AN INTRODUCTION TO THE FUNDAMENTALS OF BIO(MOLECULAR) ENGINEERING

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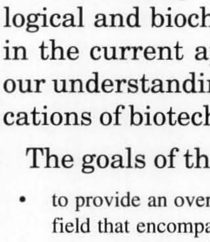
This is a course intended for first-year graduate students or seniors in chemical engineering and the physical and chemical sciences who may have a minimal background in the biological sciences and who have strong quantitative skills, including knowledge of linear algebra, calculus, and ordinary and partial differential equations. The course emphasis is on combining fundamental principles from physical chemistry, including thermodynamics and (non-linear) chemical kinetics (including irreversible thermodynamics), transport phenomena, and colloidal, interfacial, and molecular science to understanding a wide range of phenomena in biological and biochemical systems that are important in the current applications of biotechnology and in our understanding of living systems for future applications of biotechnology.

The goals of the present approach are

- to provide an overview of a wide open and rapidly developing field that encompasses material from subjects in the biological sciences, the physical and chemical sciences, and engineering
- to give the student the necessary fundamental information and skills to understand current developments
- to motivate the student to investigate areas that need further development, particularly in the area of molecular level design.

The design of structural and functional features of materials on the molecular scale is essential for modern developments in biotechnology and materials science. Examples include the development of new catalysts and sensors. The general philosophy of the course used to reach these goals involves the consideration of a hierarchy of structure from the molecular to the supracellular in light of known organizational features to illuminate gaps in our knowledge and to illustrate how our current understanding may lead to the design of functional units from the molecular to the supracellular levels.



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Fundamental aspects are stressed in order to provide a framework for further study of bioengineering in such areas as biochemical engineering, biomedical engineering, molecular (protein) engineering, metabolic engineering, and cellular engineering. This course differs considerably from conventional biochemical engineering courses offered in chemical engineering in that molecular-level concepts are incorporated within a framework of fundamental concepts of (non-linear) chemical kinetics, transport phenomena (viscoelastic fluids), and interfacial and colloidal science. In the modern chemical engineering curriculum it has become necessary for students to understand the relationships between the functional and structural properties of macromolecules; this includes not only conventional treatments of single macromolecules in solution but also dynamic systems of macromolecules functioning together in supramolecular and hierarchal structures.

The merging of chemistry and biology through rapid advances in our understanding of molecular scale events opens up the possibility for rational design of materials on the molecular level. The drive for high specificity, high selectivity, high purity, and increased quality control in the production and processing of many materials has stimulated chemists and engineers to look closely at living systems as models for building materials that have never occurred in nature. The diversity of life on earth provides a framework upon which new developments are being made. For example, our ability to develop new enzymes through site-directed mutagenesis and our understanding of molecular structure and function is giving rise to the creation of completely new artificial catalysts that promote reactions not found in natural systems.[1]

A recent work by Peacocke[2] reviews the literature on biochemical and biological organization that has arisen through the initial work of Hinshelwood in the 1940s and 1950s,[3] the work of A. Turing in the 1950s,[4] and the Brussels school of Prigogine in the 1960s to the present.[5] Peacocke overlooks the pioneering work of Rashevsky.[6,7] The emphasis of these researchers is on the use of chemical reaction kinetics and transport phenomena to describe spatial and temporal pattern formation in biochemical pathways and cellular structures. It is very revealing to the chemical engineering student that major contributions to this area have been made by chemical engineers through the analysis of chemical reactions[8-11] and that the students' own fundamental knowledge of chemical reaction kinetics and transport phenomena can be used to describe, for example, slime mold aggregation,[12,13] cell cycle oscillations,[14] the formation of zebra and leopard spots,[12] the spread of a contagious disease,[12] the functioning of the immune system[15] and cardiac arrhythmia.[16] Important developments in the analysis of chemical reactions[10,11] have also aided the advancement of the compartmental analysis of biological systems.[17] Peacocke only reveals part of the story, however, by not clearly illustrating the connection between the kinetic and systems ideas and the vast wealth of knowledge on the molecular structure of biological macromolecules that has been developed in the last twenty to thirty years. In addition, very recent developments in mechanochemical theory that links mechanical motion of molecular structures such as muscle and gel fibers to the chemical composition of the molecular structure[18,19] and solution are not fully addressed.

Fundamental aspects are stressed in order to provide a framework for further study of bioengineering in such areas as biochemical engineering, biomedical engineering, molecular (protein) engineering, metabolic engineering, and cellular engineering

TABLE 1
Outline and Major Topics

Overall Introduction

Part I: Introduction to the structure and organization of life and living systems
- Biodiversity-sources of materials and inspiration
- Structure of cells and subcellular components
- Molecular components of living systems

Part II: Molecular level interactions—biorecognition
- Physical/chemical properties of macromolecules
- Intermolecular forces that stabilize macromolecular structure
- Biological recognition-relationship between structure and function
- Macromolecular interactions with surfaces and surface forces that govern these interactions

Part III: Intracellular phenomena—The dynamics of multiple interacting macromolecules
- Metabolic pathways-multiple macromolecules working together in sequence or parallel
- Design and development of complex artificial metabolic systems

Part IV: Extracellular phenomena—The dynamics of multiple interacting cells
- Multicellular processes—chemical communication between cells
- Towards a hierarchy of direct and indirect interactions

The details of molecular structure and function arise through introductions to molecular biology,[20,21] macromolecular science,[22-24] intermolecular interactions,[25] and recent studies on mechanochemical coupling.[18] Intermolecular forces are responsible for the specificity and functioning of most biological macromolecules by giving rise to biomolecular recognition. Biomolecular recognition arises through the simultaneous action of a large number of fairly weak hydrogen bonds, and van der Waals, electrostatic, and hydrophobic interactions arrayed in unique geometrical configurations and acting cooperatively. This is a key concept that is stressed throughout the course because it is the basis for substrate binding to, for example, enzymes, cell surfaces, and antibodies.

The overall structure of the course consists of four parts that progress from a description of structure to the analysis of function (see Table 1). The first part of the course begins with an overall view of life and living systems and progresses to descriptions of cellular and molecular level features. The second part of the course seeks to develop the fundamental principles governing the interactions between macromolecules and small molecules, macromolecules and other macromolecules, and macromolecules and surfaces. The third part seeks to explore the dynamic features of many macromolecules interacting in metabolic pathways, and the fourth part seeks to explore the area of multiple interacting cells, or other subunits such as organelles, through introductions to multicellular communication through direct and indirect interactions and population models.

The mechanics of the course relies heavily on student involvement through term projects and class reports. Table 2 (next page) shows some examples of term papers. Each student is also responsible for presenting the general background material necessary for understanding the subject of their term paper. For example, the student discussing delivery of drugs to the brain also presents an introductory lecture on the analysis of facilitated diffusion.

COURSE OUTLINE AND DISCUSSION OF TOPICS

The introductory material for this course reflects a very broad and open-minded perspective on the field of biotechnology. In a general sense, one may consider biotechnology as the use of *biomaterials* (*i.e.*, molecules, combinations of molecules, cells, and tissues derived from living creatures) for feedstocks, processing tools, products, and as prototype models for new materials. Although we do not use the narrow definition of biotechnology that includes *only* the products of genetic engineering methods, it is clear that recombinant technology is making great inroads in a wide variety of new applications and that an understanding of recombinant methods is crucial. Perhaps the unique feature of this course is the concept that known biomaterials can be considered as models for the development of new materials. Protein engineering is the best known example of this; however, other examples include biomineralization, facilitated transport processes, and metabolic engineering.

From an engineering perspective, our major interest in biotechnology arises from the use of biomaterials as feedstocks, as processing tools, as products, and as an inspiration for creating new materials. Biomaterials encompass a large range of entities, from relatively simple organic compounds such as penicillin and amino acids, to complex macromolecules such as proteins and vitamins, to complete organisms such as yeasts, plants, and animals. Biomass as a feedstock for the production of alcohol and microorganisms as processing tools for food production and waste treatment have long been used. New bioprocessing tools include immobilized enzymes as industrial and consumer catalysts, recombinant bacteria for the production of eucaryotic proteins, and transgenic cows for producing human proteins.

From a long-range view, the most exciting developments use biomaterials to create new materials that have never occurred in nature. A very interesting example is the development of synthetic heme for the extraction of oxygen from water for life support in the ocean.[26] Biomimicry for synthesizing new materials is also rapidly advancing.[27] The 1988 Nobel Prize in Chemistry was awarded to D.J. Cram for his work on the design of molecular hosts and complexes. This merges synthetic organic chemistry and biochemistry to create new and exciting materials. Cram states that "evolution has produced chemical compounds that are exquisitely organized to accomplish the most complicated and delicate of tasks . . ." and his achievements demonstrate that we can build upon what evolution has produced.

TABLE 2
Sample Term Paper Projects

- The Role of Recombinant DNA Technology in the Degradation of Pesticides and Herbicides
- Biological Pattern Formation: Temporal Oscillations in the Eucaryotic Cell Cycle
- Drug Delivery to the Brain: Facilitated Transport
- Enzyme Engineering
- Biodegradation of Oil Spills
- Genetic Engineering for Enhanced Separation Processes

PART I
Introduction to the Structure and Organization of Life and Living Systems

The diversity of life that currently exists on earth, and that has ever existed on earth, is a tremendous source of substances and inspiration for the development of new materials. Prior to describing and discussing this diversity it is useful to consider the unique features of living organisms. Students generally recall from high school biology that all creatures grow, reproduce, consume, and excrete materials and energy from and to the environment, and that all living things eventually die. This is a useful beginning for the analysis of life, and the students may even recognize that there are entities such as viruses that are on the boundary of living and nonliving that are difficult to clearly classify. Other general features of life that students will easily come up with are the cell theory and the theory of evolution. The detailed discussion of these two theories is of central importance for understanding and analyzing the structure and dynamics of living systems.

Students trained in the physical and chemical sciences should be motivated at this point to ask questions such as: Do living systems obey the basic laws of physics? Certainly material and energy balances apply—but what about the second law? These ideas are succinctly expressed by Schrodinger,[28] who speculated that the dynamic aspects of living systems are related to structural aspects through large molecules, and that these structural molecules and relationships are of special significance for living systems.

> "...it has been explained that the laws of physics, as we know them are statistical laws. They have a lot to do with the natural tendency of things to go over into disorder. But, to reconcile the high durability of the hereditary substance with its minute size, we had to evade the tendency to disorder by 'inventing the molecule,' in fact, an unusually large molecule which has to be a masterpiece of highly differentiated order, safeguarded by the conjuring rod of quantum theory. The laws of chance are not invalidated by this 'invention,' but their outcome is modified. The physicist is familiar with the fact that the classical laws of physics are modified by quantum theory, especially at low temperature. There are many instances of this. Life seems to be one of them, a particularly striking one. Life seems to

> be orderly and lawful behavior of matter, not based exclusively on its tendency to go over from order to disorder, but based partly on existing order that is kept up ...

Further aspects of ideas from irreversible thermodynamics[5] will arise later in the course. However, the main idea in the beginning is to stress that there are important connections, as Schrodinger stated, between the need for macromolecules of "highly differentiated order" and dynamics of living systems, *i.e.*, the organisms' struggle against the forces of entropy. Although he referred primarily to macromolecules that carry genetic information (DNA's role and structure were unknown at the time) and the need for the long-term stability of such macromolecules, it is clear that the general ideas include other macromolecules that make up living organisms. (More recent criticisms of several other aspects of Schrodinger's ideas can be found in Kilmister.[29])

Macromolecules make up the 'first' level of structural 'order' in living systems. They are held together first of all by covalent bonds and secondly their active structure arises through a number of intermolecular forces and solution mediated interactions. Introduction to the basic classes of macromolecules, *i.e.*, nucleic acids, proteins and carbohydrates, can stress the relationship between structure and function. The assembly of lipids into membrane structures is a good example where the molecular structure of individual lipids gives rise to the structure and function of the membranes that they form. Membrane structure and the organization of lipids into micelles, liposomes, and other structures is an important area to consider in detail since it is the basis of all 'higher level' compartments (organelles) in living systems, and it has major applications in separation and reaction processes.[30]

Mere descriptions of the hierarchal structure of taxonomy,[31] cells, subcellular organelles,[32] and molecular components of living systems can be somewhat dry without constant reference to questions such as: Why are plants, animals, and cells of particular sizes? What type of interactions (*i.e.*, direct or indirect) govern the relationships between different hierarchical levels? (For this latter point, see Part IV.) The engineering student, trained in transport and kinetics and scale-up principles, should be able to postulate and test ideas to explain these and other physical biology features.[33-35] Concepts from mass transfer and fluid dynamics can be used to describe the structure of various sea creatures.[36] In addition, it benefits the student greatly if key features of various levels of description are illustrated. For example, in discussing the taxonomic levels of living organisms it is useful to describe which organisms are used directly by man and for what purpose they are used and why they are used. When discussing the structure of eucaryotic organisms, aspects of intracellular processing such as in the secretion and post translational processing of insulin[37] or the transport of materials in and out of the cell[38] can be considered in light of their effects on producing eucaryotic proteins in procaryotic cells and in analogy to the processing required in chemical plants (*i.e.*, well-defined regions for reactions and extensive material sorting and purification structures[39]).

PART II
Molecular Level Interactions—Biorecognition

Once the student has a clear idea of the multiple levels of hierarchal structure of living systems from the molecular to organelle to cellular to organism discussed above, it is useful to continue with a study of the physical/chemical properties of biological macromolecules. Basic ideas from colloidal science including thermodynamic, hydrodynamic, and electrokinetic properties can be introduced within the context of the student's understanding of transport phenomena and physical chemistry. There are a number of excellent references for this area.[22-24,40] General physical/chemical features of macromolecules such as size, surface area, charge, and shape should be considered in light of their effects on separation (chromatography, filtration, solubility) and reaction (immobilized enzymes and cell) processes, and in addition to point to further study of how these macromolecules function in groups or assemblages such as membranes, and sub-cellular organelles.

Intermolecular forces that stabilize macromolecular structure can be presented by first considering the nature and origin of intermolecular forces.[25] Many aspects of fundamental importance such as the nature of van der Waals forces, hydrogen bonding, and dipole and hydrophobic interactions can be considered. Many of the fundamental aspects have been well developed and current experiments[41] using the atomic force microscope have led to interesting advances in, for example, molecular rearrangements upon receptor ligand binding. One major area that needs further development is a quantitative treatment for the hydrophobic effects.

Biological recognition and the relationships between structure and function are key areas that can be considered in much detail. Qualitative examples such as enzyme catalysis (*e.g.*, a serine protease such as chymotrypsin[42]), antibody binding (avidin/biotin affinity chromatography[43]), cell surface interactions, and facilitated membrane transport (oxygen binding by hemoglobin and myoglobin[44]) can be described in detail. The quantitative description of these systems can be considered first from the thermodynamic approach[45-47] where binding equilibria are developed and second from the kinetic approach through Michaelis Menten type kinetics. Smoluchowski theory and Brownian motion[48] can be used to discuss diffusional limitations. In addition, recent work on the induced fit[49] and directed binding is useful in developing the dynamic approach to macromolecular recognition.

Macromolecular interactions with surfaces and surface forces that govern these interactions are vital for understanding many biochemical separation and reaction processes such as affinity chromatography and enzyme immobilization procedures. An understanding of surface interactions is also necessary for biofouling in industry, commerce, and biomedical devices. The molecular basis for adhesion of biological macromolecules on cell surfaces to inorganic matrices can be approached from the fundamental perspective as developed by Israelachvili[25] and in light of recent advances in active site directed binding.[41]

PART III

Intracellular Phenomena: The Dynamics of Multiple Interacting Macromolecules

One of the main goals of this course is to foster development of links between the dynamics of macromolecules working together and the structural features of the macromolecules and their complexes. The chemical engineering perspective for analyzing multiple linear and nonlinear chemical reactions in convective-diffusion processes can be used as a basis for analyzing metabolic pathways (lumping analysis,[50] modal analysis,[51] metabolic models,[52] cybernetic models[53] such as glycolysis, the regulation of protein synthesis, and the energetics of active transport in cell membranes[44]). This is exemplified in the development of reaction-diffusion work from both chemical engineering and biological literature. The view of the reaction processes, however, must go beyond treating the reactants as species without structure since biological structures are dynamic entities that, for example, change shape on substrate binding and that exhibit a wide range of allosteric and cooperative behaviors.

Biomechanical theories for the chemomechanical aspects of structure formation such as muscle action and cell motion can be considered within the context of advanced transport phenomena as elaborated by Murray, *et al.*[18] The swelling of (bio)polymers and the electrokinetic effects of applied electrical fields on (bio)polymers can be treated within the context of the engineering students' background in continuum mechanics as is appropriate for an introductory class.[54,55] This area is also important for the development of devices to convert chemical energy to mechanical work with little heat generation. Both of the above chemical and mechanochemical theories are useful for the design and development of complex artificial metabolic systems and structural units.

PART IV

Extracellular Phenomena: The Dynamics of Multiple Interacting Cells and Subunits

The last level considers direct and indirect interactions for multicellular and multi-subunit (*e.g.*, organelles) processes. Figure 1, a schematic view of such interactions, shows features very similar to the structure of a eucaryotic cell. Direct interactions between cells is important for a full understanding of tissue function and development as well as for such systems as immobilized cells or enzymes in membranes. Indirect interactions are important for bioreactor systems where cells, particles of immobilized cells, and particles of immobilized enzymes communicate through the bulk solution of well-mixed reactors. This area is currently not covered in detail for undergraduates; however, graduate students can appreciate these aspects through comparison to advances in chemical reactor analysis.[56] In addition, an introduction to population models[52,57,58] is necessary for understanding the growth of microbial organisms in natural and reactor processes.

CONCLUSIONS

There is currently a need for an introductory-level course for the engineering and physical and chemical sciences student that will develop the molecular and hierarchical organizational features of biotechnology, herein considered in a broad sense as the use of biomaterials (*i.e.*, molecules, combinations of molecules, cells, and tissues derived from living creatures) for feedstocks, processing tools, products, and as models for new materials. The course described in this paper seeks to integrate current and past developments from a wide range of fields into the chemical engineering curricula, to instill in the student the necessity for reading and understanding materials from a broad range of subjects and to inspire students to seek answers to unknown questions about the applications of the biosciences for improving our quality of life. This approach can be accomplished by building upon a fundamental understanding of transport phenomena and chemical kinetics through the introduction of analysis of non-linear chemical reaction-convective-diffusion processes, non-Newtonian and viscoelastic mechanics, colloid and interfacial

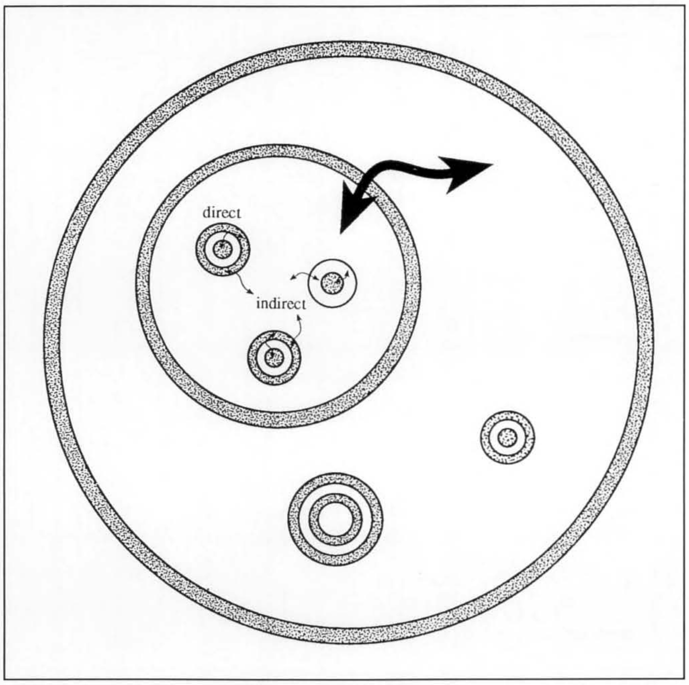

***Figure 1.** Hierarchy of direct and indirect interactions*

science, and population balance approaches. This approach will lead to additional coursework to introduce molecular transport theories,[59] statistical mechanics, and even quantum mechanics for further study of bio(molecular) design.

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two best seminars. The awards are usually books provided by the department and presented to the winners at the first seminar of the following semester. Also, pointers (useful for seminars) are given to all speakers.

The gifts express the appreciation of all department members for the effort the speakers put into their presentations. They also serve as a motivation for the graduate students to come forward and give a seminar.

SUMMARY

The graduate students in the Department of Chemical Engineering and Materials Science at Syracuse University, in collaboration with the faculty, have developed a seminar program called the "Colloquium Series in Chemical Engineering and Materials Science," with the objectives of improving the communication skills of graduate students, sharing knowledge, and exchanging ideas. Our experience has been that those objectives have been met. Furthermore, the ColCEMS program has also served as a catalyst for bringing all members of the department closer together. Intellectual relations among graduate students, research associates, and faculty have been enhanced, and everyone has had the opportunity to see beyond the technical skills of the speakers.

We feel that in an academic setting, where people are constantly coming and going over a relatively short period of time, this kind of activity is important for both educators and students. We wanted to share this experience with the readers and to urge graduate students at other schools to initiate a similar program.

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