Genome editing in livestock breeding programs: opportunities and challenges

John Bastiaansen

Henk Bovenhuis

Han Mulder

Wild type

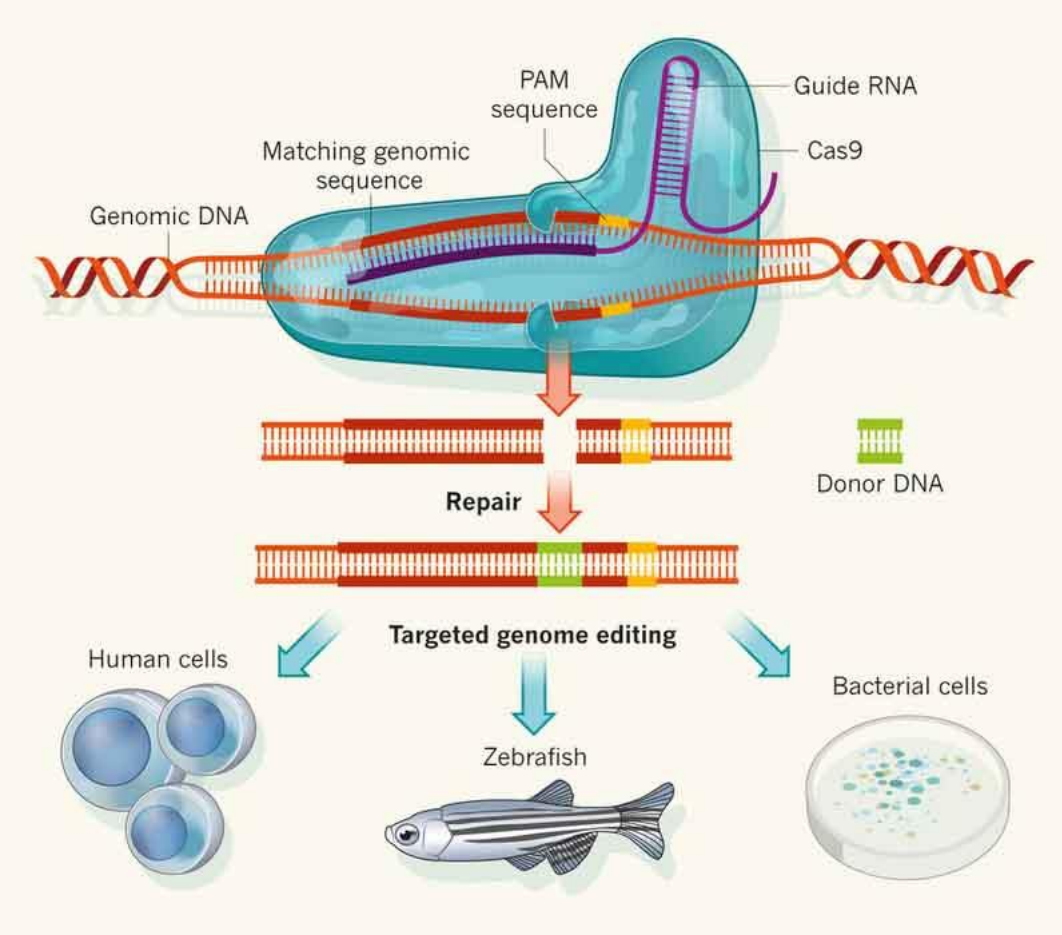
Polled variant

WAGENINGEN
UNIVERSITY & RESEARCH

BREED4FOOD

What is gene editing?

- Precise insertion, deletion or replacement of DNA using ‘molecular scissors’
- CRISPR-CAS9
- TALEN
- Zinc-fingers



WAGENINGEN
UNIVERSITY & RESEARCH

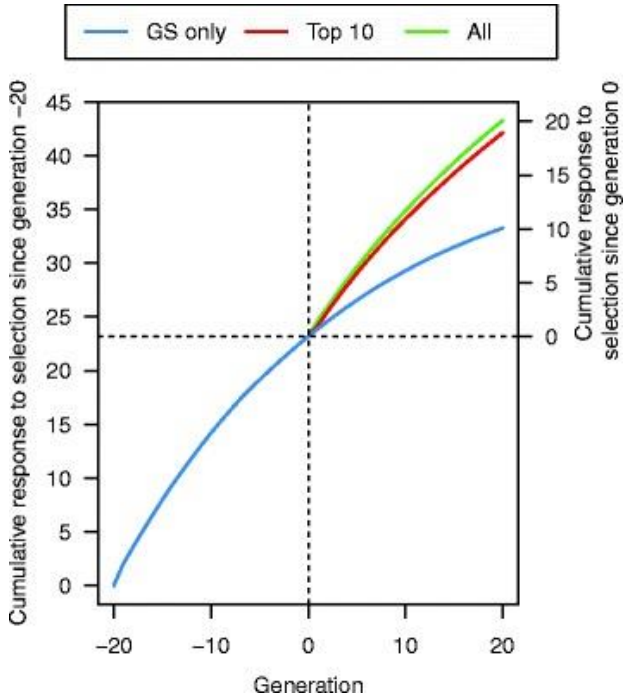
Applications in livestock breeding programs

- A gene variant is present at a very low frequency in the population or in other breeds
- A gene variant is not present in species, but present in other species
- A gene variant is unknown, but based on biological knowledge may affect trait of interest
- To enhance genetic improvement for quantitative traits

Genome editing to enhance genetic improvement for quantitative traits

- Aim in animal breeding is to improve profit
  - Increase production efficiency
  - Increase health and welfare traits
- Use of DNA markers = genomic selection

- Jenko et al. 2015 (GSE 47:55)
  - 1.08x – 4.12x more response



WAGENINGEN
UNIVERSITY & RESEARCH

Genome editing to enhance genetic improvement for quantitative traits

- Many, many genes are responsible for quantitative traits
  - >1000
- Very few causative variants are known
- Very little known about interplay between genes
- Which genes to be edited?????

Increasing polledness by genome editing and breeding for profit

Wild type

polled variant

Gene editing using TALEN

Carlson et al. (2016) Nature Biotech. 34, 479–481

WAGENINGEN
UNIVERSITY & RESEARCH

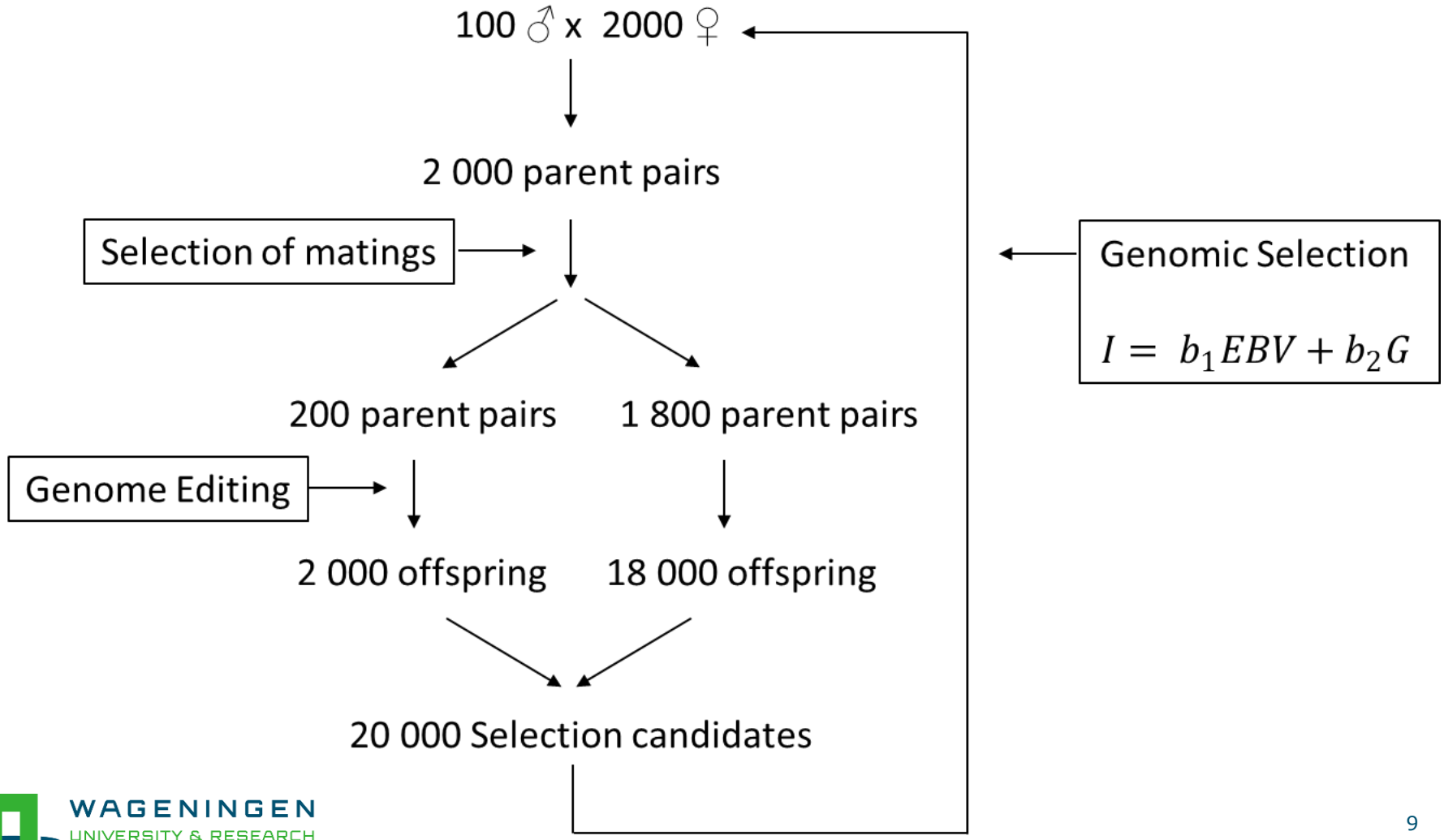
Objectives

- Investigate genome editing in livestock breeding using simulation
  - Monogenic trait (polledness in cattle)
  - Polygenic trait (profit)

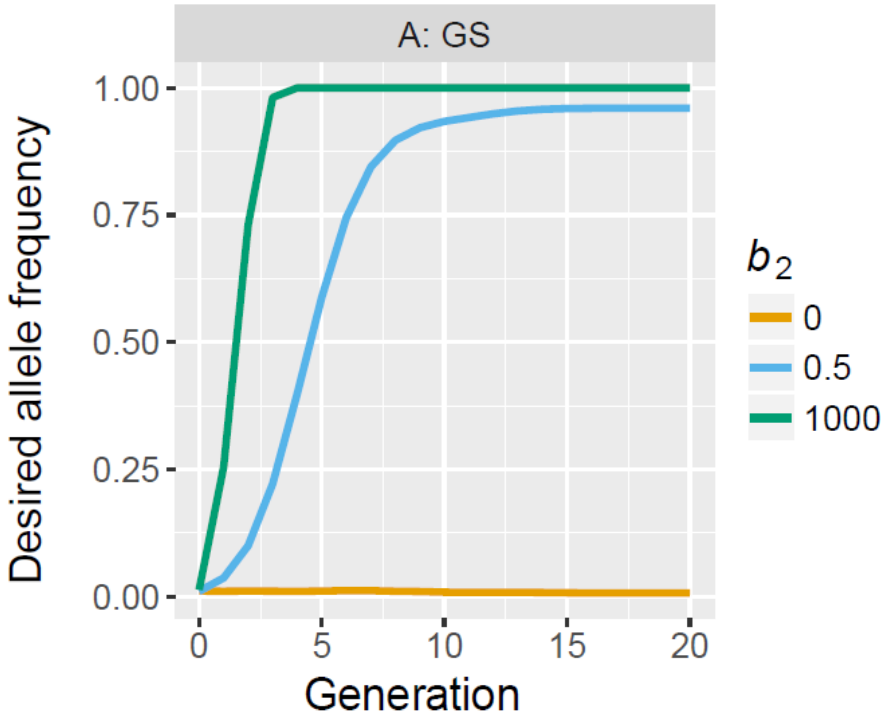
Approach

- Compare scenarios with and without genome editing
  - Allele frequency polledness
  - Genetic gain in profit
  - Rate of inbreeding
  - Cost-benefit analysis
    - Number of zygotes edited
    - Number of animals that are polled

Simulation

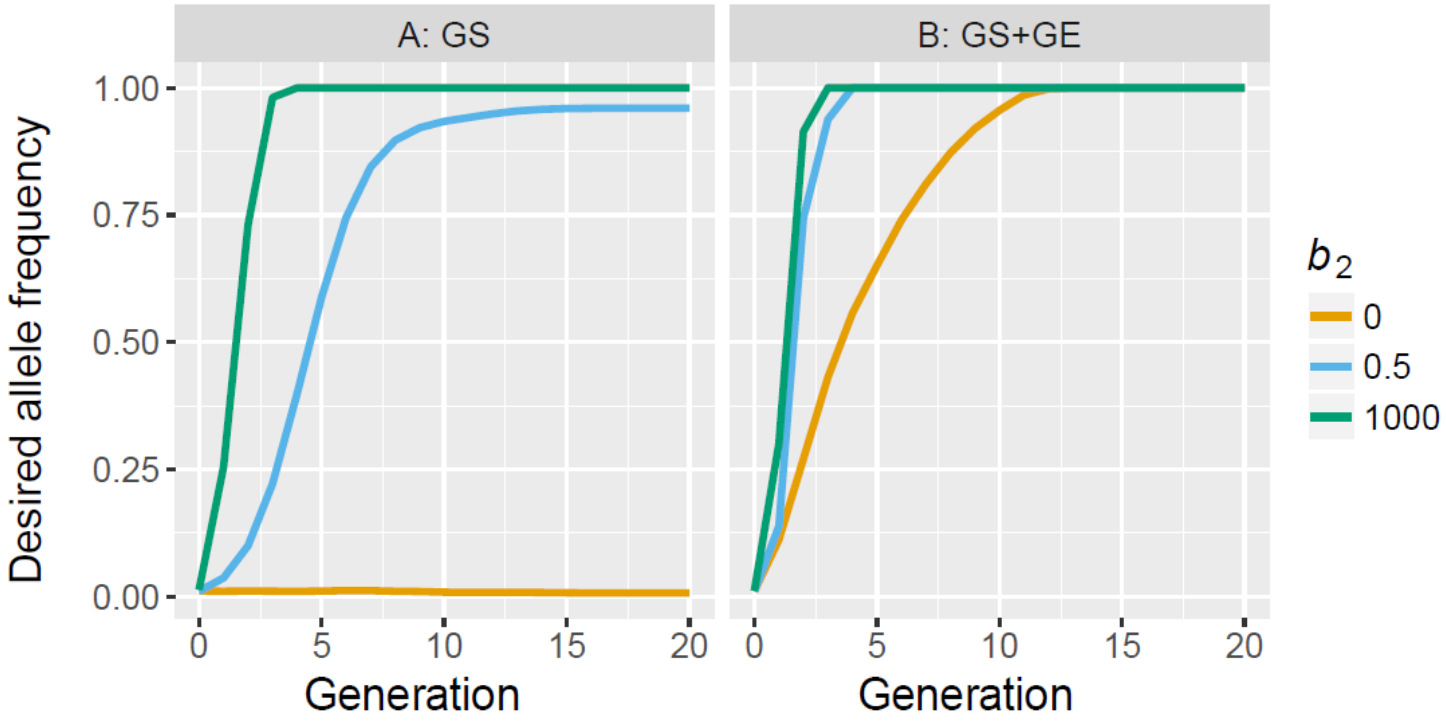

100 ♂ x 2000 ♀
2 000 parent pairs
Selection of matings
Genomic Selection
$I = b_1 EBV + b_2 G$
200 parent pairs
1 800 parent pairs
Genome Editing
2 000 offspring
18 000 offspring
20 000 Selection candidates

Monogenic allele frequency

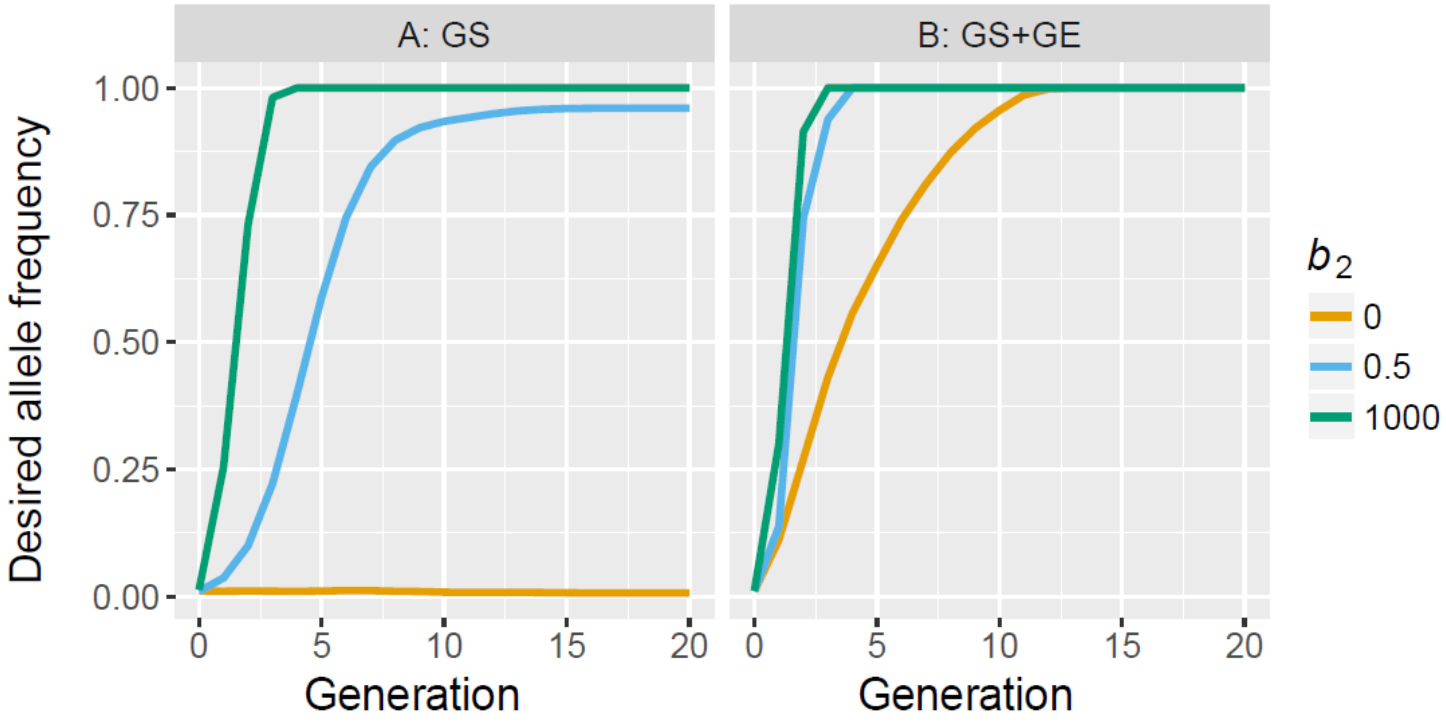


- $I = b_1 EBV + b_2 G$
- No genome editing

Monogenic allele frequency

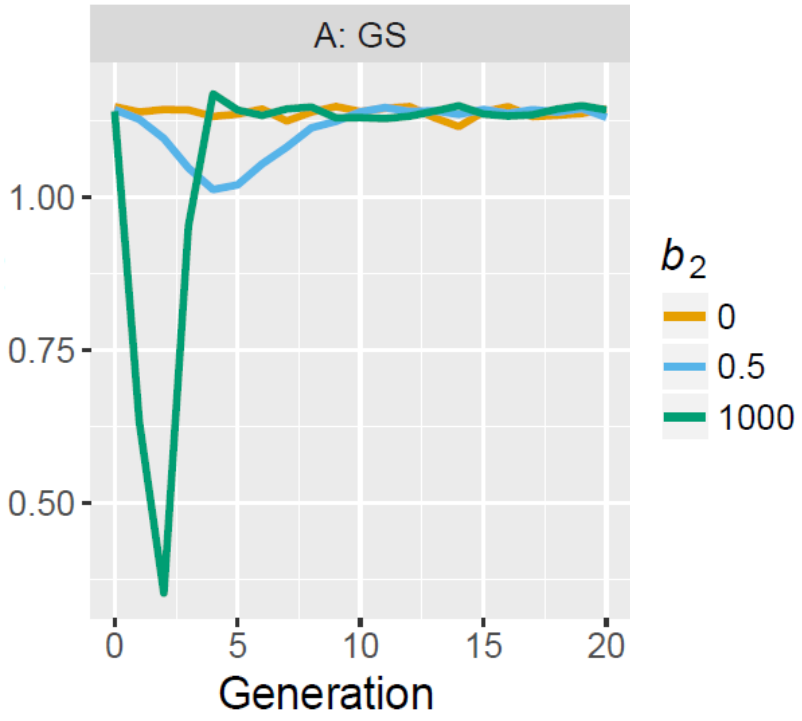


Monogenic allele frequency

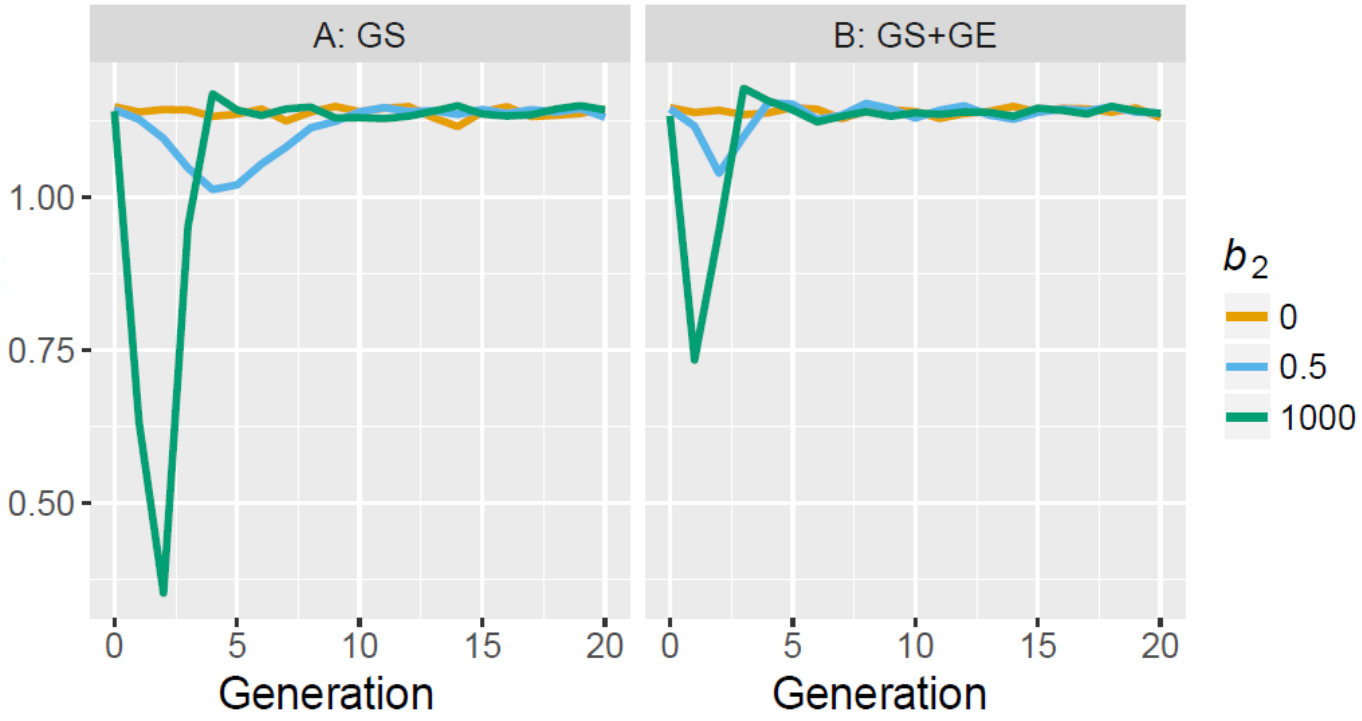


GE greatly reduced the time to fixation up to 75%

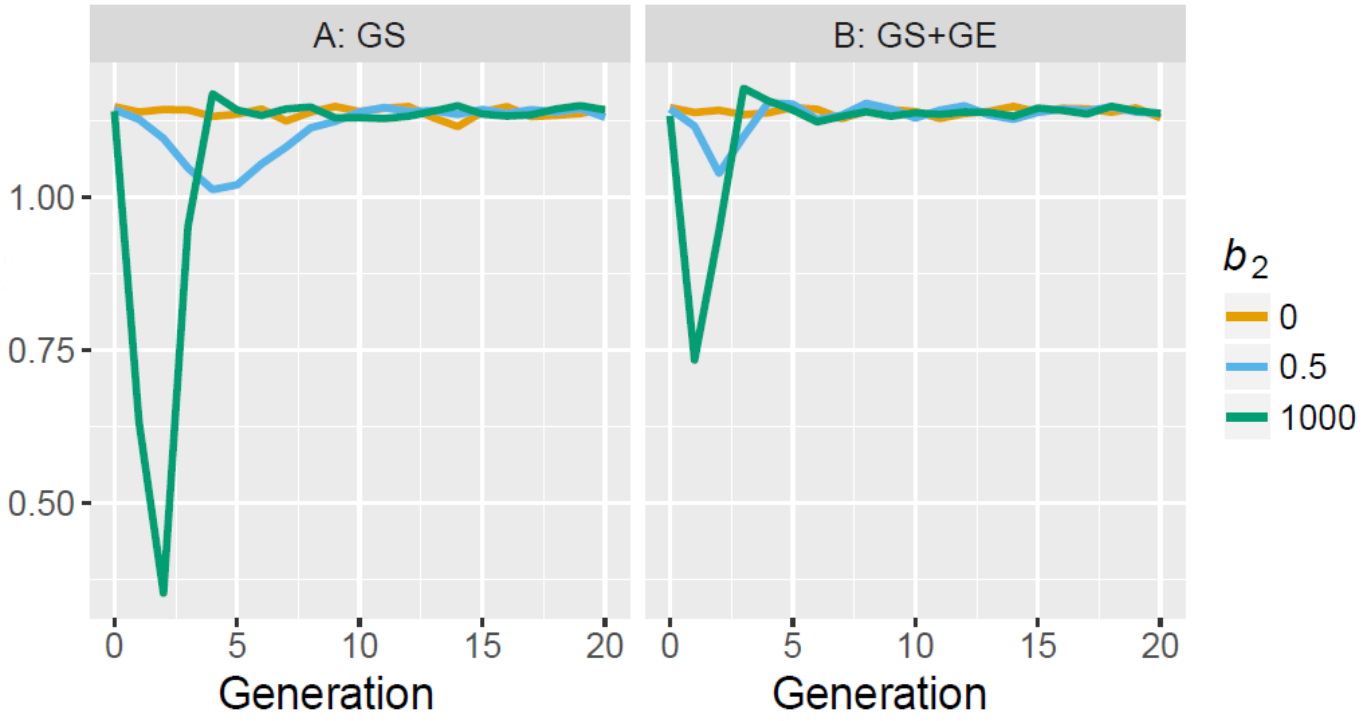
Selection response of polygenic trait (σ_A)



Selection response of polygenic trait (σ_A)

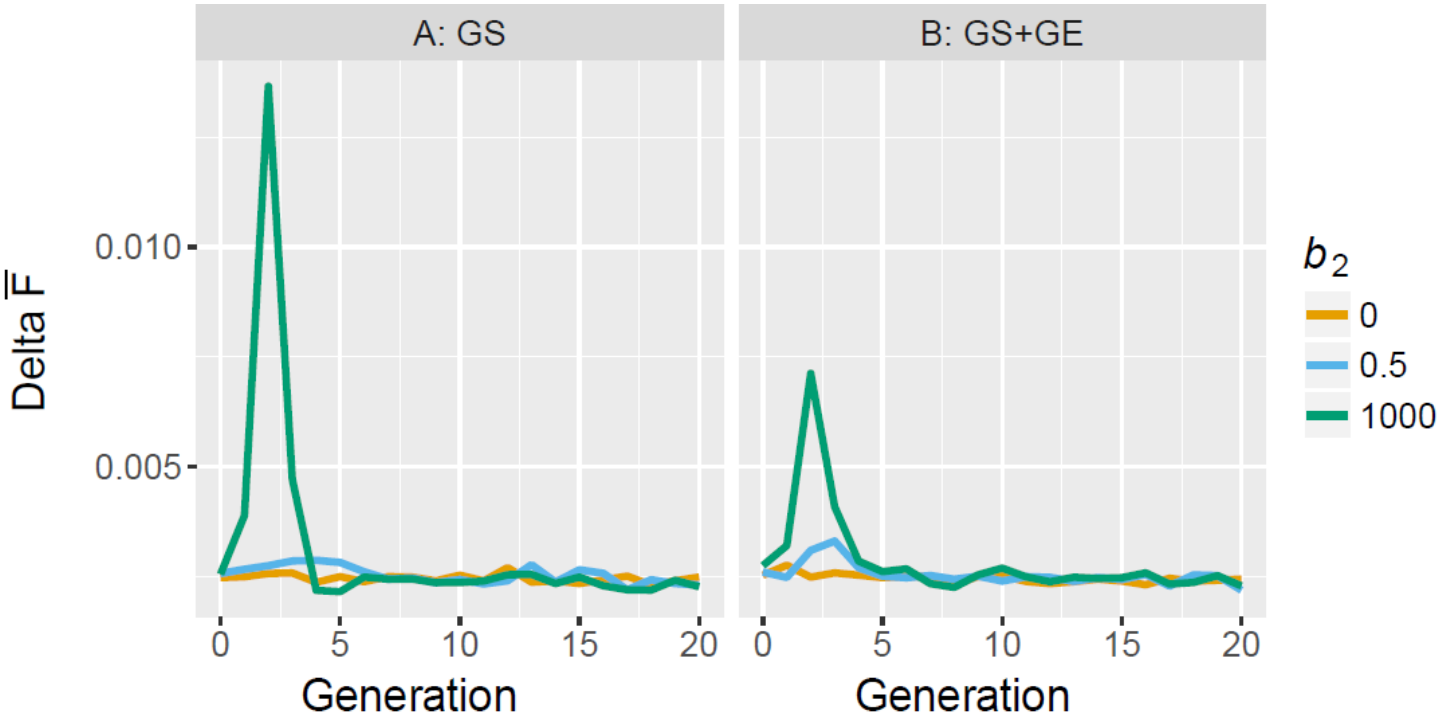


Selection response of polygenic trait (σ_A)



GE reduced the loss of response by up to 50%

Rate of inbreeding



Cost - Benefit

- Assume the monogenic trait is polled in cattle
  - Dominant trait
  - Cost of dehorning set to € 10.00
  - 5 generations evaluation horizon
    - 100,000 animals

Generation 5

Method	b_2	P
GS	0	0.01
	0.5	0.59
	1000	1
GS+GE	0	0.65
	0.5	1
	1000	1

Generation 5

Method	b_2	P	Edits
GS	0	0.01	0
	0.5	0.59	0
	1000	1	0
GS+GE	0	0.65	10,000
	0.5	1	7,080
	1000	1	3,830

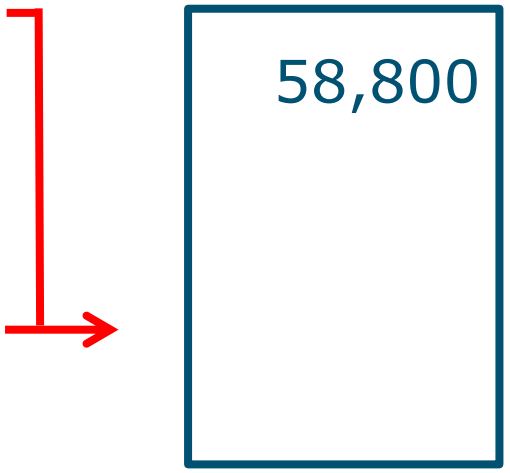
Generation 5

Method	b_2	P	Edits	Polled
GS	0	0.01	0	1,900
	0.5	0.59	0	42,400
	1000	1	0	87,700
GS+GE	0	0.65	10,000	60,700
	0.5	1	7,080	83,700
	1000	1	3,830	90,100

WAGENINGEN
UNIVERSITY & RESEARCH

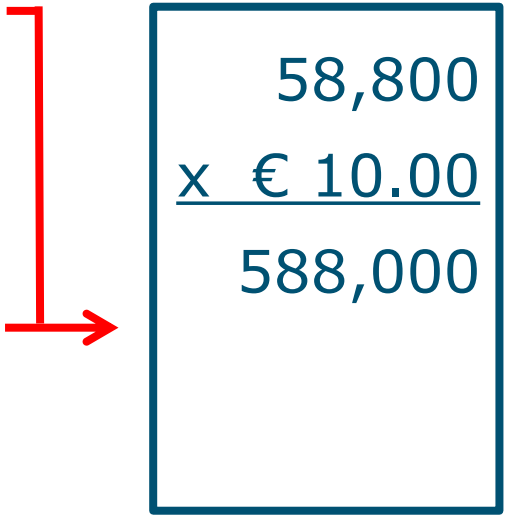
Generation 5

Method	b_2	P	Edits	Polled
GS	0	0.01	0	1,900
	0.5	0.59	0	42,400
	1000	1	0	87,700
GS+GE	0	0.65	10,000	60,700
	0.5	1	7,080	83,700
	1000	1	3,830	90,100



Generation 5

Method	b_2	P	Edits	Polled
GS	0	0.01	0	1,900
	0.5	0.59	0	42,400
	1000	1	0	87,700
GS+GE	0	0.65	10,000	60,700
	0.5	1	7,080	83,700
	1000	1	3,830	90,100



Generation 5

Method	b_2	P	Edits	Polled
GS	0	0.01	0	1,900
	0.5	0.59	0	42,400
	1000	1	0	87,700
GS+GE	0	0.65	10,000	60,700
	0.5	1	7,080	83,700
	1000	1	3,830	90,100

58,800
x € 10.00
588,000
: 10,000
€ 58.80

Generation 5

Method	b_2	P	Edits	Polled
GS	0	0.01	0	1,900
	0.5	0.59	0	42,400
	1000	1	0	87,700
GS+GE	0	0.65	10,000	60,700
	0.5	1	7,080	83,700
	1000	1	3,830	90,100

58,800
x € 10.00
588,000
: 10,000
€ 58.80

Break-even cost of € 58.80 per genome edited zygote with population size 20,000

WAGENINGEN
UNIVERSITY & RESEARCH

Conclusions simulation

- GS+GE strongly decreased time to fixation up to 75% compared to GS alone
- GS+GE reduced the loss in selection response compared to GS alone
- Break-even cost of genome editing procedure can be estimated, and depend on value of desired phenotype and the target population size

State of the art

- In vitro production of embryos is essential
  - OK in cattle
  - Not so in pigs, chickens, fish, ...
- 1 live embryo per 24 editing attempts (Stella and Montoya, *Bioessays* 2016, 38 Suppl 1:S4-S13)

  (65% more editing needed)

  (254% more loss in genetic gain)
- Mosaiks and off-target edits
  - Very difficult to detect
- Acceptance and legal issues
- Targets to edit!

Conclusions

- Genome editing has the potential to become the next game changer in animal breeding
- State of the art brings a number of concerns
  - different per species
- Ethical and welfare considerations are very important