A mathematical model of evolution of drug-induced resistance

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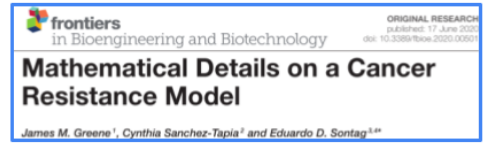
Mathematical Approach to Differentiate Spontaneous and Induced Evolution to Drug Resistance During Cancer Treatment

James M. Greene, PhD[1]; Jana L. Gevertz, PhD[2]; and Eduardo D. Sontag, PhD[3,4]

Clin Cancer Inform. © 2019 by American Society of Clinical Oncology



frontiers in Bioengineering and Biotechnology

ORIGINAL RESEARCH
published: 17 June 2020
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Mathematical Details on a Cancer Resistance Model

James M. Greene[1], Cynthia Sanchez-Tapia[2] and Eduardo D. Sontag[3,4]*

npj | systems biology and applications Article

Understanding therapeutic tolerance through a mathematical model of drug-induced resistance

Jana L. Gevertz[1,2], James M. Greene[2,3], Samantha Prosperi[2,3], Natacha Comandante-Lou[4] & Eduardo D. Sontag[2,3,4]

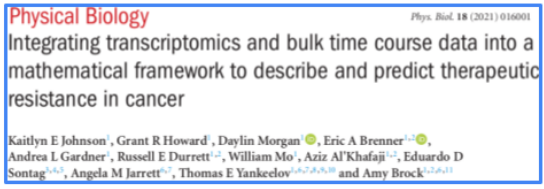
npj Systems Biology and Applications | (2025)11:30

frontiers in Immunology

ORIGINAL RESEARCH
published: 30 June 2020
doi: 10.3389/fimmu.2020.01376

Delicate Balances in Cancer Chemotherapy: Modeling Immune Recruitment and Emergence of Systemic Drug Resistance

Anh Phong Tran[1†], M. Ali Al-Radhawi[2†], Irina Kareva[3], Junjio Wu[4], David J. Waxman[5] and Eduardo D. Sontag[2,6,7]*



Physical Biology

Phys. Biol. 18 (2021) 016001

Integrating transcriptomics and bulk time course data into a mathematical framework to describe and predict therapeutic resistance in cancer

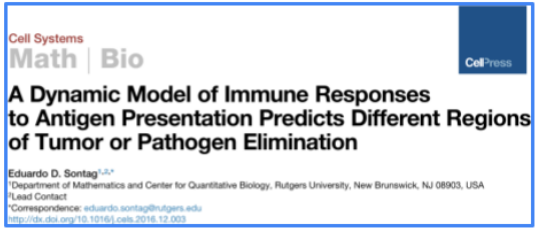
Kaitlyn E Johnson[1], Grant R Howard[1], Daylin Morgan[1], Eric A Brenner[1,2], Andrea L Gardner[1], Russell E Durrett[1,2], William Mo[1], Aziz Al'Khafaji[1,2], Eduardo D Sontag[3,4,5], Angela M Jarrett[6,7], Thomas E Yankeelov[1,6,7,8,9,10] and Amy Brock[1,2,6,11]

npj | systems biology and applications

Article | Open access | Published: 08 January 2026

Delaying cancer progression by integrating toxicity constraints in a model of adaptive therapy

Jana L. Gevertz, Harsh Vardhan Jain, Irina Kareva, Kathleen P. Wilkie, Joel Brown, Yitong Pepper Huang, Eduardo Sontag, Vladimir Vinogradov & Mark Davies



Cell Systems
Math | Bio

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A Dynamic Model of Immune Responses to Antigen Presentation Predicts Different Regions of Tumor or Pathogen Elimination

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http://dx.doi.org/10.1016/j.cels.2016.12.003

frontiers in Immunology

ORIGINAL RESEARCH
published: 28 January 2019
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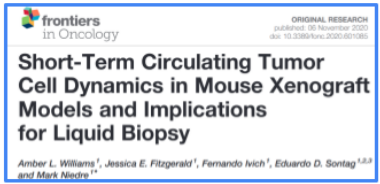
Immunobiochemical Reconstruction of Influenza Lung Infection—Melanoma Skin Cancer Interactions

*Evgeni V. Nikolaev[1,2], Andrew Zloza[3,4] and Eduardo D. Sontag[4,6,7]**



frontiers in Oncology

ORIGINAL RESEARCH
published: 06 November 2020
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Short-Term Circulating Tumor Cell Dynamics in Mouse Xenograft Models and Implications for Liquid Biopsy

*Amber L. Williams[1], Jessica E. Fitzgerald[1], Fernando Ivich[1], Eduardo D. Sontag[1,2,3] and Mark Niedre[1]**

Bulletin of Mathematical Biology (2025) 87:85
https://doi.org/10.1007/s11538-025-01455-9

Society for Mathematical Biology

Quantitative Pharmacology Methods for Bispecific T Cell Engagers

Mahdiar Sadeghi[1,2] · Irina Kareva[2,3] · Gleb Pogudin[4] · Eduardo D. Sontag[1,3,5]

PNAS

RESEARCH ARTICLE | SYSTEMS BIOLOGY PHYSICS

PNAS 2022 Vol. 119 No. 42 e2210844119

Epigenetic factor competition reshapes the EMT landscape

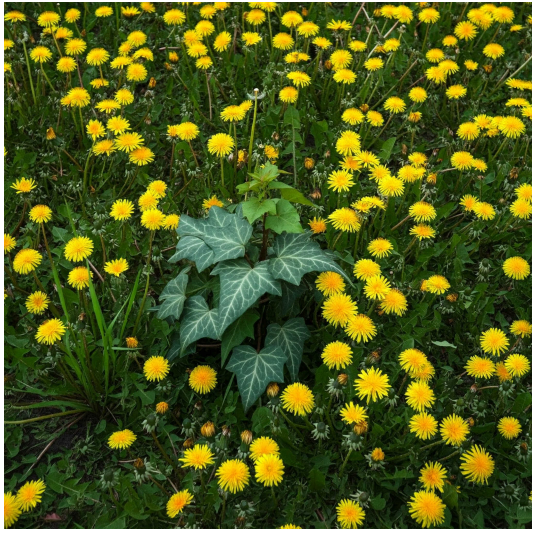
M. Ali Al-Radhawi[a,b], Shubham Tripathi[b,c,d], Yun Zhang[e,f], Eduardo D. Sontag[e,g,h,1], and Herbert Levine[b,d,g,1]

Outline

- Heterogeneity: coexisting resistant and fragile populations
- Pre-existent, spontaneous, or induced resistance
- A mathematical model of spontaneous vs. induced evolution of resistance
- Effect of induction on therapy outcome
- Some data fits
- A modified mathematical model and data fits
- Summary
- Resistance through immune damage

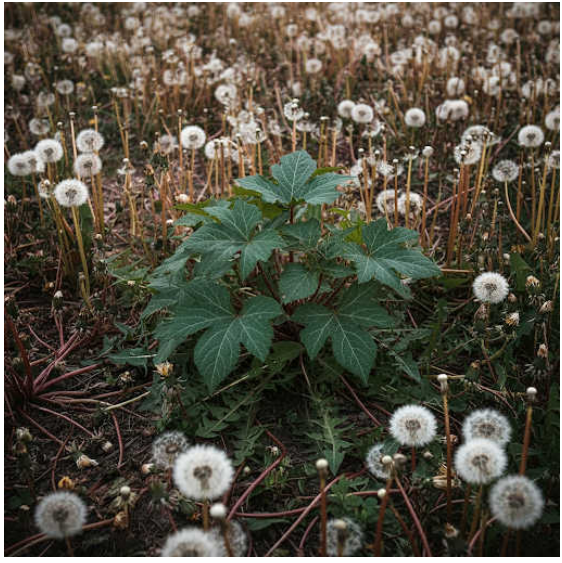
Robustness often incurs extra costs

fragile (and less resource-consuming) dandelions outcompete more robust weed



Chemical warfare!

(Temporary) success . . .



. . . but now the hard-to-kill weed can grow uncontrollably

“that which does not kill us makes us stronger” (Nietzsche)

What to do?

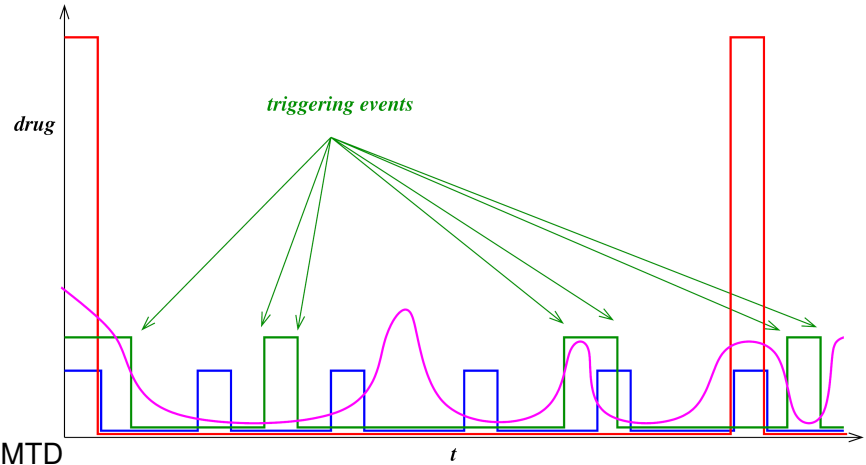
treatment holidays: don't kill all the fragile individuals / plants / cells / . . .

e.g. advantages:

- fragile population (more fit if no treatment) keeps resistant population in check
- immune system regeneration if damaged by treatment

much research in this area, including preclinical and even clinical trials

MTD / metronomic / adaptive / full feedback strategies



- red: MTD
- blue: metronomic
- green: adaptive (triggering events in adaptive: volume high/low, toxicity, . . .)
- magenta: full feedback

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Resistance is a major contributor to cancer recurrence

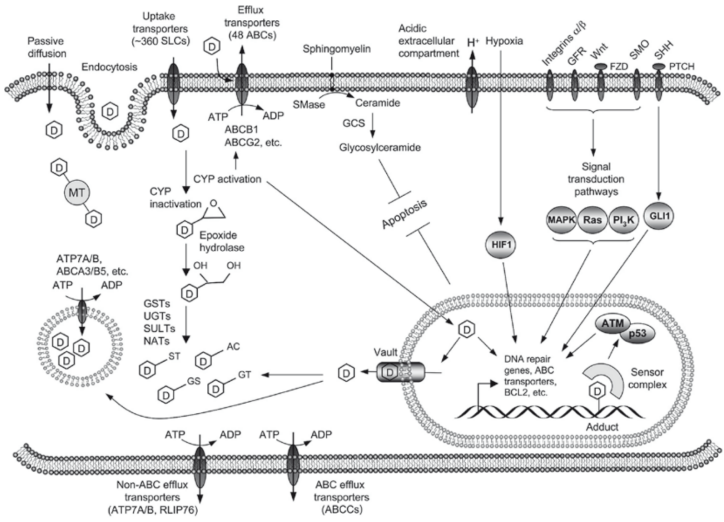
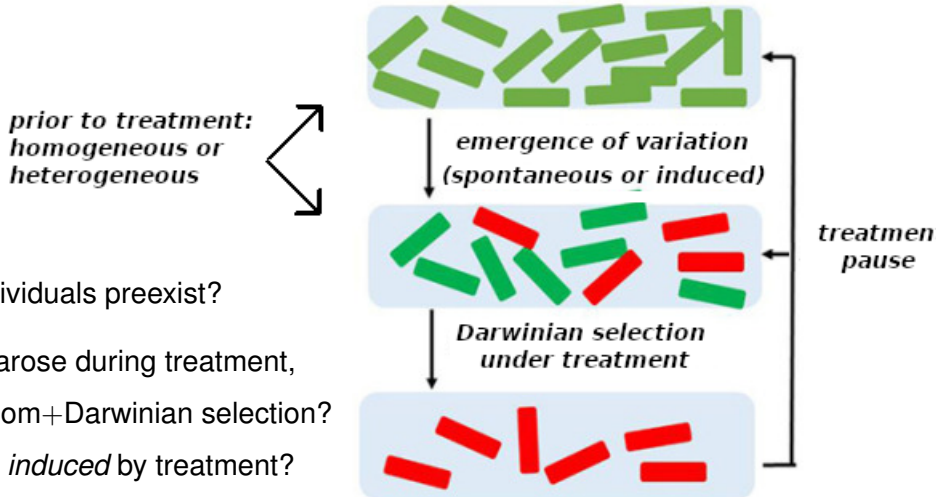


figure from Gillet et al., 2010

"90% mortality of cancer patients is attributed to drug resistance" (Bukowski at al., 2020)

Preexisting or during treatment? Darwinian or Lamarckian?



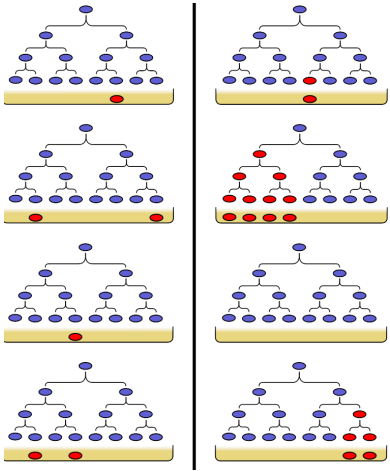
did resistant individuals preexist?

if not, and they arose during treatment,

is variation random+Darwinian selection?

or was variation *induced* by treatment?

Classical: Luria-Delbrück (bacteriophages & bacteria, 1943)



(figure modified from wikipedia)

first: parallel cultures in non-selective medium,

then: put in selective medium (bacteriophages)

left: mutations happen *during* treatment:

low variability in # of mutants ($\approx$ Poisson)

right: mutations happen *before* treatment:

high variability in # mutants

their “fluctuation experiment” showed *preexisting* resistance

Selection paradigm

random changes conferring resistance (“evolutionary rescue”) can be:

- genetic (mutation, gene amplification, chromosome translocations, . . .
- epigenetic (DNA methylation, histone modifications, . . .)

and can be:

- pre-existing (“standing variation”)
- arising during treatment (*de novo*),

both of these are *Darwinian selection* of resistant subpopulations during treatment

here we focus on a complementary aspect: *generation of variation*

Drug-induced resistance

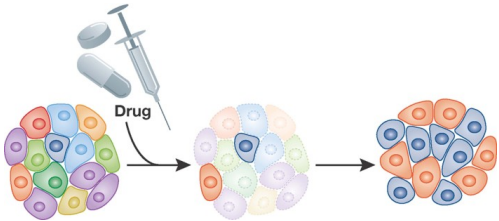
induced *genetic*: cytotoxic chemotherapies increase mutation rates

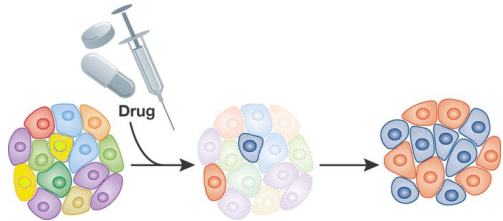
- nitrogen mustards: base substitutions, chromosome rearrangements
- Topoisomerase II inhibitors: chromose translocations
- antimetabolites: double stranded breaks, chromosome aberrations

induced *epigenetic phenotypic*: gene silencing, feedback loops, over-expression

- through DNA methylation, histone modifications, ...
- phenotypic state transitions in response to external cues (radiation, chemotherapy)
- often: rapid, dose dependent, reversible

So (at least) three possibilities



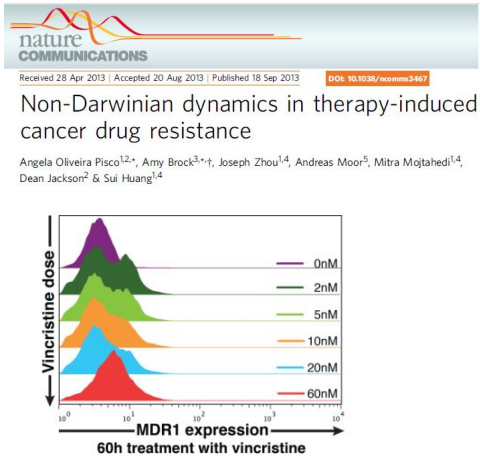


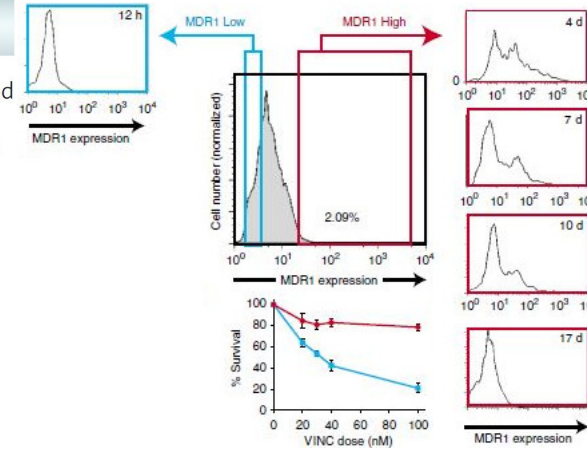
- *pre-existing* resistant clones:
  selected during therapy

- *spontaneously acquired:*
  random variations during therapy
- *induced acquired:*
  drug *causes* resistant variation to arise

of course, combinations of mechanisms likely as well

Drug-induced phenotype switching & drug resistance





heterogeneous population mix when no drug & under different drug doses

HL60 Leukemic cells, 1-2 day w/chemo vincristine, dose-dependent MDR1 resistance induced

. . . but distribution repopulated after $\approx$ 2 weeks in absence of drugs

Pisco et al. paper:

”tumour cells within a clonal population spontaneously switch between several (meta)stable attractor states, which represent different developmental states, including mesenchymal, epithelial, as well as cancer stem-cell-like states”

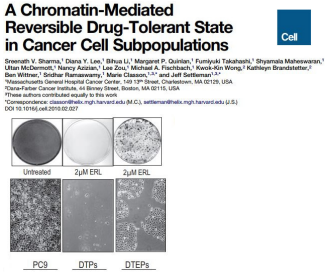
“stochastic non-genetic phenotype switching can act as a source of random variability—the substrate for Darwinian selection; cells that by chance occupy states that are more resilient to cytotoxic stress, including therapy-induced cytotoxicity, can be transiently selected for during treatment”

(but) “induction of attractor state switching by external signals opens the possibility for a Lamarckian scheme of evolution; a perturbation by cytotoxic agents may ‘instruct’ the cell to enter an attractor state that confers the stem-like, more stress-resistant phenotype”

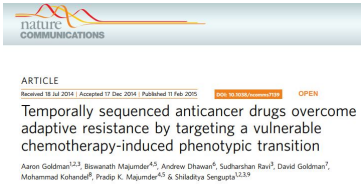
“we show by quantitative measurement and modelling that appearance of MDR1-positive cells 1–2 days after treatment with vincristine (VINC) is predominantly mediated by cell-individual induction of MDR1 expression and not by the selection of MDR1-expressing cells”

“appearance of multidrug resistance in HL60 leukemic cells following treatment with vincristine is not explained by Darwinian selection but by Lamarckian induction”

Other e.g.'s of drug-induced resistance

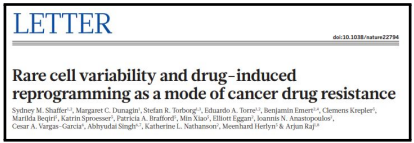


lung adenocarcinoma cell line (NSCLC, PC9)
treated with erlotinib (RTK inhibitor)
drug-tolerant persisters (DTPs) arise
reversal to drug sensitivity upon drug removal (days)



explants from breast cancer biopsies
treated w/taxanes (docetaxel)
dose-dependent transition towards
$CD44^{Hi}CD24^{Hi}$ expression status
alleviated by immediate treatment with SFK inhibitors

Other e.g.'s of drug-induced resistance

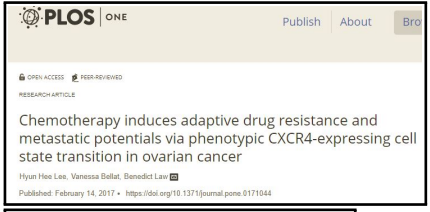


LETTER

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[1,2], Eduardo A. Torre[1,2], Benjamin Emert[1,2], Clemens Krepler[3], Marilda Beqiri[3], Katrin Sproesser[3], Patricia A. Brafford[3], Min Xiao[3], Elliott Eggan[3], Ioannis N. Anastopoulos[3], Cesar A. Vargas-Garcia[4], Abhyudai Singh[1,4], Katherine L. Nathanson[3], Meenhard Herlyn[3] & Arjun Raj[1,2]



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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

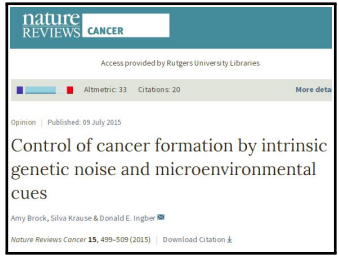
Anna C. Obenauf, Yilong Zou, Andrew L. Ji, Sakari Vanharanta, Weiping Shu, Hubing Shi, Xiangju Kong, Marcus C. Bosenberg, Thomas Wiesner, Neal Rosen, Roger S. Lo & Joan Massagué

Nature **520**, 368–372 (16 April 2015)

doi:10.1038/nature14336

Received: 26 August 2014

Accepted: 12 February 2015



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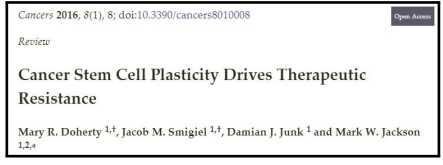
Opinion | Published: 09 July 2015

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,*]

Outline

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Differentiating selection vs. induction+selection

experimental evidence suggests induction plays a role in drug resistance

yet hard to differentiate experimentally *selection* vs. *induction*+selection

can mathematical modeling help?

one approach: precisely define and characterize the separate phenomena

- discover *qualitative* differences between origins of resistance
- possibly even suggest experiments to determine rate
- hope: suggest treatment protocols based on computed rate

references for results (+ unpublished):

- Greene, Gevertz, EDS, ASCO Clinical Cancer Informatics 2019
- Gevertz, Greene, EDS, biorXiv 2019 (otherwise unpublished)
- Greene, Sanchez-Tapia, EDS, Frontiers BioE & Biotech 2020
- Gevertz, Greene, Prosperi, Comandante-Lou, EDS, npj Systems Biology Appl 2025

Mathematical model

assume both spontaneous and induced resistance can happen:

$$\begin{aligned}\frac{dS}{dt} &= r\left(1-\frac{V}{K}\right)S - (\epsilon+\alpha u(t))\,S - du(t)S + \gamma R\\ \frac{dR}{dt} &= r_R\left(1-\frac{V}{K}\right)R + (\epsilon+\alpha u(t))\,S - d_R u(t)R - \gamma R\end{aligned}$$

where:

$$S := \text{sensitive (wild-type) cells},\ R := \text{resistant cells},\ V := S+R$$

- rescale to $K = 1$
- $u(t) =$ treatment (control), "log-kill"
- spontaneous phenotype switching: terms ϵS and γR
- rate of induction proportional to dosage: $\alpha u(t) S$
- competitive inhibition equal among all compartments
- $d_R < d$, $r_R < r$

Identifiability

parameter α may have large impact on treatment outcome

is it theoretically possible to **identify** the α value?

(from experiments in response to various inputs $u(t)$)

ideal scenario: can observe (at any time t) total tumor volume

$$V(t) = S(t) + R(t)$$

(not $S(t)$ and $R(t)$ individually; assuming $R(0) = 0$ for simplicity)

Theorem: System is structurally identifiable.

in particular, α is identifiable

so the model is a nontrivial extension of the no-induction case

Treatment evaluation

asymptotically all trajectories approach $(S, R) = (0, 1)$ (treatment fails)

but transient dynamics may be very different for different protocols ("controls")

- utilize competition to extend time so that volume $<$ critical size
- note: therapy has contradictory effects (even when $\alpha = 0$: competition if $K < \infty$)

metric to rank therapies: maximize t_c so that

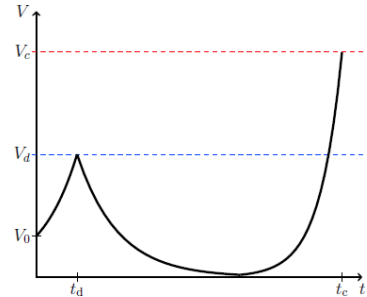
$$V(t) := S(t) + R(t) \ \leq \ V_c \text{ for all } t \leq t_c$$

first simplify:

- $d_R = 0$, i.e. complete resistance
- $\gamma = 0$, i.e. no $R \to S$

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

$V_d =$ detection threshold, $V_c =$ critical threshold



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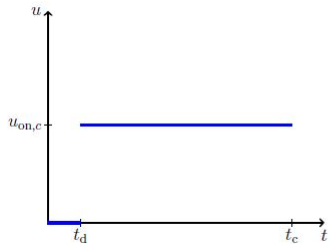
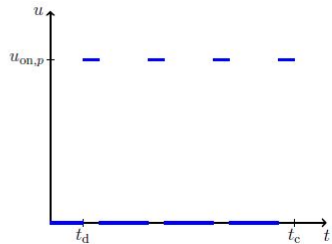
Effect of phenotype switching on therapy outcome

fundamental question:

what impact does induction (α) have efficacy?

for example, let's compare outcomes of continuous vs pulsed treatment protocols:



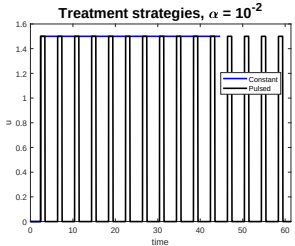


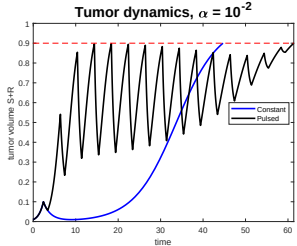
for two different scenarios:

- $\alpha = 0$ (no drug-induced competition)
- $\alpha > 0$ (there's drug-induced competition)

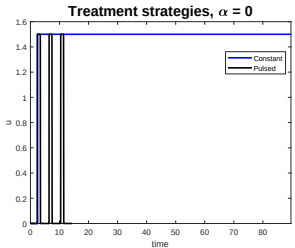
restated question: which is better, based on α?

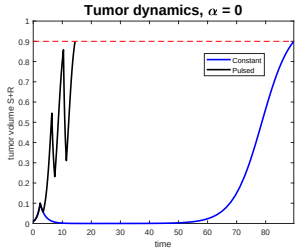
Pulsed vs. constant better depending on induction or not





pulsed better when α_i=10^{-2}
$t_{c,p} - t_{c,c} \approx 19$ (induced)





constant better when α=0
$t_{c,c} - t_{c,p} \approx 88$ (spontaneous)

(see paper for parameters)

More generally, consider optimal control problem

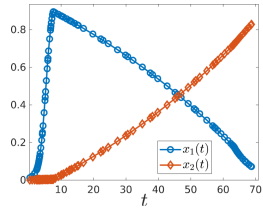
simulations indicate that more switching better as $\alpha \uparrow$

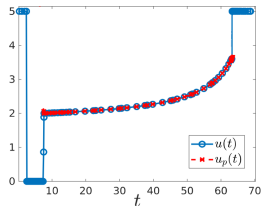
- formalize as a constrained optimal control problem
- develop theory (very technical)
- conclude: for $\alpha = 0$ optimal is bang-bang + *"boundary slide"*
- no singular (interior) trajectories can exist
- as $\alpha \neq 0$ increases, singular extremals exist, but never optimal (Legendre-Clebsch; compare times by "clock" exterior form) instead: chattering-like switching possible along extremal

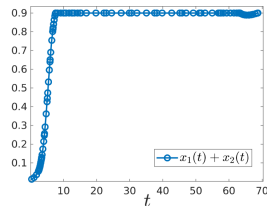
see paper for detailed optimal control analysis via PMP and Lie theory

"the oncologist has the advantage over the tumor of seeing the future and strategizing" (Bob Gatenby)

Numerical example of optimal control







sensitive (x_1)
and resistant (x_2)
temporal dynamics

control structure of form YXu_pY
X, Y are "bang" controls
($u = 0$ and $u = M$),
"sliding" $u{=}u_p$
keeps line $V{=}V_c$ invariant

volume

(see paper for parameters; here $\alpha = 0.005$)

control switches:

- maximum dosage
- no treatment (bang-bang)
- "sliding trajectory"
- maximum dosage at end

Summary of theory results

let us write:

"X" for trajectores when no drug is given ($u = 0$)

"Y" for maximal-dose trajectories ($u = M$)

"U" for a time-varying dose that allows "sliding" along $S + R = V_c$

only concatenations of trajectories that can be optimal:

$$\underbrace{YX \cdots YX}_{n \text{ iterates}} YUY \qquad \text{(for some } n \geq 1\text{)}$$

(some of the segments may not be there; e.g. YXU possible)

for $\alpha = 0$, necessarily $n = 1$: $YXYUY$

moreover, theory suggests $\frac{\partial n}{\partial \alpha} > 0$, at least for small α

Flavor of one part of proof

$$
\begin{aligned}
A(x) &:= \begin{pmatrix} f(x) & g(x) \end{pmatrix} = \begin{pmatrix} (1-(S+R)-\epsilon)S & -(\alpha+d)S \\ p_r(1-(S+R))R+\epsilon S & \alpha S \end{pmatrix} \\
\kappa(x) &:= 1-(S+R) \\
\gamma(x) &:= -\frac{(\alpha+d)S^2}{\det A(x)}\,(aS+bR-c) \\
\beta(x) &:= \frac{S^2}{\det A(x)}\Big(\alpha(1-p_r)\kappa(x)(\kappa(x)-\epsilon)+\epsilon d(S+p_rR+\kappa(x)-\epsilon)\Big) \\
a &:= \alpha\left((1-p_r)+\frac{d}{\alpha+d}\right) \\
b &:= \alpha(1-p_r)+dp_r \\
c &:= \alpha(1-p_r)+\epsilon d \\
X(x) &:= f(x) \\
Y(x) &:= f(x)+Mg(x) \quad (U=[0,M])
\end{aligned}
$$

The only possible interior singular trajectory is not optimal

line segment $\bar{\mathcal{L}} \subset \mathcal{L} = \{aS + bR = c\}$ is a singular arc
corresponding control that keeps it invariant:

$$\begin{aligned} u(x) &= M\frac{L_X\gamma(x)}{L_X\gamma(x) - L_Y\gamma(x)} \\ &= \frac{\kappa\big(x(t)\big)\Big(aS(t) + p_r bR(t)\Big) + \epsilon(b-a)S(t)}{2\alpha(1-p_r)dS(t)} \end{aligned}$$

but this the singular arc is suboptimal: it is “too fast”:

to see this, introduce one-form (“clock form”):
unique $\omega \in (T\Omega)^*$ such that

$$\omega_x(f(x)) \equiv 1\,,\ \omega_x(g(x)) \equiv 0$$

wich can be computed explicitely:

$$\omega_x = \frac{g_2(x)dx^1 - g_1(x)dx^2}{\det(f(x), g(x))}$$

Non-optimality, ctd.

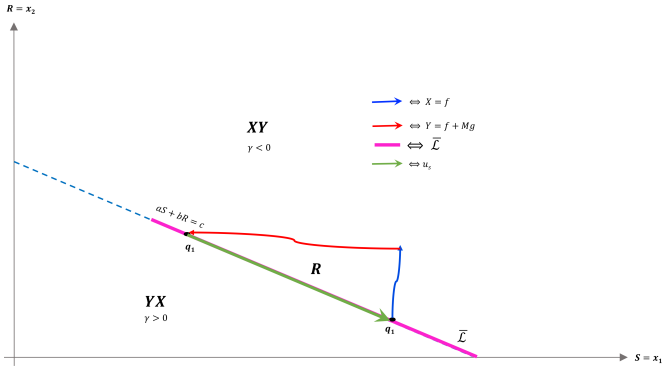
along any controlled trajectory (x, u) defined on $[t_0, t_1]$,

the integral of ω computes the time $t_1 - t_0$:

$$\begin{aligned}
\int_x \omega &= \int_{t_0}^{t_1} \omega_{x(t)}(\dot{x}(t))\,\mathrm{d}t \\
&= \int_{t_0}^{t_1} \omega_{x(t)}(f(x(t)) + u(t)g(x(t)))\,\mathrm{d}t \\
&= \int_{t_0}^{t_1} \omega_{x(t)}(f(x(t))\,\mathrm{d}t + \int_{t_0}^{t_1} u(t)\omega_{x(t)}(g(x(t)))\,\mathrm{d}t \\
&= \int_{t_0}^{t_1} \mathrm{d}t \\
&= t_1 - t_0
\end{aligned}$$

Non-optimality, ctd.

if q_1 and q_2 are sufficiently close, $\exists$ unique XY trajectory connecting them



let $\tau :=$ time spent along singular arc, $s :=$ time along X, $t :=$ time along Y arc

will show $\tau < s + t$, so time along singular arc shorter than along XY trajectory, so singular arc cannot be optimal (we are maximizing time)

Non-optimality, ctd.

curve $\Delta :=$ traverse X, Y positively, then singular arc negatively; $R :=$ its interior

by Stokes' Theorem:

$$s + t - \tau = \int_{\Delta} \omega = \int_{R} d\omega$$

where the two-form is:

$$d\omega \; = \; -\frac{\gamma}{\det(f, g)}$$

determinant is everywhere positive and R lies entirely in $\gamma < 0$,
and integral on the RHS is positive, so:

$$\tau \; < \; s + t$$

as claimed, QED

Outline

- Heterogeneity: coexisting resistant and fragile populations
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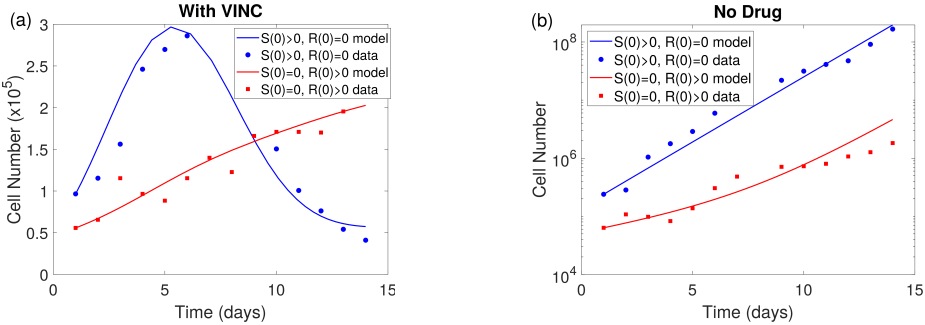
Model extremely simple, yet good fits to one set of data



left: with drug, starting with $S(0) > 0$ (blue) or $R(0) > 0$ (red)

right: without drug, using obtained parameters from left (no refit)

(added a PK-type term, not shown; omitted two obvious outliers)
(Pisco . . . Huang, "Non-Darwinian dynamics in therapy-induced cancer drug resistance," Nat Comm 2013: vincristine treated HL60 leukemic cells; resistance = MDR1 expression)

Remarkable prediction: repopulation experiments

start with a certain number of resistant cells $R(0)$, and $S(0)=0$

(as in Pisco et al. repopulation experiment)

our model predicts (with no additional fitting)

that population composed of 97.1% sensitive cells after 17 days

in *surprising agreement* with experimental data that gave 97.9%

(at same cutoff value for MDR1 expression)

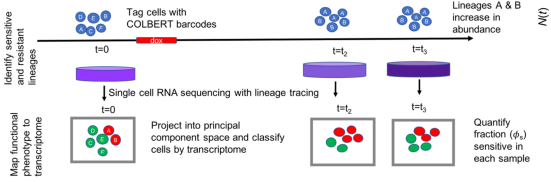
Follow-up: merging volume and resistance-labeled data

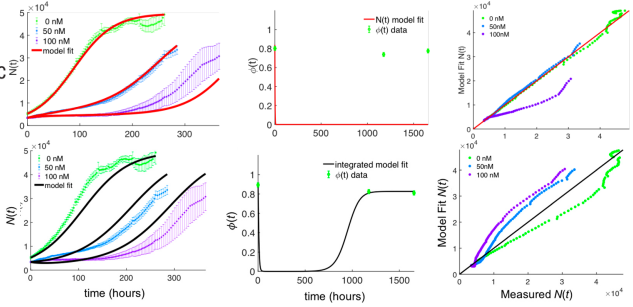
Physical Biology

Phys. Biol. **18** (2021) 016001

Integrating transcriptomics and bulk time course data into a mathematical framework to describe and predict therapeutic resistance in cancer

Kaitlyn E Johnson[1], Grant R Howard[1], Daylin Morgan[1], Eric A Brenner[1,2], Andrea L Gardner[1], Russell E Durrett[1,2], William Mo[1], Aziz Al'Khafaji[1,2], Eduardo D Sontag[3,4,5], Angela M Jarrett[6,7], Thomas E Yankeelov[1,6,7,8,9,10] and Amy Brock[1,2,6,11]





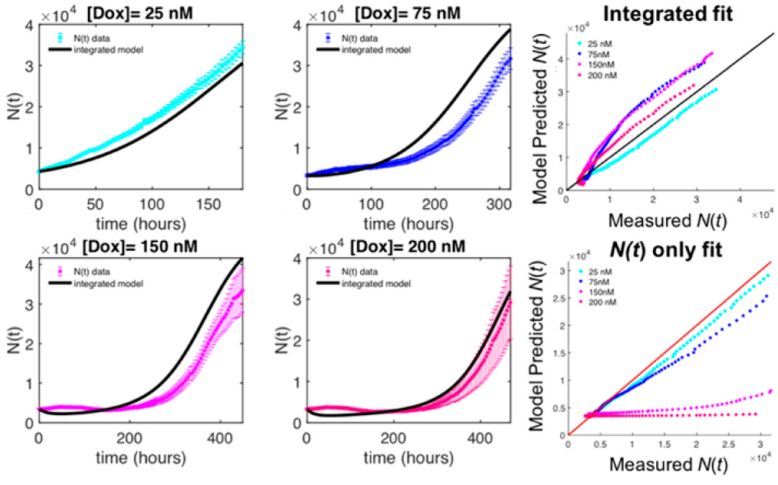
top: fit using only total cell number
bottom: using cell number and three ϕ's

human breast cancer cell line MDA-MB-231, doxorubicin

basically same model (w/$\epsilon, \gamma = 0$) and $u(t) = aUe^{-bt}$, where U = dose (doxorubicin decays)

use $t = 0$, $t = t_f$ DNA barcoded data and ML on scRNAseq data to label "resistant" fractions

Testing on dose data not used for training



reasonable predictions on dosages not trained on

better fits than with model that only used total cell data

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Recap and new work

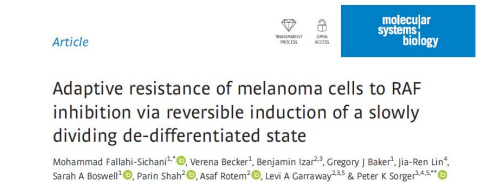
- formulated a simple model based on the most intuitive assumptions
- the type of treatment matters, depending on the level of induction
- can identify parameters in theory
- but does it fit richer data sets?
- induction rate $\propto u(t)S(t)$ too simple: try non-parametric fit
- excellent fits, parameters practically identifiable (. . . though not biologically sensible)
- found different behavior of induction on $u \rightsquigarrow$ different"optimal"

shows the importance of using phenomenological models and data:

this original model still important: started from it

of course, result very dependent on this data set
(type of cancer, treatment, etc.)

New dataset to validate/refine mathematical model

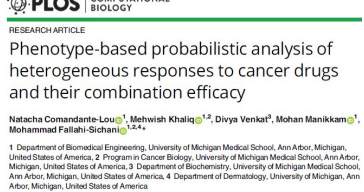


Article

molecular systems biology

Adaptive resistance of melanoma cells to RAF inhibition via reversible induction of a slowly dividing de-differentiated state

Mohammad Fallahi-Sichani[1,*], Verena Becker[1], Benjamin Izar[2,3], Gregory J Baker[1], Jia-Ren Lin[4], Sarah A Boswell[1], Parin Shah[2], Asaf Rotem[2], Levi A Garraway[2,3,5] & Peter K Sorger[1,4,5,**]



PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Phenotype-based probabilistic analysis of heterogeneous responses to cancer drugs and their combination efficacy

Natacha Comandante-Lou[1], Mehwish Khaliq[1,2], Divya Venkat[3], Mohan Manikkam[1], Mohammad Fallahi-Sichani[1,2,4]*

1 Department of Biomedical Engineering, University of Michigan Medical School, Ann Arbor, Michigan, United States of America, 2 Program in Cancer Biology, University of Michigan Medical School, Ann Arbor, Michigan, United States of America, 3 Department of Biochemistry, University of Michigan Medical School, Ann Arbor, Michigan, United States of America, 4 Department of Dermatology, University of Michigan, Ann Arbor, Michigan, United States of America

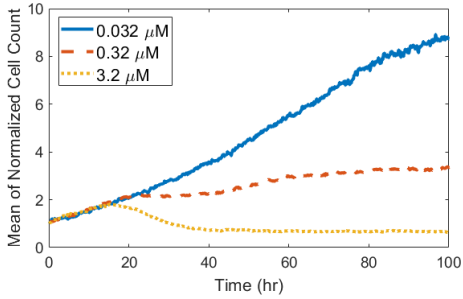
small-molecule BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) used in melanoma treatment induce resistance through reprogramming and activation of feedback loops

data set we use: COLO858 melanoma cells (BRAFV600E mutation) treated *in vitro* with vemurafenib at doses (μM): 0.032/0.1/0.32/1/3.2

(Fallahi-Sichani et al., 2017; Comandante-Lou et al., 2020)

observations of resistance even after low doses of vemurafenib reversed “non-sensitive” cells in fresh media; resistance re-induced in drug culture

Need to modify model:



responses indistinguishable for $\approx$ 24 hours suggests delay in drug action

(drug uptake? target engagement? apoptotosis initiation? cell-cycle?)

$\rightsquigarrow$ modify model: delay in drug-induced cell kill & resistance

Model with explicit activation delay

$u =$ drug concentration in *in vitro* experiment

$v =$ phenotypic effect of the dosage on cell kill and induction rates

assume dynamics of v track u with delays:

$$\begin{aligned}
\dot{S} &= r_S(u(t))S - v_{d,S}(t)S - v_\alpha(t)S \\
\dot{R} &= r_R(u(t))R + v_\alpha(t)S - v_{d,R}(t)R \\
\dot{v}_{d,S} &= \gamma_1(d_S(u(t)) - v_{d,S}) \\
\dot{v}_{d,R} &= \gamma_1(d_R(u(t)) - v_{d,R}) \\
\dot{v}_\alpha &= \gamma_2(\alpha(u(t)) - v_\alpha)
\end{aligned}$$

"effective apoptosis and induction rates" $v_{d,S}$, $v_{d,R}$, and v_α

approach asymptotic values at rate determined by γ_i

no carrying capacity: makes little difference in this *in vitro* setting

Simplify for constant doses

data: constant doses $u(t) \equiv u$ (later time-varying, for optimal control problem)

so can solve tracking equations, and just write simplified model:

$r_S := r_S(u), r_R := r_R(u), d_S := d_S(u), d_R := d_R(u), \alpha := \alpha(u)$

assuming $v_{d,S}(0) = v_{d,R}(0) = v_\alpha(0) = 0$

final model:

$$\begin{aligned} \dot{S} &= r_S S - d_S(1 - e^{-\gamma_1 t})S - \alpha(1 - e^{-\gamma_2 t})S \\ \dot{R} &= r_R R + \alpha(1 - e^{-\gamma_2 t})S - d_R(1 - e^{-\gamma_1 t})R \end{aligned}$$

take $\gamma_1 = \gamma_2 = 0.01$ (roughly 50% of maximal effect at 72 hours)

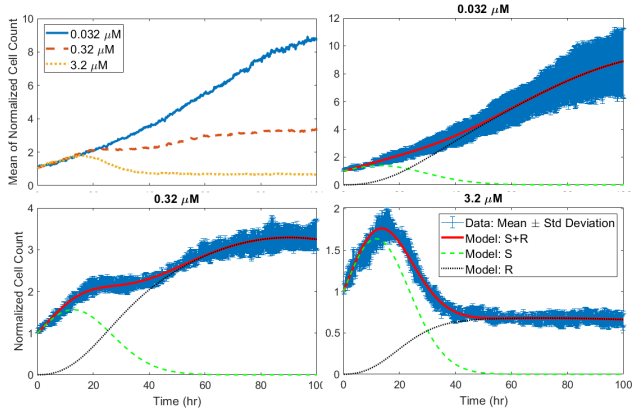
and fit all other parameters

(**small theorem:** parameters structurally identifiable)

data available is at doses 10^d with $d = -1.5, -1, -0.5, -1, 0.5$

keep intermediate red ones for validation, fit at three other doses

Model fits using 3 doses (independent fits)



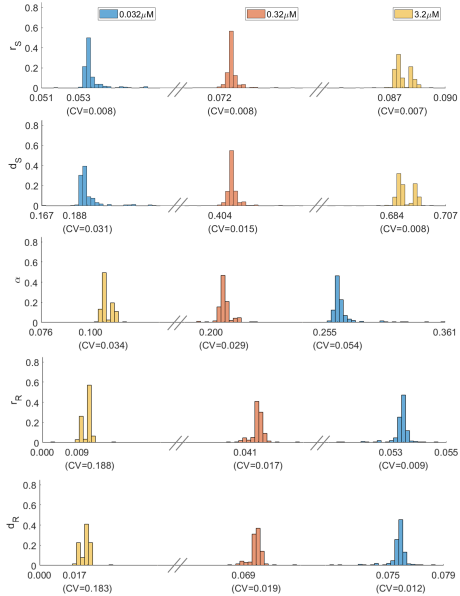
standard deviations (four replicates) are shown in blue in (b)-(d)

excellent fits

& time course predictions for sensitive and resistant subpopulations

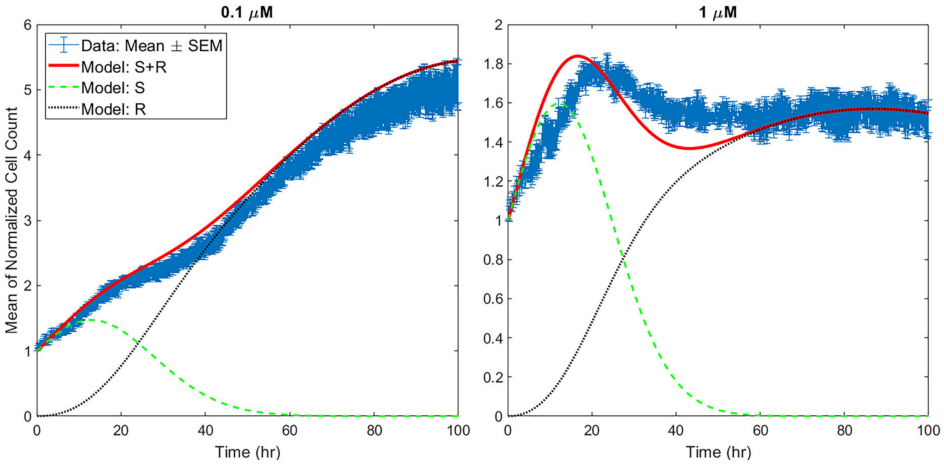
use ℓ^1 loss on means of four replicates, (Sobol-sequence) multi-start *fmincon* in MATLAB

Practical identifiability: parameters within 5% of optimal fit



Validation on unused doses

linearly interpolating parameters, good prediction:



A finer-grained three-population model

experimental data suggests subpopulation of quiescent cells distinct from resistant subpopulation

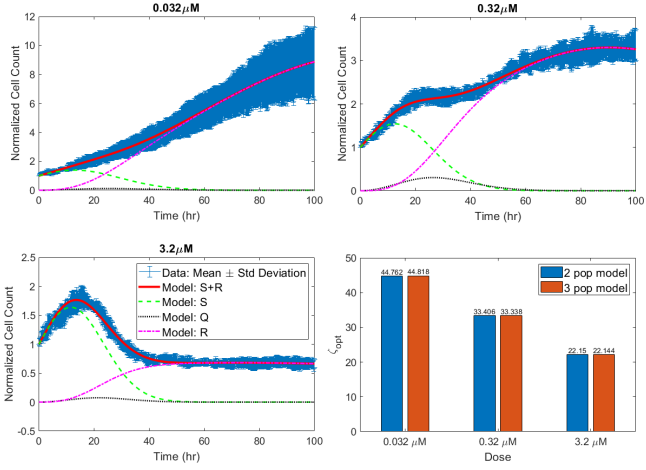
does a 3-population model better describe experimental data?

$$\begin{aligned}\dot{S} &= r_S S - d_S(1 - e^{-\gamma_1 t})S - q(1 - e^{-\gamma_2 t})S \\ \dot{Q} &= q(1 - e^{-\gamma_2 t})S - \beta Q \\ \dot{R} &= \beta Q + r_R R - d_R(1 - e^{-\gamma_1 t})R\end{aligned}$$

(must pass through the quiescent state $Q =$ on road to resistance)

also excellent fits to the data, but no real improvement!:

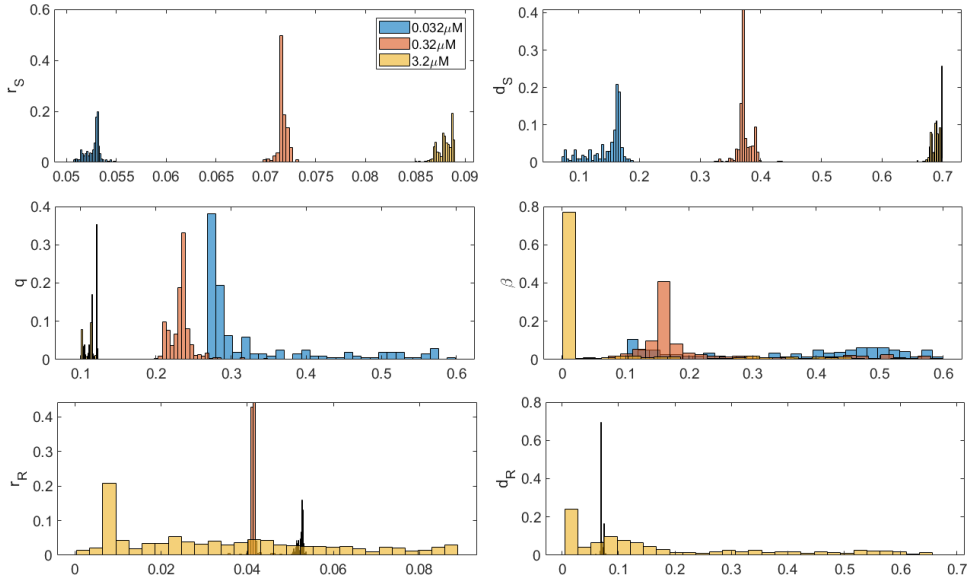
No improvement from three-population model



optimal value of the cost function doesn't change much;

in addition, model parameters become practically non-identifiable:

Wide dispersion of optimal parameters in 3-pop model



An optimal control problem

fix total AUC: 100 μM, and minimize size at $t = 100$

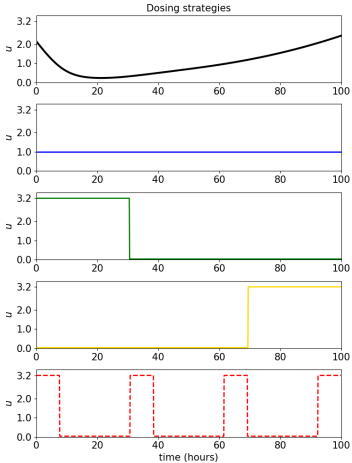
compare:

- optimal control
- constant intermediate dose
- “MTD” at onset of therapy
- “MTD” at end of therapy
- “bang-bang” metronomic

note:

optimal comparable to constant (idealized “metronomic”)

“MTD” far from optimal



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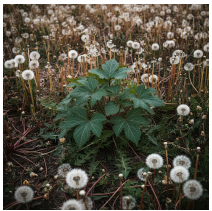
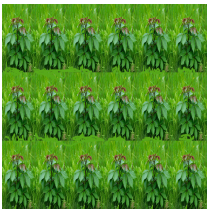
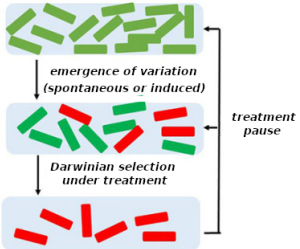
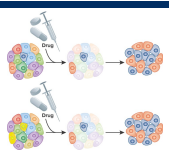
Killing the most sensitive not such a good idea



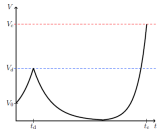




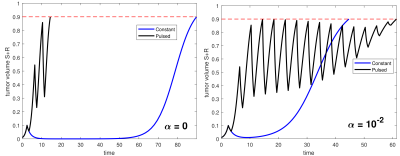
Three, not two, possibilities – consequences, models, fits



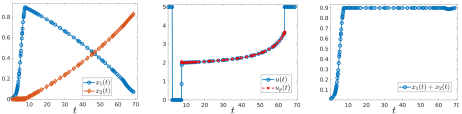
- pre-exist, selected during therapy $\dot{S} = r\left(1 - \frac{V}{K}\right) S - (\epsilon + \alpha u(t))\, S - du(t)S + \gamma R$
- random variations during therapy
- induced variation by therapy $\dot{R} = r_R\left(1 - \frac{V}{K}\right) R + (\epsilon + \alpha u(t))\, S - d_R u(t) R - \gamma R$



spontaneous: constant protocol better
induced: pulsed protocol better

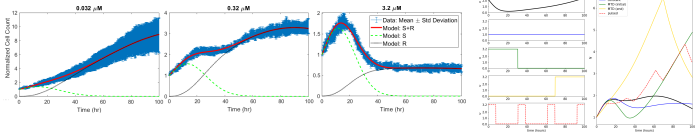


optimal:
- maximum dosage
- no treatment (bang-bang)
- "sliding trajectory"
- maximum dosage at end



- data fits
- identifiability
- Lie-based optimal control theory
- DNA barcoding combinaton

new data, model:



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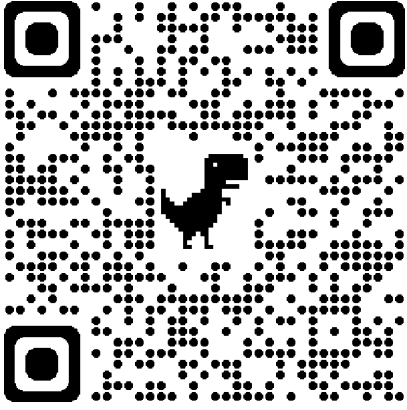

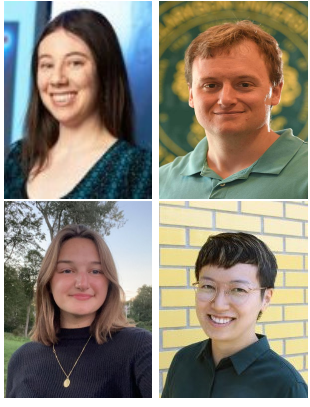

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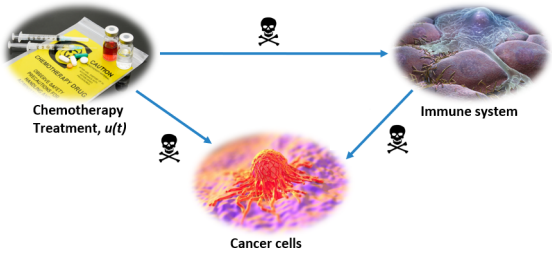
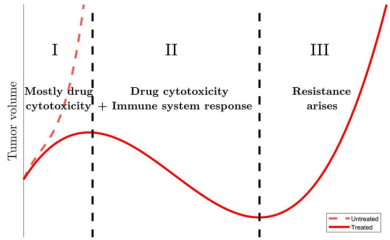
Delicate balances: cytotoxicity on immune components





drug attacks tumor . . . but negatively affects (certain) immune cells,

impairing immunogenic cell death $\rightsquigarrow$ long-term failure, rebound

ideally: balance drug-induced tumor cell kill vs immune damage

so two modes of cancer cell elimination can complement each other

our project: mathematical analysis of “metronomic” therapies

“Metronomic” therapy

high frequency, low dose: balance cytotoxicity and immunogenic cell death (ICD)

frontiers in Immunology

ORIGINAL RESEARCH
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Delicate Balances in Cancer Chemotherapy: Modeling Immune Recruitment and Emergence of Systemic Drug Resistance

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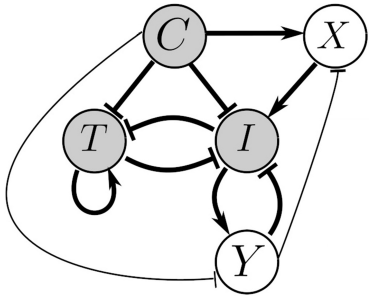
math models help tease-out effects from various players, suggest novel schedules

“toy” phenomenological model:
lumping several immunostimulatory and immunosuppressive processes

Variables in model



C :	Drug
T :	Tumor
I :	Immune Cells
X :	Immunostimulant
Y :	Immunosuppressant

thicker arrows: well-known effects, thinner: hypothesized, fit to data

experimental data fit:

volume growth curves in GL261 gliomas cells implanted in SCID mice

under varied-regimens metronomic cyclophosphamide chemotherapy

fitting *fixed* set of parameters, not adjusted for individuals or drug schedule

Equations

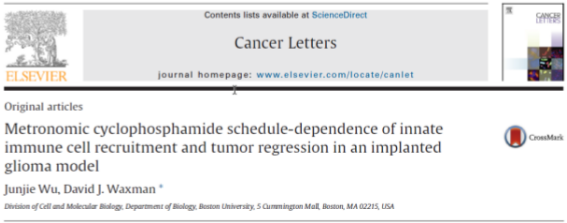
$$
\begin{aligned}
\frac{dC}{dt} &= u - \frac{k_1 C}{k_2 + C} \\
\frac{dT}{dt} &= k_a T - \frac{k_b C T}{k_c + T} - k_d T I \\
\frac{dI}{dt} &= X - k_e T I - k_f C I - k_g Y I - k_h I \\
\frac{dX}{dt} &= \frac{C}{1 + C/k_i} - k_j X - k_k X Y \\
\frac{dY}{dt} &= \frac{I}{1 + C/k_l} - k_m Y C
\end{aligned}
$$

tumor cells killed by drug $C(t)$ and immune cells $I(t)$
$-k_e T I$: tumor cells activate/inactivate immune response; fitting found inactivation (< 0)
immunosuppressive intermediate $Y(t)$ induced by I, cleared through interaction with drug
drug kills cytotoxic cells (e.g. NK, CD8+T) and immunosuppressive cells (e.g. MDSCs Tregs)
(note: carrying capacity never reached for humane reasons)

Data from Wu and Waxman 2016

GL261 glioma cells implanted in SCID mice,
then treated with cyclophosphamide (CPA)

Cyclophosphamide widely used to treat lymphoma, multiple myeloma, leukemia, ovarian, breast, small cell lung cancer, neuroblastoma, sarcoma, and autoimmune diseases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Original articles

Metronomic cyclophosphamide schedule-dependence of innate immune cell recruitment and tumor regression in an implanted glioma model

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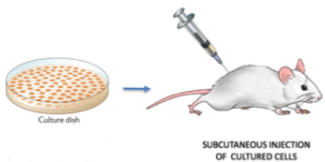
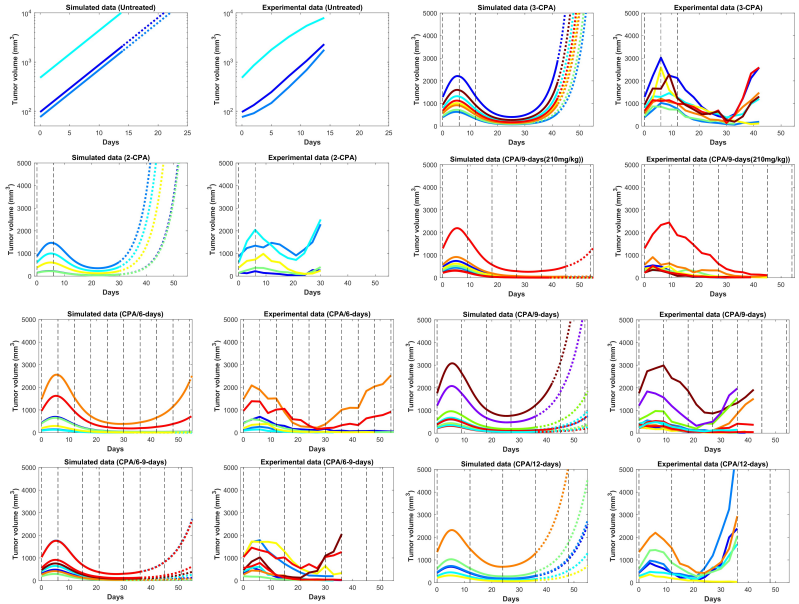


Mouse GL261 glioma cells were grown at 37°C
in a humidified 5% CO_2 atmosphere in RPMI-1640 culture

Tumor cells are then injected in **immune deficient scid mice**
(both T and B-cell deficient)

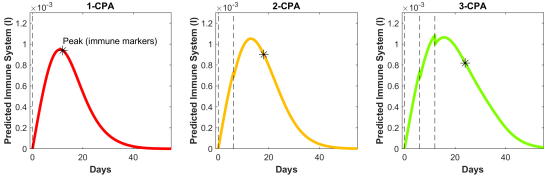
Regular dose is 140 mg CPA/kg-BW. In one case, at 9 days interval,
a dose of 210 mg/kg-BW is used

Model and data (common parameters, different treatments)

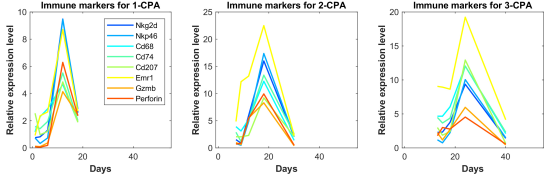


Mathematical predictions regarding the immune system

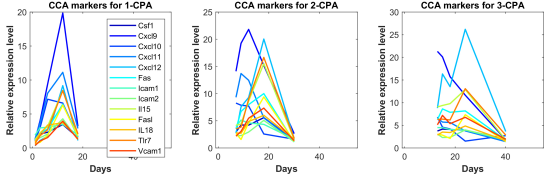
experimental immune data (from Wu/Waxman) *was not used in fitting*



model predictions



gene expression markers
for innate immunity cells
(macrophages, dendritic, NK)



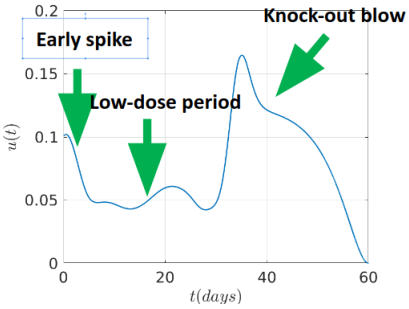
CCA =
chemokines,
cytokines,
adhesion molecules

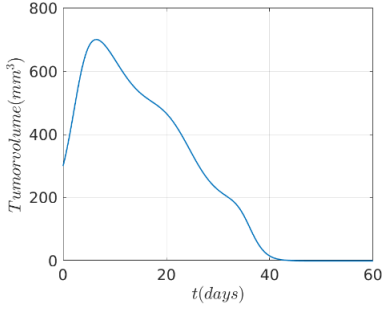
Next step: Optimal control

what about other metronomic therapies or even non-metronomic?

example:

$$\min T(t_{\text{FINAL}}) \quad \text{subject to } \dot{z} = f(z,u)\,, \int_0^{t_{\text{FINAL}}} u(s)\,ds \leq \text{dose}_{\text{max}}$$





[Background] Treatments in data, used for fits:

- 1-CPA, 2-CPA, 3-CPA:

1, 2 or 3 doses of CPA given 6 days apart; first dose on day 0

- CPA/6-days, CPA/9-days, CPA/12-days:

6, 9, or 12 days apart, respectively

- CPA/9days(210mg/kg):

210 mg/kg administered 9 days apart

- CPA/6-9days:

break of 6 days between 1sr and 2nd, break of 9 days until 3rd

[Background] Fits to data details

experimental growth curves from Wu/Waxman

initial values of states 0 except for tumor volume

using pooled mouse data for fitting, yet generally good fits

surprising that unique set population parameters captures qualitative and semi-quantitative behaviors,
for large set of different metronomic chemotherapy treatments
with induction of anti-tumor immune responses and drug resistance

[Background] Details on Wu/Waxman

tumors allowed to grow to 300 to 1000 mm^3,
then drug given on different metronomic schedules

tumor growth curves were reported for drug-free controls and:

- single CPA administration given on day 0 (1-CPA),
- two CPA treatments given on days 0 and 6 (2-CPA),
- three CPA treatments given on days 0, 6, and 12 (3-CPA)
- every 6, 9, 12 days (Q6D, Q9D, Q12D); alternating every 6 & 9

standard dose 140 mg CPA/kg-BW (body weight)
but 210 mg CPA/kg-BW Q9D (so same amount of drug as with Q6D)
to evaluate impact of schedule vs. total

reported relative gene expression levels for immune cell markers for NK and dendritic cells, and macrophages for 1-CPA, 2-CPA, 3-CPA

$n =$ 4-12 tumors per treatment group

[Background] More details on Wu/Waxman

greatest tumor burden reduction observed for Q6D

immune system: 6-12 days to significantly impact tumor growth:
so initial slowdown in tumor growth must be due to CPA

lower immune cell numbers after drug administration:
CPA cytotoxicty on immune cells

6-12 days post injection: increase in innate immune cells markers

strong correlation between loss of immune response / tumor escape

breaks in treatment $<$6 days $\rightsquigarrow$ worse performance (w/same AUC)

noted absence in immune recruitment if CPA given daily
one day after CPA, significant decrease in gene expression for
NK cells, DCs, and macrophages in TME

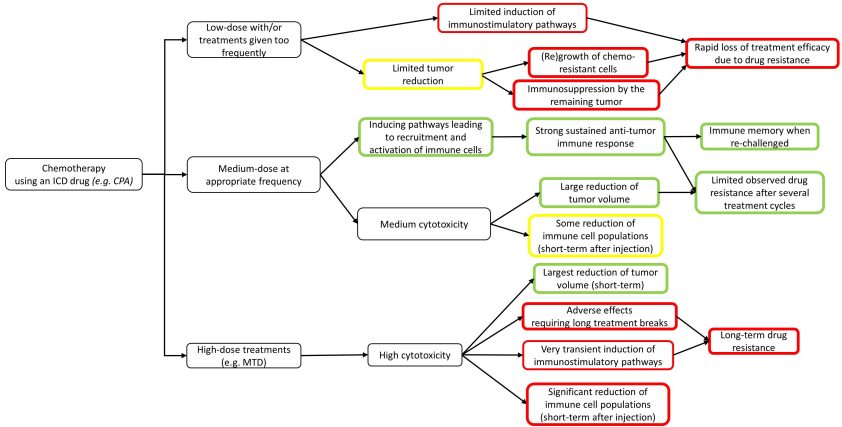
[Background] Chemo and tumor microenvironment

immune-related processes involve modifications of the TME by e.g.
increased acidity resulting from altered nutrient metabolism,
cytotoxic/regulatory immunity balance through tumor recruitment of immunosuppressive cells (Tregs, myeloid-derived suppressors)
M2 macrophages producing high levels of TGF-β, IL-10, vascular endothelial growth factor (VEGF), promoting tumor growth

immunosurveillance evaded by immunosuppressive cytokines, e.g. TGF-β suppress macrophages and monocytes

mitoxantrone, idarubicin, doxorubicin, cyclophosphamide, etc.
can induce immunogenic cancer cell death (ICD),
besides direct cancer cell cytotoxic effects,
by targeting components that regulate immune tolerance
cytotoxic effects on immunoregulatory cells, (MDSCs and Tregs)
contribute to restoration of anti-tumor immunity by decreasing suppression of T-cells and NK cells

High-level conceptual view of alternative treatments



Outline

- Heterogeneity: coexisting resistant and fragile populations
- Pre-existent, spontaneous, or induced resistance
- A mathematical model of spontaneous vs. induced evolution of resistance
- Effect of induction on therapy outcome
- Some data fits
- A modified mathematical model and data fits
- Summary
- Resistance through immune damage

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- Extra: Additional material on first model
  - More details on optimal control
  - More details on identifiability
  - Comments on multidrug and sequential therapies

(Reduced) model

we first consider a simplified (and rescaled) system

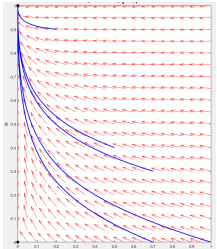
$$\frac{dS}{dt} = (1-(S+R))\,S - (\epsilon + \boxed{\alpha u(t)})S - d u(t) S$$
$$\frac{dR}{dt} = p_r\,(1-(S+R))\,R + (\epsilon + \boxed{\alpha u(t)})S$$

- no back “mutations" ($\gamma = 0$)
- complete resistance ($d_R = 0$)

note: $p_r < 1$

Asymptotic behavior

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



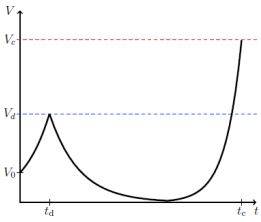
$$\Omega := \{(S,R)\,|\,0 \le S+R \le 1\}$$

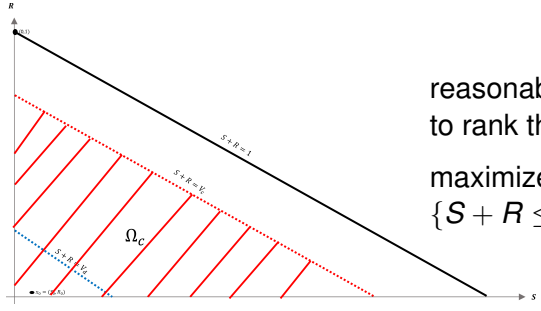
Lemma

for bounded controls $u : [0,\infty) \to [0,M]$, $M < \infty$,
and all initial conditions $(S_0, R_0) \in \Omega$,

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

Formulation





reasonable way
to rank therapies:

maximize viability of set
$\{S + R \leq V_c\}$

$$t_c(u) := \max_{t \geq 0} \{S(t) + R(t) \in \Omega_c\} \ , \quad \Omega_c := \{S + R \leq V_c\}$$

(finite because all trajectories converge to $(1, 0)$)

$$u_{\text{opt}} := \arg\max_{u(t) \in \mathcal{U}} t_c(u)$$

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

Summary of theory results

let us write:

"X" for trajectores when no drug is given ($u = 0$)

"Y" for maximal-dose trajectories ($u = M$)

"U" for a time-varying dose that allows "sliding" along $S + R = V_c$

only concatenations of trajectories that can be optimal:

$$\underbrace{YX \cdots YX}_{n \text{ iterates}} YUY \qquad \text{(for some } n \geq 1\text{)}$$

(some of the segments may not be there; e.g. YXU possible)

for $\alpha = 0$, necessarily $n = 1$: $YXYUY$

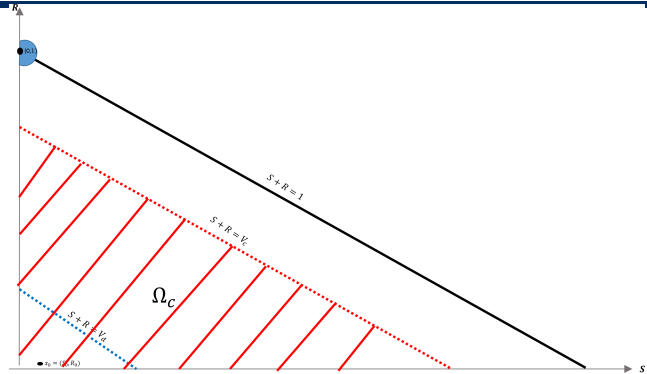
moreover, theory suggests $\frac{\partial n}{\partial \alpha} > 0$, at least for small α

Existence results

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

$$x = \begin{pmatrix} S \\ R \end{pmatrix} \in \mathbb{R}^2$$

maximize time trajectory remains inside region Ω_c

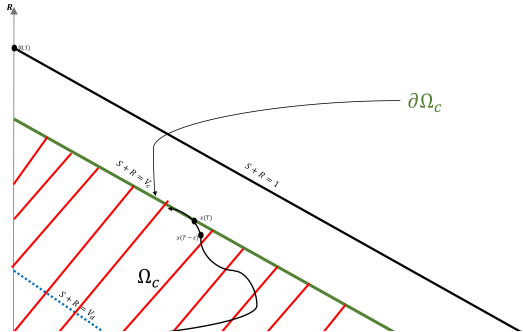


Lemma: $\sup_{u \in \mathcal{U}} t_c(u) < \infty$

by contradiction, diagonalization argument: otherwise build control that remains a fixed positive distance ϵ from $(0,1)$: $u_* = u_{1,*} * u_{2,*} * \cdots$

next apply PMP to obtain necessary conditions for extremals

Elimination of path constraints



Theorem

Suppose that x_* is an optimal trajectory. Let T be the first time such that $x(t) \in \partial\Omega_c$.
Fix (small) $0 < \epsilon < T$ and let $\xi := x(T-\epsilon)$. 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 = concatenations of:

controls obtained from unconstrained necessary conditions & controls of form: $u_p(S,R) = \frac{(1-(S+R))(S+p_r R)}{dS}$

Unconstrained maximum principle

so use PMP to derive necessary conditions for extremals in interior of Ω_c:

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

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

(converted to minimization problem to be consistent w/literature)

Basic properties of extremals (int(Ω_c))

$$H(x,u,\lambda) = -1 + \langle \lambda(t), f(x)\rangle + u\langle \lambda(t), g(x)\rangle \qquad \begin{aligned} \dot{x} &= f(x) + u(t)g(x) \\ \dot{\lambda} &= -\lambda\left(Df(x(t)) + uDg(x(t))\right) \end{aligned}$$

properties independent of α:

- $\lambda_0 = 1$, since abnormal extremals ($\lambda_0 = 0$) are simply classified ($u_*(t) \equiv 0$ or $u_*(t) \equiv M$)
- $\lambda(t) \neq 0$
- $H(t) := H(x(t), u(t), \lambda(t)) \equiv 0$ 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

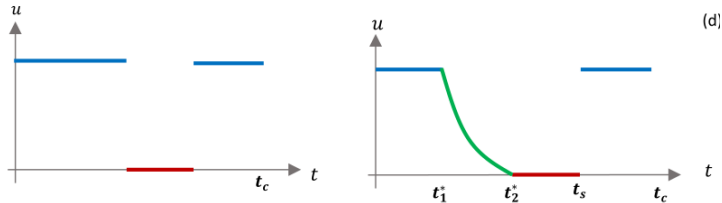
$$u_*(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0. \end{cases}$$

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

Singular arcs

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

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



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

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

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

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

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

a strong condition, implies higher-order derivatives 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)

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

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

- allows writing closed form ODEs for $x(t)$ & $\Phi(t)$ 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 a line of the form $aS + bR = c$.

Some notations

$$a = \alpha \left((1 - p_r) + \frac{d}{\alpha + d} \right) \tag{1}$$

$$b = \alpha(1 - p_r) + dp_r \tag{2}$$

$$c = \alpha(1 - p_r) + \epsilon d \tag{3}$$

$$\gamma(x) = -\frac{(\alpha + d)S^2}{\det A(x)} (aS + bR - c) \tag{4}$$

$$A(x) = \det(f(x), g(x)) \tag{5}$$

Geometry of singular arc

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

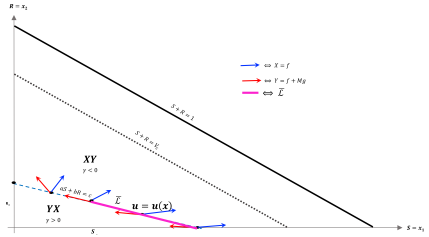
denote the "bang controls" via X and Y:

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

switching at τ such that $\Phi(\tau) = 0$

order is determined by sign of γ away from singular arcs:

$\Longrightarrow$ structure determined outside of singular arc

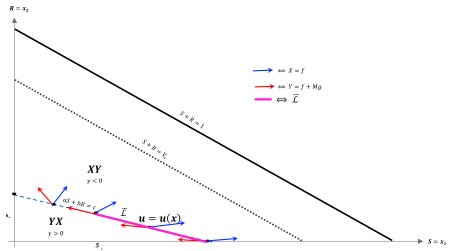


Geometry of singular arc

other properties of extremals:

- only possible singular $\subseteq \bar{\mathcal{L}}$
- control $u(x)$ is uniquely determined there via

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



reasonable assumptions on (M, ϵ) imply $\bar{\mathcal{L}}$ in Γ and feasible and extremal:

$$0 \leq u(x) \leq M$$

(last claim requires $\alpha > 0$, and will determine structure globally)

Non-induced control structure ($\alpha = 0$)

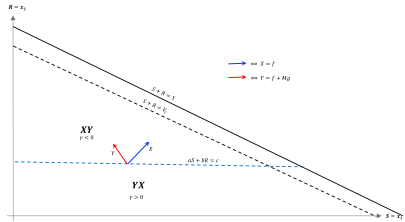
$$X := f(x) \qquad Y := f(x) + Mg(x)$$

Theorem

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

$$u = YXu_p, YXu_pY, YXYu_p, YXYu_pY$$

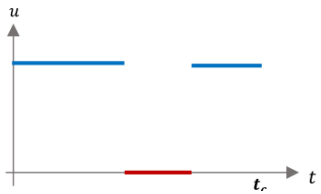
(u_p is a control that slides along $S + R = V_c$)



recall resistant population is always increasing; $a = 0$ when $\alpha = 0$

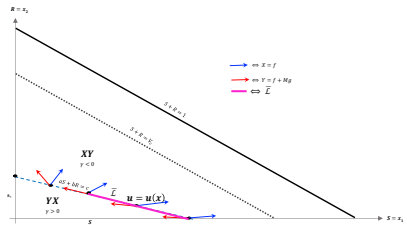
Induced control structure ($\alpha > 0$)

so: control structure in classical **drug-independent paradigm** is **bang-bang** with at most two switches before hitting boundary

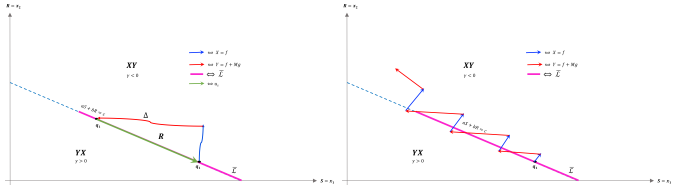


what about when $\alpha > 0$?

- are singular arcs (locally) optimal?
- does switching structure change?



Singular controls are NOT optimal



using Lie algebra structure of vf, show singular arc $\bar{\mathcal{L}}$ not optimal
i.e. $\bar{\mathcal{L}}$ 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 sliding controls.
In fact, the general control structure takes the form

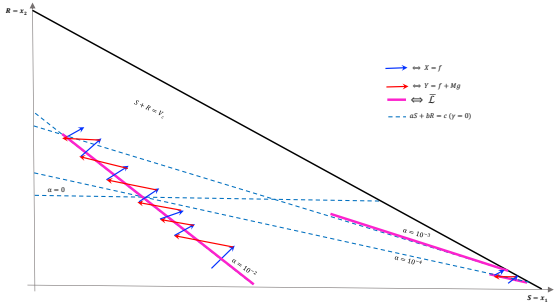
$$(YX)^n u_p Y, \tag{6}$$

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?

- $n(0) = 2$ (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)
- longer sections of $\bar{\mathcal{L}}$ are feasible as α increases

Longer sections of $\bar{\mathcal{L}}$ feasible as α increases



geometry of arc $\bar{\mathcal{L}}$ **suggests** # of switchings increases as $\alpha \uparrow$

- $\alpha = 0:\quad u = YXu_pY$
- $\alpha > 0:\quad u = (YX)^{n(\alpha)}u_pY$
- $n(\alpha)$ 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

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 mathematical framework to distinguish mechanisms by which drug resistance originates:

- random (drug-independent) (Darwinian selection only)
- induced phenotype switching (adding generation of variation)

control structure depends on strength of drug-induced induction

- $\alpha = 0$: $u = YXYu_pY$ (X, Y = respectively none or max drug)
- $\alpha > 0$: $u = (YX)^n u_p Y$, $n \geq 1$
- geometry suggests that $\frac{\partial n}{\partial \alpha} > 0$, at least initially (small α)

potential clinical relevance:

- $\neq$ treatment strategies based on how “mutagenic" chemotherapy is
- provides testable hypothesis to determine α *in vitro*
  - test which types of treatment strategies are better to infer α

Outline

- Heterogeneity: coexisting resistant and fragile populations
- Pre-existent, spontaneous, or induced resistance
- A mathematical model of spontaneous vs. induced evolution of resistance
- Effect of induction on therapy outcome
- Some data fits
- A modified mathematical model and data fits
- Summary
- Resistance through immune damage
- Extra: Additional material on first model
  - More details on optimal control
  - More details on identifiability
  - Comments on multidrug and sequential therapies

Theory results

identifiability using three constant doses plus a linearly increasing protocol:

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

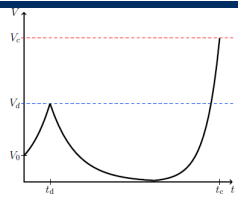
however, unrealistic experimentally (need time derivatives)

alternative, next: exploit *qualitative* differences in $\alpha = 0$ vs. $\alpha > 0$

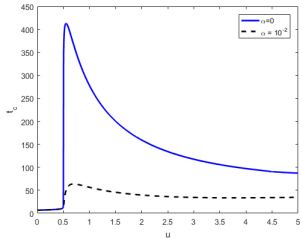
(of course, won't work well if $\alpha \approx 0$)

One heuristic for deciding if $\alpha > 0$

compute standard dose-response curves for a fixed set of parameters
only measure $\mathbf{t_c} = t_c(u, d, \alpha)$



for a fixed value of d (e.g. $d = 0.2$):

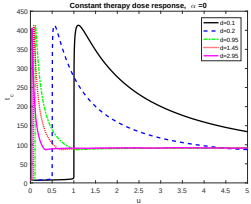


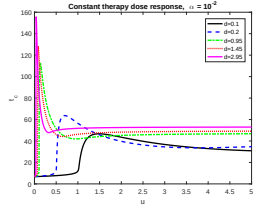
very similar qualitative dynamics for both types of scenarios
max response time occurring at **intermediate** dosage (singular controls)

A possible alternative: experiments with varying *d*

assume can (*in-vitro*) experiment by varying the drug sensitivity *d*

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





might be able to use for distinguishing that maximum response time is:

constant in *d* for $\alpha = 0$
increasing in *d* for $\alpha > 0$

Lie derivatives

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

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

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 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

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

$F_1 = F_2$ (Wang and Sontag 1989)
so, 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

thus enough to show 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, this involves measuring 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

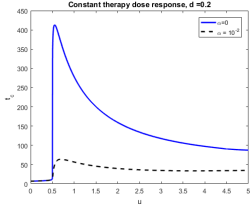
Is there another way to determine parameter α?

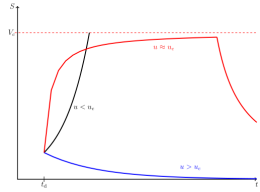
- equivalently, what are *qualitative* differences between $\alpha = 0, > 0$?
- Is there a way to distinguish utilizing only constant therapies?

Aside: maximum response dose

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

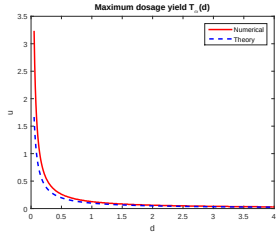
- Understand via competition between sensitive and resistant cells





critical size $V_c \approx$ carrying capacity of sensitive cells (ignoring resistant dynamics)

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

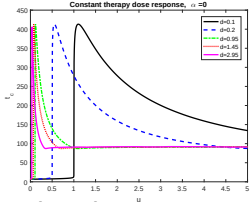


Varying *d*

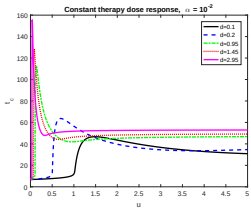
Imagine we can, *in vitro*, vary the drug sensitivity *d*

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

$\alpha_s = 0$



$\alpha_i = 10^{-2}$

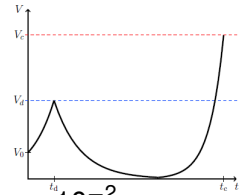


Maximum response time is:

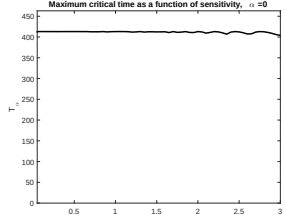
- **Constant** for $\alpha = 0$
- **Increasing in d** for $\alpha > 0$

Maximum response time

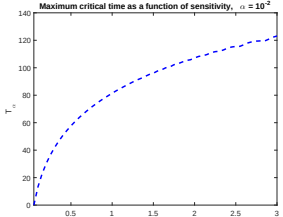
$$T_\alpha(d) := \sup_u \{t_c(u, d, \alpha)\}$$



$\alpha_s = 0$



$\alpha_i = 10^{-2}$



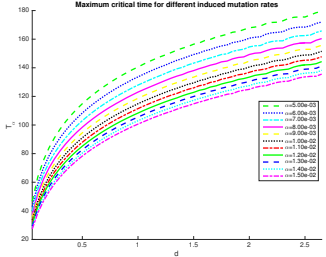
shape of max response time is indicator of phenotype-switching drug induction

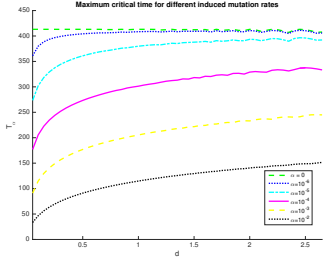
- did't even have to know anything about mechanisms

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 $u \approx u_c$

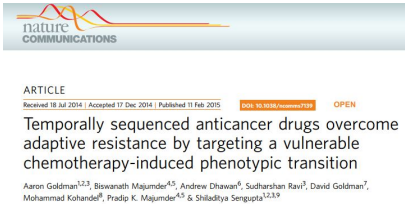
Focus on qualitative distinctions of induced drug resistance ($\alpha > 0$) under simplest treatment regime (constant)

- “Thought experiment"

Outline

- Heterogeneity: coexisting resistant and fragile populations
- Pre-existent, spontaneous, or induced resistance
- A mathematical model of spontaneous vs. induced evolution of resistance
- Effect of induction on therapy outcome
- Some data fits
- A modified mathematical model and data fits
- Summary
- Resistance through immune damage
- Extra: Additional material on first model
  - More details on optimal control
  - More details on identifiability
  - Comments on multidrug and sequential therapies

Multidrug and sequential therapy extension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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*

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

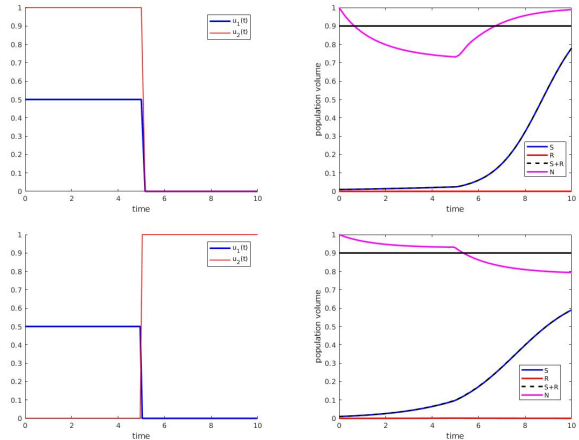
$$\dot{S} = r_S\left(1 - \frac{V}{K}\right)S - (\epsilon + \alpha u_1(t))S - d_{S,1}u_1(t)S - d_{S,2}u_2(t)S + \gamma R$$

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

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 example: sequential vs. combination therapy



sequential therapy yields small tumor volume at treatment conclusion

- order of therapy important
- natural control questions