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Fitness in the RNA World

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Life probably progressed through a primitive form based on RNA, in which RNA acted as both a genetic material and a catalyst for biochemistry. Understanding the evolution of RNA is therefore central to understanding the origin of life. Evolution can be thought of as a random walk through the space of all possible sequences. The function of fitness in sequence space is known as the 'fitness landscape.' If the fitness landscape were known, evolution could be accurately modeled as diffusion on the landscape with a tendency to drift upward due to natural selection. The fitness landscape is difficult to interrogate due to the vast size of sequence space. However, with high-throughput sequencing, we are able to map fitness landscapes for short but functional sequences of RNA, thus gaining a comprehensive 'birds-eye view' of the fitness landscape and discovering viable evolutionary pathways. One implication of our findings so far is that the ability of natural selection to optimize function across sequence space would be frustrated by the topology of the landscape, which consists of isolated islands of functional sequences. We are also studying the probability distribution of fitness and catalytic activity by analyzing the *in vitro* evolution of longer RNA sequences. This analysis reveals a log-normal distribution of rate constants, suggesting a mechanism for the emergence of function as the multiplicative result of many independent contributions. I will discuss implications of this research on understanding the probability of emergence of functional RNA and the role of chance and the repeatability of evolution in the RNA World.