The Early History of Biophysics at The University of Michigan

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Biophysics has had a long history at the University of Michigan, from its beginnings in the research of faculty members of the Department of Physics in the 1940s, through efforts to establish a department in 1950, toward the success in establishing a research institute, the Biophysics Research Division (BRD), in 1960, and to the present formation in the College of Literature, Science and the Arts (LSA) of an Enhanced Program in Biophysics (which is equivalent to a department) in 2009. My aim here is to provide an account of these early activities, which involved both the research of individuals and their persistent efforts to establish a viable academic unit at the University, the latter culminating in the formation of the BRD.

Individual Biophysical Research

The development of interest in melding the disciplines of physics and biology centered primarily on the research of scientists in the Department of Physics. It is therefore important to know the early history of this evolution in its elements of marrying the fundamentals and techniques of physics with the desire to answer basic questions in biology.

Detlev Bronk. Although the most substantive efforts in biophysical studies began in the 1940s, it would be amiss not to note the singular emergence of this disciplinary vision that is associated with Detlev Bronk This future president of the National Academy of Sciences and of the Rockefeller Institute of Medical Research started his scientific career at the University of Michigan. Although he enrolled in 1921 in the graduate program in Physics, working on studies of the infrared absorption of hydrogen chloride, by 1923 he was attracted to the idea of physical investigations of physiological mechanisms, encouraged by Chairman Harrison Randall "…in the belief that there is a large and undeveloped field in the investigation of physical laws in living organisms and [who] said that he would be glad to have such work carried on in his department…" (Brink, Jr., 1978). Bronk went on to study physiology and, with Robert Gesell, published seven papers on physiological properties of the respiratory and cardiovascular systems and on neural excitation of secretion from the salivary glands in mammals. In 1926 he received the Ph.D. in Physics and Physiology from Michigan, the first of its kind in the nation.

Bronk's subsequent research career continued with biophysical studies of physiological processes, and his advocacy of the discipline manifested itself in the transition of the Rockefeller Institute to Rockefeller University.

Harrison M. Randall. Randall's early interest in applying the discipline of physics to the solution of problems in biology developed into his own research in his later years (his 80s!). At this time he began to apply his expertise in infrared spectroscopy to a series of

studies on the characterization of compounds found in viruses and bacteria, and was publishing papers on this work (Randall, Smith, 1953). The Optical Society of America honored him for all his spectroscopic contributions with a 90th birthday issue of its Journal. He lived until almost 99.

H. Richard Crane. After getting his Ph.D. at Cal Tech and doing a post-doc there, Crane came to Michigan in 1935 and soon built an accelerator to continue his research in nuclear physics. In response to Medical School interest in the biological effects of radiation, he started a seminar on this topic and even pursued his incipient interest in biology by attending courses in biochemistry and physiology. In the early 1940s the Bacteriology Department acquired an electron microscope with funding from the Rackham Graduate School with the proviso that the Physics Department install and run it, which naturally fell to Crane. To help visualization, he "…asked [Robley Williams] if he could evaporate a little metal onto the bacteria and viruses that were to be photographed in the electron microscope, and wondered what they would look like. The effect was striking. They looked three-dimensional." (Crane, 1997). By 1945 Crane had perfected a shadow casting unit for the microscope, which Williams would exploit in his work.

After the war, Crane maintained activity in the biophysical area. In a paper on "Principles and Problems of Biological Growth" (Crane, June1950) he enunciated a basic idea: "The attachment of one [unit of a structure] to another was always done in exactly the same way, geometrically…The first and most striking thing to be noted in the models is that all of them take the form of a screw, or helix, which winds around a *straight* axis." It is intriguing to wonder if this article influenced Linus Pauling in his seminal proposals of basic protein chain structures, since he states in his first of many papers on the subject (Pauling, Corey, Branson, April 1951) that "Hence, the only configurations for a chain compatible with our postulate of equivalence of the residues are helical configurations." After the 1953 Watson and Crick discovery of the double-helical structure of DNA many scientists engaged in discussions of its biophysical properties, one of which was the 1956 Crane and Cyrus Levinthal (of the Physics Department) physical analysis of the proposed unwinding of the two strands during replication. Even though he no longer worked in this area, Crane maintained an active interest in the development of biophysics at Michigan.

Robley C. Williams. Williams came to Michigan in 1935 as an Assistant Professor of Astronomy, was recruited in 1941 for war work (during which he was introduced to viruses), and returned to Michigan in 1945 as Associate Professor of Physics. His work on evaporating an aluminum coating for telescope mirrors was what induced Crane to approach him on evaporating some on viruses for possible visualization enhancement. In 1945, together with Ralph W. G. Wyckoff of the UM Department of Epidemiology, Williams published the first electron shadow micrograph of the tobacco mosaic virus protein (Williams, Wyckoff, 1945), the forerunner of his many subsequent contributions to the study of the structure of this and other viruses.

Williams left in 1950 for Berkeley to continue his virus studies. In 1957 he was elected the first President of the recently formed Biophysical Society.

Cyrus Levinthal. After a Ph.D. at Berkeley and coming to Michigan in 1950, Levinthal turned his attention to biophysical studies. This resulted in the above-mentioned work

with Crane and in an important paper on the mechanism of DNA replication (Levinthal, 1956). In this work he used ^{32}P labeling to demonstrate that, as the replication proceeds from an initially fully labeled DNA reproducing in a non-labeled cell growing in a non-labeled medium, the label is fully retained in one strand of the double helix rather than being dispersed among the growing strands. This provided strong support for the complementary replication mechanism suggested by the double-helix DNA structure of Watson and Crick.

Levinthal left Michigan for MIT in 1957 and in 1968 he joined Columbia University as the Chairman of its newly-established Department of Biological Sciences. In subsequent work he stimulated considerations of the dynamics of how protein molecules fold into their biologically active form ("Levinthal's paradox," which points out that if the protein samples all possible conformations before finding its native structure it would require a time longer than the age of the universe); and he was the first to develop the basis of computer imaging of the three-dimensional structures of biological molecules.

Gordon B. B. M. Sutherland. Joining the Physics faculty in 1949, the eminent British scientist Gordon Sutherland quickly built one of the most prominent and diverse infrared spectroscopy laboratories in this country, providing continuity to the long-standing Michigan excellence in this field of spectroscopy started by Randall in 1911. Among his areas of research were macromolecular systems, including synthetic polymers and a continuation of his studies on biological systems. This was still the era of interpretation based on so-called group frequencies that were derived from complete analyses of the spectra of relevant small molecules, and is represented by his review on "Infrared Analysis of the Structures of Amino Acids, Polypeptides and Proteins" (Sutherland, 1952). At this point it did not seem feasible to obtain for such large molecules as polymers and proteins the kind of physical insights into structure provided by the normal mode analysis that could be implemented for small molecules. Nevertheless, he set the stage for the coming challenges to apply such analyses to the understanding of structure-spectrum correlations in macromolecules.

Sutherland left Michigan in 1956 to become director of England's National Physical Laboratory and in 1964 he became Master of Emmanuel College in Cambridge.

Samuel Krimm. One of the postdoctoral fellows in Sutherland's group was Samuel Krimm, who came in 1950 to study the infrared spectra of synthetic polymers. His initial goal was to investigate the then-unexplored far infrared region, which was accessible only at Michigan with a far-infrared vacuum spectrometer built in 1936 by Randall to obtain the long-wavelength rotation spectrum of water. Krimm's subsequent research involved obtaining experimental spectra of a range of polymers and implementing normal mode analyses for such systems based on force fields developed from small-molecule analogs. These studies led to a deeper understanding of fundamental aspects of the structure and interactions in polymers like polyethylene and polyvinyl chloride. It was this capability that induced Krimm in the early 1970s to extend his 1950s preliminary studies on protein spectra into an extensive program of normal mode analyses of the infrared and Raman spectra of polypeptides. The results of this research were summarized in a comprehensive and much-quoted review on "Vibrational Spectroscopy and Conformation of Peptides, Polypeptides, and Proteins" (Krimm, 1986). This area

remained a major component of his ongoing research program, of which other biophysically related studies included: circular dichroism investigations of the supposedly "random" chain structure of denatured proteins in solution; and theoretical studies to improve the physical accuracy of classical (so-called molecular mechanics) potential energy functions used for structure and dynamics calculations on proteins.

Other Biophysical Research Activities. During these early years other members of the Physics Department were working on biological problems. **Richard Sands,** arriving in 1957, set up a laboratory in BRD in 1963 to develop his electron paramagnetic resonance and Mössbauer studies of biologically important molecules, which continued throughout his subsequent Michigan research career. During his 1961-69 Michigan tenure, **Charles R. Worthington** embarked on incisive small-angle x-ray studies of molecular organization in collagen, muscle, and nerve myelin. While on the faculty from 1970-76, **C. M. Venkatachalam** pursued the important area of applying potential energy function computations to the determination of structure in proteins systems. In the following years, other continuing and new faculty members in the Department became engaged in a wide variety of biophysical research projects, undoubtedly contributing to and stimulated by the formation in 1973 of the Division of Biological Physics of the American Physical Society.

Academic Biophysics Units

It should be clear from the above descriptions that merging the disciplines of physics and biology was embedded from the earliest times in the vision of many members of the Department of Physics. The major players also felt strongly that the key to progress in achieving this goal would depend on a parallel effort by the University to establish an academic base for defining the discipline, developing the training of students, and promoting the acquisition of financial support for research programs. As the following chronology attests, this was not to be achieved in a timely manner, dedicated people left, and it is clear that Michigan failed to capitalize early on the revolution in molecular biology that was started by the 1953 discovery of the DNA double helix. However, it is gratifying to acknowledge that the sustained efforts to progress in this direction were eventually fruitful.

6/1949 Dean Ralph Sawyer announces the establishment of a "doctoral degree Program in Biophysics" in the Graduate School and appoints Robley Williams as the chairman of its implementation committee.

12/1949 Williams transmits to Dean Sawyer the Program's proposals for the Ph.D. in Biophysics. Its recommendations being approved, these remained the basis for the awards of future degrees.

1950 A decision is made to create a Department of Biophysics starting in the 1950-51 academic year, but the action is rescinded by the Regents following the resignation of Williams in June to go to Berkeley, attracted there by the virus work of Wendell Stanley and the opportunity to join the newly created Department of Virology. A bachelor's concentration in biophysics is established here in the Physics Department.

1/1951 Following the departure of Williams, Dean Hayward Keniston of LSA asks Sutherland to "reactivat[e] a program in biophysics" by "creating a committee which would serve to coordinate all of the interests in the field."

7/1951 Sutherland organizes a "Summer Symposium on Biophysics" at the University. Spealers include Salvatore Luria, J. Lawrence Oncley, Paul Doty, Ernest Pollard, and Max Delbruck.

11/1951 Sutherland, for the Committee on Biophysics, recommends to the Division of Biological Sciences "the early establishment of a Laboratory of Biophysics within the Physics Department with a separate allocation of funds."

1954 On behalf of the Executive Committee*, Physics Chair Ernest Barker, submits a proposal to the Administrative Officers "to sanction the formation of a Biophysics Research Unit as a separate entity in the University." Although "it would not be expected that it would be given any appropriation…it should receive due consideration in future appropriations… for research." (*H. R. Crane, R. W. Pidd, G. B. B. M. Sutherland, G. E. Uhlenbeck)

9/1955 The Regents, on request of the Department of Physics, establish in the Graduate School a Biophysics Research Center "to encourage research in biophysics and to administer funds provided for research in biophysics." Sutherland is named Director of the Center.

9/1955 The Biophysics and Biophysical Chemistry Study Section of NIH sponsors a "Conference on the Status of Biophysics" at the University "to discuss mutual research and administrative problems with leaders in the general area of biophysics."

7/1956 A "Summer Symposium on Biophysics" is held at the University. Speakers include Francis Crick, James Watson, Alex Rich, Erwin Chargaff, David Harker, Cyrus Levinthal, Gunther Stent, Seymour Benzer, Fancois Jacob, Joshua Lederberg, Sol Spiegelman, Felix Haurowitz, and many others.

12/1958 Following the departures of Sutherland and Levinthal, Samuel Krimm is appointed Director of the Biophysics Research Center.

1/1960 An application by Krimm to NIH for a graduate training grant is rejected, with the following comments: "The University of Michigan's early venture into physical biology was well known as well as are more recent difficulties which have been experienced. The failure of physical biology to develop and flourish was a source of great concern to our consultants and a cause for inquiry into why the environment was not a propitious one. [Our] consultants were of the opinion that [the Biophysics Committee] was in reality largely a paper structure which could not exercise the strong and continuing leadership in support of the proposed program which is so necessary for its success." The Center decides to urge substantive University commitment to biophysics and to the search for an eminent outside Director.

5/1960 Evolving from the impact of the NIH decision, and following intensive discussions by the Director and members of the Center with the administration, Dean Roger Heyns of LSA and Dean William Hubbard of the Medical School, with the concurrence of Dean Sawyer, submit a proposal to transfer the Center to the newly formed Institute of Science and Technology (IST). They propose that about "$75,000 of Institute funds be allocated to the support of the Center,

to be used primarily to secure one major appointment in biophysics and several younger appointments and to provide initial research support for [these]."

6/1960 The above proposal is formalized, presented to the Regents, and accepted by them to reorganize the Center as the Biophysics Research Division of IST, under the Office of the Vice-President for Research, with a Director.

6/1960 Based on earlier studies by the Center, Dugald Brown (Zoology) and Horace Davenport (Physiology) prepare an application to NIH, submitted by Dean Sawyer, for a Health Research Facilities Grant. Approval permits construction of the BRD wing of the IST building on North Campus. A committee to choose a director is formed.

9/1960 The committee to choose a Director of BRD first meets, with David Dennison of Physics as Chairman and Dean Heyns as a member.

1961 Oncley accepts the University's offer of the position of Director.

1962 Oncley arrives in Ann Arbor to assume the position of Director of BRD. The Biophysical Society, established in 1957 with Robley Williams as its first President, elects Oncley as its fourth President.

1963 The BRD wing in IST is occupied, including laboratories of several faculty groups that Oncley brings from Harvard as well as those of the Michigan groups of Krimm and Sands.

1964 An NIH Training Grant in Biophysics, with Oncley as Director, is awarded for a 5-year period to support the Ph. D. program, and is renewed in 1969.

It is evident that, with the establishment of BRD, the discipline of biophysics becomes embedded in the academic structure of the University. Its later history is another story, but it may be worth noting some highlights. **1) Interdisciplinary Chairs**: Krimm (Physics) 1976-86; Martha Ludwig (Biological Chemistry), 1982-83, 86-89, 95-96; John Langmore (Biology), 1989-95; Rowena Matthews (Biological Chemistry), 1996-2001; Erik Zuiderweg (Chemistry, Biological Chemistry), acting chair 2001-02; James Penner-Hahn (Chemistry), 2002-07; Duncan Steel (Electrical Engineering, Physics), 2007-08; Jens-Christian Meiners (Physics), 2008-. **2) Financial Support**: In addition to the University's traditional funding of faculty salaries and other administrative support for BRD, the Executive Officers approve in 1985 the establishment of a Program in Protein Structure and Design, with Krimm as Director, that includes funding for future additional BRD faculty appointments, many of them jointly with Physics. In 1986 the Program receives a $940,000 award from the State of Michigan's Research Excellence and Economic Development Fund, a portion of which is used to provide new and improved equipment in BRD. **3) Division Move**. In the interest of being located closer to participating departments, BRD is moved in 1993 from the IST building on North Campus into renovated space on the third and fourth floors of the 1908 wing of the Chemistry building on Central Campus. The move proves beneficial in all respects. **4) Organizational Change.** In view of the increasing role of teaching in the BRD mission, Provost Paul Courant initiates in 2005 a study of whether Biophysics should be more appropriately placed as a department within LSA. This results in 2009 in the creation of LSA Biophysics with Meiners as Chair, an Enhanced Program with tenure-appointing power and the inclusion of the undergraduate biophysics concentration. Progress to Departmental status is envisioned, a hopeful end to a 60-year journey.

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