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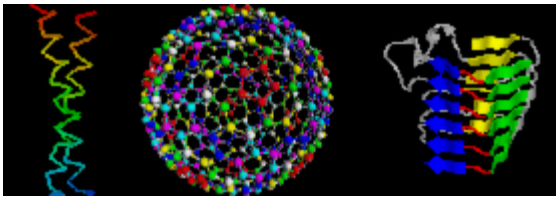

Bioinformatics Seminar

Speaker: Dr. Ye Ding, Wadsworth Center
Title: Statistical Sampling Approach to RNA Folding Prediction and Rational Design of siRNAs
Date: Monday, 15 September 2003
Time & Location
Refreshments: 11 am in the Applied Mathematics Common Room at MIT's Building 2, Room 349
Talk: 11:30 am to 1 pm in the Applied Mathematics Conference Room Building 2, Room 338
URL: http://www-math.mit.edu/compbiosem/

Abstract:

An RNA molecule, particularly a long-chain mRNA, may have a population of structures. Furthermore, multiple structures have been demonstrated to play important functional roles. Thus a representation of the ensemble of probable structures is of interest. We present a novel statistical algorithm to sample rigorously and exactly from the Boltzmann ensemble of secondary structures. We show that this algorithm overcomes inherent limitations in well-established algorithms. The algorithm enables unique tools for efficient representation of the Boltzmann ensemble through structure classification, for predicting alternative biological structures, for predicting accessible sites for RNA-targeting nucleic acids, and for predicting RNA: RNA interactions. Although the number of possible structures in the ensemble grows exponentially with the length of the RNA sequence, we show that a sample of 1,000 structures is sufficient to guarantee statistical reproducibility in the calculation of sampling statistics.

RNAi mediated by short interfering RNAs (siRNAs) has become the method of choice for sequence-specific gene knock-down in mammalian cells. Initial empirical rules have been established by the Tuschl lab for the design of siRNAs. However, large variation in the potency of siRNAs is commonly observed, and often only a small proportion of the tested siRNAs are effective. Increasingly, emerging experimental evidence suggests that secondary structure and accessibility of target RNA are important factors in determining the potency of siRNAs. With both computational analysis and experimental validation of structure-based design for antisense oligos and hammerhead ribozymes, we show that the algorithm is well suited to the prediction of target accessibility. A method is outlined for improving siRNA design, through combination of empirical rules with prediction of target accessibility. The rationale of this novel design methodology is supported by preliminary experimental validation data.

We demonstrate a new RNA software package, Sfold, developed for folding and rational design of nucleic acids. Sfold is available through Web servers at http://sfold.wadsworth.org and http://www.bioinfo.rpi.edu/applications/sfold.

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