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Book Review

Normal Mode Analysis Theoretical and Applications to Biological and Chemical Systems.
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Chapman and Hall/CRC (Mathematical and Computational Biology Series).

The realization that many of the important biochemical phenomena occur in the micro- to millisecond timescale has resulted in the need for computational methods that would extend beyond the nanosecond regime that is currently accessible with explicit-solvent molecular dynamics simulations. The normal mode analysis method, initially developed in solid-phase physics, met that need by enabling the exploration of large scale collective motions that occur in systems ranging from small proteins and nucleic acids to the bacterial ribosome. This method requires the derivation of eigenvectors and eigenvalues through the diagonalization of the Hessian matrix, which is composed of mass-weighed second derivatives of the potential energy function. The calculation and storage of the Hessian scales quadratically with the size of the system. An added benefit to normal mode analysis is the ability to determine the entropy and specific heat. These quantities are particularly useful for the estimation of the binding free energy for the association of macromolecules, as well as the binding of small molecules to macromolecules. The large memory required for the diagonalization of the Hessian matrix, which scales as the cube of the number of atoms, often exceeds the capability of most modern computers for very large systems. This has prompted the development of a series of techniques to address this problem. Many of these techniques are discussed in this book.

The book begins with a general introduction to normal mode analysis written by Konrad Hinsen. The subsequent five chapters present various extensions of the normal mode analysis methodology. These include strategies to reduce the size of Hessian matrix by partitioning the molecule into a set of blocks, such as the rotational–translational block (RTB) strategy, or the block normal mode method (BNM), which extends on the RTB approach and includes a set of low-frequency modes in addition to the translational and rotational eigenvectors of the blocks (Chapters 4 and 5). Yet another approach includes the partitioning of the Hessian into sub-blocks and using an iterative approach to arrive at the low-frequency modes (Chapter 2). Elastic network methods (ENM) figure prominently in these chapters, including offshoots of the method, such as the Gaussian network method (GNM), which is thoroughly introduced in Chapter 3 and again in Chapter 9. Some of these techniques are combined, as illustrated in Chapter 6, where ENM and RTB are used to study the motions of macromolecules and their assemblies including the bacterial ribosome. Particularly intriguing was the combination of normal mode analysis and quantum mechanics/molecular mechanics (QM/MM) potentials, to reproduce high frequency vibrations from experiment, of bonds within the active site of a protein (Chapter 4). A bit of an abrupt switch occurs subsequent to Chapter 6, whereby a description of the use of normal mode analysis in macromolecular structure refinement from X-ray diffraction and cryo-electron microscopy is presented. This is followed by a discussion of the use of normal mode analysis to study motions in x-ray crystallography data in Chapter 8. Another abrupt switch occurs in Chapter 9 where the reader is taken back to methodology, more specifically the refinement of GNM parameters, such as the cutoff distances and spring constant. In Chapter 10, a fascinating application of the normal mode analysis to DNA is presented, more specifically long DNA molecules, providing insight into how DNA of several hundred base pairs might respond to changes in nucleotide sequence and environmentally induced superhelical stress. Another application is presented in Chapter 11, again illustrating the capabilities of normal mode analysis, with the study of the motions of an entire icosahedral virus, made possible due to the clever application of group theory concepts.

The calculations were carried out on the full atomic model of the virus and included full dihedral flexibility. The rest of the book is devoted to extensions of the normal mode analysis, with emphasis on anharmonic effects and principal component analysis. In Chapter 12, for example, Akio Kiato presents the Jumping among minima (JAM) model, while Bowman discusses his driven molecular dynamics method, which precludes the determination of a Hessian (Chapter 14). Chapters 17 and 18 discuss collective coordinate approaches in conformational sampling, where principal component analysis is used to study large scale motion that would otherwise not be captured from standard molecular dynamics simulations.

This timely book brings together scientists from various backgrounds to discuss normal mode analysis and its application to biological systems. The discussion, however, was not entirely limited to normal mode analysis, which is an added benefit to the book; the final chapters of the book are devoted to methods that extend the normal mode analysis. In the process, these methods address some of the main limitations of normal mode analysis. The book is partitioned into 18 short chapters, where methodology is usually discussed first, followed by applications of the method. Chapters 7 and 8—where normal mode analysis is used to aid in the structure refinement process in X-ray diffraction—are out of place, and would be more appropriately placed after Chapter 10. Chapter 13 deals entirely with liquids, and seemed to be out of place in a book that deals entirely with biomolecules. Throughout the book, the authors do not shy away from including key equations to discuss the theory behind their methods without overburdening the reader. The chapters are in general well referenced, and include black and white illustrations of macromolecular structures, figures and tables; colored images, figures and tables are placed in the middle of the book (15 pages), between Chapters 6 and 7.

The book would be useful as a supplementary course textbook for an advanced undergraduate or graduate computational chemistry course, as well as a graduate course in statistical thermodynamics. Other courses could also benefit from this book. For example, Chapters 7 and 8 could be relevant reading during the structure refinement phase of a macromolecular crystallography course. Molecular spectroscopy applied to biological molecules could benefit from the thorough discussion of the normal mode analysis method, as well as the successful use of normal mode analysis with hybrid QM/MM potential to extract high frequency motions within the active site of a protein (see Chapter 4). General biochemistry courses could also benefit by using the book to illustrate the importance of motion and dynamics to students, and the computational means to study them. Instructors can select individual chapters from the book that relate to topic under discussion. In light of the comprehensive nature of the book, it would serve as an excellent reference book.

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