

on a continuous basis and deviations from prescribed limits of these parameters are used to record the failure of a system's performance. This approach is a popular one and exists in many working systems. The other approach is called the active approach, where, an auxiliary signal is injected into a working system and a separate detection sub-system analyses the signals of the system, enabling detection and identification of the failure. The active approach is, in a way, intrusive and can affect the dynamics of the system if the input is not carefully designed. The design of auxiliary signals, therefore, is an important aspect of the active approach of failure detection and identification in a control system.

This book deals with the optimal design of auxiliary signals for dynamical systems characterized, in general, by linear state-space models. The approach used in the book is different compared to previous literature dealing with this aspect. The book presents a systematic development of the analytical framework for auxiliary signal design, based on properties of subspaces of matrices of the state-space model.

Chapter 2 presents a clear and lucid introduction to the proposed framework of analysis for failure detection. A model is assumed for the normal working and any deviation implies occurrence of failure. The idea is to take the input and output signals and form a function which determines if the functioning of the system is 'normal' or not. This implies that the input signal needs to be 'designed' properly which would indicate failure. The framework for detecting a single failure has been developed systematically, starting from the static case and extending it to the dynamic case, with examples illustrating the methodology of design. The results presented are based on properties of matrices, with emphasis on subspace interpretation. The auxiliary signal design is formulated as an optimization problem involving the famous Riccati equation related to the state-space model. An important aspect of signal design is the real-time implementation of such methods. A section on the real-time issues is presented. The highlight of the approach presented is that it is different, novel and powerful in the analytical sense. The connection with existing work is clearly shown and emphasis is put on failure detection based on short time intervals.

Chapter 3 extends the results of the previous chapter when multiple failures are to be detected, using a multimodel approach. The highlight is the ease of extension of the framework in the previous chapter to a generalized framework. The additional constraints imposed translate into new results on signal design. A useful example illustrating the methodology is presented for the case of a vehicle suspension system design.

Chapter 4 presents the framework of signal design as a direct optimization problem. This approach is interesting and presents useful insights in terms of the trajectories of dynamical systems. The issues of numerical computation for the solutions are presented with respect to the authors' experience with packages like SOCS.

Chapter 5 summarizes the possible extensions of the proposed framework to new problems, highlighting the versatility of the framework. Sample programs using Scilab are also available for the readers to experiment.

This book is a research monograph focusing on a niche topic, written by leading researchers in the fields. The reader needs a good background of state-space modelling of dynamical systems and matrix algebra. The monograph is useful for researchers in this field and also system designers, who can benefit from the new approach to signal design, leading to good system design. The book has been written well and is almost free from spelling and grammatical errors, but for a rare error on page 15, where the word 'consistent' is used instead of 'consist'.

K. V. S. HARI

*Department of Electrical Communication Engineering,
Indian Institute of Science,
Bangalore 560 012, India
e-mail: hari@ece.iisc.ernet.in*

Calcium Channel Blockers. T. Godfraind (ed.); with a contribution by Eric Ertel. Milestones in Drug Therapy Series. Birkhauser Verlag, P.O. Box 133, CH-4010, Basel, Switzerland. 2004. 262 pp. Price not mentioned.

Ion channels are ion-specific holes in biological membranes with complex architecture. They are regulated by changes

in membrane electric field and ligands. Their importance in cellular physiology is being realized at an alarming pace. Understanding the pharmacology of ion channels is also becoming important, since by modulating their activity one can affect cellular function, and thereby regulate the function of complex tissues like the heart and the brain. Diseased conditions due to ion-channel malfunction are now classified under channelopathies.

There are not many books that are entirely devoted to ion-channel pharmacology. The more recent ones are *Molecular Physiology and Pharmacology of Cardiac Ion Channels and Transporters* by Morad *et al.*, published by Kluwer Academic Publishers (1996) and *Ion Channel Pharmacology* by Bernat Soria and Valentin Cena, published by Oxford University Press (1998). Part of the reason could be that in the last few decades more research attention has been paid to the discovery of ion-channel subtypes and splice variants of ion channels. In comparison, discovery of new molecules that modulate the ion-channel targets has been lagging behind. Combinatorial chemistry has become an important tool for discovery of new lead small organic molecules. This is now paralleled by developments in high throughput screening assays for ion-channel activity.

Among the different ion-channel types, a class of ion channels called the voltage-gated calcium channels are of immense pharmacological interest since they are found in tissues such as the heart, blood vessels, pancreas and the brain. They gate the entry of calcium inside the cell, which acts as an important second messenger regulating important functions like the contraction of individual myocytes, whose coordinated contractile activity translates into a heart beat. It is also noteworthy that although Ringer suggested the biological importance of calcium in 1883, research into the pharmacology of calcium began only forty years ago.

Godfraind, the author of this book, has been one of the key contributors to calcium pharmacology research. In the 1960s, Godfraind and co-workers demonstrated that inhibition of Ca entry into arterial tissue causes vasodilation. This book is a compendium of research on calcium-channel blockers, and their pharmacological actions on the cardiovascular system, significantly based on the results

of his own research. It is part of the Milestones in Drug Therapy Series edited by M. J. Parnham and J. Bruinvels.

The book starts with an interesting historical perspective that briefly covers the early findings in calcium physiology and pharmacology to the identification of calcium as an important signalling molecule. Among all the chapters in the book, chapter 2, written jointly with Eric Ertel is the most informative, with a good review of various kinds of calcium channels, viz. receptor-activated, ligand-gated and voltage-gated, and has more than 500 up-to-date references. It has a particularly detailed review on the different voltage-gated calcium channels and their molecular diversity. This section also has a table of the different classes of calcium antagonists, the classification being based on the criteria approved by IUPHAR Committee on Receptor Nomenclature and Drug Classification. Also included is an extensive table of the structural diversity of dihydropyridine calcium antagonists. Dihydropyridines are included under Class I antagonists and are selective for L-type calcium channels. The structural diversity of the known dihydropyridine calcium antagonists that number more than 50, is also tabulated. This would be of particular interest to organic synthetic chemists working on synthesizing lead compounds. The chapter also discusses the two important theories, viz. the modulated receptor theory and the guarded receptor theory that have been favourites of ion-channel pharmacologists, to explain the mechanisms of ion-channel block.

To understand a disease, it is important to understand its causes from the molecular level to the systems level. Similarly, to treat a disease condition with a drug, it is important to understand its action both at the molecular level and systems level. It is not uncommon in the drug discovery field, where a lead compound has yielded encouraging experimental results in isolated experimental conditions with unsuccessful clinical ap-

plication. A long time is required before a lead compound is recognized as a safe medicine. This is true of calcium-channel blockers, which are therapeutically used to treat cardiovascular and neurological conditions. Calcium-channel blockers are used to treat diseases related to hypertension, stroke and coronary diseases. The effect of calcium-channel blockers on the haemodynamic responses is discussed. The long-term effects of calcium-channel blockers have been examined, and have relevance to clinical conditions where patients have to take calcium-channel blockers for life.

It is indeed difficult to find a book where the tedious details of ion-channel blocker action from the molecular target level to the organism has been described, as given in this book. Godfraind systematically describes the cardiovascular actions of Ca-channel blockers with particular emphasis on L-type calcium channels, from the level of ion channels to systems physiology.

The action of drugs in different tissues is not uniform, and this is true of calcium-channel blockers as well. Drugs usually show varying degrees of potency, with preferential action on a particular tissue. Tissue selectivity depends on the different affinities for the different ion-channel subtypes by the same ion-channel blocker, and differs from specificity that relates to the interaction of an agent with only one type of receptor. This is quantified by examining the inhibition of different calcium current types, where calcium currents are real-time electrophysiological measures of calcium flux through calcium channels. The differences in selectivity both at the ion-channel level and tissue level are discussed. It was also quite amazing to know from this book that the inhibition of contractile response by a calcium-channel blocker is different in the human coronary artery and human internal mammary artery. However, both have contractile smooth muscle cells and do not show the extent of functional and structural diversity in

neuronal cells that is seen in brain tissues.

The last chapter aptly titled 'Beyond the cardiovascular system', briefly reviews the use of calcium antagonists to treat gastrointestinal and neuronal disorders, including the treatment of migraine, and chronic and neuropathic pain.

This is not a book for graduate courses but for a more advanced reader and would be of immense interest to practising scientists in the field of ion channels, cardiac and vascular physiology and pharmacology. To my knowledge, this is the first detailed book that examines the pharmacological effects of the blockers starting from the ion channel to the systemic level. This is particularly a significant and noteworthy effort, since such studies have become fewer in number with the shift of interest to molecular research. What is often sadly missed in this overtly enthusiastic molecular emphasis, is the fact that there are differences in tissue specificity of drug action and this only becomes evident when careful experiments at the tissue, organ and systems level are done and documented. The book by Godfraind would inspire and nudge researchers in physiology and pharmacology departments of medical colleges in the country to keep their research efforts ticking. The book conveys the message that there is a lot of good research that can still be done using simple, old and established research methodologies with an organ bath, a kymograph or a strain-gauge transducer, with immense relevance to the understanding of drug action.

This book took me back to my early days as a student of physiology, where the *in vivo* experiments were part of routine, and reviewing it has been a satisfying experience.

S. K. SIKDAR

*Molecular Biophysics Unit,
Indian Institute of Science,
Bangalore 560 012, India
e-mail: sks@mbu.iisc.ernet.in*