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Towards Personalized Prostate Cancer Therapy Using δ-Reachability Analysis

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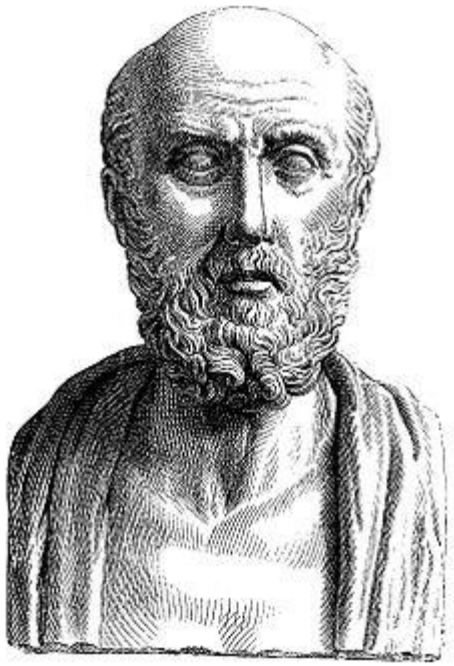
Personalized Medicine

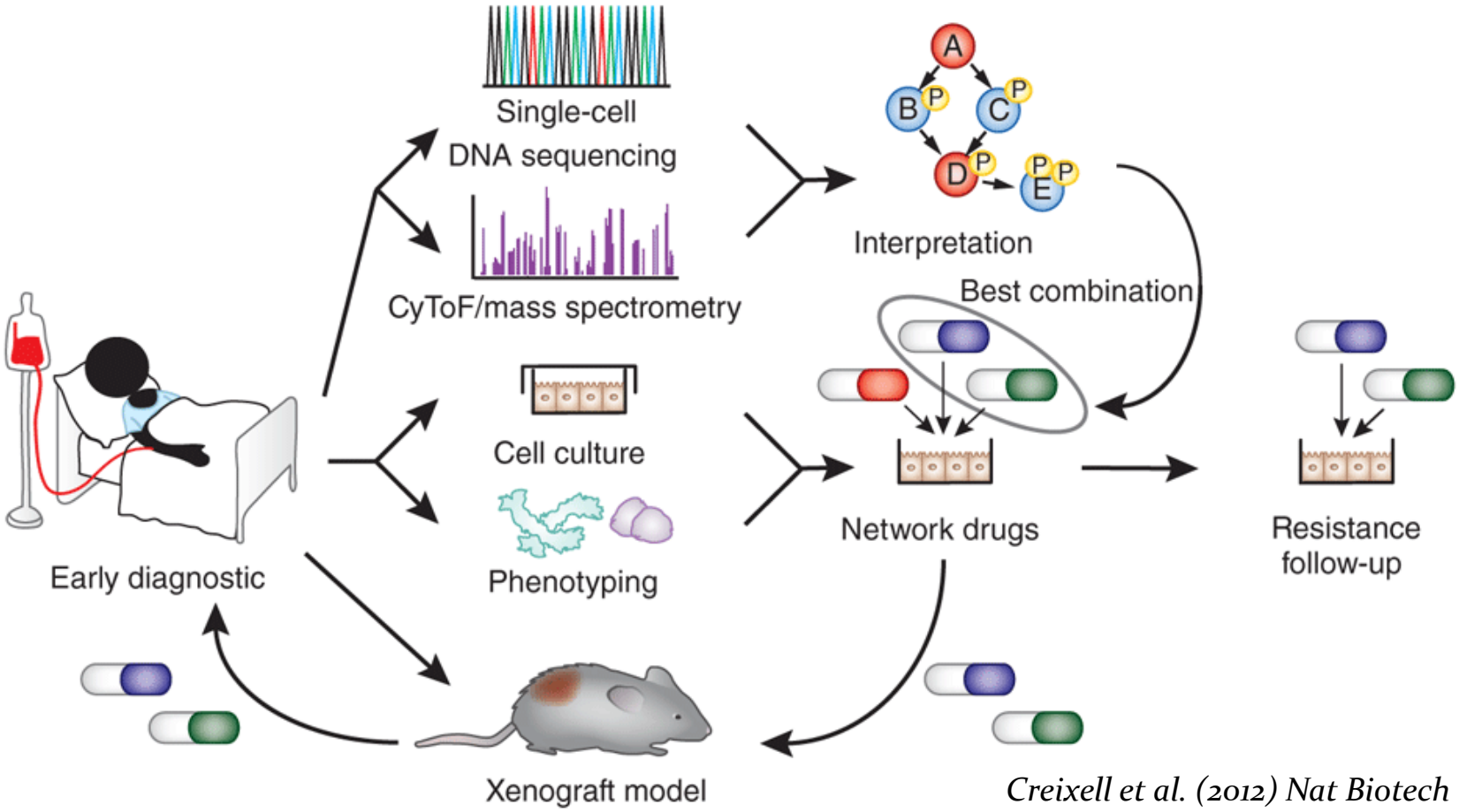
- Medical decisions, practices, and products being tailored to the individual patient

- Select optimal therapies based on the context of a patient's genetic content or other cellular analysis



Hippocrates 460BC-370BC

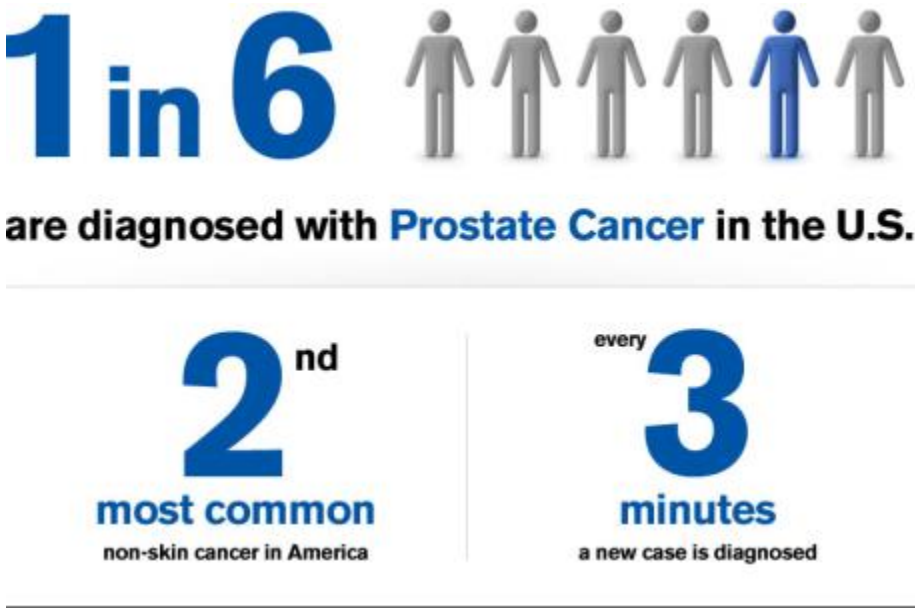
Personalized Cancer Therapy - Vision



Creixell et al. (2012) Nat Biotech

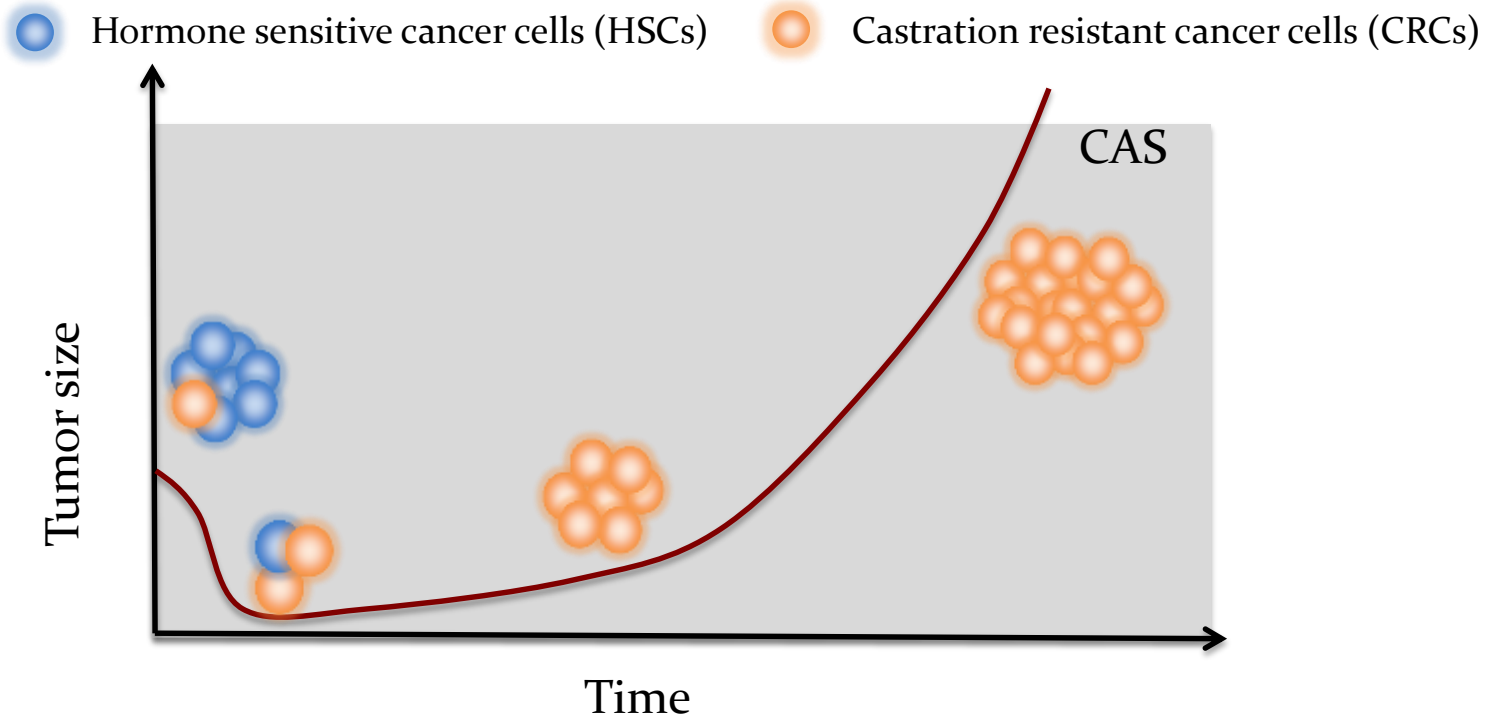
Prostate Cancer

- Second leading cause of cancer-related deaths among men in US
- Hormone therapy (androgen deprivation) has been a cornerstone of the management of advanced prostate cancer



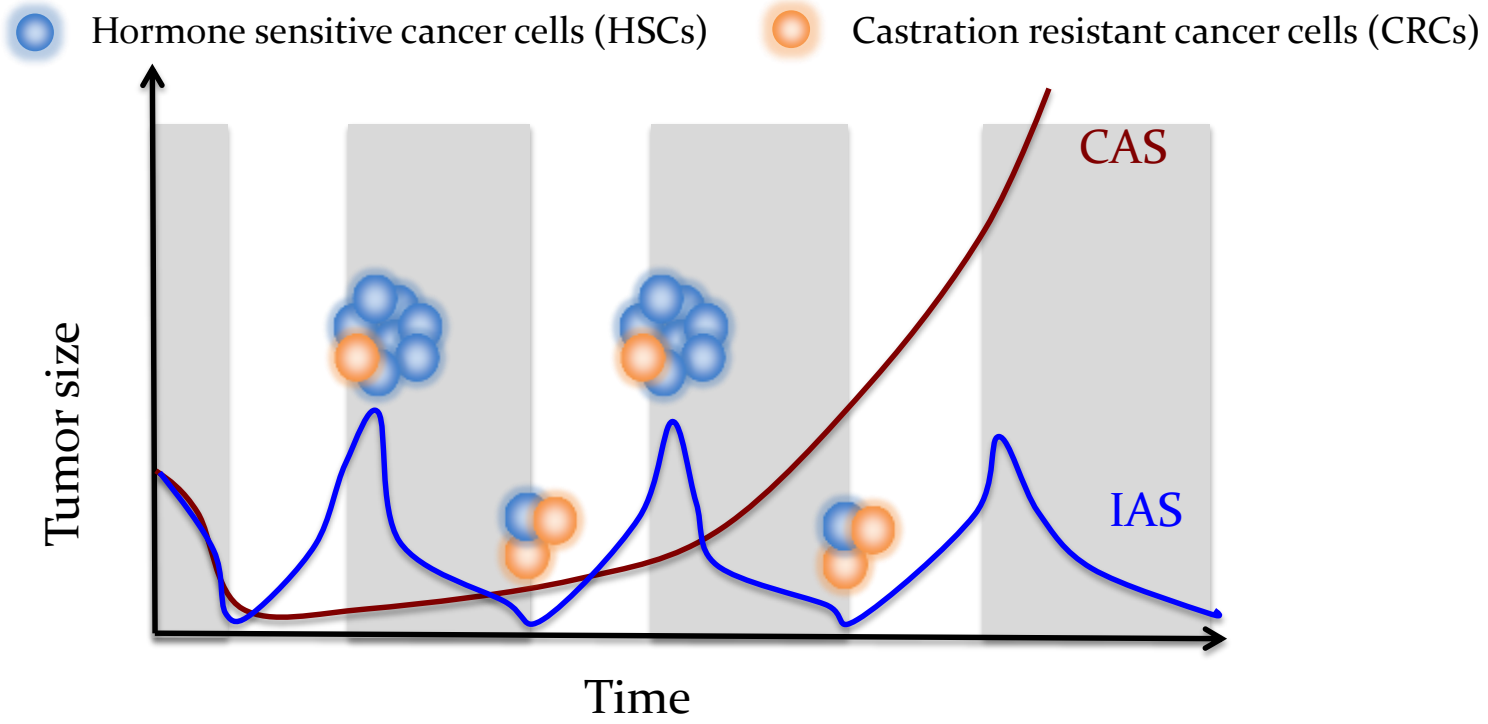
Continuous Androgen Suppression

- Many side effects: anemia, osteoporosis, impotence, etc.
- Relapse after a median duration of 18-24 months, due to the proliferation of castration resistant cancer cells (CRCs).



Intermittent Androgen Suppression

- Reduce side effects and financial cost
- May delay the time to relapse (avoid emergence of CRCs)



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?***

Modeling Cancer Progression

- Population of HSCs , CRCs, serum androgen concentration, prostate-specific antigen (PSA) level

Proliferation **Apoptosis** **Mutation**

HSC
$$\frac{dx}{dt} = \left(a_x \left(\frac{1}{1+e^{-(z-k_1)k_2}}\right) - b_x \left(\frac{1}{1+e^{-(z-k_3)k_4}}\right)\right)\left(1 - \frac{z}{z_0}\right) - l_x x + m_x$$

CRC
$$\frac{dy}{dt} = m_1\left(1 - \frac{z}{z_0}\right)x + \left(a_y\left(1 - \frac{z}{z_0}\right)\right)y - b_y y$$

Proliferation **Apoptosis**

Androgen
$$\frac{dz}{dt} = \frac{z_0 - z}{t} + m_z$$

PSA $v(t) = c_1 x(t) + c_2 y(t)$ **Biomarker**

A Hybrid Model for Hormone Therapy

- Monitoring PSA level:
  - 'PAUSE' and 'RESUME' thresholds: r_0 and r_1

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

$$x + y \le r_0 \wedge \frac{dx}{dt} + \frac{dy}{dt} < 0 \vee w \ge t_{\max}$$

Mode 1 (on-treatment)

flow_1 :

$$\frac{dx}{dt} = a_x \left(\frac{1}{1+e^{-(z-k_1)k_2}}\right) + b_x \left(\frac{1}{1+e^{-(z-k_3)k_4}}\right) + m_1\left(1 - \frac{z}{z_0}\right) - l_x x + m_x$$

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

$$\frac{dz}{dt} = \frac{-z}{t} + m_z$$

$$\frac{dv}{dt} = a_x \left(\frac{1}{1+e^{-(z-k_1)k_2}}\right) + b_x \left(\frac{1}{1+e^{-(z-k_3)k_4}}\right) + m_1\left(1 - \frac{z}{z_0}\right) - l_x x + m_x + m_1\left(1 - \frac{z}{z_0}\right) x + a_y\left(1 - d\frac{z}{z_0}\right) - b_y y$$

PAUSE

RESUME

Mode 2 (off-treatment)

flow_2 :

$$\frac{dx}{dt} = a_x \left(\frac{1}{1+e^{-(z-k_1)k_2}}\right) + b_x \left(\frac{1}{1+e^{-(z-k_3)k_4}}\right) + m_1\left(1 - \frac{z}{z_0}\right) - l_x x + m_x$$

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

$$\frac{dz}{dt} = \frac{z_0 - z}{t} + m_z$$

$$\frac{dv}{dt} = a_x \left(\frac{1}{1+e^{-(z-k_1)k_2}}\right) + b_x \left(\frac{1}{1+e^{-(z-k_3)k_4}}\right) + m_1\left(1 - \frac{z}{z_0}\right) - l_x x + m_x + m_1\left(1 - \frac{z}{z_0}\right) x + a_y\left(1 - d\frac{z}{z_0}\right) - b_y y$$

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

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

What we want to know?

- Is the model able to reproduce key observations?
- How to control the system to avoid bad states (cancer relapse)?
- … …

- Reachability/parameter synthesis problem
- Analyzing nonlinear hybrid automata is challenging
  - even simple reachability questions can be **undecidable**

δ-Reachability Analysis

- δ-complete decision: a decision procedure using numerical techniques (with an error bound δ) (Gao et al, LICS'12, IJCAR'12):
  - unsat – the formula is verifiably false
  - δ-sat – a δ-weakening version of the formula is true
  - Overcome undecidability issues by returning answers with one-side δ-bounded errors.
- A parameter synthesis framework (Liu et al. CMSB'14)
  - Encode the problem as a first-order formula over the reals
  - perform bounded model checking
  - Employ an interval constraint propagation (ICP) based algorithm to identify the resulting parameters
- dReal/dReach toolset (Gao, et al, CADE'13; Kong, et al, TACAS'15)

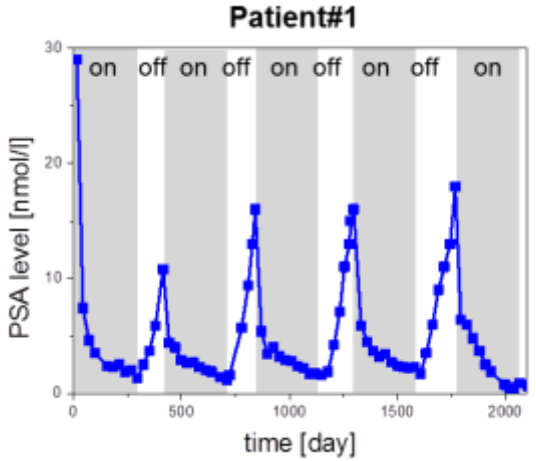
CRC Proliferation

- Hypothesis 1
  - d = 0, the grow of CRCs is independent of the androgen level
- Hypothesis 2
  - d = 1 - β_y/α_y, CRCs cease growing when the androgen level is normal
- Hypothesis 3
  - d= 1, CRCs decrease when the androgen level is normal

$$\frac{dy}{dt} = m_1 \left(1 - \frac{z}{z_0}\right)x + \underbrace{a_y \left(1 - d\frac{z}{z_0}\right)}_{\text{Proliferation}} - b_y y$$

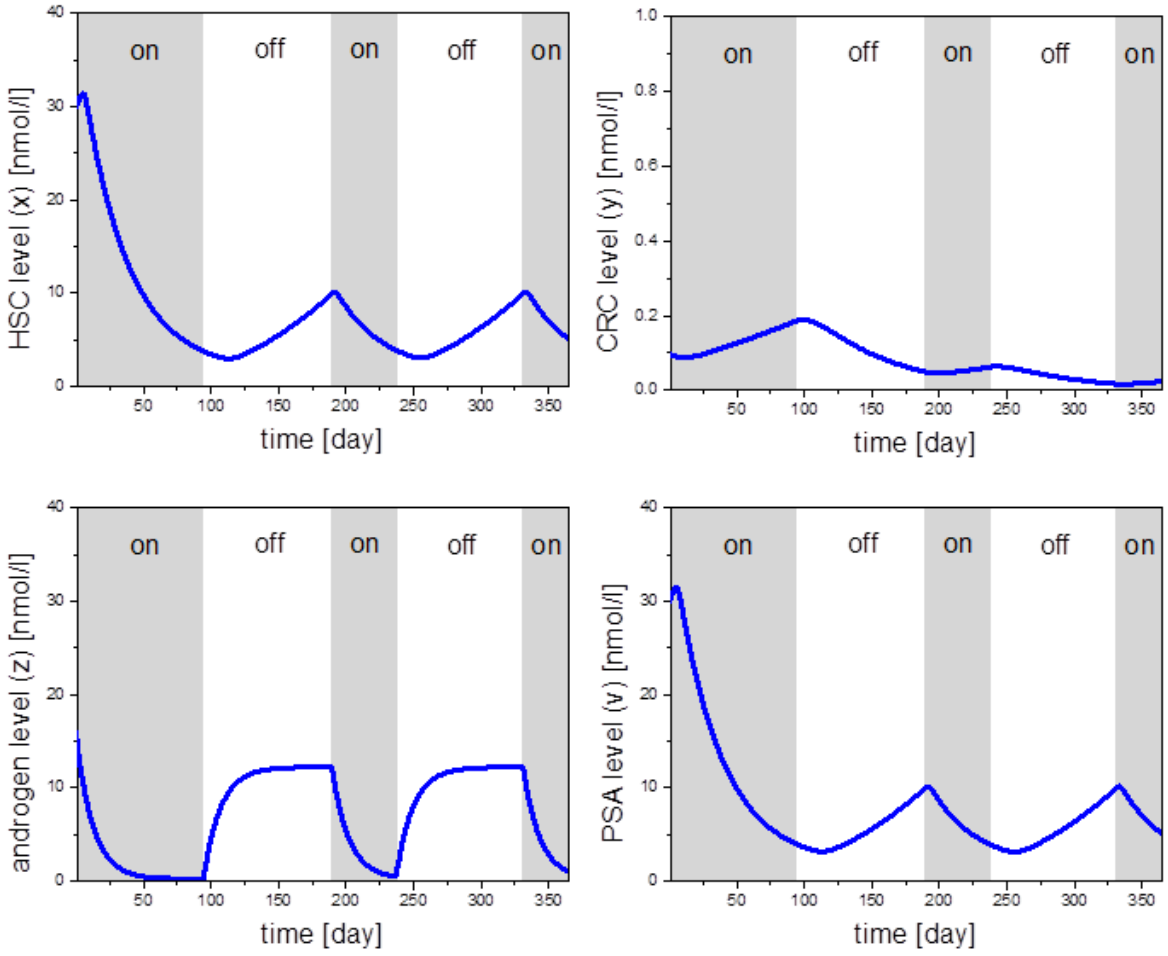
CRC Proliferation

- Observation: with proper treatment schedules, patient#1 can avoid cancer relapse for years.
- 'no cancer relapse' invariants:
  - $0 < \text{PSA level} < 30$ ng ml^{-1} $\wedge$ $0 < \text{CRC} < 1$
- Verify whether the invariants hold within a bounded time, given that $0 < r_0 < 8$ and $8 < r_1 < 15$ (ng ml^{-1})
- δ-reachability analysis results:
  - H1: unsat
  - H2: unsat
  - **H3: δ-sat**



Bruchovsky et al, Cancer, 2007

Witness Trajectories



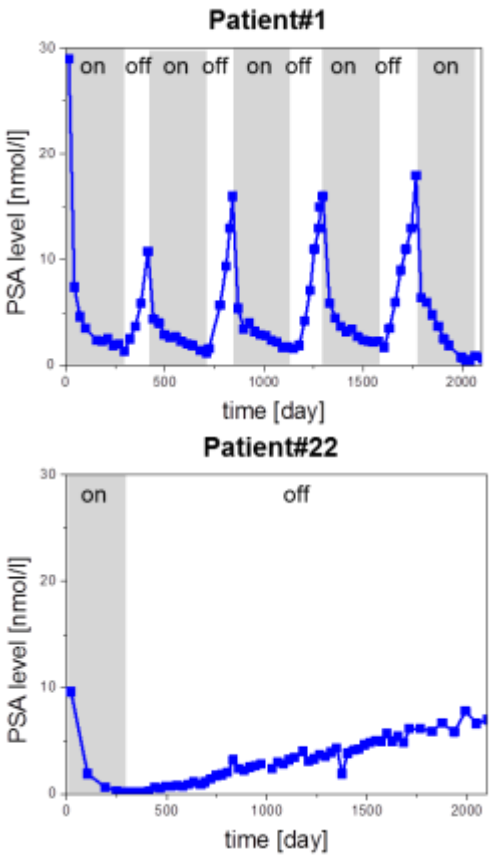
Our Model vs. Ideta's Model

- Observation: clinical data show that the half-time of PSA level under androgen suppression is less than 60 days
- Add an auxiliary mode 3, if $v(t) = v(0)/2$, the system will jump from mode 1 to mode 3
- Check the reachability of a goal state with $0 < w < 60$ days (where w is the time spend in mode 1)
  - unsat – Ideta's model
  - δ-sat – our model

Personalized Therapy Design

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

Parameter	Value	Remark
α_x	0.0204 d^{-1}	HSC proliferation
α_y	0.0242 d^{-1}	CRC proliferation
β_x	0.0201 d^{-1}	HSC apoptosis
β_y	0.0168 d^{-1}	CRC apoptosis
k_1	10.0 nM	HSC proliferation
k_2	1.0	HSC proliferation
k_3	10.0 nM	HSC apoptosis
k_4	2	HSC apoptosis
m_1	0.00005 d^{-1}	HSC to CRC conversion
z_0	12.0 nM	normal androgen level
τ	12.5 d	androgen degradation
λ_x	0.01 d^{-1}	HSC basal degradation
μ_x	0.05 d^{-1}	HSC basal production
μ_z	0.02 d^{-1}	Androgen basal production



Bruchovsky et al, Cancer, 2007

Personalized Therapy Design

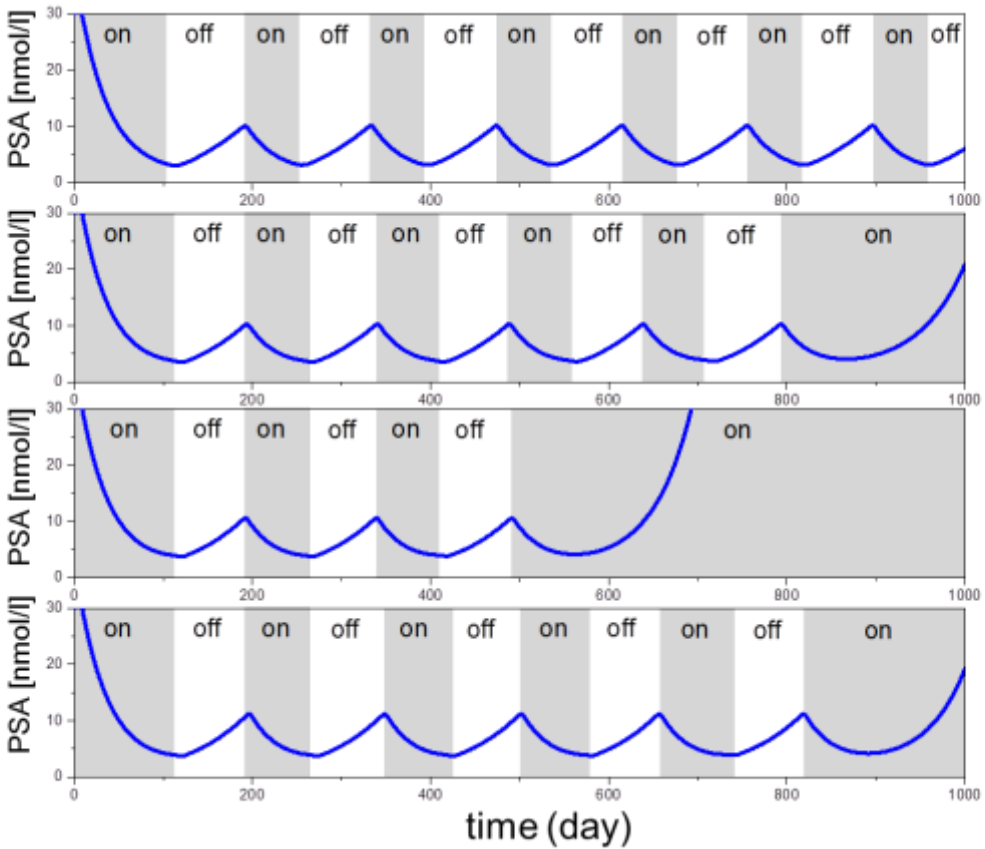
- Different patients may response differently to the same treatment scheme ($r_0 = 4$ and $r_1 = 10$)

Patient#A

Patient#B

Patient#C

Patient#C



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

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

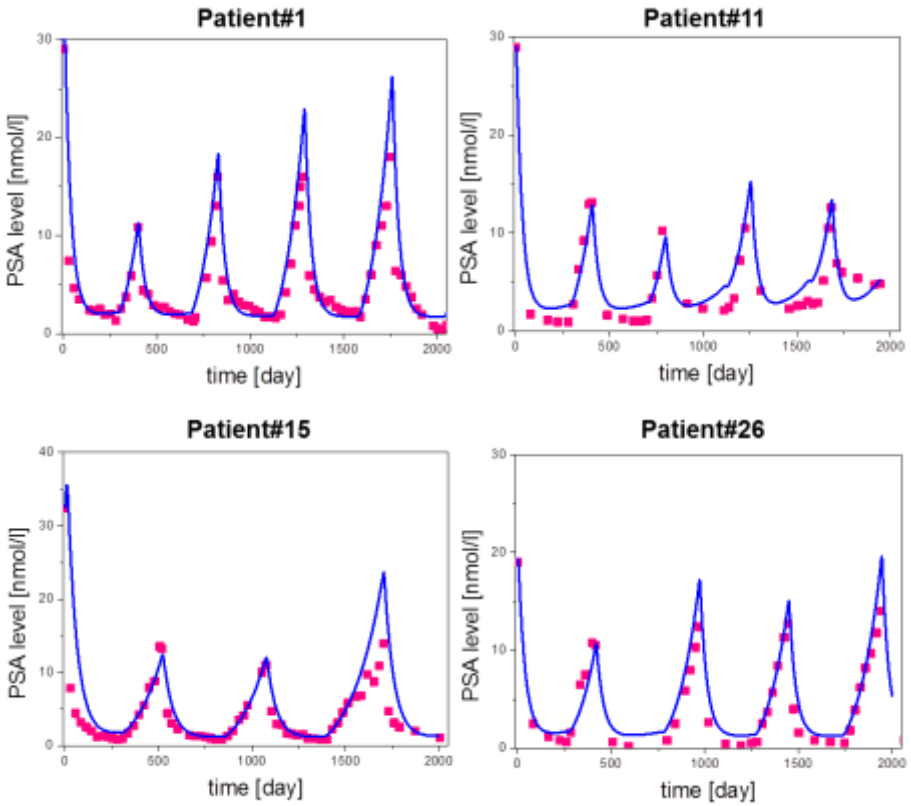
relapse ($r_0 = 4$ and $r_1 = 10$)

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 his personalized parameters by collectively fitting his PSA data.
- Given r_0 in [0,8) and r_1 in [8,15], verify if H3 can reach the goal state without violating the 'no cancer replase' invariants with in a bounded time
  - unsat: androgen suppression does not work
  - δ-sat: a feasible treatment scheme will also be returned

Results



Patient	Suggested scheme
1	$r_0 = 5.2$ and $r_1 = 10.8$
11	N/A
15	$r_0 = 1.9$ and $r_1 = 8.0$
26	$r_0 = 4.6$ and $r_1 = 10.7$

Summary

- A hybrid model of prostate cancer progression
- δ-Reachability analysis helps model construction and personalized therapy design.

What's Next

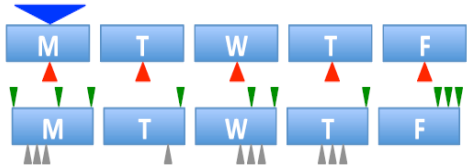
- Experimental validation?
  - Clinical trails may takes years
  - Mice (or xenograft) model is feasible
- Adaptive approach?
- Drug combination?
- Stochasticity?
- Other diseases?

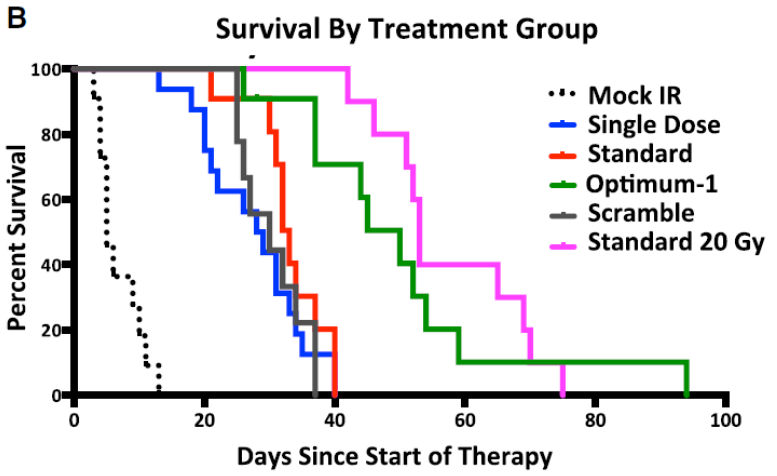
Theory

Cell

Mathematical Modeling of PDGF-Driven Glioblastoma Reveals Optimized Radiation Dosing Schedules

Leder et al, Cell, 2014

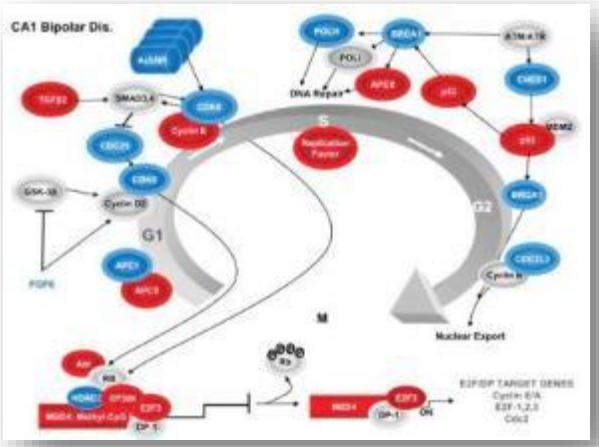


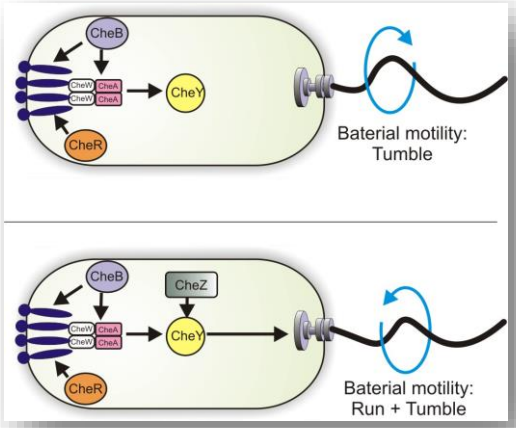


Acknowledgements

Ed Clarke

Questions?


CA1 Bipolar Dis.
DNA Repair
S
G1
G2
M
Nuclear Export


CheB
CheW
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CheR
Baterial motility:
Tumble
CheB
CheZ
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CheA
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CheR
Baterial motility:
Run + Tumble