Introduction to simulations of breeding programmes

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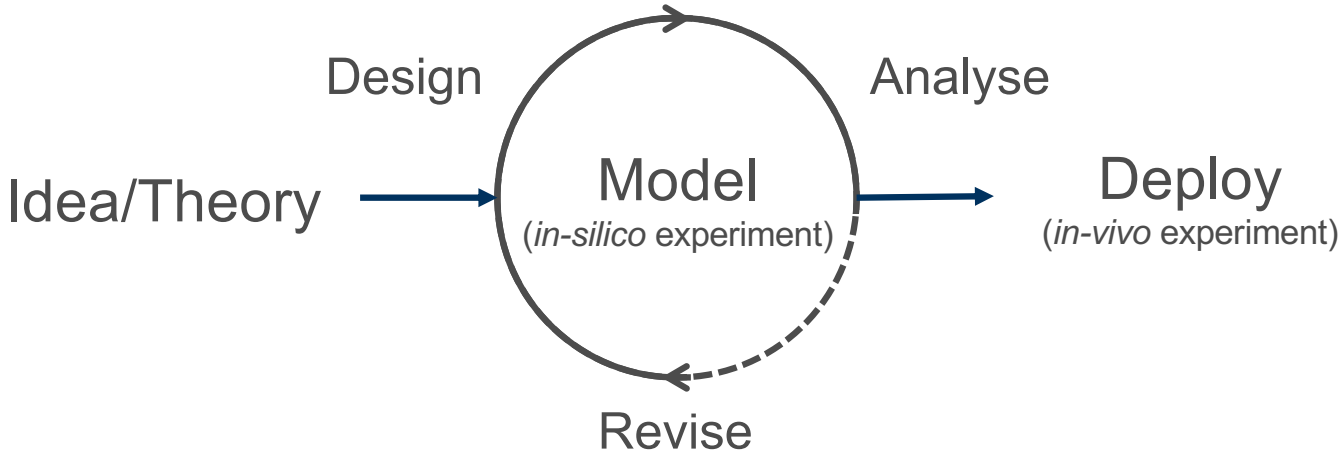
Learning objectives

- Introduce the concept of breeding simulations
- Differentiate deterministic and stochastic simulations
- Showcase one AlphaSimR simulation
- Differentiate backward- & forward-in-time simulations

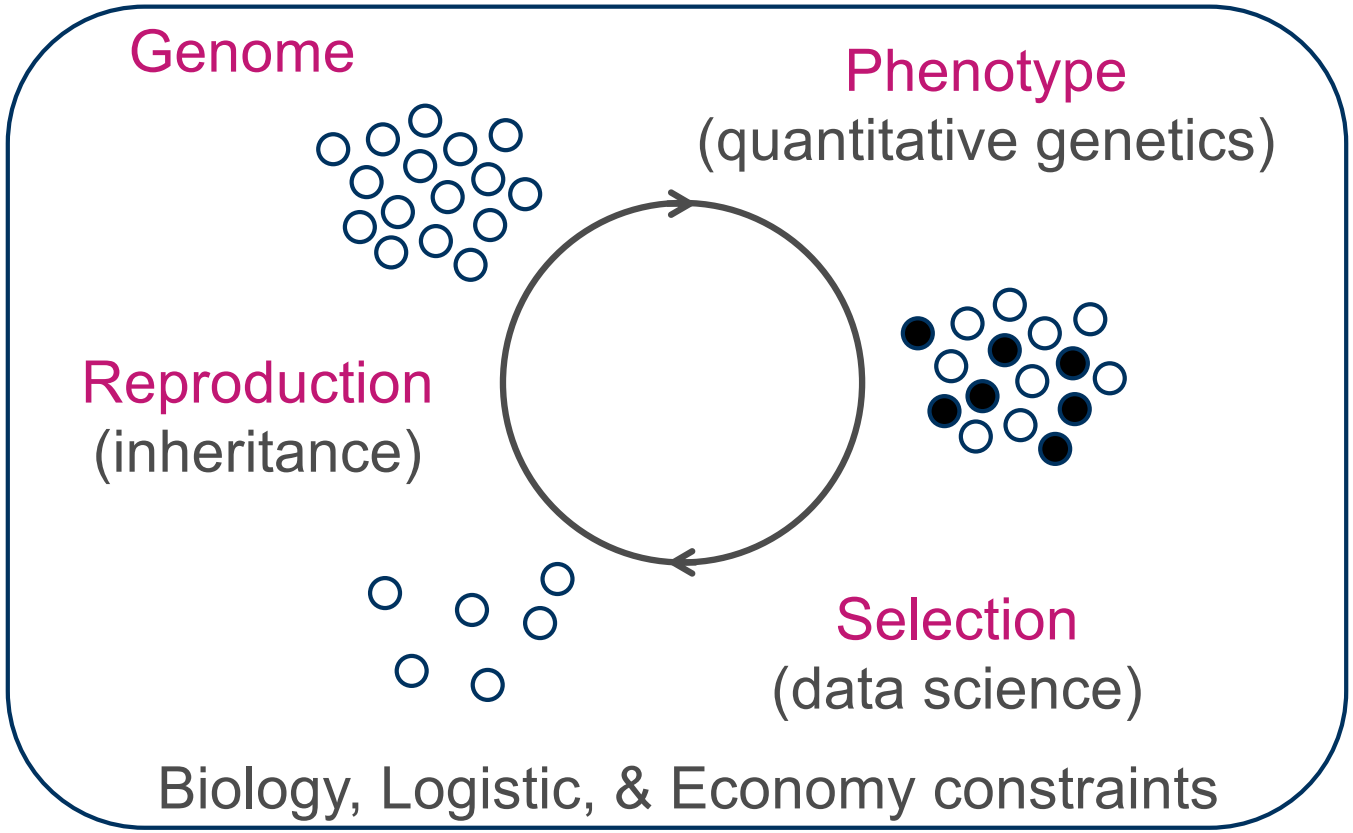
Modelling/simulation mindset in breeding

- Breeding programs are complex, costly, and can be slow!
  (genetics, reproduction, production, disease, data, statistics, …)
- A need for an *in-silico modelling sandbox*



- Capture major components to identify key drivers of population management and improvement

Basic elements of a breeding programme simulation

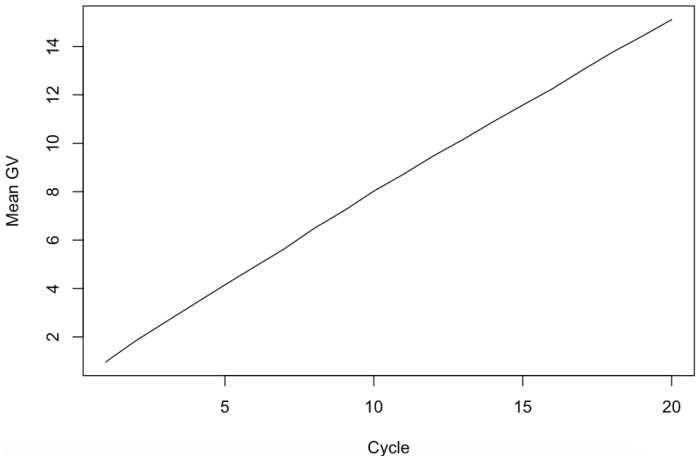


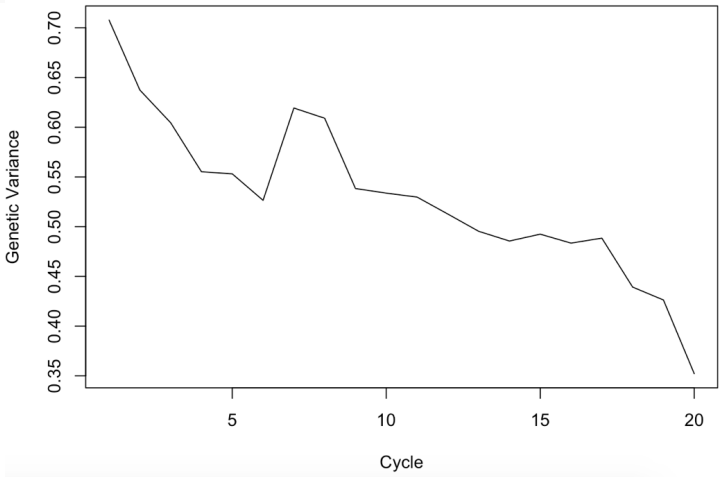
Evolution of our modelling/simulation platform

- …
- 2006 – Multi-trait polygenic breeding values in livestock
- **2008 – Genomes and markers**
- 2010 – First attempt at complex populations under selection
- 2012 – Released a simple package (*AlphaDrop*)
- 2012 – Plant breeding features and adding complexity (mating structures, etc.)
- 2014 – Released a complex package (*AlphaSim*)
- 2015 – Complex simulations required lots of “glue-scripting”
- **2017 – Migrate from Fortran to R/C++ and pop. objects - *AlphaSimR*!!!**
- 2017 – Realistic dominance model (total genetic, breeding, and dominance values)
- 2018 – Complete migration, develop many blueprints, EiB use, industry, …
- 2022 – AlphaSimR course
- 2023 – Collection of plant breeding simulations published (animal version in progress)
- …

AlphaSimR scripting

```
SP = SimParam$new(founderPop)
SP$addTraitA(nQtlPerChr=1000, mean=0, var=1)
SP$setGender("yes_sys")
pop = newPop(founderPop)
popMean = popVar = numeric(20)
for(cycle in 1:20){
  pop = selectCross(pop=pop, nFemale=500, nMale=25, use="gv", nCrosses=1000)
  popMean[cycle] = meanG(pop)
  popVar[cycle] = varG(pop)
}
plot(popMean,type="l",xlab="Cycle",ylab="Mean GV")
plot(popVar,type="l",xlab="Cycle",ylab="Genetic Variance")
```

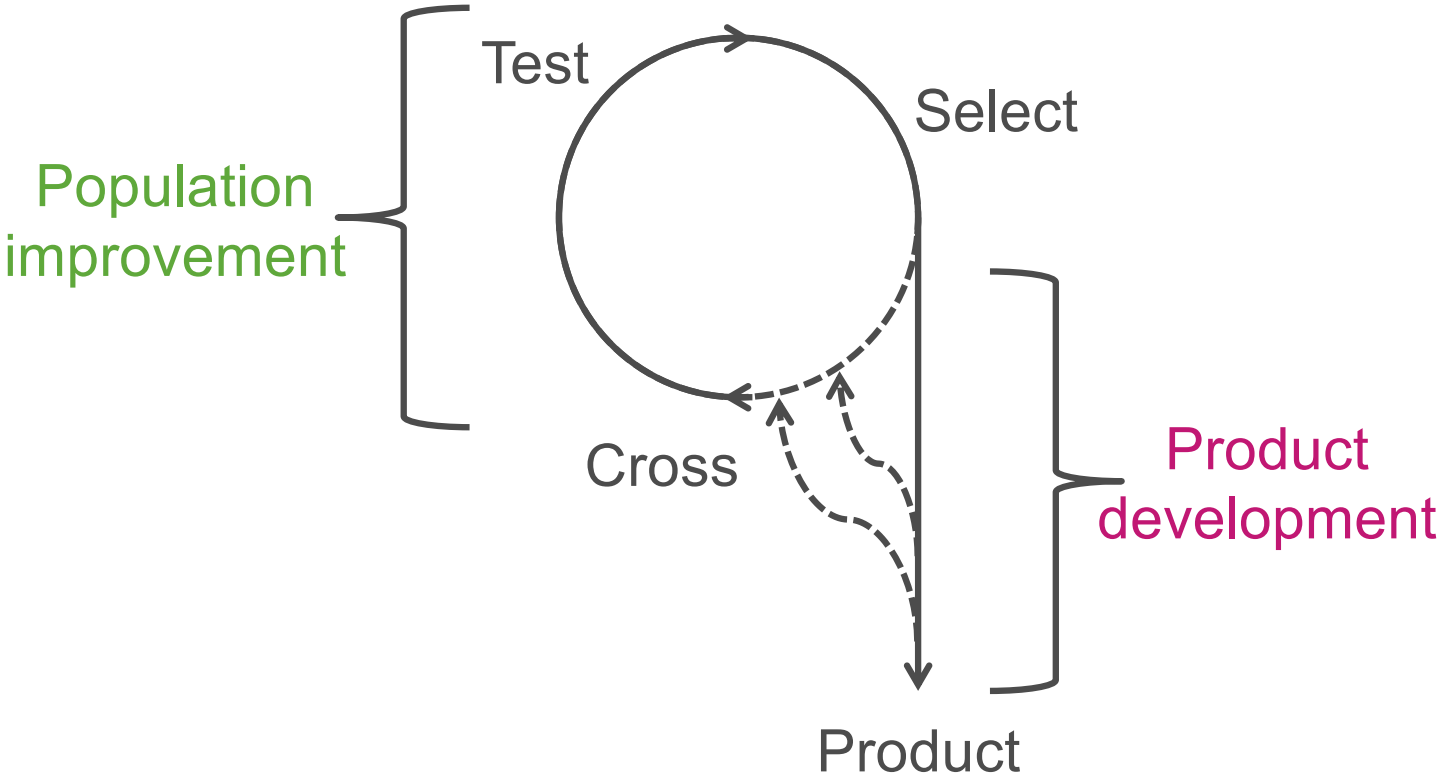




Architecture & Construction analogy

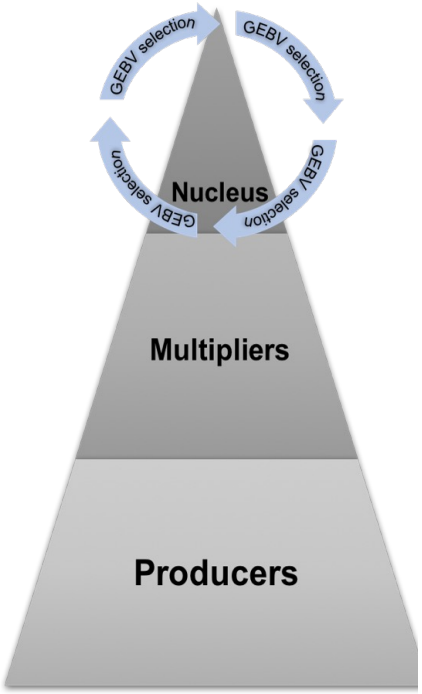
https://www.dreamstime.com/illustration/home-architecture-project-completion.html

Two core areas of every breeding programme

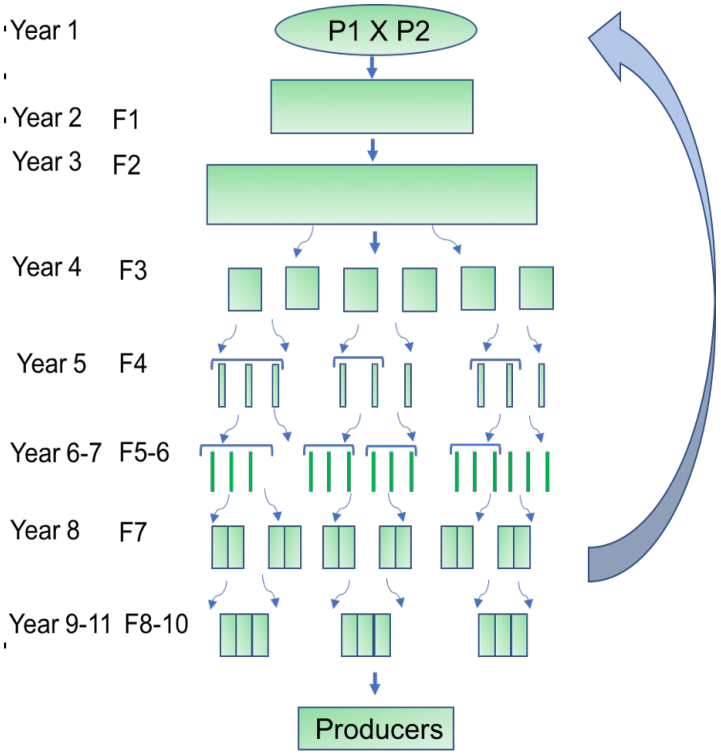


Examples

Animal breeding



Plant breeding



Used across many species

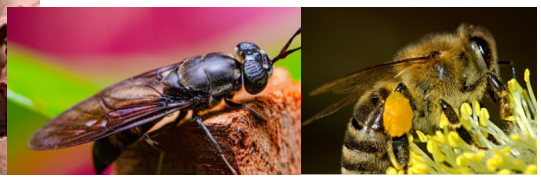




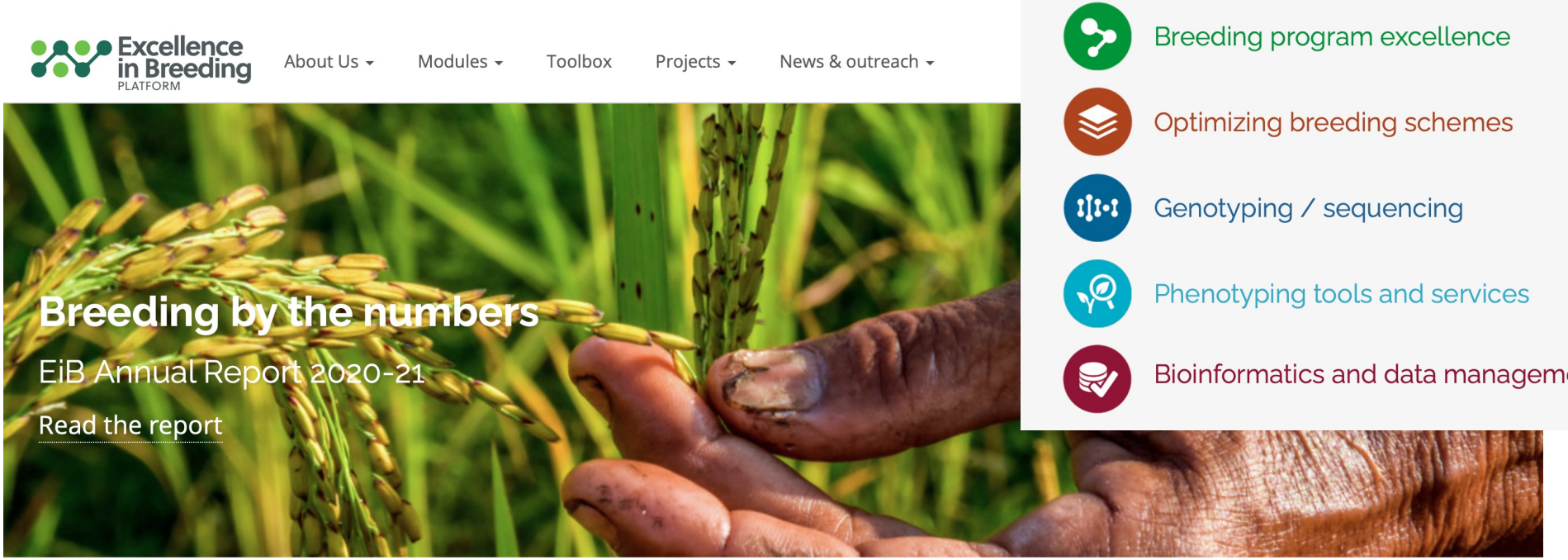









CGIAR - Excellence in Breeding Platform



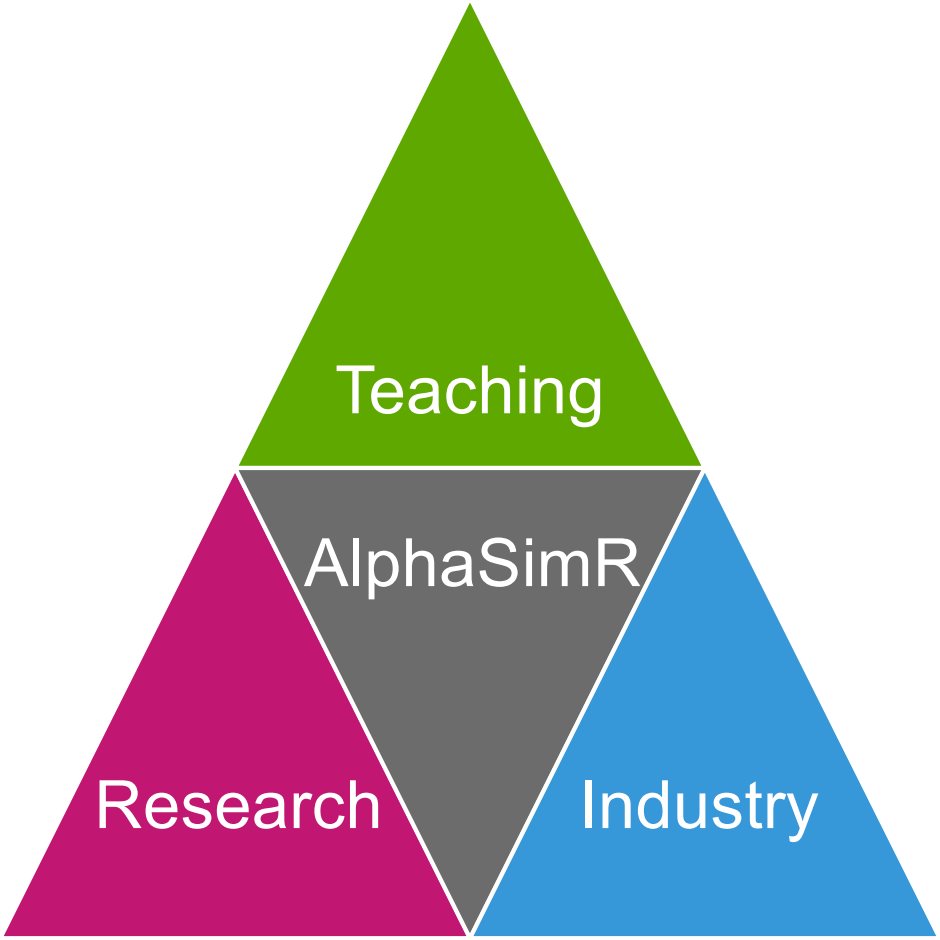
- Breeding program excellence
- Optimizing breeding schemes
- Genotyping / sequencing
- Phenotyping tools and services
- Bioinformatics and data management

CGIAR Excellence in Breeding (EiB) is accelerating the modernization of crop breeding programs that serve farmers in low- and middle-income countries. To combat hunger, poverty and climate change, farmers need diverse and **continually improving crop varieties.**

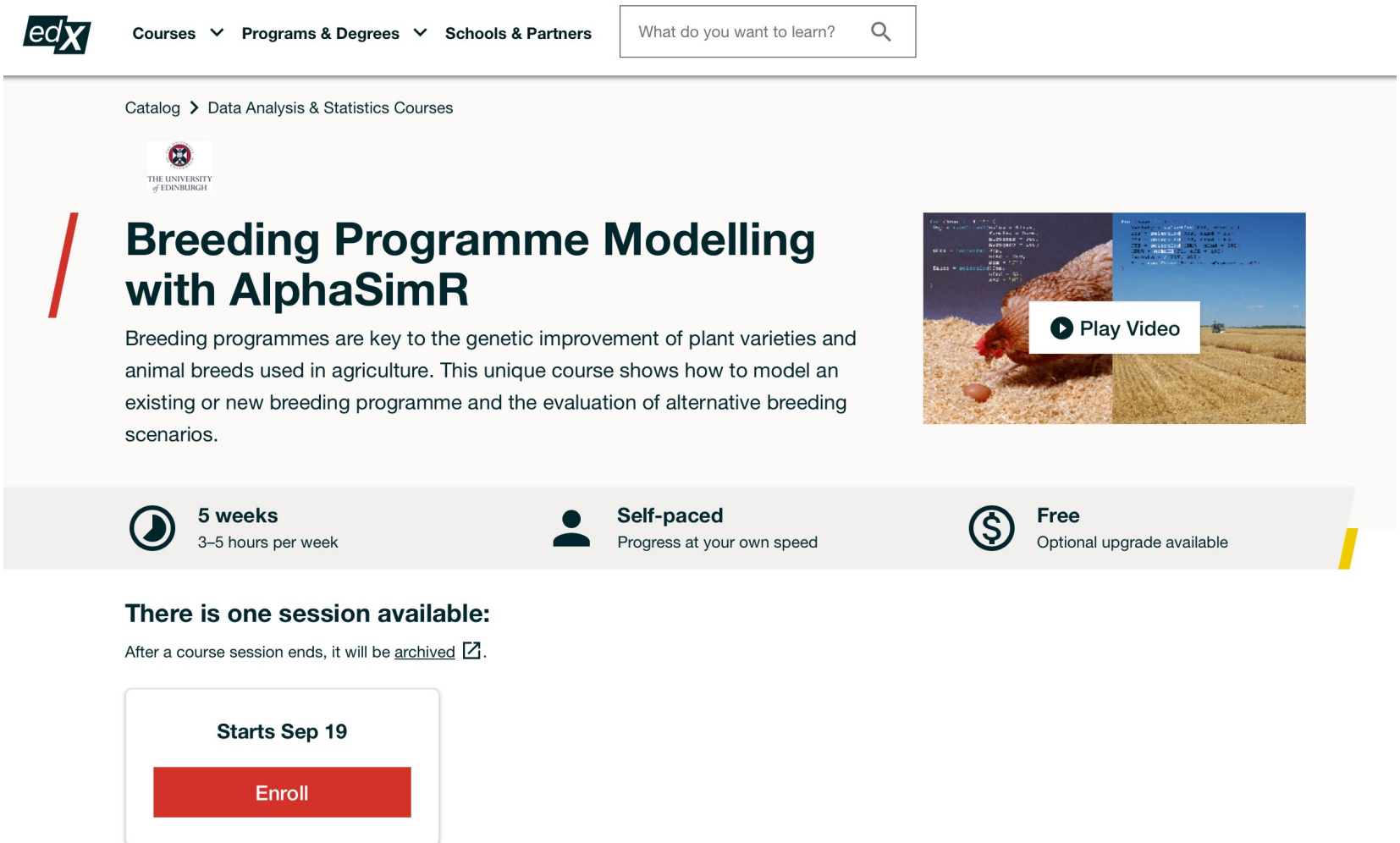
EiB provides system-level **coordination, shared services, expert guidance, resources, and access to cutting-edge innovations** to support CGIAR breeding programs to deliver on six funder requests.

CGIAR Excellence in Breeding Platform

AlphaSimR is our core tool!

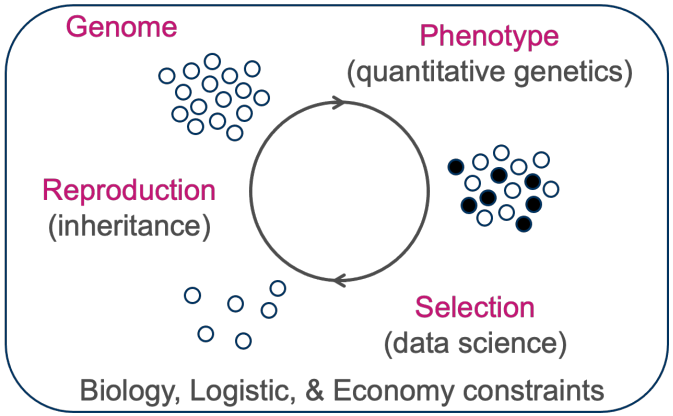


www.edx.org/course/breeding-programme-modelling-with-alphasimr



www.edx.org/course/breeding-programme-modelling-with-alphasimr

- 5 weeks, ~20h (with huge variance!)
  - Week 1: Introduction
  - Week 2: Simulation of DNA and traits
  - Week 3: DNA lottery
  - Week 4: Selection
  - Week 5: Complex breeding programmes



- Open “indefinitely” – share with colleagues & students

www.edx.org/course/breeding-programme-modelling-with-alphasimr

What is AlphaSimR?

- R package for stochastic simulation of genetics & breeding
- Two types of simulations
  - Stochastic (AlphaSimR and other fine simulators)
  - Deterministic
- Deterministic simulations are common
  - Breeder's equation
  - Optimizing multistage selection
  - Simple, until maths became unwieldy

Breeder's equation (R code)

```
# Deterministic simulation
h2 = 0.5
Va = 1
i = dnorm( qnorm(0.9) ) / 0.1 # top 10%
i * sqrt(h2) * sqrt(Va) # 1.240961

# Stochastic simulation
a = rnorm(10000, sd=1) # additive genetic values, Va = 1
e = rnorm(10000, sd=1) # environmental and non-additive genetic values
p = a + e # phenotype, h2 = 0.5
best = order(p, decreasing=TRUE)[1:1000] # top 10%
mean(a[best]) - mean(a) # ~1.240961
```

Why use stochastic simulation?

- Doesn’t require a deterministic formula
  - Long-term selection
  - Genomic prediction accuracy
  - Other complex processes

- Handles very complicated simulations
  - Whole breeding programs

Take home message no. 1

Stochastic simulations are cool and powerful!

Let’s whet your appetite!

- Genomic selection in wheat as an example
  - Template for our simulations
  - Example of interpreting results
  - Highlights strengths and weakness

Gaynor *et al.* (2017) A Two-Part Strategy for Using Genomic Selection to Develop Inbred Lines. Crop Science 57: 2372–2386.

Goal

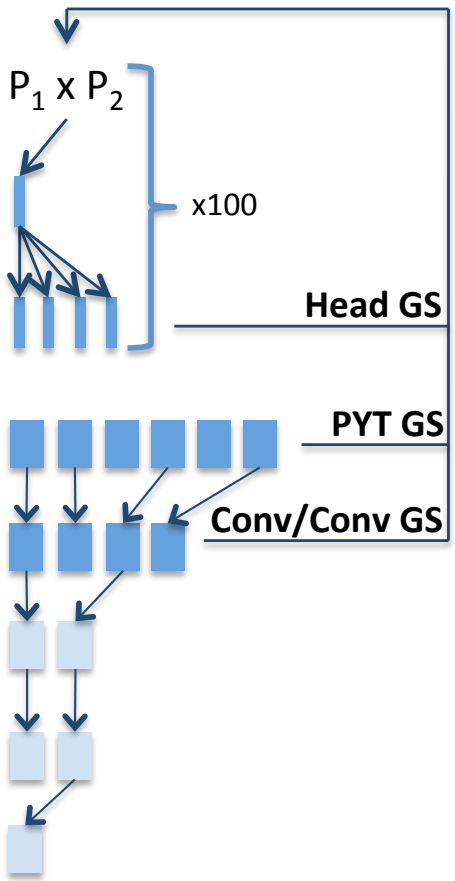
- Evaluate standard & novel approaches to genomic selection

- Two-part strategy for genomic selection
  - Splits breeding program into two components
    - Population improvement
    - Product development

- Compare against more standard designs
  - Two-part design is risky
  - Does potential justify the risk?

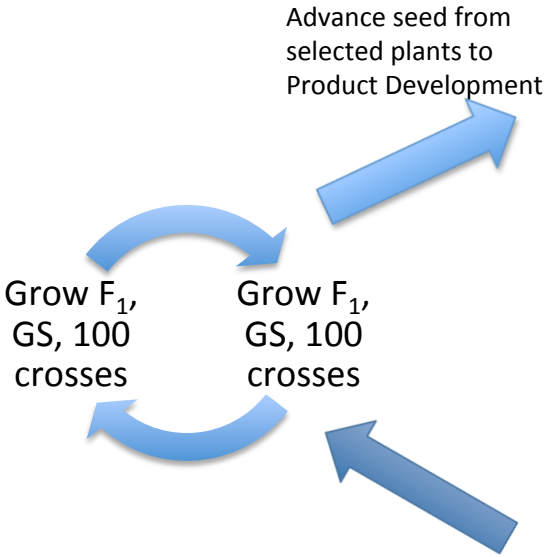
Traditional strategies

Year	Stage	Number of Plants	Action
1	Crossing	100 crosses	Make bi-parental crosses
1-2	F_1/DH	100 full-sib families	Produce DH lines
3	Headrows	100 x $N^{\dagger}$ DH lines	Advance 500 lines, genotype/cross (**Head GS**)
4	PYT	500 DH lines	Yield trial, genotype/cross (**PYT GS**)
5	AYT	50 DH lines	Yield trial, cross (**Conv**), genotype/cross (**Conv GS**)
6	EYT	10 DH lines	Yield trial
7	EYT	10 DH lines	Yield trial
8	Variety	1 DH line	Release variety

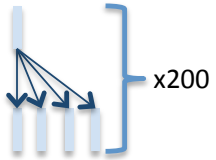
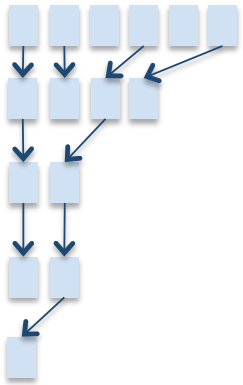


Two-part strategy

Population Improvement



Product Development

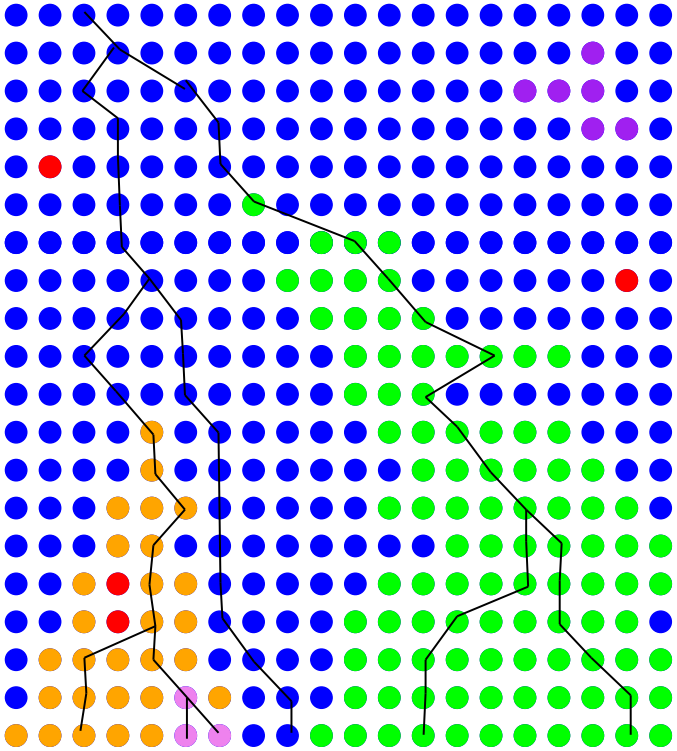
Year	Stage		Number of Plants	Action
1-2	F_1/DH		200 half-sib families	Produce DH lines
3	Headrow		200 x N^+ DH lines	Advance 500 lines, genotype (**2Part+H**)
4	PYT		500 DH lines	Yield trial, genotype (**2Part**)
5	AYT		50 DH lines	Yield trial
6	EYT		10 DH lines	Yield trial
7	EYT		10 DH lines	Yield trial
8	Variety		1 DH line	Release variety

Basic simulation scheme

1. **Coalescent simulation (MaCS)**
   - Backward-in-time
   - Model species' genome

Backward-in-time simulation of DNA

Backward-in-time stochastic process
("progeny choose their parent chromosomes" → coalescent)



AlphaSimR uses
MaCS (SMC algorithm)

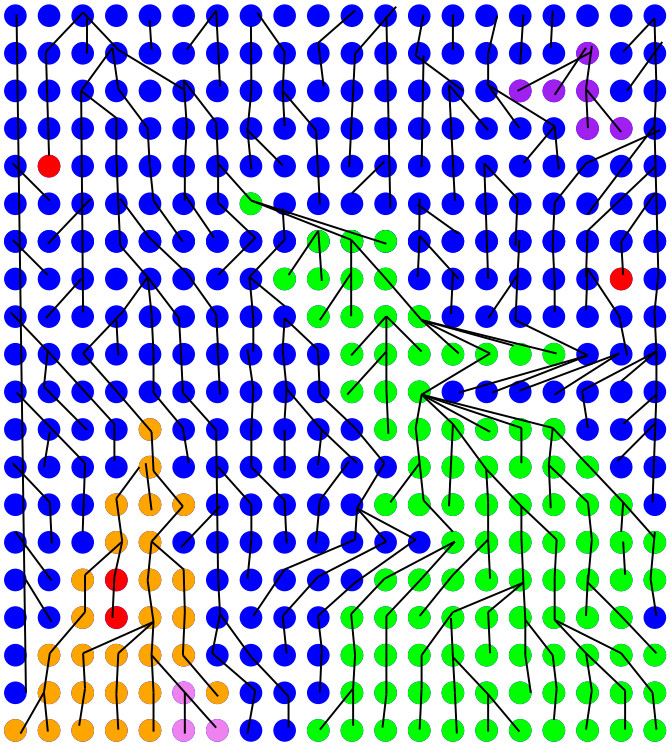
Basic simulation scheme

1. **Coalescent simulation (MaCS)**
   - Backward-in-time
   - Model species' genome

2. **Gene drop simulation (AlphaSimR)**
   - Forward-in-time
   - Model traits and genetic recombination
   - Model breeding programs

Forward-in-time simulation of DNA

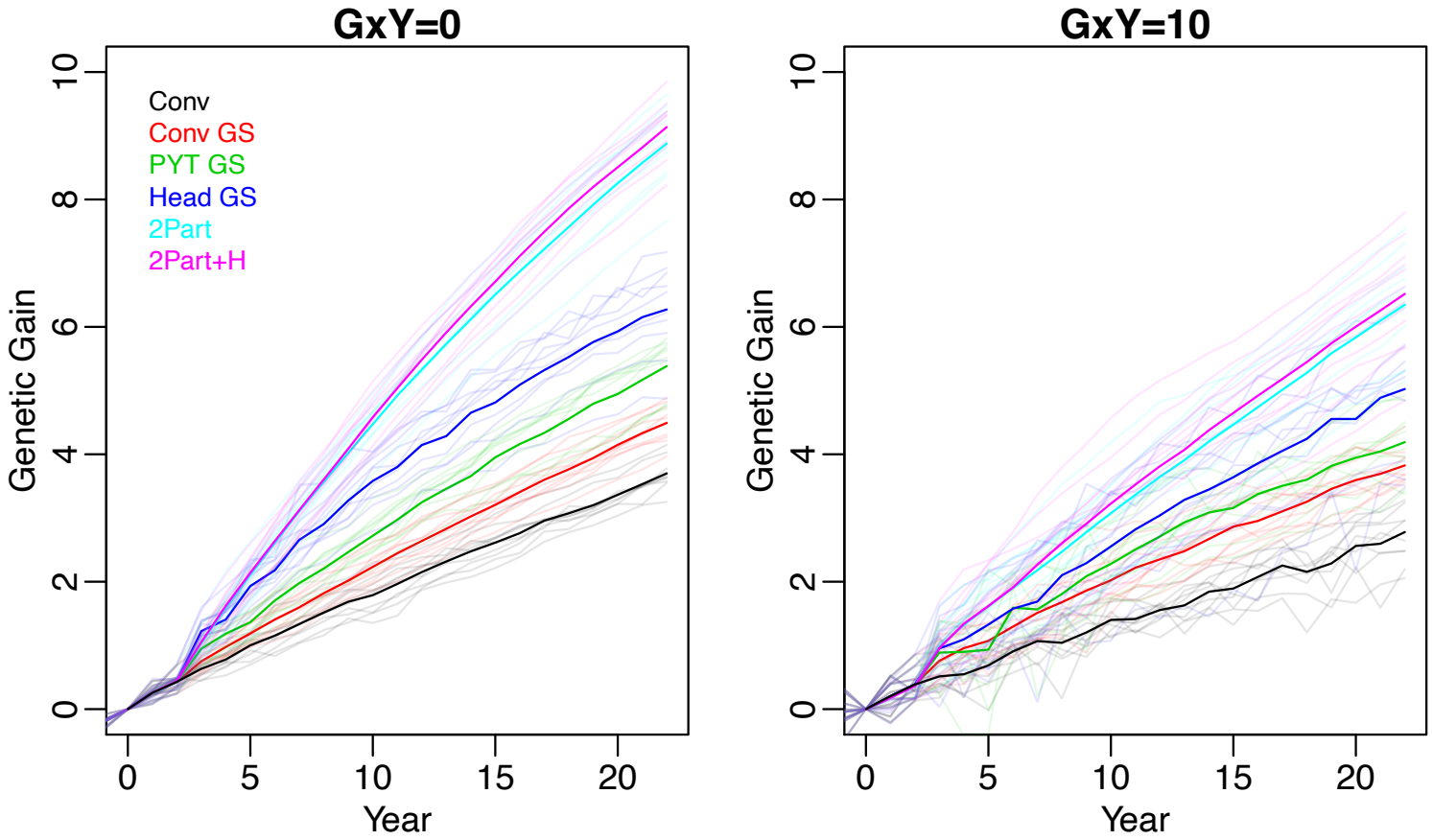
Forward-in-time stochastic process
("parents transmit chromosomes to their progeny")



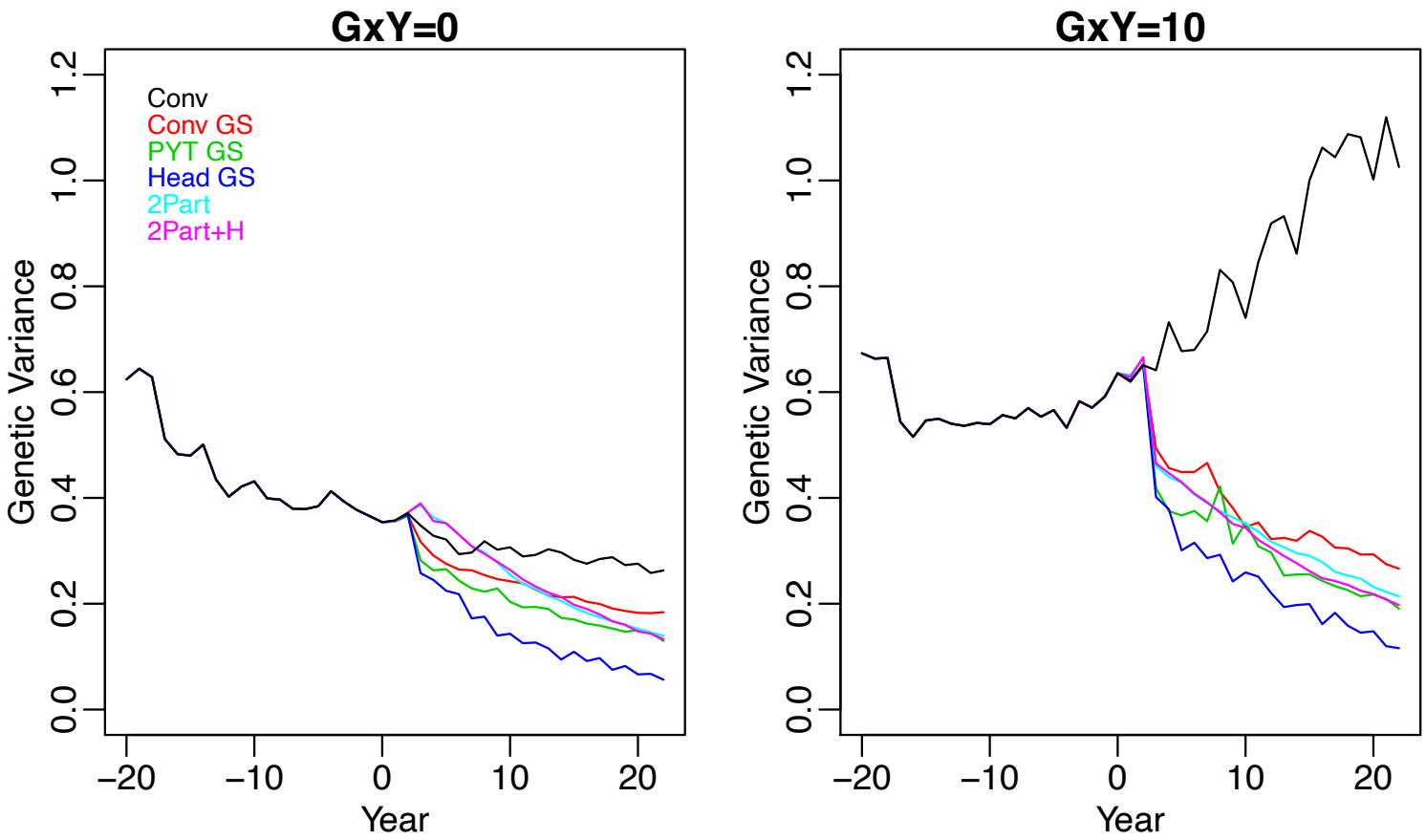
Detailed simulation scheme

	Simulation Stage	Key Features
Burn-in	Genome Sequence	100,000 generations of evolution Wheat historical effective population size 21 chromosome pairs 1.43 Morgans per chromosome $8x10^{8}$ base pairs per chromosome $2x10^{-9}$ mutation rate
	Founder Genotypes	50 inbred founders 21,000 SNP markers 21,000 QTN Normally distributed QTN effects
	Recent Breeding	20 years of modern breeding (-19 to 0) Double haploid lines No genomic selection
Evaluation	Future Breeding	20 years of breeding (1 to 20) Testing alternative breeding programs Equal cost programs Ridge regression for genomic selection

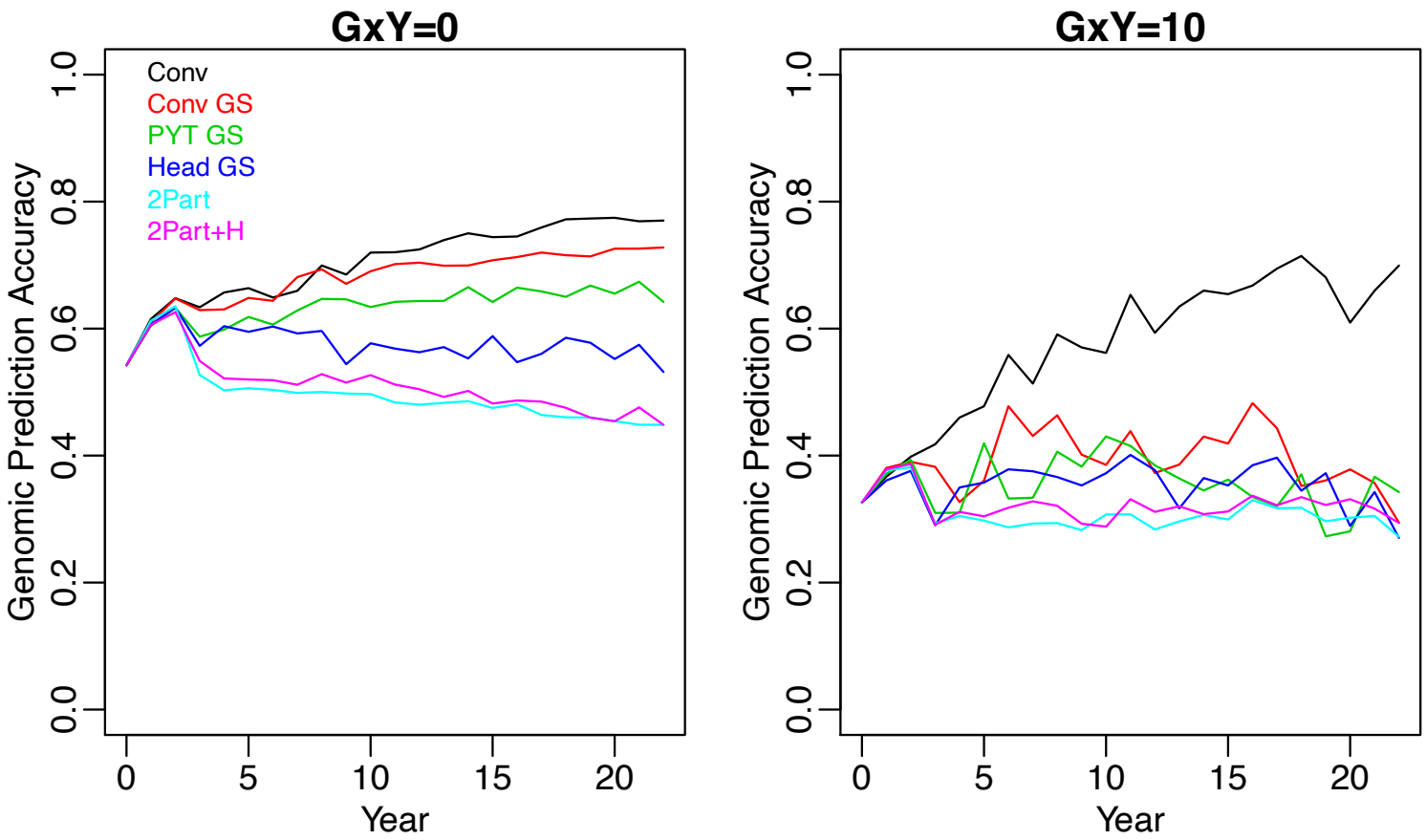
Genetic gain



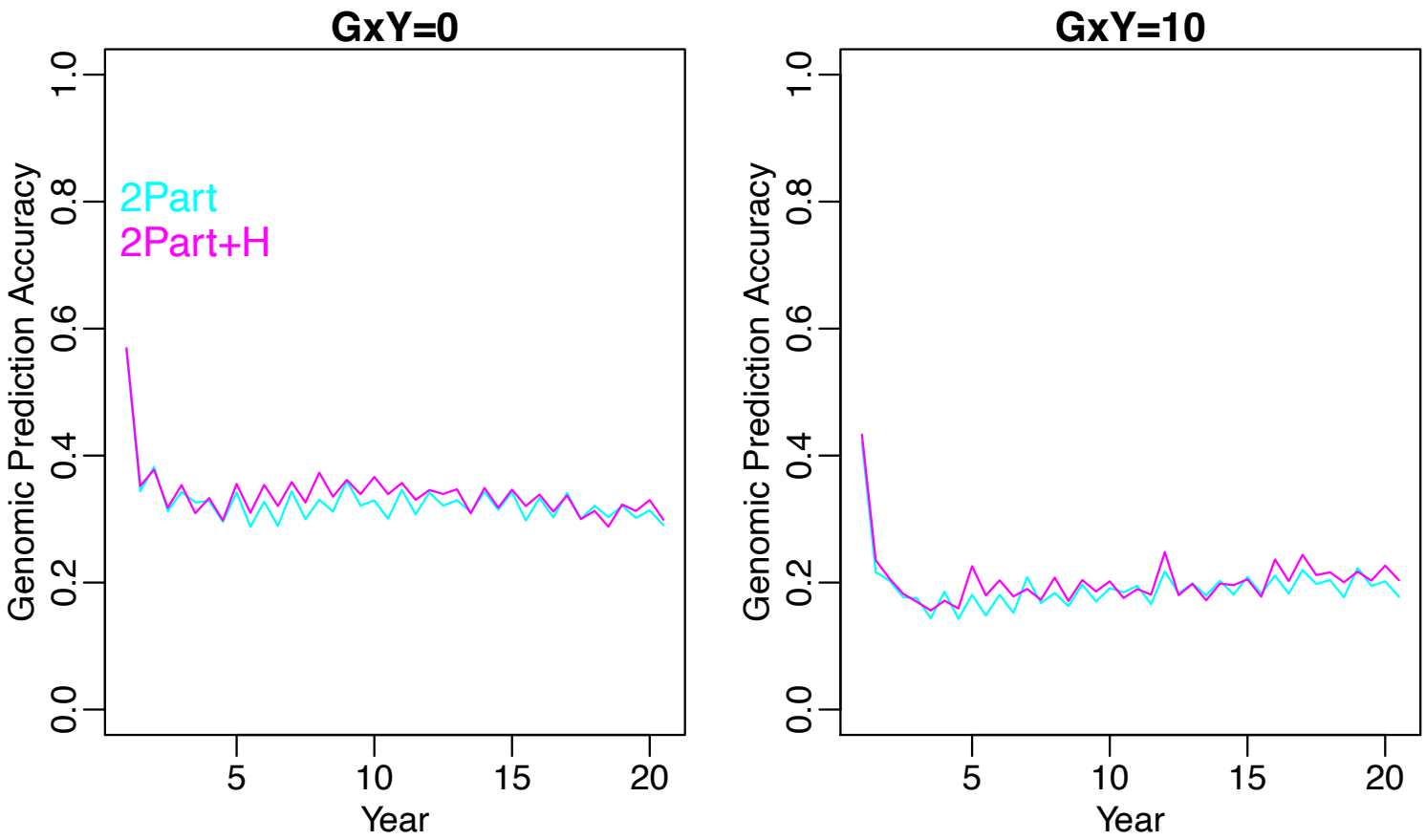
Genetic variance



GS accuracy, headrows



GS accuracy, population improvement



Main messages

- Reducing cycle time is key
  - 2-Part(+H) > Head GS > PYT GS > Conv GS
- Genomic selection can improve accuracy
  - Conv GS > Conv
- Genomic selection accuracy can rapidly decay
  - Primary limiter of two-part methods

Limitations

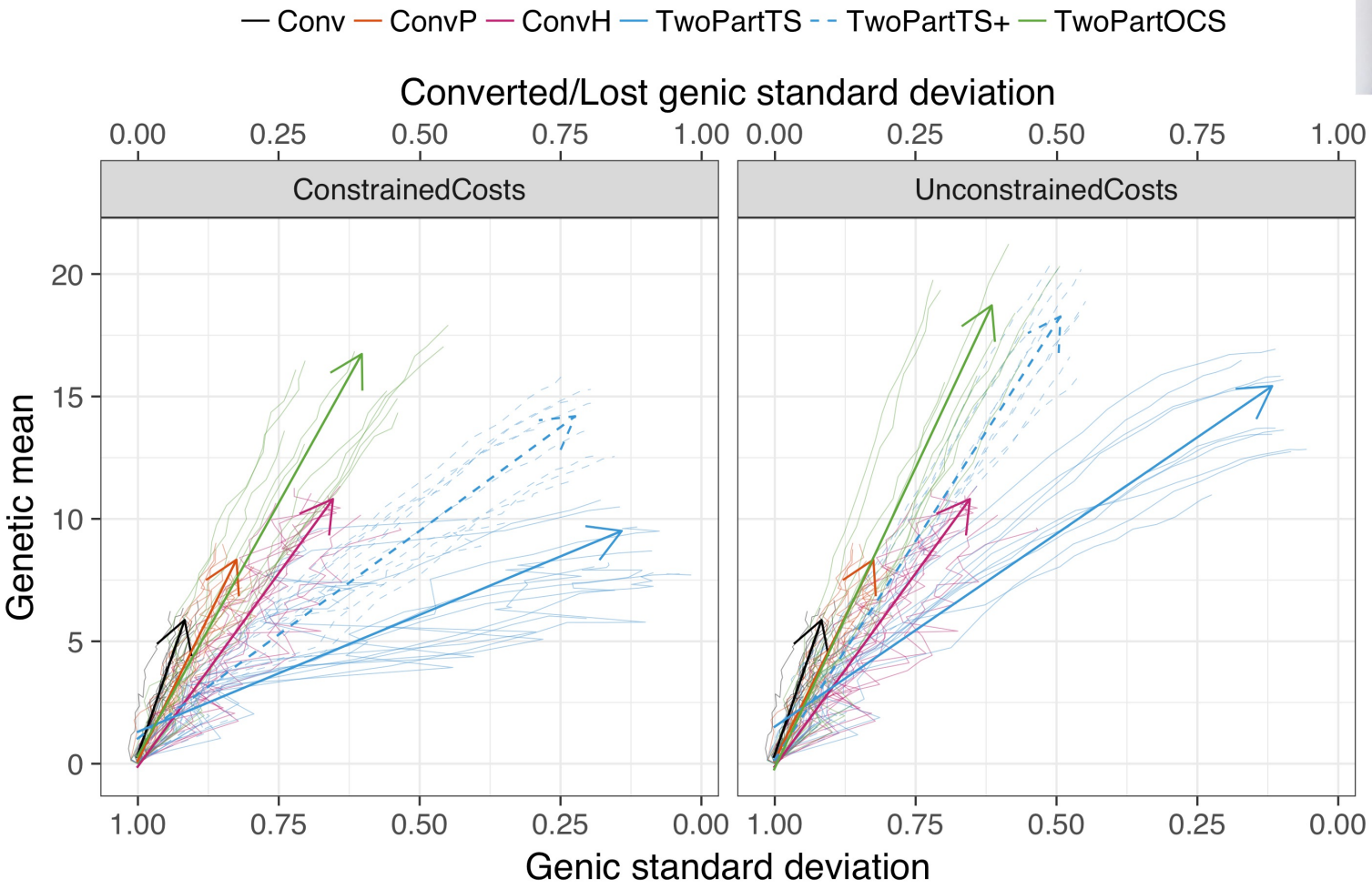
- Simple trait model
  - High genomic selection accuracy and persistence
- Only one trait (yield)
- Open questions
  - Germplasm exchange
  - Conservation of diversity
  - Lots of fine tuning

Suggestions

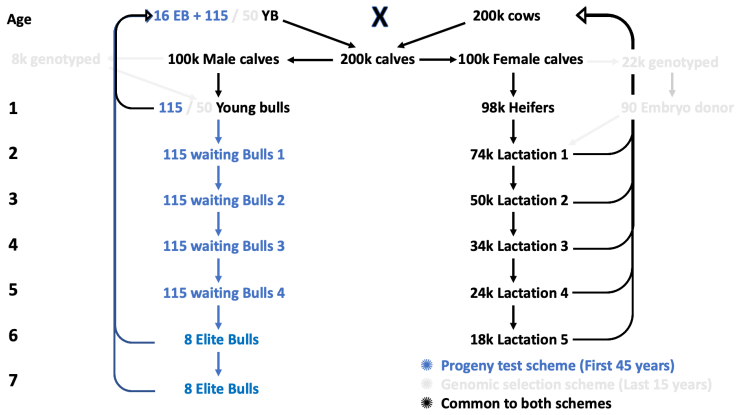
- Focus on reducing cycle time
  - Main driver of genetic gain

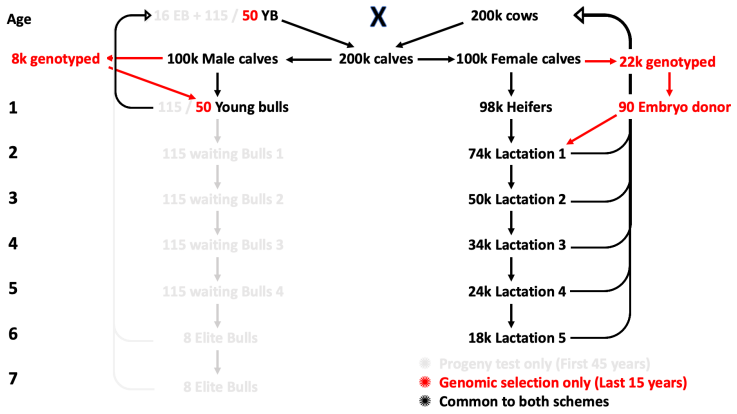
- Phased deployment of two-part strategy
  - Build infrastructure
  - Gain confidence
  - Mitigate risks

Example: Balancing selection & diversity

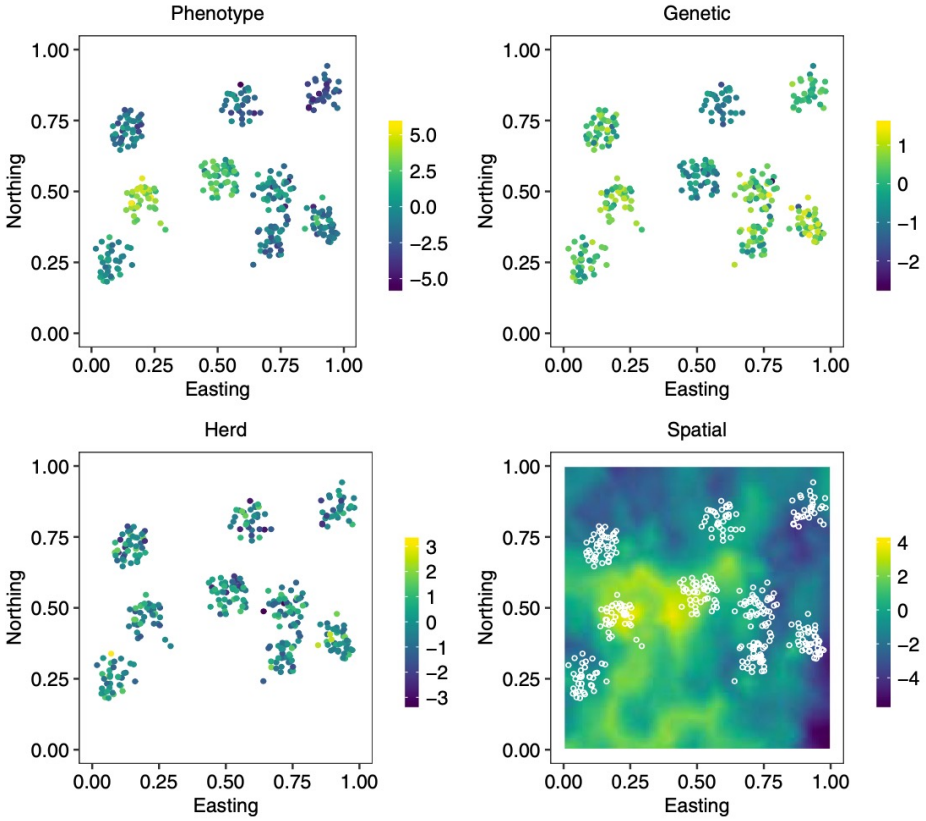


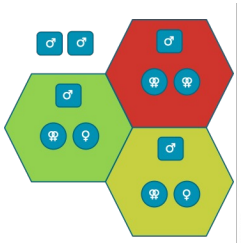
Example: Dairy cattle breeding programme

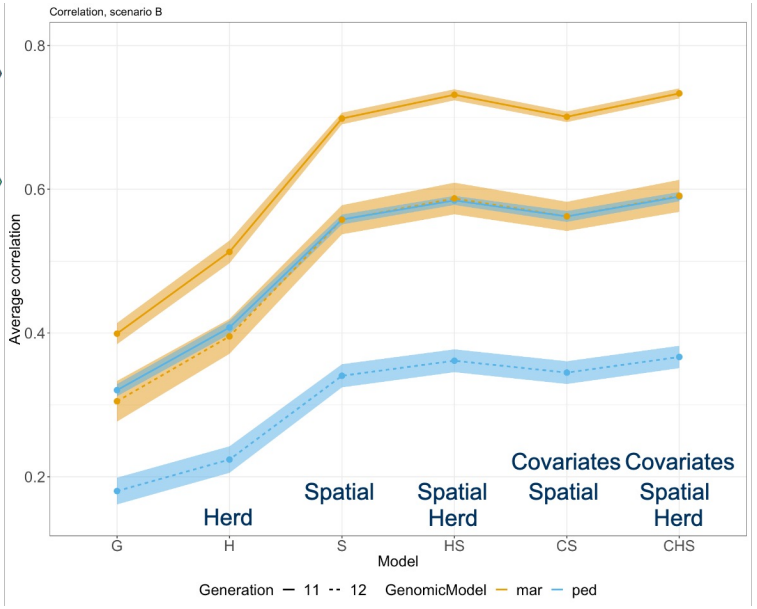




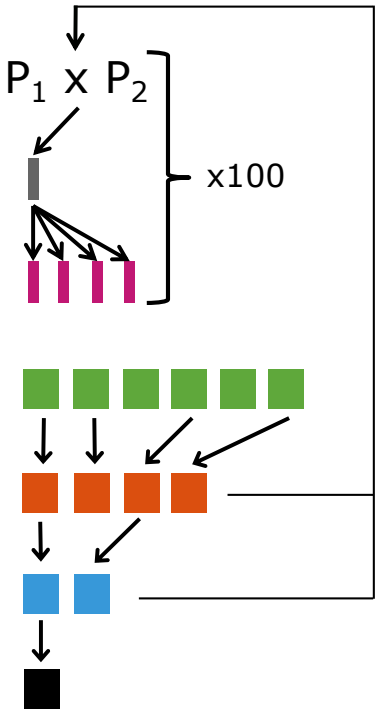
Example: Spatial modelling & smallholders

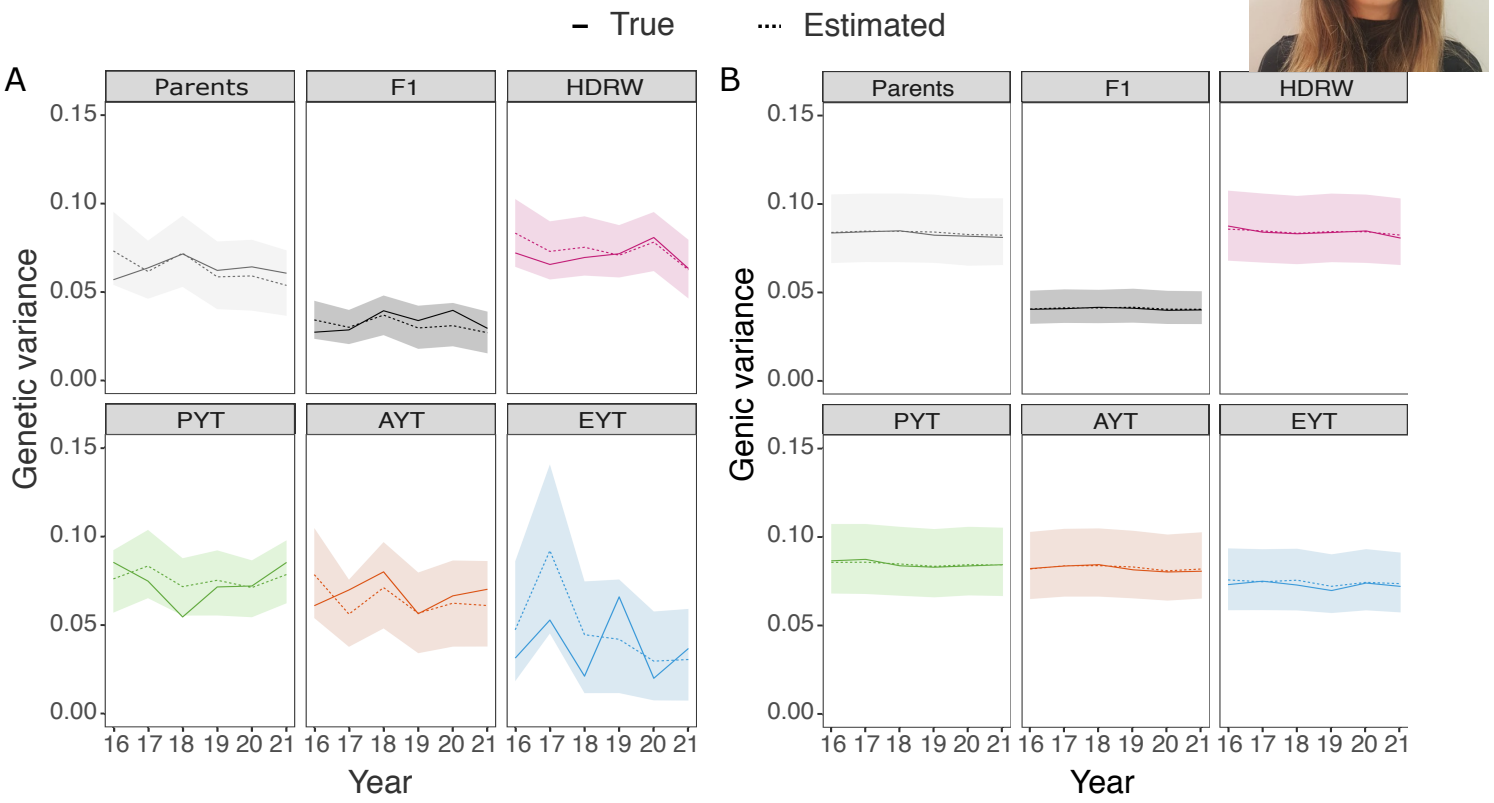




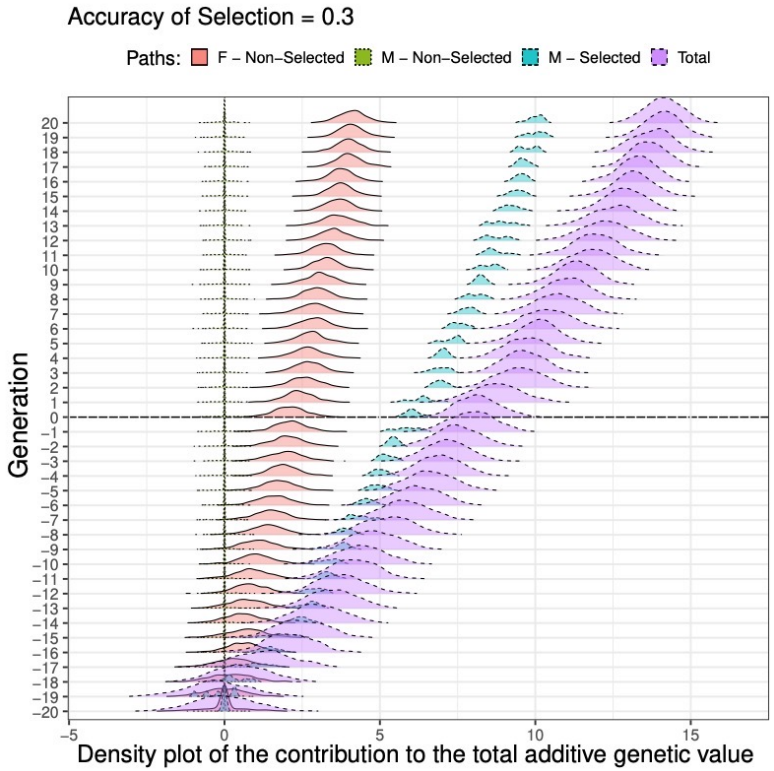


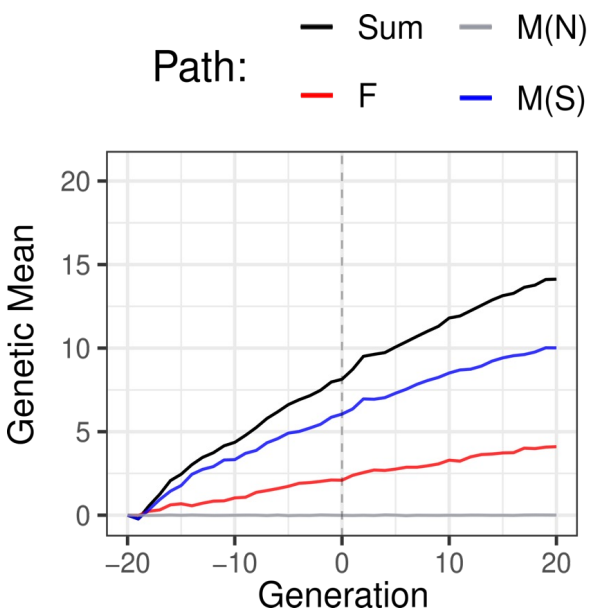
Example: Analysis of genetic variance

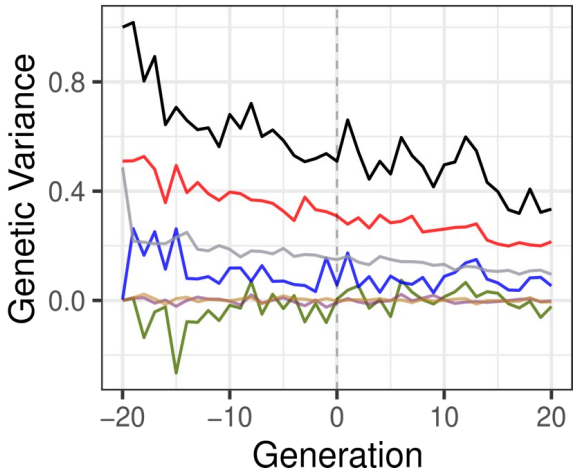




Example: Partitioning genetic trends





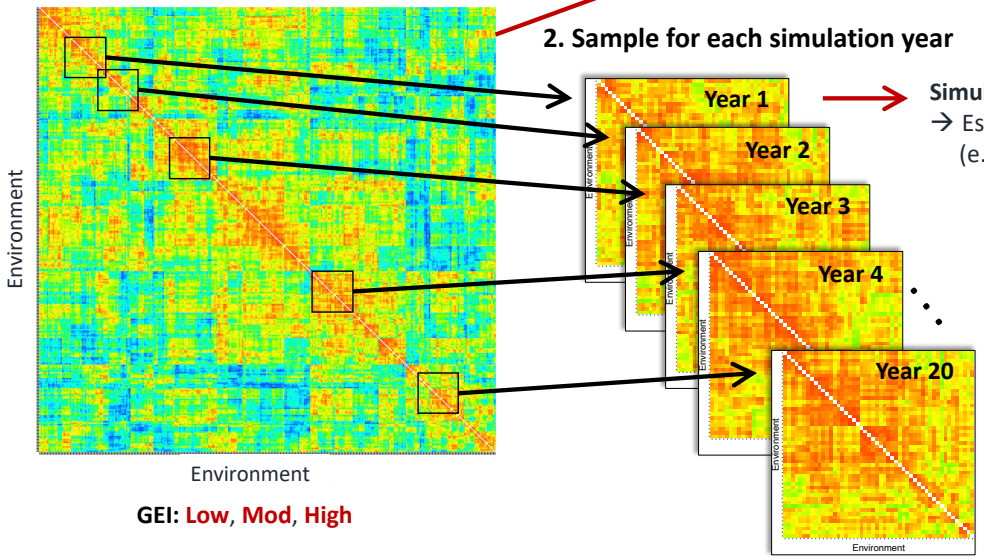


Example: GxE simulations

Simulation of TPE genetic effects
→ True performance

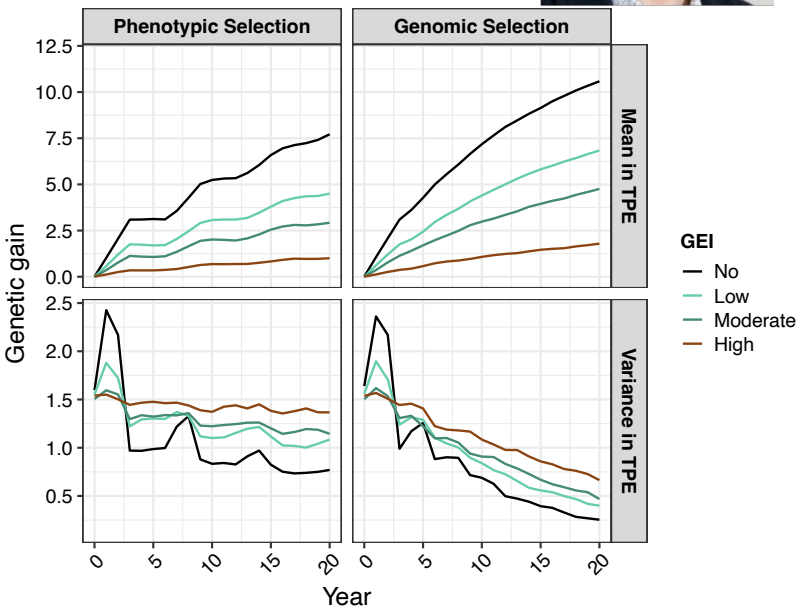
1. **Simulate 1000 x 1000 TPE**
   (constant across simulation reps)

2. Sample for each simulation year



Simulation of MET genetic effects
→ Estimated/observed performance
(e.g. Stage 1 ~ 1 env,
Stage 4 ~ 20 env)

GEI: Low, Mod, High



Example: Honey bee extension

Creating a colony

Founder Genomes → `SimParamBee$new()` → Simulation Parameters

`createVirginQueens()`

`createDrones()` `createDrones()`

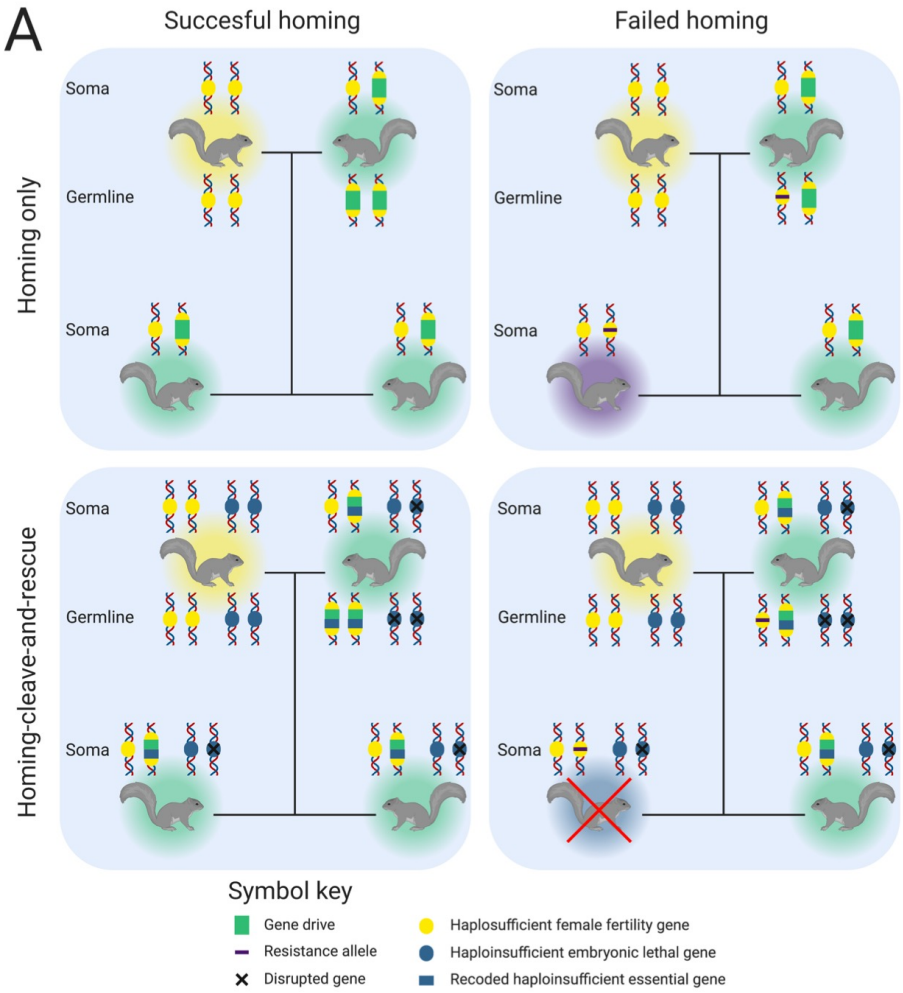
nInd nInd

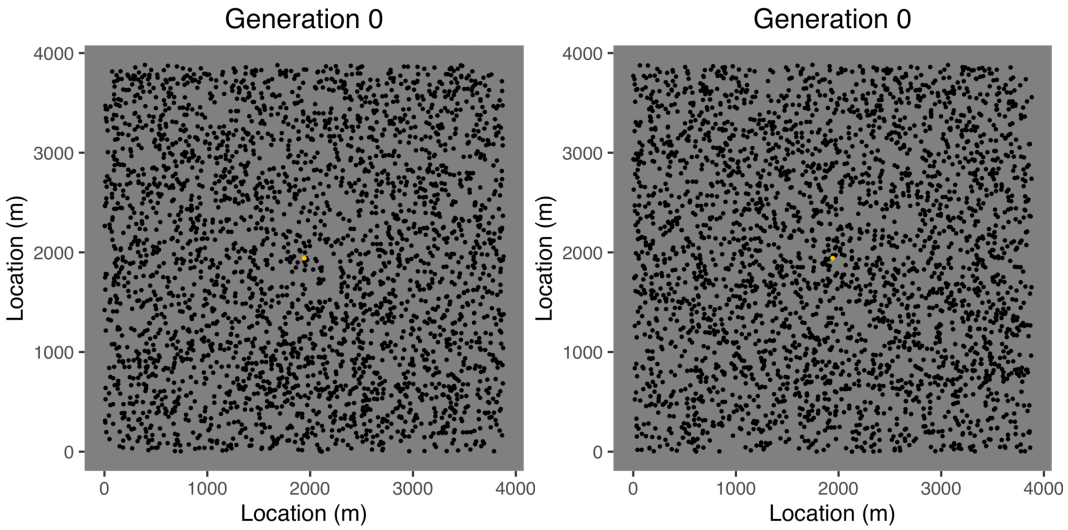
`cross()`

1 → `createColony()` → 1 0 0 0 → `buildUp()` → 1 nW nD 0

- Colony
- Mated queen
- Worker
- Drone
- Virgin queen
- nW — Number of workers
- nD — Number of drones
- p — Proportion of workers
- `function()`
- Drone congregation area
- Virgin queen population

Example: Gene drives in gray squirrels





Take home message no. 2

Stochastic simulations support development of new breeding programs / methods / theory / …!

AlphaSimR's strengths

- Very flexible
  - Not limited to preset designs
  - Access to inner workings
- Fast
  - Leverages modern computing techniques
- Alignment with classic quantitative genetics
  - Strong foundations
  - Genetic effects, values, and variance components

AlphaSimR's weaknesses

- Limitations of all simulations
  - Simplified versions of reality
- Moderate learning curve
  - Designed for scripters
  - Limited documentation of complex tasks
- Output on demand
  - Must rerun simulations if you forget something

AlphaSimR hands-on

- All examples will use R Markdown
  - We'll briefly explain how they work

- We will work through R Markdown files in folder
  - `Day_1_Intro_AlphaSimR`
    - `01Practical_DNA`
    - `02Practical_Selection`
    - `03Practical_Breeding program`

Questions?!

Other fine simulators

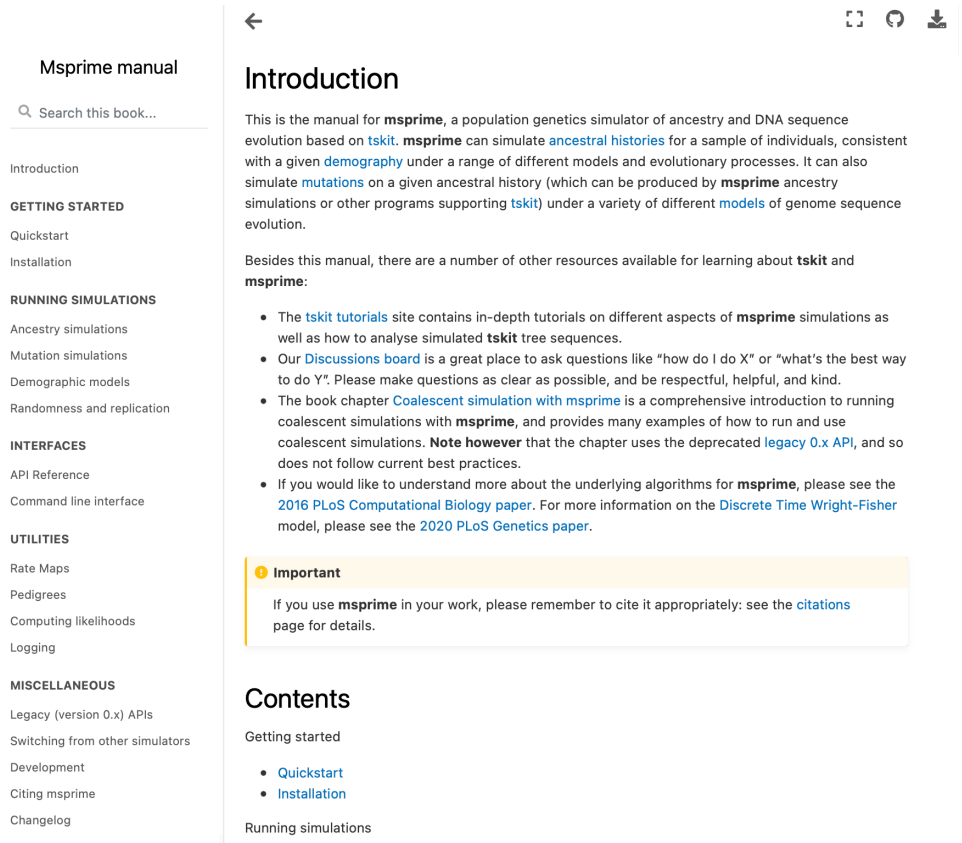
- MoPBS (R) – a competitor!
- PyBrOpS & ChromaX (Python)
- XSim & GEAS (Julia)
- Many other fine simulators!

→ Spend time on a few more or contribute to the existing? ;)

- msprime (Python/C)
- SLiM (Eidos/C++)
- stdpopsim (Python)

msprime (backward-in-time simulator)

https://pypi.org/project/msprime



Msprime manual

Search this book...

Introduction

This is the manual for **msprime**, a population genetics simulator of ancestry and DNA sequence evolution based on tskit. **msprime** can simulate ancestral histories for a sample of individuals, consistent with a given demography under a range of different models and evolutionary processes. It can also simulate mutations on a given ancestral history (which can be produced by **msprime** ancestry simulations or other programs supporting tskit) under a variety of different models of genome sequence evolution.

Besides this manual, there are a number of other resources available for learning about **tskit** and **msprime**:

- The tskit tutorials site contains in-depth tutorials on different aspects of **msprime** simulations as well as how to analyse simulated **tskit** tree sequences.
- Our Discussions board is a great place to ask questions like "how do I do X" or "what's the best way to do Y". Please make questions as clear as possible, and be respectful, helpful, and kind.
- The book chapter Coalescent simulation with msprime is a comprehensive introduction to running coalescent simulations with **msprime**, and provides many examples of how to run and use coalescent simulations. **Note however** that the chapter uses the deprecated legacy 0.x API, and so does not follow current best practices.
- If you would like to understand more about the underlying algorithms for **msprime**, please see the 2016 PLoS Computational Biology paper. For more information on the Discrete Time Wright-Fisher model, please see the 2020 PLoS Genetics paper.

Important

If you use **msprime** in your work, please remember to cite it appropriately: see the citations page for details.

Contents

Getting started

- Quickstart
- Installation

Running simulations

SLiM (forward-in-time simulator)

https://messerlab.org/slim

About SLiM

SLiM is an evolutionary simulation framework that combines a powerful engine for population genetic simulations with the capability of modeling arbitrarily complex evolutionary scenarios. Simulations are configured via the integrated Eidos scripting language that allows interactive control over practically every aspect of the simulated evolutionary scenarios. The underlying individual-based simulation engine is highly optimized to enable modeling of entire chromosomes in large populations. We also provide a graphical user interface on macOS, Linux, and Windows, for easy simulation set-up, interactive runtime control, and dynamical visualization of simulation output.

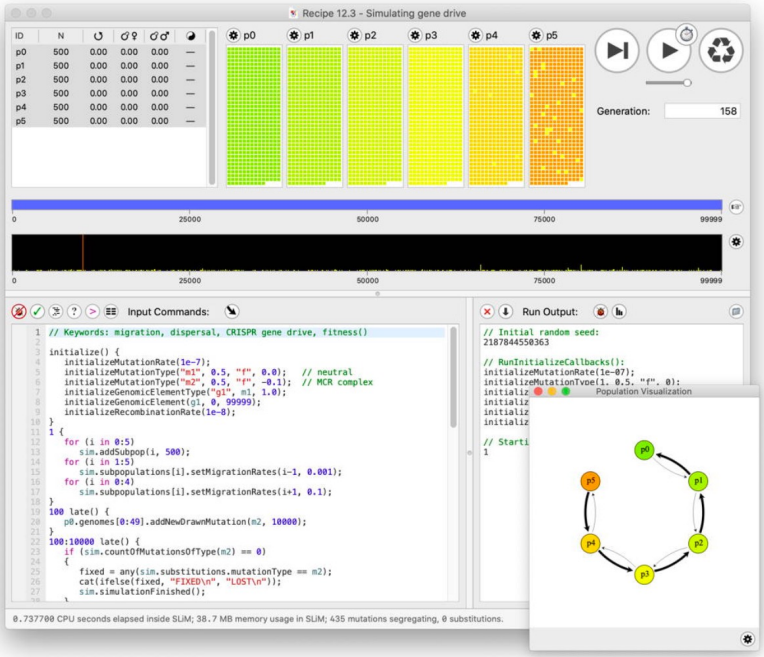
A 4–5 day SLiM Workshop is now available online. The SLiM Workshop is also offered in person from time to time; see the SLiM Workshops subsection below for more information.

Downloads (version 4.0.1)

macOS Installer | Source Code | SLiM Manual | Eidos Manual | Ref Sheets

SLiMgui

With the SLiMgui graphical modeling environment (compatible with macOS, Linux, and Windows), you can visualize your simulation as it runs and examine its parameters in real-time, allowing for much easier simulation development.

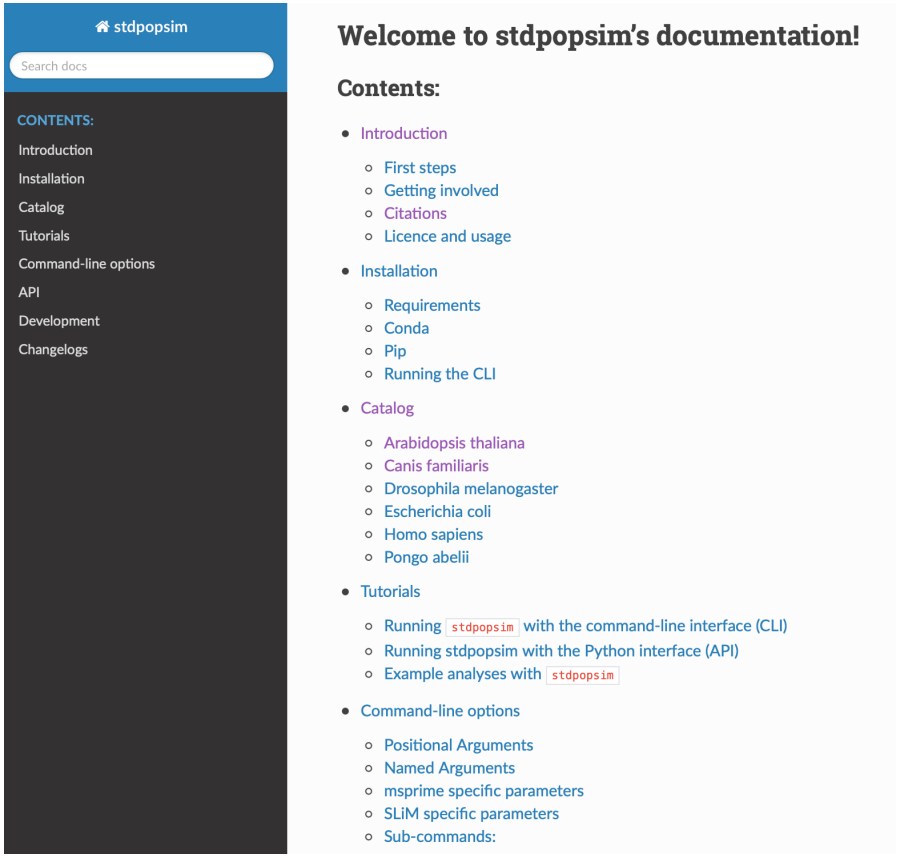


stdpopsim (standard population genetics library)

https://pypi.org/project/stdpopsim

Frontend for:

- msprime
- SLiM



Take home message no. 3

AlphaSimR is cool & there are additional fine genetics simulators!

Takeaways

- Learning objectives
  - Introduce the concept of breeding simulations
  - Differentiate deterministic and stochastic simulations
  - Showcase one AlphaSimR simulation
  - Differentiate backward- & forward-in-time simulations

- Take home messages
  - Stochastic simulations are cool and powerful!
  - Stochastic simulations support development of new breeding programs / methods / theory / …!
  - AlphaSimR is cool & there are additional fine genetics simulators!

Questions?!

Introduction to simulations of breeding programmes

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2024-02-05