An Attempt to Rebuild C. 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 he had in mind what we call "kernel models" that provide simplified views of physiology, which allowed him to make hypotheses and to draw out their logical consequences. We 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 a virtual experiment laboratory, which lets us construct and conduct virtual experiments.

1 Introduction

During the past, there have been many attempts to rationally reconstruct scientific discoveries with Artificial Intelligence techniques [5, 2]. In a way, the science of discovery results from those attempts. Nevertheless, a question remains concerning the logical status of the discovery: is it mainly an inductive, a deductive on an abductive process? Philosophers do not agree in this point; but whatever their underlying theories, it appears that inferences involved in discovery are many in number and various. 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. This paper constitutes an attempt to reconstruct some of the Claude 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.

Let us recall that Claude Bernard (1813–1878) was not only one of the most eminent 19th century physiologists, but also a theoretician who generalized his experimental method in his famous book, "Experimental Medicine" [1], which is nowadays a classic that all young students in medicine are supposed to have read. The goal of our project [3] is mainly to clarify and to generalize this experimental method by formalizing it with artificial intelligence techniques and by simulating it on computers.

More precisely, Claude Bernard had in mind an ontology of the physiology which he used to express scientific hypotheses concerning both the organ functions and the activity of toxic and/or medicinal substances. He also used this ontology to design experiments that were intended to discriminate among the different scientific hypotheses. Our first aim here is to rebuild the ontology described in the Claude Bernard's works with modern knowledge representations techniques. Then, we want to construct, on the top of this ontology, "kernel models", which simulate the experiments that Claude Bernard's had in mind when he investigated the effects of toxic substances, e.g. carbon monoxide and curare.

The first part formalizes the Bernard's medical ontology. The second is dedicated to the description of a two level model built to simulate his experimental method. The third describes the notion of "kernel model"; the fourth, the virtual laboratory on the top of which virtual experiments may be done. The final and last part envisages the hypothesis generation module and other possible generalizations.

2 The Claude Bernard's Ontology

In his writings, 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 sub-categorized 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, 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 simply be derived from these considerations. It is then easy to formulate it in an ontology description language similar to those that are nowadays used in the life sciences to represent biological and medical knowledge [7]. Note that most of the ontologies used in the biomedical community, for instance the OBO – the Open Biological Ontologies http://obofoundry.org/ – refer to three levels: one for the organs and the anatomy, the second for the cells and the third for molecules. For obvious reasons the Claude Bernard's ontology refers mainly to the first, i.e. to organs and anatomy. However, it would possible to extend our model to a three level ontology that is more appropriate in contemporaneous medicine. For instance, below are some of the previous assertions expressed with description logics [6]:

- The organs are parts of the organism: $Organ \sqsubseteq \exists PART.Organism.$
- The organs are tissues, skeleton or fibers: $Organ \equiv Tissue \sqcup Skeleton \sqcup Fiber$
- Fibers may be nerves or muscles: $Fiber \equiv Nerve \sqcup Muscle$
- Nerves may be sensitive or motor: $Nerve \equiv Sensitive\_Nerve \sqcup Motor\_Nerve$
- Epithelium, glandular tissue, mucous membrane etc. are tissues: $Tissue \sqsupseteq Epithelium \sqcup Glandular\_Tissue \sqcup \ Mucous\_Membrane \ \sqcup \ \cdots$

3 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.

To design a computational model that simulates the intellectual pathways leading Claude Bernard to his discoveries, we have supposed that he had in mind what we call "kernel models". Those "kernel models" contain basic physiological concepts — such as internal environment, organ names etc. — upon which he builds his "ideas". More precisely, "ideas" correspond to hypothetical organ functions that Claude Bernard wanted to elucidate, while "kernel models" describe the physical architecture of the simplified organisms on the top of which his experiments were designed. Claude Bernard assumed that one can use toxic substances as tools of investigation — he evoked the idea of "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. The simulation of a "kernel model" makes explicit the consequences of each working hypothesis. All his "ideas", i.e. all his working hypotheses, were then evaluated by the confrontation of their potential consequences, i.e. the consequences derived from "kernel models" simulation, to the consequences observed through empirical experiments

Our aim, in this paper, 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.

Nevertheless, other questions need to be solved when we want to rationally reconstruct the discovery process: how are "ideas", i.e. working hypotheses, generated and how are validating experiments designed? In order to answer the first question, we add to the "kernel model" a "working hypothesis management" module that has both to guide working hypothesis generation and to design experiments. The second is out of the scope of our study.

4 "Kernel Model" Simulation

The "kernel models" contain organs and connections between organs through the internal environment, mainly the blood. Both organs — e.g. muscles, hart, lung, nerves etc. — and connections between organs are represented using agents that communicate with other organs and evolves in the "milieu intérieur" viewed as the internal environment. The agents correspond to the concepts of the previously described ontology. 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. The organism, which is a set of connected organs, 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 agents belonging to the "kernel model" and their outputs are modified.

The implementation makes use of object oriented programming techniques. It helps both to simulate the "kernel model" evolutions and to conduct virtual experimenta-

tions (see next section) on those "kernel models", which fully validates our first ideas concerning the viability of the notion of "kernel model". Within this implementation, organs, i.e. instantiations of concepts of the initial ontology, and connections between organs are associated to objects that implement agents. 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 relies the discovery process, we chose to build "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 is programmed in SWI Prolog[1]. It makes use of modules to emulate object oriented programing techniques, i.e. mainly the instantiation, inheritance and message sending mechanisms.

5 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: 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. 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, which 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.

To be concrete, take a simple example of intoxication with curare that is presented in Claude Bernard's personal writings. In this experiment, Claude Bernard poisons an animal. The voluntary movements are the first to be paralyzed. This 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. etc.

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

6 Conclusion

A virtual laboratory has been programmed in PROLOG. It allows 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. As it 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 [4]). The next step is to build such an hypothesis management module.

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's empirical method are always valid, even if the ontology on which are built 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 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.

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