CYBERNARD: A Computational Reconstruction of Claude Bernard's Scientific Discoveries

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Summary. With epistemological insight and artificial intelligence techniques, our aim is to reconstruct Claude Bernard's empirical investigations with a computational model. We suppose that Claude Bernard had in mind what we call "kernel models" that contain the basic physiological concepts upon which Claude Bernard builds his general physiological theory. The "kernel models" provide a simplified view of physiology, where the internal environment – the so-called "milieu intérieur" –, mainly the blood, plays an essential role. According to this perspective, we assume that the "kernel models" allow Claude Bernard to make some hypotheses and to draw out their logical consequences. More precisely, the role of the "kernel models" is twofold: on the one hand, they help to generate and manage working hypotheses, for instance to enumerate the probable effects of a toxic substance, on the other hand, they derive, by simulation, the most plausible consequences of each of those hypotheses. We shall show how those "kernel models" can be specified using both description logics and multi-agent systems. Then, the paper will explain how it is possible to build, on these "kernel models", a virtual experiment laboratory, which lets us construct and conduct virtual experiments that play a role similar to the role of thought experiments. More generally, the paper constitutes an attempt to correlate Claude Bernard's experiments, achieved to corroborate or refute some of his working hypotheses, to virtual experiments emulated on "kernel models".

Key words: abduction, kernel model, experiments, epistemology, discovery science, multi-agent simulation

1 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") [1], which corresponds to today's principle of "homeostasis". He investigated and enlightened many phys-

iological mechanisms, e.g. the glycogenic liver function [2], effects of carbon monoxide, [3] and [4], effects of curare [5] and [3], etc. But, Claude Bernard was not only a great physiologist; he was also a theoretician who generalized his experimental method in his famous book, "Experimental Medicine" [6], which is nowadays a classic that all young students in medicine are supposed to have read.

However, there is debate in the epistemology community about the importance of the book. Some think that Claude Bernard revolutionized the physiology while others consider that he is only a great physician who successfully tried to vulgarize his scientific works. In a way, the structure of the book makes this debate possible since the first part exposes abstract principles on which relies a general experimental method, while the second exemplifies the application of the method on discoveries that are mainly derived from Claude Bernard's own work. Therefore, it could be possible to interpret the experimental method as an introduction to the description of Claude Bernard's personal scientific contribution. On the other hand, some philosophers think that the "Experimental Medicine" [6] played the same role for the 19th and 20th century physiology that the Descartes "Discourse on Method" for the 17th century physical sciences. In modern terms, it originated a "change of paradigm" in experimental medicine. Even if the knowledge of physiological mechanisms is far more detailed today than it was at the Claude Bernard's time and if the statistical techniques make the analysis of experimental data more rigorous, the principles on which relies the methodology of clinical experimentations are based on the same theoretical foundations. It is the argument of those who promote the "Experimental Medicine" as a key contribution for the modern medicine.

The CYBERNARD project aims at contributing to this debate by the achievement of a computer model and by a computer assisted diachronic analysis of Claude Bernard's texts. More precisely, the goal of the CYBERNARD project is twofold. The first is to clarify and to 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 the Claude Bernard's scientific discoveries, i.e. reconstructions of the discoveries that he has described at the end of his life, in his large audience papers. The second goal is then to confront the original Claude Bernard's scientific texts – i.e. his personal notes, scientific papers, etc. – to the reconstruction of his own work he made when he wrote the "Experimental Medicine" [6]. Our aim is to understand the effective status of the method described in the "Experimental Medicine": does it correspond to the actual method that Claude Bernard used or to an ideal reconstruction of what it should have been This confrontation can be called a diachronic reconstruction, since it is to compare the own Claude Bernard's latest reconstruction of his work to its effective ideas as they were expressed in his papers and

published articles at the time of discovery. Three teams participate to the CYBERNARD project, which is highly interdisciplinary: an artificial intelligence group headed by Jean-Gabriel Ganascia, the ACASA team, belonging to the LIP6 computer science laboratory, the epistemology department of the École Normale Supérieure directed by Claude Debru and the linguistic team of the ITEM laboratory that is specialized in genetic criticism.

This paper relates a joint work of the ACASA team and the epistemology department of École Normale Supérieure that is part of the CYBERNARD project. Within this work, our aim is to reconstruct Claude Bernard's empirical investigation with a computational model that simulates his experimental method. We are mainly interested in his investigations of carbon monoxide and curare effects. To start, we shall refer to two of Claude Bernard's texts, [5] and [3], where he rationalizes his own discoveries. In parallel, with the help of philologists, we shall confront Claude Bernard's rational reconstruction of his own previous discoveries with his former reasoning as it appeared in his writings. However, this paper focuses only on the first point.

The first part recalls the Claude Bernard's experimental method. The second is dedicated to the description of a two level model build to simulate the experimental method. The third formalizes the Bernard's medical ontology. The fourth describes the notion of "kernel model"; the fifth, the virtual laboratory on the top of which virtual experiments may be done. A sixth section presents the hypothesis generation module. The final and last part envisages possible generalizations of the experimental method and of its simulation to multi-scale "kernel models".

2 The Experimental Method

According to Claude 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, Claude 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 done.

For instance, when Claude 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. Claude Bernard does not detail the way the first idea or the initial theory is built. It corresponds to an intuition or to what he called a feeling that has to 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, Claude 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 Claude Bernard is an iterative procedure of theory refinement that proceeds in three steps, each step involving a specific scientific function:

Experimentation: an hypothesis that has 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 that can 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 : this third step is the most crucial an 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. Nowadays, it may appear that censors and computers could both help looking out and gathering data. Therefore, it is not central to the experimental method that mainly has to analyze observational data and then to generate new theories. Our point is to automate the analysis of experimental results and the hypothesis generation process that corresponds to the most crucial step. We focus on it in this paper. We assume that abduction plays an important role here, since it is to explain experimental results by modifying the current theory.

Abductive reasoning makes generally use of background knowledge on the top of which hypothesis are formulated. Considering all Claude Bernard's hypotheses and revisions, it appears that they had some resemblance; they were formulated using the same words; they seemed to be generated from the same "ontology". In the late reconstruction of his discoveries, Claude Bernard elicited the "ontology" he had in mind. The next section describes it.

3 The Claude Bernard's Ontology

To have a clear understanding of the Claude 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 the physics and the chemistry, François–Xavier Bichat (1771–1802) and François Magendie (1783–1855), who was the Claude Bernard's professor, studied the body anatomy and the organs. The 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. Claude Bernard opposed to this reduction of organs to physical bodies; he thought that organs are not only inert solid tissues, but that each of them has its autonomy and its own functions, which have to be investigated. More precisely, in his writings (cf. [3] and [4]), Claude Bernard presumes that organisms are composed of organs, themselves analogous to organisms since each of them 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, sub-subclasses etc. Each class and subclass has its own characteristics, which can easily be formulated, according to Claude Bernard's explanations.

The internal environment – i.e. the "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 Claude Bernard, the life is synonymous of exchanges. The organisms exchange through the external medium that is the air for outside animals or the water for fish. 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 to its life. Their life is also governed by exchanges; but the medium that supports exchanges is not air or water; it is the so-called

"milieu intérieur", which mainly corresponds to blood. The Claude Bernard's ontology may easily be derived from these considerations. It is then easy to formulate it in an ontology description language.

For instance, below are some of the previous assertions expressed with description logics.

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:

$$Organ \equiv Tissue \sqcup Skeleton \sqcup Fiber \tag{2}$$

$$Tissue \sqcap Fiber = \bot \tag{3}$$

$$Tissue \sqcap Skeleton = \bot \tag{4}$$

$$Fiber \sqcap Skeleton = \bot \tag{5}$$

Fibers may be nerves or muscles:

$$Fiber \equiv Nerve \sqcup Muscle \tag{6}$$

Nerves may be sensitive or motor:

$$Nerve \equiv Sensitive\_Nerve \sqcup Motor\_Nerve \tag{7}$$

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

$$Tissue \sqsupseteq Epithelium \sqcup Glandular\_Tissue \sqcup Mucous\_Membrane \sqcup etc. \tag{8}$$

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

$$Organ \sqsubseteq \exists Aliment \tag{9}$$

$$Organ \sqsubseteq \exists Poison \tag{10}$$

$$Organ \sqsubseteq \exists Action \tag{11}$$

$$etc. \tag{12}$$

The physiological ontology plays a crucial role in the way Claude 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 formulate 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. Claude 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 the ontologies are originated? What is their relevancy? And how do they evolve? Up to now, we don't 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 Claude Bernard, the ontology here described corresponds to the one he gave at the end of his scientific life, in his large audience papers (e.g. [3] or [5]) and books [6]. 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 today relevance, but its evolution during Claude Bernard's scientific career.

This paper is focused on the rational reconstruction of Claude Bernard's own discoveries that he achieved by himself when he was famous. Our ultimate goal is to go further and to confront this late and personal reconstruction of Claude Bernard's scientific discoveries to the actual Claude Bernard's discovery process as it appears through informal notes, laboratory books, scientific papers etc.

4 Two-level Model

As previously stated, abduction played a crucial role in Claude 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.

4.1 "Kernel models"

To design a computational model that simulates the intellectual pathway leading Claude Bernard to his discovery, we have supposed that he had in mind what we call "kernel models" that contain basic physiological concepts — such as internal environment, organ names etc. — upon which he builds his theories. More precisely, theories correspond to hypothetical organ functions that Claude Bernard want to elucidate, while "kernel models" describe the physical architecture of the organism.

The "kernel models" enable Claude Bernard to hypothesize tentative assumptions and draw out their logical consequences. These "kernel models" constitute the core on which the reasoning process is based; they correspond to putative architectures of the organisms. Depending on the question under investigation, they may be more or less simplified. For instance, if one want to investigate the hart function, it is not necessary to detail the precise role

of all muscles. Our aim is to build and to simulate those "Kernel 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.

4.2 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. Claude Bernard assumes that one can use toxic substances as tools of investigation — he evokes the idea of "chemical scalpel" — to dissociate and identify the functions of different organs. He presupposes, 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 lot 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 "kernel model" a working hypothesis management module that has both to guide working hypothesis generation and to design experiments. Once an hypothesis is made, virtual experiments have to simulate, on the top of the "kernel model", the probable observable consequences of this hypothesis, which helps designing real experiments. Such virtual experiments play a role 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 though 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 though experiments with computer models that can be simulated on computers.

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

5 "Kernel Model" simulation

The "kernel models" contain organs and connections between organs through the internal environment, mainly the blood, and direct connections. Both organs — e.g. muscles, hart, lung, nerves etc. — and connections between

organs are represented using automata, i.e. entities characterized by their inputs, their outputs and their internal state. A "kernel 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 usual case, e.g. for 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 [7] 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 organ activation cycle follows the blood circulation. The time is supposed to be discrete and after each period of time, the states of the different automata belonging to the "kernel model" and their outputs are modified.

A first implementation was programmed in JAVA using object oriented programming techniques. It helped both to simulate the "kernel model" evolutions and to conduct virtual experimentations (see section 6) one those "kernel models", which fully validates our first ideas concerning the viability of the notion of "kernel model". Within this implementation, organs and connections between organs are associated to objects. The instantiation and inheritance mechanisms facilitated the programming. However, since our ultimate goal is to simulate the hypothesis generation and especially the abuctive reasoning on which relies the discovery process (see section 7), we are currently rebuilding "kernel models" using logic programming techniques on which it is easy to simulate logical inferences, whatever they are, either deductive or abductive.

The logic programming implementation of the "kernel model" is programmed in SWI Prolog[3]. It makes use of modules to emulate object oriented programing techniques, i.e. mainly the 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.

[3] See http://www.swi-prolog.org/ for more details

```
:- 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).
...
```

Fig. 1. Here is the SWI Prolog code for a simplified virtual organ

6 Virtual "Thought Experiments"

Once the "kernel model" is built, it is not only possible to simulate normal organism behavior, but also to introduce pathologies (i.e. organ deficiencies) in 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 experiments, or as "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 Claude Bernard's practices, some virtual experimental operators, such as injection and ingestion of substances, application of tourniquet on members, excitations, etc.

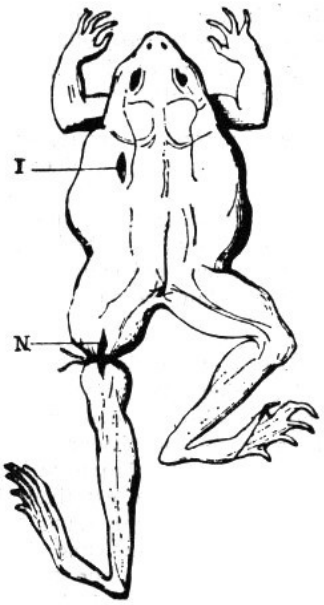

Fig. 2. This schema was published by Claude Bernard in [3]. It summarizes an experiment in which an incision has to be done on I to introduce curare, while a tourniquet is applied to the left thigh, on N.

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 "kernel model" simulation to predict the consequences of a direct injection of A combined with any combination of experimental operations (applying a tourniquet on a member and/or exciting another part of the organism before or after injecting the substance A etc.).

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 Claude Bernard in [3] with the help of figure 2. In this experiment, Claude 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 — that corresponds to one of the Claude Bernard hypotheses — but neither the sensitive nerves, nor the 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 on a "kernel model" built to model this experiment. It has to provoke a reaction on the left leg of the "kernel 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 "kernel model". One can also envisage to browse 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.

7 Abduction

The previous section presented the virtual experiment laboratory built over the "kernel 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 [8]); it is just to reconstruct the scientific steps of Claude Bernard by simulating hypothesis exploration and by providing, for each hypothesis, the key experiments carried out by Claude Bernard.

More precisely, the computer reconstruction of "kernel 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 mean 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: being given a physiological ontology and explicit theories about organ functions, it is to find out the effect of toxic substances. That 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 "kernel 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, i.e. that one can check that it is in accordance with the empirical evidences as they are mentioned by scientists. Moreover, anotations containing original experiments and observations are associated to each of the plausible hypotheses. It may help epistemologists and historians of science to understand the way research were conducted.

8 Conclusion

A first version of both the "kernel model" and the virtual laboratory are programmed in Java. They allowed us 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 done by Claude Bernard, and then to corroborate or refute working hypotheses according to the observations. As a consequence, we are able to computationally reconstruct part of Claude Bernard's intellectual pathway. A second implementation using logic programming techniques is now under construction. The reason is that is seems easier to model abductive reasoning using logic programming than traditional object oriented programming languages. We hope to reproduce the different steps of the Claude Bernard's toxic substance investigations, mainly carbon monoxide and curare.

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

We also investigate the possibility to build multi-scale "kernel models" in which physiological behaviors can be studied at different scales — organ,

cell, molecule etc. —. It should open new perspectives to modern clinical medicine. As a matter of fact, principles on which lay down Claude Bernard empirical method are always valid, even if the "kernel models" considerably changed with time. Today, the effect of new substances is usually studied at the cell or molecule scale, while the organ scale was dominant at Claude Bernard's epoch. A model that could help to simulate effects 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.

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