Modeling collaterally sensitive drug cycles: shaping heterogeneity to allow adaptive therapy

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1. Background

*Drug resistance*

![Graph showing disease burden over time with therapy started and resistance observed points highlighted.]

- **Disease burden**
- **Time**
- **Therapy started**
- **Resistance observed**
1. Background

Drug resistance

Dynamics of tumor heterogeneity
1. Background

Drug resistance

Dynamics of tumor heterogeneity

Collateral sensitivity

[Sdhawan et al., Scientific Reports, 2017]
2. Model for 2 drugs

*Fundamental modeling structure of a heterogeneous cell population*

- Dynamic variables:
  - $C_S$: sensitive cell population
  - $C_R$: resistant cell population
  - $C_S + C_R$: total tumor size, disease burden

- Parameters:
  - $s < 0$, $r > 0$: net proliferation rates for $C_S$ and $C_R$ (birth minus death, $s = b_s - d_s$, $r = b_r - d_r$)
  - $g > 0$: rate or resistance acquisition due to therapy

**Deterministic ODE system** depends on $\{s, r, g \mid C_S^0, C_R^0\}$

\[
\begin{pmatrix}
\dot{C}_S \\
\dot{C}_R
\end{pmatrix} = \begin{pmatrix}
  s - g & 0 \\
  g & r
\end{pmatrix} \begin{pmatrix}
  C_S \\
  C_R
\end{pmatrix}, \quad \begin{pmatrix}
  C_S \\
  C_R
\end{pmatrix}_{t=0} = \begin{pmatrix}
  C_S^0 \\
  C_R^0
\end{pmatrix}
\]

**Solution**

\[
\begin{align*}
C_S(t) &= C_S^0 e^{-(g-s)t} \\
C_R(t) &= A e^{-(g-s)t} + Be^{r t}
\end{align*}
\]

\[
C_S(t) + C_R(t) = A' e^{-(g-s)t} + Be^{r t}
\]

(Ex) $s=-0.05$/day, $r=0.01$/day, $g=0.02$/day
2. Model for 2 drugs

**Modeling of collateral sensitive network**

With Drug A

\[ \begin{align*}
&\text{With Drug A} \\
&\quad R_A \xrightarrow{g_A} R_B \quad s_A \xleftarrow{r_A} R_A \\
&\quad R_B \xrightarrow{g_B} R_A \quad r_B \xleftarrow{s_B} R_B
\end{align*} \]

With Drug B

\[ \begin{align*}
&\text{With Drug B} \\
&\quad R_A \xrightarrow{g_B} R_B \quad r_B \xleftarrow{s_B} R_A \\
&\quad R_B \xrightarrow{g_A} R_A \quad s_A \xleftarrow{r_A} R_B
\end{align*} \]

- **Dynamic variables:**
  - \( R_A \): resistant to Drug A sensitive to Drug B
  - \( R_B \): resistant to Drug B sensitive to Drug A
  - \( R_A + R_B \): total tumor size, disease burden

- **Parameters:**
  - \( \{s_A = b_A^s - d_A^s, r_A = b_A^r - d_A^r, g_A\} \) for Drug A
  - \( \{s_B = b_B^s - d_B^s, r_B = b_B^r - d_B^r, g_B\} \) for Drug B

- **Initial population makeup:** \( A_p B_0 = R_A^0 / R_B^0 \)

- **Drug Switches**
  - (e.g.) (A-drug, 1 week) → (B-drug, 1.5 week) → ...
2. Model for 2 drugs

Analysis: strategic drug-switch timing

1. $T_{max}$: clinical intuition

The longest time period with $Drug A$ lasting effective.

$$T_{max} \left( \{s_A, r_A, g_A\}, A p B_0 \right)$$

$$= \log \frac{(g_A - s_A)(r_A - s_A)}{r_A \left( g_A (1 + A p B_0) + A p B_0 (r_A - s_A) \right)}$$

which exists if and only if (iff) $A p B_0 < \frac{s_A}{r_A}$, where $A p B_0 = R_A(0)/R_B(0)$.

(Blue) $Drug A$ alone
(Red) $Drug B$ alone

(Used parameters)

$s_A = s_B = -0.09, r_A = r_B = 0.008,$

$g_A = g_B = 0.001, \{R^0_A, R^0_B\} = \{0.1, 0.9\}$
2. Model for 2 drugs

**Analysis: strategic drug-switch timing**

1. $T_{\text{max}}$: clinical intuition

The longest time period with Drug A lasting effective.

\[
T_{\text{max}}(\{s_A, r_A, g_A\}, ApB_0) = \log \left[ \frac{(g_A - s_A)(r_A - s_A)}{r_A(g_A(1 + ApB_0) + ApB_0(r_A - s_A))} \right],
\]

which exists if and only if (iff) $ApB_0 < |s_A/r_A|$, where $ApB_0 = R_A(0)/R_B(0)$.

2. $T_{\text{min}}$ suggests improvement

Population decreases even faster by switch from Drug A to Drug B at or after:

\[
T_{\text{min}}(\{s_A, r_A, g_A\}, \{s_B, r_B\}, ApB_0) = \log \left[ \frac{(r_A - s_A)(r_B - s_A) + g_A(r_A + r_B - s_A - s_B)}{(g_A + ApB_0(g_A + r_A - s_A))(r_A - s_B)} \right],
\]

which exists iff $ApB_0 < |(r_B - s_A)/(r_A - s_B)|$

Condition: $T_{\text{min}} < T_{\text{max}}$ iff $r_A r_B < s_A s_B$

(Blue) Drug A alone
(Red) Drug B alone
(Dashed magenta) arbitrary switch

(Used parameters)

$s_A = s_B = -0.09$, $r_A = r_B = 0.008$, $g_A = g_B = 0.001$, $\{R_A^0, R_B^0\} = \{0.1, 0.9\}$
2. Model for 2 drugs

**Analysis: strategic drug-switch timing**

1. $T_{\text{max}}$: clinical intuition

The longest time period with Drug A lasting effective.

$$T_{\text{max}}(\{s_A, r_A, g_A\}, ApB_0) = \log \left( \frac{(g_A - s_A)(r_A - s_A)}{r_A(g_A(1 + ApB_0) + ApB_0(r_A - s_A))} \right),$$

which exists if and only if (iff) $ApB_0 < |s_A/r_A|$

where $ApB_0 = R_A(0)/R_B(0)$.

2. $T_{\text{min}}$ suggests improvement

Population decreases even faster by switch from Drug A to Drug B at or after:

$$T_{\text{min}}(\{s_A, r_A, g_A\}, \{s_B, r_B\}, ApB_0) = \log \left( \frac{(r_A - s_A)(r_B - s_A) + g_A(r_A + r_B - s_A - s_B)}{(g_A + ApB_0(g_A + r_A - s_A))(r_A - s_B)} \right),$$

which exists iff $ApB_0 < |(r_B - s_A)/(r_A - s_B)|$

Condition: $T_{\text{min}} < T_{\text{max}}$ iff $r_Ar_B < s_As_B$

(Blue) Drug A alone
(Red) Drug B alone
(Dashed magenta) arbitrary switch
(Black) instantaneous switch

(Used parameters)

$s_A = s_B = -0.09$, $r_A = r_B = 0.008$,

$g_A = g_B = 0.001$, $\{R_A^0, R_B^0\} = \{0.1, 0.9\}$
2. Model for 2 drugs

Analysis: population makeup at $T_{\text{min}}$ and $T_{\text{max}}$

- Population makeup:
  \[
  ApB(t) := \frac{R_A(t)}{R_B(t)}
  \]

- \(ApB(T_{\text{min}}) = ApB(T_{\text{min}}) = \frac{r_B - s_A}{r_A - s_B} := ApB^*\),
- \(ApB(T_{\text{max}}) = \frac{-s_A}{r_A}, \quad ApB(T_{\text{max}}) = \frac{r_B}{-s_B}\)

- Drug effect at \(ApB\):
  \[
  \frac{d}{dt} P(t) \bigg|_{t=0}^{\{s_i, r_i, g_i\}, ApB_0} = P(t) = R_A(t) + R_B(t), \quad P(0) = 1 \text{ (fixed)}
  \]

when \(r_A r_B < s_A s_B\)
2. Model for 2 drugs

*Optimal control* consists of **two stages** of therapy

(Stage 1; *shaping*) until $T_{\text{min}}$, “better” drug alone

(Stage 2; *adaptive therapy*) combination of the two drugs switched in turn with a definite ratio in duration, $k$, i.e., *Drug A* for $t$ days and *Drug B* for $k$ times $t$ days.

$$k^{(t)}(\{s_A, r_A, g_A\}, \{s_B, r_B, g_B\}, \Delta t)$$

$$\lim_{\Delta t \to 0} k = \lim_{\Delta t \to 0} k' = \frac{(r_A-s_A)(r_B-s_A)+g_A(r_A+r_B-s_A-s_B)(r_A-s_B)}{(r_A-s_B)(r_B-s_B)+g_B(r_A+r_B-s_A-s_B)(r_B-s_A)} = k^*$$

- **Blue** $T_{\text{min}}$ switch (optimal)
- **Red** $T_{\text{max}}$ switch
- **Solid** Total: $R_A + R_B$
- **Dotted** $R_A$
- **Dashed** $R_B$
- **Gray area** Stage 1
- **White area** Stage 2

(Used parameters)

$$\{s_A, s_B\} = -0.09\{2,1\}, \quad \{r_A, r_B\} = 0.008\{1,2\},$$

$$\{g_A, g_B\} = 0.001\{0.75,1.25\}, \quad \{R_A^0, R_B^0\} = \{0.1,0.9\}$$
2. Model for 2 drugs

Simple analytic description of Stage 2 of the optimal control

• Differential system on Stage 2:

\[
\begin{align*}
\text{Drug A for } (k^* \Delta t)\text{-long period } \\
\frac{\dot{R}_A}{\dot{R}_B} &= \begin{pmatrix} r_B & g_B \\ s_B - g_B & 0 \end{pmatrix} \begin{pmatrix} R_A \\ R_B \end{pmatrix} := D_A \begin{pmatrix} R_A \\ R_B \end{pmatrix}, \\
\text{Drug B for } \Delta t\text{-long period } \\
\frac{\dot{R}_A}{\dot{R}_B} &= \begin{pmatrix} s_A - g_A & 0 \\ g_A & r_A \end{pmatrix} \begin{pmatrix} R_A \\ R_B \end{pmatrix} := D_B \begin{pmatrix} R_A \\ R_B \end{pmatrix},
\end{align*}
\]

\[
\begin{align*}
\text{Drug A for } (k^* \Delta t)\text{-long period }
\end{align*}
\]

... as \( \Delta t \to 0 \)

\[
\begin{align*}
\frac{\dot{R}_A}{\dot{R}_B} &= \frac{k^*}{1 + k^*} D_A + \frac{1}{1 + k^*} D_B \begin{pmatrix} R_A \\ R_B \end{pmatrix}
\end{align*}
\]

• Stage 2 starts at \( T_{\text{min}} \):

\[
A p B (T_{\text{min}}) = A p B^*
\]

• Populations on stage 2

\[
P(t + T_{\text{min}}) = P(T_{\text{min}}) \exp(\lambda \: t)
\]

for \( P \in \{R_A, R_B, R_A + R_B\} \)

where \[
\lambda = - \frac{r_A r_B - s_A s_B}{r_A + r_B + s_A + s_B}
\]

Details of the proof is shown in [Yoon et al., Bulletin of Mathematical Biology, 2018]
3. Model for \( n \) drugs

Collateral Sensitivity cycle of length \( N \):

\[
\text{Drug 1} \rightarrow \text{Drug 2} \rightarrow \cdots \rightarrow \text{Drug } N \rightarrow \text{Drug 1} \rightarrow \cdots
\]

\( N \) dynamic variables:
- \( R_i \): resistant to Drug \( i \)
- \( R_{i-1} \) (or \( R_N \)): sensitive to Drug \( i \) (or Drug 1)
- \( R_j \): neutral to Drug \( i \) \((j \notin \{i - 1, i\})\)

\( N \times 5 \) parameters:
- Proliferation rates: \( \{p_r^i > 0, p_s^i < 0, p_0^i\} \) for Drug \( i \)
- Transition rates: \( \{g_s^i, g_0^i\} \) for Drug \( i \)

![Diagram of collateral sensitivity cycle with dynamic variables and parameter interpretations](image)
3. Model for $n$ drugs

Dynamics of cell populations under Drug $i$: \[
\frac{dv}{dt} = \mathcal{M}(i) \, v \quad \text{where} \ v = (R_1, \ldots, R_N)^T
\]

\[
\mathcal{M}(i) = \begin{pmatrix}
\lambda^i_0 & 0 & \cdots & 0 & g^i_s & 0 & \cdots & \cdots & \cdots & 0 \\
0 & \ddots & \ddots & \vdots & \vdots & \ddots & \ddots & \cdots & \cdots & \ddots \\
\vdots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots & \cdots & \ddots \\
\vdots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots & \ddots \\
0 & \cdots & \cdots & 0 & \lambda^i_s & \lambda^i_r & \ddots & \ddots & \cdots & \cdots \\
g^i_0 & \cdots & \cdots & g^i_0 & 0 & \lambda^i_s & g^i_s & \cdots & \cdots & g^i_s \\
0 & \cdots & \cdots & 0 & g^i_s & 0 & \lambda^i_0 & 0 & \cdots & 0 \\
\vdots & \ddots & \cdots & \ddots & \ddots & \cdots & \ddots & \ddots & \cdots & \ddots \\
\vdots & \ddots & \cdots & \cdots & \ddots & \cdots & \ddots & \ddots & \ddots & \ddots \\
0 & \cdots & \cdots & 0 & g^i_s & 0 & \cdots & \cdots & 0 & \lambda^i_0
\end{pmatrix}
\]

With
- \((\lambda^i_r, \lambda^i_s, \lambda^i_0) = (p^i_r, p^i_s - g^i_s, p^i_0 - g^i_0)\)
- \(g^i_s = \frac{g^i_s}{N-2}\)
3. Model for $n$ drugs

**Availability of analytic derivations**

|                         | 2- drugs | n-drugs |
|-------------------------|----------|---------|
| Drug switch time ($T_{min}$) | Yes      | No      |
| Population makeup with same drug effect ($A_p B^* \text{ or } v^*$) | Yes      | Yes     |
| Relative drug period ($k^*$) | Yes      | No      |
| Metaphor problem       | $a^x = b$ (analytically solvable) | $a^x + b^x = c$ (analytically proved to have a solution; numerically solvable) |

**Total cell population with optimal therapy**

$$\frac{dv}{dt} = M \left( \arg\min_{1 \leq i \leq N} e_{fi} \right) v$$

where $e_{fi}(t) = P^i \cdot v(t)$

*Discretely solvable by finding the best drug at every discrete time point and solve $v' = M(j) \cdot v$ until the next point.*
3. Model for \( n \) drugs

Start;
\[ t \leftarrow 0 \]

Calculate \( ef_i(t) \) s, and find best drug(s):
\[ I_{best} = \{ i \mid ef_i(t) \leq ef_k(t), \ 1 \leq k \leq N \} \]

Randomly choose one best drug from \( I_{best} \)

Run the chosen drug

Time is up?
\[ t \leftarrow t + \Delta t \]

\( \uparrow \) Example of optimal therapy simulation compared to a non-optimal therapy

← Diagram to run optimal therapy over a discrete timeline
3. Model for \( n \) drugs

**Example with 4 of symmetric drugs**

\[
\{p_r, p_s, p_0\} = \{0.2, -0.7, 0.1\}, \quad \{g_s, g_0\} = \{0.1, 0.05\},
\]

\[
\{R_1^0, R_2^0, R_3^0, R_4^0\} = \{0.45, 0.3, 0.05, 0.2\}
\]

**Example 4 of asymmetric drugs**

\[
\{p_r^1, p_s^1, p_0^1\} = \{0.5, -0.7, 0.0\}, \quad \{g_s^1, g_0^1\} = \{0.01, 0.005\},
\]

\[
\{p_r^2, p_s^2, p_0^2\} = \{0.1, -0.7, 0.0\}, \quad \{g_s^2, g_0^2\} = \{0.01, 0.01\},
\]

\[
\{p_r^3, p_s^3, p_0^3\} = \{0.2, -0.3, 0.0\}, \quad \{g_s^3, g_0^3\} = \{0.05, 0.05\},
\]

\[
\{p_r^4, p_s^4, p_0^4\} = \{0.1, -0.2, 0.0\}, \quad \{g_s^4, g_0^4\} = \{0.001, 0.0005\},
\]

\[
\{R_1^0, R_2^0, R_3^0, R_4^0\} = \{0.05, 0.15, 0.2, 0.6\}
\]
3. Model for $n$ drugs

An example with symmetric drugs

\[ \{p_r, p_s, p_0\} = \{0.2, -0.7, 0.1\}, \{g_s, g_0\} = \{0.1, 0.05\}, \{R_1^0, R_2^0, R_3^0, R_4^0\} = \{0.45, 0.3, 0.05, 0.2\} \]

shaping  adaptive therapy

\[ v^* = \lambda(1, ..., 1)^T \]

Decay rate: $\frac{p_r + p_s + (N-2)p_0}{N}$
3. Model for \( n \) drugs

An example with *asymmetric* drugs

\[
\{p_r^1, p_s^1, p_0^1\} = \{0.5, -0.7, 0.0\}, \{g_s^1, g_0^1\} = \{0.01, 0.005\}, \{p_r^2, p_s^2, p_0^2\} = \{0.1, -0.7, 0.0\},
\{g_s^2, g_0^2\} = \{0.01, 0.01\}, \{p_r^3, p_s^3, p_0^3\} = \{0.2, -0.3, 0.0\}, \{g_s^3, g_0^3\} = \{0.05, 0.05\},
\{p_r^4, p_s^4, p_0^4\} = \{0.1, -0.2, 0.0\}, \{g_s^4, g_0^4\} = \{0.001, 0.0005\}, \{R_1^0, R_2^0, R_3^0, R_4^0\} = \{0.05, 0.15, 0.2, 0.6\}
\]

\[
\begin{align*}
\nu^* &= \lambda \left( (\mathcal{P}^1)^T \right)^{-1} \begin{pmatrix} 1 \\ \vdots \\ (\mathcal{P}^N)^T \end{pmatrix} \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix} \\
\text{Decay rate: ??}
\end{align*}
\]
3. Model for $n$ drugs

An example with asymmetric drugs

\[
\begin{align*}
\{p_r^1, p_s^1, p_0^1\} &= \{0.5, -0.7, 0.0\}, \{g_s^1, g_0^1\} = \{0.01, 0.005\}, \{p_r^2, p_s^2, p_0^2\} = \{0.1, -0.7, 0.0\}, \\
\{g_s^2, g_0^2\} &= \{0.01, 0.01\}, \{p_r^3, p_s^3, p_0^3\} = \{0.2, -0.3, 0.0\}, \{g_s^3, g_0^3\} = \{0.05, 0.05\}, \\
\{p_r^4, p_s^4, p_0^4\} &= \{0.1, -0.2, 0.0\}, \{g_s^4, g_0^4\} = \{0.001, 0.0005\}, \{R_1, R_2, R_3, R_4\} = \{0.05, 0.15, 0.2, 0.6\}
\end{align*}
\]

Within each stage, since the entropy graph is flat on each stage, drugs are periodically switching with relative period from the bar chart.
3. Model for \( n \) drugs

**Instantaneous drug switch** is supposed to be consistent with the **linear combination** of the dynamics with corresponding intensities (as numerically tested).

\[
v = \left( \sum_{i=1}^{N} f_i M(i) \right) v
\]

**Symmetric drugs**

**Asymmetric drugs**
4. Optimal regimen without parameters

1. Subpopulations are known (e.g., cell free DNA):

   Three equations from the explicit solutions of the ODE system, for $R_i, R_{i-1}, \sum_{j \notin \{i-1,i\}} R_j$

   Hypotheses with mutation per proliferation
   \[ g^i_0 = \alpha_0 p^i_0 \text{ and } g^i_s = \alpha_s p^i_s \]

   Calibration of 5 parameters

2. Only total population is known (e.g., Prostate Specific Antigen):

   Computational algorithm??
4. Optimal regimen without parameters

Algorithm to prescribe optimal regimen without parameters

- **Testing period**
  1. Calculate $Pop^i$s and $Der^i$s
  2. Choose good drug(s) (not just the best; $\epsilon$)
  3. Find the level of intermediate drug effect ($ef^*$)

- **Optimal therapy period**
  1. Run the best drug(s)

- Time is up?
  - yes: Still more efficient than other drug(s)?
  - no: Time is up?
    - yes: end
    - no: still more efficient than other drug(s)?
4. Optimal regimen without parameters

**Algorithm to prescribe optimal regimen without parameters**

Good consistency with $\epsilon = 0.01$

Errors of the algorithm over a range of $\epsilon$
Conclusions

• Population structure

• Numerically figured out optimal control

\[
\frac{dv}{dt} = M \left( \arg\min_{1 \leq i \leq N} e_{f_i} \right) v
\]

• Optimal prescription without drug parameters known

• Population makeup with balanced drug effects

A-drug is better

B-drug is better

\[
\begin{align*}
r_B & \quad ApB^* \\
-S_B & \quad -S_A \\
& \quad \frac{-S_A}{r_A}
\end{align*}
\]

P decreases with B-drug

P decreases with A-drug

Still more efficient than other drug(s)?

end

Time is up?

no

yes
Future work

- Considerations on the third type of cells (Areeba Khalid, Adelphi)

Differential equations:

\[
\begin{align*}
\frac{dR_A}{dt} &= r_A - g_A R_A + k_{O_A} R_O,
\frac{dR_B}{dt} &= s_A R_A - g_A R_B - h_{O_B} R_O,
\frac{dR_O}{dt} &= s_B R_B - g_B R_O - h_{O_B} R_O + h_{A_O} R_A;
\end{align*}
\]

- Find combinations of collaterally sensitive factors from RNA (miRNA), DNA, network data

- Interdisciplinary implementation of the optimal therapy in the automatic cell culturing device, Mobidostat.

- Expansion of the model considering spatial distribution of microenvironment.
Thank you all!!

Theory Division

Math & CS at Adelphi
