Optimal checkpoint strategies

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Why biological quality-control systems fail has often remained mysterious. Checkpoints in yeast and animals are overridden after prolonged arrests allowing self-replication to proceed despite the continued presence of errors. Although critical for biological systems, checkpoint override is not understood quantitatively or at the system level by experiment or theory, even though the genes and circuits involved in many checkpoints have been researched extensively.

To uncover potential patterns obeyed by error correction systems, we derived the mathematically optimal checkpoint strategy, balancing the trade-off between risk and opportunities for growth. The theory predicts the optimal override time without free parameters based on two inputs, the statistics i) of error correction and ii) of survival.

We applied the theory experimentally to the DNA damage checkpoint in budding yeast, an intensively researched model for other eukaryotes, whose override is nevertheless not understood quantitatively, functionally, or at the system level. Using a novel fluorescent construct which allowed cells with DNA breaks to be isolated by flow cytometry, we quantified i) the probability distribution of repair for a double-strand DNA break (DSB), including for the critically important, rare events deep in the tail of the distribution, as well as ii) the survival probability after override. Based on these two measurements, the optimal checkpoint theory predicted remarkably accurately the DNA damage checkpoint override times as a function of DSB numbers, which we also measured for the first time precisely. Thus, a first-principles calculation uncovered hitherto hidden patterns underlying the highly noisy checkpoint override process. Our multi-DSB results revise well-known bulk culture measurements and show that override is a more general phenomenon than previously thought. Further, we show that override is an advantageous strategy in cells with wild-type DNA repair genes.

The universal nature of the balance between risk and self-replication opportunity is in principle relevant to many other systems, including other checkpoints, developmental decisions, or reprogramming of cancer cells, suggesting potential further applications.