PROTEIN CONDENSATION

Kinetic Pathways to Crystallization and Disease

This book deals with the phase transitions, self-assembly, and aggregation of proteins in solution. Its primary purpose is to bring an interdisciplinary audience the state of the art in current research. The book discusses issues related to the production of high quality protein crystals from solution, in which the bottleneck is crystal nucleation. Since protein function is determined by protein structure, it is necessary to grow high quality crystals in order to determine their structure, usually by X-ray crystallography. The main challenge is to determine the initial solution conditions so that optimal crystal nucleation occurs. The book also discusses diseases that occur due to undesired protein condensation, an increasingly important subject. Examples include sickle cell anemia, cataracts, and Alzheimer's disease. Current experimental and theoretical work on these diseases aims to understand the diseases at a fundamental, molecular level, in order to prevent the undesired condensation from occurring. Suitable for graduate students and academic researchers in physics, chemistry, structural biology, protein crystallography, and medicine.

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To our wives, Peggy, Maria, and Martha
for their patience, love, and continued support

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Preface

This book deals with a truly interdisciplinary subject: protein condensation from solution. We use "condensation" in this book to denote one of several forms of proteins: a dense, protein-rich fluid phase, an amorphous aggregate, a gel, a crystal, or a polymer fiber. All these forms have been observed experimentally and are important in their own right. The primary purpose of the book is to bring to a wide audience the current status of research in the field, which is still evolving at a rapid rate. The bulk of the book deals with issues related to producing high quality protein crystals from solution, in which the bottleneck is crystal nucleation. Here the main challenge is to determine the initial solution conditions so that optimal crystal nucleation occurs. A second and increasingly important subject that we discuss involves diseases that occur due to undesired protein nucleation. A classic example is the nucleation of polymer fibers of sickle hemoglobin molecules within the red blood cells that distorts the cells and produces sickle cell anemia. Another example is that of age-related cataracts produced by the undesired aggregation of γ-crystallin protein molecules within the vitreous fluid of the eye. A third, somewhat different, example involves the role of amyloid β protein in Alzheimer's disease. This list is likely to grow as scientists become more aware of the molecular origins of different diseases.

As the field is interdisciplinary, the first part of the book involves several brief reviews of subjects relevant to understanding protein condensation. Readers with an expertise in these topics should omit them and begin with the second part of the book, which treats several examples of globular and membrane proteins. The third part deals with the three diseases mentioned above.

We should note what the book does not deal with. It is not a treatise on the practical art/science of growing protein crystals. The classic work on this subject is A. McPherson's book, *Crystallization of Biological Macromolecules*. The emphasis in our book is on developing a statistical mechanics theory of the equilibrium and non-equilibrium aspects of protein condensation. We do not

discuss the kinetics of crystal growth since several review articles exist on this topic.

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