Oded Maler: An odyssey from Computer Science to Biological Sciences

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Plan

"*You may have killed God beneath the weight of all that you have said*"

[The Archaeology of Knowledge, Michel Foucault]

We will talk about **some** contributions of Oded

1. Hybrid Systems
2. Applications to Systems Biology

Plan

- Much more on Oded's contributions will be said in depth by many in the coming **HSCC 2019** (April 2019, Montreal) and the **Oded Maler Memorial Day** (Sept 2019, Grenoble), and on **other** occasions related to his communities
- Acknowledgements. To **Oded** for ready material (figures, explanations, email exchanges), to **Eugene Asarin** for his comments

Hybrid Systems: Motivations

- His adviser Amir Pnueli, laureate of Turing award 1996 for introducing temporal logic as a specification language, a founder of the reactive systems domain
- Oded was curious about robotics and AI, especially technical reports by R. Brooks (MIT AI lab) advocating a behavior-based approach
- Interested in the physical world around programs, he wanted to know how to

  "*verify that a robot, following some control program, behaves correctly in an environment*"[1]

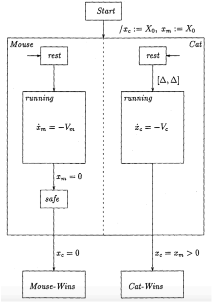
- With Amir Pnueli, he wrote a proposal, entitled "Systematic Development of Robots" (that did not pass! and he moved to France)

[1] 'Amir Pnueli and the Dawn of Hybrid Systems', Oded Maler, 2010.

First Hybrid Systems Model

- Historical context: Success of **algorithmic verification** and **emergence of timed systems**
- With Zohar Manna and Amir Pnueli, Oded proposed the model **phase-transition systems** in a seminal paper "From timed to hybrid systems" in 1992
- an extended version of temporal logic

Phase-Transition Systems



Transitions

- Discrete changes
- Take no time
- Execute by interleaving
- Defined by transition relations

Activities

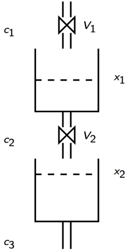
- Continuous changes
- Take time
- Execute in parallel
- Defined by differential equations

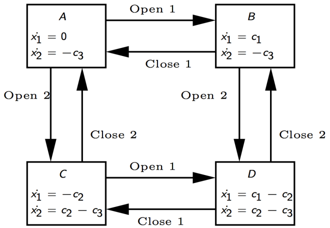
Precursor of hybrid automata

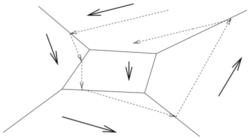
[R. Alur, C. Courcoubetis, N. Halbwachs, T.A. Henzinger, P.-H. Ho, X. Nicollin, A. Olivero, J. Sifakis, and S. Yovine. The algorithmic analysis of hybrid systems, 1995]

Verification of Hybrid Systems: PCD

- Encouraged by verification of **timed automata**
- Starting with **Piecewise-Constant Derivative systems (PCD)**
  - simple continuous dynamics
  - complexity comes from discrete dynamics switching
- Collaboration with Eugene Asarin and Amir Pnueli
- (occasion to "reinvent (independently) a version of Poincaré maps")

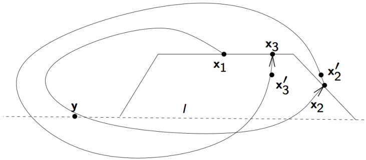






Planar PCD: Decision and Computation Problems

- Linear order: if a trajectory intersects an exit edge at three consecutive points x_1, x_2 and x_3, then $x_1 \preceq x_2$ implies $x_2 \preceq x_3$
- A trajectory cannot intersect itself (Jordan curve theorem), unlike the right figure
- For every trajectory, the sequence of edges it crosses is ultimately-periodic $\Rightarrow$ Abstract finite alphabet to describe qualitative behaviors as sequences of regions or edges



Main results

- Algorithm for deciding reachability problems (between two points, between two regions)

  [O. Maler and A. Pnueli, Reachability Analysis of Planar Multi-Linear Systems, 1993]

- Proof of undecidability for 3 dimensions by showing that PCDs can simulate any Turing Machine (2PDA)

  [E. Asarin and O. Maler, On some Relations between Dynamical Systems and Transition Systems, 1994]

- Proof (using Zeno paradox) of how all the arithmetical hierarchy can be realized by PCDs

  [E. Asarin and O. Maler, Achilles and the Tortoise Climbing Up the Arithmetical Hierarchy, 1995]

Technical Follow-ups and Impacts

- A generalization to planar differential inclusions (Asarin, Pace, Schneider and Yovine)
- Decidability boundaries for linear hybrid automata (Henzinger et al)
- Stability of Polyhedral Switched Systems (M. Viswanathan, P. Prabhakar et al.)
- Models of Computation (O. Bournez et al.)
- Approximation of continuous systems by tractable piecewise simpler derivative systems (by various researchers from both CS and control sciences)

Intellectual Impacts

These theoretical results came with

- some **disappointment** (we cannot answer anything, even about systems with such simple continuous dynamics!)
- **new motivation** for researchers in verification
  - How to handle continuous dynamics? $\Rightarrow$ Change of point of view
  - In the continuous world, seeking exact answers is not wise
  - More meaningful to seek approximate answers on more complex systems with non-trivial continuous dynamics

Intellectual Impacts

Not only theoretical results, but also **effort to look from the perspectives of the others**

"*Hopefully, this will provide control theorists and engineers with an additional perspective of their discipline as seen by a sympathetic outsider, uncommitted to the customs and traditions of the domain*" (Control from Computer Science, IFAC Annual Reviews in Control, Oded Maler, 2003)

- **attention** and **enthusiasm** in the **control theory** community who began to embrace **formal methods**
- creation of **conferences**, in particular HSCC (Hybrid Systems: Control and Computation) conference series, started in 1998
- **joint projects** (such as European projects VHS (Verification of Hybrid Systems) 2001, CC (Control and Computation) 2005, PROSYD (Property-based System Design) 2007)

Hybrid Systems II: Systems with Differential Equations

Challenge: Combination of continuous evolution and discrete changes in hybrid systems poses

- **conceptual problems**: existence of solutions, Zeno behaviors, infinitely many possible behaviors
- **computational problems**: lack of known closed-form solutions to differential equations, complexity of representation of solution sets

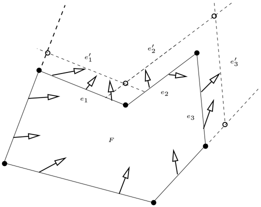
First attempts

- Approximating continuous dynamics by timed automata (UPPAAL, KRONOS) and linear hybrid automata (HYTECH) [Stursberg, Henzinger, et al.]
- The resulting approximate models are too large

It is thus important to exploit ideas from studies of continuous systems and control theory

(Ambitious) Reachable Set Computation

$$\dot{x} = f(x)$$

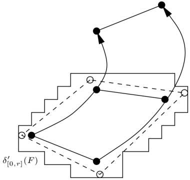


- Via face lifting due to continuity of trajectories
- Set-based Euler integration scheme

[Dang and Maler 1998]

(Less ambitious and more thoughtful) Reachable Set Computation

$$\dot{x} = Ax$$



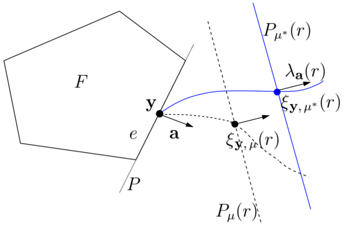
- Using convex and orthogonal polyhedra, exploiting structural properties, tool **d/dt** [Asarin, Bournez, Dang, Maler 2000]

Related work

- **CheckMate** [Chutinan, Krogh 1999] (convex-polyhedron based reachability, for abstraction purposes)
- **Ellipsoidal calculus** [Kurzhanski, Varaiya 1997], **MPT tool** [Morari et al]

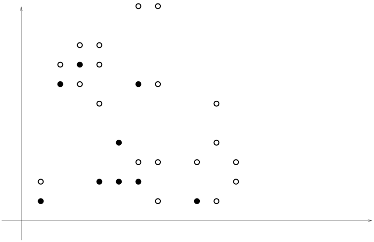
Systems with Uncertain Input - Optimal Control

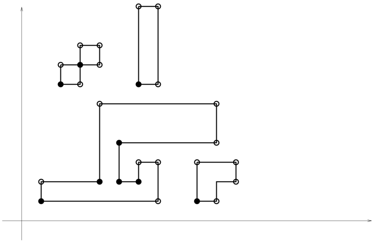
$$\dot{x} = Ax + u$$



- Adjoint system: $\dot{\lambda}_{\mathbf{a}} = -A^T \mathbf{a}$
- $\mu^*(t)$ optimal input that drives the system furthest in the direction of $\lambda_{\mathbf{a}}(t)$

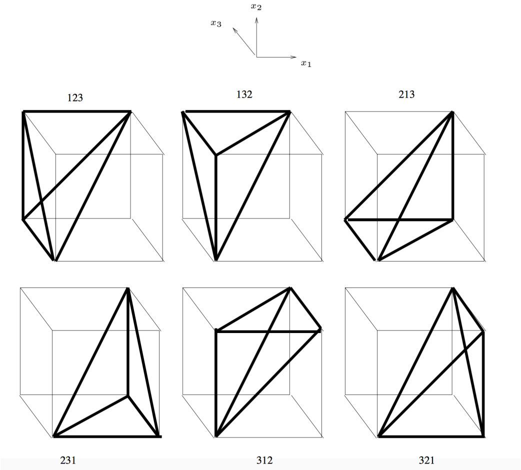
- **Non-convex** set representation, crucial ingredient
- Orthogonal polyhedra, represented by **colored vertices**
- Collaboration with Olivier Bournez
- Used for modelling constraints of timed PV programs [Dang and Genet 2006]





Timed Polyhedra

- Alternative set representation for timed automata



Reachable Set Computation - Impacts

- Opened a direction for exporting algorithmic verification to continuous and hybrid systems
- Not limited to verification, useful for **control synthesis**
- Well-accepted by both model-checking and control communities, and recently attracted researchers from program verification/abstract interpretation
- Reachable set computation has become a **central problem** in hybrid systems research

All *not* quiet on the *Timed* Front

Contributions in algorithmics, problems beyond verification, and applications

- **Controller synthesis** for timed automata
- **Scheduling** using timed automata, optimality, under stochastic uncertainty
- **Compositional** timing analysis
- Control with **bounded computational resources**
- **Multi-criteria** optimization
- **Embedded multicore**
- **Real-time** temporal logic, **timed** regular expressions
- **Monitoring**, **timed pattern matching**

Controller Synthesis for Timed Automata

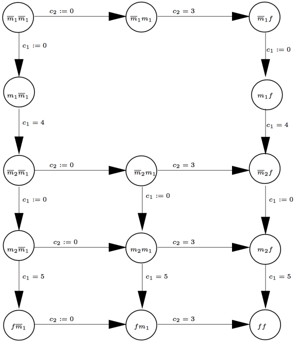
- Inspired by the work of M. Wonham and P. Ramadge for discrete-event dynamical systems
- Collaboration with Eugene Asarin, Amir Pnueli, Joseph Sifakis 1995-1998

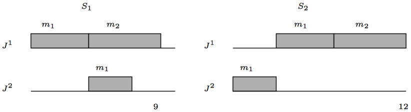
$F_0 := F$
for $i = 1, 2, \ldots,$ **repeat**
$\quad F_i := F_{i-1} \cap \pi(F_{i-1})$
until $F_i = F_{i-1}$
$F^* := F_i$

- **Controllable predecessor operator** $\pi \Rightarrow$ **Maximal** set of **winning states** (from which the system can be "safe" by one continuous time lapse or by one discrete step)
- **Optimality** criteria can be handled

Controller Synthesis for Timed Automata

- Considerable impact on researchers in control theory who began to adopt
  - computational exploration algorithms (rather than conservative analytic conditions)
  - formal specifications
  - for control systems, differential games





- Shortest path on timed automata
- Optimality criteria (performance, energy consumption...)
- With Yasmina Abdeddaïm and Eugene Asarin, 2002-2006

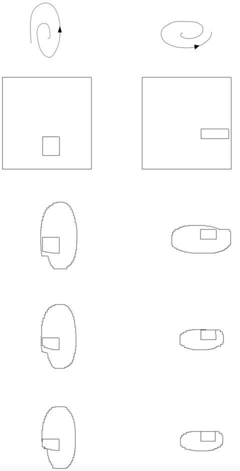
$$
\begin{array}{l}
\mathcal{P} := \emptyset; \\
\textbf{for all } q \in Q \ \{ \\
\quad X := \pi_q^\infty(\mathcal{F}_q); \\
\quad \textbf{for all } q' \neq q \ \{ \\
\qquad X := X \cup \mathcal{U}_q(\mathcal{F}_q, G_{qq'} \cap F_{q'}); \\
\quad \} \\
\quad \mathcal{P} := \mathcal{P} \cup (q, X); \\
\} \\
\textbf{return } \mathcal{P}
\end{array}
$$

- Unbounded continuous predecessor operator π_q^∞, Until operator $\mathcal{U}_q$
- These operators can be computed using variant of reachability operators

Next development: "Reach Avoid" operator for differential games [Tomlin, Lygeros, Sastry, 2000]

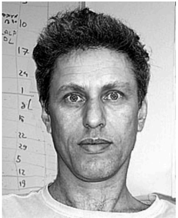
Controller Synthesis for Hybrid Systems

$\dot{x} = A_1 x \quad \dot{x} = A_2 x$



Acceptance is never easy...

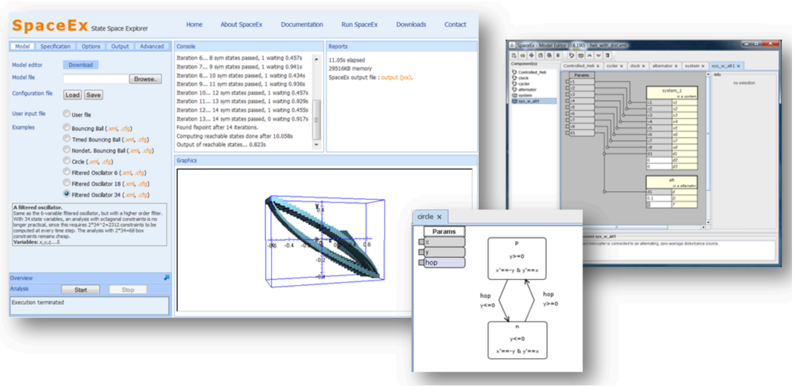
especially when a bunch of computer scientists trying to do control



(Proc of the IEEE, 2000)
"*The rest of the paper concerns the philosophy of continuous mathematics and control. Given that these philosophical remarks deserve to be exposed in a* **French cafe** *at best but not in a world class journal*", IEEE anonymous referee (2000)

SpaceEx - leading hybrid systems verification tool

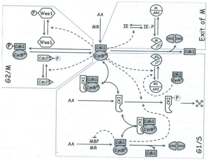
“A small step in Space, a giant leap for Mankind!” usually quoted by Oded



[Goran Frehse, Colas Le Guernic, et al.]

New exploration: Systems Biology

- Seek (conceptual and mathematical) models of dynamical systems at various levels of abstraction for **understanding** and **learning** about **underlying mechanisms**
- Relation between a dynamical system model which "explains" the mechanism AND experimentally observed behavior



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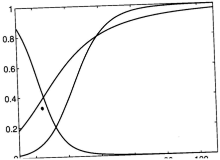
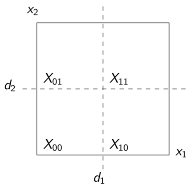


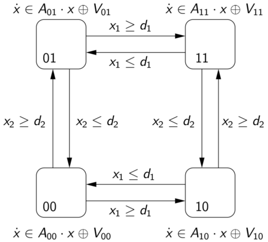
- Need of dynamical models with which we can validate/falsify **hypotheses** and **predict**

Non-Linear Challenge in Biological Models

Hybridization (Asarin, Dang, Girard, Maler, around 2010)

- $\dot{x} = f(x)$ and partition the state space into domains
- In each domain X_q, $f(x) \in A_q x \oplus V_q$ for every $x \in X_q$
- A_q is a local linearization of f with error bounded by V_q
- A piecewise linear (with uncertain input) systems





Hybridization

- Using linear techniques within a domain, until a reachable set intersects with a boundary
- Take the intersection as initial set in next domain with a new linearization

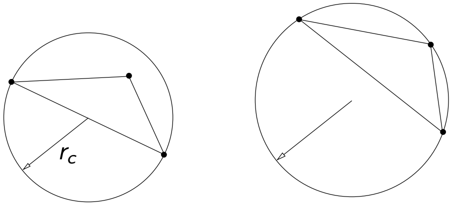
(a) (b)

Domain Construction: Using Curvature

For all $x \in \Delta$,

$$||f(x) - l(x)|| \leq \delta_\Delta \frac{r_c^2(\Delta)}{2}$$

- δ_Δ is the maximal curvature of f in Δ
- $r_c(\Delta)$ is the radius of the smallest ball containing the simplex Δ.



Smallest containment circle Circumcircle

By exploiting the curvature of $f(x)$ we can compute a larger simplex that guarantees the same error bound

Optimal domains for a class of quadratic systems

Mitochondria Theory of Aging

Mitochondria

- Generate the majority of the cellular ATP
- Produce reactive oxygen species that damage proteins, membranes and the mitochondrial DNA (mtDNA)

Damages impair ATP production but not replication of mtDNA
How defective mitochondria might accumulate?
"Survival of the slowest" hypothesis [Grey 1997]:

- Accumulation by lowering degradation rate
- Degradation depends on membrane damage

A mathematical model proposed by [Kowald and Kirkwood 2000] to examine this hypothesis

Model of Aging

$$\frac{dM_{M1}}{dt} = S\,M_{M1} + \frac{2S}{GDF+1}M_{M2} - (\alpha + (k_M + k_D)\,Rad_M)\,M_{M1}$$

$$\frac{dM_{M2}}{dt} = -\frac{2S}{GDF+1}M_{M2} + \frac{2S}{GDF}M_{M3} + k_M Rad_M\,M_{M1} - (\beta + (k_M + k_D)\,Rad_M)\,M_{M}$$

$$\frac{dM_{M3}}{dt} = -\frac{2S}{GDF}M_{M3} + k_M\,Rad_M\,M_{M2} - (\gamma + k_D\,Rad_M)\,M_{M3}$$

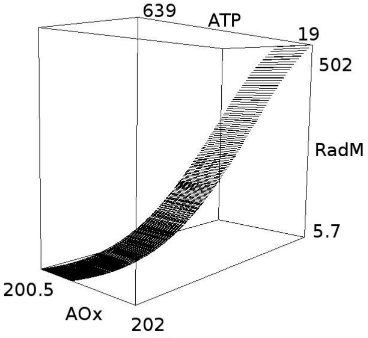
$$\frac{dM_{DM1}}{dt} = \frac{S}{GDF}(M_{DM1} + M_{DM2}) + k_D\,Rad_M\,M_{M1} - \left(\alpha + k_M\frac{RDF}{MDF}\,Rad_M\right)M_{DM1}$$

$$\frac{dM_{DM2}}{dt} = -\frac{S}{GDF}M_{DM2} + \frac{2S}{GDF}M_{DM3} + k_D Rad_M\,M_{M2} + k_M\frac{RDF}{MDF}\,Rad_M\,M_{DM1} - \left(\beta + k\right.$$

Analysis of Model of Aging

- Studying the influence of the turnover rate and initial situations on the stability of the system.

With (normalized) turnover rate too small (≤ 0.6) or too high (> 11) the system is unstable



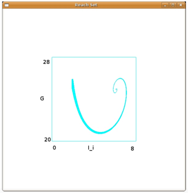
The computation time for 1000 iterations is 23.3 minutes (for standard turnover rate).

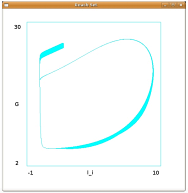
Systems Biology: Hypothesis Validation

Lac Operon [Dang and Maler 2010]

Hypothesis: existence of a limit cycle??

$$
\begin{aligned}
\dot{R}_a &= \tau - \mu * R_a - k_2 R_a O_f + k_{-2}(\chi - O_f) - k_3 R_a I_i^2 + k_8 R_i G^2 \\
\dot{O}_f &= -k_2 r_a O_f + k_{-2}(\chi - O_f) \\
\dot{E} &= \nu k_4 O_f - k_7 E \\
\dot{M} &= \nu k_4 O_f - k_6 M \\
\dot{I}_i &= -2k_3 R_a I_i^2 + 2k_{-3} F_1 + k_5 I_r M - k_{-5} I_i M - k_9 I_i E \\
\dot{G} &= -2k_8 R_i G^2 + 2k_{-8} R_a + k_9 I_i E
\end{aligned}
$$





R_a (active repressor) O_f (free operator), E(enzyme), M (mRNA), I_i (internal inducer), and G (glucose)

Systems Biology: Outcome

- Creation of Hybrid Systems Biology workshop series
- Synergy between researchers in formal methods, biology and bioinformatics (Eric Fanchon (TIMC), Jean-Marc Moulis (LBFA),...)
- Projects
  - CADMIDIA (Relation between cadmium with malfunctions of pancreatic beta cells)
  - SYMER (Metabolic and Epigenetic Regulation)
  - MoDyLAM (Dynamic modeling of iron-linked redox perturbations in Acute Myeloid Leukemia)

"*Oded was one of rare specialists in mathematical modelling who was attentive to other disciplines, and was particularly interested in systems biology*" [Uwe Schlattner, Coordinator of SYMER project]