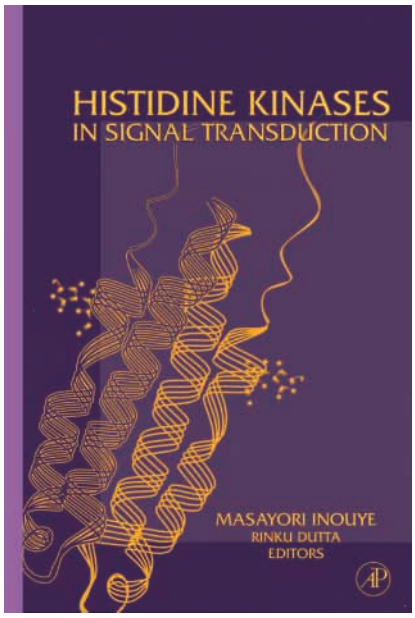
# The structure of cell signaling




## Histidine Kinases in Signal Transduction

### Edited by Masayori Inouye and Rinku Dutta

Academic Press (2003) 520 pages. ISBN 0-12-372484-8
£89.65/$129.95

Receptors involved in signal transduction fall into a few well recognized and intensively studied classes, and so it is surprising that a lot of scientists remain oddly unaware of one of the most important receptor types, the histidine kinase. Histidine Kinases in Signal Transduction is, therefore, a very welcome addition to the literature. Histidine kinases (HKs) are the first component of the widely studied 'two-component' signal transduction systems used extensively by bacteria to modify their cellular behaviour in response to their environment. The second component of these pathways, the response regulator (RR), may not be mentioned in the title of this book but it is not neglected. Nevertheless, the focus in this volume is definitely on the HK enzyme, and for good reason. In the past few years, tremendous progress has been made in determining the molecular structures of these enzymes, and this has taken our understanding of these signaling proteins into a new era. Therefore, it is no accident that at least half of the chapters in this collection of essays by leading researchers discuss, at some level, protein structures.

The signaling systems about which we know most, those involving the HK enzymes EnvZ and CheA, are dealt with first, and in the greatest detail. Partial structures of EnvZ and CheA have been solved by NMR and X-ray crystallography and have defined the HK core structure, which shows that it belongs to the GHL ATPase superfamily. The lack of a complete intact HK structure is offset somewhat by structural knowledge of other GHL ATPases, which informs our understanding of the possible HK catalytic mechanism. All of these issues are dealt with in the book by many of the people responsible for these studies. A masterful structure-based sequence analysis by Lupas and colleagues illuminates the relationships between HK families, and their deep evolutionary relationship with protein serine kinases such as pyruvate dehydrogenase kinase. These authors speculate that HKs arose from an ancestral ATPase fold and co-evolved with their signaling partners, the RRs. The RRs are discussed here by Stock and West in terms of interactions with HKs and with effector domains, and also with respect to structural changes induced by RR phosphorylation.

A major theme to emerge from the book, as expected, is the dual functionality of HK enzymes, the majority of which also act as phosphatases. Because details of the HK kinase mechanism are still hazy, even less is understood of the phosphatase activity, although this isn't simply a reversal of the kinase. Inouye discusses the kinase versus phosphatase activity, and contrasts a switch-type mechanism (i.e. kinase on – phosphatase off and vice versa) with a rheostat model encompassing many different intermediate states. The latter model is no doubt closer to the truth for most HKs, but the argument is unconvincing owing to the lack of mechanistic understanding at this time.

Despite the recent progress, fundamental questions remain. How is transmembrane signaling achieved? Wolanin and Stock address this subject with respect to bacterial chemotaxis, and discuss possible roles of helical linker regions present in receptors, as well as broader concepts, such as receptor clustering and higher order signaling. How is signaling specificity achieved in the pathways? Varughese looks at features of RR proteins that could impart specificity to their interactions with their signaling partners. By contrast, Throup and colleagues examine the common aspects of RR-HK interactions that could be useful for the design of new antibacterial drugs targeted at these signaling systems.

The later chapters of the book deal with less well-studied signaling systems (compared with chemotaxis, for example). These subjects include quorum sensing in bacteria and HK signaling systems in plants, yeast and *Dictyostelium*. These chapters are more descriptive but are highly readable and informative, and represent a useful collection of lucid and succinct reviews.

It is a truism in science that the more you know, the more you need to know, and that is the distinct impression one gets when reading this book. A much deeper understanding of the molecular operation of HKs and two-component systems is seemingly just around the corner. As Bilwes and colleagues point out, we know the structures of many individual signaling domains, which give us tantalizing clues to the way HK enzymes operate. We now need the structures of whole proteins and then the structures of protein complexes, and it is clear that these challenges are being taken up and will be met in the near future.

The editors have done a great job of assembling a stellar cast of contributors for this book, and also of achieving good coverage of the breadth and depth of the subject. All chapters are well illustrated and extensively referenced. I can highly recommend Histidine Kinases in Signal Transduction to the expert and newcomer alike.

**Peter Thomason**
Molecular Biology, Princeton University, Princeton, USA

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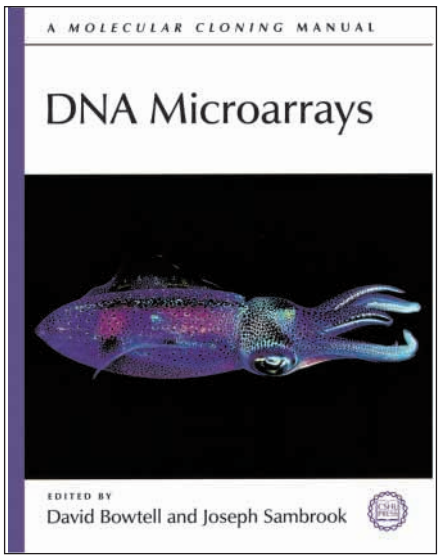
# A heavyweight guide through the array jungle




## DNA Microarrays: A Molecular Cloning Manual

### Edited by David Bowtell and Joseph Sambrook

Cold Spring Harbor Laboratory Press (2003) 712 pages. ISBN 0-870969-625-7
£100/US$135

I have to admit that I felt quite daunted when this book arrived on my desk. Over 700 pages long and weighing more than 2 kilos, it is quite a document. Is there really that much to know about microarrays? It seems there is. Just as the Molecular Cloning Manual (Sambrook et al., 2001) became a 'must have' reference in many labs, DNA Microarrays from Cold Spring Harbor Laboratory Press is set to provide the same type of in-depth information to researchers working in this relatively new field.

Bowtell and Sambrook have assembled a comprehensive collection of protocols, covering many aspects of microarray application. The protocols have been supplied by a number of contributors, many of whom are well-known authorities in the field of microarray technology. The protocols are well written and easy to follow, with extensive introductory sections to each chapter. Information panels distributed throughout the book contain very helpful and detailed background information and explain some of the jargon used in the field.

The editors have chosen to concentrate on the production of cDNA microarrays on glass surfaces and the hybridisation of cDNA and oligonucleotide arrays, both of which are covered in great detail. However, they also include a short chapter on membrane-based spotted arrays, as these seem to be more accessible for many academic labs. A large section of the book covers different methods for isolating RNA from cells and tissues, including preparing polysomal RNA for the enrichment of transcribed genes or amplifying RNA from single cells and small amounts of tissue. The description of target labelling and hybridisation methods is equally detailed, including a step-by-step guide to the tricky task of applying labelled target to glass slides. I found the troubleshooting guide at the end of the chapter particularly useful. It consists of a collection of images illustrating common problems (many of which I had come across myself) with cDNA arrays and oligonucleotide chips and lists potential causes and solutions.

In addition to the more widely used expression analysis of RNA, the manual also contains chapters on genomic analysis using microarrays, including detection of copy number and SNP genotyping and the use of microarrays in conjunction with chromatin immunoprecipitations, albeit only in yeast.

The most interesting chapter for me was the introduction to microarray bioinformatics. The authors cover every step from experimental design, image analysis, normalisation and quality control to cluster analysis and data management. In addition to excellent descriptions of different strategies and potential problems that can arise at different stages of data analysis, Bowtell and Sambrook also include examples of good and bad data, as well as references to available commercial and academic software packages.

One can argue that more and more academic labs are using microarrays from commercial sources rather than embarking on the expensive and time-consuming task of manufacturing their own. And commercial systems would usually come with recommended protocols and technical support. However, even when using an off-the-shelf system, it is very important to understand the potential of the technology and the possible pitfalls. Careful experimental design and statistical scrutiny are essential for generating usable data and can save unnecessary expense. A number of protocols in this manual also cover specialist applications that have been developed in academic labs to investigate particular biological questions. It is invaluable as a guide to how a protocol can be adjusted or optimised and to what problems can occur. Now that microarrays have evolved into a widely used technology, the appearance of this reference is timely. Bowtell and Sambrook have managed to assemble an excellent manual that should be on the shelf of anybody intending to get seriously involved in this powerful and exciting field.

**Almut Schulze**
Gene Expression Analysis Laboratory, Cancer Research UK, London, UK

**Reference**

Sambrook, J. and Russell, D. W. (2001). Molecular Cloning. New York: Cold Spring Harbor Laboratory Press.

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