mapped following the initial excitation, offers, in principle, tremendous scope for gaining insights into a large variety of chemical and biochemical reactions in the ultrafast timescale. Development of the technique further to cover a wide range of wavelengths for the stimulated Raman process and multidimensional implementation to study vibrational coherence and coupling provide an exciting future for the FSRS technique. State-to-state dynamics of elementary biomolecular reactions has been described by Yang, and spectroscopy of amino acids and nucleic acid bases has been presented by de Vries and Hobza. Duncan and Prezhdo describe recent developments in explicit time-dependent modelling of photo-induced charge separation in dye-sensitized semiconductor solar cells. The results are of importance in a variety of applications that would involve molecular electronics, analytical detection, quantum confinement devices, etc. The other review by Levine and Martinez, is on photoisomerization, the fundamental process in vision and in other processes that convert light energy into mechanical motion. Cis–trans photoisomerization about the C=C bond through conical intersection has been relooked theoretically beyond one dimension. In an interesting article aging of organic aerosols has been dealt with, where difficulties of comparing laboratory data with field measurements have been highlighted. Since climate and human health in a global scale is of prime concern today, this article by Rudich *et al.* brings out the necessity of developing an understanding of complex atmospheric chemistry/processes and their kinetics through laboratory experiments.

Two of the major topics of research in physical chemistry that have been around for quite sometime are protein folding and glass transition, both of which are discussed in this issue. Scheraga *et al.* consider the methods of folding a protein *in silico*. The area is in a state of rapid development with the introduction of new techniques, which makes it possible to study folding pathways from completely unfolded structures. The review presents algorithms for MD, and their extensions and applications to protein-folding studies using all-atom models with explicit and implicit solvent as well as reduced models of polypeptide chains. Random first-order transition theory of the glass transition is reviewed by Lubchenko and Wolynes. The authors emphasize the experimental tests of the theory and show that theory goes a long way in predicting/explaining many of the distinct phenomena associated with the transition.

Understanding complex fluids on a theoretical level is the subject of two articles. Balazs describes in detail the use of a variety of computational techniques to investigate how the self-assembly of complex mixtures can be guided by surfaces or external stimuli to form spatially regular or temporally periodic patterns. She shows how thermodynamic and hydrodynamic effects can be exploited to create regular arrays of nanowires or monodisperse, particle-filled droplets. Density functional theory is used to describe microscopic structures and phase behaviour of soft, condensed matter in the article by Wu and Li. After describing the different strategies used to formulate the free-energy functional of complex fluids, the article describes recent advances in understanding the dynamic properties of complex fluids and kinetics of phase transitions.

Cellular systems in biology, where the small molecular populations of only a few reactant species can lead to deviations from the predictions of deterministic differential equations of classical chemical kinetics have interesting internal dynamics. Gillespie reviews the theory of stochastic chemical kinetics and discusses recent advances in methods for using the theory to make numerical simulations. Qian describes statistical thermodynamics of far-from-equilibrium systems, with applications to cells and biochemical systems. He points out that the currently available models quantitatively describe energetics and theormodynamics in phosphorylation–dephosphorylation switches, GTPase timers, and specificity amplification through kinetic proofreading. Theorists' perspectives on molecular motors are presented by Kolomeisky and Fisher. Aspects of motor-protein dynamics, helpful in understanding single-molecule experiments involving biomechanical properties of such motors are presented. The field has been rapidly developing and much more is expected to happen in the area. Nanomechanical properties form the subject of an article by Mielke *et al.* who describe fracture mechanics at the nanoscale. They summarize the experimental efforts to measure fracture strengths of inorganic and carbon nanotubes, and then go on to describe the attempts to understand the measurements in terms of theory.

Although we believe that this particular issue has too many articles addressing advancements in materials science and biological chemistry, some of them are well written and provide a broad perspective of the field, while others are limited and narrow in scope. However, they all provide recent references in the field and present the background for further reading on the subject. This volume of the *Annual Review of Physical Chemistry* is certainly recommended to all libraries.

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Reading this large volume was illuminating. Twenty years ago, picking up a volume of an *Annual Review* was a must before one started working on a problem, since the information provided in a single chapter covered almost all aspects of the area of interest. What is striking now is how specific some chapter topics are, detailing a single well-defined issue. This is clearly an indication of the huge explosion in knowledge over the last two decades in specific areas, prohibiting a more broad-based coverage. Therefore, in this volume we see chapters on the allosteric regulation of G-protein coupled receptors (GPCRs), constitutive activation of GPCRs, and the use of retinoids in eye disease, along with more general topics on AMP-activated protein kinase, cell signalling and neuronal death, and the effects of estrogen on neuronal physiology.

No treatise on pharmacology and toxicology can be found without discussions on GPCRs, since the maximum number of therapeutics in the market are directed to various members of this extraordinarily large family of proteins. It is therefore pleasing to see two chapters that deal with features of GPCRs that are impor-

tant for understanding molecular aspects of activation of these receptors by their ligands. The first chapter by May *et al.* deals with allosteric activation of GPCRs by molecules that bind at sites distinct from the ligand-binding site. Such interactions can modulate the binding of the ligand and the activation of the receptor, suggesting that many of these 'allosteric' ligands can act as regulators of GPCR function. A mathematical basis for understanding receptor–ligand interaction is also provided in this chapter.

The second chapter deals with the pharmacogenomic and structural analysis of constitutive GPCR activity. It is well known now that a number of diseases are caused by point mutations in GPCRs that lead to constitutively active receptors. Many of these diseases can be treated by the use of 'inverse' agonists, and this chapter succinctly provides a summary of structural information that can explain these constitutively active conformations. With the advent of 'genome-based' therapies, namely pharmacogenomics, this chapter is especially relevant today.

A nice review of cell signalling in neuronal death by Hara and Snyder, identifies signalling pathways that can impinge on apoptosis and necrosis in the brain, such as those regulated by glutamate, nitric oxide and NMDA receptors. Interestingly, calcium appears to be the most important of intracellular messengers since it can modulate the activity of many proteins. A second chapter by Orrenius *et al.* deals with mitochondrial oxidative stress and cell death, and therefore complements nicely the earlier article. A third chapter deals with the targeting of antioxidants to the mitochondria, thereby allowing the development of mitochondria-protective therapies, which will certainly play an important role in protecting cells from death through mitochondrial misfunction. There is little overlap in these chapters, but if read together, can provide a good overview of potential therapies in the future that could modulate neurotoxicity.

However, targeting the brain with chemical therapies is difficult since an effective blood–brain barrier prevents the ready movement of compounds from the blood into the brain. Therefore, a chapter on drug targeting to the brain by de Boer and Gaillard, presents the basic physiology of the blood–brain barrier and the blood–cerebrospinal fluid barrier as well as highlights the possibility of delivering large-molecule drugs to the privileged site, i.e. the brain. Interestingly, there is possibility of viral and receptor-mediated non-viral drug delivery, and these aspects are also touched upon in this chapter.

Four chapters in this volume deal with specific enzymes and their potential as drug targets. A chapter by Hardie provides a nice overview of AMP-activated kinase (AMPK), which is important in sensing the energy levels in a cell. AMPK is the target of two classes of drugs used to treat type-2 diabetes, but these drugs activate the kinase indirectly. Therefore, there is a concerted attempt to identify newer molecules that can directly bind to AMPK, thereby retaining the therapeutic benefits of this approach, but hopefully removing side effects that are seen with the current therapies.

Matrix-metalloproteinase-2 (MMP-2) is important in degrading extracellular protein targets, but recent evidence has suggested that it has a significant role to play in the cardiomyocyte, where it is activated by oxidative stress. As a result, certain intracellular proteins are degraded and this causes contractile dysfunction. Therefore, inhibitors of MMP-2 would be interesting to develop, and the chapter by Schulz summarizes the information available in this area.

Enzymes that metabolize drugs and carcinogens include the aldo–keto reductases, and the actions of these enzymes can result in bioactivation or detoxication of different drugs. In some cases, resistance to chemotherapy is associated with the activity of these enzymes since they degrade and inactivate the drug, while in other cases, they are involved in tobacco carcinogenesis by activation of polycyclic aromatic diols to yield quinones that are toxic. The chapter by Jin and Penning provides a good overview of the properties of these enzymes and their role in drug metabolism. Continuing along a similar discussion related to the bothersome nature of carbonyl compounds, the next chapter by Oppermann deals with carbonyl reductases, which provide protective roles by inactivating xenobiotic carbonyls and quinones. Since both these enzymes (the aldo–keto reductases and the carbonyl reductases) are so important in metabolizing drugs as well as toxic molecules, they are likely to have an important role in pharmacogenomics. Therefore polymorphisms in these genes could account for the variability in responsiveness and toxicity that is seen from individual to individual.

Of even more concern in drug therapy is the phenomenon of idiosyncratic drug reactions i.e. adverse reactions that are seen in only some individuals. A chapter by Uetrecht deals with this aspect, and discusses the models that are prevalent now to explain these often life-threatening responses to drugs. The reaction is usually elicited by reactive metabolites that are formed during drug administration and are immune system-related. What researchers would hope to develop in the future are biomarkers that could predict the response of the individual to the drug, but the lack of good animal model systems could be a stumbling block to rapid progress in this area.

No discussion on pharmacology and toxicology can be complete without a discussion on modelling the pharmokinetic and pharmodynamic behaviour of drugs. This analysis does indeed play an important role in current drug discovery and development. A chapter by Danhof *et al.* deals with newer approaches to perform this modelling based on an understanding of the physiological mechanisms that underly the pharmacokinetic and pharmacodynamic properties of different drugs. This mechanism-based modelling considers aspects of receptor distribution in different tissues, the binding and activation of the target to which the drug is directed, downstream signalling events and feedback mechanisms operative *in vivo*. Examples of application of this mechanism-based modelling are provided in this chapter, which allow a critical appraisal of the use of these more sophisticated approaches to predict the behaviour of different active molecules *in vivo*.

The reviews provided in this volume are extensive in their discussion of the particular topic – almost every article cites more than 200 papers! It was also interesting to note that many of the authors provide a disclosure statement indicating their association with pharmaceutical companies. Perhaps this is heartening to the reader, since it indicates that the topics being discussed are clearly important for the pharmaceutical industry, and the authors' views are presented in the context of the development of better therapies in the years ahead.

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