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Developments in the Theory of Protein Folding Simulations

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I would argue that, on the whole, a wrong approach is being taken to computer-aided protein engineering. The reasons for this controversial view are as follows. For many years we have been developing algorithms for treating the problem of predicting the structure and behavior of molecules. To do this we have sought, borrowed and adapted ideas from several areas of science, especially mathematics. More recently some new developments in mathematics have caused us to think in a rather different way about our algorithms, or, rather, these new developments have permitted us to overcome certain difficulties that we felt were there.

In brief, these new developments are about the behavior of simulation algorithms in general and about how to describe their behavior, possibilities, and limitations in the language of topology. In fact, a great deal of this is already inherent in control theory, but a number of recent extensions of this kind of mathematical area provide a more powerful general approach.

Except for the neglect of quantum mechanical phenomena, molecular dynamics provides us with the most complete description of the conformation and behavior of a system in terms of the phase space. The conformation and behavior of the protein, which is to say the essence of its being, is represented by a trajectory in this phase space, which is a space in three dimensions consisting of three coordinates (x, y, z) and the three momenta conjugate to them (p_x, p_y, p_z) for every atom. Fundamental principles established from early this century and beyond establish the view that the main ways to envisage problems in the phase space are ways of topology (i.e., of the weaving of threads and sheets in multidimensional space). Modern developments in so-called nonlinear science, chaos theory and the like simply turn out to be in large part the sciences of solving iterative equations and interpreting their effects in terms

of topology in multidimensional space. They also explicitly reveal the first glimmerings of the nature of the simulation algorithm, how to use external information from expertise and databases to direct the simulation toward a solution, and what we mean by a "solution" anyway. In short, molecular dynamics provides a route to a unification of the seemingly disparate concepts that the computer-aided protein engineer must employ.

Major advances in our programs for calculating the structures and properties of molecules have been made possible by these developments, and examples of these studies will be presented in the lecture in order to underline the fact that these theoretical advances can quickly find tangible, practical application in biomolecular computation.

An Area-Based Algorithm for Cast Shadows on Space-Filling Molecular Models

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The area-based algorithm for space-filling molecular models has been used to produce full color pictures with realistic shadows. Previous work could only "dim" atoms proportionally to the amount they were obstructed from the light source. This approximation gave soft, penumbra-like shadows, instead of the accurate, "hard-edged" "cast-shadows" that we are now able to achieve without ray tracing. The cost of the visibility calculations is independent of the raster, and the cost of the shadow calculations grows linearly with the resolution.

Space-filling molecular models are built from intersecting spheres with radii equal to the Van der Waals radii of the atoms they represent. The equilibrium distance between two nonbonded atoms under van der Waals force is represented as spheres that just touch. Shadows provide extra visual depth cues for understanding the three-dimensional structure of the molecule when it is rendered in a raster image.

One method to achieve such realism is to repeat the visibility calculations from the point of view of the light source. The visible regions are then transformed back to the final view, where they become the illuminated regions, while the rest remain in shadow. The new algorithm computes the visible portions of the atoms at floating-point precision from both the viewer reference and from the light source view. The information from these two calculations is then merged into a color image of the space-filling molecular model with cast-shadows, self-shadows and highlights.

The output of the program is kept in a flexible format that allows it to be rendered on anything from an 8-bit frame buffer to a 24-bit film recorder. This allows one to view the output on an inexpensive raster device before putting it out to film. In addition, the resolution can