

Ask Professor Sarah Bellum

Professor Sarah Bellum answers your questions on navigating the often-uncharted waters of early career development. Do you have a question for Professor Bellum? Send it to sarah_bellum@biophysics.org. Your privacy and anonymity are assured!

Learning to Fish or Cut Bait, Experimentally

Q: *I am really worried that I might not succeed in graduate school, or if I do, it will take at least 8 years (and can that still be called "success"?). I am in my third year of the PhD program here, and my thesis project, which looked so promising at the outset, has stalled and gone nowhere in the past 9-12 months. Most of my experimental approaches are still not working. These approaches are new to my lab, but they are well established in the literature. I feel like a failure. Should I bail now and consider an alternative career, before I am asked to leave the program?*

— *Depressed in Detroit*

A: Ah, the angst-filled third year of the PhD: that magical time when, even under the best of circumstances, strong hypotheses disintegrate and method failure suddenly becomes the rate-determining step in the progress of your project!

You're not alone: Everyone experiences this to some degree: the inevitable "Nothing's working, it never will, and what's the point, anyway?" nadir between the heady excitement of first jumping into your perfectly-designed, deeply significant thesis project, and the ultimate relief of realizing that, in the end, even if it didn't work out like you initially planned, you did get several rather important things to work, and the results are actually pretty important, and hey, your advisor is recruiting a post-doc to follow up on some of your results.

So, the first step is to recognize you are in this nadir, and that it happens to everyone. The second step is to make the nadir as brief and painless as possible.

Professor Bellum's best advice for bouncing back quickly: Don't get too

attached to your hypothesis, or the experimental approaches you are using to test them. If you are already too attached, break that attachment NOW! You do not yet know if your hypothesis is correct, or if your approaches will work, so keep your brain open to alternatives. After all, there are no rules saying that if you started working on X, you have to finish X or your thesis is a failure. You need to stay open to alternatives, including both alternative hypothesis/research directions and alternative experimental approaches.

First consider: Is the problem with the hypothesis, or the approach you are using? Professor Bellum does not know of a single graduate thesis project that did not require the addition, modification, or discard of at least one experimental approach; perhaps the one you are currently grappling with is the one to discard, and it is time to look for alternatives.

Of course, it's easy to say this, but much harder to do: you've probably

already spent a year researching the literature on this method, collecting reagents, performing control experiments, and (most importantly here) banging your head — *repeatedly* — against your lab bench when this assay fails yet again, for any one of a dozen reasons. You're frustrated and depressed, but yet weirdly reluctant to give up on this approach. Part of this is pride: Other people use this approach; you know you're a good experimentalist — everyone says you have "good hands" — what's wrong with you that you can't get this to work?? There is another component, too: a feeling akin to that feeling you get in the grocery store, when the lines are long and your line is moving the slowest: Do you keep waiting, or move over to another line? Some people find it very difficult to move to another line, even if there is an obviously faster line nearby. Perhaps they stay in their slow line because they have already invested time and they feel a commitment to it. Perhaps they worry that if they abandon their line, the fates will swoop down and make their new line the slowest line.

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store, it is not productive to remain loyal to an experimental method that is proving to be intractable. Maybe there is some crucial component of your system that is different from the published systems that use this method. Maybe your detection equipment is not sensitive/fast/etc. enough to detect what needs detecting. Maybe this method, even though published, is really really really hard and only a few people in the world have the technical skills required to make it work. Rest assured: *it's probably got nothing to do with your capabilities as a scientist.*

There is, however, a very important difference between slow lines in the grocery store and intractable biophysical methods in your thesis: In your thesis, you can (and should) develop more than one method at a time (people in the grocery store tend to get mad at you for this). Many students start their thesis project with the idea that they will use a few different experimental approaches to look at various aspects of a particular problem. Yet they quickly zoom in on one particular approach, and even (perhaps particularly) when there are persistent problems, there is a tendency to stick with it, doggedly, even if it becomes clear that this particular approach is going nowhere fast.

So here is the easiest way to start breaking this cycle: Going on vacation with another method. You might pick an alternative one on your original list, but leave yourself open to the idea of trying a completely new idea that came to you last week when you were reading the literature.

If you are the kind of person who stays in the slow line (you know who you are!), console yourself with the thought that you are not abandoning the original method entirely, just putting it aside for the moment. One or more things are

likely to happen: (1) the alternative method will be a real breakthrough, and you'll never look back; (2) the new method will yield results, and one of these results may make it very clear why the original method never worked; or (3) regardless of how the alternative method works out, the process of engaging your brain differently in order to develop the method will very likely let you look back on the original method in a whole new (and hopefully helpful) light.

In general, when experiments don't work, repeatedly, it is easy to fall into the trap of doing more and more experiments and spending more and more time at the bench, in an effort to trouble-shoot every possible problem. But scientific research is a three-legged stool, and only one of those legs involves actually doing experiments. The other two legs are experiment planning and experiment analysis/write-up.

Let's focus on planning, since you have yet to produce any results to analyze. But perhaps you feel like you have already completed the planning leg: That was why you read all those papers that described the initial development, refinement, and applications of this approach, right? Wrong. Experiment planning doesn't end until the experiments end; planning is an ongoing process. And more planning is particularly important when your experiments are struggling; you will be trapped in the mental rut of failure and depression, yet in real need of breakthrough ideas. Albert Einstein said: "When I examine myself and my methods of thought, I come close to the conclusion that the gift of fantasy

has meant more to me than my talent for absorbing positive knowledge." So give yourself permission to indulge in a little scientific fantasy: what would be your dream method? "I could solve the mysteries of X, if only I had a way to..." This dream might be closer to reality than you initially imagine!

All of the problems I have described above for experimental trouble will also occur if you become attached to a

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hypothesis before it has experimental support, but this situation is a bit more devious: Your experiments are working, but they are not giving you the results you expected (i.e., the ones that support your hypothesis). How many times will you repeat these experiments, and how many orthogonal approaches will you develop, before you convince yourself that the problem is not with you, or the method, but with the hypothesis itself? Break this cycle now, before it begins: Any time you get a result you did not expect, including a negative result, keep your mind open to the possibility that you have completely misjudged the situation and your hypothesis is wrong. Another gem from Einstein: "I think and think for months and years. Ninety-nine times, the conclusion is false. The hundredth time I am right."

Whether the problem is with the approach or the hypothesis, when you learn to open your mind to alternative ideas, you begin to move from being a skilled pair of hands to being a mindful participant in the process of scientific discovery. While this transition is rarely angst-free, years later, you may look back on the process of working your way out of this situation as really the best part of graduate research.

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