PHILOSOPHY OF SCIENCE

7

This edition series is based on two guidelines. Separation lines between disciplines exist for the pleasure of crossing them and that this intrusion demand is stronger than any imposed limitations to free interaction and dialogue between fields of knowledge. Yesterday such trespassing need was true for the theories of Copernico and Darwin. Today it is valid for cosmology, biology and physics, including computer science and high technology and the boundaries set between them. The other guideline is that the most interesting philosophy, as Ludovico Geymonat liked to say, is found hidden in the creases of science. We must look in various articulations and directions of science, across any artificial boundary between "science of nature" and "human science" to find adequate and trustworthy replies to questions philosophy meets in its path.

In this general picture the single items discussed remain with many metaphorical question marks, to stimulate, as says Wittgenstein in Pensieri Diversi: "With my frequent punctuation I wish to slow down the reader's rhythm. Because I would like to be read slowly". These are not 'disposable' texts to view rapidly and in haste. We suggest you read further making yours a maxim said to be of Svetonio, an invitation to reflection: "*Festina lente*".

Marta Bertolaso

How science works

Choosing levels of explanation in biological sciences

Preface by
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Contents

Preface

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Complex biological systems, like the human body, function normally by the operation of multiple components each engaging multiple causes at different levels of organization in changing internal and external environments. Explaining scientifically how this works has generated a variety of theories, models and explanations. Some theories explain complex behavior by appeal only to properties of the simplest molecular components, others by appeal to system level properties and the interactions and processes that stabilize them. The first approach exhibits what philosophers of science have identified as reductive methodologies, the second to developmental, emergent, or systems methodologies. What all can agree upon is that the pluralism of biological explanations does not seem to be diminishing, resolving into a grand unified theory or reducing into some branch of chemistry or physics. And so the philosophical debate continues as well as to whether reductionism should, normatively, be the goal of science or not, whether unification or disunity should, normatively, characterize the relationship among different explanations or not. In my own work on these topics I have argued against reduction and unification as obligate goals and defended a position I call integrative pluralism instead (Mitchell 2003, 2009). I appeal to scientific investigations of complex biological behavior in practice as well as provide arguments for contingency, emergence, partiality of scientific representation and pragmatic components of scientific explanation in developing and defending integrative pluralism. Bertolaso is concerned with an overlapping set of issues that arise from close attention to the details of cancer research.

Understanding cancer, the targeted science for philosophical analysis in Marta Bertolaso's book, adds another source of complexity

to the story. As Tolstoy brilliantly put it "Happy families are all alike; every unhappy family is unhappy in its own way." While this does not map literally onto functional and dysfunctional behaviors (that is, a functioning complex biological system may have alternative ways to realize its "happy" state) it seems to me that *prima facie* there are many more ways to fail to function than to succeed. Thus explaining the origin, progress, and pathways of cancer presents even greater challenges for any simple explanatory strategy. As Bertolaso explains (Chapter 4), the heterogeneity of cancer tumors eludes explanation by simple models of cancer progression. This heterogeneity has led to the development of explanations that appeal to higher levels of organization. With the details of these scientific developments at hand, Bertolaso interrogates both a mechanistic account of explanation (like that of Machamer, Darden and Craver (2000)) and Schaffner's preferred causal model systems (2013a) to argue "that if reductionist-mechanistic explanations work it's because of the non-reductionist dimension that characterizes the definition of their *relata*."

Throughout the book Bertolaso refers to what she calls the "double dimension" of describing (or defining) a biological behavior and causally explaining it. She argues that the two activities are not serially independent, but rather engaged in a dialectic of revision and refinement in the experimental practice of scientists. In cancer research, providing a definition of what kind of process it is has been intimately linked with different explanatory strategies. In examining the relationship between a reductionist approach (Somatic Mutation Theory) and a system-level approach (Tissue Organization Field Theory) in Chapter 5, Bertolaso draws out general philosophical issues which motivate the chapters in this book. What are the implications for reductive strategies of the hierarchical structure that is evident in cancer ontogenesis from gene, to cell, to tissue, to organ to organism? How does the role of context, often invoked to defend emergent properties and explanations in contrast to reductive ones play out in the case of cancer? By focusing on the scientifically and philosophical salient issue of which level of explanation or description is most appropriate to the study of complex biological behavior, and using developments in cancer

research as a source for answering this question, Bertolaso provides new entries into ongoing philosophical debates, as well as opening up new questions to engage the philosopher of biology.

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Chapter I

Introduction

"It is a common idea that some choices of level of explanation or causal description are more appropriate or perspicuous than others, although there is little consensus about what exactly this means" (Woodward 2010, 296)[1]. This is the introductory statement of a well–known paper of Jim Woodward that caught my attention in the last two years and has driven my research during my visits at the University of Pittsburgh.

In this volume I collect some papers that answer that question in different ways. I have presented some of them in various conferences and I discussed these issues both in the States and in Europe. Colleagues and friends are now encouraging me to publish them all together, so that I have finally decided to share them with a wider group of readers. I have collected suggestions and have based some chapters on articles and a book already published. I have also integrated some chapters with footnotes whenever I have received comments on them in conversations with people I mention in the acknowledgments: they will be useful to further develop and articulate the discussion I am opening in these pages. I will be more than happy if others, who have already explored these issues, will be able to contribute to the discussion from these or different perspectives.

This volume is a programmatic contribution towards a clarification of *why science works* and *how it works*. In these decades, there is a trend towards a new Philosophy of Science, which is much more focused on how science works in practice and interested in the epistemological implications of scientific explanations as a means to understand the natural world. I have already addressed this philosophical claim[2], and

1. Woodward J. (2010), Causation in biology: stability, specificity, and the choice of levels of explanation, *Biology and Philosophy*, 25: 287–318.

2. Bertolaso M. (2012), *Il Cancro come questione. Modelli interpretativi e presupposti epistemologici*, FrancoAngeli, Milano.

I would like to provide in this volume some theoretical grounds for my (previous) viewpoint. I will be happy to receive comments and answers to the open questions I present at the end of the book. And to integrate and change my mind whenever different perspectives will prove to be more fruitful in accounting for the same basic scientific questions.

1.1. Which science?

When I was studying biology at the University of Milan I was told that the term *biology* was to be understood as the combination of *bios*, i.e. life, and *logos, i.e.* a principle of order and knowledge. Our training in ancient philosophy was such that none of us was actually surprised by this explanation and by the comments that some of our professors made when acknowledging that biology is not the only field of knowledge that deals with life. Life is a field for philosophical inquiry that grasps aspects of this concept that the formalisms and reductionist approach of scientific methodology can only partially address. Philosophical discussions often integrated our lessons and conversations at lunchtime and over summer school periods.

This approach to the biological world changed when I started studying philosophy. The strong commitment to believe that the scientific method, and the peculiarity of its explanatory enterprise, provided the explanatory framework for biological phenomena, which I was encouraged to embrace, contrasted strongly with my experience in lab activity. There I realized that the first challenge was rather to design the right experiment depending on the scientific problem. The relevant issue was to ask the right questions and to set the adequate experimental control to generate significant data from the experimental tools available to us.

In that period I realized that a double dimension with philosophical relevance was at stake: one related with experimental design and the other with the conceptualization and the explanatory relevance of the notion of life. The question that Woodward asked in his paper in 2010 gave me an interesting perspective to start from in trying to figure out what epistemological issues were at stake when the question was on some characteristic features of living systems and the adequate

explanatory framework to adopt to understand them. I am assuming that any biological question is characterized by the necessity to explain why something (usually identified as a system, i.e. an integrated functional unity of molecular parts) behaves in this way and not in another one. These kinds of dynamics, defined in terms of biological behaviours, are usually described in terms of inter–level regulatory or control processes. In biology it's common to distinguish a double aspect of the experimental procedure: the definition of the systems (*explananda*) and the structuring of the explanation (*explanans*), which is typically causal.

Such double dimension seemed to be overlooked in the philosophical discussion about how science works and how we know the world through science. I then decided to look at when and why research programs that addressed this kind of biological questions, related with an inter–level regulatory process, get stuck in their explanatory enterprise. In explaining a complex biological phenomenon that involves many and different levels of a biological organization, from genes to cells, up to tissues and organs' functional organization, this inquiry has been particularly interesting. Philosophical questions arise, in my opinion, when we consider that the descriptive element is a first step, necessary although propaedeutic to the discovery of a causal relationship that describes the more specific behaviour of biological systems and subsystems. At the end the question is always on the living aspect of a biological system, i.e. on its peculiar way of being, or behaving. The focus is not on the parts and their causal interactions but on the peculiar dynamics that hold them.

Training in biological science consists in developing skills in to bring these two dimensions — description of the system and articulation of causal relationships among its parts — into a unified experimental approach. The scientific outlook we have inherited from the modern era of the Renaissance in Europe is based on the idea that there are regularities and continuities of organizational principles in nature and that searching for such patterns of organization is particularly effective in exploring and understanding living systems. The notion of pattern effectively combines the dynamic aspect with the descriptive features of the systems that constitute the *explananda* as the object of scientific inquiry in biological sciences. In this volume I will explore some explanatory issues that emerge from my own expe-

rience in scientific work and my philosophical thought on it. I have to apologize for using some terms in a different way than what is sometimes considered 'the standard one' in American literature on these topics. However, I made sure that the meaning I am giving them is consistent and clarified in the papers. Others can discuss them within different philosophical traditions and consider these contributions or other perspectives they have been developing.

1.2. Structure of the book

In the next chapter, I introduce the case study. Cancer is one of the biological phenomena, to which I devoted my studies and experimental activity in the lab. The complexity of the neoplastic processes is one characteristic that appeared increasingly evident over the last few decades, both from clinical and molecular studies. Rapid advances in molecular biology have led to the acquisition of a considerable amount of data regarding the genes and proteins that are apparently involved in the progression of cancer, while the reductionist perspective — which has dominated cancer research over the last 60 years and is characterized by the attempt to explain cancer in genetic terms and through mechanistic models of interactions among biological parts — has incorporated the data into ever more detailed and complex interpretive models of the origin of cancer.

Nevertheless, an analysis of scientific literature highlights the lack of a formal definition of neoplastic pathology. Such analysis led me to explore the discussion triggered by the emergence of a number of paradoxes that have demonstrated the inadequacy of the reductionist models, particularly in explaining tumour latency and reversibility of the neoplastic phenotype. At the same time, a generalized tendency has emerged to consider cancer as a dynamic process the explication of which requires a systemic approach. In this framework, taking a certain distance from the reductionist view, often exemplified by the *Somatic Mutation Theory* (SMT), a new theory (*Tissue Organization Field Theory*, TOFT) and some new interpretive models show a clear movement toward the organic perspective. The antireductionism that characterizes these models is, to some extent, due to the historical opposition that TOFT's authors elaborate against SMT in scientific

literature but also reflects the more general opposition between reductionism and holism at the heart of contemporary Philosophy of Science in general, and of Philosophy of Biology in particular.

As hierarchical issues seem to be involved by different explanatory models of cancer, in the third chapter I confront the way they are formulated within cancer research with the well–known account of Herbert Simon on the hierarchical structure of complex and evolvable systems. The history of cancer research shows that one of the features of cancer's complexity is that tumour heterogeneity compromises the hierarchical control of the organic system. Therefore, although over the past decades the dominant paradigm has been cell centred, more recently the dynamics of cancer development and tumour cells' heterogeneity are captured by explanatory models of cancer referred to hierarchical structures. Considering that, starting from Simon's 1962 relevant paper, hierarchical organization of evolving systems has been the subject of a consistent debate in philosophical literature as well: I then analyse to what extent neoplastic and metastatic phenomena meet the near decomposability feature of hierarchical organized systems proposed by Simon, and the implications of a hierarchical account of complex biological processes. I further discuss how we should understand biological interactions in order to make sense of hierarchical phenomenology of cancer and of historical evolution of its hierarchical explanatory models.

In the forth chapter, I argue that attempts to explain higher–level properties in reductionist–mechanistic terms often fail because they are unable — they are *impassible* — to grasp the explanatory relevance of generalizations. The argument emerges from previous discussions about reductionism in biological sciences. I contend that requirements for reductions must be revised to explain how science works in practice. I consider examples from cancer research to outline a methodological and conceptual framework for our understanding of what a reduction is and how it works.

Next I explore in detail the role that the context argument plays in the structure of biological explanations. I will argue that biological explanations have a peculiar structure, which is context–dependent, and that in particular the acknowledgment of type and token context–dependency contributes greatly to clarify some points of the debate about reductionism in biology. Firstly, I analyse the terms

of the debate on explanatory reductions focused on biological behaviours. Secondly, I investigate what kind of criticism explanatory models meet when committed to explain biological behaviours and some features of their structure. Thirdly, I discuss the epistemological role the context has in explanatory models of cancer, both reductionist and anti–reductionist. I argue that acknowledging the double dimension of context–dependency can prove fruitful to understand the structure of biological explanations and the debate on the shortcomings of reductionism.

In the sixth chapter, I discuss the implications of the analysis of the scientific explanatory accounts of cancer at the beginning of the volume. The rapid evolution of such models, despite advances in cancer research, highlights the increasing effort to account for the complexity of cancer by means of different explanatory models. I then present some elements to show how our understanding of the epistemological issues that emerge in cancer research, requires an integrative approach to the neoplastic process, based on its specific dynamics. Some questions remain open suggesting directions for further research on the philosophical foundations of an integrative approach in biomedical science.

In the last section of the book I sum up the main conclusions and leave open some considerations that are programmatic in character and meant to push the debate toward a deeper understanding of the issues related with the hierarchical account of biological systems' behaviour, with the role that contingency plays in structuring levels of biological organization (ontological level) and in our understanding (epistemological level) of living systems, and with the relevance of the context argument in the explanatory scientific enterprise.

1.3. Acknowledgments

I wish to thank who has been encouraging me to explore these issues in important exchanges, allowing me to visit other universities on various occasions. First of all, I thank Alfredo Marcos and Sylvie Menard who, from a philosphical and scientific point of view respectively, followed my first steps in this field. Marco Buzzoni, Silvia Caianiello, Juan José Sanguineti, in Italy, and Sandra D. Mitchell, Jim Woodward,

Jim Lennox, Ken Schaffner in Pittsburgh, and Jean Gayon in Paris have also largely influenced my research and discussion of these topics. Their inspiring papers and litterature have been of great help to outline the main philosophical questions that constitute the framework of this book. This book also profited from many discussions with my co–fellows at Pitt last year, so that a special thank you goes to Kyle Stanford, Maria Kronfeldner and Collin Rice as well.I am also grateful to the anonymous reviewers of this volume who contributed to its final publication.

Moreover, some studies by Marjorie Grene, David Hull, Francisco Ayala also helped me to broaden my reflection. They do point toward an interesting form of integration between biology and philosophy. This can stem only from the fact that what really drives research are not specific issues in the respective fields of specialization, but their common aspects, the conditions of possibility of both fields. This kind of convergence is what I am interested in and what I find particularly useful to explore in order to understand how science works and why it works. This will improve our awareness of the powerfulness of scientific enterprise and help assess its role in the wider human challenge to understand our world and our place in it.

Finally, I wish to thank my family and friends without whose support this work would not have been possible. The discussions with some of them with different backgrounds — from engineering, to neuroscience, and from ethics to theology — had a great impact on my view of things and on the process of prioritizing the philosophical questions I have tried to address.

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