Marshall Abrams

External Examiner's Report on the Dissertation of Martin Zach
"Models and Modeling in the Biomedical Sciences"
Submitted in 2021 at the Department of Philosophy and Religious Studies
Philosophy
Charles University, Faculty of Arts

I. Brief summary of the dissertation

The dissertation falls within general philosophy of science, with a specific focus on biology. The five chapters are fairly independent, but philosophical questions concerning scientific modeling, especially mechanisms and modeling related to diseases such as cancer and COVID-19. Chapter 1 argues that research in cancer immunology uses a pattern of modeling that is different from what philosophers have previously proposed. Chapter 2 criticizes a paper by Love and Nathan that had argued that molecular biology does not provide mechanistic explanations. Chapter 3 argues for new views about the role of similarity in modeling based on mouse models in cancer research. Chapter 4 argues that some agent-based models (ABMs) of the current pandemic are models of "actual mechanisms" of the spread of SARS-CoV-2. Chapter 5 criticizes existing metaphors of the operation of the immune system, and argues for a more complex conception of the immune system.

II. Brief overall evaluation of the dissertation

This dissertation is excellent overall. It is, for the most part, carefully argued based on philosophical analysis of a large number of details of scientific research. The biological research that Zach's dissertation draws upon is extensive and is described in (appropriate) detail. This combined with the philosophical insights that he draws from the scientific research, and the philosophical insights that he applies to this research, make this an impressive work overall.

III. Detailed evaluation of the dissertation and its individual aspects

Chapter 1:

This is perhaps my favorite chapter in the dissertation. Zach argues that in some cases—cancer immunology is his example—model-based research proceeds by what he calls "experiment-driven modeling" (EDM), in which experimental data is collected, and then models are derived from the data. Implications of the models are then applied to further experimental data. Zach's focus on this kind of research in which experimentation seems to precede modeling is important, and illustrates patterns of research that philosophers of science have not taken much interest in. I am not certain that the distinction between EDM and description-driven modeling (DDM) is as clear-cut as Zach claims; I think it may be that the two conception of modeling processes should be integrated into a single conception. Zach's development of the idea of EDM and its motivation from details of cancer research are important, regardless.

(A small point: I would suggest more clearly distinguishing diagrams from models that they represent. What are the roles of captions and background models in understanding diagrams?)

Chapter 2:

For me, this was the weakest of the chapters, but it still contains valuable philosophical contributions.

A paper by Love and Nathan had argued that certain idealizations used in models in molecular biology prevent those models from capturing the kind of causal patterns that are crucial to explanation. Those models thus are not explanatory, according to the authors. Zach does an excellent job of surveying and bringing together the literature on the crucial terms "idealization" and "abstraction". Zach successfully argues that the way that Love and Nathan use "idealization" and "abstraction"—terms they take to refer to distinct scientific patterns—are somewhat confused. Zach argues that as a result, Love and Nathan's argument is unsuccessful. Zach also points to general questions about this distinction in other contexts as well.

I think it's valuable to challenge and criticize Love and Nathan's use of these technical terms, but I wasn't convinced based on the chapter that the Love/Nathan argument does not succeed. I would have preferred it if Zach had tried to charitably reconstruct one or more versions of their argument based on refining their language. This would be a valuable task even if it showed that Love and Nathan are right, but it might show that no matter how one construes their language, their argument fails—that would be particularly interesting. (I didn't follow the argument based on considering what would follow if Love and Nathan used "abstraction" instead of "idealization". Perhaps that was intended to do what I am suggesting.)

Chapter 3:

Various ideas about similarity between models and what they model have played central roles in philosophical thinking about what scientific models are and how they are used. Zach argues that in addition to similarity playing a role in selection of models to use in research, and to its role in extrapolation—in applying insights derived from models to systems being studied—similarity plays a role in creating new models. I love Zach's detailed discussion of various kinds of mouse models used in cancer research (i.e different kind of mice and different ways they are prepared). His discussion includes discussion of how these different mouse models were developed, i.e. created as new models. This kind of elaborate case study is very important for philosophy of science. Zach makes it clear that similarity and other factors play important roles in the creation of such models. I wonder, though, whether the roles of similarity in model selection and model creation are essentially the same. Perhaps we should really think of creation and selection as different phases of the same kind of process, where selection occurs once a model has already been created—perhaps a long time ago.

Chapter 4:

This chapter focuses on a detailed characterization of a particular agent-based model of the transmission of SARS-CoV-2 in Australia. (Agent-based models, or ABMs, are computer simulations in which a large number of entities with clearly defined behaviors interact. In this case, the entities include simple models of people and of viruses.) Zach argues that this model is a "model of an actual mechanism". I didn't feel that this the meaning of phrase was made sufficiently precise. Sometimes it seemed to require perfect accuracy of predictions and representations of social and disease-transmission processes, and at other times it seemed to require only approximate accuracy. Zach does a good job of arguing that this kind of model provides a fairly accurate representation of the spread of the virus in the early days of its spread in Australia, so to the extent that the latter

is what's intended, I found the argument pretty convincing.

Chapter 5:

Zach describes a large number of processes involving the immune system. I was very impressed by what he did with these summary descriptions. Using them, Zach completely undermined showing that any simplistic metaphorical conception of the immune system as a system of defense, as being stronger or weaker, or even being stronger or weaker at different times or in different respects. He does a good of arguing that these ways of thinking about the immune system are not just misleading to the public, but are probably bad for science. In place of such dominant metaphors, Zach argues that we should think of the immune system as involving context-dependence, regulatory processes, and trade-offs. This proposal is well motivated, but it's a little bit vague, and at this point I see the three factors I just mentioned as closely related. The vagueness is understandable, though. The chapter is trying to replace simple, catchy metaphors with something more realistic. I suspect that there is more that can be done develop the ideas advocated in this chapter, but the challenge is great, and I would not have expected a chapter in a dissertation to do more than what this one did. What the chapter does is quite enough.

Further remarks:

I was asked to comment on formal aspects of the dissertation: language, footnote formatting, etc. These are all exemplary. Likewise, the use of sources is excellent, and impressively detailed.

IV. Questions for the author

I feel that one of the roles of an examiner is to challenge the candidate to go further. I offer these questions in that spirit, rather than as criticisms of the dissertation, which I think is excellent overall. I don't expect that there will be time for all of these questions to be answered at the defense.

Chapter 1:

A question I have is whether the experimental stage of EDM is just an additional "stage 0" for description-driven modeling (DDM), which contains a stage in which implications of models are explored in detail. The model in the case study was very simple, but surely there are or will be cases in which a more complex model is needed, and its implications must be explored. What will the researchers do when they want their model to help them understand variation in effects between different patients? Would they then need to develop a more complex model—one that they would need to "play around with" to determine implications? (There are in fact agent-based models of the spread of cancer within bodies, agent-based models of molecular processes, and so on.) Perhaps a more complex model like this would play a role in cancer immunology, in which case it seems that stage 2 of DDM would need to be added to EDM.

Chapter 2:

Is there a way to save Love and Nathan's argument by revising their use of "idealization" and "abstraction"? Or is it impossible to use these terms consistently in support of their conclusion?

Chapter 3:

I wonder whether the roles of similarity in model selection and model creation are essentially the same. Could we think of creation and selection as different phases of the same kind of process, where selection occurs once a model has already been created?

Chapter 4:

Can you clarify what it means to be a "model of an actual mechanism"? The language surrounding this phrase varied within the chapter, I felt. Note that the pandemic model discussed in the chapter doesn't accurately represent each person and household, their behaviors, and transmission-relevant physiological features, etc. (of course). Even if it were to perfectly represent averages of these patterns, its predictions would be somewhat inaccurate. That's not a criticism of the model, but a request for clarification about relationships between model and world for the chapter's claims about the ABM. I'm wondering whether the difference between this ABM and others mentioned in the chapter is one of degree.

Chapter 5:

I don't have further questions about this chapter at this point.

V. Conclusion

This dissertation does meet the usual standard required of a doctoral dissertation. I recommend it for a public defense. I recommend the submitted dissertation with the tentative grade of Pass.

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Marshall Abrams
Associate Professor of Philosophy
University of Alabama at Birmingham, U.S.