RNA Folding Prediction Revisited: 30 Years and Counting

A 1986 AMS article on "RNA folding prediction" outlined several major questions in this area of molecular biology, and advocated "the continued need for interaction between biologists and mathematicians" to meet these challenges. Yet, despite significant advances over the past 30 years, the prediction problem remains largely unsolved. The question is deceptively simple; given an RNA sequence, predict the set of (canonical, nested) base pairs found in the native structure. Yet, a fundamental challenge was, and still is, the "ill-conditioning" of discrete optimization methods. We revisit some of the questions this raises, and present recent advances based on combinatorial models, methods, and analyses. In particular, we address denoising the structural signal when considering multiple (sub)optimal structures, incorporating auxiliary experimental data into the thermodynamic optimization, and characterizing alternative models of RNA folding.