A Reconstruction of Some of Claude Bernard's Scientific Steps

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Abstract

Our aim is to reconstruct Claude Bernard's empirical investigations with a computational model. We suppose that Bernard had in mind what we call *core models* that contain the basic physiological concepts upon which Bernard builds his general physiological theory. The core models provide a simplified view of physiology, which allows Bernard to make hypotheses and to draw out their logical consequences. We show how those core models are specified using both description logics and multi-agent systems. Then, we explain how it is possible to build, on these core models, a virtual experiment laboratory, which lets us construct and conduct virtual experiments that play a role similar to that of thought experiments. More generally, we attempt to correlate Bernard's experiments, performed to corroborate or refute some of his working hypotheses, to virtual experiments emulated on core models.

Introduction

In the past, there have been many attempts to rationally reconstruct scientific discoveries with Artificial Intelligence techniques (Feigenbaum, Buchanan, & Lederberg 1971; Langley *et al.* 1986; Shrager & Langley 1990; Kulkarni & Simon 1990). According to Simon, creativity, which is involved in the discovery process, is akin to the manner in which we find our pathway in a labyrinth (Simon 1957; 1983). From a technical point of view, creative behavior can be seen as a graph search. Even if this view is efficient and fruitful from a practical point of view, it does not tell anything concerning the logical status of the scientific discovery process. Is it mainly an inductive, deductive or abductive process? Epistemologists do not agree on this point; but whatever their underlying theories, it appears that many different kinds of inferences are inferences involved in scientific discovery. Nevertheless, up to now, most of the simulations of scientific discovery processes that have been achieved in Artificial Intelligence correspond to the simulation of inductive processes. Moreover, today, Knowledge Discovery from databases corresponds naturally to an inductive process, since it builds general knowledge from particular cases. This paper constitutes an attempt to reconstruct some of Bernard's scientific steps that are mainly abductive. It explores, with the help of Knowledge Representation and Multi-Agent techniques, some aspects of the discovery science that are not directly related to inductive processes. Our first goal is to validate our rational reconstruction with historical knowledge about Bernard's scientific discoveries. But our ultimate goal is to help scientists, especially clinical physicians, design experiments that give consideration to the fundamental theories in mind.

The CYBERNARD Project

Claude Bernard (1813–1878) was one of the most eminent 19th century physiologists. He was a pioneer in many respects. He introduced the concept of internal environment (the "Milieu intérieur") (Grmek 1997), which corresponds to today's principle of "homeostasis." He investigated and shed light on many physiological mechanisms, e.g., the glycogenic liver function (Prochiantz 1990), effects of carbon monoxide, (Bernard 1864; Grmek 1973), and the effects of curare (Bernard 1857; 1864).

But Bernard was not only a great physiologist; he was also a theoretician who generalized his experimental method in his famous book, "Experimental Medicine" (Bernard 1927), now a classic read by all students of medicine.

The goal of the CYBERNARD project (Ganascia & Debru 2007) is twofold. Firstly, the project will clarify and generalize the experimental method by formalizing it with artificial intelligence techniques and by simulating it on computers. It will then be possible to understand in what respect this method is general and can be applied to contemporaneous clinical medicine. Once this first goal will be achieved, we shall attempt synchronous reconstructions of some of Bernard's scientific discoveries, i.e., reconstructions of the discoveries that he described at the end of his life. Secondly, the project will confront Bernard's original scientific texts — i.e., his personal notes, scientific papers, etc. — and reconstruct his work in writing "Experimental Medicine." Our aim is to understand whether the method described in "Experimental Medicine" corresponds to the actual method that Bernard used or to an ideal reconstruction of what it should have been? This confrontation can be called a diachronic reconstruction, since it compares Bernard's last reconstruction of his own work with his ideas as they were expressed in his notebooks and published articles at the time of discovery. Three teams participate in the highly interdisciplinary CYBERNARD project: the ACASA team, an artificial intelligence group belonging to the LIP6 computer sci-

ence laboratory, the epistemology department of the École Normale Supérieure directed by Claude Debru, and the linguistic team of the ITEM laboratory, which specializes in genetic criticism.

This paper describes a preliminary work of the ACASA team that is to build and simulate on computers core models. Within this work, our aim is to reconstruct Bernard's empirical investigation with a computational model that simulates his experimental method. More precisely, we assume that Bernard has in mind an ontology of the physiology which is used to express scientific hypotheses concerning both the organ functions and the activity of toxic and/or medicinal substances. He uses this ontology to design experiments that are intended to discriminate among the different scientific hypotheses. Our first aim here is to build the ontology described in the Bernard's works with modern knowledge representations techniques. We want then to construct, on the top of this ontology, models that could simulate Bernard's experiments.

We are mainly interested in his investigations of carbon monoxide and curare effects. To start, we refer to two of Bernard's texts (Bernard 1857; 1864) in which he rationalizes his own discoveries. In parallel, with the help of epistemologists and philologists, we confront Bernard's computer reconstruction with his former reasoning as it appeared in his writings. However, this paper focuses only on the first point.

The first part recalls the Bernard's experimental method. The second formalizes Bernard's medical ontology. The third is dedicated to the description of a two level model built to simulate the experimental method. The fourth describes the notion of core model. The fifth introduces the virtual laboratory which hosts virtual experiments. A sixth section presents the hypothesis generation module, and the final part envisages possible generalizations of the experimental method and of its simulation to multi-scale core models.

The Experimental Method

According to Bernard's views, scientific investigation cannot be reduced to the sole observation of facts nor to the construction of theories that have not been previously confirmed by empirical evidence. In other words, Bernard is neither an inductivist who reduces the scientific activity to the pure induction of general rules from particulars, nor an idealist — or a neo-Platonist — who thinks that ideal, pure and perfect theories are given before any experimentation. The experimental method he promotes begins with an initial theory, which is usually built from passive observations or preconceived ideas. When the phenomenon is unknown, some experiments "to see" are performed.

For instance, when Bernard investigated the effects of the curare, he began with some general experiments in order to see what happened and to provide a first idea. Bernard does not detail the way the first idea or the initial theory is built. It corresponds to an intuition, or what he called a feeling, that must be validated and refined or adjusted according to empirical results generated by relevant experiments. The experimental method starts there.

In other words, once an initial theory is given, scientists must design an experimental apparatus able to test (corroborate or refute) the given theory. The experiments are viewed as "provoked" observations generated by an adequate device; those observations are compared with the expectations derived from the given theory. Their cautious analysis helps to revise, correct, refine or validate the current theory. The inferences that are involved in such an analysis clearly correspond to abduction, since it is to try to explain observations by modifying theories. However, Bernard's trail of thought cannot be simply reduced to abduction. The experimental method, iterated until the theory predicts all current experimental results, makes use of abduction, deduction, analogical reasoning and induction.

More precisely, the experimental method described by Bernard is an iterative procedure of theory refinement that proceeds in three steps, each step involving a specific scientific function:

Experimentation: A hypothesis to be validated is given. It is called an idea or a theory. For the sake of clarity, we shall refer to it as the *current theory*. The first step is to design an experimental apparatus able to generate observations to be compared to expectations derived from the current theory. In other words, the experimentation is designed to test the hypothesis under investigation, i.e., the current theory.

Observation: The second step consists in collecting observations from the designed experiments. It is not only a receptive step, since the experimenter may interpret observations and note unexpected details.

Analysis: The third step is the most crucial and original. It is to confront the current theory predictions to the observations and to generate plausible hypotheses that may transform the current theory when its predictions are not in accordance with the experimental observation.

The key question concerns the analysis and, consequently, the hypothesis generation: how, from a set of observations that invalidates a set of theories, would it be possible to generate new theories that will then be evaluated and refined until experiments will fully validate them? That step plays a crucial role in the experimental method. One has to clarify and to generalize it if we want to model and to simulate the method. In other words, designing an experiment to validate or invalidate a theory is a very complicated task that requires intuition, skill and imagination. It is out of the scope of our project to automatize such a design.

On the other hand, the observation is mainly a matter of patience. Today, it may appear that sensors and computers could help in gathering and examining data. Therefore, this step is not central to the experimental method that mainly has to analyze observational data and then to generate new theories. Our focus in this paper is to automate the analysis of experimental results and the hypothesis generation process that corresponds to the most crucial step. We assume that abduction plays an important role here, explaining experimental results by modifying the current theory.

Abductive reasoning typically makes use of background knowledge, on top of which hypotheses are formulated. All of Bernard's hypotheses and revisions appear look similar; they are formulated using the same words, and seem to be

generated from the same "ontology." In the late reconstruction of his discoveries, Bernard elicited the "ontology" he had in mind. The next section describes it.

Bernard's Ontology

To have a clear understanding of Bernard's ontology and of its originality, one has first to cast a glance at previous medical conceptions. Let us first recall that the old theory of fluids introduced by Galen (131–201), during the 2nd century, and very much developed by Santorio Sanctorius (1561–1636) in the early 1600's was prevalent in the 17th and 18th century European medical schools. According to this theory, the body is made of solid tissues and fluids, which naturally tend to become corrupted without excretions and perspiration. As a consequence, most of the diseases and of the body dysfunctions are due to fluid corruption. At the end of the 18th century, inspired by physics and chemistry, François Magendie (1783–1855), who was Bernard's professor, and François-Xavier Bichat (1771–1802) studied anatomy and the organs. Physiology was then viewed as a physical interaction between organs. As a consequence, the causes of body dysfunctions and diseases were attributed to organ damages. Post-mortem dissection could then help to diagnose the organs responsible of the diseases. Bernard opposed to this reduction of organs to physical bodies; he thought that organs are not simply inert solid tissues, but that each autonomy and unique functions which must be investigated. More precisely, in his writings (Bernard 1864; Grmek 1973), Bernard presumes that organisms are composed of organs which are themselves analogous to organisms since each has its own aliments, poisons, excitations, actions, etc.. Organs are categorized into three classes — skeleton, tissues (e.g., epithelium, glandular tissue or mucous membrane), and fibers (i.e., muscles and nerves) — that are recursively subcategorized into subclasses, subsubclasses, and so on. Each class and subclass has its own characteristics, which can easily be formulated, according to Bernard's explanations.

The internal environment ("milieu intérieur"), mainly the blood, carries organ poisons and aliments, while the organ actions may have different effects on other organs and, consequently, on the whole organism. More precisely, for Bernard, "life" is synonymous with "exchanges." Organisms exchange through and external medium, e.g., air for terrestrial animals, and water for aquatic animals. The external medium may also carry aliments, poisons etc.. Similarly, organs can be viewed as some sorts of organisms living in the body and participating in its life. Their life is also governed by exchanges, but the medium that supports exchanges is not air or water; it is the milieu intérieur, which mainly corresponds to blood. Bernard's ontology may be derived from these considerations. It is then easy to formulate it in an ontology description language similar to those that are currently used in the life sciences to represent biological and medical knowledge (Ceusters & Smith 2007). Note that most of the ontologies used in the biomedical community, e.g., OBO, the Open Biological Ontologies[1], refer mainly to three levels: the first for the organs and the anatomy, the second for the cells and the third for molecules. For obvious reasons Benard's ontology refers mainly to the first, i.e., to organs and anatomy, and sometimes to chemistry, i.e., to molecules. However, it would possible to extend our model to a three level ontology that is more appropriate in contemporary medicine.

For instance, below are some of the previous assertions expressed with description logics (Nebel & Smolka 1991).

The organs belong to the class Organ and are all parts of the organism:

$$Organ \sqsubseteq \exists PART.Organism \tag{1}$$

The organs are tissues, skeleton or fibers:

$$Organ \equiv Tissue \sqcup Skeleton \sqcup Fiber \tag{2}$$
$$Tissue \sqcap Fiber = \bot \tag{3}$$
$$Tissue \sqcap Skeleton = \bot \tag{4}$$
$$Fiber \sqcap Skeleton = \bot \tag{5}$$
$$\tag{6}$$

Fibers may be nerves or muscles:

$$Fiber \equiv Nerve \sqcup Muscle \tag{7}$$

Nerves may be sensitive or motor:

$$Nerve \equiv SensitiveNerve \sqcup MotorNerve \tag{8}$$

Epithelium, glandular tissue, mucous membrane, etc., are tissues:

$$Tissue \sqsupseteq Epithelium \sqcup GlandularTissue \sqcup MucousMembrane \sqcup \cdots \tag{9}$$

Each organ can be viewed as some sort of organism that has its own nutriments, its own poisons, its own actions, etc.:

$$Organ \sqsubseteq \exists Aliment \tag{10}$$
$$Organ \sqsubseteq \exists Poison \tag{11}$$
$$Organ \sqsubseteq \exists Action \tag{12}$$
$$\vdots$$

The physiological ontology plays a crucial role in the way Bernard erected new hypotheses. It can be considered as a clue for the discovery process. All scientific hypotheses obviously depend on the concepts with which they may be expressed. On the one hand, when a concept is lacking, one may miss some efficient hypotheses; on the other hand, the presence of some useless concepts leads to the formulation of misleading and confusing explanations. For instance, the old fluid theory precluded the observation of correlations between the evolution of the scurvy disease and the presence of fruit and vegetable in nutriments (Ganascia 2008b). Bernard himself was unable to precisely locate the effects of curare, despite his relentless work during more than twenty years; one explanation could be that the concept of *motor nerve ending* did not belong to his ontology.

The question is how ontologies originate? What is their relevance? And how do they evolve? Up to now, we do

[1] http://obofoundry.org/

not yet feel able to provide fully convincing answers, but our goal within this work is to contribute to get a better understanding of those ontology evolution processes. In the case of Bernard, the ontology described here corresponds to the one he gave in papers (Bernard 1864; 1857) and books (Bernard 1927) at the end of his scientific life. There is no doubt that it appears naive and wrong with respect to the modern medical knowledge. Nevertheless, the main question for us does not concern its relevance today, but its evolution during Bernard's scientific career.

This paper is focused on the rational reconstruction of Bernard's discoveries that he achieved during his famous career Our ultimate goal is to go further and to compare this late and personal reconstruction of his scientific discoveries to the his discovery process as it appears in informal notes, laboratory books, scientific papers, etc..

Two-level Model

As previously stated, abduction played a crucial role in Bernard's investigations. More precisely, he always considered an initial hypothesis, which he called an idea or a theory. He then tried to test it by designing *in vivo* experiments. According to the observational results of his experiments, he changed his hypotheses, until he reached a satisfying theoretical explanation of empirical phenomena.

Core Models

To design a computational model that simulates the intellectual pathway that led Bernard to his discovery, we have supposed that he had in mind core models that contain basic physiological concepts — internal environment, organ names, etc. — upon which he built his theories. More precisely, theories correspond to hypothetical organ functions that Bernard wanted to elucidate, while core models describe the physical architecture of the organism.

The core models enabled Bernard to hypothesize tentative assumptions and draw out their logical consequences. These core models constitute the basis of the reasoning process; they correspond to putative architectures of the organisms. They are built on the top of the ontologies presented in the previous section. Depending on the question under investigation, they may be more or less simplified. For instance, if one wants to investigate the heart function, it is not necessary to detail the precise role of all muscles. Our aim is to build and to simulate those core models using multi-agent architectures. Such simulations have to show, on a simplified view, both the normal behavior of the organism and the consequences of an organ dysfunction.

Working Hypotheses Management

The second level of the considered model manages hypotheses relative to the function of different organs. Each working hypothesis is evaluated through empirical experiments. Bernard assumed that one can use toxic substances as tools of investigation — he evoked the idea of a "chemical scalpel" — to dissociate and identify the functions of different organs. He presupposed, as an underlying principle, that each toxic substance neutralizes one organ first. When a toxic substance affects an organ, the anatomy of death shows how the organism behaves without the poisoned organ. Nevertheless, even when laying down such a presupposition, the investigation puzzles many physiologists, because it is a double entry enigma: they have to elucidate both the organs corrupted by toxic substances and the function of affected organs.

Two questions need to be solved when we want to rationally reconstruct the discovery process: how are working hypotheses generated and how are validating experiments designed? In order to answer these questions, we add to the core model a working hypothesis management module that has both to guide working hypothesis generation and to design experiments. Once a hypothesis is made, virtual experiments have to simulate, on the top of the core model, the probable observable consequences of this hypothesis, which helps designing real experiments. Such virtual experiments are analogous to thought experiments in traditional physics: they are required as a preliminary step to any empirical experiment. For the sake of clarity, let us recall that thought experiments are experiences that scientists do not conduct in the outside world, but only in their head. One may attempt to describe some of those thought experiments with computer models as *in silico* experiments (Ganascia 2008a), i.e., experiments that can be simulated on silicon chips.

In the case of Bernard, we have found in his writings personal notes describing ideas of experiments. Some of them correspond to experiments that have actually been achieved, while most of them remain imaginary. Our aim is to simulate those ideas of experiments with core models and to understand the place of those experiments in the discovery process with the hypothesis management module.

Core Model Simulation

The core models contain organs and connections between organs through the internal environment, mainly the blood, and direct connections. Both organs — e.g., muscles, heart, lung, and nerves — and connections between organs are represented using automata, i.e., entities characterized by their inputs, their outputs and their internal state. A core model may then be viewed as a network of automata. Each organ corresponds to an automaton with an internal environment plus external or internal excitations as inputs, organ actions and modified internal environment as outputs and a symbol characterizing the state. It is possible for the internal environment to lose or gain some substance, for instance oxygen, and some pressure when passing by an organ. In the case of muscles, the input internal environment corresponds to arterial blood while the output corresponds to venous blood. Most of the connections correspond just to transmitters that associate the outputs of some organs to the inputs of others. Nevertheless, connections may also act as crossing points, for instance, as an artery splitting or as a vein join that divide or concentrate the flow.

From a computational point of view, each organ is viewed as an agent (Russell & Norvig 1995) that communicates with other organs and evolves in the milieu intérieur viewed as the internal environment. As a consequence, the organism is modeled as a synchronous multi-agent system, where

each agent has its own inputs, transfer function and states. The agents correspond to the concepts of the previously described ontology. The organ activation cycle follows the blood circulation. Time is supposed to be discrete and after each period of time, the states of the different automata belonging to the core model and their outputs are modified.

The implementation used object oriented programming techniques. It helped both to simulate the core model evolutions and to conduct virtual experiments (see next section) on those core models, which fully validates our first ideas concerning the viability of the notion of core model. Within this implementation, organs, i.e., instances of concepts of the initial ontology, and connections between organs are associated to objects. The inheritance and instantiation mechanisms of object oriented programming facilitate the implementation of those agents. However, since our ultimate goal is to simulate the hypothesis generation and, especially, the abductive reasoning on which the discovery process relies, we chose to build core models using logic programming techniques using which it is easy to simulate logical inferences, whether deductive or abductive.

The logic programming implementation is programmed in SWI Prolog[2]. It makes use of modules to emulate object oriented programing techniques, i.e., instantiation, inheritance and message sending mechanisms. The resulting program looks like a collection of modules similar to the one given in Figure 1. Each of those modules describes a class of organs, e.g., muscles. Finally, on the top of the inheritance hierarchy of modules, there is a conjunction of literals corresponding to a virtual organism expressed as a network of connected organs. Once an initial condition and some ulterior events are given, it is possible to make the organism evolve by itself and to print states characterizing this evolution.

Virtual Thought Experiments

Once the core model is built, it is not only possible to simulate normal organism behavior, but also to introduce pathologies, i.e., organ deficiencies, into the multi-agent system that models the organism and then emulate its evolution. In a way, these abnormal behavior simulations can be viewed as virtual, or thought, experiments: they help to draw consequences of virtual situations under a working hypothesis, i.e., a supposition concerning both the effect of a substance on some organs and the function of the implied organs. In order to complete the range of virtual experiments, we introduce, according to Bernard's practices, some virtual experimental operators, such as injection and ingestion of substances, application of tourniquet on members, and excitations.

For instance, if one wants to understand the effects of a substance *A*, one can hypothesize that its concentration in the blood may affect such or such organ subclass that has such or such function in the organism. Under these hypotheses, it is possible with the core model simulation to predict the consequences of a direct injection of *A* combined with any combination of experimental operations, e.g., applying

[2]http://www.swi-prolog.org/

```
:- module(organ, []).
inherit(organ, automata).
%%%%%%%%%%%%% Output %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
output(O,E,dead,S)  :- invoke(O,transmit,[dead, E, S]).
output(O,E,fresh,S) :- invoke(O,transmit,[fresh, E, S]).
output(O,E,weary,S) :- invoke(O,transmit,[weary, E, S]).
%%%%%%%%%%%%% Transitions  %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
transition(_, _, dead, dead).
transition(O, E, fresh, fresh) :-
    invoke(O, keep_fresh, [E]),!.
transition(_, _, fresh, weary).
transition(O, E, weary, fresh) :-
    invoke(O, recovery, [E]),!.
transition(O, E, weary, weary) :-
    invoke(O, subsistence, [E]),!.
transition(_, _, weary, dead).
%%%%%%%%%%%%% Transmission  %%%%%%%%%%%%%%%%%%%%%%%%%%%%%
shift_pressure(O, E, S) :- val_al(E, blood, B),
    val_al(B, pressure, P),
    invoke(O, reduction, [pressure, R]),
    NP is P*R,
    add_al(B, [pressure, NP], NB),
    add_al(E, [blood, NB], S).
transmit(O, State, Input, S) :-
    invoke(O, shift_pressure, [Input, NE]),
    invoke(O, blood_components, [L]),
    val_al(NE, blood, B),
    invoke(O, transmit_blood, [State, L, B, NB]),
    add_al(NE, [blood, NB], S).
transmit_blood(_, _, [], B, B) :- !.
transmit_blood(O, State, [Comp | L], B, SB) :-
    invoke(O, consumption, [Comp, State, C]),
    val_al(B, Comp, VC),
    (VC > C -> NVC is VC - C; NVC is 0),
    add_al(B, [Comp, NVC], NB),!,
    invoke(O, transmit_blood, [State, L, NB, SB]).
%%%%%%%%%%%%% Procedures  %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
keep_fresh(O, E) :- invoke(O, blood_components, [L]),
    val_al(E, blood, B),
    forall(member(Comp, [pressure|L]),
        (val_al(B, Comp, V),
            invoke(O, threshold_min, [Comp, Th]),
            V >= Th)).
    forall(member(Comp, [pressure|L]),
        (val_al(B, Comp, V),
            invoke(O, threshold_recovery, [Comp, Th]),
            V >= Th)).
subsistence(O, E) :- invoke(O, blood_components, [L]),
    val_al(E, blood, B),
    forall(member(Comp, [pressure|L]),
        (val_al(B, Comp, V),
            invoke(O, threshold_subsistence, [Comp, Th]),
            V >= Th)).
%%%%%%%%%%%%% Constants  %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
blood_components(_, [oxygene, glucide, lipid]).
consumption(_, oxygene, fresh, 3).
consumption(_, oxygene, weary, 6).
...
reduction(_, pressure, 0.95).
...
```

Figure 1: SWI Prolog code implements simplified virtual organ.

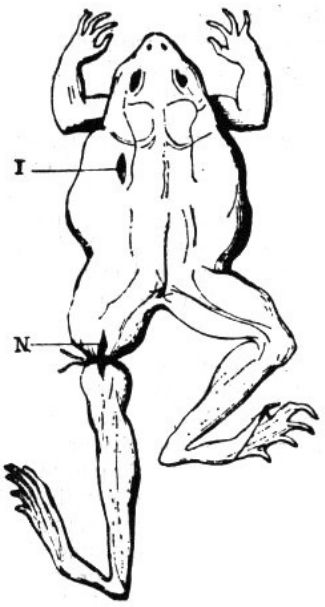

Figure 2: This schema was published by Claude Bernard in (Bernard 1864).

a tourniquet on a member, or exciting another part of the organism before or after injecting the substance *A*. In other words, it is possible to specify virtual experiments and to anticipate the subsequent model behavior under a working hypothesis.

For the sake of clarity, let us consider the experimental device described by Bernard in (1864) with the help of Figure 2. In this experiment, Bernard mentioned that curare has been introduced on *I* while a tourniquet was applied on *N*. Let us now suppose that one lay down, as a tentative hypothesis, that curare only affects the muscles — this corresponds to one of the Bernard's hypotheses — but neither the sensitive nor motor nerves, then the frog perceives excitations while the muscles belonging to all the organism are unable to move, except those on the right leg, because the tourniquet protects them from the curare effect. Let us now imagine that we excite the right leg of a core model built to model this experiment. It has to provoke a reaction on the left leg of the core model, while other virtual limbs are not able to move because of the curare effect. This can be deduced from the current hypothesis. The role of the virtual experiment is to automatically generate such evolutions from an adequate core model. One can also envisage browsing all the hypotheses, i.e., all the organ dysfunctions, which could generate the same behaviors. The virtual experiment may then prove the viability of the experiment.

To be concrete, take a simple example of intoxication with curare that is presented in Bernard's personal writings. In this experiment Bernard poisons an animal. It appears that the voluntary movements are the first to be paralysed. It is only when respiratory disorders appear, due to the paralysis of lung muscles, that the animal is asphyxiated. To simulate such an evolution, we introduced a virtual organism with a voluntary muscle, a kidney that is progressively evacuating the curare and a muscle that control the lung movements. We supposed that curare affects the muscles. We injected a dose of curare in the virtual organism and we obtained the following evolution: if the curare dose is sufficient, after 5 steps, the voluntary muscle is progressively paralyzed, but it takes more than 30 steps to see the lung paralyzed and the animal asphyxiated. If the curare dose is very low, the muscle is paralyzed, but there is no asphyxia, and the curare is evacuated.

Abduction

The previous section presented the virtual experiment laboratory built over the core model. However, as suggested, the virtual experiments are achieved under working hypotheses that assume, for instance, that a substance *A* affects such or such a function of such or such an organ class. Being given a toxic substance, one has to explore all the possible hypotheses and suggest, for each, experiments that could corroborate or refute them by showing observable consequences. It is the role of the working hypothesis management module to investigate all these hypotheses. Nevertheless, the goal is neither to achieve, nor to generate experiments, as would be the case with a robot scientist (see for instance (King *et al.* 2005)); it is just to reconstruct Bernard's scientific steps by simulating hypothesis exploration and by providing, for each hypothesis, the key experiments carried out by Bernard.

More precisely, the computer reconstruction of core models shows that tentative explanations are built on three levels. The first corresponds to the ontological level. As previously said, it is out of the scope of the present study to automatically create new concepts. In a way, the ontology transformation may be assimilated to some kind of paradigm shift. In the future, it may be a very exciting challenge to tackle this problem, but up to now it appears to be premature.

The second level covers hypothetical function of organs. The aim of scientific discovery would undoubtedly be to elucidate the organ function. The study of toxic substance effects may be viewed as a means to investigate those organ functions. However, today it seems too difficult to automate the generation of those functions. Therefore, we do not focus our study on this point.

Our present goal is more modest: given a physiological ontology and explicit theories about organ functions, find the effects of toxic substances. This corresponds to the third level of investigation. More precisely, the computer has to browse all the possible effects of a toxic substance, i.e., all the organs that may be affected by the substance of which we investigate the effects. Under each of the plausible hypotheses, experiments are formulated with core models that may be simulated on a computer and then confronted to empirical observations. It is then possible either to invalidate or to confirm each of the plausible explanations. Both explorations of all the tentative explanations and attempts to confirm or disconfirm plausible explanations belong to abductive inference processes. Let us note that one can test the consistency of our model: one can check that it is in accordance with empirical evidence as it is mentioned by scientists. Moreover, annotations containing original experiments

and observations are associated with each of the plausible hypotheses. It may help epistemologists and historians of science to understand the way scientific investigations were conducted.

Conclusion

A virtual laboratory has been programmed in Prolog. It allows scientists to build virtual experiments associated with different working hypotheses about the toxic effects of carbon monoxide and curare. It was then possible to correlate those virtual experiments to actual experiments performed by Bernard, and then to corroborate or refute working hypotheses according to the observations. As a consequence, we are able to computationally reconstruct part of Bernard's intellectual pathway.

As was previously suggested, the virtual experiments are achieved under working hypotheses that assume, for instance, that a substance *A* affects such or such a function of such or such an organ class. Being given a toxic substance, one has to explore all the possible hypotheses and, suggest, for each, experiments that could corroborate or refute them by showing observable consequences. It is the role of the working hypothesis management module to investigate all these hypotheses. Nevertheless, the goal is neither to achieve, nor to generate experiments, as would be the case with a robot scientist (see, for instance, (King *et al.* 2005)); it is just to reconstruct the Bernard's scientific steps by simulating hypothesis exploration and by providing, for each hypothesis, the key experiments carried out by Bernard. The next step is to build such an hypothesis management module.

However, this work relies on a fixed ontology, which biases the investigation and may prevent discovery. For instance, Bernard's study of curare's toxic effect was precluded by the absence of the motor nerve ending concept. Our further research will be concerned with the way that core models evolved in Bernard's research, especially the way both Bernard's ontology and the hypotheses concerning the different organ functions were transformed during Bernard's scientific life. The detailed study of Bernard's personal writings and scientific papers with genetic criticism techniques will help us in such an investigation.

We also investigate the possibility of building multi-scale core models in which physiological behaviors can be studied at different scales, e.g., organ, cell, and molecule, and should open new perspectives to modern clinical medicine. As a matter of fact, the principles on which Bernard's empirical method are based are always valid, even if the core models changed considerably with time. Today, the effect of new substances is usually studied at the cell or molecule scale, while the organ scale was dominant during Bernard's life. A model that could help to simulate the consequences of physiological dysfunctions at different levels would be of great help to determine the effects of new substances by recording different experiments and by ensuring that all the plausible hypotheses have already been explored.

Acknowledgments

I wish to thank Céline Cherici, Claude Debru and Jean-Louis Lebrave who greatly helped me in my attempts to understand Bernard's scientific work.

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