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

Thesis Defence

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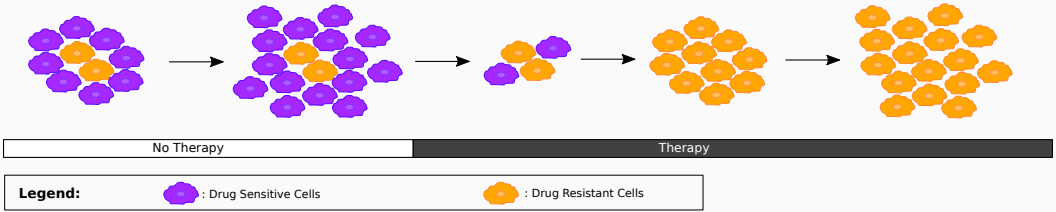
July 2021

IISER Pune

Introduction

How is cancer usually treated?



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[1] SOC: Standard-Of-Care
[2] MTD: Maximum Tolerated Dose

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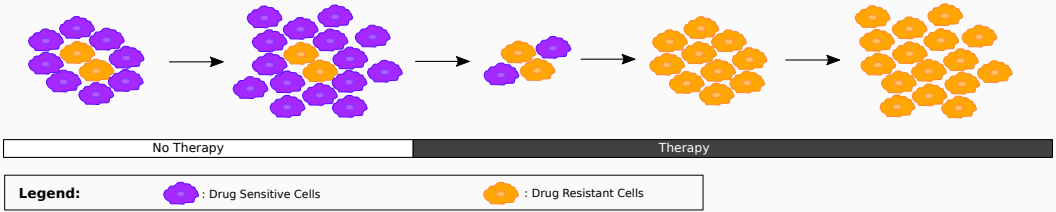

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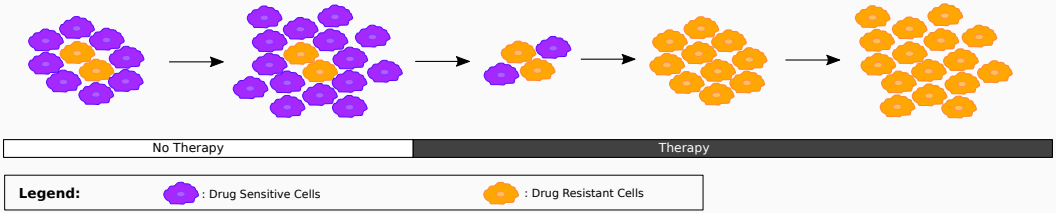

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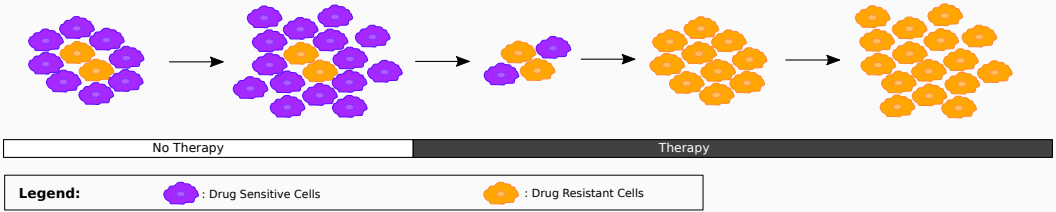

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- SOC[1]: Drugs applied at MTD[2]
- Cells have heterogeneous sensitivity → without therapy - sensitive keep resistant in check
- MTD[2] eliminates sensitive → resistant tumour doesn't respond to therapy (Scott & Marusyk, 2017)

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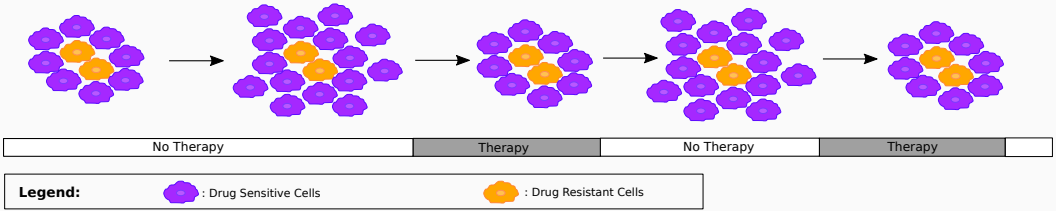
How to avoid competitive release?



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- AT[1]: apply drugs at lower, fluctuating doses (Gatenby et al., 2009)

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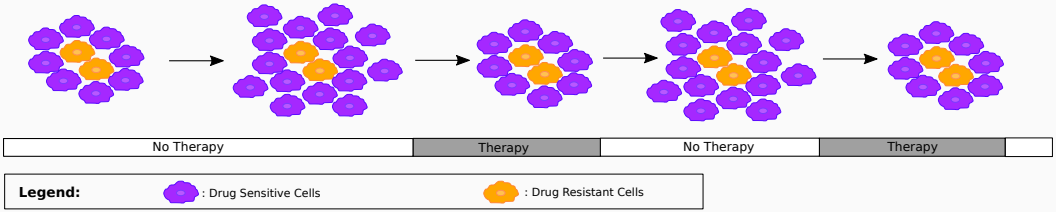

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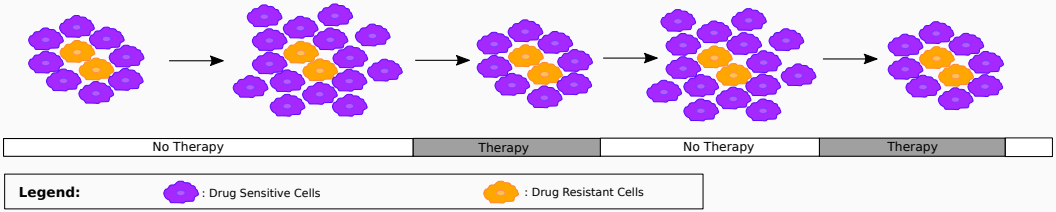

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- AT[1]: apply drugs at lower, fluctuating doses (Gatenby et al., 2009)
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- AT[1] outcome depends on competition

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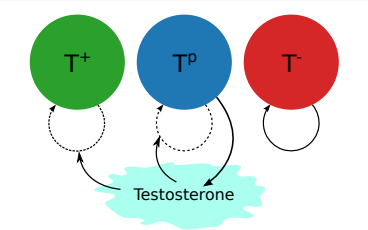

Figure 3: Schematic representation of cell types

Cell type	Testosterone dependent	Testosterone producing	Mechanism of resistance
T^+	Yes	No	N/A
T^p	Yes	Yes	Cholesterol $\xrightarrow{CYP17\alpha}$ Testosterone
T^-	No	No	AR[1] mutation

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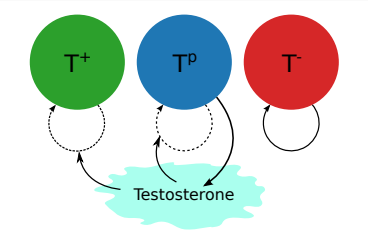
- Difficult to cure with current treatments
- Shift in goal to extend survival
- Prostate cells: AR[1] that trigger proliferation when activated by testosterone (Heinlein & Chang, 2004)



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How do we model this?

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

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[2] *ll*: lower limit, *ul*: upper limit

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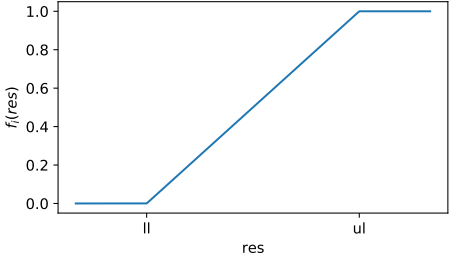

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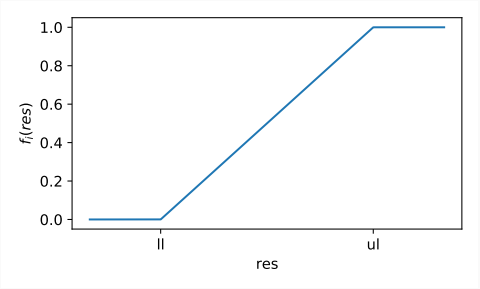
$$\frac{d(test)}{dt} = p_{test} y_{T^p} - \sum_i \mu_{test,i} y_i - \lambda_{test} test \quad (4)$$



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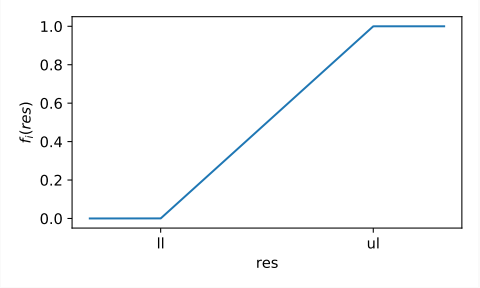

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- Assumptions: No mutation, no spatial structure, well mixed
- Defined $\mathbb{R}_{\geq 0}$, $y_i < 1 =$ extinction

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Parameters Used

- Some values directly from literature based on cell line data (Haïl et al., 2010; Jain et al., 2011)
  - T^+: LNCaP
  - T^p: 22Rv1
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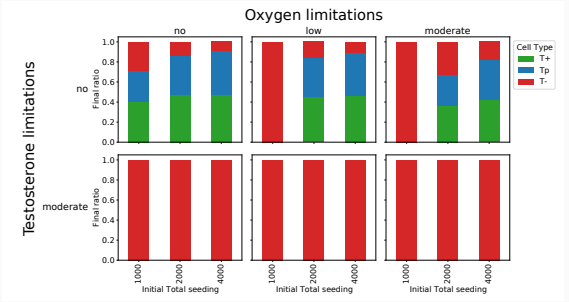
- Some values derieved from literature via contraint equations (ATCC, 2021; Stewart et al., 2010; Titus et al., 2005)
- Study Parameters:
  - Resource limitations: varied using lower and upper limits
  - Initial seeding: different ratios of cell types and total population

What happens in the absence of therapy?

All cell-type competition outcomes



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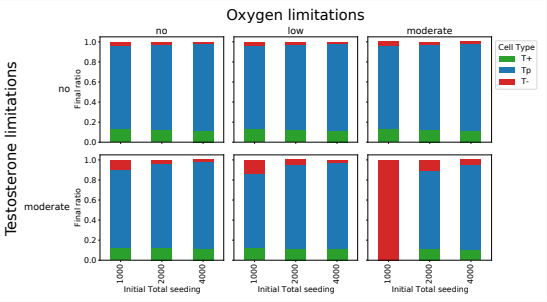

(b) High T^P seeding - 8:1:1

Figure 5: Final ratio of all cell types. (Stacked bar plot)

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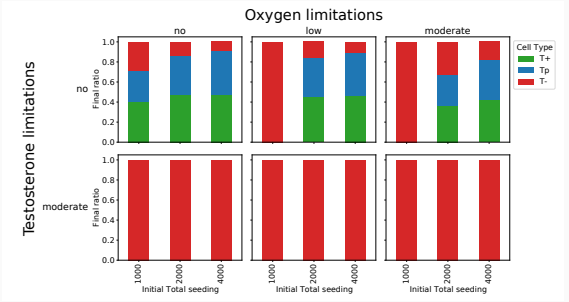

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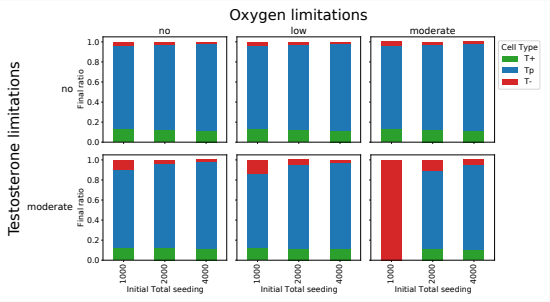

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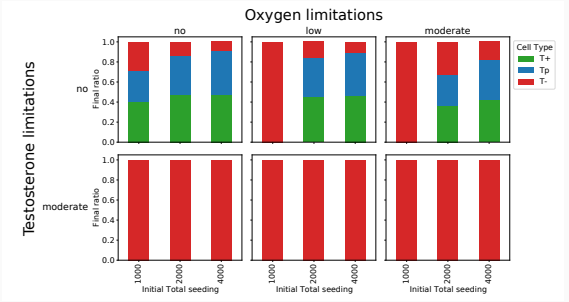

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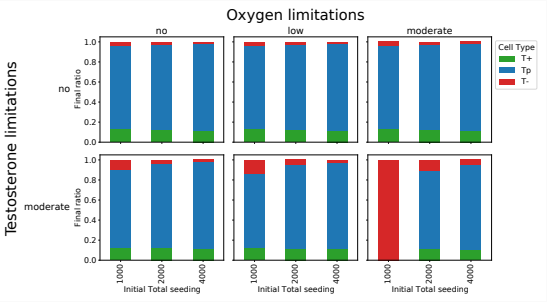

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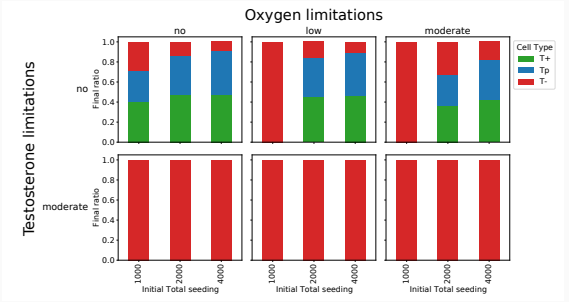

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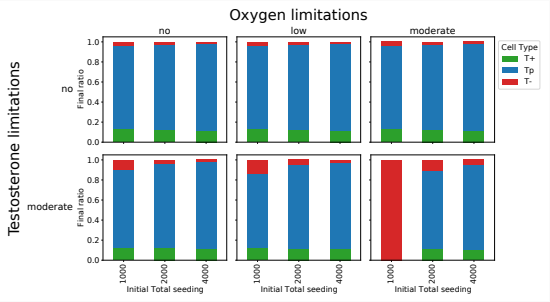

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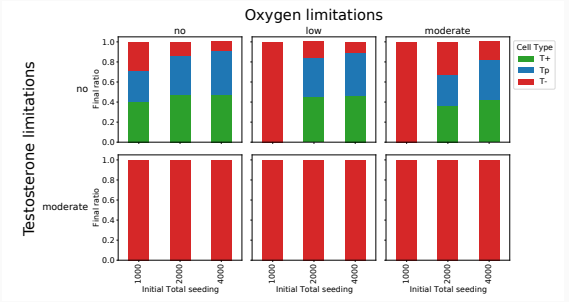

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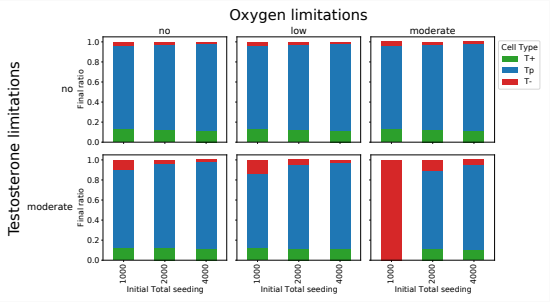

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- Oxygen: minor effect, pushes to extinction if combined limitation on the edge

What happens when we add therapy?

- Therapy: modelled as boolean

$$\begin{aligned} 1 &= \text{MTD} \\ 0 &= \text{no dose} \end{aligned} \tag{5}$$

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- AT[1]: binary mode considered
  - Dose at MTD[1] when on
  - Therapy turned on when population above On threshold
  - Therapy turned off when population below Off threshold

$$dose(y, t) = \begin{cases} 0 & \text{if } dose(y, t - \Delta t) = 0 \text{ and } y < \text{On} \\ 1 & \text{if } dose(y, t - \Delta t) = 0 \text{ and } y \geq \text{On} \\ 1 & \text{if } dose(y, t - \Delta t) = 1 \text{ and } y > \text{Off} \\ 0 & \text{if } dose(y, t - \Delta t) = 1 \text{ and } y \leq \text{Off} \end{cases} \tag{9}$$

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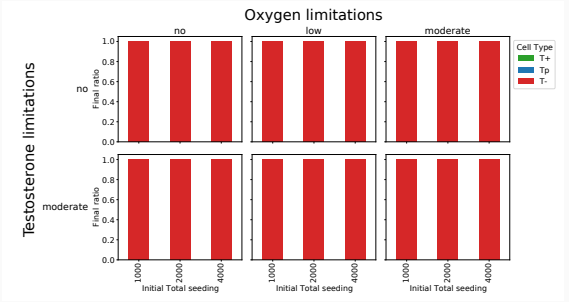
What happens with Standard-Of-Care?



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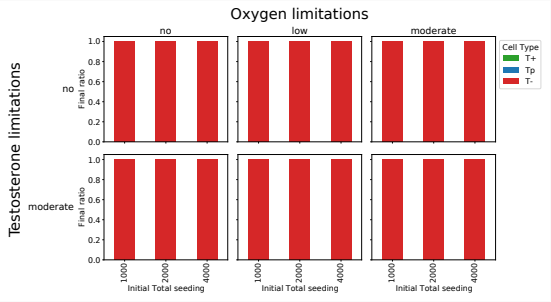


(b) High T^p seeding - 8:1:1

Figure 6: Final ratio of all cell types under standard-of-care. (Stacked bar plot)

- T^+, T^p go extinct in all cases
- Testosterone levels insufficient for growth

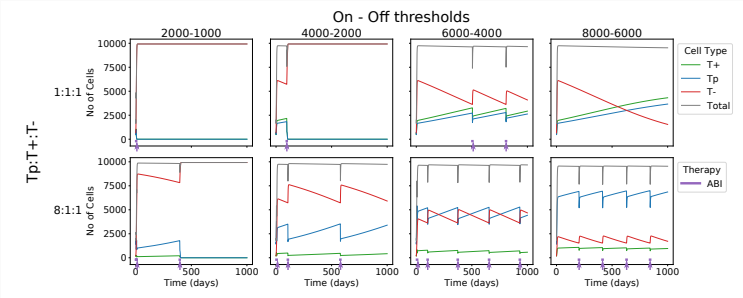
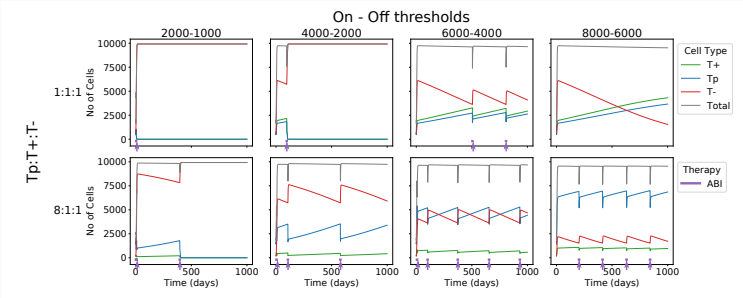


Figure 7: Standardisation of threshold for adaptive therapy

- Low threshold: T^- inhibits $T^p - T^+$ and causes extinction



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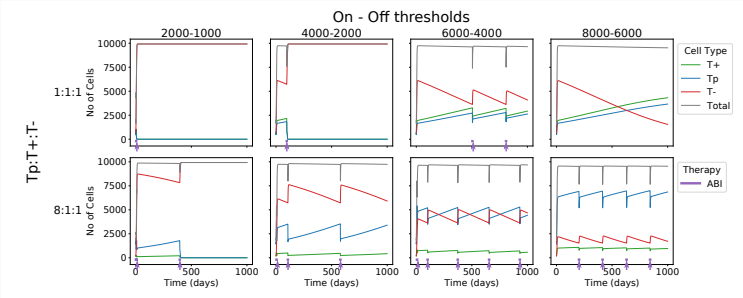

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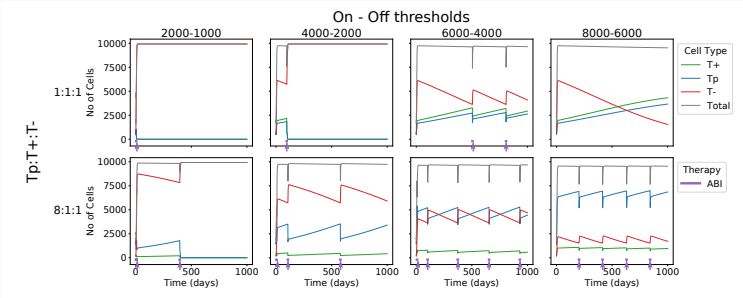

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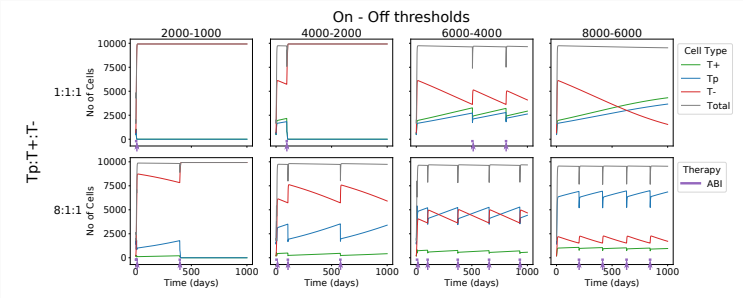
- Chosen- On: 6000, Off: 4000



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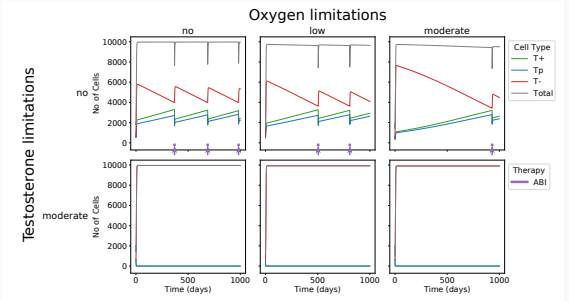
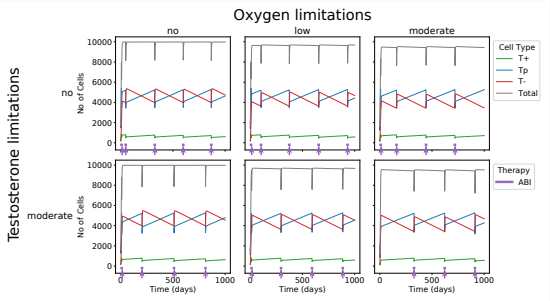
- Low threshold: T^- inhibits $T^p - T^+$ and causes extinction
- High threshold: $T^+ - T^p$ can compete with T^- (Hansen & Read, 2020)
- Too High: No therapy applied as On threshold never crossed
- Chosen- On: 6000, Off: 4000

- $T^+ + T^p$ only for threshold
- With total: $T^+ - T^p$ go extinct before therapy turned off

Is Adaptive Therapy better?



(a) Equal seeding - 1:1:1



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

Figure 8: Time-series of all cell types with adaptive therapy. (On:6000, Off:4000)

- $T^+ - T^p$ extinct just by competition: no effect

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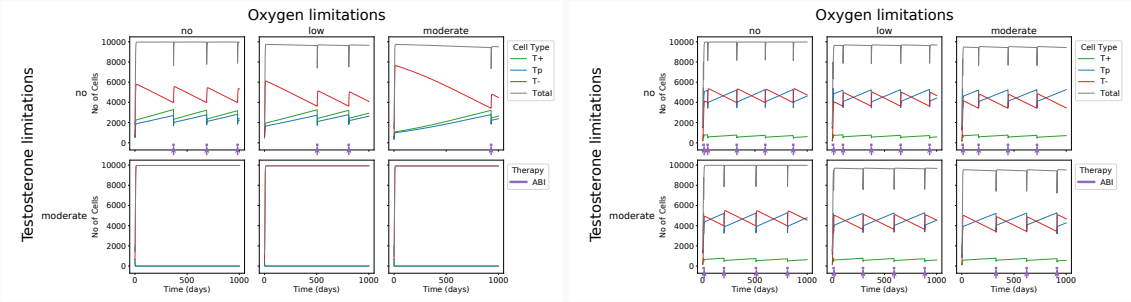

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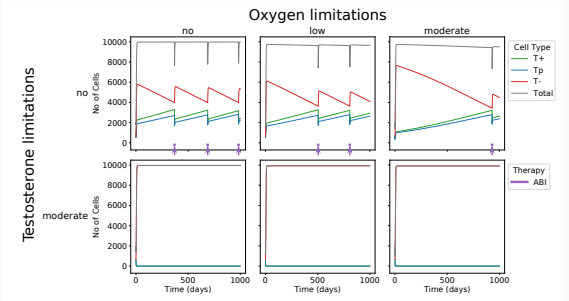

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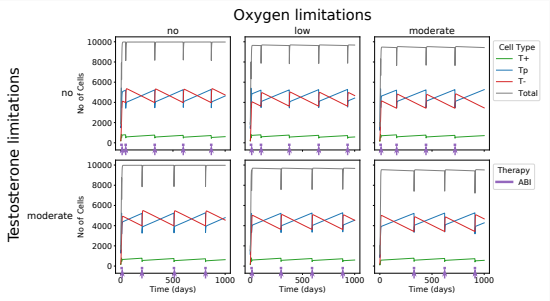

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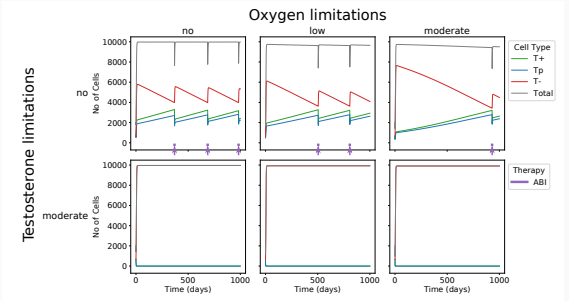

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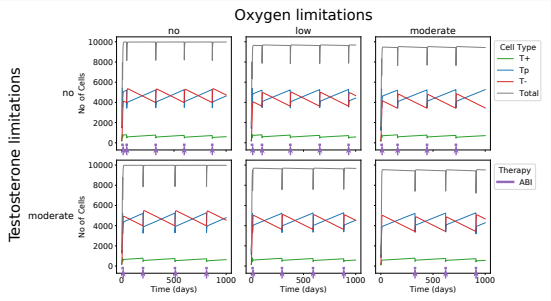

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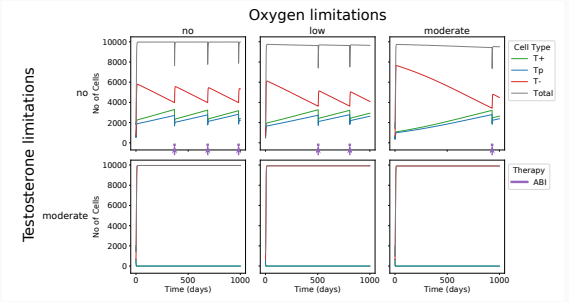

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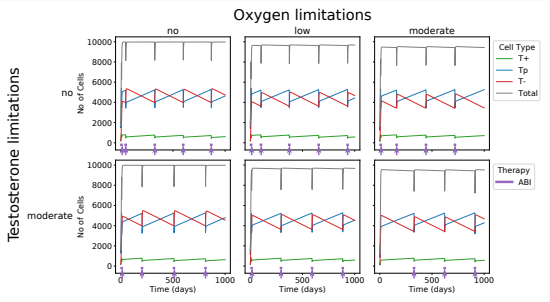

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- Success of Adaptive therapy:
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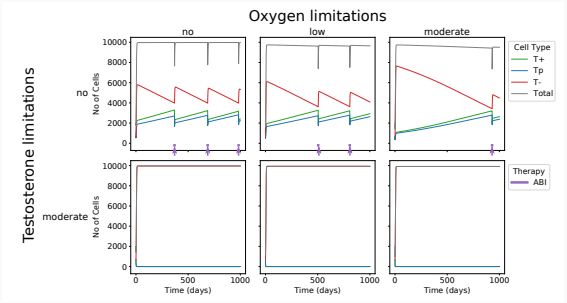
  - × Reducing tumour burden: T^- replace dead cells

Can adaptive therapy be even made better?



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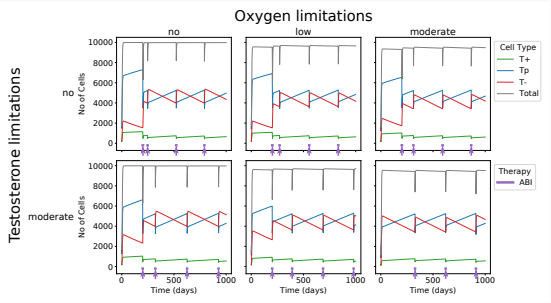

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Figure 9: Time-series of all cell types with adaptive therapy delayed by 200 days. (On:6000, Off:4000)

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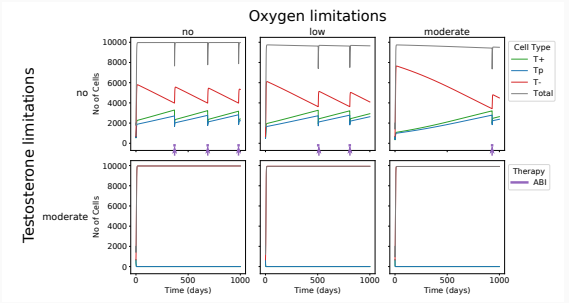
Can delaying treatment help?



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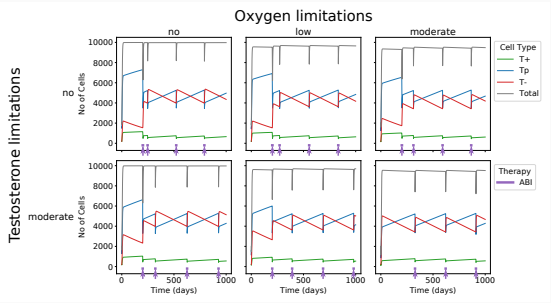

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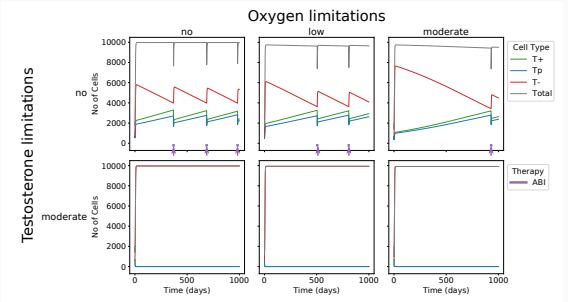

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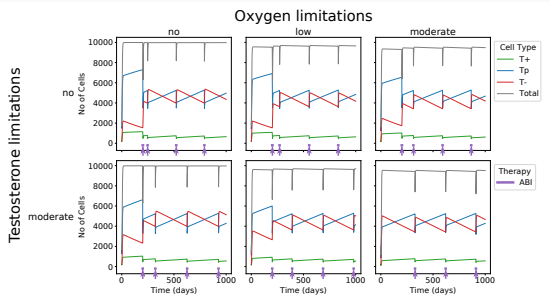

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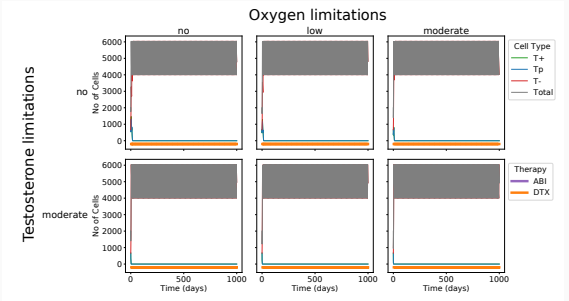

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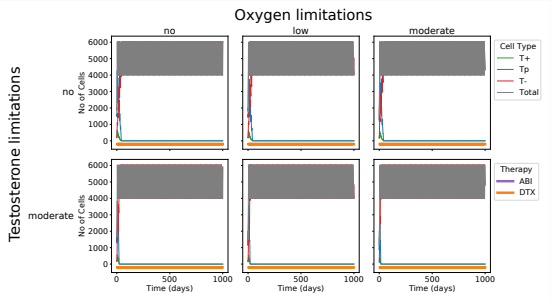

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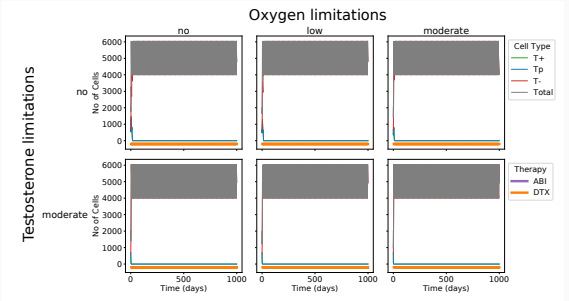

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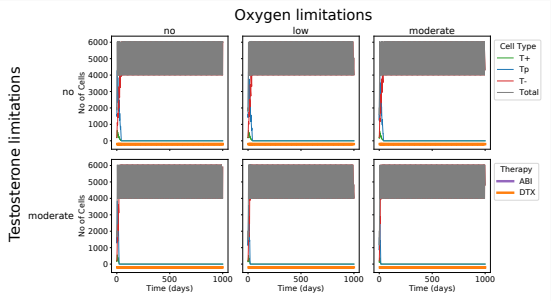

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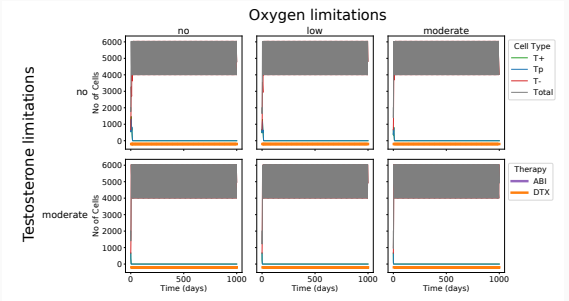

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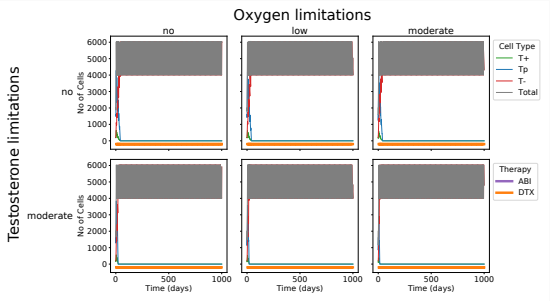

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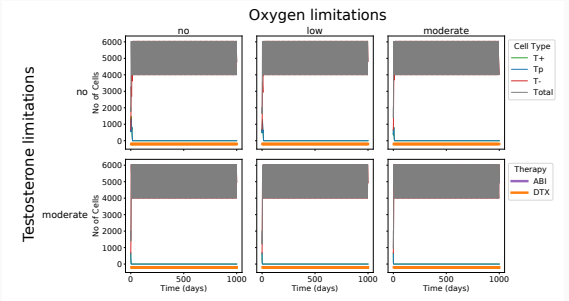

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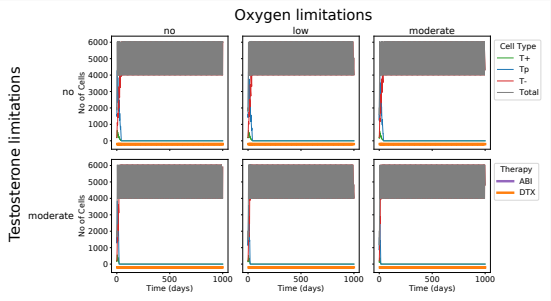

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- $-ve$ effect on coexistence by $\downarrow T^+ - T^p$ outweigh $+ve$ effect on coexistence by $\downarrow T^-$

Conclusion

Summary and Future directions

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  - Dynamic thresholds for turning on/off based on composition of the tumour
  - Different limitations for different cell types

Acknowledgement

I would like to thank the following people:

- Supervisor: Prof. Sutirth Dey
- Expert: Dr. M.S. Madhusudhan
- Mentor: Vibishan B
- PBL Members
- Friends and Family
- KVPY and IISER Pune

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