Using AI to Reconstruct Claude Bernard's Empirical Investigations

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Abstract

We propose an Artificial Intelligence architecture dedicated to the reconstruction of old scientific discoveries. This architecture is based on the notion "core models" upon which the system draws out the logical consequences of scientific hypotheses. "Core models" are based on an initial ontology that contains entities and concepts recognized by scientists. Hypotheses are tentative explanations about entities functions. Those hypotheses have to be tested by a valid model, which may realize virtual experiments, i.e. "in silico", or real-world experiments. A third module, under construction, is aimed at comparing the expectations to the experimental data and then building new working hypotheses using abduction as inference. The architecture is validated on historical data: the ultimate goal is to reconstruct parts of Claude Bernard's empirical investigations. More precisely, it is to reconstruct the main steps of his scientific inquiry. The paper presents the general architecture and the way it helps to understand some of Claude Bernards scientific steps.

Keywords: Discovery Science, Model-Based Systems, Core Models.

INTRODUCTION

The work presented in this paper is considered as the first step of a large scientific reasoning simulation. This work is aimed at developping a computational model to reconstruct scientific discoveries (Kulkarani & Simon 1988) using AI techniques (Davis & Lenat 1982). Many researches from Cognitive Science and AI focus on modeling scientific reasoning (Stefik 1981), including experimentation (Gorman 1994). The CYBERNARD project (Ganascia & Debru 2007) constitutes an attempt to reconstruct some of Claude Bernard's scientific steps with the help of Knowledge Representation and Multi-Agent techniques.

Claude Bernard (1813-1878) was not only a great physiologist of 19th century, but he was also a theoretician who generalized his experimental method illustrated in his famous book "Experimental Medicine" (Bernard 1927). Our ultimate goal is to build gradually during the project the scientific approach of Claude Beranrd. To be able to understand his scientific approach, we presume that he had in mind a general *ontology* of the physiology upon which he generated initial hypotheses and then tried to discriminate among them by building experiments. On the other hand, he reduced the physical architecture of the organism using "*core models*", which contain basic physiological concepts. Our aim here is to show how ontologies and multi-agents techniques can be used to construct "*core models*" that simulate Claude Bernard's experiments.

According to the theory of biological relativity (Kohl *et al.* 2000) explaining that there is no privileged level of causality in biological systems, it is possible to explore functionality in a quantitative manner using one specific ontology (like that of Claude Bernard) all the way from the level of genes to the physiological function of whole organism.

The paper is organized as follows: In section 2 we provide an overview of model's main features, particularly, experimental model and simulation features. We make reference in section 3 to the model's implementation and agents used in it. Next section describes our results showing a complete hypothesis simulation. Finally the conclusion summarizes our work and what our future directions are.

MAIN FEATURES

Main Experimental Model Features

Claude Bernard's Ontology According to his writings (manuscripts, notes and books of experiments), we suppose that Claude Bernard had in mind an *ontology* upon which he generated all his experiments. In his ontology, Claude Bernard presumed that organisms are composed of organs. Organs, themselves, are considered as organisms since each of them has its own aliments, poisons, excitations, actions etc. Organs are categorized into three classes: skeleton, tissues and fibers. 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, is responsible for exchanges between organs. 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.

Claude Bernard's ontology may simply be derived from these considerations. 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 & Ceusters 2006).

Claude Bernard's Experimental Method Claude Bernard invented the bases of experimental method. This method includes three principal stages:

***Experimentation*:** Before designing an experimental apparatus able to generate observations, Claude Bernard considered an initial hypothesis – or several initial hypotheses in parallel – which he was trying to discriminate using empirical evidences. These hypotheses were formulated using the above described *ontology*.

***Observation*:** this step consists of collecting observations from the designed experiments that can be compared with expectations derived from his initial hypothesis.

***Analysis*:** Once his *"in vivo"* experiments were done and according to their observational results, the scientist was able to generate new working hypotheses and, as a consequence, reconstruct new experiments validating or invalidating his observations.

In other words, we assume that abduction plays an essential role in Claude Bernard's investigations by keeping or changing his initial hypotheses according to the consequences observed through his empirical experiments.

"*Core Models*" In order to build a computational model simulating the intellectual pathways leading Claude Bernard to his scientific discoveries, we suppose that he had in mind what we call "*core models*". Those core models contain basic physiological concepts such as organs, vessels (connections between organs), blood (internal environment), etc. More precisely, core models describe the physical architecture of the organism on which the experiments were constructed depending on the understanding of Bernard prior to the experiment. The initial hypothesis itself, which he called an *"idea"* or a *"theory"*, corresponds to an hypothetical organ function that he wanted to elucidate. Our aim in this project is to construct core models as a physical architecture simulating Bernard experiments.

Main Simulation Features

Organs Both organs (muscles, heart, lungs etc.) and connections between organs (vessels) are represented using agents. Agents are implemented using automata and communicate between them using the internal environment (blood). As a result of this communication, it is possible that values of one or more of environment's components change. For instance, oxygen value in the blood changes after passing through the lungs, which can be considered as an exchange with the external medium (e.g. the air in the case of human beings).

Organism After representing organs by agents, an organism, which is a network of different organs and connections between organs, can be modeled as a synchronous multi-agent system. The model we present in this paper allows setting freely the number of agents used in our simulation and which agents are to be connected inside an organism. This free choice of organs is up to the user and it depends upon each of Claude Bernard's hypotheses that we simulate.

Virtual Laboratory and Meta-Operators Our aim, by building and simulating the core models, is not only to show the normal behavior of the organism, but also to be able to emphasize the consequences of organ dysfunction. In order to achieve this goal, a virtual laboratory will be built gradually during the project having, on one hand, many virtual experimental operators, also called meta-operators, such as toxic substance injection. The virtual laboratory should contain, from the other hand, models of the configuration of a laboratory, such as instruments for making observations. For the moment, only some meta-opertators are presented inside the virtual laboratory. It means that only the simulation of the organ system is presented in this paper and not the simulation of Barnard's abductive reasoning which is a hopful pointer to future work. The simulation of the organ system is done according to Bernard's hypotheses and 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.

Here are some meta-operators used in our virtual laboratory:

- ***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.
- ***Tourniquet application***: To be able to identify the function of one particular organ, Claude Bernard evoked the idea of tourniquet. By tightening a body member using a tourniquet, the bloodstream is cut and, as a consequence, this member will be dissociated. The dissociation of this member allowed Claude Bernard to study its function by preventing, partly or totally, a toxic substance to affect it. For this reason, the pressure of the tourniquet tightening a body member was studied. This pressure was compared with that of the vessel on which the tourniquet was applied.
- ***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 by making artificial respiration) may affect the state of the whole organism.

- ***Substance ingestion***: It is possible, for the internal environment, to lose or to gain some substances by passing through an organ or even because of organism's interactions with external medium. But it is not limited to that. Internal environment may change its components or its components' values by ingestion. Some of Claude Bernard's experiments showed that feeding "experimental animals" with some product may modify the internal medium. These modifications in the internal medium may, consequently, affect the whole organism by changing one or more of its organs' state.
- ***Excitation***: In order to complete the range of meta-operators, we introduce one last virtual experimental operator which is excitation. To be able to understand the effect of a substance, Claude Bernard used the hypothesis that its concentration in the blood may affect such or such organ. Under these hypotheses, it is possible to predict the consequences of a direct injection of this substance using any combination of experimental operators. Applying a tourniquet on a member and exciting this member before and after the injection of this substance may be an example of using a combination of two meta-operators, application of tourniquet and excitation.

THE MODEL

Overview

Organs' simulation is used by many researchers to study the functionality of one specific organ, the whole organism or even to do a full modeling of biological processes. Studies in this field are numerous, including, for example, those conducted by D. Noble establishing the first viable mathematical model of the working heart (Noble 2002). Another example of simulation, which have been applied by quite a few researchers to modeling biological processes, is that of qualitative simulation (Heidtke & S. 1997). Our goal, in this work, is different from using computer models of biological organs and organ systems to interpret physiological functions, from the molecular level to the whole organism. We aim here at constructing "*core models*" that simulate Claude Bernard's experiments. Those core models depend on Claude Bernard's own ontology and on the choice of representative organs.

The first step in our approach is to identify the agents participating in the simulation. By "identify the agents" we mean to choose the organ reduction that is necessary to represent an experiment. This reduction is done by selecting organs and by establishing their connexions, before launching simulations.

As we mentioned previously, two main sets of agents are used within our model: organs and connections between organs. As agents are represented using automata, each agent has its own inputs, outputs, transfer function and states. In our model, each organ has one main input (an artery) and one main output (a vein) except for the heart which has more than two inputs and two outputs. An organ's input is an artery's output and an organ's output is a vein's input. In other words, vessels play the role of connectors between organs in which the internal medium, mainly the blood, will be transmitted.

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. Blood components used in our model are limited for the moment to: pressure, oxygen, glucide and lipid. The organ's activation cycle follows the blood circulation. Time is supposed to be discrete and after each period of time, the states of different agents belonging to the core model and their outputs are modified.

Agents may change their states according to two cases:

- A change in a blood component's value. For instance, if oxygen's value in the blood is insufficient to keep organs' states on *fresh*, organs change their states into *weary*. Then, if oxygen's value is still insufficient, organs may change their states into *dead* and the whole organism dies.
- A change of another agent's state. For example, once the heart's state is *dead*, all other organs change also their states to *dead* and, consequently, the whole organism dies.

Model's Implementation

The implementation makes use of object oriented programming 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 [1]. It makes use of modules to emulate object oriented programing techniques, mainly the instantiation, inheritance and message sending mechanisms.

The Agents

The agents participating in the model are:

- Organs, which may be, directly or indirectly, affected by using meta operators (e.g. muscles, heart, lungs, etc.).
- Connections between organs (e.g. veins).

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

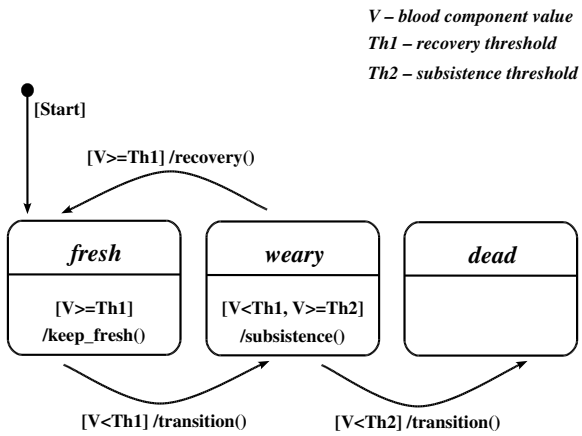

Figure 1: UML state diagram of the *Organ* agent

The *"Organ"* agent We can sum up the *Organ* agent's behaviors in the state transition diagram depicted in Figure 1.

In our model, we presume that all organs can be in one of three states:

fresh is the state of all organs in a healthy body. Organ's state does not change if blood components' values are sufficient to keep the organ's state on *fresh* according to a set of comparisons with organ's recovery thresholds for different blood components *TH1*.

weary is the state of an organ if a blood component's value is changed and the new value is less than the organ's recovery threshold for this component *TH1* but, at the same time, greater than the organ's subsistence threshold for the same component *TH2*.

dead is the state of an organ if a blood component's value is changed and the new value is less than the organ's subsistence threshold for this component *TH2*.

At the beginning of any simulation, all organs' states are initialized on *fresh* state. Each organ has, separately, its own recovery thresholds and subsistence thresholds for each blood component. The choice of these thresholds is depending on the hypotheses of Claude Bernard after doing a set of experiments. An organ's recovery threshold for one precise blood component is the minimum value of this blood component to keep the organ on *fresh* state, while an organ subsistence threshold for one precise blood component is the minimum value of this blood component to keep the organ on *weary* state. The set of these thresholds (recovery and subsistence) of an organ for each blood component is different from that of other organs. For instance, muscle's recovery threshold for a blood component is different from kidney's recovery threshold for the same blood component.

An organ keeps or changes its current state, when it is in one of these two situations: in the state of *fresh* or in the state of *weary*. An organ can not change its state when it is in the *dead* state. Thus, when blood arrives to an organ's input, all current values of blood components will be compared with organ's recovery or subsistence thresholds depending on the organ's state. As a result of these comparisons, the organ's state may be changed, as previously described.

The *"Organ which is directly affected by a toxic substance injection"* agent In our model, all organs may be directly affected by using meta operators such as: toxic substance injection, respiration or even substance ingestion. The organ that is directly affected by a toxic substance is called its target. Other organs may be indirectly affected by the dysfunction of the target. More precisely, their states change depending both on the modification of the internal medium and on the evolution of other organs's state. Organs's state can be in at least one of three states: *fresh, weary* or *dead*. However, it could be possible to add states specific to one particular organ to describe its particular dysfunctions.

Figure 2 summarizes this organ's behaviors. The upper part shows the normal behavior of these agents when no toxic substance is detected in the blood while the lower part shows that these three states *(fresh, weary, dead)* are not the only possible states for this kind of agents.

Two additional states exist:

semi-paralyzed is the organ's state if a toxic substance is detected in the blood and its value is enough to change its state from *fresh* state to *semi-paralyzed* state. Organ's state does not change if toxic substance's value is lower than the semi-paralyzed threshold *TH3*.

Once organ's state is on *semi-paralyzed* state, it is possible that an organ keep its state on *semi-paralyzed* if the toxic substance's value is still greater than the semi-paralyzed threshold *TH3* but, at the same time, lower than the paralyzed threshold *TH4*.

paralyzed is the organ's state if a toxic substance is detected in the blood and its value is enough to change its state from *semi-paralyzed* state to *paralyzed* state. It is possible that an organ keep its state on *paralyzed* if the toxic substance's value is still greater than the paralyzed threshold *TH4*.

Initial state of all organs is *fresh*. In addition to recovery thresholds and subsistence thresholds for each blood component, each organ has its own semi-paralyzed thresholds and paralyzed thresholds for every single toxic substance (e.g. curare) that may paralyze the functionality of some organs (e.g. muscles). An organ's semi-paralyzed threshold for one precise toxic substance is the minimum value of this toxic substance that is enough to turn the organ's state into *semi-paralyzed* state, while an organ paralyzed threshold for one precise toxic substance is the minimum value of this toxic substance that is enough to turn the organ's state into *paralyzed* state. These thresholds for one precise toxic substance are different from one organ to another.

An organ can keep or change its current state when it is in one of these four states: *fresh, weary, semi-paralyzed* and *paralyzed*. While *dead* state is considered as a final state. When no toxic substance is detected in the blood, the transition takes place between three states: *fresh, weary* and *dead*, as Figure 1 or also the upper part of Figure 2 show. Once a toxic substance is injected, according to its value, the transition between states takes place between all five possible

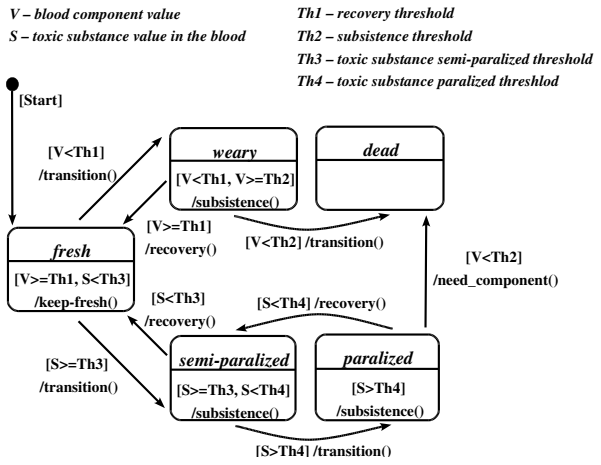

Figure 2: UML state diagram of the *Organ which is directly affected by a toxic substance injection* agent

states of an organ, as Figure 2 summarizes. As we can notice, when organ's state is *paralyzed*, two transitions are possible according to the initial value of toxic substance injected into the blood. If this value is enough to be evacuated before other organs are damaged (e.g. the lungs stop working some period after toxic substance injection), the new state is *semi-paralyzed*, otherwise it is *dead*.

For the moment, all cases are not covered by the state diagram, but as our model is based on Bernard's experiences, other cases could be added depending on senarios described by him.

The *"Connection between two organs"* agent The main functionality of these agents (e.g. veins, arteries) is to transmit blood between organs all over the organism. Many meta-operators, such as toxic substance injection or even tourniquet application, can be introduced directly on one of these agents, which affect, as a consequence, some blood component's values.

RESULTS

Recall that Claude Bernard had in mind the notion of core models based on initial ontology that contains entities and concepts. His goal was to validate or invalidate scientific hypotheses about entities functions. Our aim, in this step, is to complete entities with all functions recognized by the scientist drawing the logical consequences of each hypothesis (observations). This step is considered as the base of a future work allowing to compare these observations with expectations in order to to bulid new working hypotheses using abduction.

We show, in this section, an example of simulating observations derived from one of Claude Bernard's hypotheses. Before launching the simulation, a virtual organism is built. It corresponds to the organism reduction that takes place in Claude Bernard's thought experiment, before the actual experimentation. Once the virtual organism is constructed, meta operators simulate the experimental protocol, e.g. placement of a tourniquet at time t, injection of curare at time t', excitation of a member at time t" etc.

The phases necessary to prepare a simulation are:

- Initially, all organs' states are *fresh*.
- Virtual organisms are built with respect to different Claude Bernard's hypotheses. For instance, the organism may be reduced to one heart, one lung, two muscles: a voluntary muscle and a muscle that controls the lung movements, and one kidney that progressively evacuates toxic substances from the organism. Then, one build a virtual organism that contains agents representing one heart, one lung, etc. and their connexions.
- Two meta operators are used: the toxic substance injection and the artificial respiration, which is an interaction with the external medium meta operator.

  In the toxic substance injection, one can choose all parameters one needs to inject a toxic substance such as, *what* toxic substance to be used, *where* to inject it, *how much* of this toxic substance one needs and the *time* from which one starts the injection. In artificial respiration, only the *time*, from which the artificial respiration is started, is determined.

Complete hypothesis simulation

This simulation translates one of the many hypotheses of Claude Bernard, 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 will be subject to a reasoning process in a future phase of our project.

In his writings, he 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 an extract of one of his hypotheses taken from his personal notes (Grmek 1973):

"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 used before breathing stops and with the same dose of curare used before.

When we inject a dose of curare in the virtual organism, two cases are possible:

- If the dose of curare is very low, voluntary muscles are paralyzed but the curare is evacuated before asphyxia happens. This is not the case discussed in Claude Bernard's previous statement, however, it is in accordance with his main hypothesis and many experiments conducted by Claude Bernard simulate this script.

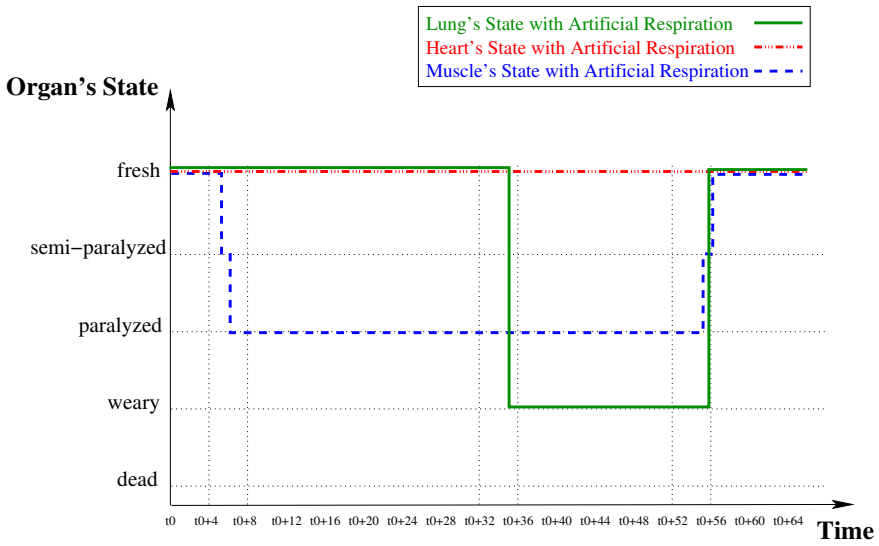

Figure 3: State of different organs in a virtual organism when an important dose of curare is injected and artificial respiration is used before breathing stops

- If the dose of curare is sufficient, voluntary muscles are progressively paralyzed and the animal is asphyxiated before the complete evacuation of curare.

Curare injection takes place at the time *t0+4* and changes the muscle's state into *semi-paralyzed* and then into *paralyzed* at the time *t0+6*. When lung's state becomes *weary*, due to lung muscles paralysis, artificial respiration is used and it provides enough oxygen to keep the heart's state *fresh* and, consequently, all other organs. Once the curare evacuation is almost done, muscle's state changes into *semi-paralyzed* and then into *fresh* at the time *t0+56*. The same happens with the lungs which change state at the same time into *fresh* and the organism is once again fresh.

CONCLUSION AND FUTURE DIRECTIONS

In this study, the work we have done till now is aimed at expressing the model of biological systems developed by Claude Bernard. We have been able to reconstruct computationally part of Claude Bernard's intellectual pathway. A virtual laboratory has been partially built allowing the construction of virtual experiments associated with different working hypotheses. The output is the observations collected after each simulation.

However, one of our future goals will be aimed at Claude Bernard's reasoning by completing our virtual laboratory with tools of configuration allowing to correlate virtual experiments to actual experiments done by Claude Bernard and then to corroborate or refute working hypotheses according to the observations.

Another further goal will concern the way upon which underlying conceptions evolve in Claude Bernard's research, especially the way both Claude Bernard's ontology and hypotheses concerning the different organ's functions were transformed during his scientific life.

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, molecule etc. 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 time. 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 working hypotheses have already been explored.

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