

# Why do female flies live longer than male flies?

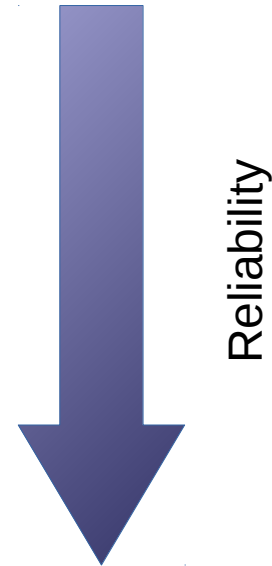
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J. Ignacio Lucas Lledó

# Introduction

# Introduction

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



# Introduction

<https://github.com/IgnasiLucas>

The screenshot shows a Mozilla Firefox browser window with the GitHub profile of J. Ignacio Lucas Lledó. The browser's address bar displays the URL <https://github.com/IgnasiLucas>, which is highlighted by a red box and a callout. The profile page features a bio section with a profile picture, name, and affiliation (Population Genomics Lab, Cavanilles Institute of Biodiversity). Below the bio are several pinned repositories, including 'fish', 'fly', 'hedgehog', 'mosquito', 'phylogenies', and 'UX'. The 'UX' repository is circled in red. At the bottom, there is a contribution activity chart showing 55 contributions in the last year.

# Introduction

IgnasiLucas/UX - Mozilla Firefox

Safata d'entrada (26.07) x Universitat de Valencia x Загрузка статьи x IgnasiLucas/UX x NASBRDI-2017-STODDEN.k x

GitHub, Inc. (US) | https://github.com/IgnasiLucas/UX 80% Search

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No description, website, or topics provided. Edit

Add topics

21 commits 1 branch 0 releases 1 contributor GPL-3.0

Branch: master New pull request Create new file Upload files Find file Clone or download

IgnasiLucas Preparing the simulations of the sexually antagonistic pleiotropy model. Latest commit 7a5ef3d 3 days ago

doc	Started preparing new simulations.	a month ago
results	Preparing the simulations of the sexually antagonistic pleiotropy model.	3 days ago
.gitignore	Finished mutation-selection balance analysis	7 days ago
LICENSE	Finished mutation-selection balance analysis	7 days ago
README.md	Finished mutation-selection balance analysis	7 days ago

README.md

## 2018-01-29

Simulations that show that the ratio between  $Cad$  and  $Va$  is actually sensitive to the allele frequencies. This is a reproduction of one of Kelly (1999) figures but with a variety of more realistic scenarios.

## 2018-04-19

Here, I repeat the last simulations with a different parameterization. The results are equivalent.

## 2018-05-22

Here I wrote a python script, 'ade structure.py', that implements the two- phases model of aad in *Drosophila*. I obtain some

# Introduction

UX/results at master · IgnasiLucas/UX - Mozilla Firefox

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GitHub, Inc. (US) | https://github.com/ignasilucas/UX/tree/master | 110% | Search

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IgnasiLucas Preparing the simulations of the sexually antagonistic pleiotropy model. Latest commit 7a59f3d 3 days ago

..

2018-01-29	Added a figure simulating ratios of Cad to Va, to prove that Kelly's ...	5 months ago
2018-04-19	Proved that X-linked variation shows in homogametic sex the propertie...	2 months ago
2018-05-22	Solved a bug in the age structure script and wrote a script for the m...	17 days ago
2018-06-07	Finished mutation-selection balance analysis	7 days ago
2018-06-21	Preparing the simulations of the sexually antagonistic pleiotropy model.	3 days ago

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# Introduction

UX/results/2018-06-07 at master · IgnasiLucas/UX - Mozilla Firefox

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GitHub, Inc. (US) | https://github.com/ignasilucas/UX/tree/master 90% ... Search

Search or jump to... Pull requests Issues Marketplace Explore

IgnasiLucas / UX Unwatch 1 Star 0 Fork 0

Code Issues 0 Pull requests 0 Projects 0 Wiki Insights Settings

Branch: master UX / results / 2018-06-07 / Create new file Upload files Find file History

IgnasiLucas Finished mutation-selection balance analysis Latest commit c9af12f 7 days ago

..

A_difference.png	Finished mutation-selection balance analysis	7 days ago
README.sh	Finished mutation-selection balance analysis	7 days ago
age_difference.png	Finished mutation-selection balance analysis	7 days ago
frequencies.png	Finished mutation-selection balance analysis	7 days ago
mutationSelectionBalance.py	Improving the mutation-selection balance script.	13 days ago
plotA.gnp	Finished mutation-selection balance analysis	7 days ago
plotAges.gnp	Finished mutation-selection balance analysis	7 days ago
plotFrequencies.gnp	Finished mutation-selection balance analysis	7 days ago

README.sh

```
#!/bin/bash
#
#
#               2018-06-07
#             =====
#
# I wrote the script mutationSelectionBalance.py, which simulates mutations
# on loci that affect the probability of becoming targeted for natural
# death. Mutant alleles all increase the parameter 'a' of the two-phases
# model of aging, and are therefore deleterious. They are recessive, and
# expressed in males if present in the X chromosome. The model includes
# recombination. The age effects are all equal and additive
```

# How I became interested in the topic



# Motivation



Dr. Pau Carazo



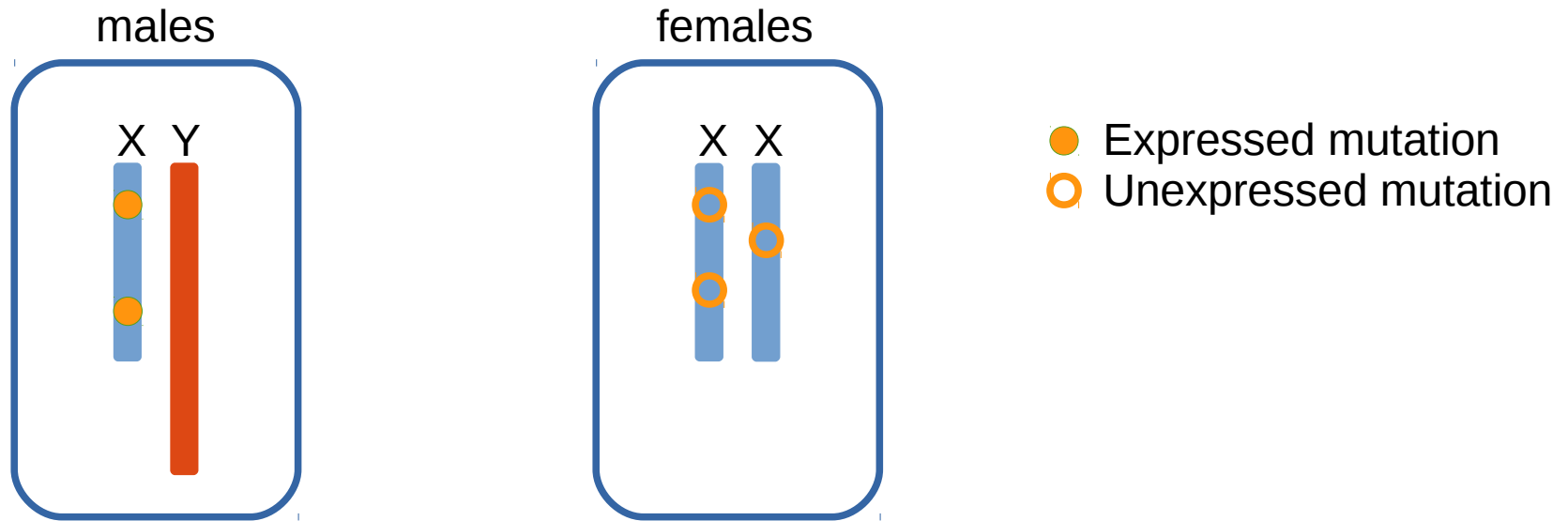
Zahida Sultanova (PhD candidate)

# The Unguarded X hypothesis

# The Unguarded X hypothesis

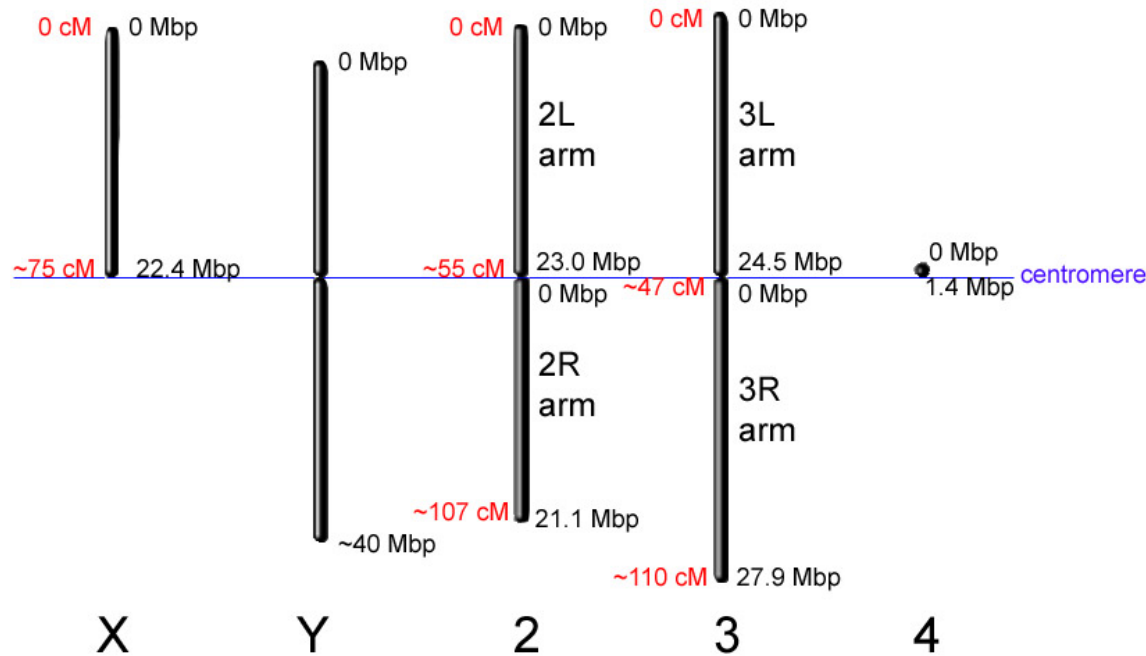
- Why do sexes age differently?
  - Adaptive processes:
    - Different optimum lifespans.
    - E.g., sexually antagonistic pleiotropy.
  - Maladaptive processes:
    - Mother's curse hypothesis.
    - Unguarded X hypothesis.

# 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



*Drosophila melanogaster* chromosomes

Data from the National Center for Biotechnology Information (NCBI) and Carvalo (2002)

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



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>

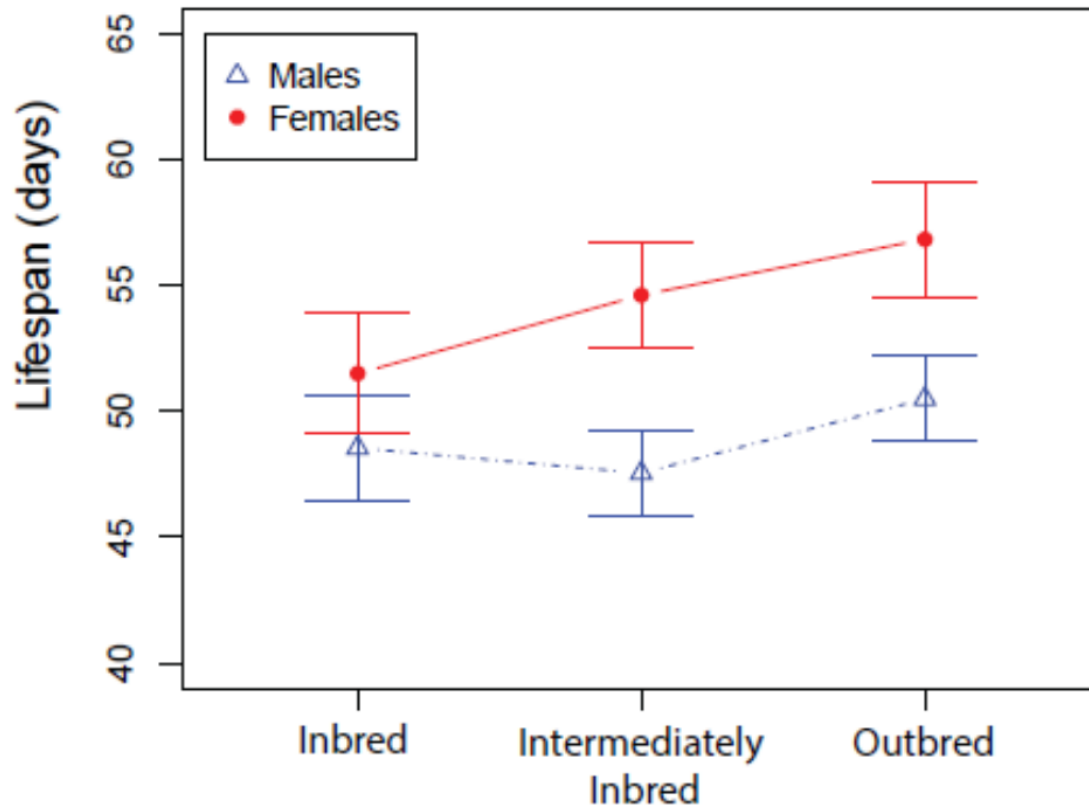
[Read the full text >](#)

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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 © 1999 Cambridge University Press 263

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

JOHN K. KELLY\*

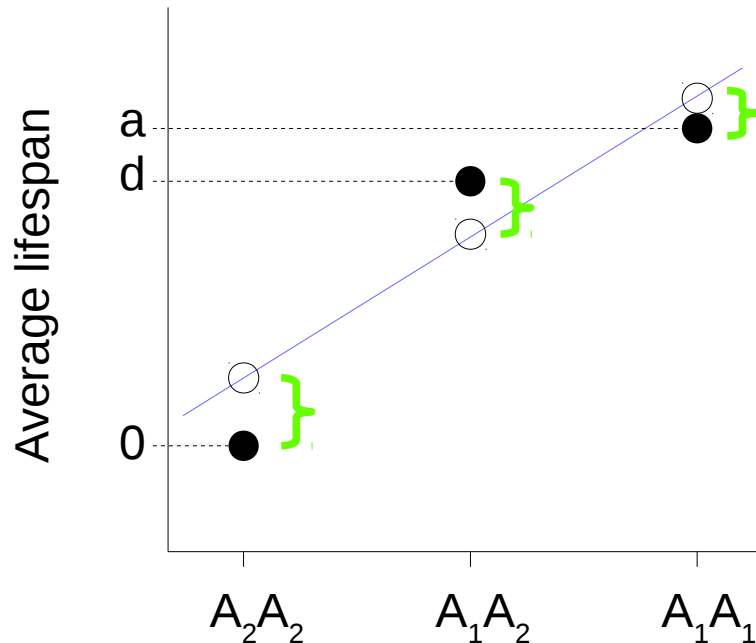
*Department of Biology, University of Oregon, Eugene, OR 97403, USA*

*(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  $A_2$ .

$\alpha_1$  = '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.

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

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

# John K. Kelly's method

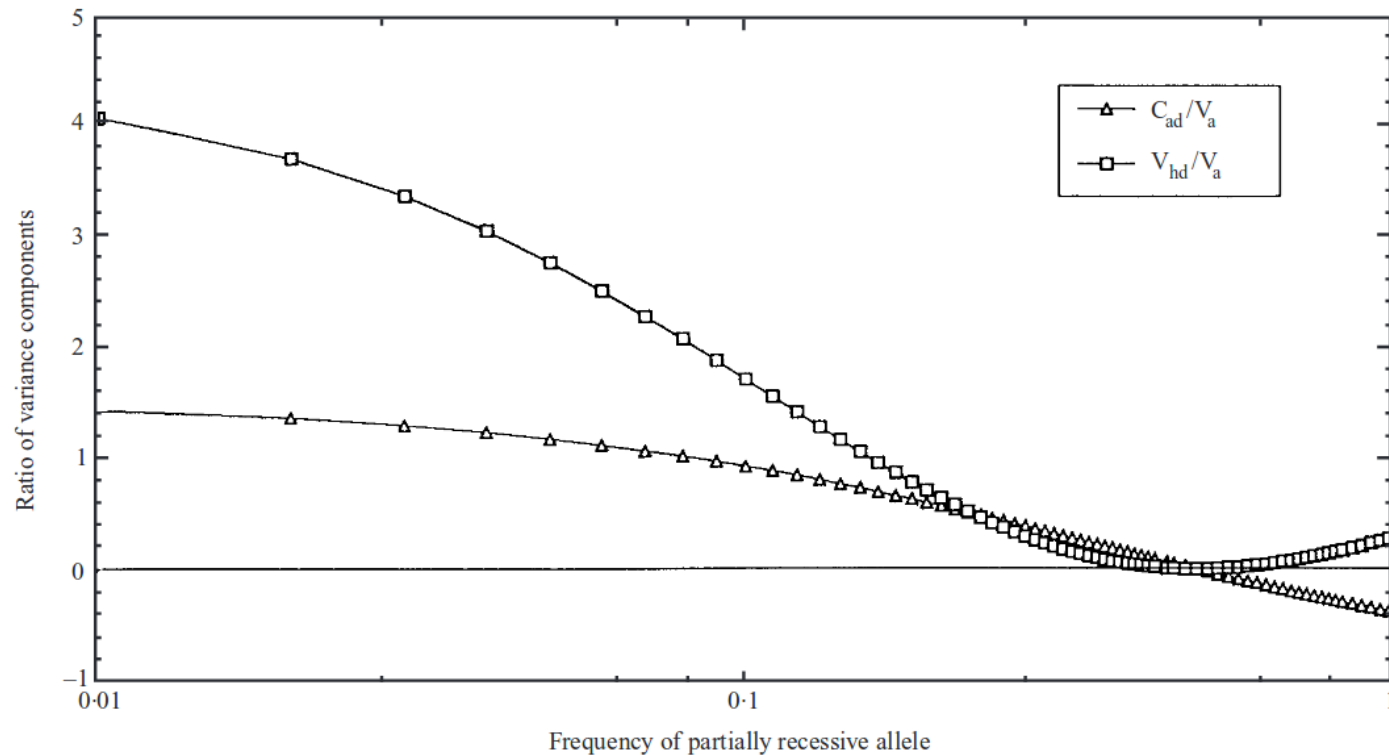
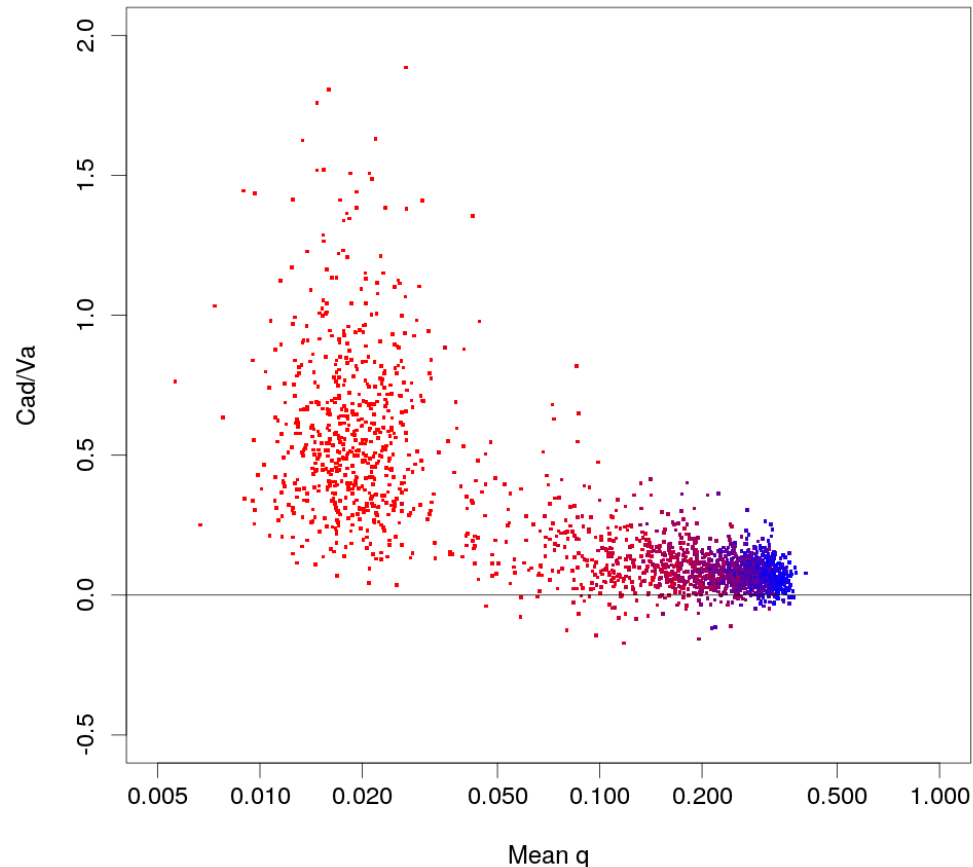


Fig. 1. The ratio of  $C_{ad}$  or  $V_{hd}$  to the additive genetic variance given the frequency of a partially recessive allele. In this case, the heterozygous effect of the allele is 20 % of its homozygous effect ( $h = 0.2$ ;  $d = -0.6a$ ).

# John K. Kelly's method



With multiple loci,  $C_{ad}$  and  $V_a$  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 simulated  $C_{ad}/V_a$  values.



# John K. Kelly's method

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

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

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

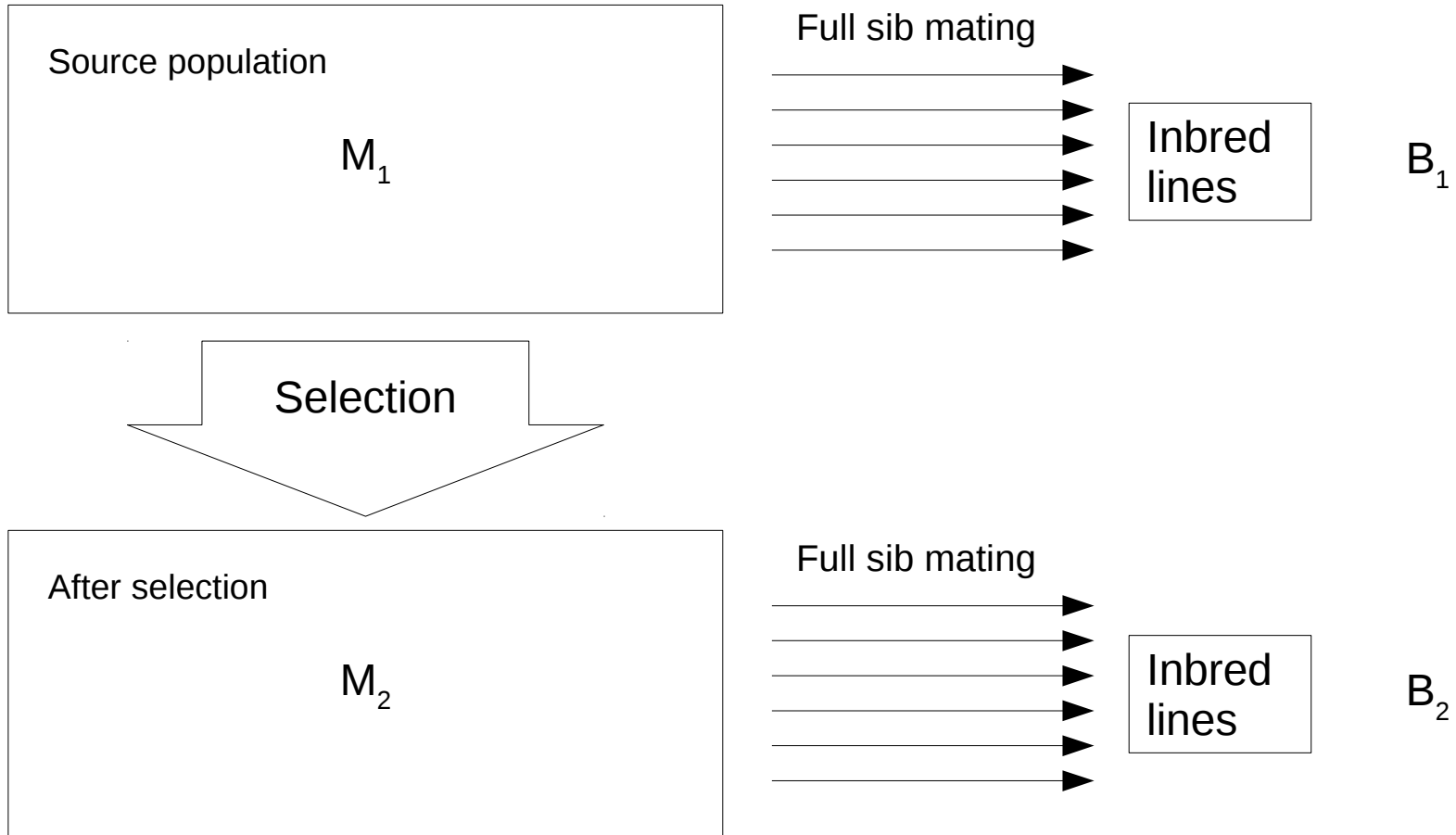
$$\frac{\Delta B}{\Delta M} = \frac{C_{ad}}{V_a}$$

$R$  = 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

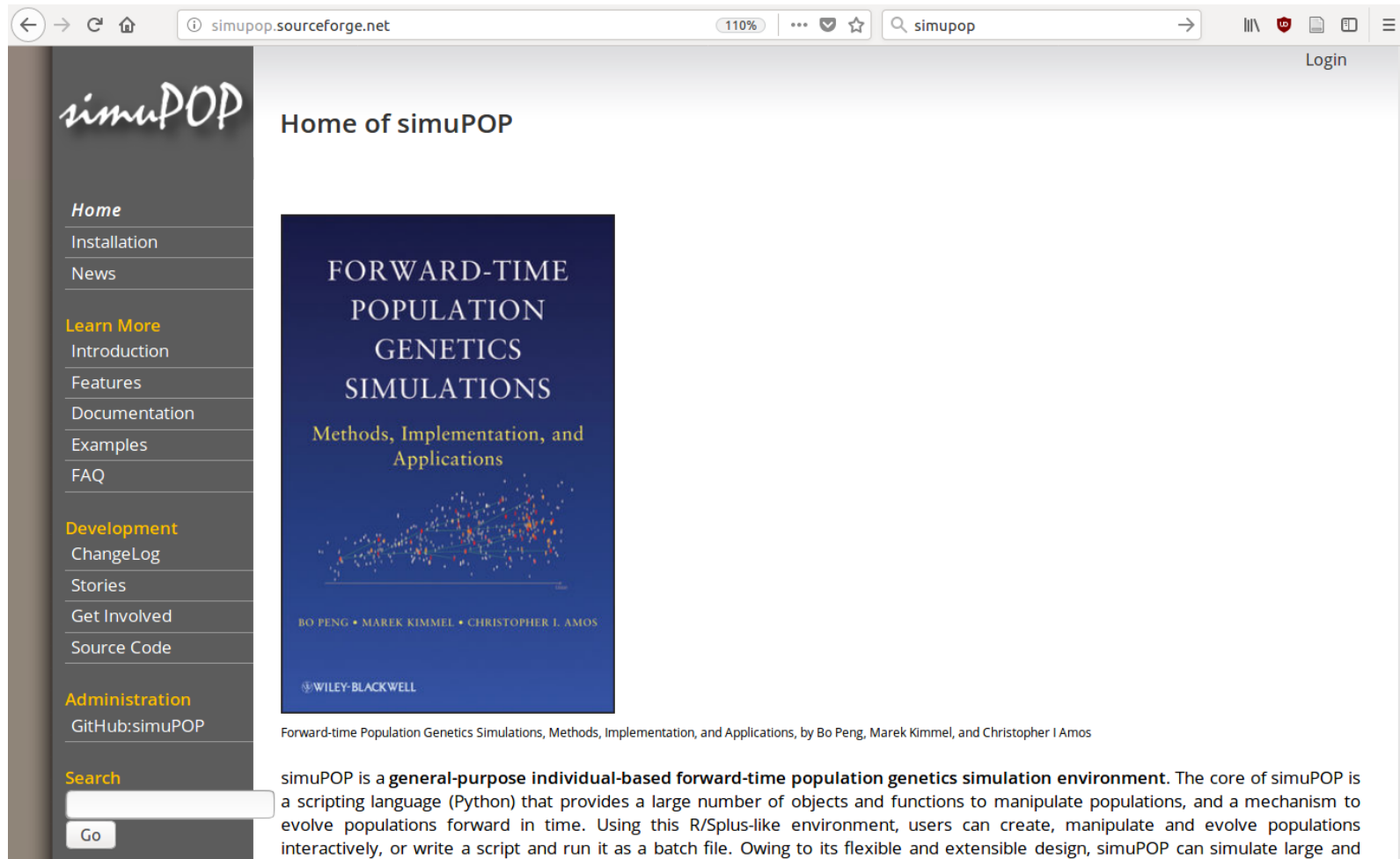
	Females			males	
Genotypes	$A_1A_1$	$A_1A_2$	$A_2A_2$	$A_1$	$A_2$
Frequencies	$p^2$	$2pq$	$q^2$	$p$	$q$
Genotypic values	$a$	$d$	$0$	$b$	$0$
Average values	$\mu_F = p^2 + 2pqd$			$\mu_M = pb$	
Estimated values	$\mu_F + 2\alpha'_{F1}$	$\mu_F + \alpha'_{F1} + \alpha'_{F2}$	$\mu_F + 2\alpha'_{F2}$	$\mu_M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



The screenshot shows a web browser window with the URL `simupop.sourceforge.net`. The page title is "Home of simuPOP". On the left is a sidebar menu with the following sections:

- Home**
  - Home
  - Installation
  - News
- Learn More**
  - Introduction
  - Features
  - Documentation
  - Examples
  - FAQ
- Development**
  - ChangeLog
  - Stories
  - Get Involved
  - Source Code
- Administration**
  - GitHub:simuPOP
- Search**
  - 
  - Go

The main content area features a book cover for "FORWARD-TIME POPULATION GENETICS SIMULATIONS: Methods, Implementation, and Applications" by Bo Peng, Marek Kimmel, and Christopher I. Amos, published by Wiley-Blackwell. Below the book cover, the text reads: "Forward-time Population Genetics Simulations, Methods, Implementation, and Applications, by Bo Peng, Marek Kimmel, and Christopher I Amos".

simuPOP is a **general-purpose individual-based forward-time population genetics simulation environment**. The core of simuPOP is a scripting language (Python) that provides a large number of objects and functions to manipulate populations, and a mechanism to evolve populations forward in time. Using this R/Plus-like environment, users can create, manipulate and evolve populations interactively, or write a script and run it as a batch file. Owing to its flexible and extensible design, simuPOP can simulate large and

# Simulations

## After-mating operations

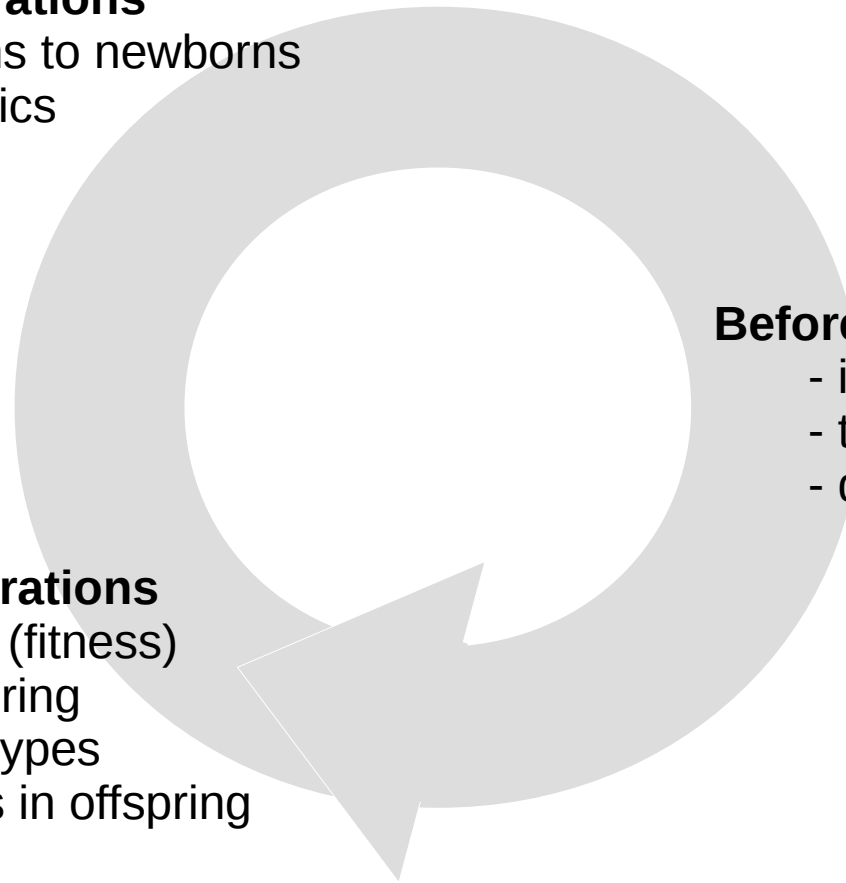
- add mutations to newborns
- output statistics

## Before-mating operations

- increase age
- target for death or not
- die or not

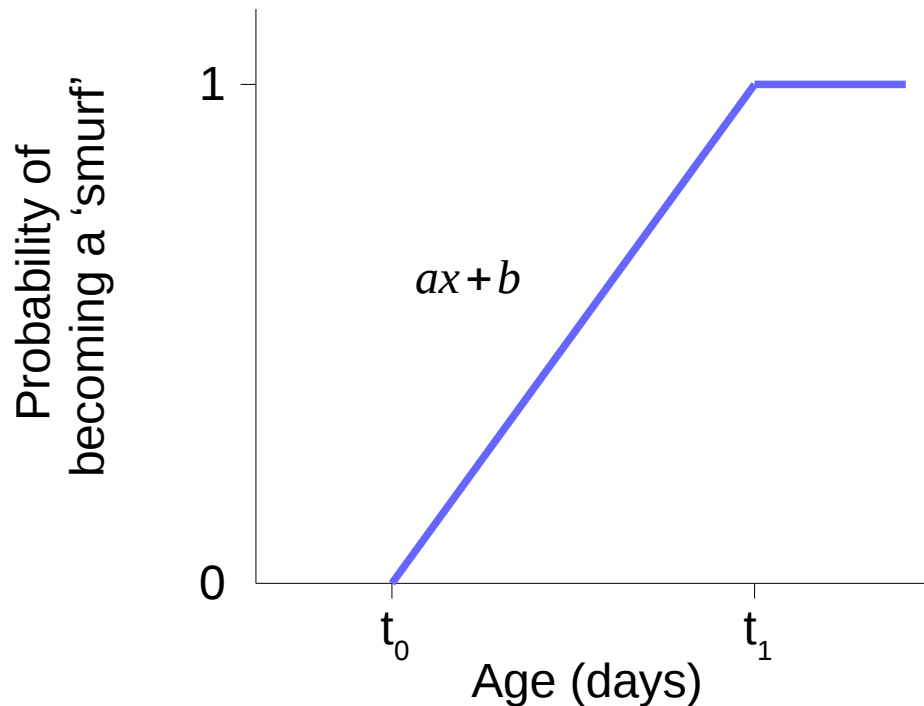
## During-mating operations

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



# Simulations. Aging model.

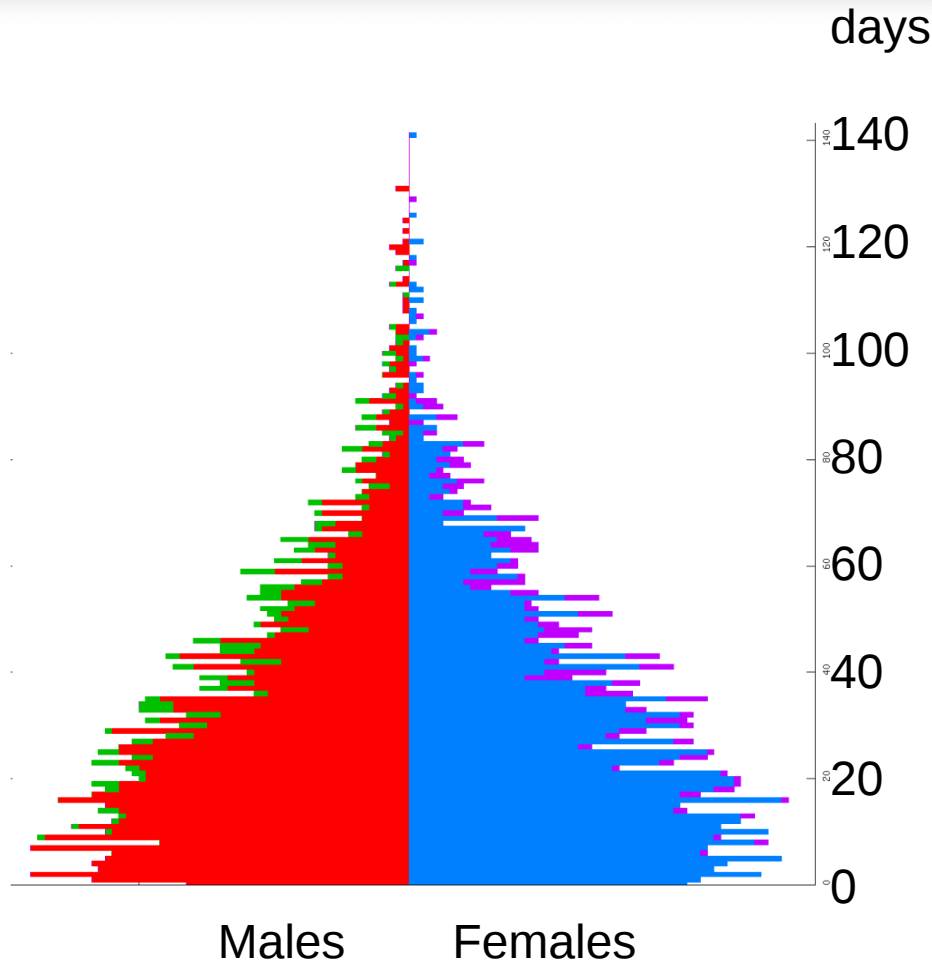
Two-phases model of aging in *D. melanogaster*



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.



$$a = 0.0039$$

$$b = -0.0190$$

$$k = 0.1911 \text{ (~5 days left)}$$

$$t_0 = 4.9 \text{ days}$$

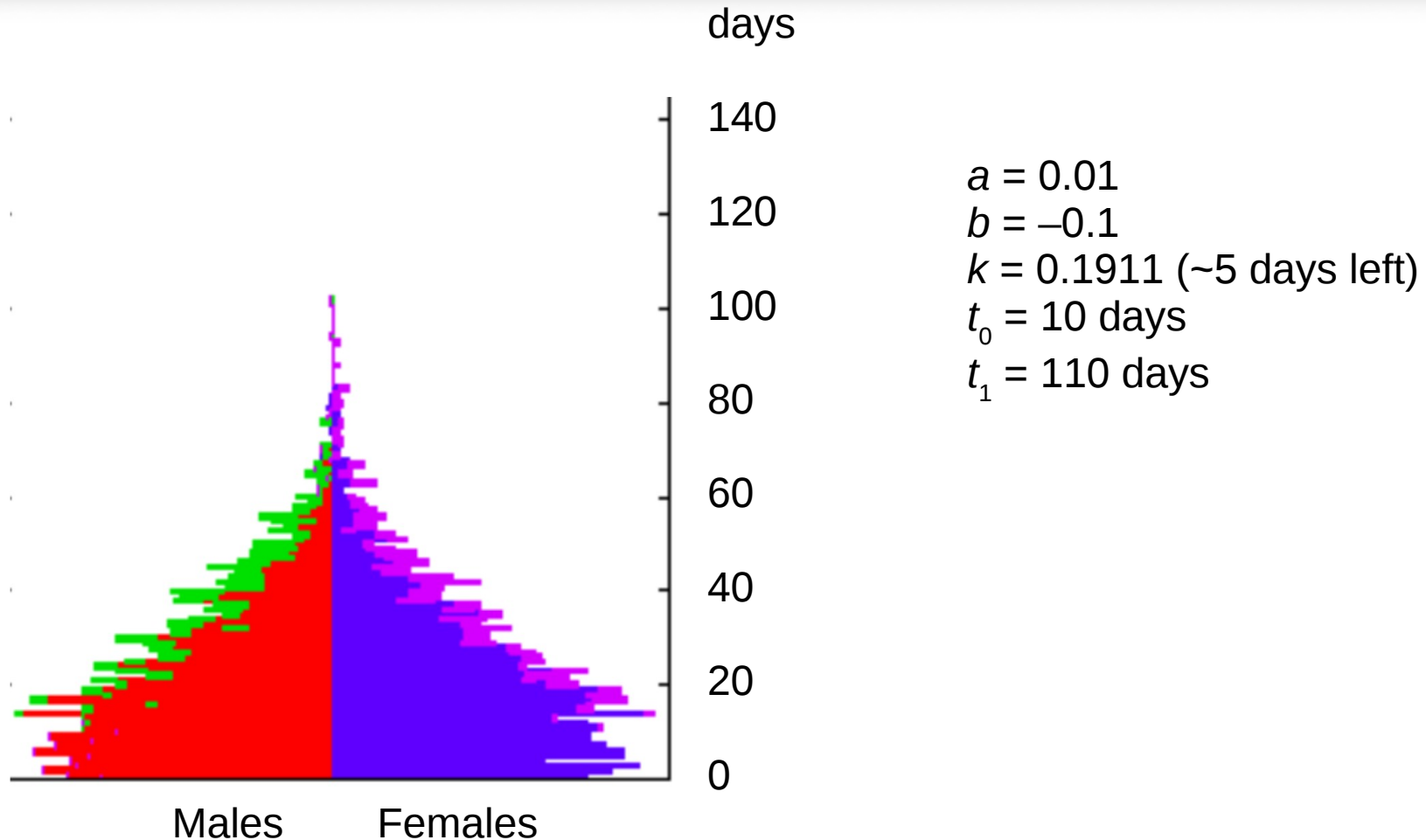
$$t_1 = 261 \text{ days}$$

(Tricoire H, Rera M (2015)

PLoS ONE 10(11): e0141920.)



# Simulations. Aging model.



# Simulations. Mutation-selection balance

7 loci in X chromosome

10 loci in autosome 2

11 loci in autosome 3

Mutation generates recessive deleterious alleles.

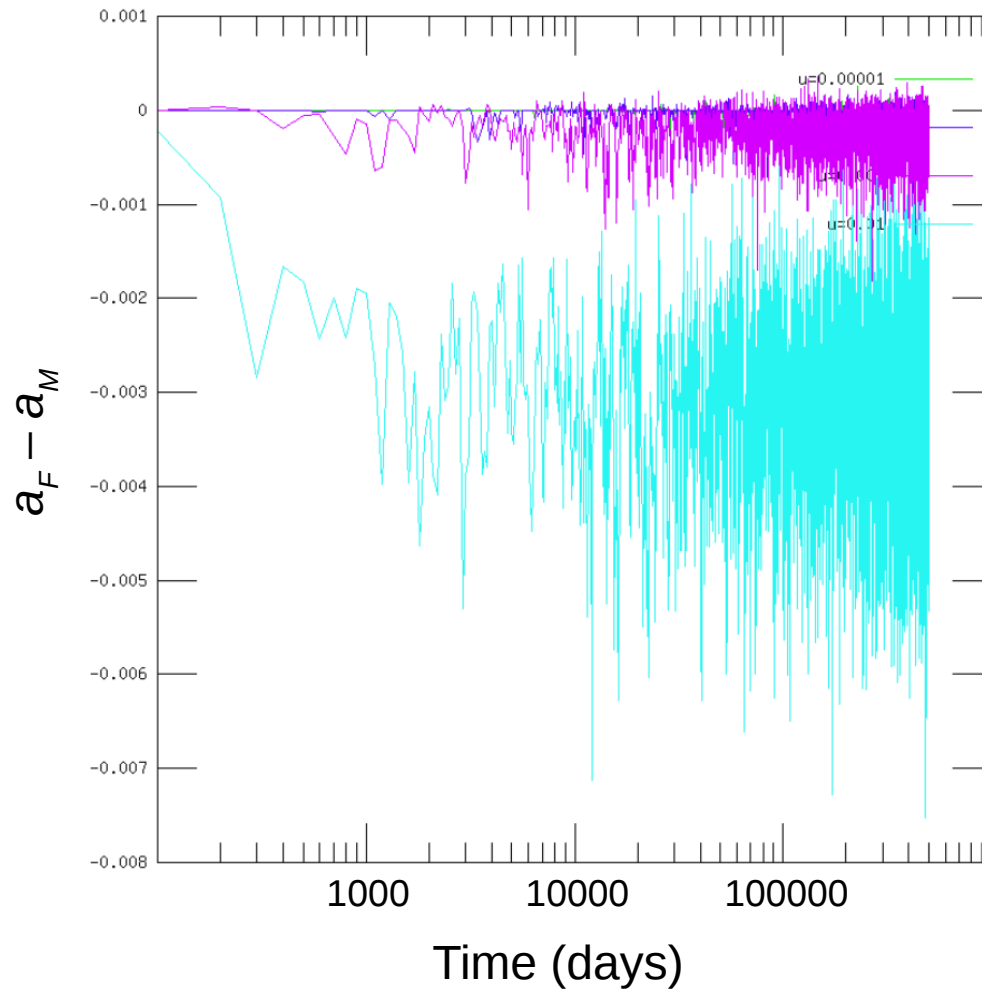
Deleterious alleles increase the rate of aging,  $a$ .

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

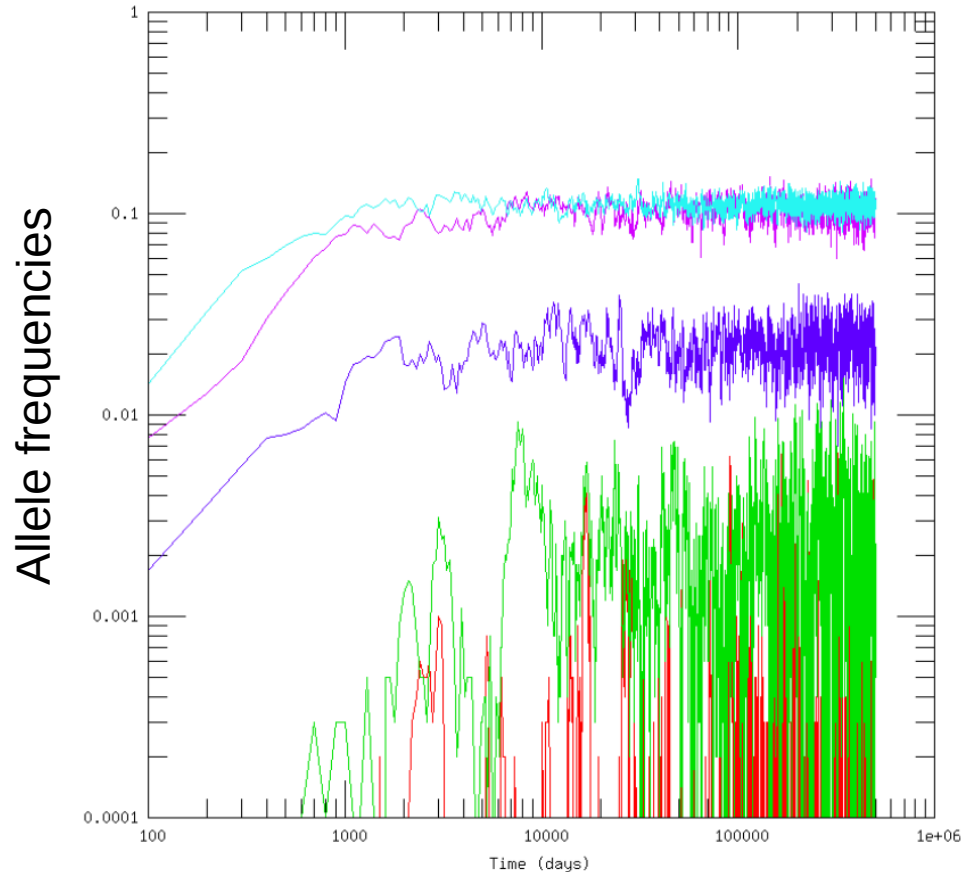


$$0.003 < a < 0.4$$

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

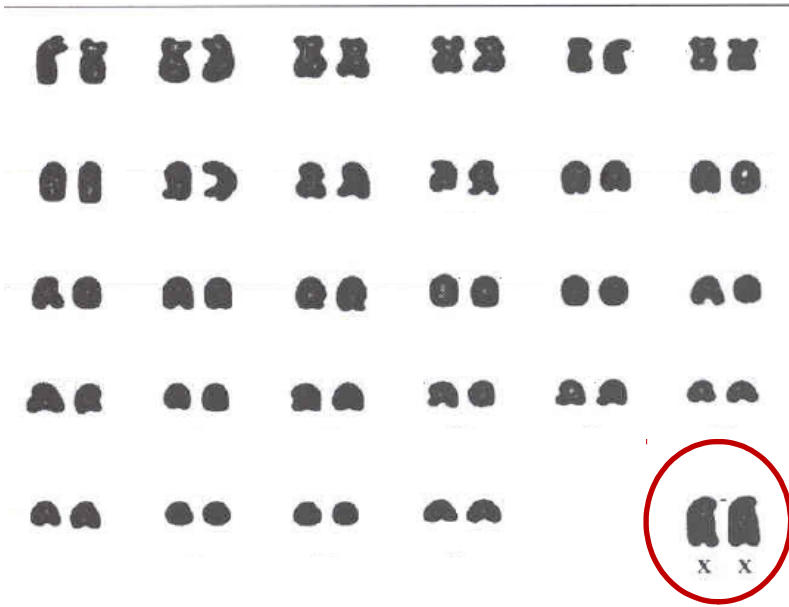
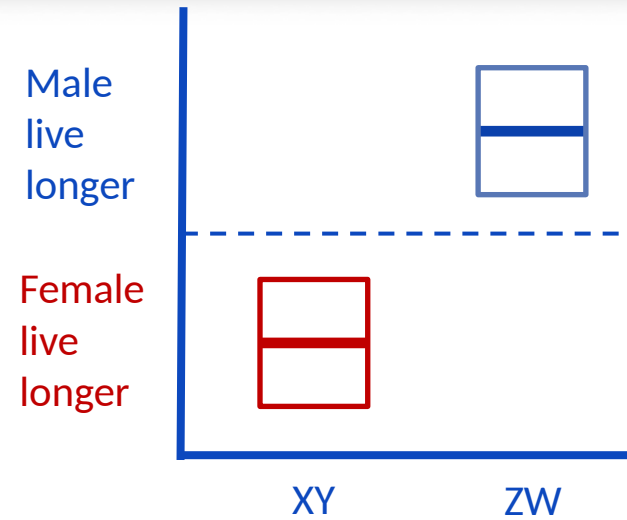
# Future steps

- 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



Pau Carazo



Zahida Sultanova



Muhammed Andic



Funding by the Spanish  
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VNIVERSITAT  
ID VALÈNCIA



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ID VALÈNCIA