Studying the effects of competition on adaptive therapy

Mid Year Presentation

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5th Year BS-MS

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Adaptive Therapy

- Conventional therapy @ MTD $\rightarrow$ min tumour burden (Frei et al. 1980)
- Heterogenous sensitivity $\rightarrow$ sensitive eliminated $\rightarrow$ resistant population (Scott et al. 2017)
- AT = lower, fluctuating dose $\rightarrow$ sensitive preserved
- AT dose = $f(\textit{tumour size})$ (Gatenby et al. 2009)

mCRPC

- System of study: Metastatic Castration-Resistant Prostate Cancer
- History of Adaptive therapy work (Cunningham et al. 2018)
- Therapy: ADT + Abiraterone

Cell type	Test. dependent	Test. Producing	Ab. sensitive	Mechanism
T^+	Yes	No	Yes	N/A
T^p	Yes	Yes	Yes	Cholestrol $\xrightarrow{CYP17\alpha}$ Testosterone
T^-	No	No	No	Androgen receptor mutations

Competition between cells

- AT outcome $\sim$ competition b/w sensitive and resistant
- sensitive keeps resistant in check
- sensitive killed by drug dose
- Competitive strategies through traits from cancer progression (Hanahan et al. 2011)
  - Higher proliferation rate
  - Better survival @ sub-optimal conditions
  - Lower death rate

ODE Model

- Starting point: forming expectations, parameterization
- Logistic framework with dynamic carrying capacity $\sim$ environmental conditions
- Environment = resource = {oxygen, testosterone}

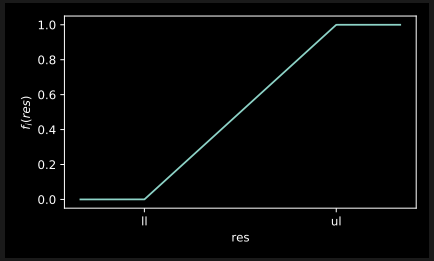


Figure 1: $f_i(res)$

$$\frac{dy_i}{dt} = r_i y_i \left(1 - \frac{\sum_j y_j}{1 + K_{i,max} f_i(O_2) f_i(test)}\right) - \delta_i y_i \quad (1)$$

$$\frac{dO_2}{dt} = p_{O_2} - \sum_i \mu_{O_2,i} y_i - \lambda_{O_2} O_2 \quad (2)$$

$$\frac{dtest}{dt} = p_{test} y_{T^p} - \sum_i \mu_{test,i} y_i - \lambda_{test} test \quad (3)$$

$$f_i(res) = \begin{cases} 1 & \text{if } ul_{res,i} \leq res \\ \frac{res - ll_{res,i}}{ul_{res,i} - ll_{res,i}} & \text{if } ll_{res,i} < res < ul_{res,i} \\ 0 & \text{if } res \leq ll_{res,i} \end{cases} \quad (4)$$

$i \in \{T^+, T^p, T^-\}$ and $res \in \{O_2, test\}$.

Parameters & Standardization

Some parameters directly from literature

- δ_i: Death rate (Jain et al. 2011)
  - T^+ 2.5×10^{-3} min^{-1}
  - T^p 2.5×10^{-3} min^{-1}
  - T^- 1.6×10^{-4} min^{-1}
- $\mu_{O_2,i}$: Oxygen uptake (Hail et al. 2010)
  - T^+ 1.63×10^{-6} $\text{min}^{-1}\text{cell}^{-1}$
  - T^p 1.63×10^{-6} $\text{min}^{-1}\text{cell}^{-1}$
  - T^- 1.04×10^{-6} $\text{min}^{-1}\text{cell}^{-1}$
- λ_{res}: Decay rate (Jain et al. 2011)
  - O_2 0.100 min^{-1}
  - *test* 0.004 min^{-1}

Parameters & Standardization

Some parameters from assumptions & constraints

- r_i: Growth rate (Eq 5)
  - T^+ 2.84×10^{-3} min^{-1}
  - T^p 2.79×10^{-3} min^{-1}
  - T^- 6.23×10^{-4} min^{-1}
- $K_{i,max}$: Maximum Carrying capacity (Eq 6)
  - T^+ 8.35×10^4
  - T^p 9.62×10^4
  - T^- 1.34×10^4
- p_{res}: Production rate (Eq 7,8)
  - O_2 0.11 min^{-1}
  - $test$ 5×10^{-7} $\text{min}^{-1}\text{cell}^{-1}$
- $\mu_{test,i}$: Testosterone uptake (Eq 8)
  - T^+ 2.34×10^{-8} $\text{min}^{-1}\text{cell}^{-1}$
  - T^p 6.00×10^{-8} $\text{min}^{-1}\text{cell}^{-1}$
  - T^- 0 $\text{min}^{-1}\text{cell}^{-1}$
- $ll_{res,i}$: Lower limit/threshold level $\in [0, 1]$
- $ul_{res,i}$: Upper limit/saturation level $\in [0, 1]$

$$r_i = \frac{ln(2)}{\tau_{d,i}} + \delta_i \tag{5}$$

$$K_{i,max} = \frac{r_i}{r_i - \delta_i} y_i^* \tag{6}$$

$$p_{O_2} = \lambda_{O_2} O_2^* + y_i^* \mu_i \tag{7}$$

$$p_{test} - \mu_{test,T^p} = \frac{test^* \lambda_{test}}{y_{T^p}^*} = 4 \times 10^{-4} \tag{8}$$

Pairwise Competition: $T^p - T^-$

1. T^p *test* & O_2 limited. T^- only O_2 limited

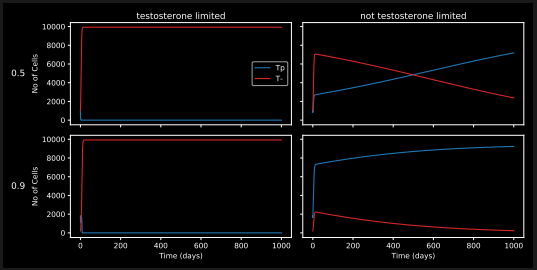
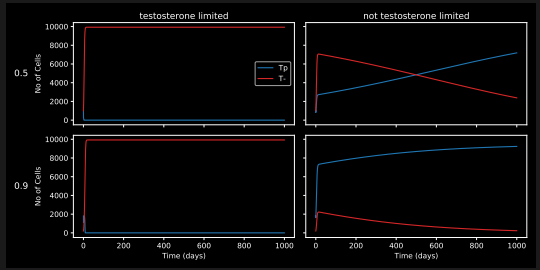


Figure 2: Pairwise $T^p - T^-$ timeseries, when T^p is testosterone limited and not testosterone limited (colums) and at different initial proportions of T^p(rows)

Pairwise Competition: $T^p - T^-$

1. T^p *test* & O_2 limited. T^- only O_2 limited
2. T^p not severely testosterone limited
   - T^p coexist or outcompete T^-
   - T^- outcompetes in other cases



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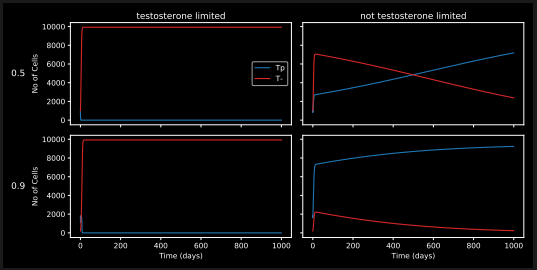

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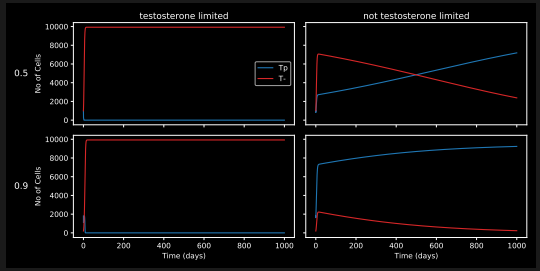
3. Outcomes dependent on the initial proportion of T^p
4. T^- strongly oxygen limited
   - T^p still testosterone limited
   - T^- wins eventually
   - Oxygen levels rise faster than testosterone



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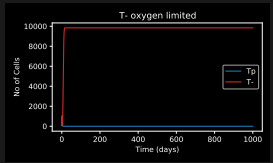


Figure 3: Pairwise $T^p - T^-$ timeseries, when T^- is severly oxygen limited

Pairwise Competition: $T^+ - T^p$

1. Both cell type limited by both resource

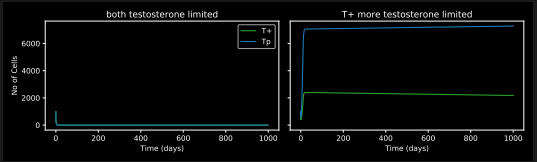
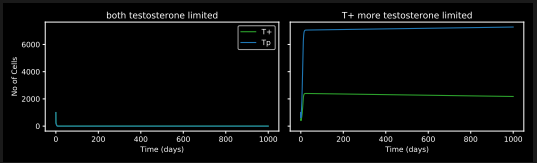


Figure 4: Pairwise $T^+ - T^p$ timeseries, when both cell types are testosterone limited and when T^+ is limited more than T^p

Pairwise Competition: $T^+ - T^p$

1. Both cell type limited by both resource
2. Both severly testosterone limited
   - T^+ consume & grows on limited testosterone
   - Density-dependent competition drive T^p extinct
   - No T^p = No testosterone $\rightarrow$ T^+ extinct



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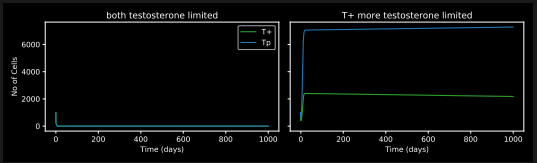
3. T^p is weakly limited by testosterone relative to T^+
   - Both coexist
   - T^p grow initially & not affected by T^+



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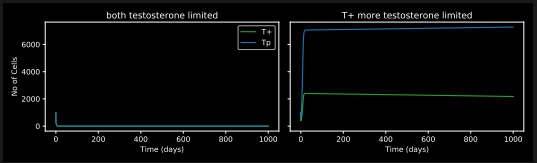
   - No T^p = No testosterone $\rightarrow$ T^+ extinct
3. T^p is weakly limited by testosterone relative to T^+
   - Both coexist
   - T^p grow initially & not affected by T^+
4. T^+ severly oxygen limited
   - T^p grow initially & secrete testosterone
   - Sustain small T^+ if not extinct



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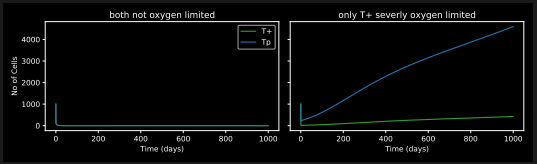

Figure 5: Pairwise $T^+ - T^p$ timeseries, when both cell types are testosterone limited and not oxygen limited and when T^+ is severly oxygen limited

Future Plans

- Testosterone limitation relaxed
- Oxygen limit exploration with lower $ul_{test,i}$
- Make oxygen more limiting than testosterone via production rates
- 3 cell-type competition
- Simulate AT regimens with therapy as $p_{test} = f(dose)$
- Replicate in ABM & Compare

Thank You

Figure 6: Meme, Original Image by USDA

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