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Explaining an Empirical Formula for Bioreaction to Similar Stimuli (Covid-19 and Beyond)

Olga Kosheleva, Vladik Kreinovich, and Nguyen Hoang Phuong

Abstract A recent comparative analysis of biological reaction to unchanging vs. rapidly changing stimuli – such as Covid-19 or flu viruses – uses an empirical formula describing how the reaction to a similar stimulus depends on the distance between the new and original stimuli. In this paper, we provide a from-first-principles explanation for this empirical formula.

1 Formulation of the Problem

Bioreactions: general reminder. Most living creatures have the ability to learn. When we first encounter some stimulus – e.g., some chemical substance or some bacteria – we do not know whether this stimulus is harmful or beneficial. This encounter – and several similar encounters – show us whether this particular stimulus is harmful, beneficial, or neutral.

We learn from this experience, so next time, when we encounter a similar stimulus, we know how to react: e.g., fight or flee if this stimulus is harmful.

Bioreaction depends on whether stimuli evolve with time. Some stimuli – e.g., smells associated with some chemicals – do not change with time. So, we learn to

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associate the smell with the corresponding stimulus – e.g., the smell of a dangerous predator with danger, and the smell of juicy edible apples of mushrooms with tasty food. Living creatures can become very selective in this association, easily distinguishing the smell of a dangerous wolf from a similar smell of a friendly dog. In such situation, an optimal strategy for a living creature would be to remember the exact stimulus – and only react to exactly this stimulus.

Other stimuli vary in our lifetime. For example, many viruses – e.g., flu and Covid-19 viruses – evolve every year. In this case, if the cells protecting our bodies from these viruses would only react to the exact shape of the viruses they encountered last year, this would leave us unprotected against even a very minor virus mutation. In such cases, it is important to react not only to the exact same stimulus as before, but also to stimuli which are similar to the ones that we previously encountered.

The closer the new stimulus to the original one, the stronger the reaction. When we encounter the exact same dangerous stimulus, we are absolutely sure that this stimulus is dangerous, so we should react with full force. On the other hand, when we encounter a stimulus which is similar to the original stimulus, we are no longer 100% sure: this new stimulus may be harmless and we may be wasting resources if we immediately launch a full-blown attack against it – resources that can be needed in the future, when a serious danger comes.

So, the farther away the new stimulus from the original one, the weaker should be the bioreaction to this stimulus – and, vice versa, the closer the new stimulus to the original dangerous one, the stronger should the bioreaction be.

An empirical formula describing this dependence. In many biological situations, there is a natural way to measure the distance d between two stimuli – e.g., we can measure the distance between the two DNAs by the total length of the parts which are specific to one of them.

Recent papers [3, 4] have shown that the observations are in good accordance with the following dependence of the reaction force f on the distance d :

$$f = F_0 \cdot \exp(-k \cdot d^\theta), \quad (1)$$

for some parameters $F_0 > 0$, $k > 0$, and $\theta > 0$ – and these papers show that the observed biological values of these parameters are close to optimal.

Problem. A natural question is: how to explain this empirical dependence?

What we do in this paper. In this paper, we provide a possible from-first-principles explanation for the empirical dependence (1).

2 General idea behind many from-first-principles explanations

Before we consider this specific problem, let us recall where many from-first-principles explanations come from.

Numerical values vs. actual values. What we want is to find dependence between the *actual* values of the corresponding quantities. However, all we can do is come up with relation between *numerical* values describing these properties.

Numerical values depend not only on the quantity itself, they also depend on the choice of the measurement scale. For example, the numerical values depend on the choice of the measuring unit. If we replace the original measuring unit with the one which is λ times smaller, then all numerical values multiply by λ : $x \mapsto \lambda \cdot x$. In particular, if we use centimeters instead of meters, then 1.7 m becomes 170 cm.

For many physical quantities like time and temperature, the numerical values also depend on the selection of the starting point. If instead of the original starting point, we choose a new starting point which is x_0 units earlier, then all numerical values are changed: $x \mapsto x + x_0$.

There may also be non-linear rescalings. In all these cases, moving to a different scale changes the numerical value, from the original numerical value x to the new value $T_c(x)$, where c is the parameter, and $T_c(x)$ is the corresponding transformation. For example, for changing the measuring unit, $T_c(x) = c \cdot x$, for changing the starting point, $T_c(x) = x + c$. etc.

Invariance: general idea. In many practical situations, there is no meaningful way to select a scale, all scales are equally reasonable. In such situations, it makes sense to require that the relation $y = f(x)$ between the two quantities x and y has the same form in all these scales.

Of course, if we re-scale x , i.e., replace it with $x' = T_c(x)$, then, to preserve the relation between x and y , we also need to re-scale y , i.e., to apply an appropriate transformation $y \mapsto y' = T'_c(y)$. Then, we can require that for every c there exists a c' for which $y = f(x)$ implies that for $x' = T_c(x)$ and $y' = T'_c(y)$, we have $y' = f(x')$.

Invariance: example. For example, the formula $a = s^2$ relating the square's area a with its side s remains valid if we replace meters with centimeters, but then, we need to correspondingly replace square meters with square centimeters. In this case, for $T_c(x) = c \cdot x$, we have $T'_c(y) = c' \cdot y$ with $c' = c^2$.

How invariance explains a dependence: example. Let us consider situations when for every c , there exists a value $c'(c)$ (depending on c) for which $y = f(x)$ implies $y' = f(x')$, where $x' = c \cdot x$ and $y' = c'(c) \cdot y$.

Substituting the expressions for x' and y' into the formula $y' = f(x')$ and taking into account that $y = f(x)$, we conclude that for every x and c , we have $f(c \cdot x) = c'(c) \cdot f(x)$. It is known (see, e.g., [1]) that every continuous (even every measurable) solution to this functional equation has the form

$$y = A \cdot x^b$$

for some A and b .

Thus, this ubiquitous *power law* can be explained by the corresponding invariance.

3 Let us apply this general idea to our problem

For our problem, what are the natural scales? To apply the above general ideas to our problem – of finding the dependence between the interaction force f and the distance d – we need to understand what are the natural scales for measuring these two quantities: distance d and force f .

Case of distance. For distance, the usual distance measures are appropriate. So, a natural change in scale in the change of the measuring unit $d \mapsto c \cdot d$.

Case of force: analysis of the problem. On the other hand, for force, the situation is not that straightforward.

In a purely mechanical environment, we can combine several forces together, so we can easily see what corresponds to 2 or 3 unit forces. So, if we select a unit force f_0 , we can talk about the force $2f_0$ which is equivalent to a joint action of two unit forces, the force $3f_0$ which is equivalent to a joint action of three unit forces, etc. In such an environment, the following will be a natural scale for measuring force: the numerical value of the force f is the number n for which the force f is equivalent to the joint action of n unit forces $f \approx n \cdot f_0$, i.e., in effect, the value $n \approx f/f_0$.

However, for biosystems, no such natural combination of forces is possible. The only thing we can do is compare two forces. Of course, if the forces are almost the same, we will not be able to distinguish them. So, if we select a unit force f_0 , then the next natural value f_1 is the smallest value $f_1 > f_0$ that can be distinguished from f_0 . After that, the next natural value f_2 is the smallest value $f_2 > f_1$ that can be distinguished from f_1 , etc.

Let us describe the above idea in precise terms. To describe these values in precise terms, we need to be able to determine, for each force f , the smallest value $g = F(f) > f$ which can be distinguished from f .

Processes involving forces do not depend on the exact choice of the physical measuring unit for a force. So, if we have $g = F(f)$ in the original units for physical force, then in a new scale, for $f' = c \cdot f$ and $g' = c \cdot g$, we should have $g' = F(f')$.

Substituting the above expressions for f' and g' into this formula and taking into account that $g = F(f)$, we conclude that $F(c \cdot f) = c \cdot F(f)$. In particular, for $f = 1$, we get $F(c) = q \cdot c$, where we denoted $q \stackrel{\text{def}}{=} F(1)$. Thus, we have $f_1 = q \cdot f_0$, $f_2 = q \cdot f_1 = q^2 \cdot f_0$, $f_3 = q \cdot f_2 = q^3 \cdot f_0$, and, in general, $f_n = q^n \cdot f_0$.

So, a natural scale for measuring the bioforce f is the number n for which f corresponds to the n -th element on this scale, i.e., for which $f \approx q^n \cdot f_0$ and

$$n \approx \log_q(f/f_0) = \frac{\ln(f/f_0)}{\ln(q)}. \quad (2)$$

Comment. It should be mentioned that the formula (2) describes what is known in physiology as Weber-Fechner Law – that the intensity of each sensation is proportional to the logarithm of its physical measure (energy or force); see, e.g., [2].

From the above somewhat simplified description to a more realistic one. In the above analysis, we implicitly assumed that for every two forces, we can either distinguish them or not. However, this implicit assumption is a simplification.

When one of the forces is much larger than the other one, then, of course, this is absolutely true. However, as the forces get closer to each other, there appears a probability that we will not be able to distinguish these forces – and the closer these forces to each other, the larger this probability. When the compared forces are very close, this probability becomes so large that, for all practical purposes, we cannot distinguish them.

In view of this fact, to describe the scale, we need to also select a confidence level with which we can distinguish the two forces. If we select this confidence level too high, then we will need a large value q – the ratio of the forces f_1/f_0 . The smaller q , the smaller the confidence level.

We arrive at different natural measurement scales for (bio)force. There is no fixed confidence level, so there is no preferred value q . In other words, we can have different natural scales of type (2) corresponding to different values q .

What is the transformation between two different natural scales for measuring (bio)force? Suppose that in addition to the scale (2) that corresponds to some value q , we also have a different scale

$$n' \approx \frac{\ln(f/f_0)}{\ln(q')} \quad (3)$$

corresponding to a different value q' . How can we transform the value n corresponding to a given physical force f on a q -based scale into a value n' corresponding to the same force f on a different q' -based natural scale?

By comparing the formulas (2) and (3), one can see that the relation between n' and n has a very simple form: $n' = c \cdot n$, where we denoted

$$c \stackrel{\text{def}}{=} \frac{\ln(q)}{\ln(q')}.$$

Which dependencies are invariant with respect to these transformations. We want to find out how force f depends on the distance d . For biosystems, a natural way to describe this dependence is by using natural scale n for bioforce. Thus, we want to describe how the bioforce n depends on the distance.

Both for the distance and for the bioforce, natural transformations have the form $x \mapsto c \cdot x$. Thus, a natural invariance of the dependence $n = N(d)$ means that for every c , there should exist some value $c'(c)$ such that $n = N(d)$ implies that $n' = N(d')$, where we denoted $d' \stackrel{\text{def}}{=} c \cdot d$ and $n' \stackrel{\text{def}}{=} c'(c) \cdot n$. We have already mentioned that this invariance implies that

$$n = A \cdot d^b \quad (4)$$

for some constants A and b .

This explains the desired dependence between f and d . Our ultimate objective is to explain the empirical dependence (1) between the physical force f and the distance d . Let us therefore see how the dependence (4) between n and d will look like in terms of the dependence between f and d .

To find this out, let us plug in the expression (4) for n into the above formula $f = f_0 \cdot q^n$, i.e., equivalently, $f = f_0 \cdot \exp(n \cdot \ln(q))$. This substitution leads to

$$f = f_0 \cdot \exp(A \cdot \ln(q) \cdot d^b).$$

This is exactly the formula (1), for $F_0 = f_0$, $k = -A \cdot \ln(q)$, and $\theta = b$.

Thus, we indeed have a from-first-principles explanation for the above empirical dependence.

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