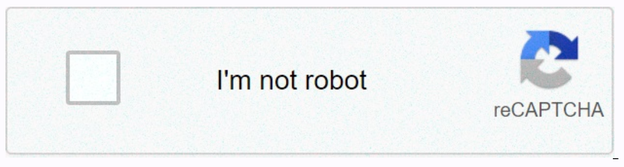

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Inputs definition biology

The classic Michaelis-Menten kinetic of chemical reactions leads to a saturation relationship between the input signal and the output response [7]. The puzzle is created at a very low input, for which Michaelis-Menten kinetics predict an almost linear output response to small changes in the input. This sensitivity at low input means that chemical reactions have almost infinite measurement accuracy for small fluctuations in the input concentration. Idealized chemical reactions do not have that infinite accuracy, and observations can follow that pattern if almost ideal conditions have been established for laboratory tests. In contrast, the actual input-output conditions of chemical reactions and more complex biological signals often differ from Michaelis-Menten kinetic. Several studies have analysed the contrast between Michaelis-Menten kinetics and observed input-output conditions of chemical reactions [2]. I will discuss some previous studies at a later stage. However, before these previous studies, it is useful to have a clearer sense of the initial puzzle and the alternative way in which the frame is the problem. An example of Michaelis-Menten kinetics michaelis-menten input-output connections is a specific example in which the higher input concentration of the signal increases the inactive molecule conversion to an active state. The different formulations of Michaelis-Menten kinetics emphasise different aspects of reactions [7]. But these different preparations all have the same basic mass action property, which assumes a spatially independent concentration of reactans. Spatially independent concentrations may be multiplied at any time to calculate spatial proximity between retantes. In my example, a signal, S, changes the inactive reactant, R, an active output, A, a reaction where the reaction rate, g, can be thought of as signal gain. In this reaction alone, if S>0, all reactant, R, is eventually transformed into the active form, A. (I use Roman fonts of different reactant species and italic font concentration of these reactantes.) However, I am particularly interested in the relationship between the input signal concentration, S, and the output signal concentration, A. So, I also have a back reaction in which the active form, A, spontaneously transforms back into inactive form, R, expressed in reaction kinetics follows, in which the exaggeration denotes the derivative in respect of time, and N=R+ A is the total concentration of inactive plus active reactant molecules. The equilibrium concentration of the output signal (A∗) is found as a function of the input signal S by solution A =0, which has m=δ/g re-reaction rate compared to the forward reaction. Note that S/(m+S) is the equilibrium of the originally inactive reactant, which is converted to an active state. At S=m, the input signal converts the inactive to the active state. in Article 1(1), the following shall be Low input signal intensity, S→0, output is strongly (linearly) sensitive to input changes, and output changes relative to S. With high signal intensity, the output is weakly (from logarithm) sensitive to input changes and the output changes in proportion to log(S). The output increases as the input is ∗→N ∗→. Figure 1Michaelis-Menten signal transmission. The reaction dynamics convert the concentration of the input signal (S) to the Eq. (2) to the equilibrium ∗ A. Half of the maximum output is at S=m input. All the restags to be converted are often different from those in 1. In particular, output is often only weakly sensitive to changes in the input signal with low input intensity. Poor sensitivity to low input values often means that the output changes in proportion to log (S) to small S values, rather than the linear connection between the input and output of small S values described by Michaelis-Menten kinetics. The Hill equation preserves the entire Michaelis-Menten pattern, but at low input it modifies the sensitivity to be logarithmic rather than linear. Remarkably, most biochemical reactions and patterns of curve shapes in more general biological input-output relationships fit fairly well with the Hill equation(difference= b xˆk + xˆk (3) or smaller variants of the equation (Table 1). The input intensity is xˆ, the measured output is yˆ, the maximum response is half xˆ=m, the response shape is determined by the K hill factor, and the response asymptotically saturates b to increase the input levels. Table 1 Conceptual bases You can simplify the expression by using y=paragraph/b substitutions, in which y is the maximum response, and x = xˆ/m, in which x returns half of the maximum response. The resulting equivalent term is replaced by the following: For k=1, the curve is the same as in 1. The increase in k narrows the input range through which the output reacts quickly (sensitively). For higher k values, rapid switching from low to high output is often referred to as a stable response, as the system output state switches almost binary between low output, OFF and OFF or ON. The bistable switching response is practically a biological transistor that is a component of a biological circuit [13]. Bistability is sometimes referred to as ultrasensitivity, as the high sensitivity of the response to small changes in inputs measured in the responsive range [14]. Figure 2Hill equation signal transmission. The input signal, x, leads to the output, y, Eq. (4) gave. The curves of the ascending slope correspond to k=1,2,4,8. Such extreme sensitivity essentially means infinite measurement accuracy at tiny input levels, which seems unlikely for realistic biological systems. As k increases, low input sensitivity will be like a threshold response, so minimal input is needed to stimulate a significant change in output. Increasing the k makes the sensitivity logarithmic at low inputs. This low input sensitivity pattern is more visible by plotting the input level on a logarithmic scale than in Figure 3. For k=1 (left curve), the sensitivity is linear, and the output continues to increase even at very low input levels, which means infinite accuracy. As k increases, the sensitivity of the low input level decreases and the required threshold is higher and sharper to trigger an output response that triggers 1% of the maximum value (y=0.01). The curves of the ascending slope correspond to k=1,2,4,8 in Eq. (4), and here is the logarithmic scaling of the input x. My goal is to understand the general properties of input-output relationships in biological systems. In order to develop this general knowledge, it is useful to continue to study the basic input-output relationships of simple chemical reactions. Presumably, most input-output connections of systems can ultimately be broken down into simple component chemical reactions. Later, I will examine how the combination of such components affects the overall response of the system. Several studies on chemical kinetics report Hill's co-ing k>1 instead of the expected Michaelis-Menten sample k=1. Solving this mysterious mismatch is the first step towards a deeper understanding of input-output patterns (Table 2). Zhang and his mtsai [2] are reviewing six specific mechanisms that could cause k>1. In this section, I will briefly summarise some of these mechanisms. See Zhang et al. [2] for references. Table 2 The conversion of a single molecule to an active state in the Hill equation literature may require simultaneous binding with multiple input signal molecules. If two signal molecules, S, are to be bound to a single inactive reactant, R, to form three molecule complexes before R is transformed into active state A, the reaction is S + S + R → g SSR → S + S + A , which by mass effect is kinetical A as Aṣ = g S 2 (N - A) - δA - δA , in which N=R+A is the total concentration of inactive active reactant molecules and the A→R back reaction δ at a low rate. The equilibrium input-output relationship is that of a Hill equation with k=2. The reaction is stychiometry, combined with two signal molecules in the reaction, the reaction rate multiplied by the signal inlet concentration. Other simple systems the concentration of the signal molecule has a multiplyrative effect on the rate of reaction. For example, the signal can increase the speed of two consecutive steps along the route, causing the signal concentration of the total speed to multiply in several steps. Some types of positive feedback also amplify the input signal multiplied. Saturation and loss of information multi-stage reaction cascadesThe previous section discussed mechanisms that multiply the signal input concentration to increase the Hill's co-value. Multiplytic interactions lead to logarithmic scaling. The K>1 Hill equation expresses logarithmic scaling of output at high and low input levels. I'll return later to the general question of logarithmic scaling. The point here is that multiplication is one of the sufficient ways to achieve logarithmic scaling. But multiplication is not necessary. Other non-multiplicative mechanisms that lead to logarithmic scaling may also fit closely with the Hill equation pattern. This section discusses two examples to which Zhang and their author [2] relate. The backpressor of weak input signals The key puzzle of the Hill equation relates to how to generate the logarithmic scaling pattern at a low input intensity. The simplest multimultiplicative mechanism stems from an initial reaction that deactivates the input signal molecule. Preprocessing signal intensity can create a filter that reduces low-intensity signals from a logarithm. For example, suppose that the suppressor can become saturated at higher input concentrations. Then the initial reaction filters out weak, low concentrations, inputs, but goes through higher input concentrations. Take an oppressor, X, which binds to the signal, S, transforms the bound complex into an inactive state, I, the reaction Can think of this reaction as a preprocessor filter for the input signal. The kinethy of this input preprocessor can be expressed by focusing on the change in the concentration of the bound, inactive complex The signal passing through the preprocessor is the amount of S that is not bound to the I complexes, which is S'=S-I. We can also properly write I= S'-S. The equilibrium between the S input (S) and the S′ output signal passing through the preprocessor can be achieved by solving Ì=0, which s (X - S + S - α (S - S) = 0 , in which α=β/γ. Figure 4a shows the relationship between the input signal, S, and the preprocessed output, S′. Knit inactive complexes, I, hold the signal molecule tightly and titrated out the activity when breaking complexes at β speed β slower than the formation of new complexes at γ speed and thus α small. Figure 4 Recycling the input signal by a suppressor reduces the sensitivity of the output to low input intensity signals. (a) Equilibrium concentration of the processed signal, S′, relative to the original signal input intensity, S, Eq. solution 5. The four curves show descending levels from the bottom up signal titration of α=0,01,0,0,0,0,0,5,1000 parameter values by the suppressor. The top curve changes very little in the initial present, so the S'≈S, which shows the consequences of an unfiltered input signal. (b) The S′ processed input signal is used in the Eq. (1) standard Michaelis-Menten reaction as kinetic process input, leading to equilibrium output, A∗. Bottom-up curves are derived from the corresponding pre-processed input signal in the top panel. The pre-processed signal can be fed by a standard Michaelis-Menten type reaction, such as reaction Eq. (1), the pre-processed signal S driving with kinetics instead of the initial input, S. The reaction chain starts with an input concentration from the initial input to the final output, from which S ' passes through the suppression filter, and S′ stimulates the active output signal concentration (A∗. to 4b. S to a lower through signal concentration, S', leads to a low sensitivity of the final output, A∗, to the initial signal input S, as long as the signal concentration does not reach the amount of repressor available titration, X.When this signal preprocessing mechanism is done, the low, essentially logarithma, sensitivity to weak input signals solves the puzzle associated with the classic Michaelis-Menten chemical kinetic in the Hill equation with sample input-output connections to the k>1. Article 4b shall be replaced by the following: However, this signal preprocessing mechanism, combined with other simple mechanisms, can result in a closer fit to the Hill equation pattern. I will discuss below the aggregation of the various mechanisms. This pre-processed signal system is associated with classical chemical kinetic mechanisms, as it is the deterministic result of a simple and explicit mass action reaction chain. However, the reactions are not inherently multiplied in terms of signal input intensity. Instead, preprocessing results in a fundamentally logarithmic transformation of scaling and information with low input signal intensity. This example shows that the original concept of multiplyrative interactions is not a necessary condition for scaling the Hill equation input-output relationships. Instead, the Hill equation pattern is simply a specific expression of the logarithmic scaling of the input-output relationship. A combination of processes that lead to similar logarithmic scaling provides similar input-output connections. Thus, the Hill equation pattern does not present any specific underlying chemical mechanism. Such input-output relationships are more of a natural consequence of the way the information is de-decontrated and are transformed relative to scaling when passing through reaction sequences that act as filters for the input signal. In contrast to forward and back-down reactionsThe previous section showed how the suppressor can reduce the sensitivity of low-intensity input signals. A similar mechanism if there is a back reaction. For example, a signal can turn an inactive reactant into an active form, and a back reaction can send the active form back to an inactive state. If the rear reaction saturates with a low signal input intensity, then the increase in signal from a very low level initially increases the concentration of the active output relatively slightly, causing a weak, logarithmic sensitivity to the intensity of the low input signal. In fact, the low input is suppressed or titrated by a strong back reaction. This opposed reaction between forward and backward reactions was one of the first specific mechanisms of classical chemical kinetics to produce a pattern of the Hill equation in the absence of direct multipical interactions to amplifying the input signal [14]. In this section, I will briefly illustrate my support for forward and back-side reactions to the Hill equation pattern. The anterior reaction, the signal, S, converts the inactive reactant, R, into an active state, A. The back reaction is catalyzed by molecule B, which converts A to r. The equilibrium effects of forward and back-way reactions in terms of saturation depend on a more pronounced kinetic of classic Michaelis-Menten kinetics than those presented above. The two reactions should be s + r δ sr → φ S + A B + A γ BA → σ B + R, in which these reactions show specifically intermediate knit complexes, SR and BA. The change rate of the output signal (A, if the dynamics follow the kinethy of the classic equilibrium Michaelis-Menten reaction) is A =φ S 0 R m + R -σ B 0 A μ + A , (6), in which S0 contains both the free signal, the S and the bound signal, SR concentration. Similarly, B0 includes the concentration of both free catalyst, B and bound catalyst, BA. The maximum reaction rate is determined by m=δ/g and μ=d/γ per hour. The degree of saturation depends on the total amount of reactant available, N= R +A, relative to the concentrations giving half-maximum reaction rate, m and μ.When the input signal S0 is small, the rear reaction dominates, potentially saturating the forward speed as the R increases. Figure 2 shows that the level of saturation determines the input-output pattern, the higher saturation increases the Hill co-value, k.5ChartBalance between forward and backward reactions leads to a high Hill-1 when the reactions are saturated. The equilibrium ∗ A is resolved in A =0 Eq. (6) as a function of the input signal S0. The symbol A dinfess=φ 0 /σ B 0 . The total volume of the retant is N=R+A. The half-maximum concentrations are set to m=μ=1. The three curves show solutions for N=1,10,100, with increasing hill-lyses for higher N values and higher reaction saturation levels. In the following sections, I will discuss alternative mechanisms that generate hill equation patterns. Before discussing these alternative mechanisms, it is useful to summarise the broader context in which cellular input-output relationships. Explicit chemical reaction mechanisms Earlier sections linked simple and explicit chemical mechanisms to certain Hill equation patterns for inputs and outputs. Each mechanism provided a separate way to increase the Hill's co-ing over one. A number of key assessments and textbooks on biochemistry and system biology stress that higher Hilli factors and increased input-output sensitivity stem from these simple and explicit deterministic mechanisms of chemical reactions [2, 7, 20]. The idea is that a particular pattern should be generated through one of the few well-defined and explicit alternative mechanisms. The explicit chemical reaction mechanisms discussed earlier are: binding of several signal molecules to stimulate individual reactions; repressors of weak input signals; and back reactions near saturation. Each of these mechanisms can in principle be separated from a particular system, analysed directly and quantitatively linked to a specific input-output scheme. Decomposition to elementary chemical kinetics and direct quantitative analysis would tie the observed sample to an explicit mechanistic process. The Hill equation is used exclusively as a description of the observed pattern In the literature, the Hill equation is also used when building models of how system outputs can react to different inputs (Table 2). Models often study how combinations of components lead to a complete input-output model of the system. To analyze such models, assumptions must be made about the input-output relationships of each component. Typically, a Hill equation is used to describe the input-output functions of components. This description does not carry any machine aspect. You simply need an input-output function to create the model or describe the properties of the component. The Hill equation is quoted because, for some reason, most observed input-output functions follow this pattern. System-wide mechanisms and deviation from mass actionA study line focuses on system properties, not input-output patterns for each component. In these studies, the sensitivity pattern of the Hill equation does not stem from a chemical mechanism in a particular reaction. Instead, sensitivity stems primarily from the overall consequences of the system (Table 2). In one example, many of the cascade's reactions combined result in hill-like sensitivity [39]. Sensitivity comes primarily from a random combination of different scales of different reactions, not from a particular chemical process. Alternatively, some studies assume that chemical kinetics differ from the assumption of classical mass act (Table 2). If the input signal tend to be spatially isolated from the reactant molecules on which they work during the reaction, then such spatial processes often create a hill-like input-output pattern by sensitivity to changes in inputs. I consider such spatial processes as an aggregate system property rather than a specific chemical mechanism because many different spatial mechanisms can limit the aggregate movement of molecules. The aggregate spatial processes of the entire system determine the deviation from mass action and the possible Hill-like sensitivity consequences, not the specific physical mechanisms that change spatial interactions. These systemic explanations are based on reaction cascades and spatially-indued variations in mass action with the potential benefit of application widely. Still, each systemic explanation itself is a particular mechanism, albeit at a higher level than previous biochemical mechanisms. In all actual cases, the higher system mechanism may or may not be applied, as each explicit chemical mechanism sometimes applies to a particular case, sometimes not. A wider perspectiveAs we accumulate more and more alternative mechanisms that fit the basic input-output pattern, we can ask if we are approaching a full explanation or missing something deeper. Is there any other way to view a problem that combines different perspectives without losing the real insight provided in any case? I think there is another, more general perspective (Table 1). At this point, I have given just enough background to outline this broader perspective. I did this for the rest of this section. However, it's too early to go through. After giving you a tip on the final view, I will return in the following sections to develop additional topics and then return to a wider analysis of input-output relationships. The K>1 hill equation delineates weak, logarithmic sensitivity at low input and high input levels with strong and essentially linear sensitivity across an intermediate range. Why should this log-linear-log pattern be so common? The broader perspective of this problem is given in the following points. Firstly, common patterns of nature are precisely those that are consistent with most alternative underlying processes [3, 40]. If many different processes lead to the same result, then this result will be common and there will be a strong connection to any particular mechanism. In any specific case, there may be a simple and clear mechanism. But the next case, with the same pattern, is likely to be mechanically separate. Secondly, measurement and transmission of information combine different mechanisms. The Domb equation uses k>1 to describe a log-linear-log measurement scale [41, 42]. The questions become: Why do biological systems, even at the lowest chemical analysis levels, often follow this measurement scaling? How does chemistry work relative to size and information transfer and loss? Why information and measurement a universal pattern of Mechanisms? Third, this broader perspective changes the way one needs to analyze biological input-output systems. In all separate cases, the specific mechanisms remain interesting and important. However, the links between the different cases and the general interpretation of the sample should be interpreted within the broader framework. As far as biological planning is concerned, natural selection is working on available variation patterns. Since some input-output relationships usually arise, natural selection works on differences around the natural contours of the input-output patterns. These natural contours of the sample and variation are determined by the universal properties of the information transmission scale (i) and its measurement scale. This limitation of variation is likely to affect the type of samples created by natural selection. To understand why some plans arise and others don't, we need to understand how the information transfer and measurement scale determines the underlying patterns of variation. I'll get back to these points later. Now, it's helpful to keep in mind these preliminary suggestions about how the various pieces will eventually come together. Aggregation Most biological input-output connections are generated through a series of reactions. Initial reactions convert the input signal into different intermediate signals, which themselves form inputs for additional reactions. The final output is generated only after several internal transformations of the initial signal. The overall input-output relationship can be thought of as a cumulative consequence of multiple reaction components. The linear reaction cascade forms a simple type of system. Kholodenko el al. [39] stressed that the cascade tends to multiply the sensitivity of each step to determine the overall sensitivity of the system. Figure 2 shows how the input-output conditions of each reaction are combined to determine the system-wide sample. Figure 6The signal processing cascade increases the Hill co-value. The parameters of each reaction were randomly selected from a beta distribution, which is referred to as a random z-B variable (α,β), resulting in values in the [0,1] range. The parameters m=100z and g=5+10z were randomly and independently selected for each reaction to beta distribution α=β=3. The k parameter for each reaction was randomly obtained as 1+z, resulting ≤ 1≤2. (a) In three different studies, different combinations of (α.β) were used for the beta distribution that created the Hill-10, k: in the first, indicated as a left distribution (α,β)=(1,6); in the second, in the middle (α,β)=(4,4); third, right (α,β)=(6,2). The preview shows that the peak heights normalized for each curve are the same to facilitate visual comparison. b) The input-to-output connection on the entire cascade. Left-to-right curves correspond to the k distribution from left to right in the previous panel. A scale is normalized, so that the maximum input value for each curve coincides with the output available for infinite input. The observed output curves reduce sensitivity more at low inputs than at high inputs compared to the hill equation, but nevertheless fit quite well. The hilly compound of the hill equation of the three curves is from left to right, k=1,7,2,2,2,2,8. In the cascade, the average Hill rate for each reaction is k=1,14,1,5,155 from left to right. Each curve shows a single concrete implementation of randomly selected reaction parameters for the underlying distributions. Article 6(2) shall be replaced by the following All reactions are Eq. (4) followed by the input-to-output ratio of the Hill equation, which at m is a semi-maximum response and a Hill k. The output of each reaction is multiplied by a gain, g. The parameters of each reaction were selected at random, as shown in Figure 6a, that the cascade significantly increases the hill-like lytic of the entire system above the average of each reaction and often well above the maximum value of each reaction. Intuitively, the most important effect is low signal input duration, because any reaction that is low sensitivity at low input reduces transmitted signal intensity, and such reductions multiply over the cascade at low input intensity, resulting in very low sensitivity to low signal input. Notice in each curve that the input signal is significantly above zero for the output signal to rise above zero. This lower tail illustrates the loss of signal information with low signal intensity. This analysis shows that weak logarithmic sensitivity at low signal inputs, which is associated with large Hill-lyses, can result from aggregation of a number of reactions. Thus, aggregation can be a partial solution to the general mystery of log-linear-log sensitivity in input-output connections. Aggregation alone leaves open the question of how the change in sensitivity arises in each reaction. Classic Michaelis-Menten reactions have linear sensitivity at low signal inputs, with a hilly co-ation k=1. The pure Michaelis-Menten cascade k=1 maintains linear sensitivity at low signal inputs at each step. The Michaelis-Menten cascade would not have the weak sensitivity to low input shown in figure 6b. How is the K>1 hill co-ed generated in each step of the cascade? The power of aggregation to induce the pattern means that it does not matter how such differences in sensitivity arise. However, it is useful to consider a few examples to get an idea of what types of processes can be put down beyond the deterministic cases you have previously specified. Signal noise and measurement noiseTwo different types of noise can affect the system's input-to-output connections. First, the initial input signal can be noisy, making it difficult for the system to distinguish between low signals and background socokytic background signal intensity [43]. The problem with the classic signal-to-noise ratio expresses this difficulty by analysing how input background noise can cover small changes in average input intensity. If the signal is weak compared to background noise, the system may be relatively insensitive to a small increase in average input at low input intensity. Secondly, for a given input intensity, the system may experience noise in signal level detection or transmission of the signal through internal processes that determine the final output. The stochasity of signal detection and transmission determines the internal measurement noise of the system. The ratio of measurement noise to signal intensity will often be higher at low signal input intensity, as weak signal detection and transmission show relatively higher noise. In this section, I look at how signal noise and measurement noise affect Michaelis-Menten processes. The question is how much this type of noise can weaken sensitivity to low-intensity signals. The weakening of the sensitivity to the low input level distorts the input-output relationship of the Michaelis-Menten process in such a way that it leads to the K>1> response-type hill equation type. Conversely, since the Hill's co-onics, k, rise above one, measurement accuracy is transformed into a log-linear-log scale, with weaker logarithmic sensitivity signal changes with low input intensity. Thus, the problem here is how signal noise or measurement noise can weaken input-output sensitivity at low input intensity. The noise of the input signal cannot change the Michaelis-Menten sensitivityThe simplified Michaelis-Menten dynamic type given in Eq is considered. (1), here for convenience repeated Aṣ = gS (R - A) - δA , where A is the output signal, S is the input signal that drives the reaction, R is the reactant converted by the input, g is the speed of the converter reaction, which is δ kind of signal amplification level, and δ the rate at which the output of the active signal is degraded into the inactive form. So far, I've been analyzing this kind of problem assuming that the input signal, S, is a constant specific reaction, and then variable S to analyze the input-output connection, given the balance of Michaelis-Menten saturation, where m= δ/g. If the intensity of the input signal is weak, so that it is m≫S, then A∗≈g S, which means that the output is linearly connected to the input. Let's say the S is actually a noisy input signal exposed to random fluctuations. How do fluctuations affect the input-to-output relationship of low average intensity inputs? Although dynamics can filter noise in different ways, it is often found that the linear input-to-output relationship remains such that the low average intensity of the average power is proportional to the average input, Â∝ S ' . Thus, signal noise does not change the fact that the system effectively measures the average input intensity linearly and with essentially infinite accuracy, even at an extremely low signal-to-noise ratio. Classical chemical kinetics generate high accuracy because mass impact presets mean that infinite changes in input concentration are immediately transformed into linear changes in the speed of collisions between possible reactantes. The puzzle of Michaelis-Menten kinetics is that mass action means high precision and linear scaling with low input intensity, while both intuition and observation suggest low accuracy and logarithmic scaling with low input intensity. The noise of the input signal alone does not usually change the high accuracy and linear scaling of mass action tics. Although the simplest Michaelis-Menten dynamics retain linearity and essentially infinite accuracy with low input, it remains unclear whether the input input-to-output connections of complex aggregate systems respond to the signal-to-noise ratio of the input. Feedback loops and reaction scades strongly affect the ways in which fluctuations between input and output are filtered. However, classical analysis of signal processing usually focuses only on the filtering properties of the systems in terms of fluctuations in the input value for the fixed mean. In contrast, the most important biological problem is how input fluctuations change the relationship between the average input intensity and the average output intensity. This main problem requires you to study the synergistic interactions between changes in average input and patterns fluctuations in the average. For noisy input signals, what are the universal characteristics of system structure and signal processing that change the relationship between average input and average output? This remains an open question. Noise in signal detection and transmission reduces measurement accuracy and sensitivity at low signal inputThe previous section examined how stochastic fluctuations in inputs could affect average performance. Simple mass action kinetics can result in infinite accuracy at low input intensity, linear scaling between average input and average power, regardless of fluctuations in noisy inputs. This section looks at the problem of noise from a different perspective, in which fluctuations arise within the system and change measurement accuracy and signal transmission. I'm going to use a simple model to illustrate the most important questions. I assume that the reaction cascade deterministic dynamics, each reaction leads to the Michaelis-Menten type equilibrium input-output given Eq. (7). To study how stotic fluctuations within the system can be input-output connections, I assume that each reaction has a certain probability that it will not transmit the input. In other words, for each reaction, the output is the equilibrium input-output input-output 1-p, and p is likely to output zero. Az Eq. (7) from its standard equilibrium state, we simplify marking using y≡A∗ for output and scale the input to x=S/m. The probability that the output is not zero is 1-p, so the expected output is: Allow the probability of error to be p=a e-bx. Note that the intensity of the input signal, x, rises, the probability of error decreases. As the signal becomes very small, the probability of reaction failure is close to the range, 0≤a≤1. Figure 2 shows that the stocastic failure of signal transmission reduces the relative sensitivity of low input signals when the signal passes through a reaction cascade. The longer the cascade of reactions, the more the total input-output relationship follows an approximate log-linear-log pattern with an increasing Hill-lytic, k. Similarly, article 8(1) shall be replaced by the following: Figure 7Stocastic error in signal transmission reduces the relative sensitivity of low intensity input signals. The lower (blue) lines show the probability p=a e-bx that the input signal will not output. The upper (red) lines show the expected equilibrium output of the dynamics of the Michaelis-Menten type, which is corrected to a probability p that the output is zero. Each panel shows a cascade of reactions (a to d) n, in which the output of each reaction forms the input of the next reaction, with an initial signal input x for the first reaction. Each reaction follows Eq. (8). In the cascade, the number of reactions increases from left to right, as n = 1,2,4,8. Az Eq. (8) other parameters are the gain per reaction(g=1.5, the maximum probability of a reaction error, since the input decreases to a very low intensity, a= 0.3, and the rate at which increasing signal intensity reduces reaction failure , b = 10. The final output signal is normalized to the maximum output of 0.8, as the input will be very large. Figure 8A higher error rate of reactions reduces sensitivity to low inputs and increases the Hill-rate, k . The curves are derived from the same analysis as the curves 7 and 8. The curves in the figure have an n=8 reaction in the cascade, a gain of g=1.5 and a decrease in failure with increasing input, b=10. The input signal scale is normalized so that the final output of each curve is 0.85 for a normalized input. The input-to-output response with a high Hill(s) leads to a switch-like function (Fig. 3). In contrast, the classic Michaelis-Menten kinetics leads to k=1, in which the output increases linearly with a small change in weak input signals – practically the opposite of the switch. Many analyses of system design focus on this distinction. The argument is that switch-like function is often a favored feature of design, allowing the system to changes between States in response to external changes [1]. Since the internal dynamics of chemistry are thought to be not a switch as a function, the classic puzzle is that the system design overcomes chemical kinetics to achieve switching function. This section of the stochastic signal error represents an alternative view. Sloppy components have a tendency not to often lead to switch-like function. Thus, if switching behavior is a preferred phenotype, it may be sufficient to use a randomly constructed signal path, coupled with poorly controlled reactions at each step. Switching, rather than a well-designed feature that requires a specific mechanistic explanation, is instead the expected result of unpredictable biological signal processing. This trend of aggregate systems is that the switching pattern does not mean that natural selection has no role and that the system design is random. Instead, the correct view may be that the aggregate signal processing and inherent stochasticity set the contours variation on which the natural selection and system design work. In particular, the most important design features may have to do with the modulating degree of negligence or stochasticity. The distribution of profit factors in each reaction and the overall pattern of stochasticity in the aggregate can also be a key design location. My argument is that systems can be well designed, but the nature of that design can only be understood in the context of natural patterns variation. The internal contours variation at the heart of the matter. I will discuss this issue later. Now, I will continue to explore processes that affect the nature of the change in system input-output patterns. Spatial correlations and variations in mass actionChemical reactions require molecules to be close to each other spatially. The overall reaction depends on the processes that determine spatial proximity and the processes that determine spatial proximity. We can pretty much think of spatial aspects in terms of motion or diffusion, and transformation in terms of spatial proximity reaction. Classical chemical kinetics typically assume that the diffusion rate is relatively high, so the spatial proximity of molecules depends only on the average concentration of distances much greater than the proximity required for the reaction. Kinecy is therefore limited by spatial proximity rather than diffusion speed. Unlike classical chemical kineticism, there is much evidence to suggest that biological molecules are often scattered relatively slowly, sometimes resulting in limited biological reactions (Table 2). In this section, we discuss how diffusion-restricted reactions can increase the Hill's chemical compound reactions, k>1. This conclusion means that the inevitable limitations in the movement of biological molecules may be sufficient to sensitivity of input-output functions and deviation from Michaelis-Menten samples. Two key points are displayed. First, limited diffusion causes potential rektans to separate spatially than expected during large diffusion and random spatial distribution. The negative spatial relationship between reactant is created because these potential reactantes tend to react close to each network, leaving fewer potential reactant than expected in the nearby spatial neighbourhood, with spatial uniformity. Negative spatial association of reacarts reduces the rate of chemical transformation. The reduction in the conversion rate is stronger at low concentrations, as low concentrations are associated with greater average spatial separation of the rektans. Thus, low signal intake can lead to a relatively significant reduction in transformation speed caused by limited diffusion. With an increase in signal intensity and concentration, this spatial effect decreases. The net consequence is the low transformation rate at low inputs, with an increasing transformation rate as the input intensity increases. This process leads to a higher Hill-like and switch-like feature with low sensitivity to input with low signal intensity. In the broader context of input-output samples, limited diffusion leads to the second key point. I recommend that limited diffusion is simply another way that systems suffer from reduced measurement accuracy and low signal intensity. The final understanding of system design and input-output function results from how to link certain mechanisms, such as diffusion or random signal loss, to wider problems with measurement and information. To understand the broader and more abstract concepts of measurement and information, it is necessary to re-work through some specific details that will lead to the loss of information by diffusion restriction. Deviation from mass act The most analyses of chemical kinets presuppose mass deeds. For example, suppose that two molecules can be combined to create a knitted complex in which the knitted complex, AB, undergoes further transformation. Mass act assumes that the ratio of AB forms is rAB, which is the product of the product of concentrations A and B multiplied by a binding factor r. The idea is that the number of collisions and potential binding reactions between A and B varies linearly by unit of time with the concentration of each reactant. Each reaction occurs in a particular place. This reaction disrupts the spatial relationship of reactant. Rektans that were accidentally close together no longer exist as free potential retant. Thus, the reaction reduces the likelihood of finding possible reactant in the vicinity, induing a negative spatial relationship with the between re-tans. To maintain the weighing rate, diffusion should be fast enough to break down spatial association. Quick Quick re-create the mutually unified spatial concentration of the re-actant, which is necessary to

maintain mass action. If diffusion is sufficiently slow, the negative spatial relationship between the reactant increases over time as the reaction continues. A decrease in the proximity of potential reactant reduces the overall reaction rate. Diffusion limited reactions therefore tend to reduce the reaction rate below the expected mass effect rate as the reaction progresses. This classic description of diffusion-limited reactions emphasizes the pattern of reaction rate over time. In contrast, I focus on the relationship between input and output. It seems obvious that the diffusion restriction may affect the input-output of the biological system. But exactly how to combine the classic analysis of diffusion restriction with the reaction rate of simple isolated reactions to the entire input-output pattern of biological systems? The relationship between diffusion and system input-output samples received relatively little attention. Some isolated studies have analyzed how the diffusion restriction increases the Hill co-ed, supporting the main discussion line (Table 2). However, a wide area of biochemical and cellular responses has almost completely ignored this issue. The following sections provide a simple illustration of how diffusion restriction can affect input-output patterns and how this effect fits into the broader context of the subject. For example, a limited diffusion of the input-output sample causes limited diffusion between spatial associations of reaktans. Spatial associations invalidate the mass action presusions. The calculation of the kinethy of the reaction without mass action shall take into account the spatially variable concentration of reactant and the related spatial changes in chemical transformations. There is no simple and general way to make spatially explicit calculations. In some cases, simple approximations give a rough picture of the result (Table 2). However, in most cases, one should study reaction kinethiki spatially explicit computer simulations. Such simulations track the spatial location of individual molecules, the reaction rate of nearby molecules, the spatial location of reaction products and the stocastic movement of individual molecules by diffusion. Several computer packages have been developed to facilitate stoocastic simulation of spatially expressed biochemical dynamics. I used the package Smoldyn [33, 44]. I was focused on how limited diffusion could increase Hill's co-ions. According to classical assumptions about chemical kinecy, diffusion rates tend to be high enough to maintain spatial uniformity, leading to michaelis-menten kinecy, with a k=1 hill-rate. Lower diffusion rates, spatial associations arise, invalidate mass Can these spatial associations lead to an increase in K>1 hilli co-ions? Figure 2 clearly shows that increased Hill co-1s are produced in a simple reaction scheme with limited diffusion. The reaction system shall be as set out in Article 9(1) and (2). Simulations can be seen in the computer package Smoldyn based on the reaction system Eqs. (9,10). The concentration of the input signal (S) is the number of molecules per volume per unit. The other concentrations are N=X=100. Diffusion rate is 10-5 for each molecule. I ran three repetitions for each input concentration, S. Each round shows the average of three repetitions. For each panel (a to f), I insert a Hill equation curve for observations, which denotes the output as a relative saturation level, A/N=sat[Sk/(mk+Sk)]. The parameters installed are: k, hill-i's co-ed; m, the concentration of the input signal which results in half of the maximum saturation; and sat, the maximum saturation level at which the emission is approximated to an asymptotic value relative to a maximum theoretical value at which it has been converted to all N A's. Due to limited diffusion, the actual saturation may be below the theoretical maximum. Panels (b) and (c) are limited to much lower output responses below the median because simulations take too long to run at higher input concentrations. Mass action is assumed to be the same dynamic as Eq. (1) With a value of - gS (N - A) - δXA - δXA, in which N=R+A is the total concentration of inactive plus active reactant molecules, in this case the reactive reaction is written as δ X, not just δ, as in the previous equation. In a spatially explicit model, we need to track the actual spatial location of each X molecule, so we need to explicitly include concentration X rather than include this concentration in a combined speed parameter. In equilibrium, the intensity of the output signal during the mass operation follows the Michaelis-Menten relationship, in which m=δ X/g. If we let x = S / m and y = A∗ / N, then we see that the reaction schema here leads to equilibrium input-output connection like Eq. (4) that follows the Hill equation k=1.I used smoldyn simulation package to study reaction dynamics when mass action assumption doesn't last. Simulations of a reaction scheme show input-output relationships with k>1 when the degree of chemical transformation is limited by diffusion. Figure 9 summarizes some smoldyn computer simulations showing k significantly larger than a certain parameter combinations. I do not go into great detail about these computer simulations, which is quite complicated. Instead, I'll briefly summarize some key points, because my goal here is simply to demonstrate that limited diffusion can increase Hill's effusions under certain reasonable circumstances. Article 9(1) shall be replaced by the following What causes the woman? It should be some aspect of spatial process, because diffusion restriction primarily causes from mass action to violating the assumption of spatial uniformity. I'm not sure what aspects of the spatial process caused the 9th Century. It appeared that in some cases most transformed output molecules, A, were considered miniature reaction centers that spontaneously formed and deteriorated. The local reaction center arose when S and R molecules approached each other, transforming into S and A. If there was a nearby X molecule as well, then X and A were restored to X and R. The R molecule may have re-reacted with the original nearby S molecule, which did not move much due to the slow diffusion rate of the reaction relative to the timescale. The cycle can then be repeated. If the formation of reaction centers increases non-linearly with signal concentration, the K>1 hill co-ation will follow. Other spatial processes were probably also important, perhaps dominant, but miniature reaction centers were the easiest to spot. In any event, spatial fluctuations in concentration caused a significant increase in the Hill-1, k, for certain parameter combinations. Limited diffusion, measurement accuracy and informationWhy does the mountain's weight variance increase? Roughly speaking, the inactive reactant, R, as a tool to measure the signal input concentration, S. The SR degree of bonding is an informative measurement. The measurement scale under linear spatial uniformity and mass effect. The measurement accuracy is essentially perfect because the SR complexes are connected exactly linearly to the S, regardless of how low the S concentration and any concentration r.Put it in another way, the mass effect means infinite linear measurement accuracy, even at the lowest signal intensity. In contrast, with limited diffusion and spatial fluctuations in concentration, the measurement accuracy varies by the scale of the intensity of the input signal. For example, imagine a low-concentration input signal that is only a few molecules in the local volume. The SR bond converts the R into A, reducing the local measurement capacity as the R molecules provide the measurement. In slow diffusion, each measurement changes the direct capacity of the additional measurement. The increase in information from the measurement is partially offset by a decrease in measurement capacity. In other words, the spatial difference in the concentration of the R meter is the loss of entropy, which is a kind of gain in unrealized potential information. Just as unrealised potential information is based on spatial variation of R, the measurement capability for S and the accumulation of information on S decrease, perhaps reflecting the principle of retention of complete information, or, equivalently, total entropy in a steady state. At low signal concentrations, each measurement reaction significantly alters the spatial distribution of molecules and the measurement capacity. As the signal overall, individual reactions have less impact on spatial differences. In other words, spatial inequalities increase with a decrease in signal intensity, which depends on the scale of measurement, in such a way that it often leads to logarithmic scaling. I'm going back to the logarithmic scaling problem below. Sensitivity and dynamic range shapingThe previous sections considered specific mechanisms that could change the sensitivity of input-output connections in such a way as to lead to log-linear-log scaling of the Hill equation. Such mechanisms include a stochastic defect in signal processing in a cascade or deviating from mass action. In many cases, these mechanisms can be important. However, my main argument stresses that the widespread occurrence of log-linear-log scaling of input-output links must go beyond each mechanism. Instead, the general properties of system architecture, measurement, and information flow are likely to explain the simple regularity of input and output connections. These general features, which operate systemically, tend to smooth out inevitable deviations from regularity, which must occur on a smaller scale. Brief overview and adjustment of the general problemIn addition to the Hill's throbbing, k, reduces sensitivity to low and high input signal intensity (Figure 2). At these intensities, small changes in input cause a small change in output. Weak sensitivity is usually logarithmic, in the sense that the output now changes logarithmically with the input. Low and high input logarithmic sensitivities often cause strong and almost linear sensitivity within an intermediate signal range, and small changes in input intensity bring about rapid change in output. The intermediate interval through which high sensitivity occurs is the dynamic range. The Hill coefficient often gives a good summary of the input-output test and is therefore a useful method for studying sensitivity and dynamic range. The general problem of understanding biological input-output systems can be described by a simple question. What processes shape patterns of sensitivity and dynamic range in biological systems? To analyze sensitivity and dynamic range, we need to consider the architecture by which biological systems convert inputs into output. A combination of multiple transformations Biological systems typically process input signals through a number of transformations before an output signal is produced. Thus, the entire input-output sample is derived from the totality of each transformation. Although the meaning of the output signal depends on the environment, meaningful outputs usually result from multiple transformations of the original input. I analyzed a simple linear cascade at an earlier stage. In this case, the cascade the original input to an output, which in turn forms the input of the next step, and so on. If each transformation in the cascade has a K>1 Hill-1, the cascade cascade the aggregated value of the total input-output pattern of the system. Reinforcement occurs because weak logarithmic sensitivity at low and high inputs usually multiply through the cascade. Multiplying the sensitivity of the logarithm in the outer ranges of the signal increases the hill coefficient, narrows the dynamic range and results in high sensitivity to intermediate inputs. This amplification of hill co-ions cascades leads back to the puzzle already emphasized throughout this article. In the case of simple chemical reactions, kinetics follow the Michaelis-Menten pattern with a k=1 hill-like value. If classic kinetics are typical, aggregated input-output relationships must also have Hill-based attributes. In contrast, most observed input-output samples have a higher hill-like value. Thus, certain aspects of the internal processing steps must move away from the classic Michaelis-Menten kinethy. There is a long history of study regarding the mechanisms by which individual chemical reactions that increased Hill's co-1s. In the first part of this article, I put together three commonly cited mechanisms of chemical kinetics that can increase the Hill's compound for individual reactions: cooperative binding, titration of the repressant, and opposing saturated forward and backward reactions. These types of deterministic mechanisms of chemical kinetics do not raise Hill's co-determinants and are likely to occur in many cases. However, the generality of the raised Hill's co-determinants seems to be too broad to be explained by such specific deterministic mechanisms. Component failureIf the classical deterministic mechanisms of chemical kinetics do not sufficiently explain the generality of the raised Hill co-ities, then what do you explain to the generality? My main argument is that input-output relationships reflect the underlying measurement and information processes. The nature of the measurement and information almost inevitably leads to a log-linear-log of the observed input-output connections. However, this argument is rather abstract. How do we combine the abstractions of measurements and information with the actual chemical processes by which biological systems convert inputs into outputs? I have set out a series of examples for the relationship between abstract concepts and the underlying mechanisms of chemical kinetics. I have already discussed the aggregation, perhaps the strongest and most important general concept. I showed that the aggregation amplifies the small variations in Michaelis-Menten kinetics (k=1) in highly log-linear-log patterns enhanced k.In the next step, it showed that when each component is an aggregate system of Michaelis-Menten kinetics, but also randomly does not transmit signals with a certain probability, the system converge an input-output sample into an elevated Hill co-ed. The main assumption is that the error rate increases as the signal input intensity Of course, the reactions of some reactions of biological systems and some of these errors correlate with the input intensity. Thus, the low and unavoidable negligence of the component performance of the aggregate system changes the nature of input-output measurement and transmission of information. Since the consequence of defects usually reproduces through a cascade, logarithmic sensitivity inevitably occurs at low signal input intensity. Instead of some specific chemical mechanisms for the universality of log-linear-log scaling, this view calls for the universality of aggregate processing and occasional component errors. I'm not saying that component errors are necessarily the primary cause of log-linear-log scaling. Rather, I would point out that such universal aspects must be common and inevitably lead to certain patterns of measurement and information processing. As soon as one starts to view the problem in this way, other aspects begin to fall into place. Deviations in mass action with limited levels of chemical diffusion often occur in biological systems. I've shown that limited diffusion can distort classic Michaelis-Menten kinenics to increase the Hill's co-ing over one. The increased Hill-rate and associated logarithmic sensitivity can be interpreted as reduced measurement accuracy of weak signals at low inputs. Regular pattern from highly unsettled mechanismsThe general conclusion is that many different mechanisms result in the same log-linear-log scaling. In all specific cases, the pattern can be converted into the classic mechanisms of mandatory cooperativity, oppressive titration, or opposing forward and backward reactions. Either the sample can result from general processes of aggregation, component failure, or deviation from bulk action. No specific mechanism is necessarily associated with log-linear-log scaling. Rather, a broader approach to the relationship between pattern and process can help. This broader view emphasises the common aspects of measurement and information for all mechanisms. The common tendency of input-output to follow log-linear-log scaling may come from the fact that so many different processes have the same consequences for measurement, scaling and information. The common patterns of nature are exactly those patterns in accordance with the widest, most different range of special mechanisms. When there is a large underlying disorder, the aggregate, rigid joint result, then this result will be widely observed, as if the result is a deterministic inevitability with some single root cause. The real root cause stems from general aspects of measurement and information, not specific chemical mechanisms. System design The inevitability of log-linear-log scaling from different underlying mechanisms suggests that the overall shape of biological input-output relationships can be strongly limited. In other words, the variation range the approach to log-linear-log scaling is singly. However, within this broad class, biological systems can tune responses in a number of different ways. Tuning by adjusting the number of reactions in a cascade, increasing the failure rate of components, using reactions significantly limited by diffusion speed, and so on. Understanding the development of input-output links should focus on such tunings within a wider range of measurement and information transmission. Proving that a particular mechanism is done in a particular system is always interesting and always limited. The location of the design and function is not the specific mechanism of a particular reaction, but the aggregate properties arise from the many mechanisms that affect the tuning of the system. Robustness The input-output pattern often reflects the narrow order resulting from the underlying anomalies. Thus, disruptions to certain mechanisms of the system can often have relatively minor consequences for the overall functioning of the system. This insensitivity to perturbation – or robustness – naturally stems from the structure of signal processing in biological systems. To study robustness, it may not be enough to look for mechanisms that reduce sensitivity to perturbation. Rather, we need to understand the aggregate nature of the variation and function and how this aggregate nature shapes the inherent tendency to insensitivity to systems [3, 4, 45]. If one understands the intrete qualities of biological systems, then we can ask how these internal properties are tuned with natural selection. Measurement and information Instinctively consider input-output connections in terms of measurement and information. However, you can ask whether measurement and information is truly useful concept or just vague and ultimately useless labeling regarding analyze biological systems. Here, I find that deep and useful concepts are the basis for measurement and information in a way that informs the study of biological design (Table 1). I'll start by developing abstract concepts more clearly. Then I tie these abstractions to the nature of biological input-output relationships. MeasurementMeasurement assigns a value to an underlying attribute or event. Thus, in biology, input-output relationships are considered measurement relationships. At first glance, this measurement emphasis may seem trivial. What do we gain by thinking of every chemical reaction, detection or dose-response curve as a measurement process? The measurement helps explain why certain similarities are constantly created in the test. When we observe common patterns, we have to face a question. Do the common aspects of the sample between different systems result from universal aspects of measurement or from chemical or sensory mechanisms shared by different systems? if we do not think about differentiation between the general characteristics of the measurement and the specific mechanisms certain chemical pathways. If we do not think about this distinction, we can try to explain what the universal property of measurement really is if we look for specific aspects of chemical kinetics, route structure or physical laws that inhibit perception in each system. In the opposite direction, we can never really recognize the role of each mechanism generating observed patterns unless we separate those aspects of the pattern that arise from the universal process. Understanding the universal aspects of the measurement pattern means more than simply analysing the evolution of observations into numbers. Instead, we need to recognise that the structure of each problem sets very strong limits on the numerical design, regardless of individual chemical or biological mechanisms. Log-linear-log scalesI've mentioned that the Hill equation is simply an expression of log-linear-log scaling. The widely recognized value of the Hill equation to describe the biological sample stems from its connection to the underlying universal measurement scale, in which small magnitudes scale linearly with logarithms, intermediate magnitudes, and large values scale logatically. Although linear and logarithmic scales are widely used and very familiar, the actual properties and meaning of such scales are rarely discussed. If we take the nature of the measurement scale directly into account, we can understand more deeply how to understand the relationships between the pattern and the process. Take his example of measuring distance [41]. Start with a ruler about the length of the hand. Use this ruler to measure the size of all objects in your office. The sizing of objects in the office is the same as the ruler length, because these objects have a natural linear scaling compared to the ruler. Now look at the distances from your office to different galaxies. Your ruler is of no use because it is not possible to distinguish whether a particular galaxy is moved further away with a ruler unit. Instead, for two galaxies, you can measure the ratio of distances between your office and each galaxy. For example, one galaxy may be twice as far from another, or usually one galaxy may be a percentage farther away than the other. The percentage changes determine the scale of the measure, which has natural units in logarithmic proportions [5]. For example, doubling the distance always adds log(2) to the logarithm of the distance, regardless of the initial distance. The measurement is naturally from linear to local nuclei to logarithmic, distant magnitúdok, in relation to some local reference scale. The transition between linear and logarithmic varies between problems. The measures of some phenomena remain primarily in the linear range, such as the degree of height and weight of people. Measures relating to other phenomena logarithmic range, such as cosmological distances. Other phenomena are linear linear in logarithmic areas, such as fluctuations in the price of financial assets [46] or the distribution of income and wealth [47]. Consider scaling in the opposite direction, from local magnitude to very small scale. The hand-length ruler has no value for small magnitudes because it cannot distinguish between the fraction of the ruler 10-4 × and the distance of 2×10-4 of the ruler. For small distances, you need a standard unit of measure of the same magnitude as the difference. The 10-4 length rule distinguishes between 10-4 and 2×10-4, but does not distinguish between 10-8 and 2×10-8. In small magnits, ratios can potentially be distinguished, causing a change in the unit of informative measurement with dimensions. Thus, small magnitúdos naturally have logarithmic scaling. As we switch from very small to medium, measurement scaling naturally changes from logarithmic to linear, and then again to logarithmic, log-linear-log scaling. The linearity location and the very small to very large meaning differ between the problems, but the overall pattern of scaling relationships remains the same. This section analyzes this characteristic scaling relative to the Hill equation and biological input-output patterns. First, I will consider more carefully what the measurement scales mean. I then combine abstract aspects of measurement with specific aspects of the Hill equation and examples of certain biological mechanisms. Invariance, the essence of the explanation We started with an observation. Many different input-output connections follow the Hill equation. We then asked: What process causes the Hill equation pattern? It turns out that many very different processes lead to the same log-linear-log pattern in the Hill equation. We need to change our question. What do very different processes have in common to generate the same overall pattern? Consider the two specific processes discussed earlier: cooperative binding and deviation from mass action. These different processes can bring hill equation patterns similar to Hill's combined, k. However, it is not clear why cooperative bonding, derogations from mass action and many other different processes lead to a very similar set of rules. Group all the different mechanisms that create a common Hill equation pattern. When faced with a new mechanism, how can we determine if it belongs to the group? We may be looking for features that are common to everyone in the group. However, this does not work. Different potential members may have important common characteristics. But the attributes that are not shared can cause one potential member to take a different pattern. Common characteristics are not sufficient. More often, joint membership stems from non-important features. Think of the circles. How do you describe whether a shape belongs to the circle class? You have to tell us what's not In the case of circles, no matter how much they are rotated, they always look the same. Circles are not capable of all rotations. Accordingly, the circles are symmetrical for each rotation. Invariance and symmetry are the same. Depending on certain constraints, if a shape is not correct for any rotation, it is a circle. If it is not an invariant for all rotations, it is not a circle. Things that don't matter define the shared, nonvariate property of a group [48-50]. Rotation is a kind of transformation. A group is defined by a set of transformations that make group members unchanged or invariant. The chemical system can be modified from cooperative bonding in the context of mass action to non-cooperative bonding by derogation from mass action, and log-linear-log scaling can be preserved. Such invariance arises because the different processes have underlying symmetry with regard to the transformation of information from inputs to output (Table 1). What aspects of the process don't matter, given causing the same log-linear-log pattern in the Hill equation? How can we recognize the underlying invarianiance that is linked to such different processes in terms of the common pattern? The Hill equation expresses the measurement scale. In order to answer our most important questions, we need to understand the meaning of the measurement scale. The measurement scale itself is an expression of invariance only. A measurement scale expresses what doesn't matter — invariance during transformation, which unites different processes for a common scaling. Invariance and measurement shall be assumed that a process converts the x inputs to G(x) output. The process can be a reading from a measuring instrument or a series of chemical transformations. In view of this process, how should we determine the related measurement scale? Definitions can, of course, be made in any way. But we have to deal with some reasonable meaning. One possible meaning of measurement is the preservation of information. In particular, we are looking for a scale on which we get the same information from the input values as from the output values. The measurement scale is the scale on which the input-output transformation does not alter the information in the signal (Table 1). Of course, information is often lost between input and output. But only certain types of information are lost. The measurement scale accurately describes what information is lost during the inlet conversion to the output and what information is retained. In other words, the measurement scale determines the invariant properties of the information, which remain unchanged through the input-output process. Different input-output processes belong to the same measurement scale if they represent the same deviation, which leaves certain aspects of the information unchanged. In the case of such processes, the information regardless of whether we have access to the original inputs or the final outputs when these values are related measurement scale. In contrast, input-output processes that change the same information ities when input and output values are given on a given measurement scale do not belong to this scale. These abstract properties define a reasonable meaning for the measurement scale. Such abstractism can be difficult to analyse. However, it is essential to express these ideas clearly, otherwise we would never understand why so many different biological processes can have such a similar input-output relationship and why other processes are not the same. It is precisely those abstract informational aspects of measurement that combine cooperative binding and departures of mass action into a common group of processes that share a similar Hill equation pattern. Measurement and informationUseful to express the general concepts in a simple equation. I created that simple summary equation starting with the components of the overall concept. Inputs are given by x. A small change in input is indicated per dx. The input specified on the measurement scale is T(x). The sensitivity of the measurement scale to the input change is that which is the change in the dT(x) measurement scale for the input change dx. This sensitivity describes the measurement scale information for input fluctuations [41, 42, 51]. You can also write an expression for incremental information related to the change in the underlying input , dx. If the scale is logarithmic, T(x)= log(x), then m x d x = d log (x) = d x x , at which the sensitivity of the measurement scale decreases as the input becomes large. On a purely logarithmic scale, the same input increment, dx, gives a lot of information if x is small and contains little information if x is large. Then express the relationship that defines the measurement scale. On the appropriate measurement scale for a given problem, the information from the input values is proportional to the information from the related output values. In other words, the measurement scale is a conversion of values that makes the information invariant, whether the input values or output values are used. The measurement scale reflects the aspects of the information that are preserved in relation to the input-output and consequently expresses the information that is lost in the input-output relationship. Although quite abstract, it is useful to complete mathematical progress before turning to a few examples in the next stage. The output is G(x) and the measurement scale converts the output using T[G(x)]. We provide for the proportionality of incremental information on the change in the input input flow, dT(x) and related output (dT[G(x)] in which the ∝ relationship shows the proportionality of the information on the sensitivity of inputs and outputs expressed on the measurement This measurement scale defines the group of g(x) input-output processes that retain the same invariant sensitivity and information properties on the T(x scale). In other words, any such G(x) input-output process that is not a variant of the T(x) measurement scale transformation belongs to this measurement scale [41, 42, 51]. In this equation, there are x inputs with the information in the said inputs, dT(x), on the T measurement scale, and the G(x) outputs in these outputs are information on the measurement scale T. We can shorten this key measurement and information balance, which the information in the dT inputs is proportional to the dT[G] output information. All G(x) input-output connections that satisfy this relationship have the same invariant information property relative to the T. Linear scale, the exact definition of linearity. Linearity requires that the same information be retrieved from the dx increment on the input scale, regardless of whether the actual value is large or small (location), and whether we evenly stretch or reduce all measurements by a constant amount. To express changes in location and uniform scaling, let which changes the initial value(x) by changing the location, and by applying a uniform stretch or scaling (scaling) b. This transformation is often referred to as linear transformation. But why is that the essence of linearity? Az Eq. (11) x d x = dT (x) = b d x ∝ d x the first part, which means that the increase in measurement provides a constant amount of information, regardless of the measurement value and that the information is uniform, apart from the constant of proportionality b. Linearity means that the information in the measurements is independent of location and uniform scaling. What input-output connections, G(x), fall within the linear measurement scale? Az Eq. (11) from the second part of dT[G(x)]∝d x, which can be extended to dT G(x) = d a + b G (x) = b dG (x) ∝ d x. Thus, any input-output relationship that belongs to the linear scale dG(x)∝dx, and any input-output relationship that does not meet this condition does not belong to the linear scale. To meet this condition, the input-to-output relationship must be in the format G(x)=α+β x, which is itself a linear transformation. Thus, only linear input-output connections are connected to a linear measurement scale. If the input-output relationship is non-linear, the corresponding measurement scale is non-linear. Logarithmic scaleThe same procedure can be run on the logarithmic measurement scale, for which a simple form is T(x)= log(x). On this scale, dT(x)=dx/x. Thus, input-output connections belong to this logarithmic scale if dT G (x) = d log G (x) = dG (x) G (x) ∝ d x x . This condition requires that the G(x)∝xk to which dG(x)∝xk-1d x. The logarithmic measurement scale applies only to input-output functions have this performance-based form (Table 1). Note that the the case of k=1 leads to linear scaling, but for other k values the scale is logarithmic. Linear-log and log-linear scales The most commonly used measurement scales are linear and logarithmic. But these scales are unnatural, because the immorality of the measurement is likely to be great. As I mentioned earlier, an office ruler is ok to take linear measurements of visible objects in the office. But if we scale up to cosmic distances or microscopic distances, we classify, of course, from linear to logarithmic. A good sense of measurement requires attention that information and input-output connections vary in magnitude [41, 42]. Let's say an input increment provides information: If x is small, m x dx≈dx, which is the linear measurement scale. If x is large, m x dx≈dx/x, which is the logarithmic scale. The related measurement scale is the T (x) ∝ log (1 + bx) and the related input-output functions correspond to G(x)∝(1+b x). This scale is continuously linear to logarithmic. Parameter b determines the relationship between magnitude and scale type. From logarithmic to low-magnitude linear, the image of scaling increases with magnitude growth, with T (x) ∝ x + b log (x). If x is small, the scale is logarithmic with T(x)≈b log(x). If x is large, the scale is linear in T(x)≈x. Biological input-output: log-linear-logI emphasized that the log-linear-log scale is probably the most natural of all scales. The information in the measurement steps is logarithmic for small and large magnits. As one moves in both extreme directions, the unit of measure varies in proportion to the magnitude of preserving consistent information. For intermediate nuclei, variable values are associated with an approximate linear measurement scale. For many biological input-to-output connections, this intermediate, linear zone is roughly the dynamic range. The Hill equation description of input-output connections is widely useful because it describes log-linear-log scaling in a simple form. To check the scale of the log, t(x)= log(x) is used in high or low input limits, which means dT(x)∝dx/x. In our basic measurement relationship, dT (x) ∝ dT G (x) = d log G (x) = k 1 x - x k - 1 1 + x k d x , If x is small, dT(x)∝dx/x, expression of input-output functions on the logarithmic scale. If x is large, dT(x)∝-dx/x, which is the expression of saturation on the logarithmic scale. For K>1, the input-to-output relationship scales linearly to intermediate x values. Different calculations can be performed to show the approximate linearity of the midrange. But the point you can see is simply looking at Figure 2.Exact linearity occurs when the second derivative of the Hill equation disappears x ∗= k - 1 k + 1 1/k (12) in figure k>1 shows that the linearity location from the low side to k→1 and x∗ →0 as the high side shifts as k→∞ and x∗ →1. Note that x∗=1 is the input answer is half the maximum response. Figure 10A position of linearity, which is the ∗ x∗ input, where the log-linear-log pattern of the Hill equation becomes exactly linear. The linearity location corresponds to the peak sensitivity of the input-output connection. At X∗=1, the output is half of the maximum response. Plot based on Eq. (12). Sensitivity is the output shape when the input is small. For the log-linear-log sample, the linearity location is often the same as the maximum sensitivity of the output relative to the input. Low and high input logarithmic systems are relatively weakly sensitive to input changes. The Hill equation is sample input, x, and output, G (x), G (x) = x k 1 + x k = 1 1 + e - k log (x) . On the right, the equivalent form is the classic logistic function, expressed in log(x) instead of x. This logarithmic form is the log-logistic function. Also note that the G(x) variable between zero and one as x increases from zero. Thus, G(x) is similar to the cumulative distribution function (cdf) derived from probability theory. These mathematical analogies will be useful for input-output curves as we continue to analyse the meaning of input-output relationships and why some patterns are particularly common. Also note that k=1 is the Michaelis-Menten pattern of chemical kinetics. The relationship between the G(x) input-output curve and chemical kinetics will be important when linking general aspects of sensitivity to the puzzles of chemical kinetics and biochemical input-output patterns. Sensitivity is the change in output relative to the input material. Thus , sensitivity is a derivative of G compared to x , which is G (x) = k x k - 1 (1 + x k) 2 . This expression is similar to the log-log log probability distribution function (pdf). Here I got the pdf as usual differentiating cdf. Noting that the pdf is the sensitivity of the CDF with small changes in value (input), there is an analogy between the sensitivity of input-output connections and the overall relationship between pdf and cdf in probability distribution. The maximum sensitivity is the maximum value of G (x) that corresponds to pdf mode. For k≤1, the maximum value is x=0, which means that the measurement sensitivity of the input-output system is highest when the input is extremely small. It seems instinctively unlikely that maximum sensitivity could be achieved if tiny input values were distinguished. For k>1, the maximum value of the logistic pattern occurs when G l (x)=0 is the point where the second derivative is zero and the input-to-output relationship is purely linear. That's the maximum Eq. (12). Probability analysis provides a connection between input-output functions, measurement, and information. The probability distribution is fully described by the information it has expressed [3, 40]. This information can be divided into two parts. Firstly, some restrictions which limit possible shapes of distribution, such as average, variance, and so on. Secondly, the measurement scale determines the sensitivity of the outputs in relation to changes in observed values or inputs in terms of randomness (entropy) and information (negative entropy) [41, 42]. Sensitivity, measurement and shape of input-output patterns The Hill equation seems almost magical in its ability to match input-output patterns in different biological processes. The magic stems from the fact that the Hill equation is a simple expression of log-linear-log scaling when the Hill co-value is k>1. The Hill-10 is the position of linearity. As k decreases towards one, the sample becomes linear-log, and linearity at low input values is converted to logarithmic as the input increases. As the k drops below one, the pattern becomes logarithmic everywhere, with a decreasing sensitivity as the input increases. The sensitivity and measurement scale are the deeper principles. The Hill equation is properly regarded as just a convenient mathematical form that expresses a particular pattern of sensitivity, measurement, and information properties of the input-output pattern. From this point of view, the question can be asked whether alternative input-output functions provide similar or better methods for expressing the underlying log-linear-log scale. Frank & Smith [41.42] demonstrated the general relationships between measurement scales and the associated probability distribution function (pdf). Because pdf is similar to expressing the sensitivity of input-output functions, we can use their system as a basis for alternatives to the Hill equation. Perhaps the most impressive general terms for log-linear-log scales come from the family of beta distributions. For example, in general beta prime distribution can be written as G (x)∝ x m α 1 + x m k - β . (13) With α=k and β=1, Eq. (3) is given a typical form of the Hill equation. Additional parameters provide α and β more flexibility in expressing different logarithmic sensitivities at high and low input levels. Frank & Smith [41, 42] also has a theory of measurement scale and probability that allows analysis of more complex measurement and sensitivity patterns. For example, a double log scale (logarithm is a logarithm) reduces sensitivity during the scaling of the classic single log. Such dual log scales offer the expression of a more extreme dissipation of signal information at low or high input levels. These sensitivity expressions have two advantages. First, they provide a wider range of empirical connections to use matching data. These empirical relationships derive from the principles of the measurement scale. Secondly, different forms of expression are hypotheses about how signal processing cascades dispel information about signals and alter patterns of sensitivity. For example, we can predict signal-scape architectures are more powerful in dispersing information and logarithmic scaling and loss of sensitivity at certain input levels. Further theory can help sort out the predicted relationships between signal processing architecture, information dissipation, and general forms of input-output connections. Policies Accessibility Press Center Support and Contact Exit Feedback Career Follow BMC BMC Twitter page BMC Facebook page BMC Weibo page page

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