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Interactive Learning from Contradictions in a Paraconsistent Logic

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Abstract. In this paper, we describe a formal logical framework which we claim as essential to prove and to revise a model produced by combined ILP techniques. The dynamic process of proof embrace the supervision of the learning machine by a human, and this framework places the interpretation of contradictions in the heart of the interactive process which leads to a model which can be discussed, justified, and proven. We illustrate and validate this framework on an industrial application in the field of Drug Discovery, combining different learning processes to predict pharmaco-kinetic properties (ADME-T) and adverse side effects of therapeutic drug molecules.

1 Introduction

The pharmaceutical industry is confronted to a pressing need to analyse ever growing quantities of collected data and **convert** them into relevant decisions, using cheminformatics methods. Most often, reliable predictions are only possible on molecules very similar to the learning set, and these predictions use descriptions which are not easy to be translated in better molecular structures.

This domain concentrates many challenges for inductive learning : the bias problem, the underfitting/overfitting problem, the constraint satisfaction problem, the multiparametric decision problem, the empirical testing and the interactive problem solving by scientists assisted by machine learning.

As there are hundreds of descriptors used to describe the surface of the molecules and thousands related to the computation of properties for a single molecule, the risk of overfitting is permanent. When we try to limitate the number of descriptors to reduce this overfitting, we create a risk of falling in the

adverse case of underfitting. So the balance between completeness and consistency corresponds to the balance between underfitting and overfitting. As learned rules in drug design conjugates more than three terms, the constraint satisfaction problem presents a transition phase between the domain where deciding with learned rules is easy but produces errors, and the domain where finding rules to decide is so difficult that the system learns by heart and can only decide for molecules which are very similar to the examples used during learning. Finally the multiparametric decision required to deal with a distributed set of constraints that is not convex leads very often to an antagonism between optimised decisions. Furthermore the regularities learned from examples which use descriptors coming from different domains do not have a unified theoretical basis to justify them by causal arguments.

Our objective is to propose a logical framework to assist researchers in supervising the proof process of inductive theories produced by learning machines. This framework enables to describe with annotations all the actions occurring during an inductive process combining different machine learning approaches. Common sense actions such as proof, refutation, conjecture, experimentation, . . . , are logically defined by their interrelation as it has been done in the logical tradition for classical reasoning **Cite. The main difference** is that we reason on actions producing knowledge. This logical framework then has to qualify the proof of a learned model from an empirical point of view as well as from a formal and subjective one; indeed, to be trusted by scientists, a model has to be empirically proven. It is formally proven when it is not producing any contradictions, and it is finally subjectively proven after the scientists eliminated properly some conjectures and postulates formulated during the learning process.

Aristotle's square (**see section ??**) is a very old formal model which puts a negation relation between modalities in the heart of a reasoning process. This square describes a syllogistic inference which occurs in classical logical reasoning. However, the square of Aristotle is not compliant with an inductive practice in which postulates are added by the user to supervise and influence the learning process, **i.e. statements which** are neither proven, nor observed or refuted. This square can't be used neither to define or take into account the fact that learned rules are conjectures, **i.e. statements which** are observed but not proven.

We discuss more precisely the problems posed by Drug discovery to inductive learning in section ??, and we propose in section ?? a cubic structure combining three Aristotle's squares defining the modalities of proof, conjectures and postulates, which are essential to obtain a framework enabling reasoning in presence of incomplete and inconsistent knowledge. However, this model doesn't take into account the confrontation between theoretical results and experimental results. So we propose in section ?? a hypercubic structure combining five Aristotle's squares designed to reason on the empirical proof of a simulation using the model resulting from the learning process. This structure merges formal, empirical and subjective reasoning. Finally, we illustrate in section ?? how this framework is

applied to the supervision of a learning process combining different ILP methods to predict ADME-T properties.

2 The problem of Drug discovery, ADME-T

Schematically, the pharmaceutical activity can be divided into three sectors: drug discovery (ie going from a target to a molecule that is ready to be tested in man), drug development (ie. the proof of concept in man and the clinical trials) and finally the marketing and monitoring of the product.

It is widely accepted that out of a hundred of drug discovery projects that are started within the industry, less than one would eventually reach the market ten to fifteen years later.

Despite over a decade of massive investment by the pharmaceutical industry into high throughput methods (Genomics, High Throughput Screening and combinatorial chemistry), efficient identification and optimization of potent and quality lead molecules is still the highest and riskiest hurdle in current drug discovery and development. The only clear outcome of high throughput methods has been an unparalleled production of large quantities of data that need to be analyzed.

In order to reduce risks in the clinical stages of development, in a typical lead optimization process, 40 to 60 assays are run in parallel or in a cascade to evaluate the potential of each candidate molecule, its specificity, its good Absorption and Distribution, good Metabolism and Excretion profiles and limited Toxicity (ADME-T). In this multi-parametric space, identifying "quality" molecules which display desirable properties is a true challenge.

The use of computational tools (data mining, predictive modeling etc) has been seen as the potential solution to this dramatic inefficiency.

QSAR (quantitative structure activity relation) equations are standard examples in predictive modelling for drug discovery where an overall fitness score is developed as a weighted sum of numerous descriptors. In Docking, the score includes ligand internal energy, interaction energy and entropic considerations in the form of a weighted sum of terms [?]. Typically the score is developed empirically by analysing a set of examples and deriving a weighted sum. The weights are fitted to the learning set and may not necessarily be relevant or precise for other complexes.

QSAR attempts to relate a numerical description of a molecular structure to a known biological activity. Large numbers of readily computable descriptors are available, in combination to sophisticated techniques that improve the initial linear regression analysis methods used in deriving QSAR equations (PCA, PLS, NN, GA, SVM etc). In general, QSAR equations relate one objective (such as activity for example) with a number of descriptors. QSAR equations are constructed by the combination of a number of weighted terms (descriptors).

These methods rely on the choices of (1) the descriptors for generalisation and (2) the examples in the learning set to avoid overfitting.

An inadequate choice of either parameters will generally lead to useless models that do not generalise or are **not** interpretable. In addition, search strategies can be compromised when confronted to **non-convex solution fronts, i.e. when a solution “between” two valid solutions might be invalid.** Furthermore scale invariance is not always true, i.e. even for a continuous property such as molecular weight, its use and therefore significance is distinct for different ranges (for example 200-600 range correspond to small molecules, a molecular weight greater than 2000 does not). This is to say that some relations are sensitive to scale. More generally, qualities can be converted into quantities (binning) but the reverse is not always true. This leads us to the necessity of defining domains of validity for all parameters, in both the search and the objective spaces. In turn the notion of domain is linked to boundaries and hence allows characterisation of paradoxical combinations or conflicts. Here, conflicts are real mutual exclusions rather than a competition between several continuous parameters.

All in all, it is fair to say that the current state of the art in cheminformatics is insufficient: “In general, reliable predictions are only possible for molecules similar to those in the training set” [?] hence undermining their predictive use and “most models [...] use descriptors that are not easily understood by the chemist and not easy to translate into better molecular structures”, and hence have little impact in drug discovery.

In next section, we present the logical framework used in such a context to control the proof process of conjectures generated by learning from examples.

3 The cube of oppositions

In the two following sections we present a logical framework which defines with modalities the different actions occurring during the dynamic process of proof. **First of all, we shall provide some intuitive interpretations of these modalities:**

- α : the formula is observed / $\neg\alpha$: the formula is not observed;
- $\Box\alpha$: the formula is proven. A *proof* is a process which enables the verification of a computation’s exactitude, or of the pertinence of problem’s solution. To prove α is to establish with reasonings the truth of α / $\neg\Box\alpha$: the formula is not proven;
- $\neg\Box\neg\alpha \wedge \neg\alpha$: the formula is a postulate. A *postulate* is a primary principle, undemonstrable or undemonstrated / $\alpha \vee \Box\neg\alpha$: the formula is not a postulate;
- $\Box\neg\alpha$: the formula is rejected, refuted. A *refutation* is a process which enables to demonstrate the falsity of an affirmation by contrary proofs / $\neg\Box\neg\alpha$: the formula is not rejected;
- $\alpha \wedge \neg\Box\alpha$: the formula is a conjecture. A *conjecture* is a simple supposition founded on appearance or probabilities, a hypothesis which has not received any confirmation / $\Box\alpha \vee \neg\alpha$: the formula is not a conjecture.

- \sim A *simulation* is a method of study and measurement consisting in replacing a studied system by a simpler model which has an analogous behaviour. Here, this model is the result of the learning process.
- $\neg\sim$ is the contrary of a simulation and can be interpreted as an experimentation. An *experimentation* is an effective test realised to study a phenomenon.
- $\neg\Box \wedge \neg\sim \wedge \neg\Box\neg$ can be interpreted as an experimental *result*, resulting from an action, a fact.
- $\Box \vee \sim \vee \Box\neg$, can be interpreted as a theoretical *result*, resulting from a computation, or a principle.

Je pense qu'on devrait dcorer le carr avec preuve et rfutation pour donner des repaires. De plus, la partie sur les 3 hexagones arrive un peu brusquement. Moins maintenant que les dfinitions sont places en dbut de section, mais tout de mme, il faudrait montrer les modalits sur le carr avant de les voir apparaitre sur les hexagones.

So a proof is the result of a dynamic process of constant revision: a new proof is interesting when it proves some conjectures or eliminate surnumerous postulates, and is reciprocally suspected when it proves some conjecture that are reputed unsolvable or false. Logicians appreciate that solvers reason with consistent and complete theories, this is why theories which take inconsistency and incompleteness model them by believes, intentions, and defaults. However, during the interactive phases of learning, it is illusory to try being consistent and complete by considering that errors are the defaults of some known consistant and complete theories, which would lead to making a theory of the whole. As we already pointed out in the title, a discovery is triggered by the resolution of a contradiction, which is a statement at the same time true and false (**Ref paraconsistent logic?**). In our formalism, it is contradictory to prove a postulate so when a postulate is proven then either it has to be removed, either the proof is false.

To express this formalism, we need to define a closed set of modalities that can be used to define a problem solving with possibly incomplete knowledge. We justify the use of a paraconsistent logic by the necessity to put into question conjectures, postulates, and even proofs, by confronting them to experimental results. A proof is then the result of a dynamic paraconsistent process of generating and putting into question new conjectures and postulates to explain new experimental results which are contradictory whith the proof in its current state.

Je pense que l'on devrait prsenter expliquer les formes de raisonnement qui interviennent durant la construction des preuves, modalits, etc... cad l'abduction, d'infrence, et la dduction. Ces formes de raisonnements ne sont elles pas les actions (non dfinies) dont on parle au dbut de ce chapitre?

3.1 Aristotle's square

The doctrine of the square of opposition originated with Aristotle in the fourth century B.C. and has occurred in logic texts ever since. It relates various quantified propositions and their negations by introducing various notions of oppositions: contradiction, contrariety and sub-contrariety. Contradiction for two terms is defined as the impossibility for them to be both true or both false at the same time. Contrariety for two terms is the impossibility for them to be both true, but the possibility to be both false. Sub-contrariety is the impossibility to be both false, but the possibility to be both true. According to these definitions, opposition is based on various degrees of truth difference. A last useful notion is sub-alternation between two terms, also better known as implication, defined as the impossibility of having the first term true without having also the second true. The square of oppositions is represented by the following geometrical relations (figure ??).

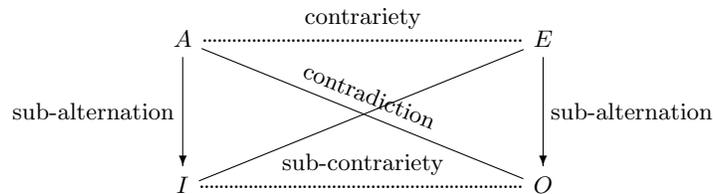


Fig. 1. Aristotle's square of oppositions

The column with A and I corresponds to affirmative propositions, while the column with E and O corresponds to negative propositions. The line with A and E corresponds to universal propositions, while the line with I and O corresponds to existential (also called particular) propositions. Several extensions have been proposed in order to palliate the logical drawbacks and develop the inference capabilities of the traditional Aristotelian square. Various modal decorations on the vertices can be found in [?]. The process which supplies evidence for the validity, or for the invalidity, of certain inferences and conversions (of a proposition into its negative) is based on this simple diagram (figure ??). Therefore the square of opposition appears as a geometrization of the inference process.

Now we introduce new modalities in order to reason in a paraconsistent and paracomplete way on the actions that occur during the dynamic construction of a proof. (i.e. **abduction, inference and deduction**)?

3.2 The cube of oppositions

In this section we define the modalities of proof, postulate and conjecture in order to reason on the pertinence of a model and on the completeness of its proof.

Working on the geometrical aspects of the so formed hexagon and its various modal decorations, [?] introduces these new modalities inside other hexagons: a paraconsistent one (in a paraconsistent logic there can exist a proposition which is true and the negation of which is true, without implying the triviality of the theory, i.e. the truth of any proposition), and a paracomplete one (in a paracomplete logic there can exist a proposition which is false and the negation of which is false, without implying triviality of the theory, i.e. the truth of any proposition).

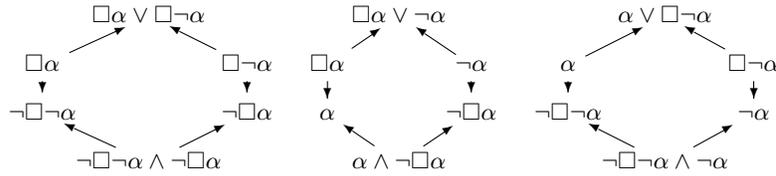


Fig. 2. The three hexagons from left to right: “classical”, “paraconsistent”, “paracomplete”.

Looking at the three hexagons [?], we have thus the most general sub-alternation relation between these various negative terms: $\Box\neg\alpha \longrightarrow \neg\alpha \longrightarrow \neg\Box\alpha$. This is no surprise, since these terms are known as expressing various kinds of negation in classical and modal proposition logics with the corresponding weakening relations: [?,?] show that $\Box\neg$ is an intuitionistic paracomplete negation, and [?] shows that $\neg\Box$ is a paraconsistent negation.

To define the modalities of conjecture and postulate, we need a richer opposition theory as the one provided by [?] and [?]. The geometrical constructions built upon this theory are various squares and hexagons among which are of course all previously discussed figures, and one logical cube, which we now focus on.

The logical cube (figure ??) is built from two distinct tetrahedra. The one of contrariety, which vertices are those from which the sub-alternation arrows start, **opposes** the proof \Box to the modalities that can be derived from its contrary $\Box\neg$, and the one of sub-contrariety which vertices are those to which the sub-alternation arrows lead, oppose the contradiction of a proof $\neg\Box$ to the modalities that can be derived from a proof. Any vertex of the cube is then contradictory to the furthest lying opposite vertex (easily obtained by central symmetry).

This logical cube is a three-dimensional generalization of the square of oppositions, and due to its construction, it contains three squares of oppositions, **visible on figure ??**, constituted by the necessity $\Box\alpha$, the impossibility $\Box\neg\alpha$ and two other cases of contingency, $\alpha \wedge \neg\Box\alpha$ and $\neg\Box\neg\alpha \wedge \neg\alpha$, which refine the case of pure contingency $\neg\Box\alpha \wedge \neg\Box\neg\alpha$ of Aristotle’s modal square, as introduced by [?].

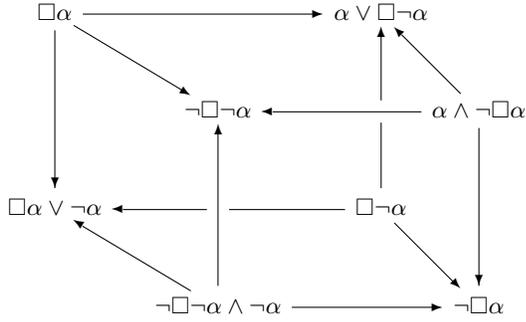


Fig. 3. The cube of oppositions

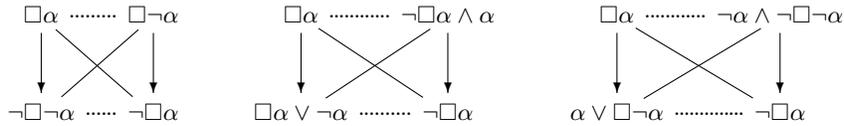


Fig. 4. from left to right: classical definition of proof towards refutation, paraconsistent definition of proof towards postulate, and paracomplete definition of proof towards conjecture

In this section, we formulated in an algebraic way a closed set of modalities to express the state of the proof of a **model, using knowledge based on observed facts and completed by conjectures and postulates**. In the following, we are concerned by the proof and refutation of a learned model, and therefore the confrontation between a simulation using this model built upon incomplete knowledge, and new knowledge coming from experimentations.

4 The Hypercube of oppositions

First of all, we identify such an approach in science philosophy. The role of contradictions in a dialectic process of discovery is well known in science philosophy. For Lakatos [?], there is always a detail level at which a statement as simple as $1+1=2$ can become arguable from a formal point of view. We introduce the use of postulates to fix some limits to what is arguable or not, and conjectures to restrain the objectives, to fix some limits to what is provable or not (for example, one could state that the conjecture $P = NP$ is not to be proved). **As Popper[?], we believe that every formal element has to be experimentally refutable by a scientific society, and that proof and refutation form the social accreditation process of a formalism. Finally, if as Bachelard, we look at truth as a corrected error, we consider an inductive pro-**

cess as resulting from the interpretation of contradictions between experimentations and theoretical results.

To take these considerations into account, we now introduce the modalities of experimental result, experimentation, simulation, and theoretical result by defining two opposition squares (only modalities are shown to simplify the diagrams), and we link them to the previous cube to build a hypercubic construction of higher-order geometrical figures of oppositions as suggested by [?] (figure ?? shows only a part of this hypercube for clarity reasons).



Fig. 5. the squares defining simulation and experimentation towards proof and refutation

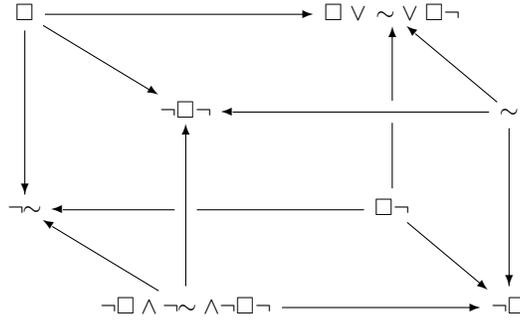


Fig. 6. One facet of the hypercube of oppositions

Both experimentation and simulation produce results, and it is the confrontation between them that puts forward an eventual contradiction between a phenomenon and the model used to simulate it, which leads to put into question proofs, conjectures, and postulates to localise the theoretical error. A first result of this methodology is to reveal the facets of the different learning techniques. On the front face, the adequacy of “experimental result” and “simulation” is related to the production of possible and contingent statements that are related with a subcontrariety relation. The corresponding learning method are version space or galois lattice techniques. The left face as the bottom face links respectively the “experimental results” to the “proof” or to the “refutation” of the model. The

three other faces are related to the analysis of the prediction. The back face is used to compare a prediction, i.e. a “theoretical result” given by a “simulation”, to an “experimentation” which concretise some “experimental results” (the fact that an object falls when it is released on earth is observable by experimenting it on a particular object in particular conditions).

In the following section we illustrate the different facetes of this supervision strategy of a learning process on an industrial application in Drug Discovery.

5 Application to the prediction of Absorption

A real application of learning in scientific discovery is from collaboration with Ariana Pharmaceuticals in Drug design [?]. KEM^{TM} can suggest specific molecular modifications to achieve multiple objectives, after analysing a multi-parametric database.

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.

To learn, KEM acts according the facet of the hypercube of oppositions visible on figure ??:

- 1)(left face) A decision tree is used to find a good segmentation of the numerical descriptors.
- 2)(front face) A Galois lattice method works on these binary descriptors in order to construct a lattice of regularities.
- 3)(upper-face) sup-irreductibles nodes are translated into logical constraints for prediction.
- 4)(backface) the prediction is confronted to the experimentation.
- 5)(right face) the study of the experimental error is done by a refutation of the simulation.

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

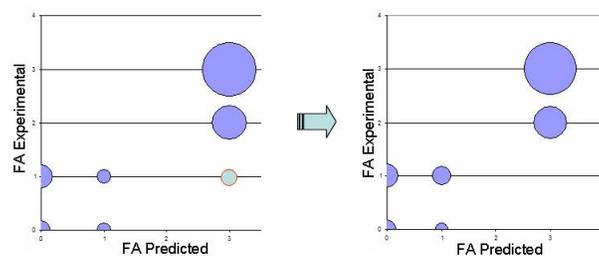


Fig. 7. Predictions A and B

A in figure ???. 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). This confrontation between a theoretical result and an experimental result puts forward a contradiction in the model.

The screenshot shows the Adme-tox Learning Structures Platform (LSP) interface. The main window displays a list of fields and their corresponding values. The fields are organized into categories: HALOGENS, VSA_POL, RADIUS, SLOGP, and FRACTION_ABSORBED_IN_MAN. The FRACTION_ABSORBED_IN_MAN field is highlighted with a red arrow. The chemical structure of Ranitidine is shown in the top right corner.

co...	sol...	type	field	viol	pr...	ab...
			Glossaire			
			AbductionPos			
			AbductionNeg			
			InductionPos			
			InductionNeg			
			HALOGENS			
			VSA_POL			
			VSA_POL_0			
			VSA_POL_1			
			VSA_POL_2			
			VSA_POL_3			
			VSA_POL_4			
			VSA_POL_5			
			VSA_POL_6			
			VSA_POL_7			
			RADIUS			
			RADIUS_0			
			RADIUS_1			
			RADIUS_2			
			RADIUS_3			
			RADIUS_4			
			RADIUS_5			
			SLOGP			
			SLOGP_0			
			SLOGP_1			
			SLOGP_2			
			SLOGP_3			
			FRACTION_ABSORBED_IN_MAN			
			FRACTION_ABSORBED_IN_MAN_0			
			FRACTION_ABSORBED_IN_MAN_1			
			FRACTION_ABSORBED_IN_MAN_2			
			FRACTION_ABSORBED_IN_MAN_3			
			TPSA			
			TPSA_0			
			TPSA_1			
			TPSA_2			
			TPSA_3			
			TPSA_4			

Fig. 8. KEMTM

Figure ?? shows this contradiction: the molecule (Ranitidine) has been predicted with *fraction absorbed in man 3* i.e. highly absorbed. However, if the user makes a postulate and forces *fraction absorbed in man 3* to be false, the system localise the error that induced the contradiction by showing that the postulate contradicts the conjectural learned rule $VSA\ pol\ 2 \rightarrow fraction\ absorbed\ in\ man\ 3$. At this stage the user realises that indeed this conjecture was true for the learning set, however this is not generally true and it can be eliminated. The user then goes back to simulating once more the test and results are shown in Figure ??, 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, and this was only possible because the user and KEMTM shared a common vocabulary to type statements.

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

6 Conclusion

We emphasised the fact that annotations are very often used by scientists to exchange points of view and communicate. We believe these annotations represent the key to a useful interaction between a learning machine and a user supervising it. We identified a closed set of modalities to represent these annotations for which we provided a logical definition. We illustrated on an example coming from Drug Discovery how these annotations of common sense, which are now logically defined, are used by a learning machine and a scientist to interactively build a model that is coherent and complete with observations and experimental results. We prone that this hypercube describes in a universal way a rational agent and enables the supervision of its computing process.

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