Automated Reasoning in Metabolic Networks with Inhibition

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Abstract. The use of artificial intelligence to represent and reason about metabolic networks has been widely investigated due to the complexity of their imbrication. Its main goal is to determine the catalytic role of genomes and their interference in the process. This paper presents a logical model for metabolic pathways capable of describing both positive and negative reactions (activations and inhibitions) based on a fragment of first order logic. We also present a translation procedure that aims to transform first order formulas into quantifier free formulas, creating an efficient automated deduction method allowing us to predict results by deduction and infer reactions and proteins states by abductive reasoning.

Keywords: Metabolic pathways, logical model, inhibition, automated reasoning.

1 Introduction

Cells in general and human body cells in particular incorporate a large series of intracellular and extracellular signalings, notably protein activations and inhibitions, that specify how they should carry out their functions. Networks formed by such biochemical reactions, often referred as *pathways*, are at the center of a cell's existence and they range from simple and chain reactions and counter reactions to simple and multiple regulations and auto regulations, that can be formed by actions defined in Figure 1. Cancer, for example, can appear as a result of a pathology in the cell's pathway, thus, the study of signalization events appears to be an important factor in biological, pharmaceutical and medical researches [14,11,7]. However, the complexity of the imbrication of such processes makes the use of a physical model as a representation seem complicated.

In the last couple of decades, scientists that used artificial intelligence to model cell pathways [10,9,16,17,6,21,15] faced many problems especially because information about biological networks contained in knowledge bases is generally incomplete and sometimes uncertain and contradictory. To deal with such issues, abduction [3] as theory completion [12] is used to revise the state of existing nodes and add new nodes and arcs to express new observations. Languages that were used to model such networks had usually limited expressivity, were specific

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to special pathways or were limited to general basic functionalities. We, in this work, present a fragment of first order logic [19] capable of representing node states and actions in term of positive and negative relation between said nodes. Then an efficient proof theory for these fragments is proposed. This method can be extended to define an abduction procedure which has been implemented in SOLAR [13], an automated deduction system for consequence finding.

For queries about the graph that contains negative actions, it is assumed that we have a complete representation of the graph. The consequence is that the negation is evaluated according to its definition in classical logic instead of some non-monotonic logic. This approach guarantees a clear meaning of answers. Since the completion of the graph is formalized a la Reiter we used the equality predicate. It is well known that equality leads to very expensive automated deductions. This problem has been resolved by replacing completed predicates by their extensions where these predicates are used to restrict the domain of quantified variables. The result of this translation is formulated without variables where consequences can be derived very fast. This is one of the main contributions of this paper.

The rest of this paper is organized as follows. Section 2 presents a basic language and proof theory capable of describing general pathways, and shows their possible extensions to address specific and real life examples. Section 3 defines a translation procedure capable of eliminating first order variables and equality predicates and shows how it can be applied to derive new axiomatic that can be used in the automated deduction process in SOLAR. Section 4 provide some case studies, and finally section 5 gives a summary and discusses future works.

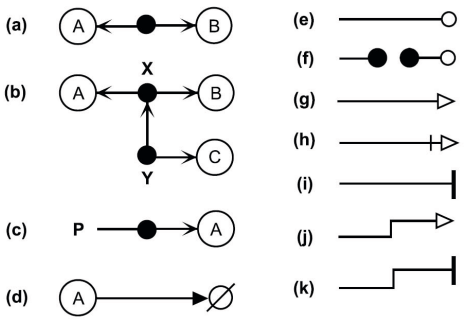

Fig. 1. Symbol definitions and map conventions

(*a*) Proteins A and B can bind to each other. The node placed on the line represents the A:B complex. (*b*) Multimolecular complexes: x is A:B and y is(A:B):C. (*c*) Covalent modification of protein A. (*d*) Degradation of protein A. (*e*) Enzymatic stimulation of a reaction. (*f*) Enzymatic stimulation in transcription. (*g*) General symbol for stimulation. (*h*) A bar behind the arrowhead signifies necessity. (*i*) General symbol for inhibition. (*j*) Shorthand symbol for transcriptional activation. (*k*) Shorthand symbol for transcriptional inhibition.

2 Logical Model

In this section we will present a basic language capable of modeling some basic positive and negative interaction between two or more proteins in some pathway. We will first focus on the stimulation and inhibition actions, points (g) and (i) of Figure 1, and then show how this language can be modified to express the different other actions described in the same figure.

2.1 Formal Language

Let's consider a fragment of first order logic with some basic predicates, boolean connectives $(\wedge)$ and, $(\vee)$ or, $(\neg)$ negation, $(\rightarrow)$ implication, $(\leftrightarrow)$ equivalence, $(\exists)$ existential and $(\forall)$ universal quantifiers, and $(=)$ equality.

The basic state predicates are:

- $A(x)$: with intended meaning that the protein x is *Active*.
- $I(x)$: with intended meaning that the protein x is *Inhibited*.

Having the basic state axiom $\forall x \neg(A(x) \wedge I(x))$ which indicates that a certain protein x can never be in both *Active* and *Inhibited* states at the same time.

An interaction between two or more different proteins is expressed by a predicate of the form $Action(protein_1, ..., protein_n)$. In our case we are interested by the simple *Activation* and *Inhibition* actions that are defined by the following predicates:

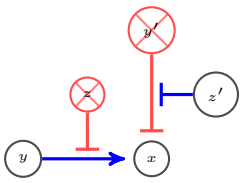

Fig. 2. Activation

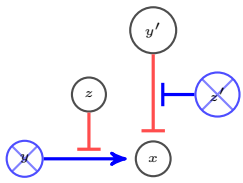

Fig. 3. Inhibition

- $CAP(y, x)$: CAP or the *Capacity of Activation* expresses that the protein y has the capacity to activate the protein x.
- $CICAP(z, y, x)$: $CICAP$ or the *Capacity to Inhibit the Capacity of Activation* expresses that the protein z has the capacity to inhibit the capacity of the activation of x by y.
- $CIP(y', x)$: CIP or the *Capacity to Inhibit a Protein* expresses that the protein y' has the capacity to inhibit the protein x.
- $CICIP(z', y', x)$: $CICIP$ or the *Capacity to Inhibit the Capacity of Inhibition of a Protein* expresses that the protein z' has the capacity to inhibit the capacity of inhibition of x by y'.

In the next section we will define the needed axioms that will be used to model the *Activation* and *Inhibition* actions.

2.2 Action Axioms

Given the fact that a node can acquire the state active or inhibited depending on different followed pathways, one of the issues answered by abduction is to know which set of proteins is required to be active of inhibited for our target protein be active or inhibited.

Axiomatic of Activation is of the following form:

$$\begin{array}{l}\forall x(\exists y(A(y) \wedge CAP(y,x) \wedge \forall z(CICAP(z,y,x) \rightarrow \neg A(z))) \wedge \\ \quad \forall y'(CIP(y',x) \rightarrow (\neg A(y') \vee \exists z'(CICIP(z',y',x) \wedge A(z')))) \rightarrow A(x)) \ .\end{array} \tag{1}$$

A protein x is active if there exists at least one *active* protein y that has the capacity to activate x, $CAP(y,x)$, **and** for every protein z that has the capacity to inhibit the capacity of activation of x by y, $CICAP(z,y,x)$, z is *not active*. **And** for every protein y' that has the capacity to inhibit x, $CIP(y',x)$, y' is *not active*, **or** there exist at least one *active* protein z' that has the capacity to inhibit the capacity of inhibition of x by y', $CICIP(z',y',x)$. (Figure 2)

Axiomatic of Inhibition is of the following form:

$$\begin{array}{l}\forall x(\exists y'(A(y') \wedge CIP(y',x) \wedge \forall z'(CICIP(z',y',x) \rightarrow \neg A(z'))) \wedge \\ \quad \forall y(CAP(y,x) \rightarrow (\neg A(y) \vee \exists z(CICAP(z,y,x) \wedge A(z)))) \rightarrow I(x)) \ .\end{array} \tag{2}$$

A protein x is inhibited if there exists at least one *active* protein y' that has the capacity to inhibit x, $CIP(y',x)$, **and** for every protein z' that has the capacity to inhibit the capacity of inhibition of x by y', $CICIP(z',y',x)$, z' is *not active*. **And** for every protein y that has the capacity to activate x, $CAP(y,x)$, y is *not active*, **or** there exist at least one *active* protein z that has the capacity to inhibit the capacity of activation of x by y, $CICAP(z,y,x)$. (Figure 3)

2.3 Extension with New States and Actions

The basic language defined in 2.1 and 2.2 can be easily extended to express different and more precise node statuses and actions. For example the action of phosphorylation can be defined by the following predicates:

- $CP(z,y,x)$: CP or the *Capacity of Phosphorylation* expresses that the protein z has the capacity to phosphorylate the protein y on a certain site, knowing that x is the result of said phosphorylation.
- $CICP(t,z,y,x)$: $CICP$ or the *Capacity to Inhibit the Capacity of Phosphorylation* expresses that the protein t has the capacity to inhibit the capacity of the phosphorylation of y by z leading to x.

We can now define the new phosphorylation axiom as:

$$\begin{array}{l}\forall x(\exists y1, y2(A(y1) \wedge A(y2) \wedge CP(y1,y2,x) \wedge \forall z(CICP(z,y1,y2,x) \rightarrow \neg A(z))) \wedge \\ \quad \forall y'(CIP(y',x) \rightarrow (\neg A(y') \vee \exists z'(CICIP(z',y',x) \wedge A(z')))) \rightarrow A(x)) \ .\end{array}$$

Auto − phosphorylation, *Dephosphorylation*, *Binding*, *Dissociation* etc. actions and some of the newly discovered ones such as *Methylation* and *Ubiquitination* [7] can formalized in a similar fashion.

3 Automated Deduction Method

In this section we define a fragment of first order logic with constants and equality, and without functions. The properties of this fragment allow us to define a procedure capable of eliminating the quantifiers in this fragment, in other words to transform the first order formulas in formulas without variables, in order to obtain an efficient automated deduction procedure with these fragments.

In the following we define a special case of *Evaluable* formulas [4] and *Domain Independent* formulas [22] called *Restricted* formulas, which are also different from *Guarded* formulas [1].

Definition 1. *Restricted formulas are formulas without free variables defined by the following grammar:*

$$\varphi ::= \forall \overline{x}(P(\overline{x},\overline{c}) \rightarrow \varphi) | \exists \overline{x}(P(\overline{x},\overline{c}) \wedge \varphi) | \psi \ . \tag{3}$$

Where $\overline{x}$ and $\overline{c}$ represent $x_1, ..., x_n$ and $c_1, ..., c_m$ respectively, and ψ is a quantifier free formula (i.e. ψ can only appear in the scope of a restricted formula). In the following the atomic formula $P(\overline{x},\overline{c})$ will be referenced as a *Domain* formula.

Examples of this kind of formulas are:
$\forall x(P(x) \rightarrow Q(x))$.
$\forall x(P(x) \rightarrow \exists y(Q(y) \wedge R(x,y)))$.

Definition 2. *A completion formula is a formula of the following form:*

$$\begin{aligned} \forall x_1, ..., x_n \ (P(x_1, ..., x_n, c_1, ..., c_p) \leftrightarrow ((x_1 = a_{1_1} \wedge ... \wedge x_n = a_{1_n}) \vee ... \vee \\ (x_1 = a_{m_1} \wedge ... \wedge x_n = a_{m_n}))) \ . \end{aligned} \tag{4}$$

Where P is a predicate symbol of arity $n + p$, and a_i are constants.

Completion formulas are similar to the completion axioms defined by Reiter in [18] where the implication is substituted by an equivalence.

Definition 3. *Given a restricted formula φ and a set of completion for the predicates in φ noted $C(\varphi)$, we say that $C(\varphi)$ saturates φ, if and only if, for each domain formula in φ, there is a unique completion formula in C.*

Definition 4. *Given a domain formula φ, we define the domain of the variables of φ, denoted $D(\mathcal{V}(\varphi), C(\varphi))$, as follows:*

if φ is of the form $P(x_1, ..., x_n, c_1, ..., c_p)$, and $C(\varphi)$ of the form:

$$\forall x_1, ..., x_m(P(x_1, ..., x_m, c_1, ..., c_l) \leftrightarrow((x_1 = a_{1_1} \wedge ... \wedge x_m = a_{1_m}) \vee ... \vee (x_1 = a_{q_1} \wedge ... \wedge x_m = a_{q_m}))) \ .$$

where $n \leq m$ and $l \leq p$.

$$\text{then } D(\mathcal{V}(\varphi), C(\varphi)) = \{< a_{1_1}, ..., a_{1_n} >, ..., < a_{q_1}, ..., a_{q_n} >\} \ . \tag{5}$$

Quantification Elimination Procedure
Let φ be a restricted formula of the following forms: $\forall \overline{x}(\varphi_1(\overline{x}) \rightarrow \varphi_2(\overline{x}))$ or $\exists \overline{x}(\varphi_1(\overline{x}) \wedge \varphi_2(\overline{x}))$, let $C(\varphi_1(\overline{x}))$ a set of completion formulas for φ_1, then we define recursively a translation $T(\varphi, C(\varphi))$, allowing to replace universal (existential) quantifiers by conjunction (disjunction) of formulas where quantified variables are substituted by constants as follows:

– if $D(\mathcal{V}(\varphi_1), C(\varphi_1)) = \{< \overline{c_1} >, ..., < \overline{c_n} >\}$ with $n > 0$:

$$T(\forall \overline{x}(\varphi_1(\overline{x}) \rightarrow \varphi_2(\overline{x})), C(\varphi)) = T(\varphi_2(\overline{c_1}), C(\varphi_2(\overline{c_1}))) \wedge ... \wedge T(\varphi_2(\overline{c_n}), C(\varphi_2(\overline{c_n}))) \ . \tag{6}$$

$$T(\exists \overline{x}(\varphi_1(\overline{x}) \wedge \varphi_2(\overline{x})), C(\varphi)) = T(\varphi_2(\overline{c_1}), C(\varphi_2(\overline{c_1}))) \vee ... \vee T(\varphi_2(\overline{c_n}), C(\varphi_2(\overline{c_n}))) \ . \tag{7}$$

– if $D(\mathcal{V}(\varphi_1), C(\varphi_1)) = \varnothing$:

$$T(\forall \overline{x} \ (\varphi_1(\overline{x}) \rightarrow \varphi_2(\overline{x})) \ , \ C(\varphi)) = True \ . \tag{8}$$

$$T(\exists \overline{x} \ (\varphi_1(\overline{x}) \wedge \varphi_2(\overline{x})) \ , \ C(\varphi)) = False \ . \tag{9}$$

Note 1. It is worth nothing that in this translation process each quantified formula is replaced in the sub formulas by constants. The consequence is that if a sub formula of a restricted formula is of the form $\forall \overline{x}(\varphi_1(\overline{x}) \rightarrow \varphi_2(\overline{x}, \overline{y}))$ or $\exists \overline{x}(\varphi_1(\overline{x}) \wedge \varphi_2(\overline{x}, \overline{y}))$ where the quantifiers $\forall \overline{x}$ or $\exists \overline{x}$ are substituted by their domain values, the variables in $\overline{y}$ must have been already substituted by its corresponding constants.

Then in the theory $\mathcal{T}$ in which we have the axioms of equality and axioms of the form $\neg(a = b)$ for each constant a and b representing different objects, which are called unique name axioms by Reiter in [18], we have the following main theorem and its corresponding lemmas:

Lemma 1. *Let F be a restricted formula of the form $F : \exists \overline{x}(\varphi(\overline{x}) \wedge \psi(\overline{x}))$ where ψ is a domain formula. There exists a translation $T(F, C(\varphi))$ for any saturated completion set $C(\varphi)$ where $D(\mathcal{V}(\varphi), C(\varphi)) \neq \varnothing$.*

Proof. The proof is constructed by induction on the number of instances of $\mathcal{V}(\varphi)$ contained in $D(\mathcal{V}(\varphi), C(\varphi))$.

Lemma 2. *Let G be a restricted formula of the form $G : \forall\overline{x}(\varphi(\overline{x}) \rightarrow \psi(\overline{x}))$ where ψ is a domain formula. There exists a translation $T(F, C(\varphi))$ for any saturated completion set $C(\varphi)$ where $D(\mathcal{V}(\varphi), C(\varphi)) \neq \varnothing$.*

Proof. The proof is constructed by induction on the number of instances of $\mathcal{V}(\varphi)$ contained in $D(\mathcal{V}(\varphi), C(\varphi))$.

Theorem 1. *Let φ be a restricted formula, and $C(\varphi)$ a completion set of formulas of the domain formulas of φ, then:*

$$\mathcal{T},\ C(\varphi) \vdash \varphi \leftrightarrow T(\varphi, C(\varphi))\ . \tag{10}$$

Proof. The proof consists of applying induction on the number of domain formulas in a restricted formula using Lemmas 1 and 2 to prove that the theorem holds for any number domain formulas.

We will now present an example of translation from first order logic formulas composed of action and state axioms to variable free formulas:

Example 1.

Let's consider the case where a protein b has the capacity to activate another protein a, and that two other proteins c_1 and c_2 have the capacity to inhibit the capacity of activation of a by b. This proposition can be expressed by the following completion axioms:

- $\forall y(CAP(y, a) \leftrightarrow y = b)$: Expresses that b is the only protein that has the capacity to activate a.
- $\forall z(CICAP(z, b, a) \leftrightarrow z = c_1 \vee z = c_2)$: Expresses that c_1 and c_2 are the only proteins that have the capacity to inhibit the capacity of activation of a by b.

Using the activation axiom defined in section 2 and the translation procedure, we can deduce:

$$\begin{aligned} &A(b) \wedge \neg A(c_1) \wedge \neg A(c_2) \wedge \\ &\forall y'(CIP(y', x) \rightarrow (\neg A(y') \vee \exists z'(CICIP(z', y', x) \wedge A(z')))) \rightarrow A(a)\ . \end{aligned} \tag{11}$$

Let's also consider that a protein d has the capacity to inhibit the protein a and that there is no proteins capable of inhibiting the capacity of inhibition of a by d. This proposition can be expressed by the following completion axioms:

- $\forall y(CIP(y, a) \leftrightarrow y = d)$: Expresses that d is the only protein that has the capacity to inhibit a.
- $\forall z(CICIP(z, d, a) \leftrightarrow false)$: Expresses that there are no proteins capable of inhibiting the capacity of inhibition of a by d.

Using the previous activation axiom and these completion axioms we can deduce:

$$A(b) \wedge \neg A(c_1) \wedge \neg A(c_2) \wedge \neg A(d) \rightarrow A(a) \ . \tag{12}$$

Which means that the protein a is active if the protein b is active and the proteins c_1, c_2, d are not active.

4 Queries and Results

From what we defined in sections 2 and 3, the resulting translated axioms are of the following type *conditions* $\rightarrow$ *results*, and can be chained together to create a series of reactions forming our pathway. Then questions of two different types can be answered using *deduction* or *abduction* reasoning.

Questions answered by deduction request all entities that satisfy a given property. A question can be of the following form: *what is the state (active or inhibited) of the proteins that result from the reactions formed by proteins in some knowledge base.*

And questions answered by abduction looks for minimal assumptions that must be added to the knowledge base to derive that a certain fact is true. A question can be of the following form: *what are the proteins and their respective states (active or inhibited) that should be present in order to derive that a certain protein is active or inhibited.*

Both types of questions can be addressed in SOLAR (SOL for Advanced Reasoning) [13] a first-order clausal consequence finding system based on SOL (Skip Ordered Linear) tableau calculus [8,20].

In the following we are going to show an example, based on figure 4, demonstrating abduction type queries where three coherent pathways have been found [11]

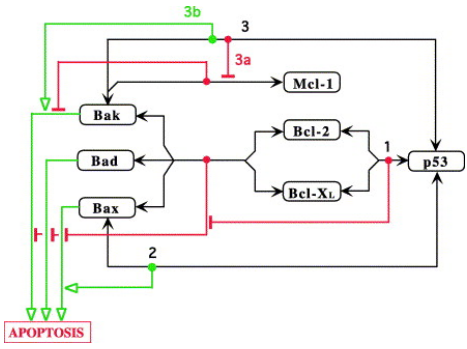

Fig. 4. Mitochondrial apoptosis induced by p53 independently of transcription

Following section 2.3 we can define new predicates to suit the needs of the pathway, as the *Capacity of Binding* $CB(z, y, x)$ and the *Capacity to Inhibit the Capacity of Binding* $CICB(t, z, y, x)$. These new predicates can be used to model the binding between p53 and Bak using the predicate $CP(p53, bak, p53\_bak)$ where p53_bak is the complex formed by such binding.

With these new predicates, new axioms can be defined that would enrich the descriptive capacities of the old ones, as seen in 2.3. Then the translation procedure applied to these axioms and to the completion axioms can be of the following form:

1. $A(p53) \wedge A(bak) \rightarrow A(bak\_p53)$
   bak_p53 is the result of the binding between p53 and Bak.
2. $A(bak\_p53) \rightarrow I(bak\_mcl)$
   bak_mcl is the result of binding between Bak and Mcl-1.
3. $A(bak\_p53) \wedge \neg A(b\_complex) \wedge \neg A(bak\_mcl) \rightarrow A(apoptosis)$
   $b\_complex$ is result of the binding between Bcl-2, Bcl-XL, Bak, Bad, and Bax.
4. $A(bak) \wedge \neg A(b\_complex) \wedge \neg A(bak\_mcl) \rightarrow A(apoptosis)$
5. $A(p53) \wedge A(bcl) \rightarrow A(p53\_bb\_complex)$
   bcl represents Bcl-2 and Bcl-XL.
   $p53\_bb\_complex$ is the result of binding between p53, Bcl-2 and Bcl-XL.
6. $A(p53\_bb\_complex) \rightarrow I(b\_complex)$
7. $A(bax) \wedge \neg A(b\_complex) \rightarrow A(apoptosis)$
8. $A(p53) \wedge A(bax) \wedge \neg A(b\_complex) \rightarrow A(apoptosis)$
9. $A(bad) \wedge \neg A(b\_complex) \rightarrow A(apoptosis)$

If we want to know what are the proteins and their respective states that should be present in order to derive that the cell reached apoptosis, the answer is given by applying abduction over the previous set of compiled clauses. In the set of consequences returned by SOLAR we can find the following:

- $A(p53) \wedge A(bcl) \wedge A(bak)$: is a plausible answer, because p53 can bind to Bcl giving the $p53\_bb\_complex$, which can in return inhibit the $b\_complex$ that is responsible of inhibiting the capacity of Bak to activate the cell's apoptosis. That is why it is sufficient to for this case to have p53, Bcl, and Bak in an active state to reach apoptosis.
- Another interpretation of the previous answer is that p53 can also bind to Bak giving the bak_p53 protein, which can in return inhibit the bak_mcl responsible of inhibiting the capacity of Bak to activate the cell's apoptosis. bak_p53 can also stimulate Bak to reach apoptosis. Without forgetting that $p53\_bb\_complex$ should be inhibiting $b\_complex$.

5 Conclusion

A new language has been defined in this paper capable of modeling both positive and negative causal effects between proteins in a metabolic pathway. We showed

how this basic language can be extended to include more specific actions that describes different relations between proteins. These extensions are important in this context, because there is always the possibility that new types of actions are discovered through biological experiments. We later showed how the axioms defined in such languages can be compiled against background knowledge, in order to form a new quantifier free axioms that could be used in either deduction or abduction reasoning. Although the first order axioms can be also well used to answer queries by deduction or abduction methods, the main advantage of translated axioms is their low computation time needed in order to derive consequences.

Future works can focus on extending the language used to define domain formulas, introducing for example the notion of time as in [2]. Trying to get as precise as possible in describing such pathways can help biologists discover contradictory informations and guide them during experiments knowing how huge the cells metabolic networks have become. One of the extensions that can also be introduced is the notion of *Aboutness* [5] that can limit and focus search results to what seems relevant to a single or a group of entities (proteins).

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