## Intelligent Bioinformatics

Intelligent Bioinformatics: The Application of Artificial Intelligence Techniques to Bioinformatics Problems
Edward Keedwell and Ajit Narayanan

© 2005 John Wiley & Sons Ltd. ISBN: 0-470-02175-6

# Intelligent Bioinformatics

The application of artificial intelligence techniques to bioinformatics problems

## Edward Keedwell and Ajit Narayanan

School of Engineering, Computer Science and Mathematics University of Exeter, UK



Copyright © 2005 John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England

Telephone (+44) 1243 779777

Email (for orders and customer service enquiries): cs-books@wiley.co.uk Visit our Home Page on www.wileyeurope.com or www.wiley.com

All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning or otherwise, except under the terms of the Copyright, Designs and Patents Act 1988 or under the terms of a licence issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1T 4LP, UK, without the permission in writing of the Publisher. Requests to the Publisher should be addressed to the Permissions Department, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England, or emailed to permreq@wiley.co.uk, or faxed to (+44) 1243 770620.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The Publisher is not associated with any product or vendor mentioned in this book.

This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the Publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

#### Other Wiley Editorial Offices

John Wiley & Sons Inc., 111 River Street, Hoboken, NJ 07030, USA

Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons Australia Ltd, 33 Park Road, Milton, Queensland 4064, Australia

John Wiley & Sons (Asia) Pte Ltd, 2 Clementi Loop #02-01, Jin Xing Distripark, Singapore 129809

John Wiley & Sons Canada Ltd, 22 Worcester Road, Etobicoke, Ontario, Canada M9W 1L1

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

#### Library of Congress Cataloguing-in-Publication Data

#### British Library Cataloguing in Publication Data

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

ISBN 0470021756

Typeset in 10.5/13.5pt Sabon by TechBooks, New Delhi, India Printed and bound in Great Britain by TJ International Ltd., Padstow, Corwall This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

## Contents

Pref Ack		dgement	ix xi
PA]	RT 1	INTRODUCTION	1
1	Intro	oduction to the Basics of Molecular Biology	3
	1.1	Basic cell architecture	3
	1.2	The structure, content and scale of deoxyribonucleic acid (DNA)	4
	1.3	History of the human genome	9
	1.4	Genes and proteins	10
	1.5	Current knowledge and the 'central dogma'	21
	1.6	Why proteins are important	23
	1.7	Gene and cell regulation	24
	1.8	When cell regulation goes wrong	26
	1.9	So, what is bioinformatics?	27
	1.10	Summary of chapter	28
	1.11	Further reading	29
2	Intro	oduction to Problems and Challenges	
		oinformatics	31
	2.1	Introduction	31
	2.2	Genome	31
	2.3	Transcriptome	40
	2.4	Proteome	50
	2.5	Interference technology, viruses and the immune system	57
	2.6	Summary of chapter	63
	2.7	Further reading	64

10.1002.07001572.1.fmatrer, Denounced from https://enlinethrary.wiley.com/doi/10.1002.07001721.fmatrer by Universidad Autonomon Merepolitum, Wiley Online Library on [06.10.2023]. See the Terms and Conditions (https://enlinethrary.wiley.com/doi/no). on Wiley Online Library or rolls of use; OA articles are governed by the applicable Creative Common License.

vi CONTENTS

3	Intro	oduction to Artificial Intelligence and	
		puter Science	65
	3.1	Introduction to search	65
	3.2	Search algorithms	66
	3.3	Heuristic search methods	72
	3.4	Optimal search strategies	76
	3.5	Problems with search techniques	83
	3.6	Complexity of search	84
	3.7	Use of graphs in bioinformatics	86
	3.8	Grammars, languages and automata	90
	3.9	Classes of problems	96
	3.10	Summary of chapter	98
	3.11	Further reading	99
PA	RT 2	CURRENT TECHNIQUES	101
4		abilistic Approaches	103
		Introduction to probability	103
		Bayes' Theorem	105
	4.3	Bayesian networks	111
		Markov networks	116
	4.5	Summary of chapter	125
	4.6	References	126
5		rest Neighbour and Clustering Approaches	127
		Introduction	127
		Nearest neighbour method	130
	5.3	Nearest neighbour approach for secondary structure protein folding prediction	132
	5.4	Clustering	135
	5.5	Advanced clustering techniques	138
	5.6	Application guidelines	144
	5.7	Summary of chapter	145
	5.8	References	146
6	Identification (Decision) Trees		147
	6.1	Method	147
	6.2	Gain criterion	152
	6.3	Over fitting and pruning	157
	6.4	Application guidelines	160
	6.5	Bioinformatics applications	163
	6.6	Background	169

10.1002/07/01572.1.fmatrer, Denounced from https://enlinethrary.wiley.com/doi/10.1002/07/01572.1.matrer by Universidad Autonoon Meropolitum, Wiley Online Library on [06.10/2023]. See the Terms and Conditions (https://enlinethrary.wiley.com/berms-md-conditions) on Wiley Online Library or rules of use; OA articles are governed by the applicable Creative Common License

CONTENTED THE	••
CONTENTS	V11

10.1002/07/01572.1.fmatrer, Dominated from https://enlinethrary.wiley.com/doi/10.1002/07/01572.1.matrer by Universidad Autonomon Merepolitum, Wiley Online Library on [06.10/2023]. See the Terms and Conditions (https://enlinethrary.wiley.com/doi/no). on Wiley Online Library or roles of use; OA articles are governed by the applicable Creative Common License.

	6.7	Summary of chapter	170
	6.8	References	170
7	Neu	ral Networks	173
	7.1	Method	173
	7.2	Application guidelines	185
	7.3	Bioinformatics applications	187
	7.4	Background	192
	7.5	Summary of chapter	193
	7.6	References	193
8	Gene	etic Algorithms	195
	8.1	Single-objective genetic algorithms – method	195
	8.2	Single-objective genetic algorithms – example	202
	8.3	Multi-objective genetic algorithms - method	205
	8.4	Application guidelines	207
	8.5	Genetic algorithms – bioinformatics applications	210
	8.6	Summary of chapter	217
	8.7	References and further reading	217
PA]	RT 3	FUTURE TECHNIQUES	219
9	Gene	etic Programming	221
	9.1	Method	221
	9.2	Application guidelines	230
	9.3	Bioinformatics applications	232
	9.4	Background	236
	9.5	Summary of chapter	236
	9.6	References	237
10	Cellu	ılar Automata	239
	10.1	Method	239
		Application guidelines	245
	10.3	Bioinformatics applications	247
	10.4	Background	251
	10.5	Summary of chapter	252
	10.6	References and further reading	252
11	Hybrid Methods		255
	11.1	Method	255
	11.2	Neural-genetic algorithm for analysing gene expression data	256
	11.3	Genetic algorithm and <i>k</i> nearest neighbour hybrid for biochemistry solvation	262

•••	
V111	CONTENTS

11.4	Genetic programming neural networks for determining	
	gene – gene interactions in epidemiology	265
11.5	Application guidelines	268
11.6	Conclusions	268
11.7	Summary of chapter	269
11.8	References and further reading	269
Index		271

10.1002/07/01572.1.fmatrer, Dominated from https://enlinethrary.wiley.com/doi/10.1002/07/01572.1.matrer by Universidad Autonomon Merepolitum, Wiley Online Library on [06.10/2023]. See the Terms and Conditions (https://enlinethrary.wiley.com/doi/no). on Wiley Online Library or roles of use; OA articles are governed by the applicable Creative Common License.

### **Preface**

It is widely recognized that the field of biology is in the midst of a 'data explosion'. A series of technical advances in recent years has increased the amount of data that biologists can record about different aspects of an organism at the genomic, transcriptomic and proteomic levels. This data is, of course, vital to advancing our knowledge. In recent years, the discipline of bioinformatics has allowed biologists to make full use of the advances in computer science and computational statistics in analysing this data. However, as the volume of data grows, the techniques used must become more sophisticated to cater for large-scale data and noise. Also, given the growth in biological data, there is a need to extract information that was not previously known from these databases to supplement current knowledge. Large databases may contain interesting patterns that, if identified and authenticated by further laboratory and clinical work, can lead to novel theories about the causes of various diseases and also possibly to new drugs for their treatment. The discipline of bioinformatics has reached the end of its first phase, and the motivation behind this book is to characterize the principles that may underlie second phase bioinformatics. That is, second phase bioinformatics is when the discipline, instead of being informed by just computer science and computational statistics, is also informed by artificial intelligence techniques.

As we show in this book, there are problems in bioinformatics and many other sciences that cannot be solved satisfactorily even with the fastest computers. Clearly, a more 'intelligent' approach is required to solve these increasingly difficult bioinformatics problems, such as gene expression analysis and protein structure prediction. This book attempts to address this by looking at the latest advances in artificial intelligence technology as applied to computational problems in biology. Artificial intelligence methods are often based on the ways in which humans solve

x PREFACE

search and optimization problems, or how nature has solved its own problems, for example by using the principles of 'survival of the fittest' in evolutionary computation.

This book is divided into three parts, each containing a number of chapters. These parts are designed to allow readers to access the material most relevant to them. The first part, Introduction, introduces the material necessary to understand the technology and biology included in the later chapters. We recognize that bioinformatics is highly crossdisciplinary and therefore some, all or none of these chapters may be relevant to the reader, depending on their background. The next part, Current Techniques, describes the established artificial intelligence techniques in bioinformatics including probabilistic, nearest neighbour and genetic algorithm approaches. The final part, Future Techniques, is intended to give the reader an impression of the latest thinking in the area of intelligent bioinformatics. Some of these approaches may not have been widely applied to problems in bioinformatics, but algorithms such as genetic programming and various hybrid approaches can be expected to make a big impact in this domain if experience in other areas of science and technology is anything to go by.

In short, this book has been written to engage and interest readers from many disciplines. Biologists are provided for in that there is a full introduction to the challenges for computer science, and computer scientists should also find the chapters on biology and bioinformatics informative. Practicing bioinformaticians are also likely to find the book enlightening, as much of the material has previously only been included in specialist publications and a collection such as this provides a single resource for many intelligent problem-solving techniques in bioinformatics. However, as with any book of this type, not every technique can be included due to space restrictions and apologies are offered to researchers whose own favourite analytical techniques are not covered in this book.

Edward Keedwell Ajit Narayanan 10.10020470015721.fmatter, Denovabed from http://ecalinelibrary.wisi.ye.om/ecil.ibrary.wisi

## Acknowledgements

The authors would like to thank everyone involved with producing this book including staff at the Department of Computer Science and Centre for Water Systems at the University of Exeter, in particular Godfrey Walters, Dragan Savic and Soon-Thiam Khu. In addition to this, we would like to thank Bjorn Olsson for his contribution to the tutorials on which this book is based, and Laetitia Jourdan for her helpful comments. Also, we would like to thank the many MSc students on the Bioinformatics programme at the University of Exeter, who contributed towards some of the material for this book. Finally we would also like to thank the editorial and production staff at Wiley, in particular Joan Marsh, Andrea Baier and Robert Hambrook for making this book possible.

We are grateful to WoltersKluwer Health for permission to adapt and re-use Figures 2.10, 6.3, 7.1, 7.2 and 7.3 and Table 5.1 from 'Artificial intelligence techniques for bioinformatics', A. Narayanan, E. C. Keedwell and B. Olsson, *Applied Bioinformatics* 2002: 1(4) 191–222.

10.1002/0470015721. Innatter, Devolveded from http://colinelibrary.wisy.com/doi/10.1000470015721. Innatter by Universidad Autonoma Meteopolitaa, Wiley Online Library on [66/10/2023]. See the Terms and Conditions (http://colinelibrary.wisy.com/terms-and-conditions) on Wiley Online Library for rule of use; OA article are governed by the applicable Creative Commons Library.

#### **Dedications**

Ed Keedwell – This book is dedicated to my family Rob, Lyn, Rich and Loveday, to Kate, and in memory of Alex Larigo.

Ajit Narayanan – This book is dedicated to Lucy, Belinda and Kieran, my mother Janaki, my brother Ramesh and sister Seetha.