

#### SReach:

How KillerRed

destroys E. coli

Lambda

A Probabilistic Bounded  $\delta$ -Reachability Analyzer for Stochastic Hybrid Systems\*

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SReach

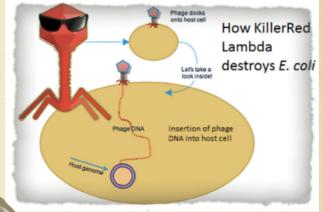
# Probabilistic Bounded Reachability Analysis

of

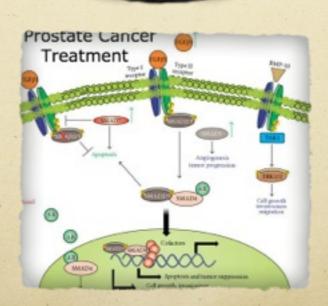
Stochastic Hybrid Systems

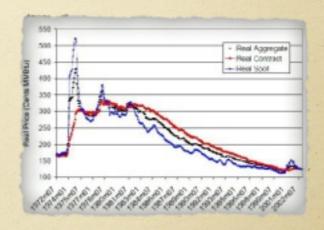


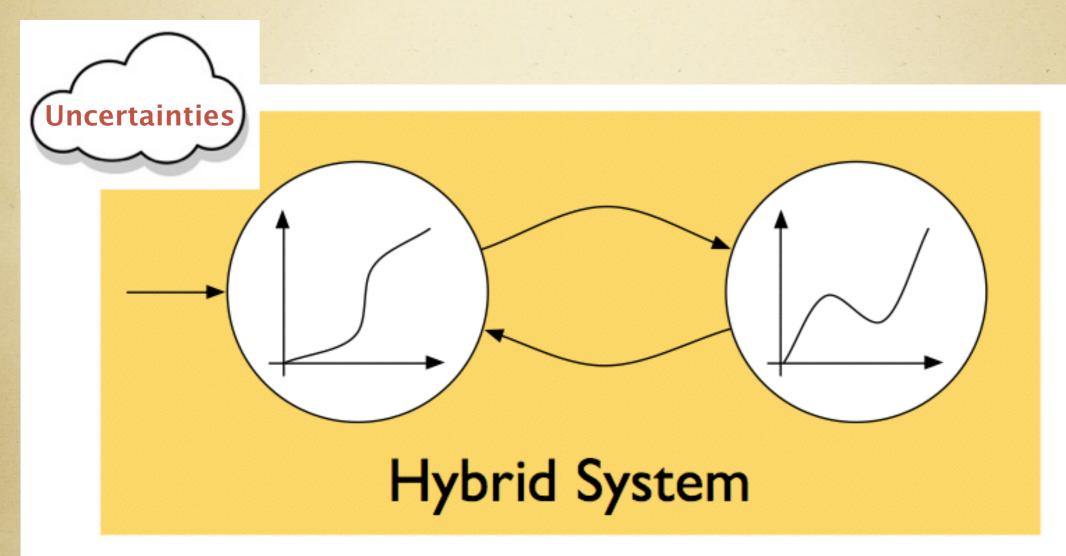




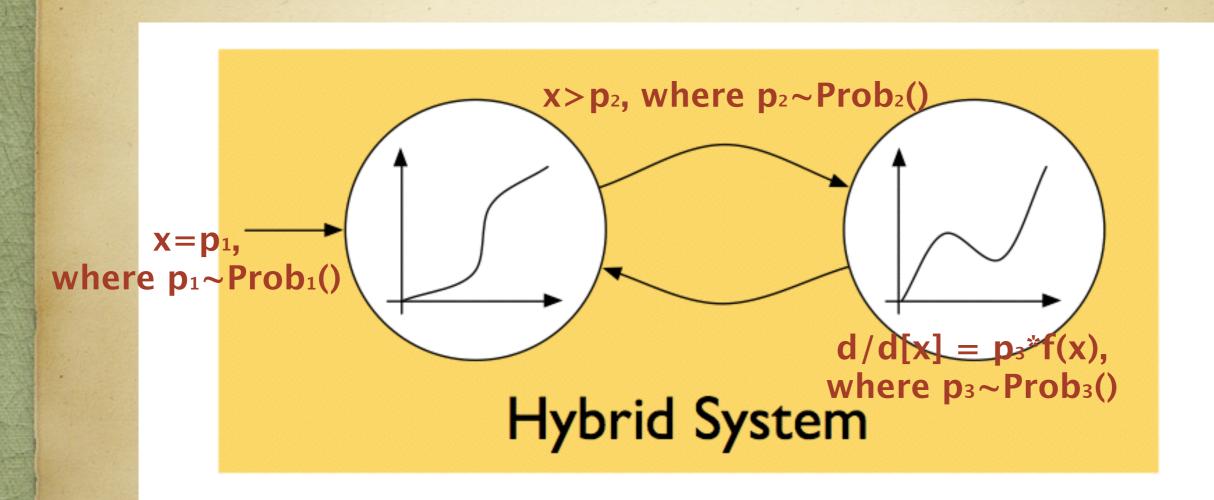
Discrete
Continuous
Stochastic



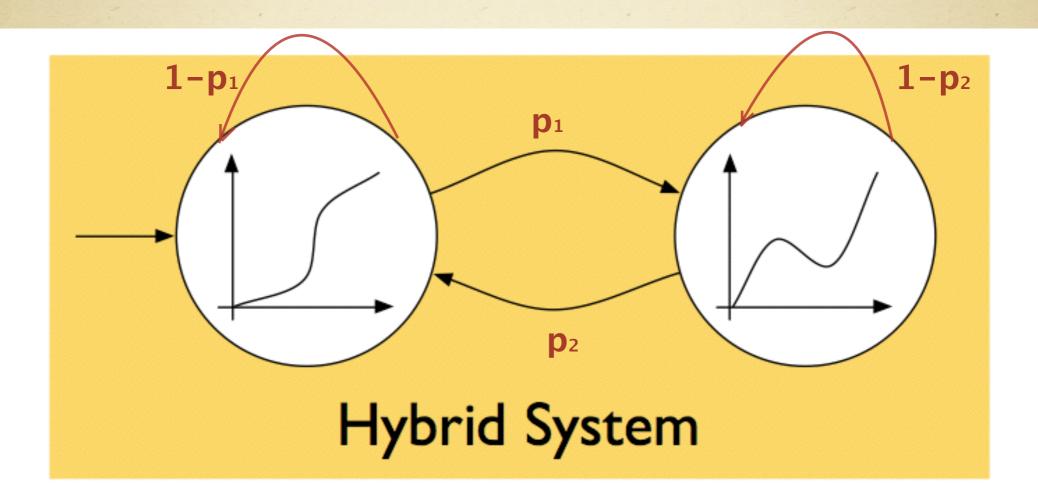




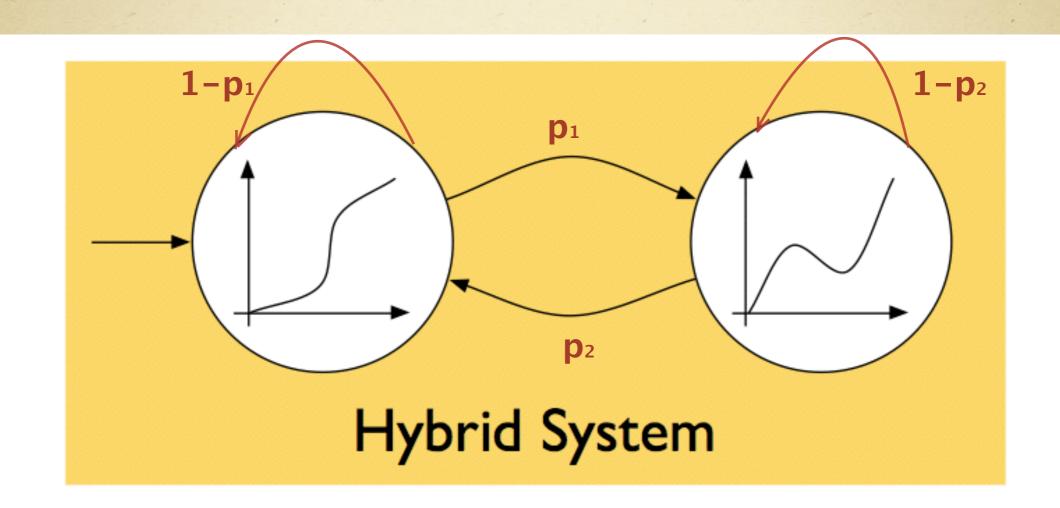
Discrete Control + Continuous Dynamics



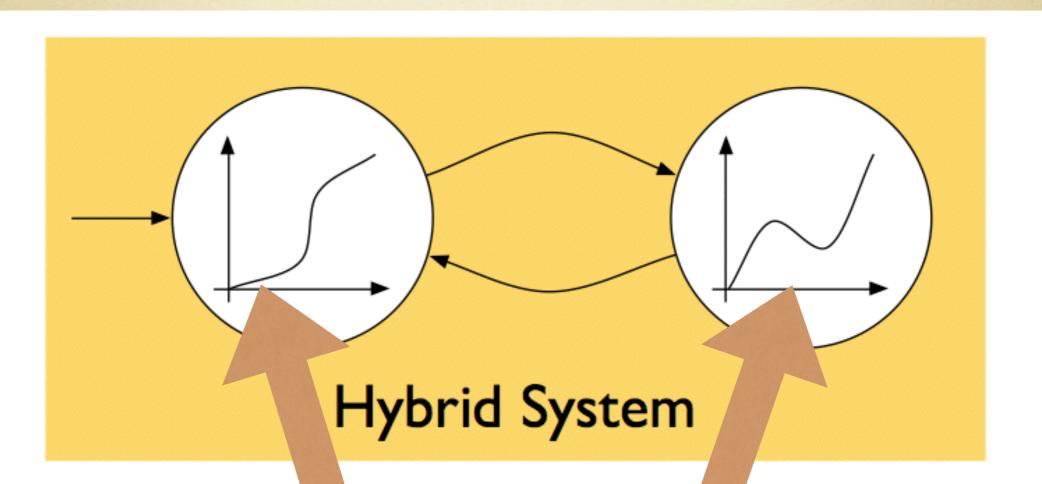
**Hybrid System with Parametric Uncertainty** 



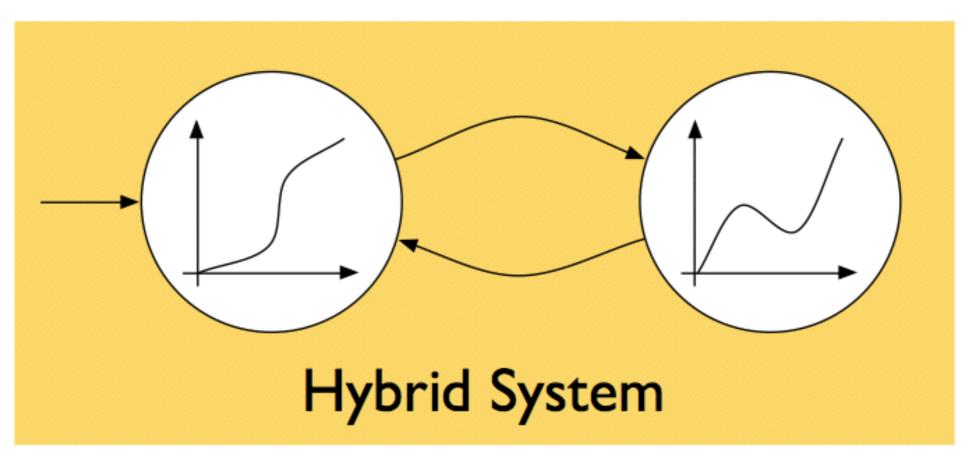
p<sub>1</sub> and p<sub>2</sub> are discrete random variables: Probabilistic Hybrid Automata



When continuous distributions are also allowed:
Stochastic Hybrid Automata



$$dX_t = \mu(X_t, t) dt + \sigma(X_t, t) dB_t,$$



When all above modifications have been applied: General Stochastic Hybrid Systems

#### SReach considers ...

**Definition 1 (HA**<sub>p</sub>). A hybrid automaton with parametric uncertainty is a tuple  $H_p = \langle (Q, E), V, RV, \text{ Init, Flow, Inv, Jump, } \Sigma \rangle$ , where

- The vertices  $Q = \{q_1, \dots, q_m\}$  is a finite set of discrete modes, and edges in E are control switches.
- $-V = \{v_1, \dots, v_n\}$  denotes a finite set of real-valued system variables. We write V to represent the first derivatives of variables during the continuous change, and write V' to denote values of variables at the conclusion of the discrete change.
- $RV = \{w_1, \dots, w_k\}$  is a finite set of independent random variables, where the distribution of  $w_i$  is denoted by  $P_i$ .
- Init, Flow, and Inv are labeling functions over Q. For each mode  $q \in Q$ , the initial condition Init(q) and invariant condition Inv(q) are predicates whose free variables are from  $V \cup RV$ , and the flow condition Flow(q) is a predicate whose free variables are from  $V \cup \dot{V} \cup RV$ .
- Jump is a transition labeling function that assigns to each transition  $e \in E$  a predicate whose free variables are from  $V \cup V' \cup RV$ .
- $\Sigma$  is a finite set of events, and an edge labeling function event :  $E \to \Sigma$  assigns to each control switch an event.

#### SReach considers ...

**Definition 2 (PHA**<sub>r</sub>). A probabilistic hybrid automaton with additional randomness  $H_r$  consists of Q, E, V, RV, Init, Flow, Inv,  $\Sigma$  as in Definition 1, and Cmds, which is a finite set of probabilistic guarded commands of the form:  $g \to p_1 : u_1 + \cdots + p_m : u_m$ , where g is a predicate representing a transition guard with free variables from

where g is a predicate representing a transition guard with free variables from V,  $p_i$  is the transition probability for the ith probabilistic choice which can be expressed by an equation involving random variable(s) in RV and the  $p_i$ 's satisfy  $\sum_{i=1}^{m} p_i = 1$ , and  $u_i$  is the corresponding transition updating function for the ith probabilistic choice, whose free variables are from  $V \cup V' \cup RV$ .

 $x \ge 5 \rightarrow p_1 : (x' = \sin(x)) + (1 - p_1) : (x' = p_x),$  $p_1 \sim U(0.2, 0.9), \text{ and } p_x \sim B(0.85)$ 

#### SReach can handle...

**Definition 3.** The probabilistic bounded k step  $\delta$ -reachability for a  $HA_p$   $H_p$  is to compute the probability that  $H_p$  reaches the target region T in k steps. Given the set of independent random variables  $\mathbf{r}$ ,  $Pr(\mathbf{r})$  a probability measure over  $\mathbf{r}$ , and  $\Omega$  the sample space of  $\mathbf{r}$ , the reachability probability is  $\int_{\Omega} I_T(\mathbf{r}) dPr(\mathbf{r})$ , where  $I_T(\mathbf{r})$  is the indicator function which is 1 if  $H_p$  with  $\mathbf{r}$  reaches T in k steps.

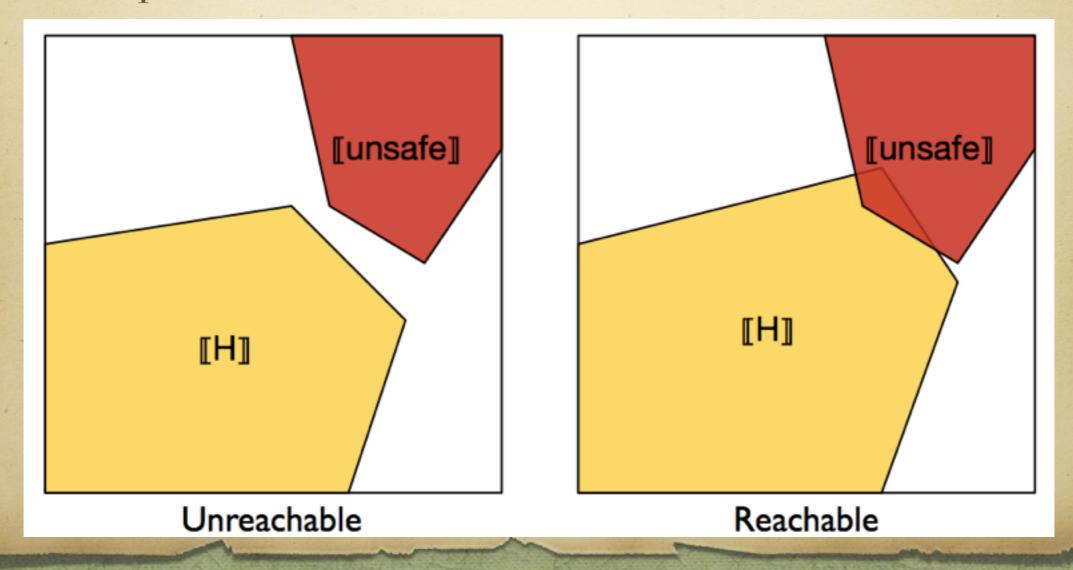
**Definition 4.** For a PHA<sub>r</sub>  $H_r$ , the probabilistic bounded k step  $\delta$ -reachability estimated by SReach is the maximal probability that  $H_r$  reaches the target region T in k steps:  $max_{\sigma \in E} Pr_{H_r,\sigma,T}^k(i)$ , where E is the set of possible executions of H starting from the initial state i, and  $\sigma$  is an execution in the set E.

## SReach's algorithm

- δ-complete bounded reachability analysis technique (dReal/dReach) + statistical testing techniques
- advance the reasoning power of SMT-based bounded model checking to probabilistic models
- > the full non-determinism and nonlinear dynamics of models will be considered
- the coverage of simulation will be increased
- > the zero-crossing problem can be avoided
- controllable error bounds on the estimated probabilities

## Reachability Analysis of Hybrid Systems

Can a hybrid system H run into a goal region of its state space?

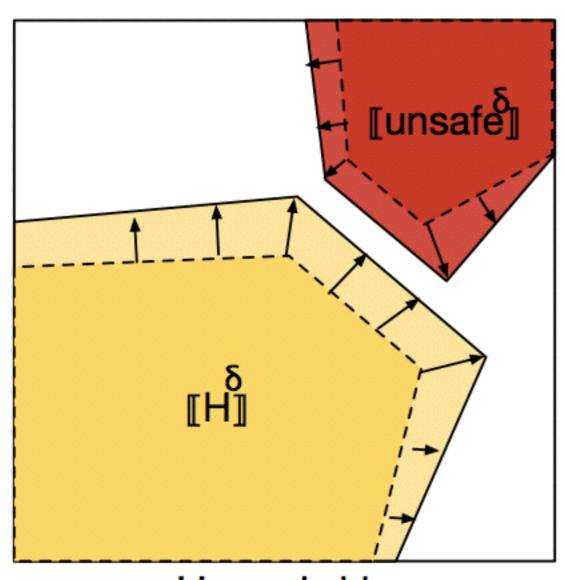


## Bounded Reachability Analysis of Hybrid Systems

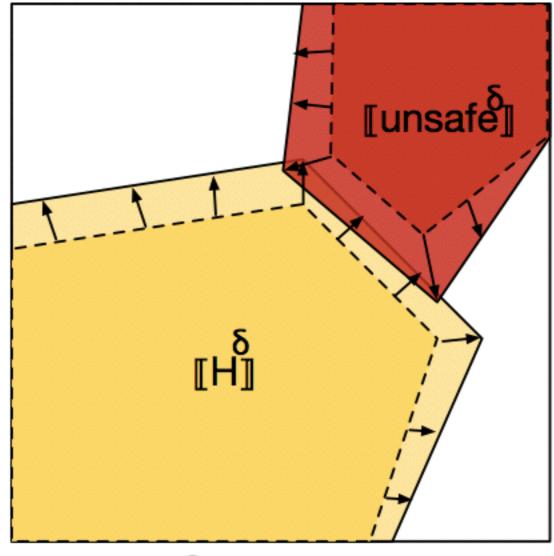
- The standard bounded reachability problems for simple hybrid systems are undecidable.
  - > 1. Give up
  - 2. Don't give Up
    - A. Find a decidable fragment and solve it
    - B. Use approximation

#### δ-Reachability Analysis of Hybrid Systems

- Solven  $\delta \in \mathbb{Q}^+$ , [H] and [Goal] over-approximate [H] and [Goal] respectively.
- > So, the δ-reachability problem asks



Unreachable



δ-reachable

#### δ-Reachability Analysis of Hybrid Systems

- > Decidable for a wide range of nonlinear hybrid systems: polynomials, log, exp, trigonometric functions, ODEs ...
- > Reasonable complexity bound (PSPACE-complete)
- > When it says
  - Unreachable the answer is sound
  - δ-Reachable may lead to an infeasible counterexample,
     you may try a smaller δ and possibly get rid of it

#### SReach's algorithm

#### Algorithm 1 SReach

```
1: function SREACH(MP, ST, \delta, k)
 2:
        if MP is a HA_p then
            MP \leftarrow EncRM_1(MP)
 3:
                                                      > encode uncertain system parameters
                                                                           \triangleright otherwise a PHA<sub>r</sub>
 4:
        else
            MP \leftarrow EncRM_2(MP) \triangleright encode probabilistic jumps and extra randomness
 5:
        end if
 6:
        Succ, N \leftarrow 0
                                               \triangleright number of \delta-sat samples and total samples
 7:
        Assgn \leftarrow \emptyset
                               > record unique sampling assignments and dReach results
 8:
        RV \leftarrow \text{ExtractRV}(MP)
                                                 9:
        repeat in parallel
10:
            S_i \leftarrow \text{Sim}(RV)
11:
                                                                      > sample the parameters
12:
            if S_i \in Assgn.sample then
13:
                Res \leftarrow Assgn(S_i).res
                                                                      ▷ no need to call dReach
14:
            else
15:
                M_i \leftarrow \operatorname{Gen}(MP, S_i)

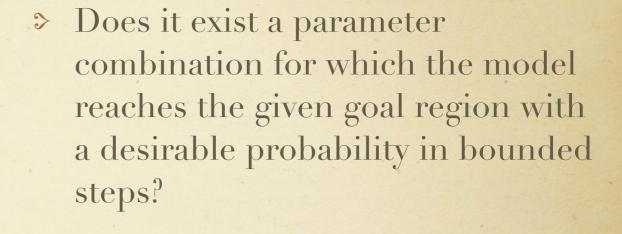
⊳ generate a dReach model

16:
                Res \leftarrow dReach(M_i, \delta, k)
                                                 \triangleright call dReach to solve k-step \delta-reachability
17:
            end if
18:
            if Res = \delta-sat then Succ \leftarrow Succ + 1
19:
            end if
            N \leftarrow N + 1
20:
        until ST.done(Succ, N)
                                                                      > perform statistical test
21:
22:
        return ST.output
23: end function
```

- > SReach can answer two types of questions:
  - (1) Does the model satisfy a given reachability property with probability greater than a certain threshold? hypothesis testing
  - > Hypothesis testing methods: Lai's test, Bayes factor test, Bayes factor test with indifference region, and Sequential probability ratio test.

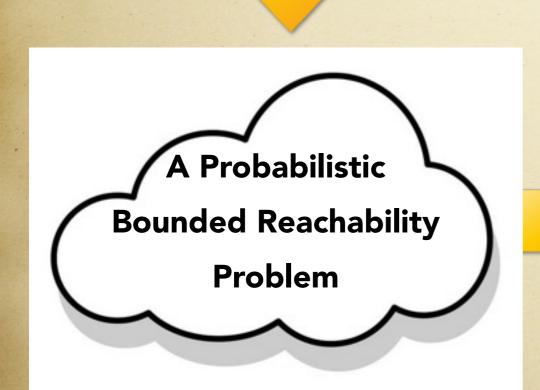
- > SReach can answer two types of questions:
  - > (2) What is the probability that the model satisfies a given reachability property? statistical estimation
  - Statistical estimation methods: Chernoff-Hoeffding bound, Bayesian interval estimation with beta prior, and Direct sampling.

Parameter Synthesis: How to control the system to reach good states with a desirable probability?



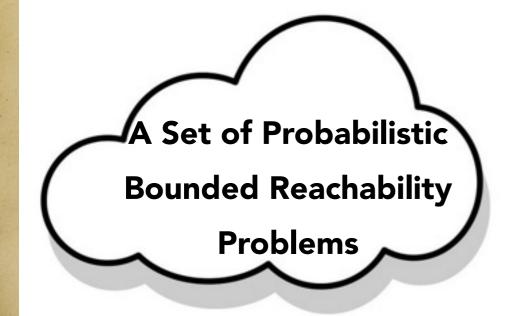
Considering an assignment of a certain set of system parameters, if a witness is returned, this assignment is potentially a good estimation for those parameters.

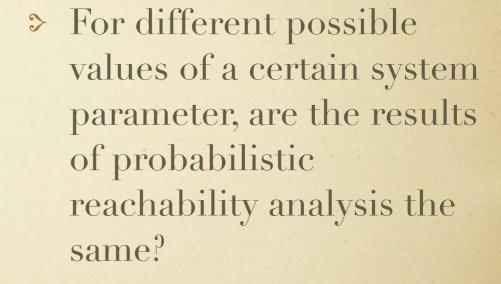
The goal here is to find an assignment with which all the given goal regions with desirable probabilities can be reached in bounded steps.

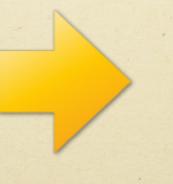


Parametric Sensitivity Analysis: Testing the robustness of the model, Understand the relationships between parameters and the model, etc.



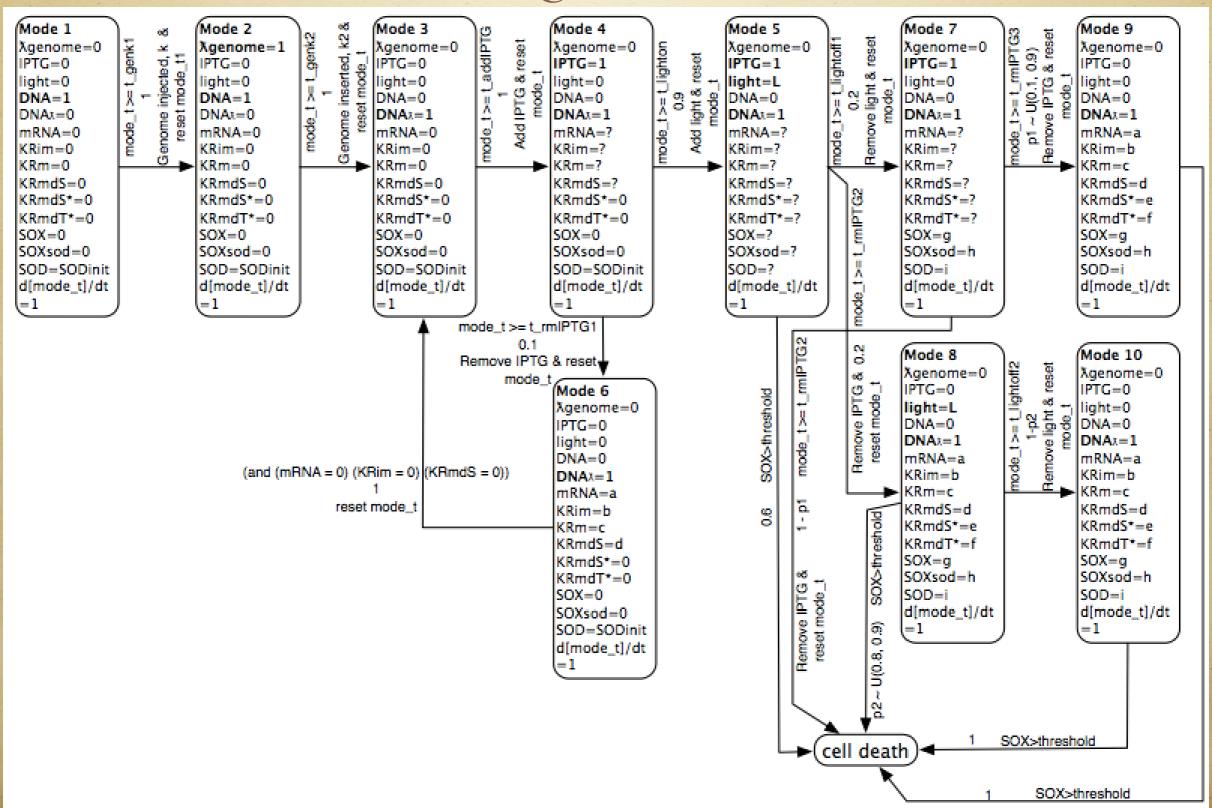






> If so, the model is insensitive to this parameter with regard to the given observations.

#### Bacteria-killing KillerRed Model



#### Bacteria-killing KillerRed Model

$$\frac{\mathrm{d}[mRNA]}{\mathrm{d}t} = k_{RNAsyn} \cdot [DNA] - k_{RNAdeg} \cdot [mRNA]$$

$$\frac{\mathrm{d}[KR_{im}]}{\mathrm{d}t} = k_{KR_{im}syn} \cdot [mRNA] - (k_{KR_m} + k_{KR_{im}deg})$$

$$\cdot [KR_{im}]$$

$$\frac{\mathrm{d}[KR_{mdS}]}{\mathrm{d}t} = k_{KR_m} \cdot [KR_{im}] - k_{KR_{mdS}deg} \cdot [KR_{mdS}] \quad \underline{\mathrm{d}[KR_{mdS}]}$$

$$\frac{\mathrm{d}[KR_{mdS}]}{\mathrm{d}t} = k_{KR_m} \cdot [KR_{im}] + k_{KR_f} \cdot [KR_{mdS^*}] \\ + k_{KR_{ic}} \cdot [KR_{mdS^*}] + k_{KR_{nrd}} \cdot [KR_{mdT^*}] \\ + k_{KR_{SOXd1}} \cdot [KR_{mdT^*}] - k_{KR_{ex}} \cdot [KR_{mdS}] \\ - k_{KR_{mdS}deg} \cdot [KR_{mdS}] \\ = k_{KR_{ex}} \cdot [KR_{mdS}] - k_{KR_f} \cdot [KR_{mdS^*}] \\ - k_{KR_{ic}} \cdot [KR_{mdS^*}] - k_{KR_{isc}} \cdot [KR_{mdS^*}] \\ - k_{KR_{mdS^*}deg} \cdot [KR_{mdS^*}] \\ = k_{KR_{isc}} \cdot [KR_{mdS^*}] - k_{KR_{nrd}} \cdot [KR_{mdT^*}] \\ - k_{KR_{SOXd1}} \cdot [KR_{mdT^*}] \\ - k_{KR_{SOXd1}} \cdot [KR_{mdT^*}] \\ - k_{KR_{SOXd2}} \cdot [KR_{mdT^*}] \\ - k_{KR_{mdT^*}deg} \cdot [KR_{mdT^*}] \\ + k_{KR_{SOXd2}} \cdot [KR_{mdT^*}] \\ + k_{KR_{SOXd2}} \cdot [KR_{mdT^*}] + k_{KR_{SOXd2}} \\ \cdot [KR_{mdT^*}] - \frac{\mathrm{d}[SOX_{sod}]}{\mathrm{d}t} \\ = k_{SOD} \cdot V_{maxSOD} \cdot \frac{[SOX]}{K_m + [SOX]}$$

#### Bacteria-killing KillerRed Model

k	Est_P	#S_S	#T_S	$Avg_{-}T(s)$	$Tot_{-}T(s)$	k	$Est_{-}P$	#S_S	#T_S	Avg_T(s)	$\overline{\mathrm{Tot}_{ ext{-}}\mathrm{T}(\mathrm{s})}$
5	0.544	8951	16452	0.074	1219.38	8	0.004	0	240	0.004	0.88
6	0.247	3045	12336	0.969	11957.12	9	0.004	0	240	0.012	2.97
7	0.096	559	5808	5.470	31770.36	10	0.004	0	240	0.013	3.18

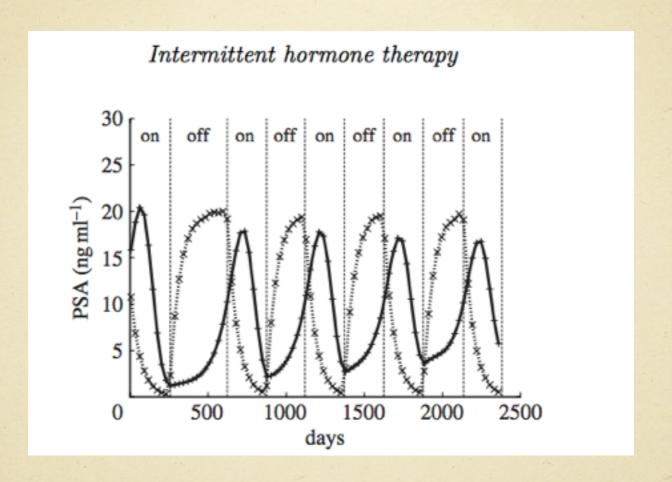
Table 3: Results for the 11-mode killerred model.

$t_{lightON}$ (t.u.)	1	2	3	4	5	6	7	8	9	10
$t_{total}$ (t.u.)	16	17.2	18.5	20	21.3	22.7	23.5	24.1	25	30
$t_{lightOFF_1}$ (t.u.)	1	2	3	4	5	6	7	8	9	10
killed bacteria cells	failed	failed	failed	succ	succ	succ	succ	succ	$\operatorname{succ}$	succ
$t_{rmIPTG_3}$ (t.u.)	1	2	3	4	5	6	7	8	9	10
killed bacteria cells	succ	succ	succ	succ	succ	succ	succ	succ	$\operatorname{succ}$	succ
$SOX_{thres}$ (M)	1e-4	2e-4	3e-4	4e-4	5e-4	6e-4	7e-4	8e-4	9e-4	1e-3
$t_{total}$ (t.u.)	5.1	5.2	5.4	17	19	48	61	71	36	42

Table 4: Formal analysis results for our KillerRed hybrid model

#S\_S = number of  $\delta$ -sat samples, #T\_S = total number of samples, Est\_P = estimated probability of property, Avg\_T(s) = average CPU time of each sample in seconds, and Tot\_T(s) = total CPU time for all samples in seconds.

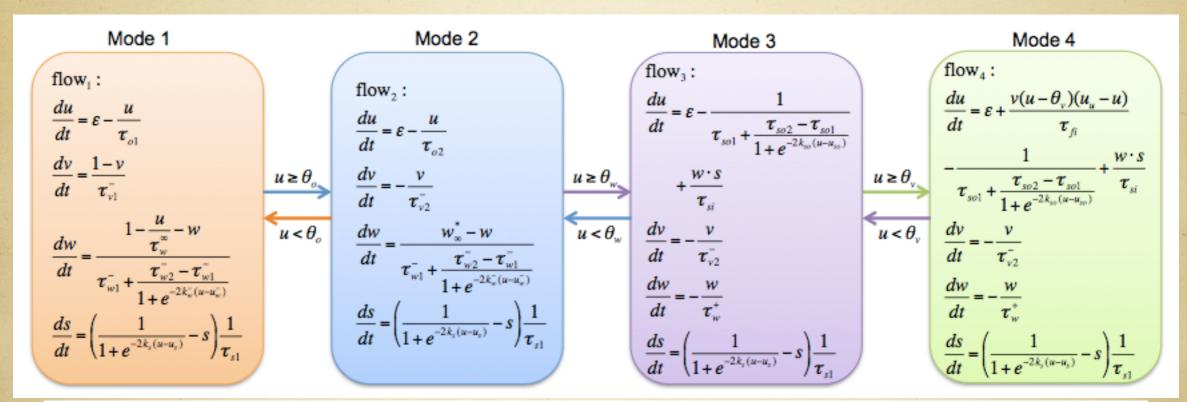
#### Prostate Cancer treatment



Model	#RVs	$r_0$	$r_1$	Est_P	#S_S	#T_S	$Avg_{-}T(s)$	$\mathrm{Tot}_{-}\mathrm{T(s)}$
PCT1	6	5.0	10.0	0.496	8226	16584	0.596	9892
PCT2	6	7.0	11.0	0.994	335	336	54.307	18247
PCT3	6	10.0	15.0	0.996	240	240	506.5	121560

Table 2: Results for the 2-mode prostate cancer treatment model (k = 2). For each sample generated, SReach analyzed systems with 41 variables and 10 ODEs in the unfolded SMT formulae.

#### Atrial Fibrillation Model



Model	#RVs	EPI_TO1	EPI_TO2	#S_S	#T_S	Est_P	$A_{-}T(s)$	$T_{-}T(s)$
$Cd_{-to1}$ s	1	U(6.1e-3, 7e-3)	6	240	240	0.996	0.270	64.80
Cd_to1_uns	1	U(5.5e-3, 5.9e-3)	6	0	240	0.004	0.042	10.08
$Cd_{-to2\_s}$	1	400	U(0.131, 6)	240	240	0.996	0.231	55.36
$Cd_{-to2\_uns}$	1	400	U(0.1, 0.129)	0	240	0.004	0.038	9.15
Cd_to12_s	2	N(400, 1e-4)	N(6, 1e-4)	240	240	0.996	0.091	21.87
Cd_to12_uns	2	N(5.5e-3, 10e-6)	N(0.11, 10e-5)	0	240	0.004	0.037	8.90

Table 1: Results for the 4-mode atrial fibrillation model (k = 3). For each sample generated, SReach analyzed systems with 62 variables and 24 ODEs in the unfolded SMT formulae. #RVs = number of random variables in the model,  $\#S\_S = number$  of  $\delta$ -sat samples,  $\#T\_S = total number of samples, <math>Est\_P = estimated$  probability of property,  $A\_T(s) = average$  CPU time of each sample in seconds, and  $T\_T(s) = total$  CPU time for all samples in seconds. Note that, we use the same notations in the remaining tables.

#### Experimental results

Benchmark	#Ms	K	#ODEs	#Vs	#RVs	δ	Est_P	#S_S	#T_S	$A_{-}T(s)$	$T_{-}T(s)$
BBK1	1	1	2	14	3	0.001			7126	0.086	612.836
BBK5	1	5	2	38	3	0.001	0.059	209	3628	0.253	917.884
BBwDv1	2	2	4	20	4	0.001	0.208	2206	10919	0.080	873.522
BBwDv2K2	2	2	4	20	3	0.001	0.845	7330	8669	0.209	1811.821
BBwDv2K8	2	8	4	56	3	0.001	0.207	2259	10901	0.858	9353.058
Tld	2	7	2	33	4	0.001	0.996	227	227	0.213	48.351
Ted	2	7	4	50	4	0.001	0.996	227	227	12.839	2914.448
DTldK3	2	3	4	26	2	0.001	0.996	227	227	0.382	86.714
DTldK5	2	5	4	38	2	0.001	0.161	1442	8961	0.280	2509.078
W4mv1	4	3	8	26	6	0.001	0.381	5953	15639	0.238	3722.082
W4mv2K3	4	3	8	26	6	0.001	0.996	227	227	0.673	152.771
W4mv2K7	4	7	8	50	6	0.001	0.004	0	227	0.120	27.240
DWK1	2	1	4	14	5	0.001	0.996	227	227	0.171	38.817
DWK3	2	3	4	26	5	0.001	0.996	227	227	0.215	48.806
DWK9	2	9	4	62	5	0.001	0.996	227	227	5.144	1167.688
Que	3	2	3	13	4	0.001	0.228	2662	11677	0.095	1109.315
3dOsc	3	2	18	48	2	0.001	0.996	227	227	8.273	1877.969
QuadC	1	0	14	44	6	0.001	0.996	227	227	825.641	187420.507
exPHA01	2	2	4	20	2	0.001	0.524	345	658	5.01	3295.82
exPHA02	2	3	2	17	1	0.001	0.900	5361	5953	0.0004	2.35
KRk5	6	5	84	194	2	0.001	0.544	8946	16457	0.122	2015.64
KRk6	8	6	112	224	6	0.001	0.246	2032	8263	1.385	11444.22
KRk7	10	7	150	271	6	0.001	0.096	558	5795	16.275	94311.18
KRk8	7	8	105	303	6	0.001	0.004	0	227	0.003	0.58
KRk9	9	9	135	335	6	0.001	0.004	0	227	0.015	3.43
KRk10	11	10	165	367	6	0.001	0.004	0	227	0.026	5.92

Table 5: #Ms = number of modes, K indicates the unfolding steps, #ODEs = number of ODEs in the unfolded formulae, #Vs = number of total variables in the unfolded formulae, #RVs = number of random variables in the model,  $\delta$  = precision used in dReach.

#### Future work

- Apply SReach to real-world models other than biological models
- Stochastic Hybrid Systems with stochastic flows: stochastic differential equations
  - introduce a type of constraints for SDEs, design a theory solver handling this type of constraints, then integrate with dReal solver.

#### Thanks!

- > https://github.com/dreal/SReach
- Questions?