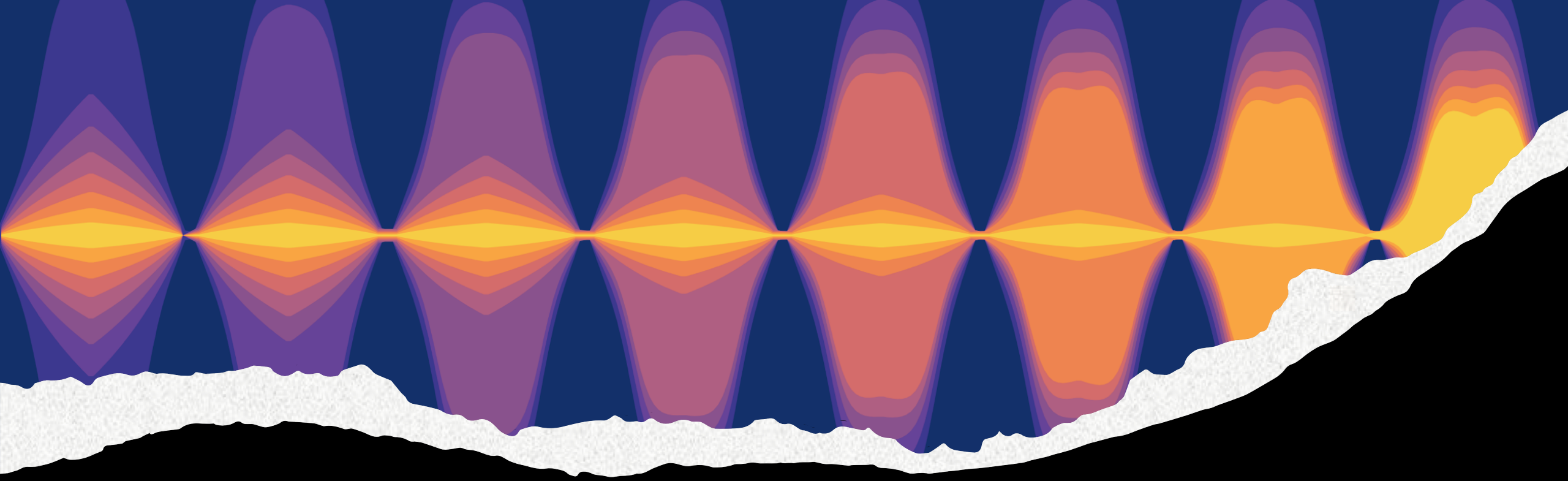

Towards multi-drug adaptive therapy

Jeffrey West (Moffitt Cancer Center)

CATMo2020

Towards multi-drug adaptive therapy

1.


CANCER RESEARCH

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Research Article

Turnover modulates the need for a cost of resistance in adaptive therapy

Maximilian A.R. Strobl, Jeffrey West, Yannick Viossat, Mehdi Damaghi, Mark Robertson-Tessi, Joel S Brown, Robert A Gatenby, Philip K Maini, and Alexander R.A. Anderson

DOI: 10.1158/0008-5472.CAN-20-0806

2.

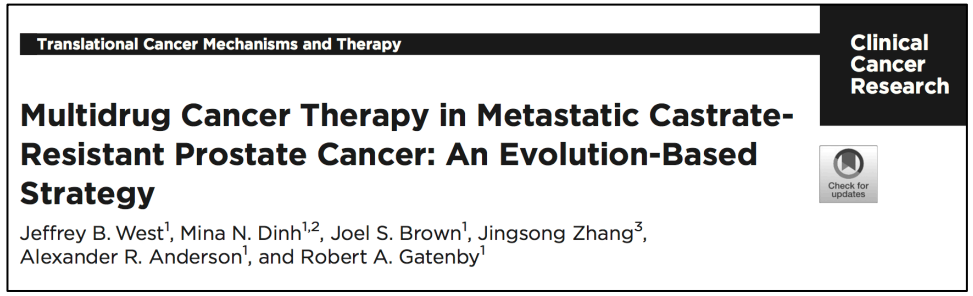

Spatial structure impacts adaptive therapy by shaping intra-tumoral competition

Maximilian A. R. Strobl, Jill Gallaher, Jeffrey West, Mark Robertson-Tessi, Philip K. Maini, Alexander R.A. Anderson

doi: https://doi.org/10.1101/2020.11.03.365163

This article is a preprint and has not been certified by peer review [**what does this mean?**].

3.

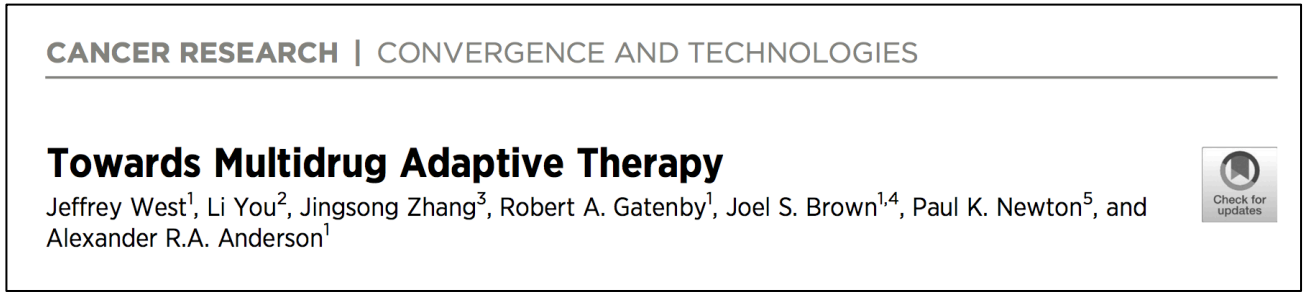

Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Multidrug Cancer Therapy in Metastatic Castrate-Resistant Prostate Cancer: An Evolution-Based Strategy

Jeffrey B. West[1], Mina N. Dinh[1,2], Joel S. Brown[1], Jingsong Zhang[3], Alexander R. Anderson[1], and Robert A. Gatenby[1]

4.


CANCER RESEARCH | CONVERGENCE AND TECHNOLOGIES

Towards Multidrug Adaptive Therapy

Jeffrey West[1], Li You[2], Jingsong Zhang[3], Robert A. Gatenby[1], Joel S. Brown[1,4], Paul K. Newton[5], and Alexander R.A. Anderson[1]

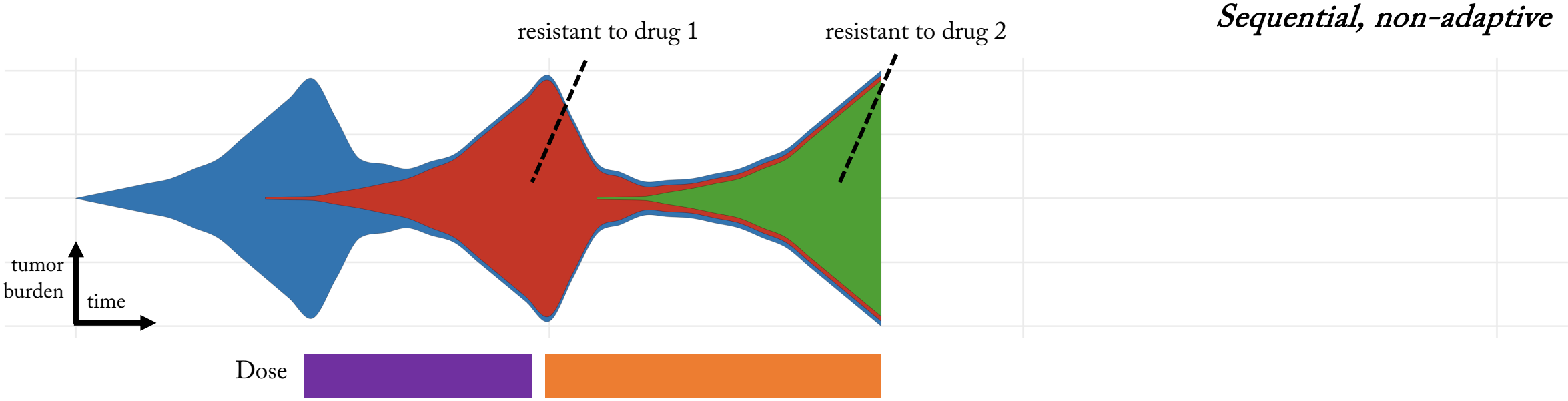
Clinically feasible today

Conceptual ideas for tomorrow

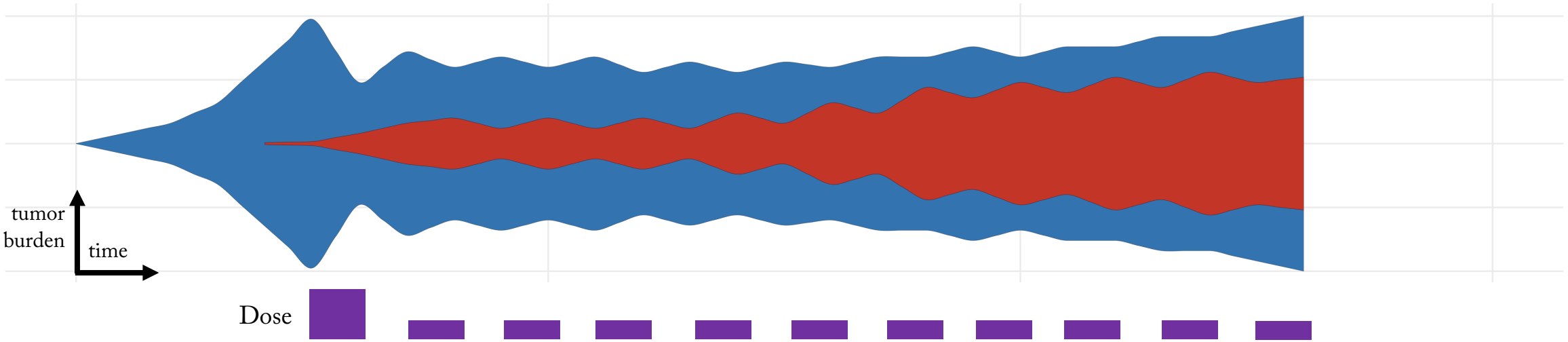
1 2 3 4

Sequential and Adaptive Therapy

Sequential, non-adaptive

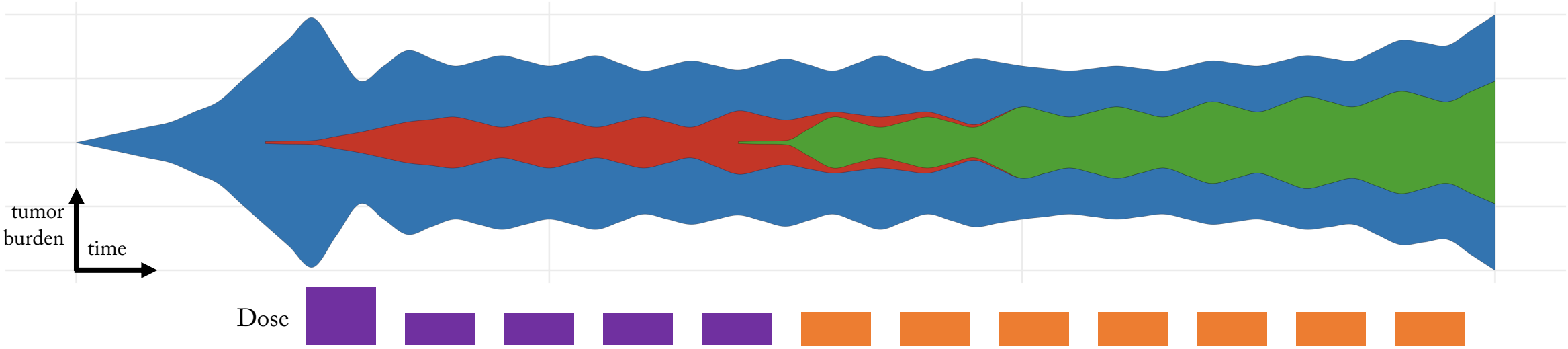


Single drug adaptive

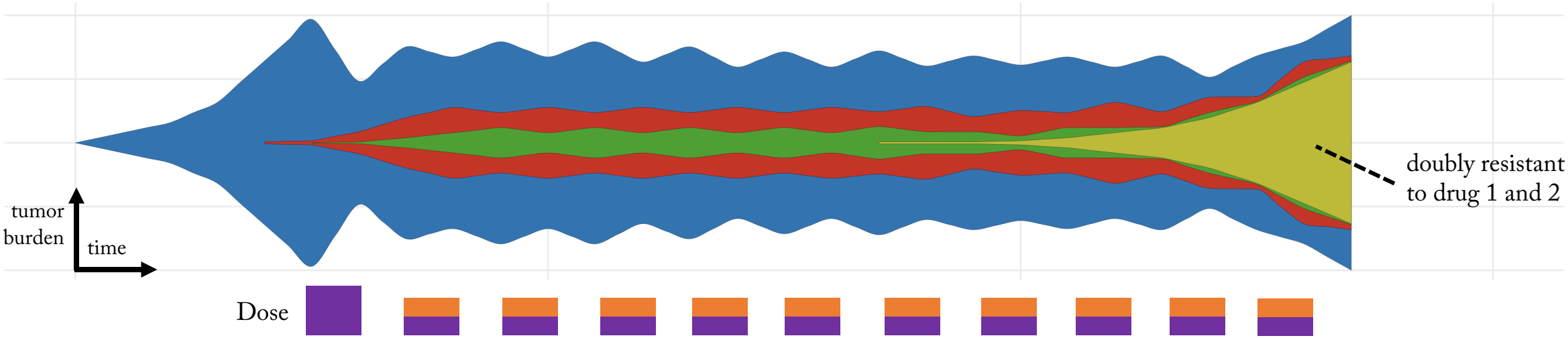


Designing Adaptive Therapy schedules w/ multiple drugs

Two drug combination adaptive



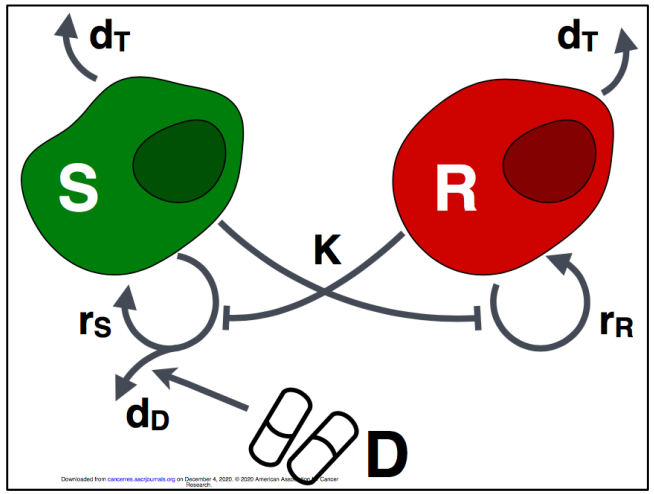
Two drug sequential adaptive



What is the purpose of adding a second drug?

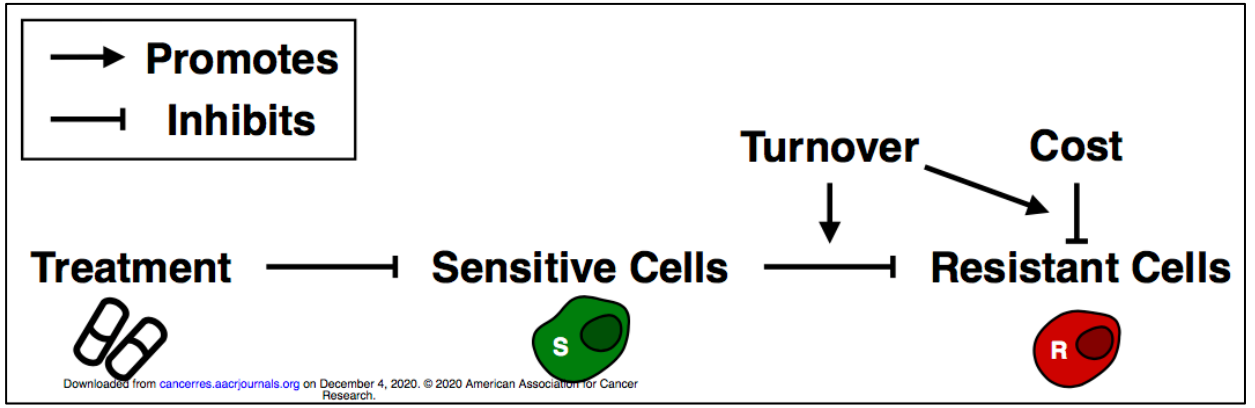
The model:

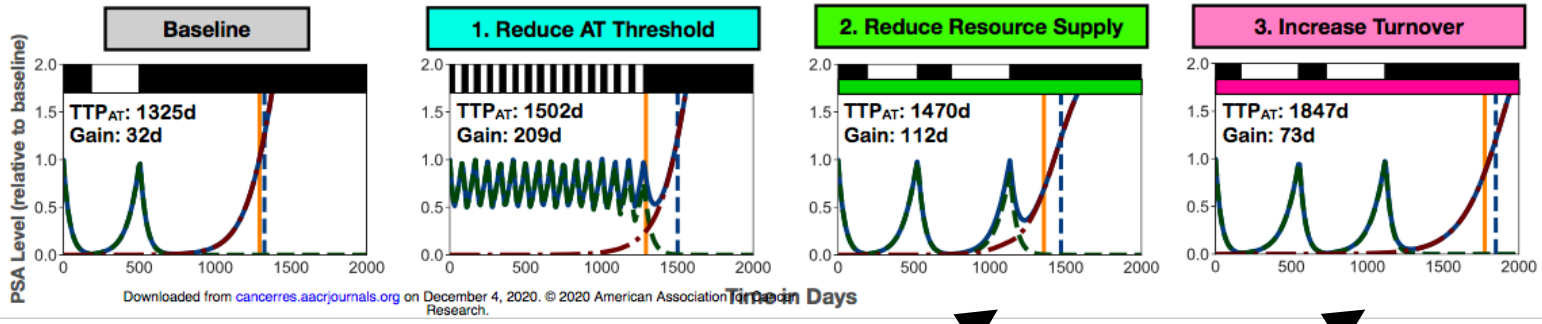
- Lotka-Volterra competition
- Norton-Simon drug effect



$$\frac{dS}{dt} = r_S\left(1-\frac{S+R}{K}\right)\left(1-\frac{2d_D}{D_{Max}}D(t)\right)S - d_T S,$$
$$\frac{dR}{dt} = r_R\left(1-\frac{R+S}{K}\right)R - d_T R,$$

(Strobl, et. al. Cancer Research 2020)





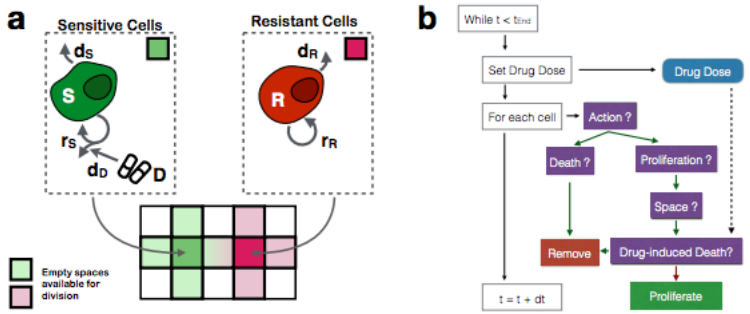
Idea:

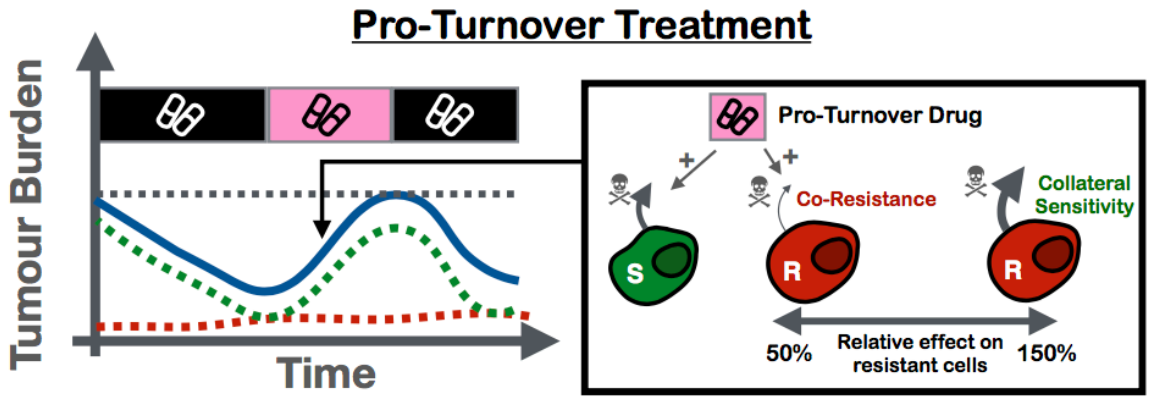
- Targeting shared resources or increasing turnover increases benefit of single drug Adaptive Therapy

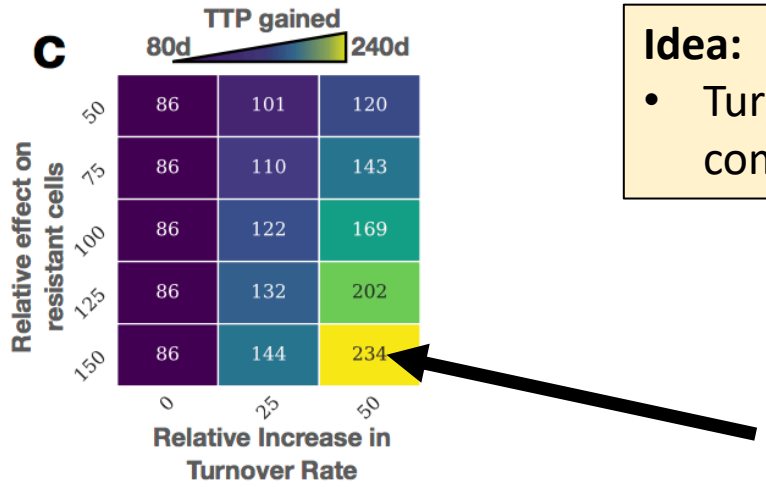
Pro-turnover treatment (off treatment cycle)

The model:

- Agent-based 2-d analog of Lotka-Volterra model







Idea:

- Turnover increases competition – can we increase competition during off treatment periods?

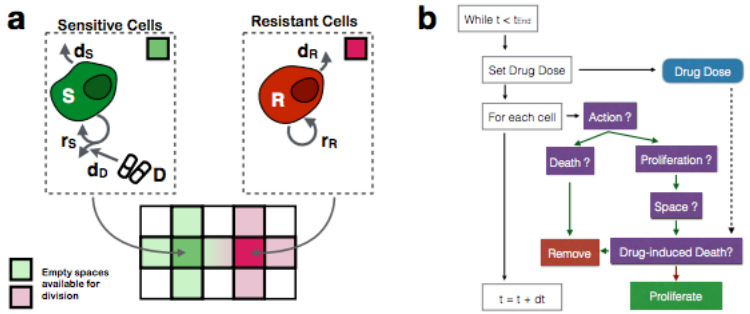
Increasing turnover, targeted to resistant cells

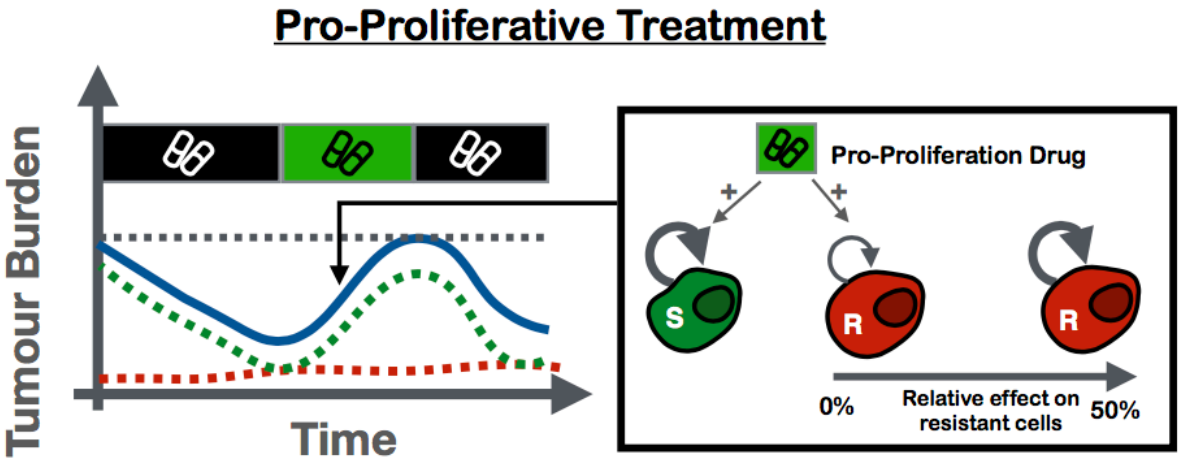
(Strobl, et. al. "Spatial structure impacts adaptive therapy by shaping intra-tumoral competition" BioRxiv, 2020)

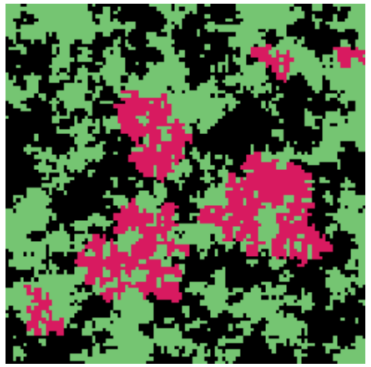
Pro-proliferation treatment (off treatment cycle)

The model:

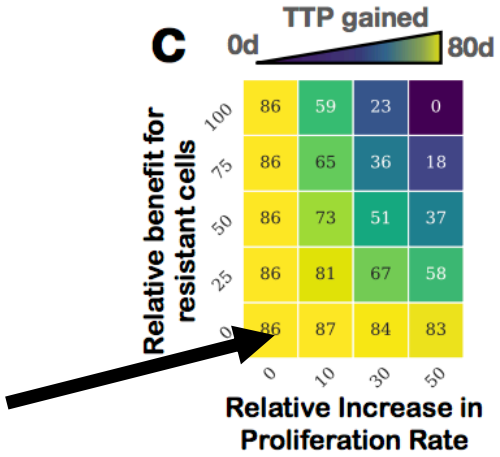
- Agent-based 2-d analog of Lotka-Volterra model







Optimal is to leave well-enough alone!



Idea:

- Sensitive cells suppress Resistant -- can we boost competition by increasing proliferation off treatment?

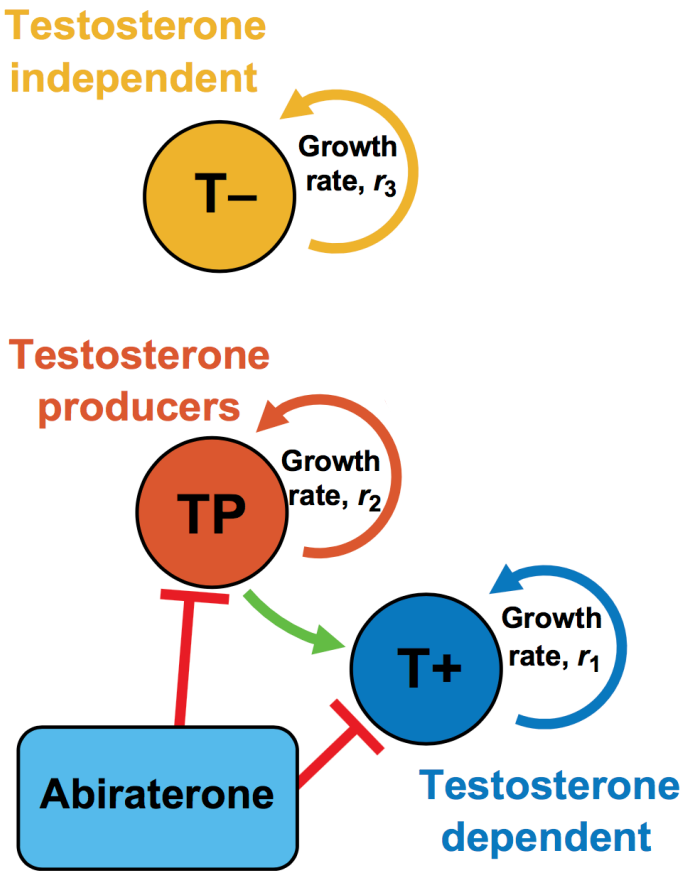
(Strobl, et. al. "Spatial structure impacts adaptive therapy by shaping intra-tumoral competition" BioRxiv, 2020)

1. Primary-secondary adaptive therapy

"What's the difference between theory and practice? Small in theory; large in practice."

- Author attribution unknown -

Primary-secondary therapy



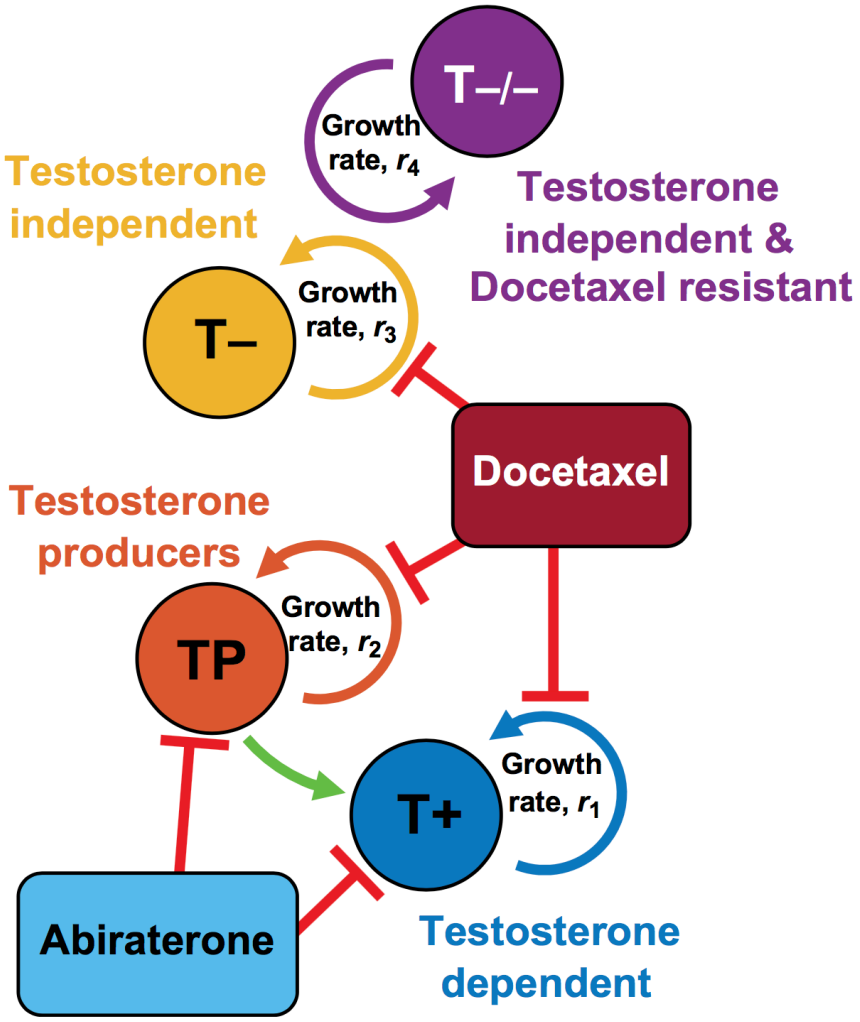
(Zhang. et. al. Nature Comm. 2017)

Cell Populations:

- Testosterone **producers** (TP)
- Testosterone **dependent** (T+)
- Testosterone **independent**

$$\dot{y}_i = r_i y_i \left(1 - \frac{\sum_{j=1}^{3} a_{ij} y_j}{K_i}\right)$$

Primary-secondary therapy



(Zhang. et. al. Nature Comm. 2017)

Cell Populations:

- Testosterone **producers** (TP)
- Testosterone **dependent** (T+)

Targeted by "Primary" drug

- Testosterone **independent**
  - **Susceptible** to Docetaxel
  - **Resistant** to Docetaxel

Targeted by "Secondary" drug

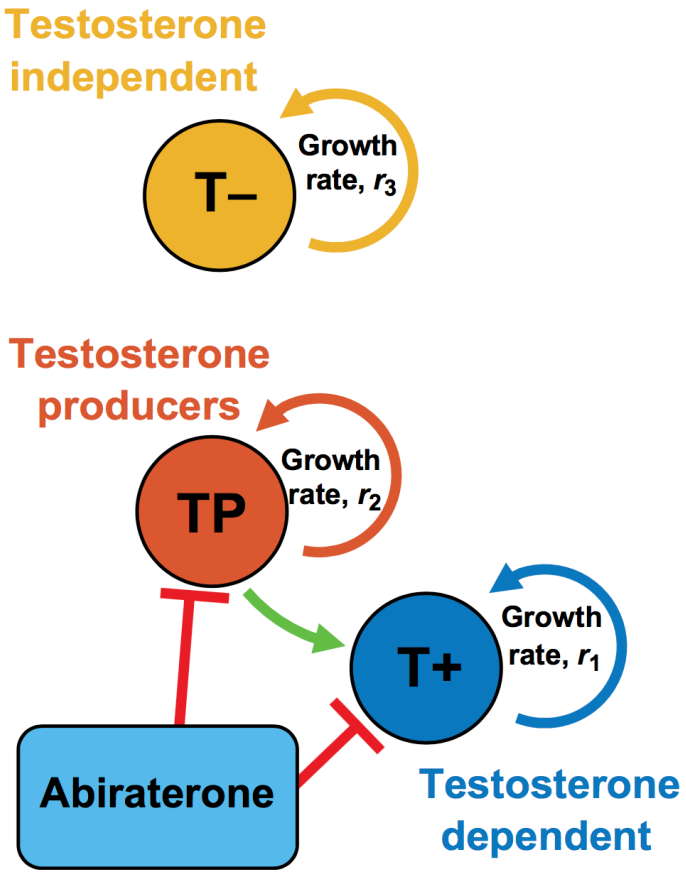
Primary drug

- Greatest efficacy and/or lower toxicity

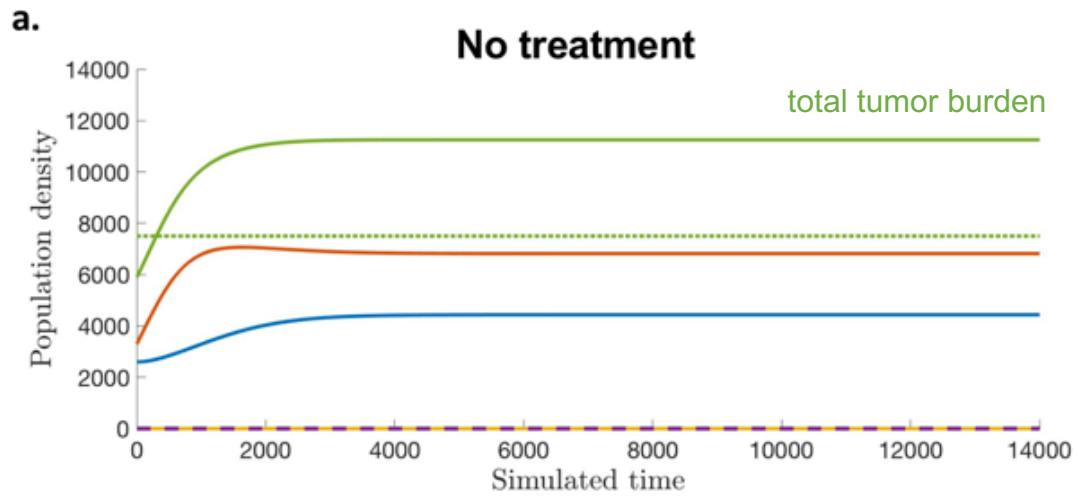
Secondary drug

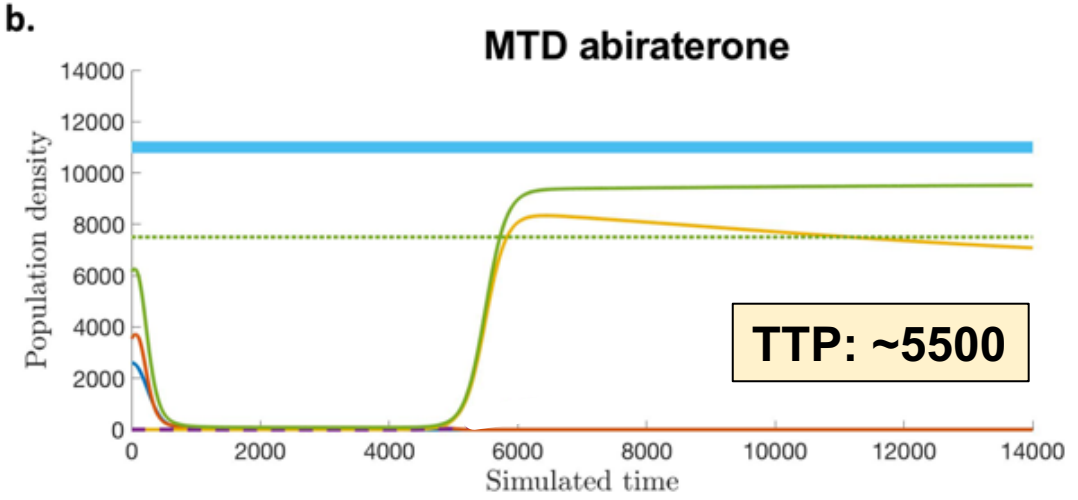
- Targets cell population which is resistant to primary drug

Primary mono-therapy



(Zhang. et. al. Nature Comm. 2017)





Co-existence

T^P + T^+

Testosterone producers

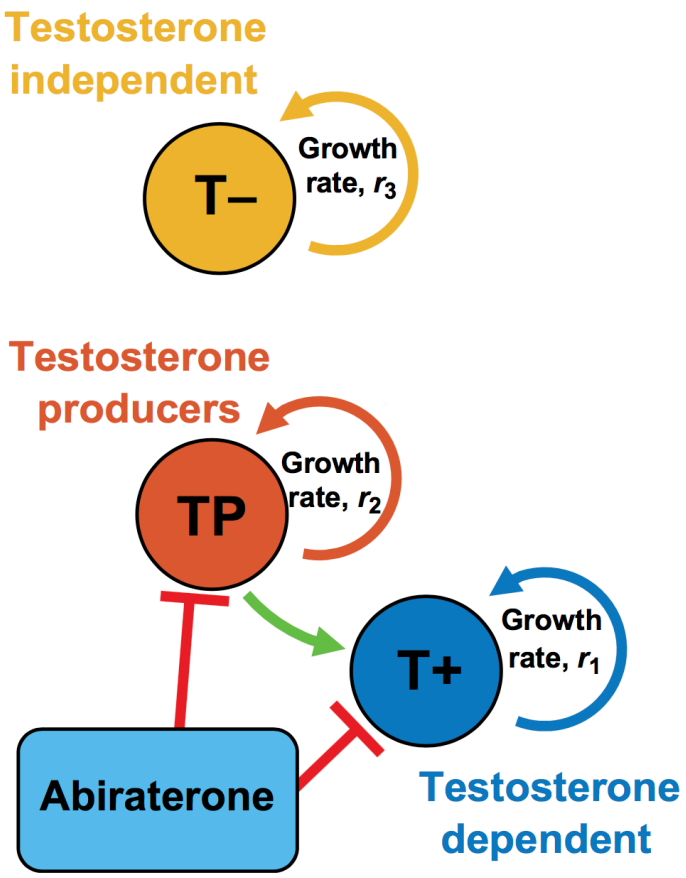
Testosterone dependent

Relapse dominated by resistance

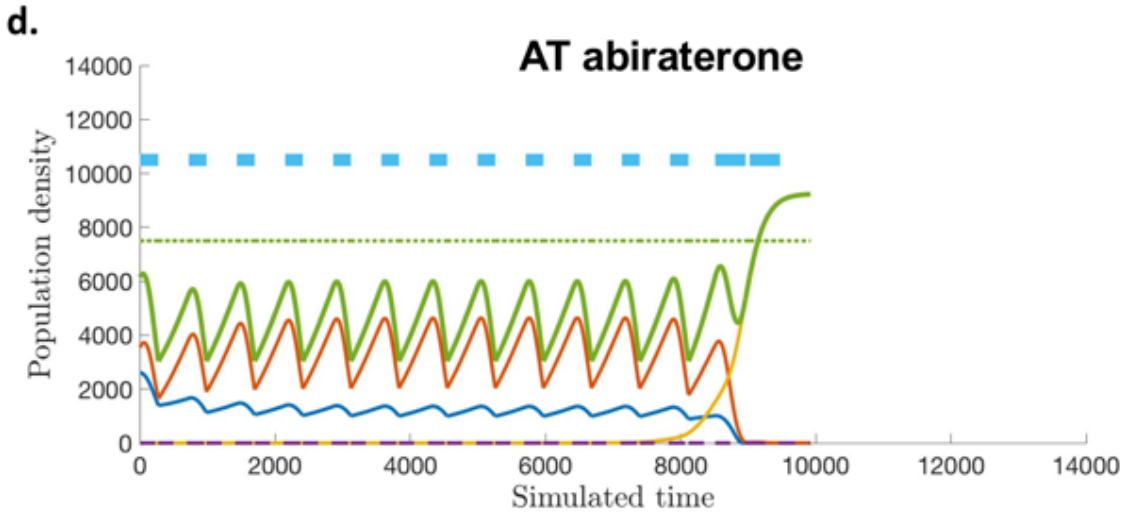
T^-

Testosterone independent

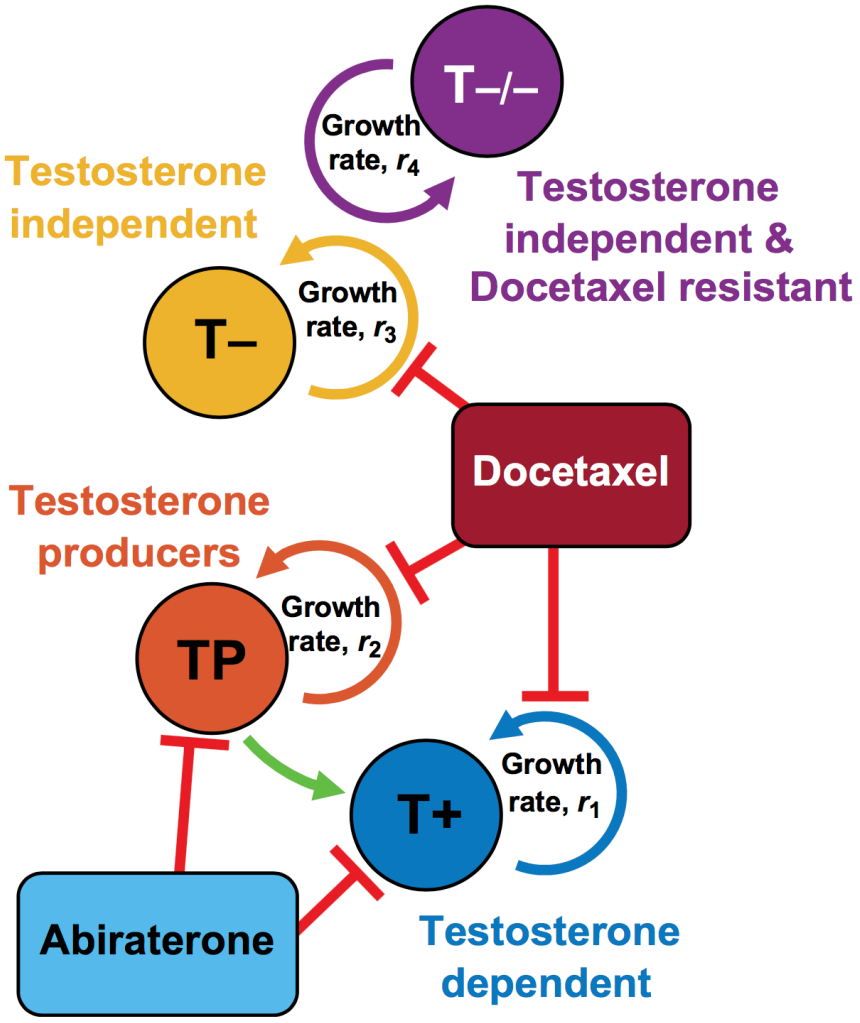
Primary mono-therapy (adaptive)



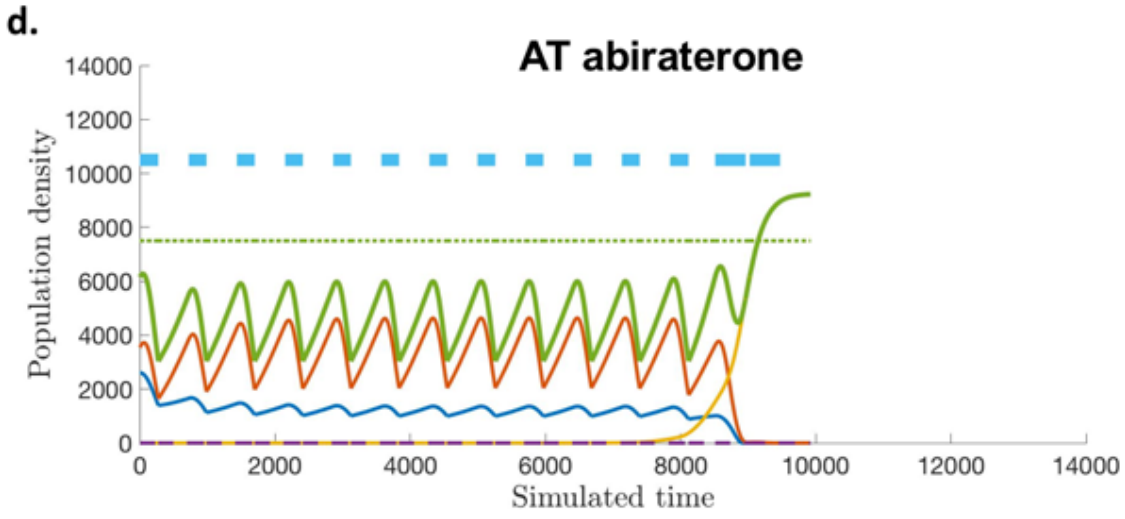
(Zhang. et. al. Nature Comm. 2017)

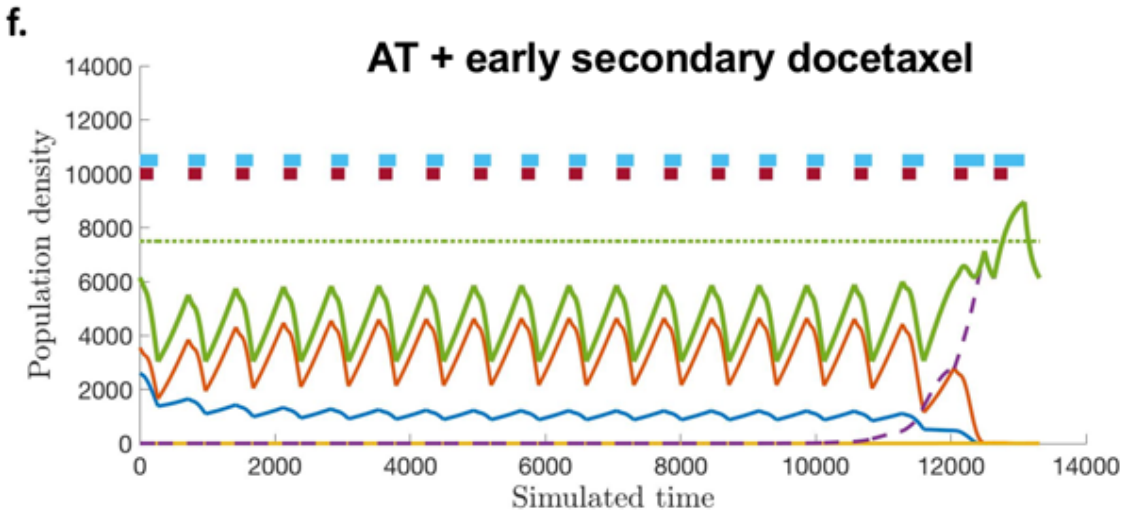


Can docetaxel be used as “Secondary” drug?



(Zhang. et. al. Nature Comm. 2017)



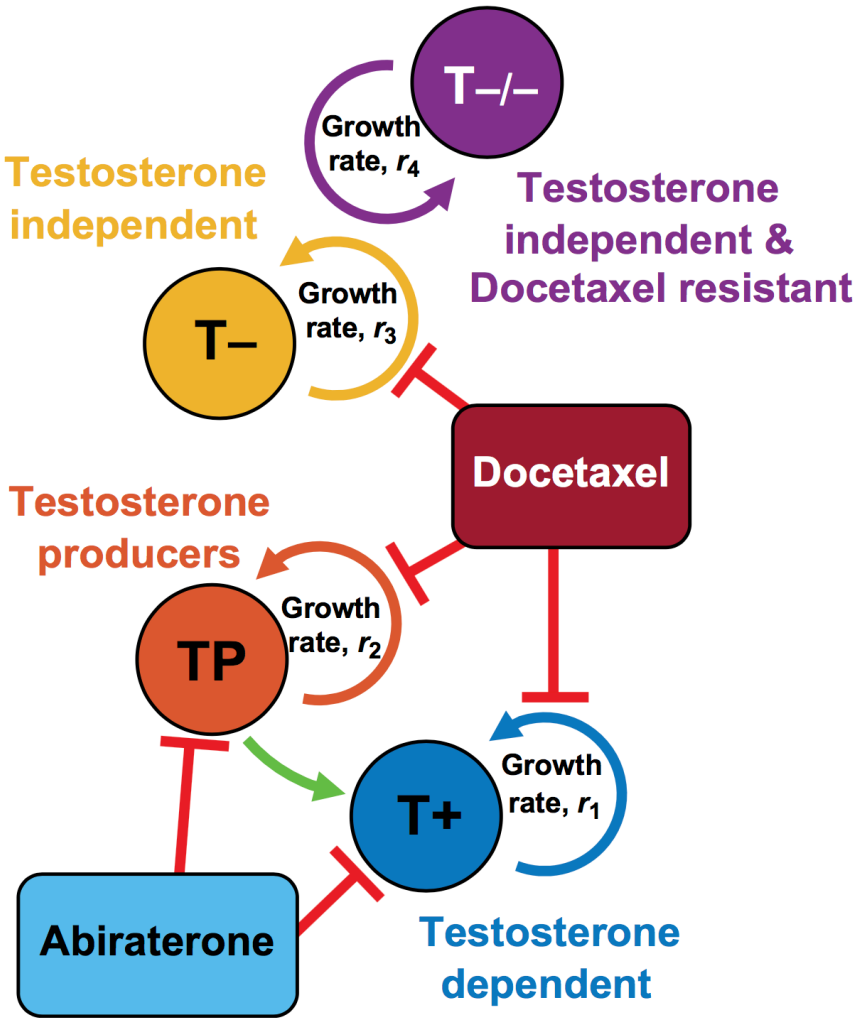


TTP_{CT}: ~5500

TTP_{AT}: ~9500

TTP_{PS}: ~13000

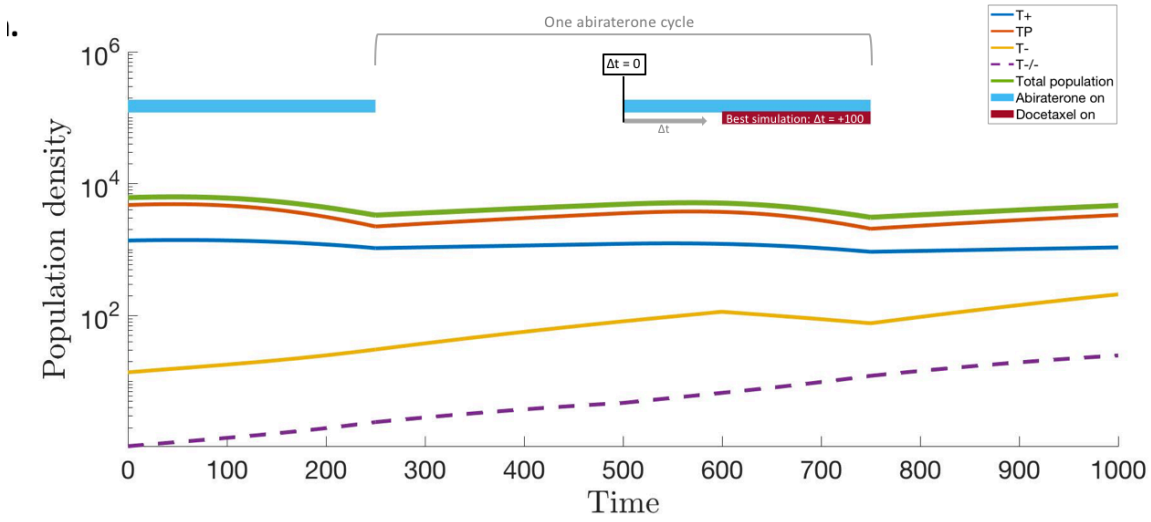
Can docetaxel be used as “Secondary” drug?

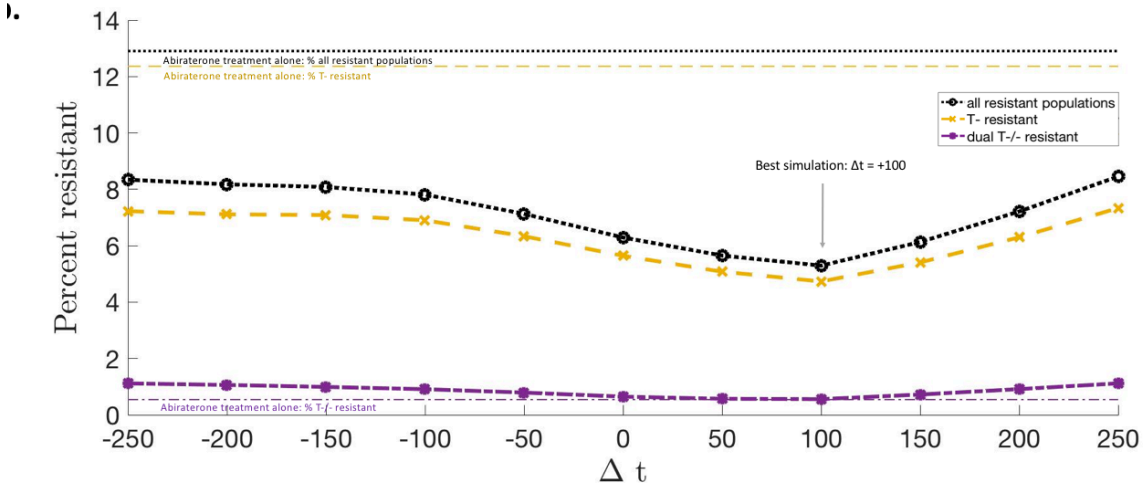


(Zhang. et. al. Nature Comm. 2017)

Problem with our secondary drug:

- Docetaxel is indiscriminately targeting 3 cell types





Delayed docetaxel:

- resistant cell type (T-) is growing
- sensitive cell types (TP, T+) are decaying

2. Evolutionary cycles

" Much is known but unfortunately in different heads."

- Werner Kollath -

Population- to frequency-dependent dynamics

Population Dynamics
Lotka-Volterra

$$\dot{y}_i = r_i y_i \left(1 - \frac{\sum_{j=1}^{3} a_{ij} y_j}{K_i}\right)$$

$$A = [a_{ij}] = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}$$

Frequency Dynamics
Replicator Dynamics

$$\dot{x}_i = (f_i - \phi) x_i$$
$$f_i = w_i (A\vec{x})_i$$
$$w_i = K_i / K_{\max}$$

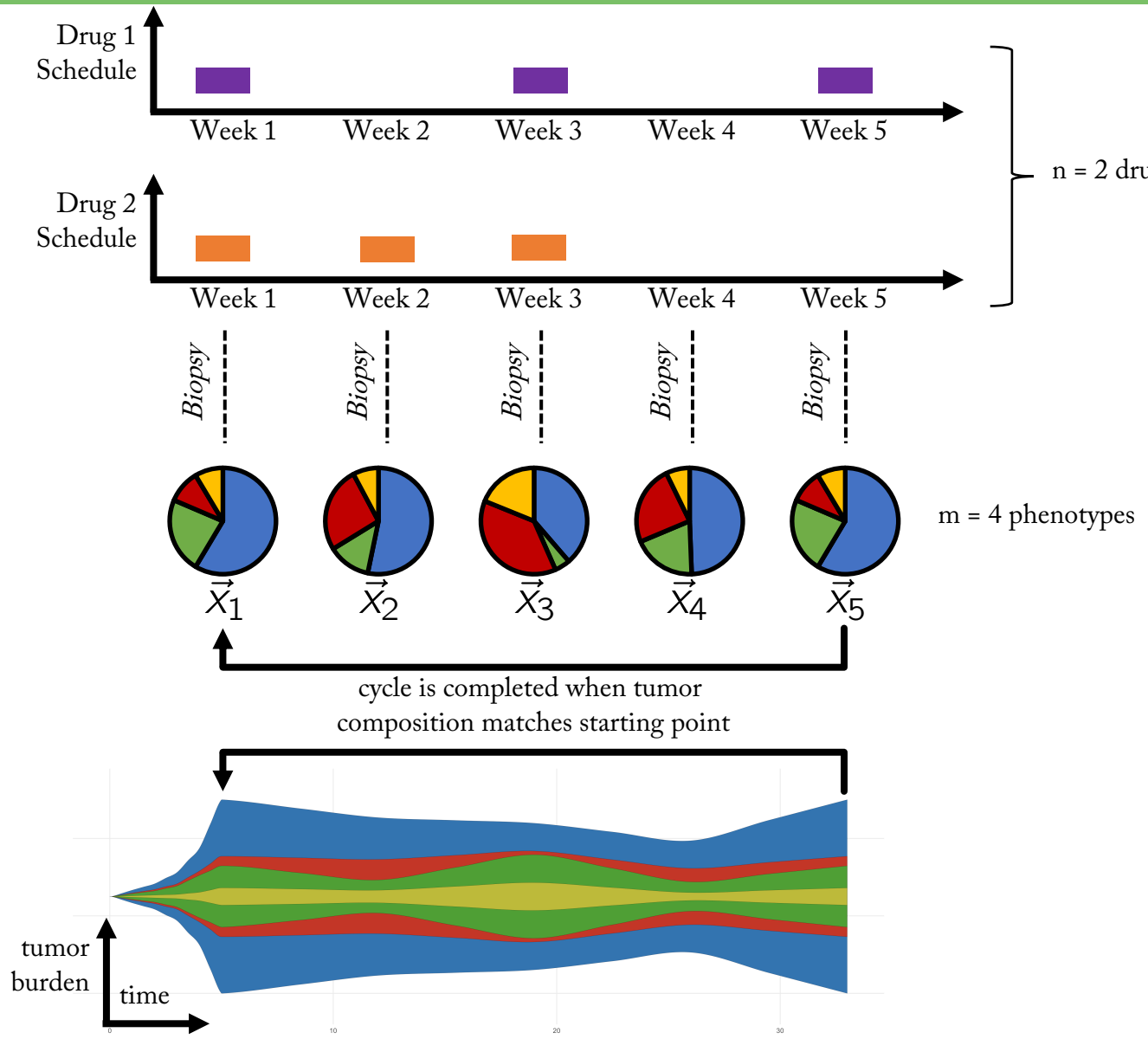
$$A = [1 - a_{ij}] = \begin{bmatrix} 1 - a_{11} & 1 - a_{12} & 1 - a_{13} \\ 1 - a_{21} & 1 - a_{22} & 1 - a_{23} \\ 1 - a_{31} & 1 - a_{32} & 1 - a_{33} \end{bmatrix}$$

**Joint work with Li You (Maastricht) & Paul Newton (Univ Southern California*

Frequency-dependent Evolutionary Cycles

Key assumption:

- since the goal of an adaptive therapy is to maintain a stable volume
- we can study frequency-dependent dynamics



What defines a treatment?

Combinations of **n** drugs:

Treatment 1

Treatment 2

Treatment 3

… and so on.

2^n possible combinations *(including no treatment)*

Controlling **m** cell types *(genotype or phenotype)*

$$\vec{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_m \end{bmatrix}$$

Frequency-dependent cycles of tumor evolution

$$\vec{x}_0 \rightarrow \vec{x}_1 \rightarrow \vec{x}_2 \rightarrow \ldots \rightarrow \vec{x}_T$$

A sequence of treatments gives rise to an evolutionary "cycle" if:

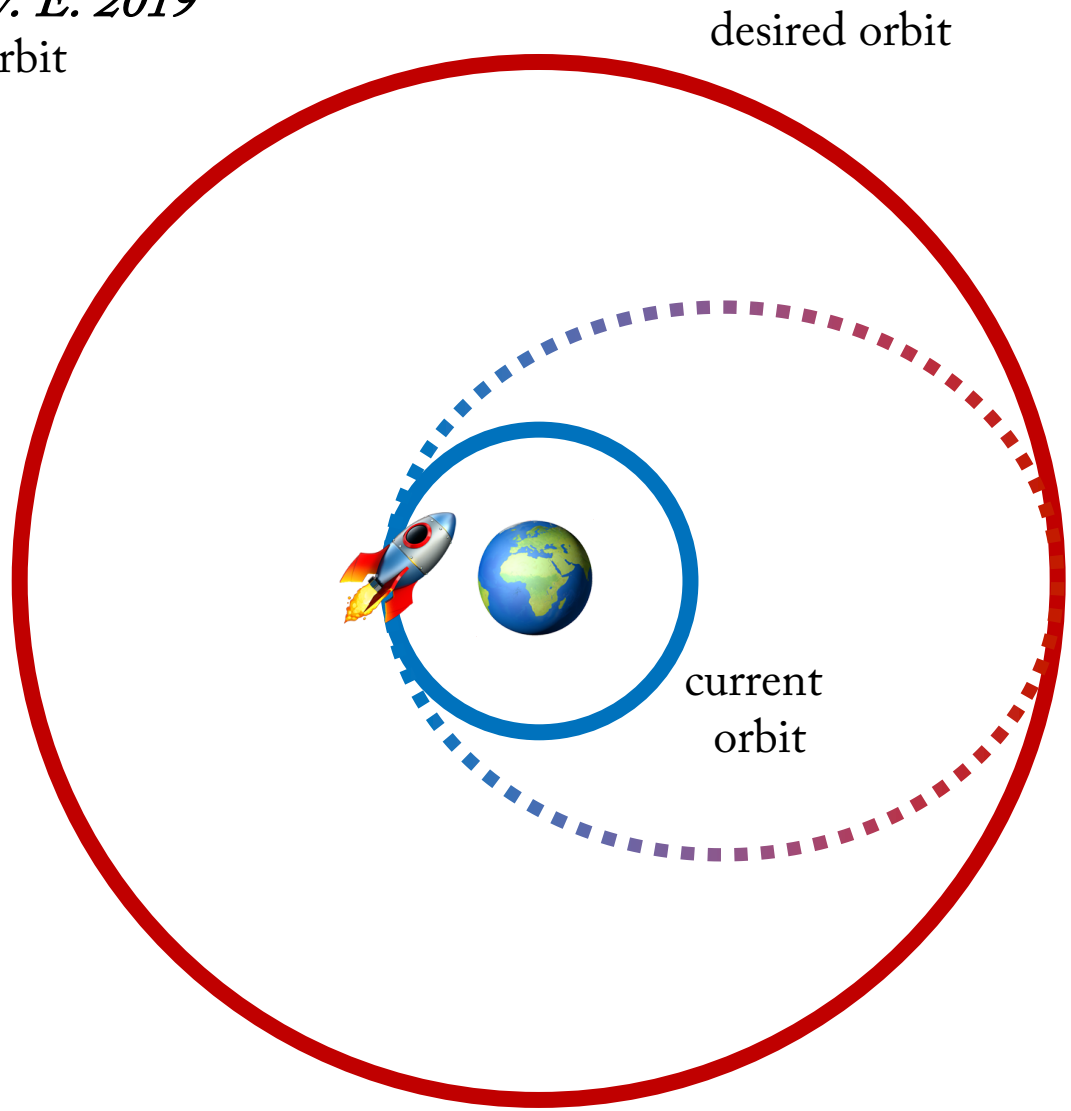
$$\vec{x}_T \approx \vec{x}_0$$

for some time period T > 0.

Drawing inspiration from orbital mechanics

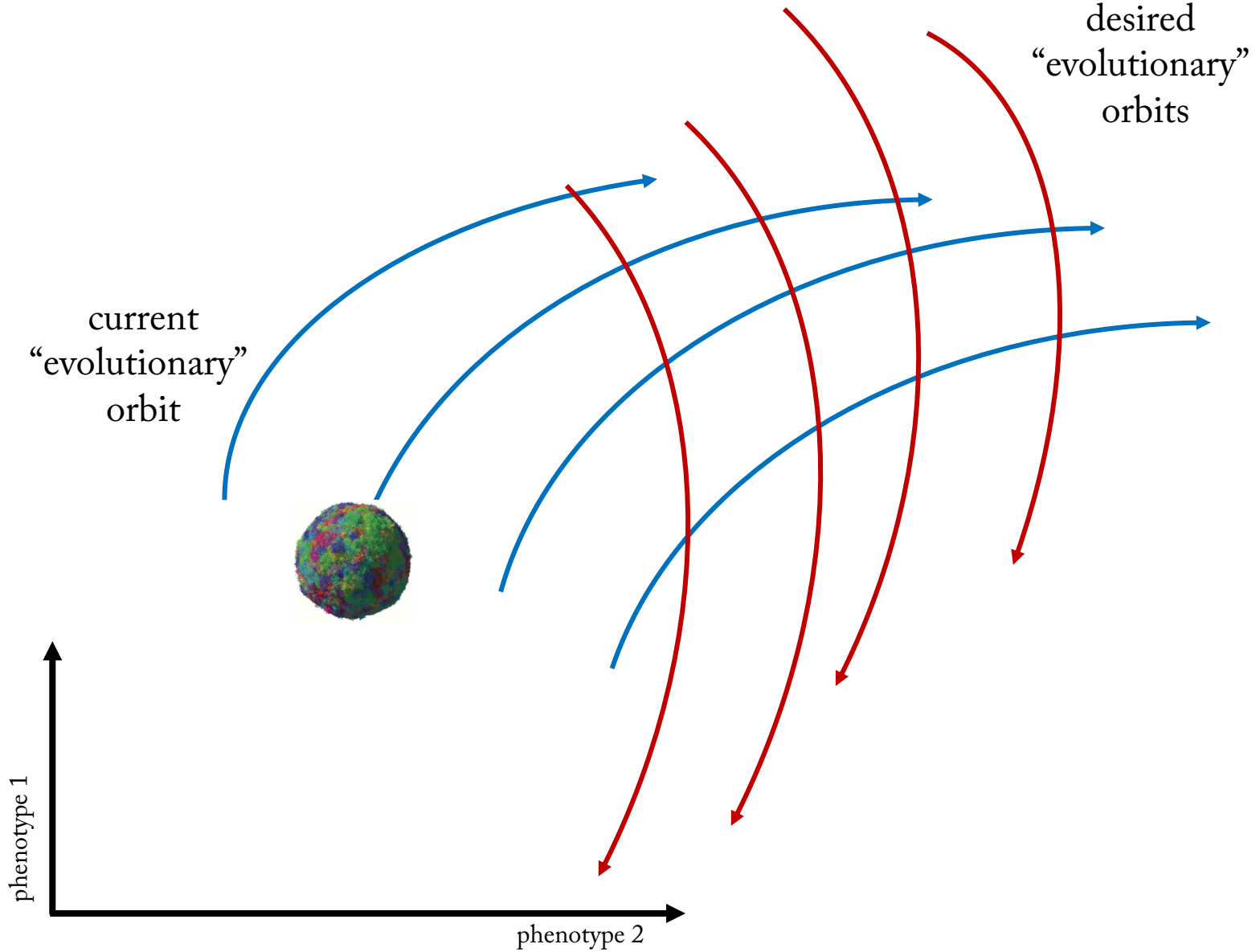
Newton et. al. Phys. Rev. E. 2019

- Hohmann Transfer Orbit



1. Current orbit is fixed & known
2. Desired orbit is fixed & known
3. The connecting orbit is tangent to current orbit and intersects desired orbit

Drawing inspiration from orbital mechanics



1. Current orbit is fixed & known
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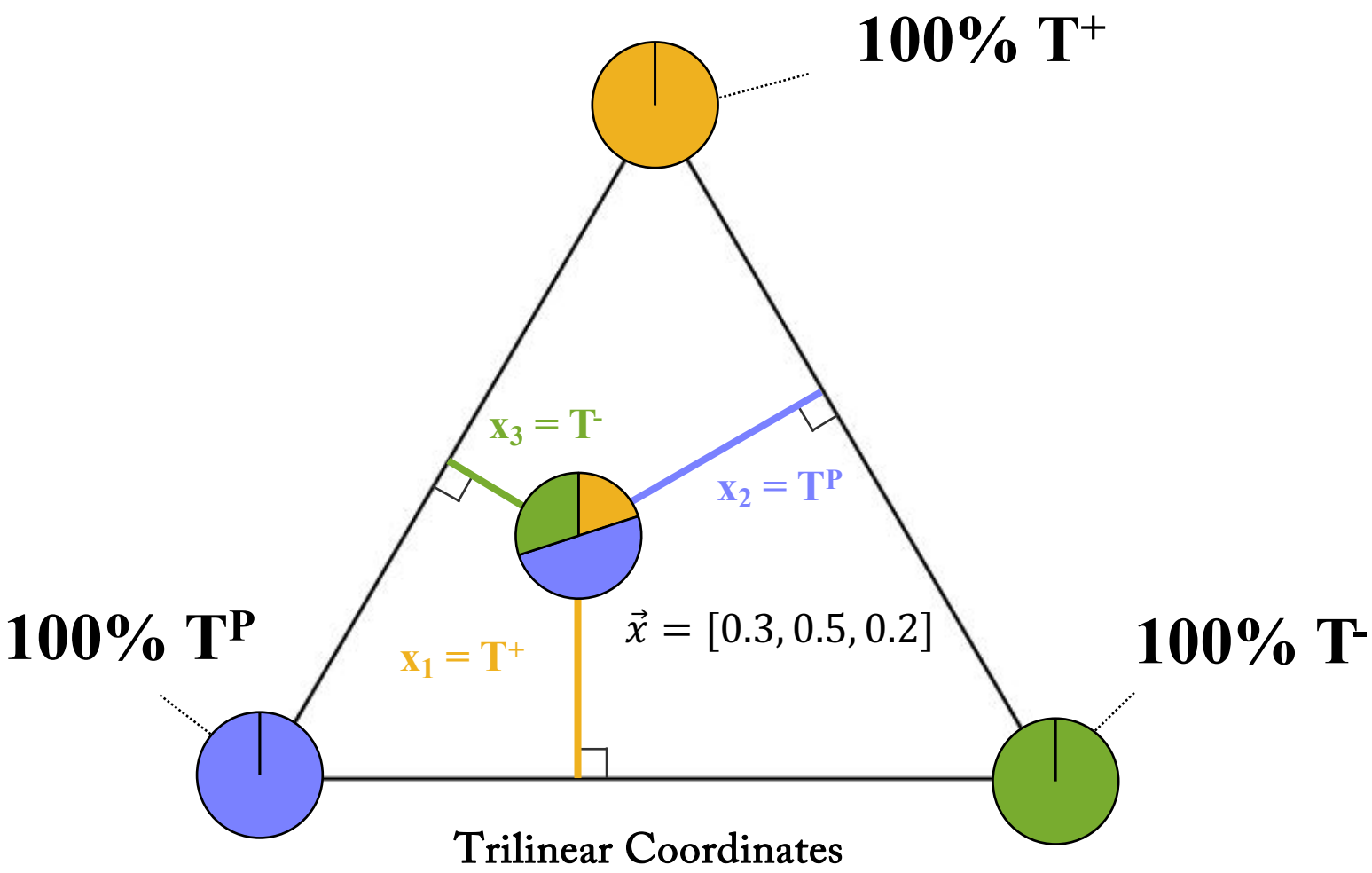
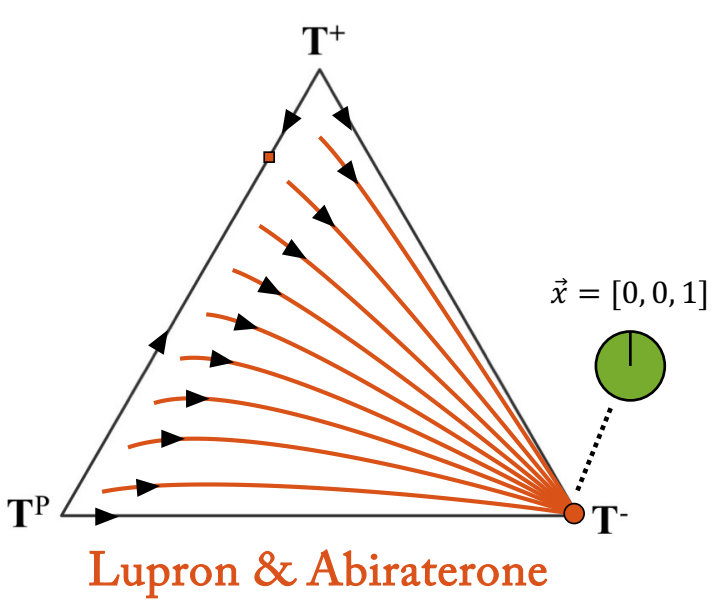
Triangular simplex

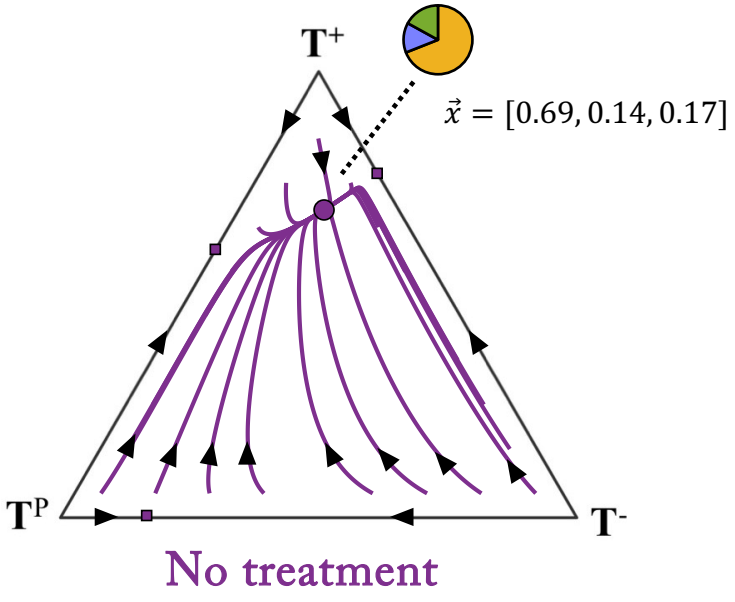


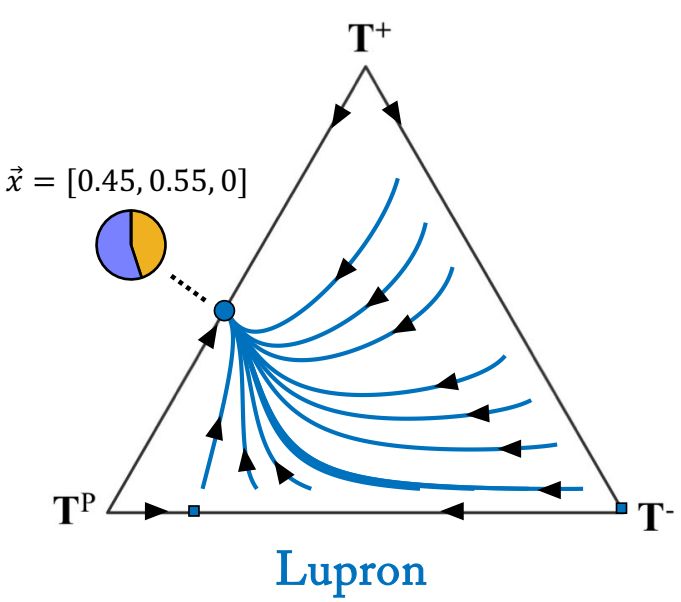
Trilinear Simplex

- The state space of all possible states of three populations
- $x_1 + x_2 + x_3 = 1$

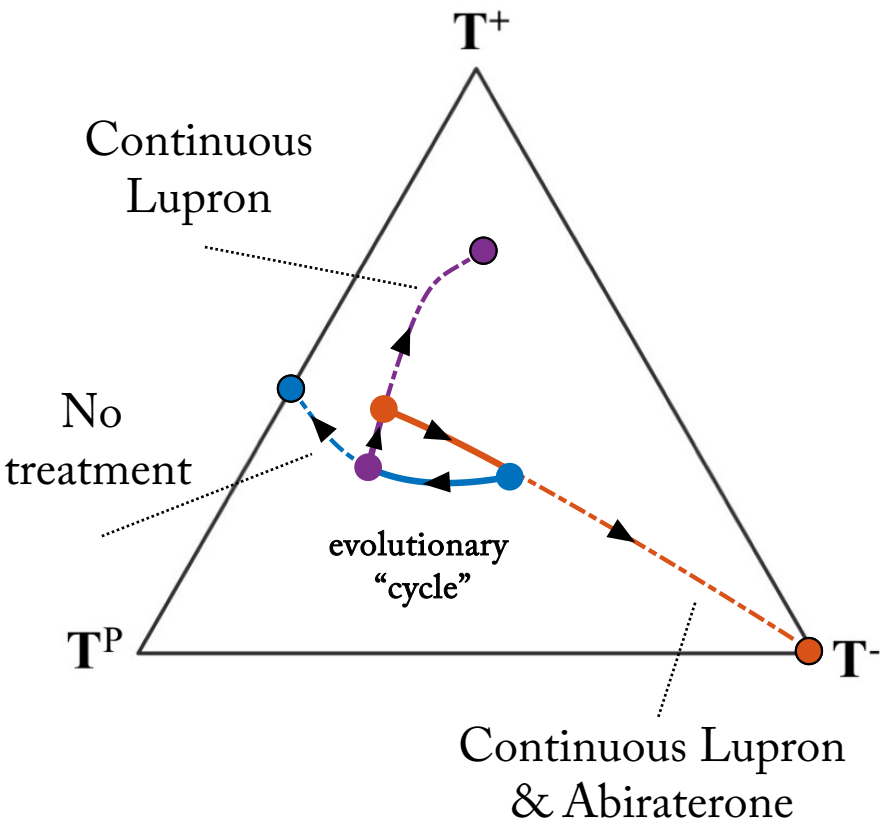
Frequency-dependent treatment dynamics

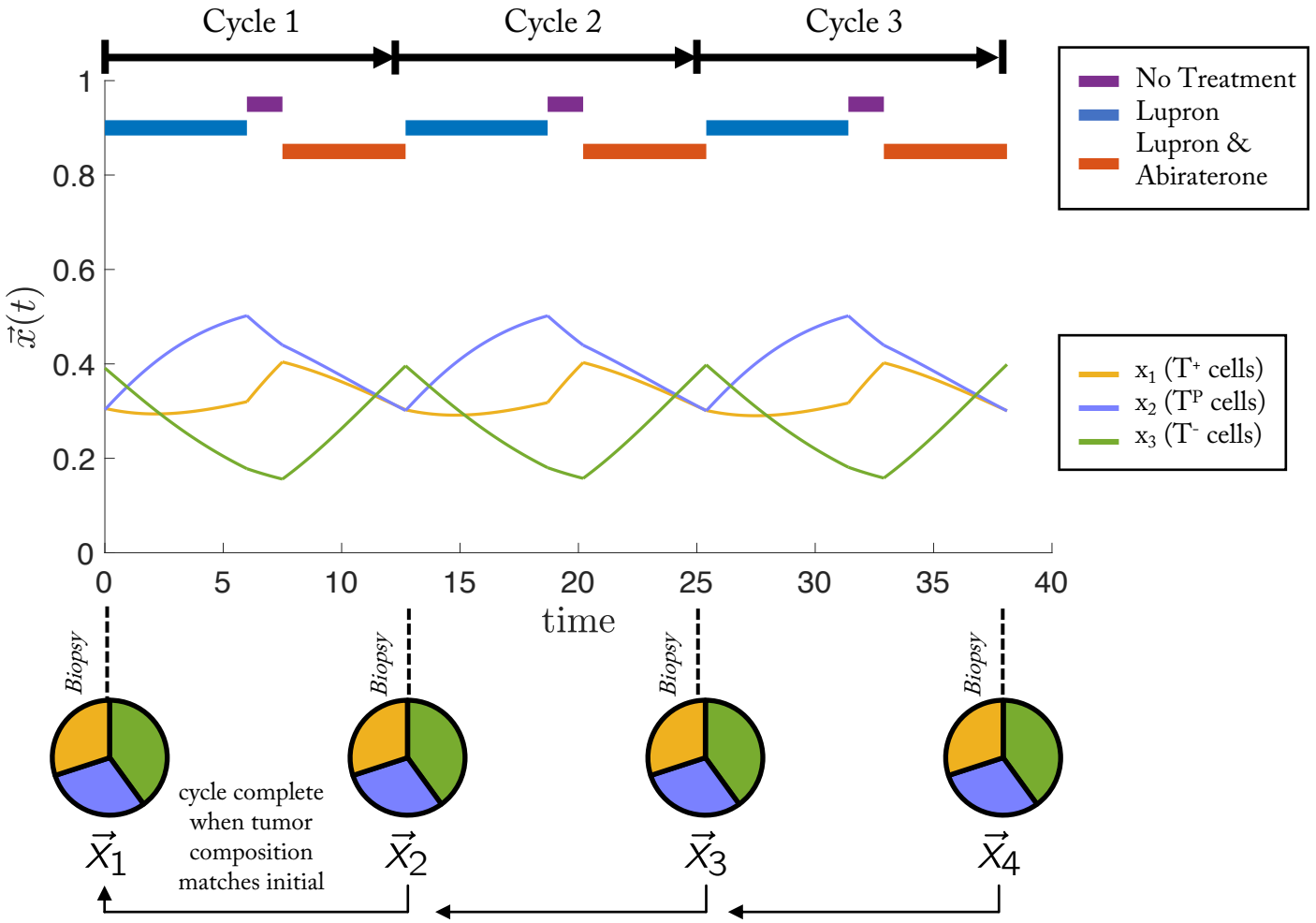




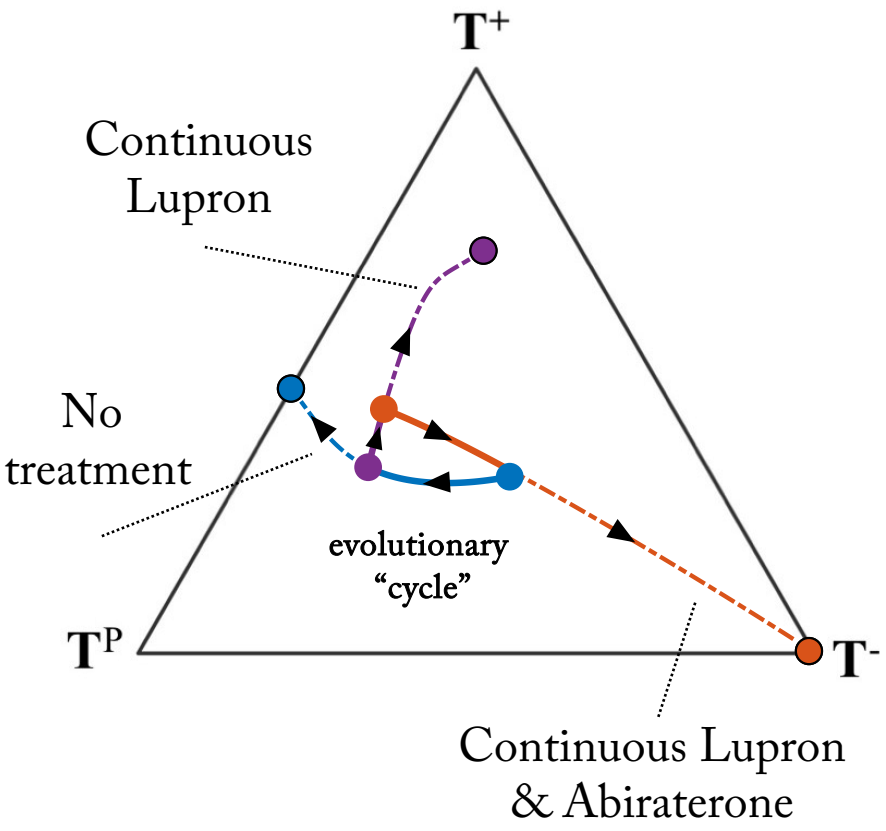


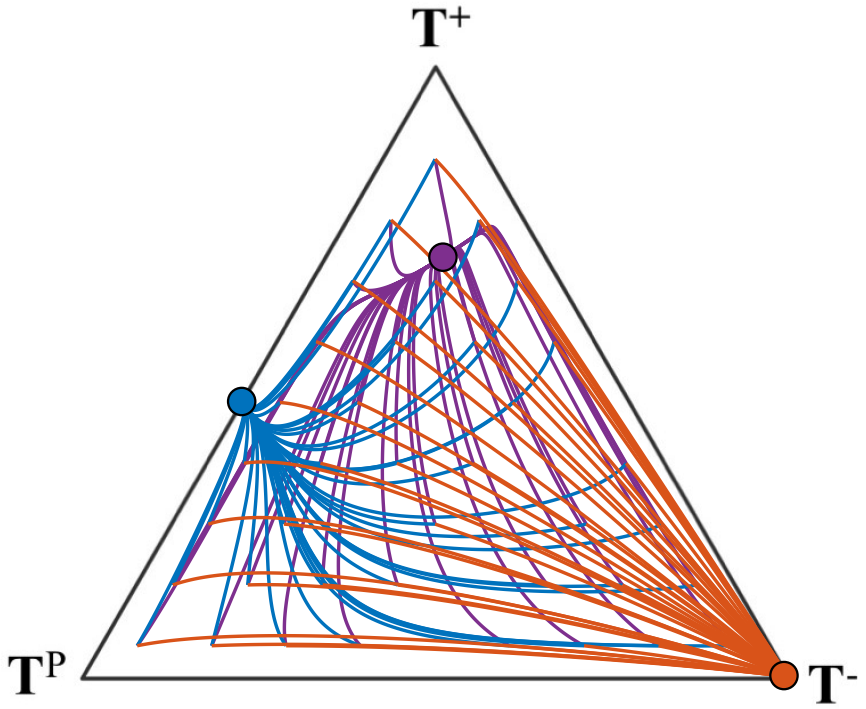
Frequency-dependent treatment dynamics





Frequency-dependent treatment dynamics





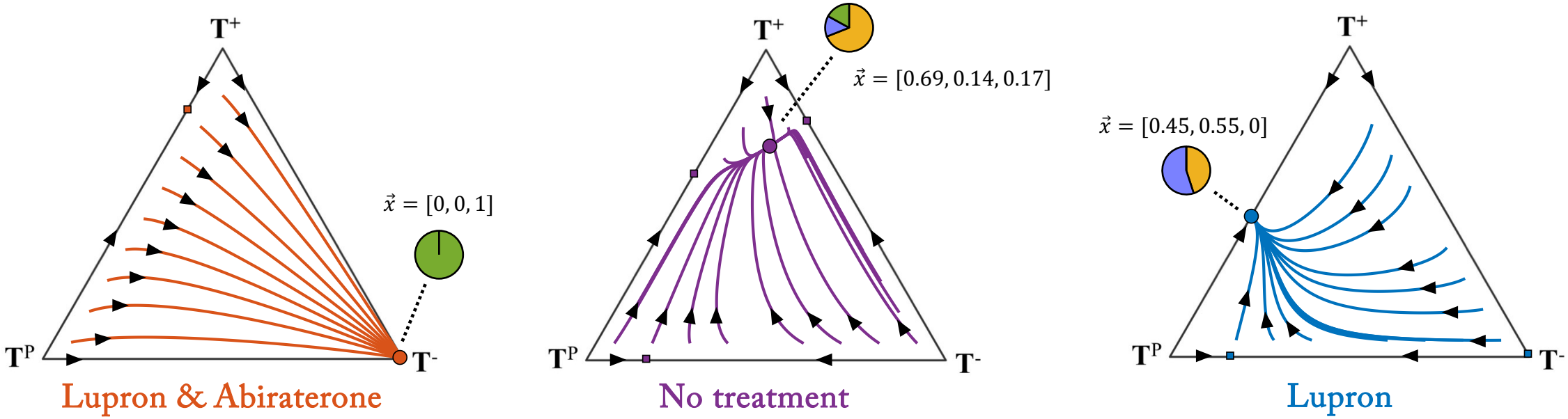
3. Evolutionary search space

" Most discoveries even today are a combination of serendipity and of searching."

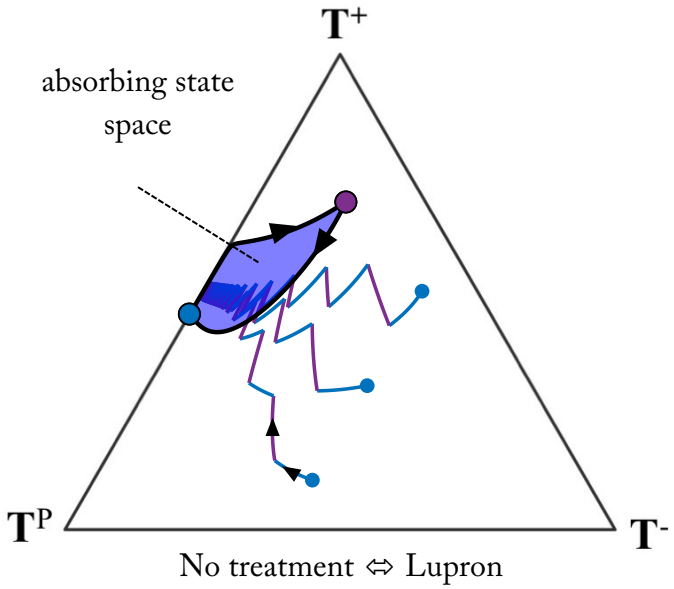
- Siddhartha Mukherjee -

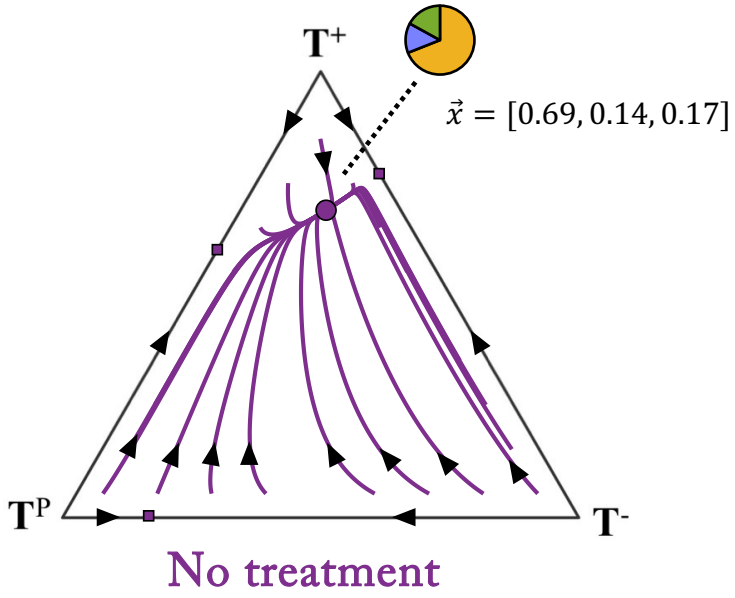
Evolutionary Search Space

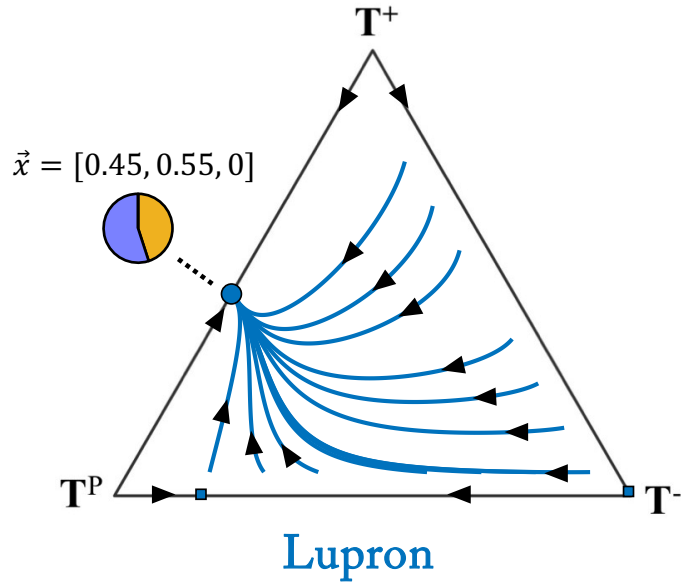
Pairwise treatment combinations



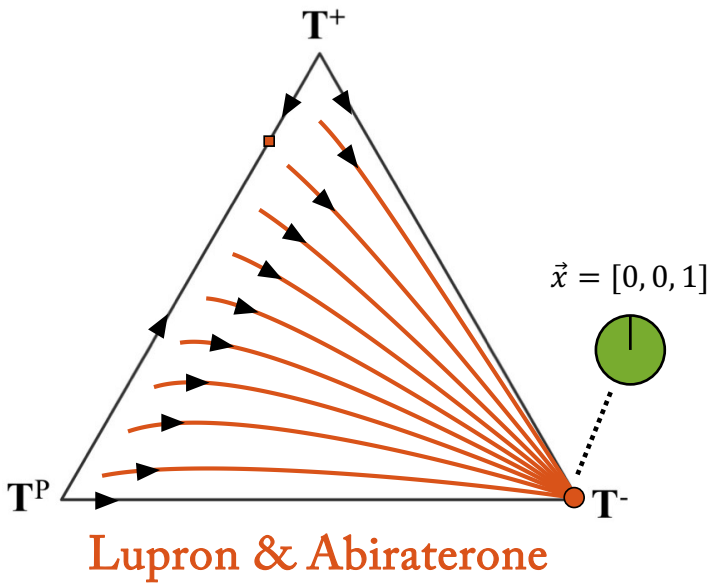
Evolutionary Search Space

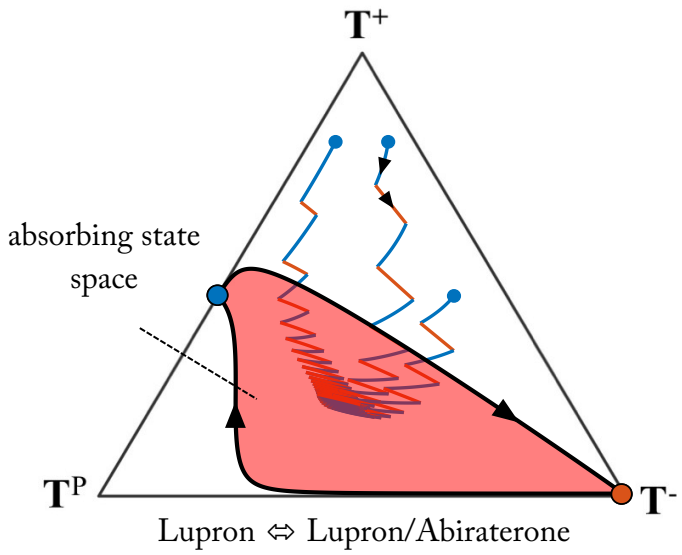


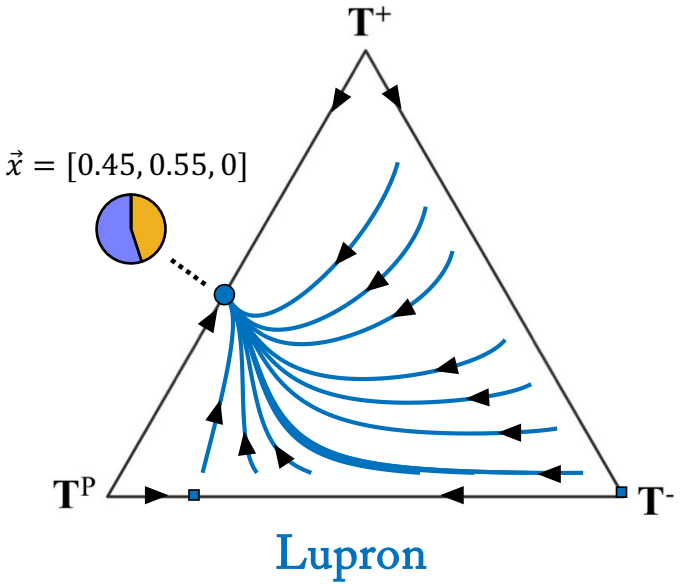




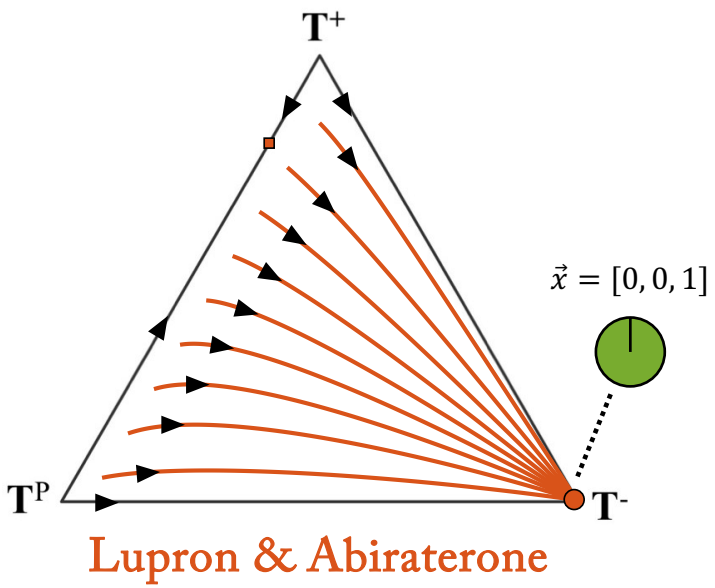
Evolutionary Search Space

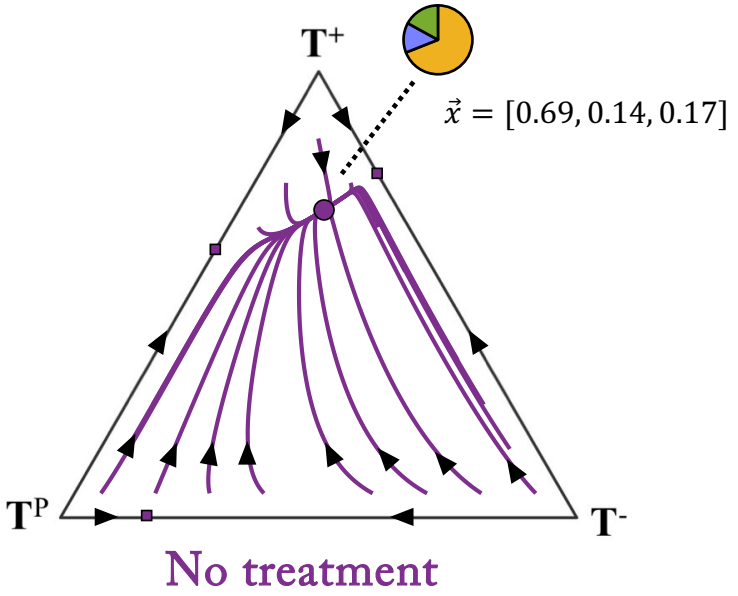


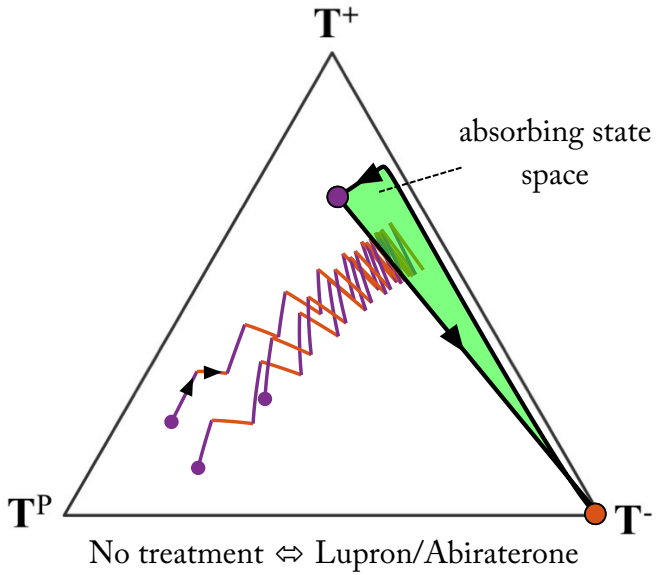




Evolutionary Search Space



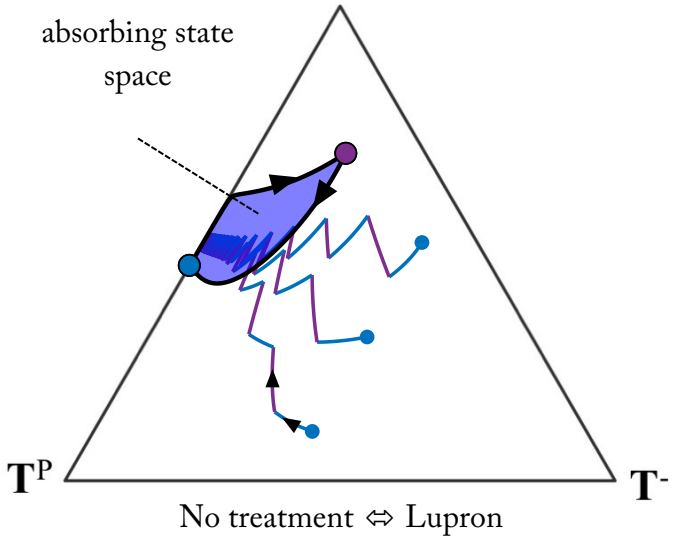


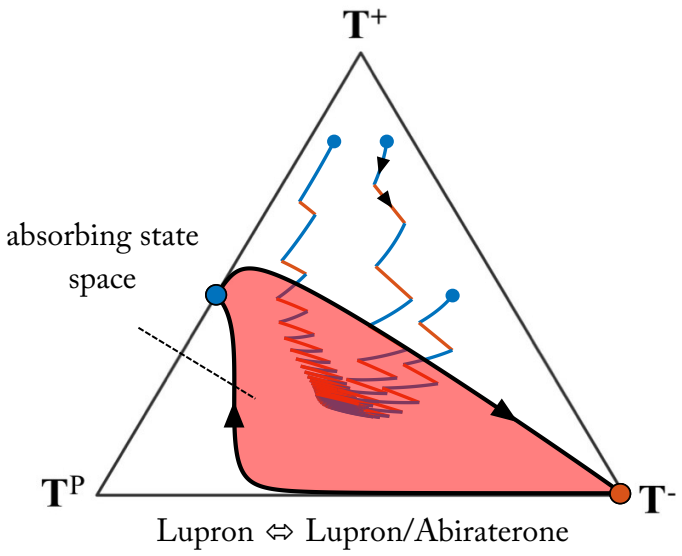


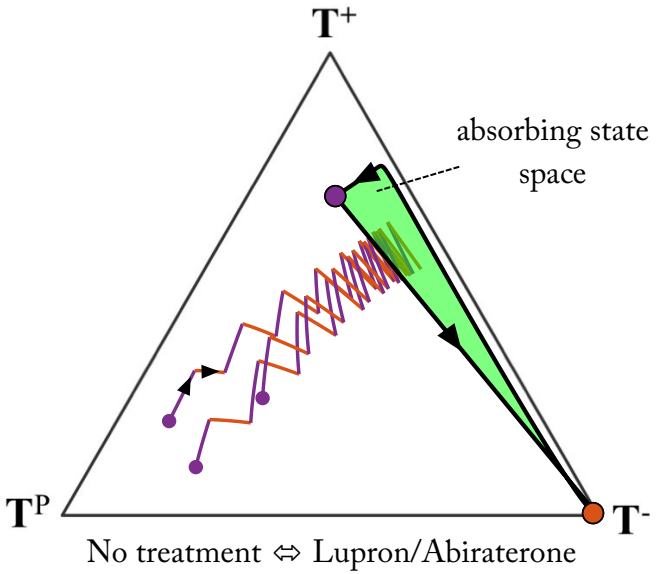
Evolutionary Search Space

Key observations:

- All possible drug sequences tend toward absorbing area
- Various drug combinations have varied size of absorbing space
- The longer time cycled, closer to absorbing space
- No treatment is an evolutionary process

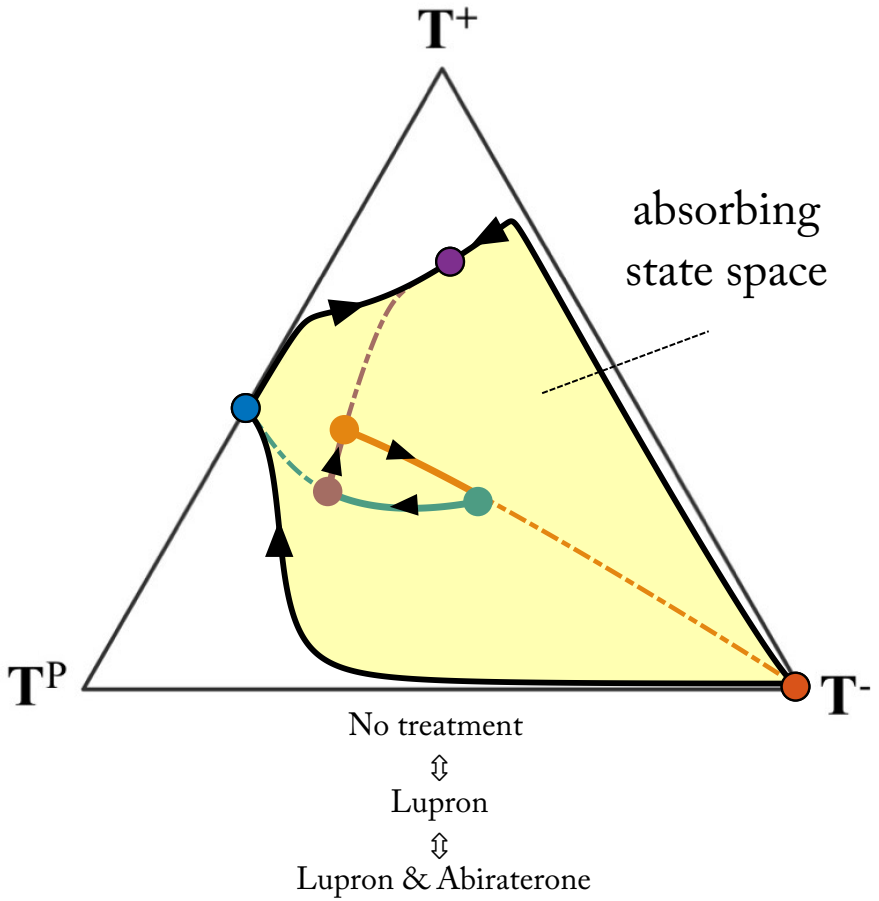






3 treatments

- Vastly expands absorbing state space
- "Orthogonal" drugs are desirable



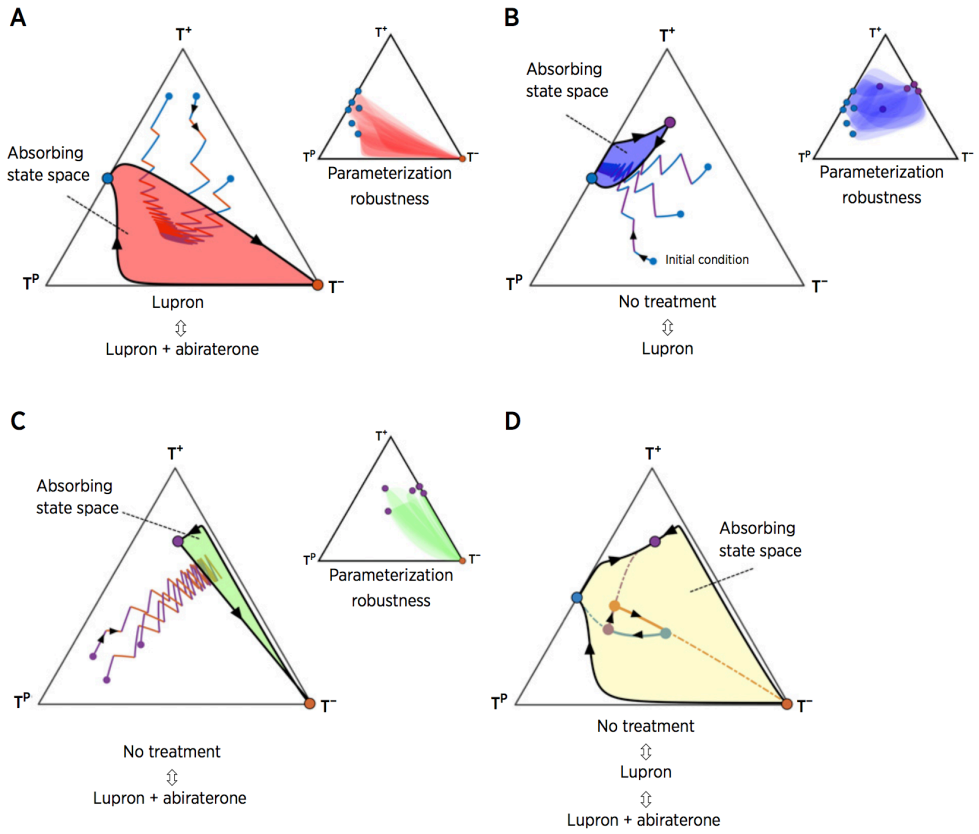
Payoff assumptions

No treatment

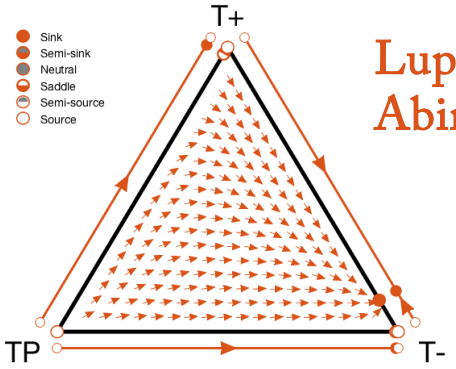
$c < e$	T^- cells have a higher fitness than T^P cells when interacting with many T^+, especially in low vasculature regions. Testosterone production by T^P production comes at some cost to provide public good to both self (T^P) and neighbor (T^+). Both c and e should decrease in the pre-treatment condition
$a > f$	T^+ cells have a higher fitness than T^- cells when interacting with many T^P, receiving advantage from the public good. The parameter a should increase in the pre-treatment condition f slightly decrease
$b > d$	T^+ cells have a higher fitness than T^P cells when interacting with many T^- because there is lack of spatial competition near vasculature for T^+ cells as testosterone is not being used
$a < b$	T^+ cells have a higher fitness competing with T^- over competition with T^P
$c < d$	Similarly, T^P cells have a higher fitness competing with T^- over competition with T^+
$e > f$	T^- cells have less competition for space in a tumor with mostly T^+ than with mostly T^P. The parameter f should decrease in the pre-treatment condition slightly

Lupron & Abiraterone

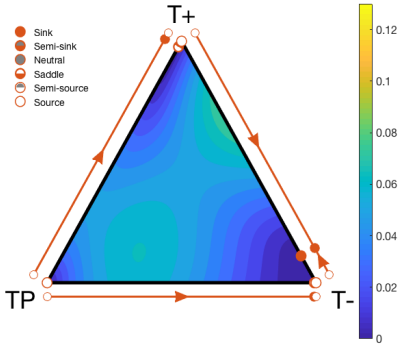
$c > e$	T^P cells have a higher fitness than T^- cells when interacting with few T^+ (absence of competition)
$a > f$	Interacting with mostly T^P cells, T^+ gains from the public good and from the new available space in low vasculature regions
$b < d$	Interacting with mostly T^- cells, T^P cells see little competition near vasculature. Payoffs to $T+$ cells, b, may be small or zero
$a > b = 0$	T^+ cells need the T^P cells to succeed in the absence of systemic testosterone
$c > d$	c is likely the largest parameter as T^P cells have the highest fitness in a mostly T^- tumor without systemic testosterone
$e > f$	Again, T^P cells outcompete T^- cells in the absence of systemic testosterone



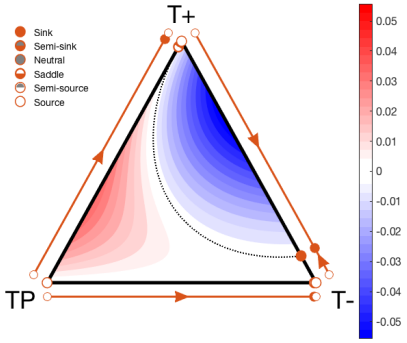
Velocity of frequency-dependent dynamics



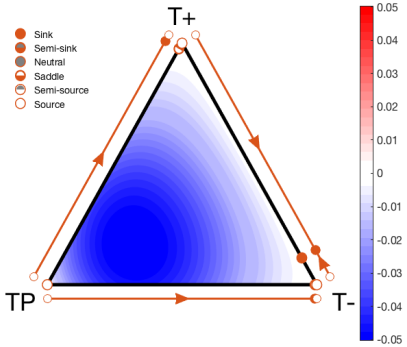
Lupron & Abiraterone



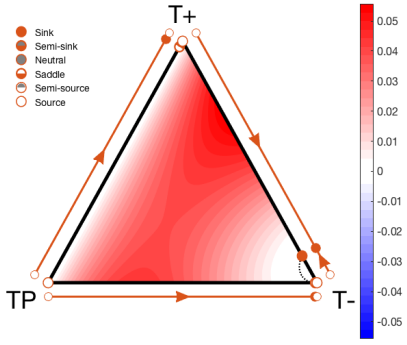
T+ velocity

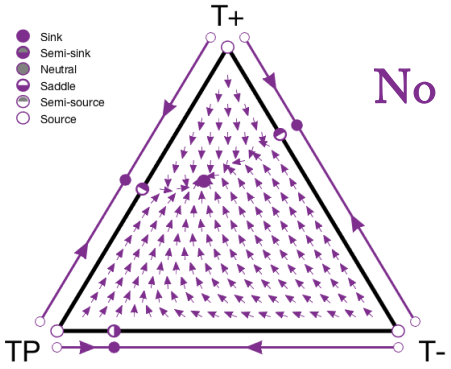


TP velocity

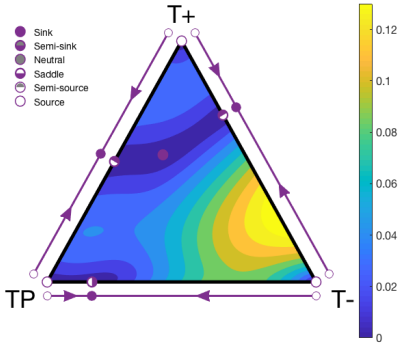


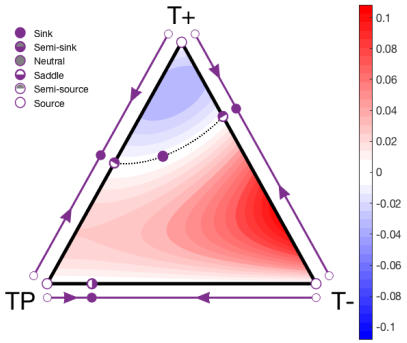
T- velocity

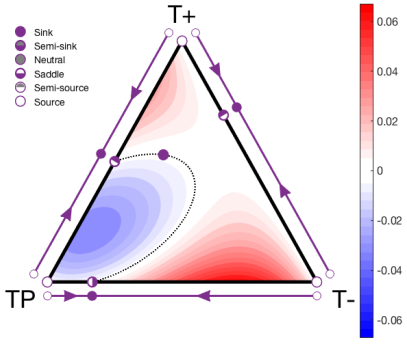


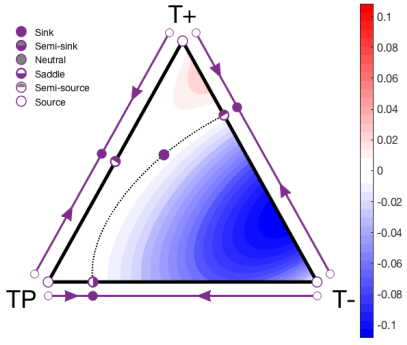


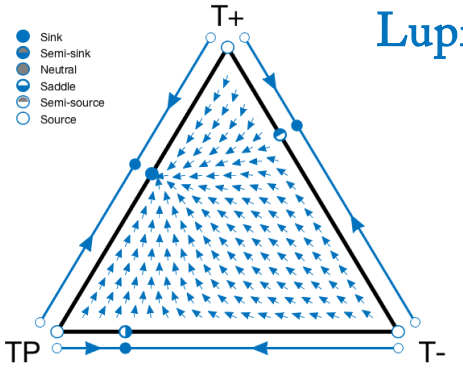
No treatment



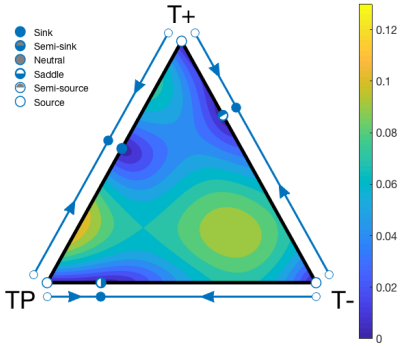


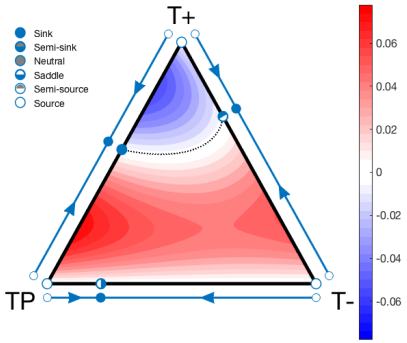


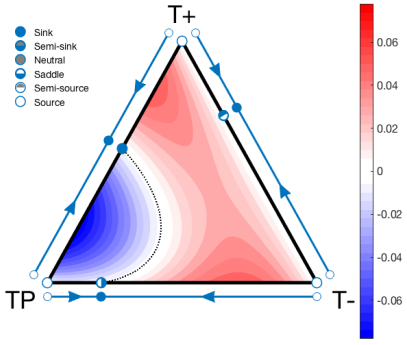


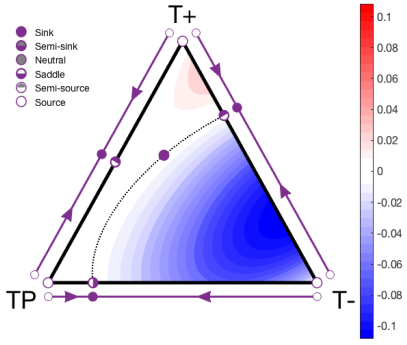


Lupron









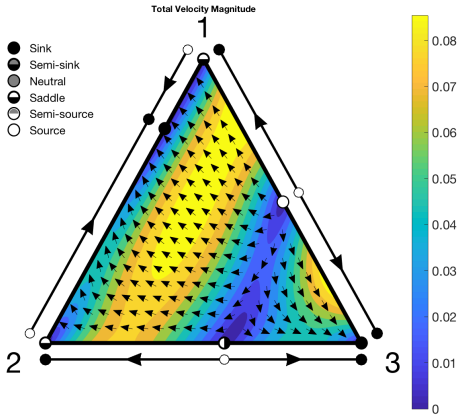
4. IsoMaTrix

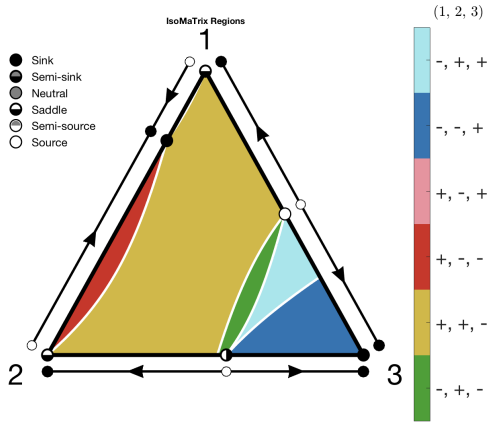
A tool for visualizing matrix games

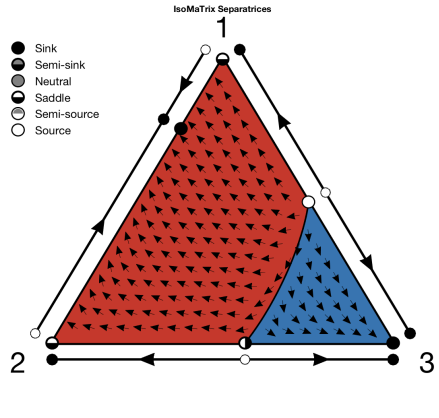
"The best investment is in the tools of own's own trade."

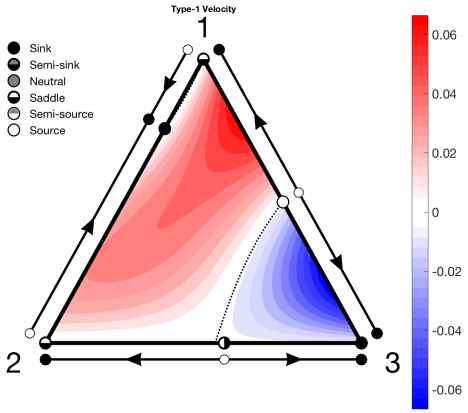
- Benjamin Franklin -

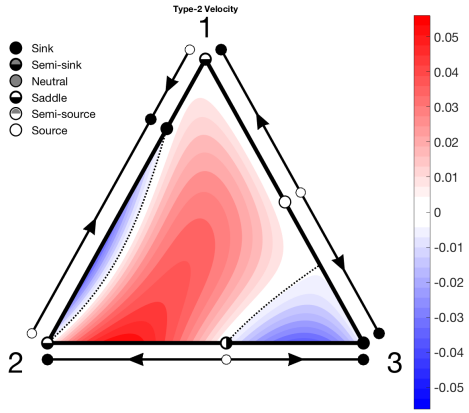
IsoMaTrix: visualizing Isoclines of Matrix games

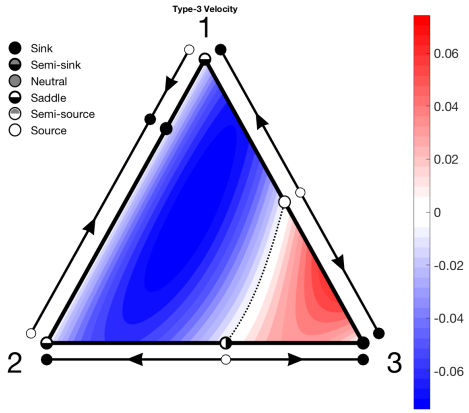












Download at:

- github.com/MathOnco/isomatrix

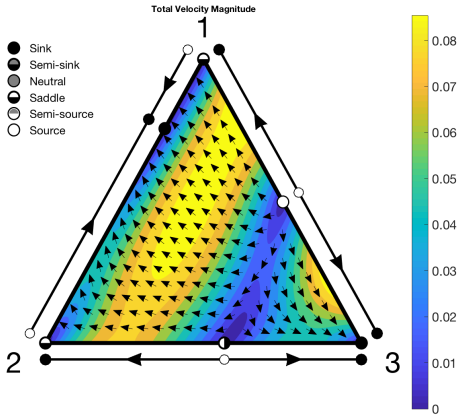
Joint work with:

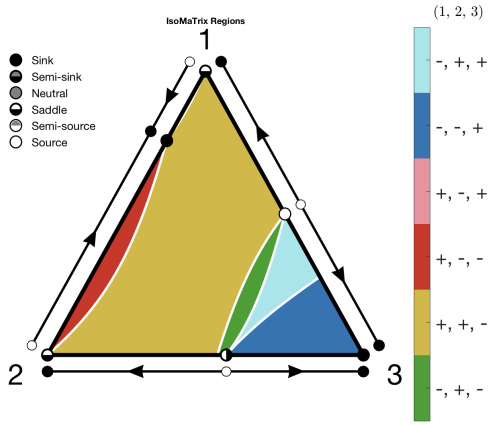
- Yongqian Ma (Univ. Southern California)
- Artem Kaznatcheev (Oxford Univ)
- Alexander Anderson (Moffitt)

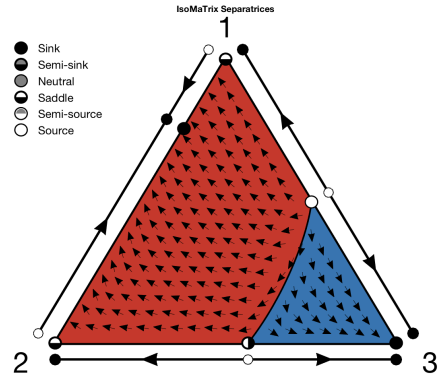
How to use:

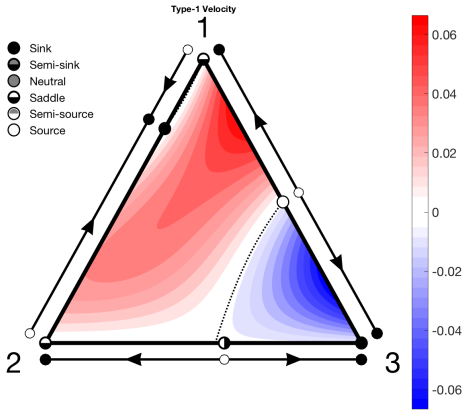
- 6 graphs with one command: isomatrix(A)

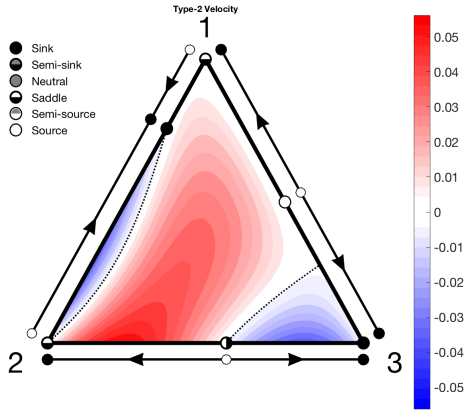
IsoMaTrix: visualizing Isoclines of Matrix games

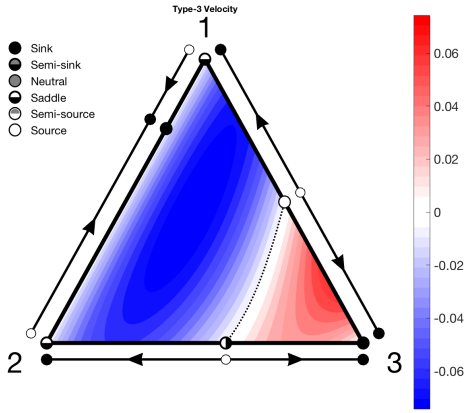












Integrated Mathematical Oncology

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