Mathematics Behind Induced Drug Resistance in Cancer Chemotherapy

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Kolchin Seminar in Differential Algebra

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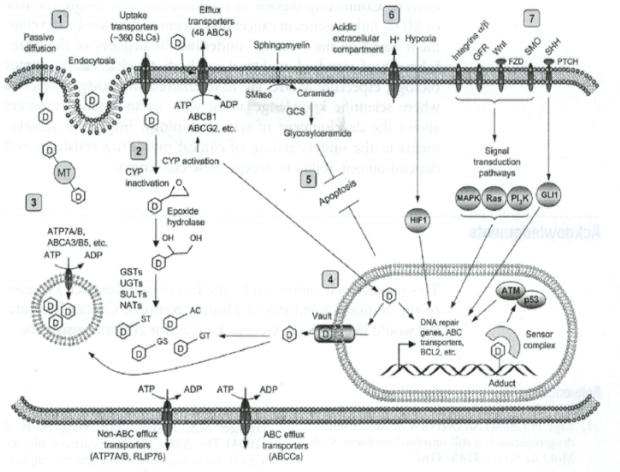
Joint work with Eduardo Sontag (NEU), Jana Gevertz (TCNJ), and Cynthia Sanchez-Tapia (RU)

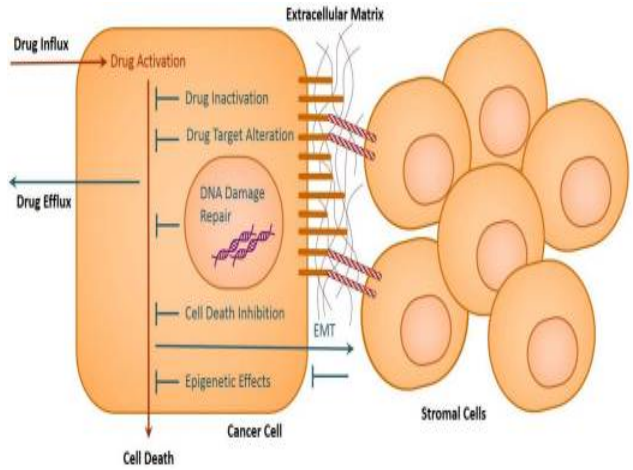
Outline

1. Drug Resistance: Mechanisms and Origins
2. Mathematical Model
3. Effect of Phenotype Switching on Therapy Outcome
4. Identifiability
   - Structural Identifiability
   - *In vitro* Identifiability
5. Optimal Control
   - Formulation
   - Technical Details
   - Basic Properties
   - Geometric Properties and Singular Arcs
   - Non-Induced Optimal Control Structure
   - Induced Optimal Control Structure
6. Conclusions and Future Work

Resistance Origins

Drug resistance is a complicated phenomena, with many **nonlinear** interacting factors





- Simplistic model to study basic properties at a very high-level

Indeed, won't even consider a specific resistance mechanism

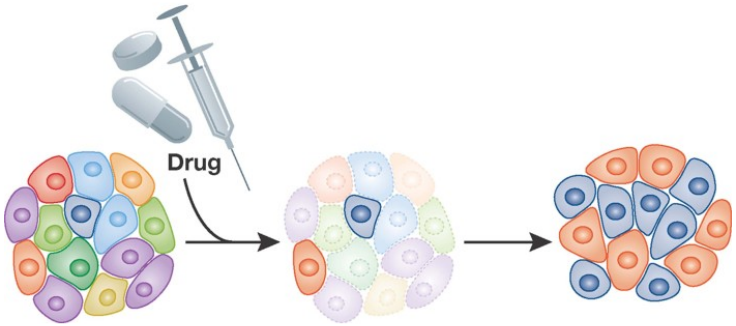
- Concerned instead with the **origin** of drug resistance
- Spontaneous (drug independent) vs. drug-induced (drug dependent)
- General competitive effects between sensitive and resistant phenotypes

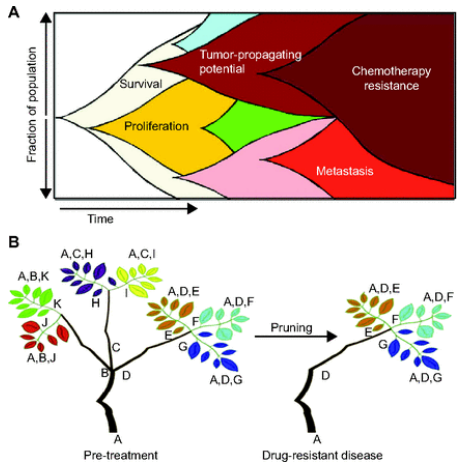
Gillet and Gottesman. Mechanisms of multidrug resistance in cancer, *Methods Mol. Biol.*, **596**: 47-76, 2010
Housman *et al.* Drug resistance in cancer, and overview, *Cancers (Basel)*, **6**(3): 1769-1792, 2014

Paradigms of Origins of Resistance

Classical: Mechanisms conferring resistance may arise via **stochastic genetic alterations** (point mutations, gene amplification, chromosomal translocations)

- Rare events
- Resistant cells are then *selected* during chemotherapy via standard Darwinian evolution





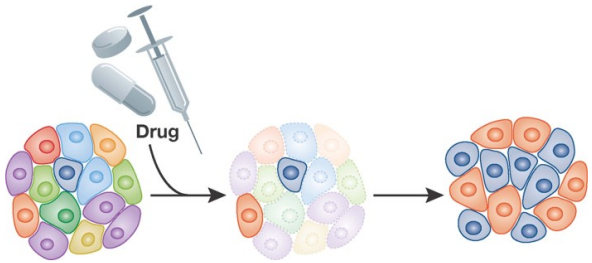
Saunders *et al.* Role of intratumoral heterogeneity in cancer drug resistance: molecular and clinical perspectives, *E.M.B.O. Mol. Med.*, **4**(8): 675-684, 2012

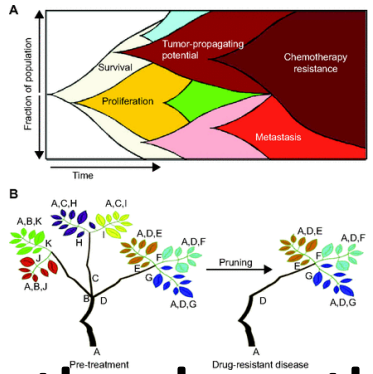
Marusyk and Polyak. Tumor heterogeneity: Causes and consequences, *Biochim Biophys Acta.*, **1805**(1): 105-117, 2010

Paradigms (continued)

More recent: Non-genetic cell-state dynamics via spontaneous switching within a clonal population (*phenotype plasticity*)

- Not necessarily rare
- Often reversible
- Importantly: *still operates via Darwinian selection*





Most recent: Phenotype plasticity **induced by the chemotherapeutic agent**

Saunders *et al.* Role of intratumoral heterogeneity in cancer drug resistance: molecular and clinical perspectives, *E.M.B.O. Mol. Med.*, **4**(8): 675-684, 2012

Marusyk and Polyak. Tumor heterogeneity: Causes and consequences, *Biochim Biophys Acta.*, **1805**(1): 105-117, 2010

Drug-induced resistance

Cytotoxic cancer chemotherapies may cause genomic mutations

- Nitrogen mustards: induce base substitutions and chromosomal rearrangements
- Topoisomerase II inhibitors: induce chromosomal translocations
- Antimetabolites: induce double stranded breaks and chromosomal aberrations

Furthermore, resistance may be induced at the epigenetic level via DNA methylation and histone modification

- Recent studies have revealed that *phenotypic state transitions* could be a consequence of external cues, including radiation and chemotherapy
- Usually rapid
- Dose dependence
- Reversible (although we don't study this yet)

Experimental Evidence of Drug-Induced Phenotype Switching and Drug Resistance

Cell

A Chromatin-Mediated Reversible Drug-Tolerant State in Cancer Cell Subpopulations

Sreenath V. Sharma,[1] Diana Y. Lee,[1] Bihua Li,[1] Margaret P. Quinlan,[1] Fumiyuki Takahashi,[1] Shyamala Maheswaran,[1] Ultan McDermott,[1] Nancy Azizian,[1] Lee Zou,[1] Michael A. Fischbach,[1] Kwok-Kin Wong,[2] Kathleyn Brandstetter,[2] Ben Wittner,[1] Sridhar Ramaswamy,[1] Marie Classon,[1,3,*] and Jeff Settleman[1,3,*]
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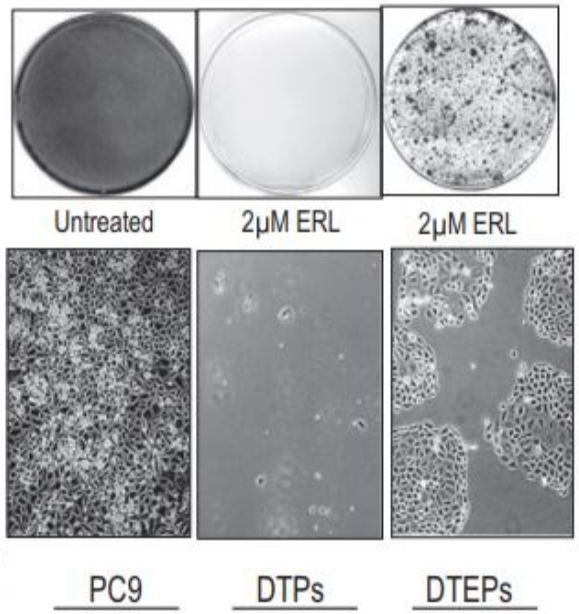
[3]These authors contributed equally to this work
*Correspondence: classon@helix.mgh.harvard.edu (M.C.), settleman@helix.mgh.harvard.edu (J.S.)
DOI 10.1016/j.cell.2010.02.027



NSCLC cell line (PC9) treated with erlotinib (2010)

- Persisters (DTPs) and DTEPs arise
- Reversal to drug sensitivity upon drug removal (days)

Experimental Evidence of Drug-Induced Phenotype Switching and Drug Resistance

nature COMMUNICATIONS

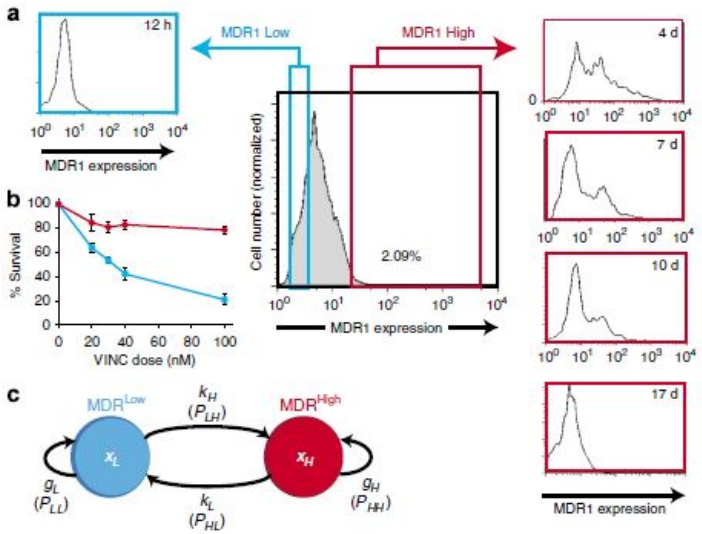
ARTICLE

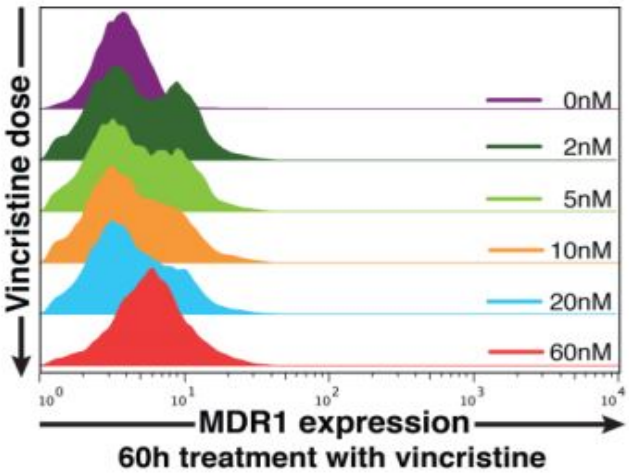
Received 28 Apr 2013 | Accepted 20 Aug 2013 | Published 18 Sep 2013

DOI: 10.1038/ncomms3467

Non-Darwinian dynamics in therapy-induced cancer drug resistance

Angela Oliveira Pisco[1,2,*], Amy Brock[3,*,†], Joseph Zhou[1,4], Andreas Moor[5], Mitra Mojtahedi[1,4],





Leukemic cells (HL60) treated with the chemotherapeutic agent vincristine (2013)

- 1-2 days of treatment: induction dominated expression of MDR1
- **NOT** by selection of MDR1-expressing cells
- Validated induction on **individual cells**

Experimental Evidence of Drug-Induced Phenotype Switching and Drug Resistance

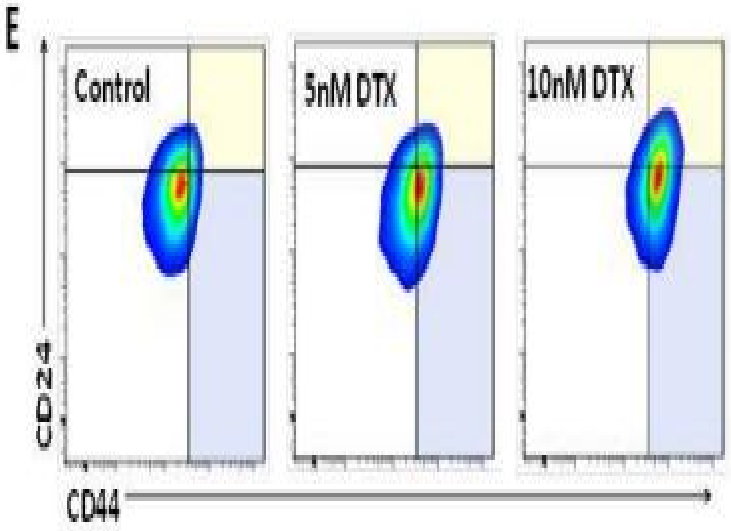
nature COMMUNICATIONS

ARTICLE

Received 18 Jul 2014 | Accepted 17 Dec 2014 | Published 11 Feb 2015 DOI: 10.1038/ncomms7139 OPEN

Temporally sequenced anticancer drugs overcome adaptive resistance by targeting a vulnerable chemotherapy-induced phenotypic transition

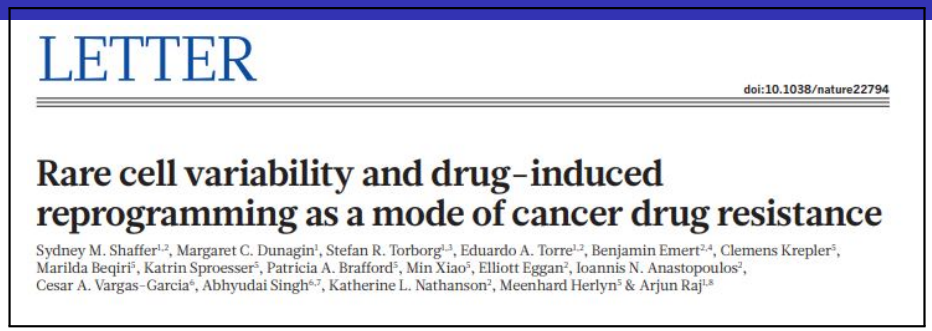
Aaron Goldman[1,2,3], Biswanath Majumder[4,5], Andrew Dhawan[6], Sudharshan Ravi[3], David Goldman[7], Mohammad Kohandel[8], Pradip K. Majumder[4,5] & Shiladitya Sengupta[1,2,3,9]



Explants derived from tumor biopsies (breast cancer) treated with taxanes (docetaxel)

- Transition towards a $CD44^{Hi}CD24^{Hi}$ expression status in dose-dependent manner
- Alleviated by immediate treatment with SFK inhibitors (dasatinib)

Experimental Evidence of Drug-Induced Phenotype Switching and Drug Resistance

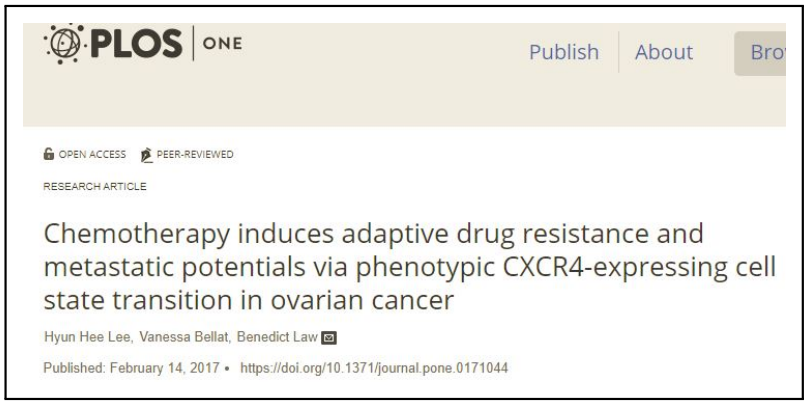


LETTER

doi:10.1038/nature22794

Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance

Sydney M. Shaffer[1,2], Margaret C. Dunagin[1], Stefan R. Torborg[1,3], Eduardo A. Torre[1,2], Benjamin Emert[2,4], Clemens Krepler[5], Marilda Beqiri[5], Katrin Sproesser[5], Patricia A. Brafford[5], Min Xiao[5], Elliott Eggan[2], Ioannis N. Anastopoulos[2], Cesar A. Vargas-Garcia[6], Abhyudai Singh[6,7], Katherine L. Nathanson[2], Meenhard Herlyn[5] & Arjun Raj[1,8]



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RESEARCH ARTICLE

Chemotherapy induces adaptive drug resistance and metastatic potentials via phenotypic CXCR4-expressing cell state transition in ovarian cancer

Hyun Hee Lee, Vanessa Bellat, Benedict Law

Published: February 14, 2017 • https://doi.org/10.1371/journal.pone.0171044

Letter

Therapy-induced tumour secretomes promote resistance and tumour progression

Anna C. Obenauf, Yilong Zou, Andrew L. Ji, Sakari Vanharanta, Weiping Shu, Hubing Shi, Xiangju Kong, Marcus C. Bosenberg, Thomas Wiesner, Neal Rosen, Roger S. Lo & Joan Massagué

Nature **520**, 368–372 (16 April 2015)
doi:10.1038/nature14336

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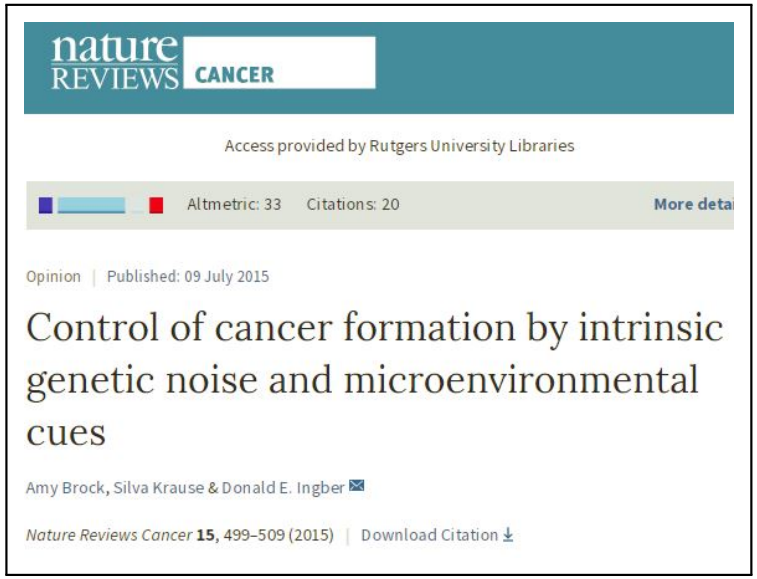
Accepted: 12 February 2015



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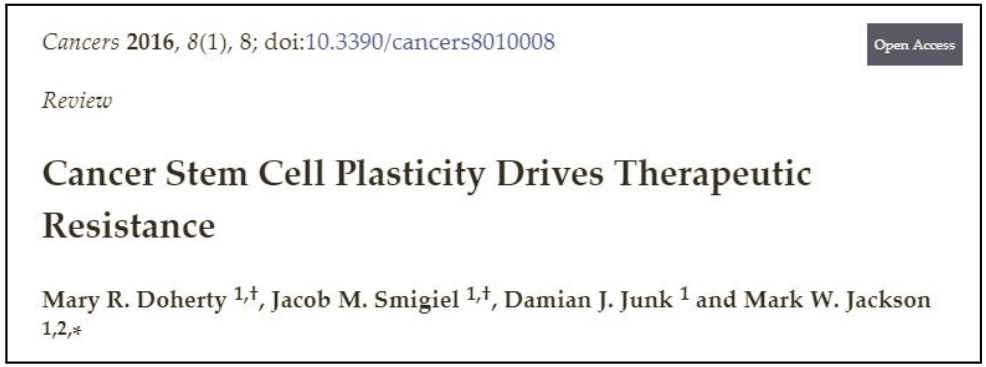
Opinion | Published: 09 July 2015

Control of cancer formation by intrinsic genetic noise and microenvironmental cues

Amy Brock, Silva Krause & Donald E. Ingber

Nature Reviews Cancer **15**, 499–509 (2015) | Download Citation



Cancers **2016**, *8*(1), 8; doi:10.3390/cancers8010008

Open Access

Review

Cancer Stem Cell Plasticity Drives Therapeutic Resistance

Mary R. Doherty [1,†], Jacob M. Smigiel [1,†], Damian J. Junk [1] and Mark W. Jackson [1,2,*]

Differentiating Selection vs. Induction

Although there is experimental evidence to suggest induction plays a role in drug resistance, it is still difficult to experimentally differentiate *selection* vs. *induction*

- *in vitro*: hard
- *in vivo*: impossible?

Mathematical modeling can assist by precisely defining and characterizing the separate phenomena

- Discover *qualitative* differences between origins of resistance
- Possibly even suggest experiments to determine rate
- Clinically: suggest treatment protocols based on discovered rate

Mathematical Model

Assume both spontaneous and induced resistance are generated

$$\frac{dS}{dt} = r\left(1 - \frac{V}{K}\right)S - \left(\epsilon + \boxed{\alpha u(t)}\right)S - du(t)S + \gamma R,$$

$$\frac{dR}{dt} = r_R\left(1 - \frac{V}{K}\right)R + \left(\epsilon + \boxed{\alpha u(t)}\right)S - d_R u(t)R - \gamma R.$$

where

$$S = \text{Sensitive (wild-type) cells}$$

$$R = \text{Resistant cells}$$

$$V = S + R$$

Basic assumptions underlying model:

- $u(t) =$ treatment (control) - bounded, measurable
- Random phenotype switching (ϵS and γR)
- Rate of induction is proportional to dosage ($\alpha u(t)S$)
- Competitive inhibition equal among all compartments

$$d_R < d.$$

(Reduced) Model

Interested in role of **induced** phenotypic alterations in treatment dynamics compared to classical drug-independent (genetic or phenotypic) changes

- Role of $\alpha u(t)S$ term in dynamics and control
- Dynamics (e.g. control structures) change as a function of α

Consider a simplified (and rescaled) system

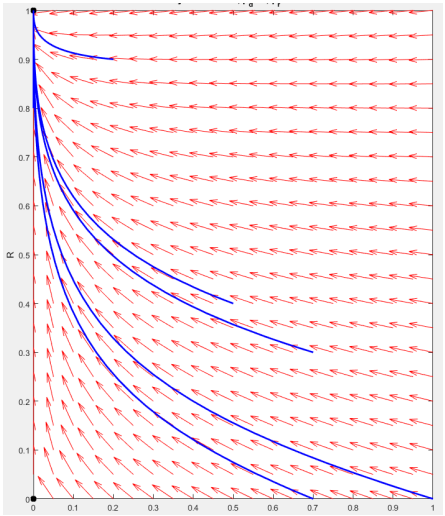
$$\frac{dS}{dt} = (1 - (S + R))\, S - (\epsilon + \boxed{\alpha u(t)})S - du(t)S,$$
$$\frac{dR}{dt} = p_r\,(1 - (S + R))\, R + (\epsilon + \boxed{\alpha u(t)})S.$$

- No back "mutations" ($\gamma = 0$)
- Complete resistance ($d_R = 0$)

Note: interesting only when $p_r < 1$.

Asymptotic Dynamics

$$\frac{dS}{dt} = (1 - (S + R))\, S - (\epsilon + \alpha u(t))S - du(t)S,$$
$$\frac{dR}{dt} = p_r\,(1 - (S + R))\, R + (\epsilon + \alpha u(t))S.$$



For all feasible controls, the long-time dynamics are invariant:

Theorem

For any bounded measurable control $u : [0, \infty) \to [0, M]$, *with* $M < \infty$, *and initial conditions* $(S_0, R_0) \in \Omega$, *solutions of the above system will approach the steady state* $(S, R) = (0, 1)$*:*

$$(S(t), R(t)) \xrightarrow{t \to \infty} (0, 1).$$

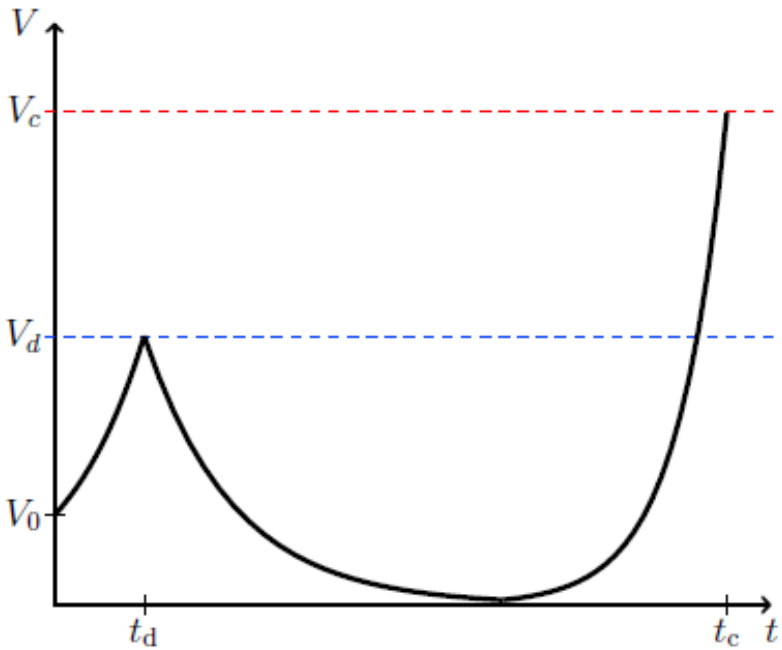
Treatment Evaluation

Even though asymptotically, all trajectories approach $(S, R) = (0, 1)$, transient dynamics may be very different for different controls

- Utilize competition to prolong patient life
- Control is still possible
- Note: therapy has contradictory effects

Metric to rank therapies: t_c defined by $V(t_c) := S(t_c) + R(t_c) = V_c$

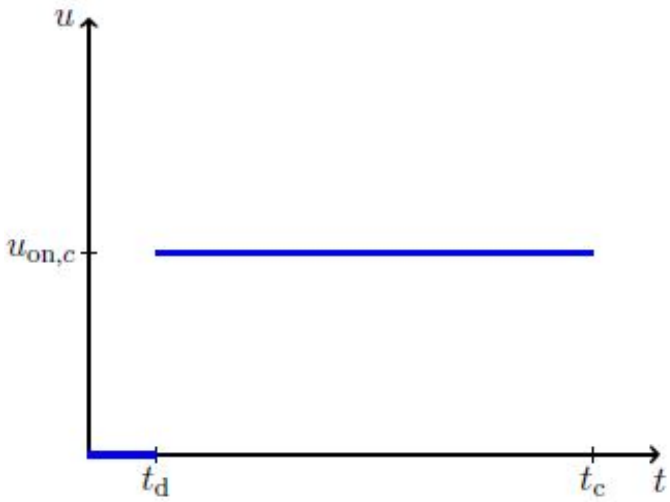
$$\frac{dS}{dt} = (1 - (S + R))\, S - (\epsilon + \alpha u(t))S - du(t)S,$$
$$\frac{dR}{dt} = p_r\,(1 - (S + R))\, R + (\epsilon + \alpha u(t))S.$$

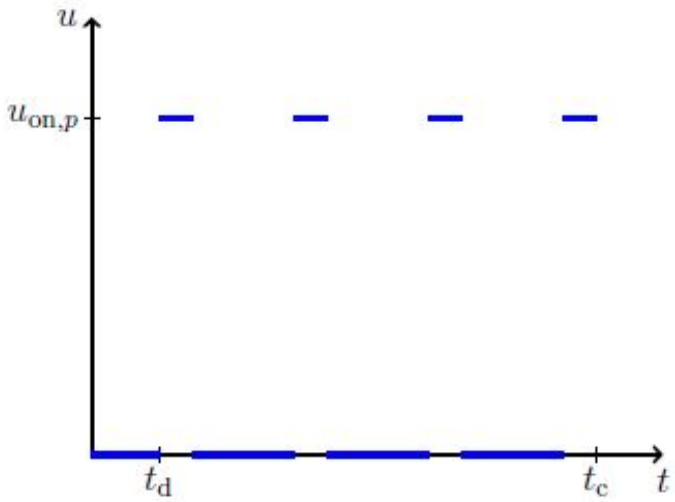


Effect of Phenotype Switching on Therapy Outcome

Fundamental question: does induction (α) have an impact on efficacy?

Compare outcomes of two standard treatment protocols:





for the two different scenarios:

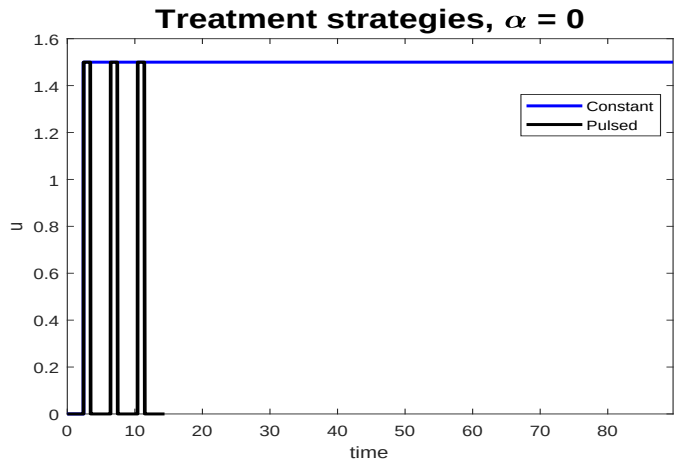
$$\alpha_s = 0, \qquad \alpha_i = 10^{-2}.$$

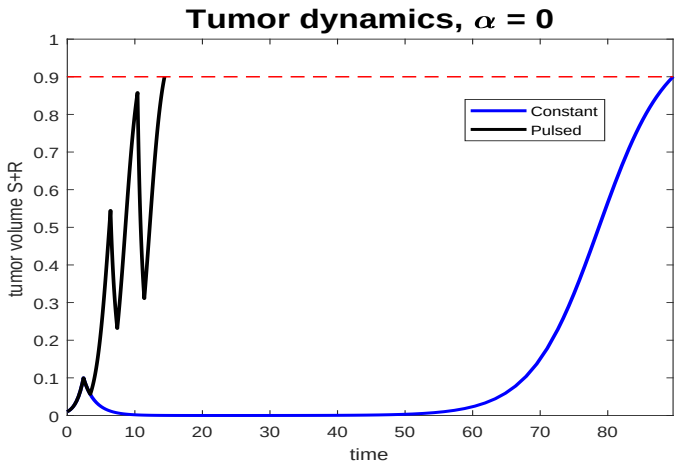
Fundamental question restated: Is there a difference on which is optimal, based solely on α?

Constant vs. Pulsed Comparison

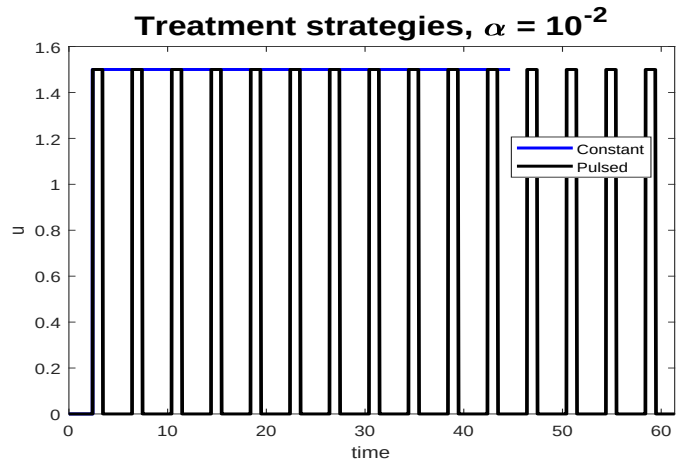
Answer: **Yes!**

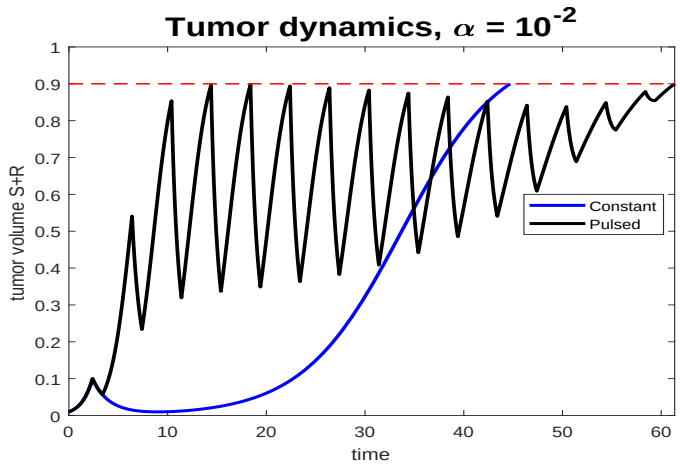
$\alpha_s = 0$





$\alpha_i = 10^{-2}$





- Constant is more successful for $\alpha_s = 0 : t_{c,c} - t_{c,p} \approx 88$
- Pulsed is more successful for $\alpha_i = 10^{-2} : t_{c,p} - t_{c,c} \approx 19$

Identifiability

Demonstrated that α parameter may have large impact on treatment outcome

Thus, a fundamental clinical goal is to **identify** it (i.e. reverse engineer) α value from various inputs $u(t)$

- Is this even possible?
- If not, not really worth studying

What are our observables?

- Time t and total tumor volume $V(t) = S(t) + R(t)$ (and derivatives, but see later)
- Don't assume we can measure sensitive and resistant subpopulations (clinical)

Lie Derivatives

We can identify all parameters (including α) using the following technique from control theory:

$$x := \begin{pmatrix} S \\ R \end{pmatrix}, f := \begin{pmatrix} (1-(x_1+x_2))x_1 - \epsilon x_1 \\ p_r(1-(x_1+x_2))x_2 + \epsilon x_1 \end{pmatrix}, g := \begin{pmatrix} -\alpha x_1 - d x_1 \\ \alpha x_1 \end{pmatrix}$$

$$\dot{x} = f(x) + u(t)g(x),$$
$$y = x_1 + x_2.$$

Idea: measure derivatives of output y at $t = 0$ for different inputs $u(t)$

- Specifically, measure $y(0), y'(0), y''(0), y'''(0)$ for $u(t) \equiv 0, 1, 2, t$
  - Call them Y_0, Y_1, Y_2, etc.
- All Lie derivatives $L_f y(0), L_g y(0), L_f^2 y(0), L_f L_g y(0)$, etc. can be written in terms of the Y_i (linear)

Lie Derivatives and Elementary Observables

$$\dot{x} = f(x) + u(t)g(x) \qquad y := h(x) = x_1 + x_2$$

Unique structural identifiability is equivalent to injectivity of the map

$$p \mapsto (u(t), y(t, p))$$

Two sets of observables are associated to the control system:

$$F_1 = \text{span}_{\mathbb{R}} \left\{ Y(x_0, U) \,|\, U \in \mathbb{R}^k, k \geq 0 \right\}$$

$$F_2 = \text{span}_{\mathbb{R}} \left\{ L_{i_1} \dots L_{i_k} h(x_0) \,|\, (i_1, \dots i_k) \in \{g, f\}^k, k \geq 0 \right\}$$

where

$$Y(x_0, U) = \left. \frac{d^k}{dt^k} \right|_{t=0} h(x(t))$$

Wang and Sontag proved that $F_1 = F_2$, so that structural identifiability is equivalent to injectivity of the map

$$p \mapsto \left(L_{i_1} \dots L_{i_k} h(x_0) \,|\, (i_1, \dots i_k) \in \{g, f\}^k, k \geq 0 \right)$$

Lie Derivatives continued

It is thus sufficient to show that the parameters may be obtained by iterated Lie derivatives (F_2):

$$
\begin{aligned}
S_0 &= h(x_0), \\
d &= -\frac{L_g h(x_0)}{S_0}, \\
\alpha &= \frac{L_g^2 h(x_0)}{d S_0} - d, \\
\epsilon &= \frac{L_f L_g h(x_0)}{d S_0} + 1 - S_0, \\
p_r &= \frac{S_0}{1 - S_0} + \frac{L_g L_f h(x_0)}{\alpha S_0 (1 - S_0)} - \left(1 + \frac{d}{\alpha}\right)\left(1 - \frac{S_0}{1 - S_0}\right).
\end{aligned}
$$

Alternatively, we may obtain via a relatively simple set of controls:

$$u(t) = 0, 1, 2, t$$

Other Methods of Identifiability

Previous: demonstrated that all parameters can be experimentally determined via relatively simple set of controls

$$u(t) \equiv 0, 1, 2, t$$

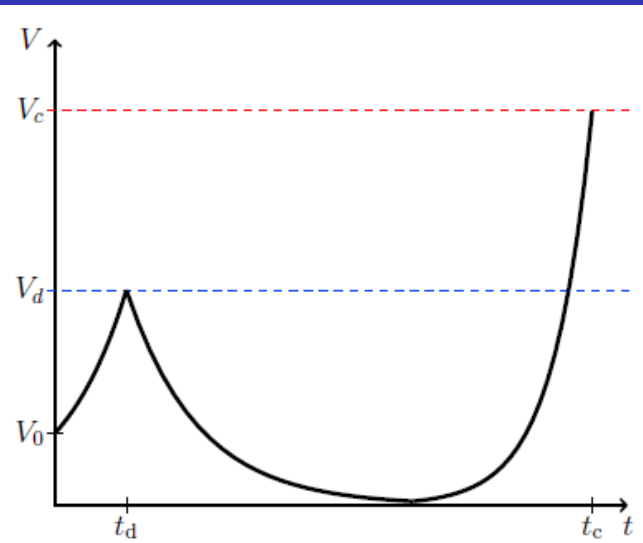
However, it is important to note that this involved measure derivatives at time $t = 0$

- $y(0), y'(0), y''(0), y'''(0)$, where $y = V$
- This may be unrealistic, especially if data is noisy

Is there another way to determine parameter α?

- Equivalently, what are the *qualitative* differences between $\alpha = 0$ and $\alpha > 0$?
- Is there a way to distinguish utilizing only constant therapies?

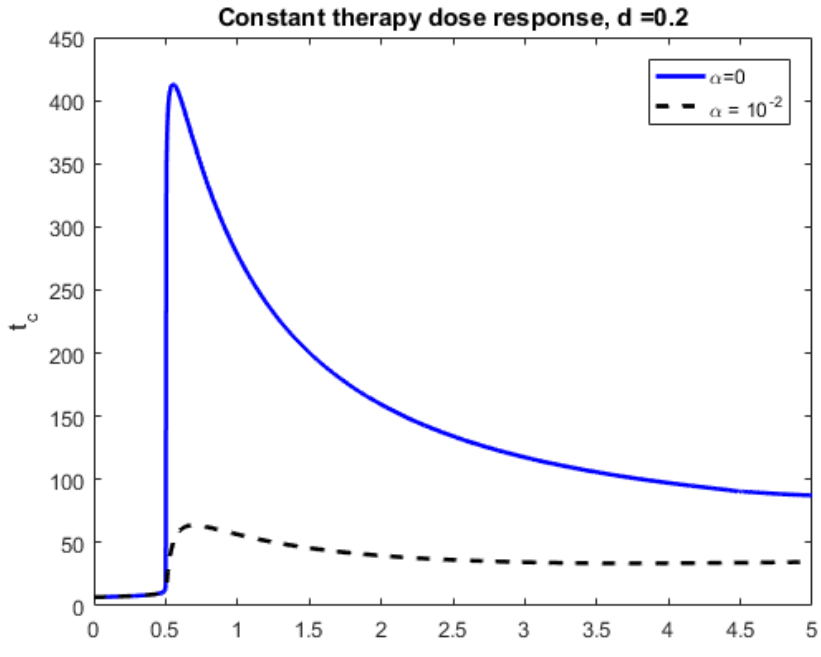
Dose-Response Curves



Compute standard dose-response curves for a fixed set of parameters

- Only measuring $\mathbf{t_c} = t_c(u, d, \alpha)$ and V_c

For a fixed value of d $(= 0.1)$:



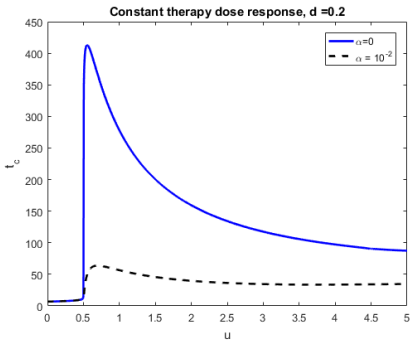
Very similar qualitative dynamics for both types of drug

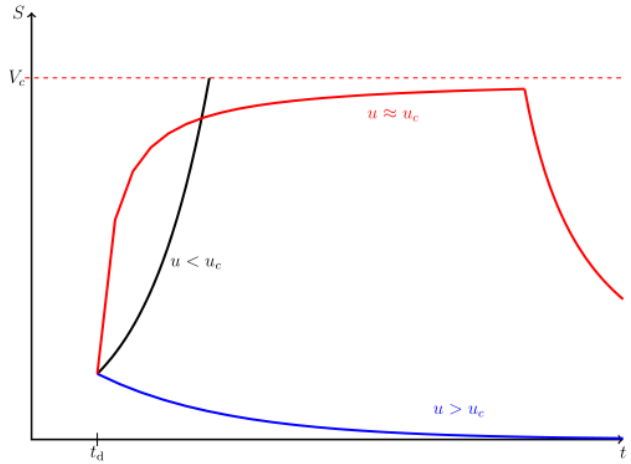
- Maximum response time occurring at **intermediate** dosage (singular controls)

Aside: Maximum Response Dose

Observed an intermediate constant dosage yielding the maximum response time (u_c)

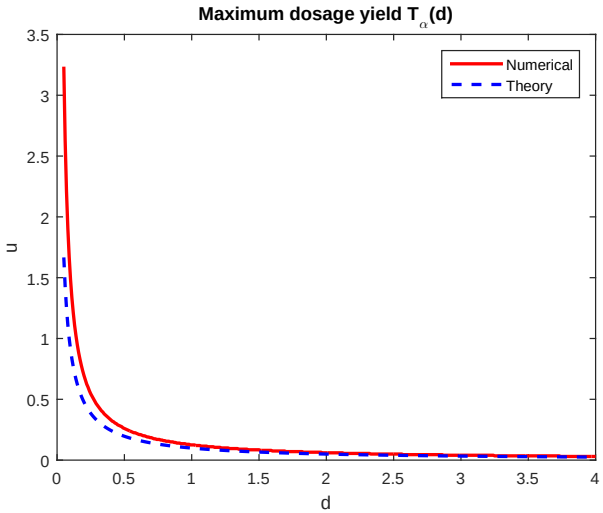
- Understand via competition between sensitive and resistant cells





Critical size V_c is approximately the carrying capacity of sensitive cells (ignoring resistant dynamics)

$$u_c \approx \frac{1 - \epsilon - V_c}{\alpha + d}$$

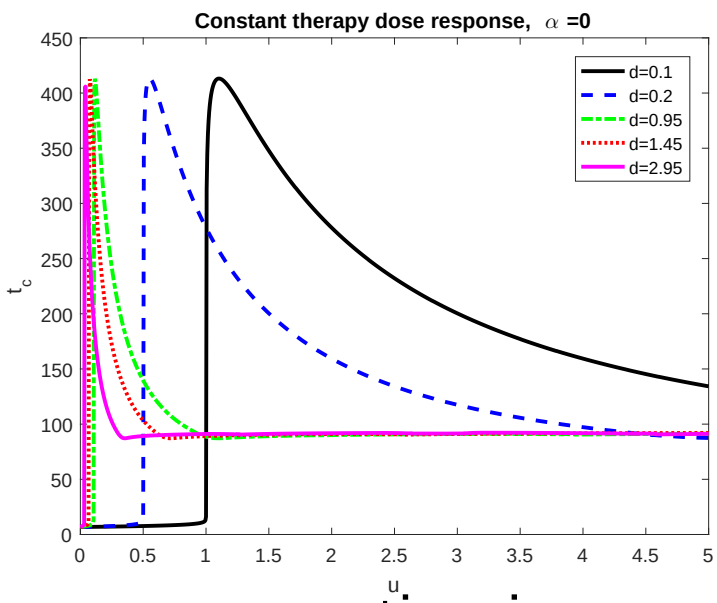


Varying d

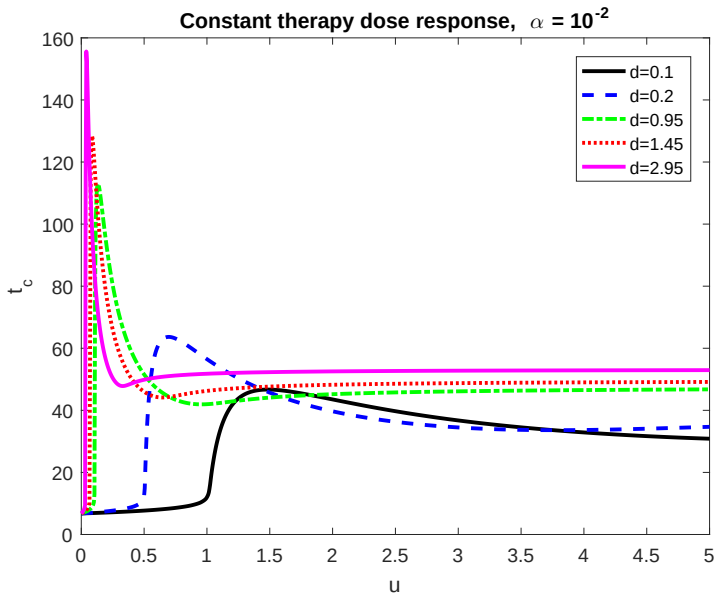
Imagine we can, *in vitro*, vary the drug sensitivity d

- May be difficult
- But may be possible to alter the expression of MDR1 via ABCBC1 or even CDX2
- Correlate d with MDR1 expression

$\alpha_s = 0$



$\alpha_i = 10^{-2}$

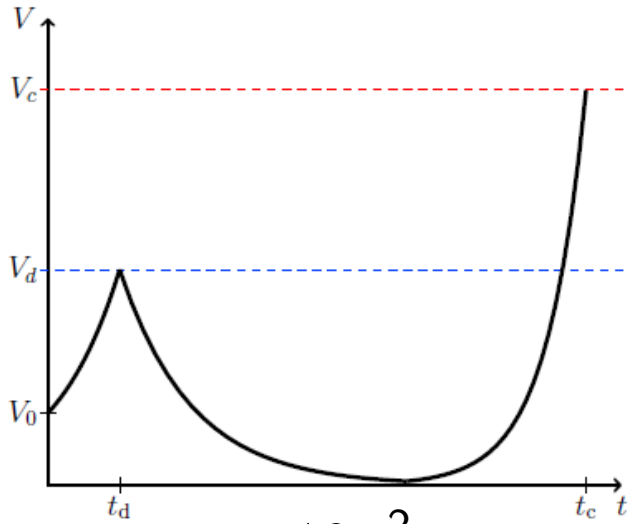


Maximum response time is:

- **Constant** for $\alpha = 0$
- **Increasing in d** for $\alpha > 0$

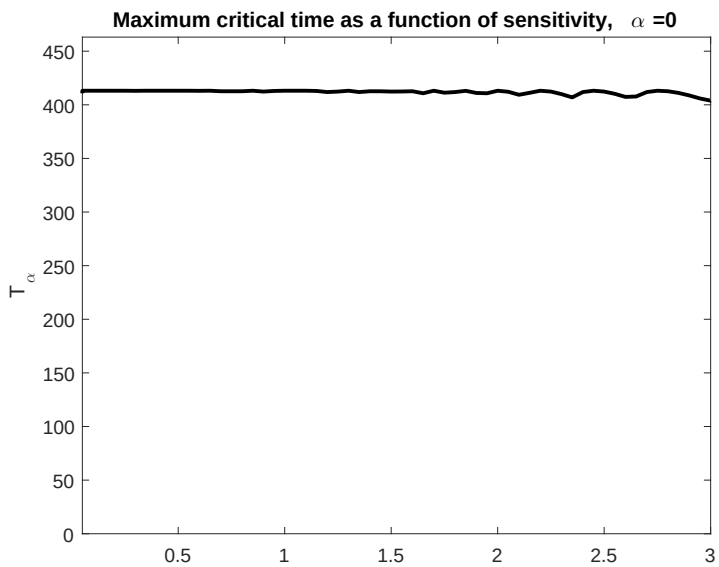
Maximum Response Time

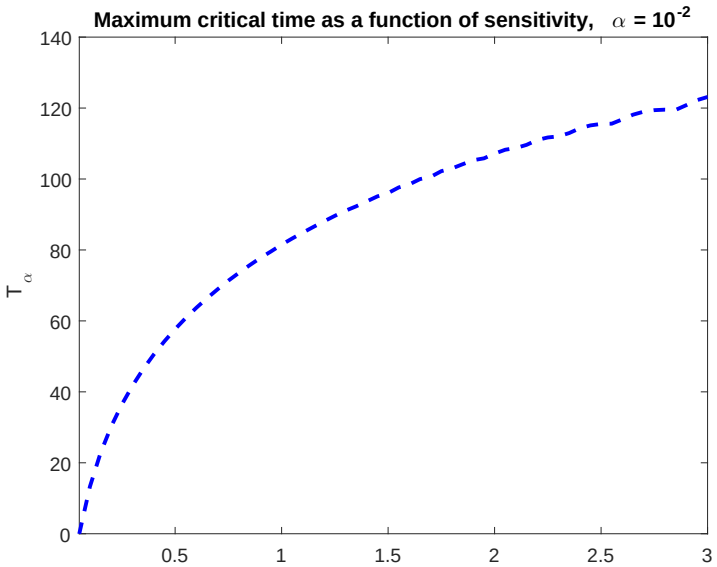
$$T_\alpha(d) := \sup_u \{t_c(u, d, \alpha)\}$$



$\alpha_s = 0$

$\alpha_i = 10^{-2}$





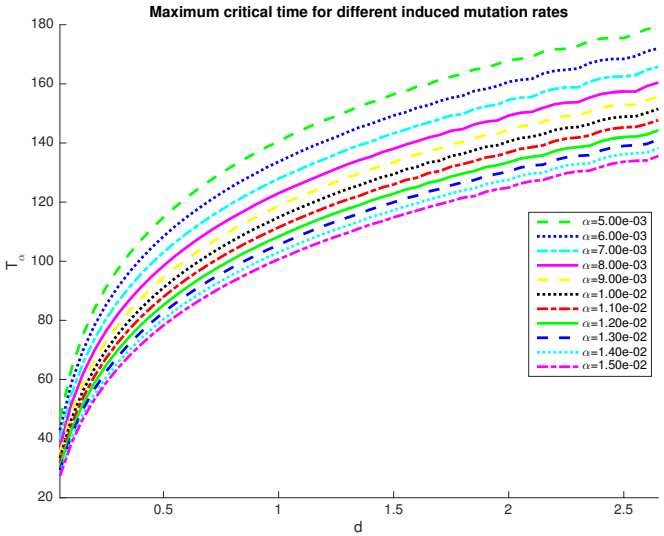
Shape of maximum response time is an indicator of phenotype-switching induction of drug

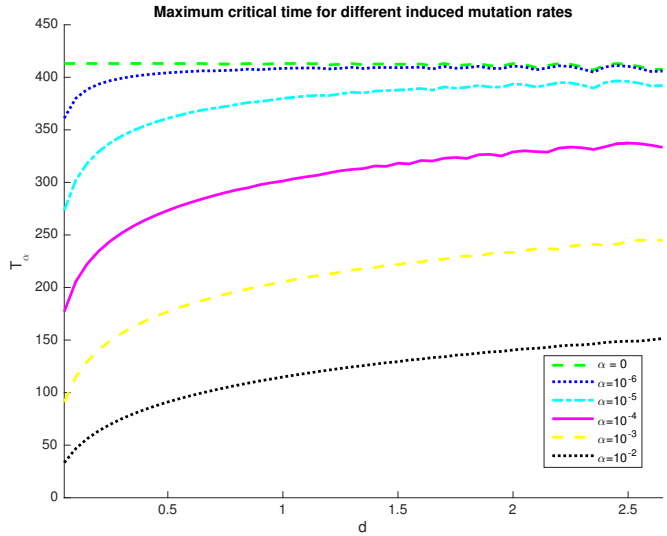
- Did not even have to know anything about mechanisms

Identifying α (Part II)

$$T_\alpha(d) := \sup_u \{t_c(u, d, \alpha)\}$$

In principle, we should be able to measure α from $T_\alpha(d)$ curve





Two possible methods:

- Increasing slope at $d = 0$ as $\alpha \to 0$

$$\frac{\partial}{\partial d}\Big|_{d=0} T_0(d) = k\delta(d)$$

- Increasing slope at $d > 0$ (away from 0) as $\alpha \uparrow$

Limitations

Practical limitations to consider:

- Difficult to precisely vary drug sensitivity d
- Measuring derivatives from experimental data is not realistic
- Control over administered dose must be exact
  - t_c has a high degree of sensitivity for $u \approx u_c$

Focus on qualitative distinctions of induced drug resistance ($\alpha > 0$) under simplest treatment regime (constant)

- "Thought experiment"

Formulation of Control Problem

Recall:

- Treatment outcome may be impacted by induction rate of treatment (α)
- We can (theoretically and "practically") identify this rate (not shown)

Natural then to ask what is the **best** therapy (i.e. optimal control problem)

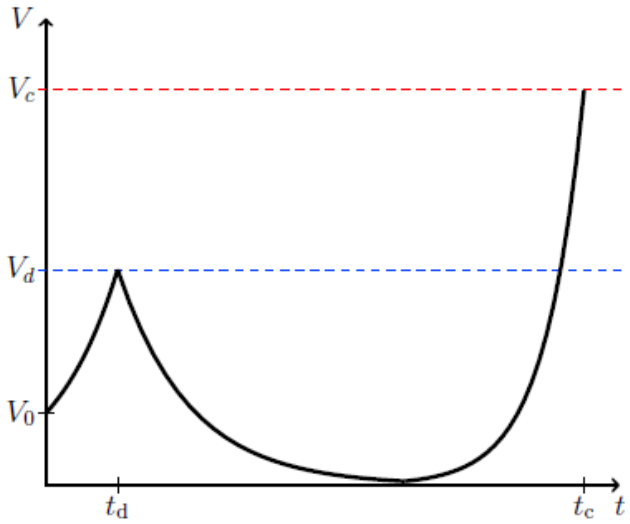
- Specifically: how (and if!) does the structure change as a function of α

$$u_\alpha(t) := u_{\text{opt}}(t; \alpha)$$

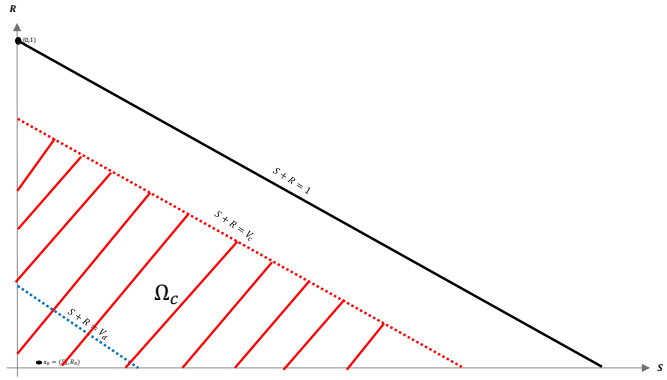
Method to characterize level of resistance induction of a drug

- Testable (*in vitro*)
- Clinically relevant!
  - Dose densification may no longer be optimal (Norton-Simon)

Formulation (continued)



$$\dot{x} = f(x) + u(t)g(x), \qquad x = \begin{pmatrix} S \\ R \end{pmatrix} \in \mathbb{R}^2$$



Only natural metric to rank therapies in **simplified** model:

$$t_c = \sup_{u(t)\in\mathcal{U}} \{J(u(t))\},$$

$$J(u(t)) = t_f = \int_0^{t_f} 1\,\mathrm{d}t,$$

$$\mathcal{U} = \{u : [0, T] \to [\mathbf{0}, \mathbf{M}] \mid T > 0, u \text{ is Lebesgue measurable}\}.$$

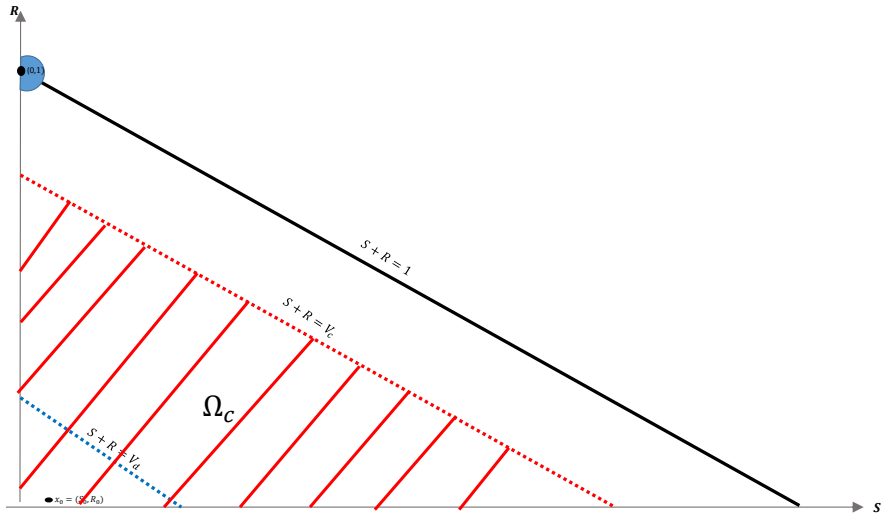
Note that a path constraint exists along the boundary $V = V_c$:

$$\psi(S(t), R(t)) := S(t) + R(t) - V_c \leq 0$$

Existence Results

$$\dot{x} = f(x) + u(t)g(x)$$

$$t_c = \sup_{u(t)\in\mathcal{U}} \left\{ \int_0^{t_f} 1 \, \mathrm{d}t \right\}$$



Maximization of time trajectory remains inside the region Ω_c

- Is this maximum obtained?

$$\sup_{u\in\mathcal{U}} t_c(u) < \infty$$

Since $(0,1)$ is globally attracting for all $u \in \mathcal{U}$: **Yes!**

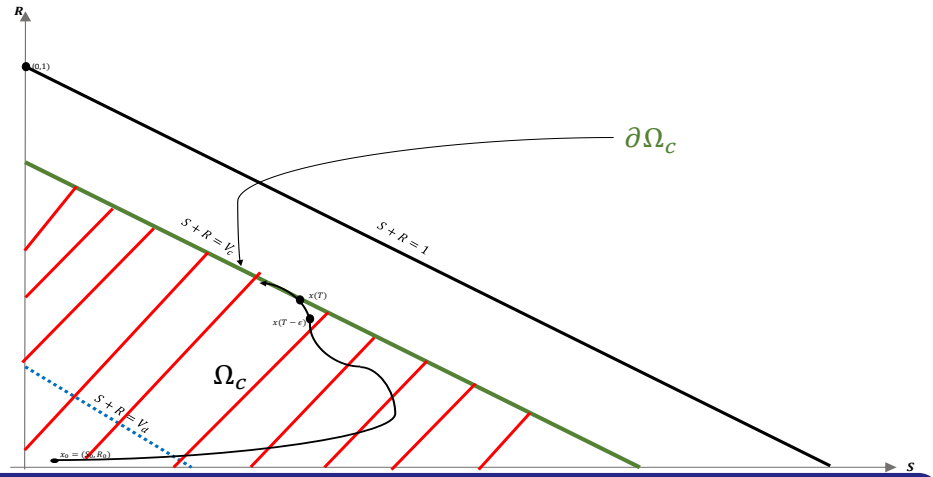
- Otherwise we could construct a control that remains a fixed positive distance ϵ from $(0,1)$:

$$u_* = u_{1,*} * u_{2,*} * \cdots$$

Thus we can apply the **Maximum Principle** to analyze necessary conditions satisfied by extremals

Elimination of Path Constraints

Synthesize unconstrained ($\text{int}(\Omega_c)$) and path-constrained ($\partial\Omega_c$) optimal controls



Theorem

Suppose that x_* is an optimal trajectory. Let T be the first time such that $x(t) \in N$. Fix $\epsilon > 0$ such that $T - \epsilon > 0$, and

$$\xi = x(T - \epsilon).$$

Define $z(t) := x_*(t)|_{t\in[0,T-\epsilon]}$. Then the trajectory z is a local solution of the corresponding time maximization problem t_f with boundary conditions $x(0) = x_0$, $x(t_f) = \xi$, and no additional path constraints.

Idea: Optimal control consists of concatenations of controls obtained from the unconstrained necessary conditions and controls of the form

$$u_p(S,R) = \frac{1}{d}\frac{(1-(S+R))(S+p_rR)}{S}.$$

Unconstrained Maximum Principle

We can then use the Maximum Principle to analyze necessary conditions satisfied by extremals at point interior to Ω_c:

- Minimize Hamiltonian $H = H(\lambda, x, u)$ pointwise w.r.t. u along extremal lifts $\Gamma = ((x, u), \lambda)$:

$$\boxed{H(x, u, \lambda) = -1 + \langle \lambda, f(x) \rangle + u \langle \lambda, g(x) \rangle}$$

Note: we have converted to a minimization problem to be consistent with the literature

Basic Properties of Extremals (int(Ω_c))

$$H(x,u,\lambda) = -1 + \langle \lambda(t), f(x)\rangle + u\langle \lambda(t), g(x)\rangle$$

$$\dot{x} = f(x) + u(t)g(x)$$
$$\dot{\lambda} = -\lambda\left(Df(x(t)) + uDg(x(t))\right)$$

Properties independent of α:

- $\lambda_0 = 1$, since abnormal extremals ($\lambda_0 = 0$) are simply classified ($u_*(t) \equiv 0, M$)
- $\lambda(t) \neq 0$
- $H(t) := H(x(t), u(t), \lambda(t)) \equiv 0$ on $[0, t_c]$ for any extremal lift Γ
- The switching function $\Phi(t)$ is given by

$$\Phi(t) = \langle \lambda(t), g(x(t))\rangle$$

along Γ, so that an extremal control must satisfy

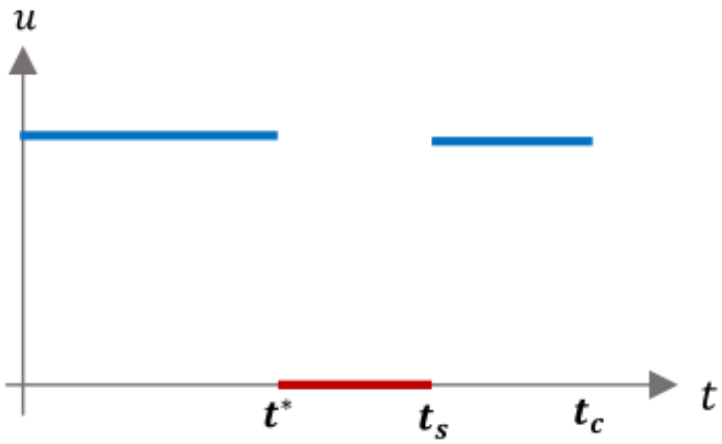
$$u_*(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0. \end{cases}$$

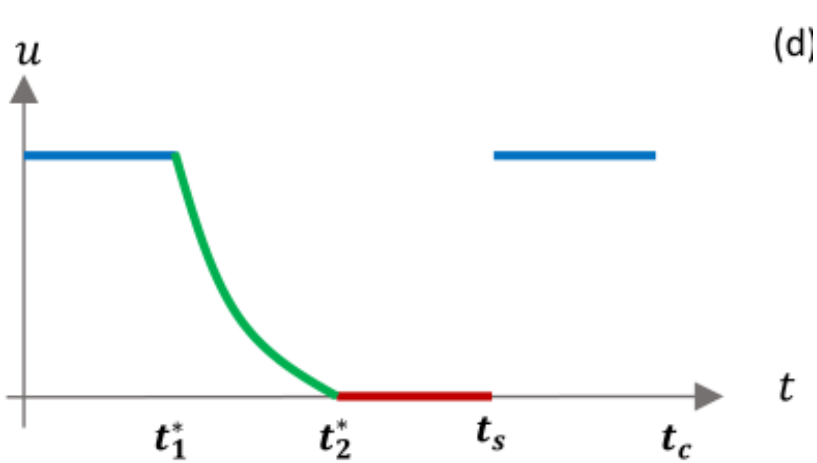
Note: $H(t) = -1 + \langle \lambda(t), f(x)\rangle + u(t)\Phi(t)$

Singular Arcs

$$u(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0. \end{cases} \qquad \dot{x} = f(x) + u(t)g(x)$$
$$\Phi(t) = \langle \lambda(t), g(x(t)) \rangle$$

Control structure is **bang-bang** ($u(t) = 0$ or $u(t) = M$) outside of possible **singular arcs** ($0 < u(t) < M$):





$\Phi(t) \equiv 0$

Questions:

- On what subsets of the SR-plane are singular arcs allowed?
- How does the geometry of the subsets depend on α?
- Are singular arcs (hence intermediate dosages) optimal?

Differential geometric arguments inspired by Sussmann (1982, 1986)

Switching Function

$$u(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0. \end{cases} \qquad \begin{aligned} \dot{x} &= f(x) + u(t)g(x) \\ \Phi(t) &= \langle \lambda(t), g(x(t)) \rangle \end{aligned}$$

On singular arcs, the switching function $\Phi(t)$ must satisfy

$$\Phi(t) \equiv 0$$

This is a strong condition, which implies all higher-order derivatives must also vanish identically:

$$\dot{\Phi}(t) \equiv 0$$

$$\ddot{\Phi}(t) \equiv 0, \quad \text{etc.}$$

Furthermore, these derivatives can be calculated via iterated Lie brackets:

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g](x(t)) \rangle$$

$$\ddot{\Phi}(t) = \langle \lambda(t), [f, [f, g]](x(t)) \rangle + u(t) \langle \lambda(t), [g, [f, g]](x(t)) \rangle$$

where

$$[f, g](x(t)) = Dg(x(t))f(x(t)) - Df(x(t))g(x(t))$$

Switching Function (continued)

$$u(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0. \end{cases} \qquad \dot{x} = f(x) + u(t)g(x) \qquad \Phi(t) = \langle \lambda(t), g(x(t)) \rangle \qquad \dot{\Phi}(t) = \langle \lambda(t), [f,g](x(t)) \rangle$$

Key observation: $f(x)$ and $g(x)$ are linearly independent in our region of interest Ω $(0 < V \leq V_c < 1)$, which implies

$$[f,g](x) = \boxed{\gamma(x)} f(x) + \beta(x) g(x)$$

$\gamma(x)$: determines geometric structure of singular arc

- Allow us to write closed form system of ODEs for $x(t)$ and $\Phi(t)$ along extremals (solutions NOT unique)
- Indeed, since $H(t) \equiv 0$, we may solve for $\langle \lambda(t), f(x) \rangle$ to obtain

$$\dot{\Phi}(t) = \gamma(x(t)) + \Big(\beta(x(t)) - u(t)\gamma(x(t))\Big)\Phi(t)$$

Theorem

Singular arcs can only occur in the SR plane where $\gamma(x) = 0$. Furthermore, in Ω, this is precisely the line $aS + bR = c$.

Geometry of Singular Arc

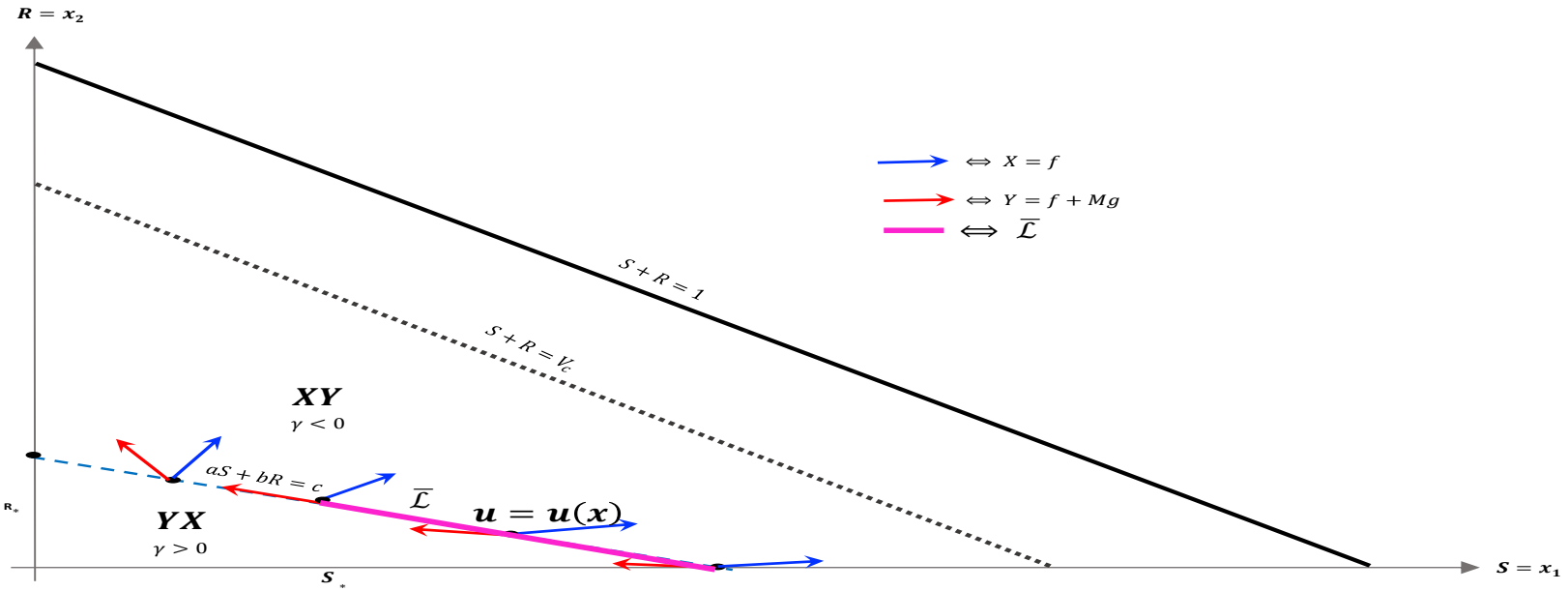
$$u(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0. \end{cases} \qquad \dot{\Phi}(t) = \boxed{\gamma(x(t))} + \Big(\beta(x(t)) - u(t)\gamma(x(t))\Big)\Phi(t)$$

Denote the bang-bang controls via X and Y:

$$X = f(x)\,(\Leftrightarrow u = 0), \qquad Y := f(x) + Mg(x)\,(\Leftrightarrow u = M)$$

Switching point (τ such that $\Phi(\tau) = 0$) order is determined by sign of γ away from singular arcs:

- $\Longrightarrow$ structure determined outside of singular arc



Geometry of Singular Arc

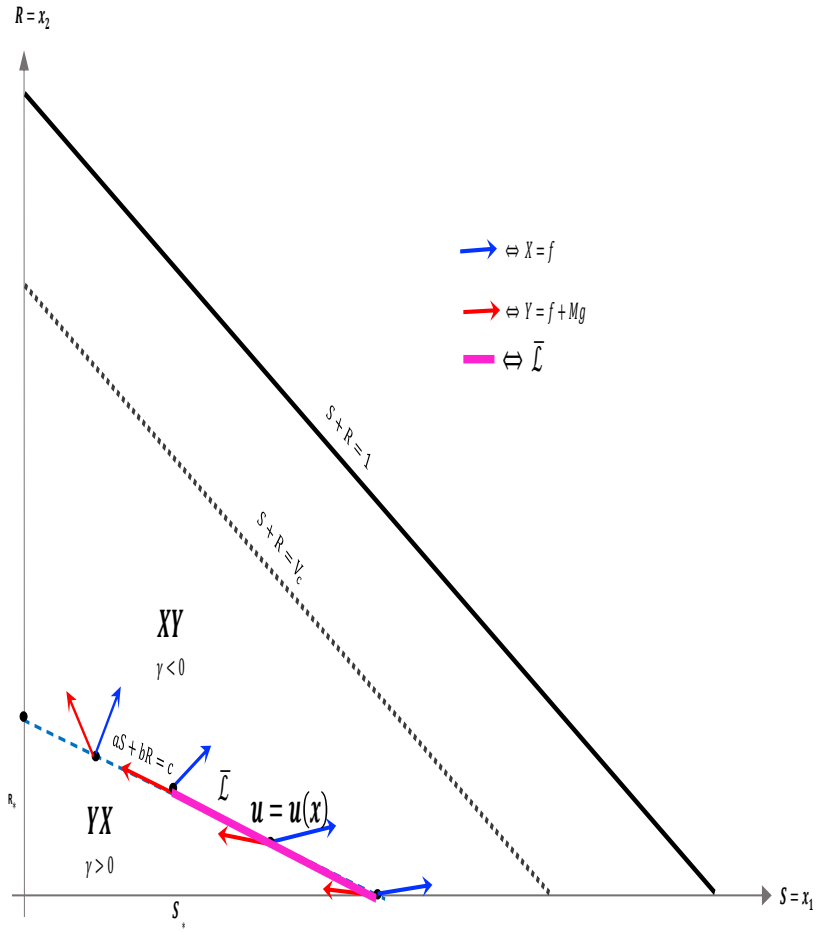
Other properties of extremals:

- Singular arc $\bar{\mathcal{L}}$ is an extremal
- Control $u(x)$ is uniquely determined there via

$$u(x) = M \frac{L_X \gamma(x)}{L_X \gamma(x) - L_Y \gamma(x)}$$

- Non-restrictive assumptions (M, ϵ) imply that $\bar{\mathcal{L}}$ is in Γ and **feasible** AND extremal:

$$0 < u(x) < M$$



Note: last claim requires $\alpha > 0$, and will determine structure globally

Non-Induced Control Structure ($\alpha = 0$)

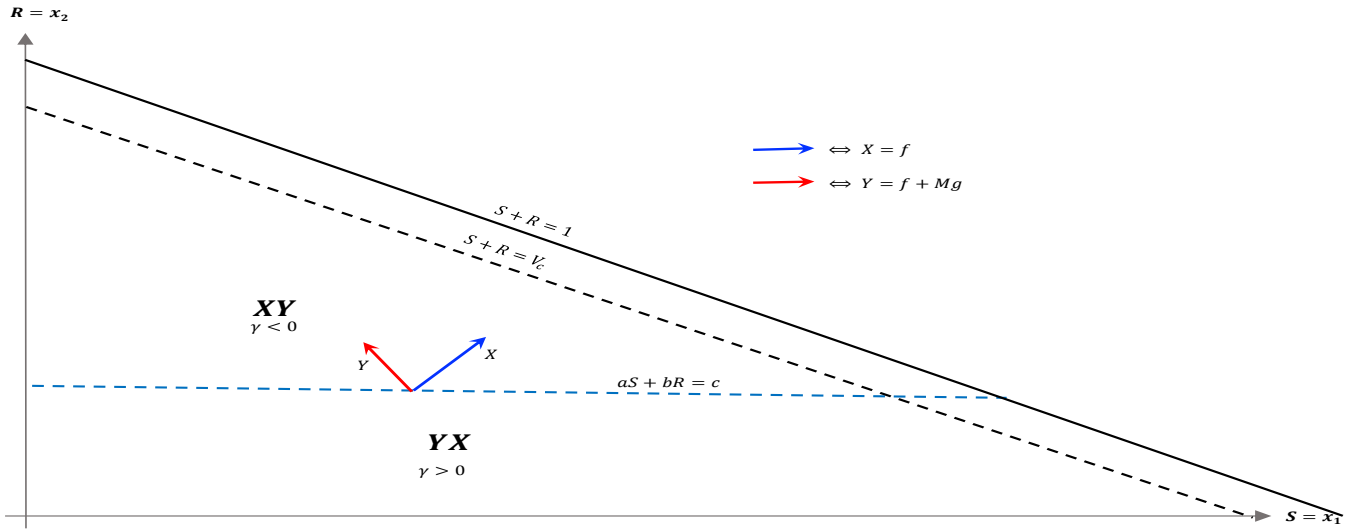
$$X := f(x) \qquad Y := f(x) + Mg(x)$$

Theorem

In the case of a non drug resistance inducing drug ($\alpha = 0$), the optimal control structure is of the form

$$u = YXu_pY$$

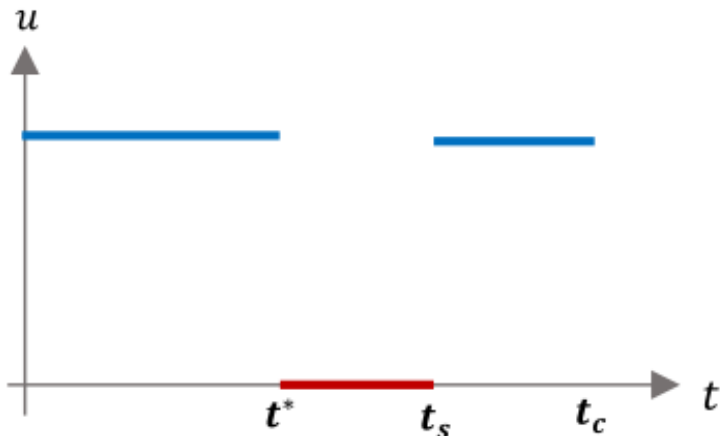
Proof



Recall that the resistant population is always increasing

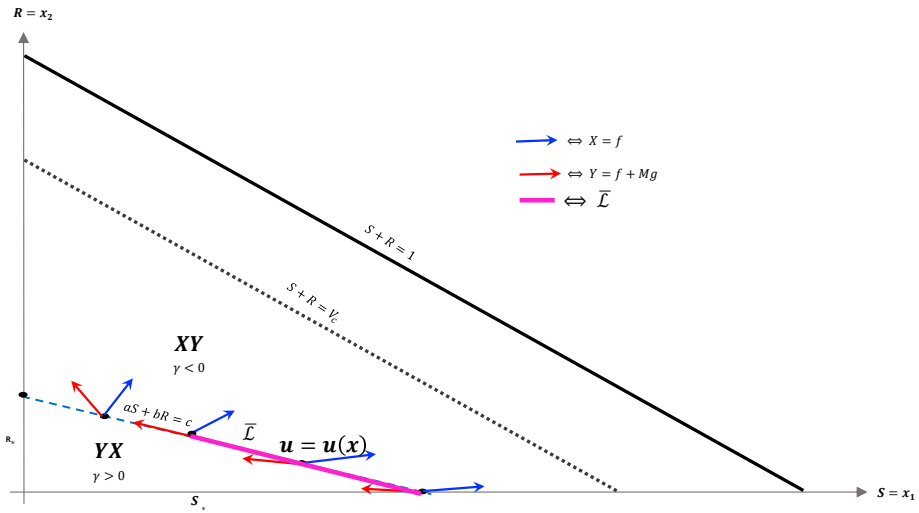
Induced control structure ($\alpha > 0$)

Proven that **control structure in classical drug-independent paradigm is bang-bang**, with at most two switches.

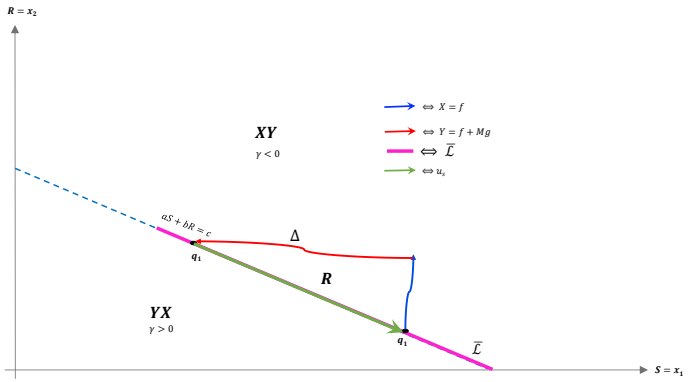


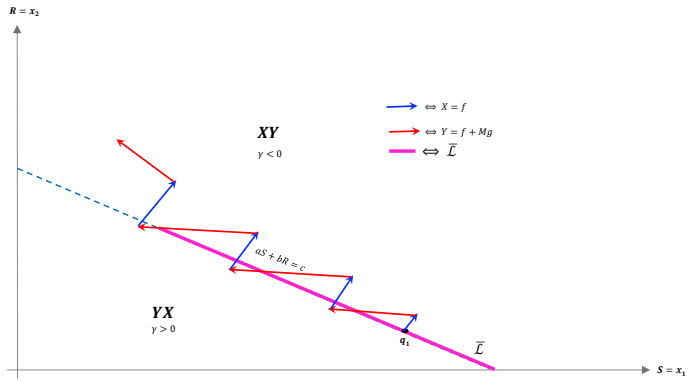
What about when $\alpha > 0$?

- Are singular arcs (locally) optimal?
- Does switching structure change?



Singular controls are NOT optimal





Using the Lie algebra structure of vector field, we can show that the singular arc $\bar{\mathcal{L}}$ is not optimal. That is, $\mathcal{L}$ is a fast singular arc.

- Legendre-Clebsch condition is violated
- Explicit clock-form $\omega \in (T\Omega)^\vee$ to compare times along bang-bang and singular arcs:

$$s + t - \tau = \int_\Delta \omega = \int_R d\omega = -\int_R \frac{\gamma}{\det(f, g)}$$

If $\alpha > 0$, optimal control is still bang locally near $\bar{\mathcal{L}}$

- **Hence global interior structure of control is bang-bang**
- However: switches through the arc $\bar{\mathcal{L}}$ are allowed

Switching Structure for $\alpha > 0$

Theorem

For any $\alpha \geq 0$, the optimal control to maximize the time to reach a critical time is a concatenation of bang-bang and path-constraint controls. In fact, the general control structure takes the form

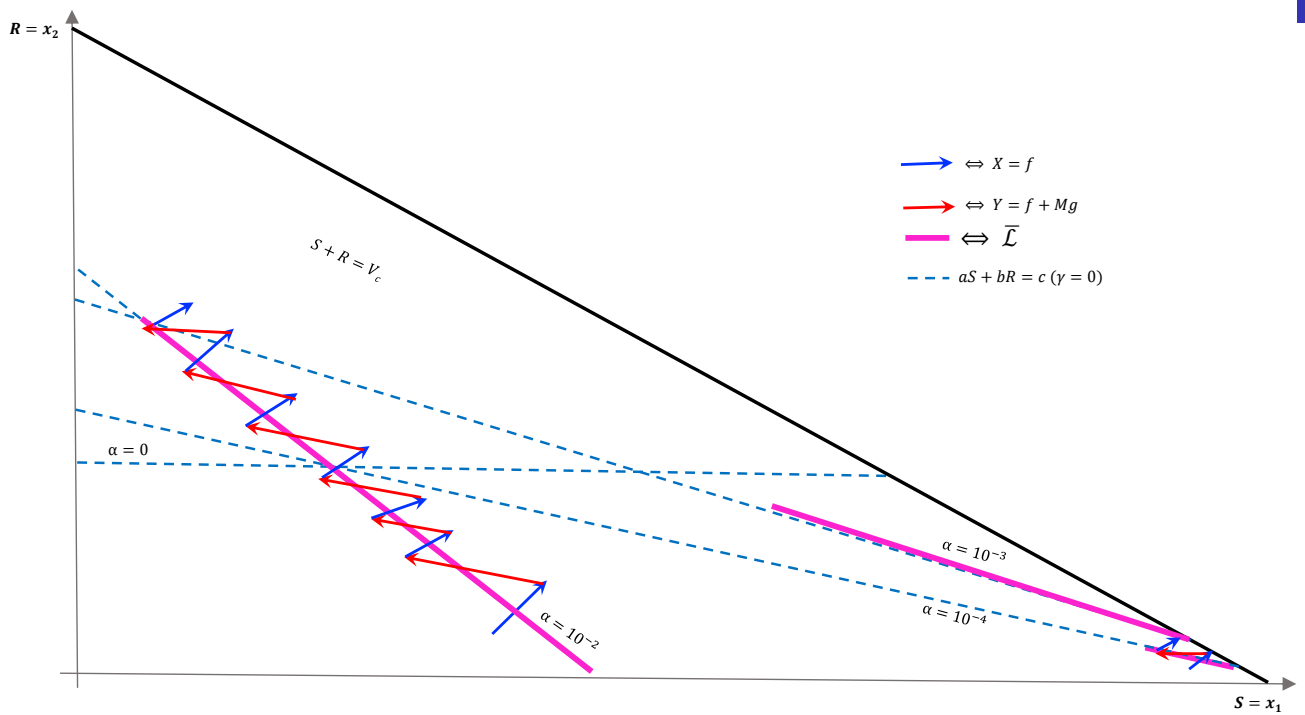
$$(YX)^n u_p Y, \tag{1}$$

where $(YX)^n := (YX)^{n-1} YX$ and $n \in \mathbb{N}$, and the order should be interpreted left to right.

How does $n = n(\alpha)$ vary as α is increased?

- $n(0) = 1$ (at most two switches in case of non-resistant inducing drug)
- Switches can only occur across singular arc $\bar{\mathcal{L}}$
  - At most one bang in a (sufficiently small) neighborhood of arc (g-conjugate points, variational vector fields)
- Larger sections $\bar{\mathcal{L}}$ lie in the control set $\mathcal{U}$ as α increases

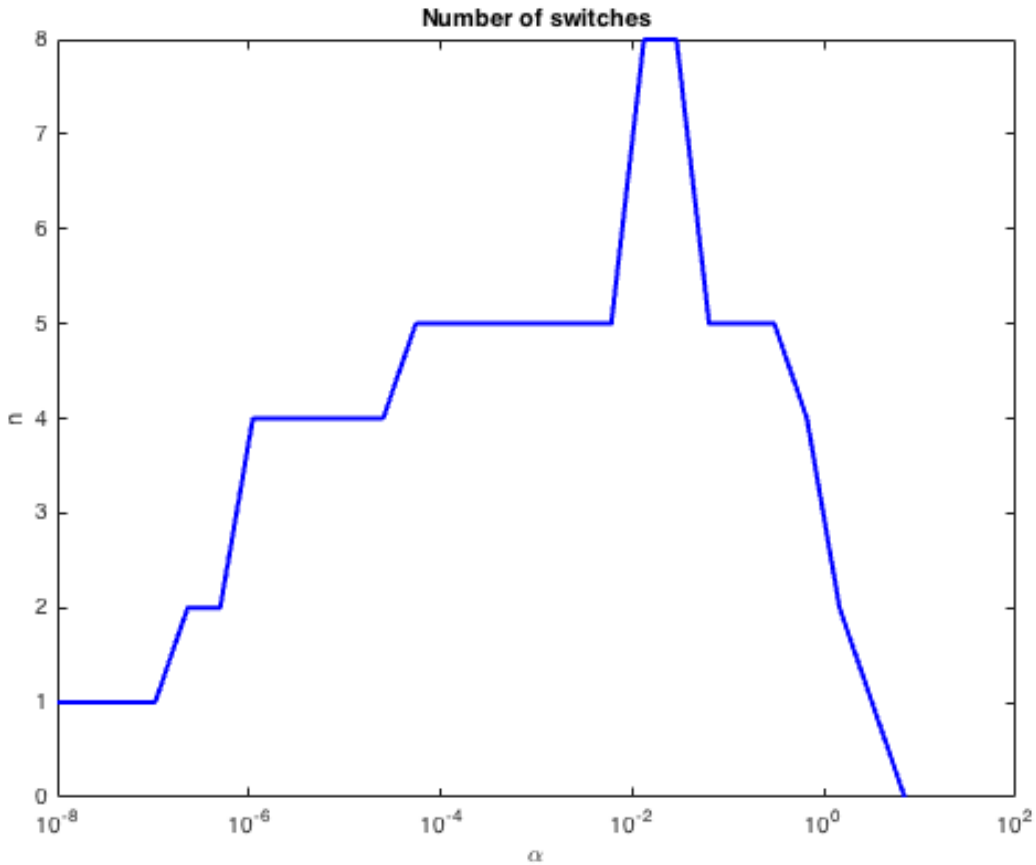
Variation in $\bar{\mathcal{L}}$



Geometry of arc $\bar{\mathcal{L}}$ **suggests** that number of switchings increases as α increases

- $\alpha = 0$: $u = YXu_pY$
- $\alpha > 0$: $u = (YX)^{n(\alpha)}u_pY$
- $n(\alpha)$ increases with induction rate α
- At least for small values of α:
  - $\bar{\mathcal{L}}$ becomes vertical (hence outside of $\mathcal{U}$) for large α

Number of Switchings



Cartoon of bang-bang structure as a function of induction rate α

- All other parameters constant
- Maximum for an intermediate α where region $\bar{\mathcal{L}}$ is largest
- Note: just a cartoon

Conclusions

$$\frac{dS}{dt} = (1 - (S + R))\, S - (\epsilon + \alpha u(t))S - du(t)S,$$
$$\frac{dR}{dt} = p_r\,(1 - (S + R))\, R + (\epsilon + \alpha u(t))S.$$

Formulated a mathematical framework to distinguish mechanisms by which drug resistance originates

- Random (drug-independent) resistance
- Induced phenotype switching

Control structure varies as a function of the degree to which the drug promotes the resistant phenotype

- $\alpha = 0$: $u = YXu_pY$
- $\alpha > 0$: $u = (YX)^n u_p Y, n \geq 1$
- Geometry suggests that $\frac{\partial n}{\partial \alpha} > 0$, at least initially (small α)

Clinically relevant:

- Suggests different treatment strategies based on how "mutagenic" chemotherapy is
- Provides testable hypothesis to determine α *in vitro*

Current and Future Work

Understand fully switching structure as a function of α

- No proofs yet
- Numerical results suggest switching is optimal, at least along some regions of $\bar{\mathcal{L}}$

Further control techniques related to **feedback**

- Switching dictated along $aS + bR = c$, which we **cannot** *a priori* measure
- Possibly approximate via volume measurements?
- Adaptive therapy, à la Gatenby

Validate and expand with experimental data

- Working with A. Pisco (CZF) utilizing *Nature Communications* data (2013)
- Extend to sequential therapy by targeting induced resistant cells

Multidrug and Sequential Therapy Extension

ARTICLE

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Temporally sequenced anticancer drugs overcome adaptive resistance by targeting a vulnerable chemotherapy-induced phenotypic transition

Aaron Goldman[1,2,3], Biswanath Majumder[4,5], Andrew Dhawan[6], Sudharshan Ravi[3], David Goldman[7], Mohammad Kohandel[8], Pradip K. Majumder[4,5] & Shiladitya Sengupta[1,2,3,9]

Leverage induction to study optimal treatment *combinations*

$$\dot{N} = r_N\left(1 - \frac{V}{K}\right)N - d_{N,1}u_1(t)N - d_{N,2}u_2(t)N$$

$$\dot{S} = r_S\left(1 - \frac{V}{K}\right)S - (\epsilon + \alpha u_1(t))S - d_{S,1}u_1(t)S - d_{S,2}u_2(t)S + \gamma R$$

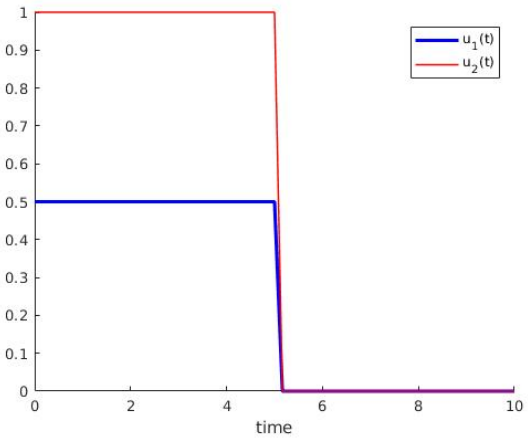
$$\dot{R} = r_R\left(1 - \frac{V}{K}\right)R + (\epsilon + \alpha u_1(t))S - \gamma R - d_{R,2}u_2(t)R$$

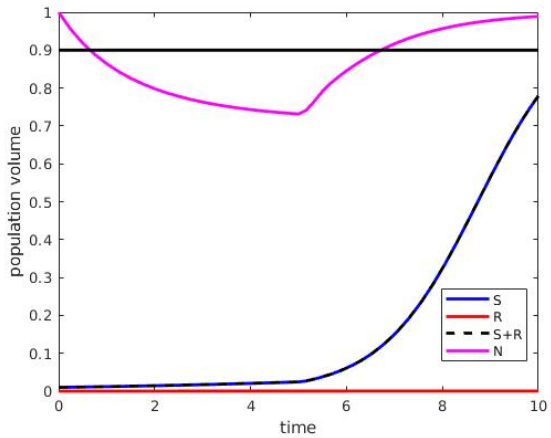
Two treatments with distinct mechanisms of action:

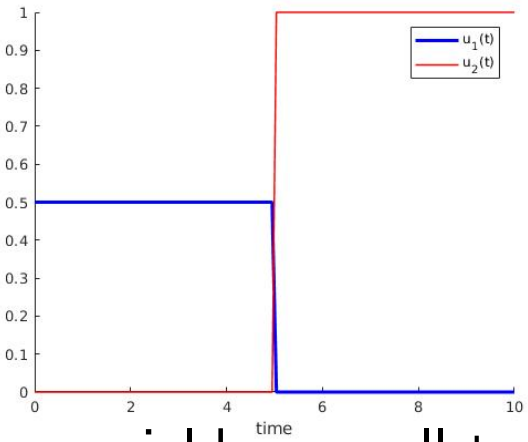
- u_1 : docetaxel (induces resistance via activation of SFK/Hck)
- u_2 : dasatinib (SFK/BCR-Abl inhibitor)

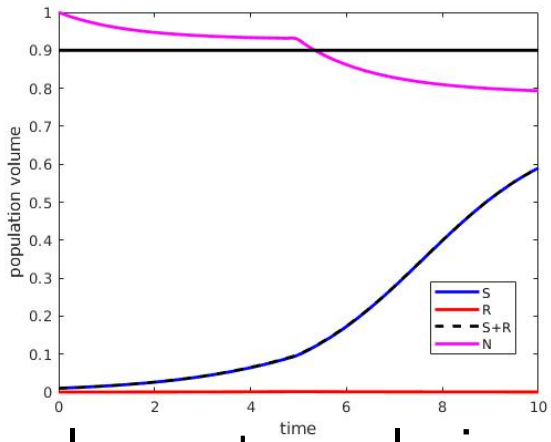
Numerical Results

Sequential versus combination therapy









Sequential therapy yields a small tumor volume at conclusion of treatment

- Order is therapy is important
- Natural control questions