A model for the intrinsic limit of cancer therapy

Duality of treatment-induced cell death and treatment-induced stemness

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Erin Angelini[†]

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[†]Department of Applied Mathematics
University of Washington
Seattle, WA

Cancer treatment paradigms: recurrence & metrics of success

- Single major cause of treatment failure in cancer therapy: emergence of treatment resistant tumor that drives recurrence
- Tacitly accepted that relapse is inevitable during the course of drug treatment
- Reflected in clinical metrics of treatment success: Kaplan-Meier Curves, progression-free survival (PFS) or time to tumor progression (TTP)
- **Prevalence of drug resistance and tumor recurrence is a driving force behind developing new approaches to cancer treatment**

Recurrence is driven by tumor evolution

- Tumor recurrence is the result of Darwinian evolution via selection for drug resistant cells
  - Genetic variability within the pretreatment tumor (increased mutation rate)
  - Certain mutations confer drug-resistance
  - Post-treatment clonal expansion of drug-resistant clones
- Competitive release of drug-resistant cells
  - Pre-treatment: sensitive and resistant cells compete for resources within tumor
  - Post-treatment: resistant cells expand into ecological niche previously occupied by sensitive cells
- **Recurrence after treatment is causatively linked to the act of treatment itself via evolutionary forces**

Phenotypic plasticity can confer resistance to treatment

- Variability in gene expression generates non-genetic heterogeneity within a single clonal, isogenic population
  - Phenotypic plasticity: sub-types not subject to extinction
- Produces distinct, robust and biologically relevant phenotypic sub-states in clonal cell populations
  - Mesenchymal, persister, or stem-like states
  - Can confer resistance, be inherited across several cell generations, & be induced by environmental signals
- **Drug treatment as a double-edge sword: drug-sensitive cells can be induced by treatment stress to enter a drug-resistant persister state, thus planting the seed for recurrence**

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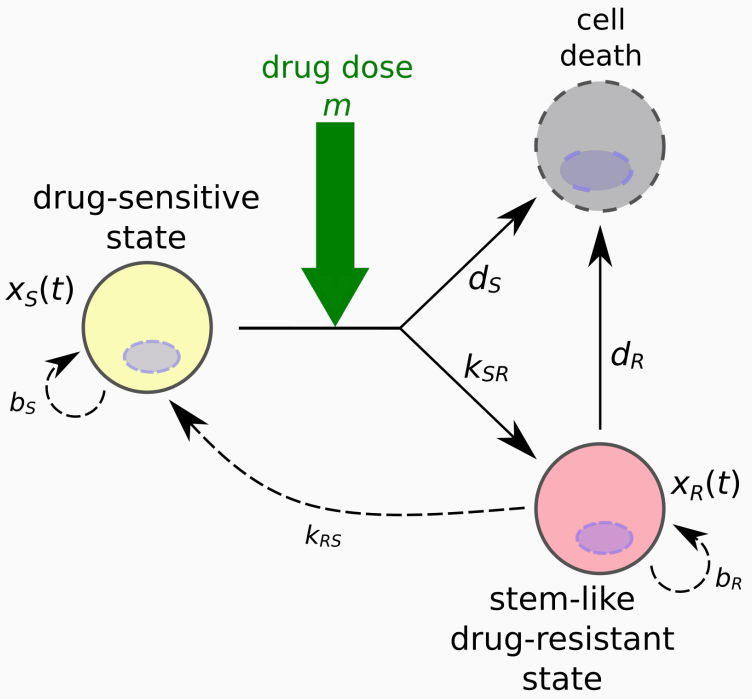
3. Quantify how these features of treatment relate to the intrinsic inevitability of recurrence, measured as time to progression (TTP)
4. **Provide a formal survey of the consequence of non-genetic induction of resistance by treatment, irrespective of the ensuing selection and (micro-)environmental influences**

Mathematical Model

Dynamical model of tumor growth

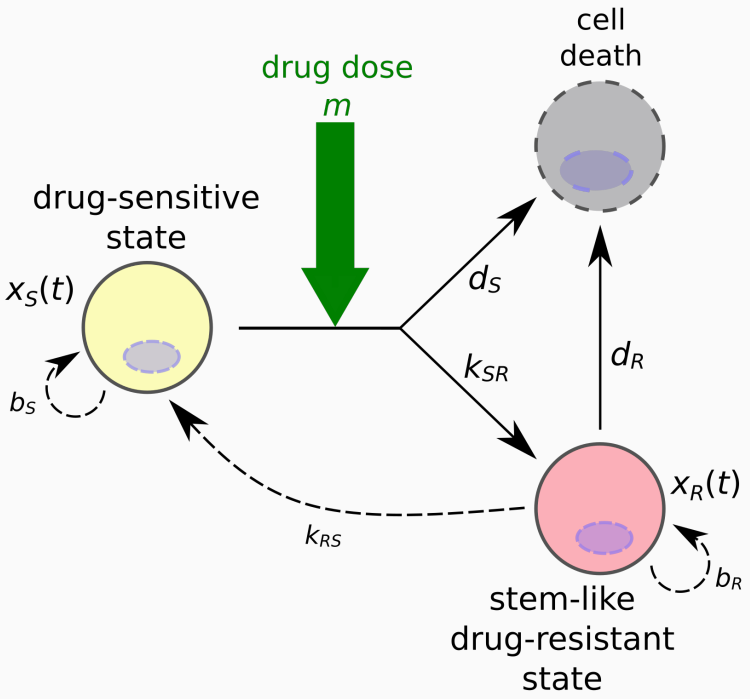


$x_S(t) = \#$ sensitive cells at time t

$x_R(t) = \#$ resistant cells at time t

$$\begin{cases} \frac{dx_S}{dt} &= (b_S - d_S - k_{SR})x_S + k_{RS}x_R \\ \frac{dx_R}{dt} &= (b_R - d_R - k_{RS})x_R + k_{SR}x_S \end{cases}$$

Dynamical model of tumor growth



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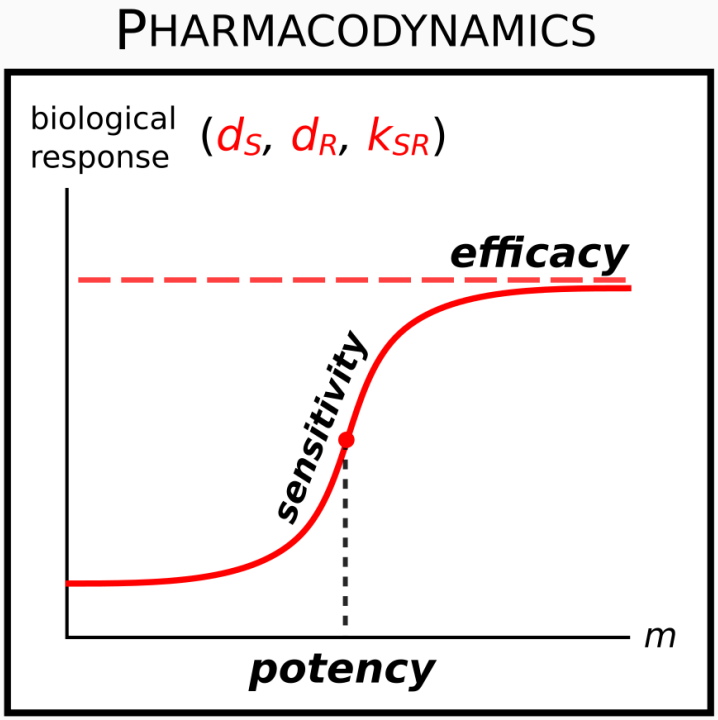
$$\frac{d\vec{x}}{dt} = A\vec{x}, \quad \vec{x} = \begin{bmatrix} x_S \\ x_R \end{bmatrix}$$

$$A = \begin{bmatrix} b_S - d_S - k_{SR} & k_{RS} \\ k_{SR} & b_R - d_R - k_{RS} \end{bmatrix}$$

Pharmacodynamic model of continuous therapy



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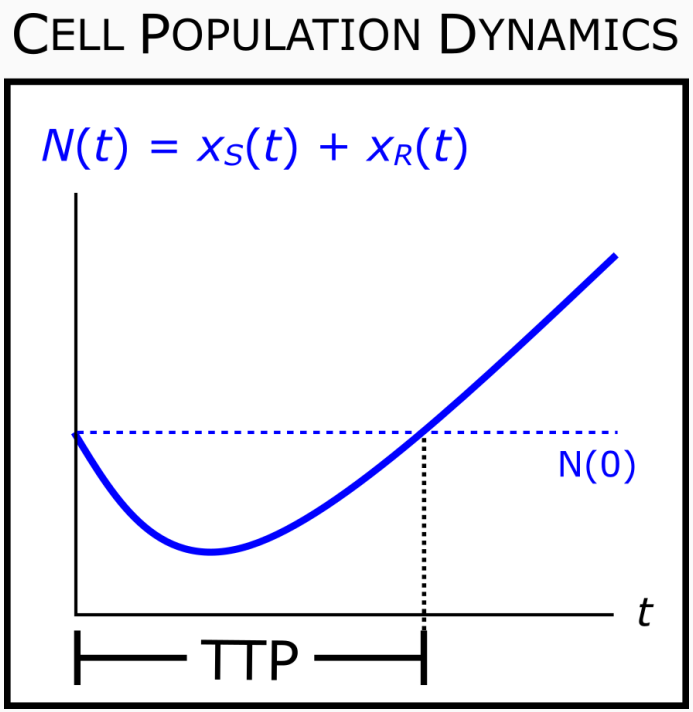
Tumor growth dynamics: time to progression



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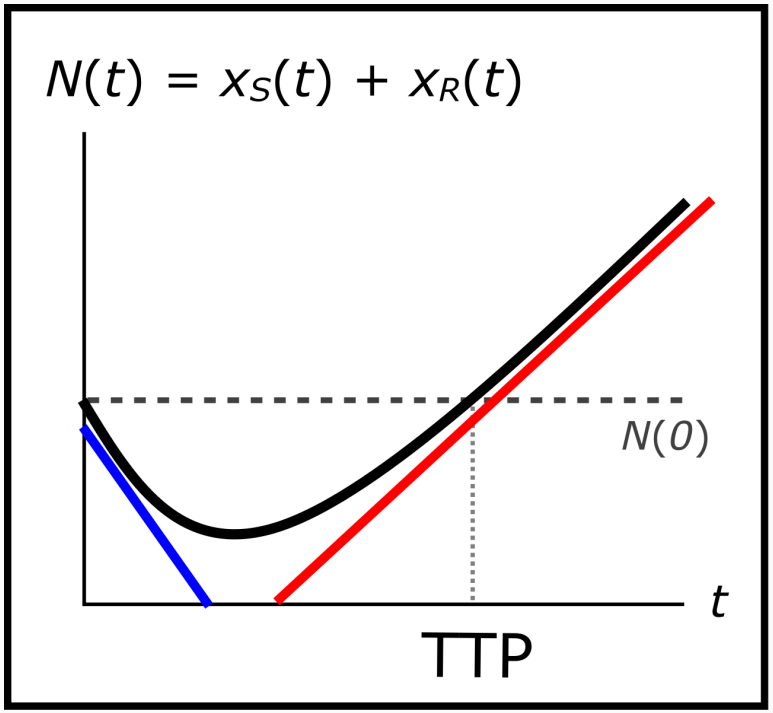
Results

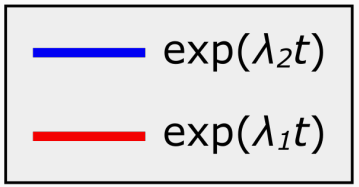
Heuristic dynamics: tumor recurrence as saddle point



$N(t) = C_1 \exp(\lambda_1 t) + C_2 \exp(\lambda_2 t)$

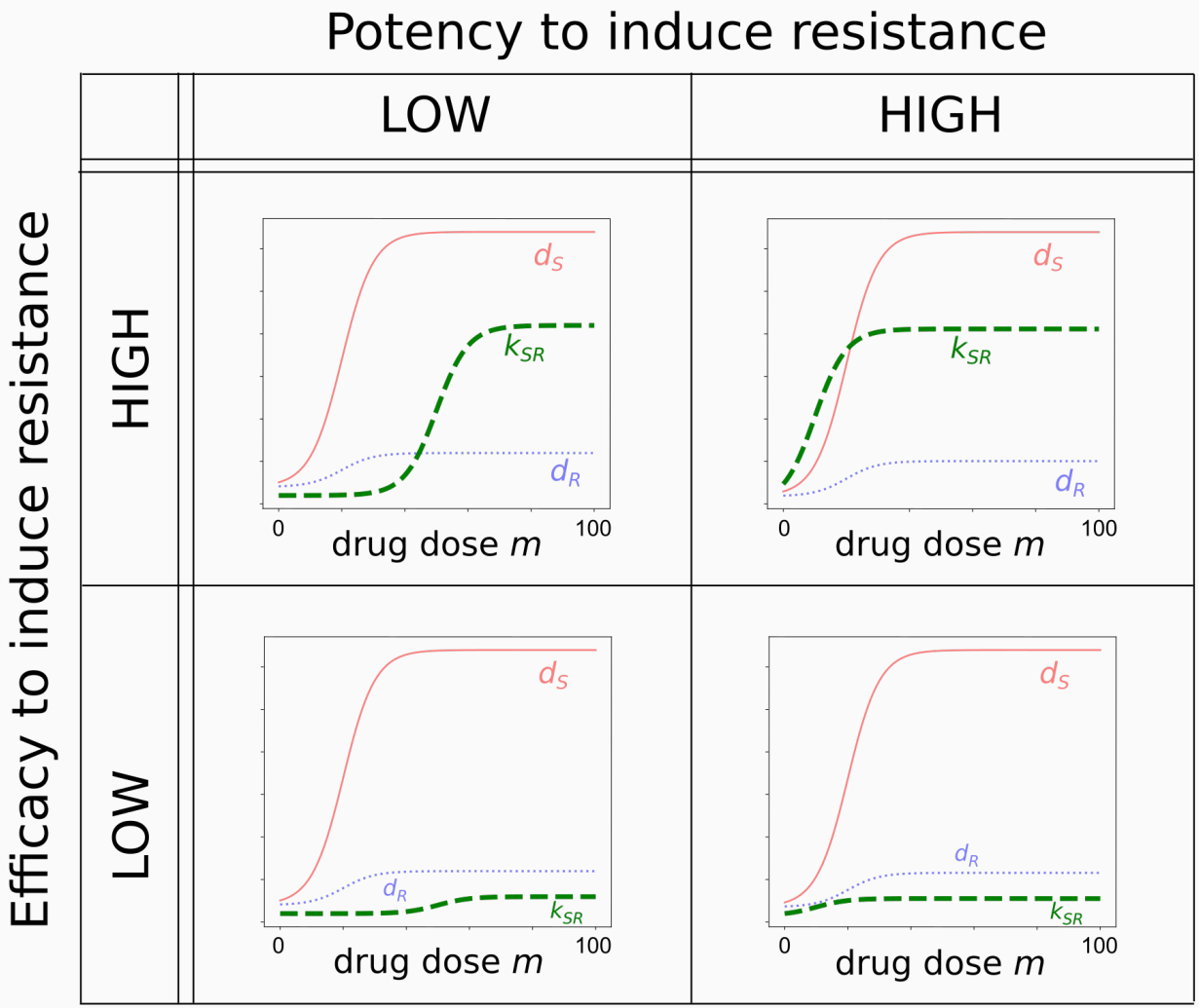
$\lambda_{1,2}$ eigenvalues of rate matrix A

- $\lambda_1 > 0$, $\lambda_2 > 0$: unchecked growth
- $\lambda_1 < 0$, $\lambda_2 < 0$: tumor eradication
- $\lambda_1 > 0$, $\lambda_2 < 0$: tumor recurrence

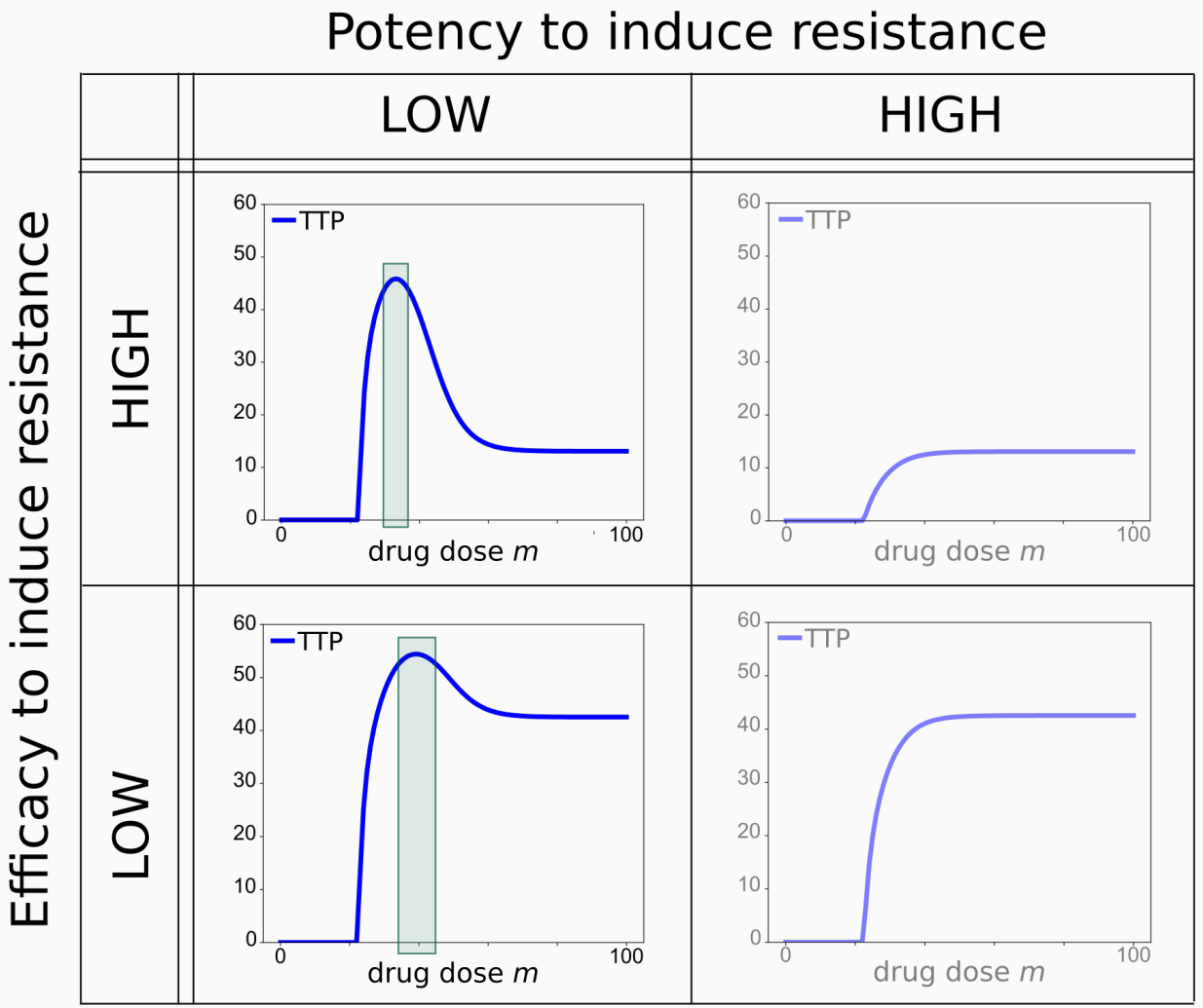


remission + regrowth

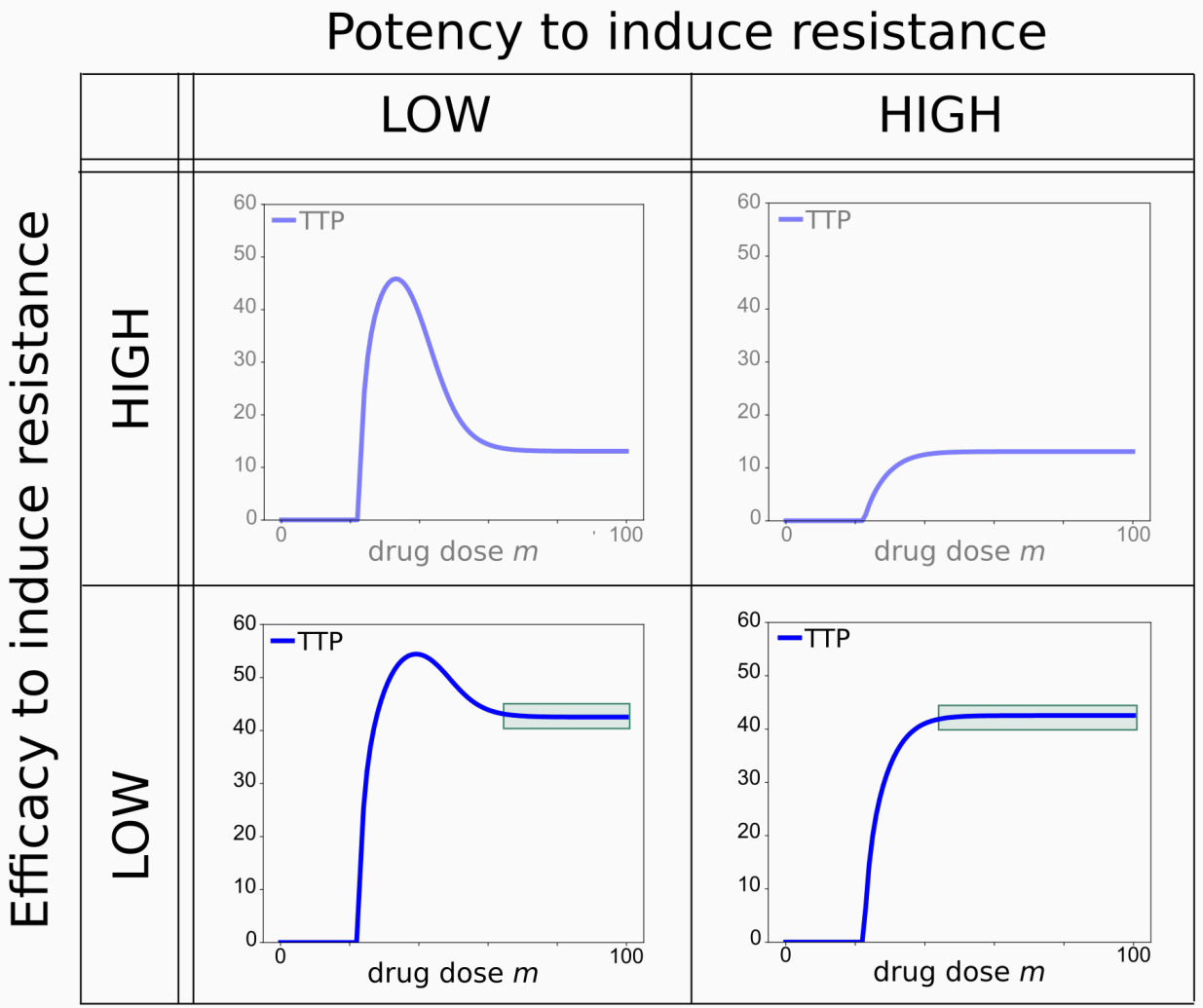
Qualitative sensitivity analysis: pharmacodynamics of drug-induced resistance



Optimal dose exists for drug with low potency to induce resistance



TTP delayed for drug with low efficacy to induce resistance



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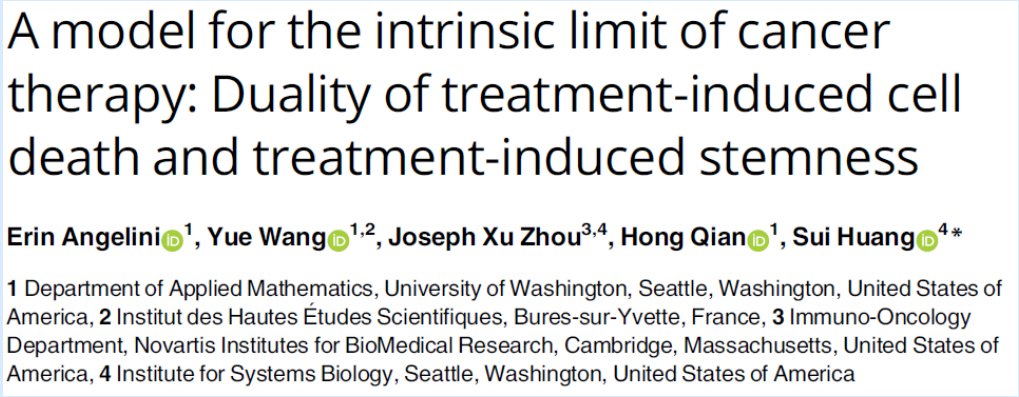
- Must ground model in (pre)clinical data in order to make meaningful predictions about optimal treatment courses
  - Estimates of population- & pharmaco-dynamic parameters
  - Statistical learning: fit parameter distributions

Questions?



A model for the intrinsic limit of cancer therapy: Duality of treatment-induced cell death and treatment-induced stemness

Erin Angelini[1], **Yue Wang**[1,2], **Joseph Xu Zhou**[3,4], **Hong Qian**[1], **Sui Huang**[4]*

1 Department of Applied Mathematics, University of Washington, Seattle, Washington, United States of America, **2** Institut des Hautes Études Scientifiques, Bures-sur-Yvette, France, **3** Immuno-Oncology Department, Novartis Institutes for BioMedical Research, Cambridge, Massachusetts, United States of America, **4** Institute for Systems Biology, Seattle, Washington, United States of America

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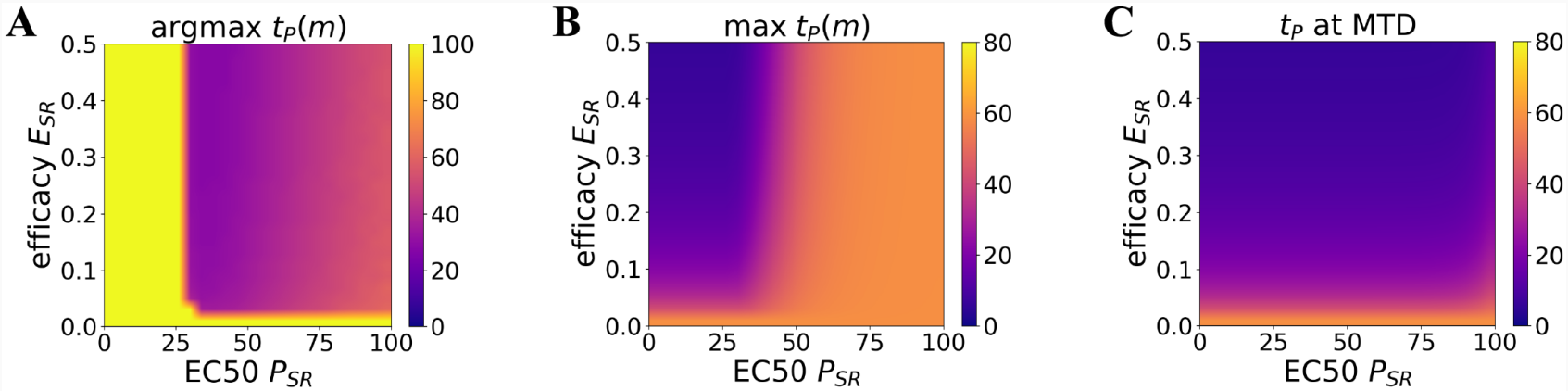
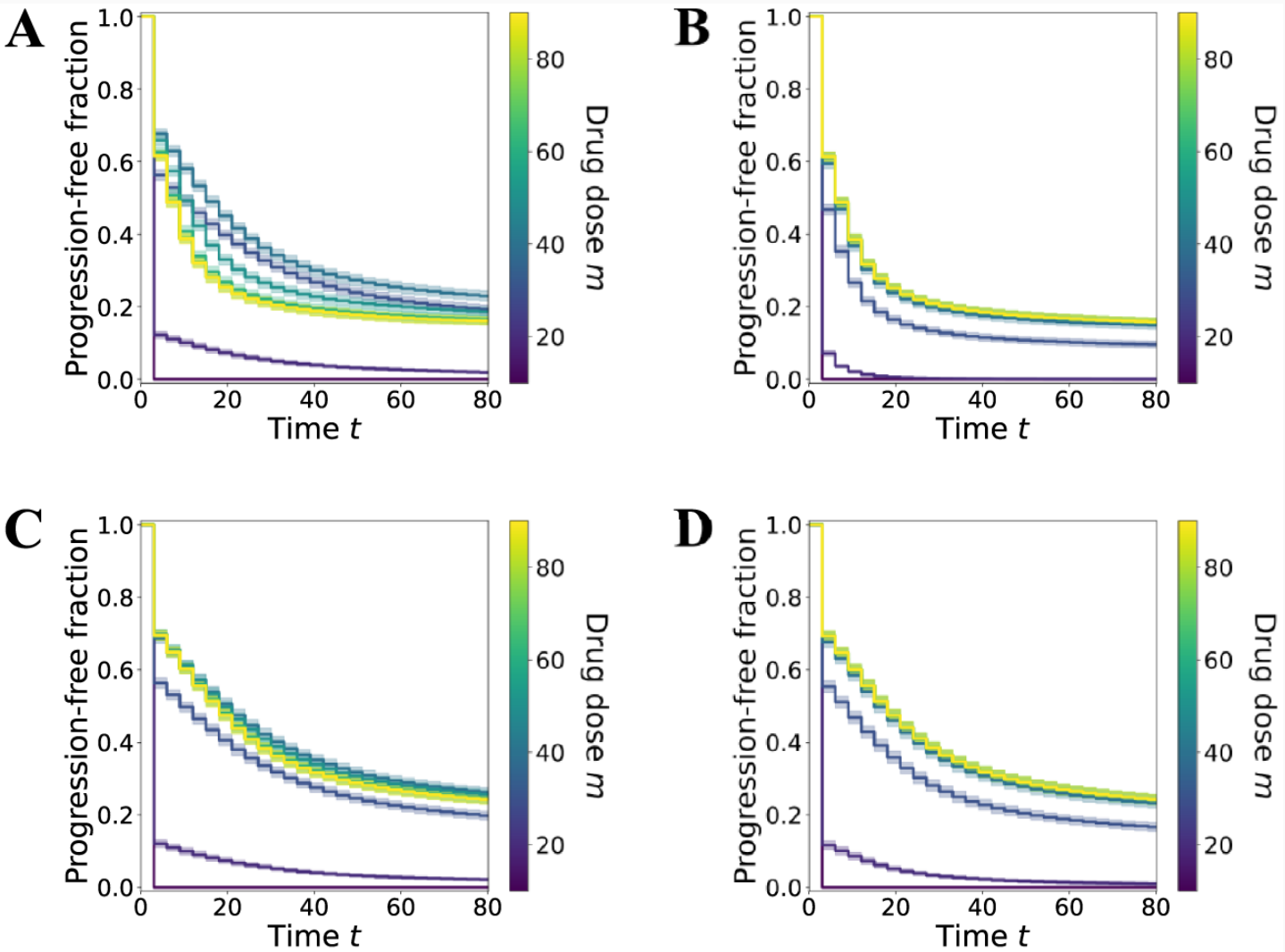
Parameter search: qualitative behavior of TTP is robust



Virtual patient cohort simulations



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References i

- S.J. Altschuler and L.F. Wu. **Cellular heterogeneity: do differences make a difference?** *Cell*, 141:559–563, 2010.
- A.R.A. Anderson, A.M. Weaver, P.T. Cummings, and V. Quaranta. **Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment.** *Cell*, 127:905–915, 2006.
- C. S-O. Attolini and F. Michor. **Evolutionary theory of cancer.** *Annals of the New York Academy of Sciences*, 1168:23–51, 2009.
- R. A. Beckman, G.S. Schemmann, and C-H. Yeang. **Impact of genetic dynamics and single-cell heterogeneity on development of nonstandard personalized medicine strategies for cancer.** *Proceedings of the National Academy of Sciences*, 109:14586–14591, 2012.
- A-M. Bleau, D. Hambardzumyan, T Ozawa, E.I. Fomchenko, J.T. Huse, C. W. Brennan, and E.C. Holland. **Pten/pi3k/akt pathway regulates the side population phenotype and abcg2 activity in glioma tumor stem-like cells.** *Cell Stem Cell*, 4:226–235, 2009.

References ii

I. Bozic. **Quantification of the selective advantage of driver mutations is dependent on the underlying model and stage of tumor evolution.** *Cancer Research*, 82:21–24, 2022.

R. Brady-Nicholls, J.D. Nagy, T.A. Gerke, T. Zhang, A.Z. Wang, J. Zhang, R.A. Gatenby, and H. Enderling. **Prostate-specific antigen dynamics predict individual responses to intermittent androgen deprivation.** *Nature Communications*, 11, 2020.

L. A. Diaz Jr, R. T. Williams, J. Wu, I. Kinde, J. R. Hecht, J. Berlin, B. Allen, I. Bozic, J. G. Reiter, M. A. Novak, K. W. Kinzler, K. S. Oliner, and B. Vogelstein. **The molecular evolution of acquired resistance to targeted egfr blockade in colorectal cancers.** *Nature*, 486:537–540, 2012.

L. González-Silva, L. Quevedo, and I. Varela. **Tumor functional heterogeneity unraveled by scrna-seq technologies.** *Trends in Cancer*, 6:13–19, 2020.

M. Greaves and C. C. Maley. **Clonal evolution in cancer.** *Nature*, 481:306–313, 2012.

J.M. Greene, C. Sanchez-Tapia, and E.D. Sontag. **Mathematical details on a cancer resistance model.** *Frontiers in Bioengineering and Biotechnology*, 8, 2020.

References iii


K. Kemper, P.L. de Goeje, D.S. Peeper, and R. van Amerongen. **Phenotype switching: tumor cell plasticity as a resistance mechanism and target for therapy.** *Cancer Research*, 74:5937–5941, 2014.


E. Kozlowska, A. Farkkila, T. Vallius, O. Carpen, J. Kemppainen, S. Grenman, R. Lehtonen, J. Hynninen, S. Hietanen, and S. Hautaniemi. **Mathematical modeling predicts response to chemotherapy and drug combinations in ovarian cancer.** *Cancer Research*, 78:4036–4044, 2018.


E. Kozlowska, R. Suwinski, M. Giglok, A. Swierniak, and M. Kimmel. **Mathematical modeling predicts response to chemotherapy in advanced non-resectable non-small cell lung cancer patients treated with platinum-based doublet.** *PLOS Computational Biology*, 16, 2020.


S. Maetani and J. M. Gamel. **Evolution of cancer survival.** *Surgical Oncology*, 19:49–51, 2010.


Y. Oren, M. Tsabar, M.S. Cuoco, L. Amir-Zilberstein, H.F. Cabanos, ..., J.S. Brugge, and A. Regev. **Cycling cancer persister cells arise from lineages with distinct programs.** *Nature*, 596:576–582, 2021.

References iv

- A.O. Pisco, A. Brock, J. Zhou, A. Moor, M. Mojtahedi, D. Jackson, and S. Huang. **Non-darwinian dynamics in therapy-induced cancer drug resistance.** *Nature Communications*, 4, 2013.
- A.O. Pisco and S. Huang. **Non-genetic cancer cell plasticity and therapy-induced stemness in tumour relapse: 'what does not kill me strengthens me'.** *British Journal of Cancer*, 112:1725–1732, 2015.
- A.F. Read, T. Day, and S. Huijben. **The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy.** *Proceedings of the National Academy of Sciences*, 108:10871–10877, 2011.
- A. Rosech, M. Fukunaga-Kalabis, E.C. Schmidt, S.E.Zabierowski, P.A. Brafford, A. Vultur, D. Basu, P. Gimotty, T. Vogt, and M. Herlyn. **A temporarily distinct subpopulation of slow-cycling melanoma cells is required for continuous tumor growth.** *Cell*, 141:583–594, 2010.
- S.M. Shaffer, M.C. Dunagin, S.R. Torborg, E.A.Torre, B. Emert, ..., and A.Raj. **Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance.** *Nature*, 546:431–435, 2017.

References v

Y. Su, W. Wei, L. Robert, M. Xue, J. Tsoi, A. Garcia-Diaz, B. H. Moreno, J. Kim, R. H. Ng, J. W. Lee, R. C. Koya, B. Comin-Anduix, T.G. Graeber, A. Ribas, and J.R. Heath. **Single-cell analysis resolves the cell state transition and signaling dynamics associated with melanoma drug-induced resistance.** *Proceedings of the National Academy of Sciences*, 114:13679–13684, 2017.

A.P. Tran, M. A. Al-Radhawi, I. Kareva, J. Wu an D.J. Waxman, and E.D. Sontag. **Delicate balances in cancer chemotherapy: modeling immune recruitment and emergence of systemic drug resistance.** *Frontiers in Immunology*, 11, 2020.

N. Vasan, J. Baselga, and D.M. Hyman. **A view on drug resistance in cancer.** *Nature*, 575:299–309, 2019.

S.J. Wang, R. Scavetta, H.J. Lenz, K. Danenberg, P.V. Danenberg, and A.H. Schönthal. **Gene amplification and multidrug resistance induced by the phosphatase-inhibitory tumor promoter, okadaic acid.** *Carcinogenesis*, 16:637–641, 1995.

J. West, Y. Ma, and P. K. Newton. **Capitalizing on competition: An evolutionary model of competitive release in metastatic castration resistant prostate cancer treatment.** *Journal of Theoretical Biology*, 455:249–260, 2018.

References vi


J. West, R.O. Schenck, C. Gatenbee, M. Robertson-Tessi, and A.R.A. Anderson. **Normal tissue architecture determines the evolutionary course of cancer.** *Nature Communications*, 12, 2021.


J. West, L. You, J. Zhang, R.A. Gatenby, J.S. Brown, P.K. Newton, and A.R.A. Anderson. **Towards multidrug adaptive therapy.** *Cancer Research*, 80:1578–1589, 2020.