Towards multi-drug adaptive therapy

Jeffrey West (Moffitt Cancer Center)
CATMo2020
Towards multi-drug adaptive therapy

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

2. Spatial structure impacts adaptive therapy by shaping intra-tumoral competition

3. Multidrug Cancer Therapy in Metastatic Castrate-Resistant Prostate Cancer: An Evolution-Based Strategy
   Jeffrey B. West, Mina N. Dinth, Joel S. Brown, Jingsong Zhang, Alexander R. Anderson, and Robert A. Gatenby

4. Towards Multidrug Adaptive Therapy
   Jeffrey West, Li You, Jingsong Zhang, Robert A. Gatenby, Joel S. Brown, Paul K. Newton, and Alexander R.A. Anderson

Clinically feasible today

Conceptual ideas for tomorrow
Sequential and Adaptive Therapy

**Sequential, non-adaptive**

![Graph showing tumor burden over time with dose levels](image1)

- Dose: 2 levels
  - Purple: Resistant to drug 1
  - Orange: Resistant to drug 2

**Single drug adaptive**

![Graph showing tumor burden over time with dose levels](image2)

- Dose: Continuous levels
  - Purple levels indicate dose changes over time
Designing Adaptive Therapy schedules w/ multiple drugs

Two drug combination adaptive

Two drug sequential adaptive
doubly resistant
to drug 1 and 2
What is the purpose of adding a second drug?

The model:
- Lotka-Volterra competition
- Norton-Simon drug effect

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

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

(Strobl, et. al. Cancer Research 2020)
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

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

Optimal is to leave well-enough alone!

(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

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

Cell Populations:
- Testosterone producers (TP)
- Testosterone dependent (T+)
- Testosterone independent
  - Susceptible to Docetaxel
  - Resistant to Docetaxel

Targeted by “Primary” drug
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

Testosterone independent

Testosterone producers

Abiraterone


Co-existence

Testosterone producers

Testosterone dependent

Relapse dominated by resistance

Testosterone independent

(a.) No treatment

(b.) MTD abiraterone

TTP: ~5500
Primary mono-therapy (adaptive)

Can docetaxel be used as “Secondary” drug?


Testosterone independent
- T–
- T+ (Testosterone dependent)
- Testosterone independent & Docetaxel resistant

Docetaxel

TTP
- CT: ~5500
- AT: ~9500

Abiraterone

TTP
- PS: ~13000

AT abiraterone

AT + early secondary docetaxel
Can docetaxel be used as “Secondary” drug?

**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

\[ \dot{x}_i = (f_i - \phi) x_i \]

\[ f_i = w_i (A\bar{x})_i \]

\[ w_i = K_i / K_{\text{max}} \]

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

*Joint work with Li You (Maastricht) & Paul Newton (Univ Southern California)*
**Key assumption:**
- since the goal of an adaptive therapy is to maintain a stable volume
- we can study frequency-dependent dynamics

**Frequency-dependent Evolutionary Cycles**

- Drug 1 Schedule
  - Week 1
  - Week 2
  - Week 3
  - Week 4
  - Week 5

- Drug 2 Schedule
  - Week 1
  - Week 2
  - Week 3
  - Week 4
  - Week 5

- Biopsy
  - Week 1
  - Week 2
  - Week 3
  - Week 4
  - Week 5

- n = 2 drugs
- m = 4 phenotypes

- Cycle is completed when tumor composition matches starting point

- Tumor burden vs. time
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
2. Desired orbit is fixed & known
3. The connecting orbit is tangent to current orbit and intersects desired orbit
Trilinear Simplex

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

$x = [0.3, 0.5, 0.2]$

Trilinear Coordinates
Frequency-dependent treatment dynamics

\[ \hat{x} = [0.0, 0.14, 0.17] \]

\[ \hat{x} = [0.45, 0.55, 0] \]
Frequency-dependent treatment dynamics

Continuous Lupron & Abiraterone

Cycles
- Cycle 1
- Cycle 2
- Cycle 3

Evolutionary "cycle"

Biopsy cycle complete when tumor composition matches initial
Frequency-dependent treatment dynamics

Continuous Lupron

No treatment

evolutionary "cycle"

Continuous Lupron & Abiraterone
3. Evolutionary search space

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

- Siddhartha Mukherjee -
Evolutionary Search Space

Pairwise treatment combinations

Lupron & Abiraterone

\[ \hat{x} = [0.45, 0.55, 0] \]

No treatment

\[ \hat{x} = [0.69, 0.14, 0.17] \]

Lupron

\[ \hat{x} = [0, 0, 1] \]
Evolutionary Search Space

No treatment $\Leftrightarrow$ Lupron

absorbing state space

$\vec{x} = (0.45, 0.55, 0)$

$\vec{x} = (0.69, 0.14, 0.17)$
\[ \vec{x} = [0,0,1] \]

Evolutionary Search Space

Lupron & Abiraterone

absorbing state space

Lupron ⬅️ Lupron/Abiraterone

\[ \vec{x} = [0.45, 0.55, 0] \]

Lupron
Evolutionary Search Space

\[ \mathbf{x} = [0, 0.69, 0.14, 0.17] \]

\[ \mathbf{x} = [0, 0, 1] \]

Lupron & Abiraterone

No treatment

No treatment ⇔ Lupron/Abiraterone

absorbing state 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c &lt; e$</td>
<td>$T^-$ cells have a higher fitness than $T^+$ cells when interacting with many $T^+$, especially in low vasculature regions. Testosterone production by $T^+$ 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.</td>
</tr>
<tr>
<td>$a &gt; f$</td>
<td>$T^+$ 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.</td>
</tr>
<tr>
<td>$b &gt; d$</td>
<td>$T^+$ 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.</td>
</tr>
<tr>
<td>$a &lt; b$</td>
<td>$T^+$ cells have a higher fitness competing with $T^-$ over competition with $T^p$.</td>
</tr>
<tr>
<td>$c &lt; d$</td>
<td>$T^p$ cells have a higher fitness competing with $T^-$ over competition with $T^+$.</td>
</tr>
<tr>
<td>$e &gt; f$</td>
<td>$T^-$ 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.</td>
</tr>
</tbody>
</table>

## Lupron & Abiraterone

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c &gt; e$</td>
<td>$T^p$ cells have a higher fitness than $T^-$ cells when interacting with few $T^+$ (absence of competition)</td>
</tr>
<tr>
<td>$a &gt; f$</td>
<td>Interacting with mostly $T^p$ cells, $T^+$ gains from the public good and from the new available space in low vasculature regions</td>
</tr>
<tr>
<td>$b &lt; d$</td>
<td>Interacting with mostly $T^-$ cells, $T^p$ cells see little competition near vasculature. Payoffs to $T^+$ cells, $b$, may be small or zero</td>
</tr>
<tr>
<td>$a &gt; b = 0$</td>
<td>$T^+$ cells need the $T^p$ cells to succeed in the absence of systemic testosterone</td>
</tr>
<tr>
<td>$c &gt; d$</td>
<td>$c$ is likely the largest parameter as $T^p$ cells have the highest fitness in a mostly $T^-$ tumor without systemic testosterone</td>
</tr>
<tr>
<td>$e &gt; f$</td>
<td>Again, $T^p$ cells outcompete $T^-$ cells in the absence of systemic testosterone</td>
</tr>
</tbody>
</table>
Velocity of frequency-dependent dynamics

Lupron & Abiraterone

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

1 IsoMaTrix (MATLAB)
   1.1 isomatrix(A)
   1.2 isomatrix_fixedpoint(A, index)
   1.3 isomatrix_quiver(A)
   1.4 isomatrix_isocline(A, id)
   1.5 isomatrix_trajectory(A, x, 0, df)
   1.6 isomatrix_velocity(A, id)
   1.7 isomatrix_fitness(A, id)
   1.8 isomatrix_region(A)
   1.9 isomatrix_surface(A, id)
   1.10 isomatrix_separatrix(A)

2 IsoMaTrix Helper Functions (MATLAB)
   2.1 Coordinate transformations
   2.2 replicator(A, x, A)
   2.3 line_plot(A, x, 0, df)
   2.4 add_labels(string, array)
   2.5 add_gridlines(gridlines)
   2.6 pairwise_fixedpoint(A)
   2.7 hessian(A, A)
   2.8 A_subset(A, types)
   2.9 Otsubaki_Nowak_transform(A, rule)

3 HAL Integration with IsoMaTrix (Java)
   3.1 Setting up Integrated Development Environment
   3.2 HALMatrixGameID and HALMatrixGame3D
   3.3 Fitness Neighborhood
   3.4 Deterministic or Stochastic Updating
   3.5 Population Update Fraction
   3.6 SingleSimulation(int timesteps)
   3.7 MeshGrid(int timesteps, int nSims)

4 Visualizing HALMatrixGames using IsoMaTrix
   4.1 HAL_isomatrix()
   4.2 HAL_isomatrix_trajectory(color)
   4.3 HAL_isomatrix_quiver(uncertainty, boolean)
   4.4 HAL_isomatrix_velocity(id)
   4.5 HAL_isomatrix_region()
   4.6 HAL_isomatrix_uncertainty(id)
Acknowledgments

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