

Obituary: Nico van Nuland 1961–2017

André Matagne¹ · Christopher M. Dobson²

Published online: 17 August 2018

© European Biophysical Societies' Association 2018

Abstract

This tribute to the life and work of Nico van Nuland highlights his interdisciplinary application of biophysical methods, especially high-resolution NMR spectroscopy and molecular dynamics simulations, to improve significantly our understanding of the structure, stability, dynamics and folding of proteins, and particularly of protein–protein interactions. His work as a colleague, team leader and collaborator highlights the importance of building scientific communities and of maintaining them, and of educating new generations of scientists.



Nico van Nuland was born into a family of farmers, on the 13th of June, 1961 in Schijndel (North Brabant), The

Netherlands. He was proud of his rural origins and he loved his native region. After graduating from secondary school, he obtained in February 1985 a teacher's degree in Chemistry and Biology from the 'Nieuw Leraren Opleiding', Moller Institute, Tilburg. He then worked until September 1986 in Oss, as a Chemistry, Biology and Mathematics teacher in a secondary school and also in an evening school for adults.

While teaching he also obtained a certificate in Mathematics, which enabled him to enroll at the Wageningen Agricultural University (now called Wageningen University and Research) in the Molecular Sciences program. He studied Physics, Physical Chemistry and Biological Chemistry, and he concluded his studies with two research projects. Thus, his master thesis was devoted to ²H-NMR studies of the interaction between the M13 coat protein and lipids, which he undertook under the supervision of Marcus Hemminga. Part of this project was conducted in the Department of Biochemistry at the University of Oxford, in collaboration with Anthony Watts. Nico also spent 3 months at the Department of Theoretical Physics of the Royal Institute of Technology, Stockholm, where he performed molecular dynamics simulations on the same protein–lipid system, under the guidance of Olle Edholm. After obtaining his diploma in Molecular Sciences on the 25th of June 1990, Nico received a PhD grant from the Netherlands Organization of Scientific Research (NWO) and joined the Departments of Biochemistry and Biophysical Chemistry at the University of Groningen. There, he wrote a thesis under the supervision of George Robillard and Ruud Scheek, describing the use of NMR spectroscopy to study the phosphocarrier HPr protein from *E. coli*; he obtained his doctorate in Mathematics and Natural Sciences on the 25th of November 1994.

✉ André Matagne
amatagne@ulg.ac.be

¹ Laboratory of Enzymology and Protein Folding, Centre for Protein Engineering, Department of Life Sciences, University of Liège, Building B6C, Quartier Agora, Allée du 6 Août, 13, 4000 Liège (Sart-Tilman), Belgium

² Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, UK

On the 16th of August, 1994, Nico joined the group of one of the authors of this article (Chris Dobson) at the Oxford Centre for Molecular Sciences (OCMS), University of Oxford, with a European Community (EC) ‘Human Capital and Mobility’ (HCM) postdoctoral fellowship for a two-year period, where he was a contemporary of the other author (André Matagne). His research project was entitled ‘The folding pathway of the histidine-containing phosphocarrier protein from *E. coli*’. Most significantly, in a close collaboration with Jochen Balbach and Vincent Forge, two other postdoctoral fellows in the Dobson group, he played a key role in the development of new NMR methods to follow protein folding in real time [see, e.g., (Balbach et al. 1995, 1996, 1997; Van Nuland et al. 1998)]. This approach involved the combined use of rapid mixing techniques and NMR spectroscopy to monitor directly, at the level of individual residues, the formation of structure during the folding of a series of representative proteins (e.g., α -lactalbumin, HPr and acylphosphatase). The results revealed the highly cooperative nature of the folding process and provided key information on the nature of folding intermediates, and on the way in which the amino acid sequence of a protein defines its ability to fold. These experiments generated a great deal of interest and enthusiasm from all participants, and there is no doubt that this work was a real highlight of the research activities being carried out in OCMS at that time. These were years of great science but also of sharing ideas, sincere friendship and true happiness in the Dobson group. Many of us have especially fond memories of those days in Oxford, a “golden era” (Carol Robinson) for many members of the group to which Nico “added an extra sparkle” (Lorna Smith).

Following the OCMS years, Nico went back to work with Ruud Scheek (University of Groningen) for one year, on a EC ‘Training and Mobility of Researchers’ (TMR) return grant. He continued the collaboration with Chris Dobson and he was involved (also with Denis Canet, Charles Lyon, George Robillard and Peter Hore) in the combination of kinetic NMR experiments with photo-CIDNP (chemically induced dynamic nuclear polarization) spectroscopy to gain information in real time about the early stages of folding. In June 1997, Nico moved to the University of Granada (Spain), where he worked until the end of 1999 in the group of Pedro Mateo, as part of a European TMR Network on protein folding and misfolding. In this context, he started collaborations with Ana Azuaga and Francisco ‘Quico’ Conejero-Lara, two former postdoctoral fellows and friends from the Dobson group. Then, from January 2000 until August 2004, Nico returned, with Ana Azuaga, to the Netherlands, where he became Supervisor of the European NMR Large-Scale Facility in the group of Robert Kaptein and Rolf Boelens, at Utrecht University. He was also Lecturer in the Faculty of Chemistry. These were years of intense scientific

productivity together with Robert Kaptein, Rolf Boelens and Alexandre Bonvin. Most significantly, Nico supervised Shang-Te Danny Hsu (a PhD student with Robert Kaptein, and subsequently another postdoctoral fellow with Chris Dobson) and published his most highly cited article (Hsu et al. 2004). Using high-resolution NMR spectroscopy, Nico and his colleagues solved the solution structure of nisin, a lanthionine-containing antibiotic with unique pore-forming activity against bacteria, in complex with the essential precursor of cell wall synthesis, lipid II. These data provided a rationale for the conservation of the lanthionine rings among several lipid II-binding lantibiotics and generated a platform for structure-based design of novel antibiotics.

Nico spent four and a half years as Supervisor of the Utrecht NMR Facility, where he demonstrated his enthusiasm for research and his networking skills, establishing strong links within the NMR community in the Netherlands and indeed internationally. During this time he also became an influential member of the Dutch NMR Discussion Group, and played a key role in organizing the first EUROMAR meeting (2005) in Veldhoven, The Netherlands. Then, at the end of 2004, Nico, Ana and their two children, Nicolas and Mara, returned to Spain, and Nico and Ana joined the Department of Physical Chemistry and the Biotechnology Institute at the University of Granada. Nico was supported by a Ramon y Cajal fellowship from the Spanish Government, and was responsible for the renovation of the NMR Centre, including the establishment of a Biomolecular NMR Facility. He revived his research activities with Ana Azuaga and Francisco Conejero-Lara, working in particular on the structure, dynamics and function of SH3 domains, together with Jose Luis Ortega-Roldan, a PhD student in the group. During this period, they developed together a robust approach to the exploitation of the unique orientational information available from RDCs in the case of weak interactions and rapid exchange between free and bound forms of SH3 domains (Candel et al. 2008; Ortega-Roldan et al. 2007, 2009, 2011, 2013).

In January 2009, Nico was appointed a Group Leader at VIB (Vlaams Instituut voor Biotechnologie) and a Research Professor at the Vrije Universiteit of Brussel (VUB), being given the task of establishing a High-Field Biomolecular NMR Centre in Belgium; it was officially opened on May 7th, 2010 and proudly named the Jean Jeener NMR Centre. Together with Remy Loris, Nico led the Molecular Recognition Group and was responsible for the establishment and management of the NMR Centre, for which, as Kristin Bartik commented, “The funds were already secured but Nico had the vision and, even more importantly, was the soul of the Centre”. These years were again very rich in terms of collaborative work and scientific output, including many co-authored papers (for a few references, see (Garcia-Pino et al. 2010; Salmon et al. 2011, 2012; Guerry et al. 2013;

Sterckx et al. 2014; Hubin et al. 2015) with Abel Garcia-Pino, Lieven Buts, Alex Volkov, Remy Loris, Tom Lenaerts, Kris Pauwels, all in Brussels, and also Martin Blackledge, in Grenoble, and Kerensa Broersen, who is now in Twente.

Nico's major scientific interests were in improving our understanding of the fundamental properties of biological systems, including the structure, stability, dynamics and folding of proteins, and particularly protein–protein interactions, using biophysical techniques, particularly high-resolution NMR spectroscopy and molecular dynamics simulations. During his years of research in a variety of prestigious European institutions, Nico collaborated with a wide range of different people, including masters and doctoral students, postdoctoral fellows, and senior scientists. He was a member of numerous scientific committees; he organized conferences, evaluated projects and participated in thesis defense committees.

Many of those people who worked closely with Nico over the years have sent comments on his unique characteristics. “He had a lot of charisma (perhaps associated in part with his mustache) and everyone could see just how much he enjoyed each and every moment shared with others, whether it was at work or at a party” (Vincent Forge). He “touched many people in his own authentic way” (Kris Pauwels) and will be remembered as a “positive, cheerful, enthusiastic, friendly and very sociable person” (Hui Lu, Lorna Smith, Carlo van Mierlo). Nico always encouraged and supported those people with whom he worked. As Kris Pauwels and Abel Garcia-Pino remember he “taught us many valuable lessons and was a great mentor”. Indeed, many young scientists consider him to have been vitally important in shaping their careers, and they cherish each and every memory of him. “Nico was a breath of fresh air for every PhD student who was completing a thesis” said Abel Garcia-Pino. “He was indeed an advocate of the importance of human relations in science, and he always encouraged young researchers to travel to meetings or workshops, or to visit other laboratories to learn new techniques.”

During his many productive years, as Abel Garcia-Pino remembers, “his office was typically full of students learning how to assign protein NMR spectra, working out the best way to overcome a particular problem or simply sharing a good cup of coffee at mid-day. Such intellectual and social exchanges permeated his whole being, and are some of the most long lasting memories from that time, together with his unwavering enthusiasm for science”. Nico was “a very passionate researcher, who used to say that NMR spectra were exciting puzzles to solve. He was always enthusiastic about new experimental challenges and it was great fun to share his excitement about the experiments and the resulting data” (Kerensa Broersen, Francesco Conejero-Lara). “Scientifically, he was imaginative and courageous, and was never scared to take on a challenge in NMR spectroscopy, no

matter how difficult or daunting the task” (Sheena Radford). As reflected in the variety of very different places in which he worked during his career, Nico was not afraid either of new and unknown environments. “He had a no-nonsense approach to problems and was always open to new ideas and fresh insights, and cultivated a distinctive image, yet again reflected in his dedication to the state of his moustache, while ensuring that everyone recognized that they could rely on him for advice and friendship. His enthusiasm to tackle new challenges and his passion to experience life to the full were evident in his work and reflected his personality” (Harmen de Jongh). “His legacy of a long list of papers and an even longer list of friends and colleagues around the world, who miss him greatly, is testament to the impact he had in his all-too-short time with us” (Sheena Radford).

Then in the Spring of 2012 came the shocking and completely unexpected news that Nico had been diagnosed as having Amyotrophic Lateral Sclerosis (ALS), a progressive and highly debilitating neurodegenerative disease that affects voluntary muscle function. Despite the progression of his illness, Nico kept working until it became physically impossible for him to do so. Many of us remember him at the University of Liège on August 31st, 2012, as a guest of the Belgian Biophysical Society, participating in the 10th one-day symposium on *Protein Folding and Stability*, organized annually by André Matagne. The conference was chaired by Roger Pain and attended by both of us together with a number of former postdoctoral fellows of the Dobson group, namely Francisco Conejero-Lara, Vincent Forge and Jochen Balbach. Nico contributed heroically to the event, delivering an extremely insightful lecture on “Communication within and between Proteins”. It was, however, a deeply moving event as the symptoms of the disease were clearly evident. Nevertheless, as Kristin Bartik recollects, “he was also in high spirits when he attended the annual gathering of the Belgian magnetic resonance communities (the 11th YBMRS) in November 2012, where his students and postdoctoral fellows proudly presented the work undertaken in his group.”

The two of us last saw Nico during a visit to his apartment in Leuven, on December 3rd, 2014, only a few weeks before he moved to a hospice in the Netherlands to be close to his family. There, on the evening of November 4th, 2017 his long and courageous fight with ALS came to an end.

All his many friends and colleagues remember Nico as an excellent scientist, a strong and endearing personality, and a warm and loyal friend. May he be where streets have no name, said Louis Matagne, playing for his favorite football team, Ajax, helping them to capture yet another international trophy, hero just for one day...

With contributions from Carol Robinson (University of Oxford), Lorna Smith (University of Oxford), Kristin

Bartik (Université libre de Bruxelles, ULB), Vincent Forge (CEA-Grenoble) Kris Pauwels (Vrije Universiteit Brussel, VUB), Hui Lu (University of Manchester), Carlo van Mierlo (University of Wageningen), Abel Garcia-Pino (Université libre de Bruxelles, ULB), Kerensa Broersen (University of Twente), Francesco Conejero-Lara (University of Granada), Sheena Radford (University of Leeds), Harmen de Jongh, and Louis Matagne.

References

- Balbach J, Forge V, van Nuland NAJ, Winder S, Hore PJ, Dobson CM (1995) Following protein folding in real time using NMR spectroscopy. *Nat Struct Biol* 10:431–437
- Balbach J, Forge V, Lau WS, van Nuland NAJ, Brew K, Dobson CM (1996) Protein folding monitored at individual residues during a 2-dimensional NMR experiment. *Science* 274:1161–1163
- Balbach J, Forge V, Lau WS, Jones J, van Nuland NAJ, Dobson CM (1997) Detection of residue contacts in a folding intermediate. *Proc Nat Acad Sci*. 94:7182–7185
- Candel AM, van Nuland NAJ, Martín-Sierra FM, Martínez JC, Conejero-Lara F (2008) Analysis of the thermodynamics of binding of an SH3 domain to proline-rich peptides using a chimeric fusion protein. *J Mol Biol* 377:117–135
- García-Pino A, Balasubramanian S, Wyns L, Gazit E, De Greve H, Magnuson RD, Charlier D, van Nuland NAJ, Loris R (2010) Allosteric and intrinsic disorder mediate transcription regulation by conditional cooperativity. *Cell* 142:101–111
- Guerry P, Salmon L, Mollica L, Ortega-Roldan JL, Markwick P, van Nuland NAJ, McCammon JA, Blackledge M (2013) Mapping the Population of Protein Conformational Energy Sub-states from NMR Dipolar Couplings. *Angew Chem Int Ed* 52:3181–3185
- Hsu S-TD, Breukink E, Tischenko E, Lutters MAG, de Kruijff B, Kaptein R, Bonvin AMJJ, van Nuland NAJ (2004) The nisin-lipid II complex reveals a pyrophosphate cage that provides a blueprint for novel antibiotics. *Nat Struct Mol Biol* 11:963–967
- Hubin E, Vanschoenwinkel B, Broersen K, De Deyn PP, Koedam N, van Nuland NAJ, Pauwels K (2015) Could ecosystem management provide a new framework for Alzheimer's disease? *Alzheimers Dement* 12(65–74):e1
- Ortega-Roldan JL, Romero-Romero ML, Ora A, Ab E, López-Mayorga O, Azuaga AI, van Nuland NAJ (2007) The high resolution NMR structure of the third SH3 domain of CD2AP. *J Biomol NMR* 39:331–336
- Ortega-Roldan JL, Ringkjøbing-Jensen M, Brutscher B, Azuaga AI, Blackledge M, van Nuland NAJ (2009) Accurate Characterization of Weak Macromolecular Interactions by Titration of NMR Residual Dipolar Couplings: application to the CD2AP SH3-C, Ubiquitin complex. *Nucl Acids Res* 37(9):e70
- Ortega-Roldan JL, Blackledge M, van Nuland NAJ, Azuaga AI (2011) Solution structure, dynamics and thermodynamics of the three SH3 domains of CD2AP. *J Biomol NMR* 50:103–117
- Ortega-Roldan JL, Casares S, Cardenas N, Ringkjøbing-Jensen M, Bravo J, Blackledge M, Azuaga AI, van Nuland NAJ (2013) Distinct ubiquitin binding modes exhibited by SH3 domains of CD2AP: molecular determinants and functional implications. *PLoS One* 8:e73018
- Salmon L, Ortega-Roldan JL, Lescop E, Licinio A, van Nuland NAJ, Ringkjøbing-Jensen M, Blackledge M (2011) Structure, dynamics and kinetics of weak protein-protein complexes from NMR spin relaxation measurements of titrated solutions. *Angew Chem Int Ed* 50:3755–3759
- Salmon L, Pierce L, Ortega-Roldan JL, Mollica L, Guerry P, Ringkjøbing-Jensen M, van Nuland NAJ, McCammon JA, Markwick PRL, Blackledge M (2012) Multi-timescale backbone dynamics of CD2AP SH3C using NMR and accelerated Molecular Dynamics. *Angew Chem Int Ed* 51:6103–6106
- Sterckx YGJ, Volkov AN, Vranken WF, Kragelj J, Ringkjøbing Jensen M, Buts L, Garcia-Pino A, Jové T, Van Melderen L, Blackledge M, van Nuland NAJ, Loris R (2014) Small-angle X-ray scattering- and nuclear magnetic resonance-derived conformational ensemble of the highly flexible antitoxin PaaA2. *Structure* 22:854–865
- Van Nuland NAJ, Forge V, Balbach J, Dobson CM (1998) Real-time NMR studies of protein folding. *Acc Chem Res* 31:773–780