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

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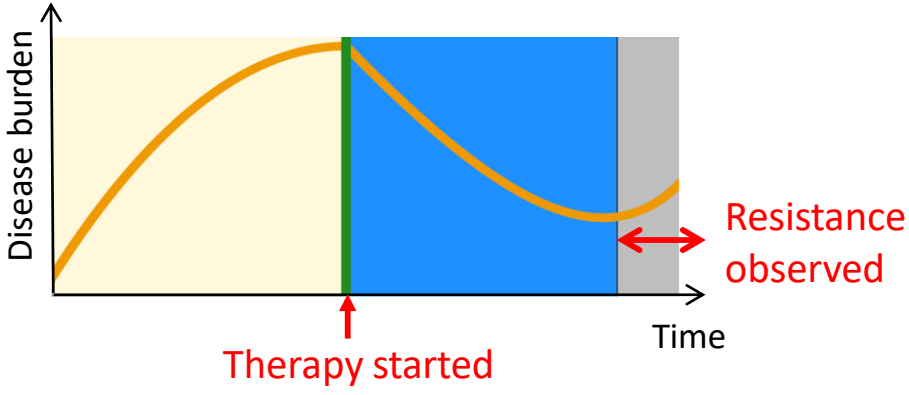
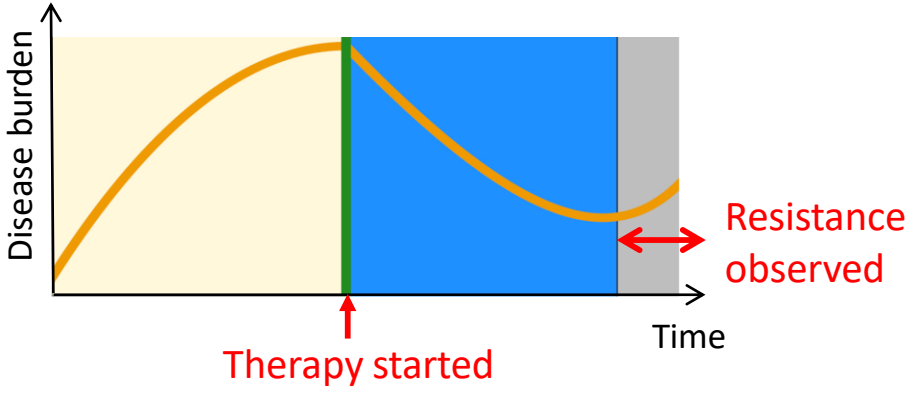
1. Background

Drug resistance

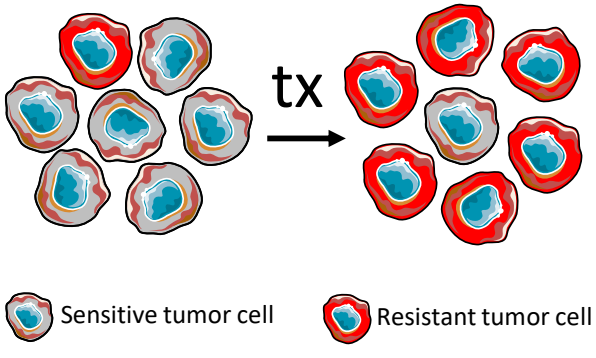


1. Background

Drug resistance

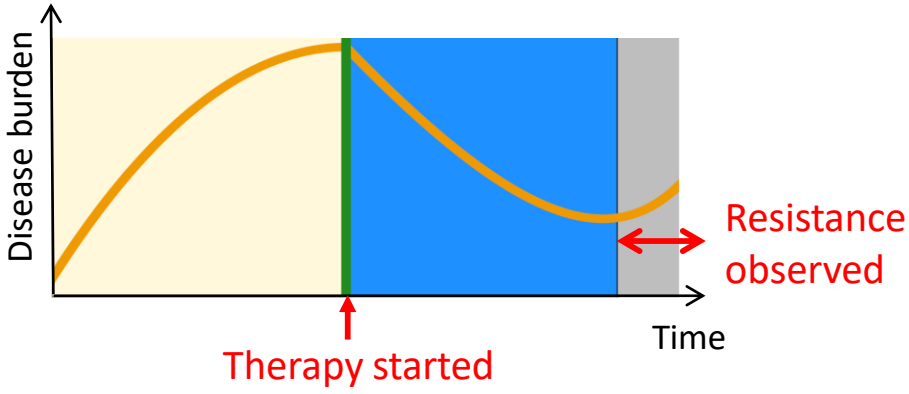


Dynamics of tumor heterogeneity

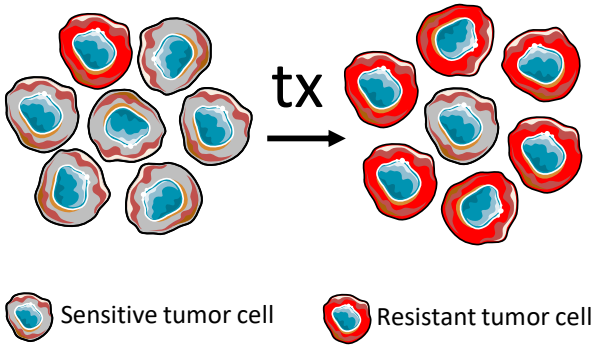


1. Background

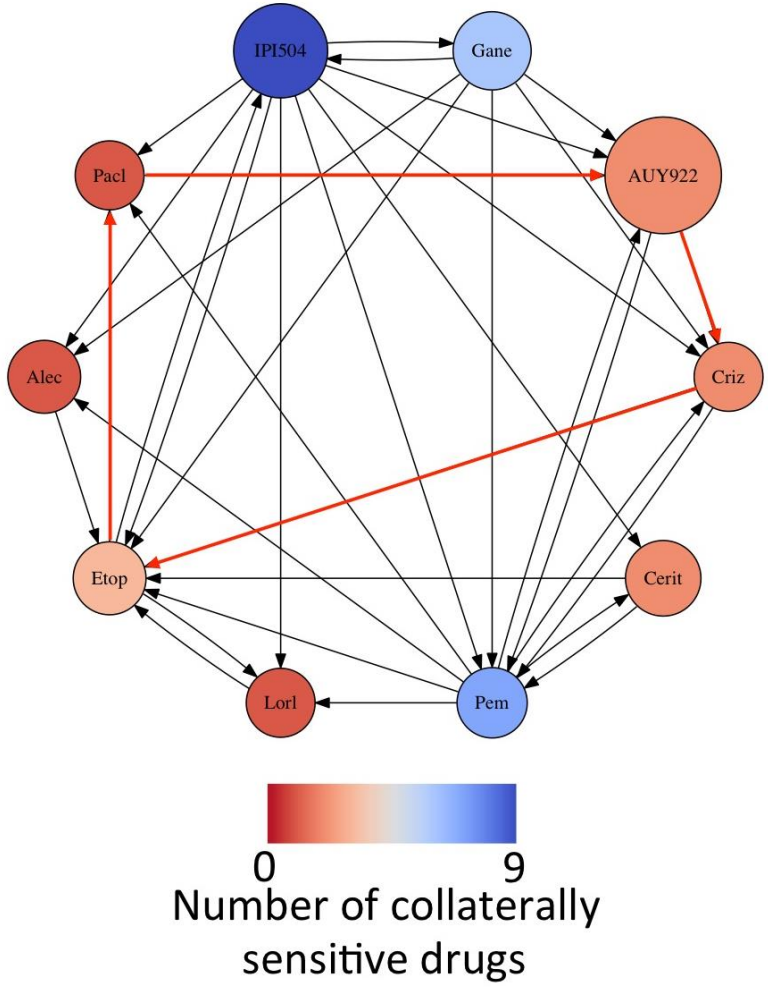
Drug resistance



Dynamics of tumor heterogeneity



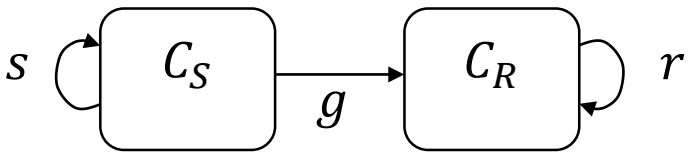
Collateral sensitivity



[Dhawan et al., Scientific Reports, 2017]

2. Model for 2 drugs

Fundamental modeling structure of a heterogeneous cell population



- Dynamic variables:
  - $\boldsymbol{C_S}$: sensitive cell population
  - $\boldsymbol{C_R}$: resistant cell population
  - $\boldsymbol{C_S + C_R}$: total tumor size, **disease burden**
- Parameters:
  - $\boldsymbol{s < 0, r > 0}$: net proliferation rates for C_S and C_R (birth *minus* death, $\boldsymbol{s = b_s - d_s, r = b_r - d_r}$)
  - $\boldsymbol{g > 0}$: rate or resistance acquisition due to therapy

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

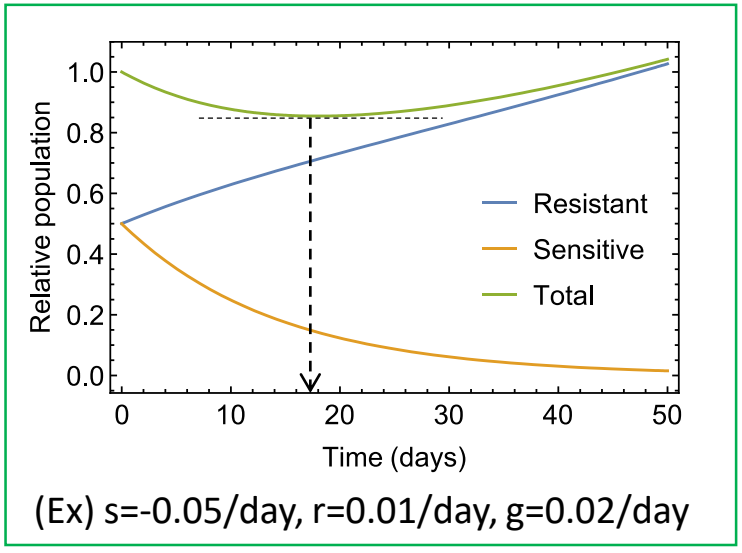
$$\begin{pmatrix}\dot{C}_S \\ \dot{C}_R\end{pmatrix} = \begin{pmatrix}s-g & 0 \\ g & r\end{pmatrix}\begin{pmatrix}C_S \\ C_R\end{pmatrix}, \quad \begin{pmatrix}C_S \\ C_R\end{pmatrix}_{t=0} = \begin{pmatrix}C_S^0 \\ C_R^0\end{pmatrix}$$

Solution

$$C_S(t) = C_S^0 e^{-(g-s)t}$$
$$C_R(t) = A\, e^{-(g-s)t} + Be^{r\,t}$$

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

positive

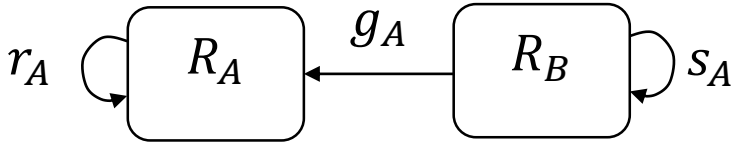


(Ex) s=-0.05/day, r=0.01/day, g=0.02/day

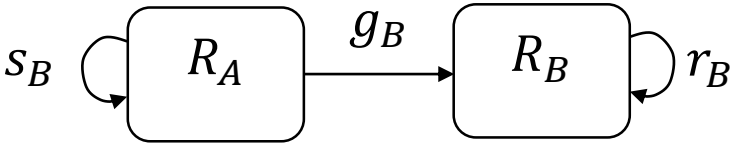
2. Model for 2 drugs

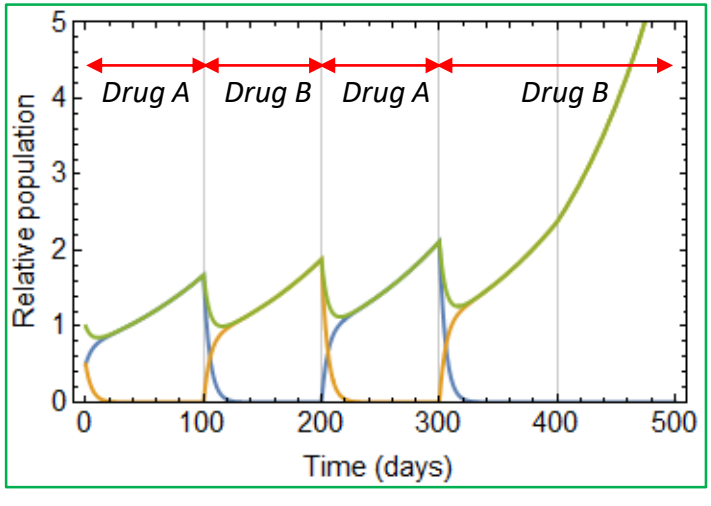
Modeling of collateral sensitive network

With Drug A



With Drug B





- 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:
  - $\{\boldsymbol{s_A} = b_A^s - d_A^s, \boldsymbol{r_A} = b_A^r - d_A^r, \boldsymbol{g_A}\}$ for *Drug A*
  - $\{\boldsymbol{s_B} = b_B^s - d_B^s, \boldsymbol{r_B} = b_B^r - d_B^r, \boldsymbol{g_B}\}$ for *Drug B*
- Initial population makeup: $ApB_0 = R_A^0/R_B^0$
- Drug Switches
  - (e.g.) (A-drug, 1 week) → (B-drug, 1.5 week) → …

2. Model for 2 drugs

Analysis: strategic drug-switch timing

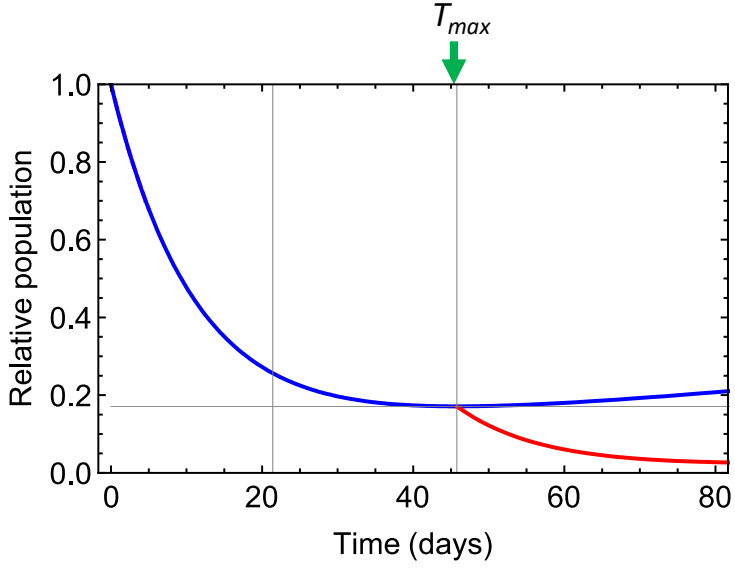
1. T_{max} : clinical intuition

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

$$\boldsymbol{T_{max}}(\{\boldsymbol{s_A}, \boldsymbol{r_A}, \boldsymbol{g_A}\}, \boldsymbol{ApB_0})$$

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

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



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

(Used parameters)

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

$g_A = g_B = 0.001, \{R_A^0, R_B^0\} = \{0.1, 0.9\}$

2. Model for 2 drugs

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

2. T_{min} suggests improvement

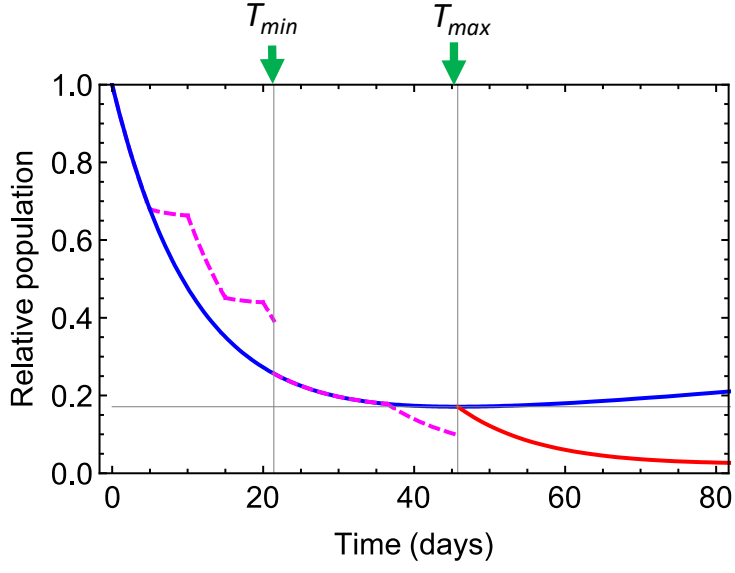
Population decreases even faster by switch from *Drug A* to *Drug B* at or after:

$$\boldsymbol{T_{min}}(\{\boldsymbol{s_A}, \boldsymbol{r_A}, \boldsymbol{g_A}\}, \{\boldsymbol{s_B}, \boldsymbol{r_B}\}, \boldsymbol{ApB_0})$$

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

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

Condition: $T_{min} < T_{max}$ 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

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

$$\boldsymbol{T_{max}}(\{\boldsymbol{s_A}, \boldsymbol{r_A}, \boldsymbol{g_A}\}, \boldsymbol{ApB_0})$$

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

which exists if and only if (iff) $ApB_0 < |s_A/r_A|$,
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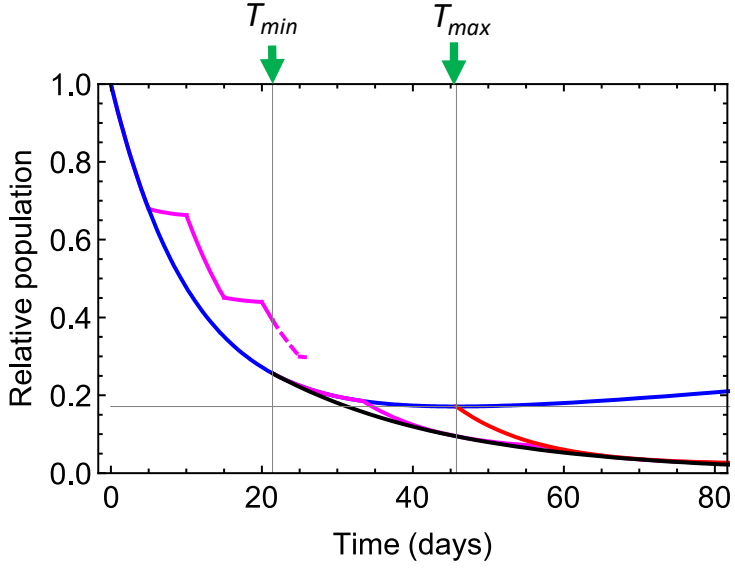
Population decreases even faster by switch from *Drug A* to *Drug B* at or after:

$$\boldsymbol{T_{min}}(\{\boldsymbol{s_A}, \boldsymbol{r_A}, \boldsymbol{g_A}\}, \{\boldsymbol{s_B}, \boldsymbol{r_B}\}, \boldsymbol{ApB_0})$$

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

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

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



(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_{min} and T_{max}

- **Population makeup**:

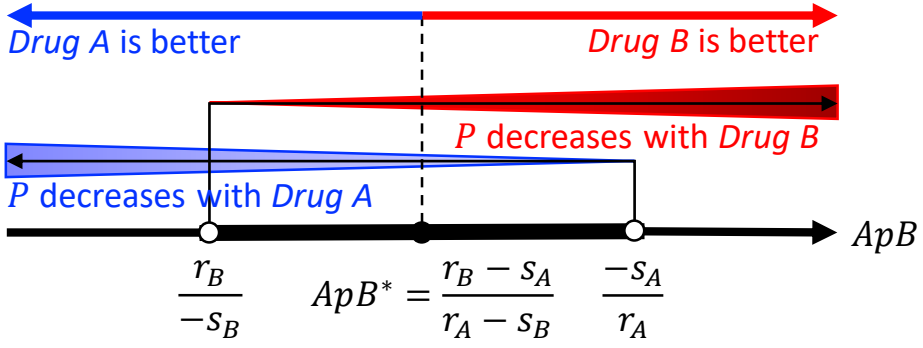
$$ApB(t) \coloneqq R_A(t)/R_B(t)$$

  - $ApB\left(T^A_{min}\right) = ApB\left(T^B_{min}\right) = \frac{\boldsymbol{r_B - s_A}}{\boldsymbol{r_A - s_B}} \coloneqq \boldsymbol{ApB^*}$,
  - $ApB(T^A_{max}) = \frac{\boldsymbol{-s_A}}{\boldsymbol{r_A}}$, $\quad ApB(T^B_{max}) = \frac{\boldsymbol{r_B}}{\boldsymbol{-s_B}}$

- **Drug effect at $\boldsymbol{ApB}$**:

$$\frac{\mathrm{d}}{\mathrm{dt}}P(t)\Big|_{t=0}^{\{s_i, r_i, g_i\}, \boldsymbol{ApB_0}}, \qquad P(t) = R_A(t) + R_B(t), \qquad P(0) = 1 \text{ (fixed)}$$

when $\boldsymbol{r_A r_B < s_A s_B}$



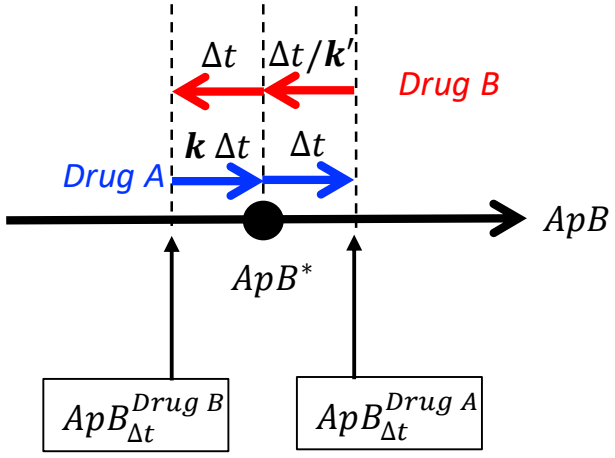
2. Model for 2 drugs

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

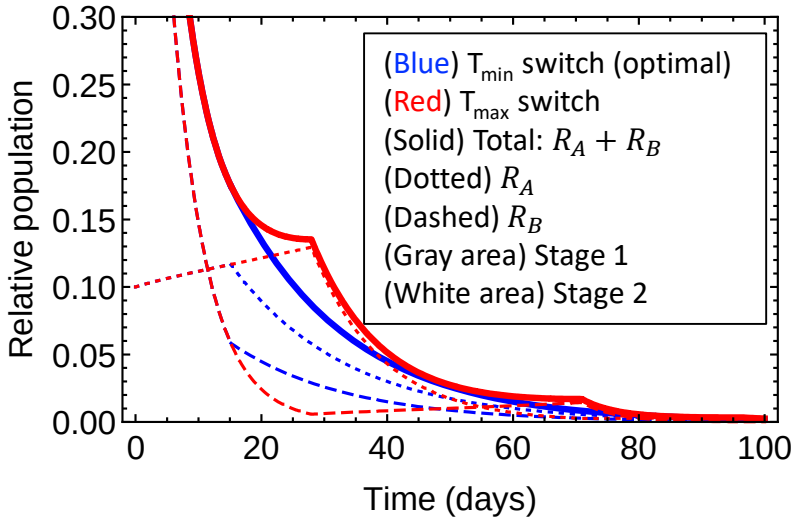
(*Stage 1; shaping*) until T_{min}, "better" drug alone

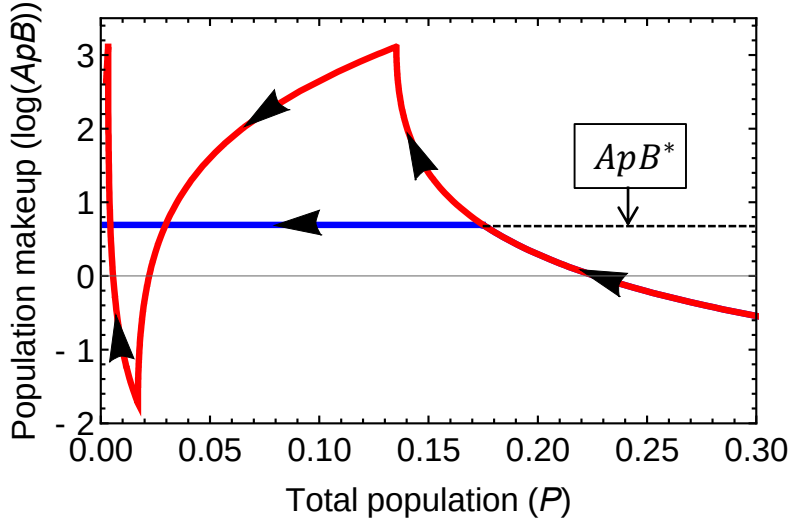
(*Stage 2; adaptive therapy*) combination of the two drugs switched in turn with a definite ratio in duration, *k*, i.e., *Drug A* for t days and *Drug B* for *k* times *t* days.

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



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





(Used parameters)

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

$\{g_A, g_B\} = 0.001\{0.75,1.25\}, \{R_A^0, R_B^0\} = \{0.1,0.9\}$

2. Model for 2 drugs

Simple analytic description of Stage 2 of the optimal control

- **Differential system on *Stage 2*:**

Drug A for $(k^*\ \Delta t)$-long period $\begin{pmatrix}\dot{R}_A\\ \dot{R}_B\end{pmatrix} = \begin{pmatrix}r_B & g_B\\ 0 & s_B - g_B\end{pmatrix}\begin{pmatrix}R_A\\ R_B\end{pmatrix} := \mathbb{D}_{\boldsymbol{A}}\begin{pmatrix}R_A\\ R_B\end{pmatrix},$

Drug B for Δt -long period $\begin{pmatrix}\dot{R}_A\\ \dot{R}_B\end{pmatrix} = \begin{pmatrix}s_A - g_A & 0\\ g_A & r_A\end{pmatrix}\begin{pmatrix}R_A\\ R_B\end{pmatrix} := \mathbb{D}_{\boldsymbol{B}}\begin{pmatrix}R_A\\ R_B\end{pmatrix}$

Drug A for $(k^*\ \Delta t)$-long period

…

as $\Delta t \to 0$

$$\begin{pmatrix}\dot{\boldsymbol{R}}_{\boldsymbol{A}}\\ \dot{\boldsymbol{R}}_{\boldsymbol{B}}\end{pmatrix} = \left[\frac{\boldsymbol{k}^*}{\boldsymbol{1+k}^*}\mathbb{D}_{\boldsymbol{A}} + \frac{\boldsymbol{1}}{\boldsymbol{1+k}^*}\mathbb{D}_{\boldsymbol{B}}\right]\begin{pmatrix}\boldsymbol{R}_{\boldsymbol{A}}\\ \boldsymbol{R}_{\boldsymbol{B}}\end{pmatrix}$$

- ***Stage 2* starts at T_{min}:**

$$ApB(T_{min}) = ApB^*$$

- **Populations on *stage 2***

$$P(t + T_{min}) = P(T_{min})\ Exp(\lambda\ t)$$

for $P \in \{R_A, R_B, R_A + R_B\}$

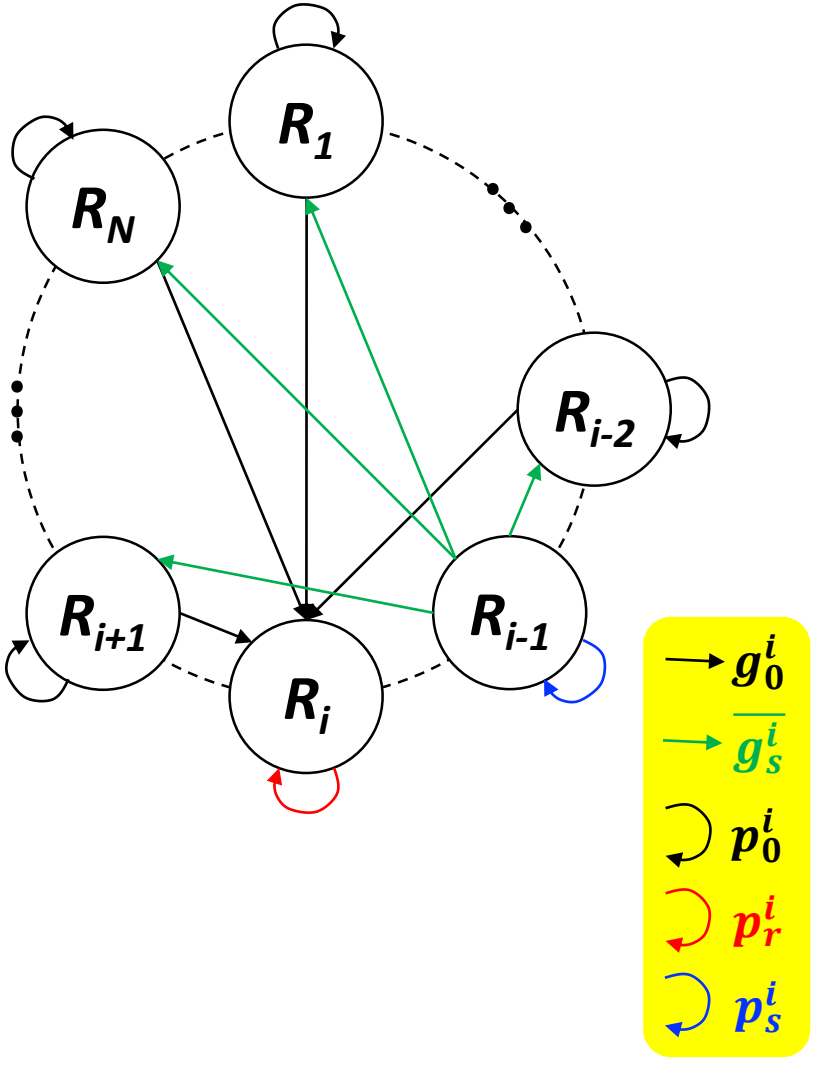
where $\lambda = -\dfrac{r_A r_B - s_A s_B}{r_A + r_B + s_A + s_B}$

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*:

Drug 1 → *Drug 2* → ⋯ → *Drug N* → *Drug 1* → ⋯

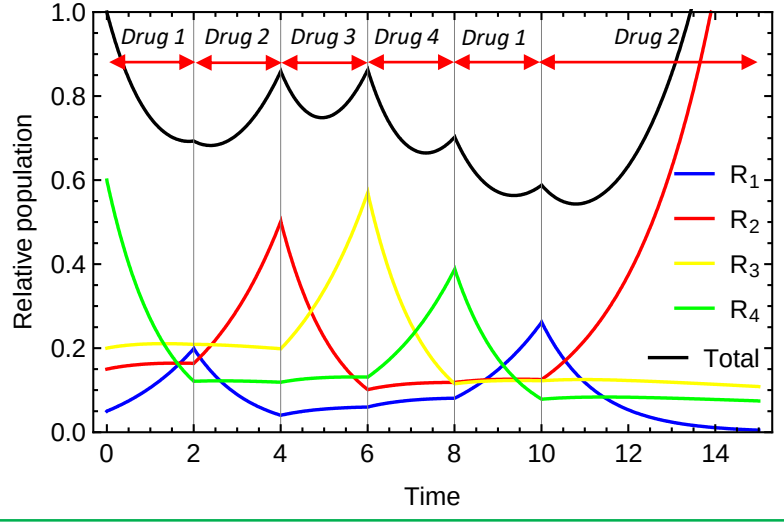


N dynamic variables:

- 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 x 5 parameters:

- Proliferation rates: $\{\boldsymbol{p_r^i} > 0, \boldsymbol{p_s^i} < 0, \boldsymbol{p_0^i}\}$ for *Drug i*
- Transition rates: $\{\boldsymbol{g_s^i}, \boldsymbol{g_0^i}\}$ for *Drug i*



3. Model for *n* drugs

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

(i-1)-th column ↓

$$\mathcal{M}(i) = \begin{pmatrix} \lambda_0^i & 0 & \cdots & 0 & \overline{g_s^i} & 0 & \cdots & \cdots & \cdots & 0 \\ 0 & \ddots & \ddots & \vdots & \vdots & \vdots & & & & \vdots \\ \vdots & \ddots & \ddots & 0 & \vdots & \vdots & & & & \vdots \\ \vdots & & \ddots & \lambda_0^i & \overline{g_s^i} & \vdots & & & & \vdots \\ 0 & \cdots & \cdots & 0 & \lambda_s^i & 0 & \cdots & \cdots & \cdots & 0 \\ g_0^i & \cdots & \cdots & g_0^i & 0 & \lambda_r^i & g_s^i & \cdots & \cdots & g_s^i \\ 0 & \cdots & \cdots & 0 & \overline{g_s^i} & 0 & \lambda_0^i & 0 & \cdots & 0 \\ \vdots & & & \vdots & \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ \vdots & & & \vdots & \vdots & \vdots & & \ddots & \ddots & 0 \\ 0 & \cdots & \cdots & 0 & \overline{g_s^i} & 0 & \cdots & \cdots & 0 & \lambda_0^i \end{pmatrix}$$

← (i-1)-th row

← i-th row

With

- $(\lambda_r^i, \lambda_s^i, \lambda_0^i) = (p_r^i, p_s^i - g_s^i, p_0^i - g_0^i)$
- $\overline{g_s^i} = \frac{g_s^i}{N-2}$

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 (ApB^* 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)

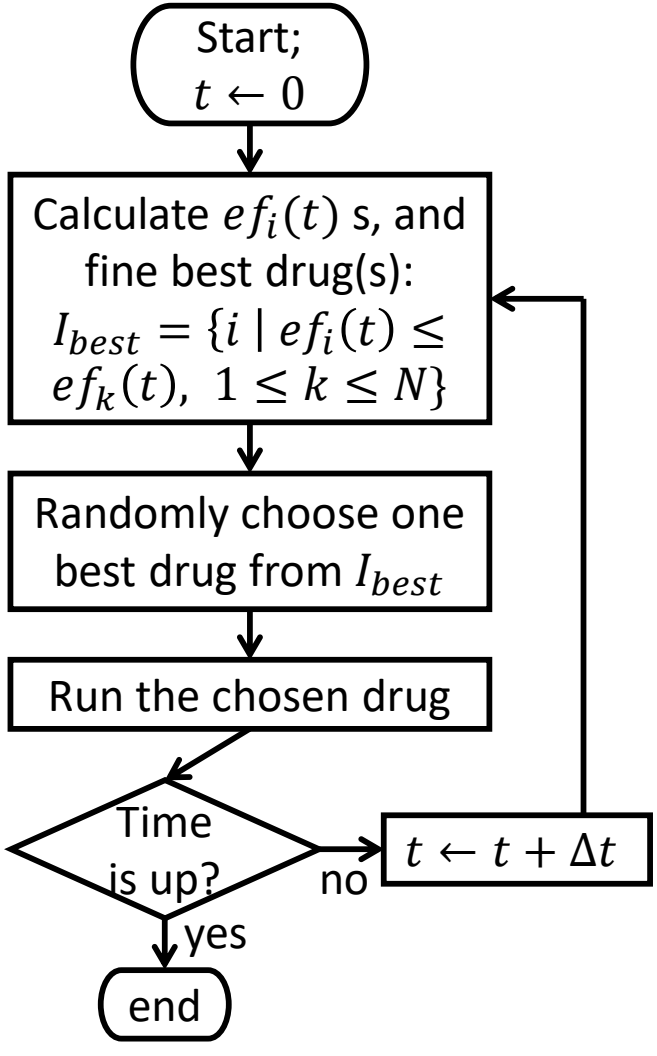
Total cell population with optimal therapy

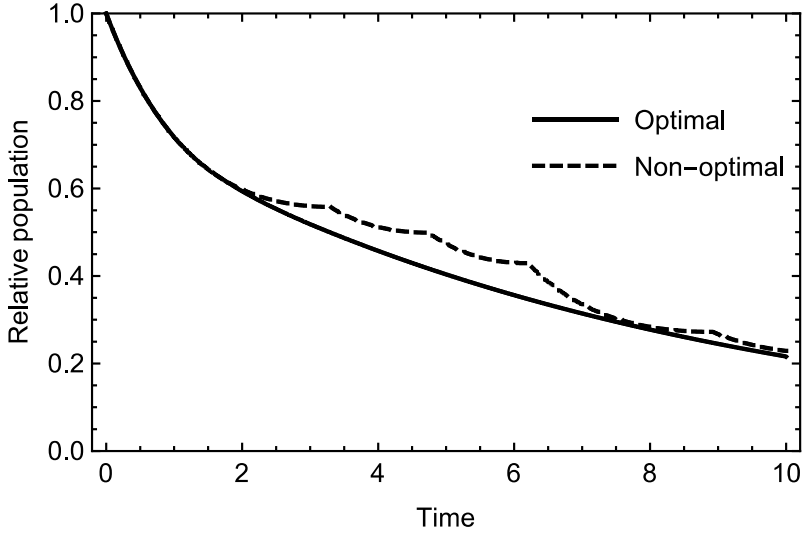
$$\frac{dv}{dt} = \mathcal{M}\left(\underset{1\le i\le N}{\operatorname{argmin}}\, ef_i\right) v$$

where $ef_i(t) = \mathcal{P}^i \cdot v(t)$

Discretely solvable by finding the best drug at every discrete time point and solve $v' = \mathcal{M}(j)\, v$ until the next point.

3. Model for *n* drugs





↑ 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*

$\{p_r, p_s, p_0\} = \{0.2, -0.7, 0.1\}, \{g_s, g_0\} = \{0.1, 0.05\},$

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

*Example 4 of **asymmetric** drugs*

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

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

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

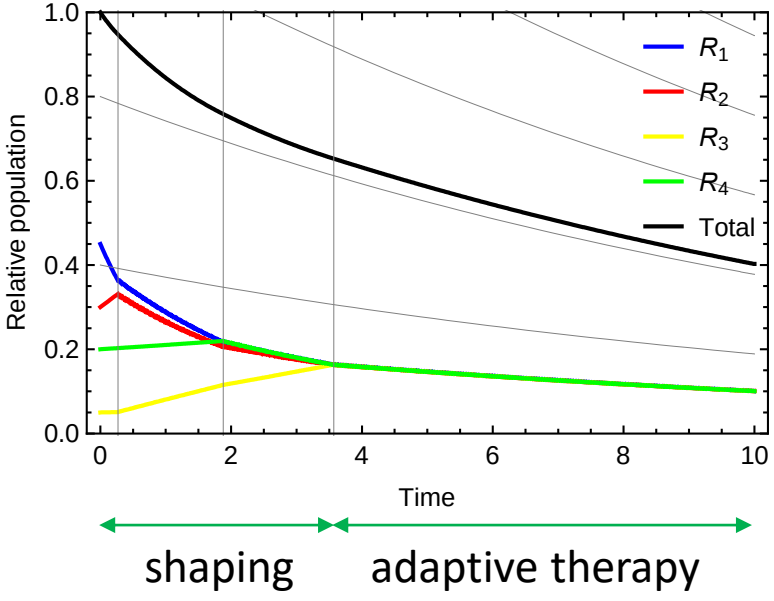
$\{p_r^4 p_s^4, p_0^4\} = \{0.1, -0.2, 0.0\}, \{g_s^4, g_0^4\} = \{0.001, 0.0005\},$

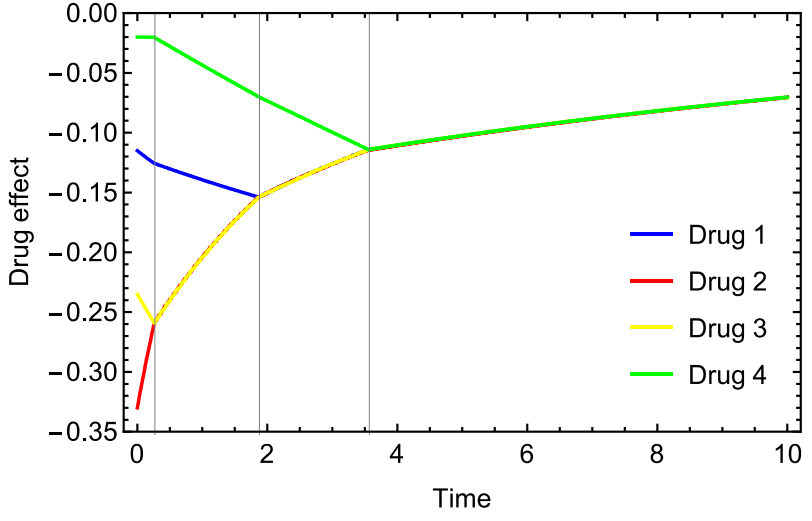
$\{R_1^0, R_2^0, R_3^0, R_4^0\} = \{0.05, 0.15, 0.2, 0.6\}$

3. Model for *n* drugs

An example with *symmetric* drugs

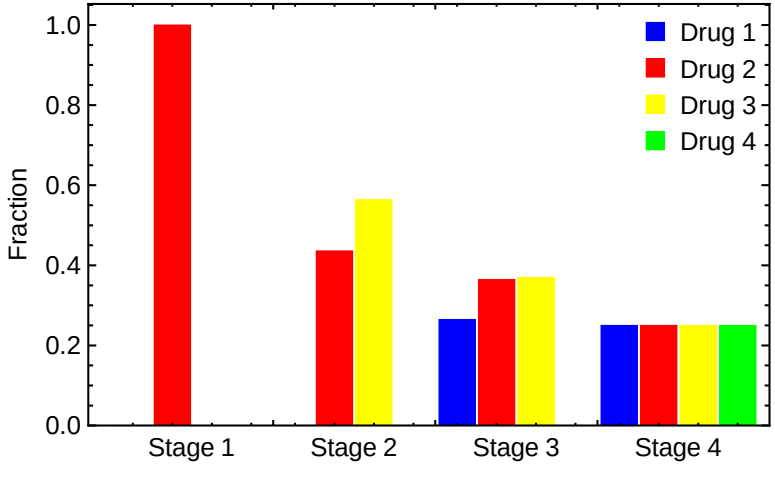
$\{p_r, p_s, p_0\} = \{0.2, -0.7, 0.1\}, \{g_s, g_0\} = \{0.1, 0.05\}, \{R_1^0, R_2^0, R_3^0, R_4^0\} = \{0.45, 0.3, 0.05, 0.2\}$





$$v^* = \lambda(1, \ldots, 1)^T$$

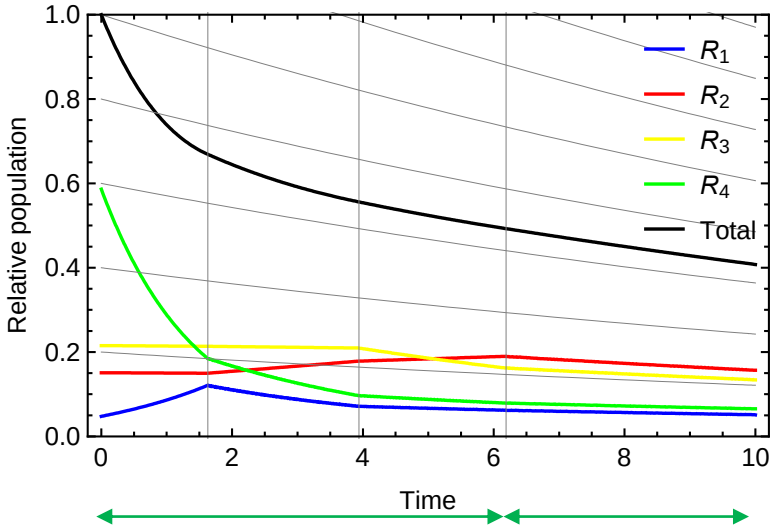
Decay rate: $\frac{p_r + p_s + (N-2)p_0}{N}$

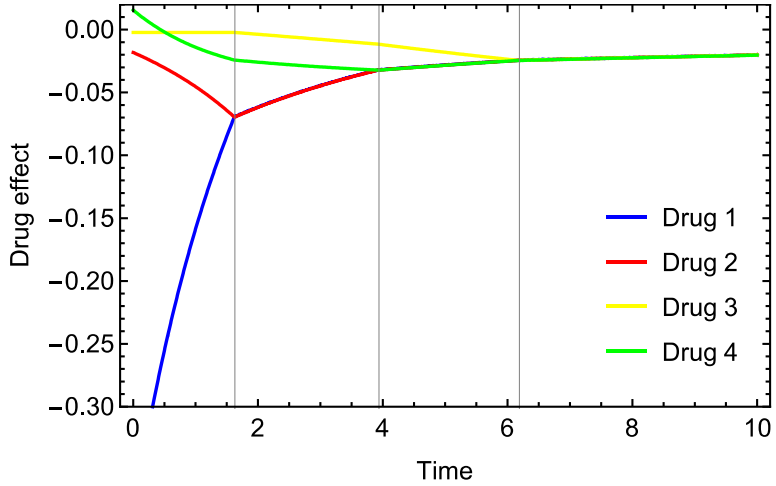


3. Model for *n* drugs

An example with *asymmetric* drugs

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





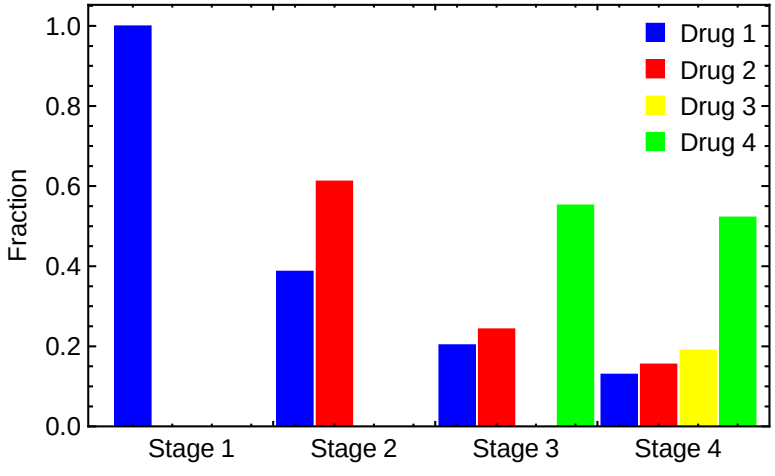
$$v^* = \lambda \begin{pmatrix} (\mathcal{P}^1)^T \\ \vdots \\ (\mathcal{P}^N)^T \end{pmatrix}^{-1} \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}$$

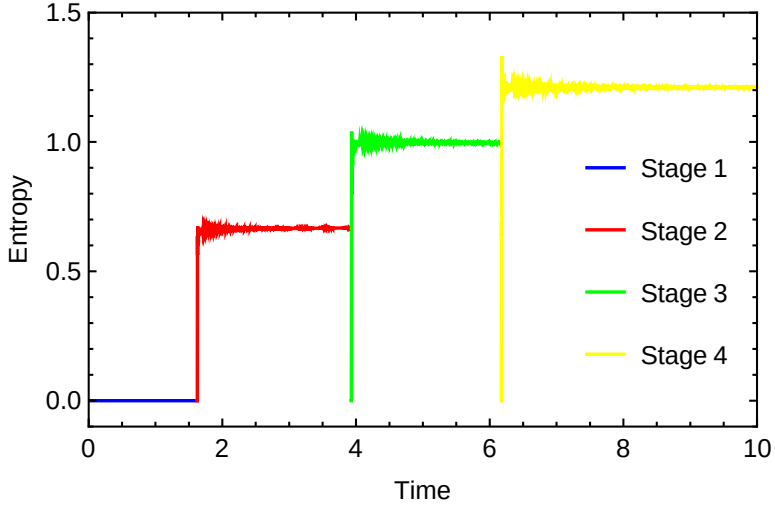
Decay rate:??

3. Model for *n* drugs

An example with *asymmetric* drugs

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





Within each stage, since the entropy graph is flat on each stage, drugs are periodically switching with relative period from the bar chart.

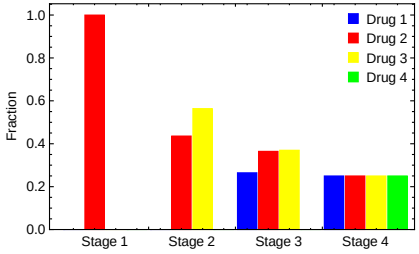
3. Model for *n* drugs

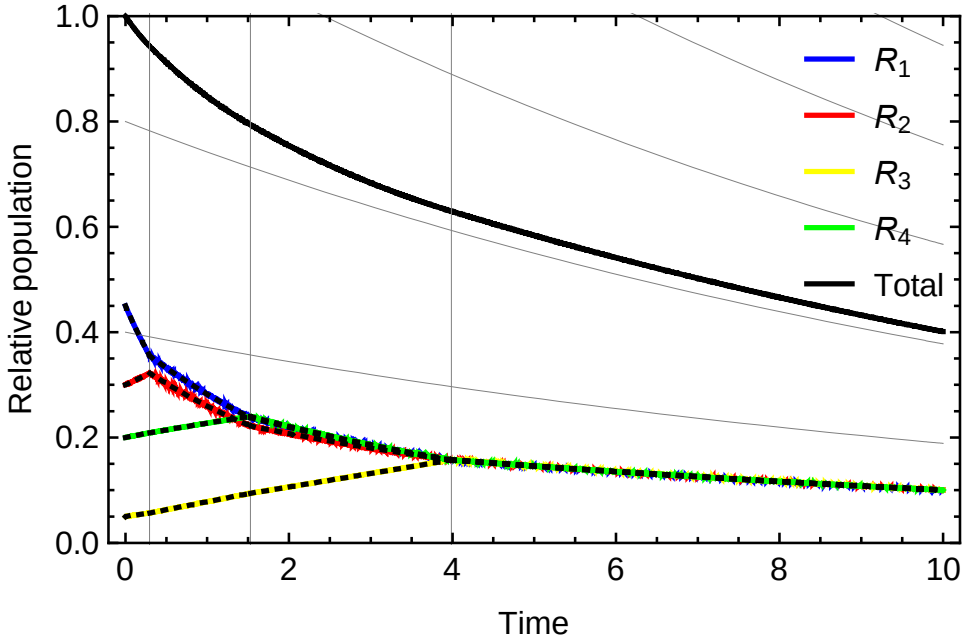
Instantaneous drug switch is supposed to be consistent with the **linear combination** of the dynamics with corresponding intensities (as numerically tested).

Drug 1 for $(f_1\ \Delta t)$-long period,
Drug 2 for $(f_2\ \Delta t)$-long period
…
Drug N for $(f_N\ \Delta t)$-long period
Drug 1 for $(f_1\ \Delta t)$-long period
…

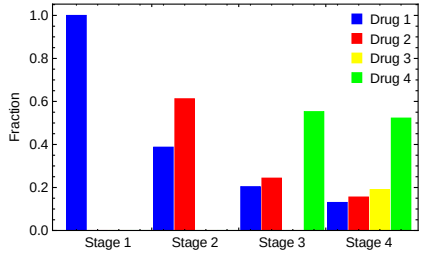
$$\boldsymbol{v} = \left(\sum_{i=1}^{N} \boldsymbol{f}_i \mathcal{M}(\boldsymbol{i})\right)\boldsymbol{v}$$

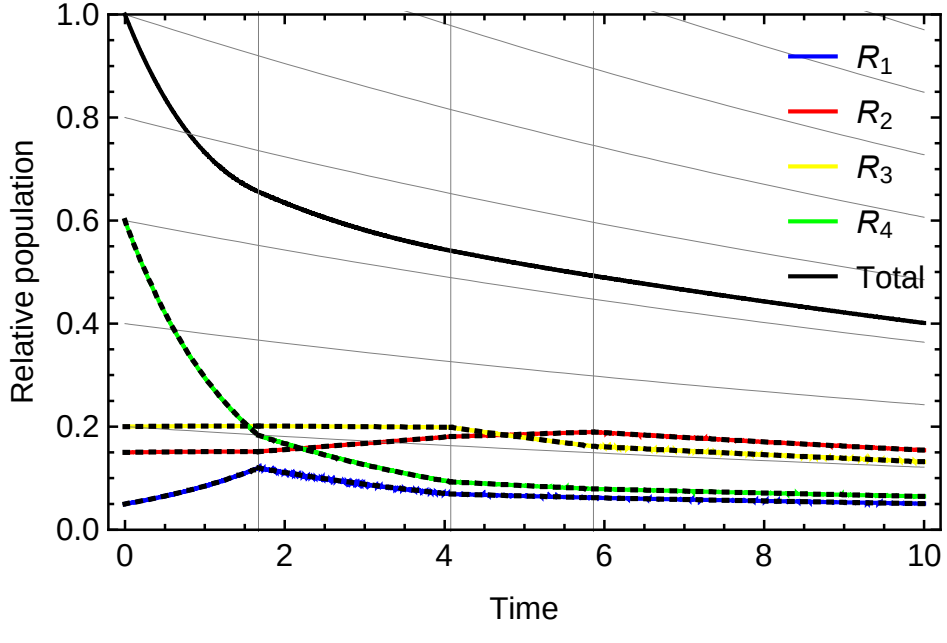
Symmetric drugs





Asymmetric drugs





4. Optimal regimen without parameters

1. Subpopulations are know (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 $g_0^i = \boldsymbol{\alpha_0} p_0^i$ and $g_s^i = \boldsymbol{\alpha_s} p_s^i$

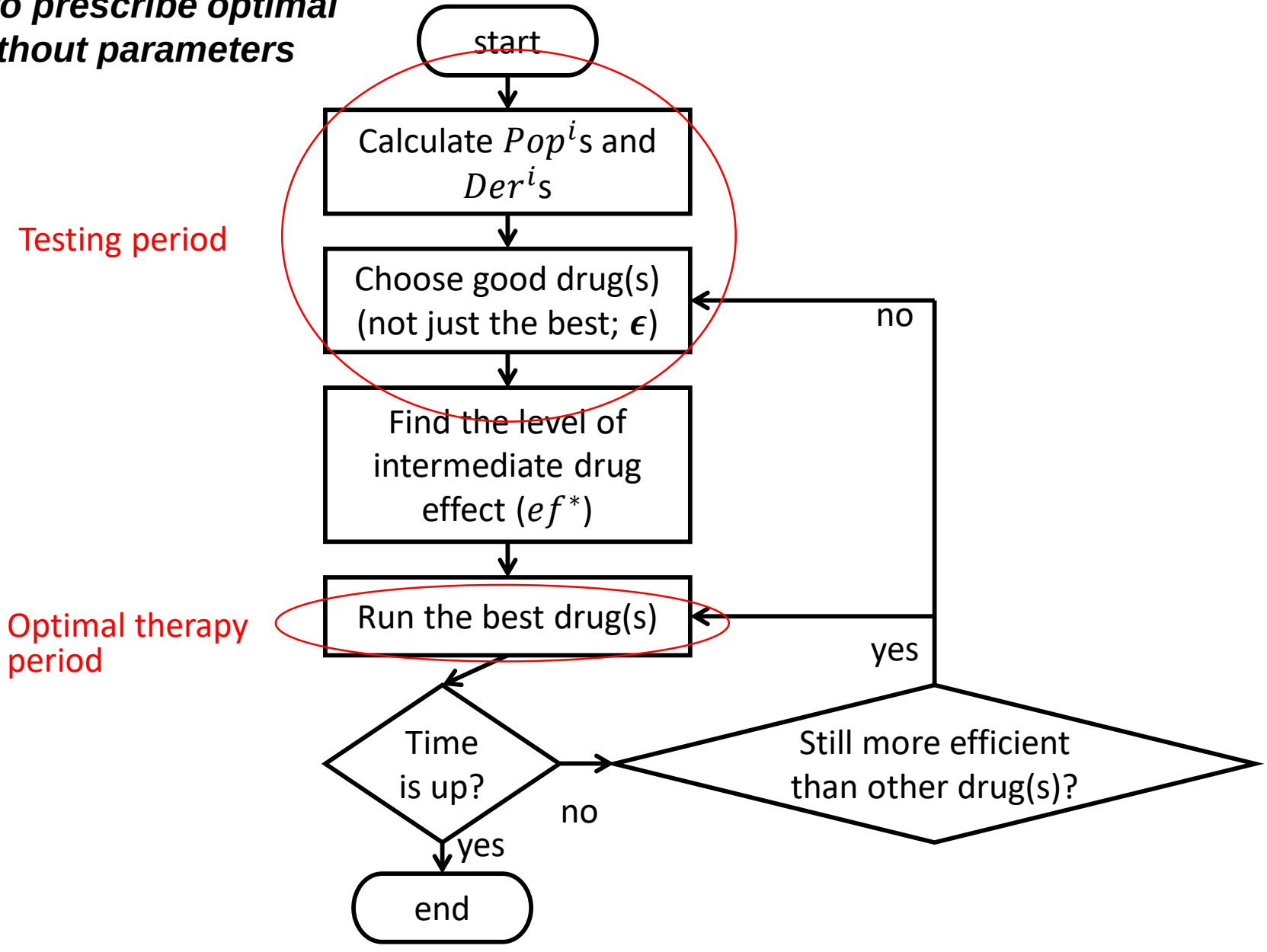
→ Calibration of **5 parameters**

2. Only total population is know (e.g., Prostate Specific Atigen):

Computational algorithm??

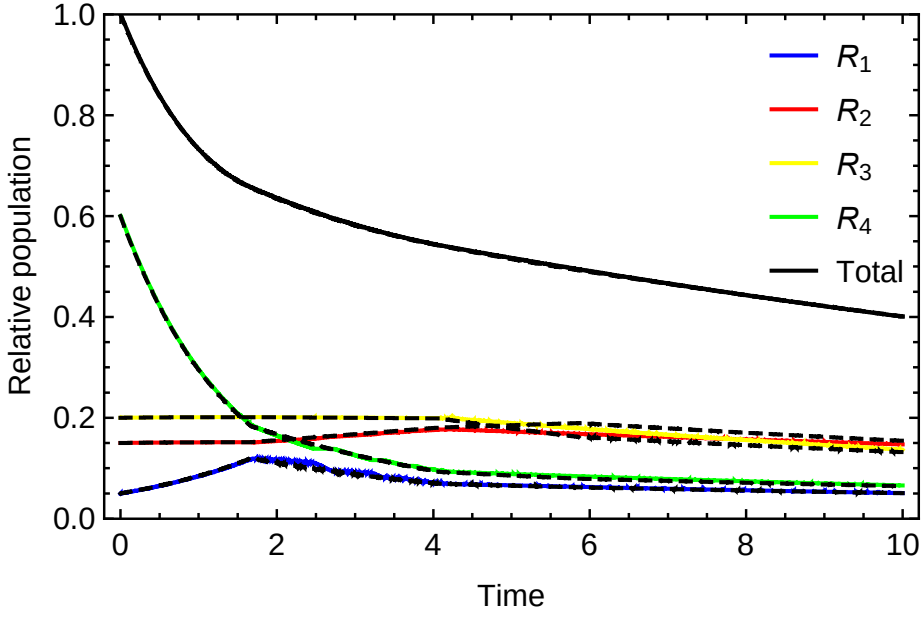
4. Optimal regimen without parameters

Algorithm to prescribe optimal regimen without parameters

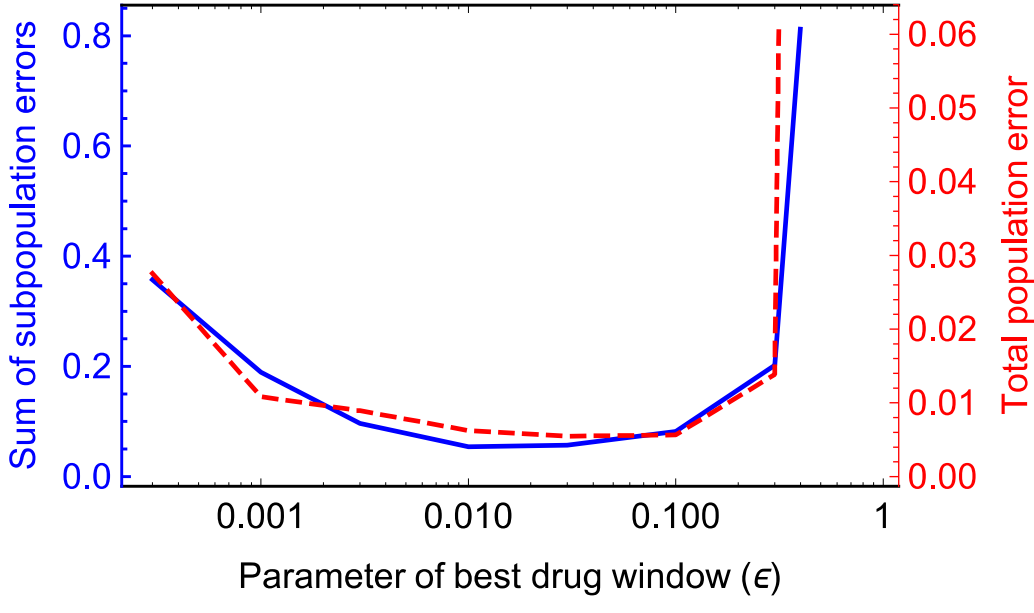


4. Optimal regimen without parameters

Algorithm to prescribe optimal regimen without parameters



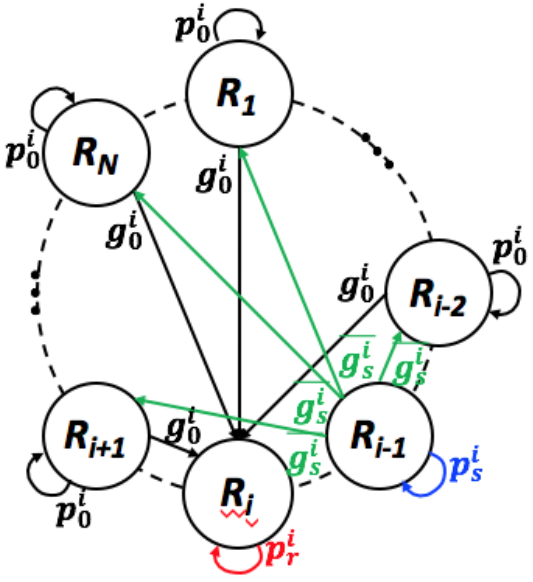
Good consistency with $\epsilon = 0.01$



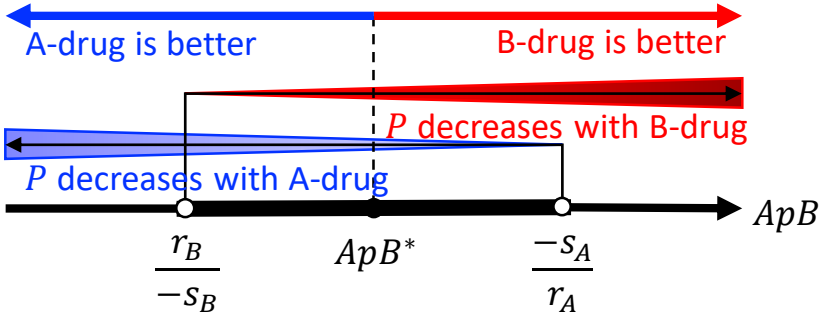
Errors of the algorithm over a range of ϵ

Conclusions

- Population structure



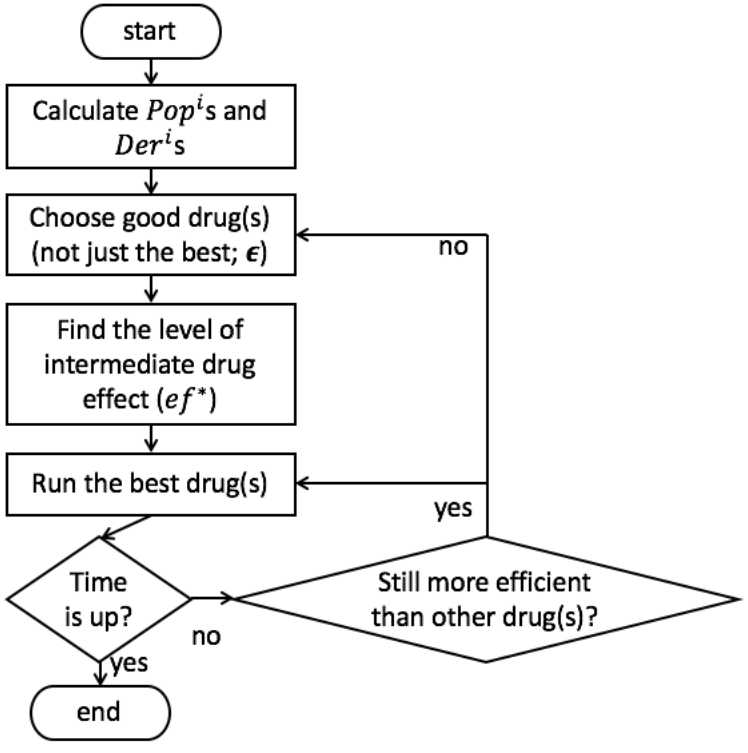
- Population makeup with balanced drug effects



- Numerically figured out optimal control

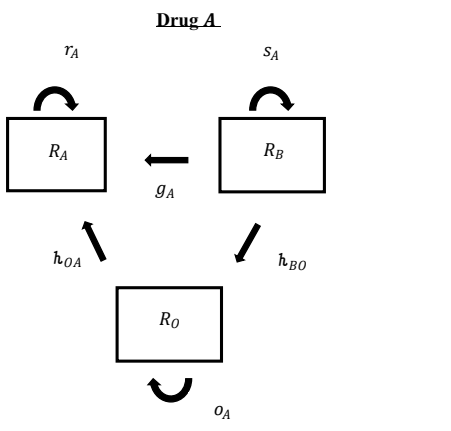
$$\frac{dv}{dt} = \mathcal{M}\left(\underset{1\le i\le N}{\operatorname{argmin}}\, ef_i\right) v$$

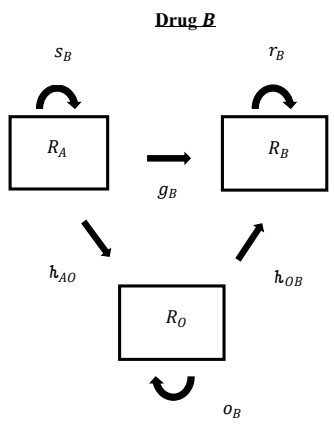
- Optimal prescription without drug parameters known

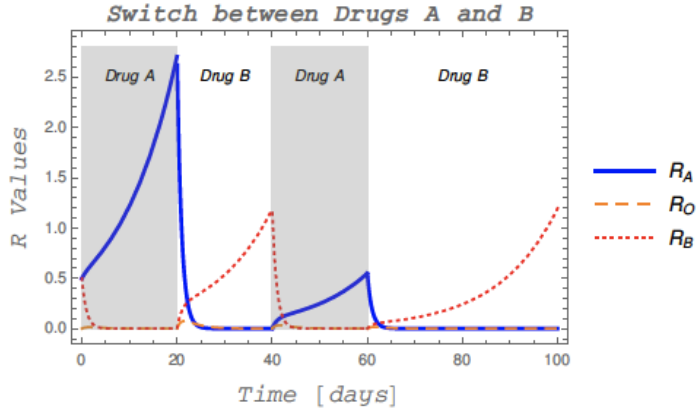


Future work

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







- **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

Thank you! Questions?