

Biology across scales: historical perspective on some Indian contributions

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Understanding Biological systems across scales, has led to two apparently contradicting approaches the reductive approach, and the holistic approach. The former attempts to understand complex systems by reducing it into smaller components, whereas the latter attempts to combine information to integrate at the systems level. Many important contributions from India have been made in these areas. I attempt to present a view of these in this article to mark celebrations 30 years of the Department of Biotechnology.

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Introduction

COMPARISONS of different scales in biology are fascinating, and I feel privileged to have been invited to write an article on this theme to celebrate 30 years of the Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India (GoI). It is inevitable that to write such an article a comprehensive overview is impossible to achieve and that subjective interpretations will appear. The examples cited here are therefore representative of personal choice, and I acknowledge that a similar article can be written by another person with completely non-overlapping set of examples. DBT has played a pivotal role in supporting life sciences in the country, and to recognize this aspect, I have chosen to quote a number of examples of work carried out in India. A historical perspective of the work carried out in life sciences over the last 100 years is presented here.

Many different biological scales over a wide range can be compared and these can be considered in any of mass, length and time. For example, one of the timescales – the evolutionary timescale, spans more than four billion years (Figure 1). Different time points on this scale form exciting areas of research, at one end – from the emergence of self-assembling and replicating molecules in the pre-biotic time period, to among the most intriguing questions being studied in the current times such as the evolution of cognitive abilities of humans. The appearance of self-assembling building block molecules, originally proposed

by Oparin¹ and Haldane², and confirmed by the famous experiment³ of Miller and Urey, forms the foundation of the research concerning the prebiotic times. One of the problems beyond the primordial soup composition is how these molecules form spontaneous self-assembly? Combined with many elegant studies, the currently accepted viewpoint suggests that the molecules emerged spontaneously in the prebiotic time period, and then formed

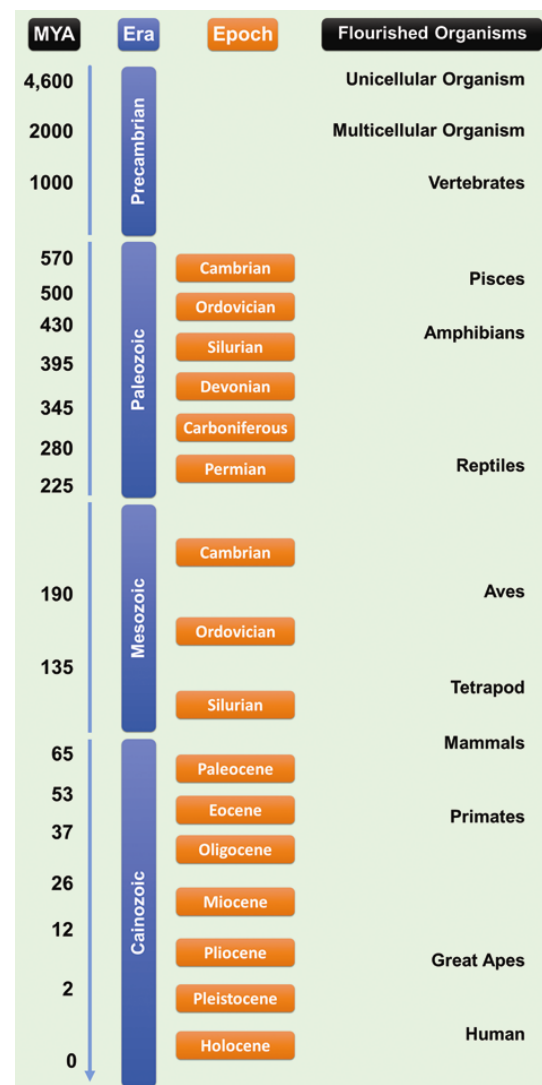


Figure 1. The approximate time scale for evolutionary events. The scale is approximate, and the major events in the evolution of different life forms are indicated.

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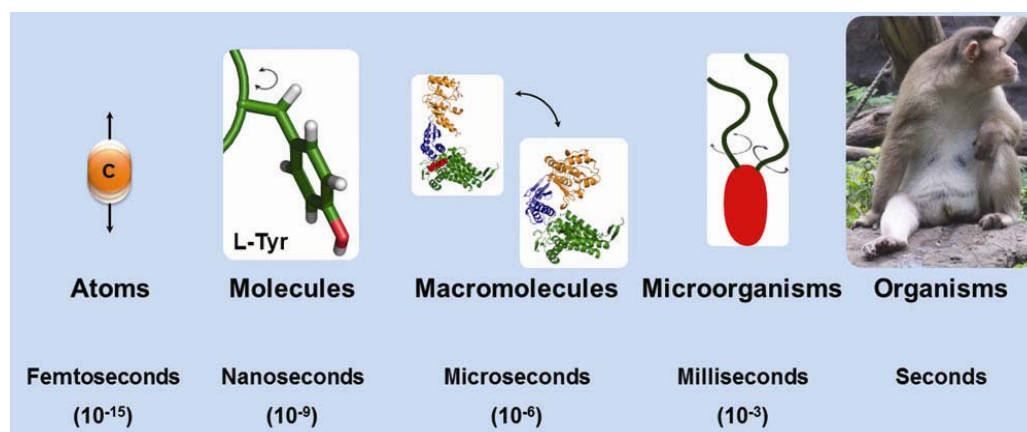


Figure 2. The time scale for biological motions. The motions which take place from femtoseconds to seconds are shown.

assemblies paving the way to the formation of early self-replicating biological molecules⁴. The Indian contributions span the entire evolutionary timescale, such as those addressed by Vijayan⁵ on spontaneous self-assembly or Gadagkar⁶ on evolution of eusociality.

Another timescale is that related to biological motions which range from femtoseconds to days/years. At one end of this scale are the apparently chaotic motions of atoms around their mean positions in biological macromolecules, which are of the order of femtoseconds. Although of very high frequency, these have profound effect on biological systems. Interestingly, the high-frequency motions are capable of giving rise to larger coordinated motions at a much lower frequency. Moreover, the femtosecond dynamics associated with the solvents in which larger molecules are immersed, has been shown to have critical effect on the structures and stability of biological macromolecules⁷. Similarly, coordinated motion of molecules, or herds of animals, approaching the other end of this timescale is another fascinating aspect of biological motion, which was shown to arise from non-specific interactions within the constituent entities⁸. Each of these areas is of great interest to discuss in detail; however, I will deal only with the length scale in the rest of the article and present some of the emerging areas in biology.

Among the earliest observations for length and mass scale in living systems were proposed by scientists such as Haldane, who attempted to rationalize the sizes of different animals⁹. He presented persuasive arguments on observations such as why the eagle is larger than the sparrow, or the hippopotamus bigger than the hare. Through these arguments he was able to justify the advantages of size in the animal kingdom. Haldane was also among the early biologists who through elegant analysis brought in quantitative aspects to biological sciences.

The length and mass scales are approximately proportional in the biological systems, with a few exceptions, and therefore it might suffice to consider only the length scale for arguments (Figure 2). One may then consider

atoms and molecules of the living systems at one end of the spectrum, and the biosphere at the other end. Between these we have myriad of biological systems, including small metabolites, amino acids, nucleotides, proteins and enzymes, linear polymers such as the DNA, branched polymers such as oligosaccharides, sub-cellular organelles, cells, multicellular organisms, collection of organism into societies and finally the biosphere. Study of any of these is a fascinating subject of biological sciences.

Until about a 100 years ago most of the studies were focused on only the objects which are visible to the human eye, or those which could be visualized by a microscope. At the same time, chemical processes defining biological principles were also being studied¹⁰. However, the last 100 years have seen the advent of technologies which now allow us to study biological systems at all the levels mentioned above. The molecular biology revolution has made it possible to address many problems that were earlier not accessible. Similarly, many new techniques have been developed in the last few decades, which have made it possible to address deeper problems of biology. Comparisons are often drawn with the developments in physics in the 1920s and 1930s to the developments that are currently being witnessed in biology.

The complexity of the biological systems has been acknowledged to be one of the major factors that precludes our complete understanding of the living systems. An approach which was originally advocated by the physicists is to study a complex system by breaking it into smaller components. Study of the smaller components is often easier, but allows obtaining insights into the functioning of the complex system on a larger scale. Also called the reductive approach, it has been immensely useful to study the complex biological systems. The reductive approach, championed by the likes of Max Delbrück, follows that a complex system such as the biosphere can be understood by studying its constituting populations, which in turn can be studied by the component organisms, which can be studied at the cellular

levels and the cells themselves can be studied at the molecular level. Timofeeff-Ressovsky *et al.*¹¹ published one of the early papers which marks the beginning of genetic reductionist approach with the conclusion that mutations are molecular rearrangements within a molecule, and the genes are a union of atoms with which the mutation can occur. The paper was popularized by Schrödinger¹² in his book *What is Life?*, which is considered to have inspired many physicists to take up biology. The reductive approach, thus described, further led to defining 'model systems' in biology, and to generalize the observations obtained from the chosen model system.

The transition of physicists into biology in India appeared soon after, with the likes of G. N. Ramachandran starting to address contemporary biological problems. Ramachandran was able to determine the atomic structure of collagen from fibre diffraction data¹³. The Madras school that he established continued their outstanding contributions with the work on protein structures in the form of the study of conformational properties measured by dihedral angles of the polypeptide backbone¹⁴. The Ramachandran map offers a powerful method to assess the conformational features of polypeptides and forms the basis of protein structure validation tools in the present time. Thus, the roots of reductionist biology were by now firmly established, and the Indian participation had gained wide acknowledgement.

Around the same time, an interesting contribution by Sambhu Nath De emerged for the understanding of cholera, and the molecular basis of its clinical manifestation. He was able to demonstrate that the manifestation of the disease was due to an exotoxin, much against the then widely held belief that the toxic effects were due to an endotoxin¹⁵. So fundamental was De's contribution that this work eventually led to the concept of enterotoxin producing *Escherichia coli*, which is now widely accepted. The roots of the role of exotoxins and their pathophysiological role can therefore be directly traced to De's work.

By the 1970s, the concept of model systems in biological research was firmly embedded, with several groups around the world making seminal contributions in genetics using *E. coli*, *Drosophila* and *Caenorhabditis elegans*, among others, as useful models. Although *Drosophila* had been proposed as a model by Castle's group in 1901, it is widely believed that this began to be used as a standard model for biological research due to the work carried out by Thomas Morgan¹⁶. He was able to refine Mendel's inheritance theory using *Drosophila* as a model, and proposed the concept of genes. Similarly, Sydney Brenner pioneered *C. elegans* as the model for understanding developmental biology using the genetics approach¹⁷. The pioneer in the use of model systems in India was Obaid Siddiqi, who began his work at the Tata Institute of Fundamental Research, Mumbai, initially with *E. coli*, but then expanded it to other models, including *Drosophila*.

He subsequently made several fundamental discoveries using these model systems. One of his earliest contributions was that of understanding recombination in *E. coli*¹⁸, before he moved to other areas using *Drosophila* as the model. Similarly, an interesting contribution of the use of *Drosophila* model from India was that in the discovery of *Wingless* mutant¹⁹. The wingless phenotype is caused by the *wg*¹ gene, the first among the seven genes that have been identified. *wg*¹ belongs to what is now called as the Wnt signalling pathway, which in many different cell types is now recognized to be of fundamental importance. Thus, these studies laid the foundation of cellular and organismal work in the post-independent India.

As one moves from whole organisms to populations, many important pieces of work have been carried out in the last 100 years in India. Of special note were the initiation of the Anthropometric Survey of the United Provinces (1941) and the Bengal Anthropometric Survey (1960) by Mahalanobis²⁰. The move of Haldane to the Indian Statistical Institute in Kolkata, further added strength to this area. An outcome of these surveys led to the outstanding invention of multivariate statistical methods by Rao²¹. Together, while the quantitative aspects as applied to whole populations were being invented in Kolkata, the process of initiating new exciting fields of statistics automatically followed. At the other end of the India, of special note of integrating the quantitative aspects into biology were those of D. D. Kosambi and L. D. Sanghvi. Kosambi's mapping function aims to estimate the recombining fractions between two loci as a function of the map distance between the loci²². Sanghvi also proposed a distance-based measure for populations based on gene frequencies²³. Apart from these important contributions, the integration of quantitative measures in population biology has left a significant impact on modern biology. Similarly, the evolutionary and conservation biology work was pioneered by Birbal Sahni (especially known for his contributions in palaeobotany), but followed in later years strongly by the likes of Gadgil²⁴. Such discussions as in this article will also be incomplete without mentioning the piloting of the green revolution by M. S. Swaminathan and his colleagues. All these works have had a strong interdisciplinary component, thus making these areas exciting.

Although immensely useful in gaining deeper insights into biology, the reductive approach has had its drawbacks (Figure 3). That studying individual components does not necessarily lead to understanding the system as a whole, has led to growing unease among biologists. Therefore, in the last couple of decades, increasing attention has been paid to integrate studies from individual components to the whole system. Typically called systems biology or integrative biology, such an approach allows gaining understanding of the emergent properties of the system. Thus, the holistic approach works in the reverse direction of the reductive approach and attempts

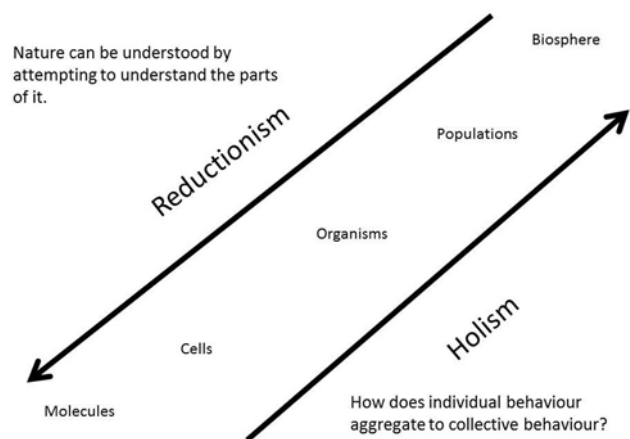


Figure 3. Schematic representation of the reductive and holistic approaches.

to understand the complex system by a combination of constituent components. In this context the holistic approach has led to some of the most pervasive questions of modern philosophy such as, 'How does individual behaviour aggregate to collective behaviour?' The question is relevant spanning across all sciences and not only to biological systems. We therefore appear to be poised for an exciting period in biological research, and hopefully important contributions from India will continue to emerge as in the past.

1. Oparin, A. I., *Priokhzhedenie Zhini Mosckovskii Rabochii*, Moscow, Reprinted and translated in Bernal, J. D., *The Origin of Life*, Weidenfeld and Nicolson, London, 1967.
2. Haldane, J. B. S., The origin of life. *Ration. Annu.*, 1929, **148**, 3–10.
3. Miller, S. L., A production of amino acids under possible primitive earth conditions. *Science*, 1953, **117**, 528–529.
4. Orgel, L. E., Evolution of the genetic apparatus. *J. Mol. Biol.*, 1968, **38**, 381–393.
5. Vijayan, M., Molecular interactions and aggregation involving amino acids and peptides and their roles in chemical evolution. *Prog. Biophys. Mol. Biol.*, 1988, **52**, 71–99.

6. Gadagkar, R., Evolution of eusociality: the advantage of assured fitness returns. *Philos. Trans. R. Soc. London*, 1990, **329**, 17–25.
7. Bagchi, B., Water dynamics in the hydration layer around proteins and micelles. *Chem. Rev.*, 2005, **105**, 3197–3219.
8. Narayan, V., Ramaswamy, S. and Menon, N., Long-lived giant number fluctuations in a swarming granular nematic. *Science*, 2007, **317**, 105–108.
9. Haldane, J. B. S., On being the right size, 1926.
10. Wilson, E. O., *On Human Nature*, Harvard University Press, USA, 1978.
11. Timofeeff-Ressovsky, N. W., Zimmer, K. G. and Delbruck, M., *Über die Natur der Genmutation und der Genstruktur*, Nachrichten von der Gesellschaft der Wissenschaften zu Göttingen: Mathematische-Physikalische Klasse, Fachgrupps VI, Biologie, 1935, pp. 189–245.
12. Schrödinger, E., *What is Life?* Cambridge University Press, 1944.
13. Ramachandran, G. N. and Kartha, G., Structure of collagen. *Nature*, 1954, **174**, 269–270.
14. Ramachandran, G. N., Ramakrishnan, C. and Sasisekharan, V., Stereochemistry of polypeptide chain configurations. *J. Mol. Biol.*, 1963, **7**, 95–99.
15. De, S. N., Enterotoxicity of bacteria-free culture of *Vibrio cholerae*. *Nature*, 1959, **183**, 1533–1534.
16. Kohler, R. E., *Lords of the Fly: Drosophila Genetics and the Experimental Life*, University of Chicago Press, USA, 1994.
17. Wood, W. B., *The Nematode Caenorhabditis elegans*, Cold Spring Harbor Laboratory Press, New York, 1988.
18. Siddiqi, O. H., Incorporation of parental DNA into genetic recombinants of *E. coli*. *Proc. Natl. Acad. Sci. USA*, 1963, **49**, 589–592.
19. Sharma, R. P., Wingless a new mutant in *Drosophila melanogaster*. *Drosophila Inf. Serv.*, 1973, **50**, 134.
20. Mahalanobis, P. C., Majumdar, D. N. and Rao, C. R., Anthropometric survey of the United Provinces, 1941: a statistical study. *Sankhya – Indian J. Stat.*, 1949, **IX**, 89–324.
21. Rao, C. R., *Advanced Statistical Methods in Biometric Research*, Oxford University Press, England, 1952, p. xii.
22. Kosambi, D. D., The estimation of map distances from recombination values. *Ann. Eugen.*, 1943, **12**, 172–175.
23. Balakrishnan, V. and Sanghvi, L. D., Distance between populations on the basis of attribute data. *Biometrics*, 1968, **24**, 859–865.
24. Gadgil, M., Dispersal: population consequences and evolution. *Ecology*, 1971, **52**, 253–161.

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