LIVING CELL THEORY AT THE WIKO

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I am currently the Distinguished Professor of Biocomplexity and Biochemistry at the University of Stellenbosch in South Africa and Co-Director of the Stellenbosch Centre for Complex Systems in Transition. I have been at Stellenbosch University since 1975. My research of the past 30 years has been in the field of theoretical systems biology, using mathematical and computational approaches to study the control and regulation of metabolism. A research highlight has been the development of supply-demand analysis, which provides a view of the functional organisation of the cell as an integrated molecular economy of coupled supply and demand systems that have evolved regulatory mechanisms that enable them to fulfil specific functions such as control of flux or homeostatic maintenance of metabolite concentrations. In recent years I have become interested in seeking ways of expressing formally the functional organisation of the cell in terms of a theory of molecular self-fabrication, a calculus of life, so to speak. This has led me to a broader study of complex systems – not only of biological systems, but also of ecological and sociological systems. – Address: Department of Biochemistry, University of Stellenbosch, Private Bag X1, 7602 Matieland, South Africa. E-mail: jhsh@sun.ac.za

What is life? This fundamental biological question has been asked since the dawn of humankind, but it is only in recent decades that we have gained enough understanding of the molecular workings of the living cell to start formulating a satisfactory answer. It was this question that I wanted to tackle during my Wiko Fellowship year and that would form the basis of a monograph. As discussed below, the first task has been accomplished to my satisfaction, and would not have been possible without the uninterrupted study

time provided by the Wiko Fellowship and without the support of the wonderful Wiko library staff, who provided me with books and papers that I would not have been able to access in South Africa. The completion of the monograph remains a future, but now urgent project (what comes to mind is the paraphrase of Robert Burns' famous line from the poem *Tae a Moose*: "The best-laid plans of mice and men / Often go awry.").

To understand just how radically this new answer to the "What is life" question changes our view of ourselves and other life-forms, it is necessary to juxtapose it with the modern reductionist view of life, namely that a living organism is essentially a machine, a view that we inherited from René Descartes and Isaac Newton and that has since then dominated Western thought. Descartes was enamoured of the hydraulic automata that were popular in his time, and from their lifelike behaviour he made the fateful deduction that life is machine-like, and so the machine metaphor of life was born. Had he but made the much more sensible conclusion that these automata were lifelike instead of that organisms were automaton-like, we would have approached biology quite differently and may have avoided many of the environmental catastrophes of the modern age.

One way of distinguishing a machine from a living cell is in terms of purpose. A machine is a deterministic system designed to fulfil a purpose set by its designer: it has no internal purpose of its own, and its parts have no purposes of their own, only purposes with respect to the machine itself. The cell, on the other hand, has a clear internal purpose of its own, and that is to persist as a material entity in the face of fragile parts that need continuous replacing. In my Wiko Colloquium I contrasted a car with the living cell. Your car is a machine built from persistent parts; when a part fails, you or a mechanic has to replace it before the car can again fulfil its function. In contrast, when a component in one of your cells fails it is replaced by the cell itself. In fact, whether we are bacterial, plant or animal, every single part in each of our cells is replaced or repaired, not from without but from within: cells are biochemical factories that uninterruptedly and autonomously fabricate and maintain themselves. The primary purpose of every living organism is therefore to fabricate itself. This insight is usually attributed to the theoretical biologist Robert Rosen and his concept of closure to efficient causation or to Humberto Maturana and Francisco Varela's concept of autopoiesis. In Rosen's terms the cell is complex, while the machine is merely complicated. Interestingly, a societal or ecological system is in many respects just like a living cell, except that its individuals are themselves complex and have purposes of their own, while the molecular components of a cell are not. But, one of the most exciting discoveries during my Wiko year was that the Jewish philosopher Hans

Jonas already articulated this view of organisms quite a bit earlier than the others in terms of his broad understanding of the concept of metabolism, from which he developed his whole philosophy, his understanding of humankind and our relation to the rest of nature. Reading Jonas made me realise for the first time what it means to escape from the machine metaphor of life and why the story that I am trying to tell is so important.

What is it that I bring to the table of self-fabrication? In a nutshell, I have developed a formal system, a calculus, through which I can capture the logic of the functional organisation of cellular processes that makes self-fabrication possible. I have followed essentially the modelling strategy of Rosen (and his erstwhile doctoral student Aloisius Louie, who has furthered Rosen's work in recent years), who seemingly approached things from the wrong direction: instead of creating a model of a known natural system, we start with a formal system and then ask whether there is a natural realisation of that formal system. Where I differ from them is my point of departure: instead of their category theory approach, I start with the notion of a formal system that uses production rules to form strings from a limited set of symbols. Cells have a fabrication strategy for making large, linear molecules using a single, conceptually straightforward chemical process – polymerisation – which is essentially string-making. These molecules can therefore formally be viewed as strings (nucleic acids being strings of nucleotides and proteins being strings of amino acids), so mine is an obvious starting point. The trick then is to ask how the production rules themselves can be created within the system: this would equate to the system being closed to efficient causation, which would, in a formal system, at the very least require the fabrication of the production rules themselves as symbol strings within the system. But, just as a linear polymer must fold into a specific three-dimensional structure before it can become functional, so a symbol string that describes a production rule must in some way acquire semantic meaning before it can do its job. This implies that just as the correct folding of a polymer requires the appropriate chemical context, so a production rule string can only acquire meaning in an appropriate formal context. For example, the rule "join symbols a and b" will only make sense in an English environment; in any other environment it would be a nonsense string. The aim is then to minimize as far as possible the role of the context and to make it clear what exactly the context does.

One of the problems of rules producing strings that become rules is the possibility of infinite regress of rule production. I was able to show formally that the only way to avoid this is to separate the description of the sequence of symbols from the construction of the sequence itself; this in turn necessitates the prior encoding of the sequence and the

subsequent translation of the encoded form of the sequence by a specialised set of rules that are also produced within the system. This is essentially what the genetic code brings to the cell. In this and all other ways, my formal system maps perfectly onto cell biochemistry as we know it, and also shows rigorously that the problem of closure to efficient causation and, therefore, of self-fabrication of a system based on sequence construction can be solved only in one way and that is the way that all life on our planet does it.

Any formal system should be able to be implemented as a computer program, and one of the major tasks that I completed was to program my formal system in the computer language Python, which served as a check on the logical coherence of my arguments and derivations. I presented both my formal system and its computer implementation in June 2015 at the second conference of the International Society of Code Biology in Jena and received excellent feedback. I also had the opportunity to discuss my work with colleagues at the Humboldt University.

Although with my Living Cell Theory project I did more reading and thinking than writing, during my stay in Berlin I did write forewords for two books, namely *Code Biology* by Marcello Barbieri and *Critical Complexity – Collected Essays* by Paul Cilliers, my late friend and colleague. I also wrote a chapter for the book *Philosophy of Systems Biology – Perspectives from Scientists and Philosophers* and co-authored with my Stellenbosch colleagues Carl Christensen and Johann Rohwer a major paper, now published in *BMC Systems Biology*, on the application of our generalised supply-demand analysis to metabolic models.

One of the first things we as new Fellows were assured of was that it was quite acceptable to end up doing projects that were not part of the original plan. While I did largely stick to my proposed project, I also took the opportunity to rekindle two former enthusiasms, namely the classical guitar and watercolour painting. To have the opportunity to practice undisturbed for an hour or so a day was priceless, and I am convinced that I was the only Fellow to discover Berlin through its wonderful art supply shops. I even relearnt all my favourite Jake Thackray songs so that I could sing them at our picnic party. And to be part of the 2014/15 Wiko choir was a real treat, even if our last concert was to happen under the very sad circumstances of Tsering's death.

Berlin, ah, Berlin. What a wonderful city and what a rich culture. There are so many memories and impressions, but what stands out is the music. As a card-carrying string quartet fanatic I had the joy of hearing some of the world's top quartets, most of them in the Kammermusiksaal, which is one of the best auditoriums I have ever been in. And

who can forget the magical and intimate concert given by András Schiff and Yuuko Shiokawa. My love of Baroque music was catered for, amongst others, by Handel's *Solomon* on authentic instruments and René Jacobs's rendition with the Akademie für Alte Musik of Telemann's opera *Emma und Eginhard*. Having the opportunity to get to know our composer Fellow in residence Hans Thomalla and explore contemporary music with him was also very special. Through him I met the members of the Arditti Quartet, especially their cellist Lucas Fels who visited the Wiko and gave a concert, and was privileged to hear them play on two occasions works that I had never heard performed live.

My other passion: bird-watching. I could do quite a bit just by looking out of my Villa Walther apartment windows, first overlooking the Herthasee and later, when I moved to a smaller apartment, the Koenigssee. Two-bird feeders on the balcony and I had the company of a nuthatch, various tits, a tree-creeper, a few jays, a bullfinch, a robin, many blackbirds and a pair of woodpeckers. But nothing compares to being serenaded night after night by a nightingale from across the amphitheatre of the Koenigssee – I never tired of it. Once, in a conversation with Meinrad Kneer, a bird expert who took Caroline McCrudden and me on a few birding trips in the vicinity of Berlin, I complained that the European robin really had a boring call, a repetitive sort of "cheep", and he denied it most indignantly. The very next day, while sitting on my balcony, a robin came and sat less than two meters away from me, singing its heart out most beautifully and proving me utterly wrong. My frequent walks around the Grunewaldsee introduced me to the great reed warbler and its beautiful song. I was also privileged to see the European cranes migrating and the bustards displaying. These are priceless memories.

I have had the good fortune to have been involved from the start in the establishment of STIAS, the Stellenbosch Institute for Advanced Study, and I have witnessed over the years just what it means to be granted a fellowship at such an institution. To now have had first-hand fellowship experience at such an august institute as the Wissenschaftskolleg has been an enormous privilege. That my wife Sukki and my daughters Clara and Nell were able to visit me during December made the long and grey winter more bearable, especially since we were able to visit Prague for a few days and enjoy all the Berlin Christmas festivities with copious cups of *Glühwein*. My daughter Nell's dream of a white Christmas was realised, albeit a day late: we woke up on Boxing Day to a white Grunewald fairyland. My personal quest to regain some proficiency in German was realised through the initial intensive course and Eva von Kügelgen's weekly classes, for which I am very grateful. Our heartfelt thanks to Luca Giuliani, Thorsten Wilhelmy, Daniel Schönpflug

and the entire Wiko staff for making this a year to be cherished and fondly remembered. I could spend another page or two thanking individual staff members who made my stay problem-free and comfortable, but there are just too many. It would however be remiss of me not to single out Sonja Grund and the Library staff, and Vera Schulze-Seeger (now Pfeffer, I see) at the *Empfang*, for whom no problem was too great and who was a mine of information. The requirement of the weekly colloquium and to have lunches and the weekly dinner together is a tradition that the Wiko should never abandon, especially since the cuisine is so excellent. It is here that I made many new Fellow friends and learnt so many new things. All in all, a perfect year.