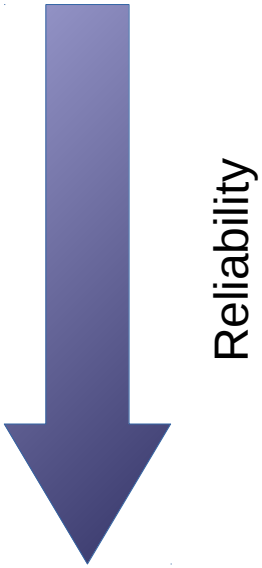
Why do female flies live longer than male flies?

J. Ignacio Lucas Lledó

Introduction

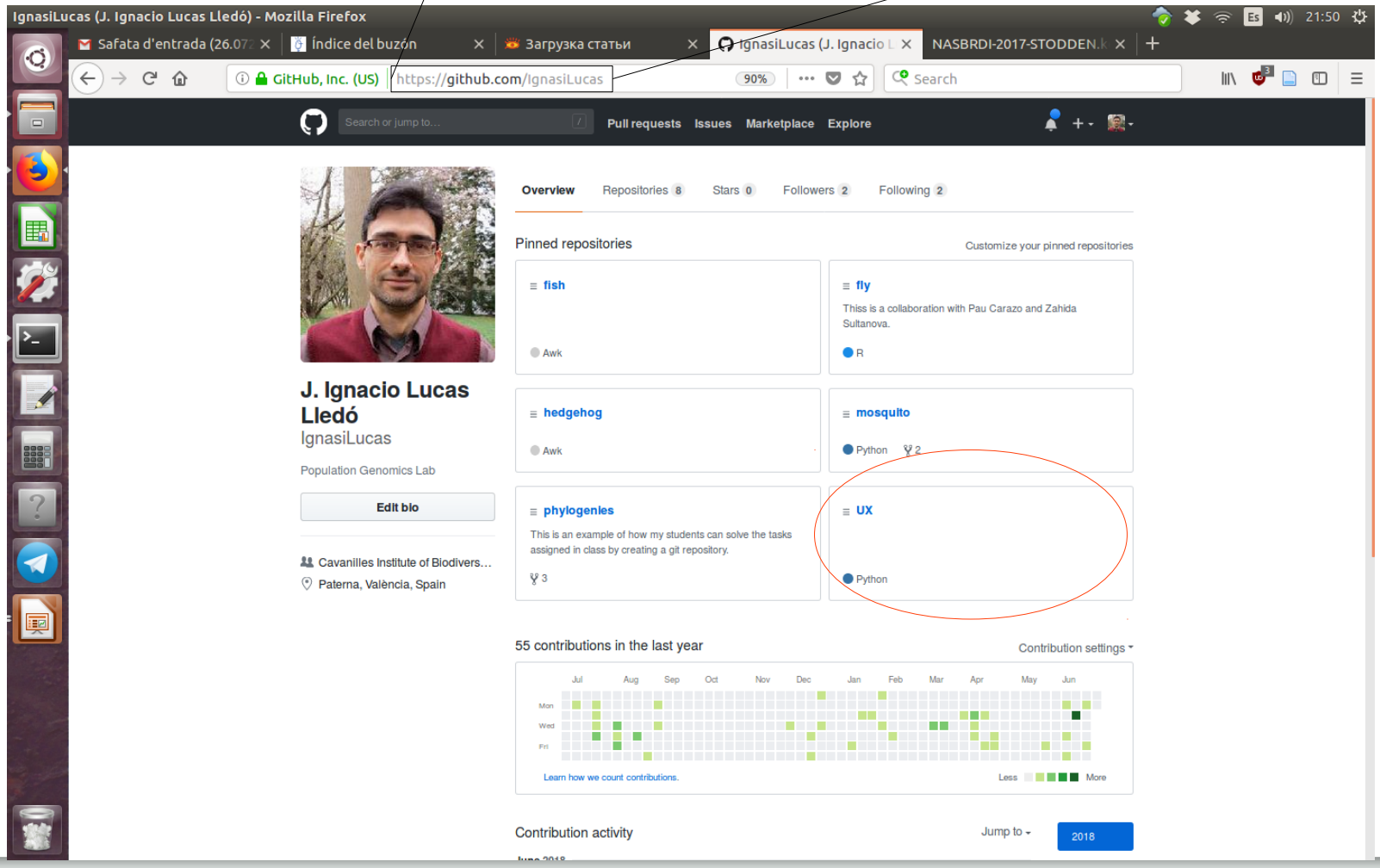
Introduction

- **Repeatability**
  - same authors, same methods.
- **Reproducibility**
  - other authors, same methods.
- **Replicability**
  - other authors, other methods.

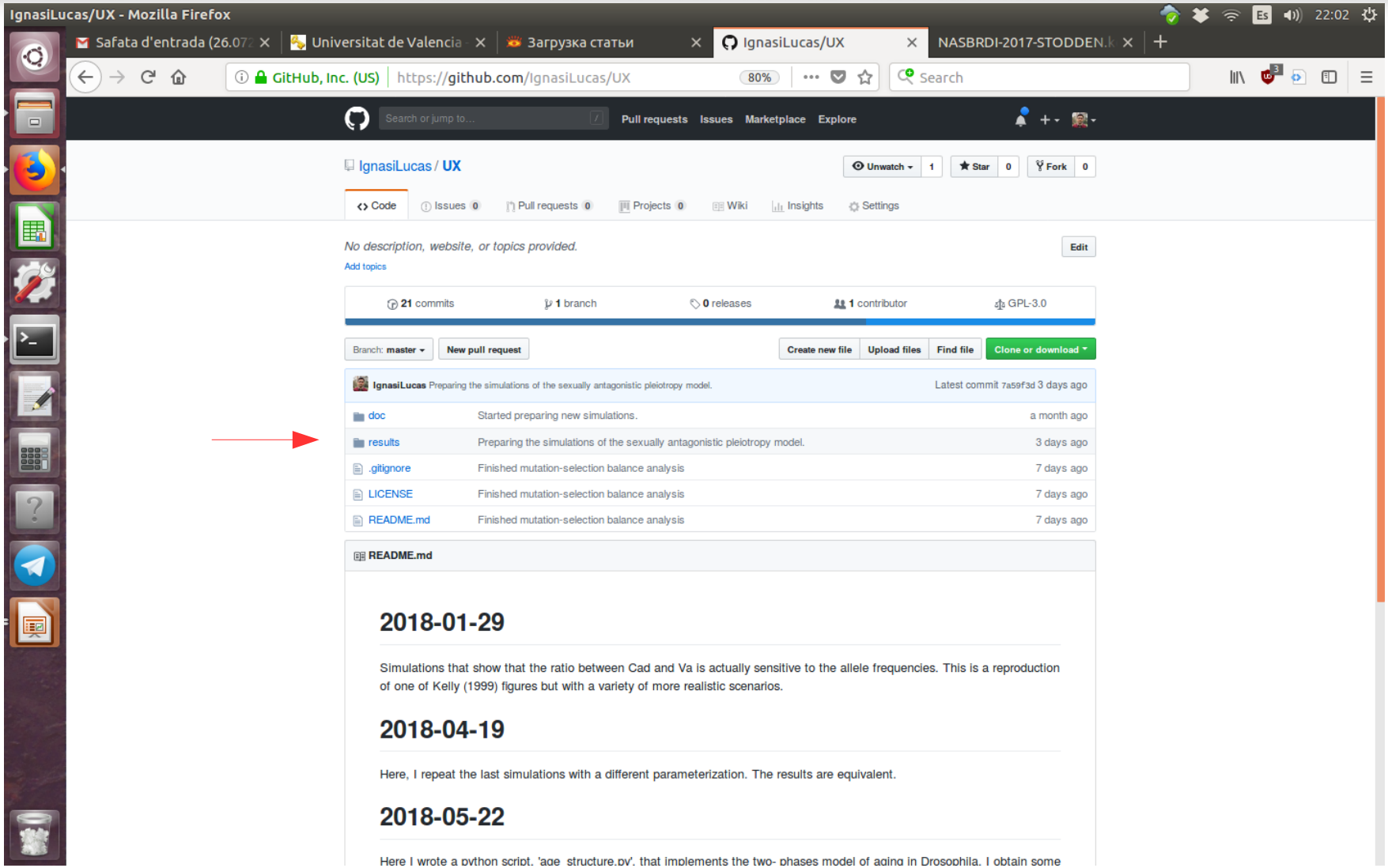


Introduction

https://github.com/IgnasiLucas



Introduction



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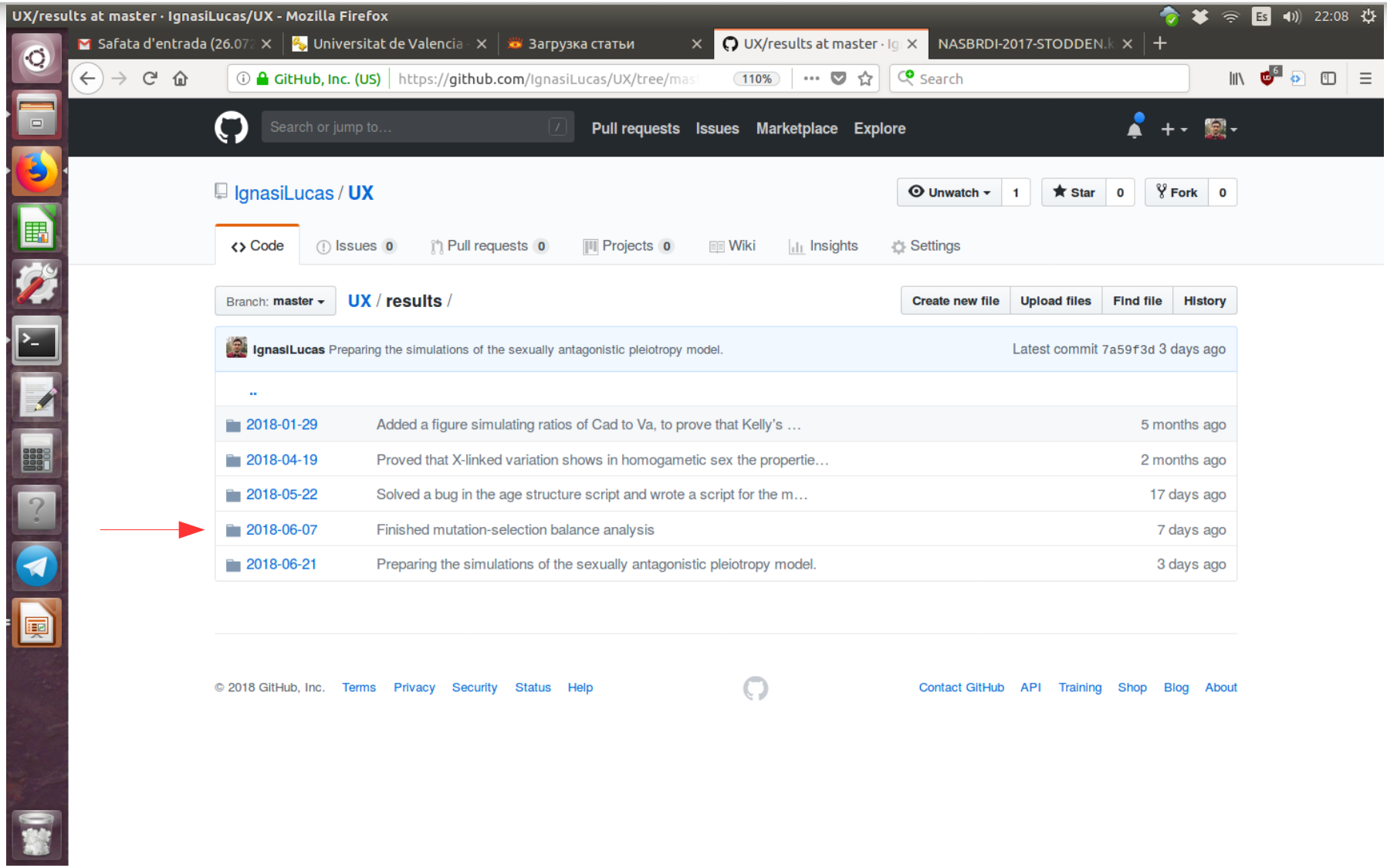
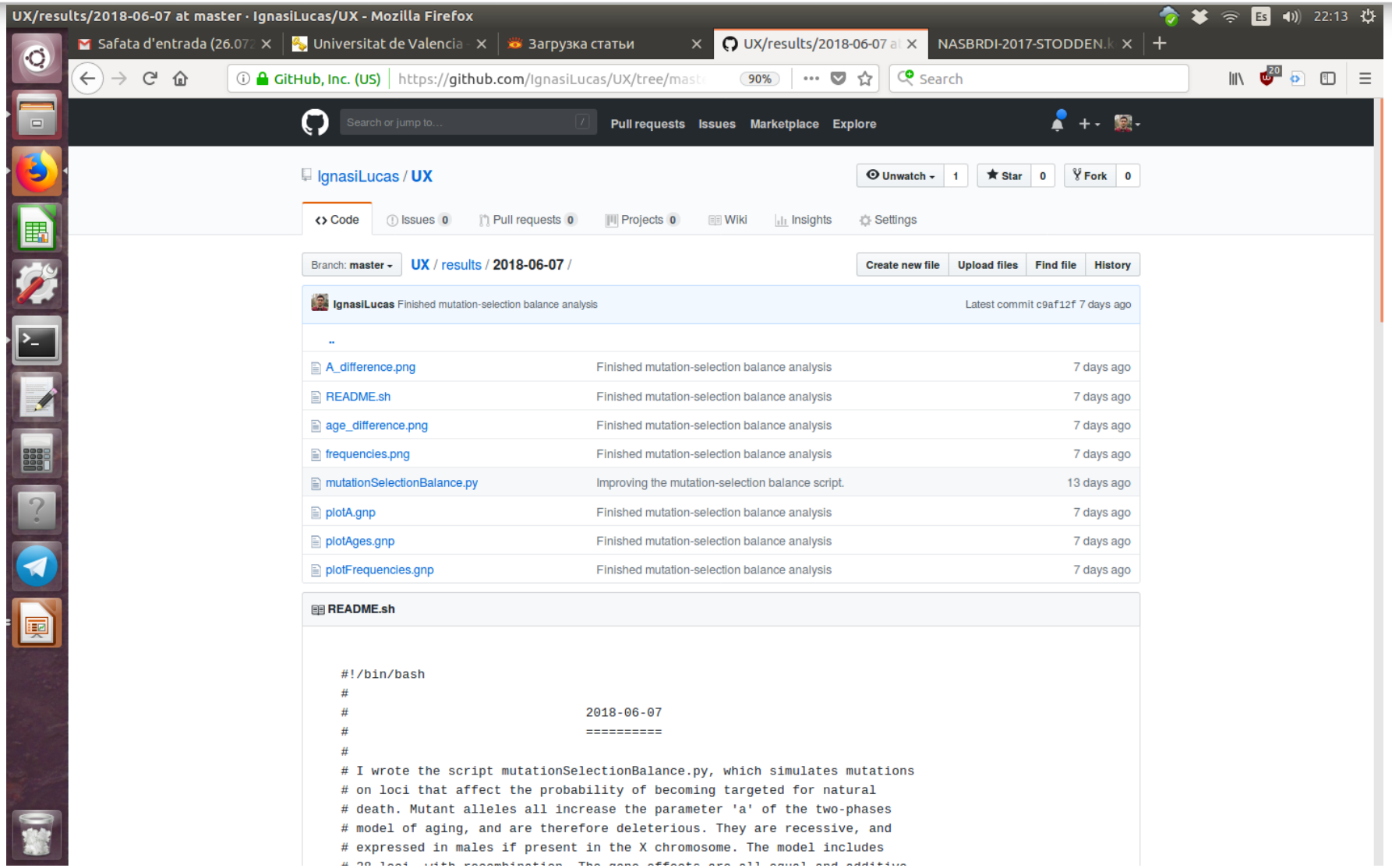


Introduction



How I became interested in the topic

Motivation

Dr. Pau Carazo

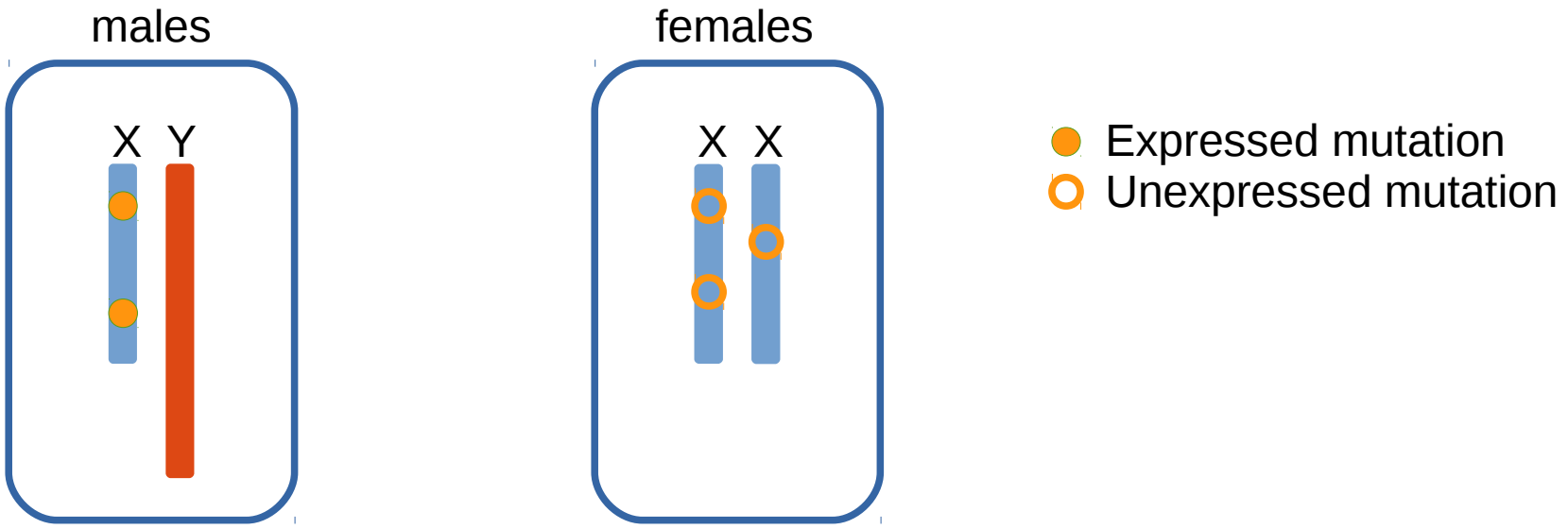
Zahida Sultanova (PhD candidate)

The Unguarded X hypothesis

The Unguarded X hypothesis

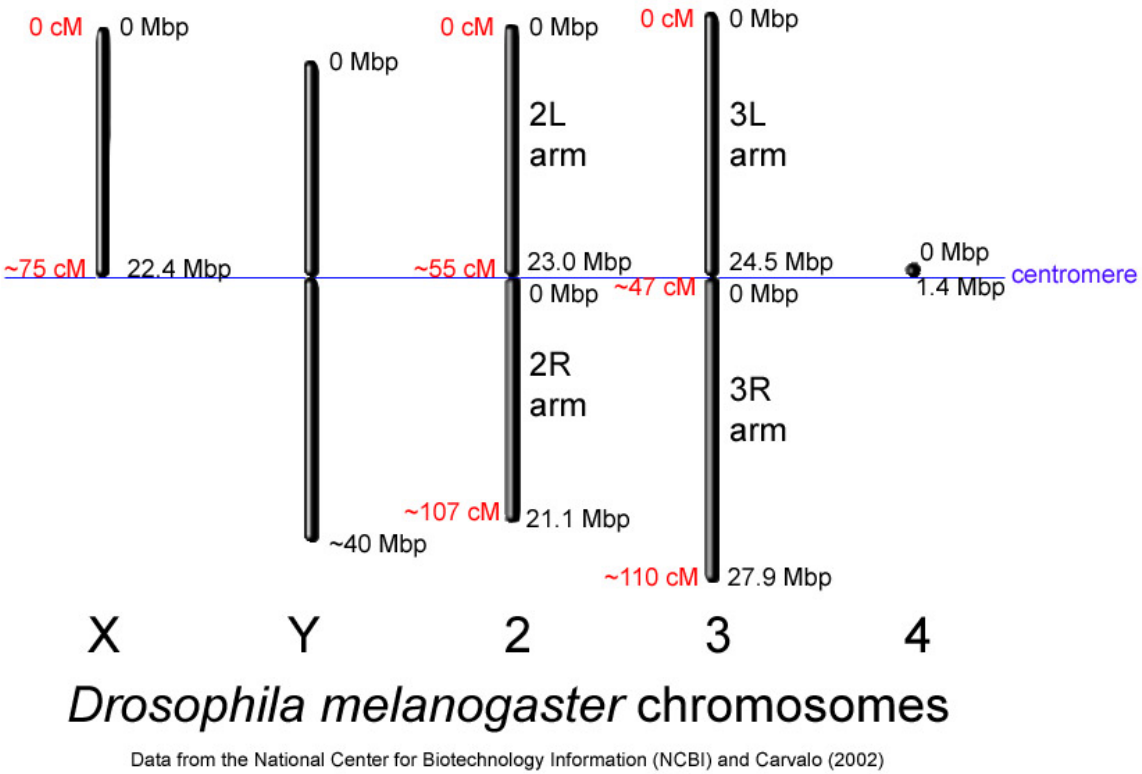
- Why do sexes age differently?
  - Adaptive processes:
    - Different optimum lifespans.
    - E.g., sexually antagonistic pleiotropy.
  - Maladaptive processes:
    - Mother's curse hypothesis.
    - Unguarded X hypothesis.

The Unguarded X hypothesis



«sex-specific ageing can be caused by the increased expression of deleterious recessive mutations in the heterogametic sex» (Sultanova et al. 2018, Evolution, 72:540-552).

The Unguarded X hypothesis



In *D. melanogaster*, the X chromosome contains about 20% of the total number of genes.

The dosage compensation system doubles the expression of X-linked genes in males.

The Unguarded X hypothesis

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ORIGINAL ARTICLE

The "unguarded-X" and the genetic architecture of lifespan: Inbreeding results in a potentially maladaptive sex-specific reduction of female lifespan in *Drosophila melanogaster*

Zahida Sultanova, Muhammed Andic, Pau Carazo

First published: 16 January 2018 | https://doi.org/10.1111/evo.13426

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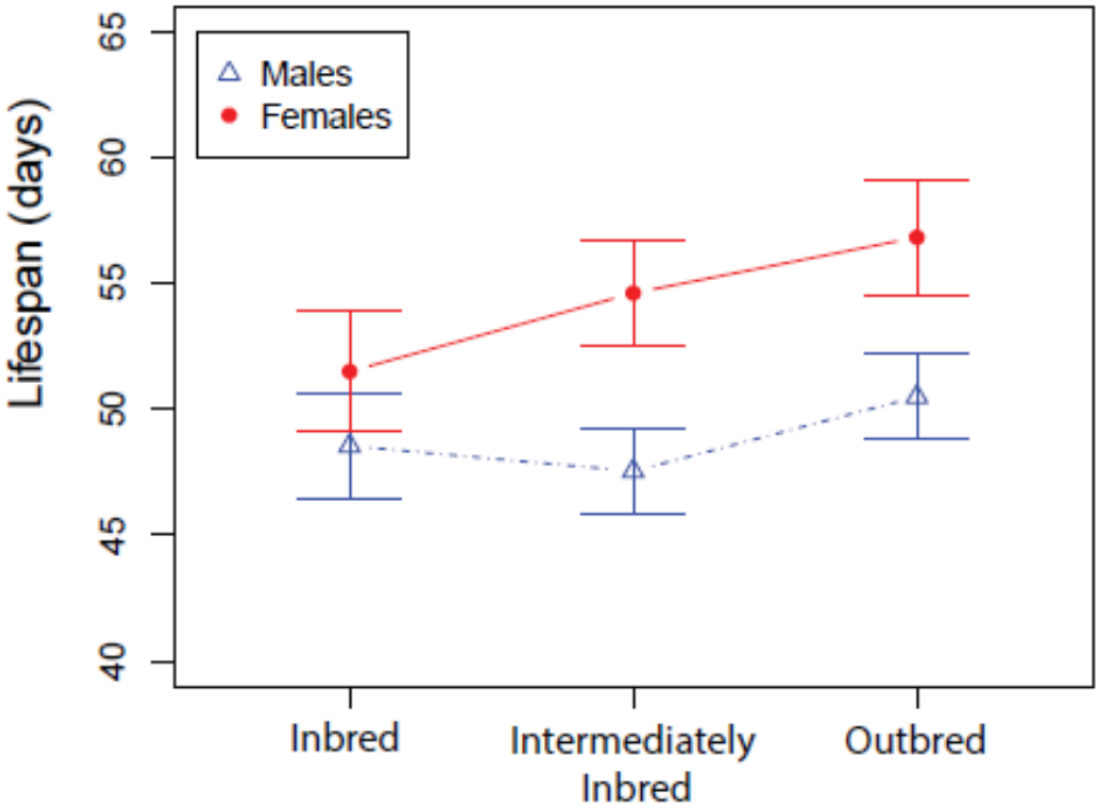
Abstract

Sex differences in ageing and lifespan are ubiquitous in nature. The "unguarded-X" hypothesis (UXh) suggests they may be partly due to the expression of recessive mutations in the hemizygous sex chromosomes of the heterogametic sex, which could help explain sex-specific ageing in a broad array of taxa. A prediction central to the UX hypothesis is that inbreeding will decrease the lifespan of the homogametic sex more than the heterogametic sex, because only in the former does inbreeding increase the expression of recessive deleterious mutations. In this study, we test this prediction by examining the effects of inbreeding on the lifespan and fitness of male and female

The Unguarded X hypothesis



Female-specific reduction of lifespan with inbreeding supports the **unguarded X hypothesis**.

However, **sexually antagonistic pleiotropy** would produce the same result.

Sultanova, Z., Andiç, M. & Carazo, P. 2018. *Evolution* 72:540-552.

Sexually antagonistic pleiotropy

Sexually antagonistic pleiotropy

In an X-linked locus, recessive allele A1 reduces female lifespan (and therefore, fitness), but increases male fitness.

When rare, it will be exposed to selection mostly in males (hemizygous), and its frequency will increase.

If abundant, the negative effects on homozygous females could overcome the benefits to males and drive a decrease of frequency.

Under these conditions, an equilibrium frequency can exist.

Sexually antagonistic pleiotropy

	Unguarded X	**Sexually antagonistic pleiotropy**
Sustained genetic variation?	Yes	Yes
Female-specific effect of inbreeding on lifespan?	Yes	Yes
Type of equilibrium	Mutation-selection balance	Selection balance
Expected frequencies of alleles affecting lifespan	**Low**	**Intermediate**

A method to evaluate the contribution of deleterious mutations to a quantitative trait

John K. Kelly's method

Genet. Res., Camb. (1999), **73**, *pp.* 263–273. *With 3 figures.* Printed in the United Kingdom

An experimental method for evaluating the contribution of deleterious mutations to quantitative trait variation

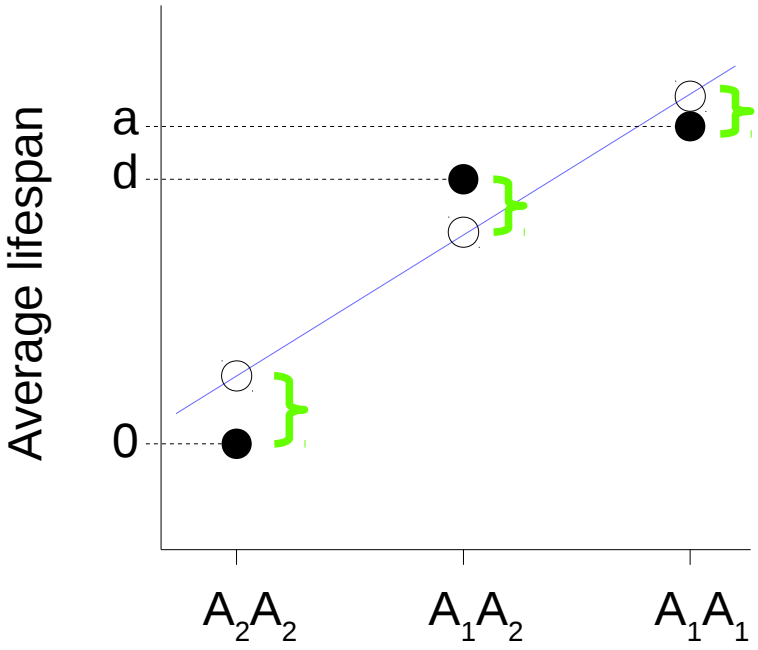
JOHN K. KELLY*
Department of Biology, University of Oregon, Eugene, OR 97403, USA

(*Received 3 August 1998 and in revised form 27 October 1998 and 8 December 1998*)

Summary

Unconditionally deleterious mutations could be an important source of variation in quantitative traits. Deleterious mutations should be rare (segregating at low frequency in the population) and at least partially recessive. In this paper, I suggest that the contribution of rare, partially recessive alleles to quantitative trait variation can be assessed by comparing the relative magnitudes of two genetic variance components: the covariance of additive and homozygous dominance effects (C_{ad}) and the additive genetic variance (V_a). If genetic variation is due to rare recessives, then the ratio of C_{ad} to V_a should be equal to or greater than 1. In contrast, C_{ad}/V_a should be close to zero or even negative if variation is caused by alleles at intermediate frequencies. The ratio of C_{ad} to V_a can be estimated from phenotypic comparisons between inbred and outbred relatives, but such estimates are likely to be highly imprecise. Selection experiments provide an alternative estimator for C_{ad}/V_a, one with favourable statistical properties. When combined with other biometrical analyses, the ratio test can provide an incisive test of the deleterious mutation model.

John K. Kelly's method



Phenotype (lifespan) measurements may be re-scaled for convenience.

Genotypic values (black dots) are represented as an additive component (empty circles) and a dominance deviation.

The linear regression depends on genotype frequencies.

John K. Kelly's method

a = genotypic value of genotype A_1A_1.

d = genotypic value of genotype A_1A_2.

p = frequency of allele A_1.

q = frequency of allele A_2.

α_1 = 'average', 'additive' or 'genic' effect of allele A_1.

Additive effect of an allele is the average deviation from the population's mean caused by that allele.

homozygous dominance effects = difference between genotypic and breeding (expected) values of homozygous genotypes, due to dominance.

$\boldsymbol{C_{ad}}$ = covariance between average effects and homozygous dominance effects. $C_{ad} = 2pq(p - q)\cdot d\cdot[a + d(q - p)]$

$\boldsymbol{V_a}$ = additive genetic variance. $V_a = 2pq[a + d(q - p)]^2$.

John K. Kelly's method

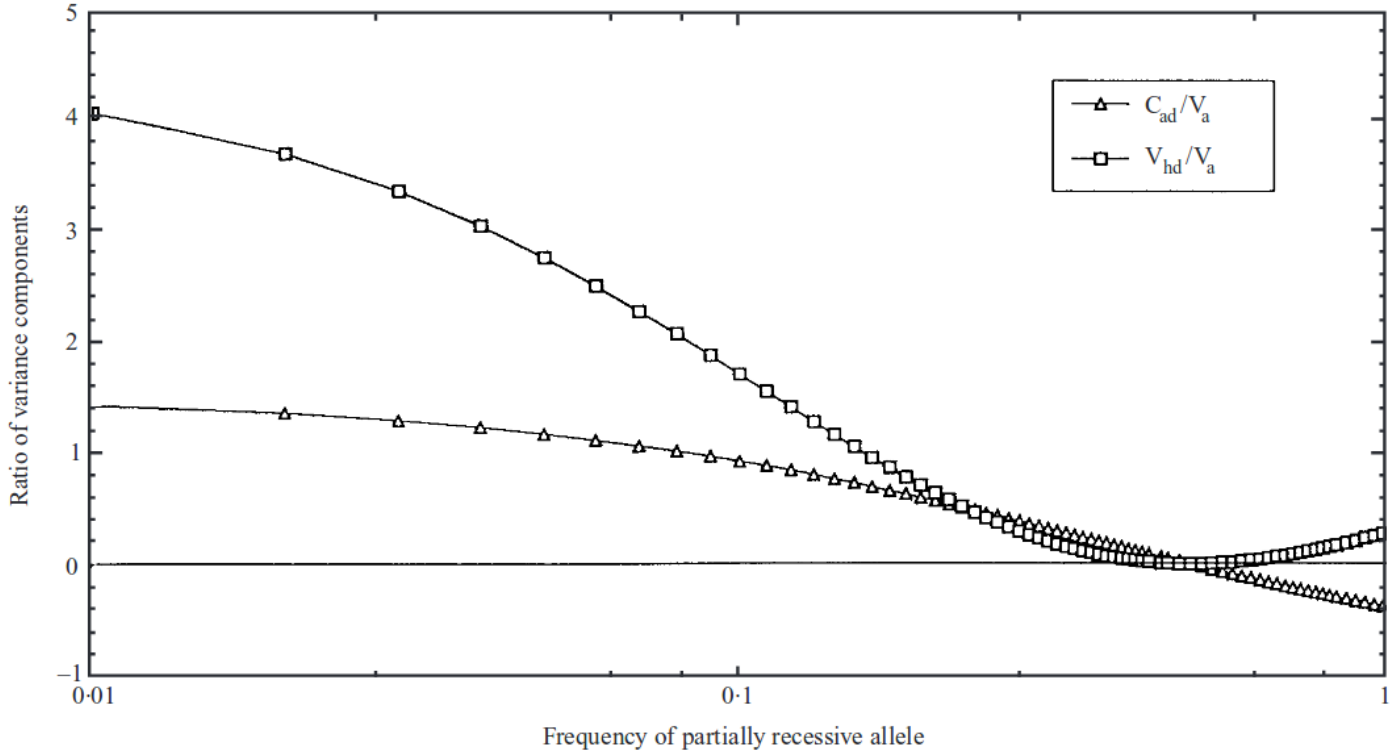
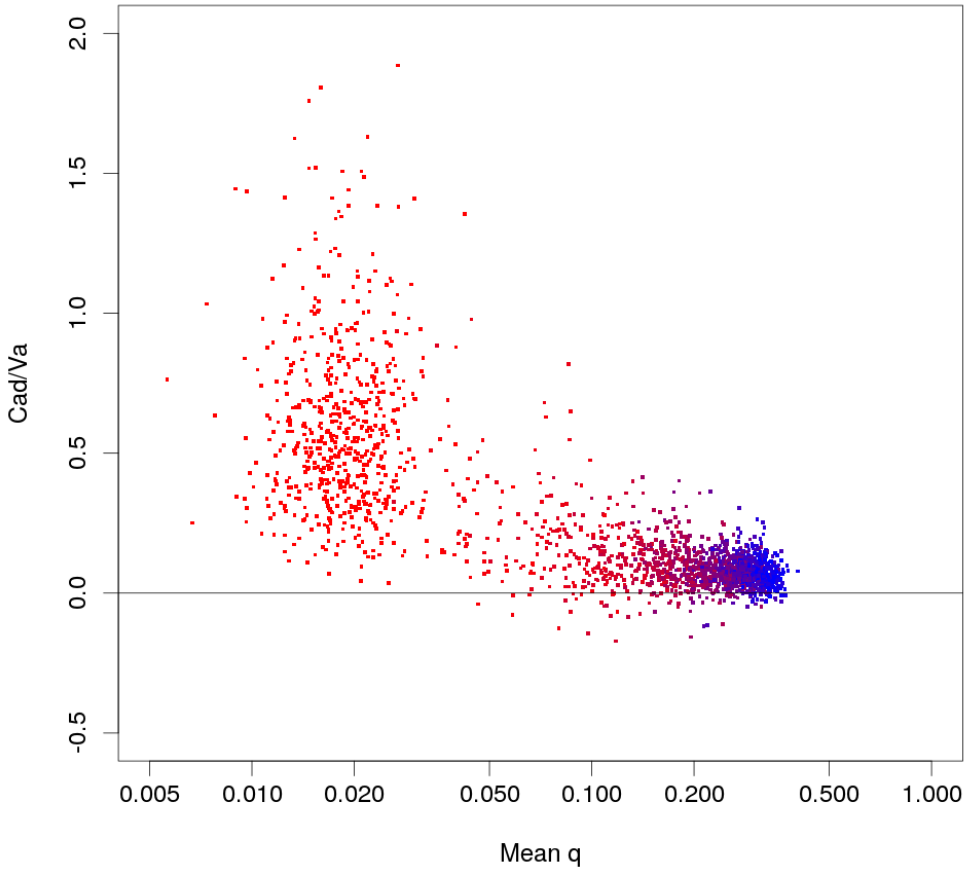


Fig. 1. The ratio of C_{ad} or V_{hd} to the additive genetic variance given the frequency of a partially recessive allele. In this case, the heterozygous effect of the allele is 20% of its homozygous effect ($h = 0{\cdot}2$; $d = -0{\cdot}6a$).

John K. Kelly's method



With multiple loci, Cad and Va are just the corresponding summations across loci.

Number of loci, genic effects, degree of dominance of the 'high' allele, proportion of loci with intermediate allele frequencies, and allele frequencies vary among simultated C_{ad}/V_a values.

John K. Kelly's method

$$R = h^2 \cdot s$$

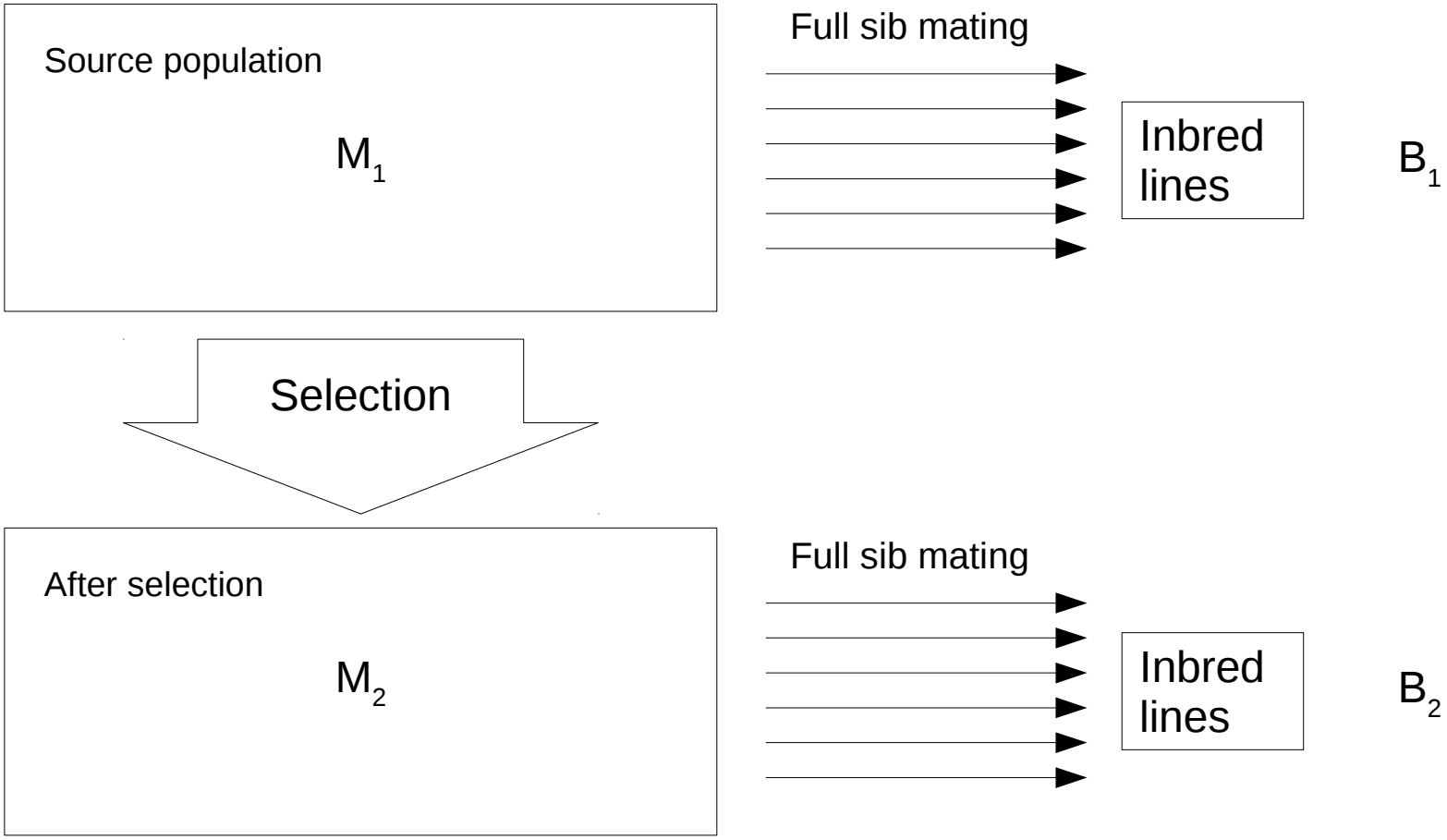
$$\Delta M = \frac{V_a}{V_p} \cdot s$$

$$\Delta B = \frac{C_{ad}}{V_p} \cdot s$$

$$\frac{\Delta B}{\Delta M} = \frac{C_{ad}}{V_a}$$

R = short term response to selection.
M = average phenotype in the population.
B = directional dominance; 'difference in mean phenotype between an outbred population and an inbred population with the same allele frequencies'.

John K. Kelly's method



John K. Kelly's method

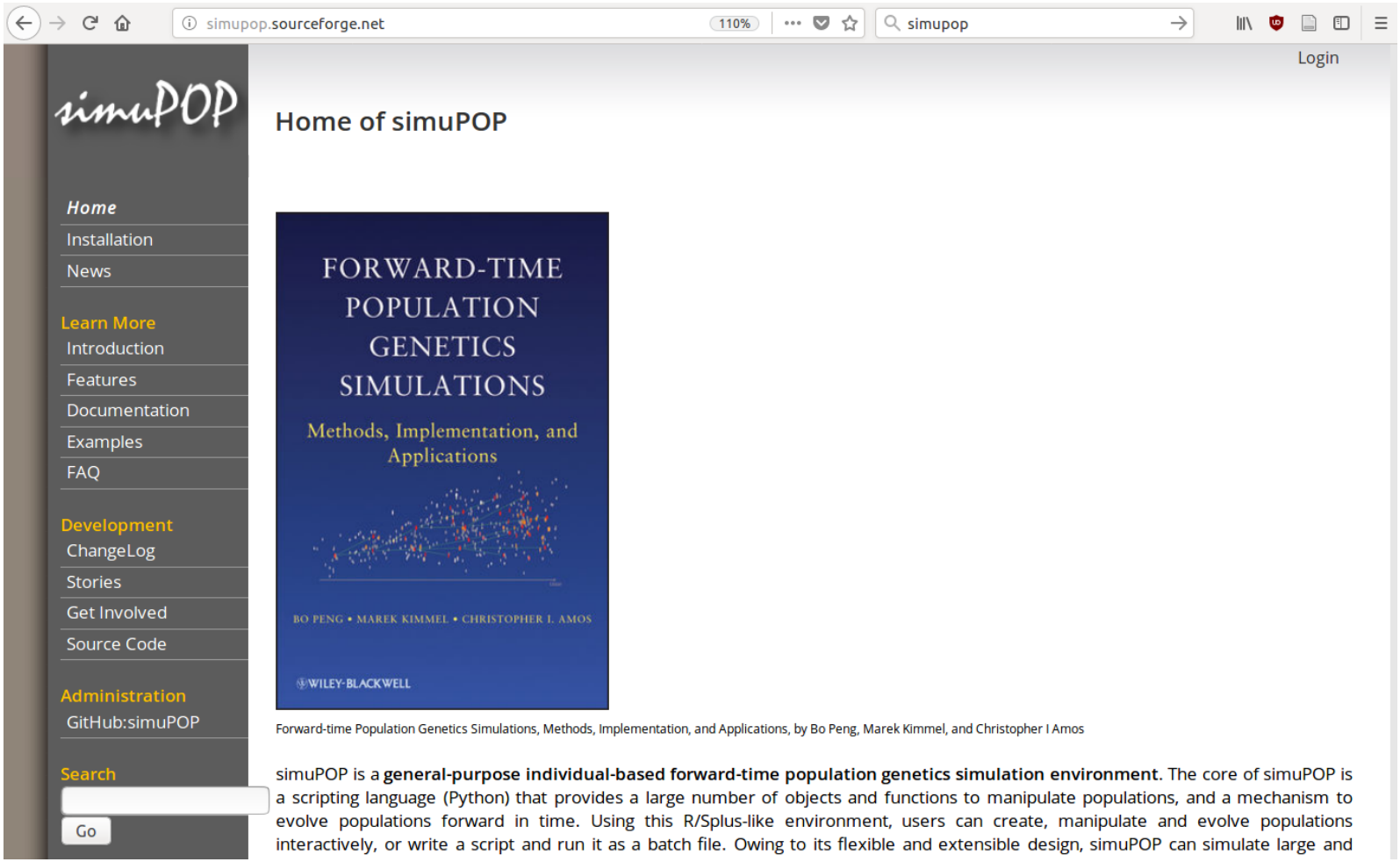
	Females			males	
Genotypes	A_1A_1	A_1A_2	A_2A_2	A_1	A_2
Frequencies	p^2	$2pq$	q^2	p	q
Genotypic values	a	d	0	b	0
Average values	$\mu_F = p^2 + 2pqd$			$\mu_M = pb$	
Estimated values	$\mu_F + 2\alpha'_{F1}$	$\mu_F + \alpha'_{F1} + \alpha'_{F2}$	$\mu_F + 2\alpha'_{F2}$	$\mu_M + \alpha'_{M1}$	$\mu_M + \alpha'_{M2}$
Dominance deviations	$q^2(2d - a)$	$-pq(2d - a)$	$p^2(2d - a)$	0	0

Similar formulas of C_{ad} / V_a apply to variation linked to the X chromosome among females. Selection experiments can be sex-limited, and even target only X-linked variation (Lund-Hansen, K.K., 2017, PhD dissertation).

However, the validity of $\frac{\Delta B}{\Delta M} = \frac{C_{ad}}{V_a}$ depends on an assumption of **linkage equilibrium**.

Simulations

Simulations

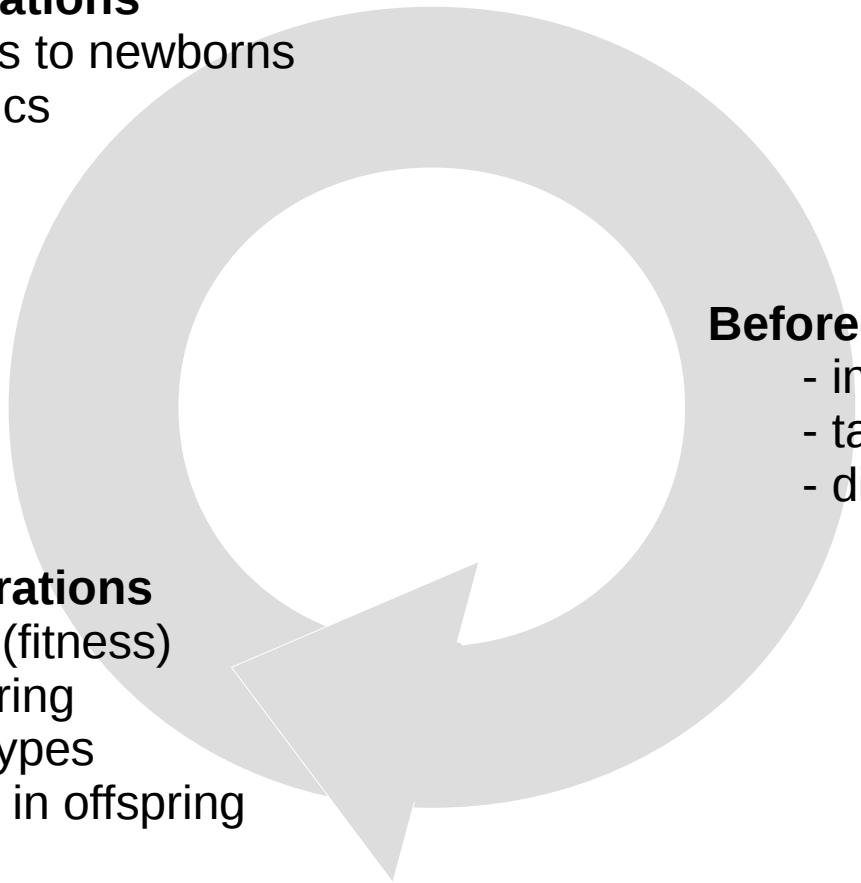


Simulations

After-mating operations
- add mutations to newborns
- output statistics

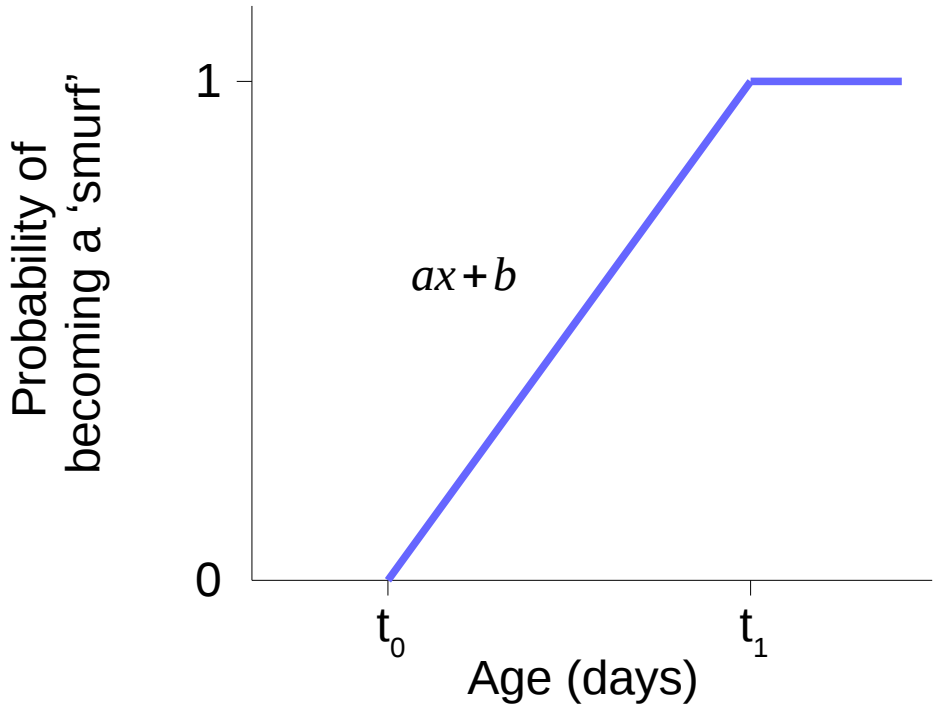
Before-mating operations
- increase age
- target for death or not
- die or not

During-mating operations
- select parents (fitness)
- generate offspring
- transmit genotypes
- set trait values in offspring



Simulations. Aging model.

Two-phases model of aging in *D. melanogaster*

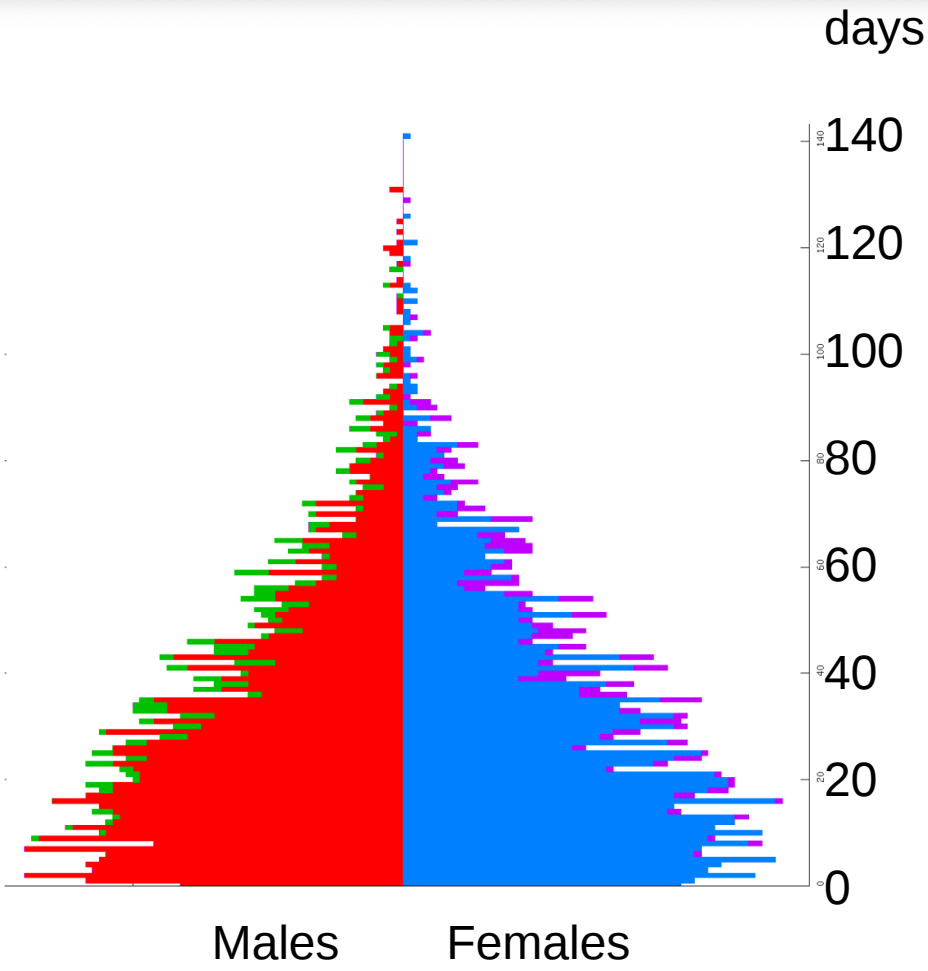


Mortality is null before becoming targeted for death (*smurf*) and constant (*k*) afterwards.

$$t_0 = -\frac{b}{a}$$

$$t_1 = \frac{1-b}{a}$$

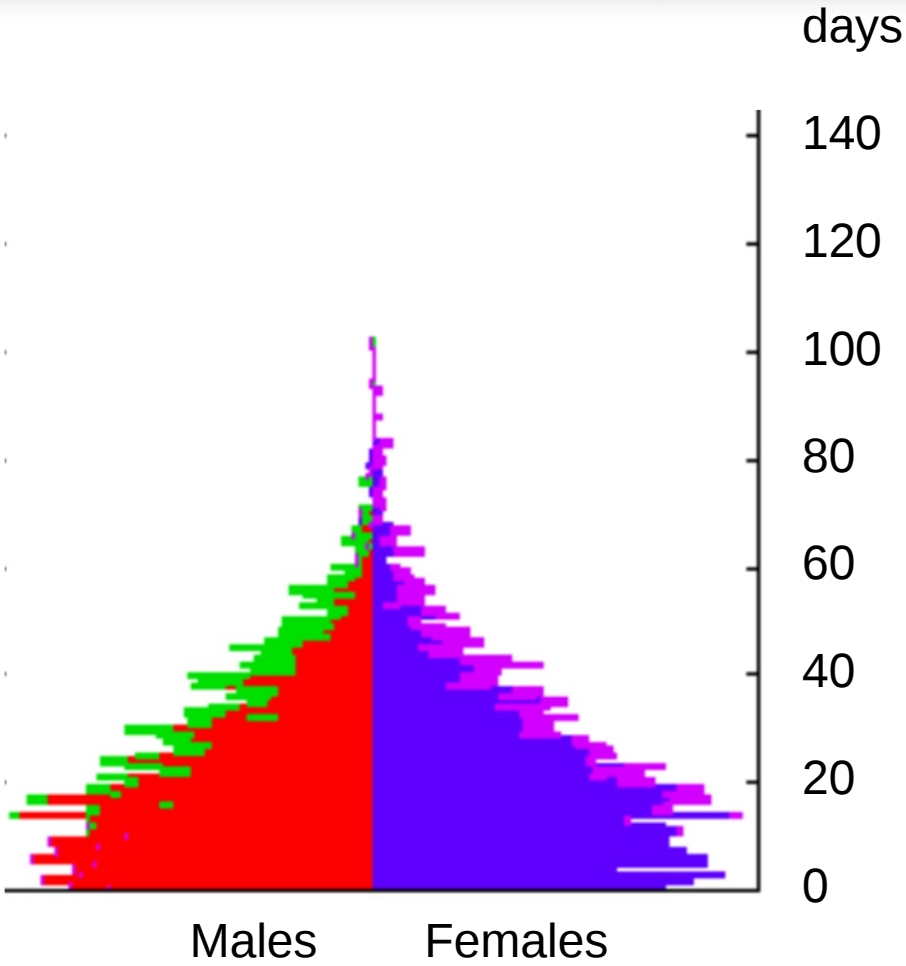
Simulations. Aging model.



a = 0.0039
b = –0.0190
k = 0.1911 (~5 days left)
t_0 = 4.9 days
t_1 = 261 days

(Tricoire H, Rera M (2015) PLoS ONE 10(11): e0141920.)

Simulations. Aging model.



a = 0.01
b = –0.1
k = 0.1911 (~5 days left)
t_0 = 10 days
t_1 = 110 days

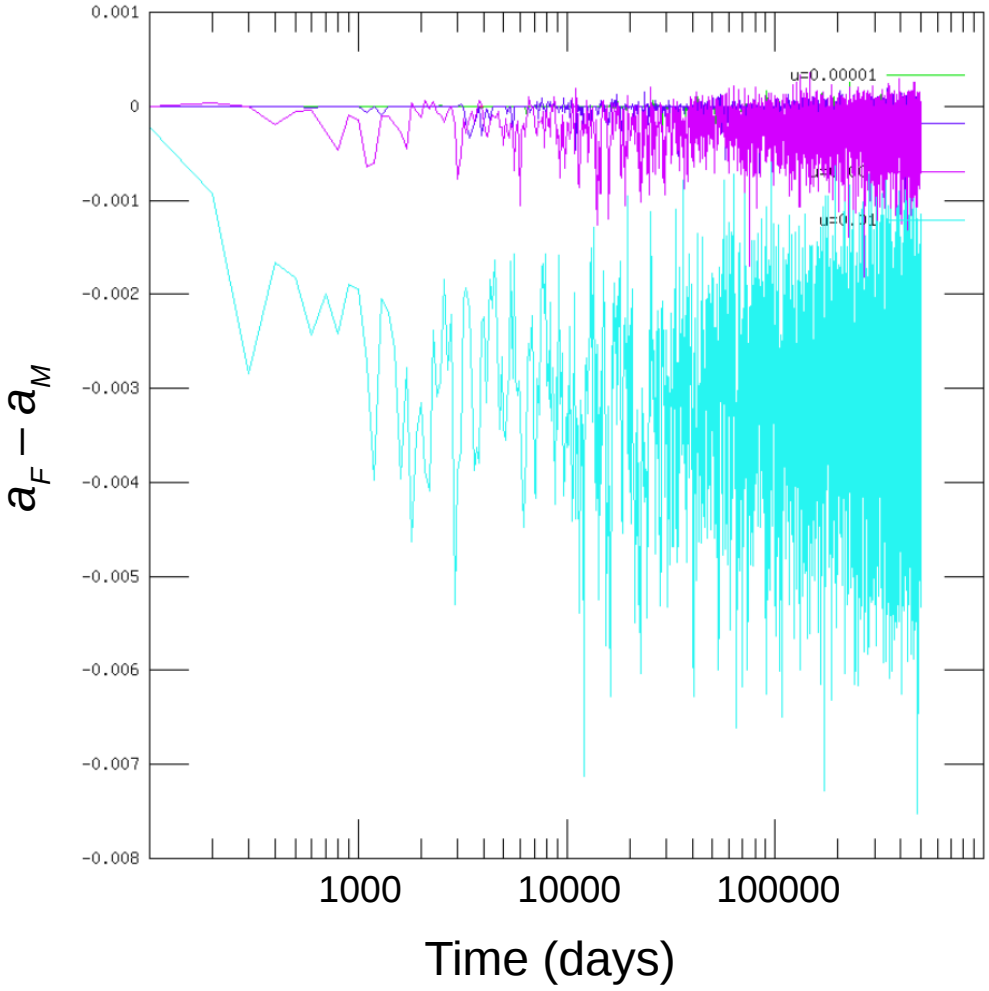
Simulations. Mutation-selection balance

7 loci in X chromosome
10 loci in autosome 2
11 loci in autosome 3

Mutation generates recessive deleterious alleles.
Deleterious alleles increase the rate of aging, *a*.
Parameter *b* is set proportional to *a*, so that $t_0 = 10$.
Reproductive success depends only on lifespan.

Simulations start without any mutation.

Simulations. Mutation-selection balance

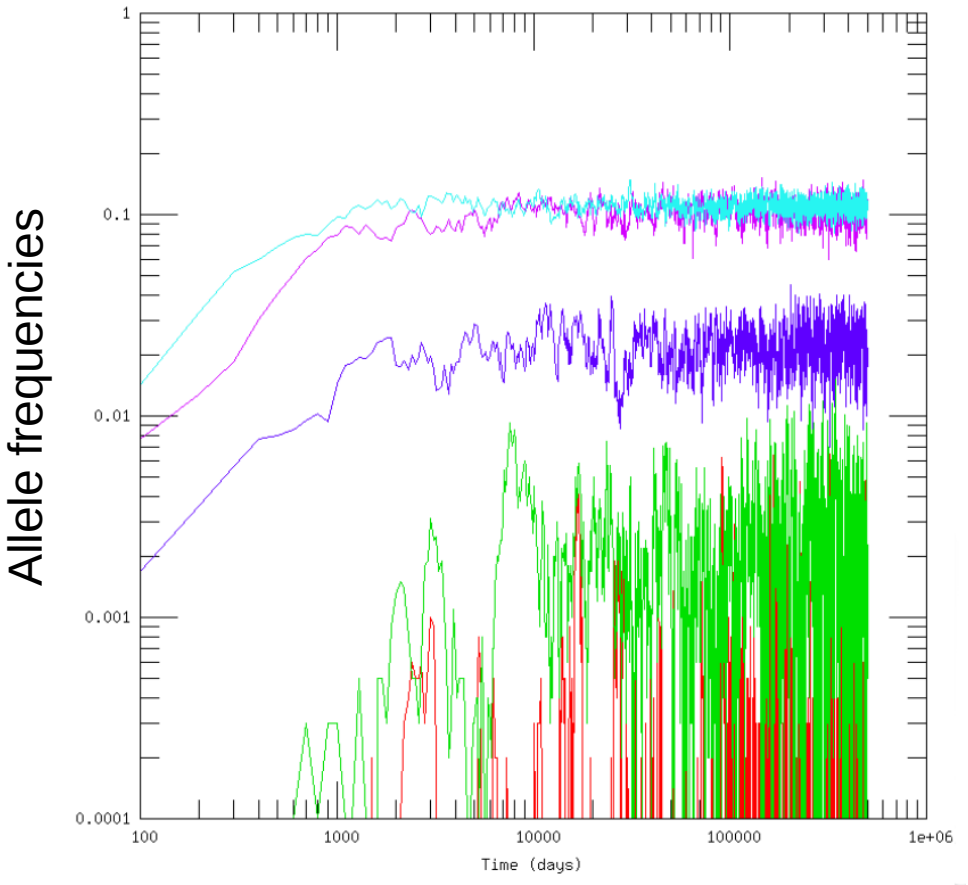


$0.003 < a < 0.4$

Unrealistically high mutation rates are required to produce a noticeable difference in aging rate between males and females.

Too few loci?
Low proportion of X-linked loci?

Simulations. Mutation-selection balance



Natural selection keeps mutant allele frequencies around the equilibrium.

Simulations. Sexually antagonistic pleiotropy.

	Males		Females		
Genotype	0Y	1Y	00	01	11
Lifespan	long	long	long	long	short
Fecundity	low	high	high	high	high

Work in progress

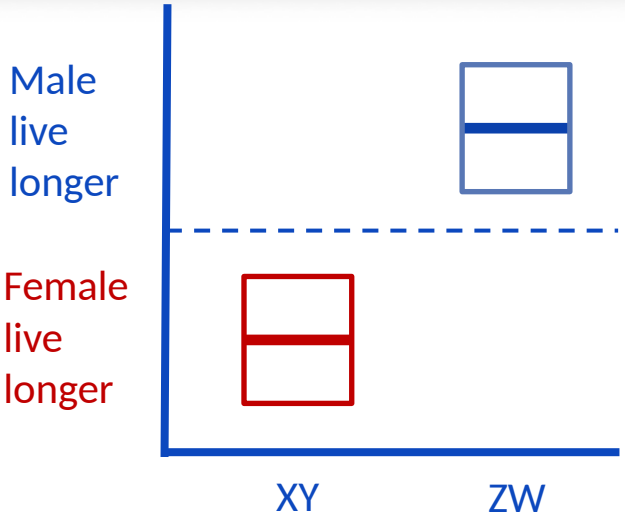
Future steps

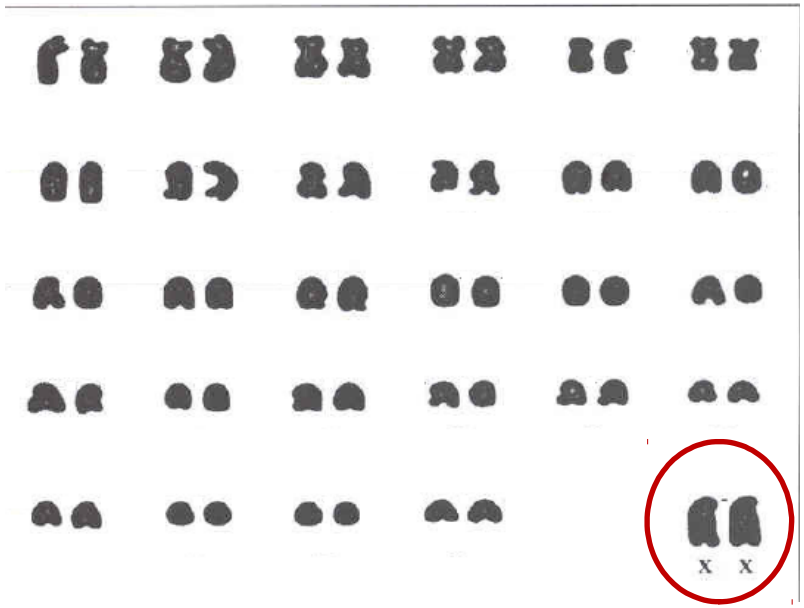
- Refine the models
- Simulate inbreeding and selection experiments
  - Check if Kelly's method works, in general
- Determine conditions for success on X-linked variation
  - Check if Kelly's method works on X chromosome
- Simulate the unguarded X under different proportions of X-linked loci

Future steps. Sultanova, Downing and Carazo, in prep.

Analysis 1

Sex-specific survival ~ Sex determination system





Analysis 2

Sex-specific survival ~ Relative importance of X/Z

Acknowledgements

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