Studying the effects of competition on adaptive therapy

Mid Year Presentation

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Adaptive Therapy

- Conventional therapy @ MTD $\rightarrow$ min tumour burden
- Heterogenous sensitivity $\rightarrow$ sensitive eliminated $\rightarrow$ resistant population (Scott et al. 2017)
- AT = lower, fluctuating dose $\rightarrow$ sensitive preserved

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	Mechanism
T^+	Yes	No	N/A
T^p	Yes	Yes	Cholestrol $\xrightarrow{CYP17\alpha}$ Testosterone
T^-	No	No	Androgen receptor mutations

Competition between cells

- AT outcome $\sim$ competition b/w sensitive and resistant
- 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 for ABM
- Computationally cheap but can't capture complex behaviour
- Logistic framework with dynamic carrying capacity $\sim$ environmental conditions
- Environment = resource = {oxygen, testosterone}

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

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

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

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

$i \in \{T^+, T^p, T^-\}$ 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 additional supplementary parameters

- τ_d: Doubling time (*ATCC: The Global Bioresource Center* n.d.)
  - T^+ 34 hr
  - T^p 40 hr
  - T^- 25 hr
- y_i^*: Equilibrium cell number (assumed)
  10000
- res^*: Equilibrium/Tissue resource levels (Stewart et al. 2010,Titus et al. 2005)
  - O_2 2.5 mmHg
  - *test* 3.74 pmol/g tissue

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
   - Testosterone limitation $\sim ll_{test,T^p}$ and ul_{test,T^p}

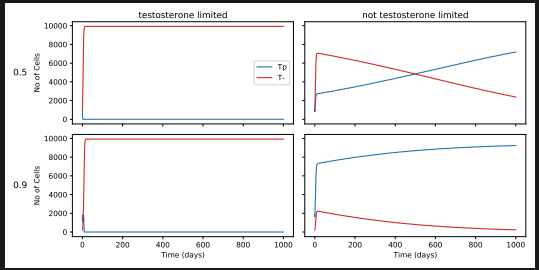

Figure: Pairwise $T^p - T^-$ timeseries, when T^p is testosterone limited and not testosterone limited (colums) and at different initial proportions of T^p(rows)

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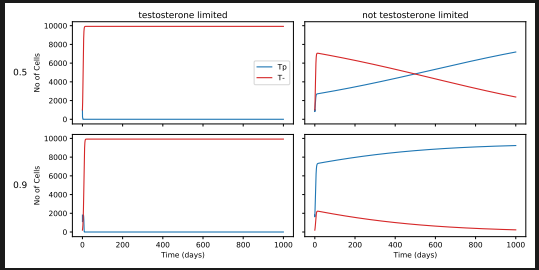
   - T^p coexist or outcompete T^-
   - T^- Outcompetes in other cases



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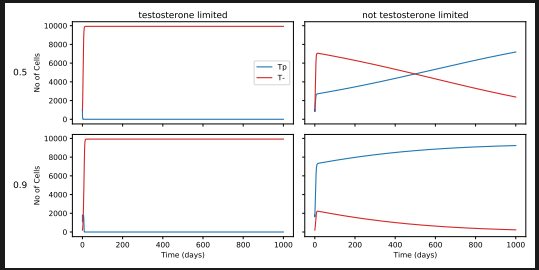
3. ll_{O_2,T^-} large
   - T^- strongly oxygen limited
   - T^p still testosterone limited
   - T^- wins eventually
   - Oxygen levels rise faster than testosterone



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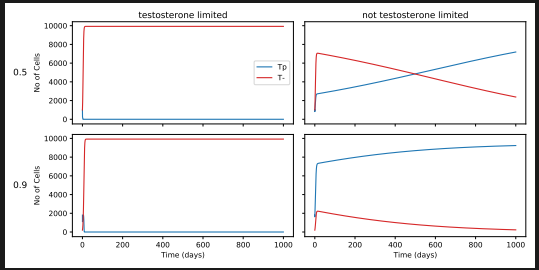
4. Outcomes dependent on the initial proportion of T^p



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

1. Both cell type limited by both resource & strength of limitation of resource through limits

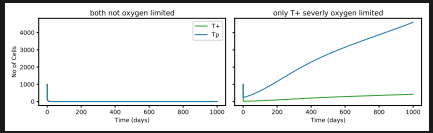


Figure: Pairwise $T^+ - T^p$ timeseries, when both cell types are testosterone limited and not oxygen limited and when T^+ is severly oxygen limited

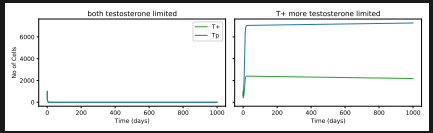
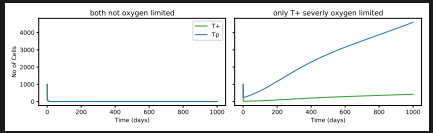


Figure: Pairwise $T^+ - T^p$ timeseries, when both cell types are testosterone limited and when T^+ is limited more than T^p

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

1. Both cell type limited by both resource & strength of limitation of resource through limits
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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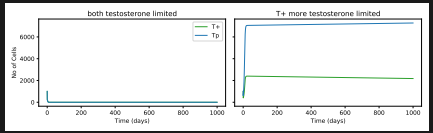

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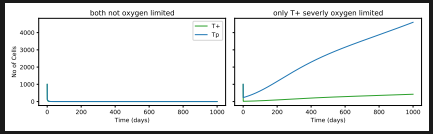
   - T^+ severly oxygen limited
   - T^p grow initially & secrete testosterone
   - Sustain small T^+ if not extinct



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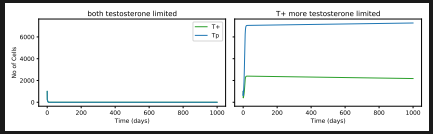

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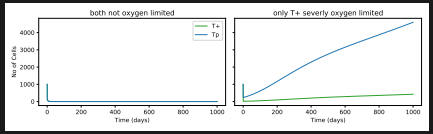
3. ll_{O_2,T^p} large
   - T^+ severly oxygen limited
   - T^p grow initially & secrete testosterone
   - Sustain small T^+ if not extinct
4. $ul_{test,T^p} \leq ul_{test,T^+}$
   - T^p is weakly limited by testosterone relative to T^+
   - Both coexist
   - T^p grow initially & not affected by T^+



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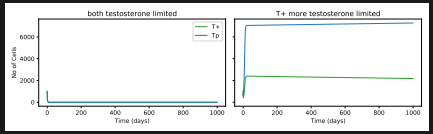

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Future Plans

- 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

References I

[1] *ATCC: The Global Bioresource Center*.

[2] Jessica J. Cunningham, Joel S. Brown, Robert A. Gatenby, and Kateřina Staňková. "Optimal control to develop therapeutic strategies for metastatic castrate resistant prostate cancer". In: *Journal of Theoretical Biology* 459 (2018), pp. 67–78.

[3] Numsen Hail, Ping Chen, and Lane R. Bushman. "Teriflunomide (Leflunomide) Promotes Cytostatic, Antioxidant, and Apoptotic Effects in Transformed Prostate Epithelial Cells: Evidence Supporting a Role for Teriflunomide in Prostate Cancer Chemoprevention". In: *Neoplasia* 12.6 (2010), pp. 464–475.

[4] Douglas Hanahan and Robert A Weinberg. "Hallmarks of cancer: the next generation". In: *cell* 144.5 (2011), pp. 646–674.

[5] Harsh Vardhan Jain, Steven K. Clinton, Arvinder Bhinder, and Avner Friedman. "Mathematical modeling of prostate cancer progression in response to androgen ablation therapy". In: *Proceedings of the National Academy of Sciences* 108.49 (2011), pp. 19701–19706.

[6] Jacob Scott and Andriy Marusyk. "Somatic clonal evolution: A selection-centric perspective". In: *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer* 1867.2 (2017). Evolutionary principles - heterogeneity in cancer?, pp. 139–150.

References II

[7] Grant D. Stewart, James A. Ross, Duncan B. McLaren, Christopher C. Parker, Fouad K. Habib, and Antony C.P. Riddick. "The relevance of a hypoxic tumour microenvironment in prostate cancer". In: *BJU International* 105.1 (2010), pp. 8–13.

[8] Mark A. Titus, Michael J. Schell, Fred B. Lih, Kenneth B. Tomer, and James L. Mohler. "Testosterone and Dihydrotestosterone Tissue Levels in Recurrent Prostate Cancer". In: *Clinical Cancer Research* 11.13 (2005), pp. 4653–4657.