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**A Complementary Account of Scientific Modelling: Modelling Mechanisms in Cancer Immunology**

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**Abstract**

According to a widely held view, scientific modelling consists in entertaining a set of model descriptions that specify a model. Rather than studying the phenomenon of interest directly, scientists investigate the phenomenon indirectly via a model in the hope of learning about some of the phenomenon’s features. I call this view the description-driven modelling (DDM) account. I argue that although an accurate description of much of scientific research, the DDM account is found wanting as regards the mechanistic modelling found in many branches of biology. By analysing research practices in cancer immunology concerning the development of mechanistic models of the process of cancer metastasis, this paper presents and argues for a complementary account of scientific modelling, herein called the experimentation-driven modelling (EDM) account. In EDM, scientists investigate a set of experimental systems and then integrate the results obtained from experiments into a mechanistic model. While EDM shares some key features with DDM, the two are epistemically very different approaches to research.

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**1 Introduction**

In the last several decades philosophers of science have made abundantly clear that much of scientific practice relies on modelling. Indeed, as Axel Gelfert claims, “models (…) are all around us, whether in the natural or social sciences, and any attempt to understand how science works had better account for, and make sense of, this basic fact about scientific practice” (Gelfert [2016], p. v).[[1]](#footnote-1) Similarly, there is now an enormous literature on the topic of mechanisms (Glennan and Illari [2018]). However, the existing literature on modelling and mechanisms has so far not been making much contact. The aim of this paper is to address this gap, and the issue that concerns us here is the nature of mechanistic modelling.

According to a widely held view, modelling is an indirect activity of scientific theorizing in which scientists first construct and then investigate a model, rather than the phenomenon itself. I call this view the *description-driven modelling (DDM) account*. In characterizing such modelling practice, some – most notably Weisberg ([2007], [2013]) and Godfrey-Smith ([2006]) – have distinguished it from a direct strategy of theorizing which they call *abstract direct representation (ADR)*. DDM fits well with much of the scientific practice of modelling. Furthermore, it appears to capture an important sociological or professional dimension of modelling - scientists who are hired and work as modellers.

However, in this paper it is argued that DDM does not account for the development of mechanistic models in certain branches of biology. Drawing on the method of participant observation and an analysis of the scientific literature, the case of the development of mechanistic models of cancer metastasis, taken from laboratory research on cancer immunology, will be discussed in detail. Consequently, a novel account will be introduced – the *experimentation-driven modelling (EDM) account* – in order to allow for the practices pertaining to mechanistic model building in many fields of biological laboratory research, including cancer immunology. In EDM one derives a model from experiments, that is, one integrates piecemeal experimental results into a unified conceptual framework that is expressed in the form of a mechanistic model, most often in the form of a diagram. It is this kind of mechanistic models that concerns us here and that is captured by the EDM account.

There are two things to note that will not figure in the arguments to follow but should nonetheless be explicitly stated. First, this is not to say that DDM cannot account for some *other* kinds of mechanistic models. Indeed, biological mechanisms can and in fact are also being investigated via the DDM approach (e.g., agent-based modelling). Second, I leave open the question whether EDM can account for modelling practices other than the mechanistic ones.

I argue that DDM and EDM are distinct modelling practices which nevertheless share several features. Although several differences will be discussed, arguably the most important of these is epistemic: EDM and DDM exhibit different research agendas with respect to modelling. Of note is the point that conflating the two modelling approaches amounts to obscuring important epistemic differences in scientific practices. It is also interesting that scientists involved in EDM are neither sociologically nor professionally recognized as modellers despite the fact that they propose various models. Finally, the proposal of EDM, much like DDM, necessarily provides only partial and incomplete picture of a scientific modelling approach – such is the nature of philosophical analysis which aims to make explicit the most salient features of scientific research. Although a closer inspection reveals that many of the features of the respective approaches constitute a difference of a degree rather than a kind, it should not obscure the fact that, on average, EDM and DDM represent two different approaches. Similarly, the fact that one may find examples of practices which exhibit aspects of EDM, DDM, and ADR does not refute the claim that many other examples represent more clear-cut cases of the respective approaches. It also does not refute the claim that EDM, DDM, and ADR are useful analytic categories.

The structure of this paper is as follows. Section 2 presents the key features of DDM that, according to some of its proponents, set it apart from other ways of theorizing. Section 3 provides a primer on cancer immunology and details some of the research practices involved in developing mechanistic models. Section 4 introduces and characterizes the EDM account and addresses, in considerable detail, the comparison with DDM and other practices. Section 5 elaborates on why EDM should be understood as a *complementary* account.

**2 The Description-Driven Modelling (DDM) Account**

The issue of the nature of modelling practices has received relatively little attention compared to many other questions concerning models.[[2]](#footnote-2) Notwithstanding a few exceptions, a consensus about the key characteristics of the modelling process has emerged. The practice of modelling is said to be unified by the representational aspect of models (Giere [1988]; Hughes [1997]; Teller [2001]; Glennan [2017]). In Teller’s words, “in principle, anything can be a model, and (…) what makes a thing a model is the fact that it is regarded or used as a representation of something by the model users” (Teller [2001], p. 397). In particular, modelling is characterized as a practice in which scientists represent the target systems *indirectly*: they engage in an indirect theoretical investigation and draw surrogative inferences (Giere [1988]; Morrison and Morgan [1999]; Godfrey-Smith [2006]; Contessa [2007]; Weisberg [2007], [2013]; Mäki [2009], [2011]; Weber [2014]; Levy and Currie [2015]; Morrison [2015]; Salis [2016], [2019]; Frigg and Nguyen [2017]; Parkkinen [2017]; Knuuttila [2017]; Knuuttila and Loettgers [2017]; Thomson‐Jones [2020]). The indirectness of modelling will become clear as soon as we look closely at the stages of the modelling process. According to Weisberg ([2007]), there are roughly three such stages, which can be described as follows:

1. *Model construction*. In the first stage, scientists construct a model by means of entertaining certain model descriptions.[[3]](#footnote-3)
2. *Model analysis*. In the second step, the properties and the dynamics of the model are investigated.
3. *Model comparison*. Finally, the model is assessed by comparing the model outcomes with its target.[[4]](#footnote-4)

Similarly, Godfrey-Smith ([2006]) describes the modelling process as consisting of the specification and investigation of a hypothetical system, i.e., a model, followed by the consideration of resemblance relations between the hypothetical and the real-world systems (see also, e.g., Frigg [2010]; Salis [2016]).

It must be noted, however, that according to Weisberg ([2013], p. 74) the stages of modelling – while conceptually distinct – do not necessarily take place in this rigid order as they may happen together or iteratively. Still, it does seem safe to assume that in order for scientists to study a model, some version of a model must first be proposed. It must also be noted that the stages of modelling are somewhat simplified, especially when modelling of complex systems is considered. For instance, some models are (or at least should be) tested not only by comparing the prediction of the model as a whole to some finding in its target system, but also by finding evidence for internal components of the model (see, e.g., Lloyd [2015]).

Thus, scientists construct models as stand-ins for phenomena, and instead of investigating the target phenomena directly, they investigate them indirectly, that is, take a detour through the model.

To illustrate this general schema, Weisberg ([2007], [2013]) introduces the Lotka-Volterra model of predator-prey dynamics.[[5]](#footnote-5) Because the activities of the fishing industry during World War I dropped off significantly, one would intuitively expect there to have been an abundance of fish after the war ended. However, once the war was over it turned out that there was a shortage of various kinds of fish in the Adriatic. Surprisingly, it was observed that the population of sharks and rays seemed to have increased, while the population of squid and cod had decreased. To understand why this was so, Lotka and Volterra, independently of one another, constructed a system of two coupled differential equations describing the hypothetical populations of predators and prey. In particular, the equations describe how the population dynamics are coupled. Following the construction and analysis of the model, Volterra figured out that whereas low levels of general biocide – which kills both predators and prey – would provide favorable circumstances for population growth in predators, high levels would contribute to population growth in prey.

Seen in this way, Weisberg argues that Volterra first constructed a model using certain model descriptions expressed in the form of mathematical equations (i.e., model construction). He then analysed the model by studying its dynamics (i.e., model analysis). Finally, the qualitative predications were matched against the available data (i.e., model comparison).

I call this view the *description-driven modelling (DDM) account* because the modelling practice proceeds by entertaining certain model descriptions, on the basis of which a model is constructed and then investigated instead of investigating the target system directly.[[6]](#footnote-6)

This indirect strategy is not the only one that scientists have at their disposal. Both Weisberg ([2007]) and Godfrey-Smith ([2006]) speak of another approach to scientific theorizing, distinct from DDM, called *abstract direct representation* *(ADR)*.[[7]](#footnote-7) In contrast to DDM, scientists engaged in ADR represent and analyse phenomena without the mediation of a model, i.e., they investigate the phenomenon directly. As Godfrey-Smith ([2006], p. 734) puts it, “one approach is to immediately try to identify and describe the actual system’s parts and their workings. A distinct approach is to deliberately describe another system, a simpler hypothetical system, and try to understand that other system’s workings first.”

An example of the ADR practice provided by Godfrey-Smith concerns a book by Leo Buss from 1987 called *The Evolution of Individuality*, which is contrasted with the DDM approach exhibited by the 1995 book, *The Major Transitions in Evolution*, by Maynard-Smith and Száthmary. Both books address the question of the origin of multi-cellularity. However, whereas Maynard-Smith and Száthmary rely on the modelling approach, Buss’ work is model-free and consists of a detailed examination and careful analysis of “the actual relations between cellular reproduction and whole-organism reproduction in known organisms” (Godfrey-Smith [2006], p. 731). Godfrey-Smith argues that Buss’ arguments, while cautious and speculative at times, are based on the causal roles and the consequences of actual cellular machineries, their environmental circumstances, and the developmental sequences, rather than on a deliberate consideration of simplified or otherwise schematic organisms. Similarly, Weisberg ([2007]) discusses the work of Mendeleev as an illustration of ADR practice. According to Weisberg, by examining the properties of chemical elements, Mendeleev created a representational system that captured a pattern exhibited by the chemical elements. Thus, in contrast to indirectly representing the phenomenon by creating and studying a model, as Volterra did, Mendeleev’s approach was direct in that he represented trends in chemical reactivity rather than trends in a model system.[[8]](#footnote-8)

Although Weisberg and Godfrey-Smith are in agreement with regard to the general distinction between DDM and ADR,[[9]](#footnote-9) they diverge on some specific issues. Weisberg ([2007], p. 228) admits that “it may be possible to take the equations that describe Volterra's model and treat them as approximate, direct representations of Adriatic predator and prey populations.” However, he further claims that the fact that “these transformations may be possible should not change our analysis of their theoretical practice” because “the contrast between modelling and ADR is about the practice, not the products of theorizing” (Weisberg [2007], p. 228). Godfrey-Smith ([2006], p. 734) appears to be somewhat more liberal, warning us that “it would be a mistake to say that the distinction is always so easy to draw” and that there are “unresolved problems to tackle in this area.” At the same time, he suggests that there is a sociological dimension to modelling, something which will be addressed in more detail in Section 5.

Thus, modelling – according to the DDM account – is an indirect strategy of scientific theorizing whereby scientists first construct a model by entertaining certain model descriptions and later devote much effort to its analysis.

**3 Cancer Immunology**

Let us now turn to a brief overview and conceptual introduction to the field of cancer immunology, followed by a discussion of experimental practices involved in research projects such as the study of the role of the myeloid-derived suppressor cells in cancer metastasis in general, and in the formation of the *pre-metastatic niche* in particular. This case study provides important lessons which will prove crucial to the introduction of the novel account of scientific modelling expounded in Section 4.

**3.1 A primer on cancer immunology**

Cancer has been a major topic of biomedical research for well over a century, but only recently has it caught the attention of philosophers.[[10]](#footnote-10) Despite its convoluted history, the idea that the immune system is implicated in tumor surveillance, destruction, but also in tumor promotion, has now been well established (see Pradeu [2019], Chap. 4, for a brief historical overview and a philosophical treatment).

One of the reasons why tumor cells can evade immune destruction and later escape is that the specific environment in which tumor cells arise, called the tumor microenvironment, is generally immunosuppressive (Weinberg [2014]).[[11]](#footnote-11) By releasing various substances with immunosuppressive potential and by actively recruiting immune cells while inducing a suppressive phenotype in them, cancer cells create a milieu which allows them to escape surveillance. Thus, the immune system actually plays a paradoxical, dual role in cancer: it eliminates tumors but may also promote tumor growth.

The immune system is implicated not only in tumorigenesis but also in the metastatic process. An intriguing observation regarding metastasis, the cause of death in 90% of all cancers, is its apparent tropism, i.e., a tumor arising in a particular tissue is likely to metastasize to a set of particular organs but not to others: for instance, it has been well established that breast cancer tends to metastasize into lungs, bone, brain and liver (Weinberg [2014]). Noting this surprising phenomenon, Stephen Paget, a 19th century British surgeon and pathologist, proposed the ‘seed and soil’ hypothesis, arguing that a tumor (the seed) can only grow if it lands on a fertile ground (the soil).[[12]](#footnote-12)

Current research indicates that the metastatic organs undergo changes before the arrival of cancer cells (Liu and Cao [2016]). Thus, rather than being a passive recipient of the ‘seed’, the ‘soil’ is actively being transformed in a complex dynamic process that gives rise to a *pre-metastatic niche* which ultimately leads to the establishment of a *secondary tumor site* (Liu and Cao [2016]). One of the immune components implicated in establishing a pre-metastatic niche are myeloid-derived suppressor cells (MDSCs), a heterogeneous population of immature cells of myeloid origin activated under pathological conditions (Gabrilovich and Nagaraj [2009]).[[13]](#footnote-13) MDSCs are thought to contribute to the establishment of the pre-metastatic niche through a variety of functions, one of which is their immunosuppressive activity. Finally, it is common to distinguish two broad sets of these cells based on different expression patterns, namely the monocytic and granulocytic MDSCs (M-MDSCs and G-MDSCs respectively), with the occasional mention of a third, early-stage population of MDSCs (Veglia *et al.* [2018]).[[14]](#footnote-14)

**3.2 Experimental inquiry into the role of myeloid-derived suppressor cells in cancer metastasis**

Inquiry into the role of MDSCs in cancer metastasis, and in particular in the establishment of a pre-metastatic niche, is an ongoing process with still many unknowns. Such research projects rely heavily upon studying experimental systems such as cell cultures and animal models and make use of a vast array of experimental assays. In what follows, I provide a brief – highly simplified, and in no way exhaustive – description of some of the common methods used in cancer immunology based in part on the use of participant observation method in an immunology lab. I take this particular case as an example for widely used 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 (see Section 4).

*Experimental systems: cell cultures*. Using cell cultures in experimental practice often involves some preparatory work, such as the use of a lentiviral vector in order to introduce the genes for the enzyme luciferase and the green fluorescent protein (GFP) in the 4T1 cell line, which is a standardized breast cancer cell line. Beyond that, various functional assays are conducted using co-culture experiments. These include studying the immunosuppressive effects of MDSCs on healthy T cells, or the migration behaviour and changes in phenotype when co-culturing MDSCs and tumor cells.

*Experimental systems: animal models*. Animal models also play an essential role in studies of aspects of cancer metastasis. For example, the BALB/c mouse strain serves as the recipient of the 4T1 cell line modified by the lentiviral vector, which results in a cohort of tumor-bearing mice models. Mice of the same strain also serve as controls and as a reservoir of healthy T cells that may be used in co-culture experiments.

*Visualization methods*. Organs are taken from both the tumor-bearing mice and the healthy controls and resected into tissue slices of approximately one cell layer (10-12 μm). These tissue slices are then subjected to immunohistochemical investigation, the goal of which is to search for and locate both the MDSCs and the metastases in lungs. Specific antibodies are used to stain the MDSCs, thus allowing for visualization. This process is repeated at different stages of tumor development to provide further data, e.g., if there are any changes over time in the number, position, and type of MDSCs. Visualization methods are also crucial when conducting *in vivo* experiments. By day 11 after injecting the immunocompetent BALB/c mice with 4T1 breast cancer cells, the mice exhibit tumors of approximately 7-10 mm. They are then injected with luciferin, a substrate that binds the luciferase enzyme expressed by the 4T1 cells, resulting in bioluminescence. This allows for the localizing of tumor cells in a living animal; and by day 20, metastases start to appear. The mice are then killed and dissected, and their organs investigated using the same imaging technique, thus providing additional precision. Imaging methods allow for important observations, yet they fail to provide other important insight into the mechanisms responsible for the observations. To that end, cells are collected from organs and subjected to further analysis using a variety of experimental instruments.

*Flow cytometry and cell sorting*. Among the essential lab equipment is the flow cytometer. A sample of cells suspended in a fluid and often labeled with fluorescent markers is injected into the flow cytometer, and flowing one at a time, the cells pass through a laser. Scattered light is then detected and processed by a computer. In short, flow cytometry is a method that enables the detection and measurement of some physical and chemical properties of cells. Fluorescence-activated cell sorting (FACS), a feature of many of the flow cytometers, allows for the gathering of cells of a particular type for later analysis. For instance, the M-MDSCs and G-MDSCs can be detected and sorted on the basis of their expression of CD11b and CD45 markers and distinguished from one another by a difference in their level of expression of Ly6C and Ly6G markers**.**[[15]](#footnote-15)

*Analysing cells: sequencing and PCR*. Selected for their surface markers, these cells can then be subjected to a variety of techniques aimed at finding out what is going on inside them. To ascertain gene expression patterns in a given sample, it has become common to rely on technologies such as RNA sequencing (RNA-seq). Another method is the polymerase chain reaction (PCR) which is used to analyse the gene expression patterns of a small set of genes of interest. The crucial difference between the two methods is that while the former provides an unbiased way to analyse all RNA (above certain abundance threshold) in a given sample, the latter requires the use of primers and as such is dependent on already known sequences. Thus, PCR is used in cases in which the researchers are interested only in a few genes. Taken from different organs at different times, MDSCs are probed, using the above methods, to reveal the set of factors that may be characteristic of them at different sites and at different times; such factors including, among others, cytokines and tissue-specific chemokines.

*Inhibition and excitation studies*. Additionally, a lot of research makes use of a variety of excitatory and inhibitory studies (see Craver and Darden [2013] for an extended discussion). For instance, studies have focused on investigating the impact of depleting MDSCs on the formation of metastasis (Ouzounova *et al.* [2017]). Likewise, knock-out experiments are conducted with the same goal in mind: for instance, one can knock out a gene coding for a membrane-bound chemokine receptor such as CXCR2 which is expressed by MDSCs and which has been implicated in recruiting MDSCs to the tumor site to see what the effect will be (Katoh *et al.* [2013]). The results show a decrease in MDSCs recruitment to the secondary site and a resulting decrease in metastatic tumor burden; conversely, transferring wild type MDSCs to CXCR2– mice leads to an increased metastatic burden (Katoh *et al.* [2013]).

*Reproducibility, robustness, and redundancy*. While reproducibility, robustness, and redundancy as such are not laboratory methods, several important remarks deserve a mention. In a given project, the same set of experiments are usually repeated several times to ensure that the results are not due to chance. Additionally, researchers also try to establish that the observation is not due to the use of a particular method: for example, inhibition of a particular signalling pathway can be achieved through a variety of methods which target a particular molecule involved in the given pathway, such as the use of inhibitory antibodies or gene knock-out technology. However, one can also frequently stumble upon seemingly conflicting results, which in many – but not all – cases may be explained away precisely by the fact that many experimental results are context-dependent, i.e., sensitive to the particular research methods and experimental systems used. Although a signalling pathway is blocked, the overall outcome may be greatly influenced by the particular molecule that has been targeted, and by the method used. Relatedly, it may also make a big difference to the outcome if the pathway is blocked up- or down-stream. It may also be the case that the results appear in conflict due to differences in the target phenomenon in question. Consider the following example. Ouzounova *et al.* ([2017]) report that whereas M-MDSCs switch on the epithelial-mesenchymal transition (EMT), thus facilitating the dissemination of tumor cells, G-MDSCs act to change the phenotype of disseminated cells through the process of mesenchymal-epithelial transition (MET), allowing for the establishment of a micro-metastasis. In contrast, referring to the study of Toh *et al.* ([2011]), Condamine *et al.* ([2015]) state that G-MDSCs rather than M-MDSCs are responsible for initiating EMT. One of the many possible explanations for this discrepancy lies in the fact that while Ouzounova *et al.* studied the 4T1-induced breast cancer mouse model, Toh *et al.*’s findings concern a mouse model of spontaneous melanoma. Thus, as noted above, some of the seemingly conflicting results may be due to the difference in the target phenomena, i.e., breast cancer as opposed to melanoma.

Finally, research is often complicated by a well-known feature of biological systems, namely redundancy. It is often the case that while the inhibition of a particular pathway may seem promising in one experimental context, it ultimately leads to disappointing results in another because a back-up pathway takes over.

**4 Introducing the Experimentation-Driven Modelling (EDM) Account**

**4.1 Mechanisms and mechanistic models**

Having provided some background context and detailed some of the experimental methods used in cancer immunology research, we may now begin formulating some philosophical conclusions. Cancer immunologists seek to discover and understand the mechanisms by which primary tumors metastasize. They propose mechanistic models which they often express by means of diagrams, which in turn are taken to represent purported mechanisms (see Figure 1). Indeed, the scientific literature is full of references to mechanisms and mechanistic models, which is also why they have been a hot topic in the philosophy of science literature for the past two decades. An ecumenical view has emerged regarding the minimal characterization of mechanisms, according to which “a mechanism for a phenomenon consists of entities and activities organized in such a way that they are responsible for the phenomenon” (Illari and Williamson [2012], p. 123).

It is important to note that the way in which cancer immunologists proceed in developing such mechanistic models as depicted in Figure 1 is to a great extent different from the modelling process described by the DDM account. In order to provide a more accurate description of modelling in various fields of biological research, another account must be proposed.



Figure 1. An example of a mechanistic model of metastasis and pre-metastatic niche, expressed in the form of a diagram. Primary tumor cells and reprogrammed stromal cells secrete a variety of factors: these include extracellular vesicles (exosomes) and tumor-derived factors (TDFs), i.e., soluble factors such as macrophage-colony stimulating factor (M-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interleukin 6 (IL-6), interferon gamma (IFN-γ), and vascular endothelial growth factor (VEGF) which circulate through blood and have systemic effects. In the bone marrow (BM), such factors act on progenitor cells and orchestrate a differentiation program that results in the production of myeloid-derived suppressor cells (MDSCs) from the granulocyte/monocyte precursor (GMP). These factors also mobilize MDSCs by enhancing actin polymerization and vascular leakiness. A variety of additional factors such as chemokines (CXCL1, CCL12, CCL2, CCL15), matrix metalloproteinases (MMPs), S100A8/A9, and tumor necrosis factor α (TNF-α) play a role in homing (chemotaxis) of MDSCs to secondary sites and in the establishment of the pre-metastatic niche. After Wang et al. ([2019]).

**4.2 What is EDM?**

I argue that the process of building mechanistic models in fields such as cancer immunology can best be captured by what I call the *experimentation-driven modelling* (EDM) account.[[16]](#footnote-16) On such an account, a variety of the experiments described above are routinely conducted on experimental systems, leading to the production of experimental results which are taken to provide some (albeit limited) insight into the nature of the studied phenomenon. When sufficient experimental results have been produced, a more complete picture begins to form, ultimately giving rise to a mechanistic model introduced to account for, at least to some extent, the target phenomenon. Thus, the EDM account is best defined as *the practice of integrating piecemeal experimental results into a comprehensive conceptual framework which is expressed in the form of a mechanistic model*.[[17]](#footnote-17)

How does such integration proceed?[[18]](#footnote-18) Given a particular phenomenon of interest, and on the basis of background knowledge, scientists set up experiments to discover and further investigate the entities, activities and their organization responsible for the phenomenon at hand. For example, in the project of Elena Rondeau from the ImmunoConcept lab in Bordeaux the goal is to investigate the mechanistic role of MDSCs which are in part responsible for the establishment of the pre-metastatic niche (the target *phenomenon*) in a mouse model of breast cancer. Such an effort consists in the characterization of MDSCs in different organs and in different time points in order to gain insight into the exact role played in that context by these cells. The *entities* in question are the different subsets of MDSCs (among other things) which are obtained from mouse models, sorted by flow cytometry, and analysed by using methods that reveal the gene expression patterns. One of the important *activities* of MDSCs is immunosuppression which is studied in co-culture assays. Finally, the spatial and temporal *organization* is brought to light by running time-series experiments, using visualization methods such as immunohistochemistry and *in vivo* imaging.

Overall, combining all these and other experiments, one can begin to generate results which help in the development of a mechanistic model of the establishment of the pre-metastatic niche.

Reflecting on the basic steps in DDM, the steps in EDM can be rendered explicit:

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 limits (and the scope) of the proposed model, scientists compare results across studies conducted on different experimental systems.

It should be noted that, just like in DDM, such a three-step process is also a great simplification of EDM. The steps in the modelling process presuppose that a phenomenon of interest has been identified and that a selection or creation of experimental systems suitable for the task of illuminating aspects of the mechanism responsible for the phenomenon in question has been achieved. One could also gain the false impression that these steps happen in this rigid order: more often than not, scientists continuously develop their model as data come in, sometimes taking a step back and following a different path than originally (and vaguely) envisioned. This much has been extensively documented in the ‘new mechanistic philosophy’: scientists usually start with a mechanistic sketch which incrementally develops into a mechanistic model, but the way in which this happens may not be straightforward or ‘linear’ (Machamer *et al.* [2000]; Craver and Darden [2013]).

Of particular interest is also the third step. Once a mechanistic model is proposed, the same or another team may want to investigate the limits (and the scope) of the model in question. Recall that the model is ‘derived’ from the experimental results which are sensitive to the particular experimental context, i.e., the experimental systems and methods used to generate the results.[[19]](#footnote-19) Thus, as already stated, it is not uncommon to find data that limit the extent to which the mechanistic model can be applied to account for what would intuitively be considered as one and the same kind of phenomenon. Consider again the discrepancy between the subtypes of MDSCs in facilitating metastasis discussed in section 3.2: whereas Ouzounova *et al.* ([2017]) report that M-MDSCs switch on EMT, Toh *et al.* ([2011]) finds that it is G-MDSCs that are responsible for switching on EMT; the explanation for which may lie in the use of mouse models of different cancer types (breast cancer and melanoma, respectively). Furthermore, the experimental systems are in many ways artificial and are subject to generating results that provide distorted pictures of what is going on in the actual full-blown phenomenon. By way of example, let us consider a set of experiments done in the 1990s concerning research on graft rejection. It was known that the presence of specific CD8 T cells is crucial for rejecting grafts. Knocking out the perforin gene in mice – one of the mechanisms by which CD8 T cells kill cells – generated T cells which lack the ability to kill graft cells *in vitro*. However, there was no observed difference in rejecting skin grafts between the perforin-less and the wild type mice, i.e., *in vivo* (Clark [2007], p. 218). What works *in vitro* may work differently, or not at all, *in vivo*, and vice versa. Given such sensitivity, it should not come as a surprise that the proposed mechanistic model may have limited scope – for that reason a comparison across studies which focus on the same kind of phenomenon is often required.

Finally, let us note that, because EDM accounts for mechanistic modelling, one should be careful not to conflate EDM with models that have been referred to by a variety of terms such as descriptive, phenomenological, or black-box models, which merely summarize data without committing to underlying mechanisms (Craver [2006]; Kaplan [2011]; Glennan [2017]).

**4.3 On the differences between EDM, DDM, and ADR**

Given the preceding discussion we can now provide a more thorough comparison between EDM, DDM, and ADR.

*Modelling steps*. The particular (simplified) steps in which mechanistic models in cancer immunology are ‘derived’ from experiments appear to differ from the (simplified) steps in DDM. Recall that in DDM, the modelling process happens in roughly three stages: scientists first use model descriptions to construct a model as a stand-in for the target phenomenon (*model construction*); they then investigate the model to find out what it implies (*model analysis*); and finally, they compare the model results with the target phenomenon (*model comparison*). Thus, one of the differences is that whereas DDM begins by constructing a model, followed by its analysis, EDM’s starting point is an experimental investigation which ultimately leads to model construction. Although neither the stages of DDM, nor of EDM must occur in this rigid order as they may happen together or iteratively, the order of steps does seem to be representative of much of the respective practices, setting them apart.

*The crux of the work*. The *crucial difference* lies in the crux of the research practices involved in the two modelling approaches: while the crux of the work in DDM is the study of the model, in EDM the work is basically considered done once a model is proposed. In other words, DDM is best characterized by ‘playing around’ with a given model, and although models also serve cognitive purposes in EDM, e.g., to provide a comprehensive picture of the mechanism, EDM does not ‘play around’ with models. This difference is further reflected in some other features of modelling such as model predictions. In many cases, by studying a model the DDM approach seeks to derive predictions which are then matched against observations, providing either confirmatory or dis-confirmatory evidence for the model. In contrast, the EDM approach does not derive model predictions to be tested: once a model is proposed, the work is considered done. Instead, the model is thought to be confirmed or validated in the process of its construction.[[20]](#footnote-20) Conflating the two modelling approaches would thus obscure important epistemic differences in scientific practices.

*Dependence on experimental data*. One may also wonder to what extent EDM and DDM are, in fact, distinct as clearly both can rely on experimental results. Recall that model descriptions that give rise to models as per the DDM approach can be not only assumptions but also empirical data, among other things. Clearly, then, the line between the two cannot be drawn on such terms. However, a closer inspection reveals an important difference not to be missed. EDM engages in the laborious processes of experimental data generation whereas DDM more often relies upon pre-existing data. Thus, the kinds of expertise required are often very different as scientists engaged in DDM usually have not acquired the necessary skills to engage in EDM and vice versa.[[21]](#footnote-21) However, it should be noted that much like DDM, EDM often also builds on pre-existing data, studies, results, and models produced by other teams (see also *hierarchy of models* for an example). Still, the respective models produced by such efforts exhibit the epistemic characteristics associated with the respective approaches (see the crux of the work).

*Indirectness*. The proponents of DDM are very keen to stress the indirectness of the modelling practice, which sets it apart from other ways of doing science, such as ADR. The question remains to what extent EDM satisfies the requirement of indirectness, a crucial feature of modelling according to the proponents of the DDM account. Should it turn out that EDM lacks this key feature, perhaps it ought not to be considered a modelling practice but either an instance of ADR or yet another, significantly different way of doing science. I argue that there are good reasons for maintaining the claim that EDM does indeed possess the feature of indirectness. The fact remains that in EDM the mechanistic model is not the central focus of scientists as it is in DDM. Thus, the purported indirectness of modelling according to the EDM account cannot stem from the same source as in DDM. However, neither in EDM does one study the phenomenon directly: the focus of investigation is a set of experimental systems that are assumed to capture – often in a highly artificial way – some aspects of the phenomenon. Thus, in EDM scientists investigate the phenomenon indirectly via a detour through the investigation of a set of simpler systems. Therefore, EDM does exhibit the feature of indirectness.

Perhaps it is less controversial to claim that a mechanistic model is the result of what I call the EDM practice here, than it is to claim that the practice is, in fact, a modelling practice. In describing the key features that distinguish modelling from ADR, Weisberg warns us about conflating the process leading up to the product with the product itself. The practices of DDM and ADR are to be:

distinguished by the actions and intentions of theorists, not by the outcome of the process of theorizing. This means that to judge whether or not a particular theorist is a modeler, it will not be sufficient to determine whether or not her theory can be represented as a model or cluster of models. We will actually need to know something about how the theory was developed and how the modeler set about trying to represent the world. (Weisberg [2007], p. 222)

Weisberg further claims that

modeling is distinguished from ADR by a theorist's construction and analysis of a model, which is used to analyze and represent a real-world phenomenon indirectly if at all. When a modeler wants to describe a real phenomenon, she begins by choosing a model, not a real phenomenon to analyze. (Weisberg [2007], p. 230)

and that in ADR

the theorist is analyzing a representation that is directly related to a real phenomenon, anything she discovers in her analysis of the representation is a discovery about the phenomenon itself, assuming that it was represented properly. There is no extra stage where the theorist must coordinate the model to a real phenomenon. (Weisberg [2007], p. 227)

However, as argued above, cancer immunologists ordinarily choose a set of experimental systems as the focus of investigation in order ultimately to learn something about the target phenomenon. They do not directly analyse the phenomenon. Rather, they intentionally pursue the indirect line of investigation because research conducted on cell cultures and animal models does not straightforwardly translate to knowledge about the target phenomenon. Thus, EDM differs from ADR.

*Role of assumptions*. In addition to comparing EDM with DDM in terms of the intentions and steps by which these practices proceed, one can also turn the spotlight onto the role of assumptions in both kinds of approaches. In DDM, assumptions serve as a kind of model description and are said to be the building blocks of models: by entertaining certain assumptions, scientists construct models. Often this is put in the following terms: scientists write down model descriptions by means of which they create or otherwise specify model systems (Godfrey-Smith [2006]; Mäki [2009]; Thomson-Jones [2010]; Weisberg [2013]; Frigg and Nguyen [2017]; Thomasson [2020]). For instance, Volterra wrote down equations (i.e., the model descriptions) describing the relations between two hypothesized populations (i.e., the model system).

In EDM, the role of assumptions is quite different. They neither define nor otherwise give rise to models. Instead of serving as building blocks for creating model systems, assumptions in EDM concern the representativeness of the experimental systems and the validity of experimental results with respect to the studied phenomenon.[[22]](#footnote-22) They also help in deciding which experimental systems to use in the study of a particular phenomenon. As noted above, much of cancer immunology research makes use of cancer cell lines such as the 4T1. Although these standardized cell lines originate from tumor biopsies, it is well known that once they have been adapted to cell culture conditions, they no longer behave like the tumors arising spontaneously *in vivo*. The genetic and/or epigenetic changes in these cells lead to cell immortalization, meaning that they can proliferate indefinitely. Cancer cell lines grow in an environment without the need for heterotypic interactions – a type of communication between different cell types which controls the proliferation of the other types of cells in the neighborhood – which sets them apart from the tumors originally found in cancer patients.[[23]](#footnote-23) The two-dimensional spatial arrangement of cell cultures and other features also introduce conditions not found *in vivo*.[[24]](#footnote-24) Recall the example of perforin-less CD8 T cells: under the *in vitro* conditions they lose their ability to reject grafts, yet they seem to do their job perfectly fine *in vivo*.

*Ontology of scientific models*. Some might wonder whether the key difference between EDM and DDM cannot be drawn along the ontological dimension. Philosophers have long distinguished physical or material models from theoretical or nonmaterial models (see, e.g., Toon [2010]; Frigg and Nguyen [2016]). Because EDM seems to concern material practices as opposed to the theoretical practices of DDM, perhaps EDM should be understood as an account of material modelling, whereas DDM could be an account of theoretical modelling. This view is mistaken for two reasons. Firstly, in EDM, material practices are involved mainly in step 1; step 2 is theoretical in that it concerns not the manipulation of material systems but the integration of piecemeal experimental results into a mechanistic model.[[25]](#footnote-25) Moreover, the mechanistic model is not a material entity in the straightforward sense; rather, it is a conceptual model expressed in the form of a diagram (see Fig. 1). Secondly, many material models are clear cases of DDM, e.g., the San Francisco Delta-Bay model (Weisberg [2013]) and the Phillips-Newlyn machine, a material model of macroeconomics (Frigg and Nguyen [2018]). These physical models are constructed as simplified versions of their target systems and are subsequently investigated in order to learn about the features of their respective targets.[[26]](#footnote-26)

*Exploratory vs hypothesis-driven research*. It would also be wrong to draw a line between EDM and DDM in terms of exploratory versus hypothesis-driven research because there are plenty of examples of both the exploratory and the hypothesis-driven instances of DDM and the same can be said of EDM (Gelfert [2016], Chapter 4). In practice, it is often the case that while some aspects of a research project can be conceived in terms of more exploratory nature (e.g., the use of RNA-seq), other aspects are more akin to hypothesis-driven nature (e.g., the use of PCR which is focused and as such presupposes *some* hypothesis in mind). Thus, the distinction may not be that sharp, and a researcher working on a project may be moving back-and-forth between the two extremes.

*Hierarchy of models*. EDM is somewhat peculiar in that the process of mechanistic modelling builds on the use of other types of models, namely the animal models and cell cultures which are also sometimes referred to as models, a point also clearly articulated in (Fagan [2016]). Arguably, while in DDM scientists sometimes also proceed by constructing a model on the basis of another model, there does not appear to be such a built-in dependency as there is in EDM. This is because while all cases of EDM exhibit the modelling hierarchy, there are clear-cut examples of DDM in which the construction proceeds without the mediation of another model or theory.[[27]](#footnote-27)

At this point it is also worth revisiting the notion of (model) robustness. In DDM, model robustness has been discussed in a number of ways (see, e.g., Lloyd [2015]). In EDM there appears to be one important sense of model robustness exemplified by some review papers in which the authors present a model that unifies otherwise diverse models. In so doing, the authors introduce another level to the model hierarchy, but this time not much different from some cases of DDM. Recall that the experimental results, and thereby also the mechanistic models are sensitive to the particular experimental systems and methods employed in a research project. Recall further the phenomenon of metastatic tropism, the explanation of which requires that there are tissue-specific features such as the different kinds of chemokines and integrins, among many others, contributing to the observed metastatic patterns (see Gao *et al.* [2019] for a depiction of several such more specific models of bone, liver, lung, and brain). The model described above (see Fig. 1) lists some of the common factors found across the spectrum of metastatic cancers, but as a general account it must remain silent on the more specific details (i.e., be *abstract*) and also retain its general *scope* (Machamer *et al.* [2000]; Levy [2018]). Similarly, the model depicted in Fig. 1 does not distinguish between different subsets of MDSCs which have been shown to play somewhat different causal roles. For instance, one of their important roles in the establishment of pre-metastatic niche is their immunosuppressive activity. However, M-MDSCs differ from G-MDSCs in the level and specificity of the immunosuppressive capacity, as well as in the mechanism by which they induce it (Gabrilovich and Nagaraj [2009]). Taken together, models such as those depicted in Fig. 1 can be viewed as expressing robustness by depicting the general causal structure, which is very much akin to what has been termed the ‘causal core’ in the literature which focuses on what I call DDM herein (see, e.g., Lloyd [2015]). Finally, the model in Fig. 1 can also be viewed as an instance of what has been termed ‘mechanism schema’ in the philosophical literature on mechanism (Machamer *et al.* [2000]).

**4.4 Experimenting and modelling**

Because experimentation is part and parcel of the EDM account, one could gain the false impression that any instance of experimentation amounts to modelling. Experimentation on its own should not be conflated with modelling; indeed, although for different reasons, this point has already been made in the existing literature (see, e.g., Weber [2014]). To give but one example, consider the case of visualizing methods which certainly count as experiments (see section 3.2). Such an experiment merely informs about the presence and location of particular cells. One can run an experiment or even a series of experiments without piecing the results together into a mechanistic model. It is only when there is an effort to understand the mechanism responsible for the phenomenon of interest by running a series of experiments, the results of which are ultimately accounted for by developing a model, that we can speak of EDM.

That said, the philosophical literature brings forth a number of interesting analogies between modelling and experimenting on the basis of which it concludes that experimenting *is* modelling (see, e.g., Mäki [2005]).[[28]](#footnote-28) One important analogy suggested by Mäki pertains to his use of the notion of isolation, the act of removing influences deemed, at least provisionally, irrelevant to the task at hand.[[29]](#footnote-29) In the case of theoretical modelling, this means employing assumptions that neutralize the influence of disturbing factors, whereas in material modelling the experimental systems are isolated in a lab and sheltered from the causal influences of the outer world. Thus, both the theoretical and the material manipulations are viewed as isolations. However, as noted before, the simple fact that abstractions, idealizations – or, in this case, isolations – are typical of modelling does not warrant the conclusion that other practices that make use of isolations should therefore be equated with modelling. For present purposes, however, there is no need to take a firm stance on this issue: what matters is that the EDM account does not rest on equating experimenting with modelling. Rather, the EDM account views modelling as the practice of integrating results obtained from experiments conducted on a set of experimental systems – material models, if you will – into a mechanistic, that is to say, a conceptual model. None of this would require commitment to the claim that experimenting, *per se*, is modelling.

**4.5 EDM: The bottom line**

Before moving on, let us summarize the key aspects of EDM. It is the practice of integrating piecemeal experimental results into a comprehensive conceptual framework which is expressed in the form of a mechanistic model, often as a diagram. In EDM, after identifying a phenomenon of interest scientists choose a set of experimental systems that, albeit in a distorted fashion, are assumed to capture some of the salient features exhibited by the target phenomenon. By running experiments, scientists produce data which shed light on the entities, activities, and organization responsible for the phenomenon in question. The results are then used to construct a mechanistic model. Rather than investigating or otherwise ‘playing around’ with the model, scientists work with a set of laboratory experimental systems: the mechanistic model is then the end product of the modelling process.

Because there is no direct investigation of the target phenomenon, EDM comprises an indirect analysis (akin to DDM, as opposed to ADR). Although EDM is not assumption-free, the role of assumptions concerns the representativeness of the experimental systems and the validity of results. In contrast to DDM, the assumptions do not give rise to models. The difference between EDM and DDM is not captured by either of the distinctions between material and non-material models, and exploratory and hypothesis-driven models, respectively. Crucially, EDM rests on model hierarchy: mechanistic models are constructed on the basis of investigating a set of experimental (model) systems. Finally, EDM does not equate experimenting with modelling.

**5 EDM as a Complementary Account of Scientific Modelling**

The EDM account of scientific modelling should be understood as complementing rather than replacing or modifying the widely held DDM account. This is because while the way in which DDM is characterized accounts for a large portion of research practice in various fields, it does not fit well with those practices employed in modelling mechanisms in many fields of biological research, such as cancer immunology. To fully defend EDM as a complementary account there are at least two problems which must be addressed.

**5.1 Between the normative and the descriptive approaches**

One may question the extent to which it is justified to speak of modelling in the context of mechanistic models based on laboratory research practices. After all, the practice of modelling seems to exhibit a sociological dimension in that “some scientists now are trained, hired, and assessed as modelers; that is their job description” and that “modelers have their own subculture within science, to some extent, and their own language” (Godfrey-Smith [2006], pp. 728–9). Indeed, seen in this way it would be difficult to maintain the claim that many cancer immunologists working in experimental labs engage in modelling, for the simple reason that they are not hired as modellers and they do not perceive themselves as such.

There is no doubt that the sociological aspect sits well with the DDM account: it is likely that most, if not all scientists who work within the DDM framework are in fact hired and assessed as modellers. In contrast, scientists whose work is best captured by the EDM account are hardly ever hired as modellers. Nevertheless, there are other (epistemically) important features shared by EDM and DDM: when building mechanistic models of phenomena, EDM scientists proceed indirectly: instead of directly analysing the target phenomenon, they construct and investigate a set of simpler systems on the basis of which they construct conceptual mechanistic models. Thus, while the sociological dimension is a unique feature of DDM, it does not prevent us from construing the EDM practices as modelling practices.

Scientific literature is notoriously loose when it comes to providing a precise clarification of some general concepts, such as a ‘model’. Given that the goals of a scientific paper can be achieved perfectly well without dwelling too much on making the meaning of these general terms more precise, the vagueness should be of no concern. However, since one of the goals of philosophical analysis lies in unpacking such general terms, it must proceed with more care. Roughly, two extreme views can be discerned in this context. Whilst philosophical analysis might espouse a strictly descriptive approach and consider anything referred to by the term ‘model’ as an instance of a model, constructed by some modelling practices, one can also stipulate the meaning of a given term by providing a philosophical analysis of a set of presumably paradigmatic examples while excluding possible alternatives. This latter approach exhibits strong normative tendencies. The EDM account, much like that of DDM, is situated somewhere between these extremes. On the one hand, it takes seriously the notion of a mechanistic model; yet on the other hand, it has built-in boundaries specified by the key characteristics described in the previous section.

**5.2 DDM and EMD as philosophical constructs**

According to some of its proponents, the DDM account should be understood as providing an incomplete picture of modelling practice. Along those lines, Weisberg argues that “just as theorists offer incomplete, idealized models of their targets, so must philosophers. Theoretical practice is rich and multilayered, and the world is often uncooperative” (Weisberg [2013], p. 6), to which he further adds that “by developing philosophical accounts of modeling, we can start to get a handle on theoretical practice. But just as in a representation of any other complex phenomenon, philosophical analysis will necessarily be partial and incomplete. Thus the accounts developed in this book are themselves models of modeling” (Weisberg [2013], p. 6).

While the EDM account helps to partially complete the picture by providing another piece of the puzzle, its proposal, much like DDM, necessarily provides only a peak into an otherwise complex and ‘messy’ scientific modelling approach – such is the nature of philosophical analysis which aims to make explicit the most salient features of scientific research. Although a closer inspection reveals that many of those features of the respective approaches constitute a difference of a degree rather than a kind, it should not obscure the fact that, on average, EDM and DDM represent two different approaches. Thus, both EDM and DDM are philosophical ‘constructs’.

**6 Conclusion**

Scientific modelling is an important tool in contemporary science. Philosophers of science have long discussed many aspects of the practice of modelling. My review of the description-driven modelling account, and my proposal of the experimentation-driven modelling account, demonstrate firstly, that DDM does not account for the practice of mechanistic modelling in laboratory fields such as cancer immunology; secondly, that EDM fits well with what is going on in cancer immunology research and beyond; and thirdly, that EDM should be understood as a complementary account which can coexist with DDM.

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1. Philosophers have addressed many perplexing questions concerning scientific modelling, such as how models explain (Bokulich [2017]) and represent (Frigg and Nguyen [2020]) phenomena and how they allow for acquiring knowledge about the world in the first place (Fumagalli [2015]; Salis [2016]; Frigg and Nguyen [2017]; Frigg and Hartmann [2020]). [↑](#footnote-ref-1)
2. For instance, Morrison and Morgan ([1999], pp. 12–3) noted that “we are given definitions of models, but remarkably few accounts of how they are constructed.” Since then, the situation has improved, although much has remained the same. This is because a large portion of the philosophy of modelling has focused on the nature of models, i.e., the ontological question, rather than on the nature of modelling as a practice. While some have explicitly drawn a distinction between the two, others have not. For instance, Weisberg ([2007], p. 208) admits that “there are many insightful discussions in the philosophical literature about the nature of models” but that “less has been written explicitly about the practice of theorizing.” On the other hand, Toon ([2010]) speaks of “the ontology of theoretical modelling,” and makes further remarks which may be viewed as collapsing the distinction, at least to some extent (see also, e.g., Thomson-Jones [2012]). [↑](#footnote-ref-2)
3. Model descriptions are taken to be assumptions, equations, parameters, pictures, empirical data, words or pieces of text or any such ‘thing’ that give rise to models or model systems, whatever the ontological status of these may be (Godfrey-Smith [2006]; Mäki [2009]; Thomson-Jones [2010]; Weisberg [2013]; Frigg and Nguyen [2017]; Thomasson [2020]). It should be noted that some authors have questioned some aspects of the distinction between model descriptions and models (Odenbaugh [2015]; Knuuttila [2017]). [↑](#footnote-ref-3)
4. Note that this third step is optional. Although it is true that such comparison often takes place, sometimes models are constructed and investigated independently of any real-world phenomenon against which they could be compared (Weisberg [2004], [2007], [2013]; Mäki [2009]; Thomson‐Jones [2020]). [↑](#footnote-ref-4)
5. For a more detailed exposition see Weisberg ([2013], pp. 10–3) and especially Knuuttila and Loettgers ([2017]) who offer a critical and more historically-oriented description. [↑](#footnote-ref-5)
6. I believe that the term *description-driven modelling* can serve as an umbrella term for a number of modelling strategies already discussed in the literature. This includes, among others, both the *theory-driven modelling* strategy, in which modelling is regulated by general theories, and the *phenomenological modelling* strategy, in which semi-empirical results and concepts beyond the theory framework are used (see Portides [2011]). It also includes *autonomous modelling*, where models are developed independently of a strongly empirically-confirmed framework theory (see Reutlinger *et al.* [2018]). In cases where data mining practices lead to the construction of network models (see Plutynski and Bertolaso [2018]), much of data-driven modelling can be also viewed as an instance of DDM. The overall modelling process mirrors the steps characteristic of DDM: the construction of a network model followed by the analysis of the features of the network (and the comparison with the phenomenon). [↑](#footnote-ref-6)
7. Note that while the great majority of authors think of modelling as an indirect activity to be distinguished from a direct, non-modelling way of doing science, there are a few authors who disagree and argue for a direct view of modelling (see Levy [2012], [2015]; Toon [2012]). [↑](#footnote-ref-7)
8. It should be noted that some authors have questioned Weisberg’s analysis of Mendeleev’s work, as well as the strict distinction between direct and indirect approaches (see Knuuttila and Loettgers [2017], p. 1012 for a discussion and a list of references). [↑](#footnote-ref-8)
9. Both agree on the indirectness of modelling and the stages in which modelling happens. They are also keen to stress that although abstraction, idealization and other tools are part and parcel of the modelling process, they are not unique to modelling (see especially Weisberg [2007], pp. 228–9). [↑](#footnote-ref-9)
10. See, for instance, the monographs by Bertolaso ([2016]), Laplane ([2016]), or Plutynski ([2018]). See also a recent entry in the Stanford Encyclopedia of Philosophy (Plutynski [2019]). [↑](#footnote-ref-10)
11. Philosophers have contributed to a key conceptual debate regarding the nature and boundaries of the tumor microenvironment (Laplane *et al.* [2018], [2019]). [↑](#footnote-ref-11)
12. This has sparked a debate in the community and multiple competing theories have been proposed to account for the observed metastatic tropism (see Fidler [2003]). According to some (e.g., Weinberg [2014]), the seed-and-soil hypothesis is promising, even though it may fail to explain certain features of the metastasis such as the rarity of contralateral metastases (i.e., tumor cells disseminated from, for example, one breast should be naturally seeded to the other breast which should provide the most hospitable environment). [↑](#footnote-ref-12)
13. As discussed by, for example, Veglia *et al.* ([2018]), MDSCs have been found to play a biological role not only in cancer but also in infectious diseases, autoimmunity disorders, obesity, and pregnancy. Although potency and the particular mechanisms by which the subsets of MDSCs mediate their immunosuppressive effects vary depending on the site (e.g., lymph node / tumor microenvironment), they do so in both an antigen-specific and nonspecific manner, and they suppress the adaptive as well as the innate immune system (Nagaraj *et al.* [2010]; Kumar *et al.* [2016]). [↑](#footnote-ref-13)
14. As is often the case when defining new cell subpopulations, some have recently questioned whether current state-of-the-art knowledge warrants the talk of MDSCs as a category of cells distinct from monocytes and neutrophils of a particular phenotype (see Garner and de Visser [2020], BOX 4). [↑](#footnote-ref-14)
15. M-MDSCs are commonly characterized as CD11b+ Ly6G– Ly6Chigh cells, whereas G-MDSCs as CD11b+ Ly6G+ Ly6Clow. Note that this is valid only for mice cells because human cells do not express Gr1 – thus, no Ly6C or Ly6G epitopes. [↑](#footnote-ref-15)
16. The terms *theory-driven models* and *experiment-driven models* appear, for instance, in the work of Mitchell and Gronenborn ([2017]), who discuss modelling approaches in the context of research on protein structures. Although similar to some extent, the way I discuss modelling in this paper differs from their approach. For Mitchell and Gronenborn, whereas theory-driven modelling concerns the practice of predicting the protein structure by means of running computations from physical and chemical principles, experiment-driven modelling pertains to algorithmically inferring models from experimental data. However, the notions of DDM and EDM as presented here are more general: DDM covers not only theory-driven approaches but also theory-independent approaches, and EDM also covers approaches that are much less, if at all, guided by any sort of algorithm and as such the derivation seems much less straightforward. [↑](#footnote-ref-16)
17. Fagan ([2016]) outlines a similar position while discussing research on human embryonic stem cells. In the context of immunology, Baetu ([2014]) has claimed that the “big picture” of some pathway or mechanism of interest is often built up as a mosaic of scientific knowledge (see also Lemoine [2017] for similar remarks). Mitchell and Gronenborn ([2017]) have discussed a variety of both theoretical and experimental approaches to modelling the structure of proteins, the ways in which these approaches may be integrated and how they complement one another. [↑](#footnote-ref-17)
18. The notion of integration here refers to a complex cognitive process, the full description of which is outside the scope of this paper. Rather than providing a detailed analysis of the cognitive process, the aim here is to outline it as a plausible account of the mechanistic model building. [↑](#footnote-ref-18)
19. There are two points to note regarding the notion of derivation. First, it should not be understood in terms of a formal logical relation. Second, it should not be conflated with the idea of applying a statistical method on a given data set. The existing philosophical literature on scientific models and modelling distinguishes ‘models of phenomena’ from a set of interrelated notions such as ‘data models’ or ‘models of experiments’ (Bogen and Woodward [1988]; Giere [2010]; La Caze [2011]; Woodward [2011]; Leonelli [2019]). Whereas the former notion concerns models of the phenomena of interest (possibly including models of mechanisms responsible for the phenomena), the latter pertains to finding patterns in the data and the use of statistical and other data processing methods. Thus, the diagrammatic representations of purported mechanisms (mechanistic models) are to be understood as ‘models of phenomena’. Such use of terminology introduces somewhat of a tension in the usual way in which these concepts figure in the literature on mechanisms and modelling, respectively, which provides further evidence for the point that the literature on mechanisms and scientific modelling have not made sufficient contact. [↑](#footnote-ref-19)
20. There are several things to note. First, although predictions can be derived from (EDM-produced) models, when they are it is often for some other, although likely related project. Thus, it is not to confirm the model. To give but one example, consider the range of conditions in which MDSCs are involved. One may find inspiring a model of MDSCs in cancer to ask questions about MDSCs in other conditions such as obesity. Second, EDM can make use of predictions in the process of model construction. For instance, at some point in an experimental investigation a result may give rise to several possibilities that could account for the given result. These possibilities are then tested and ruled out until the most plausible one is confirmed. In both these regards, EDM does not necessarily differ from some cases of DDM (Cf. Lloyd [2015]). [↑](#footnote-ref-20)
21. Once again, by such a statement I mean to suggest a difference in degree rather than a sharp dividing line, since there exist some laboratories that train researchers in both approaches. [↑](#footnote-ref-21)
22. See also Weber ([2014]) who argues that the role of assumptions in using model organisms concerns things such as the validity of the results and as such is different from the role of assumptions in mathematical modelling. [↑](#footnote-ref-22)
23. To be more precise, some carcinoma cells *in vivo* develop to the state where they no longer depend on stromal support and can grow and proliferate independently (Weinberg [2014]). [↑](#footnote-ref-23)
24. Although many labs now routinely use three-dimensional cultures, known as organoids or spheroids, they comprise only a small part of cell culture research. [↑](#footnote-ref-24)
25. At this point it is worth noting the difference between the EDM account and some of the other accounts that discuss experimental modelling, such as the experimental modelling account of Weber ([2014]). Weber claims that experimental modelling “consists of constructing model systems that are composed of living organisms (sometimes, but not necessarily, genetically modified) and that are used as *in vivo* representations of biological processes in such a way that some processes are used as stand-ins for other processes” (Weber [2014], p. 787). This, then, differs from the EDM account in two important respects. First, Weber's experimental modelling basically concerns only the first step in EDM: it is the investigation of experimental systems. Second, when Weber speaks of constructing model systems, he means the construction of experimental systems; in EDM the construction of models pertains to constructing conceptual mechanistic models (step 2). [↑](#footnote-ref-25)
26. Depending on the exact context of the research, it should also be noted that there might be cases in which it is not perfectly clear whether modelling should be thought of in terms of EDM or DDM. For example, in one of the previous footnotes the experimental modelling of the structure of proteins is discussed. Frigg and Nguyen ([2016]) discuss Kendrew’s model of myoglobin, a material model of a protein, along the lines of DDM. In their own words, although the “model was constructed on the basis of electron density data (…) it wasn’t simply a summary of these data, or a tool to communicate effectively the information the data contained. The model provided epistemic access to the tertiary structure of the molecule in a way that the electron density data alone could not” (Frigg and Nguyen [2016], p. 226). Frigg and Nguyen claim that some of the key insights regarding myoglobin came from studying its material model. Thus, at least in this case it seems natural to construe the work as consisting of constructing a model, later followed by its analysis – a picture that fits DDM. However, in other cases it might be more natural to think of the experimental modelling of proteins in terms of EDM (see Mitchell and Gronenborn [2017] for a discussion on modeling proteins). What this seems to highlight is the difference in research goals. One way or another, it is possible that the difficulty with classification may be more pertinent to models of entities than to models of mechanisms. Moreover, if some instances of modelling protein structure could be understood in terms of EDM, it would suggest that EDM may also account for non-mechanistic modelling, a question not pursued in this paper. [↑](#footnote-ref-26)
27. For instance, think of autonomous models such as Schelling’s model of social segregation (Reutlinger *et al.* [2018]). [↑](#footnote-ref-27)
28. Mäki is careful not to commit to the strong reading of this thesis, i.e., the claim that *any* modelling should count as experimenting, and vice versa. In his own words: “The equation models=experiments is not suggested to hold for all specifications of the two concepts, that of model and that of experiments. The equation rather boils down to two more specific claims: many theoretical models=experiments, and many material experiments=models” (Mäki [2005], p. 312). However, since he gives no specific examples of cases in which this analogy breaks down, I take the liberty of discussing this issue with respect to EDM. [↑](#footnote-ref-28)
29. Mäki ([2005]) lists additional analogies. However, addressing them is beyond the scope of this paper. [↑](#footnote-ref-29)