Rebecca Mertens

THE CONSTRUCTION OF ANALOGY-BASED RESEARCH PROGRAMS

The Lock-and-Key Analogy in 20th Century Biochemistry

[transcript] ScienceStudies

From:

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April 2019, 224 p., pb., ill.
34,99 € (DE), 978-3-8376-4442-5
E-Book:
PDF: 34,99 € (DE), ISBN 978-3-8394-4442-9

When the German chemist Emil Fischer presented his lock-and-key hypothesis in 1899, his analogy to describe the molecular relationship between enzymes and substrates quickly gained vast influence and provided future generations of scientists with a tool to investigate the relation between chemical structure and biological specificity.

Rebecca Mertens explains the appeal of the lock-and-key analogy by its role in model building and in the construction of long-term, cross-generational research programs. She argues that a crucial feature of these research programs, namely ascertaining the continuity of core ideas and concepts, is provided by a certain way of analogy-based modelling.

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Preface

This book has emerged from a PhD project in the philosophy and history of science at the University of Bielefeld. When I started my PhD, I wanted to conduct a study on model transfer and epistemic interrelations between chemistry and the life sciences. In the course of the project, however, my understanding of the object of study and its historical development became much more pluralistic and context-sensitive. Especially the influence that research organization and historical reconstruction have on scientific modeling has transformed the initial project idea immensely. This combination of historical and philosophical perspectives is not an unproblematic one. Diverging methodologies, styles of reasoning, arguments and goals of study have to be accommodated. Although this process was quite a challenge, especially for the philosophical study of models and their role in science, it showed that historically oriented analyses have the potential to unveil essential contexts of scientific reasoning and development. I am grateful that I had the opportunity to conduct my research in an environment that supported me to use such epistemological tensions productively.

I would especially like to thank my advisors, Maria Kronfeldner and Carsten Reinhardt, for their open-mindedness and for all their guidance and valuable feedback throughout this process. I also owe special thanks to Martin Carrier and the philosophy department at the University of Bielefeld for significantly supporting my project and for providing such a productive research environment. I further wish to warmly thank Gregor Lax, Claudia Göbel, David Rengeling, Daniel Brooks, Stephan Kopsieker and Fabian Lausen for reading and discussing many ideas and drafts of this book. I would also like to thank Kenneth C. Waters, Mary Joe Nye, Marie Kaiser, Ulrich Krohs, William Bausman, Jack Powers, Martha Halina, Mads Goddiksen and Dana Mahr for discussing my work and their constructive suggestions.

Furthermore, this book could not have been written without the support of the Rockefeller Archive Center and the Oregon State University's Special Collections & Archive Research Center as well the Archive Center of the California Institute of Technology. I am especially grateful to Lee Hiltzik and Chris Petersen for their great help and for sharing their expertise on the collections. Nor would I have been able to carry out my research without the funding and support of the DAAD and the Bielefeld Young Researchers Fund.

Finally, I would like to say thank you to my family and friends, particularly Gregor Lax and Claudia Göbel, for supporting me intellectually and emotionally in countless ways that allowed me to write and finish this book. I cannot emphasize enough how grateful I am for your companionship.

Rebecca Mertens, Bielefeld,
September 2018

1 The lock-and-key analogy and its influence on 20th century biochemistry

The present study will focus on the "molecularization" of biochemistry – i.e. the establishment of the view that biochemical phenomena can be understood and controlled by investigating the structure of macromolecules and their functions in various kinds of biological processes.[1] This view became a cornerstone for the development of molecular biology and molecular medicine in the 1950s and 60s. Yet, despite the co-dependencies of the process of "molecularization" and the foundation of molecular biology in the second half of the 20th century, one should refrain from reducing the emergence of molecular biology to the successful "molecularization" of certain biological domains, as e.g. biochemistry, neurobiology and genetics.[2] Rather, there are certain events that put the emergence of molecular biology in a unique space, for instance a novel focus on nucleic acids as carriers and determinants of genetic material, the rise of a new metaphoric terminology within the "discourse of information",[3] as well as the devel-

1 Morange (1998): A History of Molecular Biology, Cambridge (Ma), p. 180; Kay (2000): Who wrote the book of life? A History of the Genetic Code, Stanford, p. 45.

2 Morange (1998): A History, p. 1f.; Rheinberger (1995): Kurze Geschichte der Molekularbiologie, in: Preprints of the Max Planck Institute for the History of Science (24), p. 2; Kay (1993): The Molecular Vision of Life, Oxford, p. 211.

3 Kay (2000): Who wrote the Book of Life?, pp. 73-127.

opment of experimental systems and social resources that by the 60s allowed interventions into the process of protein synthesis.[4]

However, some of the episodes, research techniques and concepts of macromolecular research in the early twentieth century are known to have had a considerable impact on the constitution of molecular biology. Especially the physico-chemical study of proteins, as well as the development of new physical instruments and modeling techniques that facilitated the chemical analysis of macromolecules in the early 20th century, such as ultracentrifugation, electrophoresis, and x-ray crystallography, shaped the very idea of a macromolecule, its biological functions and systematic attempts of intervention.[5] Furthermore, the concept of specificity and its use in the field of immunology and protein biochemistry served as a conceptual basis for the combination of chemical and physiological means of understanding natural processes. [6]

Specificity can be called a "loose concept" in that it had a multiplicity of meanings in the late 19th and 20th century and due to its vagueness served as a connection point between different branches of the biochemical and bio-

4 Rheinberger (1995): Kurze Geschichte, pp. 5-8; Kay (1989): Molecular Biology and Pauling's Immunochemistry: A Neglected Dimension, in: History and Philosophy of the Life Sciences (11), p. 211.

5 See Rheinberger and Müller-Wille (2017): The Gene from Genetics to Postgenomics, London and Chicago, p. 60. For the role of ultracentrifugation and electrophoresis in the preceding period of molecular biology, see e.g. Morange (2010): What history tells us XX. Felix Haurowitz (1896-1987) – A difficult journey in the political and scientific upheavals of the 20th century, in: Journal of the Biosciences, 35 (1), pp. 17-20, here p. 17. For the interplay of x-ray cristallography and stereochemical modeling in the analysis of organic molecules in the first half of the 20th century, see James (2014): Modeling the scale of atoms and bonds: The origin of space-filling parameters, in: Klein/Reinhardt (eds.): Objects of chemical inquiry, Sagamore Beach, pp. 281-320, here p. 283.

6 For historical studies on the concept of specificity and its influence on molecular biology, see Kay (2000): Who wrote, p. 41ff., Morange (1998): A History, pp. 12ff. and 15ff, and Mazumdar (1995): Species and Specificity. An interpretation of the history of immunology, Cambridge, Chapter 3 and 9.

medical sciences.[7] The common link of these different understandings of specificity was the assumption that some organisms could selectively react to external influences, e.g. to viruses or bacteria.[8] Conceptions of how this reaction should be characterized, however, differed in crucial respects. Some scientists and physicians, like the group of Robert Koch and Paul Ehrlich, thought of it as a "rigid and complete one-to-one relationship, according to which a given organism, constant as to morphology and physiology, causes a given disease", while others like for instance Carl von Nägli, Hans Buchner, and Karl Landsteiner pointed to the gradual nature of specific processes in the living organism.[9] Despite these differences in interpretation, the concept of specificity was "omnipresent in the biology of the first half of the twentieth century."[10]

As Morange points out, in most contexts of the early 20th century the concept of specificity was interpreted in the light of chemical theories and methods.[11] At the same time, chemistry became more and more 'physicalized' in that major innovations in the chemical sciences were accompanied by the development of instruments and measuring methods, which, in turn, were often created on the basis of theories from the 'new physics'.[12] In the course of these physico-chemical influences, a wide range of biochemists

7 For the notion of "loose concepts" and their role in the history of immunology, see: Löwy (1990): The strength of loose concepts: The case of immunology, in: History of Science, 30 (90), pp. 371-396. Anne Marie Moulin and Barbara Harshav pointed to the vagueness and the multiplicity of meanings that were ascribed to the concept of specificity in the 20th century. See Moulin and Harshav (1988): Text and Context in Biology: In Pursuit of the Chimera, in: Poetics Today, 9 (1), pp. 145-161, here p. 149 and 157.

8 Mazumdar (1995): Species, p. 82.

9 Ibid., p. 80.

10 Morange (1998): A History, p. 13.

11 Ibid.

12 Here, I mainly refer to the influences of thermodynamics on organic chemistry in the late 19th century and quantum physics in the late 1920s and 30s. See Nye (1993): From chemical philosophy to theoretical chemistry: Dynamics of matter and dynamics of disciplines, 1800-1950, Berkeley/London, pp. 227-261; Nye (1999): Before big science: The pursuit of modern chemistry and physics, 1800-1940, Cambridge (Ma), pp. 88ff. and 95ff.

investigated questions concerning the structure of macromolecules, as the latter were known to play fundamental roles in biological processes. The study of macromolecules became an important aspect of biochemical research in the early 20th century, because it promised insights into the connection between chemical structure and biological function. One of the underlying assumptions was that the role of macromolecules in biological processes was determined by the complementary fit of these molecules; in other words, that molecules were selected to bind and thus cause biochemical reactions on the basis of their structural fitting relationship. The origins of this idea have been ascribed to the German chemist Emil Fischer and his introduction of the so-called lock-and-key analogy.[13] In the 1890s Fischer proposed that enzymes and substrates must have complementary structures in order to cause a fermentation reaction and compared the enzyme-substrate relationship with the relation between a lock and a key.[14] As will be shown in the course of this study, the idea that the complementary lock-and-key-like fit between macromolecules could account for almost any biological phenomenon provided a simple and easily deployable, yet vague picture of how knowledge about chemical structure could be used for the exploration and explanation of biological functions.

The lock-and-key analogy re-appeared in several biochemical and biomedical contexts, and soon dominated the study of biomolecules. Frieder W. Lichtenthaler speaks of "a dogma for explaining principal life processes" that has been "induced" by the usage of the lock-and-key analogy in the context of early 20th century biomedicine and embryology.[15] He mentions two scientists in particular who have contributed to the pervasiveness of the analogy, the physician and Nobel Prize laureate Paul Ehrlich and the embryologist Frank R. Lillie. Lichtenthaler claims that both have used the

13 Morange (1998): A history, p.13; Mazumdar (1995): Species, p. 190-196; Kay (1993): A molecular vision, p. 173f.; and Kay (2000): Who wrote the book of life, p. 43.

14 Fischer (1894): Einfluss der Configuration auf die Wirkung der Enzyme I, in: Berichte der Deutschen Chemischen Gesellschaft, Vol. 27 (1894), pp. 2.985-2993. This article was also published in: Fischer (1906): Gesammelte Werke: Untersuchungen über Kohlenhydrate und Fermente II, ed. Max Bergmann, Berlin/Heidelberg, pp. 836-844.

15 Lichtenthaler (1994): Hundert Jahre, p. 2364.

analogy in a very speculative way, which eventually led to "a rather free, uncontrolled profilation of the concept from chemistry into medicine and biology."[16] He points out that the analogy "provided successive generations of scientists with their mental picture of molecular recognition processes, and, thus has shaped to a marked degree the development not only of organic chemistry, but, by extension to basic life processes, that of biology and medicine as well."[17] Scott F. Gilbert and Jason P. Greenberg argue along similar lines. They state that the concept of stereocomplementarity, which dominated biomedicine especially in the second half of the 20th century, was introduced and made accessible to biological and medical research by the usage of the lock-and-key analogy.[18] The authors assert that it "is hard to imagine any phenomenon on the cellular or molecular level which is not governed by lock-and-key stereocomplementarity."[19]

This study will examine the influence of the lock-and-key analogy in the first half of the 20th century by reconstructing its use in three influential research programs: (1) in Emil Fischer's studies on sugar fermentation and enzymatic reactions in the late 19th century, (2) in immunology and immunochemistry from the late 19th century until the 1930s and specifically in the research of Paul Ehrlich and his contemporaries; and finally (3) in research on the physico-chemical basis of macro-molecular specificity at the California Institute of Technology (Caltech) conducted by Linus Pauling and his colleagues from the 1930s to the 1960s. The aim of this case study is to specify how the lock-and-key analogy was used in these research programs and how it contributed to the establishment and manifestation of the concept of molecular complementarity and to the "molecular revolution" in 20th century biochemistry. [20]

16 Ibid., p. 2371.

17 Ibid., p. 2364.

18 Gilbert/Greenberg (1984): Intellectual Traditions, p. 18.

19 Ibid.

20 Rheinberger (1995): Kurze Geschichte, p. 2.

1.1 STATE OF THE LITERATURE

Much of the historical work on the origins of the lock-and-key analogy in late 19th century organic- and biochemistry is conducted by the scientists of these very fields.[21] These studies serve as a valuable source for locating the fields in which the lock-and-key analogy was used and for reconstructing disciplinary thinking. However, one must take into account that they are usually written in the context of disciplinary canonization and thus, among other purposes, serve to establish historical continuity between different episodes of biochemical thinking. What is more, such disciplinary constructions of history often emphasize what in retrospect has become a success story while alternative research strategies and concepts are often disregarded once a dominant view has been established.[22] Thus, while disciplinary accounts of the history of biochemistry and biomedicine underline the pervasive significance of the lock-and-key analogy they do not specify the different usages of the analogy and the varying contexts of scientific practice in which it appeared. Furthermore, they do not provide an answer to the question of why the analogy was appealing for biochemists. In order to understand how it could gain such a broad influence on biochemical research and education under these conditions, and how this impact is to be characterized in socio-epistemological terms, I will turn to the history and philosophy of science.

Historians of science and medicine have conducted studies on the lock-and-key analogy often linked to the history of influential individual scien-

21 See e.g. Hudson (1941): Emil Fischer's Discovery of the Configuration of Glucose, in: Journal of chemical education, pp. 353-357; Hudson (1948): Historical Aspects of Emil Fischer's Fundamental Conventions for Writing Stereo-Formulas in a Plane, in: Advances in Carbohydrate Chemistry, 3, pp. 1-22; Gilbert and Greenberg (1984): Intellectual Traditions in The Life Sciences II. Stereocomplementarity, in: Perspectives in Biology and Medicine, 28 (1), pp. 18-34; Lichtenthaler (1994): Hundert Jahre Schlüssel Schloss Prinzip: Was führte Emil Fischer zu dieser Analogie?, in: Angewandte Chemie, 106, p. 2456-2467; Barnett and Lichtenthaler (2001): A history of research on yeast 3: Emil Fischer, Eduard Buchner and their contemporaries, 1880-1900, in: Yeast, 18, pp. 363-388.

22 See Butterfield (1968 {1931}): The Whig Interpretation of History, London.

tists. In particular, two of the protagonists who are commonly associated with the lock-and-key analogy, Paul Ehrlich and Linus Pauling, and their research strategies have received much attention. Ehrlich (1854-1915) was a German physician and immunologist. He is most known for his side-chain theory of immunity for which he was awarded the Nobel Prize for physiology or medicine (together with Ilya Mechnikov) in 1908 and for the development of "Salvarsarn", the first chemotherapeutic drug against syphilis.[23] In the last 20 years, there has been a growing stock of historical research on Ehrlich's person and on the social infrastructure of the "Ehrlich school", his conceptual and methodological strategies,[24] and on his usage of pictorial

23 Note that chemotherapy was at first developed as a cure for infectious diseases. It was not until the 1940s that chemotherapeutics were used for the treatment of certain types of cancer. See Bruce A. Chabner and Thomas G. Roberts, Jr. (2005): Chemotherapy and the war on cancer, pp. 65-72.

24 Axel Hüntelmann has written a biography about Ehrlich with a particular focus on the social and economic infrastructure of Ehrlich's research groups (Hüntelmann (2011): Paul Ehrlich. Leben, Forschung, Ökonomien, Netzwerke, Göttingen. See as well Hüntelmann (2010): Legend of science: External constructions by the extended family – the biography of Paul Ehrlich, in: InterDisciplines 2, pp. 13-36). Hüntelmann also recently published an article on Ehrlich's role in the arising pharmaceutical industry in the early 20th century (Hüntelmann (2013): Making Salvarsan. Experimental Therapy and the Development and Marketing of Salvarsan at the Interface between Science, Clinic, Industry and Public Health, in: Jean-Paul Gaudillière and Volker Hess (eds.): Ways of Regulating Drugs in the 19th and 20th Centuries, Basingstoke, pp. 43-65). For studies on Ehrlich's conceptual and experimental practice, see Cambrosio, Jacobi and Keating (1996): Ehrlich's "beautiful pictures" and the controversial beginnings of immunological imagery, in: Isis, 84 (4), 662-692; Ead.(2004): Intertextualité et archi-iconicité: le cas des représentations scientifiques de la réaction antigène-anticorps, in: Études de communication, 27, pp. 2-13; Travis (2008): Models for biological research: The theory and practice of Paul Ehrlich, in: History and Philosophy of the life sciences, 30, 79-98; Mazumdar (1995): Species and specificity, Chapter 5, 6, 10 and 11; and Silverstein (2002): Paul Ehrlich's receptor immunology: The magnificent obsession, San Diego. For studies on Ehrlich's connections to the German dyestuff industry, see e.g. Lenoir (1988): A magic bullet: Research for profit and growth of knowledge in Germany around 1900, in:

representations.[25] Ehrlich has been linked to the history of the lock-and-key analogy in the context of his immunological and chemotherapeutic research on receptors, which he characterized as foodstuffs that bind the cell and form an intermediate linkage point between the cell and the antibody.[26] Especially the drawings that Ehrlich had used for the representation of the relationship between antibody and antigen, and also the one between cells and receptors, have often been described as variants or successors of the lock-and-key analogy by Ehrlich's contemporaries as well as by historians of science and medicine.[27] In the existing literature it remains open, however, which exact role the lock-and-key analogy has played in Ehrlich's research.

Linus Pauling (1901-1994) is known to have "confirmed" Fischer's hypothesis on lock-and-key-stereocomplementarity with his template model of antibody-formation, which found broad application in immunology, serology, molecular biology, and embryology in the mid-20th century.[28] He was awarded the Nobel Prize in Chemistry in 1954 and also received the Peace Prize in 1963 for his political commitment against nuclear armament.

Minerva 26 (1), pp. 66-88, and Travis (1989): Science as receptor of technology: Paul Ehrlich and the Synthetic Dye Stuffs Industry, in: Science in Context, 3, pp. 383-408.

25 See Cambrosio et al. (1993): Ehrlich's "beautiful pictures" and the controversial beginnings of immunological imagery, in: Isis, 84 (4), pp. 662-692.

26 Cambrosio et al. (2004): Intertextualité et archi-iconicité, pp. 5ff.; Morange (1998): A history of molecular biology, p. 13; Mazumdar (1995): Species and specificity, pp. 195f., p. 229 and p. 236; Lenoir (1988): A magic bullet, p. 75; Silverstein (2002): Paul Ehrlich's receptor immunology: The magnificent obsession, p. 83; and Lichtenthaler (1994): 100 Years "Schlüssel-Schloss-Prinzip", p. 2371.

27 See Cambrosio et al. (1993): Ehrlich's "Beautiful pictures", p. 682f.; Cambrosio et al. (2004): Intertextualité et archi-iconicité: le cas des représentations scientifiques de la réaction antigène-anticorps, in: Études de communication, 27, pp. 2-13, here p. 5-7; Travis (2008): Models for biological research: The theory and practice of Paul Ehrlich, pp. 88ff.; Morange (2000): A history of molecular biology, p. 13; Mazumdar (2002): Species and specificity, pp. 195f., p. 229 and p. 236.

28 Morange (1998): A History, p. 15.

Especially Pauling's frequent usage of molecular models for problem solving, his interdisciplinary "style", and his role in the institutionalization of molecular biology have been picked up extensively by historians and philosophers of science.[29] Lily Kay analyzes Pauling's contribution to the formation of molecular biology and ascribes it to his leading role at the California Institute of Technology (Caltech) and his close ties to the Rockefeller Foundation.[30] She further points out that Pauling's program on the nature and function of antibodies at Caltech had a huge impact on the "new

29 Pauling's biography and his contributions to the life sciences are well captured by Thomas Hager (1995): Force of nature: The life of Linus Pauling, Michigan; and Id. (1998): Linus Pauling and the chemistry of life, Oxford. Mary Jo Nye has analyzed Pauling's modeling techniques, his usage of "paper tools", as well as his interdisciplinary style of thinking between physics, biology and chemistry (see Nye [2001]: Paper tools and molecular architecture in the chemistry of Linus Pauling, in: Klein [ed.]: Tools and modes of representation in the laboratory sciences, Boston, pp. 117-132; and Nye [2000]: Physical and biological modes of thought in the chemistry of Linus Pauling, in: Studies in the history and philosophy of science, 31, pp. 475-491). Furthermore, Nye has conducted a study on Pauling's style of textbook writing (Nye [2000]: From student to teacher: Linus Pauling and the reformulation of the principles of chemistry in the 1930s, in: Lundgren and Bensaude-Vincent [eds.]: Communicating chemistry: Textbooks and their audiences, 1789-1939, European Studies in Science History and the Arts, 3, pp. 397-414). Recently, Jeremiah James analyzed the stereochemical and physical influences on Pauling's scale-modeling techniques (James [2014]: Modeling the Scale of Atoms and Bonds: The Origins of Space-filling Parameters, in: Klein and Reinhardt [eds.]: Objects of Chemical Inquiry, Sagamore Beach, pp. 281-320). Apart from studies that aim to capture Pauling's epistemic strategies, there has been research on his activities in research management and his interactions with science administrators (see e.g. Kohler [1991]: Partners in science. Foundations and Natural Scientists, 1900-1945, Chicago; and Kay [1989]: Molecular Biology and Pauling's Immunochemistry: A Neglected Dimension, In: History and Philosophy of the Life Sciences, 11 [2], pp. 211-219; Id. [1993]: A molecular vision, and Id. [2000]: Who wrote the book of life).

30 Kay (1989): Molecular Biology and Pauling's Immunochemistry: A Neglected Dimension, in: History and Philosophy of the Life Sciences, 11 (2), pp. 211-219; and Id. (1993): A molecular vision.

biology" for which the natural science division's director of the Rockefeller Foundation, Warren Weaver, coined the term "molecular biology" in 1938.[31] Kay briefly mentions the appearance of Fischer's lock-and-key analogy in a prominent article that Pauling published with the physicist Max Delbrück on the "nature of the intermolecular forces operative in biological processes" in 1940.[32] She states that in this article Pauling and Delbrück "extended Emil Fischer's lock-and-key model beyond enzyme-substrate-relations",[33] but does not analyze the role of Fischer's model or of the lock-and-key analogy in Pauling's other writings or projects. Cambrosio et al. deal with Pauling's visual models and especially with the pictures that he used for his 1940 paper on the chemical basis of antibody formation. These drawings were created in collaboration with the artist Roger Hayward.[34] The authors link Pauling's and Hayward's drawings to Ehrlich's "beautiful pictures" and Fischer's lock-and-key analogy,[35] but just like Kay and Morange, they do not specifically analyze the role of the analogy in Pauling's immunological and molecular program. It thus remains an open question in the historical literature if and how the analogy contributed to Pauling's research practice.

In general, works that relate the successes of the lock-and-key analogy in different fields and periods in the history of biochemistry and biomedicine to each other are lacking. The appearance of lock-and-key models in different branches of biochemistry and biomedicine (such as in olfaction research, embryology, neurology, and immunology) has been noticed by historians,[36] but so far it has not been related to the influencing role of the

31 Kay (1993): A molecular vision, pp. 10-13.

32 Pauling and Delbrück (1940): The nature of the intermolecular forces operative in biological processes, in: Science, 92 (2378), pp. 77-79.

33 Kay (1993): A molecular vision, p. 173.

34 Pauling (1940): A theory of the structure and process of antibody formation, in: Journal of the American Chemical Society, 62 (10), pp. 2643-2657. Cambrosio, Jacobi, and Keating (2005) analyze Pauling's and Hayward's drawings (See Cambrosio et al. (2005): Arguing with images: Pauling's Theory of Antibody formation, in: Representations, 89 (1), pp. 94-130).

35 Cambrosio et al. (2005): Arguing with images, p. 108f.

36 Recently, Carsten Reinhardt has pointed to the influential role of stereochemical ideas on theories of olfaction in the second half of the 20th century. He notes that

analogy in the 20th century. Thus, the history of the lock-and-key analogy and associated models in biochemistry remains rather fragmentary.

In the philosophy of science literature the lock-and-key analogy has been touched upon erratically. Kenneth Schaffner briefly mentions the analogy in the context of his work on reduction and particularly in his study on the operon model in molecular genetics.[37] Anne-Sophie Barwich analyzes receptor models and modeling techniques in olfaction chemistry.[38] She states that a characteristic element of lock-and-key modeling in this field of research was the transferability of molecular models from other disciplinary contexts. Lacking empirical knowledge about the shape of odor receptors, the lock-and-key model was used to make theoretical assumptions based on knowledge about other molecular mechanisms, most prominently from the field of enzymology. In this function the lock-and-key model dominated ol-

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the so-called "stereochemical theory of olfactory perception" was based on a "rather crude 'lock-and-key' schema." In his depiction of the origins of the stereochemical theory in this field, Reinhardt focuses on the chemist John Earnest Amoore who proposed his theory in the early 1950s and thereby "adhered to a tradition of a long chain of similar attempts in chemistry, in the life sciences, and medicine, among the most famous of which was Emil Fischer's lock-and-key model of enzymatic reaction, and Paul Ehrlich's magic bullets." (Reinhardt [2014]: The olfactory object. Towards a history of smell in the 20th century, in: Klein and Reinhardt [eds.]: Objects of Chemical Inquiry, Sagamore Beach, pp. 321-341, here p. 324; 332). Furthermore, lock-and-key models have been located in other branches of neurophysiology and in the field of embryology. Gordon M. Shepherd argues that lock-and-key models played an important role in what he calls the neuroscientific revolution in the mid- and late 1950s (Shepherd [2010]: Creating modern neuroscience: The Revolutionary 1950s, New York, here p. 41f.), and Emily Martin calls attention to the ubiquity of lock-and-key models in 20th century embryology (Martin [1991]: The egg and the sperm: How science has constructed a romance based on stereotypical male-female roles, in: Signs, 16 [3], pp. 485-501, here p. 496).

37 Schaffner (1993): Discovery and Explanation in Biology and Medicine, Chicago, p. 481.

38 Barwich (2013): Making Sense of Smell: Classification and Model Thinking in Olfaction Theory, Doctoral thesis, University of Exeter, p. 155.

faction chemistry throughout the 20th century.[39] The anthropologist Emily Martin also mentions the lock-and-key analogy in her study on male/female attributions to egg and sperm concepts in the history of embryology in the 1980s.[40] Martin argues that the usage of lock-and-key terminology in this context resulted in the suppression of alternative models, especially of those that ascribed an active role to the female egg. According to this view, embryologists adopted the view that molecules of the sperm substance played an active role in the fertilization process, while the female egg molecules had a rather passive role, just like a lock that needs to be activated by the male key.[41] Although experimental results had suggested that the egg could be regarded as an active agent in the fertilization process, lock-and-key terminology played an important part in rendering these new insights invisible, which could have led embryological research into another direction.[42]

The present study shows, in line with Martin's claim, that the lock-and-key analogy indeed supported a reductionist view of biochemical processes, suggesting that biological phenomena could be sufficiently explained by the application of chemical theories and methods.[43] Yet I also argue that concentrating on this repressive role of the analogy reveals just one aspect of its history in biochemistry. In some contexts, this reductionist view left an open space for conceptual exploration and allowed cooperation between chemists and biologists. Focusing on cases of lock-and-key analogy usage in the fields of enzymology (chapter 2), immunology (chapter 3), and molecular biology (chapter 4) in the first half of the 20th century, the present study shows that the analogy also served as an instrument for the inclusion of different biochemical fields. Furthermore, it sheds light on the conditions for the analogy becoming so successful such as to suppress other concepts and models in other biochemical and biomedical contexts in the 20th century.

39 Ibid., p. 169.

40 Martin (1991): The egg and the sperm, p. 496.

41 Ibid., pp. 496ff.

42 Ibid.

43 This becomes especially clear in the context of Linus Pauling's usage of the lock-and-key analogy for the extension of his claims on stereocomplementarity to genetics, embryology and immunochemistry (See the present study, chapter 4).

In sum, although it is commonly assumed that the lock-and-key analogy had a huge influence on biochemical thought and education in the 20th century, it has not been specified yet how this influence is to be characterized. This is in part due to the lack of a long-term analysis of the analogy in its various scientific contexts. From a historical perspective, the present study can be seen as a contribution to such a long-term analysis. It concentrates on the role of the lock-and-key analogy in the making of research programs and reveals new aspects of the mutual interactions between analogy usage, model making and the organization of research in terms of epistemic, social, and political activities. I will follow the development of lock-and-key analogy usage from the 1880s to the 1960s, as in this period the lock-and-key analogy took on a bigger role in the foundation and expansion of a cross-generational research program on the molecular basis of biochemical phenomena. The aim of the historical analysis is thus to specify the various usages of the lock-and-key analogy in different stages and contexts of this program and its contributions to the molecularization of biochemistry and biomedicine in the early and mid-20th century.

1.2 THEORETICAL APPROACH: THE PHILOSOPHICAL ANALYSIS OF ANALOGIES IN SCIENCE

I will analyze the influential role of the lock-and-key analogy on biochemical research on the basis of philosophical theories about the nature and role of analogies and analogical modeling. The philosophical accounts which have hitherto been developed provide an important basis to address the relationship and mutual interrelations between analogy usage and model making in science.

My understanding of what analogies are and how they can be used in science is based on the canonical work of Max Black and Mary Hesse, and on the more recent interpretation of that work by Daniela Bailer-Jones.[44] As

44 Black (1962): Models and Metaphors, Cornell; Hesse (1966): Models and Analogies in Science, Notre Dame. Bailer-Jones discussed the work of Black and Hesse in several articles and in her book on “scientific models in the philosophy of science“ (See Bailer-Jones [2000]: Scientific Models as Metaphors, in: Hal-

Bailer-Jones points out, Black and Hesse both grasp analogies as semantic relations that can be used to make inferences from a familiar phenomenon in order to gain knowledge about a new phenomenon which needs to be investigated.[45] According to the authors, this feature of analogies has proven to be especially fruitful in scientific discovery processes and more precisely for scientific activities involved in concept formation and theory construction.[46] As opposed to other philosophical attempts towards the explanation of knowledge generation processes, Black and Hesse proposed an idea of scientific practice in which scientists are often confronted with situations of uncertainty. A common way to deal with these uncertainties is the use of analogies. Drawing analogies thus enables scientists to gain access to the phenomenon in question in situations in which the phenomenon is not fully understood or not even identified yet.[47] In such situations, it is useful to borrow knowledge and experience from domains to which one has better access, e.g. from other scientific fields or daily-life situations. As means of creativity, analogies are thus considered to be important for scientific knowledge generation.[48] According to Black's interactional view, the creative force of analogies results from an interaction between old and new meanings of an analogy and, more precisely, from the transfer of older meanings to new contexts which "forces the audience to consider the old and the new meaning together."[49]

lyn [ed.]: Metaphor and Analogy in the Sciences, Dordrecht, pp. 181-198;Bailer-Jones [2008]: Models, Metaphors, and Analogies, in: The Blackwell Guide to Philosophy of Science, Chapter 6; Bailer-Jones [2009]: Scientific Models in Philosophy of Science, Pittsburg, pp. 46-80 and 106-126).

45 Bailer-Jones (2008): Models, Metaphors, and Analogies, p. 111ff.

46 Ibid., p. 112.

47 Bailer-Jones (2009): Scientific Models in the Philosophy of Science, Pittsburgh, p. 106.

48 Ibid.

49 Black (1977): More about Metaphor, in: Ortony (ed.): Metaphor and Thought, Cambridge, p. 38.

1.2.1 Metaphors, analogies, and modeling

According to Black the "use of (theoretical) models resembles the use of metaphors in requiring analogical transfer of a vocabulary. Metaphor and model-making reveal new relationships; both are attempts to pour new content into old bottles."[50] However, citing Toulmin, Black mentions that a model, at least if it is a "good" one, will be more than a metaphor, as "it is the suggestiveness, and systematic deployability, that makes a good model something more than a simple metaphor."[51] He further illuminates the relationship of models and metaphors as follows: "Since the basic analogy or root metaphor … normally arises out of common sense, a great deal of development and refinement of a set of categories is required if they are to prove adequate for a hypothesis of unlimited scope."[52] Models are then seen as the elaborations of root metaphors and basic analogies; the goal of this elaboration being, according to Black, the creation of a hypothesis that is generalizable to all possible phenomena.

Daniela Bailer-Jones provides a compelling analysis of Black's interactional view and uses Black's depiction of the process of model-building out of "basic analogies" and "root metaphors" as a basis for her characterization of "metaphorical models".[53] Other than Black, she makes clear that there are also kinds of models which "develop in a different, non-metaphorical manner."[54] She grasps "metaphorical models" as a category of models that comprises analogical models. The basic idea behind this concept of "metaphorical models" is that they are in some ways built on the grounds of metaphorical, non-literal expressions.[55]

In line with Black, Bailer-Jones sketches the process of metaphorical model building as a process of elaboration that begins with the introduction of a metaphor and, via analogical inference between the target and the source domain, ends with a well-defined model.[56] The starting point in

50 Black (1977): More about Metaphor, p. 238f.

51 Ibid., p. 239.

52 Ibid., p. 240.

53 Bailer-Jones (2000): Scientific Models as Metaphors, p. 181; p. 186.

54 Ibid., p. 191.

55 Ibid., p. 192ff.

56 Bailer-Jones (2008): Models, Metaphors, and Analogies, p. 113f.

drawing analogies between two domains then is to be found in the conviction or even the certainty that these domains are similar in some respects. In most cases sacrifices are made, in that the resulting model is to a certain extent speculative; it "is tentative and unconfirmed in parts."[57] However, due to the initially identified similarities between the original and the new domain, the scientists using the metaphorical model would be confident that the study of these yet unconfirmed aspects leads to further clarification and discoveries.[58] In this sense the model can be called "suggestive" and "systematically deployable"; it allows to focus on hypotheses confirmed in another domain and thereby provides a system in which the study of still unknown phenomena (in the new domain) can proceed. A model which is built on the grounds of a metaphor and elaborated by analogical inference has thus "the capacity to encourage further investigative and creative development."[59]

Hence both Black and Bailer-Jones see metaphors and analogies as linked sequences in an elaborative process of modeling; while Black ascribes this process to the construction of "theoretical models",[60] Bailer-Jones prefers to narrow it to the group of "metaphorical models".[61] Yet Bailer-Jones also points to functional differences between metaphors and analogies on the one hand and metaphorical models on the other. The main purpose of models would be to enable access to scientific phenomena, whereas metaphors and analogies mainly function by transferring expressions from one domain to another.[62] In that function, the latter can also be used in order to gain access to phenomena, but it is not a mandatory element of metaphors and analogies to do that. According to Bailer-Jones, models and metaphors share that they are both descriptions,[63] whereas

57 Bailer-Jones (2000): Scientific Models as Metaphors, p. 194.

58 Black (1962): Models and Metaphors, p. 239. See also Bailer-Jones (2000): Scientific Models as Metaphors, p. 195f.

59 Bailer-Jones (2000): Scientific Models as Metaphors, p. 196.

60 Black (1962): Models and Metaphors, p. 239.

61 Bailer-Jones (2000): Scientific Models as Metaphors, p. 181.

62 Bailer-Jones (2008): Models, Metaphors, and Analogies, p. 124.

63 Ibid.

analogies "can exist as formal relationships between phenomena or rather, between the theoretical treatment of phenomena."[64]

Despite their structural differences, metaphors, models, and analogies also share a couple of functions and are often used together. Analogy, for instance "deals with resemblances of attributes, relations or processes in different domains."[65] Uncovering resemblance relations between a source and a target domain is, in turn, a beneficial and sometimes crucial condition for metaphorical transference processes and for modeling phenomena.[66] Mary Morgan also deals with the question of how metaphors, analogies and some kinds of models operate together in knowledge generation processes. In contrast to Bailer-Jones, Morgan speaks of "analogical models" instead of "metaphorical models."[67] Similar to Black and Bailer-Jones, Morgan describes the process of analogical model building as one in which a metaphor provides the basis for analogies and these, in turn, are developed into analogical models.[68] While the initial metaphor, according to Morgan, "suggests much, but tells us little", analogical models are much more concrete than analogies and metaphors; they put more constraints on "the world of the scientist."[69] Thus, the suggestiveness of metaphors provides scientists with the "raw material from which to make substantial analogies" which then allow for analogical model building.[70] But analogies already constrain the model to some extent; developing an analogical model means to use these constraints "as a way to explore the implications of that analogy."[71] Following Marcel Boumans, Morgan also speaks of developing multidimensionality when it comes to the cognitive process of turning meta-

64 Ibid., p. 111. Bailer-Jones is not always clear in her definition of analogies as relationships, as some passages suggest that analogies only "point to" or "deal with" resemblance relations. See ibid., pp. 110 and 124.

65 Ibid.

66 Ibid.

67 Morgan (2012): The World in the Model: How Economists Work and Think, Cambridge, p. 172f.

68 Ibid., p. 174.

69 Ibid., p. 173f.

70 Ibid.

71 Ibid.

phors into analogical models.[72] A metaphor is thus "something one-dimensional" – in order to arrive at an analogical model from the basis of a metaphor, "a scientist needs to develop its various possibilities or dimensions into a model", in other words, she needs to create a world out of the metaphor.[73]

1.2.2 Analogical modeling: Contexts and practices

The role of analogies in science has been an important topic in the context of the debate on the nature of models and their functions in scientific practice.[74] Especially when it comes to the creative processes that are involved in scientific modeling, analogies have been described as "archetypes", or "ideal types" for model building.[75] Amongst others, Nancy Nersessian has studied analogy use as part of model building processes.[76] In the tradition of Black and Hesse, Nersessian claims that analogies are crucial cognitive instruments for scientific productivity and innovation. One of her larger projects is to explain how reasoning by analogy works from the perspective of the cognitive sciences. According to Nersessian, analogical reasoning can best be grasped as a "model-based" strategy, meaning that it is first and foremost a means of cognitive model making.[77] This claim challenges a

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72 Ibid., p. 174. Here, Morgan is referring to Boumans (2005): How Economists Model the World to Numbers, London.

73 Ibid., p. 174.

74 Frigg and Hartmann (2012): Models in Science, in: The Stanford Encyclopedia of Philosophy: http://plato.stanford.edu/archives/fall2012/entries/models-science, 10/08/2015, 14:00.

75 See e.g. Black (1962): Models and Metaphors, pp. 219-243, and Morgan (2012): A World in the Model, p. 141.

76 Nersessian examines strategies of analogy-based modeling in several of her monographs and articles, such as, Nersessian et al. (1999): Model-based reasoning in scientific discovery, Dordrecht; Id. (1999): Model-based reasoning in conceptual change, in: Magnani, Nersessian and Thagard (eds.): Model-based reasoning in scientific discovery, New York; Id. (2002): Model-based reasoning: Science, Technology and Values, Dordrecht, and Id. (2008): Creating Scientific Concepts, Cambridge (Ma).

77 Nersessian (1999): Model-based reasoning in conceptual change, p. 20.

view which has dominated the philosophical treatment of analogies up to the late 20th century, namely that the major goal of analogical reasoning in science is the construction of arguments.[78] The logical empiricists, and most famously Rudolf Carnap, claimed that analogical arguments are less powerful than inductive arguments.[79] Nersessian argues that the advocates of this claim have failed in locating the role of analogies in science. Analogies play important roles for scientific reasoning, just not so much for argumentative reasoning. Rather "the heart of analogy is employing generic abstraction in the service of model construction, manipulation and evaluation."[80] Hence, if one wanted to understand the scientific role of analogies, one has to analyze strategies of "model-based reasoning."[81] Nersessian distinguishes three types of model-based reasoning: "Analogical reasoning", "visual reasoning" and "thought experimenting". Characteristic for all these types of reasoning is that they lead to a change of perspective(s), which is in turn crucial for scientific creativity and progress. Referring to Max Black's interactional view, she states that analogical modeling "might help us to notice what otherwise would be overlooked, to shift the relative emphasis attached to details - in short, to see new connections."[82]

Nersessian's studies, which make use of empirical knowledge from the cognitive sciences as well as from historical case studies, contribute significantly to the specification of cognitive practices and the role of analogies in scientific understanding and learning. However, what is missing in this line of research is the appreciation of the various contexts of scientific practice.[83] In addition to the characterization of the cognitive process of model-

78 Ibid.

79 Ibid.

80 Ibid.

81 Nersessian (2008): Creating Scientific Concepts, p. 12.

82 Ibid., pp. 180f.

83 More recently, Nersessian concentrates on social aspects of scientific problem solving. Particularly interesting in this context is her work with McLeod on interdisciplinary problem solving and identity formation. However, the authors stay in the realm of the cognitive sciences and social psychology and do not adopt a sociological perspective. See McLeod/Nersessian (2017): Interdisciplinary problem solving. Emerging models in Integrative Systems Biology, in: European Journal of Philosophy of Science (fc, in press). See also Osbeck/

ing by means of analogy, my study provides an answer to the question in which contexts of scientific practice and for which purposes modeling by means of an analogy becomes important. Here, I specify three of these contexts: (1) Epistemic problem solving, (2) the historical reception and retrospective canonization of scientific fields and models, and (3) research management. I propose these three categories as a first orientation for the localization of different contexts in which modeling by analogy influences the course of research programs. I am positive that there are more of these contexts which could be uncovered through other case studies. However, the point that I make by introducing these three categories is that the philosophical literature on analogical modeling has focused almost exclusively on the influencing role of analogies on models in the context of epistemic problem solving. For the case of the lock-and-key analogy, it can, however, be shown that the analogy's impact on modeling is relatively small in this context, if compared to its influence on retrospective communication and research management. Hence, if the goal is to find out more about the role of analogy usage in long-term modeling processes and research development, the consideration of these other contexts of scientific practice is vital.

Another emphasis of the case study presented here lies on the power of reconstructive activities in the making of research programs, and especially on the influential role of model reconstruction processes in this respect. As will be shown in the course of the study, there are models, which seem to be based on a particular analogy, but are in fact retrospectively reconstructed in terms of that analogy. It is important to note, though, that the analogy still plays a crucial role in these cases. In fact, I argue that – if used for such reconstruction processes – analogies can influence the course of a research program even stronger. This is due to the multiple contexts of scientific practice in which model reconstruction by analogy takes place. Other than model construction, which is usually taken to be an epistemic, inner-scientific activity, model reconstruction often exceeds the epistemic context of scientific practice and is also used for non-epistemic purposes.

Nersessian (2017): Epistemic Identities in Interdisciplinary Science, in: Perspectives on Science 25 (fc).

1.3 METHODOLOGY

I analyze lock-and-key analogy usage in the context of research programs. In the philosophical discussion, the term 'research program' goes back to Imre Lakatos, who used it to support his claim that scientific development is governed by rationalizable, methodological rules.[84]

According to Lakatos, every research program possesses a "hard core" and a set of "auxiliary hypotheses" that serve to protect this core.[85] Research programs can further be characterized by two different sets of methodological rules which orient the program towards a certain direction, the "negative" and the "positive heuristic".[86] While the negative heuristic "specifies the 'hard core' of the programme" and indicates which research paths are *not* to be followed, the positive heuristic on the other hand suggests how to proceed with research, consisting of "a partially articulated set of suggestions or hints on how to change, develop" and "modify, sophisticate, the refutable protective belt."[87]

What I take from Lakatos' conception of research programs is the idea of the importance of programmatic continuity in science; more specifically the idea that scientists aim at rescuing an established research program rather than provoking revolutions and thus use strategies which lead to that continuity.[88] Considering programmatic continuity, Lakatos' thoughts on research programs come very close to Kuhn's characterization of "normal science" as a preservation and enlargement project of knowledge, which is

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84 Carrier (2002): Explaining Scientific Progress: Lakatos' Methodological Account of Kuhnian Patterns of Theory Change, in: Kampis et al. (eds.): Appraising Lakatos: Mathematics, Methodology, and the Man, Dordrecht, pp. 53-71, here p. 10.

85 Lakatos (1970): Falsification and the Methodology of Scientific Research Programmes, in: Lakatos/Musgrave (Eds.): Criticism and the Growth of Knowledge (1970), p. 191.

86 Ibid., p. 192.

87 Ibid., p. 193.

88 Lakatos (1970): The Methodology of Scientific Research Programmes, in: Worral/Currie (eds.): Philosophical Papers, Vol. 1, p. 47.

already accepted by a respective community.[89] In this respect, Lakatos and Kuhn mainly differ in their estimation of how long the periods of continuity last and in their normative claims concerning the value of continuity for research development. While Kuhn views discontinuity and revolutionary episodes as a characteristic element of scientific projects, Lakatos emphasizes the long-term nature of successful research programs and the possibility to make scientific progress within these programs. According to Lakatos, such programs can avoid revolutions due to their inner structure. He claims that objections, anomalies or counterexamples are already expected in the beginning of research programs and that the positive heuristic is the strategy that predicts (and maybe even produces) anomalies and deals with them.[90] He further states that the amount of sophistication of such a theoretical design lies in the formulation of rules that allow for an unproblematic replacement of the initial conditions for the research program. Hence, the more sophisticated a scientific program is conceptualized and designed in the beginning; the more successful it will be in the long run.[91] This is where my account of research programs substantially differs from Lakatos'. In my understanding, continuity is established in the course of a program and is not a result of careful theoretical examination in advance and the successful application of methodological rules. Here, I follow Alan Musgrave who criticizes Lakatos for his emphasis on the conception of positive heuristics as a constitutive and empirical-autonomous preliminary for research programs.[92] As Musgrave emphasizes, Lakatos uses his considerations regarding positive heuristics as a supporting claim for the autonomy of theory

89 Kuhn (1970 {1962}): The Structure of Scientific Revolutions, Chicago, Chapter 2, here p. 10. For a better understanding of Kuhn's conception of normal science and the similarities between Kuhn and Lakatos, see Carrier (2002): Explaining Scientific Progress: Lakatos' Methodological Account of Kuhnian Patterns of Theory Change.

90 Lakatos (1970): The Methodology, p. 49f.

91 Ibid., p. 50f.

92 Other philosophers followed Musgrave in his critique on Lakatos' conception of the positive heuristics. In the 1970s a critical discussion emerged concerning whether such a heuristic can really foresee and avoid anomalies of a research program. Philosophers who have participated in this debate are e.g. Elie Zahar (1973), John Worrall (1978), Alan Chalmers (1979), and Martin Carrier (1984).

over experimental facts.[93] "It is just not true", Musgrave states, "that refutations of any specific variant of a research programme can be produced and digested by a clearly spelled out heuristic."[94] Nevertheless, he gives credit to Lakatos' concept of positive heuristics in terms of a "plan for solving [...] mathematical problem[s]."[95] Hence, "heuristic hints [...] can be found, to a greater or lesser degree, in all research programs, and [...] their importance cannot be underestimated."[96] As useful as those "heuristic hints" are, Musgrave mentions, they do not usually develop independently from the course of the respective research program (as constitutive preliminary of this research program).[97] However, the autonomy of theory over experiment is just one of the critical aspects of Lakatos' conception of research programs. The crucial point which goes beyond Musgrave's critique is that continuity within a research program is not only established by the adjustment of hypotheses and models in reaction to empirical anomalies. Rather, continuity in the long run is also a product of the re-interpretation of scientific facts and discovery processes, which in turn is a crucial part of the inner-scientific construction of history and education. This aspect of scientific development has already been mentioned by Kuhn in "The Structure of Scientific Revolutions."[98] In the context of his thoughts on the tendency of scientists to render scientific revolutions "invisible", Kuhn emphasizes that

> "scientists and laymen take much of their image of creative scientific activity from an authoritative source that systematically disguises – partly for important functional reasons – the existence and significance of scientific revolutions. [...] As the source of authority, I have in mind principally textbooks of science together with both the popularizations and the philosophical works modeled on them. All three of these categories [...] have one thing in common. They address themselves to an already ar-

93 Musgrave (1976): Method or Madness? Can the methodology of research programmes be rescued from epistemological anarchism, in: Id. (ed.): Essays in Memory of Imre Lakatos, Boston Studies in the Philosophy of Science, 39, pp. 457-491, here p. 468.

94 Musgrave (1976): Method or Madness, p. 470.

95 Ibid.

96 Ibid.

97 Ibid., p. 471.

98 Kuhn (1970 {1962}): The Structure of Scientific Revolutions, Chicago.

ticulated body of problems, data, and theory, most often to the particular set of paradigms to which the scientific community is committed at the time they are written. [...] The result is a persistent tendency to make the history of science look linear or cumulative, a tendency that even affects scientists looking back at their own research."[99]

The study presented here takes these re-interpretation processes into account and views them as crucial episodes in the establishment of programmatic continuity. I claim that the retrospective interpretation of scientific discoveries becomes especially important in transition phases in which the scope of a research program is expanded to other domains of research. As will be shown in the course of the study, analogies play an important role in these phases, as they can be used to create a linkage point between different research programs. This linkage, following the thesis, is provided by the re-interpretation and unification of models by means of analogy usage in the context of retrospective science communication.

I distinguish between two different types of research programs: Individual or single research programs which are, as the term implies, bound to the interests, questions and problems raised by individual scientists (e.g. "Fischer's stereochemical program on fermentation"), and long-term, cross-generational programs. It is important to note that individual programs can of course have many followers and that knowledge generation in these programs can certainly be seen as a social group activity. However, often these programs are associated with a founder, a scientist who has coined certain terms or who has proposed a theory or method that soon required canonical status within a scientific community. Cross-generational long-term programs, on the other hand, often have more than one founder; usually each generation ascribes groundbreaking changes to a prominent key figure (not uncommonly Nobel Laureates).[100]

For this study I looked at three individual research programs in which the lock-and-key analogy was used. Two of these research programs (Fischer's and Ehrlich's programs from the late 1880s to the early 20th century) were part of the same generation, but belong to different scientific

99 Ibid, pp. 136ff.

100 See also Kuhn (1970 {1962}): The Structure of Scientific Revolutions, p. 139f.

fields. The third program (Pauling and his co-workers at Caltech) started forty years later than the other two. There is a synchronic and a diachronic dimension of my analysis of the lock-and-key analogy. Looking at the synchronic dimension, I characterize the role of the analogy in the previously named individual programs.[101] The diachronic dimension, seen in terms of cross-generational change from Fischer through Ehrlich and Pauling to other biochemists at Caltech, allows us to see connections and differences in the previously analyzed individual research programs. Furthermore, it elucidates how scientists make references to previous programs and which role these references play in agenda setting and realization.

1.4 OUTLINE

The present study is divided into theoretical and empirical chapters. Chapter 2-4 represent cases of lock-and-key analogy usage in different, but sometimes related biochemical and biomedical research programs from the late 19th to the mid-20th century. Chapter 5 and 6 then aim to reflect and interpret the previous historical findings.

In Chapter 2, I analyze the origins of the lock-and-key analogy in enzymatic chemistry in the late 19th century and its role for the beginnings of the biochemical study of macromolecules. The focus is on the research of Emil Fischer who introduced the lock-and-key analogy in 1894 in the context of his studies on the stereochemical foundation of fermentation. I will show how Fischer used the analogy to apply the stereochemical approach that he had developed earlier in his studies on sugar classification to fermentation research. I will argue that this transfer of molecular geometry concepts from one domain of research (research on the structure of sugars) to another (research on the chemical relationship between enzymes and sugars during the process of fermentation) was facilitated by the usage of the lock-and-key analogy in a heuristic way. Specifically, I will show how

101 One might object that this is also a diachronic perspective, as these programs of individuals or locally connected groups also undergo change. This is of course true. However, these changes are smaller and different with respect to analogy usage than the ones that become visible in the cross-generational dimension.

Fischer, with the help of the analogy, applied three heuristic strategies in his research practice: incompleteness, abstraction and simplification. I argue that in this way, a new research program on the stereochemical mechanism of fermentation was established. In addition, Fischer also drew on the analogy to lay out (and thus justify) the potential of his studies envisioning the future of biochemical research as the investigation of biochemical problems in terms of lock-and-key-like macromolecular fit.

Chapter 3 deals with the use of the lock-and-key analogy in immunology and chemotherapeutic research at the end of the 19^{th} and the beginning of the 20^{th} century. Focusing on the work of Paul Ehrlich, I will examine the role of the analogy for the application of macromolecular analysis in fields of biomedicine. Ehrlich is known for his application and introduction of the lock-and-key analogy to the field of immunology and chemotherapy.[102] However, I will argue that in effect it was the historical reconstruction of Ehrlich's work by his successors that subsumed Ehrlich's ideas under the lock-and-key model of antibody-antigen reactions. I will therefore examine the construction of Ehrlich's receptor model in toxicology and immunology, which was formulated on the basis of the side chain theory of the formation of specific antibodies. Throughout this work and the subsequent transfer of concepts to the study of chemotherapeutic agents for the treatment of infectious diseases, Ehrlich did not use lock-and-key terminology but applied his own toxicological heuristics and terms. I will show that from around 1900 until the 1930s, in several phases of the reception of Ehrlich's work by successors in the fields of immunology and medicine as well as in popularization contexts, the receptor model was re-constructed as the lock-and-key model of antibody-antigen reactions.

These developments will be taken up in Chapter 4, which investigates the role of the lock-and-key analogy in the founding periods of immuno-

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102 See Cambrosio et al. (1996): Ehrlich's "Beautiful pictures", p. 682f.; Cambrosio et al. (2004): Intertextualité et archi-iconicité, p. 5-7; Travis (2008): Models for biological research, pp. 88ff.; Morange (1998): A history, p. 13; Mazumdar (2002): Species, pp. 195f., p. 229 and p. 236; Lenoir (1988): A magic bullet: Research for profit and growth of knowledge in Germany around 1900, in: Minerva 26 (1), pp. 66-88, here p. 75; Silverstein (2002): Paul Ehrlich's receptor immunology: The magnificent obsession, p. 83; and Lichtenthaler (1994): 100 Years "Schlüssel-Schloss-Prinzip", p. 2371.

chemistry and molecular biology from the 1920s to the 1960s in the United States. In the contexts under consideration, lock-and-key-like relations were generalized for the study of biologically important processes, such as fertilization, embryological development and genetic inheritance. At first, I will take a look at how immunochemists in the 1920s and 30s referred to the lock-and-key analogy in order to establish a continuum between Ehrlich's model of immunological processes and new theories of antibody formation, such as the lattice-, or framework theories. On this basis, the chemist Linus Pauling formulated the template model of antibody formation, relying on the idea of protein folding, which emerged as one of the central dogmas in molecular biology before the conceptual shift to the genetic code in the mid-1950s.[103] Pauling's template model was built on the idea of a lock-and-key-like fit between antibody and antigen. I will take a look at how this model explained the process of antibody formation as a reconfiguration that was needed to create a fit with the antigen. Furthermore, it will be shown that Pauling extrapolated from his antibody research and used the template model to ask how proteins in general are spatially transformed in order to perform different functions in the living organism. I will examine how Pauling communicated this generalized vision for the emerging cross-disciplinary field of molecular biology and how specialists from contributing disciplines, such as embryology, genetics and cell biology, took up his physico-chemical program around the study of proteins. The crucial point here is that this process of appropriation, and interdisciplinary cooperation was once more facilitated by using the lock-and-key analogy. The latter provided a fertile link between various research agendas creating major interdisciplinary research projects in the 1940s and 50s. For this context, I will analyze the use of the analogy in two exemplary cases in order to locate the role of the analogy in joint research proposals as well as on the level of research practice by the Caltech group.

After dealing with the role of the lock-and-key analogy case by case, chapters 5 and 6 will take an overarching perspective on what happened along the way from Fischer's introduction of the lock-and-key analogy in the 1890s to its usage in the context of Caltech's specificity program in the 1940s and 50s. Chapter 5 will summarize and interpret the findings from

103 Kay (2000): Who wrote the book of life, p. 51ff.; Morange (1998): A History, p. 15.

the case studies on the use of the analogy in the hitherto considered biochemical contexts in the first half of the 20th century. The main thesis that will be specified and defended in this chapter is that the lock-and-key analogy helped to establish a long-term, cross-disciplinary research program on the physico-chemical basis of macromolecular interactions. This long-term program, I argue, was a result of linking the individual research programs of Fischer, Ehrlich, and Pauling to each other by means of lock-and-key analogy usage. Chapter 6 will then elaborate on the idea that analogies can be "anchors" in the expansion of research programs.[104] Here, I will argue that analogies differ from other non-metaphorical anchors (e.g. mathematical idealizations) in that they play a crucial role in the reception and in the communication of scientific achievements to non-scientific and cross-disciplinary scientific audiences. This role of the analogy in different contexts of science (including science popularization and administration), I claim, makes a substantial difference when it comes to the expansion of a research program and to the impact of that program on other scientists and fields.

1.5 SOURCES

I have looked at both primary and secondary sources in order to specify the role of the lock-and-key analogy in the considered programs. The primary sources included published material, such as research articles, speeches, scientific monographs, popularizing science books (fictional and non-fictional), as well as archival material, i.e. laboratory notebooks, letters, research proposals and reports.

Chapters 3 and 4 are in part based on archival material, whereas chapter 2 relies on Fischer's published work and more specifically on his articles on sugar synthesis and fermentation, most of which were published in the *Reports of the German Chemical Society (Berichte der Deutschen Chemischen Gesellschaft)* between 1888 and 1907. For my analysis of Ehrlich's

104 Christopher Pincock introduced this terminology, but has only used it for the class of mathematical idealizations and models. See Pincock (2012): Mathematical models of biological patterns: Lessons from Hamilton's selfish herd, in: Biology & Philosophy, 27(4), pp. 481-496.

immunological and chemotherapeutic program (chapter 3) and the role of the lock-and-key analogy in Linus Pauling's research program at Caltech (chapter 4), I visited several archives including the Rockefeller Archive Center (RAC), the Special Collections and Archive Research Center of the Oregon State University (OSU), and the Archives of the California Institute of Technology (Caltech Archives). In order to conduct the analysis of lock-and-key analogy usage in Ehrlich's program, I made use of the *Ehrlich papers* (RAC), in particular of *Ehrlich's notebooks* and the *Ehrlich Blöcke*, a collection of 1500 cards including notes that Ehrlich had written for himself, his secretary or for his assistants. These notes allowed insights into Ehrlich's style of reasoning and administration; they were especially informative with respect to the transfer of ideas and the role of theory-laden terminology in the communication of experimental results and orders. Another source which became important in the study of Ehrlich's reception and the re-interpretation of Ehrlich's ideas in terms of the lock-and-key analogy was the collection of newspaper clippings and articles at the RAC. This collection included articles from weekly local newspapers (e.g. *Allgemeine Frankfurter Zeitung*, *Die Frankfurter Nachrichten*, *Die Illustrierte Frankfurter Woche*, *Die Wiener Freie Presse*) as well as journal articles, mostly from medical journals (e.g. *Die Deutsche Medizinische Wochenschau*, *Wiener klinische Wochenschrift*, and *Die Naturwissenschaften).*

Moreover, I made use of the *Ava Helen and Linus Pauling Papers* at the OSU Archives in order to specify the role of the lock-and-key analogy in Pauling's interactions with other scientists, in his efforts of science popularization and interdisciplinary education, as well as in his creative processes (chapter 4). In order to get insight into Pauling's administrative activities at Caltech, and his close connections to the Rockefeller Foundation, I looked at files on the *Division of Chemistry and Biology at Caltech* as well as on *Pauling's research on immunology*, all of which were located at the RAC. In particular, I have looked through the correspondence between Pauling and Warren Weaver, the director of the Natural Science Department of the Rockefeller Foundation (RF) from 1932 to 1955, at the *Warren Weaver Diaries*, as well as grant proposals and reports from Caltech to the RF. Also, the collection of the Caltech Archives related to the administrative and scientific work conducted by individual scientists and groups in Caltech's chemistry and biology departments was of special importance for chapter 4.