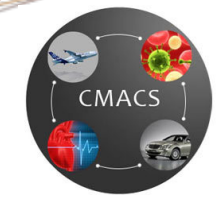


CMACS/AVACS Workshop

Parameter Identification using δ-Decisions for Hybrid Systems in Biology

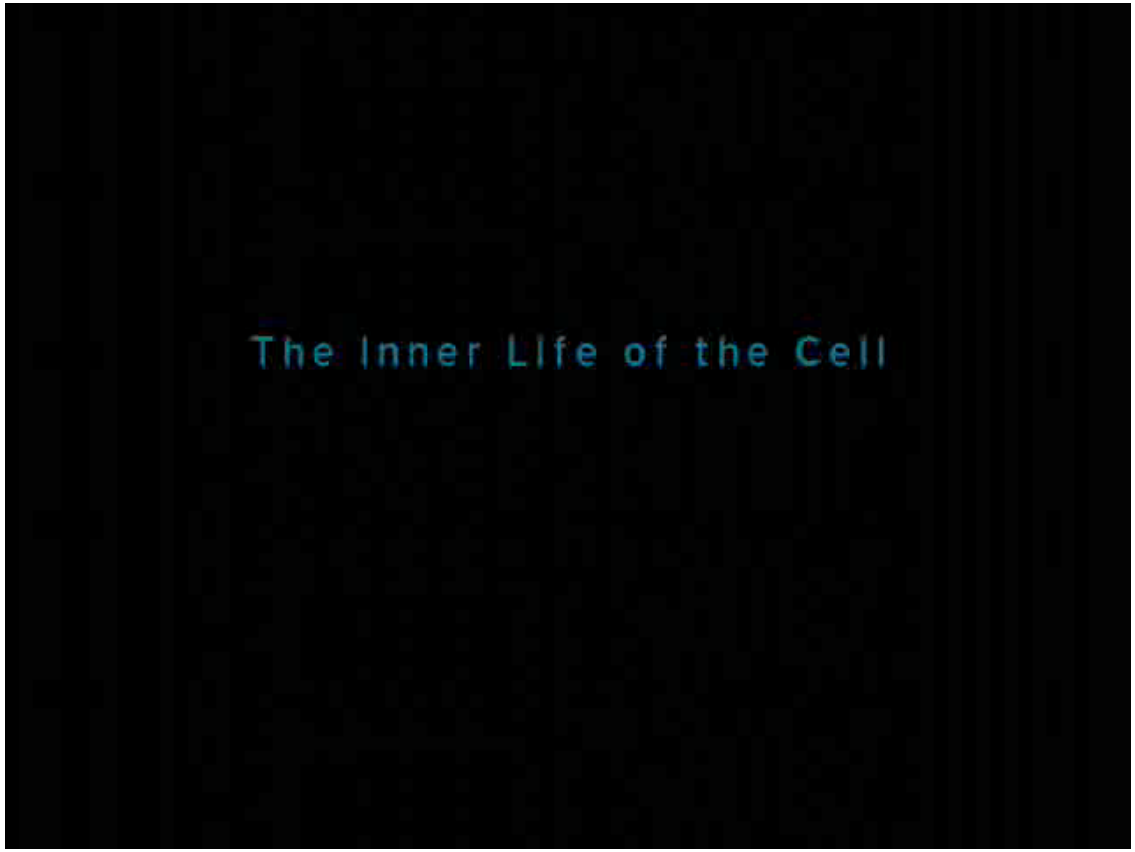
Bing Liu

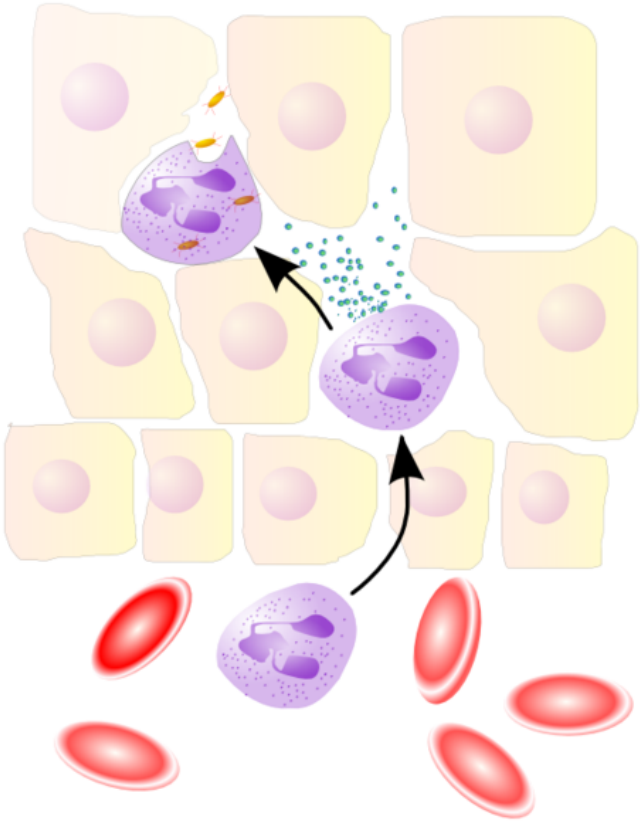
Joint work with

Soonho Kong, Sean Gao, Ed Clarke

Carnegie Mellon

Biological System

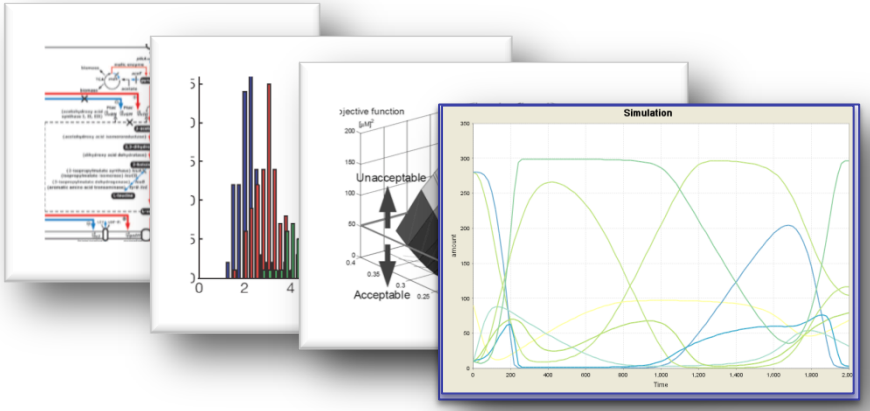


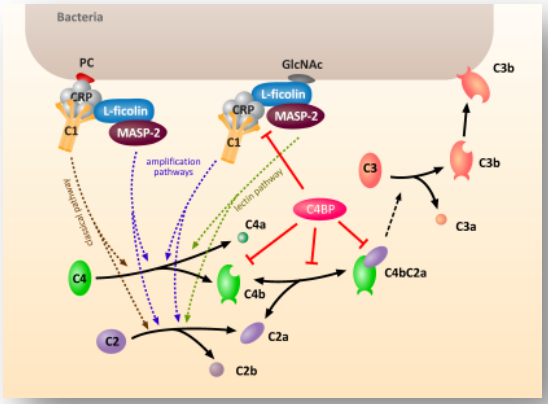


Bolinsky et al. SIGGRAPH, 2006

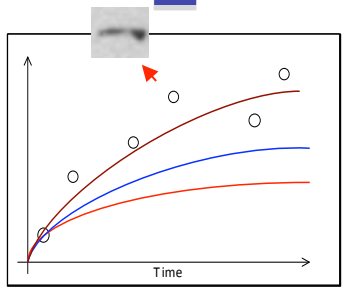
Computational Modeling

- Building a model
  - Structure
  - Calibration
    (parameter estimation)
  - Validation
- Performing analysis





$$\frac{dc_1}{dt} = -k_1.c_1.c_2 + k_2.c_3$$
$$\frac{dc_2}{dt} = -k_1.c_1.c_2 + k_2.c_3 + k_{17}.c_{18} + k_{11}.c_{11}$$
$$\frac{dc_3}{dt} = k_1.c_1.c_2 - k_2.c_3 - k_3.c_3.c_4 + k_4c_5$$
$$\frac{dc_4}{dt} = -k_3.c_3.c_4 + k_4c_5 + k_{11}.c_{11} + k_{20}.c_{21}$$
$$\frac{dc_5}{dt} = k_3.c_3.c_4 - k_4.c_5 - k_5.c_5.c_6 + k_6.c_7$$
$$\frac{dc_6}{dt} = -k_5.c_5.c_6 + k_6.c_7 + k_{11}.c_{11} + k_{20}.c_{21}$$
$$\frac{dc_7}{dt} = k_5.c_5.c_6 - k_6.c_7 - k_7.c_7.c_8 + k_8.c_9$$
$$\frac{dc_8}{dt} = -k_7.c_7.c_8 + k_8.c_9 + k_{11}.c_{11} + k_{20}.c_{21}$$
$$\frac{dc_9}{dt} = k_7.c_7.c_8 - k_8.c_9 - k_9.c_9.c_{10} + k_{10}.c_{11} - k_{15}.c_9.c_{17} + k_{16}.c_{18}$$



Computational Modeling

- Building a model
  - Structure
  - Calibration
    (parameter estimation)
  - Validation
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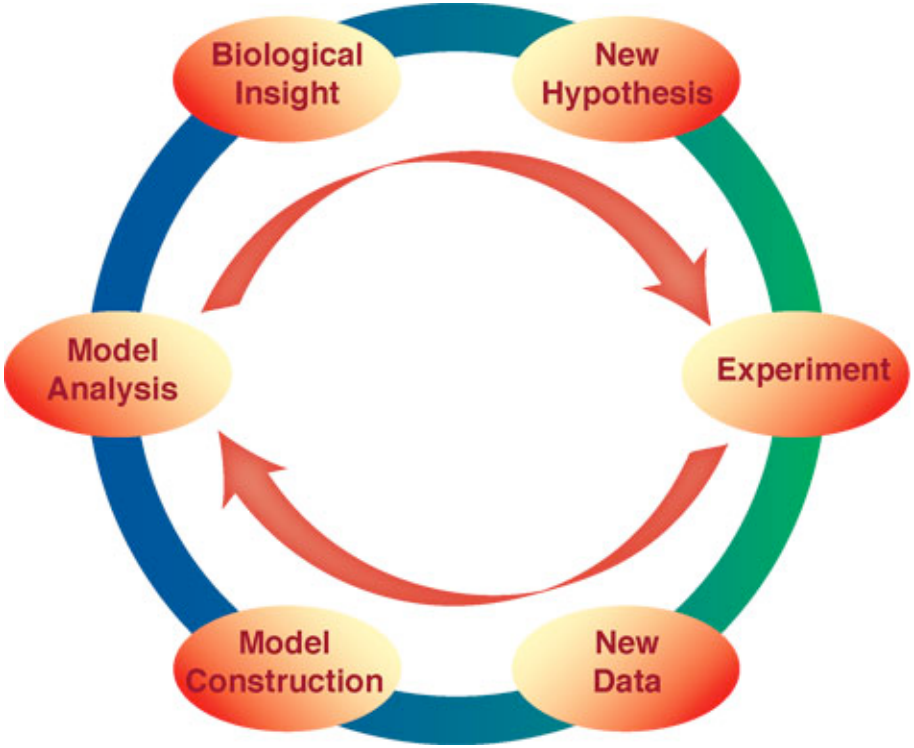
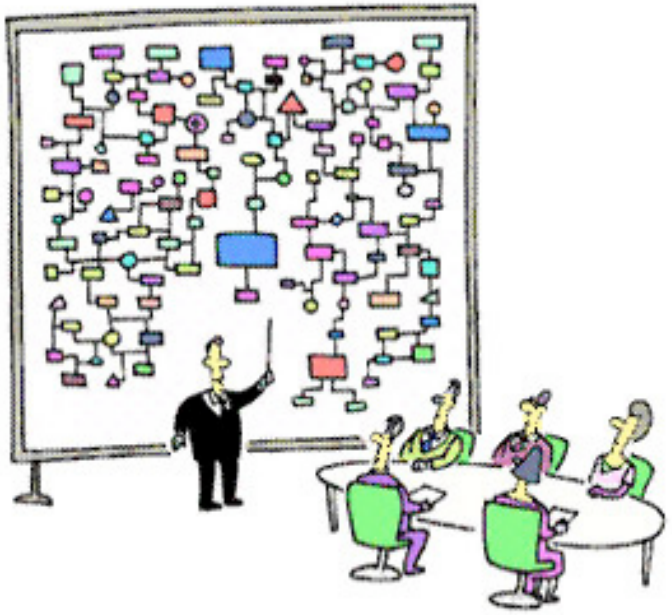


Computational Modeling

- Formalisms
  - Differential equations
  - Boolean network
  - Petri nets
  - Rule-based models
  - … …
- **Multi-mode?**

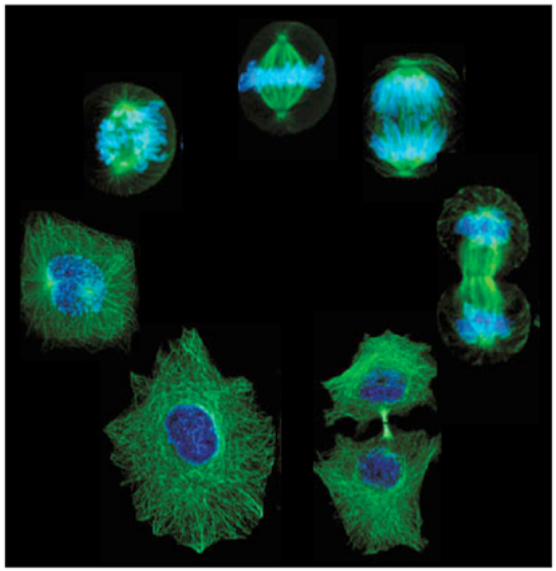


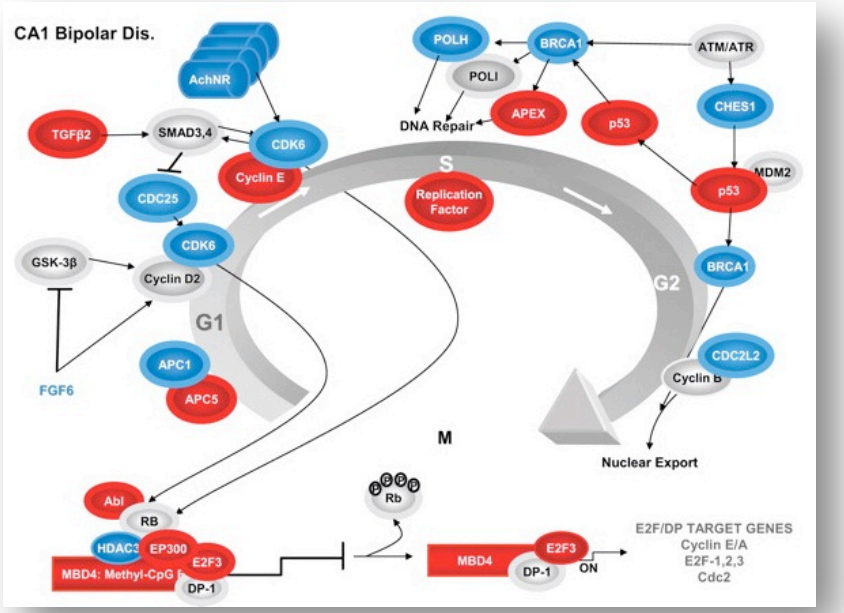
"And that's why we need a computer."

Hybrid Systems

- Activation of different networks at different stages
  - E.g. Cell cycle, Cell differentiation

Cell Cycle

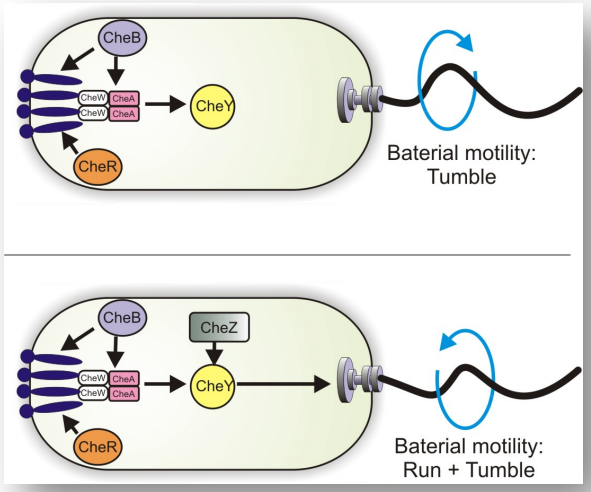


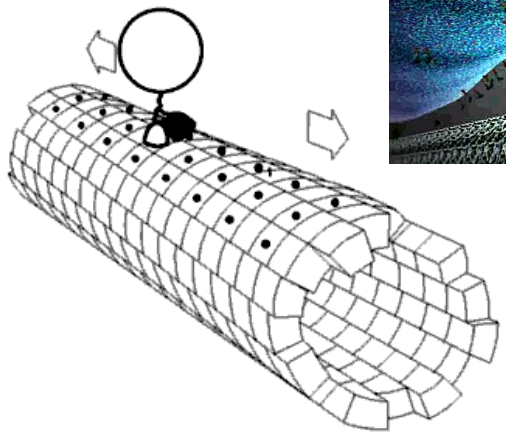


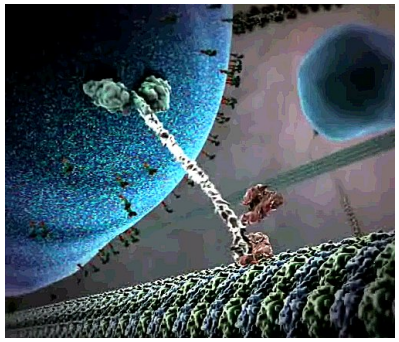
Benes et al, PNAS 2009

Hybrid Systems

- More examples:
  - *E. coli* chemotaxis, kinesin walking, gene transcription, drug treatment, … …





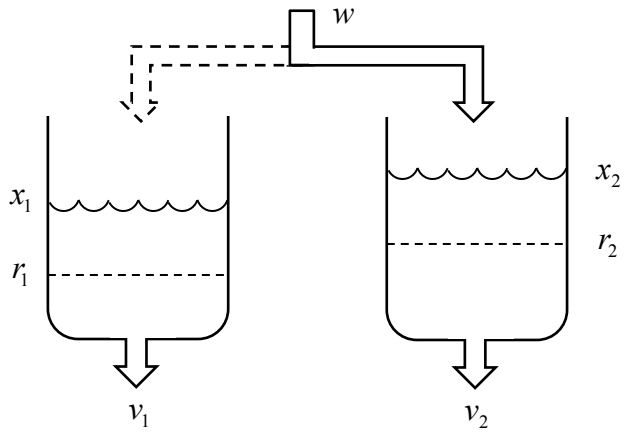


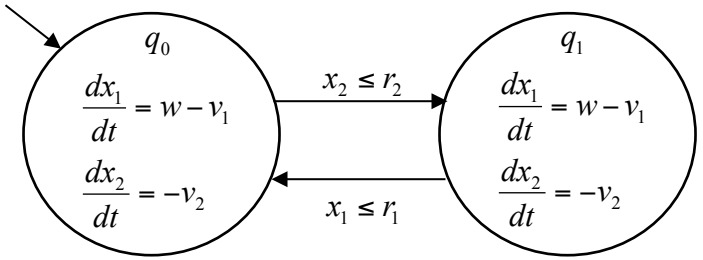
Hybrid Systems

- Evolve in a **continuous** way in each mode
- Ruled by **discrete** transitions

- Hybrid automata

$$H = \langle X, Q, \text{flow}, \text{guard}, \text{reset}, \text{inv}, \text{init} \rangle$$





Hybrid Systems

$H = \langle X, Q, \text{Init}, \text{Flow}, \text{Jump} \rangle$

- A continuous space $X \subseteq \mathbf{R}^k$ and a finite set of modes Q
- $\text{Init} \subseteq Q \times X$: initial configurations
- Flow : continuous flows
  - Each mode q is equipped with differential equations

$$\frac{d\vec{x}}{dt} = f_q(\vec{x}, t)$$

- Jump : discrete
  - The systems can be switched from to , resetting modes and variables

Hurdles

- How to answer questions such as:
  - Which model structure is better?
  - What conditions may lead to a desired state?
  - How to control the system to avoid bad states?
  - … …
- **Parameter synthesis** problem
- Analyzing nonlinear hybrid automata is challenging
  - even simple reachability questions can be **undecidable**

Our Approach

- Use **δ-complete decision procedures** to tackle the parameter synthesis problem for nonlinear hybrid models
  - Encode a parameter synthesis problem as a first-order formula over the reals
  - Perform bounded model checking
  - Employ an interval constrains propagation (ICP) based algorithm to identify the resulting parameters

Delta-Decisions

- A decision procedure using numerical techniques (with an error bound δ):
  - φ is false
  - $\varphi^{-\delta}$ is true
- The delta-decision problem is decidable for bounded first-order formulas over arbitrary Type 2 computable functions
  - exp, sin, etc, and Lipschitz-continuous ODEs

δ-Complete Bounded Model Checking

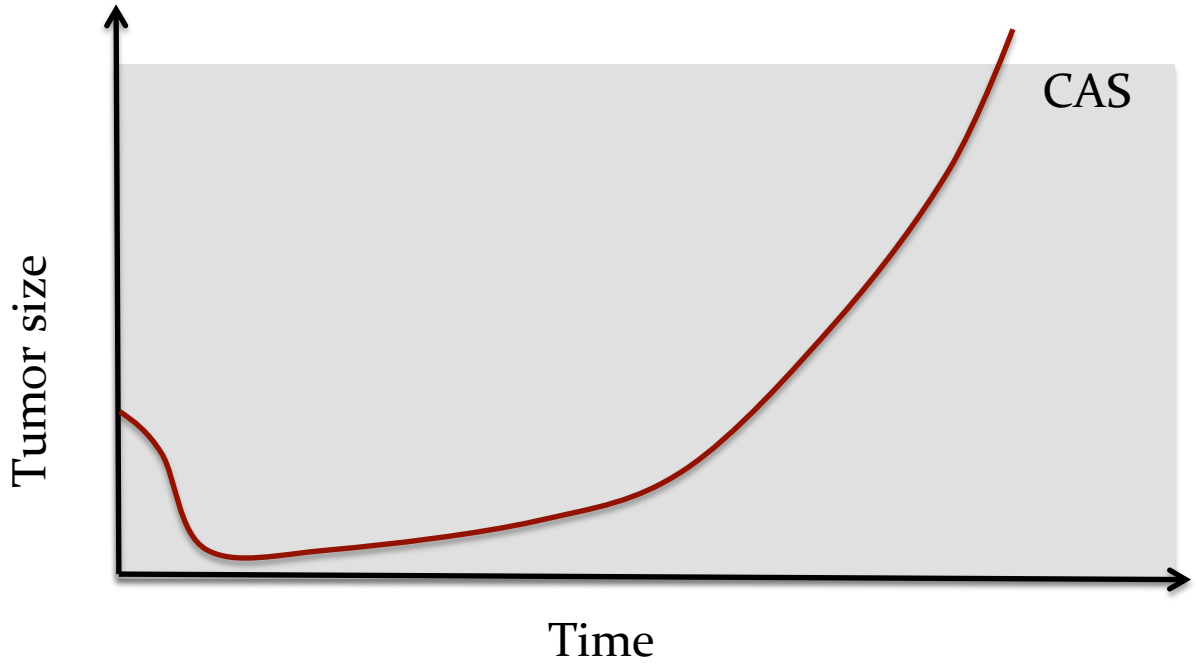
- Practical tools:
  - dReal and dReach
  - DPLL(T), interval arithmetic, constraint solving, reliable integration, etc.

Case Studies - I

- Prostate cancer
  - Second leading cause of cancer-related deaths among men in US
- Hormone therapy
  - Androgen deprivation
  - Continuous androgen suppression (CAS)
  - Intermittent androgen suppression (IAS)

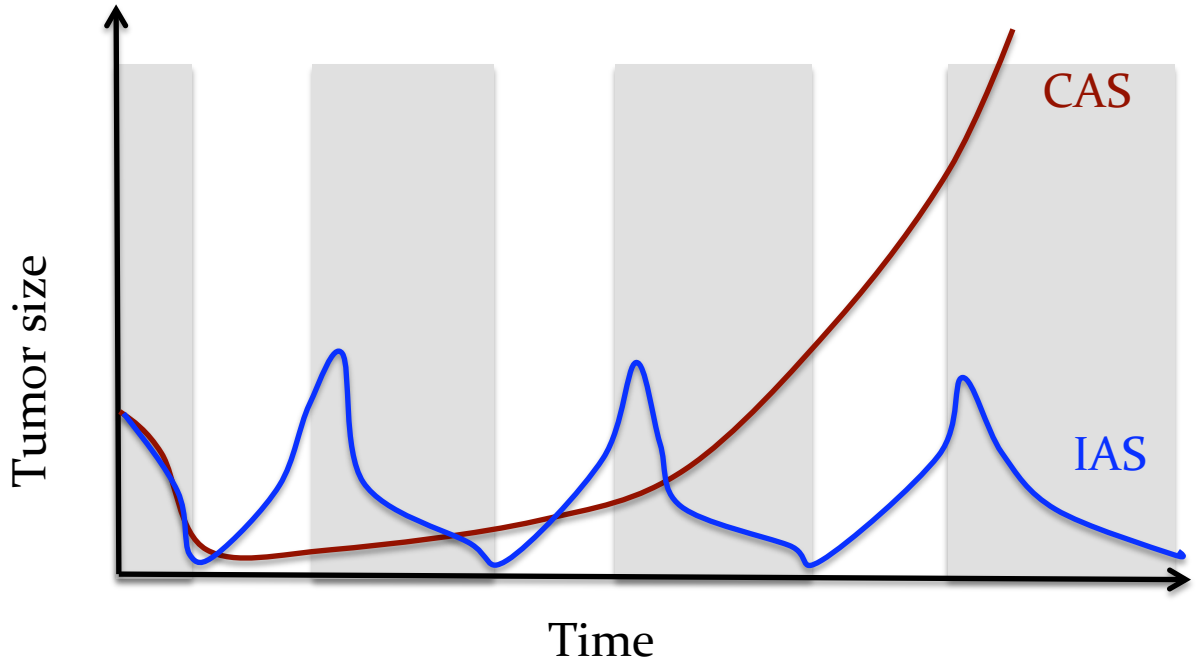
Continuous Androgen Suppression

- Side effects: anemia, osteoporosis, impotence, etc.
- Relapse after a median duration of 18-24 months, due to the proliferation of androgen independent (AI) cancer cells.



Intermittent Androgen Suppression

- Reduce side effects
- May delay the time to relapse
  - Avoid emergence of AI cells



Intermittent Androgen Suppression

- Clinical phase II and III trials confirm its advantage in terms of quality of life and cost
- For time to relapse and cancer-specific survival, its advantage depends on individual patients and the treatment scheme
- How to design a personalized treatment scheme for each individual patient?

Model

- Population of AD cells, AI cells, serum androgen concentration, PSA level (Ideta et al. 2008)

$\text{jump}_{2\to1}$:

$$x + y \geq r_1 \wedge \frac{dx}{dt} + \frac{dy}{dt} > 0$$

Mode 1 (on-treatment)

flow_1 :

$$\frac{dx}{dt} = \left(\alpha_x\left(k_1 + \frac{(1-k_1)z}{z+k_2}\right) - \beta_x\left(k_3 + \frac{(1-k_3)z}{z+k_4}\right) - m_1\left(1 - \frac{z}{z_0}\right)\right)x$$

$$\frac{dy}{dt} = m_1\left(1 - \frac{z}{z_0}\right)x + \left(\alpha_y\left(1 - d\frac{z}{z_0}\right) - \beta_y\right)y$$

$$\frac{dz}{dt} = \frac{-z}{\tau}$$

$$\frac{dv}{dt} = \left(\alpha_x\left(k_1 + \frac{(1-k_1)z}{z+k_2}\right) - \beta_x\left(k_3 + \frac{(1-k_3)z}{z+k_4}\right) - m_1\left(1 - \frac{z}{z_0}\right)\right)x + m_1\left(1 - \frac{z}{z_0}\right)x + \left(\alpha_y\left(1 - d\frac{z}{z_0}\right) - \beta_y\right)y$$

Mode 2 (off-treatment)

flow_2 :

$$\frac{dx}{dt} = \left(\alpha_x\left(k_1 + \frac{(1-k_1)z}{z+k_2}\right) - \beta_x\left(k_3 + \frac{(1-k_3)z}{z+k_4}\right) - m_1\left(1 - \frac{z}{z_0}\right)\right)x$$

$$\frac{dy}{dt} = m_1\left(1 - \frac{z}{z_0}\right)x + \left(\alpha_y\left(1 - d\frac{z}{z_0}\right) - \beta_y\right)y$$

$$\frac{dz}{dt} = \frac{z_0 - z}{\tau}$$

$$\frac{dv}{dt} = \left(\alpha_x\left(k_1 + \frac{(1-k_1)z}{z+k_2}\right) - \beta_x\left(k_3 + \frac{(1-k_3)z}{z+k_4}\right) - m_1\left(1 - \frac{z}{z_0}\right)\right)x + m_1\left(1 - \frac{z}{z_0}\right)x + \left(\alpha_y\left(1 - d\frac{z}{z_0}\right) - \beta_y\right)y$$

$\text{jump}_{1\to2}$:

$$x + y \leq r_0 \wedge \frac{dx}{dt} + \frac{dy}{dt} < 0$$

Model

- Proliferation, apoptosis, mutation rates
- Treatment thresholds: r_0 and r_1

$\text{jump}_{2\to 1}$:

$$x + y \geq r_1 \wedge \frac{dx}{dt} + \frac{dy}{dt} > 0$$

Mode 1 (on-treatment)

flow_1 :

$$\frac{dx}{dt} = \left(\alpha_x\left(k_1 + \frac{(1-k_1)z}{z+k_2}\right) - \beta_x\left(k_3 + \frac{(1-k_3)z}{z+k_4}\right) - m_1\left(1 - \frac{z}{z_0}\right)\right)x$$

$$\frac{dy}{dt} = m_1\left(1 - \frac{z}{z_0}\right)x + \left(\alpha_y\left(1 - d\frac{z}{z_0}\right) - \beta_y\right)y$$

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$$\frac{dx}{dt} = \left(\alpha_x\left(k_1 + \frac{(1-k_1)z}{z+k_2}\right) - \beta_x\left(k_3 + \frac{(1-k_3)z}{z+k_4}\right) - m_1\left(1 - \frac{z}{z_0}\right)\right)x$$

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$\text{jump}_{1\to 2}$:

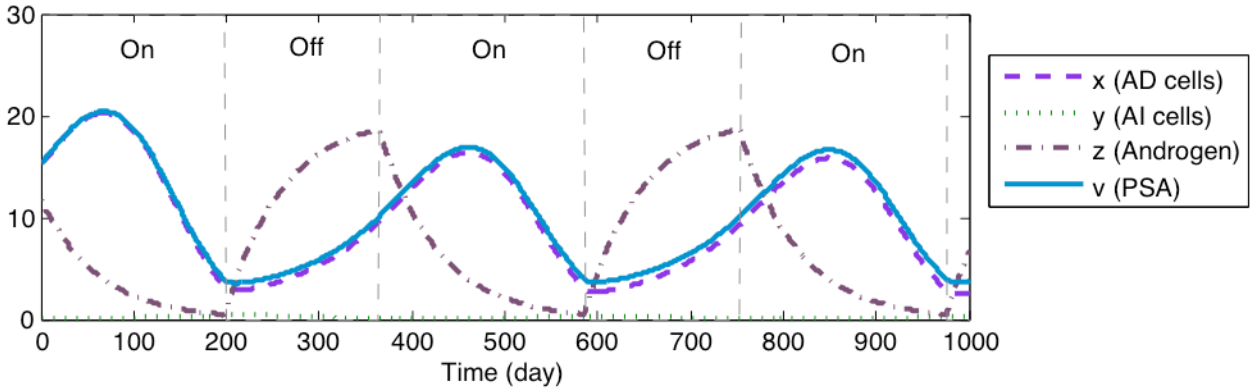
$$x + y \leq r_0 \wedge \frac{dx}{dt} + \frac{dy}{dt} < 0$$

Model Selection

- Hypothesis 1
  - AI cells grow at the constant rate independent of the androgen level
- Hypothesis 2
  - AI cells do not grow when the androgen level is normal
- Hypothesis 3
  - AI cells decrease when the androgen level is normal

Model Selection

- Observation
  - When r_0 = 4 (ng ml^{-1}) and r_1 = 10(ng ml^{-1}), cancer relapse can be avoided within 1000 days
  - Define cancer relapse: PSA level > 30 ng ml^{-1}
- Bounded model checking
  - Property: $900 \le tau \le 1000 \wedge v \le 30$
  - H1: unsat
  - H2: unsat
  - **H3: sat**



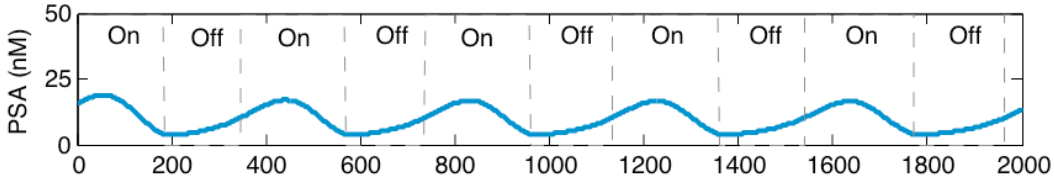
Personalized Therapy Design

- Personalized parameters
  - α_y - the proliferation rate of AI cells
  - β_y - the apoptosis rate of AI cells
  - m_1 – the mutation rate from AD to AI cells
  - $z(0)$ – the initial androgen level

Personalized Therapy Design

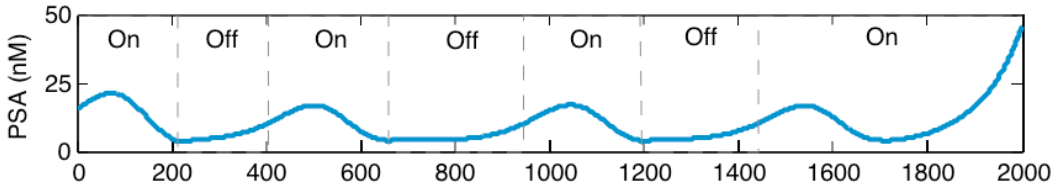
- Different patients may response differently to the same treatment scheme ($r_0 = 4$ and $r_1 = 10$)

Patient#1



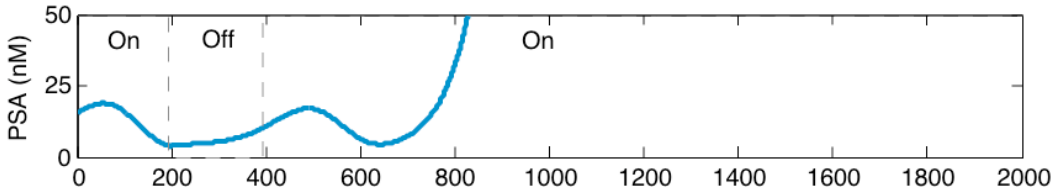
avoided ($r_0 = 4$ and $r_1 = 10$)

Patient#2



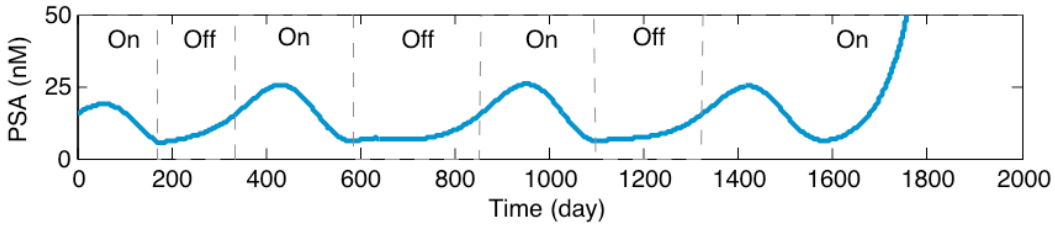
delayed ($r_0 = 4$ and $r_1 = 10$)

Patient#3



relapse ($r_0 = 4$ and $r_1 = 10$)

Patient#3



delayed ($r_0 = 5$ and $r_1 = 16$)

Personalized Therapy Design

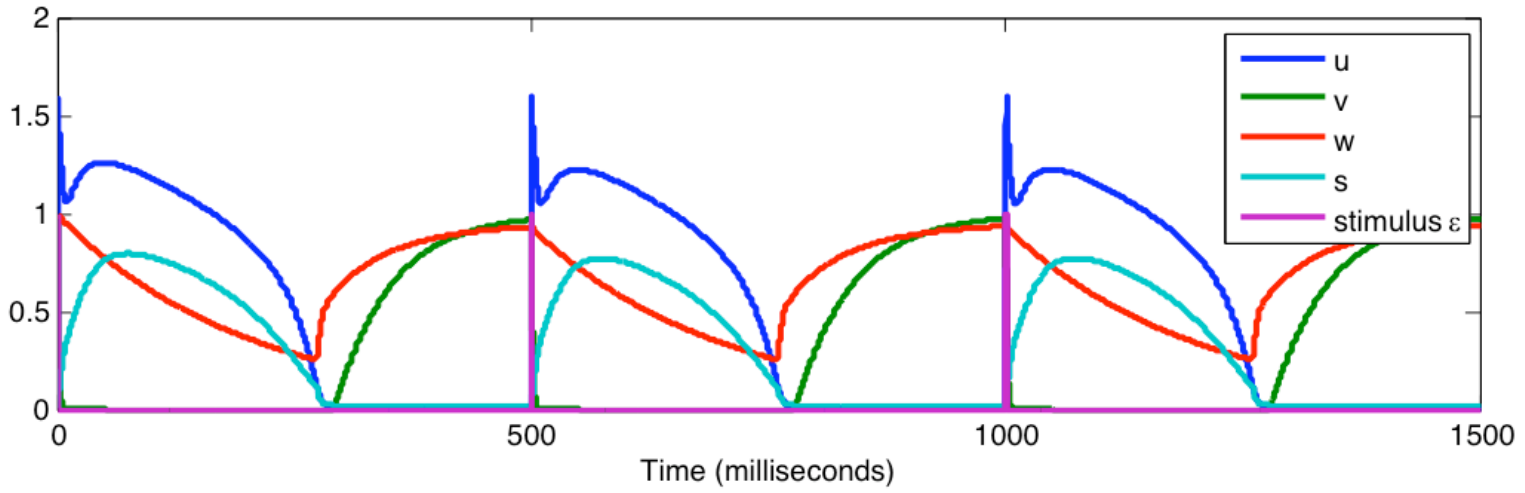
- Apply IAS therapy to a patient for 1-2 cycles and measure PSA time serials
- Estimate personalized parameters by fitting PSA data
- Given r_0 in [0,8) and r_1 in [8,15], verify if H3 can reach $900 \leq tau \leq 1000 \wedge V \leq 30$ (i.e. no relapse)
  - False: androgen suppression does not work
  - True: feasible values for r_0 *and* r_1 will be returned.

Personalized Therapy Design

- Patients dataset:
  - 109 patients
  - Phase II clinical trials (Bruchovsky et al, Cancer, 2007)
- Partial results:

Case Studies - II

- Cardiac cell
  - Minimal Resistor Model (Fenton et al, J Theor Biol, 2008)
  - The electrical activity are governed by opening and closing of ion channels



Mode 1

$$\text{flow}_1:$$

$$\frac{du}{dt} = \varepsilon - \frac{u}{\tau_{o1}}$$

$$\frac{dv}{dt} = \frac{1-v}{\tau_{v1}^{-}}$$

$$\frac{dw}{dt} = \frac{1 - \frac{u}{\tau_w^{\infty}} - w}{\tau_{w1}^{-} + \frac{\tau_{w2}^{-} - \tau_{w1}^{-}}{1 + e^{-2k_w^{-}(u-u_w^{-})}}}$$

$$\frac{ds}{dt} = \left(\frac{1}{1+e^{-2k_s(u-u_s)}} - s\right)\frac{1}{\tau_{s1}}$$

$u \geq \theta_o$

$u < \theta_o$

Mode 2

$$\text{flow}_2:$$

$$\frac{du}{dt} = \varepsilon - \frac{u}{\tau_{o2}}$$

$$\frac{dv}{dt} = -\frac{v}{\tau_{v2}^{-}}$$

$$\frac{dw}{dt} = \frac{w_{\infty}^{*} - w}{\tau_{w1}^{-} + \frac{\tau_{w2}^{-} - \tau_{w1}^{-}}{1 + e^{-2k_w^{-}(u-u_w^{-})}}}$$

$$\frac{ds}{dt} = \left(\frac{1}{1+e^{-2k_s(u-u_s)}} - s\right)\frac{1}{\tau_{s1}}$$

$u \geq \theta_w$

$u < \theta_w$

Mode 3

$$\text{flow}_3:$$

$$\frac{du}{dt} = \varepsilon - \frac{1}{\tau_{so1} + \frac{\tau_{so2} - \tau_{so1}}{1 + e^{-2k_{so}(u-u_{so})}}} + \frac{w \cdot s}{\tau_{si}}$$

$$\frac{dv}{dt} = -\frac{v}{\tau_{v2}^{-}}$$

$$\frac{dw}{dt} = -\frac{w}{\tau_w^{+}}$$

$$\frac{ds}{dt} = \left(\frac{1}{1+e^{-2k_s(u-u_s)}} - s\right)\frac{1}{\tau_{s1}}$$

$u \geq \theta_v$

$u < \theta_v$

Mode 4

$$\text{flow}_4:$$

$$\frac{du}{dt} = \varepsilon + \frac{v(u-\theta_v)(u_u - u)}{\tau_{fi}} - \frac{1}{\tau_{so1} + \frac{\tau_{so2} - \tau_{so1}}{1 + e^{-2k_{so}(u-u_{so})}}} + \frac{w \cdot s}{\tau_{si}}$$

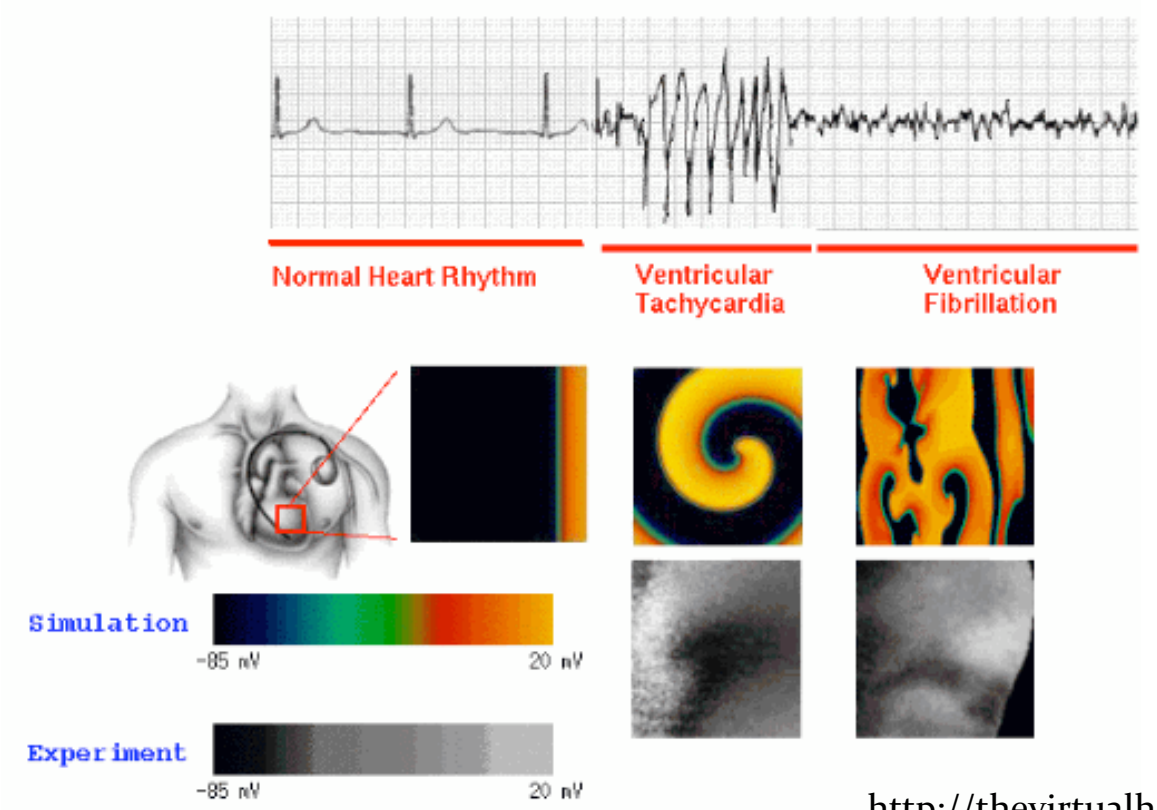
$$\frac{dv}{dt} = -\frac{v}{\tau_{v2}^{-}}$$

$$\frac{dw}{dt} = -\frac{w}{\tau_w^{+}}$$

$$\frac{ds}{dt} = \left(\frac{1}{1+e^{-2k_s(u-u_s)}} - s\right)\frac{1}{\tau_{s1}}$$

Cardiac Disorders

- When the cardiac cell loses its excitability, it will lead to disorders such as ventricular tachycardia and fibrillation

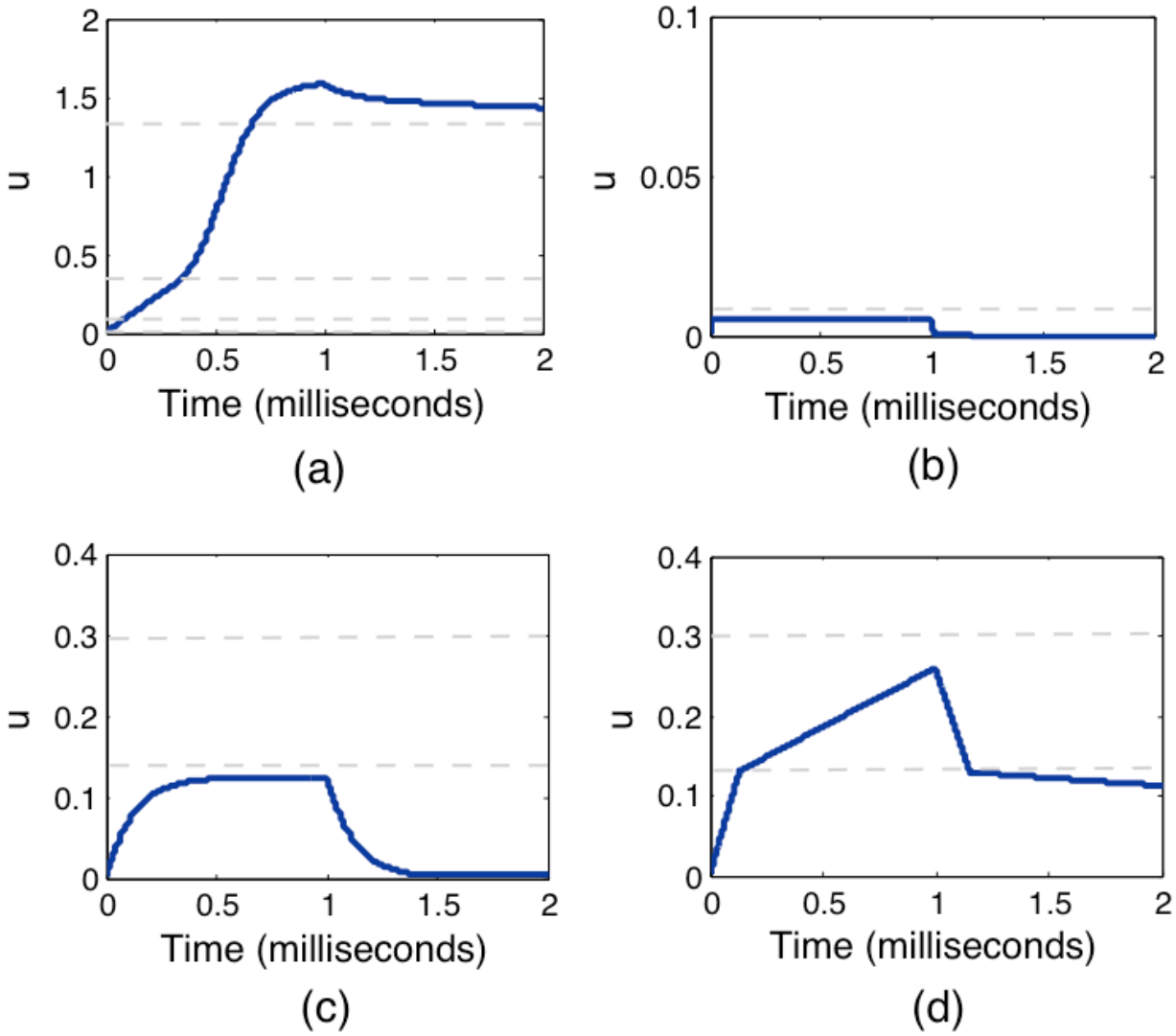


http://thevirtualheart.org/

Cardiac Disorders

- When the cardiac cell loses its excitability, it will lead to disorders such as ventricular tachycardia and fibrillation
- Under what circumstances, a cardiac cell will fail to generate a successful AP (i.e. globally $u < \theta_v$)?
  - Related parameter ranges identified by Grosu et al. CAV 2011 (**linear approximation**)
  - We answer this by identifying the ranges for parameters in the **original** nonlinear model

$$\tau_{o1} \in (0, 0.006) \vee \tau_{o2} \in (0, 0.13) \vee 6.2\tau_{o2} + \tau_{o1} \geq 9.9$$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Time (milliseconds)
(a)
(b)
(c)
(d)

Summary

- A delta-decision based framework for parameter identification
  - Model selection
  - Therapy optimization
  - Diseased-related conditions identification

- What's next
  - More analysis for cardiac cell model
  - Parameter estimation
  - DNA damage induced cellular senescence