Spotlight

Suprathreshold Stochastic Resonance behind Cancer

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To be or not to be is perhaps the most important decision a cancer cell has to make in response to a therapeutic drug. Understanding the decision process is key to the development of effective therapies because the intrinsic variability observed in cancer cell populations wickedly leads to fractional killing (i.e., some cells die, but others do not). In a recent issue of the Proceedings of the National Academy of Sciences, Suderman and colleagues presented a theoretical study of different signaling networks based on single-cell data. Using information transmission as a metric of response accuracy, they revealed that the noise present in signaling networks controlling apoptosis (mediated by the cytokine TRAIL) enhances the amount of information embodied in the cell population, but at the expense of reduced information at the single-cell level. However, by considering each cell in the population as a singular threshold system (nonlinear behavior), this result is a direct consequence of suprathreshold stochastic resonance (SSR) (Figure 1), a phenomenon already described almost two decades ago. Conventional stochastic resonance (SR) arises in a single threshold device in which the signal is too weak to be detected (subthreshold). Noise then enhances performance (transmitted information) by promoting the signal above the detection threshold. Similarly, SSR describes a noise-induced enhancement of the transmitted information but, unlike conventional SR, is not restricted to subthreshold signals: it is an aggregate effect and hence can only be observed in collectives of threshold devices. SSR is a well-known phenomenon in the fields of physics, engineering, and neuroscience, but it is also applicable to cellular biology. In quantitative models that encapsulate the SSR effect, such as those used to describe apoptosis, information transmission decays with noise in a single element (cell), but it presents a maximum upon the aggregated response of two or more elements (cells). Moreover, the logarithmic scaling of maximal information with population size is universal in such systems, and exact analytics have already been derived. Indeed, the estimated maximal information transmission of 4 bits in the case of TRAIL-mediated cell death agrees with previous calculations. Such early work has been extended to enable understanding, for instance, of why neurons within a common tissue present functional variability, which leads to uncorrelated firings but increased information transmission. Broadly, these ideas apply to any population of cells with a significant nonlinear dose–response curve; by increasing noise to some extent, this curve becomes more linear and the population captures more information. In cancer cell populations treated with TRAIL, the resulting subpopulation is greatly resistant to a second treatment immediately applied. This suggests that some thresholds, those behind inflammation, are much larger than the noisy death signal. In this scenario, only a few cells will enter apoptosis as a result of SR, and the resistant phenotype will be reinforced. The use of additional drugs may help to enhance the death signal to avoid this. However, cell proliferation in absence of TRAIL leads to recovery, in a few days, of the initial variability and susceptibility. Thus, time should also be taken into account in the design of effective therapies (i.e., shift the fraction killed with less toxicity for the organism) taking the SSR effect into consideration (Figure 1). All in all, the work of Suderman et al. is important and notable in recognizing the effect of noise and population, but setting it in the established framework of SSR builds a bridge between cellular biology and other areas of science and technology, and ultimately facilitates the permeation of ideas across multiple fields.

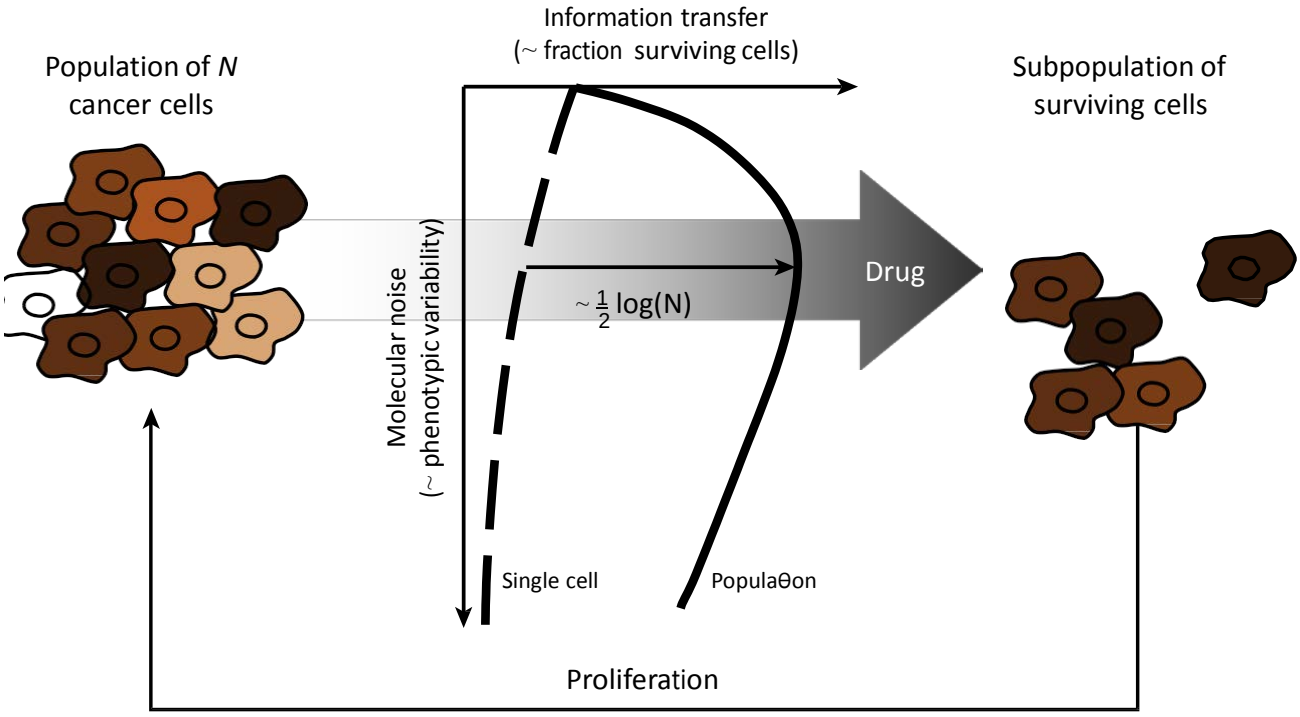

Figure 1: Schematics of Suprathreshold Stochastic Resonance behind a Cancer Cell Population Treated with a Given Drug. The extent of phenotypic variability within the population determines the fraction of surviving cells. Such variability is rapidly recovered upon proliferation.