Using Functional Languages to Study the Relationships Between Nucleic Acid Primary, Secondary and Tertiary Structure Elements

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Functional programming languages (FPLs) allow a direct implementation of mathematical definitions. Problems such as the prediction of macromolecular structures that can be naturally expressed by mathematical notations should benefit from the use of an FPL. Also in an FPL, first-class objects are functions; therefore, the abstraction order of manipulated objects is higher so that they are easier to interact with. One of these languages, MIRANDA,[1] enforces good utilization of data types and now is available in an efficient implementation, making it a very powerful programming tool.

We present our experience using MIRANDA to implement a system dealing with primary sequences, secondary and tertiary structural elements in a coherent fashion. As an example, we take the tRNA primary sequence, generate its secondary structural elements (the four stems: D, Anticodon, T and amino acceptor) and finally find its tertiary structure, which is simply the correct organization of the secondary elements in 3D space.[2] This 3D organization can be found among all plausible organizations by designing an efficient filtering process. Such processes are part of MIRANDA and are controlled by simple functions. Filter design, therefore, can be controlled easily by an expert and eventually done automatically.

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NOEMOL: Integrated Molecular Graphics and the Simulation of Nuclear Overhauser Effects in NMR Spectroscopy

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Nuclear Overhauser Effects (NOEs) are a widely used method of determining the spatial proximity of spins in Nuclear Magnetic Resonance (NMR) spectroscopy. NOEMOL is a C program developed for the SUN-3 workstation family that allows the computation of multispin NOE effects for a given molecular structure and given NMR parameters (i.e., resonance frequency and correlation time for molecular reorientation). The program combines simple molecular graphics display routines with a complete multispin relaxation matrix approach to the calculation of NOE effects, consideration of multispin effects being a prerequisite for studying macromolecules. The effects of bond rotation modifications to the molecular conformation on the NOE effects can be rapidly calculated and displayed. Using the Sun windowing system, the NOE effects can be calculated for two (or more) candidate structures, and these can be compared to experimental NMR results.

Molecular coordinate files in Brookhaven PDB format are used as raw input for the program and are converted to files containing coordinate and connectivity data by a utility program before being loaded into NOEMOL. The present version of NOEMOL accepts only protons as NMR active spins and automatically distinguishes methyl and nonmethyl protons since these have different relaxation properties. The effects of rapid internal rotations of methyl groups are handled using a formalism proposed by Tropp. NOEMOL interfaces with external data processing packages by simply using ASCII data files as an output medium. We are currently using the SAS/GRAPH package to produce plots of NOE time courses and contour plots of NOE parameters, such as spin-spin distance and cross relation rates. Examples of the application of NOEMOL to problems of determining oligosaccharide conformation(s) in solution are presented.

A Conformational and Electrostatic Potential Study of Amiloride Analogs

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Amiloride, a potent potassium-sparing diuretic, has been shown to block sodium transport in epithelial membranes.[1] In addition, amiloride is known to interact with renal alpha- and beta-adrenergic receptors.[2] A conformational study using the 3-21G* basis set has been done in order to identify the low-energy conformers and tautomers of amiloride and three closely related analogs. The analogs chosen exhibited various degrees of potency with respect to sodium-channel blocking.[3] In addition, electrostatic potential patterns using the 3-21G* basis

set are reported for the neutral and protonated forms of amiloride and these analogs. Analysis of the electrostatic potential contour maps yields information on (1) the reactive sites of these analogs, especially the possible sites of protonation in the neutral systems, and (2) the possible complementary binding sites in the sodium channel. The results of this analysis are compatible with the blocking model proposed by Cuthbert.[4] In addition, the possible reactive sites on the amiloride analogs are compared to a recently suggested putative binding site on the beta-adrenoreceptor.[5]

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