# Optimal Control to Reach Eco-Evolutionary Stability in Metastatic Castrate-Resistant Prostate Cancer

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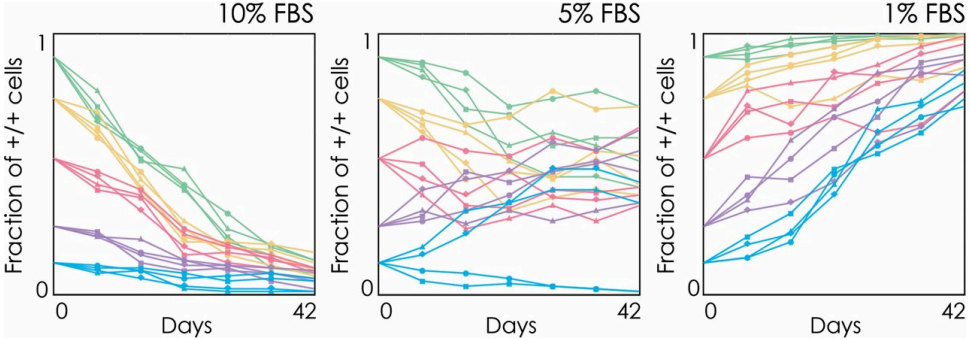
CATMO2020

# Stability: the extreme interpretation of adaptive therapy

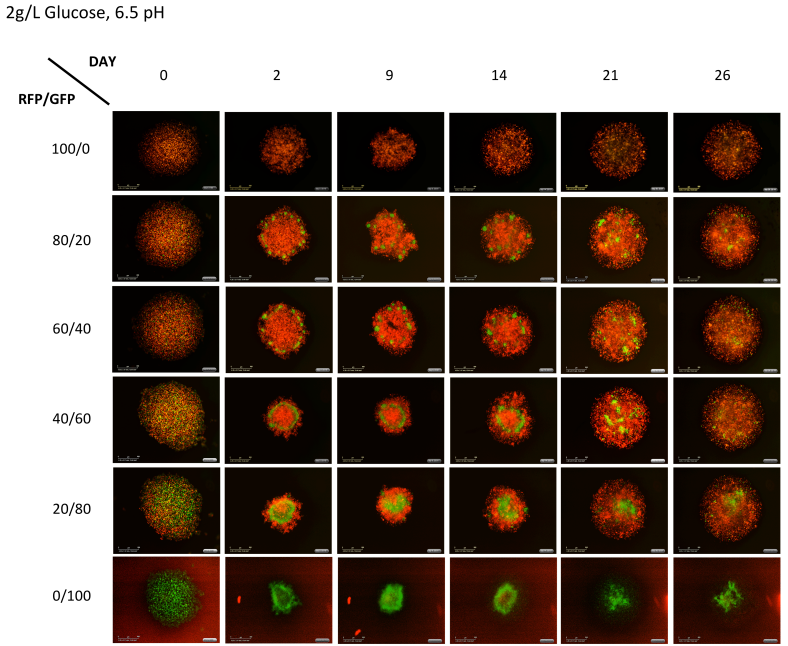
Polymorphic stability in heterogeneous tumor cell populations has been shown to exist explicitly in breast cancer and neuroendocrine pancreatic cancer in-vitro.

Can this happen in-vivo???

We can hope…




Archetti M, Ferraro DA, Christofori G. Heterogeneity for IGF-II production maintained by public goods dynamics in neuroendocrine pancreatic cancer. Proceedings of the National Academy of Sciences. 2015;112(6):1833–1838.

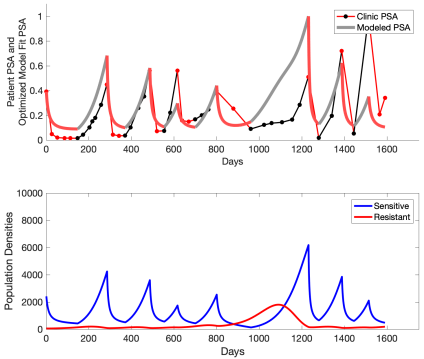


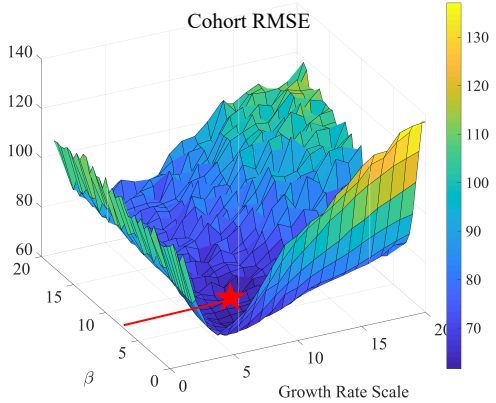

Freischel AR, Damaghi M, Cunningham JJ, Ibrahim-Hashim A, Gillies RJ, Gatenby RA, et al. Frequency-dependent interactions determine outcome of competition between two breast cancer cell lines. bioRxiv. 2020;.

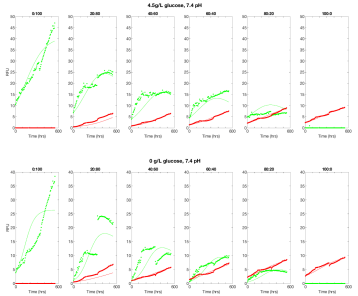
# Competition coefficients greater than 1

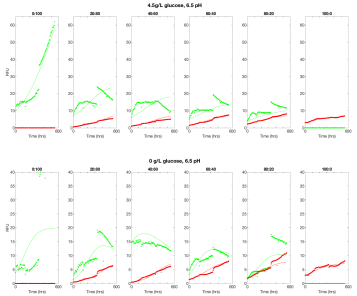
Fitting the model to clinical trial patients (unpublished) a competition coefficient for sensitive cells on resistant cells of >5 results in the best cohort fits.

From Freischel in-vitro experiments competition coefficients can be as high as 12.6!



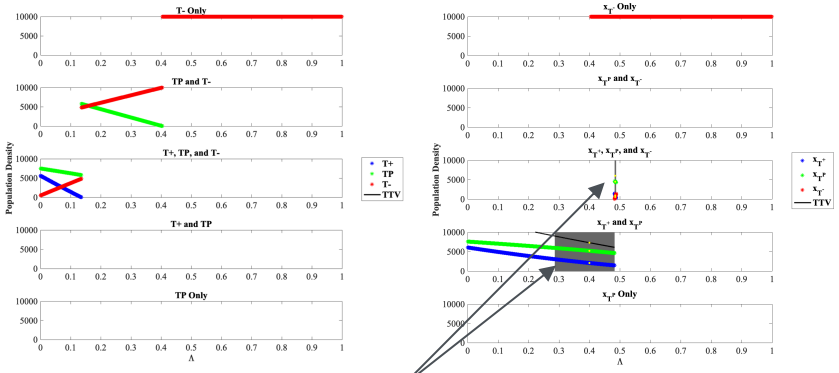


b.

| | $r_{MCF-7}$ | $r_{MDA-MB-231}$ | $K_{MCF-7}$ | $K_{MDA-MB-231}$ | α | β | Outcome |
|---|---|---|---|---|---|---|---|
| **4.5 g/L Glucose, 7.4 pH, +Glutamine** | 0.013 | 0.004 | 31.8 | 12.9 | 3.98 | -0.243 | MDA-MB-231 outcompetes MCF-7 |
| **4.5 g/L Glucose, 7.4 pH, -Glutamine** | 0.008 | 0.006 | 40.8 | 10.4 | 4.95 | 0.021 | MDA-MB-231 outcompetes MCF-7 |
| **4.5 g/L Glucose, 6.5 pH, +Glutamine** | 0.011 | 0.010 | 32.5 | 6.4 | 3.69 | 0.025 | Coexistence |
| **4.5 g/L Glucose, 6.5 pH, -Glutamine** | 0.004 | 0.006 | 112.2 | 6.8 | 12.64 | -0.066 | Coexistence |
| **0 g/L Glucose, 7.4 pH, +Glutamine** | 0.019 | 0.004 | 29.2 | 29.4 | 7.56 | -0.229 | MDA-MB-231 outcompetes MCF-7 |
| **0 g/L Glucose, 7.4 pH, -Glutamine** | 0.014 | 0.006 | 26.4 | 10.4 | 2.90 | 0.155 | MDA-MB-231 outcompetes MCF-7 |
| **0 g/L Glucose, 6.5 pH, +Glutamine** | 0.019 | 0.009 | 23.5 | 7.1 | 2.51 | 0.096 | Coexistence |
| **0 g/L Glucose, 6.5 pH, -Glutamine** | 0.012 | 0.007 | 20.0 | 7.4 | 1.34 | -0.080 | Coexistence |

# If there is stable equilibria, how do we get there?

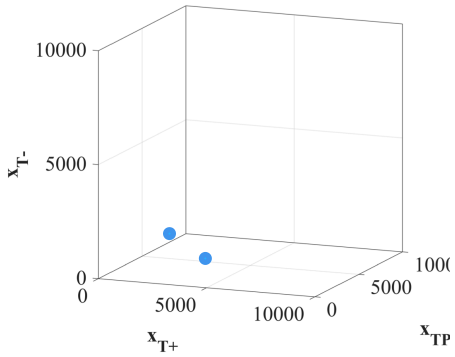
$$A = (\alpha_{ij}) = \begin{pmatrix} 1 & 0.7 & 0.8 \\ 0.4 & 1 & 0.6 \\ 0.5 & 0.9 & 1 \end{pmatrix} \qquad A = (\alpha_{ij}) = \begin{pmatrix} 1 & 0.7 & 0.8 \\ 0.4 & 1 & 0.6 \\ 0.5 & \mathbf{2} & 1 \end{pmatrix}$$

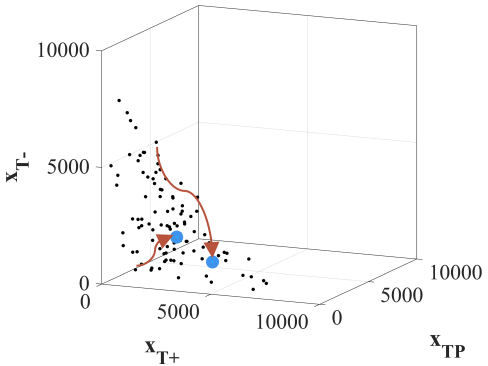



$$\sum_{i \in \mathcal{T}} x_i \leq 9000$$

Increasing the competition allows for a stable equilibria within a tolerable tumor burden.

How can we apply Abiraterone to traverse this tumor composition space to arrive and stay at these stable equilibria from any initial tumor composition???

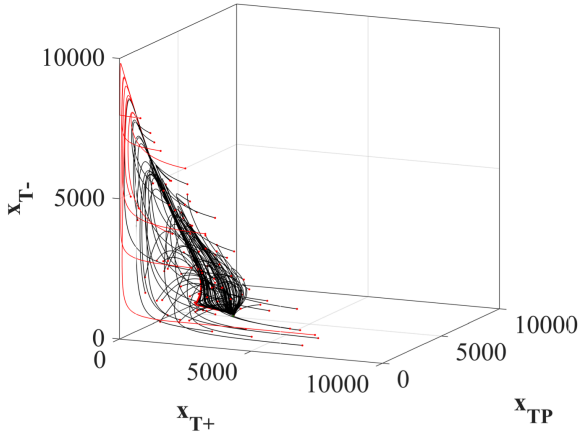


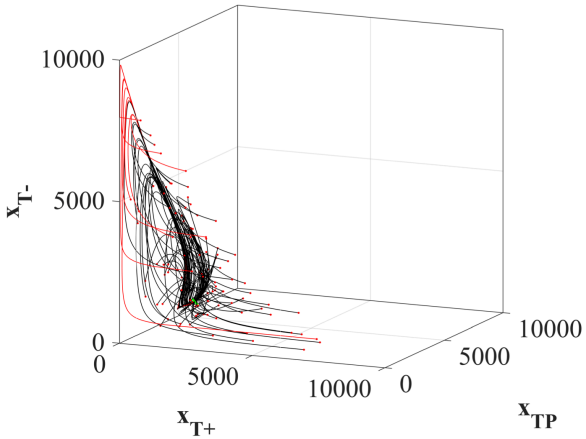



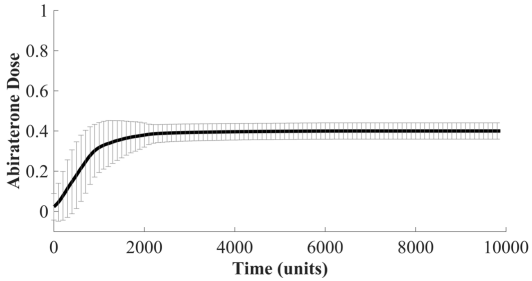
# Titration!!!

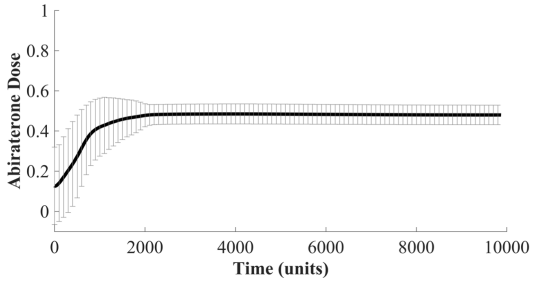
Really?... Titration? Ok.

- If the properties of the underlying biology allow stabilization (**big if…**)
- Regardless of the actual composition of the stable polymorphic tumor heterogeneity…
- **Increasing dose titration protocol may, in general, provide an appropriate dosing strategy to achieve stabilization.**



# Titration isn't new!

- Most notably in oncology, a 'ramp-up' protocol for Venetoclax is used in patients with chronic lymphocytic leukemia in order to limit tumor lysis syndrome (physical toxicity).

- In patients with hepatocellular carcinoma a dose titration of sorafenib is used to significantly lower overall cost (financial toxicity) while maintaining equivalent survival.

- Titration of axitinib resulted in a greater proportion of patients with metastatic renal cell carcinoma achieving an objective response.

- Incredibly, titration of regorafenib in patients with metastatic colorectal cancer actually increased median overall survival from 5.9 months (initiating treatment at standard dose) to 9.0 months.

# Can we do this with no information (aka in the clinic)?

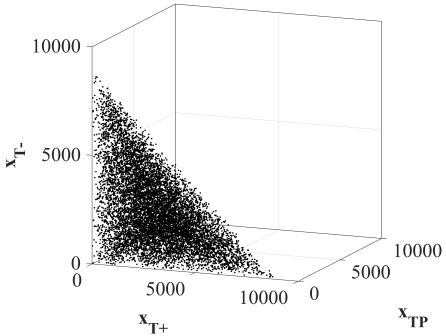
1. Maximum tolerated dose
2. Adaptive therapy cutting the initial volume by 50%.
3. Stabilization at initial tumor volume $V_a$, with $\Lambda(t_0) = 1$.
4. Stabilization at initial tumor volume $V_a$ with $\Lambda(t_0) = 0$.

$V_a = \sum_{i \in \mathcal{T}} x_i(t_0)$

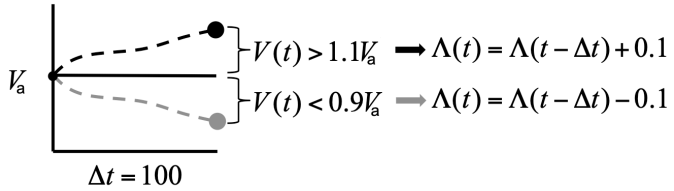
5. Stabilization at maximum tolerated tumor volume $V_b$ with $\Lambda(t_0) = 1$.
6. Stabilization at maximum tolerated tumor volume $V_b$ with $\Lambda(t_0) = 0$.

$V_b = 7000$

Initial Tumor Compositions

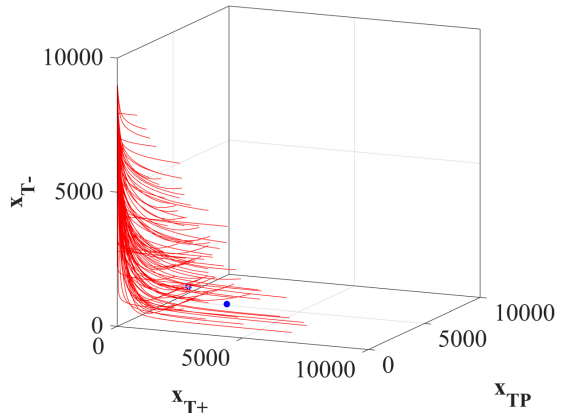


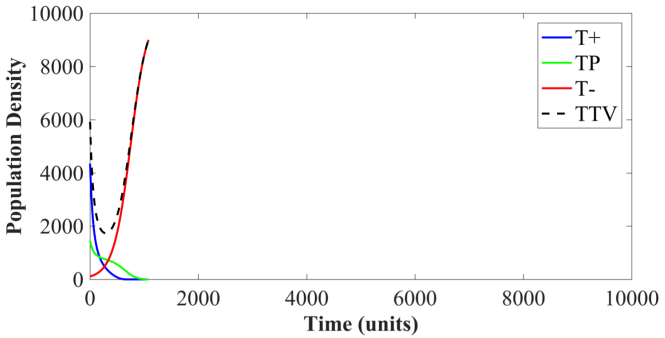

Stabilization Protocol



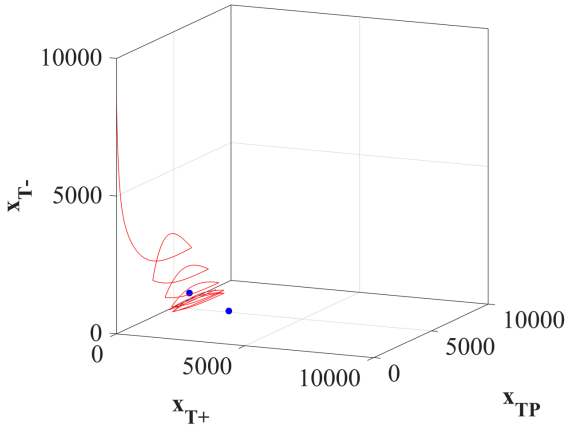
# Standard of Care and 50% Adaptive Therapy

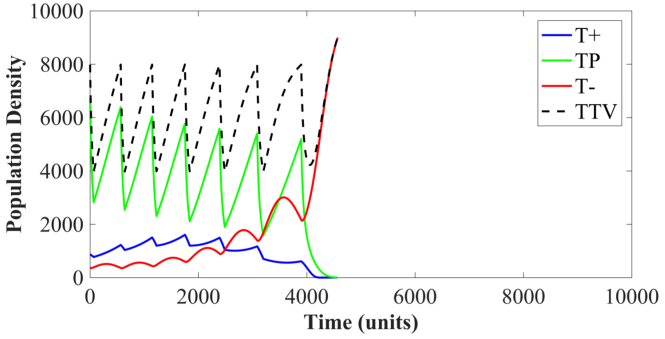
MTD



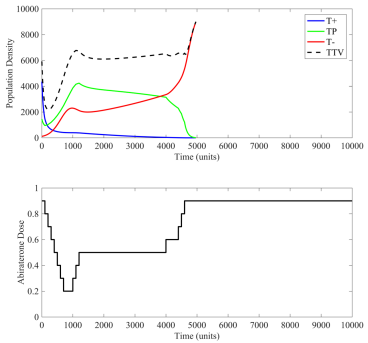

Adaptive Therapy



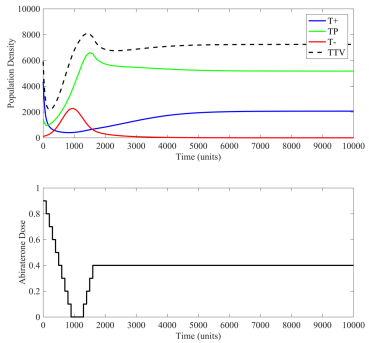



# Dose titration protocols for a single patient.

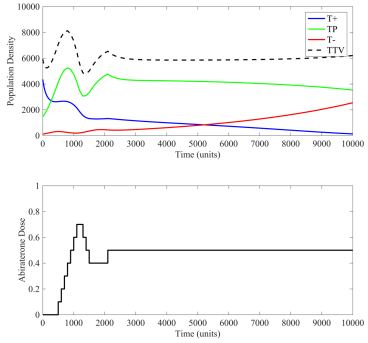
$V_a$, with $\Lambda(t_0) = 1$



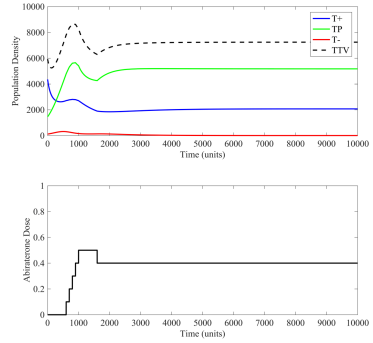

$V_b$ with $\Lambda(t_0) = 1$

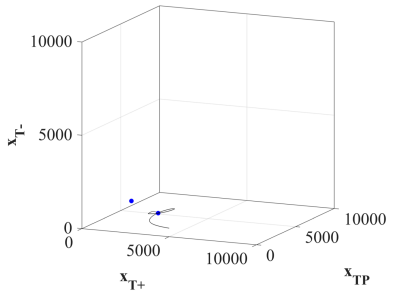



$V_a$ with $\Lambda(t_0) = 0$




$V_b$ with $\Lambda(t_0) = 0$



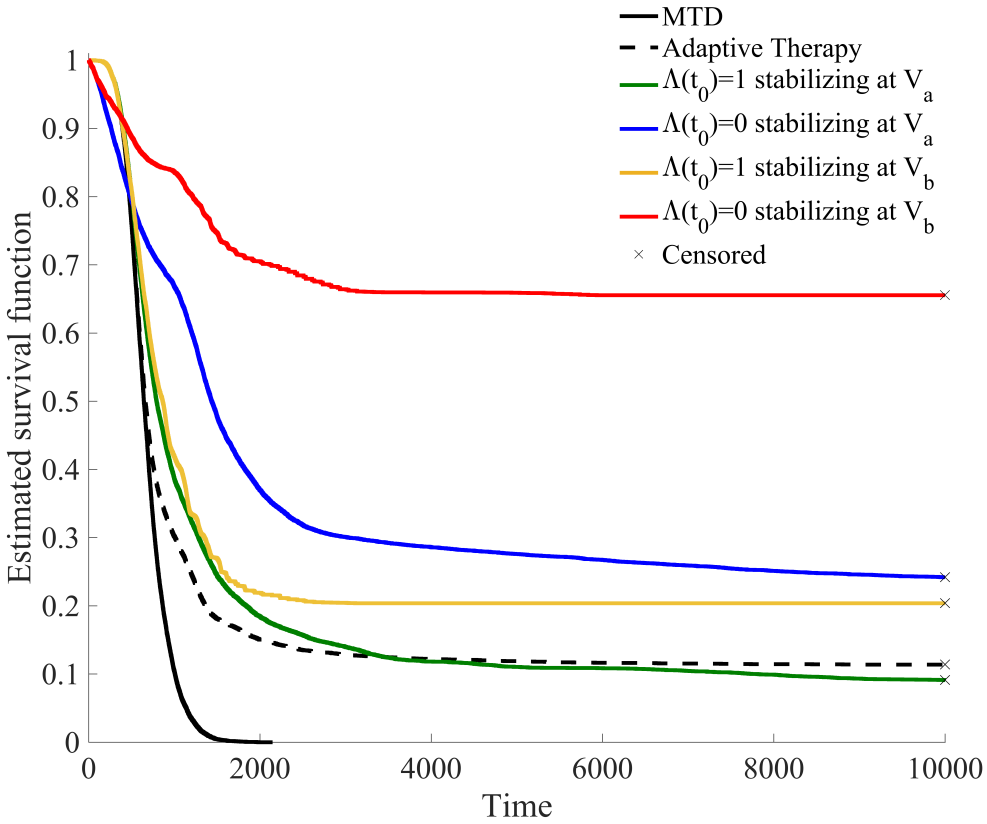

Stabilizing at a low volume (~6000) and starting at MTD results in competitive release.

Increasing the attempted stabilization volume to 7000 saves this patient, even with MTD as initial dose.

Stabilizing at low volume and starting at minimum dose works (but you can see that we are slowly failing).

Stabilizing at high volume and using this titration arrives at stable equilibrium.

# Kaplan Meier of six clinically feasible treatments



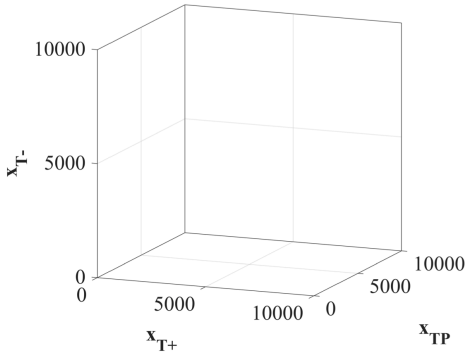
# Who lives and who dies?

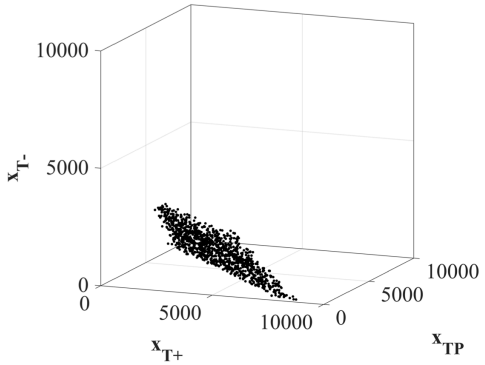
MTD

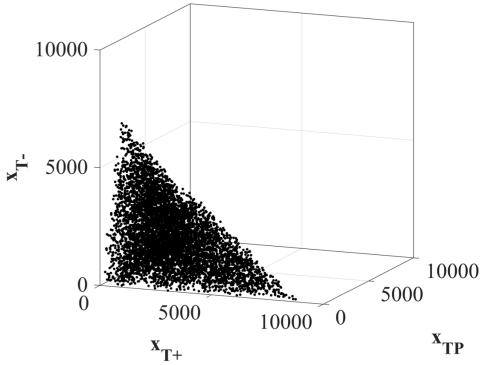
50% Adaptive Therapy

Increasing Dose Titration to Max Tolerable Tumor Volume

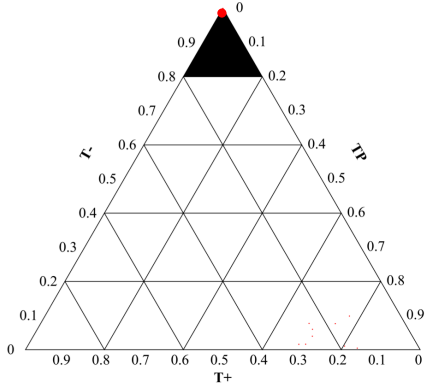
Initial conditions of surviving patients

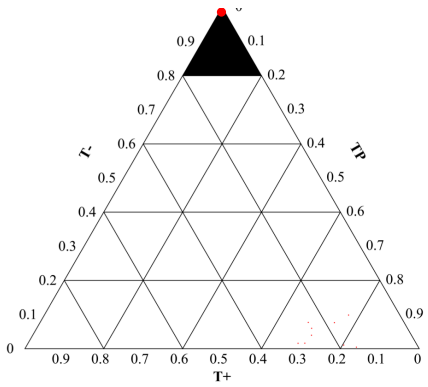


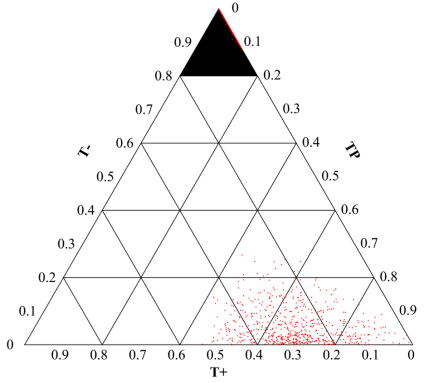




Final conditions of deceased patients

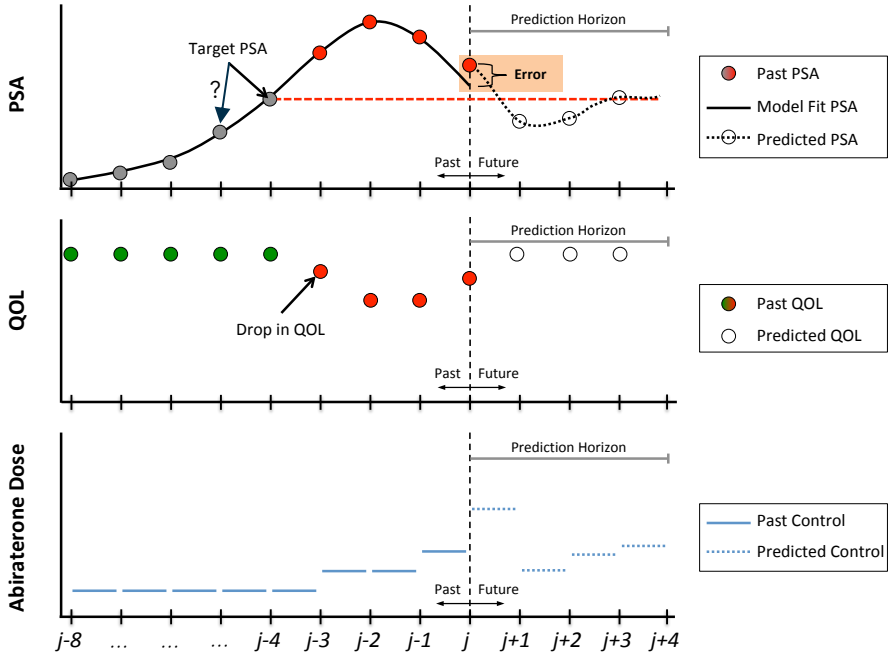


# Conclusions

- Theoretically, an increasing dose titration could provide benefit beyond a standard adaptive therapy.
- We could potentially implement this clinically with little/no additional information.
- When we reject "cure" we must replace our definition of success.
- For this method **quality of life** becomes paramount. Stabilize at the largest tumor the patient is comfortable with. There are so many factors that go into this.
- While maximum tolerable tumor burden is theoretically ideal, *minimum containable tumor burden* would no doubt be clinically ideal.



# “The purpose of models is not to fit the data but to sharpen the question.” — Samuel Karlin

Is PSA alone good enough? (That’d be nice...) CTC’s? Can we even capture tumor composition with CTC?

What about in cancers that don’t have easily available biomarkers?

Can we use imaging instead/alongside? FDG-PET compared with PSMA/DHT-PET?

Inter-lesion and intra-lesion spatial organization?

What in the world is “maximum tolerable tumor volume?” IACUC for humans?

How often should we make treatment decisions?

Can we safely administer intermediate doses?

Are we creating new monsters?

Do we just live with it forever? Should we attempt extinction once stabilized?

Psychological implications.. Would you do this?

# So many thanks…

MOFFITT CANCER CENTER

IMO

UIC University of Illinois at Chicago

Maastricht University