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Roles of Entropic Funnels and Irreversibility in RecA Mediated Homology Recognition

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The self-assembly complex systems requiring the correct pairing of more than approximately 3 distinct binding sites faces significant entropic barriers and can suffer from kinetic trapping in conformations containing some correct pairings. If the pairings have energies of the order of the thermal energy kT, then thermodynamic pairing cannot provide the stringencies required for biological systems. It is well known that kinetic proofreading systems can provide much better stringency by including an irreversible step; however, simple versions of such systems fundamentally tradeoff speed and stringency. RecA mediated homology recognition is an example of a system that can provide excellent rapid recognition that can last for days without irreversibility. The combination of speed and stability in the absence of irreversibility depends on the probability that accidental matches extend over of m contiguous binding sites. If the probability decreases sufficiently strongly with m, rapid and efficient homology recognition can occur via a system of checkpoints that limit the number of binding sites that can come in contact, which provides enthalpic and entropic advantages. Increasing the number of contacts requires passing sequence dependent energy barriers. The simplest version of such a system is an initial weakly bound state that is independent of site matching, which is separated from the next conformation by a sequence dependent barrier. The sequence dependent barrier for correct matches must be low enough for the correct match to progress to the next conformation before unbinding from the initial state, whereas the barrier for mismatches must be high enough that it is highly probable that the mismatch will unbind before they pass through the barrier. RecA employs a series of several sequence dependent barriers. The energy gap that reduces the need for irreversibility is the result of the correct pairing having orders of magnitude more contiguous matching sites than the nearest mismatch present in the sample.