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 whose series provides linear relationship between signal and response over arbitrary range of signal. The motif also reproduces the neuronal data of numerosity detection study on monkey. The series of this motif provides a general mechanism for 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 Weber's 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 (see the section *Weber's Law*) [2]. Another model which can also account for Weber's 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 bacterial 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 using the reduced model demonstrated the presence of Weber's law in *E. coli*'s chemotaxis. [5].

Thus, inspired from the connection between Weber's law and exact adaptation in the bacterium, Weber's law was 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 is 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. If k is replaced with f, this leads to a contradiction in a system which shows FCD but does not adapt exactly. 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 sense 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.

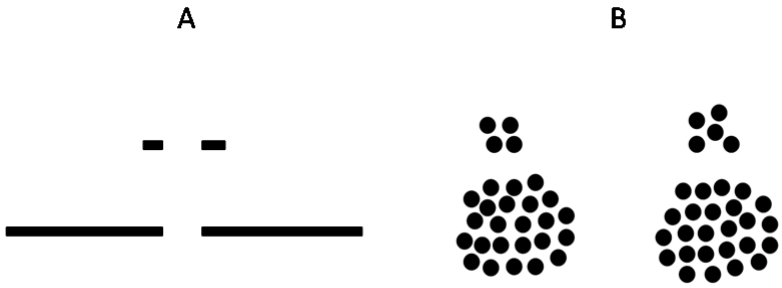

Figure 1: (**A**) Two pairs of rectangular strips which differ by the same length (20% of the smaller strip of the upper pair). (**B**) Two pairs of collection of discs numbering (i) 4 and 5; (ii) 24 and 25.

Weber's law is also observed in size (length/area/volume) perception, for which two examples are presented now. The first example demonstrates that a difference of 1 unit between two rectangular strips of 5 and 6 units is perceptible to the human eye, whereas the same difference between two rectangular strips of 40 and 41 units is not (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]. As with weight perception, the perception of size and number does not come back to some resting value. Because it is not clear how scale-invariance with respect to the maximum amplitude or exact adaptation 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 either scale-invariance with respect to the maximum amplitude or exact adaptation. Additionally, 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, ideal relationship between a signal and the response should be a straight line with the slope of one. Because sensory systems operate over several orders of magnitude, the system 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). Clearly, the output (i.e., the production rate of Z, β_1) of the receptor meant

to respond to signal of higher strength 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

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

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

$$Z_{eq} = \sum_{i=1}^{N} \left[\frac{10^i \frac{X}{10^i}}{1 + \frac{X}{10^i}} \right] \tag{3}$$

Let's assume that the value of the signal has the order of magnitude two. The receptor with Kd_{XZ} equal to 10^3 should 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

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

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

The expression in the second pair of brackets on the right hand side (RHS) 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 RHS 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.

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

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

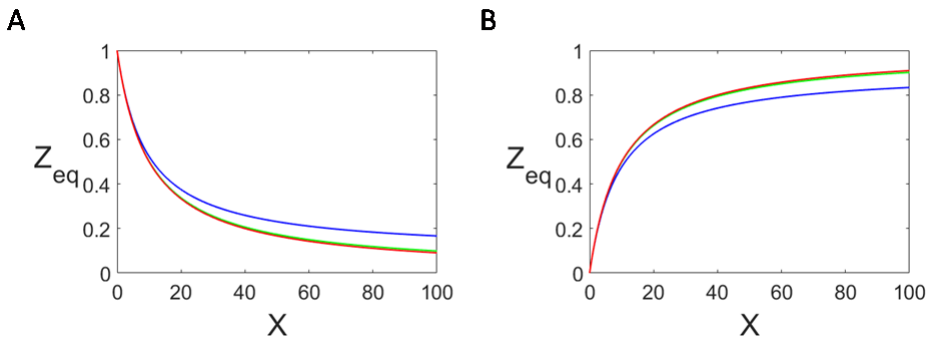

Figure 2: (**A**) The blue curve represents the expression $1/(1+10((x/100)/(1+(x/100))))$. The green curve: $1/(1+100((x/1000)/(1+(x/1000))))$. The red curve: $1/(1+(x/10))$. (**B**) The blue curve represents the expression $10((x/100)/(1+(x/100)))/(1+10((x/100)/(1+(x/100))))$. The green curve: $100((x/1000)/(1+(x/1000)))/(1+100((x/1000)/(1+(x/1000))))$.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

After applying the approximation, equation 7 becomes

$$Z_{eq} = \left[\frac{\frac{\beta_1}{\alpha_1}\frac{X}{Kd_{XZ}}}{1+\frac{X}{Kd_{XZ}}}\right] \cdot \left[\frac{1}{1+\left(\left(\frac{1}{Kd_{YZ}}\frac{\beta_2}{\alpha_2}\right)\frac{X}{Kd_{XY}}\right)^n}\right] \tag{10}$$

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

$$Z_{eq} = \sum_{i=1}^{N} \left[\frac{10^i \frac{X}{10^i}}{1 + \frac{X}{10^i}} \right] \cdot \left[\frac{1}{1 + \frac{X}{10^i}} \right] \tag{11}$$

The following is non-approximated form of the above equation

$$Z_{eq} = \sum_{i=1}^{N} \left[\frac{10^i \frac{X}{10^i}}{1 + \frac{X}{10^i}} \right] \cdot \left[\frac{1}{1 + \frac{10^2 \frac{X}{10^{i+2}}}{1 + \frac{X}{10^{i+2}}}} \right] \tag{12}$$

However, a signal can generate the output Z 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 the output from the receptors whose Kd_{XZ} is equal to 10^4 and 10^5 arb. units, respectively. Output Z_{eq} generated by each of the two receptors is approximately equal to 10^2 arb. units, which is of the same order as Z_{eq} generated by the receptor whose Kd_{XZ} is equal to 10^3 arb. units. The output from 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.

$$\frac{dV}{dt} = \frac{\beta_3 \frac{X}{Kd_{XV}}}{1 + \frac{X}{Kd_{XV}}} - \alpha_3 V \tag{13}$$

$$\frac{dY}{dt} = \frac{\beta_2 \frac{X}{Kd_{XY}}}{1 + \frac{X}{Kd_{XY}}} - \alpha_2 Y \tag{14}$$

$$\frac{dZ}{dt} = \left[\frac{\beta_1 \frac{X}{Kd_{XZ}}}{1 + \frac{X}{Kd_{XZ}}}\right] \cdot \left[\frac{\left(\frac{V}{Kd_{VZ}}\right)^m}{1 + \left(\frac{V}{Kd_{VZ}}\right)^m}\right] \cdot \left[\frac{1}{1 + \left(\frac{Y}{Kd_{YZ}}\right)^n}\right] - \alpha_1 Z \tag{15}$$

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

$$V_{eq} = \frac{\frac{\beta_3}{\alpha_3} \frac{X}{Kd_{XV}}}{1 + \frac{X}{Kd_{XV}}} \tag{16}$$

$$Y_{eq} = \frac{\frac{\beta_2}{\alpha_2} \frac{X}{Kd_{XY}}}{1 + \frac{X}{Kd_{XY}}} \tag{17}$$

$$Z_{eq} = \left[\frac{\frac{\beta_1}{\alpha_1} \frac{X}{Kd_{XZ}}}{1 + \frac{X}{Kd_{XZ}}}\right] \cdot \left[\frac{\left(\frac{\left(\frac{1}{Kd_{VZ}} \frac{\beta_3}{\alpha_3}\right) \frac{X}{Kd_{XV}}}{1 + \frac{X}{Kd_{XV}}}\right)^m}{1 + \left(\frac{\left(\frac{1}{Kd_{VZ}} \frac{\beta_3}{\alpha_3}\right) \frac{X}{Kd_{XV}}}{1 + \frac{X}{Kd_{XV}}}\right)^m}\right] \cdot \left[\frac{1}{1 + \left(\frac{\left(\frac{1}{Kd_{YZ}} \frac{\beta_2}{\alpha_2}\right) \frac{X}{Kd_{XY}}}{1 + \frac{X}{Kd_{XY}}}\right)^n}\right] \tag{18}$$

The formulation demands that the expression in the second pair of brackets on the RHS of the equality in equation 18, representing the generation of output Z_{eq} 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. The expression in the second pair of brackets on the RHS of the equality in equation 18 is approximately equal to the expression 19 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.

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

$$\left[\frac{\left(\frac{\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)}{1+\frac{X}{Kd_{XV}}}\right)^m}{1+\left(\frac{\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)}{1+\frac{X}{Kd_{XV}}}\right)^m}\right] \approx \left[\frac{\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)^m}{1+\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)^m}\right] \tag{20}$$

After applying the approximation, equation 18 becomes

$$Z_{eq} = \left[\frac{\frac{\beta_1}{\alpha_1}\frac{X}{Kd_{XZ}}}{1+\frac{X}{Kd_{XZ}}}\right]\cdot\left[\frac{\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)^m}{1+\left(\left(\frac{1}{Kd_{VZ}}\frac{\beta_3}{\alpha_3}\right)\frac{X}{Kd_{XV}}\right)^m}\right]\cdot\left[\frac{1}{1+\left(\left(\frac{1}{Kd_{YZ}}\frac{\beta_2}{\alpha_2}\right)\frac{X}{Kd_{XY}}\right)^n}\right] \tag{21}$$

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

$$Z_{eq} = \sum_{i=1}^{N}\left[\frac{10^i\frac{X}{10^i}}{1+\frac{X}{10^i}}\right]\cdot\left[\frac{\frac{X}{10^{i-1}}}{1+\frac{X}{10^{i-1}}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^i}}\right] \tag{22}$$

The following is non-approximated form of the above equation

$$Z_{eq} = \sum_{i=1}^{N} \left[\frac{10^{i} \frac{X}{10^{i}}}{1 + \frac{X}{10^{i}}} \right] \cdot \left[\frac{\frac{10^{2} \frac{X}{10^{i+1}}}{1 + \frac{X}{10^{i+1}}}}{1 + \frac{10^{2} \frac{X}{10^{i+1}}}{1 + \frac{X}{10^{i+1}}}} \right] \cdot \left[\frac{1}{1 + \frac{10^{2} \frac{X}{10^{i+2}}}{1 + \frac{X}{10^{i+2}}}} \right] \tag{23}$$

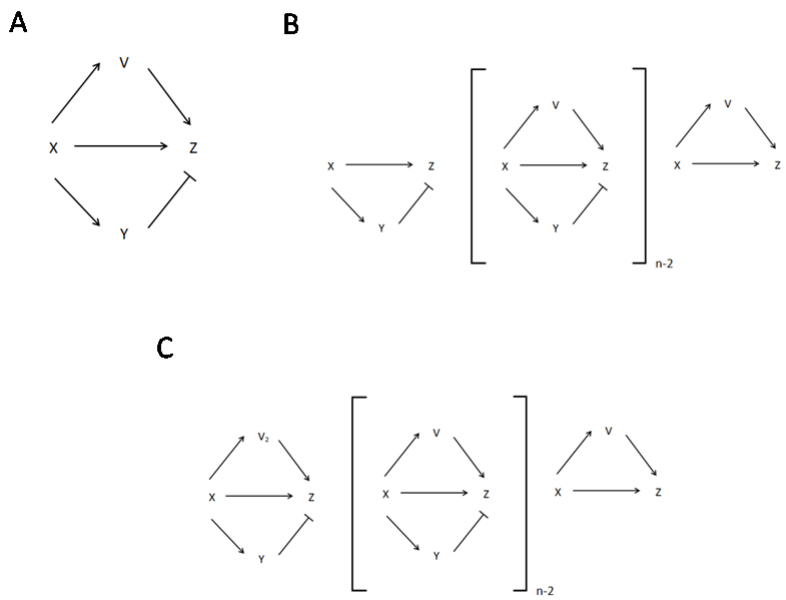

Figure 3: (**A**) The four-node motif which in series can generate linear signal-response relationship and compute logarithm. (**B**) The series for generating linear signal-response relationship. (**C**) The series for computing logarithm.

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) $Kd_{XY}=100\cdot Kd_{XZ}$, c) $Kd_{XV}=10\cdot Kd_{XZ}$, and $Kd_{YZ}\cdot(\beta_2/\alpha_2)$ and $Kd_{VZ}\cdot(\beta_3/\alpha_3)$ are equal to 100, 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 output Z_{eq} 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:-

$$Z_{eq} = \left[\frac{10^1\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^1}}\right]+\sum_{i=2}^{N-1}\left[\frac{10^i\frac{X}{10^i}}{1+\frac{X}{10^i}}\right]\cdot\left[\frac{\frac{X}{10^{i-1}}}{1+\frac{X}{10^{i-1}}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^i}}\right]+\left[\frac{10^N\frac{X}{10^N}}{1+\frac{X}{10^N}}\right]\cdot\left[\frac{\frac{X}{10^{N-1}}}{1+\frac{X}{10^{N-1}}}\right] \quad (24)$$

The following is non-approximated form of the above equation

$$Z_{eq} = \left[\frac{10^1\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{1}{1+\frac{10^2\frac{X}{10^3}}{1+\frac{X}{10^3}}}\right]+\sum_{i=2}^{N-1}\left[\frac{10^i\frac{X}{10^i}}{1+\frac{X}{10^i}}\right]\cdot\left[\frac{\frac{10^2\frac{X}{10^{i+1}}}{1+\frac{X}{10^{i+1}}}}{1+\frac{10^2\frac{X}{10^{i+1}}}{1+\frac{X}{10^{i+1}}}}\right]\cdot\left[\frac{1}{1+\frac{10^2\frac{X}{10^{i+2}}}{1+\frac{X}{10^{i+2}}}}\right]+\left[\frac{10^N\frac{X}{10^N}}{1+\frac{X}{10^N}}\right]\cdot\left[\frac{\frac{10^2\frac{X}{10^{N+1}}}{1+\frac{X}{10^{N+1}}}}{1+\frac{10^2\frac{X}{10^{N+1}}}{1+\frac{X}{10^{N+1}}}}\right] \quad (25)$$

It could be observed that output Z_{eq} of equation 24 with the Hill-coefficients m and n being equal to one is 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

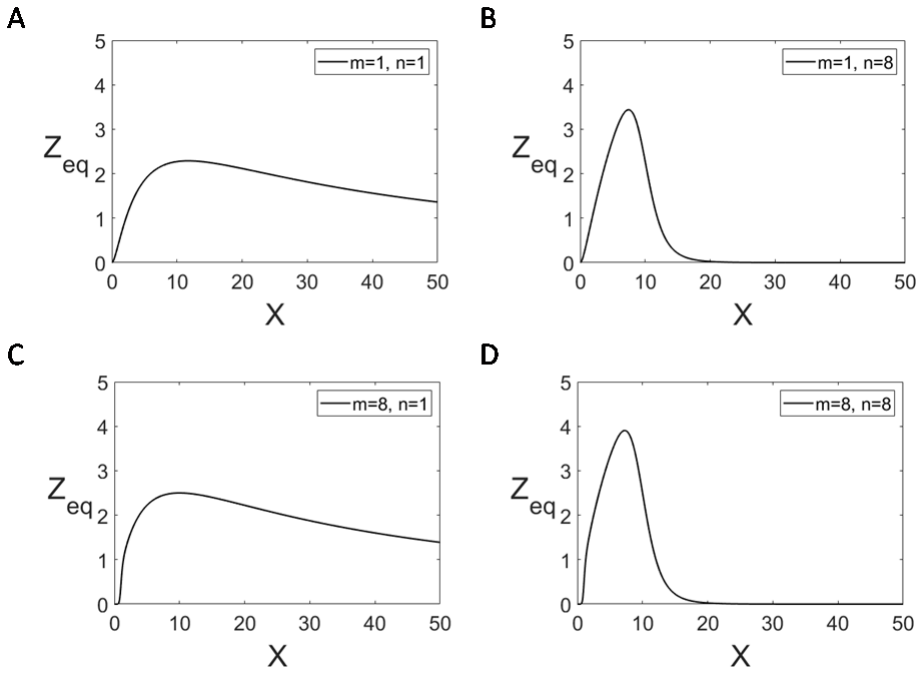

Figure 4: (**A-D**) The output of the four-node motif defined by the equation $[10 \cdot (X/10)/(1 + X/10)] \cdot [(X/1)^m/(1 + (X/1)^m)] \cdot [1/(1 + (X/10)^n)]$ with different values of the Hill-coefficients m and n.

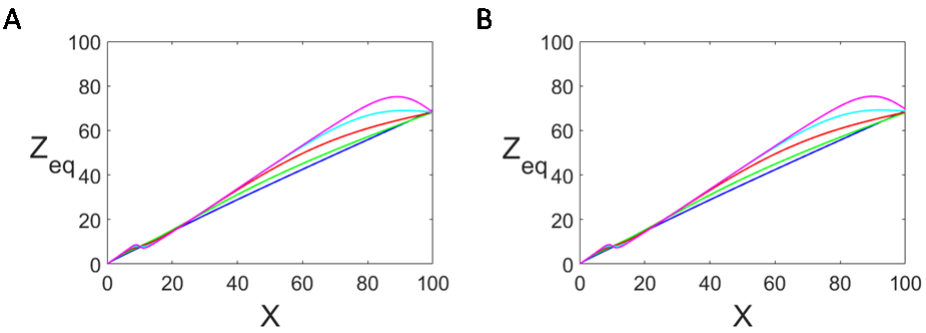

Figure 5: The output from the first three receptors for the approximated form (**A**) and non-approximated form (**B**) when m=1, n=1 (blue); m=1, n=2 (green); m=1, n=4 (red); m=1, n=8 (cyan); m=1, n=16 (pink).

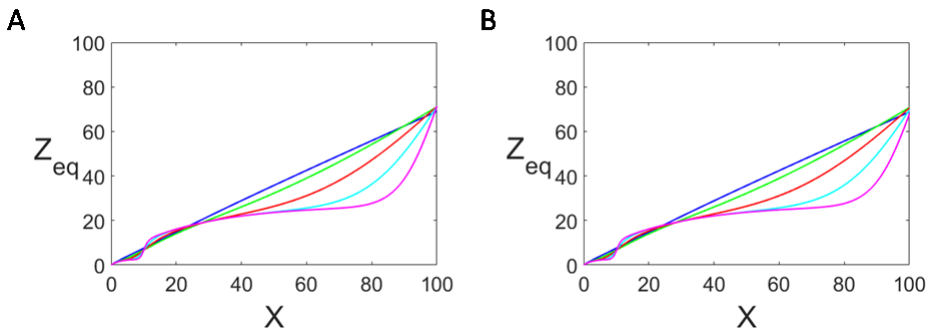

Figure 6: The output from the first three receptors for the approximated form (**A**) and non-approximated form (**B**) when m=1, n=1 (blue); m=2, n=1 (green); m=4, n=1 (red); m=8, n=1 (cyan); m=16, n=1 (pink).

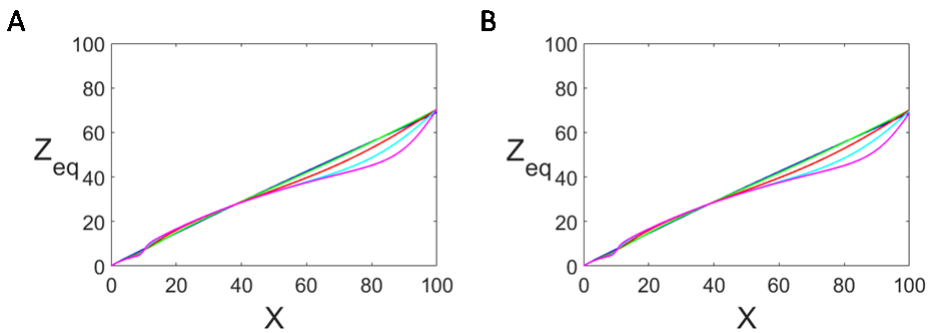

Figure 7: The output from the first three receptors for the approximated form (**A**) and non-approximated form (**B**) when m=1, n=1 (blue); m=2, n=2 (green); m=4, n=4 (red); m=8, n=8 (cyan); m=16, n=16 (pink).

represented by the term infinity.

In order to assess how well equation 24 approximates equation 25, output Z_{eq} given by equation 25 for N=5 was regressed on the expression on the RHS of the equality in equation 24 for N=5 having each of its term multiplied with a coefficient (equation 26). If equation 24 is a good approximation of equation 25, the value of the coefficients should turn out to be around one, besides goodness-of-fit (r^2) being close to one. Because Z_{eq} given by equation 24 (and hence also by equation 25) begins to plateau as the signal's value goes beyond Kd_{XZ} of the penultimate receptor (whose value is 10^4 when N=5), the signal's values at which Z_{eq} given by equation 25 was generated for the purpose of regression were 1, 2, 5, 10, 20, 50, 10^2, $2{\cdot}10^2$, $5{\cdot}10^2$, 10^3, $2{\cdot}10^3$, $5{\cdot}10^3$, 10^4. Except for the value of the coefficient C_1 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 of m and n were close to one. The goodness-of-fit was equal to one for all the combinations (Supplementary Information, Table 1-3). Specifically, for m and n equal to one, the value of C_1, C_2, C_3, C_4, C_5 were 1.0075, 0.9948, 0.9974, 0.9968, 0.9963, respectively.

$$Z_{eq} = C_1 \left[\frac{10^1 \frac{X}{10^1}}{1 + \frac{X}{10^1}} \right] \cdot \left[\frac{1}{1 + \frac{X}{10^1}} \right] + \sum_{i=2}^{4} C_i \left[\frac{10^i \frac{X}{10^i}}{1 + \frac{X}{10^i}} \right] \cdot \left[\frac{\frac{X}{10^{i-1}}}{1 + \frac{X}{10^{i-1}}} \right] \cdot \left[\frac{1}{1 + \frac{X}{10^i}} \right] + C_5 \left[\frac{10^5 \frac{X}{10^5}}{1 + \frac{X}{10^5}} \right] \cdot \left[\frac{\frac{X}{10^4}}{1 + \frac{X}{10^4}} \right] \tag{26}$$

As stated above, in order to provide sensitive detection, ideal relationship between a signal and the response should be a straight line with the slope of one, but output Z_{eq} given by equation 24 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, straight line was fitted with output Z_{eq} given by equation 24 for various ranges of Kd_{XZ} and signal (Table 1). For a given range of signal, the output was generated at the input values

which were powers of 10. 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 linear regression of output Z_{eq} on the input values 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. Specifically, to provide linear signal-response relationship over the range 10^{a}-10^{b} (where, a < b and both are integers), series of receptors whose Kd_{XZ} ranges at least from 10^{a-5} to 10^{b+5} is required. In other words, if output Z_{eq} of this series is multiplied by the reciprocal of 0.7466, one gets a straight line with the slope of 1 over the signal's range 10^{a}-10^{b}. 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 in a sensory system the response should be zero when the signal is zero, a non-zero y-intercept can be considered an error; that is, 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 24, which, when multiplied by the factor of (1/0.7466), yields $Z_{eq} = X$ for intermediate range of values of X. Given a signal ($X = \mu$), the output (Z_{eq}) 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 $\mu_2 - \mu_1 = \sigma_1$; that is, when the difference between the mean of the current signal and the 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

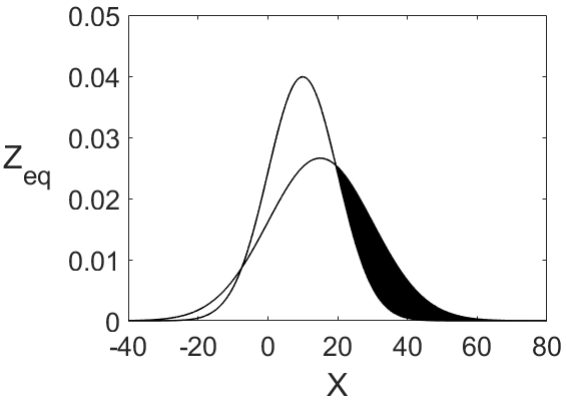

Figure 8: The Gaussian on the left has mean μ_1=10, and the Gaussian on the right has mean μ_2=15. The shaded portion is the non-overlapping region, R

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 Z_{eq}, given by equation 24, is the sum of Z_{eq} of 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.

$$\frac{1}{\sqrt{2\pi\sigma_1^2}} e^{-\frac{(p-\mu_1)^2}{2\sigma_1^2}} = \frac{1}{\sqrt{2\pi\sigma_2^2}} e^{-\frac{(p-\mu_2)^2}{2\sigma_2^2}} \tag{27}$$

$$\ln\left|\frac{\sigma_2}{\sigma_1}\right| = \frac{(p-\mu_1)^2}{2\sigma_1^2} - \frac{(p-\mu_2)^2}{2\sigma_2^2} \tag{28}$$

$$\frac{\ln\left|\frac{\sigma_2}{\sigma_1}\right|}{\left(\frac{1}{\sigma_1} - \frac{1}{\sigma_2}\right)} = p\left[\left(\frac{1}{\sigma_1} + \frac{1}{\sigma_2}\right)p - \frac{2}{f}\right] \tag{29}$$

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

Equation 29 becomes

$$C = p[Ap - B] \quad \text{or} \quad Ap^2 - Bp - C = 0 \tag{30}$$

$$p_{1,2} = \frac{B \pm \sqrt{B^2 4AC}}{2A} \tag{31}$$

$$p_2 = \frac{\frac{2}{f} + \sqrt{\left(\frac{2}{f}\right)^2 + 4\left(\frac{1}{\sigma_1} + \frac{1}{\sigma_2}\right)\frac{\ln\left|\frac{\sigma_2}{\sigma_1}\right|}{\left(\frac{1}{\sigma_1} - \frac{1}{\sigma_2}\right)}}}{2\left(\frac{1}{\sigma_1} + \frac{1}{\sigma_2}\right)} \tag{32}$$

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

$$p_2 = \frac{\mu_1\left(1 + \sqrt{1 + f(2 + f)\ln|1 + f|}\right)}{\left(1 + \frac{1}{1 + f}\right)} \tag{33}$$

The expression 33 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

$$R = \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{p_2 - \mu_1}{\sigma_1\sqrt{2}}\right)\right] - \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{p_2 - \mu_2}{\sigma_2\sqrt{2}}\right)\right] \tag{34}$$

Inserting the value of p_2 in equation 34

$$R = \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{\mu_1 g(f) - \mu_1}{\sigma_1\sqrt{2}}\right)\right] - \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{\mu_1 g(f) - \mu_2}{\sigma_2\sqrt{2}}\right)\right] \tag{35}$$

$$R = \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{g(f) - 1}{f\sqrt{2}}\right)\right] - \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{g(f)/(1 + f) - 1}{f\sqrt{2}}\right)\right] \tag{36}$$

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.

$$\frac{\Delta X_{min}}{X_{background}} = \frac{\mu_2 - \mu_1}{\mu_1} = \frac{\sigma_1}{\mu_1} = f = h^{-1}(R) \tag{37}$$

In the formalism presented here (i.e., the linear model), 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 function of a constant increment in the response.

$$Z_0 = \log(X_0) \tag{38}$$

$$Z_1 = \log(X_0 + \Delta X_{min}) \tag{39}$$

$$\Delta Z = Z_1 - Z_0 = \log\left(1 + \frac{\Delta X_{min}}{X_0}\right) \tag{40}$$

$$e^{\Delta Z} - 1 = \frac{\Delta X_{min}}{X_0} = f \tag{41}$$

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 converted the signal to an equally valued response.

In order to validate the above-stated formalism for Weber's law, which assumes output Z_{eq} given by equation 25 (approximated as equation 24) to be noisy and thus considers it to be equivalent

to sampling from Gaussian distribution centered on the signal's value, output Z_{eq} of equation 25 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 standard deviation equal to the Weber fraction times the respective mean.

Then, with the value of X, V and Y, Z_{eq} 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 standard deviation equal to the Weber fraction times the expression. Adding output Z_{eq} of all receptors of the series and multiplying it 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 times 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 among 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 $\beta_2/(\alpha_2 \cdot Kd_{YZ})$ and $\beta_3/(\alpha_3 \cdot Kd_{VZ})$ were set equal to 100 in order to carry out

the approximations (equations 9 and 20), 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 the mean (X) and the Weber fraction (f), ten thousand values of Z_{eq} were generated from this sampling procedure and used to fit a Gaussian distribution. This procedure was carried out for thirty times. For a given value of f, the average of (thirty) means of the Gaussian fit 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 regressed on the following values: 0.1, 1, and 10. Similarly, for a given value of f, the average of (thirty) standard deviations got from the same procedure were regressed on the following values: f·0.1, f·1, and f·10. The values of f taken are as follows: 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 at worst), and R^2 was equal to 1 for all the nine combinations (of $\beta_2/(\alpha_2 \cdot Kd_{YZ})$ and β_3/α_3 and Kd_{VZ}) for both mean and standard deviation up to f equal to 0.2 (Supplementary Information, Tables 6-12). For higher values of f (i.e., 0.5 and 1), the fit became progressively poor. Curiously, the values of standard deviation of the fitted Gaussian were consistently approximately $1/\sqrt{2}$ times (instead of being equal to) the value of f·mean that was used as the standard deviation to generate values from the Gaussian random variable generator.

As the control, for a given combination of the value of mean and f, ten thousand values of Z_{eq} were generated 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) and f equal to 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, and 1. The values of Z_{eq} were fitted with a Gaussian distribution to get the mean and standard deviation. For a given value of f, the values of mean were regressed against the following values: 0.1, 1, 10, and the values of standard deviation were regressed

against the following values: f·0.1, f·1, and f·10. The R^2 for both fits was equal to 1. For the regression of mean and standard deviation, the biggest y-intercept was of the order of magnitude -3 and -2, respectively. The slope for the regression of mean and standard deviation were very close to 1 (Supplementary Information, Table 13 and 14).

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. Additionally, on the logarithmic scale, the variance of numerosity filters was approximately constant with increasing preferred numerosity when the amplitude was kept constant .

Receptors considered in the present study so far produce the maximum at values which are powers of ten (for example, receptors which constitute the series represented by equations 24 and 25 have maximum at the values 10^1, 10^2, 10^3, and so on up to 10^N, respectively). Thus, in order to have the receptors produce maximum at integral values, such as 1, 2, 3, etc, and also possess a certain mathematical property, a few combinations of the equilibrium dissociation constants and the Hill-coefficients were tried. The mathematical property that the expression for output Z_{eq} of the individual receptors needed to possess is $f_{N+1}(X) = f_N(X/C_N)$

when β_1/α_1 is kept constant. f_N and f_{N+1} are the expressions for output Z_{eq} of consecutive receptors, respectively, and C_N is a coefficient which may depend on N. This property makes the output of the individual receptors with constant β_1/α_1 have equal variance when plotted on a logarithm scale, as can be readily seen.

$$f_{N+1}(\exp(X)) = f_N(\exp(X - \ln C_N)) \tag{42}$$

The latter function can be got from the former by the transformation $X \rightarrow X+\ln C_N$; hence the standard deviation remains the same. The following expression turned out to satisfy both requirements

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

C_N for this function is equal to (N+1)/N.

The following is non-approximated form of the above expression

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

As in the study [12], R^2 values of the Gaussian fit of the expression 43 having constant β_1/α_1 (i.e., set equal to 1) for N=1,2,3 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 the first, second, and third term on the RHS of the equality in equation 22 (Supplementary Information, Table 5).

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 when β_1/α_1 is kept constant: $f_{N+1}(X) = f_N(X/C_N)$, where f is the expression of the output with β_1/α_1 set equal to one and N is the receptor's number. C_N for this function is independent of N and is equal to 10. Thus, because output Z_{eq} of the receptor whose series produces linear signal-response relationship follows the above-stated mathematical property when β_1/α_1 is kept constant, the output have constant variance when plotted on a logarithm scale.

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 two 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 of this series were determined by linearly regressing uniformly spaced values on output Z_{eq} of series of ten receptors which produce maximum at integral values; that is, from 1-10. Receptors of this series are defined by equation 43. The uniformly spaced values ranged from 0.25 to 10 with the difference of 0.25 between two consecutive values. It turned out that the values of β_1/α_1 varied over 6 orders of magnitude, which does not seem biologically plausible. When the series of twenty such receptors were considered, the values of β_1/α_1 varied over 5 orders of magnitude. Thus, the present work is unable to explain the behavioural data.

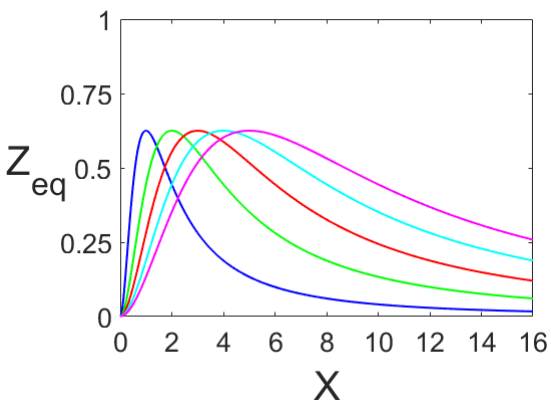

Figure 9: Output Z_{eq} of the receptors which produce the maximum at integral values. The outputs are of the expression 43 for N=1,2,3,4,5 respectively.

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

As shown in the section *Linear Signal-Response Relationship Over Arbitrary Range*, for the series which generates linear signal-response relationship (Figure 3B), b-a+11 receptors are required to provide linear signal-relationship over the range 10^a-10^b. This implies that when b-a is large and both b and a are also large, 10^b-$10^a \gg$ b-a+11; and consequently, the generation of linear signal-response relationship becomes an example of bow-tie architecture. For example, when a=0 and b=5, the range of signal and response (10^5-1) is four orders of magnitude larger than the number of receptors (16). Therefore, a class of bow-tie architecture can be defined: a class in which the number of receptors is much smaller than the range of signal and response.

The range of output Z_{eq} 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. But 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 value. Figure 10B shows a biologically realistic form of the outputs.

Figure 10C shows output Z_{eq} of a series of the four-node motif which qualitatively matches figure 10B and, thus, provides sensitive detection over arbitrary range of signal while the output has an upper limit. The four-node motif in this series has the following properties: β_1/α_1 (K) 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 expression 45 defines the general form of this receptor. Z_{eq} of this four-node motif fits Gaussian distribution very well. R^2 for the Gaussian fit of the expression 45 for N=1,2,3,4,5 are 0.9965, 0.9955, 0.9954, 0.9953, and 0.9953, respectively. Although the outputs when m=2, n=10 and m=1, m=8, for equilibrium dissociation constants equal to 1, give slightly better R^2 (Supplementary Information: Table 15), they are visibly less symmetric than the output when m=2, n=8 (Figure 11).

$$\left[\frac{K\frac{X}{2^{N-1}}}{1+\frac{X}{2^{N-1}}}\right]\cdot\left[\frac{\left(\frac{X}{2^{N-1}}\right)^2}{1+\left(\frac{X}{2^{N-1}}\right)^2}\right]\cdot\left[\frac{1}{1+\left(\frac{X}{2^{N-1}}\right)^8}\right] \tag{45}$$

The following is non-approximated form of the above expression

$$\left[\frac{K\frac{X}{2^{N-1}}}{1+\frac{X}{2^{N-1}}}\right]\cdot\left[\frac{\left(\frac{10^2\frac{X}{2^{N-1}\cdot 10^2}}{1+\frac{X}{2^{N-1}\cdot 10^2}}\right)^2}{1+\left(\frac{10^2\frac{X}{2^{N-1}\cdot 10^2}}{1+\frac{X}{2^{N-1}\cdot 10^2}}\right)^2}\right]\cdot\left[\frac{1}{1+\left(\frac{10^2\frac{X}{2^{N-1}\cdot 10^2}}{1+\frac{X}{2^{N-1}\cdot 10^2}}\right)^8}\right] \tag{46}$$

Because the expression 45, whose β_1/α_1 is already a constant, possesses the mathematical property $f_{N+1}(X) = f_N(X/C_N)$, where C_N is independent of N and is equal to 2, the coefficient of variation of Gaussians they are approximately equivalent to is constant. That is, the mean and variance of a receptor is C_N times the mean and variance of the preceding receptor. Further, between the mean of the first receptor and the antepenultimate receptor, the total output of the series of this receptor 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 the mean of the approximate Gaussians they form. It should be noted that even though the output's range has an upper limit, the range of response is still proportional to the signal's range as for the series which generates linear signal-response relationship. 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.

Assuming the equilibrium dissociation constant of the first and the last receptor to be 2^a and 2^b, respectively; arguably, the range in which signal can be detected sensitively is $\mu_1\cdot(2^b-2^a) + (1/2)\cdot\sigma_1\cdot(2^a+2^b)$, where b > a and both are integers, and μ_1 (= 0.8461) and σ_1 (= 0.2748) are the mean and standard deviation of the Gaussian distribution which fits output Z_{eq} of the receptor whose equilibrium dissociation constants are equal to 1 (i.e., N=1 in the expression 45). The number of receptors in this series is equal to b-a+1. This implies that when b-a is large

and both b and a are also large, $\mu_1 \cdot (2^b - 2^a) + (1/2) \cdot \sigma_1 \cdot (2^a + 2^b) \gg b-a+1$; and consequently, the signal-response relationship becomes an example of bow-tie architecture. For example, when a=0 and b=10, the range of signal and response (1006.4) is three orders of magnitude larger than the number of receptors (11). 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 expression of the three receptors are in the figure's legend.

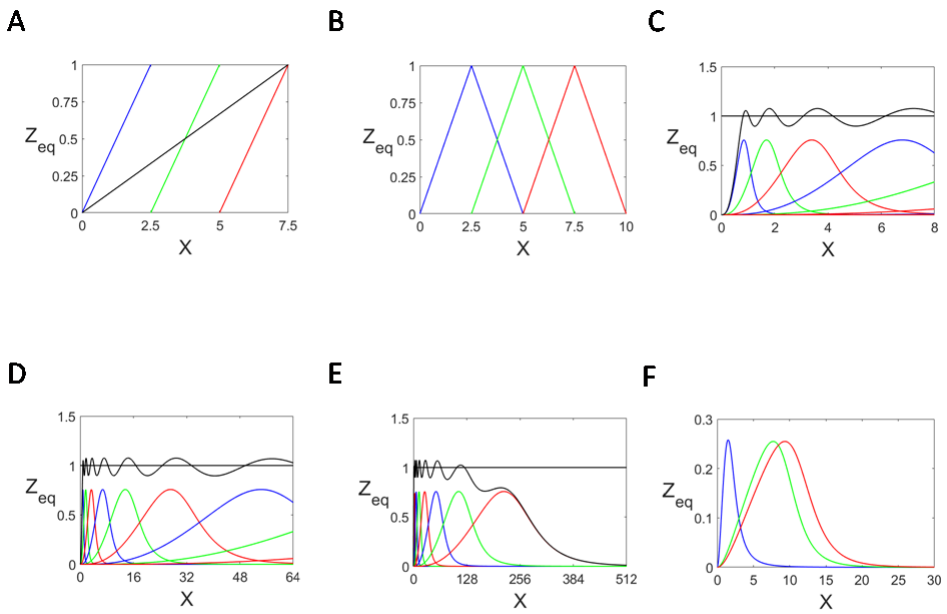

Figure 10: **A** The black line shows that, when the output has an upper limit, sensitivity of linear signal-response relationship reduces with increase in the range of signal. The blue, green, and red lines are minimal ideal hypothetical signal-response relationship, i.e., which maintain high sensitivity throughout the signal's range. **B** Biologically realistic form of the ideal hypothetical signal-response relationship. **C-E** Output Z_{eq} of the series of receptors defined by the expression 45 (with K=5) for various ranges of N. The individual 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 expressions of the three receptors are: $[3.6 \cdot (X/4)/(1 + X/4)] \cdot [(X/8)^2/(1 + (X/8)^2)] \cdot [1/(1 + (X/8)^8)]$; $[5 \cdot (X/20)/(1 + X/20)] \cdot [(X/20)^2/(1 + (X/20)^2)] \cdot [1/(1 + (X/20)^8)]$; $[5 \cdot (X/24)/(1 + X/24)] \cdot [(X/24)^2/(1 + (X/24)^2)] \cdot [1/(1 + (X/24)^8)]$

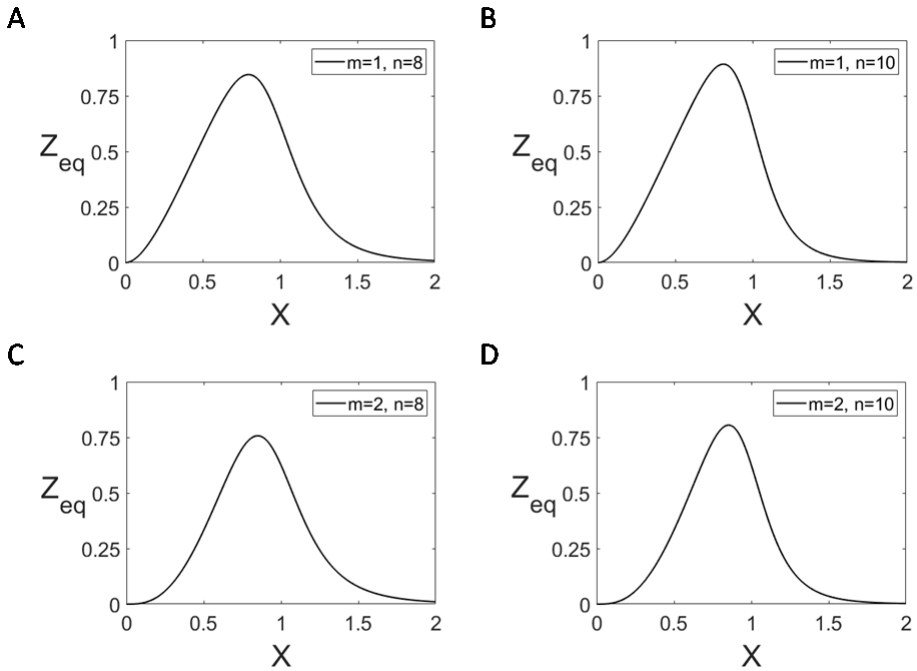

Figure 11: (**A-D**) Output Z_{eq} of the four-node motif defined by the expression $[5 \cdot (X/1)/(1 + X/1)] \cdot [(X/1)^m/(1 + (X/1)^m)] \cdot [1/(1 + (X/1)^n)]$ with different values of the Hill-coefficients m and n.

2.5. The Four-node Motif and Logarithm Computation

When the ratio β_1/α_1 in the expression 21 increases as powers of ten, the series of the four-node motif defined by equation 24 produces a straight line. And when the ratio β_1/α_1 increases linearly, the output of the same series is a strongly concave curve. Thus it was suspected that with rational choice of β_1/α_1, the output could be equal to 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 (equation 24) 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.

The functions $\log_{10}$ and $\log_e$ were regressed on the expression on the RHS of the equality in equation 47. The logarithms and the expression were evaluated at values which were powers of 2 ranging from 0 to 14 (i.e., the values ranging from 1 to 8192). 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 receptor. On the other hand, when, for the purpose of regression, $\log_{10}$, $\log_e$ and the expression were evaluated at values which were powers of 10, 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 produce figures 13 and 14 are from using logarithm of powers of 2 for regression, because this way more data points were 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.

The computation of logarithm by a series of the four-node motif raises the possibility that, with rational choice of β_1/α_1, such a series might also 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 computing 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.

$$Z_{eq} = C_1\left[\frac{10^1\frac{X}{10^1}}{1+\frac{X}{10^1}}\right]\cdot\left[\frac{\left(\frac{X}{10^0}\right)^2}{1+\left(\frac{X}{10^0}\right)^2}\right]\cdot\left[\frac{1}{1+\frac{X}{10^1}}\right]+\sum_{i=2}^{4}C_i\left[\frac{10^i\frac{X}{10^i}}{1+\frac{X}{10^i}}\right]\cdot\left[\frac{\frac{X}{10^{i-1}}}{1+\frac{X}{10^{i-1}}}\right]\cdot\left[\frac{1}{1+\frac{X}{10^i}}\right]+C_5\left[\frac{10^5\frac{X}{10^5}}{1+\frac{X}{10^5}}\right]\cdot\left[\frac{\frac{X}{10^4}}{1+\frac{X}{10^4}}\right] \tag{47}$$

Table 2 depicts how the parameters of the series based on the four-node motif scale with the motif's number. In all the cases, the value of $Kd_{YZ}\cdot\beta_2/\alpha_2$ and $Kd_{VZ}\cdot\beta_3/\alpha_3$ is equal to 100.

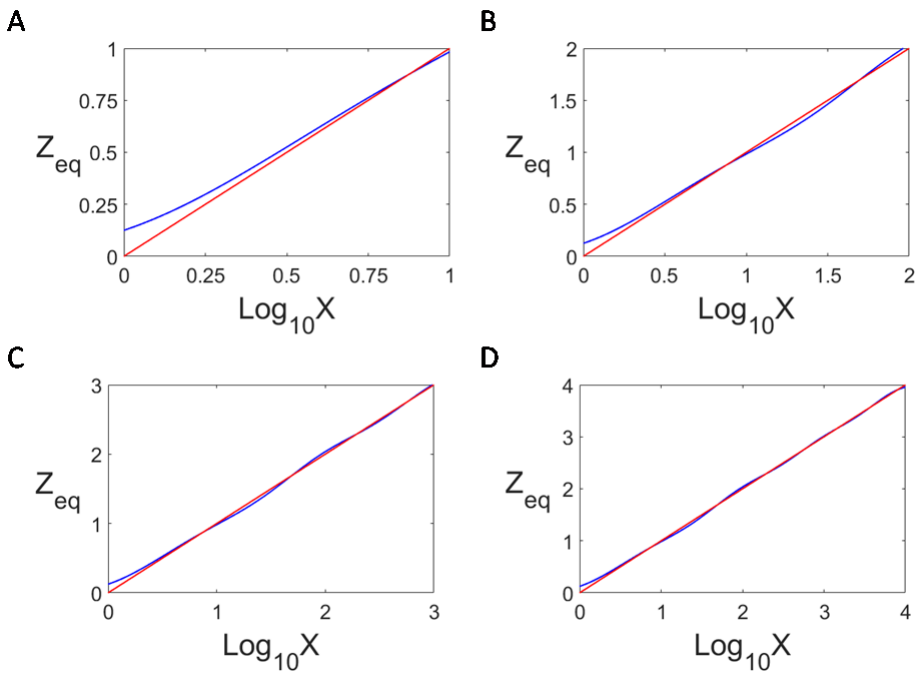

Figure 12: (**A-D**) The series which computes $\log_{10}$. The total output (blue) of the first five receptors for various range of signal plotted on $\log_{10}$-transformed abscissa. The straight line (red) is drawn for comparison. The last receptor lacks the negative arm. The first receptor possesses 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.

Table 2: Type of Series and the Values of its Parameters

Series Type	β_1/α_1	Kd_{XZ}	Kd_{XY}	Kd_{XV}	m	n
Linear Signal-Response	Kd_{XZ}	Powers of 10	$100 \cdot Kd_{XZ}$	$10 \cdot Kd_{XZ}$	1	1
Numerosity Processing in Monkey	Kd_{XZ}	Integral values	$100 \cdot Kd_{XZ}$	$10 \cdot Kd_{XZ}$	1	2
Sensitive Detection when the Output has an Upper Limit	Constant	Powers of 2	$100 \cdot Kd_{XZ}$	$10 \cdot Kd_{XZ}$	2	8
Logarithm Computation	Determined by Linear Regression	Powers of 10	$100 \cdot Kd_{XZ}$	$10 \cdot Kd_{XZ}$	1	1

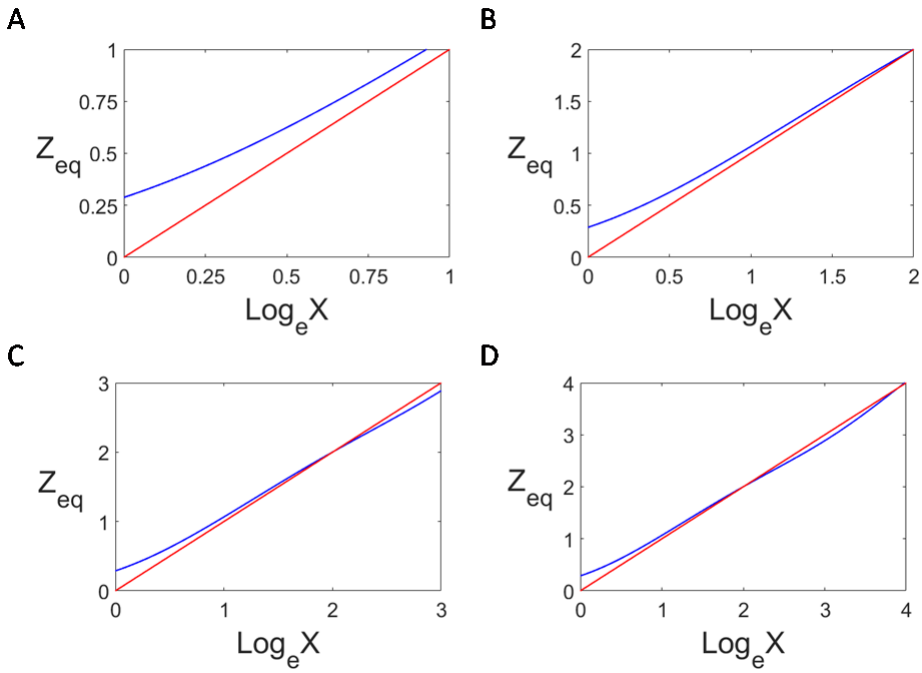

Figure 13: (**A-D**) The series which computes $\log_e$. The total output (blue) of the first five receptors for various range of signal plotted on $\log_e$-transformed abscissa. As earlier, the last receptor lacks the negative arm and the first receptor possesses the positive arm with m=2. β_1/α_1 of the five receptors were: 6.654, 14.5, 19.77, 28.47, 19.15, respectively. The R^2 was 0.9989.

3. Discussion

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 (the time rate of change in methylation must be a monotonically decreasing function of the kinase activity), 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 (and thus decreases the tumbling frequency), 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 is responsible for Weber's law observed in E coli's chemotaxis. The two differences are as follow. Firstly, 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. Secondly, 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. Because higher-order sensory processes such as weight perception, size perception, and numerosity processing sense a signal in absolute manner and should not involve exact adaptation (as argued in the section *Introduction*), a sensory mechanism based on exact adaptation cannot explain Weber's law observed in the three higher-order sensory processes. Thus the mechanism proposed here is, to the author's knowledge, the only plausible 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 18) 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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