A theoretical study of the implications of resource competition for adaptive therapy of castration-resistant prostate cancer

Thesis Defence

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Introduction

- Conventional therapy @ MTD $\rightarrow$ $\downarrow$ tumour burden (Frei & Canellos, 1980)
- Heterogenous sensitivity $\rightarrow$ sens. $\times \rightarrow$ resst. (Scott & Marusyk, 2017)
- AT = $\downarrow$, $\sim$ dose $\rightarrow$ sens. $\checkmark$ (Gatenby et al., 2009)
- Drug holiday - sens. $\rightarrow \downarrow$ resst.
- AT outcome $\leftarrow$ competition

Figure 1: Competitive release under SOC

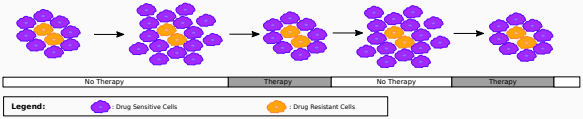


Figure 2: Control under AT

- Castration-Resistant Prostate Cancer (CRPC)
- AR pathway: prostate cells $\rightarrow$ cancer (Heinlein & Chang, 2004)
- Therapy: ADT + Abiraterone

Cell type	Test. dependent	Test. Producing	Ab. sensitive	Mechanism
T^+	Yes	No	Yes	N/A
T^p	Yes	Yes	Yes	Cholesterol $\xrightarrow{CYP17\alpha}$ Test.
T^-	No	No	No	AR μ^n

- Logistic framework w/ dynamic carrying capacity ≈ env. condn.
- Environment = resource = $\{O_2, test\}$
- No μ^n, no spatial structure, well mixed
- Defined $\mathbb{R}_{\geq 0}$, $y_i < 1 =$ extinction

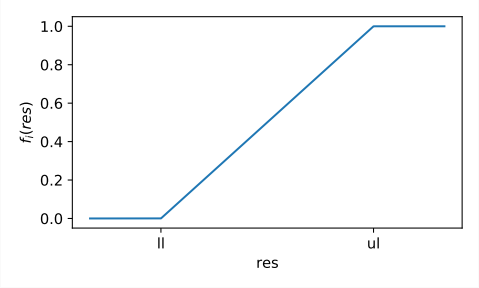


Figure 3: $f_i(res)$

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

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

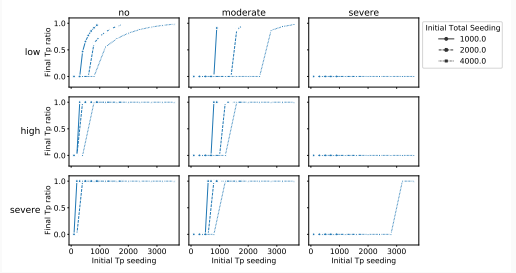
$$\frac{dtest}{dt} = p_{test} y_{T^p} - \sum_i \mu_{test,i} y_i - \lambda_{test} test \quad (3)$$

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

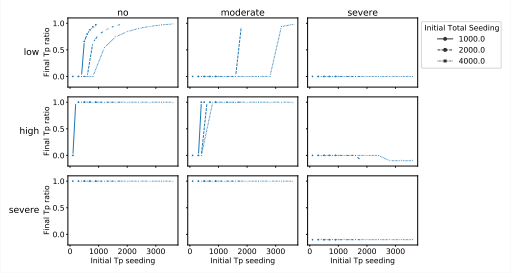
$i \in \{T^+, T^p, T^-\}$ and $res \in \{O_2, test\}$.

Cell-types Interactions and Competition outcomes

T^p - T^- Cases



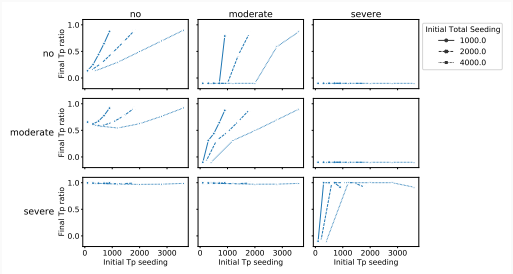
(a) normal prodn.



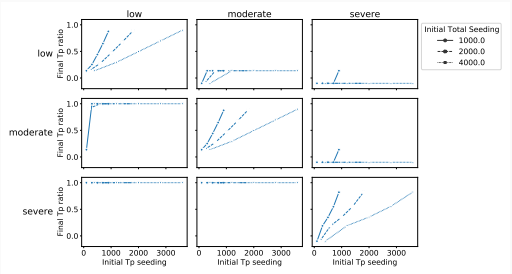
(b) poor prodn.

Figure 4: Final T^p ratio of pairwise $T^p - T^-$. SF: O_2 prodn., C: T^p *test* limits, R: T^- O_2 limits.

- Coexist: T^p no/mod. + T^- low
- Tot. popn. vs Initial propn.



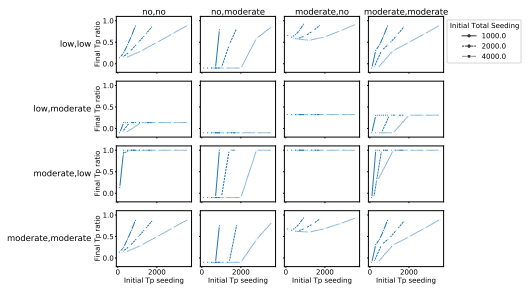
(a) *test* limits. C: T^p *test* limits, R: T^+ *test* limits



(b) O_2 limits. C: T^p O_2 limits, R: T^+ O_2 limits

Figure 5: Final T^p ratio of pairwise $T^+ - T^p$

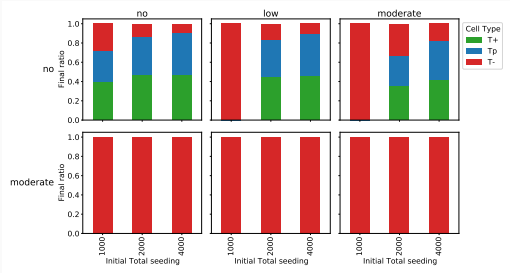
- Coexist: limitation same
- Coexist: mod.



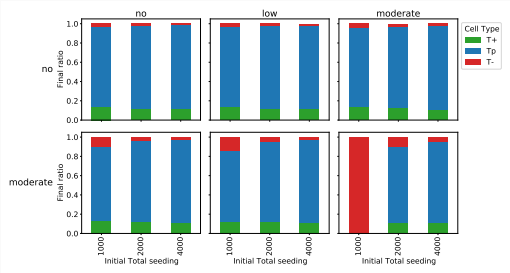
(c) Combination limits. C: T^+, T^p *test* limits, R: T^+, T^p O_2 limits

Figure 5: Final T^p ratio of pairwise $T^+ - T^p$

- Similar: symmetric limitation



(a) Equal seeding - 1:1:1



(b) High T^D seeding - 8:1:1

Figure 6: Final ratio of all cell types. C: O_2 limits , R: *test* limits and SF: seeding propn.

- Homogenous: *test* private resource
- No vs Mod: Weak vs Strong interspecific

- O_2: 3 zones of effect

Therapy

- Therapy: boolean - 1 = MTD

$$p_{test}(abi) = \begin{cases} p_{test,max} & \text{if } abi = 0 \\ p_{test,min} & \text{if } abi = 1 \end{cases} \quad (5)$$

$$r_i(dtx) = \begin{cases} r_{i,max} & \text{if } dtx = 0 \\ r_{i,min} & \text{if } dtx = 1 \end{cases} \quad (6)$$

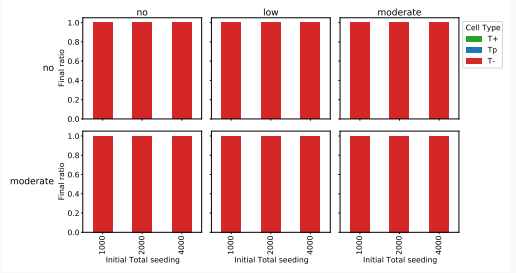
- SOC: dose at MTD from start

$$dose(x,t) = 1 \quad \forall\, t, x \quad (7)$$

- AT: binary mode, switch on/off therapy

$$dose(x,t) = \begin{cases} 0 & \text{if } dose(x, t-\Delta t) = 0 \text{ and } x < \text{On} \\ 1 & \text{if } dose(x, t-\Delta t) = 0 \text{ and } x \geq \text{On} \\ 1 & \text{if } dose(x, t-\Delta t) = 1 \text{ and } x > \text{Off} \\ 0 & \text{if } dose(x, t-\Delta t) = 1 \text{ and } x \leq \text{Off} \end{cases} \quad (8)$$

Standard of care (SOC)



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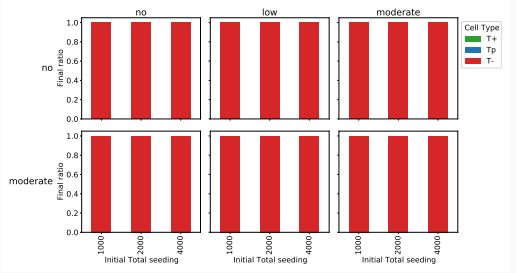


(b) High T^p seeding - 8:1:1

Figure 7: Final ratio of all cell types under standard-of-care. C: O_2 limits , R: *test* limits and SF: seeding propn.

- T^+, T^p extinct: all cases
- *test*: insufficient

Adaptive Therapy (AT) thresholds

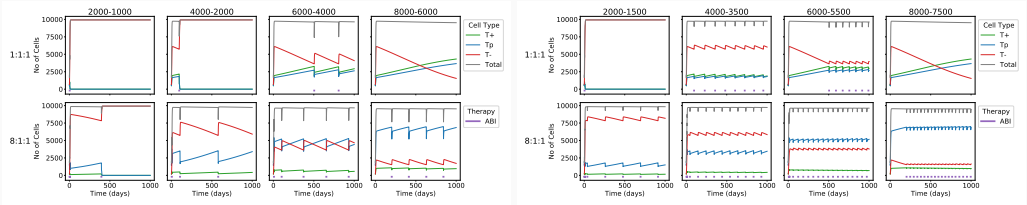
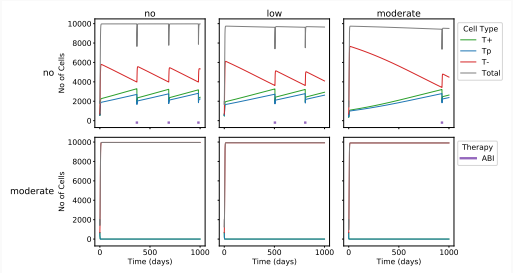


Figure 8: Standardisation of threshold for AT, C: On-Off threshold, R: $T^p : T^+ : T^-$ Seeding

- 50% rule
- Low threshold: T^- inhibits
- High threshold: better (Hansen & Read, 2020)

- Too high: no therapy
- On: 6000, Off: 4000
- Popn. size $T^+ - T^p$



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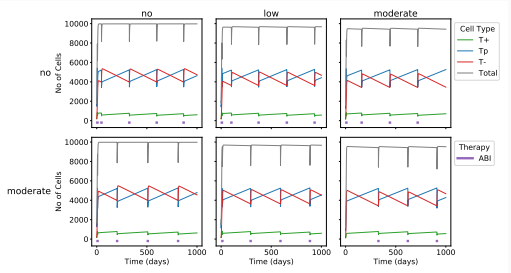
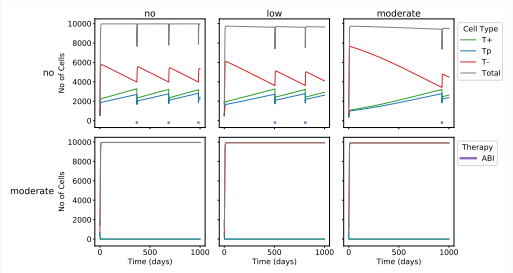


(b) High T^p seeding - 8:1:1

Figure 9: Time-series of all cell types with AT. C: O_2 limits, R: *test* limits and SF: seeding propn. (On:6000, Off:4000)

- Higher $T^+ - T^p$: more treatable
- *test* mod.: extinct from comp.

- Apply therapy - T^- quickly replace $\rightarrow$ tot. popn. high



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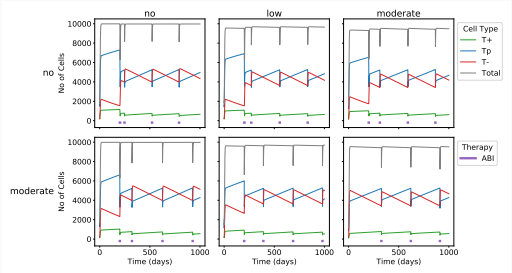


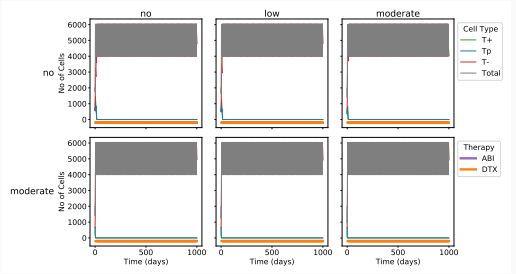
(b) High T^p seeding - 8:1:1

Figure 10: Time-series of all cell types with AT delayed by 200 days. C: O_2 limits, R: *test* limits and SF: seeding propn. (On:6000, Off:4000)

- Speculate: delay $\rightarrow T^+ - T^p \uparrow$

- No advantage $\leftarrow$ no variability
- Physiological cost

Combination AT



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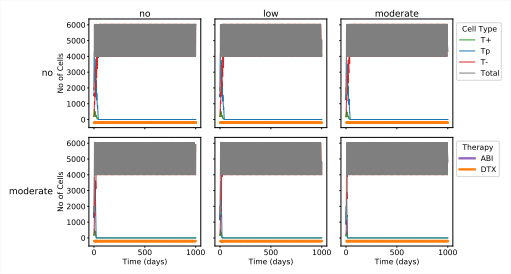

(b) High T^p seeding - 8:1:1

Figure 11: Time-series of all cell types with combination AT of abi and dtx. C: O_2 limits, R: *test* limits and SF: seeding propn. abi(On:6000, Off:4000; $T^+ + T^p$), dtx(On:6000, Off:4000; $T^+ + T^p + T^-$)

- Hormone-specific + cytoxic (West et al., 2019)
- Test-of-concept: abi - $T^+ - T^p$, dtx - total

- $-ve$ effect on $T^+ - T^p$ vs $+ve$ effect $\downarrow T^-$

Conclusion

Summary

- Res. levels $\rightarrow$ compe. strength
- Limit balance $\rightarrow$ coexist
- SOC: $\uparrow$ *test* limit
- AT: influence $\propto T^{+} - T^{p}$
- Higher threshold: $\uparrow$ success, $\uparrow$ physiological cost
- Assumptions: carrying capacity
- Mechanistic vs Data-driven
- Future work: IBM, Spatial, Plasticity, Heterogeneity

References

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