A Pragmatic Logic of Scientific Discovery

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Abstract. To the best of our knowledge, this paper is the first attempt to formalise a pragmatic logic of scientific discovery in a manner such that it can be realised by scientists assisted by machines. Using Institution Agents, we define a dialectic process to manage contradiction. This allows autoepistemic Institution Agents to learn from a supervised teaching process. We present an industrial application in the field of Drug Discovery, applying our system in the prediction of pharmaco-kinetic properties (ADME-T) and adverse side effects of therapeutic drug molecules.

1 Introduction

Scientific discovery is a collective process made possible by the tracability of judgment, positive and negative results, theories and conjecture through their publication and evaluation within a community. Without this tracability, scientific results will not last long enough to influence others, and there would be no science. This tracability is the key to localise points of debate between members of a community, to open new research fields, to put forward problems and paradoxes that need further investigation and the establishment of a consensual frame of reference. This collective process leads to a social organisation in which some members specialise in publishing, refuting, or proving results, and have gained credit which defines them as a reference in the community.

The logic of scientific discovery presented by Popper [1] or Lakatos [2], and discussed by the Vienna Circle puts forward the elaboration of norms and the break-points taking place during the formation of scientific theories. However, to formalise scientific discovery, one has to define logically notions such as paradox, postulate, result and conjecture, which was not possible whithout using a logical system allowing to reason non trivially in presence of contradictions. Moreover, the process of scientific discovery is a collective process that can only be formalized by taking interaction into account in a constructive way, as in multi-agent theories. Finally, scientific discovery is an interactive adaptive process, and it is only very recently that Angluin's works on machine learning theory gave a formal basis to the convergence analysis of such a process. To the best of our knowledge, this paper is the first attempt to merge these three domains in order to formulate a pragmatic logic of scientific discovery.

In section 2, we propose a cubic model to express judgment about statements in the context of scientific discovery. We then show that the set of judgments is closed when the underlying logic is a paraconsistent logic C1. In section 3, we assume that this logic is applied independently by different institutions, and we present their properties fixed by their interaction protocol: the respect of a hierarchy, the pair evaluation, and finally the auto evaluation. This enables to tune these institutions in order to match a specific context on knowledge construction and representation. In section 4, we assess the learnability of scientific theories by scientists assisted by learning machines during an interaction following this protocol, and we present an industrial application in the field of Drug Discovery, applying our system in the prediction of pharmaco-kinetic properties (ADME-T) and adverse side effects of therapeutic drug molecules.

2 Logical expectations: Cube of judgments

We assume that the form of reasoning used in science is the same for every institution and every scientist. This form is given by a modality attributed to a statement beyond the following: paradox, proof, refutation, result, conjecture, postulate, contingent, and possible. This set of modalities is assumed complete and closed by negation. In this section, we define with these modalities the cube of judgments and we have to work with paraconsistent logic.

2.1 Square of modalities

The figure 1 expresses Aristotle's *square of modalities*. Aristotle's logic is said to be *ontic* since every modality is expressed from a single modality $\Box$ and negation $\neg$ and the square of oppositions is closed by doubling this negation: $\Box = \neg\neg\Box$. The top modalities (Necessary, Impossible) are used to express universal statements whereas the lower modalities (Possible, Contingent) are used to express particular statements.

$$\begin{tikzcd}
Necessary = \Box A \arrow[d, "D"'] \arrow[dr, leftrightarrow, "\neg"] & Impossible = \Box\neg A \arrow[d, "D"] \arrow[dl, leftrightarrow] \\
Possible = \neg\Box\neg A & Contingent = \neg\Box A
\end{tikzcd}$$

Fig. 1. Aristotle's square of modalities

We can make a parallel with Scientific Discovery and the theory of proof and refutation as follow:

- ”‘A is necessary”’ = A is proven: $\Box A$
- ”‘A is impossible”’ = ”‘A is refuted”’: $\Box\neg A$
- ”‘A is possible”’ = ”‘A has not been refuted”’: $\neg\Box\neg A$

– ”‘A is contingent”’ = ”‘A has not been proven”’: $\neg\Box A$

To link these modalities, epistemic logic uses axioms: the axiom D describes the vertical relations between necessary and possible, and between impossible and contingent”. By following two different paths on the square of oppositions, we can reach the same point, and we define consistency constraints by considering that these two paths lead to the same result:

– What is necessary is possible and therefore is not impossible.
– What is impossible is contingent and therefore is not necessary.

In intuitionistic logic, the negation of a concept A is not a concept but an application from this concept into a *contradiction*, which is a statement both true and false ($A \wedge \neg A$). In the same way, a paradox is a statement which is both proven and refuted. For instance, a bike without $wheel \vee frame \vee handlebar$ would be contradictory. Classical logic becomes trivial in the presence of a single contradiction, following the principle of contradiction: *given two contradictory propositions, one being the negation of the other, only one of them is false*. On the opposite, paraconsistent logic allows reasoning in a non trivial way in the presence of contradictions [3] [4] [5].

2.2 Paraconsistent logic

Paradoxes have often been at the source of scientific discoveries, and have often lead to new approaches and revisions of the frame of reference. This only happened when the whole theory used to explain the concerned domain did not completely collapse under the weight of its contradictions, and that is why we need to use paraconsistent logic to formalise a logic of scientific discovery. Paraconsistent logic uses different negations associated with different levels of contradiction to allow reasoning in the presence of contradictions as in classical logic with no contradictory statement. Given a theory T, we call '*formal antinomy*' any meta-theoretical result showing that T is trivial. A '*formal paradox*' is the derivation of two contradictory results of T. Paraconsistent logic can be paradoxical without being antinomic: an *informal paradox* is an acceptable argument for which premises are acceptable (they seem true), argument is acceptable (valid), and the conclusion unacceptable (seems false).

To achieve our goal of producing a complete judgment system, taking into account contradictions, we need to complete the set of modalities with those of paradox and conjecture, hypothesis and result. The square of oppositions then becomes a cube of judgments for which the square is a diagonal plane as shown in figures 2 and 3.

Definition 1. *The* ***cube of judgments*** $Cube = (\Box, \neg)$ *is the set of ontic modalities derivable from a modality* $\Box$ *and a negation* $\neg$.

Property 1 *In a paraconsistent logic C1, this cube of judgments is complete and closed by negation.*

This property, highlighted by the diagonal planes of the cube on figure 2 is given by the following two principles of abstraction that caracterise C1 logic [6], from which a paraconsistent interpretation of the Morgan's laws can be verified:

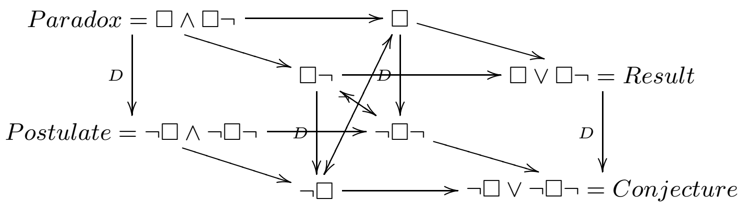

Fig. 2. Square of deontic judgments as a diagonal plane of the $Cube$

The weak principle of abstraction: If two propositions are not contradictory, then none of the logical relations between them is contradictory:

- What is not a non contradictory postulate is a *result*:

$$\neg : \neg\Box \wedge \neg\Box\neg \longrightarrow \Box \vee \Box\neg.$$

- What is not a non contradictory paradox is a *conjecture*:

$$\neg : \Box \wedge \Box\neg \longrightarrow \neg\Box \vee \neg\Box\neg$$

The strong principle of abstraction: Out of two propositions, if one is not contradictory, then none of the logical relations between them is contradictory:

- What is not a non contradictory conjecture is a *paradox*:

$$\neg : \neg\Box \vee \neg\Box\neg \longrightarrow \Box \wedge \Box\neg.$$

- What is not a non contradictory result is a *postulate*:

$$\neg : \Box \vee \Box\neg \longrightarrow \neg\Box \wedge \neg\Box\neg.$$

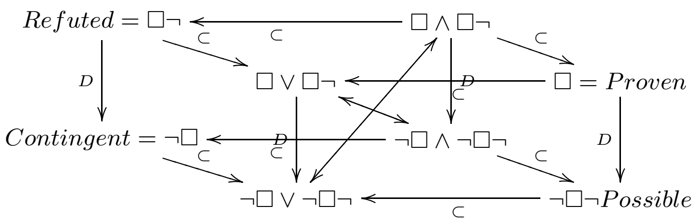

Fig. 3. Square of oppositions resulting from C1 logic, as a diagonal plane of the $Cube$

This cube of judgments expresses a set of modalities closed by negation that can judge any statement, object, or situation, formulated in the language upon which this logic is applied.

3 The Institution Agent social game

Section 2 presented the properties of a closed system producing judgments and taking into account contradiction. Such a system can be used to model the decision process of an agent holding incomplete knowledge, and we call such an agent an *”Institution Agent” (IA).*

Definition 2 (IA). *An IA is an agent using the $Cube$ to judge statements.*

We assume that the logic used during this decision process is the same for every IA, and we focus on the adaptation and the interaction of IAs sharing a vocabulary and trying to build a common language or frame of reference with this vocabulary.

Three logical properties are needed to qualify this interaction protocol and to add a logical control to the adaptation process:

- deontic: an IA must be able to attribute credits to another IA, to interact, and to teach another IA,
- defeasible: Lower IAs must be able to adapt their behavior to the norms imposed by the higher ones,
- autoepistemic: an IA can be seen as composed by at least two interacting IAs and can therefore learn its own hierarchy of norms and auto-adapt.

In this section, we suppose that each IA can be represented by a particular normative system resulting from its own experience and adaptation during an interaction with other IAs.

Definition 3. *We call a* ***Normative System (NS)*** *the couple* (L, $Cube$) *formed by:*

- *L: a language formed by a hierarchy of concepts and the relations between them*
- *$Cube$: a cube of judgments*

3.1 Deontic logic

Often used in multi-agent systems to constrain an agent’s behaviour, annotable deontic logic uses modalities expressing obligation, interdiction, advice, and warning. According to Frege’s definition, these statements express a judgment, ie. the recognition of the type of truth of the statement [7]. Imputations (gains or losses, risk estimation) are used to estimate the risk incurred in a given situation to decide what action to take or what behaviour to adopt. A modality and an imputation have to be used to express statements of the following form: ”The obligation to respect the speed limit is attached to a imputation of x”. A credit value can also be associated to IAs, ordering them hierarchically, to define which one is the most qualified to rule in a given context, for example by defining a social organisation as a government with a parliament, a senate, ...

Scientific discovery is a collective process, and needs interaction between researchers to exchange their points of view and judgments. That’s how IAs interact: by exchanging judgments about statements. More exactly, by asking another IA if it agrees with a particular judgment: ”this statement is a conjecture, is it not?”, to which the answer is ”yes” or ”no, it is a result”. Exchanging judgments creates the negation in the common

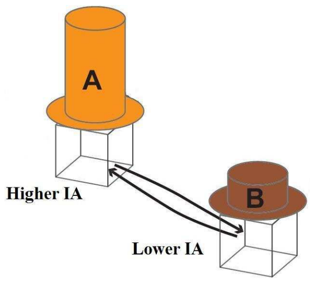

Fig. 4. IA's credit

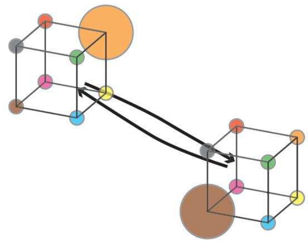

Fig. 5. Exchanging judgments

frame of reference (language), and the revision of the normative system associated with one IA or the other. Two judgments are especially important: *judging one's conjecture as being a paradox*, and *judging one's postulate as already being a result*. KEM^{TM}, presented in section 4.2, illustrates this control by a scientist over the IA assisting him.

3.2 Defeasible logic

It is possible to link two NS by respecting a defeasible logic to take into account a hierarchy of Institution Agents. The resulting hierarchy of IAs has to be brought together with the transitivity axiom, that stands as follows: "What is necessary in a normative system of proof and refutation is also necessary in a lower normative system". In other words, no one should be unaware of the law, no one should go against a superior law. [8] gives a concrete usage of defeasible logic, that allows us to order rules and to supervise an IA, for example with another higher IA, as illustrated on figure 6.

$$\begin{tikzcd}
O_1 = \Box_1 \arrow[d, "D"] & I_1 = \Box_1 \neg \arrow[d, "D"] & HigherIA \\
O_2 = \Box_2 \subset C_1 = \neg\Box_1\neg \arrow[ur] \arrow[d, "D"'] \arrow[dr, <->] & I_2 = \Box_2\neg \subset A_1 = \neg\Box_1 \arrow[ul] \arrow[d, "D"] \arrow[dl, <->, "\neg"] & \\
C_2 = \neg\Box_2\neg & A_2 = \neg\Box_2 & LowerIA
\end{tikzcd}$$

Fig. 6. Normative system hierarchy

- Every Obligation of a lower IA belongs to the superior IA's advice.
- Every Interdiction of a lower IA belongs to the superior IA's warnings.

The middle line shows the conditions according to which an IA can be supervised by another one. The violation of this constraint ($O_2 = \Box_2 \subset I_1 = \Box_1\neg$ or $I_2 = \Box_2\neg \subset O_1 = \Box_1$) can put forward contradictions between the two IA's normative system. We present in section 4 how IAs can learn and adapt their normative systems. Finding a contradiction, and trying to eliminate it, leads to the initiation of a transaction between the two IAs, during which they adapt their normative system. When no contradiction remains, a new IA can be created, formed by the association of the two precedent IAs, and this process ensures the tracability of all the events leading to an IA's creation.

3.3 Autoepistemic logic

Aristotle distinguishes endophasy as an inner dialog. This is a constructive manner to build an intelligent agent as the result of an auto-adaptation. The inner IAs can be interpreted as managing believes, desires or intentions (BDI), for example. By applying the dialectic and deontic interaction presented in section 3.1, an IA is able to acquire its own NS, which prepares an efficient learning, and even enable self learning from examples.

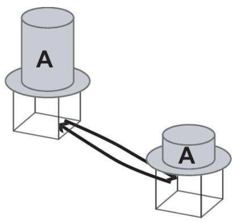

Fig. 7. Autoepistemic dialog

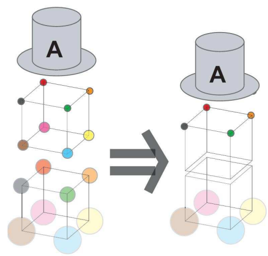

Fig. 8. IA formation

In this section, we presented how an interaction process and a hierarchical control can be used to build an agent able to adapt its defeasible deontic and autoepistemic Normative System.

4 Learnability

To estimate the complexity of an IA's creation, we embrace machine learning theories, and we discuss the learnability of a normative system by an Institution Agent. We illustrate various learning methods as decision trees or version spaces, then we show that this system is related to Angluin's theories on learning monotonous functions by querying, and learning from different teachers [9] [10] [11]. Finally, we present an industrial application dedicated to Drug Discovery.

4.1 Learning a scientific theory

Definition 4. *A* ***scientific theory*** *is an application :* $F : L \longrightarrow \Omega$ *such that* $(L, F(L))$ *is a normative system, associating to every statement* $x \in L$ *a scientific judgment* $F(x) \in \Omega$*.*

Definition 5. *We call T^{cube} the lattice obtained by "forgetting" the negation links coming from the weak and strong principles of abstraction (section 2.2). T^0 (figure 9 is the truth lattice underlying a classical logic. T^1 and T^2 (respectively in bold and italic characters on figure 10)are the lower and upper sub-lattices of T^{cube}.*

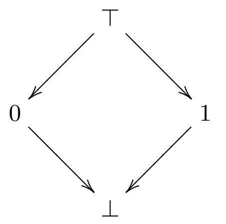

Fig. 9. T^0: the lattice underlying classic logic

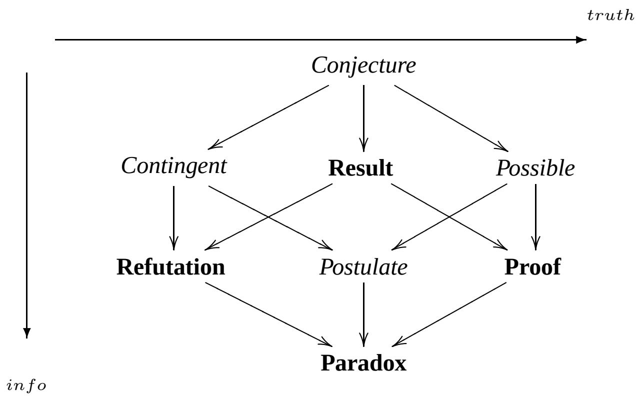

Fig. 10. T^{cube}: the lattice underlying the cube's logic

Definition 6. *A **scientific theory learned by an IA** is an application : $F_{IA} : L \longrightarrow T^{Cube}$ such that $(L, F_{IA}(L))$ is a normative system, associating to every statement $x \in L$ a scientific judgment $F_{IA}(x) \in T^{cube}$.*

Remark 1. If we assume that a *paradox* (bottom of the lattice) is more informative than a *conjecture* (top of the lattice) and that a *proof* (right) is more true than an *refutation* (left), this lattice can be oriented following a vertical axis representing the information level and an horizontal axis representing the truth level.

Remark 2. T^1 represents the modalities used by the teacher during Angluin's protocol [11]. The interactive process used in the following cases is an interaction using only membership queries. The furtherance of science can never be the result of an isolated scientist who cannot verify the interest of his theory. Reference theories of machine learning use as well Equivalence Queries EQs, which should compare two scientific theories $F_{I.A._1}$ and $F_{I.A._2}$. The protocol defined in section 3, depends on the use of EQs in which case putting forward a contradiction answered an EQ: an interaction between two hierarchicaly ordered IAs allows the confrontation of two non comparable theories through the confrontation of their hypotheses and conjectures on the one hand, with paradoxes and results on the other.

Property 2 *Since T^{cube} is a modular lattice, a scientific theory F_{IA} is learnable in a polynomial time using membership queries.*

The following cases show the generality of this approach.

Case 1 *Given a set L of boolean and real variables, a* ***scientific theory learned by a decision tree*** *is an application $F_{DT} : L \longrightarrow T^0$ such that $(L, F_{DT}(L))$ is a normative system.*

Case 2 *Given a set L of boolean variables, a* ***scientific theory learned by a version space*** *is an application $F_{VS} : L \longrightarrow T^1$ such that $(L, F_{VS}(L))$ is a normative system.*

Case 3 *Given a set L of boolean variables, a* ***scientific theory learned by a galois lattice*** *is an application : $F_{GL} : L \longrightarrow T^{Cube}$ such that $(L, F_{GL}(L))$ is a normative system.*

Case 4 *Given a set L of boolean and real variables, given a set of results coming from a decision tree method,* ***a scientific theory learned by*** *DT/GL is an application : $F_{DT/GL} : L \longrightarrow T^{0,2}$ such that $(L, F_{DT/GL}(L))$ is a normative system.*

All these cases of scientific theories are monotonous functions and are therefore learnable. However, only cases 3 and 4, which take into account dialectical aspects required to manage the norms and the ruptures in scientific discovery, are learnable by an IA. The following section develops the case 4.

4.2 Dialectic protocol and application in drug design

A real application of learning in scientific discovery, is from collaboration with Ariana Pharmaceuticals in Drug design [12].

KEM^{TM} can suggest specific molecular modifications to achieve multiple objectives, after analysing a multi-parametric database. Data mining is performed with an Institution Agent using DT/GL to learn. KEM^{TM} is an Institution Agent resulting from the interaction of an $IA_{DT/GL}$ and a expert scientist, who has in mind his own normative system. To teach KEM^{TM} how to learn his normative system, the expert scientist describes each example by way of a set of non paradoxical results. KEM^{TM} learns from these examples a scientific theory, and the scientist uses $(x, F_{DT/GL}(x))$ as a rational mirror of his own normative system. In a dialectic way, KEM^{TM} evolves and adapts to create a new IA from the learning process.

To assist the learning process, KEM^{TM} selects an hypothesis that is not a paradox and, more specifically, KEM^{TM} selects a conjecture within this hypothesis that is not a result. Then the scientist admits new examples to eliminate the conjecture as a result or modifies his own normative system to eliminate the hypothesis as a paradox. Such a method has been tried and succesfully tested in a legal context where the "learners" are humans, to build efficient normative systems [13] [14].

Designing novel therapeutic molecules is a challenging task since one needs not only to select an active molecule, the molecule needs also to be absorbed, needs to be stable within the body (i.e. not metabolized too rapidly) and finally it needs to have low toxicity and side effects. This is called improving the ADME-T profile (Absorption, Distribution, Metabolism, Excretion and Toxicity).

In this example we focus on the prediction of Absorption, a key issue in drug design since this is one of the important and early causes of failure in the drug discovery process. Indeed molecules need to be absorbed before they can perform any desired activity. Absorption is a complex process involving both passive (diffusion) and active (through transporter proteins) accross cellular membranes. For passive transport, molecules need to be soluble (hydrophilic) in water and at the same time they need to be greacy (hydrophobic) to penetrate cellular membranes that are formed of lipids. This contradicting requirement is modulated by active transport, where molecules need to be recognized (i.e. complementarity of shape and charge) by a another molecule (transporter) that helps them through membranes.

Although no one can for sure predict the absorption of a new molecule, a number of empirical rules are known. This is an interesting context for applying our IA since our key requirement is to capture knowledge from the experimental data and then evolve and improve this model in a consistent manner.

To illustrate our approach we focus on a set of 169 molecules for which the absorption in man has been experimentally evaluated (4 classes. 0 not absorbed, 3 highly absorbed). These molecules are described using a set of physico chemical properties such as molecular radius, different calculated measures of their total polar surface accessible to water (*TPSA* and *VSA POL*), their hydrophobicity (*SLOGP*), presence of halogens etc.

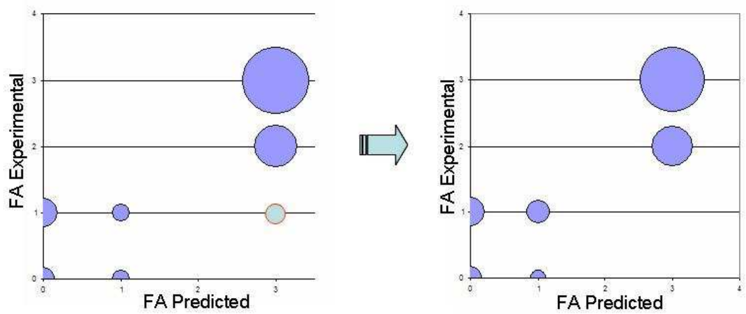

Fig. 11. Predictions A and B

Initially, the system learns from the dataset a set of rules linking the structure of the molecule to the absorption. The quality of the prediction is tested in a subsequent stage on a novel set of molecules. The results are shown on prediction A in figure 11. Ideally the predictions should be on the diagonal. An error of one class is tolerated. However, it is clear that for one molecule, the error is larger (ie experimental : class 1 vs predicted class 3).

Figure 12 shows that the molecule (Ranitidine) has been predicted with *fraction absorbed in man 3* i.e. highly absorbed. However, if the user forces *fraction absorbed in man 3* to be false, the system shows that this contradicts a learned rule *VSA pol 2* $\rightarrow$ *fraction absorbed in man 3*. At this stage the user realises that indeed this rule was true

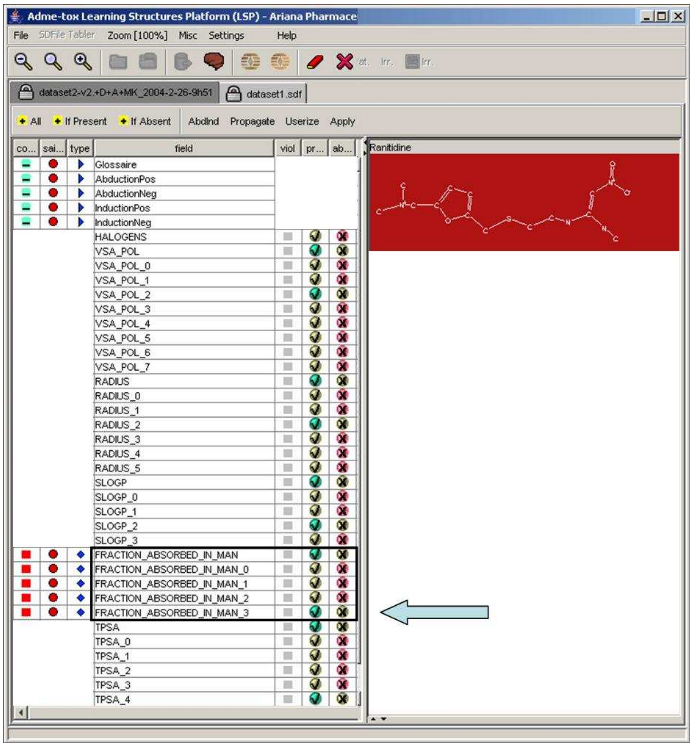

Fig. 12. KEM^{TM}

for the learning set, however this is not generally true and it can be eliminated. Once this rule has been eliminated, the user goes back to predicting once more the test set and results are shown in Figure 11, prediction B. As expected, the results have been improved. The important point is that the improvement has been done in a controlled way under the user's supervision.

In scientific discovery, there are in general no Oracles who can say a priori whether a prediction is correct or not. Experimentalists design a hypothesis that is consistent with existing empirical data and then set about to test it. We beleive that the key for a computational system is to adhere to the same process i.e. build up an explanation / reasons for suggesting for predicting an outcome. If the system is able to provide enough arguments, the user will "trust" it and try the experience.

KEM^{TM} is an Institution Agent resulting from a process combining both human and machine learning. It is very interesting to log the various adaptations of the learned normative system coming from the addition of examples or normative theories and to analyse process of the formation of such an IA. This method also give a compliance record of the various processes chosen or rejected in the formation of the resulting IA.

5 Conclusion

We propose a pragmatic logic to manage scientific judgment. This set of judgments is closed by negation when using paraconsistent logic C1. Using Institution Agents, we define a dialectic process to manage contradiction. This allows autoepistemic Institution Agents to learn from a supervised teaching process. This methodology is now tried and tested in various domains: in drug design, in Law[14], and even in mathematical games [15].

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