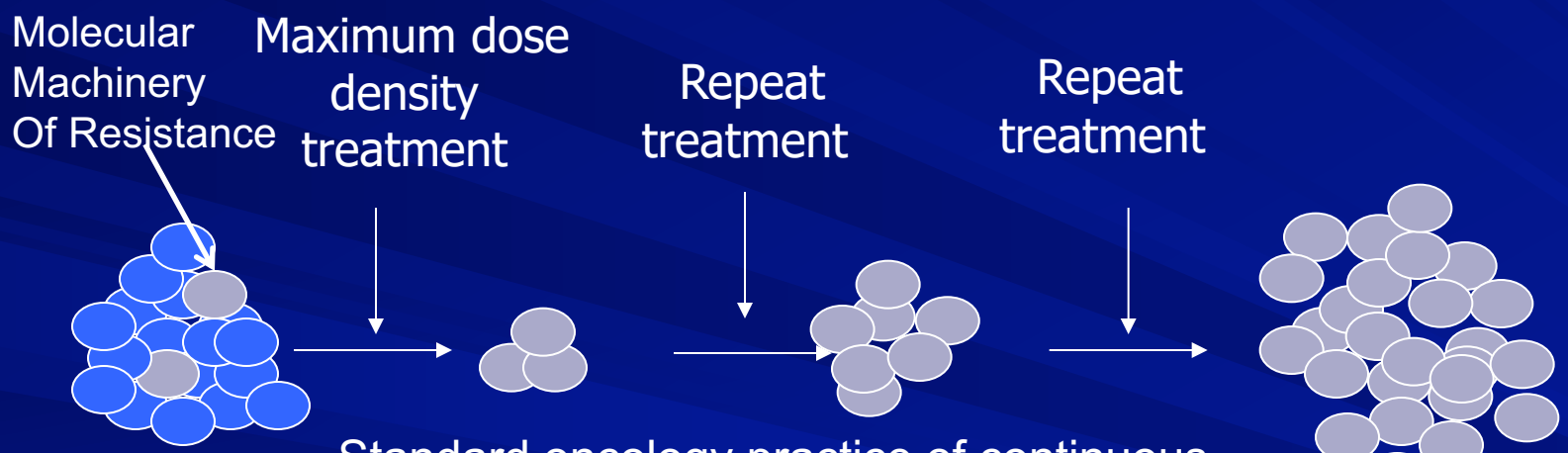
Evolutionary Dynamics in Prostate Cancer Control and Cure

IMAGING RESEARCH
MOFFITT CANCER CENTER

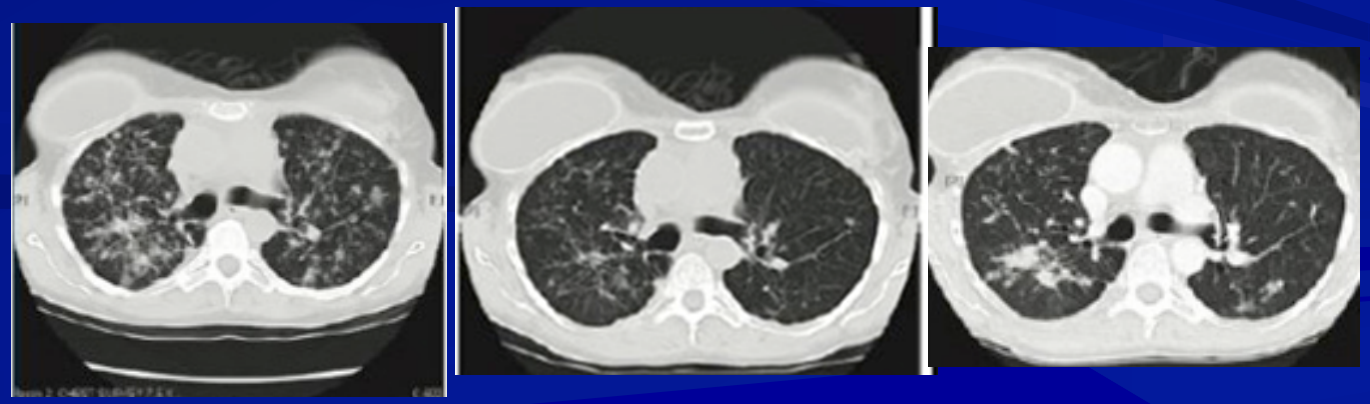
Combining personalized medicine and game theory models: MTD kills maximum numbers of cancer cells but selects for resistance and eliminates competitors – "competitive release"



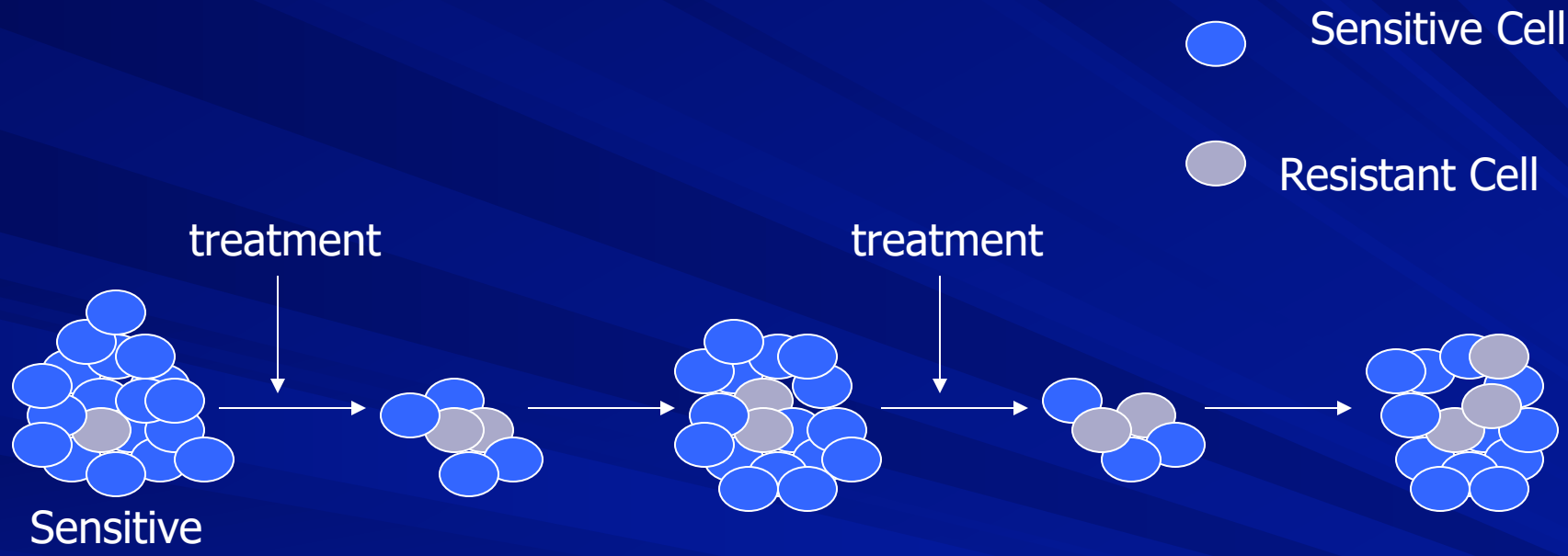
Standard oncology practice of continuous cycles of the same drugs at MTD until progression is <u>usually</u> evolutionarily unwise

Sensitive Cell

Resistant Cell



Adaptive therapy - exploiting the cost of resistance in clinical cancer treatment



- Limited administration of therapy to maintain sensitive cell population
- Sensitive cells, without the phenotypic cost of resistance, suppress resistant cells during no treatment.
- Treatment is a *forcing function* that, *when applied at the correct time,* induces oscillating near steady state

First clinical application: Abiraterone blocks androgen synthesis in mCRPC. In large trials 62% of men with mCRPC respond (radiographic TTP 8 to 16 months)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

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ABSTRACT

BACKGROUND

The androgen-receptor isoform encoded by splice variant 7 lacks the ligand-binding domain, which is the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor. We hypothesized that detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from men with advanced prostate cancer would be associated with resistance to enzalutamide and abiraterone.

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Evolution-based mathematical models to design trial

Define mCRPC subpopulations based on androgen dynamics:

- T+ cells require exogenous testosterone (sensitive to ADT)
- TP cells produce testosterone (sensitive to Abi) and promote T+ cells
- T- cells proliferate independent of testosterone (bad guys!)

Evolution mathematical models define intratumoral Darwinian dynamics during therapy

The oncologist-tumor "game" is modeled as a payoff matrix

The fitness function is set up as follows:

$$G_i = r_i\left(\frac{K_i - (1 - E_i)\sum x_j}{K_i}\right)$$

where $\sum x_j = x_1 + x_2 + x_3$.

The population dynamics are a simple difference equation.

$$\Delta x_i = x_i G_i$$

The PSA dynamics are shown below.

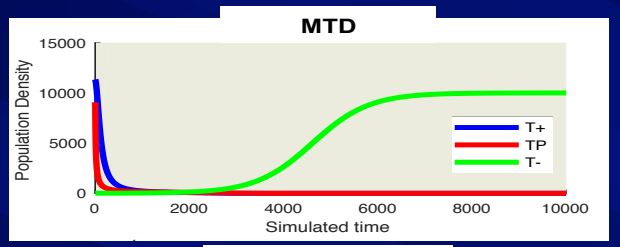
$$\frac{dPSA}{dt} = f_1 x_1 + f_2 x_2 + f_3 x_3 - \sigma_{PSA} \cdot PSA$$

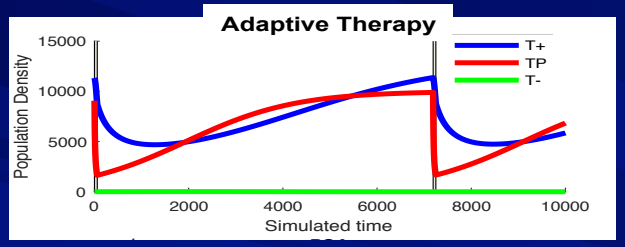
where $\sigma_{PSA} = 0.3$ and
where f_i is the PSA production per cell based on the frequency of TP cells.

	T+	TP	T-
T+	0	*a*	*b*
TP	*c*	*0*	*d*
T-	*e*	*f*	0

ADT Inequalities	
c > e	a > b
a > f	c > d
b < d	e > f

Integrating adaptive therapy mathematical model into clinical oncology practice

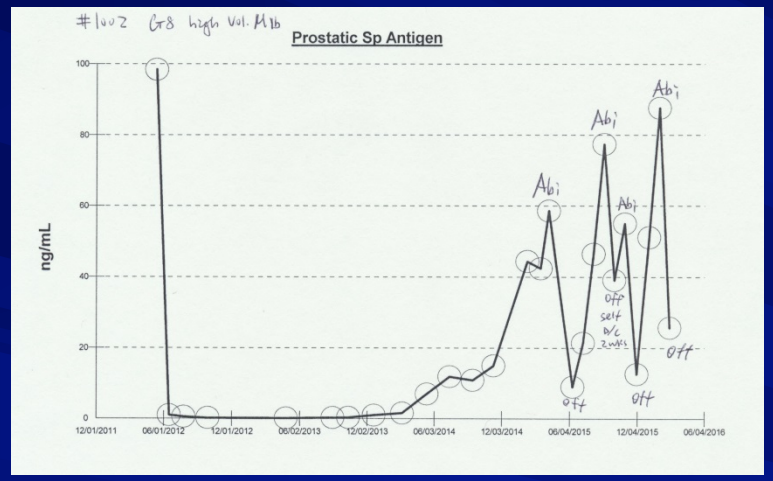


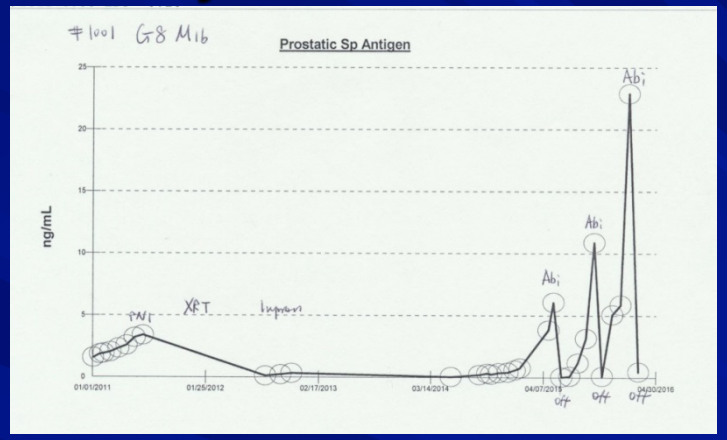


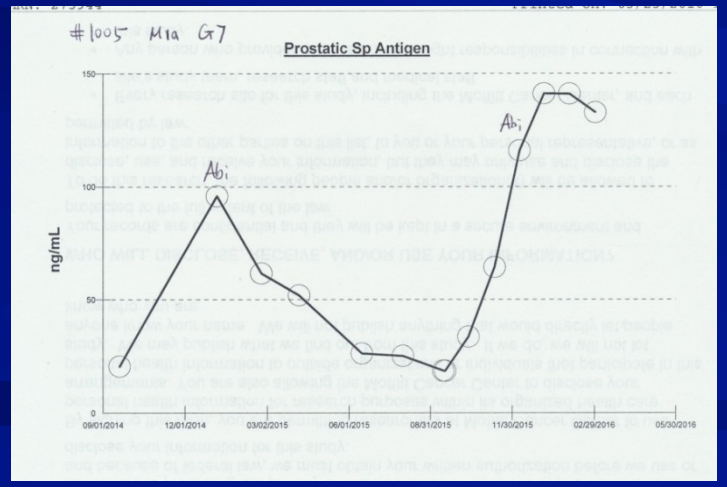
Jingsong Zhang, MD PhD

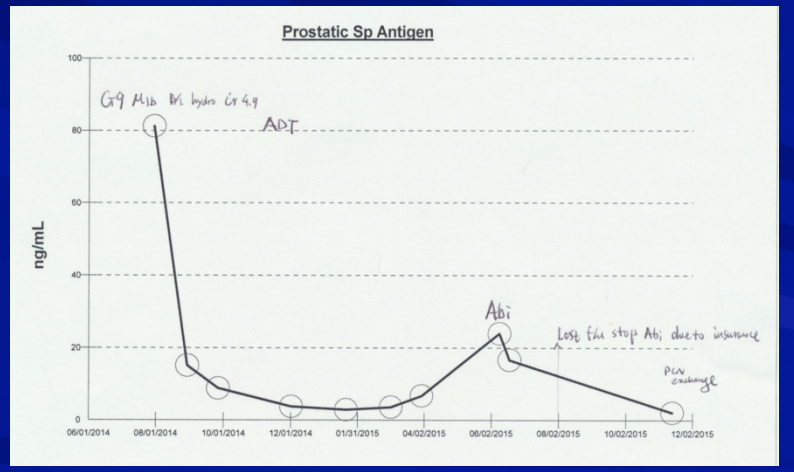
- Initial administration of abiraterone
- When PSA is <50% of pretreatment value, discontinue abiraterone
- Tumor grows but treatment sensitive cells (TP and cheater T+) suppress growth of the resistant T- cells in the absence of treatment
- Resume abiraterone when PSA returns to the pretreatment level and start the cycle over
- Simulations predict control for 2 to 20 cycles

Accrual goals met: Cycle length 4 to 14 months. Earliest recurrence at 2 cycles. Some patients still on treatment at 14 cycles





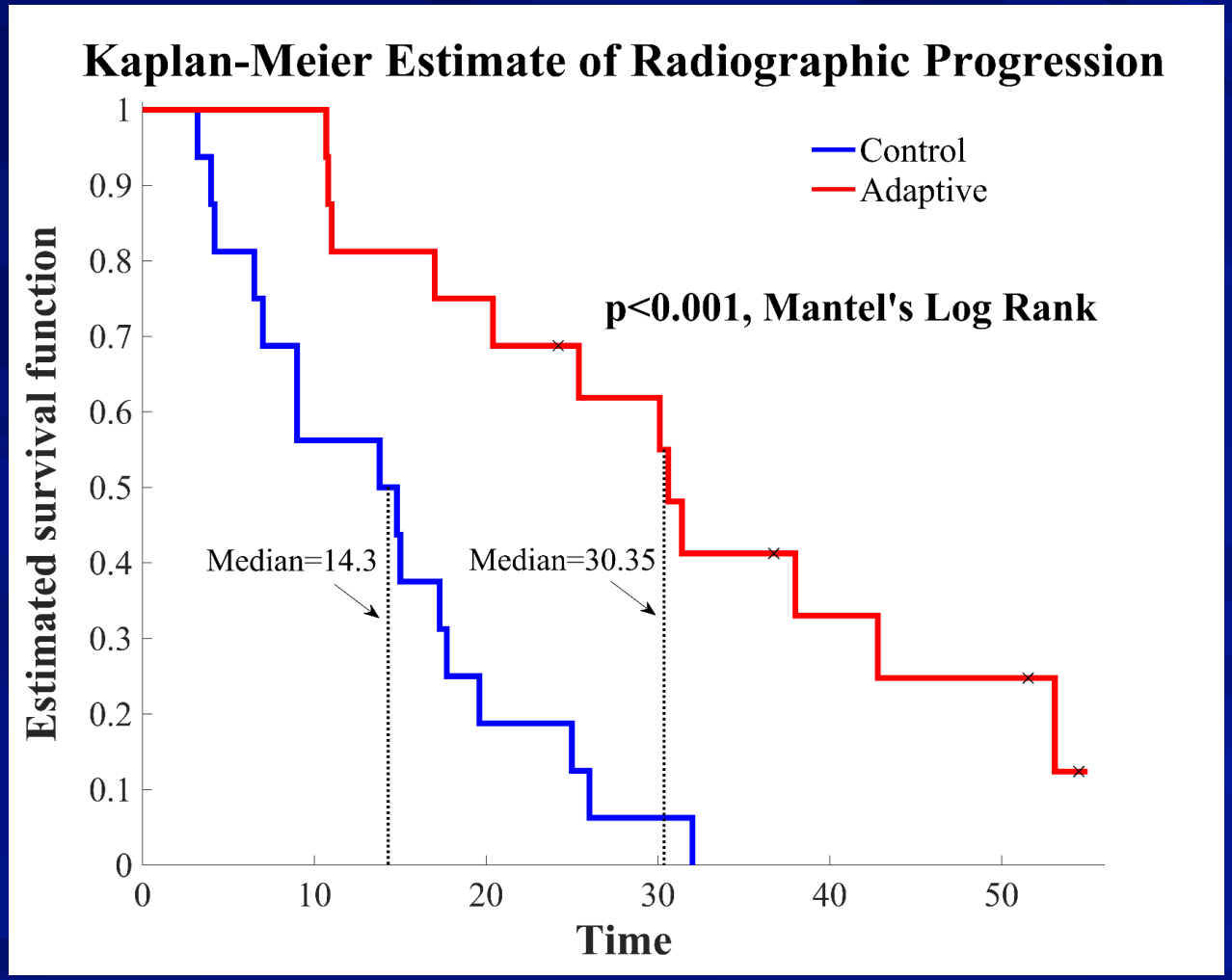




About 1 in 4 patients had long delay in upcycle after decline suggesting achievement of new steady state

The novel eco-evolutionary dynamics of small populations

Current status



Adaptive therapy patients received 41% (22-66%) of SOC

Average cost reduction: $50,00 per patient per year

Treatment sensitive cells have a non-zero (positive) competition coefficient (α_{SR}) for resistant cells in the absence of treatment

Total suppression is function of $\alpha_{SR}N_S$, where N_S is the number of resistant cells.

1 Collapsing Model to Sensitive and Resistant

The system of equations that describes the interactions between T^+, T^P, and T^- cell types, $i \in T = \{T^+, T^P, T^-\}$ is reduced to a two species model containing dynamics for the resistant T^- cells and combining the T^+ and T^P cell in to a singular equation. The instantaneous rate of change in the population size of each cell type $i \in T$, $\dot{x}_i = \frac{dx_i}{dt}$ is given by

$$\dot{x_S} = sr_S x_S \left(1 - \frac{x_S + \alpha x_R}{10000 - 9000\Lambda}\right) \tag{1}$$

$$\dot{x_R} = sr_R x_R \left(1 - \frac{\beta x_S + x_R}{10000}\right) \tag{2}$$

Λ is the dose of abiraterone. For this case it's always either 0 for no treatment or 1 for treatment. We simplify further and consider the case where $\alpha = 1$, meaning that the competition of resistant cells to sensitive cells is the same as the intra-type (diagonal) competition.

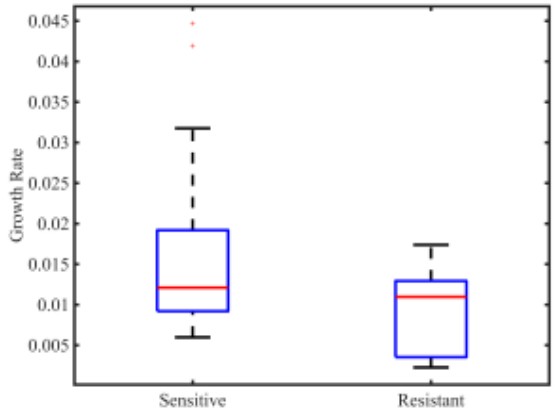


Figure 1: Growth Rates

The mean sensitive growth rate is 0.0156 and the mean resistant growth rate is 0.0091. These are statistically different with a p-value = 0.0407. In this way we set $r_S = 0.0156$ and $r_R = 0.0091$. Because the extracted growth rates don't consider that there may be limits to growth as they were assumed to be exponential growth, the actual growth rate within the Lotka-Volterra model could be quite higher to explain the data. That is why there is the extra parameters s presented as a scale to the ecological dynamics.

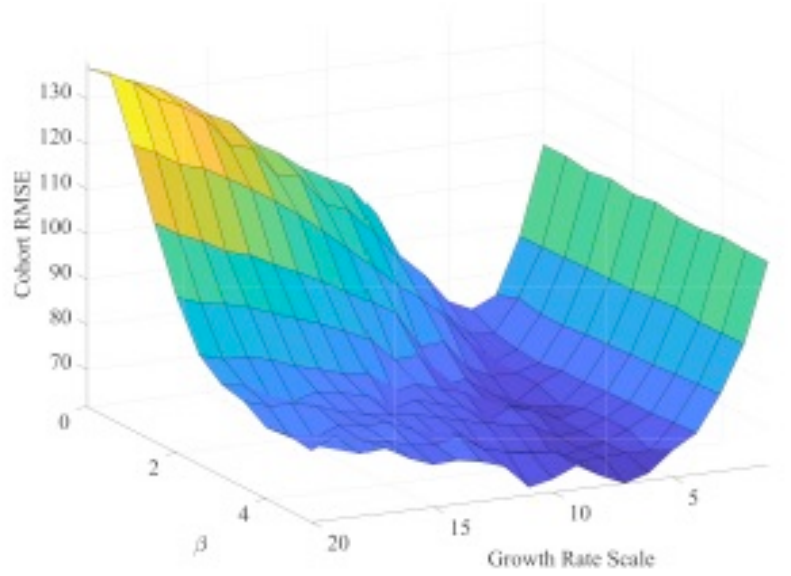


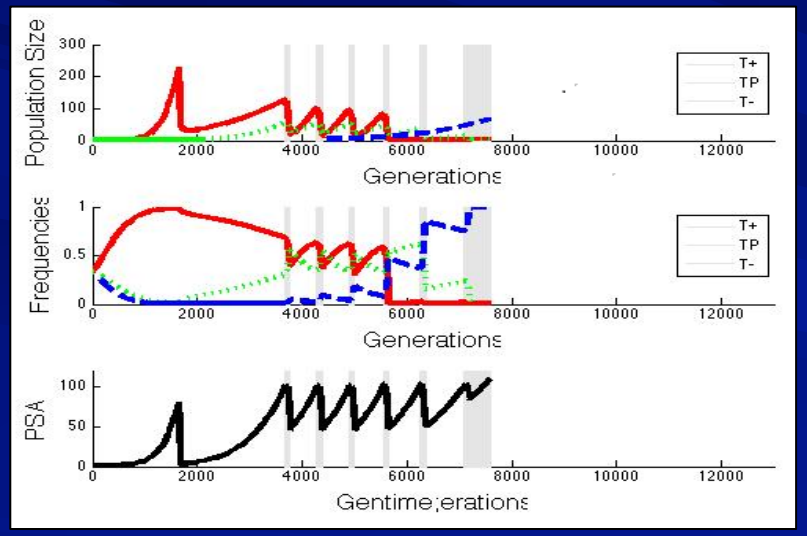
Figure 2: Grid Search for β and s.

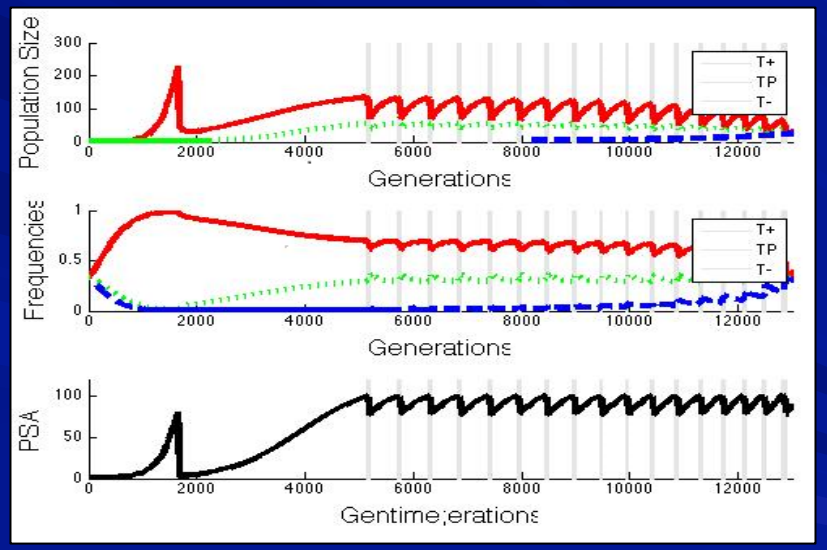
Here we see that the optimal combination of β and s is $\beta = 5$, and s=7.

Beyond cohort analysis: Investigating each patient using the trial mathematical model

Inverse problem approach: Run the model backward from outcome to initial conditions followed by computational exploration of treatment parameter space to improve outcomes (West et al. Clin. Cancer Res. 2019).

Subject 1010 progressed after 6 cycles (30 months)





Modeling recommendation: Stop abiraterone at 80% of pre-treatment value.
Cycle time shorter but control maintained for 58 cycles ~ 63 months

Mathematical analysis of evolution dynamics suggests future trial strategies and can investigate outcomes when other agents are added.