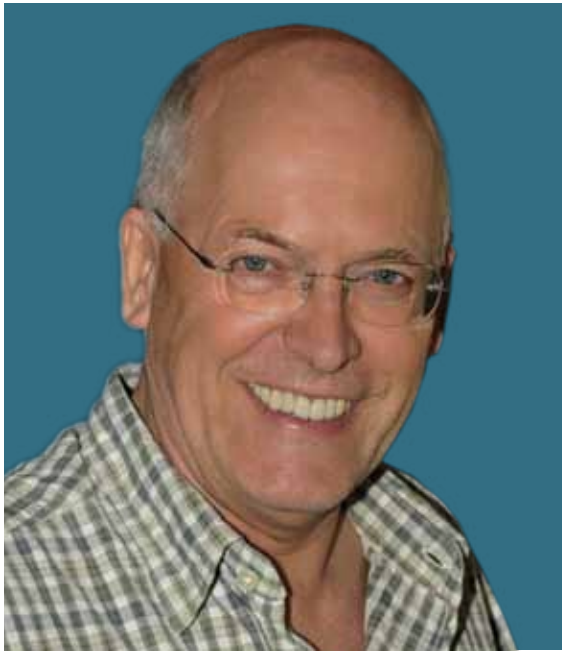
JAN-HENDRIK HOFMEYR



TOP THREE AWARDS

- Harry Oppenheimer Fellowship Award and Gold Medal, 2002
- Beckman-Coulter Gold Medal of the South African Society for Biochemistry and Molecular Biology, 2003
- Havenga Prize for Biological Sciences from the *Suid-Afrikaanse Akademie vir Wetenskap en Kuns*, 2009

DEFINING MOMENT

"All my defining moments were linked to books." He reveres the authors who have influenced him and is very deliberate in pointing out which thoughts belong to others in his field, which thoughts are his, and how his thoughts have been shaped by the works of others.

WHAT PEOPLE DO NOT KNOW

Hofmeyr is a musician, cabaret artist and actor, and he helped launch Afrikaans *Kabaret* in the 1970s and 80s in South Africa. "Music and theatre keep me sane. But I don't have time to practise the flute and guitar every day. And if you can't practise every day, your technique goes to the dogs."

PERSPECTIVES ARE TO BE SHIFTED

In academia, change often happens slowly. Academics are born into a paradigm and, more often than not, they maintain that paradigm rather than interrogating and critiquing it. It is rare to find a researcher who is willing, much less eager, to look outside of his or her field and recognise when a paradigm can be improved upon or discarded entirely. Such an academic is Jannie Hofmeyr, Distinguished Professor at Stellenbosch University (SU).

Hofmeyr is unique in his constantly shifting perspective on his field and on science in general. He has moved from experimental to theoretical, from parts to the whole, from a dedicated discipline to interdisciplinarity. "What I like is to start something," he said, "to be out there where the buses don't run in the first place. That for me is fun. Then I start something and see if I can build it up and then I try something else. I've made big jumps in my life."

Perhaps his willingness to embrace change was instilled in him from a young age. Hofmeyr was born in Durban and lived in Pietermaritzburg until his father became the immigration attaché in Holland. Hofmeyr then lived in Holland until he was seven before coming back to South Africa where his family settled in Johannesburg. After matriculating and spending a year in the navy, Hofmeyr moved to Stellenbosch. From his well-travelled childhood, it may surprise some that he stayed at SU and has been there for 41 years. While it is common, even advised, for young academics to split their training among several institutions, Hofmeyr has never regretted staying put. "Stellenbosch is such a fantastic place. You get to go everywhere in the world anyway for research and conferences, so I've never regretted staying."

Hofmeyr began his academic career during his Honours year. After obtaining his BSc biochemistry/microbiology (*cum laude*) from Stellenbosch in 1974, he started his Honours and began working in the Biochemistry Department. "I was appointed temporary junior lecturer. Lower than that, you cannot start." From this lowest point, he has expanded outwards and upwards until reaching the status of Distinguished Professor with an NRF A-rating since 1999. He has served many roles at the university, including Acting Head of Department (1991), Departmental Chair (1995 – 1998, 2002), Deputy Dean of the Faculty of Science (1999), and currently is the Co-Director of Stellenbosch University's Centre for Complex Systems in Transition. Hofmeyr's first transition in academia was from biochemistry to systems biology. Hofmeyr describes biochemistry as the most reductionist biological science. In the classic approach to understanding metabolic reactions, the building blocks and products of a single reaction are treated in isolation of the system that contains it. However, these reactions are rarely (if ever) isolated in a living system and have interactions influenced by factors at a reaction level, a cell level and an organism level. "You have to have an understanding of how all the pieces work together."

While he was grappling with this paradigm of biochemistry, Hofmeyr read a paper that changed his life. *The Control of Flux* by Henrik Kacser and Jim Burns (1973) described how the rate of a metabolic pathway could be influenced by the change in amount and activities of the enzymes in the pathway. The authors shared Hofmeyr's misgivings about treating metabolic systems and enzymes in isolation and attributing metabolic fluxes to a single, predictable control mechanism. "When I read that, I thought – this is mind-blowing, this explains most of what has been bothering me about the control and regulation of metabolic pathways."

The paper led Hofmeyr to become interested in the behaviour of biochemical systems and to understand what happens when systems are coupled together. To study these systems properly, he also bought his first computer (a ZX81 by Sinclair) and learned to code. "I realised you had to simulate the dynamic behaviour of metabolic pathways because it was very difficult, especially at that stage, to study it experimentally." He took the reductionist properties derived from biochemistry and tested how they behaved when put into a model.

EMERGING FIELD

The theoretical field that Hofmeyr entered was unnamed at the time. It later became systems biology. Hofmeyr remembers when there were only five or six people in the world with this focus. He brought this emerging field

into South Africa and established the first systems biology group, the Triple-J Group for Molecular Cell Physiology, dedicated to studying the control and regulation of cellular processes using theory, modelling and experimental approaches. "Systems biology was unique is South Africa, and then it became a huge thing internationally. It was the word you put in your grant proposals to get money; it was the cash cow."

Nonetheless, Hofmeyr seems to have outgrown systems biology. Over time, he saw the field fall into description rather than explanation. "The human genome project was this huge thing, it promised to tell us everything about life, which of course it doesn't." While it is important to look at the whole picture, seeing the whole picture doesn't necessarily explain the relationships between the individual elements. "What happened was all these high throughput technologies got developed. You can now measure virtually everything in a cell." Hofmeyr calls this system-wide biology and complains that just because you can measure it doesn't mean you know how it works and interacts with different elements in the system. "Systems biology needs a new view, a new way of looking at systems, not in terms of looking at the components, but looking at the relationships between."

This of course is the hallmark of complexity, where the relationships between components have characteristics that would not be predicted by looking at only the isolated parts. "If you have a system like that where the relationships are also important, then that system as a whole has properties that you cannot find in any individual component." This is what is described as emergent properties. Hofmeyr learned from complexity theory that while modelling may be helpful in some cases, modelling cannot always capture emergent properties.

Hofmeyr was introduced to complexity by Paul Cilliers. They became fast friends and were very interested in working together. However, the university was not an easy place to collaborate across faculty boundaries. "The snag was that I was in the Faculty of Science, he was in the Faculty of Humanities, and never the twain shall meet." Hofmeyr and Cilliers applied for funding for a Centre for Studies in Complexity. It started off with just the two of them and Rika Preiser as their research assistant. "The goal was to keep it small and develop modules for courses that have to do with systems and complexity." One lecture they taught was called *Complexity – from Molecules to Morality*. "That's what you had to cover. It's a very broad topic." Although Cilliers passed away in 2011, the essence of his teaching can still be found embedded in the lectures Hofmeyr continues to give.

CHANGED BY A BOOK

In 1996, Hofmeyr was again changed by a book. He remembers walking into a local bookshop in Stellenbosch and stumbling upon a book called *Life Itself*: *A Comprehensive Inquiry into the Nature, Origin, and Fabrication of Life* by Robert Rosen (1991). "I had heard of him before because he had written a book called *Dynamical Systems Theory* which addressed the sort of things I had been doing with my modelling." Rosen, a theoretical biologist and trained mathematician, had written *Life Itself* as a pursuit of a central problem he had spent his career interrogating – What is the difference between living and non-living systems? The book is rooted in category theory, which Hofmeyr had to learn in order to really understand and appreciate Rosen's perspective. "That really took over my life. That's what I did in the evenings."

Reading the book changed how Hofmeyr viewed the complexity of life. "Even coming from a systems point of view, it was still so radical." The main lesson he derived from Rosen was that a living system is able to remake itself in the face of complete turnover. Living things are like factories that remake the entire factory floor from raw materials as every single instrument decays and all the machinery gets replaced autonomously without any help from outside. "We all know that, but we don't think about how special that is. That's what makes us different from the factories that we build. It means a very special functional organisation, fabricating itself as it goes along."

While Hofmeyr was inspired by this new outlook, he still had questions. Rosen had handled the concept in a very abstract way without getting down to the details of functionality. Hofmeyr saw that he could contribute to this understanding with his training as a biochemist. "I know what's inside cells, I want to know how self-fabrication works at that level." Hofmeyr's

excitement for the subject shows in how he describes it. "While you are sitting there, you are making yourself. Every part of you is fragile. You persist longer than any molecule in your life. In a year's time, virtually all of your atoms will have been replaced, but you will still be you."

In an attempt to address this gap between abstract and functional, Hofmeyr has come up with a new way of modelling. It's a linguistic model to describe and capture the functional organisation of life. He has just returned from overseas where he had dedicated his time to writing a book on the subject. While he wasn't able to finish his book, he has worked out the model and has presented it at conferences. He describes it as "a model that captures the idea of self-fabrication in terms of what we know happens inside the cell".

While much of modern science is geared towards application and improvement of society, Hofmeyr's contributions to biocomplexity and biochemistry are about improvements in thinking. "We are living creatures, we want to understand what we are." Hofmeyr explained that from the days of Descartes, machines have been a metaphor for life. Descartes was fascinated by hydraulic automata that mimicked living organisms. These automata can be interpreted in two ways. The first that automata are very life-like, or the second, that life is very automata-like and we are really machines. "Unfortunately he took the second route, but the other one is more obvious to me. These things simulate aspects of life, but of course we are much more complex than that." Regardless of how obvious it is, we have been living for centuries with the machine metaphor for life. "That makes you think about yourself and about other organisms in a particular way – which I think is very bad." Hofmeyr and others in his field have been turning that metaphor around and showing that life is a complex set of interactions that must be understood on its own terms.

Beyond the experimental and theoretical contributions, Hofmeyr has also contributed to the growth of a new generation of scientists through teaching and supervising. Another contribution is his building of spaces that facilitate the work of others. He has been instrumental in developing the Biochemistry Department, the Stellenbosch Institute for Advanced Study (STIAS), and the Centre for Studies in Complexity. He has also helped to put together a proposal for the university's NRF Flagship Programme, the heart of which is a new research centre called the Centre for Complex Systems in Transition. The centre is dedicated to integrating the research fields of complexity, sustainability and transdisciplinary methodology and their application in water management, cities, renewable energy, and food systems. "For me, this is really about developing the platform for our fantastic young people to do their thing."

Hofmeyr wants young people to follow their dreams rather than be forced to conform to a particular way of thinking or a narrow area of study. "Don't let yourself be bamboozled into a straightjacket." He believes that you need dreams in order to pursue science and that pursuit must be framed by a question that drives the research. "Oh," he adds, "and learn how to write. Research is only half of the output. Reporting that research is the other half. Then, in a world where so much nonsense is written, try and maximise your signal-to-noise ratio."

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