Determination of RNA Folding Pathway Functional Intermediates using a Massively Parallel Genetic Algorithm

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ABSTRACT

RNA folding pathways are proving to be quite important in the determination of RNA function. Studies indicate that RNA may enter intermediate conformational states that are key to its functionality. These states may have a significant impact on gene expression. It is known that the biologically functional states of RNA molecules may not correspond to their minimum energy state. Specifically, kinetic barriers may exist that trap the molecule in a local minimum. In addition, folding often occurs during transcription, and cases exist in which a molecule will undergo transitions between one or more functional conformations before reaching its native state. Thus, methods for simulating the folding pathway of an RNA molecule and locating significant intermediate states are important for the prediction of RNA structure and its associated function.

A generalizable methodology that utilizes a massively parallel Genetic Algorithm (GA) [2-5,7-9], that operates on populations of thousands of RNA structures, has proven successful for determining RNA functional intermediates. Some of the features incorporated in the GA are the ability to simulate the impact on folding pathways of chain elongation, 3' terminal processing obtained from multiphase computations, and protein stabilization effects. To analyze the data generated by algorithms such as the GA, an RNA structure analysis workbench, STRUCTURELAB [6] was used. Specifically, Stem Trace [1], an interactive tool for the analysis and visualization of a database of RNA structure solutions, has proven very useful for extracting and interpreting the large amount of information generated by the GA. Computational results produced by the application of these methodologies are consistent with those derived from biological experiments and have illuminated some novel phylogenetically conserved interactions.

Keywords

RNA structure, folding pathways, massively parallel genetic algorithm, RNA structure prediction, RNA structure analysis

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