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Signaling pathways and the propagation of information in cells

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Introduction

Signaling pathways are essential to cells in adjusting to their environment. An extracellular signal, for example a ligand concentration, when in contact with a cell and its receptor proteins can initiate a signaling cascade. In turn, several membrane bound proteins respond by activating and using the input of the extracellular signal as a catalyst to inevitably bind to a target protein and activate an output layer that will obtain an element of response from the cell.

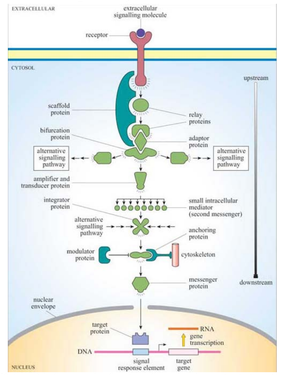


Fig.(1) *A model of a cascade of proteins from signal receptor to target protein.*

Objective

There are many forms of signaling systems, however the purpose of the following is to quantitatively model these activated and deactivated concentrations throughout their course of transmission. Studying the information transmission through the signal transduction of cells.

Methodology and Analysis

Through the usage of chemical kinetics as well as Langevin equations, it's possible to formulate an approximate model of the behavior in steady state.
For an initial understanding, one can reduce the cascade of signal transmission to a one step process, in which an assumption of total concentration of active and inactive output proteins as constant is made. In such case,

$$\textit{An input activates an output ...} \quad I + O \longrightarrow_{k_{11}} I + O^*$$

$$\textit{While a background deactivation occurs ...} \quad O^* \longrightarrow_{\alpha} O$$

$$(\textit{The parameters of the reaction and rate constants}) \ldots \quad k_{11}, \alpha$$

$$\textit{Chemical kinetic equation ...} \quad \frac{d[O^*]}{dt} = k_{11} I[O] - \alpha[O^*]$$

$[O]$ *representing the unactivated output and* $[O^*]$ *activated*
From the assumption made that total concentration is a constant taken to be 1

$$\frac{d[O^*]}{dt} = k_{11} I[1 - [O^*]] - \alpha[O^*]$$

$$\textit{The stable fixed point yeilded by the kinetic equation ...} \quad [O^*]_o = \frac{k_{11} I}{k_{11} I + \alpha}$$

This obtains a direct relationship between the activated output concentration and the input concentration for this simplified version of a signal pathway. The activated output concentration eventually saturates under this system that contains no feedback and no randomness. This deterministic model can be generalized to a signaling cascade with multiple steps (i.e., receptors that transmit activated concentrations to varying proteins through a multi step process). It would imply additional kinetic equations regarding the specific intermediate step coupled with the initial equation. Figures 2 and 3 give visuals of the concentration of a two-step signaling cascade under these conditions.

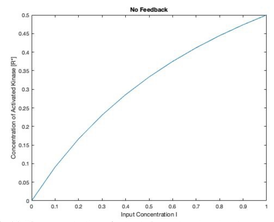


Fig.(2) *The concentration of activated receptor given input concentration*

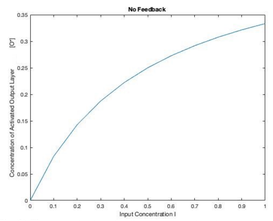
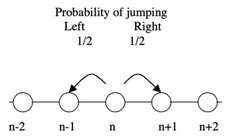


Fig.(3) *The concentration of activated output given input concentration through activation of intermediate receptor.*

Inherent in the activation of proteins is an aspect of randomness. Every time a protein is activated or deactivated the total number of proteins activated is either increasing by one or decreasing, respectively. These individual protein activations are stochastic. The deterministic equation investigated prior simply can be considered as an average value of activation. Shannon's model of communication identifies a factor of noise within the channel between the transmitter of a signal and the receiver of a signal. This noise term will be a standard deviation in the dynamical equation of activated concentration.



Fig(4). *The random walks or "jumps" in positive or negative direction depicted here are analogous to the independent activation or deactivation of proteins and their stochastic aspect*

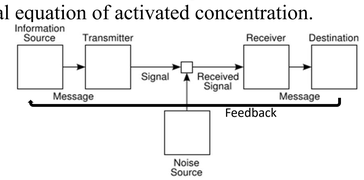


Fig.(5) *A diagram of Shannon-Weaver model of communication*

The exact time interval between these stochastic activations is unknown while the average time is known. Considered as a Poisson process, its variance is equivalent to the average number of activations. Because the formulation gathered is that of concentrations, the variance generally equates as the deterministic kinetic equation divided by a concentration volume – the average. With such an application as a Langevin Equation can be made to such that it better approximates the dynamic behavior of a mixture in steady state.

$$\textit{Langevin Equation ...} \quad \frac{d[O^*]}{dt} = \underbrace{k_{11} I[1 - [O^*]] - \alpha[O^*]}_{\textit{Deterministic-"A"}} + \underbrace{\sqrt{\frac{k_{11} I[1 - [O^*]] - \alpha[O^*]}{V}}\,\xi(t)}_{\textit{Stochastic-"B"}}$$

$$\textit{Acting as "strength" of noise component ...} \quad \xi(t)$$

The probability of an activated concentration given an input concentration, at steady state should be a gaussian distribution, with a peak at the average value. When averaged over, the noise goes to zero, $\langle \xi(t) \rangle = 0$, and what is left is the deterministic portion of the equation. In this case, the fixed point would be that average. Allowing for a model of activation of concentrates and to a generalized extent, the transmission of information.

$$\textit{Probability of random variable with gaussian distribution...} \quad P(x) = \frac{1}{\sqrt{2\pi\sigma^2}}\, e^{\frac{-(x-\mu)^2}{2\sigma^2}}$$

$$\textit{Conditional Probability of activated output concentration given input concentration ...} \quad P([O^*]|I) = \frac{1}{\sqrt{2\pi\sigma^2}}\, e^{\frac{-([O^*]-[O^*]_o)^2}{2\sigma^2}}$$

Once the variance (σ^2) is obtained, with this probability distribution of the activated output concentration the mutual information between and input concentration and activated output concentration can thus be derived through first the obtainment of the joint probability and then the marginal distribution $P([O^*])$.

$$\textit{Joint Probability ...} \quad P(I, [O^*]) = P([O^*]|I) P(I)$$

$$\textit{Mutual Information ...} \quad I(I; [O^*]) = \iint P(I, [O^*]) log \frac{P(I, [O^*])}{P(I) P([O^*])}\, dI\, d[O^*]$$

A linearization of both components of the Langevin equation about the calculated fixed point and changing to discrete time intervals can provide the foundation for obtaining the variance of this conditional probability distribution between activated output and input.

$$\frac{d([O^*] - [O^*]_o)}{dt} = \underbrace{\underbrace{A|_{[O^*]_o}}_{0} + \underbrace{\frac{dA}{d[O^*]}|_{[O^*]}}_{W}\underbrace{([O^*] - [O^*]_o)}_{\delta C}}_{\textit{Linearized deterministic}} + \underbrace{(\underbrace{\frac{k_{11} I(1 - [O^*]_o) + \alpha[O^*]_o}{V}}_{B})^{\frac{1}{2}}\xi(t)}_{\textit{Linearized noise}}$$

$$\frac{\delta C_{t+1} - \delta C_t}{\Delta t} = W \delta C_t + \frac{1}{\sqrt{\Delta t}} N_t \qquad N_t = B\epsilon \qquad \textit{where } \xi(t) \textit{ has been discretized to } \frac{\epsilon}{\sqrt{\Delta t}}$$

$$\langle \delta C^2{}_{t+1} \rangle = (1 + \Delta t W) \langle \delta C^2{}_t \rangle + \Delta t \langle N^2{}_t \rangle \quad \textit{it is a good approx. as } \Delta t \to 0 \textit{ that ...}$$

$$\sigma^2 = \langle \delta C^2{}_t \rangle = \langle \delta C^2{}_{t+1} \rangle = \frac{\langle N^2{}_t \rangle}{-2W} = \frac{B^2}{-2W}$$

For the case of the one step signaling pathway using the results of the stable fixed point calculated earlier the variance will be,

$$\sigma^2 = \frac{(k_{11} I \alpha)}{(V)(k_{11} I + \alpha)^2}$$

Continuing the use of the one step process as reference, all relevant parts of the equation are known to create the conditional probability distribution.

$$P([O^*]|I) = \frac{1}{\sqrt{2\pi(\frac{(k_{11} I \alpha)}{(V)(k_{11} I + \alpha)^2})}}\, e^{\frac{-([O^*]-(\frac{k_{11} I}{k_{11} I + \alpha}))^2}{2(\frac{(k_{11} I \alpha)}{(V)(k_{11} I + \alpha)^2})}} = \frac{1}{\sqrt{2\pi(\frac{(k_{11} I \alpha)}{(V)(k_{11} I + \alpha)^2})}}\, e^{\frac{-([O^*] k_{11} I + [O^*] \alpha - k_{11} I)^2 V}{2(k_{11} I \alpha)}}$$

Although the input concentration is a probabilistic function, if it were to be taken as a constant one could visualize the distribution that the probability density of an activated output, shown in figure 6.

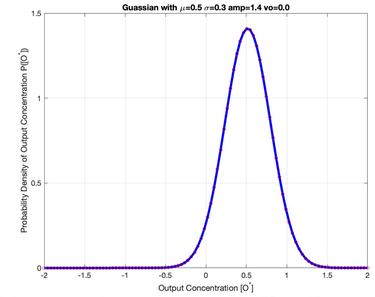


Fig.(6) *A visualization of the gaussian distribution at fixed rate constants* $\alpha = 0.7, k_{11} = 1.5$, *fixed input concentration* $I = 0.5$ *and fixed volume* $V = 20$ *of the activated output concentration for one step signaling process. Plotted using Matlab.*

To further the understanding of information propagating through this one step signal, now one must think of input concentration not as a constant but as a distribution. In any case, it is an input that is brought upon the system and so not derived from it. If the gaussian distribution of the input concentration were to take on the form,

$$P(I) = \frac{1}{\sqrt{2\pi(0.2)^2}}\, e^{\frac{-(I-0.5)^2}{2(0.2)^2}} \qquad \textit{Std. Deviation } \sigma = 0.2 \qquad \textit{Mean Value } \mu = 0.5 \qquad \textit{Range from } 0 \to 1$$

$$P(I, [O^*]) = \underbrace{\frac{1}{\sqrt{2\pi(\frac{(k_{11} I \alpha)}{(V)(k_{11} I + \alpha)^2})}}\, e^{\frac{-([O^*] k_{11} I + [O^*] \alpha - k_{11} I)^2 V}{2(k_{11} I \alpha)}}}_{P([O^*]|I)} \cdot \underbrace{\frac{1}{\sqrt{2\pi(0.2)^2}}\, e^{\frac{-(I-0.5)^2}{2(0.2)^2}}}_{P(I)}$$

By then integrating the joint probability over the range of input concentrations a marginal probability distribution is then acquired $P([O^*])$
With this, all the necessary components arise such that the mutual information can finally be calculated for this one step signal, (refer to mutual information equation).

Conclusion

The mutual information between an input concentration and its activation of an output concentration is obtainable and for the simple one step process shown. The mutual information can be considered as a quantitative measure of information understood about one random variable given another. It is the crossroads of Information theory and chemical kinetics that presents a way to grasp aspects of signal transduction such as noise. This allows for a better understanding of how rate constants of the chemical reactions surrounding the cell can be used to understand the fashion at which signals propagate to the cell and its reaction to those environmental stimuli.
Further exploration which is currently being conducted is the application of this to a two-step signal pathway. An intermediate activation of a receptor protein will be coupled with the output concentration, making the system more complex however more approximate to a cascading system.

$$I + R \longrightarrow_{k_{1r}} I + O^* \qquad R^* \longrightarrow_{\alpha} R \qquad \frac{d[R^*]}{dt} = k_{1r} I[1 - [R^*]] - k_{r0}[O^*]^h[R^*] - \alpha[R^*] + \sqrt{\frac{k_{1r} I[1 - [R^*]] - \alpha[R^*]}{V}}\,\xi_1(t)$$

$$R^* + O \longrightarrow_{k_{r0}} R^* + O^* \qquad O^* \longrightarrow_{\beta} O \qquad \frac{d[O^*]}{dt} = k_{r0} R^*[1 - [O^*]] - \beta[O^*] + \sqrt{\frac{k_{1r} R^*[1 - [O^*]] - \beta[O^*]}{V}}\,\xi_2(t)$$

These coupled equations signify a two-step process, further study can apply the notion of feedback, which is the term added the dynamic equations that signifies an effect of the output on the input loop which can be negative or positive. Example shown is that of negative feedback. With the incorporation of the feedback element of communication, how do the results differ when compared to the process of no output feedback? What does the mutual information for positive feedback scenario and negative feedback scenario look like in comparison to no feedback. Can something be learned about the nature of these differing signal cascading systems by their mutual information ?