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The AASERT research dealt with (i) the molecular structure prediction via global optimization mtehods, (ii) the sensitivity analysis, and (iii) molecular dynamic simulations. Rigrous global optimization methods were proposed and applied to oligopeptides, and solvated peptides. Molecular dynamics simulations and tools were introduced at the active site of myoglobin under photolytic decarboxylation.

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FINAL TECHNICAL REPORT

AASERT ACTIVITIES : 07/15/94 - 08/31/97

Project Title : AASERT-Global Optimization and Sensitivity Analysis in Molecular Structure Determination

Award: AASERT-F49620-94-1-0389

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Objectives

The AASERT research by two partially supported graduate students is concerned with the dual problems of identifying the global optimal structure and molecular aggregates, as well as determining the critical variables defining the optimum structure.

Final Report on Accomplishments

Substantial progress has been achieved in both the global optimization and sensitivity analysis of molecular structures. This is briefly summarized in the following:

1. A deterministic global optimization approach has been introduced for dipeptides and for oligopeptides [1.2]. This approach combines the atomistic modeling force filed ECEPP/3 with the global optimization method αBB. The minimization of the total potential energy is based on the dihedral angles, and consists of a novel branch and bound scheme in which convex valid underestimators are derived. The proposed approach is shown to converge to the global optimum with theoretical guarantee.

2. A branch and bound global optimization method, αBB for general constrained NLPs is proposed, [3]. The nonlinear terms are classified as (i) bilniear, fractional, signomial for which special underestimators are derived, and (ii) general nonconvex terms for which novel convex underestimators that employ a novel DC transformation are derived. The proposed approach is shown to converge to the global optimum in a finite number of steps, and extensive computational experience with a variety of applications demonstrate its potential.

3. A novel theoretical approach was proposed for the generation of valid convex underestimators for general twice-differentiable problems, [4]. This approach is based on the generating interval hessian matrices. Rigorous lower bounds are obtained on the minimum eigenvalue of these matrices, and a variety of methods were proposed for obtaining rigorous eigenvalue bounds. Application of these bounding techniques to highly nonconvex problems that arise in molecular modelling indicated that the obtained bounds are reasonably tight to achieve convergence to the global solution within reasonable computational effort.

4. A global optimization method is described for identifying the global minimum energy conformation, as well as lower and upper bounds on the global minimum conformer of solvated peptides [5]. Potential energy contributions are calculated using the ECEPP/3 force field model. In considering the effects of hydration, two implicit free energy models are compared. One method is based on the calculation of solvent–accessible surface

areas, while the other uses information on the solvent–accessible volume of hydration shells. Detailed information on the potential and solvation energy contributions is presented for the terminally blocked single residue peptides. In addition, based on a procedure that allows the exclusion of domains of the (ϕ, ψ) space, a number of oligopeptide structure prediction problems are considered, and the role of the solvation model in defining global minimum conformations is addressed.

5. A computatinally efficient algorithm to calculate the energy flux in a large multi-bodied system is developed [6], along with a visualization program SHOWFLOW. This program is interfaced with the existing Molecular Dynamics packages and results are presented for the energy flow in myoglobin upon photolytic decarboxylation.

6. A molecular dynamics study in the active site of myoglobin is presented [7]. The fluxes were calculated from the energy density derivatives, while the photolytic decarboxylation was simulated by placing the carbon monoxide group on an excited-state potential energy surface till the molecule had reached a certain distance from the hemeiron. An ensemble of twenty seven runs were averaged to distinguish concerted energy flows from random fluctuations.

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7. O.C. Braun, F. Bergasa-Caceres, T.A. Ronneberg and H. Rabitz, "A Molecular Dynamics Study of the Energy Flow in the Active Site of Myoglobin Upon Photolytic Decarboxylation", Submitted for publication (1997).