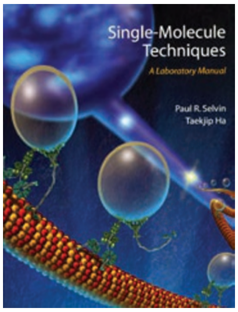
Single molecule for the people



Single-Molecule Techniques

Edited by Paul R. Selvin & Taekjip Ha

Cold Spring Harbor Laboratory Press, 2008 Price: $165/£120

Robert Cross

I don't believe I have ever before read a microscopy textbook from cover to cover — but this one, reader, I did. Its two editors, Taekjip Ha and Paul Selvin, have set out to assemble a manual for cell biologists who want to extend their technical repertoires to include single-molecule techniques. They have succeeded admirably, and as a bonus the book provides a fascinating insight into where the technical limits lie, of how we stand — as the authors suggest in their introduction — at the beginning of a new era of single-molecule-based cell biology.

If molecular cell biology had an agenda, then near the top of the list would be the need to understand how the biology of cells arises out of the properties and behaviours of individual molecules. Single molecules still hold considerable mystery. For the most part, the world of our everyday experience comprises multimolecule phenomena, and the familiar language of cell biology is adapted to describe these phenomena. As we zoom in to the single-molecule level, unfamiliar things start to happen. Events become stochastic. Structures become probabilistic distributions of different structures. Everything jiggles about, so that even the idea of a given object being in a particular fixed position needs careful consideration and qualification.

We don't ordinarily have to worry about such things because traditional methods inherently report the average properties of an ensemble of molecules. But to understand how the characteristics of an ensemble arise from the behaviour of its constituent molecules, we need to study the individual molecules, preferably in context, within the ensemble. Some of the most revealing recent work is being done in this way, but most cell biology labs are still some way from being able to make their own single molecule measurements. One problem is that, to do so, it is usually necessary to build a custom one, or at least to modify a commercially available microscope. This typically requires a considerable commitment of time and effort, but it is nonetheless not nearly as forbidding an enterprise as it seems. The expressed hope of the editors is that their book will encourage more labs to upgrade to single-molecule techniques. I think that indeed it will.

Roughly half the chapters of this book are dedicated to single-molecule nano-manipulation and mechanics, and the other half deal with the use of fluorescent and other labels to signal conformational changes and track the positions of molecules. Every chapter consists of an introductory commentary, followed by a set of detailed protocols, each with a troubleshooting guide dealing with common pitfalls. These kinds of specifics are typically buried in the supplementary information of primary papers, and are sometimes not described at all. The format of this book gives its authors space to expand on what is important and what is not in the construction and operation of a particular apparatus, as well as to discuss and impart the tricks of their trades. The authors have seized the day: indeed, their enthusiasm and their urge to share, fairly glow from the pages of this book. All the contributors have gone out of their way to explain how, after much toil, single molecules can be made to reveal themselves.

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Single-molecule measurements will surely get easier, but for the moment they tend to be 'challenging', to use a fashionably upbeat term, or 'slow, maddeningly difficult, or both', to be more accurate. Constructing a new microscope is challenging, but it is also educational and fun. This excellent book will be invaluable to anyone who is already competent at multimolecule data collection and interested in getting down to molecular mechanisms. The book's only weakness is its rather limited index — but this is a quibble; here is all you need to dissolve the technical barriers surrounding single-molecule cell biology.

The chief remaining barriers to single-molecule success reside in the wetware, the biological molecules and the biological person trying to measure their properties. Physicists expect to spend time constructing their equipment before they can do an experiment. Biologists, in my experience, do not. Aside from this psychological or cultural barrier, the actual doing of the experiment itself can take a while. Not uncommonly, by the time a worker has all the parts of the microscope pointing in the right direction, and has persuaded the interesting biological molecules to pose attractively, it is, all too soon, time to retire for a restorative sleep — a scenario that can repeat itself for weeks or months until satisfactory data are finally collected. Here, we can learn something from the living cell, which typically works around the vagaries of single biomolecules by assembling them into teams. In my own field — molecular motors — motor domains are typically arranged thus, and members of the team collaborate, to great effect. Perhaps in the coming era of widespread single-molecule cell biology, molecular cell biologists ought to do the same.

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