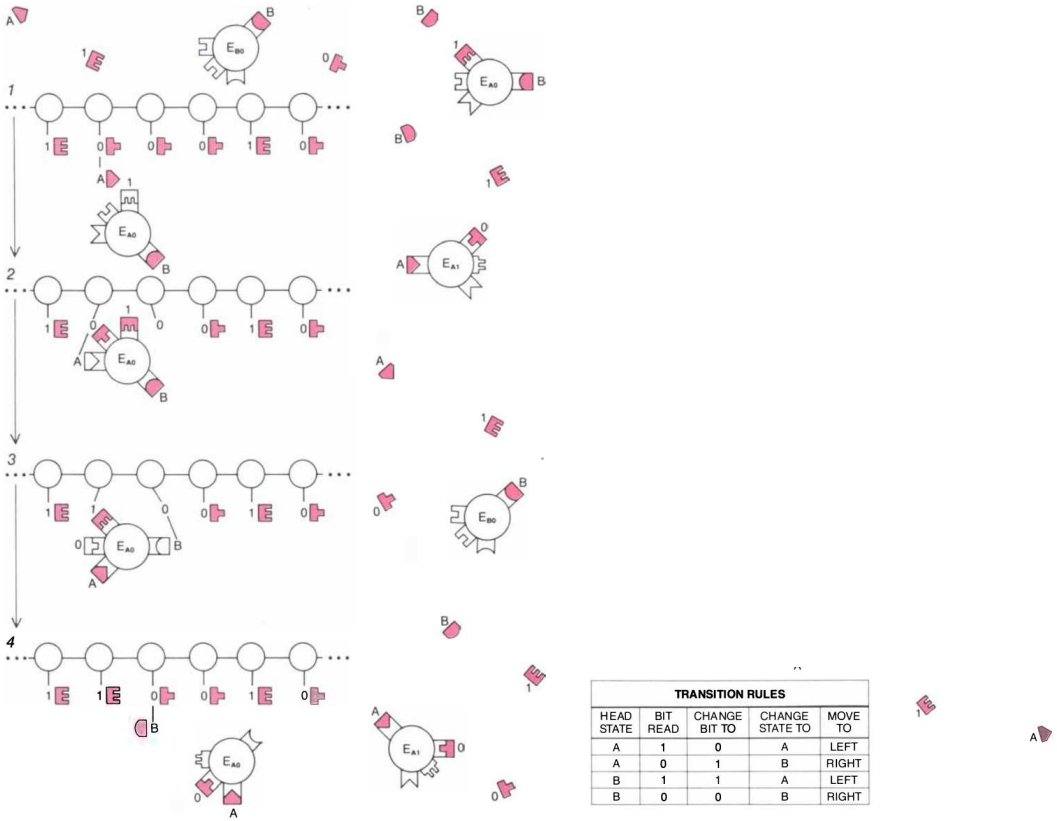
The basic insight so far

Deterministic computation comes at a cost in energy.

Brownian computers

Bennett's *Brownian computers*[1]

- Exploit thermal noise in order to perform a computation
- Energy input is necessary in order to drive them at a finite speed.
- Examples: DNA copying, transcription, translation . . .



TRANSITION RULES

HEAD STATE	BIT READ	CHANGE BIT TO	CHANGE STATE TO	MOVE TO
A	1	0	A	LEFT
A	0	1	B	RIGHT
B	1	1	A	LEFT
B	0	0	B	RIGHT

[1] C. Bennett (1982). "The thermodynamics of computation. A review". In: *International Journal of Theoretical Physics* 21.12, pp. 905–940.

Sensing as an example of biological computing

- One important example of biological computation is **sensing**.
- Cells need to gather and process information about their environment so as to adapt internal conditions.
- Examples are:
  - Concentration detectors for external nutrient molecules (cell infers concentration of molecules)
  - Gradient sensing during chemotaxis (cell infers direction of a gradient)
  - Quorum sensing (cell infers density of cells in environment)

Biological sensing and its limits

Sensing (of internal or external molecular concentrations) has become a paradigm case for biological computation.

- Berg-Purcell[2] limit.

$$\frac{\delta c}{c} = \sqrt{\frac{1}{Dac\tau_{\text{int}}}}$$

- This result has proved rather general and was later refined by Bialek[3] and Kaizu[4].
- Govern and co-workers[5] connected this to resource limitations (e.g. time, molecular copy numbers, energy).
- Kinetic proofreading: Recognition of cognate vs non-cognate ligands can be improved beyond free energy difference by adding dissipative pathways[6]
- Adaptation during chemotaxis requires constant energy input in order to sustain efficient computation[7].

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[2] H. C. Berg and E. M. Purcell (1977). "Physics of chemoreception." eng. In: *Biophys J* 20.2, pp. 193–219.

[3] W. Bialek and S. Setayeshgar (2005). "Physical limits to biochemical signaling." In: *Proceedings of the National Academy of Science USA* 102.29, pp. 10040–10045.

[4] Kazunari Kaizu et al. (2014). "The Berg-Purcell limit revisited." eng. In: *Biophysical Journal* 106.4, pp. 976–985.

[5] C. Govern and P. ten Wolde (2014). "Optimal resource allocation in cellular sensing systems." eng. In: *Proceedings of the National Academy of Science USA* 111.49, pp. 17486–17491.

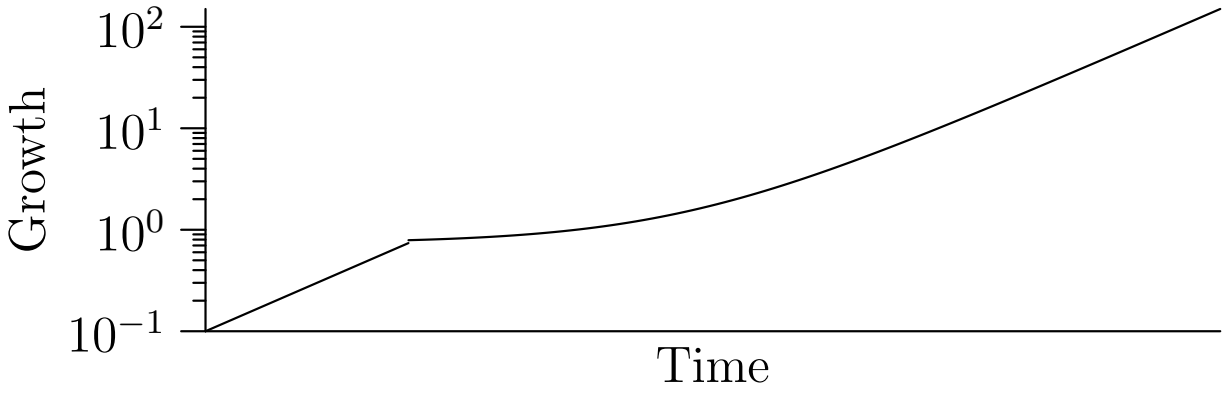
[6] J. Ninio (1975). "Kinetic amplification of enzyme discrimination." eng. In: *Biochimie* 57.5, pp. 587–595.

[7] G. Lan et al. (2012). "The energy-speed-accuracy trade-off in sensory adaptation". In: *Nature physics* 8.5, pp. 422–428.

A biological example

Diauxic growth aka “glucose effect”

Diauxic growth is the phenomenon whereby a population of microbes, when presented with two carbon sources (e.g. glucose and lactose), exhibits bi-phasic exponential growth intermitted by a *lag phase* of minimal growth.



- The lag-phase is usually interpreted as a collective growth arrest.
- The evolutionary rationale of the lag phase is unclear! Perhaps related to “computational” cost of switching between two nutrient sources.

Diauxic growth

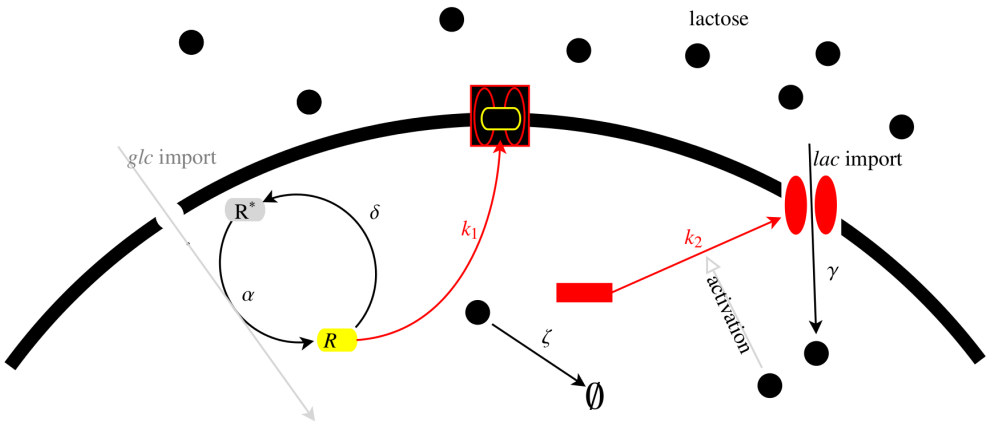
- The effect is well known going back to Monod
- It is traditionally interpreted as an adaptation to maximise growth in multi-nutrient environments.
- Recent experimental work[8] has provided new insights:
  - During lag-phase the population is heterogeneous.
  - The lag-phase seems to be under evolutionary control and can be manipulated experimentally.
  - Cells start to switch to the secondary nutrient before the primary nutrient is exhausted.
  - The earlier they switch, the shorter the lag-phase.
  - Faster switching between nutrients means slower growth (at all times).

[8] J. Wang et al. (2015). "Natural variation in preparation for nutrient depletion reveals a cost-benefit tradeoff." eng. In: *PLoS Biology* 13.1, e1002041; O. Venturelli et al. (2015). "Population diversification in a yeast metabolic program promotes anticipation of environmental shifts." eng. In: *PLoS Biology* 13.1, e1002042.

Preemptying the results

- We will later show that all these qualitative effects can be reproduced with a minimal mathematical model.
- Diauxic growth is in essence a sensing problem.
- The lag-phase can be understood as a consequence of inefficient sensing.
- Efficient sensing ($\approx$ accurate computation) comes at a cost in energy and reduces growth **at all times**.
- Switching fast between nutrient sources is only possible at a high energy expense.

A mathematical model to show the connection between leak-rate/sensing and cost.



- Glucose (glc) is the primary nutrient, taken up via specialised porins.
- Lactose (lac) is the secondary nutrient, taken up via specialised porins.
- Uptake of glc coincides with de-phosphorylation (chemical modification) of R.
- R (but not R^*) blocks porins for lactose.
- Lactose once in the cell activates expression of porin for lactose.

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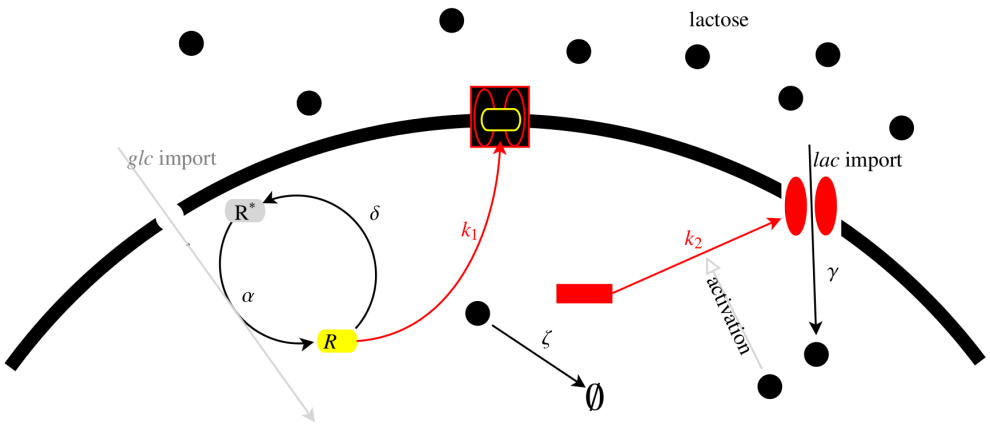
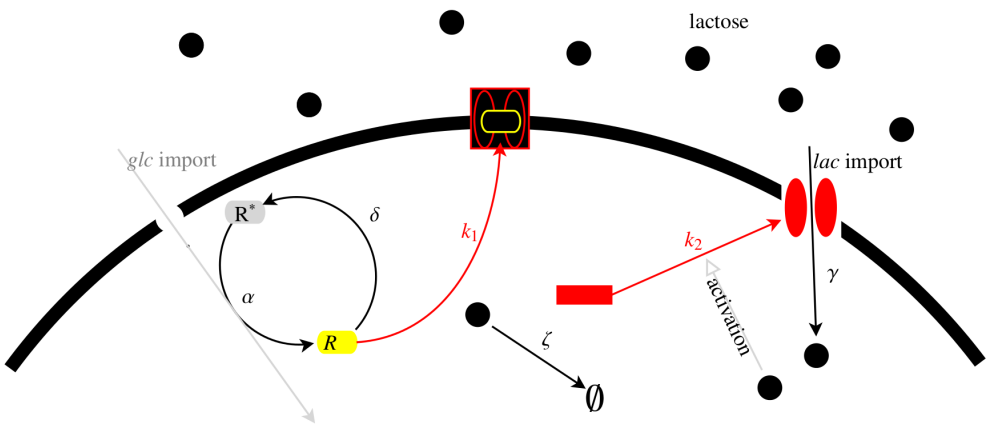


- Abundance of R indicates external concentration of glc.
- When the concentration is 0 (or very low) the cell needs to switch from glc to lac metabolism.
- The system needs to sense R.
- The sensor is the autoactivation of lac-permeases.
- The **leak expression** is the sampling frequency of the sensor.

A mathematical model to show the connection between leak-rate/sensing and cost.



$$
\begin{aligned}
\dot{P}_{R,n,l} \quad = \quad & k_1^0(R+1)(n+1)P_{R,n,l} + k_2 P_{R,n-1,l} - (k_1^0 Rn + k_2)P_{R,n,l} + \\
& \alpha(P_{R-1,n,l} - P_{R,n,l}) + \delta((R+1)P_{R+1,n,l} - RP_{R,n,l}) \\
& \gamma n P_{R,n,l-1} + \zeta(l+1)P_{R,n,l+1} - (\gamma n + \zeta l)P_{R,n,l}
\end{aligned}
$$

After a number of simplifications and approximations...

..this can be reduced to a birth-death process.

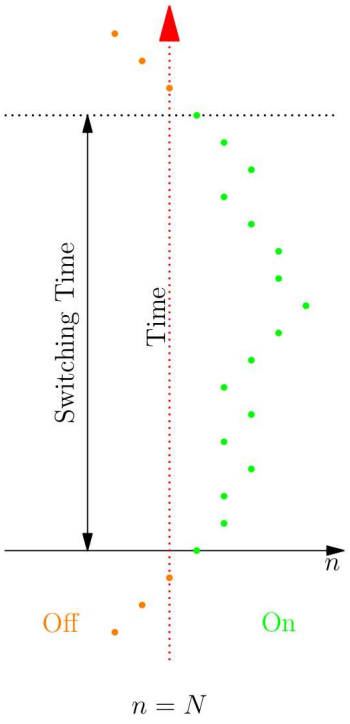
$$\dot{P}(n,t) = k_1^0 R(n+1)P(n+1,t) + k_2 P(n-1,t) - (Rnk_1^0 + k_2)P(n,t)$$

n ... the number of (*lac*) permeases
R ... the number of repressors (a proxy for the glucose uptake rate)
k_1^0 ... rate constant of R binding to lac permeases
k_2 ... the leak rate. It represents the sampling rate of the binary sensor.

What we are interested in

1. What is the probability that the lac metabolism is switched on, given a certain concentration of glc?
2. How long does it take for the system to switch on (or off), once the glc concentration has changed?

Mean-time to switch



- We assume that the system is on, when a threshold number of N permeases are expressed.
- We can now calculate the expected switching times from on to off and *vice versa*.

Computing the MFPT

We start by defining:

$$S(n_0, t) := \sum_{n=a}^{b} P(n, t|n_0, 0)$$

Here a is the **reflecting** boundary of the interval, b is absorbing.

$$T(n_0) = \langle T \rangle = \int_0^\infty S(n_0, t)dt$$

Summing over all n in the backwards master equation, we obtain an equation for S.

$$\frac{dS(n_0, t)}{dt} = \omega_+(n_0)[S(n_0+1, t)-S(n_0, t)]+\omega_-(n_0)[S(n_0-1, t)-S(n_0, t)]$$

We can now integrate over all t, to obtain a formula for the mean time to absorption:

$$-1 = \omega_+(n_0)[T(n_0 + 1) - T(n_0)] - \omega_-(n_0)[T(n_0) - T(n_0 - 1)]$$

Computing the MFPT

If we now introduce the helper function $U(n)$ defined by

$$U(n) := T(n) - T(n-1) \tag{1}$$

, then we obtain a recursive relationship for $U(n)$:

$$\omega_+(n)U(n+1) - \omega_-(n_0)U(n) = -1$$

For the boundary condition $a < b$ and a absorbing and b reflecting this leads to a general formula for any $U(n)$:

$$U(n) = \sum_{i=n}^{b} \psi(n,i) \qquad \text{, where} \quad \psi(n,i) := \frac{1}{\omega_-(i)} \left(\prod_{j=n}^{i-1} \frac{\omega_+(j)}{\omega_-(j)} \right)$$

Altogether, we then obtain the final formula for the mean first passage time at a:

$$T(n) = \sum_{y=a}^{n} \sum_{j=y}^{b} \left(\frac{1}{\omega_+(j)} \prod_{i=y}^{j} \frac{\omega_+(i)}{\omega_-(i)} \right)$$

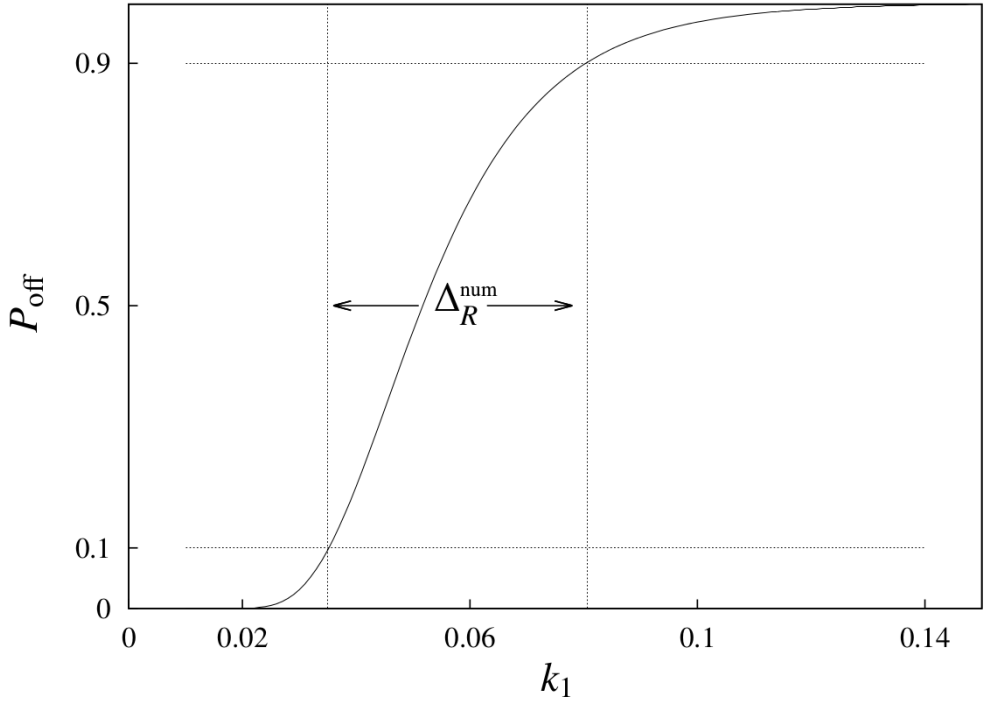
Calculating the switching probability

- Now we need to calculate the MFPT coming from above (same technique).
- Then insert the specific values for ω_+ and ω_- from our master equations.
- Match the two MFPT at the boundary.
- The MFPT now allow us to calculate the macroscopic rate of switching on and off as a function of R.
- From this we can calculate the probability of being switched off.

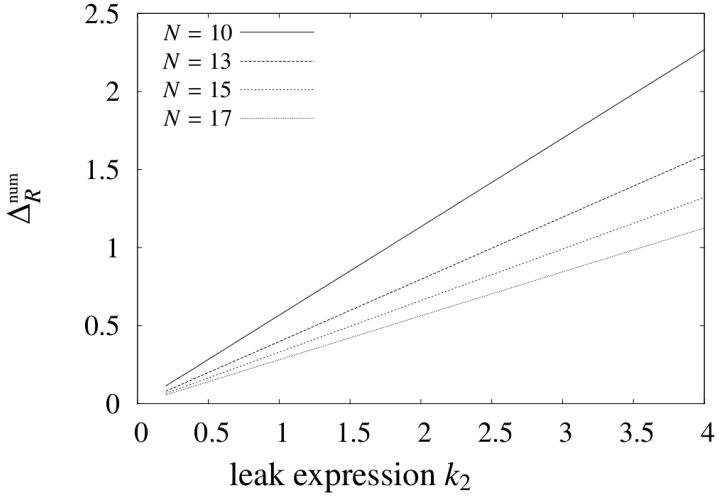
Digested results

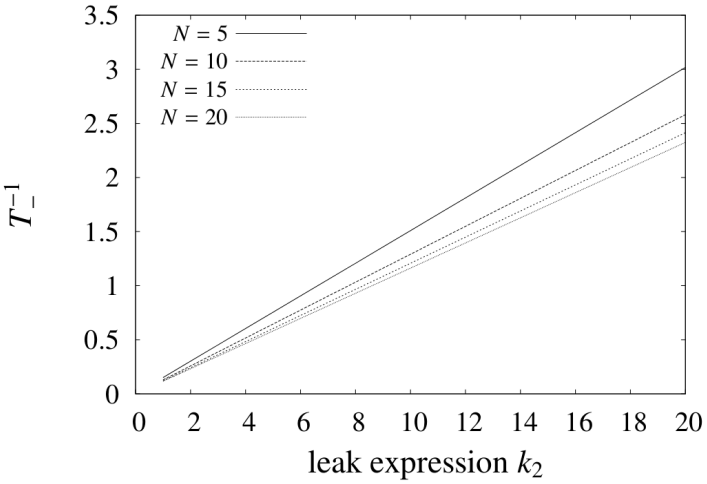
..using this, we can then calculate the probability of the system being switched on/off as a function of the number of R (the "glucose uptake rate").

$$P_{\text{off}} = \frac{\Gamma\left(N, \frac{k_2}{Rk_1^0}\right)}{\Gamma(N)}$$



Results





R: Indicator for uptake rate of primary nutrient.

Δ_R: Uncertainty about activation state/lag-phase/population heterogeneity.

k_2: Leak expression and hence metabolic cost of regulation.

Main insights

- The system cannot switch accurately **and** fast.
- $$R_{\mathrm{sw}} = \frac{k_2}{k_1^0} \cdot \frac{1}{N+1}$$

  A certain degree of premature switching to the secondary nutrient is therefore unavoidable and a direct consequence of the limitations of stochastic systems.
- Rapid switching to the secondary nutrient requires high leak expression and hence implies cost. This is the evolutionary driver for the lag-phase.
- Rapid switching means higher inaccuracy (ΔR).

Conclusions

We could predict a variety of known phenomena simply based on considerations of the cost of cellular computing.

- The lag-phase can be thought of as a consequence of the cost of computing.
- The parameter that controls this cost is the leak rate of the secondary permease.
- The leak rate acts as a sampling frequency for the sensor.
- Heterogeneity of population $\leftrightarrow$ uncertainty of state.
- Switching fast $\leftrightarrow$ start to switch early.
- Switching fast implies energetic cost.
- The minimal mathematical model predicts qualitatively experimental phenomena.
- Quantitative prediction requires more extensive models.

Outlook

- It seems to emerge that sensing is not just an example of a biological computer but of fundamental importance to any type of chemical computing.
- Sensing amounts to measuring the state of the environment and emerges as a dominant cost factor in microscopic computing.
- There are fundamental relations that show that accurate sensing is not possible at finite resource usage.
- More on this later....