Brigitte Lohff   Jochen Schaefer

Cardio-physiology Challenging Empirical Philosophy

Three Essays

In collaboration with Johann Kuhtz-Buschbeck
Bernhard Thalheim Ekkehart Rumberger

IIfTC

Reha-Kliniken Küppelsmühle, Bad Orb[1]

These three essays are dedicated to the co-founders of the International Institute for Theoretical Cardiology Daniel Burkhoff, Michael R. Franz and David T. Yue as well as Ulrich Freund. It is also dedicated to the students of IIfTC, friends, and collaborators.

We remember with gratitude The Johns Hopkins School of Medicine, Baltimore, and its evolving Division of Cardiology in the 1960s under the guidance of Richard S. Ross.

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[1] Photo of the Reha-Klinken Küppelsmühle was kindly provided by Anne-Kathrin Dieulangard, Haitz-Gelnhausen // Cover Logo: International Institute for Theoretical Cardiology [IIfTC], https://www.iiftc.de

The authors

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Jochen Schaefer, born 1930, studied medicine in Freiburg/Brsg. and doctorate in 1955; subsequently postdoc in pathology and pharmacology (FU Berlin).1960-1962 training at the evolving Division of Cardiology, Johns Hopkins Hospital, Baltimore, under Richard S. Ross; 1962 residency at I. Med. University Hospital, Kiel, to establish a division of modern cardiology; 1966 habilitation; 1970 Professor and Head of Special Cardiology at the CAU; 1985 leaving the service of the state of Schleswig-Holstein. 1981 to 1996 chief physician of the rehabilitation clinics-Küppelsmühle Bad Orb - Scientific interests: the interdisciplinarity of medicine and philosophy.

Johann P. Kuhtz-Buschbeck, born 1961, studied medicine from 1982 to 1989 in Kiel. He received his doctorate in the field of Pediatric Cardiology, where he worked as an assistant until 1991. Since then he has worked at the Institute of Physiology of CAU Kiel and as a postdoc guest researcher at the Karolinska Institute in Stockholm. His main research interest has been sensorimotor control (habilitation on locomotion in 2000), and he is also interested in the history of physiology.

Bernhard Thalheim, born 1952, studied mathematics at the TU Dresden. He received his PhD in discrete mathematics from the Lomonosov University, Moscow, in 1979. His habilitation followed in 1985 at the Technical University of Dresden. This was followed by professorships in Dresden Kuwait, Rostock and Cottbus before he took over the Chair of Information Systems Technology at CAU Kiel from 2003 to 2020. Visiting professorships led him for example to the University of Klagenfurt in Austria, to the Hungarian Academy of Sciences and to Massey University in New Zealand. His research area is the theory of conceptual modeling.

Ekkehart Rumberger, born 1939 in Chemnitz/Saxonia, received the PhD in Internal Medicine in 1971; 1977–2003 Professor and Director of the Department of Physiology at the Faculty of Medicine at the University Hamburg [Eppendorf]. Main research interests: The cardiovascular system and the Force-Interval Relationship (FIR). He retired in 2004.

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PREFACE

The book we are now presenting, *Cardio-physiology Challenging Empirical Philosophy*, is published forty years after the founding symposium of the International Institute for Theoretical Cardiology in April 1982. Its cardio-physiological origins can be traced back to 1960. During these more than sixty years, many friends and scientists have actively accompanied its projects and, thus, contributed to interest-ing insights and suggestions, which have also become the subject of our essays. Given the complexity of the broad subject matter, we ask the reader to forgive occasional redundancies and repetitions.

We would like to thank them all for their contribution. In this acknowledgement, we want to make special mention of the participants at our Thursday Round Table, which has existed for more than twenty-five years, and their lively discussions between: Wolfgang Deppert, Anne-Kathrin Dieulangard, Hans-Carl Jongebloed, Claus Köhnlein, Björn Kralemann, Johann Kuhtz-Buschbeck, Claas Lattmann, Brigitte Lohff, Siegfried Munz, Klaus-Jürgen Nordmann, Brigitte Schaefer, Jochen Schaefer, Tim Schaefer, Bernhard Thalheim, Nicolaus Wilder.

The truly interdisciplinary diversity of opinions, views and works represented by them was and is an essential stimulant of the IIfTC.

1. Introductory remarks

With this volume of essays, we want to create an opportunity for dialogue between different disciplines by taking a closer look at three cardio-physiological examples. In the essays presented, we will look at the exploration of different cardiological topics from the 20th century, all of which have contributed to a better understanding of certain aspects of cardiac activity. Not only do these insights provide a more complete picture of the phenomena of cardiac activity, but it is also within this context that we can look for and into the patterns of regularities which govern living organisms. Our goal is to stimulate a dialogue on the philosophy of science in the spirit of Reichenbach. For Hans Reichenbach, as well as for László Kocsis and Adam Tamas Tuboly, the continuity between science and philosophy was bidirectional.[2] Philosophy had to learn from the sciences and proceed from them, but still had its own role to play: "But a philosophy that draws its facts from science, that is able to shed light on the mysteries of scientific research and to clarify for the researcher, on the basis of his own achievements, the aims and methods of his work, can only be a welcome ally on the path to knowledge." [3]

A few more reflections on the history of science introduce these essays to remind the reader that from the middle of the 19th century onwards, scientific experimentation became the guiding principle of medical biological research. The rapid increase in knowledge through experimentation required the integration of these new findings into necessarily changing views of what constitutes a healthy and sick human being.

1.1. The challenging of empirical philosophy by empirical physiology

It is an unwritten rule in biological-medical research that the question of what is the meaning of a physiological function should not be asked, rather only the "how" of the physiological mechanism should be answered. Since the middle of the 19th century, excluding the “why”-question was seen as a necessary prerequisite for expanding the stock of validated knowledge in physiology, which at that time was still in its infancy. As the field of physiology matured, a discussion was raised on how to make it comparable to the other natural sciences. Within this discussion, a critical debate was ignited surrounding the appropriateness of “how” vs. “why” questions within biomedical research. The physiologist and anatomist Johannes Müller (1801–1858), who became one of the most important teachers of physiologists from the middle of the 19th century, played a central role in this debate. His *Handbuch der Physiologie des Menschen und der Thiere*[4] (Handbook of the Physiology of Man and Animals) and his reports on the progress of anatomy and physiology in *Müller's Archiv der Physiologie und wissenschaftlichen Medizin*[5] became integral research-guiding writings for the anatomists, physiologists, and zoologists who followed him. As early as 1827, in his *Grundriß der Vorlesungen über die Physiologie* (Basic Lectures on Physiology), Müller formulated the claim that physiological research should be carried out according to scientific criteria to be recognized as natural science: "Such a work, if it is to be complete, [must] indicate the scope of this science in consistently equal and complete treatment and at the same time the achievements to date as well as those still possible and necessary to be demanded."[6] However, research should not stop at the description of individual observations; rather it should place them in a superordinate context. In Müller's view, the recognition of the universal[7] can only succeed if physiological and philosophical thinking is combined.[8] To recognize a general principle or general rules from individual facts, Müller requires various categories of thought: "The teaching of physiology [...] cannot do without the logic of the essential or of speculation such as dialectics [...] And all material that has become empirically known can, if it is to be understood, be considered in that threefold way of thinking."[9]

A "logical connection of empirical facts" is not sufficient in and of itself, but „true physiology thinks life into right experience; through experience as well as through philosophical thinking, physiology comes about, to itself."[10] [Only when] the different categories of thought mentioned above have been applied to all empirically known substances "does science come into being"[11]. This thought process was summarized by Müller in the guiding principle: "The physiologist experiences nature so that he thinks it."[12] The classification of individual physiological phenomena into a concept of the "Aliveness of the organism" – i.e. in our terminology, the question of meaning – is necessary from Müller's point of view for the following reason: Speculative thinking allows us to understand the concepts or functions developed in reflection, in which "the becoming, the procedure of the general into the particular"[13] contained therein are to be grasped.

Müller, however, thought that physiologists in his era still had to abstain from utilizing a speculative system on the 'physics of life': "Indeed, empirical physiology does not solve the final questions about life, but neither does philosophy solve them in such a way that we could make use of this solution in empirical science".[14] Indeed, one cannot expect metaphysical theories from empirical science, but rather proof of whether a theory is true or false. But according to Müller, it does not make sense if the physiologist, out of "anxiety and caution", merely enumerates the facts rather than dare to say more about the knowledge gained."[15] However, the classification into a superordinate system only makes sense if the assumptions contained therein agree with the empirical observations.[16]

Müller was a very influential scientist and built up an important school of anatomists and physiologists in the 19th century.[17] The researchers of the following generation adhered to the demand to produce empirically proven facts, abstaining from interpretation and reflection on the question of how individual pieces of knowledge can be classified in a system of organic life. The overwhelming success of physiology from the 1840s onwards was continued by the prominent school of Carl Ludwig (1816–1895) in Vienna and Leipzig.[18] Researchers from the second half of the 19th century concentrated their creative and systematic experiments primarily on the production of proven facts. This focus further relegated the classification of facts into a superordinate context of meaning into the background. The limitation of empirical and experimentally verifiable connections or mechanisms led to an explosive expansion of new insights into the biological processes of an organism. At the same time, this development was accompanied by an abundance of new measuring and recording methods that helped verify the knowledge gained through experiments.

This "quasi-ban" of examining the meaning or purpose of a physiological function continues to have an effect to this day. As it turns out, limiting physiological thought to the "how" question has proven to be successful. However, it seems to have been forgotten that Johannes Müller did not exclude the question of meaning, but rather had relegated it to the field of philosophical reflection. With the increasing number of individual observations, an epistemological discussion – as demanded by Ernst Cassirer (1874–1945) – was also lost in addressing this question to "transform the world of sensual impressions [...] first into a spiritual world, into a world of ideas and meanings."[19]

1.2. The hiatus between research and epistemological classification of examples from cardio-physiology

This “reluctance” to include “why” questions had consequences which prevented a dialogue to use insights gained from the natural sciences to create an epistemological classification. Classifying the biologic phenomena to understand the organic only occurred to a limited extent. The concepts presented by Hans Driesch (1847–1941), who dared to make this attempt with his *Philosophy of the Organic* in 1909, were widely refuted. Although he was recognized as an expert in developmental mechanics, but his concept of teleology for understanding and classifying observations in developmental biology received little recognition among biologists.[20]

This complex relationship between scientific research results and their epistemological classification can also be seen within research results from cardiac physiology. Hans Reichenbach’s introduction of the journal *Erkenntnis* in 1930 announced: "It has always been a program of the '*Annals*' to pursue philosophy not as an isolated science, but in close connection with the individual specialist sciences [...]."[21] However, this promise could only be fulfilled to a limited extent, at least for cardio-physiology. In the philosophy of science, the pumping function of the heart has been used repeatedly and rather superficially as an example of teleological thinking in science up to the present. The fundamentally new understanding of the physiology of heart mechanics in the 20th century has hardly been taken into account in epistemological analyses.[22]

Carl Gustav Hempel (1905–1997) demonstrates his concept of an explanatory model of the biological sciences using the phenomenon of a heartbeat:

> "Historically speaking, functional analysis is a modification of teleological explanation, i.e., of explanation not by reference to causes which ‚bring about' the event in question, but by reference to ends which determine its course. Intuitively, it seems quite plausible that a teleological approach might be required for an adequate understanding of purposive and other goal-directed behavior; and teleological explanation has always had its advocates in this context."[23]

Regarding the "function" of the heart, he states: "The heartbeat in vertebrates has the function of circulating blood through the organism."[24] Hempel summarized his considerations in the following statement: "The heartbeat has the effect of circulating the blood, and this ensures the satisfaction of certain conditions (supply of nutrients and removal of waste) which are necessary for the proper working of the organism."[25] Analytically speaking, his statement about the significance of the heartbeat is a summary of the "function of the heartbeat", which has been accepted in physiology since Harvey's theory of blood circulation in 1628. Through the causally based concept of blood circulation, the phenomenon of the pulse could be related to the contraction of the heart muscle. The idea that the blood serves to transport and distribute nutrients to maintain the viability of the organs has been accepted since the times of ancient doctors like Galen, even if the explanatory model of that time did not apply.[26]

Twelve years after Hempel's explanations, Ernest Nagel (1901–1985) also used the "blood pumping function" of the heart to illustrate the teleological explanation in science.[27] This discussion continued within the philosophy of science. Ultimately, the term "function" was considered in its various semantic validations to determine its epistemological classification: "What is being asserted by this attribution of function? It might be held that all the information conveyed by a sentence such as can be expressed just as well by substituting the word 'effect' for the word 'function'. [28] In the philosophy of science literature, other words are used in addition to the term "function" in the same context as to *why, how, goals, aims, purposes, mechanisms, teleology, teleonomy*.[29] Different positions have been taken as to whether biomedical scientists are obliged to use an epistemologically sound definition for their terms – in this context the term in question is "function". Ghiselin (2001) asserted his view for the contra-argument: "A stipulative re-definition of a term that we biologists routinely use to say what we mean can only lead to misunderstandings and confusion. Philosophers have no right to arrogate the role of determining how language shall be used in order to further their own metaphysical agendas."[30]

David Buller[31] pointed out in 2002 that definitions of terms in the philosophy of science have developed primarily from the epistemological analysis of physics, which cannot simply be transferred to biology.[32] It is inherent in biological manifestations that the principle of evolution, selection, and changeability in time is an indispensable part of the constitution of the living. Consequently, the teleological, as well as the historical, argument is inherent in the epistemological consideration of biological laws. "Buller's response is to note that any token of a trait has numerous effects, so one has to single out those which contribute to the fitness of the organism, and this can only be done historically. This looks to be an epistemological rather than definitional concern."[33] When reviewing statements in the philosophy of science on the concept of function[34] it becomes clear that the reference to the cardiovascular system served the authors for a certain type of scientific explanation. They ultimately did not push forward knowledge past the late 17th century. The question posed by Hempel: "What does the statement [the heartbeat has function of circulating the blood] mean,"[35] has not been tested on other "functions" of the heart mechanics.

Using selected examples from cardio-physiology, we ask the question of whether the lack of a scientific-philosophical classification of experimentally and theoretically gained knowledge has consequences for the understanding of organic phenomena or, taking into account current cardio-physiological experience, can be a useful addition to both an empirical philosophy of science[36] and cardio-physiology.

1.3. Brief summary of the contents of the three essays

The present first Essay on the history of the force-interval relationship (FIR) is the first in a three-part series. While performing our study on partial aspects of cardiac mechanics, stimulation and periodicity of cardiac activity we came to the following conclusion: Our aim was not only to trace the path of different discoveries of cardiac function, including J.S’s own research-history of the last 60 years, rather, we want to further explore the context of how progress was taking place. Using the discoveries in cardio-physiology, we have to ask ourselves the question of what practices were accepted and further pursued by the scientific community to gain insights into the special aspects of the cardiac function. We have asked ourselves e.g.: Why were at the same time some ideas and results "overlooked" as being of little interest? Why often decades passed until already existing concepts were taken up again? As a result, the original ideas were often forgotten, so that no reference was made to insights already gained and many things were "re-explored".

By exploring these three essays we want to illustrate the "jumps and turns"[37] of progress and stimulate a scientific-philosophical discussion on current biomedical findings.

The second Essay is intended to describe the field of research in which physiologists have been working for over a hundred years to provide a complete description of the mechanical cardiac activity within the cardiovascular system. It began with Otto Frank's lecture in Munich "The work of the heart and its determination by the heart indicator" on Nov. 29, 1898: "The mechanical states into which the heart muscle enters would be fully described if we knew the tensions and lengths of the single elements at every moment of its activity."[38]

In the following 120 years there were extensive efforts – parallel to the development of new measuring methods – to elucidate the mechanics of the heart experimentally and mathematically. In the process of elucidating the mechanics we will take a closer look at Frank's students and scientists such as Hermann Straub, Kiichi Sagawa, Hiroyuki Suga and Daniel Burkhoff. They helped to create the mathematical and experimental conditions to gradually realize the goals Otto Frank had set for himself in 1898. Using Otto Frank's pressure-volume diagram, electronic and computerized models have been developed since the 1990s to determine their significance for cardiac mechanics even more precisely. These models led to the electronic HARVI-Simulation program, which was presented by Daniel Burkhoff in 2005 and has since been further developed, and which can be interpreted as a realization of Frank's visions. – In parallel with the HARVI Simulation program, it was possible to present a technology for cardiac-assist-systems/assisted circulation systems that can be successfully used to relieve both pressure and volume of the failing heart – which can hardly be influenced by medication.

The last field of research – which will be presented in the third Essay – is based on observations of the effects of rehabilitation medicine from cardiac patients. In the broadest sense, this is a future-oriented concept for implementing the importance of restricted heart rhythm variability (HRV) in the prognosis for individual patients with cardiovascular diseases. A prerequisite for such a concept is that one must first understand the phases of heartbeat and respiratory synchronization – which involves experimental mathematical modeling. The latest technical developments seem to confirm the ideas of Wolfgang Deppert, who in 2002 expressed the idea of a system time clock. With such a system it could be possible to determine the individual system times of a patient and then be able to classify them in their chronobiological pattern. In order to be able to develop such a concept, it is necessary to understand the phases of the synchronization of heartbeat and respiration – including experimental mathematical modelling. In this part we will present the different aspects from a historical and epistemology perspective of the cardiology, their theoretical concepts and experiments of the last 150 years.

1.4. References

Burkhoff, Daniel /Israel Mirsky/Hiroyuki Suga: Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers, in: Am J Physiol Heart Circ Physiol 289(2005):H501-H512, https://doi.org10.1152/ajpheart.00138.2005.

Buller, David J.: Function and Design Revisited, in: AriewAndrew /Robert Cummins/Mark Perlman (eds.): Functions: New Essays in the Philosophy of Psychology and Biology, Oxford 2002, pp. 225–243.

Cassirer, Ernst: Wesen und Wirken des Symbolbegriffs [1925], Darmstadt:Wissenschaftliche Buchgesellschaft 1994.

Frank, Otto: Die Arbeit des Herzens und ihre Bestimmung durch den Herzindicator (Vorgetragen am 29. November 1898) in: Sitzungsberichte Gesell. Morph. Physiol. München, 14(1898):147–156. Translation in: Kuhtz-Buschbeck, Rediscovery of Otto Frank's, 2018, Appendix A. Supplementary data, https://doi.org/10.1016/j.yjmcc.2018.04.017

Ghiselin M.T., Can biologists and philosophers see eye to eye in function, Hist. Phil. Life Sciences, 2001, pp. 279–284.

Hempel, Carl Gustav: Aspects of scientific explanation – Another essay in the philosophy of science, New York 1970.

Johansson, Ingvar/Niels Lynøe: Medicine & Philosophy – A Twenty-First Century Introduction, Frankfurt/Paris/Brunswik 2001.

Kocsis László /Adam Tamas Tuboly: The liberation of nature and knowledge: a case study on Hans Reichenbach's naturalism, in: Synthese 199(2021):951–978, https://doi.org/10.1007/s11229-021-03224-2.

Lohff; Brigitte: Die Suche nach der Wissenschaftlichkeit der Medizin in der Zeit der Romantik. [Medizin in Geschichte und Kultur, 17], Stuttgart 1990.

Lohff, Brigitte: Facts and Philosophy in Neurophysiology. The 200th Anniversary of Johannes Müller (1801–1858), in: Journal History Neuroscience 10(2001): 277–292.

Lohff, Brigitte: Johannes Müller – Integration und Transformation naturphilosophischer Naturinterpretation, in: Olaf Breidbach/Thomas Bach (Hg.): Naturphilosophie nach Schelling, Frankfurt 2005, pp. 331–370.

Lohff, Brigitte: Die Josephs-Akademie im Wiener Josephinum. Die medizinischchirurgische Militärakademie im Spannungsfeld von Wissenschaft und Politik 1785–1874, Wien: Böhlau 2019, pp. 225–236, https://www.vr-elibrary.de/doi/pdf/10.7767/9783205232773.

Mac Donald, Graham: [Review] Andre Ariew/Robert Cummins/Mark Perlman (eds.): Functions: New Essays in the Philosophy of Psychology and Biology, in: Philosophical Reviews 2003.07.01, https://ndpr.nd.edu/news/functions-new-essays-in-philosophy-of-psychology-and-biology.

Müller, Johannes: Ueber das Bedürfniß der Physiologie nach einer philosophischen Naturbetrachtung (1824), in: Johannes Müller, Zur vergleichenden Physiologie des Gesichtssinnes des Menschen und der Thiere, Bonn: Cnoblauch 1826, S. 1–36.

Müller, Johannes: Grundriß der Vorlesungen über die Physiologie, Bonn: Cnoblauch 1827.

Müller, Johannes: Handbuch der Physiologie des Menschen und Thiere, Bd. 1, 2. Theil, Koblenz: Hölscher 1834.

Nagel, Ernest: Functional Explanations in Biology, in: The Journal of Philosophy 74, 5(1977): 280–301, https://doi.org/10.2307/2025746

Nagel, Ernest: Teleology revisited: Goal directed processes in biology, in: The Journal of Philosophy 74, 5(1977):261–279, https://www.jstor.org/stable/2025745.

Nagel, Goal directed processes in biology, 1977, p.263; Andre Ariew et al (eds.): Functions: New Essays 2002, p. 2; 157-171.

Reichenbach, Hans: The aims and methods of physical knowledge [1929], in: Marie Reichenbach/ R. S. Cohen (eds.): Selected writings 1909–1953, Vol. 2, Dordrecht: D. Reidel, 1978, pp. 118–166.

Reichenbach, Hans: Zur Einführung, in: Erkenntnis, 1(1930): I–V.

Schaffner, Kenneth F.: Theory structure, reduction, and disciplinary integration in biology, in: Biology and Philosophy, 8 (3) (1993): 319–347, https://doi.org/10.1007/BF00860432

Schröer, Heinz: Carl Ludwig, Begründer der messenden Experimentalphysiologie [Große Naturforscher, 33], Stuttgart 1967.

Wagenknecht, Susann/Nancy J. Nersessian/ Hanne Andersen (Eds.): Empirical Philosophy of Science-Introducing Qualitative Methods into Philosophy of Science, Heidelberg/New York 2015.

Weber, Marcel: Hans Drieschs Argumente für den Vitalismus, in: Philosophia Naturalis 36(1999): 263–293.

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[2] Kocsis/Tuboly, The liberation of nature and knowledge, 2021, pp. 951–978.

[3] Reichenbach, The aims and methods of physical knowledge, in: Selected writings, 1978, p. 123.

[4] The *Handbuch der Physiologie* was published in two volumes; the first volume from 1833–1844 in four revised editions, in each of which Müller incorporated current research.

[5] Cf. Lohff, Facts and Philosophy in Neurophysiology, J. Hist. Neuroscience, 2001, 277–292 – Lohff, Integration und Transformation naturphilosophischer Naturinterpretation, 2005, pp. 331–370.

[6] „Eine solche Arbeit, wenn sie Vollständiges leistet, [muss] den Umfang dieser Wissenschaft in durchgängig gleicher und vollständiger Bearbeitung und zugleich die bisherigen sowie die noch möglichen und notwendigen zu fordernden Leistungen bezeichnen." Müller, Grundriß der Vorlesungen über die Physiologie, 1827, p. I.

[7] For the researchers of this time, the concept of the universal was associated with the question of how individual observations could be placed in the context of the meaning of living matter as opposed to dead matter.

[8] „Jenes Allgemeine, welches nicht im Gegensatze ist mit dem Besonderen, sondern das Einzeln aus sich hervorbringt […], dieses ist das Prinzip der philosophischen Naturbetrachtung und dasjenige allein, was die Philosophie mit der Physiologie verbindet." ["The universal, which is not in opposition to the particular, but produces the individual from itself [...], this is the principle of philosophical observation of nature and that alone which connects philosophy with physiology."]. Müller, Ueber das Bedürfniß der Physiologie nach einer philosophischen Naturbetrachtung, 1824, p. 7.

[9] Die Lehre der Physiologie […] kann der Logik des Wesenhaften oder der Speculation wie der Dialektik nicht entbehren […] Und aller empirisch bekannt gewordener Stoff läßt sich, wenn er begriffen werden soll, in jener dreifachen Weise des Denkens betrachten." Müller, Grundriß, 1827, p. V.

[10] „die wahre Physiologie denkt das Leben in die richtige Erfahrung; durch die Erfahrung sowohl als durch das philosophische Denken kommt die Physiologie zustande, zu sich selbst." Müller, Von dem Bedürfniß, 1824, p. 37.

[11] Müller, Grundriß, 1827, p. IV.

[12] „Der Physiolog erfährt die Natur, damit er sie denkt." Müller, Von dem Bedürfniß, 1824, p. 34.

[13] „das Werden, Procediren des Allgemeinen zum Besonderen" Müller, Grundriß, 1827, p. 76.

[14] „Es ist wahr, die empirische Physiologie löst die letzten Fragen über das Leben nicht, aber die Philosophie löst sie auch nicht auf eine solche Art, dass wir von dieser Lösung in einer Erfahrungswissenschaft Gebrauch machen könnten," Johannes Müller, Handbuch der Physiologie, Bd. 1, Theil 2; 1834, p. VI.

[15] Müller, Handbuch, Bd. 1, 1834, p. VII.

[16] Müller, Handbuch, Bd. 1, 1834, p. VII.

[17] Among Müller's students were, for example: Hermann von Helmholtz, Emil Du-Bois-Reymond, Ernst Brücke, Theodor Schwann, Jacob Henle and Rudolf Virchow.

[18] Cf. Schröer, Carl Ludwig, Begründer der messenden Experimentalphysiologie, 1967 – Lohff, Die Josephs-Akademie, 2019, p. 225-236. In France Claude Bernard plays a comparably central role in the implementation of modern physiology.

[19] „die Welt der sinnlichen Eindrücke […], erst zu einer geistigen Welt, zu einer Welt der Vorstellungen und Bedeutungen umzuschaffen“ Ernst Cassirer, Wesen und Wirken des Symbolbegriffs, [1925], p. 99.

[20] Cf. Weber, Drieschs Vitalismus, Philosophia Naturalis, 1999, 263–293.

[21] Reichenbach, Zur Einführung, Erkenntnis, 1930, p. I.

[22] Nagel, Teleology revisited, Journal of Philosophy, 1977, 261–279.

[23] Hempel, Aspects of scientific explanation, 1970, p. 304.

[24] Ibid., p. 305

[25] Ibid

[26] Cf. to the history of the cardiovascular system, Johansson/ Lynøe, Medicine & Philosophy, 2001, 33–39; 142–151.

[27] Nagel, Functional Explanations in Biology, Journal of Philosophy, 1977, 283–286.

[28] Hempel, Scientific explanation, 1970, p.305.

[29] In this list the term "biological law" is missing, although biologists use this term to describe the consistent observation of regularly occurring and predictable biological phenomena. Examples for the use of the term law are: "Starling’s Law of the heart"; "Frank’s Law of the heart"; "Kleiber’s Law."

[30] Ghiselin, Can biologists and philosophers see eye to eye in function, Hist. Phil. Life Sciences, 2001, p. 280.

[31] Buller, Function and Design Revisited, 2002, 225–243.

[32] For the complex issue of the structure of biological theories, cf. Schaffner, Theory structure, reduction, and disciplinary integration in biology, Biology and Philosophie 1993.

[33] Cf. MacDonald, [Review] Andre Ariew et al., Functions, Philosophical Review, 2003, 07.01.

[34] Cf. Nagel, Goal directed processes in biology, 1977, p.263 – Ariew et al (eds.): Functions: New Essays 2002, p. 2; 157–171.

[35] Hempel, Scientific explanation, 1965, p. 305.

[36] Cf. Wagenknecht et al., Empirical Philosophy of Science 2015.

[37] The aphorism "jumps and turns" is used for the multiple changes of direction of an animal that crosses the original track or returns to it.

[38] Frank, Die Arbeit des Herzens,1898, p.147.

CARDIO-PHYSIOLOGY CHALLENGING EMPIRICAL PHILOSOPHY

ESSAY I

The Physiological Function of the Force-Interval Relationship: A Forbidden Question?

Brigitte Lohff / Jochen Schaefer
In cooperation with Johann P. Kuhtz-Buschbeck and Ekkehart Rumberger

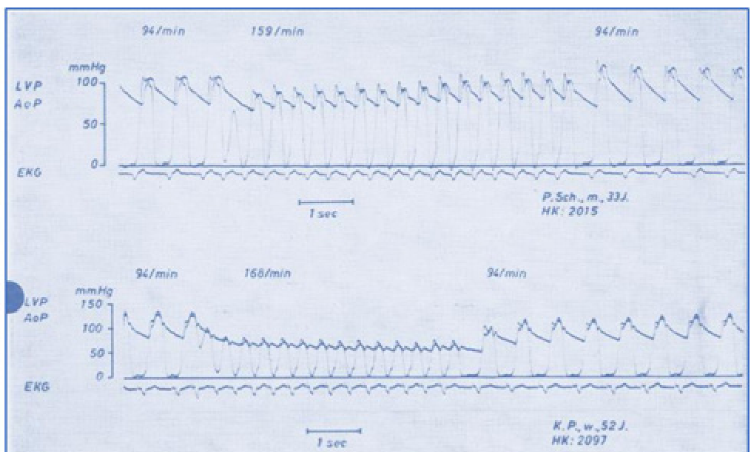

Abb. 1. Verhalten des Aorten (AoP)- und des linksventrikulären (LVP) Druckes bei Umschaltung von niedriger auf hohe Impulsfrequenz und zurück (Stimulation vom rechten Ventrikel aus).
Oben: Herzgesund. Unten: Zustand nach Vorderwandinfarkt.

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Cover picture: Scheme of the Heart ©B. Lohff/ Fig. from: J. Schaefer: Darstellung des Aortendrucks, 1971, p. 357 (Permission to reprint by Springer Nature)

1. Introduction

In 1983, Arnold M. Katz wrote a historical review of the 30-year development of research into the *Regulation of Myocardial Contractility* from the perspective of a "brief and personal history." Katz paraphrased this history of research with a playful yet apt metaphorical subtitle, calling it "An Odyssey".[39] Jochen Schaefer has been working on the force-interval relationship of the heart [FIR] in clinical research since the 1960s, both theoretically and practically. As a member of a research group of cardio-physiologists, he has also experienced an odyssey in the elucidation of the function of the FIR and has personally helped to shape it. The following paper uses a historical perspective to trace the development of hypotheses, experiments, and knowledge on the role of the FIR in cardiac mechanics. The written sources of the last 60 years of research on FIR will be underpinned and supplemented, taking into account the personal perspective on this history of research.

1.1. The historical background of the Force-Interval Relationship

The intensive study of the phenomenon of the force-frequency/interval relationship [Force-Interval Relationship = FIR][40] resulted from the therapeutic application possibilities of pacemaker technology, which have been emerging since the 1960s. The evolving technology of the artificial stimulation of the heart (electrostimulation, cardiac excitation) also contributed to the intensive study of FIR. The artificial, and also the natural, excitation of the heart muscle are due to electro-mechanical coupling. The basic principles and current understanding of electromechanical coupling (e-c coupling = excitation-contraction-coupling), underlying the phenomenon of the force-frequency relationship FIR, are often presented in the recently published corresponding diagrams, such as for instance by Bers.[41] The well-known simultaneously records of the course of the action potential, the influx of calcium ions and the resulting contraction illustrate the interdependence and the time sequence of three different parameters: The action potential [AP measured in the unit mV], which is the trigger for the influx of calcium ion [Ca^{2+} measured in the unit nMol] into the cell. The influx of Ca^{2+} triggers the cellular processes that lead to muscle contraction. The course of the contraction is recorded schematically via the percentage change in the length of the heart muscle cell.

The dependence of the force development of a heart muscle on the (preceding) stimulus interval (i.e., the frequency) during electrostimulation – later known as the staircase phenomenon – was first described in 1871 by Carl Ludwig's American student Henry Pickering Bowditch (1840–1911)[42] at the Leipzig Physiological Laboratory.[43] The following experimental observation was thus described - as summarized by Schütz in 1958:

> "He [Bowditch] observed that the first amplitude of contractions after a longer resting period was lower than the amplitudes of the contractions registered before the period of rest. The contractions following the first beat gradually increased in amplitude again. This staircase phenomenon occurs especially after prolonged cardiac arrest."[44]

Bowditch had already suspected a far-reaching significance of the staircase phenomenon for the understanding of heart