A Logical Framework for Systems Biology

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LSB, FLOC, July 13, 2014

Motivation : Modeling and Analysis of Biological Systems

Specialized logistic systems (temporal logics: Computation Tree Logic CTL*, CTL, LTL, Probabilistic CTL,...)

- Modeling in dedicated languages (stochastic π-calculus, biocham, kappa, brane, ...) or in differential equations
  $\hookrightarrow$ transition systems
- Express properties in temporal logic
- Verify properties against traces - external simulator
  $\hookrightarrow$ model checking.

$\hookrightarrow$ *Reasoning is not done directly on the models.*

Approach

An unified framework:

- modeling systems of biochemical reactions as transition systems: linear logic (ILL)
- transitions with (temporal, stochastic, ...) constraints
- modal extension of ILL: *Hybrid Linear Logic (HyLL)*
- HyLL has a cut admitting sequent calculus, focused rules,...
- induction and mechanized proofs: the Coq proof assistant
- proofs: Coq λ-terms containing HyLL proof trees

$\hookrightarrow$ A logical framework for constrained transition systems.

$\hookrightarrow$ *A logical framework for systems biology.*

Outline

Defined Modal Connectives - delay

- Defined 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*:
  Derived right rule:

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

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Hybrid Logic

- A form of modal logic that allows *naming of worlds*.
- Very general idea. Can be applied for
  - Almost all known modal and temporal logics
  - Many substructural logics (eg. linear logic)
- Ideas go back to Prior (1960s) and Allen (1980s)
  — but still active and recently energized area

Ordinary Logic

- Start with ordinary first-order (intuitionistic) logic

$$t, \ldots ::= c \mid x \mid f(t_1, \ldots, t_n) \qquad \textit{Ex: } \texttt{gene}(a)$$

$$A, B, \ldots ::= p(t_1, \ldots, t_k) \mid \top \mid \bot \mid A \wedge B \mid A \vee B \mid A \Rightarrow B \mid \forall x.A \mid \exists x.A$$

$$\textit{Ex: } \texttt{pres}(x) \wedge \texttt{abs}(y)$$

- Judgements are of the form: $A_1, \ldots, A_n \vdash C$

  C is true assuming the hypotheses $A_1 \cdots A_n$ are true

  Ex: $\texttt{pres}(\texttt{x}), \texttt{abs}(\texttt{y}) \vdash \texttt{pres}(\texttt{z})$

- Connectives specified as usual, in the Sequent Calculus style

$$\Gamma, A \vdash A \; [hyp] \qquad \frac{\Gamma \vdash A \quad \Gamma \vdash B}{\Gamma \vdash A \wedge B} \wedge_R \qquad \frac{\Gamma, A \vdash C}{\Gamma, A \wedge B \vdash C} \wedge_{L1} \qquad \frac{\Gamma, B \vdash C}{\Gamma, A \wedge B \vdash C} \wedge_{L2}$$

$$\frac{\Gamma, A \vdash B}{\Gamma \vdash A \Rightarrow B} [\Rightarrow_R] \qquad \frac{\Gamma \vdash A \quad \Gamma, B \vdash C}{\Gamma, A \Rightarrow B \vdash C} [\Rightarrow_L]$$

Hybrid Logic

- Add a new metasyntactic class of *worlds*, written "w":

Definition

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, $\preceq$-initial, represents the lack of any constraints: ILL $\subseteq$ HyLL[ι] $\subset$ HyLL[W].
- Ex: Time: $\mathcal{T} = \langle \boldsymbol{N}, +, 0 \rangle$ or $\langle \mathbb{R}^+, +, 0 \rangle$

Hybrid Logic

- Make all judgements situated *at a world*: $A \mathbin{@} w$

  A is true at world w

$$A_1 \mathbin{@} w_1, \ldots, A_n \mathbin{@} w_n \vdash C \mathbin{@} w$$

- All ordinary rules continue essentially unchanged.

$$\Gamma, A \mathbin{@} w \vdash A \mathbin{@} w \; [hyp]$$

$$\frac{\Gamma \vdash A \mathbin{@} w \quad \Gamma \vdash B \mathbin{@} w}{\Gamma \vdash A \wedge B \mathbin{@} w} [\wedge_R]$$

$$\frac{\Gamma, A \mathbin{@} w \vdash C \mathbin{@} w}{\Gamma, A \wedge B \mathbin{@} w \vdash C \mathbin{@} w} [\wedge_{L1}] \qquad \frac{\Gamma, B \mathbin{@} w \vdash C \mathbin{@} w}{\Gamma, A \wedge B \mathbin{@} w \vdash C \mathbin{@} w} [\wedge_{L2}]$$

$$\frac{\Gamma, A \mathbin{@} w \vdash B \mathbin{@} w}{\Gamma \vdash A \Rightarrow B \mathbin{@} w} [\Rightarrow_R] \qquad \frac{\Gamma \vdash A \mathbin{@} w \quad \Gamma, B \mathbin{@} w \vdash C \mathbin{@} w}{\Gamma, A \Rightarrow B \mathbin{@} w \vdash C \mathbin{@} w} [\Rightarrow_L]$$

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Hybrid Connectives

- Make the claim that "A is true at world w" a *mobile* proposition in terms of a *satisfaction* connective:

$$A, B, \ldots ::= \quad \ldots \mid A \text{ at } w \mid \downarrow u.\ A$$

Satisfaction

- To introduce the *satisfaction* proposition $(A \ \mathtt{at}\ u)$ (at any world v), the proposition A must be true in the world u:

$$\frac{\Gamma; \Delta \vdash A \ @ \ u}{\Gamma; \Delta \vdash (A \ \mathtt{at}\ u) \ @ \ v} \ \mathtt{at}\ R$$

- The proposition $(A \ \mathtt{at}\ u)$ itself is then true at any world, not just in the world u.
- i.e. $(A \ \mathtt{at}\ u)$ carries with it the world at which it is true. Therefore, suppose we know that $(A \ \mathtt{at}\ u)$ is true (at any world v); then, we also know that $A \ @ \ u$:

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

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Localisation

- The other hybrid connective of *localisation*, $\downarrow u.\ A$, is intended to be able to name the current world:
- If $\downarrow u.\ A$ is true at world w, then the variable u stands for w in the body A:

$$\frac{\Gamma; \Delta \vdash [w/u]A \ @\ w}{\Gamma; \Delta \vdash \downarrow u.A \ @\ w} \downarrow R$$

- Suppose we have a proof of $\downarrow u.A \ @\ v$ for some world v; Then, we also know $[v/u]A \ @\ v$:

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Linear Logic

- Terms:

$$
\begin{aligned}
t &::= \; c \mid x \mid f(\vec{t}) \\
A, B, \ldots &::= \; p(\vec{t}) \mid A \otimes B \mid \mathbf{1} \mid A \multimap B \mid A \,\&\, B \mid \top \mid A \oplus B \mid \mathbf{0} \\
& \quad\;\; !A \mid \forall x.\, A \mid \exists x.\, A
\end{aligned}
$$

- Judgements are of the form: $\Gamma; \Delta \vdash C$, where
  Γ is the *unrestricted context*
  its hypotheses can be consumed any number of times.
  Δ (a *multiset*) is a *linear context*
  every hypothesis in it must be consumed singly in the proof.
- Judgemental rules:

$$
\Gamma, p(\vec{t}) \vdash p(\vec{t}) \; [init] \qquad \frac{\Gamma, A; \Delta, A \vdash C}{\Gamma, A \vdash C} \; copy
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Sequent Calculus for Linear Logic [1]

- Exponentials:

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

- Multiplicatives:

$$\frac{\Gamma; \Delta, A \vdash B}{\Gamma; \Delta \vdash A \rightarrow B} \; [\rightarrow_R] \qquad \frac{\Gamma; \Delta \vdash A \quad \Gamma; \Delta', B \vdash C}{\Gamma; \Delta, \Delta', A \rightarrow B \vdash C} \; [\rightarrow_L]$$

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

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Sequent Calculus for Linear Logic [2]

- Additives:

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

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

Example

- *Activation*:

$$\mathtt{Active}(a, b) \stackrel{\text{def}}{=} \mathtt{pres}(a) \to \delta_1(\mathtt{pres}(a) \otimes \mathtt{pres}(b)).$$

- *Inhibition*

$$\mathtt{Inhib}(V, a, b) \stackrel{\text{def}}{=} \mathtt{pres}(a) \to \delta_1(\mathtt{pres}(a) \otimes \mathtt{abs}(b)).$$

Hybrid Linear Logic (HyLL)

- Terms:

$$\begin{aligned} t &::= \quad c \mid x \mid f(\vec{t}) \\ A, B, \ldots &::= \quad \ldots \mid A \ \mathtt{at}\ w \mid \downarrow u.\ A \mid \forall u.\ A \mid \exists u.\ A \end{aligned}$$

- Judgements are of the form: $\Gamma ; \Delta \vdash C @ w$, where Γ and Δ are sets of judgements of the form $A @ w$

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Sequent Calculus for HyLL [1]

- Judgement: $\Gamma; \Delta \vdash A \,@\, w$
- Judgemental rules

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

- Exponentials rules

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

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Sequent Calculus for HyLL [2]

- Multiplicatives

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

- Additives

$$\frac{\Gamma ; \Delta \vdash A \ @\ w \qquad \Gamma ; \Delta \vdash B \ @\ w}{\Gamma ; \Delta \vdash A \,\&\, B \ @\ w} \,\&\, R$$

$$\frac{\Gamma ; \Delta, A_i \ @\ u \vdash C \ @\ w}{\Gamma ; \Delta, A_1 \,\&\, A_2 \ @\ u \vdash C \ @\ w} \,\&\, L_i \qquad \frac{\Gamma ; \Delta \vdash A_i \ @\ w}{\Gamma ; \Delta \vdash A_1 \oplus A_2 \ @\ w} \oplus R_i$$

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Sequent Calculus for HyLL [3]

- Hybrid connectives

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

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

Properties of the Sequent Calculus System [1]

Theorem

1. *If* $\Gamma ; \Delta \vdash C \mathbin{@} w$, *then* $\Gamma, \Gamma' ; \Delta \vdash C \mathbin{@} w$ *(weakening)*
2. *If* $\Gamma, A \mathbin{@} u, A \mathbin{@} u ; \Delta \vdash C \mathbin{@} w$, *then* $\Gamma, A \mathbin{@} u ; \Delta \vdash C \mathbin{@} w$ *(contraction)*
3. $\Gamma ; A \mathbin{@} w \vdash A \mathbin{@} w$ *(identity)*

Theorem (cut)

1. *If* $\Gamma ; \Delta \vdash A \mathbin{@} u$ *and* $\Gamma ; \Delta', A \mathbin{@} u \vdash C \mathbin{@} w$, *then* $\Gamma ; \Delta, \Delta' \vdash C \mathbin{@} w$.
2. *If* $\Gamma ; . \vdash A \mathbin{@} u$ *and* $\Gamma, A \mathbin{@} u ; \Delta \vdash C \mathbin{@} w$, *then* $\Gamma ; \Delta \vdash C \mathbin{@} w$.

Properties of the Sequent Calculus System [2]

Theorem (invertibility)

- *On the right:* $\&R$, $\top R$, $\to R$, $\forall R$, $\downarrow R$ *and* $\mathtt{at}\ R$;
- *On the left:* $\otimes L$, $\mathbf{1}L$, $\oplus L$, $\mathbf{0}L$, $\exists L$, $!L$, $\downarrow L$ *and* $\mathtt{at}\ L$

Theorem

1. *(consistency) There is no proof of* $.;. \vdash \mathbf{0} \ @\ w$.
2. *(conservativity) For "pure" contexts* Γ *and* Δ *and "pure" proposition* A*:* $\Gamma; \Delta \vdash_{ILL} A$.

Theorem (HyLL is -at least as powerful as- S5)

$.; \Diamond A \ @\ w \vdash \Box\Diamond A \ @\ w$.

Defined Modal Connectives - delay

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

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

- The connective δ represents a form of *delay*:
  Derived right rule:

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

Oscillation

$$A \wedge \mathrm{EF}(B \wedge \mathrm{EF}A)$$

Definition (one oscillation)

$$\mathrm{oscillate}_1\,(A, B, u, v) \stackrel{\mathrm{def}}{=} A \;\&\; \delta_u(B \;\&\; \delta_v\, A) \;\&\; (A \,\&\, B \to 0).$$

Definition (oscillation - object)

$$\mathrm{oscillate}_h\,(A, B, u, v)$$
$$\stackrel{\mathrm{def}}{=} \dagger[(A \to \delta_u\, B) \;\&\; (B \to \delta_v\, A)] \;\&\; (A \,\&\, B \to 0).$$

Definition (oscillation - meta)

$$\mathrm{oscillate}\,(A, B, u, v)$$
$\stackrel{\mathrm{def}}{=}$ for any w, $(A \;@\; w \vdash B \;@\; w.u)$, $(B \;@\; w.u \vdash A \;@\; w.u.v)$, and $(\vdash A \,\&\, B \to 0 \;@\; w)$.

Activation/Inhibition Rules (Boolean Model) [1]

- *Without consumption*:

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

- *More precise*:

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

- *Looping*:

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

- *General*:

$$\begin{aligned} &\mathtt{active}(a,b) \\ &\quad \stackrel{\text{def}}{=} (\mathtt{pres}(a) \oplus (\mathtt{pres}(a) \otimes \mathtt{pres}(b)) \oplus (\mathtt{pres}(a) \otimes \mathtt{abs}(b))) \\ &\qquad \to \delta_1 \;(\mathtt{pres}(a) \otimes \mathtt{pres}(b)). \end{aligned}$$

Activation/Inhibition Rules [2]

- *With consumption*:

$$\mathtt{s\_active}_c(a,b) \stackrel{\text{def}}{=} \mathtt{pres}(a) \otimes \mathtt{abs}(b) \multimap \delta_1(\mathtt{abs}(a) \otimes \mathtt{pres}(b)).$$

- *Strong activation*:

$$\mathtt{s\_active}_s(a,b) \stackrel{\text{def}}{=} \mathtt{abs}(a) \otimes \mathtt{pres}(b) \multimap \delta_1(\mathtt{abs}(a) \otimes \mathtt{abs}(b)).$$

- *Inhibition*

$$w\_\mathtt{inhib}(V,a,b) \stackrel{\text{def}}{=} \mathtt{pres}(a) \multimap \delta_1(\mathtt{pres}(a) \otimes \mathtt{abs}(b)).$$

- *...*

Example - Definition (Boolean Model)

The P53/Mdm2 DNA-damage repair mechanism.

P53 is a tumor suppressor protein that is activated in reply to DNA damage. $\mathtt{C}(p53)$ is controlled by another protein, Mdm2.

DNA damage increases the degradation rate of Mdm2 so that the control of this protein on P53 becomes weaker and (after ev. oscillations) the concentration of p53 can increase. P53 can thus either repair DNA damage or provoke apoptosis.

Boolean Model:

Initial states: P53 is absent and Mdm2 is present.

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

Specification in HyLL [1]

In HyLL$[\langle \mathbb{N}, +, 0\rangle]$

$$
\begin{aligned}
\mathtt{unchanged}(x, w) &\stackrel{\text{def}}{=} \; ! \, [(\mathtt{pres}(x) \; \mathbf{at} \; w \to \mathtt{pres}(x) \; \mathbf{at} \; w.1) \; \& \\
&\qquad (\mathtt{abs}(x) \; \mathbf{at} \; w \to \mathtt{abs}(x) \; \mathbf{at} \; w.1)]. \\
\mathtt{unchanged}(V, w) &\stackrel{\text{def}}{=} \; \otimes_{x \in V} \mathtt{unchanged}(x, w).
\end{aligned}
$$

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

$$
\mathtt{active}_c(V, a, b) \stackrel{\text{def}}{=} \; \ldots
$$

$\ldots$

Specification in HyLL [2]

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

Specification in HyLL [3]

- *The system*:

$$\begin{aligned}
\mathtt{vars} &\stackrel{\text{def}}{=} \{\mathtt{p53}, \mathtt{Mdm2}, \mathtt{DNAdam}\}.\\
\mathtt{rule}(1) &\stackrel{\text{def}}{=} \mathtt{inhib}(\mathtt{vars}, \mathtt{DNAdam}, \mathtt{Mdm2}).\\
\mathtt{rule}(2) &\stackrel{\text{def}}{=} \mathtt{inhib_s}(\mathtt{vars}, \mathtt{Mdm2}, \mathtt{p53}).\\
\mathtt{rule}(3) &\stackrel{\text{def}}{=} \mathtt{active}(\mathtt{vars}, \mathtt{p53}, \mathtt{Mdm2}).\\
\mathtt{rule}(4) &\stackrel{\text{def}}{=} \mathtt{inhib}(\mathtt{vars}, \mathtt{Mdm2}, \mathtt{p53}).\\
\mathtt{rule}(5) &\stackrel{\text{def}}{=} \mathtt{inhib_c}(\mathtt{vars}, \mathtt{p53}, \mathtt{DNAdam}).\\
\mathtt{rule}(6) &\stackrel{\text{def}}{=} \mathtt{inhib_s}(\mathtt{vars}, \mathtt{DNAdam}, \mathtt{Mdm2}).
\end{aligned}$$

$$\begin{aligned}
\mathtt{system} \stackrel{\text{def}}{=} \quad & \mathtt{vars}, \mathtt{rule}(1), \mathtt{rule}(2), \mathtt{rule}(3),\\
& \mathtt{rule}(4), \mathtt{rule}(5), \mathtt{rule}(6), \mathtt{well_defined}(\mathtt{vars}).
\end{aligned}$$

- *Initial state*:

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

Informal Proofs

Linear Logic $\hookrightarrow$ we sometimes need, in the theorems:

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

In the proofs:

Case analysis on the possible values of variables (using $\mathtt{well\_defined}_1$*).*

Definitions:

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

Property 1

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

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:

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

Proposition (Property 1, Version 2)

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

$$\dagger\, system \;@\; 0 \;;\; state_1 \;@\; w.u \vdash state_0 \;@\; w.u.v$$

Property 2

DNA damage can be quickly recovered.

Proposition (Property 2)

For any world w, there exists a world u such that u is less than 5 and the following holds:

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

Induction/Case Analysis

Case analysis on the set of fireable rules:

$$\mathtt{fireable_s}(1) \stackrel{\text{def}}{=} \mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2}) \otimes \mathtt{dont\_care}(\mathtt{p53})$$

$$\mathtt{not\_fireable_s}(1) \stackrel{\text{def}}{=} ((\mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2})) \oplus (\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2})) \oplus (\mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2}))) \otimes \mathtt{dont\_care}(\mathtt{p53})$$

$$\mathtt{fireable}(1) \stackrel{\text{def}}{=} (\mathtt{pres}(\mathtt{DNAdam}) \oplus (\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{pres}(\mathtt{Mdm2})) \oplus (\mathtt{pres}(\mathtt{DNAdam}) \otimes \mathtt{abs}(\mathtt{Mdm2}))) \otimes \mathtt{dont\_care}(\mathtt{p53})$$

$$\mathtt{not\_fireable}(1) \stackrel{\text{def}}{=} \mathtt{abs}(\mathtt{DNAdam}) \otimes \mathtt{dont\_care}(\{\mathtt{Mdm2}, \mathtt{p53}\})$$

"for any *fireable rule* r, P"

for any rule r in $[1..6]$, $(\mathtt{fireable}(r)\ \&\ P) \oplus \mathtt{not\_fireable}(r)$

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:
$\dagger\, \mathit{system} \,@\, 0, \mathtt{abs(DNAdam)} \,@\, 0 \vdash \mathit{state}_0 \otimes \mathtt{abs(DNAdam)} \,@\, w$.

We want to prove that if $\mathtt{abs(DNAdam)} \,@\, 0$ then $\mathit{state}_0 \otimes \mathtt{abs(DNAdam)} \,@\, w$ 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.

Property 3 (con't)

Proposition (Property 3)

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

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

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.

$\hookrightarrow$ *strong* inhibition and activation rules:

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

Property 4 (con't)

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

from $\mathcal{L}$ we can only go to $\mathcal{R}$, *no matter which rule is fired*.

$\hookrightarrow$ *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; .
$\vdash \mathcal{L} \rightarrow (s\mathtt{\_fireable}(r) \,\&\, \delta_1\, \mathcal{R}) \oplus s\mathtt{\_not\_fireable}(r)$ @ w

Formal Proofs [1]

Proofs fully formalized in *Coq*,
using a *λProlog prover* to help with *partial automation* of the proofs.

The λProlog prover is
a (generic) tactic-style interactive theorem prover,
instantiated with tactics implementing HyLL's inference rules.

$\hookrightarrow$ Both prove *meta-level* properties of HyLL (ex: weakening)
and reason at the *object-level* (i.e. prove HyLL sequents).

Two-level style of reasoning, with HyLL as the *specification logic*.

Formal Proofs [2]

HyLL is implemented as an inductive predicate in Coq.

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

Coq's `apply` tactic requires arguments to be given explicitly for the instantiation of A, B, Δ, etc.

λProlog's tactics use unification to infer these arguments.

$\hookrightarrow$ The λProlog prover
(interactively) applies the HyLL inference rules, and then automatically generates proof scripts for Coq.

Formal Proofs [3]

Let `Gamma` and `PP` be the Coq encodings of (resp.)
$\dagger$ *system* @ 0 and (*state*$_0$ $\otimes$ abs(`DNAdam`)).

Theorem Property3 : forall w:world,
seq Gamma ((PP @ 0)::nil) ((PP at 0) @ w) and
forall (n:nat) (A B:oo_), fireable n A $\rightarrow$ not_fireable n B $\rightarrow$
seq Gamma nil ((PP $\rightarrow_o$ ((A &a step PP) +o B)) @ w).

The Coq proof of the 2nd conjunct proceeds by case analysis on `n`, then 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.

Comparison with Model Checking

Model checking:

- encode the biological system as a finite transition system,
- specify properties in propositional temporal logic, and
- verify properties by exhaustive enumeration of all reachable S

+ efficient tools

CCind-λProlog-HyLL:

+ HyLL has a very traditional proof theoretic pedigree: sequent calculus, cut-elimination and focusing;
+ unified framework to encode both transition rules and (both statements and proofs of) temporal properties;
+ *all* the models containing the rules satisfy a ($\exists$) property.

- theorem proving can be time consuming and needs expert. Can however provide partial, and sometimes complete, automation of the proofs.

Temporal Operators

Encoding of temporal logic operators in $\mathrm{HyLL}[\mathcal{T}]$, where $\mathcal{T} = \langle \boldsymbol{N}, +, 0 \rangle$, representing instants of time:

- State quantifiers

$$\mathsf{F} \Leftrightarrow \Diamond, \quad \mathsf{G} \Leftrightarrow \Box \quad \text{and} \quad \mathsf{X}P \Leftrightarrow \delta_1 P$$

$$P_1 \mathsf{U} P_2 \Leftrightarrow \downarrow u.\ \exists v.\ P_2 \ \mathtt{at}\ u.v \otimes \forall w < v.\ P_1 \ \mathtt{at}\ u.w$$

- Path quantifiers

  E corresponds to the existence of a proof: $\mathsf{EF} \Leftrightarrow \Diamond$, $\mathsf{EG} \Leftrightarrow \Box$

  A: consider all the possible rules to be applied at each step. Let R be the set of rules of our transition system.

  - $\mathsf{AX}P$ is encoded as $\forall r \in R\ \delta_1 P$. More precisely: $\mathsf{AX}P \Leftrightarrow \forall r \in R\ (\mathtt{fireable}(r)\ \&\ \delta_1 P) \oplus \mathtt{not\_fireable}(r)$
  - $\mathsf{AG}P \leftrightarrow P \wedge \mathsf{AG}(P \rightarrow \mathsf{AX}(P))$. $\mathsf{AG}P \Leftrightarrow P \otimes \forall n (P\ \mathit{at}\ n) \rightarrow \forall r \in R (P\ \mathtt{at}\ n+1)$.

Temporal Operators (con't)

- $\mathrm{AF}P \leftrightarrow P \vee \mathrm{AX}(\mathrm{AF}P)$.
  If we have a bound k on the number of steps needed:
  $P \vee \mathrm{AX}(P \vee \mathrm{AX}(\ldots \mathrm{AX}P))$, with k nested occurrences of AX.
  $\mathrm{AF}P \Leftrightarrow P \oplus \forall r \in R(\delta_1 P \oplus (\forall r \in R(\ldots \delta_k P)))$.
- $\mathrm{A}(P_1 \mathrm{U} P_2) \leftrightarrow P_2 \vee (P_1 \wedge \mathrm{AX}(P_1 \mathrm{U} P_2)$.
  If we have a bound k on the number of steps needed:
  $P_2 \vee (P_1 \wedge \mathrm{AX}(P_2 \vee (P_1 \wedge \mathrm{AX}(\ldots \mathrm{AX}P_2))))$, with k nested occurrences of AX.
  $$\mathrm{A}(P_1 \mathrm{U} P_2) \Leftrightarrow P_2 \oplus (P_1 \otimes \forall r \in R(\delta_1 P_2 \oplus (\delta_1 P_1 \otimes \forall r \in R(\ldots \delta_k P_2))))$$

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

Further Advantages w.r.t Model Checking

- We do not need to blindly try all possible rules at each step but we can guide the proof.
- Proof of a property of the system which is not desirable: we can look for the rules to be removed/modified among those that have been used in the proof.
- "P is true at every even state of an infinite path": $\forall n = 2k.\ P\ at\ n.$
- Couple our models with other models sharing some variables.

Future Work

- Other examples.
- Multivalued biological models: $\mathtt{C}(A, x)$.
- Continuous / stochastic constraints.
- Automate the choice between fireable rules - Gillespie.
- Axioms for external events.
- ...
- *A resource-aware stochastic or probabilistic λ-calculus that has HyLL propositions as (behavioral) types.*

Thanks for your attention