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Defects and DNA replication: a role for stochasticity[1]

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When a cell replicates its DNA, each base must be copied once and only once per cell cycle. A failure to complete replication normally can lead to cell death, or worse. In this talk, I will discuss how ideas from statistical physics can help understand how replication is organized and controlled. In particular, we describe a formalism based on rate equations similar to those used to describe the kinetics of crystal growth and show how it can describe the normal course of DNA replication. In practice, replication must also deal with numerous kinds of problems. For example, the machinery of replication may stall or strands may be broken. We show how to extend our formalism to include the effects of such damage and conclude that there are two regimes: a normal regime, where the influence of defects is local, and an initiation-limited regime, where the influence of defects is long range. In the latter regime, defects have a global impact on replication. We show that normal, healthy cells have defect densities in the normal regime but cells with "problems" have defect densities that approach the crossover value. The overall conclusion is that passive stochastic control and physical effects such as diffusion are more relevant for DNA replication than had been believed until recently.

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