Modelling in Systems Biology : An analysis of the Relevance of Rosen's Relational Viewpoint for Current Systems Biology

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Abstract
Systems Biology aims to take up the challenge of the post-genome era by developing means to handle the data flood in the contemporary 'omic' sciences. One of the challenges is to 'turn data into knowledge', which gives rise to the question of the functional meaning of the structural data. Systems Biology tries to answer this question by capturing the organisation of a biological system through mathematical and computational modelling. In this regard, however, there is some ambiguity concerning the notions of function, wholeness and system. In this paper, we intend to discuss this ambiguity by analysing the status of modelling in Systems Biology. We do so by articulating the source of the tensions between a relational and a mechanistic approach of living systems, and will inquire upon the potential relevance of a relational account for current Systems Biology. We draw upon Robert Rosen's relational account, in which functionality is an intrinsic and essential part of the organisation of a living system. An organism is complex, e.g. not amenable to a mechanistic, classical or engineering analysis. In this viewpoint, which is quite similar to Kant's, functionality has to be *presupposed* in order to 'save' the organism as a *living* system. It is the status of this presupposition that qualitatively distinguishes a mechanistic from a relational account, and it is the potentiality of that idea which deserves further investigation in current Systems Biology.
Keywords: Robert Rosen, Systems Biology, modelling, complexity, function.

1 Introduction

New technological means, mathematical and computational modelling techniques, have enabled molecular biologists over the past decennia to sequence quickly and at relatively low cost the genomes of various living systems. The sequencing of the human genome is certainly the most notorious example among these. Initially, huge expectations arose around these sequencing capacities, as if the production of genetic (structural) data, would in and of itself lead to a sufficient understanding and explanation of the (functional) processes characteristic of living systems. These were the high days of gene-reductionism, in which an identification of unique, *material*, molecular components was thought to be sufficient for an adequate account of the *functionality* of living beings. That is what the idea of a genetic blueprint, originating in evolutionary processes guided by blind variation and natural selection, mainly referred to.

However, difficulties and limitations of this approach became more and more apparent over the years. The study of epigenetic phenomena, complexity issues, regulatory processes of various kinds regulating the expression of the so-called information contained in the genetic data, ... countered the linear causal view expressed in the Central Dogma. It lead to the insight that even the most systematic sequencing, even the vastest production of structural data, would eventually not be sufficient to attain the goal of unravelling the functional secrets of life. Genome projects, including the one concerning the human genome, did not fulfil the expectations. With a linear view on genetic causality having become untenable, within the impossibility to capture in one stroke material as well as functional characteristics through genetic sequencing, molecular genetics entered the post-genomic era. What became fundamentally question-begging was the idea of function being reducible to a set of material components, that is, the idea of function conflating with purely materially (molecularly) identified parts. Instead of considering genetic data as a basis in itself dictating, instructing or sufficiently informing the functioning of living systems, the functionality of genes was to be understood on the basis of more encompassing organizational contexts that were in a certain sense *independent* from the underlying material parts. In various ways, this issue was explored from within molecular genetics. The regulative workings of more or less proximate, organizational layers were and are articulated, leading to the development of the disciplines nowadays identified as the 'omic' sciences (cf. Vidal, 2001). However, until this day, these 'omic' sciences contribute mainly to the proliferation of still more data, beyond those related to the sequencing at the genetic level. Therefore, it can be said that even if the reductionist dream initially linked up with the orthodox paradigm has changed in tune, its key-note seems to have stayed intact: if the genes don't dictate the functionality of living beings, then perhaps the structural data of the 'omic' sciences eventually might do the job.

This is where Systems Biology enters the scene. With the advent of the 'omic' sciences, it had become obvious that a context, a perspective, a frame, a theory is needed to interpret and understand the huge amount of available structural data. The general, official aim of Systems Biology is now "to turn data into knowledge", by focusing primarily on the *relations* between data, on their *system's* aspect, more than on the data themselves (Kitano, 2001; Wolkenhauer, 2001; Huang, 2004; Mesarovic, 2004). Beyond the knowledge about materially or structurally identified parts, it explicitly wishes to take into account the idea of an interconnectedness, an interaction, a systematicity, an organization of these parts, within which their behaviour can be *meaningfully* described. In other words, Systems Biology purports to provide a *global* account within which the behaviour of locally identified and materially described parts can be coherently interpreted and explained.

This is the general picture, motivated by a clearly stated *ideal* of wholes being in some sense more than the sum of the parts. When looking at what actually happens in Systems Biology, however, things are less straightforward.

2 Systems Biology: Top-down and Bottom-up

The idea of a whole being more than the sum of the parts, is of course not new. Current Systems Biology was preceded by earlier, quite similar ideas formulated in a general way in Systems Theory. What Mesarovic stated already in 1968, namely that systems theory is needed to explain biological phenomena in terms of information and decision making or control concepts, that it studies how objects are related more than how they are internally composed, is equally true of current Systems Biology. The latter, however, has in addition a quite specific ambition, as indicated earlier: to overcome the relative failures of the genome projects on the one hand, and to interpret the huge amount of data that became available in the new high-throughput technologies. That is the ground upon which Systems Biology is making its way. Its most pregnant question is therefore that of functionality, as it aims to "bring genomes to life"[1], that is, to discover or recover function in a world of material sequencing and functionless data production.[2]

As can be expected, the field of Systems Biology is not uniform. Various approaches can be distinguished, expressing differences in viewpoint on biology as a science, and often implying different assumptions on what counts as a living system. There is for example no clear viewpoint on what modelling precisely involves, even if mathematical modelling by computational means is of the inner heart of Systems Biology. Or else, Systems Biology is often described in terms of bottom-up and top-down approaches (O'Malley & Dupré, 2005), but the meaning of these terms varies quite drastically. For Ideker (2001), bottom-up refers to the idea that the genes or the genomic level are taken as a starting point, for Noble (2001), it means starting from "the properties of individual molecules" and for Krohs & Callebaut (2007) the bottom-up approach begins from some meaningful biological process. These different identifications of the bottom level of the system indicate that a different weight is given to the hierarchical levels of the system, and this has implications for the viewpoint on functionality. So, for Ideker, taking the genome as the bottom level of the system leads to what we could call an 'extended central dogma'. It implies a linear view on the information flow in the system, and continues to conflate function and (extended) materially identified parts. Noble clearly sees functionality as located at the top of the system, leaving the particles to physics and chemistry, which has the implication of introducing functionality somewhere up in the hierarchy. Similar differences exist concerning the top-down approaches.

Considering this conceptual variety, we believe that, in addition to its discourse in terms of integration and systematisation, Systems Biology might gain from a more

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[1] Cf. The "Bringing Genomes to Life Program" of the United States Department of Energy. http://www.sc.doe.gov/ober/berac/genome-to-life-rpt.html

[2] Eisenberg *et al* (2000, p. 823) state it as follows: "Faced with the avalanche of genomic sequences and data on messenger RNA expression, biological scientists are confronting a frightening prospect: piles of information but only flakes of knowledge. How can the thousands of sequences being determined and deposited, and the thousands of expression profiles being generated by the new array methods, be synthesized into useful knowledge? What form will this knowledge take?"

explicit, biologically informed, account of functionality. Data are not automatically transformed into functional knowledge, and it is therefore advisable to keep the biologists in the driver's seat (Keller, 2005; Werner, 2003) of Systems Biology. This means that biology is likely to provide for specific and important insights in relation to the functionality of living systems, beyond those provided through efforts of physicalistic reduction.

In this paper, we stick to the account of modelling discussed by Krohs & Callebaut (2007) because it allows us to outline the ambiguity in relation to the issue of functionality most clearly. According to these authors, the *bottom-up* approach seeks biological meaningfulness starting from *local* functional data. It attempts to turn the structural data of the 'omic' sciences into something biologically meaningful by using these as resources to extend traditional pathway modelling in molecular biology, resulting in an ever growing network. It subscribes to the idea that the complexity of the living has to be and will be approached "from below", from the parts, but it sees this as a matter of gradualness. In that regard, it is true that the idea remains intact that a bottom-level can be identified that serves as a starting point to assess the regulative impact of large scale networks, but this starting point is considered from the beginning as functionally relevant in as far as it is functionally embedded in a local context.

The *top-down* approach on the other hand considers that the system's nature of living beings has implications from the very start, in that the whole is seen to have a major impact on the workings of the levels below. The roots of the top-down approach are biological cybernetics and systems theory, and its focus is primarily on the regularities at the *global* level. In this, the role of the 'omic' sciences is more substantial than in the bottom-up approach. The data are considered as global data spanning over the whole system at a certain time point. The top-down modelling approach starts its analyses from these global, structural data and tries to make them functionally meaningful by an engineering analogy in terms of design principles such as modularity, control concepts, redundancy, complex engineering, etc.

The question here arises whether there is still a "free" bottom level from which global wholes at a later stage emerge. Quite understandably, the challenge is to come to a "clear concept of wholeness" and to address "the ontological question of how to define wholeness" (Krohs and Callebaut, 2007, p. 209). It is true that Systems Biologists have more concerns for the "biological reality" than was the case in the times of cybernetics or system's theory, mainly because of the fact that more "biological" data are available nowadays. But nevertheless the problem of the top-down approach is still to recover biologically embedded functional organization starting from the global level. The underlying hope is in this regard that the modules or units identified in the bottom-up approach will eventually *converge* with the modules identified top-down, or that experimental research will converge with the computational analyses of structural data.[3]

This presentation allows us to see how crucial the issue of functionality is to current Systems Biology. The bottom-up approach is operating in the middle of a *given*

[3] This in itself can indicate that bottom-up as well as top-down approaches assume that there is eventually one and the same "reality" to be covered.

biological functionality – to our knowledge, no biologist will ever deny that living beings are essentially functional – without making explicit what functionality or wholeness consists in, without "transcending" the level of biological functioning and its close modelling.[4] The top-down approach on the other hand is confronted with the generality of its descriptions of overall regularities of networks, and has problems to "descend" to relevant and detailed biologically functioning processes. In other words, the bottom-up strategy is immersed in a functionality that it assumes rather than explaining it, the top-down strategy is not immersed in function but cannot but adopt a design reasoning (most likely framed in an engineering perspective) that as such remains external to the system. The distinction between bottom-up and top-down moreover shows how Systems Biology subscribes to the idea that it is possible ánd biologically relevant to define local data independently from their global organization, and vice versa. This explains its current research agenda, but it also illustrates how it remains basically focussed on two strategies: *either* it looks, top-down, for a substantification of wholeness that will allow for an adequate understanding of the parts, *or* it sticks to the parts and attempts to generate and understand organized wholes on that basis.

Is this divergence between bottom-up and top-down then a real problem for Systems Biology? Well yes, it is, to the extent that it considers that an integration or a unification of both approaches is advisable (cf. O'Malley & Dupré, 2005), ánd to the extent that it considers the conflation of structure and function, that was the case in classical molecular biology, as no longer tenable.

As indicated earlier, the conflation between structural data and functional organization is of the essence in classical molecular biology; it was actually this conflation that generated the field. At the heart of it lies the modern gene concept, and more specifically, the gene reductionism of molecular biology. At least two different modes of reductionism were at work in this regard, and they return in current Systems Biology. The first is the one undertaken by Mendel, who broke an organism apart in terms of phenotypic traits (characters), which were in turn reduced to the working of *factors.*[5] The second form of reductionism subscribes to the possibility of breaking down the biological organism to its basic material constituents, its molecules. These two modes of reductionism eventually converged in the modern gene concept, which implied the identification of a Mendelian factor with a special molecule, the gene.[6] So,

[4] Krohs & Callebaut (2007, p. 184) suggest something along these lines when stating that structural data are generated without theory and are very poor in generating theory.

[5] By this, Mendel did not try to establish a universal theory for all of biology. Instead he tried to provide breeders with a conceptual instrument. (see Falk 1991, 1995 and Moss 2003).

[6] Lenny Moss (2003) comes to a similar conclusion when he makes the Gene-P/Gene-D distinction, even if his historical analysis goes further back in time and is centred around the preformationism and epigenesis debate. He states: "The preformationist gene (Gene-P) predicts phenotypes but only on an instrumental basis where immediate medical and/or economic benefits can be had. The gene of epigenesis (Gene-D), by contrast, is a developmental resource that provides possible *templates* for RNA and protein synthesis but has in itself no determinate relationship to organismal phenotypes. The seemingly prevalent idea that genes constitute information for traits (and blueprints for organisms) is based, I argue, on an

the combination of the two gave rise, not just to all the molecules of the system (this would be only a material reductionism), neither just to functional entities (which would consist of only a part-whole reductionism) but to a piece of matter which contains an inherent encoding – the sequence of the base pairs of the molecule – of the whole functional organism. A detailed knowledge of the encoding pieces would then allow to know the whole system as a living, functional entity. This is the ideal explicitly pursued by the genome projects.[7]

Through the vast amount of structural data, as well as through the acknowledgment of the need, and of the difficulty, to interpret them coherently in more global terms, Systems Biology precisely *reveals* the untenability of such a conflation. However, it is unlikely that the renewed and impressive modelling efforts of Systems Biology will as such change anything substantial in the classical agenda. At this stage, Systems Biology appears to be a witness of a conflation it can no longer explicitly subscribe to, but for which it has not succeeded thus far in formulating a genuine, positive alternative. We suggests therefore that an epistemological reflection on, and a revision of, the status of functionality in its relation to structural data, is what Systems Biology is really in need of today. In an attempt to contribute to this epistemological reflection, we now turn to Rosen's relational account of living systems, which is critical towards the conflation between function and structure we discussed, and purports to develop an alternative account.

3 Robert Rosen

The functional organisation of a living system is precisely the problem Robert Rosen set himself to resolve during his entire career. It is perhaps not a coincidence that after decennia of neglect on behalf of the molecular biologists his theoretical ideas now gain more and more attention (see for example Boogerd *et al*, 2007). There are many reasons for this neglect, but the fact that Rosen had to establish a whole new idea of science in order to tackle the question 'What is Life?', was certainly not very beneficial for the proliferation of his ideas. In *Fundamentals of Measurement* (1978) he devised a 'relational systems theory' opposing the Newtonian Paradigm. This was inspired by his mentor Nicolas Rashevsky who coined the term 'relational biology' for his mathematical biology. Rashevsky came to believe that an investigation of the parts of an organism (for instance, you can investigate how the heart works or how diffusion is involved in cell division) can never result in an idea of life as such. In a way, Robert Rosen extended the idea of a relational biology to the whole of science and in this he has given the notion of function, excluded in a Newtonian framework as being unscientific, a proper place. Our discussion of Rosen starts with his viewpoint on

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unwarranted conflation of these two meanings which is, in effect, held together by rhetorical glue." (Lenny Moss, 2003, xiv).

[7] In the brochure entitled 'To know ourselves', distributed by the Human Genome Project consortium, this ideal is rendered in the following, typical, statement: "(…) the goal of the human genome project is a truly profound molecular level understanding of how we develop from embryo to adult and what makes us work". (http://www.ornl.gov/sci/techresources/Human_Genome/publicat/tko/index.html.)

component systems, as that contains in our opinion the core of his theory of functionality of living systems.

3.1 Components: the Functional Parts

According to Rosen, a living, functional, organisation cannot be dealt with from within a science that follows the Newtonian scheme. Instead of starting from well identified parts and describing the behaviour of systems in terms of recursive state sequences, organisms require a kind of decomposition that is basically the opposite: first focus on the organization, that is, throw away the idea of neatly identifiable and separable parts from which to start, and just stick to the organization. If you will not give up the idea of an identifiable, intrinsically non-functional material basis, not only will you not be able to recover organization afterwards, you will have lost it in an irretrievable way. This is what Bergson's metaphor of the tree suggests: if you reduce a tree into sawdust, don't hope to reconstruct it afterwards from these, well identified, material parts... This is the idea of the whole being more than the sum of the parts.

Biologists of course know this and will not overlook this particular phenomenology of the living. But Rosen's point is quite radical, as it attempts to develop rigorously the epistemology needed to think adequately about organisms. The point is indeed not to deny the possibility of arriving at identifiable parts – you can saw any tree into pieces – the point is to look for the most adequate or relevant way of looking at parts and wholes in relation to the living. At stake is, to use Rosen's words, to look for the correct decomposition. In contradistinction to a Newtonian worldview, that subscribes to the possibility of identifying unique material entities that are universal and objective, Rosen stresses the fact that there are many ways to decompose a system. With him, decomposition becomes a matter of choice and of interest, a matter of perspective. A model is never neutral but needs to be argued for in each context. Moreover, the question of choice does not seem to be simply settled in pragmatical terms, as the idea is to do justice to what is encountered at a certain phenomenal level, within certain contexts of experience. In this case, a living system is apparently not a Newtonian system, and the challenge is to attempt to grasp the living system *as* a living system.[8]

Let us first explain in a bit more detail what the core is of Rosen's account, that is, what exactly the point is where he essentially differentiates thinking about organisms from thinking about mechanical systems. There are various possibilities of entrance into his viewpoint. As we are dealing with parts and wholes, let us have a look at what he says about components, because that is the term he uses to refer to the functional parts of living systems, as different from the non-functional parts of mechanical systems.

In *Life itself* (1991), Rosen states that it is relatively easy to objectify the concept of *function*. "Suppose, for example, we are given a system, or better, a state, that is perceptibly heterogeneous; one part looks different, or behaves differently, from another

[8] To us, this is fundamentally a Kantian way of reasoning, and we believe Kant's overall account of objectivity is useful in this regard, but a detailed treatment of this issue falls outside the scope of this paper. We can refer in this regard to Van de Vijver et al. (2003, 2005); Kolen & Van de Vijver (2007)

part. If we leave the system alone, some autonomous behaviour will ensue. On the other hand, we can ask a question like: *if we were to remove, or change, one of these distinguishable parts, what would be the effect on that behavior?"* (Ibidem, p. 116)[9]. Rosen considers this a pregnant question, because it involves a new element, "not merely observation, but willfull, active intervention" (Ibidem, p. 116).

We shall not enter the discussion about the difference between observation and willfull intervention here. Let us just mention that we would rather think that all observation or perception is active intervention, as von Helmholtz, to name only one, already pointed out. Moreover, we would be tempted to think about willfull interventions as just a special case of perception or observation. But that is not the main point of interest here. What Rosen correctly stresses, is the following: "The result of that intervention is, in effect, the creation of a *new system*, which can be regarded as a kind of perturbation or mutilation of the original one. But supposing this can be done (...), we can compare the behaviors of these two systems, the original one, and the new one, with some original part ablated. Any discrepancy between these behaviors defines the *function* of the removed part. Indeed, as we shall see, *it provides us with another way of describing that part*, a new way of encoding that part into a formalism." (Ibidem, p. 116) Rosen will call any part of a systems that can be assigned a function in the above sense henceforth a *component*.

What is here to be stressed?

Firstly, a functional definition of a part, a component, can only be provided for on the basis of an intervention. Activity is needed, and not just mechanical activity but, as we would interpret it, directed, organised activity. Things go somewhere.

Secondly, what is interesting is that the function of a part can only be defined in a negative way. Or perhaps more correctly, it cannot be substantified. There is no possibility to define the function of a part by taking it apart and attributing a certain role to it, then called function. Functions are not to be attributed to parts, they are the result of a comparison between two types of global behavior of a system, one in which the part is present, the other in which the part is not present. Comparison between the behaviour of at least two systems is needed to determine the function of a component; it is undefined by any system alone.

Thirdly, the definition of functional parts expresses as much about the part as about the whole, more correctly it expresses a *difference*. There is no other way of substantifying the difference between parts and wholes than by making a comparison between two behaviours. The only thing that rests is ultimately a stabilisation of behaviour. Rosen (2001, p. 116) states the latter explicitly: "From a formal point of view, the concept of *function*, and its embodiment in terms of *components*, is a part of stability theory. Namely, we are comparing two different situations: an original unperturbed one, and a second one, arising as the perturbation of the first. The discrepancy defines the concept of *component*; the discrepancy between the two *behaviors* defines the *function* of the component."

[9] By adopting such a strategy Rosen tries to avoid the pitfalls and keep the benefits of both an internal structural description (as in physics) and an external functional description (as in the engineering sciences) by combining them in an *internal* description of functional activities (See Rosen, 1972).

And finally, if we wish to develop an adequate theory of the living, we can only reason from the viewpoint of actively moving beings, that is, we can only reason from within, as actively engaged within the living activity. We have to investigate, explore and carry our particular capacities of (perceptually) relating to certain things, living and non-living, without considering that it is in itself a unique and universal, detached, point of view. Instead, we can attempt to push as far as possible our ways of understanding parts and wholes by being actively part of the living dynamics and by attempting to objectify these patterns of interaction in the form of an ever renewable stabilisation.

3.2 Relational Biology

The idea that it is impossible to substantify function has important epistemological consequences. It implies in particular that the issue of reduction has to be considered in terms of the relative adequacy of fractionations, much more than in terms of a solid and independently defined material basis below, that is then to be made convergent with a functional organization at the top (or vice versa). Rosen exemplifies this idea through his viewpoint on modelling (2000, p. 46-53). The issue of reductionism is presented as follows. Let Ω be an organism (e.g. a pea plant). There exist accordingly two modes of fractioning the organism: the molecular one in terms of genes (A), and the Mendelian one in terms of factors (B). The question is, is it possible to draw the arrow $\theta : A \rightarrow B$? If this is possible, then there is in fact a reduction of one of the encodings to the other. If this is not possible, then the different encodings are irreducible and complementary: neither of the encodings captures all the causal processes in Ω (Figure 1).

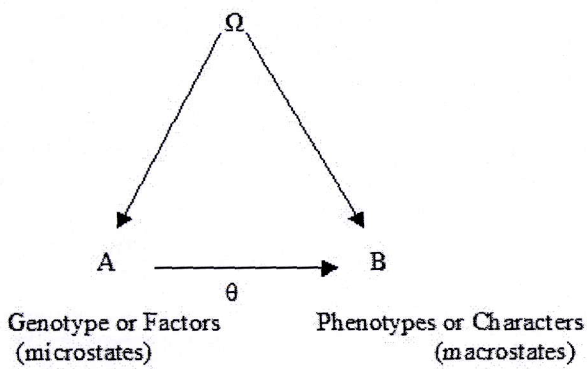

Figure 1: Different fractionations of an organism (Rosen, 2000, p. 49)

Of course, the idea of a natural system will play a crucial role in considering reduction as possible or not. For Rosen (1985, p. 45), "a natural system comprises some aspect of the external world which we wish to study". This statement implies two 'basic dualisms', grounding the whole of science. The first dualism consists of the *self*, the internal, subjective world which we apprehend in a direct manner, and the *ambient*, the external world.[10] Science consists in pulling aspects of the external world into the internal world, where it *constitutes* a model. The second dualism is the one between a system and its environment, the latter being everything which is not included in the system (its complement). The important point here is that there is no guiding principle of how the self divides the ambient world in systems. Moreover, system and environment are defined relative to one another. A system is a collection of percepts or sensory impressions (qualities or observables) that seems to belong together from the viewpoint of an observer. The unity, if any, is imposed by the self on the percepts. This is not unproblematic, as the relations – the organisation of percepts – reflect the properties of the mind as well as those of the external world. At this point, Rosen (1985, p. 46) suggests: "What does seem to be true, however, is the following: that the mind behaves *as if* a relation it establishes between percepts were itself a percept. Consequently, it behaves *as if* such a relation between percepts arises from a corresponding relation between qualities in the external world".[11] In other words, the perceptual act of a relation between qualities is the imputation of the relation by the mind.[12]

As already indicated, this viewpoint on modelling implies a quite drastic change in perspective regarding the study of living systems, at least in comparison to accounts that are either reductionist or holistic. As a matter of fact, the ideal here is no longer to look for an independently defined, solid material basis – to look for more and more structural data – that could as such explain the whole functionality of the living. Neither is it to look for functionality at the top level and to consider material identification of the living as belonging to another domain (physical or chemical). Instead, the ideal is to look for a modelling of living systems that accounts for their specific organizational (functional) nature given the fact that this modelling is itself an intrinsic part of the living, interactive, perceptual dynamics. The core of the relational epistemology is that it takes as a starting point the interactive dynamics, and considers from there on structure as well as function as possible stabilised endpoints, that are intrinsically defined in relation to one another. The challenge here is to understand how structure as well as function can be in some sense distinguishable if they are taken to arise from interactive living processes. What they are, how they acquire a meaning at various levels, how we can understand or know them as distinct, becomes fundamentally question-begging. The identification of parts (structure), and their interrelatedness

[10] This viewpoint is as such not unproblematic, as could be argued in more general philosophical terms on the basis of the difference between Brentano and Husserl's account of intentionality and consciousness. This would require, however, a totally different development than the one under discussion here.

[11] The move Rosen is making here, is kantian or more generally transcendental, in that it subscribes to the idea that a (natural) thing is only knowable to the extent that a question is asked, obliging an as yet undetermined x to answer, and leading to a determination of something that cannot but fit within the range of the question.

[12] The moment Rosen makes the assumption that the relations the mind imputes on the percepts correspond with certain relations (such as causal and temporal relations) between observables (the correlates of the percepts in a natural system), he can establish his 'scientific' modelling relation, which is crucial for his discussion on anticipatory systems (see Rosen, 1985). For a discussion of modelling and anticipation, see also Van de Vijver (1998).

(function) can at no moment be considered as detachable. They are certainly not the more or less neatly separated terms between which a convergence or a unification needs to be established, as is apparently the case in current Systems Biology. On the contrary, decisions regarding structure and function, depend on decisions regarding the ways of fractionating systems and the choices underlying these fractionations, and they lead to the question of the compatibility or the priority between different fractionations.

4 Conclusion

By asking the question of the meaning of the structural data Systems Biology reveals a conflation between structure and function that remained largely implicit in molecular biology. It becomes clearer now how the materialisation of the Mendelian gene in molecular biology involved a different epistemological project, with a basically different question-begging starting-point, and with a different ideal upon which all research efforts were directed. By identifying the Mendelian fractionation with the molecular factor, the materialistic perspective became the new ideal of molecular biology. Even if the molecular gene concept (together with neo-Darwinian theory) did not deny the functionality of an organism, it attempted to localise function in particular molecules. The idea of the organism as a whole became from then on in a way dispensable or at least secondary, and the fact that any material identification of the gene at some point required the functional context of the organism was more or less silenced. Will Systems Biology continue to operate in line with this historical background? Will it continue to subscribe to the (dualistic) option: *either* to look top-down, for a substantification of wholeness that will allow for an adequate understanding of the parts, *or* sticking to the parts in an attempt to generate and understand organized wholes on that basis?

What Rosen's relational viewpoint illustrates is that living systems need an account of function and structure that is developed in some sense *from within,* that is, in the absence of a designer that would decide about function on external grounds, and in the abandonment of the idea that parts are always the same parts that can serve as unambiguous building blocks, no matter which context surrounds them. A relational account implies the idea that a component is already a global notion, and as such it goes beyond the dichotomy between parts and wholes. To look for an ontology of systems or for a sound concept of wholeness starting from objectified parts becomes pointless in this regard. The relational epistemology sees the production of the structural data as the result of a certain perspective, by means of the modelling relation. It is an epistemology which is not trapped into an objectivism *or* a subjectivism but is grounded in the idea of interaction as a necessary characteristic of the dynamics of life. The structural data can therefore be seen as stabilized, objectified, endpoints of an intentional processes, grounded in a subjective necessity. And the question of function, of the meaning in living systems, is addressed from the start in a relational perspective; it is not something which has to be added afterwards on top of something which is not functional. If the living organism is seen as an ongoing process, constantly generating meaning for itself – which biologists will not deny – isn't it more appropriate then to attempt to think of them in relational terms, as more or less stabilized entities, that depend on stabilizing conditions and actively co-determining these conditions in their turn? Would it not be more appropriate to establish an epistemology that is faithful to that basic idea of relative stabilisation *from within*, an epistemology that as such refuses to collapse into either objectivism or subjectivism that accepts stabilisation *from without*?

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