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

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1. 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.

2. 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 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.
- They easily distinguish 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.

3. Bioreaction depends on whether stimuli evolve with time (cont-d)

- 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.

4. 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.
- We may be wasting resources if we immediately launch a full-blown attack against it.

5. The closer the new stimulus to the original one, the stronger the reaction (cont-d)

- These resources can be needed in the future, when a serious danger comes.
- So, the father away the new stimulus from the original one, the weaker should be the bioreaction to this stimulus.
- Vice versa, the closer to the new stimulus to the original dangerous one, the stronger should the bioreaction be.

6. 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.
- The observations are in good accordance with the following dependence of the reaction force f on the distance d:

$$f = F_0 \cdot \exp\left(-k \cdot d^{\theta}\right).$$

- The recent papers show that the observed biological values of these parameters are close to optimal.

7. Problem

- A natural question is: how to explain this empirical dependence?
- In this talk, we provide a possible from-first-principles explanation for the above empirical dependence.
- Before we consider this specific problem, let us recall where many from-first-principles explanations come from.

8. 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.

9. Numerical values vs. actual values (cont-d)

- 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 news 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.

10. 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 $y \mapsto y' = T'_{c'}(y)$.

11. Invariance: general idea (cont-d)

- 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 $y' = f(x')$.

12. Invariance: example

- The formula $a = s^2$ relating the square's area a with its side s remains valid if we replace meters with centimeters.
- However 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 $c' = c^2$.

13. 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 $y' = c'(c) \cdot y$.
- Now:
  - 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 that every continuous (even every measurable) solution to this functional equation has the form $y = A \cdot x^b$.
- Thus, this ubiquitous *power law* can be explained by the corresponding invariance.

14. For our problem, what are the natural scales?

- Our problem is to find the dependence between the interaction force f and the distance d.
- So, we need to understand what are the natural scales for measuring these two quantities: distance d and force f.
- For distance, the usual distance measures are appropriate.
- So, a natural change in scale in the change of the measuring unit:

$$d \mapsto c \cdot d.$$

15. Case of force: analysis of the problem

- 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.

16. Case of force: analysis of the problem (cont-d)

- 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 $n \approx f/f_0$.

17. Case of force: analysis of the problem (cont-d)

- 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.

18. 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

$$g' = F(f').$$

19. Let us describe the above idea in precise terms (cont-d)

- Now:
  - 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 $f_1 = q \cdot f_0$, $f_2 = q \cdot f_1 = q^2 \cdot f_0$, $f_3 = q \cdot f_2 = q^2 \cdot f_0$, 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

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

20. Let us describe the above idea in precise terms (cont-d)

- It should be mentioned that this formula 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).

21. 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.
- The closer these forces to each other, the larger this probability.
- When the compared forces are very close, this probability becomes very close to 1.
- Then, for all practical purposes, we cannot distinguish them.

22. From the above somewhat simplified description to a more realistic one (cont-d)

- 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.

23. 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 corresponding to different values q.
- What is the transformation between two different natural scales for measuring (bio)force?
- One can see that $n' = c \cdot n$, where we denoted

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

24. 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 $n = A \cdot d^b$ for some constants A and b.

25. This explains the desired dependence between f and d

- Our ultimate objective is to explain the empirical dependence between the physical force f and the distance d.
- Let us therefore see how the above dependence 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 above expression 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 desired formula $f = F_0 \cdot \exp\left(-k \cdot d^\theta\right)$, 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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27. Acknowledgments

- This work was supported in part by the National Science Foundation grants:
  - 1623190 (A Model of Change for Preparing a New Generation for Professional Practice in Computer Science), and
  - HRD-1834620 and HRD-2034030 (CAHSI Includes).
- It was also supported by the AT&T Fellowship in Information Technology.
- It was also supported by the program of the development of the Scientific-Educational Mathematical Center of Volga Federal District No. 075-02-2020-1478.