Invariant Verification of Nonlinear Hybrid Automata Networks of Cardiac Cells

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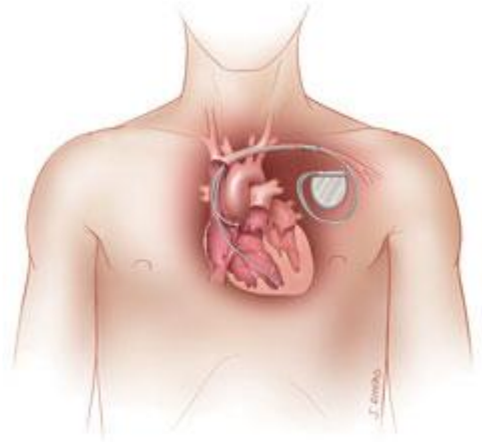
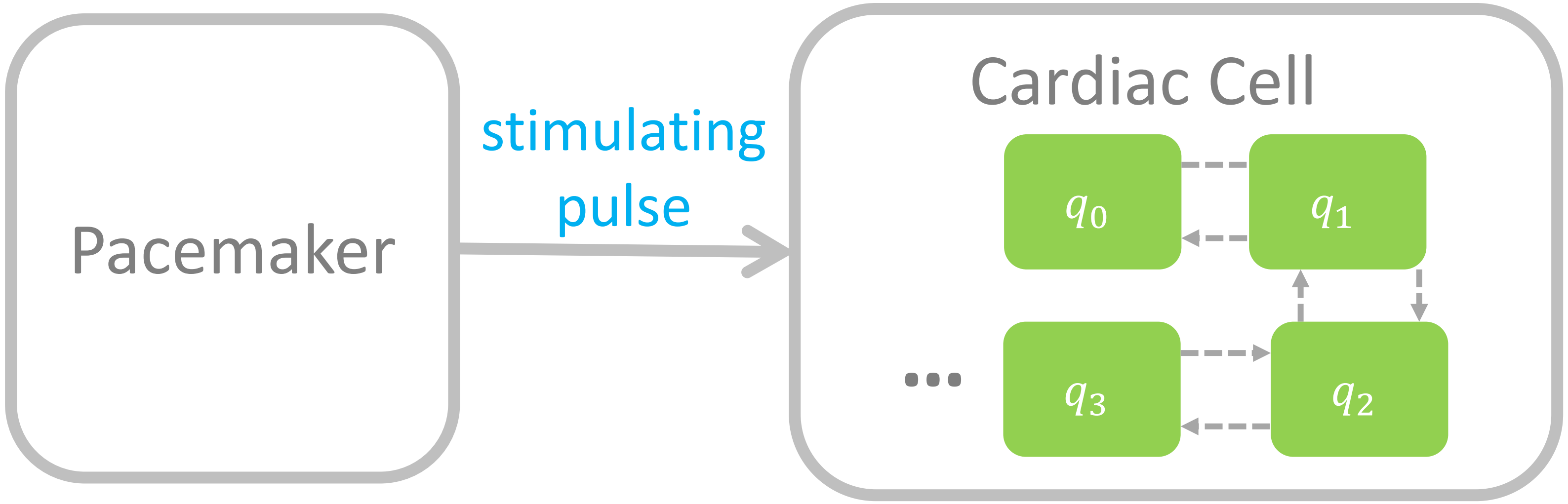
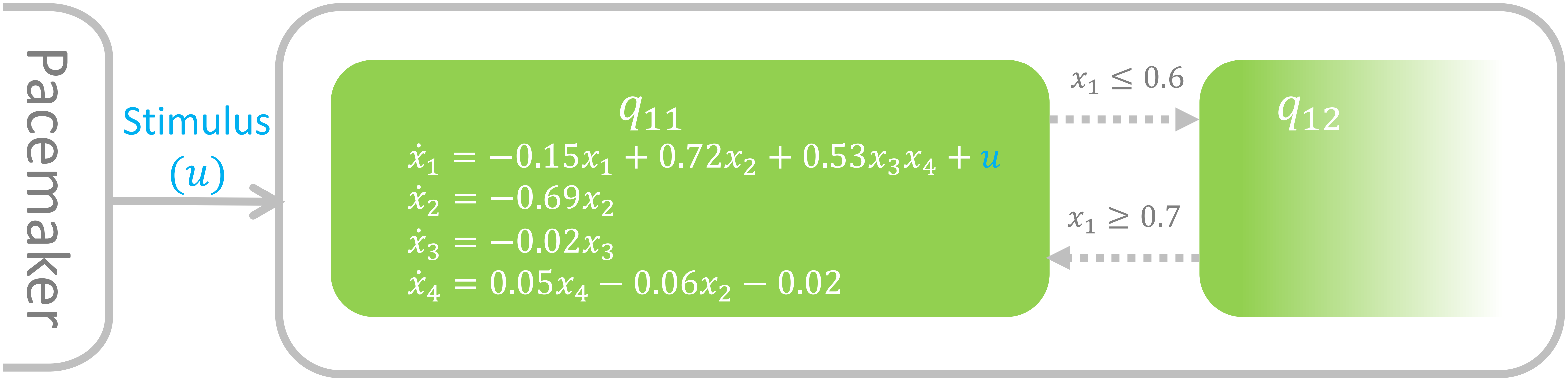
Hybrid Automata (HA)

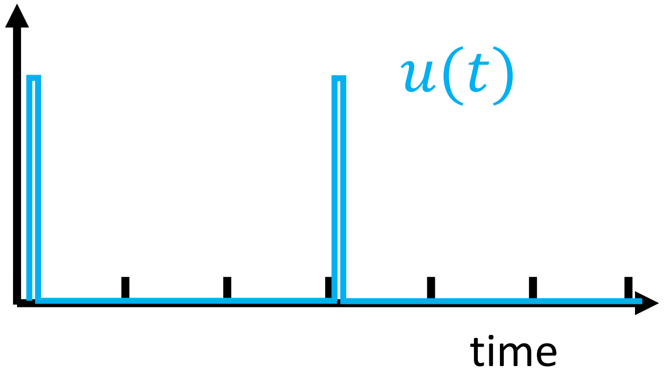


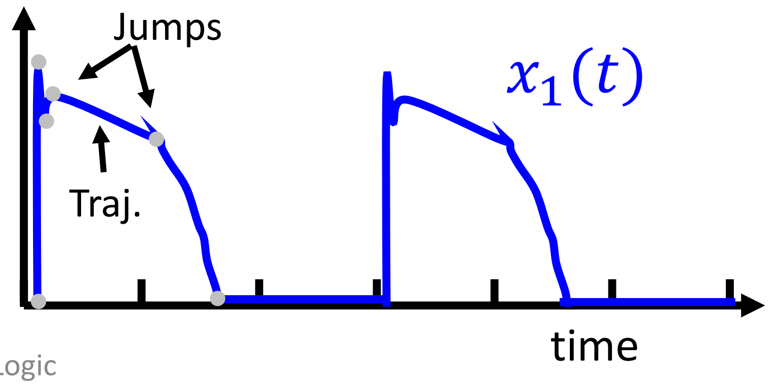


HA = Finite-State Machine + Differential Equation

Hybrid Automata Model of Cardiac Cells [Grosu12]







Invariant Verification for Hybrid Automata

Computing reach set exactly is undecidable [Henzinger]

- Over-approximations
- Bounded time

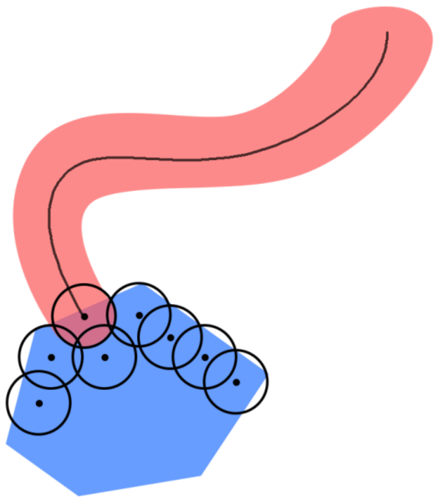
- Static analysis and symbolic approaches
  - E.g. HyTech[Henzinger97], CheckMate[Silva00], d/dt[Dang98], SpaceEx[Frehse11], flow*[Chen13]

- Dynamic+Static analysis using numerical simulations
  - E.g. Breach[Donzé10], S-TaLiRo[Annapureddy11], C2E2[Duggirala13]

Simulation-Based Bounded Reachability

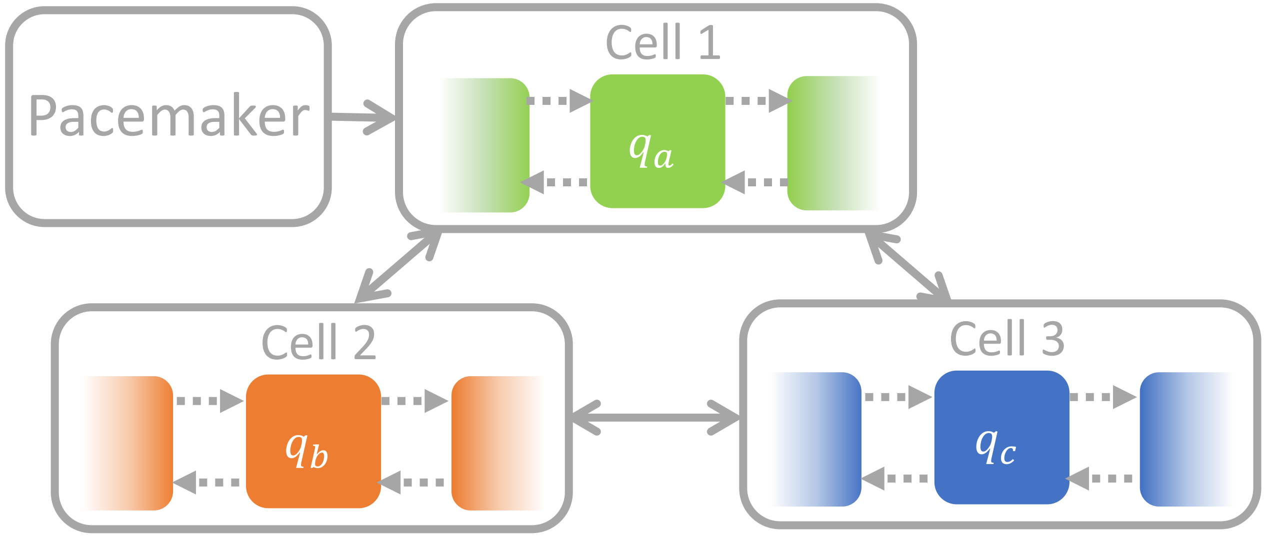
$$\dot{x} = f(x), \Theta \subseteq R^n$$

- Finite cover of Θ
- Simulate from the center of each cover
- Bloat the simulation with some factor, such that the bloated tube contains all trajectories starting from the cover
- Union of all such tubes gives an over-approximation of reach set



- The bloating factor can be computed using sensitivity analysis [Donzé07]
- Or given as an annotation for the model [Duggirala13,Huang14].

Challenge: HA Network

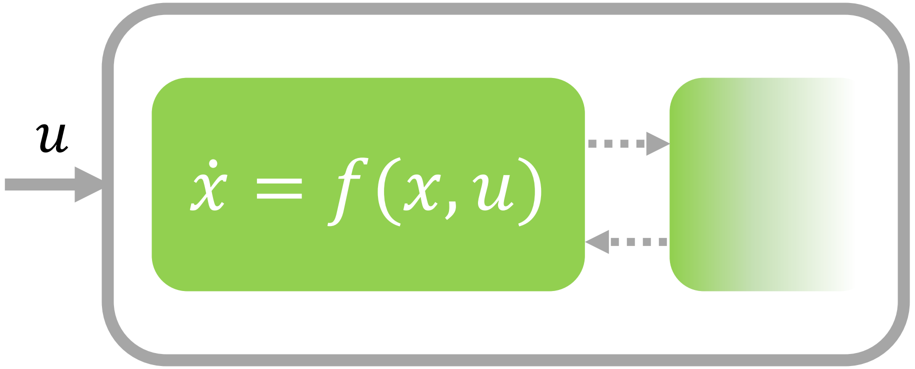


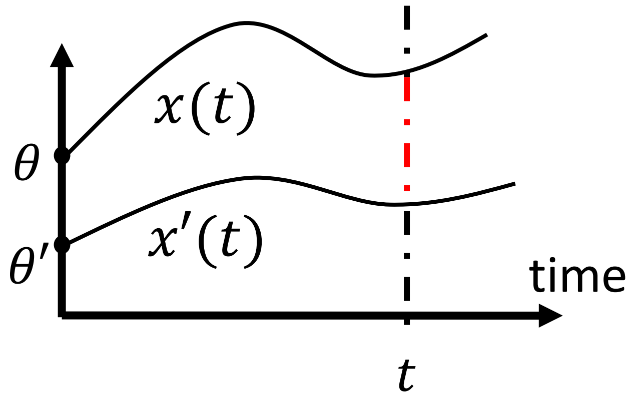
$$
\begin{aligned}
\dot{x}_{11} &= -0.13x_{11} + 0.53x_{13}x_{14} + 0.01x_{21} + 0.01x_{31} + \mathit{stim} \\
\dot{x}_{12} &= -0.69x_{12} \\
\dot{x}_{13} &= -0.25x_{13} \\
\dot{x}_{14} &= 0.53x_{14} - 0.63x_{12} - 0.19 \\
\hline
\dot{x}_{21} &= -1.67x_{21} + 0.24x_{21}x_{22}x_{23} + 0.01x_{11} + 0.01x_{31} \\
\dot{x}_{22} &= -0.09x_{22} \\
\dot{x}_{23} &= -0.25x_{23} \\
\dot{x}_{24} &= 0.22x_{21} - 0.63x_{24} - 0.21 \\
\hline
\dot{x}_{31} &= -0.81x_{31} + 10x_{32} - 6x_{31}x_{32} + 0.01x_{11} + 0.01x_{21} \\
\dot{x}_{32} &= -0.69x_{32} \\
\dot{x}_{33} &= -0.25x_{33} \\
\dot{x}_{34} &= 0.58x_{31} - 0.625x_{34} - 0.19
\end{aligned}
$$

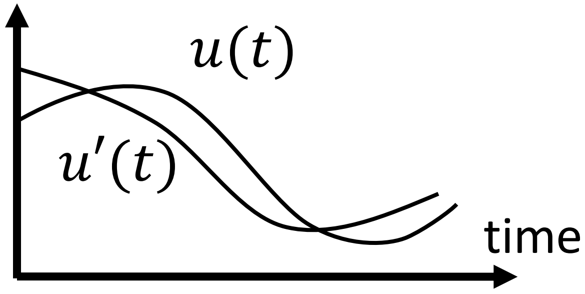
$$\times L^N$$

We assume the network is annotated by the user per automaton per mode.

Annotation: Input-to-State (IS) Discrepancy





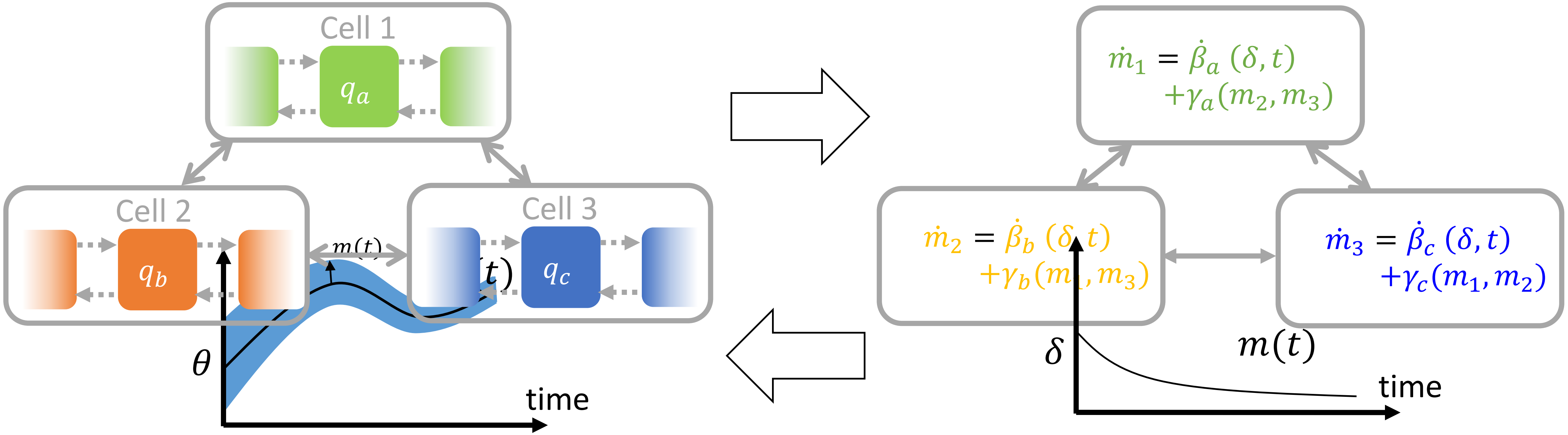


Definition[Duggirala13,Huang14]. IS discrepancy is defined by β and γ such that for any initial states θ, θ' and any inputs u, u',

$$|x(t) - x'(t)| \leq \beta(|\theta - \theta'|, t) + \int_0^t \gamma(|u(s) - u'(s)|)ds$$

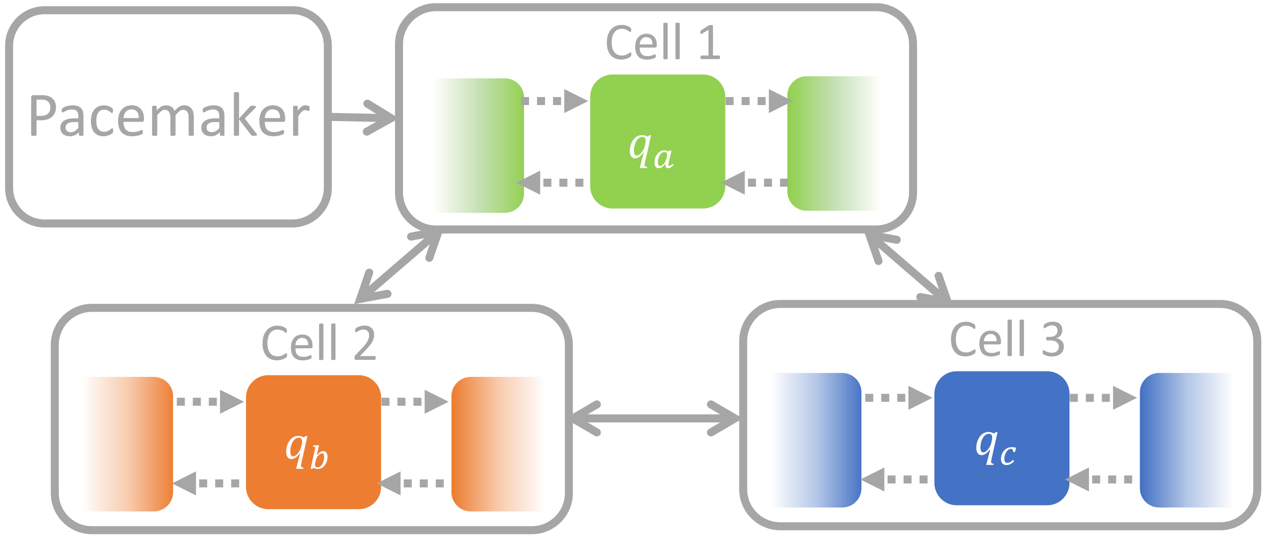
- $\beta \to 0$ as $\theta \to \theta'$, and $\gamma \to 0$ as $u \to u'$
- Linear $f()$: found automatically
- Nonlinear $f()$: several heuristics were proposed

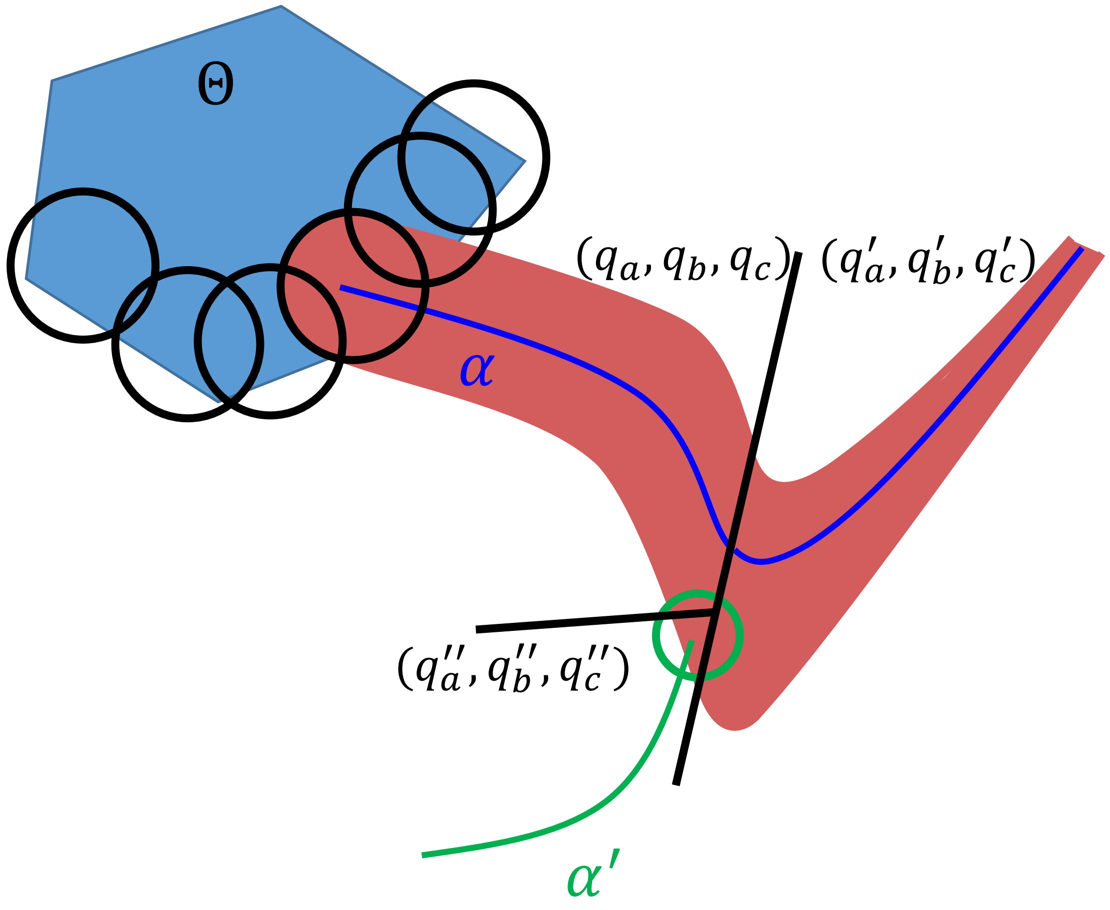
Bloating a Trajectory with IS Discrepancy



- The bloated tube contains all trajectories start from the δ-ball of θ.
- The over-approximation can be computed arbitrarily precise.

Reachability Algorithm for HA Networks





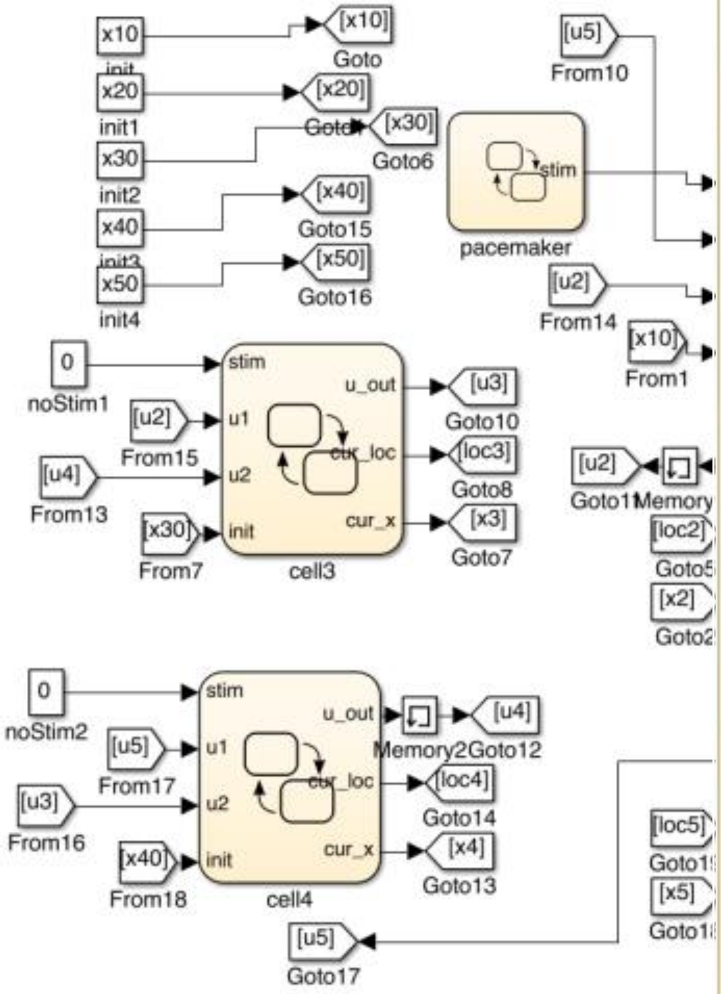
- Bloat α piece-wisely
- Generate α' for missing jumps
- Refinement
  - finer initial cover
  - more precise numerical simulation

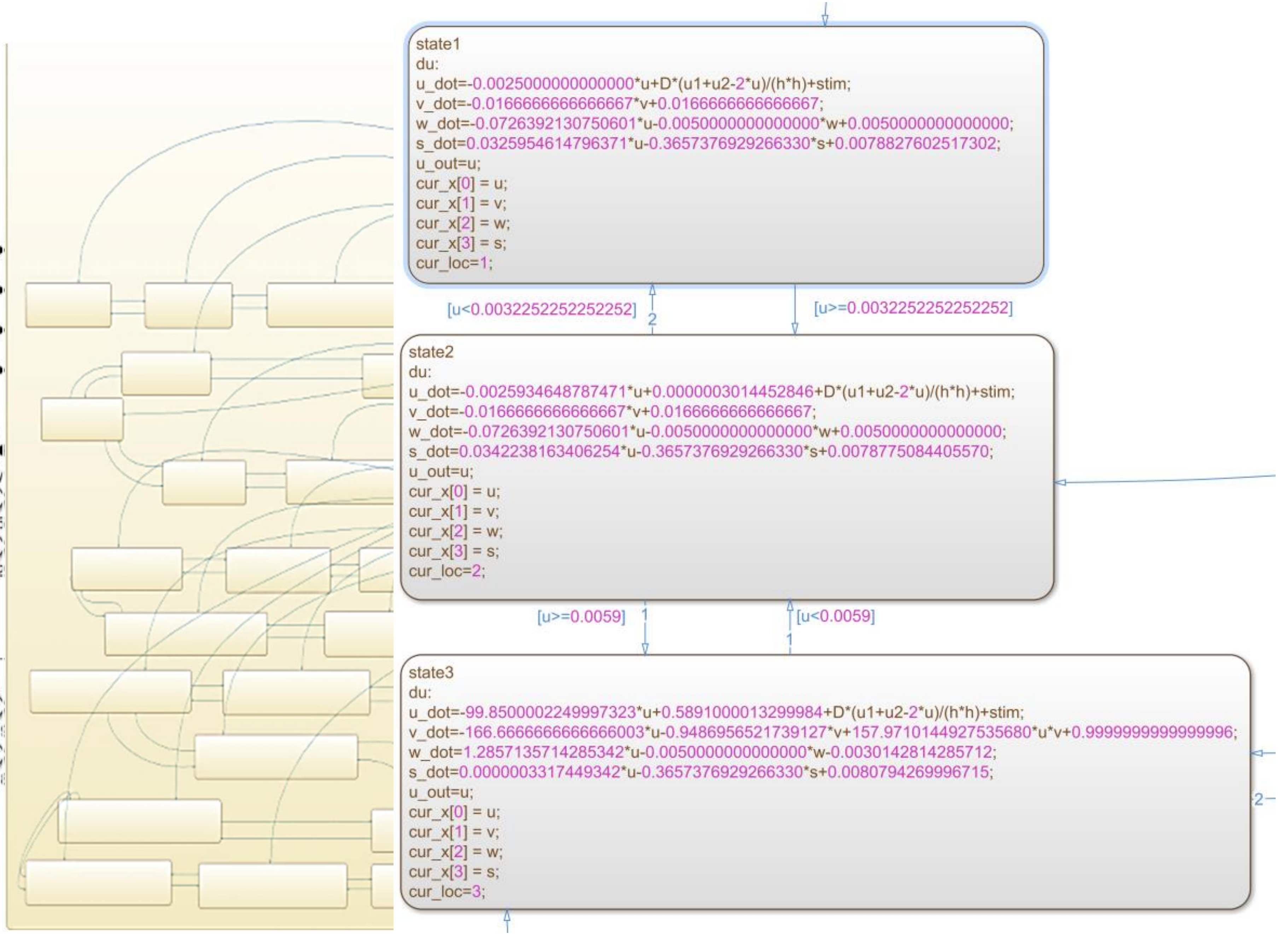
Soundness and Relative Completeness

- Definition. $c\text{-perturb}(A)$ is the set of all HA A', such that A' and A are identical except that
  - The initial sets: $\mathrm{d_H}(\Theta_A, \Theta_{A'}) \leq c$, and
  - The differential equations in every mode: $\mathrm{d}_\infty(f_A, f_{A'}) \leq c$
- Definition. A Robustly satisfies (violates) Inv iff there exists $c > 0$ such that all $c\text{-perturb}(A)$ satisfy (violate) Inv.

- **Theorem**: the algorithm is sound and relatively complete.
  - i.e. the algorithm terminates if A robustly satisfies (violates) Inv.

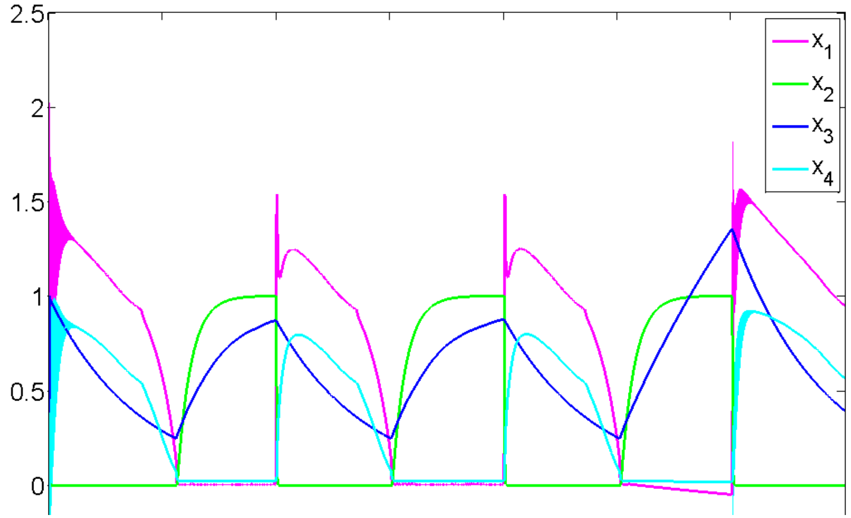
Benchmark

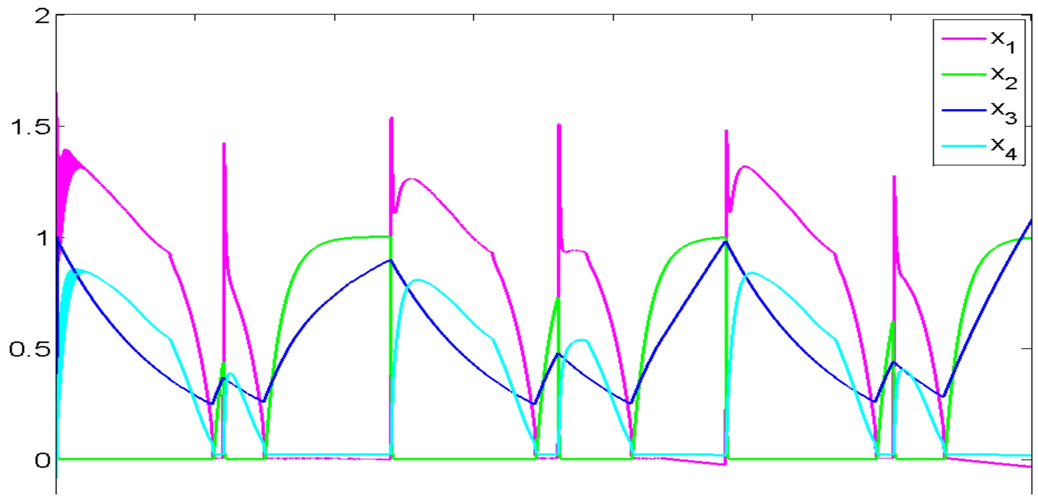

x10
init
[x10]
Goto
x20
init1
[x20]
Goto
[x30]
x30
init2
Goto6
x40
[x40]
Goto15
x50
init4
[x50]
Goto16
stim
pacemaker
[u5]
From10
[u2]
From14
[x10]
From1
0
noStim1
[u2]
From15
[u4]
From13
[x30]
From7
stim
u1
u2
init
u_out
cur_loc
cur_x
cell3
[u3]
Goto10
[loc3]
Goto8
[x3]
Goto7
[u2]
Goto11
Memory
[loc2]
[x2]
0
noStim2
[u5]
From17
[u3]
From16
[x40]
From18
stim
u1
u2
init
u_out
cur_loc
cur_x
cell4
Memory2
[u4]
Goto12
[loc4]
Goto14
[x4]
Goto13
[u5]
Goto17
[loc5]
[x5]


state1
du:
u_dot=-0.0025000000000000*u+D*(u1+u2-2*u)/(h*h)+stim;
v_dot=-0.0166666666666667*v+0.0166666666666667;
w_dot=-0.0726392130750601*u-0.0050000000000000*w+0.0050000000000000;
s_dot=0.0325954614796371*u-0.3657376929266330*s+0.0078827602517302;
u_out=u;
cur_x[0] = u;
cur_x[1] = v;
cur_x[2] = w;
cur_x[3] = s;
cur_loc=1;
[u<0.0032252252252252]
2
[u>=0.0032252252252252]
state2
du:
u_dot=-0.0025934648787471*u+0.0000003014452846+D*(u1+u2-2*u)/(h*h)+stim;
v_dot=-0.0166666666666667*v+0.0166666666666667;
w_dot=-0.0726392130750601*u-0.0050000000000000*w+0.0050000000000000;
s_dot=0.0342238163406254*u-0.3657376929266330*s+0.0078775084405570;
u_out=u;
cur_x[0] = u;
cur_x[1] = v;
cur_x[2] = w;
cur_x[3] = s;
cur_loc=2;
[u>=0.0059]
1
[u<0.0059]
1
state3
du:
u_dot=-99.8500002249997323*u+0.5891000013299984+D*(u1+u2-2*u)/(h*h)+stim;
v_dot=-166.6666666666666003*u-0.9486956521739127*v+157.9710144927535680*u*v+0.9999999999999996;
w_dot=1.2857135714285342*u-0.0050000000000000*w-0.0030142814285712;
s_dot=0.0000003317449342*u-0.3657376929266330*s+0.0080794269996715;
u_out=u;
cur_x[0] = u;
cur_x[1] = v;
cur_x[2] = w;
cur_x[3] = s;
cur_loc=3;
2

Experiments

Network	# Variables	# Modes	# Sims	Run Time (s)
8 cells (FH)	16	1	24	33
3 cells	12	2.4×10^4	16	105
5 cells	20	2.1×10^7	170	945
8 cells	32	5.0×10^{10}	73	2377





Discussion and Future work

- A scalable technique to verify nonlinear hybrid automata networks using annotations
  - IS discrepancies are used to construct a reduced model of the overall network whose trajectory gives the bloating factor
  - Both original network and the reduced model
  - Sound and relatively complete algorithm
- Cardiac cell networks upto 8 cells, 32 var. and 29^8 modes are verified using 29 annotations

- Future work:
  - Find IS discrepancy automatically
  - Verify properties of more biological importance