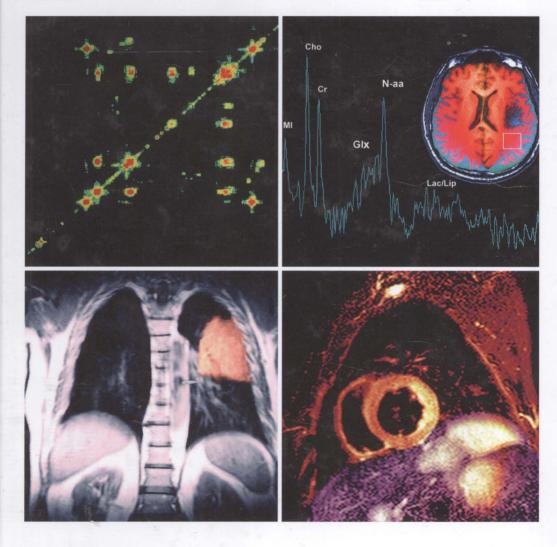
Edited by Leoncio Garrido and Nicolau Beckmann

New Applications of NMR in Drug Discovery and Development



RSCPublishing

New Applications of NMR in Drug Discovery and Development

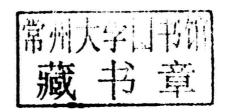
Edited by

Leoncio Garrido

Consejo Superior de Investigaciones Científicas, Spain Email: lgarrido@cetef.csic.es

Nicolau Beckmann

Novartis Institutes for BioMedical Research, Switzerland Email: nicolau.beckmann@novartis.com



New Developments in NMR No. 2

ISBN: 978-1-84973-444-8

ISSN: 2044-253X

A catalogue record for this book is available from the British Library

© The Royal Society of Chemistry 2013

All rights reserved

Apart from fair dealing for the purposes of research for non-commercial purposes or for private study, criticism or review, as permitted under the Copyright, Designs and Patents Act 1988 and the Copyright and Related Rights Regulations 2003, this publication may not be reproduced, stored or transmitted, in any form or by any means, without the prior permission in writing of The Royal Society of Chemistry or the copyright owner, or in the case of reproduction in accordance with the terms of licences issued by the Copyright Licensing Agency in the UK, or in accordance with the terms of the licences issued by the appropriate Reproduction Rights Organization outside the UK. Enquiries concerning reproduction outside the terms stated here should be sent to The Royal Society of Chemistry at the address printed on this page.

The RSC is not responsible for individual opinions expressed in this work.

Published by The Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge CB4 0WF, UK

Registered Charity Number 207890

For further information see our website at www.rsc.org

New Applications of NMR in Drug Discovery and Development

New Developments in NMR

Editor-in-Chief:

Professor William S. Price, University of Western Sydney, Australia

Series Editors:

Professor Bruce Balcom, University of New Brunswick, Canada Professor István Furó, Industrial NMR Centre at KTH, Sweden Professor Masatsune Kainosho, Nagoya University, Japan Professor Maili Liu, Chinese Academy of Sciences, Wuhan, China

Titles in the Series:

- 1: Contemporary Computer-Assisted Approaches to Molecular Structure Elucidation
- 2: New Applications of NMR in Drug Discovery and Development

How to obtain future titles on publication:

A standing order plan is available for this series. A standing order will bring delivery of each new volume immediately on publication.

For further information please contact:

Book Sales Department, Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, CB4 0WF, UK

Telephone: +44 (0)1223 420066, Fax: +44 (0)1223 420247

Email: booksales@rsc.org

Visit our website at www.rsc.org/books

Preface

Nuclear Magnetic Resonance (NMR) is a most informative tool for gaining insight into the inner workings of nature and is useful in many fields of applied science. The gained knowledge allows us to develop advanced medical methods of treating diseases and to develop preventive procedures. Often NMR represents even the ultimate tool of insight in drug discovery and development, for example. The information gained by NMR is in the correct form expected by a medical scientist and it can be applied directly for discovering new potential drugs and for working out prescriptions of their optimum application to treat diseases.

The comprehension of biomedical effects, induced by drugs, requires a molecular view. Molecules are interacting and are leading to beneficial results or to harmful side effects. In this sense, pharmaceutical science is part of applied chemistry where molecules are the objects of central interest. Without a molecular view, it is difficult to understand the functioning of drugs. There is a fortuitous match between the demands of pharmaceutical practice and the outstanding features of NMR as an investigative tool. The results of NMR experiments are also best understood in terms of molecular interactions. This is one of the reasons for the unique importance of NMR in biomedicine. Comprehension is often a question of using the correct language and the proper terms that can be understood and applied directly in the relevant biomedical context.

The match between measurement results and the biomedical needs is implemented rather perfectly in the various chapters of this comprehensive treatise. The *Part I. Small Molecules, Proteins, Cellular Systems*, reflects the fact that many of the most potent drugs are small molecules. Indeed, nature takes advantage of small molecules as agents and transporters with their multivariate functions that adapt well to the needs of the biomedical organism. Small molecules are easier to tailor-make to match the requirements, their

New Developments in NMR No. 2 New Applications of NMR in Drug Discovery and Development Edited by Leoncio Garrido and Nicolau Beckmann © The Royal Society of Chemistry 2013 Published by the Royal Society of Chemistry, www.rsc.org vi Preface

synthesis is manageable in an industrial environment and they are easier to comprehend. Small proteins are the first choices of nature as well as of the drug designer who has to take into account the specific properties of the cellular environment where the drugs must exert their action.

In many, if not in most circumstances, an extreme reductionist approach of analytical science is inappropriate. Physiological action involves the entire biological organism and can not be understood solely in terms of its parts. This view is reflected in *Part II*. The Whole Organism in Vivo, where it is attempted to balance an analytical approach with a holistic view of the entire organism. Again, NMR is astonishingly adaptive to the various degrees of focusing. NMR technology acts like a universal microscope that can be adapted to macroscopic objects, such as a human heart or a brain, or focused onto nanoscale objects, such as cells and tissues, or used to explore truly molecular processes, like the interaction of proteins and nucleic acids. Various tools of magnetic resonance allow the focusing onto the features of actual interest. Many of them are described in this book. They lead to the remarkable adaptability of NMR to the actual practical situation.

In Part III. Translational drug discovery: From Biological Models to the Clinics, the possibilities of NMR and MRI are discussed in the context of a number of relevant clinical applications of magnetic resonance techniques, from tissue engineering, to the exploration of psychiatric disorder, to neuro-degenerative diseases, to respiratory diseases, to cardiac MR, and finally to MR applications in cancer.

This volume convincingly demonstrates the enormous breadth of MRI applications in biomedicine. The utility of modern NMR and MRI becomes even more impressive when one realizes that biomedicine is only one of the potential fields of fruitful application of magnetic resonance technology. Other fields are developing equally rapidly today, including magnetic resonance studies of battery materials, NMR in the context of nanotechnology, and materials research in general, to mention just a few. One of the most important fields is and will remain the study of protein and nucleic acid interactions for biomedical understanding and for drug design.

In summary, the volume "New Applications of NMR in Drug Discovery and Development" represents an important addition to the bookshelf of anybody seriously interested in drug discovery and development. It will remain a reliable source of information in this important field for many years to come. I would like to congratulate and thank Nicolau Beckmann and Leoncio Garrido for their efforts towards such a comprehensive survey on this field of remarkable current activity.

Richard R. Ernst Laboratorium für Physikalische Chemie ETH Zürich, Switzerland

Contents

| Introduction Leoncio Garrido and Nicolau Beckmann | | | | |
|--|--------------------|--|--|----|
| | Par | I Small Molecul | es, Proteins, Cellular Systems | |
| Chapter 1 | Disc Mai Áng | very and Develop Ta del Carmen Fern | igh-Resolution NMR in Drug ment ández-Alonso, Manuel Alvaro Berbis, Ardá, Francisco Javier Cañada and | 7 |
| | 1.1 1.2 | | Historical Perspective s for Molecular Recognition | 7 |
| | | - | Monitoring Ligand Resonances | 9 |
| | | 1.2.1 Fundamer | itals | 9 |
| | | | dware Description Experiments: STD, WaterLOGSY | 13 |
| | | and Their | | 13 |
| | | 1.2.4 Further D | evelopments | 18 |
| | | | g Other Nuclei (19F) | 23 |
| | 1.3 | NMR Techniques | s and Applications Based on | |
| | | Monitoring the R | eceptor Resonances | 25 |
| | | 1.3.1 Fundamer | ntals: A Brief Overview of | |
| | | Biomolecu | lar Structure Elucidation by NMR | 25 |
| | | | d Their Variants. SAR by NMR | 26 |
| | 1.4 | Mixed Protocols | | 27 |
| | | 1.4.1 Screening. | Fragment-Based Drug Design | 27 |

New Developments in NMR No. 2

New Applications of NMR in Drug Discovery and Development

Edited by Leoncio Garrido and Nicolau Beckmann

Published by the Royal Society of Chemistry, www.rsc.org

[©] The Royal Society of Chemistry 2013

viii Contents

| | 1.5 | Frontiers 1.5.1 Towards Larger and Larger Systems: Labeling | 31 |
|-----------|------|--|-----|
| | | Strategies and Instrumentation | 31 |
| | | 1.5.2 Membrane Proteins | 34 |
| | 1.6 | | 36 |
| | | erences | 36 |
| Chapter 2 | | d-State NMR in Drug Discovery and Development derick G. Vogt | 43 |
| | 2.1 | Introduction | 43 |
| | 2.2 | Background | 44 |
| | | 2.2.1 Theoretical Background | 44 |
| | | 2.2.2 Instrumentation | 52 |
| | | 2.2.3 Experimental Methods | 54 |
| | | 2.2.4 Computational Methods | 64 |
| | | 2.2.5 Special Processing Methods | 68 |
| | 2.3 | Applications to Drug Discovery | 68 |
| | | 2.3.1 Labeled Biomolecules | 69 |
| | | 2.3.2 Oriented Biomolecules | 72 |
| | | 2.3.3 Metal Sites in Proteins and Other Biological | 72 |
| | | Macromolecules | 73 |
| | | 2.3.4 Drug–Receptor Interactions2.3.5 Protein–Protein Interactions and Interactions | 75 |
| | | 2.3.5 Protein–Protein Interactions and Interactions Between Biomolecules | 76 |
| | | 2.3.6 Future Directions | 78 |
| | 2.4 | Applications to Drug Development | 78 |
| | 2.7 | 2.4.1 Polymorphism | 79 |
| | | 2.4.2 Hydrates, Solvates, Salts and Cocrystals | 84 |
| | | 2.4.3 Disordered Forms | 85 |
| | | 2.4.4 Amorphous Drugs | 85 |
| | | 2.4.5 Excipients | 87 |
| | | 2.4.6 Formulations and Dispersions of Drugs | 88 |
| | | 2.4.7 Crystal Structure Determination | 89 |
| | | 2.4.8 Future Directions | 90 |
| | 2.5 | Conclusions | 90 |
| | Refe | erences | 91 |
| Chapter 3 | Disc | n-Resolution NMR-Based Metabolic Profiling in Drug covery and Development and J. Waters | 101 |
| | 3.1 | Background to Metabolic Profiling by NMR | |
| | | Spectroscopy | 101 |
| | 3.2 | Advancements in NMR Spectroscopy | 104 |

Contents ix

| | | Applications in Drug Discovery and Development | 110 |
|-----------|---------|--|------------|
| | 1 | 3.3.1 Understanding of Disease Etiology in | |
| | | Pre-Clinical Models | 110 |
| | | 3.3.2 Toxicology and Safety Assessment | 118 |
| | | 3.3.3 Drug Metabolism and Pharmacokinetics | 121 |
| | | 3.3.4 Clinical Applications | 123 |
| | | Summary and Future Directions | 126 |
| | | owledgements | 127 |
| | Refere | ences | 127 |
| Chapter 4 | | l NMR Spectroscopy to Study Protein-Drug | |
| | Intera | | 134 |
| | | eline D. Washington, David S. Burz and | |
| | Alexa | nder Shekhtman | |
| | | ntroduction | 134 |
| | | n-Cell NMR Spectroscopy | 135 |
| | | 4.2.1 Cell Types | 136 |
| | | 4.2.2 Target Labeling | 138 |
| | | 4.2.3 In-Cell Delivery of Protein Target Molecules | 139 |
| | | Methods and Applications | 144 |
| | | 4.3.1 STructural INTeractions NMR (STINT-NMR) | 144 |
| | | 4.3.2 Protein Maturation | 146 |
| | | 4.3.3 Metabolic Processing of Proteins | 148 |
| | | 4.3.4 Regulation of Post-Translational | 1.40 |
| | , | Modifications (In-Cell Biochemistry) 4.3.5 <i>De Novo</i> Structure Determination | 149 |
| | | | 152 |
| | | Orug Screening 4.4.1 In-Cell Delivery of Drug Molecules | 153 |
| | | , , | 153 |
| | - | | 155 |
| | 4.5 | Library NMR (SMILI-NMR) Conclusions | 155 157 |
| | Refere | | |
| | Refere | ences | 158 |
| | | Part II The Whole Organism In Vivo | |
| Ana | tomy, I | Function, Metabolism and Cellular/Molecular Imaging | |
| Chapter 5 | Applic | sed Sensitivity Using Cryogenic Radiofrequency Coils: eation to In Vivo Phenotyping of Mice ohs, A. Seuwen, A. Schröter, D. Marek and M. Rudin | 165 |
| | 5.1 I | ntroduction | 165 |
| | | 5.1.1 Mouse Models in Biomedical Research | 165 |
| | 4 | 5.1.2 Challenges in MRI Phenotyping of Mice | 166 |

X

| | 5.2 | Cryog | enic RF Colls as a Tool in Small | | |
|-----------|--|----------------|--|-----|--|
| | | Anima | al MRI | 167 | |
| | | 5.2.1 | Improving Signal-to-Noise Ratio by Lowering the Coil Temperature: Theoretical | 167 | |
| | | 5.2.2 | Background Comparison of Signal-to-Noise Ratio Obtained with Room Temperature and Cryogenic RF | 167 | |
| | | | Coils | 171 | |
| | 5.3 | Cryog 5.3.1 | enic RF Coils for Mouse Phenotyping Application of Cryogenic RF Coils for | 172 | |
| | | 5.3.2 | High-Resolution MR Imaging The Use of Cryogenic RF Coils for Functional | 172 | |
| | | | MRI of the Mouse Brain | 174 | |
| | | 5.3.3 | Metabolic Phenotyping Using MRS and Chemical Shift Imaging | 177 | |
| | | 5.3.4 | Advantages and Limitations of Cryogenic RF | | |
| | | | Coils for Mouse Phenotyping | 178 | |
| | Refe | erences | 71 0 | 181 | |
| | | | | | |
| Chapter 6 | Recent Developments of Contrast Agents, CEST and | | | | |
| | Low Fields S. Aime and D. L. Longo | | | | |
| | 6.1 | Introd | luction | 184 | |
| | 6.2 | | I)-Based Contrast Agents | 185 | |
| | | 6.2.1 | | 185 | |
| | | 6.2.2 | | 188 | |
| | | | Nanosized Carriers | 189 | |
| | 6.3 | | (Chemical Exchange Saturation Transfer) | | |
| | | Agent | | 190 | |
| | | 6.3.1 | Iopamidol and Iopromide as DIACEST | | |
| | | 0.0.1 | Agents | 191 | |
| | | 6.3.2 | AN AND THE PROPERTY AND AND AN AND AN AND AN ANALYSIS OF THE PROPERTY AND AN | 194 | |
| | | | Multiplexing Detection of Cells Labeled with | | |
| | | | PARACEST Agents | 194 | |
| | 6.4 | Contr | ast Agents & Low Fields MRI Scanners | 196 | |
| | | 6.4.1 | Low-density Lipoproteins as Carriers of | | |
| | | | Amphiphilic Gd(III) Complexes | 197 | |
| | | 6.4.2 | Blood-Pool Agents for DCE-MRI | | |
| | | cus secret | Applications | 198 | |
| | 6.5 | Concl | usions | 200 | |
| | | | | | |
| | Ack | nowled | gements | 200 | |

Contents

| Chapter / | | | | | |
|-----------|-------------|--|-----|--|--|
| | Development | | | | |
| | Alexandre | Coimbra, Richard Baumgartner and | | | |
| | Adam J. S. | chwarz | | | |
| | | duction | 204 | | |
| | 7.2 Physic | ology of fMRI | 205 | | |
| | | Techniques | 206 | | |
| | 7.3.1 | | 206 | | |
| | 7.3.2 | | 207 | | |
| | 7.3.3 | | 207 | | |
| | | Applications in Drug Research: Principles | | | |
| | and E | Examples | 208 | | |
| | 7.4.1 | Pre-Clinical Drug Discovery | 208 | | |
| | 7.4.2 | | 211 | | |
| | 7.4.3 | | 214 | | |
| | 7.5 Good | Imaging Practice (GIP) for fMRI | | | |
| | in Dr | ug Studies | 216 | | |
| | 7.6 Analy | rtical Tools for Functional Magnetic Resonance | | | |
| | Imagi | ng (fMRI) in Pharmacological Experiments | 217 | | |
| | 7.6.1 | ALL SELECTION OF THE SE | 218 | | |
| | 7.6.2 | Task-Based fMRI and phMRI Experiments | 219 | | |
| | 7.6.3 | | 220 | | |
| | 7.6.4 | • | 222 | | |
| | 7.7 Challe | | 222 | | |
| | References | | 224 | | |
| Chapter 8 | In Viva Dra | oton MR Spectroscopy: Animal and Human | | | |
| Chapter 6 | | s at High Fields | 230 | | |
| | | and Gülin Öz | 230 | | |
| | 8.1 Introd | duction | 230 | | |
| | | odology of Proton MRS at High Fields | 231 | | |
| | 8.2.1 | Potentials for Neurochemical Profiling | 231 | | |
| | 1710700 01 | Data Acquisition | 232 | | |
| | 8.2.3 | | 235 | | |
| | 8.2.4 | Metabolite Quantification | 236 | | |
| | | cations of Proton MRS at High Fields | 238 | | |
| | 8.3.1 | Neurochemical Profiling in the | 200 | | |
| | 0.011 | Animal Brain | 238 | | |
| | 8.3.2 | Neurochemical Profiling in the | | | |
| | 5 AB A.E. | Human Brain | 244 | | |
| | 8.4 Conc | lusions | 248 | | |
| | References | | 249 | | |

xii Contents

| Chapter 9 | Hyperpolarization: Concepts, Techniques and Applications Arnaud Comment | | | | |
|------------|--|----------|---|-----|--|
| | 9.1 | What | is Hyperpolarization and Why Bother Using It? | 252 | |
| | 2.1 | 9.1.1 | Thermodynamic Considerations | 255 | |
| | | 9.1.2 | The Principles of Hyperpolarization and | 233 | |
| | | 7.1.2 | Dynamic Nuclear Polarization Methods | 256 | |
| | | 9.1.3 | The Importance of Spin Relaxation | 258 | |
| | | 9.1.4 | Other Limitations | 261 | |
| | 9.2 | How t | to Hyperpolarize Nuclear Spins? | 262 | |
| | | 9.2.1 | Brute Force Method | 262 | |
| | | 9.2.2 | Dissolution Dynamic Nuclear Polarization | 262 | |
| | | 9.2.3 | Parahydrogen-Induced Polarization | 263 | |
| | 9.3 | Applic | cations of Hyperpolarized Magnetic | | |
| | | Reson | ance in Drug Research | 264 | |
| | | 9.3.1 | In Vitro Applications | 265 | |
| | | 9.3.2 | In Vivo Applications | 266 | |
| | | 9.3.3 | Perspectives for Clinical Applications | 268 | |
| | 9.4 | Concl | usions | 268 | |
| | | owledge | ments | 269 | |
| | Refere | ences | | 269 | |
| Chanter 10 | Comb | ined PE | T/MRI for Improving Quantitative Imaging | 273 | |
| Chapter 10 | Tim D. Fryer | | | | |
| | 10.1 | Introd | luction | 273 | |
| | 10.2 | | ined PET/MRI Designs | 274 | |
| | 10.3 | | MR Registration | 276 | |
| | 10.4 | | uation Correction | 276 | |
| | 10.5 | Motio | n Correction | 278 | |
| | 10.6 | Anato | mically Guided Image Reconstruction | 281 | |
| | 10.7 | Anato | mically Driven Post-Reconstruction | | |
| | | Resolu | ation Recovery and Denoising | 281 | |
| | 10.8 | Image | -Based Input Function Estimation | 283 | |
| | 10.9 | Comb | ined Functional Imaging | 284 | |
| | 10.10 | Clinic | al/Pre-Clinical Applications | 285 | |
| | | Concl | | 285 | |
| | | owledge | ments | 286 | |
| | Refere | ences | | 286 | |
| Chapter 11 | Magn | etic Res | onance-Based Cell Imaging Using Contrast | | |
| | _ | | porter Genes | 293 | |
| | | | Velde and Uwe Himmelreich | | |
| | 11.1 | Introdu | action | 293 | |

| 11.2.1 Contrast Generation in MRI 11.2.2 Contrast Generation in MR Spectroscopic Imaging 29 11.3 MRI Contrast for Cellular and Molecular Imaging 11.3.1 Labeling Cells with Contrast Agents for MRI 29 | 98 99 99 |
|--|----------------|
| Imaging 29 11.3 MRI Contrast for Cellular and Molecular Imaging 29 11.3.1 Labeling Cells with Contrast Agents for MRI 29 |)9)9 |
| 11.3 MRI Contrast for Cellular and Molecular Imaging 11.3.1 Labeling Cells with Contrast Agents for MRI 29 |)9)9 |
| 11.3.1 Labeling Cells with Contrast Agents for MRI 29 | 99 |
| MRI 29 | |
| | |
| | |
| 11.3.2 MRI Contrast Agents Targeting Specific Cell Types 30 | |
| Cell Types 30 11.3.3 Contrast Agents Responsive to Chemical |)2 |
| Modification 30 |)4 |
| 11.3.4 Genetic Reporter Systems 31 | |
| 11.3.5 Direct Monitoring of Metabolic Pathways 31 | |
| 11.4 Limitations and Perspectives 31 | |
| Acknowledgements 32 | 20 |
| References 32 | 20 |
| | |
| Part III Translational Drug Discovery: From Biological Models to the Clinics | S |
| | E |
| Chapter 12 Translational Magnetic Resonance Imaging and | |
| Spectroscopy: Opportunities and Challenges 33 | 53 |
| John C. Waterton | |
| 12.1 Translational Magnetic Resonance Imaging and | |
| Spectroscopy 33 | 33 |
| 12.2 NMR Measurements as Biomarkers 33 | 36 |
| 12.2.1 Biomarker Definition 33 | 36 |
| 12.2.2 Biomarker Qualification 33 | 38 |
| 12.2.3 Technical Validity 34 | 46 |
| 12.2.4 Biological Validity 35 | |
| | 53 |
| | 53 |
| References 35 | 54 |
| | |
| Chapter 13 In Vivo MRI/S for the Safety Evaluation of | |
| | 61 |
| Paul D. Hockings and Helen Powell | |
| 13.1 Introduction 36 | 61 |
| | 64 |
| | 65 |
| • | 67 |
| | 69 |
| • | 71 |
| References 37 | 73 |

xiv Contents

| Chapter 14 | | | MRI and MRS in Cartilage Therapeutics and | |
|------------|--------|-----------|---|------|
| | | Engine | | 376 |
| | David | l A. Reit | er and Richard G. Spencer | |
| | 14.1 | Introdu | ction | 376 |
| | 14.2 | Hollow | Fiber Bioreactor Studies | 377 |
| | | 14.2.1 | ¹ H MRI Studies of Hollow Fiber Bioreactor | |
| | | | Cartilage | 380 |
| | | 14.2.2 | Hollow Fiber Bioreactor Studies Using | |
| | | | Complementary Spectroscopic and Imaging | |
| | | | Techniques | 380 |
| | 14.3 | | tion of Neocartilage Growth | 386 |
| | | 14.3.1 | Nutrients, Anabolic Agents and Growth | |
| | | | Factors | 386 |
| | | 14.3.2 | Mechanical Stimulation | 387 |
| | | | Catabolic Agents | 389 |
| | 14.4 | | tional Studies: Tissue Integration and | |
| | | | nent Using MRI | 389 |
| | 14.5 | | ity and Specificity Improvements in Proton | |
| | | MRI | | 392 |
| | | 14.5.1 | Alternative Models of Transverse | |
| | | 1450 | Relaxation | 392 |
| | | 14.5.2 | Multivariate Machine Learning Analysis of | 20.4 |
| | | 1450 | MRI Parameters | 394 |
| | | 14.5.3 | Combined Multivariate and | 200 |
| | 146 | C - 1 | Multiexponential Analysis | 398 |
| | 14.6 | | | 398 |
| | Refer | owledgei | nent | 398 |
| | Refer | ences | | 399 |
| Chapter 15 | Applie | cations o | f Magnetic Resonance Spectroscopy to | |
| | | iatric Di | | 405 |
| | Richa | rd A. Ko | omoroski | |
| | 15.1 | Introdu | ction | 405 |
| | | 15.1.1 | Scope | 405 |
| | | 15.1.2 | In Vivo MRS in the Study of Psychiatric | |
| | | | Disorders | 406 |
| | | 15.1.3 | Animal Models and Ex Vivo Studies | 407 |
| | 15.2 | Informa | ation Content of In Vivo MRS of Brain | 408 |
| | | 15.2.1 | ¹ H MRS | 408 |
| | | 15.2.2 | ³¹ P MRS | 410 |
| | | 15.2.3 | ¹³ C MRS | 411 |
| | | 15.2.4 | Direct Detection of Psychoactive Drugs by | |
| | | | ¹⁹ F and ⁷ Li MRS | 412 |

Contents

| | 15.3 | Applications to Specific Disorders | 414 |
|------------|---------|---|-----|
| | | 15.3.1 Schizophrenia | 414 |
| | | 15.3.2 Bipolar Disorder (BPD) | 415 |
| | | 15.3.3 Major Depressive Disorder (MDD) | 416 |
| | | 15.3.4 Other Psychiatric Disorders | 416 |
| | 15.4 | Future Directions | 417 |
| | | 15.4.1 Technically Oriented Directions | 417 |
| | | 15.4.2 Clinically Oriented Directions | 417 |
| | Ackn | owledgements | 418 |
| | Refer | ences | 418 |
| Chapter 16 | Struc | tural Magnetic Resonance Imaging Biomarkers in | |
| - | | odegenerative Disease | 422 |
| | | a K. McEvoy, Dominic Holland and Anders M. Dale | |
| | 16.1 | Introduction | 422 |
| | 16.2 | Technical Considerations | 423 |
| | | 16.2.1 Standardized Data Acquisition Protocols | 423 |
| | | 16.2.2 Artifact Minimization | 424 |
| | | 16.2.3 Automated Image Segmentation and | |
| | | Quantification | 427 |
| | | 16.2.4 Longitudinal Image Analysis | 428 |
| | 16.3 | Clinical Trial Design | 429 |
| | | 16.3.1 MRI for Clinical Trial Enrichment | 430 |
| | a san a | 16.3.2 MRI as an Outcome Variable | 431 |
| | 16.4 | | 433 |
| | Refer | ences | 434 |
| Chapter 17 | Magn | netic Resonance Imaging in Respiratory Diseases: From | |
| | | nosis to Pharmaceutical Research and Development | 441 |
| | | lau Beckmann, Alexandre Trifilieff, Christine Egger and | |
| | Yann | ick Crémillieux | |
| | 17.1 | Introduction | 441 |
| | 17.2 | Lung Imaging: Basic Considerations | 442 |
| | 17.3 | MRI in Respiratory Diseases: From Animal Models | |
| | | to Patients | 444 |
| | | 17.3.1 Airway Inflammation | 445 |
| | | 17.3.2 Mucus Secretion and Clearance | 447 |
| | | 17.3.3 Emphysema | 449 |
| | | 17.3.4 Lung Ventilation and Perfusion | 453 |
| | | 17.3.5 Lung Fibrosis | 457 |
| | | 17.3.6 Infections | 459 |
| | | 17.3.7 Pulmonary Arterial Hypertension | 461 |

xvi Contents

| | | 17.3.8 | Side Effects from Inhaled Pollutants or Particles | 462 |
|------------|-------|-----------|--|-----|
| | 17.4 | Final R | | 464 |
| | Refer | | onara | 465 |
| Chapter 18 | Cardi | ovascular | Magnetic Resonance | 472 |
| | | | Theodoros D. Karamitsos, Jürgen E. Schneider | |
| | and S | stefan Ne | ubauer | |
| | 18.1 | | f the Problem: the Global Burden of | |
| | | | ascular Disease | 472 |
| | 18.2 | | on of CMR and an Overview of the Clinical | 172 |
| | 18.3 | Role of | w of the Current Status of CMR (Imaging | 472 |
| | 10.5 | | ectroscopy) and the Rationale for the Use of | |
| | | ~ | n Drug Evaluation | 473 |
| | 18.4 | | Pre-Clinical Drug Development | 475 |
| | 18.5 | | Clinical Drug Development: Current Status | |
| | | of CMR | R for Interrogating Aspects of Cardiovascular | |
| | | | and Function | 476 |
| | | | Vascular Imaging | 476 |
| | | | Ischemic Heart Disease | 478 |
| | 18.6 | | Cardiomyopathy ions of CMR | 480 |
| | | | Perspectives: Emerging CMR Techniques | 482 |
| | 10.7 | | o Aid Evaluation of Emerging Therapies | |
| | | - | nical and Clinical Sections) | 483 |
| | Ackn | owledger | *. | 484 |
| | Refer | _ | | 484 |
| Chapter 19 | Magn | etic Reso | onance Imaging Techniques in Cancer | 490 |
| • | | | , J. P. B. O'Connor and A. Jackson | |
| | 19.1 | Overvie | w | 490 |
| | 19.2 | Relaxat | ion Times and Proton Density | 491 |
| | | | Clinical Use of "Weighted" Sequences | 492 |
| | | 19.2.2 | Quantifying T_1 and T_2^* | 494 |
| | 19.3 | | ic Contrast Enhanced MRI (DCE-MRI) | 495 |
| | | 19.3.1 | Dynamic Susceptibility Contrast Enhanced-MRI (DSCE-MRI) | 495 |
| | | 19.3.2 | Dynamic Relaxivity Contrast Enhanced | 493 |
| | | 17.5.2 | MRI (DRCE-MRI) | 498 |
| | 19.4 | Diffusio | on Weighted Imaging | 501 |
| | | 19.4.1 | Apparent Diffusion Coefficient | 501 |
| | | 19.4.2 | Clinical Applications | 502 |