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Project knowledge and its resituation in the design of research projects: Seymour Benzer's behavioral genetics, 1965-1974

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Abstract

The article introduces a framework for analyzing the knowledge that researchers draw upon when designing a research project by distinguishing four types of "project knowledge": goal knowledge, which concerns possible outcomes, and three forms of implementation knowledge that concern the realization of the project: 1) methodological knowledge that specifies possible experimental and non-experimental strategies to achieve the chosen goal; 2) representational knowledge that suggests ways to represent data, hypotheses, or outcomes; and 3) organizational knowledge that helps to build or navigate the material and social structures that enable a project. In the design of research projects such knowledge will be transferred from other successful projects and these processes will be analyzed in terms of modes of resituating knowledge. The account is developed by analyzing a case from the history of biology. In a reciprocal manner, it enables a better understanding of the historical episode in question: around 1970, several researchers who had made successful careers in the emerging field of molecular biology, working with bacterial model systems, attempted to create a molecular biology of the physiological processes in multicellular organisms. One of them was Seymour Benzer, who designed a research project addressing the physiological processes underlying behavior in *Drosophila*.

Keywords: Project knowledge; Resituating Knowledge; Method; Seymour Benzer; *Drosophila*; Behavior

1. Introduction

In 1968, Seymour Benzer (1921-2007) provided the first proposition of a new research program on which he had embarked formally only one year earlier: the "search for defects in non-phototactic mutants describes the outline of a research program to attack the mechanisms underlying behavior by genetic methods" (Benzer, 1968, p. 52). A research program, or rather an actual project informed by a program, is a complex arrangement. As the quotation makes clear, it addresses a domain of phenomena under investigation (behavior), and typically a subset of the phenomena that can be studied in an exemplary manner (phototaxis), and it is based on an idea about the appropriate form of result (mechanistic explanation) and a suitable methodology (genetic methods). The goals (here, the mechanistic explanation) will be divided in several subtasks and the methods to achieve these tasks will involve several techniques specific to the material at hand that involve suitable instruments (e.g., behavioral screening devices), reagents (e.g., mutagens), and, in biology, typically an

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experimental organism (in this case, the fruit fly *Drosophila melanogaster*). Furthermore, employing the techniques, making the organisms available, and coordinating the work in a collective requires the project to be embedded in physical infrastructures, institutions, and social relations (in this case, a lab at the California Institute of Technology (Caltech), the social hierarchy of a principle investigator and the postdocs and graduate students working in the lab, and the *Drosophila* community and its systems of communication and exchange of protocols, mutant stocks, and other resources). In part 1 of this article, I will develop a framework for analyzing the kind of knowledge researchers draw on when designing and embedding a research project. The proposed account facilitates the identification of the sources of such "project knowledge" and the analysis of the processes of its resituation. The framework is developed from the case of Benzer's work in behavioral genetics presented in part 2, and in turn helps to understand how new research programs emerged around 1970 in biology and engendered conceptual change. The study thus also contributes to the history of this period, which was characterized not only by a molecularization of physiological processes, but also by the encounter of molecular biology with higher organisms, as well as new models of gene action (Morange, 1997; Burian and Thieffry, 2000; Suárez-Díaz and García-Deister, 2015). It furthermore contributes to the history of behavioral biology broadly construed.

2. The resituation of project knowledge in the design of research projects

2.1. Project knowledge in the design of research projects

"Research program" and "research project" are both actors' terms.[1] Sometimes "research program" and "research project" can be used interchangeably, but they are not synonymous. "Research program" refers to the generalized plan underlying a project that can in principle be taken up by other researchers at other times to inform their respective projects. Both Sydney Brenner (b. 1927) and George Streisinger (1927-1984), for instance, refer to Benzer's research program in the exposition of their respective projects (Brenner, 1974; Streisinger et al., 1981). A research project, instead, is intended and carried out by a particular person or group at a given time. It makes sense to speak of several sub-projects, tackling individual problems or delivering partial results under the umbrella of a larger project informed by a research program. The term "project" still emphasizes the plan and its execution (one may have a project before embarking on it, but one can also actively pursue a project); the expression "research process" is probably most appropriate to refer to the actual embodied and materialized actions and events, including reasoning and symbolic activities that occur when a project is carried out. Much of scientific activity takes the form of research projects pursued in a lab or field site by smaller (often hierarchically organized) teams of researchers associated with one or more institutions. Projects can often be identified insofar as they are acknowledged as such in grant proposals, reports, notebooks, correspondence, publications of results or personal recollections; they typically consist of a series of experiments or other forms of inquiry and result in a single article or, more often, a series of research articles.[2] Projects address a domain of phenomena, such as ontogenetic development or the behavior of organisms, by asking

[1] The meaning of "research program" is narrower than in Imre Lakatos' (1978) use of the term in the sense that it addresses what underlies particular projects rather than larger disciplinary formations. It is also more centered on methodological approaches rather than theories. Rheinberger (2000) uses "project" in the sense intended here in an analysis that inspired the present account.

[2] This seems to be true at least for the natural sciences in the twentieth century, but even here there are other forms of research. One may ask if the framework provided here also applies to "big science" projects, e.g., the Human Genome Project. Furthermore, collection-based work, for instance in systematics, might exhibit quite different forms of organization and temporality.

specific questions that can be addressed with an appropriate methodology. The same domain might also be addressed by other researchers asking different questions and applying different methods, i.e., it might be the subject of other research projects.[3] Projects are episodes of research that inquire into open questions pertaining to epistemic things, i.e., previously identified entities or processes within a domain that "embody what one does not yet know" (Rheinberger 1997, p. 28). Epistemic things emerge in a domain often from the perspective of one set of questions or methods, but can – once identified – become the subject of other approaches and can also become seen as relevant entities in a different domain.

Questions, concepts and methods, instruments and reagents, institutions and communities – all of these heterogeneous elements are assembled in a research project. They are brought into new constellations and are often transformed in this process. This implies that most if not all of them have a history: elements that enter a research project are transferred from one context to another; novelty arises from recombination. Paul Rabinow writes: "However, from time to time, new forms emerge that have something significant about them, something that catalyzes previously present actors, things, institutions into a new mode of existence, a new assemblage, an assemblage that made things work in a different manner" (Rabinow, 2000, p. 44). "Assemblage" refers to the result, emphasizing the novelty that is enabled by an assemblage, which cannot be reduced to the effect of the individual elements. Nonetheless, many authors are interested in the emergence of the socio-techno-natural assemblages formed in a research project. Detailed accounts of research episodes in the history of science show how various elements are brought together in research projects and they often trace the origins or genealogies of these elements. However, studies focusing on material practices typically do not explicitly distinguish the transfer of research materials and technologies from the transfer of knowledge about how to plan experiments, prepare materials, construct devices, etc. Similarly, authors who emphasize social practices do not always distinguish the building of new or the use of existing infrastructures, or the mobilization of a social formation from transferring knowledge about how to set up, transform, or utilize such contexts and conditions. Studies on knowledge transfer, finally, often look at the way scientific concepts or data travel between contexts, but rarely address scientists' knowledge about how to develop research questions and appropriate methods, or how to adjust a research project in the face of unexpected findings. In this study, I aim to show that researchers either already possess or actively seek knowledge that enables them to design a research project or to amend it in the face of emerging constraints and opportunities. I will refer to such knowledge as "project knowledge."[4] What is the nature of such knowledge? Are there different types of project knowledge? How do researchers acquire it and how do they transfer it from one research context to another? These are the questions that will be

[3] I use the term "domain" with reference to Dudley Shapere (1984), Ch. 13. Shapere was interested more in the concept of a scientific theory than in goals and methods informing practices. What he points out, however, is that certain phenomena are the subject matter of research, but at the same time cannot be identified independently of (changing) scientific perspectives, i.e., domains are not given. For two research groups to address "the same domain" with different questions and by different means, thus always implies a shared interpretation on some broader level.

[4] The advantage of "project knowledge" is that it facilitates the comparison of projects aimed at generating knowledge with projects of, say, producing an artwork or developing technologies or services. One of the realms where the term is used (albeit often in a less specified manner) is knowledge management in organisations (see, e.g., Schindler and Eppler, 2003).

addressed through the further explication of the notion of "project knowledge" and the analysis of a case from the history of biology.

2.2. Project knowledge and other project relevant knowledge

Projects materialize in a series of activities performed by the researchers, i.e., the actual research process. Project knowledge can thus at first instance be characterized as knowledge that informs the activities necessary to carry out a project. A useful distinction is that between knowledge about the possible goals of a project and knowledge about how to accomplish that goal, i.e., how to implement the project. This distinction can be drawn for many kinds of projects. In research projects "goal knowledge" concerns the kinds of knowledge that can be achieved. What might be more generally referred to as "implementation knowledge," instead, concerns the methods applied, but also other activities related to a project (see 1.3, below). Unlike "procedural knowledge," it is not restricted to experimental activities but includes a broader range of activities that are necessary to implement a project. Furthermore, procedural knowledge is usually contrasted with declarative knowledge, whereas implementation knowledge can often take the form of explicit instructions (Gooding, 1990, pp. 8-9). Indeed, carrying out a research project often requires embodied skills in handling certain instruments or materials. Such skills are acquired through practice and in principle skills pertaining to a given material or instrument can become helpful when handling novel objects and are in that sense transferred. Nonetheless, implementation knowledge, as it is understood here, although it might be tacit in many cases, is acquired not from practicing experimental gestures, but from understanding the steps necessary to achieve a goal and can in principle be made explicit. Hence it is transferred in different ways from procedural knowledge (see 1.5).

While project knowledge is not knowledge-how, it is knowledge about possible goals and how to achieve them. As such, it can be very generic, specifying what can be known about any or at least many domains of phenomena as well as generic strategies for obtaining knowledge of different kinds. More often, however, project knowledge will be more specific for a given domain and even if generic project knowledge constitutes the starting point it needs to be adjusted to the case at hand (see 1.4). Where project knowledge contains domain-specific knowledge, it needs to be distinguished from other knowledge specific for the phenomena that enters a research project. Certainly, researchers start from reviewing what is already known about the phenomena or specific epistemic things in a domain of interest. Furthermore, specific data, say about the chromosomal position of a gene, might be necessary to plan an intervention. But goal knowledge is knowledge about how to generate research questions from what is already known (i.e., to specify what is not known). If, for instance, the elements participating in a physiological process have been identified, knowledge about mechanistic explanations might prompt a researcher to ask how they interact. Similarly, implementation knowledge pertaining to the methodological approach draws on very specific knowledge about the research material as well as the instruments or other elements, but it is not identical with this knowledge. It is knowledge about how to employ such information to generate approaches that yield the kind of knowledge specified as the goal of a project.

2.3. Types of project knowledge and their function

Project knowledge can be addressed in terms of "schemata," a term that is borrowed from cognitive science and is meant to point out that the knowledge in question is richly structured.[5] Goal knowledge has already been distinguished from implementation knowledge. Goal schemata codify knowledge about problems and results; such schemata characterize possible forms of empirical knowledge that can be the outcome of a project. The schemata define relations between abstract (or concrete, i.e., domain-specific) placeholders that can potentially be instantiated (or, respectively, replaced) by objects or events in a (different) domain. Such schemata can represent outcomes of projects in various degrees of complexity (e.g., similarity elations or taxonomies, localizations or topologies, causal correlations or mechanisms, etc.). They concern the form of empirical knowledge rather than its specific content and enable researchers to formulate a question with respect to a domain of interest.[6]

Regarding implementation knowledge, from the function of project knowledge to inform research activity it follows that a typology can be achieved by reflecting on the kinds of activities that make up the research process. Research activities can, of course, be parsed and classified in many ways. The following suggested classifications reflect different aspects of research that have been highlighted in recent, practice-oriented history and philosophy of science:

a) Activities involving the specific research materials and technology. These are, for instance, the activities of experimentation that are performed in the context of experimental systems (Rheinberger 1997).[7] While for the purpose of this article it is sufficient to speak of experimental systems as the spaces where this kind of activity happens, the spaces of action created through decisions and technologies in the context of field studies, for instance, can be addressed as observational systems, and the relevant activities can also be performed in the context of computational or other kinds of model systems (Keller, 2003; Burkhardt, 2005).

b) Activities of crafting representations. These activities are closely intertwined with the activities in a). They aim at recording and displaying data, or representing more complex research for reasoning (e.g., drawing diagrams of hypothetical mechanisms), distribution (e.g., preparing data for databases), or communication (e.g., narrating an explanation for a journal article).

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[5] Marvin Minsky, who uses the term "frame," wrote: "When one encounters a new situation (or makes a substantial change in one's view of the present problem) one selects from memory a structure called a *frame*. This is a remembered framework to be adapted to fit reality by changing details as necessary. A *frame* is a data-structure for representing a stereotyped situation […]. We can think of a frame as a network of nodes and relations. The 'top levels' of a frame are fixed, and represent things that are always true about the supposed situation. The lower levels have many *terminals*–'slots' that must be filled by specific instances or data. Each terminal can specify conditions its assignments must meet. (The assignments themselves are usually smaller 'sub-frames.')" (Minsky, 1988, p. 156)

[6] Some philosophers speak of schemata in a similar way, but are restricted to forms of explanation (e.g., Thagard, 2003; Craver and Darden, 2013).

[7] See, e.g., Radder (2009) for a review of the literature on the history and philosophy of experimentation.

Representations can be constructed in various media, symbol systems, and formats (Vorms, 2013; Abrahamsen and Bechtel 2015).[8]

c) Activities of establishing, maintaining, and using material infrastructures and social institutions that enable the experimental (or observational, or modelling) work, i.e., provide the context in which the activities addressed in a) and b) can happen. These are the activities aimed at organizing or navigating communities and institutions (including gaining funding for research), setting up and handling material repositories or databases, interacting with instrument makers or service facilities, etc. These activities naturally often happen on the community level and they are pursued independently and beyond the time and locality of individual experiments, in order to enable many projects by many researchers.[9]

It is now possible to identify three types of implementation knowledge that scientists draw upon to develop a research project, which inform the three kinds of activities, respectively.

1) Knowledge about how to solve a problem or achieve a result (methodological schemata): Such schemata characterize possible (technologically mediated) strategies to make entities appear as instances of a specific goal schema a methodological schema is associated with (e.g., *collect and compare* for achieving a taxonomy, *intervening on one element in a system and observe changes in another* for finding causal correlations, etc.). To execute the methodological strategy will require further specific domain knowledge (e.g., how to manipulate the objects in question) and possibly also skills in handling the materials.[10]

2) Knowledge about how to represent knowledge of a given form (notational schemata): Such schemata characterize the media, symbol systems, and formats of notations that can be used to express knowledge as specified by the goal schema that selected an associated notational schema (e.g., tables for taxonomies, maps for spatial composition, arrow diagrams or certain types of narratives for causal/mechanistic explanations, etc.). To produce the representations will require additional knowledge about the media in question or skills in working with the tools involved.[11]

3) Knowledge about how to organize research work (organizational schemata): Such schemata characterize possible strategies for establishing, choosing, maintaining, or navigating material infrastructure, social rules, and institutions (e.g., museum collections, laboratories, field stations,

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[8] Hentschel (2014) reviews much of the literature on visual culture in science, but narrative and other textual genres are also relevant here (see Morgan and Wise, 2017).

[9] Rachel Ankeny and Sabina Leonelli show how social and material structures enabling research might emerge from individual research projects, but transcend them and provide continuity even under substantial shifts in theory and experimental practice (Ankeny & Leonelli, 2016). They also emphasize the role of these factors in collaboration and integration across research projects. While I agree with their points, my perspective here is inverse: I am interested in how researchers use these structures, or take them as models for building new ones.

[10] The notion of strategy implies knowledge that informs activities. Philosophers and historians have looked at many strategies to acquire knowledge in particular cases, or for specific forms of knowledge. See, e.g., Müller-Wille (2007) for taxonomies, Woodward (2003) for causal correlations, or Bechtel and Richardson (2010) for mechanistic explanations.

[11] Hentschel (2014), Ch. 5, also addresses cases of transfer of visual techniques, which implies that knowledge about visual techniques can be identified.

etc., and the technological and social arrangements that they require) which are necessary to create the conditions for realizing the strategy specified by the methodological schemata that selected an appropriate organizational schema. Entrenching their research in socio-material structures based on such knowledge is not only important for scientists to make their work physically possible, but also to gain acceptance and support.[12]

The following section will further elaborate on the nature of project knowledge before the question of resituating such knowledge is addressed (1.5).

2.4. Project knowledge bundles, domain specificity, and the dynamic character of research projects

In the sense that these kinds of schemata are closely associated, knowledge of types of goals, methods, representations, and organizational structures often comes in bundles. Such bundles can, however, be unpacked and elements can be recombined or new elements can be introduced. Very generic schemata bundles like those mentioned above enable researchers to approach new domains of phenomena because, not knowing anything about them, they still know what could be known about them (e.g., what entities there are, how they are composed and distributed, how they interact, etc.), how to go about investigating them (make collections, intervene on parameters, etc.), and how to organize the work (building research sites or repositories, founding institutions, etc.). It also allows researchers to switch fields and make their previous experiences fruitful. More often, however, the project knowledge researchers rely on will consist of schemata specific for the domain for which they were trained to pose and solve research problems, i.e., schemata will be encoded with the respective placeholders in the structures filled with representations of actual, concrete realizations (e.g., knowledge of how to classify based on morphological characters, or how to intervene on the genetic level etc.). Furthermore, actual goals of research projects will consist of complex combinations of goal schemata (the schema of a mechanistic explanation, for instance, is composed of sub-schemata of composition, localization, causal interactions, etc.) and hence entail more complex methodological, representational, and organizational schemata. Researchers are not necessarily aware of the generic structures or principles behind their goals and strategies, but if there is no applicable specific schema available to them they typically reason on the basis of a more generic schema derived by abstraction from a domain-specific schema. Finding new research questions, developing new methods to approach problems, or devising new technologies – hence creativity in science – can be understood as based on abstraction, analogies and recombination on the level of such schemata.

Karin Knorr-Cetina (1981), who is also attentive to the role of analogy in the process, points to the activities of assembling a project by invoking the notion of tinkering. Hans-Jörg Rheinberger (1997) emphasizes the role of unprecedented events in experimentation over the intentions of the researchers and Friedrich Steinle (1997) described the often exploratory character of research. In this way, however, these authors highlight the opportunistic over the planned character of research. Emphasizing the knowledge that researchers mobilize to define their goals and inform the activities necessary to achieve them seems, instead, to depict research as a planned and hence predetermined endeavor. The proposed account of project knowledge is consistent with the above observations, however, in that: a) goal schemata often only assume that entities have properties, are composed of

[12] Scholars in science and technology studies have been particularly attentive to the strategies scientists follow in this respect (e.g., Latour, 1987).

parts, are involved in productive interactions, etc., which is not in contradiction with exploratory experimentation or the unexpected appearance of entities, properties, parts, or interactions; b) unprecedented events can only become perceived in the context of planned, systematic activity; and c) in response to such events goals are often abandoned, but new goals (and appropriate methods, etc.) are chosen and pursued, again, in a planned manner. Project knowledge does not inform a rigid plan. Instead, when the project develops, new project knowledge is often activated or sought to amend the project in a dynamic way. This dynamic character of creativity can be even better appreciated by attending to the project knowledge that drives the often-observed changes in strategy.

2.5. The resituation of project knowledge

How is project knowledge transferred? Mary Morgan (2014) offers an account of knowledge transfer by articulating the notion of resituating knowledge. The account provides an alternative to a simple model of knowledge diffusion. The problem arises because knowledge is always produced in specific local settings and therefore does not generalize or apply to other cases in an obvious manner. Whereas probably most instances of knowledge transfer, in contrast to mere diffusion of knowledge, involve decoupling knowledge from the context of its origin and adjusting it to the target context, the notion of resituation can be understood to emphasize the effectiveness of transferred knowledge in shaping the target context and is thus stronger than the notion of transfer. Project knowledge certainly creates the new research situation in the first place, when it is transferred to a new context. Morgan suggests three strategies that scientists use to resituate knowledge. Making knowledge produced in one locality relevant for use in another situation may be achieved by: a) "establishing comparable sites where the local specific knowledge may apply directly"; b) "extracting—desituating—some causal or conceptual knowledge from local findings that can then be resituated in comparable sites elsewhere"; or c) "establishing local knowledge as 'typical' and thence available to be used in many other comparable (or contrasting) sites" (Morgan, 2014, p. 1014). Morgan is interested in knowledge in terms of results of research – that is, knowledge that has been generated about certain entities or processes in a local setting. Project knowledge, which is knowledge about how to generate knowledge, is distinct from such knowledge, even if it can be more or less domain-specific (see 1.2, above). Nonetheless, it is plausible to expect similar strategies to be employed by scientists when attempting to make goals, methods, notations, or organizational principles developed in one situation available in other situations.

The present account is concerned with knowledge about how to conceive of, set up, and run a research project: How are questions or problems that have been posed in one situation transferred to other situations to generate new goals? How are methods of observation, experimentation or modelling, or techniques of representation of data and results that have been developed to produce certain results or solve certain problems in one domain applied to another domain or other objects in a given domain? How can strategies to organize work developed in one context be applied in another? Next to Morgan's account, other models of knowledge transfer and circulation have been suggested in the literature. Sabina Leonelli's notion of data journeys, for instance, apart from being concerned with results of research episodes or high-through-put data acquisition process, is different from the account of resituation because it focuses on the packaging of data for re-use (Leonelli 2016, Ch. 1.2). In the case of project knowledge, those at the source, i.e., researchers who have successfully developed goals and implementation strategies to some degree, package their project knowledge for re-use in research articles (in the "methods and materials," but also often in the "results" or equivalent sections). However, this mainly applies to direct replicability of specific

procedures.[13] When researchers embarking on a new project resituate project knowledge, more often they need to seek it at its source and de-situate it themselves by performing some form of abstraction. Hence, unlike in the case of curated databases, the necessary steps for resituation are provided neither by the researchers at the source nor by some mediators. Other accounts of knowledge circulation emphasize standardization and ready-made solutions. Joan Fujimura speaks of "standardized packages," which consist of a "scientific theory and a standardized set of technologies" (Fujimura, 1992, p. 169), while Peter Keating and Alberto Cambrosio speak of "biomedical platforms" as "combinations of techniques, instruments, reagents, skills, constituent entities (morphologies, cell-surface markers, genes), spaces of representations, diagnostic, prognostic, and therapeutic indications, and related etiologic accounts" (Keating and Cambrosio, 2003, p. 4). Focusing on packages, these accounts do not discriminate between circulating material (research kits, instruments) and circulating knowledge, nor between project knowledge and other relevant knowledge. Furthermore, they emphasize the stabilization of standards and routines in similar contexts, whereas the present account is interested more in processes of creativity and recombination where researchers draw from heterogenous sources, leading to a diversification of research programs.[14]

The case study displays several modes of resituating project knowledge, which can be located in Morgan's typology and will be summarized in the conclusion. Before attending to the case (part 2, below), the choice of Benzer's research in behavioral genetics will be justified both in terms of its suitability for the philosophical purpose and its relevance for the history of molecular biology and behavioral biology. Furthermore, the advantages of the project knowledge framework for both philosophy and history of science will be pointed out.

2.6. The case study and the value of the framework for philosophy of science and for history of science

It is possible that many cases of knowledge transfer, which at first sight appear as a resituation of research findings, in fact turn out to be more accurately described as a resituation of research approaches and hence of project knowledge. When results from research on model organisms is transferred to other organisms or possibly human cell cultures, the task is often not to extrapolate knowledge in an act of reasoning, but to recreate a similar experimental access to the entities or processes in question in the target experimental system (see also Bechtel, 2009). For this reason, an account of project knowledge can facilitate the study of modes of resituating knowledge. Furthermore, the notion of project knowledge taken together with modes of its resituation provides an important complement to studies on creativity, innovation, and discovery in science. Previous accounts have typically either emphasized aspects of conceptual reasoning, for instance in terms of analogy, or material practice, showing, for instance, how novel entities emerge in novel experimental systems (see, e.g., Meheus and Nickles, 2009). An account of project knowledge expands this work and provides a link between such studies by pointing to the reasoning that informs novel practices, which in turn can give rise to novel concepts. Given that project knowledge is often imported into a

[13] More generic accounts of methods might be provided in textbooks.

[14] The notion of bundles introduced in sect. 1.4, unlike "packages" in Fujimura's sense, is meant to point less to standardization and more to the learned association of types of goals and suitable strategies for achieving them (both generic and domain-specific).

project from different disciplines, in some cases by different project participants, the account should also enrich the study of interdisciplinarity (MacLeod, 2016).

Historical case studies are essential for a philosophical understanding of the formation of novel approaches in science because the latter process is historical in nature, i.e., extended in time and situated in specific geographical and social constellations. Furthermore, these processes can only be understood from the perspective of their consequences in terms of broader changes in the scientific landscape. A case study should thus not simply be seen as an example from history, but as displaying the historicity of the process. This implies, on the one hand, that an account of the formation of new research programs is important for a philosophical understanding of scientific change that is based on practices rather than theories and acknowledges complex patterns of merging and diverging approaches. On the other hand, it makes clear why such an account is useful for writing the history of specific changes in a discipline such as biology. In part 2 of the article, I will analyze the resituation of project knowledge in the formation of Benzer's research program in behavioral genetics.[15] The case is particularly suitable for investigating these processes.[16] Typically researchers gradually transform their research activities, reacting to opportunities that arise from their experimental systems or to technical or conceptual developments in their broader field or in other areas of science. Benzer, instead, explicitly abandoned his successful research program in phage genetics and set out to make contributions in another field, or rather in a niche at the intersection of various fields that he considered unoccupied. For this reason, he established a new research program in a relatively short time. In this concentrated form, the process of resituating project knowledge becomes easily visible. Frederic Holmes acknowledges that Benzer seems unique in switching fields two times in his career, first from solid-state physics to phage genetics, and later from the latter field to behavior genetics, working with a metazoan model organism. Holmes points out that "[…] even when making such leaps from field to field, Benzer found transition pathways that enabled him to cross from one main line to another without losing all the investments that he had made in his previous research activity" (Holmes, 2004, p. 22). This implies that Benzer resituated knowledge from one field in another. Given that the domains of phenomena are quite distinct (although less so in the second case), the relevant kind of knowledge must in part be relative generic project knowledge rather than accumulated knowledge about the domain.

The case of Benzer's research program in behavioral genetics not only serves as a suitable case for the study of project knowledge and its modes of resituation, but is furthermore relevant for the understanding of the period that has been referred to as the ''long 1970s'' (1969–1983) by Edna Suárez-Díaz and Vivette García-Deister. These authors characterize it as "an important though often overlooked period in the development of a rich landscape in the research of metabolism, development, and evolution" (2015, p. 503). Whereas these authors focus on the emergence of models of gene regulation (e.g., those of Eric H. Davison, 1937-2015), they acknowledge the presence

[15] Obviously, the reasoning processes involving project knowledge cannot be observed directly, but can only be inferred from the available sources. It has been pointed out that the rationale of a project is often constructed in retrospect when writing up the research publication (e.g., Gooding, 1990; Holmes et al., 2003). And yet, starting from Benzer's programmatic statements published in a very early phase and comparing them to later research articles makes it possible to get an idea of the planning of the project and its subsequent dynamic development.

[16] The questions of resituating approaches and results applies to research in philosophy of science as much as in science. Under what conditions a philosophical analysis developed based on a case study can be generalized or applied to different cases is subject to methodological debate (see, e.g., Scholl and Räz, 2016).

at the time of more reductionist approaches put forward by members of the first generation of molecular biologists. These researchers had worked with bacteria and were driven by the "expectation that molecular genetics could be extrapolated from bacteria to eukaryotic cells" (p. 507). Among them were next to Benzer also François Jacob (1920-2013), as well as Brenner and Streisinger. While of these Brenner's work with *c. elegans* was the most successful and became the subject of some philosophical and historical literature (Ankeny, 2000; de Chadarevian, 1998; Schaffner, 1998), Benzer's work with *Drosophila* has not received much attention.[17] The latter had, however, a different focus from the work of Brenner, who aimed for a complete description of neural development. Benzer's work was highly influential in its own way and opened many new research avenues and the reconstruction of his approach thus adds to the historical analysis of this line of work.[18] Given Benzer's emphasis on behavior, rather than neuro-physiology, at least in the beginning, and later research on behavior taking up his approach, the given study also expands the literature on the history of behavioral biology that has so far mainly concentrated on behaviorism and ethology (see, e.g., Burkhardt, 2005).

Michel Morange (1997) associates the work of Jacob, Brenner, and Benzer with a crisis in molecular biology. Complementary to the notion of a molecularization of the physiology of development and other processes in multicellular organisms, Morange emphasizes the "deep transformations which occurred in molecular biology and which led from a molecular biology of the gene to a molecular biology of the cell" (p. 370). The experience of crisis that Morange identifies at the beginning of this process was not only induced by the notion that, on the level of the gene, nothing was left to discover, but also by the lack of technologies that would enable molecular biologists to tackle metazoan physiology on a molecular level. In addition, Morange argues, "what happened during these years was the progressive definition by molecular biologists of what had to be explained and what would constitute an explanation" (p. 372). It is exactly when grappling with such questions that the resituation of project knowledge becomes relevant. Hence the philosophical account developed based on the historical episode in turn allows a better understanding of what drove this particular historical development. In this sense, this article constitutes a study in integrated HPS, or, since the latter term has been used in many ways in recent years (see, e.g., Scholl and Räz, 2016), what I would call "reciprocal HPS."

3. Designing a research project: Seymour Benzer's behavioral genetics

3.1. The researcher: Benzer's investigative pathway from bacteriophage to a metazoan model system

A central aspect of a research project is, of course, the individual researcher, or, more often, the group of researchers, who are part of communities and institutions, carry out the relevant activities, and communicate results to their peers. Most importantly, researchers possess or actively acquire

[17] Weiner (1999) provides a journalistic account of Benzer's work in this period; for Streisinger's work with Zebrafish, see Meunier (2012); for Jacob's work with mice, see Morange (2000a).

[18] As many obituaries and reviews indicate, Benzer is generally seen as a "founding father" or "pioneer" in behavioral genetics ("the single gene approach") and neuro-genetics (see, e.g., Sokolowski, 2001; Vosshall, 2007; Greenspan, 2009). Also the genealogy of more specific fields can be traced back to individual mutants that were first described in his lab, such as the circadian rhythm mutant *period*, which helped to initiate a field that has recently been in the spotlight due to the awarding of the 2017 Nobel Prize in Physiology or Medicine (Abrahamsen and Bechtel, 2015; http://www.nobelprize.org/nobel_prizes/medicine/laureates/2017, accessed 21 Dec 2017).

the knowledge relevant to design their research project. Which knowledge they possess or which resources they are likely to draw from to acquire new knowledge strongly depends on their previous experience. Before attending to the project knowledge underlying Benzer's research project, I shall therefore briefly contextualize his work regarding his biography, or rather his investigative pathway (Holmes, 2004). When Benzer turned to *Drosophila* to address the phenomena of behavior by genetic means, he was already a celebrated scientist. He had mapped the fine structure of a gene in bacteriophage (Benzer, 1955), an achievement not only pivotal to the development of molecular genetics, but also often cited as constituting an important conceptual and methodological bridge between classical and molecular genetics.[19] Like many other protagonists of early molecular biology, Benzer started his career in physics and, like others, he cited Erwin Schrödinger's (1887-1961) *What is life?* (Schrödinger, 1944) as an important influence for changing fields in his autobiographical narrative (Benzer, 1991, p. 15). While working as an assistant professor in physics at Purdue University (where he had obtained his PhD in 1947) doing research on the semiconductor properties of Germanium, Benzer took the summer course in phage genetics at the Cold Spring Harbor Laboratory in 1948. Subsequently, he spent much time on leave from Purdue to work at various institutions, among them Caltech in Pasadena, CA, USA, the Medical Research Council (MRC) Unit for the Study of the Molecular Structure of Biological Systems at the Cavendish Laboratory in Cambridge, UK, as well as the Institute Pasteur in Paris, France, to familiarize himself with microbiology and biochemistry techniques. Gradually, he became one of the central figures in the "Phage Group" around Max Delbrück (1906-1981).[20] Benzer pursued several questions reaching from phage replication and host range to phenotypic expression (plaque morphology) in the context of the broader hypothesis that phage could be characterized best in terms of genetic material, which had informed the work of the group from the beginning. The plan to map the fine structure of the *rII* region of *E. coli* phage T4 (a locus associated with the rapid destruction of the host cell) grew gradually in spring 1954. Benzer developed a method based on collecting as many mutations in the respective region as possible (an approach that required large numbers and fast phenotypic screens that could not be achieved in metazoan systems), on calculations based on recombination events, and on employing a variation of the *cis-trans* test that was developed by Edward Lewis (1918-2004) for *Drosophila*, to test whether two mutations occupy the same locus. Among the most important implications of these results was that not only the genes on the chromosomes, but also the constituents of individual genes were arranged in linear order. His results thus strongly supported the Watson-Crick model of DNA, as well as Crick's later sequence hypothesis, according to which the sequence of bases in a strand of DNA or RNA determines the linear basis of the sequence of amino acids in proteins. The results also implied, however, that the genetic unit of recombination and the unit of function, i.e., physiological activity, are not identical, thus complicating the definition of the gene (Holmes, 2006). Benzer made further important contributions to molecular biology that had a stronger biochemical aspect, one of them being the elucidation of the role of aminoacyl tRNA synthetases in translating the genetic code, and another the demonstration of the degeneracy of the genetic code (Greenspan, 2009).

[19] For a detailed reconstruction of Benzer's phage work see Holmes (2006), and for a biographical overview see Greenspan (2009). This section is based on these accounts as well as on an interview with Benzer conducted by Heidi Aspaturian (Benzer, 1991).

[20] The CSHL phage course was a regular event organized by Delbrück since 1945. For the significance of the phage group, see Kay (1993), Ch. 8, and Morange (2000b), Ch. 4.

Nonetheless, Benzer developed an interest in questions of neuro-physiology and behavior. In his autobiographical account, he named several influences, among them Dean E. Wooldridge's (1913-2006) *Machinery of the Brain* (Wooldridge, 1963), the effect of which on his thinking he likened to that of Schrödinger's book. Wooldridge was not a neuro-scientist but an engineer, and he reasoned about the brain in terms of design principles for information processing, drawing on the pervasive analogy of brains and computers. Benzer also mentioned the fact that he had observed personality differences in his daughters (Benzer, 1991, p. 79). These influences might or might not be seen as retrospective, narrative rationalizations of the scientific biography. What was probably more important was a broader trend in his community. Other researchers in molecular biology turned to higher organisms and became interested in complex physiological processes, hoping that these, since they were already partly characterized in biochemical terms, could be related to the findings of molecular genetics. Among those who moved from experimental systems grounded in microbiology to multicellular organisms were Delbrück, who started working with *Phycomyces*, Jacob, who embarked on research in mice, Gunther Stent (1924-2008), who turned to *Drosophila*, as well as Brenner and Streisinger, who introduced new organisms (*C. elegans* and Zebrafish, respectively) that were to become important model systems in the last quarter of the twentieth century. A recurrent theme was the impression that "all the molecular biology problems were on the verge of being solved," at least on the basic level, having to do with the structural and informational basis of the replication and synthesis of cellular molecules (Benzer, 1991, p. 79).[21]

Benzer first seriously engaged with neuro-biology when he spent a sabbatical at the lab of Roger Sperry (1913-1994) at Caltech in 1965. Sperry, who would receive the Nobel Prize for Medicine or Physiology in 1981 for his work on split-brain patients, was at the time mainly known for the chemoaffinity hypothesis. According to the latter, neurons possess cytochemical markers that define their type and allow them to connect selectively with their targets (see Meyer, 1998). This was what made Benzer think that making a connection between genes, brains, and behavior could be quite straightforward. If the wiring of the brain would be guided by specific molecules and those molecules would be synthesized on the basis of genetic information, then it would be immediately clear how the brain's structure and thus the behavior it generates would be programmed into the genome, or so Benzer thought. Making this connection was what constituted Benzer's initial research question:

> The genes contain the information for the circuit diagram, but little is known about the relationship between this primary information and its conversion into the end result. (Benzer, 1968, p. 50)

In 1967 Benzer joined the Caltech faculty and established his own lab, built around a genetic approach to *Drosophila* behavior and neuro-physiology.

3.2. Organizational knowledge, infrastructures and institutions: Caltech and the *Drosophila* community

Benzer needed to implement his project in a material and social context that would enable the envisioned approach. His experience with bacteriophage clearly influenced his choice of the *Drosophila* model system and provided him with knowledge of how to navigate such a system and exploit its features to support his goals. Sperry's lab neither worked with *Drosophila* nor applied a

[21] See also Stent (1968), p. 160, and Brenner (1998 [1963]), p. x, as well as Morange (1997), p. 370, and de Chadarevian, (1998, p. 85), Fn 11.

genetic approach. In fact, members of the lab were quite skeptical towards genetics as a means to investigate neuro-physiology, as Benzer reported (Benzer, 1991, p. 87). Benzer, while being a guest in Sperry's lab, initially had worked on frogs, an experimental animal used by the group next to others. Why Benzer eventually chose to work with *Drosophila* is not entirely clear. His rationalization reads like this:

> The fruit fly *Drosophila melanogaster* represents a compromise. In mass, in number of nerve cells, in amount of DNA and in generation time it stands roughly halfway on a logarithmic scale between the colon bacillus *Escherichia coli* (which can be regarded as having a one-neuron nervous system) and man. (Benzer, 1973, p. 24)

But similar arguments regarding optimal compromises have been made by other researchers with respect to other organisms, for instance by Brenner (1974) and Streisinger (Streisinger et al., 1981) regarding *C. elegans* and Zebrafish, respectively. It is more likely that Benzer chose *Drosophila* because he knew from his work with the *E. coli* phage system that it was essential not only to have protocols for basic steps of the relevant experiments worked out instead of setting up the right conditions in a long trial and error procedure, but also to have the mutagens, instruments, and, most importantly, a large number of mutant stocks in place, as well as an infrastructure for sharing them among researchers. The fact that *Drosophila* as a system – in the sense of a model organism that is embedded in a material and social infrastructure – was well established, in particular at Caltech where the direct legacy of the group around Thomas Hunt Morgan (1866-1945) was located and materialized in collections and personified mainly through Alfred Sturtevant (1891-1970) and Lewis, made the organism a plausible choice:

> The wealth of genetic knowledge of the fruit fly *Drosophila*, and the availability of many mutants and special chromosomal arrangements make it an organism of choice for the genetic approach. (Benzer, 1968, p. 50)

Analyzing the research project of Walter Gehring (1939-2014), Marcel Weber concludes that "*Drosophila* played such an important role in the molecularization of developmental biology not so much because of antecedently existing theoretical knowledge on its embryology, but mainly due to the enormous experimental resources accumulated by generations of geneticists" (Weber, 2004, p. 74). *Drosophila* was thus more than just an element in the experimental system. A community had formed around the species that developed stocks of mutants and an infrastructure to distribute them, codified and recorded not only anatomical and genetic knowledge about the organism but also practical knowledge about how to maintain and manipulate the organism, and set up infrastructures to distribute all available information.[22]

Benzer did not resituate knowledge (organizational schemata) about how to build such a community and an infrastructure that allows the collection and exchange of knowledge and stocks. But that this sometimes happens is illustrated by the cases of Brenner and Streisinger, who introduced new organisms for research and clearly envisioned such organized communities and means for the exchange of information and resources. Both researchers drew on their experience of working with the *E. coli* phage system and being members of the respective community, as well as on their

[22] See Kohler (1994) for the history of the *Drosophila* community, and in particular the community's exchange network (Ch. 5). For the general role of communities and infrastructures in model organism research, see also Ankeny and Leonelli (2011). Kay (1993) provides a history of Caltech and its social and material culture.

knowledge about the *Drosophila* community. Benzer himself can probably be best described as tapping into an existing social and material structure by adopting the *Drosophila* system. And yet, he still had to draw on his organizational knowledge about model systems and their communities to see the advantage, navigate the structures successfully, and turn them into supportive context for his project.

3.3. Goal knowledge and the domain of phenomena: Benzer's understanding of behavior and its explanation

> Much of human personality is determined by heredity. For instance, recent studies have revealed that inmates of institutions for the criminally insane show an unusually high frequency of chromosomal abnormalities – suggesting that undue emphasis might have been placed on environmental factors in causing their behavior. (Benzer, 1968, p. 50)

This is how Benzer began his above cited first published exposition of his new research program. The sentence sounds much like a caricature of genetics as an overly positivistic and reductionist science. In fact, it not only expresses an explicit genetic determinism with respect to human behavior, but has a rather eugenic ring to it, suggesting the possibility of a biological handle on social problems.[23] Such statements, displaying a simplistic understanding of the relation of genes and behaviors that probably neither Benzer nor many other geneticists actually held at the time, were of course problematic when taken to inform public opinion and policies in the context of complex social problems. More interesting for the present question is how the perception of human behavior influenced the construction of the research questions regarding *Drosophila* genetics. Such statements might be seen as rhetorical maneuvers in establishing the relevance of basic research, rather than motivations for the research design. Yet the notion of normalcy and deviance implicit in the statement fuses with geneticists' focus on phenotypic difference between the normal "wild type" and the deviant mutant in forming the notion of behavior that informed Benzer's research.[24] In fact, Benzer often equated behavior with personality, or "temperament" in this context. As mentioned, he referred to the personality differences between his daughters as a phenomenon that prompted him to become interested in the subject (Benzer, 1991, p. 79). And after describing fly mutations that alter the circadian rhythm, i.e., the molecular mechanism regulating the timing of physiological processes in relation to the rhythm of day and night, Benzer remarked laconically:

> In a normal world, these mutants would appear always to wake up too early or too late. One need not look far to find human analogs of these types. It is possible that genetics may be a strong component of this personality trait. (Benzer, 1972, p. 7)

These examples point out that behavioral characters were not conceived of as species specific, but in terms of individual differences. Such mutations might also drive speciation – in Darwinian theory there is a way from individual variation to species differences – but Benzer's interest was not in the evolution of behavior. He was concerned with causation in the sense of "How does it work?", according to Niko Tinbergen's (1907-1988) classification of questions regarding behavior, or with

[23] Benzer does not provide a reference, but so called XYY males and the potential connection of the condition with aggressive behavior was the topic of the day in human genetics (Nielsen et al., 1968; see Denno, 1988).

[24] See Holmes (2017) on the concept of wild type.

proximate causes in Ernst Mayr's (1904-2005) sense (Mayr, 1961; Tinbergen, 1963). But Benzer's understanding of behavioral characters was decidedly different from the way that behavior was understood in ethology, a discipline that was probably at the peak of its popularity at the time.[25] Ethologists were not only mainly interested in ultimate causes, they also conceptualized behavior in terms of instinct, and they did not conceive of behavior in terms of individual, but of species differences.[26] Lorenz wrote:

> A species-specific behavior pattern is not something that animals may or may not perform; it is a character that the systematic group concerned simply has, just as it has claws, bills, or wings of a particular form! (Lorenz, 1996 [1944 - 1948], p. 238)

There was, of course, another highly influential field of research on behavior, namely behaviorism. Behaviorists emphasized environmental influence and theorized that behavioral patterns were mainly learned. Benzer did not deny the influence of environment, but he thought that behavioral tendencies are "to a large degree" inherited.

> It should not be surprising if, to a large degree, the genes also determine behavioral temperament, although, of course, environmental influences can also play a large role. All behavior is inevitably the resultant of both components. To discern the genetic contribution clearly, the thing to do is to keep the environment constant and change the genes. (Benzer, 1972, p. 4)

Behavior has been a theme in the study of heredity since its beginning. From Francis Galton (1822-1911) to Charles Davenport (1866-1944), tracing behavioral deviation in families was common and the close link to eugenic motivations is obvious. Behavior in *Drosophila* has been studied since the early twentieth century (Carpenter, 1905) and mutants showing behavioral peculiarities have been described frequently in *Drosophila* genetics (e.g., McEwen, 1918). In classical genetics of the Morgan school the emphasis was, however, less on the explanation of characters than on the use of characters to identify genes and their mode of inheritance, which was explained through chromosomal mechanics. Later explorations of developmental genetics aimed at an explanation of the phenotype, but focused on anatomical structures. The study of the genetics of behavior in *Drosophila* became a serious research subject only in the late 1950s. Jerry Hirsch (1922-2008) is credited with pioneering quantitative studies, focusing on phototaxis and geotaxis (Hirsch and Erlenmeyer-Kimling, 1961). Hirsch's research was also concerned with individual differences, as opposed to the ethologists' species-specific behaviors, and he rejected the behaviorist emphasis on learning. Unlike Benzer, however, Hirsch was not interested in the effect of single genes. His work was rooted in quantitative population genetics and he focused on heritability in selection experiments. Benzer saw his work as complementing the work done by Hirsch. Hirsch, instead, was highly critical of Benzer's work and saw the single gene approach as misguided in studying behavior. As a result, the relation between the two approaches became seen as a major tension in behavioral

[25] For instance, Konrad Lorenz (1903-1989), Tinbergen, and Karl von Frisch (1886-1982) will receive the Nobel Prize for Physiology or Medicine in 1973.

[26] See Burkhardt (2005) on the program of ethology.

genetics (see Tully, 1996).[27] What Benzer imported from Hirsch's research project was the more specific phenomena that were studied in an exemplary manner to find general principles that apply to the relation of genes, the nervous system, and behavior. These might be called model phenomena, in this case geotaxis and phototaxis. Hirsch had studied both, while Benzer focused on the latter in his first experiments. These phenomena had been observed and studied before. In fact, Benzer cites both early studies on the genetics of *Drosophila* behavior mentioned above, which are concerned with the reaction of flies to light and gravity, as well as a text book on animal orientation (Fraenkel and Gunn, 1961).[28] Nonetheless, the clue that Benzer got from Hirsch's approach was that these behavioral phenotypes could be conveniently operationalized by putting flies in tubes and orienting the tubes in various ways towards the source of stimulation (although Benzer's design of the screening device differed from that of Hirsch, reflecting the different interest in qualitative as opposed to quantitative evaluations of the phenotype).

Coming back to the comparison of Benzer's understanding of behavior with that of ethology, an additional point can be made. Not only did Benzer focus on individual variation and its genetic basis in single mutations, he also held a view of behavior that equated the organism with a machine that performs certain movements unless some parts are broken such that the movements are inhibited. This becomes obvious in the way he describes the different types of phototactic mutants he identified. If the notion of behavior is based on the idea of instinct as in ethology, a negatively phototactic mutant running away from the light would be perceived as having an altered instinct. Regarding a mutant that runs neither towards nor away from the light, but simply moves randomly in both directions because the fly is blind and does not see the light, the instinct perspective would suggest that the instinct is probably unaltered, and that it is only a physiological function that is impaired, which prevents the otherwise unaltered behavioral tendency from being actualized. For Benzer (e.g., 1973, p. 29), instead, these cases were on a par. In both cases, some element in the machinery of the molecular and neural mechanisms is defective and therefore the organism *qua* machine cannot generate the patterns of movements in the standard way. Here the influence of Wooldridge's *Machinery of the Brain,* which was written from an engineer's perspective, might have been relevant. This mechanistic view also informs the kind of explanations aimed for and the overall strategies employed to achieve these goals.[29] Benzer wrote: "Once assembled, the functioning nervous system embodies a complex of interacting electrical and biochemical events to generate behavior" (Benzer, 1968, p. 50). This fits well with the way that philosophers of science have characterized mechanistic explanations in terms of entities and activities interacting in a spatial and temporal organization that is productive of the phenomena that constitute the explanandum.[30] As these authors have also pointed out, this understanding of explanations is closely tied to strategies of

[27] The notions of complementation and tension implied that the researchers considered their projects to be concerned with the same domain (see Fn 3, above).

[28] These works are influenced by Jacques Loeb's (1859-1924) studies on tropism (Loeb, 1905; see Pauly, 1987).

[29] The reductionism and determinism involved in the genetic approach to behavior has been criticized from within science, as well as by philosophers. Next to Hirsch, Stent (1981) demanded caution in the interpretation of the results derived from the single gene approach. Kenneth Schaffner (1998) discusses the implications of a reductionist approach in the case of Brenner's program. I am concerned here only with the question of how the ideas of the genetic approach and mechanistic explanation shaped the design of the research project.

[30] On mechanistic explanations and the associated experimental strategies and notational practices, see Bechtel and Richardson (2010) and Craver and Darden (2013).

discovering mechanism thus conceived. In terms of project knowledge, goal schemata (in this case the very generic schema of a mechanistic explanation) and methodological schemata (in this case an intervention schema based on introducing defects) are transferred into the project as closely associated bundles. They will be considered in more detail in the following section.

3.4. Goal knowledge and methodological knowledge bundles: Pathways and the genetic approach

> The fine structure and interlacing of even the simplest nervous systems are such that to dissect them requires a very fine scalpel indeed. Gene mutation can provide such a microsurgical tool; with it one might hope to analyze the system in a manner analogous to the one which has proven so successful in unravelling biochemical pathways and control mechanisms at the molecular level. (Benzer, 1968, p. 50)

This is how Benzer continued the first description of his research program. It can be observed that the explanatory goals are limited to neither the neural nor to the molecular realm. Benzer employed several notions to characterize the explanatory goal of the project, i.e., the mechanisms to be elucidated, which are relevant for behavior on the physiological level, that is on the level of cell interactions facilitated by molecular interactions. For instance, he spoke of the "circuit components of behavior, from sensory receptors to central nervous system to effector muscles," which "are constructed under direction of the genes" (Hotta and Benzer, 1972, p. 527). Again, the influence of Wooldridge is obvious: the nervous system is likened to a computer. A more pervasive notion, however, is that of a pathway. While in the quote opening this section the pathway is associated with metabolism, Benzer also spoke of the "visual pathway" (Benzer, 1973, p. 28), a common term at the time, of the "behavioral pathway" (Benzer, 1974, p. 11), and the "whole pathway between the light and the response" (Benzer, 1991, p. 86) or the "pathway from input to output" (Hotta and Benzer, 1970, p. 1156). In both cases, the biochemical and the neuro-physiological, the pathway metaphor suggests a series of events (chemical reactions, transmissions of signals in the nervous system) that are explanatory of the end result (e.g., a functional molecule, a motor response). Both concepts, the neural pathway and the biochemical pathway, go back at least to the 1920s (Thagard, 2003). According to Paul Thagard, biochemical pathways can be understood as figuring in "explanation schemas," which characterize mechanistic explanations (Ibid., pp. 235 and 237). The notion of pathway not only expresses linearity as a simplifying assumption about the mechanisms in question, but when applied on the biochemical and the physiological level constructs a connection between the mechanisms. In the simplest case, the synthesis of functional molecules from genes builds crucial parts of the physiological mechanisms, i.e., the path consisting of "receptor response, central nervous system integration, and motor output" (Hotta and Benzer, 1970, p. 1156). The vertical biochemical pathways explain the elements in the horizontal physiological pathways (mainly by explaining the properties and capacities of neurons and other cells), while the horizontal physiological pathways from sensory input to motor output explain the behavioral response. The goal is thus an inter-level integration of mechanisms (Craver and Darden, 2013, Ch. 10).

The explanatory schema suggested a methodology. Benzer spoke of "dissection" of the nervous system. He had used the term "dissection" already regarding his investigation of the fine structure of genes. The work of George Beadle (1903-1989) and Edward Tatum (1909-1975) on *Neurospora crassa* (Beadle and Tatum, 1941, see also Kohler, 1994, Ch. 7) provided an exemplar for the genetic dissection of biochemical pathways by genetic means (although they did not use the term "dissection"). The basic idea was to mutagenize many individual organisms and select mutations that interrupt the same metabolic pathway to identify the elements and determine the temporal order of steps in the reaction. On a more generic level, the strategy has been described as the genetic approach: it aims to "discover naturally occurring or artificially produced mutants that exhibited a

difference relevant to some biological process of interest and then carrying out genetic analyses of the mutants" (Waters, 2004, p. 799). Benzer made use of this strategy in many ways, which always involved some form of adjustment to the specific task. In a manner analog to the dissection of biochemical pathways, it was possible to dissect a physiological pathway by collecting many mutations that affect the same physiological process, presumably because they interrupt one of the molecular pathways necessary for the cells in the physiological pathways to fulfill their functions.[31] The horizontal pathway is thus not only constructed under the "direction of the genes," but it can also be dissected by disabling the vertical pathway through mutagenesis. The notion of dissection suggests that a first intermediary goal in the analysis is to determine what elements there are in the pathway, i.e., decomposition.

Another central notion is that of a map, pointing to the aspect of localization. Benzer and Yoshiki Hotta (b. 1938), a postdoc in his lab, used fate maps representing the parts of the early embryo in terms of the structures they will give rise to in the larva and in the adult organism, to determine the site in the adult fly at which a gene involved in the generation of behavior is active and thereby, of course, also which anatomical parts are involved in the first place. They called this site "focus" and this became the central epistemic object in the early phase of Benzer's new program (Hotta and Benzer, 1972). Foci were epistemic objects in so far as they are embedded and contained in an experimental system and "embody what one does not yet know" (Rheinberger, 1997, p. 28). What is the identity of the gene active at the site, what is its product, what is the function of the product, how does it interact with other molecules, how does this interaction determine the function of the cells, and how does the cell function integrate in the larger physiological process generating behavior? These were the questions that could be asked based on mapping the focus. To achieve the goal of localization, Benzer and his co-workers adopted a specific method based on genetic mosaicism, i.e., of generating organisms that contain tissues with different genotypes. As Hotta and Benzer summarized the project in an article titled "Mapping of Behaviour in *Drosophila* Mosaics": "By making genetic mosaics and constructing embryonic 'fate maps' it is possible to locate the anatomical site of abnormalities affecting behaviour" (Hotta and Benzer, 1972, p. 527). The notion of mapping thus expressed another intermediary goal in the search for mechanisms, the method to achieve this goal, as well as the form representation of the result. The methodological combination of mutations and mosaics employed to achieve the intermediate goals can thus be characterized as decomposition and localization (Bechtel and Richardson, 2010). Mechanistic explanations can be seen as constituting already quite complex goal schemata that can be broken down into several intermediary goals, each associated with an appropriate methodological schema, which are then combined into complex methodological schemata accordingly. While mechanistic explanations and associated intervention strategies are generic goals and methods, molecular and neural pathways and mutagenesis are domain-specific renderings of these goal and method bundles. Nonetheless, they constitute a fairly abstract approach applicable to many problems. The mapping approach based on mosaics is an example of a method on the level of a specific technique. In the following section I shall explain the approach in more detail, reconstruct how the relevant knowledge was resituated, and show how methodological and notational schemata are closely associated in this case.

[31] Already Benzer's (1955) dissection of the gene relied on the strategy of collecting as many mutants as possible that, in this case, affect the same gene. The method of genetic dissection was thus scalable from genes to biosynthetic pathways, to physiological processes.

3.5. Intermediary goals, methodological and representational knowledge: Mapping the "focus" of gene action

On the assumption that non-phototactic mutants are blind, the question could be asked which point in the pathway of reception, transmission, and processing of the visual signal is affected. One of the procedures applied was an elctroretinogram (ERG) recording. Based on this technique, Hotta and Benzer were able to identify various non-phototactic mutants which seemed to show an effect in the photoreceptor cells and others which seemed to have deficient second-order neurons (Hotta and Benzer, 1969). There were, however, other behavioral mutants for which it was not easy to detect the anatomical structures that were affected because the relevant structures might be hidden deeper inside the body of the fly, showing no histological aberrations (or one wasn't sure where to look for them). A further complication was that not all effects were cell autonomous, i.e., tissues that were genotypically wild type could still show aberrations as secondary effects of a gene defect elsewhere in the body that prevented the production of a circulating substance, for instance, that was necessary for the former structure to develop or function normally. Here is how Benzer defined the task:

> [I]f one knows that a certain behavior (nonphototactic, say) is produced by a single-gene mutation and that it seems to be explained by an anatomical fault (the degenerated receptors), one still cannot say with certainty what is the primary "focus" of that genetic alteration, that is, the site in the body at which the mutant gene exerts its primary effect. (Benzer, 1973, p. 28)

To solve the problem, Hotta and Benzer adopted and expanded a methodology that was introduced by Sturtevant more than 30 years before. Sturtevant (1920) had used flies (*Drosophila simulans*) that were genetically mosaic, i.e., which consisted of tissue areas that were genotypically different, to demonstrate non-autonomy of the *vermilion* character. By drawing a methodological analogy from his earlier work where he mapped the relative distance of genes on the chromosomes on the basis of the frequency of recombination (Sturtevant, 1913; see also Vorms, 2013), Sturtevant went on to devise a technique that allowed him to infer the relative distances between regions in the early embryo that would give rise to certain parts of the fly (Sturtevant, 1929). Antonio García-Bellido (b. 1936) and John R. Merriam, who were working as postdocs in Lewis lab at Caltech, re-worked Sturtevant's partly unpublished data to create more advanced fate maps (García-Bellido and Merriam, 1969). In the zygote of the fly many nuclear divisions occur before the nuclei migrate to the boundary of the egg where membranes are formed, resulting in a spherical single cell layer – the blastoderm. It happens occasionally (and more frequently in certain mutants) that an X chromosome is lost in nuclear division, resulting in nuclei with different genotypes. Since the position of the axis of the first nuclear division relative to the axis of the egg is random and determines the distribution of the nuclei with different genotypes in the blastoderm, the lines dividing areas in the blastoderm with different genotypes are hence randomly distributed. Two areas that lie closer together in the blastoderm are less likely to be of a different genotype. Accordingly, one can use the frequency of any two structures of the adult fly showing the same or a different phenotype to calculate the relative distance in the blastoderm of the cells that give rise to the respective adult structures. The blastoderm is for that purpose conceptualized as the two-dimensional surface of a sphere. If the relative distances of blastoderm loci can be related to known positions or dimensions in the blastoderm, such as the dorsal and ventral midline, the result would be a fate map of the blastoderm, i.e., a map indicating the physical positions of areas in the blastoderm that give rise to different structures (thus having different fates). These maps could then be related to other fate maps that were constructed by embryological techniques, such as marking cells with vital dyes and

tracking the movement in the developing embryo or observing where in the larval or adult organism traces of the dye could be found.[32]

To create a fate map based on mosaic analysis, it was necessary to determine the genotype of the anatomical structures in the adult fly. This was straightforward in the case of surface structures that reveal their genotype through marker phenotypes such as cuticle color, bristle shape, or eye color. It was less clear how the methodology could be applied to determine the relative position of blastoderm regions that give rise to internal structures. Benzer and Hotta, working in close vicinity to García-Bellido and Merriam, adopted the mosaic methodology, expanded its scope, and applied it to behavioral phenotypes (Hotta and Benzer, 1970 and 1972). They constructed a fate map for *Drosophila melanogaster* based on surface phenotypes. These figured as "landmarks," as they called them, in mapping internal structures that influenced behavior by recording the frequency by which a behavioral mutant phenotype co-occurs with a surface phenotype. This was the basis for calculating the relative distance between the regions in the blastoderm that gave rise to the surface landmarks and those giving rise to the anatomical structures that caused the behavioral abnormality when dysfunctional due to carrying the mutant genotype. Through triangulating distances between landmarks and behavior related blastoderm regions, it was possible to locate the latter on the fate map. Since the fate map based on the mosaic methodology could be related to embryological fate maps based on lineage tracing, it was often possible to conclude, from the location of the region associated with the behavioral phenotype in the blastoderm and the knowledge of its fate, where in the adult body the gene was active that in its mutant form resulted in the aberrant behavior. Hence the pathway of inference ran from the behavior to the blastoderm and back to the anatomical structures involved in generating behavior.One mutant analyzed by Hotta and Benzer, to give an example, was called *drop-dead*.[33] The flies carrying the mutation would behave normally for one or two days, but after some time (varying among affected individuals) they would move less and more erratically and finally fall on their back and die. As Hotta and Benzer observed, "*[a] priori*, symptoms such as these could result from malfunction in almost any part of the body of the fly, such as blockage of the gut, a general biochemical disturbance, or a nervous disorder" (Hotta and Benzer, 1972, p. 531). By mapping the blastoderm region associated with the phenotype, they could infer, based on existing fate maps, that it lies in a region that was found to give rise to the brain by embryologists (see Fig. 1, left side). Histological analysis confirmed the localization in that, after the onset of the *drop-dead* behavior, affected individuals showed signs of degeneration in the brain. However, without the mosaic analysis it would not have been possible to determine whether this was a primary effect of the disturbed gene function in the brain cells (i.e., if the effect was autonomous), or a secondary effect of the mutation causing deficiencies at another site in the body.

[32] See Galperin (1998) and Griesemer (2007) for the history and epistemology of lineage tracing and fate mapping.

[33] Phototaxis was the first phenotype for which Benzer collected mutants. As the project progressed, more and more behavioral phenotypes appeared. The mutant *drop-dead* is also an example of a phenotype that would not have been classified as behavioral in other areas of behavioral biology.

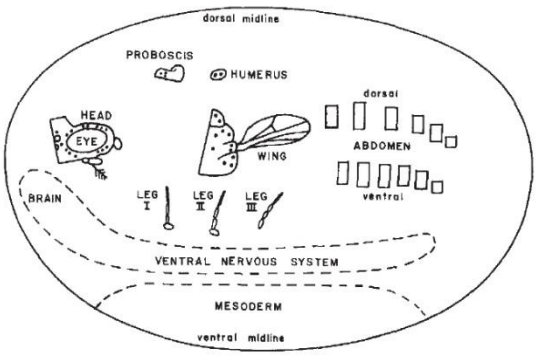

Fig. 6 Pictorial sketch of the external parts of an adult fly derived from various sites on the blastoderm, based on the fate map. This represents only the right half of the fly; the left parts are formed from the other half of the embryo. Dotted lines indicate areas which, according to embryological studies, give rise to the nervous system and the mesoderm.

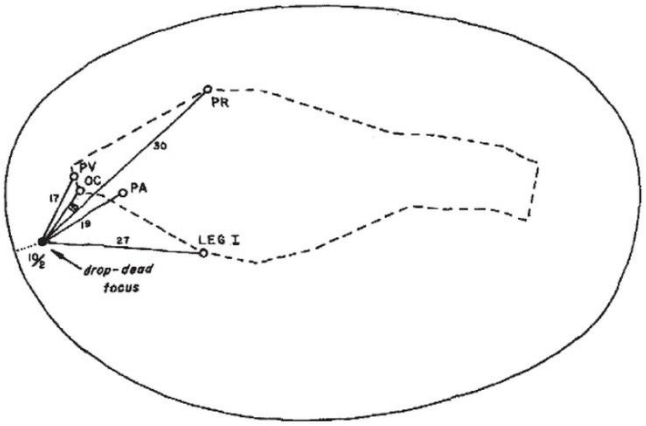

Fig. 10 Fate map of the *drop-dead* mutant focus.

Fig. 1. The representational techniques of fate mapping: Fig. 6 (left) and 10 (right) from Hotta and Benzer (1972, pp. 529 and 533) with original captions. The left diagram shows how the parts of the adult fly were mapped on regions in the blastoderm that will give rise to these structures. This made it possible to map a behavioral phenotype on the blastoderm and infer in which part of the adult body the gene that produces the phenotype when mutated is active. The right diagram shows a fate map locating the blastoderm focus for the *drop-dead* mutant in a region that (according to the left diagram) should give rise to the brain. Reprinted by permission from Springer Nature: Hotta, Y., and Benzer, S. (1972). Mapping of Behaviour in *Drosophila* Mosaics. *Nature*, 240(5383), 527–535. Copyright 1972.

The generic strategy of using the genetic approach for mapping, i.e., for not only identifying but also localizing entities relative to each other and in a larger structure of which they are part, was familiar to Benzer from his earlier work on the fine structure of a phage gene. This enabled him to evaluate the potential of the specific method of mosaic analysis developed by his colleagues at Caltech. He acquired knowledge about the technique through direct communication and the relevant publications. Using project knowledge on this specific level amounts to reproducing an experiment, albeit in a differential manner that embeds it in the context of different goals and combines it with different techniques (in this case, behavioral screens and ERGs, etc.).[34] Knowledge of the mosaic method came with knowledge of procedures for analyzing the data and of notational practices for recording the data and representing the result. The construction of the resulting maps was informed by two domain-specific mapping schemata: one derived from genetics and hence familiar to Benzer, representing the relative distances between entities (in the case of genes these maps were one-dimensional, here they became two dimensional), and one from embryology, representing the blastula as a two-dimensional space consisting of regions with differential developmental fate (Galperin, 1998). The introduction of the mapping strategy also demonstrates the dynamic character of research projects and hence of the recruitment of relevant project knowledge. The (intermediary) goals of the project became adjusted in response to the constraints and opportunities that emerged in the course of its implementation. The idea of hitting upon cytochemical markers that determine the wiring pattern of the nervous system through mutation that motivated the project initially was not entertained anymore once the project gained traction. Instead, the mapping strategy was taken up in an opportunistic manner. The spatial proximity of researchers enabled by the institution played

[34] On differential reproduction, see Rheinberger (1997), Ch. 5.

an important role here.[35] The approach allowed Benzer and Hotta to achieve the intermediary goal of localizing the site of action of genes that affect behavior, or what they called its "focus." This was seen as a step towards elucidating the biochemical pathways the gene and its product are involved in, and how they interact with other genes and their products to build the neuro-physiological mechanisms that generate behavior.

4. Conclusion: Modes of resituating project knowledge in the attempt to create a molecular biology of multicellular organisms

Mary Morgan's (2014) account of resituating knowledge distinguishes between instances in which knowledge is transferred from one local setting to another, similar setting, and instances where a form of abstraction takes place that de-contextualizes a local finding, creating some causal or conceptual knowledge that can then be resituated in many, as well as less comparable, localities. This matches with the notion, supported by the case study, that project knowledge can be domain-specific or generic (see 1.4). Some project knowledge is rather abstract, specifying on the one hand forms of knowledge in the broadest sense in terms of possible relations between entities that can be the subject of scientific knowledge, and on the other hand generic strategies for achieving knowledge of that form. Knowing the generic structure of a mechanistic explanation and the basic experimental strategies that can be employed to investigate mechanisms would be an example of highly abstract project knowledge. The case study suggests that researchers often reason about the design of research projects on the basis of more domain-specific project knowledge, specifying on the one hand possible outcomes of research in terms of the entities or processes that make up the domain, and on the other hand specific operations of intervening or registering that pertain to these entities or processes, as well as specific forms of representing hypotheses or results and of organizing the work. A more specific mechanism schema, for instance, will encode what is considered an adequate mechanistic explanation in a community investigating a domain. Benzer began his reasoning (at least to the extent that it is documented in his published writings) with the notion of biochemical pathways and their investigation by means of genetic analysis, which was familiar to him from his earlier work in the emerging field of molecular genetics. Nonetheless, when he thought of mechanisms on multiple levels, including neural mechanisms, he presumably relied on a more generic understanding of mechanisms. Instead, when it comes to selecting appropriate methodological strategies for investigating higher level mechanisms, the strategy was not to derive an abstract notion of introducing a defect in the system from the specific strategy of mutagenesis, but rather to use this specific strategy to intervene on the higher level mechanism.[36] While the notions of biochemical pathways and genetic analysis, albeit domain-specific, are still fairly abstract, knowledge about detailed experimental designs is often resituated directly from one local setting to another. Benzer's adoption of the mosaic-based mapping strategy and the representational techniques associated with it are a case in point. Here experiments, calculations, and drawings performed by Sturtevant, García-Bellido, and Merriam were reproduced. The purpose was not, however, to replicate an experiment to show that it is valid, but rather to produce the same kind of information regarding the physiological processes and genes of interest to Benzer and his group. In the course of the application of the procedure, the experimental design was adapted to their

[35] On local contingencies, see Knorr-Cetina (1981), Ch. 2.

[36] Intervening on the level of parts of the nervous system would have been an alternative. The group of Sperry, for instance, followed the same broad method, but their approach was more rooted in classical ablation experiments of physiology.

purposes and expanded in its scope. This form of resituation of project knowledge is thus well captured by Rheinberger's notion of differential reproduction of experimental systems (Rheinberger, 1997, Ch. 5).

Regarding the more abstract forms of project knowledge discussed above, one question is whether such knowledge circulates in research communities and researchers acquire it in its abstract form, or whether they learn by working on instances of research problems and through these gain an abstract understanding. Presumably, both ways of project knowledge acquisition play a role. Textbooks and teaching provide generic notions of research problems and suitable experimental designs. In this case the step of de-situation by abstraction has already been made by others and researchers only resituate the knowledge when designing a new project. But researchers also learn from experience in earlier work on specific problems and perform both steps in this kind of resituation via abstraction. Another route might be provided by exemplars. Morgan further distinguishes instances of resituation where local knowledge is established or at least perceived as typical or exemplary. Some ways of carrying out research projects can certainly be described as functioning as exemplars. If the project knowledge that these exemplars embody is carried over to another situation, this requires the same work as in cases of local-local transfer or cases that involve abstraction, depending on how similar the target situation is to the exemplary situation. For this reason, the distinction with the other modes of resituating knowledge cannot be drawn sharply, at least for project knowledge. The notion of exemplars is nonetheless justified for experiments, representations, or research enabling structures that are well known in a community. There might often be more recent or more elaborate approaches, but when researchers are not aware of them (or they simply don't come to mind), they resort to well-known exemplars. These serve as a source for relevant project knowledge especially when researchers are not yet looking for more specific procedures, i.e., when they have to choose a research environment and frame a problem in the first place. Once a project is initiated on the basis of exemplars, more specific project knowledge will be sought. The *Drosophila* and phage communities and their networks of exchange certainly often served as exemplars when new model organisms have been introduced or refashioned (as was the case for Brenner and Streisinger). Particular experimental approaches also frequently figure in that way. Sturtevant's analysis of the non-autonomous expression of the vermilion character or Beadle's and Tatum's experiments with *neurospora crassa*, despite being somewhat dated at the time, clearly were exemplars that came to Benzer's mind when reasoning in terms of genetic analysis. These latter cases of exemplary problems and solutions are reminiscent of Kuhn's notion of exemplars as one of the central meanings of the term "paradigm" (Kuhn, 1970, p. 187). It needs to be emphasized, though, that the present account differs from Kuhn's. Kuhn draws an image of, on the one hand, largely hermetic communities of "normal science" that share an understanding of puzzle solving and, on the other hand, of scientific change in terms of replacement of one such community by another, sharing a different understanding, based on novel exemplars. The emphasis in the present account is on a constantly merging and diverging flow of project knowledge that helps to construct familiar problems and solutions in novel domains, or recombine methods to forge new approaches. Scientific change, at least in twentieth-century biology, seems to be better described as a constant merging and diverging of approaches and domains, much more in line with Rheinberger's notions of conjunctures, hybrids, bifurcations, and the formation of experimental cultures (Rheinberger 1997, Ch. 9). The account of project knowledge provided here helps to reconstruct the reasoning that underlies these processes.

Regarding the history of biology, the result of the present study seems to confirm the notion that early hopes for making the new molecular biology fruitful for questions of metazoan physiology, in particular concerning development and the neural basis of complex behaviors, were not easily fulfilled (Morange, 1997; Suárez-Díaz and García-Deister, 2015). Indeed, the results produced by

Benzer and his colleagues mainly relied on genetic analysis and were not very molecular in nature. One might say that developmental and neuro-genetics only became molecular after new techniques, in particular those derived from recombinant DNA techniques, were established towards the end of the 1970s (Morange, 1997; Weber, 2004). Important were, for instance, positional cloning to identify genes, or *in situ* hybridization to observe gene expression, and monoclonal antibodies to identify proteins, but also many other new ways to analyze regulatory components of the genome, the structure and function of gene products, and their regulation and cell function related interactions. Benzer's own work subsequently narrowed down to the development and neuro-physiology of the visual system, with questions of behavior moving to the background. This work would take full advantage of the new molecular techniques (see, e.g., Fujita et al., 1982). Nonetheless, the focus on the role of the resituation of project knowledge in designing new research projects makes clear how reasoning about new experimental approaches was often informed by the successes in the bacterial or fungal models of early molecular biology and biochemical genetics. Furthermore, it brings to the fore how biologists at the time around 1970 pushed classic genetic tools to ever more fine-grained analysis, creating, among other things, new ways to trace cell lineage. Clonal analysis was a major approach in developmental biology and while strategies based on genetic mosaics developed by García-Bellido, Benzer, and others were but one approach, they proved to be highly effective and in many ways provided the conditions for relating molecular data to regulatory and cellular functions in development and neuro-physiology (Galperin, 1998).

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