Pavlovian Conditioning in Microbes

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Abstract

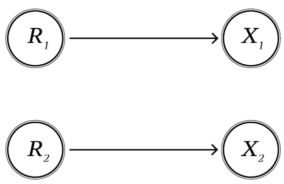
The aim of this project is to develop a simple model for Pavlov Conditioning of microbes, and to assess its feasibility using cost-benefit analysis. The goal is to predict whether or not a particular set of environmental changes will lead to conditioning in the cell.

Introduction

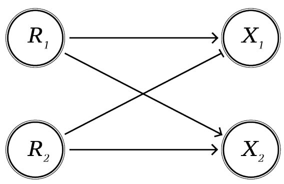
When a cell encounters a change in environment which is almost always succeeded by another change in the environment, which may or may not be causal, the cell adapts (read: evolves) to prepare to respond to the second change even before encountering it. This is referred to as conditioning, and was first observed and reported in dogs by Pavlov [1].

Problem Formulation

Consider a cell which encounters a environmental signal S_1, which is followed by signal S_2, with a probability p. The signals individually result in transcription factors R_1 and R_2, which start the production of proteins X_1 and X_2, respectively.



If conditioned, R_1 should start the production of X_2 and R_2 should curb the production of X_1.



The rate of production and degeneration/dilution of protein X_i depends on the concentration of the transcription factor R_j and itself as [2]:

$$\frac{d[X_i]}{dt} = \frac{\beta_{ji}[R_j]}{K_{ji} + [R_j]} - K_i[X_i]$$

For each case, we use cost-benefit analysis to study the feasibility of conditioning. The cost here refers to the resources spent in the production of the proteins. The benefit refers to the advantage a cell gets by producing the right proteins at the right time. Let Net Benefit be the difference between the Benefit and Cost. If the Expected Net Benefit in a conditioned cell($E[NB]_P$) is greater than the Expected Net Benefit in an unconditioned cell($E[NB]_N$), then natural selection will lead to conditioning of the cell.

Assumptions

- As long as the signal(S_i) is present, the concentration of the respective transcription factor(r_i) is assumed to be constant with value r_i.
- For protein X_i, the cost(C) of production is $c_i \int_0^\infty r_i(t)dt$, and benefit($B$) is $b_i \int_0^\infty \mathbb{1}_{S_i}(t) r_i(t)dt$, where $[P]$ represents the concentration of protein P, and $\mathbb{1}_{S_i}$ is 1 when S_i is present and 0 when S_i is absent.
- Initially, no protein X_i is present, i.e., $[X_i](0) = 0$.
- S_1 is present from $t = 0$ to $t = t_0$, at which point S_1 dies out and S_2 appears instantaneously and stays for time t_1 till $t = t_0 + t_1$.

Solution

We know that the solution of

$$\frac{dx(t)}{dt} = Q - Px(t) \tag{1}$$

given initial condition $x(0) = x_0$ is given by

$$x(t) = x_0 e^{-Pt} + \frac{Q}{P}(1 - e^{-Pt}) \tag{2}$$

This will be useful later. Now, let us compute the Expected Net Benefits for the below cases.

Case 1 (No Conditioning)

Case 1.1 (S_2 does not appear)

The differential equation satisfied by $[X_1]$ is:

$$\frac{d[X_1]}{dt} = \begin{cases} \frac{\beta_{11} r_1}{K_{11} + r_1} - \alpha_1 [X_1], & \text{if } t \leq t_0 \\ -\alpha_1 [X_1], & \text{if } t > t_0 \end{cases} \tag{3}$$

while $[X_2] = 0 \ \forall\ t$ since there is no signal S_2 and no conditioning.

Since Equation 3 is of the form of Equation 1, the solution will be given by Equation 2, as

$$X_1(t) = \begin{cases} \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1 - e^{-\alpha_1 t}), & \text{if } t \le t_0 \\ \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1 - e^{-\alpha_1 t_0})e^{-\alpha_1 (t - t_0)}, & \text{if } t > t_0 \end{cases} \tag{4}$$

The cost C_1 is given by:

$$C_1 = \frac{c_1}{\alpha_1} \times \frac{\beta_{11} r_1}{K_{11} + r_1} t_0 \tag{5}$$

Similarly, the benefit B_1 is given by:

$$B_1 = \frac{b_1}{\alpha_1} \left(\frac{\beta_{11} r_1}{K_{11} + r_1} t_0 - \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1 - e^{-\alpha_1 t_0}) \right) \tag{6}$$

From Equations 5 and 6:

$$NB_1 = \frac{b_1}{\alpha_1} \left(\frac{\beta_{11} r_1}{K_{11} + r_1} t_0 - \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1 - e^{-\alpha_1 t_0}) \right) - \frac{c_1}{\alpha_1} \times \frac{\beta_{11} r_1}{K_{11} + r_1} t_0 \tag{7}$$

Case 1.2 (S_2 appears at $t = t_0$)

The differential equation satisfied by $[X_2]$ is:

$$\frac{d[X_2]}{dt} = \begin{cases} -\alpha_2 [X_2], & \text{if } t \le t_0 \\ \frac{\beta_{22} r_2}{K_{22}+r_2} - \alpha_2 [X_2], & \text{if } t_0 < t \le t_0 + t_1 \\ -\alpha_2 [X_2], & \text{if } t_0 + t_1 < t \end{cases} \tag{8}$$

We know from Case 1.1 that:

$$X_1(t) = \begin{cases} \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1 - e^{-\alpha_1 t}), & \text{if } t \le t_0 \\ \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1 - e^{-\alpha_1 t_0})e^{-\alpha_1 (t - t_0)}, & \text{if } t > t_0 \end{cases} \tag{9}$$

Since Equation 8 is of the form of Equation 1, the solution will be given by Equation 2, as

$$X_2(t) = \begin{cases} 0, & \text{if } t \le t_0 \\ \frac{\frac{\beta_{22} r_2}{K_{22}+r_2}}{\alpha_2}(1 - e^{-\alpha_2 (t - t_0)}), & \text{if } t_0 < t \le t_0 + t_1 \\ \frac{\frac{\beta_{22} r_2}{K_{22}+r_2}}{\alpha_2}(1 - e^{-\alpha_2 t_1})e^{-\alpha_2 (t - t_0 - t_1)}, & \text{if } t_0 + t_1 < t \end{cases} \tag{10}$$

The cost C_2 is given by:

$$C_2 = \frac{c_1}{\alpha_1} \times \frac{\beta_{11} r_1}{K_{11} + r_1} t_0 + \frac{c_2}{\alpha_2} \times \frac{\beta_{22} r_2}{K_{22} + r_2} t_1 \tag{11}$$

Similarly, the benefit B_2 is given by:

$$\begin{aligned} B_2 = \frac{b_1}{\alpha_1}\left(\frac{\beta_{11}r_1}{K_{11}+r_1}t_0 - \frac{\frac{\beta_{11}r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})\right) \\ + \frac{b_2}{\alpha_2}\left(\frac{\beta_{22}r_2}{K_{22}+r_2}t_1 - \frac{\frac{\beta_{22}r_2}{K_{22}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t_1})\right) \end{aligned} \tag{12}$$

From Equations 11 and 12:

$$\begin{aligned} NB_2 = \frac{b_1}{\alpha_1}\left(\frac{\beta_{11}r_1}{K_{11}+r_1}t_0 - \frac{\frac{\beta_{11}r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})\right) \\ + \frac{b_2}{\alpha_2}\left(\frac{\beta_{22}r_2}{K_{22}+r_2}t_1 - \frac{\frac{\beta_{22}r_2}{K_{22}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t_1})\right) \\ - \frac{c_1}{\alpha_1}\times\frac{\beta_{11}r_1}{K_{11}+r_1}t_0 - \frac{c_2}{\alpha_2}\times\frac{\beta_{22}r_2}{K_{22}+r_2}t_1 \end{aligned} \tag{13}$$

From Equations 7 and 13, the Expected Net Benefit is given by:

$$\begin{aligned} E[NB_N] &= (1-p)NB_1 + pNB_2 \\ &= \frac{b_1}{\alpha_1}\left(\frac{\beta_{11}r_1}{K_{11}+r_1}t_0 - \frac{\frac{\beta_{11}r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})\right) - \frac{c_1}{\alpha_1}\times\frac{\beta_{11}r_1}{K_{11}+r_1}t_0 \\ &+ p\left(\frac{b_2}{\alpha_2}\left(\frac{\beta_{22}r_2}{K_{22}+r_2}t_1 - \frac{\frac{\beta_{22}r_2}{K_{22}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t_1})\right) - \frac{c_2}{\alpha_2}\times\frac{\beta_{22}r_2}{K_{22}+r_2}t_1\right) \end{aligned} \tag{14}$$

Case 2 (With Conditioning)

Case 2.1 (S_2 does not appear)

The differential equation satisfied by $[X_1]$ is:

$$\frac{d[X_1]}{dt} = \begin{cases} \frac{\beta_{11}r_1}{K_{11}+r_1} - \alpha_1[X_1], & \text{if } t \le t_0 \\ -\alpha_1[X_1], & \text{if } t > t_0 \end{cases} \tag{15}$$

and that of X_2 is:

$$\frac{d[X_2]}{dt} = \begin{cases} \frac{\beta_{12}r_1}{K_{12}+r_1} - \alpha_2[X_2], & \text{if } t \le t_0 \\ -\alpha_2[X_2], & \text{if } t > t_0 \end{cases} \tag{16}$$

Since Equation 15 and 16 are of the form of Equation 1, the solutions will be given by Equation 2, as

$$X_1(t) = \begin{cases} \frac{\frac{\beta_{11}r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t}), & \text{if } t \le t_0 \\ \frac{\frac{\beta_{11}r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})e^{-\alpha_1(t-t_0)}, & \text{if } t > t_0 \end{cases} \tag{17}$$

and

$$X_2(t) = \begin{cases} \frac{\frac{\beta_{12} r_2}{K_{12}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t}), & \text{if } t \le t_0 \\ \frac{\frac{\beta_{12} r_2}{K_{12}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t_0})e^{-\alpha_2(t-t_0)}, & \text{if } t > t_0 \end{cases} \tag{18}$$

The cost C_1 is given by:

$$C_1 = \frac{c_1}{\alpha_1} \times \frac{\beta_{11} r_1}{K_{11}+r_1} t_0 + \frac{c_2}{\alpha_2} \times \frac{\beta_{12} r_2}{K_{12}+r_2} t_0 \tag{19}$$

Similarly, the benefit B_1 is given by:

$$B_1 = \frac{b_1}{\alpha_1}\left(\frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})\right) \tag{20}$$

From Equations 19 and 20:

$$\begin{aligned} NB_1 = {} & \frac{b_1}{\alpha_1}\left(\frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})\right) \\ & - \frac{c_1}{\alpha_1} \times \frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{c_2}{\alpha_2} \times \frac{\beta_{12} r_2}{K_{12}+r_2} t_0 \end{aligned} \tag{21}$$

Case 2.2 (S_2 appears at $t = t_0$)

The differential equation satisfied by $[X_2]$ is:

$$\frac{d[X_1]}{dt} = \begin{cases} \frac{\beta_{11} r_1}{K_{11}+r_1} - \alpha_1[X_1], & \text{if } t \le t_0 \\ -\frac{\beta_{21}[K_{21}]}{K_{21}+[R_{21}]} - \alpha_1[X_1], & \text{if } t \le t_0 \\ -\alpha_1[X_1], & \text{if } t > t_0 \end{cases} \tag{22}$$

and that of X_2 is:

$$\frac{d[X_2]}{dt} = \begin{cases} \frac{\beta_{12} r_1}{K_{12}+r_1} - \alpha_2[X_2], & \text{if } t \le t_0 \\ \frac{\beta_{22} r_2}{K_{22}+r_2} - \alpha_2[X_2], & \text{if } t_0 < t \le t_1 + t_0 \\ -\alpha_2[X_2], & \text{if } t_1 + t_0 < t \end{cases} \tag{23}$$

Since Equation 22 and 23 are of the form of Equation 1, the solutions will be given by Equation 2, as:

$$X_1(t) = \begin{cases} \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t}), & \text{if } t \le t_0 \\ \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t}) - \frac{\frac{\beta_{21} r_2}{K_{21}+r_2}}{\alpha_1}(1-e^{-\alpha_1(t-t_0)}), & \text{if } t_0 < t \le t_0 + t_1 \\ \left(\frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1(t_0+t_1)}) - \frac{\frac{\beta_{21} r_2}{K_{21}+r_2}}{\alpha_1}(1-e^{-\alpha_1 t_1})\right) e^{-\alpha_1(t-t_0-t_1)}, & \text{if } t > t_0 + t_1 \end{cases} \tag{24}$$

and similarly:

$$X_2(t) = \begin{cases} \frac{\frac{\beta_{12} r_1}{K_{12}+r_1}}{\alpha_2}(1-e^{-\alpha_2 t}), & \text{if } t \leq t_0 \\ \frac{\frac{\beta_{12} r_1}{K_{12}+r_1}}{\alpha_2}(1-e^{-\alpha_2 t}) + \frac{\frac{\beta_{22} r_2}{K_{22}+r_2}}{\alpha_2}(1-e^{-\alpha_2 (t-t_0)}), & \text{if } t_0 < t \leq t_0+t_1 \\ \left(\frac{\frac{\beta_{12} r_1}{K_{12}+r_1}}{\alpha_1}(1-e^{-\alpha_2 (t_0+t_1)}) + \frac{\frac{\beta_{22} r_2}{K_{22}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t_1})\right) e^{-\alpha_2(t-t_0-t_1)}, & \text{if } t > t_0+t_1 \end{cases} \tag{25}$$

The cost C_2 is given by:

$$\begin{aligned} C_2 = {} & \frac{c_1}{\alpha_1}\left(\frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{\beta_{21} r_2}{K_{21}+r_2} t_1\right) \\ & + \frac{c_2}{\alpha_2}\left(\frac{\beta_{12} r_1}{K_{12}+r_1} t_0 + \frac{\beta_{22} r_2}{K_{22}+r_2} t_1\right) \end{aligned} \tag{26}$$

Similarly, the benefit B_2 is given by:

$$\begin{aligned} B_2 = {} & \frac{b_1}{\alpha_1}\left(\frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})\right) \\ & + \frac{b_2}{\alpha_2}\left(\frac{\beta_{22} r_2}{K_{22}+r_2} t_1 - \frac{\frac{\beta_{12} r_1}{K_{12}+r_1}}{\alpha_1}(1-e^{-\alpha_2 t_1})e^{-\alpha_2 t_0} - \frac{\frac{\beta_{22} r_2}{K_{22}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t_1})\right) \end{aligned} \tag{27}$$

From Equations 26 and 27:

$$\begin{aligned} NB_2 = {} & \frac{b_1}{\alpha_1}\left(\frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})\right) \\ & + \frac{b_2}{\alpha_2}\left(\frac{\beta_{22} r_2}{K_{22}+r_2} t_1 - \frac{\frac{\beta_{12} r_1}{K_{12}+r_1}}{\alpha_1}(1-e^{-\alpha_2 t_1})e^{-\alpha_2 t_0} - \frac{\frac{\beta_{22} r_2}{K_{22}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t_1})\right) \\ & - \frac{c_1}{\alpha_1}\left(\frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{\beta_{21} r_2}{K_{21}+r_2} t_1\right) \\ & - \frac{c_2}{\alpha_2}\left(\frac{\beta_{12} r_1}{K_{12}+r_1} t_0 + \frac{\beta_{22} r_2}{K_{22}+r_2} t_1\right) \end{aligned} \tag{28}$$

From Equations 21 and 28, the Expected Net Benefit is given by:

$$\begin{aligned} E[NB_P] &= (1-p)NB_1 + pNB_2 \\ &= \frac{b_1}{\alpha_1}\left(\frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{\frac{\beta_{11} r_1}{K_{11}+r_1}}{\alpha_1}(1-e^{-\alpha_1 t_0})\right) \\ &\quad - \frac{c_1}{\alpha_1} \times \frac{\beta_{11} r_1}{K_{11}+r_1} t_0 - \frac{c_2}{\alpha_2} \times \frac{\beta_{12} r_2}{K_{12}+r_2} t_0 \\ &\quad + p\frac{b_2}{\alpha_2}\left(\frac{\beta_{22} r_2}{K_{22}+r_2} t_1 - \frac{\frac{\beta_{12} r_1}{K_{12}+r_1}}{\alpha_1}(1-e^{-\alpha_2 t_1})e^{-\alpha_2 t_0} - \frac{\frac{\beta_{22} r_2}{K_{22}+r_2}}{\alpha_2}(1-e^{-\alpha_2 t_1})\right) \\ &\quad + p\left(\frac{c_1}{\alpha_1}\frac{\beta_{21} r_2}{K_{21}+r_2} t_1 - \frac{c_2}{\alpha_2}\frac{\beta_{22} r_2}{K_{22}+r_2} t_1\right) \end{aligned} \tag{29}$$

For conditioning to be naturally selected, $E[NB]_P > E[NB]_N$. From Equations 14 and 29, this condition translates to:

$$p_0 > \frac{\frac{c_2}{\alpha_2} \times \frac{\beta_{12} r_2}{K_{12} + r_2} t_0}{\frac{c_1}{\alpha_1} \times \frac{\beta_{21} r_2}{K_{21} + r_2} t_1 - \frac{b_2}{\alpha_2} \times \frac{\frac{\beta_{12} r_1}{K_{12} + r_1}}{\alpha_1} (1 - e^{-\alpha_2 t_1}) e^{-\alpha_2 t_0}} \tag{30}$$

Conclusion

Given a biological phenomenon that is a candidate for conditioning, we find that the feasibility of conditioning depends on the relative regularity of the two events occurring succeedingly. If this regularity is modelled by a Bernoulli Distribution with success probability p, then the microbe is likely to get conditioned if this probability is greater than the threshold defined by Equation 30, i.e., $p > p_0$.

References

[1] Pavlov, I. P. (1927/1960). *Conditional Reflexes*. New York: Dover Publications (the 1960 edition is not an unaltered republication of the 1927 translation by Oxford University Press http://psychclassics.yorku.ca/Pavlov/).

[2] Alon, Uri. *Introduction to Systems Biology*. Chapman & Hall, 2006.