FINAL TECHNICAL REPORT

02/02/94 - 01/31/98

Project Title: New Tools for Molecular Structure Determination:
Global Optimization and Identification of Critical Variables.

Award: F49620-94-1-0138

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Objectives

This research was 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 was made in both the global optimization and sensitivity analysis of molecular structures. This is briefly summarized in the following:

1. A deterministic global optimization approach was introduced for dipeptides and for oligopeptides [1,2]. This approach combined the atomistic modeling force field ECEPP/3 with the global optimization method αBB. The minimization of the total potential energy was based on the dihedral angles and consisted of a novel branch and bound scheme in which convex valid underestimators were derived. The proposed approach was shown to converge to the global optimum with theoretical guarantee.

2. A branch and bound global optimization method, αBB for general constraint NLPs was proposed [3]. The nonlinear terms were classified as (1) bilinear, fractional, signomial for which special underestimators were derived, and (ii) general nonconvex terms for which novel convex underestimators that employ a novel DC transformation were derived. The proposed approach was shown to converge to the global optimum in a finite number of steps, and extensive computational experience with a variety of applications demonstrated its potential.

3. A novel theoretical approach was proposed for the generation of valid convex underestimators for general twice-differentiable problems [4]. This approach was based on the generating interval Hessian matrices. Rigorous lower bounds were

proposed for obtaining rigorous eigenvalue bounds. Application of these bounding techniques to highly nonconvex problems that arise in molecular modeling indicated that the obtained bounds are reasonably tight to achieve convergence to the global solution within reasonable computational effort.

4. A global optimization method was 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 were calculated using the ECEPP/3 force field model. In considering the effects of hydration, two implicit free energy models were compared. One method was based on the calculation of solvent-accessible surface areas, while the other used information on the solvent-accessible volume of hydration shells. Detailed information on the potential and solvation energy contributions was presented for the terminally blocked single residue peptides. In addition, based on a procedure that allows the exclusion of domains of the (ϕ,φ) space, a number of oligopeptide structure prediction problems were considered, and the role of the solvation model in defining global minimum conformations was addressed.

5. A computationally efficient algorithm to calculate the energy flux in a large multibodied system was developed [6], along with a visualization program SHOWFLOW. This program was interfaced with the existing molecular dynamics packages, and results were presented for the energy flow in myoglobin upon photolytic decarboxylation.

6. A molecular dynamics study in the active site of myoglobin was 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 until the molecule had reached a certain distance from the hemeiron. An ensemble of 27 runs were average to distinguish concerted energy flows from random fluctuations.

Publications

1. C.D. Maranas, I.P. Androulakis, and C.A. Floudas, "A Deterministic Global Optimization Approach for the Protein Folding Problem," DIMACS Series in Discrete Mathematics and Theoretical Computer Science, pp. 133-150 (1995).

2. I.P. Androulakis, C.D. Maranas, and C.A. Floudas, "Prediction of Oligopeptide Conformations via Deterministic Global Optimization," *Journal of Global Optimization*, 11, pp. 1-34 (1997).

3. I.P. Androulakis, C.D. Maranas, and C.A. Floudas, "aBB: A Global Optimization Method for General Constrained Nonconvex Problems," *Journal of Global Optimization*, 7, pp. 337-363 (1995).

4. C.S. Adjiman and C.A. Floudas, "Rigorous Convex Underestimators for General Twice-Differentiable Problems," *Journal of Global Optimization*, 9, 23-40 (1996).

5. J.L. Klepeis, I.A. Androulakis, M.G. Ierapetritou, and C.A. Floudas, "Predicting Solvated Peptide Conformations via Global Minimization of Energetic Atom-to-Atom Interactions," *Computers + Chemical Engineering*, 22, 765-788 (1998).

6. O.C. Braun, F. Bergasa-Caceres, T.A. Ronneberg, and H. Rabitz, "SHOWFLOW: A Graphical Tool to Depict the Flow of Energy in Molecular Dynamics," submitted for publication, 2000.

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, 2000.

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REPORT DOCUMENTATION PAGE

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for review needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any othe burden to Washington Headquarters Services, Directorate for Information Operatio^s and Repo^s, 1215 Jefferson Davis Highwe. Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 05/01/00	3. REPORT TYPE AND DATES COVERED Final Technical Report 2/1/94-1/31/98

4. TITLE AND SUBTITLE New Tools for Molecular Structure Determination: Global Optimization and Identification of Critical Variables.	5. FUNDING NUMBERS F49620-94-1-0138
6. AUTHOR(S) C..A. Floudas and H. Rabitz	

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Department of Chemical Engineering and Department of Chemistry Princeton University Princeton, NJ 08544	8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) Air Force Office of Scientific Research AFOSR/NL 801 North Randolph Street, Room 732 Arlington, VA 22203-1977	10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT APPROVED FOR PUBLIC RELEASE: DISTRIBUTION UNLIMITED	12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

This research dealt with (i) the molecular structure prediction via global optimization methods, (ii) the sensitivity analysis, and (iii) molecular dynamic simulations. Rigorous 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.

14. SUBJECT TERMS Global Optimization, Sensitivity Analysis; Molecular Structure; Molecular Dynamics			15. NUMBER OF PAGES 3
			16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102