Chapter 11
Multiple Means of Determination and Multiple Constraints of Construction: Robustness and Strategies for Modeling Macromolecular Objects

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11.1 Introduction

As Wimsatt has repeatedly and explicitly pointed out,[1] one of the main sources of his interest in the concept of robustness and in the procedures of robustness analysis is constituted by the work of Levins (1966, 1968) on "robust theorems" in the context of model building in population biology. If Wimsatt has expanded the notion of robustness to a much broader set of procedures and contexts of use than what was intended for by Levins' discussion,[2] the work of Levins still seems to be a good resource to discuss robustness in model-based scientific activities. More generally, the overall discussion within which the notion of robustness analysis is introduced in Levins (1966) is of great interest when discussing practices of modeling (Weisberg 2006a).

It is within a discussion of the practical limitations population biologists face when constructing and analyzing models that Levins (1966) has emphasized the interest of robustness analysis. Because the systems encountered in population biology are complex, the construction of *manageable* models of these systems requires *tradeoffs*. As Odenbaugh (2006) has convincingly argued, "(. . .) Levins' discussion of tradeoffs in biological modeling concerns the tension between our own limitations with respect to what we can compute, measure, and understand, the aims we bring to our science, and the complexity of the systems themselves" (Odenbaugh 2006, p. 618). After having emphasized such specific constraints of the

[1] See Wimsatt (1981), for example p. 124 or p. 126. See also Wimsatt (1994) or (2001).

[2] Wimsatt (1981) wrote: "The family of criteria and procedures which I seek to describe in their various uses might be called *robustness analysis*. (. . .) I will call things which are invariant under this analysis 'robust', extending the usage of Levins (1966, p. 423), who first introduced me to the term and idea and who, after Campbell, has probably contributed most to its analysis" (p. 126).

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epistemological context in population biology, Levins (1966) analyzes the modeling practices of population biologists and considers that three different modeling strategies, implying different tradeoffs, are developed in this field. One of these strategies is the one Levins uses and prefers, as a modeler. It is within this strategy, where "very flexible models" (as Levins 1966, p. 19, calls them) are constructed, that robustness analysis emerges.

In this chapter, I will present and analyze a theoretical procedure developed during the 1960s and 1970s within the field of protein chemistry. The interest of this case study is definitely linked with such a picture of science interested by the limitations scientists encounter and the "in practice" strategies they then devise in order to study "messy systems" (a wimsattian expression[3]). So, it will be necessary to grasp the epistemological context within which such theoretical procedure, which constitutes a type of protein modeling, has been set up by scientists: what are the specific problems scientists were faced with when constructing this procedure? For theoretical chemists, proteins are truly complex objects, and the construction of a theoretical method to gain knowledge on the properties of these objects by devising models of their structures faces them with different kinds of limitations (notably computational limitations). As Levins has made for population biology, I will therefore describe the tension between the limitations protein scientists encountered, their aims for constructing models, and the complexity of proteinic objects. In so doing, I will discuss and analyze the strategy protein scientists worked out in order to manage this tension and to construct, then, what became, for them, a stable and efficient procedure of modeling.

With that interest in modeling practices, it seems then interesting to go back to Levins' work, which ties up model building and robustness analysis. In order to understand and analyze the procedure protein scientists have set up for constructing theoretical models of protein structure, as well as some properties of the models built, I will use Levins' analysis of modeling practices in population biology, which differentiates three main modeling strategies. But if Levins' analytical framework constitutes an interesting resource for discussing, in another scientific field, the type of modeling procedures used and the characteristics of the models constructed when using them, it seems also worthwhile to contrast the modeling strategy Levins uses and prefers, as a "population biology" modeler, and the modeling strategy worked out by protein scientists.

When contrasting these two approaches, it becomes notably clear that robustness analysis is a tool particularly well suited to Levins' modeling strategy. This is not the case with the modeling procedure protein scientists have set up within the strategy they chose. So, if the fruitfulness of the modeling strategy of Levins is partially related to idea that robustness analysis may provide a resource for determining which results are robust and, then, which models are trustworthy, the fruitfulness of protein scientists' modeling strategy and the stabilization of their modeling procedure have to be found elsewhere. One factor that seems have been important in the stabilization of this procedure of modeling is that the three limited resources

[3] See Wimsatt (2007), p. 6.

proteins scientists have used for devising the procedure have been mutually and iteratively adjusted. Such a mutual and iterative adjustment of theoretical, empirical and computational constraints has been implied in the stabilization of the modeling procedure, and, in so doing, in scientists' recognition that their procedure was efficient and their strategy fruitful.

So, my aim is to describe and analyze how, in a constrained epistemological context, protein scientists have used and mutually adjusted limited resources in order to construct what became, for them, an efficient procedure of modeling protein structure. As the efficiency of this procedure is partly related with its stabilization, I will pick out two factors implied in this stabilization. Thus, I will mention the mutual adjustments of the three constraints above-mentioned as well as the impact of the computational nature of the procedure on its evolving status, and on its diffusion within the scientific community. But if these two factors seem interesting for understanding to some extend how the modeling procedure has been stabilized and then conceived, by scientists, as being efficient, a real discussion of the trustworthiness of that procedure would require an analysis of the way the predictions produced with the models constructed have been tested against empirical data. Within the limited scope of this chapter, I will not discuss this point. I propose, then, a more modest approach, emphasizing some factors implied in the stabilization of the modeling procedure.

This chapter then discusses how practicing scientists, with limited resources, have exploited multiple constraints of construction and the limited tools computers are in order to construct and stabilize a modeling procedure. In so doing, I want to show that beside the justification of modeling results by robustness analysis and, more generally, the stabilization of a scientific procedure by a robustness scheme, others strategies of construction and stabilization of a scientific tool exist and have to be characterized. The strategy used by protein scientists to construct and stabilize their modeling procedure has been to manage multiple constraints of construction by mutually and iteratively adjusting, in a computational way, these theoretical, empirical and computational limited resources.

So as to understand more clearly the epistemological situation of modeling practices described by Levins for population biology, the nature of the tradeoffs he discussed, and the different strategies of model building he presented, I will, first, discuss Levins (1966) in Section 11.2. This discussion will be useful in order to specify, by using Levins' analytical framework, the type of modeling strategy used by protein scientists. Secondly, I will discuss, in Section 11.3, the specific constraints of the epistemological context within which theoretical approaches in protein chemistry have been developed. I will also specify, here, scientists' epistemic aims for constructing models of protein structure. Finally, I will analyze, in Section 11.4, the nature of the modeling procedure and of the models that protein scientists have constructed during the 1960s and 1970s. I will discuss, here, the theoretical, empirical and technological limited resources they could and had to take into account. To conclude, I will discuss, in Section 11.5, what is robustness for Levins and for Wimsatt in order to show, by contrast, the specificity of the strategy devised by protein scientists for constructing and stabilizing their theoretical procedure. I

will emphasize, here, that the construction of the modeling procedure of proteins is based, and its stability depends, on a mutual and iterative adjustment of theoretical, empirical and technological constraints and on its special characteristics due to its computational nature.

11.2 Complex Systems, Brute Force Approach and Tradeoffs in Model Building

As Odenbaugh (2006) has argued, Richard Levins' article "The Strategy of Model Building in Population Biology" can be seen as a defense of a style of theorizing in population biology that Levins has developed during the 1960s with others biologists (Robert MacArthur, Richard Lewontin, E.O. Wilson, and others). His methodological essay is in particular composed of an analysis of three different strategies of modeling in the field of population biology. Levins argues that all these three strategies are relevant and important, and that it will not be beneficial to abolish this diversity in favor of one unique strategy. Levins' methodological discussion can then be seen as a defense of the richness of plural modeling strategies in population biology. As Odenbaugh (2006) writes: "(. . .) the target of Levins' 1966 article is ultimately *model monism* – that there is a single correct model type for successfully representing evolutionary-ecological systems" (p. 616, italics in the original). In defending this kind of "pragmatic pluralism" in theorizing,[4] Levins tries then to show that the modeling strategy he prefers and uses (which is one of the three strategies) is legitimate.

Levins considers that this pluralism is necessary for population biology (at least in the 1960s) because the way biological populations are described in his project (shared with others) of integrating population genetics and population ecology leads to have to "(. . .) deal simultaneously with genetic, physiological, and age heterogeneity within species of multi-species systems changing demographically and evolving under the fluctuating influences of other species in a heterogeneous environment" (Levins 1966, p. 18). As Weisberg (2006a) has noted, the core of Levins' article is constituted by the recognition of this complexity and by the two main options that are then discussed in order to deal with it.

Thus, Levins indicates that one way of modeling such a complex system would be "(. . .) to set up a mathematical model which is a faithful, one-to-one reflection of this complexity" (Levins 1966, p. 18). The aim of this first approach is to construct models that offer a representation as complete as possible of the complex system of interest. In this kind of models, every features of the system has to be represented within the model constructed. In order to reach this "ideal of completeness"[5] as far as possible when modeling the systems of population biology, one must then

[4] Wimsatt (2001) uses this expression, "pragmatic pluralism", when he discusses Levins' strategies of model building.

[5] This notion of an "ideal of completeness" is introduced and discussed by Weisberg (2006a, p. 626).

construct models constituted of a very large number of simultaneous partial differential equations with a lot of parameters. Once such a model has been constructed, it is then necessary to solve the equations to obtain numerical predictions, which have to be compared with known quantified properties of the system. Levins names this first way to deal with the complex systems of population biology "the brute force approach". But for him, such an approach is impracticable because too many parameters must be measured, because the equations are not analytically soluble and cannot be solved by the computers of that time, and because, even if solutions could be obtained, the results expressed in a long list of numbers would have no meaning for scientists.[6] Thus, Levins considers that this first approach cannot be followed, because of the complexity of the models *and* of the limitations of scientists.[7] Oppositely to the unreachable goal of this "brute force approach" – to construct a definitive model representing biological populations in their environment – a satisfactory theory in population biology is then, for him, what he calls "a cluster of models", that is a global coordination of different *idealized* models representing different sets of phenomena.[8] Levins' recognition of the impracticability of the "brute force approach" constitutes, thus, the core of his defense of model pluralism in population biology.

As Levins considers that this "brute force approach" cannot be followed, he then thinks that it is necessary to simplify the models constructed so as to work with manageable ones. This second approach is named by Weisberg (2006a) the "idealization approach". *It is within this second approach that Levins introduces a differentiation between three strategies of modeling*, which depends on the sacrifice made, concerning one of three desiderata of model building, when constructing simplified models. For Levins, besides the requirement of manageability of models, necessarily implied by the "idealization approach" chosen, the three desiderata of model building are generality, realism and precision.[9] Nevertheless, he considers that if it is desirable to maximize all these three aspects of models, it is not possible in practice; hence the tradeoffs in model building.[10] As these three aspects cannot be maximized if one wants to construct a manageable (then necessarily simplified) model, a sacrifice concerning one of these three aspects has to be made. Three strategies are thus possible: (1) "sacrifice generality to realism and precision"; (2) "sacrifice realism to generality and precision"; (3) "sacrifice precision to realism and generality" (Levins 1966, p. 19). Each of these strategies is then exemplified by the works of different groups of scientists interested in population biology. For the first one, Levins cites notably the works done in systems ecology. The second one is referred to the works

[6] For the precise formulations used by Levins, see Levins (1966, pp. 18–19.)

[7] Odenbaugh (2006) has convincingly defended this point.

[8] See Levins (1966, pp. 26–27), in particular Fig. 3 on p. 26.

[9] See the next paragraph for a discussion of the meaning of the terms "generality", "realism" and "precision".

[10] For a discussion of the logical versus in practice impossibility of such a maximization (i.e. of the logical versus in practice necessity of the tradeoffs), see Weisberg (2006a, p. 636).

of physicists-turned-ecologists. The third strategy is the one favored by Levins (and others). So, the three strategies identified set up something like a panorama of the different styles of theorizing represented in 1960s population biology.

The question of the meaning of the terms "precision", "realism" and "generality" used by Levins remains. In his chapter, he doesn't discuss precisely these terms and he uses these notions in a somewhat ambiguous way. Weisberg (2006a) has clearly picked out this situation and has then proposed an in-depth discussion of these notions. For him, generality corresponds to "(. . .) the number of target systems that a model can be applied to" (Weisberg 2006a, p. 634), realism to an assessment "(. . .) of how well the structure of the model represents the structure of the world or (. . .) an assessment of how close the output of the model matches some aspect of the target phenomenon" (Weisberg 2006a, p. 635), and precision corresponds to "(. . .) the fineness of specification of the parameters, variables, and other parts of model descriptions" (Weisberg 2006a, p. 636). So, the generality of a model is a property corresponding to the number of target systems this model describes or can describe. Concerning realism, it is a notion which corresponds to the accuracy of a model, understood (in Levins' uses of the term realism) *either* as the accuracy of the representation offered by the model *or* as the accuracy of the predictions of the model.[11] So as to distinguish these two meanings of the term realism, I will use, in what follows, "representational accuracy" (or "representational fidelity" – see the preceding footnote) and "predictive accuracy" (or "dynamical fidelity" – see the preceding footnote). Concerning now precision, it seems important to note that this notion is used in order to characterize model descriptions and not the outputs of models. Precision is then different from predictive accuracy because, in Levins' sense, precision doesn't characterize the output of a model.[12] It is also different from "representational accuracy" because precision concerns the fineness of specification (in particular of "quantitative specification") of the description used to model the system of interest, which is not equivalent to the quality of the representation of the system's structure offered by the structure of the model description (i.e. "representational accuracy").

It seems interesting to consider in some details the nature of the three modeling strategies in order to understand more precisely to what generality, realism and precision refer, and how these terms are used.[13] Models built within the first strategy maximize realism and precision and sacrifice generality. Here, we find

[11] Weisberg (2006a, p. 635) analyzes this ambiguity of the term realism in this way. See also Matthewson and Weisberg (2009, p. 181), who speak of "representational fidelity" of a model (which concerns "how well a model describes the causal structure of the target system") and of "dynamical fidelity" of a model (which concerns model's "predictions about the quantities of measurable attributes" of the target system).

[12] In this context, it will not make sense to speak of "predictive precision". It is then useless to speak of "representational precision", because precision is exclusively understood as "representational precision" (and not as "predictive precision").

[13] Here again, for an in-depth discussion of each of the three strategies, see Weisberg (2006a, pp. 637–640). I use Weisberg's discussion for my rough description of the three strategies.

the models of systems ecology, which are complex mathematical models describing in great details, with a lot of precisely specified quantitative parameters, very specific systems in order to provide accurate predictions. They lack generality because they are tailored to particular real systems, and they maximize realism (i.e. "predictive accuracy") and precision because they respectively produce accurate predictions, and describe with a high degree of specification the system of interest. Within this first strategy, computers are used to solve numerically the equations of the models.

Concerning now models built within the second strategy, they maximize generality and precision and sacrifice realism. Levins considers here that this is the strategy used by physicists-turned-ecologists, who construct models by "(. . .) setting up quite general equations from which precise results may be obtained" (Levins 1966, p. 19). These models lack realism (i.e. "representational accuracy") because the simple equations they use describe highly idealized systems (as it is the case, in physics, with frictionless systems or perfect gases, as Levins mentions). Nevertheless, these simplified systems are precisely specified (in particular in a quantitative way) within the models, which can, therefore, maximize precision. Furthermore, these precisely specified models could be applied to many systems, whence their generality. Within this strategy, it is sometimes possible to resolve analytically the equations. This can lead to compare the results then obtained with measured properties of the systems and to analyze precisely, as Weisberg (2006a) puts forward, the mathematical structure of the model used. It is then possible to try to construct less idealized models (i.e. more realistic ones).

Finally, with the third and last strategy, "very flexible models", as Levins calls them, are built. These models are often graphical rather than described by mathematical equation(s), and the parameters used in the model description are often only qualitative. The results produced are then qualitative and express often tendencies of evolution and contrasts between two situations in the form of inequalities. These models maximize generality because they are constructed in order to compare, for example, the effects of the same parameter on distinct phenomena. So, they have to be applicable to different analogous systems. Moreover, they maximize realism (i.e. "representational accuracy") because the aim of constructing this type of models is to test explanatory hypotheses concerning the ways a particular system evolves. It seems then necessary that such models characterize accurately these ways of evolving if we want the assumption to be explanatory. Nevertheless, as these models are deliberately qualitative ones, they don't offer a precise specification of the system being modeled, because the precise values for the parameters are not fixed. Thus, precision is sacrificed within this third strategy of model building, exemplified by Levins' works.

If the notions of "generality", "realism", and "precision" used by Levins remains perhaps somewhat ambiguous, they nevertheless enable to understand, at least intuitively, what are the characteristics of each strategy and the differences between all three. Moreover, by considering which specific tradeoff has been chosen when constructing a model, we can grasp the main goal assigned to model building by such or such scientists. For example, the first strategy is used when someone wants to make

quantitative predictions about a very specific system, whereas the third strategy is used for trying to explain general features of phenomena.[14]

It is after having presented and discussed these three strategies that Levins introduces the notion of "robust theorem" and the idea of what we now call "robustness analysis". As robustness analysis in the sense of Levins will be discussed in conclusion, I will not develop at length, here, the way this notion is introduced. I just want to indicate what is a robust theorem and that robustness analysis fit in relatively well with the defense, by Levins, of model pragmatic pluralism. A robust theorem is not, for Levins, a theorem in the common sense of the term. It is more simply an explanatory hypothesis concerning the ways a particular biological system evolves. Levins takes for example the following statement to be a robust theorem: "in an uncertain environment species will evolve broad niches and tend toward polymorphism" (Levins 1966, p. 20). If several models, with different simplifications for describing the phenomenon but all incorporating the same biological hypothesis for trying to explain it, lead to similar results, then, in that case, these results don't depend on the particular simplifications of each model but on the biological explanatory hypothesis. This explanatory hypothesis, which consequences, when derived by various models with different simplifications, are similar, can then be considered as a robust theorem. As Levins puts it: "(. . .) if these models, despite their different assumptions, lead to similar results, we have what we can call a robust theorem that is relatively free of the details of the model. Hence, our truth is the intersection of independent lies" (p. 20).

So, the introduction of the notion of a robust theorem and of the underlying procedure of robustness analysis depends on the recognition that models are artificial constructions, which include artificial assumptions. It is because all models have artificial assumptions that constructing several alternative models of a same phenomenon becomes, for Levins, necessary, in order to try to secure a "theorem". Moreover, it has to be emphasized, here, that the recognition of this artificial character of models leads Levins to a defense of model pluralism, which is congruent with the way robustness analysis is conducted (by analyzing if a same result is obtained with *several alternatives models* using different assumptions and simplifications, in order to judge if this result can then be seen as trustworthy (i.e. robust)). So, robustness analysis is typically a tool linked with the model pragmatic pluralism defended by Levins, and this tool is particularly well suited to the third strategy of model building, exemplified by Levins' own works, because constructing different qualitative models of the same system is, here, relatively easy (it requires, nevertheless, that interesting assumptions are used). We could probably say, then, that the fruitfulness of this particular strategy of model building ("sacrifice precision to realism and generality" by constructing "very flexible models") is, in part, linked with the relatively easy possibility it offers to use robustness analysis.

In the two next sections, I will develop my case study on modeling practices in protein chemistry in the 1960s and 1970s. In so doing, I will try to show, as Levins

[14] In his presentation of the three strategies, Weisberg (2006a, pp. 637–640), discuss in more details the goals associated with each strategy.

has made for population biology, how the epistemological context, which articulates complexity of the modeled object *and* scientists' limitations, is important in order to understand the strategy protein scientists have devised for constructing theoretical models of proteins structure, as well as the status of the models built. I will examine some properties of these models, notably their generality and realism. Levins' essay constitutes therefore an interesting resource for discussing model-based activities in another scientific field.

11.3 Epistemological Situation of Theoretical Approaches in Protein Chemistry

In order to understand the epistemological situation of the theoretical approaches to proteins properties in the 1960s and 1970s, it seems necessary to present, schematically, what kind of molecular object proteins are. Proteins are organic compounds that play different fundamental functions within cells. These organic compounds are biological *macro*molecules, typically made of thousands of atoms. These biopolymers are composed of repeating structural units. Twenty such natural occurring structural units, named "amino acids", exist. Most proteins have the property of naturally folding into a precisely defined three-dimensional structure: scientists speak of the native *conformation* of a protein for this naturally occurring structure. A conformation of a molecule is thus a particular three-dimensional arrangement of its atoms. For one protein, different conformations are theoretically possible because of the various possible rotations around certain chemical bonds. The native conformation is then one among the great number of theoretically possible conformations of a protein: this collection of theoretically possible conformations of one protein is called its "conformational space", typically of an order of 3^{100} for a protein of 101 amino-acids.

The three-dimensional native structure of a protein is complex. It can be noted here that this structural complexity has immediately been recognized by the scientists (John Kendrew and Max Perutz) who, using X-rays scattering experiments, were able to propose in 1960 the first structures at atomic resolution of two proteins, namely myoglobin and hemoglobin.[15]

This molecular complexity of proteinic objects (huge number of atoms, intricacy of the folded structure, size of the conformational space) helps us understanding the epistemological situation of theoretical approaches in protein chemistry during the 1960s and 1970s. If, in order to grasp and deal with the complexity of the structures experimentally produced, some theoretical approaches were needed, and called for

[15] See Kendrew et al. (1960) and Perutz et al. (1960). Concerning the complexity of the structure, Kendrew wrote: "Perhaps the most remarkable features of the molecule are its complexity and its lack of symmetry. The arrangement seems to be almost totally lacking in the kind of regularities which one instinctively anticipates, and it is more complicated than has been predicted by any theory of protein structure" (Kendrew et al. 1958, p. 665). On the works of Perutz and Kendrew, see de Chadarevian (2002) and Debru (1983).

by scientists, the theory that *in principle* governs the properties of proteins, just as for any other molecular objects, was nevertheless not applicable *in practice* because of computational intractability. As shown by philosophers and historians interested in the question of the possible reduction of chemistry to physics, or more simply in quantum chemistry, the application of quantum mechanics to molecular systems has always been problematic and has led to increasingly complex and laborious computations.[16] That explains the central character of computers in the culture and practices of quantum chemistry after World War II. As quantum theory was already very difficult to apply to molecular systems of three, five or ten atoms, its use, even in conjunction with the specific theoretical descriptions and computational procedures developed between approximately 1930 and 1960 in quantum chemistry,[17] was clearly seen, by scientists, as definitively impracticable for proteins.

So, as for the situation in population biology described by Levins, there is a tension in protein chemistry between the complexity of the system under study *and* the limitations of scientists (the fact, here, that they are not computationally omnipotent). This tension has then led to the necessary development of a special modeling procedure, which doesn't use, at least directly, the theoretical formulations of quantum mechanics. Within this particular and constrained theoretical context, the impracticable approach (equivalent to the brute force approach criticized by Levins) is, more clearly than in the case of population biology, a (brute force) *theoretical application*. The modeling procedure devised by protein scientists is then an alternative approach, set up for allowing the construction of computationally manageable models.

Before the 1960s, a relatively long tradition of modeling structure and possible conformations of proteins already existed, but it was, within this tradition, *material* molecular models that were constructed (as for example by the famous chemist Linus Pauling).[18] Although material models were still used in the 1960s and 1970s, notably for representing the structures obtained by processing and interpreting X-rays experimental data,[19] practices of *theoretical* modeling also emerge during the 1960s. It is within such practices that the modeling procedure I am interested in has been developed.

As for all processes of emergence of a scientific practice, several factors can be put forward to understand this specific one. I will only mention here the scientists' epistemic aims that led to such an emergence. From the scientists' point of view, as noted above, the first need was the development of tools to analyze the great intricacy of the first structures experimentally obtained, and to test and refine the

[16] See in particular Scerri and McIntyre (1997), Schweber and Wächter (2000), and Park (2009, 2003).

[17] On these theoretical descriptions, which use various approximations, and these computational procedures developed in quantum chemistry, see for example Park (2009, 2003), Ramsey (2000, 1997) and Simoes (2003).

[18] See Francoeur (1997, 2001) for an historical analysis of material molecular models in chemistry (including protein chemistry).

[19] See de Chadarevian (2004).

structures that were constructed by processing and interpreting X-rays data: a very difficult task.[20] But, secondly, there was also a hope: if sufficiently good theoretical models of proteins could be devised on the basis of structural experimental data already obtained, then it would be possible, by exploring the conformational space of these macromolecules, to predict the native conformation of proteins – seen as the active one in cells – on the unique basis of a knowledge of their amino acids sequence. This would have potentially led to avoid the really laborious work to experimentally determine the three-dimensional structure of proteins. Moreover, this specific epistemic aim fitted in with the then current agenda of Molecular Biology.[21] Molecular Biology was interested, within the so-called "central dogma", in an understanding of genetic information flow from the one-dimensional structure of DNA (the sequence of bases) to the three-dimensional structure of proteins. The problem of predicting the 3-D structure of a protein from the knowledge of his sequence is known as the "protein folding problem",[22] a typically hot question for Molecular Biology in the 1960s and 1970s, and still today within structural genomics.

11.4 "Empirical Models" of Proteins: Status of the Procedure of Modeling and Resources for Its Construction

So far, we have seen what epistemic aims led scientists to construct theoretical models of protein conformations. But what resources could they exploit for such a construction? As noted above, since the use of theoretical formulations from quantum mechanics lead to non-manageable equations, even with the introduction of

[20] The construction of a three-dimensional structure of a molecule from X-rays data is a difficult work. Notably, the electronic density distribution of the molecule is calculated from the diffraction pattern, the electronic density distribution is then represented on electronic density maps, and a three-dimensional model of the molecule is constructed by using these maps. Thus, the structure proposed is the result of a complex analysis of X-rays data. When such a structure has been constructed, scientists try to test it, notably against stereochemical rules already adopted by the community. These tests lead to a refinement of the structure proposed. The modeling procedure I am interested in has been used in order to test and refine the structures proposed for various proteins. Others methods have also been used. For precisions concerning (the complexity of) X-rays data analysis, and structure refinement, see Perutz (1964), de Chadarevian (2002) Chapter 4, and de Chadarevian (2004).

[21] As Kendrew wrote in his Nobel lecture: "The geneticists now believe – though the point is not yet rigorously proved – that the hereditary material determines only the amino acid sequence of a protein, not its three-dimensional structure. That is to say, the polypeptide chain, once synthesized, should be capable of folding itself up without being provided with additional information; this capacity has, in fact, recently been demonstrated by Anfinsen *in vitro* for one protein, namely ribonuclease. If the postulate is true it follows that one should be able to predict the three dimensional structure of a protein from a knowledge of its amino acid sequence alone" (Kendrew 1964, pp. 676–98).

[22] The protein folding problem is called a problem because proteins have so many degrees of freedom; remember the size of the conformational space.

the approximations developed in quantum chemistry methods of ab initio or semi-empirical calculations, protein scientists have to find other theoretical resources. As the goal of constructing models of proteins was to gain knowledge of protein's conformations stability, protein scientists used a very simple theoretical formulation that has been proposed at the end of the 1940s,[23] and has been mainly used during the second half of the 1950s,[24] in order to understand the stereochemistry of organic compounds within the field of physical organic chemistry. It is not the place here to precisely discuss the origins, uses, transformations according to different contexts and the diffusion of this theoretical formulation.[25] This formulation stems notably from some attempts to interpret infrared spectra of (organic) molecules[26] and has been used, as already noted, in organic stereochemistry as well as in polymer chemistry. It seems more interesting, for the purpose of the present chapter, to write down this formulation in order to understand the characteristics exhibited by the models of molecules based on it.

The formulation defines a potential energy for a molecule for every set of positions of the atoms, that is for every conformation, as follows:

$$\mathrm{E} = \Sigma \left(u_0 (r_0/r)^{12} - 2u_0 (r_0/r)^6 \right) + \Sigma \tfrac{1}{2} k_s (l - l_0)^2 + \Sigma \tfrac{1}{2} \mathrm{k_b} (\theta - \theta_0)^2$$

where l is a chemical bond distance, θ a bond angle, k_s and k_b are force constants, l_0 and θ_0 are equilibrium values of the bond length and angle, r is the distance between two interacting atoms, and $-u_0$ is the minimum value of the interaction energy (at $r = r_0$). The sum, for the first term, is made over all pairs of non-bonded atoms. For the second and third terms, the sums are made, respectively, over all pairs of bonded atoms and over all bond angles.

So, this simple formulation, at the heart of the models of protein that were constructed, involves a particular representation of matter: molecules are constituted of valence-bonded 'atoms' (and not of nucleus and electrons as in quantum mechanics), and are roughly speaking represented by a system of balls connected by springs. This particular idealization shows that the question of the very accuracy of the representation offered by that type of protein models is not a priority for scientists. They obviously know that this representation is not accurate, but they adopt it precisely because it is useful, because it is the unique representation at hand that can lead to computationally manageable models, but, also, because it is a representation which is consistent with a classical conception of molecules, as conveyed, for example, by material molecular models and by some analysis of molecular vibrations. For scientists, the models constructed on the basis of this formulation use a relatively usual idealization in chemistry. The representation they offer is then acceptable but not

[23] See Hill (1946) and Westheimer (1947).

[24] See Westheimer (1956).

[25] For details, see Wieber (2005), Chapters 6 and 7.

[26] See for example the pioneering works of physical chemist Bjerrum, as described by Assmus (1992), and the subsequent works of Wilson et al. (1955).

accurate. Thus, the validity of the models can only be above all pragmatic: it will only be possible, for scientists, to test their validity by using these models and by comparing, then, the predictions obtained with known and accepted empirical data.

We can then see, here, that the modeling strategy devised by protein scientists sacrifices the realism of the representation of molecules (i.e. the "representational accuracy" of models) to computational imperatives. But scientists hope that if sufficiently good parameters were used, the predictions obtained would be reasonably accurate. If the models constructed on the basis of this simple theoretical formulation are not realists, in the sense of "representational accuracy", they could nevertheless "numerically describe", with sufficient accuracy, the structural properties of proteins. These models of protein structure could then be viewed as being realists in the sense of "predictive accuracy". The double meaning of Levins' "realism" ("representational accuracy" *or* "predictive accuracy") is here particularly manifest, because, in this context, a well-confirmed theory, with a precise ontology, governs the systems of interest but cannot be applied to these systems. So, because the manageable models that can be constructed use another ontology, they lack "representational accuracy". But scientists hope that these models could nevertheless offer accurate predictions, that they will have a good "predictive accuracy".

There is a second interesting and, for scientists, fundamental characteristic of the simple theoretical formulation used within the modeling strategy. In order to construct a model of a particular protein (the theoretical formulation is obviously not, by itself, a model of protein), one has inevitably to fix the values of parameters appearing in the theoretical formulation, for all pairs of non-bonded atoms, for all pairs of bonded atoms and for all bond angles. And the number of parameters is really important, because a protein is made of different types of atoms and of chemical bonds. As the parameters used are *empirical parameters*, we have thus to note here, firstly, that this modeling procedure is called by scientists "empirical modeling", and, secondly and more importantly, that the strategy of using this modeling procedure is very dependent on the availability of the empirical data required. We recognize, here, the problem of the measurement of a great number of parameters that Levins has stressed when discussing the brute force approach in population biology.

For protein models, as well as for models of other organic molecules, different types of empirical data are needed: infrared spectroscopic data, crystallographic data, thermodynamic data *etc.*. . . Thus, scientists who want to construct a model for a particular molecule must find, one the one hand, what data are available for that molecule, and choose, and the other hand, which values of data it seems preferable to use when different values are available for one type of data. Of course, all the data needed are never at hand for the particular molecule of interest, and they are then estimated and adjusted, by some kind of theoretical tinkering, to the specific case of that particular molecule of interest, from the data available for other molecules. It is important here to stress that such modeling practice of molecular objects couldn't have been developed without the revolution of physical instrumentation in chemistry

since the 1930s.[27] But it is equally necessary to remind here the complexity of proteinic objects. Since these objects are constituted of a huge number of atoms, the use of physical instrumentation to obtain typical data for these molecules was very difficult; hence the amount of data necessary to parameterize a model of protein was really thin. The work of estimating and adjusting empirical data was thus more extensive in protein chemistry than in organic chemistry, where more data were available, because smaller molecules are studied. To conclude this point, we can stress that for constructing models of molecules within this modeling strategy, scientists had to exploit creatively, within a practice of theoretical tinkering, some empirical resources. The parameterization is the central stage in the procedure of modeling, and it demands a good knowledge of empirical results for such or such type of molecule, and specific skills to make and justify the choices and adjustments of data.[28] Finally, different research teams made these choices locally, and different sets of parameters have been constructed during the 1960s, in organic chemistry as well as in protein chemistry.[29] Scientists speak of a "force field" for a set of parameters and equations, because a parameterized equation describes the potential energy for a molecule.

I turn now to the third resource that protein scientists used when constructing their "empirical models". This third resource is a technological one, namely computers. So, if a protein scientist has made the choice of using the theoretical formulation we have seen above, and has constructed a model for a molecule by choosing, estimating, adapting, adjusting different types of empirical data, he can now use this model to study the stability of some conformations or to refine (by minimizing the potential energy of the molecule) the structure proposed when interpreting X-rays patterns. But to do all that, it is necessary to calculate the potential energy of one or several conformations. When the modeling strategy was used in organic chemistry in the 1950s without the help of computers, the task of calculating all the chemical bonds geometries and energies and all the interactions between all pairs of non-bonded atoms was still complex and really laborious. But a pencil and paper application of the method to bigger organic molecules and a fortiori to proteins was

[27] On the transformations in chemistry induced by the spreading of physical instrumentation, see Morris and Travis (2003).

[28] Choosing and adjusting empirical data in order to construct a set of parameters demands a good knowledge of empirical results in chemistry, a good appreciation of the validity of such or such empirical technique for measuring such or such property of such and such molecule, as well as analogical reasoning and extrapolations in order to decide, for example, how to construct a particular parameter concerning an interaction between two "atoms" within a particular molecule from the empirical value of that interaction between this two same (or chemically similar) "atoms" in another molecule.

[29] For details about the situation at the end of the 1960s, and references, see the review of Williams et al. (1968) for organic chemistry, and the review of Scheraga (1968) for protein chemistry. During the 1970s, sets of parameters continued to be developed and refined. For references, see Wieber (2005), Chapters 6 and 7.

out of reach.[30] The development and spread out of that type of modeling practices in protein chemistry (and more generally in chemistry) has thus been fully dependent of the use of computers. These practices would not have been efficient if these technological instruments of computation had not been available.

But if computers were needed for that efficiency, the use of these calculating machines altered modeling practices in turn. So, to define precisely the characteristics of each atom inside a protein according to their molecular surrounding, scientists were able to use an increasingly large number of parameters stored in databanks, which the computer program could access quickly. A mode of calculation based on pencil and paper would not have allowed such increase in the number of parameters used for modeling, because it would not have been manageable. And with this greater number of parameters quickly accessible, models of more and more proteins could then be conveniently constructed and used. Finally, the computational nature of the modeling practices has also allowed a type of crystallization and spreading of the choices made locally concerning the empirical parameters, and more generally a stabilization of the modeling procedure, thanks to the construction and dissemination of computer programs packages.[31]

This partial black-boxing as computer software of this procedure seems fundamental in order to understand its increasing stability. With the construction and dissemination of these computer programs packages integrating the procedure of modeling, the community of its users has been broadened. In this process, the theoretical tools constructed have been integrated, thanks to their computational nature, to the classical toolbox used by experimenters for processing and interpreting empirical data of molecular structure. The procedure of modeling has then participated to the production of more and more experimental results. In this sense, many experimental results depend, today, on this procedure. Following Wimsatt (2007), it seems then possible to consider that the procedure of modeling has gained in stability by being "generatively entrenched".[32]

We can now conclude on this strategy of modeling in protein chemistry by discussing the status of the procedure of modeling, the properties of the models devised within this strategy, and the fundamental character of the *computational* nature of these models. As we have seen, these models don't offer "representational accuracy" because they are not constructed by applying the theory that governs protein properties. As an application of this theory is not possible in practice, scientists sacrifice

[30] Hendrickson (1961) constitutes the first *computational* application of this procedure of modeling in organic chemistry. For proteins, the development of this modeling procedure has always been computational; see for example Scott and Scheraga (1966).

[31] For modeling proteins (and more generally biological macromolecules and even organic molecules), three main packages were developed during the 1970s, by three different research teams: see Momany et al. (1975), Weiner and Kollman (1981), and Brooks et al. (1983). Packages specifically dedicated to modeling organic molecules were also developed during the 1970s.

[32] Wimsatt (2007) defines "generative entrenchment" in this way: "A deeply generatively entrenched feature of a structure is one that has many other things depending on it because it has played a role in generating them" (pp. 133–134).

deliberately this type of accuracy by choosing another theoretical formulation, which is applicable to the systems of interest and could conduct to relatively accurate predictions. If this choice of theoretical formulation impacts the status of the models constructed by defining what kind of realism they will hold, it has equally interesting consequences concerning the generality of the models and of the procedure of modeling. Thus, this choice of theoretical formulation leads to a lot of empirical parameters. But the parameters used with success for modeling one particular molecule cannot be used, strictly speaking, to construct a model for another molecule: each parameterized term in the formulation has no real meaning in itself, and only global numerical results obtained when applying the whole parameterized formulation can have a real meaning if they are accurate, that is if they are considered as good predictions. So, the parameters chosen, estimated and adjusted for one protein, within a practice of theoretical tinkering, are theoretically not transferable for another one. In that respect, the models constructed within this procedure of modeling greatly lack generality. But this is not the whole story. As the procedure would not be useful if it was necessary to reconstruct, each time, for each new protein, the parameters, a hypothesis of transferability is made.[33] With such hypothesis, a gain in generality is obtained, not for each model constructed, but for the procedure of modeling. However, the in practice transferability of each parameters has to be shown pragmatically by using these parameters for constructing more and more models of different proteins and by testing against empirical results the outputs obtained with these models. The computerization of the procedure of modeling is then really fundamental: with more and more models constructed and effective calculations executed, scientists have been able to increasingly test the results produced against empirical data in order to *iteratively optimize* the parameters chosen for modeling. Moreover, a large number of different parameters, suitable for more and more types of molecules, have been stored in computer programs, as indicated above. So, the use of computers has allowed an increase in generality of the "force fields" elaborated, and the construction of models that scientists consider as more trustworthy. Nevertheless, the procedure of modeling is such that a "force field" is only validated by its usage, by the accurate predictions obtained for circumscribed families of molecules, and its generality is then inevitably limited. Scientists are then lead to perpetually refine the parameters stored in computer programs, and the choice of a particular "force field" depends on the type of molecule studied and on the question asked concerning this molecule.

11.5 Conclusion

As noted in introduction as well as in Section 11.2, robustness analysis emerges, in Levins' works, within a discussion concerning the constraints set on modeling practices by the specific epistemological context in population biology. These constraints

[33] On the question of the transferability of parameters, see Burkert and Allinger (1982, pp. 3–4).

have led to the development of three different modeling strategies, implying different tradeoffs. It is because Levins (1966) considers that all models have artificial assumptions, and that "there is always room to doubt whether a result depends on the essential of a model or on the details of simplifying assumptions" (p. 20), that a method becomes then necessary in order to judge the trustworthiness of a particular result obtained when using one particular model. Robustness analysis is precisely, for Levins, such a method: if a same result is obtained with several alternatives models using different assumptions and simplifications, this result can then be seen as trustworthy (i.e. robust). Thus, robustness analysis has to be understood as the final stage of an epistemological strategy where multiple alternative models of a same system are deliberately, and initially, constructed. Robustness analysis is based on the examination of the results produced when using these multiple alternative models, and constitutes the core of the strategy. We can speak of a heuristic procedure for this "robustness strategy", which is developed in order to take into account that all models have artificial assumptions.

This characteristic of models follows from the above-mentioned specific constraints of the epistemological context in population biology. It is because scientists face practical limitations with respect to what they can compute, measure and understand when modeling the complex systems of population biology that the models they construct entail simplifications and artificial assumptions, whose consequences are managed by using the heuristic strategy which includes robustness analysis. And if such a strategy is used, and a result said to be robust, we are then more confident with respect to the trustworthiness of the models that have led to this particular result. As Weisberg (2006b) considers, this method is then useful "(. . .) for determining which models make trustworthy predictions and which models can reliably be used in explanations" (p. 731).[34]

Wimsatt has expanded the notion of robustness to a broader set of procedures and contexts of use. When he speaks of robustness, a general scheme concerning the constitution of the solidity[35] of an entity, or a property, or a relation, or a proposition is used. As Soler points out in Chapter 1, Wimsatt's notion of robustness "(. . .) refers to the idea of the invariance of a result under multiple independent determinations". For Wimsatt, this scheme is conceived as being very general, and it can be used in different contexts in order to distinguish "(. . .) that which is regarded as ontologically and epistemologically trustworthy and valuable from that which is unreliable, ungeneralizable, worthless, and fleeting" (Wimsatt 1981, p. 128). Wimsatt considers that "a family of criteria and procedures" (Wimsatt 1981, p. 126), based on

[34] It seems interesting to note, here, that Weisberg (2006b) considers robustness analysis to be an important method in sciences where complex systems "(. . .) have yet to be described by comprehensive theories" (p. 731). When we construct models of a system which is governed by a well-developed theory, this theory "(. . .) could be used to determine how much distortion was introduced by each idealization [in each model]" (p. 731). As he puts it: "(. . .) theories have the resources to estimate the effect of various idealizations, providing guidance about what must be included when particular degrees of accuracy and precision are required" (p. 731).

[35] I use, here, the term "solidity", as introduced by Soler in Chapter 1.

this robustness scheme, are used to this end. He mentions a long list of such procedures, for example: "(a) using different sensory modalities to detect the same property or entity (…); (b) using different experimental procedures to verify the same empirical relationships or generate the same phenomenon […]; (c) using different assumptions, models, or axiomatizations to derive the same result or theorem (…)" (Wimsatt 1981, pp. 126–127). All these procedures can be called, for Wimsatt, "robustness analysis". Thus, when someone uses such a procedure, he or she analyzes what has been obtained with different (at least partially) independent derivations in order to establish if a robustness scheme could be find. If such a scheme is found, Wimsatt considers that we have more reasons, then, to judge the result as being reliable.

So, Wimsatt has proposed a fruitful generalization of the notion of robustness with respect to its more restricted sense in Levins' works. By delimiting a general robustness scheme, robustness analysis can then be extended to others procedures – notably to the "triangulation" of a same result by different empirical procedures – which was not discussed in the very specific context of modeling in population biology. Moreover, robustness analysis is then not only a procedure used by practicing scientists in order to judge the trustworthiness of their results and models, but it becomes also, for philosophers of science, an explicit scheme for describing the way scientists try to secure the results they produce and a good starting point for discussing scientists' judgments of robustness and possible bias in the methodologies and reasoning they have used for producing such or such result. Finally, if the notion of robustness is more general for Wimsatt, it seems equally that he uses the term "robustness" with multiple senses, exploiting then fully the resources offered by the most general form of that notion.[36]

We have seen that Levins' robustness analysis really makes sense within a strategy, which is developed because models have limitations imposed by a constrained epistemological context in biological modeling. Here again, Wimsatt generalizes this idea of robustness as an epistemological strategy, in the context of a conception of science within which the limited capacities of practicing scientists are fully recognized. Thus, the importance of robustness (and more generally of heuristic procedures) is linked, for Wimsatt, with the necessary recognition that the world is complex, that practicing scientists have limited capabilities and are fallible, that they are not omniscient and computationally omnipotent, and that the tools they

[36] In his recent review of Wimsatt (2007), Calcott (2011) distinguishes three kinds of robustness, each occurring in Wimsatt's book: robust theorems (in the sense of "robustness" conveyed by Levins' robustness analysis), robust detection (or triangulation, that is to say, the production of the same result by different and at least partially independent empirical procedures), and robust phenomena (in the sense that a system, a mechanism, is robust when it "continues to function reliably, despite perturbations or interventions", as Calcott wrote). So, the sense of "robustness" used by Wimsatt presents some kind of multiplicity, but behind that multiplicity, there is probably a common structure to all these kinds of robustness, as Calcott suggests and discusses.

use have limitations.[37] When we recognize this overall situation, when we resist "in principle" claims about the way science works, then robustness analysis really makes sense and becomes the core of an important strategy (among others).

The case study on modeling practices in protein chemistry I have presented and discussed is definitively linked with this picture of science interested by the limitations scientists encounter and the "in practice" strategies they have then to devise in order to study complex systems. Nevertheless, the strategy used by protein scientists to construct and stabilize their modeling procedure cannot be described by a robustness scheme. But before pointing out the particular scheme of construction and stabilization that emerges from my case study, it seems interesting to go back to Levins' analytical framework of modeling practices.

This framework, devised for analyzing different styles of theorizing in population biology, constitutes an interesting resource for discussing the modeling procedure developed in protein chemistry during the 1960s and 1970s and the characteristics of the models constructed when using it, by examining their realism, precision, and generality. As we have seen in Section 11.4, these models lack generality (even if the hypothesis of transferability of parameters and the use of computers have allowed an increase in generality of the *procedure* of modeling) as well as they lack realism (in the sense of "representational accuracy"). But scientists try to construct and use realist (in the sense of "predictive accuracy") and precise models (because the representation used to model the system of interest is precisely specified, with quantitative parameters). So, the strategy devised by protein scientists seems close to the first model building strategy discussed by Levins ("sacrifice generality to realism and precision"). Moreover, as it has been emphasized, the use of computers was indispensable for developing and using the protein modeling procedure set up within the chosen strategy, as it was also the case for the models of systems ecology, which exemplify, for Levins, the models constructed within the first strategy he discussed. Levins' analytical framework is then an interesting tool for characterizing the modeling strategy used by protein scientists. And such characterization is finally interesting because it leads us to contrast this strategy with the one defended by Levins, and to ask what made these two strategies fruitful and efficient strategies.

Robustness analysis is typically an argument showing the fruitfulness and efficiency of the type of qualitative modeling strategy Levins practiced, because it is a tool particularly well suited to this modeling strategy: with "very flexible models", multiple models of a same system can be constructed in a relatively easy way. Concerning the strategy devised by protein scientists, its fruitfulness is not associated with robustness analysis but with its stabilization, which cannot be described by using a general robustness scheme.

[37] See, for example, Wimsatt (2007), in particular the introduction and the epilogue, or Wimsatt (1981, pp. 151–153). It seems worth noting here that all scientific tools have, for Wimsatt, limitations. So, models have limitations (as Levins points out), as it is equally the case for our sensory modalities, our measurement apparatuses, etc. . .. Within such a generalized constrained epistemological context, the importance of "robustness strategy" is also generalized.

Here, we have to recognize how the *computational* nature of the procedure of modeling devised in protein chemistry has been fundamental in its stabilization, which has participated to the recognition, by scientists, that this procedure was efficient and fruitful. So, as I have tried to show, its computerization has allowed the construction of more and more models and the effectuation of more and more effective calculations. Scientists have then been able to increasingly test the results produced against empirical data in order to iteratively optimize the parameters chosen for modeling. With such a computational optimization of parameters, and with the large numbers of parameters stored in computer databanks and quickly accessible by the computer program, the procedure of modeling has gained a (limited) *generality*, which seems have been important in its stabilization and in the widest recognition of its relevance. After all, it is possible to consider that this procedure has acquired stability within a process of mutual and iterative adjustment of theoretical, empirical and computational constraints, because the three kinds of limited resource protein scientists have used for devising the procedure of modeling were mutually dependent, and limited: computational limitations has led to the adoption of a theoretical formulation which requires to fix, within a practice of theoretical tinkering (necessary because the amount of data necessary to parameterize a model of protein is thin), the values of a lot of empirical parameters which are then computationally optimized. . . But if an adjustment of these different constraints has been fundamental for the constitution of a stable procedure of modeling protein structural properties, the partial black-boxing as computer software of this procedure has also, as we have seen, increased its stabilization: the dissemination of computer programs packages integrating this procedure has broadened the community of its users.

Here again, we can emphasize that the computational nature of these modeling tools is obviously important. More generally, the technological characteristics of computers – the way they function, the limitations of their processing power, their accessibility for scientists – have a great impact on the evolving epistemic status of that kind of modeling practices, which have led to the emergence of what has been considered, by scientists, as a theoretical knowledge about proteins structure and stability.

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References

Assmus, A. 1992. “The Molecular Tradition in Early Quantum Theory.” *Historical Studies in the Physical and Biological Sciences* 22:209–31.

Brooks, B.R., R.E. Bruccoleri, B.D. Olafson, D.J. States, S. Swaminathan, and M. Karplus. 1983. “CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations.” *Journal of Computational Chemistry* 4:187–217.

Burkert, U., and N.L. Allinger. 1982. *Molecular Mechanics*. Washington, DC: American Chemical Society.

Calcott, B. 2011. “Wimsatt and the Robustness Family: Review of Wimsatt’s Re-engineering Philosophy for Limited Beings.” *Biology and Philosophy* 26:281–93.

Debru, C. 1983. *L'Esprit des Protéines*. Paris: Hermann.
De Chadarevian, S. 2002. *Designs for Life. Molecular Biology After World War II*. Cambridge: Cambridge University Press.
De Chadarevian, S. 2004. "Models and the Making of Molecular Biology." In *Models. The Third Dimension of Science*, edited by S. de Chadarevian and N. Hopwood, 339–68. Stanford: Stanford University Press.
Francoeur, E. 1997. "The Forgotten Tool: The Design and Use of Molecular Models." *Social Studies of Science* 27:7–40.
Francoeur, E. 2001. "Molecular Models and the Articulation of Structural Constraints in Chemistry." In *Tools and Modes of Representation in the Laboratory Sciences (Boston Studies in the Philosophy of Science, Volume 222)*, edited by U. Klein, 95–116. Dordrecht: Kluwer.
Hendrickson, J.B. 1961. "Molecular Geometry. I. Machine Computation of the Common Rings." *Journal of the American Chemical Society* 83:4537–47.
Hill, T.L. 1946. "On Steric Effects." *Journal of Chemical Physics* 14:465.
Kendrew, J.C. 1964. "Myoglobin and the Structure of Proteins. Nobel Lecture, December 11, 1962." In *Nobel Lectures, Chemistry 1942–1962*, 676–98. Amsterdam: Elsevier.
Kendrew, J.C., G. Bodo, H.M. Dintzis, R.G. Parrish, H.W. Wyckoff, and D.C. Phihips. 1958. "A Three-Dimensional Model of the Myoglobin Molecule Obtained by X-Ray Analysis." *Nature* 181:662–6.
Kendrew, J.C., R.E. Dickerson, B.E. Strandberg, R.G. Hart, D.R. Davies, D.C. Phillips, and V.C. Shore. 1960. "Structure of Myoglobin: A Three-Dimensional Fourier Synthesis at 2 Å resolution." *Nature* 185:422–7.
Levins, R. 1966. "The Strategy of Model Building in Population Biology." Reprinted in *Conceptual Issues in Evolutionary Biology*, 1st ed. (1984), edited by E. Sober, 18–27. Cambridge: MIT Press.
Levins, R. 1968. *Evolution in Changing Environments*. Princeton, NJ: Princeton University Press.
Matthewson, J., and M. Weisberg. 2009. "The Structure of Tradeoffs in Model Building." *Synthese* 170:169–90.
Momany, F.A., R.F. McGuire, A.W. Burgess, and H.A. Scheraga. 1975. "Energy Parameters in Polypeptides. VII. Geometric Parameters, Partial Atomic Charges, Nonbonded Interactions, Hydrogen Bond Interactions, and Intrinsic Torsional Potentials for the Naturally Occurring Amino Acids." *Journal of Physical Chemistry* 79:2361–81.
Morris, P.J.T., and A.S. Travis. 2003. "The Role of Physical Instrumentation in Structural Organic Chemistry." In *Companion to Science in the Twentieth Century*, edited by J. Krige and D. Pestre, 715–40. Londres: Routledge.
Odenbaugh, J. 2006. "The Strategy of 'The Strategy of Model Building in Population Biology'." *Biology and Philosophy* 21:607–21.
Park, B.S. 2003. "The 'Hyperbola of Quantum Chemistry': The Changing Practice and Identity of a Scientific Discipline in the Early Years of Electronic Digital Computers, 1945–65." *Annals of Science* 60:219–47.
Park, B.S. 2009. "Between Accuracy and Manageability: Computational Imperatives in Quantum Chemistry." *Historical Studies in the Natural Sciences* 39:32–62.
Perutz, M. 1964. "X-Ray Analysis of Haemoglobin. Nobel Lecture, December 11, 1962." In *Nobel Lectures, Chemistry 1942–1962*, 653–73. Amsterdam: Elsevier.
Perutz, M.F., M.G. Rossmann, A.F. Cullis, H. Muirhead, G. Will, and A.C.T. North. 1960. "Structure of Haemoglobin. A Three-Dimensional Fourier Synthesis at 5,5 Å Resolution, Obtained by X-Ray Analysis." *Nature* 185:416–22.
Ramsey, J.L. 1997. "Between the Fundamental and the Phenomenological: The Challenge of 'Semi-Empirical' Methods." *Philosophy of Science* 64:627–53.
Ramsey, J.L. 2000. "Of Parameters and Principles: Producing Theory in Twentieth Century Physics and Chemistry." *Studies in History and Philosophy of Modern Physics* 31:549–67.
Scerri, E.R., and L. McIntyre. 1997. "The Case for the Philosophy of Chemistry." *Synthese* 111:213–32.

Scheraga, H.A. 1968. “Calculations of Conformations of Polypeptides.” *Advances in Physical Organic Chemistry* 6:103–84.

Schweber, S., and M. Wächter. 2000. “Complex Systems, Modelling and Simulation.” *Studies in History and Philosophy of Modern Physics* 31:583–609.

Scott, R.A., and H.A. Scheraga. 1966. “Conformational Analysis of Macromolecules. III. Helical Structures of Polyglycine and Poly-L-Alanine.” *Journal of Chemical Physics* 45:2091–101.

Simoes, A. 2003. “Chemical Physics and Quantum Chemistry in the Twentieth Century.” In *The Cambridge History of Science, vol. V. The Modern Physical and Mathematical Sciences*, edited by M.J. Nye, 394–412. Cambridge: Cambridge University Press.

Weiner, P.K., and P.A. Kollman. 1981. “AMBER: Assisted Model Building with Energy Refinement. A General Program for Modeling Molecules and Their Interactions.” *Journal of Computational Chemistry* 2:287–303.

Weisberg, M. 2006a. “Forty Years of ‘The Strategy’: Levins on Model Building and Idealization.” *Biology and Philosophy* 21:623–45.

Weisberg, M. 2006b. “Robustness Analysis.” *Philosophy of Science* 73:730–42.

Westheimer, F.H. 1947. “A Calculation of the Energy of Activation for the Racemization of 2,2′-Dibromo-4,4′-Dicarboxydiphenyl.” *Journal of Chemical Physics* 15:252–60.

Westheimer, F.H. 1956. “Calculation of the Magnitude of Steric Effects.” In *Steric Effects in Organic Chemistry*, edited by M.S. Newman, 523–55. New York: Wiley.

Wieber, F. 2005. “Construction et Applicabilité Théoriques en Chimie des Proteins (1960–1990). Essai Epistémologique et Historique.” PhD thesis, Paris: Paris Diderot University.

Williams, J.E., P.J. Stang, and P. von R. Schleyer. 1968. “Physical Organic Chemistry: Quantitative Conformational Analysis; Calculation Methods.” *Annual Review of Physical Chemistry* 19:531–58.

Wilson, Jr. E.B., J.C. Decius, and P.C. Cross. 1955. *Molecular Vibrations. The Theory of Infrared and Raman Vibrational Spectra*. New York: McGraw-Hill.

Wimsatt, W.C. 1981. “Robustness, Reliability, and Overdetermination.” In *Scientific Inquiry and the Social Sciences*, edited by M.B. Brewer and B.E. Collins, 124–63. San Francisco, CA: Jossey-Bass.

Wimsatt, W.C. 1994. “The Ontology of Complex Systems: Levels of Organization, Perspectives, and Causal Thickets.” In *Biology and Society: Reflections on Methodology, Canadian Journal of Philosophy*, Supplementary Vol. 20, edited by M. Matthen and R. Ware, 207–74.

Wimsatt, W.C. 2001. “Richard Levins as Philosophical Revolutionary.” *Biology and Philosophy* 16:103–8.

Wimsatt, W.C. 2007. *Re-Engineering Philosophy for Limited Beings. Piecewise Approximations to Reality*. Cambridge: Harvard University Press.