

Weber's Law for Biological Responses in Autocatalytic Networks of Chemical Reactions

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Biological responses often obey Weber's law, according to which the magnitude of the response depends only on the fold change in the external input. In this study, we demonstrate that a system involving a simple autocatalytic reaction shows such a response when a chemical is slowly synthesized by the reaction from a faster influx process. We also show that an autocatalytic reaction process occurring in series or in parallel can obey Weber's law with an oscillatory adaptive response. Considering the simplicity and ubiquity of the autocatalytic process, our proposed mechanism is thought to be commonly observed in biological reactions.

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Adaptation is ubiquitous in biological systems. In perfect adaptation, some state variables of a biological system change in response to a change in the external conditions but slowly come back to their original values [1]. Such adaptation is observed in signal transduction, sensory, neural systems, and so forth. Several theoretical studies have investigated such adaptation by using a set of ordinary differential equations, in which certain variables return to their original values independently of the parameter values representing the external condition [2–5].

Responses in a biological system have another ubiquitous characteristic: the degree of response is often proportional to the ratio of an external stimulus before and after it is applied, rather than the absolute difference. In other words, the response detects the fold change, which is commonly known as Weber's law. This kind of response was discovered in the field of psychology, wherein it was observed that our sensory response is proportional to the logarithm of the magnitude of an external stimulus.

Recently, Weber's law was also observed to be obeyed by cellular responses in microorganisms [6]. Shoval *et al.* [7] further defined fold-change detection (FCD) in a sense stronger than Weber's law: not only the magnitude of the response peak but also the entire relaxation profile over time depends only on the change ratio of the stimuli. The relaxation profile over time is identical as long as the ratio is constant, irrespective of the absolute magnitude of stimuli. Shoval *et al.* also developed a theoretical model for such FCD by using a feed-forward gene regulation network. However, ubiquity of this FCD is not yet confirmed, in contrast to universality of Weber's law.

An adaptive response usually has two components: rapid response to a change and slow relaxation to the original state. Oosawa and Nakaoka confirmed the existence of these distinct timescales in the adaptive response of *Paramecium* to chemotaxis and also the relevance of their existence to chemotaxis [8] (see also [5]). It is therefore

important to elucidate the relevance of such a timescale difference to Weber's law for adaptation.

Most biochemical reactions are catalytic, while replication of molecules as well as allosteric enzymatic reactions often involve autocatalytic regulation [9–11]. In the present Letter, we show that a simple system with autocatalytic reactions exhibits an adaptive response according to Weber's law if the autocatalytic process is slow. Because the autocatalytic process often involves several steps and requires a long time for completion, the ubiquity of adaptive responses obeying Weber's law of a cell can be easily understood from this simple system. We also demonstrate Weber's law in a system of chained or parallel-connected autocatalytic reactions. In addition, we explore oscillatory adaptation with Weber's law and establish a condition for it. Finally, we discuss the relevance of the results to biological responses.

First, we study a simple reaction model of two chemicals X_0 and X_1 with the following autocatalytic reaction, as introduced in [5]: $X_0 + X_1 \rightarrow 2X_1$; the model also includes (a) the synthesis of X_0 from an external resource chemical S as $S \rightarrow X_0$ and (b) the degradation of X_0 and X_1 . By representing the concentrations of the two chemicals as x_0 and x_1 and suitably scaling the time and concentration variables, we get the rate equation as

$$dx_0/dt = S - x_0x_1 - x_0, \quad dx_1/dt = (x_0x_1 - x_1)/\tau. \quad (1)$$

Among the two fixed-point solutions of Eq. (1), we focus on the steady state $x_0^* = 1, x_1^* = S - 1$ [12]. According to a linear stability analysis, this state is stable when $S > 1$, i.e., as long as $x_1^* > 0$. It should be noted that x_0^* is independent of S . The chemical concentration responds to the concentration of the external signal, S ; when S increases (decreases), x_0 increases (decreases) from its steady-state value but later returns to the original value. Thus, X_0 always shows an adaptive response, whereas the steady-state concentration of X_1 changes with S .

To examine Weber's law, we study the response of x_0 when S changes as $S_0 \rightarrow pS_0$ ($p > 0$), and calculate the dependence of the peak value of x_0 during this change in S . We assume $\tau \gg 1$, which is required to ensure a fast response and slow adaptation. Under the adiabatic limit, x_1 changes more slowly than x_0 does. During the fast response of x_0 to the change in S , x_1 can be assumed to remain at the steady-state value under the condition of $S = S_0$. Then, the peak value of x_0 is obtained from $(dx_0/dt)_{x_0=x_0^{\text{peak}}} = 0$ by fixing the value of x_1 to $S_0 - 1$.

A straightforward calculation gives us $x_0^{\text{peak}} = p$. In a similar way, the peak time t^{peak} is estimated from $(dx_0/dt) \sim S - S_0 x_0$ and t^{peak} is given by $\sim 1/S_0$ [13]. Hence, x_0 changes from the original value $x_0^* = 1$ to $x_0^{\text{peak}} = p$ and returns to the original value. This amplitude of the response depends only on p , i.e., the ratio of the shift in S , and is independent of the S_0 value. Thus, our model demonstrates Weber's law under the adiabatic condition.

The time scale for adaptation is estimated from the Jacobi matrix at the fixed point (x_0^*, x_1^*) . As its eigenvalue with a smaller absolute value is given by $\sim -1/\tau$ for large S , the time scale for adaptation is given by $\sim \tau$ and is independent of S . However, the peak time t^{peak} is given by $\sim 1/S_0$. Thus, the temporal profile of the response depends not only on p but also on S_0 . In this sense, our considered model does not satisfy the condition for FCD in [7].

We note that the adiabatic condition need not be rigid in order for Weber's law to be demonstrated reasonably well. Figure 1 shows a plot of the peak-value ratio $(x_0^{\text{peak}1} - x_0^*) / (x_0^{\text{peak}2} - x_0^*)$ obtained by multiplying S p -fold from S_0^1 or S_0^2 , respectively, as a function of τ . The ratio is close to unity; it is independent of the initial S_0 as long as $\tau/t^{\text{peak}} \sim \tau S_0 \geq 100$. In a previous study, we determined that for efficient chemotaxis [5], the ratio of the relaxation time to the response time to sense the environmental changes is on the order of 100, at several microorganisms such as *Paramecium* [8] and *E. coli* [14].

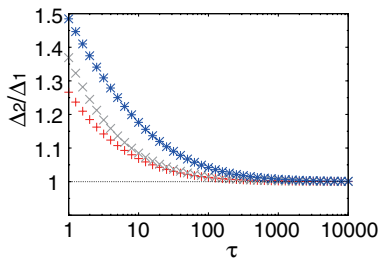


FIG. 1 (color online). Plot of ratio of maximum response amplitude Δ_2/Δ_1 (ordinate axis) versus τ (abscissa axis). $\Delta_i = x_0^{\text{peak}i} - x_0^*$ with the change $S_0^i \rightarrow pS_0^i$. $\Delta_2/\Delta_1 = 1$ implies the independence of the response amplitude from the S_0^i value, or Weber's law. Data with three different (S_0^1, S_0^2, p) sets are shown: $(S_0^1, S_0^2, p) = (5, 50, 2)$ for +, $(S_0^1, S_0^2, p) = (5, 500, 2)$ for x, and $(S_0^1, S_0^2, p) = (5, 50, 10)$ for *.

Thus, as estimated above, Weber's law is approximately satisfied for this time scale.

Adaptation obeying Weber's law is not restricted to this two-component reaction system; in fact, it is generally observed in a system with autocatalytic reactions with a slower timescale. We study several extensions of autocatalytic reaction networks showing adaptation with Weber's law. First, we consider an autocatalytic reaction occurring in series with N chemicals, as $S \rightarrow X_0 \rightarrow X_1 \rightarrow \dots \rightarrow X_{N-1}$. The rate equations are given by

$$\begin{aligned} dx_0/dt &= (S - \beta_1 x_0 x_1 - x_0)/\tau_0, \\ dx_i/dt &= (\beta_i x_{i-1} x_i - \beta_{i+1} x_i x_{i+1} - x_i)/\tau_i \quad (i \neq 0, N-1), \\ dx_{N-1}/dt &= (\beta_{N-1} x_{N-2} x_{N-1} - x_{N-1})/\tau_{N-1}. \end{aligned} \quad (2)$$

Then, the steady-state concentrations are obtained as $x_0^* = S/(\beta_1 x_1^* + 1)$, $x_i^* = (\beta_{i+2} x_{i+2}^* + 1)/\beta_{i+1}$ ($i \neq 0, N-2$), and $x_{N-2}^* = 1/\beta_{N-1}$. Accordingly, both the steady-state concentrations x_{N-2}^* and x_{N-2m}^* ($m > 1$) are independent of the external-signal concentration S , and these results show the adaptive response to the change in S . Here, we also note that the adaptation alone of the chemical x_{N-2} depends only on the reaction process $X_{N-3} \rightarrow X_{N-2} \rightarrow X_{N-1}$. As long as this chain reaction is autocatalytic and X_{N-2} increases with S , x_{N-2} undergoes perfect adaptation. We can modify other reaction processes while retaining the adaptive response of X_{N-2} .

First, we study the case of $N = 3$ in detail. For simplicity, we use $\beta_i = 1$. Suppose $x_i > 0$; the steady state is given by $x_0^* = S/2$, $x_1^* = 1$, and $x_2^* = (S-2)/2$, which is linearly stable if $S > 2$ and x_1 shows adaptive response to the change in S . The relaxation process to the state, however, depends on the time scale, as is confirmed from the eigenvalues of the Jacobi matrix (Fig. 2). To achieve a normal adaptive response with monotonic relaxation, $\tau_0 \ll \tau_1, \tau_2$ is required (for large S , $8\tau_0 < \tau_2$ and $\tau_0/2 < \tau_1/S < \tau_2/32$ [15]): otherwise, the system would show an adaptive response with damped oscillation.

An adaptive response with damped oscillation has often been observed in experiments, e.g., in [16,17]. In contrast, theoretical models for such oscillatory adaptation have

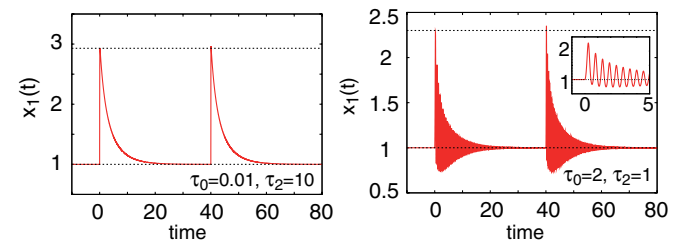


FIG. 2 (color online). Behaviors of an adaptive variable (x_1) in the $N = 3$ case. Responses corresponding to $S = 100 \rightarrow 200$ at $t = 0$ and $S = 200 \rightarrow 400$ at $t = 40$ are shown, respectively. (Left) $\tau_0 = 0.01$, $\tau_1 = 1$, $\tau_2 = 10$ and (Right) $\tau_0 = 2$, $\tau_1 = 1$, $\tau_2 = 1$, zoomed in the inset.

rarely been explored. Our proposed model provides a simple example of an oscillatory adaptive response.

In an autocatalytic reaction chain as well, Weber's law for responses is obeyed for only a certain range of parameters. Here, we study the conditions for Weber's law in the $N = 3$ case as an example. To analyze this case, we again study the system response to the change in S as $S_0 \rightarrow pS_0$ ($p > 0$). By setting $\tau_0 \ll \tau_1 \ll \tau_2$, we study the dynamics of x_1 and its peak value (x_1^{peak}) during an adaptive response. Since the change in x_0 is much faster than that in x_1 , x_0 is assumed to take the equilibrium value defined from the present x_1 value, and hence, x_0 is obtained from $dx_0/dt = 0$ as $x_0 = pS_0/(1 + x_1)$ for given x_1 . However, x_2 still remains at the equilibrium value under the condition $S = S_0$, i.e., $x_2 = (S_0 - 2)/2$. Using these values, x_1^{peak} that satisfies $(dx_1/dt)_{x_1=x_1^{\text{peak}}} = 0$ is given by $x_1^{\text{peak}} = 2p - 1$.

Accordingly, $x_1^{\text{peak}} - x_1^* = 2(p - 1)$ depends only on the ratio of change in S and not on the S_0 value itself. Thus, the model given by Eq. (2) with $N = 3$ obeys Weber's law under the limits of $\tau_0/\tau_1 \rightarrow 0$ and $\tau_2/\tau_1 \rightarrow \infty$.

To examine the validity of the above approximation, we numerically studied the peak-amplitude ratio of x_1 under varying τ_2 and τ_0 and constant τ_1 . This condition corresponds to the upper-left area in Fig. 3, where Weber's law is confirmed and x_1 shows a monotonic relaxation. In Fig. 3, however, we find another regime that (approximately) satisfies Weber's law in the lower-right triangle, where x_1 shows a damped oscillation and the above adiabatic conditions are not satisfied. Indeed, in this case, Weber's law is well obeyed for large S and τ_0 .

We now consider the response in the case that S changes as $S_0 \rightarrow pS_0$ ($p > 0$) with $\tau_0 \gg \tau_1$, τ_2 and $S_0 \gg 1$. We solve Eq. (2) with the initial condition $x_0(0) = S_0/2$, $x_1(0) = 1$, and $x_2(0) = (S_0 - 2)/2$ to obtain the first peak in x_1 at $t = t^{\text{peak}}$, which is expected to be $t^{\text{peak}} \ll 1$ because S is sufficiently large. From the assumption of large S and $\tau_0 \gg \tau_1$, x_0 is solved approximately as $x_0(t) \sim \frac{S_0}{2} + \frac{(p-1)S_0}{\tau_0} t$ for small t . Then, we get

$$\frac{d \ln x_1}{dt} \sim \frac{S_0(p-1)}{\tau_0 \tau_1} t - \frac{S_0}{(S_0 - 2)\tau_1} \{x_2(t) - x_2(0)\}. \quad (3)$$

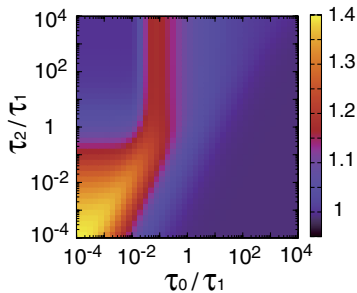


FIG. 3 (color online). Phase diagram with τ_0/τ_1 (abscissa axis) and τ_2/τ_1 (ordinate axis). Ratio of the maximum response amplitude, Δ_2/Δ_1 , is shown. $\Delta_2 = x_1^{\text{peak}} - x_1^*$ with $S = 200 \rightarrow 400$ and Δ_1 with $S = 100 \rightarrow 200$.

Temporarily neglecting the latter term for small t , we get $x_1 \sim \exp[S_0(p-1)t^2/(2\tau_0\tau_1)]$. By substituting this in $d(\ln x_2)/dt = (x_1 - 1)/\tau_2$, we get $x_2 = x_2(0) \exp[(p-1)S_0 t^3/(6\tau_0\tau_1\tau_2)]$. Now, with this increase in x_2 , the second term in Eq. (3) is no longer negligible, as a result of which the sign of Eq. (3) changes to negative and x_1 stops increasing. Thus, the time of occurrence of the first peak in x_1 is estimated from the time when the first term is equal to the second one as $(t^{\text{peak}})^2 \sim 12\tau_1\tau_2/S_0$. By substituting this value in the expression of x_1 , the peak value of x_1 is roughly estimated as $x_1^{\text{peak}} \sim \exp\{6(p-1)\tau_2/\tau_0\}$. Hence, the maximum amplitude depends on the change ratio of S and not on S_0 . Next, we numerically verified the dependence of the peak amplitude on τ 's from the original equation [Eq. (2)]. As shown in Fig. 4, the above approximations give good estimates for the peak position and explain the validity of Weber's law.

Note that we need to satisfy $t^{\text{peak}} \ll \tau_0$ as τ_0 takes the largest value among the three in this area. Then, we get

$$\tau_1\tau_2/\tau_0^2 \ll S_0/12, \quad (4)$$

which explains the boundary condition in the lower-right area. Note that the peak value itself increases as τ_2/τ_0 increases. Hence, to achieve an oscillatory response with a large amplitude, the value on the left-hand side of Eq. (4) should preferably be large. Then, an oscillatory response with Weber's law with a relatively large peak will be obtained at the border of the above condition.

For $N > 3$ as well, x_{N-2} shows an adaptive response with both monotonic relaxation and damped oscillation. For the former case, by carrying out similar analysis with $N = 3$ case, Weber's law is shown to hold under the condition of $\tau_0, \dots, \tau_{N-3} \ll \tau_{N-2} \ll \tau_{N-1}$. According to Eq. (2), x_{N-2m} ($m > 1$) also shows an adaptive response, and Weber's law for x_{N-2m} is satisfied when $\tau_0, \dots, \tau_{N-2m-1} \ll \tau_{N-2m} \ll \tau_{N-2m+1}$, i.e., if all processes of influx are fast and only the next runoff process

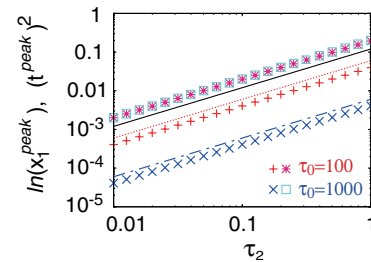


FIG. 4 (color online). Comparison between results of numerical simulation (points) and approximate calculation (lines). $\ln(x_1^{\text{peak}})$ and $(t^{\text{peak}})^2$ are shown as a function of τ_2 with τ_1 fixed to 1. $\ln(x_1^{\text{peak}})$ with $\tau_0 = 100$ (+) and $\tau_0 = 1000$ (x) and $(t^{\text{peak}})^2$ with $\tau_0 = 100$ (*) and $\tau_0 = 1000$ (□) are taken from the numerical simulation. The estimates of $\ln(x_1^{\text{peak}})$ with $\tau_0 = 100$ (dotted line) and $\tau_0 = 1000$ (broken line) and $(t^{\text{peak}})^2$ (straight line) in the text are also shown.

is slow. Weber's law with damped oscillation is also satisfied for large S and τ_0 .

We also studied the case of catalytic reaction networks having parallel paths. Two types of extensions are possible. In one extension, many terminal chemicals exist instead of a single x_1 in Eq. (1), which are reached in parallel from x_0 ($S \rightarrow X_0 \rightarrow X_1^1, X_1^2, X_1^3, \dots, X_1^k$). It can be straightforwardly shown that variable x_0 shows an adaptive response, since the mean field of all x_1^j 's acts as the variable of x_1 in the original two-variable case. Moreover, in this type of extension, each catalytic reaction need not be autocatalytic; that is, the reaction from x_0 to x_1^j can be catalyzed by x_1^m with $j \neq m$. Adaptation obeying Weber's law is possible in the adiabatic limit. The other extension includes reaction paths in two or more rows, each of which is a series reaction, as in the case of variable N ($S \rightarrow Y_0 \rightarrow A_1 \rightarrow \dots \rightarrow A_N \rightarrow Y_1$ and $S \rightarrow Y_0 \rightarrow B_1 \rightarrow \dots \rightarrow B_M \rightarrow Y_1$). Here, both an input variable (y_0) and an output variable (y_1) can show adaptive responses only when there are an odd number of elements in each row (N and M). In this case, adaptation obeying Weber's law is again possible, but there usually are more restrictions on the parameter values.

In this Letter, we have demonstrated that a simple autocatalytic reaction process in a system leads to its adaptation that obeys Weber's law. We first confirmed such an adaptation in an autocatalytic reaction of two variables. Coupling of one more variable to the reaction led to oscillatory adaptation obeying Weber's law. It would be interesting to explore such an adaptive response experimentally. Indeed, such an oscillatory adaptation was observed in cAMP concentration in *Dictyostelium* cells [16].

Generally, cells undergo autocatalytic reactions to replicate themselves, where complex autocatalytic reactions are often slower than simple catalytic ones. For example, in a sequential reaction process for the synthesis of a biopolymer that has catalytic activity for this chain reaction, more time would generally be required for a longer polymer. Also, the autocatalytic regulation exists in a system with allosteric enzyme reaction [11], and the (chain) autocatalytic reaction as in our model is known to exist in glycolytic reaction [11,18], as well as in the response to cAMP in *Dictyostelium* [19]. The results of this study suggest that adaptive response obeying Weber's law is generally observed in such systems with slow autocatalytic reactions.

Adaptation or habituation refers to a general property of a biological system to exhibit homeostasis, whereas Weber's law is applicable to a system exhibiting a sensory response over a wide range of environmental conditions. The variation in an external parameter S will often increase with its value. Then, if the response were just proportional to the difference in the external parameter before and after the input, it would be too sensitive to large S and would not be able to generate a reliable response under external noise. Thus, a response to fold change with Weber's law is applicable to sensory systems in general.

Here, Weber's law was obeyed in an autocatalytic reaction system with time scale differences, without any special design or tuning of the parameters. Because of its simplicity, the present mechanism is expected to have a wide range of applications. It may also offer fresh perspectives on Weber's law in general, including psychological and neural perspectives. Indeed, our proposed model can be regarded simply as a system with self-positive feedback and is not necessarily restricted to chemical reactions.

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