Stochastic Hybrid Systems: Modelling Prostate Cancer and Psoriasis

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Introduction

- We use hybrid systems for modelling and verifying systems biology models
- Hybrid systems combine continuous dynamics with discrete state changes
  - *Parametric* hybrid systems feature random and nondeterministic parameters
- Reachability is one of the central properties of hybrid systems
  - **Undecidable** even for linear hybrid systems (Alur, Courcoubetis, Henzinger, Ho. 1993)
  - Bounded reachability – number of discrete transitions is finite

Bounded Reachability

Does the hybrid system reach the *goal* state within a finite number of (discrete) steps?

- Nonlinear arithmetics over the reals is **undecidable** (Richardson, 1968)
- Bounded reachability is δ-**decidable**
  - δ-complete decision procedure (Gao, Avigad, Clarke. LICS 2012)
- Used for parameter set identification in parametric hybrid systems

Parametric Hybrid Systems (PHS)

$$H =< Q, T, X, P, Y, R, \text{jump}, \text{ goal} >$$

- $Q = \{q_0, \cdots, q_m\}$ a set of modes (discrete components of the system),
- $T = \{(q, q') : q, q' \in Q\}$ a set of transitions between the modes,
- $X = [u_1, v_1] \times \cdots \times [u_n, v_n] \subset \mathbb{R}^n$ a domain of continuous variables,
- $P = [a_1, b_1] \times \cdots \times [a_k, b_k] \subset \mathbb{R}^k$ the **parameter space** of the system,
- $Y = \{\mathbf{y}_q(\mathbf{x_0}, t) : q \in Q, \mathbf{x_0} \in X \times P, t \in [0, \mathcal{T}]\}$ the continuous dynamics,
- $R = \{\mathbf{g}_{(q,q')}(\mathbf{x}, t) : (q, q') \in T, \mathbf{x} \in X \times P, t \in [0, \mathcal{T}]\}$ 'reset' functions,

and predicates (or relations)

- $\text{jump}_{(q,q')}(\mathbf{x})$ defines a discrete transition $(q, q') \in T$
- $\text{goal}_q(\mathbf{x})$ defines the goal state $\mathbf{x}$ in mode q.

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Bounded reachability can be encoded as the following (π a path and $B \subseteq P$):

$$\phi(\pi, B) := \exists^B \mathbf{p}, \exists^{[0,\mathcal{T}]} t_0, \cdots, \exists^{[0,\mathcal{T}]} t_{|\pi|-1} : \left(\mathbf{x}^t_{\pi(0)} = \mathbf{y}_{\pi(0)}(\mathbf{p}, t_0)\right) \wedge$$

$$\bigwedge_{i=0}^{|\pi|-2} \left[\text{jump}_{(\pi(i),\pi(i+1))}(\mathbf{x}^t_{\pi(i)}) \wedge \left(\mathbf{x}^t_{\pi(i+1)} = \mathbf{y}_{\pi(i)}(\mathbf{g}_{(\pi(i),\pi(i+1))}(\mathbf{x}^t_{\pi(i)}), t_{i+1})\right)\right]$$

$$\wedge\ \text{goal}_{\pi(|\pi|-1)}(\mathbf{x}^t_{\pi(|\pi|-1)})$$

Parameter Set Identification (I)

- **Parameter set identification** can be encoded by the formula:

$$\phi^{\forall}(\pi, B) := \forall^{B}\mathbf{p}, \exists^{[0,\mathcal{T}]}t_0, \cdots, \exists^{[0,\mathcal{T}]}t_{|\pi|-1} : \left(\mathbf{x}^{t}_{\pi(0)} = \mathbf{y}_{\pi(0)}(\mathbf{p}, t_0)\right) \wedge$$
$$\bigwedge_{i=0}^{|\pi|-2} \left[\mathrm{jump}_{(\pi(i),\pi(i+1))}(\mathbf{x}^{t}_{\pi(i)}) \wedge \left(\mathbf{x}^{t}_{\pi(i+1)} = \mathbf{y}_{\pi(i)}(\mathbf{g}_{(\pi(i),\pi(i+1))}(\mathbf{x}^{t}_{\pi(i)}), t_{i+1})\right)\right]$$
$$\wedge\ \mathrm{goal}_{\pi(|\pi|-1)}(\mathbf{x}^{t}_{\pi(|\pi|-1)})$$

- *Problem:* parameter **p** is quantified **universally**
  - δ-complete decision procedures currently support formulae with universal quantification over a single variable only

Parameter Set Identification (II)

- We solve a series of formulae $\psi_j(\pi, B)$:

$$\psi_j(\pi, B) := \exists^B \mathbf{p}, \exists^{[0,\mathcal{T}]} t_0, \cdots, \forall^{[0,\mathcal{T}]} t_j : \left(\mathbf{x}^t_{\pi(0)} = \mathbf{y}_{\pi(0)}(\mathbf{p}, t_0)\right) \wedge$$

$$\bigwedge_{i=0}^{j-1} \left[\mathbf{x}^t_{\pi(i+1)} = \mathbf{y}_{\pi(i)}(\mathbf{g}_{(\pi(i),\pi(i+1))}(\mathbf{x}^t_{\pi(i)}), t_{i+1})\right] \wedge \neg \mathrm{jump}_{(\pi(j),\pi(j+1))}(\mathbf{x}^t_{\pi(j)})$$

if $j < |\pi| - 1$ and

$$\psi_j(\pi, B) := \exists^B \mathbf{p}, \exists^{[0,\mathcal{T}]} t_0, \cdots, \forall^{[0,\mathcal{T}]} t_j : \left(\mathbf{x}^t_{\pi(0)} = \mathbf{y}_{\pi(0)}(\mathbf{p}, t_0)\right) \wedge$$

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if $j = |\pi| - 1$.

$$\bigwedge_{j=0}^{|\pi|-1} \neg \psi_j(\pi, B) \;\Rightarrow\; \phi^{\forall}(\pi, B)$$

Parameter Set Identification (III)

input: H - PHS, l - reachability depth, B - subset of parameter space, δ - precision;
output: **sat** / **unsat** / **undet**;
Path$(l) = \textit{get\_all\_paths}(H, l)$; // `compute all paths of length` l `for` H
for $\pi \in$ **Path**(l) **do**
    if $\phi(\pi, B)$ - δ-**sat then**
        for $i \in [0, l]$ **do**
            if $\psi_i(\pi, B)$ - δ-**sat then**
                return undet;
        return sat; // `all` $\psi_i(\pi, B)$ `are` **unsat**
return unsat; // `all` $\phi(\pi, B)$ `are` **unsat**

- **sat** – goal reached in l steps for **all** parameter values in B
- **unsat** – goal reached in l steps for **no** parameter values in B
- **undet** – goal reached in l steps for **some** parameter values in B
  - This can also mean a *false* alarm due to large value of δ
- B can be a singleton
  - Strengthening δ-**sat** answer (δ-**sat** $\Leftrightarrow$ **sat**)
  - Necessary for *statistical* model checking

Parameter Set Identification Application

Parameter Set Synthesis

- Given a parametric hybrid system find a subset of parameter space satisfying the given time series data

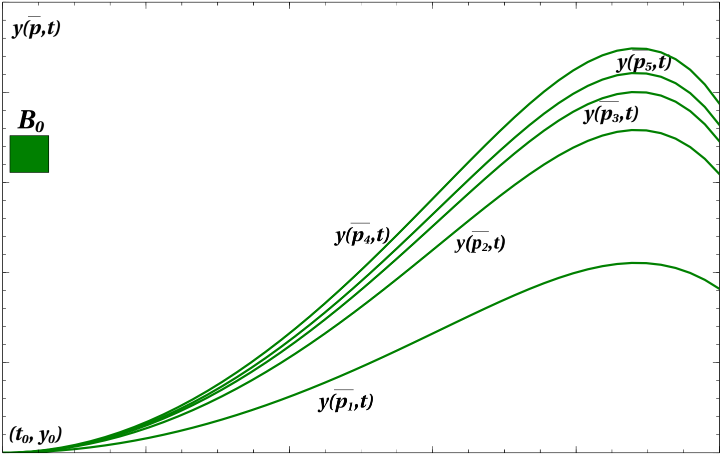
Probabilistic Bounded Reachability

- What is the maximum (minimum) probability that the system reaches the *goal* state in a finite number of discrete steps?

Parameter Set Synthesis

- **Parameter Set Synthesis** in continuous (*no* discrete transitions) biological systems

Curtis Madsen, Fedor Shmarov and Paolo Zuliani, *CMSB 2015*



- This approach was extended to parameter set synthesis in hybrid systems

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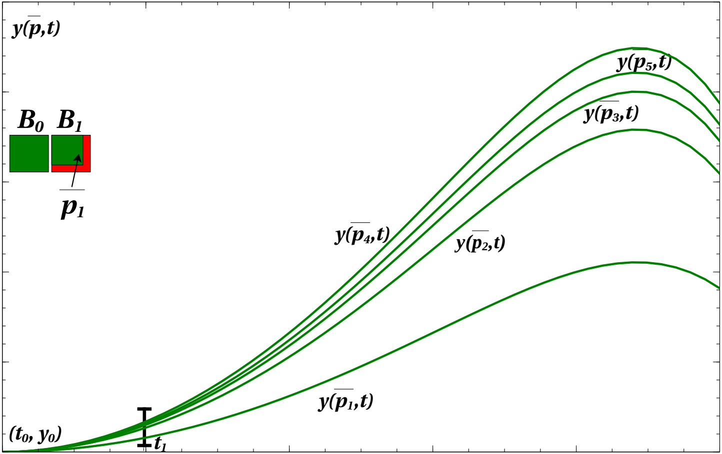

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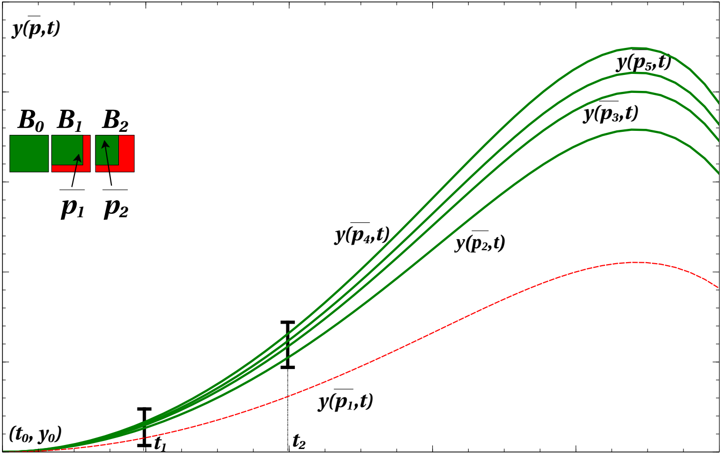

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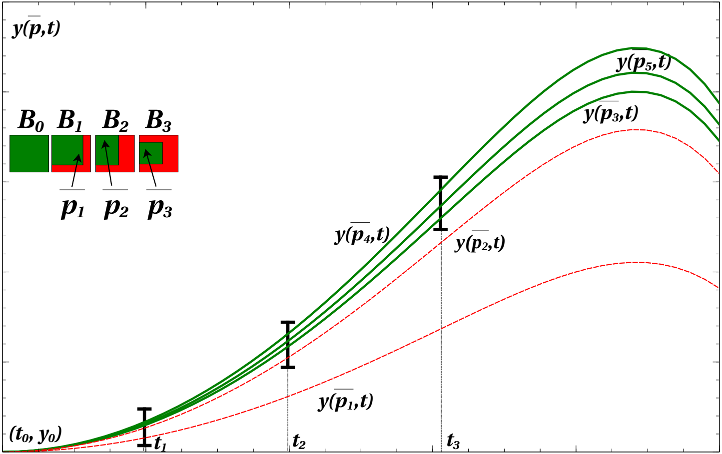

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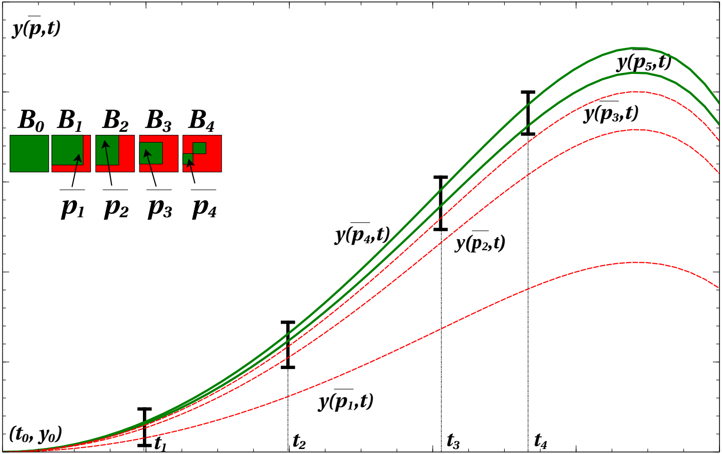

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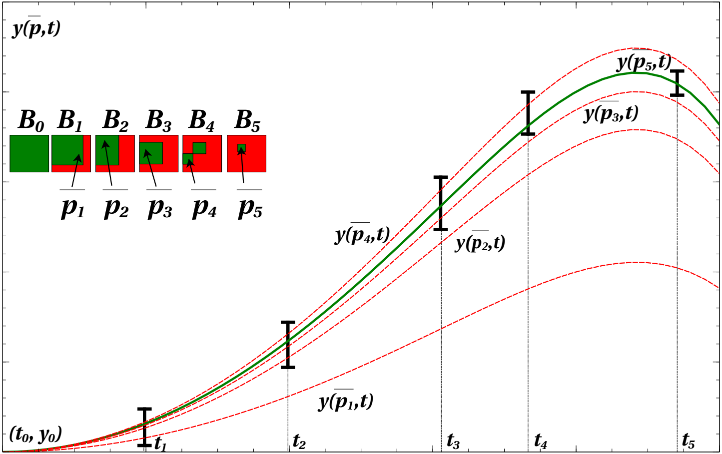

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Probabilistic Bounded Reachability

Formal approach

- Integrating probability measure
- Returns a list of enclosures $P(B_N) = [P_{lower}, P_{upper}]$
  - For all $\mathbf{p}_N \in B_N : \mathbf{Pr}(\mathbf{p}_N) \in P(B_N)$
  - $P(B_N)$ can be arbitrarily small (up to user defined $\epsilon > 0$) when
    - Probability function is continuous *or*
    - Only random parameters are present
- Exponential complexity with respect to the number of parameters

Fedor Shmarov and Paolo Zuliani, *HSCC 2015*

Statistical/formal approach

- Bayesian Estimations Algorithm (probability)
- Cross-Entropy Algorithm (nondeterminism)
- Returns a confidence interval $[P_{lower}, P_{upper}]$ containing the maximum (minimum) probability value with the user-defined confidence $c \in (0, 1)$.
- Constant complexity with respect to the number of parameters

Fedor Shmarov and Paolo Zuliani, *HVC 2016*

Our Software

`ProbReach`

- Parameter Set Synthesis in Hybrid Systems
- Probabilistic Bounded Reachability in Hybrid Systems

  `https://github.com/dreal/probreach`

`BioPSy`

- Parameter Set Synthesis in Continuous Systems (no discrete transitions)
  - SBML file as input,
  - Graphical User Interface.

  `https://github.com/dreal/biology`

Personalized Prostate Cancer Therapy

- **Identification:** prostate-specific antigen (PSA) – tumor marker
- **Therapy:** androgen suppression
  - Low androgen level causes growth of castration resistant cells (CRC)
- **Solution:** alternation between *treatment* and *rest* episodes

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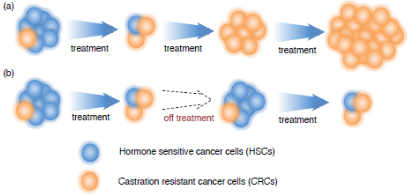

Prostate cancer progression in response to a) continuous and b) intermittent androgen suppression treatments

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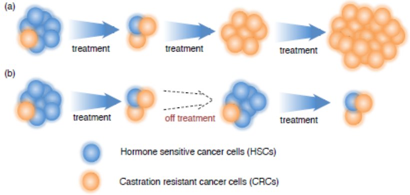

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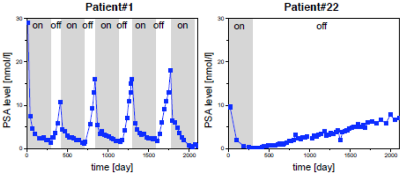

The serum level of prostate-specific antigen (PSA)

Liu, B., Kong, S., Gao, S., Zuliani, P., Clarke, E.M.: Towards personalized cancer therapy using delta-reachability analysis. In: HSCC. pp. 227–232. ACM (2015)

Personalized Prostate Cancer Therapy Model

on-therapy

$$\frac{dx}{dt} = \left(\frac{\alpha_x}{1 + e^{(k_1 - z)k_2}} - \frac{\beta_x}{1 + e^{(z - k_3)k_4}} - m_1\left(1 - \frac{z}{z_0}\right) - c_1\right)x + c$$
$$\frac{dy}{dt} = m_1\left(1 - \frac{z}{z_0}\right)x + \left(\alpha_y\left(1 - \frac{d_0 z}{z_0}\right) - \beta_y\right)y$$
$$\frac{dz}{dt} = -z\gamma + c_3$$
$$\frac{dv}{dt} = \frac{dx}{dt} + \frac{dy}{dt}$$

$v \le r_0$

$v \ge r_1$

off-therapy

$$\frac{dx}{dt} = \left(\frac{\alpha_x}{1 + e^{(k_1 - z)k_2}} - \frac{\beta_x}{1 + e^{(z - k_3)k_4}} - m_1\left(1 - \frac{z}{z_0}\right) - c_1\right)x + c$$
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$$\frac{dz}{dt} = (z_0 - z)\gamma + c_3$$
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υ - *prostate specific antigen* (PSA)
x - *hormone sensitive cells* (HSCs)
y - *castration resistant cells* (CRCs)
z - androgen

Personalized Prostate Cancer Therapy Model

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v - *prostate specific antigen* (PSA)
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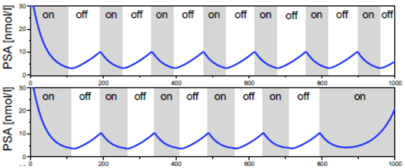
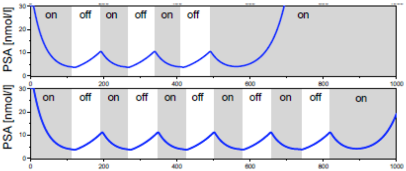


Model simulation for two different patients (days)



Model simulation for two different therapies (days)

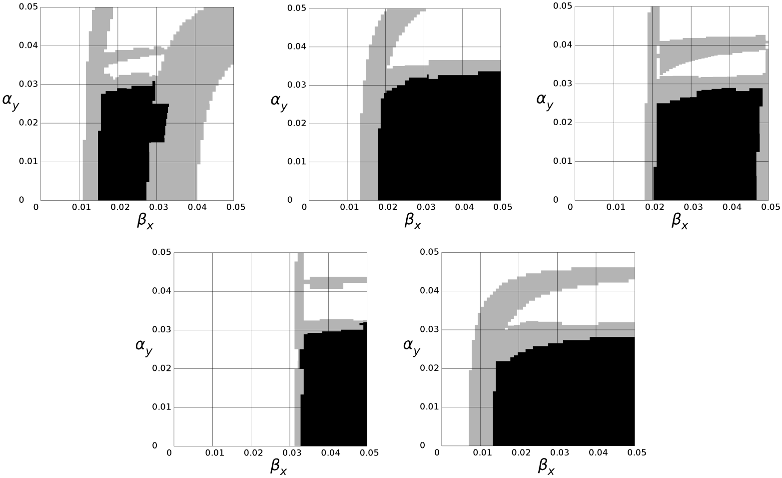
Ideta, A.M., Tanaka, G., Takeuchi, T., Aihara, K.: A mathematical model of intermittent androgen suppression for prostate cancer. Journal of Nonlinear Science 18(6), 593–614 (2008)

Parameter Set Synthesis (I)

- A prostate cancer patient was on treatment for 5 nonconsecutive times throughout 6 years and monitored every month (such as PSA and androgen levels were documented).
- Every period of time-series data contains around 4-5 time points.
- Parameter synthesis was performed using **real clinical data**[1].
- For each time-series, we synthesise $\alpha_y \times \beta_x \in [0.0, 0.05] \times [0.0, 0.05]$ with:
  - Tolerable amount of noise, $\eta = 1.4$;
  - Parameter synthesis precision, $\epsilon = 10^{-3}$; and
  - SMT solver precision, $\delta = 10^{-3}$.

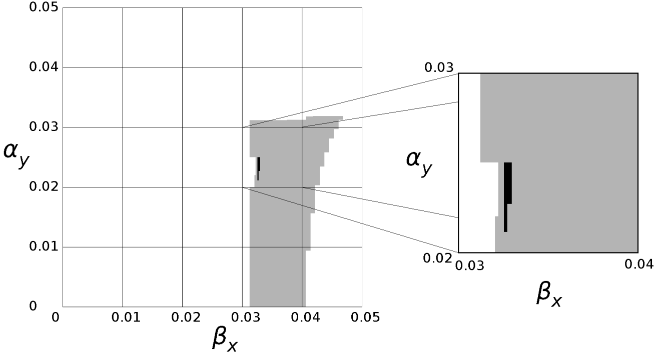
[1] `http://www.nicholasbruchovsky.com/clinicalResearch.html`

Parameter Set Synthesis (II)



white - infeasible boxes; **black** - feasible boxes; and **gray** - undetermined boxes. **Runtime**: 12 hours for set of time-series data.

Parameter Set Synthesis (III)



white - infeasible boxes; **black** - feasible boxes; and **gray** - undetermined boxes.

- The feasible set:
  $\alpha_y \times \beta_x \in [0.0225, 0.025] \times [0.0325, 0.0332031] \bigcup [0.0210938, 0.0225] \times [0.0325, 0.0327344]$.

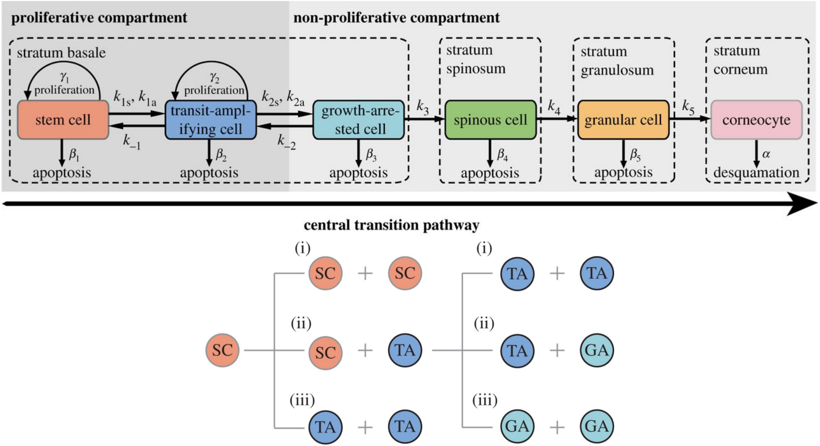
Parameter Checking

- Checking parameter values is easier than synthesising parameter sets.
- Parameter values in this study were obtained using `COPASI` and verified with `BioPSy`.

Method	α_x	α_y	β_x	β_y	BioPSy				
					S_1	S_2	S_3	S_4	S_5
Evolut. Prog.	-0.216	-2.68×10^{-6}	0.0272	0.000135	n	y	y	n	y
Hooke & Jeeves	-0.309	-0.279	0.029	-0.24	y	y	y	y	y
Levenberg-Marquardt	-0.17	-32.0	0.00661	-10.5	n	n	n	n	n
Praxis	-0.233	-0.00698	0.0240	0.187	y	y	y	n	y
Scatter Search	-0.17	-31.9	0.00661	-10.5	n	n	n	n	n
Simulated Annealing	-0.249	6.4×10^{149}	0.0227	-2.27×10^{148}	n	n	n	n	n
Truncated Newton	-0.236	-0.00792	0.0244	0.0116	y	y	y	n	y

Psoriasis Model

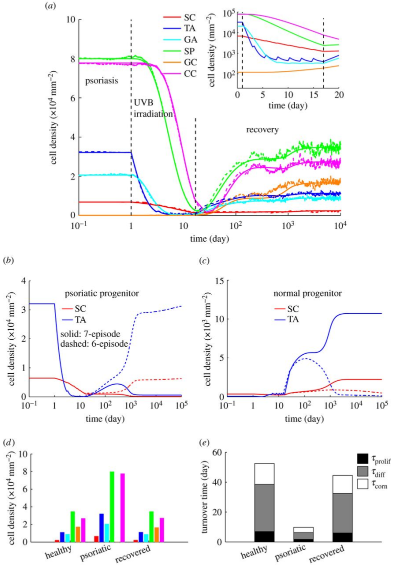
- **Psoriasis** – complex epidermal disorder characterized by keratinocyte hyperproliferation and abnormal differentiation



H. Zhang, W. Hou, L. Henrot, S. Schnebert, M. Dumas, C. Heusele, and J. Yang. Modelling epidermis homoeostasis and psoriasis pathogenesis. Journal of The Royal Society Interface, 12(103), 2015.

UVB Irradiation Therapy

- Based on UVB irradiation for inducing apoptosis in SCs and TA cells
- Patient is exposed to UVB irradiation for τ_{UVB} followed by τ_{rest} of rest
- The number of cycles is crucial for postponing the relapse



H. Zhang, W. Hou, L. Henrot, S. Schnebert, M. Dumas, C. Heusele, and J. Yang. Modelling epidermis homoeostasis and psoriasis pathogenesis. Journal of The Royal Society Interface, 12(103), 2015.

UVB Irradiation Therapy Model

- **Therapy:** 48 hours of irradiation + 8 hours of rest
- **Model:** simplified version (6 ODEs instead of 10)

$$SC' = \gamma_1 \frac{\omega(1 - \frac{SC+\lambda SC_d}{SC_{max}})SC}{1 + (\omega - 1)(\frac{TA+TA_d}{P_{ta,h}})^n} - \beta_1 In_A SC - \frac{k_{1s}\omega}{1 + (\omega - 1)(\frac{TA+TA_d}{P_{ta,h}})^n SC + k_1 TA}$$

$$TA' = \frac{k_{1a,s}\omega SC}{1 + (\omega - 1)(\frac{TA+TA_d}{P_{ta,h}})^n} + \frac{2k_{1s\omega}}{1 + (\omega - 1)(\frac{TA+TA_d}{P_{ta,h}})^n + \gamma_2 GA - \beta_2 In_A TA - k_{2s} TA - k_1 TA}$$

$$GA' = (k_{2a,s} + 2k_{2s}) TA - k_2 GA - k_3 GA - \beta_3 GA$$

$$SC_d' = \gamma_{1d}(1 - \frac{SC + SC_d}{SC_{max,t}} SC_d - \beta_{1d} In_A SC_d - k_{1sd} SC_d - \frac{k_p SC_d^2}{k_a^2 + SC_d^2} + k_{1d} TA_d)$$

$$TA_d' = k_{1a,sd} SC_d + 2k_{1sd} SC_d + \gamma_{2d} TA_d + k_{2d} GA_d - \beta_{2d} In_A TA_d - k_{2sd} TA_d - k_{1d} TA_d$$

$$GA_d' = (k_{2a,sd} + 2k_{2sd}) TA_d - k_{2d} GA_d - k_{3d} GA_d - \beta_{3d} GA_d$$

- **Irradiation:** increase β_1 and β_2 by In_A (constant)

Parameter Set Synthesis (I)

Time series data (65 times points) was obtained from simulation:

- $In_A = 60000$ – characterizes strength of irradiation
- $\lambda = 0.28571$ – characterizes strength of psoriatic stem cells

Parameters:

- $In_A \in [55000, 65000]$
- $\lambda \in [0.2, 0.4]$

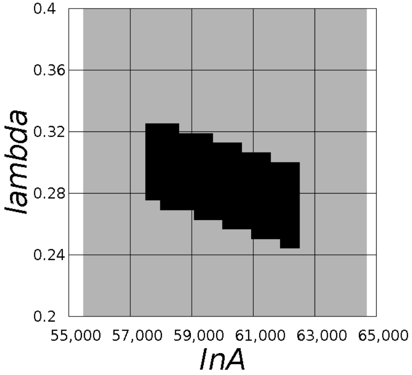
Precision vector:

- $\overline{\epsilon} = \{200, 0.01\}$

Noise vector:

- $\overline{\eta} = \{1, 1, 1, 5, 5, 5\}$

Parameter Set Synthesis (II)



white - infeasible boxes; **black** - feasible boxes; and **gray** - undetermined boxes. **Runtime:** 195 minutes (∼3 hours)[2]

- 276 boxes (**black** color) satisfy the time series data

[2] 32-core (2.9GHz) Linux machine

Probabilistic Bounded Reachability

Parameters:

- $In_A \sim N(6 \cdot 10^4, 10^4)$ – continuous random
- $\lambda \in [0.1, 0.5]$ – nondeterministic

Goal:

- What are the maximum and minimum probabilities of a psoriasis relapse within 2000 days after five therapy episodes?

λ	**Conf. Interval**	s_R	s_N	Time	**Formal Interval**	Time[3]
0.4953	[0.8268,1]	3,118	24	13,492	[0.9049,0.9274]	38,700
0.1303	[0,0.1086]	2,880	23	12,550	[0.0008,0.03806]	38,700

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Conclusions

- We presented techniques for
  - Parameter set synthesis
  - Probabilistic reachability analysis
- We demonstrated their applications to
  - Personalized prostate cancer therapy
  - UVB irradiation therapy for psoriasis treatment
- A lot to do
  - Biological systems with stochastic dynamics (Stochastic Differential Equations)

Demonstration

Human Starvation Model tracks the amount of fat, protein in muscle mass, and ketone bodies in the human body after glucose reserves have been depleted.

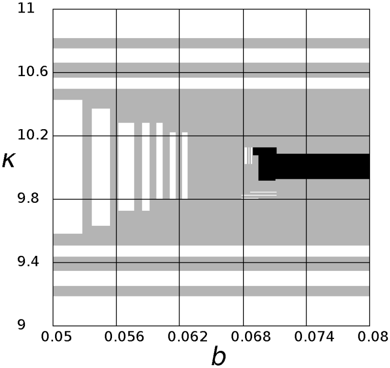
$$\frac{dF}{dt} = F\left(\frac{-a}{1+K} - \frac{1}{\lambda_F}\left(\frac{C+gL_0}{F+M} + \kappa\right)\right)$$
$$\frac{dM}{dt} = -\frac{M}{\lambda_M}\left(\frac{C+\kappa L_0}{F+M} + \kappa\right)$$
$$\frac{dK}{dt} = \frac{VaF}{1+K} - b$$

Parameter Set Synthesis:

- **Parameters:** $\kappa \times b \in [9, 11] \times [0.05, 0.08]$
- **Noise:** $\eta = 0.1$,
- **Precision:** $\epsilon = 0.1$,
- **Time-series:** 25 time points,
- **Solver precision:** $\delta = 10^{-3}$.

Song, B., Thomas, D.: Dynamics of starvation in humans. Journal of Mathematical Biology 54(1), 27–43 (2007)

Parameter Set Synthesis



white - infeasible boxes; **black** - feasible boxes; and **gray** - undetermined boxes. **Runtime**: 5 minutes[4].

- The feasible set:
  $\kappa \times b \in [9.88077, 9.8832] \times [0.0764844, 0.0771875] \bigcup [9.92213, 10] \times [0.0785938, 0.08] \bigcup \ldots.$

[4] 32-core (2.9GHz) Linux machine

Probabilistic Reachability

- **Parameters:** $\tau \in [20, 27]$, $\kappa \sim N(10.96, 1)$
- **Goal:** What are the minimum and maximum probabilities that muscle mass will decrease by 40% within τ days?

τ_g	**Conf. Int.**	s_R	s_N	Time	**Form. Int.**	Time
20.2264	[0,0.0057]	408,061	31	2,703	[0.00139,0.0014]	12
26.4713	[0.99131,1]	485,721	34	4,360	[0.993659,0.993668]	21

Thank You

Questions?