(Mathematical) Logic for Systems Biology

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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 Kripke models
  or traces ($\rightarrow$ external simulator)
  $\hookrightarrow$ model checking.

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

General Approach

An unified framework:

- modeling systems of biochemical reactions as transition systems: Linear Logic (LL)
- transitions with (temporal, location, stochastic,...) constraints
- modal extensions of LL: *Hybrid Linear Logic (HyLL)* or *Subexponential Linear Logic (SELL)*
- Both HyLL and SELL have a cut admitting sequent calculus, focused rules, ... *– modern logic*
- Proofs by induction and mechanized proofs: the Coq or Isabelle proof assistant *– future work: automatic proofs*
- proofs: Coq λ-terms containing HyLL/SELL proof trees

$\hookrightarrow$ *A logical framework*$^{(*)}$ *for systems biology.*

(*) A logic for encoding deductive systems and reasoning about them.

Outline

Example

- *Activation*:

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

- *Inhibition*

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

Note. This is not Biocham/Kappa/...

Linear Logic

- Terms:

$$t, \ldots ::= \quad c \mid x \mid f(\vec{t}) \qquad \textit{Ex: } \texttt{P53},\ \texttt{ph}(\texttt{MAPK}), \texttt{complex}(\texttt{PER1}, \texttt{CRY1})$$

- Propositions

$$A, B, \ldots ::= \quad p(\vec{t}) \mid A \otimes B \mid \mathbf{1} \mid A \rightarrow B \mid A \,\&\, B \mid \top \mid A \oplus B \mid \mathbf{0}$$
$$!A \mid \forall x.\ A \mid \exists x.\ A$$
$$\textit{Ex: } \mathcal{C}(\texttt{P53}, 0.2),\ \texttt{pres}(x) \otimes \texttt{abs}(y)$$

- 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.
  C is true assuming the hypotheses Γ and Δ *are true*
  Ex: $\texttt{bio\_system};\ \texttt{pres}(\texttt{x}), \texttt{abs}(\texttt{y}) \vdash \texttt{pres}(\texttt{z})$

"C" is a proposition, "C is true" is a judgement [Martin-Löf 83-96]

Sequent Calculus for Linear Logic [1]

- Judgemental rules:

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

- Multiplicatives:

$$\Gamma; . \vdash 1\ [1\ R] \quad \frac{\Gamma; \Delta \vdash C}{\Gamma; \Delta, 1 \vdash C}\ 1\ L$$

$$\frac{\Gamma; \Delta, A \vdash B}{\Gamma; \Delta \vdash A \to B}\ [\to_R] \qquad \frac{\Gamma; \Delta \vdash A \quad \Gamma; \Delta', B \vdash C}{\Gamma; \Delta, \Delta', A \to B \vdash C}\ [\to_L]$$

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

Sequent Calculus for Linear Logic [2]

- Additives:

$$\Gamma ; \Delta \vdash \top \ [\top R] \qquad \Gamma ; \Delta, \mathbf{0} \vdash C \ [\mathbf{0}L]$$

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

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

- Exponentials: $\dfrac{\Gamma ; . \vdash A}{\Gamma ; . \vdash !A} \, !R \qquad \dfrac{\Gamma, A ; \Delta \vdash C}{\Gamma ; \Delta, !A \vdash C} \, !L$

Proofs are proof-trees, eventually including recursion (not described here).

Pure syntactic part of logic; no models.

Sequent calculus is ideally suited for proof-search [Gentzen 1935-1969]

Example

- *Activation*:

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

- *Inhibition*

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Hybrid Linear Logic [1]

HyLL

- 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 $\langle \mathbb{R}^+, +, 0\rangle$

J. D. and Kaustuv Chaudhuri.
A hybrid linear logic for constrained transition systems.
In *Post-Proceedings of TYPES'2013*, 2014.

Hybrid Linear Logic [2]

- Make all judgements situated *at a world*: $A \;@\; w$

  A is true at world w
- Judgements are of the form:

  $$\Gamma ; \Delta \vdash C \;@\; w,$$

  where Γ and Δ are sets of judgements of the form $A \;@\; w$
- All ordinary rules continue essentially unchanged:

$$\frac{\Gamma ; \Delta, A \;@\; w \vdash B \;@\; w}{\Gamma ; \Delta \vdash A \to B \;@\; w} \; [\to_R]$$

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

$$\ldots$$

Hybrid Connectives

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

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

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 $A \ @ \ u$:

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

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 $[v/u]A \ @ \ v$:

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

Properties of the Sequent Calculus System [1]

Lemma

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

Theorem (identity - syntactic completeness)

$\Gamma; A \ @ \ w \vdash A \ @ \ w$

Theorem (cut - syntactic soundness)

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* $\Gamma; \Delta \vdash C \ @ \ w$.

Properties of the Sequent Calculus System [2]

Lemma (invertibility)

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

Theorem (consistency)

There is no proof of $.;. \vdash \mathbf{0} \ @\ w$.

Theorem (conservativity)

For "pure" contexts Γ *and* Δ *and "pure" (in ILL) proposition* A*:*
if $\Gamma; \Delta \vdash_{HyLL} A \ @\ w$ *then* $\Gamma; \Delta \vdash_{ILL} A$.

Properties of the Sequent Calculus System [3]

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

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

Theorem (HyLL admits a - sound and complete - focused system)

Focusing reduces non-determinism during proof search.
$\hookrightarrow$ normal form of proofs.
$\hookrightarrow$ (full) adequacy (i.e. soundness and completeness) of encodings.

Theorem (adequacy)

$S\pi$ can be fully adequately encoded in (focused) HyLL

Defined Modal Connectives - Delay

- Defined modal connectives:

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

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

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

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

Example

- *Activation*:

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

- *Inhibition*

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

Modeling Approach

In a first experiment:

- Boolean models
  - (i) a set of boolean variables,
  - (ii) a (partially defined) initial state, and
  - (iii) a set of rules of the form $L_i \Rightarrow R_i$
- Rules are asynchronous (one rule can be fired at a time).
- Encode both the model and the property in HyLL, and prove the property in HyLL + Coq.

Elisabetta de Maria, J. D., and Amy Felty.
A logical framework for systems biology.
In *FMMB*, 2014.

Activation/Inhibition Rules [1]

- *Lack of information*:
$$0\_\mathtt{active}(a, b) \stackrel{\text{def}}{=} \mathtt{pres}(a) \multimap \delta_1\, \mathtt{pres}(b).$$
- *Without consumption*:
$$w\_\mathtt{active}(a, b) \stackrel{\text{def}}{=} \mathtt{pres}(a) \multimap \delta_1(\mathtt{pres}(a) \otimes \mathtt{pres}(b)).$$
- *More precise*:
$$s\_\mathtt{active}(a, b) \stackrel{\text{def}}{=} \mathtt{pres}(a) \otimes \mathtt{abs}(b) \multimap \delta_1(\mathtt{pres}(a) \otimes \mathtt{pres}(b)).$$
- *Looping*:
$$l\_\mathtt{active}(a, b) \stackrel{\text{def}}{=} \mathtt{pres}(a) \otimes \mathtt{pres}(b) \multimap \delta_1(\mathtt{pres}(a) \otimes \mathtt{pres}(b)).$$
- *General*:
$$\begin{aligned}&\mathtt{active}(a, b)\\ &\stackrel{\text{def}}{=} (\mathtt{pres}(a) \oplus (\mathtt{pres}(a) \otimes \mathtt{pres}(b)) \oplus (\mathtt{pres}(a) \otimes \mathtt{abs}(b)))\\ &\qquad \multimap \delta_1\ (\mathtt{pres}(a) \otimes \mathtt{pres}(b)).\end{aligned}$$

Activation/Inhibition Rules [2]

- *Inhibition*:

$$\begin{aligned}&\texttt{inhib}(V, a, b)\\ &\quad\stackrel{\text{def}}{=} \texttt{pres}(a) \oplus (\texttt{pres}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{pres}(a) \otimes \texttt{abs}(b)))\\ &\qquad \multimap \delta_1 \ (\texttt{pres}(a) \otimes \texttt{abs}(b)).\end{aligned}$$

- *Inhibition with consumption*:

$$\begin{aligned}&\texttt{inhib}_c(V, a, b)\\ &\quad\stackrel{\text{def}}{=} (\texttt{pres}(a) \oplus (\texttt{pres}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{pres}(a) \otimes \texttt{abs}(b)))\\ &\qquad \multimap \delta_1 \ (\texttt{abs}(a) \otimes \texttt{abs}(b)).\end{aligned}$$

- *Strong inhibition*

$$\begin{aligned}&\texttt{inhib}_s(V, a, b)\\ &\quad\stackrel{\text{def}}{=} (\texttt{abs}(a) \oplus (\texttt{abs}(a) \otimes \texttt{pres}(b)) \oplus (\texttt{abs}(a) \otimes \texttt{abs}(b)))\\ &\qquad \multimap \delta_1 \ (\texttt{abs}(a) \otimes \texttt{pres}(b)).\end{aligned}$$

- ...

Oscillation

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

Definition (one oscillation)

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

Definition (oscillation - object)

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

Definition (oscillation - meta)

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

Example - Definition

The P53/Mdm2 DNA-damage repair mechanism

P53 is a tumor suppressor protein that is activated in reply to DNA damage. 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, in Biocham:

Initial states: P53 is absent and Mdm2 is present.

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

Specification in HyLL [1]

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

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

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

Specification in HyLL [2]

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

Specification in HyLL [3]

- *The system*:

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

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

- *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:

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

Alternative: prove $(\cdots \otimes \top)$.

In the proofs:

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

Definitions:

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

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:

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

Induction/Case Analysis

Case analysis on the set of fireable rules:

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

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

...

"for any *fireable rule* r, P"

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

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

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

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:

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

Property 4 (con't)

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

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:*

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

Formal Proofs

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

Two-level style of reasoning, with HyLL as the *specification logic*
(HyLL is implemented as an inductive predicate in Coq).

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

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.

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.

Subexponentials in Linear Logic

SELL [V. Danos, J.-B. Joinet and H. Schellinx, 93]

Subexponential Signature

$\Sigma = \langle I, \preceq, U \rangle$ where I is a set of labels, $U \subseteq I$ set of unbounded subexp and $\preceq$ is a pre-order among the elements of I.
$\preceq$ is upwardly closed wrt U [if $a \in U$ and $a \preceq b$, then $b \in U$]

$$F \quad ::= \quad \mathbf{0} \mid 1 \mid \top \mid \bot \mid p(\vec{t}) \mid F_1 \otimes F_2 \mid F_1 \oplus F_2 \mid F_1 \parr F_2 \mid F_1 \,\&\, F_2 \mid \exists x.F \mid \forall x.F \mid\, !^a F \mid\, ?^a F \mid \forall x : a.F \mid \exists x : a.F$$

$!^a F$ means that F holds in a.
$!^s ?^s F$ means that F is confined to s.
Moreover if $a \in U$ then $!^a F$ is a classical formula (as $!\,F$ in LL)
Assume two independent spatial domains a and b ($a \not\preceq b$). Then,

$$(!^a C \multimap !^b D), !^b C \not\vdash !^b D$$

Quantification on Subexponentials

$\mathrm{SELL}^{\forall}$ [V. Nigam and C. Olarte and E. Pimentel, 2011-2016]

$$F \quad ::= \quad \cdots \mid \forall x : a.F \mid \exists x : a.F$$

- Creating "new" locations: $\Gamma, \exists l.(F) \vdash G$
- Asserting something about all locations: $\Gamma, \forall l.(F) \vdash G$
- Proving that all locations satisfies G: $\Gamma \vdash \forall l.(G)$
- Proving that G holds in some location: $\Gamma \vdash \exists l.(G)$

Theorem (Cut-elimination)

For any signature Σ, the proof system $\mathrm{SELL}^{\forall}$ admits cut-elimination.

HyLL and SELL$^{\forall}$

- Linear logic defines two kind of contexts: classical (unbounded) and linear.
- SELL generalizes this idea by slitting the context in as many parts as needed.
- Subexponentials are not canonical: $!^a F \not\Leftrightarrow\, !^b F$, thus SELL as a logical framework is more expressive than LL.
- What about HyLL? Do the worlds in HyLL add more expressive power?

J. D., Carlos Olarte, and Elaine Pimentel.
Hybrid and subexponential linear logics.
In *LSFA*, 2016.

Modal Connectives

- Defined modal connectives in HyLL:

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

- in SELL$^{\forall}$:

$$\Box_u A \stackrel{\text{def}}{=} \forall l : u.\ !^{l} A \qquad \Diamond_u A \stackrel{\text{def}}{=} \exists l : u.\ !^{l} A$$
$$\Box A \stackrel{\text{def}}{=} \forall t : \infty.\ !^{t} A \qquad \Diamond A \stackrel{\text{def}}{=} \exists t : \infty.\ !^{t} A$$
$$[\![\delta_v\, A]\!]_u \stackrel{\text{def}}{=} [\![A]\!]_{u.v} \qquad [\![\dagger\, A]\!]_u \stackrel{\text{def}}{=} \forall u : \infty. [\![A]\!]_u$$

Bio Example

- *Inhibition* in HyLL

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

- *Inhibition* in classical SELL$^\forall$

$$\mathtt{Inhib}(a,b) \stackrel{\text{def}}{=} \forall t : \infty.\ !^{t}\mathtt{a} \multimap\ !^{t+1}(\mathtt{a} \ \otimes \ \mathtt{b}^\perp)$$

$$\begin{array}{rl} \mathtt{Inhib}(a,b,c) \stackrel{\text{def}}{=} & \forall t : \infty. \\ & [!^{t}\mathtt{a} \otimes (\mathtt{b} \oplus \mathtt{b}^\perp) \otimes \mathtt{c} \multimap\ !^{t+1}(\mathtt{a} \ \otimes \ \mathtt{b}^\perp) \otimes \mathtt{c}]\ \& \\ & [!^{t}\mathtt{a} \otimes (\mathtt{b} \oplus \mathtt{b}^\perp) \otimes \mathtt{c}^\perp \multimap\ !^{t+1}(\mathtt{a} \ \otimes \ \mathtt{b}^\perp) \otimes \mathtt{c}^\perp] \end{array}$$

- *Inhibition* in SELL$^\forall$

$$\mathtt{Inhib}(x,y,z) \stackrel{\text{def}}{=} \forall t : \infty.\ !^{t}\mathtt{count}(1,y,z) \multimap !^{t+1}\mathtt{count}(1,0,z)$$

More Examples

- HyLL has been used to
  encode transition systems (Sπ calculus) and
  to specify/verify biological interacting systems.
  Biological example with formal proofs in Coq.
- SELL$^{\forall}$ has been used to
  represent contexts of proof systems
  to specify systems with temporal, epistemic
  and spatial modalities
  and soft-constraints or preferences;
  to specify bigraphs and
  to specify/verify biological/multimedia interacting systems.

Encodings in Linear Logic

Two meta-level predicates $\lfloor \cdot \rfloor$ and $\lceil \cdot \rceil$ for identifying objects that appear on the left or right side of the sequents in the object logic.

Rules

$$\frac{\Delta, A \longrightarrow \Gamma}{\Delta, A \wedge B \longrightarrow \Gamma} \wedge_{L1} \quad \frac{\Delta, B \longrightarrow \Gamma}{\Delta, A \wedge B \longrightarrow \Gamma} \wedge_{L2} \quad \frac{\Delta \longrightarrow \Gamma, A \quad \Delta \longrightarrow \Gamma, B}{\Delta \longrightarrow \Gamma, A \wedge B} \wedge_{R}$$

are specified in LL as

$$\wedge_L : \exists A, B.(\lfloor A \wedge B \rfloor^{\perp} \otimes (\lfloor A \rfloor \oplus \lfloor B \rfloor))$$

$$\wedge_R : \exists A, B.(\lceil A \wedge B \rceil^{\perp} \otimes (\lceil A \rceil \mathbin{\&} \lceil B \rceil))$$

The linear logic connectives indicate how these object level formulas are connected: contexts are copied ($\&$) or split ($\otimes$), in different inference rules ($\oplus$) or in the same sequent ($\invamp$).

HyLL and Linear Logic

HyLL rules can be encoded in LL as:

$$
\begin{array}{lcl}
\otimes\, R & : & \exists C, C', w.(\lceil (C \otimes C')@w \rceil^{\perp} \otimes \lceil C@w \rceil \otimes \lceil C'@w \rceil) \\
\otimes\, L & : & \exists C, C', w.(\lfloor (C \otimes C')@w \rfloor^{\perp} \otimes (\lfloor C@w \rfloor \parr \lfloor C'@w \rfloor)) \\
\mathtt{at}\ R & : & \exists C, u, w.(\lceil (C\ \mathtt{at}\ u)@w \rceil^{\perp} \otimes \lceil C@u \rceil) \\
\mathtt{at}\ L & : & \exists C, u, w.(\lfloor (C\ \mathtt{at}\ u)@w \rfloor^{\perp} \otimes \lfloor C@u \rfloor) \\
\downarrow R & : & \exists A, u, w.(\lceil \downarrow u.A@w \rceil^{\perp} \otimes \lceil (A\ w)@w \rceil) \\
\downarrow L & : & \exists A, u, w.(\lfloor \downarrow u.A@w \rfloor^{\perp} \otimes \lfloor (A\ w)@w \rfloor)
\end{array}
$$

Theorem (Adequacy)

Let Υ be the set of above clauses. The sequent $\Gamma; \Delta \vdash F@w$ is provable in HyLL iff $\vdash ?\Upsilon, ?\lfloor \Gamma \rfloor, \lfloor \Delta \rfloor, \lceil F@w \rceil$ is provable in LL.
The adequacy of the encodings is on the level of derivations *[i.e. when focusing on a LL specification clause, the (bipole) derivation corresponds exactly to applying the introduction rule at the object level].*

HyLL and SELL

HyLL rules into SELL$^{\forall}$:

$$
\begin{array}{lcl}
\otimes\, R & : & \exists C, C'.\exists w : \infty.(!^{w}\lceil (C \otimes C')@w\rceil^{\perp} \otimes ?^{w}\lceil C@w\rceil \otimes ?^{w}\lceil C'@w\rceil \\
\mathtt{at}\ R & : & \exists A.\exists u : \infty, w : \infty.(!^{w}\lceil (A\ \mathtt{at}\ u)@w\rceil^{\perp} \otimes ?^{u}\lceil A@u\rceil) \\
\mathtt{at}\ L & : & \exists A.\exists u : \infty, w : \infty.(!^{w}\lfloor (A\ \mathtt{at}\ u)@w\rfloor^{\perp} \otimes ?^{u}\lfloor A@u\rfloor) \\
\downarrow R & : & \exists A.\exists u : \infty, w : \infty.(!^{w}\lceil \downarrow u.A@w\rceil^{\perp} \otimes ?^{w}\lceil (A\ w)@w\rceil) \\
\downarrow L & : & \exists A.\exists u : \infty, w : \infty.(!^{w}\lfloor \downarrow u.A@w\rfloor^{\perp} \otimes ?^{w}\lfloor (A\ w)@w\rfloor)
\end{array}
$$

Theorem (Adequacy)

Let Υ be the set of formulas resulting from the encoding in the above definition. The sequent $\Gamma; \Delta \vdash F@w$ is provable in HyLL iff $\vdash ?^{c}\Upsilon, ?^{c}\lfloor\Gamma\rfloor, \lfloor\Delta\rfloor, ?^{w}\lceil F@w\rceil$ is provable in $SELL^{\forall}$. Moreover, the adequacy of the encodings is on the level of derivations.

Information Confinement

- Information confinement in SELL:
  inconsistency is local: $!^w ?^w \mathbf{0} \nvdash \mathbf{0}$
  inconsistency is not propagated: $!^w ?^w \mathbf{0} \nvdash !^v ?^v \mathbf{0}$
- In HyLL it is not possible to confine inconsistency:
  even if we exchange the rule $\mathbf{0}L$ by

$$\Gamma; \Delta, \mathbf{0}@w \vdash F@w \; [0_L]$$

the rule $\mathbf{0}L$ would still be admissible:

$$\dfrac{\Gamma; \Delta, \mathbf{0}@w \vdash (\mathbf{0} \text{ at } v)@w \;\; 0_L \qquad \dfrac{\Gamma; \Delta, \mathbf{0}@v \vdash F@v \;\; 0_L}{\Gamma; \Delta, (\mathbf{0} \text{ at } v)@w \vdash F@v} \, at_L}{\Gamma; \Delta, \mathbf{0}@w \vdash F@v} \, \mathrm{cut}$$

CTL in HyLL [1]

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

- State quantifiers

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

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

- Path quantifiers

  E corresponds to the existence of a proof: EF $\Leftrightarrow \Diamond$, 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.

  - AXP is encoded as $\mathrm{forall}\ r\ \mathrm{in}\ R\ \delta_1 P$. More precisely: AX$P \Leftrightarrow \mathrm{forall}\ r\ \mathrm{in}\ R\ (\mathtt{fireable}(r)\ \&\ \delta_1 P) \oplus \mathtt{not_fireable}(r)$
  - AG$P \leftrightarrow P \wedge \mathrm{AG}(P \multimap \mathrm{AX}(P))$. AG$P \Leftrightarrow P \ \otimes\ \forall n.\ (P\ at\ n) \multimap \mathrm{forall}\ r\ \mathrm{in}\ R\ (P\ \mathtt{at}\ n+1)$.
  - AF$P \leftrightarrow P \vee \mathrm{AX}(\mathrm{AF}P)$. for a bound k on the number of steps needed.

CTL in HyLL [2]

Let $\mathtt{V} = \{a_1, ..., a_n\}$ propositional variables and $\mathtt{s} = \mathtt{p}_1(a_1) \wedge \cdots \wedge \mathtt{p}_n(a_n)$ represent a state where $\mathtt{p}_i \in \{\mathtt{pres}, \mathtt{abs}\}$ and $r : \mathtt{s} \to \mathtt{s}'$ be a state transition.
Encoding $[\![\cdot]\!]$ from CTL states and state transitions to HyLL:

$$[\![\mathtt{pres}(a_i)]\!] = \mathtt{pres}(a_i) \quad [\![\mathtt{abs}(a_i)]\!] = \mathtt{abs}(a_i)$$
$$[\![\mathtt{s}]\!] = \bigotimes_{i \in 1..n} [\![\mathtt{p}_i(a_i)]\!] \qquad [\![r : \mathtt{s} \to \mathtt{s}']\!] = \forall w. (([\![\mathtt{s}]\!] \ \mathtt{at}\ w) \multimap \delta_1([\![\mathtt{s}']\!]) \ \mathtt{at}\ w$$

Let F, G be CTL formulas built from states and $\wedge, \vee, \mathrm{U}, \mathrm{EX}, \mathrm{EF}$.

$$\begin{array}{lcllcl}
\mathcal{C}[\![\mathtt{s}]\!] & = & [\![\mathtt{s}]\!] & \mathcal{C}[\![F \wedge G]\!] & = & \mathcal{C}[\![F]\!] \,\&\, \mathcal{C}[\![G]\!] \\
\mathcal{C}[\![F \vee G]\!] & = & \mathcal{C}[\![F]\!] \oplus \mathcal{C}[\![G]\!] & \mathcal{C}[\![\mathrm{E}[F \mathrm{U} G]]\!] & = & \mathcal{C}[\![F]\!] \mathrm{U}\ \mathcal{C}[\![G]\!] \\
\mathcal{C}[\![\mathrm{EX}F]\!] & = & \delta_1\, \mathcal{C}[\![F]\!] & \mathcal{C}[\![\mathrm{EF}F]\!] & = & \Diamond \mathcal{C}[\![F]\!]
\end{array}$$

Such encodings are *faithful*, i.e. a CTL formula F holds at state $\mathtt{s}$ in $\mathcal{R}$ iff $[\![\mathcal{R}]\!]@0; [\![\mathtt{s}]\!]@w \vdash \mathcal{C}[\![F]\!]@w$ is provable in HyLL.

CTL in μMALL

MALL is the core of LL: without exponentials (! and ?).
μMALL: extension of MALL with (least and greatest) fixed points

$$\frac{\Sigma \vdash \Delta, S\vec{t} \qquad \vec{x} \vdash B\ S\vec{x}, (S\vec{x})^{\perp}}{\Sigma \vdash \Delta, \nu B\vec{t}}\ \nu \qquad \frac{\Sigma \vdash \Delta, B(\mu B)\vec{t}}{\Sigma \vdash \Delta, \mu B\vec{t}}\ \mu$$

where S is the (co)inductive invariant. The μ rule corresponds to unfolding while ν allows for (co)induction. Σ represents the (first-order) signature.

CTL in μMALL [1]

Path quantifiers as fixpoints:

$$
\begin{array}{rcl}
\mathrm{EF}F & = & \mu Y.F \vee \mathrm{EX}Y \\
\mathrm{EG}F & = & \nu Y.F \wedge \mathrm{EX}Y
\end{array}
\qquad
\mathrm{E}[F \mathrm{U} G] = \mu Y.G \vee (F \wedge \mathrm{EX}Y)
$$

$$
\begin{array}{rcl}
\mathrm{AF}F & = & \mu Y.F \vee \mathrm{AX}Y \\
\mathrm{AG}F & = & \nu Y.F \wedge \mathrm{AX}Y
\end{array}
\qquad
\mathrm{A}[F \mathrm{U} G] = \mu Y.G \vee (F \wedge \mathrm{AX}Y)
$$

CTL in μMALL [2]

Definition (CTL into μMALL)

Let $\mathcal{R}$ be of transition rules and a state $\mathtt{s} = \mathtt{p}_1(a_1) \wedge \cdots \wedge \mathtt{p}_n(a_n)$.

$$
\begin{array}{lcl}
[\![\mathtt{pres}(a_i)]\!] = a_i \qquad [\![\mathtt{abs}(a_i)]\!] = a_i^\perp \qquad [\![p]\!] = \mathtt{pos}(p) \\
[\![s]\!] & = & [\![\mathtt{p}_1(a_1)]\!]^\perp \parr \cdots \parr [\![\mathtt{p}_n(a_n)]\!]^\perp \\
\mathtt{pos(s)} & = & [\![\mathtt{p}_1(a_1)]\!] \otimes \cdots \otimes [\![\mathtt{p}_n(a_n)]\!] \\
\mathtt{neg(s)} & = & ([\![\mathtt{p}_1(a_1)]\!]^\perp \otimes \top) \oplus \cdots \oplus ([\![\mathtt{p}_n(a_n)]\!]^\perp \otimes \top)
\end{array}
$$

p is a state formula. $\mathtt{pos(s)}$ (resp. $\mathtt{neg(s)}$) tests if r can (resp. cannot) be fired at the current state.
We map CTL $\wedge$ [resp. $\vee$] into & [resp. $\oplus$].

$$
\begin{array}{lcl}
\mathcal{C}[\![\mathsf{AX}F]\!]_{\mathcal{R}} & = & \mathop{\&}_{\mathtt{s} \to \mathtt{s}' \in \mathcal{R}} (\mathtt{neg(s)} \oplus (\mathtt{pos(s)} \otimes ([\![\mathtt{s}']\!] \parr \phi))) \\
\mathcal{C}[\![\mathsf{EX}F]\!]_{\mathcal{R}} & = & \bigoplus_{\mathtt{s} \to \mathtt{s}' \in \mathcal{R}} (\mathtt{pos(s)} \otimes ([\![\mathtt{s}']\!] \parr \phi))
\end{array}
$$

CTL in μMALL [3]

Definition (CTL into μMALL (con't))

$$\begin{aligned}
\mathcal{C}[\![\mathsf{AF}F]\!]_{\mathcal{R}} &= \mu Y.\ \phi \oplus \mathop{\&}_{s \to s' \in \mathcal{R}} (\mathrm{neg}(s) \oplus (\mathrm{pos}(s) \otimes ([\![s']\!] \parr Y))) \\
\mathcal{C}[\![\mathsf{EF}F]\!]_{\mathcal{R}} &= \mu Y.\ \phi \oplus \bigoplus_{s \to s' \in \mathcal{R}} (\mathrm{pos}(s) \otimes ([\![s']\!] \parr Y)) \\
\mathcal{C}[\![\mathsf{AG}F]\!]_{\mathcal{R}} &= \nu Y.\ \phi \mathbin{\&} \mathop{\&}_{s \to s' \in \mathcal{R}} (\mathrm{neg}(s) \oplus (\mathrm{pos}(s) \otimes ([\![s']\!] \parr Y))) \\
\mathcal{C}[\![\mathsf{EG}F]\!]_{\mathcal{R}} &= \nu Y.\ \phi \mathbin{\&} \bigoplus_{s \to s' \in \mathcal{R}} (\mathrm{pos}(s) \otimes ([\![s']\!] \parr Y)) \\
\mathcal{C}[\![\mathsf{A}[F \mathsf{U} G]]\!]_{\mathcal{R}} &= \mu Y. \psi \oplus \left(\phi \mathbin{\&} \mathop{\&}_{s \to s' \in \mathcal{R}} (\mathrm{neg}(s) \oplus (\mathrm{pos}(s) \otimes ([\![s']\!] \parr Y)) \right) \\
\mathcal{C}[\![\mathsf{E}[F \mathsf{U} G]]\!]_{\mathcal{R}} &= \mu Y. \psi \oplus \left(\phi \mathbin{\&} \bigoplus_{s \to s' \in \mathcal{R}} (\mathrm{pos}(s) \otimes ([\![s']\!] \parr Y)) \right)
\end{aligned}$$

CTL in μMALL [4]

Let $s \models^{\mathcal{R}}_{CTL} F$ denote "the CTL formula F holds at state s in $\mathcal{R}$".

Theorem (Adequacy)

Let $V = \{a_1, \ldots, a_n\}$ be a set of propositional variables, $\mathcal{R}$ be a set of transition rules on V and F be a CTL formula. Then, $s \models^{\mathcal{R}}_{CTL} F$ iff the sequent $\vdash [\![s]\!], \mathcal{C}[\![F]\!]_{\mathcal{R}}$ is provable in μMALL.

Example in Biomedicine

[Ongoing joint work with P. Lio']
Formalizing the evolution of cancer cells - driver or passenger mutations.

An intravasating Circulating Tumour Cell:

$$\text{In HyLL:} \quad \mathtt{C}(n, \mathit{breast}, f, [\mathtt{EPCAM}]) \multimap \delta_d\ \mathtt{C}(n, \mathit{blood}, 1, [\mathtt{EPCAM}])$$

$$\text{In SELL}^{\forall}\text{:} \quad \forall t : \infty. \; !^{t}!^{br}\mathtt{C}(n, f, [\mathtt{EPCAM}]) \multimap !^{t+d}!^{bl}\mathtt{C}(n, 1, [\mathtt{EPCAM}])$$

where f is a fitness parameter.

Our long term goal here is the design of a Logical Framework for disease diagnosis and therapy prognosis.

Conclusion and Future Work

- Done: HyLL and SELL$^{\forall}$ for biology (first steps), HyLL vs SELL$^{\forall}$ (HyLL into LL, HyLL into SELL$^{\forall}$, simplicity/efficiency vs expressiveness/localities), CTL into μMALL.
- Claim: Logical Frameworks are safe and general frameworks, for specifying and verifying properties of a large number of systems.
- To do: automatic proofs for HyLL/SELL$^{\forall}$ for biology, biomedicine (diagnosis and prognosis), neuroscience, ...
- and also: external events, stochastic constraints, formal proofs of (meta-theoretical) properties of HyLL/SELL (in Coq), ..., *a resource-aware stochastic or probabilistic λ-calculus that has HyLL propositions as (behavioral) types.* $\rightsquigarrow$ type-theory.

Thanks for your attention

J. D. and Kaustuv Chaudhuri.
A hybrid linear logic for constrained transition systems.
In *Post-Proceedings of TYPES'2013*, 2014.

Elisabetta de Maria, J. D., and Amy Felty.
A logical framework for systems biology.
In *FMMB*, 2014.

J. D., Carlos Olarte, and Elaine Pimentel.
Hybrid and subexponential linear logics.
In *LSFA*, 2016.