Squishy matter and active chemistry: understanding membrane organization

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I had just established my laboratory at the National Centre for Biological Sciences (NCBS) in Bangalore, and was recovering from the inevitable stress, when a very cheerful character dropped into my office. He asked if I would be able to explain the properties of cell membranes to him, as he was a physicist from the neighbouring Raman Research Institute, and had just moved from Madras to explore the scientific environs of Bangalore and to see if there were any biologists who knew anything about cell membranes. Just as I began to get rid of him, saying that the chemistry of the cell membrane was complex enough and I did not understand very much about the physical properties of cell membranes, he threw a squishy jelly-like object that looked like a lizard at the ceiling. To our amazement, it stuck there and refused to come down. Until then I had been quite unaware of the whole field of squishy (soft condensed) matter and if I had known it existed, I would have imagined that it would help in the development of face creams and toothpaste. I certainly knew nothing about the huge strides made in this field in exploring 'active' systems, situated away from equilibrium. While we waited for the lizard to detach, a conversation ensued between Madan Rao and myself, which has led to an exciting dialogue that has lasted many years. And one that has been a turning point in my attempts to understand the connection between the chemistry of biomolecules and their behaviour in living cells.

When I was an undergraduate, I went to an engineering school, the Indian Institute of Technology (IIT, Bombay), and found myself in the positivist world of engineering solutions where heat transfer efficiencies and an understanding of fluid mechanics were the order of the day. However, I found myself at odds with the dominant preoccupations in my academic environment and yearned to study biology. I began taking almost every course and elective offered that could provide a whiff of anything biological; I even equated chemistry with biology and immersed myself in the lore of physical and organic chemistry, equilibrium thermodynamics and chemical kinetics. For my undergraduate thesis, I joined the laboratory of (the late) Dr Anil Lala, an enthusiastic bioorganic chemist who was developing photoactivatable probes to study how proteins could insert into membranes. However, when I finally arrived in a pure biology laboratory for my doctorate at the Rockefeller University, I found it deeply intellectually disorienting: there seemed to be more to the story than a chemist's view of biological systems as assemblages of molecules subject to laws so neatly laid out in physical and organic chemistry textbooks.

Extraordinary things were being discovered in biological systems that violated all the chemistry I had learnt: for example in Gunter Blobel's laboratory the world's most complex nano-machine — the ribosome — was busy not only making proteins but also engaging with the translocation machinery as a gatekeeper of protein secretion. How could systems as complex as these ever work or be understood? I decided to stick to simpler biochemistry that I might hope to understand. (I would ask authors to make cuts here done)

I joined the laboratory of George Cross. At the time his laboratory had discovered the structure of a strange glycolipid whose only apparent function was to keep the protective surface coat protein of the trypanosome parasite attached to the membrane. With Anant Menon, a biophysicist from Cornell, I embarked on a 'simple' (bio)chemical expedition to understand how the GPI-anchor of the major variant surface glycoprotein (VSG) is assembled. The rationale was noble: understanding the chemistry of this specific attachment mechanism and identifying a 'chemical' that could poison it to render the parasite defenceless and rid the world of sleeping sickness. Within a year, the GPI-anchor had been discovered in almost all eukaryotic systems as a general, alternative mechanism of permanently anchoring proteins to membranes. I had learnt an important lesson: nothing in biology is either simple or unique. The biology of any organism is a consequence of evolution and survival — something that a chemical system simply does not even have to consider.

For my postdoctoral work with Fredrick Maxfield, I elected to study how GPI-anchored proteins behave in their own special milieu — the membrane — which I have subsequently discovered requires deep understanding of local lipid dynamics and composition in the living cell. Back in India, I set up my own laboratory, focusing on GPI-anchored protein organization in time and space in living cells, which I believe may lead us to discover a new chemical language that cells use to regulate their local molecular environment.

Although the jury is still out, the special chemistry and physics of 'squishy matter' may be key to understanding the mechanism underlying how cells create such crazy molecular assemblies — even if they are made of the same 'chemicals' as artificial membranes. The squishy lizard proved to be the beginning of a rich collaboration with Madan Rao, to explore how active processes that maintain systems far from equilibrium can create cellular structures and regulate composition in living cell membranes.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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