The Series of a Four-node Motif can Provide Sensitive Detection over Arbitrary Range of Signal, thereby Explain Weber's Law in Higher-Order Sensory Processes, and Compute Logarithm

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Abstract

Weber's law states that the ratio of the smallest perceptual change in a signal and the background signal is constant. The law is observed across the perception of weight, light intensity, and sound intensity and pitch. Conventionally, two models of perception have been proposed to explain Weber's law, namely the logarithmic and the linear model. Later, another formulation of Weber's law was proposed which links it with exact adaptation. This paper argues in favour of the linear model, which requires the sensory system to generate linear signal-response relationship over several orders of magnitude. To this end, a four-node motif is constructed from first principles which in series provides linear relationship between signal and response over arbitrary range of signal. The motif also reproduces the neuronal data of numerosity detection studies on monkey. The series of this motif provides a general mechanism of sensitive detection over arbitrary range of signal. The series also provides a general basis for a class of bow-tie architecture where the number of receptors is much lower than the range of signal and response. Besides numerosity processing, another example of this class of bow-tie architecture that the series of this motif is able to produce is absorption spectra of cone opsins of humans. Further, the series can compute logarithm over arbitrary range of signal.

Keywords: Sensitive detection, Weber's law, linear model, bow-tie architecture, numerosity processing, human cone cell, logarithm

1. Introduction

Ernst Weber discovered that the ratio of the smallest noticeable difference in a signal and the background signal is constant, a phenomenon now known as WeberCHAR13s law [1]. Later, Fechner showed that Weber's law could be explained by assuming that the perception is proportional to the logarithm of the signal (discussed in the section *Weber's Law*) [2]. Another model which can also account for WeberCHAR13s law is the linear model, according to which the response is equal to the signal plus noise which is proportional to the signal. In 1973, work of Mesibov et al. on bacterial chemotaxis suggested that *Escherichia coli* exhibits Weber's law, in that the bacteria response was dependent on the gradient of the logarithmic ligand concentration [3]. A theoretical study of a reduced model of *Escherichia coli*'s chemotaxis machinery showed that exact adaptation is necessary, though not sufficient, for the bacterial chemotaxis to exhibit Weber's law [4]. Later, an experimental and theoretical modelling study validated the reduced model [5].

Thus, inspired from the connection between Weber's law and exact adaptation in the bacterium, Weber's law has been formulated as an exactly adapting system generating identical maximum amplitude as a response to a signal if the ratio of the current signal to the background signal is constant [6,7]. The formulation has been applied to explain modified versions of Weber-Fechner and Stevens laws, found in human sensory systems [8]. However, it is doubtful that all higher-order sensory processes which show Weber's law exhibit scale-invariance with respect to the maximum amplitude. For example, consider the case of weight perception. Suppose the just noticeable difference (JND) for weight perception is 5% of the background, so that a subject holding a weight of 100 gm can feel the change in the weight if at least 5 gm of weight is added. The JND when the subject is holding 1 kg of weight is 50 gm. Although the ratio of the JND to the background signal is constant, the subject is able to sense the background weight and the additional weight in the absolute sense. The subject is not, if at all, just calculating the ratio between the two signals.

It has also been claimed that fold-change detection (FCD) entails Weber's law [6]. A system capable of providing FCD also shows exact adaptation, in which the response to a new input signal returns to the resting value of the system even when the signal persists. That FCD implies exact adaptation can be proven in the following way. Consider a system equilibrated at a stimulus X_0. Its baseline output is Z_0. It generates a certain output when a stimulus X_1 is provided. The ratio X_1/X_0 being the fold change, f. If the system does not show exact adaptation, the resting output of the system, equilibrated at stimulus X_1 (or fX_0), will not be equal to Z_0. If the system is capable of providing FCD, it will show identical response when the two stimuli are replaced by kX_0 and kX_1, respectively, where k is a scalar. Clearly, the output of the system equilibrated at stimulus kX_0 should be Z_0. This, then, leads to a contradiction if k is replaced with f. That is, when the stimulus is fX_0, the resting output of the system is Z_0 in the latter scenario, whereas it is not equal to Z_0 in the former scenario. Therefore, a system which shows FCD will also show exact adaptation.

However, it is doubtful that all higher-order sensory processes which show Weber's law exhibit exact adaptation. Again considering the case of weight perception, a subject holding a certain amount of weight continues to perceive the same amount of signal; that is, the perception of the weight does not come back to some resting value. The same argument applies also to the perception of sound intensity and brightness.

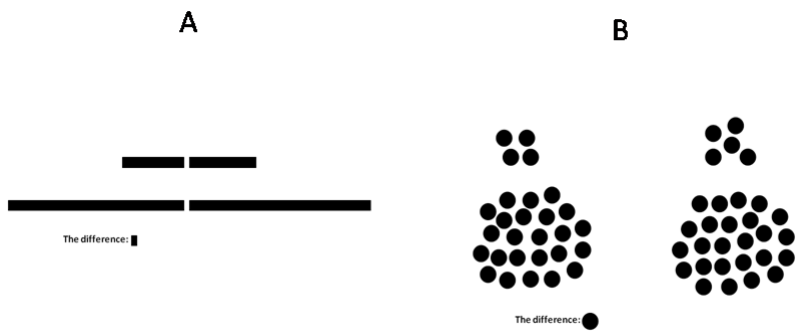

Figure 1: (**A**) Two pairs of rectangular strips which differ by the same length. (**B**) Two pairs of collections of discs numbering (i) 4 and 5; (ii) 24 and 25.

Weber's law is also observed in size (length/area/volume) perception, for which two examples are presented now. The first example demonstrates that the detection of difference between the length of two rectangular strips becomes more difficult with the increase in their lengths keeping the difference constant (Figure 1A). The second example shows that the human eye can easily notice the difference of one disc between collections of 4 and 5 such identical discs on a quick glance, whereas doing so is virtually impossible between collections of 24 ad 25 discs (Figure 1B). Weber's law is also observed in numerosity processing [9]. Because it is not clear how exact adaptation or scale-invariance with respect to the maximum amplitude could be present in weight perception, size perception, and numerosity processing; arguably, a general mechanism for Weber's law is needed which does not involve exact adaptation or scale-invariance with respect to the maximum amplitude. It also implies that such a mechanism should be able to generate linear signal-response relationship over several orders of magnitude.

2. Results

2.1. Linear Signal-Response Relationship Over Arbitrary Range

In order for a system to respond sensitively throughout the whole range of signal, the ideal relationship between a signal and the response should be a straight line with the slope of one. Such a formulation is presented now. Because sensory systems operate over several orders of magnitude, the formulation should be able to generate linear signal-response relationship over several orders of magnitude. This is achieved in the following way. Consider a collection of five receptors which bind a certain ligand, representing the signal, with the equilibrium dissociation constant (K_{da}) equal to 10^1, 10^2, 10^3, 10^4, and 10^5 arb. units, respectively. The signal, X, causes the *Z* producer (an imaginary generic form of gene) to produce Z. In order to have sensitive detection, that receptor should contribute to the output, Z, whose K_{da} is an order of magnitude larger than the strength of the signal (the concentration of X). Because the receptors meant to respond to signal of higher strength have lower binding affinities (larger K_{da}), their contribution to the output (or the production rate of Z, β_1) should be proportionally larger.

$$\frac{dZ}{dt} = \frac{\beta_1 \frac{X}{Kd_{XZ}}}{1 + \frac{X}{Kd_{XZ}}} - \alpha_1 Z \tag{1}$$

where, β_1 is the rate constant for production of Z by X. α_1 is the degradation rate of Z. Kd_{XZ} is the equilibrium dissociation constant for the binding of X to the producer element (an imaginary generic form of promoter) of Z, which causes Z production.

The equilibrium value of Z is

$$Z = \left[\frac{\frac{\beta_1}{\alpha_1} \frac{X}{Kd_{XZ}}}{1 + \frac{X}{Kd_{XZ}}} \right] \tag{2}$$

Choosing appropriate values of β_1/α_1 and Kd_{XZ}, the total output from the five receptors is

$$Z = \left[\frac{10 \frac{X}{10^1}}{1 + \frac{X}{10^1}} \right] + \left[\frac{10^2 \frac{X}{10^2}}{1 + \frac{X}{10^2}} \right] + \left[\frac{10^3 \frac{X}{10^3}}{1 + \frac{X}{10^3}} \right] + \left[\frac{10^4 \frac{X}{10^4}}{1 + \frac{X}{10^4}} \right] + \left[\frac{10^5 \frac{X}{10^5}}{1 + \frac{X}{10^5}} \right] \tag{3}$$

Let's assume that the value of the signal is of the order of magnitude of two. The receptor with Kd_{xz} equal to 10^3 is ought to generate output from the signal of this value. However, the receptors with Kd_{xz} equal to 10^1 and 10^2 arb. units, respectively, saturated by the signal, also contribute to the output. Thus, output from the receptors whose Kd_{xz} is either equal to or less than the order of magnitude of the signal should be removed. This is achieved by adding to the motif a “negative arm”: the signal X engenders production of the molecule Y which suppresses the output Z from such receptors. The signal X and the molecule Y bind to the producer element of Z in mutually exclusive manner. The resulting motif is type-1 incoherent feed-forward loop. Parameters of the negative arm are such that it suppresses the output mainly from the receptors whose Kd_{xz} is either equal to or less than the order of magnitude of the signal.

$$\frac{dY}{dt} = \frac{\beta_2 \frac{X}{Kd_{XY}}}{1 + \frac{X}{Kd_{XY}}} - \alpha_2 Y \tag{4}$$

$$\frac{dZ}{dt} = \left[\frac{\beta_1 \frac{X}{Kd_{XZ}}}{1 + \frac{X}{Kd_{XZ}}} \right] \cdot \left[\frac{1}{1 + \left(\frac{Y}{Kd_{YZ}} \right)^n} \right] - \alpha_1 Z \tag{5}$$

where, β_2 is the rate constant for production of Y by X. α_2 is the degradation rate of Y. Kd_{XY} is the equilibrium dissociation constant for the binding of X to the producer element of Y, which causes Y production. Kd_{YZ} is the equilibrium dissociation constant for the binding of Y to the producer element of Z, leading to suppression of Z production.

The equilibrium value of Y and Z are

$$Y = \frac{\frac{\beta_2}{\alpha_2} \frac{X}{Kd_{XY}}}{1 + \frac{X}{Kd_{XY}}} \tag{6}$$

$$Z = \left[\frac{\frac{\beta_1}{\alpha_1} \frac{X}{Kd_{XZ}}}{1 + \frac{X}{Kd_{XZ}}} \right] \cdot \left[\frac{1}{1 + \left(\frac{\left(\frac{1}{Kd_{YZ}} \frac{\beta_2}{\alpha_2} \right) \frac{X}{Kd_{XY}}}{1 + \frac{X}{Kd_{XY}}} \right)^n} \right] \tag{7}$$

The expression in the second pair of brackets on the right hand side of the equality in equation 7, representing suppression of the output by the signal, reaches an asymptotic value because the denominator in the expression reaches an asymptotic value. On the other hand, the formulation demands the expression to keep decreasing with increasing X. That is, the expression should be of the form: $1/(1+X)^n$. This is achieved in the following way. The expression in the second pair of brackets on the right hand side of the equality in equation 7 is approximately equal to

the expression 8, which is of the required form, at least in the parameter range of interest if the order of magnitude of $\left(\frac{1}{Kd_{YZ}}\frac{\beta_2}{\alpha_2}\right)$ is at least two (Figure 2A). This is because X/Kd_{XY} remains much less than 1 until the saturation has occurred.

$$\left[\frac{1}{1+\left(\left(\frac{1}{Kd_{YZ}}\frac{\beta_2}{\alpha_2}\right)\frac{X}{Kd_{XY}}\right)^n}\right] \tag{8}$$

$$\left[\frac{1}{1+\left(\frac{\left(\frac{1}{Kd_{YZ}}\frac{\beta_2}{\alpha_2}\right)\frac{X}{Kd_{XY}}}{1+\frac{X}{Kd_{XY}}}\right)^n}\right] \approx \left[\frac{1}{1+\left(\left(\frac{1}{Kd_{YZ}}\frac{\beta_2}{\alpha_2}\right)\frac{X}{Kd_{XY}}\right)^n}\right] \tag{9}$$

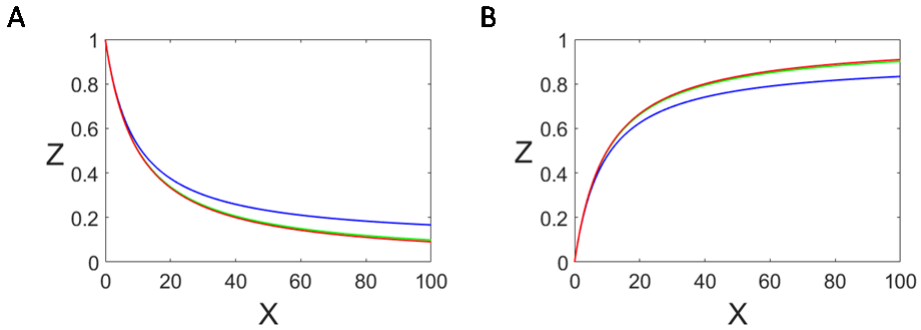

Figure 2: (**A**) The blue curve represents the expression $1/(1 + 10((x/100)/(1 + (x/100))))$. The green curve: $1/(1 + 100((x/1000)/(1 + (x/1000))))$. The red curve: $1/(1 + (x/10))$. (**B**) The blue curve represents the expression $10((x/100)/(1+(x/100)))/(1+10((x/100)/(1+(x/100))))$. The green curve: $100((x/1000)/(1 + (x/1000)))/(1 + 100((x/1000)/(1 + (x/1000))))$. The red curve: $(x/10)/(1 + (x/10))$.

To fulfill the aforementioned demand on the value of parameters of the negative arm, $Kd_{YZ}\left(\frac{\alpha_2}{\beta_2}\right)Kd_{XY}$, the effective equilibrium dissociation constant of this arm, is set equal to Kd_{XZ}. The total output from the five receptors is

$$Z = \left[\frac{10^1\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^1}}\right] + \left[\frac{10^2\frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^2}}\right] + \left[\frac{10^3\frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^3}}\right]$$

$$+\left[\frac{10^4\frac{X}{10^4}}{1+\frac{X}{10^4}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^4}}\right]+\left[\frac{10^5\frac{X}{10^5}}{1+\frac{X}{10^5}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^5}}\right] \tag{10}$$

The following is non-approximated form of the above equation

$$Z=\left[\frac{10^1\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{1}{1+\frac{10^2\frac{X}{10^3}}{1+\frac{X}{10^3}}}\right]+\left[\frac{10^2\frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{1}{1+\frac{10^2\frac{X}{10^4}}{1+\frac{X}{10^4}}}\right]+\left[\frac{10^3\frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{1}{1+\frac{10^2\frac{X}{10^5}}{1+\frac{X}{10^5}}}\right]+$$

$$\left[\frac{10^4\frac{X}{10^4}}{1+\frac{X}{10^4}}\right]\cdot\left[\frac{1}{1+\frac{10^2\frac{X}{10^6}}{1+\frac{X}{10^6}}}\right]+\left[\frac{10^5\frac{X}{10^5}}{1+\frac{X}{10^5}}\right]\cdot\left[\frac{1}{1+\frac{10^2\frac{X}{10^7}}{1+\frac{X}{10^7}}}\right] \tag{11}$$

However, a signal can generate output from those receptors also whose Kd_{xz} is larger than the signal by more than one order of magnitude. In the current case, this means that the signal of 10^2 arb. units being able to generate output from the receptors whose Kd_{xz} is equal to 10^4 and 10^5 arb. units, respectively. Output generated by each of the two receptors is approximately equal to 10^2 arb. units, which is of the same order as output generated by the receptor whose Kd_{xz} is equal to 10^3 arb. units. Output by the receptors whose Kd_{xz} is larger than the signal by more than one order of magnitude is removed by adding to the motif a “positive arm”: the signal X engenders production of the molecule V, which must also be bound along with X to the producer element of Z in order to engender Z production. Parameters of the positive arm are such that it lets mainly those receptors generate the output whose Kd_{xz} is at most one order of magnitude larger than the signal.

$$\frac{dV}{dt} = \frac{\beta_3 \frac{X}{Kd_{XV}}}{1 + \frac{X}{Kd_{XV}}} - \alpha_3 V \tag{12}$$

$$\frac{dY}{dt} = \frac{\beta_2 \frac{X}{Kd_{XY}}}{1 + \frac{X}{Kd_{XY}}} - \alpha_2 Y \tag{13}$$

$$\frac{dZ}{dt} = \left[\frac{\beta_1 \frac{X}{Kd_{XZ}}}{1 + \frac{X}{Kd_{XZ}}}\right] \cdot \left[\frac{\left(\frac{V}{Kd_{VZ}}\right)^m}{1 + \left(\frac{V}{Kd_{VZ}}\right)^m}\right] \cdot \left[\frac{1}{1 + \left(\frac{Y}{Kd_{YZ}}\right)^n}\right] - \alpha_1 Z \tag{14}$$

where, β_1, β_2, and β_3 are the rate constants for production of Z, Y, an V, respectively, by X. α_1, α_2, and α_3 are the degradation rates of Z, Y, and V, respectively. Kd_{XZ}, Kd_{XY}, and Kd_{XV} are the equilibrium dissociation constants for the binding of X to the element of Z, Y, and V, respectively, which causes production of Z, Y, and V, respectively. Kd_{YZ} and Kd_{VZ} are the equilibrium dissociation constants for the binding of Y and V, respectively, to the element of Z, which causes Z production.

The equilibrium value of V, Y, and Z

$$V = \frac{\frac{\beta_3}{\alpha_3} \frac{X}{Kd_{XV}}}{1 + \frac{X}{Kd_{XV}}} \tag{15}$$

$$Y = \frac{\frac{\beta_2}{\alpha_2} \frac{X}{Kd_{XY}}}{1 + \frac{X}{Kd_{XY}}} \tag{16}$$

$$Z = \left[\frac{\frac{\beta_1}{\alpha_1}\frac{X}{Kd_{XZ}}}{1+\frac{X}{Kd_{XZ}}}\right] \cdot \left[\frac{\left(\frac{\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}}{1+\frac{X}{Kd_{XV}}}\right)^m}{1+\left(\frac{\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}}{1+\frac{X}{Kd_{XV}}}\right)^m}\right] \cdot \left[\frac{1}{1+\left(\frac{\left(\frac{1}{Kd_{YZ}}\frac{\beta_2}{\alpha_2}\right)\frac{X}{Kd_{XY}}}{1+\frac{X}{Kd_{XY}}}\right)^n}\right] \tag{17}$$

The formulation demands that the expression in the second pair of brackets on the right hand side of the equality in equation 17, representing the generation of the output by the signal X and the molecule V according to the AND logic, should be of the form $X^n/(1 + X)^n$. This is achieved in the following way. As previously, the expression in the second pair of brackets on the right hand side of the equality in equation 17 is approximately equal to the expression 18 at least in the parameter range of interest if the order of magnitude of $\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)$ is at least two (Figure 2B). This is because X/Kd_{XV} remains much less than 1 until the saturation has occurred.

$$\left[\frac{\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)^m}{1+\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)^m}\right] \tag{18}$$

$$\left[\frac{\left(\frac{\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}}{1+\frac{X}{Kd_{XV}}}\right)^m}{1+\left(\frac{\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}}{1+\frac{X}{Kd_{XV}}}\right)^m}\right] \approx \left[\frac{\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)^m}{1+\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)^m}\right] \tag{19}$$

To fulfill the aforementioned demand on the value of parameters of the positive arm, $Kd_{VZ}\left(\frac{\alpha_3}{\beta_3}\right)Kd_{XV}$, the effective equilibrium dissociation constant of this arm, is set equal to $Kd_{XZ}/10$. The total

output from the five receptors is

$$Z = \left[\frac{10^1 \frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{\frac{X}{10^0}}{1+\frac{X}{10^0}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^1}}\right]+\left[\frac{10^2 \frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^2}}\right]+\left[\frac{10^3 \frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{\frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^3}}\right]$$

$$+\left[\frac{10^4 \frac{X}{10^4}}{1+\frac{X}{10^4}}\right]\cdot\left[\frac{\frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^4}}\right]+\left[\frac{10^5 \frac{X}{10^5}}{1+\frac{X}{10^5}}\right]\cdot\left[\frac{\frac{X}{10^4}}{1+\frac{X}{10^4}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^5}}\right] \tag{20}$$

The following is non-approximated form of the above equation

$$Z = \left[\frac{10^1 \frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{\frac{10^2 \frac{X}{10^2}}{1+\frac{X}{10^2}}}{1+\frac{10^2 \frac{X}{10^2}}{1+\frac{X}{10^2}}}\right]\cdot\left[\frac{1}{1+\frac{10^2 \frac{X}{10^3}}{1+\frac{X}{10^3}}}\right]+\left[\frac{10^2 \frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{\frac{10^2 \frac{X}{10^3}}{1+\frac{X}{10^3}}}{1+\frac{10^2 \frac{X}{10^3}}{1+\frac{X}{10^3}}}\right]\cdot\left[\frac{1}{1+\frac{10^2 \frac{X}{10^4}}{1+\frac{X}{10^4}}}\right]+$$

$$\left[\frac{10^3 \frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{\frac{10^2 \frac{X}{10^4}}{1+\frac{X}{10^4}}}{1+\frac{10^2 \frac{X}{10^4}}{1+\frac{X}{10^4}}}\right]\cdot\left[\frac{1}{1+\frac{10^2 \frac{X}{10^5}}{1+\frac{X}{10^5}}}\right]+\left[\frac{10^4 \frac{X}{10^4}}{1+\frac{X}{10^4}}\right]\cdot\left[\frac{\frac{10^2 \frac{X}{10^5}}{1+\frac{X}{10^5}}}{1+\frac{10^2 \frac{X}{10^5}}{1+\frac{X}{10^5}}}\right]\cdot\left[\frac{1}{1+\frac{10^2 \frac{X}{10^6}}{1+\frac{X}{10^6}}}\right]+$$

$$\left[\frac{10^5 \frac{X}{10^5}}{1+\frac{X}{10^5}}\right]\cdot\left[\frac{\frac{10^2 \frac{X}{10^6}}{1+\frac{X}{10^6}}}{1+\frac{10^2 \frac{X}{10^6}}{1+\frac{X}{10^6}}}\right]\cdot\left[\frac{1}{1+\frac{10^2 \frac{X}{10^7}}{1+\frac{X}{10^7}}}\right] \tag{21}$$

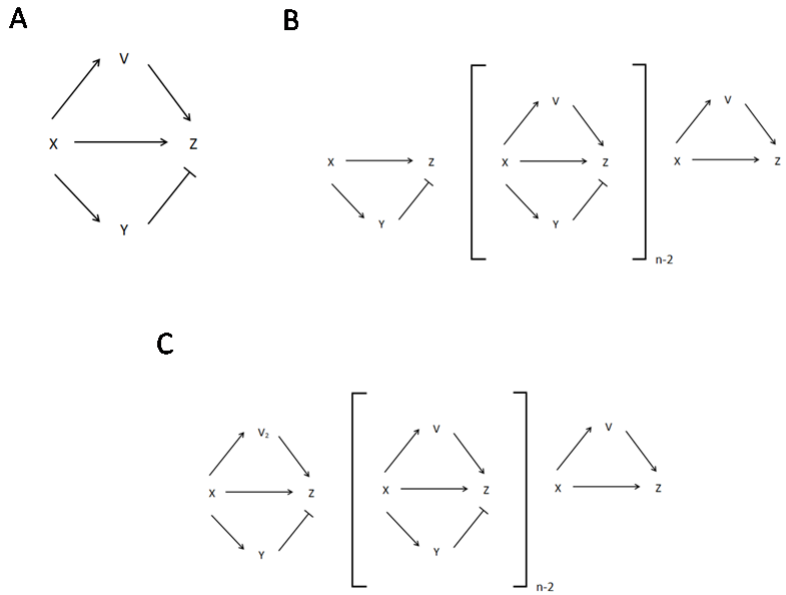

Figure 3: (**A**) The four-node motif which in series can generate linear signal-response relationship and compute logarithm. (**B**) The series for generating linear signal-response relationship. (**C**) The series for computing logarithm.

Hence, together the negative arm and the positive arm create a window which shows maximum response to signal of a particular order of magnitude and whose response declines progressively as the distance between the preferred order of magnitude and the order of magnitude of signal increases in either direction. Further, the signal-response curve is right-skewed. Figure 4 shows signal-response relationship of a single four-node motif with four combinations of the Hill-coefficients. Increasing the value of m introduces steepness at the leftmost end of the output, whereas increasing the value of n causes the output to have higher and sharper peak and decline quickly. Notably, because a) β_1/α_1 is equal to Kd_{xz}, b) the effective equilibrium dissociation constant of the negative arm is equal to Kd_{xz}, c) the effective equilibrium dissociation constant of the positive arm is equal to $Kd_{xz}/10$, the value of Kd_{xz} is sufficient to specify all other parameters of the four-node motif whose series produces linear signal-response relationship, as shown below. Since the first receptor does not need the positive arm (nor it should have the positive arm because the arm causes the output of the series to further deviate from linearity in the leftmost end of the output) and the last receptor should not have the negative arm (otherwise

a very large signal will generate a very small output), the expression for the output should be:-

$$Z = \left[\frac{10^1 \frac{X}{10^1}}{1 + \frac{X}{10^1}}\right] \cdot \left[\frac{1}{1 + \frac{X}{10^1}}\right] + \left[\frac{10^2 \frac{X}{10^2}}{1 + \frac{X}{10^2}}\right] \cdot \left[\frac{\frac{X}{10^1}}{1 + \frac{X}{10^1}}\right] \cdot \left[\frac{1}{1 + \frac{X}{10^2}}\right] + \left[\frac{10^3 \frac{X}{10^3}}{1 + \frac{X}{10^3}}\right] \cdot \left[\frac{\frac{X}{10^2}}{1 + \frac{X}{10^2}}\right] \cdot \left[\frac{1}{1 + \frac{X}{10^3}}\right]$$

$$+ \left[\frac{10^4 \frac{X}{10^4}}{1 + \frac{X}{10^4}}\right] \cdot \left[\frac{\frac{X}{10^3}}{1 + \frac{X}{10^3}}\right] \cdot \left[\frac{1}{1 + \frac{X}{10^4}}\right] + \left[\frac{10^5 \frac{X}{10^5}}{1 + \frac{X}{10^5}}\right] \cdot \left[\frac{\frac{X}{10^4}}{1 + \frac{X}{10^4}}\right] \tag{22}$$

The following is non-approximated form of the above equation

$$Z = \left[\frac{10^1 \frac{X}{10^1}}{1 + \frac{X}{10^1}}\right] \cdot \left[\frac{1}{1 + \frac{10^2 \frac{X}{10^3}}{1 + \frac{X}{10^3}}}\right] + \left[\frac{10^2 \frac{X}{10^2}}{1 + \frac{X}{10^2}}\right] \cdot \left[\frac{\frac{10^2 \frac{X}{10^3}}{1 + \frac{X}{10^3}}}{1 + \frac{10^2 \frac{X}{10^3}}{1 + \frac{X}{10^3}}}\right] \cdot \left[\frac{1}{1 + \frac{10^2 \frac{X}{10^4}}{1 + \frac{X}{10^4}}}\right] +$$

$$\left[\frac{10^3 \frac{X}{10^3}}{1 + \frac{X}{10^3}}\right] \cdot \left[\frac{\frac{10^2 \frac{X}{10^4}}{1 + \frac{X}{10^4}}}{1 + \frac{10^2 \frac{X}{10^4}}{1 + \frac{X}{10^4}}}\right] \cdot \left[\frac{1}{1 + \frac{10^2 \frac{X}{10^5}}{1 + \frac{X}{10^5}}}\right] + \left[\frac{10^4 \frac{X}{10^4}}{1 + \frac{X}{10^4}}\right] \cdot \left[\frac{\frac{10^2 \frac{X}{10^5}}{1 + \frac{X}{10^5}}}{1 + \frac{10^2 \frac{X}{10^5}}{1 + \frac{X}{10^5}}}\right] \cdot \left[\frac{1}{1 + \frac{10^2 \frac{X}{10^6}}{1 + \frac{X}{10^6}}}\right] +$$

$$\left[\frac{10^5 \frac{X}{10^5}}{1 + \frac{X}{10^5}}\right] \cdot \left[\frac{\frac{10^2 \frac{X}{10^6}}{1 + \frac{X}{10^6}}}{1 + \frac{10^2 \frac{X}{10^6}}{1 + \frac{X}{10^6}}}\right] \tag{23}$$

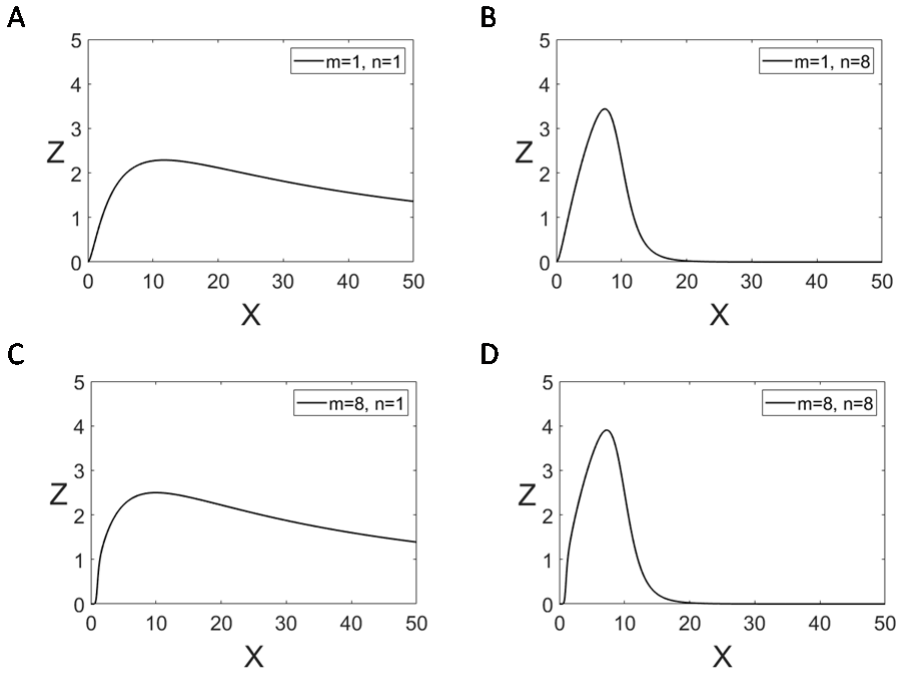

Figure 4: (**A-D**) Output of the four-node motif defined by the equation $[10 \cdot (X/10)/(1+X/10)] \cdot [(X/1)^m/(1+(X/1)^m)] \cdot [1/(1+(X/10)^n)]$ with different values of the Hill-coefficients m and n.

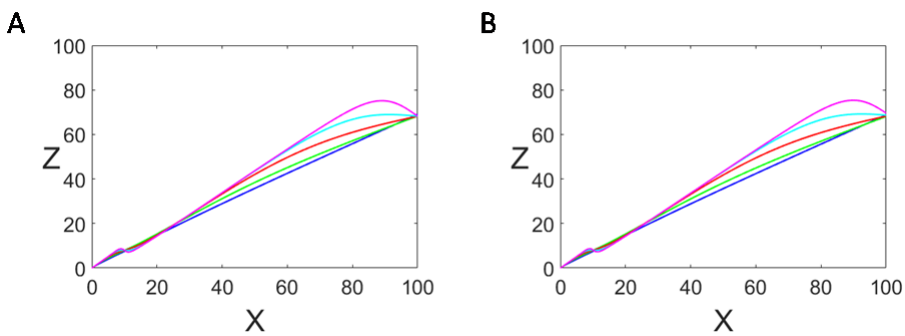

Figure 5: Output from the first three receptors for the approximated form (**A**) and non-approximated form (**B**) when m=1, n=1 (blue); m=1, n=2 (green); m=1, n=4 (red); m=1, n=8 (cyan); m=1, n=16 (pink).

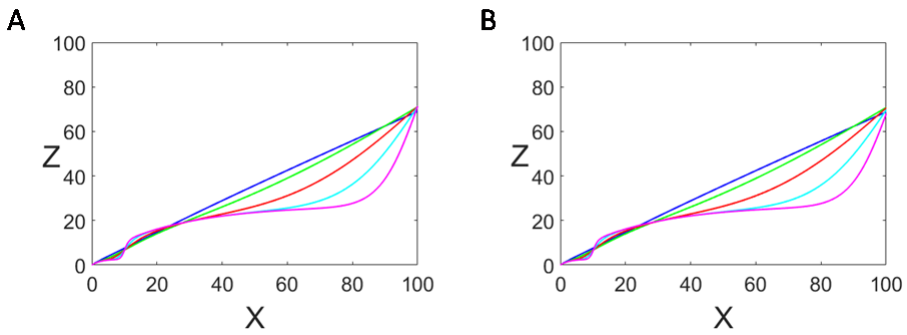

Figure 6: Output from the first three receptors for the approximated form (**A**) and non-approximated form (**B**) when m=1, n=1 (blue); m=2, n=1 (green); m=4, n=1 (red); m=8, n=1 (cyan); m=16, n=1 (pink).

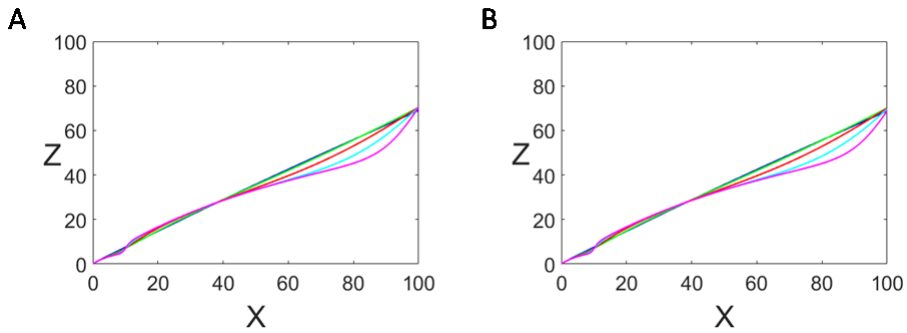

Figure 7: Output from the first three receptors for the approximated form (**A**) and non-approximated form (**B**) when m=1, n=1 (blue); m=2, n=2 (green); m=4, n=4 (red); m=8, n=8 (cyan); m=16, n=16 (pink).

It could be observed that output of equation 22 with the Hill-coefficients m and n being equal to one was a curve with a slight concavity for signal's values up to one order of magnitude less than Kd_{xz} of the last receptor. As the signal's value increases further, the output for all the combinations of m and n starts to plateau. That the output plateaus for very large signal may explain why humans do not have a refined sense for very large numbers, and thus they are represented by the term infinity.

In order to assess how well equation 23 approximates equation 22, output of equation 23 was fitted with equation 22 having each of its term multiplied with a coefficient (equation 24). If equation 23 is a good approximation of equation 22, the value of the coefficients should turn out to be around one, besides goodness-of-fit (r^2) being close to one. Because output of equation 22 (and hence also equation 23) begins to plateau as the signal's value goes beyond Kd_{xz} of the penultimate receptor (whose value is 10^4), the signal's values at which output of equation 23 was generated for the purpose of fitting were 1, 2, 5, 10, 20, 50, 10^2, $2\cdot10^2$, $5\cdot10^2$, 10^3, $2\cdot10^3$, $5\cdot10^3$, 10^4. Except for the value of the coefficient A for m=2, n=1; m=4, n=1; m=8, n=1; and m=16, n=1, the values of all the coefficients for all the combinations m and n were close to one and goodness-of-fit was equal to one (Supplementary Information, Table 1-3). Specifically, for m and n equal to one, the value of A, B, C, D, E were 1.0075, 0.9948, 0.9974, 0.9968, 0.9963, respectively.

$$Z = A\cdot\left[\frac{10^1\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^1}}\right]+B\cdot\left[\frac{10^2\frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^2}}\right]+C\cdot\left[\frac{10^3\frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{\frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^3}}\right]$$

$$+D\cdot\left[\frac{10^4\frac{X}{10^4}}{1+\frac{X}{10^4}}\right]\cdot\left[\frac{\frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^4}}\right]+E\cdot\left[\frac{10^5\frac{X}{10^5}}{1+\frac{X}{10^5}}\right]\cdot\left[\frac{\frac{X}{10^4}}{1+\frac{X}{10^4}}\right] \quad (24)$$

As stated above, the ideal relationship between a signal and the response should be a straight line with the slope of one, but output of equation 22 with m=1, n=1 has a slight concavity up until the signal's value is less than Kd_{xz} of the penultimate receptor (after which it plateaus). Thus, in order to assess if, given a range of Kd_{xz}, there is a range of signal in which the series could generate linear signal-response relationship, the output was fitted with straight line for various ranges of Kd_{xz} and signal (Table 1). For a given range of signal, the values at which the output was generated for the purpose of fitting were taken as powers of ten. For example, for the range 10^{-1}–10^{3}, the output was generated at the following values: 10^{-1}, 10^{0}, 10^{1}, 10^{2}, and 10^{3}.

Table 1: Slope and goodness of fit (R^2) for the fit of the output with straight line for various ranges of signal and Kd_{xz}.

Signal Range (across) **Kd_{xz} Range (down)**	10^{0}–10^{2}	10^{-1}–10^{3}	10^{-2}–10^{4}	10^{-3}–10^{5}	10^{-4}–10^{6}
10^{-2}–10^{4}	0.736 (1.0000)	0.6867 (1.0000)	0.4573 (0.9975)	NA	NA
10^{-3}–10^{5}	0.7455 (1.0000)	0.7363 (1.0000)	0.6872 (1.0000)	0.4585 (0.9975)	NA
10^{-4}–10^{6}	0.7465 (1.0000)	0.7455 (1.0000)	0.7364 (1.0000)	0.6875 (1.0000)	0.4591 (0.9975)
10^{-5}–10^{7}	0.7466 (1.0000)	0.7465 (1.0000)	0.7455 (1.000)	0.7365 (1.0000)	0.6876 (0.9999)
10^{-6}–10^{8}	0.7466 (1.0000)	0.7466 (1.0000)	0.7465 (1.0000)	0.7455 (1.0000)	0.7365 (1.0000)

For the middle intervals, the slope converges to the value 0.7466. In other words, if the output is multiplied by the reciprocal of this value, one gets a straight line with the slope of 1 for the middle intervals. Because there is no limit on the number of the receptors, the series can generate linear signal-response relationship over arbitrary range of signal. For the values of m and/or n being more than one, the output becomes oscillatory around the output generated with m=1 and n=1 (Figures 5, 6, and 7). Therefore, I posit that V and Y molecules should be present as monomers in a real system.

The exact same result was got when the range of Kd_{xz} and concomitantly the range of signal were shifted by the factor of 0.01, 0.1, 10, and 100. That is, for example, for the second case the new ranges of Kd_{xz} were 10^{-3}–10^{3}, 10^{-4}–10^{4}, 10^{-5}–10^{5}, 10^{-6}–10^{6}, and 10^{-7}–10^{7}. And the new ranges of signal were 10^{-1}–10^{1}, 10^{-2}–10^{2}, 10^{-3}–10^{3}, 10^{-4}–10^{4}, and 10^{-5}–10^{5}. Similarly, for the third case the new ranges of Kd_{xz} were 10^{-1}–10^{5}, 10^{-2}–10^{6}, 10^{-3}–10^{7}, 10^{-4}–10^{8}, and 10^{-5}–10^{9}. And the new ranges of signal were 10^{1}–10^{3}, 10^{0}–10^{4}, 10^{-1}–10^{5}, 10^{-2}–10^{6}, and 10^{-3}–10^{7}. As the ranges of Kd_{xz} were multiplied by the factor of 0.01, 0.1, 10, and 100, the y-intercept of the fitted line were 0.01, 0.1, 10, and 100 times the previous y-intercept, respectively. Explanation of this observation is as follows. The first transformation, for example, is $f(x) \rightarrow 0.01 \cdot f(x/0.01)$. Because the y-intercept should be zero when x is zero, it can be considered as the deviation of the output from the straight line. The multiplicative factor of 0.01 implies that the error also gets multiplied by 0.01; hence the y-intercept is 0.01 times it was before the transformation. In other words, $y = mx + c \rightarrow y = 0.01 \cdot mx/0.01 + 0.01 \cdot c$

2.2. Weber's Law

Now I present a formalism to get Weber's law from equation 22, which, when multiplied by the factor of (1/0.7466), yields $Z = X$ for intermediate range of values of X. Given a signal ($X = \mu$), the output (Z) is considered to be the result of sampling from a Gaussian distribution with mean equal to μ and standard deviation linearly proportional to μ; that is, $\sigma = f\mu$, where f is the Weber fraction, the ratio of the smallest perceptual change in a signal (ΔX_{min}) and the background signal ($X_{background}$): $\Delta X_{min}/X_{background} = f$. It is posited here that the subject is able to perceive a change in the signal when the ratio of non-overlapping region of the Gaussian centered on μ_2 to the right of the Gaussian centered on μ_1 and the area under the Gaussian centered on μ_1, is above a certain threshold (figure 8). Because the Gaussians in consideration are normalized, the ratio is equal to the non-overlapping region.

As is defined now, the non-overlapping region is just below the threshold when $\mu_2 - \mu_1 = \sigma_1$;

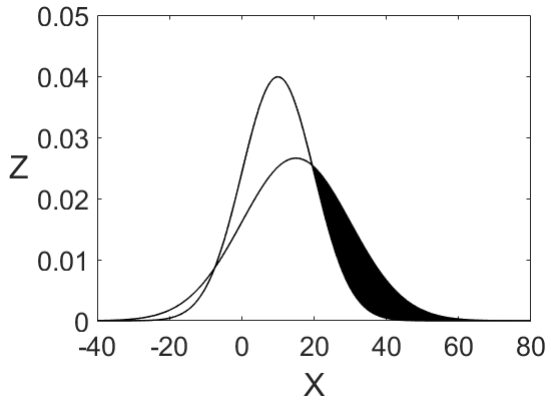

Figure 8: The Gaussian on the left has mean μ_1=10, and the Gaussian on the right has mean μ_2=15. The shaded portion is the non-overlapping region, R

that is, when the difference between mean of the current signal and mean of the background signal is equal to the standard deviation of the background signal. In other words, σ_1 is the just noticeable difference (JND). The non-overlapping area (R) is $F_1(p_2)$ - $F_2(p_2)$, where F(X) is the cumulative distribution function of Gaussian distribution and p_2 is the farther point of intersection of the two Gaussians when $\mu_2 - \mu_1 = \sigma_1$. That is, this point is the bigger-valued solution of the quadratic equation below. It should be noted that the total output, given by equation 22, consists of the sum of outputs by individual receptors. But that still does not affect the formalism above because the individual outputs are independent, and thus the sum of the individual means is μ and the sum of the individual standard deviations is σ.

$$\frac{1}{\sqrt{2\pi\sigma_1^2}} e^{-\frac{(p-\mu_1)^2}{2\sigma_1^2}} = \frac{1}{\sqrt{2\pi\sigma_2^2}} e^{-\frac{(p-\mu_2)^2}{2\sigma_2^2}} \tag{25}$$

$$\ln\left|\frac{\sigma_2}{\sigma_1}\right| = \frac{(p-\mu_1)^2}{2\sigma_1^2} - \frac{(p-\mu_2)^2}{2\sigma_2^2} \tag{26}$$

$$\frac{\ln\left|\frac{\sigma_2}{\sigma_1}\right|}{\left(\frac{1}{\sigma_1} - \frac{1}{\sigma_2}\right)} = p\left[\left(\frac{1}{\sigma_1} + \frac{1}{\sigma_2}\right)p - \frac{2}{f}\right] \tag{27}$$

Setting $C = \dfrac{\ln\left|\dfrac{\sigma_2}{\sigma_1}\right|}{\left(\dfrac{1}{\sigma_1} - \dfrac{1}{\sigma_2}\right)}$, $A = \left(\dfrac{1}{\sigma_1} + \dfrac{1}{\sigma_2}\right)$, $B = \dfrac{2}{f}$

Equation 27 becomes

$$C = p[Ap - B] \quad \text{or} \quad Ap^2 - Bp - C = 0 \tag{28}$$

$$p_{1,2} = \frac{B \pm \sqrt{B^2 4AC}}{2A} \tag{29}$$

$$p_2 = \frac{\dfrac{2}{f} + \sqrt{\left(\dfrac{2}{f}\right)^2 + 4\left(\dfrac{1}{\sigma_1} + \dfrac{1}{\sigma_2}\right)\dfrac{\ln\left|\dfrac{\sigma_2}{\sigma_1}\right|}{\left(\dfrac{1}{\sigma_1} - \dfrac{1}{\sigma_2}\right)}}}{2\left(\dfrac{1}{\sigma_1} + \dfrac{1}{\sigma_2}\right)} \tag{30}$$

Setting $\dfrac{\sigma_2}{\sigma_1} = 1 + f$

$$p_2 = \frac{\mu_1\left(1 + \sqrt{1 + f(2 + f)\ln|1 + f|}\right)}{\left(1 + \dfrac{1}{1 + f}\right)} \tag{31}$$

The expression 31 can be written as $p_2 = \mu_1 g(f)$

The CDF of a Gaussian distribution with mean μ and variance σ^2 is

$$F(Y) = \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{Y - \mu}{\sigma\sqrt{2}}\right)\right]$$

Hence

$$R = \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{p_2 - \mu_1}{\sigma_1\sqrt{2}}\right)\right] - \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{p_2 - \mu_2}{\sigma_2\sqrt{2}}\right)\right] \tag{32}$$

Inserting the value of p_2 in equation 32

$$R = \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{\mu_1 g(f) - \mu_1}{\sigma_1\sqrt{2}}\right)\right] - \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{\mu_1 g(f) - \mu_2}{\sigma_2\sqrt{2}}\right)\right] \tag{33}$$

$$R = \frac{1}{2}\left[1 + \mathrm{erf}\left(\frac{g(f) - 1}{f\sqrt{2}}\right)\right] - \frac{1}{2}\left[1 + \mathrm{erf}\left(\frac{g(f)/(1 + f) - 1}{f\sqrt{2}}\right)\right] \tag{34}$$

Being a function of f alone, R can be written as $R = h(f)$. It also implies that the value of R remains the same when the two means are multiplied by a scalar. This is because the two Gaussians become flatter, whereas the point p_2 goes farther. Hence, the non-overlapping region stays constant when the two signals are multiplied by a scalar, which is Weber' law.

$$\frac{\Delta X_{\mathrm{min}}}{X_{\mathrm{background}}} = \frac{\mu_2 - \mu_1}{\mu_1} = \frac{\sigma_1}{\mu_1} = f = h^{-1}(R) \tag{35}$$

In the formalism presented here, Weber's law is the result of internal noise whose standard deviation is proportional to the signal. On the other hand, Fechner's explanation is based on the assumption that the response is proportional to a logarithm of the signal, and JND therefore is a constant increment in the response.

$$Z_0 = \log(X_0) \tag{36}$$

$$Z_1 = \log(X_0 + \Delta X_{\mathrm{min}}) \tag{37}$$

$$\Delta Z = Z_1 - Z_0 = \log\left(1 + \frac{\Delta X_{\mathrm{min}}}{X_0}\right) \tag{38}$$

$$e^{\Delta Z} - 1 = \frac{\Delta X_{\mathrm{min}}}{X_0} = f \tag{39}$$

However, Fechner's formulation does not provide a biological basis of the relation between the Weber fraction and ΔZ. Also, the response being logarithm of the signal does not seem natural. Two Wildebeests butting their head against each other should not compute logarithm of the force that they receive from the other in the process. Otherwise, a force four times as large will appear larger by only log4. With such a sensory system the weaker animal will be much more injured at the end of the fight than if the sensory system were to convert the signal to an equally valued response.

In order to validate the above-stated formalism for Weber's law, which assumes output of equation 23 (approximated as equation 22) to be noisy and thus considers it to be equivalent to sampling from Gaussian distribution centered on the signal's value, output of equation 23 should be shown to be a Gaussian distribution with mean equal to the signal's value and standard deviation proportional to the mean when output generated by individual components of the four-node motif are considered to be the result of sampling from their corresponding Gaussian distributions. That is, given the signal X, the value of V and Y are generated from Gaussian distribution with mean equal to $\frac{\beta_3}{\alpha_3}\frac{X}{Kd_{XV}}\Big/\left(1+\frac{X}{Kd_{XV}}\right)$ and $\frac{\beta_2}{\alpha_2}\frac{X}{Kd_{XY}}\Big/\left(1+\frac{X}{Kd_{XY}}\right)$ respectively, and the standard deviation equal to Weber fraction times the respective mean.

Then, with the value of X, V and Y, Z is generated from Gaussian with mean equal to

$$\left[\frac{\beta_1\frac{X}{Kd_{XZ}}}{1+\frac{X}{Kd_{XZ}}}\right]\cdot\left[\frac{\left(\frac{V}{Kd_{VZ}}\right)^m}{1+\left(\frac{V}{Kd_{VZ}}\right)^m}\right]\cdot\left[\frac{1}{1+\left(\frac{Y}{Kd_{YZ}}\right)^n}\right]$$

and the standard deviation equal to Weber fraction times the expression. Adding output of all receptors and multiplying by the reciprocal of 0.7466 should turn out to be equivalent to sampling from a Gaussian centered on the signal X and standard deviation equal to a constant time mean. It should be noted that because the signal-response curve is linear only for the middle values of signal, the order of magnitude of X should be the preferred order of magnitude of the middle receptors.

The expanded form of the expression is

$$\left[\frac{\frac{\beta_1}{\alpha_1}\frac{X}{Kd_{XZ}}}{1+\frac{X}{Kd_{XZ}}}\right]\cdot\left[\frac{\left(\frac{\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}}{1+\frac{X}{Kd_{XV}}}\right)^m}{1+\left(\frac{\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}}{1+\frac{X}{Kd_{XV}}}\right)^m}\right]\cdot\left[\frac{1}{1+\left(\frac{\left(\frac{1}{Kd_{YZ}}\frac{\beta_2}{\alpha_2}\right)\frac{X}{Kd_{XY}}}{1+\frac{X}{Kd_{XY}}}\right)^n}\right]$$

The value of $\beta_2/\alpha_2 Kd_{YZ}$ and $\beta_3/\alpha_3 Kd_{VZ}$ were set equal to 100 in order to carry out the approximations (equations 9 and 19), respectively. However, values of β_2/α_2 and β_3/α_3, required to generate the value of V and Y from the signal X, are not known individually. Therefore I considered three combinations of β_2/α_2 and Kd_{YZ} while keeping the value of their product equal to 100. The combinations are β_2/α_2=100 and Kd_{YZ}=1, β_2/α_2=10 and Kd_{YZ}=10, and β_2/α_2=1, Kd_{YZ}=100. The same was done with β_3/α_3 and Kd_{VZ}.

Given a value of mean (X) and Weber fraction (f), ten thousand values of Z were generated from this sampling procedure and fitted with a Gaussian distribution. This procedure was carried out for thirty times. For a given value of f, the average of mean and standard deviation of the fitted Gaussian for mean equal to 0.1, 1, and 10 (and therefore, standard deviation equal to f·0.1, f·1, and f·10, respectively) were fitted with straight line (i.e, regressed against output of p1+p2·mean and p1+p2·f·mean, respectively). The value of f taken were 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, and 1. As expected, the slope of the fit was very close of 1, the y-intercept was very close to zero (of the order of magnitude -4), and R^2 was equal to 1 for all the nine combinations up to f equal to 0.2 for both mean and standard deviation (Supplementary Information, Tables 7-13). Curiously, given a value of f, the straight line fit of standard deviation of the Gaussian fit of ten thousand values sampled from the Gaussian random variable generator for mean equal to 0.1, 1, and 10 (and therefore, standard deviation equal to f·0.1, f·1, and f·10, respectively) was consistently approximately 1.4 times the value of f, instead of being equal to it (Table 15, Supplementary Information, Table 15).

2.3. Explaining Numerosity Processing Data

In 2002, two studies [10,11], investigating parietal cortex and prefrontal cortex, respectively, observed the presence of neurons whose firing rate was tuned to a specific numerosity. In a study by Nieder and Miller [12], the activity of neurons from the lateral prefrontal cortex displayed a maximum at a preferred number and declined progressively as the numerical distance from that preferred number was increased, thereby forming numerosity filter function. The tuning curves, which were skewed towards the right on a linear scale, were plotted on nonlinear scales, namely a power function with an exponent of 0.5, a power function with an exponent of 0.33, and a logarithmic scale. The new distributions along with the original distribution (linear scale) were fitted with a Gaussian distribution. The mean goodness-of-fit (R^2) values were in ascending order when arranged from left to right for the linear scale, the power function with an exponent of 0.5, the power function with an exponent of 0.33, and the logarithmic scale. On the logarithmic scale, the variance of numerosity filters was approximately constant with increasing preferred numerosity.

Receptors considered in the current study until now produce the maximum at values which are powers of ten (for example, the receptors which constitute the series represented by equations 22 and 23 have maximum at the values 10^1, 10^2, 10^3, 10^4, and 10^5, respectively). Thus, in order to have the receptors produce maximum at the values 1, 2, 3, etc, and also possess a certain mathematical property, a few combinations of equilibrium dissociation constant and Hill-coefficient were tried. The mathematical property that the expression of output of the individual receptors having constant β_1/α_1 needed to possess is $f_n(X) = f_{n+1}(X/c)$, where f_n and f_{n+1} are outputs of consecutive receptors, respectively. This property makes output of the individual receptors have equal variance when plotted on a logarithm scale [12]. The following expression turned out to satisfy both requirements

$$\left[\frac{1\frac{X}{1}}{1+\frac{X}{1}}\right]\cdot\left[\frac{\frac{X}{1}}{1+\frac{X}{1}}\right]\cdot\left[\frac{1}{1+\left(\frac{X}{1}\right)^2}\right] \tag{40}$$

$$\left[\frac{2\frac{X}{2}}{1+\frac{X}{2}}\right]\cdot\left[\frac{\frac{X}{2}}{1+\frac{X}{2}}\right]\cdot\left[\frac{1}{1+\left(\frac{X}{2}\right)^2}\right] \tag{41}$$

$$\left[\frac{3\frac{X}{3}}{1+\frac{X}{3}}\right]\cdot\left[\frac{\frac{X}{3}}{1+\frac{X}{3}}\right]\cdot\left[\frac{1}{1+\left(\frac{X}{3}\right)^2}\right] \tag{42}$$

As in the study [12], R^2 values of the Gaussian fit of output of the expressions 40-42 plotted on the linear scale, the power function with an exponent of 0.5, the power function with an exponent of 0.33, and the logarithmic scale were in ascending order when arranged from left to right (Supplementary Information, Table 4). The same result was obtained with respective output of the first three terms of equation 20 (Supplementary Information, Table 5).

The following are non-approximated forms of the above three equations

$$\left[\frac{1\frac{X}{1}}{1+\frac{X}{1}}\right]\cdot\left[\frac{\frac{10^2\frac{X}{10^2}}{1+\frac{X}{10^2}}}{1+\frac{10^2\frac{X}{10^2}}{1+\frac{X}{10^2}}}\right]\cdot\left[\frac{1}{1+\left(\frac{10^2\frac{X}{10^2}}{1+\frac{X}{10^2}}\right)^2}\right] \tag{43}$$

$$\left[\frac{2\frac{X}{2}}{1+\frac{X}{2}}\right]\cdot\left[\frac{\frac{10^2\frac{X}{2\cdot 10^2}}{1+\frac{X}{2\cdot 10^2}}}{1+\frac{10^2\frac{X}{2\cdot 10^2}}{1+\frac{X}{2\cdot 10^2}}}\right]\cdot\left[\frac{1}{1+\left(\frac{10^2\frac{X}{2\cdot 10^2}}{1+\frac{X}{2\cdot 10^2}}\right)^2\cdot 10^2}\right] \tag{44}$$

$$\left[\frac{3\frac{X}{3}}{1+\frac{X}{3}}\right]\cdot\left[\frac{\frac{10^2\frac{X}{3\cdot 10^2}}{1+\frac{X}{3\cdot 10^2}}}{1+\frac{10^2\frac{X}{3\cdot 10^2}}{1+\frac{X}{3\cdot 10^2}}}\right]\cdot\left[\frac{1}{1+\left(\frac{10^2\frac{X}{3\cdot 10^2}}{1+\frac{X}{3\cdot 10^2}}\right)^2}\right] \tag{45}$$

In their experiments, monkeys were shown a set of dots, and then, after a short delay, were presented with another set of dots, which they had to distinguish from the first set. The percentage of trials on which they judged the second number to be indistinguishable from the first number, which varied between 2-6, was plotted as a function of the second number. Monkeys' performance –percentage of trials on which they reported the two sets to be of the same numerosity– declined progressively as the t*wo sets became numerically more distant. For larger numerosities, the two sets had to be proportionally larger in order to keep the level of performance the same, thereby translating to Weber' law. The distributions of both monkey's performance had positive skew, but assumed a more symmetric shape when plotted on nonlinear scales, namely a power function with an exponent of 0.5, a power function with an exponent of 0.33, and a logarithmic scale. The mean goodness-of-fit values for the linear scale, the power function with an exponent of 0.5, the power function with an exponent of 0.33, and the logarithmic scale were 0.93, 0.97, 0.98, and 0.98, respectively. Further, the variance of the distributions for each numerosity was constant when the data was plotted on a power function scale with 0.33 exponent and the logarithmic scale.

Because the above-stated formulation of Weber's law requires the signal-response relationship to be linear, the series of the receptors which produce maximum at integral values must be able to produce linear signal-response relationship in order to explain behavioural data of the study by Nieder and Miller [12]. The values of β_1/α_1 were determined by fitting the output with straight line. It turned out that the values vary over 5 orders of magnitude, which does not seem biologically plausible. Thus, the present work is unable to explain the behavioural data.

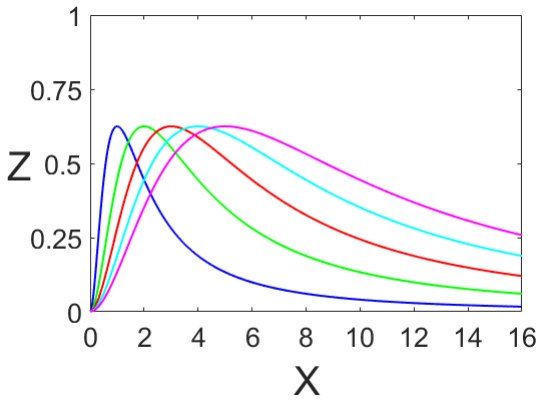

Figure 9: Output of the receptors which produce the maximum at integral values. The first three outputs are of the expressions 40, 41, and 42, respectively.

After logarithmic-compression of abscissa, the expression 41 and 42 become

$$\left[\frac{\frac{\exp(X)}{2}}{1+\frac{\exp(X)}{2}}\right]\cdot\left[\frac{\frac{\exp(X)}{2}}{1+\frac{\exp(X)}{2}}\right]\cdot\left[\frac{1}{1+\left(\frac{\exp(X)}{2}\right)^2}\right] \tag{46}$$

$$\left[\frac{\frac{\exp(X)}{3}}{1+\frac{\exp(X)}{3}}\right]\cdot\left[\frac{\frac{\exp(X)}{3}}{1+\frac{\exp(X)}{3}}\right]\cdot\left[\frac{1}{1+\left(\frac{\exp(X)}{3}\right)^2}\right] \tag{47}$$

The two expressions can be written as

$$\left[\frac{\exp(X-\log_e 2)}{1+\exp(X-\log_e 2)}\right]\cdot\left[\frac{\exp(X-\log_e 2)}{1+\exp(X-\log_e 2)}\right]\cdot\left[\frac{1}{1+\exp(X-\log_e 2)}\right] \tag{48}$$

$$\left[\frac{\exp(X-\log_e 3)}{1+\exp(X-\log_e 3)}\right]\cdot\left[\frac{\exp(X-\log_e 3)}{1+\exp(X-\log_e 3)}\right]\cdot\left[\frac{1}{1+\exp(X-\log_e 3)}\right] \tag{49}$$

The latter function can be got from the former by the transformation $X \rightarrow X+\log_e 2-\log_e 3$; hence the standard deviation remains the same. Notably, barring the first and last receptor (which do not possess both arms), receptors of the series which gives linear signal-response relationship are related in the following way: $f_n(X) = c\cdot f_{n+1}(X/c)$, where f is the expression of the output and n is the receptor's number. Thus, output of the receptor follows the above-stated

mathematical property when β_1/α_1 is kept constant, and consequently the output have constant variance when plotted on a logarithm scale.

On a logarithmic abscissa, the expressions

$$\left[\frac{1\frac{X}{10}}{1+\frac{X}{10}}\right]\cdot\left[\frac{\frac{X}{1}}{1+\frac{X}{1}}\right]\cdot\left[\frac{1}{1+\frac{X}{10}}\right] \tag{50}$$

and

$$\left[\frac{1\frac{X}{100}}{1+\frac{X}{100}}\right]\cdot\left[\frac{\frac{X}{10}}{1+\frac{X}{10}}\right]\cdot\left[\frac{1}{1+\frac{X}{100}}\right] \tag{51}$$

become

$$\left[\frac{\frac{\exp(X)}{10}}{1+\frac{\exp(X)}{10}}\right]\cdot\left[\frac{\frac{\exp(X)}{1}}{1+\frac{\exp(X)}{1}}\right]\cdot\left[\frac{1}{1+\frac{\exp(X)}{10}}\right] \tag{52}$$

$$\left[\frac{\frac{\exp(X)}{100}}{1+\frac{\exp(X)}{100}}\right]\cdot\left[\frac{\frac{\exp(X)}{10}}{1+\frac{\exp(X)}{10}}\right]\cdot\left[\frac{1}{1+\frac{\exp(X)}{100}}\right] \tag{53}$$

The two expressions can be written as

$$\left[\frac{\exp(X-\log_e 10)}{1+\exp(X-\log_e 10)}\right]\cdot\left[\frac{\exp(X)}{1+\exp(X)}\right]\cdot\left[\frac{1}{1+\exp(X-\log_e 10)}\right] \tag{54}$$

$$\left[\frac{\exp(X-2\log_e 10)}{1+\exp(X-2\log_e 10)}\right]\cdot\left[\frac{\exp(X-\log_e 10)}{1+\exp(X-\log_e 10)}\right]\cdot\left[\frac{1}{1+\exp(X-2\log_e 10)}\right] \tag{55}$$

The latter function can be got from the former by the transformation $X \rightarrow X\text{-}\log_e 10$, which leaves the standard deviation unchanged.

2.4. The Four-node Motif and a Class of Bow-Tie Architecture

For the series generating linear signal-response relationship (figure 3B), assuming the signal's range is 10^n-10^m (n > m and both are integers), the number of receptors (i.e., the four-node motifs) is equal to n-m+10. When $m \geqslant 0$, the generation of linear signal-response relationship becomes an example of bow-tie architecture. Therefore, a class of bow-tie architecture could be defined: a class in which the number of receptors is much smaller than the range of signal and consequently the range of response.

The range of output generated by the series in figure 3B is identical to the signal's range. In contrast to that, now I consider a hypothetical requirement of sensitive detection over wide range of signal while the output has an upper limit. Black line in figure 10A depicts that when the output has an upper limit, sensitivity of a mechanism generating single linear signal-response relationship reduces as the signal's range increases. However, the sensitivity is maintained if a mechanism generates multiple linear signal-response outputs, each of which is from its corresponding receptor and covers corresponding limited range of signal. The blue, green, and red lines are ideal hypothetical outputs which together provide sensitive detection over a wide range of signal. However, the outputs are not biologically realistic, as they terminate abruptly at their maximum. Figure 10B shows a biologically realistic form of the outputs.

Figure 10C shows output of a series of the four-node motif which qualitatively matches figure 10B and, thus, provides sensitive detection over arbitrary range of signal. The four-node motif in this series has the following properties: β_1/α_1 is constant, the Hill coefficients m and n are equal to 2 and 8, respectively, all equilibrium dissociation constants of a given receptor are equal, and the value of equilibrium dissociation constants of a receptor are twice those of the preceding receptor. The expressions 56-58 define the first three receptors. Output of such a four-node motif fits Gaussian distribution very well. R^2 for the Gaussian fit of output of the three expressions are 0.9967, 0.996, and 0.9959, respectively. Because eqs. 56-58, when

keeping β_1/α_1 constant, possess the mathematical property $f_n(X) = f_{n+1}(X/c)$, the coefficient of variation of Gaussians fitted by them are equal. Further, output of such a series oscillates with constant amplitude and decreasing frequency around a flat line. It should be noted that the individual outputs in figure 10B have constant width at half height (WAHH); whereas, because WAHH is equal to $4 \cdot \ln 2 \cdot \sigma$, WAHH of the outputs in figure 10C are proportional to mean of the approximate Gaussians they form. Although the output's range is constant, the range of response is still proportional to the signal's range as in the previous example. That's because, for a given signal the total output is a unique combination of the individual output of the receptors. Thus, for a given signal a unique response can be reconstituted from the individual output of the receptors. It also implies that this mechanism belongs to the above-defined class of bow-tie architecture.

Assuming the equilibrium dissociation constants of the first and the last receptor are 2^m and 2^n, respectively; arguably, the range in which signal can be detected sensitively is $\mu_1 \cdot (2^n - 2^m) + (1/2) \cdot \sigma_1 \cdot (2^m + 2^n)$, where $n > m$ and both are integers, and μ_1 and σ_1 are mean and standard deviation of the Gaussian distribution which fits output of the defining expression of the receptor whose equilibrium dissociation constants are equal to 1. When $m \geqslant 0$, the signal-response relationship becomes an example of bow-tie architecture, as for the signal's range being $\mu_1 \cdot (2^n - 2^m) + (1/2) \cdot \sigma_1 \cdot (2^m + 2^n)$, the number of receptors is equal to n-m+1. Figure 10D shows that, with some modifications, a series of three such four-node motifs is able to produce a signal-response relationship which qualitatively matches absorption spectra of three cone opsins of humans [13]. The defining expressions of the three receptors are in the figure's legend.

$$\left[\frac{5\frac{X}{1}}{1+\frac{X}{1}}\right] \cdot \left[\frac{\left(\frac{X}{1}\right)^2}{1+\left(\frac{X}{1}\right)^2}\right] \cdot \left[\frac{1}{1+\left(\frac{X}{1}\right)^8}\right] \tag{56}$$

$$\left[\frac{5\frac{X}{2}}{1+\frac{X}{2}}\right]\cdot\left[\frac{\left(\frac{X}{2}\right)^2}{1+\left(\frac{X}{2}\right)^2}\right]\cdot\left[\frac{1}{1+\left(\frac{X}{2}\right)^8}\right] \tag{57}$$

$$\left[\frac{5\frac{X}{4}}{1+\frac{X}{4}}\right]\cdot\left[\frac{\left(\frac{X}{4}\right)^2}{1+\left(\frac{X}{4}\right)^2}\right]\cdot\left[\frac{1}{1+\left(\frac{X}{4}\right)^8}\right] \tag{58}$$

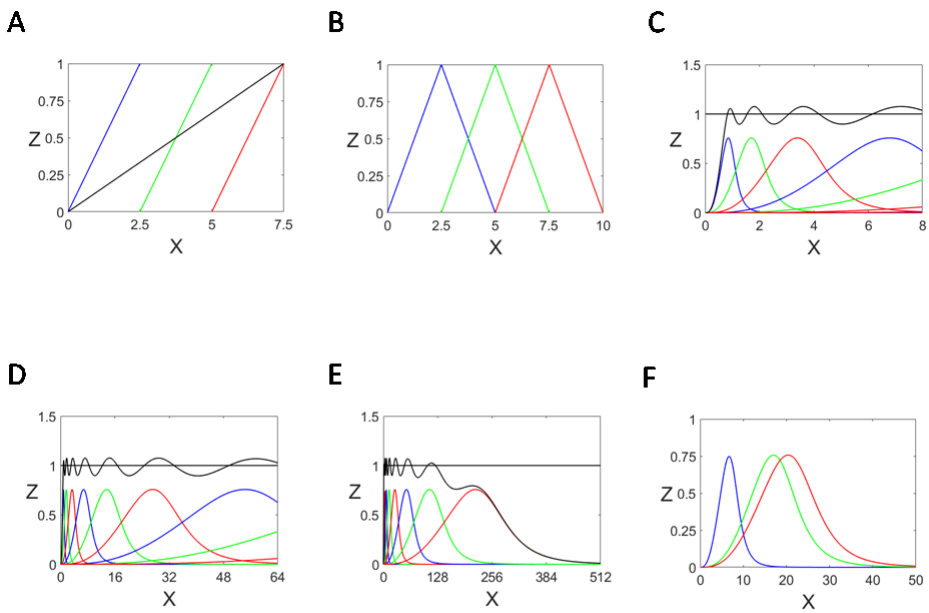

Figure 10: **A** The black line shows that, when the range of response is constant, sensitivity of linear signal-response relationship reduces with increase in the range of signal. The blue, green, and red lines are minimal ideal hypothetical signal-response relationship, i.e., which maintain high sensitivity throughout the signal's range. **B** Biologically realistic form of ideal hypothetical signal-response relationship. **C-E** Output of the receptors defined by equations of the form specified by eqs. 56-58. The total output of the series oscillates around a flat line up to the antepenultimate receptor. The outputs are approximately Gaussian and have constant coefficient of variation. **F** A series of three four-node motifs is able to qualitatively generate the absorption spectra of human cone cells. The equations of the three receptors are: $[3.6 \cdot (X/4)/(1 + X/4)] \cdot [(X/8)^2/(1 + (X/8)^2)] \cdot [1/(1 + (X/8)^8)]$; $[5 \cdot (X/20)/(1 + X/20)] \cdot [(X/20)^2/(1 + (X/20)^2)] \cdot [1/(1 + (X/20)^8)]$; $[5 \cdot (X/24)/(1 + X/24)] \cdot [(X/24)^2/(1 + (X/24)^2)] \cdot [1/(1 + (X/24)^8)]$

2.5. The Four-node Motif and Logarithm Computation

When β_1/α_1 increase as powers of ten, the series of the four-node motif produces a straight line. Therefore, when β_1/α_1 increases linearly, the output is a strongly concave curve. Thus, it may be suspected that with rational choice of β_1/α_1, the output could be the logarithm of the signal. Because a series was sought which could compute logarithm of signal ranging between 1 and 10^4, series of five four-node motifs having Kd_{xz} equal to 10^1, 10^2, 10^3, 10^4, and 10^5, respectively, was considered. The values of β_1/α_1 of the series which compute logarithm with the base ten and the natural logarithm were estimated by linear regression. $\log_{10}$ and $\log_e$ of powers of 2 ranging from 0 to 14 (i.e., the values ranging from 1 to 8192) were regressed against output of equation 59. It was observed that β_1/α_1 of all the receptors were positive only when the signal range was from 1 to a value which was slightly larger than Kd_{xz} of the antepenultimate. On the other hand, when $\log_{10}$ and $\log_e$ of powers of 10 were regressed against output of equation 59, the signal range had to be from 1 to slightly larger than Kd_{xz} of the penultimate receptor in order for β_1/α_1 of all the receptors to be positive. β_1/α_1 used to generate figures 13 and 14 are from regressing logarithm of powers of 2, because this way more data points are available for the procedure.

Because the logarithm of values that lie between 0 and 1 is negative, a biologically unrealistic scenario, the output in this range was suppressed. This was done by adding a positive arm with m=2 to the first receptor. This raises the possibility of a series of the four-node motif being able to compute the exponential of signal. To achieve this, the value of β_1/α_1 of the successive receptor should increase much faster than the corresponding value of Kd_{xz}. As before, linear regression was used to find out the values of β_1/α_1. However, β_1/α_1 of the first receptor turned out to be negative. This result alone rules out the possibility of a series of the four-node motif to compute exponential. Moreover, the regression gave a poor R^2 value. The four-node motif in series being able to compute logarithm but unable to compute exponential might be due to positive skew in its output.

$$Z = \left[\frac{A\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\left[\frac{\left(\frac{X}{10^0}\right)^2}{1+\left(\frac{X}{10^0}\right)^2}\right]\cdot\left[\frac{1}{1+\frac{X}{10^1}}\right]+\left[\frac{B\frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^2}}\right]+\left[\frac{C\frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{\frac{X}{10^2}}{1+\frac{X}{10^2}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^3}}\right]$$

$$+\left[\frac{D\frac{X}{10^4}}{1+\frac{X}{10^4}}\right]\cdot\left[\frac{\frac{X}{10^3}}{1+\frac{X}{10^3}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^4}}\right]+\left[\frac{E\frac{X}{10^5}}{1+\frac{X}{10^5}}\right]\cdot\left[\frac{\frac{X}{10^4}}{1+\frac{X}{10^4}}\right] \tag{59}$$

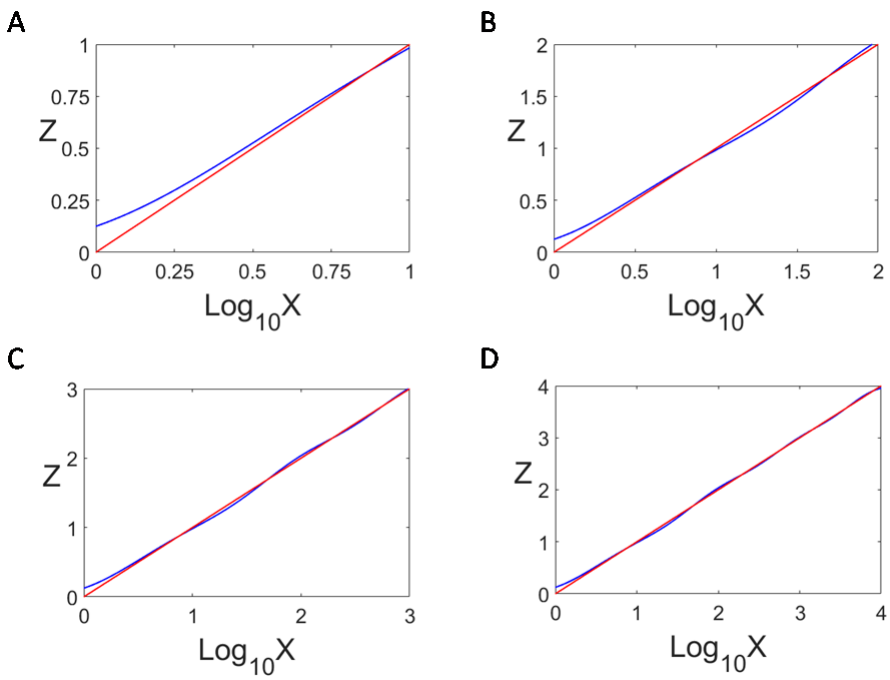

Figure 11: (**A-D**) The series which computes $\log_{10}$. The total output (blue) of the first five receptors for various range of signal plotted on $\log_{10}$-transformed abscissa. The straight line (red) is drawn for comparison. The last receptor lacks the negative arm. The first receptor possesses the positive arm, with m=2, in order to dampen the output when signal is below one. β_1/α_1 of the five receptors were: 2.89, 6.299, 8.587, 12.36, 8.317, respectively. The R^2 was 0.9989.

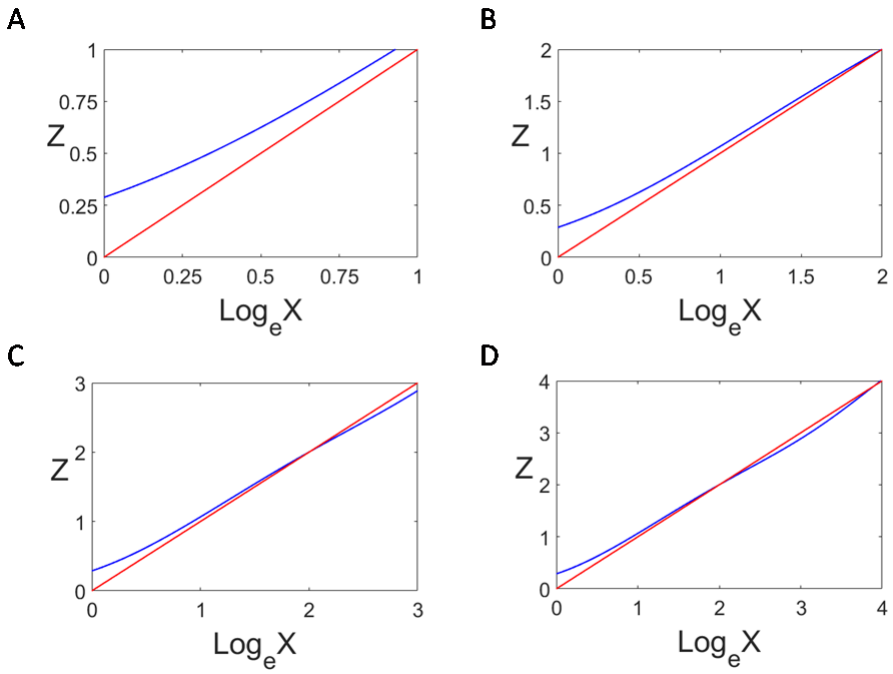

Figure 12: (**A-D**) The series which computes $\log_e$. The total output (blue) of the first five receptors for various range of signal plotted on $\log_e$-transformed abscissa. As earlier, the last receptor lacks the negative arm and the first receptor possesses the positive arm with m=2. β_1/α_1 of the five receptors were: 6.654, 14.5, 19.77, 28.47, 19.15, respectively. The R^2 was 0.9989.

3. Concluding Remarks

Sensory systems need to respond to stimuli which vary over several orders of magnitude. One way to achieve this is by “resetting” the system, that is, by employing the mechanism of exact adaptation. A prominent example of this strategy is *Escherichia coli*'s chemotaxis. Tu and co-workers [4] presented a three-variable reduced model of the bacterial chemotaxis, whose features are: 1) attractant ligand (L(t)) binding reduces the average kinase activity (a(t)), 2) the kinase activates demethylation machinery, and 3) attractant ligand binding affinity is a decreasing function of the average methylation level (m(t)). Binding of an attractant ligand lowers the average kinase activity, leading to reduction of demethylation rate, and the resultant increased level of methylation restores the average kinase activity back to its resting value.

The sensory mechanism presented in this work in order to explain Weber's law in higher-order sensory processes differs fundamentally from the exact adaptation based mechanism which forms the basis of Weber's law observed in E coli's chemotaxis. The two overlapping differences are as follow. Firstly, in the latter mechanism it's the transient response of the system that possesses information about the signal, as the system's output returns back to its resting value. On the other hand, in the former mechanism the equilibrium state of the system possesses information about the signal. Secondly, in the latter mechanism a signal is sensed relative to the previous signal, at which the system was equilibrated to. By contrast, in the former mechanism a signal is sensed in absolute manner. Because a mechanism based on exact adaptation cannot be the basis of weight perception, size perception, and numerosity processing, the mechanism proposed here is, to the author's knowledge, the only known mechanism which can explain Weber's law observed in the three higher-order sensory processes.

It should be noted that there has to be an upper limit on the production rate (β_1). However, because the expression 2 (and hence also 17) is linear in β_1, the overall output can be increased by having the signal engender the production from multiple Z producers. There also has to be

an upper limit on the value of the equilibrium dissociation constants, so that the free energy of binding remains significantly different from the thermal energy. Thus, some mechanism has to exist such that the apparent value of the equilibrium dissociation constants increases even when the equilibrium dissociation constants for the actual binding reach an upper limit. This can be achieved, for example, by having a mechanism in which the signal has to occupy multiple producer elements of the producer Z at the same time in order to engender production of Z. An implication of these two considerations is that the four-node motif is likely to be present in a hidden form in biological networks.

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