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Essay

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The Roots of Bio-Molecular Simulation: The Eight-Week CECAM Workshop 'Models for Protein Dynamics' of 1976

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This essay is dedicated to Herman Berendsen *at the occasion of his 85th birthday, 22 September 2019*

This year, the Centre Européen de Calcul Atomique et Moléculaire (CECAM) celebrates its 50-th anniversary. Founded in 1969 in Orsay near Paris, it later moved to Lyon and in 2008 to Lausanne. It is an organization devoted to the promotion of fundamental research on advanced computational methods and their application in condensed matter science. Its main vehicle to this end is the organization of workshops. The key role of an eight-week workshop held forty-three years ago, characterized by an open exchange of scientific ideas and a foresight regarding the topics relevant to a proper dynamic simulation of bio-molecules such as proteins, is remembered, together with the issues discussed at the time. These are still relevant today.

Keywords: molecular dynamics, proteins, water, sharing, cooperation.

Introduction

Fifty-one years ago, *Shneior Lifson* and *Arieh Warshel* published their first paper[1] on the development of a classical force field that would represent the inter-atomic interactions determining the structure and behavior of bio-molecules. During the same years, *Anees Rahman* explored ways to solve *Newton*'s equations of motion to simulate the dynamics of atoms and molecules in the condensed phase on a computer, first for liquid argon[2] and then for liquid water.[3] This led *Herman Berendsen* of the University of Groningen, The Netherlands, to organize in 1976 an eight-week workshop[4] 'Models for Protein Dynamics' with about 20 participants, to be held at CECAM, the Centre Européen de Calcul Atomique et Moléculaire, based in Orsay near Paris, directed and driven by the late *Carl Moser*. Based on his experience with the measurement of NMR spectra of proteins, *Herman Berendsen* had the vision that the dynamics of bio-molecules such as proteins could be and had to be simulated using computers. In order to materialize this vision, he organized in October 1975 a two-day CECAM discussion meeting in Bilthoven, The Netherlands, where he presented his ideas (*Figure 1*) for the eight-week CECAM workshop in Orsay in the spring of 1976.

CECAM: Purpose and Means

In the 1984 and 1985 annual reports of CECAM, Carl *Moser*, its inspiring director, wrote: '*CECAM's purpose in the scientific world is to concentrate on problem areas in which only numerical solutions exist and for which larger and larger scale computing power becomes necessary for progress.*' and '*A main scientific purpose of CECAM has always been to encourage a cooperative goal towards scientific development.*'.[5] CECAM's activities have been of the following types: 1) individual visits and scientific cooperation resulting from these visits, 2) specialized discussion meetings, 3) preparatory meetings for workshops, and 4) workshops. Over the years, the emphasis on various kinds of activities and the nature of these activities has changed. In the early seventies the usual duration of a workshop was at least one, often two months. This allowed the participants to extensively interact, to work together on computational algorithms and software, and to use the outstanding computer power available in Orsay. In later years the willingness to spend such long periods at CECAM has waned due to the relative decline of the computer facilities at CECAM during the eighties. This changed the character of the workshops: instead of doing a lot of innovative work during a workshop,

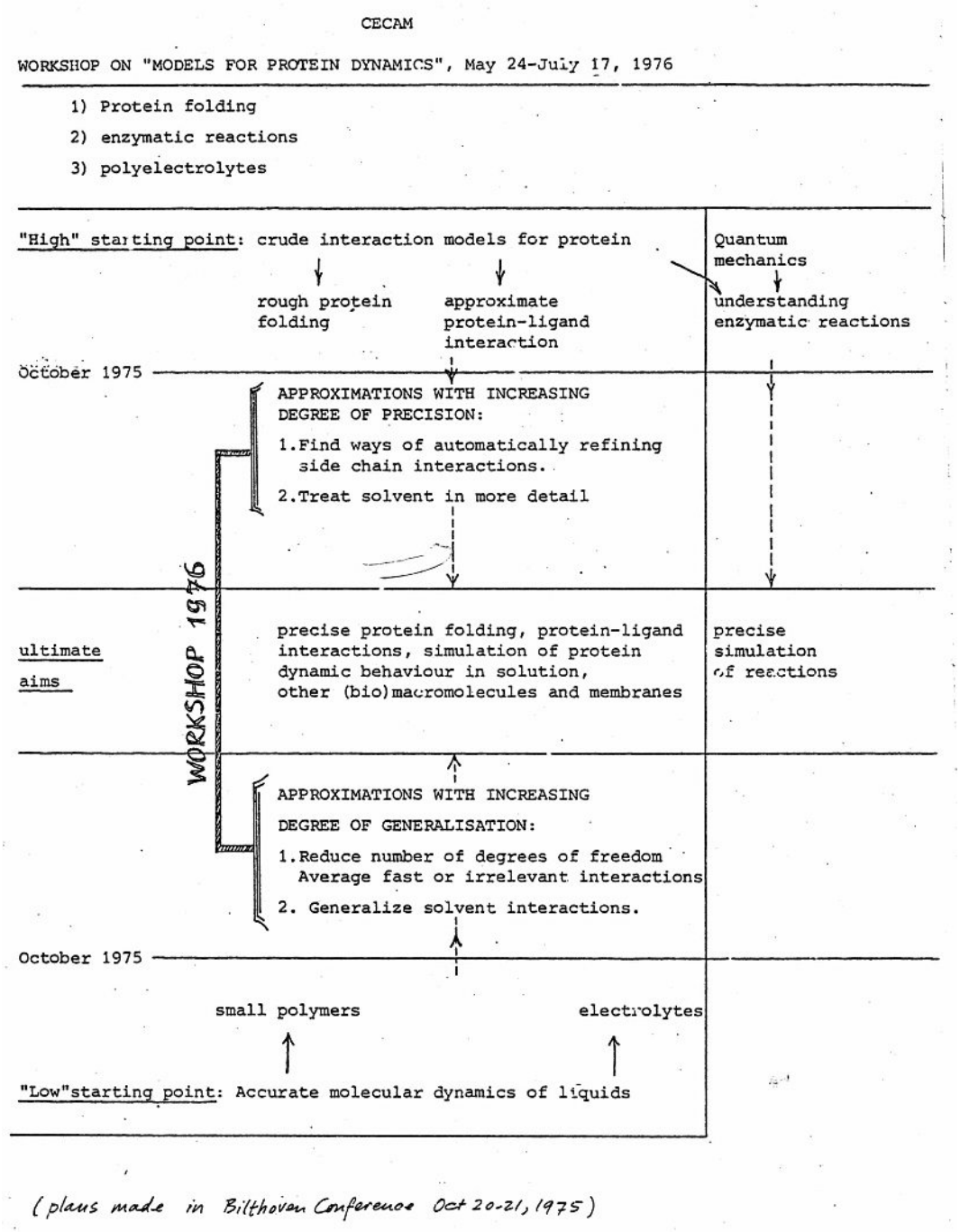

Figure 1. The vision regarding the future development of bio-molecular modeling formulated by *Herman Berendsen* on a transparency for the two-day CECAM discussion meeting held in Bilthoven, The Netherlands, he organized in 1975 in preparation of the eight-week 1976 CECAM workshop 'Models for Protein Dynamics', held in Orsay near Paris.

people generated and absorbed ideas at CECAM and worked them out in their home institutions. This change is also due to the advent of the internet easing scientific exchange from home, and to the maturation of the field, requiring larger and more sophisticated computer programs that cannot be generated on the spot. This means that being present at CECAM is immaterial for the purpose of using computers, but is

essential for the exchange of scientific ideas. Unfortunately, the current practice of three- to four-day workshops packed with participants, leading to a lack of leisurely discussion time at the coffee machine, is eroding the second original goal of CECAM: being a driving force on scientists from different fields who may contribute their expertise and insights to achieve new goals by freely interacting with each other.

The 1976 Workshop on Models for Protein Dynamics: Goals and Strategy

Simulation of atomic and molecular systems in the condensed phase started in 1972 at CECAM with a two-month workshop (seven participants) on Molecular Dynamics and Monte Carlo methods on water,[6] at which the presence of *Aneesur Rahman* was pivotal, through his sincere personality and scientific depth setting an example to all.[7] This workshop showed that simulation of water was possible. Simulation of water contains already the major difficulties of treating long-range electrostatic interactions, polarizability and hydrogen bonding, all crucial to the simulation of biological macromolecules. If you cannot simulate water, biological macromolecules will be hopeless. If you can, the latter may just be more complex, not more complicated.[7] Molecular dynamics then developed along two lines: 1) treatment of simple systems to test and extend methods of statistical mechanics through simulation of simple liquids, ionic liquids, stochastic dynamics, and non-equilibrium behavior, and 2) the approximate treatment of models of the real world to understand and predict properties of realistic systems, *e.g.*, through the simulation of proteins, DNA, carbohydrates, and lipid membranes. In 1974 a four-week CECAM workshop (nine participants) on the simulation of long time scale events[8] addressed as yet unexplored issues such as separation of fast and slow motions, the use of approximations leading to a significant decrease of computer time per MD time step and methods designed to avoid the explicit calculation of rapid motions in molecules. In 1974 *Levitt* and *Warshel* used an incredibly crude – and hence unreliable – model for the interactions within a protein, but managed to obtain some kind of folding of the macromolecule.[9] The method resembled an inaccurate type of dynamics; it was wrong and controversial but brave, and stimulated many people at the time.[7] This led *Herman Berendsen* to hold a CECAM discussion meeting in 1975 to see if the two approaches, accurate simulations on small molecular systems and crude simulations on biological macromolecules, could be brought together. They could and they were in the 1976 CECAM workshop on Models for Protein Dynamics.

Figure 1 shows in the middle the ultimate goals, such as the precise simulation of protein folding, protein-ligand interaction, the dynamics in membranes, and an understanding of enzymatic reactions. These goals were to be approached from two sides: 1) from a coarse-grained level through finding approximations with increasing degree of precision, *i.e.*, the refinement of crude interaction models for proteins towards more detail, and 2) from a fine-grained level through finding approximations with increasing degree of generalization, *i.e.*, by reducing the number of degrees of freedom. These are all topics still relevant and being addressed these days. The CECAM workshop resulted in the first molecular dynamics simulation of a protein,[10] bovine pancreatic trypsin inhibitor (BPTI), and can be considered the start of the field of bio-molecular simulation.

Thus one can argue that the roots of bio-molecular simulation lie in the following fundamental contributions:

1) At the end of the sixties and in the early seventies of the last century the *Lifson* group in Israel worked on the development of interaction functions or so-called force fields for alkanes[1] and the other molecules that contain functional groups[11] of bio-molecules.
2) In the same period, the late *Anees Rahman* explored the simulation technique of molecular dynamics (MD), first for atomic liquids[2] and then for the bio-molecular solvent water.[3]
3) The initiative and vision of *Herman Berendsen* who, with his interest in water and the interpretation of (NMR) spectroscopic measurements, wanted to base the latter on a detailed simulation of the dynamics of bio-molecules, and thus organized and led the 1976 CECAM workshop[4] to that end.

The 1976 Workshop on Models for Protein Dynamics: Problems Addressed

Figure 2 shows the participants of the workshop 'Models for Protein Dynamics' of 1976. Those participants that stayed for the whole two-months duration of the workshop did not only enjoy the cultural and culinary qualities of Paris, but also the close cooperation during eight weeks between scientists contributing different expertise to make progress towards the

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*for part of the workshop
**visitor

Note. Many reports contain some work done in a few months after the workshop ended.
In some cases this has involved cooperation with non-participants of the workshop, who are then listed as coauthors of the report.

Figure 2. Participants[4] of the eight-week CECAM workshop 'Models for Protein Dynamics' held in Orsay, near Paris in the spring of 1976, where the foundation of bio-molecular simulation was laid out: *C. Bennett, H. J. C. Berendsen, G. Careri, G. Ciccotti, C. Chothia, D. Elkkoubi, A. Englert, D. L. Ermak, D. R. Ferro, W. F. van Gunsteren, J. Hermans, M. Leclerc, M. Levitt, B. Maigret, J. A. McCammon, K. Nagano, J. Orban, S. Prémilat, A. Rahman, P. Rossky, J. P. Ryckaert, P. Turq, S. Wodak.*

goal of simulating the behavior of bio-molecular systems. It goes without saying that *Herman Berendsen* was instrumental to this process of interaction. His wide interests, vast knowledge of physics, chemistry, and biology, his ability to clearly formulate issues, combined with an open mind and a generosity of

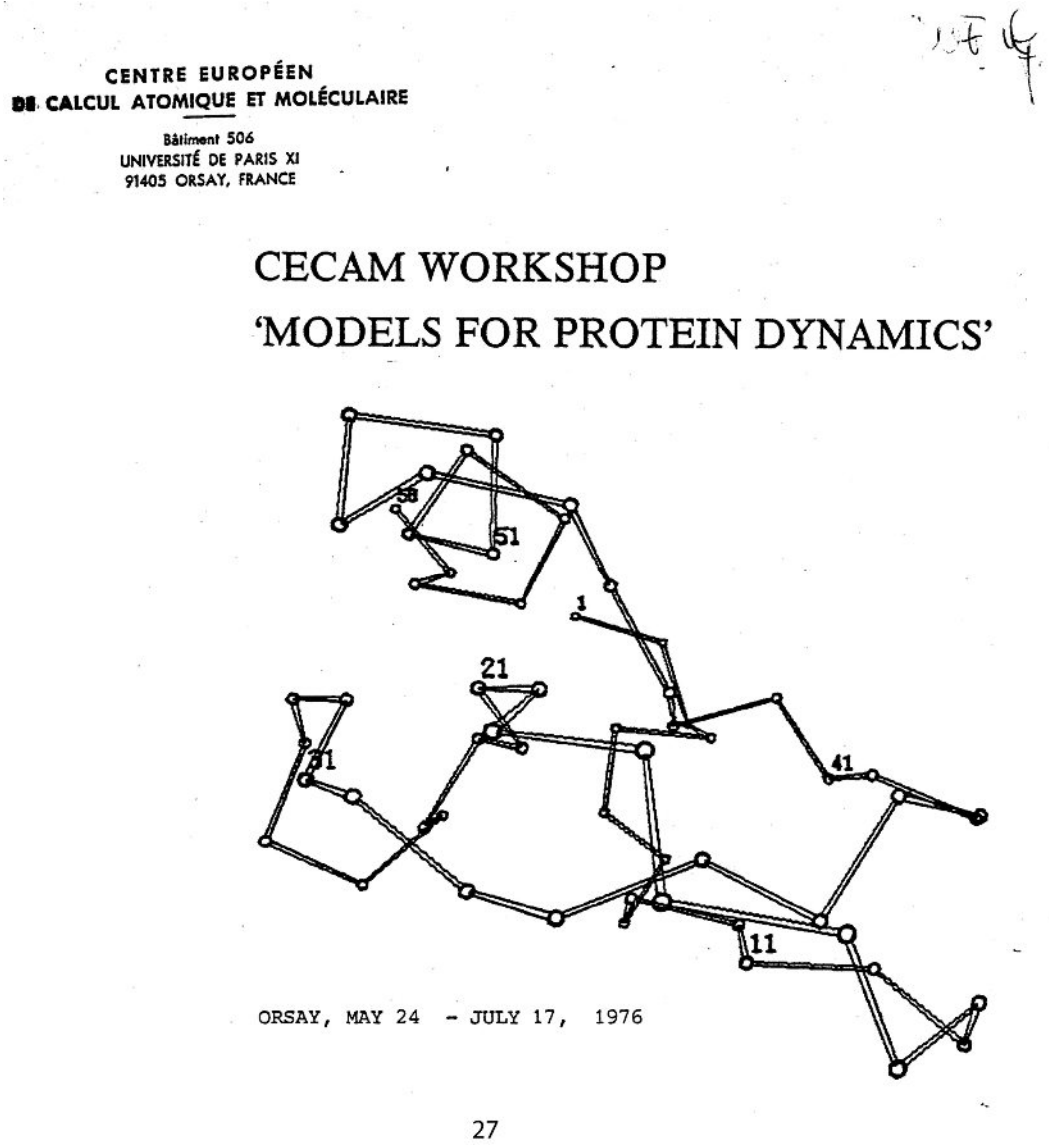

Figure 3. The cover of the 1976 CECAM workshop report[4] (available at the Natural Sciences Library of the ETH). It contains a coarse-grained model of the protein bovine pancreatic trypsin inhibitor, one bead per amino acid residue.

sharing his insights, made him a powerful inspiration for working together towards a common goal. *Anees Rahman* worked with *Jan Hermans* from Chapel Hill on the dynamics of water molecules in a crystal of BPTI, and with *Peter Rossky*, then at Harvard, on the dynamics of a dipeptide in water, using *Rahman* and *Stillinger*'s ST2 model for liquid water.[3] *Don Ermak* used his algorithm for solving stochastic equations of motion and *Andy McCammon* from Harvard simulated BPTI *in vacuo*. My own task during the workshop was, as a novice to the field – I had just completed my Ph.D. work on the nuclear quasi-particle model – to implement and test the constraint algorithm SHAKE[12] in the MD program.[13] Since the 1976 workshop, the field of bio-molecular simulation has seen a rapid development in terms of algorithms and force fields, with an ever expanding set of applications. Methodological developments necessary for bio-molecular simulation involved algorithms to efficiently integrate equations of motion, to apply constraints, to couple the molecular system to temperature and pressure baths, to treat long-range electrostatic interactions adequately, to compute free energy and entropy, to refine protein structure based on NMR data (in a 1983 CECAM workshop[14]), to mention a few. *Figure 3* shows the cover of the 1976 CECAM workshop report.[4] It

contains a coarse-grained model of the protein bovine pancreatic trypsin inhibitor, one bead per amino acid residue. At the workshop, this representation was considered to be awfully inaccurate[5] and the poor representation only served as pretty picture without physical content offering an impression of the molecule that was simulated.

The CECAM Workshops on Molecular Dynamics of the Seventies

In the mentioned CECAM workshops, scientific puzzles and problems were addressed that remained relevant for decades:[15–18] how to treat properly, *i.e.*, inducing minimal artifacts, the long-ranged *Coulomb* interactions that are proportional to the inverse of the distance between two charges; how to calculate the dielectric permittivity from the dipole fluctuations in a simulation using a cut-off for non-bonded electrostatic interactions; how to coarse-grain an atomic model into a supra-atomic or supra-molecular one by neglecting or averaging over atomic-level forces without incurring a severe loss of accuracy; how to enlarge the time step in MD simulations, *e.g.*, by multi-range, multi-step integration algorithms; how to incorporate constraints in a MD simulation, *etc.*

The participants of these workshops continued to further develop molecular simulation techniques at their home institutions for the following decades, inspired by the atmosphere typical for CECAM at the time: bringing together scientists from a wide variety of areas to induce cross fertilization with an eye to a common goal, spending much time to understand each other's ideas and work, not hampered by competitive attitudes or secretiveness. The location of CECAM in Orsay was a perfect one. The train rides from and to Paris enabled – or rather forced – the participants to discussions in an informal and *ad hoc* manner. During the 1983 workshop on Nucleic Acid Structure and Dynamics,[14] the basic idea of refinement of protein structure by MD using 2D-NMR proton-proton NOE (nuclear *Overhauser* effect) distance restraints came up in discussions with *Rob Kaptein* during our daily train trips.

Computational Challenges in Chemistry, Biochemistry, Molecular Biology, and Physics

There are several reasons why molecular simulation in chemistry is much more difficult and challenging than in the technical sciences such as aeronautics or civil engineering.

1) Degrees of freedom governing chemical processes are electronic, nuclear, atomic, molecular, and supra-molecular, and the corresponding particles have different masses and sizes.
2) Interactions are governed by quantum mechanics: the *Dirac* or *Schrödinger* equations of motion, for not too small mass or too low temperature by classical equations of motion.
3) At non-zero temperatures, the behavior of particles is governed by statistical mechanics: *Fermi-Dirac*, *Bose-Einstein*, or *Boltzmann* ensembles of configurations are to be considered, not single structures.
4) The *Coulomb* interaction is rather long-ranged (~ distance^{-1}) and induces many-body effects that make accurate modeling rather expensive.
5) (Free) energy differences that drive processes can be very small compared to the total energy of the interacting particles of a system.
6) Time scales of processes easily span 15 orders of magnitude (10^{-15} sec to seconds).

These features of molecular modeling and simulation require many approximations to be made and thus it is mandatory to strike an appropriate balance between accuracy attained and affordable computational cost, while maintaining a physically correct mechanism of the process of interest.

A popular answer to the mentioned challenges is to use 'big data', *i.e.*, the plethora of data becoming available and accessible these days through the increase of computing power and storage capacity. However, attempts to detect the degrees of freedom and the dominant interactions of a molecular system that are essential for a proper modeling of the properties of interest to be calculated is generally not an easy, if not impossible,[19] task. Averaging over many data may enhance the statistical precision of properties or correlations found, but overlooks by definition outliers that may hold the key to an understanding of their origin.

Another popular answer to the mentioned challenges is to use 'machine learning' or 'artificial intelligence' applied to 'big data'. As for humans, there exists a limit though to what an algorithm can 'learn': Using the mathematical foundations of machine learning it can be demonstrated that learnability can be undecidable, in other words 'the notion of learnability is vulnerable'.[20]

A less popular but essential issue regarding answering the mentioned challenges is the validation of the results of molecular simulations.[15] How can one

detect simulation artifacts due to approximations made and compensation of errors? Regarding validation by comparison of simulated with experimental data various issues are to be considered: 1) generally, there are less experimentally determined values of observable quantities available for comparison than the number of molecular model parameters for which values were chosen, 2) *pseudo*-validation based on the use of the same data for parameter calibration and model testing, 3) *pseudo*-validation based on comparison of simulated to non-observed data, 4) what is the statistical uncertainty of the calculated properties or the observed correlations. And, is the popularity of a molecular model or simulation software an appropriate validation criterion?

The increase of available computing power can be used 1) to simulate larger systems allowing for longer-range electrostatic interactions to be incorporated in a simulation, 2) to increase the number of simulations of a particular system in order to enhance the statistical precision of the properties calculated from the ensemble of configurations, 3) to extend the time scale of simulations, and 4) to incorporate quantum-mechanical treatment of electronic or nuclear degrees of freedom in a system while simulating chemical or enzymatic reactions.

Challenges for the next decades of molecular simulation are the following:

1) Simulation of correlated electron and proton motion (no *Born-Oppenheimer* approximation).
2) Improvement of hybrid quantum/classical dynamics simulation (reconciliation of a probabilistic *versus* a deterministic picture).
3) Accurate calculation of entropic contributions to molecular processes, at any level of resolution.
4) Development of yet more accurate energy functions (force fields) for (bio-)molecular simulation, at any level of resolution.
5) Development of computationally efficient methods to sample (*Boltzmann*) relevant bio-molecular conformations.
6) Maintaining the quality of software used in molecular modeling and simulation research.
7) Maintaining the quality of the simulation literature by requiring proper validation of simulation results to be published.

Sharing of Scientific Ideas

Due to the increasing pressure on scientists to publish papers and generate citations[21] in order to enhance their own so-called 'performance indices', rather than those of colleagues, the willingness to share thoughts, ideas, data, and results seems to be declining, which is unfortunate because impeding the progress of science. It is therefore desirable that scientific organizations, such as national science foundations or CECAM, refrain from using popularity indices for evaluation, facilitate, and (financially) stimulate the free exchange and sharing of ideas and data between scientists, and that plagiarism, *i.e.*, theft of ideas, is denounced.[22]

Herman Berendsen practiced sharing his ideas, continued to initiate and lead CECAM workshops, made essential contributions[23] to simulation methodology, and indeed has, with a handful of others, given the field of bio-molecular simulation its present shape. Milestones are his iterative SHAKE algorithm to perform molecular dynamics simulation in Cartesian coordinates with constraints, one of the most widely used water models, namely, the simple (three-)point-charge (SPC) model for liquid water, his pioneering study of free energy perturbation methods for computing hydration free energy through simulation, the *Berendsen* thermostat and barostat for simulation at constant temperature and pressure, and his density matrix evolution method for hybrid quantum/classical dynamics simulation. The simulation of membranes was pioneered by the *Berendsen* group in the early eighties. Undoubtedly, *Herman Berendsen* represents the best academic tradition of probing the unknown, of seeking both insight and improved methodology, but always with an eye to possible practical application. In this endeavor, he has never hesitated to share his insights, knowledge, and ideas with others, as is best illustrated by the series of 13 CECAM workshops and discussion meetings he has organized and led since 1972. His scientific work is above all characterized by an exceptional scope,[24] from mathematics, computer science, and physics to chemistry, biochemistry, molecular biology, and medical applications, and by a clear vision and foresight. It is these characteristics that gave the 1976 CECAM workshop 'Models for Protein Dynamics' its far-reaching impact.

Author and Biographical Statement

The author (PhD, Free University Amsterdam) is professor emeritus of computer-aided chemistry at the Swiss Federal Institute of Technology (ETH) in Zurich, Switzerland. His major research interest is the development of methodology to simulate the behavior of bio-molecular systems, using his GROMOS bio-molecular simulation software as research vehicle. He has authored more than 600 research papers and served in several functions at the ETH, at last as ombudsperson of the ETH.

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