

Molecular Biophysics Unit, Indian Institute of Science: the first thirty years (1971–2000)

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The Molecular Biophysics Unit (MBU) of the Indian Institute of Science was established by G. N. Ramachandran in 1971. He assembled a well-balanced team of faculty members in the first half of the 1970s. After Ramachandran and a couple of others left, MBU continued its journey with six comparatively undecorated and young faculty members as the core group in 1979. Subsequently, and with the addition of more faculty members, it grew into a vibrant, coherent team and came to be considered as an outstanding department. This journey, outlined here, perhaps holds some lessons to the scientific community.

Background

The Molecular Biophysics Unit (MBU) of the Indian Institute of Science (IISc), Bengaluru was founded by G. N. Ramachandran (GNR) in 1971. He was perhaps the most distinguished scientist to have worked in independent India. He took his D Sc under the supervision of C. V. Raman from the Physics Department of IISc in 1947. Subsequently, he earned another doctorate from the University of Cambridge, UK in 1949. After his return to India, GNR worked as a faculty member in the Physics Department of IISc. In 1952, he joined the University of Madras as Professor and Founder-Head of the Department of Physics (from which the present Department of Crystallography and Biophysics originated) at the invitation of its Vice-Chancellor, Lakshmanaswamy Mudaliar. Moreover, Mudaliar provided all the necessary administrative and financial support to GNR and the latter's mandate was to establish a world-class research centre at Madras. This is precisely what he did. Partly on account of prodding from J. D. Bernal, GNR entered the field involving the study of biological molecules. He relied primarily on computational biophysics and crystallography for his studies. He was globally a pioneer in investigations on biomolecular conformation. The Madras group determined the crystal structures of several important biomolecules. Furthermore, GNR and his colleagues made substantial contributions to the methodology of crystal structure analysis.

The first major contribution to emanate from the Madras group was the determination of the structure of collagen in the mid-1950s. Among the three important types of fibrous proteins, collagen is the one which defied structure

solution even in the hands of veterans like Linus Pauling and Francis Crick. The enunciation of the triple helical coiled-coil structure of collagen was a landmark in the history of structural biology. Some controversies in relation to this structure, which turned out to be substantially irrelevant, eventually led GNR and his colleagues to propose the celebrated Ramachandran map in 1963. This map still remains the simplest descriptor and tool for validation of protein structures. During the less than two decades he was in Madras, GNR and his colleagues made several outstanding contributions to the structure and conformation of different types of biopolymers.

After the retirement of Mudaliar and on account of other external factors, the ambience at the University of Madras drastically changed in the second half of the 1960s. GNR could no longer work comfortably there. He left Madras for a sabbatical at the University of Chicago, USA, in 1970. On his return, he joined IISc in 1971. At the Institute, his intention was to have a small research group christened as the 'Molecular Biophysics Unit'. It is another matter that the group developed into a full-fledged department rapidly. However, the name 'Molecular Biophysics Unit' was retained.

Early years

The earliest colleagues of GNR at MBU were V. S. Ananthanarayanan and K. R. K. Easwaran, both of whom returned from postdoctoral stints abroad to ad hoc positions. In 1972, their positions were regularized as Assistant Professors. In the same year, three of his former colleagues in Madras, viz. V. Sasisekharan, V. S. R. Rao and C. Ramakrishnan, joined MBU, the first two as Professors and the third as Assistant Professor. I

was then occupying an ad hoc position in the Physics Department at IISc and moved to MBU for all practical purposes in 1973. I was made an Assistant Professor in 1974. In the meantime, P. Balaram joined MBU as a Lecturer in 1973. The last appointment during that phase was that of R. Chandrasekharan in 1974 as an Assistant Professor. For a few years, K. Venkatesan of the Organic Chemistry Department at the Institute was associated with MBU as an adjunct faculty.

Thus, MBU had grown within a span of less than three years from its inception into a full-fledged department with nine faculty members and their students and associates (Figures 1 and 2). The team was well balanced with different strands of molecular biophysics, currently referred to as structural biology, represented in it. The age distribution of the faculty members was also optimal. Serious scientific research started from the very beginning. However, the rapid expansion of MBU inevitably created some turbulence, the most important of which had to do with space. To start with, MBU had four rooms in the lecture hall complex with no provision for experimental investigations. After much prodding, by the end of 1970s two more locations were acquired for occupation. Thus, the X-ray laboratory and the workshop were located in a hall kindly lent by the Department of Civil Engineering at the Institute. The experimentalists had their office space and wet laboratories in the old Chemical Engineering building which was vacated by the members of that Department when a building was constructed. This was not a very convenient arrangement. For example, I had to shuttle among three locations every day: the departmental office in the lecture hall complex, the X-ray laboratory in the Civil Engineering Department and the wet lab and office in

the upper floors of the old Chemical Engineering building. MBU had no lecture hall of its own. The Microbiology and Cell Biology Laboratory was kind enough to lend its lecture hall to us, as and when required. We used to make use of bigger lecture halls in other departments also, when distinguished visitors gave talks. In spite of these constraints, research efforts at MBU progressed at a reasonable pace.

The period 1977–79 was a time of attrition. Chandrasekharan left MBU for USA in 1977. Ananthanarayanan followed suit in 1979, to take up a position

in Canada. Most importantly, GNR himself left the unit in 1978. During 1977–78, he was a Fogarty Fellow at the National Institutes of Health, USA. That probably provided him with an opportunity to think about his future endeavours. On his return from USA, he called all of us and indicated his desire to leave MBU. Naturally, we were all stunned. Subsequently, I had discussions with GNR as to why he took such a drastic decision. He said that he felt he had nothing more to offer to structural biology. Therefore, he wanted to explore other pastures in subsequent years. The

best way to do so was to make a clean break. After leaving MBU, GNR concentrated on subjects like mathematical philosophy and scientific logic.

We were devastated by the departure of GNR. The situation was akin to Hamlet without the Prince of Denmark. An event of this consequence naturally led to a spate of rumours and speculations. Some felt that GNR left as he was not satisfied with our performance, while some others felt that we had not been sufficiently solicitous about him. In the middle of this cacophony, we as a young group felt defenceless. It was important to establish that the relation between GNR and the rest of us was cordial. An opportunity for doing so arose when Dorothy Hodgkin, the celebrated British Nobel laureate, visited IISc in 1979. On account of my close association with Hodgkin, I was largely responsible for organizing her programme. One of the major events we organized was a symposium on the structure and conformation of DNA. That was the hot topic then in view of the major contributions Sasisekharan made in the area. We requested Dorothy to inaugurate the symposium. GNR greatly admired Dorothy. She, considerably senior to GNR, had always been a calming influence on him. GNR readily accepted our invitation to chair the inaugural function. We therefore had two stalwarts gracing the function. GNR was all praise for us in his presidential address and also extended his best wishes to us. That effectively put an end to the unpleasant discussions on the departure of GNR from MBU.



Figure 1. Members of MBU with Dorothy Hodgkin in 1973. Sitting: (L to R) V. S. Ananthanarayanan, C. Ramakrishnan, V. S. R. Rao, G. N. Ramachandran, Dorothy Hodgkin, K. Venkatesan, V. Sasisekharan and M. Vijayan. P. Balam is second from right in the last row. Manju Bansal, then a student, is behind K. Venkatesan.



Figure 2. Some members of MBU with Elkan Blout (third from left in the first row) in the mid 1970s. K. R. K. Easwaran is to the left of G. N. Ramachandran. Samir Brahmachari, then a student, is at the extreme left.

Expansion and consolidation

After the departure of three colleagues, including GNR, we were six faculty members in MBU. Among them, Sasisekharan and Rao were in the 40s. Ramakrishnan, Easwaran and myself were in the latter half of 30s. While Balam was just about 30. We were by and large an undecorated team and had hardly any influence to speak of. Yet, we received considerable appreciation and support on the basis of performance. The team was well balanced, not only in age, but also in subjects of specialization. Half of the team consisted of primarily computational biologists, all with the Madras background, while the remaining three were primarily experimentalists. Among

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these three, one was a crystallographer, another could be described as an expert in physico-chemical studies and the third was a bio-organic chemist. These six faculty members formed the core group which started the journey of MBU as a coherent department. In the meantime, part of the new MBU building got ready. In addition to space for general facilities, the then new building had six separate laboratories for the six existing faculty members. Five of us moved into the new building and Balaram chose to remain in the old Chemical Engineering building. The MBU building was subsequently expanded stage by stage to what it is today.

With the completion of the first part of the new building and the prospect of further expanding it, MBU was set for the next expansion. Five appointments were made during 1981–1984. There was a felt need for a biochemical component in MBU. Thus, one appointee was A. Surolia, who already had established collaborative arrangements with MBU for structural studies on proteins. S. K. Brahmachari, an old student and a new faculty appointee, had by then added biochemistry and molecular biology to his repertoire. The need for strengthening the computational biology component prompted the appointment of Manju Bansal, an old student, and Saraswathi Vishveshwara. Finally, M. R. N. Murthy was recruited with the avowed intention of initiating virus crystallography. A period of several years was allowed for the new appointees to settle down and develop a rapport with the existing faculty, before further appointments were made.

K. Suguna, a crystallographer, joined in the late 80s, while S. K. Sikdar and Raghavan Varadarajan were appointed in the early 90s. Sikdar added expertise in neuro biophysics to MBU and Varadarajan enhanced the already existing expertise in biophysical chemistry and molecular biology. In the meantime, Sasisekharan and Rao retired from service leaving a void in the area of computational biology. This void was partly filled up by the appointment of N. Srinivasan, an old student, towards the end of the 90s. Brahmachari, by then a Professor, left to take up position as the Director of a CSIR laboratory. In his place, Dipankar Chatterji was appointed as Professor. By then, he was already well established in Indian science. Thus, at the turn of the century, MBU consisted of about a dozen faculty members and their students and associates. Of course, by then we had ceased to be the young, green horns that the six from the original group were in the late 70s.

As long as GNR was at MBU, he provided the leadership. Sasisekharan was the chairman of MBU when GNR left. From then on till the end of 1984, he led MBU with great distinction. The transition of MBU from an unit primarily centred around a pre-eminent leader to a normal department was effected under Sasisekharan's leadership. After relinquishing the chairmanship of MBU, Sasisekharan went on to become the Dean of the Science Faculty and subsequently the first Chairman of the newly organized Division of Biological Sciences at IISc. Later, Rao also served

as the Dean of the Science Faculty. I was the Chairman of MBU from January 1985 till March 1992. That was a period of consolidation. I was followed by Easwaran. In the first half of 1993, I became the Chairman of the Division of Biological Sciences. Easwaran continued as the Chairman of MBU till 1995. He was succeeded by Balaram. Subsequently, Balaram succeeded me as the Chairman of the Division of Biological Sciences in 2000, when I became the Associate Director of the Institute. The subsequent changes in the leadership of MBU are beyond the period of current consideration. Balaram, of course, went on to become the Director of IISc. Happily, all the leadership changes in MBU were smooth and based on consensus among the faculty.

Research theme

It is impossible even to outline the research work carried out by more than a dozen faculty members and their students over about 30 years and described in well over a thousand research publications. By deliberate choice, the work was almost entirely concerned with structural biology which deals with the structure, conformation, assembly and interactions of biomolecules, and their relation to function. The scope of the effort has been inclusive and involved nucleic acids, proteins, polysaccharides and the biomembrane. The strategy has been to bring to bear all available methods on the central theme. The faculty and their associates at MBU constituted a truly interdisciplinary team during the period under discussion. A major component of the effort was computational biology. The faculty included scientists with expertise in X-ray crystallography, spectroscopy, other areas of biophysical chemistry, biochemistry and molecular biology, and organic synthesis. This engendered extensive collaborative interactions among the members of MBU as well as with other research groups inside and outside the Institute. Over the years, scientists at MBU grew into a reasonably integrated and coherent research team with a great deal of commonality in their approach.

Most of GNR's contributions to structural biology were made at the University of Madras, but many contributions by him emanated from Bengaluru as well (Figure 3).



Figure 3. At the Royal Society, London, when G. N. Ramachandran was conferred the Fellowship of the Society, in 1977. (L to R) M. Vijayan, Tom Blundell, G. N. Ramachandran, Mrs Ramachandran, unidentified and Dorothy Hodgkin.

The most notable among them is perhaps the elucidation of the role of hydroxyproline in collagen. That, among other things, settled a long-standing dispute on a specific detail of the structure of collagen. There have also been detailed studies on the structural requirements for proline hydroxylation.

A significant result to emanate from MBU was on the structural flexibility of DNA. Although there were some indications to the contrary, DNA was thought to be a monotonic double helix. It is to a substantial extent, the thorough computational and related investigations of Sasisekharan and his colleagues, who included some young faculty members, that demolished this notion. Different types of DNA conformations are now invoked to explain many phenomena. Sasisekharan and his colleagues were primarily responsible for, so to say, opening up the structure of DNA. This effort was followed up by several others, including that on the role of the secondary structure of DNA in gene expression. Structural and related studies on DNA continued to be an important component of the research activities at MBU.

Polysaccharides, which are polymers of sugars, have received much less attention than nucleic acids and proteins. The systematics of sugar and polypeptide conformation developed by Rao and his colleagues, have had considerable global impact. The group also explored, using computational techniques, protein–sugar interactions, lactam antibiotics and complex carbohydrates as determinants of specificity. Computational approaches to general protein–ligand interactions were also developed by them. Another unique component of computational studies at MBU was the systematic and thorough studies on the conformation of different cyclic peptides, carried out by Ramakrishnan and his students. The detailed analysis of the geometrical features of hydrogen bonds has also been noteworthy.

Proteins occupy the pride of place in terms of structural and functional diversity. Even before crystal structures of proteins began to emerge from India, many faculty members of MBU started analysing information available in the Protein Data Bank. Some of the results obtained from the analysis have had considerable impact. Early crystallographic studies at MBU related to proteins have been on the supramolecular association

and specific interactions involving amino acids and peptides, and their implications to chemical evolution and self-assembly. Subsequently, MBU played a major role in initiating and developing macromolecular crystallography in India. The first definitive result in the area to emanate from MBU was concerned with protein hydration and its consequences. Research on proteins entered into a different orbit when collaborative efforts on the biochemistry, physical chemistry and crystallography of lectins, quintessential carbohydrate-binding proteins, got off the ground. Towards the close of the last century, serious efforts at biochemical and structural investigations on proteins from microbial pathogens also began to yield results. Design of peptides using conformationally restrictive amino acids had already been part of the research work at MBU. Major efforts in protein folding were also underway by this time.

Membrane biophysics has been an important component of research at MBU. In particular, extensive physico-chemical, spectroscopic, crystallographic and synthetic studies on ionophores and their analogs have been carried out. The scope of the work included carrier ionophores and transmembrane peptide channels. Electro-physiological studies at the molecular level added a new dimension to the effort.

Peer recognition

Although MBU started its uninterrupted journey as a coherent department with a small group of relative green horns at the core, eventually members of MBU turned out to be a highly decorated group. Among the 16 faculty members who worked at MBU during 1980–2000, 10 obtained the Bhatnagar Prize. Almost an equal number were elected to all the three science academies of India. From among them, half a dozen are fellows of The World Academy of Sciences. The President of India awarded Padmashri and Padma Bhushan to one and Padmashri to two others. Those who occupied important positions at the Institute have already been referred to. One of the faculty members became the President of the Indian National Science Academy, another the President of the Indian Academy of Sciences and yet another the Director General of the Council of Scientific and Industrial Research. Many in

MBU occupied important positions in international organizations as well. Several former students of MBU have also been recognized with awards, fellowships and important positions.

Concluding remarks

From a somewhat disorganized, and to an extent turbulent, beginning in the 1970s, how did MBU emerge as a well-recognized department by the end of the 80s and also remain so subsequently? There is no simple answer to this question. While what is given in the foregoing is substantially a factual narrative, the attempt to answer the above question is primarily based on my personal observations and opinions.

The fact that MBU was founded by the great scientist GNR by itself gave it a head start. The rapid expansion in the first couple of years led to considerable disorder, but did not affect the high level of scientific operations that the involvement of GNR engendered. His choice of faculty members was well balanced. All computational biophysicists among them were his former students/colleagues from the University of Madras, while the experimentalists came from different institutions with varied backgrounds. Thus GNR assembled a team of young faculty members with complementary expertise among them, to pursue a common theme in research. Such a potent group could have been brought together within a couple of years, only by GNR. It is another matter that the whole group did not remain intact for long. As indicated earlier, only six of us remained at MBU by the end of the 70s. By then, we had inculcated a tradition involving synergy between that bequeathed by GNR and those brought by some of us from other internationally famous research schools.

In further faculty appointments at MBU, care was taken to see that proper balance within the organization was maintained. During the period under consideration, the research activities in MBU could be roughly categorized into three streams: (a) computational biology, (b) X-ray crystallography and (c) physico-chemical, biochemical and spectroscopic studies. Although this division was by no means watertight, an effort was made to ensure a reasonable balance among the three streams. Within each stream, the attempt was to ensure a spread of age groups in order to avoid

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unhealthy competition among the faculty. To an extent, the older members functioned as mentors of junior faculty. The proper balance among different disciplines and age groups facilitated extensive collaboration among the members of MBU faculty.

Coherence within a department needs to be preserved and promoted by deliberate action; it does not often happen automatically. In any group, particularly in those made up of brilliant self-driven persons, disagreements do occur. The responsibility of the leadership is to try to resolve them expeditiously and ensure that they do not degenerate into permanent squabbles. In this respect, MBU has been reasonably successful. It was per-

haps commonality of the research theme of the different groups, the complementary expertise of different faculty members which engendered extensive collaboration among them and the camaraderie among the members of the unit, that enabled MBU to orchestrate as a single entity.

What I have outlined above is a brief history of MBU till the turn of the century and what I perceive as the factors which helped it to perform well. The period beyond 2000 is too close to the present time to be assessed objectively. Furthermore, although MBU continued to be the platform for my research and engagement with Indian and international science, I naturally dissociated myself

from the administration of MBU after my formal retirement in 2004 (incidentally, as Raja Ramanna used to say, I have since then retired from different positions several times!). In any case, hopefully, the story of MBU holds some lessons for the scientific community.

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