Extreme statistics may govern avalanche-type biological reactions

Comment on "Redundancy principle and the role of extreme statistics in molecular and cellular biology" by Z. Schuss, K. Basnayakey, D. Holcman.

Dmitri A. Rusakov, Leonid P. Savtchenko

Queen Square UCL Institute of Neurology, University College London, Queen Square, London WC1N 3BG, United Kingdom

In many biological systems, a chemical or physiological reaction can be triggered in full by a singular event when a motile agent, be it a diffusing molecule or a swimming cell, reaches and interacts with its target. When multiple copies of the agent are released to move freely by some physiological act, this low-threshold, avalanche-type reaction will be induced by the agent entity which happens to find the fastest route to the target. Thus, the expected reaction-diffusion onset time will be determined by the statistics of the sole first-past-the-post winner rather than by the average population behavior which gives rise to the traditional case of linear reaction kinetics. A quantitative probabilistic evaluation of the first-passage times belongs to the area of extreme-value statistics, which has historically been developed to study extreme events in weather or in materials [1].

In their informative and timely review [2], Schuss et al explore a theory of extreme-value statistics with a view on biological reactions involving stochastic molecular movement or transformations. The review follows several pioneering studies carried out by the group, which have advanced the field in its applications to theoretical neuroscience and molecular biology [3-6]. The authors discuss and examine several common biological scenarios in which a non-linear target reaction is triggered by the first reagent molecule reaching the target. They also present closed-form expressions that can be employed to estimate the extreme-event timing as a function of various parameters in the diffusion-reaction system under study.

The review thus focuses on avalanche-type mechanisms with the activation threshold represented by a single (or perhaps very few) reagent molecule. Whilst this is a relatively common case in live systems, there are numerous reaction types in biology that rely on linear interactions with large numbers of reagent molecules and therefore follow the classical mass-average (concentration) kinetics. For instance, the waveform

of synaptic currents in neurons is generated by dozens of receptor ion channels responding to thousands of released neurotransmitter molecules, and thus could be well described by the mean-field approximation statistics of Brownian diffusion or electrodiffusion [7-9]. It could be important, therefore, for an investigator to understand what criteria or conditions would classify the reaction under study as the avalanche-type to which the extreme-value statistics are applicable. For instance, activation of the most common synaptic receptors in the brain requires two bound neurotransmitter molecules rather than one [10-12], and the number of calcium ions required to activate ubiquitous ryanodine receptors remains subject of debate [13, 14]. The corresponding reaction-diffusion statistics will therefore involve the first two (or more) fastest arrivals. To what degree such relatively common scenarios fall into the extreme-value statistics category is an important and intriguing question.

Somewhat related to this subject is the knowledge of the activation rate displayed by the target avalanche-type reaction itself. When this rate is significantly slower than the disparity between the first-passage and the mass-average time for the diffusing reagents, the reaction outcome could be insensitive to such a disparity. In this respect, the important derivation shown by the authors for the mean first-passage-time of a Brownian particle (Equation 8 in [2]) could be further explored to evaluate variability of this mean quantity.

Another interesting issue is the concomitant effects arising from the medium environment. For instance, calcium ion diffusion inside brain cells often encounters a high concentration of calcium-buffering proteins, i.e., numerous binding sites interacting with diffusing molecules. These interactions, where present, have a strong effect on calcium diffusion kinetics hence rapid physiological responses in the host cells [15-17]. It could be therefore of great interest to understand how this binding and related phenomena impact on the first-passage time estimates.

Throughout their explorations, Schloss and colleagues [2] come to an important, even though intuitively evident, conclusion that the first-passage time is positively correlated with the number of reagent molecules designated for the reaction in question. Based on this universal observation, the authors put forward a heuristic hypothesis that the disproportionately large numbers of reagents in natural processes serve the purpose of generating the fastest possible response. This important and intriguing conclusion might benefit from additional clarification. In some cases, producing (or recycling) large amounts of biological material could be too costly for a biological system to gain a small advantage in speed, and in many instances nature uses physically limited delivery channels to speed up mass or signal transfer. Ensuring a reliable, as well as rapid, response could also be thought of as a natural purpose of having massive amounts of reagents. Whilst these theoretical questions are a matter for a motivating discussion, there is little doubt that the review by Schloss and colleagues [2] provides an important and highly informative guide to the kinetics of all-or-none, avalanche-type reactions in

biology, equipping researchers with novel and potentially influential concepts pertinent to the extreme-value statistical estimators.

References

[1] Clusel M, Bertin E. Global fluctuations in physical systems: A subtle interplay between sum and extreme value statistics. International Journal of Modern Physics B 2008;22:3311-68.

[2] Schuss Z, Basnayake K, Holcman D. Redundancy principle and the role of extreme statistics in molecular and cellular biology. Physics of Life Reviews 2019 ***** [this issue].

[3] Basnayake K, Hubl A, Schuss Z, Holcman D. Extreme Narrow Escape: Shortest paths for the first particles among n to reach a target window. Physics Letters A 2018;382:3449-54.

[4] Holcman D, Parutto P, Chambers JE, Fantham M, Young LJ, Marciniak SJ, et al. Single particle trajectories reveal active endoplasmic reticulum luminal flow. Nature Cell Biology 2018;20:1118-25.

[5] Guerrier C, Holcman D. The First 100 nm Inside the Pre-synaptic Terminal Where Calcium Diffusion Triggers Vesicular Release. Frontiers in Synaptic Neurosciece 2018;10:23.

[6] Amitai A, Holcman D. Encounter times of chromatin loci influenced by polymer decondensation. Physical Review E 2018;97(1-3).

[7] Savtchenko LP, Sylantyev S, Rusakov DA. Central synapses release a resource-efficient amount of glutamate. Nature Neuroscience 2013;16:10-2.

[8] Sylantyev S, Savtchenko LP, Ermolyuk Y, Michaluk P, Rusakov DA. Spike-Driven Glutamate Electrodiffusion Triggers Synaptic Potentiation via a Homer-Dependent mGluR-NMDAR Link. Neuron 2013;77:528-41.

[9] Zheng K, Rusakov DA. Efficient integration of synaptic events by NMDA receptors in three-dimensional neuropil. Biophysical Journal 2015;108:2457-64.

[10] Jonas P, Major G, Sakmann B. Quantal components of unitary EPSCs at the mossy fibre synapse on CA3 pyramidal cells of rat hippocampus. Journal of Physiology 1993;472:615-63.

[11] Lester RAJ, Tong G, Jahr CE. Interactions between the glycine and glutamate binding sites of the NMDA receptor. Journal Neuroscience 1993;13:1088-96.

[12] Wadiche JI, Jahr CE. Multivesicular release at climbing fiber-Purkinje cell synapses. Neuron 2001;32:301-13.

[13] Zahradnik I, Gyorke S, Zahradnikova A. Calcium activation of ryanodine receptor channels - Reconciling RyR Gating models with tetrameric channel structure. Journal of General Physiology 2005;126:515-27.

[14] Meissner G. The structural basis of ryanodine receptor ion channel function. Journal of General Physiology 2017;149:1065-89.
[15] Sala F, Hernandez-Cruz A. Calcium diffusion modeling in a spherical neuron. Relevance of buffering properties. Biophysical Journal 1990;57:313-24.
[16] Rusakov DA. Ca^{2+}-dependent mechanisms of presynaptic control at central synapses. Neuroscientist 2006;12:317-26.
[17] Savtchenko LP, Bard L, Jensen TP, Reynolds JP, Kraev I, Medvedev N, et al. Disentangling astroglial physiology with a realistic cell model in silico. Nature Communications 2018;9:3554.