External Examiner's Report on the Dissertation of Martin Zach

Models and Modeling in the Biomedical Sciences

Submitted in 2021

This thesis consists of five chapters brought together under the general heading of philosophy of biological and biomedical models. While the chapters have clearly been written for publication as separate units, the author does an admirable job of bringing them together as parts of a wider picture of biomedical modelling. The results are certainly insightful, well-written and convincing contributions to the philosophy of science. This is particularly notable given that the thesis focuses on some of the most well-trodden grounds in philosophy (philosophy of modelling, mechanistic reasoning, idealisation, the use of metaphors), making it particularly difficult to develop an original position. The author manages this feat while also building cogently on existing philosophical and scientific literature, and thus displaying his mastery of the field to the level required for a PhD. I am therefore strongly in favour of awarding the author a PhD in philosophy.

The structure of the thesis is admirable. The thesis very clearly outlines its focus and objectives at the start, and achieves these objectives through a systematic examination of key issues in relation to modelling in the biomedical sciences and particularly cancer immunology. Topics identified are cogent and well-chosen, as they are indeed among the most challenging issues in the field. Formally, the thesis is also well-presented, with a good use of conventions and formats, and correct language as well as referencing.

The candidate's knowledge of the relevant literature is detailed and up to date. It is notable that the candidate managed to elaborate a critical, well-justified viewpoint on many branches of relevant literature. It is also notable how he managed in a short amount of time to redeploy such knowledge towards the analysis of COVID modelling, and particularly the AceMod model – work which again displays his maturity and promise as an emerging scholar in the field. The chapter in question, Chapter 4, is somewhat of an outlier in the thesis as it is the only one to go beyond immunology and venture into a brand new "modelling territory", so to speak – but the circumstances and execution make this a brave and well-justified choice.

The methods adopted within the thesis, alongside traditional critical discourse as typical of philosophy, are an in-depth analysis of scientific sources as well as some ethnographic/collaborative encounter with biological practices and practitioners. This methodology is one I would have liked to hear more about from the author (in the introduction, methods are very summarily introduced in a single paragraph – though the author points to a publication of his where methodological issues are discussed in more detail). I would have liked to see a more detailed and focused account of the methods used to bring together the empirical materials used in this thesis, as well as a statement on what the author thinks the relation between science and philosophy is, and how scientific

evidence can and should be used for philosophical purposes. This is particularly important since many chapters build so strongly on specific renditions of the scientific literature. There are some additional details on such matters within the chapters themselves, but not a well-developed justification for how scientific sources were chosen, what was included/excluded and what the author means by "participant observation" (in Bordeaux) and how this has informed his work. Also, a reflection on what the use of very specific cases to exemplify much broader trends would be desirable (e.g. on p. 18: "Elena Rondeau, in which the goal is to provide the characterization of MDSCs in different organs and in different time points in metastatic breast cancer in order to gain insight into the exact role played in that context by MDSCs.. this particular example should be understood as exemplifying the practice found across many different (biological and other) fields in which much of the focus is devoted to wet lab research, allowing us to draw general lessons and to formulate a philosophical account of the practices involved"). We will discuss this further in the viva.

In my view, the key contributions of the thesis to the existing body of literature are:

- The exploratory-descriptive account of modelling (EDM), which is certainly a useful distinction and comparator to add to the DDM approach (I personally would not quite think that DDM encompasses most approaches to modelling, as argued in this thesis – it does not fit my own approach nor others such as Morrison or Morgan - but I think the author provides a convincing argument that it encompasses many);
- the critique to Love and Nathan, in chapter 2, is nicely developed and certainly publishable (again I am not convinced that it deals as devastating a blow to the account as it claims, but this is a matter for interesting debate);
- the model selection/ creation/ extrapolation distinction utilised to structure the analysis of mouse models in chapter 3 is very useful to characterise the existing literature and re-think ongoing debates, especially around the usefulness of similarity as a mark of predictive accuracy (which I completely agree with the author, is not central or even that relevant for model selection/creation)
- the conceptual model of the immune system proposed in Chapter 5, encompassing contextuality, regulation and trade-offs (and moving away from antagonistic metaphors). This is again very useful. The final argument of this chapter, on the value of metaphors and particularly the notion of strong and weak immunity, comes as something of a surprise given the initial tone of the chapter, and the chapter could have been more tightly structured to support that point – nevertheless, the analysis is rigorous and easy to follow.

One aspect of this work that is particularly striking, and the author could have highlighted further in his introduction and conclusions, is the extent to which such a study of cancer immunology practice is, indeed, innovative. As the author notes, there have been philosophers delving into that realm – but still few and far between, and this work is certainly adding a great deal of careful analytic understanding of the field of cancer immunology from the philosophical perspective. One wonders why the thesis title does not reflect that – it is a strength of this thesis that it focuses so rigorously and comprehensively on this particular – important and understudied, from the philosophical viewpoint – domain, and this should be emphasised. The analysis of cancer immunological practices is interspersed with philosophical analysis throughout, providing an essential counterpoint to the philosophical arguments. This raises questions around how one generalises from this, of

course – questions which this thesis does not have to satisfy, given its already impressive scope, but which we will explore in more detail in the viva.

My questions for the author concern the following topics:

- Methods in cancer immunology research, and the author's take on naturalism (the extent to which philosophers can and should be trusted in rendering the scientific literature to make it act as evidence for philosophical arguments);
- Generalising from cancer immunology to biomedicine;
- Generalising from biomedical methods to science as a whole;
- EDM: why does the author think that comparisons among experimental systems need to happen through model comparison? This seems an important assumption in your framework, but not always warranted in my view (e.g. data comparisons, methods comparisons, samples, etc). How much of this view hangs on the prominence accorded to models here?

[EDM as formulated in chapter 1:

1. *Analysis of experimental systems. Experimental systems are manipulated to generate experimental results.*
2. *Model construction. Experimental results serve as building blocks in the construction of a mechanistic model which accounts for the studied phenomenon.*
3. *Model comparison. To estimate the extent to which the model adequately accounts for its target, scientists often conduct further experiments in addition to changing the experimental context.]*

- Distinction between EDM and DDM: two key issues that separate them, on p. 21, are the different relationship to data and the extent to which the model is a finished product or a starting point for the respective scientists. These are really interesting points, but it is not entirely clear where they come from – are they exemplified by the examples? How?
- Also, it is argued on p.22 that DDM investigates the systém indirectly because the investigationn happens via an experimental systém. Why could one not argue that the experimental systém is, in fact, the model? (and thus, this is a case of DIRECT representation). The author argues that the materiál features of the model do not imply that this is a direct representation also on p.24, but I would like to discuss the point further.
- On p.26 the idea of a „model hierarchy" is mentioned for EDM. Why a hierarchy? I understand stressing the plurality of models here, but why should the mechanistic model be primary with respect to other models here? Why is the mechanistic model necessarily the key goal?
- On the critique to Love and Nathan, in chapter 2: as much as the argument on the inconcistent use of the terms abstraction/.idealisation holds water (e.g. p.38), I am not sure it really defies the key argument of these authors, which is against treating the explanation as mechanistic. Can the author summarise again why his critique amounts to a rejection of their conclusions/main point?
- The characterisation of ACEMod (and more generally, agent-based models) as mechanistic is rather controversial. The author is right that they broadly fit the very broad definition provided by Glennan, but this may be an argument against that definition in the first place... what would it také for such a population-level model NOT to be mechanistic? Is it really enough to connect some causal factors in ways

informed/calibrated by data, in order to be a mechanistic model? Also: to which extent do ABMs siuch as ACEMod incorporate social factors? And finally: while I am in complete agreement that „mechanistic" evidence such as provided by these models needs to be taken into account by policy, why should be také them to be „the best existing evidence", as claimed on p.71? After all, as the author himself acknowledges, epidemiological models focused on the social impact of mitigation measures may be best equipped to provide an assessment of measures to take.

To sum up, I recommend the submitted dissertation with the tentative grade of pass.

Sabina Leonelli