The Reasoning Process about Claude Bernard's Scientific Discoveries

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Abstract

This paper presents an attempt to rationaly rebuild the discovery process in medicine. Our aim is to reconstruct Claude Bernard's intellectual pathway leading to important discoveries, in particular his understanding of the effects of curare. Achieved in collaboration with epistemologists, we refer to the notebooks where Bernard recorded his experiments. Based on this material, this paper presents a computational model of Bernard's activity. Our study shows that Bernard did not only used inductions, but also deductions and abductions. The deductions anticipate the consequences of working hypothesis; experiments attempt to confirm or to infirm those hypothesis; then abductions generate new hypothesis that explained unexpected observations. We focus here on the deductive part of this process, with a virtual laboratory that allows the construction of virtual experiments associated with different working hypotheses. Then, we show how this deductive part takes place in the discovery process and how it is related to the abductive and the inductive steps.

1 Introduction

In the past, there have been many attempts to rationally reconstruct scientific discoveries with Artificial Intelligence techniques [Feigenbaum *et al.*, 1971; Langley *et al.*, 1986; Shrager and Langley, 1990; Kulkarani and Simon, 1988]. According to Herbert 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, a deductive on an abductive process? Epistemologists do not agree in this point; but whatever their underlying theories, it appears that many different kind of inferences are 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 [Corruble and Ganascia, 1994]. Moreover, today, Knowledge Discovery from Data Bases corresponds naturally to an inductive process, since it builds general knowledge from pieces of information that describe particular cases. The Cybernard project [Ganascia and Debru, 2007] constitutes an attempt to reconstruct some of Bernard's scientific steps that are mainly abductive [Josephson and Josephson, 1996] . It explores with the help of Knowledge Representation and Multi-Agent techniques, some aspects of the discovery process that are not directly related to inductive processes. Our 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, to design their experimentations in consideration of the fundamental theory they have in mind.

In previous papers, we began the study of the process of scientific discovery [Ganascia and Debru, 2007; Habib and Ganascia, 2008] by implementing a virtual laboratory that is able to anticipate the consequences of an hypothesis. It corresponds to a deductive process. The aim of our present study is to focus on the way this deductive process can be articulated to the abductive process, i.e. to the hypothesis generation.

The paper is organized as follows: In Section 2 we provide an overview of Claude Bernard's ontology and how his ontology has changed during his career. We make reference in Section 3 to our virtual laboratory containing core models and meta-operators. Then, we present the model, agents used in it and how our model has changed to take into account the changes in Claude Bernard's ontology. Next Section describes our results simulating one of Claude Bernard's experiments. Finally the conclusion summarizes our work and what our future directions are.

2 Epistemological Study on Claude Bernard's Manuscripts and Knowledge Represenation

As previously introduced, the focus of our work is on Claude Bernard's discovery about the effects of curare. Our work is based on data gathered from his notebooks and manuscripts between 1845 and 1875. Since Claude Bernard's manuscripts contain descriptions of experiments in natural language, it was necessary to abstract from these descriptions a number of attributes (experimental criteria), which are rich enough to reflect the complexity of the original descriptions, and sufficiently representative of their variability. An attribute is created if this potential attribute intervenes in a significant proposition of available experiments.

Claude Bernard's manuscripts have been the subject of an epistemological study, which consists of several steps:

- The transcription of these manuscripts using a text editor. These manuscripts contain experiments using curare or strychnine as a toxic substance;
- The surrender of this work in a chronological order;
- The formalization of an Excel table in which Claude Bernard's experiments are annexed according to several experimental criteria (attributes) such as : weight, age, dose, animal, preparation/manipulation, point of insertion, date, ideas of experiments, observations, hypotheses and references.

The identification of the main attributes allowed us to formalize Claude Bernard's experiments. This is a preliminary step to the simulation of these experiments in a virtual laboratory previously built [Habib and Ganascia, 2008]. Prior to the simulation, Claude Bernard's experiments are classified into several sets of experiments. The classification of experiments may be done according to one precise criterion; for instance, the set of experiments using dogs as experimental animals, or even the set of experiments including some nerve manipulations, etc. This classification is a methodological problem, because it constitutes an important step in the process of empirical discovery that concerns us, but it is not systematic, and even less, automatic.

Since Claude Bernard does not write down all the details about preparation, observations or even less about the deduced hypotheses, some experiments are not complete comparing to others in the same set of experiments. Hence comes the idea to complete experiments' descriptions by fusing them with descriptions about other experiments from the same set, which are compatible [Laudy *et al.*,].

Fusion allows us, on the one hand, to reduce the number of experiments within a set of experiments and thus, to reduce the number of possible simulations in a particular set of experiments since each experiment may be the object of a simulation. On the other hand, fusion allows to complete descriptions about some experiments with information of a great interest in our reasoning process. After the fusion step, information includes not only the complete set of observations resulting from experiment takes place but also the hypotheses deduced by Claude Bernard.

3 Claude Bernard's Ontology

According to his writings (manuscripts, notebooks, etc.), we suppose that Claude Bernard had in mind an ontology upon which he generated all his experiments. His ontology has changed gradually during more than twenty years of his scientific career. Claude Bernard's ontology is considered as the core of his knowledge base upon which he constructed his reasoning process.

Since Claude Bernard did not always explicitly describe his ontology, many ontologies can be derived by studying his experiments at different points of his career. Then, it is easy to formulate it using an ontology description language similar to those that are nowadays used in life sciences to represent biological and medical knowledge [Smith and Ceusters, 2006].In his ontology, organs, vessels or even the nervous system are seen as classes. These classes are, in their turn, subcategorized into subclasses, sub-subclasses etc. Each class and subclass has its own characteristics, which can be easily formulated according to Claude Bernard's explanations. He considered that internal environment, mainly the blood, the responsible for exchanges between organs via vessels. Blood carries all organ's aliments and poisons. As a consequence, interactions between blood and one of the organs may have different effects on other organs and, as a result, on the whole organism.

Note that most of ontologies used in the biomedical community, for instance the OBO (Open Biological Ontologies) refers mainly to three levels: one for the organs and the anatomy, the second for the cells and the third for molecules. For obvious reasons Claude Bernard's ontology refers mainly to the first. However, it would be possible to extend our model to a three level ontology that is more appropriate in contemporaneous medicine.

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.

4 Claude Bernard's Experimental Method

This Section recalls Peirce's inferential theory and situates Claude Bernard's scientific approach comparing to this theory.

The modern classification of logical reasoning into abduction, induction and deduction is due to the American Pragmatist C.S. Peirce (1839-1914) [Hartshorne *et al.*, 1931]. Around 1900, Peirce was led to his so-called inferential theory, where abduction and induction are seen as complementary processes cooperating with deduction and experiment in a cycle of scientific knowledge discovery.

As shown in Figure 1, the cycle usually begins with an anomaly that is not explicable by one's existing knowledge. Some plausible hypothesis must then be sought to account for this fact. This process of hypothesis is what Peirce now calls abduction. Testable predictions must then be extracted that would follow if the hypothesis were true. This process of prediction is the task of deduction. The predictions must then be compared against the result of experiment. Support for the predictions may justify the acceptance of the hypothesis as part of one's growing knowledge, but insufficient support may rule out one hypothesis in favour of another and may result in the discovery of new anomalies in need of further explanation (thereby invoking a new cycle). This process of evaluation is what Peirce now calls induction.

Claude Bernard's experimental method corresponds, at a grosser or finer level of approximation, to the above described cycle. His experimental method usually begins with an initial hypothesis he had, most of the time, even before some inexplicable anomalies are given. Claude Bernard does not

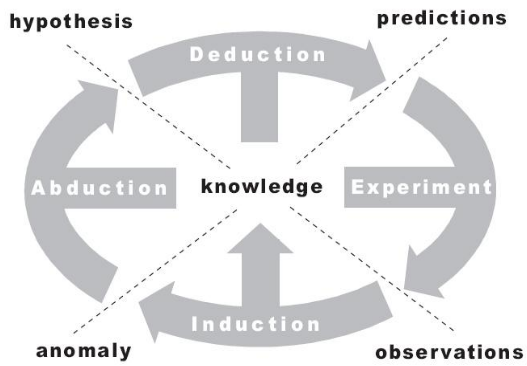

Figure 1: Peirce's 'Inferential Theory'

detail all the time the way his initial hypothesis is built. It corresponds to an intuition that has to be validated, refined or adjusted according to empirical results generated by relevant experiments.

Once Claude Bernard has an initial theory, his experimental method begins and it proceeds in three steps, each step involving a specific scientific function:

***Experimentation*:** After considering an initial hypothesis or several initial hypotheses in parallel , Claude Bernard designs an experimental apparatus able to generate observations that can be compared to predictions derived from the current theory. These hypotheses were formulated using the above described *ontology* consisting the core of Claude Beranrd knowledge base. This step corresponds to the experiment step in Peirce's cycle.

***Observation*:** This step consists in collecting observations from the designed experiments that can be compared with predictions derived from his initial hypothesis. As he rarely gave the predictions in his notebooks, the deduction was not that clear in his scientific approach.

***Analysis*:** The third step is the most crucial and original. it is to confront the predictions extracted from the initial theory to the observations. According to the observational results, the scientist was able to generate, on the one hand, new theories to add to his knowledge base which corresponds to the induction in Peirce's cycle. On the other hand, he generates new working hypotheses from anomalies he might obtain, this step coressponds to the abduction in Peirce's cycle. As a consequence, he reconstructs new experiments validating or invalidating his new working hypotheses.

Claude Bernard's experimental method is an iterative procedure of theory refinement. The role of the induction in his experimental method is limited to the refinement of some thresholds, such as the dose of curare used in paralysis, after repeating the same experiment and adding new thresholds values to his knowledge base. That leaves un with the abduction as the main logical reasoning model used in his scientific approach. We describe by an example how we used Abductive Logic Programming (APL) [Kakas *et al.*, 1992] to find some hypotheses using one of Claude Bernard's experiments.

5 Experiment Design

We have devoted a great part of our work designing our experiment by constructing a virtual laboratory simulating Claude Bernard's experiments which corresponds to the experiment in Peirce's cycle. This virtual laboratory allows us to construct virtual experiments where the input is some attributes formalizing Claude Bernard's experiment and the output is the observations he obtained after doing the experiment.

5.1 The virtual laboratory

In order to construct virtual experiments based on Claude Bernard's notebooks, a virtual laboratory has been built. We will continue to refine it gradually during the project to take into consideration all of Claude Bernard's studied cases. This virtual laboratory has some core models describing the physical architecture of the organism on which the experiments are constructed. It has also many experimental operators, called meta-operators, such as toxic substance injection. The virtual laboratory should contain, as well, models of the configuration of a laboratory, such as instruments for making observations. The simulation of the organ system is done according to Bernard's hypotheses. Observations are the output of each simulation. The choice of both core models and meta-operators depends on Claude Bernard's experiments. Nevertheless, the ontology, on which core models are built, is previously given and evolves very slowly during the Claude Bernard's career.

After building the virtual laboratory, we can choose our own ingredients, from organs to meta-operators, which are needed in our recipe, according to Claude Bernard's scenarios.

Many meta-operators are presented in our virtual laboratory including: toxic substance injection, tourniquet application, interaction with the external medium, substance ingestion and excitation. Here are, in more details, some of these meta-operators used in our simulations showed in the Section devoted to the results:

- ***Toxic substance injection***: In his experiments, Claude Bernard used toxic substances as tools of investigation. He assumed, as underlying principle, that each toxic substance neutralizes the function of one particular organ. He then studied the consequences of organ's dysfunction on other organs and, consequently, on the functionality of the whole organism. Claude Bernard evoked the idea of toxic substances as (chemical scalpel), because they were used to isolate each organ's function. In practice, Claude Bernard took into account the percentage of toxic substance injected and where to inject it. For instance, he devoted an important time of his experiments to the study of *curare*'s effects as one of these toxic substances.

  This operator is presented in the virtual laboratory using the the following predicate:

$$injection(V, [ToxSub, Val], T) \tag{1}$$

$$\begin{cases} ToxSub\text{: the toxic substance injected} \\ V\text{: the vessel in which the toxic substance is injected} \\ Val\text{: the dose of the toxic substance} \\ T\text{: time at which the injection is applied} \end{cases}$$

- ***Interaction with the external medium***: As previously seen, Claude Bernard considered internal environment as a medium of exchanges between organs. But his studies were not focused only on the internal medium but also on external medium, which is the air for outside animals. The fact that external medium may carry aliments, poisons, etc, introduced external medium as a way of exchanges for organisms. As a consequence, changing the nature of the gas breathed (e.g. by adding carbon monoxide) or even carrying artificial respiration may affect the state of the whole organism.

  This operator can take different forms. One of these forms is artificial respiration which can be formalized by the following predicate:

$$artificial\_respiration(T1, T2) \qquad (2)$$

$$\begin{cases} T1\text{: time at which the artificial respiration is carried} \\ T2\text{: time at which the artificial respiration is stopped} \end{cases}$$

5.2 The virtual laboratory implementation

In our model, organs, connections between organs and nervous system components are represented by agents. Agents are represented using automata, each agent has its own inputs, outputs, transfer function and states. Blood is represented by a *list* of blood components and their associated values. These values may be changed according to blood circulation through the organism. Time is discrete and after each period of time, the states of different agents belonging to the core model and their outputs are modified.

Claude Bernard's experiments are represented using a number of attributes. Since his manuscripts contain descriptions of experiments in natural language, it was necessary to abstract from these descriptions a number of attributes (experimental criteria). An attribute is created if this potential attribute intervenes in a significant proposition of available experiments.

The implementation makes use of object oriented programming (OOP) techniques. Inheritance and instantiation mechanisms of object oriented programming facilitate the implementation of those agents. It helps both to simulate the "*core model*" evolutions and to conduct virtual experimentations on it, which fully validates our first ideas concerning the viability of the concept of "*core model*".

Within this implementation, organs and connections between organs are associated to objects that implement agents. Organs and connections between organs are instantiations of concepts of the initial ontology. However, since our ultimate goal is to simulate the hypothesis generation and especially the abductive reasoning on which relies the discovery process, we have chosen to build "core models" using logic programming techniques on which it is easy to simulate logical inferences, whatever they are, either deductive or abductive.

The agents are implemented in SWI Prolog. It makes use of modules to emulate object oriented programing techniques, mainly the instantiation, inheritance and message sending mechanisms. The choice of logic programming techniques was motivated by our ultimate goal that is to simulate the abdutive way of reasoning that explores the hypothesis space.

6 Reasoning: Abductive Logic Programming (ALP) Task

ALP is the field of Artificial Intelligence concerned with finding hypotheses Δ to explain a goal G with respect to a theory T and integrity constraints IC. In brief, the goal G is a set of literals to be explained, the theory T is a normal program expressing some prior knowledge, and the integrity constraints IC are a set of formulae that restrict the acceptable hypotheses. Informally, the explanation Δ is a set of ground atoms that, relative to T, 'cover' G and are 'consistent' with IC. Typically, Δ is restricted to the ground instances A of some given set of abducible predicates.

Definition 6.1 An abductive context is a tuple $\langle T, G, IC, A \rangle$ where T is a normal program, G is a set of literals, IC is a set of closed first-order formulae, and A is a set of ground atoms.

Definition 6.2 Suppose that $X = \langle T, G, IC, A \rangle$ is an abductive context. Then an abductive explanation of X is a set of ground atoms $\Delta \subseteq A$ for which there exists a stable model M of $T \cup \Delta$ and a ground instance $G\theta$ of G such that $M \models G\theta$ and $M \models IC$.

Definition 6.3 Let X be an abductive context $\langle T, G, IC, A \rangle$, Δ be an abductive explanation of X, and Y be the abductive context $\langle T, \Delta, IC, A \rangle$. Then Δ is *minimal* iff there is no $\Delta' \subset \Delta$ such as Δ' is an explantion for X; and Δ is *basic* iff there is no explanation Δ' of Y such that $\Delta \nsubseteq \Delta'$.

A detailed example is given in the next Section devoted to results.

7 Case of Study

The first part of the simulation translates one of Claude Bernard's experiments, concerning the intoxication with the curare, into a virtual experiment. The construction of virtual experiments allows, gradually, the complement of organism's entities with different linked functions. These entities is the subject of the reasoning process.

In his writings [Grmek, 1973], Claude Bernard had an initial hypothesis that he tried to improve by constructing an experiment. Then, he validated or rejected his initial hypothesis according to the observational results of the experiment.

Here is the first part of an extract of one of his experiments and the corresponding hypothesis taken from his notebooks:

Experiment: *"We introduce under the skin of a frog's thigh a small piece of dry curare. Three minutes later, paralysis occurs. Six minutes later, the nerves, by pinching or by electricity, don't determine any kind of contraction in*

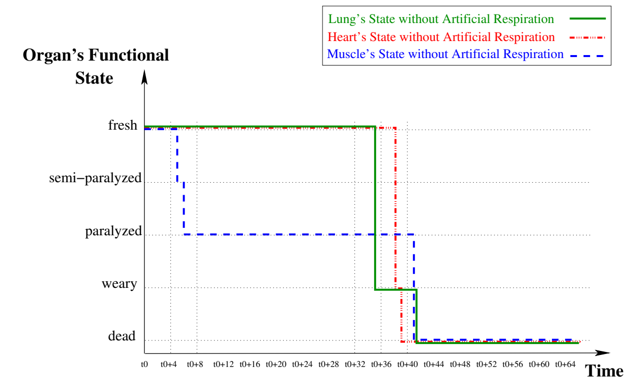

Figure 2: State of different organs in a virtual organism when an important dose of curare is injected and no artificial respiration is carried

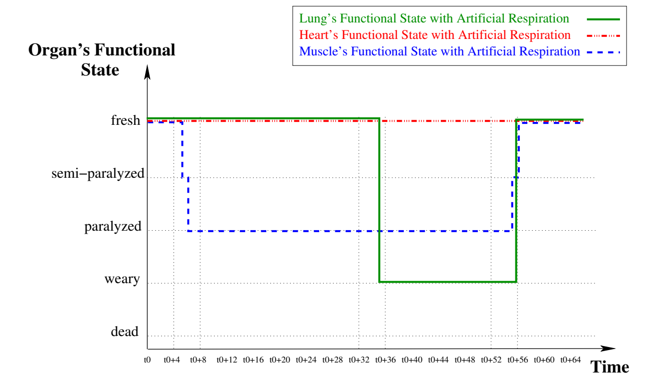

Figure 3: State of different organs in a virtual organism when an important dose of curare is injected and artificial respiration is carried before breathing stops

the muscles. Nine minutes later, the heart stops contracting and the frog died."

Hypothesis: *"In curare poisoning, voluntary motor nerves are much more quickly extinguished than the nerves of organic life. But when respiratory movements are, themselves, paralyzed, then asphyxia occurs and quickly paralyzes motor nerves of organic life ..."*

The translation of Claude Bernard's experiment into a virtual experiment is illustrated in Figure 2 which shows the state of different organs during the simulation.

According to the observations and knowing that the curare is injected in the animal's blood and its dose is sufficient to paralyze the animal, he gives a hypothesis considering the asphyxia as the main reason about the animal's death. So he repeats the same experimnts using artificial respiration before breathing stops.

The second part of the simulation shows how results change when the scenario proposed by Claude Bernard changes by using artificial respiration.

Here is the complete extract of the experiment previously described and the corresponding hypothesis:

Experiment: *"We introduce under the skin of a frog's thigh a small piece of dry curare. Three minutes later, paralysis occurs. Before breathing stops, we just replace it with artificial respiration. Nine minutes later, the nerves, by pinching or by electricity, don't determine any kind of contraction in the muscles. The heart contracts all alone again after one hour."*

Hypothesis: *"In curare poisoning, voluntary motor nerves are much more quickly extinguished than the nerves of organic life. But when respiratory movements are, themselves, paralyzed, then asphyxia occurs and quickly paralyzes motor nerves of organic life.* ***But if, when breathing stops, we just replace it with artificial respiration, then the nerves of organic life awake while the nerves of animal life will paralyze more."***

The translation of Claude Bernard's complete hypothesis into a virtual experiment is illustrated in Figure 3. This figure shows what could happen to organs if artificial respiration is carried before breathing stops and with the same dose of curare used before.

Let us reprensent now the previous example using ALP. Let $X = \langle T, G, IC, A \rangle$ be an abductive context. The theory T contains four clauses describe the domaine. The first rule states that a paralysis occurs when an efficient injcetion takes place and an artificial respiration is carried. The second rule states that for an injection to be efficient, the poison's dose has to be sufficient (comparing to some thresholds) and the injection takes place in the animal's blood. The remaining facts state that the poison's dose is sufficient and is injected in the frog's blood.

$$T = \begin{cases} paralysis(x) \leftarrow effInjection(x), artRes(x) \\ effInjection(x) \leftarrow suffDose(x), inBlood(x) \\ suffDose(frog) \\ inBlood(frog) \end{cases}$$

$$G = \{paralysis(frog)\} \tag{3}$$

$$IC = \{\leftarrow artRes(x), \neg alive(x)\} \tag{4}$$

$$A = \{artRes/1, alive/1\} \tag{5}$$

The abducibles A allow assumptions of the form *artRes(t)* and *alive(t)*, where t is a ground atom; but the integrity constraint *IC* requires that *artRes* can only be carried if the animal is still *alive*. The goal G can be regarded as asking whether there is an explanation of the fact *paralysis(frog)*. With reference to Definitions 6.2 and 6.3, above, it can be shown that the hypothesis Δ, below, is an abductive explanation of X that is both minimal and basic.

$$\Delta = \begin{cases} artRes(frog) \\ alive(frog) \end{cases}$$

8 Conclusion and Future Directions

In this study, a virtual laboratory has been built allowing the construction of virtual experiments associated with different working hypotheses. It was then possible to correlate those virtual experiments to actual experiments done by Claude Bernard. As a consequence, we are able to reconstruct computationally part of Claude Bernard's intellectual pathway. We showed also how we have changed our virtual laboratory to take into account the way upon which underlying conceptions evolve in Claude Bernard's ontology concerning the different organ's functions.

To achieve our ultimate goal concerning the rational reconstruction of Claude Bernard's scientific process, we must first complete the construction of our virtual laboratory. To do so, we are working on making a categorization of the experiments according to different core models, and identify some key attributes allowing the formalization of these sets of experiments and then simulating them. This allows the expert, on one hand, to select the virtual organism on which experiments will be conducted, without having to build it again at the beginning of each experiment. On the other hand, he can choose the key attributes necessary for the simulation of the experiment among the key attributes corresponding to a category of experiments.

However, our further research concerns the reasoning process of the formation of Claude Bernard's hypotheses and theories. That requires to study Claude Bernard's reasoning process and to choose the adapted algorithms. We want to provide input cases described in Claude Bernard's manuscripts before reaching valid hypotheses. Then, we compare the results of these experiments to validate the algorithm which will complete our model.

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