



Box 2 | Conclusions are conditional

A mathematician, a biologist and a physicist are sitting in a street café watching people going in and coming out of the house on the other side of the street.

First they see two people going into the house. Time passes. After a while, they notice three people coming out of the house.

“The measurement wasn’t accurate,” says the physicist.

“No, no,” says the biologist, “they have reproduced.”

“I don’t think so,” says the mathematician. “If exactly one person now enters the house, then it will be empty again.”

This joke was posted on [Profession jokes](#).

fellows are doing. I know what experiments they’ve done recently, and what we discussed they should probably do next (it’s their decision), but on a day-to-day basis, I really don’t know. Just watching them pipetting something or looking into a microscope, whatever the purpose, puts a smile on my face — they might discover something today!

So when the experiment doesn’t work, put the data in your notebook (the failure will probably be useful down the road) and don’t tell your PI. On the rare occasion when the experiment gives you a glorious result, you will have the great pleasure of strolling into the PI’s office with a broad grin on your face and asking (magnanimously, of course) whether they would care to see the data from the ‘experiment that would never work’. Only a control freak PI (see figure 2 in Part I (REF. 1)) could fail to share your joy and excitement. In fact, when you are a PI yourself be careful when discouraging your mentees from performing experiments, no matter how spectacularly flawed they might seem. There is simply no substitute for enthusiasm in science, and you douse it both at your own peril and at the peril of those whose careers are your responsibility.

Size matters. Having a good idea (or even a bad idea, sometimes any idea will do, as they can all lead to serendipity) is only the start. Designing experiments is an art that you will continue to improve for as long as you work at the bench or supervise those who do. The size of the experiment is crucial (FIG. 1). It should be just large enough to have a sufficient number of repeat samples and positive and negative controls for you to interpret the results with confidence. Small experiments are much more likely to work than big ones, as there is less to go wrong. Furthermore, no matter how much thought you give to the experiment, the crucial controls will occur to you after doing the experiment, typically only after many repetitions, if at all. Rare is the scientist who has not been confronted with an essential control when the work is presented in a seminar or for publication. By doing a series of small experiments with constant modifications based on each preceding experiment, you will progress much more rapidly than by performing larger experiments that try to anticipate all of the problems and possible outcomes. An important psychological advantage of small, rapid experiments is that failure (the typical fate of new experiments) is much less depressing than after spending huge amounts of time and energy in a much larger but equally unsuccessful effort.

Doing experiments

Golden eyes. Every well-established laboratory has a ‘Hall of Fame’ of legendary alumni with ‘golden hands’. Golden hands? Golden eyes is closer to the mark. Experimental science does not demand the dexterity of neurosurgery, but it does demand the neurosurgeon’s focus on the task at hand. The key to being a good experimentalist is obsessive attention to detail. They are constantly thinking about the matter at hand (and not about dinner, their next work-out or the cute student in the next laboratory). They constantly use their eyes to monitor every relevant detail. For example, is the water bath too hot? Is the CO₂ setting in the incubator correct? Is the buffer cloudy or off-colour? In cell-based experiments, the golden eyed pay close attention to the cells. They have a feel for how cultured cells look when they are thriving and for how to keep cells in tip-top shape for each experiment. They are constantly scrutinizing the cells during the experiment, even using the microscope when convenient to monitor cell happiness (and to make the odd discovery based on the macrobehaviour of cells). They notice the size, colour and texture of the cell pellets and how they disperse. Details, details, details!

Good experimenters understand every part of an experiment (including buffer and detergent selection) and quickly learn to recognize which are the most important aspects of an experiment and which steps can be shortened or even discarded. While doing the experiment they are already planning how each step could be improved or done more efficiently (doing things more quickly allows more samples to be included or more experiments to be performed, and can be crucial for making discoveries).

Although the repetition of experiments is an essential step to gain confidence in a finding, it is a poor experimenter who does not frequently make at least minor changes to their protocol. In fact, making the same finding after modifying an experiment bolsters the validity of the finding. Above all, as an experimental scientist, you must be certain that your observations are reproducible (BOX 1).

Laboratory notebook: the scientist’s best friend. An essential part of each experiment is to record accurate and appropriately detailed notes. Start each experiment entry with a statement regarding the hypothesis you are testing. In describing your actions, make sure you include all of the unique details of the experiment that you will need in order to repeat it. Those who don’t heed

this advice are fated to make an incredibly exciting finding that they will never be able to repeat. Believe me, this really hurts.

Record the important events that occurred that will help you interpret your findings (such as when the centrifuge tube cap flew off in the centrifuge and (Argh!) weird material collected in your cell pellet). Neatly write or tape data into your notebook. After careful thought, force yourself to write a conclusion: what went right, what went wrong, how does your hypothesis look now and what is the next step. Writing the conclusion is important — it is all too easy to fall into the trap of working hard without thinking hard. If you are going to be an independent scientist, you must do both.

There is an element of luck behind most great discoveries. Your luck will be proportional, however, to the number of well-conceived and expertly performed experiments that you execute and on how prepared your mind is to process unexpected findings. As famously attributed to Louis Pasteur, one of the greatest experimentalists of all time, “Dans les champs de l’observation, le hasard ne favorise que les esprits préparés” (in the fields of observation, chance favours only the prepared mind).

Interpreting experiments

Think big. Discoveries are not physical entities, but the products of cogitation. Making discoveries is the best part of science: it hooks you as a student and never lets you go. Some discoveries hit you like a frying pan and don’t require a huge amount of thought. These are a real kick, so enjoy the initial glow because sooner or later doubts will tarnish your bright, shiny, discovery as you carefully consider its implications. Other discoveries are more subtle, at least given our mindset, which is hobbled by existing paradigms. To break

Box 3 | Staying happy and sane in the laboratory

- Your default opinion of others should be that they, like you, are sincere, well meaning individuals. Assume that dust-ups stem from an easily resolved misunderstanding. Wait before confronting. Most problems solve themselves in a few days. If not, patiently plan a conservative course of action. For advice, consult senior members of the laboratory or department. Involve your principal investigator (PI) only when absolutely necessary. Why? Whatever the issue, it will probably not reflect well on you, regardless of your innocence. Having the PI intervene will permanently mar your relationship with the other laboratory member and negatively affect laboratory esprit.
- Never write an emotional e-mail: have your confrontations on the phone or, better still, in person, as you will have the benefit of visual clues that will allow you to determine the effect of your words on your antagonist. Because of the imperfection of memory, spoken words (unlike written words) remain shrouded in the mists of uncertainty.
- Your career will be much easier if you develop a thick skin. You should embrace valid criticism, because it can improve your science and qualities as a scientist and a person. Of course, not all criticism is valid. With time you will develop a sense for legitimate criticism that needs to be addressed, and other criticism that should be ignored (with no malice to the source).
- If possible, avoid intra-laboratory romances, which typically lead to awkward break ups. Yes, only another scientist will truly understand you, but try to find your soul mate in another laboratory!
- Daily exercise will enhance your energy levels and improve your mood. No matter how brief or easy the workout, it is better than no workout at all. Vacations are essential to maintain your mental health and enthusiasm for science. Get as far away from laboratory life as possible and stay away from your e-mail!

the shackles of convention, the first thing you should do with fresh data is to come up with the most interesting possible interpretation of the results. This has several benefits. First, occasionally, you will actually be right. A surprising number of great discoveries were missed by previous investigators who made the same findings but never made the intellectual leap. Go to enough meetings and you will hear somebody lament “Oh, we saw that too, but didn’t make anything of it”. Second, even when the most interesting interpretation is wrong, thinking creatively will help you to place your findings in their proper context and will pay large dividends in designing and interpreting future experiments. Third, it is fun, particularly if it leads to brain storming with your mentor and other members of the research team.

Repetition trumps p values. Experiments have two general outcomes. Either they are interesting or they aren’t. If they are interesting, you need to repeat them to the point where you are sure they are correct. It is far better to repeat a given phenomenon in a series of slightly imperfect experiments than to rely on a single experiment with perfect replicates that yield impeccable p values. Although statistics are important, don’t be blinded by them — they are only as good as the assumptions they are based on. Statistically significant differences between samples only mean that something was different between the samples. The something might be the thing you were testing, or

it might be something you didn’t consider, like the temporal or spatial order in which you set up the samples.

Yes you can! You’ve done a superb experiment and your brilliant and subtle interpretation has led to an important discovery. This step actually trips up many young scientists, who lack the confidence to believe that their own two hands and brain could achieve such a thing. You need to get over this attitude immediately. Although oversized egos are as big a problem in science as in any profession, you need a healthy ego to be successful in science. You have got to believe that you have good ideas and can make an important contribution to your field (and don’t fret, it’s really true).

Embrace serendipity. What if your great discovery is not on the list of specific aims? Frequently, the best discoveries are serendipitous. Serendipity is easiest to embrace if it provides insight into your question of interest, but it often leads you into other fields. You should seriously consider pursuing these leads, but the final decision will have to be made by your PI. After all, it is your PI who is paying the bills. When you are a PI, these will be some of your more difficult scientific decisions. When you are in this position, remember that an excursion into a new field need not be permanent, but can be an exploratory expedition that may or may not lead to a permanent shift in direction.

Avoid the P-word. Without going off the philosophical deep end, it is useful to occasionally step away from the trenches of day-to-day research and contemplate the nature of discoveries. Observations are statistical phenomena that can be verified beyond a shadow of doubt. For example, a dead mouse is really and truly dead. By contrast, conclusions are the product of human thought based on an existing theoretical framework that is imposed on a system (that is, nature) that is inchoate and therefore essentially unknowable — for inspiration, see Huxley’s translation of Goethe’s view of nature (the system), which is the opening essay in the very first issue of *Nature* (the journal)². Conclusions, therefore, are conditional; they are always wrong or incomplete in some manner, it’s just a question of the degree to which they are incomplete (BOX 2). Do not fall into the all too common habit of stating that your findings ‘prove’ a given conclusion. They don’t, and thinking this way closes your mind to alternative explanations and future discoveries.

Remember — science should be fun

Well, that’s about it. Here’s one last bit of advice — science is much more enjoyable and productive when it’s fun (BOX 3). Maintain your sense of humour, particularly about yourself. Above all, pass on the joy of science to the next generation.

Now go and discover something that shocks everybody and makes your mother proud.

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1. Yewdell, J. W. How to succeed in science: a concise guide for young scientists. Part I: taking the plunge. *Nature Rev. Mol. Cell Biol.* 10 April 2008 (doi:10.1038/nrm2389).
2. Huxley, T. H. Nature: aphorisms by Goethe, *Nature* 1, 9–11 (1869).
3. Goodman, A. *Intuition* (The Dial Press, Bantam Dell Publishing Group, 2007).

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