7.345 Are There Inherent Limits to Our Understanding in Biology? A Challenge and Exploration Based on Diseases of the Nervous System

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Molecular biology over the past two decades has experienced significant changes in both methods and understanding, with major technical innovations facilitating diverse breakthroughs. For example, high-throughput techniques and genome sequencing, introduced in the 1990s, have generated vast quantities of data and valuable insights concerning the workings of the cell under normal and disease conditions. The impact of these findings in the context of human disease has been greatest in the case of single-gene disorders (e.g., cystic fibrosis), which in general are relatively rare. However, most common human diseases, ranging from solid tumors (e.g., sarcomas and carcinomas) to cardiovascular, neurodegenerative and neuropsychiatric pathologies, have remained refractory to non-symptomatic therapeutic interventions, mostly because researchers have been unable to identify simple causative mechanisms. In other words, most common diseases have proved to be both heterogeneous in origin and mechanistically complex. Why is this the case, and what is preventing us from reaching an understanding of the pathologies of these disorders -- a scientific understanding that is not merely descriptive but rather founded on mechanism? This course aims to examine current challenges in the field of pathobiology (the study of the molecular and physiological mechanisms of disease). Students will discuss, through detailed analysis of the primary research literature, whether these challenges possess an underlying commonality. For example, have ultimate causes of many diseases remained elusive because of (i) limitations in experimental or computational methodology, (ii) limitations in our ability to interpret complex data, and/or (iii) some unknown facet of the diseases themselves? Can we identify a common thread in the answers to these questions for multiple diseases? In our efforts to answer such questions, might we discover some inherent limitation to human understanding -- a cognitive limitation similar to that which a rodent faces when fruitlessly attempting to learn to navigate a prime-number maze? If the answer is yes, can we do anything to overcome that limitation? If the answer is no, does that mean that there are no upper limits to what science can reveal and to what we can comprehend, e.g., concerning the etiology of a disease? We will focus on disorders of the nervous system, such as neurodegenerative diseases and cancers of the central nervous system. Our discussions will be framed by two general themes: (i) the quantification and meaning of uncertainty in experimental biology and (ii) a potential limit to scientific understanding. The primary goals of this course are for students to enhance their skills in critically evaluating the primary research literature and to think about the relationship between objective realities as typified by experimental data and human cognitive abilities and limits. The course will include a field trip to a computational/theoretical biology laboratory focused on the structures of proteins to observe how theoretical studies of protein structures can help reveal novel facets of pathological protein-protein interactions in neurodegenerative disorders.