Models of Insecticide Resistance Evolution; narrowing the gap to field data.

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Andy South & Ian Hastings

RBM Vector Control Working Group, February 2018

IVCC
Building Partnerships
Creating Solutions
Saving Lives

Models of insecticide resistance evolution

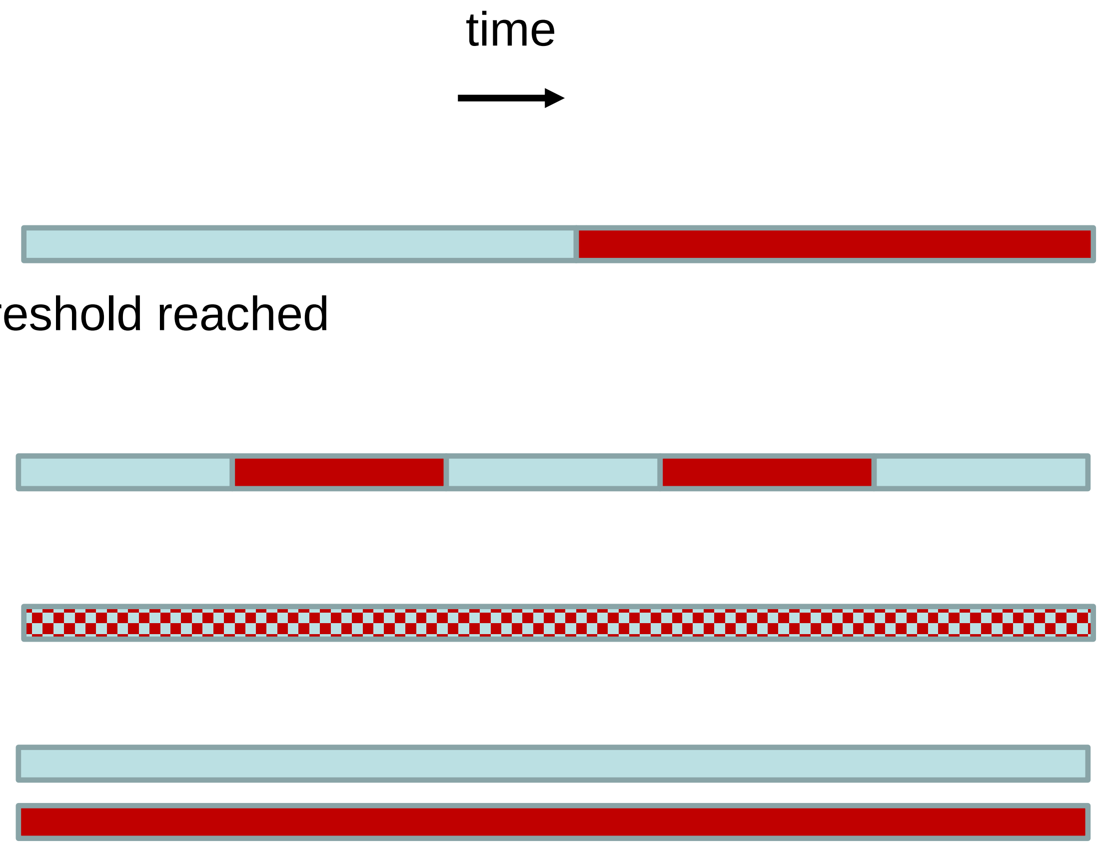
Our models are research tools

Uncertainty in model structure and input data

Potential to address operational questions in future

Useful for us to know what the operational questions are

Insecticide use strategies



Sequence

use until resistance threshold reached

Rotation

Mixture

Mosaic

Insecticide 1, 2

Detailed paper : January 2017
Lay-persons guide : January 2018 accepted Malaria Journal

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PLOS | COMPUTATIONAL BIOLOGY

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RESEARCH ARTICLE

A Two-Locus Model of the Evolution of Insecticide Resistance to Inform and Optimise Public Health Insecticide Deployment Strategies

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Abstract

We develop a flexible, two-locus model for the spread of insecticide resistance applicable to mosquito species that transmit human diseases such as malaria. The model allows differential exposure of males and females, allows them to encounter high or low concentrations of insecticide, and allows selection pressures and dominance values to differ depending on the concentration of insecticide encountered. We demonstrate its application by investigating the relative merits of sequential use of insecticides versus their deployment as a mixture to minimise the spread of resistance. We recover previously published results as subsets of

Our models

Resistance to each insecticide coded by one gene

Resistance already present at low frequencies

Standard population genetic methods

Most relevant to new active ingredients

Flexibility to include cross resistance but not yet done

Genotypes

Alleles

Susceptible (S) or Resistant (R)

1 insecticide : 3 genotypes SS SR RR

2 insecticides : 9 genotypes

main model inputs

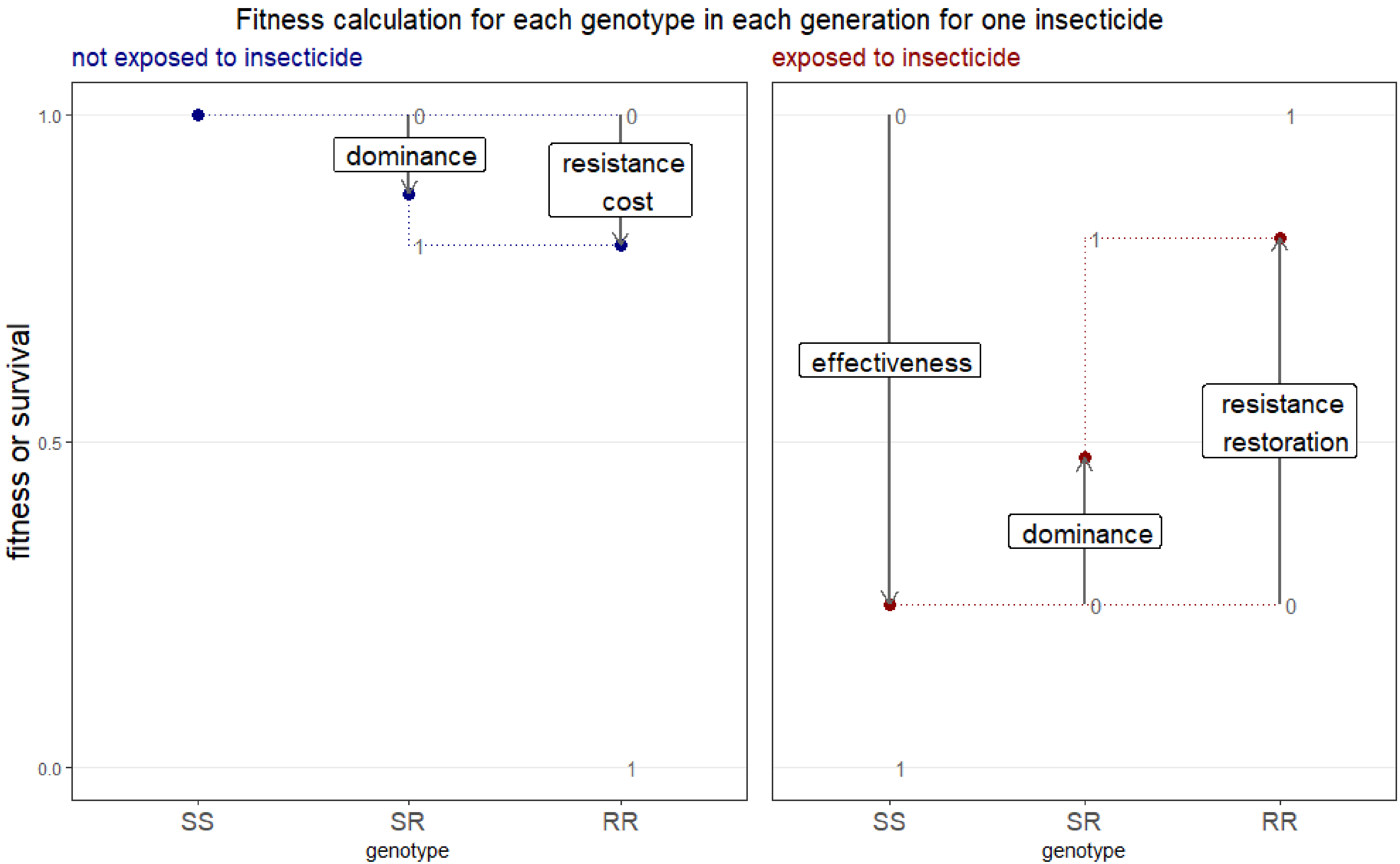
Exposure proportion of insects exposed to insecticide

Effectiveness proportion of susceptible (SS) insects killed by exposure to insecticide

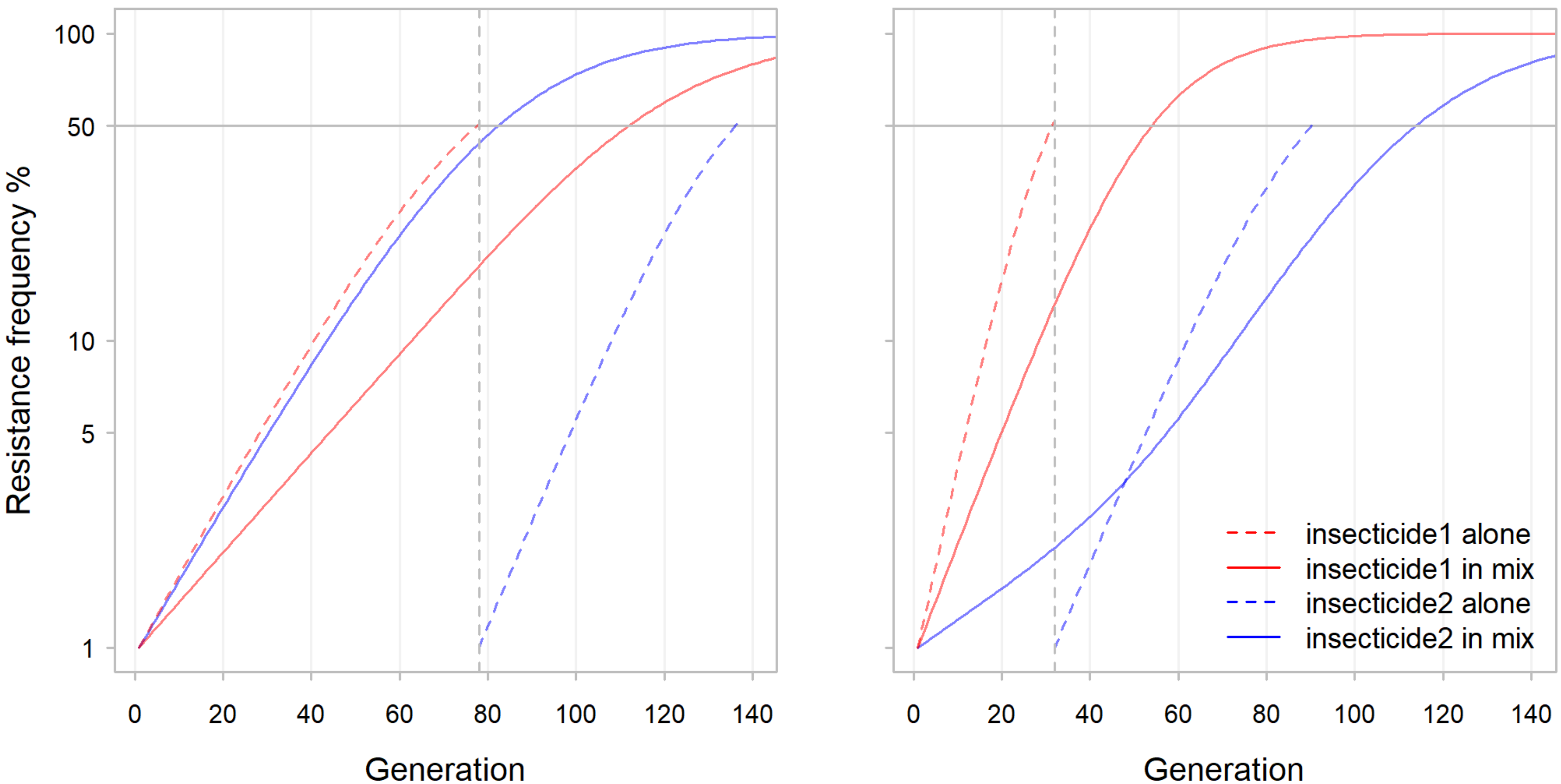
Resistance restoration ability of resistance (RR) to restore fitness when exposed to insecticide

Cost of resistance decrease in fitness of resistance (RR) insects not exposed to insecticide

Dominance determines fitness of heterozygotes (SR)

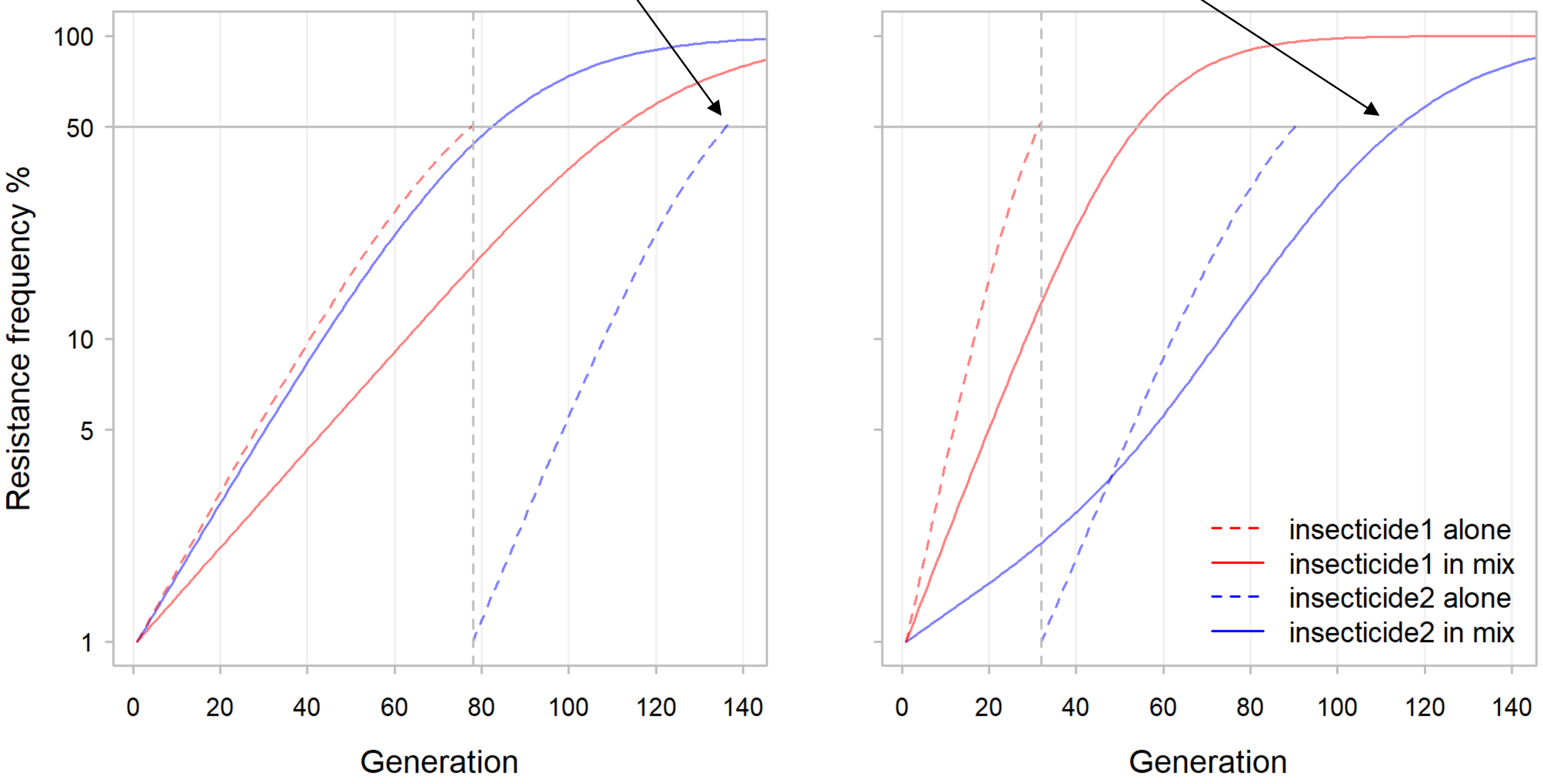

Fitness calculation for each genotype in each generation for one insecticide
not exposed to insecticide
exposed to insecticide
fitness or survival
1.0
0.5
0.0
dominance
resistance cost
effectiveness
dominance
resistance restoration
0
1
SS
SR
RR
genotype

solid lines = Mixture
dashed = Sequence



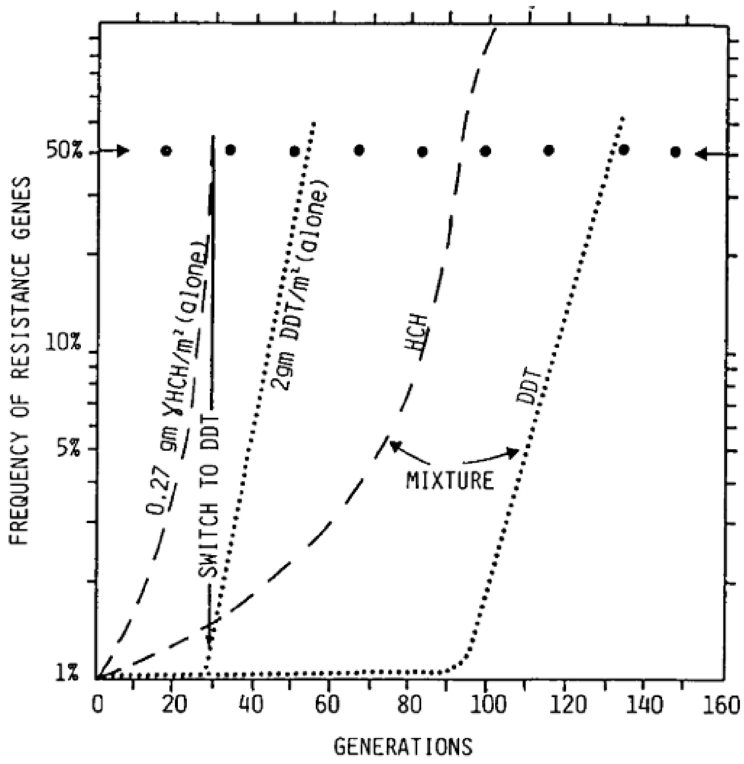
Low effectiveness of insecticide 1 : sequence slows evolution of resistance to both.

High effectiveness of insecticide 1 : mixture slows evolution of resistance to both.



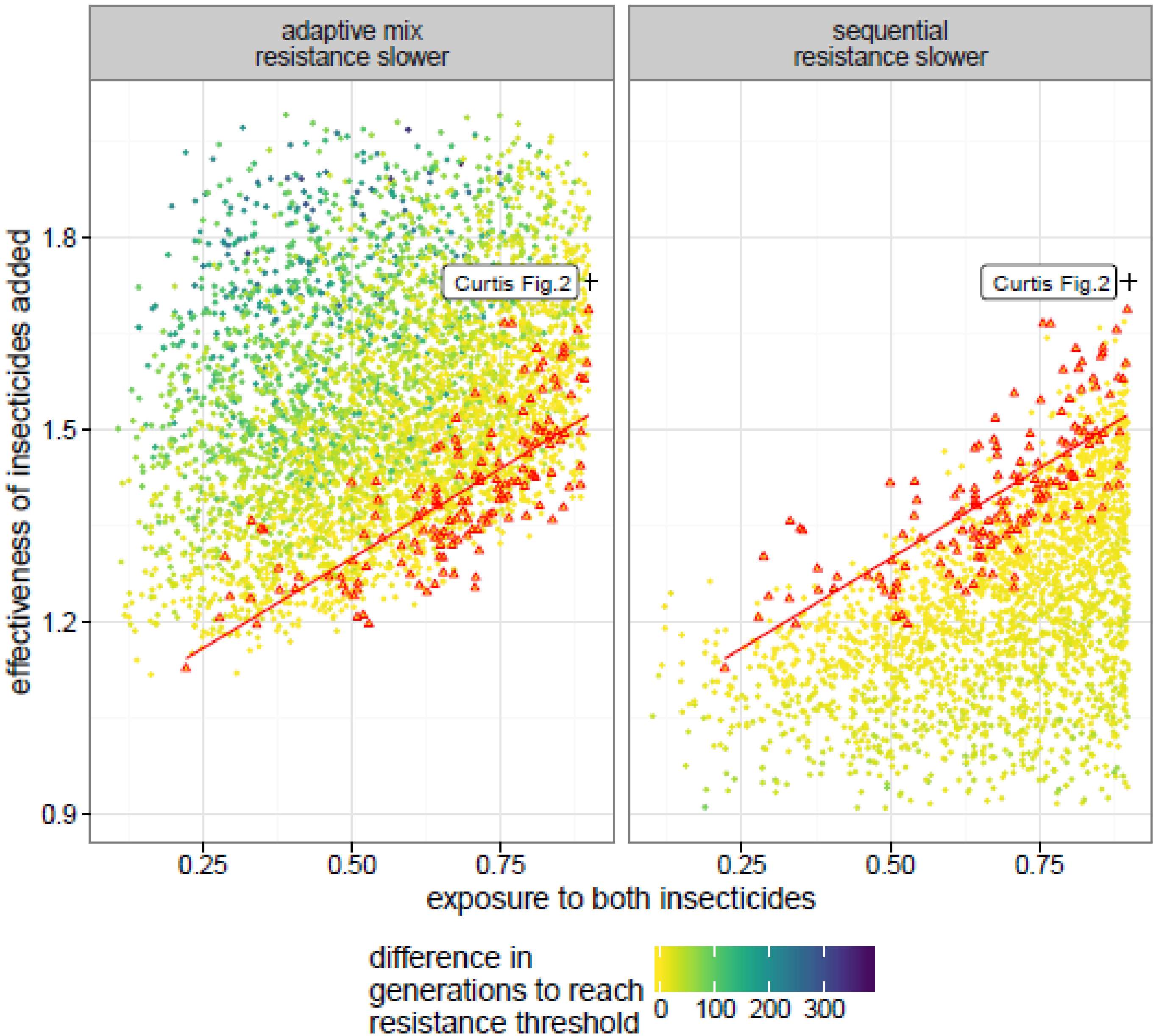
Mechanism : Higher effectiveness of insecticide 1 in right panel speeds up evolution to itself in the mixture but slows down evolution of resistance to the partner.

Curtis(1985), a mixture is better …



Curtis, C. F. (1985). "Theoretical models of the use of insecticide mixtures for the management of resistance." Bulletin of Entomological Research 75(2): 259-265.

Levick, South, Hastings (2017) … that depends.



10,000 runs

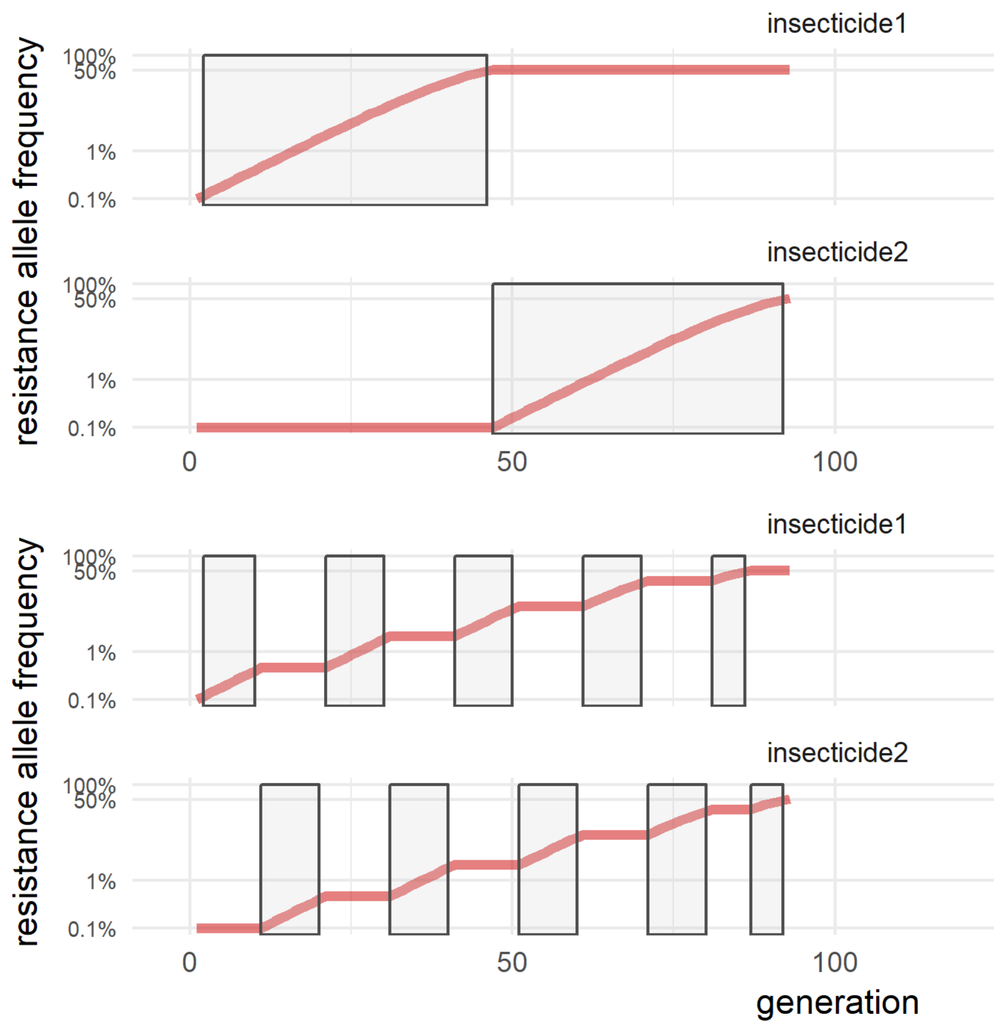
sequences vs rotations

Preliminary work shows little difference between them in terms of slowing evolution of insecticide resistance.

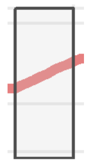
sequences vs rotations
no costs of resistance or refugia

Sequence

Rotation



key :

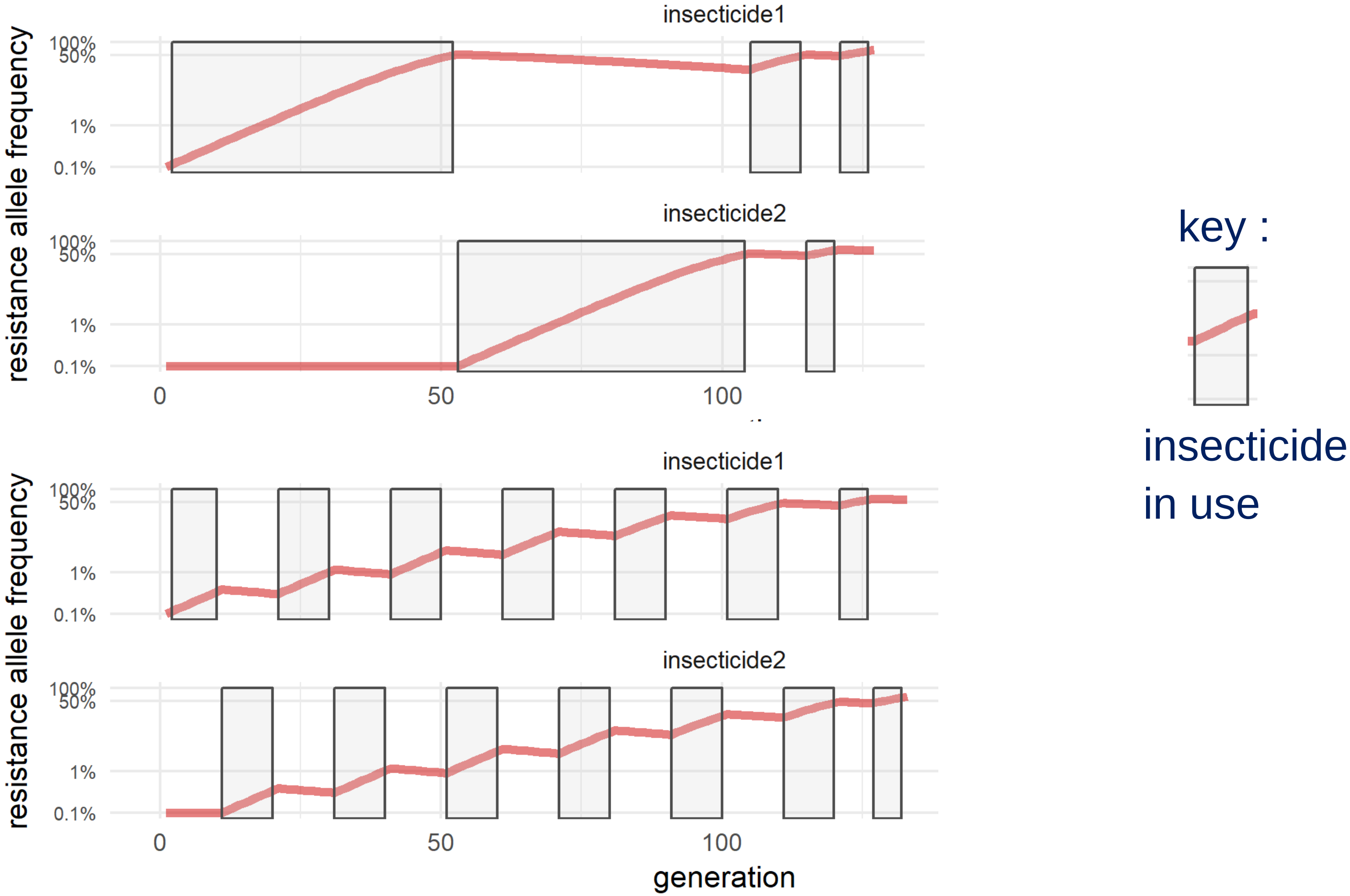


insecticide in use

Costs of resistance cause resistance to decline when an insecticide not in use

Sequence

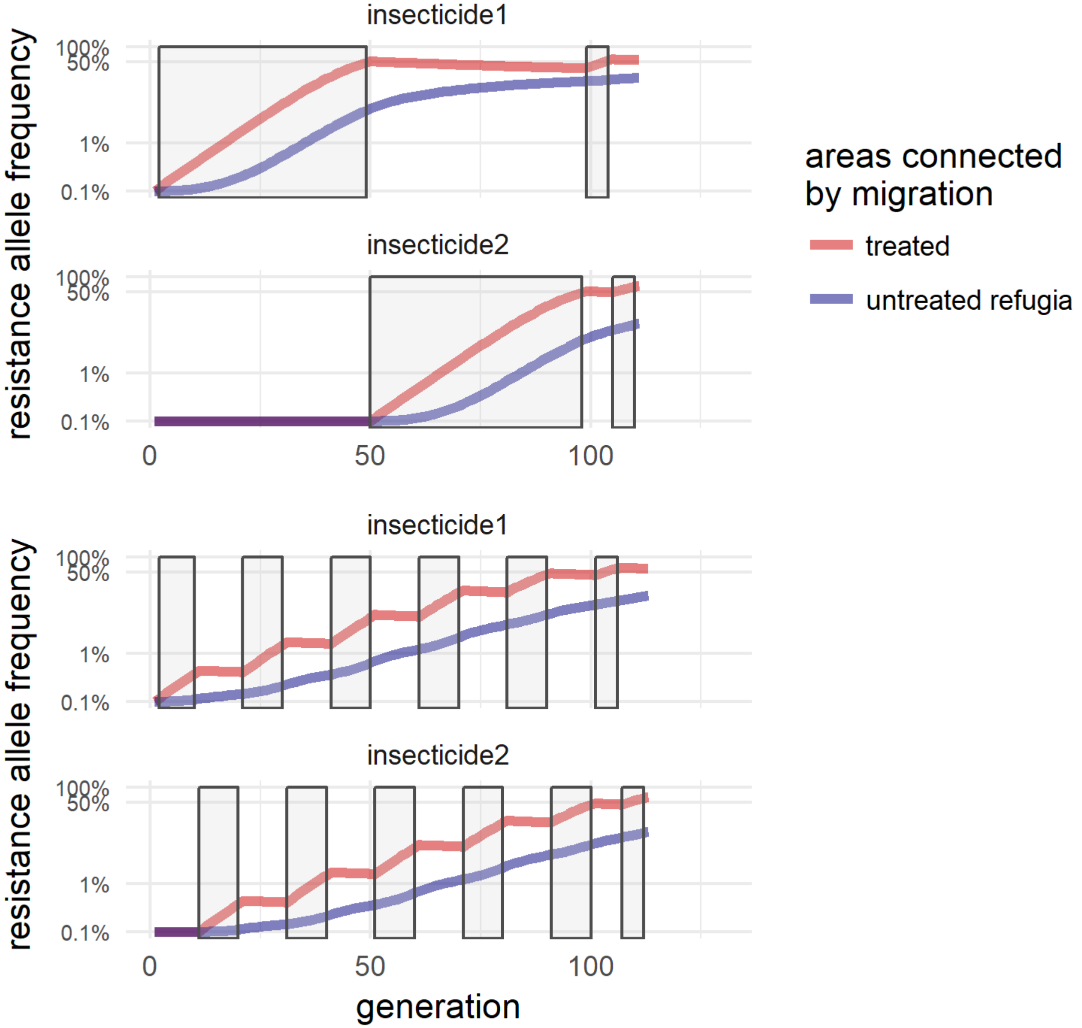
Rotation



Untreated areas (refugia) and dispersal also lead resistance to decline when insecticide not in use

Sequence

Rotation



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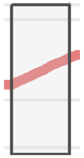
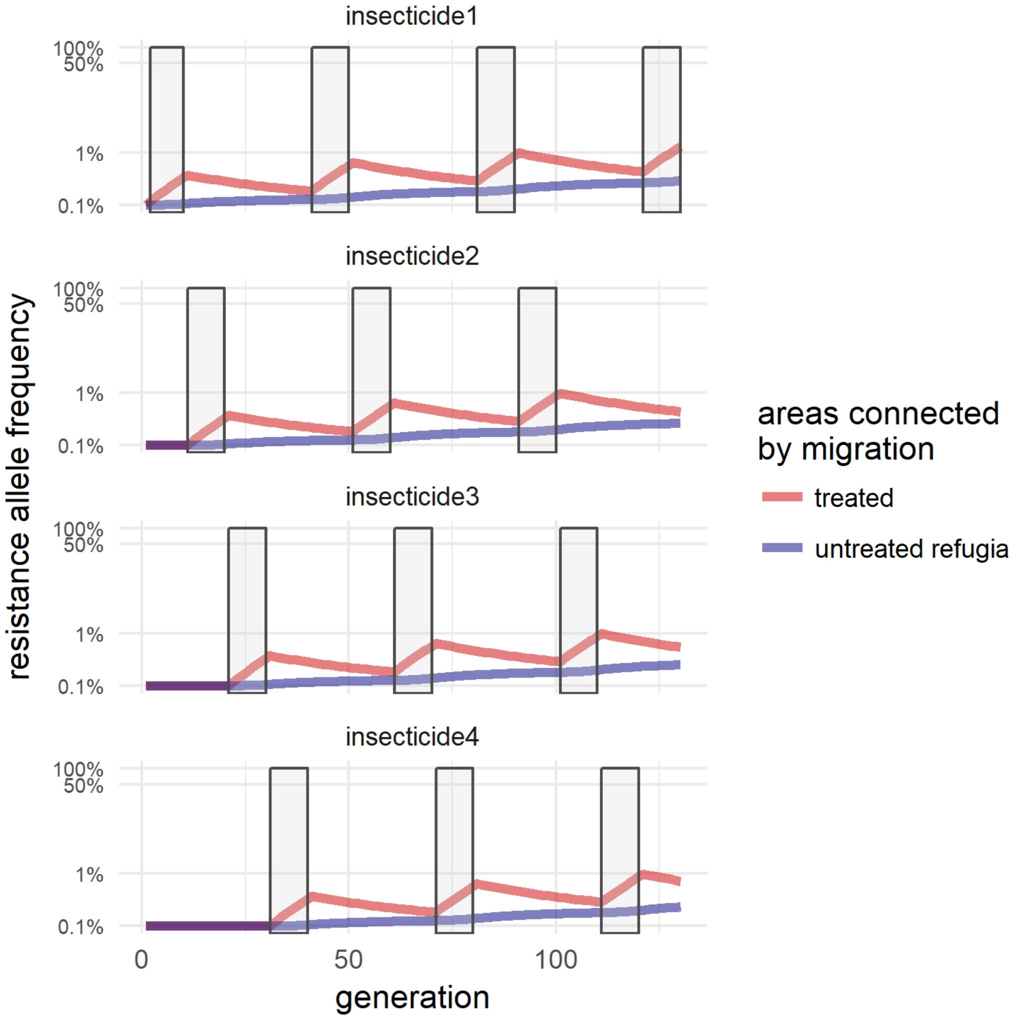


insecticide in use

Larger refugia, more dispersal and more insecticides can lead to resistance staying lower for longer



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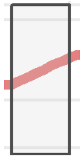


insecticide in use

Early results

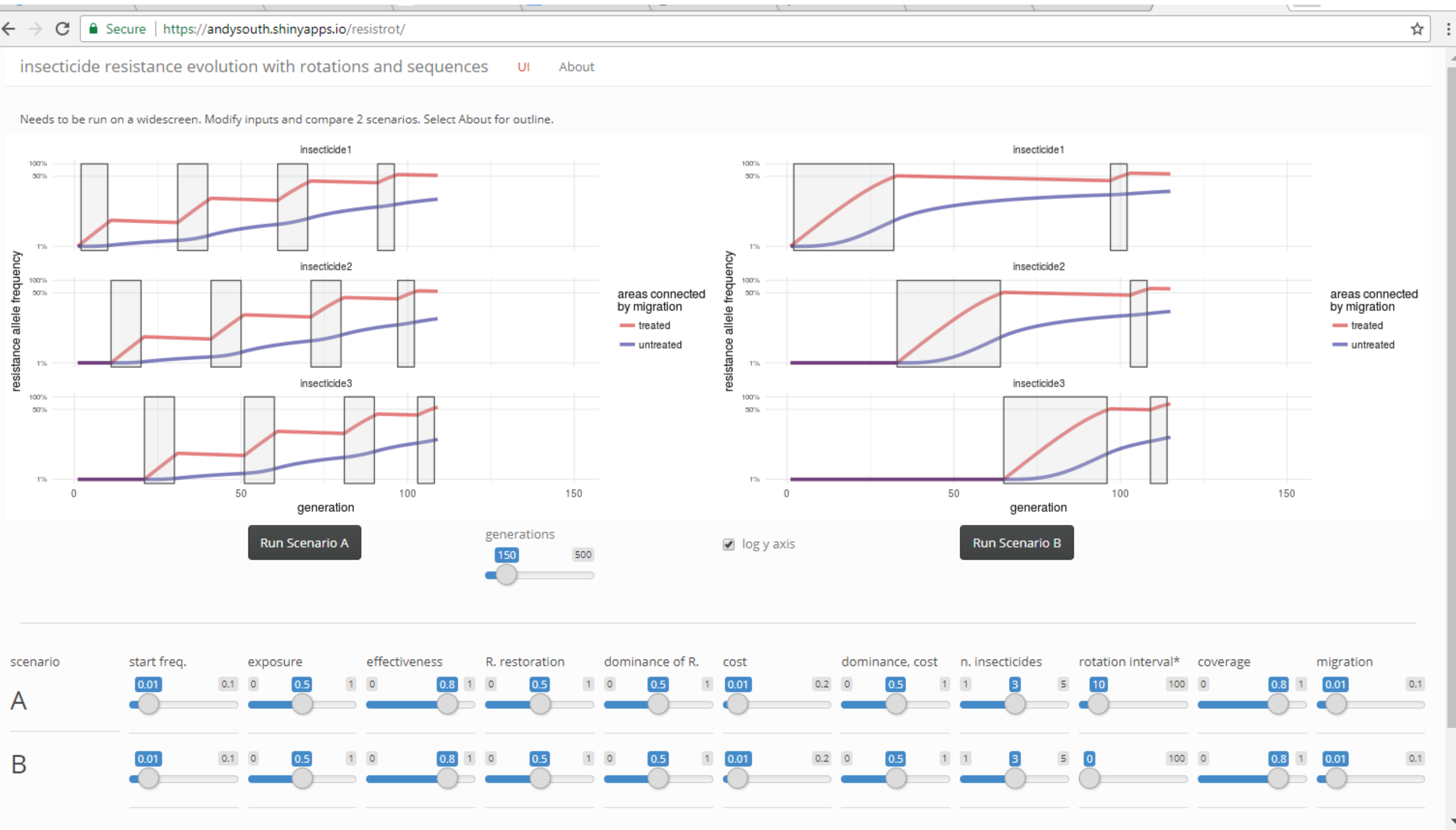
No simple answer to whether mixtures, sequences or rotations are ‘better’

1. Very effective insecticides are needed to favour mixtures
2. High exposure of less effective insecticides favours sequences
3. Little difference between sequences and rotations

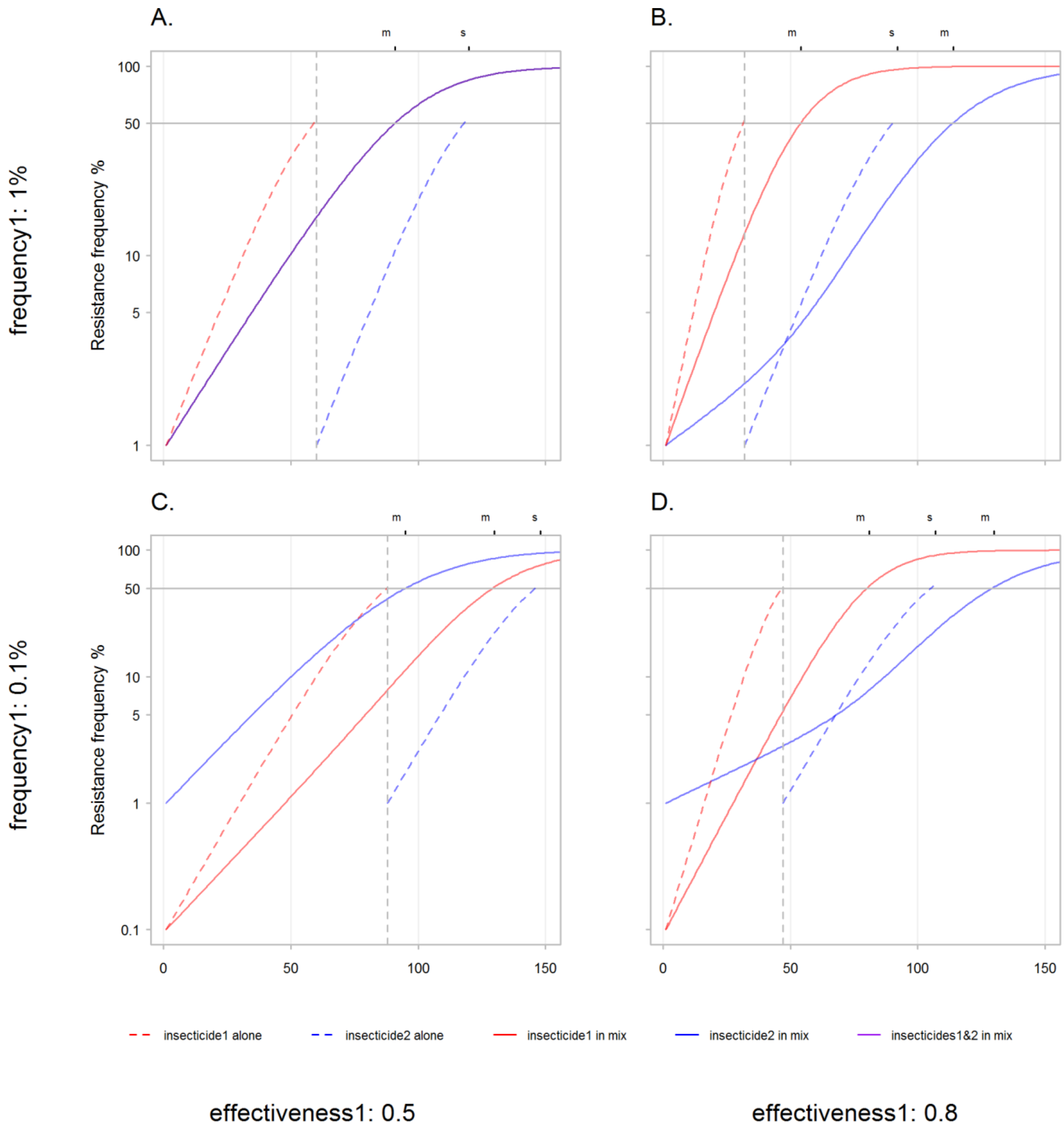
Model user interfaces :

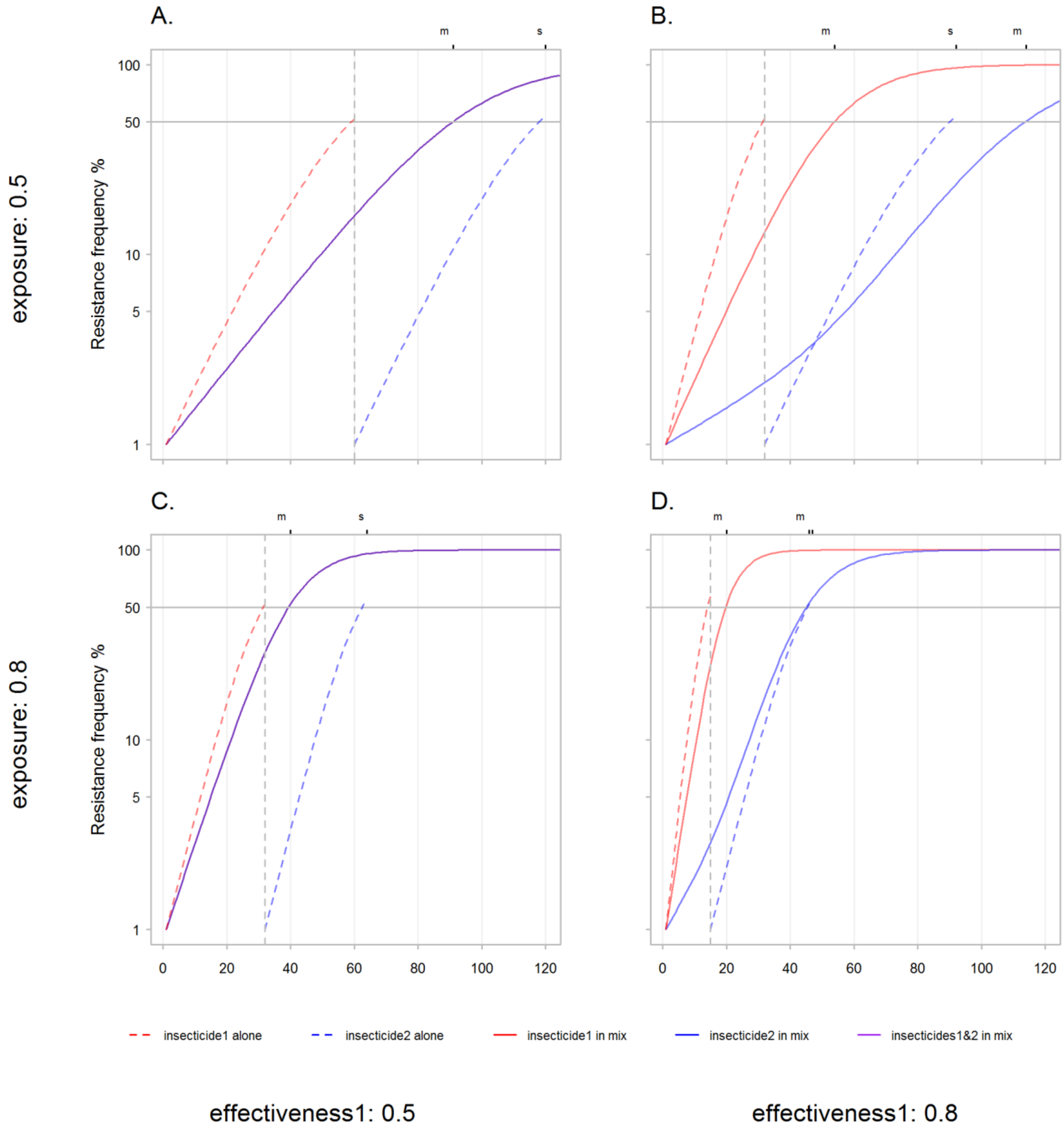
Mixtures : https://andysouth.shinyapps.io/resistmixseq/

Rotations : https://andysouth.shinyapps.io/resistrot/


Secure | https://andysouth.shinyapps.io/resistrot/
insecticide resistance evolution with rotations and sequences
UI
About
Needs to be run on a widescreen. Modify inputs and compare 2 scenarios. Select About for outline.
insecticide1
insecticide2
insecticide3
resistance allele frequency
100%
50%
1%
0
50
100
150
generation
areas connected by migration
treated
untreated
Run Scenario A
generations
150
500
log y axis
Run Scenario B
scenario
start freq.
exposure
effectiveness
R. restoration
dominance of R.
cost
dominance, cost
n. insecticides
rotation interval*
coverage
migration
A
0.01 0.1
0 0.5 1
0 0.8 1
0 0.5 1
0 0.5 1
0.01 0.2
0 0.5 1
1 3 5
10 100
0 0.8 1
0.01 0.1
B
0.01 0.1
0 0.5 1
0 0.8 1
0 0.5 1
0 0.5 1
0.01 0.2
0 0.5 1
1 3 5
0 100
0 0.8 1
0.01 0.1

END


frequency1: 1%
frequency1: 0.1%
A.
B.
C.
D.
Resistance frequency %
m
s
100
50
10
5
1
0.1
0
50
100
150
insecticide1 alone
insecticide2 alone
insecticide1 in mix
insecticide2 in mix
insecticides1&2 in mix
effectiveness1: 0.5
effectiveness1: 0.8


A.
B.
C.
D.
m
s
m
s
m
m
m
s
m
m
100
50
10
5
1
Resistance frequency %
0
20
40
60
80
100
120
exposure: 0.5
exposure: 0.8
insecticide1 alone
insecticide2 alone
insecticide1 in mix
insecticide2 in mix
insecticides1&2 in mix
effectiveness1: 0.5
effectiveness1: 0.8

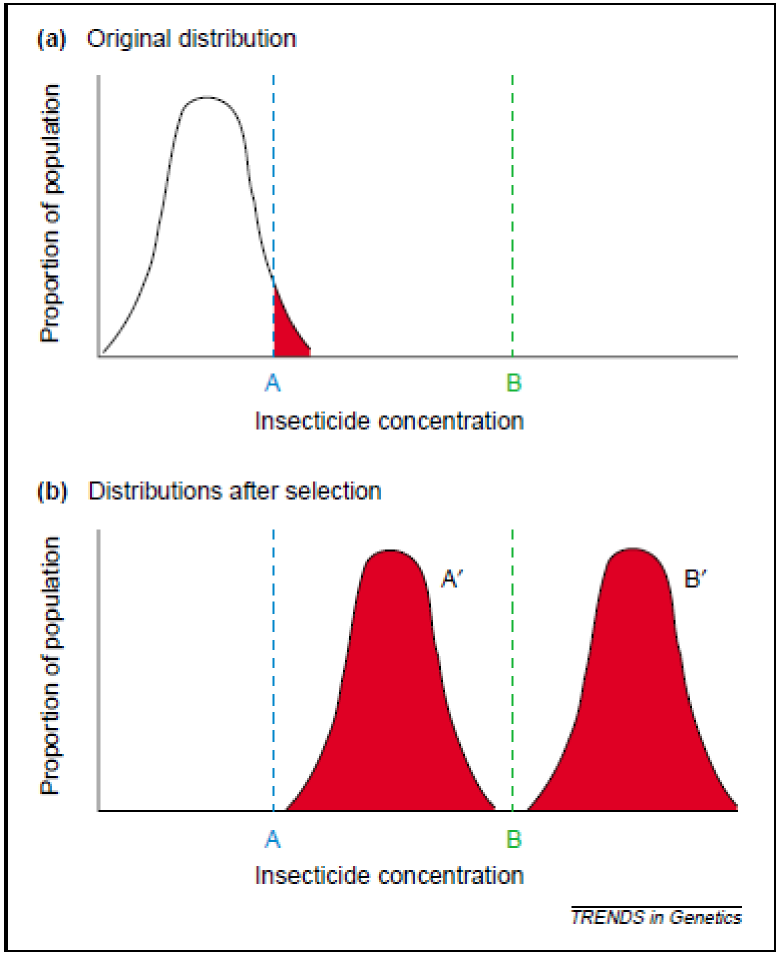


Figure 1. Selection within, and outside of, the normal response of an insect population. Selection within the normal distribution of insecticide tolerance at a concentration indicated by broken line (A) results in the survival of a large number of individuals. These individuals show a marginally enhanced tolerance to insecticide after selection (distribution A′). When repeatedly applied to the same population, such doses of insecticide select for several different resistance traits of minor effect that act cumulatively (polygenic resistance). Selection outside of the normal distribution of tolerance (concentration indicated by the line B) results in the selection of rare mutations that have a major effect within single genes (monogenic resistance). Such mutants show a tolerance distribution (distribution

ELSEVIER Review TRENDS in Genetics Vol.20 No.3 March 2004

The genetics and genomics of insecticide resistance

Richard H. ffrench-Constant, Phillip J. Daborn and Gaelle Le Goff