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Editorial

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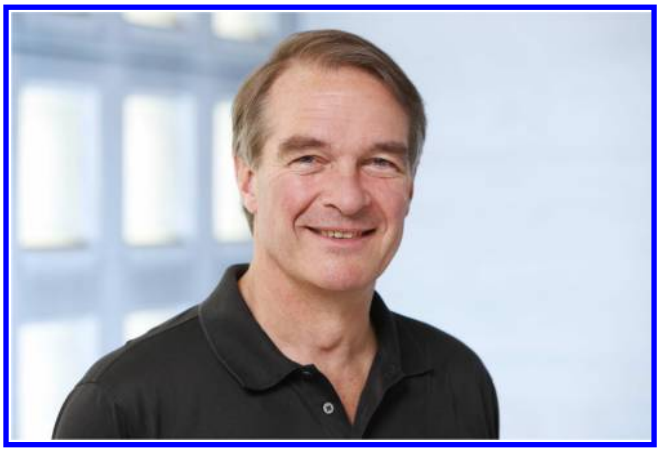
Wilfred van Gunsteren: 35 Years of Biomolecular Simulation



Photograph of Wilfred van Gunsteren: Giulia Marthaler/ETH Zürich

This special issue of the *Journal of Chemical Theory and Computation* is dedicated to one of the founders of the field of biomolecular simulation, Prof. Wilfred F. van Gunsteren, in honor of his 65th birthday and 35 years of research in this field.

The description of biological processes at the molecular level is one of the greatest challenges in theoretical biology, and the key to understanding how biomolecules, biomolecular systems, cells, and, ultimately, living organisms function. In turn, the description of molecular properties at the (sub)atomic level is rooted in the field of theoretical physics, namely, in the laws of quantum mechanics or of its classical Newtonian approximation, the connection between microscopic and macroscopic levels being provided by statistical mechanics. Biomolecular simulation therefore bridges a broad spectrum of scientific disciplines, and it is not surprising to see that many key players in this field, such as Wilfred, combine a strong background in physics with a deep appreciation of both chemistry and biology.

Biomolecular simulation is nowadays a well-established yet still rapidly evolving field. Scientists happily dwelling in a mature scientific area generally do so because they are standing "on the shoulders of giants", in this case, the pioneers who dreamed once about simulating the molecules of life based on the laws of physics, designed the basic methods and algorithms to do so, programmed them into computers, and made their dream come true. It is beyond doubt that Wilfred was one of these pioneers. His contributions to the toolkit, the applications, and even the "philosophy" of biomolecular simulation over more than three decades are extensive and varied. Owing to his innovative mind, scientific rigor, unbounded energy, and strong personal charisma, Wilfred is definitely one of the "giants" of the field.

Wilfred was born on August 7, 1947, in the town of Wassenaar in The Netherlands as Willem Frederik van Gunsteren, youngest child in a family of eight. As an undergraduate, he studied physics at the Free University of Amsterdam ("Vrije Universiteit Amsterdam"), obtaining his bachelor's degree ("kandidaats") in 1968 and his master's degree ("doctoraal") *cum laude* in 1972. Wilfred undertook his doctoral work in nuclear physics under the supervision of Prof. Dr. Egbert Boeker, was awarded the Royal Dutch–Shell Prize (1975) for this work, and obtained his Ph. D. *cum laude* in 1976. In addition to studying physics, Wilfred also prepared (without actually following the lectures!) a master's degree in law ("meester in de rechten"), which he obtained in 1974. While he never formally worked as a lawyer, the unusual combination of law and physics has been visible throughout his later career, in the form of a keen interest in matters of correctness, integrity, and justice, and in the careful formulation of arguments.

Despite having just completed a highly successful Ph. D., Wilfred was unsure whether he wanted to pursue a career in nuclear physics. It was at this point that he met Prof. Herman J. C. Berendsen, professor of physical chemistry at the University of Groningen. Herman convinced Wilfred that his skills in physics and computation might enable him to address fundamental questions in biology, a new and radical idea for the time. Wilfred worked with Herman at the University of Groningen as a postdoctoral fellow from 1976 to 1978, developing the basic algorithms and programs needed to efficiently simulate (bio)-molecular systems. This period was followed by a second postdoctoral stay from 1978 to 1980 in the group of Prof. Martin Karplus at Harvard University, another leading center in this rapidly developing field. These years were important ones, not only scientifically but also privately: Wilfred and his wife Jolande, who had married in December 1970, became parents of two children, Job, born in 1976, and Eva, born in 1978.

It was at Harvard that Wilfred began to write the code that would ultimately form the basis of the GROMOS (GROningen MOlecular Simulation) package, which he was to develop and refine over the course of his career. He returned from the U.S. in 1980 to take a position of senior lecturer at the University of Groningen, and became professor of physical chemistry at this university in 1987. From 1987 to 1988, he also spent one year at the University of California in San Francisco (UCSF), where he worked with his friend, the late Prof. Peter A. Kollman. In early 1990, Wilfred accepted an offer of the Eidgenössische Technische Hochschule (ETH) in Zürich and moved to Switzerland to become professor of computer-aided chemistry ("informatikgestützte chemie") in September of that year.

Wilfred has received numerous honors and prizes. Notable examples include the gold medal of the Royal Dutch Union of Chemists (1987) and the Max-Planck Forschungspreis für Chemie and Pharmazie (2002). Wilfred was also made Stiftungsgastprofessur für Chemie and Medizin of the Johann Wolfgang Goethe-Universität in Frankfurt (1988), corresponding member of the Royal Dutch Academy of Arts and Sciences (1995), 73rd Priestly Lecturer of Penn State University (1999), and 10th Huygens Lecturer of the Dutch Science Foundation (2001). Last but not least, Wilfred recently received the Golden Tricycle award of the Academic Association of Scientific Staff at ETH Zürich (2009), a unique prize awarded to group leaders at ETH for their support of family friendly policies. Wilfred has supervised nearly 50 Ph. D. students and as many postdoctoral

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fellows, and published over 530 research articles (see full publication list on the IGC Web site[1]).

The three following sections provide an account of Wilfred's career from 1976 until now, intermingling biographical and scientific components, and divided according to three main periods: The Groningen and Harvard years (1976−1990), the years spent at ETH-Zentrum (1990−2001), and the years spent at ETH-Hönggerberg (2001−present). These three sections are written by Herman Berendsen, Alan Mark, and Philippe Hünenberger, respectively.

THE GRONINGEN AND HARVARD YEARS (1976−1990)

It must have been early 1976 when Wilfred's promotor at the Free University of Amsterdam, the nuclear physicist Egbert Boeker, called me in Groningen with a somewhat unusual request: "I have a very talented Ph. D. candidate who is about to finish his dissertation on a quasi-particle model for atomic nuclei. But he sees no future in nuclear physics and considers the study of many-particle systems instead. Could he come and talk with you?" Of course he could, and soon after, Wilfred and I had a long and inspiring conversation in Groningen. We agreed that the physics of large many-particle systems stood before a major breakthrough as a result of the rapidly increasing computational power that was then becoming available to the scientific community. But I also warned him that he would need a fair knowledge of chemistry, on the one hand, and of biology, on the other, because the most challenging problems ahead would be of a biophysical nature. This did not scare him away at all: after all, he had mastered most of his physics courses without actually attending the lectures, and he had, as a side interest, obtained a law degree more or less in his spare time. So why bother about picking up chemistry and biology?

It so happened that this conversation took place at a time of turmoil in the development of computational sciences. Computational methods in physics and chemistry were rapidly developing to a level of practical usefulness. In several places, large computer centers had been or were being set up to serve the scientific community. In France, a regional computer center in Orsay also hosted the European organization CECAM (Centre Européen de Calcul Atomique et Moléculaire) that organized "workshops" where scientists would work together on a scientific computational topic using the regional "super"computer at Orsay. At first, the topics concerned quantum chemistry and X-ray diffraction but soon extended to other fields including the application of molecular dynamics (MD) and Monte Carlo methods to condensed-phase systems. I had organized several workshops since 1972 and learned the trade mainly from Aneesur Rahman, one of the founding fathers of molecular dynamics. Anees had published (with Frank Stillinger) the first MD simulation of liquid water in 1971 and initiated several other innovations in molecular dynamics, until his untimely death in 1987.

For the summer of 1976, we had planned an extensive workshop[2] involving 20 scientists from both the physical and the biological sciences with a duration of eight weeks(!). Its title was "Models for Proteins," and its aim was to investigate the possibilities of simulating biological systems by bringing physicists and biochemists together in a stimulating, open, and interactive environment. The participants included—among several others—Aneesur Rahman, Giovanni Ciccotti, Charles Bennett, Andy McCammon, Michael Levitt, and Jan Hermans, while Martin Karplus was a frequent visitor. For Wilfred, participation in this workshop was the ideal introduction into the field and preparation for a postdoc position in Groningen. So it happened. During the workshop, Wilfred and I worked on the incorporation of the then recently developed SHAKE method for enforcing constraints into the MD code, thus abandoning the complicated Euler dynamics used in Rahman's programs and allowing larger time steps for protein dynamics. We all shared our knowledge; Andy McCammon (then a postdoc in Martin Karplus' lab) came with an MD program and protein force field from Harvard, and actually performed the first simulation of a protein, bovine pancreatic trypsin inhibitor (BPTI), during the workshop.

How about Wilfred's chemistry and biology? He was extremely eager to learn and picked up the necessary knowledge on the way. On more than one occasion, we made the eight-hour-long trip from Paris to Groningen by car together, discussing incessantly the basics of (quantum) chemistry and biochemistry. By the end of the summer, Wilfred was ready for a career in a new field and joined my group as a postdoc. The following 14 years, mostly in Groningen, turned out to be very productive. We had an effective collaboration on many methodological topics, ranging from integrator algorithms, constraints and thermostats to force fields, and free-energy determinations. It was real fun and exciting to explore this mostly uncharted territory.

In Groningen, there was much interest to keep Wilfred in a permanent staff position, but there was no vacancy and the strict faculty policy made a direct promotion from a temporary to a tenured position impossible. So, Wilfred left Groningen and took up a postdoc position with Martin Karplus at Harvard University (1978−1980), submerging in a stimulating and demanding, but competitive, environment quite distinct from the almost naively open scientific atmosphere he was used to. At Harvard, Wilfred concentrated on the effects of constraints on macromolecular behavior and on the simulation of biomolecules in explicit solvent.

In 1982, he accepted a position of associate professor in Groningen, where he became full professor in 1987. Around the same time, he was also appointed part-time as visiting professor at his Alma Mater, the Free University of Amsterdam, a position he kept until 1992. In 1987−1988, he went for a sabbatical to Peter Kollman at UCSF. It is during this second period in Groningen (1982−1990) that Wilfred carried out pioneering work in the field of biomolecular structure refinement using MD based on nuclear magnetic resonance (NMR) data. He was also one of the first to apply MD to the refinement of structures from X-ray diffraction data. Then, in 1990, he got an offer from the ETH in Zürich that he could not resist, and he left Groningen for good, while keeping strong scientific ties with his former colleagues. As one of his last achievements while still in Groningen, Wilfred wrote for *Angewandte Chemie* a comprehensive and much-quoted review on MD,[3] which remains highly relevant even today and, in the mean time, has inspired many newcomers in the field.

The GROMOS program was born in the late 1970s, written entirely (in Fortran) and maintained exclusively by Wilfred. It started at the 1976 CECAM workshop with elements from the Harvard program that later evolved into CHARMM and was also a basis for AMBER, further developed by Peter Kollman. While the three popular programs were to progress independently thereafter, considering their joint roots, it is not surprising that they still have many features in common. By 1986, GROMOS had become so popular and widespread (also in industry) that Wilfred sought for means to streamline its existence and generate some funds for its distribution, maintenance, and innovation. Stimulated by the University and the Science Park Foundation in Groningen,

a software firm "BIOMOS B.V." was established in September of 1986. GROMOS was then distributed for a fee to industrial customers, including the first real GROMOS manual,[4] but still essentially for free to academic users. After 1990, GROMOS was further developed at the ETH. The software development in Groningen followed its own path: the focus was on special-purpose parallel hardware, which required a rewrite (GROMACS), written in C with parallel extensions and distributed in the public domain.

I think that, on the one hand, Wilfred enjoyed being the CEO of an official firm, but on the other hand, he and I agreed fully on the principle that the results of publicly funded scientific developments should be freely available to the scientific community. So he did not obtain a salary from the firm and neither did the trustees! The income of the firm was spent on a part-time secretary, on distribution and installation, on some hardware, and occasionally on some programming help, but—since 1990, when Wilfred took up his position at the ETH—mostly on the yearly organization of a joint symposium between the Groningen and Zürich groups in the German castle *Burg Arras* near Alf-Bullay on the Mosel, located close to the mean of the Groningen and Zürich coordinates. The informal and stimulating *Burg Arras* meetings persisted for 20 years! The BIOMOS meetings continue nowadays along the very same tradition but, since 2011, in the village of Ausserberg in the Swiss Alps. **Herman J.C. Berendsen**

THE ETH-ZENTRUM YEARS (1990−2001)

I first met Wilfred when he visited Australia in 1987. I joined him and Herman Berendsen in Groningen in 1989, and moved with Wilfred to Zürich in 1990. The move to Zürich was not an easy decision. Wilfred cherished his interaction with Herman, and the very close collaboration between leading groups in NMR, X-ray crystallography, electron microscopy, and computational sciences that existed in Groningen at the time was rare. In contrast, ETH offered independence and the resources needed to sustain an internationally competitive research program. Ultimately, it was the proactive approach taken by ETH compared with what Wilfred saw as the failure to sufficiently recognize and support what had been created in Groningen that determined his decision.

This difference helped shape Wilfred's own approach to leading groups, departments, and institutions. He was decisive and always willing to seize opportunities. Nevertheless, Wilfred knew the opportunities his time in Groningen had given him and, before leaving, organized a party for the department providing not only the food and venue but also the entertainment, playing the drums in his band with Jolande, his wife, singing. Such acts of generosity were common. Among his first acts at ETH was to organize a Dutch "borrel" for the new department. These became regular if not somewhat notorious events to which all were invited.

The new group at ETH-Zentrum consisted of Andrew Torda, Alan Mark, Piet Gros, Paul King, and Roger Brunne, representing Australia, The Netherlands, England, and Germany. This core quickly expanded to include Swiss, Italian, French, American, Indian, and Chinese nationals. Having a mixture of skills, genders, and nationalities was of particular importance to Wilfred. Most were invited to join the group based on a specific personal relationship. As far as I can recall, only once was a position actually advertised.

Scientifically, the group focused on exploring and testing novel methodology. New search techniques such as potential-energy annealing conformational search, four-dimensional molecular dynamics, and local elevation (rebadged by others as conformational flooding and later meta-dynamics) were developed. Approaches to enhance free-energy calculations were introduced, including a simple soft-core approach to avoid singularities as atoms were created or deleted, and single-step perturbation methods for evaluating multiple free-energy differences from a single simulation. Enhancements in umbrella-sampling techniques and methods for estimating configurational entropies were examined. The treatment of electrostatic interactions was a major focus. A generalized reaction-field method was developed, and particle-mesh approaches were investigated. Work also continued on the use of time- and ensemble-averaging in structure refinement. Other topics of interest included protein unfolding, simulations of polymers, mixed quantum-classical methods, implicit-solvent models, and force field development. Refinements in the force field during this period led to the ability to reversibly fold small peptides. This shed new light on the conformational properties of peptides in solution, in particular concerning the nature of the unfolded state, a topic that became a major focus in the following years. The ability to sample the phase space of a peptide so extensively also led to the possibility of directly computing experimental properties such as NMR order parameters and resonance cross-relaxation rates from simulation trajectories in which the molecule would fold and unfold spontaneously and tumble freely.

Rigor was central to all of this work. The ability to reproduce experimentally determined quantities was critically assessed, and often it had to be concluded that the available experimental data were simply insufficient to support claims that had been made in the literature. Equally, alternative theoretical approaches were rigorously analyzed. Wilfred was never afraid to challenge preconceived notions. He would often hold colleagues, friends, and even previous mentors to account, which more than once led to disputes in the literature. When simulating biomolecular systems, it is easy to choose the methodology or conditions to obtain the answer you desire. Wilfred felt that for the good of the field, such work must be challenged.[5] He would also not distribute code he did not trust, and before 1990, he had personally written and maintained almost all of the 40 000 lines of code in the GROMOS87 simulation package.[4] In Zürich, this was no longer possible. The development of GROMOS as a tool within the group blossomed, but its position as a leading code in terms of speed and functionality diminished. This changed in 1995 when the effort of the entire group was focused on what would become GROMOS96.[6]

Ties with Groningen remained strong. Since 1990 and over 20 years, the annual BIOMOS meeting gathered the Zürich and Groningen groups each autumn at the castle *Burg Arras*. These meetings were an opportunity to discuss the latest trends in simulation techniques, to develop new ideas, and to promote long-term friendships. Funded initially from the proceeds of GROMOS, the meetings embodied Wilfred's desire to maintain and nurture an expanded community. BIOMOS meetings were special. Discipline was strict, attendance was mandatory, and the talks, projected against striped wallpaper, were exactly 20 minutes.

Ultimately, research groups reflect the personalities of their leaders. The group Wilfred established at ETH-Zentrum was, on the one hand, talented, hard-working, and competitive and, on the other, supportive and fun-loving. To Wilfred, personal relationships are crucial. Family came first. After this, from ski weekends to farewell parties, the group was central. Many of the people who worked with Wilfred during the early days at ETH-Zentrum have gone on to become professors in their own right.

However, while Wilfred was very supportive of those students and postdocs who wanted an academic career, his primary aim was not his personal legacy. He was equally supportive of students who ultimately ended up writing software for banks, in the chemical industries, or raising families. To all, Wilfred was not only a supervisor and mentor but also a friend and confidant. It was this generosity of spirit along with Wilfred's scientific ability and vision that made the time at ETH-Zentrum for all those involved special. **Alan E. Mark**

THE ETH-HÖNGGERBERG YEARS (2001-PRESENT)

In the summer of 2001, the Department of Chemistry moved from ETH-Zentrum to the ETH-Hönggerberg campus, more remote from the city center but nicely surrounded by fields and woods. In the bright new chemistry building, the Informatikgestützte Chemie (IGC) group of Wilfred organized itself around a beautifully located group-meeting room facing the Uetliberg and the Alps, and occupied three "laboratories", six smaller offices, and two computer rooms, dubbed the "zoo".

Wilfred always secured state-of-the-art computational equipment for IGC. The previous decade at ETH-Zentrum had been that of the "big fridges". The new decade was to be that of the more cost-effective multinode clusters, with sufficient disk space to tackle larger and larger problems. Wilfred insisted that the computers be managed by group members, as specified in the yearly edition of the IGC group responsibility list (document C17, for the connoisseurs), rather than given to a permanent technician or outsourced. In this way, the group developed and maintained a high level of technical expertise, which also turned out to be an asset for many former group members in their post-IGC academic or professional lives.

The drive to embrace modernity also affected the GROMOS code. Shortly after the GROMOS96 release,[6] a group of young Ph. D. students started to develop C^{++} routines, labeled GROMOS^{++}, for the preprocessing and analysis of MD trajectories, replacing the original Fortran routines written by Wilfred. This effort was soon followed by the development of a full-blown C^{++} MD engine, labeled MD^{++}. Initially, Wilfred was skeptical about the merits of these efforts, knowing that the development of a reliable simulation code requires not only computational skills but also a great deal of physical insight, follow-through, common sense, and experience. However, he could also see the advantages of a code in C^{++} for developing new methodology. Judging that the project had gathered sufficient collectiveness, competence, and momentum to be viable, he finally gave it its legitimity. The MD^{++} engine and the GROMOS^{++} library were documented in an article in 2005 and, after a major finalization effort now involving the entire group, became the official GROMOS release in 2011, including an updated force-field version and a detailed manual of nearly 1200 pages.[7]

Over these 11 years at ETH-Hönggerberg, the group was extremely productive, Wilfred's research covering all relevant areas of atom-based (bio)molecular simulations and extending in part beyond.[8] In the domain of conformational sampling and structure refinement, the group explored and extended the use of, among other approaches, soft constraints, NOE intensity calculations, time-averaging, adiabatic-decoupling, and multigraining. The critical examination of the relationship between experimental and simulated observables was also a key theme in Wilfred's research. Numerous practical examples underlined a common important message: be it in the context of nuclear magnetic resonance, X-ray crystallography, or circular dichroism, experimental observables are properties of a conformational ensemble. Their interpretation in terms of a single structure often leads to conclusions that range from inaccurate to entirely incorrect. In the domain of free-energy calculations, work was continued on the single-step perturbation method, on the design of improved nonbonded scaling schemes, and on the calculation of potentials of mean force. New approaches were also developed such as the hidden restraints and the enveloping distribution sampling (EDS) methods. Entropy calculations also represented an important research line of the group, considering in particular the covariance-matrix and the solvent−solvent entropy−enthalpy cancellation approaches. Force-field development, in terms of both methodology and parametrization, was extended along the lines of atomistic, polarizable, implicit-solvent, and coarse-grained models. Contributions in the domain of electrostatic interactions as well as excursions in the domain of mixed quantum-classical methods may also be mentioned. The application of new methodologies extended over a broad spectrum of organic and biological (macro)molecules, including peptides and proteins, but also nucleic acids, lipids, and carbohydrates.

In these Hönggerberg years, the IGC group comprised an average of about 20−30 group members. As an efficient, pleasant, and well-guided group, it also attracted many shorter-term students and visitors, from ETH and from abroad. The ability of Wilfred to lead a group of this size while remaining available and personal to everyone, and without introducing any "pyramidal" hierarchical structure, is truly remarkable. Everyone in the group enjoyed the direct involvement of Wilfred in his or her project. All meetings were systematically summarized in a corresponding "yellow note", written by Wilfred with one of his numerous hard-mine pencils, in a handwriting that became progressively more decipherable to a student with the time spent at IGC.

The popularity and attractiveness of the IGC group to students within and outside ETH certainly also had a lot to do with Wilfred's skills as a speaker and teacher. All gathered in a quite busy fall semester, the four courses taught by Wilfred were quite popular among the students. Equally popular were the one-week courses on biomolecular modeling that he organized between 2008 and 2012, three times in Kandersteg (Switzerland) and twice in Hefei (China). In these workshops, graduate students, predominantly from experimental groups, could benefit from a hands-on introduction to MD techniques and to GROMOS, in a setting that associated theory lectures and practical projects with scientific and social interactions in a rather unique fashion.

Over the past 22 years at ETH, Wilfred has also taken a very active part in the political and administrative life of the institution, always representing an influential, positive, and common-sense oriented driving force. Just to mention a few, he took mandates of head of the Competence Centre for Computational Chemistry (1993−2005), head of the Laboratory of Physical Chemistry (1995−1997), and president of the Informatikkommission (1997−2005), and was twice head of the Department of Chemistry (2000−2002 and 2006−2008).

After the celebration of his 60th birthday in 2007, including a special colloquium organized by the Laboratory of Physical Chemistry and a surprise event at the "Ruderclub" of Zürich organized by the IGC group members and alumni, Wilfred had to start slowly thinking about the time of retirement. Not necessarily an easy perspective for someone so active and energetic as Wilfred, and so socially involved in his scientific community, colleague circle, and research group. At present, although the size of the IGC group is progressively decreasing, it is quite clear that retirement from ETH is by no means an end, but rather another step in his career. Wilfred will certainly remain very active in

science and still has many ideas in reserve to go on developing the research field he pioneered 35 years ago.

But to all those who have interacted with him over these years, as mentors, colleagues, alumni, or friends, the influence of Wilfred has been personal as much as scientific. People have always been as important to Wilfred as science. Owing to his generosity and ease in social contact, his scientific colleagues see him as a friend, and all the past and present IGC group members have the feeling of belonging to one big family. **Philippe H. Hünenberger**

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Notes
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■ REFERENCES

(1) van Gunsteren, W. F. Group for computer-aided chemistry (Informatikgestützte Chemie, IGC), established at the Department of Chemistry of the ETH Zürich in 1990 by Wilfred van Gunsteren. http://www.igc.ethz.ch (accessed August 2012).
(2) Berendsen, H. J. C. *Report of the CECAM workshop on models for protein dynamics*; Berendsen, H. J. C., Ed.; CECAM: Orsay, France, 1976.
(3) van Gunsteren, W. F.; Berendsen, H. J. C. Computer simulation of molecular dynamics: Methodology, applications and perspectives in chemistry. *Angew. Chem., Int. Ed.* **1990**, *29*, 992−1023.
(4) van Gunsteren, W. F.; Berendsen, H. J. C. *Groningen Molecular Simulation (GROMOS) Library Manual*; BIOMOS: Groningen, The Netherlands, 1987.
(5) van Gunsteren, W. F.; Mark, A. E. Validation of molecular dynamics simulation. *J. Chem. Phys.* **1998**, *108*, 6109−6116.
(6) van Gunsteren, W. F.; Billeter, S. R.; Eising, A. A.; Hünenberger, P. H.; Krüger, P.; Mark, A. E.; Scott, W. R. P.; Tironi, I. G. *Biomolecular Simulation: The GROMOS96 Manual and User Guide.*; Verlag der Fachvereine: Zürich, Switzerland, 1996.
(7) van Gunsteren, W. F. The GROMOS software for biomolecular simulation. http://www.gromos.net (accessed August 2012).
(8) van Gunsteren, W. F.; Bakowies, D.; Baron, R.; Chandrasekhar, I; Christen, M.; Daura, X.; Gee, P.; Geerke, D. P.; Glättli, A.; Hünenberger, P. H.; Kastenholz, M. A.; Oostenbrink, C.; Schenk, M.; Trzesniak, D.; van der Vegt, N. F. A.; Yu, H. B. Biomolecular modelling: goals, problems, perspectives. *Angew. Chem., Int. Ed.* **2006**, *45*, 4064−4092.