DOI: 10.1002/prot.25659

WILEY PROTEINS

IN MEMORIAM

Jan Hermans (1933-2018): Red-blooded Biophysicists study Hemoglobin*

Jan Hermans received his PhD in Physical Chemistry from the University of Leiden in 1958 and then had a 2-year postdoctoral fellowship at Cornell with Harold Scheraga. Next, he worked for 2 years at American Viscose Corporation. In 1964, after a year in Genoa with Gianni Rialdi he joined the Department of Biochemistry and Nutrition at the University of North Carolina at Chapel Hill, where he immediately attracted the first of 17 graduate students and 24 postdoctoral trainees he would mentor.

Jan's enduring interest was in studies of protein structure and dynamics. While still a graduate student at Leiden, John Kendrew or Max Perutz came to Leiden for a seminar on protein crystallography work. But Jan missed the talk as his advisor told him that the work was uninteresting. He later often remarked that he regretted not having had the opportunity to study crystallography, and his future work made fundamental contributions to the interpretations of electron density maps and macromolecular simulations.

Jan's choice of research projects reflected something he repeatedly told associates: you must make something useful. His research contributions confirm that he was truly motivated by this belief: his researches can be grouped into tool development and the use of theoretical and computational approaches to help understand the physics of biochemical processes.

His articles are imaginatively resourceful, yet constrained by a high regard for experimental data. An early example is an article coauthored with Harold Scheraga and Nobel laureate Melvin Calvin,[1] observing that, whereas thermal melting temperatures themselves are not directly related to thermodynamic parameters, melting temperature differences induced by shifts in pH, deuteration, and more recently by mutagenesis, are proportional via the overall enthalpy change to changes in the free energy of folding.

Denaturation

His early independent work focused on experimental studies of the thermodynamic parameters of α-helix formation and protein folding via studies of denaturation. His articles from that era were notable for incorporating statistical thermodynamics into his interpretations[2] and for detailed consideration of the important question of two-state behavior.[3] An especially prescient article,[4] given recent interest in natively disordered proteins, reported data from denaturation of lysozyme and myoglobin consistent with the notion that incompletely denatured proteins maintain approximately the same secondary structures observed in the folded protein.

Coagulation

The University of North Carolina has for a long time had an exceptional research epicenter for the study of bleeding disorders and thrombosis. For a number of years Hermans played an important role in that unique focus, which led him to study the physical chemistry of polymer-protein interactions. That work included a statistical-mechanical treatment of

*"Redblooded Biophysicists Study Hemoglobin" Epigram from Chapter 11, "Allostery" *Kinetics and Equilibria of Biological Macromolecules*, Jan Hermans and Barry Lentz

how polymer exclusion limits protein solubility.[5] At the time of its publication, Jan viewed this article as his finest achievement.

Protein crystallography and refinement

Recognizing the central importance of experimental data on protein structures, Jan joined the American Crystallographic Association in the late 1960s. With considerable foresight, he published a solution to the computational problem of retaining the underlying modularity of macromolecules for purposes of modifying their atomic coordinates.[6] That algorithm revolutionized macromolecular crystallography because it became central to the development, first in the UNC Department of Computer Science GRIP system and subsequently Alwyn Jones's widely-used Frodo and O programs implementing user-interfaced computer graphic representations to automate construction and refinement of protein models. He co-authored the first publication to successfully interpret an electron density map entirely via computer graphics.[7]

Molecular dynamics

His interests in crystallography led him to recruit the first crystallographers to UNC, and to take up the problem of crystallographic refinement in a sabbatical with Lyle Jenson at the University of Washington, Seattle, where he began a long-standing collaboration with Keith Watenpaugh, leading to the development of a multipurpose refinement and molecular dynamics program called SIGMA. He re-directed his entire research team to solving problems associated with molecular dynamics, and organized the first workshop on this topic in the United States at UNC in 1984.[8] He served as associate editor and later on the Editorial Board of *Proteins: Structure, Function and Genetics*. His influence made that journal a top-tier venue for articles on molecular dynamics.

Single point charge water model

Key to the efficient use of computing power to model protein behavior was the challenging problem of how to represent water. Hermans solved this problem in a seminal article with Herman Berendsen, Wilfred van Gunsteren, and Johan Postma.[9] This work was announced in Jan's most highly cited article,[10] which has been cited more than 5500 times. As with the computer representation of protein as a tree,[6] this computer modeling algorithm remains essential today.

Free energies from simulations

Jan was one of the first to grasp the opportunity that simulations presented for enumerating all states, and hence for estimating free energy changes for various processes. He returned repeatedly to the problem of ensuring that simulations accurately represent equilibria, in order to maximize what simulations tell us about thermodynamics. He showed that MD simulations could produce realistic free energies for simple systems like the alanine dipeptide.[11] He also was first to tackle the difficult problem of using simulations to estimate binding free energies.[12] An essential and recurring requirement for larger scale simulations of folded proteins was to treat solvent water as realistically as possible. This required artful blending of discrete and continuum models for solvent water,[13–15] which he rapidly validated by establishing that decoys from CASP competition had higher free energies than the corresponding crystal structures.[16]

Estimating forces from natural backbone and side chain variances

One of the more useful of his later efforts came from his preoccupation with how different sources of variance impact simulations.[17] That enquiry later gave rise to several publications in which he used results from simulations to characterize the natural variation in protein backbone[18] and side chain configurations from the structural database.[19,20] These semi-empirical studies provided a unique estimate of the forces that can result from intramolecular packing interactions, and defined, apparently for the first time, the extent to which distortions observed in crystal structures could result from such effects.[21]

Hermans and Lentz

Jan famously maintained that you can never hope to really understand thermodynamics, you can just know it. Nevertheless, he explained its implications with clarity, helping others to steer between the rocks and shoals of physical biochemistry without scraping their bottoms too badly. Gary Pielak put it this way: "Jan was one of the most brilliant people I ever met. He would tell me something, and I would not understand. Three days later it would come to me, because it involved about 10 steps. He saw all ten, in order, at once." His logical train was indeed very much like that of a computer program, making even simple programs he wrote quite difficult to follow because they approximated machine language.

Nowhere was this more clarity more evident than in the textbook written for the central course in the UNC Biophysics Program.[22] Co-author Barry Lentz recalls that "Sharing the writing of that book was special. Imagine such an extensive collaboration between a stubborn Dutchman and a fiery and equally stubborn Irishman." Indeed, publication of Hermans and Lentz was a prolonged process, in part because it charts such a remarkable path through those rocks and shoals.

Living large

Jan's life was finely balanced. He had an outsized enthusiasm for family, fellowship, music, adventure, and the scientific method. His role as father showed brightly when he took a detour to Dallas en route to his sabbatical in Seattle to outfit his daughter, Janneke, with a prom dress from Neiman Marcus. "I remember that trip to Neiman Marcus like it was yesterday," Janneke remembers. "Friso and I were wearing look-alike jeans and jean jackets and hair cuts, and had been on the road for many days, most of which, it felt like, had been in Texas. At Neiman Marcus, Jan bought me a very stylish dress that I can picture clearly, and then we had a luncheon on the top floor, topped off with a desert of swan-shaped meringues floating in a red strawberry sauce. Real fancy and ladylike, until we had to hit the road again." He leaves a wife, Cynthia, two of his own children, three adopted children, and seven grandchildren. Jan's life-long love of sailing took many of his

scientific friends on his two ocean-going sloops, the Scimitar and the Dogstar as far off the east coast as Bermuda, as far north as New England and as far south as the Caribbean. In addition, there were sailboat charters in the Salish Sea, the Virgin Islands, and the Aegean Sea with colleagues and friends. His unerring judgment deferred local maneuvering near moorings squarely in the hands of his wife, Cynthia. After a day of sailing and safe anchoring, Dutch chocolate, cheeses, and rum drinks were frequently enjoyed in a "happy hour." In the evenings he and Cynthia infected many of their friends with the dice-game 5000, whose outcome fascinated Jan because it is an endlessly enchanting blend of chance and skill.

Hooft; Lucretius

Jan was also a well-versed linguist with a more than passing knowledge of Latin and Greek, Dutch, German, Italian and French. Prompted by a luncheon discussion, he joined a group led by a classics professor at UNC who were translating page by page *De rerum natura*, the splendid 6000-line poem of Lucretius. After his retirement as Professor of Biochemistry in 2011, Jan undertook a major effort to translate *Nederlandsche Historiën*, by P.C. Hooft (1581-1647) from old Dutch into English. The original is a contemporary, 1100-page history of the Dutch revolution in the period 1555 to 1587, half of which first appeared 1642, and the other half posthumously in 1654.

Jan died at home December 20, 2018 after a long battle with pancreatic cancer. He expressed a desire that gifts be directed to organizations like Compassion and Choices and The Death with Dignity Center.

Charlie Carter[1]
Richard Wolfenden[1]
Michael Caplow[2]
Barry Lentz[2]
Gary Pielak[3]
Keith Watenpaugh[4]
Hao Hu[5]
David Puett[6]

[1]*Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*
[2]*Emeritus, Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*
[3]*Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*
[4]*Emeritus, Pharmacia-Upjohn Pharmaceutical, Kalamazoo, Michigan*
[5]*SAS Institute Inc. 100 SAS Campus Drive Cary, North Carolina*
[6]*Emeritus Regents Professor of Biochemistry and Molecular Biology, University of Georgia, Athens, Georgia*

REFERENCES

1. Calvin M, Hermans J, Scheraga HA. Effect of deuterium on the strength of hydrogen bonds. *J Am Chem Soc*. 1959;81:5048-5050.
2. Hermans J, Lohr D, Ferro D. Unfolding and hydrogen exchange of proteins: the three-dimensional ising lattice as a model. *Nature*. 1969;224:175-177.
3. Jan Hermans J, Acampora G. Reversible denaturation of sperm whale myoglobin. II. Thermodynamic analysis. *J Am Chem Soc*. 1967;89:1547-1552
4. Hermans J Jr, Puett D, Acampora G. On the conformation of denatured proteins. *Biochemistry*. 1969;8:22-30.
5. Hermans J. Excluded-volume theory of polymer–protein interactions based on polymer chain statistics. *J Chem Phys*. 1982;77:2193-2203.
6. Hermans J, Ferro D. Representation of a protein molecule as a tree and application to modular computer programs which calculate and modify atomic coordinates. *Biopolymers*. 1971;10:1121-1185.
7. Tsernoglou D, Petsko GA, McQueen JE Jr, Hermans J Jr. Molecular graphics: Application to the structure determination of a snake venom neurotoxin. *Science*. 1977;197:1378-1380.
8. Hermans J, ed. *Molecular dynamics and protein structure: proceedings of a workshop held 13–May 18, 1984 at the*. University of North Carolina; Fort Belvoir, VA: Defense Technical Information Center. 1984.
9. Hermans J, Berendsen HJC, van Gunsteren WF, Postma JPM. A consistent empirical potential for water-protein interactions. *Biopolymers*. 1984;23:1513-1518.
10. Berendsen, H. J. C., Postma, J. P. M., van Gunsteren, W. F., and Hermans, J. (1981) Interaction models for water in relation to protein hydration. In: *Jerusalem Symposia on Quantum Chemistry and Biochemistry*. Riedel
11. Anderson AG, Hermans J. Microfolding: conformational probability map for the alanine dipeptide in water from molecular dynamics simulations. *PROTEINS: Struct Funct Gen*. 1988;3:262-265.
12. Hermans J, Wang L. Inclusion of loss of translational and rotational freedom in theoretical estimates of free energies of binding. Application to a complex of benzene and mutant T4 lysozyme. *J Am Chem Soc*. 1997;119:2707-2714.
13. Vorobjev YN, Scheraga HA. A fast adaptive multigrid boundary element method for macromolecular electrostatics in a solvent. *J Comput Chem*. 1997;18:569-583.
14. Vorobjev YN, Grant JA, Scheraga HA. A combined iterative and boundary element approach for solution of the nonlinear Poisson-Boltzmann equation. *J Am Chem Soc*. 1992;114:3189-3196.
15. Vorobjev YN, Hermans J. ES/IS, Estimation of conformational free energy by combining dynamics simulations with explicit solvent with an implicit solvent continuum model. *Biophys Chem*. 1999;78:195-205.
16. Vorobjev YN, Almagro JC, Hermans J. Discrimination between native and intentionally misfolded conformations of proteins: ES/IS, a new method for calculating conformational free energy that uses both dynamics simulations with an explicit solvent and an implicit solvent continuum model. *PROTEINS: Struct Funct Gen*. 1998;32:399-413.
17. Hermans J. Simple analysis of noise and hysteresis in (Slow-Growth) free energy simulations. *J Phys Chem*. 1991;95:9029-9032.
18. O'Connell TM, Wang L, Tropsha A, Hermans J. The "Random-Coil" state of proteins: comparison of database statistics and molecular simulations. *PROTEINS: Struct Funct Gen*. 1999;36:407-418.
19. Butterfoss GL, Richardson JS, Hermans J. Protein imperfections: separating intrinsic from extrinsic variation of torsion angles. *Acta Cryst*. 2005;D61:88-98.
20. Butterfoss GL, Hermans J. Boltzmann-type distribution of side-chain conformation in proteins. *Prot Sci*. 2003;12:2719-2731.
21. Kapustina M, Hermans J, Carter CW Jr. Potential of mean force estimation of the relative magnitude of the effect of errors in molecular mechanics approximations. *J Mol Biol*. 2006;362:1177-1180.
22. Hermans J, Lentz B. *Equilibria and Kinetics of Biochemical Macromolecules*. Hoboken, NJ: John Wiley & Sons; 2014.