The Discovery of the Causes of Leprosy: a Computational Analysis

Vincent Corruble, Jean-Gabriel Ganascia

LAFORIA-IBP, Université Paris VI
4, Place Jussieu - Boîte 169
75252 PARIS Cedex 05, FRANCE
{corruble,ganascia}@laforia.ibp.fr

Abstract

The role played by the inductive inference has been studied extensively in the field of Scientific Discovery. The work presented here tackles the problem of induction in medical research. The discovery of the causes of leprosy is analyzed and simulated using computational means. An inductive algorithm is proposed, which is successful in simulating some essential steps in the progress of the understanding of the disease. It also allows us to simulate the false reasoning of previous centuries through the introduction of some medical *a priori* inherited form archaic medicine. Corroborating previous research, this problem illustrates the importance of the social and cultural environment on the way the inductive inference is performed in medicine.

Introduction

In some previous work (Corruble & Ganascia 1993, 1994), we investigated the role of induction in an important medical discovery. It appeared that an algorithm could, through a simple pure induction, dicover the cause of scurvy using a number of cases from 19th century medical literature. In that respect, our work was in the direct line of the data-driven approach to the computational study of scientific discovery. Pat Langley and Jan Zytkow have summarized in (Langley & Zytkow 1989) some of the key systems based on this approach. They defined the commonality of these systems as « the use of data-driven heuristics to direct their searches through the space of theoretical terms and numeric laws ».

On the other hand, we also showed in this study that, in order to reconstruct rationally some of the false reasoning of the 18th and 19th century about scurvy, it was necessary to introduce some implicit background knowledge inherited from pre-clinical medicine that influenced the inductive reasoning of those physicians. Thus we questioned the validity of a purely data-driven induction for the rational reconstruction of medical discoveries and we introduced the concept of *medical system,* a body of knowledge that influences, in some cases implicitly, the inductive reasoning of physicians.

In the study presented here, our original aim was to investigate whether the results obtained on the discovery of the causes of scurvy would also apply to the discovery of the causes of leprosy. The central role played by the cultural environment on the inductive process is illustrated with this example: it has been necessary to formalize some implicit background knowledge concerning the nature of the concept of disease to reach a plausible computational account of the Nineteenth century reasoning on leprosy cases.

In addition, we are to show that the rational reconstruction of the reasoning on the leprosy cases available requires the use of a type of induction which allows for the representation of exceptions. We consider these exceptions as radically different from the noise traditionally studied in the fields of statistics and machine learning. Although medical science was not advanced enough in the Nineteenth century to elaborate a fully satisfactory etiology for the disease, we show that some crucial improvement in the understanding of leprosy could have been reached based on the data then available. The primary lesson drawn from our experiment is that induction in science needs to be considered as an inference taking place within a dynamic context influenced by the previous stages of the domain, and aiming at overcoming its limitations.

We begin this paper by giving some perspective on the history of leprosy and of the research regarding, chiefly, its etiology. Then we analyze some specific issues concerning induction in this discovery. More specifically, we show that useful inductions were produced in history despite the presence of obvious counter-examples which were not caused by noise. We then use PASTEUR, a new inductive algorithm, in two simulations on leprosy data collected in Nineteenth century medical literature. First we get some surprising results which can be understood in the light of modern leprosy research. Second, we reproduce the false reasoning of the Nineteenth century by introducing *a priori* knowledge on the concept of disease. We then sketch the basics of PASTEUR, and highlight its advantages over other classical learning algorithms for the task considered.

A Brief History of Leprosy

History of leprosy dates back to ancient China and India. We will not dwell here upon its origins (readers interested can refer for example to (Skinsnes 1973)), but an important fact to notice is that the concept of leprosy was ill-defined

for many centuries because it seems to have been confused with some other diseases until more recent times.

Research on leprosy has followed a particularly interesting path. Modern western medicine was increasingly confronted with the disease during the development of colonialism in the Nineteenth century. In the past century, the main theory on the etiology of leprosy referred to heredity as the main and often only explanation of the disease (see for example (Royal College of Physicians 1867)). It made a lot of sense since the disease would often affect many members of the same families. The other hypothesis, the one of contagion, was also proposed early (Drognat-Landré 1869), but was contradicted by the fact that many people (for example some nurses) in close contact with lepers were not affected, so that, for a long time, this hypothesis was considered unscientific.

However insightful these theories were, they were not confirmed by laboratory experiments and were thus merely hypotheses. It is not until 1872 with Hansen's discovery of the infectious agent causing leprosy (Hansen 1875) that the theory of contagion gained significant ground. The question was not solved though because this discovery did not explain how the agent was transmitted. Heredity and contagion were still opposed as two distinct potential explanations. One reason for this debate was the impossibility of *in vivo* experimentation on animals: the only environment in which Hansen's bacillus could survive was the human body. Hansen went as far as trying to contaminate some healthy patients in his hospital by pricking their eyes with a contaminated object, but he was not successful in obtaining any result (except that of being found guilty of unethical medical practice by a Danish court).

As shown in (Waters 1993), the most radical advances in our century in the understanding of leprosy were produced in the early 60's by, on the one hand, the discovery of the possibility of *in vivo* experimentation in the mouse footpad, and on the other hand, the progress of immunology and the new classification of leprosy proposed in (Ridley & Jopling 1966), which focuses on individuals' immune reaction. The new main axis of research on leprosy then became the study of the human immune system's reaction to the leprosy bacillus.

Induction and Leprosy Research

To summarize the history of leprosy and focus on the development of hypotheses, we can isolate three major theories: the theory of heredity, the theory of contagion, and the theory of immunity. What was the role of induction on the formation of these theories? It is clear from reading the works of physicians that these hypotheses result from the observation of patients. However, the underlying inductive reasoning was not described precisely so that it could be directly formalized. Nevertheless, the previous account of the history of the disease tells us that the induction performed in the 19th century did not abide by the rules of the type of logical inference which proved useful in simulating other medical discoveries (Corruble & Ganascia 1993, 1994).

Both theories, the one of heredity and the one of contagion obviously had some counter-examples known to most physicians. Some people got ill even though none of their ascendants had been diagnosed as a leper, so that, in fact, the hypothesis of heredity was directly invalidated. Some health workers or close relatives had been in contact with lepers for the major part of their lives and were still in perfect health. This « fact » invalidated the contagion theory. Despite these limitations, the hypotheses were produced, and proved useful, because they constituted significant steps towards the next breakthroughs.

We have designed a new algorithm in order to permit a computational account of the reasoning performed last century. Also, the same algorithm is used to study whether the same computational techniques could have been of significant help to the physicians.

The Need for Indulgent Induction

Here we introduce a new inductive inference, indulgent induction, which departs significantly from the classical generalization-based induction in its ability to model explicitly exceptions. We will then present an algorithm which performs this inference, and which has been used in our experiments on leprosy.

One of the most widely recognized frameworks for the study of induction, in the field of Machine Learning, is the Version Space approach (Mitchell 1982). In this framework, induction is seen as a search for an hypothesis which is consistent with the pre-classified set of examples and counter-examples. This constraint is generally accepted in the community as a primary requirement. However, (Mitchell 1982) recognizes the limitations of the approach in the case of inconsistency, which can be of two kinds: inconsistency can result from (1) an insufficient description language, or (2) error in the training instances.

The second case has lead to a huge amount of work, from statistics to machine learning, on induction from noisy data. However, in medical research, it is common to reason within a framework characterized by an insufficient description language. Furthermore, even though Mitchell suggests that other approaches are needed in the case of the impossibility of hypotheses consistent with all the examples, it seems that they should also be considered if consistent hypotheses are available. This opinion is directly linked to the theory of *satisficing* developed in (Simon 1980): confronted with a complex phenomenon, a scientist has to come up with an hypothesis which favors simplicity over pure logic or optimality. The theories of heredity, and of contagion are two examples of « satisficing theories », which are both wrong, but yet simple enough to enable the researcher to structure his reasoning toward more elaborate and accurate theories.

Therefore, we need to define another type of induction for which strict consistency with the data is not considered

as a prerequisite. We have named this new inference *indulgent induction*, because, as an indulgent father in real life, an indulgent hypothesis will make exceptions for its children. Also, it is through the violation of the consistency constraint that innovative hypotheses which depart radically from the current theory (implicitly encoded in the data) can be suggested. The interest and the validity of these hypotheses are of course not guaranteed, but it is the role of the search heuristics to maximize the chances that they be so. In the next section, we present our experiments on the discovery of leprosy with PASTEUR, an algorithm that implements the principle of indulgent induction. PASTEUR is presented in some detail in the last section of this article.

Experimentation on leprosy

In this section, we present our experiments with PASTEUR on inductive reasoning on the causes of leprosy. The study is based on a compilation of cases carried out in an Indian leprosy asylum in the 1880's reported and analyzed in (Phineas 1889). This study came at a time when the theory of contagion was beginning to challenge the prevalent theory of heredity, but it is worth noticing that, in this specific study, as Phineas mentions, the investigator seems to favor the theory of heredity. An evidence of this bias lies in the care taken in researching the list of relatives affected by the disease. The question that we ask ourselves in these experiments is: can we, given observational data on the disease acquired and reported with a pro-heredity bias, obtain through automated induction the suggestion of other interesting hypotheses. The first « other hypothesis » that could be expected is the contagion theory. We will however see in the following that our experimental results are quite surprising in that respect.

The material used for the experiments

.Most of the cases available are supposed to have leprosy even though, for some, the diagnosis seems more than doubtful (for example, one patient is said to have no symptom of the disease, but is convinced of having it).
However, all these cases are of a great interest because of the care taken to research a number of features potentially relevant to the etiology of the disease. Among them, we have available the sex, the caste, the age of the patient, the variety and duration of the disease, then the relatives affected, some information on the children and spouse, a description of how the disease started, and also the fish diet (considered by some as a key factor in the Nineteenth century). These features are summarized in Figure 1. The more specific question asked in this experiment is: Can the system propose an exploratory model linking the description of the patient and of his/her environment to the health of his/her children ? In other words, can it predict (in an exploratory mode) whether some of the patient's children will be sick or whether all of them will be healthy.

The 61 cases selected have been used in two experiments using PASTEUR. The first experiment aims at testing which hypotheses can be induced on the cause of the disease. The second one is concerned with the reconstruction of Nineteenth century reasoning as it happened in history.

Attribute	Type	Domain
name	string	NA
sex	unordered set	m, f
caste	unordered set	Mussulman Sweeper Jheur Kohle Jat Rajpoot Musician Do_potter Do_teli Bahte
age	integer	NA
disease_type	unordered set	mixed do_ anaesthetic tuberc
duration	integer	
father_affected	unordered set	yes, no
mother_affected	unordered set	yes, no
father_side	unordered set	yes, no
mother_side	unordered set	yes, no
spouse	hierarchy	no yes (healthy, sick)
children	unordered set	some_sick, all_healthy
fish_diet	ordered set	never, rarely, sometimes, often, very_often plenty, in_excess
initial_location	unordered set	body, arm, leg, hand, foot, joints, face

Figure 1. List of attributes with their characteristics

Indulgent induction on leprosy

In this experiment, we give to PASTEUR the description of the 61 patients available. The question posed is formulated as such: given the description of a patient and his/her family, the system is asked to build an exploratory model predicting the health of the children on the basis of other observable features. In this experiment, the results which we would find interesting are of two kinds, as for our experiments on scurvy:

- from a descriptive point of view, do the hypotheses produced account for the theories proposed at the time of the observations ?
- from a normative point of view, do the hypotheses produced suggest a more advanced theory than the ones from the Nineteenth century ?

In this latter case, the kind of theory that we would expect to be suggested is, considering the medical debate of the Nineteenth century, the theory of contagion. It would be interesting if the simulation suggested contagion from the material available since these observations were acquired with a pro-heredity bias.
Results. The results are shown in Figure 2 (the decision graphs proposed by the algorithm have been translated into an equivalent set of rules). R1 and R2, the two main rules proposed (out of 5) are given. R2 solves some exceptions resulting from the general rule R1.

```
R1: IF father_affected = No                THEN children = all_healthy
R2: IF father_affected = No                THEN children = some_sick
       Mother_side = yes
       age > 35
       disease_type = aneasthetic
+ 3 minor rules
```

Figure 2. Model induced by PASTEUR

Analysis. The model tells us that in the general case, it is sufficient to know that the father of the patient is NOT ill to conclude that his children are healthy (rule R1). This general rule has exceptions however, and these are partly resolved by the more specific rule (R2), which says that among these patients with a healthy father, the ones having ill relatives on the mother's side, being ill with the anesthetic type of disease, and being over 35 years old, have ill children.

The theory of heredity appears in the model induced, since the first feature of interest appears to be the health of a direct ascendant. In that respect, our simulation is close to the models proposed in the Nineteenth century. There are however two major differences. The first one is that the theory of contagion does not appear directly in the hypothesis. The second difference appears critical in the light of modern research on leprosy: What the model proposes is to reason on the *absence* of the disease. The first rule, R1, tells us that it is relevant to consider that the fact that somebody is *healthy* tells us something about the disease. We have to put ourselves back in the context of the Nineteenth century to realize how this idea would have been *revolutionary* then, and we have to use our knowledge of contemporary leprosy research to understand how *relevant* this revolution could have been. Before studying why this hypothesis was not proposed at the time, let us examine why it would have been particularly relevant.

Modern leprosy research, as we suggested earlier, aims at understanding the immune system's reaction to the bacillus, so that the current accepted classification of the disease is based mainly on the characteristics of this reaction, even though it is initiated by an infectious agent. The absence of the disease is, in that context, an active process in which the human metabolism is fully involved.

This point of view could not be articulated in the Nineteenth century for two main reasons: The first, obvious one, is that the domain language did not include the vocabulary needed to describe adequately the phenomenon of immunity. The second one requires the help of history of medicine

Historical reconstruction

A study in the history of medicine helps us to understand this phenomenon. In [Grmek 1995], a history of the concept of disease is attempted. In archaic western medicine (before Hippocrates, 6th cent. BC), Grmek isolates the primitive ontological conceptualization. In this framework, a disease is identified as one entity which penetrates the organism. This "thing" can be inanimate (corpuscular theory), a material living being (parasite theory) or an immaterial being (demon theory). The disease and its cause are thus naturally confounded.

Hippocratic medicine introduced a new concept of disease. Being brought back into the field of nature, diseases are then considered as resulting from a bad mix of some essential humors. Indeed the passing from fitness to illness takes place through the change from a fair mix[1] (*symmetria*) to a bad one (*dyskrasia*). What is important to notice is that, even after this new dominant framework was introduced, the original view on the nature of diseases remained in the background, and was sometimes particularly vivid.

If we hypothesize that these two views on the nature of diseases coexisted and could have influenced the reasoning on leprosy, we need to find a formalization for each of them in order to carry out an experimentation. The archaic concept of disease is best represented by a predicate. In the case of leprosy, "patient X has the disease" is considered as a property that can be expressed as the predicate `leper(X)`. On the other hand, if the disease is defined by a bad mix (Hippocratic concept), a good representation is an attribute-value one expressing that `mix_X = bad` if X is ill, and `mix_X = if X is healthy`.

The choice of a formalism over the other one can be considered as an *a priori* on the nature of the disease. As such, we can formalize it by constructing the features describing if a relative is affected instead of considering them as given in the description. What the description tells us concerns only symptoms (or syndromes). The disease itself is defined by the axioms of Figure 3 (archaic ontological concept) or of Figure 4 (Hippocratic dynamic concept) for *father_affected*. The same axioms apply also for the other attributes (*mother_affected*, *father_side*, *mother_side*, and *spouse*).

```
IF leprosy_symptom_father = yes  THEN father_affected = yes
```

Figure 3. Axioms constructing the concept of leprosy (1)

```
IF leprosy_symptom_father = yes  THEN mix_father = bad
IF leprosy_symptom_father = no   THEN mix_father = good
IF mix_father = bad              THEN father_affected = yes
IF mix_father = good             THEN father_affected = no
```

Figure 4. Axioms constructing the concept of leprosy (2)

In our first experiment, through a naive representation of our examples, we eluded a major a priori inherited from archaic medicine. By representing the health status of a family member as a Boolean feature (yes or no, for healthy or ill), we gave as much importance to the presence and to the absence of the disease, implicitly using the Hippocratic dynamic concept of disease. This hypothesis of the importance of the representation chosen is tested in our next experiment.

[1] What the elements of this mix are remained ill-defined, but took a more precise shape within the humor theory which defined two pairs of humorus as its four basic elements.

Induction with a priori medical knowledge

This experiment aims at testing our hypothesis about the role of the conceptualization of disease. We are interested in testing the impact on induction of the use of the archaic concept of disease, and its correspondance with history. This is simulated in this experiment by constructing the attributes describing the health of relatives according to the axioms of Figure 3.

Results. With this description language, PASTEUR induces the following model:

R2:	IF	disease_type = do.	THEN	children = all_healthy
R4:	IF	disease_type = do ∧ mother_affected = yes	THEN	children = some_sick
R5:	IF	disease_type = do ∧ father_affected = yes	THEN	children = some_sick
R1:	IF	disease_type = anesth.	THEN	children = all_healthy
R3:	IF	disease_type = tuberc.	THEN	children = all_healthy
R6:	IF	disease_type = mixed	THEN	children = all_healthy

Figure 5. Model induced by PASTEUR given the archaic concept of disease

Analysis. These results are interesting because they account for the theory proposed in the Nineteenth century on the etiology of leprosy. The two main characteristics are, on the one hand, the importance of the disease type which appears here as a key feature to explain the disease (so that, this classification in types of leprosy finds some kind of posterior justification in the context of Nineteenth century medicine). On the other hand, the heredity theory appears in full force to claim that the ill children are, among the children of those patients having the "do." type of disease, the children of patients also having a parent affected by the disease.

In this experiment, we see that by introducing some appropriate bias concerning the nature of the concept of disease, we can induce a model which is very similar to the one proposed in the Nineteenth century.

PASTEUR, algorithm for indulgent induction

Indulgent induction has been recognized as important to overcome the limitations of a domain language within the dynamic context of a science in the making such as medicine confronted with the etiology of leprosy. PASTEUR is a new inductive algorithm based on CHARADE (Ganascia 1991), which implements the principles of indulgent induction. It introduces a new hypothesis space and new heuristics for searching the description space. Here, we will only give an idea of the functioning of the algorithm, insisting on the way hypothesis space and search heuristics are both geared toward the design of exploratory *satisficing* theories, and toward an explicit modeling of exceptions.

A basic idea behind the new hypothesis space is to use the properties of the description space. All the nodes of the description space are connected according to a general to specific relation, and this relation is used to ensure a top-down search.

All the rules induced by the algorithm can therefore be represented as a set of directed graphs of rules connected by a specialization relation. We call these graphs *decision graphs* by reference to the more constrained decision lists and decision trees. Decision graphs are acyclic graphs made of a rule at each one of their nodes. Two rules are connected if the premise of one rule is more specific than the premise of the other rule. Among all the rules whose premises are satisfied by an example, only the most specific ones, are activated. A voting scheme among these rules is then used to assign a class to the example.

Structures similar to decision graphs have been proposed recently in (Gaines 1995) to address the same kind of problem through a post-processing of existing rule bases induced by various algorithms. The decision graphs used here are however in spirit closer to the "ripple-down rules" proposed in (Compton 1991).

Input: E a set of preclassified examples
D a set of elementary "attribute-value" pairs
Output: Rset, a set of rules structured in decision graphs

Procedure PASTEUR(E)
Set nodeset to D, initialize fuel to fuelmax
PASTEUR-aux(E,nodeset,Ø)

Procedure PASTEUR-aux(E,nodeset,Rset)
If nodeset is empty or If fuel=0 then return Rset
decrement fuel
Select node N in Inf(nodeset) that maximizes B(fuel,N,Rset).H1(N,Rset,E)
Construct R from N
If H2(E, Rset, Rset ∪ R) > X_α
then **insert** R in Rset and reset fuel to fuelmax
Specialize N
Set nodeset to nodeset \ {N} ∪ {d & N, d ∈ D}
strip nodeset of "useless" nodes
PASTEUR-aux(E,nodeset,Rset)

Figure 6. PASTEUR algorithm (2-class case)

Some simple heuristics have been developed to explore the space of decision graphs. The description space is explored according to a best-first top-down search. Two elements are taken into account when selecting a new node for evaluation. The first element (H1) measures the interest of a node taking into account the examples it covers from a global perspective, selecting the one that maximizes the number of cases that will be correctly classified, minus the number of cases that will be misclassified.

The second element (B) is a bias toward graph construction: the exceptions created by a rule are corrected in priority by refinement of the decision graph. This bias decreases linearly so that after repeated failures, the algorithm is given more flexibility so that it can explore other parts of the description space to initiate new graphs. This flexibility is a distinctive feature of PASTEUR whose search is directed by exceptions *and* coverage.

Each candidate rule is evaluated, and inserted in the current decision graph if it satisfies a criterion (H2) based on the global improvement of the coverage of the learning cases. This criterion takes into account that what seems to

be at first an approximation can be refined by the insertion of more specific rules.

PASTEUR in our experiments

Here, we briefly justify the use of PASTEUR in our experiments by comparison with other standard inductive algorithms. We do this by showing that the hypotheses proposed by PASTEUR are not in the search spaces of other classical algorithms. This appears best in the model proposed in Figure 5. This model uses a combination of properties which is not shared by other approaches.

Figure 7 summarizes three properties needed to induce this model, which are characteristic of PASTEUR but not shared by other classical learning algorithms. The properties reviewed are the "Separate and Conquer" feature (SC) characteristic of algorithms learning Disjnuctive Normal Form (DNF) hypotheses, the ability to learn default hypotheses (characteristic marginally shown by algorithms designed to handle noisy data), and the ability to model explicitly exceptions to default rules. PASTEUR is compared to approaches learning Decision Trees (e.g. C4.5 (Quinlan 1992)), Decision Lists (e.g. CN2 (Clark & Niblett 1989)), and DNF (e.g. CHARADE) hypotheses.

Property	DT	DL	DNF	PASTEUR	Rules involved
SC		X	X	X	R2,R1,R3,R6
Default	X	X	X	X	R2
Exception				X	R4, R5

Figure 7. Properties needed to induce the model of Figure 5 and comparison with other algorithms

Conclusion

Our experiments on the discovery of the causes of leprosy have shown that a general inductive algorithm being given patients' descriptions collected in the 19th century could produce hypotheses corroborated by 20th century medicine on the etiology of the disease. Even though last century's descriptions were incomplete and collected with a pro-heredity bias, PASTEUR detects the importance of the absence of the disease, and hence, of immunity to predict the children's health. Our second experiment, confirming previous research, shows that computational simulations can be used to give a dynamic account of the Nineteenth century medical reasoning by taking into account some knowledge on the nature of the concept of disease.

Acknowledgments

The initial stages of this research were made possible thanks to a grant from the *Fondation de France*. We are grateful to Jacques Lebbe and the reviewers for their helpful comments on earlier drafts of this article.

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