#### Hybrid and Networked Systems Lab



#### Formal Verification and Synthesis of Piecewise Affine Systems with Applications to Gene Networks

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> Joint work with **Boyan Yordanov** Biomedical Engineering, Boston University (→ Microsoft Research, Cambridge, UK)

#### Synthetic Biology is

A) the design and construction of new biological parts, devices, and systems, andB) the re-design of existing, natural biological systems for useful purposes.



http://syntheticbiology.org/

- Bioremediation
- Biosensing
- Nanofabrication
- Therapeutics
- Biofabrication
- Biocomputing



Examples: toggle switch (Gardner 2000), oscillator (Elowitz 2000), logical gates (Weiss 2002), sensing and communication mechanisms (Weiss 2000), pulse generator (Basu 2004).





NSF CCF-0432070: "Collaborative Research: Rational Design of Synthetic Gene Networks using Formal Analysis of Hybrid Systems"

Aim: tune the parameters of a set of existing synthetic circuits such that all possible behaviors of the circuits satisfy a given specification



#### Specification:

if aTc < low, then eventually always YFP > high, and if aTc > high, then eventually always YFP < low



ONR MURI: Utilizing Synthetic Biology to Create Programmable Micro-Bio-Robots





ONR MURI: Utilizing Synthetic Biology to Create Programmable Micro-Bio-Robots

**One specific aim:** from a set of available parts, construct a circuit satisfying a given specification



Registry of Standard Biological Parts http://partsregistry.org/

#### Specification:

Eventually, the concentration of *eyfp* starts oscillating between values above 100 and below 10, i.e.,

"Always eventually eyfp > 100 and always eventually eyfp < 10"





ONR MURI: Utilizing Synthetic Biology to Create Programmable Micro-Bio-Robots

1. In silico construction of all biologically feasible circuits





ONR MURI: Utilizing Synthetic Biology to Create Programmable Micro-Bio-Robots

2. For each circuit, using the available information on the kinetic parameters and/or experimental data, check the satisfaction of the specification for a mathematical model of the circuit



### Approach

#### Draw inspiration from formal analysis (verification)

Specification

"Is deadlock ever possible?" "If a request is received, make sure it is eventually granted." if aTc < low, then eventually always YFP > high, and if aTc > high, then eventually always YFP < low

#### Process



#include<time.h>

#### main()

clock\_t time,deltime; long junk,i; float secs;

- LOOP: printf("input loop count: "); scanf("%id",6junk); time = clock(); for(1=0;i<junk;i++); time = clock();
  - class = clock(); for(i=0;i<junk;i++) deltime = clock() - time; secs = (floct) deltime/CLOCKS\_PER\_SEC; printf("for %id loops, #tics = %id, time acto LOOP;
- return 0;



### Approach

#### Draw inspiration from formal analysis (verification)

Specification

"Is deadlock ever possible?" "If a request is received, make sure it is eventually granted."

> Model checking (SPIN, NuSMV)

if aTc < low, then eventually always YFP > high, and if aTc > high, then eventually always YFP < low

#### Model



Process



#include<time.h>

main()

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:
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scanf("%id",≤junk);
time = clock();
for(1=0;i<junk);
deltime = clock() - time;
secs = (float) deltime/CLOCKS\_PER\_SEC;
printf("for %id loops, \$tics = %id, time
goto LOOP;
return 0;</pre>





### Approach

#### Draw inspiration from formal analysis (verification)

Specification

"Is deadlock ever possible?" "If a request is received, make sure it is eventually granted."

Model checking (SPIN NuSMV)

if aTc < low, then eventually always YFP > high, and if aTc > high, then eventually always YFP < low



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



Model





#include<time.h>

main()

clock\_t time, deltime; long junk,i;
float secs; LOOP: printf("input loop count: "); scanf("%ld", &junk); time = clock(); for(i=0;i<junk;i++) delete= clock();

deltime = clock() - time; secs = (float) deltime/CLOCKS\_PER\_SEC; printf("for %ld loops, #tics = %ld, time goto LOOP; return 0;

## Outline

- 1) LTL verification and control for finite systems
- 2) PWA Systems
- 3) Verification of PWA Systems
- 4) Parameter Synthesis for PWA Systems
- 5) LTL Control of PWA Systems

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Transition systems with finitely many states and actions



Transition systems with finitely many states and actions



D-D: deterministic fully observable transition system

Transition systems with finitely many states and actions



N-D: nondeterministic fully observable transition system

Transition systems with finitely many states and actions



P-D: Markov Decision Process (MDP)

Transition systems with finitely many states and actions



P-P: Partially Observable Markov Decision Process (POMDP)

Transition systems with finitely many states and actions



#### In this talk:

D-D: deterministic fully observable transition system

N-D: nondeterministic fully observable transition system

Linear Temporal Logic (LTL)

Syntax



#### Semantics

Run (trajectory):  $q_1, q_4, q_3, q_3, ...$ Word:  $\pi_1 \pi_2 \pi_3 \pi_3 \dots \pi_3 \pi_4 \pi_4$ Language: the set of all words



Given a transition system and an LTL formula over its set of propositions, check if the language of the transition system starting from all initial states satisfies the formula.



SPIN, NuSMV, ...

Given a transition system and an LTL formula over its set of propositions, find a set of initial states and a control strategy for all initial states such that the produced language of the transition system satisfies the formula.



Given a transition system and an LTL formula over its set of propositions, find a set of initial states and a control strategy for all initial states such that the produced language of the transition system satisfies the formula.



• for deterministic systems the solution is a simple adaptation of LTL model checking algorithms

• for nondeterministic systems the solution is based on Buchi and Rabin games

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**Syntax** 



All the sets are polyhedral subsets of Euclidean spaces of appropriate dimensions.

Semantics



Semantics



Can be checked against the satisfaction of LTL formulae over  $\Pi$ 

#### Why PWA systems?

• PWA systems can approximate nonlinear systems with arbitrary accuracy [Lin and Unbehauen, 1992].

• Under mild assumptions, PWA systems are equivalent with several other classes of hybrid systems, including mixed logical dynamical (MLD), linear complementarity (LC), extended linear complementarity (ELC), and maxmin-plus-scaling (MMPS) systems [Heemels et al., 2001, Geyer et al., 2003].

• There exist tools for the identification of PWA systems from experimental data [Paoletti, Juloski, Ferrari-Trecate, Vidal, 2007]



#### Why PWA systems?

• Specific classes of PWA models can be directly derived from first principles



• PWA systems admit finite quotients and can be formally analyzed / controlled

## Outline

- 1) LTL verification and control for finite systems
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Problem formulation: Find the largest subset of  $\mathcal X$  such that all trajectories originating there satisfy an LTL formula  $\phi$  over L while always staying inside  $\mathcal X$ 



Embed the PWA system into an infinite deterministic transition system  $T_e$  with set of observations  $L \cup \{Out\}$ 

Construct the observational equivalence quotient  $T_e/{\sim}$ 





Construct the observational equivalence quotient  $T_e/{\sim}$ 



 $(X, X') \in \to_{e,\sim}$  if and only if  $\operatorname{Post}_{T_e}(\operatorname{con}(X)) \cap \operatorname{con}(X') \neq \emptyset$   $\operatorname{Post}_{T_e}$  is computable  $\operatorname{Post}_{T_e}(\operatorname{con}(X_l)) = A_l X_l + b_l$ 

Construct the observational equivalence quotient  $T_e/{\sim}$ 



 $Post_{T_e}(con(X_1)) = A_1X_1 + b_1$ 

 $(X, X') \in \to_{e,\sim}$  if and only if  $\operatorname{Post}_{T_e}(\operatorname{con}(X)) \cap \operatorname{con}(X') \neq \emptyset$ 

# Verification of PWA Systems with Fixed Parameters solve the problem on $T_e/\sim$



 $T_e/\sim$  simulates  $T_e$ 

LTL formula " $\bigcirc$  []7"

1) solve the problem on  $T_e/_{\sim}$ 

2) map the solution to  $T_e\,$  -> satisfying region for  $T_e\,$  but not the largest
# Verification of PWA Systems with Fixed Parameters solve the problem on $T_e/\sim$



if  $T_e/\sim$  was a bisimulation quotient

LTL formula "

solving the problem on  $\,T_e/_{\sim}\,$  is equivalent to solving it on  $T_e$ 

### Verification of PWA Systems with Fixed Parameters

#### **Bisimulation algorithm**





Algorithm 1 ~=BISIMULATION( $\mathcal{T}$ ): Coarsest bisimulation ~ of  $\mathcal{T}$ 

- 1: Initialize  $\sim$  with observational equivalence
- 2: while there exist  $X, X' \in Q/_{\sim}$  such that  $\emptyset \subset con(X) \cap Pre_{\mathcal{T}}(con(X')) \subset con(X)$  do
- 3: Construct state  $X_1$  such that  $con(X_1) := con(X) \bigcap Pre_{\mathcal{T}}(con(X'));$
- 4: Construct state  $X_1$  such that  $con(X_2) := con(X) \setminus Pre_{\mathcal{T}}(con(X'));$
- 5:  $Q/_{\sim} := Q/_{\sim} \setminus \{X\} \bigcup \{X_1, X_2\};$

6: end while

7: return  $\sim$ ;

## Verification of PWA Systems with Fixed Parameters Can the bisimulation algorithm be used to solve the problem?



A. Chutinan and B. H. Krogh, "Verification of infinite-state dynamic systems using approximate quotient transition systems," IEEE Transactions on automatic control, vol. 46, no. 9, pp. 1401–1410, 2001.

### Verification of PWA Systems with Fixed Parameters



 $con(X_{l_1}) \cap Pre(con(X_{l_2})) = X_{l_1} \cap A_{l_1}^{-1}(con(X_{l_2}) - b_{l_1})$ 

### Verification of PWA Systems with Fixed Parameters A better approach



 Expand the satisfying region
 Do not refine satisfying regions
 Construct satisfying sets for both the LTL formula and its negation simultaneously

Yordanov, B., Batt, G., and Belta, C., ECC '07

Yordanov, B. and Belta, C., IEEE Trans. Autom. Control, 2010

### Verification of PWA Systems with Fixed Parameters A better approach



LTL formula " $\bigcirc \Box$ 7"

This procedure might terminate when the bisimulation algorithm does not the idea of formula guided refinement (formula equivalent quotients).

Yordanov, B., Tumova, J., Belta, C., Cerna, I., and Barnat, J., CDC '10

### Verification of PWA Systems with Fixed Parameters

Example: toggle switch - model with fixed parameters



 $\bigcirc \square(\mathsf{R}_1 > 80 \land \mathsf{R}_2 < 20)$  $\bigcirc \square(\mathsf{R}_1 < 40 \land \mathsf{R}_2 > 50)$ 



### Verification of PWA Systems with Fixed Parameters

Example: toggle switch - model with fixed parameters



(hyness.bu.edu/software)

#### Verification of PWA Systems with Additive Uncertainty



Problem formulation: Find the largest subset of  $\mathcal X$  such that all trajectories originating there satisfy an LTL formula  $\phi$  over L while always staying inside  $\mathcal X$ 

#### Verification of PWA Systems with Additive Uncertainty

Construct the observational equivalence quotient  $T_e/{\sim}$ 





 $(X, X') \in \to_{e,\sim}$  if and only if  $\operatorname{Post}_{T_e}(\operatorname{con}(X)) \cap \operatorname{con}(X') \neq \emptyset$ 

Post<sub>T<sub>e</sub></sub> is still computable and therefore  $T_e/\sim$  is computable Post<sub>T<sub>e</sub></sub>(con(X<sub>l</sub>)) =  $A_lX_l + P_l^b$ 

#### Verification of PWA Systems with Additive Uncertainty

#### Refinement





Pre is still computable

 $con(X_1) \cap Pre_{T_e}(con(X_2))$ 

$$con(X_{l_1}) \cap Pre_{T_e}(con(X_{l_2}) = A_{l_1}^{-1}(con(X_{l_2}) - P_{l_1}^b)$$

The only difference from the fixed parameter case is that there will be more states and more transitions (nondeterminism) in the quotient at each step of the refinement

#### Verification of PWA Systems with Uncertain Parameters



Problem formulation: Find the largest subset of  $\mathcal{X}$  such that all trajectories originating there satisfy an LTL formula  $\phi$  over L while always staying inside  $\mathcal{X}$ 

Yordanov, B. and Belta, C., ACC '08

Yordanov, B. and Belta, C., IEEE Trans. Autom. Control, 2010

#### Verification of PWA Systems with Uncertain Parameters

Construct an over-approximation of the observational equivalence quotient  $T_e/$ 



 $(X, X') \in \to_{e,\sim}$  if and only if  $\operatorname{Post}_{T_e}(\operatorname{con}(X)) \cap \operatorname{con}(X') \neq \emptyset$   $\operatorname{Post}_{T_e}$  is not computable and therefore  $T_e/\sim$  is not computable An over-aproximation  $\overline{\operatorname{Post}}_{T_e}(\operatorname{con}(X_l)) = hull(\{A_lX_l \mid A \in V(P_l^A)\}) + P_l^b$  is computable An over-aproximation  $\overline{T}_e/\sim$  of  $T_e/\sim$  is computable

#### Verification of PWA Systems with Uncertain Parameters

#### Refinement



Pre is not computable and any partition scheme that does not capture the dynamics can be used, e.g., quad-tree partition.

#### Verification of PWA Systems Example: toggle switch - model with uncertain parameters



#### Example: repressilator





$$\square(((R_3>60))))$$

#### Example: repressilator



Fixed parameters: 99.8% of state space was satisfying Computation time was 11 min 1% parameter noise:
69% of state space was satisfying Computation time was 3 h

Matlab tool: "FaPAS" (hyness.bu.edu/software)

Example: selection of devices built from parts Parts list



Example: selection of devices built from parts Biologically feasible devices







Example: selection of devices built from parts Selection of possible repressilators



	□(�(cl<1000)∧�(cl>20000))			□ (♦ (lacl<1000) ∧♦ (lacl>250000))		
	Satisfying	Violating	Time	Satisfying	Violating	Time
Without aTc	0%	100%	2.5 sec	0%	99.96%	1.5 sec
With aTc	0%	99.8%	1.5 sec	0%	99.96%	1.5 sec

Example: selection of devices built from parts Selection of possible toggle switches



	Satisfying	Violating	Time		
Without aTc	0%	100%	1.5 sec		
With aTc	0%	100%	1.0 sec		

Example: selection of devices built from parts Selection of possible toggle switches



	Satisfying	Violating	Time	Satisfying	Violating	Time
Without aTc	0%	100%	1.0 sec	100%	0%	4 sec
With aTc	99.9%	0%	1.0 sec	0%	99.9%	1.0 sec

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### Parameter Synthesis for PWA Systems Problem formulation

Given a LTL formula  $\varphi$  over linear predicates in the state, find a subset of the parameter sets, such that all trajectories of the system satisfy the formula.



Approach

- Embed PWA system into  $T_e$
- Construct an over-approximation  $\overline{T_e}/_{\sim}$  of  $T_e/_{\sim}$
- While there exist violating runs in  $\overline{T}_e/_{\sim}$ 
  - Trim  $\overline{T}_e/_{\sim}$  to remove a transition of a violating run
  - Limit the parameter values in the PWA to ensure the removal of the transition
- End While
- Result:  $\overline{T}_{e}^{\phi}/_{\sim}$

#### The language of the obtained PWA is included in the language of $\overline{T}^{\phi}_{e}/_{\sim}$

E. Clarke, A. Fehnker, Z. Han, B. Krogh, J. Ouaknine, O. Stursberg, and M. Theobald, "Abstraction and counterexampleguided refinement in model checking of hybrid systems," International Journal of Foundations of Computer Science, vol. 14, no. 4, pp. 583–604, 2003.

Frehse, Jha, Krogh. A Counterexample-Guided Approach to Parameter Synthesis for Linear Hybrid Automata. In HSCC 2008

Yordanov, B. and Belta, C., HSCC '08

Counterexample - guided transition elimination



When a transition is removed, the set of parameters of the PWA system is restricted 1) Other transitions might be disabled as a side effect

2) Some states might become blocking - the transitions to these states need to removed as well by further restricting the parameters of the PWA system

Satisfying quotients tree





Non-satisfying finite quotients that generate further counterexamples

Finite quotients with blocking initial states (no more counterexamples can be generated but the formula is not satisfied) Satisfying finite quotients without any reachable blocking states

Parameter sets disabling transitions in  $\overline{T}_e/_{\sim}$ 

Let  $P^{X_i \not\rightarrow X_j}$  denote the set of all parameters for which  $Post(X_i) \cap X_j = \emptyset$ Removing a transition means restricting the parameters to  $P^{X_i \not\rightarrow X_j}$  $P^{X_i \not\rightarrow X_j}$  is not computable

An under-approximation  $P^{X_i \not\rightarrow X_j}$  can be computed





#### Example



**Specification**: "Keep surveying all regions except 5, which should never be visited", i.e., "always (eventually 1 and eventually 2 ... and eventually 4 and eventually 6 ... and eventually 9) and always not 5. Do not go out of the  $[-10,10] \times [-10 \ 10]$  rectangle."

#### Example



#### Example

Trimmed  $\overline{T}_e/\sim$ 



9

10

28 Transitions total

Sets of parameters producing a bisimulation quotient

Let  $P^{X_i \to X_j}$  denote the set of all parameters for which  $Post(X_i) \subseteq X_j$  $P^{X_i \to X_j}$  is computable



#### Parameter synthesis



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## LTL Control of PWA Systems

#### **Problem formulation**

Find a set of initial states and a state-feedback control strategy such that all the trajectories of the system satisfy an arbitrary LTL formula over linear predicates over the states.


#### Approach



#### State abstraction



#### State abstraction



#### State abstraction













Finite control transition system



1: Compute states (state equivalence classes) 2: For each state:

- 2.1: Compute inputs (input equivalence classes)
- 2.2: Remove inputs that are "too small"
- 2.3: Keep only "most deterministic" inputs3: Generate control strategy for control TS4: Adapt the control strategy to the PWA system (language inclusion)

The finite control transition system  $T_C$  can be constructed using polyhedral operations only.

Yordanov, B. and Belta, C., CDC '09

Tumova, J., Yordanov, B., Belta, C., Cerna, I., and Barnat, J., CDC '10 Yordanov, B. and Belta, C., Accepted in IEEE Trans. Autom. Control, 2011

Example: Buchi game



•3182 input regions were "large enough" (limit=0.05)

·260 input regions induce deterministic transitions only

(do not lead to a solution from any state - no solution can be found if the game is avoided!!)

•691 "most deterministic" input regions were included (control strategies were found from all 36 states)

Example: Buchi game

 $\phi = \Diamond \mathcal{X}_1 \land \Diamond \mathcal{X}_{10} \land \Diamond \mathcal{X}_{27} \land \Diamond \mathcal{X}_{36}$ 



#### Improving the solution: stuttering phenomena



- For nondeterministic transitions in the control transition system that contain self-loops, the adversary can use the self-loop to win the game.
- We can characterize the input sets that are stuttering (guarantee to leave the region in finitely many steps)
- Stuttering inputs can be used in the game

Example: Rabin game



Matlab tool: "conPAS" (hyness.bu.edu/software)

If stuttering is not accounted for, only 10 is a satisfying initial region.

### Acknowledgements



Boyan Yordanov



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