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Solution 2

Release: 19.04.2023
Due: 25.04.2023

Question 1: Slow and Fast Time Scales

Recall the reversible isomerization reaction $S_1 \underset{c_2}{\overset{c_1}{\rightleftharpoons}} S_2$, where S_1 and S_2 are the two isomeric species and c_1 and c_2 are the corresponding reaction rates. x_T denotes the constant total number of molecules of the two species, $x(t)$ the time-varying number of S_1, and $x(0) = x_0$ the initial value.

a) For large numbers of the chemical species the time evolution of their number is well approximated by the law of mass action. The ODE describing the evolution of $x(t)$ is then given by:

$$\frac{dx}{dt} = -c_1 x + c_2(x_T - x) = -(c_1 + c_2)x + c_2 x_T \tag{1}$$

Here, we have an inhomogeneous, linear differential equation which can be solved analytically. One approach is to use Lagrange's idea of variation of constants. For simplicity, set $a = -(c_1 + c_2)$ and $b = c_2 x_T$. The *homogenous problem* $\frac{dx_H}{dt} = a x_H$ has solutions of the form

$$x_H(t) = e^{at} \cdot k \tag{2}$$

with some constant k. Now use Lagrange's idea of variation of constants for the full problem (1). For that, assume the solution (1) is of the form

$$x(t) = e^{at} \cdot k(t). \tag{3}$$

Differentiating (3)

$$\frac{dx}{dt} = \frac{d}{dt}(e^{at} \cdot k(t)) = \underline{a e^{at} \cdot k(t) + e^{at}\frac{dk}{dt}} \tag{4}$$

Plugging (3) in the ODE (1)

$$\frac{dx}{dt} = ax + b = \underline{a e^{at} \cdot k(t) + b} \tag{5}$$

Setting (4) equal to (5) yields

$$a e^{at} \cdot k(t) + e^{at}\frac{dk}{dt} = a e^{at} \cdot k(t) + b \tag{6}$$

$$\frac{dk}{dt} = b e^{-at} \tag{7}$$

$$k(t) - k(0) = \frac{b}{-a}\left(e^{-at} - 1\right) \tag{8}$$

The full solution hence reads

$$x(t) = e^{at}\left[k(0) + \frac{b}{-a}\left(e^{-at} - 1\right)\right] = -\frac{b}{a} + \left[k(0) + \frac{b}{a}\right]e^{at} \tag{9}$$

$$x(t) = \frac{c_2 x_T}{c_1 + c_2} + \left[k(0) - \frac{c_2 x_T}{c_1 + c_2}\right]e^{-(c_1+c_2)t} \tag{10}$$

From the initial value $x(0) = x_0$ follows $k(0) = x_0$, hence the final solution is

$$x(t) = \frac{c_2 x_T}{c_1 + c_2} + \left(x_0 - \frac{c_2 x_T}{c_1 + c_2}\right)e^{-(c_1+c_2)t}. \tag{11}$$

b) Inspection of Equation (11) for $t \to \infty$ relaxes to the asymptotic value $\frac{c_2 x_T}{c_1+c_2}$ independent of the initial value of x_0 in a time of order $(c_1 + c_2)^{-1}$. Hence, the system is considered stiff if the term $(c_1 + c_2)$ assumes large values.

c) Figure 1 shows numerical solutions of (1). If the time step Δt exceeds 1 the solution gets unstable. The asymptotic value for $x(t)$ is $\frac{c_2 x_T}{c_1+c_2} = \frac{1\times 2\times 10^5}{1+1} = 1 \times 10^5$.

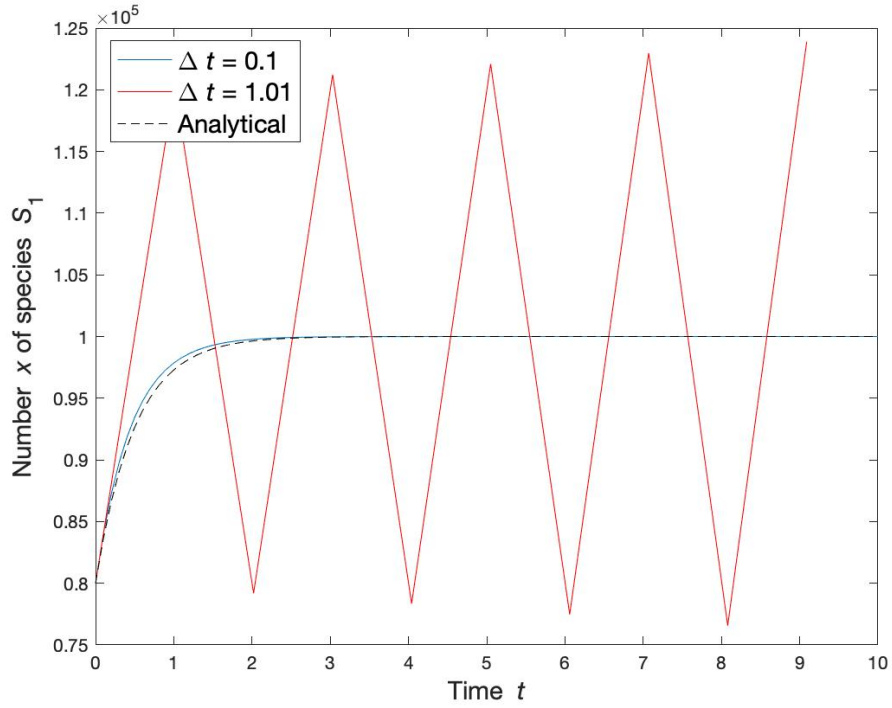

Figure 1: Numerical solution of Equation (1) for $c_1 = c_2 = 1$, $x_T = 2\times 10^5$ and $x_0 = 0.8\times 10^5$ and $\Delta t = 0.1$ resp. 1.01. Note that the peaks of the numerical solution for $\Delta t = 1.01$ grow over time.

d) The explicit Euler method for (1) reads:

$$x_n = x_{n-1} - \Delta t(c_1 + c_2)x_{n-1} + \Delta t c_2 x_T \tag{12}$$

where $x_n = x(t_n)$ of the numerical solution. If we expand the true solution $x(t)$ in a Taylor series about t_{n-1}, we get:

$$x(t_n) = x(t_{n-1}) - \Delta t(c_1 + c_2)x(t_{n-1}) + \Delta t c_2 x_T + O(\Delta t^2) \tag{13}$$

Substracting (13) from (12), and defining the error $e_n = x(t_n) - x_n$, leads to:

$$e_n = e_{n-1} - \Delta t(c_1 + c_2)e_{n-1} + O(\Delta t^2) \tag{14}$$

Thus, the recurrence formula for e_n is given by:

$$e_n = (1 - \Delta t(c_1 + c_2))e_{n-1} + O(\Delta t^2) \tag{15}$$

From (15) we can derive constraints for the maximum time step size, namely:

$$|1 - \Delta t(c_1 + c_2)| < 1 \Leftrightarrow 0 < \Delta t(c_1 + c_2) < 2 \tag{16}$$

Hence $\Delta t < 2(c_1 + c_2)^{-1}$ to ensure convergence of e_n. Assuming $c_1 = c_2 = 1$ from c) leads to the observed maximum step size $\Delta t_{max} = 1$.

Question 2: Time Scales in the QS system

We consider the submodel for the binding of LuxR / AHL-n-mer to DNA found in the 2005 draft of the QS model, Section 2.1.

a) The promoter region of the DNA can assume two possible states. Either the LuxR / AHL-n-mer is bound to the region (state A) or not (state B), so $P(A)+P(B)=1$. Two processes influence the probability to bind to the promoter site. Independent of the concentration of the LuxR / AHL-n-mer, a constant dissociation rate κ_-between n-mer and DNA is assumed, i.e. it is only dependent on the affinity of the n-mer to the DNA. The association of protein and DNA however depends highly on the actual concentration y_n of the protein and an association constant κ_+. Thererfore, the evolution of the $P(A)$ can be modeled as follows:

$$\frac{d}{dt}P(A) = -\kappa_- P(A) + \kappa_+ y_n P(B) = -\kappa_- P(A) + \kappa_+ y_n (1 - P(A)) \tag{17}$$

To get a simplified expression for $P(A)$ we have to conduct an *asymptotic analysis of time scales*. In the latter part of the section 2.1 we find the ODE for the concentration y_n:

$$\frac{d}{dt}y_n = -\pi_n^- y_n + \pi_n^+ y_1 y_{n-1} \tag{18}$$

Let us assume that the process of polymerization of the LuxR / AHL-n-mer takes much longer than the association and dissociation of protein and DNA. In mathematical terms this means:

$$\pi_n^-, \pi_n^+ \ll \kappa_-, \kappa_+ \tag{19}$$

To non-dimensionalize time using the slow time scale we set $\hat{t} = \pi_n^+ t$ and define a small $\epsilon = \frac{\pi_n^+}{\kappa_+}$. Introducing $\hat{t}$ and dividing equations (17) and (18) by κ_+ yields:

$$\epsilon \frac{d}{d\hat{t}}P(A) = -\frac{\kappa_-}{\kappa_+}P(A) + y_n(1 - P(A)) \tag{20}$$

$$\epsilon \frac{d}{d\hat{t}}y_n = -\frac{\pi_n^-}{\kappa_+}y_n + \epsilon\, y_1 y_{n-1} \tag{21}$$

The objective of *asymptotic analysis* is to treat ϵ not as fixed number but as a parameter that can be varied. In the asymptotic limit $\epsilon \to 0$ we find that the right hand side of (21) approximates zero where in (20) this is not the case! Note that $\frac{\pi_n^-}{\kappa_+}$ is small too and $\frac{\kappa_-}{\kappa_+}$ is not.
This is the lowest-order solution in the asymptotic analysis on the slow time scale. It is called the *quasi-steady state* approximation, where "quasi" emphasizes that $-\kappa_- P(A) + \kappa_+ y_n(1 - P(A))$ is nearly, but not exactly, zero!
Using this result in (17) yields

$$0 \approx -\kappa_- P(A) + \kappa_+ y_n(1 - P(A)) \Leftrightarrow (\kappa_- + \kappa_+ y_n)P(A) \approx \kappa_+ y_n \Leftrightarrow P(A) \approx \frac{\kappa_+ y_n}{(\kappa_- + \kappa_+ y_n)}$$

which is exactly the statement of the paper.
Whether or not assumption (19) is reasonable is not an easy thing to decide. It requires fundamental knowledge of the biochemical processes involved.

Alternative approach: Solve linear inhomogeneous differential equation (17) using an *integrating factor*

$$\frac{d}{dt}P(A) = -\kappa_- P(A) + \kappa_+ y_n(1 - P(A)) = P(A)(-\kappa_- + \kappa_+ y_n) + \kappa_+ y_n = P(A)a + b \quad (22)$$

$$\frac{d}{dt}P(A) - aP(A) = b \quad (23)$$

Get *integrating factor* u

$$u = e^{\int -a \ dt} = e^{-at} \quad (24)$$

Multiply both sides with u and integrate

$$(e^{-at}P(A))' = e^{-at} \ b \quad (25)$$

$$\int (e^{-at}P(A))' \ dt = \int e^{-at} b \ dt \quad (26)$$

$$e^{-at}P(A) = \frac{b}{-a}e^{-at} + c \quad (27)$$

Obtain the *general* solution for $P(A)$:

$$P(A) = -\frac{b}{a} + c \quad (28)$$

with arbitrary constant c. Since the probability for the bound state (A) is zero if the association constant $\kappa_+ = 0$, we get $c = 0$. Thus,

$$P(A) = -\frac{b}{a} = \frac{\kappa_+ y_n}{(\kappa_- + \kappa_+ y_n)} \quad (29)$$

b) The authors use again time scale arguments in the latter part of the section to simplify the model. As we have seen for the analysis of $P(A)$, they derive a model in quasi-steady state where only the dynamics of the internal and external AHL concentration, denoted by x_c and x_e, are considered slow. Thus, the same logic as in 2 a) has been applied leading to the simplified model system.
In addition, several individual parameters have been lumped together.

Just for further information follows below an overview of timescales relevant to cell biology. Other branches of biology deal with even longer time scales, for example population dynamics (hours to years), ecosystem dynamics (years to thousands of years to hundreds of thousands of years) and evolutional biology (millions of years to about one billion years).

SnapShot: Timescales in Cell Biology

Cell

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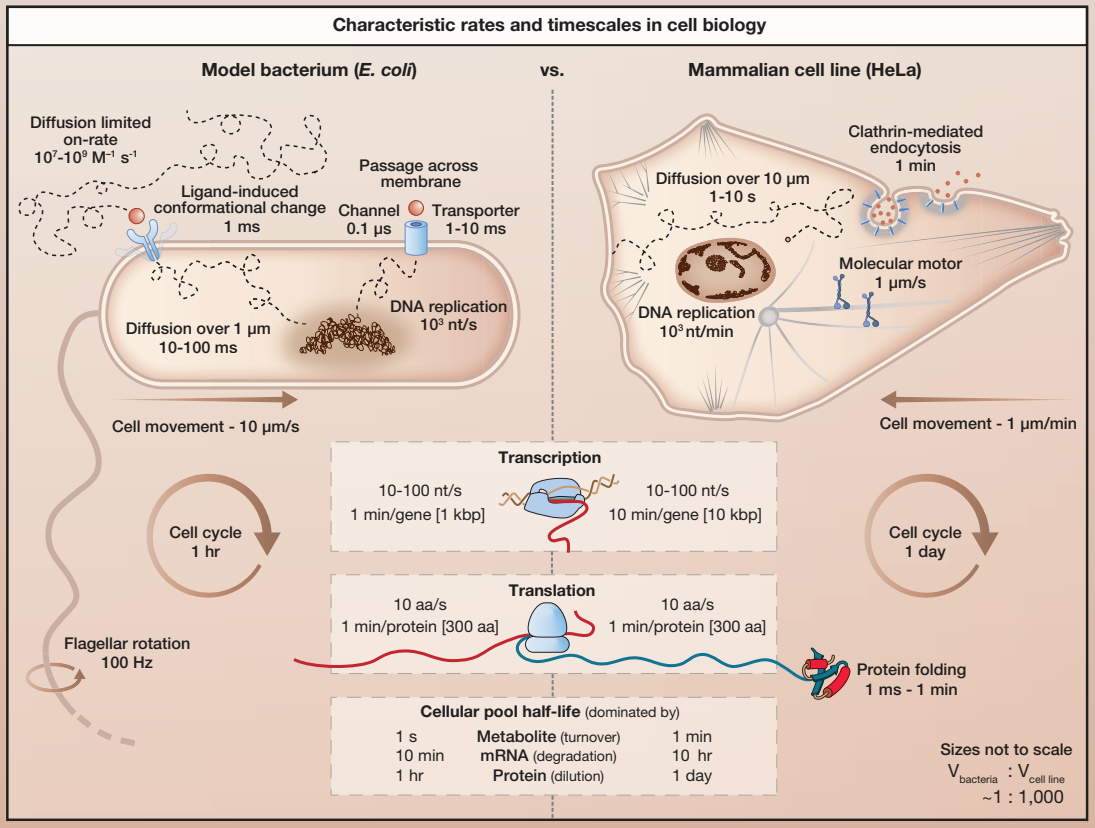
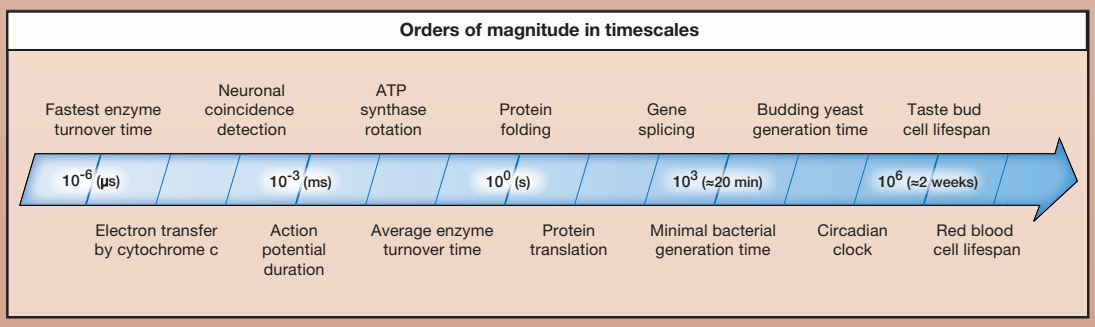
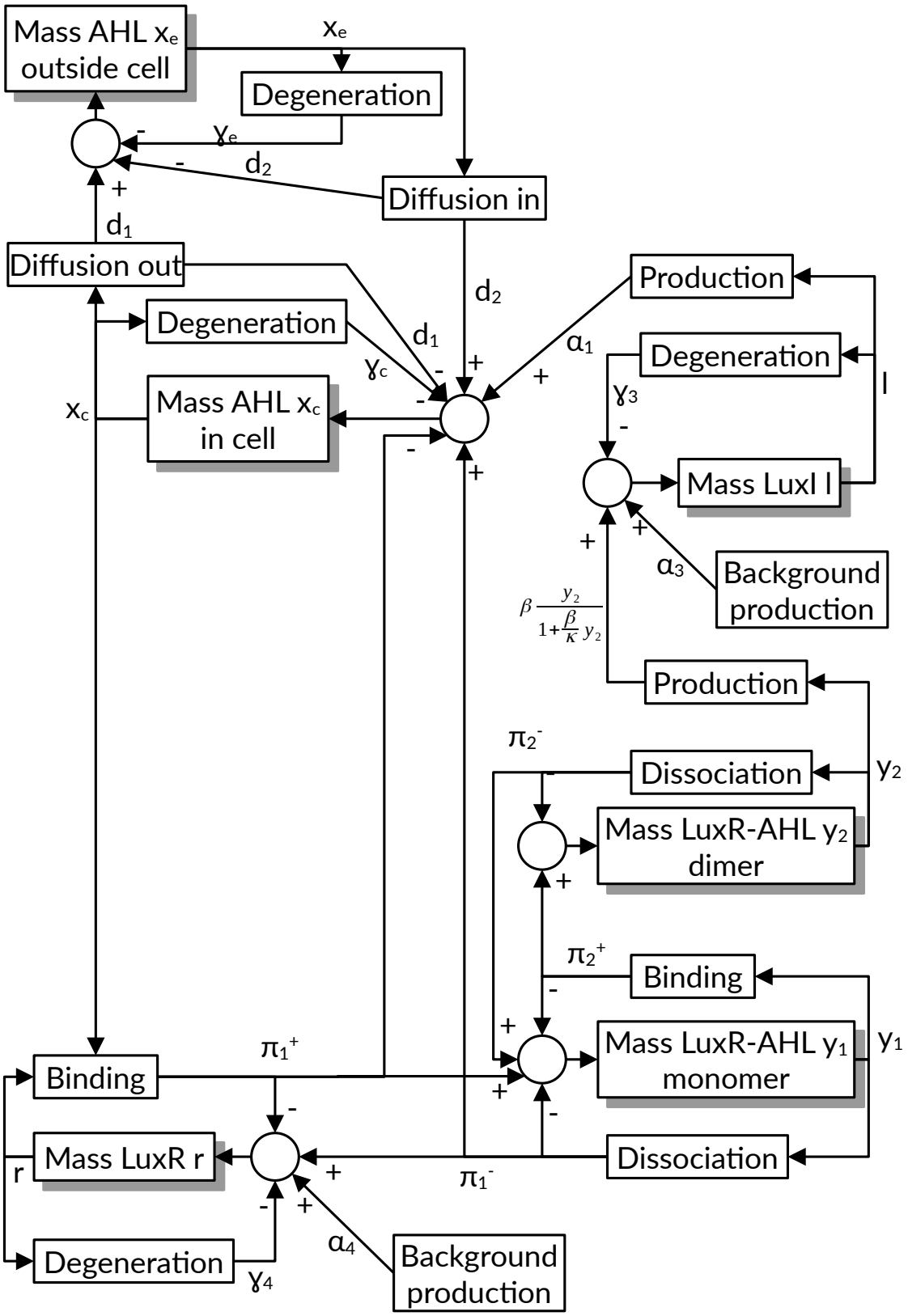




See online version for legend and references.

Question 3: Flows, Reservoirs and Causality Diagrams of the QS model

a) Causality Diagram of the QS model



b) Simplified Causality Diagram of the QS model