Abstract simulation of ODEs

Athénaïs Vaginay
Université de Caen

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Modelling biology with reaction networks

$\mathcal{R} = \{\mathcal{R}_i : R_i \xrightarrow{e_i} P_i \mid i = 1 \dots m\}$

reaction, reactants, products, kinetics

Ordinary Differential Equations (ODE)

$\left\{\dot{X} = \sum_{i \in 1 \dots m} e_i \times (P_i(X) - R_i(X)) \mid X \in \mathcal{S}\right\}$

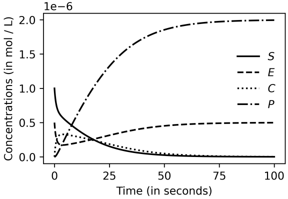
(numerical) solving $\rightarrow$ continuous time and values

Example

$$\mathcal{S} = \{S, E, C, P\}$$

$$\boldsymbol{\mathcal{R}}_{enz} = \left\{ \begin{array}{l} \mathcal{R}_{on} : S + E \xrightarrow{e_{on}} C \\ \mathcal{R}_{off} : C \xrightarrow{e_{off}} S + E \\ \mathcal{R}_{cat} : C \xrightarrow{e_{cat}} E + 2 \times P \end{array} \right\}$$

$$\mathrm{ode}_{\boldsymbol{\mathcal{R}}_{enz}} = \begin{cases} \dot{S} = -e_{on} + e_{off} \\ \dot{E} = -e_{on} + e_{off} + e_{cat} \\ \dot{C} = e_{on} - e_{off} + e_{cat} \\ \dot{P} = 2 \times e_{cat} \end{cases}$$



Problem with numerical solving

- Kinetic parameters are hard to measure / estimate
- Can't picture the whole behavior of the systems (simulation with an infinitly many combinations of initial conditions)
- Technical problems: which integration method ? hyperparameters ? Stiffness, float representation...
- We lose the causality of events (except with Euler, which is inefficient), necessary to reason qualitatively on the dynamics

Example

$$\boldsymbol{\mathcal{R}}_{\mathsf{enz}} = \begin{Bmatrix} \mathcal{R}_{\mathrm{on}} : \mathsf{S} + \mathsf{E} \xrightarrow{e_{\mathrm{on}}} \mathsf{C} \\ \mathcal{R}_{\mathrm{off}} : \mathsf{C} \xrightarrow{e_{\mathrm{off}}} \mathsf{S} + \mathsf{E} \\ \mathcal{R}_{\mathrm{cat}} : \mathsf{C} \xrightarrow{e_{\mathrm{cat}}} \mathsf{E} + 2 \times \mathsf{P} \end{Bmatrix}$$

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$$\boldsymbol{\mathcal{R}}_{\mathsf{enz}} = \left\{ \begin{array}{l} \mathcal{R}_{\mathrm{on}} : \mathsf{S} + \mathsf{E} \xrightarrow{\mathrm{k_{on}} \times \mathsf{S} \times \mathsf{E}} \mathsf{C} \\ \mathcal{R}_{\mathrm{off}} : \mathsf{C} \xrightarrow{\mathrm{k_{off}} \times \mathsf{C}} \mathsf{S} + \mathsf{E} \\ \mathcal{R}_{\mathrm{cat}} : \mathsf{C} \xrightarrow{\mathrm{k_{cat}} \times \mathsf{C}} \mathsf{E} + 2 \times \mathsf{P} \end{array} \right\}$$

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Example

$$\boldsymbol{\mathcal{R}}_{\mathsf{enz}} = \begin{cases} \mathcal{R}_{\text{on}} : \mathsf{S} + \mathsf{E} \xrightarrow{10^6 \times \mathsf{S} \times \mathsf{E}} \mathsf{C} \\ \mathcal{R}_{\text{off}} : \mathsf{C} \xrightarrow{0.2 \times \mathsf{C}} \mathsf{S} + \mathsf{E} \\ \mathcal{R}_{\text{cat}} : \mathsf{C} \xrightarrow{0.1 \times \mathsf{C}} \mathsf{E} + 2 \times \mathsf{P} \end{cases}$$

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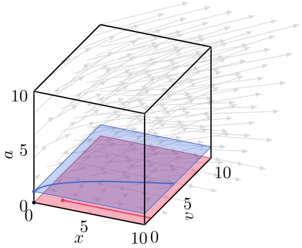
Example

Point moving along an axis : $\dot{a} = 0; \quad \dot{v} = a; \quad \dot{x} = v$
Analytical solution : $a(t) = 1; \quad v(t) = t; \quad x(t) = t^2/2$



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Analytical solution

t	0	1	2	3
a	1	1	1	1
v	0	1	2	3
x	0	0.5	2	4.5

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Analytical solution and clever solvers*

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Euler with $\Delta = 1$

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Abstract simulation [Niehren et al., 2022]

Euler algo:

$\mathcal{V} = \left\{ \mathsf{X}, \dot{\mathsf{X}}, \underset{\mathrm{next}}{\mathsf{X}}, \underset{\mathrm{next}}{\dot{\mathsf{X}}} \mid \mathsf{X} \in \mathcal{S} \right\}$, interpreted over reals.

(1) X (2) $\dot{\mathsf{X}} = f\left(\mathbb{R}_+^{|\mathcal{S}|}\right)$ (3) $\underset{\mathrm{next}}{\mathsf{X}} = \mathsf{X} + \dot{\mathsf{X}} \times \Delta$

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- Analogy with abstract interpretation of programs [Cousot, Cousot, 1977]
- Causal relationship encoded in a first order logic formula ϕ

FOBNN: First-Order Boolean Networks with Nondeterm. updates

- A model of ϕ on $\mathbb{S} = \{-1, 0, 1\}$ projected on $\mathcal{S} \cup \underset{\text{next}}{\mathcal{S}}$
  $\rightsquigarrow$ a transition $\mathbb{B}^n \to \mathbb{B}^n$ over discrete time

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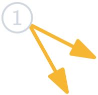

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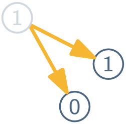

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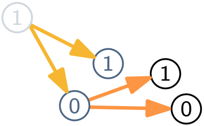


Example on $\boldsymbol{\mathcal{R}}_{\mathsf{enz}}$ – reactions and odes

$\mathcal{S} = \{\mathsf{S}, \mathsf{E}, \mathsf{C}, \mathsf{P}\}$

$$\boldsymbol{\mathcal{R}}_{\mathsf{enz}}$$

$$\left\{\begin{array}{l} \mathcal{R}_{\mathrm{on}} : \mathsf{S} + \mathsf{E} \xrightarrow{e_{\mathrm{on}}} \mathsf{C} \\ \mathcal{R}_{\mathrm{off}} : \mathsf{C} \xrightarrow{e_{\mathrm{off}}} \mathsf{S} + \mathsf{E} \\ \mathcal{R}_{\mathrm{cat}} : \mathsf{C} \xrightarrow{e_{\mathrm{cat}}} \mathsf{E} + 2 \times \mathsf{P} \end{array}\right\}$$

$$\mathrm{ode}_{\boldsymbol{\mathcal{R}}_{\mathsf{enz}}}$$

$$\begin{cases} \dot{\mathsf{S}} = -e_{\mathrm{on}} + e_{\mathrm{off}} \\ \dot{\mathsf{E}} = -e_{\mathrm{on}} + e_{\mathrm{off}} + e_{\mathrm{cat}} \\ \dot{\mathsf{C}} = e_{\mathrm{on}} - e_{\mathrm{off}} + e_{\mathrm{cat}} \\ \dot{\mathsf{P}} = 2 \times e_{\mathrm{cat}} \end{cases}$$

e: mass action law

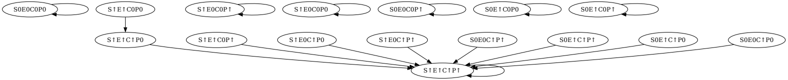
Example on $\mathcal{R}_{\text{enz}}$ – FOBNN

$$
\begin{aligned}
& \mathring{S} = -e_{\text{on}} + e_{\text{off}} && \wedge\ \underset{\text{next}}{\mathring{S}} = -\underset{\text{next}}{e_{\text{on}}} + \underset{\text{next}}{e_{\text{off}}} \\
\wedge\ & \mathring{E} = -e_{\text{on}} + e_{\text{off}} + e_{\text{cat}} && \wedge\ \underset{\text{next}}{\mathring{E}} = -\underset{\text{next}}{e_{\text{on}}} + \underset{\text{next}}{e_{\text{off}}} + \underset{\text{next}}{e_{\text{cat}}} \\
\wedge\ & \mathring{C} = e_{\text{on}} - e_{\text{off}} - e_{\text{cat}} && \wedge\ \underset{\text{next}}{\mathring{C}} = \underset{\text{next}}{e_{\text{on}}} - \underset{\text{next}}{e_{\text{off}}} - \underset{\text{next}}{e_{\text{cat}}} \\
\wedge\ & \mathring{P} = e_{\text{cat}} && \wedge\ \underset{\text{next}}{\mathring{P}} = \underset{\text{next}}{e_{\text{cat}}}
\end{aligned}
$$

$$
\begin{aligned}
\wedge\ & \underset{\text{next}}{S} = S + \mathring{S} && \wedge\ S \leq \underset{\text{next}}{S} \\
\wedge\ & \underset{\text{next}}{E} = E + \mathring{E} && \wedge\ E \leq \underset{\text{next}}{E} \\
\wedge\ & \underset{\text{next}}{C} = C + \mathring{C} && \wedge\ C \leq \underset{\text{next}}{C} \\
\wedge\ & \underset{\text{next}}{P} = P + \mathring{P} && \wedge\ P \leq \underset{\text{next}}{P}
\end{aligned}
$$

e: mass action law

Example on $\mathcal{R}_{enz}$ – computed transition graph



with mass action law constraint

From FOBNN to Propositional BNN

FOBNN: First-Order Boolean Networks with Nondeterministic updates
terms + existential quantifiers + the finite domain of sign

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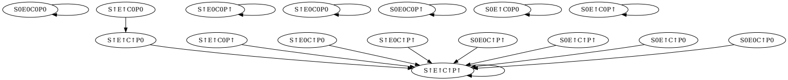
$\Longrightarrow$ satisfiability is decidable and an FOBNN can be **effectively translated** into a **propositional** logic formula.

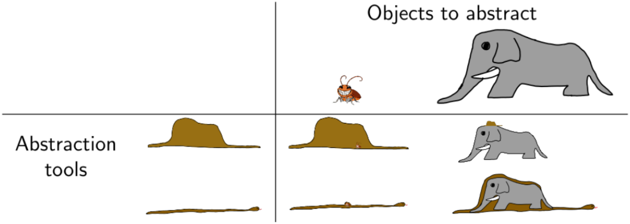
Joint work with Hans-Jörg Schurr (univ. Iowa) : sound and complete translation to propositional logics + implementation with a SAT solver.

- Fast enumeration of transitions
- Find fixed-points (inescapable configurations)

Summary of the workflow

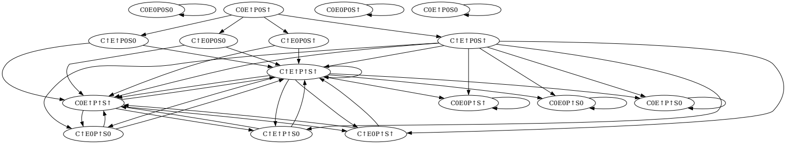
An ODE system → an FO formula → an equisatifiable propositional formula → a transition graph → model checking





Figures inspired from [Saint-Exupery 1943]

- hat is not complete nor tight
- snake is complete and tight.
- FOBNN are complete but not tight (indeterminacies)



$\mathcal{R}_{\mathsf{enz}}$ without the mass action constraint

Conclusion

- Abstract simulation to reason qualitatively on the dynamics of ODEs
- FOBNN soundly overapproximate the ODEs traces with Euler
- Translation to propositional logics $\rightarrow$ SAT-based model checking technics

Future work

- Use FO/P-BNN to anticipate other dynamical properties (beyond fixed-points : limit cycles, stability of steady-states)
- Refine the abstraction (eg : add logical consequences of the equations)
- Further comparison to other Boolean abstraction of biological systems (Boolean semantics of Biocham, Boolean automata networks)

Thank you for your attention.

FO to P

- flatten the equations
- translate the equations using 2 propositional variables for each term.

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