Annual RAC meeting

Vibishan B.

20163448

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

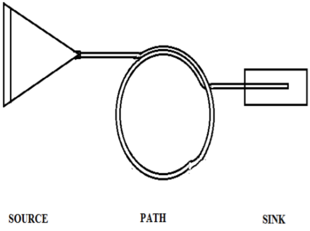
Outline

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

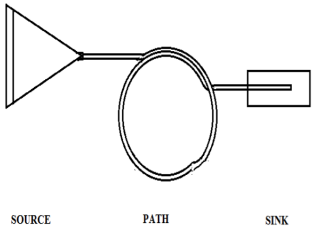
1. Dispersal selection
   - Work done up to 2020
   - Post-pandemic data and future directions
2. Cancer theory
   - Adaptive therapy
   - Other theory work in cancer

Background



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

Background

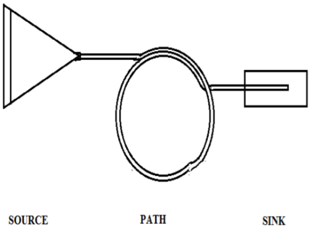


- Existing setup for dispersal selection
- Large outbred populations of *Drosophila melanogaster*

Tradeoffs against dispersal

- Previous work in normal food showed largely cost-free selection response.

Background



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

Tradeoffs against dispersal

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

Background

- Dispersal evolution with the same setup, but with larval malnutrition
- Malnutrition $\implies$ development in food with one-third yeast concentration

Background

- Dispersal evolution with the same setup, but with larval malnutrition
- Malnutrition $\implies$ development in food with one-third yeast concentration

Selection line populations

- **MD**$_{1\text{-}4}$-Malnourished Dispersers
- **MC**$_{1\text{-}4}$-Malnourished Control

Background

- Dispersal evolution with the same setup, but with larval malnutrition
- Malnutrition $\implies$ development in food with one-third yeast concentration

Response at generation 42

- Dispersal response seen-MD were nearly twice as likely to initiate dispersal and covered nearly twice the distance as MC.
- Locomotor activity higher in MD than in MC, but no costs in body weight or fecundity

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

Lockdown and suspension of selection

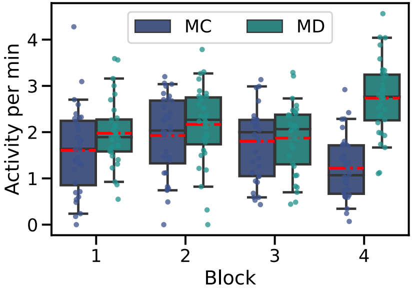
- Dispersal selection suspended from March to November 2020 spanning 11 generations

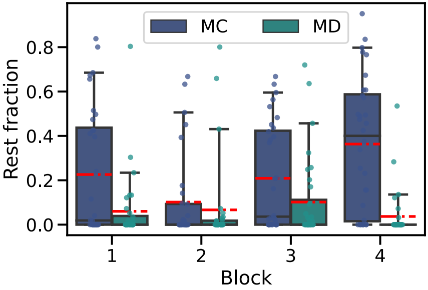
Lockdown and suspension of selection

- Dispersal selection suspended from March to November 2020 spanning 11 generations
- Two assays to assess loss of phenotype before continuing selection-*dry body weight* and *locomotor activity*

Lockdown and suspension of selection

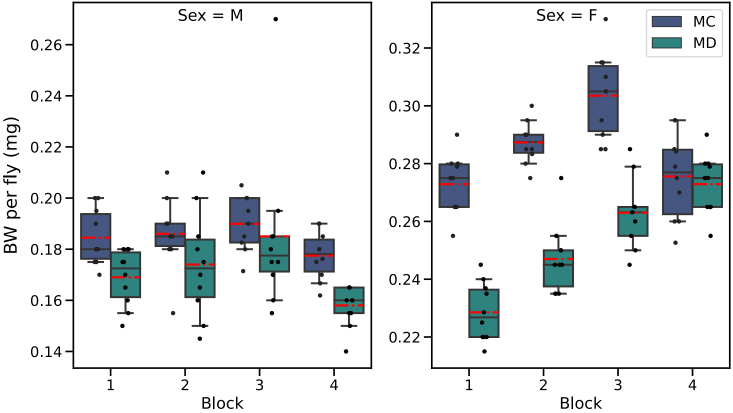
Activity signal is weaker, but the difference in rest fraction is still detected.





Lockdown and suspension of selection

MC body weight is higher than that of MD, which hasn't been seen before.



Resuming selection

- Locomotor phenotype is still detectable, body weight trends are unclear.
- About 20 more generations of dispersal have now been carried out-62 generations of selection in total

Resuming selection

- Locomotor phenotype is still detectable, body weight trends are unclear.
- About 20 more generations of dispersal have now been carried out-62 generations of selection in total
- Bigger set of assays need to be repeated-dispersal kernel, body weight and fecundity
- I plan to conduct smaller experiments for the time being-exploration and male-male aggression, and kit-based estimation of total glucose and triglyceride content.

Resuming selection

- Locomotor phenotype is still detectable, body weight trends are unclear.
- About 20 more generations of dispersal have now been carried out-62 generations of selection in total
- Bigger set of assays need to be repeated-dispersal kernel, body weight and fecundity
- I plan to conduct smaller experiments for the time being-exploration and male-male aggression, and kit-based estimation of total glucose and triglyceride content.
- Standardisation-consumption rate based on coloured dye uptake and recording-based approaches to measure time to starvation or dessication

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

Conventional vs adaptive therapy

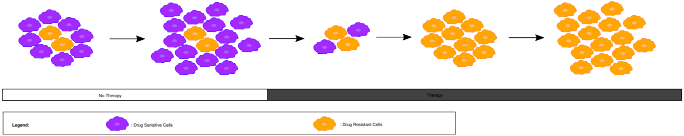


Figure 1: Drug at maximum dose-competitive release of resistant cells[1]

[1] Image credit: Harshavardhan BV

Conventional vs adaptive therapy

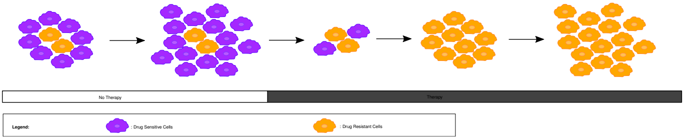


Figure 1: Drug at maximum dose-competitive release of resistant cells[1]

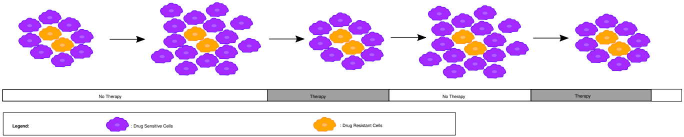


Figure 2: Adaptive therapy and *control through competition*[1]

[1] Image credit: Harshavardhan BV

Interactions in castration-resistant prostate cancer

- Early prostate cancer cells-dependent on testosterone supply for growth-treated by chemical castration

Interactions in castration-resistant prostate cancer

- Early prostate cancer cells-dependent on testosterone supply for growth-treated by chemical castration
- Some cells acquire testosterone synthesis $\implies$ castration resistance-treated with specific inhibitors

Interactions in castration-resistant prostate cancer

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

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
- Doubling rates scale as $T^{-} < T^{+} < T^{p}$.

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

Competition is tuned by resource limitation

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

Competition is tuned by resource limitation

- Doubling rates scale as $T^{-} < T^{+} < T^{p}$, but T^{-} doesn't win by default.
- Resource limitations can be used to tune co-existence.
- Testosterone is the stronger limiting resource in this system.

Competition is tuned by resource limitation

- Doubling rates scale as $T^- < T^+ < T^p$, but T^- doesn't win by default.
- 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 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

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

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.

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

Patterns in cancer incidence

- Across species-

Patterns in cancer incidence

- Across species-
  - How does greater number of cells or cell division cycles affect risk of mutation and cancer?
  - Selection on somatic mutations and clonal expansion are uncommon in current theory (Nowell, 1976).
  - Neutral vs non-neutral somatic mutation accumulation in a model

Patterns in cancer incidence

- Across species-
  - How does greater number of cells or cell division cycles affect risk of mutation and cancer?
  - Selection on somatic mutations and clonal expansion are uncommon in current theory (Nowell, 1976).
  - Neutral vs non-neutral somatic mutation accumulation in a model
- Within species-

Patterns in cancer incidence

- Across species-
  - How does greater number of cells or cell division cycles affect risk of mutation and cancer?
  - Selection on somatic mutations and clonal expansion are uncommon in current theory (Nowell, 1976).
  - Neutral vs non-neutral somatic mutation accumulation in a model
- Within species-
  - Incidence of cancer in humans rises near mid-life, peaks around 70 years and then declines (Harding et al., 2012).

Patterns in cancer incidence

- Across species-
  - How does greater number of cells or cell division cycles affect risk of mutation and cancer?
  - Selection on somatic mutations and clonal expansion are uncommon in current theory (Nowell, 1976).
  - Neutral vs non-neutral somatic mutation accumulation in a model
- Within species-
  - Incidence of cancer in humans rises near mid-life, peaks around 70 years and then declines (Harding et al., 2012).
  - What roles do temporal patterns of turnover play in mutation accumulation? (Rozhok and DeGregori, 2019)

Patterns in cancer incidence

- Across species-
  - How does greater number of cells or cell division cycles affect risk of mutation and cancer?
  - Selection on somatic mutations and clonal expansion are uncommon in current theory (Nowell, 1976).
  - Neutral vs non-neutral somatic mutation accumulation in a model
- Within species-
  - Incidence of cancer in humans rises near mid-life, peaks around 70 years and then declines (Harding et al., 2012).
  - What roles do temporal patterns of turnover play in mutation accumulation? (Rozhok and DeGregori, 2019)

Work on developing an agent-based model based on Erten and Kokko (2020) for both these questions is ongoing with a Master's student.

Timeline

- Lab change in 2019
- Pandemic and lockdown in 2020
- Multiple lines of active work that would take at least a year from now to complete

Erten, E. Y. and Kokko, H. (2020). From zygote to a multicellular soma: Body size affects optimal growth strategies under cancer risk. Evolutionary Applications *13*, 1593–1604.

Harding, C., Pompei, F. and Wilson, R. (2012). Peak and decline in cancer incidence, mortality, and prevalence at old ages. Cancer *118*, 1371–1386.

Nowell, P. (1976). The clonal evolution of tumor cell populations. Science *194*, 23–28.

Rozhok, A. and DeGregori, J. (2019). A generalized theory of age-dependent carcinogenesis. eLife *8*, e39950.

Thank you.

Statistical analysis

Locomotor activity

Activity (Two-way mixed-effects ANOVA); Population main effect: $F_{1,6} = 4.938;\, p = 0.068$
Rest (linear mixed-effects binomial model); Population main effect: $z = -3.990; p = 6.61e - 05$

Dry body weight

Three-way mixed-effects ANOVA
Population main effect: $F_{1,150} = 73.186; p = 1.233e - 14$
Sex main effect: $F_{1,150} = 1189.076; p < 2.2e - 16$
Popn-sex interaction: $F_{1,150} = 12.778; p = 0.0004713$

A mathematical framework

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

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

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

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

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

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

A mathematical framework

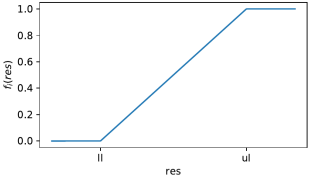


Figure 3: Response function for change in carrying capacity against resource concentration

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.