MULTI-LEVEL ORGANISATION OF BIOLOGICAL SYSTEMS

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A system consists of components (or, elements), which are interacting, interrelated, or interdependent in order to facilitate the flow of information, matter, or energy to form a complex "whole". In other words, it is an assemblage of inter-related elements that work together giving rise to a functional and structural entity. When the "whole" is simply the sum of its parts it is known as a *Linear System*, where the "Principle of Superposition" holds. It means that the behaviour of the system can be understood by simply adding up the effect of each part independently, and a change on one part of the system induces proportional change in the other. In the other hand, a system is designated as a *Complex System*, when the "whole" is not a simple sum of its parts. Complex systems generally consist of a large number of interacting dynamical parts with interactions that are of nonlinear in nature. In such systems, the effect of a change on one part of the system does not have a proportionate relationship with change in the other. Even though making a catalogue of all parts of a system may help in understanding what it is made up of, yet investigation of the respective parts in isolation may not be useful in knowing how they work to give the system behaviour [**1**].

In Figure 1(A) is shown a cartoon where a child's curiosity to understand how the toy car works by taking it apart only leads to a collection of parts, which do not work any more.

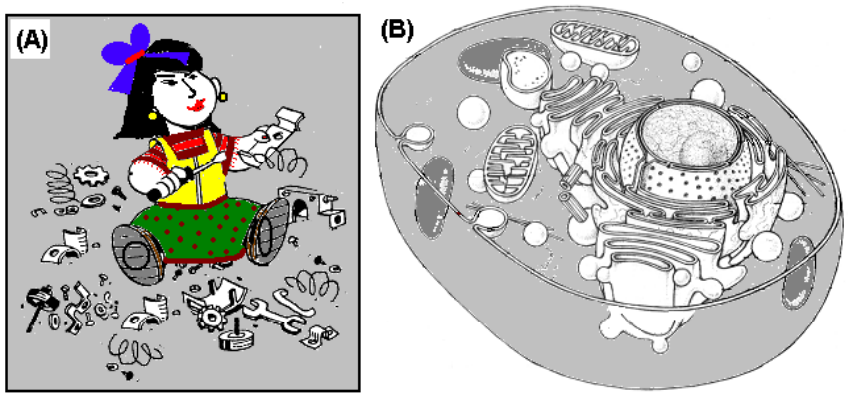

Figure 1: Reductionist Approach: (A) Taking apart the toy car to see how it works leads to only knowing its parts; (B) Isolation and characterisation of all organelles and molecules that make up a cell only gives a "part list".

Similarly, a biological cell, shown in Figure 1(B), is made up of many different types of organelles, such as plasma membrane, nucleus, mitochondrion, golgi apparatus, endoplasmic reticulum, lysosome, cytoskeleton, peroxisome, etc, which, in turn, are organised assemblies of different types of molecules. But, simply putting together all these organelles do not make a functional cell. The dynamic interactions, influence of contacts/couplings, different structural environment, etc, regulate the interaction among the parts, and hence the overall behaviour. A "system's approach" requires unification of structure and dynamics of individual parts to understand or predict about the whole system. Thus, the structural and functional organisation of a system involves transfer of information among its parts and their regulation. The lower level entities interact according to certain rules and patterns, which, in turn, can also modulate the behaviour of the constituent entities.

Biological systems are spectacular examples of Complex Systems. Life on earth is organised in multiple layers—from ecosystem to populations to organisms to cells to molecules that make up the cells (see Figure 2). The reductionist approach of molecular biology has been a major success in unraveling the layers of organisation in physiological systems—from whole organisms to molecules that carry genetic information and regulate biochemical functions. A lot is known about biological functions and their regulation at the genetic and biochemical level. With all this information in hand, now the major challenge is to rebuild or ''reverse engineer'' the levels of organisation upward. At any higher level of organisation, the emergent properties of the biological structure is largely determined by the interacting constituent elements/modules (molecules, cells, populations), and the individual behaviour of the entity, and the collective behaviour of the "whole" may be quite different. Network theory has been used quite successfully to describe interacting entities [**2**]. A large body of literature has accumulated over the past few years on how networks of amino acids [**3**], genes [**4**], proteins [**5**], and biochemical pathways [**6,7**] behave when the information of the individual constituents are known. The high throughput experimental technology, such as microarray, proteomics, etc has been essential in reaching this state. At higher levels of organisation, social interactions [**8**], and ecological networks, such as food webs [**9**] have also been described using network theory. There has not been much study, using this framework, at the intermediate level where many cells interact to form a multicellular structure/group such as, tissues, organs, organisms and cell populations.

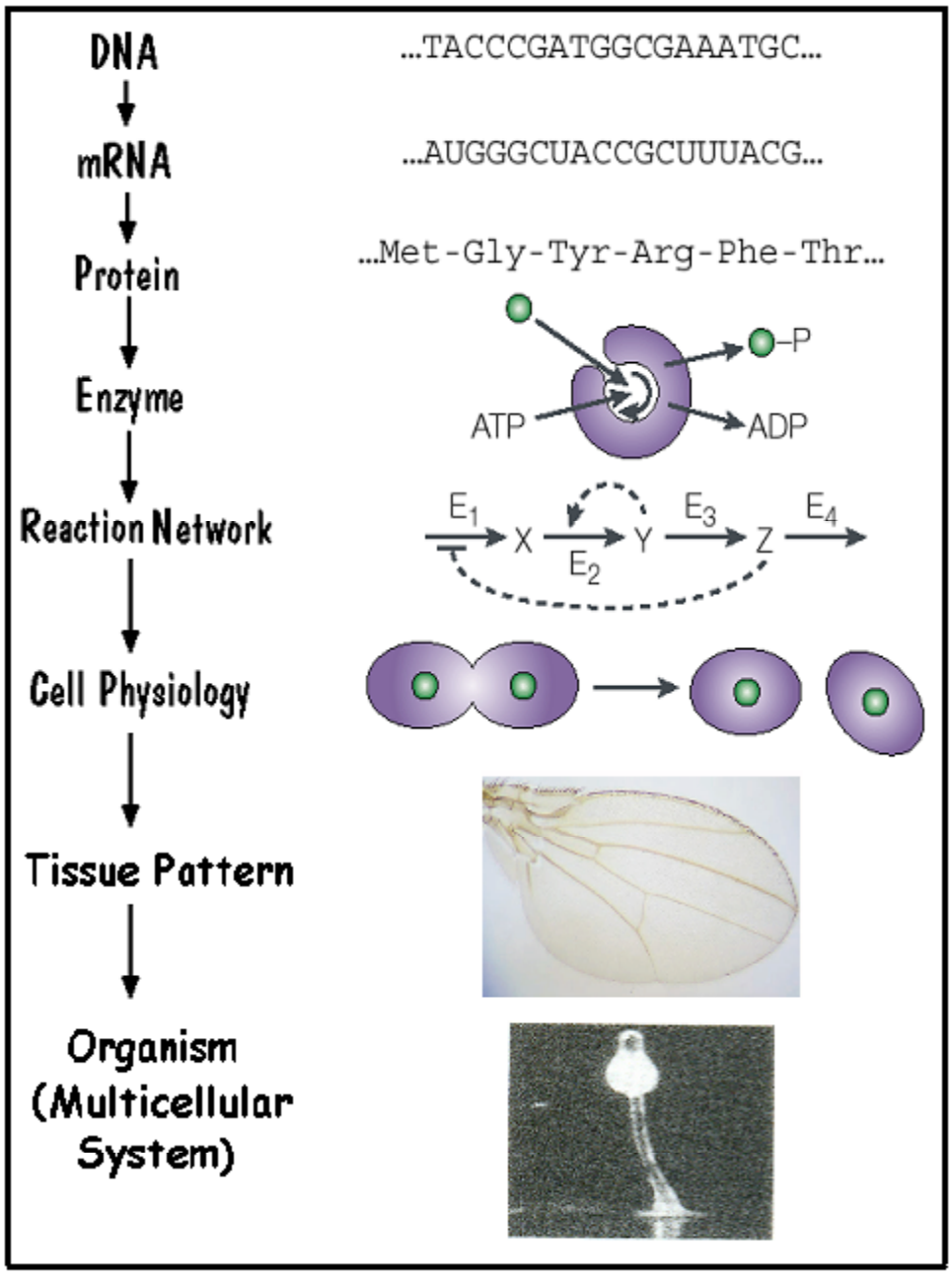

Figure 2: Multilevel organisation of biological systems – from genetic material to organism.

Transition from single to multi-cellular life has been a major milestone in the evolution of life on earth. Living cells organize themselves into various types of spatial structures to suit their milieu and functions. Sophisticated modes of communication, well-organized social behaviour, and division of labour among the constituent cells are prerequisite for such structures to function. Modes of communication among the cells in such organised multi-cell systems can be both direct

and indirect. Direct signalling involves interaction between membrane-bound molecules (receptors), or via gap junctions for facilitating ion exchange. Indirect communication can be through secreted chemicals or matrix mediated. Inter-cellular signalling during any physiological process uses any one, or combination of the above-mentioned mechanisms [**10**].

Structured groups of cells or organized assemblies, tissues and organs, are the most common form of multi-cell system known to us, where the arrangement and types of contacts complement their specific functions. But other types of organizations, such as cell colonies, and aggregates of cells exhibiting density dependent population behaviour are also quite common among organisms performing various tasks. Community Effect [**11**], Quorum Sensing [**12**], and Biofilms [**13**]) are examples of cell density-dependent behaviour, where a population of similar cells responds to a signal factor by inducing new gene expression only when the number of cells reach a certain density. An impressive example of an organised assembly of cells are the Pancreatic islets, consisting of primarily beta cells, which secrete insulin in a pulsatile manner in response to elevated glucose level in the blood. It is known that well synchronised electrical activity of the beta cell membranes precedes insulin secretion in the islet. Any defect in the

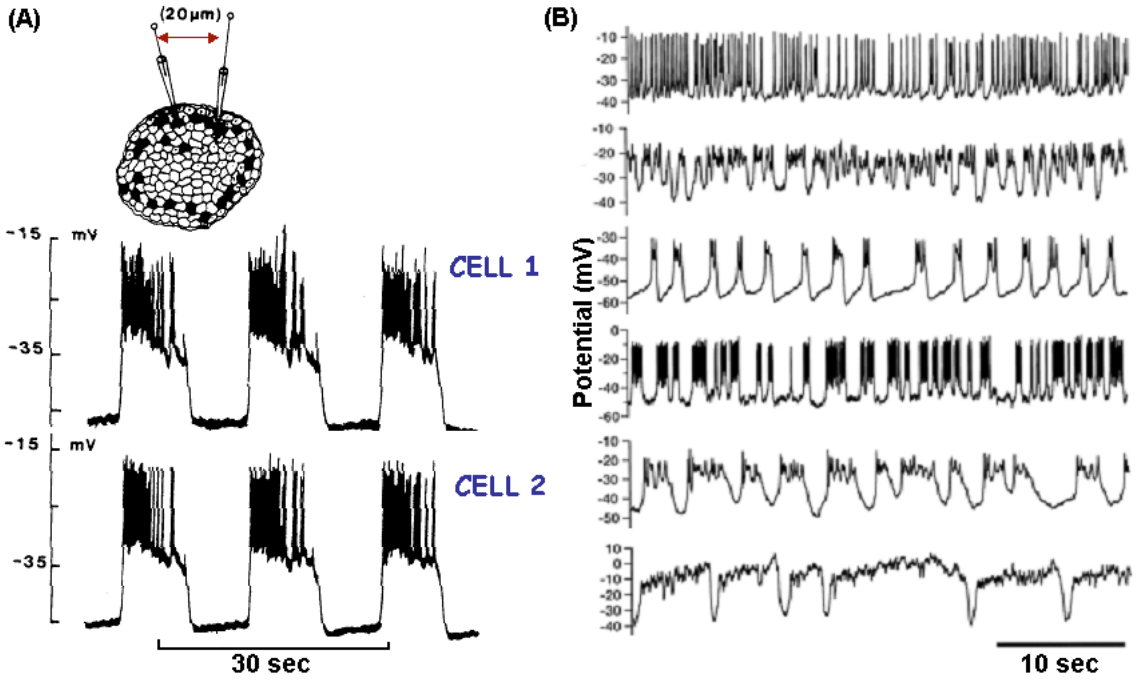

Figure 3: Bursting electrical activity in single beta cells when - (A) dispersed (from [16]), and (B) two cells 20 micrometer apart inside the islet (from [15]).

electrical activity can interfere with insulin secretion [**14**]. Electrophysiological measurements have shown that each cell in the islet exhibit electrical activity of voltage oscillations with the same frequency and amplitude [**15**], as shown in Figure 3(A). This synchronized activity allows all beta cells in the islet to act synchronously and secrete insulin in pulsatile packets. Interestingly, it has also been shown [**16**] that when the constituent beta cells of the islet are dispersed to single cells and their membrane potential measured, they exhibit electrical activity with very different frequencies and do not secrete insulin effectively (shown in Figure 3(B). Thus dynamics of dispersed single beta cells are varied and they cannot function effectively. In fact none of them show the frequency of voltage oscillations that the islet cells exhibit. Inside the islet, the same cells when coupled to each other in an organised structure give rise to the collective synchronized behaviour functionally effective for insulin secretion. This clearly shows that the system's (i.e., the islet) behaviour cannot be obtained by breaking it apart in to its consituents (single beta cells) and measuring their activity. The dynamic coupling of the cells and the structural features of the cells regulate the islet behaviour.

Computational Systems Biology addresses similar problems in which, based on the dynamic behaviour of the constituents in isolation, the collective behaviour of the system is modeled. An example of the islet model is shown in Figure 4. Figure 4(A) shows a simple representation of an islet modeled as a linear lattice of cells. Here each cell (i) interacts with its nearest neighbours (i+1, i-1) through sharing voltage experienced across the gap junctions. Electrically active cells are modeled using electrical Resistor-Capacitor circuits in accordance with the Hodgkin-Huxley equations proposed to model neural activities [**17**]. The ionic currents in each cell through the Resistor (I_R), Capacitor (I_{cap}) contribute to their voltage differences and they communicate with each other through the gap junctional current ((I_{coup}). Figure 4(B) shows the voltage oscillations in a model islet of 50 cells. The left panel shows examples of electrical activities of few of the uncoupled model islet cells (5, 10, 25, and 40^{th} cells), having different frequencies of voltage oscillations – fast and slow. The right panel shows that the same cells, when coupled through the gap junctional currents of their nearest neighbours, organize their inherent electrical activities to give rise to beautiful collective synchronized bursts of medium frequency (about 25 sec). Cell-cell communications through gap junctions suppress individual cell's behaviour, and yield the emergent synchronized dynamics characteristic of the system behaviour. This illustrates that the intercellular communication in the organised islet structure is

a necessary prerequisite for effective functioning, i.e., synchronized collective bursts of electrical activity required for insulin secretion.

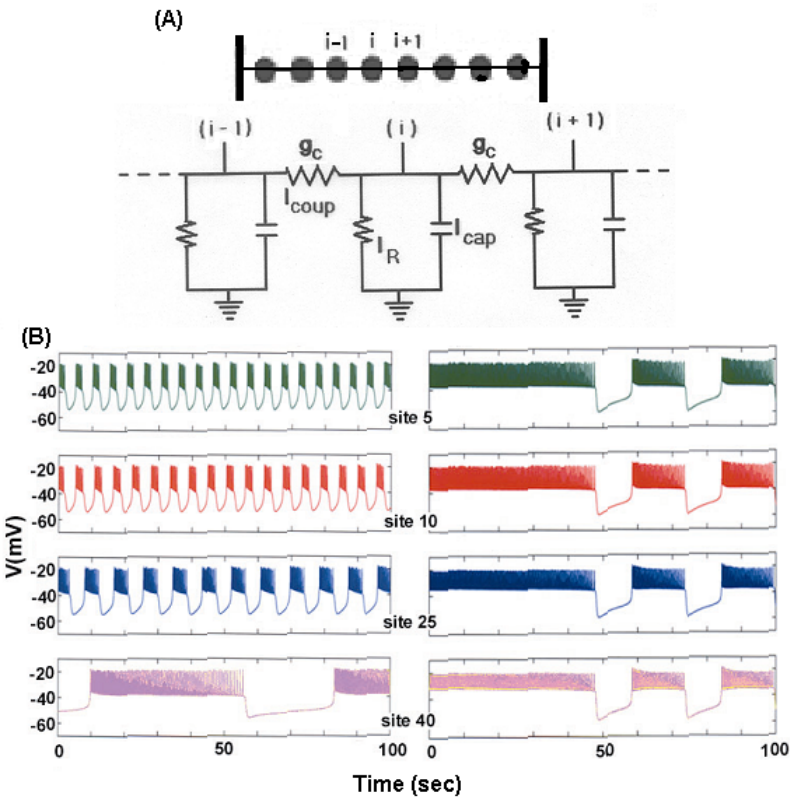

Figure 4: Model islet of beta cells – (A) One-dimensional lattice as a simple model of islet of 50 cells, and the beta cells as model electrical RC circuits coupled through gap junctions (see text for details). (B) Electrical activity of - uncoupled single beta cells (left panel), and coupled cells in the islet (right panel).

That information transfer among the parts of the system can regulate the constituent entity's behaviour leading to the emergent synchronized dynamics, has been shown for other biological systems also, using computational modeling [**18,19**]. Many diseases are due to the loss of cell communication or abnormal cell–cell interactions in the tissue. In real biological tissue or multi-cellular systems, large variations in structure and function exist. The tissue behaviour may not always be the same as the constituent single cell dynamics. The collective dynamics is generally robust even if the single cell behaviour is not [**20**]. Such a property confers functional advantage to the system in natural noisy environment.

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