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Comment

First among equals
Comment on “Redundancy principle and the role of extreme statistics in molecular and cellular biology” by Z. Schuss, K. Basnayake and D. Holcman

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Imagine a stranded applied mathematician on a desert island, whose only supplies are a ream of paper, a pencil and a crate of empty bottles.[1] Her only means of escape is to toss a message into the ocean and hope that the motion of the bottle among the waves – let’s say the motion is random and uncorrelated – will carry it back to civilisation. How long must she wait? The traditional mathematical approach to this problem has been to model the motion of the message-carrying bottle as a simple Brownian motion, and then solve the *mean first passage time* problem for random motion from a starting point (the point of release on the desert island) to a capture region (civilisation). This approach has been the subject of expository reviews [1,2]. However, our hero is not particularly interested in the mean time for a message to reach home. She will write multiple copies of her message and send them in independent bottles, and she will be rescued when the *first* message arrives home. Obviously, sending multiple messages is not expected to be slower than sending a single message. In fact, if she were to send enough messages, each diffusing randomly and independently around the ocean, then she could expect that one of the bottles would travel close to an optimal (geodesic) path back to her home! The mathematical problem in question is thus to estimate the *fastest arrival time* of her messages. This is an example of an *extreme statistics problem*, and has been much less studied in the mathematical literature.

In this fascinating review paper, Schuss, Basnayake and Holcman [3] describe several important situations in cell biology where the fastest arrival time is a much more important and relevant statistic than the mean arrival time. Consider, for example, the random generation of antibodies by genetic recombination within a B cell undergoing somatic hypermutation [4]. In this process, several copies of a gene segment are made, but only the first of such segments to reach and bind to a particular macromolecular complex will ultimately be used as a template for generating antibodies. There is effectively a race, and while only the winner of the race will take the spoils, the process can be expected to work more quickly and efficiently if there are multiple competitors. A similar situation occurs during fertilization of an ovum by sperm [5]. Due to the large number of sperm in the race, we can expect the time to

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[1] If the bottles were full, the urgency of the situation would be much reduced.

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fertilization to be much lower than the mean time for a single sperm to reach the ovum, and the winning sperm will usually have taken a rather direct route.

The arrival time of the first randomly moving particle, among N such particles, to arrive at a given target region is, in general, a tricky mathematical question. In their review, Schuss et al. show the analytical expression for a one-dimensional problem (corresponding to diffusion down a channel) based on an explicit eigenfunction expansion, and validate their solution by comparison with simulations. Unfortunately, the eigenfunction expansion solution is not very suitable for building intuition around the effects of N on the first arrival time. However, by applying asympotics valid in the limit of large N, the formula

$$\bar{t}^1 \simeq \frac{a^2}{16D \ln\left(\frac{2N}{\sqrt{\pi}}\right)}$$

is achieved for the mean first arrival time, where a is the length of the channel and D is the diffusion coefficient of the particles. This formula shows how the fundamental timescale a^2/D is modulated as more and more messenger particles are released. Reassuringly, the time decays only as $1/\ln N$, so the winning time of the race among particles effectively cannot be too short. In two- and three-dimensional scenarios, asymptotic expansions are almost always required to find the mean first arrival time. These problems also highlight the question of how the winning particle should behave during the race: it must travel close to the shortest possible path. Schuss et al. show how this intuitive result can be derived heuristically from properties of Brownian paths.

Much work remains to be done to bring the concept of the first arrival time, and extreme statistics in general, to its proper place in the theory of biological processes. At larger length- and time-scales than those countenanced in this review paper, biological species are observed to invade new habitats. We can easily imagine that the first few animals or plant seeds that reach a new and favourable habitat might reproduce rapidly, and thus the first arrival time is much more relevant than a mean first passage time for randomly moving species, as has often been calculated [6–8]. If rapidly finding new habitats is an important part of the life-cycle of a species, then we can also predict that individuals of that species might make costly investments into large numbers of mobile offspring. In this regard, the results described in this review paper precisely determine the limits of returns on such investments. As another example, we have previously used first passage time statistics to describe the search of a T cell for cognate antigen within a mammalian lymph node [9]. However, the concept of first arrival time is also highly relevant to this problem, because the T cell immune response will begin at the first encounter. Extending the first arrival time calculations to such new situations will provide great insights into the regulation of biological processes by transport effects at the organelle, cell, tissue and ecosystem scales.

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