



Reply to comment

# Fastest among equals: a novel paradigm in biology

## Reply to comments: Redundancy principle and the role of extreme statistics in molecular and cellular biology

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We have appreciated the six insightful and complementary commentaries on our review [19] that have also proposed novel applications and suggested to reinforce the theoretical developments of the redundancy principle we formulated: to be successful for their physiological function, molecular processes require many redundant copies so that the first one to arrive to a small target can occur in time. This time of arrival defines the rate of the physiological process and thus having many copies of the same individual is not a waste of resources, but is probably achieved through evolution to guarantee that the underlying physiological function will happen on time with maximal chances. We discussed several examples such as fast calcium transduction in synapses where the time scale is given by the fastest travelling ions, in neurotransmitter release at synapses that have to open receptors and in fertility where the fastest spermatozoa will reach the ovum and also in gene activation mediated by promoter interaction. As we all recognize, this redundancy theory and concepts are only emerging and the manifestations of extreme statistics in biology is quite a new topic used to estimate reaction rates, to determine the underlying molecular organization and to reveal an intimate interplay between geometry and the number of participating molecules.

The theory that underlies the redundancy principle is extreme statistics that describes the statistics of the fastest or the slowest among many independent stochastic particles. Extreme statistics theory is well-summarized by three generic distributions: Gumbel (exponential tail of the extreme distributions), Fréchet (heavy tail with algebraic decay) and Weibull (light tail) [18]. Although explicit expressions for the distributions, the moments and the mean time of the fastest were known for some stochastic processes in one dimension such as classical Brownian motion [18,12] (see also the commentary by S. Redner and B. Meerson [14]), much less was known in higher dimensions, and in particular about the interplay between the number of particles and the local geometry of the narrow search target [3]. The redundancy principle suggests that it would be more accurate to define time scale by focusing on short- or

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long-tailed distributions inside experimental data rather than estimating mean quantities such as the first or the second moments (mean diffusion).

Considering extreme statistics in dimensions higher than one has revealed [1] that trajectories associated to the fastest are concentrated near optimal paths for a variational formulation that remains to be found. Indeed the formal path-integral representation of the shortest trajectories is certainly insufficient to derive a variational problem that would predict the dynamics of the fastest, as noticed in the commentary of Redner & Meerson [14] and explained in [1]. Neither does the variational problem fall into the large deviation principle as explained in the comment of I. Sokolov [20], because this is not about deviation from a mean behavior but we start directly with the extreme one, located in the tail of the distribution. To conclude, Euler's variational approach, from which the dynamical equations of physical processes are derived, is not applicable for processes following extreme statistics because the law of motion is not physical but results from the complete atypical behavior of the extremes. Therefore, extreme events in cellular biology mediated by stochastic molecular trajectories do not fall into the physical description of the average. We wonder whether a variational formulation is possible and this question should indeed attract the attention of mathematics and theoretical physics communities.

In his commentary, D. Coombs [4] gives first a very didactic scenario about the number of messages calling for help that a person should send in order to be rescued from a desert island and the time it would take for the messages to be received by chance. This toy example explains the context of extreme statistics in a very practical sense. Perhaps, we could argue that, in the case of no additional information, the time to find a hiding terrorist could also fall into extreme statistics where the search time would decay with the logarithm of the number of called police officers. To enlarge the perspective of the review, D. Coombs offers also an example from ecology, highlighting that reaching the first new habitats could have pushed reproduction for more progenitures. Timescales here are in months, years, or could even be much longer. Finally, Coombs brings another fundamental and interesting example about triggering a fast response of the immune system: the first encounter between a T-cell and an antigen in a mammalian lymph node triggers the cell immune response. This example proposes also to develop computations for the first arrival time when the initial number is not fixed but growing with time.

A central part of I. Sokolov's commentary [20] emphasizes that a cell is not a well-stirred chemical compartment and thus descriptions based on the well homogenization of material is not very much relevant in cellular physiology. In particular, the rate of arrival of the first particles to a small target, computed from extreme statistics is more appropriate than the classical Smoluchowski's rate that was considered as the gold standard to define activation rates [7]. In particular, the famous Gillespie's algorithm [6] that samples the rate of activation by the mean forward rate should be revisited. In the light of extreme statistics, this clearly cannot reproduce the extreme statistics of the fastest. These considerations should also have consequences in molecular networks that should be modeled and simulated using extreme statistics, especially for transient regimes. Another question that should be impacted by extreme statistics is the search of a promoter by a transcription factor [22,10,9,16] which can switch between 1D motion on chromatin and 3D diffusion inside the nucleus. The search time here is indeed the search time of the fastest and not of the mean. In contrast to classical stochastic theory, where a deterministic behavior emerges in the average limit of large numbers, in our examples the deterministic behavior ensues due to extreme events, which are despite being rare, but are in fact the ones that activate the biological function.

L.M. Martyushev's comment [11] highlighted the importance of expanding the extreme statistics and redundancy principle into a broader context: the sigmoidal response of biochemical processes suggests that the production occurs at the highest possible rate. It seems that the relationship between the cause and the response of a nonequilibrium system can be derived from maximizing the local entropy production (Maximum Entropy Production Principle). It would be interesting to see if extreme trajectories can be derived from such principles.

D. Rusakov and L.P. Savtchenko focus their commentary [17] on applications of extreme statistics to neuroscience. Indeed the commentary recalls that the use of mass-average concentration kinetics is limited by the few numbers of calcium ions. Interestingly, the presence of calcium buffers can change some of the properties of the fastest-diffusing calcium ions because the fastest have to avoid buffers or otherwise the time lost bound to a buffer is too long compared to the diffusion time. However, the effect of buffers can be compensated by increasing the initial number of calcium ions. Conversely the large amount of calcium buffers might be sufficient to avoid any calcium avalanche triggered by residual calcium. We expect that the time scale of spontaneous activity in neuronal cells and astrocytes might be specifically defined by these residual concentrations of calcium and buffers (work still ongoing).

D. Rusakov and L.P. Savtchenko also makes an interesting comment that for receptor activation during synaptic transmission, extreme statistics may not be very relevant because the mean-field theory is sufficient to obtain the time course and the number of activated receptors. However, the role of extreme statistics in that case is more relevant to explain the numbers: it requires around  $10^3$  neurotransmitters to activate few receptors because the probability that they bind before escaping the synaptic cleft is in the order of  $10^{-4}$  [15]. Neurotransmitter redundancy guarantees that some of the receptors will indeed be activated. Interestingly, diminishing the number of neurotransmitters by 30%, which can be associated to a ketogenic diet [8,5] can lead to a change in the neuronal network activity.

The commentary of M.V. Tamm [21], highlights that if the Gumbell, Weibull and Fréchet distributions are classical, no direct applications in biology were known. More is to learn from the extreme values of correlated stochastic processes [12]. In particular, by selecting shortest random walks of Brownian motions that avoid a semi-circle, the approach of [13] is actually to condition on extreme trajectories and thus fluctuations of the trajectories are non-Gaussian and fall into KPZ universality class. This example highlights that the statistics of correlated stochastic particles could lead to a more atypical behavior that remains to be found.

Finally, we invite to read our review with all the commentaries and also to watch the recordings of the Pisa conference titled “Probabilistic methods in statistical physics for extreme statistics and rare events” associated to these topics (<http://www.crm.sns.it/event/420/>). Extreme statistics and redundancy principle have already led to the discovery of the molecular nanometer organization in dendritic spines [2]. We expect much more findings, especially in the scenarios where there are random searchers for small targets, a step followed by an amplification. We conclude by emphasizing the idea that living cells are not chemical factories because of the role played by geometry, as also summarized here by I. Sokolov: “One cannot grow a chick from a scrambled egg”.

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