Chapter 2
Basic Concepts of Systems Biology as Seen Through Systems Biologists' Eyes: Metaphorical Imagination and Epistemic Presuppositions

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Abstract After the successful structural analysis of the human and other organisms' genomes the last decade witnessed a fundamental shift in the area of research in molecular biology: the move into Omics. It produced a plethora of data that require methodological and conceptual approaches to systematize, integrate, and interpret data which go beyond a linear understanding of biological processes and systems. The promise of the rapidly developing field of systems biology is to extend—if not overcome—the methodological and theoretical limits set by previous research undertaken in molecular biology. Taking this contemporary development seriously, this chapter investigates the framing of basic epistemic concepts (life, system, reductionism, holism, and model) by scientists working in systems biology. Based on a corpus of written evidence and interviews conducted with system biologists in Germany, we analyze the metaphorical frameworks underlying their conceptualization to tackle implicit meanings and the practical relevance ascribed to them. It becomes apparent that (to some extent) different professional backgrounds bear an impact on the framing of different concepts and heterogeneous interpretation prevails. The results underline the need for theoretical clarification of basic epistemic concepts in systems biology and the implementation of a science philosophy curriculum as a basic ingredient of university education. Both aspects are important to avoid methodological and theoretical fallacies that restrict the innovative potential of systems biology.

Keywords Systems biology • Basic concepts • Conceptual analysis • Metaphor

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Science and any branch of it are practically based upon a certain number of relevant or basic concepts. These concepts may take different forms in different disciplines, but within a specific discipline they are commonly shared and exhibit an imaginative mindset upon which basic methods and interpretations rest. This is also the case in the present context of systems biology. Generally conceived as a successor of molecular biology and heavily influenced by information and communication technology (ICT), it conceptually merged these two research fields promising not only new insights into the workings of biological systems but also a variety of innovations ranging from new medical or pharmacological applications to the development of new methods in biology (Sect. 5.1). The ICT-driven approach in systems biology represents a technologically induced and data-driven remathematization of biology that aims at a deeper understanding and better prediction of molecular processes at, between, and above all levels of biological organization. It is thus not surprising that the ambitious enterprise of systems biology has been welcomed at the wake of the new millennium as an improved approach of addressing and dealing with biological complexity.

The question, however, is what basic concepts systems biology exactly relies upon and what their content and practical use is. Both aspects are dealt with in this chapter by using an empirical approach based on a combination of discursive and linguistic approaches that provide insight into the conceptualization of important concepts used and applied in systems biology. The chapter addresses thus the following questions:

- What are basic concepts in systems biology?
- How are they framed and semantically conceptualized by scientists working in the field of systems biology?
- Are there any significant con- or divergences between scientists holding different professional backgrounds? If so, why and how do the concepts analyzed di- or converge?
- What are the possible implications contained in these basic concepts?

For this to be done, we start with a short overview of how epistemic concepts in biology have been analyzed to date (Sect. 2.1.1). Against this background, we outline the theoretical aspects of our language-oriented approach, which is mainly based on the analysis of metaphors and metaphorical concepts that are conceived of as basic mechanisms to produce, maintain, and share meaning (Sect. 2.1.2). This section is followed by methodological considerations about the data gathered and their analysis before we turn to the systematic investigation and interpretation of the concepts and their metaphorical expression encountered in expert interviews. Paradigmatic examples taken from the interviews are used to illustrate the metaphorical concepts that permeate and semantically structure the basic concepts analyzed. These are life (Sect. 2.2), system (Sect. 2.3), reductionism (Sect. 2.4), holism (Sect. 2.5), and model (Sect. 2.6). Once they have been analyzed, the final section of this chapter (Sect. 2.7) summarizes the findings and provides an assessment of the basic concepts as seen through systems biologists' eyes. It analyzes the aspects of intangible creativity nestling in the metaphorical conceptualizations of the basic concepts and partly compares them with everyday practices as alluded to in the interviews. Let us now turn to an impressionistic overview of research undertaken in the philosophy of biology and systems biology. Here, we outline the theoretical and methodological aspects of our analysis which are then applied throughout this chapter.

2.1 Basic Concepts and Implications

Questions about the epistemic dimensions of biology have been raised by a variety of scientists stemming from disciplines such as the philosophy or sociology of science, science and technology studies, the history of science, and other disciplines. They mostly converge in the fact that they understand scientific knowledge as an experiential, socially, and culturally generated construct. Even though there are different theoretical and methodological approaches within these different branches, science studies or the social study of science in general investigate the sociocultural and historical contingencies underlying the production, maintenance, and dispersion of scientific knowledge. The new philosophy of biology represents within this framework a subdiscipline that emerged at the start of the 1970s (Byron 2007) as a reaction to the traditional philosophy of science which was grounded in logical positivism and mainly addressed in physics. This led to fruitful debates and interactions of scientists and philosophers introducing a critical and above all reflexive perspective on the scientific enterprise of biology. Questions addressed in the philosophy of biology revolve around the structure and content of concepts or particular kinds of explanation that are, again and again, combined with questions addressing methodological or practical aspects. At the beginning, the philosophy of biology focused on evolutionary biology and biological systematics, but the philosophical grounding of molecular and experimental biology also received considerable attention. This was due to the advent of genetics and molecular biology, and a consequence of debates on whether biological disciplines could be reduced to molecular biology.[1] The further development of biology and the emergence of the life and biomedical sciences, including the previously mentioned Omics approaches, contributed to the development of a field that was—because of its tremendous methodical and technical advances—leading to ever better insights into genetic structures and mechanisms. However, it also provoked far- reaching ethical, social, and legal questions.[2] As a consequence, more and more scholars started to address and investigate such aspects innate in modern biology and medicine.

[1] We can only provide an impressionistic overview of the developments here. For further information see Sattler (1986), Sober (1993), Sterelny and Griffiths (1999), Hull and Ruse (2007) and Ayala and Arp (2009).

[2] Examples of this extensive body of work are Marteau and Richards (1996); Tutton and Corrigan (2004); or Forgó et al. (2010).

In this context, the recent advent of the interdisciplinary endeavor of systems biology represents an attempt to reintroduce a holistic perspective.[3] Based on a new technologically driven guise it mainly attracted attention from some researchers working in the overlapping areas such as the philosophy of biology, science and technology studies, and the history of science. Interest in the area of science studies was rather moderate even though different aspects have been investigated since 2005 by a rather small group of researchers. O'Malley et al. (2007) were among the first who addressed the issue of systems biology and they provided a fruitful conceptual overview of its socioethical issues. Dupré and O'Malley (2007) investigated questions about metagenomics and the impact of this discipline on reshaping biological categories and ontologies. O'Malley and Dupré (2005, 1250) also investigated fundamental issues in systems biology studying the identification of systems and the different causalities that operate at different levels of organization. Besides these more or less philosophical approaches Calvert and Fujimura (2011) studied epistemic problems and issues emerging in the interdisciplinary context of systems biology whereas Kastenhofer (2013) applied to this newly emerging approach the concept of epistemic cultures[4] (Knorr Cetina 1999) in order to analyze differences between systems and synthetic biology. Calvert (2007) also examined questions of patenting and problematized aspects of data-driven research (Calvert and Joly 2011) and De Backer et al. (2010) explored the conceptual and disciplinary borders between molecular systems biology. Ofran (2008) analyzed the emergentist's and reductionist's views underlying systems and molecular biology whereas Fujimura (2005) referred, though not systematically, to the relevance of metaphors in the conceptual language of post-genomic research and systems biology. Fox Keller (2002) provided a diachronic and conceptual analysis of synthetic and systems biology. She emphasized the importance of metaphors and models for making sense of observational and experimental data in biology providing a large overview and a deep insight into the development of biological thinking. The only paper explicitly investigating a basic concept is O'Malley's and Soyer's (2012) paper on integration in molecular systems biology: they and Green and Wolkenhauer (2012) depict the different meanings of integration and show how it has been discussed from scientific and philosophical points of view (O'Malley and Soyer 2012, 58; McLeod and Nersessian 2014).

Against this background, this chapter aims at an empirical analysis of life, system, reductionism, holism, and model as basic concepts in systems biology. Such an analysis has, to our knowledge, not been carried out to date. Emphasis is put on a grounded approach which means that data were gathered during qualitative expert interviews. These interviews were transcribed and thoroughly analyzed according to the converging requirements as outlined in grounded theory (Charmaz 2006;

[3] The notion of holism is further contextualized and explained in Sect. 2.5.

[4] The notion of epistemic cultures refers to the analysis of how scientific disciplines create knowledge. The concept refers to the idea that different disciplines possess intermingled scientific processes and social rationales which determine the way they do science and bear an impact on what kind of knowledge is created.

Clarke 2005; Corbin and Strauss 2008) and in the systematic analysis of metaphor (Schmitt 2000, 2005, 2011; Döring 2014). It is, furthermore, important to bear in mind that two fundamental assumptions underlie this chapter: first, that metaphors are a ubiquitous phenomenon in scientific language and thinking and, second, that the analysis of these linguistic images provides a valuable insight into the unconscious and implicit dimensions underlying the scientific theories, models, and concepts implicated in both (Paton 1996). A systematic analysis of metaphor thus holds the potential to unravel implicit foundations and connected presuppositions informing scientific thinking and acting because scientific language, like all sorts of human language and discourse, is permeated by metaphor. The systematic analysis of metaphor hence offers a constructive way to make transparent the semantic content of basic concepts in systems biology and it helps to better understand the styles of thought (Fleck 2011) in systems biology. These subconscious styles of thought and their structuration are of particular interest here as they bear an impact on how research in systems biology is done and by what kind of basic concept it is informed. It is, however, necessary to explain our analytical concept of metaphor as an essential ingredient in the workings of science in more detail. We therefore turn in the next section to a more general outline of its functions in language, thought, and action before we briefly describe the methods we applied to our data.

2.1.1 Science, Tacit Knowledge, and Linguistic Imagery

Nowadays it is a truism to state that metaphors and other kinds of linguistic imagery pervade and are creatively applied in scientific thinking (Brown 2008; Katherndahl 2014). Numerous scholars working in science and technology studies, in philosophy of science, and the social study of science have undertaken research on the constitutive role of metaphors and metonymies for scientific thinking, the development of concepts, theories, and methods of science. Important publications have paved the way for further research on the use of metaphor in biotechnological and biomedical science.[5] Especially this scientific field took up speed in the context of the human genome project at the turn of the century when attention was redrawn to the constitutive role of metaphors for science.

Numerous articles have since then been published on all sorts of aspects revolving around a large variety of topics ranging from the role of linguistic imagery in scientific thought or everyday practices via the pervasive role of metaphor in policy and regulatory discourses to the media-metaphorical framings of biotechnological developments and innovations. Especially the latter, often running under the heading of "public understanding of science", received considerable attention and this is why it is simply impossible to review all theoretical and methodological approaches

[5] See for example Black (1962), Gentner and Jeziorski (1993), Hesse (1970, 2005), Fox Keller (1992, 2002), Haraway (2004), Kay (1997, 2000), Knorr Cetina (1981), Maasen and Weingart (2000) and Nerlich et al. (2009).

applied to analyses. A closer look at the main bulk of research undertaken, however, indicates it in many cases lacks a systematic methodological approach and theoretical rigor about what analytical notion or theoretical concept of metaphor had been applied to the data gathered. It has, furthermore, been taken for granted that metaphor is an essential ingredient in constructing scientific meaning whereas its philosophical implications in terms of constructivism and objectivism are often omitted. It is thus not astonishing that important questions have not been investigated, such as, for instance: is there an existing reality or is the notion of reality just a construct science lives by? In this study, we take an experientialist position based on the assumption that our observations of biological phenomena are deeply shaped by social, cultural, and many other factors which thus contribute to form the knowledge and practices with which human beings wend their way through the world.

The philosophical implications of constructivism and objectivism have again and again been addressed by philosophers and psychologists such as Kant (1993), Giam Battista Vico (1990), Ernst Cassirer (1923), Karl Bühler (1934), and Nelson Goodman (1968), but it was mainly the historian and philosopher Michael Polanyi (1958) who started to identify and outline the shortcomings of so-called objectivism or logical empiricism in the 1950s. Polanyi himself was an experienced scientist and did not reject the notion of an existing reality. Adhering to an experiential notion of reality (Polanyi 1966), he was convinced that scientists in their daily life develop scientific theories and concepts on the basis of ideas about a hidden reality underneath the phenomena perceived. Following this conviction, ideas or visions are determined by imagination and intuition (Polanyi 1958) which define a so-called tacit knowledge. This tacit knowledge is based on experiences gathered from all kinds of encounters that are not communicable and provide a conceptual background which informs scientific thought and action (Polanyi 1966). This concept has much in common with early developmental psychology as outlined by Jean Piaget (1954) and Lew Vigotsky (2012) as Polanyi's work develops a comparable interactive and dynamic understanding of knowledge based on physical and social experiences and the humanly embodied conceptual framework. It is thus an experience-based approach that highlights the body in the mind (Johnson 1987). This experienced approach has (though not consciously) been revitalized by the philosopher Mark Johnson (1987, 2007) and the linguist George Lakoff (1987) in series of coedited and single-authored monographs (Johnson 1987, 2007; Lakoff and Johnson 1980, 1999; Lakoff 1987). Similar to Polanyi, Johnson and Lakoff underline the relevance of the human imaginative capacities and an embodied experience to construct what they call mental representations. They too build on the premise that imaginative capacities and an embodied experience are the basic ingredients for a subconscious form of tacit knowledge which materializes in spoken language and provides an interpretative access to so-called conceptual metaphors used in scientific reasoning. The distinction of linguistic and conceptual metaphors is of importance here because the latter could be understood as configurations underlying and structuring what Polanyi calls tacit knowledge. This means that the analysis of metaphor holds the possibility to reveal and analyze the cognitive patterns and processes used to reason about a scientific problem or concept. In this view, science and scientific reasoning should be understood as embodied processes of metaphorical reasoning that transforms knowledge into so-called experientially gained structures. This view obviously holds philosophical implications for notions such as objectivity and truth as they are not awaiting discovery (Putnam 1981, 1991, 1993). Thus, scientific facts are consequently a product of embodied and experiential metaphorical reasoning that provides a fragmentary but nevertheless important perspective towards reality.

Lakoff's and Johnson's experiential approach might hold serious epistemological limitations because metaphor as one of these experientially gained structures has long been conceived as a mere linguistic decorum and rhetorical device that contributes to the confusion of categorical distinctions between words and reality. Seen from this perspective of mere language games, the outlook is rather purely constructivist. Here, the experiential approach as created by Polanyi and put forward by Lakoff and Johnson offers a productive perspective because metaphor holds a great conceptual "[…] power to evoke images and complex ideas" (Chawla 2001, 115). It could be understood as a dynamic device or embodied mechanism anchored in experience that enables scientists to interpret and analyze their scientific problem under review in productive, imaginative, creative, and new ways. Scientific work and thought experiments basically involve imagination, and imagination is thus an endeavor based on accumulated and embodied experiences canalized and structured by scientific training. The resulting mental representations are of vital interest because they are metaphorical in character and hold the potential to provide access to tacit or unconscious or submerged knowledge at work in scientists' minds and practices. The aim consequently consists in uncovering and assessing the metaphorical forms of scientific reasoning and knowledge as reflected in the language and its imaginary use by scientists. In the next section, we take a closer look at the conceptual theory of metaphor and introduce the analytical tools that are used later in the analysis of basic concepts encountered in systems biology.

2.1.2 A Theoretical Slant on Metaphor

One central thesis of this chapter is that metaphorical reasoning lies at the heart of what scientists do in their everyday lives. Scientists rely on metaphors and metaphorical thinking when they communicate about and design experiments, formulate theories, develop models, make discoveries, and think about and apply basic concepts. Especially the latter are of specific interest as they provide an unconscious social and embodied knowledge against which scientific endeavors are carried out. Following the classical perspective, metaphor was long regarded as a purely rhetorical phenomenon acting on the level of words and linked only to poetic discourse or the aesthetic creativity of writers. It was therefore not considered as referring to a linguistically describable reality and rather relegated to the artistic use of language. However, according to most linguistic research on metaphor, it can no longer be regarded as a mere aesthetic figure in poetic discourse but must be understood as a ubiquitous phenomenon and constitutive element of cognition in everyday life that pervades and structures all kinds of discourse. This becomes apparent if we look at the following linguistic examples taken from a corpus of spoken language:

1. My assumption about the omnipresence of metaphor in science completely *collapsed* because my supervisor has questioned […].
2. The results taken from her research *undermine*, at least to some extent, the argument that cancer could be, ah yes that it could be understood as genetically determined […].

Both examples literally do not make sense but it is nevertheless astonishing that, as soon as one reads them, one understands their meaning immediately. The process of understanding these linguistic metaphors is in fact quite easy for most people who read these sentences and what is even more striking about them is the fact that the structures marked in the examples do not really appear to the reader or listener as metaphorical. Their metaphorical content only becomes obvious at second glance and provides an underlying image of arguments as objects or buildings that can collapse or be undermined. What is involved in the two examples quoted above is actually the very basic ingredient of metaphor, the metaphorical mapping. This means that a concrete domain of discourse (a building), called the *source domain*, projects its information and connected associations on an abstract domain of discourse (conceptualization of cancer), called the *target domain*. Thus, abstract entities, assumptions, or arguments could metaphorically be framed as buildings or objects which entail that they can collapse or be undermined even though they do not do such things in reality. What is interesting about the examples is not only the mapping process as a mechanism that conceptualizes abstract domains of knowledge but the intangible background knowledge implicated in it. The metaphorical transfer and its "[…] implication complexes […]" (Black 1993, 28) enable a wide range of possible associations that open up avenues for creative thinking and acting. It is thus possible to talk about the foundation of an argument or, more creatively, to understand a theory as a building that lacks a roof. Another example taken from molecular biology might be illustrative and has been taken up as an example inter alia by Brown (2008, 25–26) because it shows how everyday language and practice might have once entered the realm of science. Brown states that one of the most active fields in molecular biology nowadays is devoted to research on how proteins change their shape and constitution in a solution. This branch of research investigates how proteins active in biological systems rearrange their chain lengths to maintain their characteristic shape. This active process was called *folding* due to a comparison or analogy between the process taking place within a protein and folding practices in the human world. In brief, the folding practices encountered in the human world were metaphorically mapped on the more abstract biological process taking place on the molecular level. As Brown (2008, 25) states, the metaphorical projection of the everyday concept of folding on a molecular biological process provoked a variety of questions that exerted an impact on further experimental arrangements and research undertaken and, at the same time, added an extra shade of meaning to the semantics of the verb "folding". What becomes clear is that the metaphorically used language creatively connects everyday discourse with scientific discourse. Metaphors thus "[…] play

[…] an essential role in establishing links between scientific language and [experiences taken from; the authors] the world" (Kuhn 1993, 539).

Thus far, we have encountered two analytically important characteristics of metaphor, namely that metaphor is—according to its etymology—a cognitive mapping mechanism which carries meaning from one domain of knowledge to another and structures the semantics of the target domain by using social, cultural, and bodily experiences.[6] A closer look, however, uncovers other important elements (Jäkel 1997, 40–42) which are relevant for our analysis. One is that metaphors, as already alluded to, hold a creative potential for thinking and acting due to the background knowledge implicated in them. To understand this process in more detail, it is important to see that the use of a linguistic imagery semantically highlights certain aspects while it hides others. Framing the way chemicals take to pass through a cell membrane metaphorically as a *channel* emphasizes the functionality of such a structure for transporting ions (see Brown 2008, 100–120). It is interesting that the noun "channel" was taken from everyday experiences because other words such as "corridor" or "tunnel" would have been available as well. The use of the word "channel", however, seemed to fit best due to the original idea of water or fluids in which ions can flow. With regard to extending the image, the metaphorical use of "channel" offers further opportunities to reframe or explore its implications. Thus, the introduction of certain membrane proteins to be conceptualized as sluices might hold the potential to block the transfer of ions and unintended reactions between molecules on the molecular waterway could be metaphorically framed as shipping accidents in the channel. The implications inherent in the channel image thus offer a variety of ways to postulate and explore creatively the functioning of the cell and possible ways to understand processes running on the molecular level as outlined in the shipping accident metaphor.

What is astonishing is that some of these images are self-explanatory whereas others such as the shipping accident metaphor require a certain amount of reflection to be understood. It follows that some images are more accessible than others in the sense that they conform more to experimental results than others. Furthermore it seems that the aspects of accuracy and comprehensibility are directly related to the important aspect of conventionality. What becomes thus apparent in the previous examples is the fact that the channel metaphor is rather easy to understand and it is nowadays an integral part in research. Lakoff and Johnson (1980) stated that scientific discourses are replete with and based on so-called *conventional metaphors* which semantically structure their content. This neatly links up with the previous example because the channel metaphor shows that a certain domain of discourse is structured by it even though empirical research indicates whole domains of discourse are based on a restricted set of conventionalized metaphors. Other good examples are the pervasive text and script metaphors used in the press coverage during the sequencing of the human genome (Nerlich et al. 2002; Nerlich and Clarke

[6] The notion of embodiment refers to the fact that the semantic content of metaphors is inter alia motivated by the human biological body.

2003; Döring 2005). They became a conventionalized image to convey the chemical structure of the DNA is information that could be read, understood, and—to use another metaphor—be rewritten in research. Another illustrative is the noun *cell* which denotes a small and functional biological unit that can be perceived through the microscope. Although the word nowadays rather appears to be a conventional noun, in the nineteenth century it was used first in the metaphorical sense because the elements perceived through the microscope in a monastery by a monk structurally resembled his cell. The initial metaphorical mapping has hence disappeared during the last decades as it underwent a process of standardization that finally changed the metaphor into a standalone word. Generally speaking, there are thus two kinds of metaphors: the novel ones that can be encountered at any time but also the *conventional metaphors* that often go unnoticed. Conventional metaphors, especially, develop underlying systems or models that deserve further attention due to their structuring force, inbuilt implications, and connected associations. This means certain domains of discourse are based on an underlying system of *conceptual metaphors* that materialize in the form of a variety of linguistic instantiations. Conceptual metaphors are thus to be conceived as cognitive meaning structures that help to make an abstract domain accessible. This aspect becomes visible in the conceptual metaphors used to frame mental activity. Jäkel (1997, 184–188) has shown that mental activity has been depicted in conventional metaphors such as IDEAS ARE OBJECTS, THINKING IS WORKING ON PROBLEM-OBJECTS WITH THE MIND-TOOL, or FORMING IDEAS IS SHAPING RAW MATERIAL whereas doing science has been metaphorically framed in terms of SCIENCE IS A JOURNEY or as SCIENCE IS THE STRUGGLE FOR THE SURVIVAL OF THE FITTEST. These conceptual metaphors develop coherent models or so-called cognitive models that represent experiential simplifications of an even more complex reality and at the same time provide a semantic structure which pervades scientific thought and practice.

In this brief overview of the conceptual theory of metaphor we have identified some basic characteristics of and assumptions on metaphor and types that are of vital importance for our analysis of basic concepts in systems biology. These are:

- Metaphors are based on a cognitive mapping process in which more concrete experiences are projected upon an abstract domain to make it semantically and cognitively accessible. The analysis of these mapping processes provides insight into the experientially informed processes of meaning making while it also opens up the possibility of analyzing and assessing possible implications transferred to the target domain.
- Metaphor is a ubiquitous phenomenon that pervades scientific discourses too. They are not an element that could be relegated to the realm of artistic discourses or poetics. Of special interest are the conventional metaphorical concepts because they subliminally shape a domain of discourse and often pass unnoticed.
- Metaphors possess a focusing function. They highlight certain semantic aspects of the discursive domain while hiding others. This offers the opportunity to analyze how a certain domain of discourse is framed and at the same time opens up the possibility to question current framings and to develop alternative ones.

- Metaphors are creative mechanisms for the production and shaping of meaning. This meaning and semantic productivity cannot be reduced to the propositions of the words involved. This aspect refers to the important aspect of malleability because metaphors hold the power to change or restructure ingrained thought patterns. In science, they clearly possess a heuristic function.
- Conceptual metaphors form so-called cognitive models. These models provide an experiential and simplified structure that semantically conceptualizes a whole domain of discourse. Cognitive models could be understood as cultural models of thought that determine the worldview of a social group or scientific discipline.

Having outlined the relevant and sometimes overlapping characteristics of metaphor here does not mean this list is exhaustive. It, however, provides a practical overview of the analytical aspects and assumptions of the conceptual theory of metaphor as first outlined by Lakoff and Johnson (1980). This plays an important role in the current context inasmuch as systems biology introduced a change in at least some biological concepts that is "accompanied by a change in some of the relevant metaphors in the corresponding parts of the network of similarities" (Kuhn 1993, 539). Our aim, consequently, consists in unraveling, analyzing, and critically assessing these metaphorical networks that inform the basic concepts of systems biology. But before we turn to our empirical analysis it is necessary to outline our methodological approach for the analysis of linguistic imagery. This is done in the next section.

2.1.3 Tracking and Analyzing Metaphor in Scientific Discourse

As we have outlined in the previous sections, metaphorical language and thought are deeply rooted in physical, social, and cultural experiences and play an essential role in science. How can data on these processes be raised and analyzed and what kind of method should be applied to do justice to the data raised? The methodological approach we chose to take represents a combination of linguistic (Jäkel 1997, 141–146; Döring 2005; Steen et al. 2010) and discourse analytical approaches[7] (Semino 2008; Döring 2014). These have been informed by recent attempts to analyze metaphor from a social science perspective systematically (Maasen and Weingart 2000; Kruse et al. 2012; Schmitt 2010, 2011, 2014).

The question we had was whether there are metaphors to be found in the scientific discourse on systems biology. For this to be partly answered, we started analyzing scientific reviews and edited volumes on systems biology to get a preliminary insight

[7] Discourse analytical approaches (as referred to here) investigate from an empirical point of view the language used to describe and frame a problem, situation, or prevailing topic under question. The analysis of different linguistic structures in the language reappearing helps us to better understand the social ascription and contesting of meanings.

into the current state of the art while at the same time a provisional analysis of metaphor was carried out. This procedure resulted in the insight that metaphors are at work in the discourse and led us at the same time to papers written inter alia by Ouzounis and Mazière (2006) and Bruggeman et al. (2005). The authors of the former made explicit reference to metaphor in their title "Maps, Books and Other Metaphors for Systems Biology" (Ouzounis and Mazière 2006, 6) however, the latter outlined that they "think that it is important to reveal the philosophy of notions such as life or cell to broaden the—sometimes—too narrow scope of systems biologists" (Bruggeman et al. 2005, 395). Both papers have in common that they emphasize the relevance of a reflexive perspective to analyze the philosophical and cultural embeddedness of systems biology. Having Polanyi's notion of tacit knowledge in mind, these statements provided by scientists working in the area of systems biology motivated us to start a systematic literature research to get a better understanding of systems biology. We thus gathered different kinds of written evidence such as conference proceedings, edited volumes, textbooks, scientific articles, and reviews to get a deeper insight into current topics and debates of systems biology. The literature search on scientific reviews was undertaken with the help of the search tool *Pubmed-Pubmed-Reminer* which offers a variety of search options to combine keywords and fine tune the search according to different parameters such as the date of publication, relevant journals, main scientists working in the field, and the main topics addressed. This helped us to set up a database of written sources that was then read and tentatively pre-structured. This procedure provided a first structure of the field of systems biology and also showed that basic concepts such as life, system, reductionism, holism, and model were quite often used. This led us to conclude that these concepts are of vital interest to the scientific community. Astonishingly, they are extensively used in the systems biology literature, but definitions or thorough discussions of them are more or less lacking. We come back to this point later on.

With this provisional result in mind and using the concept boundary object[8] (Griesemer and Star 1989; Bowker and Star 2000) as a heuristic device we decided to concentrate on such basic concepts as the main object of research. The aim was to address and assess their embeddedness and metaphorical structure (Ouzounis and Mazière 2006; Bruggeman et al. 2005) from an empirical point of view. For this to be done, we established a dataset of scientists working in systems biology in Germany whom we had identified during our literature research. We furthermore extended this list by undertaking an extensive search on the Internet that provided us with information about the contact details and, more important, with the main fields of research, the current professional status, and important publications of the respective scientists. To guarantee an adequate social distribution, representative scientists from different career levels in Germany were chosen, some of them coming from other countries than Germany. Twenty-five semi-structured interviews

[8] Boundary objects are socially constructed entities or things around which scientists or other social actors unite and which enable communication and coordinated action towards a commonly conceived goal. It is interesting though that the conceptions of such a boundary object vary considerably among the parties involved.

addressing the history and development of the discipline, the understanding of basic biological concepts, disciplinary controversies within the field, national idiosyncrasies, and the future potentials of systems biology were carried out. Interviews lasted between 1½ and 2 h, were tape-recorded and transcribed. The section addressing the conceptualization of basic concepts was cut out and analytical emphasis was put on the metaphors used by the scientists to explain their notion of the above-mentioned concepts.

The method used to analyze the metaphors started with an initial cursory reading of the transcript. The next step consisted in a close line-by-line reading trying to reveal all metaphors occurring in speech. The linguistic imagery encountered was transferred into a table where the mapping processes were analyzed. This procedure explored the degree of metaphoricity and at the same time helped us to study which source domains were used to conceptualize the target domain. Once the mappings were analyzed, all metaphors were—if possible—divided into different categories and grouped under so-called conceptual metaphors. These elements, to be understood as generic structures that pervade each concept, were studied with regard to what they highlight and hide. The final analytical step consisted in comparing whether certain kinds of conceptual metaphors could be associated with disciplinary backgrounds of interviewees and possibly refer to conventional modes of conceptualizing the basic notion under question.

The following scheme provides an overview of the different steps undertaken during our investigation and shows how these steps analytically build upon one another.

- Choose a domain of discourse in science, a discipline, or a specific research project → predefine your research object.
- Immerse yourself in the discourse by gathering different kinds of written material and iteratively read through the written evidence gathered → contextualize yourself.
- Take notes of all kinds of aspects that attract your attention and systematize them after having read through your sources → open up the field in a structured way.
- Define a tentative research question and reanalyze whether and, if so, how the research question fits → assess your research question.
- Develop a systematic database of written evidence and immerse yourself systematically in the domain of discourse → get a deep conceptual insight into the domain of discourse and develop a questionnaire for semi-structured interviews.
- Set up a table in which you note main actors in the field, their affiliation, scientific topics addressed, their current professional status, and the most important publications → become familiar with the main actors in the field.
- Choose a representative sample of scientists according to their professional status and their disciplinary backgrounds → gather a representative group of interviewees.
- Do interviews, transcribe them, and read them → iterative approximation to the interviews.

- Analyze the interviews on a line-by-line basis and gather the metaphors encountered in a table → systematically search for linguistic metaphors.
- Analyze the mapping processes in the metaphors → assess the metaphoricity of each metaphorical instantiation.
- Check whether some metaphors could be subsumed under one heading → definition of conceptual metaphors.
- Discuss aspects of highlighting and hiding → assess the possible implications of the metaphorically triggered styles of thought and propose alternatives.
- Check whether certain kinds of conceptual metaphors can be connected to disciplinary backgrounds → attribute metaphorically informed thought styles.

In sum, the approach outlined here aims at meeting the complex requirements for a detailed and methodological sound metaphor analysis of the complex issue of basic concepts in systems biology. It tries to provide a systematic examination of metaphor in scientific discourses which so far has been applied by Döring (2014) to assess and analyze metaphors in media discourses on synthetic biology. In the next section we now turn to the metaphorical framing of the notion of life by systems biologists.

2.2 The Conceptual Framing of Life in Systems Biology

As we have seen in the previous section, metaphors are a basic ingredient in scientific as well as in everyday discourses. They run through all stages of scientific thinking and acting. This also holds true for systems biology. Having read through a representative bulk of publications dealing with systems biology and having tackled the prevalent concepts of life, system, reductionism, holism, and model we now turn to the analysis of the understanding of life in systems biology. Life represents a multifaceted concept that has been described, defined, and explained in many fields such as biology, philosophy, religion, psychology, and many more. These studies are extremely interesting in themselves. However, the empirical question remains of how life is conceptualized by members of different scientific disciplines in their academic and scientific work? Is the notion of life relevant to them? If so, how do scientists working in the area of systems biology conceptualize life? An empirical investigation of these questions seems vital inasmuch as the concept of life is not plainly based on a definition or theory of life as outlined by Oparin (1924), Schrödinger (2012), Crick (1981), Monod (1970), Maynard-Smith (1986), and others. On the contrary, it is often based on scientists' associations and attitudes that in many cases are not overtly articulated. They rather reside in the unconscious and represent different kinds of tacit knowledge (Polanyi 1958, 1967), styles of thought (Fleck 2011), or cultural presumptions (Kather 2003) that are often not explicitly formulated and thought through, but nevertheless hinge on and display a certain mind-set. The task thus consists in empirically investigating conceptions and framings of life by systems biologists. Because systems biology considers itself as a highly interdisciplinary endeavor the question remains as to how the different disciplinary backgrounds and related styles of thought exert an explicit or implicit impact on the conception of life. In this section we show that the different characteristics of the concept of life play an important role, but these are merged with conceptualizations connected to scientific training and professional background. As a result, it seems appropriate to hypothesize that systems biology introduces new facets to the multifaceted concept of life.

2.2.1 Life and Its Characteristics in Biology: An Impressionistic Overview

Before we start to analyze the differing concepts of life in systems biology, we provide an impressionistic introduction to the different understandings of life in biology. Life represents a generic concept that is semantically difficult to grasp. It designates a phenomenon that often is explained as a property, especially as a property of organisms (see Table 2.1).

Box 2.1: Meanings of and Distinction Between Term, Notion, and Concept

In this chapter, we use specific names or terms in order to label abstract or mental constructs such as *notion* or *concept*. In scholarly discourse these constructs are not always clearly defined. Their use varies and they may have different meanings. In order to be as clear as possible in our terminology, we use the following definitions.

- A **term** is a word or compound word that in specific contexts is given a specific meaning. This may deviate from the meaning the same word may have in other contexts and in everyday language. Terminology studies the development of terms, their interrelationships, and their use.
- A **notion** in philosophy is a reflection in the mind of real objects and phenomena in their essential features and relations. Notions are usually described in terms of scope and content. Notions are often created in response to empirical observations (or experiments) of covarying trends among variables.
- A **concept** (or conception) is an abstract idea, mental representation, or mental symbol that exists in the brain. The terms concept and conception are sometimes used interchangeably. However, a conception may also be more encompassing and detailed than a concept with regard to considered factors and theoretical reflections. In metaphysics, and especially ontology, a concept is a fundamental category of existence.

When biologists try to give details about the nature of life, they refer in many cases to a set of criteria or a list of features that exemplify living organisms (see , e.g., Deamer 2010; Ganti 2003, 76–80; Mayr 1997, 20–23). Throughout the history of biology numerous efforts have been undertaken to elucidate what life is or could be (Kather 2003; Toepfer 2005) with this kind of feature-procedure ranging from Bernard's (1878) properties (organization, reproduction, development, nutrition, and vulnerability) via Crick's characteristics (reproduction, genetics, evolution, and metabolism) to Gibson et al. (2010), who understands life as exclusively based on reproduction. What becomes apparent is that biologists use these central features with the aim of exploring what life is, even though this task seems to be rather speculative and has led now and then to attempts to develop a universally shared definition. One of these endeavors was, for example, undertaken in Murphy's and O'Neill's (1997) book entitled, *What is Life? The Next Fifty Years. Speculations on the Future of Biology*. The book simply showed that it is impossible to agree and rely on a fixed set of basic features. As indicated by the subtitle, the endeavor of defining what life is via a fixed or agreed-upon set of characteristics rather represents a speculative task as these are in many cases context or temporally bound features emerging in a specific historical, social, technological, and scientific milieu, although certain features (for instance, reproduction) remain constant and can be found in almost any set of life-defining features. Having this in mind, one might conclude that investigating the notion of life is a useless venture. However, we would like to reject this conclusion inasmuch as we are interested in exactly this sociocultural contextuality. Features assigned to life are markers that meander through history and display a prevalent conception of life in a certain sociotemporal context. This sociotemporal context not only engenders a specific understanding of life but also determines questions, methods, and instruments employed in order to analyze it and to deploy its parts and processes for human goals. Different conceptions of life therefore may have different implications for science and society, and this is but one of the many reasons why it is worthwhile to re-explore them in detail once relevant framework conditions changed. Interestingly enough, some of these markers mentioned above were also encountered in the interviews we led with systems biologists in Germany. To sum up, there is a large diversity of features that have been used by different disciplines to describe and define life which reflect the richness of scientific and cultural perception of this seemingly unfathomable phenomenon. On the other hand, there is a historically generated set of so-called canonical features, which serve as indicators for life (see Table 2.1).

As collectively shared and combined markers, these canonical features fulfill the function of providing a common ground for partially defining when an entity should be considered to be alive. It is thus necessary for the analysis undertaken here to provide a thorough nonexhaustive but still representative insight into the basic characteristics of life.

The features outlined here could be conceived as discrete characteristics, but most of them are conceptually related. Therefore, some compilations or lists about basic features of life merge characteristics whereas others are divided into two or even more discrete traits overlooking that scientists more often tend to use their

Table 2.1 Defining 'life' via certain characteristics (cf. Kather 2003; Toepfer 2005)

Author	Characteristic(s)
Bernard (1878)	Organization, reproduction, development, nutrition, and vulnerability.
Oparin (1924)	Organization, metabolism, reproduction, irritability.
Crick (1981)	Reproduction, genetics, evolution, metabolism.
Monod (1970)	Teleonomy, morphogenesis, reproduction.
Maynard-Smith (1986)	Metabolism, different segments holding functions.
Gibson et al. (2010)	Reproduction

self-defined idiosyncratic features. In sum, the characteristics described above attribute basic abilities to living organisms such as to form, to develop, and to reproduce on the basis of a natural layout, which makes organisms forms of being that exist in principle independent of any kind of human or other assistance.[9]

Thus far, we have outlined in a nonexhaustive attempt the so-called traditional features of life prevalent in biology as well as in or traditional biotechnology. Systems biology, however, applies a different and perhaps more fundamental perspective on organisms, organs, cells, or even single metabolic pathways. Although not to be conceived as a uniform scientific approach, it holds its own history and has emerged in the context of different disciplines such as molecular biology, genomics, biochemistry, computer science, and engineering. The heritage from its predecessors as well as the ideas and approaches from other scientific disciplines contributed to an expansion or possible reformulation of concepts of life in the context of systems biology. We now explore and analyze the metaphorical conceptualization of life encountered in interviews with systems biologists.

2.2.2 Depicting Life as Seen Through Systems Biologists' Eyes

As we have seen in the previous section, life is perceived as a fuzzy concept comprising certain characteristics but undergoing change throughout time. In systems biology, the word *life* frequently appears in the titles of conference talks or scientific reviews, often in combination with other words such as elements, principles, basics, and so on. Furthermore, books dealing with systems biology in general as well as textbooks and articles use the notion of life in their titles or devote a considerable section or chapter to it (see, e.g., Ideker et al. 2001; Kaneko 2006; Noble 2008a; Westerhoff et al. 2009). A closer look at a representative bulk of the literature paradoxically revealed that neither characteristics nor explanations of the notion of life

[9] This holds true no matter whether a specific animal or plant has evolved naturally or by breeding or genetic engineering. The ensuing organism is alive, although it may represent a new version of its natural predecessor.

are given. Systems biologists seemingly wish to make scientific statements about life, but without describing the object of inquiry more accurately. Furthermore, in scientific practice, they focus on elucidating complex networks, processes, or (emergent) functions, but not on "life" as such, whatever that means. One could obviously argue life is a concept too complex to explain or simply not relevant in the context of systems biology. But why then is it so often used in the corresponding scientific literature? Is it only referred to for scientific marketing purposes with the aim of pushing the newly emerging approach as *the* approach that provides an answer to what life is? This does not seem to be true as a search on the ISI-Web of Knowledge and PubMed indicated the notion is constantly in use and not only employed during the starting period of systems biology. It could also be possible the notion does not apply to everyday problems and practices encountered in scientific work. This mismatch, however, attracted our attention.

Given the fact that studies devoted to the empirical conceptualization of life are still rare (see Fox-Keller 1995, 2002; Gutman 2008; Hesse 1966; Kay 2000; Bock von Wülfingen 2007; Bölker et al. 2010) and that no preliminary answers to the so-called life-question could be deduced from the scientific literature analyzed, we decided to ask the life-question during the interviews led with systems biologists. Our hypothesis was that either the life-question would simply be rejected or an interesting discussion might emerge in which metaphors are used to conceptualize and communicate the framings of life by our interviewees. We thus hypothesized that a systematic analysis of metaphor might reveal the hidden meanings nestling in the language used to depict life. Consequently, a manual for semi-structured interviews was designed in which we first asked what systems biology is, how it developed since its advent in the German context, and what its future potentials might be. This section was deliberately used to instigate a thought process that led to a self-contextualization of the interviewee. Having outlined and discussed the individual framings of systems biology's pasts, presents, and futures, the life-question was asked in the following section. The question was carefully introduced by the interviewer using a polite and cautious language which indicated that it is a complex but nevertheless relevant query. The query was informed by insights provided by prototype theory (Rosch 1973, 1978; Rosch et al. 1976). The aim consisted in initiating a thought process that psychologically reduced the complexity of the question and provided an implicit offer to start with the features outlined in the previous section: In doing so, a shared communicative grounding between interviewee and interviewer developed. Not astonishingly, most interview partners initially answered that reproduction and metabolism represent the basic features of life. However, a subcutaneous tension emerged in the course of the interview which becomes apparent in the following two representative quotes.

> This is a question we do not get often, hmm, because, well, we are just on the technical side of it, err, yes, but it's a good question one as well, as yes, we are so immersed in our daily hassle. Yeah, you know that we lose track of these, yes philosophical but relevant questions […]. (Scientist A)
>
> German original: Das ist eine Frage, die uns nicht oft gestellt wird, hm, weil, ja, wir befinden uns auf der technischen Seite, err, aber es ist eine gute Frage, weil ja, wir sind ja

so in unserem Alltag gefangen. Ja, wir verlieren den Kontakt zu diesen, ja philosophischen, aber relevanten Fragen […].

Life? Oh yes, big concept, loooong history and no clear answers […] hahahaha […] what a mess. I think that the concept does not really play an important role in our daily working life. We make a cut in our brains and just concentrate on this and this pathway […] but the big picture, yes, I think that we should address this mess […]. (Scientist J)

German original: Leben? Oh ja, eine großes Konzept, laaange Geschichte und keine klaren Antworten […] hahahaha [..] was für ein Durcheinander. Ich glaube, dass das Konzept nicht wirklich eine wichtige Rolle in unserem Arbeitsalltag spielt. Wir unterteilen unsere Gehirne und konzentrieren uns lediglich auf diesen oder diesen Pathway, aber das Große und Ganze, ja, ich denke dass wir uns darum auch kümmern sollten.

The two quotes show that the life-question appears quite relevant but at the same time too big to deal with. In the first quote reference is made to daily workloads that prevent the interviewee from addressing the question of what life could be, however, the second evidently refers to his historical knowledge. Scientist J also ironically plays with the life-question but in the end concludes that the question is, at least, of interest to him. However, it is not an explicit subject for experimental or theoretical inquiry. Withstanding the tension and attempts to resolve it, the interviewer remained in these situations often silent but provided feedback channeling with the aim of keeping the thought process going. This leads, on the side of the interviewee, to a differentiation of the previously said with the help of spontaneous metaphors that were systematized and analyzed in the transcribed interview data according to the methodological procedure previously depicted. This analysis yielded the following seven conceptual metaphors framing life: LIFE IS A MACHINERY, LIFE IS A SYSTEM, LIFE IS INTERACTION AMONG SYSTEM COMPONENTS, LIFE IS A NETWORK, LIFE IS A FORCE, LIFE IS A RIDDLE, and LIFE IS A SECRET.

To start with, life has metaphorically been depicted in terms of machinery. Words metaphorically used comprise lexical items such as machine, machinery that is projected upon the domain of life, as could be seen in the following two quotes.

Life? Yes, that is tricky to explain. I would say that what we do is **understanding life as machinery**. I mean, there are all these processes which we try to understand and I think that machinery captures it quite good. (Scientist A)[10]

German original: Leben? Ja, das ich nicht einfach zu erklären. Ich würde sagen, dass das was wir machen ist dass wir **versuchen Leben als Maschine zu verstehen**. Ich meine, da sind all diese Prozesse, die wir wir versuchen sie zu zu verstehen und ich glaube, dass Maschine das ganz gut ausdrückt.

Well that's difficult […], I would say. Well, well one might **think of life as some sort of a machine or better machinery** where different bits and pieces work together. Hm, yes, one could understand life in this way. (Scientists K)

German original: Ja, das ist schwer […], ich ich würde sagen. Gut, gut, man könnte sich **Leben als eine Art Maschine oder besser als Maschinerie vorstellen**, in der unterschiedliche Stücke und Teile zusammen arbeiten. Hm, ja, auf diese Weise könnte man Leben verstehen.

[10] Letters in bold indicate the metaphor or metaphorical phrase.

What have been highlighted by these metaphors are clearly technical and engineering aspects. This includes a constant need for energy and at the same time relates to old images of the mitochondria as power stations of the cell, a culturally well-engrained idea in the German context. The second quote, furthermore, differentiates between machines on the one hand and then introduces the noun machinery as a generic concept. The metaphorical transfer visibly highlights images of steel, oil, gearwheels, and lubrication but also develops on a connotative level a relation to cellular and biochemical processes. In sum, the conceptual metaphor and its inherent transfer convey images of factories.

Life has also been metaphorically depicted as a system. In this case, the metaphorical transfer relies on an abstract notion used in a variety of ways ranging from economics via politics and the German waste disposal system to scientific systems. In the present context, however, the interpretative background refers to systems theory and systems biology.

> Life? Oh dear! Ok, I think **life is a system**, a fuzzy system. It is hard to explain but to me it's a structured whole. (Scientist D)
>
> German original: Leben? Oh je! Ok, Ich denke, **dass Leben ein System**, äh ein unscharfes System ist. Es, es ist wirklich schwer zu erklären, aber für mich, äh, ist es ein strukturiertes Ganzes.
>
> Life, that's a difficult notion. I see, ah […] **life for me is a system**. Yeah, that's what it is. (Scientist E)
>
> German original: Leben, das ist ein ein schwieriger Begriff. Ich sehe ah […] **Leben als ein System**. Ja, so könnte man es ausdrücken.

The systems metaphor, though semantically opaque, highlights aspects of structured or organized entities. These, in turn, develop out of smaller components that hold functional relations among these entities and are governed by principles in a functional way. The explanatory value of the system metaphor, however, remains small due to its imprecise meaning and open semantic content.

In addition to these first two conceptual metaphors, life is also metaphorically framed as interaction between system components. The notion of system appears in the following two cases again, but is now determined by the metaphorical use of the word "interaction". Moreover, the quotes are more precise than the previous two because they indicate who interacts with whom.

> Well, for what I now say probably a lot of people would kill me, but […] haha […] anyway. So in my version, **the interaction between the DNA and the proteins**, that's what I think is life. (Scientist M)
>
> German original: Gut, für das, was ich jetzt sage würden mich wahrscheinlich viele Leute umbringen, aber […] haha […] egal. So, meine Version von **Leben ist**, **ist die Interaktion zwischen der DNA und den Proteinen**, ich denke, dass das Leben ist.
>
> Yes, life is to me rather small and **rather interaction on the molecular level**, you know. That is my version of the whole thing. (Scientist F)
>
> German original: Ja, Leben ist für mich eher klein und und **eher Interaktion auf der molekularen Ebene**, verstehen sie. Das ist meine Version dieser ganzen Sache.

The metaphorical use of interaction highlights relational and mutual aspects of interdependence and cooperation. Interaction furthermore holds obvious connotations and refers to life-world experiences of social and communicative interplay and exchange. The conceptual metaphor, LIFE IS INTERACTION AMONG SYSTEM COMPONENTS, thus subcutaneously introduces a social aspect.

Furthermore, scientists in systems biology frame the notion of life using a network metaphor. The metaphorical concept, LIFE IS A NETWORK, appears to be prominent among researchers holding an IT background as the following two quotes indicate.

> The concept of life? That's a tricky question but **in my view it is rather a network**, the interaction and regulation of metabolic networks; it is this functional coupling thing that we have to deal with, we have to understand. (Scientist K)
>
> German original: Das Konzept Leben? Das ist eine schwierige Frage, aber ich sehe **es eher als Netzwerk an**, die Interaktion und Regulierung metabolischer Netzwerke; es ist dieses funktional verbindende Moment, mit dem wir uns beschäftigen, das wir verstehen sollten.
>
> That is an exciting question […]. Well, I am quite pragmatic and I interpret life from my point of view in terms of a **network**. I mean, it is the only way I can think about it, and, yes, that is what I am interested in and how I can imagine it. (Scientist O)
>
> German orginal: Ja, das ist eine spannende Frage […]. Also ich bin da eher pragmatisch und interpretiere aus meiner Arbeit heraus das **Konzept Leben als eine Art Netzwerk**, ok? Ich meine, ich kann das so denken und metabolische Netzwerke, ja, das ist was mich interessiert und wie ich es mir vorstellen kann.

The first interview excerpt metaphorically depicts life in terms of a network metaphor. A closer look at the example, however, refers to the implication complex of the metaphor as it could be seen in the use of the phrase "functional coupling". Here, the network metaphor is elaborated upon as connections in the system are highlighted, the integration of different levels in the system is alluded to, and the link between inside and outside is referenced. The second quote, on the contrary, displays a pragmatic and technologically driven access to the complex notion of life and at the same time outlines a quasi meta-reflection on why this metaphor has been applied: it is the work experience with IC technology that plays a vital role. The metaphor itself connects the notion of life to the semantic field of information technologies and highlights, on a connotative level, lexical items such as computers, hardware, Internets, computer programs, connections, knots, and knotting. These, although unmentioned aspects of the semantic field, resonate with each other and bear an impact on conceptualizing the notion of life using the characteristic feature of life, namely metabolism. It could thus be hypothesized that the conceptual metaphor, LIFE IS A NETWORK, theoretically merges a technologically driven vision of work experience with a biologically informed framing constitutive for systems biology.

However, in addition to such technologically driven images culturally well-established aspects of framing life emerge. The abstract metaphorical framing of LIFE IS A FORCE materializes in many interviews and often appears in conversations with interviewees trained in physics. Although not theoretically explaining the notion of life, these scientists metaphorically highlight the—to use another image—gear or impulse of life:

> We already understand complex living processes, but what is this **secret force of life** that keeps plants, humans, well all of this going? That is really, yeah, that is such a basic and interesting question and we know not much about it. (Scientist J)
>
> German original: Wir verstehen Lebensprozesse eigentlich schon ganz gut, aber was ist denn bloß diese **geheime Kraft des Lebens** die Pflanzen, uns Menschen und alles am Laufen hält? Das ist wirklich, ja, das ist eine so grundlegende und spannende Frage und wir wissen nicht wirklich viel darüber.
>
> Life, the **force of life**. That is really strange and fascinating at the same time. What agent, what kind of force keeps all these metabolic and other processes running?, Well, you can try and explain this with the law of energy conservation, but where comes this from, you understand? We have not really started yet. (Scientist A)
>
> German original: Leben, ja **die Kaft des Lebens**. Das ist schon merkwürdig und faszinierend zugleich. Welches Mittel, welche Kraft hält diese ganzen metabolischen und anderen Prozesse am Laufen, verstehen Sie? Ja, man kann das mit Energiesätzen erklären, aber woher kommt die dann. Wir sind da noch nicht mal am Anfang.

A close look at the sections in the interviews dealing with the conceptual metaphor, LIFE IS A FORCE, displays an emotional engagement. This is linguistically expressed by adjective constructions such as "[…] that is such a basic and interesting question […]" and feedback channeling such as "[…] you understand […]." However, the force-metaphor uses a generic concept that highlights the aspect of a physical and vectorial quantity which is necessary to perform work that changes the energy level of a physical system. This change in energy levels and directionality could be connected to the energy needed to provide work power for basic characteristics of life such as metabolism and reproduction. These aspects are, however, hypothetical and require further corroboration through in-depth interviews and analysis. What is interesting, however, is that the generic concept of force is used to explain the generic concept of life. Both concepts could be situated on an abstract conceptual level which might explain why the metaphorical categorization oscillates between abstract fuzziness on the one hand and human bodily experiences with forces. The conceptual metaphor thus holds an abstract concreteness based in the present case on the professional origin of the interviewee.

The penultimate conceptual metaphor we have to deal with in this section is the metaphorical concept, LIFE IS A RIDDLE. This culturally engrained concept looks back at a long history and is used in many interviews and the two quotes below are representative examples of how the metaphor is used by scientists working in the field of systems biology:

> **The concept life is a riddle to me**, you understand? What keeps replication going, ah, reproduction going on? That is so fascinating and we really have to think deeply to solve this riddle, yeah! (Scientist D)
>
> German original: Das **Konzept Leben gibt mir immer noch Rätsel auf**, verstehen sie? Was hält die Replikation, äh, die Reproduction am Laufen? Das ist so faszinierend wir sollten nach wie vor eingehend bemühen dieses Rätsel zu lösen, ja!

> It, it is still **a riddle to me** and I am sure that we will not solve it. But it is a fascinating thing, this life and, I do not know why, but it keeps me going and pesters me, this life question. (Scientist G)
>
> German original: Es, es **ist immer noch ein Rätsel für mich** und ich bin mir sicher, dass wir es nicht lösen werden. Aber es ist ein faszinierendes Ding, dieses Leben und ich weiß nicht warum, aber es hält mich am Laufen und stellt mir auch nach, diese Frage nach dem Lebensbegriff.

The conceptual metaphor of LIFE IS A RIDDLE alludes to a task or question that has logically to be solved by the process of thinking. The metaphor holds strong ties with science because of associated connotations such as scientist, to solve, to decipher, mysterious, mystery, and unresolved, and also refers to the pedagogical tasks of a riddle in terms of strategic problem-solving and education. Riddles hold a haunting if not stalking potential, as we see in the second quote where "riddle" pesters the scientist interviewed. The aspect of entertainment and pastime stemming from everyday experience with riddles or riddle magazines are not highlighted here but enable a conceptual connection between the realm of science and daily life: the abstract entity of life is conceptualized via the experienced and cultural domain of riddles.

The last metaphorical concept discussed in this section is the conceptual metaphor, LIFE IS A SECRET. This metaphor holds strong semantic ties with the analyzed concept of LIFE IS A RIDDLE. At first sight, both concepts contain connotations already encountered such as scientist, to solve, to decipher, mysterious, mystery, and unresolved, but on close inspection there are some considerable differences: secrets could reveal horrible things, are sometimes open, best-kept, and (at least in the German language) often lie in the dark. These aspects also emerged during the interviews:

> The question of what life **is or could be**? **This will remain a secret** and always stay in the dark. It might be possible that we can bring some light into darkness but that will take some time. (Scientist P)
>
> German original: Die Frage nach dem was Leben ist oder sein könnte? **Das wird ein Geheimnis bleiben** und im Dunklen bleiben. Möglicherweise kriegen wir etwas Lichts ins Dunkel, aber das wird noch dauern.
>
> The concept of life is not really interesting for us. We are working on another concrete level; this is **some sort of a secret** that will always stay in the dark. (Scientist P)
>
> German original: Das Konzept Leben ist für uns hier nicht wirklich interessant. Wir arbeiten auf einer anderen konkreteren Ebene; **das ist so eine Art Geheimnis**, das immer im Dunklen bleiben wird.

What becomes apparent in the interview extracts is that the conceptual metaphor, LIFE IS A SECRET, is often combined with linguistic light metaphors. These figurative speech patterns are based on the conceptual metaphor, LIGHT IS KNOWLEDGE, and develop a close alliance with the conceptual metaphor, LIFE IS A SECRET. The secret-metaphor again, as in the other cases, conceptually blends the abstract entity "life" with the cultural experiences revolving around the notion of secret. The quotes, however, differ considerably as the first one displays a slightly positive perspective on solving the secret of life whereas in the second quote the combination of light and secret-metaphors is used to express that the attempt to unravel the secret of life is a useless endeavor: an all-embracing concept of life seems impossible.

In summary, the metaphorical concepts analyzed demonstrate that scientists also use metaphors to conceptualize abstract scientific entities such as life. Even though it might have been problematic to ask the complex life-question, not a single interviewee rejected reflecting on it and answering it. On the contrary, the question—primarily philosophical in its character (Kather 2003; Toepfer 2005)—was in many cases conceived to be relevant and the systematic analysis of the transcripts revealed a creative and skillfull variety of ways of dealing and coping with this question, which may finally not be an explicit research subject of systems biology but nevertheless an important philosophical question for systems biologists. We now turn, in the next and final section of this subchapter to a more systematized overview of the conceptual metaphors of life analyzed. The aim consists in providing a structured overview and interpreting what kind of implications may reside in the metaphorically framed concepts.

2.2.3 Assessing Metaphorically Informed Visions of Life

The preceding analysis has shown how scientists working in the area of systems biology use metaphors to ascribe meaning to the basic notion of life. The conceptual metaphors analyzed depicted an interrelated conceptual and shared network endowing the abstract concept with meanings (see Fig. 2.1).

The interpretation of representative examples, furthermore, revealed the semantic complexities and associative networks nestling in the metaphorical concepts studied. These results offered a first insight into how and by which means a representative group of scientists working in the area of systems biology attributes meaning to the

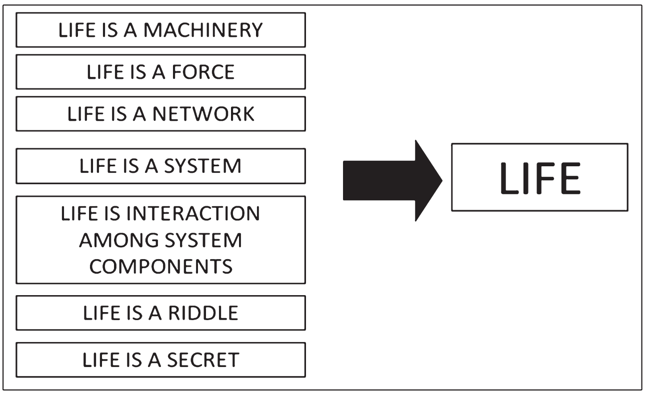

Fig. 2.1 Conceptual metaphors used to frame the notion of life

abstract notion of life in biology. The results are interesting in themselves but the question remains of what one could conclude from such a study that discloses underlying semantic networks and how such a sociocultural investigation could contribute to developing deeper insights?

First of all, we emphasize that empirical studies on the metaphorical framing of basic categories in biology as undertaken in the present context are rare. A closer look at the analyzed semantic network and its interpretation opens up the possibility for an empirically informed overview over the conceptual structure of the field. If one considers again the analyzed imagery in view of the underlying transfer processes, it shows the first three conceptual metaphors are motivated by engineering science: one is shaped by science, one stems from interpersonal experience, and two fall back on culturally established experience reports in the broadest sense of the meaning (see Fig. 2.2).

This clearly shows that in systems biology, the concept of life exhibits characteristics that are primarily technological or engineering–scientific in nature, yet there is a shift in meaning towards dynamization and complexity with the frequently encountered interaction metaphor. In view of the diverse metaphorical framings of biological relationships and their functional processes, the force metaphor highlights the gear of life and the ambiguity of the riddle or secret metaphors underlines difficulties encountered to define what life means and is. The analysis of imagery and its transfer processes therefore makes it possible to reveal a metaphorically motivated "heuristic fiction" (Black 1962, 229) with which the notion of life is explored. If one considers that in most cases the metaphors and their underlying transfer processes take place in the subconscious as elements of an implicit knowledge (Cassirer 1985, 1993; Polanyi 1966) then the possibility arises of slightly deepening the analysis in the present context. This means if we correlate the target domains with the professional backgrounds of those interviewed another interesting picture comes into view, namely that the professional backgrounds of the interviewees

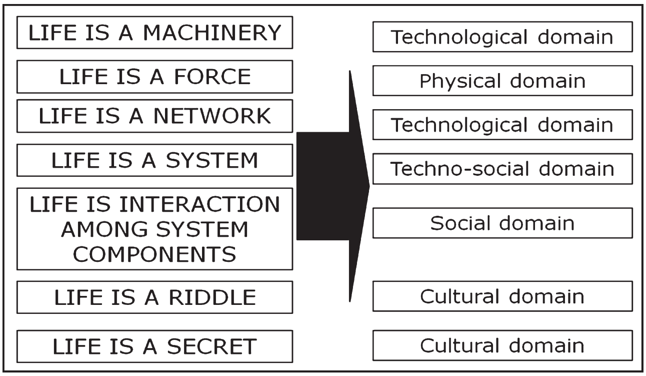

Fig. 2.2 Conceptual metaphors and corresponding source domains

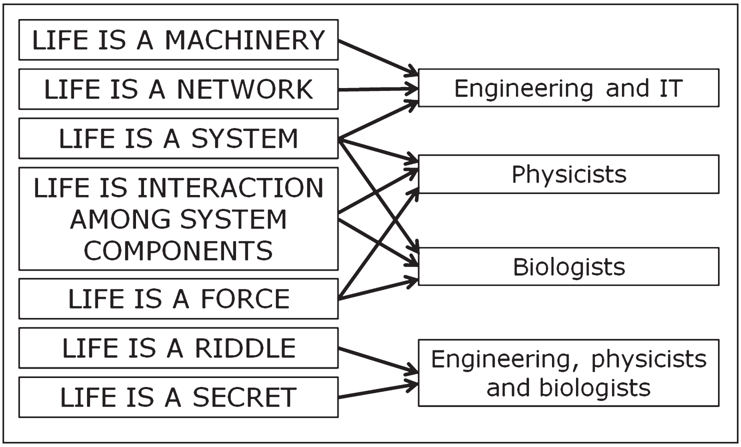

Fig. 2.3 Dispersion of conceptual metaphors among disciplinary backgrounds of scientists

influence their ways of conceptualizing the notion of life as most of those using technological source domains hold an engineering or physics background (see Fig. 2.3).

But the distinction is not as easy as that because the sociocultural target domains such as life is a riddle and life is a secret permeate all interviews. In brief, the notion of life as analyzed here is a mix of professional as well as of sociocultural experiences and knowledge, although the impact of technology-driven approaches on biology—as already outlined—becomes partly visible. Furthermore, a closer look at the transfer processes holds the potential to, though from an interpretative point of view, raise awareness about implications nestling in the transfer processes of the imagery used. Thus, the target domain of machinery clearly highlights aspects of cooperative parts, mechanical engineering, or cog wheels and the riddle metaphor alludes to implicit aspects such as playful solution, systematic deciphering and the like. Hence, the possibility arises within the framework of a critical assessment of conceptual metaphors to disclose and question these meaningful elements to a certain extent and to discuss with systems biologists various paths of technological development and their implications.

To summarize, it might have become clear in this section that metaphors play an important role in the conceptualization of abstract knowledge domains because they capture abstract circumstances with tangible representations facilitated by transfer processes. The analysis and interpretation of these processes of generating meaning provides an opportunity to reveal unconsciously constructed meanings of the notion of life and their implications for debate. The approach aims to create a form of meta-knowledge, which provides the foundation for the negotiation of evaluating technology with those working in systems biology. In this respect, an empirically grounded analysis of conceptual metaphors offers the opportunity to address implications of current, but still implicit visions of life. Even though such an analysis is still in its infancy, we now turn in the following section to an analysis of conceptual metaphors used to frame the notion of system in systems biology.

2.3 Envisioning the Notion of System in Systems Biology

The main aim of this section is to unravel the meanings attributed to the concept of system with the help of metaphor analysis. The notion of system is part of almost all sciences and each disciplinary approach developed its more or less own conceptions and applications. Consequently, system represents a multilayered concept that has been used as a heuristic tool in many disciplines ranging from sociology and economics to ecosystem or even earth system analysis. It officially gathered momentum in biology since the 1950s with the wider recognition of Ludwig von Bertalanffy's General Systems Theory (von Bertalanffy 1932, 1949) and Paul A. Weiss' *The Science of Life: The Living System—A System of Living* (Weiss 1973). These insights were taken up and put forward by theoretical biologists such as Robert Rosen (1970a, b) or Jacques Monod and Ernest Bornek (1971). The systems concept, thus, possesses a considerable theoretical history and wide range of practical applications. With regard to systems biology, the notion of system has so far not undergone a detailed theoretical clarification and empirical examination in terms of its meanings, operationalizations, and applications. Nevertheless, it has become an unquestioned and socially accepted boundary object (Griesemer and Star 1989; Bowker and Star 2000) among scientists in systems biology. However, some contemporary systems biologists such as Boogerd et al. (2007a, b), Wolkenhauer (2001, 2007a, b), and Wolkenhauer and Mesarovic (2005) already aimed—partially together with historians and philosophers of science (Drack and Wolkenhauer 2011)—for conceptual clarification and application: they address theoretical and methodological questions while providing first steps towards a philosophical examination of the notion of system in systems biology. Our task, however, is to tackle the contemporary framings of the notion of system by systems biologists. Such an empirical question concerning the system concept has to date to our knowledge rarely been addressed by system biologists or by scientists working in the area of science studies, technology assessment, and science and technology studies. To better understand how scientists working in systems biology conceive systems is important because nonarticulated conceptual differences may create misunderstandings and hamper the progress of research. We therefore try to answer the following questions. Is there some sort of a conceptual agreement on the abstract notion of system among systems biologists? Does a differentiated set of concepts exist? Furthermore, what kind of unconscious attitudes are bound to the idea of system and could they be connected to a specific professional mindset or scientific identity?

In the following analysis we show how the notion of system is conceptually framed and informed by different conceptual metaphors to disclose the otherwise intangible structures and meanings implicated in the linguistic imagery. It is, however, necessary to historically contextualize the system concept in biology to unfold its different dimensions and meanings before we turn to the empirical analysis. Consequently, the following section provides a (though nonexhaustive) diachronic insight into the notion of system and its features in systems biology. Against this backdrop, metaphors and conceptual metaphors in a representative set of interview extracts are analyzed to reveal implicit conceptualization inbuilt in the notion of system in systems biology.

2.3.1 The Systems Notion in Old and New Systems Biology: A Sketchy Overview

Generally speaking, a system could be conceived as a network of components that are interconnected and represent an interacting whole or unified entity. Systems normally demonstrate some sort of an emergent behavior holding a characteristic or property not shared by or implicated in its constituting elements. This is also a major aspect alluded to in systems biology. There seems, however, to be little awareness among systems biologists about the conceptual history of systems and theoretical impacts of so-called predecessors.[11] This is a problem because a lack in historical and conceptual awareness might lead to theoretical and methodological shortcomings that in turn bear an impact on research which currently develops many ways into biochemistry, genetics, ecology, and the like. As a result, the capacity to understand and to virtually construct complex biological systems might be affected and should hence be based on thorough theoretical, methodological, and historical knowledge about systems theory in general and in biology, especially. This obviously represents a challenge for scientists working in systems biology but holds the potential to develop historically rooted and conceptually sound models of biological systems.

It might sound counterintuitive but one has to go back to the end of the nineteenth century to understand two important concepts stemming from the seventeenth century that underpin biology and even today's systems biology. The first can be identified with René Descartes who stated that complex questions could be analyzed by reducing them to manageable pieces. Descartes' paved the way towards a reductionism that was thought to provide the relevant answers to mathematical and physical problems. Today, it still is an important principle in the sciences in general, and in biology or systems biology in particular. With regard to systems, the basic assumption of reductionism consists in the idea that characteristics of higher system levels could easily be explained by the behavior of lower biological levels (see Sect. 2.4 for more details on reductionism). This conceptual understanding was taken over by proponents of mechanistic biology which concurrently surfaced in the seventeenth century. Based on Descartes' ideas, the emergence and the development of *clockworks* enabled a mechanistic thinking of organisms or biological entities as clockwork-like. The clockwork metaphor facilitated a deterministic view that was able to draw on ideas of disassembling and reassembling and by doing so to explain the characteristics of a system via its parts (Haber 1975; Nicholson 2013). This understanding influenced many scientists such as the plant biologist Jacques Loeb (1964) whose work was based on mechanistic attitudes.

In reaction to Loeb's mechanistic ideas some concerns were articulated by a small group of theoretical and other biologists at the start of the twentieth century (Roll-Hansen 1984; Nicholson 2012). Biologists such as Woodger (2001, 31–84), Weiss (1940), and von Bertalanffy (1950a, 23; 1950b, 140; 1968, 87–89) expressed

[11] This became visible during the interviews conducted for this study.

a twofold concern with the concept of mechanistic biology (Hein 1972). They first outlined—with reference to Aristotle—that the whole is just more than its constitutive parts. This view had dominated up to the seventeenth century but vanished with the advent of experimental physics and biology. To denominate this phenomenon, the term holism was introduced by the statesman and philosopher, Jan Christiaan Smuts (1926). It included the idea that wholes such as cells or tissues, for example, hold properties which could not be understood by reference to the composition of their constituting elements. Thus, reductionism was, according to Smuts, thought to be unable to explain emerging properties of wholes based on mere information about its components.

It was Paul A. Weiss (1925) who experimentally questioned Loeb's mechanistic ideas. Weiss analyzed in his dissertation the impact of light and gravity on insect behavior and was able to show that, although all individuals displayed an identical final response, this response was achieved by unique behavioral ways. Furthermore, Roger Williams (1956) worked on biochemical individuality. He propounded molecular, physiological, and anatomic individuality in animals showing that these vary considerably in terms of chemical, hormonal, and physiological parameters. Consequently, the concept of mechanistic biology was challenged in favor of a more dynamic system-oriented conception because living cells could not be conceived of as deterministic machines but should be envisaged as adaptive and variable entities holding typical characteristics while exhibiting individual responses.

In addition to the typical characteristics, the individuality and reactivity of living systems, their hierarchical organization or structure represents an important aspect or property from a systems perspective. The theoretical biologist Joseph Henry Woodger emphasized in his book entitled, *Biological Principles* (Woodger 2001, 283–298), that higher biological entities start their life cycle from single cells and the development of complex entities follows a typical developmental order. There seem to be restricted developmental routes or constraints that are organized and controlled on a higher level. A system such as a tissue is thus constructed out of single cells and the principle underlying this development is the interaction among the constituents of the lower level that is organized and structured by a higher system level. This hierarchical organization does not follow bottom-up rules but pursues a system logic in which interactions on one level lead to emergent properties on a higher level and vice versa.

Also Paul A. Weiss (1973) aimed at unraveling important characteristics of biological systems referring to the recognition of hierarchical structures in biological systems but focused on evolutionary implications. Weiss emphasized two important aspects: he first outlined that greater variation exists at lower levels of systems and that individual metabolic pathways appear to be more ordered within a system than they would be outside a system. Especially the latter characteristic proves that molecular behaviors depend on and are coordinated by higher system levels. Comparable ideas were also expressed by Gregory Bateson (1972) who pointed to the fact that all organisms are able to adapt and deal with unpredictable environmental incidents. Later, in his book, *Steps to an Ecology of Mind*, Bateson (1972, 343–377) also refers to the gene–environment interaction. Such a systems perspective exerted a vital impact on the interpretation and understanding of evolutionary mechanisms because the interaction of an organism with a complex and variable environment was scientifically reframed as the evolutionary force of nature (Vrba and Gould 1986).

After having clarified and extensively investigated the hierarchical structure of systems, Ludwig von Bertalanffy (1950b, 1968) suggested that, among other important aspects, all complex systems are based on the common property of representing a compilation of interlinked components. This meant there are correspondences if not detailed similarities in the structure and control design of systems. Bertalanffy's outline of a General Systems Theory (von Bertalanffy 1968) gathered momentum due to its emphasis on the relevance of so-called hubs and connectors (Barabasi 2002, 63–64). These components represent the basic ingredients for a stable system structure: Hubs are thought to be connected to many connectors and these in turn are linked to only a few supplementary components (Barabasi 2002, 55–64). Bertalanffy's ideas of a general systems theory proved to be very productive because it emphasized the interconnectedness and interaction of different components: by bringing such properties of systems to the fore he aimed at explaining how they contribute to building a unified whole consisting of different levels. The interaction between different levels was also explicitly addressed by Michael Polanyi (1968) who theoretically showed that adjacent levels do restrict but not determine each other. His basic idea framed upper levels as availing entities that make constituents of lower levels perform functions or behaviors which they would not carry out on their own. Using language as an example, Polanyi (1968, 1311) showed the meaning of a sentence is an emergent property and this property restricts the use of the words to be used to express that meaning. Meaning here holds a top-down function as it bears an impact on the choice of words whereas the words themselves determine the scope of meaning to be constructed. This example can easily be transferred to biological systems and clearly explains how upward and downward causation work when mutations in the DNA appear (Polanyi 1968, 1310).

In addition to upward and downward causation, aspects of control design in systems turned out to be of vital importance. Control is carried out with the help of negative feedback and homeostasis (Cannon 1963, 98–167) which sustain a biological entity. Negative feedback is conceived to be one of the most important elements to control a system because information about the actual reactions of and performances in a system is constantly observed. Feedback controls and loops were also acknowledged by Bernard (1878) and Cannon's book, *The Wisdom of the Body* (Cannon 1963), proved to be highly influential for early proponents of systems theory such as Norbert Wiener (1948) because it anticipated basic ideas later developed in cybernetics. Wiener's book, *Cybernetics or Control and Communication in the Animal and the Machine*, cites Cannon's work (Wiener 1948, 1, 17 and 115) and conceptually owes much to it.

Inbuilt in these emerging ideas of feedback and homeostasis is the concept of stability which was thought to be an intrinsic characteristic of a biological system. Stability is conceived to be based on informational entropy which is envisaged as a driver generating a state of best stability (Beer 1965). There is, however, a problem because the subsystems' intention to aim for its own stability is in many cases overruled by interactions with higher system levels. Such aspects clearly exhibit the shortcomings of reductionist approaches that are based on invariant bottom-up behavior of internal and external system components because real-life processes seem to be more complex and interactive across a vast array of system levels. Early conceptual models of biological systems, however, took up the idea of stability and emphasized that organisms should be conceived of as open systems sustained by a recurrent stream of energy and matter (von Bertalanffy 1950a, 23; Denbigh 1951). The approach, besides its conceptual problems, paved the way towards mathematically systems-oriented *relational biology* as proposed by Robert Rosen (1970a) in his book, *Dynamical System Theory in Biology*.

At about the same time Mihaijlo Mesarovic's (1968) book, *System Theory and Biology*, appeared and his following publications such as *Mathematical Theory of General Systems* (Mesarovic and Takahara 1972), *General Systems Theory* (Mesarovic and Takahara 1975) or *Abstract Systems Theory* (Mesarovic and Takahara 1988) laid grounds for a mathematically inspired systems approach to biology. Based on the—although not new—idea that system dynamics and organizing principles of complex biological phenomena give rise to the functioning and function of cells (Wolkenhauer and Mesarovic 2005, 14), emphasis was put on the understanding of temporal aspects triggering functions of cells such as growth, differentiation, division, and apoptosis. In doing so, the need to understand the functioning of the cell from a systems perspective was stressed. The advent of bioinformatics as well as genomics and other Omics approaches driven by new ICT technologies provided biology with a plethora of genetic and genomic data and rekindled the interest in systems approaches at the end of the 1990s. Albeit their identification procedures, characterizations of main components making up cells, and first approaches to construct domain-specific ontologies provided substantive benefit for systems biology because they supplied the basic ingredients for refocusing on biological interactions, processes, and dynamics. Especially the information made available by proteomics, the listing of all proteins active in a certain state of a cell or organism and on different system levels, instigated a reconceptualization of organisms, cells, genes, and proteins as independent entities whose characteristics and relations are established and determined by their function in a whole. This conception clearly mirrors a general systems definition in which a system is conceived as a discrete number of components and the relations among them (Klir 1991). "Systems theory is then the study of organization and behavior per se and a natural conclusion therefore to consider systems biology as the application of systems theory to genomics" (Wolkenhauer 2001, 258). This concept emerged and was put forward by main proponents of the new systems biology such as Hood (2000), Kitano (2002a, b), and Wolkenhauer (2001) with the aim of developing mathematical or so-called computational models for biology.

The theoretical background to this development stems from the 1960s and is based on a conceptual transfer from physics to biology when theoretical biologists used the then contemporary systems approaches to find and analyze biological laws that govern the behavior and evolution of living entities. Analogous to the relation between physical laws and living matter, biological systems were conceived of as representing a special case of physical systems. Criticism was raised and resulted in a comprehensive discussion of systems biology by Robert Rosen (1978, 1985, 2000). Nonetheless, biologists beginning to become interested in re-emerging systems biology more than a decade ago realized there is a need to approach complex and dynamic systems in a way for which existing reductionist approaches were not suitable. Against this backdrop, the return to systems-theoretical approaches by the end of the twentieth century appears logically consistent as the plethora of data made available by advances in Omics required a conceptual rather than an empirical approach that investigates the relationship between state variables. Emphasis was in this context not put on entities themselves but on the connections between them, their functional relations, and the outcomes of these relations. These insights, along with the increase of computing capacities, initiated and promoted an interest in the mathematical modeling of biological systems. Such modeling aims at establishing rules working on different levels, thereby postulating so-called causal laws that, for example, explained functional dependencies among genes or gene products instead of describing them in terms of mere associations. Hence, the aim consisted in the description of organized and probably repeated process patterns that were envisioned to help better understand the interaction, functioning, and development of a set of biological variables on one and/or across different levels. Looking at biological processes through the system-theoretical lens thus proved to be conceptually productive and led to the first steps into mathematical modeling of biological processes. It is, however, important to bear in mind that the notion of system in biology with all its theoretical implications and recent practical transfer to mathematical modeling offers explanations that refer to the limits of the new systems biology.

Thus far, we have tried to provide a sketchy overview of the history of the systems' idea in biology and systems biology. It became apparent that the notion of system holds a long conceptual history which can be traced back in essence to antiquity and more concretely to the seventeenth century. The most important insight consists in the Aristotelian understanding that the thing is more than the sum of its constituents, a view which was abandoned with the development of Cartesian reductionism and taken up again at the start of the last century in the works of Ludwig von Bertalanffy and Paul A. Weiss. The development and application of the systems idea in biology has, as roughly depicted in this section, progressed via a variety of intermediate steps and cumulated at the end of the 1960s with the rediscovery of Ludwig von Bertalanffy's general systems theory. Bertalanffy's ideas were partly reconceptualized and mathematically put forward by Robert Rosen's and Mihaijlo Mesarovic's publications. Their mathematically inspired system approaches contributed to paving the way to what nowadays is called the "new" systems biology. Even though the works of Bertalanffy, Weiss, Rosen, and Mesarovic are rarely referred to,[12] they provided the conceptual grounding for a mathematically

[12] An exception to this rule are Westerhoff and Palsson (2004), Alberghina and Westerhoff (2005), Boogerd et al. (2007a, b), Ullah and Wolkenhauer (2007), Drack and Apfalter (2007), Drack (2009, 2013), and Drack and Wolkenhauer (2011). The authors mentioned regularly refer to the "founders" of the new systems biology.

informed understanding and modeling of systems in biology. The notion of biological systems, however, remains ambiguous and is tied to daily practices and ICT contexts. It is, hence, worth exploring how the notion of system is metaphorically conceptualized by systems biologists of different disciplines to uncover the various meanings attributed to this basic notion. This aspect is explored in the following sections.

2.3.2 Systems Biologists Picturing the Notion of System in Systems Biology

The previous section depicted a (though limited) historical and conceptual insight into the system notion that paved the way towards new systems biology. It became apparent that it theoretically owes a lot to the Aristotelian notion of system (wholes), to general systems theory as outlined by Ludwig von Bertalanffy and Paul A. Weiss, to cybernetics developed by Norbert Wiener, as well as to Robert Rosen and to Mihaijlo Mesarovic, who both provided important theoretical grounds for the mathematization of current systems biology. Although the system notion itself is constitutive for the discipline, its historization in new systems biology is still lacking and has also rarely received philosophical investigation. This is an astonishing fact because the concept is constitutive for the approach itself and analytically used in many ways for exploring and analyzing the functioning of systems in biology ranging from genes, cells, and organs to entire organisms. Frequent are quotes—such as the following—explaining what new systems biology is and at the same time giving an implicit idea of what a system is supposed to be.

> Systems biology is the coordinated study of biological systems by (1) investigating the components of cellular networks and their interactions, (2) applying experimental high-throughput and whole genome techniques, and (3) integrating computational methods with experimental efforts. […] The systematic approach to biology is not new, but it has recently gained new attraction due to emerging experimental and computational methods. (Klipp et al. 2005, V)

Here we find a description of some important characteristics of systems: systems biology is depicted as a systematic study of components, their interrelation on and beyond system levels, and the experimentally grounded simulation of their interactions. Even though this textbook extract aims at introducing systems biology to students, its historical depth is reduced to just mentioning that there is a historical background which was remotivated due to emerging methods and technical innovation (Ideker et al. 2001, 345–346). One could argue that such a general outline of what systems biology is and what the systems notion means meets the needs of undergraduate students in this context. A detailed and perhaps historical introduction might simply place too much strain on undergraduates but depictions of systems in systems biology remain in many cases on a general and descriptive level.

Especially a limited outline of the historical roots often appears in the form of the following two quotes.

> Since the day of Norbert Wiener, system-level understanding has been a recurrent theme in biological science. The major reason it is gaining renewed interest today is that progress in molecular biology, particularly in genome sequencing and high-throughput measurements, enable us to collect comprehensive data sets on system performance and gain underlying information on the underlying molecules. This was not possible in the days of Wiener, when molecular biology was still an emerging discipline. (Kitano 2002a, 1662)
>
> Whereas the foundations of systems biology-at-large are generally recognized as being as far apart as of 19th century whole-organism embryology and network mathematics, there is a school of thought that systems biology of the living cell has its origin in the expansion of molecular biology to genome-wide analyses. From this perspective, the emergence of this 'new' field constitutes a 'paradigm shift' for molecular biology, which ironically has often focused on reductionist thinking. (Westerhoff and Palsson 2004, 1249)

Reference is often made to well-known scientists such as Norbert Wiener and temporal indications such as "nineteenth century" chronologically situate genealogies and disciplinary development paths. In addition to these aspects, disciplines such as molecular biology and emerging technological and methodological innovations form important narrative structures in which the notion of system is only alluded to superficially. Although these rhetoric devices refer to well-known discursive strategies of newly emerging disciplines, this is not to say that systems biologists use rather naive system conceptions. On the contrary, scientists working in the interdisciplinary field of systems biology dispose over a tacit and everyday knowledge (Polanyi 1958) of what systems are and how they should be used, but this knowledge does not appear in scientific articles or in books or is not explicitly expressed, respectively. This is why a historical anchoring and philosophical theoreticization of the systems notion in systems biology might be helpful for the reflection on presuppositions inbuilt in ideas of or about systems. This aspect has to date rarely been addressed and motivated us to explore system conceptions distributed among systems biologists.

Based on these insights, we situated the so-called systems part of our manual for the semi-structured interviews after a question addressing the conceptualization of bottom-up, top-down, and middle range approaches. This was done implicitly to allude to levels, system borders, and so on, and prepare the ground for the complicated question about what a system represents for the interview partner. The methodological procedure was triggered by the hypothesis that an organized analysis of metaphors might disclose subliminal system conceptions distributed among our interviewees whereas the aim of the question consisted in instigating a thought process in which most salient features or characteristics of systems were discursively explored. A close look at the interview transcripts corroborates the usefulness of this approach because most interviewees generally started with a typical description of the characteristics of systems such as the different layers and levels of a system, and then swiftly outlined aspects of wholeness, system borders, and interaction among system components, among others. These aspects were in many cases supplemented by focusing on current research undertaken by the interview partner and back references to technological innovation in computation technologies and methods. Once the question was conceptually grounded, a subcutaneous tension appeared as displayed in the two following interview extracts.

> You are really asking tricky questions…hmm. Well, I mean the question is really basic and I have to admit that we do not often address it because we are immersed in all these different technicalities. But now, as I start to think about it, I think that we should address this question in our seminars because I am pretty sure that, at least in our group, the meaning and the characteristics of what a system is has not been addressed. (Scientist D)
>
> German original: Sie stellen aber wirklich schwierige Fragen… Ich muss zugeben, dass die Frage wirklich grundlegend ist und wir tauchen hier immer in diese technischen Fragen ab. Aber wenn ich jetzt so darüber nachdenke, dann sollten wir schon einmal diese Frage in unserem Seminar stellen, denn ich bin mir sicher, dass zumindest in unserer Gruppe die Bedeutung und Eigenschaften von dem, was ein System ist, nicht wirklich behandelt wurden.
>
> You want to know what I think a system is? OK, we are going now in medias res, eh? Ok the whole discipline is built on this idea and I sometimes feel quite unsatisfied with the theoretical outcomes or concepts of what my colleagues think a system is. I mean, there is a diversity of system notions. Sometimes it feels like a zoo where lots of system notions are around. (Scientist F)
>
> German original: Sie wollen also von mir wissen was ein System ist? Ok, jetzt geht's aber wirklich in medias res, oder? Ok, die ganze Disziplin baut ja auf dem Begriff auf und ich bin manchmal ziemlich unbefriedigt mit theoretischen Ergebnissen oder Systemkonzepten meiner Kollegen. Ich meine, da ist eine ziemliche Diversität an Systembegriffen unterwegs. Manchmal habe ich das Gefühl, dass ich in einem Zoo bin und dort jede Menge Systembegriffe antreffe. (Scientist J)

The two quotes indicate that the question asked about the meaning of what a system is appears to be difficult. Especially in the first excerpt the phrase "tricky questions" indicates this to some extent and in the second quote the scientist interviewed refers via the phrase "in medias res" to a perceived intensity. Furthermore, both excerpts exhibit a certain amount of dissatisfaction with the conceptual framing of the systems notion in biology, as expressed by scientist J with his ironic metaphor of a zoo, whereas scientist F expresses that there is a need for further clarification. The tension, however, remained in many interviews and withstanding its resolution by the interviewer, the interviewees started giving an insight into their system notions. As a system is an abstract entity, metaphors were used to conceptualize and communicate it. This led to spontaneously used metaphors that were systematized and analyzed. The analysis of the transcribed interviews gave rise to the following five conceptual metaphors that were utilized to semantically depict what a system is. The conceptual metaphors encountered are A SYSTEM IS A WHOLE, A SYSTEM IS A STRUCTURED ENTITY, A SYSTEM IS THE RELATION OF RELATED AND INTERACTING OBJECTS, A SYSTEM IS A MACHINE, A SYSTEM IS A CYBERNETIC MACHINE, and A SYSTEM IS A BIG PICTURE.

To start with, the notion of systems was metaphorically depicted as a whole. This imagery used lexical items such as whole ("*Ganzheit*") or the big picture ("*Große und Ganze*") which are in many cases sidelined by adjectives such as entire ("*ganz*"), complete ("*komplett*"), or full ("*voll und ganz*"). These words are projected upon the abstract entity of system, as could be seen in the two following quotes.

> **For me**, **a system is some sort of a whole thing**, **a whole** which you can deconstruct to its constituents. And here you can look for what interacts with what, well, what components interact and what comes out of it or, yes, what evolves from it. (Scientist A)
>
> German original: **Also für mich ist ein System eine Art Ganzes**, **so'ne Ganzheit**, das man analytisch in seine Bestandteile auflösen kann. Und hier kann man dann schauen was mit wem, also welche Komponenten miteinander interagieren und was dabei herauskommt oder sich, ja, irgendwie entwickelt. (Scientist A)
>
> Well, **a system that is a whole or an entity** for me that possesses borders in a way, and it's a functional unit within them. It can function and has whatever output which keeps the unit going. Yeah, this is really a rough description I would say. (Scientist K)
>
> German original: Gut, **ein System**, **das ist für mich ein Ganzes oder eine Einheit**, die für mich Grenzen hat, äh eine funktionelle Einheit innerhalb dieser Grenzen. Es funktioniert und hat eine wie auch immer gearteten Output, der die Einheit am Laufen hält. Naja, das ist eine ziemlich grobe Beschreibung, würde ich sagen.

What becomes apparent in these quotes is that it seems to be quite difficult to describe the abstract entity system. What stimulated our interest is that the abstract notion of system is metaphorically conceptualized by other abstract lexical items such as whole or entity. A closer look at the linguistic structures indicates these words hold spatial implications that, roughly speaking, map out what a system is and at the same time reify it. This becomes especially apparent in the second quote where borders are mentioned on the word level and the used adjective "within" alludes to spatial structures. In sum, the conceptual metaphor, A SYSTEM IS A WHOLE, cognitively realizes systems as entities with a certain spatial extension.

Systems have also metaphorically been depicted in terms of a structured entity. An aspect which also – though implicitly – appeared in the previous quotes but is emphasized in the following three excerpts where words such as "divided into" ("unterteilt in"), "structured" ("strukturiert") or "segmented" ("segmentiert") propose an internal order.

> **Systems are structured entities** for me, you know. They possess some sort of an internal structure comprising functional entities which stand in relationship to each other and interact. (Scientist N)
>
> German original: **Systeme sind für mich strukturierte Einheiten**, verstehen sie das? Sie besitzen so eine Art interne Struktur, die funktionelle Einheiten umfassen und miteinander in Beziehung stehen und interagieren.
>
> A system, phew, good question… Well I would say **that it could be understood as a whole which could be divided into functional elements**. Take for example the cell and its components which make it up. (Scientist P)
>
> German original: Ein System, phuu, gute Frage… Gut, ich würde sagen, dass **es als ein Ganzes verstanden werden kann**, **das in funktionelle Elemente unterteilt werden kann**. Nehmen wir z.B. die Zelle und die unterschiedlichen Komponenten, aus denen sie besteht.
>
> **A system is a structured arrangement of components** that, to my knowledge, interact and holds certain functions which emerge out of their interaction. But it's still a big question and just a definition which requires in depth thinking. (Scientist D)
>
> German original: **Ein System ist eine Art strukturiertes Arrangement von Komponenten**, das, meinem Wissen nach, das zu Funktionen führt, die der Interaktion der Komponenten entspringen. Aber das ist immer noch eine grundlegende Frage und nur eine Definition, über die wirklich einmal intensiv nachgedacht werden sollte.

The conceptual metaphor, A SYSTEM IS A STRUCTURED ENTITY, offers another possibility to make the abstract notion of system more concrete. It holds spatial implications but implicitly refers to smaller scales and a higher degree of segmentation. Both aspects become apparent in the frequent use of the words "component" and "elements" appearing in the interview transcripts. In brief, the spatio-metaphorical downscaling provides a higher degree of segmentation which makes the system concept cognitively manageable.

The previous conceptual metaphor is further elaborated on by another one which we called, A SYSTEM IS THE RELATION OF RELATED AND INTERACTING OBJECTS. This concept goes back to the work of Mihaijlo Mesarovic who developed mathematical explanations for elucidating functional relations between associated and interacting objects in biological systems. His metaphorical concept has, although sometimes implicitly, been taken over in systems biology and points to the aspect of interaction and dynamization not covered in the previous two metaphorical concepts.

> Yes, well that's quite simple because that is Mike Mesarovic's work who developed a comprehensive theory of systems. He simply said that **a system is the sum of related and interacting objects**. (Scientist E)
>
> German original: Ja. Äh, das ist ganz einfach weil das eben Mike Mesarovics Arbeit ist, der eine umfassende Theorie von System entwickelt hat. Er hat einfach gesagt, dass ein System eine Menge von ineinander in Beziehung stehender und interagierender Objekte ist.
>
> The system notion I adhere to is the one that emphasises the fact that **a system consists of the relations among objects**. I mean, their relation and the inherent interaction, you understand? (Scientist H)
>
> German original: Der Systembegriff, dem ich anhänge, betont die Beziehung der Objekte untereinander. Ich meine jetzt so deren Beziehung und Interaktion, verstehen sie?

In addition to these more abstract metaphors that frame systems in terms of spatial structures, reify them in terms of an entity and apply more dynamic ideas to them, the conceptual metaphor A SYSTEM IS A MACHINE appears quite frequently. This is seen in the following two quotes.

> If you like, as **system could also be understood as a machine**. Well I have now Kitano's image of an airplane in mind. There are all these subsystems consisting of their elements and components. And the whole and its subsystems work together, are interlinked and in the end the system works properly. Well, in Kitano's case, the airplane flies, if you will. (Scientist L)
>
> German original: Wenn Sie so wollen, kann man **ein System auch als eine Maschine sehen**. Also ich meine jetzt dieses Flugzeugbild von Kitano. Das sind alle diese Subsysteme und deren Elemente und Komponenten, die zusammengesetzt sind. Und das Ganze und seine Untersystems arbeiten zusammen, greifen ineinander und am Ende arbeitet das System dann. Also gut, bei Kitano fliegt das Flugzeug dann, wenn Sie so wollen.
>
> A system, yes, err, how could I explain this? For me, it's, **well not solely**, **a machine**. It's a functional unit that can work on its own but that could also be linked to other units. Well, it could also be a big and overarching entity. (Scientist F)
>
> German original: Ein System, ja, äh, wie könnte ich das beschreiben? **Für mich ist das**, **also nicht ausschließlich**, **aber auch eine Maschine**. So eine funktionelle Einheit, die in sich selber arbeitet, aber auch mit anderen Einheiten vernetzt ist und arbeitet. Naja, ist eine große und übergreifende Einheit halt.

The machine metaphor clearly emphasizes the technical and engineering aspect of the system notion as it is outlined in the first quote with intertextual reference to Kitano's (2002a) paper. Kitano used the image of an airplane to explain what the aim of systems biology is and how a systems-oriented approach to biology could work. The plane functions here as a metaphor for a biological system constituted out of different components or subsystems which brings about a metabolism to work or a plane to fly. The machine metaphor conceptualizes the abstract domain with the help of a concrete domain and differs in this respect from prior conceptual metaphors that relied on an abstract to less abstract metaphorical mapping. It, however, holds technical and mechanistic implications that are critically assessed in the second extract. Thus, the machine metaphor seems to hold a certain explanatory potential but is also viewed critically.

This critical aspect is raised and elaborated upon in some interviews where the conception of machine is further refined into the conceptual metaphor, A SYSTEM IS A CYBERNETIC MACHINE. Here, reference is made to Norbert Wiener's cybernetics and the work done by Heinz von Foerster. Their research offered insight into the working of systems as nonlinear machines because the entities under review exposed different reactions after having received a series of the same inputs. This aspect is stressed in the following two interview sections.

> And there is an interesting story. There is, ah, an interesting American cyberneticist, Heinz von Foerster. And he coined the notion of a non-trivial machine. The non-trivial machine is a machine that – even though it gets the same input – generates different outputs. Why is this so? Well, he says that each input changes the state of the machine. **Yes, it thus is not a simple converter and biological systems are also not a simple converter**, they are not physical machines. (Scientist H)
>
> German original: Und da gibt's 'ne interessante Geschichte. Es gibt ähm einen bekannten ähm amerikanischen Kybernetiker, Heinz Foerster. Und der hat den Begriff geprägt der sogenannten nicht trivialen Maschine. Die nicht triviale Maschine ist eine Maschine, die – obwohl sie den gleichen Input bekommt – mehrmals hintereinander jedes Mal einen anderen Output produziert. Und warum ist das so? Weil er sagt, weil jeder Input, den sie kriegt, ändert den inneren Zustand der Maschine. **Ja, es ist also kein simpler Konverter und das sind biologische Systeme auch nicht**, die sind keine physikalische Maschine.
>
> You know, we have to deal with different outputs although the system is fed with the same input. I would say that this is the basics of cybernetics as outlined by Bertalanffy and von Foerster. **Biological systems are cybernetic machines** in that the hold a history and this history or experience changes the outputs even though the input is the same. Quite complicated to understand, eh? (Scientist J).
>
> German original: Wissen sie, wir haben es hier mit unterschiedlichen outputs zu tun, und dass obwohl das System mit dem gleichen Input versorgt wurde. Ich würde sagen, dass wir es hier mit den Grundlagen von Bertalanffy und von Foerster zu tun haben. **Biologische Systeme sind kybernetische Maschinen**, die eine Geschichte haben und diese Geschichte oder Erfahrungen verändern den Output auch wenn der Input gleich bleibt. Ziemlich kompliziert zu verstehen, was?

What becomes apparent in this metaphorical concept is a complex understanding of systems as nontrivial, nonlinear, and nonmechanistic entities. In fact, the machine metaphor in combination with the concept of cybernetics evokes an understanding of systems as the relation of related and interacting objects. The metaphor clearly displays some sort of cognitive dissonance because the notion of a machine holds functional and deterministic implications that cybernetic machines do not. The metaphor could thus be understood as a productive contradiction *in adjecto* or heuristic device for systems biologists as it conceptually merges a certain degree of functionality with the idea of nonlinearity.

However, along with these more technical metaphors, the visually oriented conceptual metaphor, A SYSTEM IS A BIG PICTURE, materialized in the interviews. It stresses aspects of visual perception and its relevance for the research process, and features aspects of detailed overview and insight:

> "The **system perspective really provides the big picture**, it's some sort of a vista where you can switch back and forth, from small scale to big scale, back and forth." (Scientist C)
>
> German original: Also, die **Systemperspektive führt uns wirklich zum großen Bild**, es ist so eine Art Überblick in dem man vom Ganzen ins Detail gehen kann, also einfach hin und her schalten.
>
> I mean, **the system view really is the big picture**. We can go into detail and at the same time think about the overall perspective and then see how this all evolves, the whole system. Sometimes its leads me to a new humility… because of these multifaceted interactions that make up things like petals or resistant plants such as glasswort. (Scientist G)
>
> German original: Ich finde, dass **die Systemperspektive wirklich das große und ganze Bild** ist. Wir können uns Detail gehen und zur gleichen Zeit über die übergreifende Perspektive nachdenken und schauen, wie das alles entsteht, also das System. Manchmal führt das bei mir zu einer neuen Bescheidenheit… weil, diese vielfältigen Prozesse die Blütenblätter entstehen lassen oder zu so resistenten Pflanzen wie Queller führen.

What becomes evident in the previous interview excerpts is that the conceptual metaphor, A SYSTEM IS A BIG PICTURE, is often combined with lexical items stemming from the semantic field of vision. Thus, words such as "perspective" (*Perspektive*), "systems perspective" (*Systemperspektive*), and "overview" (*Überblick*) develop a connection with the conceptual metaphor and strengthen its visual scope in terms of an improved understanding. This aspect of an improved understanding is subcutaneously endorsed by culturally well-engrained metaphorical concepts such as, UNDERSTANDING IS SEEING, and, UNDERSTANDING IS LIGHT, which relate to the visual aspect semantically inherent in the metaphorical concept, A SYSTEM IS A BIG PICTURE.

Concluding this section, we now turn to a broader picture of the conceptual metaphors encountered and analyzed in this section. The aim first consists in providing a structured overview and second in interpreting what kind of implications may reside in the metaphorical framing of the system concept.

2.3.3 Assessing Metaphorically Informed Concepts of System

As we have seen in the previous section, scientists use different metaphorical concepts to grasp and elaborate semantically upon what the abstract notion system means to them. The—sometimes—detailed analysis and interpretation revealed hidden aspects that do not appear on the word level. Although the question asked was complex and led in some cases to a short period of reflection, not a single

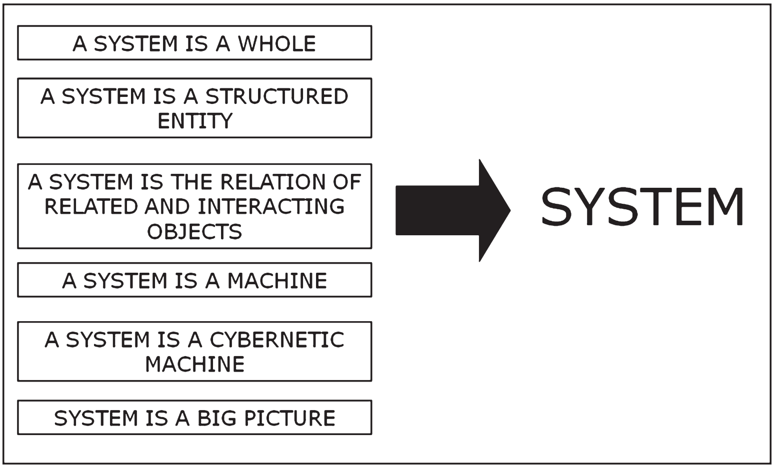

Fig. 2.4 Conceptual metaphors used to frame the notion of system

interviewee refused to answer the question. On the contrary, some scientists enjoyed exploring and depicting their understanding of what system means to them and expressed in the aftermath of the interviews that more time should be devoted to what one interviewee called “theoretical playing and exploring.”

The preceding analysis, furthermore, provided insight into how the abstract notion of system was endowed with meanings, albeit different ones. These results offered a first insight into how and by which means a representative group of scientists working in the area of systems biology frames the concept of system in systems biology (see Fig. 2.4).

If one considers again the analyzed imagery in view of the underlying transfer processes, it showed that the first two conceptual metaphors were based on an implicit spatiality that contributed to reifying what a system is and applied a spatial structure to what a system could be. The aim here consisted in making the rather static system concept manageable. Meanwhile, a certain degree of dynamization was tackled in the conceptual metaphor, A SYSTEM IS THE RELATION OF RELATED AND INTERACTING OBJECTS, and in the A SYSTEM IS A CYBERNETIC MACHINE. The latter especially seemed to counteract the mechanistic implications nestling in the conceptual metaphor, A SYSTEM IS A MACHINE, by merging mechanistic aspects with a nonlinear understanding of systems. In brief, the conceptual metaphors exhibited a process of dynamization of the systems notion and this provided a bigger picture as encountered in the conceptual metaphor, A SYSTEM IS A BIG PICTURE (see Fig. 2.5).

To summarize, it should have become clear in this section that metaphors play—again—a vital role in the conceptualization of abstract knowledge domains because they capture the abstract notion of system with the help of six metaphorical concepts. Interestingly enough, the metaphorical concepts could not be connected to the scientific disciplines to which the interviewees belonged. The analysis and interpretation of the metaphorical mapping processes, furthermore, provided an

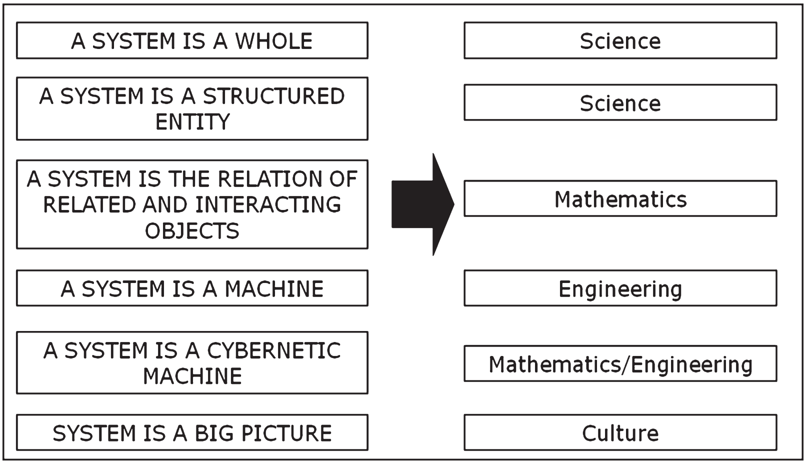

Fig. 2.5 Conceptual metaphors and source domains

opportunity to reveal the generally shared and unconsciously generated meaning constructions that seem to revolve around the aspect of "dynamizing" the understanding of biological processes with the aid of a systems concept. As the approach to systematically analyze metaphors proved to be practical and productive, we now turn to the systematic exploration of the abstract notion of reductionism.

2.4 Reimaging Reductionism in Systems Biology

The notion of reductionism seems to run counter to the logic of complexity and multilevel interaction, inbuilt in systems biology, and also to contradict the intuitions evoked by the term holism which is connected to systems biology. Reductionism refers to a concept which could roughly be characterized by the idea that the development, maintenance, and functioning of an entity can be understood and explained with reference to a basic and restricted set of underlying components. These indivisible and invisible elements such as genes (or the DNA-sequences coding for proteins or control elements, respectively) are conceived of as representing material endpoints that help to understand and explicate phenomena which go beyond them. Thus, higher levels of biological organization and their phenomena causally rely on these endpoints and represent their ostensible epiphenomena. The concept of reductionism, thus, aims at explaining complex and multifaceted phenomena of the natural world by reducing them to simpler structures of matter. It was introduced into Western thinking by René Descartes and his clockwork metaphor (Descartes 2000, 42–43 and 270–271), which we already encountered in the previous section on the concept of system in systems biology. Simply put, Descartes' idea of a clockworks is based on the belief that God, when creating the world, had a clockwork mechanism in mind (Snobelen 2012) which could be used to explain the mechanical functioning of physical, chemical, and biological systems. Reductionism, to be understood as a heuristic and philosophical standpoint, offered a rationale in which things were conceived of as being composed of a restricted set of substances (ontological reductionism), that one has to break down a system to its constituents and then to functionally reconstruct it (methodological reductionism). This procedure was thought to be a promising approach to unravel and understand the organized parts and their functionality in a comprehensive system (Pigliucci 2014). A third version of reductionism holds that concepts, laws, and theories are tied to a certain level of organization and explanations found at one level could be absorbed by theories of higher levels, or, the other way around: an explanation relevant to one level could be reduced to theories formulated for lower system levels (theoretical reductionism).

Methodical reductionism especially was adopted in molecular biology and triggered an understanding of individual components as based on their structural chemical and physical properties.[13] However, developments in biology, medicine, genomics, and proteomics indicate since the 1990s that the approach is about to arrive or already has arrived at its limits. Consequently, reductionist frameworks appear unable to explain and unravel the nature of complex phenotypes or diseases such as cancer, and efforts to explicate the complexity and indeterminacy of the human brain based on reductionist assumptions did not prove to be successful. Furthermore, certain properties inherent to biological systems could not be explained with the help of a reductionist heuristic because

> […] proteins with identical or similar biochemical properties do not automatically also have similar biological functions. This specific protein, as found in the fruit fly, apparently catalyzes the folding of a pigment which is involved in vision, whereas the protein found in mammalian life forms seems to be involved in the regulation of the maturation of immune cells. This means that one enzyme (and the relevant gene) can influence very different biological phenomena with a different ecological relevance, depending on the genetic, cellular or phylogenetic context in which it is found […] (Kollek 1990, 128)
>
> and because
>
> […] biological activity does not arise from the specificity of the individual molecules that are involved, as these components frequently function in many different processes. For instance, genes that affect memory formation in the fruit fly encode proteins in the cyclic AMP (cAMP) signaling pathway that are not specific to memory (van Regenmortel 2004, 1016).

Such insights instigated interest in more comprehensive and systemic approaches that materialized in the new systems biology at the end of the 1990s. Systems biology is, however, rooted in reductionist thinking which has been extremely important to molecular biology. Westerhoff and Palsson (2004, 1249) estimate that at least two reductionist roots have been important for systems biology:

> [The first] stemmed from fundamental discoveries about the nature of genetic material, structural characterization of macromolecules and later developments in recombinant and high-throughput technologies [while the second] sprung from non-equilibrium thermodynamics theory in the 1940s, the elucidation of biochemical pathways and feedback controls in unicellular organisms and the emerging recognition of networks in biology.

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[13] It must be stated, however, that there were always currents in biology critical to an overarching methodical reductionism as, for instance, in physiology (Stange 2005) or which rejected ontological reductionism.

Reductionism and molecular biology, however, underwent considerable criticism in systems biology, even though its relevance for the development of a systems approach in biology has generally been acknowledged. The empirical question, nevertheless, remains of how contemporary scientists working in systems biology frame the notion of reductionism. Although this question has already been addressed by Calvert and Fujimura (2011) in their analysis of how scientists working in systems biology separate their discipline from molecular biology, our analysis has different aims: first, we want to elucidate how the abstract notion of reductionism is metaphorically framed by systems biologists, and second, whether different implications nestling in conceptual metaphors display a critical or positive view of reductionism. Furthermore, do these metaphorical concepts contribute to building up a professional identity or difference (Bourdieu 1976) between molecular biology and systems biology?

The overall aim therefore consists in disclosing and interpreting the intangible structure implicated in the linguistic imagery used. It is, however, necessary to provide an insight into the different theoretical backgrounds of reductionism and its current relevance in systems biology before we turn to our empirical analysis as only knowledge about its conceptual history can help to contextualize and better understand current ideas of reductionism. We therefore present in the following section a—though compressed—diachronic and synchronic insight into the notion of reductionism and its use in systems biology. Against this background, linguistic and conceptual metaphors taken from the interviews conducted are analyzed to reveal the current conceptualization of reductionism in systems biology.

2.4.1 Reductionism in Biology and Systems Biology: A Short Overview

Reductionism is a basic concept in modern sciences such as physics, chemistry, or biology since the days of Descartes and Newton, and debates revolving around it question "whether specific scientific entities, concepts or relations can replace other entities, concepts or relations. Attempts at such reductions from one area of inquiry to another have been an integral part of much modern science" (Andersen 2001, 153). Reductionism, thus, represents a historically consolidated concept that goes back to the seventeenth century where, for example, developments in mechanical philosophy used a mechanical logic to explain optical phenomena, whereas physicists at the end of the nineteenth century tried to explain the thermodynamics of ideal gases by analyzing the mechanical activities of constituting molecules.

There is thus a well-established tendency to study complex natural phenomena in relation to elements that are conceived of as constituting parts. According to this view, the world could be interpreted as a nested structure of reductive levels where the laws of higher systems levels could be reduced to the ones of lower system levels. This position is also termed *theoretical reductionism*, which aims at reducing one explanation or theory to another, simpler, but more comprehensive idea (Andersen 2001). The strongest version of this view was put forward in the 1930s by the logical positivists adhering to the ideas of linearity, causality, and the cumulative aspect of nested structures (Feigl 1981a). It remained an important approach until the late 1950s and had a considerable impact on science (Feigl 1981b). The approach is best expressed in Oppenheimer's and Putnam's (1958, 3) paper entitled, "The Unity of Science as a Working Hypothesis." The authors stress that

> [i]t is not absurd to suppose that psychological laws may eventually be explained in terms of the behavior of individual neurons of the brain; that the behavior of individual cells – including neurons – may eventually be explained in terms of their biochemical constitution; and that the behavior of molecules – including the macro-molecules that make up living cells – may eventually be explained in terms of atomic physics.

Contemporary concepts of reduction and reductionism are highly influenced by the logical empiricist Ernest Nagel. Nagel aimed at developing a formal framework for reduction in his essay "The Meaning of Reduction in the Natural Sciences" (Nagel 1960, 99) and in his book entitled, *The Structure of Science. Problems in the Logic of Scientific Explanation* (Nagel 1961). He described reduction as "the explanation of a theory or set of experimental laws established in one area of inquiry, by a theory usually though not invariably formulated for some other domain" (Nagel 1961, 338). This concept is based on a not unproblematic logical empiricist background because it is unable to explain why phenomena could not be reduced to the components or workings of lower system levels. To overcome these logical shortcomings, Nagel developed the idea of the condition of connectability and the condition of derivability with which he aimed at first allowing an assumption that connects functionally discrete entities, and second provides the basis logically to derive laws of the lower system from the higher system (Klein 2009; Peacocke 1976). Nagel's thinking is an important point of reference in philosophical discussions of reductionism that could be, according to Ayala (1974) and as already mentioned, divided into methodological, theoretical, and ontological reductionism. Although these subcategories are in reality intertwined and almost always appear in combination, they nevertheless represent, from an analytical point of view, discrete analytical concepts running through past and present philosophical analyses of scientific research and reasoning.

Ontological reductionism is based on the monist idea that all natural phenomena are composed of a minimum number of kinds of entities or substances. In essence, it is a metaphysical position claiming that all objects, properties, and processes are finally reducible to a single substance. In general, it holds that knowledge about the most basic level and the functionality of its constituting elements suffices to explain phenomena emerging at higher levels of natural entities. These phenomena are called epiphenomena and their complexity is resolved by reducing them to ever-simpler structures of matter which means that the evolution and behavior of higher levels of complexity are driven by basic laws that govern the configuration of basic elements. Change in the structure of elements and their relations is conceptualized as movement in space and the geometrical rearrangement is ruled by cause and effect (Schaffner 1993a, b).

Methodological reductionism, in addition, often builds upon ontological reductionism in that it is unconsciously implicated in the former. The concept of methodological reductionism is based on the conviction that it is a scientifically sound and sensible way to analyze any system at its lowest level. The approach consists in breaking a whole system down to its constituting elements to investigate the structures and functions of its components, and then to reconstruct it with the aim of understanding their functional interaction in the context of the whole entity (Peacocke 1985).

The French physiologist Claude Bernard may be considered one of the first scientists to apply these central principles of experimental philosophy (Böhme et al. 1977) to biology and medicine. In his *Introduction to the Study of Experimental Medicine* (Bernard 1983), he outlined his approach and research methods in the field of experimental physiology: Experimental reasoning, whose different terms we have examined in the preceding section, sets itself the same goal in all the sciences. Experimenters try to reach determinism; with the help of reasoning and of experiment they try to connect natural phenomena with their necessary conditions, or, in other words, with their immediate causes. By these means they reach the law which enables them to master phenomena (Bernard 1983, 57). Research in modern analytical biology and medicine has for the most part followed this pattern since then.

In addition to these two concepts of reductionism, theoretical or epistemological reductionism (Ayala 1974) presupposes that epistemic units such as laws or theories are tied to a certain level of organization and could be explained by implementing the rules of reduction taken from epistemic units at lower levels of the system (Nagel 1961). Epistemological reductionism clearly possesses hierarchical characteristics and obviously holds strong ties with the previous two kinds of reductionism. To summarize, there is thus not a single concept of reductionism but mainly three concepts that inform and permeate scientific discourses and practices of all sorts (Stöckler 1991). In scientific discourse, however, the difference between the analytically discrete concepts usually is neither appreciated nor consciously discussed. Rather, they are often mingled together which does not help to clarify the debate about reductionism.

Inbuilt in all concepts of reductionism outlined here are basic ideas of linear causality and predictability. They hold strong ties with a deterministic worldview in which any phenomenon of nature is tied to pre-existing causes: knowing the initial conditions and the mechanical laws triggering the behavior of the entities hence leads to predictability of the system. Both concepts—reductionism and determinism—had an impact on biology and played an important role in the rise of molecular biology which was mainly propelled by scientists trained in physics (Morange 2000, 2009) and computer sciences (Kay 2000). Consequently, genetic information was conceived to be a straight representation of the genetic code and the structure of the DNA. In this model causal linear flows trigger the transcription of genetic information from the DNA to RNA to proteins (Crick 1958). These information flows were thought to be unidirectional and were conceived of as the central dogma of molecular biology (Schaffner 2002) regardless of the fact that control genes or feedback loops were detected later on. As a result, the molecule-centered perspective of biology was coupled with a molecular-reductionist perspective which suggested that the identification of relevant molecules and their laws of interaction are the relevant units of biological analysis for understanding the functioning of biological entities (Rosenberg 1997).

Reductionism possessed and still possesses a considerable explanatory power, and it enabled scientists working in biology to explore important molecular and cellular processes. Many scientists working in molecular biology to date still rely on reductionist models (Parry and Dupré 2010; Fox Keller 2010). However, a critical point for excessive reductionism was reached when evidence was provided that gene products are not linear representations of genetic information (Falk 1986, 2010) and that their function depends on the spatiotemporal patterns of their expression and on their interactions with other genes. As a consequence, genes (and their products) today have to be conceived of as elements of complex networks on different levels, and that these levels bear an impact on their context-specific activity in cells, tissues or organs. In summary, genes have different functional purposes in an organism depending on their place and position in time. What becomes apparent is the fact that research deconstructed the belief that complex processes could be reduced to unidirectional processes or to the workings of the lower-level elements (Laubichler and Wagner 2001).

A good example for the tendency to simplify complex issues consists in the fact that the reductionist approach removes the object of investigation from its natural context (Kollek 1990; Bonß et al. 1993, 1994; Rheinberger 1997, 2009, 2010). The disciplinization of the research object for specific research purposes reduces the validity of scientific results and can lead to over-interpretation and misleading conclusions. According to this view, it appears impossible to explain processes of life by reducing them to the molecular or genetic level.

This is precisely where systems biology comes into play because it is based on the idea that biological systems are complex and interactive entities with a multitude of structural and functional entities distributed over different system levels. This approach questions the idea of a central control unit and decentralizes it, and also sheds doubts on a hierarchical mode of control and "democratizes" it even though it does not mean that scientists working in systems biology did throw out the baby with the bathwater. The systems approach leads to developing new questions (van Regenmortel 2004) and the application of novel methods. Thus, scientists working in systems biology try to detach themselves from the molecular tradition of linear causality and upward causation by generating ideas of downward causation and distributed causality and control. This change in approaching problems was instigated by the advent of innovations in IC technologies, high-throughput technologies and enhanced possibilities of simulating complex systems or biological networks with the help of mathematical models (Alm and Arkin 2003). No matter how elaborated the positions and reflections are in detail, what becomes apparent is the new conviction that the behavior of a complex system cannot be explained by the structural analysis of the systems components alone, although knowledge about these components is indispensable. But still, although a different mindset in the context of systems biology emerged, an explicit and critical reflection of reductionism and its subcategories for systems biology in general and molecular systems biology in particular is still pending.

In summary, we have tried to provide a somewhat reduced historical and synchronic overview of the main aspects and concepts of reductionism in biology and, as far as possible, systems biology. It became clear that the notion of reductionism holds a long history dating back to the days of René Descartes and Isaac Newton. Descartes' clockwork metaphor, especially, paved grounds for a mechanistic and reductionist logic that was taken up and conceptually redefined in the nineteenth and twentieth centuries by a variety of scientists and philosophers of biology and science. The three analytically discrete but in reality intertwined subconcepts of ontological, methodological, and epistemological (resp., theoretical) reductionism (Ayala 1974) were tackled in which constitutive aspects such as predictability, linear causality, upward causation, and the idea of a central control unit nestled. These aspects became constitutive elements in the rationale of molecular biology and considerably contributed to its development. Results from research and technological developments such as the advent of high-throughput technologies put superficial reductionist rationales into question but a closer look at approaches and concepts in systems biology indicates methodological reductionism cannot be relinquished and still constitutes an important research strategy, whereas epistemological reductionism has implicitly been accepted, but its challenges have not really been tackled yet by the research community. Although systems biology is thought to emphasize that biological processes are characterized by upward as well as by downward causation across system levels, distributed causality, and disseminated control, the different forms of reductionism are still at work in scientists' minds and research carried out. The notion and concept of reductionism in systems biology, however, has not received much critical inspection or in-depth reflection to date. In order to explore what is meant by reductionism in systems biology it is thus important to study its metaphorical conceptualization by systems biologists as it surely is a basic heuristic and practical ingredient in their daily scientific work. This is done in the following section where a paradigmatic set of interview excerpts displays conceptual metaphors used to conceptualize reductionism.

2.4.2 *Systems Biologists' Imaging Reductionism*

In the previous section we encountered the different dimensions of reductionism and their basic conceptual ingredients. It became apparent that the general notion of reductionism is based on three subconcepts such as ontological reductionism, methodological reductionism, and epistemic reductionism. Taking these aspects into consideration, it is remarkable that a historical, theoretical, and philosophical investigation of reductionism in systems biology has rarely been addressed.[14] Quotes, such as the following, often depict some sort of historical overview in which different concepts are generally mentioned with regard to molecular biology, but not further analyzed:

> Much of twentieth-century biology has been an attempt to reduce biological phenomena as an investigation into the inheritance of variation, such as differences in the color of pea seeds and fly eyes. From these studies, geneticists inferred the existence of genes and many

[14] For exceptions see Andersen (2001), Fang and Casadevall (2011) and Kaiser (2011).

> of their properties, such as their linear arrangement along the length of a chromosome. Further analysis led to the principles that each gene controls the synthesis of one protein, that DNA contains genetic information, and that the genetic code links the sequence of DNA to the structure of proteins. Despite the enormous success of this approach, a discrete biological function can only rarely be attributed to an individual molecule in the sense that the main purpose of hemoglobin is to transport gas molecules in the bloodstream. In contrast, most biological functions arise from interactions among many components. (Hartwell et al. 1999, C47)

This paradigmatic description of twentieth-century biology clearly refers to molecular biology and displays some of the characteristics of reductionism outlined in the preceding section such as central control by genes or the attribution of discrete biological functions to a single molecule. What remains in the dark is what this means for systems biology and in what way the systems approach differs from theoretical implications of reductionism inherent in molecular biology. This aspect is historically referred to in the following quote of a paper written by Westerhoff and Palsson:

> Whereas the foundations of systems biology-at-large are generally recognized as being as far apart as 19th century whole-organism embryology and network mathematics, there is a school of thought that systems biology of the living cell has its origin in the expansion of molecular biology to genome-wide analyses. From this perspective, the emergence of this 'new' field constitutes a 'paradigm shift' for molecular biology, which ironically has often focused on reductionist thinking. Systems thinking in molecular biology will likely be dominated by formal integrative analysis going forward rather than solely being driven by high-throughput technologies. (Westerhoff and Palsson 2004, 1249)

Generic reference is made to well-known historical developments to situate the genealogy of systems biology: nineteenth century whole-organism embryology is conceptually coupled with recent advancements such as network mathematics whereas reductionism is explicitly alluded to in the phrase "reductionist thinking". In fact, a closer inspection of the relation between the concepts of reductionism and holism is lacking in many papers on systems biology which often follow the rhetorical logic of a short historical introduction to be initially pursued by the specific problem under investigation. These rhetoric devices contribute to developing a narrative of systems biology as already existing and then re-emerging due to the shortcomings of the reductionist agenda inherent in molecular biology. Although this rhetoric appears to be constitutive for the discipline of systems biology, one has to bear a mind that there is a great difference between the written form of scientific papers or reviews and the knowledge of systems biologists in their scientific everyday life on the other hand. Scientists possess an implicit and pragmatic knowledge about reductionism; it is relevant for them and whether and how it should be applied to scientific problems. This kind of knowledge does not materialize in reviewed scientific papers or books but in cognitive strategies of problem-solving and scientific practices. Two interview excerpts taken from our dataset clearly indicate that reductionism is a ubiquitous phenomenon in systems biology:

> You now, everyone criticizes reductionism or this reductionist agenda but honestly speaking, we have to reduce the problem to make it manageable. We can only start with the smallest units and then go up to the next level to try to understand it. I mean the small parts constitute the overall entity, which naturally has an impact back on the smaller units. (Scientist D)

German original: Wissens Sie, jeder kritisiert den Reduktionismus oder diese reduktionistische Agenda, aber ehrlich gesagt müssen wir das Problem reduzieren um es handhabbar zu machen. Wir können doch nur mit den kleinsten Einheiten anfangen und dann auf die nächst höherer Ebene gehen, um diese zu erklären. Ich meine, die kleinsten Einheiten bringen doch die übergreifende Einheit hervor, die natürlich wieder auf die kleineren Einheiten zurückwirkt.

The quote clearly displays an ontological reductionism by indicating that the "small parts constitute the overall entity" and methodological reductionism appears in the phrase "we have to reduce the problem to make it manageable." A comparable mixture of reductionist dimensions appears in the following quote where "to start with the elements" refers to ontological reductionism and, "I think that we have to be pragmatic to structure the research process," clearly refers to methodological reductionism.

I think that we need this kind of daily reductionism to solve problems. I really do not subscribe to the idea that the parts constitute the whole but I think that we have to be pragmatic to structure the research process. So we start with the elements and see what happens on the next system level, and then we try to understand this process or the interaction between the elements and the system levels. (Scientist G)

German original: Ich bin der Meinung, dass wir eine Art Reduktionismus für die Problemlösung brauchen. Ich bin wirklich kein Fan der Idee, dass die Teile das Ganze konstituieren, aber ich glaube, dass wir pragmatisch sein sollten, um den Forschungsprozess zu strukturieren. Also beginnen wir mit den Komponenten und gucken dann, was auf der nächsten Systemebene passiert. Und dann versuchen wir diesen Prozess oder die Interaktion zwischen den Komponenten und den Ebenen zu verstehen.

What is even more interesting is that in both quotes, nonreductionist and reductionist thinking surface at the same time. It looks as though systems biologists insist on methodical reductionism, which they think is essential to their work, while having problems to detach themselves from ontological reductionism.

Taking these results into consideration, we think it might be of vital interest for systems biologists to reflect philosophically upon the notion of reductionism with the aim of developing a clearer picture of what reductionism is and what role it plays in their daily work and their conceptionalization of biological research objects. As reductionism is an abstract concept, metaphors are used to concretize and to communicate it. This led to spontaneously generated metaphors that were analyzed and systematized by examining the transcribed interviews and led to four conceptual four conceptual metaphors. These are REDUCTIONISM IS AN ENTITY, REDUCTIONISM IS AN ANCESTOR, REDUCTIONISM IS A PREDECESSOR, and REDUCTIONISM IS AN ADVERSARY.

To start with, reductionism has been metaphorically framed as an entity by using the conceptual metaphor of REDUCTIONISM IS AN ENTITY. This imagery uses words such as "entity" (*eine Sache*), "scientific entity" (*wissenschaftlicher Gegenstand*), and "scientific concept" (*wissenschaftliches Konzept*) which often appear in the interview quotes. These words are projected upon the abstract entity reductionism to make it cognitively accessible and manageable:

Ehm, **reductionism**, **well that is some sort of entity** which is really tricky to handle. It has been and is so influential in science and even though it proved to be wrong. I do not want to throw out the baby with the bathtub because it has been important to research in biology. (Scientist A)

German original: Äh, der **Reduktionismus**, **das ist so eine schwierige Sache zu handhaben**. Er war und ist so einflussreich in der Wissenschaft auch wenn er sich in vielen Fällen als falsch erwies. Ich möchte nicht das Baby mit dem Bad ausschütten denn er war schon sehr wichtig für die Forschung in der Biologie.

Reductionism has been highly influential in my scientific life. **It's a scientific entity or a concept which** has been quite helpful and brought biology forward. I would say that it has been an influential concept. (Scientist M)

German original: Der Reduktionismus war in für mein wissenschaftliches Leben sehr wichtig. **Das ist ein wissenschaftlicher Gegenstand oder so ein Konzept**, das sehr hilfreich war und die Biologie wirklich vorangebracht hat. Ich würde sagen, dass es ein einflussreiches Konzept war.

What one can see in these quotes is that it is quite difficult to describe the abstract entity of reductionism, and ontological metaphors help to constitute it as a thing. Furthermore, a closer look at the quotes indicates an implicit historicization: tenses used such as "has been," "proved," and "has been and is" develop a temporal image of a past to which reductionism is implicitly relegated.

The ontological metaphor, however, is quite important as it prepares the conceptual ground for the following two conceptual metaphors which are mainly based on personifications (Jäkel 1997). Personification, to be understood as a subcategory of ontological metaphors, conceptualize an abstract entity in terms of a human being and open up the possibility to ascribe human characteristics to it. This becomes apparent in the following quotes where reductionism (and sometimes molecular biology) is metaphorically framed as an ancestor.

The concept reductionism has been around for decades and **I see it partly as an ancestor of systems biology**. It has indeed contributed so much to the development of biology and the sciences, I mean in the context of molecular biology, but it did not manage to solve the problems detected by it. Somehow a funny development. (Scientist H)

German original: Das Konzept des Reduktionismus kennen wir ja schon seit Jahrzehnten und **ich sehe es teilweise als eine Art Vorfahre der Systembiologie**. Es hat wirklich sehr viel zur Biologie und der Entwicklung der Wissenschaft beigetragen, ich meine im Zusammenhang mit der Molekularbiologie, auch wenn diese nicht die Probleme lösen konnte, die sie aufgeworfen hat. Auch irgendwie eine komische Entwicklung.

It [reductionism] **could be understood as an ancestor** that led the way to systems biology, to complexity and all these interesting questions, you know. (Scientist E)

German original: Er [der Reduktionismus] **könnte als eine Art Vorfahren verstanden werden** der den Weg zur Systembiologie bereitet hat, zur Komplexität und all diesen spannenden Fragen, wissen Sie.

The personification, REDUCTIONISM IS AN ANCESTOR, offers a further possibility to structure the concept of reductionism semantically. It develops human genealogy and situates systems biology at the end of family tree which began in the past with molecular biology.

The following personification, REDUCTIONISM IS A PREDECESSOR, elaborates on the previous concepts but introduces a more neutral aspect on the genealogical aspect because predecessors can be family members but also people not belonging to the family.

Reductionism and obviously **molecular biology are predecessors of systems biology**. I see it as such and I know that many colleagues would subscribe to this view. (Scientist I)

German original: Der Reduktionismus und natürlich auch **die Molekularbiologie sind Vorläufer der Systembiologie**. Ich sehe es zumindest so und ich weiß, dass viele Kollegen es auch so sehen.

For me, reductionism is, together with molecular biology, well, yeah, **they are predecessors of systems biology**. (Scientist N)

German original: Für mich ist der Reduktionismus, zusammen mit der Molekularbiologie, ja, also das sind Vorläufer der Systembiologie.

This personification again puts emphasis on the temporal aspect of succession and the development of scientific theories. What is even more important is the fact that both personifications, REDUCTIONISM IS AN ANCESTOR, and REDUCTIONISM IS A PREDECESSOR, construct a succession of events starting in the past and contributing to bringing about systems biology in its current state, at least in systems biology.

Personification can also be critically used because other theories or approaches can become enemies or adversaries threatening their own scientific agenda or even existence. The conceptual metaphor, REDUCTIONISM IS AN ADVERSARY, appeared not as often as the previous personifications, but it is worth noting here as it could be interpreted as some sort of a relict of former scientific struggles or enforcement techniques.

Reductionism has long been seen as an adversary. I see it today much more as a useful development which then paved the way towards new approaches such as metabolomics, network biology or systems biology. (Scientist J)

German original: **Der Reduktionismus wurde lang als Gegner angesehen**. Ich sehe es heute eher so als eine sinnvolle Entwicklung, die den Weg für Ansätze wie metabolomics, die network biology oder auch die Systembiologie freigemacht hat.

At the beginning, there was a lot dispute and **reductionism and molecular biology were conceived as an adversary**, if one can say it in this way… (Scientist B)

German original: Zu Anfang gab's schon ziemlich viel Streit **und der Reduktionismus sowie die Molekularbiologie wurden schon als Gegner verstanden**, also wenn man das so sagen kann.

What is interesting in the previous quotes is the fact that reductionism and molecular biology are metaphorically framed as adversaries of the past. The use of the past tense or the past progressive indicates the differences between systems and molecular biologists already came to an end. So, the images of reductionism and molecular biology as adversaries fade and more prominent images such as REDUCTIONISM IS AN ANCESTOR and REDUCTIONISM IS A PREDECESSOR indicate a reconciliation of both approaches.

We now turn, in concluding this section, to a short and systematized overview of the conceptual metaphors encountered and analyzed in this section.

2.4.3 Evaluating Metaphorically Informed Images of Reductionism

As we have seen in the preceding empirical section, the conceptual metaphors encountered and analyzed demonstrate that scientists, in fact, use a somewhat restricted set of metaphors to frame the abstract concept of reductionism. The conceptual metaphors

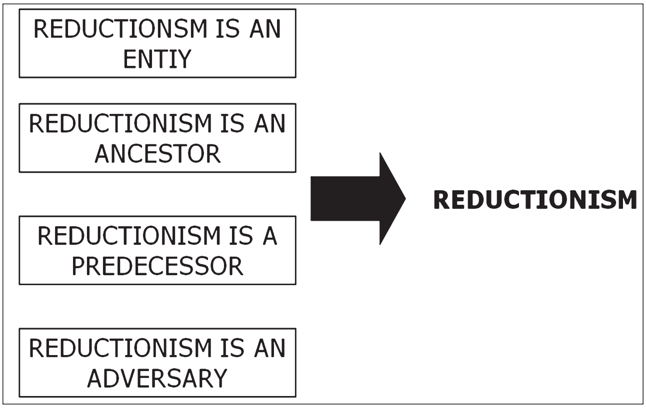

Fig. 2.6 Conceptual metaphors and personifications used to frame the notion of reductionism

REDUCTIONISM IS A THING, REDUCTIONISM IS AN ANCESTOR, REDUCTIONISM IS A PREDECESSOR, and REDUCTIONISM IS AN ADVERSARY were generally used to express and frame the relation of system biologists towards the concept of reductionism and—in many cases—molecular biology (see Fig. 2.6). This seems to indicate that a close conceptual relation between reductionism and the overarching discipline of molecular biology exists because at some stages in the interviews, reductionism almost became a metonym for molecular biology. It, furthermore, became evident that almost exclusively personifications were used as linguistic devices to frame what reductionism is. Thus, the ontological metaphor, REDUCTIONISM IS AN ENTITY, prepares grounds—metaphorically speaking—to substantiate the concept of reductionism. Based on this conceptual grounding, the two personifications, REDUCTIONISM IS AN ANCESTOR and REDUCTIONISM IS A PREDECESSOR, develop a genealogical image of advance supported by the fading personification, REDUCTIONISM IS AN ADVERSARY.

The analysis of the conceptual metaphors, moreover, showed that the ongoing quarrels between molecular and systems biology have been reassured. This was deducted from the personifications as well as from surrounding linguistic context which displayed an extensive use of verbs in the past tense and the past progressive. In brief, reductionism is no longer conceived of as an adversary but a relict of former times that has been incorporated but not overcome by systems biology.

To summarize, we have seen how metaphors and two of its special subcategories, ontological metaphors and personifications, contribute to semantically making the abstract concept of reductionism accessible. The analysis and interpretation of the metaphorical mapping processes inherent in the personifications provided an opportunity to disclose the shared meaning constructions that seem to revolve around the aspect of reconciling systems biology with reductionism, in some cases at least to be understood as a metonym for molecular biology. To complement and contrast the analysis in this section, we now turn to the analysis of imagery framing the abstract notion of holism.

2.5 The Concept of Holism in Systems Biology

As we have seen in the previous section, reductionism in systems biology is metaphorically framed as an entity and personified as an ancestor, a predecessor, and an adversary. These metaphorical notions and their delimiting implications now make it necessary to contrast reductionism with the opposite notion of holism as conceptualized by systems biologists. It is not our academic endeavor (at least not in this section) to show that systems biology is more holistic than molecular biology. It is, however, interesting that such claims, which are made by quite a number of researchers working in systems biology (see Sect. 1.1.2) often lack a theoretical consideration or explanation of what holism means for systems biologists and how they apply the concept in their scientific work. As a result, it is, first, not surprising that the reductionist–holist debate has made a limited reappearance in the context of systems biology and, second, that the notion of holism is in many cases mainly superficially used. This aspect is corroborated by the fact that 32 articles use the notion of holistic, holism, whole, or wholes in their titles and abstracts in the period from 2000 to 2014.[15] Furthermore, a close reading of the articles indicates that theoretical or conceptual considerations are often lacking while they frequently provide an ahistorical understanding of the reductionism–holism debate: it is in many cases framed as closely related to the advent of systems biology. This is astonishing as systems biology had already made contact with the concept of holism in the context of general systems theory. Ludwig von Bertalanffy, Paul A. Weiss, and Robert Rosen, to mention just a few, already addressed in the 1950s and 1960s the question of how holistic views or concepts could be integrated into systems theory and theoretical biology. Not taking these theoretical and conceptual insights into consideration (Drack and Apfalter 2007; Drack 2009) seems to have led to a certain degree of semantic confusion, conceptual inconsistency, and historical misunderstanding about the meaning of holism and from where it originates.[16] We, thus, aim at providing in the following section an insight into how systems biologists metaphorically frame the notion of holism. This investigation provides us with a synchronic insight which is then used as a backdrop for a historical contextualization and conceptual comparison with scientific precursors such as vitalism, classical holism, and modern holism. The main aim of this historically inverse procedure consists in disclosing the intangible structures implicated in the linguistic imagery and in the analysis whether and how system biologists relate to scientific predecessors. Although similar questions have already been empirically addressed by Calvert and Fujimura (2011) and Mazzochi (2012) with regard to systems biology, the scope of the present section differs from these studies as it puts emphasis on the conceptual analysis

[15] See, for example, Stange (2005), Verpoorte et al. (2005), Bennett and Monk (2008), Hood et al. (2008), Federoff and Gostin (2009) and Greek and Rice (2012).

[16] We would like to refer among others to the works of Ayala (1974), Schaffner (1969), Zucker (1981), Ruse (1988), Andersen (2001), and Allen (2005) who provided historical and philosophical insight into the different theoretical concepts and arguments underlying the debates on holism and reductionism.

of the notion of holism as used by systems biologists in their daily language. So let us now turn to study how the notion of holism is metaphorically framed in paradigmatic interview excerpts.

2.5.1 Systems Biologists' Metaphorical Frameworks of Holism

As outlined in the introduction, holism represents a theoretical concept that appears to be of interest to scientists working in systems biology even though not much theoretical activity has been devoted to clarifying what holism means for them. It is astonishing, however, that systems biology appears rather to be informed by idiosyncratic and sometimes tentative concepts of holism which lack historical, theoretical, and philosophical precision. Quotes such as the following are paradigmatic in that they represent general thoughts about holism by redepicting the holism–reductionism dichotomy and characterizing systems biology per se as holistic. What is lacking here is theoretical or conceptual elaboration on why systems biology has to be conceived as holistic.

> I would like to make the point that to obtain the evidence for the activity of traditional medicine we should not follow the reductionist approach, but go back to the holistic in vivo approach. This can be done in two different ways, one is via clinical trials. The other is through animal experiments. Besides the classic physiological observations that can be made in such in vivo experiments, e.g. blood pressure, analgesic activity, sedation, etc. nowadays we also have the possibility to measure gene expression, the proteome and the metabolome. These methods open a complete new world of possibilities, giving a much better insight in possible changes in the organism, i.e. in a holistic way. It will give us the possibilities to better understand the mode of action by comparing the changes in the transcriptome, proteome and metabolome patterns if compared to those observed with known drugs. Such an approach is now known as a systems biology approach (Verpoorte et al. 2005, 54).

Although the phrase "go back to the holistic in vivo approach" implicitly refers to historical predecessors, the quote in general appears to be a colorful conglomeration of buzzwords.

The holistic approach of systems biology is also often introduced by using visual metaphors such as holistic perspective or holistic view, as in the next quote. This all-encompassing perspective, however, neither expresses nor attracts any theoretical analysis of holism or possible implication nestling in the concept itself. This aspect becomes apparent in the following quote where the conceptual shift from genomics towards systems biology is metaphorically depicted as a revolution:

> At a ***first glance the*** present 'Western' medical approach may seem very different from holistic forms of traditional medicine. Western medicine relies on a detailed classification of diseases, empirical investigations and treatments targeting those disorders. However, the revolution in genomics that has taken place in life sciences during the past decade has provided considerable support for a ***more holistic view*** on diagnosis and treatment (Wang et al. 2005, 173).

Even though this quote stems from an article combining TCM with systems biology, it provides a typical way of vaguely outlining the value and meaning of holism. In addition to the narrative structure that often uses technical lexical elements such as "genetics," "genomics," "proteomics," and the like, the visual metaphor "first glance" opens the quote and the adjective "more" gradually characterizes the concept of holism at the end of the quote. This perspective with regard to holism, however, remains imprecise if not unclear and a closer look at the interview transcripts indicates not much reflection has been devoted to the concept of holism. This becomes apparent in the following two quotes which are spontaneous reactions to the interviewer's question of what holism means in systems biology:

> I have to admit that I did not really devote much reflection to that topic. I would say that we simply scaled the analytical levels up and tried to broaden the perspective. (Scientist F)
>
> German original: Ich habe da noch nie so wirklich drüber nachgedacht, muss ich gestehen. Wir haben einfach die Skalen oder Level erhöht und die Perspektive etwas erweitert, würde ich sagen.
>
> No, albeit this is important for our group, we have not theorized the holistic aspect. The interest, if you would like to call it holistic, emerged from the fact that we came under pressure for failing to offer explanations and were discontent with the current conceptual framework. (Scientist B)
>
> German original: Nö, das ist jetzt für unser Gruppe hier zwar wichtig, aber theoretisiert haben wir das nicht. Das Interesse, wenn man es holistisch nennen möchte, entstand eher aus der Tatsache, dass wir in Erklärungsnot kamen und auf einer konzeptuellen Ebene unzufrieden waren.

What becomes apparent in these quotes is that the concept of holism does not explicitly represent a theoretical problem: it is rather the practical side which is emphasized as the main driver to address conceptual problems implicated in research. What one witnesses here is a tentative knowledge that leads to a kind of practicotheoretical reflection in view of undertaking scientific work on a daily basis. This is an interesting fact and in the course of the interview questions on holism a theoretical reflection started in which the three conceptual metaphors, HOLISM IS AN ENTITY, HOLISM IS A BUILDING, and HOLISM IS A PERSPECTIVE, emerged.

To start with, holism was, similar to reductionism, metaphorically depicted as an entity. This designation emerged in almost all interviews and aimed at making an abstract entity cognitively manageable. This imagery is based on generic lexical items such as "entity" (*Entität*) or "thing" (*Ding*) which can be found in the following quotes.

> Holism, ok, I would say **that it is a kind of entity**, **a constructed entity** which helps to better understand or sheds light on emergent properties which develop and cannot be explained by the underlying parts. (Scientist H)
>
> German original: Holismus, ok. Ich würde sagen, **dass das so eine Art Entität ist**, **eine konstruierte Entität**, die uns ein besseres Verständnis ermöglicht und Licht ins Dunkel emergierender Eigenschaften bringt, die nicht aus den einzelnen Teilen erklärt werden können.
>
> For me holism is **some sort of a philosophical thing or better**, **a theoretical entity**, yes a theory. I think it goes back to Smuts and this Vitalist thinking, I think. (Scientist L)
>
> German original: Für mich ist **Holismus eine Art philosophisches Ding**, **also eine theoretische Entität**, ja eine Theorie. Ich glaube, dass die auf Smuts zurückgeht und vitalistisches Denken, das glaube ich.

Although references to theoretical predecessors and schools of thought rarely appear, the quotes partly outline the uneasiness in defining what holism is. It is for this reason that it is, first, metaphorically reified in terms of an entity and then, second, conceptually relegated via the adjective “theoretical” to a more abstract and theoretical level.

The reification, however, initiated in some interviews a more structured thought process in which the concept of holism was metaphorically framed in terms of a building. Thus, theories or concepts become structured and fabricated entities known from everyday life.

> Well, I do not know the **theoretical building of holism** in detail. […] This does not mean that I know, if you will, the house as a whole but at least some rooms and perhaps one or two floors. (Scientist E)
>
> German original: Also, ich kenne das **theoretische Gebäude des Holismus** nicht en detail. […] Das bedeutet nicht, dass ich das Haus als Ganzes kenne, aber wenigstens einige Räume und vielleicht ein oder zwei Etagen.
>
> If you wish, I would say that I do not really **know the theoretical building holism**. I know the notion has been around but it rather is not of everyday relevance for me. (Scientist G)
>
> German original: Wenn sie so wollen, dann kann ich nur sagen, **dass ich diese Theoriegebäude nicht wirklich kenne**. Es ist mir zwar begrifflich bekannt, aber es hat für mich eher keine alltägliche Relevanz.

What becomes apparent in the quotes is that the conceptual metaphor, HOLISM IS BUILDING, reifies holism as a structured but still abstract entity. This view quite roughly implies that one could home-in on such a building because buildings normally have doors to enter them and rooms to live in, but it can also remain a rather empty concept as in the last quotation. Here no inner differentiation or structure appears and it therefore comes near to the conceptual metaphor, HOLISM IS AN ENTITY. This aspect is also corroborated by the second sentence in the quote in which the theoretical building is framed as not being relevant for daily scientific work.

Finally, holism is in many cases metaphorically portrayed by the conceptual metaphor, HOLISM IS A PERSPECTIVE. This metaphor obviously emphasizes visual aspects and implicitly refers to a possibly higher standpoint from which the analytical aspect is investigated by the scientist. This can be seen in the following interview excerpts.

> The **holistic perspective on biological processes** aims at being all comprising. It tries to explain emergent properties which appear on higher levels but are determined by lower ones. (Scientist D)
>
> German original: **Die holistische Perspektive auf biologische Prozesse** versucht übergreifend zu sein. Sie versucht Eigenschaften zu erklären die sich auf höheren Ebenen abspielen und durch untere bestimmt sind.
>
> **The holistic view on biology** has been always been around but not very prominent in times of molecular biology. I mean, molecular biology has provided an important framework but I think that it is now time to broaden the scope and see what is possible. (Scientist C)
>
> German original: **Die holistische Perspektive** war eigentlich immer da, wenn auch nicht sehr prominent vertreten in Zeiten molekularbiologischer Forschung. Ich meine, die Molekularbiologie hat wichtige Konzepte entwickelt, aber ich denke dass es jetzt an der Zeit ist den Ausschnitt wieder zu vergrößern um zu schauen, was möglich ist.

Both quotes exhibit the linguistic metaphor "holistic" view. Although the first quote provides an unspecific or general example that prevails in the corpus, the second offers a relatively detailed example with regard to content. The verb "to see," furthermore, conceptually links up with the metaphorically induced visual aspects, and therefore to the conceptual metaphor, UNDERSTANDING IS SEEING (Sweetser 1990).

In sum, the interview excerpts show the concept of holism is framed by the three conceptual metaphors, HOLISM IS AN ENTITY, HOLISM IS A BUILDING, and HOLISM IS A PERSPECTIVE. The first concept clearly puts emphasis on the aspect of manageability and reification of an abstract entity whereas the other two implicitly map their inherent structure partly on the abstract entity of holism. The conceptual metaphor, HOLISM IS A BUILDING, thus offers an encultured mapping and reification by using an entity encountered in daily life that implicitly holds the potentials of conceptual differentiation in terms of doors, rooms, and windows. HOLISM IS A PERSPECTIVE, moreover, highlights visual aspects while implicitly referring to a higher viewpoint and sight with which a better overview could be gained: two important aspects for a holistic approach. In sum, it becomes evident that at least a limited theoretical knowledge about holism exists among systems biologists. This is clearly mirrored in the general metaphors used to depict what holism is and in the lack of inner differentiation that might provide entry points for further elaboration and differentiation. With these aspects in mind, we now turn to a historical and conceptual contextualization of holism. The aim here consists in providing an interpretative background against which the conceptual metaphors encountered in this section are analyzed.

2.5.2 An Incomprehensive Insight into Holism in Biology and Systems Biology

After having empirically analyzed the limited set of metaphorical framings used to ascribe meaning to the concept of holism in systems biology, it is now time to take a look at the different theoretical threads that emerged in the conceptual history of holism. This might help to better understand the current semantic void of the concept in systems biology. Generally speaking, holism is based on three interrelated theories that historically overlap and inform each other: vitalism, classical holism, and modern holism.

Vitalism (the first concept to be outlined here) is informed by the belief that a special life-force provides a necessary difference to separate living matter from inanimate entities (De Klerk 1979). The basic idea or premise of vitalism (Benton 1974; Williams 2003) is the assumption of the irreducibility of life which was conceived as being brought forth by an anti-materialist power process which could not be explained by an in-depth understanding of underlying physical, chemical or biological processes. This antimaterialist concept of a vital principle or vital force was put forward by Paul-Joseph Barthez (1806) at the end of the eighteenth century

(Canghuilhem 1994) and appeared in its most recent form in the work of Henri Bergson (1911). One of the last scientific proponents of vitalism was Hans Driesch (1914), a biologist and natural philosopher, who considerably contributed to mould developmental biology out of descriptive embryological anatomy. Driesch's vitalist concept in biology declined when Eduard Buchner (Ukrow 2004) discovered in 1897 cell-free fermentation and by doing so laid grounds for modern biochemistry as a foundation of molecular biology (Kohler 1971, 1972). Buchner's materialistic discovery more or less provided food for thought for a mechanic-materialistic understanding of life as expressed by Jacques Loeb. According to Loeb (1964, 430) living processes should and could be explained as physico-chemical processes. With regard to these and other insights provided by biological research, vitalism was abandoned due to its theoretical shortcomings and the prevalent mechanistic logic paved the way towards a variety of experimental possibilities. In brief, the mechanistic logic became the conceptual foundation of the theoretical debate in biology.[17]

In addition to vitalism a second antimechanistic and antireductionist approach entered the stage by the end of the nineteenth century. Proponents of neo-Lamarckism[18] emphasized an interactionist approach which interpreted development as the outcome of a lifelong interaction between an organism and its environment. Although neo-Darwinian ideas were gaining more and more attention in the 1920s, neo-Lamarckian concepts were prominently brought forward by Lloyd Morgan (1923) among others. His antireductionist idea of emergent evolution (Morgan 1923) became influential in debates about the dichotomy of reductionism and holism, although his theory of holism perished with the advent of a neo-Darwinism proposed by R. A. Fisher (1930) (Box 1978; Mayr and Provine 1988; Tabery 2008). What unites the turning away from vitalist and neo-Lamarckian concepts in the history of biology is the fact that approaches such as neo-Darwinism, mechanistic, and materialistic interpretations of biological functioning and development offered practicalities for doing research in the lab.

It was in this mechanistic context that Jan Smuts, a proponent of classical holism, first published his concept of holism (Smuts 1926). Based on the Greek concept of wholes, Smuts' ideas overlapped with Lloyd Morgan's theory of emergent evolution. Smuts' theory, however, was based on the concept that the universe has a tendency to form stable wholes on the basis of constituting parts. Thus, the tendency for stability was conceived to run through all levels of an entity ranging from comprising atoms to whole biological systems. His conception of life clearly differs from that of the early vitalists in that it is assumed to be triggered by a force which drives evolution and development towards upper and more complex levels of living organisms.

[17] Mechanistic biology describes the causal relationship of interacting components in a biological system that produce changes and effects in it (see Nicholson 2012). Allen (2005) investigates the importance of the context for mechanism, vitalism, and organicism in late nineteenth- and twentieth-century biology.

[18] Jean Baptiste Lamarck (1744–1829) is known for the theory of inheritance of acquired characteristics, also called Lamarckism.

This diversifying force was consequently interpreted as a materially inherent characteristic of systems and not understood in terms of a mechanistic interaction of biological parts. Smuts (1926), however, aimed for an all-comprising understanding of holism[19] and is thus not astonishing that he did not subscribe to mechanistic interpretations of biological processes and the positivist research agenda as outlined by Auguste Compte and the Viennese Circle. Their attempt to develop a unified and hierarchically ordered science was based on a mechanistic understanding of biological and other processes and in which physics was conceived of as providing the philosophical endpoint (Carnap 2011). The Viennese Circle thus proposed a layered model of reductionism that envisaged chemistry as based on physics, biology as based on chemistry, and human sciences as based on biology. This kind of step-by-step reductionism was put forward by one of the Circle's disciples, Ernest Nagel (1961) in the 1960s. It is astonishing that attempts have seldom been made to apply conceptually the Viennese reductionist framework to real cases in the biological sciences.[20] Assertions such as Crick's (1966, 10) statement that "the ultimate aim of the modern movement of biology is in fact to explain all biology in terms of physics and chemistry" have been taken for granted within the then emerging field of molecular biology and provided a comfortable and ideal philosophical background. However, reductionist conceptions clearly superseded holistic approaches even though von Bertalanffy and Rosen were publishing their work on general systems theory and the mathematization of biology.

Meanwhile, the notion of a more modern holism was taken up by scientists opposed to ontological and theoretical reductionism and skeptical of the epistemic value of methodical reductionism and its advances (Polanyi 1968; Waddington 1968, 1975; Baedke 2013). The so-called postwar holists envisaged reductionism as ill-treating complex biological and other biological phenomena while they basically rejected the idea of explaining them solely on the basis of molecular interactions (MacCay 1965). The reductionists, on the contrary, accused holists to use an, ironically speaking, include-all rationale that lacks any specific explanation why emergent

[19] Smuts developed the orthogenetic theory which is a biological theory based on the hypothesis that life has an innate tendency to evolve in an unlinear fashion due to some internal or external driving force (for an introduction into the theoretical foundations and the spread of orthogenetic theory between 1880 and 1926 see Ulett 2014).

[20] One of the few exceptions is represented by Kenneth F. Schaffner's early work on the reduction of biology to chemistry and physics. There he states that "[t]he outcome of this account of the development of molecular genetics—which I have characterised as being both stimulated and unified by the Watson-Crick model of DNA—is to warrant as a working hypothesis a biological principle of reduction. This principle, it seems, holds not only for genetics, but also for other biological theories. The principle can be stated as follows: given an organism composed out of chemical constituents, the present behaviour of that organism is a function of the constituents as they are characterisable in isolation plus the topological causal inter-structure of the chemical constituents (The environment must of course, in certain conditions, be specified.)" (Schaffner 1969, 346). Studying the reducibility of more complex phenomena, however, he stated later on: "It would thus seem that for the present and the foreseeable future neurobiology as well as general biology will not be fully reducible sciences. This is a position which I believe can be described as a form of as 'weak emergentism'" (Schaffner 1993a, b, 342).

properties materialize. One has, however, to bear in mind that there was not one agreed philosophical framework among those who subscribed to holism. In fact, it was rarely the case that the philosophical foundations completely converged among so-called modern holists. One good example of this variety was Erwin László (1972), a Hungarian systems theoretician and philosopher of science, who did not principally deny reductionism but questions its practicability. László used the example of car accident on specific dates to explain his conceptual problem with reductionism. Addressing the individual level of drivers such as driver's abilities or journey lengths, and so on, for the analysis of why car accidents occur might be useful but not feasible due to the complex amount of data to be gathered and conceptually coupled. Lázló argued that it might be more reasonable and practicable to use and analyze so-called middle-range data such as weather in the respective locations, the alcohol consumption of drivers during the day, and place-specific accident statistics to estimate the probability of car accidents. Obviously, László preferred another analytical level in the analysis of the car accident system which followed the idea of reducing the amount of data to be gathered and coupled for the sake of practicality. His kind of "reductionist holism" received considerable attention and others adopted the idea of ontological antireductionism.

The notion of ontological antireductionism (Nagel 1998) refers to the fact that things do not simply exist and work on the basis of their mechanical functions. This would mean, for example, that a cellist's musical performance could not solely be analyzed and understood by the physics of playing the cello. There is more to such a performance; the spiritual and musical aspects, for instance, often go unnoticed but play a vital role for the performance of a whole piece of music. Another branch, that of explanatory ontological antireductionism (Nagel 1998), provides a fuller picture as it accepts the vitality of the cellist's performance but also draws attention to the physical aspects of it and that there are emerging laws governing the presentation of a cello suite. This understanding is not based on deterministic or bottom-up ideas but rather a dynamic version of deterministic and nondeterministic thinking. In brief, the physics of performing a piece of music is as important as the processes and governing laws that emerge in the course of the presentation such as phrasing and spirituality. The latter aspects are, in principle, nonreducible elements as they emerge in practice.

Higher-level properties thus appear to be connected to low-level properties but not in a deterministic way: the laws of the higher level could not be deduced from the laws of the lower level. Comparable aspects have been addressed by the German-American physicist Walter Elsasser (1958, 1961, 1998) who coined the term of biotonic laws (Olby 1971). Biotonic laws are biological laws compatible with physical laws but they cannot be deduced from them. This conceptual framework considerably contributed to the idea that biological processes could work in terms of top-down and bottom-up causation (Drack and Apfalter 2007), a concept that runs counter to reductionist thinking and was put forward by Michael Polanyi (1968) who emphasized that knowledge about constituting parts does not fully explain properties appearing on higher system levels (Porsch 1986).[21]

[21] In modern systems biology, the idea of bottom-up and top-down causations working in parallel has mainly been propagated and substantiated by Denis Noble (Noble 2008b).

In the meantime, molecular biology proliferated into the main biological paradigm relying on a concept one could frame as "tentative reductionism" (Morange 2000, 2009). Whereas the focus was first on single gene analysis, it shifted towards the study of genomics and protein expression (proteomics) later on. The production of vast amounts of data on increasingly complex structures coming along with this development brought the reductionist–holism debate back into biology, via the medium of systems approaches. Many proponents of systems biology made general statements that it provides a more holistic approach to biology than molecular biology by generally outlining molecular biology as reductionist and deterministic (see, e.g., Li 2009; Lu et al. 2012). Systems biology was and still is thought to complement or even replace molecular biology. All these claims have considerably contributed to the framing of systems biology in terms of a fundamental paradigm shift (Seth and Thaker 2014) that will result in a biology which is done in a different and more comprehensive way. The death of molecular biology (Morange 2008) was propagated and some authors also outlined that one witnesses in biology a similar shift like the one from classical to modern physics. These claims are obviously exaggerated and a new humility surfaced in recent years in which such claims only randomly appear. Thus, not everybody working in systems biology agreed and concerns have been raised as the concept of systems biology's holism is not holistic enough (Cornish-Bowden et al. 2004; Mesarovic et al. 2004). A small group of dissidents, however, also disagrees with the concept of holism and argued for more reductionist approaches (Bose 2013; Tin and Poon 2014) and others expressed considerable skepticism towards the holistic paradigm shift induced by systems biology (Bennett and Monk 2008).

Hence, the notion of holism is in current systems biology far from being precise or clear. Although some authors have been enthusiastic about it, it has still to be explicated what holistic-oriented systems biology exactly represents. This aspect is also mirrored in the interviews in which general statements about holism appear. They show that different kinds of holism in systems biology are at work and that many proponents do not reflect their concept of holism: where theoretical reflection, however, is done, ontological explanatory antireductionism surfaces (Ahn et al. 2006; Conti et al. 2007).

To sum up, we have tried in this section to provide a limited diachronic and synchronic overview of the main concepts and characteristics of holism. They show the notion of holism holds a long, complex, and varying conceptual history in which the dichotomy of holism and reductionism proved to be productive for the differentiation of both concepts. After a short overview of vitalism which was envisaged as a theoretical predecessor for different kinds of holism we showed that at least two holisms exist: classical and modern holism. The latter was subdivided into ontological antireductionism and ontological explanatory antireductionism which theoretically differ in view of their implicit reductionism. Whereas ontological explanatory antireductionism aims at productively combining bottom-up and top-down causation to explain emergent biological phenomena and laws, ontological antireductionism theoretically remains on the level of vitalism emphasizing emergent properties without an attempt to explain them in terms of multilevel interaction. In the emerging discourse on systems biology holism can rather be conceived of as a strategically

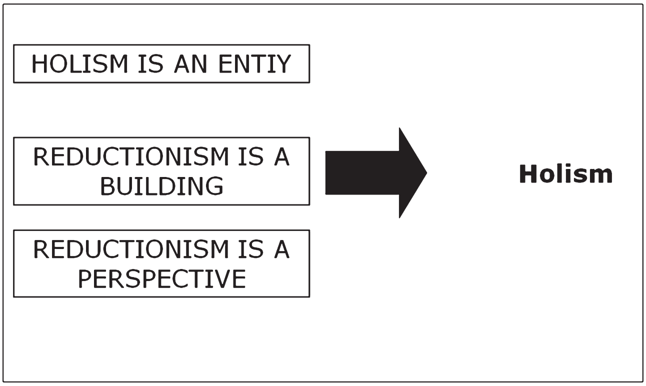

Fig. 2.7 Conceptual metaphors used to frame the notion of holism

used boundary object (Griesemer and Star 1989; Bowker and Star 2000). Although semantically vague it provides a fairly limited theoretical anchoring which, as we have seen, does not materialize in the analysis of the interview excerpts. Only a limited number of scientists working in systems biology theoretically reflect their conception of holism or reductionism; most systems biologists appear to be immersed in their daily work and devote no time to the philosophy of biology or epistemic deliberations. We now turn to the assessment of the concept of holism in systems biology.

2.5.3 Assessing the Concept of Holism in Systems Biology

The preceding section provided an overview of the conceptual history of holism in biology. It became apparent that different strands and developments of holism existed in history which finally culminated in ideas of ontological antireductionism and ontological explanatory antireductionism. Both concepts mainly materialized subcutaneously and contributed to building a somewhat vague and sometimes unconscious rationale underlying different research strands in systems biology. The conceptual and semantic imprecision of the term holism throughout its history is also mirrored in the empirical findings of the interviews with system biologists. Conceptual metaphors such as HOLISM IS AN ENTITY, HOLISM IS A BUILDING, and HOLISM IS A PERSPECTIVE demonstrated that the scientists interviewed use a quite restricted set of unspecific metaphors to frame the abstract concept of holism: these conceptually highlight aspects of reification, manageability, and perspective or sight (see Fig. 2.7).

This low metaphorical complexity and differentiation coheres with the fact that the historically generated concept of holism to date did not attract much philosophical and theoretical reflection in systems biology. This is somewhat astonishing because the main proponents of systems biology portray the approach as holistic or quasi-holistic. Even though different theoretical conceptions of holism exist in systems biology, the main bulk of research seems to subscribe unconsciously to the concept of ontological antireductionism and only a minority favors the more reductionist concept of explanatory ontological antireductionism. In brief, the concept of holism in systems biology remains unspecific and requires clarification to better understand the epistemological assumptions inherent in systems biology. After having analyzed the concepts of reductionism and holism, we now turn to the analysis of the theoretical notion of model in systems biology.

2.6 Images of Models in Systems Biology

The final section of this chapter on the understanding of basic concepts in systems biology aims at analyzing how scientists working in systems biology metaphorically conceptualize the notion of model. Models could be conceived as cognitive, epistemic, practical, and technical devices used in a variety of scientific disciplines ranging from meteorology and climate science to the social sciences to better understand a system's structure, state, behavior, and development. The term model implies, according to its theoretical outline and contextualized scientific use, different functions and applications. In brief, every scientific approach or discipline uses models as abstractions of real-world processes to understand and solve problems.

This also applies to systems biology where models are both important cognitive concepts and technical devices used for problem solving. The fact that modeling in many cases is perceived as an evidence-based technical process of depicting real-world phenomena with the help of numerics, differential equations, and computation, however, constitutes a problem because models always are also social and cultural constructions. The cultural dimensions and philosophical implications of models and modeling in systems biology hitherto did not receive much attention (Fox Keller 2002). Questions such as Wolkenhauer's (2014, 1) "Why modeling?" are rarely asked as they require a considerable effort to reconsider one's concepts used in modeling, their limiting implications for the scientific endeavor undertaken, and for its application to real-world phenomena (Boogerd et al. 2007a, b). An additional problem consists in the fact that nowadays a huge variety of different kinds of models such as stochastic models, rate equation models, multiscale models, mechanistic models, mathematical models, and the like are in use. This "zoo of models" (Wolkenhauer 2014, 3) makes it extremely difficult to maintain an overview over all types of models used and track the changes they undergo in scientific problem settings.

In addition to these more theoretical aspects, a substantial part of the scientific literature in systems biology is devoted to the practical dimensions of modeling and models. An analysis of the publications with the keywords "systems biology," "modeling," "systems biology model" on the Pubmed database conducted in May 2014 displays more than 1187 publications. This result goes hand in hand with a growing number of monographs and edited volumes devoted to modeling and models in systems biology (see, e.g., Palsson 2011; Patel and Nagl 2010; Koch et al. 2011; Ingalls 2013). Most of these publications are, however, problem-oriented and seldom address philosophical aspects of modeling. If they do so, the phrase philosophy rather refers to the structured process of defining, assessing, selecting, and functionally combining elements of biological systems without explicitly addressing underlying theoretical concepts and assumptions that inform the fabrication of a model. This perspective thus stands in sharp contrast to what is understood to be the principles and philosophy of modeling in biology (Massoud et al. 1998). The empirical question thus remains: how do scientists working in systems biology frame the notion of model and what kind of philosophical implications and tacit knowledge could be deduced from their framings?

This question might be of interest to systems biologists as it has rarely been addressed by research carried out in theoretical systems biology and studies conducted in the sociology of science (Hesse 1966) and the philosophy of science (Giere 2004; Morrison 2009; Suárez 2009). This is the reason why we took up the challenge and explored how the notion of model is framed by systems biologists. The aim of this exploration first is to analyze the metaphors used by systems biologists and second to disclose the implications inherent in them from an interpretative point of view. Yet, it is still necessary partly to contextualize the notion of model and provide an insight into the different conceptual dimensions of models. Against this background, we then turn to the analysis and interpretation of the different conceptual metaphors used by scientists in systems biology to depict what the notion of model means to them.

2.6.1 Models in Science and in Systems Biology

The use of models in biology has gained momentum in the last two decades. For systems biologists, they represent a familiar device. Currently, the development and use of models represents a daily practice in many areas of biological research such as ecosystem analysis or systems biology: they are descriptive abstractions and reduced ways of understanding a complex reality that materialize through heuristic media such as diagrams, chemical formulae, graphs, and so on. The concept of model, thus, applies to hypotheses developed by scientists in the course of scientific work carried out as well as to theories (Black 1962) to be projected upon a scientific issue. A closer inspection of the term model, however, shows a large variety of different model conceptions. There are, for example, complex numerical or mathematical models that could be implemented on computers, they can also have an epistemic function as devices for theoretical reflection, and they all converge in their potential to provide an intentionally reduced representation and explanation of dynamic processes in biology. One has, however, to bear in mind that models develop and are used in social contexts and represent outcomes of socioscientific processes that can become powerful instruments (Hastrup and Skrydstrup 2012) beyond the realm of science. Yet, for biologists, the use of models in research is still unfathomable because modeling has not been a core topic in biology. The last 40 years were mainly shaped by molecular biology and only the interpretative problems generated by genomics and other Omics approaches rekindled the interest in modeling in biology. Bearing in mind that conceptual models were already developed from the 1930s onwards (von Bertalanffy 1932, 1949; Weiss 1973; Rosen 1970a, b), the current use of mathematical and other modeling approaches in biology is developed in special contexts and for particular purposes. This problem-oriented use of modeling makes it difficult to provide an all-comprising conceptual history of the notion of model in systems biology (an exception is Krohs 2013) because there is simply an abundance of models around. Although attempts have been undertaken to investigate characteristics of models in systems biology systematically (Krohs and Callebaut 2007; Richardson and Stephan 2007; Schaffner 2007; Ullah and Wolkenhauer 2007), we think that it would increase the understanding of the model concept in systems biology if we approach it from a theoretical point of view by studying its semantic, ontological, and epistemological dimensions. Questions to be asked are the following: how do models represent processes or things? What could be learned with the help of models? How do theory and models relate to each other? What functions do they serve?

A theoretical look at the functions of models clearly indicates two aspects: they are designed to represent a selected extract from a perceived reality and, at the same time, they embody theory meaning that a model could be seen as an interpretation of empirical findings exhibiting the laws and axioms implicated in a theoretical framework. Although one might agree that scientific models are characterized by a limited perception of a phenomenon or process to be encountered in the world, the notion of phenomenon represents a generic term that scientifically refers to features of the world. Thus, the theoretical problem of scientific depictions concerns the question of what a model actually represents or what it stands for (Frigg 2006). This ontological question becomes even more difficult to be answered if we envisage models as not purely linguistically determined. We then have to clarify what kind of medium is used for the purpose of representing a scientific issue under investigation (Suárez and Solé 2006) and this goes hand in hand with the variety of representational styles by which biological entities or things could be depicted. In brief, different kinds of models are different ways of addressing and skillfully representing a certain aspect or perspective on the world. In brief, models are theoretically informed, fragmentary, and stylistic representations of a phenomenon under investigation.

Connected to the aspect of different styles of representation are different kinds of models. Scale models, for example, are basically reduced or small copies of a system to be investigated. Thus, cardboard models of housing estates are naturalistic replica or copies of such things. Scale models could be conceived of as generally restricted visions whereas idealized models contain deliberate simplifications. Such simplifications aim at constructing something less complicated to make a certain problem easier to understand. Economic theories based on the assumption of rational choice represent such idealized models of individuals whose motivation to perform any kind of action is based on calculating the profit to be generated by a certain act. Analogical models (Black 1962), moreover, are based on the idea of shared properties. Thus, the brain could metaphorically be conceived of as a computer because there are relevant similarities that could be projected upon a different domain of discourse. Thus, discussions could be framed as fights or even wars that not only share certain features but abstractly require the development of formal analogies and comparable patterns. Such analogies are important for science as they are thought-provoking heuristic devices that play a vital role in the development of theories (Gentner and Jeziorski 1993; Bailer-Jones 2003). Finally, there are phenomenological models that only represent observable properties. They refrain from analyzing underlying mechanisms that trigger a system even though they often incorporate laws and principles. The question of how models relate to reality has partly been addressed in so-called models of data (Suppes 1962). This concept simply states that the model has been derived from raw data through processes of correction, rectification, and idealization and confirms a tentative theoretical outline or approach. Such models are often constructed in systems biology and represent complicated constructions. Their development requires the application of sophistical statistical procedures that raise philosophical and methodological questions (Harris 2003). Questions such as, "What data should be included in the model?" and, "How should the functional relation between aggregated data be designed?" range among the easier questions to be addressed in models of data.

In addition to questions of what kinds of models exist and how they represent an issue under investigation, the most relevant question arises of what models actually are. Ontologically speaking, models are conceived to be physical, fictional, structural, and descriptive in nature. Physical models are thus material representations of something else such as the replication of a mammoth by a paleontologist. There are also enlived models such as knock-out mice in cancer research or certain kinds of yeast often used in experiments about heat resistance (Leonelli and Ankeny 2012). Such examples do not really provoke any difficulties with the ontological status of models as they can objectively be experienced. There are, however, nonmaterial or fictional models (Fine 1993) as well. Bohr's model of the atom only existed in his mind and exerted a considerable impact on physics. Such models appear to be purely fictional even though they—as in the case of Bohr—can exert a vital impact on a discipline (Giere 1988) and are open to modification through any kind of discussion or interaction. Fictional models cognitively reify entities and represent intangible vehicles and productive devices of research to develop or deepen scientific thinking. Although the conception of models as fictions has gathered interest in research undertaken in science and technology studies and the philosophy of science, their ontological status is to date far from clear. Important though for biology and systems biology (Lloyd 1984, 1994) are models that appear to be based on set-theoretic structures (Suppes 1960). These models are closely tied to mathematically oriented models and envisaged as a specific set and functional combination of structures. Finally, models can also take the ontological shape of descriptions. These often appear in scientifically stylized presentations, papers, and textbooks of a system under investigation. The problem here lies in the fact that the description is often confused with the model: the description becomes the model. The problem inherent in the duality between description and model is one of descriptive properties. Models do not per se possess such properties but achieve them through a kind of medium used to portray and this bears an impact on its ontological status and assessment. Different models therefore hold discrete ontological statuses that in many cases overlap. They can ontologically reside in scientists' minds and at the same time appear as drawing on a blackboard or as virtual constructs in a computer.

Finally, models also possess an epistemic and learning function as they are skillfully designed entities to acquire knowledge. Today, significant parts of research undertaken in science are based on the development of models. Thus, an important part of scientific research is carried out on (virtual) models and not on (material) reality itself. As surrogate entities, models instigate what one might call a process of model-based reasoning (Magnani and Nersessian 2002) which comprises aspects of denotation, demonstration, and interpretation (Hughes 1997). The process of learning starts by developing a representation that links the model with a targeted system to be investigated. This denotative process is followed by the demonstrative procedure in which features of the model and their relation to theoretical claims are thought through. Finally, the claims achieved will have to be projected upon the targeted system and converted into assertions about it. This interpretative procedure is intrinsic in learning about models on the one hand and in converting knowledge about the model on the targeted system. Thus, learning about the model happens in the course of its construction and manipulation which is devoted to the model's properties. It obviously depends on what kind of methodology is applied and what activities are carried out to structure the model. Hence, material models do not prompt questions that go beyond questions of experimentation. Most important, mathematical models help scientists to derive results or equations analytically. Computers and their ability to perform simulations and preliminary results are of great value at this point as they provide the opportunity to tinker with equations and test them. This means computers offer an opportunity to learn something about the model and its functioning by using simulations. Simulations could therefore be conceived of as a kind of methodology that might raise philosophical problems (Frigg and Reiss 2009) but are of enormous practical relevance because they often generate an improved understanding of dynamical models. Although the relational differences and convergences between computer simulation and experiments have not yet been resolved, current experimental setups in systems biology combine an in silico and in vivo rationale to learn more about the calibration of models (Franceschelli and Imbert 2009) and test trustworthiness. The aspect of trustworthiness addresses the question of whether equations used in the computer models adequately represent the functioning of the targeted system. In addition to these aspects, computer simulations appear to possess a considerable heuristic value as they contribute to generating theoretical improvements, amend models, and develop hypotheses. Once knowledge about a model has been amended, the knowledge generated has to be integrated into existing knowledge about the targeted system. This procedure is implicitly controlled by the scientifically informed assumption that analogies or idealizations in the model have converging counterparts in the real world.

To sum up, we have provided a tour de force on a variety of aspects connected to the notion of model. We started with the aspect of representation and the problem of what a model actually represents. It became clear that models are theoretically informed and fragmentary constructs of a certain research object. Ways or styles of representation differ according to the estimated relation between model and research object. These are, furthermore, influenced by the kind of model used and its ontological status. It, thus, matters if a model resides in scientists' minds or whether it virtually exists in a computer because experiments and falsifications carried out differ. Finally, the investigation of the epistemological dimension referred to two kinds of learning: leaning about the model itself and model-informed learning about the system or phenomenon under investigation. Although these two aspects could analytically be understood as discrete, they in reality appear as intermingled processes in scientific work and reveal the often hidden but nevertheless complex procedures at work in building and working with models. The notion of model and the philosophical aspects and practices tied to it make it now advisable to explore them in our analysis of the expert interviews. The analysis of the conceptual metaphors used not only reveals how models are conceptualized by systems biologists but also enable us—at least to some extent—to reveal and analyze theoretical aspects outlined in this section.

2.6.2 Systems Biologists Picturing Models

The previous section sketched out the different theoretical and conceptual issues inherent in models and modeling. Looking at it through the lens of philosophy of science and science and technology studies, it became clear that models have a variety of implications on different levels. They concern basic theoretical aspects such as representation, different kinds of models, and their ontological and epistemological status. Only few systems biologists and theoreticians have to date touched upon the philosophical aspects implicated in it (Boogerd et al. 2007a, b; Krohs 2004, 2013; Ullah and Wolkenhauer 2007; Wolkenhauer 2014). This is astonishing as the notion is constitutive for the discipline that aims at modeling genetic networks, cells, or even organs. There are, however, many references in papers on different kinds of models and the importance of modeling for systems biology. The general relevance of models is, for example, outlined by Kitano (2002b, 206) as follows.

> There are still issues to be resolved, but computational modeling and analysis are now able to provide useful biological insights and predictions for well understood targets such as bifurcation analysis of the cell cycle, metabolic analysis or comparative studies of robustness of biological oscillation circuits.

Bearing in mind that the quote stems from the start of the century, it outlines gaps in research on models and how they could be used in the context of systems biology. It displays narrative elements to legitimize why models are important in and for biological research by highlighting two aspects: it implicitly emphasizes the epistemological aspect of models (useful biological insights) and alludes to the process of how knowledge generated with the model could be turned into knowledge about the biological processes to be modeled. In addition to such strategic explanations and outlines, textbooks in systems biology devote whole chapters to the topic of models to be explained to students. Rhetorical questions of what models represent are answered as follows.

> What is a model? The answer to this question will differ among communities of researchers. In a broad sense, a model is an abstract representation of objects or processes that explains features of these processes […]. A biochemical reaction network can be represented by graphical sketch showing dots for metabolites and arrows for reactions; the same network could also be described by a system of differential equations, which allows simulating and predicting the dynamic behavior of that network. (Klipp et al. 2009, 5)

What we encounter here are far more aspects about models than we have taken from the previous more strategic excerpt. First, the notion "model" is depicted as an entity standing in close connection to its scientific users (communities of researchers) and is envisaged to be differently framed by different scientists. General reference is made to phenomena (objects, processes, and features), and these abstract aspects are then explained by means of two types of models (graphical and mathematical). The descriptive measures of the models appear to stand in an isomorphic relationship to real entities or processes (arrows–reactions, equations–behavior, dots–metabolites) and their epistemic status is alluded to by indicating that the model aims at a dynamic prediction of the behavior of the target network (biochemical reaction network). What is fascinating about this excerpt of just 83 words is that it is a complex mixture of underlying philosophical assumptions of modeling which draw on means of representation, facets of isomorphism, different kinds of models, and epistemological considerations. Such aspects should not be underestimated as they permeate the varying discourses of systems biology, are basic ingredients in scientists' everyday knowledge and practices: they display, in a way, a subliminal philosophy of modeling.

Comparable aspects also materialized in the interviews conducted where system biologists were asked to explain what the term model means to them.:

> We are interested in metabolic pathways and their functioning. This means that we have to define the biological entities involved in certain reactions and functionally relate them. We do this quite often by drawing pictures or using special programs on the computer. Once we have sorted things out which means that we have decided what kind of biological units we include, discussion starts how this could be integrated in a mathematical model. (Scientist K)
>
> German original: Wir interessieren uns vor allem für Stoffwechselwege und deren Funktionen. Das bedeutet, dass wir die biologischen Substanzen, die in Reaktionen involviert sind, erst einmal herausfinden und dann funktionell verbinden müssen. Dafür fertigen wir einfach Zeichnungen an oder nutzen diese speziellen Computerprogramme. Wenn das dann klar ist, also welche biologischen Einheiten wir in das mathematische Modell einbeziehen, dann beginnt die Diskussion, wie wir das ins Modell integrieren können.

Different theoretical aspects of models are combined here: its starts with the question of what has to be represented. This process of selection goes hand in hand with the heuristic use of different models (drawing pictures, mathematical) which display different ways of representing the problem under investigation. The same holds true for the following quote in which a rather complicated way of developing and improving a model is outlined.

> The models used are more or less the same. I mean that we have to fine-tune them to the process or whatever aspect we investigate. We use quite a complicated setup as we model and then do the experiments and then go back to the model to improve it. The aim is to get a well-balanced model which helps us to better understand the processes we investigate. Failures are quite important as they help us to better understand what goes on in the system. (Scientist B)
>
> German original: Die Modelle, die wir hier nutzen, sind mehr oder minder dieselben. Ich meine, dass wir die natürlich an das anpassen müssen, was wir gerade untersuchen. Wir nutzen dafür einen ziemlich komplizierten Versuchsaufbau, da wird ein Modell entwickelt und dann Experimente durchgeführt, um dann wieder das Modell zu verbessern. Ziel ist es, dass wir ein gut ausbalanciertes Modell bekommen, das uns ein besseres Verstehen oder Verständnis von den Prozessen gibt, die wir untersuchen. Misserfolge sind übrigens ziemlich wichtig, denn die helfen uns besser zu verstehen, was im System los ist.

What we can see here is a procedure used in the area of in silico and in vivo experimentation. The aim consists in calibrating the model with the help of so-called lab models. This means different kinds of models holding distinct ontological statuses are combined with the epistemic aim to know more about the respective model and the natural entity to be analyzed. The two showcase examples visibly exhibit the manifold conceptual and amalgamated theoretical processes at work in developing models of biological processes.

In addition to the analysis of these subliminal philosophical and theoretical aspects at work in modeling biological processes, it is also of vital interest to analyze how scientists in systems biology frame the entity model itself because here further aspects of what a model represents become analytically accessible. The systematic investigation of the interviews conducted gave rise to five conceptual metaphors: A MODEL IS A CONSTRUCT, A MODEL IS A HEURISTIC DEVICE, A MODEL IS A HEURISTIC MACHINE, A MODEL IS A TOY, and A MODEL IS AN INTEGRATING ENTITY.

To start with, the notion of model has been metaphorically depicted as a construct that highlights the aspects of abstraction and the selection of relevant units to become functional parts of the model.

> […], **it [a model] is a construct of a natural process** that we aim to understand. There are lots of things going on in the area of modeling and we always check first what kind of models are around, what their characteristics are and for what purposes they have been used. At the same time we start to try to understand the constituents of the system and how they relate. (Scientist G)
>
> German original: […], **das ist ein Abstraktionsprozess von natürlichen Prozessen**, den wir verstehen möchten. Im Modellbereich passiert derzeit viel und wir schauen immer, was für Modelle gerade benutzt werden, was deren Eigenschaften sind und für welche Zwecke die benutzt wurden. Aber gleichzeitig schauen wir uns natürlich auch das System und seine Elemente an, in welcher Beziehung die stehen.

The example clearly displays the metaphorical concept, A MODEL IS A CONSTRUCT, and explains in the rest of the quote the different processes underlying the development of a model: the monitoring of model development, their area of application, and the comparison with the entity to be modeled. Such complex aspects also appear in the following quote, although here emphasis is put on the status of the model as a construct.

> **Models are constructs**. I always have to emphasize this because many students and colleagues often shift from model to reality and back without drawing a line between the natural process which we cannot tackle as a whole and the scientific construction we make of it. (Scientist M)
>
> German original: **Modelle sind Konstruktionen**. Ich muss das immer wieder betonen und viele Studenten und Kollegen wechseln zwischen Modell und Realität hin und her, ohne zwischen dem natürlichen Prozess, den wir als Ganzes eben nicht verstehen können und der wissenschaftlichen Konstruktion, zu unterscheiden.

Here, the aspect of construction is again highlighted but puts emphasis on the problem of confusing the model and the real biological process. What becomes apparent is that, as a construct, a model is partial simulation but not a representation of nature. The distinction between these two aspects is implicated in the metaphorical mapping but it still requires critical reflection and emphasis.

Building on the metaphorical concept, A MODEL IS A CONSTRUCT, the mapping inherent in the conceptual metaphor, A MODEL IS HEURISTIC DEVICE, more evidently plays with the aspect of construction albeit it emphasizes a more technical aspect.

> There is a lot happening at the moment in our group. We have some PhD students coming from informatics which bear a positive impact. I mean, **models are for me some sort of a heuristic device** which helps me to understand not only the phenomenon under investigation but also my thinking about it. (Scientist I)
>
> German original: Ins unserer Gruppe passiert gerade sehr viel. Wir haben da diese Doktoranden aus der Informatik, das wirkt sehr positiv. Ich meine, also für mich sind Modelle **eine Art heuristisches Instrument** das mir nicht nur hilft, das Phänomen zu verstehen, sondern auch mein eigenes Denken über den Forschungsgegenstand.

Models, metaphorically to be understood in terms of a heuristic device, exhibit a certain degree of theoretical reflection because they are conceived to be instrumental. Such aspects are involved in the mapping of the lexical item device on the notion of model. Furthermore, theoretical repercussions models might bear on the scientific process and scientific thinking become quite evident in the quote. This interaction is also highlighted in the following excerpt.

> The modeling is very important, I would say. I mean it is some sort of a way to think and do something about a scientific problem. A model is always a construct, but built according to a scientific logic or convention. **It is a way or a heuristic device** to better understand things in manifold ways as a model replicates but is not a one to one representation. (Scientist Q)
>
> German original: Die Modellierung ist sehr wichtig, würde ich sagen. Ich meine, das ist eine Art und Weise über ein wissenschaftliches Problem nachzudenken und was zu machen. Ein Model ist immer ein Konstrukt, das einer bestimmten wissenschaftlichen Logik und Konvention folgt. **Das ist ein Weg oder ein heuristisches Instrument**, einen Sache aus vielen Richtungen zu verstehen und es überträgt ja und stellt es nicht so dar wie es ist.

Here, we clearly witness a process of pondering what a model actually is. The concealed metaphorical concept, A MODEL IS HEURISTIC DEVICE, drives a reflection on the different aspects of models whereas at the end of the quote a variety of theoretical reflections appears. This metaphorical concept is technically elaborated upon in the following quote where models are metaphorically framed as heuristic machines.

> You know, technically speaking it [model] is **some sort of a heuristic machine** with which we come to grips with scientific problems. They often appear to me as skillfully designed constructs in which we invest a lot of time. (Scientists N)
>
> German original: Wissen sie, technisch gesprochen sind sie **eine Art heuristische Maschine** mit der wir wissenschaftliche Problem in den Griff bekommen. Für mich sind das gekonnt entwickelte Konstrukte in die viel Zeit reingeht.

The conceptual metaphor, A MODEL IS A HEURISTIC MACHINE, appears here again and maps technical aspects on the domain of models. The linguistic element "some sort of" in the quote indicates the metaphor is deliberately used to explain what the interviewee means. The technical implications nestling in the metaphorical mapping are not further discussed and models are again abstractly framed as constructs, but in this case as a skillful construct.

Such aspects are, however, critically discussed in the following interview section where the potential of models is obviously stressed but also critically assessed.

> To me, **models are very important because they are a background or heuristic machine** against which I can better understand the processes and phenomena we investigate. But this machine, well the computer, is just a man made machine. It can help us to better understand a biological system but also it helps us to improve our ways of approaching scientific problem in terms of what is relevant to be modeled and what not. (Scientists O)
>
> German original: Für mich **sind Modelle sehr wichtig weil sie eine Art Hintergrund oder heuristische Maschine sind**, mit der wir besser die Prozesse und Phänomene verstehen können, die wir untersuchen. Aber diese Maschine, also der Computer, ist eine menschgemachte Maschine. Sie kann uns helfen eine biologisches System besser zu verstehen, aber sie hilft uns auch dabei, ein wissenschaftliches Problem besser anzugehen, also in dem Sinne, was wichtig für das Modell und die Modellierung ist und was nicht.

The machine metaphor here holds an epistemological status as it instigates a critical reflection on what kind of knowledge is generated about the biological process under investigation. Furthermore, the model is depicted as computational and manmade machine that helps to revisit methodologically whether the selected components in the model are acute (improve our ways of approach a scientific problem).

In addition to the more technical aspects as expressed by the metaphorical use of machine or device, models are also metaphorically portrayed as toys. The metaphorical transfer of toy onto the target domain model semantically infuses it with ideas revolving around childhood and, more important, playing. This aspect is accentuated in the following quote.

> For some scientists, **their model is a toy** they have been playing with for a long time. My colleagues really invest a lot of time in building them and we share a considerable amount of our scientific lifetime with them. (Scientist D)
>
> German original: Also für einige Wissenschaftler ist **ein Modell ihr Spielzeug** mit dem sie lange Zeit herumgespielt haben. Meine Kollegen investieren wirklich viel Zeit in die Entwicklung und wir verbringen wirkliche eine nicht zu unterschätzende Zeit unseres wissenschaftlichen Lebens mit ihnen.

What we can take from this quote is the fact that there is, first, a perceived close relationship between the model and the scientist who works on it and, second, that playing is metaphorically used to frame the more sober process of constructing. It is interesting that the metaphorical use of playing is informed by the context in which it is carried out: a scientifically informed tinkering to develop or improve a model. Such aspects are also found in the next excerpt:

> Sometimes a **model also takes the shape of a toy**. You develop it and then you play with it to see whether it works and how it has to be amended. This takes some time and can also be a fun part – well sometimes obviously not. (Scientist L)
>
> German original: Manchmal **nimmt ein Modell auch die Gestalt eines Spielzeugs an**. Du entwickelst es und dann spielst Du mit ihm herum, um zu sehen, ob es funktioniert und wie es verbessert werden könnte. Das verbraucht viel Zeit und kann Spaß machen – manchmal aber auch nicht.

This quote still refers to the play- or joyful development of models, but underlines the act of playing as a scientifically guided procedure to improve them which can also turn into a laborious exercise of amending or revising elements of a model.

Finally, models also appear to hold a social function as an integrating device because they are, metaphorically speaking, personified entities that gather scientists around them. This could clearly be seen in the following two quotes where the conceptual metaphor, A MODEL IS AN INTEGRATING ENTITY was tackled:

> Sometime we literally gather around a model, well a sketch of it and discuss it. Deep thinking sometimes occurs and an exchange of ideas materializes that, at least in my view, tightens the bonds in the group. I mean, we all learn from this thinking together and **the model really brings us together**. (Scientist M)
>
> German original: Manchmal versammeln wir ich buchstäblich um ein Model herum, also um eine Skizze und dann diskutieren wir die. Da werden oft wichtige und essentielle Überlegungen ausgetauscht und das, so sehe ich das zumindest, trägt schon dazu bei, dass sich Beziehungen entwickeln. Ich finde, dass wir alle **von diesem gemeinsamen Durchdenken lernen und das Modell bringt uns zusammen**.
>
> Certain approaches and **models really bring people together** while they sometimes exclude others. There is this what I have called a model culture but this is perhaps too general. (Scientist P)
>
> German original: Also einige Ansätze und **Modelle bringen die Leute wirklich zusammen** und natürlich grenzen die auch aus. Da gibt es halt auch diese Modellkulturen, auch wenn das vielleicht zu generell ausgedrückt ist.

Models are thus not only technical devices but entities that are envisioned to exert an integrating function. Certain practices and routines are tied to them which contribute to establishing human interaction and bonds while, at the same time, model cultures and scientific identities are built. In sum, the metaphorical concept A MODEL IS AN INTEGRATING ENTITY not only refers to the integration of data and functions, but more important, conceptualizes the social process of bonding among scientists.

The previously outlined metaphorical concepts of A MODEL IS A CONSTRUCT, A MODEL IS A HEURISTIC DEVICE, and A MODEL IS A HEURISTIC MACHINE, clearly revealed more technical images of what models are and sometimes disclosed knowledge-theoretical aspects revolving around the questions of what one learns about the model, what about the targeted biological entity, and about one's own epistemological assumptions. Albeit these conceptions prevail in the interviews, it is interesting that models are also metaphorically envisaged as toys in A MODEL IS A TOY, and as socially integrating devices in A MODEL IS AN INTEGRATING ENTITY. The toy metaphors stress aspects of scientific and creative tinkering whereas the personification of models as integrating social agents underline the bonding effect they might exert on the scientific community. We now turn to the concluding section to provide a more systematized overview over the conceptual metaphors of model encountered here. The aim consists in summarizing the outcomes, in interpreting what kind of results nestle in the metaphorical concepts, and in analyzing whether a specific set of metaphorical concepts could be connected to scientists holding a particular scientific background or training. This might help us to develop a clearer picture about and grasp the multifaceted dimensions of the notion of model in systems biology.

2.6.3 Picturing Metaphorically Informed Images of Models

The previous section depicted five metaphorical concepts that were encountered and analyzed in the course of the study conducted. The analysis showed how the abstract entity of model was metaphorically conceptualized and demonstrated how scientists try to grasp and elaborate upon the notion of model. Having roughly outlined the philosophical aspects of models and modeling before, the metaphorical analysis provided insight into the theoretical playing and exploring of what models mean to scientists working in systems biology. The analysis, thus, gave way to an interrelated and mostly shared conceptual network that endowed the abstract entity of model with meaning and at the same time offered insight into the theoretical processes underlying the development and idea of models. Interestingly though, it was not possible to relate specific metaphorical concepts to a particular scientific training or background. All concepts were shared among the scientists interviewed and represent a rather limited insight into how people working in systems biology frame the notion of model (see Fig. 2.8).

Considering the imagery analyzed in view of the underlying metaphorical mappings, one might say that the first three metaphors elaborated upon convey the idea of models as technical constructs whereas the latter two were refined by developing a more instrumental and mechanistic perspective. Although one might be tempted to hypothesize that scientists holding an engineering background preferably use these images, the evidence provided did not corroborate this claim: the imagery was shared by almost all interviewees. The concept of model as construct, as heuristic device, and heuristic machine thus appears to be mainly structured by a more technical imagery. One has, however, to bear in mind that the conceptual mappings in the metaphors, A MODEL IS A TOY and A MODEL IS AN INTEGRATING ENTITY, highlight other and complementing aspects: creative scientific tinkering and the social dimension of models and modeling. Both counteract the subliminal technical and mechanistic

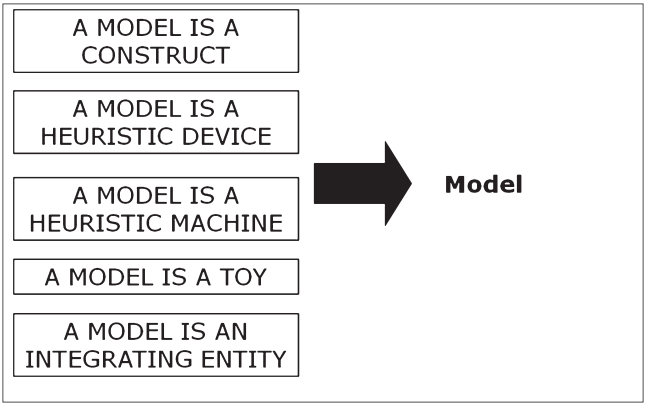

Fig. 2.8 Conceptual metaphors used by scientists to frame the notion of model

rationale of models and modeling and might deserve further scrutiny in terms of models and modeling as imaginative and social activities. To finish this chapter, we now turn to an overall summary of all basic notions analyzed in this chapter.

2.7 Concluding Remarks: Basic Concepts, Metaphors, and Scientific Imagination

The previous sections provided thought-provoking insights into the framing of basic biological concepts by systems biologists. Although the scope of the study was limited[22] and most of the time we were only able to scratch the surface of complex issues to be further investigated, the systematic analysis and contextualization of conceptual metaphors revealed a network of intangible but effective characteristics connected to five basic notions in systems biology. Thus, the analysis of the concept of life discovered a complex network of seven conceptual metaphors used to frame it (see Fig. 2.9). First of all, they made the concept of life accessible by applying a variety of technological, social, and cultural source domains to it that semantically permeate it.

A closer look at the mapping processes indicated that meaning was in many cases determined by metaphors stemming from a technological source domain. This could suggest that life might undergo a technological reframing within the field of systems biology due to the influx of scientists coming from engineering, physics, mathematics, and computer science, but the almost ubiquitous presence of

[22] Results are based on 25 interviews conducted with German scientists, on an extensive analysis of the scientific literature published on the topic of systems biology, a reading of historical precursors, and the analysis of it with the help of secondary literature that dealt with them.

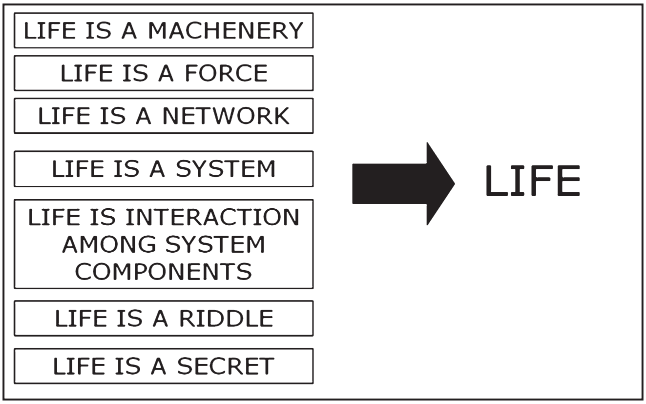

Fig. 2.9 Conceptual metaphors used to frame the notion of life

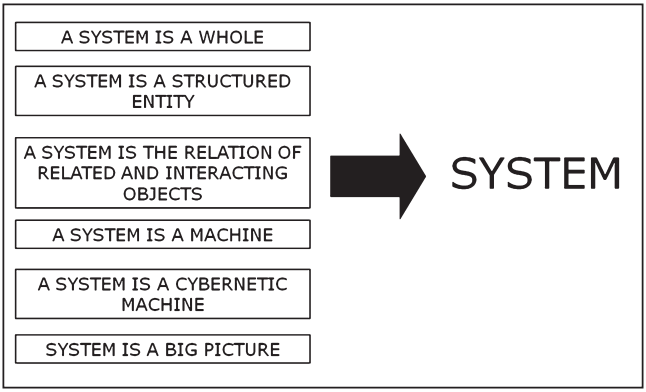

Fig. 2.10 Conceptual metaphors used to frame the notion of system

the conceptual metaphors, LIFE IS A RIDDLE and LIFE IS A SECRET, seemed to counteract this hypothesis: They give the impression that a conceptual path towards a technological understanding of life is stepped on, at least at the period of the interviews, but that the complexity of the life-issue to date remains unresolved and still represents a riddle. One could, however, hypothesize that the prevalence of technological metaphors and their implications in the long run might reshape the notion of life or hold the potential to solve the riddle or secret of life. Further discussion among systems biologists is needed as to whether these conceptualizations of life represent accurate ways of approaching the life-problem from a reflexive point of view.

With regard to the metaphors used to frame the abstract notion of system, six conceptual metaphors were revealed by the analysis (see Fig. 2.10). The transfer processes underlying the imagery reified the notion of system as an entity and applied a spatial structure to it. In using the metaphorical concepts, A SYSTEM IS A WHOLE and A SYSTEM IS A STRUCTURED ENTITY, the notion system became a cognitively manageable entity.

Furthermore, efforts of dynamization are implicated in the conceptual metaphors, A SYSTEM IS THE RELATION OF RELATED AND INTERACTING OBJECTS and A SYSTEM IS A CYBERNETIC MACHINE. Especially the latter appears to counteract the mechanistic implications inherent in the conceptual metaphor, A SYSTEM IS A MACHINE, because it merges a rather mechanistic conception of systems with a nonlinear, complex, and dynamic understanding of systems. What can be deduced from the conceptual metaphors are efforts to increase dynamization which is conceived to lead to an improved understanding of complex processes constituting biological systems. One could try to pursue this way of a metaphorically induced dynamization by developing alternative or complementing metaphors with systems biologists. Such an enterprise could build upon existing conceptual metaphors and help to reconsider reflexively the implications nestling in them to develop alternatively perspectives and approaches based on critically revised system conceptions.

The turn towards the important concept of reductionism exposed four conceptual metaphors used to frame what reductionism represents (see Fig. 2.11). Here, interesting aspects emerged in the course of the analysis which first disclosed reductionism as an entity. The conceptual metaphor, REDUCTIONISM IS AN ENTITY, made the abstract entity reductionism manageable for further clarification and discussion. Indeed, the reification appeared to be a basic process of meaning ascription by which the following metaphorical concepts, REDUCTIONISM IS AN ANCESTOR, REDUCTIONISM IS A PREDECESSOR, and REDUCTIONISM IS AN ADVERSARY were applied to create a relationship of systems biology towards the concept of reductionism. Implicated in the personifications, REDUCTIONISM IS AN ANCESTOR and REDUCTIONISM IS A PREDECESSOR, are genealogical images that subliminally depict the more holistic approach of systems biology

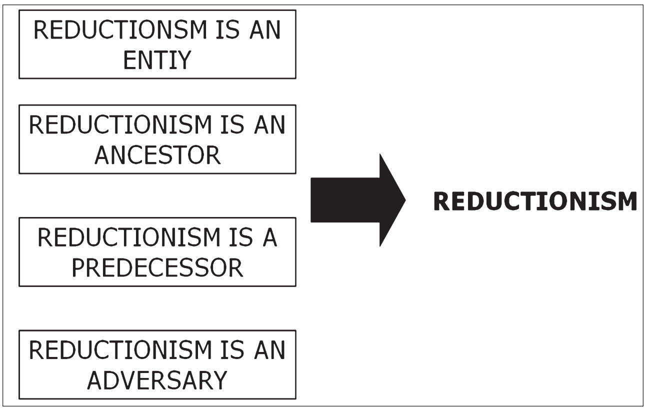

Fig. 2.11 Conceptual metaphors and personifications used to frame the notion of reductionism

as some sort of offspring. Albeit reductionism is now and then metaphorically depicted as an adversary, such an attribution was rare.

Surprisingly, theoretical awareness of the different subconcepts of reductionism was rather less marked in the interviews. The lack in awareness about ontological, methodological, and epistemological reductionism, so it seems, was concealed by the metaphorically motivated dissociation from a reductionist framework. In theoretical terms, this is problematic because approaches in systems biology are and also will in future be based on methodological reductionism. Nevertheless, it must face the challenges posed by the implicit epistemic (theoretical) reductionism found to be prevalent among systems biologists in order not to impede progress with regard to theoretical and experimental or practical progress. Therefore an open reflection of what kind of reductionism is necessary to tackle a certain scientific problem might be important to outline clearly the scope of results that can be achieved. A critical reflection of the conceptual metaphors in view of different subconcepts of reductionism might also help to divulge important theoretical aspects productively for doing research, help to examine concepts of holism in systems biology critically, and inspect the invention of a holistic tradition (Hobsbawm and Ranger 1992) or conceptual framework.

The analysis of holism displayed the three conceptual metaphors, HOLISM IS AN ENTITY, HOLISM IS A BUILDING, and HOLISM IS A PERSPECTIVE (see Fig. 2.12). These metaphors conceptually highlighted aspects of reification, manageability, perspective, and sight. A closer look at the conceptual metaphors, however, disclosed a low degree of metaphorical and semantic differentiation which was an astonishing fact because the concept of holism forms an important theoretical anchor in systems biology.

This shows that although systems biologists are thought to be holistically oriented, they in many cases undertake their research in view of unconscious reductionist frameworks. Those who theoretically reflect on holistic concepts mainly apply the concept of ontological antireductionism and work on the basis of their mechanical

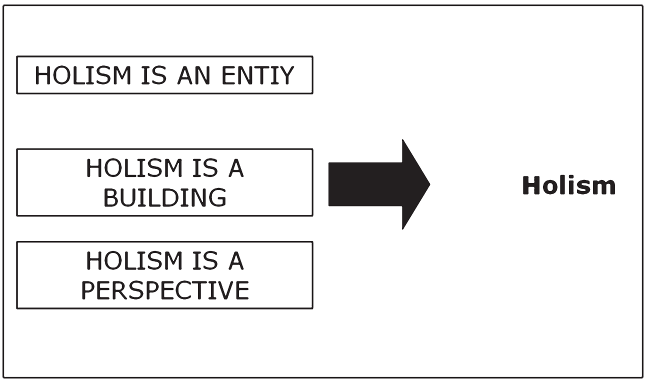

Fig. 2.12 Conceptual metaphors used to frame the notion of holism

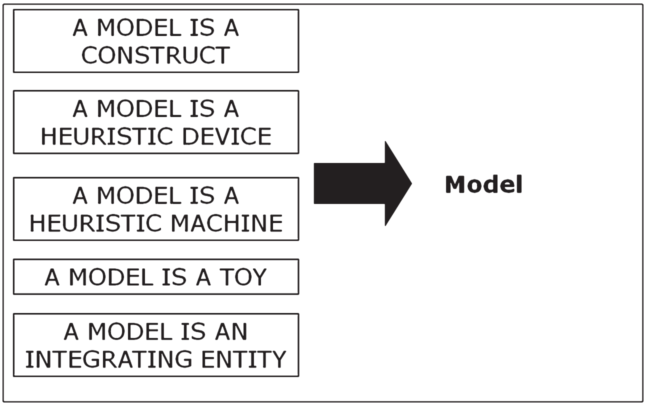

Fig. 2.13 Conceptual metaphors used to frame the notion of model

functions. However, this antimechanistic mindset was rare and encountered in the interviews only now and then together with different kinds of subconcepts of reductionism. Such a theoretical imprecision also surfaced in the metaphorical concepts and it would be important to elaborate on the different kinds of holism to define more precisely the underlying holistic rationale to be applied in research undertaken in systems biology. The metaphors could be taken here as starting point for analyzing the tacit knowledge[23] among system biologists about holism to be aligned with theoretical conceptions of holism. This would help to develop a situated and bottom-up definition of holism obviously implicitly inherent in research.

Finally, the analysis of the notion of model exposed five metaphorical concepts (see Fig. 2.13). The conceptual metaphors, A MODEL IS A CONSTRUCT, A MODEL IS A HEURISTIC DEVICE, and A MODEL IS A HEURISTIC MACHINE, elaborate that models are technical constructs and the latter two emphasize more instrumental aspects. It is, however, important to stress that in the three concepts awareness materialized that models do not represent exact replications but are abstract constructs of biological processes based on system components considered to be relevant. Although one might be tempted to hypothesize that scientists holding an engineering background preferably use these images, this does not hold true as the imagery was mainly shared by all interviewees.

Equally important are the conceptual metaphors, A MODEL IS A TOY and A MODEL IS AN INTEGRATING ENTITY, because they highlight aspects of scientific tinkering and the social dimension of models and modeling: they might deserve further scrutiny in terms of models and modeling as nonrationalist imaginative and social activities.

The number of these metaphorical concepts of systems biologists is by far not comprehensive and others such as interaction, dynamism, emergence, integration

[23] Tacit knowledge is a kind of knowledge that is difficult to be verbalized or communicated to others. It is gained through experience and not formalized.

(Green and Wolkenhauer 2012; O'Malley and Soyer 2012), and basic principles (Wolkenhauer and Green 2013) await further and much deeper linguistic, sociological, and philosophical analysis. However, the investigation of the figurative language used in speech in this chapter revealed how scientists semantically frame basic biological concepts and explain it to the scientifically informed interviewer.[24] The systematization of these linguistic images as conceptual metaphors proved to be methodologically useful and productive as they uncovered a wide range of interpretations and exposed to a certain degree the dynamics of knowledge (Maasen and Weingart 2000) inherent in the basic biological concepts discussed. It should have become clear that the conceptual metaphors "create what we would call cultural cosmologies or meaning-worlds that, once built, for better or for worse become the 'homes' in which we reason and act […]" (Harrington 1995, 359). They exhibit the poetics of scientists' minds (Bono 1999; Gibbs 1994) and disclose a culture in mind (Shore 1996) that generates the mindset to manufacture scientific knowledge (Knorr Cetina 1981) and the development of epistemic cultures (Knorr Cetina 1999). Hence, the conceptual metaphors encountered in the previous sections partially depicted the cultural, social, and philosophical grounding or metaphysics of scientific work undertaken in systems biology.

In addition to the previous aspect which mainly addresses the cognitive dimension in the conceptual theory of metaphor, images in speech are also ways of doing things with words (Austin 1962). This means the process of ascribing meanings to abstract entities entails different kinds of action or practices connected to or inherent in it. Thus, metaphors could be understood as "[…] a field of embodied, materially interwoven practices centrally organized around shared practical understandings" (Schatzki 2001, 3). Consequently, possible kinds of actions or practices (Bourdieu 1976; Pickering 1995; Schatzki 1996; Schatzki et al. 2001) could interpretatively be deduced from the conceptual metaphors informing practical understandings. Hence, metaphorically framing, for example, a model as a toy, possibly leads literally to playing around with a model on a computer to improve it scientifically whereas conceptualizing reductionism as an enemy brings about defensive attitudes towards certain experimental procedures in research or even the stigmatization or exclusion of colleagues subscribing to it. Michael Polanyi's (1967) tacit dimension comes into play here as it outlines the idea of knowing without being able to express this knowledge. In brief, he refers to knowledge that triggers action and practices where the individual is only partly able to explicate it verbally. Here metaphor as a meaning generating function of language gets into the game again. Although Polanyi is not explicit on the relevance of metaphor (Polanyi 1977, 66–81), for his concept of tacit knowledge, we would like to indicate that metaphors represent a way to verbalize the inexpressible partly. This means that the diversity of conceptual metaphors

[24] One has to keep in mind that the interview-setting represents in some way an unbalanced situation as the interviewer was not scientifically trained but conducted extensive research on the scientific and social aspects of systems biology. The interviews should thus be seen as sophisticated encounters in which scholars explain their framings of basic biological concepts in an interdisciplinary setting.

encountered in the preceding sections represent incorporated (Johnson 1987) tacit knowledge which is expressed and held together by daily behavioral routines of scientific work. Thus, metaphors could be understood as dialectical entities because daily practices and thinking hold them together. Therefore conceptual metaphors, as taken from the interviews, could also be understood as socially stabilized constructs constituted by acting and thinking at the same time: they represent in our study the diversity of dialectical knowledge systems underlying basic biological concepts in systems biology. These conceptual frameworks play an important role as they are "subconscious forms of understanding [manifest] in the metaphorical reasoning, as reflected in the language used in reasoning and communicating about science" (Brown 2008, 11).

Such a theoretical perspective on metaphor holds important philosophical and practical implications for science, policy, and the public. As embodied structures (Lakoff 1987; Johnson 1987, 1993; Lakoff and Johnson 1999), conceptual metaphors challenge the concept of scientific work as a logically driven and disembodied enterprise. Indeed, the mapping processes encountered in the previous sections display a wide range of bodily experiences and sociocultural reservoirs used to make abstract concepts meaningful and apply them to scientific problems. It is thus not surprising that both reductionism and holism are metaphorically conceptualized as entities or buildings because the metaphors give them concrete shape. But what follows from these insights?

First those basic biological concepts are perceived "through the lenses of embodied and social experience" (Brown 2008, 195) and second a rejection of objectivism (Putnam 1988) in favor of an experientialist perspective. This means in the context of this study that the basic biological concepts analyzed are grounded in and structured by conceptual metaphors. Such a position might sound too relativistic but many technological developments ranging from airplanes to medical therapies clearly show that metaphorically informed scientific knowledge is indeed able to solve problems and develop useful technologies or drugs. John Ziman (2000, 6) eloquently summarizes that imagery "is the vital link between the social and epistemic dimensions of science." This is an important point as Ziman (2000) refers to the productive analysis of metaphors that could be applied in metaphor assessment (Döring 2013; Jäkel 1997; Mambrey and Tepper 2000; Katherndahl 2014). Critical metaphor assessment helps to broach the subject of implications and assumptions nestling in basic biological concepts in order to empirically analyze and critically reflect on them. This could, for example, be seen in the previous sections of metaphors framing reductionism and holism where we took stock of conceptual metaphors to tackle how the biological concepts were framed. Complemented with a philosophical analysis, the assessment of conceptual metaphors revealed the subconscious rationales at work on system biologists' minds. Such an approach offers space for critical reflection and theoretical development. The complex problems addressed by the interdisciplinary enterprise of systems biology could obviously profit from such an assessment as it possesses the means to unravel hidden rationales driving research and the metaphorically generated professional backgrounds of the disciplines involved in research. As seen in the sections on life and systems, disciplinary framings were based upon occupation-related conceptual metaphors. An integration of these professional perspectives and attitudes could be brought forward once metaphors are shared, critically inspected, and reframed (Liebert 1995). Such a process holds the potential to contribute to a better mutual understanding, to initiate integrative problem understanding, to explore cooperative ways to approach scientific problems more creatively and to develop new or improved methods and theories for systems biology. The question, however, remains of how one could approach the theoretical diversity encountered in the previous sections from a reflexive point of view.

One way to instigate a reflective process would consist in providing scientists during workshops with the philosophical grounding of their scientific thinking and discuss the theoretical and practical implications nestling in it. This could create awareness about the impact of metaphorically coined worldviews on doing scientific research. Furthermore, courses on the philosophy of science and the relevance of language as a framing device in the curriculum of systems biology appear to be quite important as they could provide tools to develop a reflexive understanding of the epistemological and theoretical foundations innate in doing systems biology. These elements would theoretically and practically complement the worldwide mushrooming curricula of systems biology and productively match their existing interdisciplinary scope from a reflexive point of view. In fact, the theory of conceptual metaphor could pave the way towards an integrative or even experientialist teaching practice and open up interdisciplinary avenues of doing science. Such curricula would do justice to the complex issues addressed by systems biology from a very practical point of view because the analysis of metaphorically generated basic concepts in systems biology could quite easily be combined with a historical perspective. In doing so, new generations of systems biologists would learn about the diachronic and synchronic elements of their epistemologies and that enables them to reflect on their philosophical grounding of doing science. Thus, a course on different concepts of life, their philosophical sources together with the metaphorical framings of students, might help them to better understand and contextualize the origins of their thinking. To conceptualize life as machinery or a network holds certain implications but could also be seen as creative ways to rethink or improve one's scientific thinking. Hence, a curriculum that includes embodied experiences of students offers the opportunity comprehensively to educate and prepare them for the complex endeavor of systems biology.

In summary, we have tried in this chapter synchronically and diachronically to contextualize five important biological concepts permeating systems biology. The analysis provided a rich framework of different meanings metaphorically ascribed to the respective concepts under review. Philosophically grounded in experientialism (Johnson 1987) that emphasizes "that we know the world only in terms of perceptions, categorizations, and reasoning, both conscious and unconscious, grounded in our bodily capacities and life experiences" (Brown 2008, 187), metaphor was conceived as an analogical anchor in reality. And this anchor truly deserves more attention with regard to the analysis of basic biological concepts.

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