Structure of Ribonucleic Acids

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A. Research Results

During the final year of the grant, the following things were accomplished:

We completed our model for the mitochondrial ribosome from *Bos taurus*, based on the cryo-electron density map provided by our collaborator, Dr. Rajendra Agrawal. This was a collaborative effort with people in Dr. Agrawal's laboratory, and with Dr. Robin Gutell, whose efforts were critical to the establishment of the RNA secondary structure. The model reveals evolutionary changes in RNA structure required to keep critical functional regions at the same relative positions in three-dimensional space even though the mitochondrial ribosomal RNA is much smaller than its cytoplasmic counterpart. It also reveals evidence of the co-evolution of ribosomal RNA and transfer RNA. The work has been published (Mears *et al*., 2006).

In collaboration with David Case's group, we developed a coarse-grained model for the ribosome that greatly accelerates dynamic simulations, while successfully reproducing critical motions. The results of that work were also published (Qui *et al*., 2006).

We have just completed the developoment of the first all-atom models for the *E. coli* ribosome in two functional states, immediately before and after accommodation. This work was done in collaboration with Dr. Joachim Frank's group, who provided the cryo-electron microscopy density maps for the two states and was based on the recently published crystal structure of the *E. coli* ribosome. Our models include both the A- and P-site tRNAs and the mRNA. Accommodation is the motion of tRNA into the peptidyl transferase center and is the step when the second reading of the codon-anticodon interaction (proofreading) takes place. It is consequently critical to the fidelity of translation. Prior to these models, the structural basis of proofreading has not been known, but our models have allowed us to develop a hypothesis explaining that. The hypothesis can be tested both experimentally and by computer simulation, and we have begun the critical simulations. The final draft of the manuscript is in the hands of Dr. Frank, and we hope to submit it shortly (Devkota *et al*., in preparation).

For several years we have participated in the RNA Ontology Consortium, a group that has been working (1) to integrate sequence and structural databases; (2) to facilitate communication between different computational tools; (3) to create powerful software tools bringing advanced computational methods to the bench scientist; and (4) to facilitate precise searches for all relevant information pertaining to RNA. The Consortium published a report on our work to date, along with an invitation to all members of the RNA community to join in our efforts (Leontis *et al*., 2006).

B. Publications:

J.A. Mears, M.R. Sharma, R.R. Gutell, A.S. McCook, P.E. Richardson, T.R. Caulfield, R.K. Agrawal and S.C. Harvey, "Structural Evolution in Mitochondrial Ribosomes," *J. Mol. Biol. 358,* 193-212 (2006).

Q. Cui, R.K.Z. Tan, S.C. Harvey and D.A. Case, "Low-resolution Molecular Dynamics Simulations of the 30S Ribosomal Subunit," *Multiscale Modeling Simul. 5,* 1248-1263 (2006).

N. Leontis, R. Altman, H.M. Berman, S.E. Brenner, J. Brown, D. Engelke, S.C. Harvey, S.R. Holbrook, F. Jossinet, S.E. Lewis, F. Major, D.H. Mathews, J. Richardson, J.R. Williamson and E. Westhof, "The RNA Ontology Consortium: An Open Invitation to the RNA Community," *RNA 12*, 533-541 (2006).

B. Devkota, T.R. Caulfield, R.K.Z. Tan, W. Li, J. Sengupta, J. Frank and S.C. Harvey, "The Structure of the *E. coli* Ribosome Immediately Before and After Accommodation," (in preparation).

C. Project-Generated Resources: None

D. Inventions and Patents: None