Foreword

Mechanosensitivity in Cells and Tissues as an Overall Regulatory System

Kamkin and Kiseleva's assembly of leaders in the mechanosensitivity field provides an excellent broad based and up-to-date book, with chapters in the first part discussing mechanically gated channels (mechanogated), mechanosensitive channels (MGC, MSC) systems (as the editors air the nomenclature in their editorial), the second describing their signaling, and the third presenting aspects of cell mechanobiology. Conceptually starting with tension at the surface membrane, the book's theme moves on to some molecular mechanisms, and then on to MSC as initiating complex cell signal cascades, sometimes invoking signalsomes. Mechanosensitivity is also described in organs.

Mechanosensitivity does not only relate to very soft deformable tissue, but chapters also focuses on cells and tissues concerned essentially with skeletal growth and development. The state of the art covered in the book heralds, to me, a slant to mechanosensitivity in general.

Galileo remarked in 1638 that longer bones were thicker for a given structural strength (Galilei, 1638) (translation in (Crewew & da Silavio, 1939)), and this was followed in 1859 by Darwin's noting that flying ducks have underdeveloped legs as compared with terrestrial bound ones (Darwin, 1859).

These early observations were already suggesting a compensatory homeostatic feedback system applying to the whole organism. Based on the wide-ranging and authoritative chapters, I propose that mechanogated, mechanosensitive systems in biology as a whole preserves physiological, integrative homeostasis as closed feedback control systems, and Fig. 1 is indication of how this could fit into system biology. Feedback interaction is between the mechanosensor to spatiotemporal integration of systems and organs. Mechanoelectric Feedback in heart has already been similarly viewed and invokes mechanosensitivity as the detector/transducer in feedback control of electrophysiology. (Lab, 1999) Although I have applied the homeostatic feedback notion to heart, this book suggests that I can broaden this mechanical homeostatic process to biology in general, for mechanosensitivity exists throughout the phyla - bacteria to mammalian tissue.

In pursuing this notion, I used a type of meta-analyses — an accepted method to address a defined clinical topic, sometimes as a hypothesis (treatment X works). The current approach is roughly analogous, examining this book as well as the literature with the proposal in mind. My analysis roughly encompasses literature over 20 years or so, using "Entrez Pubmed," with search terms such as "Mechanotransduction,"

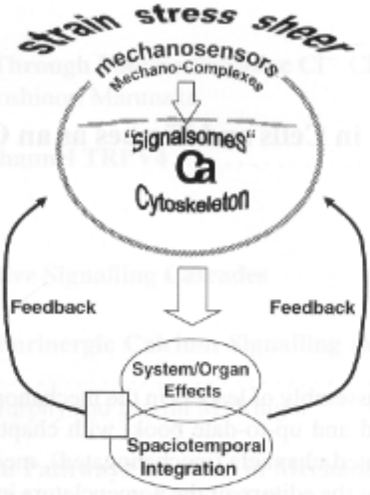

Fig. 1 Stress,strain, and sheer forces (very top) affect the membrane Mechanosensors / Mechano-complexes and then into the cell, feeding down (top block arrow - "feed-forward") down signal-somes and signal cascades often involving calcium. Importantly, influences via the cytoskeleton modulate (bottom block arrow) organ and spatiotemporal integration. These feed back ("return" - outside curved black arrows) via the same or alternate paths to modulate the consequences of the initiating mechanical changes

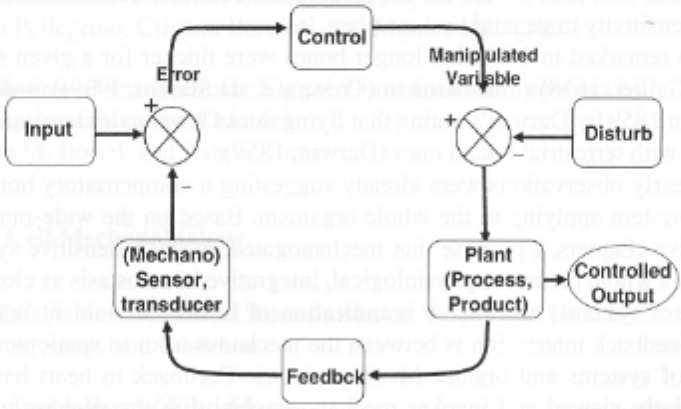

Fig. 2 Simplified block diagram of mechanosensitivity as a homeostatic feedback control system. The mechanosensors or transducers (bottom left element in loop) have mechanical inputs (top left) to a summing point (left crossed circle in loop). These via the control mechanisms and transfer functions going clockwise reach another summing point, interacting with the factors disturbing the system (top right – "disturb"). The product of these interactions (bottom left element – "plant", in loop) would produce a controlled output (elipse – bottom right). The plant/process element feeds back to influence the mechanosensor or transducer.element

"Mechanosensitivity," "Mechanogated channels," and "Stretch activated channels", and "Mechano Feedback." The findings were then organised into appropriate components of feedback control loops, see Fig. 2.

The "feedback" label in heart (Lab, 1999) was negative and when the Feedback Loop is altered (gain changes) it heralds pathology, with arrhythmia, hypertrophy.

It can also apply in the vasculature with its regulatory flow dynamics (Lehoux *et al.*, 2006). In this case an altered loop can produce atherosclerosis. Growth & proliferation, repair and regeneration can also be treated in analogous fashion, and altered loop gains here produce cancer.

Although several elegant reviews covering aspects of mechanobiology (for example (Ingber, 2003; Ingber, 2006)) offer an open system view with feed forward descriptions, my current proposal in this article is for mechanosensitivity to involve closed negative feedback systems. As a homeostatic regulatory system, it has several putative characteristics found in other regulatory systems with biophysical, biochemical and physiological regulatory functions, operating from the molecule to the organ/system.

References

Crewew H & da Silavio A (1939). *Dialogue concerning two new sciences*. Northwestern University Press.

Darwin C (1859). *On the origin of species by means of natural selection. London: John Murray* John Murray, London.

Galilei G (1638). *Discorsi e dimonstrazioni mathematichia intorno a due nuove scienze*. Lieda: Elsevier.

Ingber DE (2006). Cellular mechanotransduction: putting all the pieces together again. *FASEB J* **20**, 811–827.

Ingber DE (2003). Tensegrity II. How structural networks influence cellular information processing networks. *J Cell Sci* **116**, 1397–1408.

Lab MJ (1999). Mechanosensitivity as an integrative system in the heart: an audit. *Prog Biophysics & Molec Biol* **71**, 7–27.

Lehoux S, Castier Y, & Tedgui A (2006). Molecular mechanisms of the vascular responses to haemodynamic forces. *J Intern Med* **259**, 381–392.

Max J Lab
Imperial College London, National Heart & Lung Institute and Nanomedicine Research Laboratory — (Hammersmith Campus), Charing Cross, London W6 8RF, UK

Foreword

The book "Mechanosensitivity in Cells and Tissues: Mechanosensitive Ion Channels" edited by Andre Kamkin and Irina Kiseleva impressively demonstrates the diversity of cellular effects depending on mechanical stimuli. Coming from basic biophysical mechanisms of mechanosensitivity of the lipid bilayer, ionic channels including K^+, Cl^-, and nonselective channels in bacteria as well as in eukaryotic multicellular organisms are reviewed. Examples demonstrating the physiological role of mechanosensitive channels in cellular and organ physiology include odontoblasts and chondrocytes. Moreover information is given on mechanosensitive signaling cascades in articular chondrocytes, osteoblastic and mesenchymal stem cells as well as on in neuronal and cardiac cells where mechanosensitive cation channels are described.

When I was asked to write the foreword to this compelling book I doubted about what I as a stem cell researcher could say about mechanosensitivity of cells? But looking at the more recent studies in this field, and in particular on detailed insights in the earliest events of cellular development in the embryo – eureka - mechanical effects including migration and mechanosensitivity turn out to be ones of the most primal and archaic mechanisms of self organisation. Cellular mechanosensitivity is probably the most basic biological principle that is presumably expressed in every cellular phenotype and plays a pivotal role in manifold physiological mechanisms and especially in early embryonic development. There is compelling evidence that physical forces, including gravity, tension, compression, pressure and shear forces influence growth and remodelling in nearly all living tissues on a cellular level. Proliferation, growth, differentiation, secretion, movement, signalling as well as gene expression have been shown to be altered by applying mechanical stress directly to the respective cells. In parallel with the identification of more and more cellular targets of mechanosensitivity there is an increasing interest of basic and applied scientists in this field. Just looking at the number of publications in Pubmed[1] as a measure of the scientific impact which well reflects the interest of the scientific community in this specified research area, one can identify a dramatic rise of interest within the last year. While the field of mechanosensitivity attracted around 100 papers per annum from 2000 to 2005 the number immensely jumped to more than 450 in the year 2006.

[1] Pubmed-listed publications with the term "mechanosensitivity" in the title/abstract

This might also be due to the fact that great technological advances in areas such as nanotechnology, micromanipulation, biological imaging and computer modelling have enabled us to analyze mechanotransduction: how forces affect the biochemical activities of individual molecules, both in isolation and within living cells. Also, the detailed analysis of mechanosensitive ionic channels using 2D crystallography, electronparamagnetic resonance spectroscopy, fluorescence resonance energy transfer spectroscopy as well as computational modelling based on molecular dynamics and Brownian dynamics gave a new impact in this field. Mechano-regulation is once again becoming a central focus in fields ranging from molecular biophysics and cell biology to human physiology and clinical medicine.

The present book demonstrates the various aspects of mechanosensitivity. It thus considerably contributes to a better understanding of the primary processes in cellular mechanosensitivity and highlights the electrophysiological responses. Together with other well known signalling cascades directly coupled to the cytoskeleton and thus to cellular mechanical responses our picture on these important signalling processes becomes more and more detailed and hopefully will integrate into the complex cellular processes such as embryonic development and differentiation of cells as well into the complex physiological organic functions.

Jürgen Hescheler
Institut für Neurophysiologie. Universität zu Köln. Robert-Koch Str. 39 D-50931
Köln, Germany