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A career of taking biological species for a spin

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Ahead of his 70th birthday, Adriaan (Ad) Bax, Distinguished Investigator at the National Institutes of Health (NIH), spoke about his career in science.

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How did you decide on a career in science?

I grew up on a farm in the somewhat impoverished southern part of the Netherlands. I was the third of six children and the only one to go directly to university, although my elder sister later obtained a law degree after an initial career as a nutritional assistant.

While I received a chemistry set for one of my birthdays before high school, I did not find it particularly interesting. Instead, my older brother and I explored more exciting hands-on chemistry: building small explosives from fertilizer and diesel fuel, both readily available on the farm. My real interests were in mathematics, which came naturally to me and required little memorization. I was even selected to represent the Netherlands at the International Mathematical Olympiad.

Because I had skipped a grade in elementary school, I had to pick a major at age sixteen, when I entered Delft University of Technology. Thanks to a fabulous high school physics teacher, who asked us to solve problems, I decided to study applied physics. My initial laboratory work involved fluid mechanics and experiments related to nuclear reactor engineering, but that quickly lost its charm. After taking courses in theoretical physics and quantum mechanics, I found the use of NMR spectroscopy as a playground for those fascinating theoretical concepts far more exciting.

Shortly after the death of my father and not wishing to disappoint my mother by abandoning nuclear physics, switching to nuclear magnetic resonance seemed an ideal solution – and until her death, she never knew the difference.

My advisor, Toon Mehlkopf, was a true engineering genius. He was building a futuristic NMR spectrometer capable of carrying out experiments that had not even been invented yet and at least a decade ahead of the commercial manufacturers Bruker and Varian. Richard Ernst in Zurich and Ray Freeman in Oxford were the international leaders in solution NMR at the time, both pioneering two-dimensional NMR methods. While working on improvements of Ernst's future Nobel Prize-winning experiments, Ray heard about Mehlkopf's 'miracle instrument' and invited me to Oxford for what was supposed to be a short visit. It eventually turned into nearly three years, with me periodically taking the ferry back to Holland to carry out Ray's latest crazy experiments. Being surrounded by exceptionally bright peers in Ray's group, together with his wonderful mentoring style – he basically gave us free rein to explore – convinced me that academic research was where I belonged.

How did you decide to focus your research efforts on analysing the structure and dynamics of complex biological species?

During my PhD work in Oxford, it became clear that although advanced NMR applications to organic chemistry were interesting, the truly important challenge was applying NMR to proteins and nucleic acids. This became even more obvious through my interactions with international leaders Iain Campbell, Chris Dobson and their groups. However, with only a 200 MHz spectrometer available, we simply were not capable of doing anything very useful in that area.

A few years later, during my postdoctoral work with Gary Maciel at the US National Solid-State NMR Center at Colorado State University, Rich Griffey, a student of Dale Poulter, was trying to carry out painstaking double-resonance experiments on a ^{15}N-labelled tRNA sample using the Center's 360 MHz spectrometer. I realized that two-dimensional (2D) NMR was the perfect solution for this problem and with help from Bruce Hawkins, who rebuilt the equipment for this purpose, we obtained 2D ^{1}H–^{15}N correlation spectra on what at the time was considered an extremely dilute sample.

That work pulled me away from the attention-grabbing solid-state NMR experiments I had been pursuing and got me excited again about biological systems in solution.

What breakthroughs have you been most proud of in your career so far?

I have been fortunate to stumble onto several fortuitous findings, mostly – but not entirely – related to technically challenging advances in NMR that later turned out to have long-term impact.

Indirect detection of weak ^{13}C and ^{15}N signals through the much more sensitive attached protons had already been proposed by Richard Ernst but demonstrating that this actually worked for molecules such as tRNA was one early highlight of my work. Another was the development of triple-resonance NMR methods that made it possible to analyse proteins far too complex for existing proton-only methods. Our experiments also opened the door to detailed studies of internal protein dynamics.

A problem I had wrestled with since my postdoctoral days in Colorado was how to merge the dipolar coupling information accessible in solids with the superb spectral resolution available in solution NMR. While listening to a talk by Olle Söderman on zeolites – a subject I was not particularly interested in and attended mostly to pass time before my own lecture – it suddenly occurred to me that dissolving proteins in an aqueous suspension of Olle's magnetically oriented particles might allow precise measurement of dipolar couplings. That unexpected connection ultimately transformed both protein and nucleic acid NMR and remains one of the highlights of my career.

More recently, during the COVID-19 pandemic, the issue of airborne virus transmission caught my attention. Sophisticated epidemiological models based on superspreading events seemed incompatible with what medicine considered the required infectious dose of virus. Inspired by my wife, a sociolinguist, we suspected ordinary speech might generate far more airborne particles than appreciated. Together with my colleague Phil Anfinrud, we used his laser scattering setup – originally designed for optical protein studies – to visualize speech droplets directly. We found particle concentrations orders of magnitude higher than detected by standard aerosol counters and showed that after rapid dehydration these particles remained airborne for many minutes. What this meant was that not only was airborne COVID transmission entirely feasible but also that ordinary speaking was likely to be its main driver. At the time, this was tremendously exciting with immediate real-life applications.

Given the interdisciplinary nature of your research, how do you go about communicating your science to those in different fields and members of the public?
I must admit that communicating my ideas outside my own area of expertise is one of my weaker points. Modern science has become highly specialized, with each field developing its own jargon and assumptions. In that respect, the COVID pandemic was eye-opening as I realized that we frequently erroneously assume that our colleagues in other fields share the same knowledge and perspective. I try to improve such cross-disciplinary dialog by focusing on solving a shared problem. As far as communicating my science to the public, as you know, as a government employee I am highly restricted when talking to media organizations. But again, the knowledge gap is even more pronounced. The public expects quick and definitive answers to a problem while we as scientists deal much more in data and nuance. I try to explain my work by using examples that describe how my discoveries might impact people's lives and health. My wife is a good sounding board in that respect.

What is your approach to deciding research directions?
I tend to jump on questions that I find interesting, even if the payoff is not immediately obvious, and I have been extraordinarily fortunate that my position at the NIH has allowed me to do exactly that. Because our funding is based largely on retrospective evaluation, I have had the freedom to pursue new ideas without delay instead of spending years writing grant applications first.

What do you see as the interesting avenues for future research?
Over the past four decades, the complexity of systems that NMR can study in extraordinary detail has grown exponentially, often with little competition from other technologies. However, training of young spectroscopists has not kept pace with these developments, making it difficult to fully exploit the power of modern NMR methods.

Quantitative studies of molecular motions – for example atomic-level motions associated with ligand binding and signal transduction – remain among the lowest-hanging fruit.

More generally, how has the culture of science changed over your career?
I am not sure whether it is truly a cultural change, but younger scientists today seem to approach career planning very differently from when I started, partially due to increased competition. I never planned more than a few weeks or months ahead and did not worry much about where I would end up. Today there is much greater emphasis on systematic career planning, job security and salary considerations, which of course puts science at a disadvantage relative to more financially rewarding professions.

Another change is that with increasingly complex real-life problems, science has, and must, shift towards collaboration across a wide range of disciplines, including the behavioural and social sciences.

What would be your advice for the next generation of scientists?
I would encourage young scientists to choose problems, not fashions. Some of the most rewarding work comes from questions that initially look unfashionable or are not easily solved by artificial intelligence.

I also think it is essential to develop a deep understanding of fundamentals. Techniques evolve rapidly, but intuition grounded in physics, chemistry and quantitative reasoning remains invaluable.

It is equally important to remain intellectually flexible. Increasingly, the most interesting science happens at the interfaces between disciplines. When I began my career, the boundaries between chemistry, physics, biology and computation were much sharper than they are today. Young scientists now have extraordinary opportunities to move between fields and combine ideas in new ways.

Finally, science requires patience and resilience. Research often progresses much more slowly than expected, and setbacks are unavoidable. Several of my own projects, including the measurement of dipolar couplings, appeared unsuccessful for a very long time. Persistence matters, but so does maintaining curiosity and enjoyment in the process itself.

What is next for you?
I sometimes wish I had another seventy years because there are more promising ideas now than ever before.

Realistically, I hope to round out several ongoing NMR projects related to protein motions and amyloid formation, together with two medically oriented projects involving diagnostics of lung disease and prevention of pneumonia. The latter began with NMR studies of chemical tracers but now has gradually evolved into collaborative clinical work. Fortunately, there still seem to be far more interesting problems than remaining time.

Ad Bax was interviewed by Stephanie Greed

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Competing interests
A.B. declares no competing interests.