HPLS (2015) 36(3):321–334
DOI 10.1007/s40656-014-0049-3

ORIGINAL PAPER

Preparations, models, and simulations

Hans-Jörg Rheinberger

Received: 30 August 2014 / Accepted: 9 September 2014 / Published online: 23 December 2014

Abstract This paper proposes an outline for a typology of the different forms that scientific objects can take in the life sciences. The first section discusses preparations (or specimens)—a form of scientific object that accompanied the development of modern biology in different guises from the seventeenth century to the present: as anatomical–morphological specimens, as microscopic cuts, and as biochemical preparations. In the second section, the characteristics of models in biology are discussed. They became prominent from the end of the nineteenth century onwards. Some remarks on the role of simulations—characterising the life sciences of the turn from the twentieth to the twenty-first century—conclude the paper.

Keywords Preparations · Models · Simulations · Virtual experimentation · Structure–function

For Christiane, curatress, amongst many other things, of specimens.

The following thoughts on preparations and other scientific objects such as models and simulations take their starting point from the sentences with which Gilles Deleuze opened his dissertation (1968, p. 11):

> Difference and repetition have taken the place of the identical and the negative, of identity and contradiction. For difference implies the negative and therefore leads to contradiction to the extent only that its subordination under the identical is maintained. The primacy of identity, however conceived, defines the world of representation. But modern thought is born out of the shattering of representation; out of the loss of identities and of the discovery of all those forces that act beneath the representation of the identical.

H.-J. Rheinberger (✉)
Max Planck Institute for the History of Science, Boltzmannstr. 22, 14195 Berlin, Germany
e-mail: rheinbg@mpiwg-berlin.mpg.de

Like so many others, including Jacques Derrida, Deleuze had passed through the school of historian of biology Georges Canguilhem. That it took a quarter of a century until this book appeared in German (1992) and English (1995) is certainly not due to its lack of substance, but rather a symptom of the fact that translation in the realm of the humanities between France, Britain, and Germany in the second half of the twentieth century, despite the formation of the European Union, has become something of a game of dice. If we compare this situation with the time around 1900, one is surprised that there was a not too distant time in which this was substantially different.

What reads like a sign of the times was, and is, a starting point for me to think about the constitution of scientific objects. If one decides not to do that within the logical sphere of identity and contradiction, but in the praxeological sphere of repetition and difference, then aspects of the process of the formation of knowledge become graspable that allow us to move in the space of just those forces that "act beneath the representation of the identical," as Deleuze expressed it. This is exactly the space in which the objects of science take shape. On the one hand they are leaning toward repetition, but on the other hand they are of epistemic relevance only as long as they allow for the emergence of difference. Thus, difference and repetition are mutually dependent upon each other. They are always concerned with the formation and configuration of similes, but they can acquire very different contours over the course of time.

In what follows, I would like to deal in some detail with three classes of epistemic objects.[1] In the language of the sciences, they come under the labels of preparation (or specimen), model, and simulation. They each exhibit and carry their own specific forms of repetition and differentiation. They are by no means reducible to each other and are therefore in need of closer inspection; and they have their own peculiar histories in the different scientific disciplines. Above all, however, they are closely interwoven with the technologies to which the objects in question owe their formation. I would like to stress in particular that the relationship between scientific objects and the tools of their processing, manipulation, and development is not an exterior and purely instrumental one, but is, rather, constitutive for the objects in question. Constitutivity thereby runs in both directions. Whilst object and rendering technology do not *produce* each other, they could be said to *provoke* each other. The examples which I would like to use to develop my reflections and thus to form and gain a concept of preparation, model, and simulation, respectively, are taken from the realm of the history of the life sciences. There is a simple reason for this: familiarity. But I think that the message holds true for a much wider range of the empirically oriented sciences.

There is one more thing that should be stated in advance: the perspective taken here on preparations, models, and simulations is that of the production of data, for it is from this perspective that the specific differences between them are best made visible. Elsewhere I have shown in more detail that typically, what comes first in an experiment is the creation of traces; they are the immediate product of the means and media of investigation that are brought into play. As the starting points of the

[1] For a German version of this paper see Rheinberger (in press).

experimental semiosis in the spaces of the infra-experimental, they are, however, generally of a volatile nature. Therefore, they have to be made durable, in one way or another, if they are to serve as what we are used to calling data (Rheinberger 2007a, b). Data, in turn, are then integrated into objects of knowledge (Rheinberger 2011). There are multiple ways in which this can happen. The typology that will be presented here proceeds from this perspective.

1 Preparations

Let us begin with a consideration of preparations. Preparations can be described as self-configured traces made durable. In the case of preparations, the traces participate in, are part of, the very materiality of the object under scrutiny, and they rely on some of their physical, chemical, or biological properties for their configuration. They stick, so to speak, to the object. With that, they exhibit at the same time a particular indexicality: we could say they point at themselves. They are renderings, not representations. They are manifestations of facts of the matter that are subject to the game of repetition and difference in a rather specific manner.

I will not here characterise anatomical preparations, nor microscopical, nor biochemical forms of preparation, as has been done in some detail in a couple of earlier papers (Rheinberger 2006, chap. 12; see also 2003). Instead, I will concentrate in an exemplary fashion on a form of micro-preparation that played a crucial role in the development of molecular genetics and that is of particular interest here. In contrast to anatomical, microscopical, or biochemical preparations it could be described as, paradoxically formulated, a living preparation: a bacterial culture in a petri dish. As a living preparation, it carries with it a very particular form of visualisation. Preparations of this kind bring about a macroscopic rendering of the presence of viruses, submicroscopic particles whose structure otherwise can only be made visible, to a certain extent, by the electron microscope. A simple principle of visualisation comes into play here that is characteristic for many forms of technical enhancement in scientific work, both observational and experimental. It reads: what is too small for investigation must be enlarged. Elsewhere, I have called this the principle of "dilatation" (Rheinberger 2009). The reverse, of course, also holds true: what is too big must be downsized according to a principle of "compression" or "condensation".

There is more than the visualisation of molecules at stake here, however. It is also and essentially a visualisation of *variants* of molecules. The principle is as follows: bacteriophages can be regarded as genetic packages that in order to multiply have to enter bacteria. There they induce the genetic apparatus of the bacterial cell to occupy itself with the procreation of the molecular parasite, instead of its own genome. The bacterium fills with virus particles until it bursts. The phages thus freed can then enter neighbouring bacterial cells, and the cycle is repeated. If one now spreads appropriately diluted virus particles on a bacterial lawn grown in a Petri dish, the phages do their work and thus form holes in the bacterial lawn, so-called plaques, at the very place where the multiplication of a single virus started. These holes can, according to particular variants of the virus, assume different

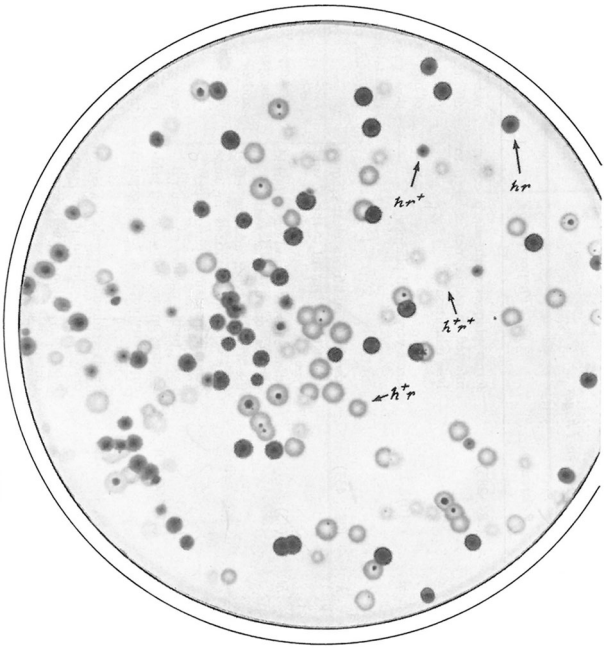

Fig. 1 Culture of *Escherichia coli* bacteria infected with phage T2 (Stent 1963, p. 185; also in Watson 1965, Figs. 7–18)

shadings, granulation, and fringes. The principle is shown in Fig. 1. On it one can distinguish four different genetic mutants of bacteriophage T2, the *Escherichia coli* phage on which the group around Max Delbrück at the California Institute of Technology in Pasadena specialized in the 1940s and 1950s. The picture is from a textbook on phages by molecular genetician Gunther Stent (1963, p. 185). Since only two different T2-phages—type hr and h^+r^+—were used in this experiment, the preparation additionally indicates that in the course of multiplication, genetic recombination had taken place. It results in the discrimination of four different plaques caused by the two types hr and h^+r^+ on the one hand, and the mixed types h^+r and hr^+ on the other.

This virus preparation thus embodies a rather complex knowledge about the genetic constitution and behaviour of bacterial viruses. But at the same time it is also a procedure for the identification of new, hitherto unknown mutants, by the identification and isolation of which the experimental process of genetic knowledge acquisition is driven forward. The existence of different genetic types of the virus is rendered visible by the characteristic structure of those parts of the bacterial lawn that have been devastated by the respective types. They are the result of an interaction between virus and bacterium as well as the interaction of viruses amongst each other. Here, I have only described the pattern produced by different types of virus. The representational arsenal of this kind of preparation—we could call it molecular-analytic—is, however, extended by the fact that bacteria with

different susceptibility, as well as bacterial mixtures, can also produce different effects. In this way, in the continuous iteration of the process, permanently new differences can be created that lead to new characterisations that in turn determine the ensuing iterative course of the experiments. This is, as it were, typical for productive experimental series and the rendering procedures that characterise them. They have, in principle, little in common with the traditional idea of representation as depiction. And yet, molecular processes that otherwise would defy all imagery, are rendered plainly visible in this way. The structural characteristics of visible contours and areas of spots, in the example just shown, come to stand for certain molecular processes—genetic recombination events.

2 Models

Another class of scientific objects that shall be briefly presented here are models. They play a particularly important role in many different sciences (Rheinberger 2010). A first general characteristic of models is that they presuppose a change of medium—this distinguishes them from preparations which, as we have seen, participate in the materiality of the object of knowledge in question, or in other words are a real configuration (*Realkonfiguration*) of it. In contrast, the model is located in a medium that is different from that of the research material on which it bears and with which it becomes connected.[2] With that, however, nothing is yet said about the medium of models. Here we observe a huge amount of variations. Biochemical models of partial reactions of biological processes can be seen as a boundary case. On the one hand, their medium is the test tube, not the organism, on the other hand they rely on materials derived from organisms. This example reminds us of the precariousness of any generalising typology. More straightforwardly, models can be purely schematic and realised essentially on paper. They can also take the form of material working models with which one tinkers. Today, computer models are ubiquitous in the laboratories of the world.

Let us concentrate on the straightforward cases. In a model, experimental data become interconnected. This is the second specificity of a model. Models are not only located in a different medium, they are, to use another expression, data configurations. In a model, data are connected more or less deliberately, they no longer configure themselves. If preparations can essentially be seen as self-configurations of traces, models constitutively presuppose the transition from traces to data. Data are traces made durable. This transition is connected with a change of medium. What models basically enable is an overview at one glance of a multiplicity of data and of how they interrelate. They thus form a scaffold that sensibly reacts as a whole if alterations in one of its parts are introduced. Through their connection they affect other points of the network of data, and thus the model. The questions that arise by tinkering with the data components of the model can

[2] In a recent research note, Hoffmann (2012) has argued that models should be regarded as the overarching genus. Preparations would therefore be "models in one's own material", classical models, accordingly, "models in another material."

themselves give rise to changes in an ongoing stream of the production of traces, and accordingly, of data. In this way, yet another loop of repetition and difference is established that consists of a permanent oscillation, from the model to the experiment, and from the experiment to the model. I do not of course claim to do justice to all forms and filiations of models in the sciences with this description, but I think that it gives us a good starting point. It will lead to further differentiations, one of which is the distinction between functional and structural models. Let me give an example of each of them here.

Both examples are derived from the history of protein synthesis research on which I will concentrate in the remainder of this paper. The functional model circles around the central enzymatic step by which polypeptides are formed in an orderly fashion from amino acids along a coding chain of ribonucleic acid. The basic features of the model acquired contours in the two decades between 1945 and 1965. It is a curiosity of these functional models that they essentially represent molecular-chemical processes as mechanisms. The biochemical aspects of the process—for instance the catalytic properties of the components of the ribosome, the organelle on which all this happens, and the energy transformations involved—thereby completely recede into the background. This becomes particularly visible when looking at the metallic, three-dimensional realisation of such a model (Fig. 2) as presented by Alexander Spirin at a symposium on protein synthesis in Cold Spring Harbor in 1969. This restriction, however, is at the same time the advantage of these models. On the basis of these fixations—frozen instances we might call them—predictions can be derived that in turn can be addressed experimentally, in the sense of the repetitive and differential circularity sketched above. The model thus serves as an indirect source for an iterative process of the generation of new traces and

Fig. 2 Mechanical model of a translating ribosome (Spirin 1969, Fig. 1 on p. 199)

their fixation as data that again can be interrogated in terms of their compatibility with the existing model. They can become incorporated into the model, modifying it at the same time, and so on. To serve this function, the model, as can be seen in this example, does not necessarily have to be 'realistic': in its concentration on a particular aspect of the process it may well display a thoroughly metaphorical character.

The functional analysis leading to these models historically went hand in hand with the identification of the molecular components making up the protein synthesis organelle. A proliferation of structural models ensued. Figure 3 shows an early protein model of the small subunit of the ribosomal particle. In this model the proteins of different molecular weight are represented by polystyrene balls of different sizes, numbered from 1 to 21, and connected by differently hatched and shaded bars. The bars stand for different experimental approaches to determine the neighbourhoods of the components: chemical cross-linking after the whole particle was soaked with a particular reagent; reconstitution dependencies arrived at through assembly in the test tube; protection from chemical interaction by stepwise in vitro assembly, and the like, thus defining what is side by side, what is inside, and what outside.

With models such as these, attempts were made to represent the *inner* constitution of the particle. Other efforts were undertaken to model its *outer* shape. Here the method of choice was transmission electron microscopy. Comparison, series formation, and superposition of images led to a number of competing three-

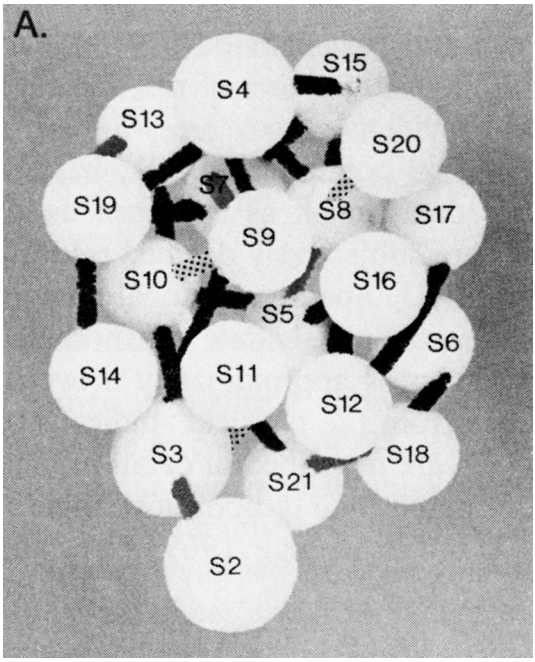

Fig. 3 Polystyrene ball model of the small ribosomal subunit (Traut et al. 1974, Fig. 1 on p. 273)

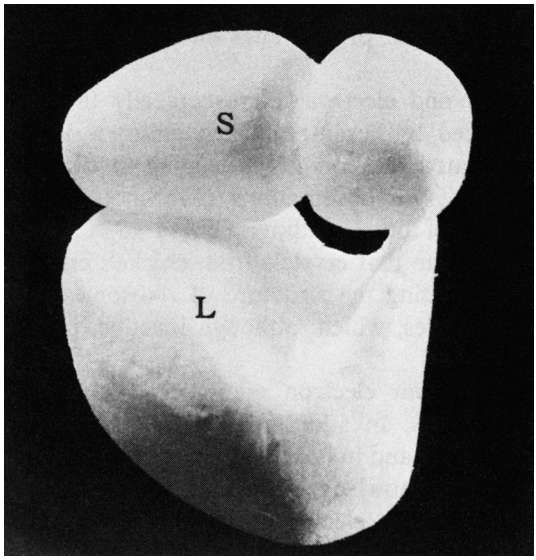

Fig. 4 Styrofoam model of both small and large ribosomal subunits in association (Lake et al. 1974, Fig. 1 on p. 544)

dimensional models, one of which, again made from polystyrene, is shown in the following figure with its clearly asymmetric subunits (Fig. 4).

With that, the two parameters are named that form the basis of these structural models: the external shape in three-dimensional space, and the internal articulation and positioning of the components with respect to each other—often addressed as quaternary structure. What is at stake here is the relation and arrangement between macromolecules that are already three-dimensional by themselves—a never-ending task given the number of more than fifty components in the whole particle. Consequently, this modeling process stretched over decades.

Finally, these different models, functional and structural, came to bear on each other. Figure 5 gives an example. Here, particular functional states of the active ribosome running through a synthesis cycle—to the left—are correlated with the corresponding positioning of messenger RNA at the interface between the two subunits—on the right.

We are at a point where we can sum up. In research processes like the historical example given here, there is not only a cyclical feedback between models and the production of data, but also a kind of second-order feedback, namely that between different models that rest on different data sets. The confrontation between models can reveal incongruities that in turn can lead to the production of new data, and to the further alignment and adjustment of models. Here we are less concerned with how a referent relates to its reference, where in the end one asks for its *meaning*, but rather with the relationship between different referents, where something—to make use of Gottlob Frege's (1966) distinction—rather makes, or does not make, *sense: Sinn* in German.

On the one hand, it seems that with models we clearly move in the world of representation, as Bas van Fraassen defines it, and as it is usually taken to be

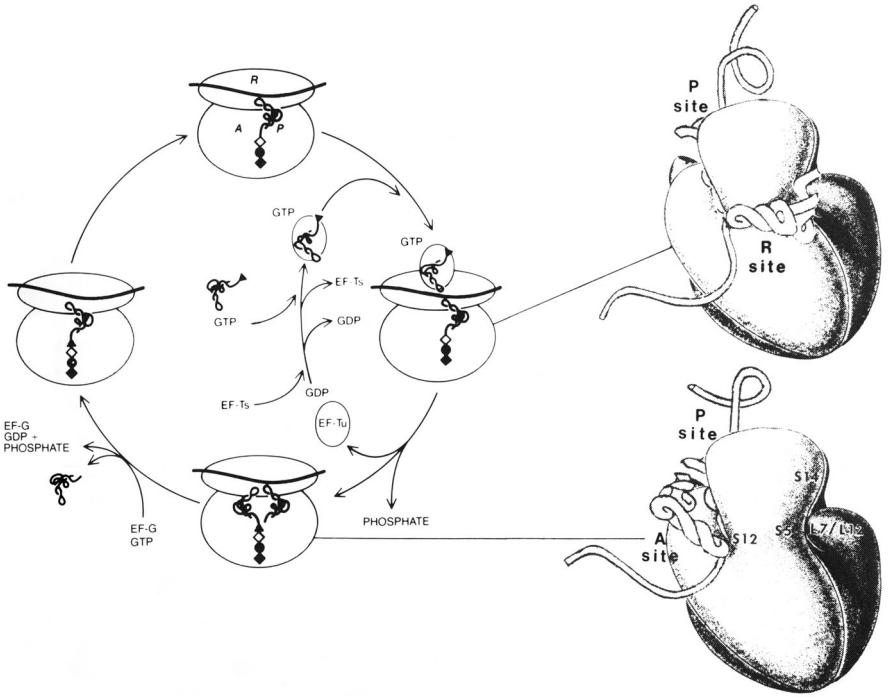

Fig. 5 Combination of functional and structural models of the ribosome (Oakes et al. 1986, Fig. 3.10 on p. 57)

characteristic for science as a whole. According to this definition, the representation of something means "the production of another object that intentionally refers to the former. Thereby a certain coding relation is assumed that determines what rightly counts as similar" (van Fraassen and Sigman 1993, p. 74). On the other hand, however, this seeming unambiguousness is permanently subverted in the process of modelling. Epistemically productive models live from and with the permanent failure of representation, the "shattering of representation" to come back to the words of Deleuze. They live from the fact that they leave something to be desired. "It appears," as Georges Canguilhem (1968, p. 313) once put it, "that in biology it is even harder than in physics to resist the temptation to ascribe to a model a value of representation." He continues, "It looks as if not only popularisers of science have the tendency to forget that a model is nothing else than its function. This function consists in imputing its own mechanism to another object without installing itself as the canon". In other words, the epistemic fertility of a model lies exactly in the maintenance of an irreducible difference between the model and the modelled, eventually doubled between that of a model to another model, differences that are inevitably due to the alleged media transition, regardless of whether the coding relation mentioned by van Fraassen is of an iconic or of a purely symbolic nature. As we have seen, both options, and shades and grades between them, are

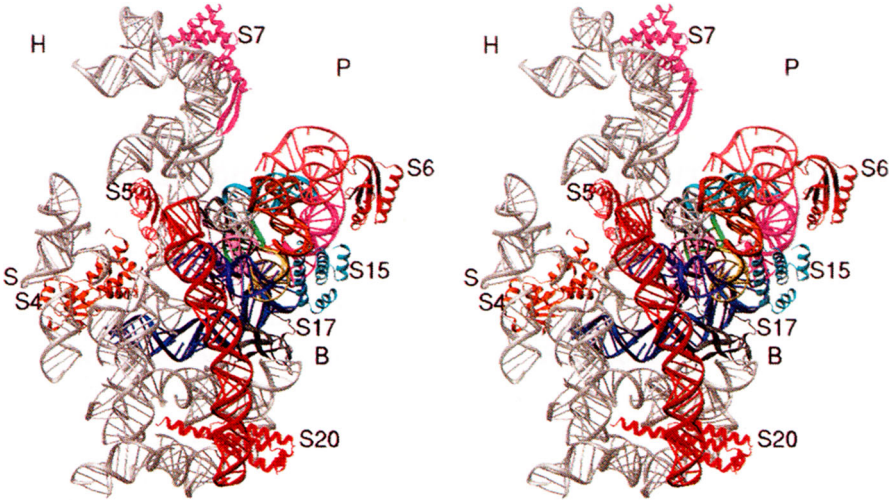

Fig. 6 Model of the small ribosomal subunit using molecular secondary structure elements (Ramakrishnan et al. 2000, Fig. 6 on p. 7)

characteristic of models, in contrast to preparations, where the indexical mode prevails.[3]

3 Simulations

The knowledge objects—preparations, models—considered so far were of a rather passive, stilling, fixing nature. Today, a kind of epistemic objects proliferate that are of a more and more intrinsically active nature: computer models. Of course there are aspects of computer modelling that have been carried over from traditional modelling. To give an example—staying with the ribosome—let us look at a computer-graphic representation in which RNA and proteins are rendered in the standardised form of their secondary structure—single stranded and double helical parts for RNA, alpha-helices and beta-sheets for proteins (Fig. 6). These elements are themselves now folded in three-dimensional space and can also be stereoscopically viewed in three dimensions. Alternatively, Fig. 7 shows a compact surface representation of the large ribosomal subunit, whereas Fig. 8 gives an electron density model of the small subunit in comparison to models derived from electron microscopy.

These are features that were already in use in earlier spatial models. There are, however, two additional aspects that lend computer modelling its peculiar character and that appear to justify distinguishing them from traditional models as a separate category—let us call them simulations. The first aspect is their basic mobility in

[3] I here stick to the triadic distinction of "index", "icon", and "symbol" made by Charles Sanders Peirce (1955).

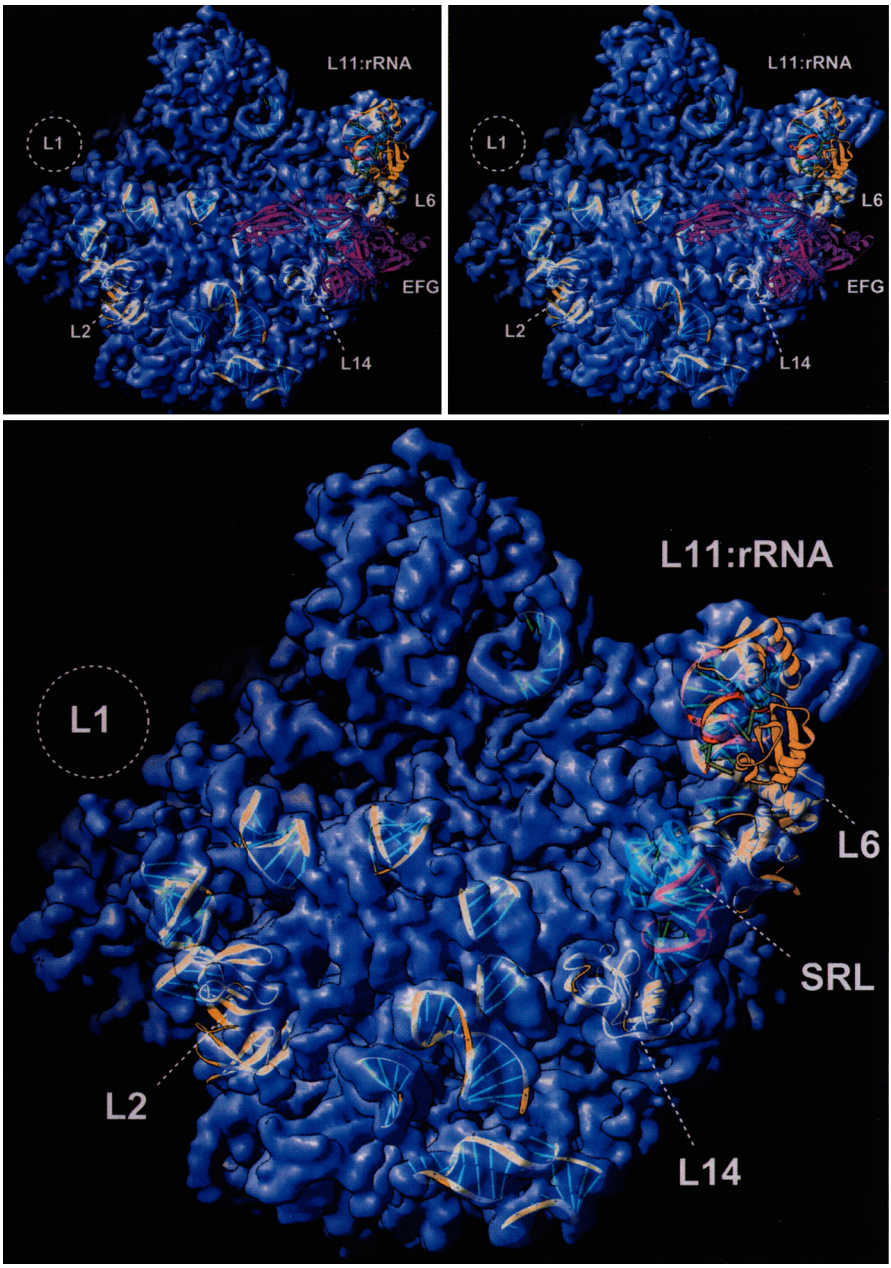

Fig. 7 Space-filling molecular model of the large ribosomal subunit (Ban et al. 2000, Fig. 2 on p. 15)

virtual space. This mobility makes it possible to simulate functional states and their sequence in time. With that, processes of a cyclical nature—such as protein synthesis—but also those of a non-cyclical nature can be visualised, for instance developmental processes.

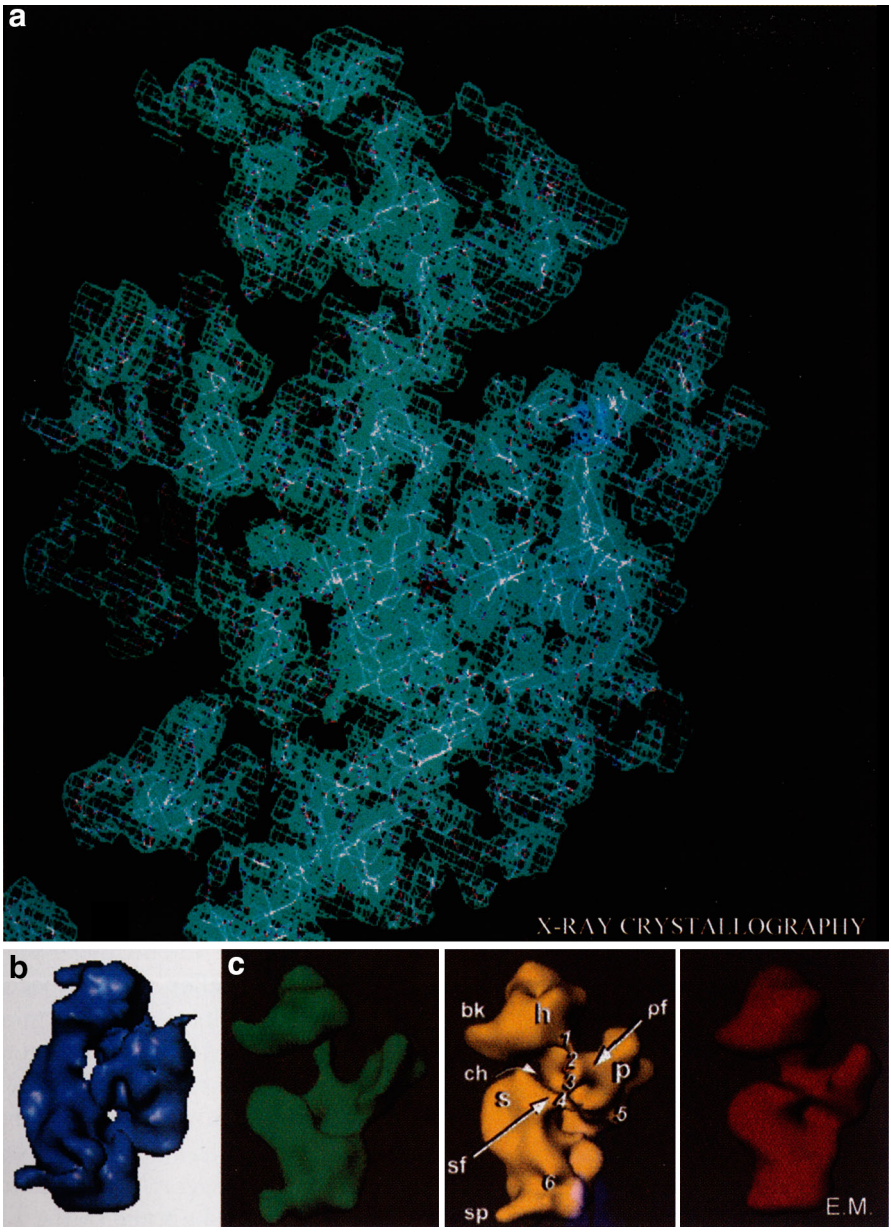

Fig. 8 Electron density map of the ribosome (Bashan et al. 2000, Fig. 1 on p. 23)

The second aspect goes even further. Preparations as well as traditional models are principally of a data *processing* nature, albeit, as we have seen, in very different forms. Here, however, we are concerned with models that, in principle, not only *process* data, but can also *generate* data. With that, simulations tend to completely

operate in the virtual, where they also produce the data of which they consist. The model literally takes on a life of its own and develops into a reality of its own. Just as with the preparation, we are again here concerned with a self-configuration of data, only now on the side of the model. With that, the concept of representation is once more undermined, is broken, if not to say inverted. As expressed by Baudrillard (1983, pp. 31–32) 30 years ago, "We are in a logic of simulation that has nothing to do with a logic of facts and an order of reasons. Simulation is characterized by a *precession of the model*. […] Facts no longer have their own trajectory, they arise at the interface of the models." He concludes, "The definition of the real itself now becomes: *that of which an equivalent reproduction can be given*. At the boundary of this process of reproducibility the real not only becomes something that can become reproduced, but something that is always already reproduced. The hyperreal" (ibid., p. 146).

We know the precessivity of the model in another realm of culture with which we are quite familiar: art and architecture. Here the relationship between the model and the modelled is always already inverted. If in a different manner for each of the two realms, the model is a precept and not a result. What does it mean, in the long run, for the sciences to have been overtaken by the precession of the model? What does this mean in particular for the relationship between the sciences and the arts? The last word appears not to have yet been spoken.

References

Ban, N., et al. (2000). Crystal structure of the large ribosomal subunit at 5-Ångstrom resolution. In R. Garrett, et al. (Eds.), *The ribosome. Structure, function, antibiotics, and cellular interactions* (pp. 11–20). Washington DC: ASM Press.

Bashan, A., et al. (2000). Identification of selected ribosomal compounds in crystallographic maps of procaryotic ribosomal subunits at medium resolution. In R. Garrett, et al. (Eds.), *The ribosome. Structure, function, antibiotics, and cellular interactions* (pp. 21–33). Washington DC: ASM Press.

Baudrillard, J. (1983). *Simulations*. New York: Semiotext(e).

Canguilhem, G. (1968). Modèles et analogies dans la découverte en biologie. In G. Canguilhem (Ed.), *Etudes d'histoire et de philosophie des sciences* (pp. 305–318). Paris: Vrin.

Deleuze, G. (1968). *Différence et répétition*. Paris: Presses Universitaires de France.

Deleuze, G. (1992). *Differenz und Wiederholung* (trans: Vogl, J.). München: Fink.

Deleuze, G. (1995). *Difference and repetition* (trans: Patton, P.). New York: Columbia University Press.

Frege, G. (1966). Über Sinn und Bedeutung. In G. Frege (Ed.), *Funktion, Begriff, Bedeutung: Fünf logische Studien* (pp. 40–65). Göttingen: Vandenhoeck & Ruprecht.

Hoffmann, C. (2012). Probe, Konservat, Modell—Präparat? In K. Ammann & P. Gisler (Eds.), *Präparat Bergsturz* (pp. 61–69). Luzern/Poschiavo & Chur: Edizioni Periferia & Bündner Kunstmuseum.

Lake, J. A., et al. (1974). Ribosome structure as studied by electron microscopy. In M. Nomura, et al. (Eds.), *Ribosomes* (pp. 543–557). New York: Cold Spring Harbor Laboratory Press.

Oakes, M., et al. (1986). Ribosome structure, function, and evolution: Mapping ribosomal RNA, proteins, and functional sites in three dimensions. In B. Hardesty & G. Kramer (Eds.), *Structure, function, and genetics of ribosomes* (pp. 47–67). New York: Springer.

Peirce, C. S. (1955). Logic as semiotic: The theory of signs. In J. Buchler (Ed.), *Philosophical writings of Peirce* (pp. 98–119). New York: Dover.

Ramakrishnan, V., et al. (2000). Progress toward the crystal structure of a bacterial 30S ribosomal subunit. In R. Garrett, et al. (Eds.), *The ribosome. Structure, function, antibiotics, and cellular interactions* (pp. 3–9). Washington DC: ASM Press.

Rheinberger, H.-J. (2003). Präparate—'Bilder' ihrer selbst. Eine bildtheoretische Glosse. *Bildwelten des Wissens, Kunsthistorisches Jahrbuch für Bildkritik, 1*(2), 9–19.

Rheinberger, H.-J. (2006). *Epistemologie des Konkreten*. Frankfurt a.M: Suhrkamp.

Rheinberger, H.-J. (2007a). Spurenlesen im Experimentalsystem. In S. Krämer, W. Kogge, & G. Grube (Eds.), *Spur: Spurenlesen als Orientierungstechnik und Wissenskunst* (pp. 293–308). Frankfurt a.M: Suhrkamp.

Rheinberger, H.-J. (2007b). Wie werden aus Spuren Daten, und wie verhalten sich Daten zu Fakten? In: *Nach Feierabend* (*Züricher Jahrbuch für Wissensgeschichte*) (Vol. 3, pp. 117–125). Zürich: Diaphanes.

Rheinberger, H.-J. (2009). Sichtbar Machen: Visualisierung in den Naturwissenschaften. In K. Sachs-Hombach (Ed.), *Bildtheorien: Anthropologische und kulturelle Grundlagen des Visualistic Turn* (pp. 127–145). Frankfurt a.M: Suhrkamp.

Rheinberger, H.-J. (2010). Molekulare Modelle als epistemische Objekte. Ribosomen im Spiegel von 50 Jahren Forschung. In J. Hennig & U. Andraschke (Eds.), *Weltwissen. 300 Jahre Wissenschaften in Berlin. Ausstellungskatalog* (pp. 76–81). München: Hirmer.

Rheinberger, H.-J. (2011). Infra-experimentality: From traces to data, from data to patterning facts. *History of Science, 49*, 337–348.

Rheinberger, H.-J. (in press). *Über den Eigensinn epistemischer Dinge*. Berlin: Neofelis.

Spirin, A. S. (1969). A model of the functioning ribosome: Locking and unlocking of the ribosome subparticles. The mechanism of protein synthesis. *Cold Spring Harbor Symposia on Quantitative Biology, 34*, 197–207.

Stent, G. S. (1963). *Molecular biology of bacterial viruses*. San Francisco: Freeman.

Traut, R. R., et al. (1974). Protein topography of ribosomal subunit from *Escherichia coli*. In M. Nomura, et al. (Eds.), *Ribosomes* (pp. 271–308). New York, NY: Cold Spring Harbor Laboratory Press.

van Fraassen, B. C., & Sigman, J. (1993). Interpretation in science and in the arts. In G. Levine (Ed.), *Realism and representation* (pp. 73–99). Madison, NY: University of Wisconsin Press.

Watson, J. D. (1965). *Molecular biology of the gene*. New York, NY: Benjamin.