Raimond Winslow

Raimond Winslow is an outstanding cardiovascular expert and professor in the Department of Biomedical Engineering, Johns Hopkins University School of Medicine, USA. *Current Science* interviewed him to comprehend cellular ion-exchange mechanisms, especially the important role of calcium signalling when faced with a heart failure and other cardiac diseases.

Winslow did BS in electrical engineering from Worcester Polytechnic Institute (1978) and Ph D in biomedical engineering (BME) from The Johns Hopkins University (1985). After training in Washington University in St Louis School of Medicine in the fields of biomedical computing and neurology (1986–87), he returned as a faculty to his alma mater, the Department of Biomedical Engineering, in 1991 and became a professor in 2000. He holds additional positions in the Whiting School of Engineering and School of Medicine (Johns Hopkins University) as Director of the Institute for Computational Medicine and of the Center for Cardiovascular Bioinformatics and Modeling.

His research interests include computational modelling of intracellular signalling, metabolism and electrical excitability in cardiac myocytes; integrative modeling of cardiac function in healthy and diseased micro-environments; grid computing and data sharing; development of personalized diagnostic kits for critical patients, and biomedical data representation and database design.

He is a fellow of the American Institute for Medical and Biological Engineering (2000), the American Heart Association (2001), the inaugural fellow of the Biomedical Engineering Society (2005), and a member of the Biophysical Society. He is on the editorial board of several scientific journals, including *Circulation Research*, *Journal of Molecular and Cellular Cardiology*, *IET Systems Biology*, and *International Journal of Computational Medicine and Healthcare*. He is also the reviewer of several notable journals.

Winslow is also the recipient of eminent awards like Johns Hopkins University School of Medicine Paul Erhlich Graduate Student Award, First Prize, 1985; Computerworld/Smithsonian Information Technology Innovations Award for Digital Heart category Medicine, 1998; The Richard Skalak Memorial Lecturer, Department of Biomedical engineering, The University of California San Diego; 2002.

Winslow gave us an insight into his research interests, especially his work in understanding cardiac diseases, developing customized diagnostics, the CardioVascular Grid system and his criteria for selecting research students.

Could you tell us about your current research and what motivated you to pursue it?

There are three major areas of research in my laboratory.

The first is studying the nature of calcium signalling in cardiac myocytes and its relationship to arrhythmia. Deficiencies of calcium signalling are involved in every form of heart disease. This is because of the many different roles of calcium in cardiac muscle cells. Its signals determine the strength of muscle contraction and feedback to regulate the electrical activity of the myocyte. Calcium also activates intracellular signalling pathways and controls gene expression. We have recently expanded this research beyond the cardiac myocyte to study a type of synapse found in the nervous system known as the 'c-synapse'. Remarkably, these c-synapses structures are similar to those of the fundamental structures in cardiac myocytes involved in calcium release – the dyads. Because of this similarity, the tools and analytical methods we have developed for studying calcium signalling in myocytes can be applied to understand these synapses and how they process information in the nervous system.

The second area of research spans a different concern. Intensive care unit (ICU) patients are the most heavily instrumented patients in any hospital, and are configured with sensors that monitor many different physiological signals such as the ECG, respiration, various forms of blood pressure, blood gas levels, etc. These are likely to be the most informative signals that we measure in patients since they relate directly to the physiological state of a patient. Nonetheless, these signals are 'ephemeral', i.e. they are displayed on a bedside monitor and are then lost forever. This severely limits our ability to learn how these signals can be interpreted to infer the underlying state of the patient. This is incredibly important for the ICU setting as the state of a critically ill patient can change over a time course of tens of minutes. These are the only signals that are measured at a faster timescale and are therefore the only measurements we have that can inform us quickly about these state changes. In common ICU diseases such as sepsis, every missed hour of diagnosis increases mortality by 8% and hence early detection is critical. Therefore, to address this problem, we are developing informatics systems to capture these data, and also developing early detection algorithms that perform optimally to detect early patient state changes. Our approach will be to fit models of the cardiopulmonary system to individual patient datasets, and then use the personalized models to inform disease diagnosis and therapy selection.

Finally, we lead a national project called the CardioVascular Research Grid Project. This is funded by the NIH National Heart Lung and Blood Institute as a national resource to provide an informatics infrastructure for sharing and analysing cardiovascular clinical research data (cvrgrid.org).

Among all the other biologically significant molecules like sodium and potassium in the body, why does calcium play the most significant role in heart failure through the calcium-induced calcium-release (CICR) pathway?

This is because calcium regulates so many different intracellular processes. At its root, heart failure is a disease of

altered calcium handling. The pumps that sequester calcium into the intracellular organelle which stores it for release to drive muscle contraction (the junctional sarcoplasmic reticulum; JSR), are downregulated in heart failure for unknown reasons. Less calcium is stored in the JSR for release. Since calcium feedbacks to regulate cardiac action potential duration (APD), these changes prolong APD which is pro-arrhythmic. Since there is less calcium available for release from the JSR on each heart beat, muscle contraction is weaker and less blood is pumped by the heart. Altered calcium signals can also drive changes in gene expression during heart failure.

Is the CICR pathway common for all causes of heart failure?

The cellular phenotype is a final common end-point in heart failure. Regardless of the cause, end-stage heart failure is characterized by reduced amplitude of calcium transients (less availability for release during each heart beat), prolonged APD (less released calcium produces less inhibition of the inward calcium current, prolonging the AP), weaker heart contraction (smaller calcium release causes less cross-bridge cycling and contraction of cardiac muscle).

How can calcium signalling be compared in an 80-year-old versus a 20-year-old with heart failure?

End-stage heart failure (HF) is similar in both cases. However, the causes are likely to be very different for these two age groups. HF that appears so early is more likely to result from a genetic mutation that is predisposed to HF (there are familial forms of dilated cardiomyopathy). HF in later years is more likely to arise from other factors such as underlying developing ischaemic heart disease.

What is the relation between calcium deficiency and the calcium signalling pattern in heart failure? Do supplements help and if so, what is the mechanism? Are calcium supplements the new potential preventives of heart failures?

Calcium supplements do not help because a fundamental deficit is reduced expression of the pump that transports it from the cytosol into the JSR. Clinical trials are underway in which viral gene delivery methods are being used to upregulate the expression of this pump. This approach rescues the normal calcium phenotype in animal models of HF.

If calcium deficiency is a factor, then heart failure should be more common in women; but males are more affected. Why?

Calcium deficiency is not the key factor. The key factor is normal expression of the pump that transports it from the cytosol of the cardiac muscle cell into the JSR. When that pump is downregulated, there is a limit on how much calcium can be transported into the JSR.

It is also important to understand that at high levels calcium is toxic to cells. All cells have homeostatic mechanisms that keep it at remarkably low resting levels. Diastolic calcium levels in the cardiac myocyte and many other cell types are about 100–150 nmol, which is very low. Cells die when their levels become abnormally high.

Does trauma regulate calcium levels in the body and then lead to heart failure?

No, trauma does not regulate calcium levels.

How does calcium signalling in the heart, during a heart failure, affect the brain?

HF renders the heart less able to pump blood. As HF advances, the heart contracts less vigorously and in a rather uncoordinated way. Less blood is ejected per heart beat. The body becomes deprived of oxygen because less oxygenated blood is pumped from the heart. Blood can pool within the heart due to this less vigorous contraction, increasing the risk of a blood clot formation, and thus increasing the risk of stroke.

What pattern is followed when a person gets a 'mild' heart attack? What happens to calcium signalling in a series of heart attacks?

A very complex question as too many things happen than I cannot describe here. There are many different types of 'heart attacks' – which is a very generic term.

Is the pattern of the CICR process similar in animals as seen in human beings?

Qualitatively yes.

Can you elaborate on how mitochondrial calcium mismanagement leads to scarcity of ROS (reactive oxygen species) scavengers? Is this the only effect on ROS production or does it have a direct influence on increase in ROS?

Calcium regulates the activity of some key enzymes in the tricarboxylic acid (TCA) as Krebs cycle. In heart failure, for reasons we do not yet understand, cytosolic sodium levels are much higher than normal. There is a transporter protein in the mitochondrial inner membrane known as the sodium–calcium exchanger (NCXm). It extrudes one calcium ion from the mitochondria at the cost of importing three sodium ions per cycle. When the cytosolic sodium is elevated, it causes NCXm to extrude calcium from the mitochondria. Reduced mitochondrial calcium reduces the production of nicotin-amide adenine dinucleotide phosphate by the TCA cycle. Through a long cascade of complex reactions, this increases production of ROS which is released from the mitochondria. ROS is a signalling molecule that targets and regulates many other proteins in the myocyte that are important for its function. These effects are only beginning to be understood.

Can you elaborate on the cardiac beta-adrenergic pathway?

Books have been written about this pathway. In general, this is a pathway by which the sympathetic nervous system controls the rate of contraction of the heart as well as contractile strength. Epinephrine released from sympathetic nerve terminals binds to beta-adrenergic receptors. This stimulates production of cAMP by adenylyl cyclase. cAMP binds to the regulatory subunits of protein kinase A, thus activating it. PKA is then available to phosphorylate its targets. The B-AR system produces its effects through the actions of PKA. The sinoatrial node is the pacemaker region of the heart where cells spontaneously generate action potentials. Their frequency determines heart rate. PKA activation causes this frequency of oscillation to increase, that is, heart rate increases and so more blood is pumped per unit time. In the ventricular myocardium, the actions of PKA are to increase calcium loading into JSR. More

calcium is released per beat, contraction is stronger per beat, and more blood is pumped per beat. These two major actions work together to increase blood flow to tissues as part of the 'flight or fight response'.

What is your view about the medical applications of bioengineering and computational biology in future?

Medicine is becoming a computational science. The ways in which biological systems are perturbed in disease are simply too complex to be understood without the use of computational models. Over the long term, computational models constrained by data from individual patients will inform both the disease diagnosis and choice of treatment for that patient.

How effectively can the systems biology approach be used to diagnose and treat diseases in the near future?

Gene and protein networks are highly interconnected and complex. Understanding their dynamic behaviour can only be achieved through development and application of mechanistic models. This modelling approach is, to me, the essence of systems biology. Systems biologists who limit their work to collecting large-scale 'ohmics' datasets are not really doing systems biology; they are doing stamp-collecting. The complex nature of these datasets cries out for quantitative analytical and modelling-based approaches to their analysis. I will replace the word 'effective' with 'necessary'. Systems biology is a necessary approach to understanding disease. How effective it will be over what time course remains to be seen. What I know is that it is a necessary approach.

As a reviewer of a number of significant scientific journals, what would you suggest to aspiring scientists for successful research papers?

I have never written a paper with the driving motivation being to place it in *Science*, *Nature*, *PNAS*, etc. When I write a paper, my motivation is to present our work in as crystal-clear a way as possible, to accurately communicate our results, and to be as objective as possible in presenting these results (meaning not over-selling them or crying out 'this is a first'). The best papers are those that clearly and effectively communicate important findings. They present work in a way that assures it can be reproduced by others. They make all the research products openly available for use by the entire community. These are the papers that will be read and cited by others. There are plenty of examples of *Science* papers that receive a handful of citations over their lifetime. There are innumerable examples of papers in what would be considered as second-tier, but still good journals that receive thousands of citations over their lifetime. Citations are the metric of impact.

What are your criteria while selecting graduate or doctoral students for research?

Strong academic performance. Evidence of focused interest in their written statement of purpose. Solid letters of recommendation from the faculty with whom the applicants have done research. Our BME Ph D program requires all applicants to be interviewed. In the interview, students need to impress me with their ability to think on their feet.

What is your research vision for the coming year?

To develop the work I described above on personalized modelling of ICU patients, to improve disease detection and therapy selection.

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