From Pacing the Heart to the Pace of Evolution

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The first mathematical model of heart rhythm (Noble 1962) generated beautiful voltage traces reproducing Purkinje fibre rhythm. It did so with only four channel mechanisms. We now know that cardiac electrophysiology is vastly more complex, as a later model of mine showed (DiFrancesco & Noble, 1985), and we now know even more ion channels and related mechanisms, many of them from the work of Yoram Rudy's group here at Washington University. The complexity arose from iterative interactions between experiments and modelling (Noble & Rudy 2001). So why did the 1960-2 model work so well, and what was so seriously wrong with it?

In this lecture, I also want to ask a deeper, developmental question: why did Nature develop such extensive complexity? One answer is robustness of function. Multi-mechanism interpretations of cardiac pacemaker function reveal the extent to which many physiological functions are buffered against genomic change. The first stage of the lecture will show how an evolutionary perspective informs electrophysiology and how it led to the development of a useful medication.

The conclusion of the lecture will show that this perspective also requires fundamental changes in the theory of evolution. Contrary to Schrödinger's claim in *What is Life?* (1944), which led to the Central Dogma of Molecular Biology (Crick 1970), biological functions at higher levels harness stochasticity at lower levels. This harnessing of stochasticity is a pre-requisite for the processes by which the pace of evolution can be accelerated through guided control of mutation rates and of buffering by regulatory networks in organisms. It is mathematical modelling that has shown how this buffering works. Could future developmental models reproduce this feature of organisms? If so, would that be AI (Artificial Intelligence) or would it be AA (Artificial Agency -- Noble & Noble, 2019)? To update Schrödinger, could it be life itself? Might you fall in love with it – her/him?

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