Gene drive modified insects: hopes, fears, gene drive systems and the problem formulation concept

Fred Gould
North Carolina State University

Outline

1) Hopes and Fears
2) Types of gene drive systems
3) Mechanisms behind unrestricted drives
4) Mechanisms behind spatially restricted drives
5) Problem formulation

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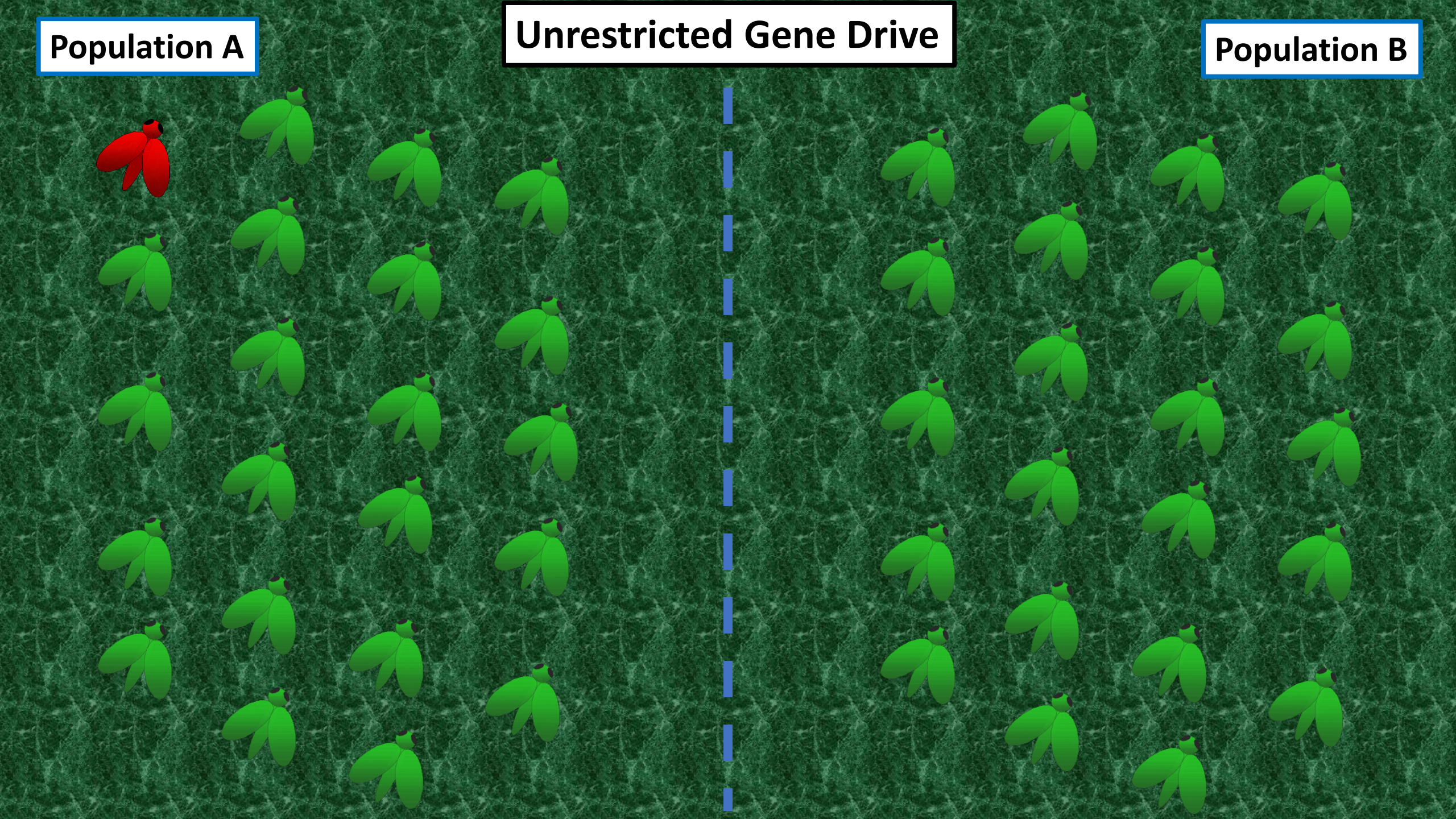
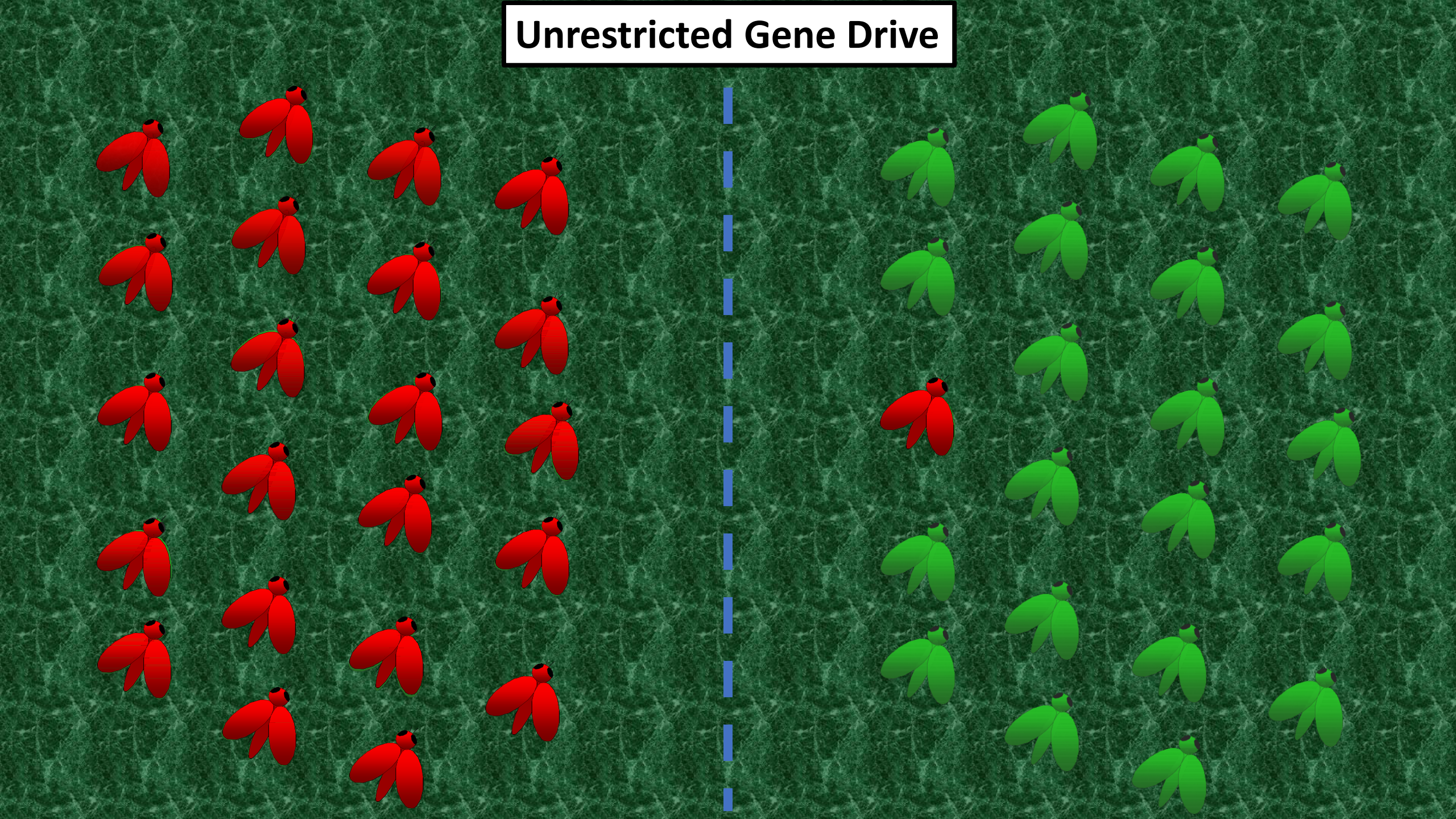
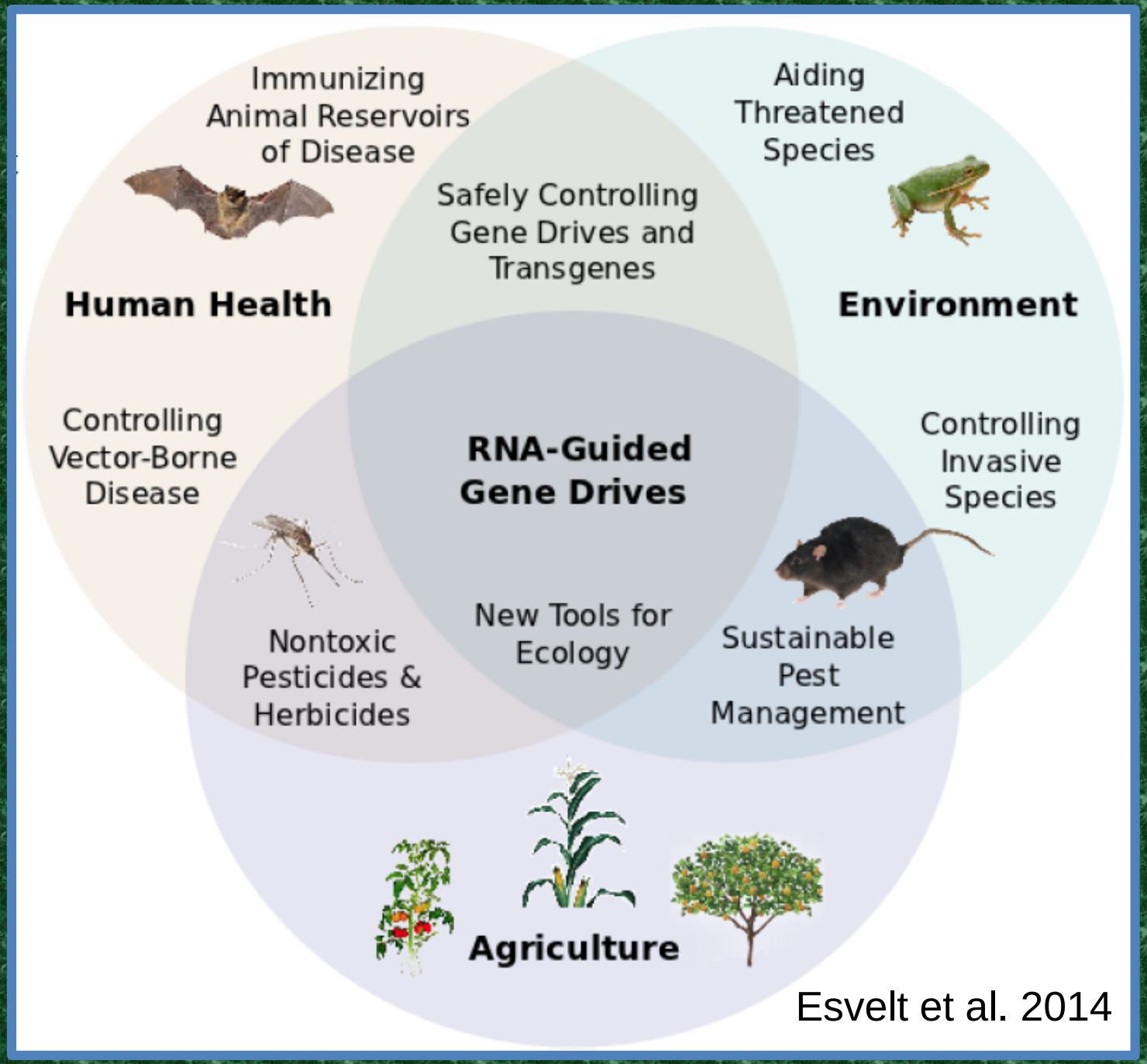

Population A
Unrestricted Gene Drive
Population B

Unrestricted Gene Drive



Unrestricted Gene Drive

A Multitude of Hopes



Esvelt et al. 2014

Malaria

435,000 Deaths

219,000,000 Cases

$ 3.1 Billion Cost (US)

Malaria

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219,000,000 Cases

$ 3.1 Billion Cost (US)

TARGET MALARIA

A Vector Control Research Alliance

The Fears

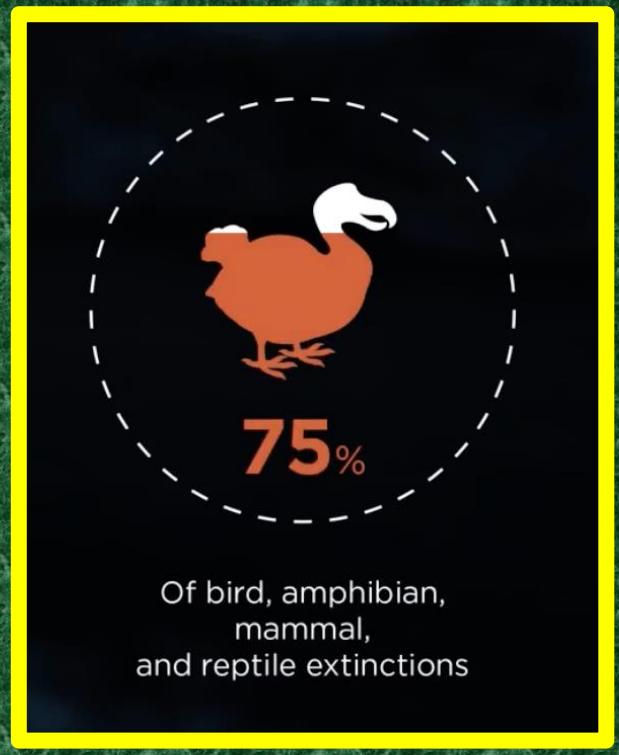
1) Ecosystem disruption
2) Resurgence
3) Others

TARGET MALARIA

A Vector Control Research Alliance

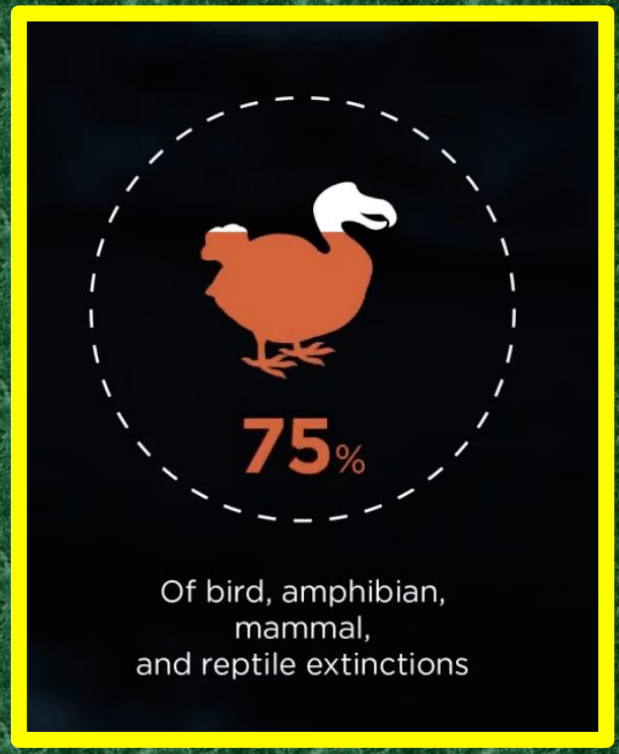
Hopes

Eradicate Invasives



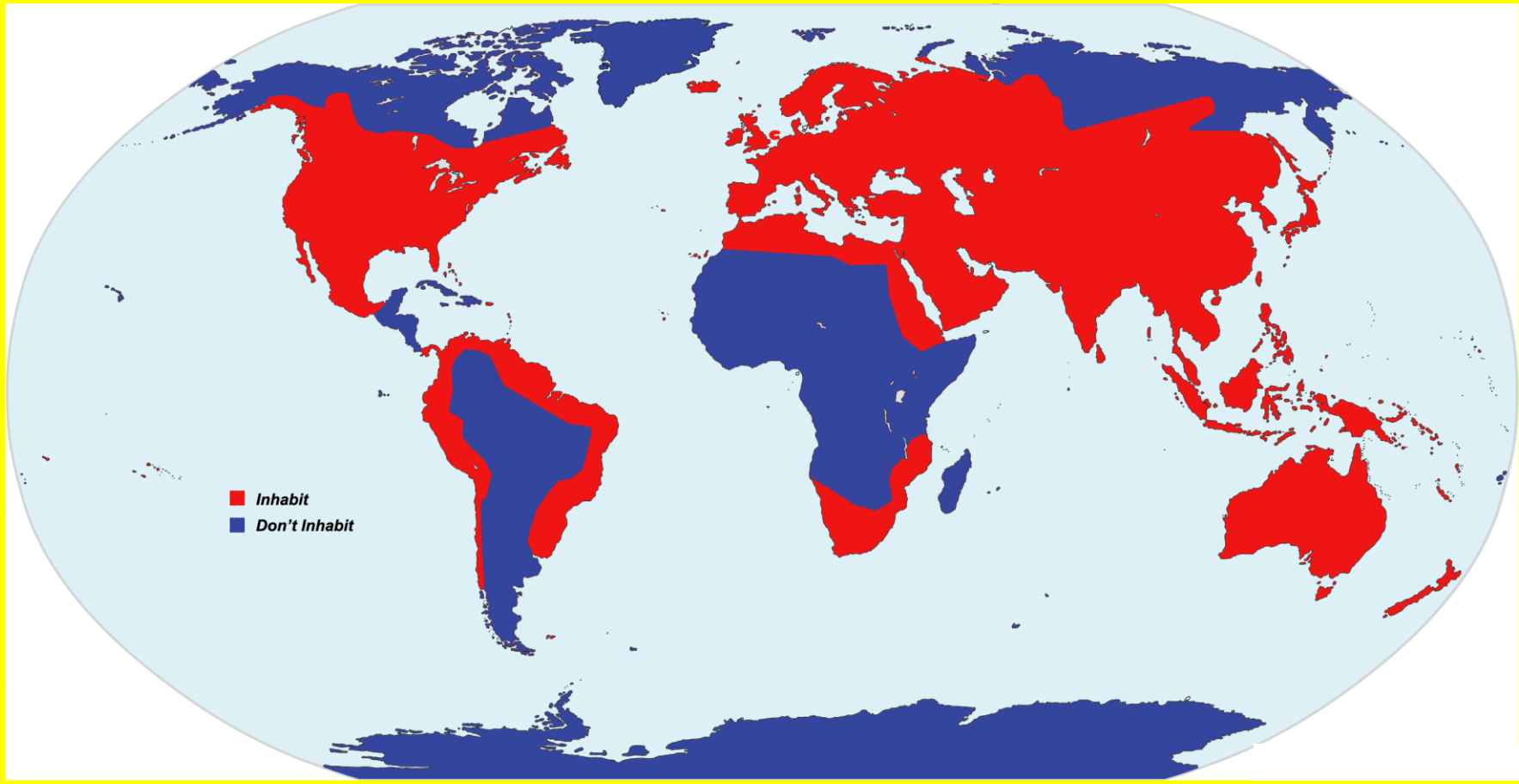
Hopes

Eradicate Invasives



The Fear

Global House Mouse Distribution



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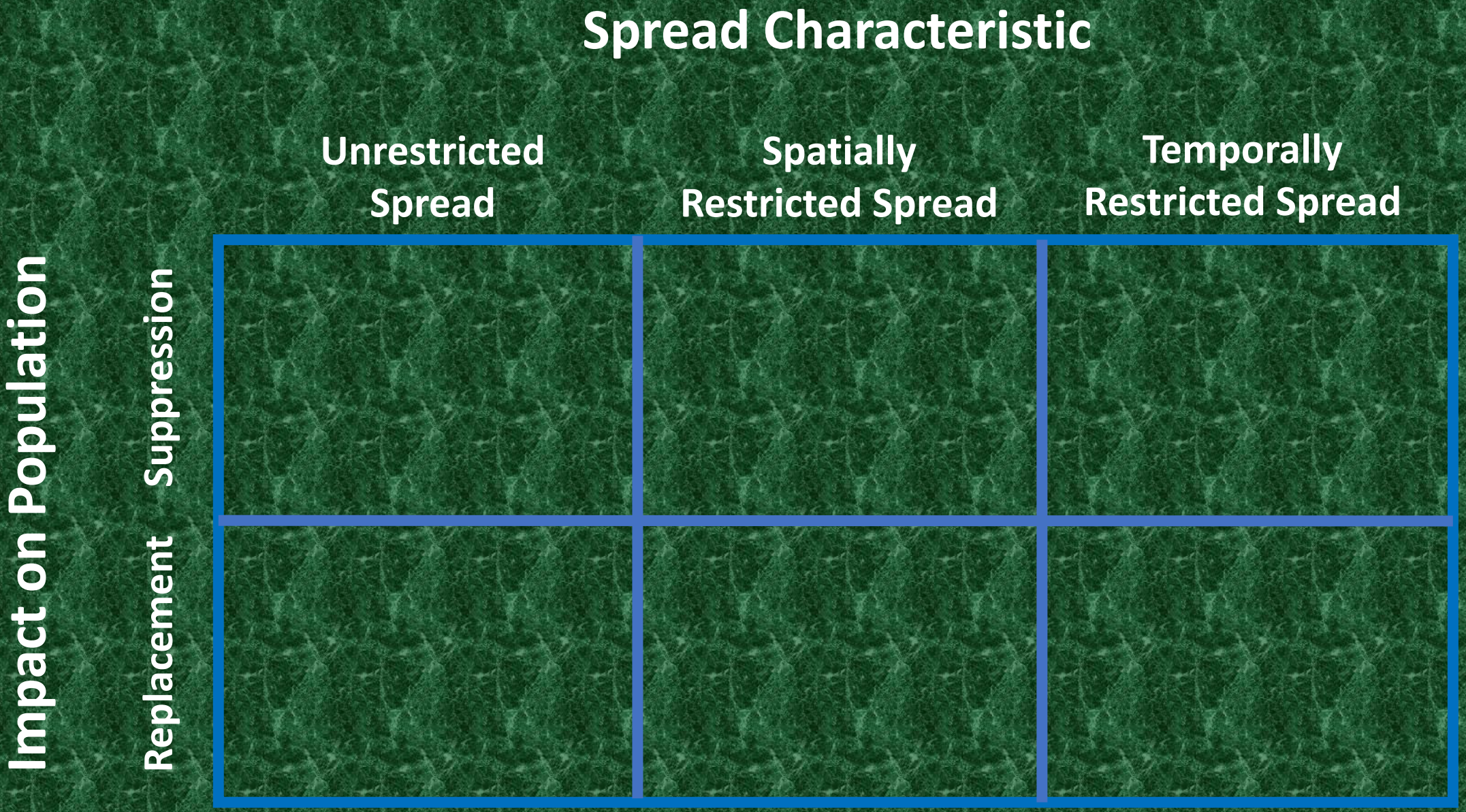
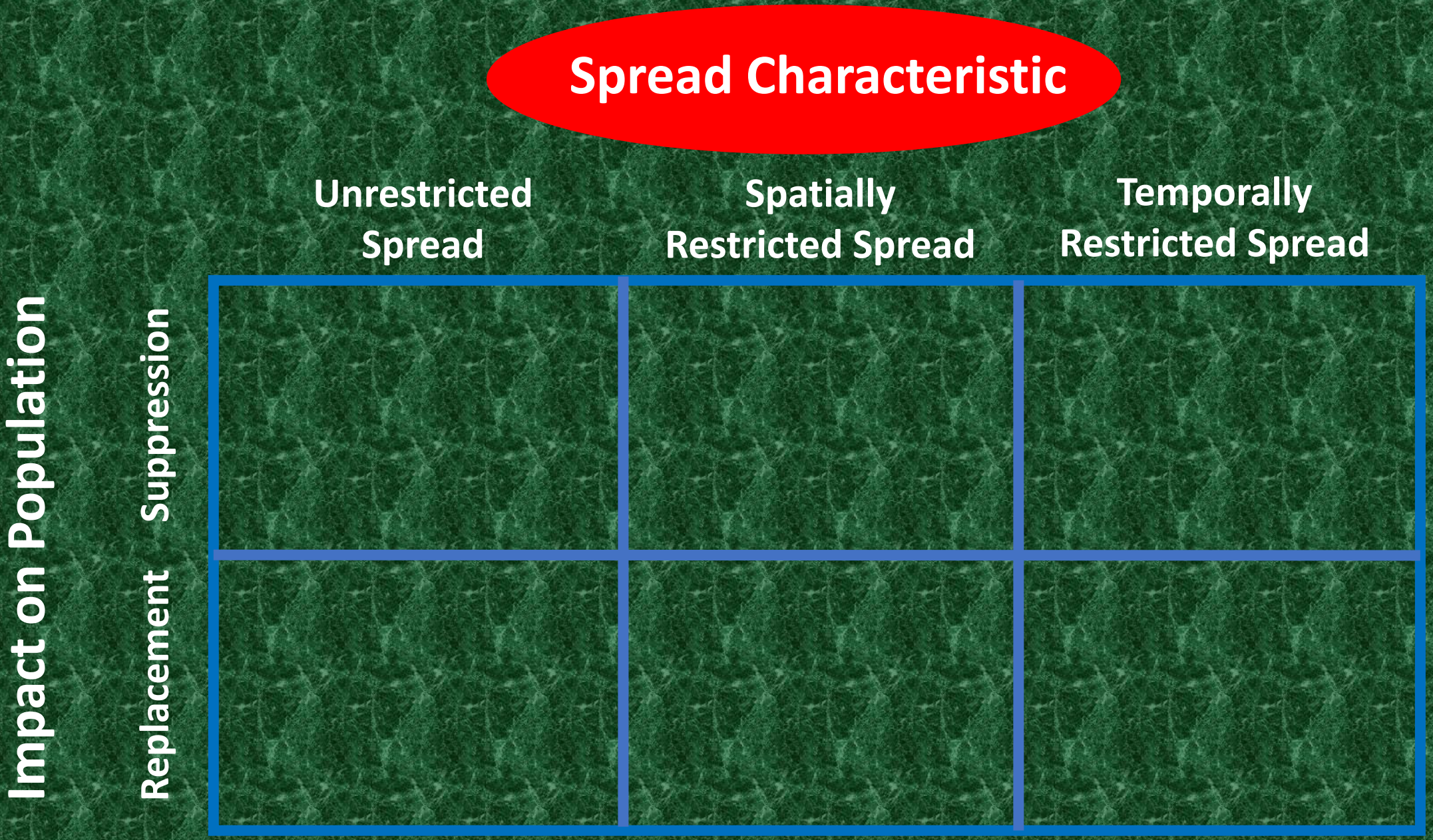

Spread Characteristic
Unrestricted Spread
Spatially Restricted Spread
Temporally Restricted Spread
Impact on Population
Suppression
Replacement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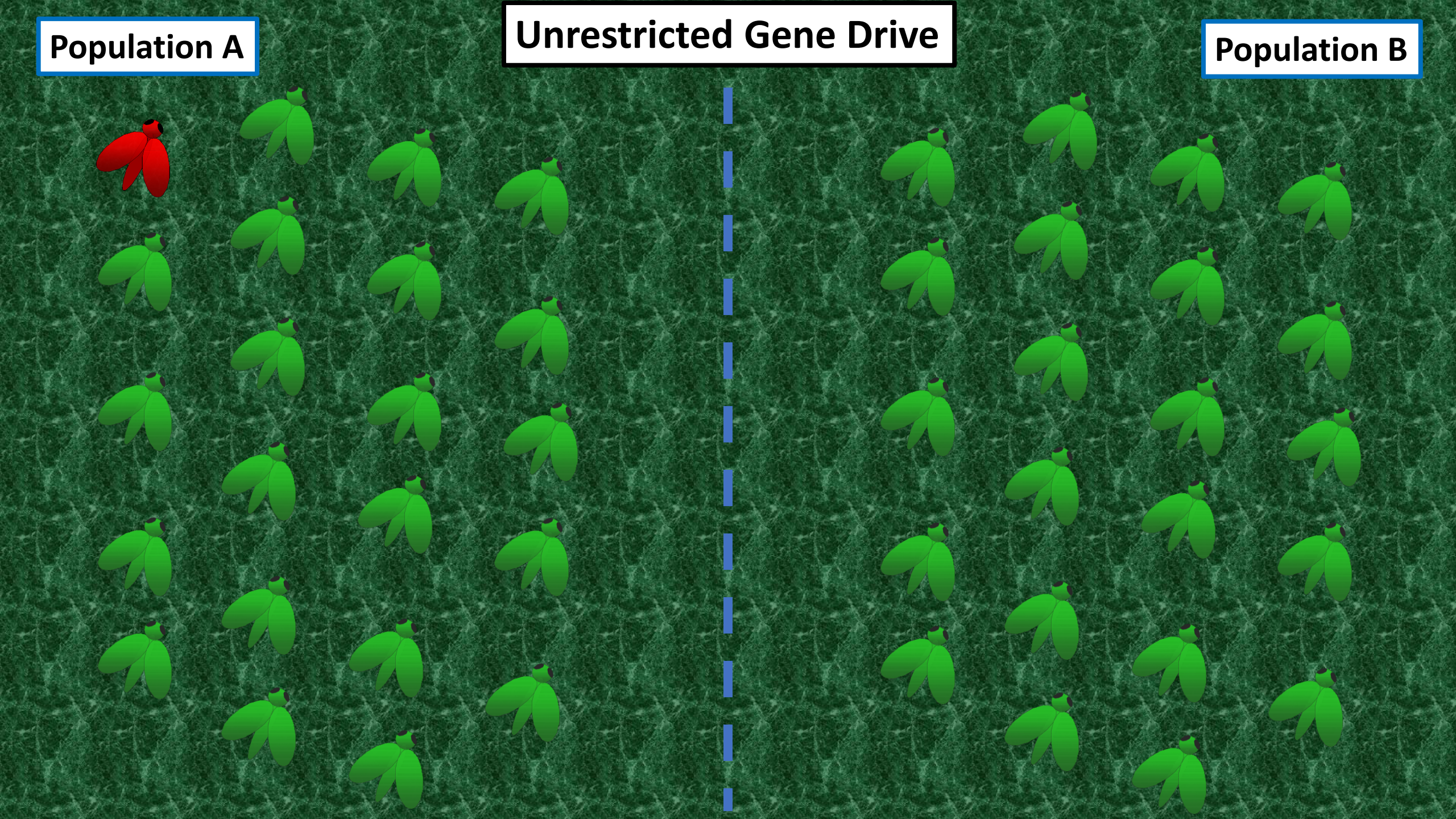
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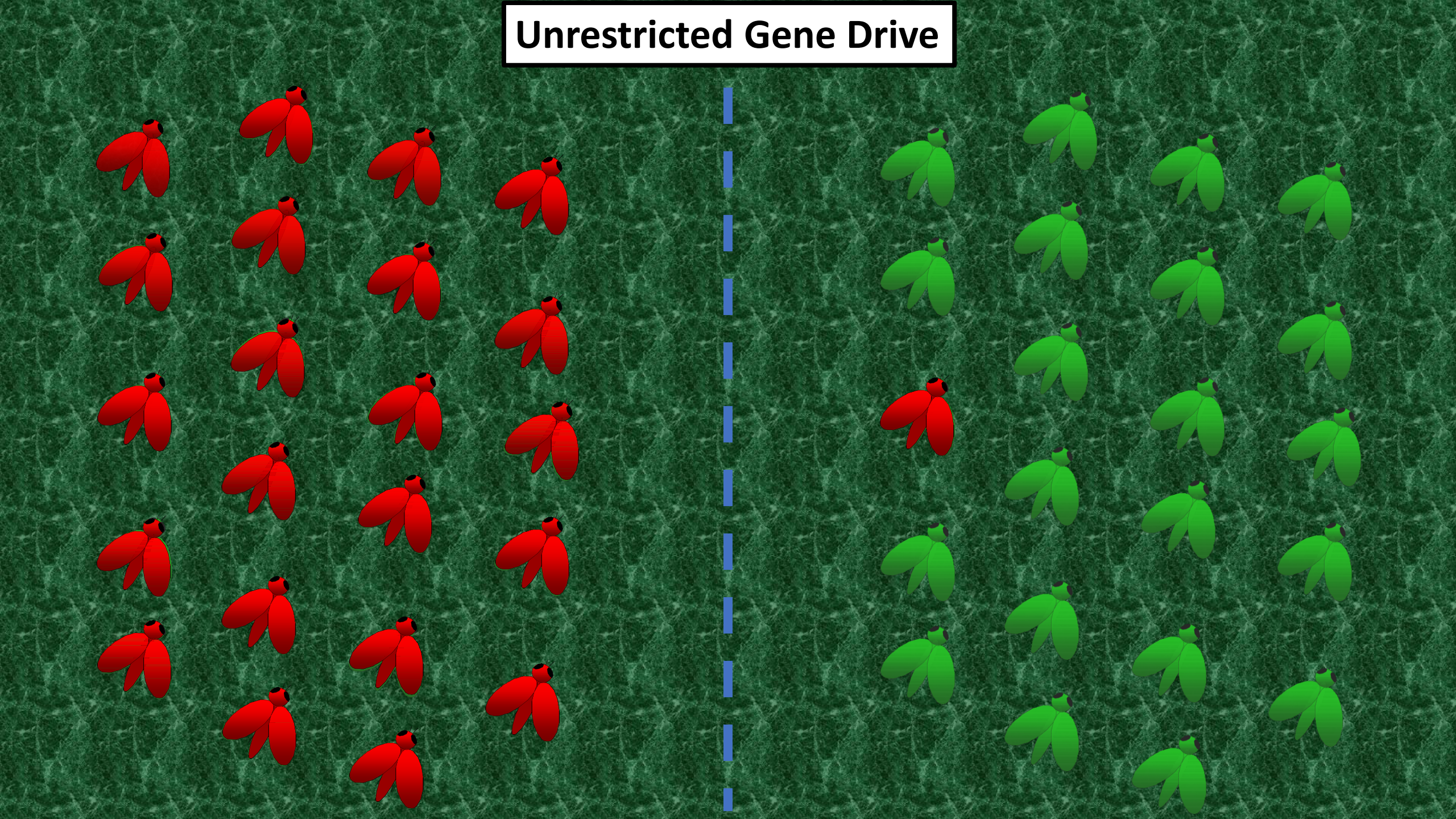
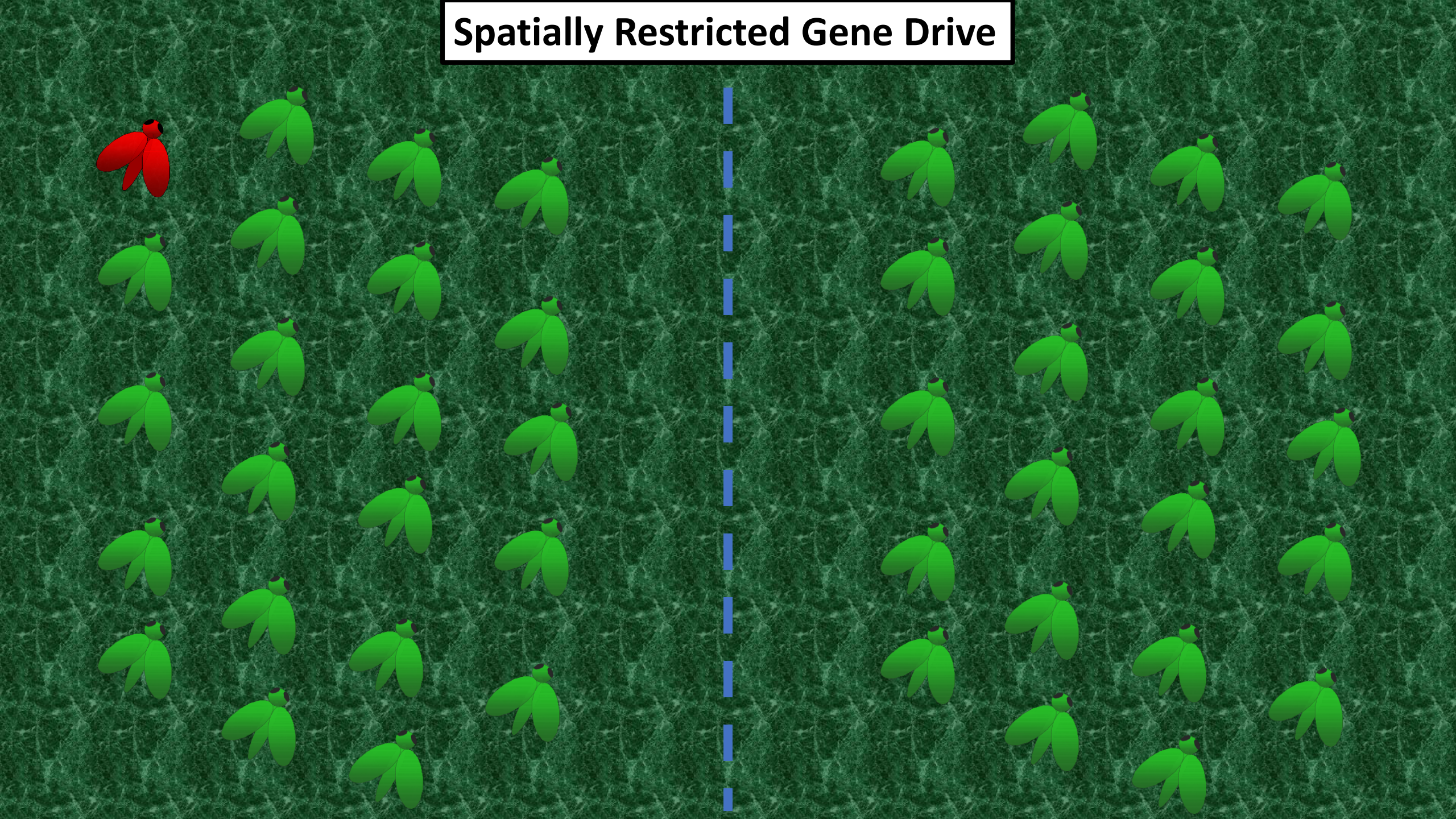
Unrestricted Gene Drive

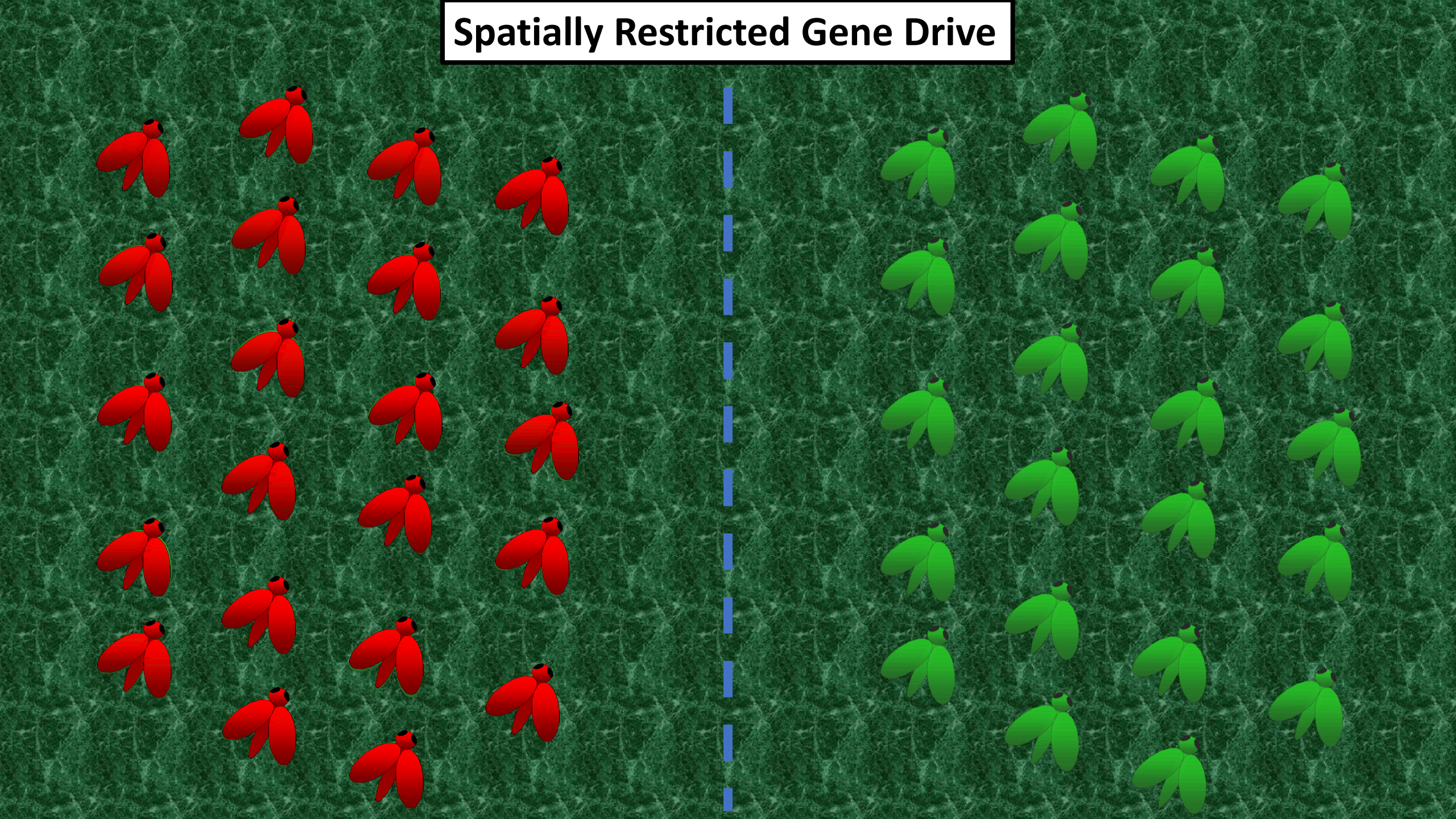


Unrestricted Gene Drive

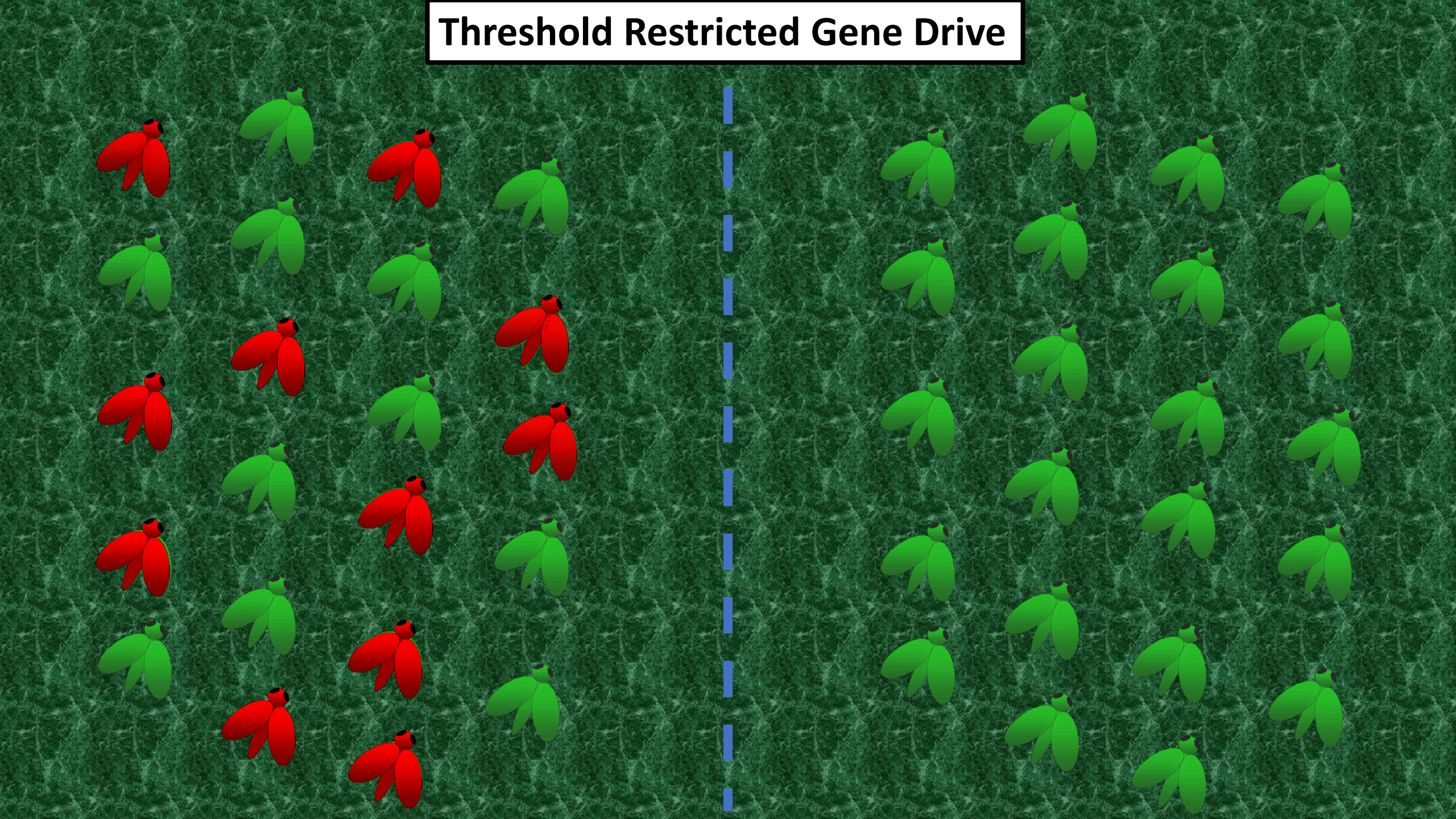
Spatially Restricted Gene Drive



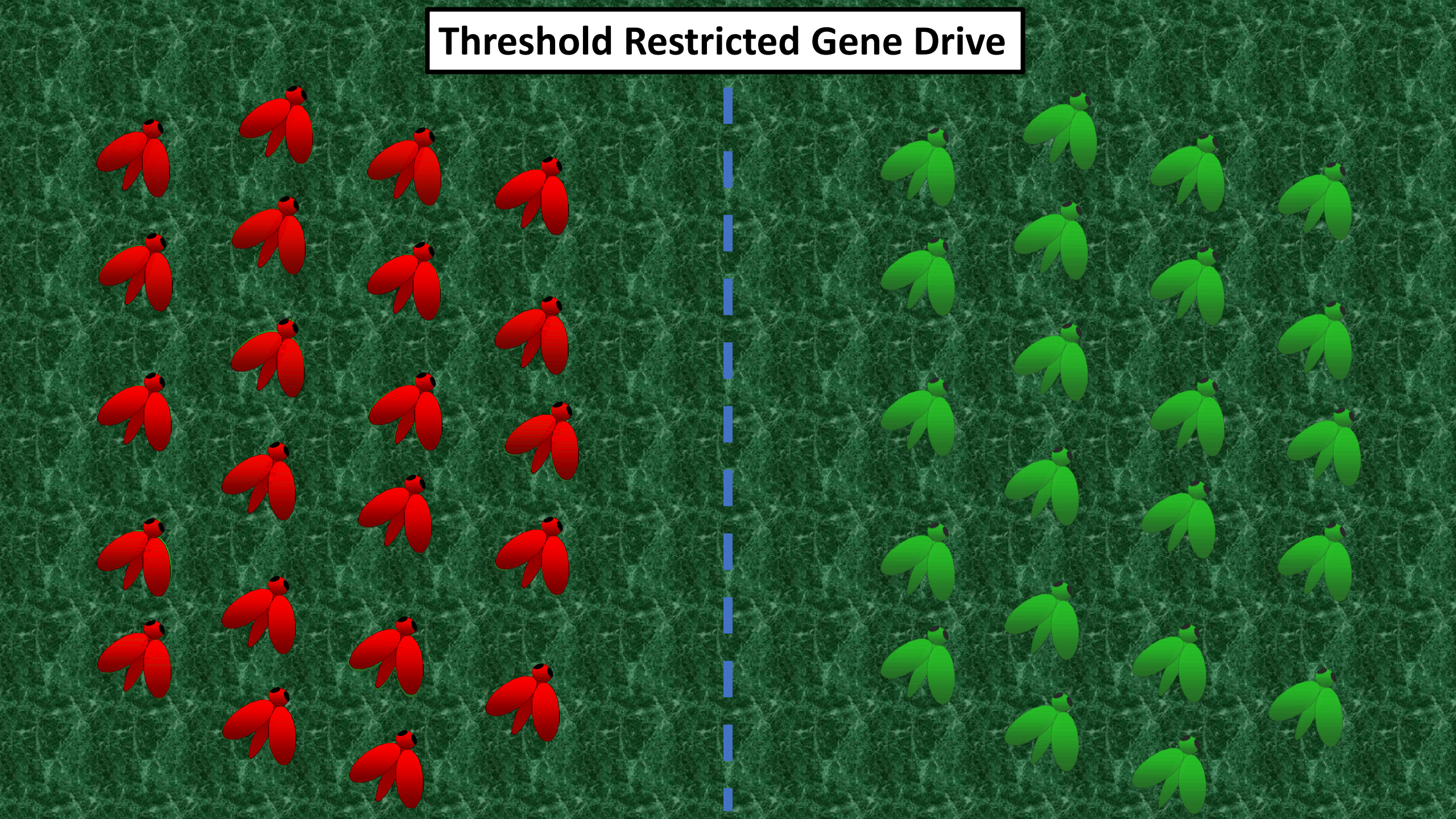
Spatially Restricted Gene Drive



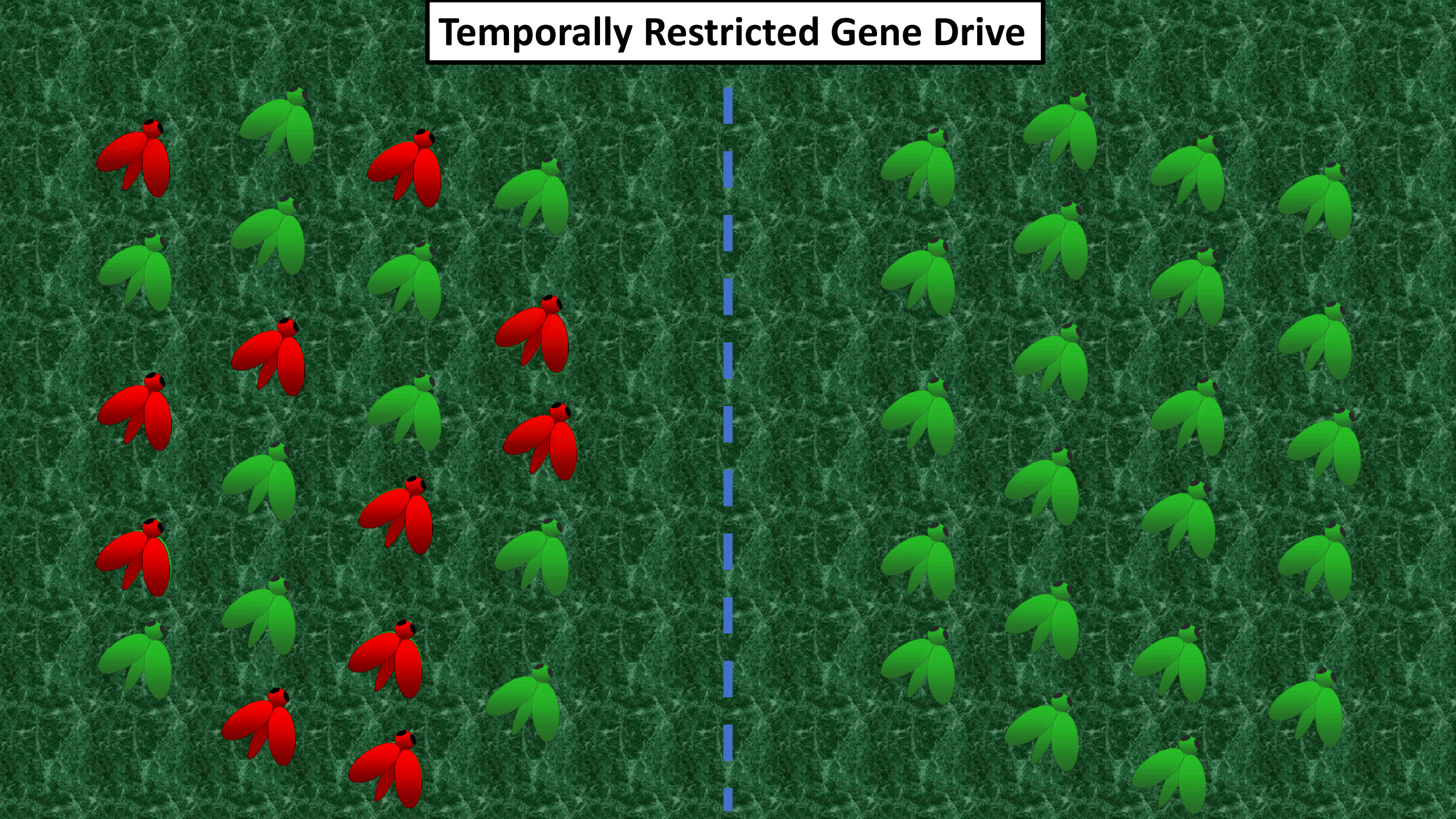
Threshold Restricted Gene Drive



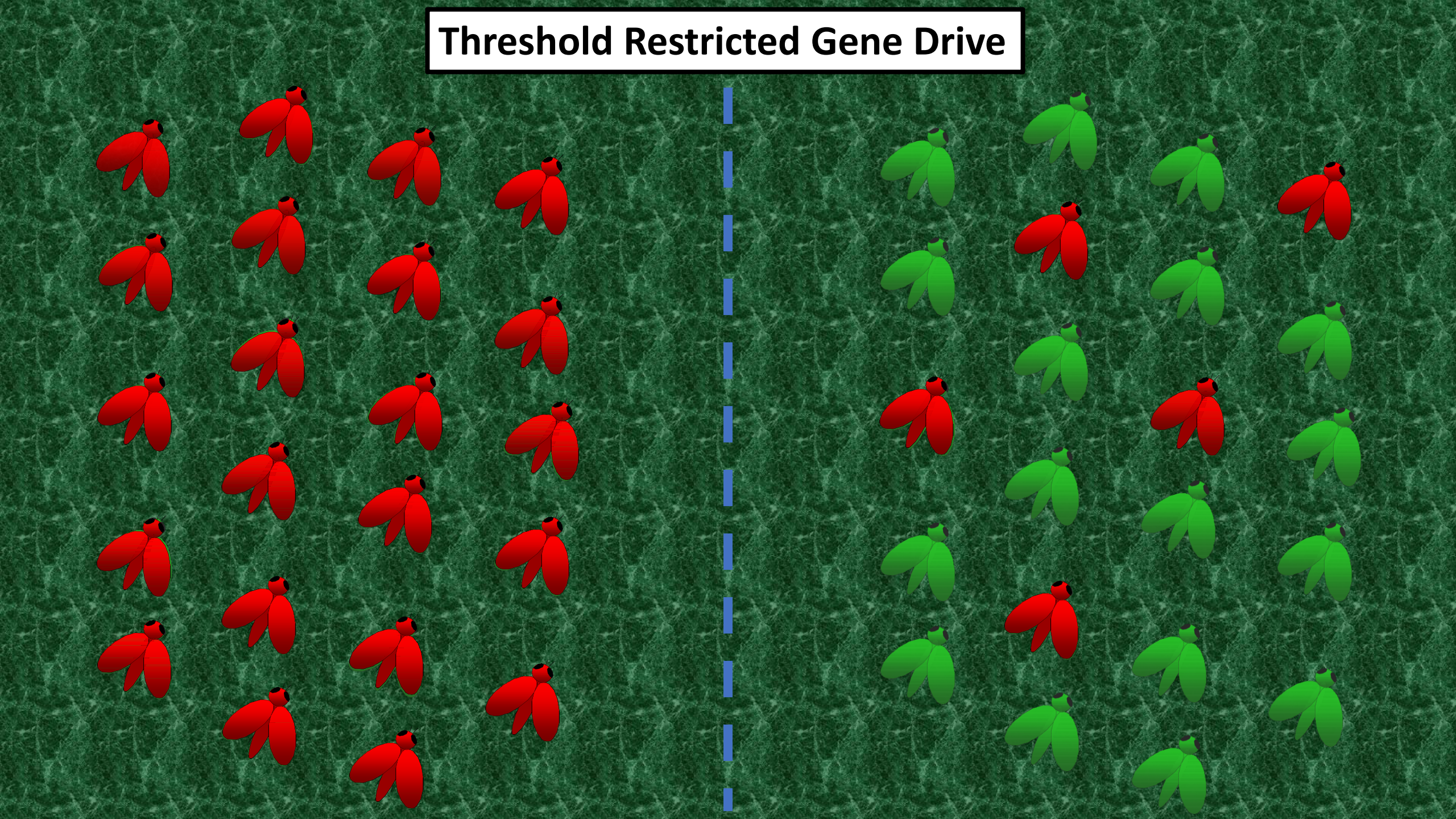
Threshold Restricted Gene Drive



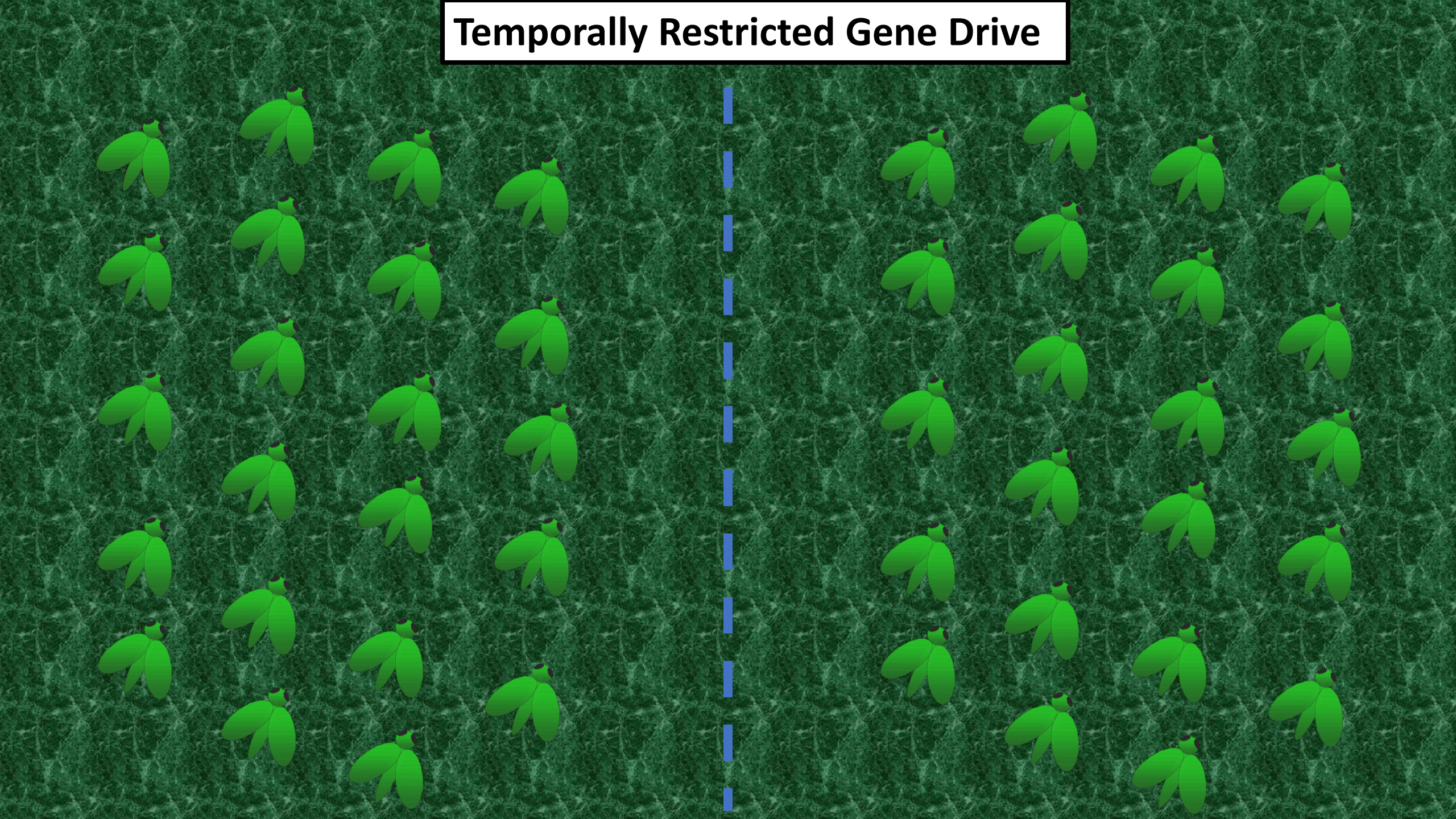
Temporally Restricted Gene Drive

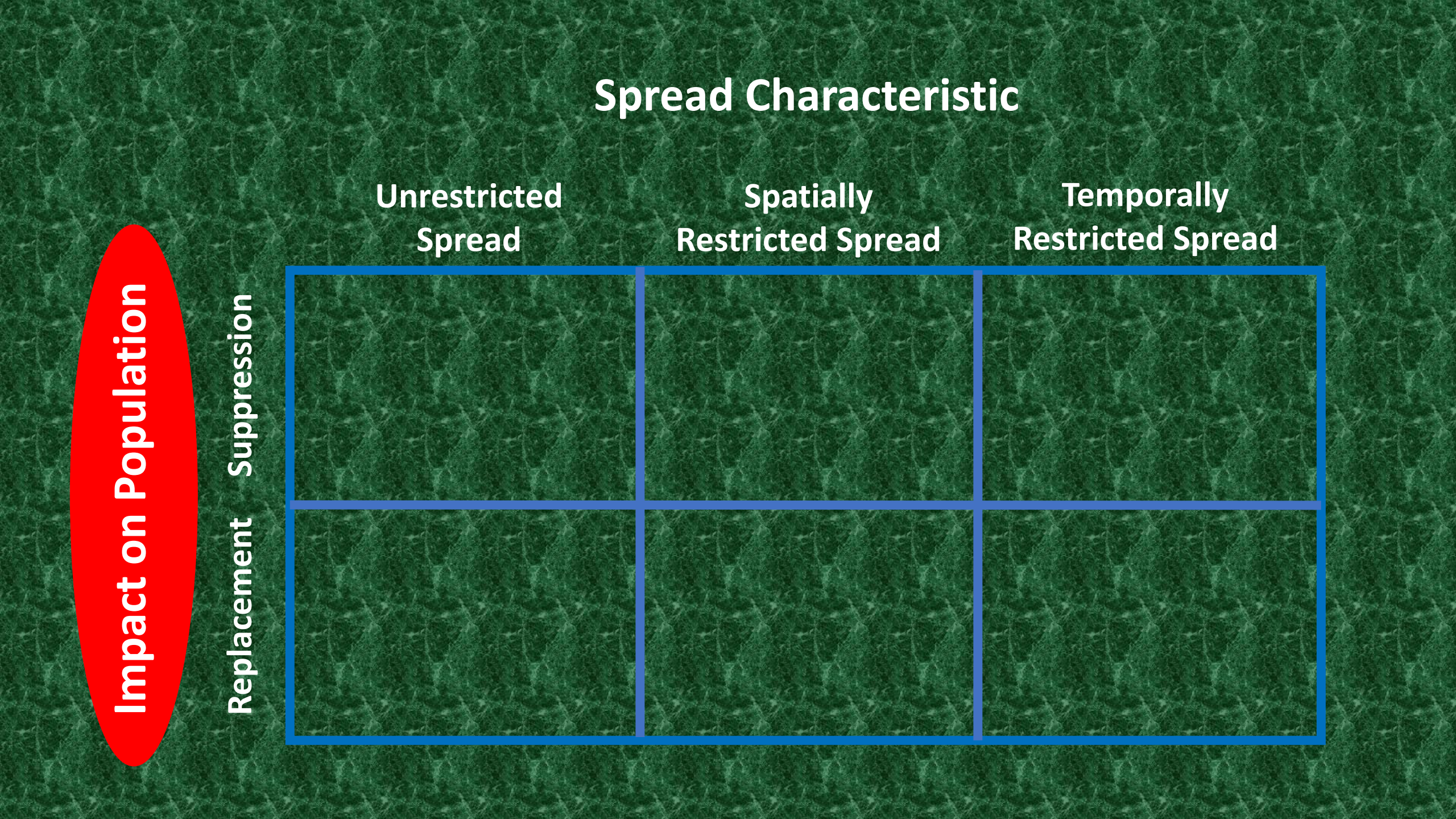


Threshold Restricted Gene Drive



Temporally Restricted Gene Drive

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Replacement

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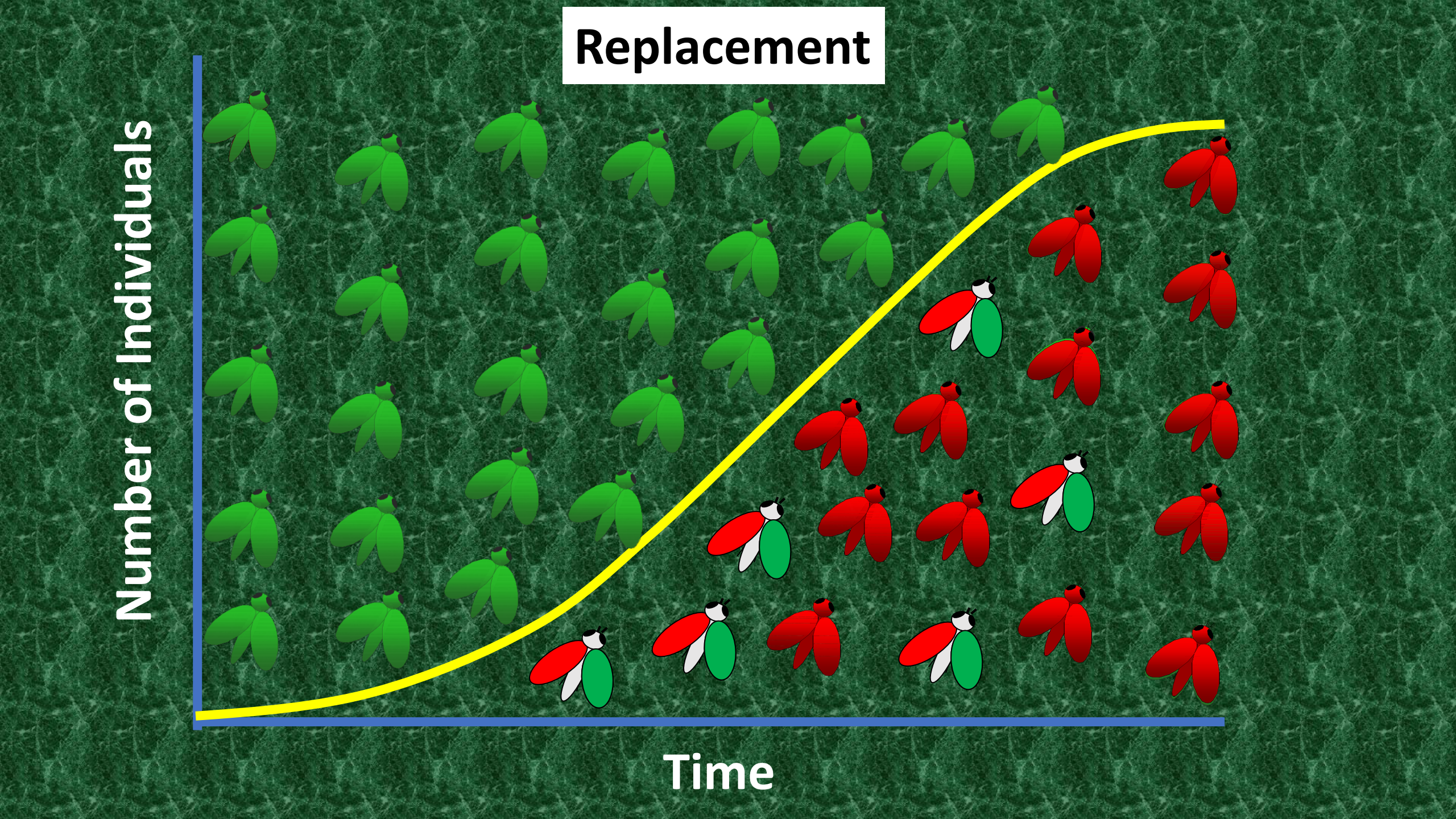
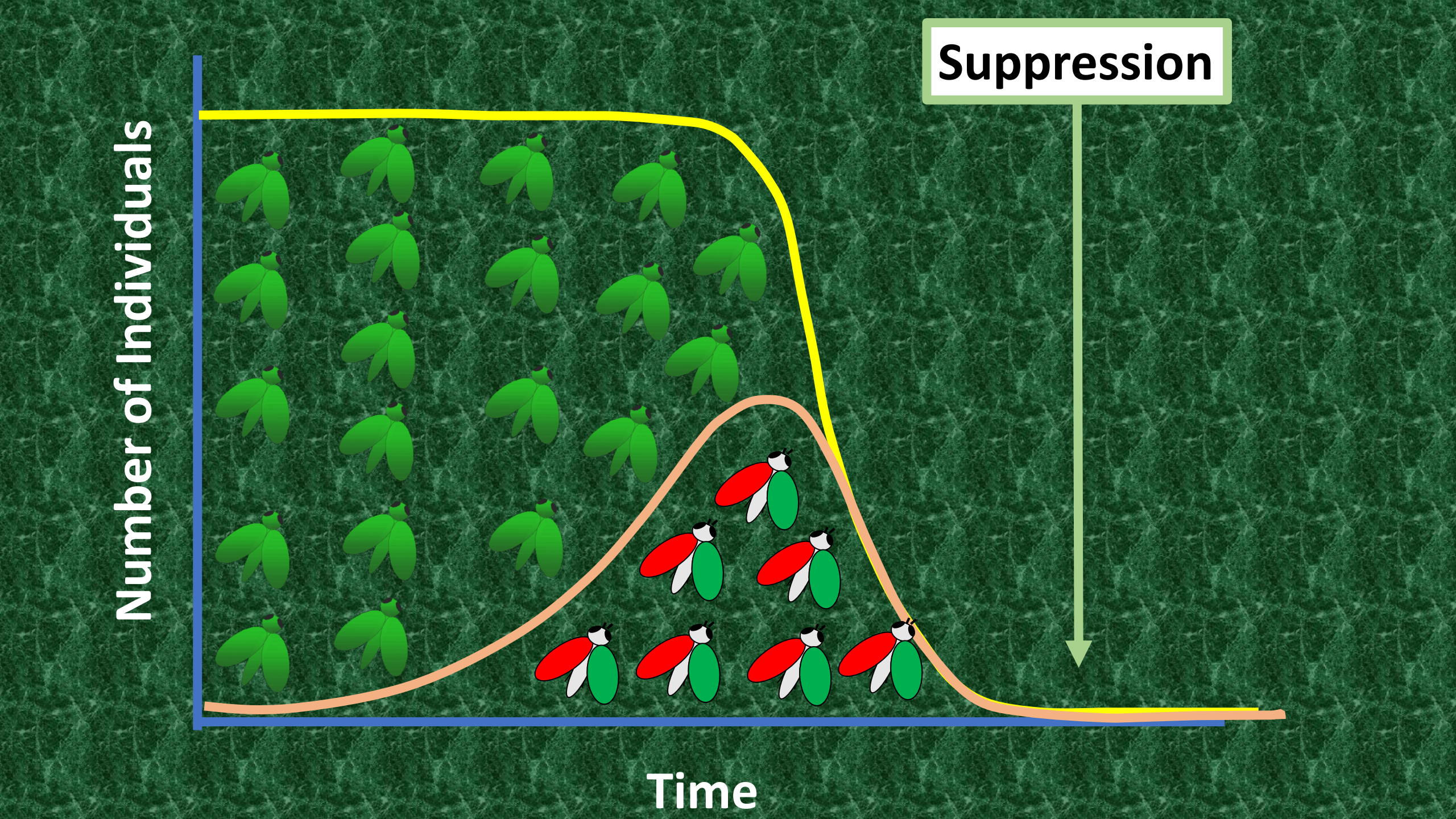
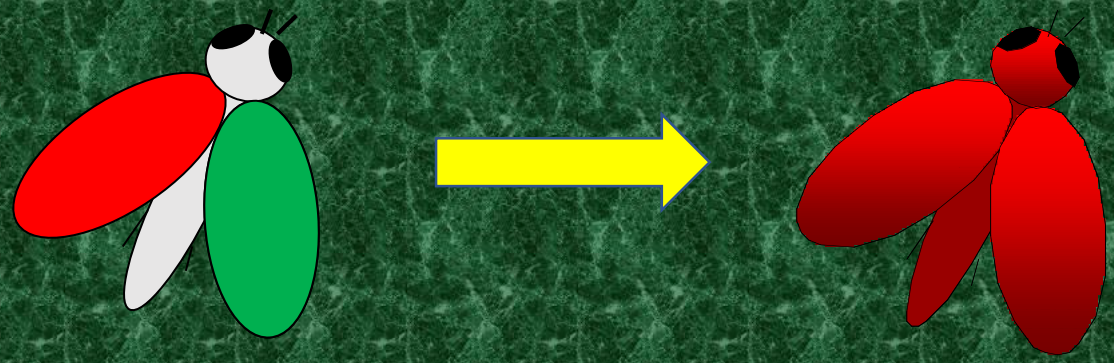



Suppression
Number of Individuals
Time

The Mechanism Behind the Magic

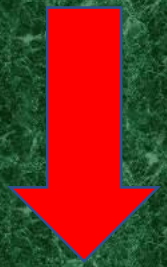
The Mechanism Behind the Magic



The Mechanism Behind the Magic

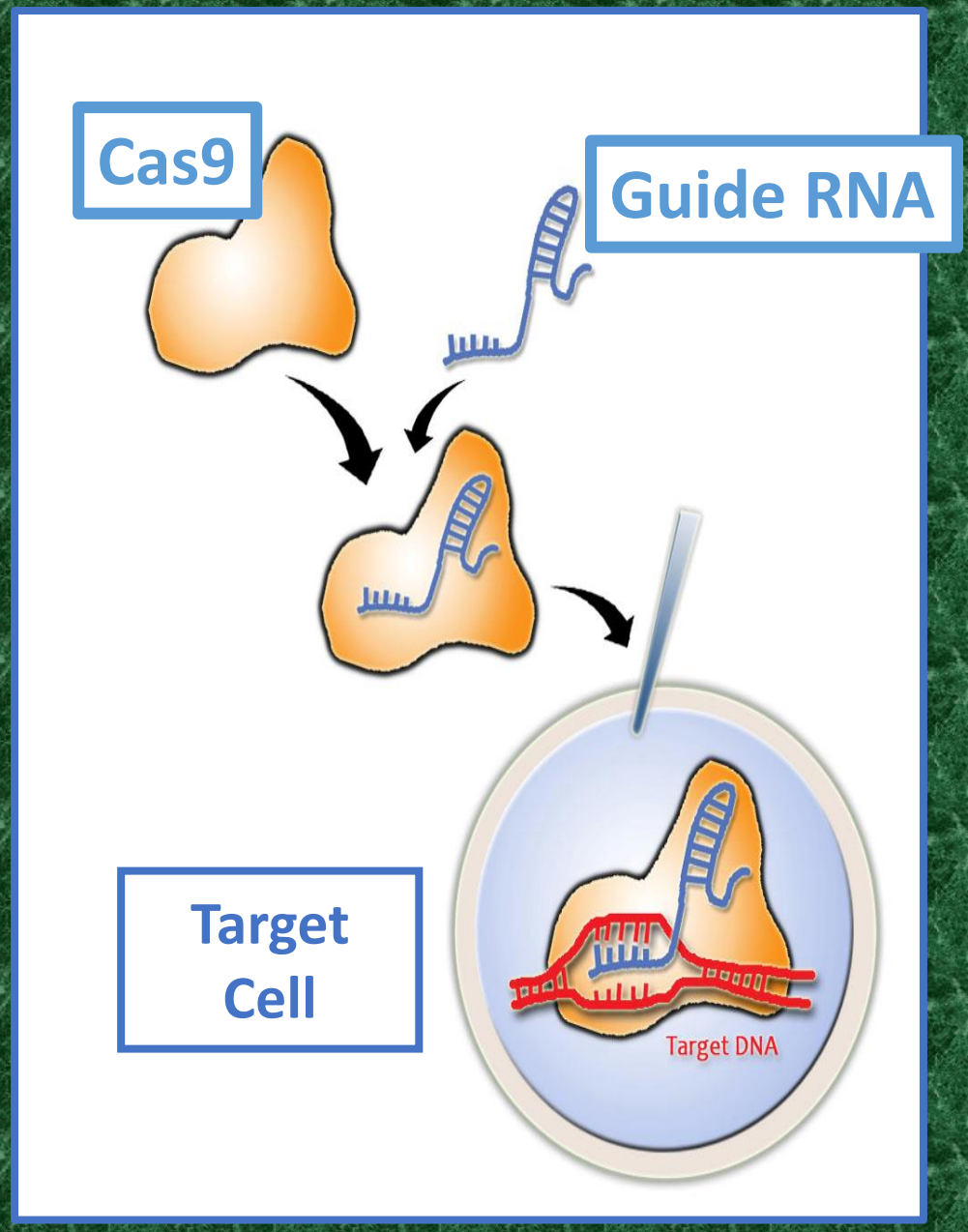
Spatially Unrestricted Gene Drives

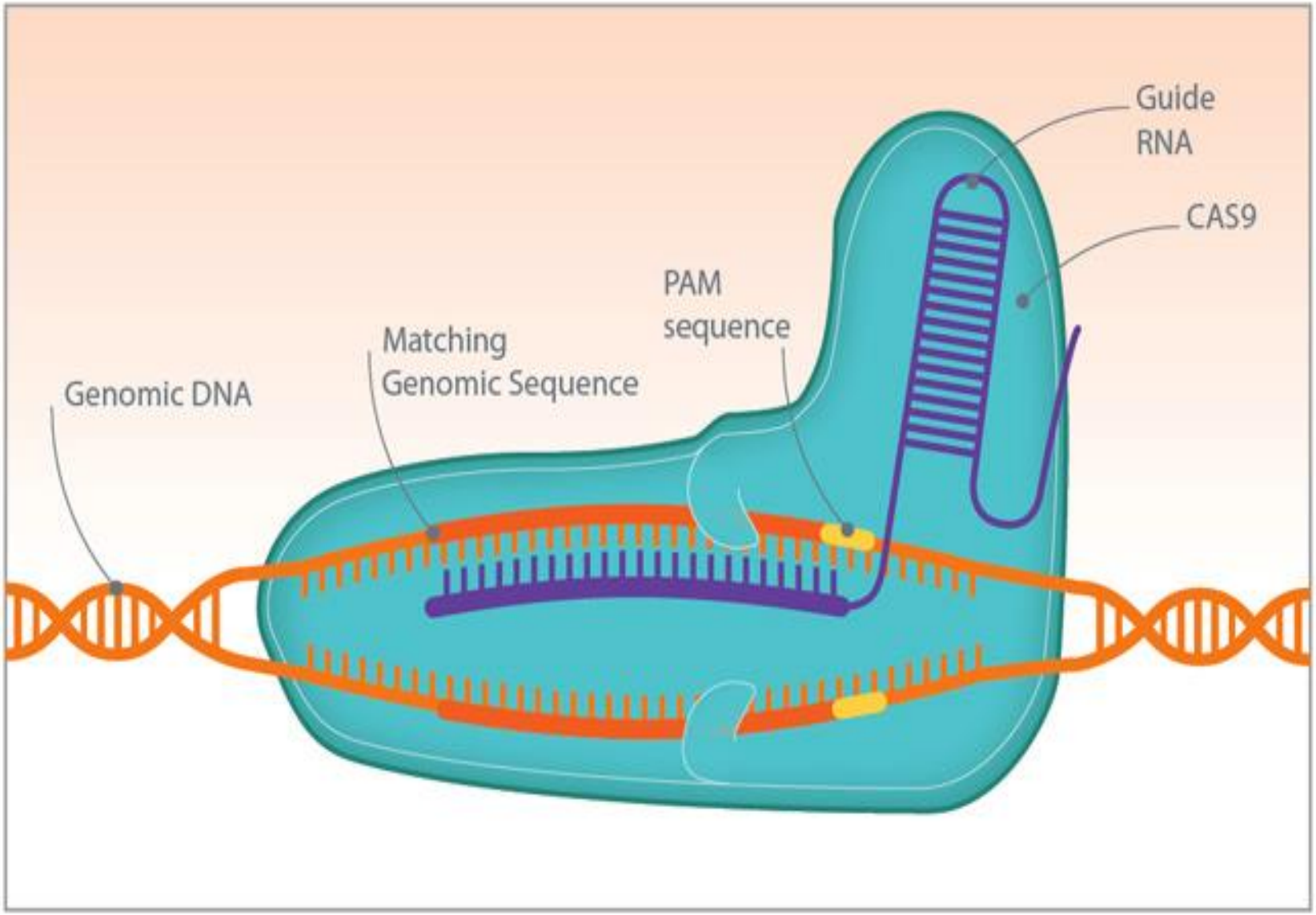
CRISPR for Crop Breeding



CRISPR for Gene Drive

CRISPR/Cas9



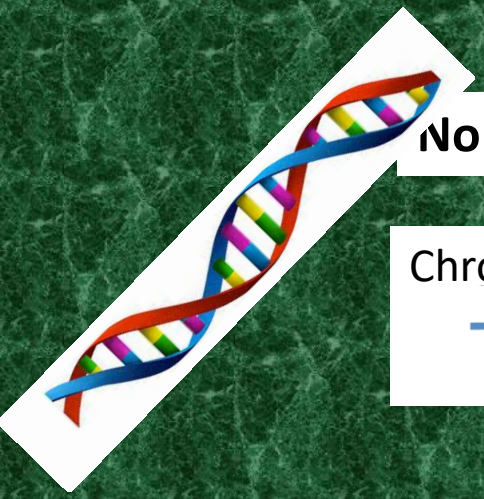

Guide
RNA
CAS9
PAM
sequence
Matching
Genomic Sequence
Genomic DNA

Non-Homologous End-Joining (NHEJ)

Homology-Directed Repair (HDR)

Non-Homologous End-Joining (NHEJ)

Homology-Directed Repair (HDR)



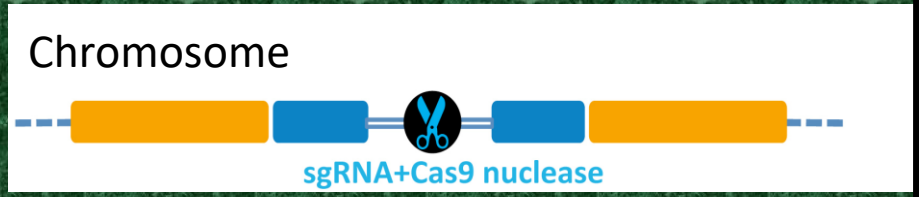
Non-Homologous End-Joining (NHEJ)

Chromosome

Homology-Directed Repair (HDR)

Non-Homologous End-Joining (NHEJ)

Homology-Directed Repair (HDR)



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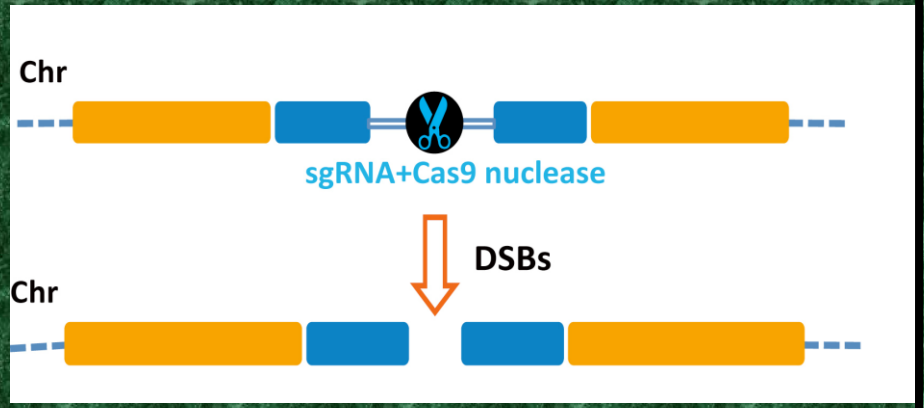

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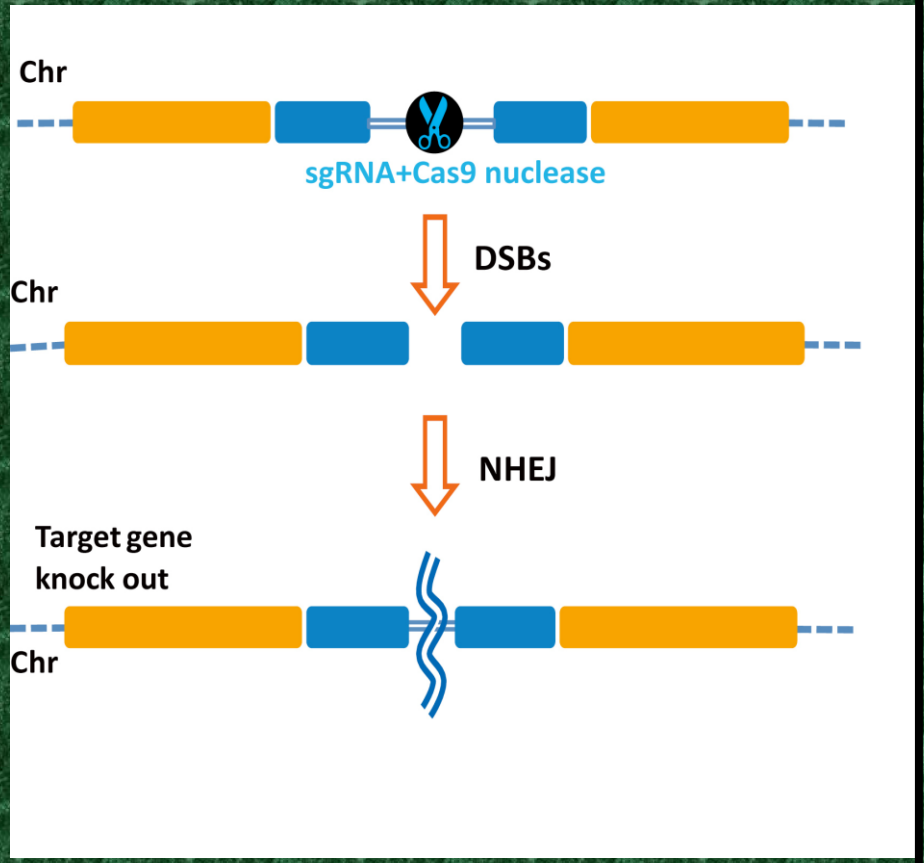
Non-Homologous End-Joining (NHEJ)



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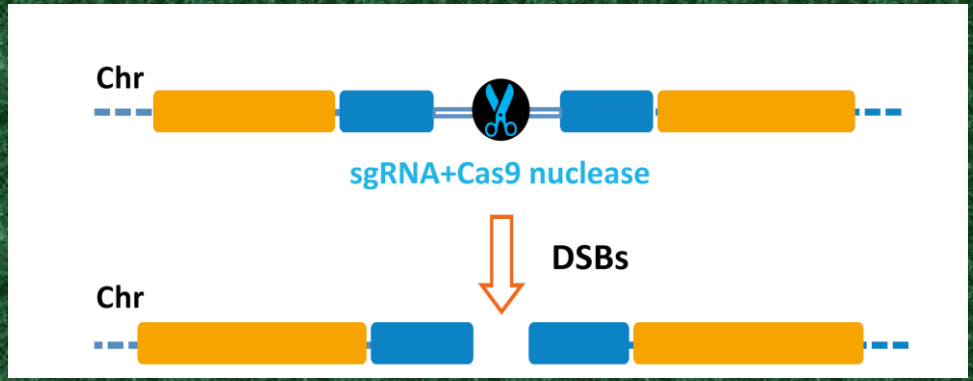
Non-Homologous End-Joining (NHEJ)

Homology-Directed Repair (HDR)



Slide series adapted from
Gantz and Bier 2015

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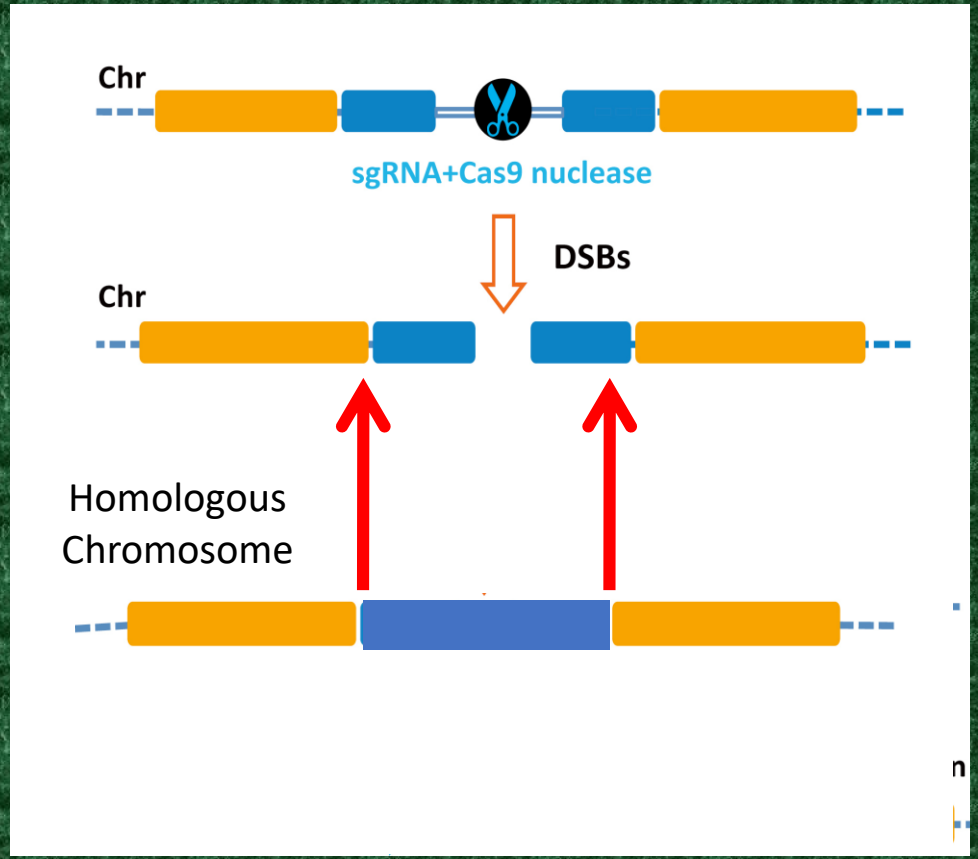
Homology-Directed Repair (HDR)



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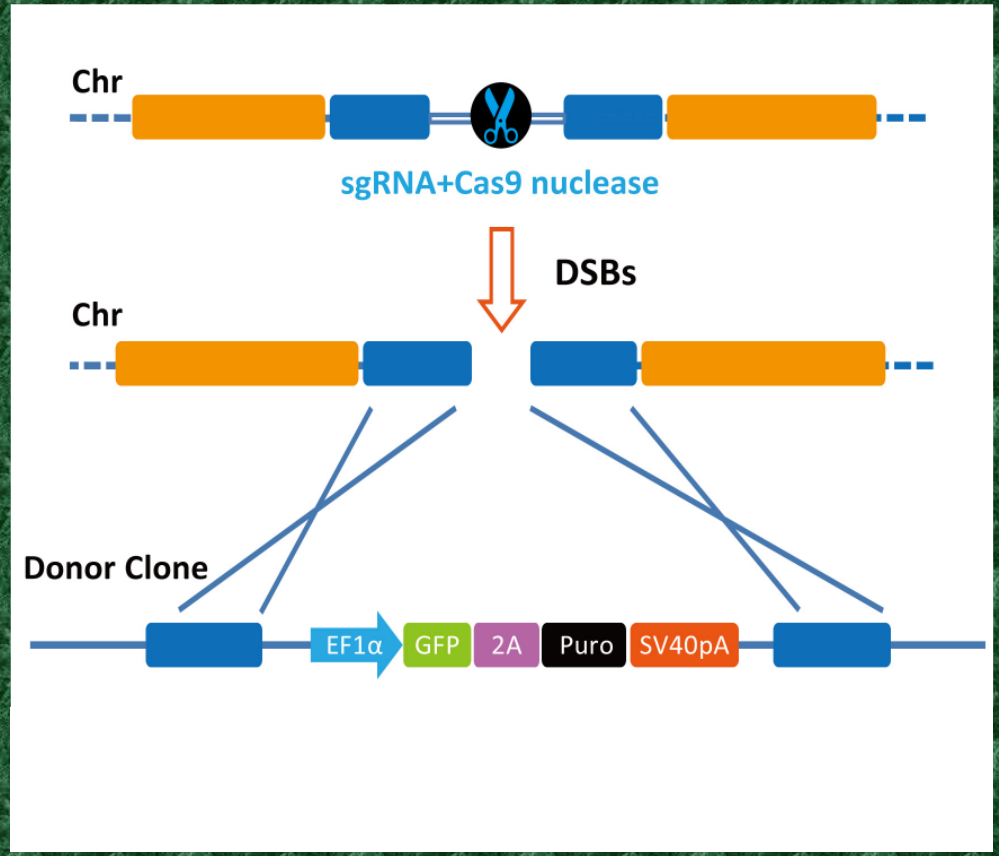

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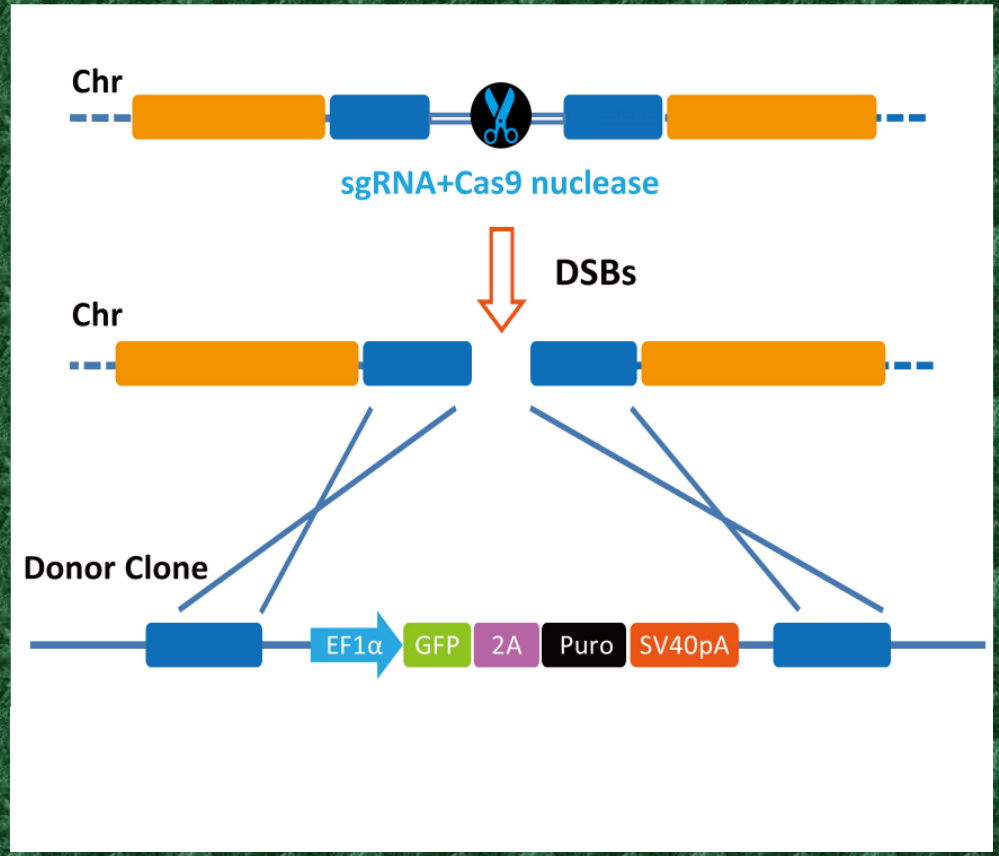
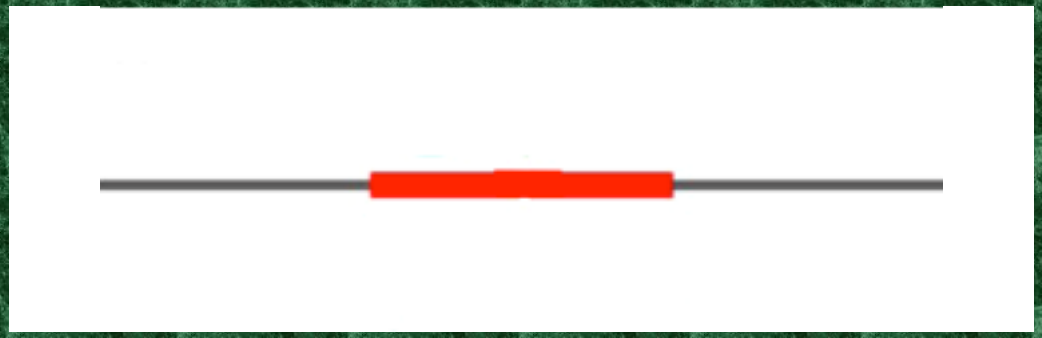
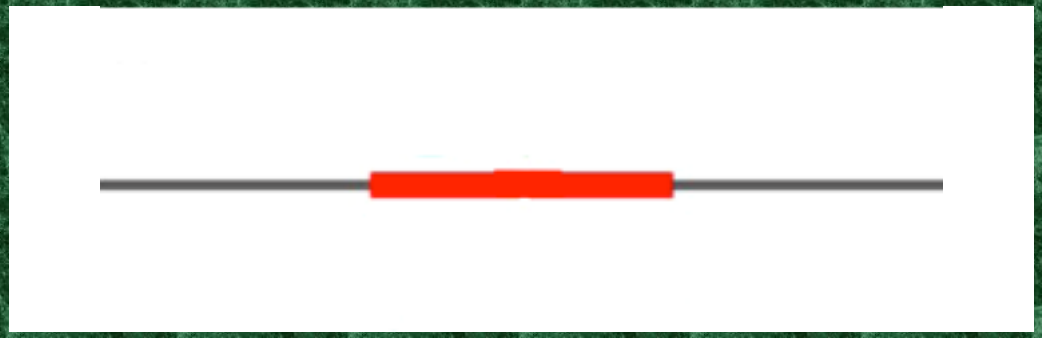


Chromosome segment with target sequence

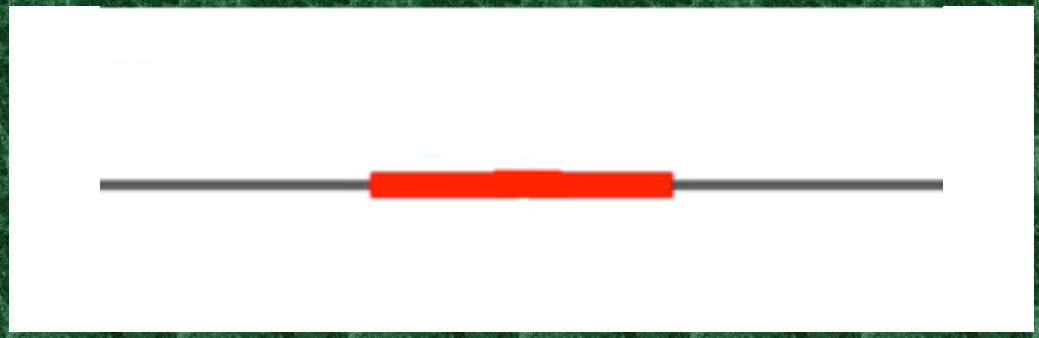


Chromosome segment with target sequence

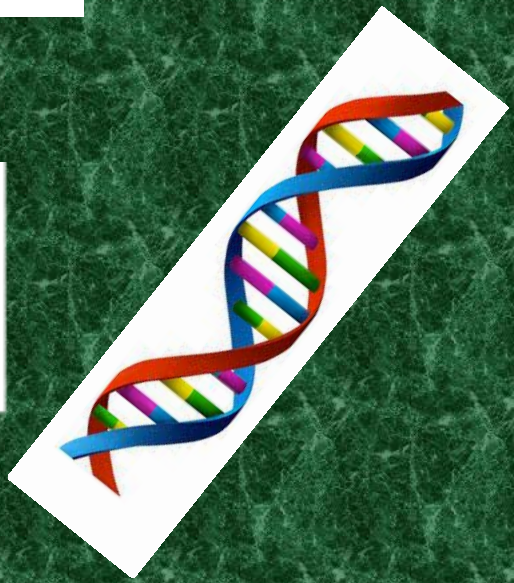


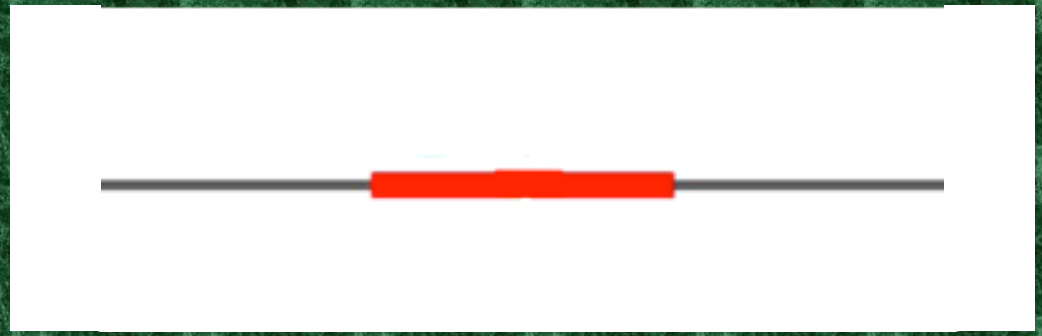
Plasmid with desired gene

Chromosome segment with target sequence

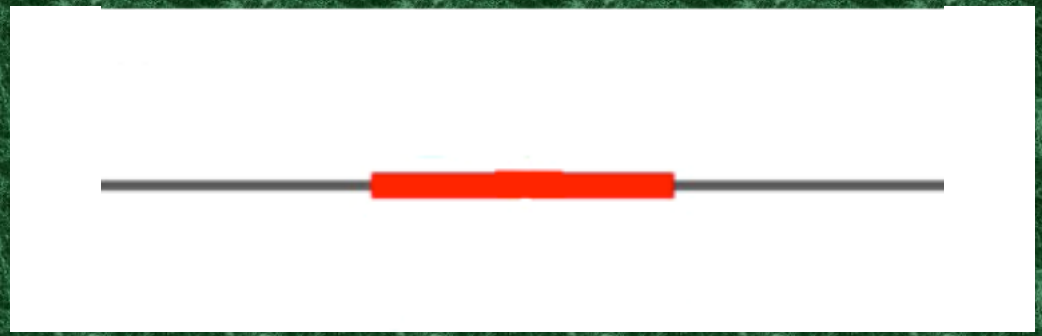


Plasmid with desired gene






HA1
EF1α
GFP
2A
Puro
SV40pA
HA2

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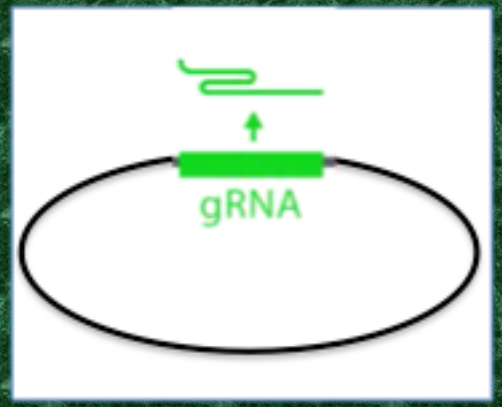
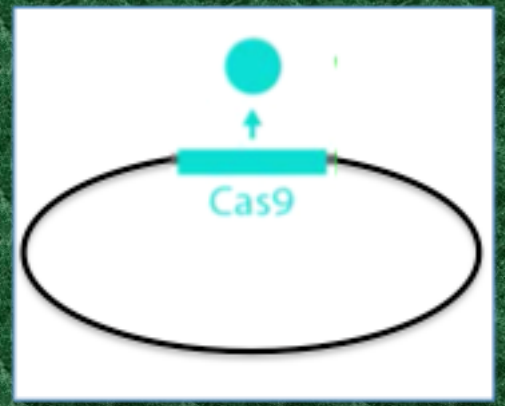
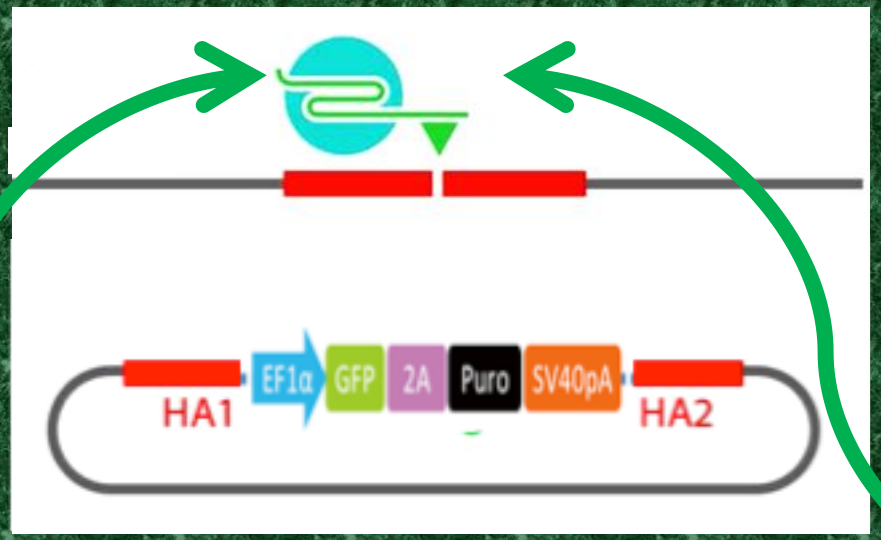

gRNA


Cas9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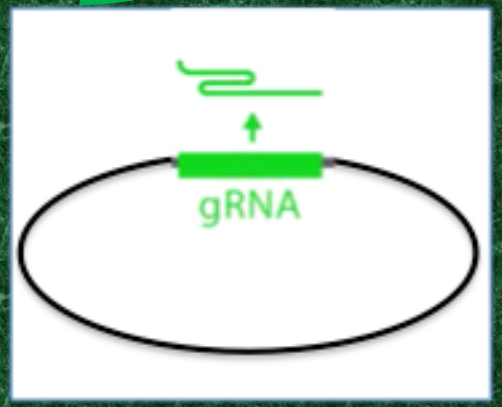
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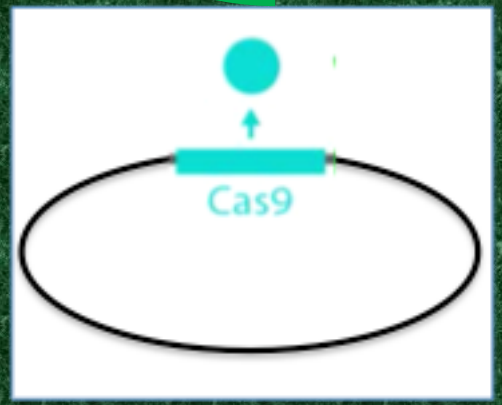
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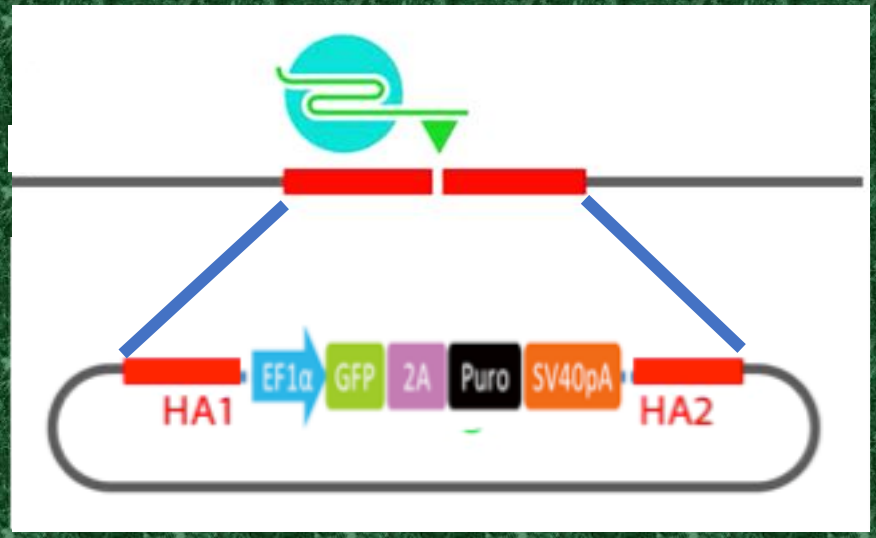
EF1α
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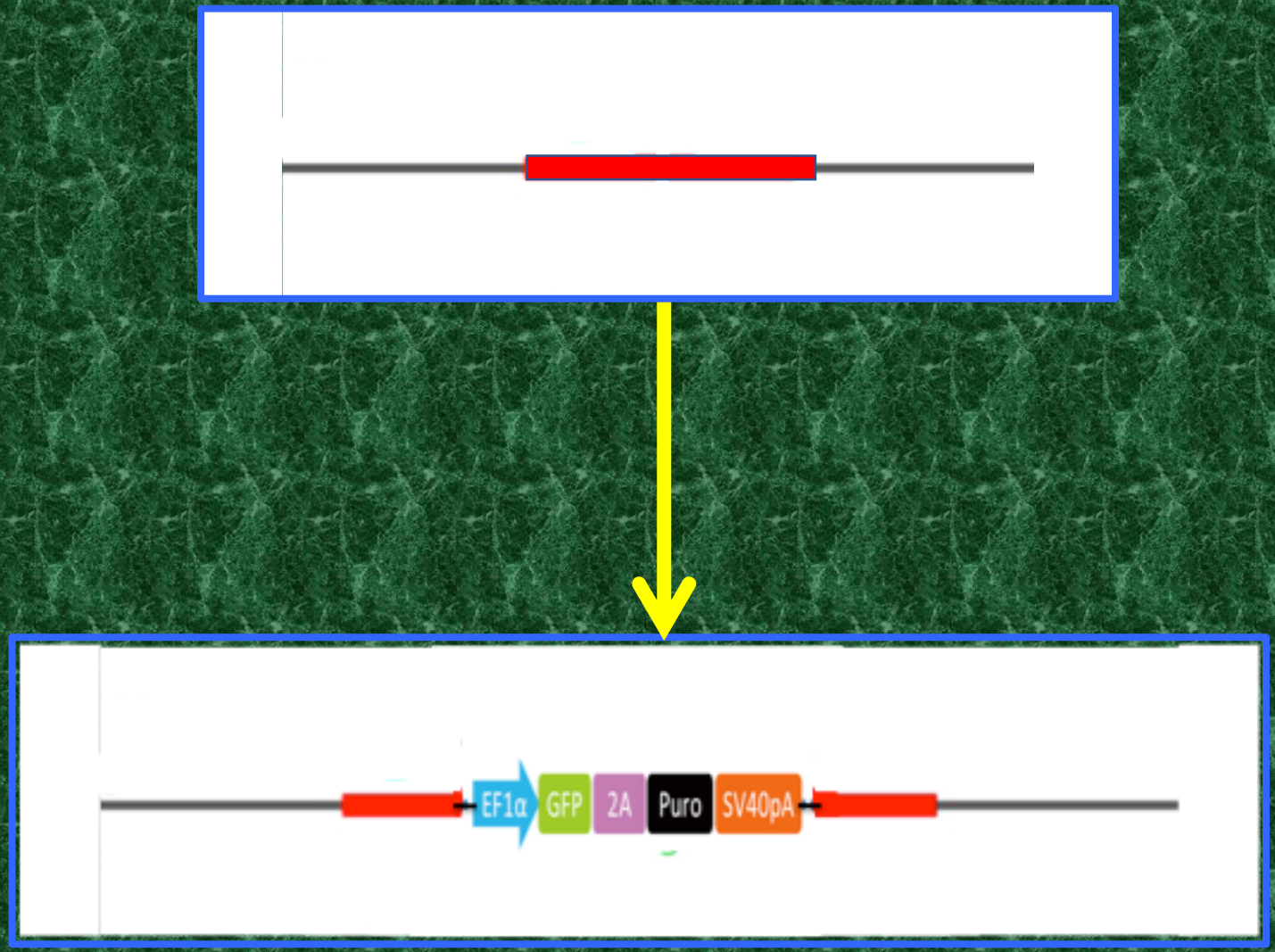
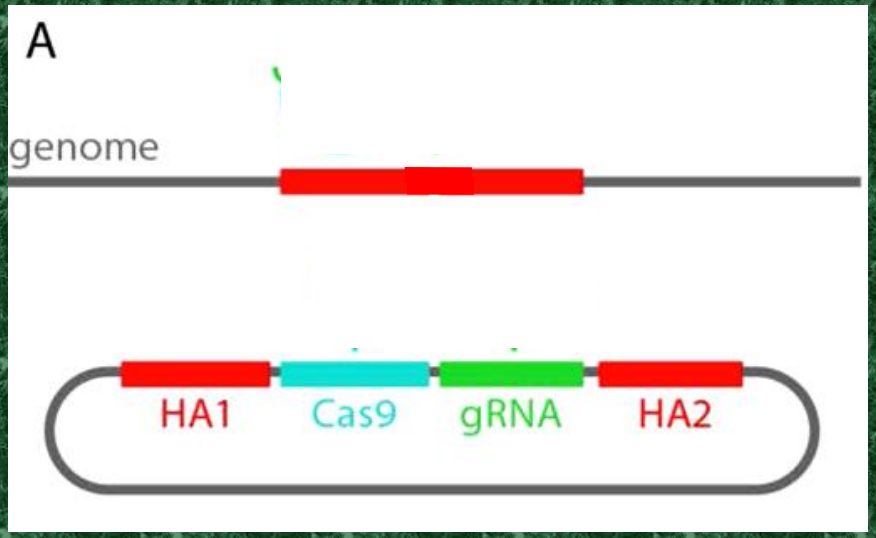
HA1
HA2

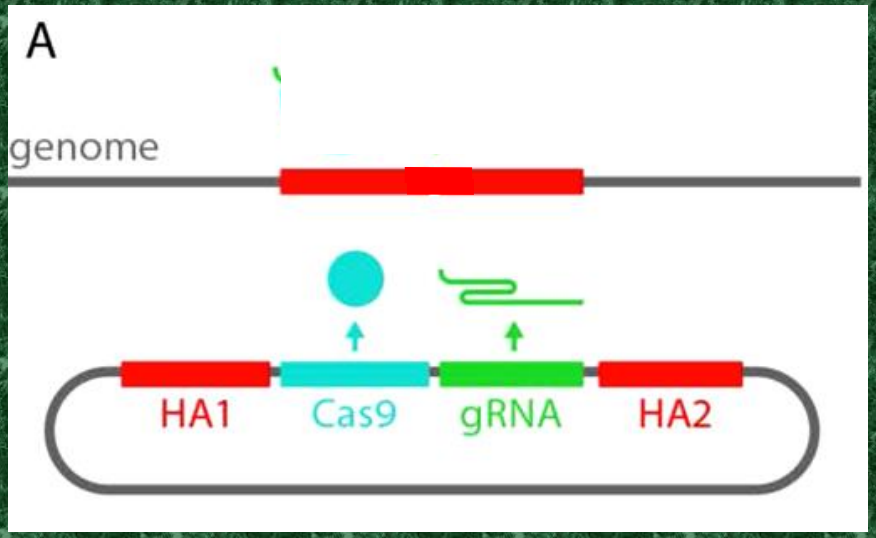

EF1α
GFP
2A
Puro
SV40pA

CRISPR for Gene Drive

Homologue #1



Homologue #1



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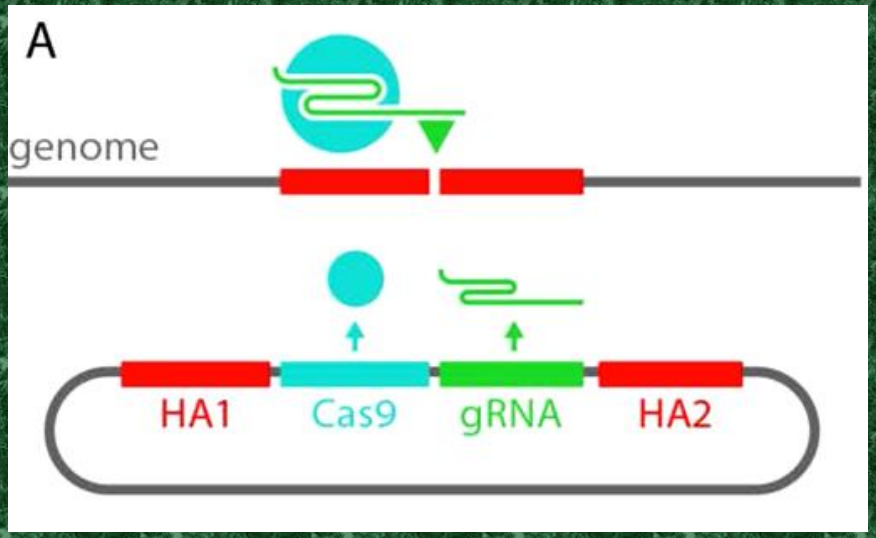

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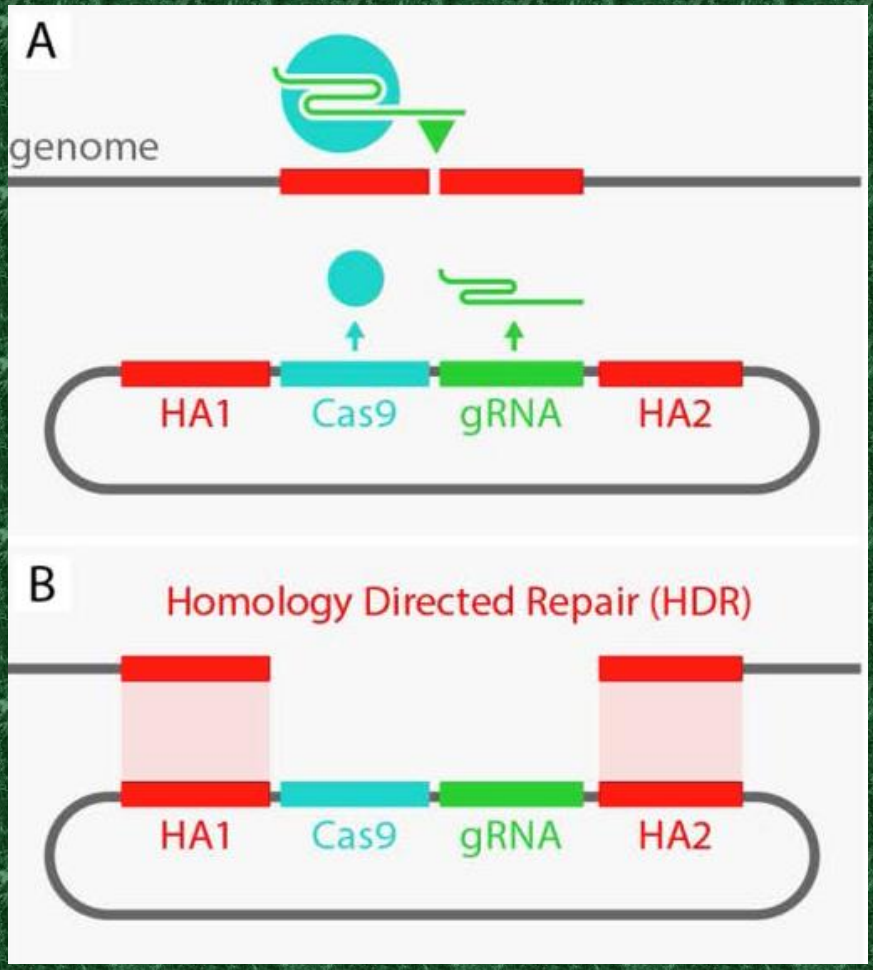
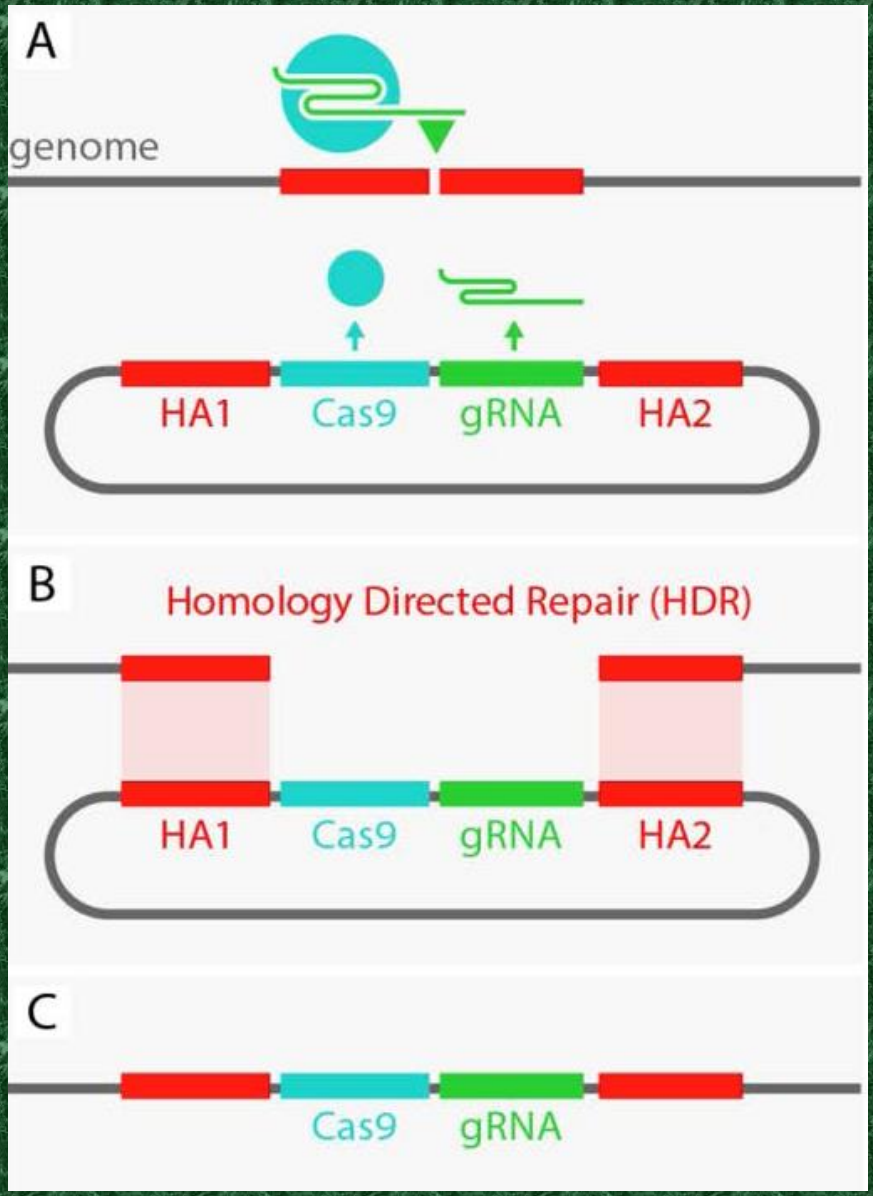
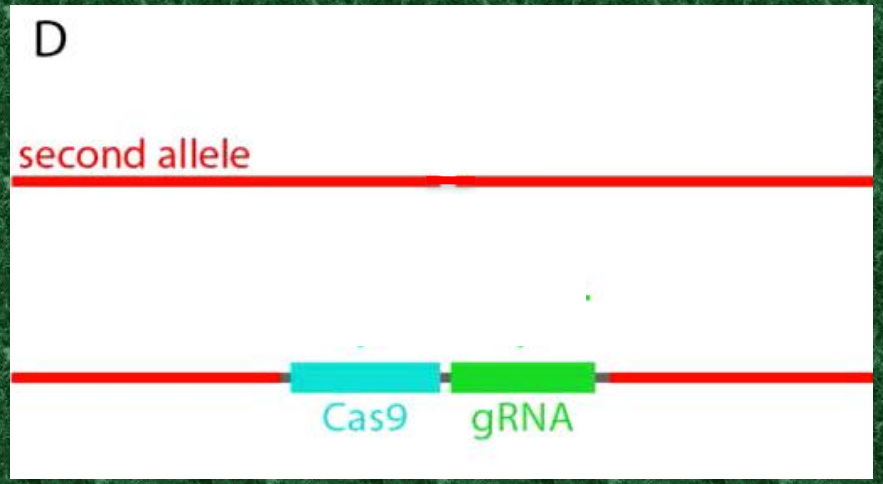

A
genome
HA1
Cas9
gRNA
HA2
B
Homology Directed Repair (HDR)
HA1
Cas9
gRNA
HA2

Homologue #1


A
genome
HA1
Cas9
gRNA
HA2
B
Homology Directed Repair (HDR)
HA1
Cas9
gRNA
HA2
C
Cas9
gRNA

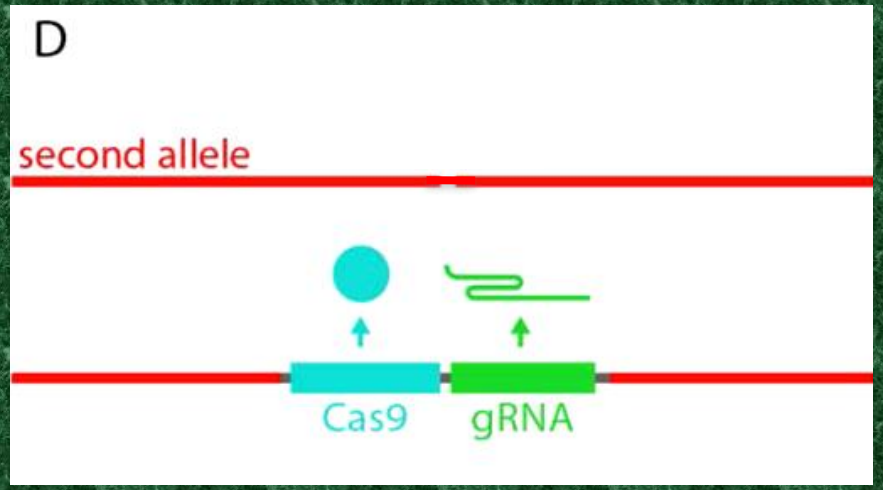
Homologue #2

Homologue #1



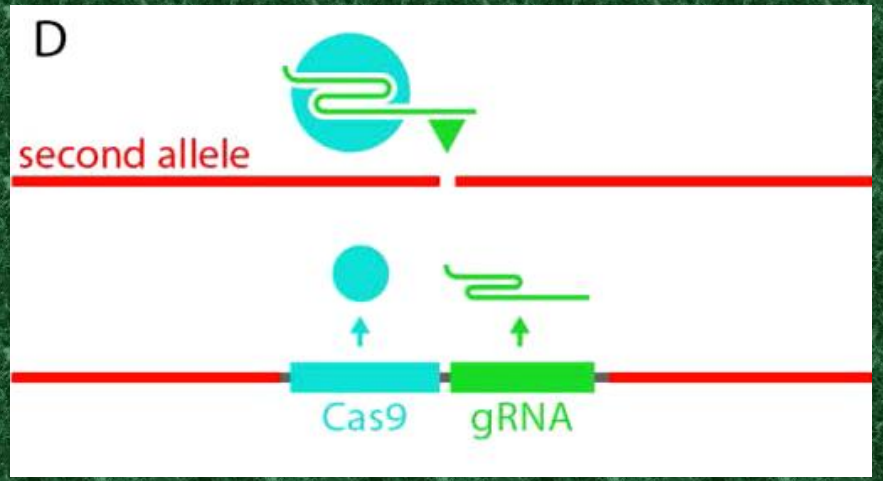
Homologue #2

Homologue #1



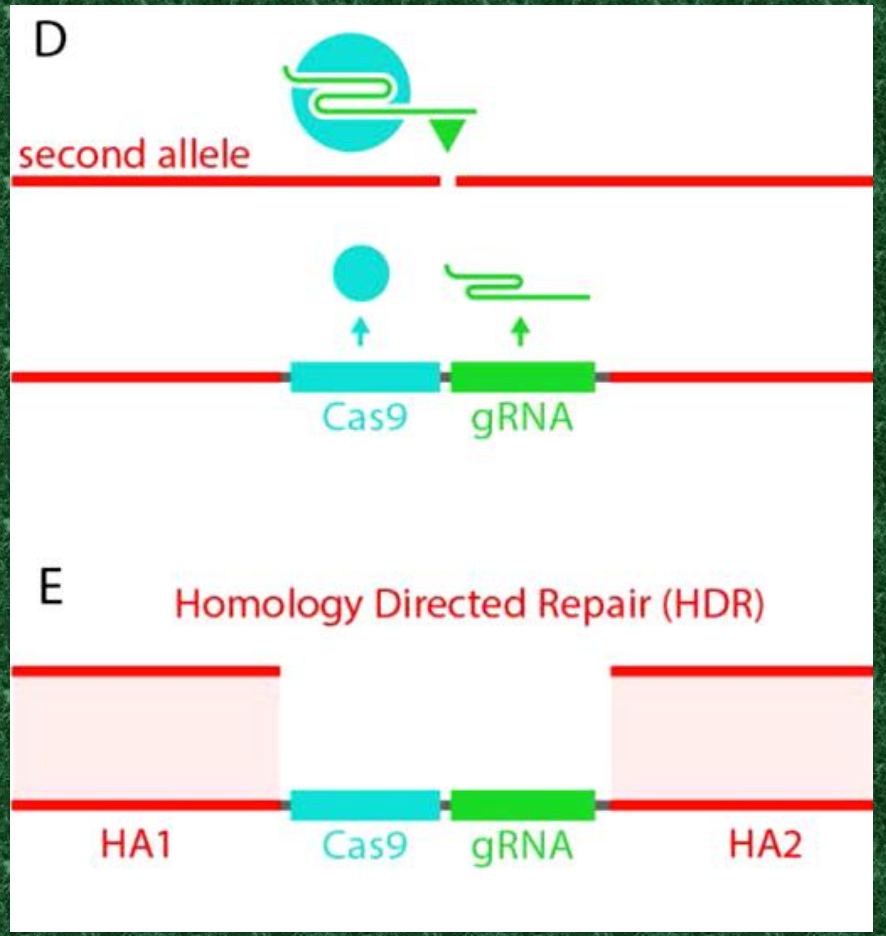
Homologue #2

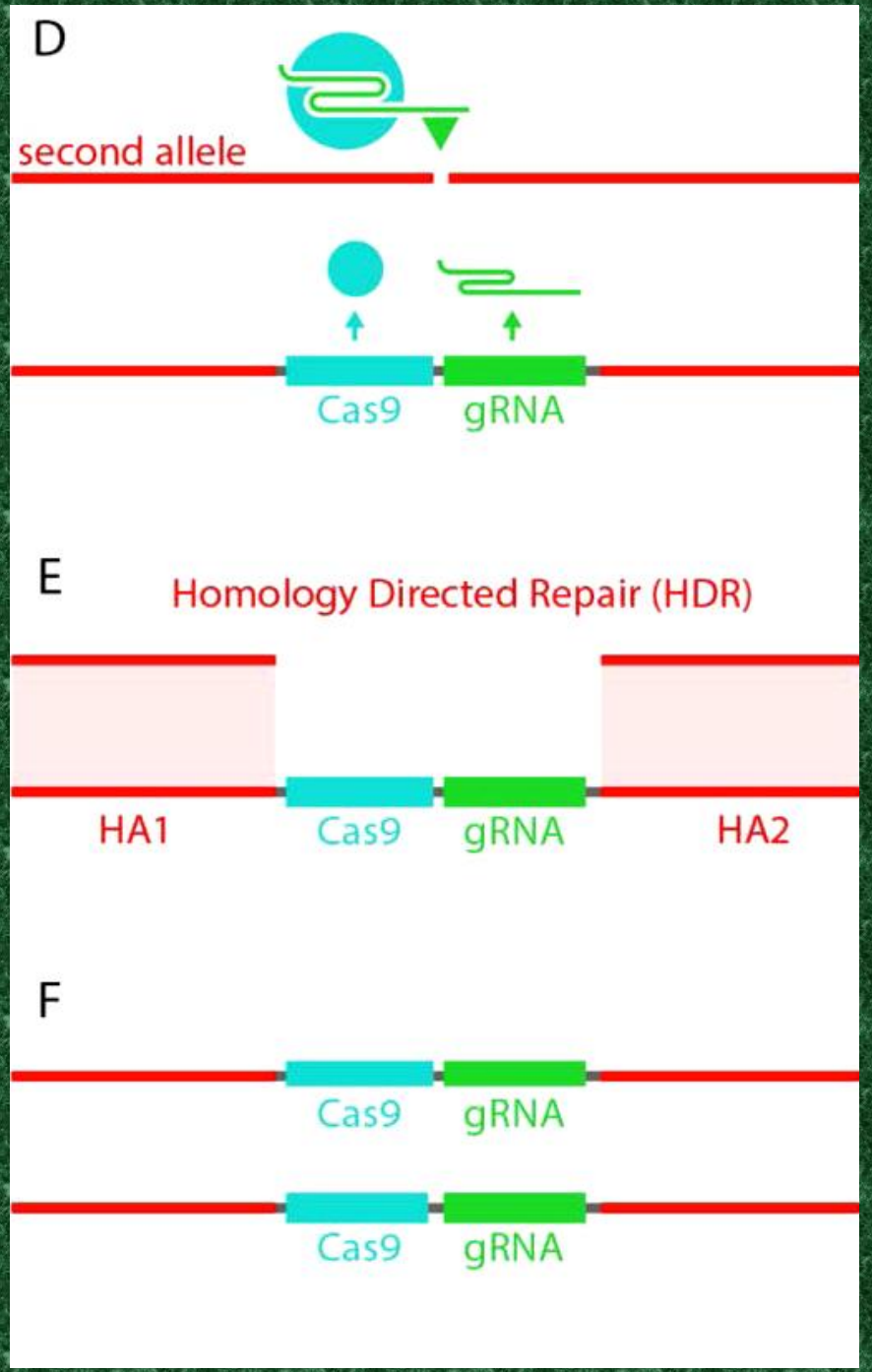
Homologue #1



Homologue #2

Homologue #1





Homologue #2

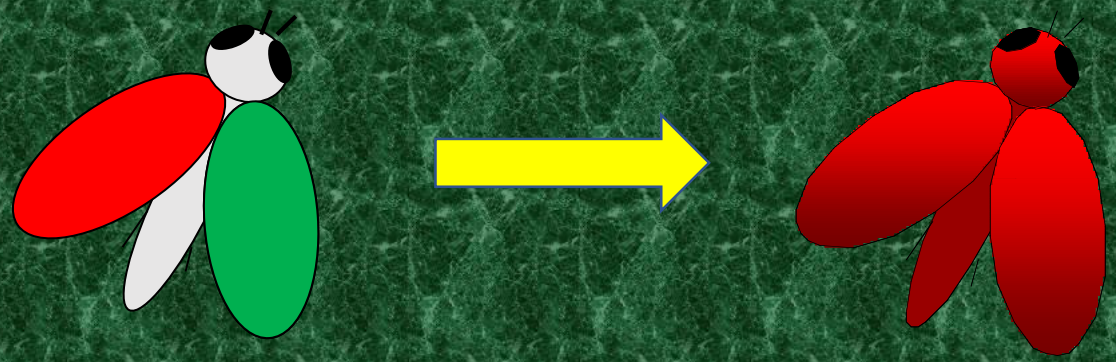
Homologue #1

March 2015

Sciencexpress

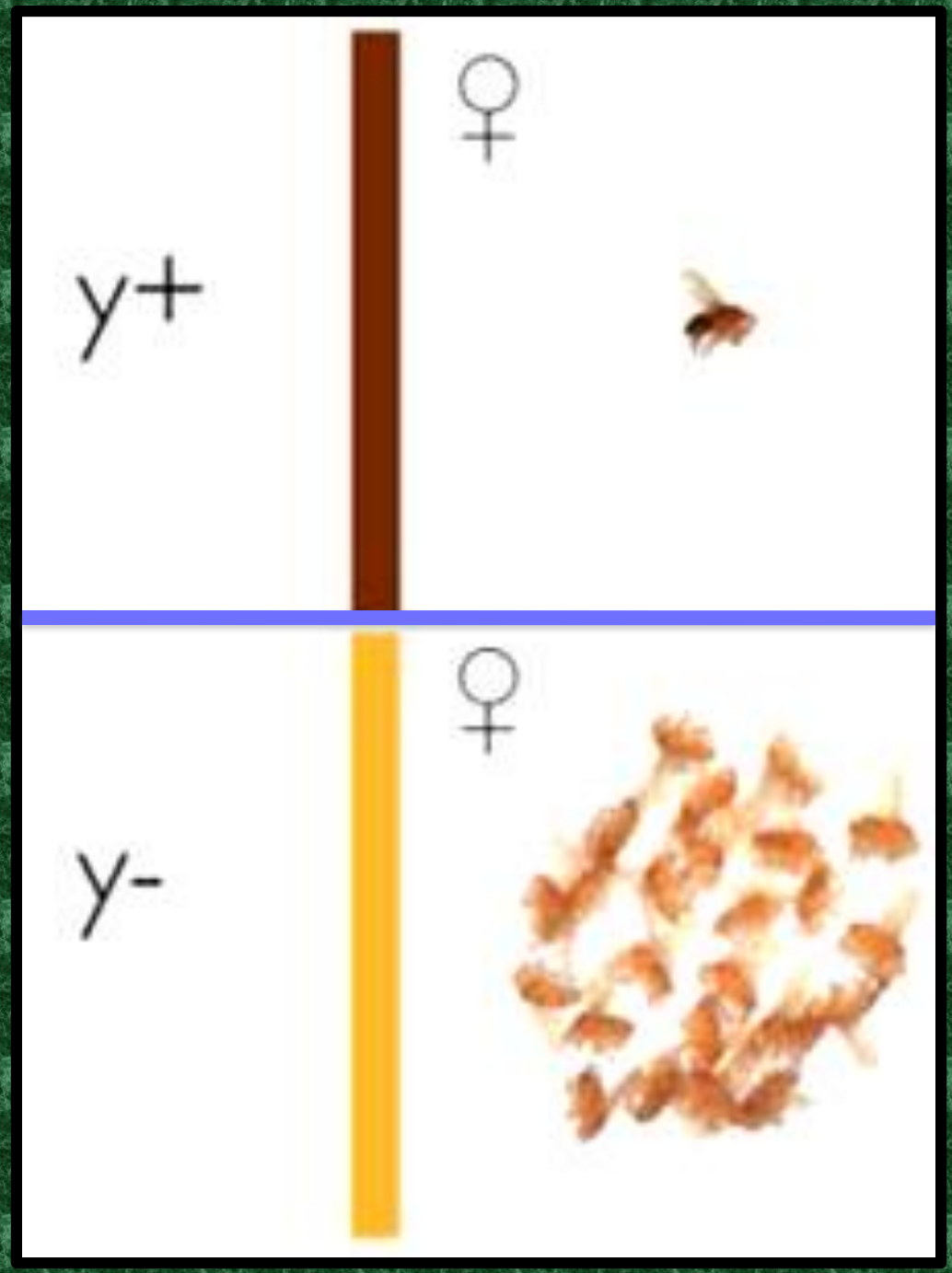
The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations

Valentino M. Gantz* and Ethan Bier*

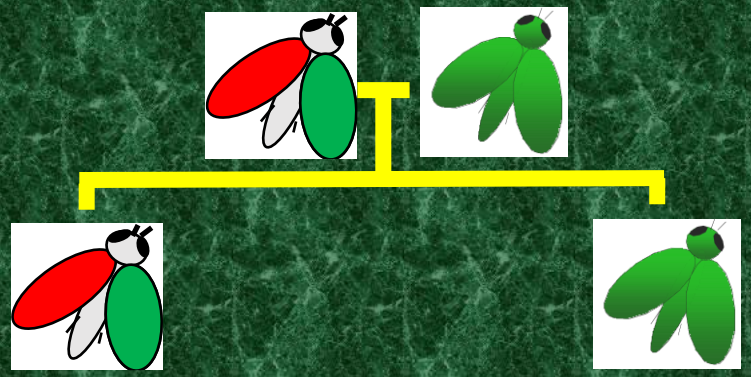


Wild Type
or
Heterozygote

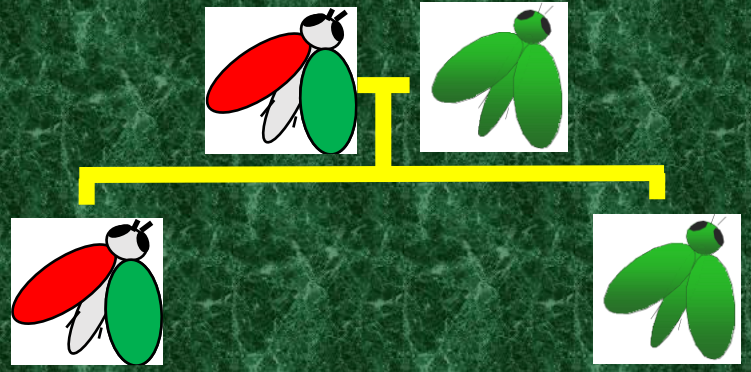
Homozygous
mutant


y+
♀
y-
♀

Mendelian Inheritance



Mendelian Inheritance



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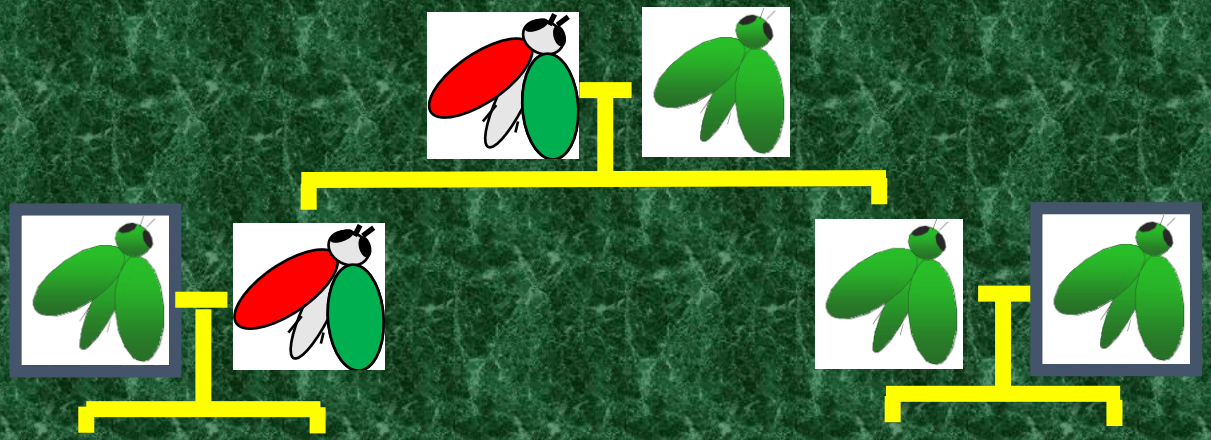

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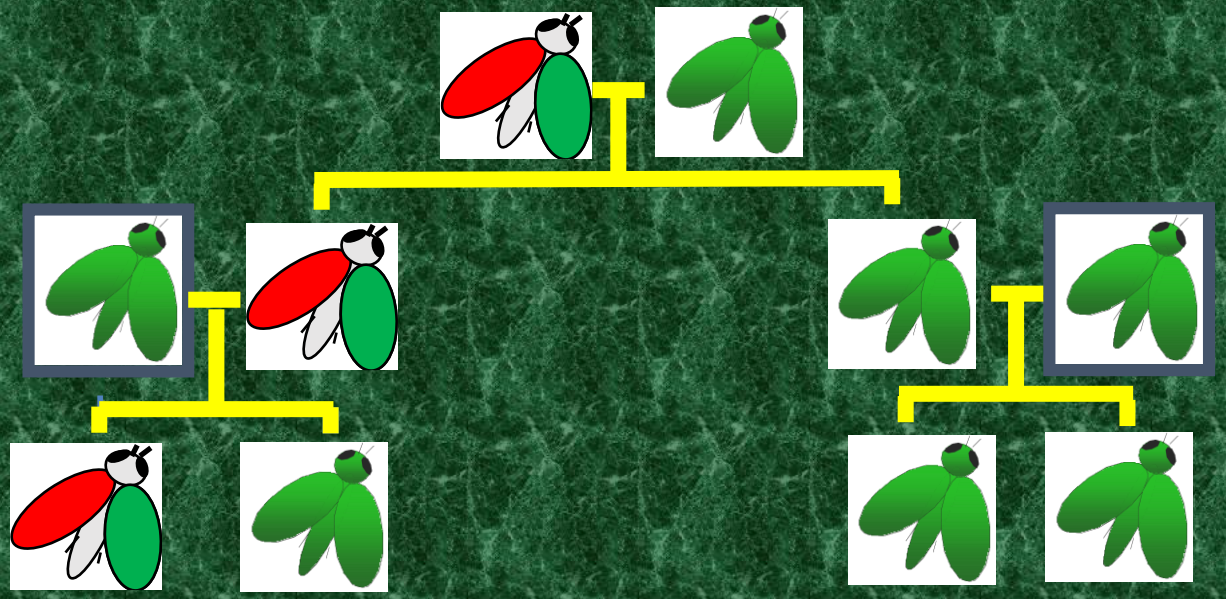

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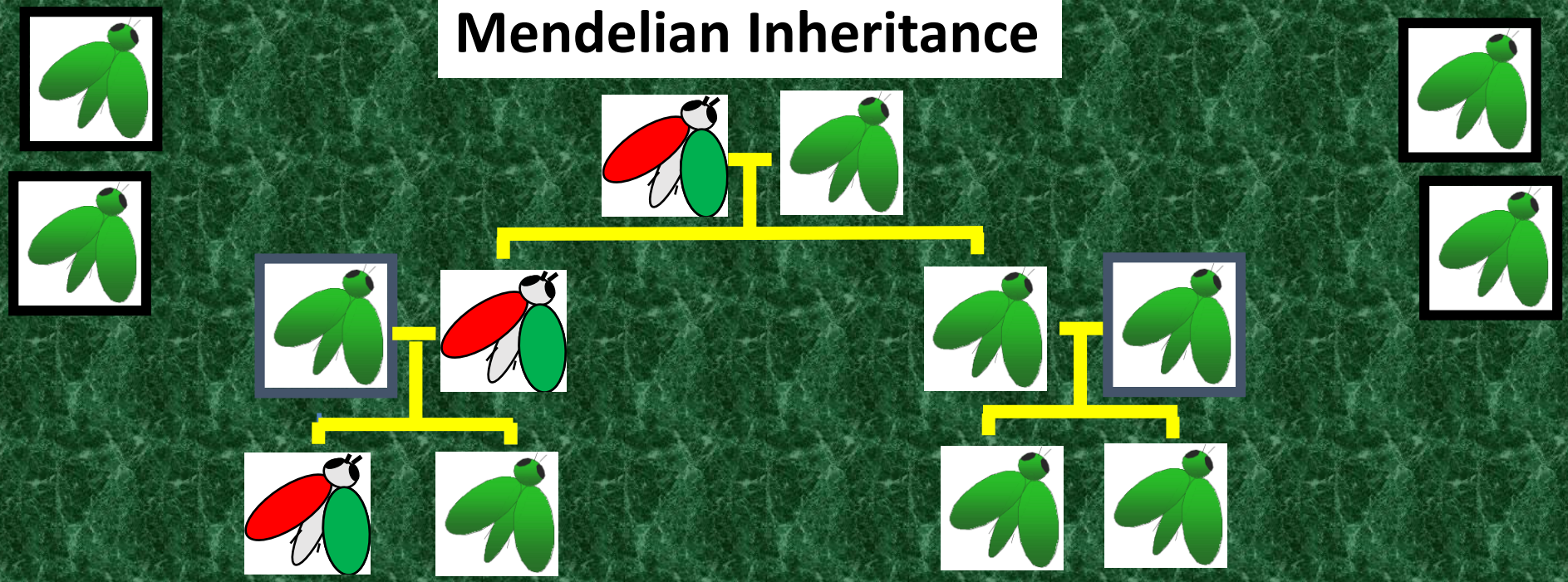
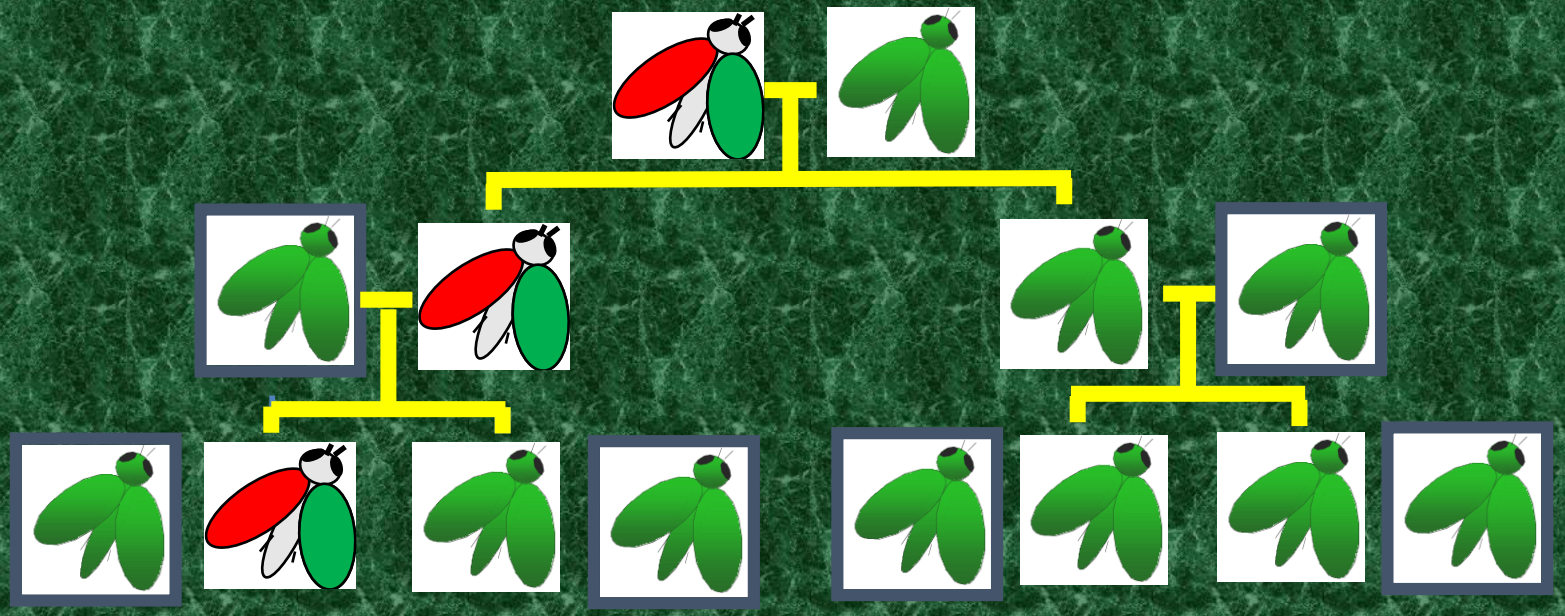
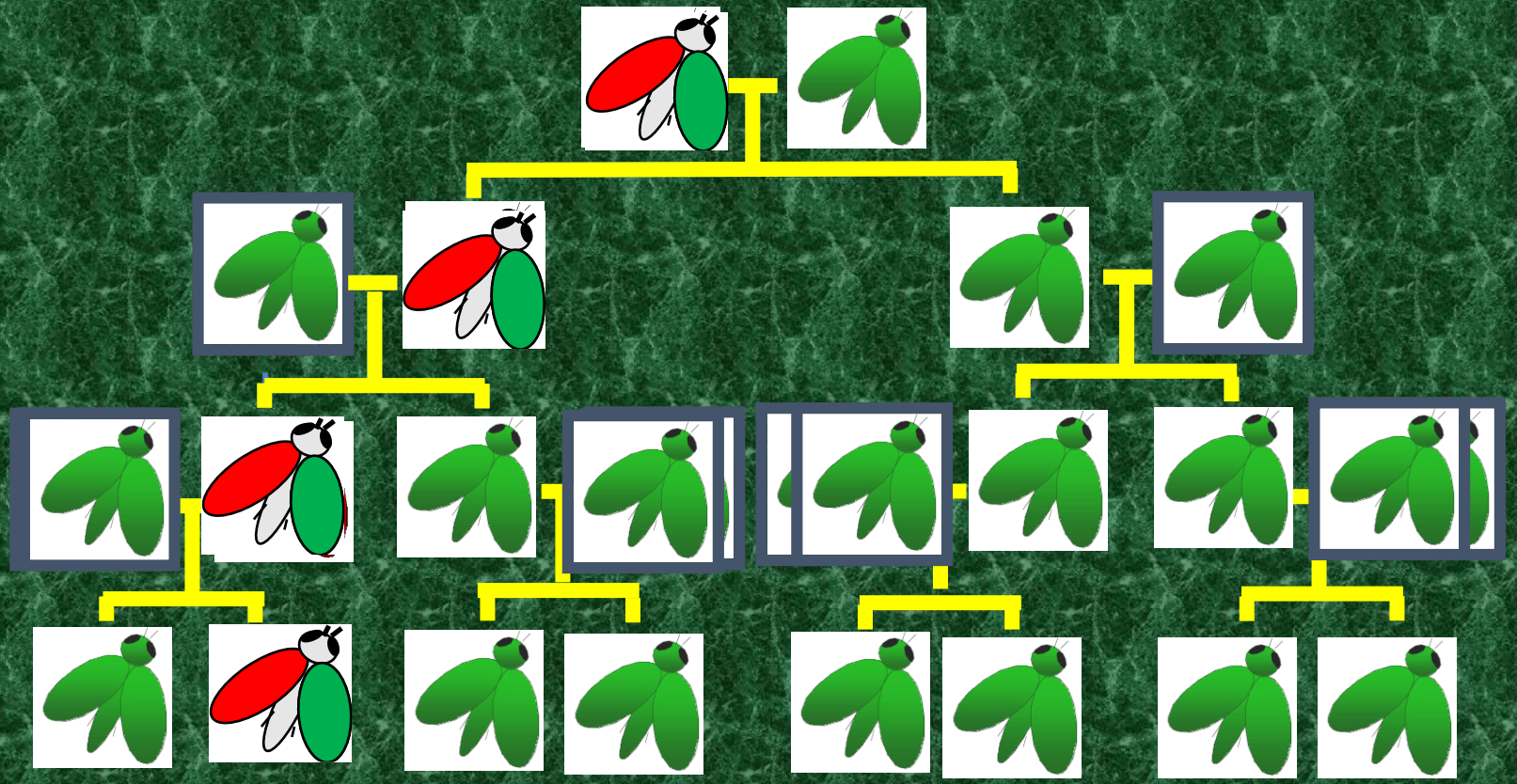


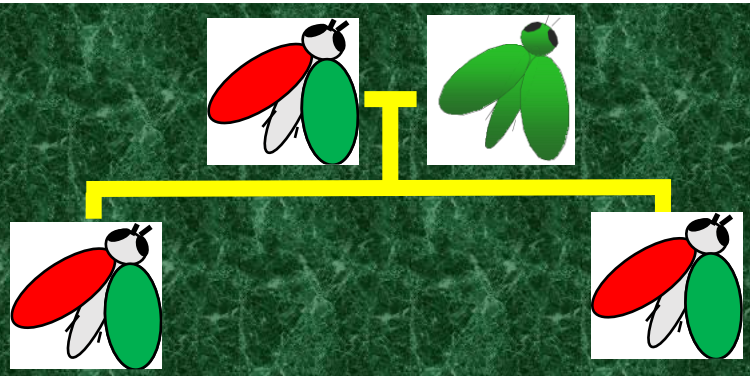
Mendelian Inheritance



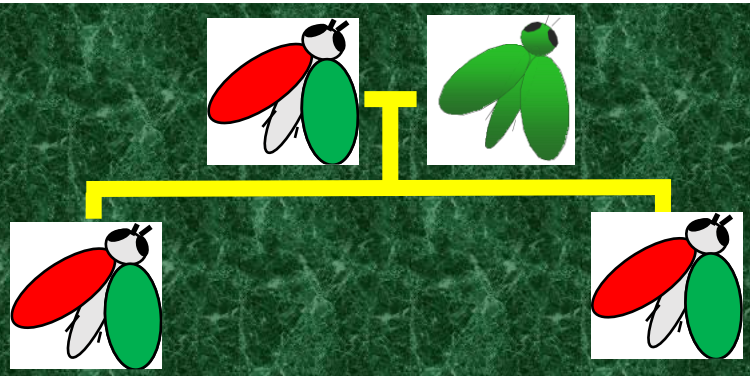
Mendelian Inheritance

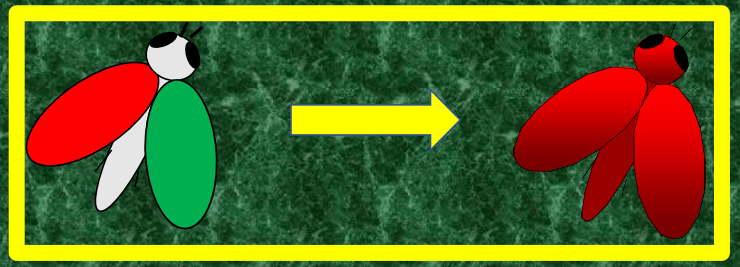


Super-Mendelian Inheritance



Super-Mendelian Inheritance





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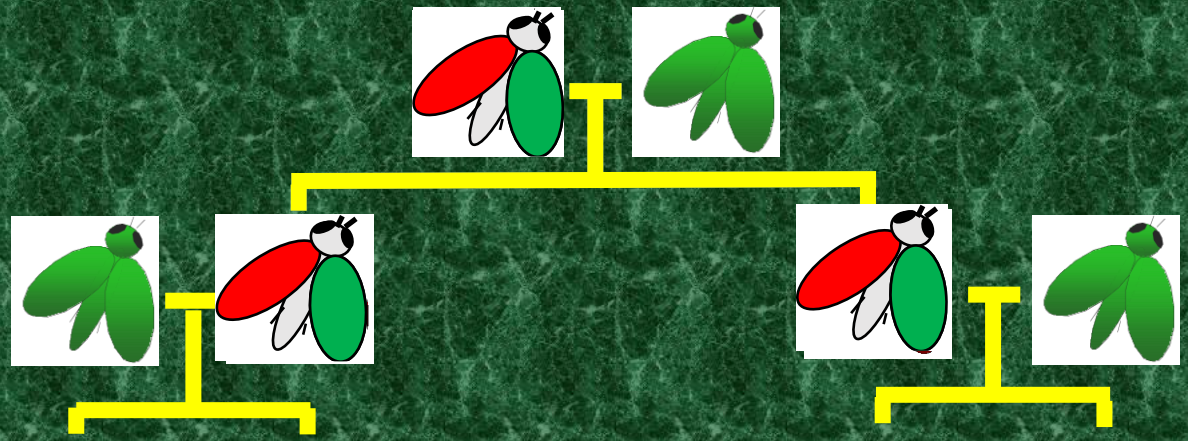

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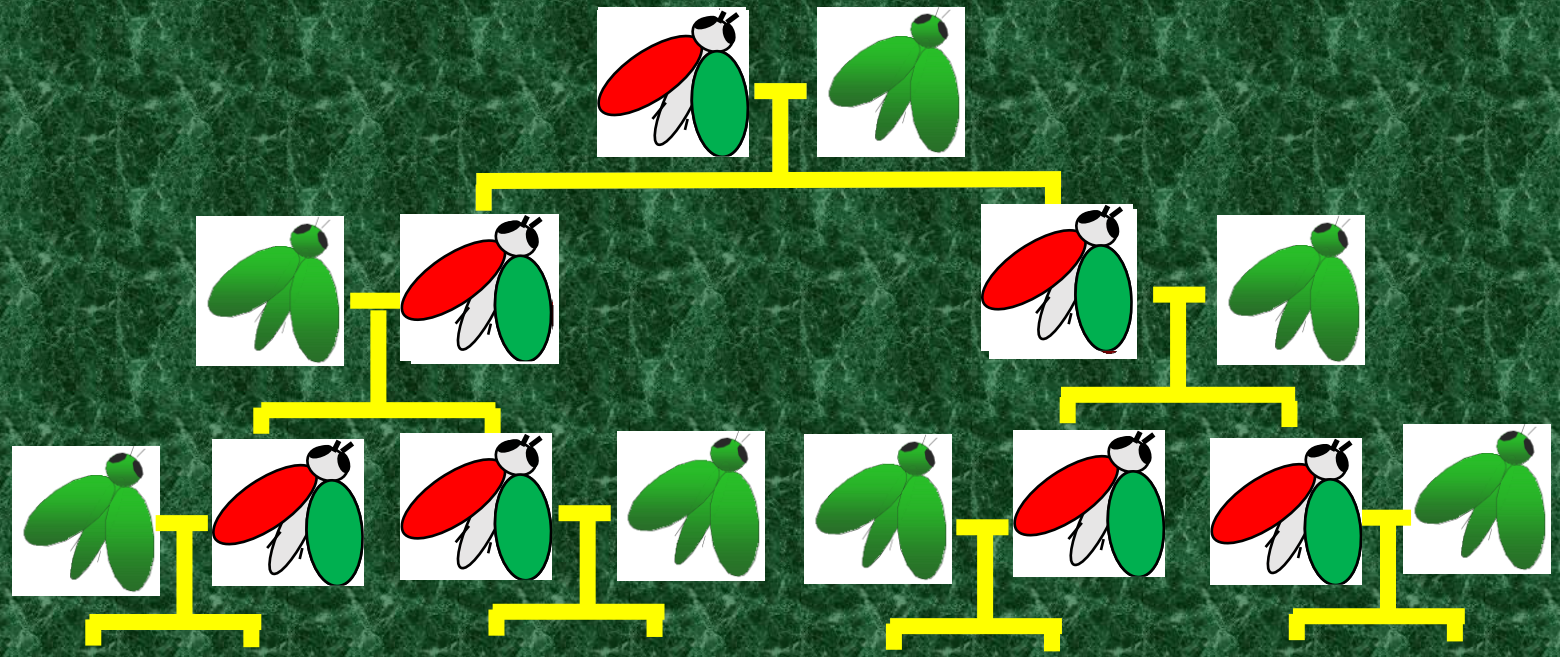

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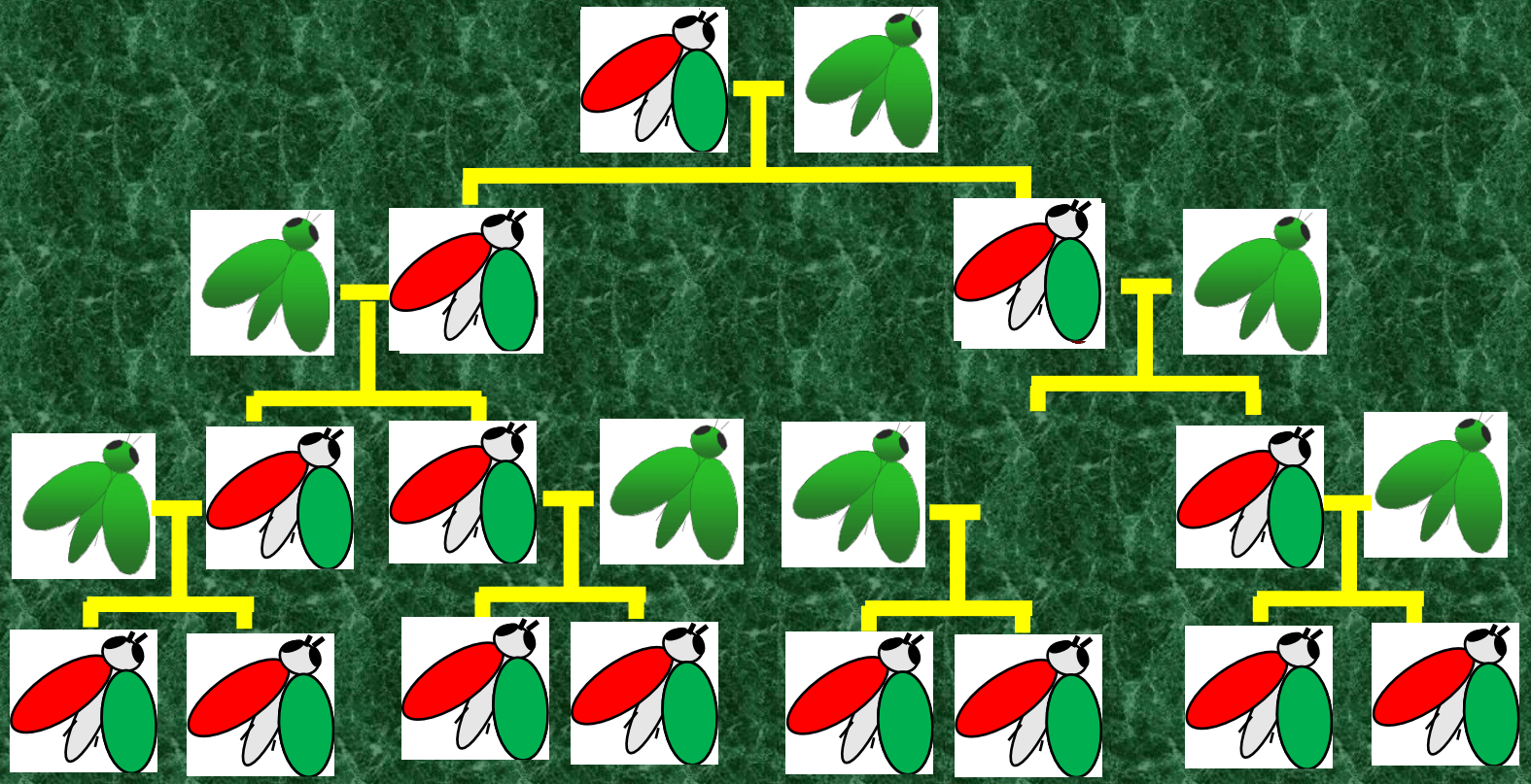
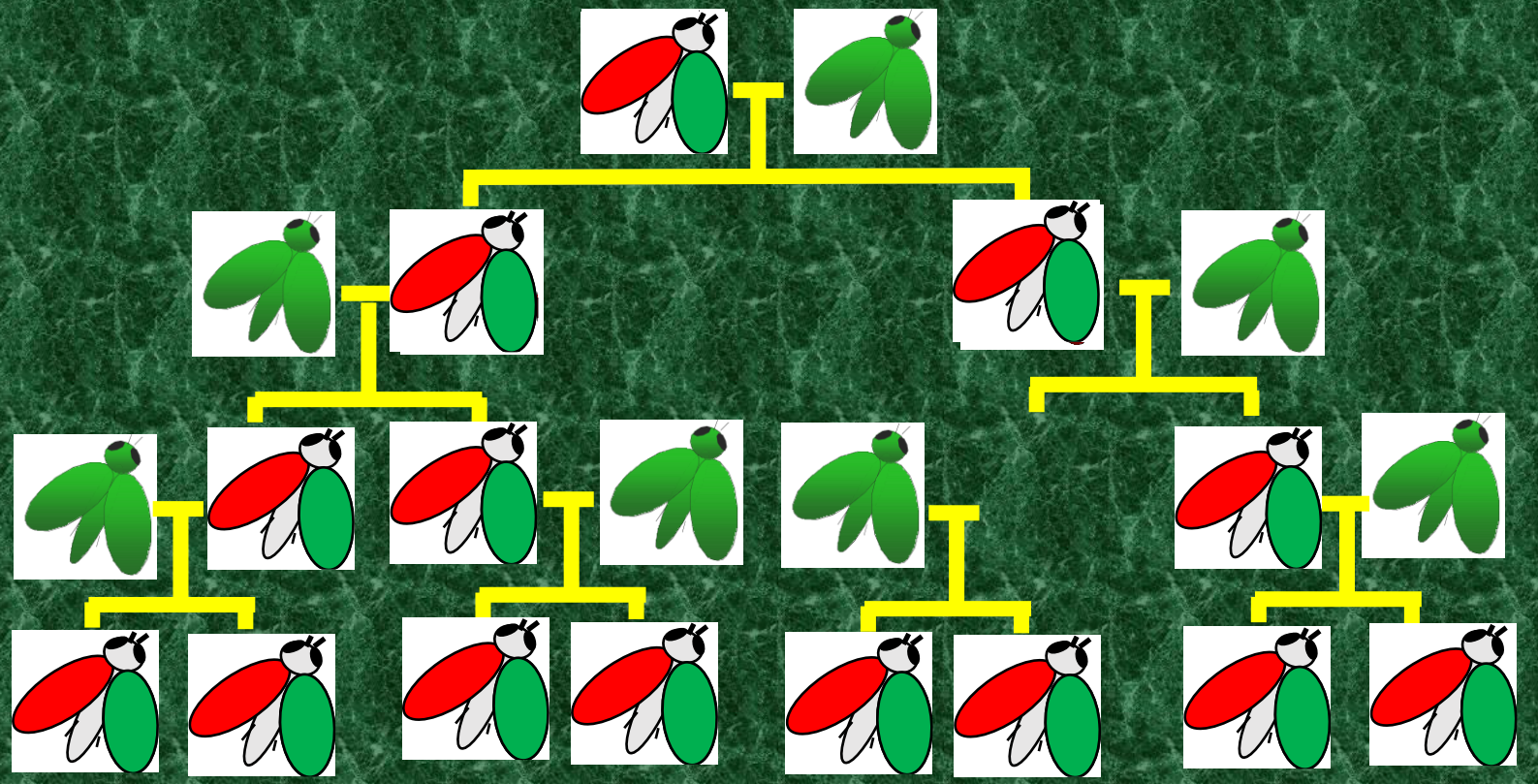
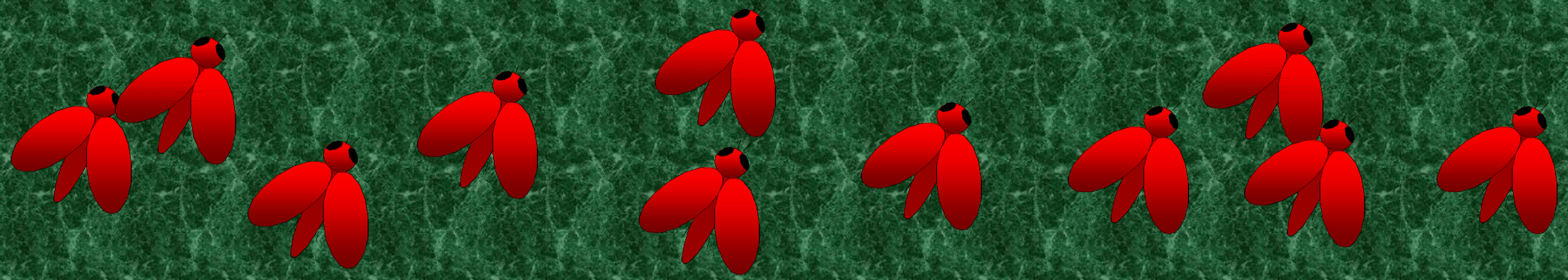


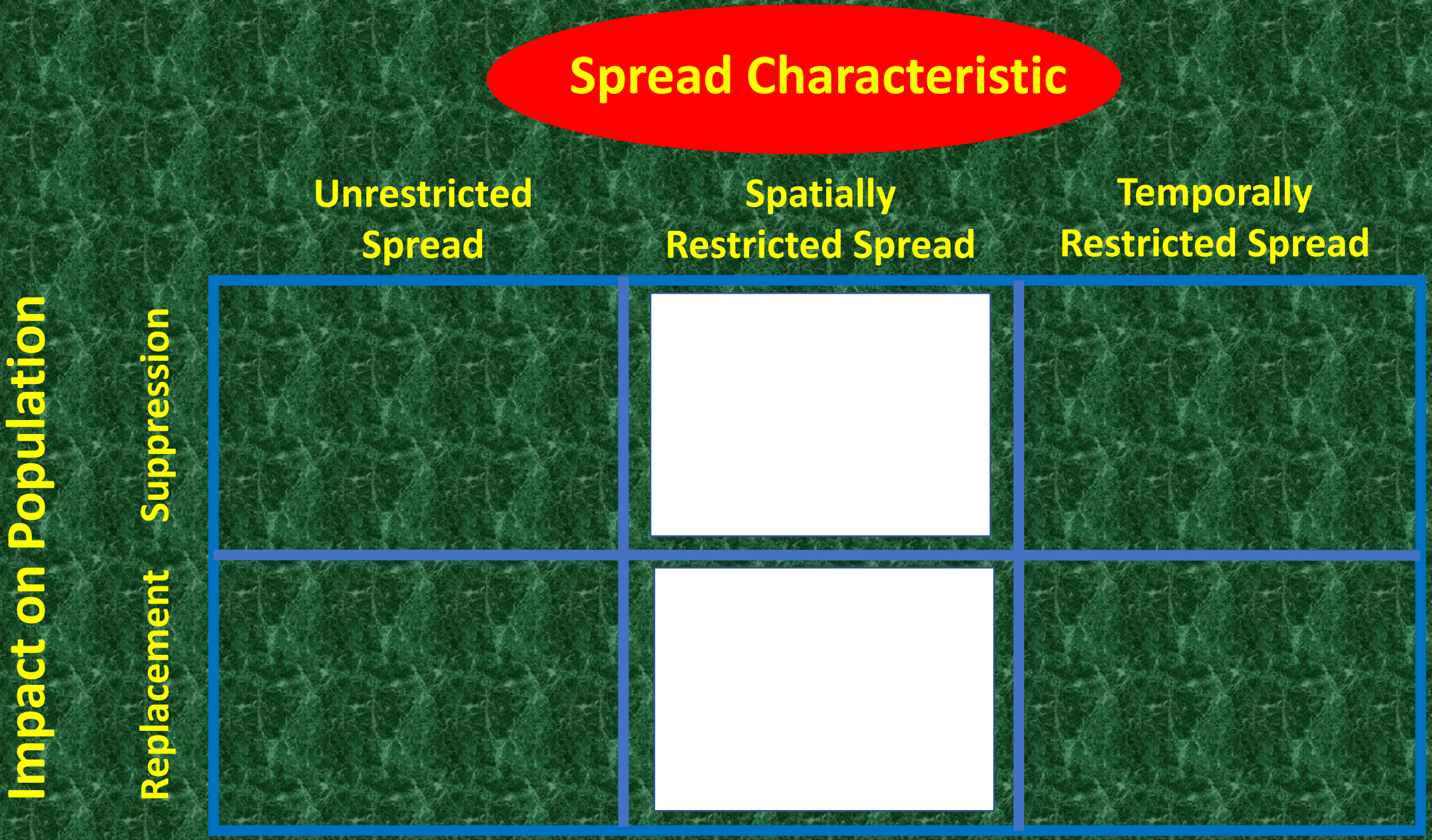
Super-Mendelian Inheritance



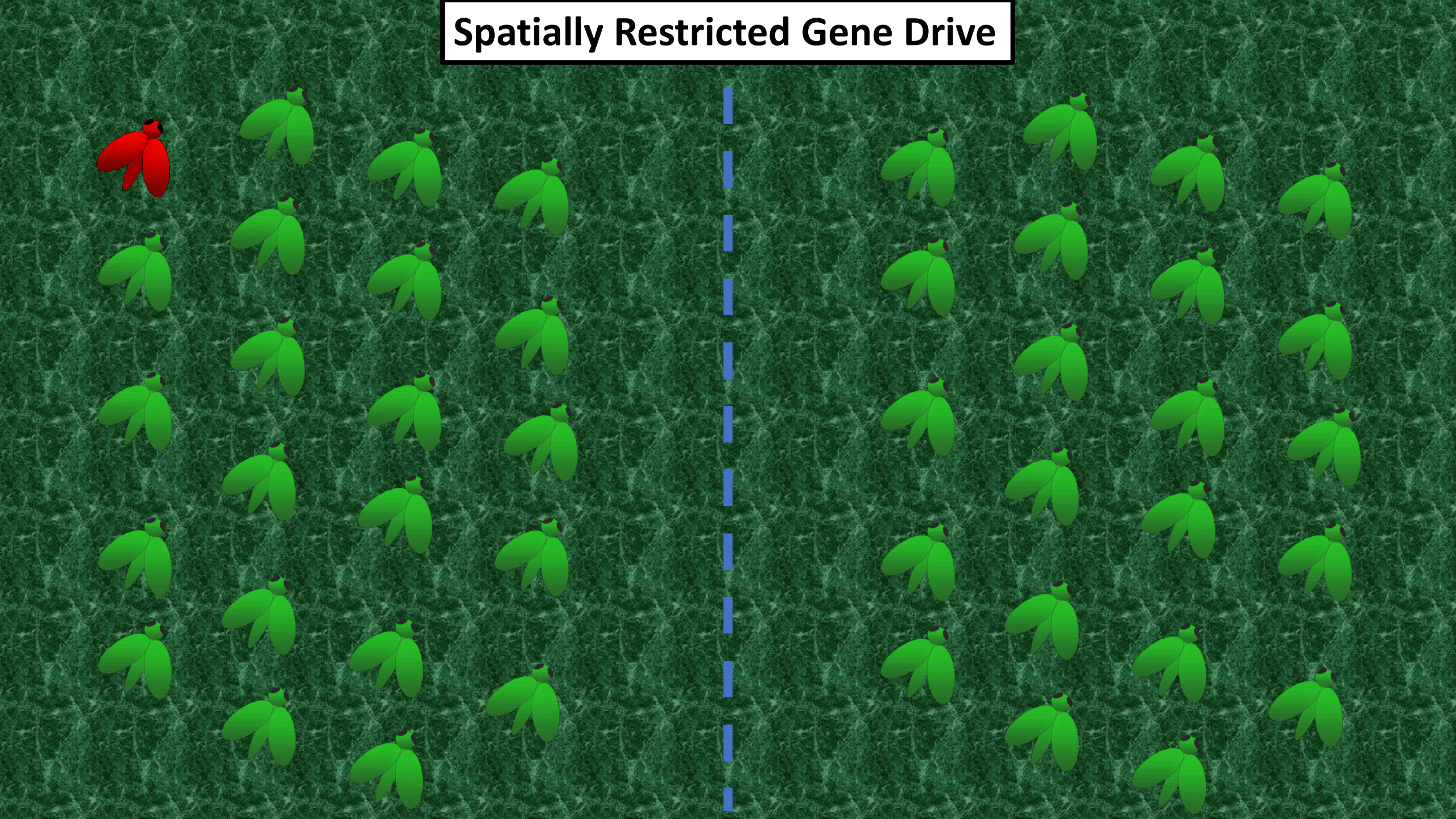


Spread Characteristic

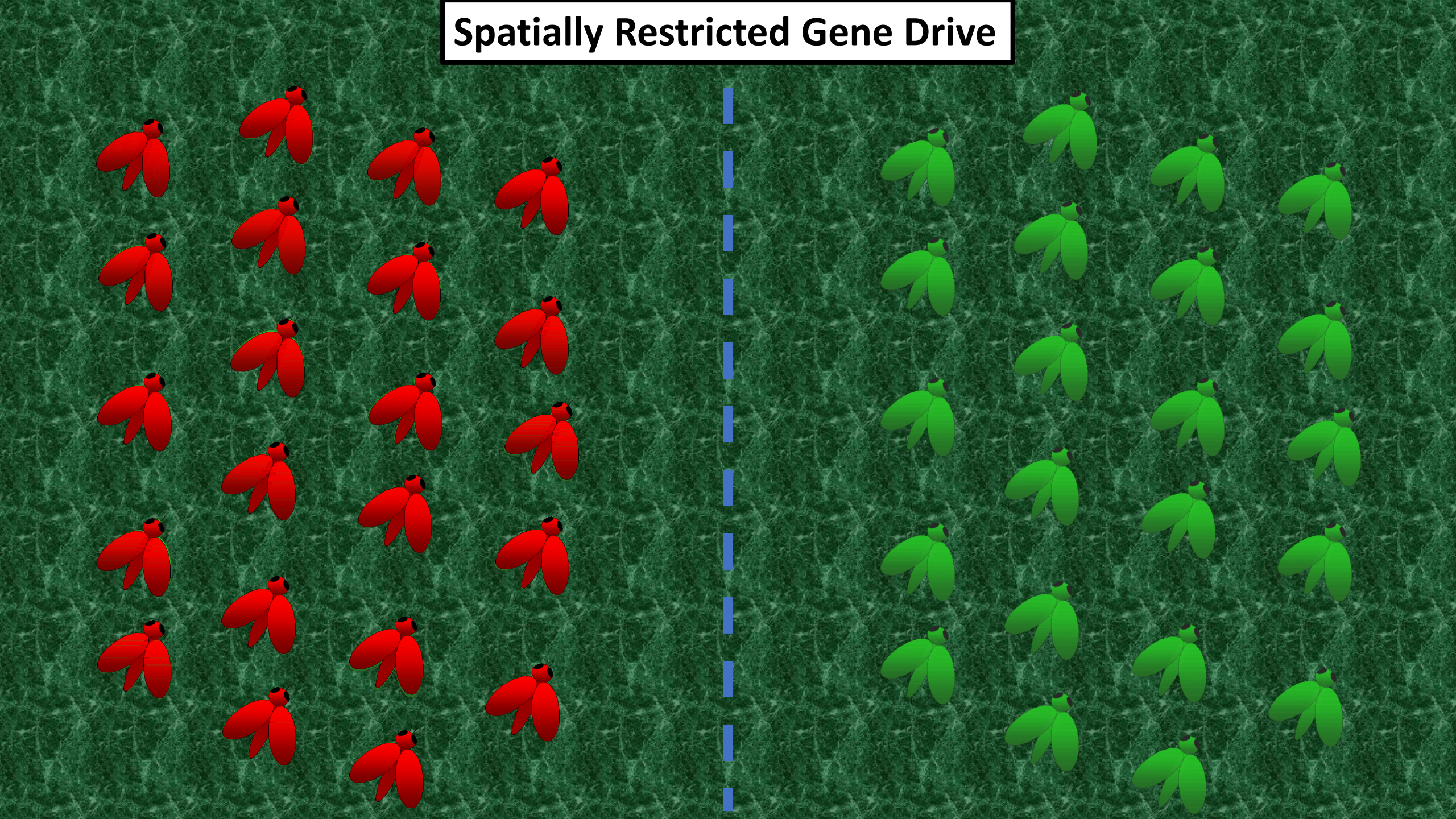
Impact on Population	Unrestricted Spread	Spatially Restricted Spread	Temporally Restricted Spread
Suppression			
Replacement			


Spread Characteristic
Unrestricted Spread
Spatially Restricted Spread
Temporally Restricted Spread
Impact on Population
Suppression
Replacement

Spatially Restricted Gene Drive



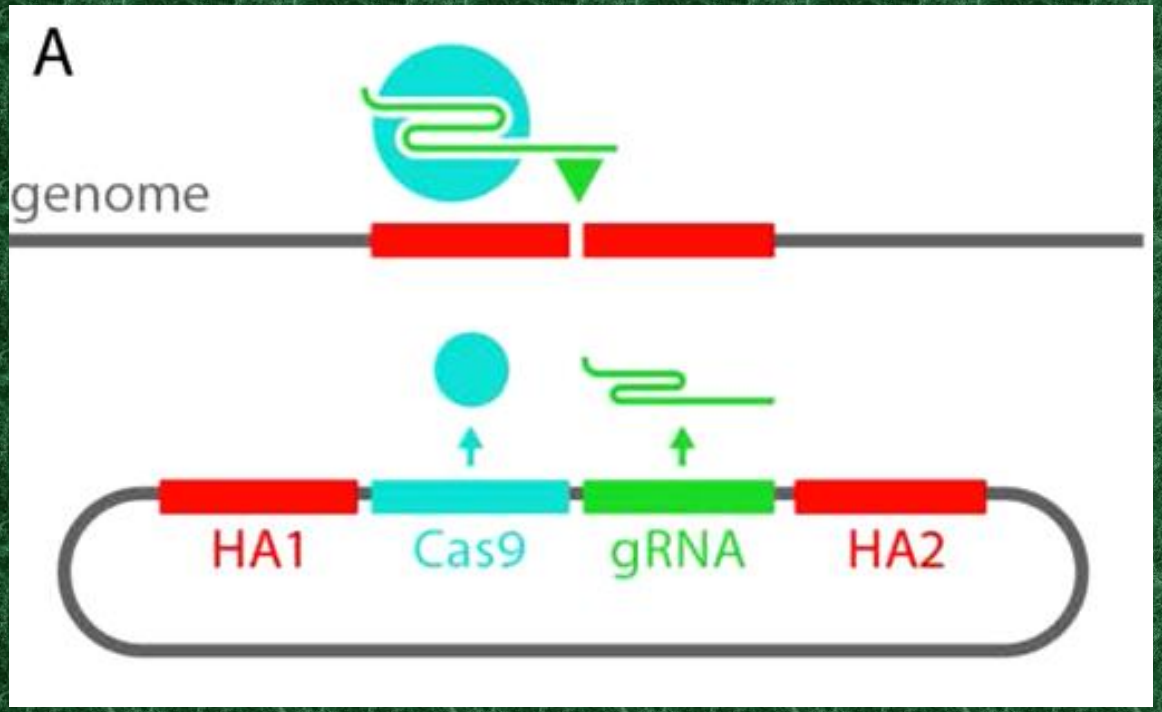
Spatially Restricted Gene Drive



Locally Fixed Alleles: A method to localize gene drive to island populations

Jaye Sudweeks, Brandon Hollingsworth, Dimitri V. Blondel, Karl J. Campbell, Sumit Dhole, John D. Eisemann, Owain Edwards, John Godwin, Gregg R. Howald, Kevin Oh, Antoinette J. Piaggio, Thomas A. A. Prowse, Joshua V. Ross, J. Royden Saah, Aaron B. Shiels, Paul Thomas, David W. Threadgill, Michael R. Vella, Fred Gould, Alun L. Lloyd

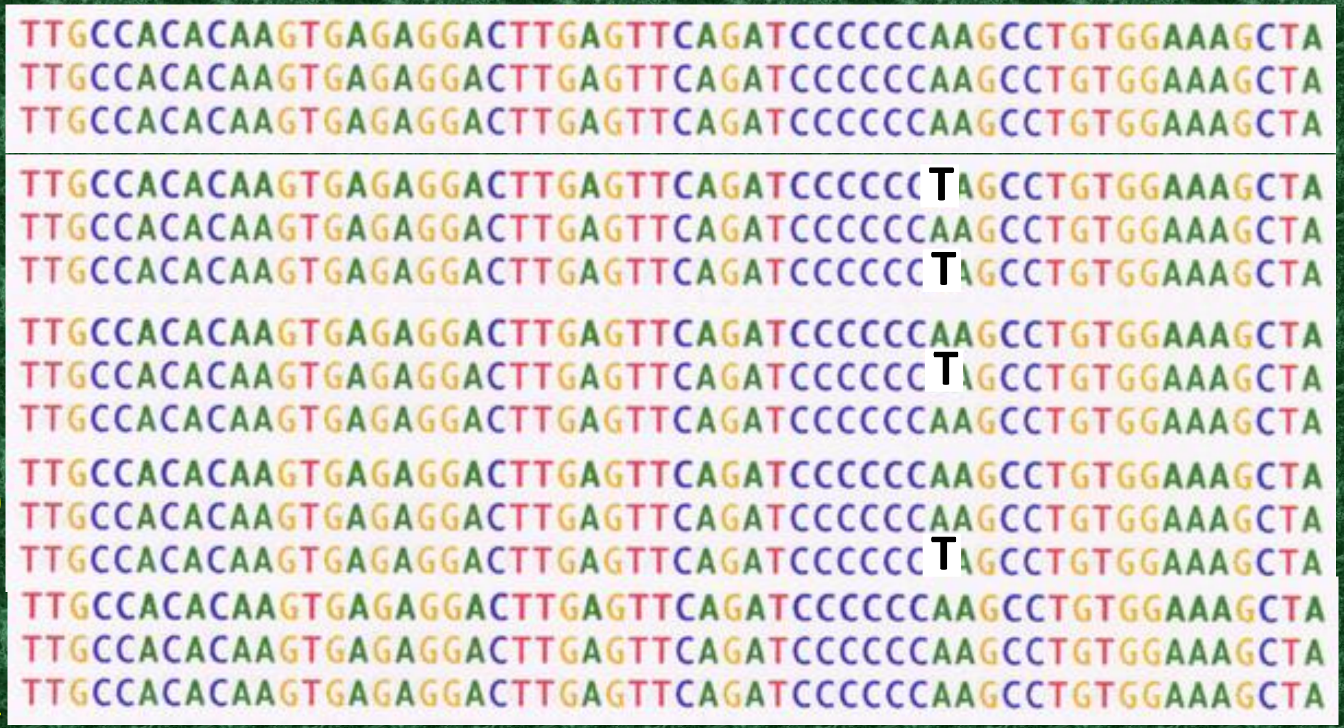
doi: https://doi.org/10.1101/509364



Island

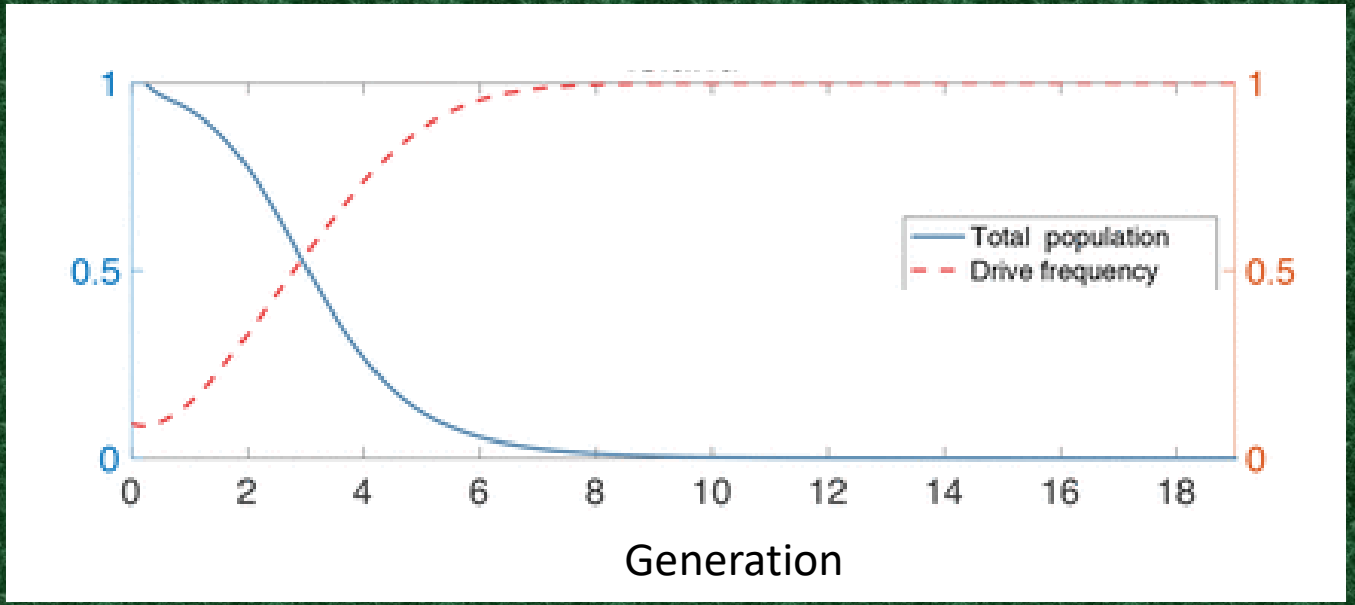

1
2
3
4
5
6
7
8
9
10
11
12
13
14
TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA

Mainland

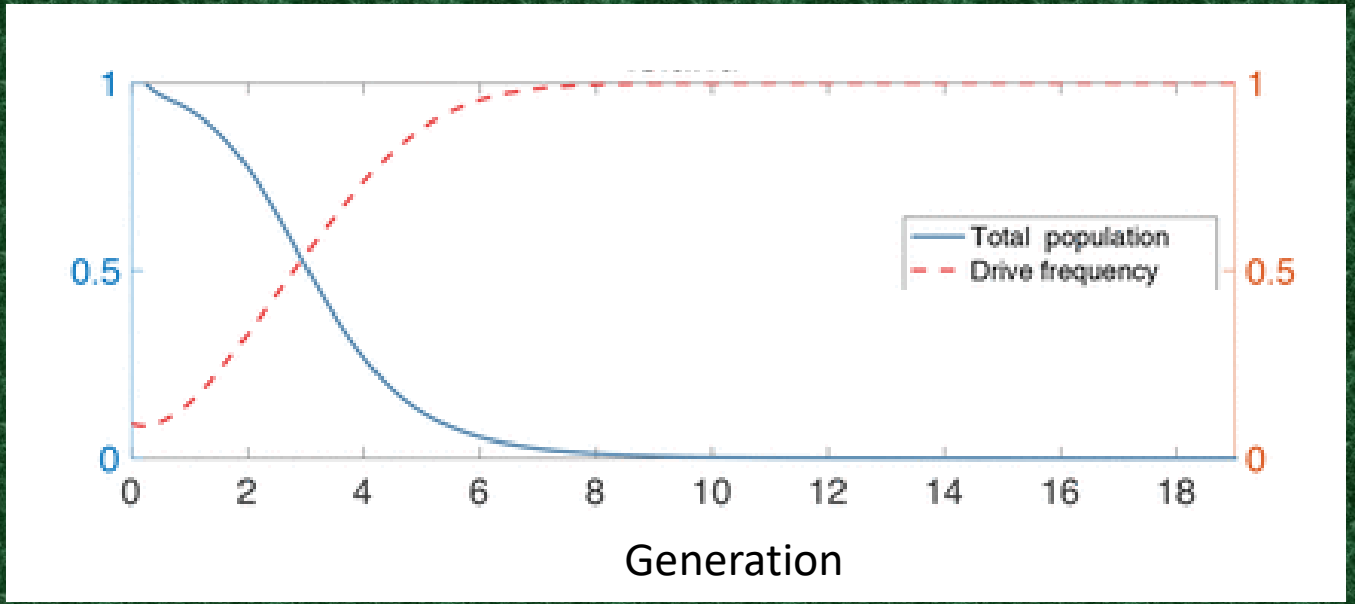


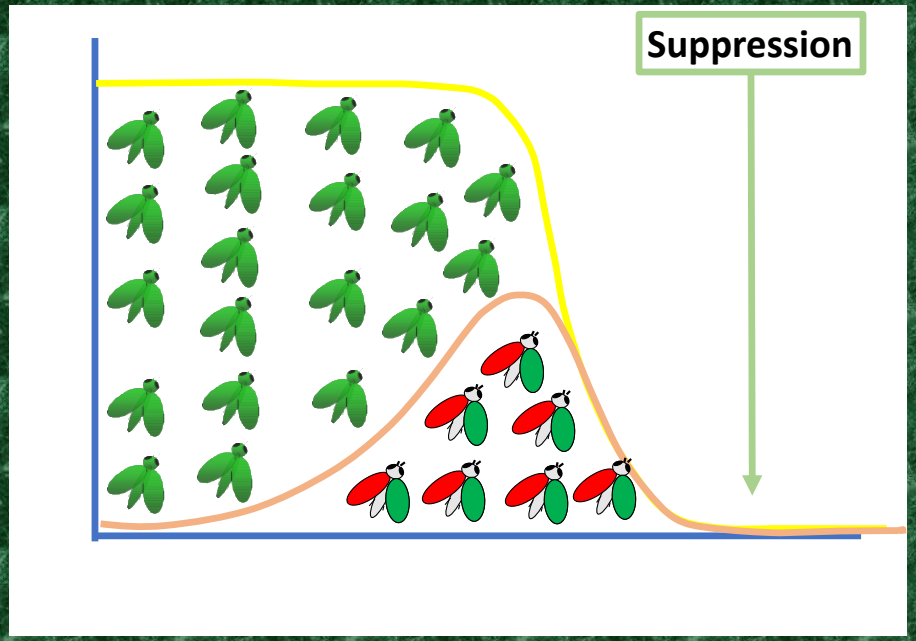
1
2
3
4
5
6
7
8
9
10
11
12
13
14

Island

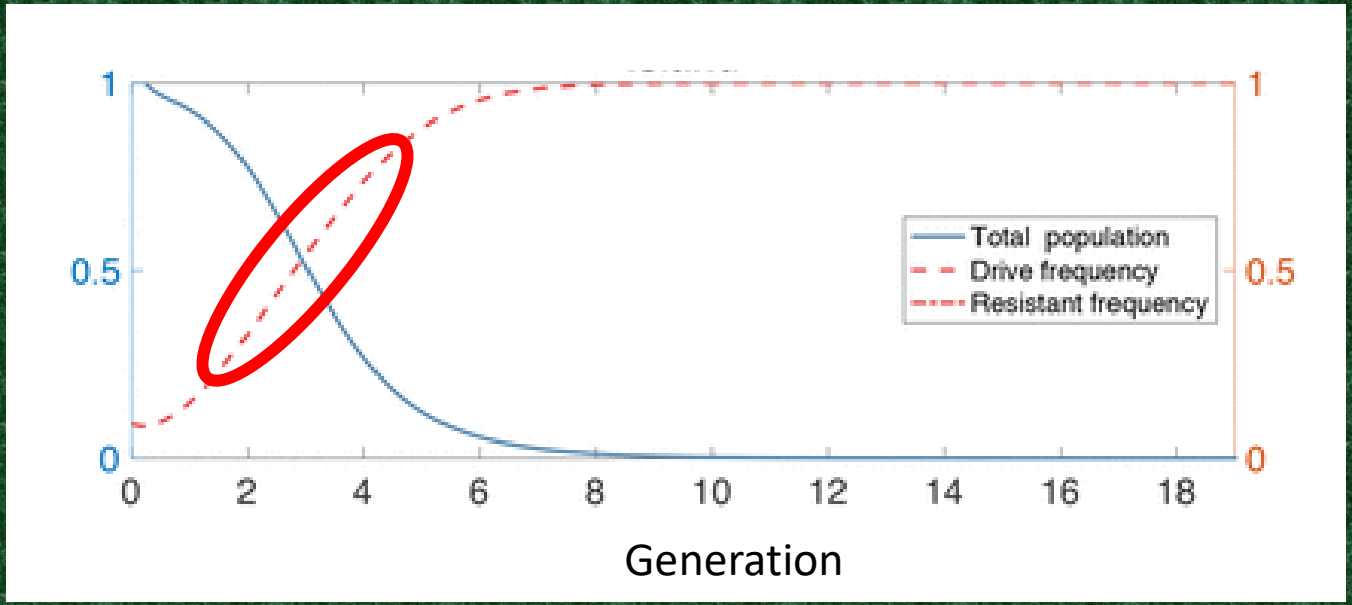

1
0.5
0
1
0.5
0
0
2
4
6
8
10
12
14
16
18
Total population
Drive frequency
Generation

Island


1
0.5
0
1
0.5
0
0
2
4
6
8
10
12
14
16
18
Total population
Drive frequency
Generation


Suppression

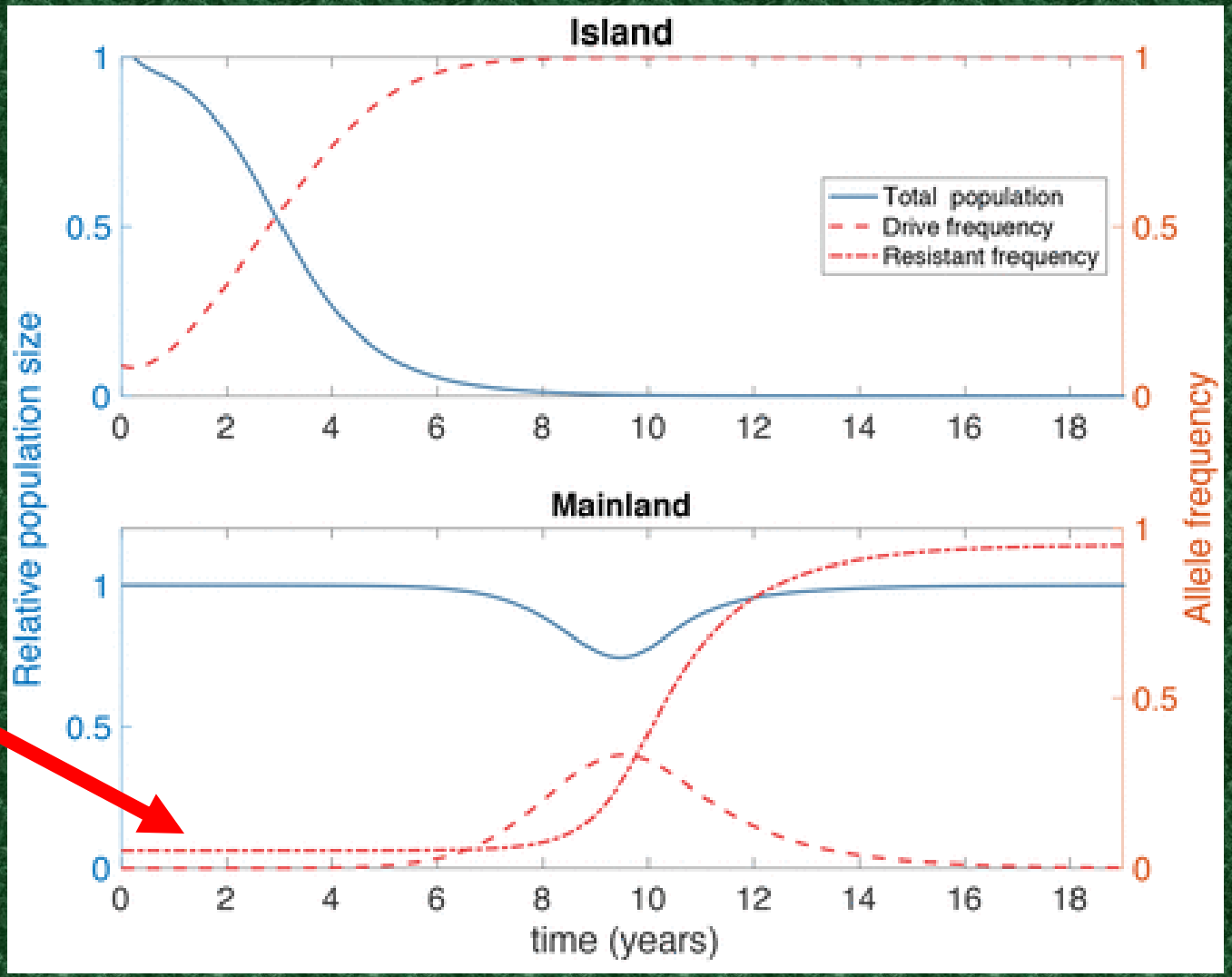
Island


1
0.5
0
1
0.5
0
0
2
4
6
8
10
12
14
16
18
Total population
Drive frequency
Resistant frequency
Generation

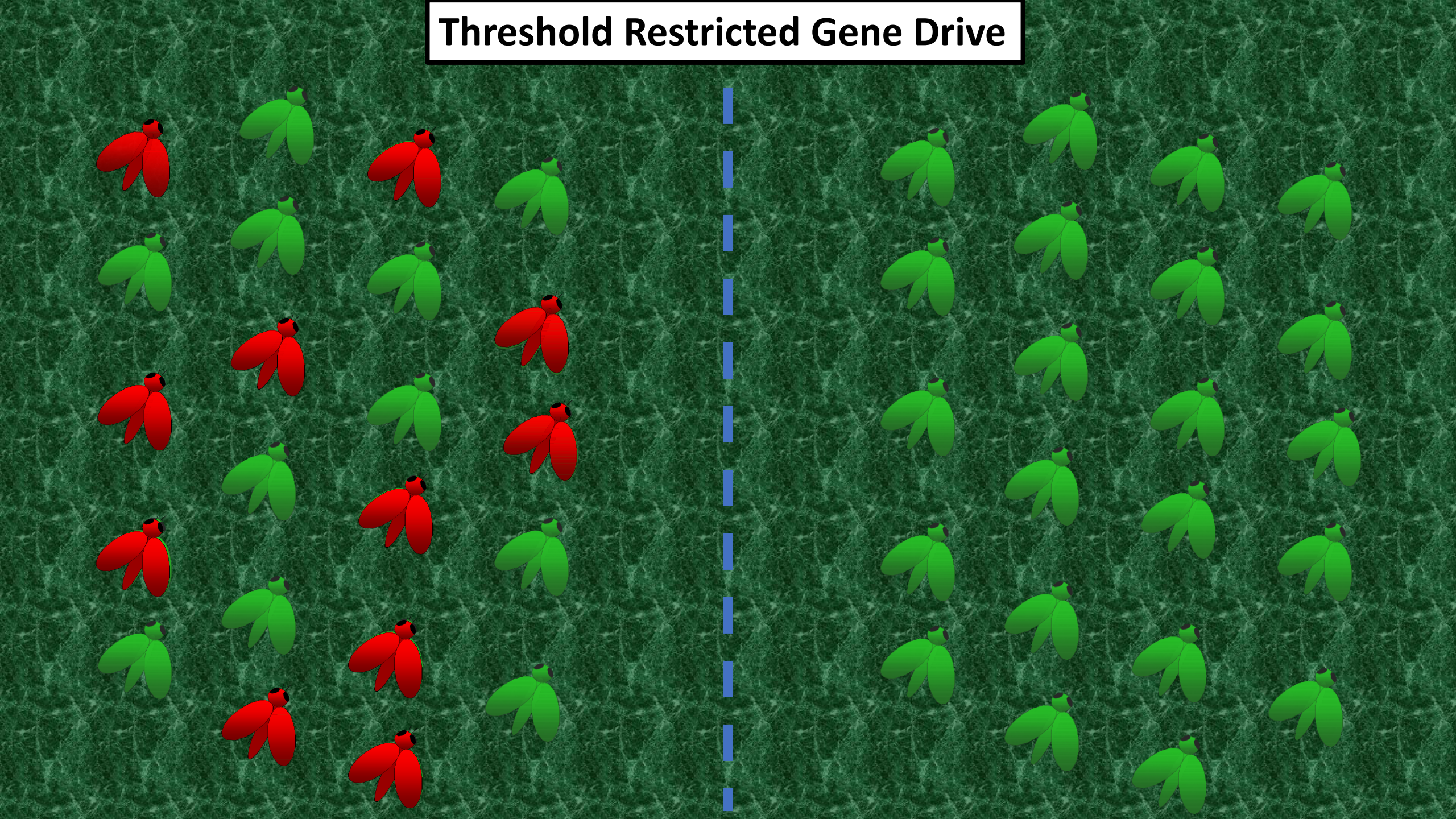
Mainland

1 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
2 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
3 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
4 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCTAGCCTGTGGAAAGCTA
5 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
6 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCTAGCCTGTGGAAAGCTA
7 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
8 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCTAGCCTGTGGAAAGCTA
9 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
10 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
11 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCTAGCCTGTGGAAAGCTA
12 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
13 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA
14 TTGCCACACAAGTGAGAGGACTTGAGTTCAGATCCCCCCAAGCCTGTGGAAAGCTA

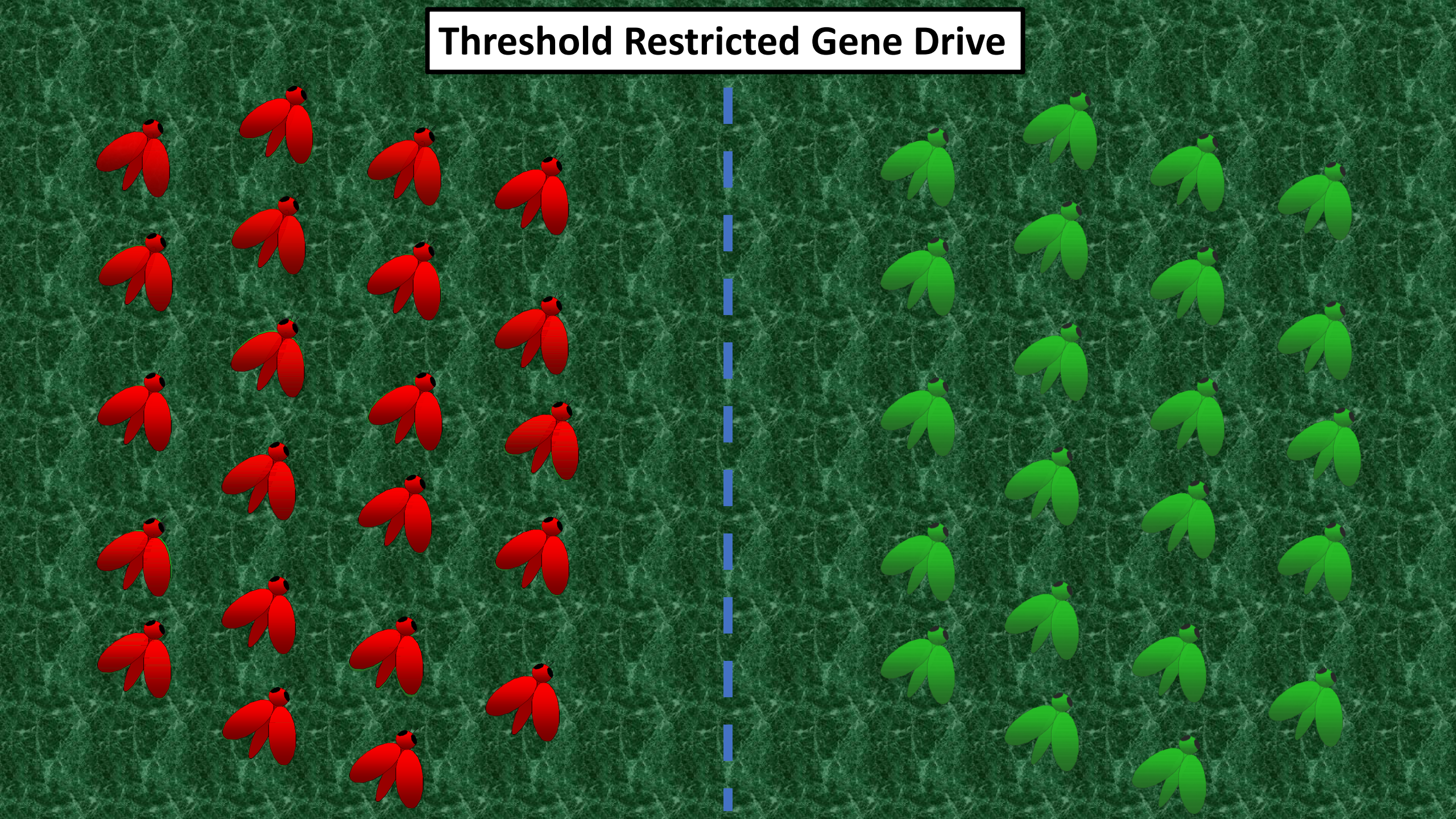
Resistant Allele

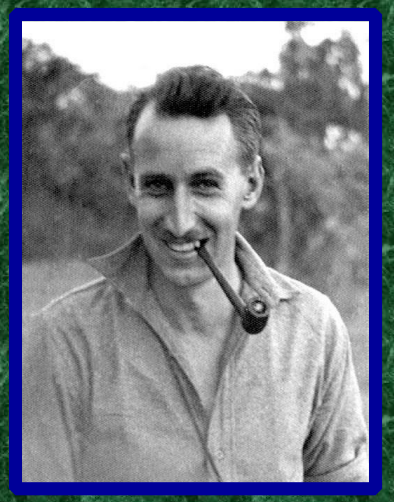


Threshold Restricted Gene Drive

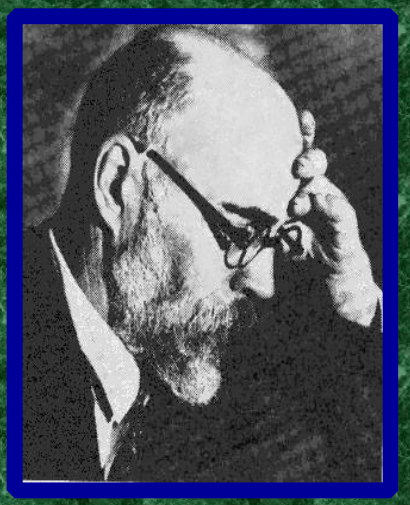


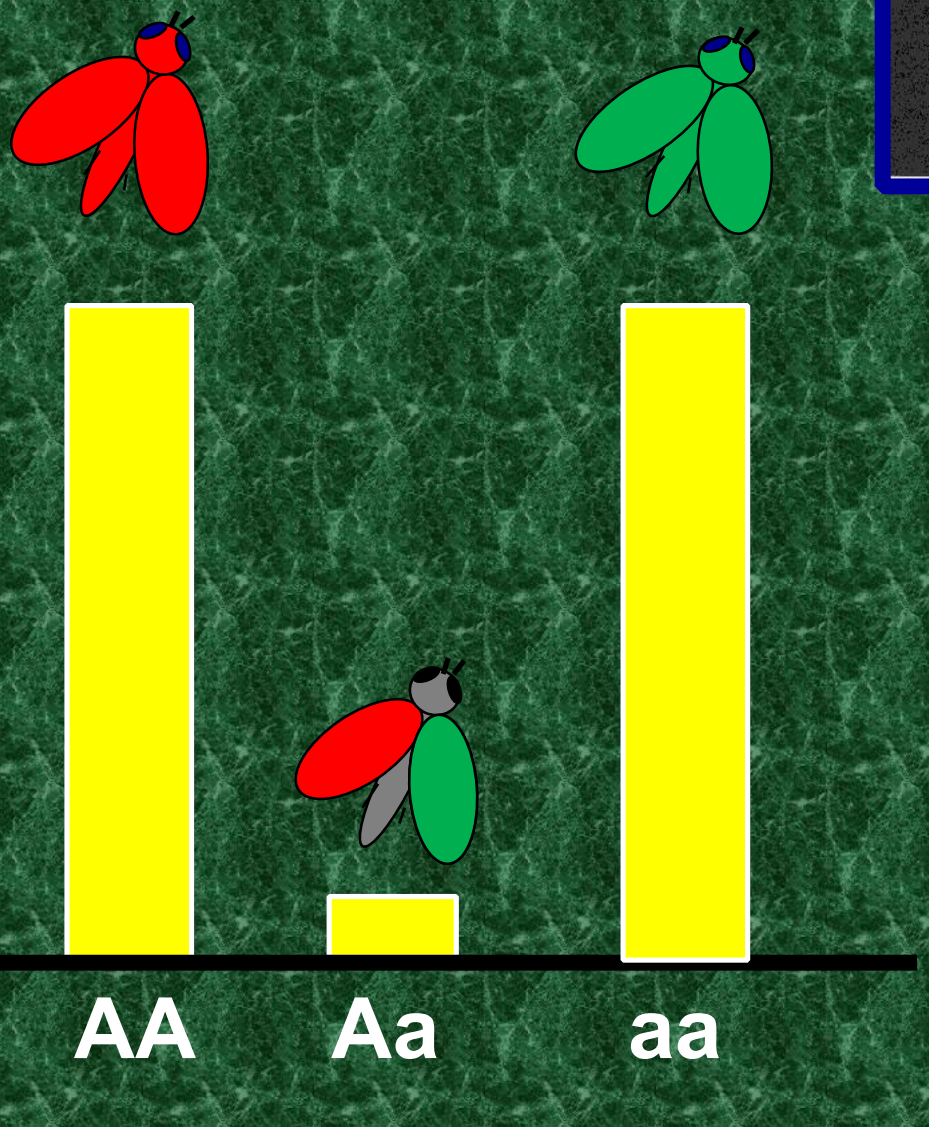
Threshold Restricted Gene Drive



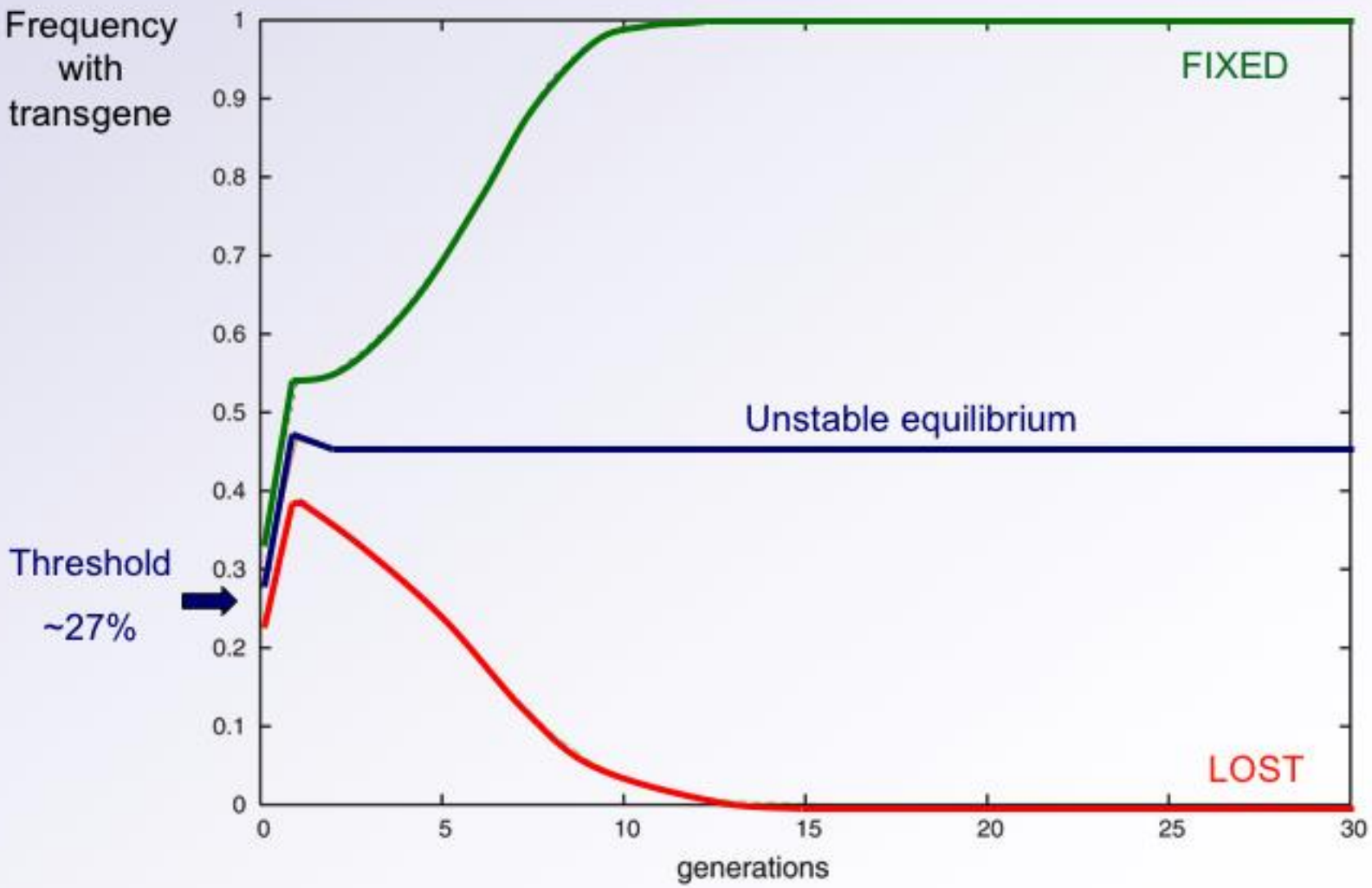


Underdominance



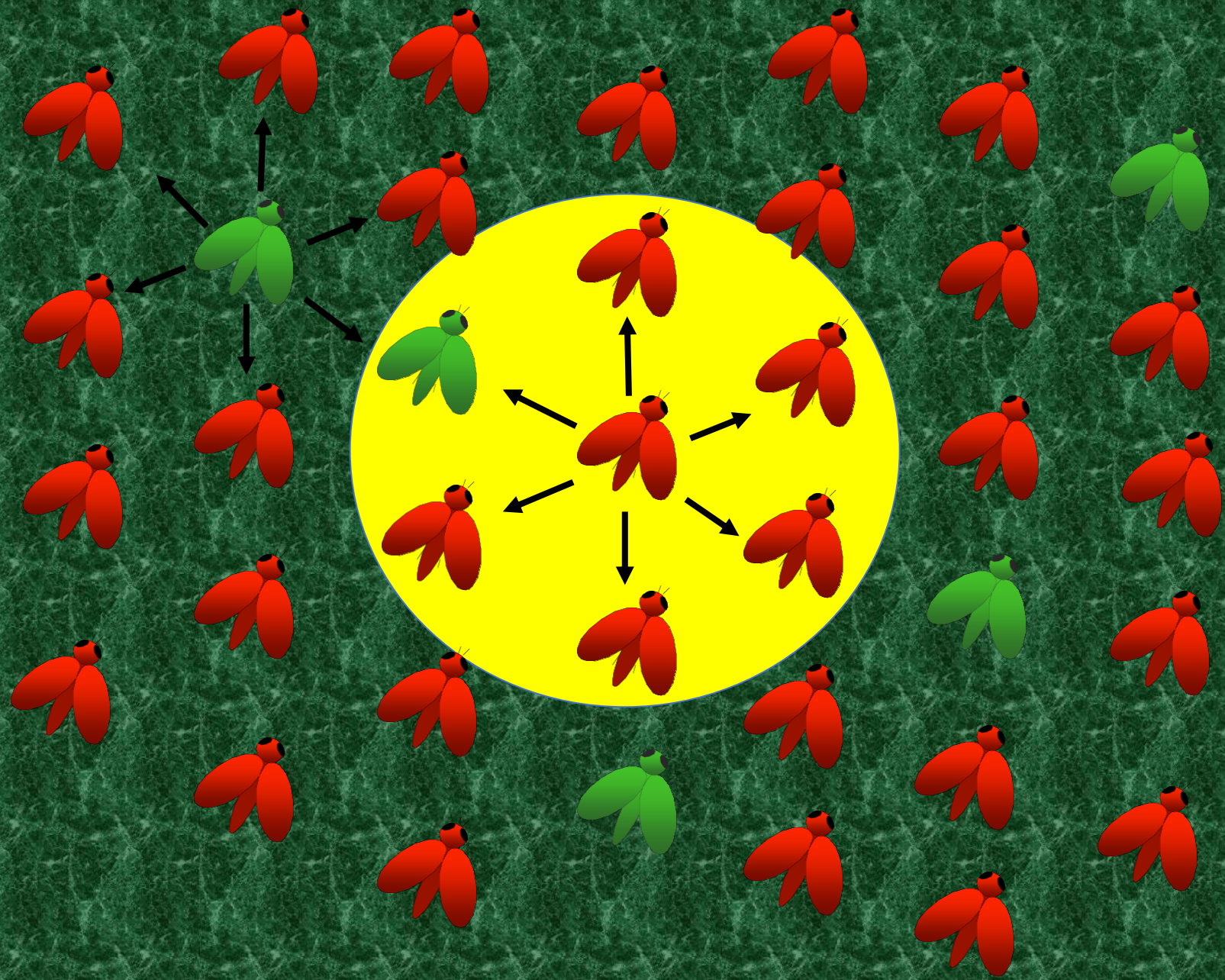


Engineered Underdominance – No cost

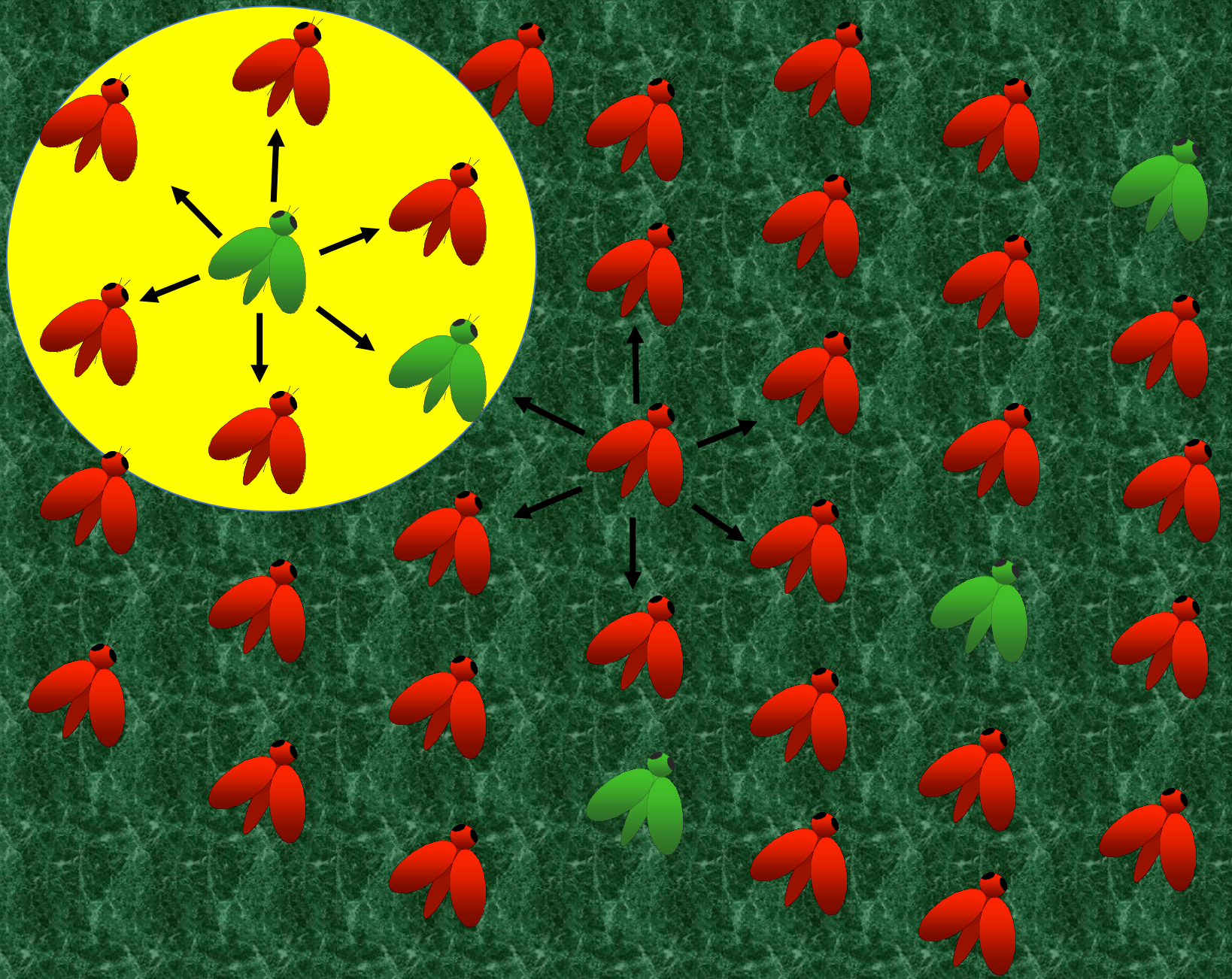


Large numbers of transgenic genotypes released

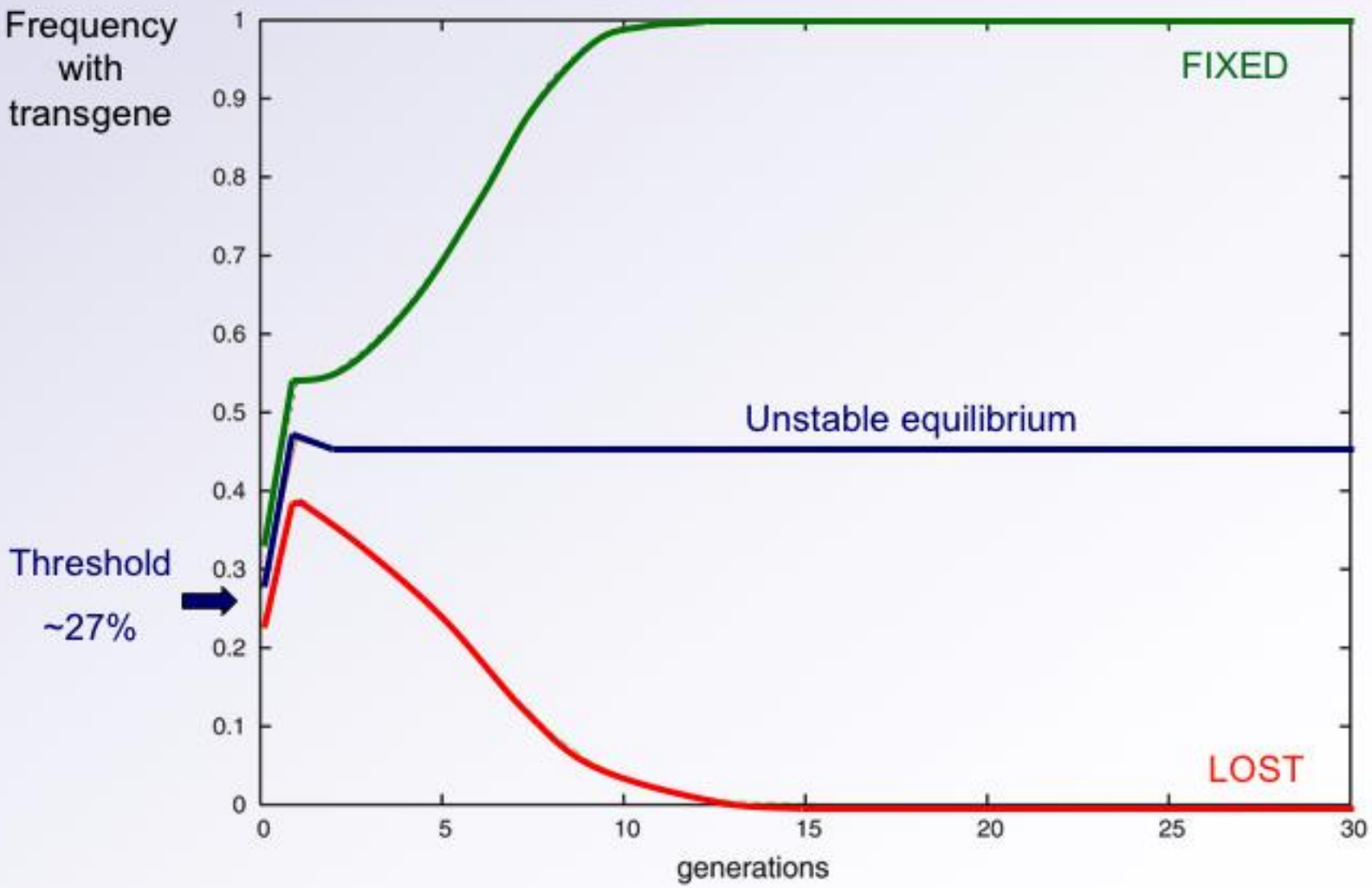
A transgenic Individual is likely to mate with another transgenic individual

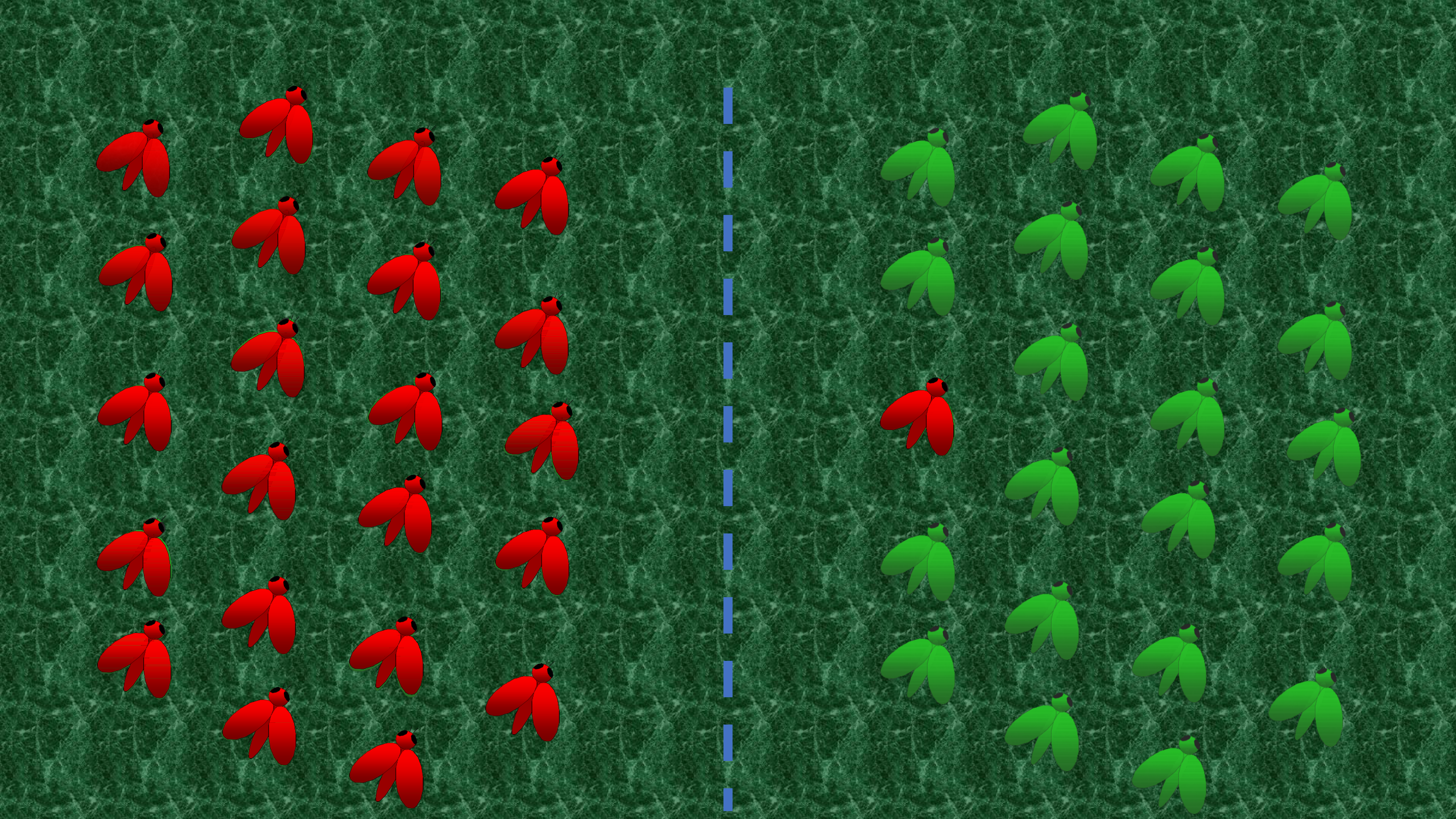


A wildtype individual is likely to mate with a transgenic individual



Engineered Underdominance – No cost





1) Hopes and Fears
2) Types of gene drive systems
3) Mechanisms behind unrestricted drives (CRISPR)
    A) Current state of the art
    B) Models of spread
4) Mechanisms behind spatially restricted drives (Fixed alleles/Underdominance)
    A) Current state of the art
    B) Models of spread
5) **Problem formulation**

Problem Formulation

1) Formally devise plausible pathways that describe how the deployment of gene drive modified insects could be harmful

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2) Formulate risk hypotheses about the likelihood and severity of such events

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1) Formally devise plausible pathways that describe how the deployment of gene drive modified insects could be harmful

2) Formulate risk hypotheses about the likelihood and severity of such events

3) Identify the information that will be useful to test these risk hypotheses.

Take Home Message

When "devising plausible pathways" keep in mind that….

Not All Gene Drives Are Created Equal