Annual RAC meeting

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8th July, 2021

Outline

1. Dispersal selection
   - Work done up to 2020
   - Post-pandemic data and future directions
2. Cancer theory
   - Adaptive therapy
   - Other theory work in cancer

Outline

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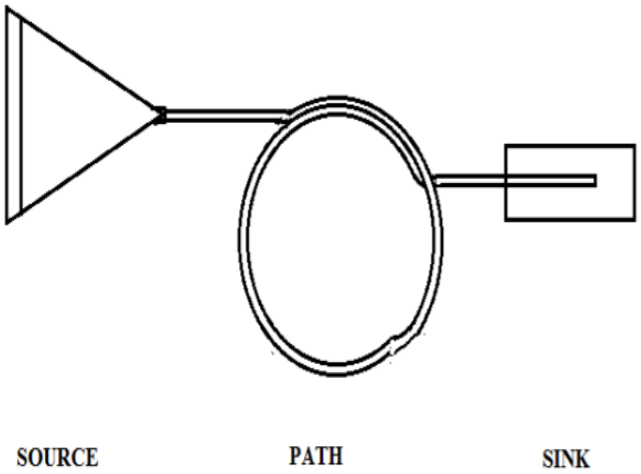
Background



- Existing setup for dispersal selection
- Large outbred population of *Drosophila melanogaster*

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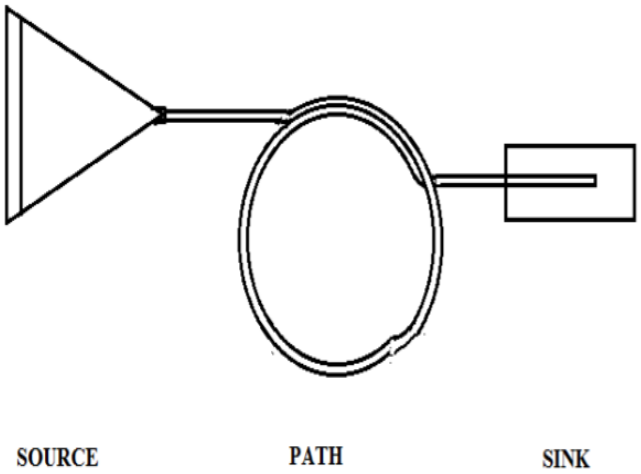

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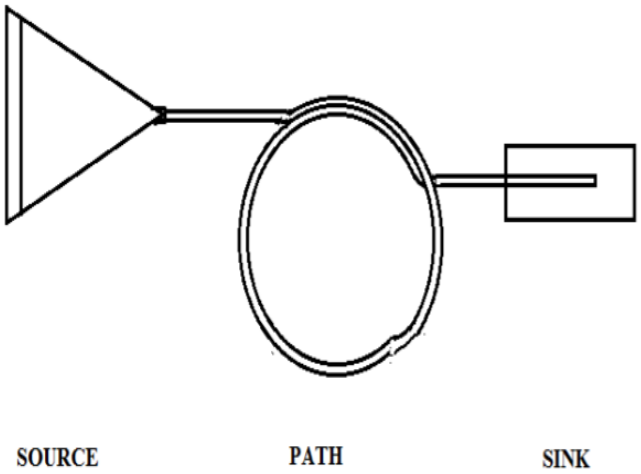

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Tradeoffs against dispersal

- Previous work in normal food showed largely cost-free selection response.
- *Could costs be detected in a nutritionally-deprived context?*

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Selection line populations

- **MD**-Malnourished Dispersers
- **MC**-Malnourished Control

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- Malnutrition $\Longrightarrow$ development in food with one-third yeast concentration

Response at generation 42

- Dispersal response seen-MD were more likely to initiate dispersal and dispersed over longer distances than MC.
- Locomotor activity higher in MD than in MC, but no costs in body weight or fecundity

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Lockdown and suspension of selection

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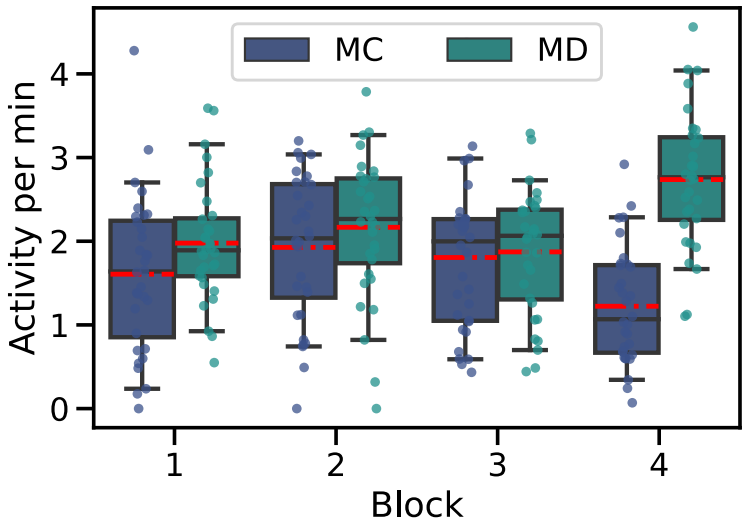
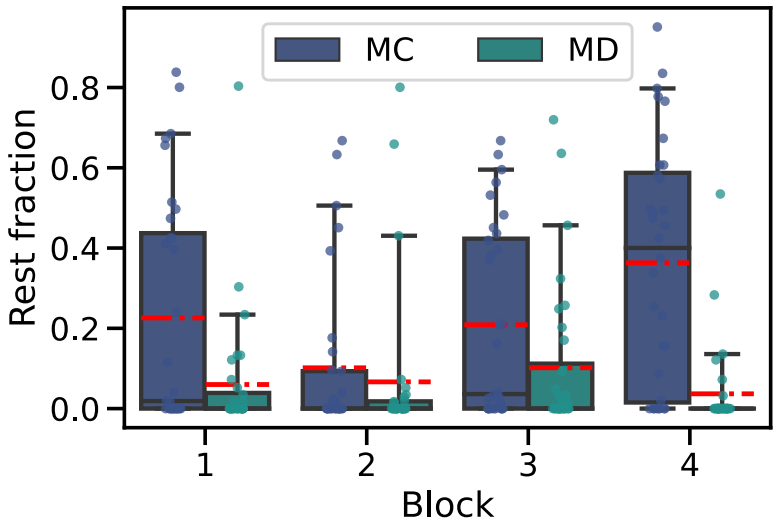
- Two assays to assess loss of phenotype before continuing selection-*dry body weight and locomotor activity*

Lockdown and suspension of selection

Locomotor activity

ANOVA numbers here





Lockdown and suspension of selection

Dry body weight

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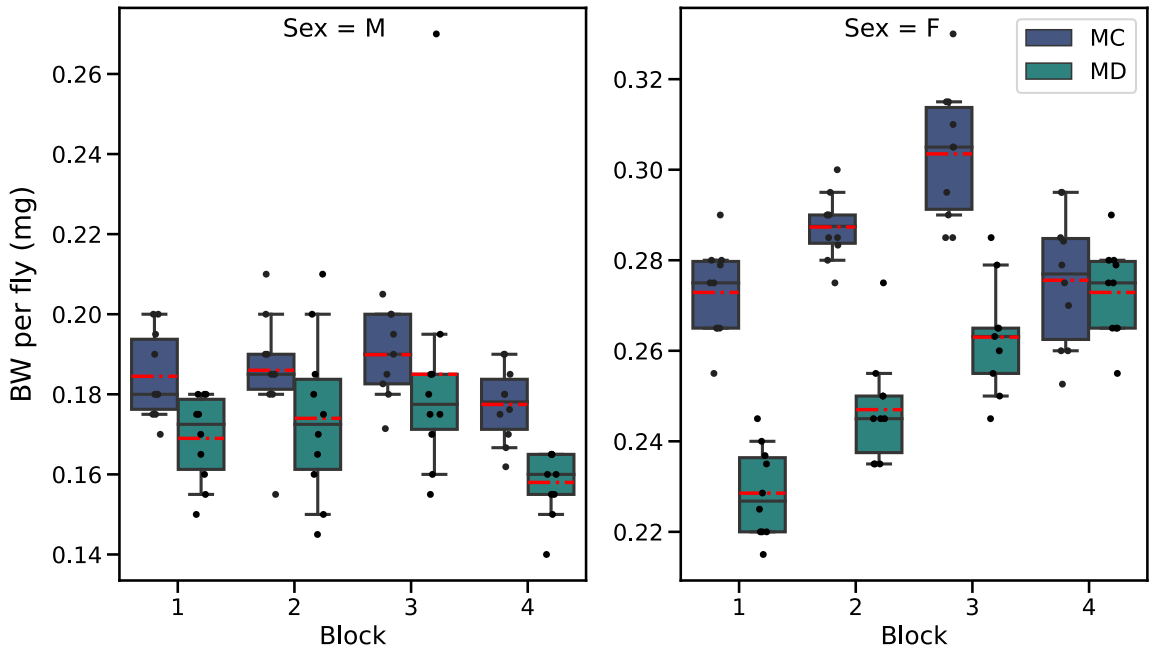

Resuming selection

- Locomotor phenotype is still detectable, body weight trends are unclear.
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- Standardisation-consumption rate based on coloured dye uptake and recording-based approaches to measure time to starvation or dessication

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Conventional vs adaptive therapy

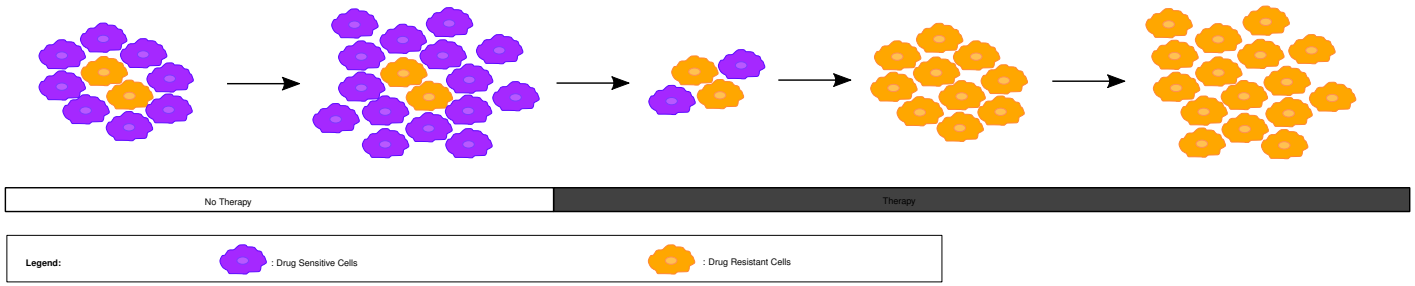
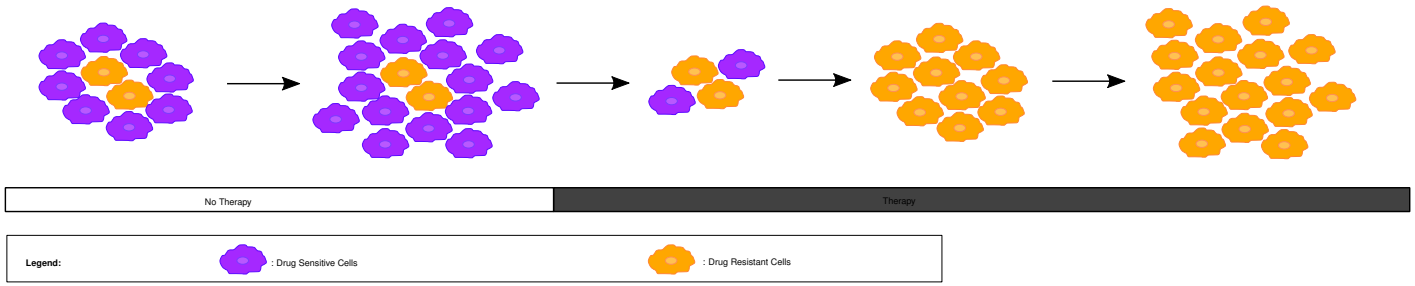


Figure 1: Drug at maximum dose-competitive release of resistant cells

Conventional vs adaptive therapy



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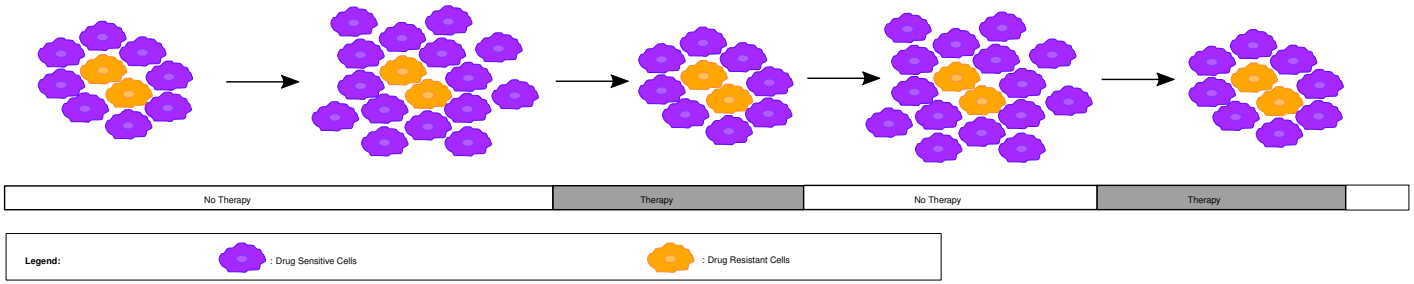

Figure 2: Adaptive therapy and *control through competition*

Ecological interactions in castration-resistant prostate cancer

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- Early prostate cancer cells-dependent on testosterone supply for growth-treated by chemical castration
- Some cells acquire testosterone synthesis $\Longrightarrow$ castration resistance-treated with specific inhibitors
- Other cells become testosterone-independent in growth $\Longrightarrow$ resistant to inhibitors-treatment?

Ecological interactions in castration-resistant prostate cancer

Three cell types and two resources

- Oxygen-externally-supplied resource
- Testosterone-produced internally
- T^+-testosterone-dependent, but not producing
- T^p-testosterone-dependent, also producing as a public good
- T^--testosterone-independent

This work was done with Harsha, a Master's student in the lab.

A mathematical framework

For $i \in \{T^+, T^p, T^-\}$

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

For $R \in \{O_2, T\}$

$$f_i(R) = \begin{cases} 1 & \text{if } ul_{R,i} \leq R \\ \frac{R - ll_{R,i}}{ul_{R,i} - ll_{R,i}} & \text{if } ll_{R,i} < R < ul_{R,i} \\ 0 & \text{if } R \leq ll_{R,i} \end{cases} \quad (2)$$

$$\frac{dO_2}{dt} = p_{O_2} - \sum_i \mu_{O_2,i} y_i - \lambda_{O_2} O_2 \quad (3)$$

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

A mathematical framework

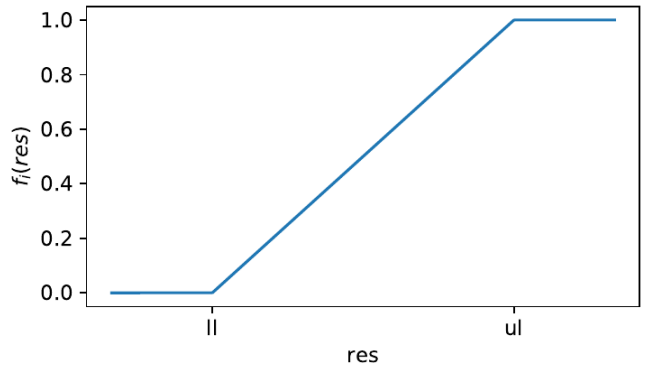
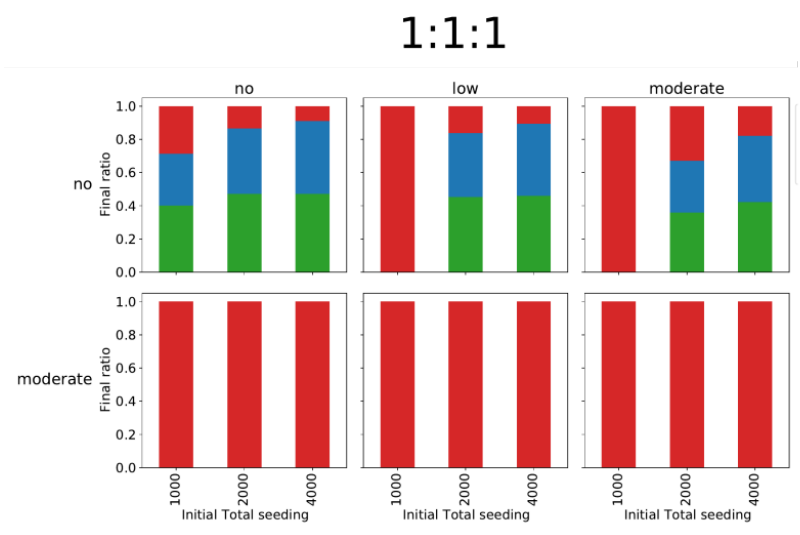


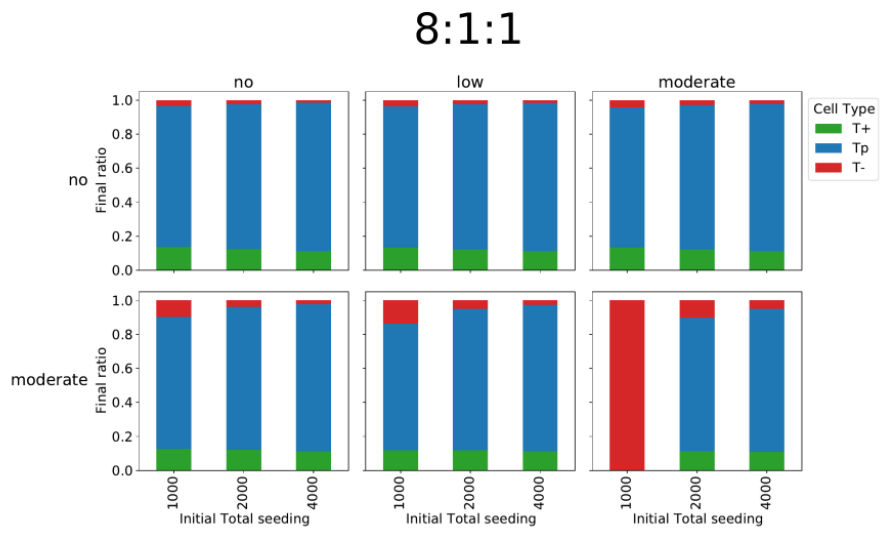
Figure 3: Response function for change in carrying capacity against resource concentration

Parameterisation

Doubling times, consumption rates for oxgen and testosterone, and testosterone production rate for T^p were all derived from literature sources reporting empirical measurements in cell lines.

Competition is tuned by resource limitation





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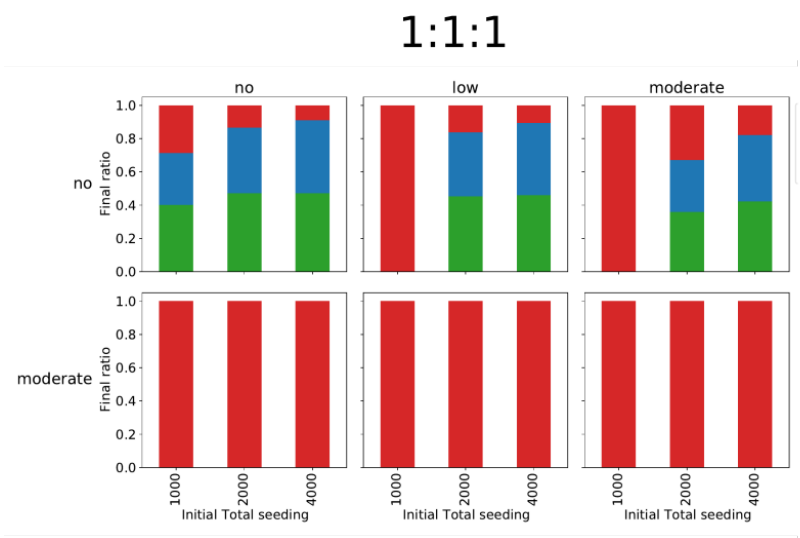

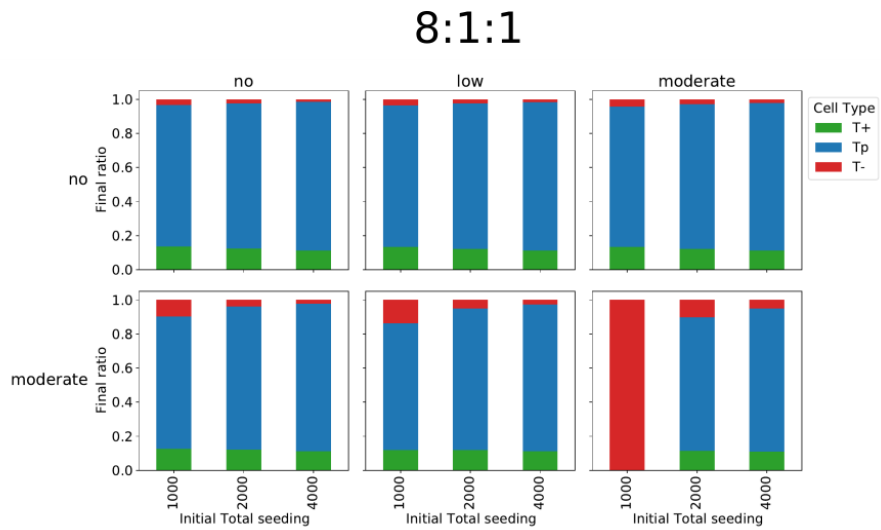

- Doubling rates scale as $T^{-}<T^{+}<T^{p}$, but T^{-} doesn't win by default.
- Resource limitations can be used to tune co-existence.

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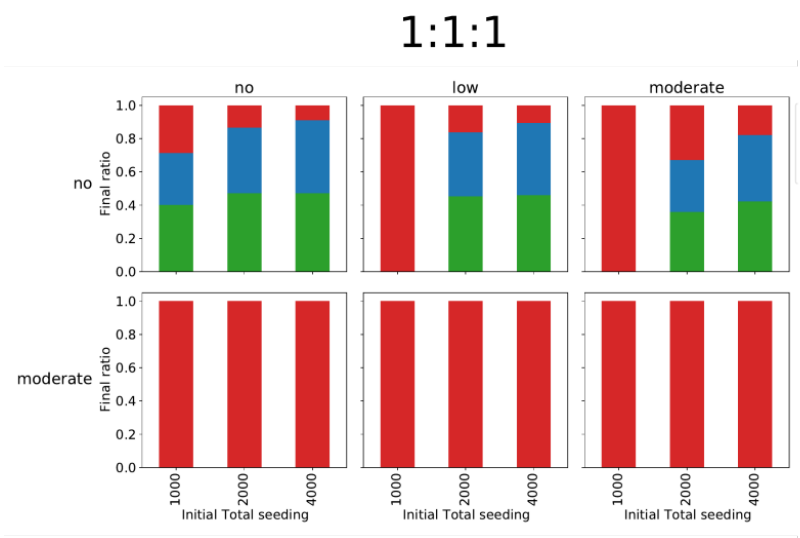

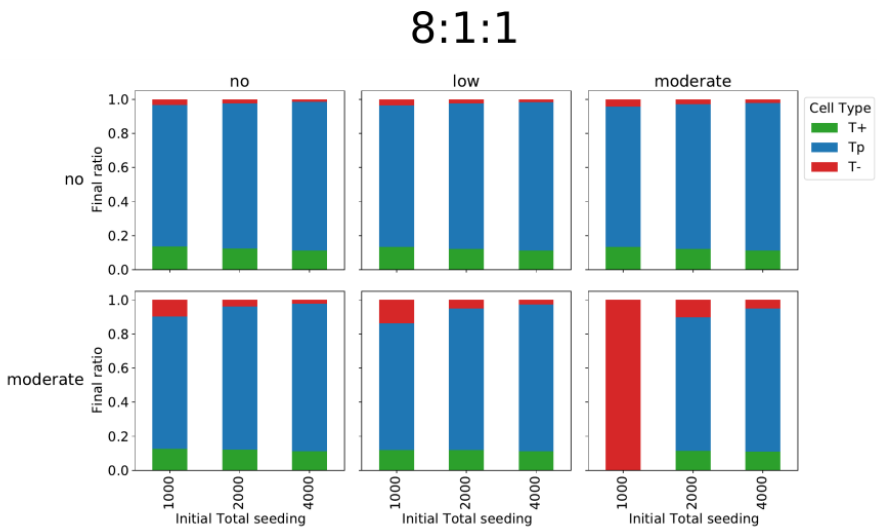

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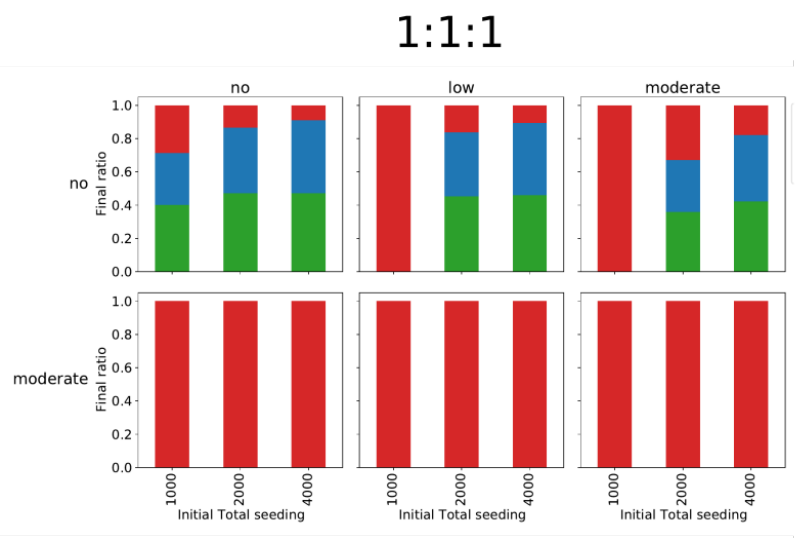

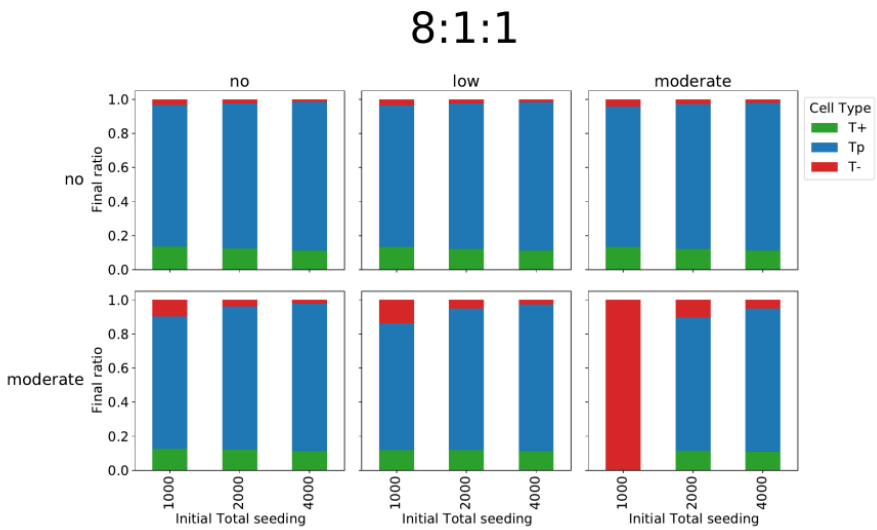

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- Resource limitations can be used to tune co-existence.
- Testosterone is the stronger limiting resource in this system.
- Higher T^- proportion makes tumours harder to treat and more unresponsive.

Further development

- A resource-consumer model without explicit carrying capacity terms-parameterisation is ongoing
- Further exploration of therapy parameters in the same model-rules of on and off, frequency, multi-drug combinations
- Spatial dynamics-a discrete reaction-diffusion system is being considered at the moment

All three lines are being developed with undergraduate students from IISER Pune.

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Patterns in cancer incidence

Trends across species

- Body size as well as lifespan varies widely across species and taxa.
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Timeline

Thank you for your attention.