Evolutionary Dynamics in Prostate Cancer Control and Cure
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 usually evolutionarily unwise
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)
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!)

The oncologist-tumor “game” is modeled as a payoff matrix

<table>
<thead>
<tr>
<th></th>
<th>T+</th>
<th>TP</th>
<th>T-</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T+</strong></td>
<td>0</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>TP</td>
<td>c</td>
<td>0</td>
<td>d</td>
</tr>
<tr>
<td>T-</td>
<td>e</td>
<td>f</td>
<td>0</td>
</tr>
</tbody>
</table>

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

The fitness function is set up as follows:

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

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.

\[ \frac{dPSA}{dt} = f_s x_1 + f_2 x_2 + f_3 x_3 - \sigma_{PSA} \cdot PSA \]

where \( \sigma_{PSA} = 0.3 \) and \( f_s \) is the PSA production per cell based on the frequency of TP cells.
Integrating adaptive therapy mathematical model into clinical oncology practice

- 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

Kaplan-Meier Estimate of Radiographic Progression

- Control
- Adaptive

p<0.001, Mantel's Log Rank

Estimated survival function

- Median=14.3
- Median=30.35

Time

0 10 20 30 40 50

Treatment sensitive cells have a non-zero (positive) competition coefficient ($\alpha_{SR}$) 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 $i \in T$, $x_i$, is given by

$$
\begin{align*}
x_S &= \sigma r \tau g \left( 1 - \frac{x_S + \sigma r}{1000} \right) \\
x_R &= \sigma r \tau g \left( 1 - \frac{\beta r x_S + \tau r}{1000} \right)
\end{align*}
$$

(1)

(2)

$A$ 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](image)

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 extraneous 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 parameter $\alpha$ presented as a scale to the ecological dynamics.
Figure 2: Grid Search for $\beta$ and $s$.

Here we see that the optimal combination of $\beta$ and $s$ is $\beta = 5$, and $s=7$. 
Beyond cohort analysis: Investigating each patient using the trial mathematical model


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.