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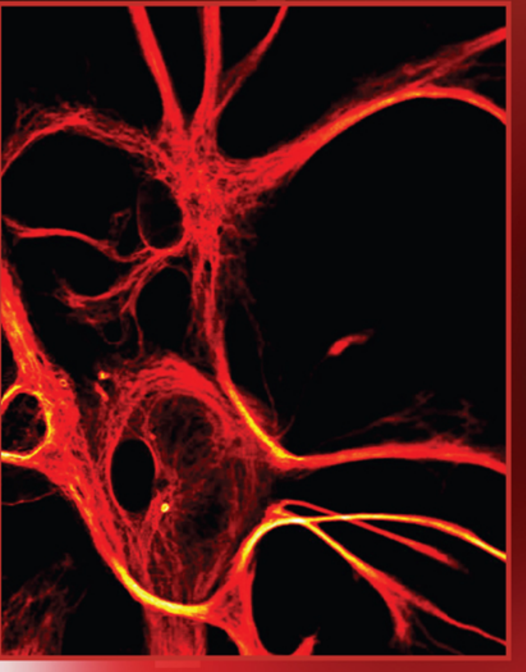
Philip D. Langton



Essential Guide to Reading Biomedical Papers

Recognising and Interpreting Best Practice

WILEY-BLACKWELL

Essential Guide to Reading Biomedical Papers

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Editor

Phil Langton

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Foreword

Biological research is an experimental science in which the testing of hypotheses through experiments generates knowledge and ultimately, understanding. However, while the construction of a hypothesis is open to the imagination, the experiments that produce the data to be analysed in the light of the hypothesis are only useful if they are reliable, accurate, reproducible, and come from carefully designed and controlled experiments. In the acquisition of data, therefore, there is no room for the imagination and even less for wishful thinking – the vice that reads the data to fit the hypothesis and not the other way around. Therefore, although it is true that a hypothesis guides the gathering of information, the primacy of the data is obvious since without them all hypotheses remain in the "to be done" drawer.

Biological research nowadays can be approached using a variety of techniques, the majority of which have been developed in the last 50–60 years. The power of these new techniques is such that biologists often forget two fundamental things, (1) that the usefulness of the technique does not lie so much in its intrinsic power but in the way it is applied to a biological question and (2) that all techniques have been designed for a specific purpose and therefore have limitations. There is not a single technique that can inform us about the whole of a biological problem and therefore it is advisable, wherever possible, to use more than one complementary technique.

These are the reasons why the present book by Langton and colleagues is so important. It is not merely about techniques; it puts techniques into context – their potential, their limitations and possible pitfalls. This is accompanied by useful primers on the philosophy of science, on experimental design and on statistics. As such, this volume will undoubtedly be of great interest and value, not only to the novice scientist but also to the experienced investigator and mentor.

I highly recommend this book to all practitioners of biological research.

Professor Sir Salvador Moncada
FMedSci, FRS
27th July, 2012

Preface

Imagine you are interested in buying a used car. Are you likely to be entirely trusting of the person selling the vehicle? Will you accept everything they tell you without question and without evidence? I suspect not. I suspect that you will have a *healthy scepticism*. The seller wants your money and it is your responsibility to ensure that you are satisfied with the trade – hence the phrase '*caveat emptor*', which means '*let the buyer beware*'.

I would argue that you should regard journal articles with the same healthy scepticism, but I imagine your reaction to this is either disbelief or a mixture of confusion and panic. If you are sceptical, good! I need to provide evidence for my argument. If you are confused, let me explain.

How is a journal article like a used car? It is easier to consider how the seller equates to the author(s) of a journal article. The seller wishes to get the best price and is unlikely to point out defects and flaws; certainly not with the same enthusiasm as they have for the *plus points*. The authors of a journal article are also selling something – their interpretation of their experiments, including their underlying assumptions. It is hugely important that the authors win the reader's confidence; that they convince *you* that their work is showing true facts (see Primer 1 for an expansion of this idea). Science is big business and careers depend on how widely and how securely the views of the authors are endorsed by the scientific community. In some ways, it is possible to regard journal articles as advertisements for a particular doctrine.

Some of you will have picked up a counter-argument in the shape of the *peer-review process*. Good for you, you are reading with scepticism. Surely the peer-review process means the reader can have confidence that an article in a peer-reviewed journal is accurate and true – at least at the time it was published? Sadly, this would not be a safe assumption. Though it is arguably the best system we have to ensure the quality and validity of what is published, peer-review is very far from perfect and even the most prestigious journals make mistakes.

Science makes use of an approach that has become known as the Scientific Method (see Primers 1 and 2). It was developed into something we can recognize today in a process that can be traced back nearly 400 years to a succession of great thinkers and great philosophers. In 1601, Francis Bacon (1561–1626) wrote:

> *'Read not to contradict and confute; nor to believe and take for granted; nor to find talk and discourse; but to weigh and consider.'*
>
> From Bacon's essay *of Studies* (published in full in [1]Madden, 2007).

It is too easy to read and simply accept as facts those things that are offered as such. It is highly likely that excellence in your written work, which relies upon your interpretation of the academic literature, will be judged on your ability be demonstrate that you are '*critical of what you read*'.

Unless you have knowledge of the experimental techniques used in a study, however, you will find it difficult to discriminate between studies that are well designed and/or controlled and those that are not, and you will find it hard to be critical. Therefore, in essence, each primer in this book is intended to provide you with the means to be critical about studies described in journal articles.

Aims of each primer

It is important that you are aware of the aims of these primers. Each one is designed to:

- ✓ provide orientation and guidance to readers who have no experience of the technique;
- ✓ suggest reasons/motives for electing to use a specific technique;
- ✓ provide details of a method only where detailed knowledge is required;
- ✓ provide limits on what can 'reasonably' be claimed of data – specificity, selectivity, etc.;
- ✓ describe control experiments that *should* be included in a journal article;
- ✓ explain why particular controls are performed;
- ✓ list other techniques that are commonly used in conjunction;
- ✓ list common misconceptions about a technique or the data produced by a technique;
- ✓ list some caveats about interpretation of data [where appropriate].

[1] Madden, P. (Ed., 2007). *Quotidiana* (http://essays.quotidiana.org/bacon/studies/). Accessed 22 Apr 2012.

However, they are *not*:

✘ intended to be encyclopaedic manuals or reviews;

✘ 'how to' guides;

✘ sufficient in themselves as resources (hence the further reading);

✘ likely to be useful to persons experienced with the technique.

I want to end this preface with another quotation from Francis Bacon:

> *"If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties."*
>
> From Bacon's [2]*The Advancement of Learning* (1605) book 1, primer 5, section 8

What I take from this quotation is that it is *not* healthy for scientists to believe too fiercely in what appears today to be true. We must be prepared to question anything; there should be no [3]dogma in science, because our current understanding reflects a continuum beginning with the tentative '*more probable than not*' and moving to greater and greater probability of being accurate or true – but *never reaching certainty*. Ultimately, nothing is ever proved.

Phil Langton

[2] Available from: www.lifesmith.com/Berkeley%20Teaching/The%20Oxford%20Dictionary%20Of%20Quotations.pdf; accessed 22nd April, 2012.

[3] ***Dogma*** – 'a principle or set of principles laid down by an authority as incontrovertibly true'. Source: Oxford Dictionaries.

Acknowledgements

This book can trace its origins back to about 10 years, to learning and teaching resources for undergraduate students studying anatomy, neuroscience or physiological science at the University of Bristol and this explains in large part why Bristol academics are involved with the majority of the primers you will find listed. The aim for the book is simple, as it was for the original resource; to communicate some of the practical wisdom that can only come with years of experience and scholarship in laboratory research. It does not pretend to make the reader an expert or to train the reader to use these research techniques but it does provide insight into the assumptions and issues that can lie beneath the surface of seemingly transparent and persuasive research reports. In editing the book, I have been surprised on a daily basis by the scope and significance of the aspects highlighted by my colleagues. Indeed, I have learned so much that I would now view with extreme scepticism the claim that one can read contemporary research reports without, as minimum, the sort of insight that this book aims to provide.

The original resource would not have been possible without the enthusiastic support of my colleagues in the University of Bristol and it is to them that I am most deeply grateful. I wish also to thank the team at Wiley-Blackwell who saw the potential for a book and the independent reviewers who reacted so positively to the preliminary outline and example primers. The first edition required a significant expansion from the original resource and had involved a large number of people from Universities in the United Kingdom, Australia and North America to whom I am enormously and sincerely grateful.

I wish to express my gratitude to the University of Bristol for its encouragement of excellence in learning and teaching as well as excellence in research. For some time the prevailing wind within UK HE has benefitted a focus on research above all else and yet Bristol has striven consistently to promote the interests of its students and the education they receive. This book reflects the ethos of enquiry and excellence that is so typical of the University of Bristol.

I need to acknowledge the support (and patience) of my partner, Rosie, without whom this project would have failed. Finally, I gratefully acknowledge my parents who taught me to respect the potential in dedication and hard work and the value of integrity; attributes that no research scientist should ignore. Lastly to Alice, Polly and Jess who just wanted to see their names in print.

Dr Phil Langton
August, 2012

Introduction

Phil Langton

This introduction explains the structure of most of this publication (Primers 4 to 35). The first three primers escape this structure, as their aim is different. These first three primers cover:

1. The philosophy of science
2. Experimental design
3. Statistics

These are topics of fundamental importance in science. Reading these first will allow maximum benefit from the other primers and indeed from every journal article you read in future. Switch on your scepticism!

As Claude Bernard said in his [1]textbook, "*L'expérimentateur doit douter, fuir les idées fixes et garder toujours sa liberté d'esprit", which means "the investigator should doubt, avoid preconceptions, and always keep an open mind*"

Primers 4 to 35 will have the following structure:

- **Basic 'how-to-do' and 'why-do' section**
  This section will cover what the technique is used for. For some techniques, the answer is far from obvious. If there are facets of the technique that require insight into how the experiments are done, then they will be included in this section. It will be basic – just enough to make sections on *required controls* and *pitfalls in execution or interpretation* intelligible and to help you tackle articles in the reference section.
- **Required controls**
  If your eyes have at tendency to glaze over at the mere mention of '*experimental controls*', then give yourself a slap and read on. Without well-judged experimental design and comprehensive controls, the results of an experiment are next to useless. There will endless possible interpretations – so much so that the experiment will not advance our understanding. Each

[1] '*Introduction à l'étude de la médecine expérimentale*', 1865.

primer will list the controls that should be present, and particularly those that require special attention, because these are frequently absent or poorly designed in published articles. If appropriate, the section will indicate what failure of a particular control might indicate. For example, failure of the negative control in a PCR experiment suggests contamination of the RNA by genomic DNA – mRNA implies ongoing transcription, but the presence of genomic DNA says nothing about transcription.

- **Common problems or errors in literature**
  The errors pointed out should be findable by undergraduate students who have little or no practical experience of the technique. This does not mean there are not others – just that you will not be able to recognise them without first-hand experience, i.e. without using the technique to perform experiments.
- **Pitfalls in execution or interpretation**
  If you think that the peer-review process prevents the publication of studies that contain significant errors then, again, give yourself a slap – you're being naïve! Consider this example: a study uses immunocytochemistry (Primer 13) to provide evidence that a protein is expressed in sections of tissue or in isolated/cultured cells; it then goes on to do immunoblotting (Primer 15) to back up the immunocytochemistry (demonstrating that the protein bound by the antibody has the correct apparent mass), *but* uses different primary antibodies for the immunocytochemistry and immunoblots. Yes, it does happen! If the significance of this logical error is lost on you, then you need to read Primers 12 to 15.
- **Complementary and/or adjunct techniques**
  This will list techniques that are often used together.
- **Further reading and resources**
  Some of the articles will be those cited in the text, while others will be suggestions for further reading. You need to keep in mind that these techniques require years of careful scholarship and training to master. The primers have been written by researchers who have developed true expertise with each technique but each primer is very short and of limited scope – hence the term, '[2]*primer*'.

[2] **Primer**: a book (or text) that covers the basic elements of a subject. Source: OED.

Section A

Basic Principles

1
Philosophy of Science

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1.1 What is science?

Dictionary definitions speak of a systematic body of knowledge, and the word '*science*' comes from the Latin word for knowledge. However, not any old collection of facts – even one that is organized – constitutes a science. For example, an alphabetical list of all the words that are used in this book and all the others published on the same day would make no contribution to scientific knowledge. Something else is needed, and there are two obvious supplements to what has been said so far:

- First, the subject matter must be the workings of the physical world. There must be discovery of natural laws and the relations of cause and effect that give rise to the phenomena that we observe.
- Second, the relevant theories must be generated in the right way.

In fact, most philosophers of science and scientists define science in terms of its methods of production; science is knowledge produced by the scientific method. For many people then, asking the question with which we began really amounts to asking, '*What is the scientific method?*'

There are, of course, many methods, and this book is about some of them. The techniques and procedures of the laboratory and experimental trials and the measurement, recording and representation of data, as well as its statistical analysis, form at least as much a part of science as what it tells us about the world as a result. Clearly, the methods of geology and astrophysics differ from those of cell biology or pharmacology.

However, all the sciences we now take for granted have really only reached maturity and separation from each other within the last few hundred years. For example, biochemistry and neuroscience have only become separate disciplines in

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the last century, and whole areas of enquiry were impossible before the invention of electron microscopy and magnetic resonance imaging. Our gigantic science faculties, with their highly specialized disciplines, originated in the ancient and medieval systems of knowledge, and these made very few of the distinctions in subject matter that we now would. for example, many posited connections between the planets and human diseases and other conditions where we find none. Nonetheless, we can find some original truths from many subjects discussed a long time ago. For example, Aristotle recorded that bees pollinate flowers, and the 28-day cycle of the Moon's phases has been known since prehistory.

Modern science is usually regarded as having originated at the turn of the 16th and 17th centuries. At this time, the established ways of predicting the motions of the planets, which placed the Earth at the centre of the solar system, were replaced by the Copernican theory placing the Sun at the centre, which was then modified by Kepler to incorporate elliptical orbits. The latter's laws were precise mathematical statements that fitted very well with the detailed data that had recently been gathered using new optical technology. In the years that followed, telescopes, microscopes, the air pump and clockwork and other mechanical devices were invented and, over the next few generations, knowledge of chemistry, biology, medicine, physics and the rest of what was then called 'natural philosophy' grew enormously.

An amazing thing about all the scientific knowledge that we now take for granted is that the founders of modern science envisaged its production by the collaborative endeavour of people following the scientific method. They argued that there was a common core to all the methods mentioned above, and they advocated the collective use of a single set of principles or rules for investigation, whatever the subject matter. Different people had different ideas about exactly what the method should be, but everyone agreed that testing by experiment is fundamental to science. The task, therefore, is to say what exactly 'testing by experiment' means.

There two general kinds of answer:

- **Positive**, according to which the job of scientists is to gather data from which to infer theories, or at least to find out which theories are supported by it.
- **Negative**, according to which the real task is to try and prove theories false.

The latter may sound strange, but in fact many scientists put more emphasis on it than the former. The reason for that is that there is a very great tendency in human thought to find confirmation of preconceptions and received ideas by being selective in what is taken into account.

The phenomenon known as 'confirmation bias' has been studied extensively in psychology; it is manifested in many ways, including by people selectively remembering or prioritizing information that supports their beliefs. It is very difficult to overcome this tendency, so some people argue that science should always be sceptical and that attempts to prove theories false should be at its heart.

Modern science began with the upturning of many entrenched beliefs about the world, but since then the history of science has repeatedly involved the overturning of cherished doctrines and the acceptance of previously heretical ideas. Examples include the motion of the Earth, the common ancestry of the great apes and human beings, the expansion of the universe and its acceleration, the relativity of space and time, and the utter randomness of radioactive decay. Even the greatest scientific theories, such as Newton's physics and Lavoisier's chemistry, have been subject to substantial correction.

Hence, many scientists follow the philosopher of science Karl Popper in saying that the scientific method consists in the generation of hypotheses, from which are deduced predictions that can, in principle, be falsified by an experiment. When an experiment does not falsify the hypothesis, it may tentatively be employed to make predictions – but the aim should be to seek new kinds of test that may prove it false. A theory that makes specific and precise predictions is more liable to falsification than one that makes only general and vague claims; so, according to Popper, scientists should strive to formulate hypotheses from which very exact statements about experimental outcomes can be derived, and to say in advance what would count as falsification.

Popper emphasized that scientific knowledge is always revisable in the light of new empirical findings, and that science has succeeded in increasing its accuracy, depth and breadth, because even well-established theories are not regarded as immune from correction and revision. Science is not compatible with absolute certainty and the refusal to question.

However, it is also true that in practice, scientists do not immediately abandon core theories when experiments go against them. For example, Newton's law of universal gravitation, the famous inverse-square law, gave beautifully accurate predictions for the paths of the planets in night sky and improved on those of Kepler, as well as generating successful new predictions such as the return of Halley's comet and the flattening of the curvature of the Earth at the poles. However, in the 18th century it was found that the orbit of Uranus was not as predicted, but astronomers did not abandon Newtonian mechanics as a result. Instead, they looked at the other assumptions that they had made in order to calculate the orbit. They had assumed that only the gravitation attraction of the Sun and six other planets needed to be taken into account. If there was another planet, that might explain the anomaly; therefore, Neptune was looked for and found.

Modifying a theory to take account of data that contradicts the original is not, in itself, bad practice. In the case just mentioned, the modification led to a new prediction that could be tested. Science often proceeds like this and, indeed, Pluto was found in the same way. It is now common in astronomy to infer the existence of unobservable objects because of their hypothetical gravitational effect on observable ones.

These examples illustrate an extremely important feature of science, which is that predictions and, hence, tests are never of single hypotheses but always of a collection thereof. To predict the orbit of a planet, one must know all the bodies to whose gravitational attraction it is appreciably subject, and also all of their masses and its mass. If the data do not fit, then logic dictates that there is a problem with at least one of the laws or the other assumptions – although not which one. This is called the Duhem problem (after Pierre Duhem). Scientists face this every day, but they rarely consider that a central theoretical component is false as Popper imagines. To do so would not be sensible, because those core beliefs have been at the centre of a vast number of successful predictions. On the other hand, there will often be many other plausible culprits among the other assumptions involved, and the art and practice of science involves teasing them apart and finding out which to amend.

It is not plausible to argue, as Popper did, that no matter how much a hypothesis has agreed with experiment and survived attempts to show it to be false, there are no positive grounds for belief in it. Since Francis Bacon proposed his new logic of 'induction', many others have sought to develop an account of how evidence can be said to support or confirm a theory. Thus we have two extreme positions:

- *Falsificationism* says science is about showing theories to be false.
- *Inductivism* says science is about showing theories to be true.

It is tempting to seek a happy medium able to incorporate the importance of both, but clearly we cannot do this without some notion of confirmation in science. It is often the case that we look to science to tell us positive facts, such as that a drug is efficacious and safe, or that a particular pathogen is the cause of some medical problem. Bayesian statistics provides measures for how much a given body of evidence supports a given hypothesis. On the other hand, statistical methods are also sometimes used in a falsificationist spirit, as when they are used to calculate the probability of the so-called 'null hypothesis', according to which some potential causal factor has no effect.

The fundamental problem with the scientific method is that it cannot tell us how confident we need to be in a theory before we accept it. Nor, if a research programme is in trouble, can it tell us exactly when to abandon it. For example, in the 19th century, more accurate measurements revealed that the orbit of Mercury did not fit with the predictions of Newtonian gravitation. The trick of positing another planet was tried but, because Mercury is so close to us, any such new planet ought to have been immediately obvious. Thus, it was thought that perhaps it was always the other side of the Sun from us. As it turned out, there is no such planet, and it took Einstein's then new theory of General Relativity to solve the problem.

Similarly, when the evidence begins to come in about the efficacy of a new drug, there is no mathematical formula that can say when we should regard it as '*known*' to be effective. Some scientists may feel sure very early on in the trials, and there may be patients who could benefit from its immediate prescription. However, others will insist that larger studies need to be done before the evidence is compelling. In the end, a committee will set the bar at some level, perhaps demanding that the probability of the null hypothesis for the drug acting on the condition be shown to be less than 0.05 per cent. That is reasonable, but it could also be set at 0.5 per cent or 0.005 per cent, or any other small value and which value is chosen is to some extent arbitrary. Clearly. if the chance of a drug being completely useless is 50 per cent. it should not be prescribed, and if it is .0000000005 per cent then it should be; but where exactly the line should be drawn between these extremes is a matter of choice and judgment.

It is therefore important to be very clear about the limitations of the scientific method, as well as its great power. How much evidence we demand before reaching a conclusion depends in part on whether we are more keen *to have true beliefs* or *to avoid false ones*. If all we care about is having true beliefs, then, for example, above all else we will wish to avoid failing to believe a drug works when it does; if all we care about is not having false beliefs, then, for example, we will wish above all else to avoid believing that a drug works when it does not. The former attitude emphasizes avoiding false negatives and the latter emphasizes avoiding false positives, and in general doing well in respect of one is at the cost of doing badly in respect of the other. Falsificationists emphasize avoiding false positives, so they always think of scientific theories as not yet falsified rather than as confirmed.

The problem is that, both in life and in science, we often need to stick our necks out and commit to the truth of a theory, because if we always wait for one more trial, patients will be denied treatments they need. Part of being a good scientist is developing good judgment about such matters, and it is also necessary to learn where reasonable disagreement is possible, how to identify the crux of such disputes, and how to use the scientific method to refine the evidential basis on which they can be resolved.

Further reading

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