The lag-phase during diauxic growth as a consequence of the cost of computing.

Dominique Chu

School of Computing
University of Kent, UK
D.F.Chu@kent.ac.uk

2016 Annual Meeting of the Society for Mathematical Biology and European Conference for Mathematical and Theoretical Biology

Outline

Background
- Biological computers
- Diauxic growth

Results
- A computational simulation model
- Artificial evolution
- Diauxic growth as a birth-death process
- Results

Conclusions

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 . . .

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

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

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].

---

[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.

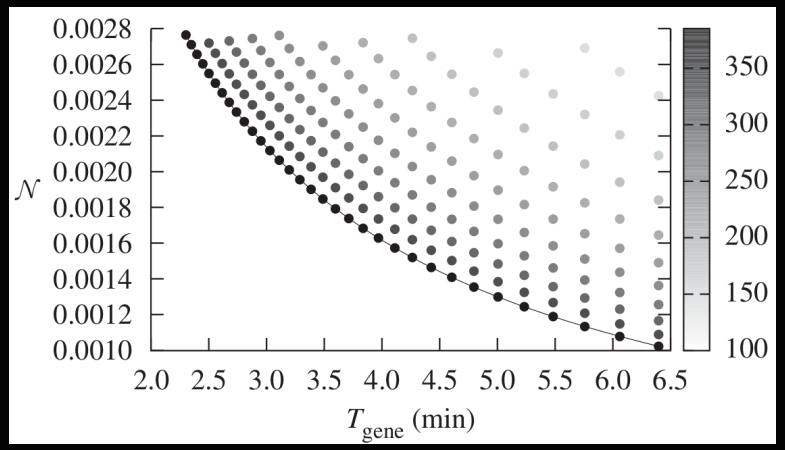
[7] G. Lan et al. (2012). "The energy-speed-accuracy trade-off in sensory adaptation". In: *Nature physics* 8.5, pp. 422–428.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

Minimal example: Binary computing in cells with noise

- A gene g can be either in state "on" or "off."
- Gene g is controlled by external input, which can itself be either "on" or "off."
- The output of g is then a processed form of the input (say a `NOT` gate).

Question: How fast can such a computer compute when gene regulation is noisy[8]?



It depends on the noise and energy input that one is willing to accept.

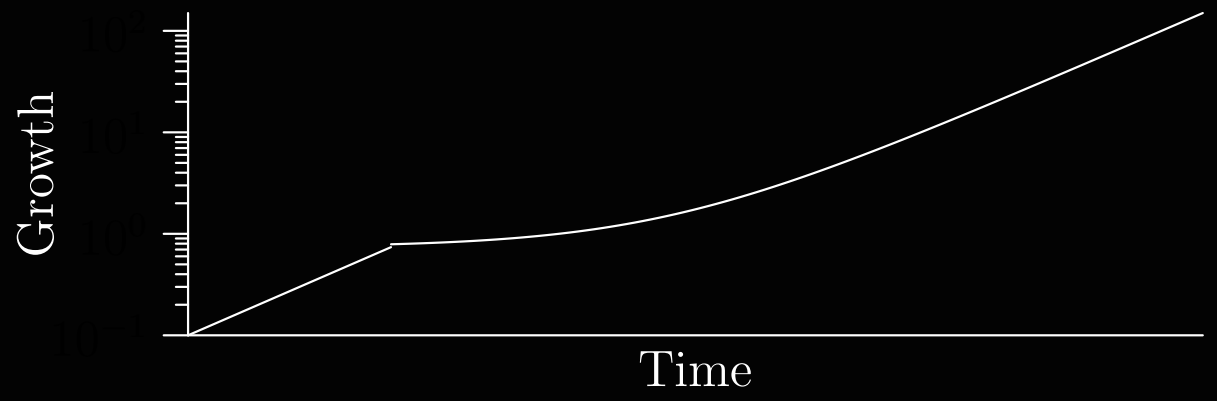
[8] N. Zabet and D. Chu (2010). "Computational limits to binary genes." eng. In: *Journal of the Royal Society Interface* 7.47, pp. 945–954.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

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.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

Diauxic growth

The effect is well known going back to Monod, but recent work[9] 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.
- (Yeast-)cells start to switch to the secondary nutrient before the primary nutrient is exhausted.
- The length of the lag-phase depends on when the cells start to switch not how long the switching takes.

[9] 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.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

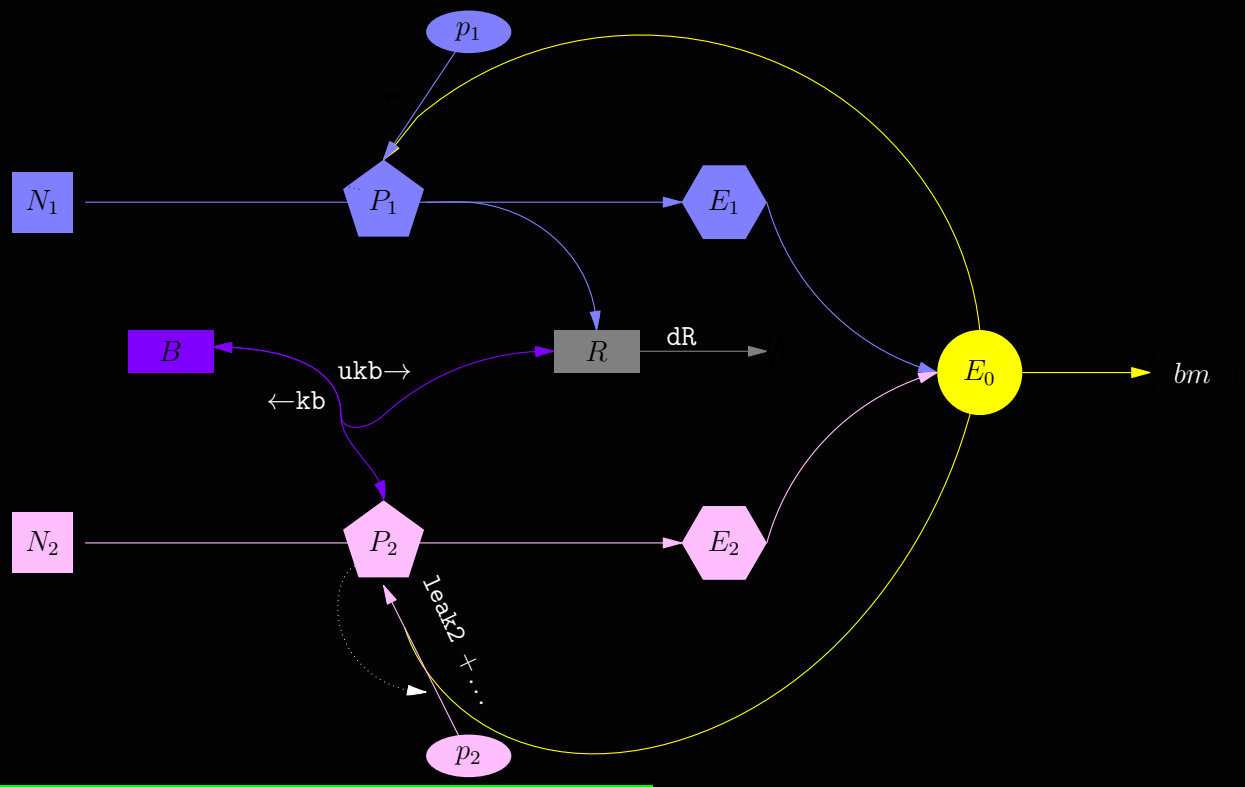
Preemptying the results

- We will later show that all these qualitative effects can be reproduced with a minimal mathematical model.
- The leak-expression rate of permease is important.
  - It is related to long-term growth prospects (the higher the leak, the lower the peak growth rate on any nutrient).
  - Higher leak rate improves sensing of secondary nutrient and shortens the lag-phase.
- There is a trade-off between the ability to switch rapidly and the ability to grow fast.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

A computational model of diauxic growth and the phosphotransferase system[10]

- Nutrient $N1$ and $N2$ have specialised permeases $P1$ and $P2$.
- Both are activated by their respective metabolite.
- Uptake of $N1$ represses uptake via $N2$
- $P1$ and $P2$ are expressed at a leak rate when not activated. This will turn out to be the driver of the evolution of the lag-phase.
- All synthesis has to be "paid" for (metabolic cost).



[10] D. Chu (2015). "In silico evolution of diauxic growth." eng. In: *BMC Evolutionary Biology* 15, p. 211.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

Simulation model

- *Agent-based* model simulating a population of cells that grow and divide if sufficient nutrient is available.
- For each cell we simulate the internal biochemistry using exact Gillespie-type stochastic simulation algorithms (SSA).
- Individual agents undergo mutation upon division and thus change.
- The model thus supports simulated evolution.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

The software[11] (an aside)

- Essentially it is an SSA with some added on meta-control.
- Birth and death of cells are “events”.
- When birth/death happens then:
  - Halt the simulation and record its state.
  - Add/remove a new set of reactions and new “species” corresponding to the internal chemical of the cell to be removed/born.
  - A mutation is a slight change of the reaction rate constants.
  - After birth, initialise new variables, corresponding to resource sharing between parent and offspring.
  - Re-start simulation.
- The agent-based paradigm supports heterogeneity of rates between cells and supports implicit evolution.
- Model supports its own specification language to specify individual agents. **very easy to use!!**
- Model also supports parallel computing (on multi-core machines and clusters).

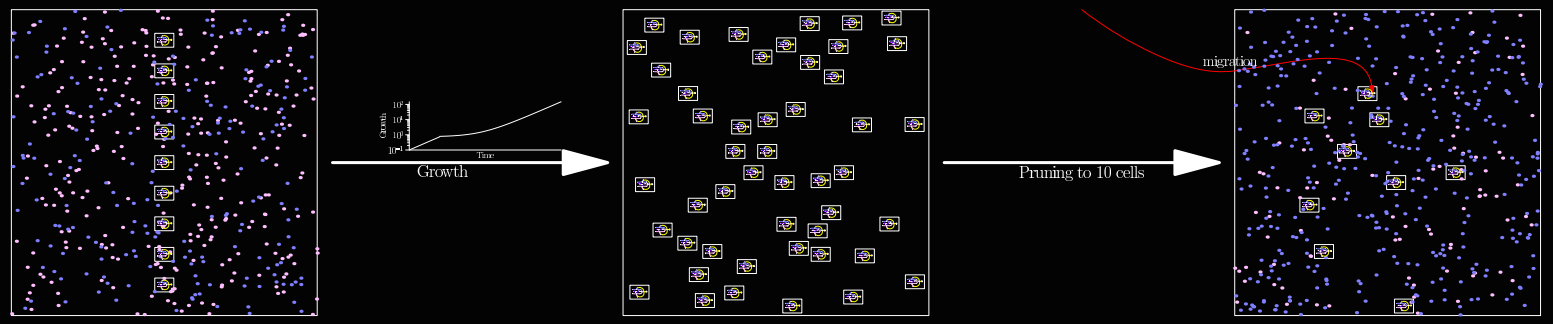
Software is written in Java and available on request.

[11] Dominique Chu and David J. Barnes (2016). “The lag-phase during diauxic growth is a trade-off between fast adaptation and high growth rate.” eng. In: *Scientific Reports* 6, p. 25191.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

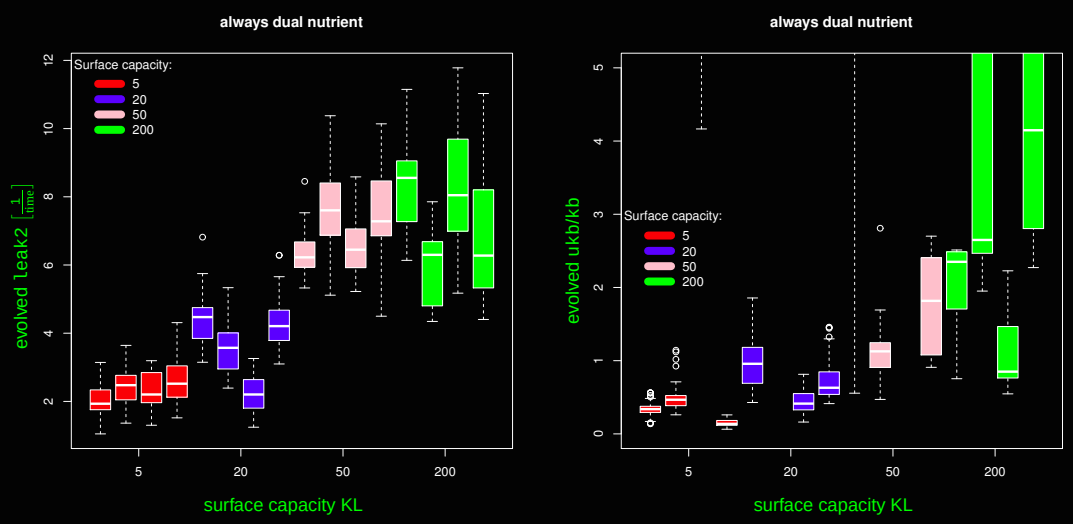
Implicit Evolution

- Start with 1 cell and a mix of $N1$ and $N2$.
- Grow a population (with mutation).
- When all nutrient exhausted, select a small number of random cells as seeds for the next population.

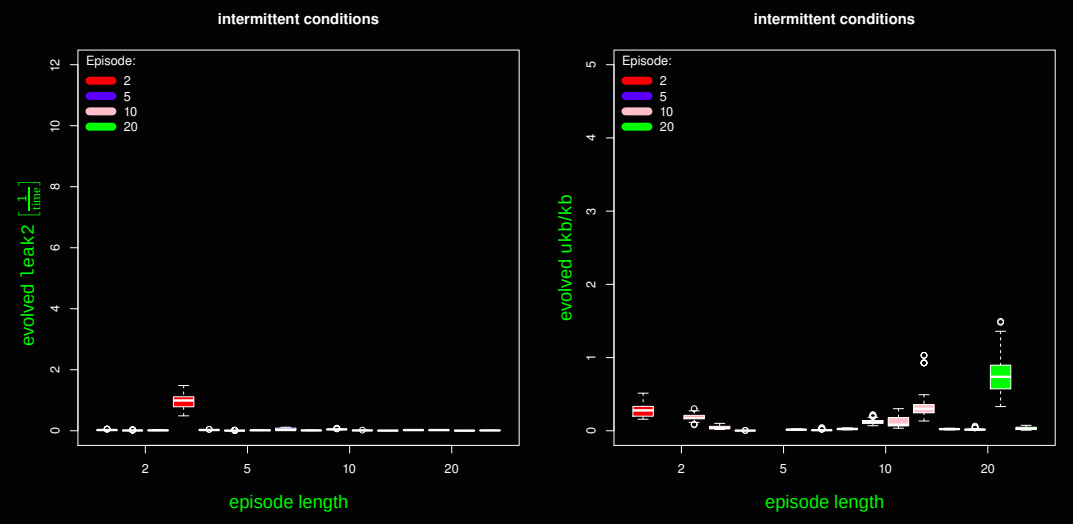


Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

(*i*) Evolution leads to a lag-phase



(a) (b)

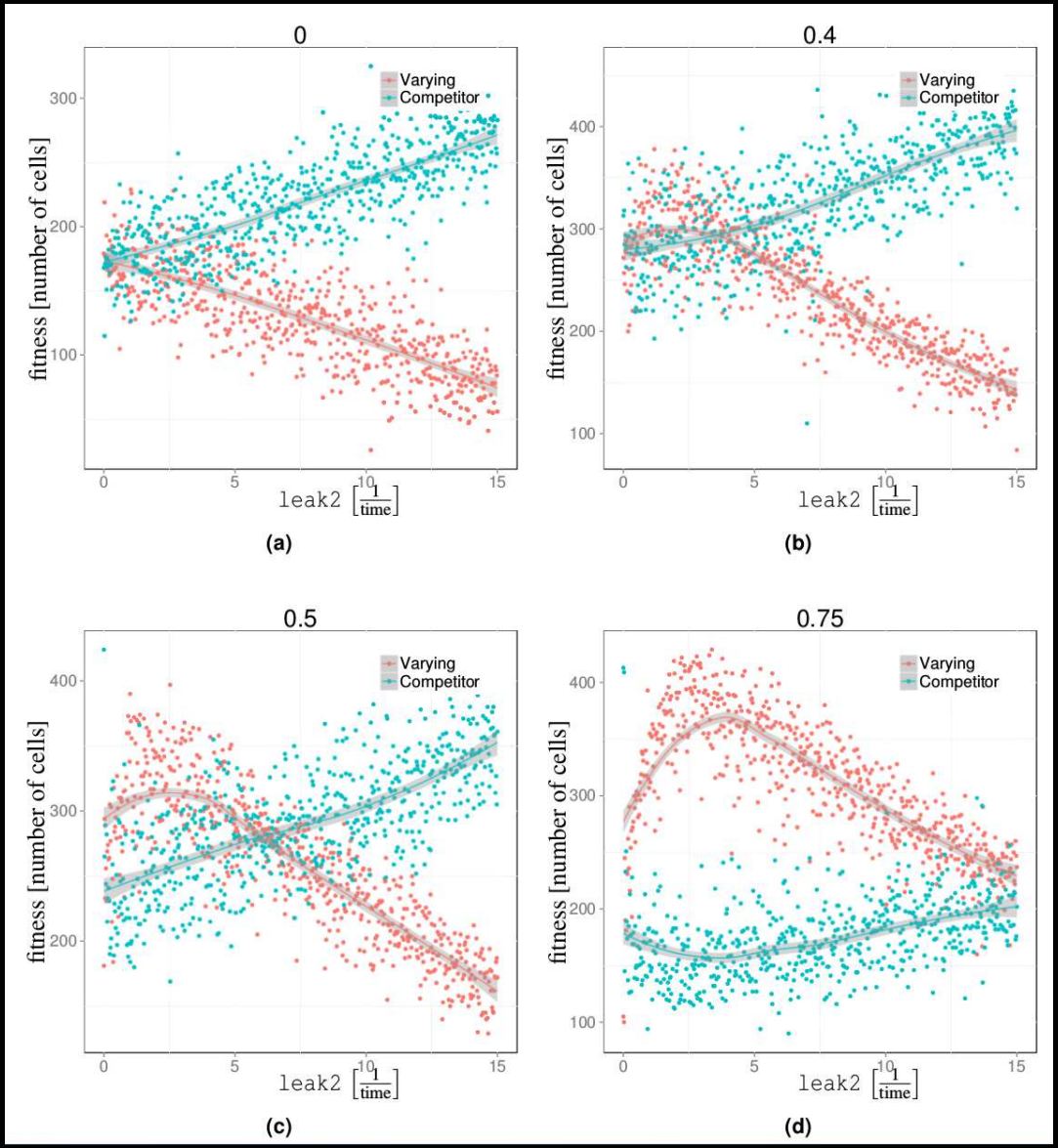


(c) (d)

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

(*ii*) There is an optimal lag-phase

The optimal lag-phase balances the immediate cost due to episodic lost growth during the switch with the long-term costs of sensing.



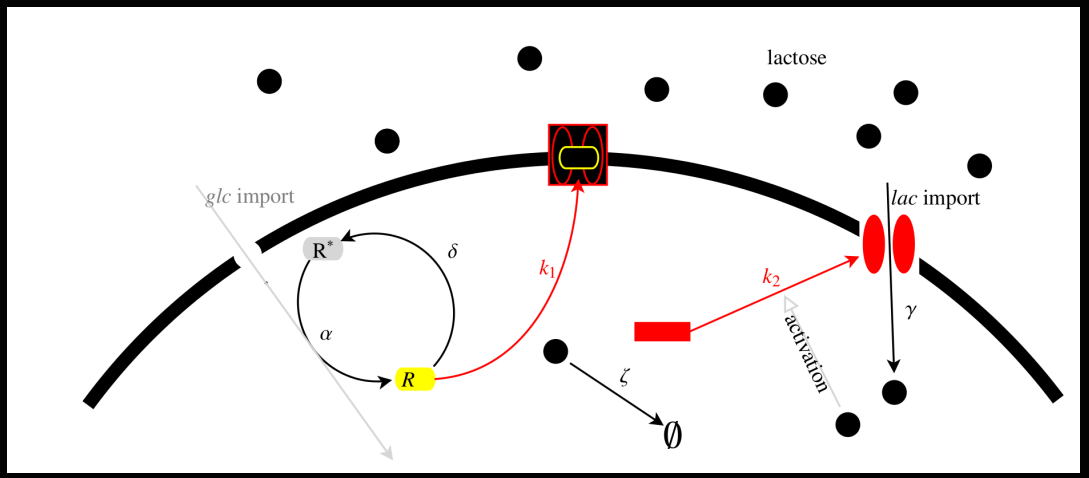
Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

Insights

- There is an optimal lag-phase balancing the ability to switch and growth potential.
  - A long lag-phase implies a dramatic fitness cost at the moment of switching.
  - A short lag-phase requires high leak rate and implies a permanent cost when growing on any nutrient.
- When the cell only experiences dual nutrient conditions, then no lag-phase will evolve. :-)

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

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



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

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

After a number of simplifications and approximations...

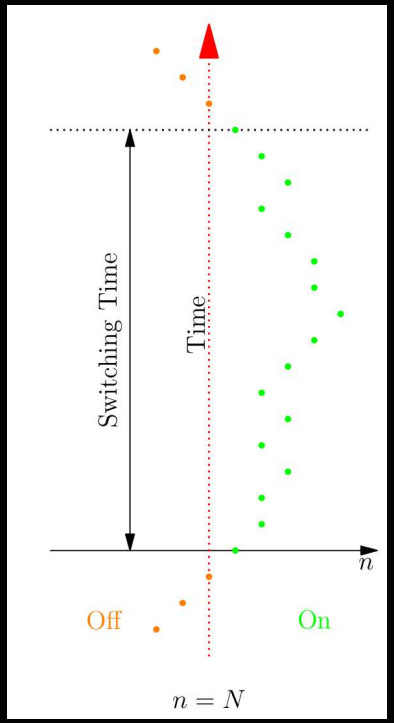
..this can be reduced to a birth-death process.

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

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.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

Mean-time to switch



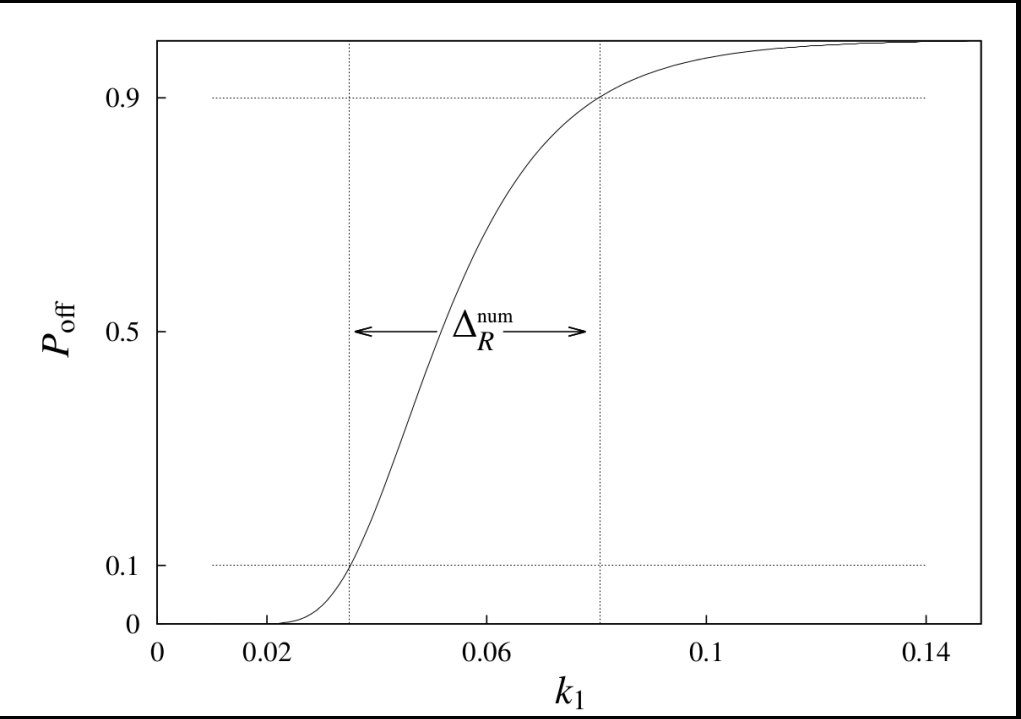
- We assume that the system is on, when a threshold number of N permeases are expressed.
- We can now calculate the expected switching times from on to off and *vice versa*.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

Digested results

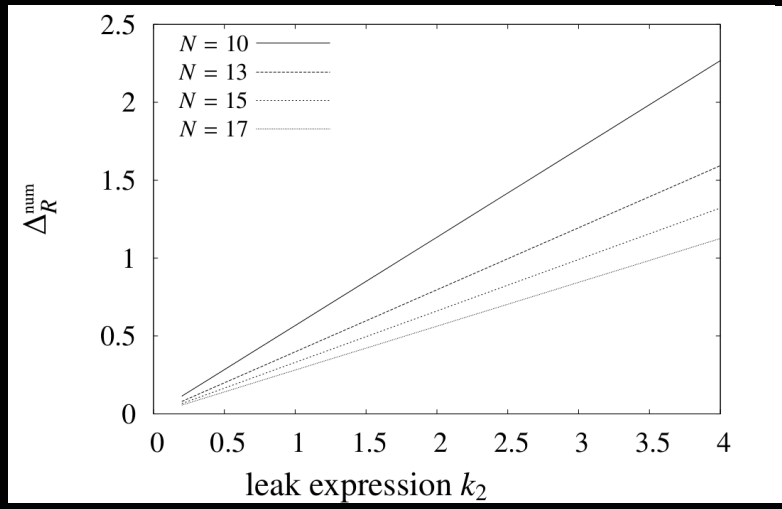
..using this, we can then calculate the probability of the system being switched on/off as a function of the number of R (the "glucose uptake rate").

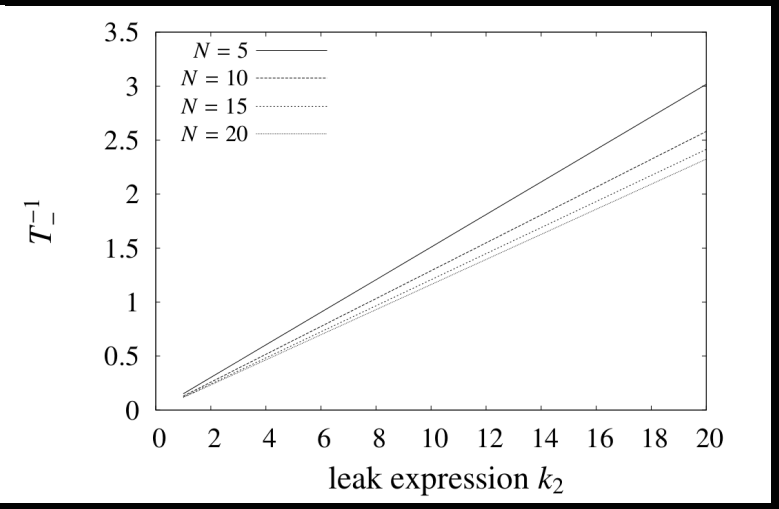
$$P_{\text{off}} = \frac{\Gamma\left(N, \frac{k_2}{Rk_1^0}\right)}{\Gamma(N)}$$



Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

Results





R: Indicator for uptake rate of primary nutrient.

ΔR: Uncertainty about activations state/lag-phase/population heterogeneity.

k_2: Leak expression and hence metabolic cost of regulation.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

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).

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions

Conclusions

- The lag-phase can be thought of as a consequence of the cost of sensing.
- The parameter that controls this cost is the leak rate of the secondary permease.
- The leak-rate can also be thought of as a sampling rate for the binary sensor (i.e. Is secondary nutrient present?).
- The lag-phase then is a manifestation of a trade-off between episodic fitness-loss and long-term low-growth.
- The minimal mathematical model predicts qualitatively empirical data by Wang and co-workers and Venturelli and co-workers.
- Quantitative prediction requires more extensive models.

Background
Biological computers
Diauxic growth
Results
A computational simulation model
Artificial evolution
Diauxic growth as a birth-death process
Results
Conclusions