This article has been accepted for publication. Please cite: Boon M. (forthcoming). *An Engineering Paradigm in the Biomedical Sciences: Knowledge as Epistemic Tool*. In: *Progress in Biophysics and Molecular Biology* (special issue: Validation and Models in Computational Biomedical Science: Philosophy, Engineering and Science, A. Carusi and B. Rodriquez eds.).

Information provided by publisher: Article title: *An engineering paradigm in the biomedical sciences: Knowledge as epistemic tool.* Article reference: *JPBM1190.* Journal title: *Progress in Biophysics and Molecular Biology* Corresponding author: *Prof Mieke Boon* First author: *Prof Mieke Boon* Online publication complete: 12-APR-2017 *DOI information: http://dx.doi.org/10.1016/j.pbiomolbio.2017.04.001* or http://www.sciencedirect.com/science/article/pii/S007961071630044X

An engineering paradigm in the biomedical sciences: Knowledge as epistemic tool

MIEKE BOON

Department of Philosophy, University of Twente, PO Box 217, 7500 AE Enschede, The Netherlands. m.boon@utwente.nl

Abstract

In order to deal with the complexity of biological systems and attempts to generate applicable results, current biomedical sciences are adopting concepts and methods from the engineering sciences. Philosophers of science have interpreted this as the emergence of an engineering paradigm, in particular in systems biology and synthetic biology. This article aims at the articulation of the supposed engineering paradigm by contrast with the physics paradigm that supported the rise of biochemistry and molecular biology. This articulation starts from Kuhn's notion of a disciplinary matrix, which indicates what constitutes a paradigm. It is argued that the core of the physics paradigm is its metaphysical and ontological presuppositions, whereas the core of the engineering paradigm is the epistemic aim of producing useful knowledge for solving problems external to the scientific practice. Therefore, the two paradigms involve distinct notions of knowledge. Whereas the physics paradigm entails a representational notion of knowledge, the engineering paradigm involves the notion of 'knowledge as epistemic tool'.

Key words: philosophy of science; engineering sciences; paradigm; disciplinary matrix; Kuhn; model construction; *epistêmê* and *technê*; systems biology; synthetic biology.

1. Introduction

Scientific practices are guided by presuppositions concerning the nature and value of scientific knowledge as well as the reliability and effectiveness of methodologies in producing such knowledge. Thomas Kuhn (1970a) coined the term *paradigm* to account for a kind of background picture that guides practitioners in their common problem-solving activities, which consists of the established and commonly adopted *fundamentals* of a field. Kuhn's thoughts were revolutionary because he convincingly showed that these fundamentals have the character of a body of productive but indemonstrable presuppositions and beliefs.

Recently, philosophers of science have claimed the emergence of an *engineering paradigm* in new fields in the biomedical and biological sciences – in particular, integrative systems biology and synthetic biology – since these fields have adopted engineering models, methods, concepts, technologies, strategies and epistemic principles, possibly at the cost of traditional approaches to investigate biological phenomena in the biological sciences.[1] This article aims to explore and elaborate on this claim, and is structured as follows.

Section 2 presents an overview of engineering approaches in the biological sciences as explained by leading scientific researchers and philosophers of science. Section 3 summarizes Kuhn's notion of paradigm and his more cautious account of paradigms as *disciplinary matrices*. Section 4 presents a brief sketch of paradigm changes in biology. Whereas in the first half of the 20th century a *physics paradigm* was adopted, current changes seem to imply the emergence of an *engineering paradigm* of science. In Section 5, the point is made that a paradigm also entails philosophical and normative ideas about science, that is, about what science 'really' is or should be. It will be argued that the traditional conceptual distinction between science and technology as two different kinds of knowledge justifies the dominance of what can be called a *physics paradigm of science*. Analysis of the Aristotelean distinction between two types of knowledge, *epistêmê* and *technê* elucidates why an *engineering paradigm of science* sounds like an oxymoron and may even come across as provocative. The philosophical and normative issue is how the ubiquitous presence of engineering concepts, methods and goals in systems biology and synthetic biology should be interpreted. I aim to defend that the emergence of these new fields in the biomedical sciences goes hand-in-hand with the emergence of a new paradigm of science, called an engineering paradigm of science that incorporates philosophical and normative ideas commonly attributed to the engineering sciences. This view is developed by expanding on Kuhn's disciplinary matrix, turning it into an extended list of mutually cohering elements (i.e., elements listed in the first column of the schema in Section 5.2) in terms of which specific paradigms of science can be fleshed out. Accordingly, this matrix is used to tentatively articulate an engineering paradigm of science, which in important respects contrasts with a physics paradigm of science. In particular, I will defend an engineering paradigm of which the most salient aspect is the currently emerging notion of scientific knowledge as *epistemic tool*, which aims to be a viable alternative to a *representational view* (in a correspondence sense) traditionally dominant in a physics paradigm of science. Characterising knowledge as epistemic tool is entangled with and supported by the other elements of the engineering paradigm – firstly with the aim of science, but also with presuppositions at the metaphysical, epistemological and methodological levels. The proposed

---

[1] The notion of an emerging engineering paradigm was introduced at the workshop *(Re)Engineering Biology: The Emerging Engineering Paradigm in Biomedical Engineering, Systems Biology, and Synthetic Biology*, at Center for Philosophy of Science, University of Pittsburgh, 15 - 16 April 2016, organized by Nancy Nersessian, Miles MacLeod et al.

engineering paradigm enables to recognize aspects of the biological and biomedical sciences that remain unnoticed, neglected or even rejected in the physics paradigm.

2. Engineering in biology

2.1 Engineering concepts and methods

From an outsiders perspective, a salient aspect of systems biology and synthetic biology is their use of engineering *concepts*. Biological objects are described as functional modules common in engineering, such as *system*, *network, circuit, program, module, machinery, mechanism, signal, pathway, transduction-network,* and *network-motif*. Similarly, engineering concepts are used to describe properties of biological entities in functional terms, such as *robustness, adaptation, amplification, activation, insulation, signal-transduction, oscillation, dynamics, regulation,* and *communication*. Indeed, authors such as Hartwell et al. (1999) have already argued that the most effective language to describe biological components and their interactions will be derived from computer science or engineering, in which function appears naturally. Figure 1 illustrates the ubiquitous use of engineering concepts in systems biology, and thereby aims to underpin in a visual manner the emergence of an engineering paradigm in systems biology.

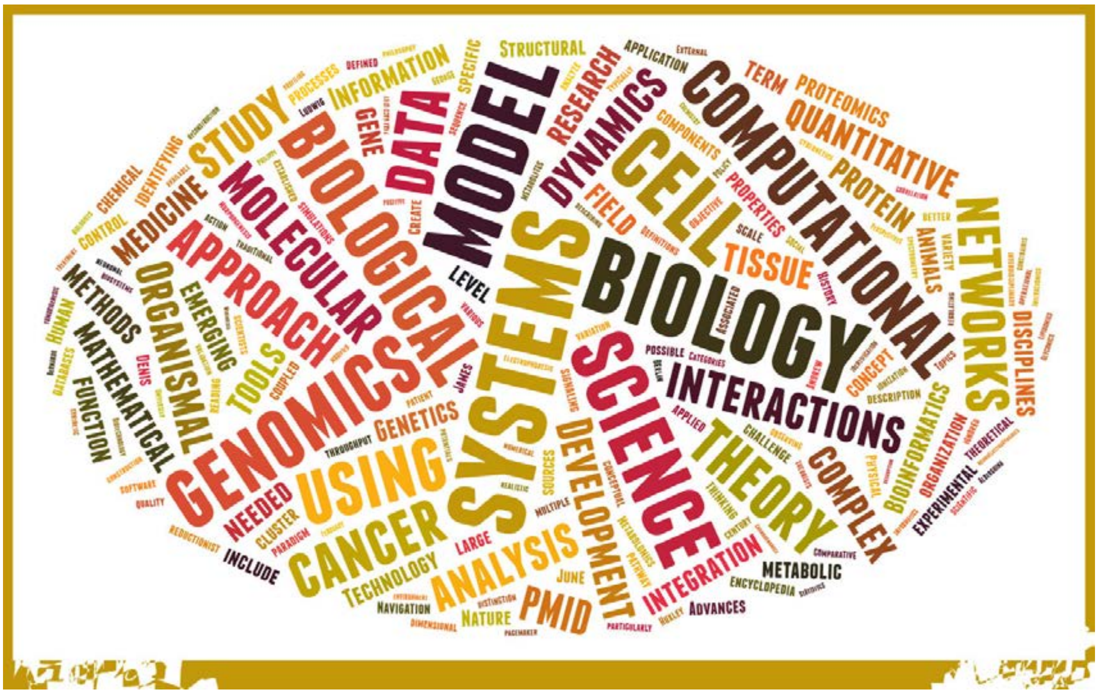

Figure 1. This word-cloud has been produced using the full text of the Wikipedia website on Systems biology https://en.wikipedia.org/wiki/Systems_biology and the word-cloud program http://www.tagxedo.com/ It illustrate the ubiquitous use of engineering concepts in systems biology.

An important if not crucial reason for the role of engineering concepts and methods in the biological and biomedical sciences is dealing with the *complexity* of biological systems (Mitchell 2003, 2009; Brigandt and Love 20015; Dev 2015). Within biology the modelling of mechanisms, for instance, is facing a number of obstacles. Systemic behaviour is typically not determined by the behaviour of a single component, but by a number of causally interacting components, each with unique and characteristic capacities, together forming an interactive causal network. Control over systemic biological and biochemical processes is therefore distributed rather than local, requiring detailed analysis of the design and dynamics of intracellular molecular networks by systems biology using concepts from physics, engineering and mathematics (Boogerd et al. 2013, also see Bruggeman and Westerhoff 2006). Another major challenge is understanding and modelling higher-level properties such as the *robustness* of biological systems, which involves for example that some components of the system appear to have multiple roles (also see Kitano 2002a-b). Although crucial from an evolutionary point of view, the downside from a scientific and (biomedical) application point of view is that biological systems become very difficult to predict, as, according to common scientific methodology, in order to adequately explain and predict their behaviour we usually tend to rely on reproducible causal behaviour of lower-level entities (e.g., the entities distinguished in molecular biology).

These features make the scientific understanding and modelling of biological systems very hard, and scientists needed to develop new kinds of methods and methodological strategies, found in the engineering sciences. *Computational modelling and simulations*, which has been used for decades already in the engineering sciences for modelling, ‘mimicking’, explaining and optimizing the behaviour of multi-level complex systems (e.g., industrial processes in chemical engineering), has been promoted as a viable method in the biological sciences by authors such as Ideker et.al. (2001), Kitano (2002a) and Kremling & Saez-Rodriguez (2007). Basically, computer modelling and simulation involves crafting mathematical descriptions of networks that consist of at least two interconnected (biological) components. The state of each component is described by differential mathematical equations, while their dynamic interactions are described by connecting these equations in the mathematical model that is run in a computer simulation. The engineering sciences have refined this general strategy of building mathematical models and running computer simulations. In order to keep these models manageable, common strategies of so-called model reduction have been developed, which aim at the reduction of their complexity. Examples are, the use of macro-states rather than micro-states (e.g., at the molecular level), modular model reduction (subdividing the system into interacting modules), using conservation relationships (which allows for algebraic calculations of unknown or unmeasurable quantities), and time-scaling (distinguishing between processes that are dynamic, static or quasi steady-state within the time window). Other relevant mathematical and computational methods have been developed in engineering fields such as systems control, which for instance aim to model ‘integral feedback’ or higher-level properties such as stability or multi-stability, or aim to deal with uncertainties concerning the components involved (Kremling and Saez-Rodriguez 2007). *Reverse engineering* is another strategy for dealing with the interplay of complexity and robustness of biological systems borrowed from the engineering sciences, which is a method for the identification of the structure of a (biochemical) network from experimental data. In this approach, mathematical models of dynamic systems are build, based on experimental data in which the response of the system to changes in their environment is measured (e.g., Csete and Doyle, 2002; Ingolia and Weissman, 2008). Still another method common in the engineering sciences is to *build complex artificial biological systems* (consisting of synthetic, yet physical systems and in silico computer simulations) to investigate natural biological phenomena. The goal is to extend or modify the behaviour of biological components or organisms and engineer them to perform new tasks for a variety of applications (also see Hartwell et al. 1999, Ideker et al. 2001, Endy 2005, Sismour and Benner 2005, and Andrianantoandro et al. 2006). A paradigm example is provided by Elowitz & Leibner (2000), who have *engineered* a synthetic regulatory system in *E. coli* which functions as a synthetic oscillator, a predetermined network model, to study the gene-regulatory system.

Within the philosophy of science, authors have aimed to characterize these newly emerging scientific practices of systems biology and synthetic biology, and some have pointed at the indispensable role of engineering concepts and methods. Nersessian (2009), for instance, counts designing, building, and experimenting with physical simulation models as typical of engineering approaches. Additionally, philosophers have studied these practices, and indicated typical engineering strategies of using combinations of methods that mutually support each other in investigating and modelling complex systems. MacLeod and Nersessian (2013 and 2015) point out how the use of computational methods generates novel methodological strategies for managing complexity, and show how the coupling of experiment, computational modelling and simulation enabled a researcher to build and validate models. Similarly, Carusi et al. (2013) have analysed in great detail a typical engineering methodology of interrelated modelling, computer simulation and experimentation, which can be used to mimic the mechanisms of physiological processes (in this instance cardiac processes). Based on this analysis, they suggest that this could also be a viable approach in systems biology. In fact, this is the kind of engineering strategy that Knuuttila and Loettgers (2013b) have studied in synthetic biology. They call it combinational modelling, by which they mean that experiments on model organisms and mathematical/computational models are combined with a new type of model—a synthetic model.

2.2 Engineering goals

Typical of the engineering sciences is an emphasis on the usefulness of knowledge and technologies produced in scientific research, which is another reason for aiming to learn from them in the biomedical sciences. Several authors hold that understanding complex biological systems by means of systems biology and synthetic biology will lead to practical innovations in medicine, drug discovery and biomedical engineering (e.g., Ideker et.al. 2001, Kitano 2002a, Benner and Sismour 2005, Somvanshi and Venkatesh 2014, Carusi 2014, Dev 2015, Viceconti et al. 2016). Somvanshi and Venkatesh (2014), for instance, defend in their *Conceptual Review on Systems Biology in Health and Diseases – from Biological Networks to Modern Therapeutics* that understanding diseases at systems level – which they conceptualize as 'disease systems engineering' – will facilitate work on cures for diseases, for instance, "by identification of rational drug targets, effective drug design with least side effects, effective therapeutic strategies, diagnosis of actual source of disease state, treatment on disease source rather than symptoms, early and reliable diagnosis of diseases using predictive models, rational toxicological and drug safety assessments leading to improved healthcare." These authors believe that 'disease systems engineering,' which emerges from system biology, has got tremendous potential in biomedical research and pharmaceutical industries wherein the efforts of clinical trial studies can be drastically minimized. Their focus is networks and modelling approaches to address human diseases. Another example of these high expectations on practical applicability of systems and synthetic biology is the Virtual Physiological Human (VPH) project. According to the *European Commission*: "The Virtual Physiological Human will revolutionise the way health knowledge is produced, stored and managed as well as the way in which healthcare is currently delivered." The VPH is a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system. It is a framework that aims to be descriptive, integrative and predictive, and so have the potential to deliver personalized care solutions, reduced need for experiments on animals, more holistic approach to medicine, and preventative approach to treatment of disease" (http://www.vph-institute.org/what-is-vph-institute.html). Related to this ambition is a recent roadmap by the Avicenna Alliance (2016): *In silico Clinical Trials: How Computer Simulation will Transform the Biomedical Industry* (http://www.vph-institute.org/documents.html; Viceconti et al., 2016). In this document, the term '*in silico* clinical trials' refers to the use of individualized computer simulation (i.e., *in silico* medicine technologies) in the development or regulatory evaluation of a medicinal product, medical device or medical intervention (Avicenna roadmap 2016, 10).

As a consequence and similar to the engineering sciences, biomedical sciences not only aim to understand biological systems out of scientific curiosity, but also to generate knowledge and technologies for practical (biomedical) applications. Systems biology and synthetic biology have adopted, for instance, the *goal of generating desired properties or particular functions* by design-methodologies typical of the engineering sciences. Ideker et al. (2001) have reviewed examples in which mechanistic models of a naturally occurring biological system were constructed (i.e., material *synthetic models*), which allow for investigating properties of a *naturally* occurring biological system. They call this approach 'reverse engineering.' Here, slightly different from the notion mentioned above, reverse engineering means that one alters the synthetic model to best fit the properties of the naturally occurring biological system. Conversely, according to these authors, this approach can equally be used to construct a synthetic system in which, based on predictive scientific or mathematical models, the biological system is altered in order to produce new properties or particular functions – they call this 'forward engineering'. Eventually, the two approaches to studying the properties of existing biological systems by means of engineered synthetic models, and re-engineering biological systems by means of predictive theoretical models to produce new properties or functions, will converge. Ideker et al. (2001, 364) believe that this "dualistic approach is one of the 'holy grails' of biology and medicine in which a predictive model of a complex disease pathway is used to design and test cellular modifications that can, ultimately, ameliorate the disease response." Similar strategies are defended for synthetic biology. Benner and Sismour (2005) claim for instance that synthetic biologists use unnatural molecules to reproduce emergent behaviours from natural biology, with the goal to seek interchangeable parts from natural biology to assemble into systems that function unnaturally. Also these approaches resemble common strategies in the engineering sciences (e.g., the development of chemical processes to synthesize unnatural compounds replacing natural ones), adopted in the biomedical sciences to produce knowledge and technologies for biomedical applications.

3. Paradigms in Science

3.1 Paradigms versus methodological rules

Kuhn (1962, 1970) postulated the notion of paradigm after observing remarkable differences between the social and the natural sciences. Whereas the social sciences were having fierce debates on fundamentals in the social sciences —such as, what counts as legitimate scientific questions and methods— similar controversies seemed absent in the natural sciences. Kuhn's attempts to discover the source of these differences led him to recognize the role in scientific research of what he then started to call 'paradigms.' Paradigms, according to Kuhn, entail universally recognized scientific achievements that for a time provide model problems and solutions to a community of practitioners as well as their rules and standards. In matured scientific practices, there is a shared paradigm to which practitioners are committed and which prepares the student for their membership, and this explains why practitioners are often reluctant to raise doubts about or disagree with the fundamentals. In newly emerging and changing scientific fields such as systems biology and synthetic biology, however, the fundamentals *are* being discussed – such as illustrated by authors cited in Section 2 – and there is every chance that a new paradigm will emerge.

Kuhn proposed the notion of paradigm as an *alternative* to the idea that the functioning of scientific practices can be sufficiently grasped as being governed by explicit methodological *rules and procedures*. Yet, this does not mean that a paradigm cannot be articulated or analysed. A paradigm is similar to the idea of methodological rules and procedures in the sense that it is operative in a practice, but it does not consist of rules, nor is it a theory; it is more like a 'picture,' a 'perspective', or a 'conceptual framework.' Accordingly, the paradigm can be considered as the background within which a scientific practice of a specific discipline is embedded, and which guides and enables that practice. This idea has been visualized in Figure 2. It depicts the widely adopted schema of scientific research methodology that we teach our students, but the paradigm surrounding it enables and guides the dynamics of scientific practices on all levels depicted in this schema: at the level of 'observations' some phenomena are noticed and not others; at the level of questions some types of questions are raised and not others. Also at the level of formulating hypotheses some types of explanations can be crafted and not others. Furthermore, specific types of experimental techniques and technological, mathematical and representational instruments adopted in a scientific discipline enable specific kinds of tests and not others. Finally, instead of a clear-cut 'true' or 'false' outcome of a test, background values and more fundamental beliefs that are also part of the paradigm will be taken into account in the evaluation of the test of a hypothesis.

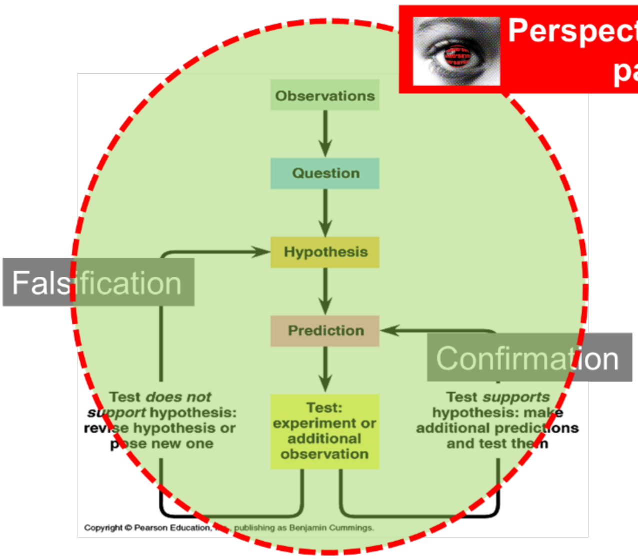

Figure 2: Visualization of how a scientific research practice – schematically pictured as the *research-cycle* or *empirical cycle* commonly used to sketch scientific methodology – is embedded in a paradigm. A paradigm consists of a (loose, non-rigid) set of interlocking aspects that mutually support and reinforce each other. A scientific practice is embedded in a paradigm, and conversely, the paradigm is maintained by a scientific practice. Rather than being guided by strict methodological rules only, the paradigm enables and guides research in scientific practice. Elements in terms of which a paradigm of science can be articulated – e.g., elements of the disciplinary matrix as proposed in this article – are listed in the first column of the schema in Section 5.2.

Central to Kuhn's notion of paradigm is the notion of a *paradigm shift*. Revolutionary new theories, such as in the Copernican, Newtonian, chemical and Einsteinian 'revolutions' could not have emerged or become accepted within the existing paradigm of their days – they involved its change. Kuhn argues that such changes are usually due to *anomalies*, for instance, newly discovered phenomena that cannot be explained by existing theory. Anomalies, therefore, are occurrences that seem to violate aspects of the paradigm of a scientific discipline. In the Newtonian revolution, the fundamental metaphysical belief, 'that there cannot be action at a distance' was violated, and in quantum mechanics common notions of causality needed to be abandoned. Below, in Section 4, anomalies that seem to violate the *physics paradigm* held in biological and biomedical science will be discussed.

Importantly – anticipating the contrast between the two paradigms of science proposed in Section 5 – even if an engineering paradigm is adopted in the newly emerging sub-disciplines of the biological and biomedical sciences, a physics paradigm of science may remain dominant in some more traditional sub-disciplines like molecular biology. Kuhn admits that a new paradigm does not necessarily mean the older paradigm becomes extinct. Two paradigms can coexist peacefully in the later period. Also, a new paradigm may adopt or integrate or expand on valuable elements of the former.

3.2 Paradigms as a disciplinary matrices

In the *Postscript* to the second edition of *The Structure of Scientific Revolutions*, Kuhn (1970) aimed to specify the notion of paradigm, as some readers of the earlier edition had found the concept hard to grasp and over the years Kuhn's paradigm received a lot of philosophical critique. Therefore, he proposed to specify it in terms of a *disciplinary matrix*. With regards the term 'disciplinary matrix' he wrote: "For present purposes I suggest 'disciplinary matrix': 'disciplinary' because it refers to the common possession of the practitioners of a particular discipline; 'matrix' because it is *composed of ordered elements of various sorts*, each requiring further specification" (1970, 182, my emphasis). In several texts (1970a&b; 1974), Kuhn stresses that he does not attempt an exhaustive list, but only notes the main sorts of components of a disciplinary matrix (e.g., 1970a, 182).

The first type of component is what he labels 'symbolic generalizations,' which refers to the theoretical content of the discipline such as its (logically formalizable) laws (e.g. F=m.a, or V=I.R). The second type of component is the 'metaphysical part of paradigms,' which consists of the shared commitments to such beliefs as: "all perceptible phenomena are due to the interaction of qualitatively neutral atoms in the void," or, alternatively, "to matter and force," or "to fields." Importantly, Kuhn stresses that scientific models explaining the phenomena may be taken metaphysically (i.e., literally) or heuristically, as in cases where the model is clearly intended as an analogy, a 'seeing-as', such as in 'the molecules of a gas *behave like* tiny elastic billiard balls in random motion.' According to Kuhn, "the degree of a community's commitment varies as one goes from heuristic to metaphysical models, but the nature of the models' cognitive functions seems to remain the same" (1974, 462). In this manner, he not only avoids any claim on whether practitioners are committed to these models because they take them literally or merely heuristically, but also suggests that philosophical considerations of whether they are to be taken as literal or heuristic models do not matter to scientific practices. In Section 6, I will push the idea that a distinction between metaphysical and heuristic interpretations of scientific knowledge makes sense in the physics paradigm, in particular if true or adequate scientific knowledge is considered to, more or less literally, describe or ‘represent’ the purported target object – notably, a view held stronger in disciplines such as biochemistry and molecular biology than in physics –, whereas an engineering paradigm is better served by the notion of ‘knowledge as epistemic tool.’

Kuhn describes the third sort of component as ‘values’ used to judge theories, rebutting the idea that ‘truth’ is the ultimate epistemic value by which theories are accepted or rejected. In later work, he summarizes the values a good theory ought to possess as: accuracy, consistency, scope, simplicity and fruitfulness (Kuhn 1977). Crucially, theories cannot possess all these values at once or in the same degree, which implies that theory-choice – and, as I will argue, specific ways in which scientific knowledge is constructed – also involves pragmatic aspects already indicated in his list of values. Also, Kuhn takes it, and I follow him in this opinion, that these values are not specific to a discipline but are held in science at large. Nevertheless, as will become obvious in the construction of the engineering paradigm of science, the significance of specific values may differ between paradigms. ‘Usefulness’ for actual problem solving, for instance, is more important in an engineering paradigm of science than in a physics paradigm. The fourth and last component that Kuhn (1970, 1974) points out, he calls ‘exemplars.’ Exemplars are illustrations of the symbolic generalizations. They are examples of problem-solutions by means of which students, first, learn how to relate symbolic generalizations to problems (e.g., the inclined plane, the conical pendulum, and Keplerian orbits), and next, by learning to see new problems as similar to those of the exemplars, will be able to apply the problem-solution strategies illustrated by means of the exemplar to new situations.

3.3 Expanding on Kuhn’s disciplinary matrix

A paradigm or disciplinary matrix consists of heterogeneous elements (or constituents as Kuhn also calls them). They are different types of things that at the same time support and reinforce each other, which is the sense in which they *cohere* in the paradigm. Kuhn, by means of his notion of disciplinary matrices suggested that philosophers of science could analyse paradigms in scientific practices, which is the approach that will be taken in this article. Yet, in discerning these elements Kuhn took revolutionary changes of theories in physics as exemplary, which leaves more general elements in which physics may differ from other sciences unnoticed. In this article, I defend that these other elements belong to *paradigms of science* as well. The four constituents of a disciplinary matrix proposed by Kuhn were not meant to be exhaustive, which offers the possibility for elaboration. Accordingly, Kuhn’s disciplinary matrix for which physics has been exemplary will be expanded with additional elements that account for other types of philosophical and normative presuppositions and beliefs about science and scientific practices more generally. In the remainder of this article, this matrix will be developed, and used to articulate both a paradigm of science prevalent in the more traditional biological sciences (called a physics paradigm), as well as a paradigm of science that suits better to current biomedical and biological sciences (called and engineering paradigm).

4. A physics paradigm in biology

4.1 Reductionism

A physics paradigm of science has been around for quite some time, but only in the second half of the twentieth century, it got accepted in the biological sciences. Schrödinger's (1944) *What is life*, articulates and defends the then emerging view that biology in spite of its complexity can be accounted for by physics and chemistry. This view proposes new fundamentals for that field and new ways of conceptualizing life, and can therefore be considered as a changing paradigm in the biological sciences. Schrödinger's book is widely regarded as a decisive impetus for the emergence of biogenetics, biophysics and systems biology (Gumbrechts et al. 2011 p1; also see Frauenfelder et al. 1999, and Frauenfelder 2014). Sketchily put, and certainly not doing justice to his more subtly phrased ideas, Schrödinger defended a metaphysical and ontological view according to which living systems consist of the same basic stuff and obey the same basic laws of nature as the entities and laws discovered in physics and chemistry. This *metaphysical view* on how the world is implies an *epistemology* according to which scientific knowledge about physical and biological systems can be unified, meaning that knowledge in biology can be reduced to, or deduced from the more basic knowledge of physics and chemistry. This view also motivated a reductionist *methodology* according to which scientists aim to discover the basic entities and laws that determine life. The physics paradigm of science in biology just sketched is often characterized as reductionist, but also as unificationist, determinist, materialist, physicalist and essentialist (also see Dupré 1995).

This brief sketch aims to illustrate how physicists such as Schrödinger promoted a physics paradigm for biology. The point of calling it a paradigm-change is that it not only promoted the use of scientific knowledge from physics and chemistry in biology, but also, to *see biological systems as physical systems*, and to study them by the same concepts and methods as those used in physics and chemistry, and thereby, to adopt presuppositions typical of a physics paradigm. In particular, this physics paradigm involves *reductionism* at the ontological, the epistemological and the methodological level, which – although not necessarily implying each other (cf. Brigandt and Love, 2015) – reinforce each other within the physics paradigm. Taken together, it involves the belief that nature ultimately consists of independently existing fundamental building-blocks, governed by basic laws from which everything else is built and generated (i.e., the metaphysical belief of a reductionist ontology), and therefore, these building-blocks and the workings of laws governing them must be discovered and studied in isolation (i.e., a reductionist methodology of science). Through such an investigation fundamental knowledge of the basic constituents of living organisms is gained, from which knowledge (e.g., descriptions, explanations or predictions) of more complex biological phenomena can be deduced (i.e., a reductionist epistemology). The physics paradigm is hierarchical in the sense that 'higher-level' phenomena result from (i.e., are caused by) those at 'lower-levels', while it excludes the possibility of any influence in the opposite direction, i.e., that 'higher-level' phenomena have a causal effect on 'lower-level' phenomena.

4.2 Anomalies in biological sciences: Reductionism under attack

The reductionist take on research in biology has been enormously productive. In the Human Genome Project (HGP) the sequence of 3 billion DNA base pairs that make up the human genome has been analysed, and the estimated 20,000 to 25,000 human genes —which are generally defined as stretches of DNA that code for particular proteins— have been identified (HGP 2004, https://www.genome.gov/12513430). However, the initial presupposition that the HGP gave us the ability, for the first time, to read nature's complete genetic blueprint for building a human being (https://www.genome.gov/10001772/all-about-the--human-genome-project-hgp/) appeared too optimistic. Biological systems happen to be much more complex in the sense that hardly any reliable predictions can be made about their behaviour on the basis of knowledge of genes. The interesting issue is that the HGP was motivated by the kind of physics paradigm just sketched, which justified the belief that identification of genes provides scientists with 'a complete genetic blueprint for building a human being' and with knowledge for explaining biological systems that would also be of enormous value for biomedical applications. Within the sketched physics paradigm, the notion of a blueprint made perfect sense.

For Kuhn, a paradigm itself cannot be proven or disproven, but if anomalies arise scientists may wish to abandon or try to revise the paradigm. The discrepancy between the belief that the genome constitutes a blueprint and the recognition that this belief does not bring us closer to a fuller understanding of the whole organism, is an example of such an anomaly. In this instance, it appears that the accepted physics paradigm no longer serves us well and may need revision.

Ideker (2001, 343) has written elegantly on this anomaly and the emergence of a new paradigm — which he calls a new view of biology: "Perhaps the most important consequence of the Human Genome Project is that it is pushing scientists toward a new view of biology—what we call the systems approach. Systems biology does not investigate individual genes or proteins one at a time, as has been the highly successful mode of biology for the past 30 years. Rather, it investigates the behaviour and relationships of all of the elements in a particular biological system while it is functioning." Also Noble (2010) presents in a very comprehensive manner several findings in molecular biology which have revealed that the idea of a determinate genetic program in the DNA, controlling the development and functioning of the organism, similar to the digital code of a computer program, was seductive, but not correct. He summarizes six examples, which each show that genes do not determine processes as there is no strict causal relationship between genes and biochemical behaviour. Instead, how a gene acts is also determined by its ever changing environment. Furthermore, phenomena at the level of the cell or organism, such as the *robustness* of biological systems (including their resistance to damage from mutations and knockouts), cannot be explained in terms of genes (also see Kitano 2002a-b). Therefore, Noble (2010, 1127, citing Sydney Brenner) suggests: "The fundamental unit, the correct level of abstraction, is the cell and not the genome." This certainly is a rift with a physics paradigm, which holds that the knowledge of more complex systems can be derived in principle from knowledge about entities and processes at lower levels. Indeed, Noble (2010) believes that the next stage in the development of biological science will be revolutionary in its conceptual foundations and be strongly mathematical in its methods. Also other authors have defended similar visions on fundamental conceptual changes needed to get progress in the biological sciences (e.g., Hartwell et al. 1999, Andrianantoandro et al. 2006, Somvanshi and Venkatesh 2014).

4.3 The metaphysical fundamentals of the physics paradigm under attack

Additionally, a paradigm can come under attack when its fundamentals are criticized in a direct manner. In the philosophy of science, *reductionism* at the metaphysical, epistemological and methodological level has come under attack (see Brigandt and Love 2015 for an overview). Dupré

(1993), for instance, calls it a mechanistic world-view, which consists of three cohering ideas: that everything that happens should ultimately be understood or explained in terms of basic constituents of matter (*materialist reductionism*), and is determined by the causal behaviour of the constituent parts only (*determinism*), which also entails the metaphysical belief that there is a pre-determined structure in the world consisting of a unique and objective set of natural kind (*essentialism*). Against essentialism, Dupré argues that the way in which biologists divide up (i.e., categorize) the biological world is not determined by nature – instead, classification is much more instrumental, and principles of classification are determined by pragmatic reasons as well. Against determinism, Dupré holds that we have good reasons for believing in the causal efficacy of *higher-level* objects. Furthermore, as an alternative to reductionism in general, he proposes *pluralism* at these different levels. Similarly, Mitchell (2009) has argued against reductive explanations. She advocates *integrative pluralism*, which is the idea that an explanation consists of a fabric of many levels and different kinds of explanations that are integrated with one another to ground effective prediction and action. Crucial to this alternative is the assumption that explanations are evaluated in view of their capacity to effectively and reliably *predict* in specific contexts and for specific uses. This is a pragmatic criterion, and contrasts with the criteria of *truth*, *universality* and *simplicity* (as aimed at in reductive explanations) that were motivated by the metaphysical and ontological presuppositions of the physics paradigm.

Related to the former, another important aspect of the critique by these philosophers of science is that, instead of adopting scientific concepts and methods that suit our metaphysical presuppositions, the job of science is to develop concepts and methods that fit our epistemic needs, such as the need to deal with complexity by generating knowledge capable of effective prediction, and the need for knowledge to be intelligible. Robert (2004), in a critical paper, explains the issue in a straightforward manner by including a methodological perspective on the matter. He acknowledges the need for reductionist methodologies and epistemologies as a strategy of simplification, since otherwise research programs in biology would not be possible. A common strategy is to simplify the *context* by controlling the environment and focus on simple components of a system. In this manner, higher-level (more complex) components and systems are concealed, while lower-level (more simple) components and systems are made prominent. However, this asymmetry between simple components and their environment causes a bias towards reductionist explanations at the danger of generating causal stories about genes in which the causal significance of the environment is neglected. The point is that, when studying genes while holding all other factors of the biological system fixed, the causal influence of these factors is just not studied, which may wrongly suggest that these factors do not play a causal role. Therefore, methodological reductionism is not rejected in an engineering paradigm, but instead, is one strategy amongst others, the use of which is pragmatically rather than metaphysically motivated, and should always be evaluated in view of the epistemic aim and values of the scientific research project.

4.4 The emergence of a new paradigm

Based on the analysis so far, I claim that the emergence of new fields in the biomedical sciences (in particular, systems biology and synthetic biology) goes hand-in-hand with the emergence of a new paradigm, called an engineering paradigm. This entangled development is attributed to a combination of factors, consisting of (i) severe anomalies encountered in the biological sciences that demonstrate that the original expectations supported by the physics paradigm are violated, (ii) philosophical critique on the metaphysical and epistemological presuppositions of the physics paradigm, and (iii) actual technological and conceptual developments in which visionary promotion and implementation of engineering concepts, methods and goals allow for new scientific approaches in biology that are not merely instrumental and technological, but which also involve new ways of 'seeing' and theorizing about biological systems. Next to the availability of new experimental techniques such as synthetic modelling and efficient measurement instruments by means of which new kinds of data can be generated in huge amounts ('big data'), the adoption of mathematical modelling, and computer simulations are crucial in processing and organizing these data. Taken together, these new means make it possible to deal with higher complexity thus opening up new venues for research.

5. An engineering paradigm versus a physics paradigm in biology

5.1 The character of knowledge in science and engineering: epistêmê versus technê

Although Kuhn does not explicitly mention the aim of science as part of the paradigm, a paradigm does entail a view of 'what science is' and 'what its aim is.' Here, I will argue that this aim is entangled with the other fundamentals of a paradigm.

Traditionally, there has been a rather strict distinction between science and technology according to which the ultimate aim of science is *true* knowledge, not, *useful* or *applicable* knowledge. In accordance with this idea, *engineering sciences* such as mechanical, chemical and electrical engineering used not be easily recognized as science but rather as technology in the sense of engineering and design (Boon 2011).[2] The common phrasing that 'science aims at truth whereas technology aims at use,' echoes the classical Aristotelian distinction between *epistêmê* and *technê*. Usually, *epistêmê* is translated as science or scientific knowledge or theoretical (pure) knowledge, and *technê* as art or craft or (experience based) practical knowledge. Crucial to the argument made here, Aristotle distinguishes *epistêmê* and *technê* as two kinds of *knowledge* having distinct objects (or things) as their aim. *Epistêmê* or scientific knowledge is about things that exist out of necessity, 'things that are universal, eternal, ungenerated, and imperishable – that is, things that do not admit of change.' *Technê* or technological knowledge is knowledge about 'things that have their origin in their maker – i.e., things that are variable, generated, and perishable.'

---

[2] On the term *engineering sciences*, readers may have different understandings, with either emphasis on the *engineering* part or on the *science* part of the term. Here it is assumed that the term *engineering sciences* is not to be taken as synonymous with *engineering*. Instead, engineering sciences are scientific research practices, often defined as "scientific research in the context of technological applications" (e.g., Boon 2011). When called *engineering sciences*, chemical, electrical and mechanical engineering are distinct scientific disciplines. Additionally, when called *engineering*, chemical, electrical and mechanical engineering are specialisms within engineering. The notion of an *engineering paradigm of science* is wrongly understood if considered as based on a common understanding of *engineering* (e.g., as in engineering and design practices). Instead, in this article, the engineering paradigm of science is developed by focus on specific features of existing scientific practices in the *engineering sciences*. This also involves the claim – although not explicitly made in this article – that not only systems biology, synthetic biology and biomedical sciences are better understood through an engineering paradigm of science, but also the engineering sciences themselves.

Aristotle's distinction is useful for understanding that the aim of science is an inherent part of a paradigm of science, bringing with it presuppositions on the character and subject matter of knowledge. On the one hand, the notion of *epistêmê* suits the idea that science aims at discovering the furniture of the world such as atoms and genes, but not at knowledge of complex, ever changing systems. On the other hand, the notion of *technê* is a better fit for the biomedical sciences such as systems biology and synthetic biology, which have adopted as an important goal to produce knowledge that is useful for generating things, i.e., knowledge for how to manipulate and change things and how to solve practical problems.

The Aristotelian distinction between *epistêmê* and *technê* as two different types of knowledge also involves that both their *subject matter* and the *epistemic criteria* for accepting knowledge are different. The idea expressed by *epistêmê* that the subject-matter of science is 'things that exist out of necessity and that are universal, eternal, ungenerated and imperishable' – an idea that is in striking agreement with commonly held ideas about fundamental physics that also motivated the physics paradigm, first in chemistry and later on in biology (as in Schrödinger 1944) – licenses the idea that scientific knowledge is not firstly evaluated for its usefulness, relevance and predictive reliability as to 'real world' systems, but rather for how it meets epistemic criteria such as truth, simplicity and universality. Conversely, *technê* expresses the idea that the subject matter of scientific research is 'things that are variable, generated, and perishable.' In accordance with this idea, the subject matter of *technê* is phenomena that are considered as 'functions' or 'functional phenomena' that can be generated by means of (technological) manipulation and intervention, or as 'problems' or 'problematic phenomena' in need of change or control. The production and epistemic uses of this kind of knowledge calls for epistemic tasks such as modelling and designing 'non-existing' things in such manner that the 'envisioned' things (phenomena and functions) can actually be created or changed. Performing these epistemic tasks involves using and generating knowledge suitable to these tasks, while epistemic criteria for evaluating the quality of knowledge thus produced are its usefulness and relevance to these epistemic uses, as well as its predictive 'productiveness' and adequacy for the behaviour of 'real world' systems.

Assuming that scientific practices can produce different types of knowledge, and also, that our understanding of the character of this knowledge is entangled with philosophical and normative ideas, implies that Kuhn's original set of elements of a disciplinary matrix that make up a paradigm needs to be expanded with additional *kinds* of presuppositions. The expanded matrix consists of the types of elements listed in the first column of the schema in Section 5.2, in which the elements II, IV, V and X agree to Kuhn's original set, while the other elements have been added.

5.2 The disciplinary matrix – expanding on Kuhn

The core of Kuhn's notion of scientific paradigms is that a scientific practice is embedded in a paradigm that enables and guides it (as illustrated in Figure 2), rather than being guided by strict methodological rules alone. Conversely, the paradigm is maintained and reinforced by the practice. A paradigm consists of a loose, non-rigid set of interlocking elements that mutually support and reinforce each other. Also, a paradigm is a kind of self-fulfilling prophecy that cannot be proven or disproven in a straightforward manner. Nonetheless, it can be articulated, analysed and disputed, and in the course of time new paradigms may replace more established ones.

The remainder of this article aims at articulating an engineering paradigm of science in contrast with a physics paradigm. This will be done in two steps. Firstly, the distinct elements of the extended disciplinary matrix will be listed, and each element will be filled in for the physics and the engineering paradigm in a contrastive manner, which results in the schema below. The construction of the disciplinary matrix and the substantiation of each element for the two paradigms builds on ideas and information presented in the previous sections. The content of the schema also aims to make obvious how distinct elements cohere and often support each other. Therefore, rather than discussing the mutual relationships between elements listed in the schema – in order to spell out how they are forged into a coherent whole called the physics and the engineering paradigm, respectively – focus will be on explaining how the elements of the engineering paradigm entail and support its most salient aspects as compared to the physics paradigm, which concerns the epistemic aim of science, and related to it, the character of knowledge for which the notion *knowledge as epistemic tool* is introduced. This is the second step (in Sections 5.3-5.5).

The content of the schema is not meant to be a complete description in the sense of presenting the necessary and sufficient contents of the two paradigms. Also, it is not meant to claim that molecular biology versus systems and synthetic biology agree one to one to the physics and engineering paradigm, respectively. Nor is it suggested that there are scientists or philosophers who would entirely adopt one or the other. The two paradigms have been constructed in a comparative and contrastive manner (at the same time aiming at their internal coherence), while the distinct scientific disciplines will have elements of both. Rather, the presented articulation is meant to promote philosophical reflection on, and further exploration of our ideas about science and scientific knowledge in these scientific practices.

This schema presents the proposed elements of the disciplinary matrix (first column), and their substantiation for the two paradigms of science, using biological and biomedical sciences as example

Elements constituting the paradigm	**A. Physics paradigm (e.g. as reconstructed from Schrödinger)**	**B. Engineering paradigm (as reconstructed from current authors)**
I. Epistemic aim(s) of scientific research	1. *Discovery* of basic physical entities (basic 'building-blocks' of nature), fundamental principles and general laws that govern nature. 2. *Explanation and prediction* of observed phenomena in terms of theories (fundamental principles and general laws). 3. *Unification* of theories.	1. *Construction of epistemic tools*: Knowledge production (e.g., concepts, laws and models) for practical uses, including epistemic uses that aim to discover *how* to generate and manipulate (biological or technological) functions for practical uses (e.g., as in medicine, agriculture and biotechnology). 2. *Explanation and prediction* of natural and technologically generated phenomena and functions in terms of concepts, laws and theories, thereby generating models that enable actual design, production and manipulation of these phenomena and functions. 3. *Interdisciplinarity* (rather than unification), which concerns the epistemic aim of generating scientific models in view of specific epistemic purposes (for practical uses).
II. Epistemic values & criteria for the acceptance of knowledge (Kuhn's third element)	1. truth (and empirical adequacy) 2. simplicity in the sense of generality 3. universality, 4. explanatory & predictive power, 5. logical consistency, 6. coherency with accepted knowledge, 7. derivability of knowledge at higher levels from knowledge at lower levels, 8. testability.	1. empirical adequacy, reliability and relevance in view of epistemic purposes (for practical uses), 2. simplicity in the sense of manageability & tractability, 3. balance between generality & specificity in view of epistemic aims, 4. explanatory & predictive reliability, 5. logical consistency, 6. coherence with accepted knowledge relevant to epistemic uses, 7. integration of knowledge from different fields and levels, 8. validation in view of epistemic uses.
III. Basic and 'regulative' principles (i.e., basic assumptions and rules guiding scientific research)**.**	1. *Unification*: 'aim at unity of knowledge.' 2. *Reductive explanation* i.e., 'aim at explanation of phenomena in terms of general laws and basic physical entities' (e.g., as in Human Genome project). 3. *Generalization* (inductive inference) based on reproducibility and the *ceteris paribus* principle, which involve, e.g., *testing* generalizability through reproducibility in a carefully controlled and stable (non-dynamic) environment (e.g., Robert 2004). 4. *Invariance*: i.e., 'search for physical phenomena that are stable at a variety of relevant physical conditions' (also see Woodward 2001).	1. *Integrative pluralism* & *pragmatism* (e.g., Mitchell 2009) 2. *Construction of models* for diverse epistemic purposes (e.g., explanation, prediction, building experimental models and computer simulations) 3. *Generalization* based on reproducibility and the regulative principle of *same conditions – same effects* (Boon 2012b), which involves, e.g. testing generalizability of knowledge in relevant, new, physical conditions, thus taking into account unforeseen interactions. 4. *Invariance* (next to reproducibility): 'search for physical phenomena that are stable at a variety of relevant physical conditions' (also see Woodward 2001).
IV. Theoretical principles of a discipline (Kuhn's symbolic generalizations)	1. Basic laws of a discipline, especially physics, such as Newton's laws of motion, Maxwell's laws of electricity and magnetism, the fundamental laws of thermodynamics, and the Schrödinger equation in quantum mechanics. 2. Laws such as PV(T)=c(T); V=I.R.	1. Basic laws are employed in model building (for specific types of target systems). 2. Phenomenological concepts and laws (derived from specific experimental set-ups, Feest 2010, Boon 2012a) are employed in model building. 3. Fundamental law-like presuppositions, such as, the conservation of mass, energy and atoms, or, as in thermodynamics 'heat cannot spontaneously flow from cold to hot,' are employed in (mathematical) model building.

		4. Typical engineering principles in modelling a specific system in order to reduce complexity, for example, distinguishing between dynamic, semi-steady state and steady state within a certain 'time-window' (cf. Kremling and Saez-Rodriguez 2007).
V. Metaphysical pre-suppositions (Kuhn's second element)	1. The world has a simple, hierarchical structure and is well ordered. 2. The world consists of a hierarchy of basic entities and general laws at lower levels that 'govern' objects & phenomena at higher levels. 3. *Physicalism*: each particular physical system (including biological systems) is constituted by nothing but physical and chemical entities and their interactions	1. The world has a complex, non-hierarchical structure: "large numbers of functionally diverse, and frequently multifunctional, sets of elements interact selectively and nonlinearly to produce coherent rather than complex behaviours" (Kitano 2002a). 2. Physical phenomena are composed of physical and chemical entities and governed by laws of nature. However, phenomena do not exist nor emerge independently, but in an interaction with their environment. 3. Biological systems are governed by their physical structure as well as by their higher-order functions.
VI. Ontology (i.e., how the subject-matter of research is conceptualized)	1. The physical world is conceptualized in term of objects, their properties and their causal workings. 2. *Ontological reductionism* (agrees with metaphysical presuppositions): Higher-level objects, their properties and their causal behaviour supervene on lower-level physical objects and properties (i.e., no difference in a biological property without a difference in some underlying physical property), and each particular biological process is metaphysically identical to some particular physico-chemical process (Brigandt and Love 2015).	1. In current systems biology and synthetic biology, *phenomena* (objects, properties, and processes) are usually conceptualized in terms of their function (see examples in Figure 1). 2. Biological structures are seen through an engineering perspective, calling them complex 'biological *systems*,´ which are conceptualized in terms of their function using engineering analogies (e.g., Figure 1), such as 'mechanisms,' 'modules,' 'informational systems' (Ideker et al. 2001), 'modular circuits' (Kitano 2002a), and different kinds of networks such as 'cybernetic networks' (Kauffman 1971), 'gene / metabolic / signal transduction networks' (Kitano 2002b), 'molecular networks' (Boogerd et al. 2013), and 'biological networks' (Somvanshi and Venkatesh 2014).
VII. Subject-matter (i.e., types of 'things' studied in scientific research)	1. Biological phenomena in nature. Focus is on fundamental, 'causally explanatory' basic entities: (e.g., genes and their molecular structure), 2. Basic entities are considered as independently existing. They are studied in isolation, at controlled, static environmental conditions (Roberts 2004).	1. Biological phenomena and systems, both in nature and those generated in (material) synthetic models. Focus is on different kinds of entities (e.g., basic genetic and non-genetic molecules, mechanisms, pathways, biological circuits and different kinds of networks). 2. Dynamics of biological phenomena and systems. 3. Biological functions and function*ing*. 4. Technological production and manipulation of (artificial) biological phenomena and functions by means of interlocking modelling techniques (using experimental, theoretical, mathematical and computer models, e.g. Nersessian 2009).
VIII. Epistemology	1. Scientific research aims at 'truth'. 2. Scientific research aims at theories and explanations. *Theoretical* and *explanatory reductionism* (Sarkar 1991, also see Brigandt and Love 2015): Strict laws (universal, exceptionless, spatio-temporally unrestricted) are required for explanation, and *why-necessary* explanations are better than *how-possible* explanations (Rosenberg 2006). Higher-level theories must be reduced to – and deduced from lower-level theories, and explanations of higher-level phenomena are in terms of at lower levels.	1. Scientific research aims at 'use': *How* and *How possible* 2. Scientific research aims at *epistemic tools*: Epistemic results (theories, models, laws, concepts) are epistemic tools constructed for epistemic uses such as construction of explanations and predictions, model-building (e.g., mechanistic, mathematical, experimental and synthetic models), creative thinking, problem-solving, computer simulations, and design of experimental equipment (Boon and Knuuttila 2009, Knuuttila and Boon 2011, Boon 2012a, Green 2013). 3. *Integration* of knowledge: Knowledge of dynamics, which involves spatial and temporal relations. This also allows for reductive causal explanations of lower-level phenomena in terms of higher-level

	3. *Hierarchy* of knowledge. Knowledge of basic constituents and their properties, which is a-temporal. Higher-level theories must be reduced to – and deduced from lower-level theories, and explanations of higher-level phenomena are in terms of lower-levels. 4. Theories and models aim to be ‘*true*’ *representations* of the real world (e.g., as in Boogerd et al. 2013: “a successful causal model is a mechanism responsible for the systemic behaviour articulated in terms of ‘real’ processes and parts.”).	properties (Hütterman and Love 2011). Furthermore, biological phenomena are conceptualized in terms of their structure and their function (cf. concept of dual nature, Kroes 1998, 2010). 4. Scientific knowledge is not necessarily ‘true’ representations – it does not necessarily refer to real parts and processes. It could resemble a control diagram an engineer would draw to study general properties of feedback (e.g., Boogerd et al. 2013; also see Isaac 2012).
IX. Methodology	1. *Methodological reduction* is the idea that biological systems are most fruitfully investigated at the lowest possible level, and that experimental studies should be aimed at uncovering molecular and biochemical causes. A common example of this type of strategy is the decomposition of a complex system into parts (e.g. Bechtel and Richardson 1993).	1. *Methodological reduction* is a pragmatic strategy in which a phenomenon is studied at controlled conditions. Many other strategies are used to study the complexity of biological systems (MacLeod and Nersessian 2013, 2015, also see Humphreys 2004 on the use of mathematical templates).
X. Exemplars of *science* (rather than exemplars of *theories*, as in Kuhn’s fourth element)	1. Physics (Schrödinger, 1944). 2. Analytical and physical chemistry.	1. Synthetic chemistry (e.g., Bensaude-Vincent, 2015). 2. Engineering sciences such as chemical engineering, mechanical engineering, electrical engineering, computer sciences, biotechnology, and nanotechnology.
XI. Role attributed to experiments and technological instruments	1. Experiments to discover and test theories. 2. (Development of) instruments to generate novel phenomena, to study phenomena, and to measure phenomena of nature (Boon 2004 calls these roles of instruments: *Manufacture*, *Model*, *Measure*).	1. Experiments to test models and quantify specific parameters, but also to simulate and manipulate in order to generate or control (functional and artificial) phenomena. 2. (Development and understanding of) technological instruments that produce specific (artificial and functional) phenomena (Boon 2017).
XII. Results / products of scientific research	1. *Epistemic*: Theories and laws. 2. *Physical*: Discovery of physical phenomena.	1. *Epistemic*: data-sets, phenomenological laws, scientific concepts, mechanistic and mathematical models, as well as scientific models of (the workings of) technological instruments and experimental set-ups. 2. *Physical*: Physical phenomena that may be of functional interest. 3. *Material*: Technological instruments and experimental model-systems. 4. *Virtual*: Mathematical tools and models, and computer models.
XIII. Justification	1. Aim is to *test* (confirm or falsify) a hypothesis, 2. basically, through the hypothetical-deductive method (as in Figure 2), which tests predictions deduced from the hypothesis by means of experiments, often also using computer simulations.	1. Aim is to *validate* epistemic results such as scientific models but also computer models (of complex multi-level systems), that is, to assess whether they meet the intended epistemic uses (also see Mitchell 2009 and Section 4.3 above). 2. How to *validate* computer models for biomedical applications, for instance, is the topic of this special issue. Knuuttila and Boon (2011) argue that much of the justification of a scientific model takes place when building it (rather than by experimental tests only).

5.3 The epistemic aim and values of science (element I and II)

The engineering paradigm encompasses the idea that the *epistemic aim of science* is to produce useful knowledge for solving problems and producing new things (element I-B), which is also reflected in the changed *epistemic values and criteria for accepting knowledge* (element II-B). Hence, besides meeting general epistemic criteria such as consistency and coherency, knowledge must also be relevant, useful and predictively adequate. Although these ‘pragmatic’ rather than ‘epistemic’ criteria were not explicitly included in the traditional physics paradigm, there has been a strong tendency to believe that ‘true’ knowledge would automatically be useful, and that explanation is symmetrical to prediction (also see Boon forthcoming). This belief is supported by the reductionist metaphysical and epistemological presuppositions of the physics paradigm (elements V-A and VIII-A), such as the idea that lower-level entities determine the behaviour at higher levels, which implies that ‘real world’ phenomena can, at least in principle, be explained and predicted by means of scientific knowledge generated by typical reductive methodologies (element A-IX). The former sections have outlined several examples and arguments of why this belief seems to be flawed. A huge problem for using knowledge in practical (biomedical) applications is the lack of understanding about how the entities studied in sciences such as molecular biology interact with their environment – i.e., in applications we lack knowledge on how the environment, which is kept constant in commonly accepted ‘traditional’ reductive methodologies, plays a role in *causing* the lower-level phenomena and on how these phenomena will respond to a changing environment (cf., Robert 2004).

5.4 What is knowledge? Knowledge as epistemic tool (element I-B and element VII)

The analysis of *epistêmê* and *technê* (Section 5.1) shows that the meaning of knowledge also concerns the *subject matter* of knowledge (element VII), which at the same time involves an ontology, i.e., concepts that ‘describe’ the subject matter of research (element VI). Whereas the physics paradigm puts emphasis on discovering fundamental entities and laws, the engineering paradigm stresses the production of knowledge and technological instruments by means of which ‘nature’ (physical phenomena) and technology (instruments that measure and/or technologically produce physical phenomena) can be created, manipulated and controlled (Boon, 2017). In other words, according to the engineering paradigm, scientific research also aims at knowledge *of* and *for* ‘man-made things.’

In view of the practical purpose of producing scientific knowledge for problem-solving and creating new things and functions, some philosophers of science have proposed to revise our conception of knowledge (such as theories and scientific models, laws and concepts). Instead of scientific knowledge firstly being a *representation* of how the world is independent of humans, they propose to characterize knowledge as *epistemic tools* (Nersessian 2009, Boon and Knuuttila 2009, Feest 2010, Knuuttila and Boon 2011, Boon 2012a, Green 2013).[3] Here, it is suggested that ‘knowledge as representation’ (in a

---

[3] An instrumental notion of knowledge has been around much longer. It has been defended by authors who aimed to avoid metaphysical notions (i.e., logical positivism and logical empiricism), and also Kuhn (1970) suggested this notion. Current philosophers of science, meanwhile, have developed the notion further, both as a viable alternative to a representational view of knowledge (e.g., as in scientific models) as well as to a definitional (conventionalist) view (as in scientific concepts).

correspondence sense) is deeply embedded in the physics paradigm whereas 'knowledge as epistemic tool' is central to the engineering paradigm. When knowledge is understood as an epistemic tool, then humans *construct* scientific knowledge for more or less specific epistemic uses, instead of somehow passively (but objectively!) mirroring the (unobservable) world as it really is (Boon forthcoming). Hence, the notion of knowledge as epistemic tool emphasizes the tripartite relationship between 'world' – knowledge – knowledge-user, rather than assuming a mere representational (and supposedly objective) 'world – knowledge' relationship (also see De Regt and Dieks 2005; De Regt et al. 2009). This view also means that knowledge must suit both the knowledge-user and the world in the sense that it enables epistemic uses in solving problems (which includes generating knowledge about 'real world' target systems) and creating new things in the world.

Some philosophers have begun to use this kind of thinking when developing alternatives to *representational* accounts of scientific *models* and *definitional* accounts of scientific *concepts*. Nersessian (2009), for instance, has used detailed history of science studies to argue that novel scientific *concepts* arise from attempts to solve specific problems, where scientists utilize conceptual ideas (such as analogies), and analytical and material resources. Feest (2010), Chang (2004, 2011) and Boon (2012a) add that in many cases the initial conceptual content of a scientific concept is determined by the 'paradigmatic experiment' in which its purported phenomenon manifests and is investigated. An example (not given by these authors) is the concept of 'yield' of micro-organisms (i.e., the amount of substrate consumed for its growth). This concept *derives from* experimental measurements of cell-growth and substrate consumption over time. It was further developed by Pirt (1965), who found in a *similar experimental set-up* that the yield is not a constant value but varies with the growth rate of micro-organism, which he interpreted as the amount of energy and substrate needed for the 'maintenance' of cells. The relationships found in his experimental data could be *described mathematically* by distinguishing between three scientific concepts: 'observed' yield, 'true' yield and maintenance. By this method, Pirt constructed the concepts of 'true yield' and 'maintenance,' which subsequently became *characteristic quantitative properties* of micro-organisms. Still, these concepts were not rigidly defined but developed further, for instance, by connecting them to concepts and properties in thermodynamics, which allowed for defining the 'thermodynamic efficiency' of growth (e.g., Roels 1980). The way in which scientific concepts emerge and develop sketched here is typical of the engineering sciences (e.g., chemical engineering, materials sciences and biotechnology), where it is commonly used in establishing *characteristic properties* of materials, processes and systems. The presented example illustrates that such scientific concepts are not determined by nature alone, but also by the experimental set-up and technological instruments to measure the relevant variables. Furthermore, it illustrates that a preliminary scientific concept such as 'yield,' is an epistemic tool as it allows for epistemic uses in further research, by which the content of the scientific concepts becomes enriched and refined.

The engineering concepts to 'describe' and explain biological phenomena presented in Section 2.1 are other examples. They are functional concepts with engineering connotations, which were *not* introduced because scientists literally believe that the biological phenomenon is a technological object or system. Instead, these engineering concepts facilitate different ways of reasoning about the biological phenomena, which in turn opens the way to new kinds of hypotheses. By using the concept in epistemic tasks, the content of scientific concepts develops, and eventually may gain a different meaning in the technological context.

Additionally, unlike the idea that scientific *models* are 'true' *representations* of an (unobservable) target phenomenon or system, the notion of knowledge as epistemic tool considers scientific models (and scientific knowledge in general) as constructed entities that enable different kinds of reasoning in problem solving. Scientific models of mechanisms, for instance, must be such that the model allows for inferential and creative reasoning about the causal workings of the target object, as well as how it could be manipulated in order to produce new (artificial and functional) phenomena.

According to Boon and Knuuttila (2009), the construction of a scientific model involves the integration of heterogeneous aspects into a coherent whole, utilizing relevant epistemic content (i.e., results of previous scientific research, see element XI-B, first point), with a specific epistemic purpose in mind (element I) and aiming to meet epistemic criteria relevant to that purpose (element II). The construction of scientific models is also guided by relevant principles (such as basic and regulative principles, see element III; and, theoretical principles, see element IV). An example of theoretical principles is the use of 'conservation-principles,' such as the conservation of mass, chemical atoms and charge, momentum and energy, which is crucial in the modelling of dynamic systems as these principles allow for the construction of 'balance-equations,' which in turn, enable mathematical descriptions of causal interactions between phenomena at different levels ('higher' and 'lower') in space and time (e.g., by means of diagrammatic models, see Boon 2008). What is more, as has been argued by Knuuttila and Boon (2011), much of the *justification* of scientific models comes from *how* it is constructed, while it is only partially put through empirical tests (element XIII-B). Therefore, different specializations may produce different types of knowledge (e.g., different kinds of explanatory models) that cannot be compared in a straightforward manner – or, in Kuhn's vocabulary, distinct explanations of the same phenomenon (e.g., explanations put forward by distinct scientific disciplines) are 'incommensurable.' Nevertheless, this does not imply that 'anything goes.' Very similar to the physics paradigm, the engineering paradigm entails that epistemic, physical, material and 'virtual' results of scientific research (element XII) are constrained and guided by regulative principles (see element III) and epistemic criteria (element II), and are ultimately assessed on how well they perform in view of specific epistemic aims (element I).

Obviously, what counts as results of scientific research (element XII) according to the engineering paradigm does not fit well with the expectations of the physics paradigm. For instance, the results do not consist of simple universal causal laws or relatively straightforward 'universal' mechanistic models (e.g., as in Machamer et al. 2000), and they often cannot be understood as a literally true story (a 'true' representation) of how the observed biological phenomenon or function is produced. The notion of knowledge as epistemic tool puts emphasis on the fact that scientific knowledge is *constructed*, rather than *discovered*. Also, it emphasizes the aspect of *technê* according to which knowledge is constructed *for* and *by means of* technologically creating and manipulating phenomena, such as the manipulation of DNA, and the synthetic or virtual production of biological functions (also see Boon 2015, forthcoming; Knuuttila and Loettgers 2013 a, b, 2014; and Section 2.2).

5.5 Metaphysical and epistemological presuppositions (element V and VIII)

The notion of knowledge as an epistemic tool does not easily fit with the physics paradigm, in which it tends to mean something more trivial, to wit, that scientific knowledge (such as a scientific model) can also be used as a tool, since knowledge allows for correct derivations *by virtue of* being a correct representation. Defenders of knowledge as epistemic tool reject the idea that knowledge is useful as a result of its representational qualities in a correspondence sense (Knuuttila and Boon 2011). Similarly, scientific knowledge is not *explanatory* by virtue of being a correct representation, but rather by virtue of it being *intelligible* in the sense that it allows knowledge-users to reason from it, for instance by drawing predictive conclusions about the behaviour of a system, or by crafting ideas about how to manipulate or build the system (also see De Regt 2015).

The notion of *knowledge as epistemic tool* is also easily misunderstood as being equivalent to having heuristic functions rather than representative ones, which would make it a rather thin notion. This and other misunderstandings are reinforced by the physics paradigm. In both paradigms of science, the distinction between knowledge (e.g., scientific concepts or models) that is merely heuristic (as a tool that helps to learn or solve problems, or that guides in discovery or investigation) and knowledge that is a ‘truthful’ or ‘adequate’ representations is meaningful. However, unlike ‘knowledge having a mere heuristic function,’ in order to be accepted as knowledge, knowledge understood as epistemic tool must meet certain epistemic values and criteria (element II). Although these criteria overlap between the two paradigms, the engineering paradigm puts more emphasis on the usefulness, relevance and predictive reliability of knowledge in view of its epistemic uses. Next to common uses in scientific reasoning (e.g., deductive, explanatory and predictive reasoning) taken for granted in the physics paradigm, this also encompasses constructive and creative reasoning by means of which scientific models and concepts for specific, still other epistemic uses are constructed or refined (e.g., scientific models of a biological mechanism by means of which the physical object can be manipulated, or scientific models of the workings of a synthetic model by means of which the physical object can be build). Accordingly, the engineering paradigm characterizes knowledge to function as an epistemic tool in generating more specific knowledge about a target system, which in turn, is an epistemic tool in the sense of giving directions on how to build, change or manipulate aspects of the target system.

Furthermore, common ideas on the character of scientific knowledge are part of a paradigm of science in the sense of being entangled with epistemological and metaphysical presuppositions, which also entail ideas on semantics, i.e., on how knowledge is linked to the real world. In the so-called realism debate, *scientific realists* distinguish between scientific knowledge that must be taken literally and therefore is *true*, versus knowledge that is only meant heuristically. Conversely, *anti-realists* such as Van Fraassen (1980) defend that scientific knowledge cannot be taken literally but merely needs to be *adequate* as to what can be *deduced* or *inferred* from it – i.e., scientific knowledge is at most ‘empirically adequate,’ rather than ‘true’ (see element II). Clearly, the anti-realist position is coherent with the idea of knowledge as epistemic tools, whereas opposition to this idea may partly be due to holding on to a realist position.

An example in biology is when scientists and philosophers of science are reluctant to accept mathematical models as explanatory, since full-blown scientific explanations must involve some kind of *literal* story of how the ‘real’ mechanism brings about biological phenomena (e.g., Craver 2006). Conversely, other researchers such as Brigandt (2013) adopt a pragmatic view on explanation: since mathematical models allow for predicting biological phenomena that result from the dynamics of a system, they must be considered as explanatory of the observed behaviour. Accordingly, Brigandt emphasizes the explanatory and predictive *usefulness* of mathematical models, which agrees with the notion of knowledge as epistemic tool. Indeed, when knowledge is viewed as epistemic tool, epistemic results (element XII-B) are constructed such that they allow for specific types of reasoning about a target, but it is often much harder to see *what* the knowledge *represents* exactly (see Carusi et al. 2013 for a detailed analysis of the representational relationships between model and target).

Hence, whereas the metaphysical and epistemological presuppositions of a physics paradigm suggest exclusiveness on what kind of knowledge is acceptable and what counts as 'real' explanations, the engineering paradigm allows for different types of knowledge and explanations about the same target, and evaluates them for their epistemic usefulness such as for explaining, predicting, generating or manipulating relevant phenomena, or for building physical systems (e.g., synthetic models) to produce specific phenomena.

6. Conclusions

Systems biology and synthetic biology are newly emerging disciplines within the broader context of the biomedical sciences. Although they can be considered as springing from established disciplines such a biochemistry and molecular biology, their character qua science is very different. The emergence of these new disciplines has been prompted by scientists who came to see that biological systems are much more complex than the isolated objects studied in molecular biology (e.g., genes), and also, that knowledge of these isolated objects, even when complete in regard of the make-up of the human genome, lacks crucial information for actually utilizing it in biomedical applications, such as those foreseen in the *Human Genome Project*. Leading scientists consider the use of engineering concepts and methods crucial to the successful development of these disciplines, while philosophers of sciences have interpreted the ubiquitous utilization of engineering concepts and methods as a change of paradigm within the biomedical sciences. This article has aimed to flesh-out this idea by explaining the notion of paradigm, and by articulating in a comparative and contrastive manner, a physics paradigm that gave rise to earlier successful disciplines in biomedical sciences (biochemistry and molecular biology), versus an engineering paradigm that supposedly promotes current systems biology and synthetic biology.

The established paradigm of a scientific practice confines what can be observed, asked and explained, while a change of paradigm enables new types of observations, questions and explanations (as was visualized in Figure 2). Hence, an engineering paradigm enables observation of new kinds of phenomena such as the robustness of a system, raises new kinds of questions such as how robustness is generated, offers concepts from engineering for crafting explanations of biological phenomena, and facilitates the incorporation of engineering methods such as mathematical modelling, synthetic modelling and computer simulations, and epistemic strategies such as reductive, iterative, integrative and instrumental approaches in knowledge generation. Also, a paradigm involves new ontological and epistemological principles, which open the way for biological systems being considered as primarily 'functional' and 'purposeful,' rather than as physical processes that can and must be explained in terms of ever more fundamental physical entities and laws. Accordingly, an engineering paradigm steps away from the idea of a blueprint of life that was supported by metaphysical and ontological presuppositions of the physics paradigm, and allows for explanations that start from the function and functionality of a system. This functional perspective enables observation of the *functional* properties of a system and crafting of explanations in terms of nature's *design strategies* in generating these properties, without the need to take these notions literally or metaphysically. Altogether, the emergence of a new paradigm goes hand-in-hand with the transformation process of the scientific practice – that is, innovations such as new concepts, methods and technological instruments adopted in a practice may give rise to a new paradigm, which in turn shapes the practice. Eventually, this may result into new ideas about 'what biological science is.'

Furthermore, although the two paradigms are developed contrastively and symmetrically, they are not symmetrical in what is to be taken as the core that to some extent motivates the content of the other elements of the paradigm. Central to the physics paradigm is its metaphysical and ontological presuppositions, whereas central to the engineering paradigm is the epistemic aim of science (i.e., producing useful knowledge and technological instruments). As a consequence, metaphysical and ontological presuppositions are less important in the engineering paradigm, whereas the epistemic aim 'external' to the scientific discipline is a less important element in the physics paradigm.

At the core of articulating the engineering paradigm is the claim that it involves another notion of knowledge. A preliminary explanation of this idea was given by means of the Aristotelean distinction between two types of knowledge, *epistêmê* and *technê*. Next, the notion of *knowledge as epistemic tool* was introduced. It was argued that this notion of knowledge agrees with the central idea of the engineering paradigm, which is that the aim of science is to produce knowledge and technological instruments for epistemic uses 'external' to scientific practices (e.g., in solving societal problems and in *making* things) in such a manner that it suits the needs and cognitive abilities of knowledge-users. The latter requires, for instance, that knowledge is intelligible (as otherwise knowledge-users will not be able to use it as a tool for reasoning) but does not favour any one type of knowledge (e.g. causal-mechanistic explanations) over another (e.g., mathematical models). Also, 'knowledge as epistemic tool' is an alternative to a commonly held idea in the physics paradigm that knowledge can be used by virtue of it being a correct representation of how the world 'really' is. Indeed, this misconceived understanding of 'knowledge as epistemic tool' suggested by the physics paradigm is difficult to overcome since it is motivated and supported by the metaphysical and ontological presuppositions of the physics paradigm. Nonetheless, knowledge as epistemic tool is a very productive idea for scientific practices aiming at knowledge that meets the epistemic criteria of the engineering paradigm. Accordingly, the engineering paradigm involves a thoroughly pragmatic notion of knowledge that, on the one hand, urges us to meet challenging quality criteria (the epistemic criteria, but also the needs of knowledge-users, such as 'intelligibility'), and on the other hand, liberates us from rigid, and sometimes unproductive ideas of what 'real' scientific knowledge is, as regimented by the physics paradigm of science. An engineering paradigm invites us to try-out whatever works best in constructing epistemic tools, such as using engineering concepts in trying to understand biological phenomena. But this does not mean that 'anything-goes'. The engineering paradigm requires us to remain very critical with regard to relevant epistemic criteria and the aim of science. It makes it possible for a science to be loved and admired, not for agreeing to the physics paradigm, but for being creative, innovative, productive and useful.

Acknowledgements

An early version of this paper has been presented at the Wellcome Trust Funded workshop *Validation and Models in Computational Biomedical Science: Philosophy, Engineering and Science*, held on November 30, 2015 at the University of Sheffield, co-hosted by Medical Humanities Sheffield and the Computational Cardiovascular Sciences Team, University of Oxford. I wish to thank Annamaria Carusi, Blanca Rodriguez and the Insigneo Institute for In Silico Medicine for organizing this workshop. The second version was presented at the conference *(Re)Engineering Biology*, held on April 15-16, 2016 in the Center for Philosophy of Science at the University of Pittsburgh, organized by Nancy Nersessian et al., for which I wish to thank them. This paper was also presented at the biennial conference of the Society for Philosophy of Science in Practice (SPSP2016). I also wish to thank Henk Procee and two anonymous referees for their thorough critique and suggestions on earlier versions. This work is financed by an Aspasia grant (2012-2017) of the Dutch National Science Foundation (NWO) for the project “Philosophy of Science for the Engineering Sciences.”

References

Andrianantoandro, E., Basu, S., Karig, D. K., & Weiss, R. (2006). Synthetic biology: new engineering rules for an emerging discipline. *Molecular Systems Biology, 2*(1). doi:10.1038/msb4100073

Aristotle. (1999). *Nichomachean Ethics, second edition, trans. Terence Irwin*. Indianapolis: Hackett Publishing Co.

Benner, S. A., & Sismour, A. M. (2005). Synthetic biology. *Nat Rev Genet, 6*(7), 533-543. Retrieved from http://dx.doi.org/10.1038/nrg1637

Bensaude-Vincent, B. (2015). Synthetic Biology As a Replica of Synthetic Chemistry? Uses and Misuses of History. *Biological Theory, 4*(4), 314-318. doi:10.1162/BIOT_a_00007

Boogerd, F. C., Bruggeman, F. J., & Richardson, R. C. (2013). Mechanistic Explanations and Models in Molecular Systems Biology. *Foundations of Science, 18*(4), 725-744. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=phl&AN=PHL2217175&site=ehost-live

Boon, M. (2004). Technological Instruments in Scientific Experimentation. *International Studies in the Philosophy of Science*. 18(2&3): 221-230.

Boon, M. (2008). Diagrammatic Models in the Engineering Sciences. *Foundations of Science, 20*(1), 27-47.

Boon, M., & Knuuttila, T. (2009). Models as epistemic tools in engineering sciences: a pragmatic approach. In A. Meijers (Ed.), *Philosophy of technology and engineering sciences. Handbook of the philosophy of science* (Vol. 9, pp. 687-720): Elsevier/North-Holland.

Boon, M. (2011). In Defense of Engineering Sciences: On the Epistemological Relations Between Science and Technology. *Techné: Research in Philosophy and Technology, 15*(1), 49-71.

Boon, M. (2012a). Scientific Concepts in the Engineering Sciences: Epistemic Tools for Creating and Intervening with Phenomena. In U. Feest & F. Steinle (Eds.), *Scientific Concepts and Investigative Practice* (pp. 219 - 243). Berlin: De Gruyter.

Boon, M. (2012b). Understanding Scientific Practices: The Role of Robustness Notions. In L. Soler, E. Trizio, Th. Nickles, & W. Wimsatt (Eds.), *Characterizing the Robustness of Science after the Practical Turn of the Philosophy of Science* (pp. 289-315): Springer: Boston Studies in the Philosophy of Science.

Boon, M. (2015). The Scientific Use of Technological Instruments. In S. O. Hansson (Ed.), *The Role of Technology in Science: Philosophical Perspectives* (18 ed., pp. 55-80). Dordrecht/Heidelberg: Springer.

Boon M. (2017) Measurements in the Engineering Sciences: An Epistemology of Producing Knowledge of Physical Phenomena**.** Chapter 15 in: *Reasoning in Measurement*, N. Mößner and A. Nordmann (eds.) Series "History and Philosophy of Technoscience". London and New York: Routledge, 203-219.

Boon M. (forthcoming). Philosophy of Science in Practice: A Proposal for Epistemological Constructivism. Chapter 16 in: *Proceedings of the 15th Congress of Logic, Methodology, and Philosophy of Science (CLMPS) 2015*, pp 289-310.

Brigandt, I. (2013). Systems Biology and the Integration of Mechanistic Explanation and Mathematical Explanation. *Studies in History and Philosophy of Biological and Biomedical Sciences, 44*(4), 477-492. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=phl&AN=PHL2219558&site=ehost-live

Brigandt, I., & Love, A. (2015). Reductionism in Biology. In E. N. Zalta (Ed.), *The Stanford Encyclopedia of Philosophy*: http://plato.stanford.edu/archives/fall2015/entries/reduction-biology/

Bruggeman, F. J. and H. V. Westerhoff (2007). "The nature of systems biology." Trends in Microbiology **15**(1): 45-50.

Carusi, A. (2014). Validation and variability: Dual challenges on the path from systems biology to systems medicine. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 48, Part A*, 28-37. doi:http://dx.doi.org/10.1016/j.shpsc.2014.08.008

Carusi, A., Rodriguez, B., & Burrage, K. (2013). Model Systems in Comptational Systems Biology. In J. M. Durán & E. Arnold (Eds.), *Computer Simulations and the Changing Face of Scientific Experimentation* (pp. 118-144): Cambridge Scholars Publishing.

Chang, H. (2004). *Inventing Temperature: Measurement and Scientific Progress*. Oxford: Oxford University Press.

Chang, H. (2011). The Persistence of Epistemic Objects Through Scientific Change. *Erkenntnis*, 75, 413-429. doi: 10.1007/s10670-011-9340-9.

Craver, C. F. (2006). When mechanistic models explain. *Synthese, 153*, 355-376. doi:10.1007/s11229-006-9097-x

Csete, M. E. and J. C. Doyle (2002). "Reverse engineering of biological complexity." Science **295**(5560): 1664-1669.

De Regt, H. W., & Dieks, D. (2005). A contextual approach to scientific understanding. *Synthese*, 144, 137-170. doi:DOI: 10.1007/s11229-005-5000-4

De Regt, H. W., Leonelli, S., & Eigner, K. (Eds.). (2009). *Scientific Understanding - Philosophical Perspectives*. Pittsburgh: Pittsburgh University Press.

De Regt, H. W. (2015). Scientific understanding: truth or dare? *Synthese*, 192(12), 3781-3797. doi:10.1007/s11229-014-0538-7.

Dev, S. B. (2015). Unsolved problems in biology—The state of current thinking. *Progress in Biophysics and Molecular Biology, 117*(2–3), 232-239. doi:http://dx.doi.org/10.1016/j.pbiomolbio.2015.02.001

Dupré, J. (1993). *The Disorder of Things: Metaphysical Foundations of the Disunity of Science*. Cambridge MA: Harvard University Press.

Dupré, J. (1995). *The Disorder of Things:* Metaphysical Foundations of the Disunity of Science. *Proceedings and Addresses of the American Philosophical Association*, APA 68(3): 84-86.

Elowitz, M. B., & Leibler, S. (2000). A synthetic oscillatory network of transcriptional regulators. *Nature, 403*(6767), 335-338. doi:10.1038/35002125

Endy, D. (2005). Foundations for engineering biology. *Nature, 438*(7067), 449-453. Retrieved from http://dx.doi.org/10.1038/nature04342

Feest, U. (2010). Concepts as Tools in the Experimental Generation of Knowledge in Cognitive Neuropsychology. *Spontaneous Generations, 4*(1), 173-190.

Frauenfelder, H. (2014). Ask not what physics can do for biology—ask what biology can do for physics. *Physical Biology, 11*(5), 053004. Retrieved from http://stacks.iop.org/1478-3975/11/i=5/a=053004

Frauenfelder, H., Wolynes, P. G., & Austin, R. H. (1999). Biological Physics. *Reviews of Modern Physics, 71*(2), S419-S430. Retrieved from http://link.aps.org/doi/10.1103/RevModPhys.71.S419

Green, S. (2013). When one model is not enough: Combining epistemic tools in systems biology. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 44*(2), 170-180. doi:http://dx.doi.org/10.1016/j.shpsc.2013.03.012

Gumbrecht, H. U. (2011). *What is Life?: The Intellectual Pertinence of Erwin Schrödinger*: Stanford University Press.

Hartwell, L. H., Hopfield, J. J., Leibler, S., & Murray, A. W. (1999). From molecular to modular cell biology. *Nature*. Retrieved from http://www.nature.com/nature/journal/v402/n6761supp/full/402c47a0.html?message=remove&WT.mc_id=FBK_NatureReviews

Humphreys, P. (2004). *Extending Ourselves: Computational Science, Empiricism, and Scientific Method*. New York, NY: Oxford University Press.

Hüttemann, A., & Love, A. C. (2011). Aspects of Reductive Explanation in Biological Science: Intrinsicality, Fundamentality, and Temporality. *The British Journal for the Philosophy of Science, 62*(3), 519-549. doi:10.1093/bjps/axr006

Ideker, T., Galitski, T., & Hood, L. (2001). A new approach to decoding life: systems biology. *Annual review of genomics and human genetics, 2*(1), 343-372. doi:DOI: 10.1146/annurev.genom.2.1.343

Ingolia, N. T. and J. S. Weissman (2008). "Systems biology: Reverse engineering the cell." Nature **454**(7208): 1059-1062.

Isaac, A. M. C. (2012). Modeling without representation. *Synthese, 190*(16), 3611-3623. doi:10.1007/s11229-012-0213-9

Kauffman, S. A. (1971). Articulation of parts explanations in biology and the rational search for them. In R. C. Buck & R. S. Cohen (Eds.), *PSA 1970, Boston Studies in Philosophy of Science, Volume 8* (pp. 257–272). Dordrecht: Reidel.

Kitano, H. (2002a). Computational systems biology. *Nature, 420*(6912), 206-210. Retrieved from http://dx.doi.org/10.1038/nature01254

Kitano, H. (2002b). Looking beyond the details: a rise in system-oriented approaches in genetics and molecular biology. *Current Genetics, 41*(1), 1-10. doi:10.1007/s00294-002-0285-z

Knuuttila, T., & Boon, M. (2011). How do models give us knowledge? The case of Carnot's ideal heat engine. *European Journal for Philosophy of Science, 1*(3), 309-334. doi:10.1007/s13194-011-0029-3

Knuuttila, T., & Loettgers, A. (2013a). Basic Science Through Engineering? Synthetic Modeling and the Idea of Biology-Inspired Engineering. *Studies in History and Philosophy of Biological and Biomedical Sciences, 44*(2), 158-169. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=phl&AN=PHL2209057&site=ehost-live

Knuuttila, T., & Loettgers, A. (2013b). Synthetic Modeling and Mechanistic Account: Material Recombination and Beyond. *philosophy of science, 80*(5), 874-885. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=phl&AN=PHL2218080&site=ehost-live

Knuuttila, T., & Loettgers, A. (2014). Varieties of Noise: Analogical Reasoning in Synthetic Biology. *Studies in History and Philosophy of Science, 48*, 76-88. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=phl&AN=PHL2235107&site=ehost-live

Kremling, A. and J. Saez-Rodriguez (2007). "Systems biology - An engineering perspective." Journal of Biotechnology **129**(2): 329-351.

Kroes, P. (1998). Technological Explanations: The Relation between Structure and Function of Technological Objects. *Techné: Research in Philosophy and Technology, 3*(3), 124-134. doi:10.5840/techne19983325

Kroes, P. (2010). Engineering and the dual nature of technical artefacts. *Cambridge Journal of Economics, 34*(1), 51-62. doi:10.1093/cje/bep019

Kuhn, T. S. (1970a). *The Structure of Scientific Revolutions, second edition*. Chicago: The University of Chicago Press.

Kuhn, T. S. (1970b). *Reflections on my critics*. In I. Lakatos & A. Musgrave (Eds.), *Criticism and the Growth of Knowledge.* (pp. 231-278): Cambridge University Press.

Kuhn, T. S. (1974). *Second thoughts on paradigms*. In F. Suppe (Ed.), *The structure of scientific theories* (Vol. 2, pp. 459-482). Urbana, ILL: University of Illinois Press.

Kuhn, T. S. (1977). Objectivity, Value Judgment, and Theory Choice. In: *The Essential Tension: Selected Studies in Scientific Tradition and Change* (pp. 320-339). Chicago: The University of Chicago Press.

Machamer, P., Darden, L., & Craver, C. F. (2000). Thinking about Mechanisms. *Philosophy of Science, 67*(1), 1-25.

MacLeod, M., & Nersessian, N. J. (2013). Coupling simulation and experiment: The bimodal strategy in integrative systems biology. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 44*(4, Part A), 572-584. doi:http://dx.doi.org/10.1016/j.shpsc.2013.07.001

MacLeod, M., & Nersessian, N. J. (2015). Modeling systems-level dynamics: Understanding without mechanistic explanation in integrative systems biology. *Studies in History and Philosophy of*

Biological and Biomedical Sciences, 49, 1-11. doi:http://dx.doi.org/10.1016/j.shpsc.2014.10.004

Mitchell, S.D. (2003), *Biological complexity and integrative pluralism*. New York: Cambridge University Press.

Mitchell, S. D. (2009). *Unsimple Truths, Science Complexity and Policy*. Chicago and Londen: The University of Chicago Press.

Nersessian, N. J. (2009). How Do Engineering Scientists Think? Model-Based Simulation in Biomedical Engineering Research Laboratories. *Topics in Cognitive Science, 1*(4), 730-757. doi:10.1111/j.1756-8765.2009.01032.x

Noble, D. (2010). Biophysics and systems biology. *Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences, 368*(1914), 1125-1139. doi:DOI: 10.1098/rsta.2009.0245

Pirt, S. J. (1965). The Maintenance Energy of Bacteria in Growing Cultures. *Proceedings of the Royal Society of London. Series B, Biological Sciences, 163*(991), 224-231. Retrieved from http://www.jstor.org/stable/75569

Robert, J. S. (2004). *Embryology, Epigenesis, and Evolution - Taking Development Seriously*. Cambridge UK: Cambridge University Press.

Roels, J. A. (1980). Application of macroscopic principles to microbial metabolism. *Biotechnology and Bioengineering, 22*(12), 2457–2514. doi:10.1002/bit.260221202.

Rosenberg A. (2006), *Darwinian reductionism: or, how to stop worrying and love molecular biology*. Chicago: University of Chicago Press.

Sarkar, S. (1991). Models of reduction and categories of reductionism. *Synthese, 91*(3), 167-194. doi:10.1007/bf00413566

Schrödinger, E. (1944). *What is Life?* : Cambridge University Press.

Sismour, A. M., & Benner, S. A. (2005). Synthetic biology. *Expert opinion on biological therapy, 5*(11), 1409-1414.

Somvanshi, P. R., & Venkatesh, K. V. (2014). A conceptual review on systems biology in health and diseases: from biological networks to modern therapeutics. *Systems and Synthetic Biology, 8*(1), 99-116. doi: 10.1007/s11693-013-9125-3

Van Fraassen, B. C. (1980). *The Scientific Image*. Oxford: Clarendon Press.

Viceconti, M., Henney, A., Morley-Fletcher, E., & Consortium), e. a. T. A. (2016). *Avicenna Roadmap: "in silico Clinical Trials: How Computer Simulation will Transform the Biomedical Industry"*. Retrieved from http://www.vph-institute.org/ , https://www.researchgate.net/publication/289522507_in_silico_Clinical_Trials_How_Computer_Simulation_will_Transform_the_Biomedical_Industry

Woodward, J. (2001). Law and Explanation in Biology: Invariance Is the Kind of Stability That Matters. *Philosophy of Science* 68(1), 1-20.