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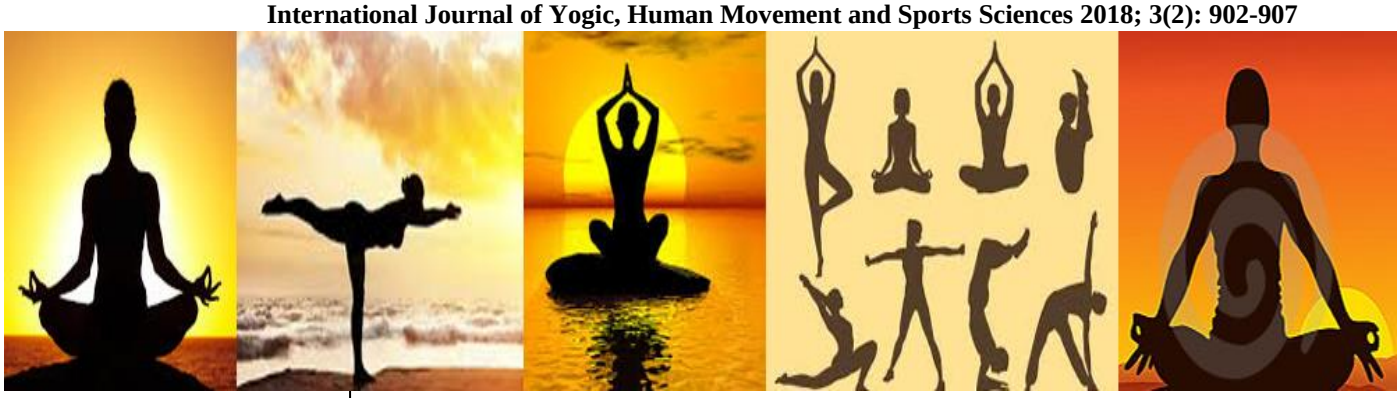

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Bioinformatics- mathematical and computational modeling in biology

Dr. Amitabha Kar and Dr. Partha Majumder

Abstract
A variety of topics are reviewed in the area of mathematical and computational modeling in biology, covering the range of scales from populations of organisms to electrons in atoms. The use of maximum entropy as an inference tool in the fields of biology and drug discovery is discussed. Mathematical and computational methods and models in the areas of epidemiology, cell physiology and cancer are surveyed. The technique of molecular dynamics is covered, with special attention to force fields for protein simulations and methods for the calculation of solvation free energies. The utility of quantum mechanical methods in biophysical and biochemical modeling is explored. The field of computational enzymology is examined.

Keywords: Mathematical biology, epidemiological models, cellular physiological models, molecular dynamics, solvation free energies, computational enzymology

Introduction
Mathematical, computational and physical methods have been applied in biology and medicine to study phenomena at a wide range of size scales, from the global human population all the way down to the level of individual atoms within a biomolecule. Concomitant with this range of sizes between global to atomistic, the relevant modeling methods span time scales varying between years and picoseconds, depending on the area of interest (from evolutionary to atomistic effects) and relevance. This review will cover some of the most common and useful mathematical and computational methods. Firstly, we outline the maximum entropy principle as an inference tool for the study of phenomena at different scales, from gene evolution and gene networks to protein-drug molecular interactions, followed with a survey of the methods used for large scale systems—populations, organisms, and cells—and then zooming down to the methods used to study individual biomolecules—proteins and drugs. To study the large systems, the most common and reliable mathematical technique is to develop systems of differential equations. At the molecular scale, molecular dynamics is often used to model biomolecules as a system of moving Newtonian particles with interactions defined by a force field, with various methods employed to handle the challenge of solvent effects. In some cases, pure quantum mechanics methods can and should be used, which describe molecules using either wave functions or electron densities, although computational costs in time and resources may be prohibitive, so hybrid classical-quantum methods are often more appropriate. Quantum methods can be particularly valuable in the study of enzymes and enzymatic reactions.

Maximum execution in biology and drug discovery
Two reasoning methods, deduction and inductive inference, have been utilized in the development of theories to interpret phenomena we observe in nature, and to make predictions about complex systems. Deduction allows us to draw conclusions when sufficient information is available, and is contrasted with inductive inference (also known as inductive logic or probable inference). Inductive inference provides a least biased way to reason when the available information is insufficient for deduction. It is called “inference” when we make estimates of quantities for which we do not have enough information to use deductive reasoning, and “induction” when we are generalizing from special cases [1].

When we deal with complex systems, for example either many-body interactions at the microscopic level, complicated regulatory protein-protein networks at the mesoscopic level, or population genetics at the macroscopic level, we never have enough knowledge to completely understand the system. Therefore, we normally rely on inductive inference based on the available information to infer the most preferred solution to problems related to these systems. Particularly, we are interested in a mathematical tool for inductive inference based on the Bayesian interpretation of probability, the rules of probability theory, and the concept of entropy. Bayesian interpretation treats probability as a degree of our knowledge about a system of interest, rather than the frequency of appearance of an event. Cox demonstrated that this type of probability can be manipulated by the rules of standard probability theory [2]. This forms the building blocks of inductive inference, termed Bayesian inference. Moreover, Caticha and Giffin have shown that Bayesian inference is a special case of entropy-based inference [3]. Therefore, our discussion in this section will be founded on entropy-based inference.

Entropy as an information measure

Shannon's pioneering work on the quantification of information loss during communication established a new viewpoint on entropy, which was until then only known as a measure of randomness in thermodynamics [8]. Since then, using entropy as an information measure has attracted much attention not only in signal processing, but also in the field of biology.

Information in genomic evolution

With the advance of genomic sequencing technology there is more and more genomic sequence data available for species across the three domains: Bacteria, Archaea, and Eukaryota. The question is, how do we compare complete genomes and extract useful information from the sequencing data?

To address the question of genome comparison, Chang *et al*. [4] proposed an entropy-based scheme for complete genome comparison. The foundation of their approach is to define the probability distribution that represents our current state of knowledge regarding the occurrence of different combinations of the four bases in DNA sequences. Chang *et al*. [4] specified that *k*-mer nucleotides in the sequence encode genetic information, where *k* is an arbitrary number. The occurrence of *k*-mers in a DNA sequence characterizes that sequence. Based on this definition, information in sequences can be quantified with Shannon information. Furthermore, Chang *et al*. [4] introduced the concept of reduced Shannon information, which is defined as the ratio of the Shannon information of the genome to the Shannon information of random sequences, so as to quantify to what extent the information contained in the genome is different from the information in a random DNA sequence. Note that this concept is similar to the concept of relative entropy, which is discussed in the next section. Based on reduced Shannon information (or relative entropy), a universal feature across three taxonomic domains was observed; namely, the effective root-sequence length of a genome, which is defined as the ratio of genome length and reduced Shannon information, linearly depended on *k*, and was a genome-independent constant. Furthermore, this study revealed a possible genome growth mechanism: at an early stage of evolution, a genome is likely to utilize random segmental duplication, which would maximize reduced Shannon information. These insights not only provide a clue to the origin of evolution but also may shed light on further questions, such as which genes are responsible for drug resistance.

Entropy in molecular docking

Our first example of applying entropy for inductive inference is *in silico* drug discovery. Virtual screening has attracted much attention in the pharmaceutical industry [12, 13]. It provides a more economical way to screen diverse chemicals as drug candidates compared with a wet-lab approach. Basically, it consists of the creation of a chemical library, followed by searching optimal ligand-receptor binding modes through docking algorithms, and finally the evaluation of binding affinities. There are three criteria that are required to successfully identify drug candidates. First, the chemical library needs to be large and contain diverse chemical structures. Second, conformational search algorithms need to be able to search possible binding modes within a reasonable time. Third, an appropriate scoring function needs to be utilized to correctly evaluate the binding affinity of the chemical structures. In the framework of information theory, the first and third criteria are the fundamental information required in virtual screening process. The second criterion then can be treated as an information processing guideline. The efficiency and accuracy of this step will depend on the methods of information processing.

Genetic algorithms, which borrow from the concept of genomic evolution processes to search conformations of complex targets and chemical structures, are commonly used in docking protocols, such as AutoDock [14]. Chang *et al*. have offered a better alternative, MEDock [6]. Although MEDock did not completely exploit entropic-based inductive inference for searching, it does utilize the maximum entropy principle as a guideline to make decisions during this process. The fundamental question asked in MEDock is "What is the probability of finding the deepest energy valley in a ligand-target interaction energy landscape?" Maximum entropy provides a direction to update the initial guess of binding modes (described by an almost uniform distribution) to the optimal mode (a localized distribution around the global energy minimum).

Mathematical and computational models for biological systems:

In recent years, mathematical biology has emerged as a prominent area of interdisciplinary scientific research. It is not a new area of research, but with recent advances in medical and computational methods, it has grown extensively, being applied to solve many health related problems across a spectrum of life sciences. Areas of mathematical biology where modeling has made contributions to biology and medicine include epidemiology, cell physiology, cancer modeling, genetics, cellular biology, and biochemistry. Because there is such a broad range of topics and methods that can be discussed, we limit ourselves to a discussion of how differential equations have been used to solve important biological problems in epidemiology, cell physiology, and cancer modeling, and briefly discuss some of the clinical advances that have arisen from such efforts. For a more extensive review on mathematical modeling for each of these branches of science, we refer the reader to recent books on these topics [20, 21, 22, 23]. For the reader who is interested in learning more about mathematical biology from a beginner's perspective, books by Edelstein-Keshet [24], Murray [25, 26], and Britton [27] are also recommended.

Here, we highlight only a few of the models that have been developed to study epidemiological, physiological, and cancer problems. The reader is encouraged to look more extensively into the literature regarding other models that have been developed and successfully applied to improve present medical treatments.

One key assumption of this model is that the total population N ($N = S + I + R$) is constant and that there is no death or birth. Many models have since been developed to include such population demographics [30], the first being completed by Soper in an attempt to understand the dynamics of measles.

A number of extensions have been made to describe a wider class of infections. For example, the SIRS and SIS models allow for the movement of individuals back into a susceptible class S, meaning there may be no immunity to re-infection [30]. Such models are useful in studying bacterial-type infections like tuberculosis and gonorrhea. Other models, referred to as SEIR and SEIRS models, where "E" stands for a latent class of individuals (exposed but not showing symptoms), can be used to describe a disease where a delayed time of infection may exist. For example, this is often the case with individuals suffering from malaria.

A disadvantage of ODE-based modeling is that it assumes the well mixing of large populations of individuals. Also, such models are deterministic, meaning that the outcome is determined solely on the initial conditions and the parameters that govern the dynamics. For some populations, where contacts and transmission rates between individuals may vary, agent based stochastic or network type models may be more useful. Also, age-structured models may be more appropriate for diseases that depend on age, such as AIDS.

Another disadvantage of ODE-based modeling is that it does not describe the movement of individuals through space. This information is extremely important because a disease may not just spread within a single population, but may spread from one location to another. Examples of models that incorporate spatial dynamics include partial differential equations (PDEs). These models have been used to study the outbreak of rabies in continental Europe in the early 1940s, as well as to study the more recent outbreak of the West Nile Virus in 1999 in New York State. Other models used to study the spatial spread of disease include patch model. In the patch model of Lloyd and May the authors consider an SEIR modeling approach.

Mathematical models have influenced protocol in disease control and management. Now, such modeling is part of epidemiology policy decision making in many countries. Some important modeling contributions include the design and analysis of epidemiology surveys, determining data that should be collected, identifying trends and forecasting outbreaks, as well as estimating the uncertainty in these outbreaks.

Physiological models at the cellular level: enzyme kinetics, ion channels, and cell excitability

The field of physiology is arguably the number one biological field where mathematics has had the greatest impact. Two broad areas of physiology where mathematics has made a profound impact are cell physiology and systems physiology. Here, we focus on cell physiology, and restrict ourselves to the topics of enzyme kinetics, ion channels, and cell excitability. For an excellent review on systems physiology, the reader is referred to Keener and Sneyd [22].

The rate of change of a simple chemical reaction can be described by the law of mass action, a law that describes the behavior of solutions in dynamic equilibrium.

Computational systems biology has been creating a series of tools that are useful for application to enzyme kinetics. This is particularly true in the area of parameter estimation where several algorithms have been shown to be useful to enzyme kinetics. The availability of increasingly sophisticated and standardized modeling and simulation software will undoubtedly benefit enzyme kinetics.

Biochemical networks are sets of reactions that are linked by common substrates and products. The dynamics of biochemical networks are frequently described as sets of coupled ODEs, similar to those given by equations (13) through (16) that represent the rate of change of concentrations of the chemical species involved in the network. The right-hand side in these ODEs is typically the algebraic sum of the rate laws of the reactions that produce or consume the chemical species (positive when it is produced, negative when consumed). There is formally no difference between a biochemical network and an enzyme reaction mechanism, as both conform to this description. For systems biology studies, it is sufficient to represent each enzyme-catalyzed reaction as a single step and associate it with an appropriate integrated rate law. The systems biologist should be cautioned, though, that mechanistic details may indeed affect the dynamics, as is the case with competitive versus uncompetitive inhibitor drugs.

The Systems Biology Markup Language (SBML) is a standard format to encode the information required to express a biochemical network model including its kinetics. SBML is based on the Extended Markup Language (XML), which is itself a standard widely adopted on the Internet. After a series of progressive developments, there are now several compatible software packages available to model biochemical networks. Some are generic and provide many algorithms, while others are more specialized. This includes not only simulators, but also packages for graphical depiction and analysis of networks, and databases of reactions and kinetic parameters, to name but a few examples. In some cases these packages can even work in an integrated way, such as in the Systems Biology Workbench (SBW) suite.

Another area of cell physiology where mathematical modeling has been used to describe complex molecular-scale dynamics is the study of ion channels. Molecules (both large and small) move back and forth across a cell membrane, to ensure that conditions for homeostasis are met. Some molecules are small enough (and soluble to lipids) to diffuse across the membrane, while others require energy, working against electrochemical gradients between the outside and the inside of the cell. For example, differences in ionic potential across a cell membrane can drive ionic current.

Much of the work completed on ion channels and cell excitability has been used to study diseases that are associated with malfunction of ion channels. As a result, such channels have become new targets for drug discovery. One example of a disease caused by the disruption of the action potential of cardiac myocytes is cardiac arrhythmia. Certain drugs used in the treatment of arrhythmias, such as lidocaine and flecainide, are sodium channel blockers, and so interfere with open sodium channels. Although these drugs have been used in treatment for cardiac arrhythmias, their exact mode of action is not well understood. Current computational models are being developed to understand the function of these, as well as other anti-arrhythmia drugs. Another example of a disease caused by the disruption of ion channels is cystic fibrosis

(CF), which has been found to be associated with malfunctions in chloride channel operation. Although there is still no cure for CF, new directions for treatment protocols are being developed.

The models discussed above describe the spatial and temporal changes of certain quantities that are of interest in various biological systems. In particular, the differential equations described above give temporally dependent solutions (and spatially dependent solutions in the case of the PDEs described) for various quantities, including the total populations of individuals, the total number/density of cells, or the total molecular concentration of a certain compound. Many of the successes and limitations of a differential equation modeling approach are highlighted above. One limitation, not highlighted in the above sections, is that such methods (those that use only a handful of differential equations) are not appropriate for describing the smaller scale movements of molecules. The movement and structure of an individual molecule is based on the many complex interactions between the individual atoms within a molecule, as well as its interactions with surrounding molecules. In order to follow the motions of every atom and molecule over extremely small timescales, computational methods such as molecular dynamic simulations (designed to solve extremely large systems of differential equations over very small timescales) can be applied.

Molecular dynamics

The sophistication of the model used to study a given system depends on the property of interest. Often, a 3D model of a molecule or complex that shows the spatial relationships between atoms is the best way to understand a system. Such computational models provide a means of observing the structure and motion of individual atoms within complex biomolecular systems. Although a physical model of a small molecule with less than 20 atoms can be easily made from plastic or wire in a few minutes, a similar model of a protein or an enzyme involves hundreds or thousands of atoms. Over the last decade improvements in a combination of computer graphics programs, and molecular modeling techniques and hardware have resulted in an unprecedented power to create and manipulate 3D models of molecules.

Molecular dynamics (MD) simulations follow the motions of atoms and molecules, and provide a means of investigating biological problems at a molecular level. This is achieved by solving Newton's equations of motion (EOM) for interacting atoms and evolving a system through time and space. Changes in atomic positions and velocities over time, usually ranging from nano- to milliseconds, result in a trajectory. In simple cases with few atoms, analytic solutions to Newton's EOM can be obtained, giving a trajectory that is a continuous function of time. However, in a computer simulation with many atoms, the EOM are solved numerically. Forces are evaluated for discrete intervals, or time steps on the order of femtoseconds, where the forces are considered constant over a given time step. The goal is to follow the continuous function of time as closely as possible, which requires small time steps to ensure the motions of all atoms are resolved.

The forces on each atom are derived from the potential energy of the system, which can be described with quantum or classical mechanics. Since quantal descriptions are generally limited to small systems, classical descriptions are commonly used when studying biological systems and will be discussed in this section. It is worth noting that MD is a deterministic approach for exploring the potential energy surface of a system, while a stochastic approach can be obtained using Monte Carlo methods.

Calculation of solvation free energies

The calculation of solvation free energies is a challenging problems in MD simulations. Determining solvation free energy is especially difficult in aqueous bio-systems due to the size of the system. Solvation free energy, ΔG_{solv}, is a thermodynamic property defined as the net energy change upon transferring a molecule from the gas phase into a solvent with which it equilibrates. Solvation effects can change the physical and chemical properties of biomolecules including charge distribution, geometry, vibrational frequencies, electronic transition energies, NMR constants and chemical reactivity.

Several methods have been developed for modeling solvation and one can select the most advantageous choice among them based on the required accuracy and computational cost. To simulate effects of solvent on biomolecules, one can use explicit or implicit solvent models. While explicit solvent models include solvent molecules in the system, implicit models use a mean field approach. Although explicit solvent simulations are computationally expensive because of the enormous numbers of atoms involved, they provide a more realistic picture of solute-solvent interactions, reflecting the molecular complexity of the biomolecule and its environment. In comparison, implicit solvent models increase the speed of the simulation since the Newtonian equations of motion are not solved for additional solvent molecules.

Quantum mechanics in biophysical modelling

Quantum mechanics (QM) calculations, being highly accurate and rigorous, are an essential tool in computational chemistry studies. Unfortunately, the prohibitive size of many biological systems has limited theoretical and computational studies of them to the realm of classical mechanics, largely utilizing non-polarizable force fields in MD simulations. This has necessarily reduced the scope of studies to conformational or structural aspects of these bio-systems, rather than more complex problems such as chemical reactions or quantum phenomena (excited states and charge-transfer, for example). Although hybrid quantum mechanics/molecular mechanics (QM/MM) approaches have increased accuracy, recent improvements in software, hardware and theory have allowed for full quantum mechanical studies of biochemical systems.

Fragment-based quantum mechanics methods

One approach to making QM methods more tractable to biological and medicinal applications is the modification of methods so that they scale linearly with system size. One such approach is based on fragmentation methods, which have been developed to facilitate the application of wave function and density functional methods to macromolecular structures. These methods partition a macromolecular system and perform QM calculations on each fragment to obtain their wave functions and properties, which are then combined to arrive at properties of the macromolecular system as a whole. Fragmentation methods also benefit from their ability to be massively parallelized. A comprehensive summary of the many fragmentation methods available, with many applications to biological systems, can be found in a recent review.

Of the electronic structure software available, the GAMESS program includes the greatest variety of fragmentation methods, which include the effective fragment potential (EFP)

methods, the fragment molecular orbital (FMO) method, the elongation (ELG) method, and divide and conquer (DC) approaches. Although the EFP methods utilize intermolecular potentials, these are distinct from those in force fields since they are rigorously derived from *ab initio* calculations rather than empirical parameters. Of these fragmentation methods, the FMO approach is arguably the most robust and has been widely applied to biological systems, which include drug discovery, protein-ligand binding, protein-protein interactions, enzymatic catalysis, and DNA.

Application of quantum mechanics/molecular mechanics to computational enzymology

Enzymology investigates, among other topics, enzyme kinetics and mechanisms of inhibition in steady-state turnover. Advances in technology and methods have led to more detailed information about enzyme structures and mechanisms. With an explosion in the number of novel and uncharacterized enzymes identified from the vast number of genome sequences, it has become evident that the structural and functional properties of these enzymes need to be elucidated to establish precisely their mechanisms of action and how the enzymes fit into the complex webs of metabolic reactions found in even the simplest of organisms.

Vast changes have occurred in the science of enzymology since molecular simulations and modeling were first developed. Calculations can provide detailed, atomic-level insights into the fundamental mechanisms of biological catalysis. Computational enzymology was launched in the 1970s. The pioneering studies of Warshel are particularly notable. By the early 1990s the number of computational mechanistic studies of enzymes was still relatively small, but recently there have been a great number of computational studies of enzymatic reaction mechanisms published. Currently, computational enzymology is a rapidly developing area, focused on testing theories of catalysis, challenging "textbook" mechanisms, and identifying novel catalytic mechanisms.

The choice of an appropriate method for the particular enzyme being modeled is vital. Quantitative predictions of reaction rates or the effects of mutations remain very challenging, but with appropriate methods, useful predictions can be made with some confidence. Careful testing and experimental validation are important. For example, a comparison of calculated barriers for a series of alternative substrates with experimentally determined activation energies demonstrated good correlation validating mechanistic calculations. Some enzymes have become important model systems in the development and testing of computational methods and protocols; these include chorismate mutate, citrate synthase, P450, para-hydroxybenzoate hydroxylase and triosephosphate isomerase.

Modeling enzyme-catalyzed reactions

The usual starting point for modeling an enzyme-catalyzed reaction is an enzyme structure from X-ray crystallography. When this is not available, sometimes a model may be constructed based on homology to other structures that have been solved, though such models should be treated with much more caution. The first step in studying an enzyme-catalyzed reaction is to establish its chemical mechanism. Its goal is to determine the functions of catalytic residues, which are often not obvious. Even the identities of many important groups may not be certain. Any specific interactions that stabilize transition states or reactive intermediates should also be identified and analyzed.

Enzymes, representing usually large molecules, need sophisticated modeling steps as the reactions that they catalyze are complex. This can be complicated further by the need to include a part of a particular enzyme's molecular environment, such as the surrounding solvent, cofactors, other proteins, a lipid membrane, or DNA. There are many practical considerations in simulating such complex systems, such as the proper interpretation of crystal structures and the choice of protonation states for ionizable amino acids. Here, we illustrate these challenges with recent examples of modeling enzyme-catalyzed reactions.

Calculating free energy profiles for enzyme-catalysed reactions

According to transition state theory, the rate constant of a reaction is related to the free energy barrier. The techniques described previously calculate potential energy barriers for a particular conformation. Techniques that illustrate configurations along a reaction coordinate give a more sophisticated and extensive description by taking account of multiple conformations and estimating entropic effects, and can be essential for modeling enzyme reactions. Simulations of this type provide estimates of the free energy profile along a specific reaction coordinate, which is often referred to as the potential of mean force. MD and Monte Carlo methods allow such illustration, but do not provide a sufficiently detailed view of high energy regions, such as those in the vicinity of transition states. Conformational illustration of processes of chemical change requires specialized techniques, e.g., to bias the simulation to sample the transition state region. Umbrella sampling, which is widely used in MD simulations, when combined with QM/MM techniques, can be used to model enzymatic reactions. QM/MM umbrella sampling simulations are possible with semi-empirical molecular orbital methods (e.g., AM1 or PM3). Often, such methods are highly inaccurate for reaction barriers and energies but their accuracy can be improved significantly by re-parameterization for a specific reaction.

Conclusions

This review paper has aimed to provide a comprehensive guide to a plethora of mathematical and computational methods developed in the past few decades to tackle key quantitative problems in the life sciences. Our critical overview covers methods used across the life sciences, starting from macroscopic systems such as those in evolutionary biology, and ending with atomic level descriptions of biomolecules including quantum mechanical or hybrid classical/quantum approaches. Particular attention was given to large-scale computational methods, such as molecular dynamics, which play pivotal roles in the development of our understanding of molecular mechanisms at the level of molecular, structural, and cell biology. Important applications in medicine and pharmaceutical sciences have been discussed, in particular in the context of extracting crucial conclusions about complex system behavior with information limitations. We hope the reader will be encouraged to explore particular topics at a deeper level using the information and references provided in this review.

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