Computing with stochastic systems.

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Outline

What to expect

How energy considerations apply to classical models of computing

Energy consumption of biochemical computers

Natural computation as a theory of biology
  Results

Conclusions and Outlook
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 $W = k_B T \ln(2)$. 

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

\[ \spadesuit \, \triangledown \quad \mapsto \quad \triangledown \]
\[ \triangledown \quad \mapsto \quad \spadesuit \, \# \]
\[ \star \, \Box \quad \mapsto \quad \diamond \, b \]
\[ \# \, b \quad \mapsto \quad \$ \, \star \]
Formal systems

Inference rules

\[
\begin{align*}
\spadesuit & \quad \rightarrow \quad \bigtriangledown \\
\bigtriangledown & \quad \rightarrow \quad \spadesuit \ # \\
\star \ & \quad \rightarrow \quad \diamond b \\
\# b & \quad \rightarrow \quad \spadesuit \star \\
\end{align*}
\]

Theorems

\[
\begin{align*}
\spadesuit \ & \quad \# b \quad \ldots \\
\bigtriangledown \ & \quad \# b \quad \ldots \\
\bigtriangledown \ & \quad \spadesuit \star \quad \ldots \\
\spadesuit \ # & \quad \bigtriangledown \ spadesuit \star \quad \ldots \\
\ldots & \quad \\
\end{align*}
\]
Formal systems

Formally this is similar to enzymatic reactions.

\[ E + A \rightarrow C \rightarrow E + B \]

Only that the reactions should be reversible.

\[ E + A \Leftrightarrow C \Leftrightarrow E + B \]

- 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.
Assume the following system

$$A \xleftrightarrow{k^+} B \xleftrightarrow{k^-}$$

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 mean 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 . . .

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.

\[
\frac{\delta c}{c} = \sqrt{\frac{1}{Da c \tau_{int}}}
\]

- 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\(^7\).


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).

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

- 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.

\[
\dot{P}_{R,n,l} = k_1^0 (R + 1)(n + 1)P_{R,n,l} + k_2 P_{R,n-1,l} - (k_1^0 Rn + k_2)P_{R,n,l} + \alpha(P_{R-1,n,l} - P_{R,n,l}) + \delta((R + 1)P_{R+1,n,l} - RP_{R,n,l}) + \gamma nP_{R,n,l-1} + \zeta(l + 1)P_{R,n,l+1} - (\gamma n + \zeta l)P_{R,n,l}
\]
After a number of simplifications and approximations...

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

\[
\dot{P}(n, t) = k_1^0 R(n + 1)P(n + 1, t) + k_2 P(n - 1, t) - (Rn k_1^0 + k_2)P(n, t)
\]

\[n\ldots\text{the number of (lac) permeases}\]
\[R\ldots\text{the number of repressors (a proxy for the glucose uptake rate)}\]
\[k_1^0\ldots\text{rate constant of } R\text{ binding to lac permeases}\]
\[k_2\ldots\text{the leak rate. It represents the sampling rate of the binary sensor.}\]
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 \textbf{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

$$U(n) := T(n) - T(n - 1)$$

(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 $U(n)$:

$$U(n) = \sum_{i=n}^{b} \psi(n, i)$$

, where

$$\psi(n, i) := \frac{1}{\omega_-(i)} \left( \prod_{j=n}^{i-1} \frac{\omega_+(j)}{\omega_-(j)} \right)$$

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 $\omega_+$ and $\omega_-$ 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”).

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

$R$: Indicator for uptake rate of primary nutrient.

$\Delta R$: 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.

\[ R_{sw} = \frac{k_2}{k_1^0} \cdot \frac{1}{N + 1} \]

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 ($\Delta R$).
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....