A Logical Framework for Systems Biology

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Abstract

We propose a novel approach for the formal verification of biological systems based on the use of a modal linear logic. We show how such a logic can be used, with worlds as instants of time, as an unified framework to encode both biological systems and temporal properties of their dynamic behaviour. To illustrate our methodology, we consider a model of the P53/Mdm2 DNA-damage repair mechanism. We prove several properties that are important for such a model to satisfy and serve to illustrate the promise of our approach. We formalize the proofs of these properties in the Coq Proof Assistant, with the help of a Lambda Prolog prover for partial automation of the proofs.

1 Introduction

In this paper, we consider the question of reasoning about biological systems in a modal linear logic. We show that a new logic, called Hybrid Linear Logic (HyLL) developed by the second author in joint work with K. Chaudhuri [CD13, DC14], is particularly well-suited to this purpose. HyLL provides a unified framework to encode biological systems, to express temporal properties of their dynamic behaviour, and to prove these properties. By constructing proofs in the HyLL logic, we directly witness reachability as logical entailment. This approach is in contrast to most current approaches to applying formal methods to systems biology, which generally encode biological systems either in a dedicated programming language or in differential equations, express properties in a temporal logic, and then verify these properties against some form of traces built using an external simulator. In the next subsection, we review in some detail the state of the art of such approaches, in order to further situate and motivate our new approach. In subsection 1.2, we motivate our choice of linear logic in general and HyLL in particular. Then in subsection 1.3, we further outline our contributions as well as the overall organization of the rest of the paper.

1.1 Formal Methods for Systems Biology

Computational systems biology provides a variety of methods for understanding the structure of biological systems and for studying their dynamics, that is, the temporal evolution of the involved entities. According to the chosen abstraction level, several formalisms have been proposed in the literature to model biological networks (e.g., gene regulatory networks, metabolic networks, or signal transduction networks).

To capture the qualitative nature of dynamics, Thomas introduced a Boolean approach for regulatory networks (an entity is present or absent) [Tho73] and subsequently generalized it to multivalued levels of concentration [TTK95]. Contrary to Petri nets, which are based on synchronous updating techniques [RML93], Thomas' discrete models are asynchronous. Other purely qualitative approaches are π-calculus [RSS01], bio-ambients [RPS$^+$04], and reaction rules [DL04, CRCD$^+$04].

To describe the dynamics from a quantitative point of view, ordinary or stochastic differential equations are heavily used. More recent approaches include hybrid Petri nets [HT98] and automata [ABI+01], stochastic π-calculus [PC05], and rule-based languages with continuous/stochastic dynamics such as Kappa [DL04], Biocham [FS08], or BioNetGen [BFGH04].

The Biochemical Abstract Machine Biocham [FSCR04] is a framework that allows the description of a biochemical system in terms of reaction rules and the interpretion of it at different levels of abstraction, by either an asynchronous Boolean transition system (Boolean semantics), a continuous time Markov chain (stochastic semantics), or a system of ordinary differential equations over molecular concentrations (differential semantics). In this paper, taking inspiration from Biocham reaction rules to model regulatory networks, we formalize the Biocham language (in the boolean case) in logic.

One of the most common approaches to the formal verification of biological systems is model checking [CGP99]. Model checking allows one to verify desirable properties of a system by an exhaustive enumeration of all the states reachable by the system. In order to apply such a technique, the biological system should be encoded as a finite transition system and relevant system properties should be specified using propositional temporal logic. Formally, a transition system over a set AP of atomic propositions is a tuple $M = (Q, T, L)$, where Q is a finite set of states, $T \subseteq Q \times Q$ is a total transition relation (that is, for every state $q \in Q$ there is a state $q' \in Q$ such that $T(q, q')$), and $L : Q \to 2^{AP}$ is a labeling function that maps every state into the set of atomic propositions that hold at that state.

Temporal logics are formalisms for describing sequences of transitions between states [Eme95]. The computation tree logic CTL* allows one to describe properties of computation trees. Its formulas are obtained by (repeatedly) applying Boolean connectives, *path quantifiers*, and *state quantifiers* to atomic formulas. The path quantifier A (resp., E) can be used to state that all paths (resp., some path) starting from a given state have some property. The state quantifiers are the next time operator X, which can be used to impose that a property holds at the next state of a path, the operator F (sometimes in the future), that requires that a property holds at some state on the path, the operator G (always in the future), that specifies that a property is true at every state on the path, and the until binary operator U, which holds if there is a state on the path where the second of its argument properties holds and, at every preceding state on the path, the first of its two argument properties holds. The branching time logic CTL is a fragment of CTL* that allows quantification over the paths starting from a given state. Unlike CTL*, it constrains every state quantifier to be immediately preceded by a path quantifier. The linear time logic LTL is another known fragment of CTL* where one may only describe events along a single computation path. Its formulas are of the form $\mathsf{A}\varphi$, where φ does not contain path quantifiers, but it allows the nesting of state quantifiers. The Probabilistic Computation Tree Logic PCTL quantifies the different paths by replacing the E and A modalities of CTL by probabilities.

In Biocham [FS08], CTL, LTL, and a fragment of PCTL with numerical constraints are used in the three semantics of reaction models, respectively, in the boolean semantics, in the differential semantics and in the stochastic semantics.

Given a transition system $M = (Q, T, L)$, a state $q \in Q$, and a temporal logic formula φ expressing some desirable property of the system, the *model checking problem* consists of establishing whether φ holds at q or not, namely, whether $M, q \models \varphi$. Another formulation of the model checking problem consists of finding all the states $q \in Q$ such that $M, q \models \varphi$. Observe that the second formulation is more general than the first one.

There exist several tools for checking if a finite state system verifies a given CTL, LTL, or PCTL formula, e.g., NuSMV [CCGR99], SPIN [Hol03], and PRISM [HKNP06].

In contrast to the above approaches, in our new technique we encode both biological systems and temporal properties in HyLL, and prove that the properties can be derived from the system. We focus on Boolean systems and in this case a time unit corresponds to a transition in the system. We believe that discrete modeling is crucial in systems biology because it allows taking into account some phenomena that have a very low chance of happening (and could thus be neglected by differential approaches), but which may have a strong impact on system behavior.

1.2 Linear Logic

Linear Logic (LL) [Gir87] is particularly well suited for describing state transition systems. LL has been successfully used to model such diverse systems as: planning [SP07], Petri nets, CCS, the π-calculus [CPWW03,Mil93], concurrent ML [CPWW03], security protocols [Boz02], multi-set rewriting, graph traversal algorithms [SP08], and games.

In the area of biology, for example, a rule of activation (e.g., a protein activates a gene or the transcription of another protein) can be modeled by the following LL axiom:

$$\texttt{active}(a, b) \stackrel{\text{def}}{=} \texttt{pres}(a) \to (\texttt{pres}(a) \otimes \texttt{pres}(b)).$$

The formula $\texttt{active}(a, b)$ describes the fact that a state where $\texttt{pres}(a)$ is true can evolve into a state where both $\texttt{pres}(a)$ and $\texttt{pres}(b)$ are true.

Propositions such as $\texttt{pres}(a)$ are called *resources*, and a rule in the logic can be viewed as a rewrite rule from a set of resources into another set of resources, where a set of resources describes a state of the system. Thus, a particular state transition system can be modeled by a set of rules of the above shape. The rules of the logic then allow us to prove some desired properties of the system, such as, for example, the existence of a stable state.

However, linear implication is timeless: there is no way to correlate two concurrent transitions. If resources have lifetimes and state changes have temporal, probabilistic or stochastic *constraints*, then the logic will allow inferences that may not be realizable in the system being modeled. This was the motivation of the development of HyLL, which was designed to represent constrained transition systems.

1.3 Contributions and Organization

In this work, we present some first applications of HyLL to systems biology. We present HyLL in Section 2 and the overall approach to the application domain in Section 3. We choose a simple yet representative biological example concerning the DNA-damage repair mechanism based on proteins p53 and Mdm2, and present and prove several properties of this system (Section 4). We fully formalize these proofs in a theorem prover we have implemented in the Coq Proof Assistant [BC04] and λProlog [MN12] (Section 5). This prover is designed to both reason in HyLL and to formalize meta-theoretic properties about it.

We discuss the merits and eventual drawbacks of this new approach compared to approaches using temporal logic and model checking. To better illustrate the correspondence with such approaches, which all use temporal logic to reason about (simulations of models of) the biological systems described, we also present in some detail the encoding of temporal logic operators in HyLL (Section 6).

We conclude and discuss future work in Section 7.

In appendix B, we give the sequent proofs of the properties of our biological system; the formalization of these proofs is available in our electronic appendix: `www.eecs.uottawa.ca/~afelty/fmmb14/`.

2 A Hybrid Linear Logic

HyLL is a conservative extension of intuitionistic first-order linear logic (LL) [Gir87] where the truth judgements are parameterized on a *constraint domain*. Instead of the ordinary judgement "A is true", for a proposition A, judgements of HyLL are of the form "A is true under constraint w", abbreviated as A @ w. A typical example of such a judgement is "A is true at time t", or "with probability p."

2.1 HyLL Syntax

Like in the linear logic LL, propositions are interpreted as *resources* which may be composed into a *state* using the usual linear connectives, and the linear implication ($\to$) denotes a transition between states. The world

label w of a judgement $A \mathbin{@} w$ represents a constraint on states and state transitions; particular choices for the worlds produce particular instances of HyLL. The common component in all the instances of HyLL is the proof theory, which is fixed once and for all. The minimal requirement on the kinds of constraints that HyLL can deal with is defined as follows:

Definition 1. *A* constraint domain $\mathcal{W}$ *is a monoid structure* $\langle W, ., \iota \rangle$*. The elements of* W *are called* worlds*, and the partial order* $\preceq : W \times W$ *—defined as* $u \preceq w$ *if there exists* $v \in W$ *such that* $u.v = w$ *—is the* reachability relation *in* $\mathcal{W}$*.*

The identity world ι is $\preceq$-initial and is intended to represent the lack of any constraints. Thus, the ordinary first-order linear logic is embeddable into any instance of HyLL by setting all world labels to the identity. A typical and simple example of constraint domain is $\mathcal{T} = \langle \Re^+, +, 0 \rangle$, or $\langle I\!N, +, 0 \rangle$, representing instants of time.

Atomic propositions are written using lowercase $(a, b, ...)$ applied to a sequence of *terms* $(s, t, \ldots)$, which are drawn from an untyped term language containing term variables $(x, y, \ldots)$ and function symbols $(f, g, ...)$ applied to a list of terms. Non-atomic propositions are constructed from the connectives of first-order intuitionistic linear logic and the two hybrid connectives *satisfaction* (`at`), which states that a proposition is true at a given world $(w, \iota, u.v, \ldots)$, and *localization* $(\downarrow)$, which binds a name for the (current) world the proposition is true at. The following grammar summarizes the syntax of HyLL terms and propositions.

$$
\begin{array}{lll}
t & ::= & c \mid x \mid f(\vec{t}) \\
A, B & ::= & p(\vec{t}) \mid A \otimes B \mid \mathbf{1} \mid A \to B \mid A \,\&\, B \mid \top \mid A \oplus B \mid \mathbf{0} \mid\, !A \mid \\
 & & \forall x.\ A \mid \exists x.\ A \mid (A \ \texttt{at}\ w) \mid \downarrow u.\ A \mid \forall u.\ A \mid \exists u.\ A
\end{array}
$$

Note that in the propositions $\downarrow u.A$, $\forall u.\ A$ and $\exists u.\ A$, world u is bound in A. World variables cannot be used in terms, and neither can term variables occur in worlds; this restriction is important for the modular design of HyLL because it keeps purely logical truth separate from constraint truth. We let α range over variables of either kind. Note that the $\downarrow$ connective commutes with every propositional connective, including itself [CD13]. That is, $\downarrow u.\ (A * B)$ is equivalent to $(\downarrow u.\ A) * (\downarrow u.\ B)$ for all binary connectives $*$, and $\downarrow u.\ * A$ is equivalent to $*(\downarrow u.\ A)$ for every unary connective $*$, assuming the commutation will not cause an unsound capture of u. It is purely a matter of taste where to place the $\downarrow$, and repetitions are harmless. Note that $\downarrow$ and `at` commute freely with all non-hybrid connectives [CD13].

2.2 Sequent Calculus for HyLL

We present the syntax of hybrid logic in a sequent calculus style, using Martin-Löf's principle of separating judgements (here: $A@w$) and logical connectives (here: $\otimes, \to$, ..., `at`, ...) [ML96]. We use sequents of the form $\Gamma; \Delta \vdash C \mathbin{@} w$ where Γ and Δ are sets of judgements of the form $A \mathbin{@} w$, with Δ being moreover a *multiset*. Γ is called the *unrestricted context*: its hypotheses can be consumed any number of times. Δ is a *linear context*: every hypothesis in it must be consumed singly in the proof. Note that in a judgement $A \mathbin{@} w$ (as in a proposition A `at` w), w can be any expression in $\mathcal{W}$, not only a variable. The notation $A[\tau/\alpha]$ stands for the replacement of all free occurrences of the variable α in A with the expression τ, avoiding capture. The expressions in the rules are to be read up to alpha-conversion.

The full collection of inference rules are in Fig. 1. The rules for the linear connectives are borrowed from [CCP03] where they are discussed at length, so we omit a more thorough discussion here. The rules for the first-order quantifiers are completely standard. A brief discussion of the hybrid rules follows. To introduce the *satisfaction* proposition (A `at` u) (at any world w) on the right, the proposition A must be true in the world u. The proposition (A `at` u) itself is then true at any world, not just in the world u. In other words, (A `at` u) carries with it the world at which it is true. Therefore, suppose we know that (A `at` u) is true (at any world v); then, we also know that $A \mathbin{@} u$, and we can use this hypothesis (rule "at L"). These two introduction rules (on the right and on the lelft) match up precisely to (de)construct the information in the $A \mathbin{@} w$ judgement. The other hybrid connective of *localisation*, $\downarrow$, is intended to be able to name the current world. That is, if $\downarrow u.\ A$ is true at world w, then the variable u stands for w in the body A. This interpretation is reflected in its right

Judgemental rules

$$\Gamma; p(\vec{t}) \mathbin{@} w \vdash p(\vec{t}) \mathbin{@} w \ [init] \qquad \frac{\Gamma, A \mathbin{@} u; \Delta, A \mathbin{@} u \vdash C \mathbin{@} w}{\Gamma, A \mathbin{@} u; \Delta \vdash C \mathbin{@} w} \ copy$$

Multiplicative

$$\frac{\Gamma; \Delta \vdash A \mathbin{@} w \quad \Gamma; \Delta' \vdash B \mathbin{@} w}{\Gamma; \Delta, \Delta' \vdash A \otimes B \mathbin{@} w} \otimes R \quad \frac{\Gamma; \Delta, A \mathbin{@} u, B \mathbin{@} u \vdash C \mathbin{@} w}{\Gamma; \Delta, A \otimes B \mathbin{@} u \vdash C \mathbin{@} w} \otimes L$$

$$\Gamma; . \vdash \mathbf{1} \mathbin{@} w \ [\mathbf{1}R] \quad \frac{\Gamma; \Delta \vdash C \mathbin{@} w}{\Gamma; \Delta, 1 \mathbin{@} u \vdash C \mathbin{@} w} \, 1L$$

$$\frac{\Gamma; \Delta, \ A \mathbin{@} w \vdash B \mathbin{@} w}{\Gamma; \Delta \vdash A \to B \mathbin{@} w} \to R \qquad \frac{\Gamma; \Delta \vdash A \mathbin{@} u \quad \Gamma; \Delta', B \mathbin{@} u \vdash C \mathbin{@} w}{\Gamma; \Delta, \Delta', A \to B \mathbin{@} u \vdash C \mathbin{@} w} \to L$$

Additive

$$\Gamma; \Delta \vdash T \mathbin{@} w \ [T \ R] \qquad \Gamma; \Delta, \mathbf{0} \mathbin{@} u \vdash C \mathbin{@} w \ [\mathbf{0}L]$$

$$\frac{\Gamma; \Delta \vdash A \mathbin{@} w \qquad \Gamma; \Delta \vdash B \mathbin{@} w}{\Gamma; \Delta \vdash A \,\&\, B \mathbin{@} w} \,\& R \qquad \frac{\Gamma; \Delta, A_i \mathbin{@} u \vdash C \mathbin{@} w}{\Gamma; \Delta, A_1 \,\&\, A_2 \mathbin{@} u \vdash C \mathbin{@} w} \,\& L_i$$

$$\frac{\Gamma; \Delta \vdash A_i \mathbin{@} w}{\Gamma; \Delta \vdash A_1 \oplus A_2 \mathbin{@} w} \oplus R_i \quad \frac{\Gamma; \Delta, A \mathbin{@} u \vdash C \mathbin{@} w \quad \Gamma; \Delta, B \mathbin{@} u \vdash C \mathbin{@} w}{\Gamma; \Delta, A \oplus B \mathbin{@} u \vdash C \mathbin{@} w} \oplus L$$

Quantifiers

$$\frac{\Gamma; \Delta \vdash A \mathbin{@} w}{\Gamma; \Delta \vdash \forall \alpha.\ A \mathbin{@} w} \ [\forall R^{\alpha}] \qquad \frac{\Gamma; \Delta, A[\tau/\alpha] \mathbin{@} u \vdash C \mathbin{@} w}{\Gamma; \Delta, \forall \alpha.\ A \mathbin{@} u \vdash C \mathbin{@} w} \ [\forall L]$$

$$\frac{\Gamma; \Delta \vdash A[\tau/\alpha] \mathbin{@} w}{\Gamma; \Delta \vdash \exists \alpha.\ A \mathbin{@} w} \ [\exists R] \qquad \frac{\Gamma; \Delta, A \mathbin{@} u \vdash C \mathbin{@} w}{\Gamma; \Delta, \exists \alpha.\ A \mathbin{@} u \vdash C \mathbin{@} w} \ [\exists L^{\alpha}]$$

For $\forall R^{\alpha}$ and $\exists L^{\alpha}$, α is assumed to be fresh with respect to Γ, Δ, and C.
For $\exists R$ and $\forall L$, τ stands for a term or world, as appropriate.

Exponentials rules

$$\frac{\Gamma; . \vdash A \mathbin{@} w}{\Gamma; . \vdash !A \mathbin{@} w} \ !R \qquad \frac{\Gamma, A \mathbin{@} u; \Delta \vdash C \mathbin{@} w}{\Gamma; \Delta, !A \mathbin{@} u \vdash C \mathbin{@} w} \ !L$$

Hybrid connectives

$$\frac{\Gamma; \Delta \vdash A \mathbin{@} u}{\Gamma; \Delta \vdash (A \ \mathtt{at}\ u) \mathbin{@} w} \ [\mathtt{at}\ R] \qquad \frac{\Gamma; \Delta, A \mathbin{@} u \vdash C \mathbin{@} w}{\Gamma; \Delta, (A \ \mathtt{at}\ u) \mathbin{@} v \vdash C \mathbin{@} w} \ [\mathtt{at}\ L]$$

$$\frac{\Gamma; \Delta \vdash A[w/u] \mathbin{@} w}{\Gamma; \Delta \vdash \downarrow u.A \mathbin{@} w} \ [\downarrow R] \qquad \frac{\Gamma; \Delta, A[v/u] \mathbin{@} v \vdash C \mathbin{@} w}{\Gamma; \Delta, \downarrow u.A \mathbin{@} v \vdash C \mathbin{@} w} \ [\downarrow L]$$

Figure 1: Sequent calculus for HyLL

introduction rule $\downarrow R$. For left introduction, suppose we have a proof of $\downarrow u.\ A\ @\ v$ for some world v. Then, we also know, and thus can use $A[v/u]\ @\ v$.

There are only two structural rules: the init rule infers an atomic initial sequent, and the copy rule introduces a contracted copy of an unrestricted assumption into the linear context (reading from conclusion to premise). Weakening and contraction are admissible rules. Their proofs are straightforward, by induction on the structure of the given derivations [CD13].

Theorem 2 (structural properties)**.**

- *If* $\Gamma; \Delta \vdash C\ @\ w$*, then* $\Gamma, \Gamma'; \Delta \vdash C\ @\ w$*. (weakening)*
- *If* $\Gamma, A\ @\ u, A\ @\ u; \Delta \vdash C\ @\ w$*, then* $\Gamma, A\ @\ u; \Delta \vdash C\ @\ w$*. (contraction)*

The most important structural properties are the admissibility of the identity and cut theorem. Thanks to the cut-admissibility theorem, the proof of the consistency of the logic is reduced to the observation that there is no cut-free derivation of $.; . \vdash 0\ @\ w$.

The identity theorem is the general case of the init rule. Its proof is straightforward, by induction on the structure of A.

Theorem 3 (identity)**.** $\Gamma, A\ @\ w \vdash A\ @\ w$.

Theorem 4 (cut)**.**
1. *If* $\Gamma; \Delta \vdash A\ @\ u$ *and* $\Gamma; \Delta', A\ @\ u \vdash C\ @\ w$*, then* $\Gamma; \Delta, \Delta' \vdash C\ @\ w$
2. *If* $\Gamma; . \vdash A\ @\ u$ *and* $\Gamma, A\ @\ u; \Delta \vdash C\ @\ w$*, then* $\Gamma; \Delta \vdash C\ @\ w$.

Proof. By lexicographic structural induction on the given derivations, with cuts of kind 2 additionally allowed to justify cuts of kind 1. See [CD13] for the details. □

We can use the admissible cut rules to show that the following rules are invertible: $\mathbf{1}L$, $\mathbf{0}L$, $\otimes L$, $\oplus L$, $!L$, $\exists L$, $\top R$, $\rightarrow R$, $\&R$, and $\forall R$. In addition, the four hybrid rules, $\mathtt{at}R$, $\mathtt{at}L$, $\downarrow R$, and $\downarrow L$ are invertible [CD13].

Corollary 5 (consistency)**.** *There is no proof of* $.; . \vdash 0\ @\ w$.

Proof. Suppose $.; . \vdash 0\ @\ w$ is derivable. Then, by the cut-admissibility theorem (4) on the sequent calculus, the sequent $.; . \vdash 0\ @\ w$ must have a cut-free proof. However we can see by simple inspection on the inference rules that this cannot be the case, as this sequent cannot be the conclusion of any rule of inference in the calculus. Therefore, $.; . \vdash 0\ @\ w$ is not derivable. □

Note also that HyLL is conservative with respect to intuitionistic linear logic: as long as no hybrid connectives are used, the proofs in HyLL are identical to those in LL [CD13].

An example of derived statements, true in every semantics for worlds, is the following:

Proposition 6 (relocalisation)**.** *Any true judgement can be relocated at any time in the future:*

$$\frac{\Gamma; A_1\ @\ w_1 \cdots A_k\ @\ w_k \vdash B\ @\ v}{\Gamma; A_1\ @\ u.w_1 \cdots A_k\ @\ u.w_k \vdash B\ @\ u.v}$$

This property is particularly well suited to applications in biology. The interested reader can find proofs and further meta-theoretical theorems about HyLL in [CD13].

2.3 Some Definitions for Biology

We can define modal connectives in HyLL as follows:

Definition 7 (modal connectives)**.**

$$\Box A \stackrel{\text{def}}{=} \downarrow u.\ \forall w.\ (A\ \mathtt{at}\ u.w) \qquad \Diamond A \stackrel{\text{def}}{=} \downarrow u.\ \exists w.\ (A\ \mathtt{at}\ u.w)$$
$$\delta_v\, A \stackrel{\text{def}}{=} \downarrow u.\ (A\ \mathtt{at}\ u.v) \qquad \dagger\, A \stackrel{\text{def}}{=} \forall u.\ (A\ \mathtt{at}\ u)$$

The connective δ represents a form of delay. Note its derived right rule:

$$\frac{\Gamma \vdash A\ @\ w.v}{\Gamma \vdash \delta_v\, A\ @\ w}\ [\delta R]$$

The proposition $\delta_v\, A$ thus stands for an *intermediate state* in a transition to A. Informally it can be thought to be "v before A". The modally unrestricted proposition $\dagger\, A$ represents a resource that is consumable in any world; it is mainly used to make transition rules applicable at all worlds.

It is worth remarking that HyLL proof theory can be seen as at least as powerful as S5 [CD13]. Obviously HyLL is more expressive as it allows direct manipulation of the worlds using the hybrid connectives: for example, the δ connective is not definable in S5.

Oscillation is one of the typical properties of interest in biological systems (illustrated here by Property 1 in Sect 4.3.1). In our logic, we can define one oscillation between A and B, with respective delays u and v, as follows:

Definition 8 (one oscillation)**.** $\mathit{oscillate}_1\,(A, B, u, v) \stackrel{\text{def}}{=} A\ \ \&\ \ \delta_u(B\ \ \&\ \ \delta_v\, A)\ \ \&\ \ (A \,\&\, B \to 0)$.

Note that the above HyLL proposition closely corresponds to the temporal formula $A \wedge \mathsf{EF}(B \wedge \mathsf{EF}A)$.

Oscillation can be more generally defined by the following proposition in HyLL:

Definition 9 (oscillation)**.** $\mathit{oscillate}_h\,(A, B, u, v) \stackrel{\text{def}}{=} \dagger[(A \to \delta_u\, B)\ \ \&\ \ (B \to \delta_v\, A)]\ \ \&\ \ (A \,\&\, B \to 0)$.

However, since oscillation can be considered a meta-level property of the biological systems modeled in HyLL, this property is perhaps more naturally defined as follows:

Definition 10 (oscillation)**.** $\mathit{oscillate}\,(A, B, u, v) \stackrel{\text{def}}{=}$ *for any* w, $(A\ @\ w \vdash B\ @\ w.u)$, $(B\ @\ w.u \vdash A\ @\ w.u.v)$, *and* $(\vdash A \,\&\, B \to 0\ \ @\ w)$.

2.4 Temporal Constraints

In this paper, we only consider the constraint domain $\mathcal{T} = \langle \mathbb{N}, +, 0\rangle$ representing (discrete) instants of time, and we write HyLL[$\mathcal{T}$] for this instantiation of HyLL. Delay (Definition 7) in HyLL[$\mathcal{T}$] represents intervals of time; $\delta_d\, A$ means "A will become available after delay d". This domain is very permissive because addition is commutative, resulting in the equivalence of $\delta_u\, \delta_v\, A$ and $\delta_v\, \delta_u\, A$. The "forward-looking" connectives G and F of temporal logic are precisely $\Box$ and $\Diamond$ of defn. 7. For further discussion on the comparison with temporal logic and model checking, see Sec 6. For our temporal specifications the notion of addition on times is fundamental.

Considering other constraint domains such as $\mathcal{T}_r = \langle \Re^+, +, 0\rangle$, or probabilistic constraints (as discussed in [CD13]) is left to future work.

3 Approach

In this work we take into consideration Boolean models consisting of (i) a set of Boolean variables, (ii) a (partially defined) initial state denoting the presence/absence of (some) variables, and (iii) a set of rules of the form $L_i \Rightarrow R_i$, where the left (resp. right) hand side of the rule L_i (resp. R_i) is the conjunction of a set of predicates concerning the presence/absence of variables. For example, $x_1 \wedge x_2 \Rightarrow \neg x_3$ is a valid rule. This kind of rule can be used to describe state transitions involving control variables or abstract processes. In Biocham [FSCR04], they are mostly used to represent biochemical reactions (observe that Biocham rules are more restrictive, they do not express the absence of a variable). In this paper, we take advantage of these rules to express influence rules (e.g. activations and inhibitions) in a biological system.

Observe that, given a Boolean model of this kind, although we do not do it, it is always possible to build a transition system where the set of states is the set of all tuples of Boolean values denoting the presence/absence of the different variables, and a pair of states (s,s') belongs to the relation if and only if there exists a rule i such that s satisfies L_i, s' satisfies R_i, and all the variables not involved in rule i have the same value in s and s'.

If L_i speaks about the presence of a variable x, nothing can be said about the presence/absence of x in s'. In other words, nothing can be inferred about the consumption of variables appearing in the left hand side of rules. If we want to force consumption/not consumption, we have to specify it explicitly. Furthermore, our rules are asynchronous: one rule can be fired at a time. If several rules can be taken from a given state, one of them is non-deterministically chosen. As in Biocham, we choose an asynchronous semantics in order to eliminate the risk of affecting fundamental biological phenomena such as the masking of a relation by another one and the consequent inhibition/activation of biological processes.

To verify whether a Boolean model satisfies a given temporal property, our approach consists of encoding both the model and the property in the HyLL logic and producing a proof. Observe that we do not explicitly build the transition system, we just give a set of variables and rules. Proving temporal properties can result in building a sub-part of the system. There is an analogy with on-the-fly model checking [CVWY92], a technique that in many cases avoids the construction of the entire state space of the system (because the property to test guides the construction of the system). However, on-the-fly model checkers mainly deal with LTL formulas.

4 Example

In this section we focus on the P53/Mdm2 DNA-damage repair mechanism. P53 is a tumor suppressor protein that is activated in reply to DNA damage. In normal conditions, the concentration of p53 in the nucleus of a cell is weak: its level is controlled by another protein, Mdm2. These two proteins present a loop of negative regulation. In fact, P53 activates the transcription of Mdm2 while the latter accelerates the degradation of the former.

DNA damage increases the degradation rate of Mdm2 so that the control of this protein on P53 becomes weaker and the concentration of p53 can increase. P53 can thus exercise its functions, either stopping the cell cycle to allow DNA repair, or provoking apoptosis, if damage is too heavy. This is possible if the control of Mdm2 on p53 weakens. As written above, in most of cases this happens for phosphorylation of p53 and Mdm2 through ATM.

When Mdm2 loosens its influence on P53, it is possible to observe some oscillations of P53 and Mdm2 concentrations. The answer to a stronger damage is a bigger number of oscillations. In the literature, several models have been proposed to model the oscillatory behaviour of proteins P53 and Mdm2 (see those introduced by Chickermane et al. [CRSN07], by Ciliberto et al. [CNT05], and by Geva-Zatorsky et al. [GZRI$^+$06]). In the context of cancer therapies, in [MFRS11] it is shown how a coupled model of the P53/Mdm2 DNA-damage repair mechanism, of the cell cycle, of the circadian clock, and of an anticancer drug can be a valuable tool to investigate the drug influence on the cell cycle.

The concentration of P53 in healthy cells is weak because this protein is responsible for the activation of

many mechanisms that could be dangerous for cells. In an indirect way, it stops the DNA synthesis process, it activates the production of proteins charged with DNA reparation, and it can lead to apoptosis (cell death).

4.1 Definition

In the following we propose a simple Boolean model considering the presence/absence of the three variables DNAdam, P53, and MdM2. The corresponding transition system woud thus consist of eight states, each one associated to a 3-tuple of Boolean values denoting the presence/absence of the three variables. Initial states are the ones where P53 is absent and Mdm2 is present.

The behaviour of the biological system is specified by the six following rules:

1) Dnadam $\Rightarrow \neg$Mdm2	4) Mdm2 $\Rightarrow \neg$P53
2) $\neg$Mdm2 $\Rightarrow$ P53	5) P53 $\Rightarrow_C \neg$Dnadam
3) P53 $\Rightarrow$ Mdm2	6) $\neg$Dnadam $\Rightarrow$ Mdm2

In rule 5, we use $\Rightarrow_C$ to force consumption, i.e., if P53 is present, after firing the rule both P53 and Dnadam are absent. Note that, if Dnadam is present in the initial state, this rule (that refers to damage repair) can be non-deterministically fired after one, a few, or several P53/MdM2 oscillations. This is consistent with experiments, where the number of oscillations preceding damage repair depends on the damage entity. In the other rules we assume there is no comsumption.

4.2 Specification in HyLL

The biological system is modeled in HyLL by a set of axioms of two kinds. First, each rule of the biological system is modeled by a formula in HyLL, as it would be in ordinary linear logic, with the additional use of the delay operator δ_v, making precise the delay taken by the corresponding transition. The domain of world is $\mathcal{T} = \langle I\!N, +, 0\rangle$ and we fix all time delays to 1. Then we add a set of axioms stating some well-definedness conditions and the initial state. To encode the basic Boolean model, we use two predicates: $\texttt{pres}(a)$ (seen earlier) and $\texttt{abs}(a)$ to indicate the presence or absence of variable a. The full model is given in Fig. 2.

4.2.1 Activation/Inhibition Rules

For the sake of clarity, we first define generic activation/inhibition actions. These actions can be defined in various ways. A first attempt at describing an activation rule without consumption, for example, might be the following:

$$w\_\texttt{active}(a,b) \stackrel{\text{def}}{=} \texttt{pres}(a) \multimap \delta_1\ \ (\texttt{pres}(a) \otimes \texttt{pres}(b)).$$

This rule does not make any assumption on the value of b: this kind of rule corresponds to the case of partial knowledge of the current state of the system. Note however that in the case where b is present, the above rule does not modify the state. In order to avoid uninteresting proofs, we might alternatively define our activation rule in a more precise way, as follows:

$$s\_\texttt{active}(a,b) \stackrel{\text{def}}{=} \texttt{pres}(a) \otimes \texttt{abs}(b) \multimap \delta_1(\texttt{pres}(a) \otimes \texttt{pres}(b)).$$

We call the first kind of rules *weak* rules, and the second one *strong* rules.

For the sake of completeness, let us mention a third kind of rules, that we might call *useless*, although they are indeed needed to formalize loops in a state (see our Property 3 below):

$$u\_\texttt{active}(a,b) \stackrel{\text{def}}{=} \texttt{pres}(a) \otimes \texttt{pres}(b) \multimap \delta_1(\texttt{pres}(a) \otimes \texttt{pres}(b)).$$

The *general* form of an activation rule, taking in account the various possible values of b, and our eventual missing knowledge of this, is then the following:

$$\begin{array}{rcl} \texttt{active}(a,b) & \stackrel{\text{def}}{=} & (\texttt{pres}(a) \oplus (\texttt{pres}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{pres}(a) \otimes \texttt{abs}(b))) \\ & & \rightarrow \delta_1 \ (\texttt{pres}(a) \otimes \texttt{pres}(b)). \end{array}$$

The properties stated in the present paper will all use the general form of the biological rules, except Property 4, which is only valid for strong rules.

There are further alternatives for the activation/inhibition rules. Let us consider the above strong variant $s\_\texttt{active}(a,b)$. We can define an *activation with consumption* (of the product a) as follows:

$$s\_\texttt{active}_c(a,b) \stackrel{\text{def}}{=} \texttt{pres}(a) \otimes \texttt{abs}(b) \rightarrow \delta_1(\texttt{abs}(a) \otimes \texttt{pres}(b)),$$

while a *strong activation* will have an inhibitor effect, in case of absence of a:

$$s\_\texttt{active}_s(a,b) \stackrel{\text{def}}{=} \texttt{abs}(a) \otimes \texttt{pres}(b) \rightarrow \delta_1(\texttt{abs}(a) \otimes \texttt{abs}(b)).$$

Our example also uses the corresponding three kinds of rules for the inhibition actions (see Fig. 2). Of course, we could also define activation/inhibition rules accounting for a lack of information concerning consumption.

4.2.2 The System

Before giving the complete definition of our system, we need to additionally specify, in each rule, that if a variable is not touched, then its value remains the same in the next state. This is the purpose of the `unchanged` predicate, which in turn leads us to introduce a parameter `vars`, specifying the set of variables of the biological system.

Note that the definition of the `unchanged` predicate relies on the hypothesis (discussed earlier, in Sec 3) that only one rule of the biological system can fire at a time. Note also the use of the ! and & operators in its definition: this is an intuitionistic predicate.

We define our biological system (with rules in their general form) by the set of HyLL axioms given in Fig. 2.

4.3 Proofs

Although linear logic is well suited to describing transition systems, as we do here in the area of biology, this logic can sometimes be too precise in its resource management for our needs. To solve this constraint, we sometimes make precise that we do not care about the value of some variables. We define a `dont_care` predicate for this purpose:

$$\texttt{dont\_care}(x) \stackrel{\text{def}}{=} \texttt{pres}(x) \oplus \texttt{abs}(x) \qquad \texttt{dont\_care}(V) \stackrel{\text{def}}{=} \otimes_{x \in V} \texttt{dont\_care}(x).$$

This predicate is used in the statement of two of the four properties we present in this paper (Properties 1 and 4).

Additionally, in some proofs, when we do not know the value of some variables of the system, we sometimes need to perform a case analysis on their two possible values, using the $\texttt{well\_defined}_1$ predicate introduced for this purpose.

Finally let us give two definitions in order to further shorten propositions and proofs ($state_0$ is a state equivalent to the initial state):

$$state_0 \stackrel{\text{def}}{=} \texttt{abs}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})$$
$$state_1 \stackrel{\text{def}}{=} \texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{Mdm2}).$$

- *Variables*:

$$\texttt{unchanged}(x,w) \stackrel{\text{def}}{=} \ !\ [(\texttt{pres}(x)\ \texttt{at}\ w \to \texttt{pres}(x)\ \texttt{at}\ w.1)\ \ \&\ \ (\texttt{abs}(x)\ \texttt{at}\ w \to \texttt{abs}(x)\ \texttt{at}\ w.1)].$$
$$\texttt{unchanged}(V,w) \stackrel{\text{def}}{=} \otimes_{x\in V}\texttt{unchanged}(x,w).$$

- *Activation*:

$$\begin{aligned}\texttt{active}(V,a,b) \stackrel{\text{def}}{=}\ & (\texttt{pres}(a) \oplus (\texttt{pres}(a)\otimes\texttt{pres}(b)) \oplus (\texttt{pres}(a)\otimes\texttt{abs}(b)))\\ & \to \delta_1\ \ (\texttt{pres}(a)\otimes\texttt{pres}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).\end{aligned}$$

- *Activation with consumption*:

$$\begin{aligned}\texttt{active}_c(V,a,b) \stackrel{\text{def}}{=}\ & (\texttt{pres}(a) \oplus (\texttt{pres}(a)\otimes\texttt{pres}(b)) \oplus (\texttt{pres}(a)\otimes\texttt{abs}(b)))\\ & \to \delta_1\ \ (\texttt{abs}(a)\otimes\texttt{pres}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).\end{aligned}$$

- *Strong activation*:

$$\begin{aligned}\texttt{active}_s(V,a,b) \stackrel{\text{def}}{=}\ & (\texttt{abs}(a) \oplus (\texttt{abs}(a)\otimes\texttt{pres}(b)) \oplus (\texttt{abs}(a)\otimes\texttt{abs}(b)))\\ & \to \delta_1\ \ (\texttt{abs}(a)\otimes\texttt{abs}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).\end{aligned}$$

- *Inhibition*:

$$\begin{aligned}\texttt{inhib}(V,a,b) \stackrel{\text{def}}{=}\ & (\texttt{pres}(a) \oplus (\texttt{pres}(a)\otimes\texttt{pres}(b)) \oplus (\texttt{pres}(a)\otimes\texttt{abs}(b)))\\ & \to \delta_1\ \ (\texttt{pres}(a)\otimes\texttt{abs}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).\end{aligned}$$

- *Inhibition with consumption*:

$$\begin{aligned}\texttt{inhib}_c(V,a,b) \stackrel{\text{def}}{=}\ & (\texttt{pres}(a) \oplus (\texttt{pres}(a)\otimes\texttt{pres}(b)) \oplus (\texttt{pres}(a)\otimes\texttt{abs}(b)))\\ & \to \delta_1\ \ (\texttt{abs}(a)\otimes\texttt{abs}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).\end{aligned}$$

- *Strong inhibition*:

$$\begin{aligned}\texttt{inhib}_s(V,a,b) \stackrel{\text{def}}{=}\ & (\texttt{abs}(a) \oplus (\texttt{abs}(a)\otimes\texttt{pres}(b)) \oplus (\texttt{abs}(a)\otimes\texttt{abs}(b)))\\ & \to \delta_1\ \ (\texttt{abs}(a)\otimes\texttt{pres}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).\end{aligned}$$

- *Well definedness*:

$$\texttt{well\_defined}_0(V) \stackrel{\text{def}}{=} \forall a \in V.\ [\texttt{pres}(a)\otimes\texttt{abs}(a) \to 0].$$
$$\texttt{well\_defined}_1(V) \stackrel{\text{def}}{=} \forall a \in V.\ [\texttt{pres}(a)\oplus\texttt{abs}(a)].$$
$$\texttt{well\_defined}(V) \stackrel{\text{def}}{=} \texttt{well\_defined}_0(V), \texttt{well\_defined}_1(V).$$

- *The system*:

$$\texttt{vars} \stackrel{\text{def}}{=} \{\texttt{p53}, \texttt{Mdm2}, \texttt{DNAdam}\}.$$
$$\texttt{rule}(1) \stackrel{\text{def}}{=} \texttt{inhib}(\texttt{vars}, \texttt{DNAdam}, \texttt{Mdm2}). \qquad \texttt{rule}(4) \stackrel{\text{def}}{=} \texttt{inhib}(\texttt{vars}, \texttt{Mdm2}, \texttt{p53}).$$
$$\texttt{rule}(2) \stackrel{\text{def}}{=} \texttt{inhib}_\texttt{s}(\texttt{vars}, \texttt{Mdm2}, \texttt{p53}). \qquad \texttt{rule}(5) \stackrel{\text{def}}{=} \texttt{inhib}_\texttt{c}(\texttt{vars}, \texttt{p53}, \texttt{DNAdam}).$$
$$\texttt{rule}(3) \stackrel{\text{def}}{=} \texttt{active}(\texttt{vars}, \texttt{p53}, \texttt{Mdm2}). \qquad \texttt{rule}(6) \stackrel{\text{def}}{=} \texttt{inhib}_\texttt{s}(\texttt{vars}, \texttt{DNAdam}, \texttt{Mdm2}).$$

$$\texttt{system} \stackrel{\text{def}}{=} \texttt{vars}, \texttt{rule}(1), \texttt{rule}(2), \texttt{rule}(3), \texttt{rule}(4), \texttt{rule}(5), \texttt{rule}(6), \texttt{well\_defined}(\texttt{vars}).$$

- *Initial state*:

$$\texttt{initial\_state} \stackrel{\text{def}}{=} \texttt{abs}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2}), \quad \texttt{initial\_state}\ \texttt{at}\ 0.$$

Figure 2: Representation of the System in HyLL

4.3.1 Property 1

As long as there is DNA damage, the above system can oscillate (with a short period) from $state_0$ to $state_1$ and back again. We outline the proof informally below. The sequent proofs can be found in Appendix B; we refer the reader to the electronic appendix for their formalization.

From $state_0$ and $\texttt{pres}(\texttt{DNAdam})$ we get $\texttt{abs}(\texttt{p53})$, $\texttt{abs}(\texttt{Mdm2})$, and $\texttt{pres}(\texttt{DNAdam})$ by rule 1. Then $\texttt{pres}(\texttt{p53})$, $\texttt{abs}(\texttt{Mdm2})$, and $\texttt{pres}(\texttt{DNAdam})$ ($state_1$) by rule 2. Then $\texttt{pres}(\texttt{p53})$, $\texttt{pres}(\texttt{Mdm2})$, and $\texttt{pres}(\texttt{DNAdam})$ by rule 3, and finally $\texttt{abs}(\texttt{p53})$, $\texttt{pres}(\texttt{Mdm2})$, and $\texttt{pres}(\texttt{DNAdam})$ ($state_0$) by rule 4.

We define (and prove) our property in the two possible ways discussed earlier (Sec 4.2), roughly corresponding to Definitions 8 and 10, respectively. The difference here is that our initial state (the one from which the oscillation starts) includes the presence of DNA damage.

Proposition (Property 1, Version 1)**.** *For any world w, there exists two worlds u and v such that both u and v are less than* 3 *and the following holds:*

$$\dagger\, system \;@\; 0 \;;\; state_0 \;\otimes\; \texttt{pres}(\texttt{DNAdam}) \;@\; w \\ \vdash \delta_u\; [(state_1 \;\otimes\; \texttt{dont\_care}(\texttt{DNAdam}))\;\&\;(\delta_v\;(state_0 \;\otimes\; \texttt{dont\_care}(\texttt{DNAdam})))] \;@\; w$$

Aternatively, our property can be defined:

Proposition (Property 1, Version 2)**.** *For any world w, there exists two worlds u and v such that both u and v are less than* 3 *and the following holds:*

$$\dagger\, system \;@\; 0 \;;\; state_0 \;\otimes\; \texttt{pres}(\texttt{DNAdam}) \;@\; w \vdash state_1 \;\otimes\; \texttt{dont\_care}(\texttt{DNAdam}) \;@\; w.u \quad \textit{and}$$
$$\dagger\, system \;@\; 0 \;;\; state_1 \;@\; w.u \vdash state_0 \;@\; w.u.v$$

There are no $\texttt{dont\_care}$'s needed in the conclusion of the second sequent because only rules 3 and 4 are used, which don't involve DNAdam.

4.3.2 Property 2

DNA damage can be quickly recovered.

From $state_0$ and $\texttt{pres}(\texttt{DNAdam})$ we get $\texttt{abs}(\texttt{p53})$, $\texttt{abs}(\texttt{Mdm2})$, and $\texttt{pres}(\texttt{DNAdam})$ by rule 1. Then $\texttt{pres}(\texttt{p53})$ and $\texttt{abs}(\texttt{Mdm2})$ ($state_1$) and $\texttt{pres}(\texttt{DNAdam})$ by rule 2. Then $\texttt{abs}(\texttt{p53})$, $\texttt{abs}(\texttt{Mdm2})$, and $\texttt{abs}(\texttt{DNAdam})$ by rule 5, and finally $\texttt{abs}(\texttt{p53})$ and $\texttt{pres}(\texttt{Mdm2})$ ($state_0$) and $\texttt{abs}(\texttt{DNAdam})$ by rule 6.

Our property can be stated directly as follows.

Proposition (Property 2)**.** *For any world w, there exists a world u such that u is less than* 5 *and the following holds:*

$$\dagger\, system \;@\; 0;\; state_0 \;\otimes\; \texttt{pres}(\texttt{DNAdam}) \;@\; w \vdash state_0 \otimes \texttt{abs}(\texttt{DNAdam}) \;@\; w.u$$

4.3.3 Induction/Case Analysis

Most of interesting proofs require case analysis or induction; this is the case for Properties 3 and 4 below. More precisely, we need here *case analysis on the set of fireable rules*. We implement this by a case analysis on the interval [1..6] of our six rules, together with a new predicate $\texttt{fireable}$ defining the necessary conditions for each rule to fire. We shall also need the negation of this predicate: $\texttt{not\_fireable}$[1]. We give here the definitions of these predicates for the first rule of our system, for both (strong and general) styles of the rules used in the present paper (the complete definitions can be found in Appendix A):

[1]The definition of $\texttt{not\_fireable}$ relies on the $\texttt{well\_defined}_1$ hypothesis $\forall a.\ \texttt{pres}(a) \oplus \texttt{abs}(a)$ for all the variables not involved in the hypothesis of the rules.

$$
\begin{array}{ll}
\texttt{fireable}_{\texttt{s}}(1) & \stackrel{\text{def}}{=} \texttt{pres}(\texttt{DNAdam}) \otimes \texttt{pres}(\texttt{Mdm2}) \otimes \texttt{dont\_care}(\texttt{p53}) \\
\texttt{not\_fireable}_{\texttt{s}}(1) & \stackrel{\text{def}}{=} ((\texttt{abs}(\texttt{DNAdam}) \otimes \texttt{pres}(\texttt{Mdm2})) \ \oplus \ (\texttt{pres}(\texttt{DNAdam}) \otimes \texttt{abs}(\texttt{Mdm2})) \\
 & \quad \oplus \ (\texttt{abs}(\texttt{DNAdam}) \otimes \texttt{abs}(\texttt{Mdm2}))) \ \otimes \ \texttt{dont\_care}(\texttt{p53}) \\
 & \\
\texttt{fireable}(1) & \stackrel{\text{def}}{=} (\texttt{pres}(\texttt{DNAdam}) \ \oplus \ (\texttt{pres}(\texttt{DNAdam}) \otimes \texttt{pres}(\texttt{Mdm2})) \\
 & \quad \oplus \ (\texttt{pres}(\texttt{DNAdam}) \otimes \texttt{abs}(\texttt{Mdm2}))) \ \otimes \ \texttt{dont\_care}(\texttt{p53}) \\
\texttt{not\_fireable}(1) & \stackrel{\text{def}}{=} \texttt{abs}(\texttt{DNAdam}) \ \otimes \ \texttt{dont\_care}(\{\texttt{Mdm2}, \texttt{p53}\})
\end{array}
$$

An (informal) formula like "for any *fireable rule* r, P" will be written as "for any rule r in the interval [1..6], $(\texttt{fireable}(r) \ \& \ P) \oplus \texttt{not\_fireable}(r)$", which can be expressed fairly directly in the Coq formalization. Note that both definitions of `fireable` and `not_fireable` could be generated from the definitions of the biological rules, as the rules we consider in the present paper always have the same shape.

4.3.4 Property 3

If there is no DNA damage, the system remains in the initial state. A first attempt at formalizing this property might be:

For any world w, the following holds: $\dagger\, system \ @ \ 0;\ \texttt{abs}(\texttt{DNAdam}) \ @ \ 0 \vdash state_0 \otimes \texttt{abs}(\texttt{DNAdam}) \ @ \ w$.

However, the above statement does not model our property. We want to prove that if $\texttt{abs}(\texttt{DNAdam}) \ @ \ 0$ then $state_0 \otimes \texttt{abs}(\texttt{DNAdam}) \ @ \ w$ holds, for all worlds w, *no matter which rule is fired* to get to w. Thus our property requires a *case analysis* on the rules of the biological system.

Proposition (Property 3)**.** *Let $\mathcal{P}$ denote the formula $state_0 \ \otimes \ \texttt{abs}(\texttt{DNAdam})$. For any world w, the following holds: $\dagger\, system \ @ \ 0,\ \mathcal{P} \ @ \ 0 \ \vdash \mathcal{P}$ `at` $0 \ @ \ w$;*
and for any world w, for any rule r in the interval [1..6]*, the following holds:*

$$\dagger\, system \ @ \ 0 \vdash \mathcal{P} \rightarrow (\texttt{fireable}(r) \ \& \ \delta_1 \, \mathcal{P}) \ \oplus \ \texttt{not\_fireable}(r) \ @ \ w$$

The proof of the second statement proceeds by case analysis on the rules (r) of the biological system.

To prove that $\mathcal{P} \ @ \ n \vdash \mathcal{P} \ @ \ n+1$, for each `fireable` rule r, we have to prove that, if $\texttt{abs}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{DNAdam}) \ @ \ n$ then $\texttt{abs}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{DNAdam}) \ @ \ (n+1)$, no matter which rule is fired.

At state n, `DNAdam` is absent, thus the only effet it can have is to strongly inhibate `Mdm2` (`rule`(6)), making it present in the next state. However, `Mdm2` being already initialy present, this first applicable rule has no effect.

At state n, `p53` is also absent, thus no rule involving `p53` can apply.

At state n, the only present product is `Mdm2`. The only (second) applicable rule is $\texttt{inhib}(\texttt{Mdm2}, \texttt{p53})$ (`rule`(4)), which, after an interval of time 1, makes `p53` absent and leaves `Mdm2` present. As `p53` was already absent, and `Mdm2` present, the next state is, here again, equivalent to the previous state.

Thus, there are only two fireable rules: `rule`(4) and `rule`(6), and none of them modifies the current state of the system, which thus remains in its initial state.

4.3.5 Property 4

There is no path with two consecutive states where `p53` and `Mdm2` are both present or both absent. In other words: from any state where `p53` and `Mdm2` are both present or both absent, we can only go to a state where either `p53` is present and `Mdm2` is absent or `p53` is absent and `Mdm2` is present.

This requires a stronger (natural) hypothesis: we need the property that each rule modifies at least one entity in the system. In order to achieve this, we shall use the strong style of definitions for our inhibition and activation rules discussed earlier (sec. 4.2.1). For example, the activation rule will be defined as follows:

$$s\_\texttt{active}(V, a, b) \stackrel{\text{def}}{=} \texttt{pres}(a) \otimes \texttt{abs}(b) \rightarrow \ \delta_1(\texttt{pres}(a) \otimes \texttt{pres}(b)) \otimes \downarrow u. \ \texttt{unchanged}(V \setminus \{a, b\}, u)).$$

The complete set of strong rules can be found in Appendix A.

Let $\mathcal{L}$ and $\mathcal{R}$ denote the following two formulas:

$$\mathcal{L} := (\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \oplus (\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)})$$
$$\mathcal{R} := ((\texttt{pres(p53)} \otimes \texttt{abs(Mdm2)}) \oplus (\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)})) \otimes \texttt{dont\_care(DNAdam)}$$

We want to prove that from state $\mathcal{L}$ we can only go to state $\mathcal{R}$, *no matter which rule is fired*. Here again, we need *case analysis on the set of fireable rules*:

Proposition (Property 4)**.** *For any world w, for any rule r in the interval* [1..6]*, the following holds:*

$$\dagger\, system \ @\ 0;\ . \vdash \mathcal{L} \to (s\_\texttt{fireable}(r)\ \&\ \delta_1\, \mathcal{R}) \ \oplus\ s\_\texttt{not\_fireable}(r)\ @\ w$$

Property 4 could be written as the CTL formula $\mathsf{AG}(\mathcal{L} \to \mathsf{AX}\mathcal{R})$ (see Sec 6 for the encoding of such a formula in HyLL). Nevertheless, to simplify the proof we can observe that the argument property of AG contains an implication and thus all the possible states verifying the left hand side of the implication should be taken into account in the proof. As a matter of fact, at each step we do not make assumptions on the state where $\mathcal{L}$ holds, we suppose to be in a generic state. The system satisfies Property 4 if all its states satisfy $\mathcal{L} \to \mathsf{AX}\mathcal{R}$. Since in our transition system all the states are reachable from the initial states, this corresponds to requiring the satisfaction of Property 4 at (that is, from) the initial states. In case we want to test such a property at a state S_i that is not connected to all the other states, we only need to prove the property in the subtree of the transition system rooted in S_i. Thus, we are only interested in the set of states reachable from S_i. In HyLL, we should prove the following theorem: *if* $reachable(S, S_i)$ *then* $S \vdash \mathcal{L} \to \forall r \in R\ \delta_1 \mathcal{R}$, where $reachable(S, S_i) \stackrel{\text{def}}{=} \exists u.\ S_i \to \delta_u S$.

5 Formal Proofs

As mentioned, we use a combination of the Coq Proof Assistant and a theorem prover written in the higher-order logic programming language λProlog to formalize the properties presented in the previous section. We first describe the overall approach (Sect. 5.1), and then describe the encoding of the biological system in Coq (Sect. 5.2).

5.1 A Combined Theorem Prover

Our approach is to fully formalize proofs in Coq, using the λProlog prover to help with partial automation of the proofs. The λProlog prover is a tactic-style interactive theorem prover implemented in the manner described in [Fel93], also given as an example in Sect. 9.4 of [MN12]. The code described there can be viewed as a logical framework, implementing a tactic-style architecture. We use this code directly, and instantiate the framework with tactics implementing the basic inference rules of HyLL.

We use Coq for two reasons. First, we can build libraries in Coq that allow us to reason at two levels. We can prove meta-level properties of HyLL (for example, we have formalized Theorem 2 -weakening), and we can reason at the object-level, which in this case means that we can prove HyLL sequents directly. To do so, we adopt the two-level style of reasoning used in Hybrid [FM12] where the logic we want to reason in and about is called the *specification logic* and is implemented as an inductive predicate in Coq. The inductive predicate in this case defines HyLL sequents, and its definition is a fairly direct modification of the ordered linear logic in [FM12]. Second, once a proof is complete, Coq provides a *proof certificate*. In particular, Coq implements the calculus of inductive contstructions (CIC), where a property is stated as a type in CIC and a proof is a λ-term inhabiting that type. This λ-term serves as a certificate, which can be stored and checked independently.

It is, of course, possible to prove the properties in Sect. 4 only using Coq, but in general, proofs in Coq of HyLL sequents quickly become cumbersome because of the amount of detail required to apply each inference rule of HyLL. The λProlog prover is used to automatically infer much of this detail. For example, because

we implement HyLL directly as an inductive predicate in Coq, in order to apply the $\otimes L$ rule (see Figure 1), Coq's `apply` tactic requires arguments to be given explicitly for the instantiation of formulas A and B, world u, and multisets Δ and $\Delta, A \mathbin{@} u, B \mathbin{@} u$. As a result, the Coq proofs are verbose and often contain redundant information. In λProlog on the other hand, our primitive tactics for applying HyLL inference rules use unification to infer these arguments. We could instead program a more automated version of the `apply` tactic in Coq, tailored to applying HyLL rules using Coq's Ltac facility, but this task would likely be more complex and adhoc, since unification is not one of the primitive operations of Coq.

It is also straightforward to represent HyLL proof terms in λProlog, and implement the construction of these proof terms as part of the implementation of the primitive tactics. In our λProlog prover, we construct such proof terms and then translate them to strings representing Coq proof script. This translation is also implemented in λProlog. These automatically generated proof scripts are imported into Coq, and then after some fine-tuning of the script, we obtain a proof certificate for the entire proof.

To illustrate the approach, we briefly summarize our proof of Proposition 4.3.2 (Property 2) using this combined prover. The statement of the property is expressed fairly directly in Coq, and then after a few steps in Coq (very few in this case), the HyLL sequent:

$$\dagger\, system \mathbin{@} 0;\ state_0 \ \otimes\ \mathtt{pres(DNAdam)} \mathbin{@} w \vdash state_0 \otimes \mathtt{abs(DNAdam)} \mathbin{@} w.4$$

is given to the λProlog prover. (Currently this step is done by hand, but we could of course automate the translation of a Coq subgoal to a λProlog one.) In the λProlog version w is an arbitrary constant that does not appear anywhere else in the sequent, generated by the meta-level universal quantifier of λProlog. After the proof is completed, the λProlog prover generates and then outputs the Coq script to a file. This file is imported by hand into the Coq proof and modified slightly using a small number of emacs macros as well as some fine tuning of proofs, mainly about multiset equality. Automating these last details is left for future work.

Note that we do not use λProlog to fully automate proofs; the λProlog prover is also interactive. The user indicates what HyLL rule to apply at each step, possibly with some other basic information such as the position in Δ of the formula to which the rule is to be applied. The arguments needed to apply the rule are then inferred automatically. We could build more automation into the prover, possibly in the style of the linear logic programming language presented in [HM94] for general automation, with the addition of heuristics tailored to our application. Again, this is left for future work.

5.2 Representing the System in Coq

We summarize the encoding of our biological system in Coq. This section fills in some of the details of our approach to formalizing proofs for readers familiar with interactive proof assistants and inductive definitions. Due to space restrictions, we do not describe in detail the formalization of HyLL itself, but instead refer the reader to [FM12], which uses a *higher-order abstract syntax* approach to representing formulas and a specification logic for implementing inference rules, as we do here. We just note here that formulas of HyLL are encoded as an inductive definition called `oo` and `seq` is the inductive predicate defining the inference rules of HyLL. Sequents have the form `(seq Gamma Delta (A @ W))`. In this sequent, `Gamma` is a list of formulas of type `oo` (using the built-in lists of Coq). `Delta` is a multiset of elements of type `oo`, where we build our own custom multiset library. Finally, `A` is a formula (type `oo`) and `W` is a world, where worlds are encoded using Coq's built-in type for natural numbers.

In order to instantiate our encoding of HyLL to the example model we consider here, we must introduce Coq sets representing the variables and the biological system and the predicates expressing presence and absence of these variables. We define both as inductive types, and also add some definitions for some convenient abbreviations. Note that constant names ending in an underscore in the Coq code below represent direct instantiations (whose definitions we omit) of the constants used to define the general version of HyLL. For example, the `atom_` constant is the instantiated version of the part of the HyLL encoding used to coerce atoms (type `atm`) to the instantiated version of HyLL formulas (type `oo_`).

```
Inductive tm:Set := p53 | mdm2 | dNAdam.
Inductive atm:Set := pres_atm: tm -> atm | abs_atm: tm -> atm.
Definition vars := (p53::mdm2::dNAdam::nil).
Definition pres (x:tm): oo_ := (atom_ (pres_atm x)).
Definition abs (x:tm): oo_ := (atom_ (abs_atm x)).
```

Definitions such as those in Sect. 4.3 and Figure 2 are straightforward to encode in Coq. As an example, we show the definition of `dont_care`, both the direct version and the version with multiple variable arguments. The latter is defined recursively using Coq's fixpoint operator. The symbols `+o` and `*o` represent the HyLL connectives $\oplus$ and $\otimes$, respectively.

```
Definition dont_care (t:tm): oo_ := (pres t +o abs t).
Fixpoint dont_cares (V:list tm): oo_ :=
  match V with
  | nil => One
  | (t::nil) => (dont_care t)
  | (t::ts) => ((dont_care t) *o (dont_cares ts))
  end.
```

The definition of `unchanged` is similarly encoded, with `unchanged1` and `unchanged` as the names of the direct and multiple-argument versions, respectively.

We show one example each of an activation/inhibition predicate and rule in Coq:

```
Definition inhib (V:list tm) (a b:tm): oo_ :=
 ((pres a +o (pres a *o pres b) +o (pres a *o abs b)) ->>
  ((step (pres a *o abs b)) *o (Down (fun u => unchanged (minustm_ V (a::b::nil)) u)))).
Definition rule1 := inhib vars dNAdam mdm2.
```

The symbols `->>`, `step`, and `Down` represent the HyLL operators $\rightarrow$, δ_1, and $\downarrow$, respectively. The $\downarrow$ operator binds a variable, and thus its higher-order abstract syntax representation `Down` takes a functional argument. The function `minustm_` implements set difference for type `tm`.

In order to do induction and case analysis on rules, we define `fireable` and `not_fireable` as inductive predicates whose first argument is the rule number. The first clause of the general versions of each is shown below.

```
Inductive fireable: nat -> oo_ -> Prop :=
| f1: fireable 1 ((pres dNAdam +o (pres dNAdam *o pres mdm2) +o (pres dNAdam *o abs mdm2)) *o
                  (dont_care p53))
| ...

Inductive not_fireable: nat -> oo_ -> Prop :=
| nf1: not_fireable 1 (abs dNAdam *o (dont_cares (mdm2::p53::nil)))
| ...
```

To illustrate their use, we state the Coq version of `Gamma` and `PP` are the Coq encodings of (resp.) $\dagger\, system \mathbin{@} 0$ and $(state_0 \otimes \texttt{abs(DNAdam)})$.

```
Theorem Property3 : forall w:world,
  seq Gamma ((PP @ 0)::nil) ((PP at 0) @ w) /\
  forall (n:nat) (A B:oo_), fireable n A -> not_fireable n B ->
  seq Gamma nil ((PP ->> ((A &a step PP) +o B)) @ w).
```

The Coq proof of the second conjunct proceeds by case analysis on `n`, followed by inversion on `(fireable n A)` and `(not_fireable n B)`, which provides instantiations for `A` and `B` (the conditions that express whether the rule is fireable or not). The resulting 6 subgoals are sent to the λProlog prover, whose output is imported back into Coq as described above.

6 Comparison with model checking

While temporal logics such as LTL, CTL, or CTL* have been very successful in practice with efficient model checking tools, the proof theory of these logics is very complex. In contrast, HyLL has a very traditional proof theoretic pedigree: it is presented in the sequent calculus and enjoys cut-elimination and focusing [CD13]. A further advantage of our approach with respect to model checking is that it provides an unified framework to encode both transition rules and (both statements and proofs of) temporal properties.

Let us examine both approaches in more details.

6.1 Temporal Operators

We propose the following encoding of temporal logic operators in HyLL$[\mathcal{T}]$, where $\mathcal{T} = \langle \mathbb{N}, +, 0 \rangle$, representing instants of time. While this domain does not have any branching structure like CTL, it is expressive enough for many common idioms because of the branching structure of derivations involving $\oplus$.

State quantifiers can be easily mapped. There is a clear correspondence between F (resp. G) and $\Diamond$ (resp. $\Box$), see Definition 7. The encodings of X and U are the following ones: $\mathsf{X}P \Leftrightarrow \delta_1 P$ and $P_1 \mathsf{U} P_2 \Leftrightarrow\downarrow u.\ \exists v.\ P_2\ \mathtt{at}\ u.v \otimes \forall w < v.\ P_1\ \mathtt{at}\ u.w.$ where P, P_1, and P_2 are some propositions (not necessarily atomic ones).[2]

As for path quantifiers, the question is more subtle. The idea is that E corresponds to the existence of a proof, while for A it is necessary to look at a proof considering all the possible rules to be applied at each step (at each step of the proof, the chosen rule should not influence the property satisfaction).

We came to the conclusion that the encoding of A in HyLL depends on the state quantifier following it. Let R be the set of rules of our transition system. The mapping we propose is the following one:

- $\mathsf{AX}P$. In HyLL, we write $\forall r \in R\ \delta_1 P$. More precisely, the encoding contemplating fireable rules is $\forall r \in R\ (\mathtt{fireable}(r)\ \&\ \delta_1 P) \oplus \mathtt{not\_fireable}(r)$ (see Sect. 4.3.3). For the sake of simplicity, in the following we omit such details concerning fireable rules.
- $\mathsf{AG}P$. It is equivalent to $P \wedge \mathsf{AG}(P \rightarrow \mathsf{AX}(P))$. In HyLL, we write $P \otimes \forall n(P\ at\ n) \rightarrow \forall r \in R(P\ \text{at}\ n+1)$.
- $\mathsf{AF}P$. It is equivalent to $P \vee \mathsf{AX}(\mathsf{AF}P)$. If we have a bound k on the number of steps needed to satisfy the property, we can expand this formula by obtaining: $P \vee \mathsf{AX}(P \vee \mathsf{AX}(\ldots \mathsf{AX}P))$, with k nested occurrences of AX. In HyLL, we write $P \oplus \forall r \in R(\delta_1 P \oplus (\forall r \in R(\ldots \delta_k P)))$. Notice that another alternative is to express the F operator by using U ($\mathsf{F}P \Leftrightarrow \text{true}\ \mathsf{U}P$).
- $\mathsf{A}(P_1 \mathsf{U} P_2)$. It is equivalent to $P_2 \vee (P_1 \wedge \mathsf{AX}(P_1 \mathsf{U} P_2)$. If we have a bound k on the number of steps needed to satisfy the property, we can expand this formula by obtaining: $P_2 \vee (P_1 \wedge \mathsf{AX}(P_2 \vee (P_1 \wedge \mathsf{AX}(\ldots \mathsf{AX}P_2))))$, with k nested occurrences of AX. In HyLL, we write $P_2 \oplus (P_1 \otimes \forall r \in R(\delta_1 P_2 \oplus (\delta_1 P_1 \otimes \forall r \in R(\ldots \delta_k P_2))))$.

In addition to the future connectives, the domain $\mathcal{T}$ also admits past connectives if we add saturating subtraction (*i. e.*, $a - b = 0$ if $b \geq a$) to the language of worlds. We can then define the duals H (historically) and O (once) of G and F as:

$$\mathsf{H}\ P \stackrel{\text{def}}{=}\downarrow u.\forall w.(P\ \mathtt{at}\ u - w) \qquad \mathsf{O}\ P \stackrel{\text{def}}{=}\downarrow u.\exists w.(P\ \mathtt{at}\ u - w)$$

6.2 Model Checking

A strength of our approach with respect to model checking is that, when we prove an existential property using certain rules of a model, we have the guarantee that *all* the models containing such rules satisfy the property. This is important because in biology we often deal with incomplete information. It is also worth noting that in model checking, all objects are finite: both the number of states, and the number of transitions in the state graph. In HyLL, objects can potentially be infinite; in particular, we can have an infinite number of states.

[2] Observe that a proposition characterizes a set of states.

Let us point out further advantages of our approach with respect to model checking. First of all, when proving a given property we do not need to blindly try all possible rules at each step but we can guide the proof (see section 7). Observe that a successful proof of a given property can be exploited to prove similar properties. Furthermore, suppose we are able to prove a property of the system which is not desirable. In this case the proof we get can help us in understanding what should be modified in the system so that the property is not satisfied. More precisely, we can look for the rules to be removed/modified among those that have been used in the proof. In model checking, when a property turns out to be true, the reason is not investigated. Finally, in [Wol83], temporal logic is extended to allow the expression of properties such as "P is true at every even state of an infinite path." A decision procedure for this extended logic is also defined, but to the best of our knowledge, there is no model checking tool for it. In HyLL, if we add equality on worlds, we can write $\forall n = 2k.\ P\ at\ n$.

Note that in some of the temporal properties we test, there is a bound on the number of time units, and thus on the length of the proof. In this particular case, there is a strong analogy with "bounded model checking" [BCC$^+$03], where the user can limit the length of paths leading from the initial state to states which satisfy the property to be tested. Observe that we could easily couple our model with other models sharing some variables. As an example, we could consider a Boolean model of the cell cycle and add the following linking rules: p53 activates p21 and p21 inhibits CycA and CycE, where the last three compounds belong to the cell cycle model [MFRS11].

A drawback of theorem proving with respect to model checking is that this method can be time consuming and needs an expert. Recent advances in both proof theory and systems however provide us with at least partial, and sometimes complete, automation of the proofs.

7 Conclusion and Future Work

In this paper we argued that the HyLL logic can be successfully exploited for formally verifying Boolean biological systems. This work is a first experiment along this new line of research (although we already provide fully mechanized proofs). We focussed on a simple regulatory network but our framework could be adopted to model several other kinds of biological networks (e.g., neuronal, predator-prey, or ecological networks).

A natural extension of this work consists of applying our methodology to multivalued, continuous, and stochastic biological models. As far as the first case is concerned, the extension is straightforward, we just need to replace present/absent predicates by predicates indicating the discrete values of variables: $\mathtt{C}(A, x)$. The last two cases are more involved. We could try to use the domain of world $\mathcal{W} = \langle \Re^+, +, 0 \rangle$, use predicates $\mathtt{C}$ to represent variable concentrations and express the evolution of each variable in terms of functions involving kinetic expressions such us the mass action law, Hill, or Michaelis-Menten kinetics. [CD13] also discuss several alternatives for the worlds in the probabilistic case. In any case, the challenge would consist of being able to perform symbolic calculus as much as possible without evaluating functions.

With regard to formal proofs, an alternative to using Coq with HyLL implemented as the specification logic is to use Abella [Gac09], which also is a two-level system, with $\mathcal{G}$ as the meta-logic in which one can define a specification logic. This requires replacing Abella's current higher-order intuitionistic specification logic with HyLL and implementing support for building proofs using this logic.

Proofs of properties such as 1 and 2 require finding a path through the system, which here means specifying a series of rules that can be applied in a particular order. At each step, there may be a choice between several potential fireable rules. In the interactive proofs, such choices were made by hand. Our future work includes building automated procedures (e.g., Coq tactics) to guide the proof. We would also like to extend our model to include axioms for events such as those considered in Biocham, which make it possible to change the value of some variables under certain special conditions. Such events often correspond to external inputs and have priority over the ordinary rules of a model.

We were looking for the logical essence of biochemical reactions. What we envision for the domain of "biological computation" is a resource-aware stochastic or probabilistic λ-calculus that has HyLL propositions as (behavioral) types.

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References

[ABI+01] Rajeev Alur, Calin Belta, Franjo Ivanicic, Vijay Kumar, Max Mintz, George J. Pappas, Harvey Rubin, and Jonathan Schug. Hybrid modeling and simulation of biomolecular networks. In Springer-Verlag, editor, *Proceedings of the 4th Intl. Workshop on Hybrid Systems: Computation and Control, HSCC'01*, volume 2034 of *Lecture Notes in Computer Science*, Rome, Italy, 2001.

[BC04] Yves Bertot and Pierre Castéran. *Interactive Theorem Proving and Program Development. Coq'Art: The Calculus of Inductive Constructions*. Springer, 2004.

[BCC+03] Armin Biere, Alessandro Cimatti, Edmund M. Clarke, Ofer Strichman, and Yunshan Zhu. Bounded model checking. In Marvin Zelkowitz, editor, *Highly Dependable Software*, number 58 in Advances in Computers, chapter 3. Academic Press, 2003.

[BFGH04] Michael L. Blinov, James R. Faeder, Byron Goldstein, and William S. Hlavacek. BioNetGen: software for rule-based modeling of signal transduction based on the interactions of molecular domains. *Bioinformatics*, 20(17):3289–3291, 2004. Applications note.

[Boz02] Marco Bozzano. *A Logic-Based Approach to Model Checking of Parameterized and Infinite-State Systems*. PhD thesis, DISI, Università di Genova, 2002.

[CCGR99] Alessandro Cimatti, Edmund M. Clarke, Fausto Giunchiglia, and Marco Roveri. Nusmv: A new symbolic model verifier. In *Proceedings of the 11th Intl. Conference on Computer Aided Verification*, CAV '99, pages 495–499, London, UK, UK, 1999. Springer-Verlag.

[CCP03] Bor-Yuh Evan Chang, Kaustuv Chaudhuri, and Frank Pfenning. A judgmental analysis of linear logic. Technical Report CMU-CS-03-131R, Carnegie Mellon University, December 2003.

[CD13] Kaustuv Chaudhuri and Joëlle Despeyroux. A hybrid linear logic for constrained transition systems with applications to molecular biology. Technical Report inria-00402942, INRIA-HAL, October 2013.

[CGP99] Edmund M. Clarke, Jr., Orna Grumberg, and Doron A. Peled. *Model checking*. MIT Press, Cambridge, MA, USA, 1999.

[CNT05] Andrea Ciliberto, Béla Novák, and John J. Tyson. Steady states and oscillations in the p53/mdm2 network. *Cell Cycle*, 4(3), March 2005.

[CPWW03] Iliano Cervesato, Frank Pfenning, David Walker, and Kevin Watkins. A concurrent logical framework II: Examples and applications. Technical Report CMU-CS-02-102, Carnegie Mellon University, 2003. Revised, May 2003.

[CRCD+04] Nathalie Chabrier-Rivier, Marc Chiaverini, Vincent Danos, François Fages, and Vincent Schächter. Modeling and querying biochemical interaction networks. *Theoretical Computer Science*, 325(1):25–44, September 2004.

[CRSN07] Vijay Chickarmane, Animesh Ray, Herbert M. Sauro, and Ali Nadim. A model for p53 dynamics triggered by dna damage. *SIAM Journal on Applied Dynamical Systems*, 6:61–78, 2007.

[CVWY92] Costas Courcoubetis, Moshe Y. Vardi, Pierre Wolper, and Mihalis Yannakakis. Memory-efficient algorithms for the verification of temporal properties. *Formal Methods in System Design*, 1(2/3):275–288, 1992.

[DC14] Joëlle Despeyroux and Kaustuv Chaudhuri. A hybrid linear logic for constrained transition systems, 2014. To appear in Types for Proofs and Programs, post-proceedings of TYPES 2013, LIPIcs (Leibniz International Proceedings in Informatics).

[DL04] Vincent Danos and Cosimo Laneve. Formal molecular biology. *Theoretical Computer Science*, 325(1):69–110, 2004.

[Eme95] E. Allen Emerson. Temporal and modal logic. In *Handbook of Theoretical Computer Science*, pages 995–1072. Elsevier, 1995.

[Fel93] Amy Felty. Implementing tactics and tacticals in a higher-order logic programming language. *Journal of Automated Reasoning*, 11(1):43–81, August 1993.

[FM12] Amy P. Felty and Alberto Momigliano. Hybrid: A definitional two-level approach to reasoning with higher-order abstract syntax. *Journal of Automated Reasoning*, 48(1):43–105, 2012.

[FS08] François Fages and Sylvain Soliman. Formal cell biology in BIOCHAM. In M. Bernardo, P. Degano, and G. Zavattaro, editors, *8th Intl. School on Formal Methods for the Design of Computer, Communication and Software Systems: Computational Systems Biology SFM'08*, volume 5016 of *Lecture Notes in Computer Science*, pages 54–80, Bertinoro, Italy, February 2008. Springer-Verlag.

[FSCR04] François Fages, Sylvain Soliman, and Nathalie Chabrier-Rivier. Modelling and querying interaction networks in the biochemical abstract machine BIOCHAM. *Journal of Biological Physics and Chemistry*, 4(2), 2004.

[Gac09] Andrew Gacek. *A Framework for Specifying, Prototyping, and Reasoning about Computational Systems*. PhD thesis, University of Minnesota, September 2009.

[Gir87] Jean-Yves. Girard. Linear logic. *Theoretical Computer Science*, 50:1–102, 1987.

[GZRI+06] N. Geva-Zatorsky, N. Rosenfeld, S. Itzkovitz, R. Milo, A. Sigal, E. Dekel, T. Yarnitzky, Y. Liton, P. Polak, G. Lahav, and U. Alon. Oscillations and variability in the p53 system. *Molecular Systems Biology*, 2, 2006.

[HKNP06] Andrew Hinton, Marta Kwiatkowska, Gethin Norman, and David Parker. Prism: A tool for automatic verification of probabilistic systems. In *Proc. 12th Intl. Conference on Tools and Algorithms for the Construction and Analysis of Systems (TACAS'06)*, volume 3920 of *LNCS*. Springer, 2006.

[HM94] Joshua S. Hodas and Dale Miller. Logic programming in a fragment of intuitionistic linear logic. *Journal of Information and Computation*, 110(2):327–365, 1994.

[Hol03] Gerard Holzmann. *Spin Model Checker, the: Primer and Reference Manual*. Addison-Wesley Professional, first edition, 2003.

[HT98] Ralf Hofestädt and S. Thelen. Quantitative modeling of biochemical networks. In *In Silico Biology*, volume 1, pages 39–53. IOS Press, 1998.

[MFRS11] Elisabetta De Maria, François Fages, Aurélien Rizk, and Sylvain Soliman. Design, optimization and predictions of a coupled model of the cell cycle, circadian clock, dna repair system, irinotecan metabolism and exposure control under temporal logic constraints. *Theor. Comput. Sci.*, 412(21):2108–2127, 2011.

[Mil93] Dale Miller. The π-calculus as a theory in linear logic: Preliminary results. In *3rd Workshop on Extensions to Logic Programming*, number 660 in LNCS, pages 242–265. Springer, 1993.

[ML96] Per Martin-Löf. On the meanings of the logical constants and the justifications of the logical laws. *Nordic Journal of Philosophical Logic*, 1(1):11–60, 1996. Lecture notes to a short course at Università degli Studi di Siena, April 1983.

[MN12] Dale Miller and Gopalan Nadathur. *Programming with Higher-Order Logic*. Cambridge University Press, 2012.

[PC05] Andrew Phillips and Luca Cardelli. A correct abstract machine for the stochastic pi-calculus. *Transactions on Computational Systems Biology*, 2005. Special issue of BioConcur 2004.

[RML93] V. N. Reddy, M. L. Mavrovouniotis, and M. N. Liebman. Petri net representations in metabolic pathways. In *Proceedings of the 1st Intl. Conference on Intelligent Systems for Molecular Biology (ISMB)*, pages 328–336. AAAI Press, 1993.

[RPS+04] Aviv Regev, Ekaterina M. Panina, William Silverman, Luca Cardelli, and Ehud Shapiro. Bioambients: An abstraction for biological compartments. *Theoretical Computer Science*, 325(1):141–167, September 2004.

[RSS01] Aviv Regev, William Silverman, and Ehud Y. Shapiro. Representation and simulation of biochemical processes using the pi-calculus process algebra. In *Proceedings of the sixth Pacific Symposium of Biocomputing*, 2001.

[SP07] Uluç Saranli and Frank Pfenning. Using constrained intuitionistic linear logic for hybrid robotic planning problems. In *IEEE Intl. Conference on Robotics and Automation (ICRA)*, pages 3705–3710. IEEE, 2007.

[SP08] Robert J. Simmons and Frank Pfenning. Linear logical algorithms. In Luca Aceto, Ivan Damgård, Leslie Ann Goldberg, Magnús M. Halldórsson, Anna Ingólfsdóttir, and Igor Walukiewicz, editors, *ICALP 2008: 35th Intl. Colloquium Automata, Languages and Programming, Reykjavik, Iceland*, volume 5126 of *Lecture Notes in Computer Science*, pages 336–347. Springer, July 2008.

[Tho73] René Thomas. Boolean formalization of genetic control circuits. *Journal of Theoretical Biology*, 42(3):563–85, December 1973.

[TTK95] René Thomas, Denis Thieffry, and Marcelle Kaufman. Dynamical behaviour of biological regulatory networks-i. biological role of feedback loops and practical use of the concept of the loop-characteristic state. *Bulletin of Mathematical Biology*, 57(2):247–276, 1995.

[Wol83] Pierre Wolper. Temporal logic can be more expressive. *Information and Control*, 56(1/2):72–99, 1983.

A Example Specification in HyLL

A.1 Strong Rules

- *Variables*:

$$\texttt{unchanged}(x,w) \stackrel{\text{def}}{=} \,!\,[(\texttt{pres}(x)\ \texttt{at}\ w \to \texttt{pres}(x)\ \texttt{at}\ w.1)\ \ \&\ \ (\texttt{abs}(x)\ \texttt{at}\ w \to \texttt{abs}(x)\ \texttt{at}\ w.1)].$$
$$\texttt{unchanged}(V,w) \stackrel{\text{def}}{=} \otimes_{x\in V}\texttt{unchanged}(x,w).$$

- *Activation*:

$$s\_\texttt{active}(V,a,b) \stackrel{\text{def}}{=} \texttt{pres}(a)\otimes\texttt{abs}(b) \to \delta_1(\texttt{pres}(a)\otimes\texttt{pres}(b))\otimes\downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).$$

- *Activation with consumption*:

$$s\_\texttt{active}_c(V,a,b) \stackrel{\text{def}}{=} \texttt{pres}(a)\otimes\texttt{abs}(b) \to \delta_1(\texttt{abs}(a)\otimes\texttt{pres}(b)))\otimes\downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).$$

- *Strong activation*:

$$s\_\texttt{active}_s(V,a,b) \stackrel{\text{def}}{=} \texttt{abs}(a)\otimes\texttt{pres}(b) \to \delta_1(\texttt{abs}(a)\otimes\texttt{abs}(b))\otimes\downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).$$

- *Inhibition*:

$$s\_\texttt{inhib}(V,a,b) \stackrel{\text{def}}{=} \texttt{pres}(a)\otimes\texttt{pres}(b) \to \delta_1(\texttt{pres}(a)\otimes\texttt{abs}(b))\otimes\downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).$$

- *Inhibition with consumption*:

$$s\_\texttt{inhib}_c(V,a,b) \stackrel{\text{def}}{=} \texttt{pres}(a)\otimes\texttt{pres}(b) \to \delta_1(\texttt{abs}(a)\otimes\texttt{abs}(b))\otimes\downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).$$

- *Strong inhibition*:

$$s\_\texttt{inhib}_s(V,a,b) \stackrel{\text{def}}{=} \texttt{abs}(a)\otimes\texttt{abs}(b) \to \delta_1(\texttt{abs}(a)\otimes\texttt{pres}(b))\otimes\downarrow u.\ \texttt{unchanged}(V\setminus\{a,b\},u)).$$

- *Well definedness*:

$$\texttt{well\_defined}_0(V) \stackrel{\text{def}}{=} \forall a\in V.\ [\texttt{pres}(a)\otimes\texttt{abs}(a)\to 0].$$
$$\texttt{well\_defined}_1(V) \stackrel{\text{def}}{=} \forall a\in V.\ [\texttt{pres}(a)\oplus\texttt{abs}(a)].$$
$$\texttt{well\_defined}(V) \stackrel{\text{def}}{=} \texttt{well\_defined}_0(V),\texttt{well\_defined}_1(V).$$

- *The system*

$$\begin{aligned}
\texttt{vars} &\stackrel{\text{def}}{=} \{\texttt{p53},\texttt{Mdm2},\texttt{DNAdam}\}\\
s_\texttt{rule}(1) &\stackrel{\text{def}}{=} s_\texttt{inhib}(\texttt{vars},\texttt{DNAdam},\texttt{Mdm2})\\
&\stackrel{\text{def}}{=} \texttt{pres}(\texttt{DNAdam})\otimes\texttt{pres}(\texttt{Mdm2})\to\delta_1(\texttt{pres}(\texttt{DNAdam})\otimes\texttt{abs}(\texttt{Mdm2}))\otimes\downarrow u.\ \texttt{unchanged}(\texttt{p53},u)\\
s_\texttt{rule}(2) &\stackrel{\text{def}}{=} \texttt{Inhib}_\texttt{s}(\texttt{vars},\texttt{Mdm2},\texttt{p53})\\
&\stackrel{\text{def}}{=} \texttt{abs}(\texttt{Mdm2})\otimes\texttt{abs}(\texttt{p53})\to\delta_1(\texttt{abs}(\texttt{Mdm2})\otimes\texttt{pres}(\texttt{p53}))\otimes\downarrow u.\ \texttt{unchanged}(\texttt{DNAdam},u))\\
s_\texttt{rule}(3) &\stackrel{\text{def}}{=} s_\texttt{active}(\texttt{vars},\texttt{p53},\texttt{Mdm2})\\
&\stackrel{\text{def}}{=} \texttt{pres}(\texttt{p53})\otimes\texttt{abs}(\texttt{Mdm2})\to\delta_1(\texttt{pres}(\texttt{p53})\otimes\texttt{pres}(\texttt{Mdm2}))\otimes\downarrow u.\ \texttt{unchanged}(\texttt{DNAdam},u))\\
s_\texttt{rule}(4) &\stackrel{\text{def}}{=} s_\texttt{inhib}(\texttt{vars},\texttt{Mdm2},\texttt{p53})\\
&\stackrel{\text{def}}{=} \texttt{pres}(\texttt{Mdm2})\otimes\texttt{pres}(\texttt{p53})\to\delta_1(\texttt{pres}(\texttt{Mdm2})\otimes\texttt{abs}(\texttt{p53}))\otimes\downarrow u.\ \texttt{unchanged}(\texttt{DNAdam},u))\\
s_\texttt{rule}(5) &\stackrel{\text{def}}{=} \texttt{Inhib}_\texttt{c}(\texttt{vars},\texttt{p53},\texttt{DNAdam})\\
&\stackrel{\text{def}}{=} \texttt{pres}(\texttt{p53})\otimes\texttt{pres}(\texttt{DNAdam})\to\delta_1(\texttt{abs}(\texttt{p53})\otimes\texttt{abs}(\texttt{DNAdam}))\otimes\downarrow u.\ \texttt{unchanged}(\texttt{Mdm2},u))
\end{aligned}$$

$$s\_\mathtt{rule}(6) \stackrel{\text{def}}{=} \mathtt{Inhib_s}(\mathtt{vars}, \mathtt{DNAdam}, \mathtt{Mdm2})$$
$$\stackrel{\text{def}}{=} \mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2}) \to \delta_1(\mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2})) \otimes \downarrow u.\ \mathtt{unchanged}(\mathtt{p53}, u))$$

$$\mathtt{system} \stackrel{\text{def}}{=} \mathtt{vars}, s\_\mathtt{rule}(1), s\_\mathtt{rule}(2), s\_\mathtt{rule}(3), s\_\mathtt{rule}(4), s\_\mathtt{rule}(5), s\_\mathtt{rule}(6), \mathtt{well\_defined}(\mathtt{vars}).$$

- *Initial state*:

$$\mathtt{initial\_state} \stackrel{\text{def}}{=} \mathtt{abs}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{Mdm2}),$$
$$\mathtt{initial\_state}\ \mathtt{at}\ 0.$$

- *Hypothesis (with strong rules)*:

$$\mathtt{dont\_care}(x) \stackrel{\text{def}}{=} \mathtt{pres}(x) \oplus \mathtt{abs}(x)$$
$$\mathtt{dont\_care}(V) \stackrel{\text{def}}{=} \otimes_{x \in V} \mathtt{dont\_care}(x)$$

$$s\_\mathtt{fireable}(1) \stackrel{\text{def}}{=} \mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2}) \otimes \mathtt{dont\_care}(\mathtt{p53})$$
$$s\_\mathtt{fireable}(2) \stackrel{\text{def}}{=} \mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{abs}(\mathtt{p53}) \otimes \mathtt{dont\_care}(\mathtt{DNAdam})$$
$$s\_\mathtt{fireable}(3) \stackrel{\text{def}}{=} \mathtt{pres}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{dont\_care}(\mathtt{DNAdam})$$
$$s\_\mathtt{fireable}(4) \stackrel{\text{def}}{=} \mathtt{pres}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53}) \otimes \mathtt{dont\_care}(\mathtt{DNAdam})$$
$$s\_\mathtt{fireable}(5) \stackrel{\text{def}}{=} \mathtt{pres}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{dont\_care}(\mathtt{Mdm2})$$
$$s\_\mathtt{fireable}(6) \stackrel{\text{def}}{=} \mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{dont\_care}(\mathtt{p53})$$

$$s\_\mathtt{not\_fireable}(1) \stackrel{\text{def}}{=}$$
$$((\mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2})) \oplus (\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2})) \oplus (\mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2}))) \otimes \mathtt{dont\_care}(\mathtt{p53})$$
$$s\_\mathtt{not\_fireable}(2) \stackrel{\text{def}}{=}$$
$$((\mathtt{pres}(\mathtt{Mdm2}) \otimes \mathtt{abs}(\mathtt{p53})) \oplus (\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \oplus (\mathtt{pres}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \otimes \mathtt{dont\_care}(\mathtt{DNAdam})$$
$$s\_\mathtt{not\_fireable}(3) \stackrel{\text{def}}{=}$$
$$((\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2})) \oplus (\mathtt{pres}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{Mdm2})) \oplus (\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{Mdm2}))) \otimes \mathtt{dont\_care}(\mathtt{DNAdam})$$
$$s\_\mathtt{not\_fireable}(4) \stackrel{\text{def}}{=}$$
$$((\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \oplus (\mathtt{pres}(\mathtt{Mdm2}) \otimes \mathtt{abs}(\mathtt{p53})) \oplus (\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{abs}(\mathtt{p53}))) \otimes \mathtt{dont\_care}(\mathtt{DNAdam})$$
$$s\_\mathtt{not\_fireable}(5) \stackrel{\text{def}}{=}$$
$$((\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{DNAdam})) \oplus (\mathtt{pres}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{DNAdam})) \oplus (\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{DNAdam}))) \otimes \mathtt{dont\_care}(\mathtt{Mdm2})$$
$$s\_\mathtt{not\_fireable}(6) \stackrel{\text{def}}{=}$$
$$((\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2})) \oplus (\mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2})) \oplus (\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2}))) \otimes \mathtt{dont\_care}(\mathtt{p53})$$

A.2 General Rules

- *Variables*:

$$\texttt{unchanged}(x, w) \stackrel{\text{def}}{=} \,!\,[(\texttt{pres}(x)\ \texttt{at}\ w \to \texttt{pres}(x)\ \texttt{at}\ w.1)\ \ \&\ \ (\texttt{abs}(x)\ \texttt{at}\ w \to \texttt{abs}(x)\ \texttt{at}\ w.1)].$$
$$\texttt{unchanged}(V, w) \stackrel{\text{def}}{=} \otimes_{x \in V} \texttt{unchanged}(x, w).$$

- *Activation*:

$$\begin{aligned}\texttt{active}(V, a, b) \stackrel{\text{def}}{=}\ & (\texttt{pres}(a) \oplus (\texttt{pres}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{pres}(a) \otimes \texttt{abs}(b))) \\ & \to \delta_1\ \ (\texttt{pres}(a) \otimes \texttt{pres}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V \setminus \{a, b\}, u)).\end{aligned}$$

- *Activation with consumption*:

$$\begin{aligned}\texttt{active}_c(V, a, b) \stackrel{\text{def}}{=}\ & (\texttt{pres}(a) \oplus (\texttt{pres}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{pres}(a) \otimes \texttt{abs}(b))) \\ & \to \delta_1\ \ (\texttt{abs}(a) \otimes \texttt{pres}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V \setminus \{a, b\}, u)).\end{aligned}$$

- *Strong activation*:

$$\begin{aligned}\texttt{active}_s(V, a, b) \stackrel{\text{def}}{=}\ & (\texttt{abs}(a) \oplus (\texttt{abs}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{abs}(a) \otimes \texttt{abs}(b))) \\ & \to \delta_1\ \ (\texttt{abs}(a) \otimes \texttt{abs}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V \setminus \{a, b\}, u)).\end{aligned}$$

- *Inhibition*:

$$\begin{aligned}\texttt{inhib}(V, a, b) \stackrel{\text{def}}{=}\ & (\texttt{pres}(a) \oplus (\texttt{pres}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{pres}(a) \otimes \texttt{abs}(b))) \\ & \to \delta_1\ \ (\texttt{pres}(a) \otimes \texttt{abs}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V \setminus \{a, b\}, u)).\end{aligned}$$

- *Inhibition with consumption*:

$$\begin{aligned}\texttt{inhib}_c(V, a, b) \stackrel{\text{def}}{=}\ & (\texttt{pres}(a) \oplus (\texttt{pres}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{pres}(a) \otimes \texttt{abs}(b))) \\ & \to \delta_1\ \ (\texttt{abs}(a) \otimes \texttt{abs}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V \setminus \{a, b\}, u)).\end{aligned}$$

- *Strong inhibition*:

$$\begin{aligned}\texttt{inhib}_s(V, a, b) \stackrel{\text{def}}{=}\ & (\texttt{abs}(a) \oplus (\texttt{abs}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{abs}(a) \otimes \texttt{abs}(b))) \\ & \to \delta_1\ \ (\texttt{abs}(a) \otimes \texttt{pres}(b)) \otimes \downarrow u.\ \texttt{unchanged}(V \setminus \{a, b\}, u)).\end{aligned}$$

- *Well definedness*:

$$\texttt{well\_defined}_0(V) \stackrel{\text{def}}{=} \forall a \in V.\ [\texttt{pres}(a) \otimes \texttt{abs}(a) \to 0].$$
$$\texttt{well\_defined}_1(V) \stackrel{\text{def}}{=} \forall a \in V.\ [\texttt{pres}(a) \oplus \texttt{abs}(a)].$$
$$\texttt{well\_defined}(V) \stackrel{\text{def}}{=} \texttt{well\_defined}_0(V), \texttt{well\_defined}_1(V).$$

- *The system*

$$\begin{aligned}\texttt{vars} &\stackrel{\text{def}}{=} \{\texttt{p53}, \texttt{Mdm2}, \texttt{DNAdam}\} \\ \texttt{rule}(1) &\stackrel{\text{def}}{=} \texttt{inhib}(\texttt{vars}, \texttt{DNAdam}, \texttt{Mdm2}) \\ &\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{DNAdam}) \oplus (\texttt{pres}(\texttt{DNAdam}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{pres}(\texttt{DNAdam}) \otimes \texttt{abs}(\texttt{Mdm2}))) \\ &\quad \to \delta_1(\texttt{pres}(\texttt{DNAdam}) \otimes \texttt{abs}(\texttt{Mdm2})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{p53}, u) \\ \texttt{rule}(2) &\stackrel{\text{def}}{=} \texttt{inhib}_\texttt{s}(\texttt{vars}, \texttt{Mdm2}, \texttt{p53}) \\ &\stackrel{\text{def}}{=} (\texttt{abs}(\texttt{Mdm2}) \oplus (\texttt{abs}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53})) \oplus (\texttt{abs}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53}))) \\ &\quad \to \delta_1(\texttt{abs}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{DNAdam}, u))\end{aligned}$$

$$
\begin{aligned}
\texttt{rule}(3) &\stackrel{\text{def}}{=} \texttt{active}(\texttt{vars}, \texttt{p53}, \texttt{Mdm2}) \\
&\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{p53}) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{Mdm2}))) \\
&\quad \rightarrow \delta_1(\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{DNAdam}, u)) \\
\texttt{rule}(4) &\stackrel{\text{def}}{=} \texttt{inhib}(\texttt{vars}, \texttt{Mdm2}, \texttt{p53}) \\
&\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{Mdm2}) \oplus (\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53})) \oplus (\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53}))) \\
&\quad \rightarrow \delta_1(\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{DNAdam}, u)) \\
\texttt{rule}(5) &\stackrel{\text{def}}{=} \texttt{inhib}_{\texttt{c}}(\texttt{vars}, \texttt{p53}, \texttt{DNAdam}) \\
&\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{p53}) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{DNAdam})) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{DNAdam}))) \\
&\quad \rightarrow \delta_1(\texttt{abs}(\texttt{p53}) \otimes \texttt{abs}(\texttt{DNAdam})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{Mdm2}, u)) \\
\texttt{rule}(6) &\stackrel{\text{def}}{=} \texttt{inhib}_{\texttt{s}}(\texttt{vars}, \texttt{DNAdam}, \texttt{Mdm2}) \\
&\stackrel{\text{def}}{=} (\texttt{abs}(\texttt{DNAdam}) \oplus (\texttt{abs}(\texttt{DNAdam}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{abs}(\texttt{DNAdam}) \otimes \texttt{abs}(\texttt{Mdm2}))) \\
&\quad \rightarrow \delta_1(\texttt{abs}(\texttt{DNAdam}) \otimes \texttt{pres}(\texttt{Mdm2})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{p53}, u))
\end{aligned}
$$

$$
\texttt{system} \stackrel{\text{def}}{=} \texttt{vars}, \texttt{rule}(1), \texttt{rule}(2), \texttt{rule}(3), \texttt{rule}(4), \texttt{rule}(5), \texttt{rule}(6), \texttt{well\_defined}(\texttt{vars}).
$$

- *Initial state*:

$$
\begin{aligned}
&\texttt{initial\_state} \stackrel{\text{def}}{=} \texttt{abs}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2}), \\
&\texttt{initial\_state at } 0.
\end{aligned}
$$

- *Hypothesis*:

$$
\begin{aligned}
&\texttt{dont\_care}(x) \stackrel{\text{def}}{=} \texttt{pres}(x) \oplus \texttt{abs}(x) \\
&\texttt{dont\_care}(V) \stackrel{\text{def}}{=} \otimes_{x \in V} \texttt{dont\_care}(x)
\end{aligned}
$$

$$
\begin{aligned}
\texttt{fireable}(1) &\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{DNAdam}) \oplus (\texttt{pres}(\texttt{DNAdam}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{pres}(\texttt{DNAdam}) \otimes \texttt{abs}(\texttt{Mdm2}))) \otimes \texttt{dont\_care}(\texttt{p53}) \\
\texttt{fireable}(2) &\stackrel{\text{def}}{=} (\texttt{abs}(\texttt{Mdm2}) \oplus (\texttt{abs}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53})) \oplus (\texttt{abs}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53}))) \otimes \texttt{dont\_care}(\texttt{DNAdam}) \\
\texttt{fireable}(3) &\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{p53}) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{Mdm2}))) \otimes \texttt{dont\_care}(\texttt{DNAdam}) \\
\texttt{fireable}(4) &\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{Mdm2}) \oplus (\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53})) \oplus (\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53}))) \otimes \texttt{dont\_care}(\texttt{DNAdam}) \\
\texttt{fireable}(5) &\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{p53}) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{DNAdam})) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{DNAdam}))) \otimes \texttt{dont\_care}(\texttt{Mdm2}) \\
\texttt{fireable}(6) &\stackrel{\text{def}}{=} (\texttt{abs}(\texttt{DNAdam}) \oplus (\texttt{abs}(\texttt{DNAdam}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{abs}(\texttt{DNAdam}) \otimes \texttt{abs}(\texttt{Mdm2}))) \otimes \texttt{dont\_care}(\texttt{p53})
\end{aligned}
$$

$$
\begin{aligned}
&\texttt{not\_fireable}(1) \stackrel{\text{def}}{=} \texttt{abs}(\texttt{DNAdam}) \otimes \texttt{dont\_care}(\{\texttt{Mdm2}, \texttt{p53}\}) \\
&\texttt{not\_fireable}(2) \stackrel{\text{def}}{=} \texttt{pres}(\texttt{Mdm2}) \otimes \texttt{dont\_care}(\{\texttt{p53}, \texttt{DNAdam}\}) \\
&\texttt{not\_fireable}(3) \stackrel{\text{def}}{=} \texttt{abs}(\texttt{p53}) \otimes \texttt{dont\_care}(\{\texttt{Mdm2}, \texttt{DNAdam}\}) \\
&\texttt{not\_fireable}(4) \stackrel{\text{def}}{=} \texttt{abs}(\texttt{Mdm2}) \otimes \texttt{dont\_care}(\{\texttt{p53}, \texttt{DNAdam}\}) \\
&\texttt{not\_fireable}(5) \stackrel{\text{def}}{=} \texttt{abs}(\texttt{p53}) \otimes \texttt{dont\_care}(\{\texttt{DNAdam}, \texttt{Mdm2}\}) \\
&\texttt{not\_fireable}(6) \stackrel{\text{def}}{=} \texttt{pres}(\texttt{DNAdam}) \otimes \texttt{dont\_care}(\{\texttt{Mdm2}, \texttt{p53}\})
\end{aligned}
$$

B Example Proofs

In most of the following proofs, we omit the intuitionistic constant environment $\dagger\, system \ @\ 0$ (from which we can deduce $system \ @\ w$ at any state w). We also omit trivial proofs (called "hyp") consisting in using hypothesis from the (intuitionistic or linear) context.

Note that several proofs implicitly use the `unchanged` predicate, which, for example, enable to pr'ove $\mathtt{abs(p53)} \ @\ w.1$ from $\mathtt{abs(p53)} \ @\ w$ in the P_1 part of the proof of Property 1. We shall also sometimes need (and implicitly use) the `well_defined` hypothesis $\forall a.\ \mathtt{pres}(a) \oplus \mathtt{abs}(a)$ (see the proof of Property 4).

B.1 Property 1

As long as there is DNA damage, the above system can oscillate (with a short period) from $state_0$ to $state_1$ and back again.

From $state_0$ and $\mathtt{pres(DNAdam)}$ we get $\mathtt{abs(p53)}$, $\mathtt{abs(Mdm2)}$, and $\mathtt{pres(DNAdam)}$ by rule 1. Then $\mathtt{pres(p53)}$, $\mathtt{abs(Mdm2)}$, and $\mathtt{pres(DNAdam)}$ ($state_1$) by rule 2. Then $\mathtt{pres(p53)}$, $\mathtt{pres(Mdm2)}$, and $\mathtt{pres(DNAdam)}$ by rule 3, and finally $\mathtt{abs(p53)}$, $\mathtt{pres(Mdm2)}$, and $\mathtt{pres(DNAdam)}$ ($state_0$) by rule 4.

Proposition (Property 1, Version 1)**.** *For any world w, there exists two worlds u and v such that both u and v are less than 3 and the following holds:*

$$\dagger\, system \ @\ 0 \ ;\ state_0 \ \otimes\ \mathtt{pres(DNAdam)} \ @\ w \\ \vdash \delta_u\ [(state_1 \ \otimes\ \mathtt{dont\_care(DNAdam)})\ \&\ (\delta_v\ (state_0 \ \otimes\ \mathtt{dont\_care(DNAdam)}))] \ @\ w$$

Proof. Let S_0 denote $state_0 \ \otimes\ \mathtt{pres(DNAdam)}$ where $state_0$ is $\mathtt{abs(p53)} \otimes \mathtt{pres(Mdm2)}$
in

$$\dfrac{\dfrac{P_1}{S_0 \ @\ w \vdash state_1 \ \otimes\ \mathtt{dont\_care(DNAdam)} \ @\ w.u} \qquad \dfrac{\dfrac{P_2}{S_0 \ @\ w \vdash state_0 \ \otimes\ \mathtt{dont\_care(DNAdam)} \ @\ w.u.v}}{S_0 \ @\ w \vdash \delta_v\ (state_0 \ \otimes\ \mathtt{dont\_care(DNAdam)}) \ @\ w.u}\ \&R}{S_0 \ @\ w \vdash (state_1 \ \otimes\ \mathtt{dont\_care(DNAdam)})\ \&\ \delta_v\ (state_0 \ \otimes\ \mathtt{dont\_care(DNAdam)}) \ @\ w.u}}{S_0 \ @\ w \vdash \delta_u\ [(state_1 \ \otimes\ \mathtt{dont\_care(DNAdam)})\ \&\ (\delta_v\ (state_0 \ \otimes\ \mathtt{dont\_care(DNAdam)}))] \ @\ w}$$

where P_1 is
let us remind that

$$\begin{aligned} \mathtt{rule}(1) &\stackrel{\text{def}}{=} \mathtt{inhib}(\mathtt{vars}, \mathtt{DNAdam}, \mathtt{Mdm2}) \\ &\stackrel{\text{def}}{=} (\mathtt{pres(DNAdam)} \oplus (\mathtt{pres(DNAdam)} \otimes \mathtt{pres(Mdm2)}) \oplus (\mathtt{pres(DNAdam)} \otimes \mathtt{abs(Mdm2)})) \\ &\quad \to \delta_1(\mathtt{pres(DNAdam)} \otimes \mathtt{abs(Mdm2)}) \otimes \downarrow u.\ \mathtt{unchanged(p53}, u), \end{aligned}$$

let H_1 denote $\mathtt{pres(DNAdam)} \oplus (\mathtt{pres(DNAdam)} \otimes \mathtt{pres(Mdm2)}) \oplus (\mathtt{pres(DNAdam)} \otimes \mathtt{abs(Mdm2)})$ (hyp. of $\mathtt{rule}(1)$),
C_1 denote $\delta_1(\mathtt{pres(DNAdam)} \otimes \mathtt{abs(Mdm2)}) \otimes \downarrow u.\ \mathtt{unchanged(p53}, u)$ (conclusion of $\mathtt{rule}(1)$),
and R_1 denote $state_1 \ \otimes\ \mathtt{dont\_care(DNAdam)}$ where $state_1$ is $\mathtt{pres(p53)}$, $\mathtt{abs(Mdm2)}$
in

$$\dfrac{\dfrac{\ldots \vdash \mathtt{pres(DNAdam)} \otimes \mathtt{pres(Mdm2)} \ @\ w}{\mathtt{pres(Mdm2)} \otimes \mathtt{pres(DNAdam)} \ @\ w \vdash H_1 \ @\ w}\ \oplus R_1 \qquad \dfrac{P_{11}}{\mathtt{abs(p53)} \ @\ w,\ C_1 \ @\ w \vdash R_1 \ @\ w.u}}{\mathtt{abs(p53)} \otimes \mathtt{pres(Mdm2)} \otimes \mathtt{pres(DNAdam)} \ @\ w, \mathtt{rule}(1) \ @\ w \vdash state_1 \ \otimes\ \mathtt{dont\_care(DNAdam)} \ @\ w.u}\ \to L$$

with P_{11}

$$\dfrac{\dfrac{P_{12}}{\mathtt{abs(p53)} \otimes \mathtt{abs(Mdm2)} \otimes \mathtt{pres(DNAdam)} \ @\ w.1 \vdash R_1 \ @\ w.u}}{\mathtt{abs(p53)} \ @\ w,\ \mathtt{pres(DNAdam)} \otimes \mathtt{abs(Mdm2)} \ @\ w.1,\ \mathtt{unchanged(p53}, w) \ @\ w \vdash R_1 \ @\ w.u}$$

P_{12}:
let us remind that
$\mathtt{rule}(2) \stackrel{\text{def}}{=} \mathtt{inhib_s}(\mathtt{vars}, \mathtt{Mdm2}, \mathtt{p53})$
$\stackrel{\text{def}}{=} (\mathtt{abs}(\mathtt{Mdm2}) \oplus (\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \oplus (\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{abs}(\mathtt{p53})))$
$\quad \to \delta_1(\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \otimes \downarrow u.\ \mathtt{unchanged}(\mathtt{DNAdam}, u))$,
let H_2 denote $\mathtt{abs}(\mathtt{Mdm2}) \oplus (\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \oplus (\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{abs}(\mathtt{p53}))$ (hypothesis of $\mathtt{rule}(2)$),
and C_2 denote $\delta_1(\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \otimes \downarrow u.\ \mathtt{unchanged}(\mathtt{DNAdam}, u))$ (conclusion of $\mathtt{rule}(2)$),
in

$$\dfrac{\dfrac{\ldots \vdash \mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2})\ @\ w.1}{\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2})\ @\ w.1 \vdash H_2\ @\ w.1}\ P_{12c}}{\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{DNAdam})\ @\ w.1,\ \mathtt{rule}(2)\ @\ w.1 \vdash R_1\ @\ w.u}\ \to L$$

with P_{12c}:

$$\dfrac{\dfrac{state_1\ @\ w.2 \vdash state_1\ @\ w.2 \quad \mathtt{pres}(\mathtt{DNAdam})\ @\ w.2 \vdash \mathtt{dont\_care}(\mathtt{DNAdam})\ @\ w.2\ [u = 2]}{\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{DNAdam})\ @\ w.2 \vdash R_1\ @\ w.u}\ \otimes R}{\dfrac{\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})\ @\ w.2,\ \mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{unchanged}(\mathtt{DNAdam}, w.1)\ @\ w.1 \vdash R_1\ @\ w.u}{\mathtt{pres}(\mathtt{DNAdam}) \otimes C_2\ @\ w.1 \vdash R_1\ @\ w.u}}$$

and P_2 is
(P_2 is P_1 where $R_1\ @\ w.u$ is replaced by $R_2\ @\ w.u.v$ and P_{12c} is replaced by P_{23}.)
let H_1 denote $\mathtt{pres}(\mathtt{DNAdam}) \oplus (\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2})) \oplus (\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2}))$ (hyp. of $\mathtt{rule}(1)$),
C_1 denote $\delta_1(\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2})) \otimes \downarrow u.\ \mathtt{unchanged}(\mathtt{p53}, u)$ (conclusion of $\mathtt{rule}(1)$),
and R_2 denote $state_0 \otimes \mathtt{dont\_care}(\mathtt{DNAdam})$ where $state_p$ is $\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{Mdm2})$
in

$$\dfrac{\dfrac{\ldots \vdash \mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2})\ @\ w}{\mathtt{pres}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{DNAdam})\ @\ w \vdash H_1\ @\ w}\ \oplus R_1 \qquad \dfrac{P_{21}}{\mathtt{abs}(\mathtt{p53})\ @\ w,\ C_1\ @\ w \vdash R_2\ @\ w.u.v}}{\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{DNAdam})\ @\ w, \mathtt{rule}(1)\ @\ w \vdash state_0 \otimes \mathtt{dont\_care}(\mathtt{DNAdam})\ @\ w.u}\ \to L$$

with P_{21}

$$\dfrac{\dfrac{P_{22}}{\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{DNAdam})\ @\ w.1 \vdash R_2\ @\ w.u.v}}{\mathtt{abs}(\mathtt{p53})\ @\ w,\ \mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2})\ @\ w.1,\ \mathtt{unchanged}(\mathtt{p53}, w)\ @\ w \vdash R_2\ @\ w.u.v}$$

P_{22}:
let H_2 denote $(\mathtt{abs}(\mathtt{Mdm2}) \oplus (\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \oplus (\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{abs}(\mathtt{p53})))$ (hypothesis of $\mathtt{rule}(2)$),
and C_2 denote $\delta_1(\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})) \otimes \downarrow u.\ \mathtt{unchanged}(\mathtt{DNAdam}, u))$ (conclusion of $\mathtt{rule}(2)$),
in

$$\dfrac{\dfrac{\ldots \vdash \mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2})\ @\ w.1}{\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2})\ @\ w.1 \vdash H_2\ @\ w.1}\ P_{22c}}{\mathtt{abs}(\mathtt{p53}) \otimes \mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{DNAdam})\ @\ w.1,\ \mathtt{rule}(2)\ @\ w.1 \vdash R_2\ @\ w.u.v}\ \to L$$

with P_{22c}:

$$\dfrac{\dfrac{P_{23}}{\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53}) \otimes \mathtt{pres}(\mathtt{DNAdam})\ @\ w.2 \vdash R_2\ @\ w.u.v}}{\dfrac{\mathtt{abs}(\mathtt{Mdm2}) \otimes \mathtt{pres}(\mathtt{p53})\ @\ w.2,\ \mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{unchanged}(\mathtt{DNAdam}, w.1)\ @\ w.1 \vdash R_2\ @\ w.u.v}{\mathtt{pres}(\mathtt{DNAdam}) \otimes C_2\ @\ w.1 \vdash R_2\ @\ w.u}}$$

P_{23}:
let us remind that
$\texttt{rule}(3) \stackrel{\text{def}}{=} \texttt{active}(\texttt{vars}, \texttt{p53}, \texttt{Mdm2})$
$\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{p53}) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{Mdm2})))$
$\rightarrow \delta_1(\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{DNAdam}, u))$,
let H_3 denote $\texttt{pres}(\texttt{p53}) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{Mdm2}))$ (hyp. of $\texttt{rule}(3)$),
and C_3 denote $\delta_1(\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{DNAdam}, u))$ (conclusion of $\texttt{rule}(3)$)
in

$$\dfrac{\dfrac{\ldots \vdash \texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{Mdm2}) \ @\ w.2}{\texttt{abs}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53}) \ @\ w.2 \vdash H_3 \ @\ w.2} \qquad \dfrac{P_{24}}{\dfrac{\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{DNAdam}) \ @\ w.3 \vdash R_2 \ @\ w.u.v}{\texttt{pres}(\texttt{DNAdam}) \ @\ w.2,\ C_3 \ @\ w.2 \vdash R_2 \ @\ w.u.v}}{\texttt{abs}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{DNAdam}) \ @\ w.2,\ \texttt{rule}(3) \ @\ w.2 \vdash R_2 \ @\ w.u.v}$$

P_{24}:
let us remind that
$\texttt{rule}(4) \stackrel{\text{def}}{=} \texttt{inhib}(\texttt{vars}, \texttt{Mdm2}, \texttt{p53})$
$\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{Mdm2}) \oplus (\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53})) \oplus (\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53})))$,
$\rightarrow \delta_1(\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{DNAdam}, u))$
and R_2 is $state_0 \otimes \texttt{dont\_care}(\texttt{DNAdam})$ where $state_p$ is $\texttt{abs}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})$,
let H_4 denote $\texttt{pres}(\texttt{Mdm2}) \oplus (\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53})) \oplus (\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53}))$ (hyp. of $\texttt{rule}(4)$),
and C_4 denote $\delta_1(\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{DNAdam}, u))$ (conclusion of $\texttt{rule}(4)$)
in

$$\dfrac{\dfrac{\ldots \vdash \texttt{pres}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{p53}) \ @\ w.3}{\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2}) \ @\ w.3 \vdash H_4 \ @\ w.3} \qquad \dfrac{\texttt{pres}(\texttt{Mdm2}) \otimes \texttt{abs}(\texttt{p53}) \otimes \texttt{pres}(\texttt{DNAdam}) \ @\ w.4 \vdash R_2 \ @\ w.u.v \ [v=2]}{\texttt{pres}(\texttt{DNAdam}) \ @\ w.3,\ C_4 \ @\ w.3 \vdash R_2 \ @\ w.u.v}}{\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2}) \otimes \texttt{pres}(\texttt{DNAdam}) \ @\ w.3,\ \texttt{rule}(4) \ @\ w.3 \vdash R_2 \ @\ w.u.v \ \ [u=2; v=2]}$$

□

Proposition (Property 1, Version 2)**.** *For any world w, there exists two worlds u and v such that both u and v are less than 3 and the following holds:*

$$\dagger\, system \ @\ 0\ ;\ state_0 \otimes \texttt{pres}(\texttt{DNAdam}) \ @\ w \vdash state_1 \otimes \texttt{dont\_care}(\texttt{DNAdam}) \ @\ w.u \quad (1) \quad \textit{and}$$
$$\dagger\, system \ @\ 0\ ;\ state_1 \ @\ w.u \vdash state_0 \ @\ w.u.v \quad (2)$$

Note. There are no $\texttt{dont\_care}$'s needed in the conclusion of the second sequent because only rules 3 and 4 are used, which don't involve DNAdam.

Let us first prove the first statement (1):

Proof.

$$\dfrac{P_1}{state_0 \otimes \texttt{pres}(\texttt{DNAdam}) \ @\ w \vdash state_1 \otimes \texttt{dont\_care}(\texttt{DNAdam}) \ @\ w.u \ \ [u=2]}$$

where P_1 is the same proof P_1 used in the proof of Property 1, Version 1, above. □

Let us prove the second statement (2):

Proof. let us remind that
$\texttt{rule}(3) \stackrel{\text{def}}{=} \texttt{active}(\texttt{vars}, \texttt{p53}, \texttt{Mdm2})$
$\stackrel{\text{def}}{=} (\texttt{pres}(\texttt{p53}) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \oplus (\texttt{pres}(\texttt{p53}) \otimes \texttt{abs}(\texttt{Mdm2})))$
$\rightarrow \delta_1(\texttt{pres}(\texttt{p53}) \otimes \texttt{pres}(\texttt{Mdm2})) \otimes \downarrow u.\ \texttt{unchanged}(\texttt{DNAdam}, u))$,

let H_3 denote $\texttt{pres(p53)} \oplus (\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \oplus (\texttt{pres(p53)} \otimes \texttt{abs(Mdm2)})$ (hyp. of $\texttt{rule}(3)$), and C_3 denote $\delta_1(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \otimes \downarrow u.\ \texttt{unchanged(DNAdam}, u))$ (conclusion of $\texttt{rule}(3)$) in

$$\dfrac{\dfrac{\ldots \vdash \texttt{pres(p53)} \otimes \texttt{abs(Mdm2)} \ @\ w.2}{\texttt{abs(Mdm2)} \otimes \texttt{pres(p53)} \ @\ w.2 \vdash H_3 \ @\ w.2} \quad \dfrac{P_{24}}{\dfrac{\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \ @\ w.3 \vdash \mathit{state}_0 \ @\ w.2.v}{C_3 \ @\ w.2 \vdash \mathit{state}_0 \ @\ w.2.v}}}{\dfrac{\texttt{abs(Mdm2)} \otimes \texttt{pres(p53)} \ @\ w.2,\ \texttt{rule}(3) \ @\ w.2 \vdash \mathit{state}_0 \ @\ w.2.v}{\mathit{state}_1 \ @\ w.2 \vdash \mathit{state}_0 \ @\ w.2.v \ \ [v = 2]}}$$

P_{24}:
let us remind that

$$\begin{aligned}\texttt{rule}(4) &\stackrel{\text{def}}{=} \texttt{inhib(vars, Mdm2, p53)}\\ &\stackrel{\text{def}}{=} (\texttt{pres(Mdm2)} \oplus (\texttt{pres(Mdm2)} \otimes \texttt{pres(p53)}) \oplus (\texttt{pres(Mdm2)} \otimes \texttt{abs(p53)}))\\ &\quad \to \delta_1(\texttt{pres(Mdm2)} \otimes \texttt{abs(p53)}) \otimes \downarrow u.\ \texttt{unchanged(DNAdam}, u)),\end{aligned}$$

let H_4 denote $\texttt{pres(Mdm2)} \oplus (\texttt{pres(Mdm2)} \otimes \texttt{pres(p53)}) \oplus (\texttt{pres(Mdm2)} \otimes \texttt{abs(p53)})$ (hyp. of $\texttt{rule}(4)$), and C_4 denote $\delta_1(\texttt{pres(Mdm2)} \otimes \texttt{abs(p53)}) \otimes \downarrow u.\ \texttt{unchanged(DNAdam}, u))$ (conclusion of $\texttt{rule}(4)$) in

$$\dfrac{\dfrac{\ldots \vdash \texttt{pres(Mdm2)} \otimes \texttt{pres(p53)} \ @\ w.3}{\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \ @\ w.3 \vdash H_4 \ @\ w.3} \quad \dfrac{\texttt{pres(Mdm2)} \otimes \texttt{abs(p53)} \ @\ w.4 \vdash \mathit{state}_0 \ @\ w.2.v \ [v = 2]}{C_4 \ @\ w.3 \vdash \mathit{state}_0 \ @\ w.2.v}}{\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \ @\ w.3,\ \texttt{rule}(4) \ @\ w.3 \vdash \mathit{state}_0 \ @\ w.2.v \ \ [v = 2]}$$

□

B.2 Property 2

DNA damage can be quickly recovered.

From state_0 and $\texttt{pres(DNAdam)}$ we get $\texttt{abs(p53)}$, $\texttt{abs(Mdm2)}$, and $\texttt{pres(DNAdam)}$ by rule 1. Then $\texttt{pres(p53)}$ and $\texttt{abs(Mdm2)}$ (state_1) and $\texttt{pres(DNAdam)}$ by rule 2. Then $\texttt{abs(p53)}$, $\texttt{abs(Mdm2)}$, and $\texttt{abs(DNAdam)}$ by rule 5, and finally $\texttt{abs(p53)}$ and $\texttt{pres(Mdm2)}$ (state_0) and $\texttt{abs(DNAdam)}$ by rule 6.

Proposition 11 (Property 2)**.** *For any world w, there exists a world u such that u is less than 5 and the following holds:*

$$\dagger\, \mathit{system} \ @\ 0;\ \mathit{state}_0 \ \otimes\ \texttt{pres(DNAdam)} \ @\ w \vdash \mathit{state}_0 \otimes \texttt{abs(DNAdam)} \ @\ w.u$$

Proof. Let R denote $\mathit{state}_0 \otimes \texttt{abs(DNAdam)} \ @\ w.4$ where state_0 is $\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)}$ in

$$\dfrac{P_1 \quad \dfrac{P_2 \quad \dfrac{P_5 \quad \dfrac{P_6 \quad \dfrac{\mathit{state}_0 \otimes \texttt{abs(DNAdam)} \ @\ w.4 \vdash \mathit{state}_0 \otimes \texttt{abs(DNAdam)} \ @\ w.4 \ \ [\mathit{hyp}]}{\texttt{abs(p53)} \ @\ w.3,\ \texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \ @\ w.4,\ \texttt{unchanged(p53}, w.3) \ @\ w.3 \vdash R}}{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \otimes \texttt{abs(DNAdam)} \ @\ w.3, \texttt{rule}(6) \ @\ w.3 \vdash R}}{\texttt{abs(Mdm2)} \ @\ w.2,\ \texttt{abs(p53)} \otimes \texttt{abs(DNAdam)} \ @\ w.3,\ \texttt{unchanged(Mdm2}, w.2) \ @\ w.2 \vdash R}}{\texttt{pres(p53)} \otimes \texttt{abs(Mdm2)} \otimes \texttt{pres(DNAdam)} \ @\ w.2,\ \texttt{rule}(5) \ @\ w.2 \vdash R}}{\texttt{pres(DNAdam)} \ @\ w.1,\ \texttt{pres(p53)} \otimes \texttt{abs(Mdm2)} \ @\ w.2,\ \texttt{unchanged(DNAdam}, w.1) \ @\ w.1 \vdash R}}{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \otimes \texttt{pres(DNAdam)} \ @\ w.1,\ \texttt{rule}(2) \ @\ w.1 \vdash R}}{\texttt{abs(p53)} \ @\ w,\ \texttt{abs(Mdm2)} \otimes \texttt{pres(DNAdam)} \ @\ w.1,\ \texttt{unchanged(p53}, w) \ @\ w \vdash R} \to L}{\mathit{state}_0 \ \otimes\ \texttt{pres(DNAdam)} \ @\ w,\ \texttt{rule}(1) \ @\ w \vdash R}}{\mathit{state}_0 \ \otimes\ \texttt{pres(DNAdam)} \ @\ w \vdash \mathit{state}_0 \otimes \texttt{abs(DNAdam)} \ @\ w.4}$$

where P_1 is

$$\texttt{pres(Mdm2)} \ @\ w,\ \texttt{pres(DNAdam)} \ @\ w \vdash \cdots \oplus (\texttt{pres(Mdm2)} \otimes \texttt{pres(DNAdam)}) \oplus \cdots \ @\ w,$$

P_2 is

$$\texttt{abs(p53)} \ @ \ w.1, \ \texttt{abs(Mdm2)} \ @ \ w.1 \vdash (\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \oplus \cdots \oplus \cdots \ @ \ w.1,$$

P_5 is

$$\texttt{pres(p53)} \ @ \ w.2, \ \texttt{pres(DNAdam)} \ @ \ w.2 \vdash \cdots \oplus (\texttt{pres(p53)} \otimes \texttt{pres(DNAdam)}) \oplus \cdots \ @ \ w.2,$$

and P_6 is

$$\texttt{abs(Mdm2)} \ @ \ w.3, \ \texttt{abs(DNAdam)} \ @ \ w.3 \vdash (\texttt{abs(Mdm2)} \otimes \texttt{abs(DNAdam)}) \oplus \cdots \oplus \cdots \ @ \ w.3$$

□

B.3 Property 3

If there is no DNA damage, the system remains in the initial state.

Proposition (Property 3)**.** *Let $\mathcal{P}$ denote the formula $state_0 \otimes \texttt{abs(DNAdam)}$. For any world w, the following holds:*

$$\dagger \, system \ @ \ 0; \ \mathcal{P} \ @ \ 0 \ \vdash \mathcal{P} \ \texttt{at} \ 0 \ @ \ w;$$

and for any world w, for any rule r in the interval $[1..6]$, the following holds:

$$\dagger \, system \ @ \ 0; \ . \vdash \mathcal{P} \rightarrow (\texttt{fireable}(r) \ \& \ \delta_1 \, \mathcal{P}) \ \oplus \ \texttt{not\_fireable}(r) \ @ \ w$$

The proof of the second statement proceeds by case analysis on the rules (r) of the biological system. There are only two fireable rules: $\texttt{rule}(4)$ and $\texttt{rule}(6)$.

Proof. Let $\mathcal{P}$ denote $state_0 \otimes \texttt{abs(DNAdam)}$ where $state_0$ is $\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)}$ in

$$\dfrac{\dfrac{\dfrac{P_1 \quad P_2 \quad P_3 \quad P_4 \quad P_5 \quad P_6}{\mathcal{P} \ @ \ w \vdash \forall r : [1..6]. \ (\texttt{fireable}(r) \ \& \ \delta_1 \, \mathcal{P}) \ \oplus \ \texttt{not\_fireable}(r) \ @ \ w} \ case_r}{\vdash \mathcal{P} \rightarrow \forall r : [1..6]. \ (\texttt{fireable}(r) \ \& \ \delta_1 \, \mathcal{P}) \ \oplus \ \texttt{not\_fireable}(r) \ @ \ w} \rightarrow R$$

where P_1 is

$$\dfrac{\dfrac{\texttt{abs(DNAdam)} \ @ \ w \vdash \texttt{abs(DNAdam)} \ @ \ w \qquad \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ w \vdash \texttt{dont\_care}(\{\texttt{Mdm2}, \texttt{p53}\}) \ @ \ w}{\mathcal{P} \ @ \ w \vdash \texttt{not\_fireable}(1) \ @ \ w} \oplus R}{\mathcal{P} \ @ \ w \vdash (\texttt{fireable}(1) \ \& \ \delta_1 \, \mathcal{P}) \ \oplus \ \texttt{not\_fireable}(1) \ @ \ w}$$

P_2 is

$$\dfrac{\dfrac{\texttt{abs(DNAdam)} \ @ \ w \vdash \texttt{dont\_care(DNAdam)} \ @ \ w \qquad \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ w \vdash \texttt{pres(Mdm2)} \ \otimes \ \texttt{dont\_care(p53)} \ @ \ w}{\mathcal{P} \ @ \ w \vdash \texttt{not\_fireable}(2) \ @ \ w} \oplus R}{\mathcal{P} \ @ \ w \vdash (\texttt{fireable}(2) \ \& \ \delta_1 \, \mathcal{P}) \ \oplus \ \texttt{not\_fireable}(2) \ @ \ w}$$

P_3 is

$$\dfrac{\dfrac{\texttt{abs(DNAdam)} \ @ \ w \vdash \texttt{dont\_care(DNAdam)} \ @ \ w \qquad \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ w \vdash \texttt{abs(p53)} \ \otimes \ \texttt{dont\_care(Mdm2)} \ @ \ w}{\mathcal{P} \ @ \ w \vdash \texttt{not\_fireable}(3) \ @ \ w} \oplus R}{\mathcal{P} \ @ \ w \vdash (\texttt{fireable}(3) \ \& \ \delta_1 \, \mathcal{P}) \ \oplus \ \texttt{not\_fireable}(3) \ @ \ w}$$

P_4 is

$$\dfrac{\dfrac{P_{4f} \qquad P_{4r}}{\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \ @ \ w \vdash \texttt{fireable}(4) \ \& \ \delta_1 \, \mathcal{P} \ @ \ w} \ \& \, R}{\mathcal{P} \ @ \ w \vdash \ (\texttt{fireable}(4) \ \& \ \delta_1 \, \mathcal{P}) \oplus \texttt{not\_fireable}(4) \ @ \ w} \oplus R_1$$

P_{4f} :

$$\frac{\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w \vdash \texttt{pres(Mdm2)} \otimes \texttt{abs(p53)} \mathbin{@} w \qquad \texttt{abs(DNAdam)} \mathbin{@} n \vdash \texttt{dont\_care(DNAdam)} \mathbin{@} w}{\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} n \vdash \texttt{fireable}(4) \mathbin{@} w} \otimes R$$

P_{4r} :

$$\frac{\begin{array}{l}\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w \\ \vdash \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w\end{array} \qquad \frac{\cdots \vdash \texttt{abs(DNAdam))} \mathbin{@} w+1 \qquad \cdots \vdash \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w+1}{\texttt{abs(DNAdam)} \mathbin{@} w,\ \texttt{pres(Mdm2)} \otimes \texttt{abs(p53)} \mathbin{@} w+1,\ \texttt{unchanged(DNAdam)} \mathbin{@} w \vdash \mathcal{P} \mathbin{@} w+1}}{s\_\texttt{rule}(4) \mathbin{@} w,\ \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} w \vdash \delta_1 \mathcal{P} \mathbin{@} w} \to L$$

P_5 is

$$\frac{\dfrac{\texttt{abs(DNAdam)} \mathbin{@} w \vdash \texttt{dont\_care(DNAdam)} \mathbin{@} w \qquad \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w \vdash \texttt{abs(p53)} \otimes \texttt{dont\_care(Mdm2)} \mathbin{@} w}{\mathcal{P} \mathbin{@} w \vdash \texttt{not\_fireable}(5) \mathbin{@} w} \oplus R}{\mathcal{P} \mathbin{@} w \vdash (\texttt{fireable}(5) \,\&\, \delta_1 \mathcal{P}) \oplus \texttt{not\_fireable}(5) \mathbin{@} w}$$

P_6 is

$$\frac{\dfrac{P_{6f} \qquad P_{6r}}{\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} w \vdash \texttt{fireable}(6) \,\&\, \delta_1 \mathcal{P} \mathbin{@} w} \,\&\, R}{\mathcal{P} \mathbin{@} w \vdash\ (\texttt{fireable}(6) \,\&\, \delta_1 \mathcal{P}) \oplus \texttt{not\_fireable}(6) \mathbin{@} w} \oplus R_1$$

P_{6f} :

$$\frac{\texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} w \vdash \texttt{abs(DNAdam)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w \qquad \texttt{abs(p53)} \mathbin{@} n \vdash \texttt{dont\_care(p53)} \mathbin{@} w}{\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} n \vdash \texttt{fireable}(6) \mathbin{@} w} \otimes R$$

P_{6r} :

$$\frac{\begin{array}{l}\texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} w \\ \vdash \texttt{abs(DNAdam)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w\end{array} \qquad \frac{\cdots \vdash \texttt{abs(DNAdam))} \mathbin{@} w+1 \qquad \cdots \vdash \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w+1}{\texttt{abs(p53)} \mathbin{@} n,\ \texttt{abs(DNAdam)} \otimes \texttt{pres(Mdm2)} \mathbin{@} w+1,\ \texttt{unchanged(p53)} \mathbin{@} w \vdash \mathcal{P} \mathbin{@} w+1}}{s\_\texttt{rule}(6) \mathbin{@} w,\ \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} w \vdash \delta_1 \mathcal{P} \mathbin{@} w} \to L$$

□

B.4 Property 4

There is no path with two consecutive states where p53 and Mdm2 are both present or both absent. In other words: from any state where p53 and Mdm2 are both present or both absent, we can only go to a state where either p53 is present and Mdm2 is absent or p53 is absent and Mdm2 is present. This property is only valid for strong rules.

Proposition 12 (Property 4)**.** *For any world n, the following holds:*

$$\dagger\, system \mathbin{@} 0;\ . \vdash \mathcal{L} \to \forall r : [1..6].\ (s\_\texttt{fireable}(r) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(r) \mathbin{@} n$$

The proof proceeds by case analysis on the rules (r) of the biological system.

Note that we need (and sometimes implicitly use) here the well_defined hypothesis $\forall a \in \texttt{vars}.\ (\texttt{pres}(a) \oplus \texttt{abs}(a))$. For example, the proof P_1 below uses the hypothesis $\texttt{pres(DNAdam)} \oplus \texttt{abs(DNAdam)}$.

Proof. Let $\mathcal{L}$ denote $(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \oplus (\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)})$
and $\mathcal{R}$ be $((\texttt{pres(p53)} \otimes \texttt{abs(Mdm2)}) \oplus (\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)})) \otimes \texttt{dont\_care(DNAdam)}$
in

$$\frac{\dfrac{P_1 \quad P_2}{\mathcal{L} \mathbin{@} n \vdash \forall r : [1..6].\ (s\_\texttt{fireable}(r) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(r) \mathbin{@} n} \oplus L}{\vdash \mathcal{L} \to \forall r : [1..6].\ (s\_\texttt{fireable}(r) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(r) \mathbin{@} n} \to R$$

where P_1 is

$$\frac{P_{11} \quad P_{12} \quad P_{13} \quad P_{14} \quad P_{15} \quad P_{16}}{(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \ @ \ n \vdash \forall r : [1..6].\ (s\_\texttt{fireable}(r) \ \& \ \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(r) \ @ \ n}\ case_r$$

with P_{11} :

$$\frac{\dfrac{P_{11F} \qquad P_{11N}}{(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \ @ \ n, (\texttt{pres(DNAdam)} \oplus \texttt{abs(DNAdam)}) \ @ \ n \vdash \cdots \oplus \cdots \ @ \ n}\ \oplus L}{(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \ @ \ n \vdash \ (s\_\texttt{fireable}(1) \ \& \ \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(1) \ @ \ n}$$

P_{11F} :

$$\frac{\dfrac{P_{11Ff} \qquad P_{11Fr}}{\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{pres(DNAdam)} \ @ \ n \vdash s\_\texttt{fireable}(1) \ \& \ \delta_1 \mathcal{R} \ @ \ n}\ \& R}{(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \ @ \ n, \texttt{pres(DNAdam)} \ @ \ n \vdash (s\_\texttt{fireable}(1) \ \& \ \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(1) \ @ \ n}\ \oplus R_1$$

P_{11Ff} :

$$\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{pres(DNAdam)} \ @ \ n \vdash s\_\texttt{fireable}(1) \ @ \ n \quad [...; hyp]$$

P_{11Fr} :

$$\frac{\begin{array}{c}\texttt{pres(DNAdam)} \otimes \texttt{pres(Mdm2)} \ @ \ n \\ \vdash \texttt{pres(DNAdam)} \otimes \texttt{pres(Mdm2)} \ @ \ n\end{array} \qquad \dfrac{\dfrac{\cdots \vdash \texttt{pres(p53)} \otimes \texttt{abs(Mdm2)} \ @ \ n+1}{\cdots \vdash (\texttt{pres(p53)} \otimes \texttt{abs(Mdm2)}) \oplus \cdots \ @ \ n+1}\ \oplus R \quad \dfrac{\cdots \vdash \texttt{pres(DNAdam)} \ @ \ n+1}{\cdots \vdash \texttt{dont\_care(DNAdam)} \ @ \ n+1}\ \oplus R}{\texttt{pres(p53)} \ @ \ n, \ (\texttt{pres(DNAdam)} \ \otimes \ \texttt{abs(Mdm2)}) \ @ \ n+1, \ \texttt{unchanged(p53)} \ @ \ n \vdash \mathcal{R} \ @ \ n+1}\ \rightarrow L}{s\_\texttt{rule}(1) \ @ \ n, \ (\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)} \ \otimes \ \texttt{pres(DNAdam)}) \ @ \ n \vdash \delta_1 \mathcal{R} \ @ \ n}$$

P_{11N} :

$$\frac{\texttt{pres(p53)} \ @ \ n, (\texttt{abs(DNAdam)} \ \otimes \ \texttt{pres(Mdm2)}) \ @ \ n \vdash s\_\texttt{not\_fireable}(1) \ @ \ n \quad [...; hyp]}{(\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)}) \ @ \ n, \texttt{abs(DNAdam)} \ @ \ n \vdash (s\_\texttt{fireable}(1) \ \& \ \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(1) \ @ \ n}\ \oplus R_2$$

P_{12} :

$$\frac{\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)} \ @ \ n \vdash s\_\texttt{not\_fireable}(2) \ @ \ n \quad [hyp]}{\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)} \ @ \ n \vdash \ (s\_\texttt{fireable}(2) \ \& \ \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(2) \ @ \ n}\ \oplus R_2$$

P_{13} :

$$\frac{\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)} \ @ \ n \vdash s\_\texttt{not\_fireable}(3) \ @ \ n \quad [hyp]}{\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)} \ @ \ n \vdash \ (s\_\texttt{fireable}(3) \ \& \ \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(3) \ @ \ n}\ \oplus R_2$$

P_{14} :

$$\frac{\dfrac{P_{14f} \qquad P_{14r}}{(\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)}) \ @ \ n \vdash s\_\texttt{fireable}(4) \ \& \ \delta_1 \mathcal{R} \ @ \ n}\ \& R}{(\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)}) \ @ \ n \vdash \ (s\_\texttt{fireable}(4) \ \& \ \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(4) \ @ \ n}\ \oplus R_1$$

P_{14f} :

$$\frac{\cdots \vdash \texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)} \ @ \ n \quad [hyp] \qquad \texttt{well\_defined}_1\texttt{(DNAdam)} \ @ \ n \vdash \texttt{dont\_care(DNAdam)} \ @ \ n}{\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)} \ @ \ n \vdash s\_\texttt{fireable}(4) \ @ \ n}$$

P_{14r} :

$$\frac{\begin{array}{c}\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ n \\ \vdash \texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ n\end{array} \qquad \dfrac{\dfrac{\cdots \vdash \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ n+1}{\cdots \vdash (\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)}) \oplus \cdots \ @ \ n+1} \quad \dfrac{\texttt{well\_defined}_1\texttt{(DNAdam)} \ @ \ n+1 \vdash \cdots}{\vdash \texttt{dont\_care(DNAdam)} \ @ \ n+1}}{\texttt{pres(Mdm2)} \ \otimes \ \texttt{abs(p53)} \ @ \ n+1, \ \texttt{unchanged(DNAdam)} \ @ \ n \vdash \mathcal{R} \ @ \ n+1}\ \rightarrow L}{s\_\texttt{rule}(4) \ @ \ n, \ (\texttt{pres(p53)} \ \otimes \ \texttt{pres(Mdm2)}) \ @ \ n \vdash \delta_1 \mathcal{R} \ @ \ n}$$

P_{15} :

$$\frac{P_{15F} \qquad P_{15N}}{(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \ @ \ n, (\texttt{pres(DNAdam)} \oplus \texttt{abs(DNAdam)}) \ @ \ n \vdash \cdots \oplus \cdots \ @ \ n} \oplus L$$
$$(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \ @ \ n \vdash (s\_\texttt{fireable}(5) \ \& \ \delta_1 \ \mathcal{R}) \oplus s\_\texttt{not\_fireable}(5) \ @ \ n$$

P_{15F} :

$$\frac{\dfrac{P_{15Ff} \qquad P_{15Fr}}{\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{pres(DNAdam)} \ @ \ n \vdash s\_\texttt{fireable}(5) \ \& \ \delta_1 \ \mathcal{R} \ @ \ n} \ \& R}{(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \ @ \ n, \texttt{pres(DNAdam)} \ @ \ n \vdash (s\_\texttt{fireable}(5) \ \& \ \delta_1 \ \mathcal{R}) \oplus s\_\texttt{not\_fireable}(5) \ @ \ n} \oplus R_1$$

P_{15Ff} :

$$\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{pres(DNAdam)} \ @ \ n \vdash s\_\texttt{fireable}(5) \ @ \ n \quad [...; hyp]$$

P_{15Fr} :

$$\frac{\begin{array}{c}\texttt{pres(p53)} \otimes \texttt{pres(DNAdam)} \ @ \ n \\ \vdash \texttt{pres(p53)} \otimes \texttt{pres(DNAdam)} \ @ \ n\end{array} \qquad \dfrac{\dfrac{\cdots \vdash \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ n+1}{\cdots \vdash (\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)}) \oplus \cdots \ @ \ n+1} \oplus R \quad \dfrac{\cdots \vdash \texttt{pres(DNAdam)} \ @ \ n+1}{\cdots \vdash \texttt{dont\_care(DNAdam)} \ @ \ n+1} \oplus R}{\texttt{pres(Mdm2)} \ @ \ n, \ (\texttt{abs(p53)} \otimes \texttt{abs(DNAdam)}) \ @ \ n+1, \ \texttt{unchanged(Mdm2)} \ @ \ n \vdash \mathcal{R} \ @ \ n+1} \rightarrow L}{s\_\texttt{rule}(5) \ @ \ n, \ (\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \otimes \texttt{pres(DNAdam)}) \ @ \ n \vdash \delta_1 \ \mathcal{R} \ @ \ n}$$

P_{15N} :

$$\frac{\texttt{pres(p53)} \otimes \texttt{abs(DNAdam)} \ @ \ n, \ \texttt{pres(Mdm2)} \ @ \ n \vdash s\_\texttt{not\_fireable}(5) \ @ \ n \quad [...; hyp]}{(\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)}) \ @ \ n, \texttt{abs(DNAdam)} \ @ \ n \vdash (s\_\texttt{fireable}(5) \ \& \ \delta_1 \ \mathcal{R}) \oplus s\_\texttt{not\_fireable}(5) \ @ \ n} \oplus R_2$$

P_{16} :

$$\frac{\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ n \vdash s\_\texttt{not\_fireable}(6) \ @ \ n \quad [hyp]}{\texttt{pres(p53)} \otimes \texttt{pres(Mdm2)} \ @ \ n \vdash (s\_\texttt{fireable}(6) \ \& \ \delta_1 \ \mathcal{R}) \oplus s\_\texttt{not\_fireable}(6) \ @ \ n} \oplus R_2$$

and P_2 is

$$\frac{P_{21} \quad P_{22} \quad P_{23} \quad P_{24} \quad P_{25} \quad P_{26}}{(\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \ @ \ n \vdash \forall r : [1..6]. \ (s\_\texttt{fireable}(r) \ \& \ \delta_1 \ \mathcal{R}) \oplus s\_\texttt{not\_fireable}(r) \ @ \ n} \ case_r$$

with P_{21} :

$$\frac{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \ @ \ n \vdash s\_\texttt{not\_fireable}(1) \ @ \ n}{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \ @ \ n \vdash (s\_\texttt{fireable}(1) \ \& \ \delta_1 \ \mathcal{R}) \oplus s\_\texttt{not\_fireable}(1) \ @ \ n} \oplus R_2$$

P_{22} :

$$\frac{\dfrac{P_{22f} \qquad P_{22r}}{(\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \ @ \ n \vdash s\_\texttt{fireable}(2) \ \& \ \delta_1 \ \mathcal{R} \ @ \ n} \ \& R}{(\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \ @ \ n \vdash (s\_\texttt{fireable}(2) \ \& \ \delta_1 \ \mathcal{R}) \oplus s\_\texttt{not\_fireable}(2) \ @ \ n} \oplus R_1$$

P_{22f} :

$$\frac{\cdots \vdash \texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \ @ \ n \quad [hyp] \qquad \texttt{well\_defined}_1\texttt{(DNAdam)} \ @ \ n \vdash \texttt{dont\_care(DNAdam)} \ @ \ n}{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \ @ \ n \vdash s\_\texttt{fireable}(2) \ @ \ n}$$

P_{22r} :

$$\frac{\begin{array}{c}\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \ @ \ n \\ \vdash \texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \ @ \ n\end{array} \qquad \dfrac{\dfrac{\cdots \vdash \texttt{pres(p53)} \otimes \texttt{abs(Mdm2)} \ @ \ n+1}{\cdots \vdash (\texttt{pres(p53)} \otimes \texttt{abs(Mdm2)}) \oplus \cdots \ @ \ n+1} \quad \dfrac{\texttt{well\_defined}_1\texttt{(DNAdam)} \ @ \ n+1 \vdash \cdots}{\vdash \texttt{dont\_care(DNAdam)} \ @ \ n+1}}{\texttt{abs(Mdm2)} \otimes \texttt{pres(p53)} \ @ \ n+1, \ \texttt{unchanged(DNAdam)} \ @ \ n \vdash \mathcal{R} \ @ \ n+1} \rightarrow L}{s\_\texttt{rule}(2) \ @ \ n, \ (\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \ @ \ n \vdash \delta_1 \ \mathcal{R} \ @ \ n}$$

P_{23} :

$$\frac{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n \vdash s\_\texttt{not\_fireable}(3) \mathbin{@} n}{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n \vdash (s\_\texttt{fireable}(3) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(3) \mathbin{@} n} \oplus R_2$$

P_{24} :

$$\frac{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n \vdash s\_\texttt{not\_fireable}(4) \mathbin{@} n}{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n \vdash (s\_\texttt{fireable}(4) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(4) \mathbin{@} n} \oplus R_2$$

P_{25} :

$$\frac{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n \vdash s\_\texttt{not\_fireable}(5) \mathbin{@} n}{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n \vdash (s\_\texttt{fireable}(5) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(5) \mathbin{@} n} \oplus R_2$$

P_{26} :

$$\frac{\dfrac{P_{26F} \qquad P_{26N}}{(\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \mathbin{@} n, (\texttt{pres(DNAdam)} \oplus \texttt{abs(DNAdam)}) \mathbin{@} n \vdash \cdots \oplus \cdots \mathbin{@} n} \oplus L}{(\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \mathbin{@} n \vdash (s\_\texttt{fireable}(6) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(6) \mathbin{@} n}$$

P_{26F} :

$$\frac{\dfrac{P_{26Ff} \qquad P_{26Fr}}{\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} n \vdash s\_\texttt{fireable}(6) \,\&\, \delta_1 \mathcal{R} \mathbin{@} n} \,\&\, R}{(\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \mathbin{@} n, \texttt{abs(DNAdam)} \mathbin{@} n \vdash (s\_\texttt{fireable}(6) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(6) \mathbin{@} n} \oplus R_1$$

P_{26Ff} :

$$\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \otimes \texttt{abs(DNAdam)} \mathbin{@} n \vdash s\_\texttt{fireable}(6) \mathbin{@} n \quad [...; hyp]$$

P_{26Fr} :

$$\frac{\begin{array}{l}\texttt{abs(DNAdam)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n \\ \vdash \texttt{abs(DNAdam)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n\end{array} \qquad \dfrac{\dfrac{\cdots \vdash \texttt{abs(p53)} \otimes \texttt{pres(Mdm2)} \mathbin{@} n+1}{\cdots \vdash (\texttt{abs(p53)} \otimes \texttt{pres(Mdm2)}) \oplus \cdots \mathbin{@} n+1} \oplus R \quad \dfrac{\cdots \vdash \texttt{abs(DNAdam)} \mathbin{@} n+1}{\cdots \vdash \texttt{dont\_care(DNAdam)} \mathbin{@} n+1} \oplus R}{\texttt{abs(p53)} \mathbin{@} n,\ (\texttt{abs(DNAdam)} \otimes \texttt{pres(Mdm2)}) \mathbin{@} n+1,\ \texttt{unchanged(p53)} \mathbin{@} n \vdash \mathcal{R} \mathbin{@} n+1}}{s\_\texttt{rule}(6) \mathbin{@} n,\ (\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)} \otimes \texttt{abs(DNAdam)}) \mathbin{@} n \vdash \delta_1 \mathcal{R} \mathbin{@} n} \to L$$

P_{26N} :

$$\frac{\texttt{pres(DNAdam)} \otimes \texttt{abs(Mdm2)} \mathbin{@} n,\ \texttt{abs(p53)} \mathbin{@} n \vdash s\_\texttt{not\_fireable}(6) \mathbin{@} n \quad [...; hyp]}{(\texttt{abs(p53)} \otimes \texttt{abs(Mdm2)}) \mathbin{@} n, \texttt{pres(DNAdam)} \mathbin{@} n \vdash (s\_\texttt{fireable}(6) \,\&\, \delta_1 \mathcal{R}) \oplus s\_\texttt{not\_fireable}(6) \mathbin{@} n} \oplus R_2$$

□