

Underdominance Predictions and Genetically Transforming a Population

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Genetic Pest Management (GPM)

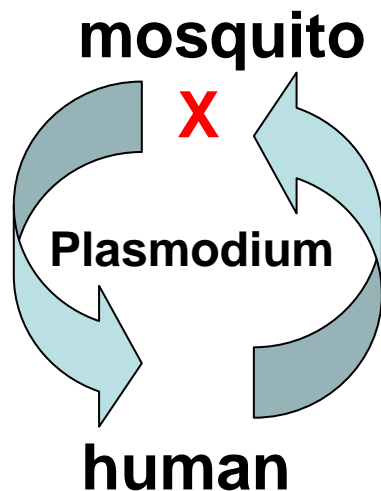
Many diseases vectored by insects are taking a huge humanitarian toll

Malaria kills 1 million people a year, antimalarial drug resistance is evolving and spreading, and no effective vaccine has been developed.

Dengue fever is rapidly spreading, no effective vaccine has been developed.

West Nile virus is spreading across N. America, no vaccine for humans exists.



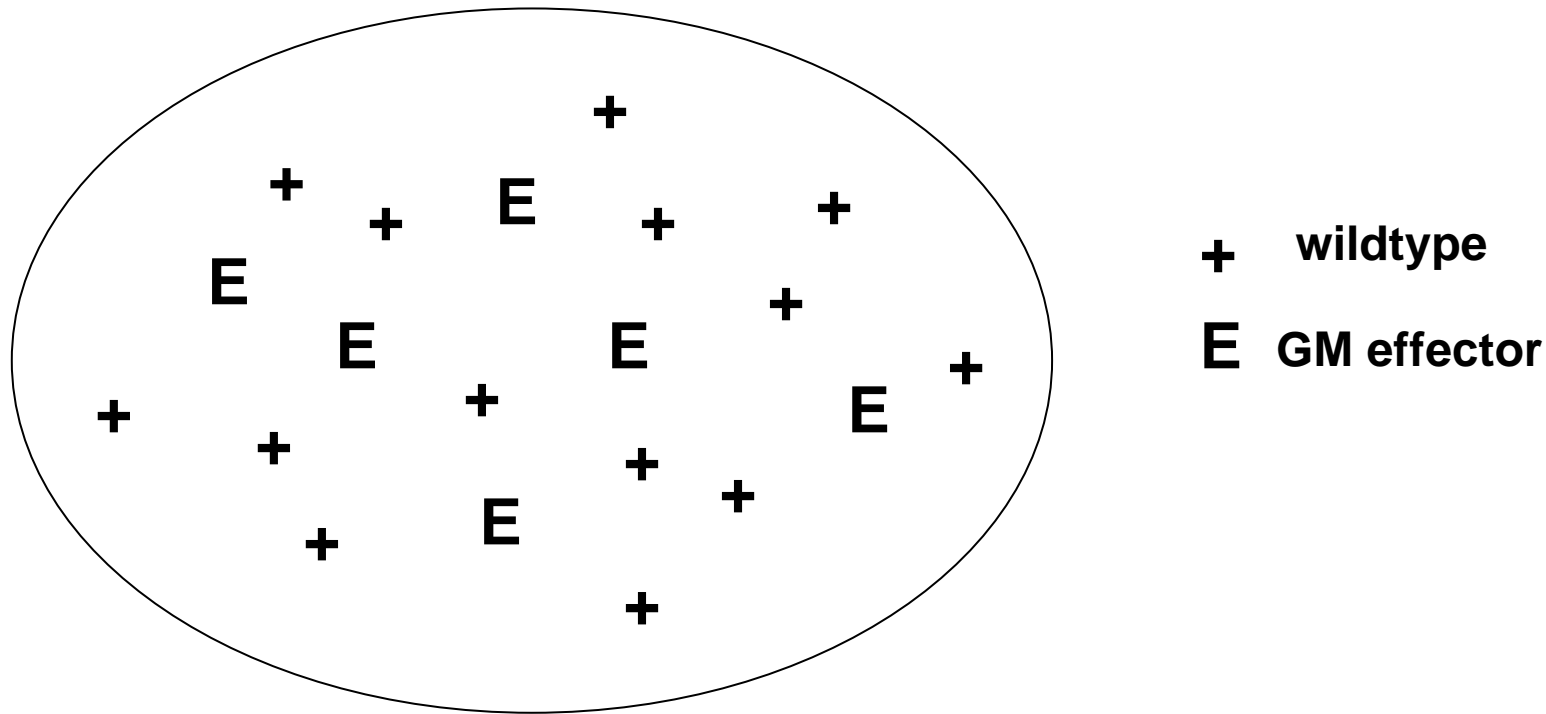


In theory, an insect that vectors a harmful disease can be genetically modified to be resistant to infection and no longer transmit the disease.

There has been success in developing refractory constructs in *Anopheles* against *Plasmodium falciparum* (Corby-Harris *et al.* 2010), and in *Aedes* against *P. gallinaceum* (Jasinskiene *et al.* 2007).

We can refer to this genetic modification as an “effector.”

Effectors can be released into a wild population:

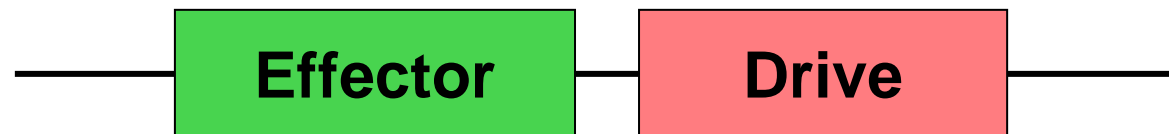


But, if there is no fitness advantage, and especially likely, if there is a fitness cost, they are unlikely to reach fixation and may be quickly lost from the wild.

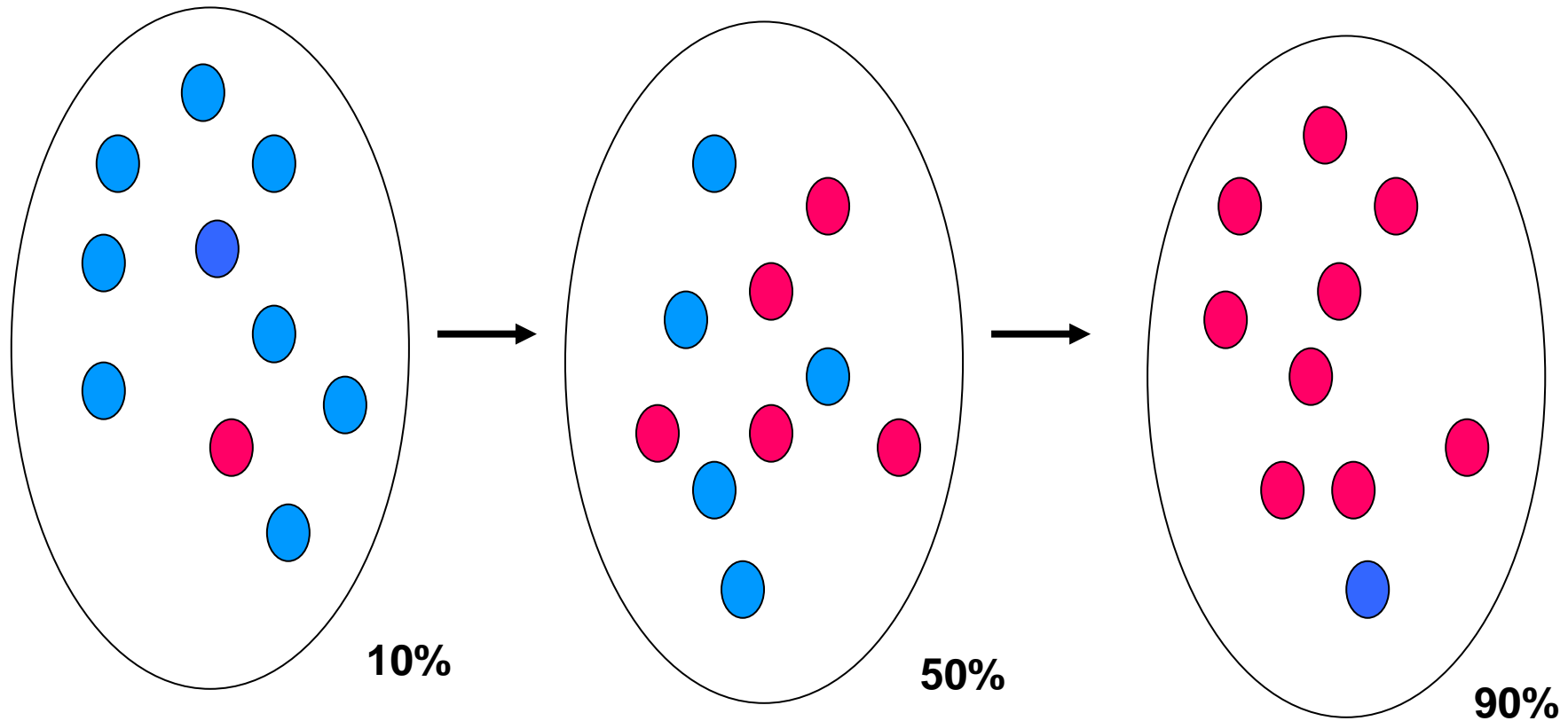
It may be next to impossible to engineer a construct with higher fitness than wildtype (in the adaptive sense).

However, there are types of selfish genetic elements that can increase in frequency without an adaptive fitness advantage (e.g. meiotic drive, TEs, Wolbachia, Medea, ...?).

These may be utilized as “drive” mechanisms linked to effector constructs to push effectors to high frequency or fixation in the wild.



The Wright--Fisher “bean bag” model.



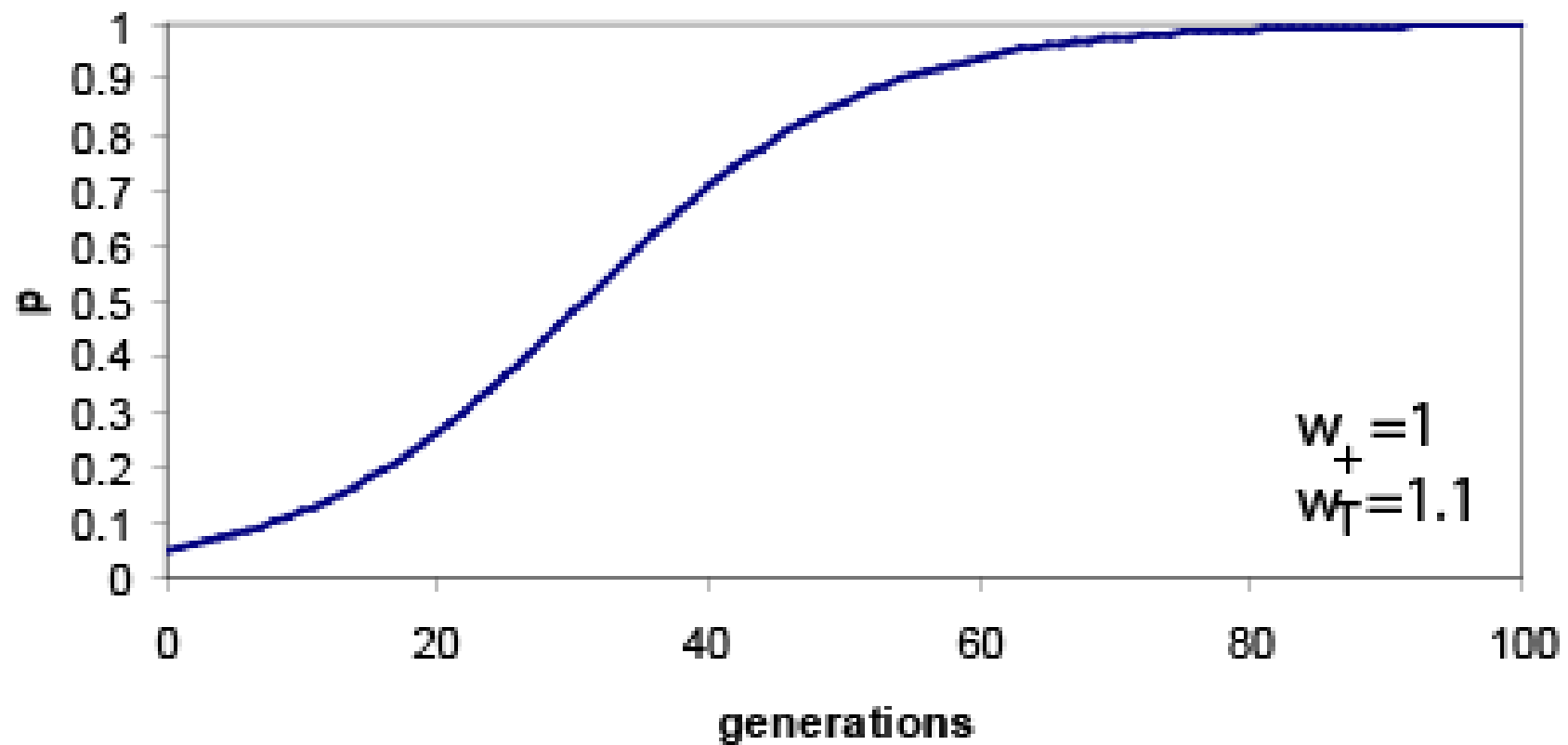
Natural selection changes allele frequencies in a population over time.

Say there is a mutant allele, T, at a frequency of p with a fitness of w_T . The predicted frequency in the next generation is simply its frequency multiplied by fitness and normalized by the average fitness in the population.

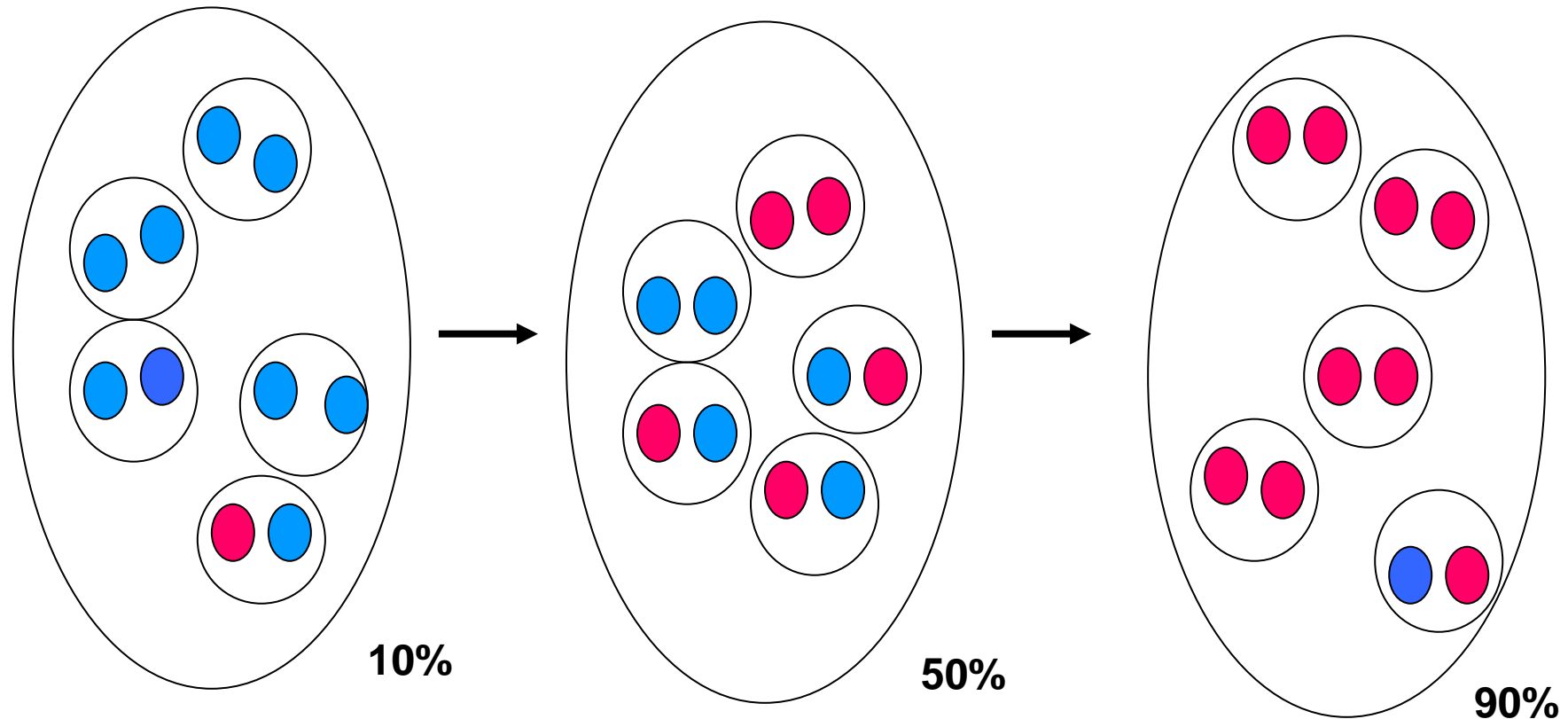
$$p' = \frac{w_T p}{\bar{w}}$$

If an allele has a higher than average fitness it will increase in the population.

With a simple fitness advantage, one allele replaces the other over the following generations.



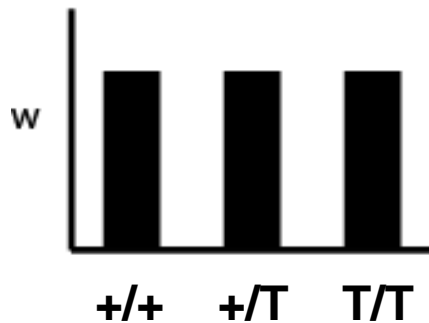
Of course things are not so simple (diploids)



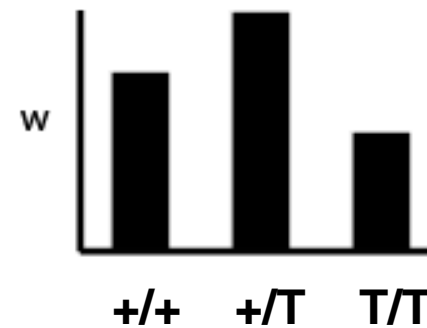
In diploids alleles are paired into individuals, rare alleles tend to be heterozygous.

Two alleles give three genotypes and four different fitness configurations.

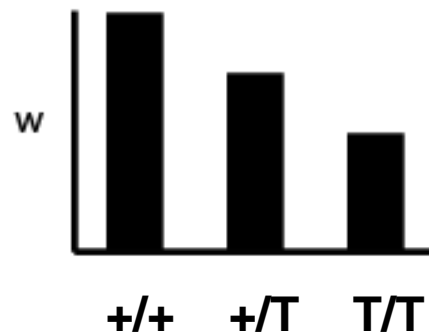
1) Neutrality



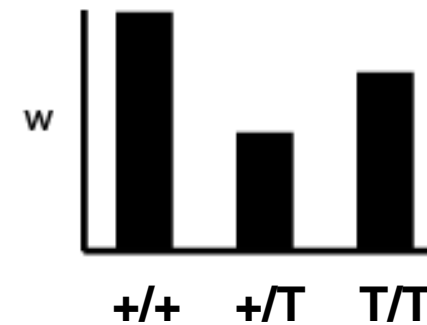
3) Overdominance



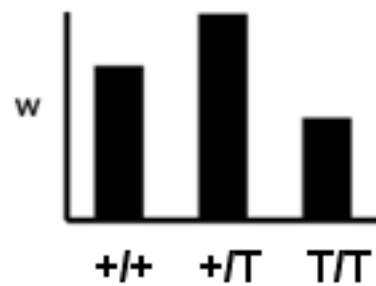
2) Directional



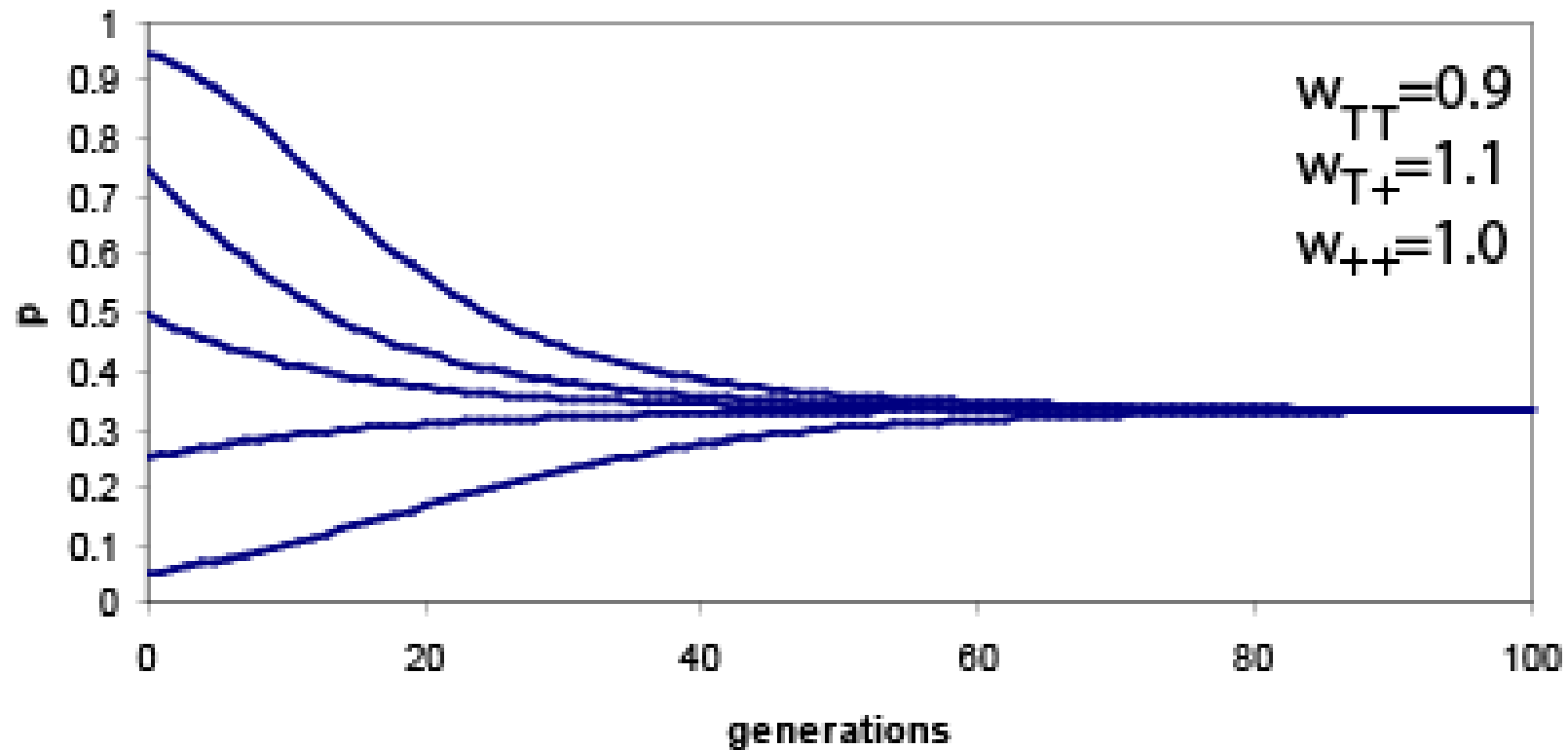
4) Underdominance



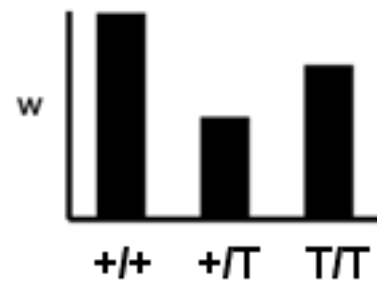
3) Overdominance



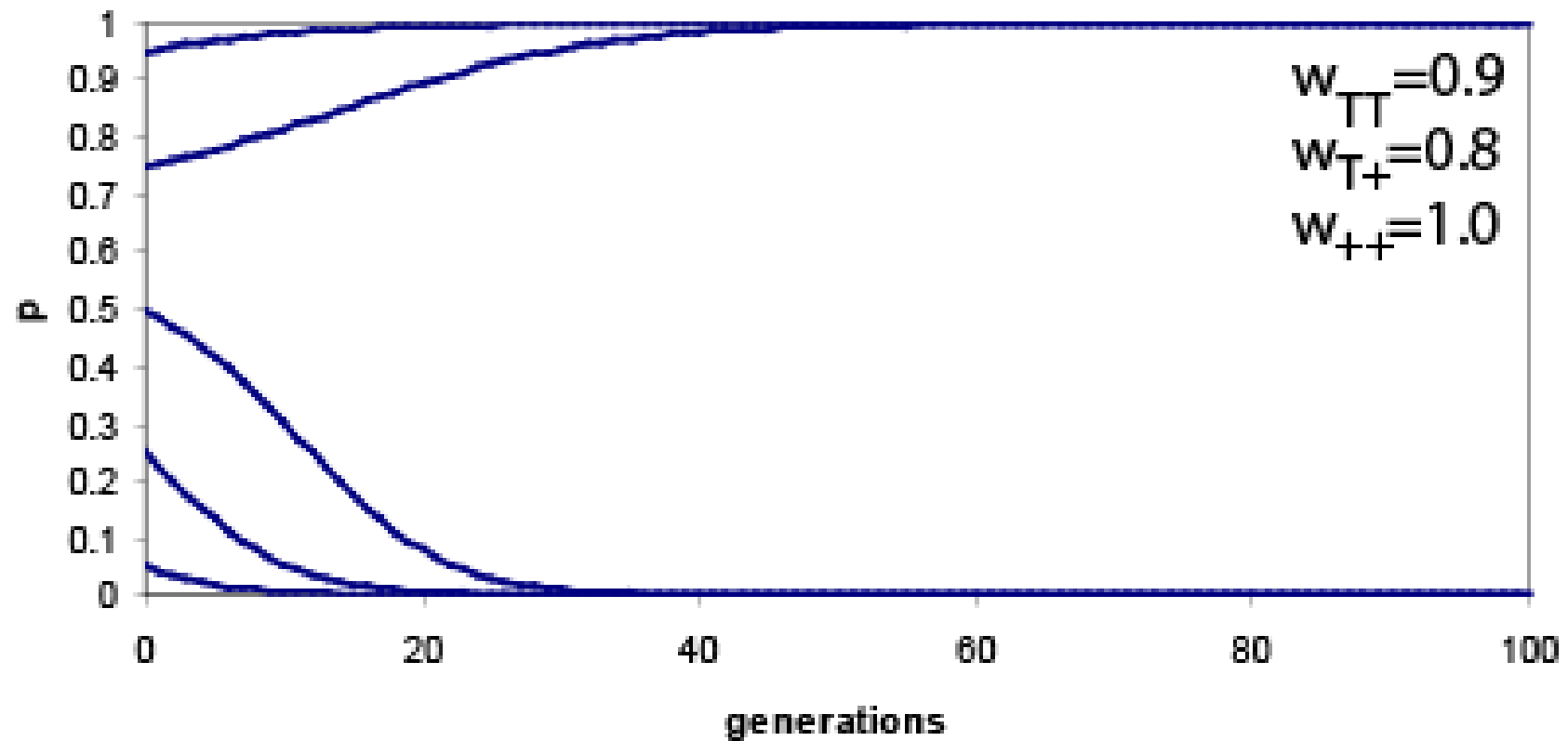
A heterozygote advantage leads to a stable equilibrium.



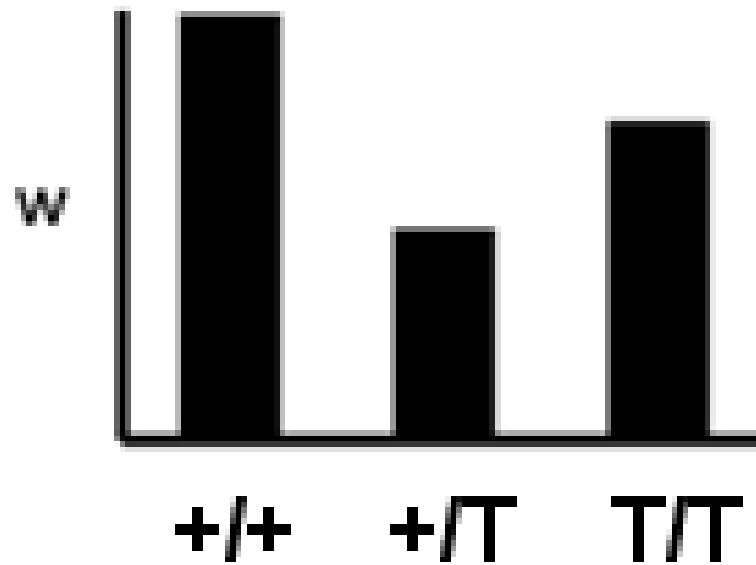
4) Underdominance



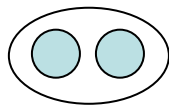
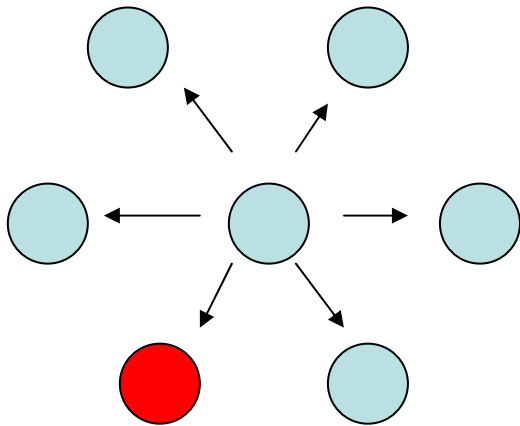
A heterozygote disadvantage leads to an unstable equilibrium.



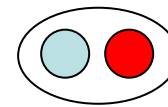
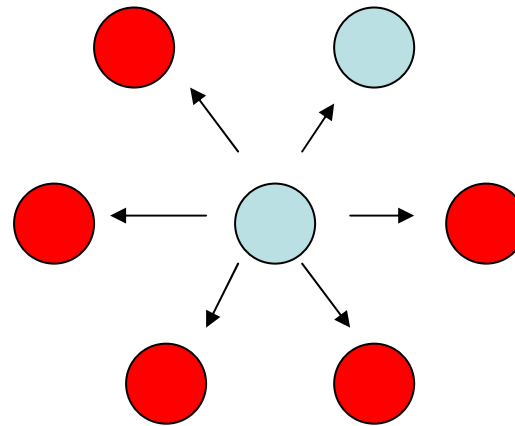
Because of this bistable nature, underdominance can be an alternative to the types of “selfish drive” systems mentioned before.



Possible allele pairings in a population



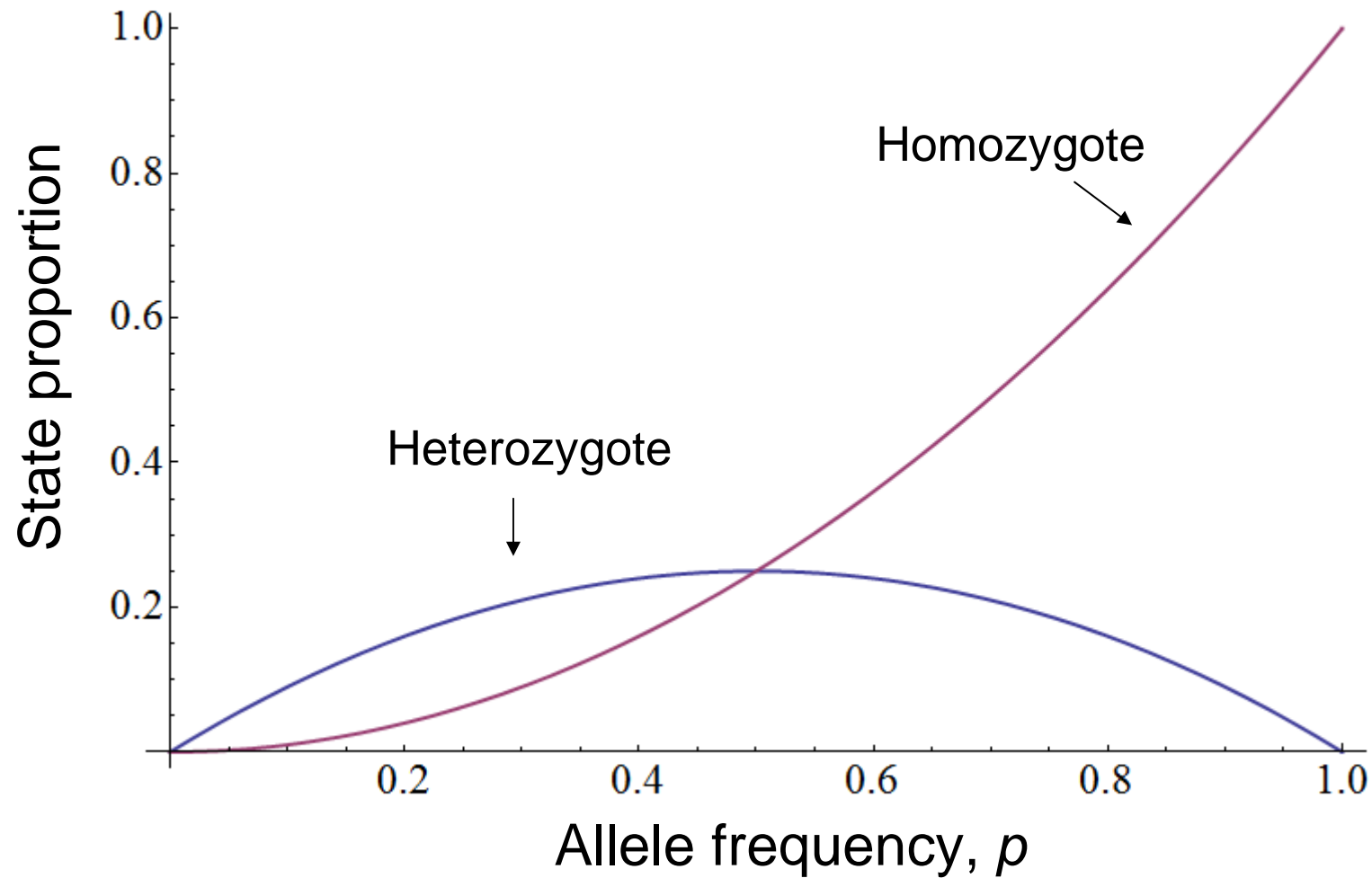
Homozygote



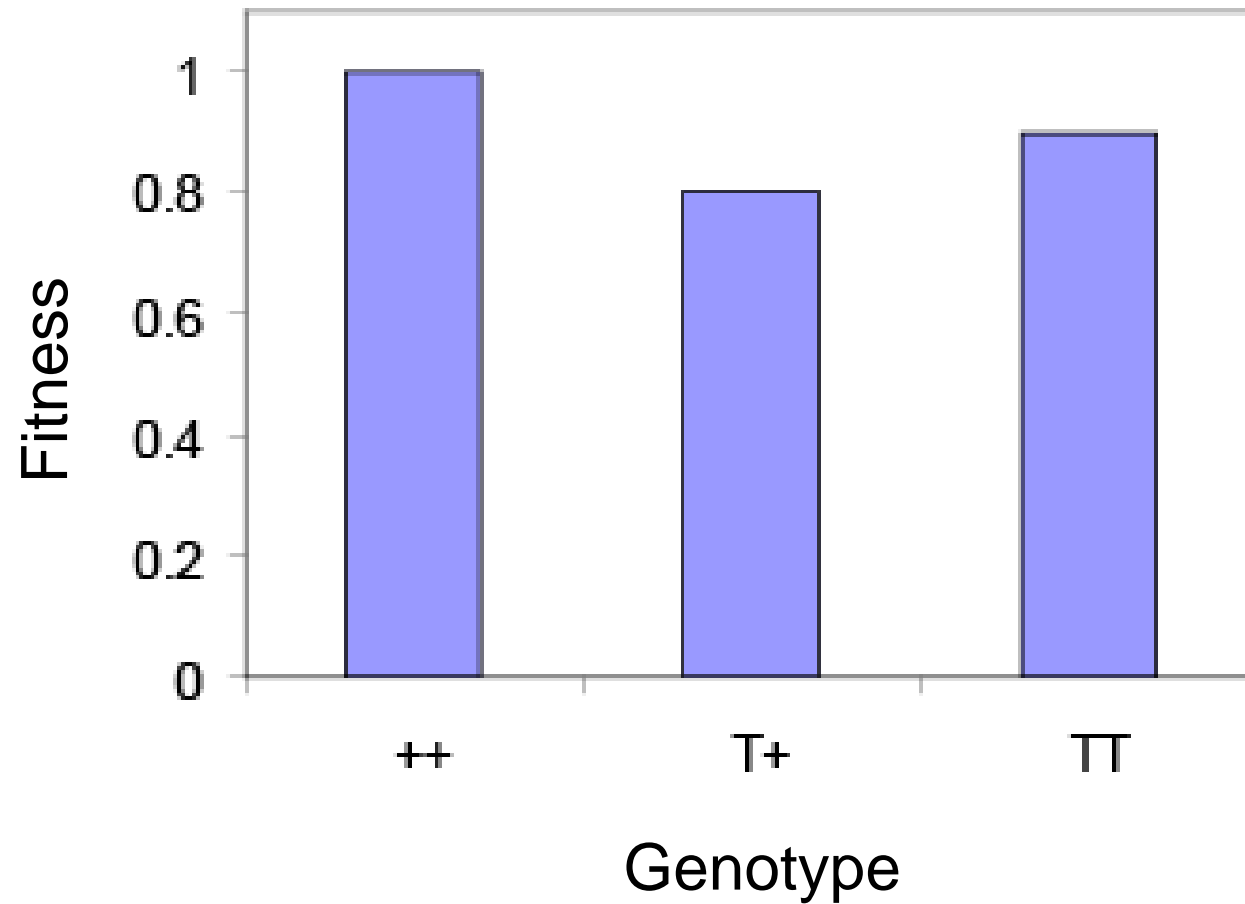
Heterozygote

Common alleles are present most often as homozygotes, rare alleles are present most often as heterozygotes.

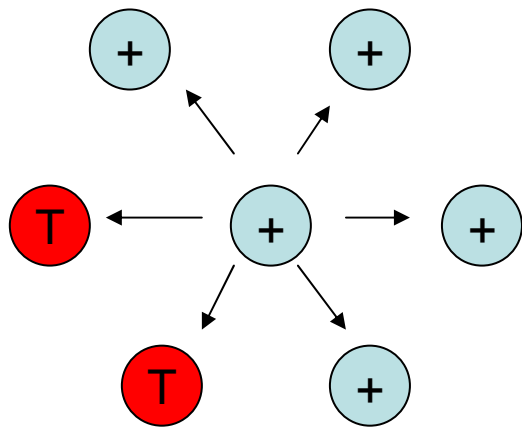
A rare allele spends more time as a heterozygote than a homozygote



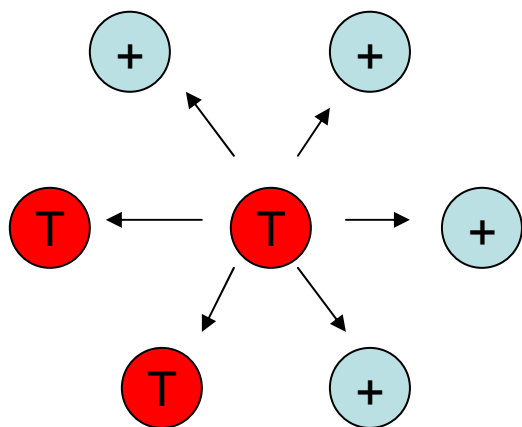
A heterozygote disadvantage corresponds to a rare allele disadvantage



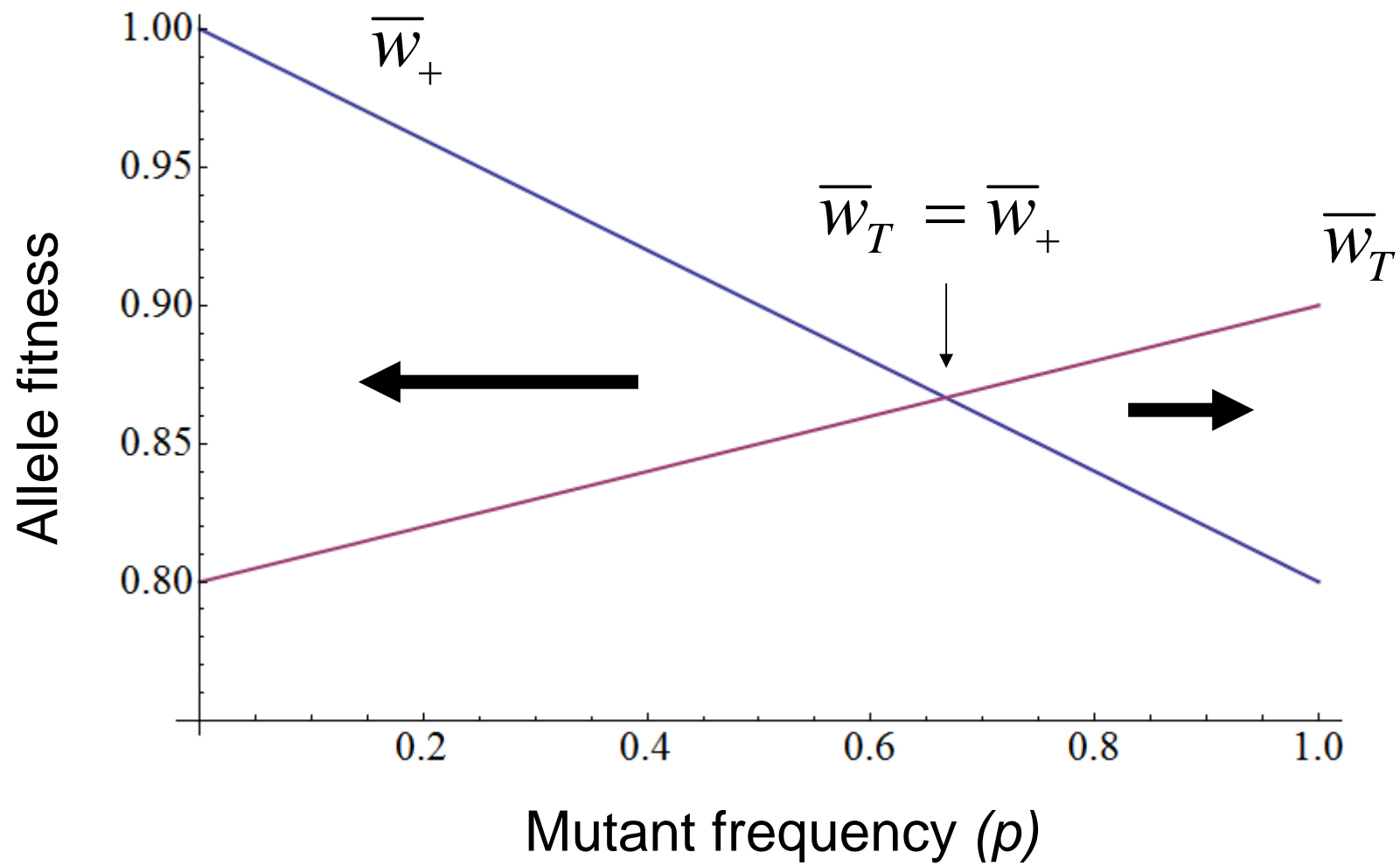
We can estimate the average fitness of each allele



$$\bar{w}_+ = w_{T+} p + w_{++} (1 - p)$$



$$\bar{w}_T = w_{TT} p + w_{T+} (1 - p)$$



Equilibrium value

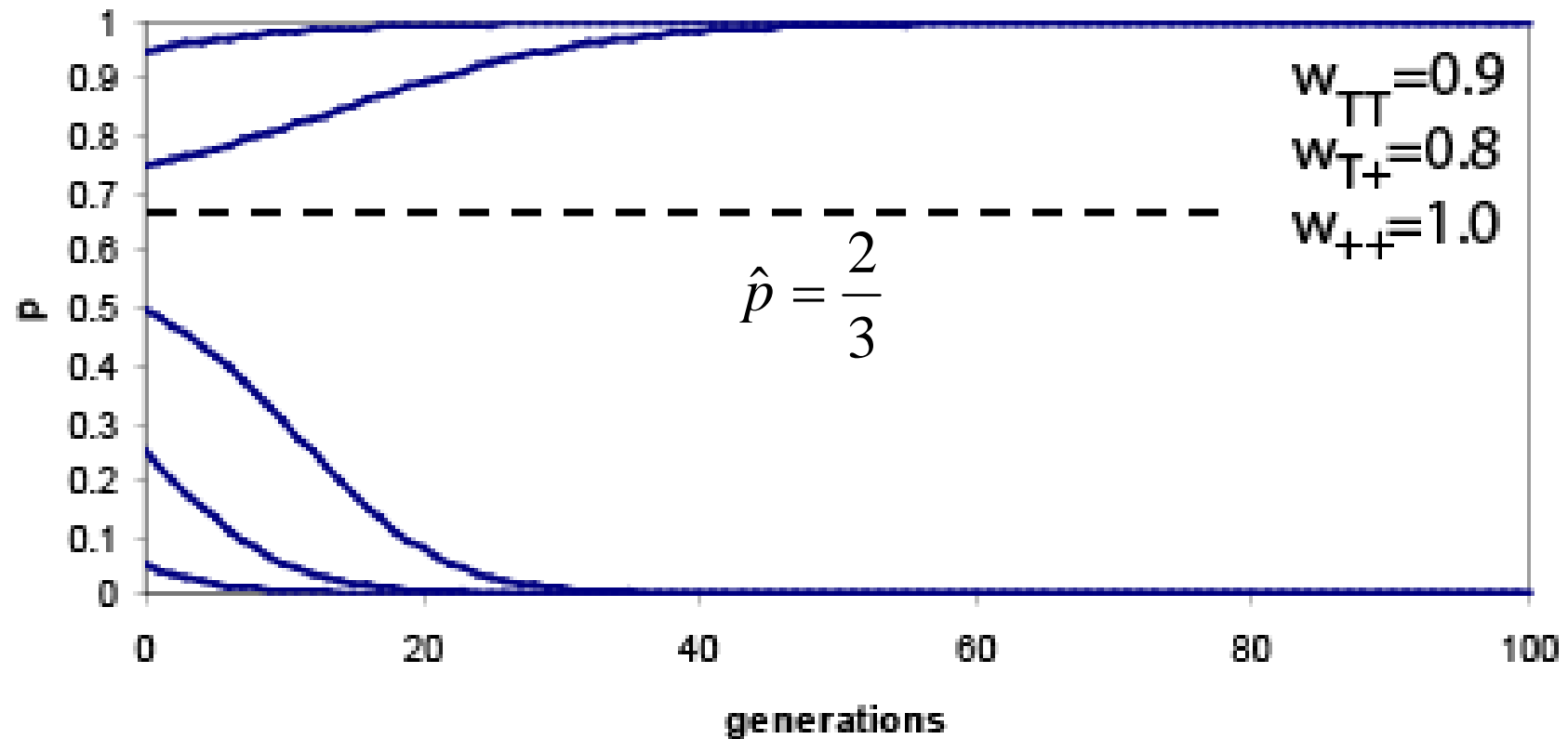
$$\overline{w}_T = \overline{w}_+$$

$$w_{TT} p + w_{T+} (1 - p) = w_{T+} p + w_{++} (1 - p)$$

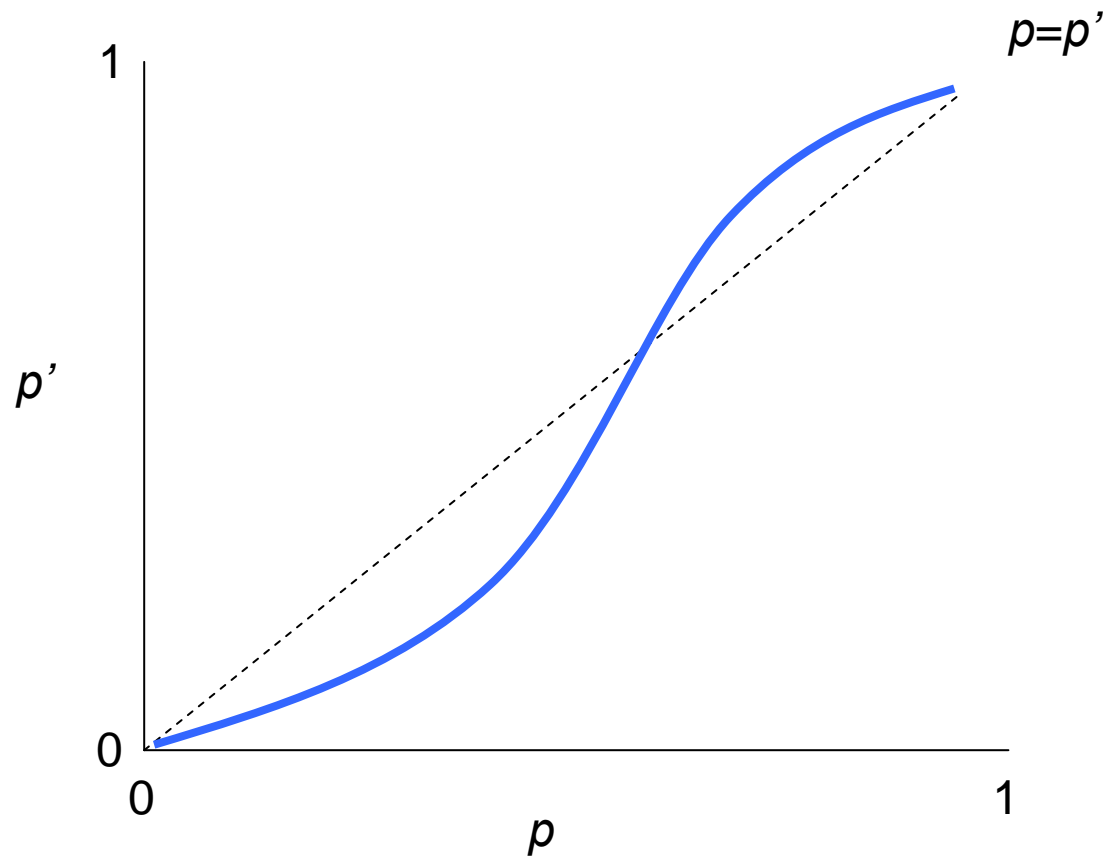


$$\hat{p} = \frac{w_{++} - w_{T+}}{w_{++} - 2w_{T+} + w_{TT}}$$

If starting at a frequency above this value, an allele less fit than wildtype can stably fix in a population.

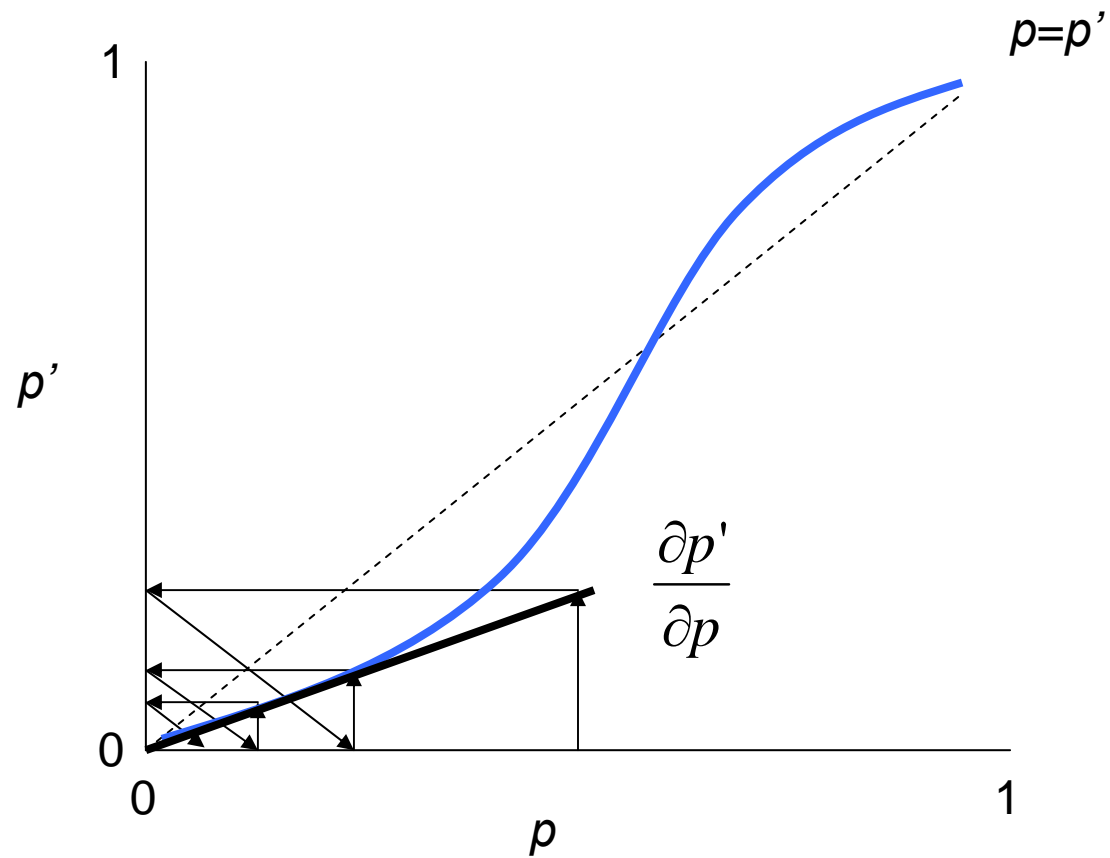


A different way to visualize underdominance

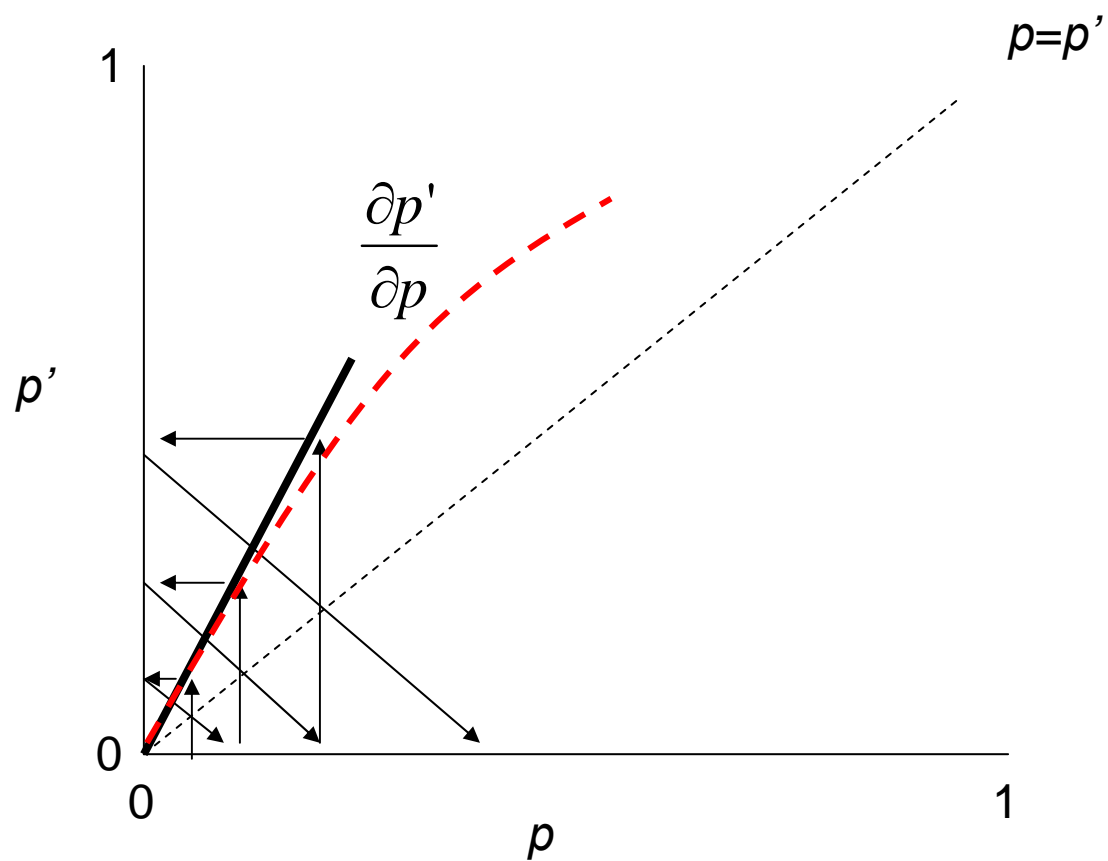


$$p' = \frac{w_T p}{\bar{w}}$$

Stable equilibrium at $p=0$



Unstable equilibrium at $p=0$



To describe the stability near the point $p=0$

Find $\frac{\partial p'}{\partial p}$

Substitute in $p=0$

Set it equal to 1 and solve for w :

$$w_{T+} = 1$$

If w_{T+} is less than one (wildtype fitness) the allele will be lost (near $p=0$).

To describe the stability near the point $p=0$

Find $\frac{\partial p'}{\partial p}$

Substitute in $p=0$

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$$w_{T+} = 1$$

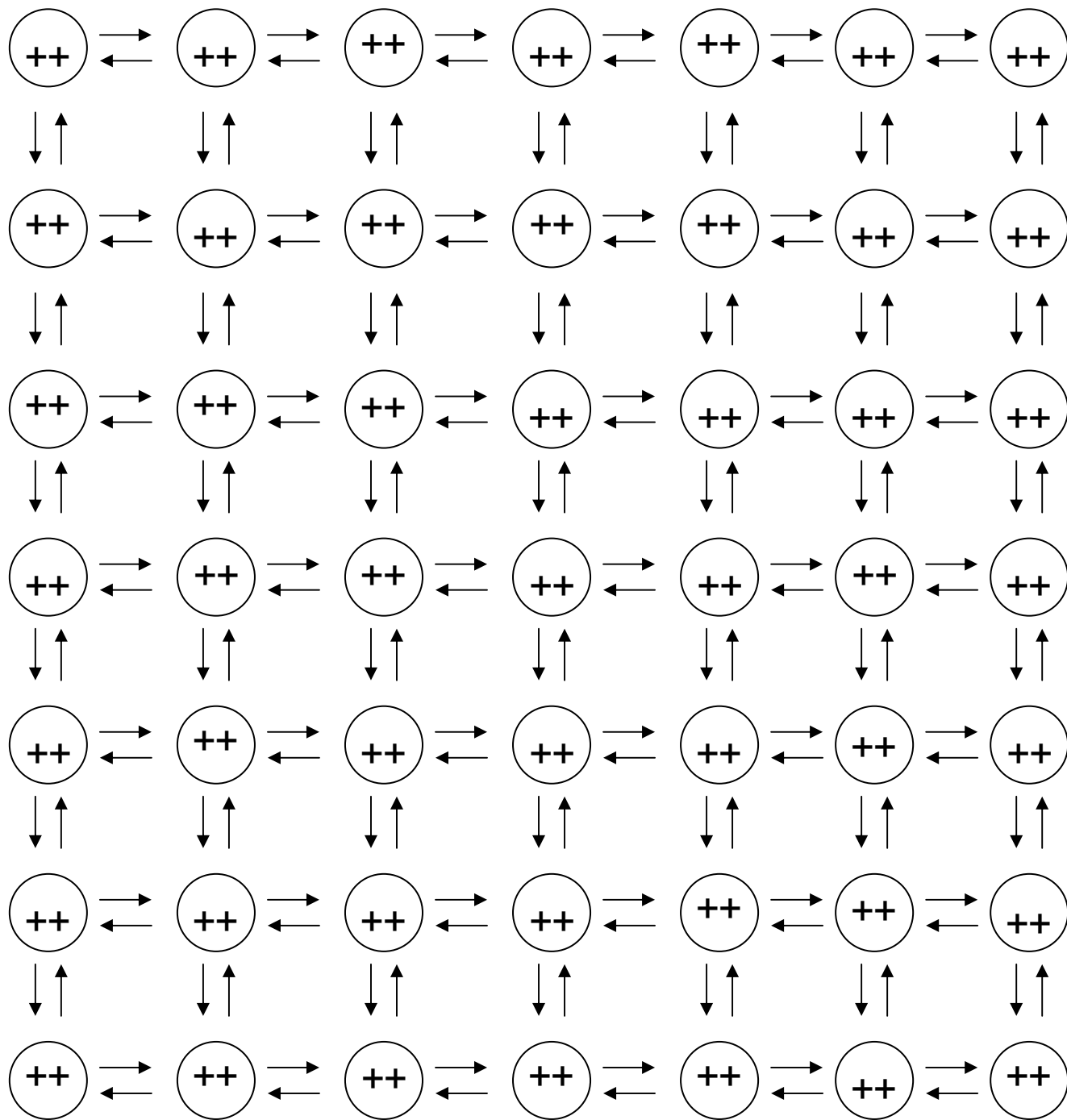
If w_{T+} is less than one (wildtype fitness) the allele will be lost (near $p=0$).

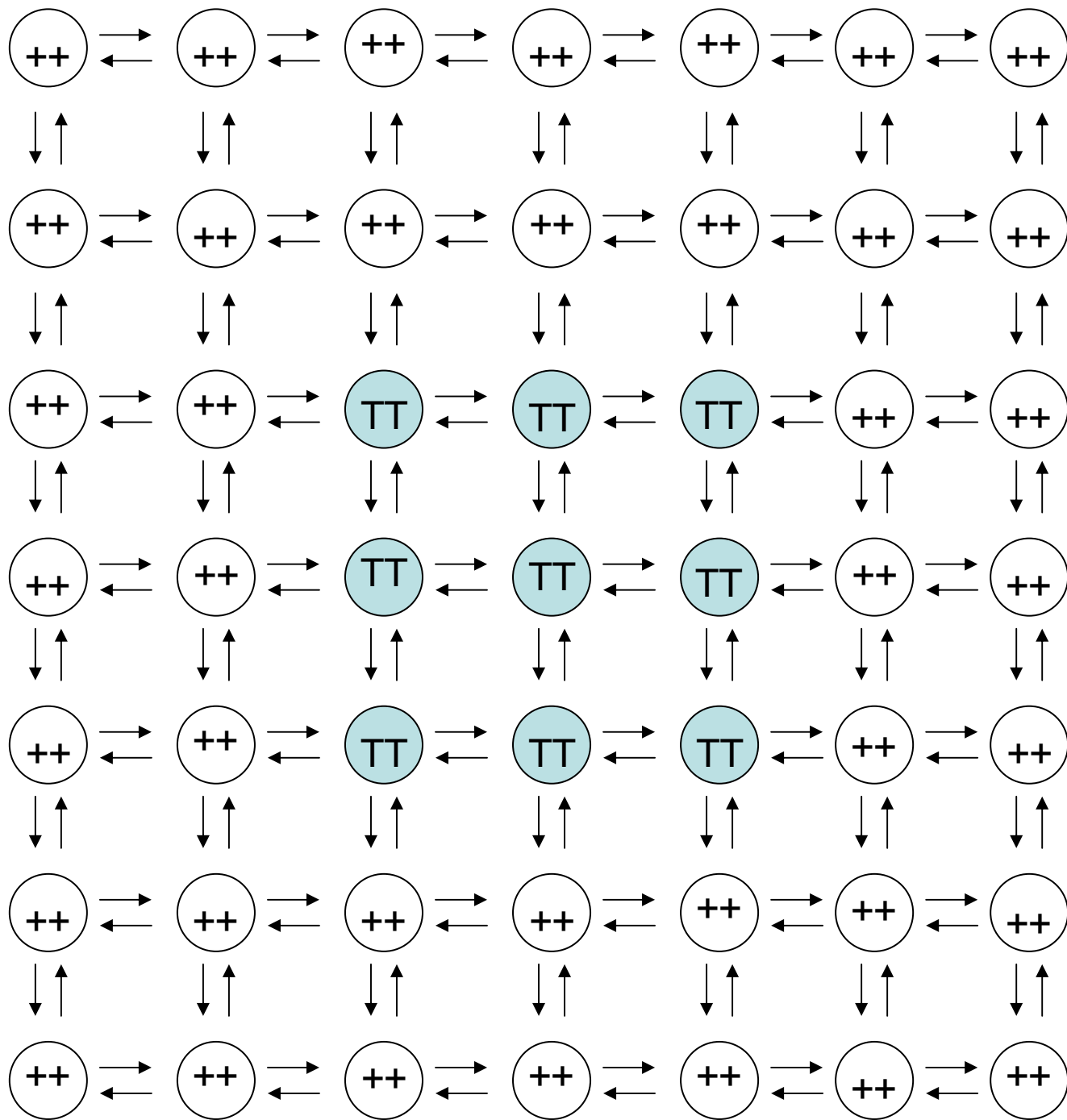
At $p=1$...

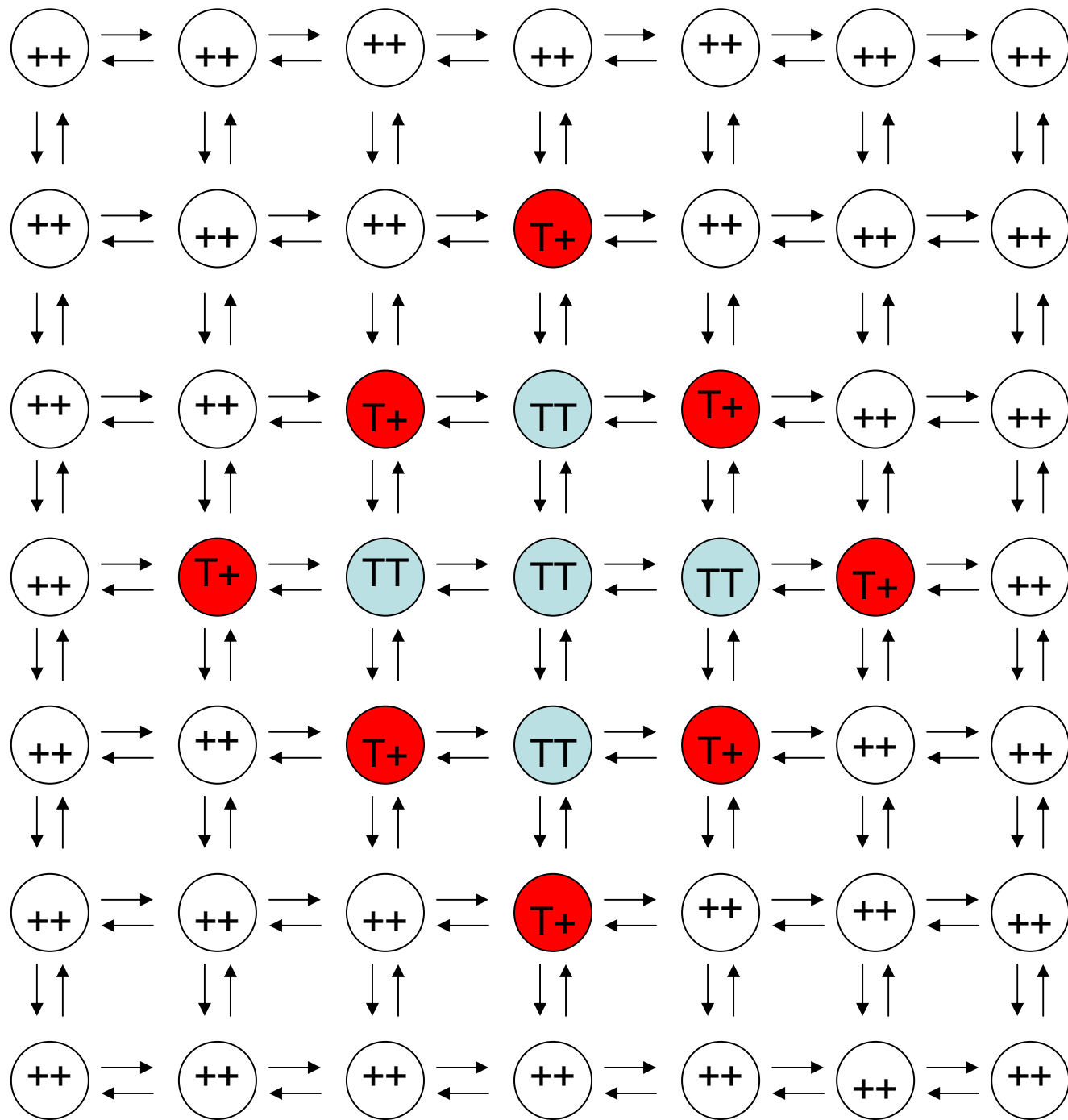
$$w_{T+} = w_{TT}$$

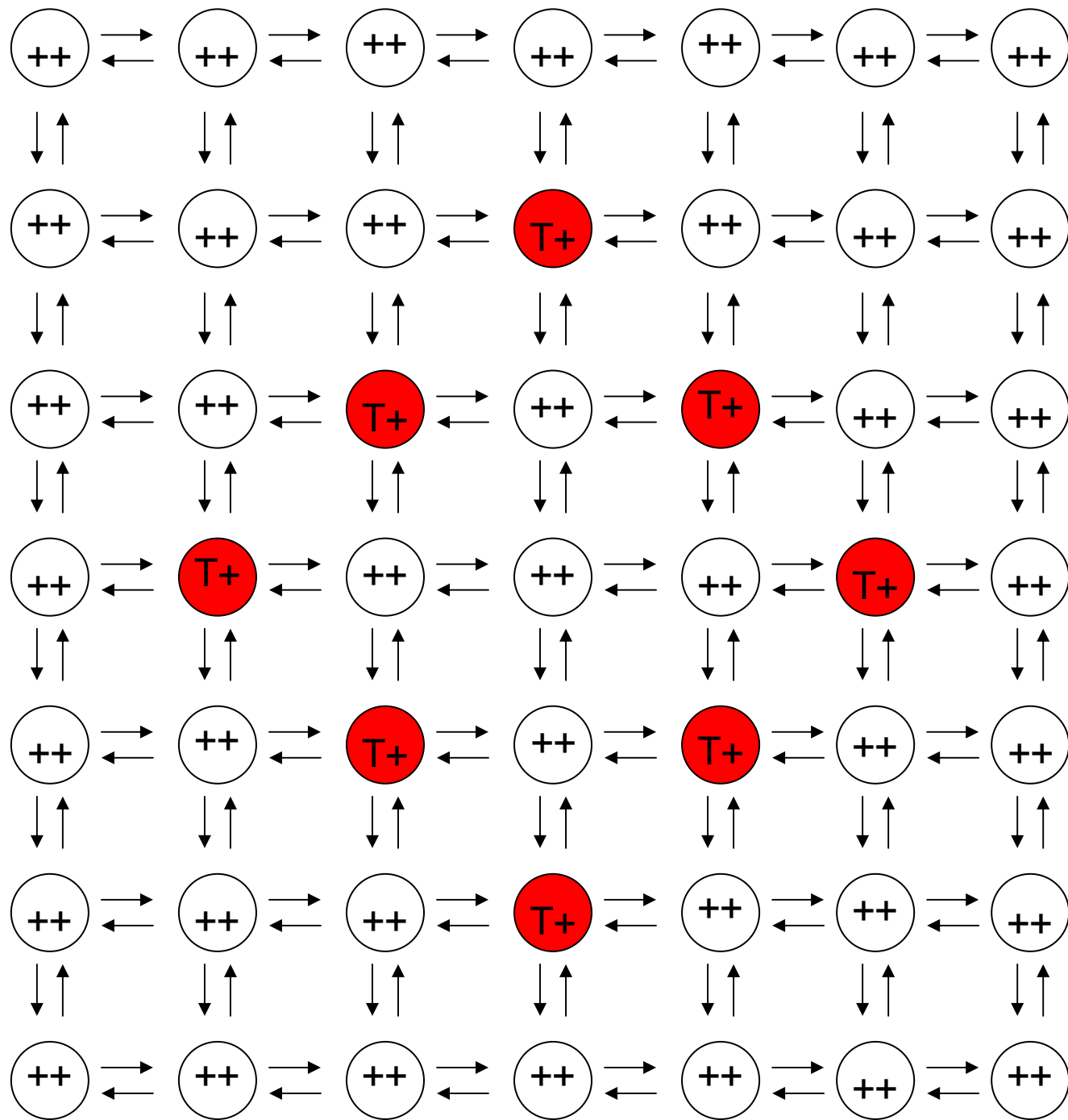
If w_{T+} is less than w_{TT} the allele will fix in the population (near $p=1$)

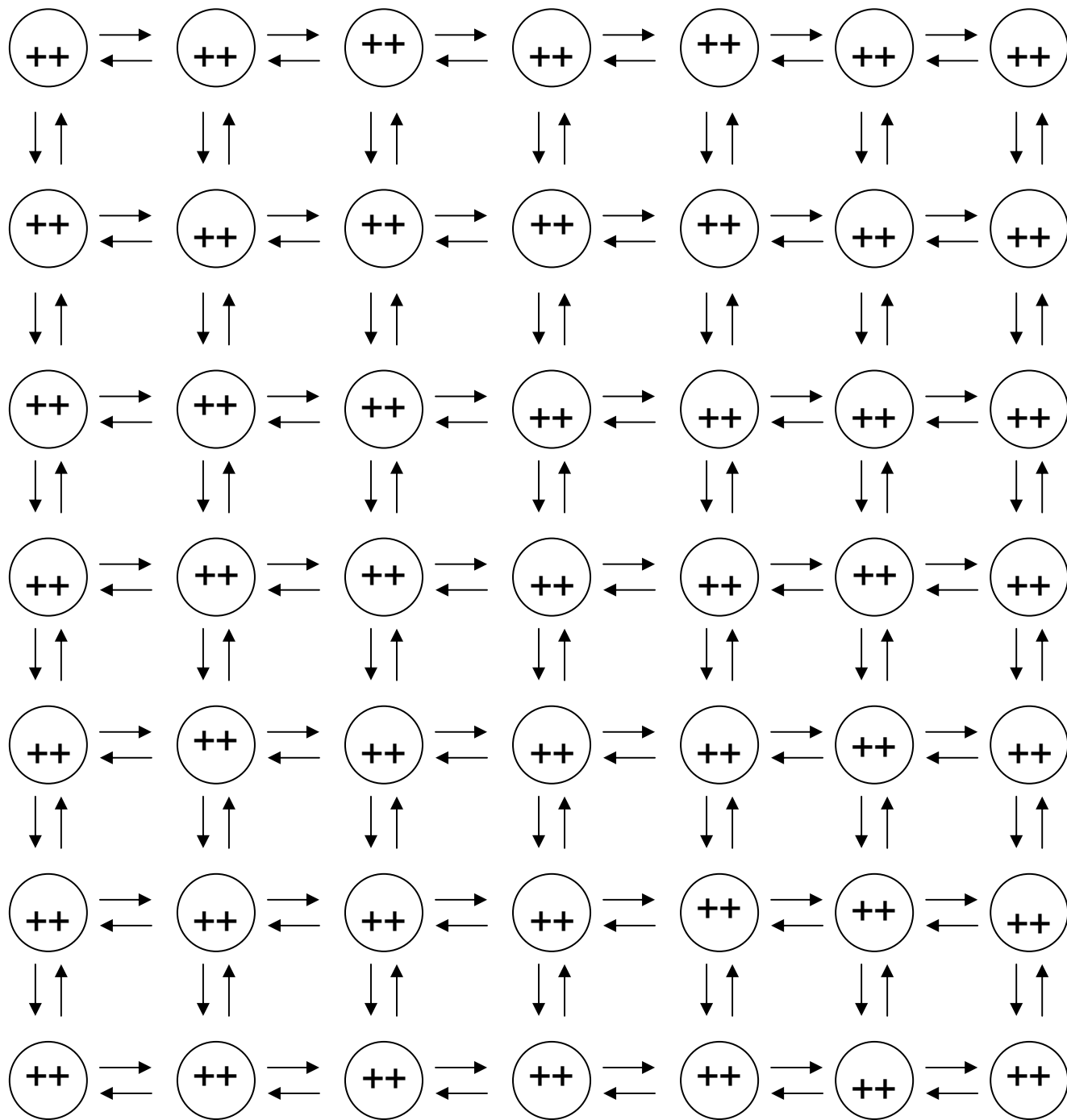
Underdominance has useful spatial properties for testing effector systems.



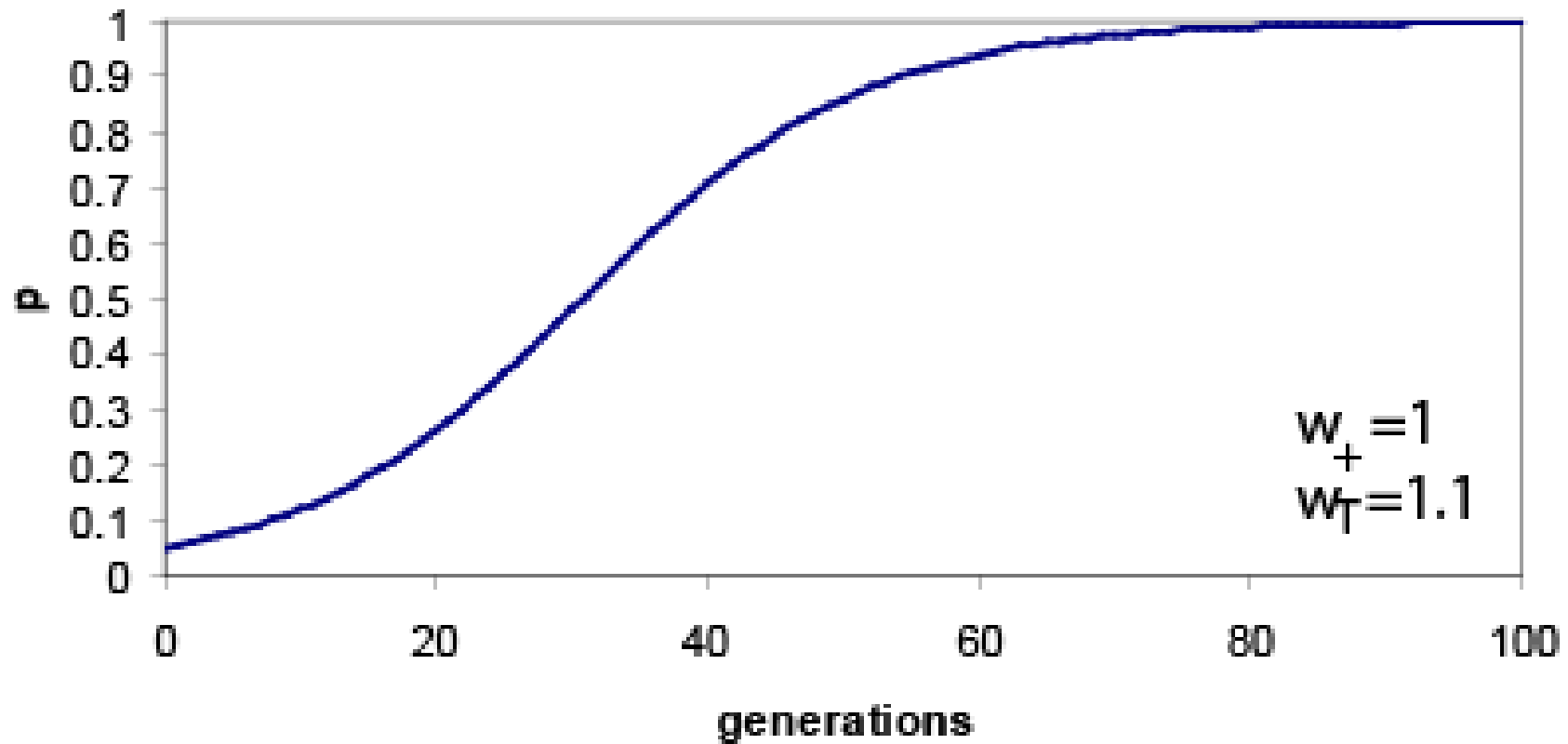


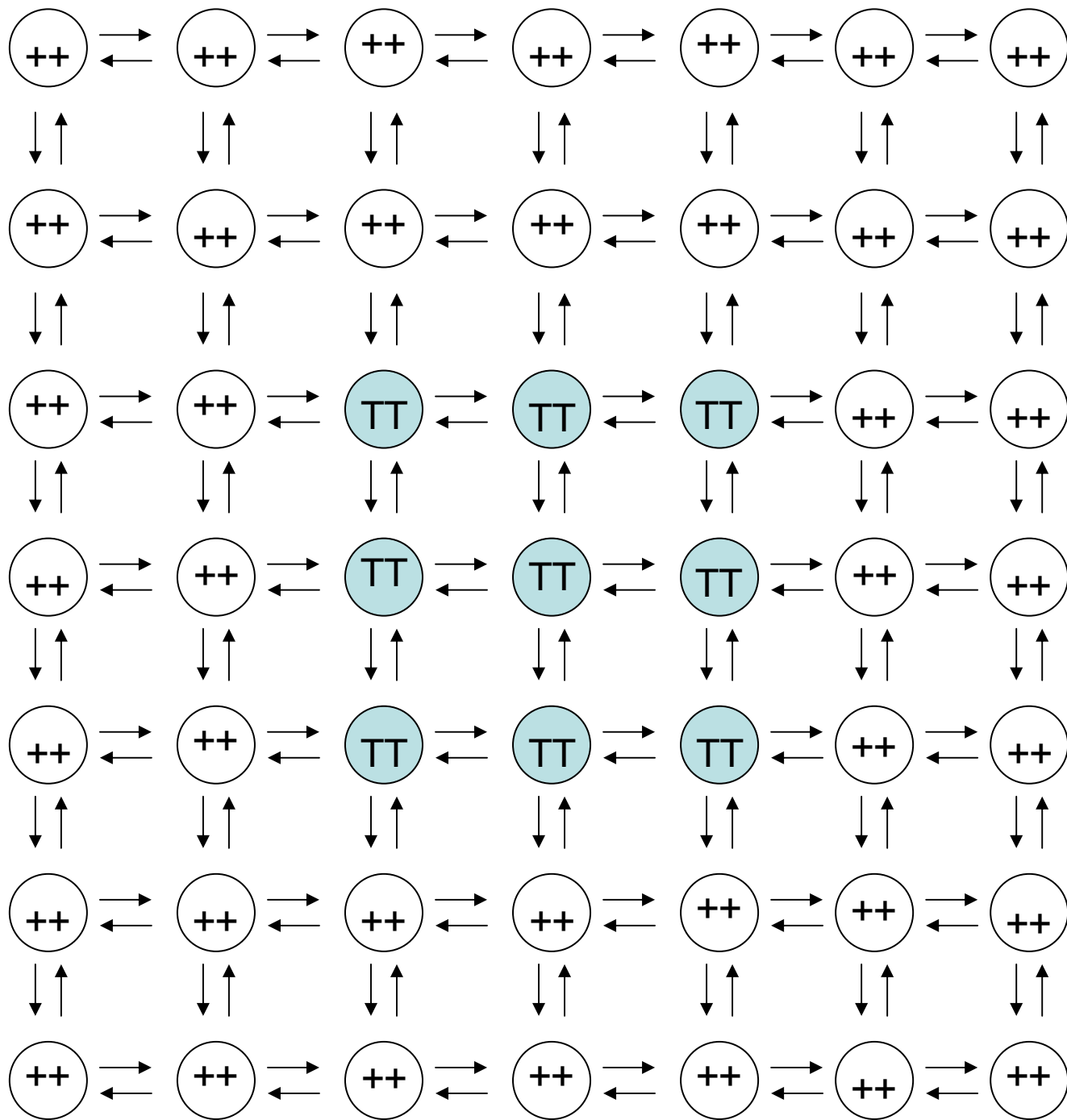


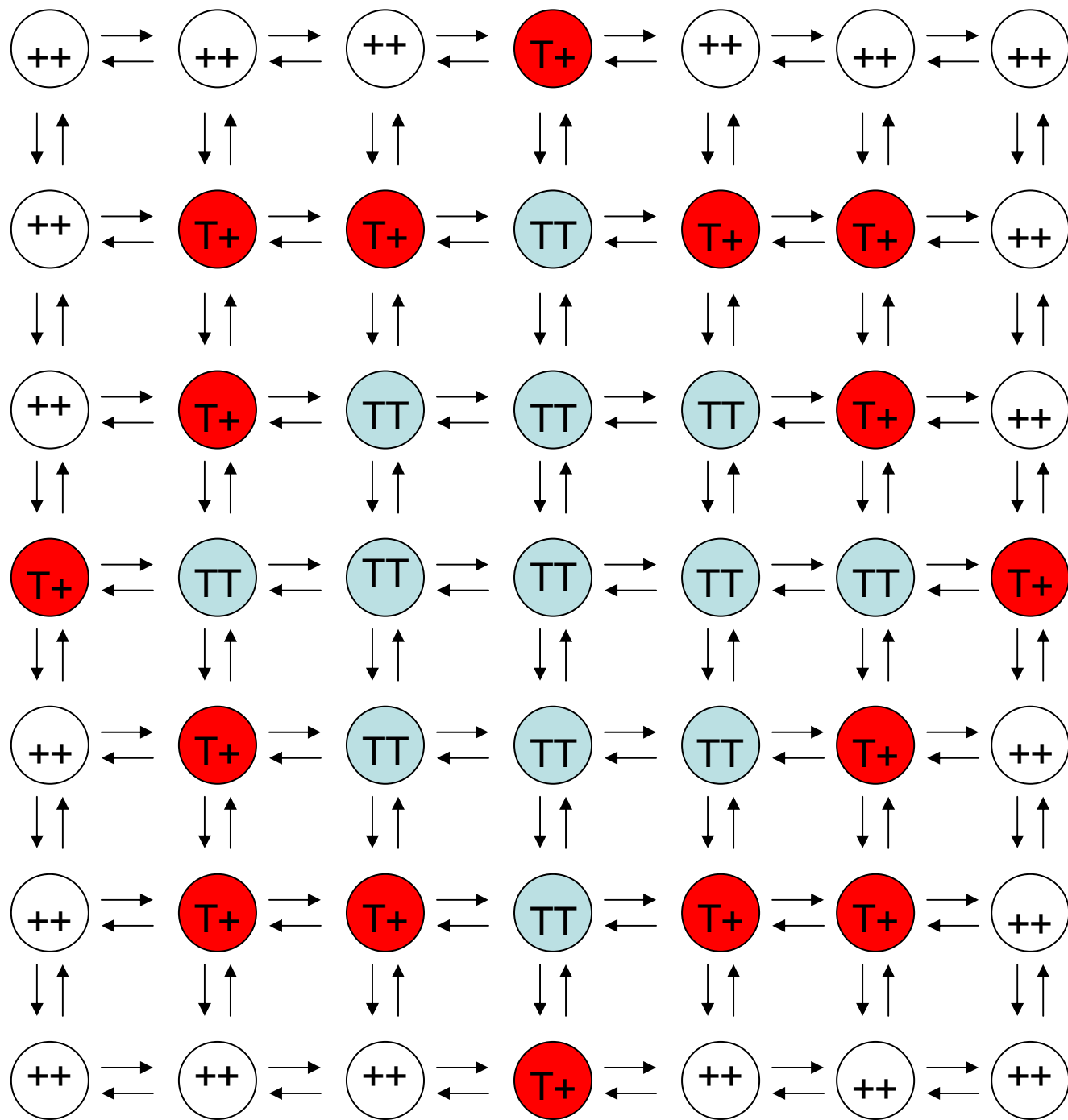


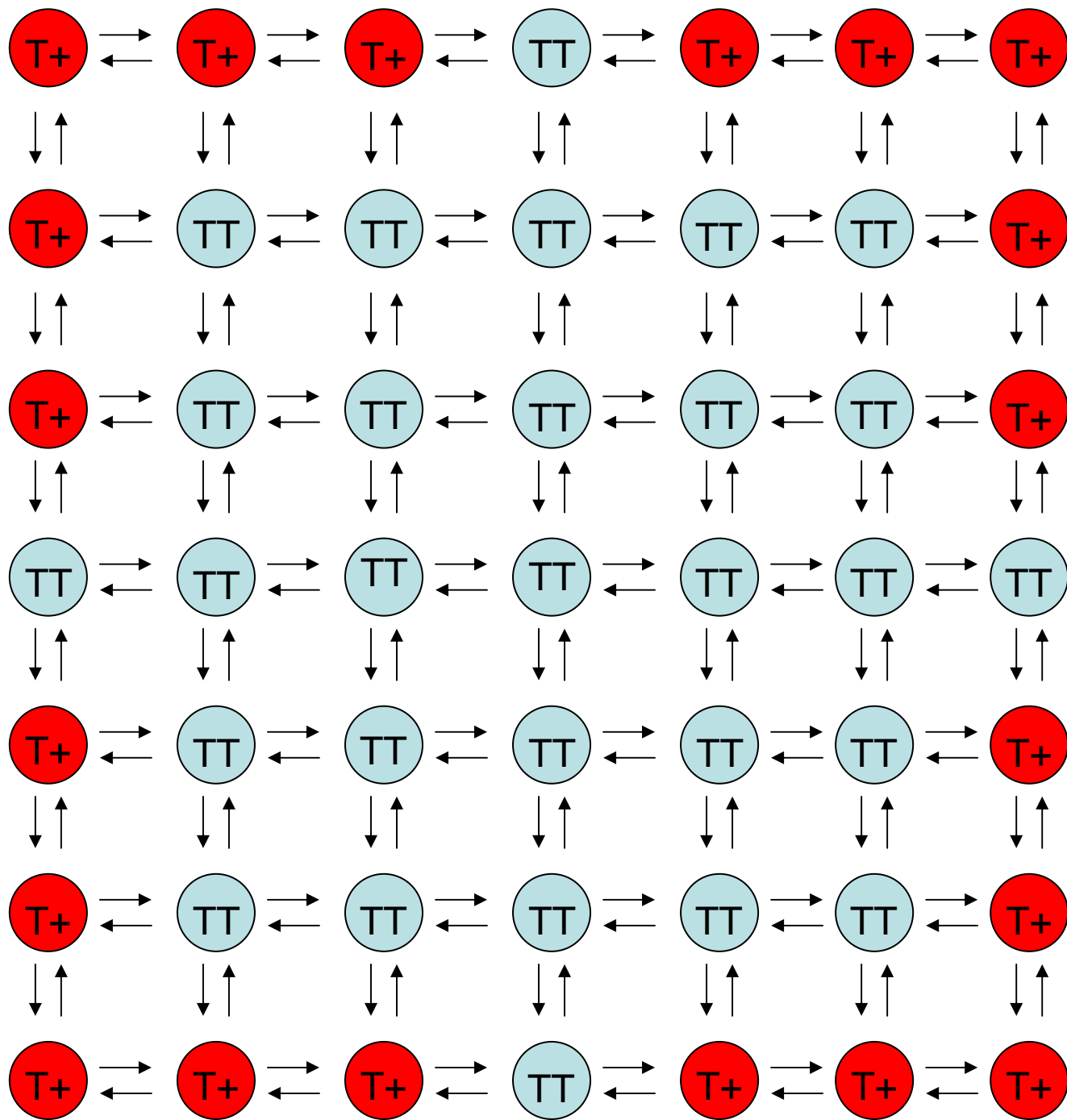


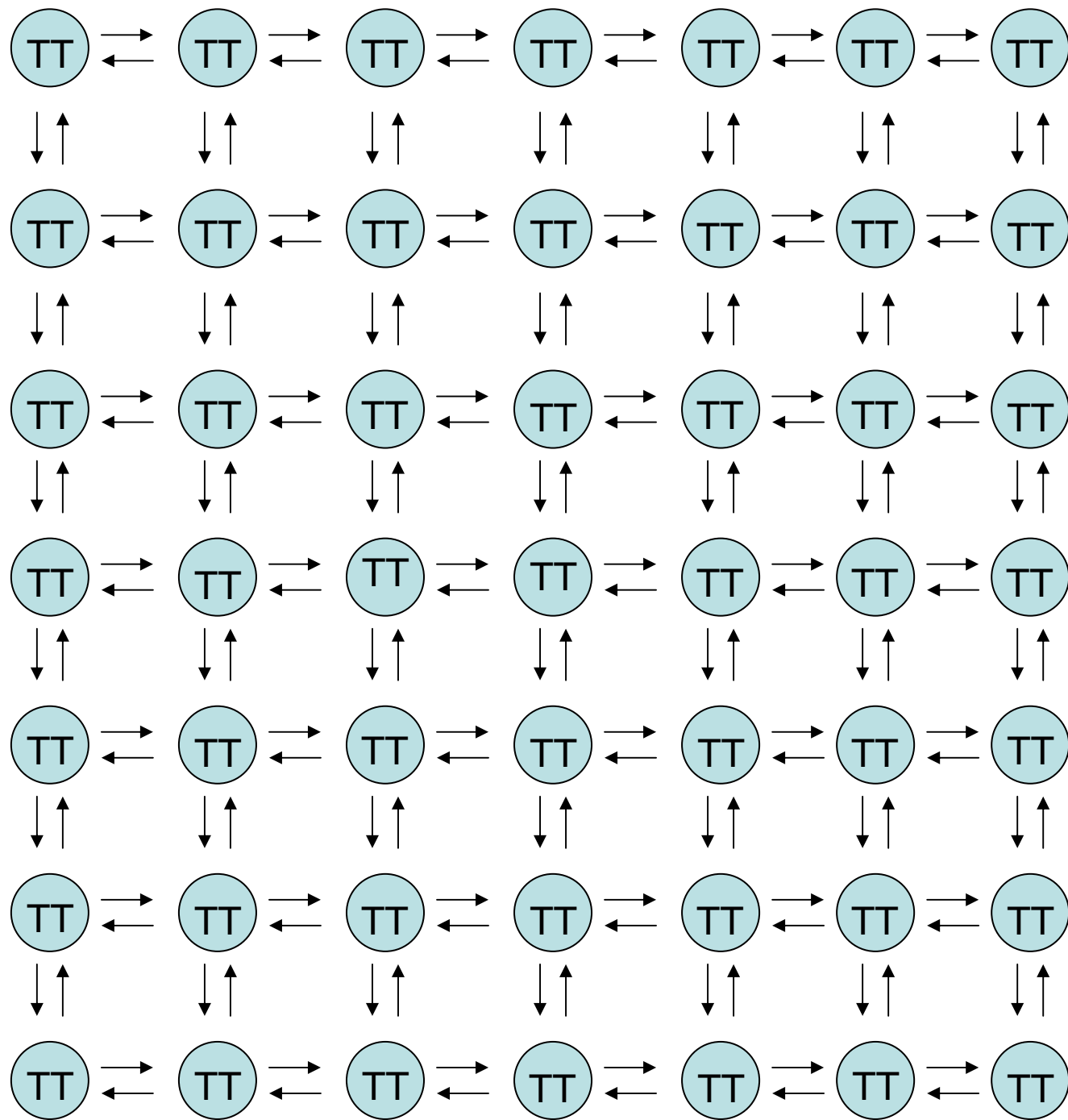
Alternative gene-drive methods have been proposed that can invade a population from very low frequencies

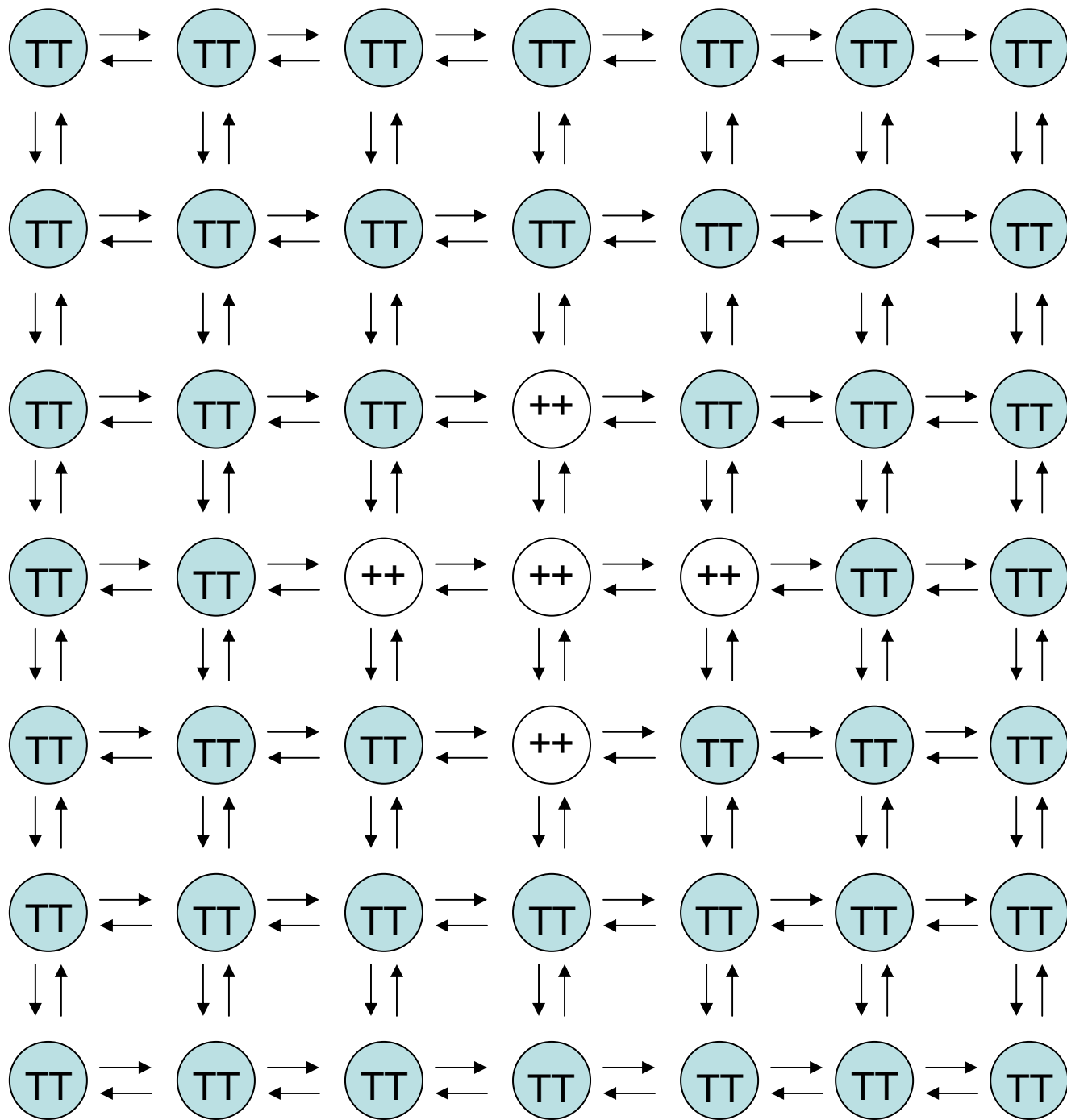


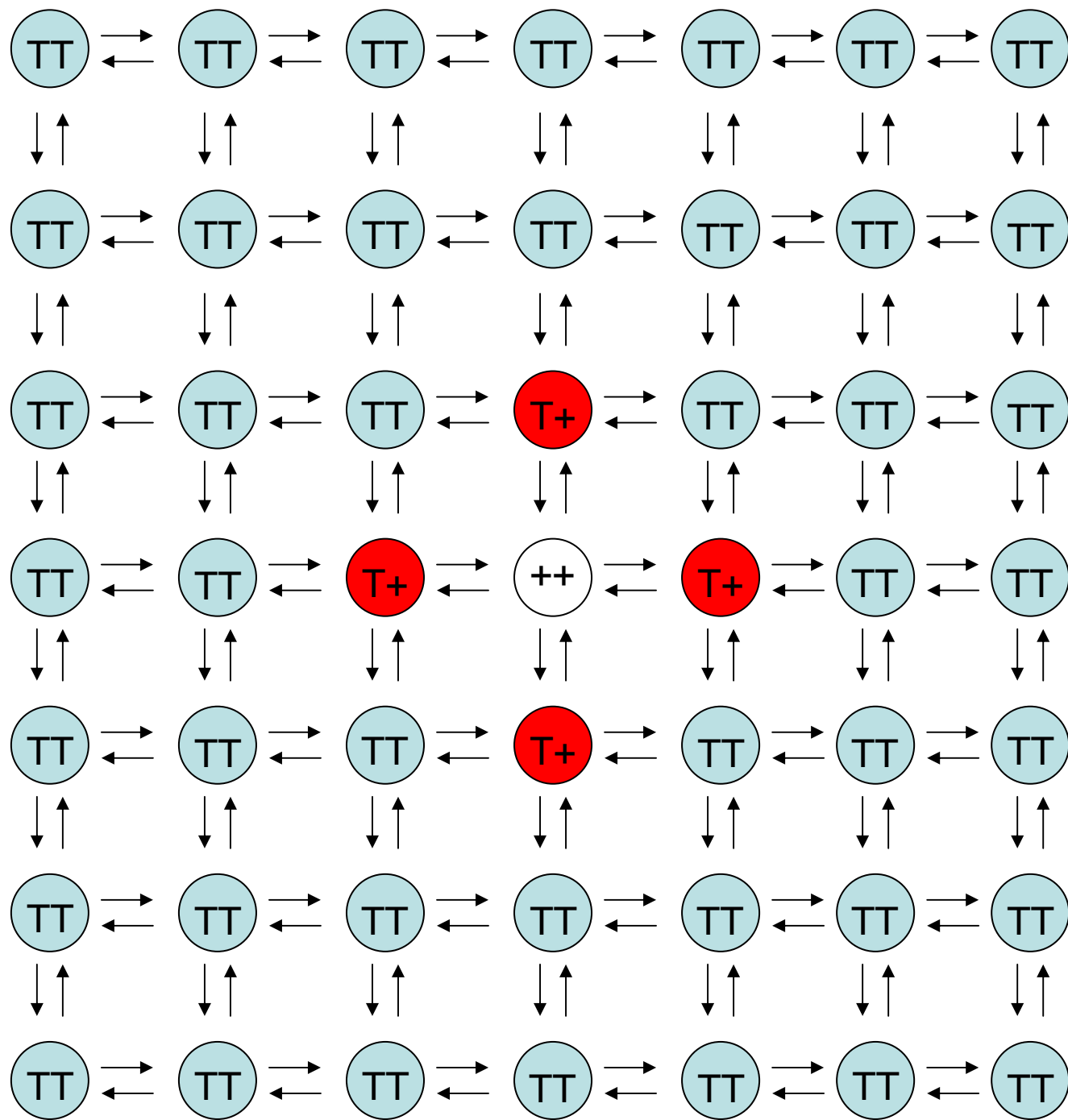


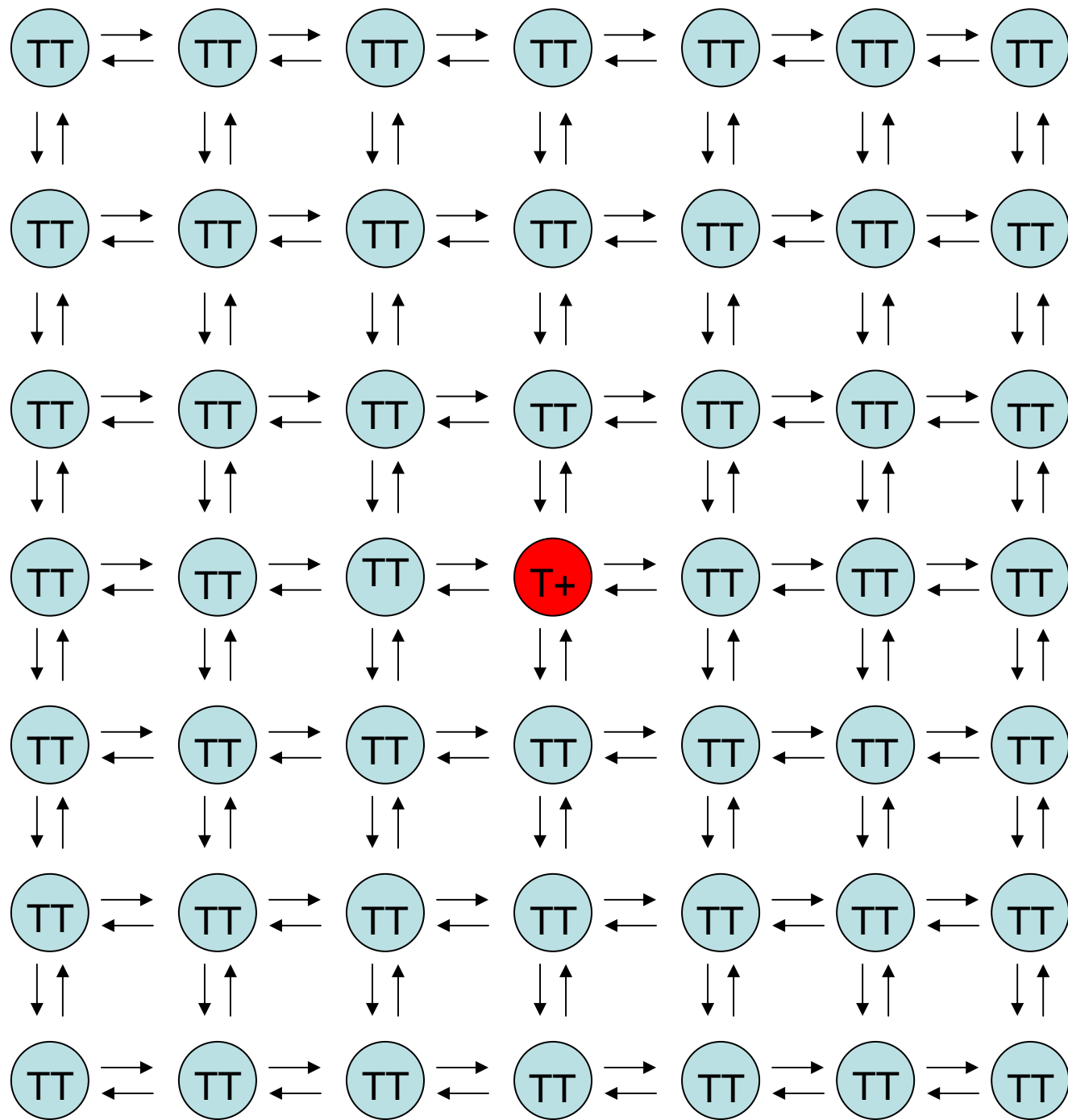


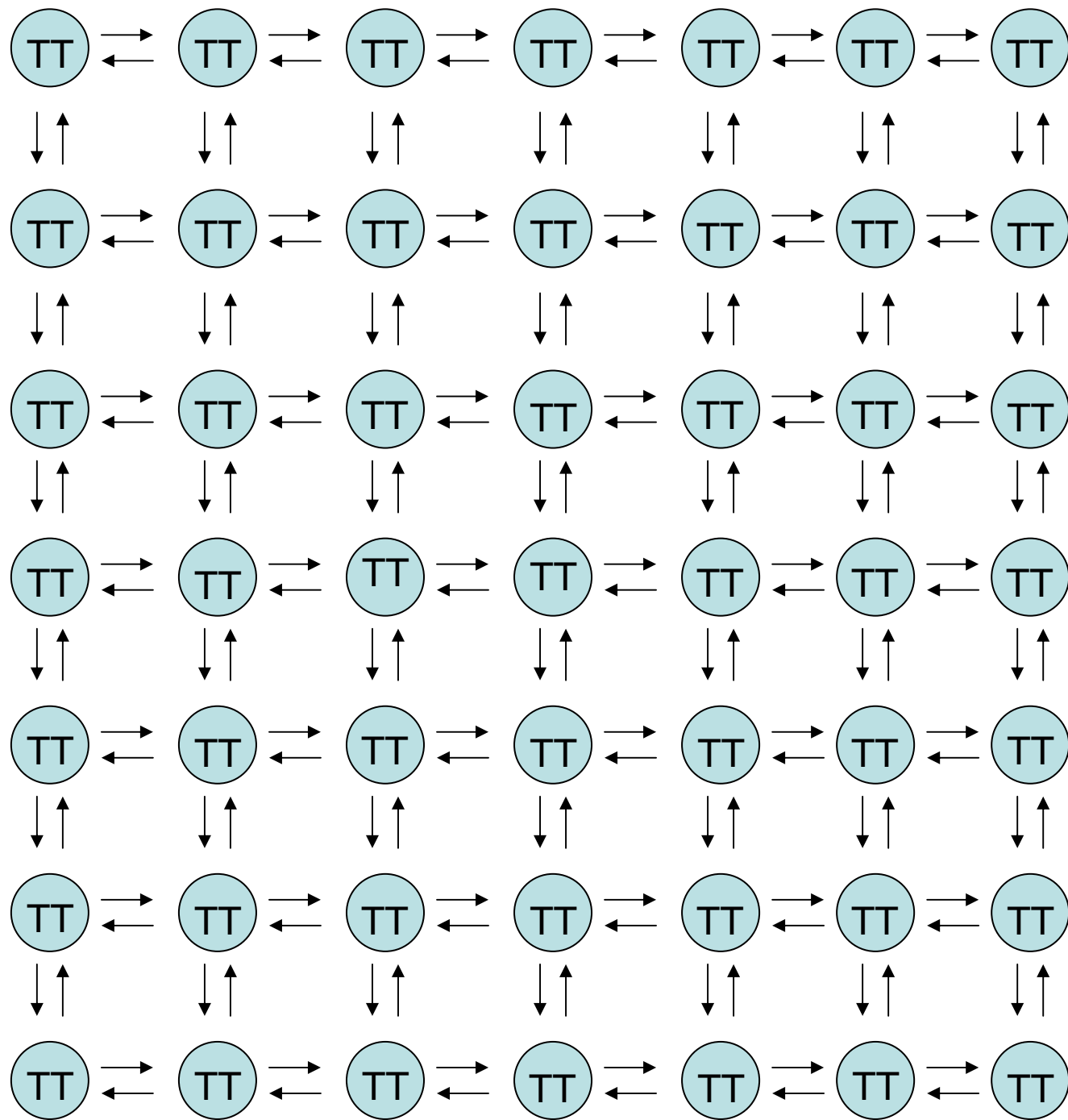




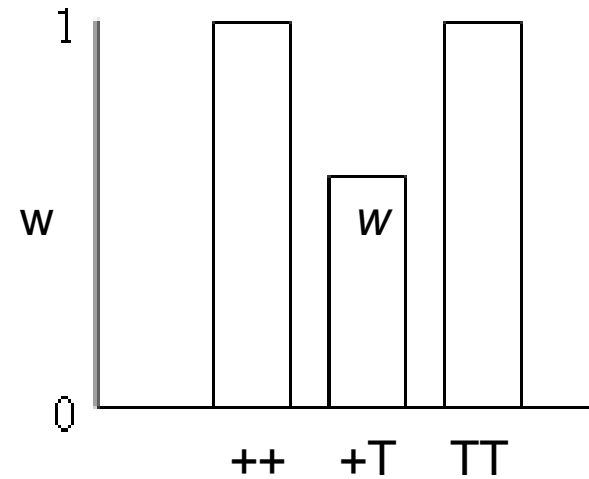
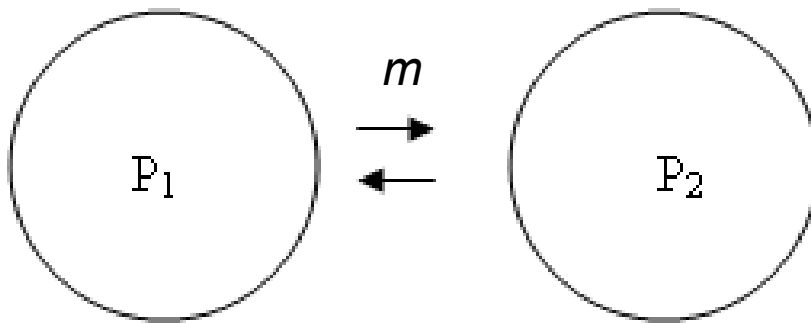




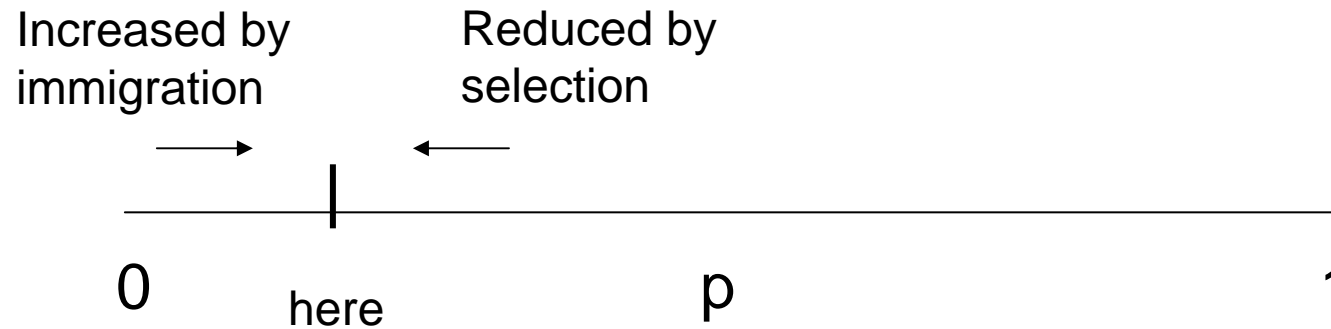




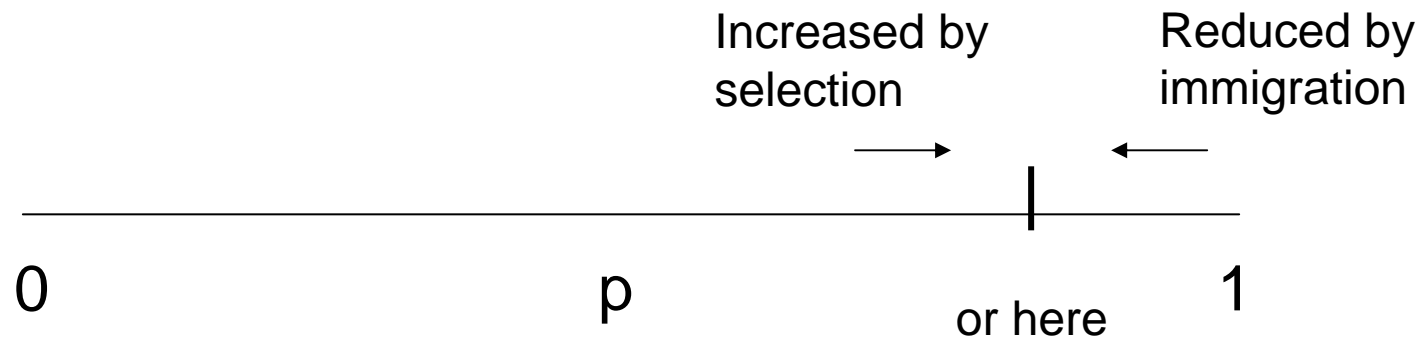
The simplest model to investigate the spatial properties of underdominance is one of a single locus in two populations exchanging migrants each generation (and equal homozygote fitness).



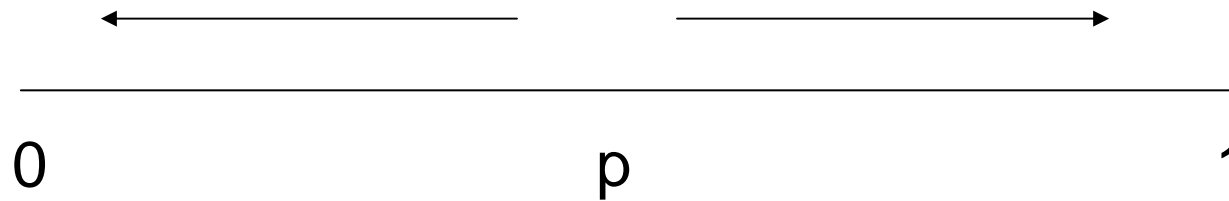
In contrast to the single-population prediction, underdominance can maintain a stable polymorphism among multiple populations connected by migration.



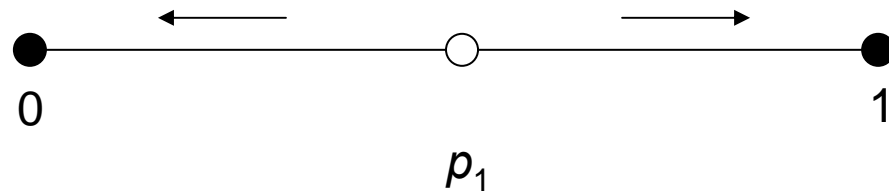
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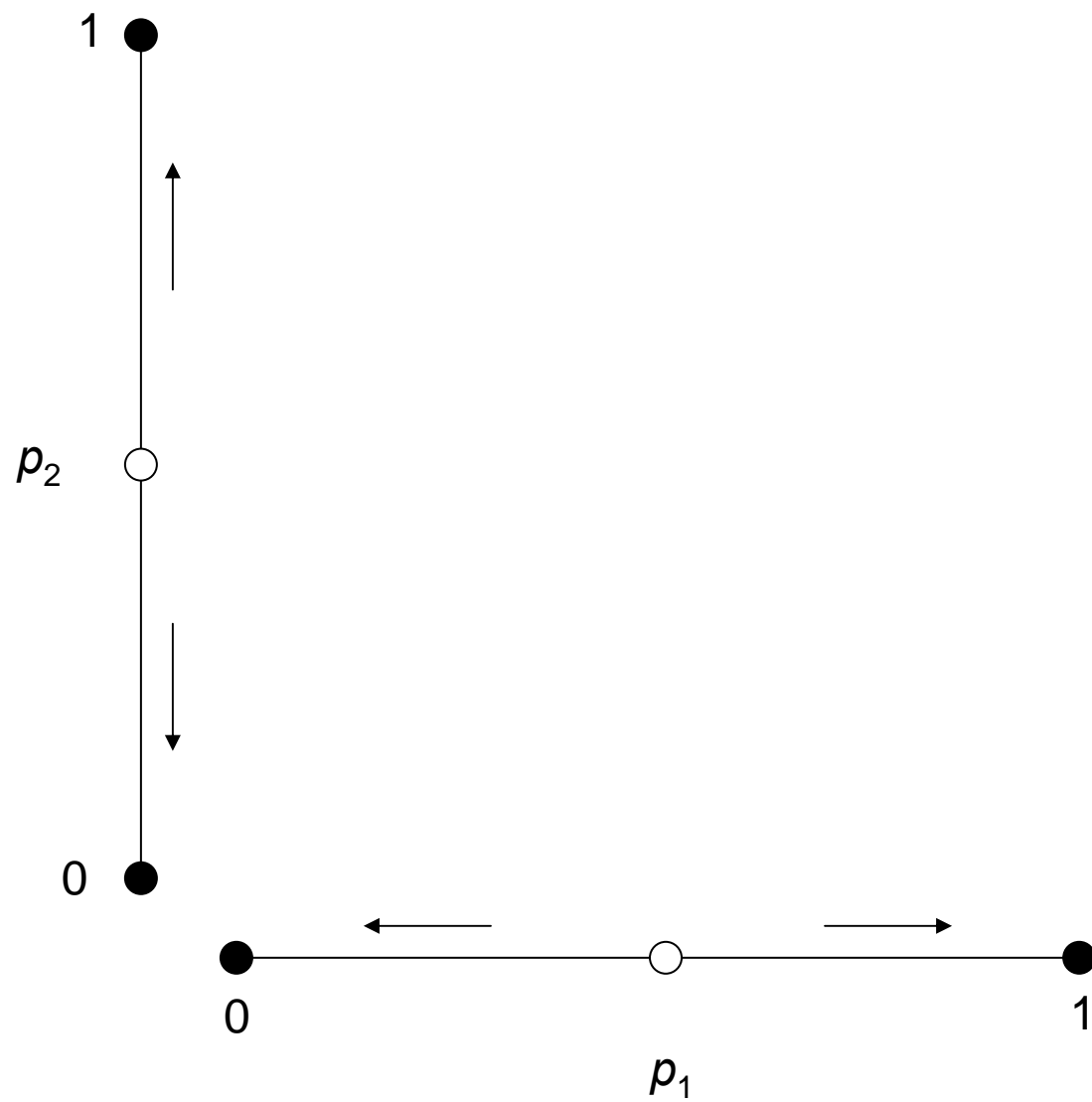


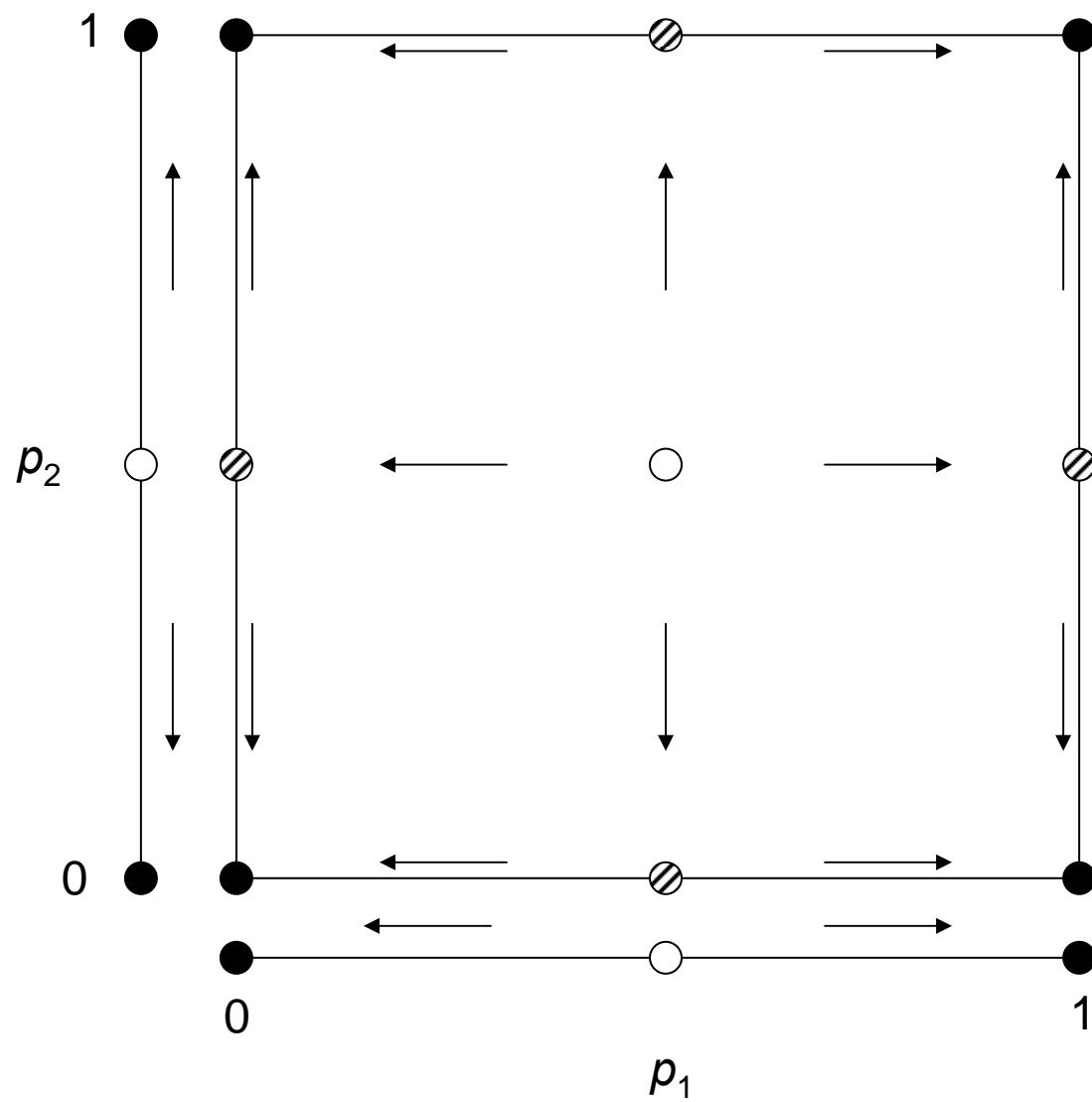
In contrast to the single-population prediction, underdominance can maintain a stable polymorphism among multiple populations connected by migration.

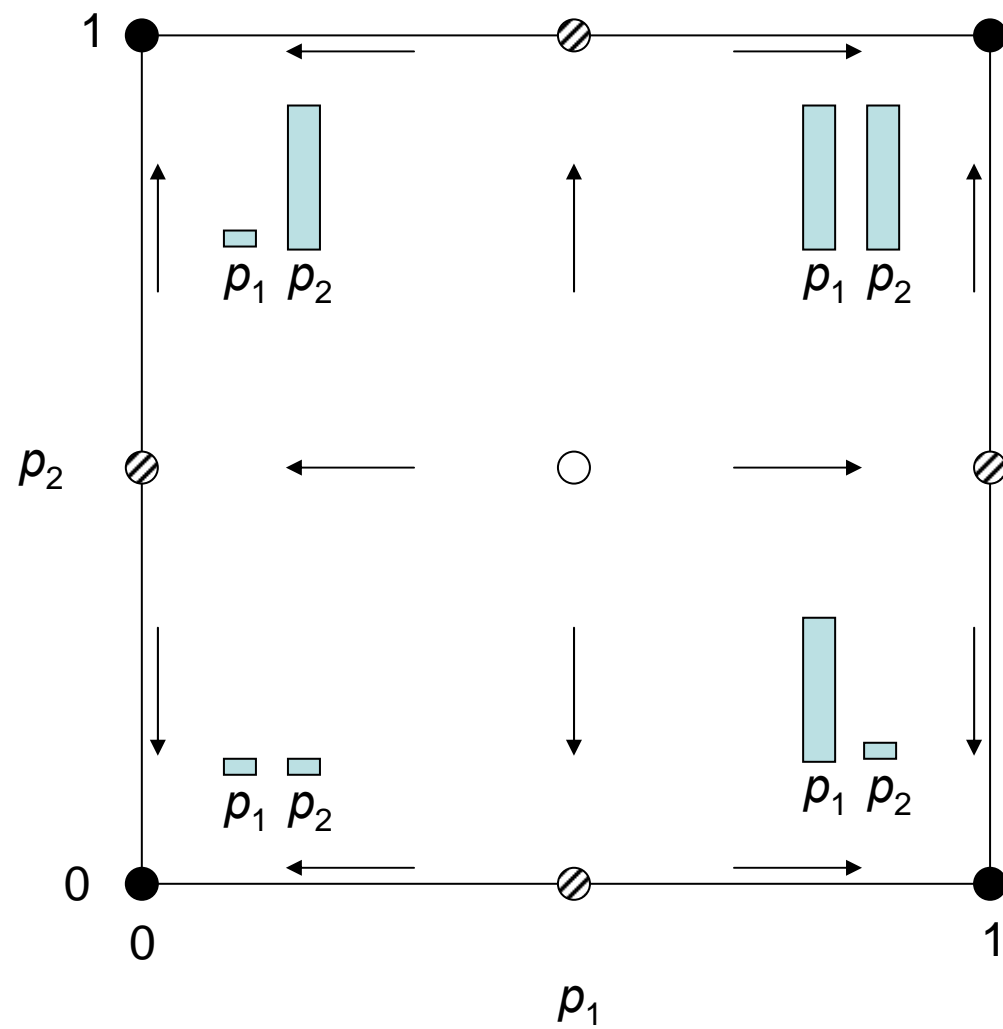


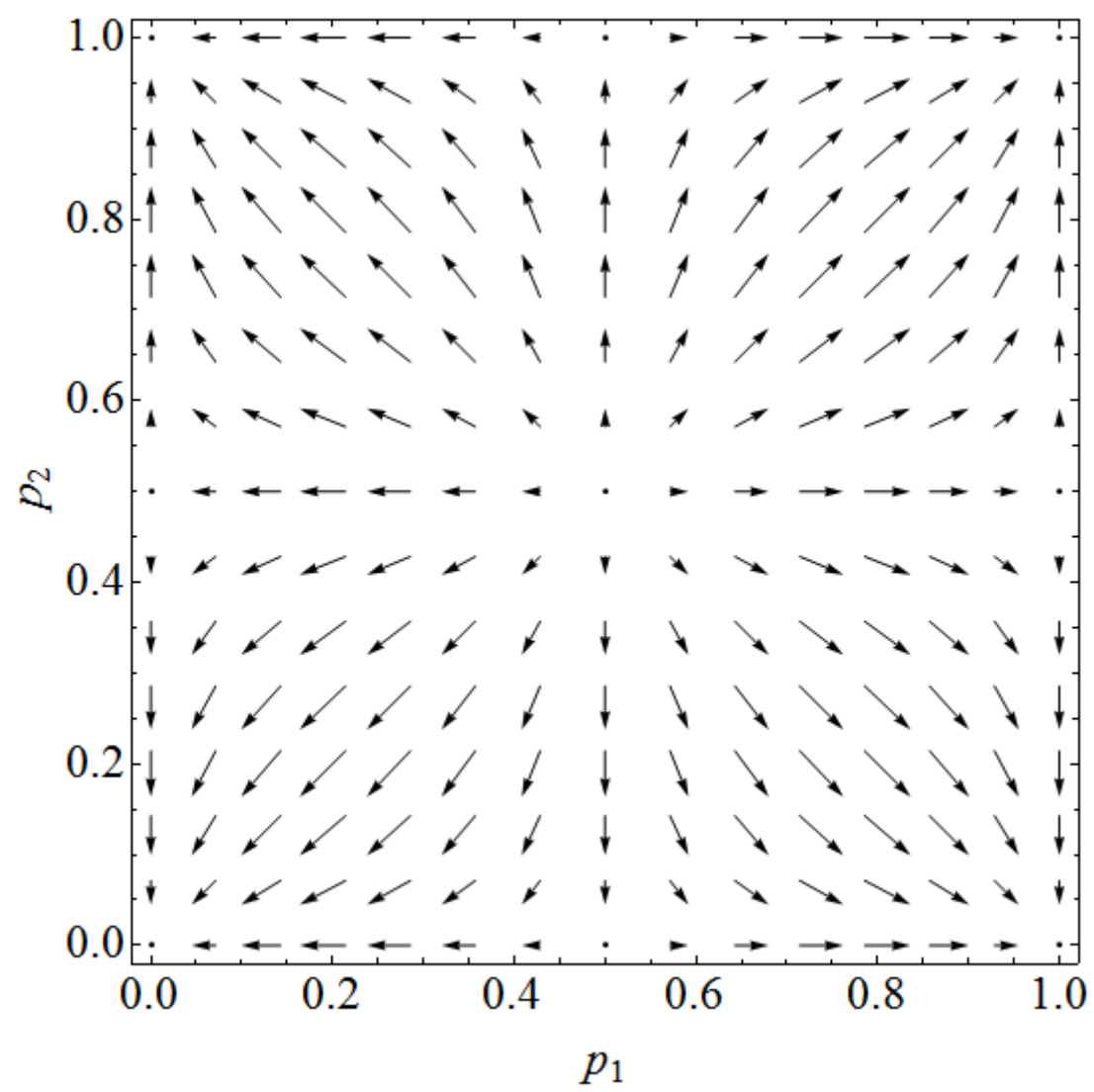
However, if the migration rate is too high, the system behaves like a single population and polymorphism is lost.

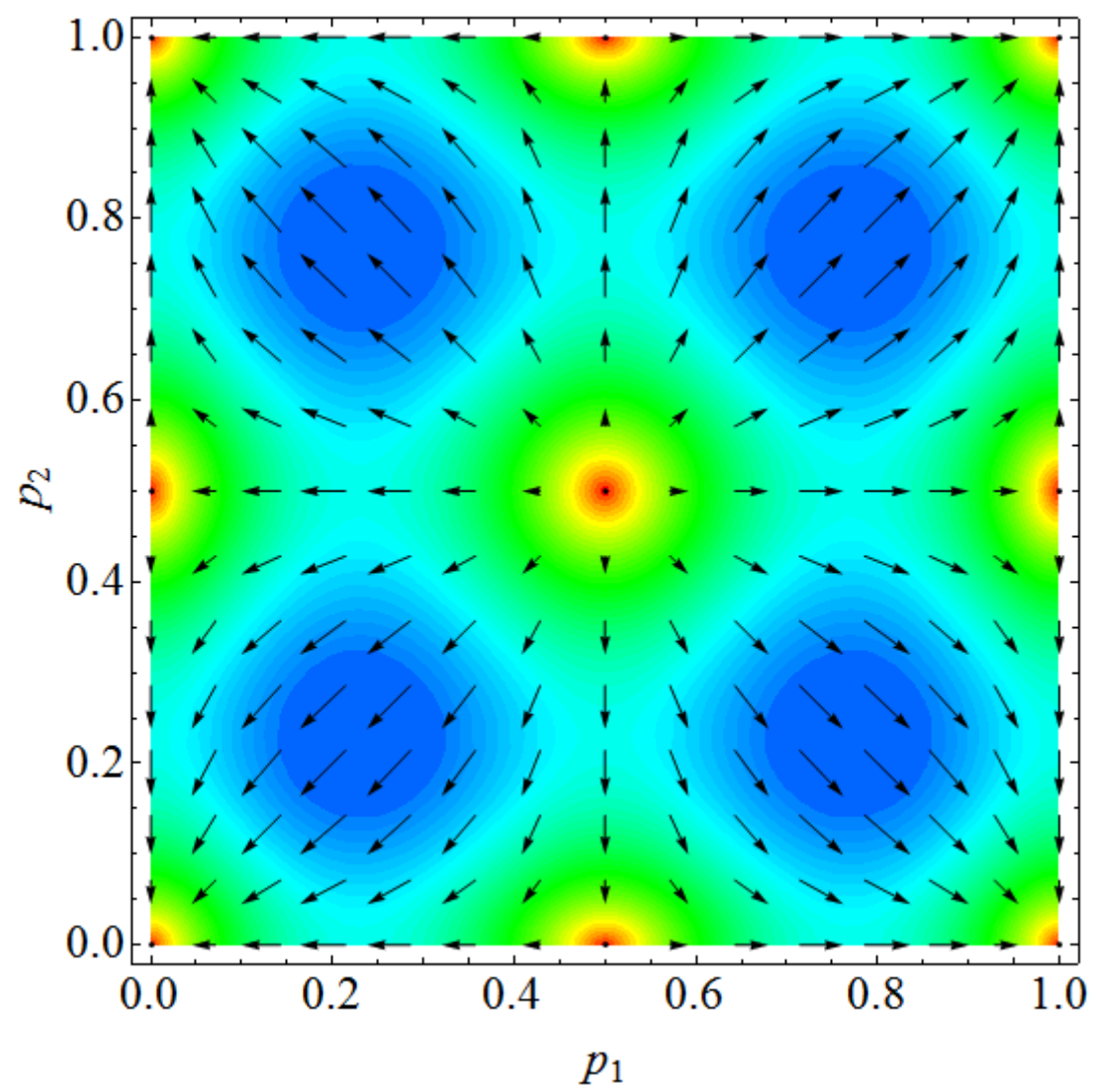






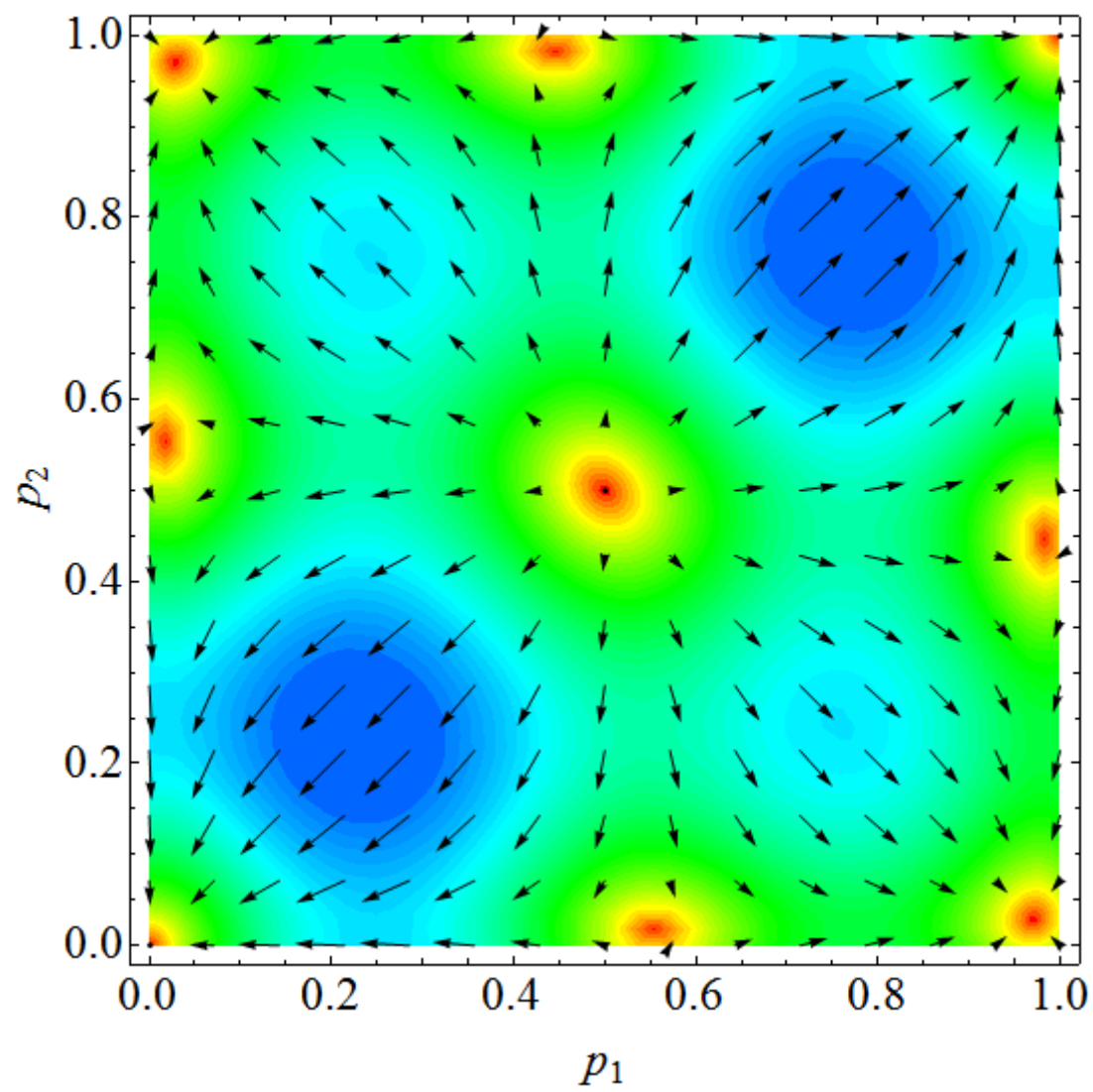






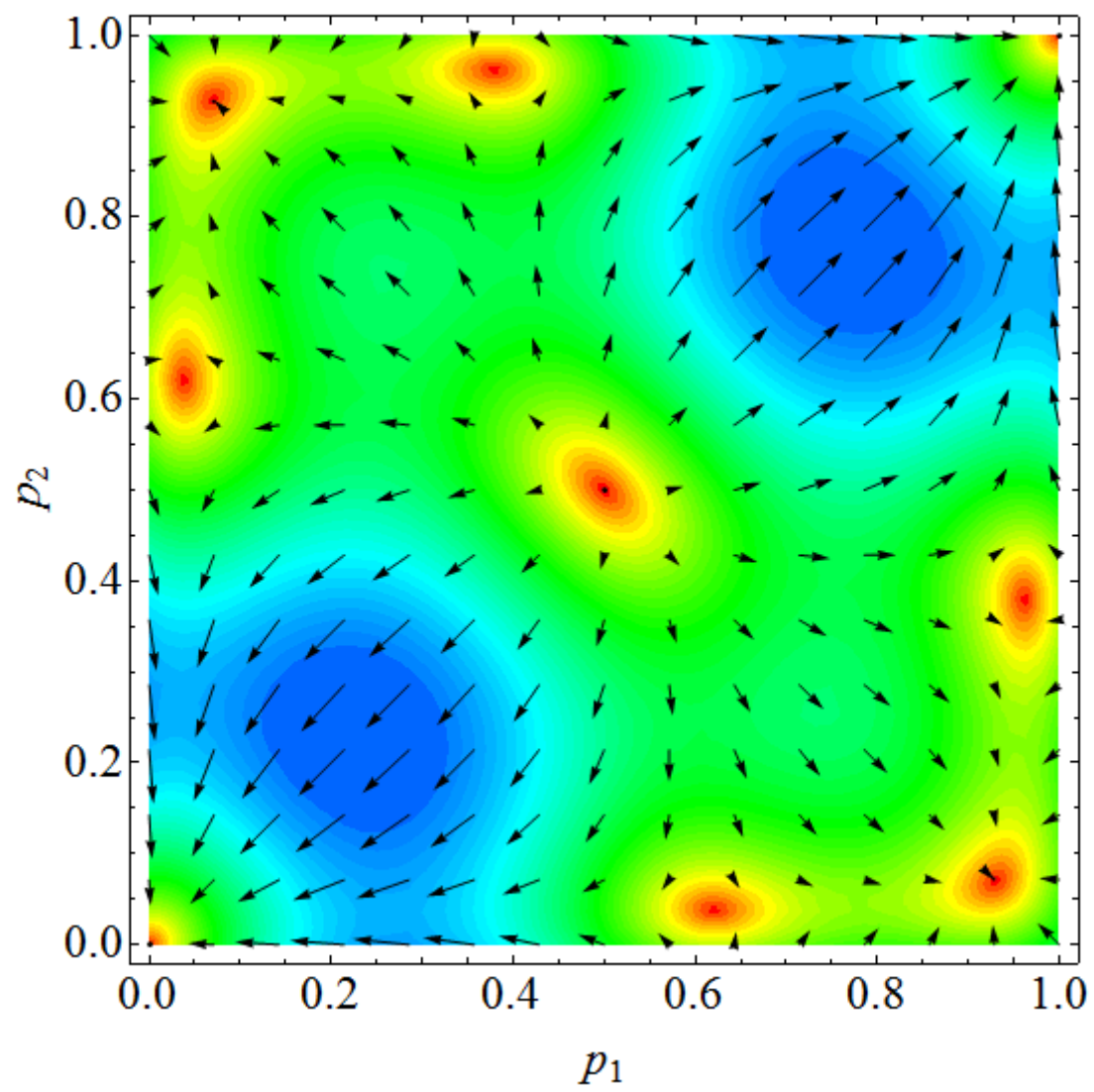
$$w_{T+}=0.5$$

$$m=0$$



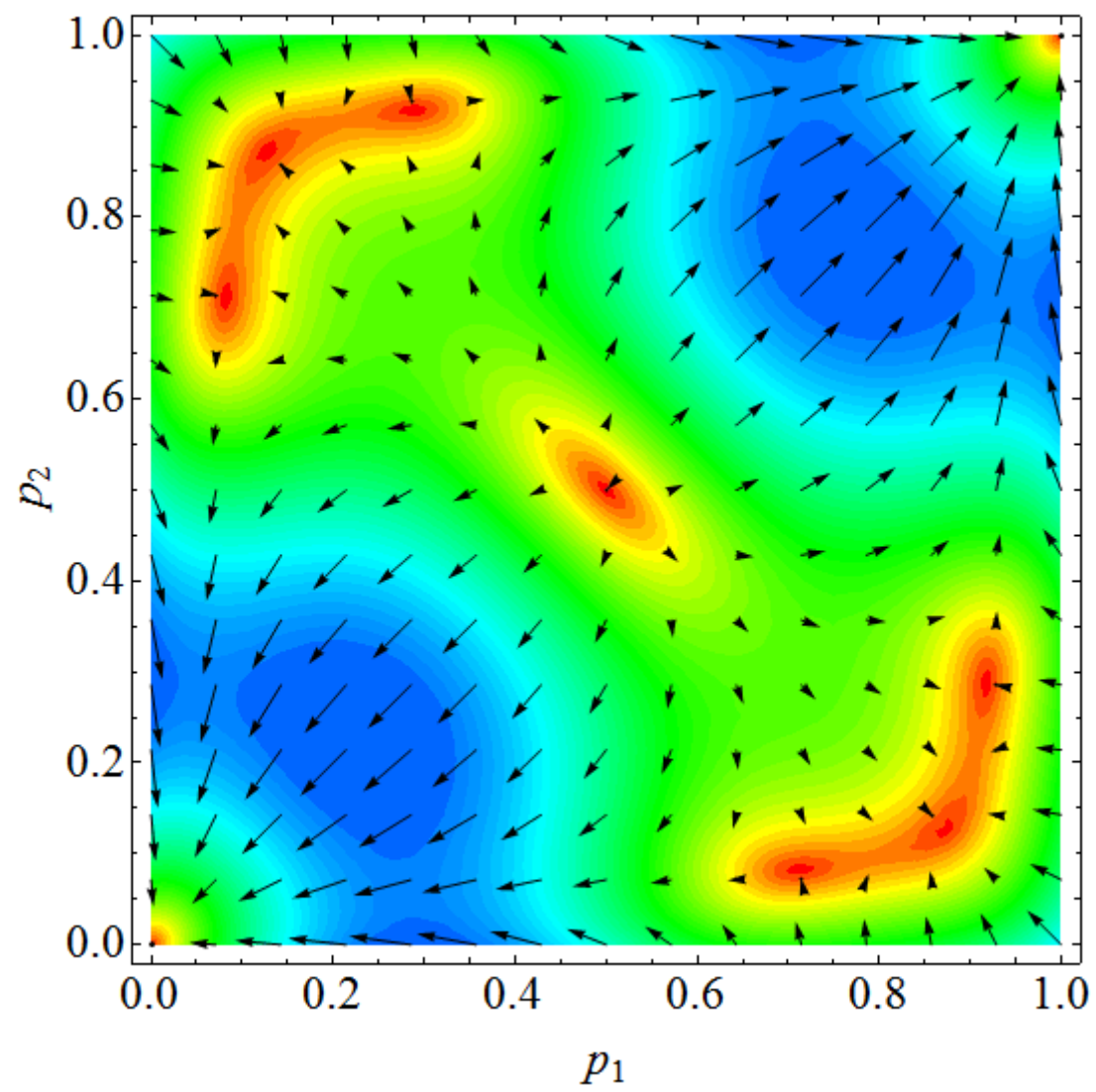
$$w_{T+}=0.5$$

$$m=0.025$$



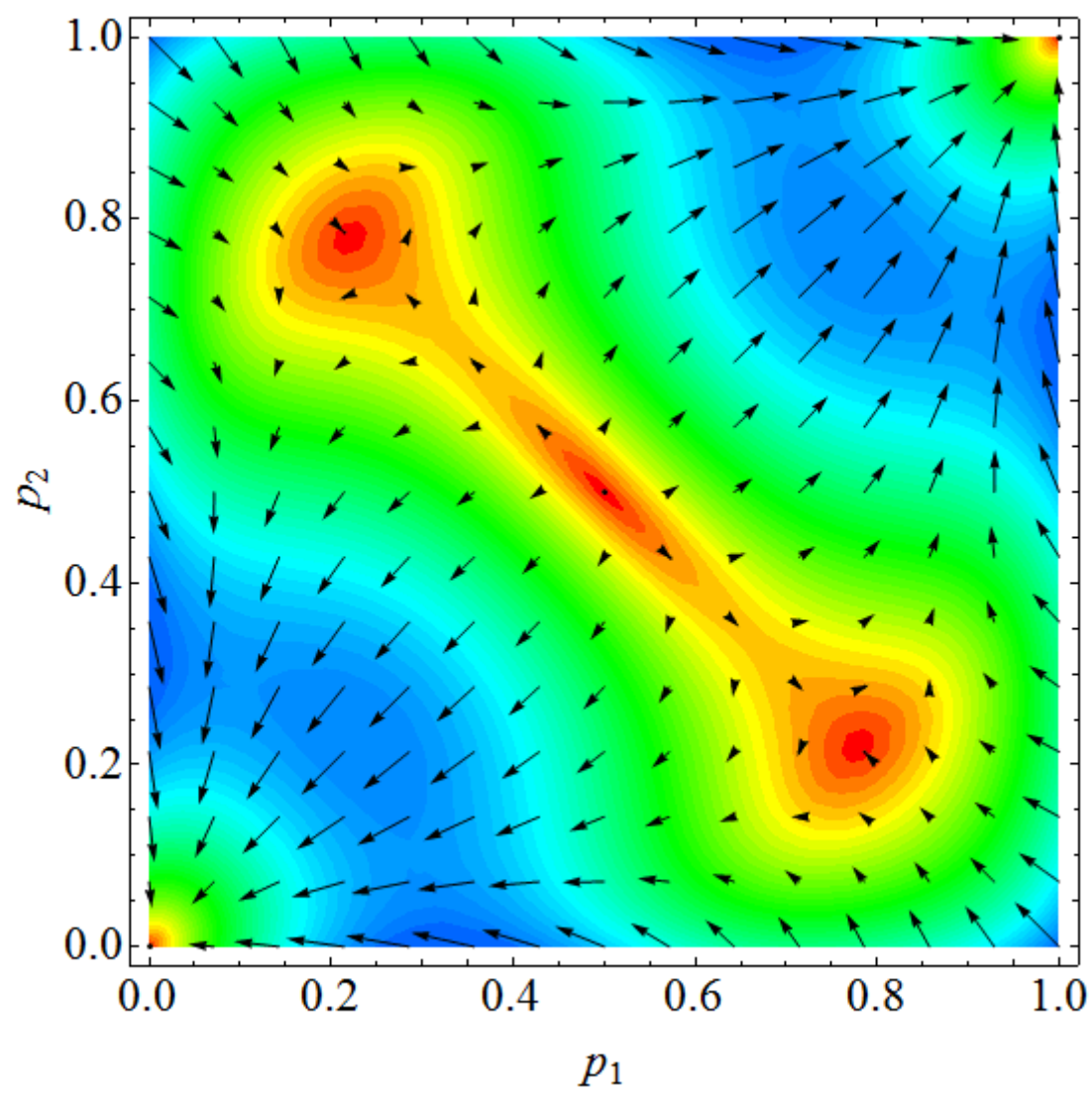
$$w_{T+}=0.5$$

$$m=0.05$$



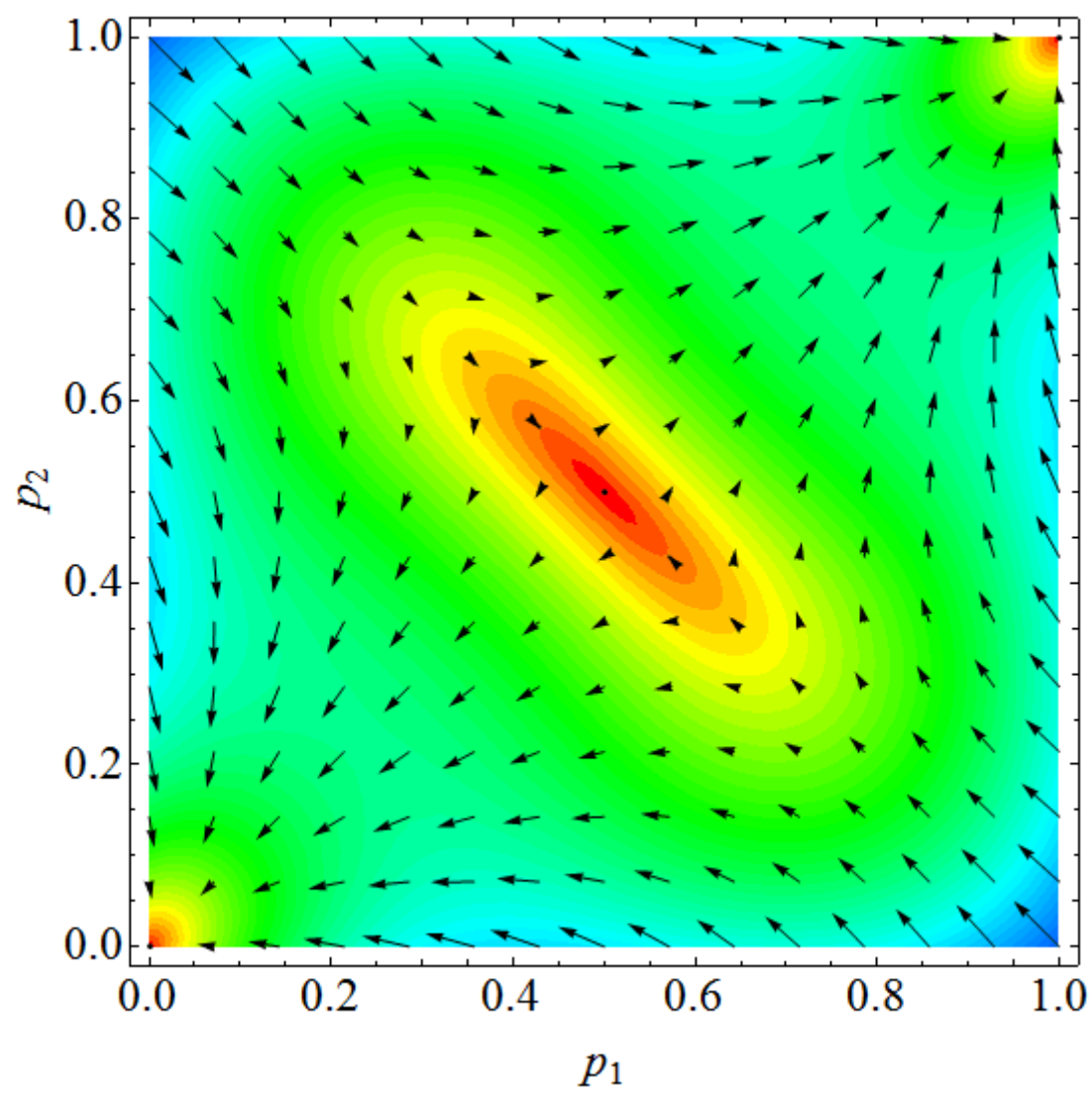
$$w_{T+}=0.5$$

$$m=0.075$$



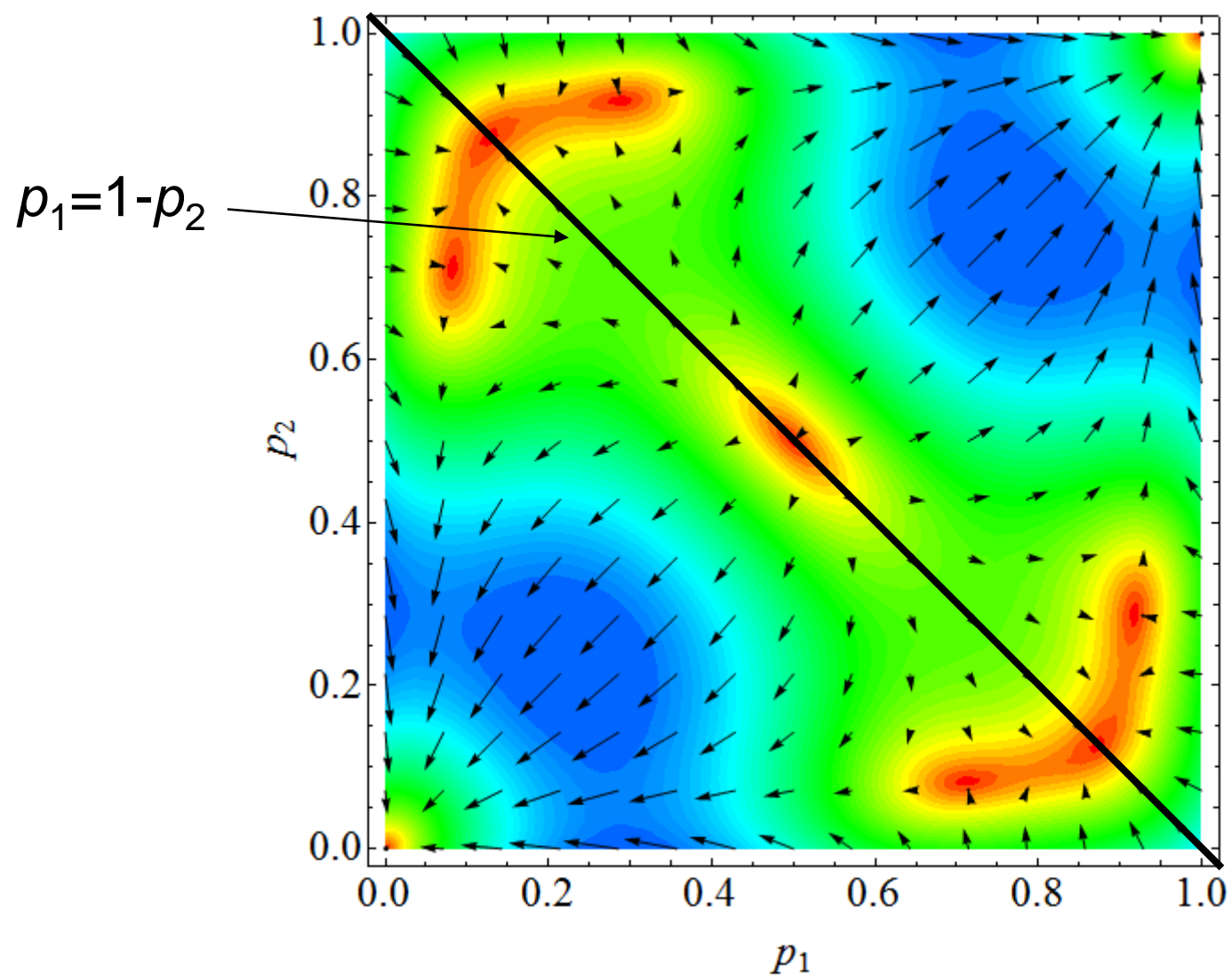
$$w_{T+}=0.5$$

$$m=0.1$$



$$w_{T+}=0.5$$

$$m=0.15$$



$$w_{T+}=0.5$$

$$m=0.075$$

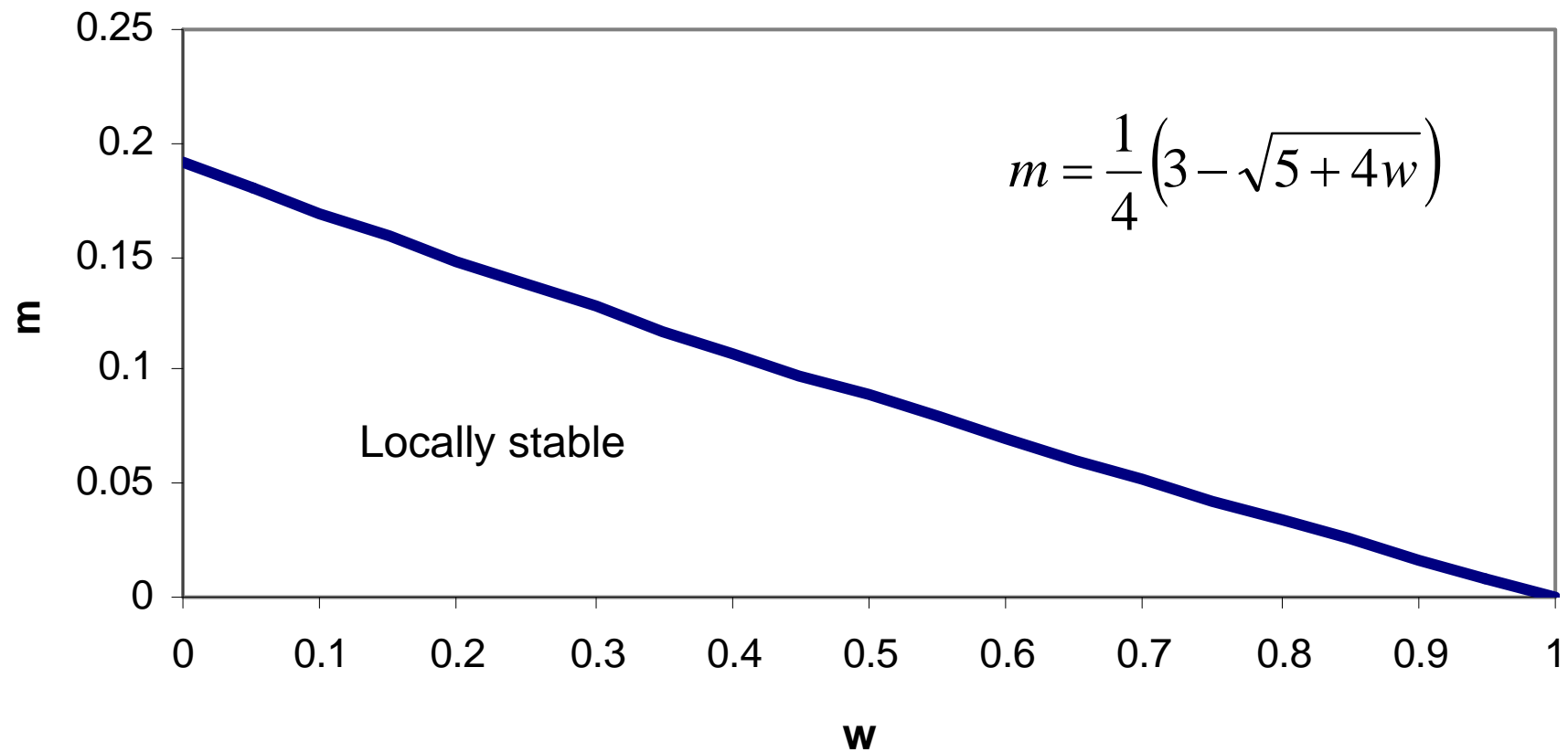
A Jacobian matrix of partial derivatives can be used to create a linear approximation of the system.

$$J = \begin{bmatrix} \frac{\partial p'_1}{\partial p_1} & \frac{\partial p'_1}{\partial p_2} \\ \frac{\partial p'_2}{\partial p_1} & \frac{\partial p'_2}{\partial p_2} \end{bmatrix}$$

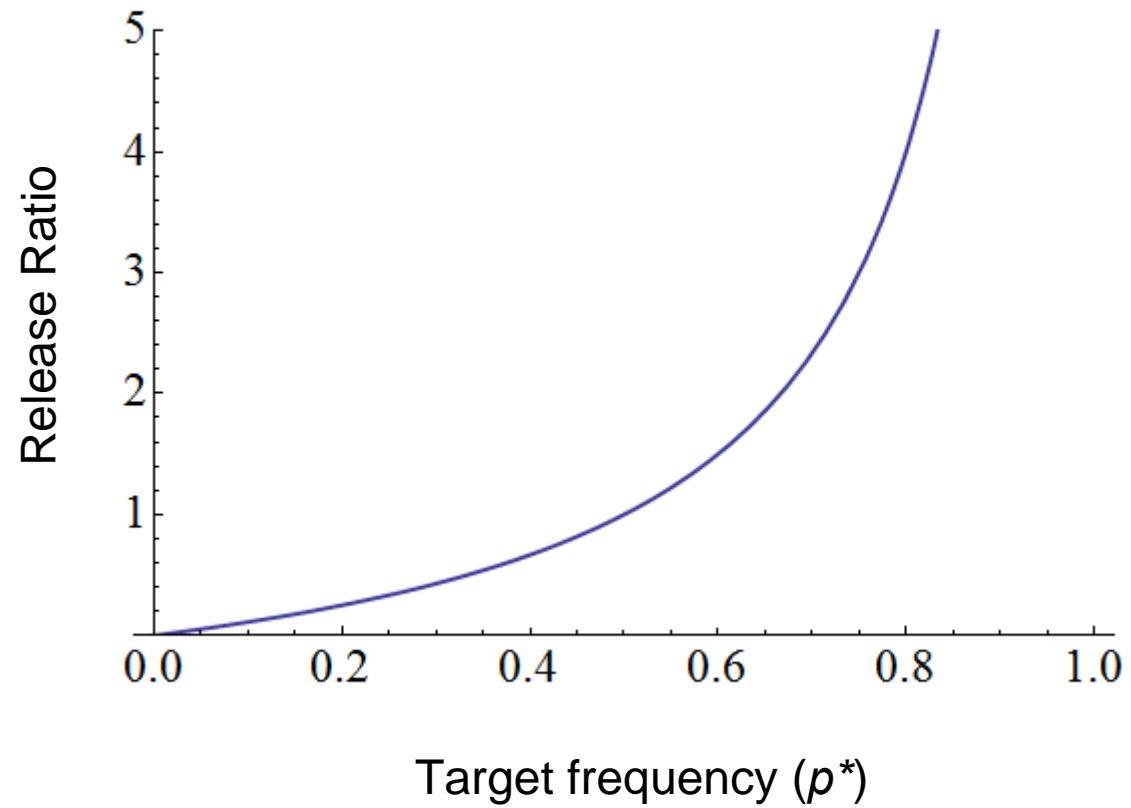
Substituting $p_1=1-p_2$ into the system simplifies it enough to be tractable and the resulting eigenvalues yield the following relationship.

$$m = \frac{1}{4} \left(3 - \sqrt{5 + 4w_{T+}} \right)$$

The maximum migration rate that allows local underdominant stability.

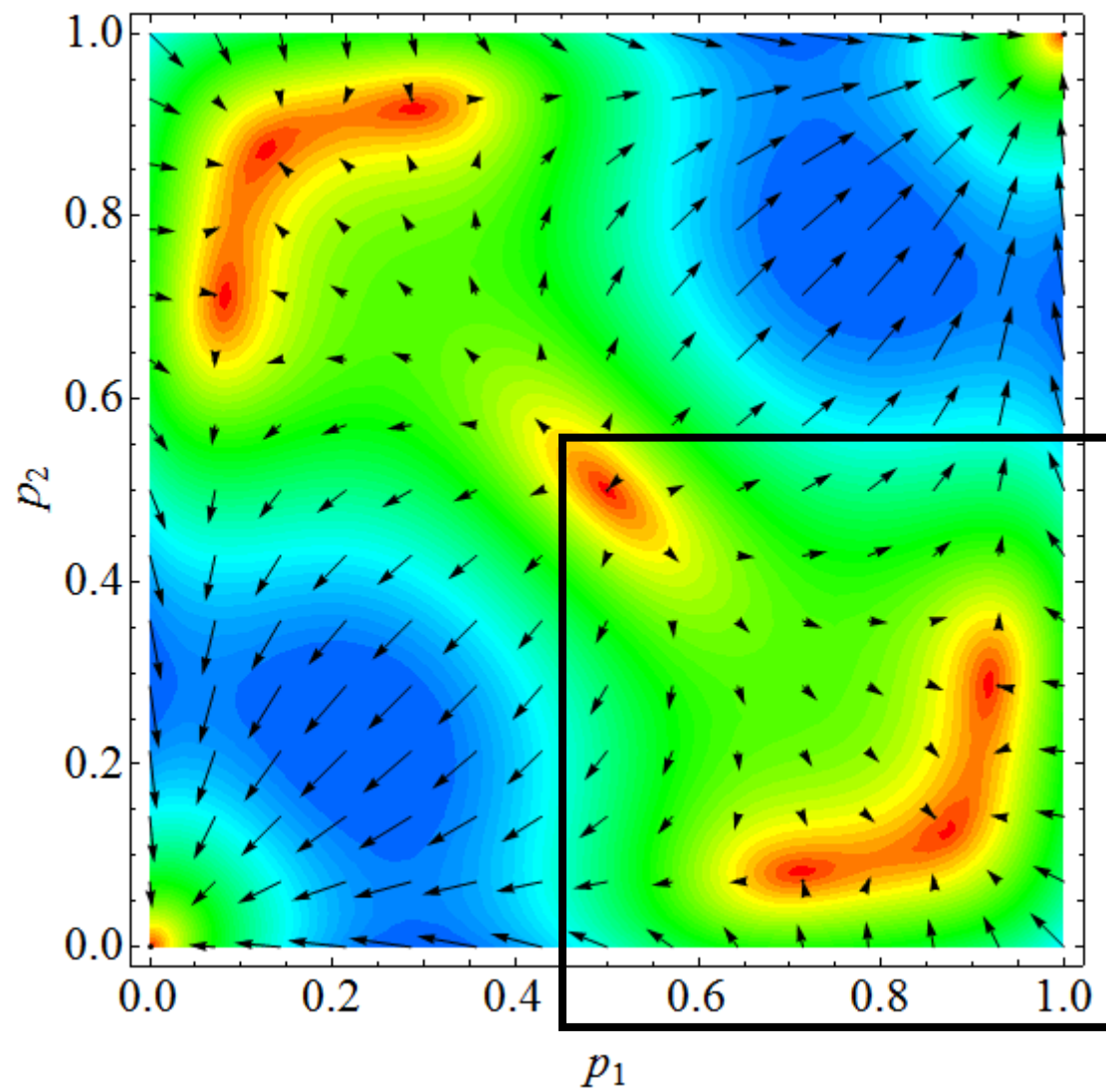


Strategy to enter the basin.



$$R = p^* / (1 - p^*)$$

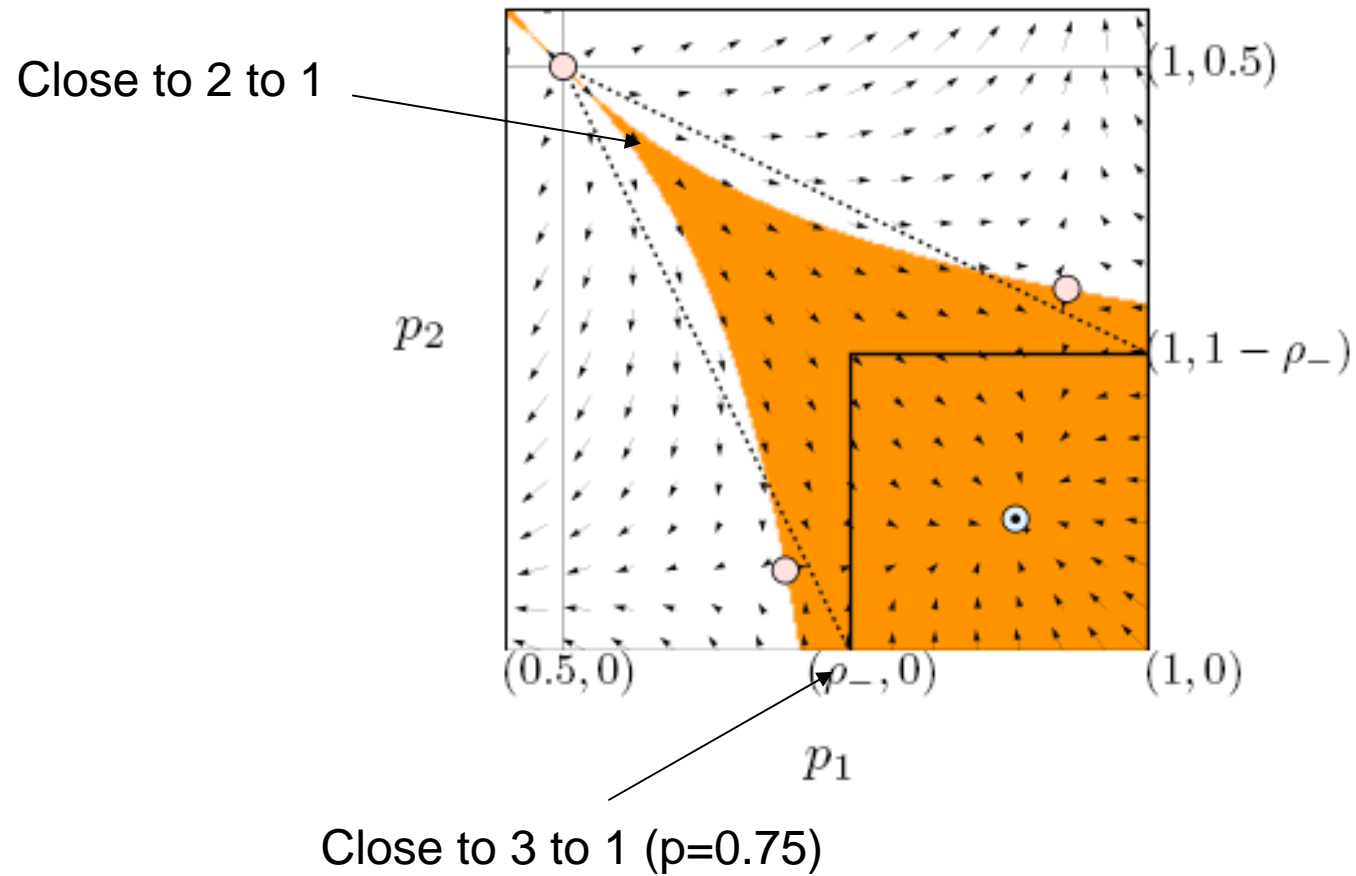
Strategy to enter the basin.



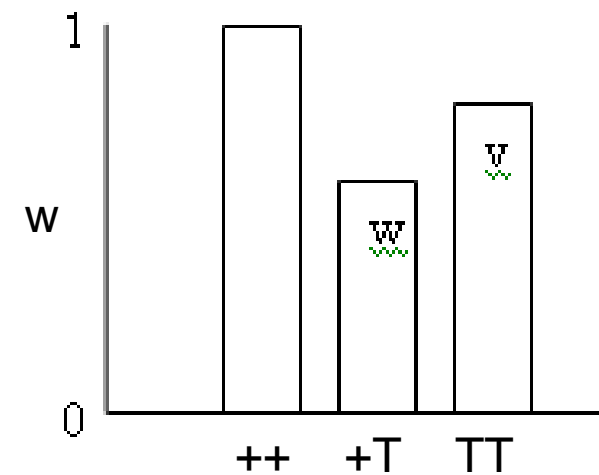
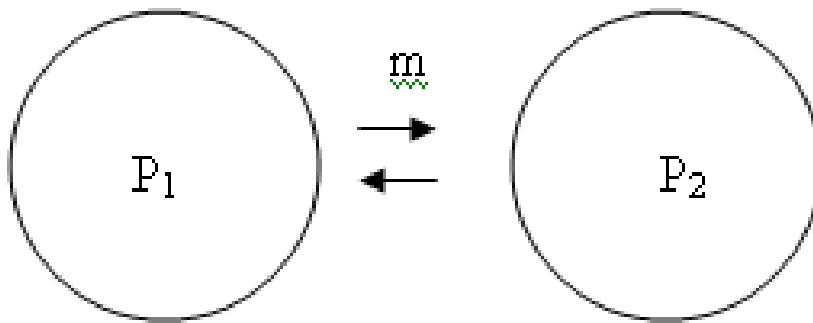
$$w_{T+}=0.5$$

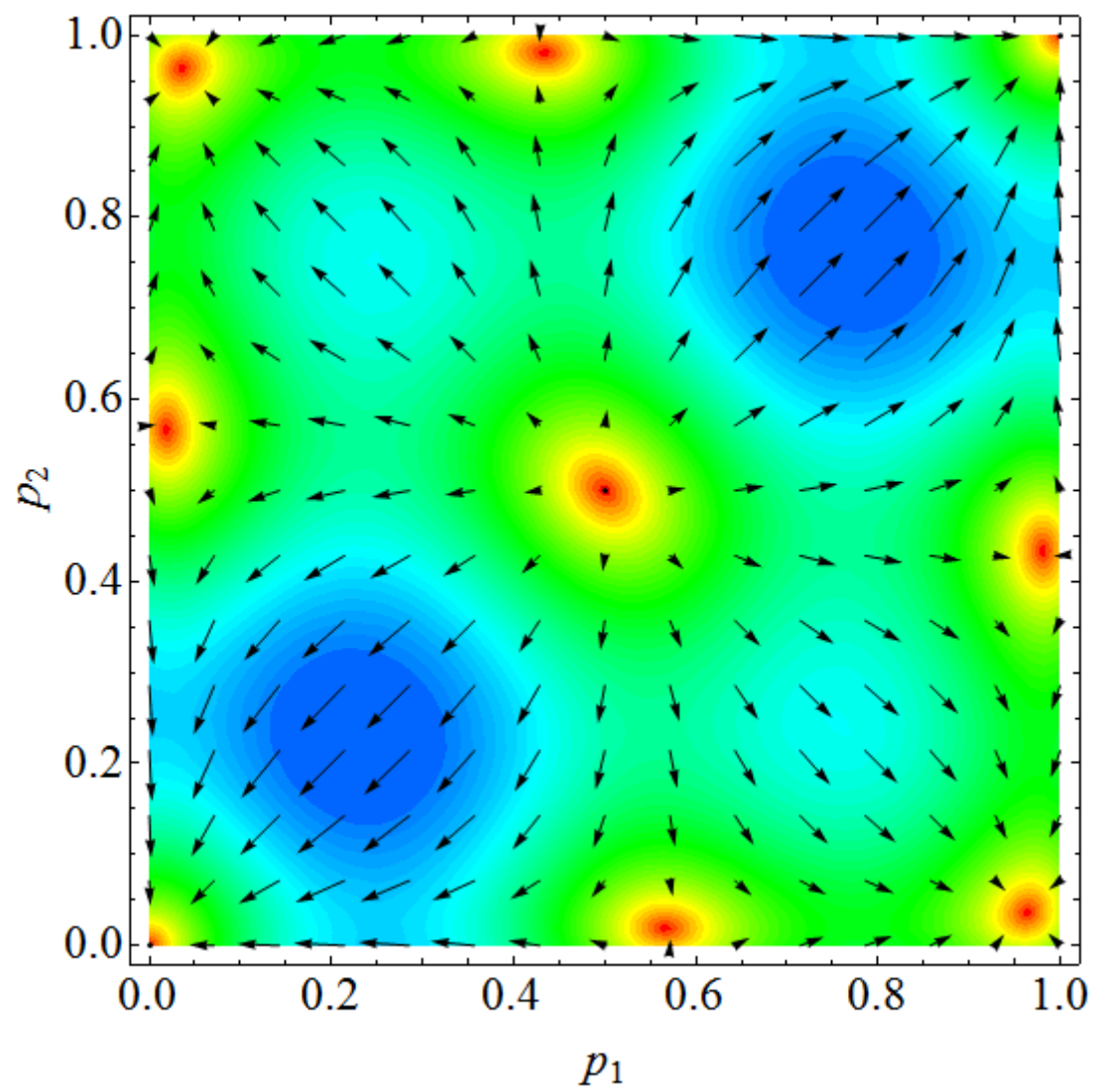
$$m=0.075$$

Strategy to enter the basin.



A slightly more complicated model, homozygote fitnesses are not equal.

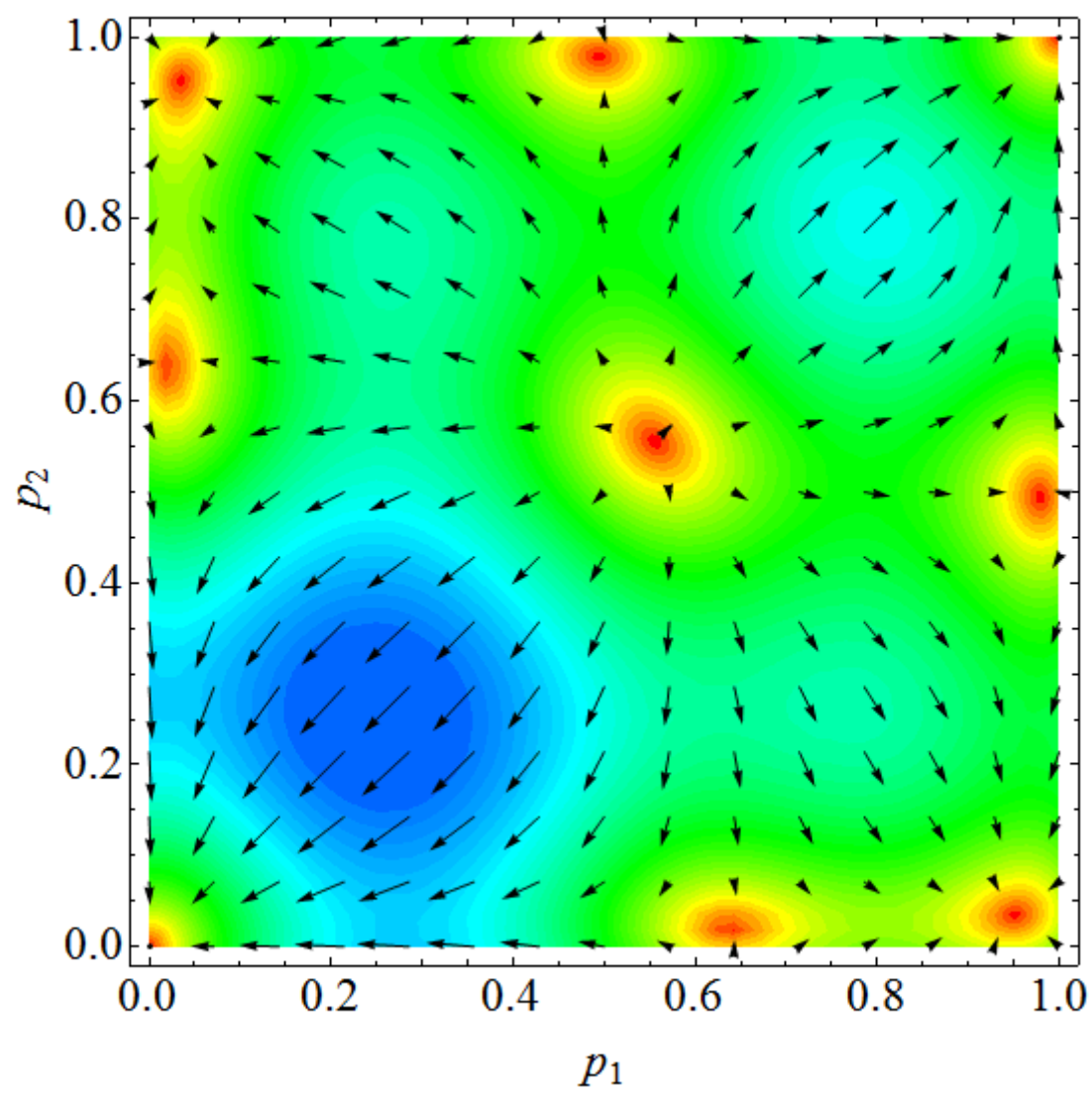




$$w_{\text{TT}}=1$$

$$w_{\text{T}+}=0.5$$

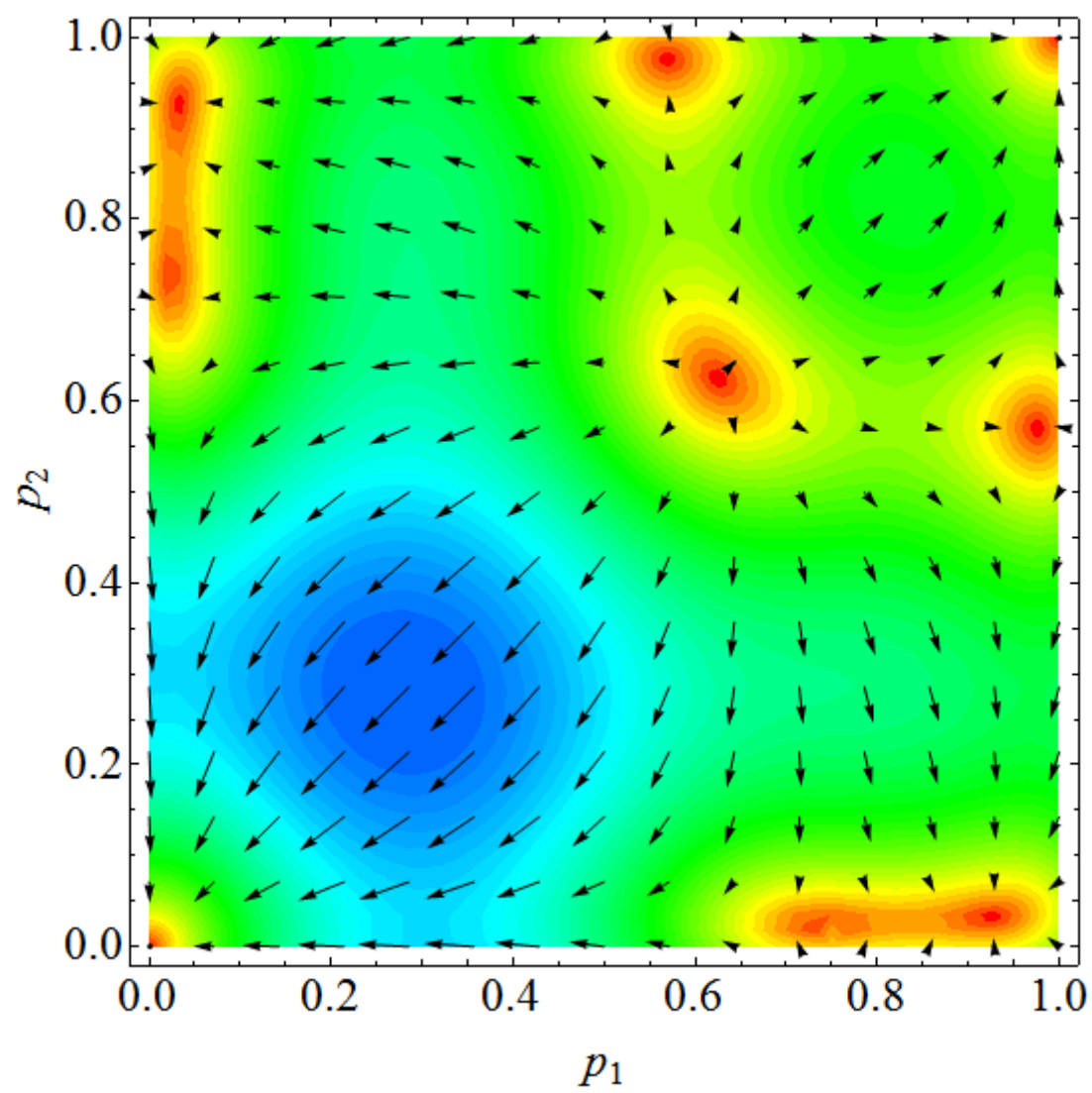
$$m=0.075$$



$$w_{\text{TT}}=0.9$$

$$w_{\text{T}+}=0.5$$

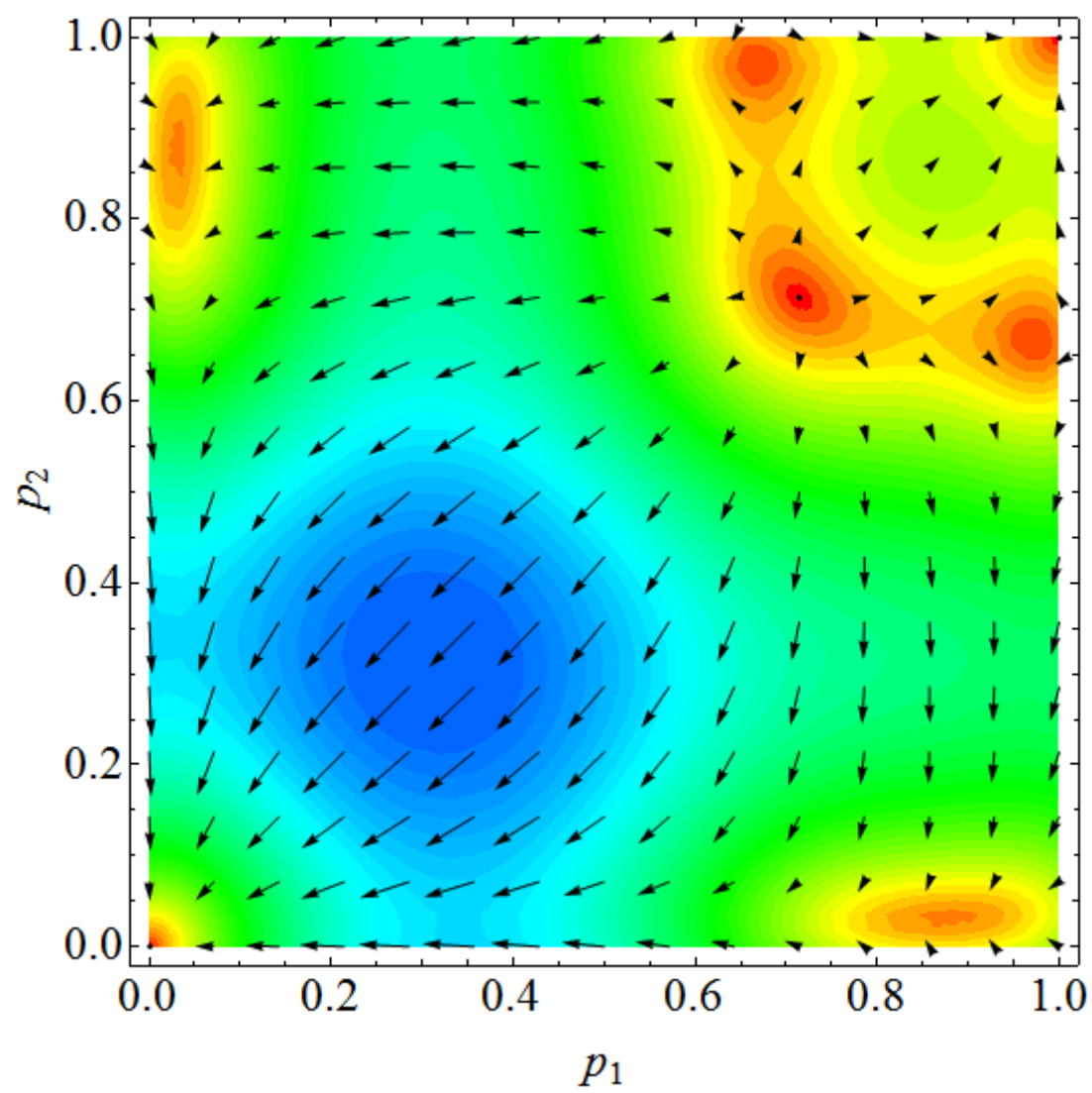
$$m=0.075$$



$$w_{\text{TT}}=0.8$$

$$w_{\text{T}+}=0.5$$

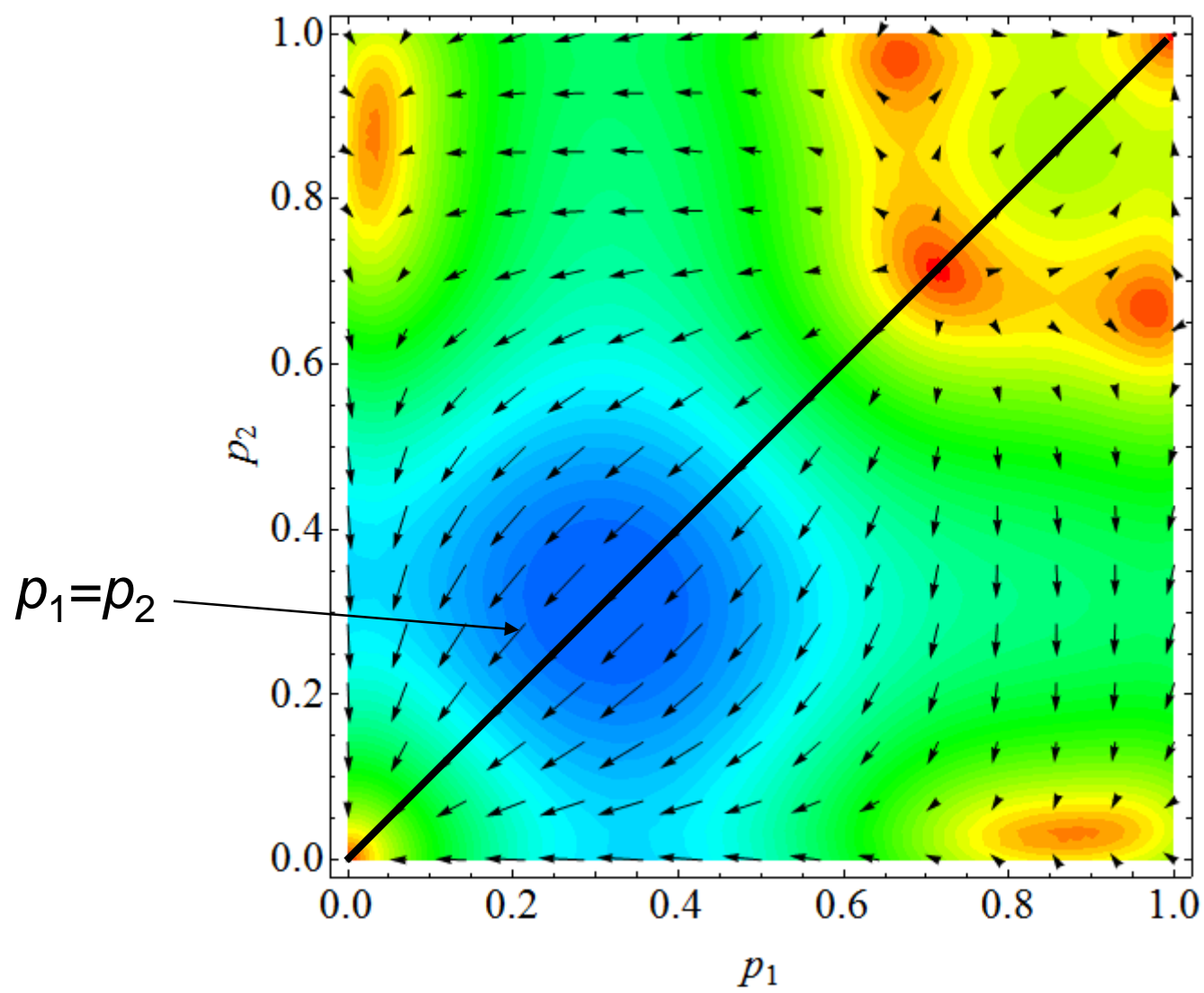
$$m=0.075$$



$$w_{\text{TT}}=0.7$$

$$w_{\text{T}+}=0.5$$

$$m=0.075$$



$$w_{\text{TT}}=0.7$$

$$w_{\text{T}+}=0.5$$

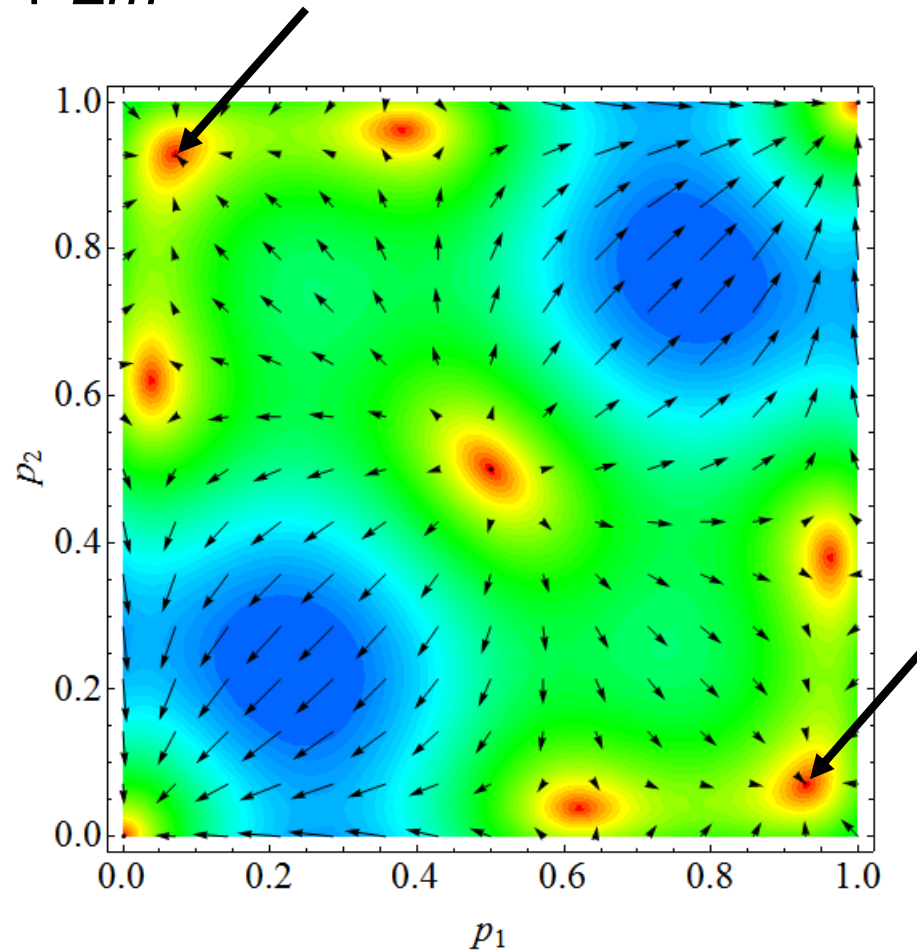
$$m=0.075$$

Solving for the unstable equilibrium in this case yields

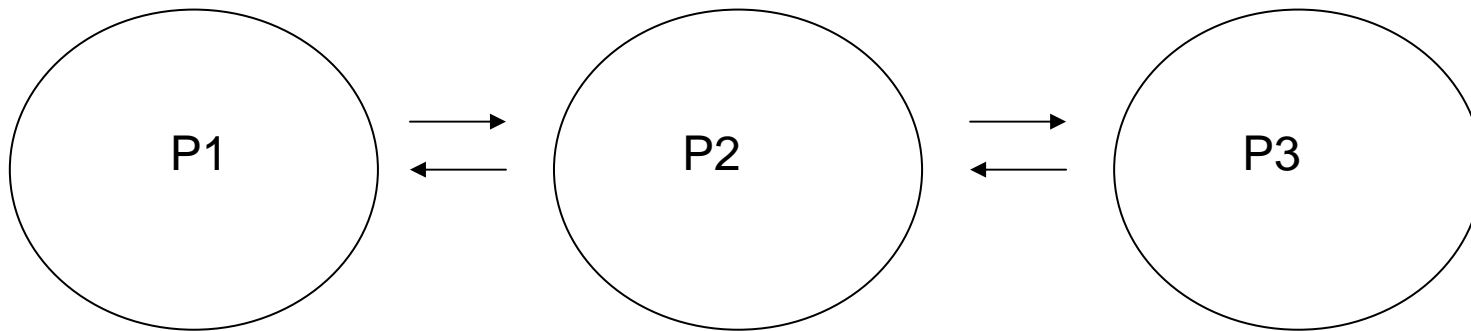
$$\hat{p}_1 = \hat{p}_2 = \frac{w_{T+} - w_{TT}}{2w_{T+} - 1 - w_{TT}}$$

This is independent of the migration rate and equivalent to the single population case given in the introduction.

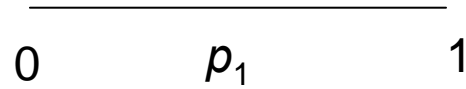
Incidentally, the average fitness at the non-trivial stable equilibrium is independent of the genotype fitnesses and is only a function of the migration rate. $\bar{w} = 1 - 2m$



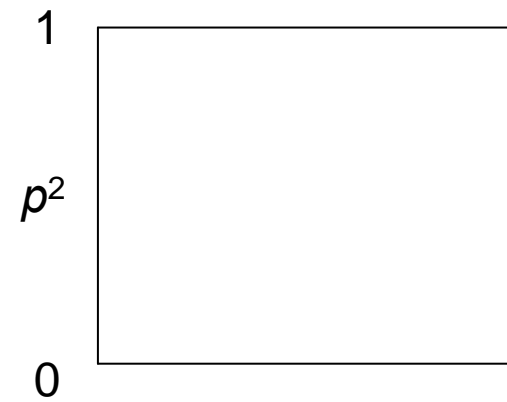
What about more populations?



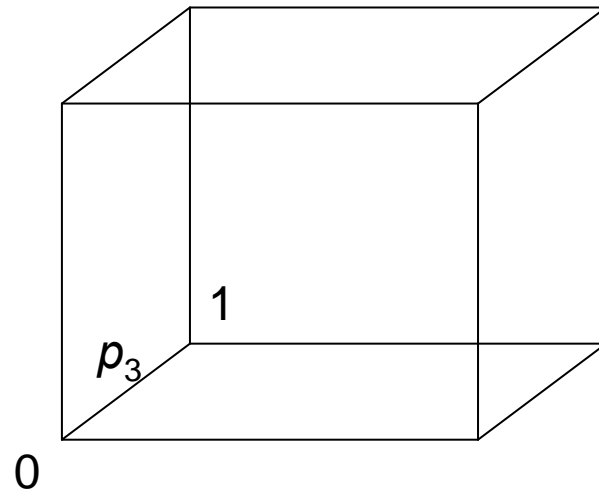
1 population = 1 dimensional system

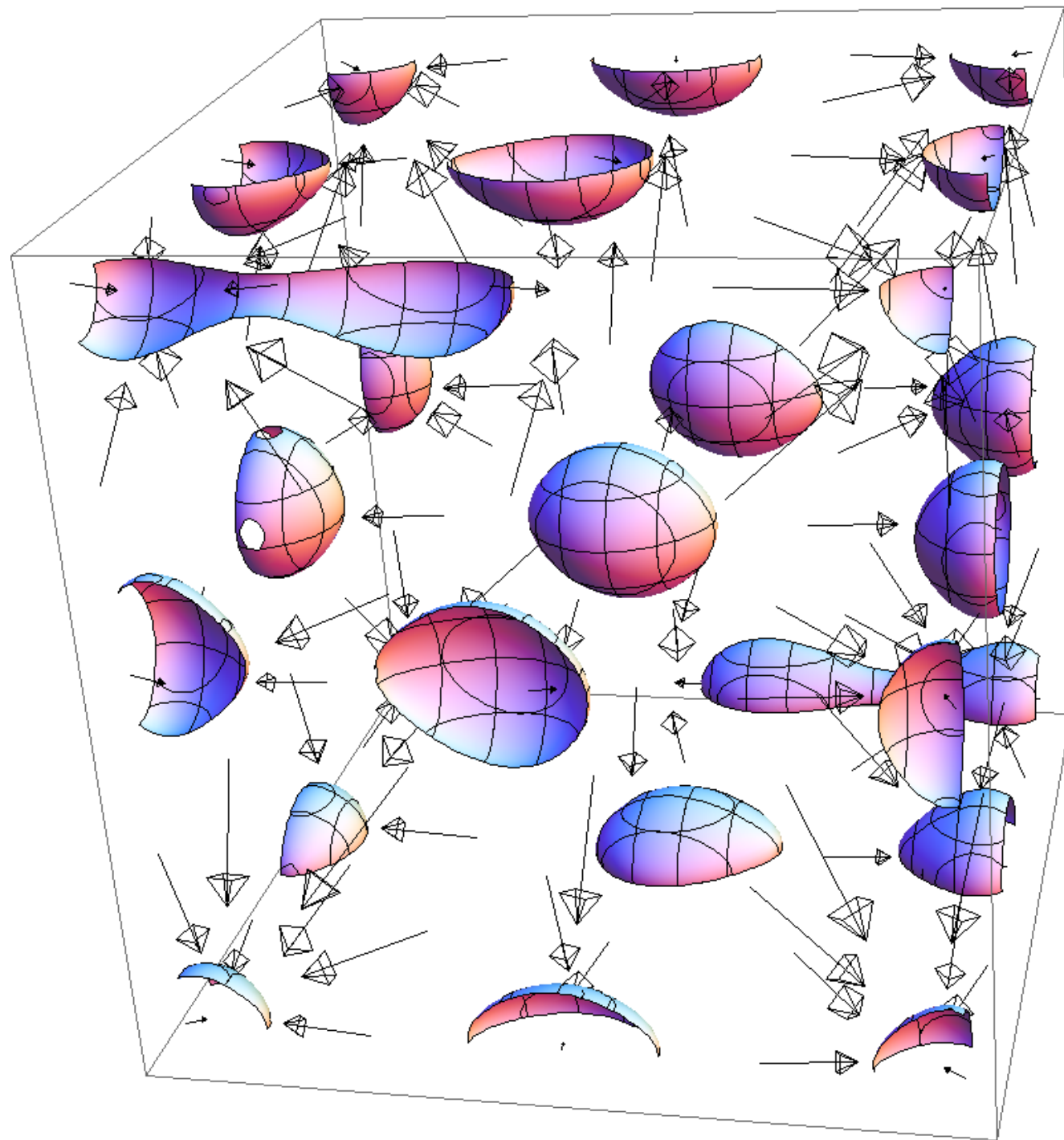


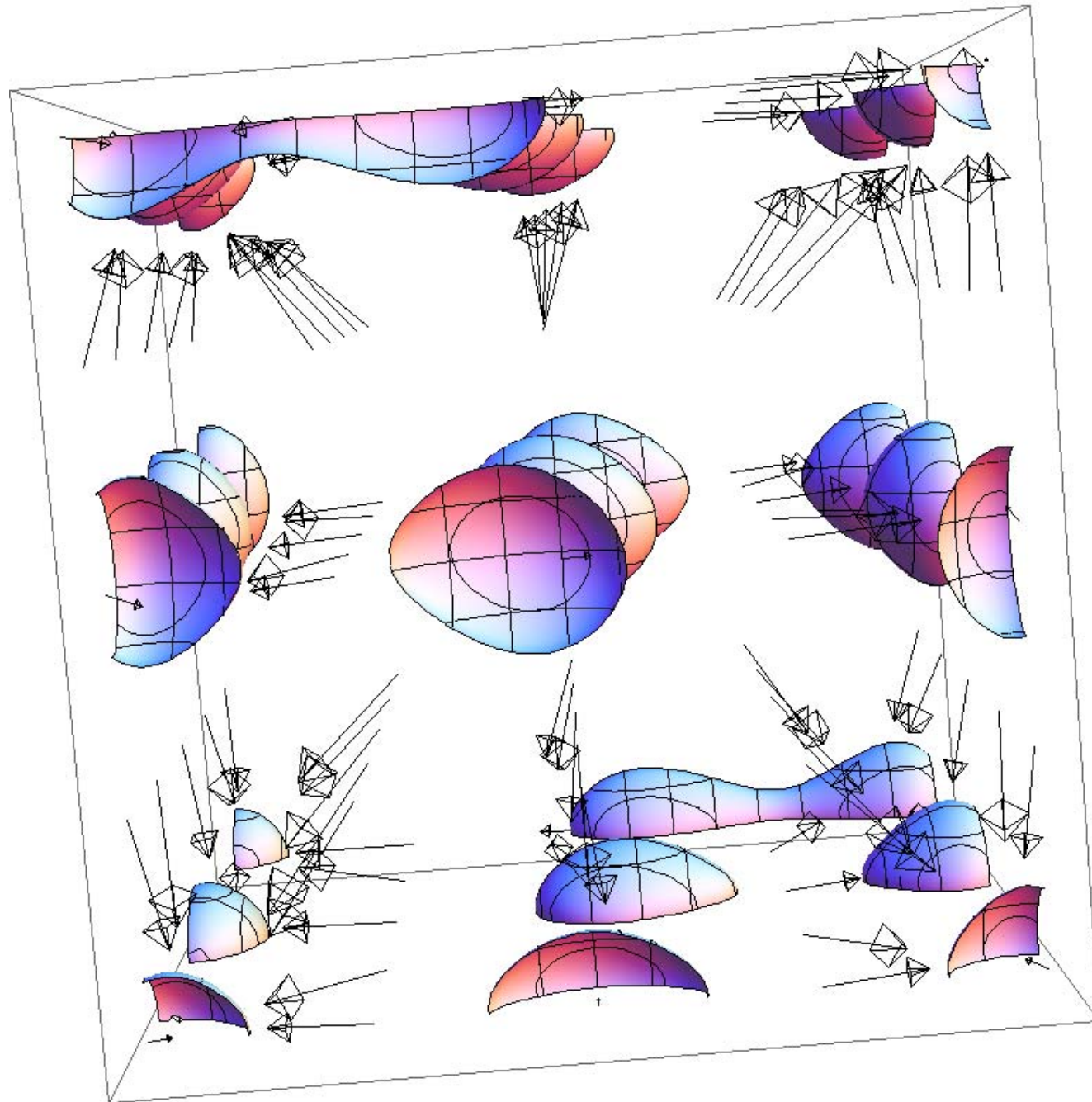
2 populations = 2 dimensional system



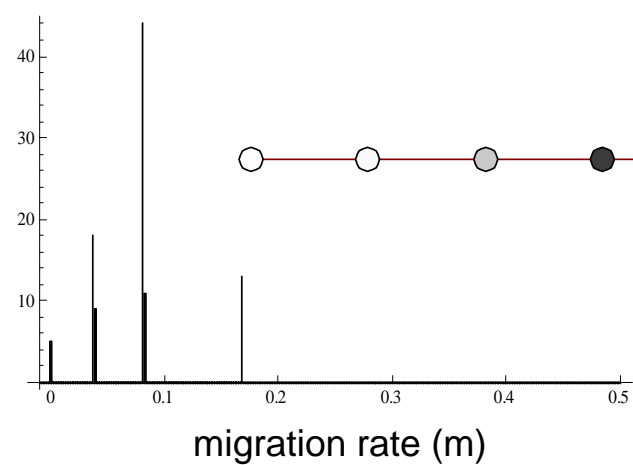
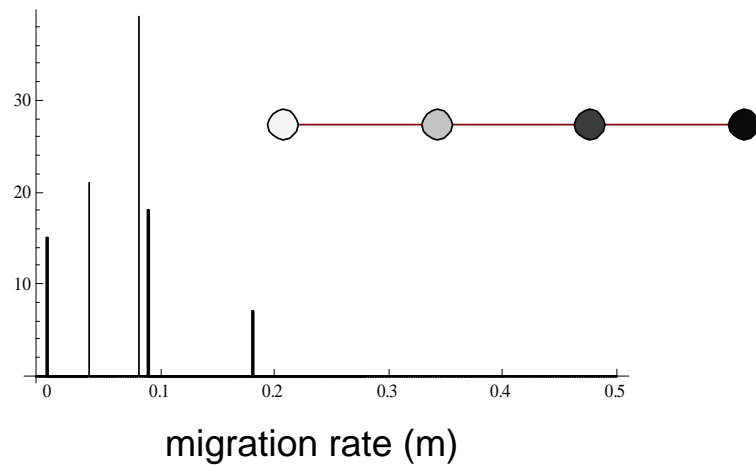
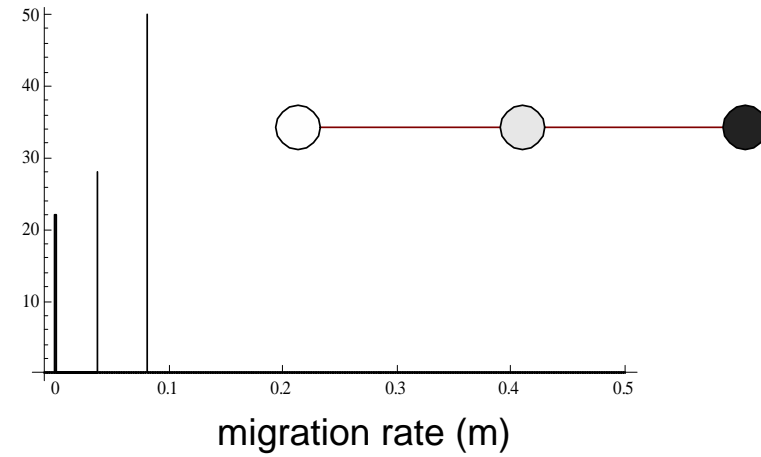
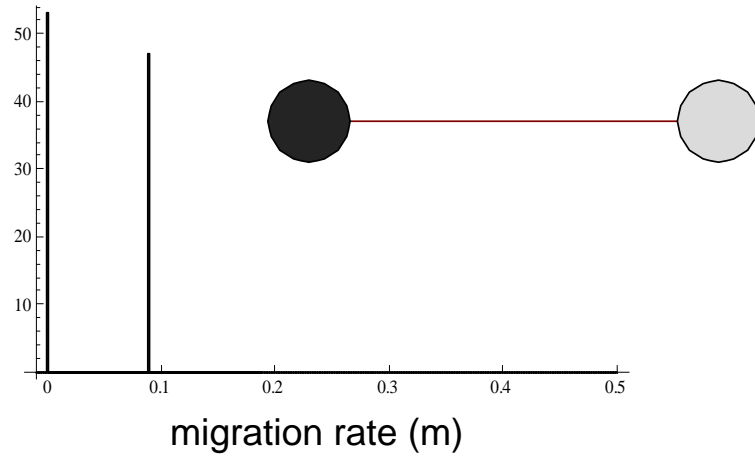
3 populations = 3 dimensional system



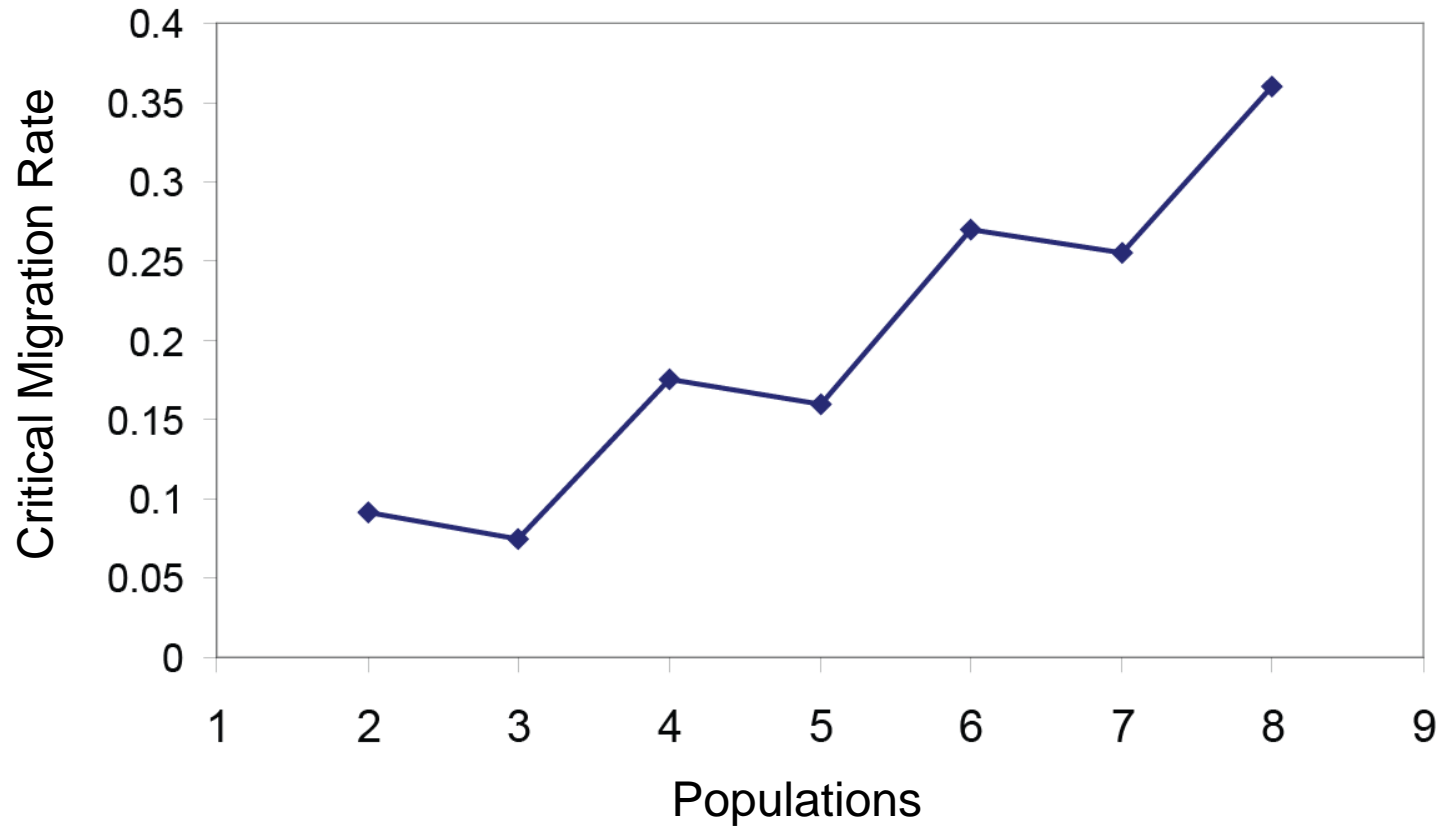




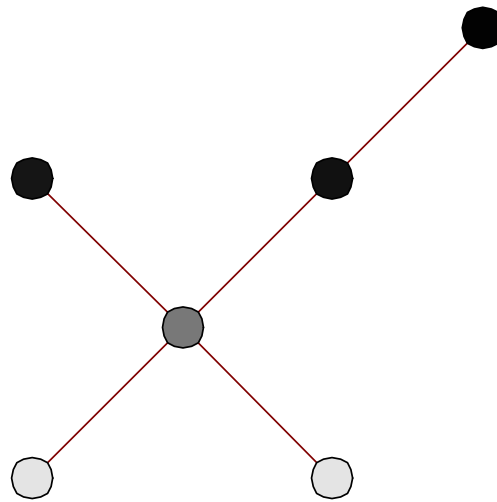
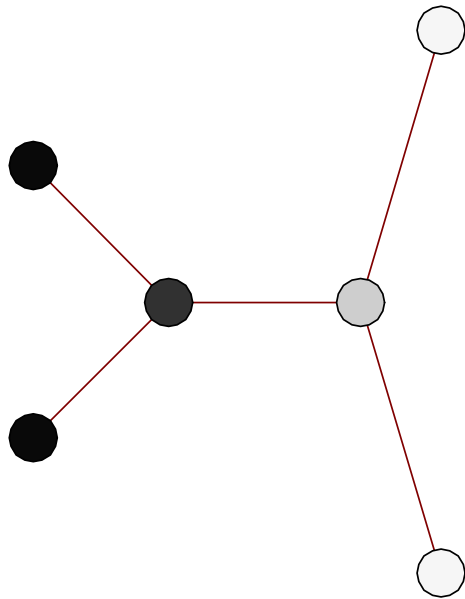
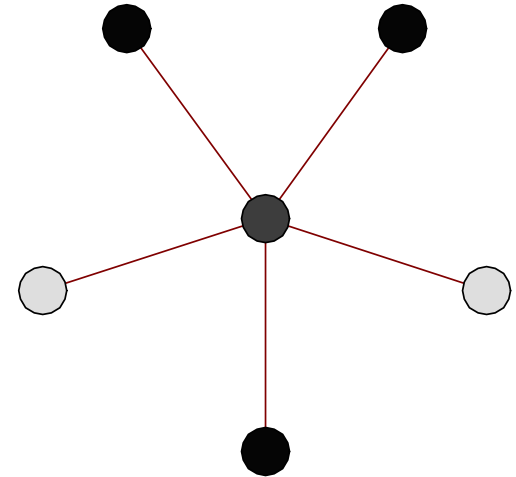
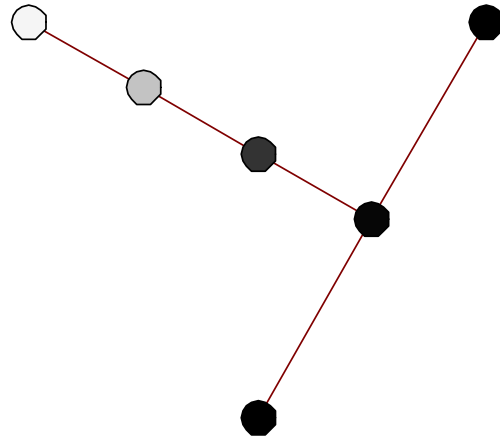
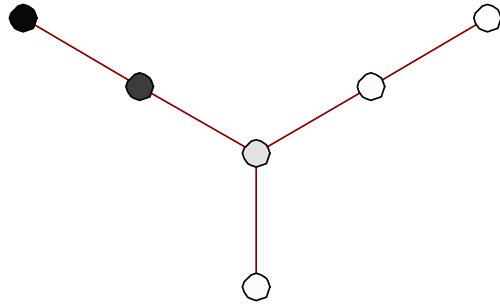
Extending from two populations in one dimension ($w=0.5$).

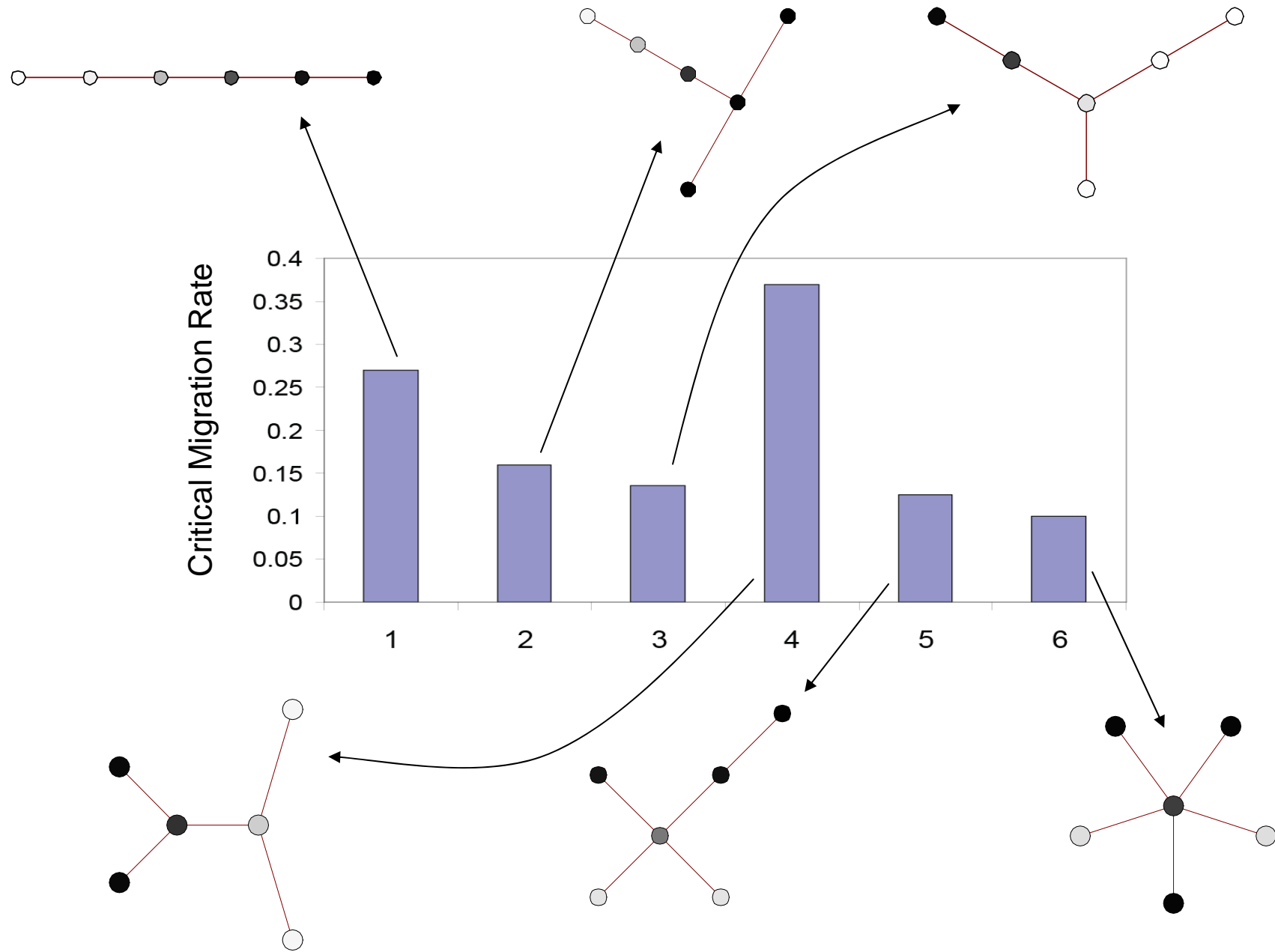


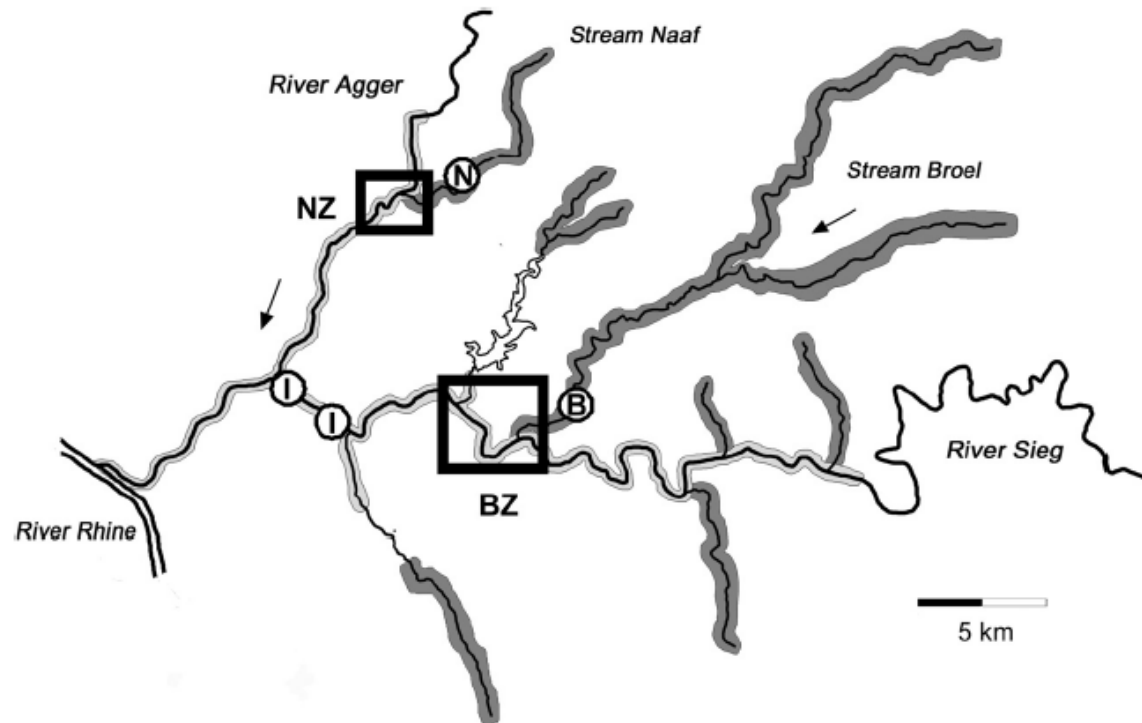
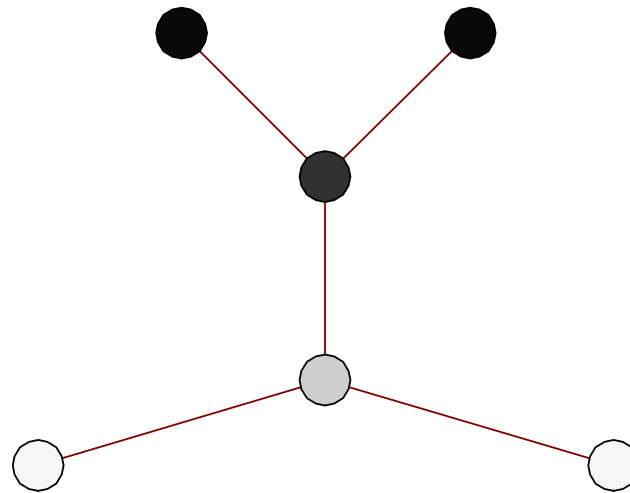
An even-odd sawtooth stability pattern appears.

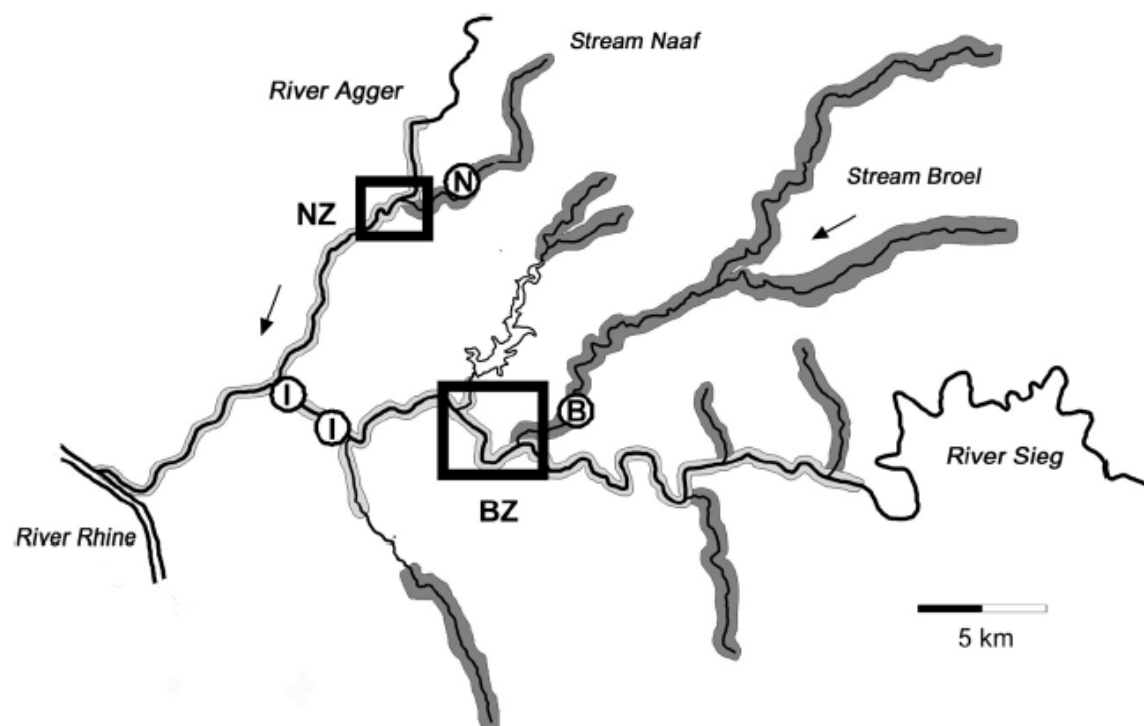


Two buffer populations are better than one or three?











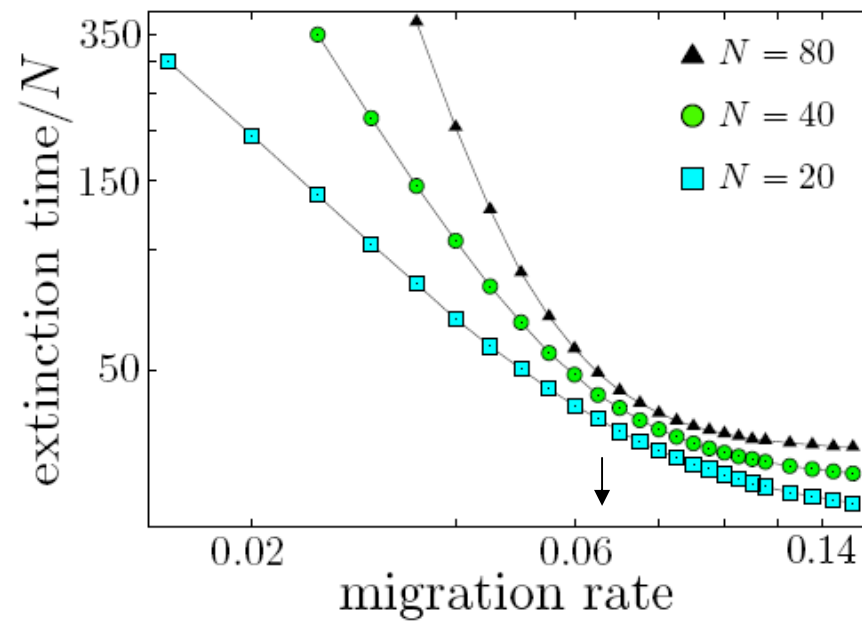
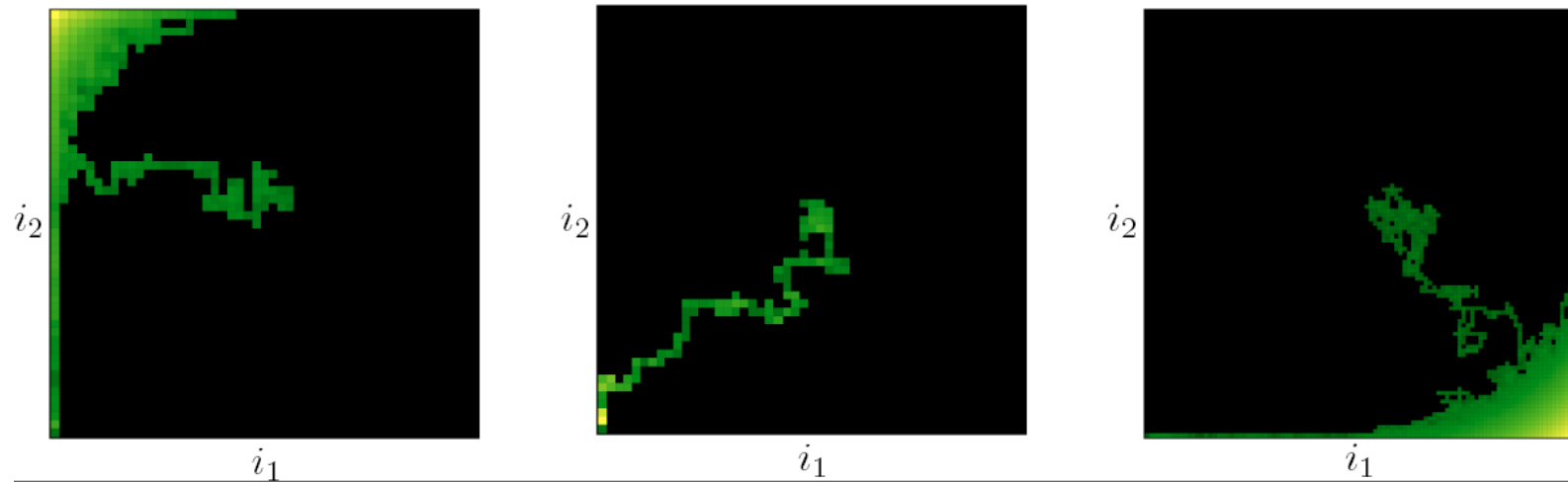
Molecular Ecology (2009) 18, 2615–2627

Variable patterns of introgression in two sculpin hybrid zones suggest that genomic isolation differs among populations

A. W. NOLTE,* Z. GOMPERT† and C. A. BUERKLE†

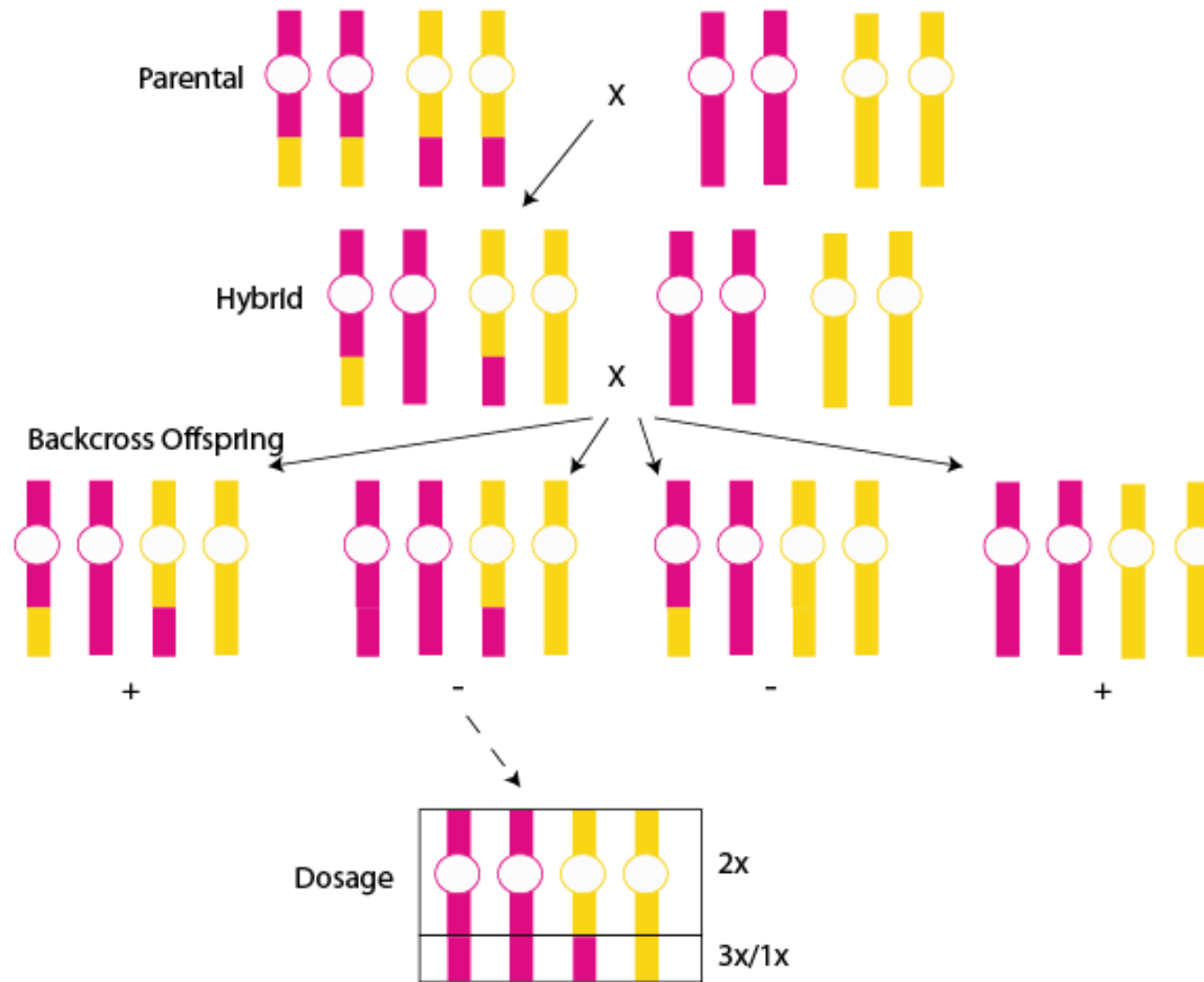
Results suggest widespread underdominance between *Cottus* populations.

Stochastic/Finite Population Predictions



How to engineer underdominance?

Translocations are a Natural Form of Underdominance



Possible Use of Translocations to fix Desirable Genes in Insect Pest Populations

CHROMOSOME translocation heterozygotes ($T/+$) are usually semisterile, but translocation homozygotes (T/T) if viable are usually fully fertile. If such a viable translocation were produced in an insect pest, T/T insects could be reared in captivity and released into the wild, where matings with wild types ($+/+$) would produce $T/+$ progeny. ...

C. F. CURTIS

Tsetse Research Laboratory,
University of Bristol,
Langford, near Bristol.

Early work failed to achieve underdominance with wildtype heterozygotes.

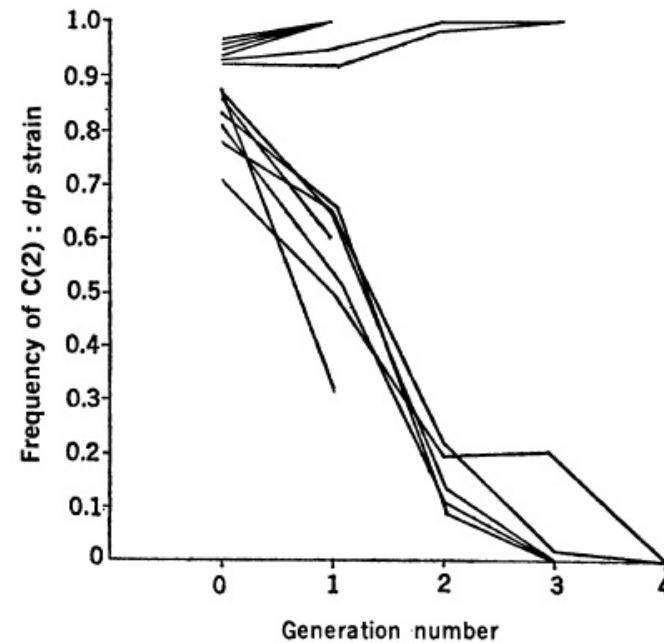
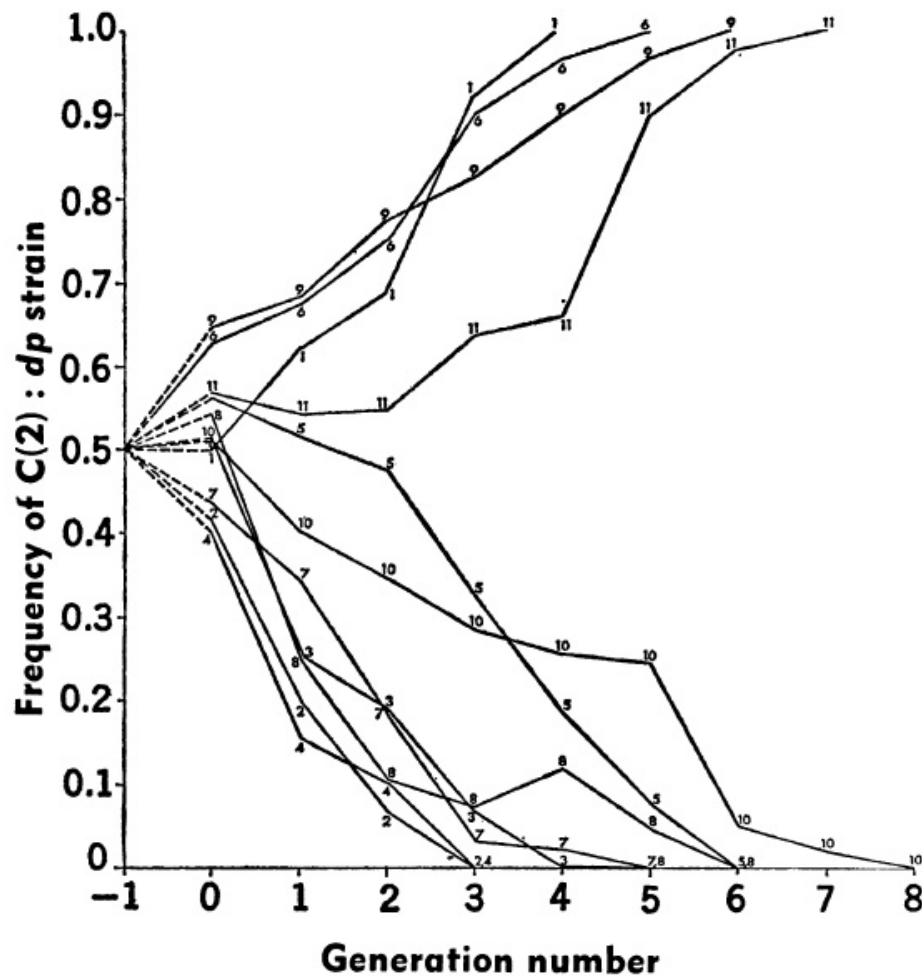
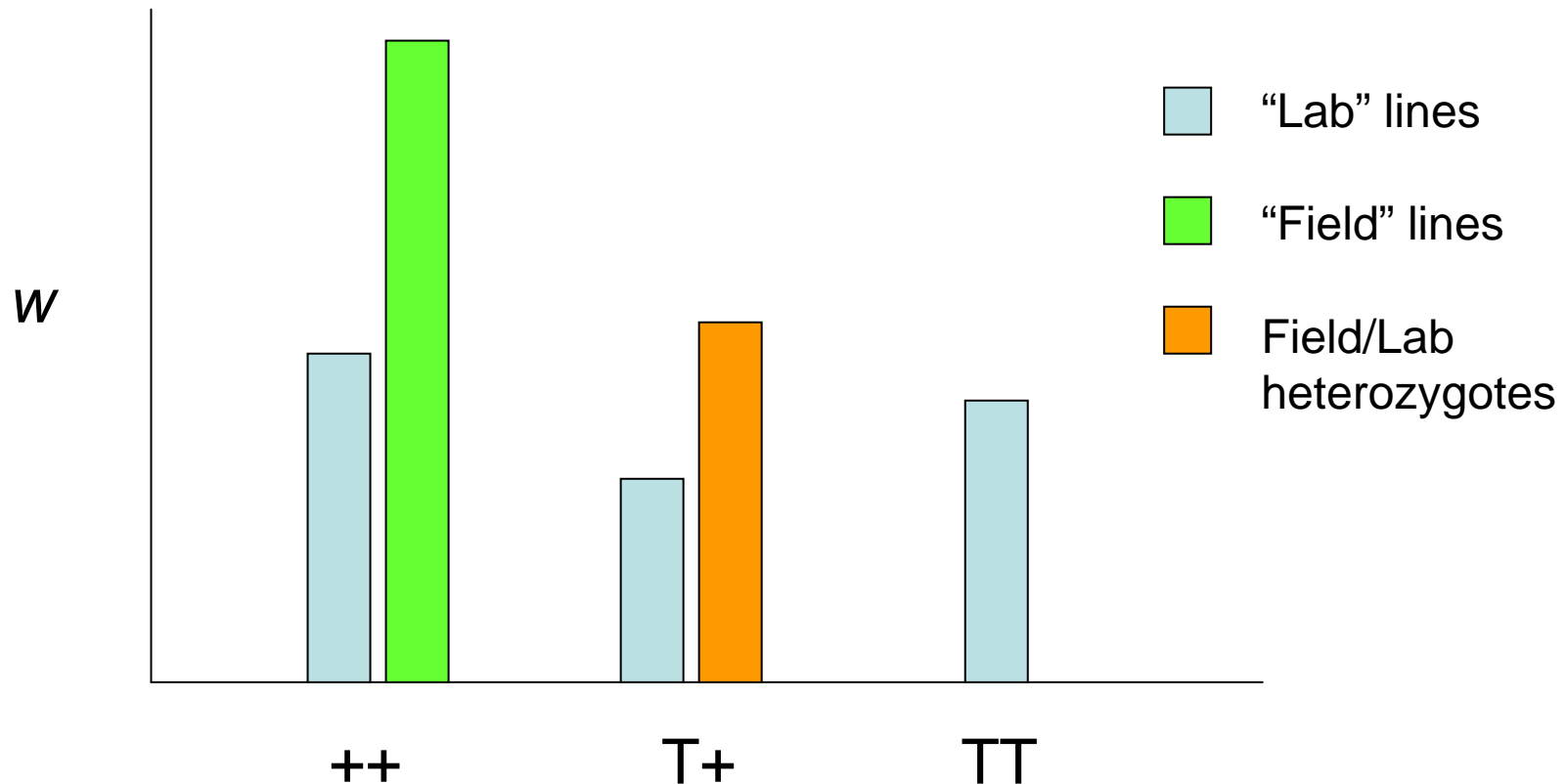


Fig. 6 (left). Change in frequency of C(2):dp strain in competition with C(3):ri strain. The unstable point is about 0.5. Fig. 7 (right). Change in frequency of C(2):dp strain in competition with structurally wild-type strain. The unstable point is about 0.9.

Foster et al. (1972)

Lab lines, especially ones exposed to radiation and made homozygous are much less fit than wild flies (*cf.* Boussy 1988).

(In one dramatic case the lab homozygous fitnesses were so low that there was a heterozygote advantage, despite a translocation!)



In recent years other alternatives have been proposed.

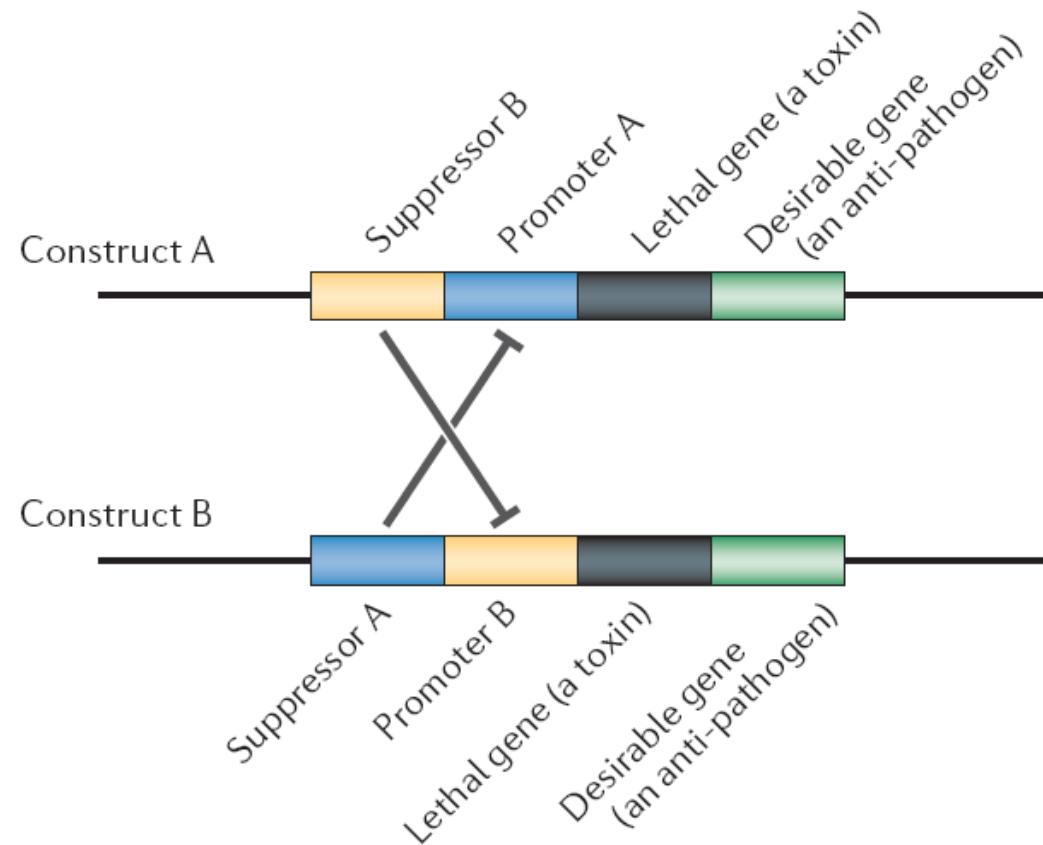
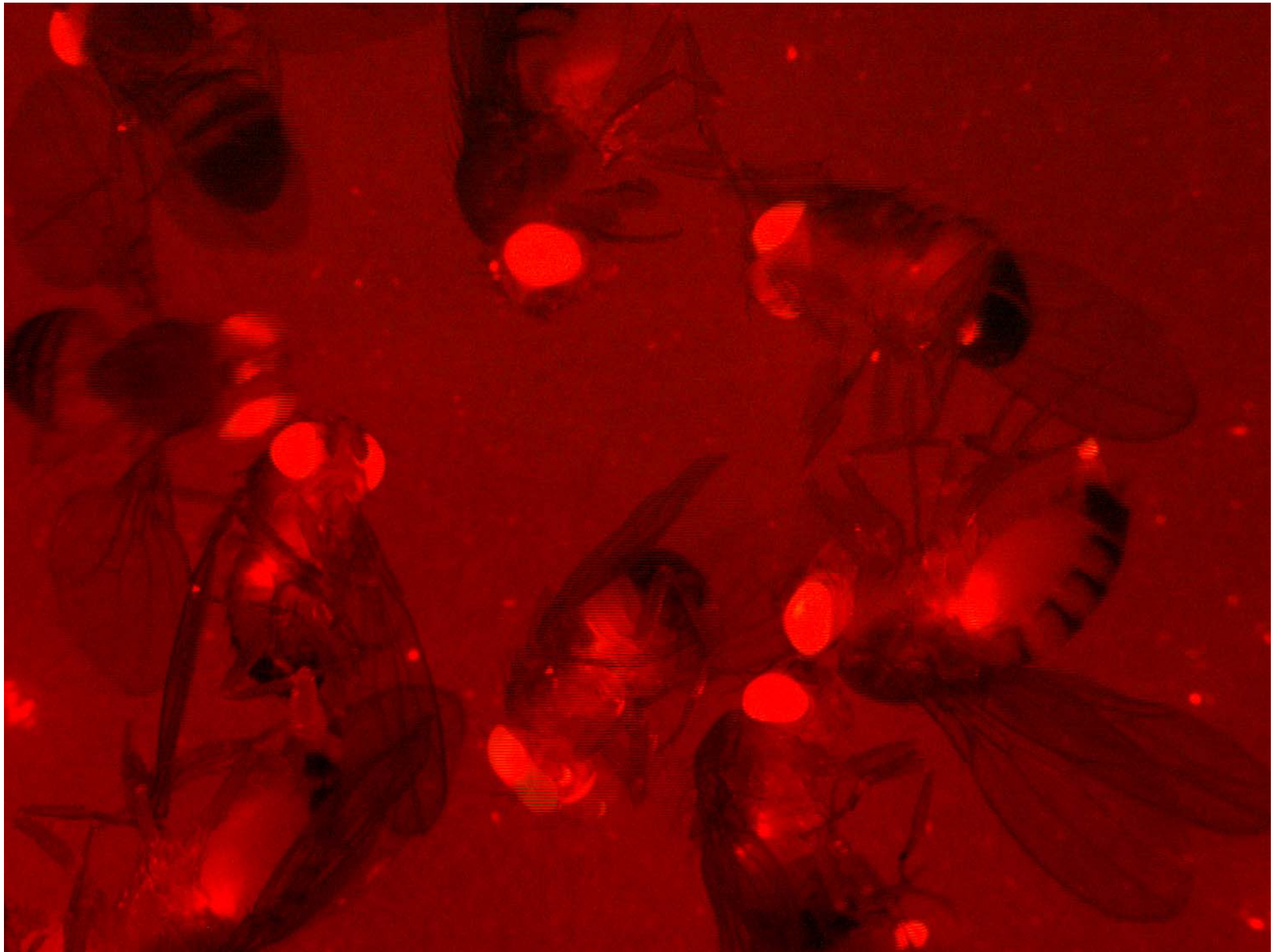


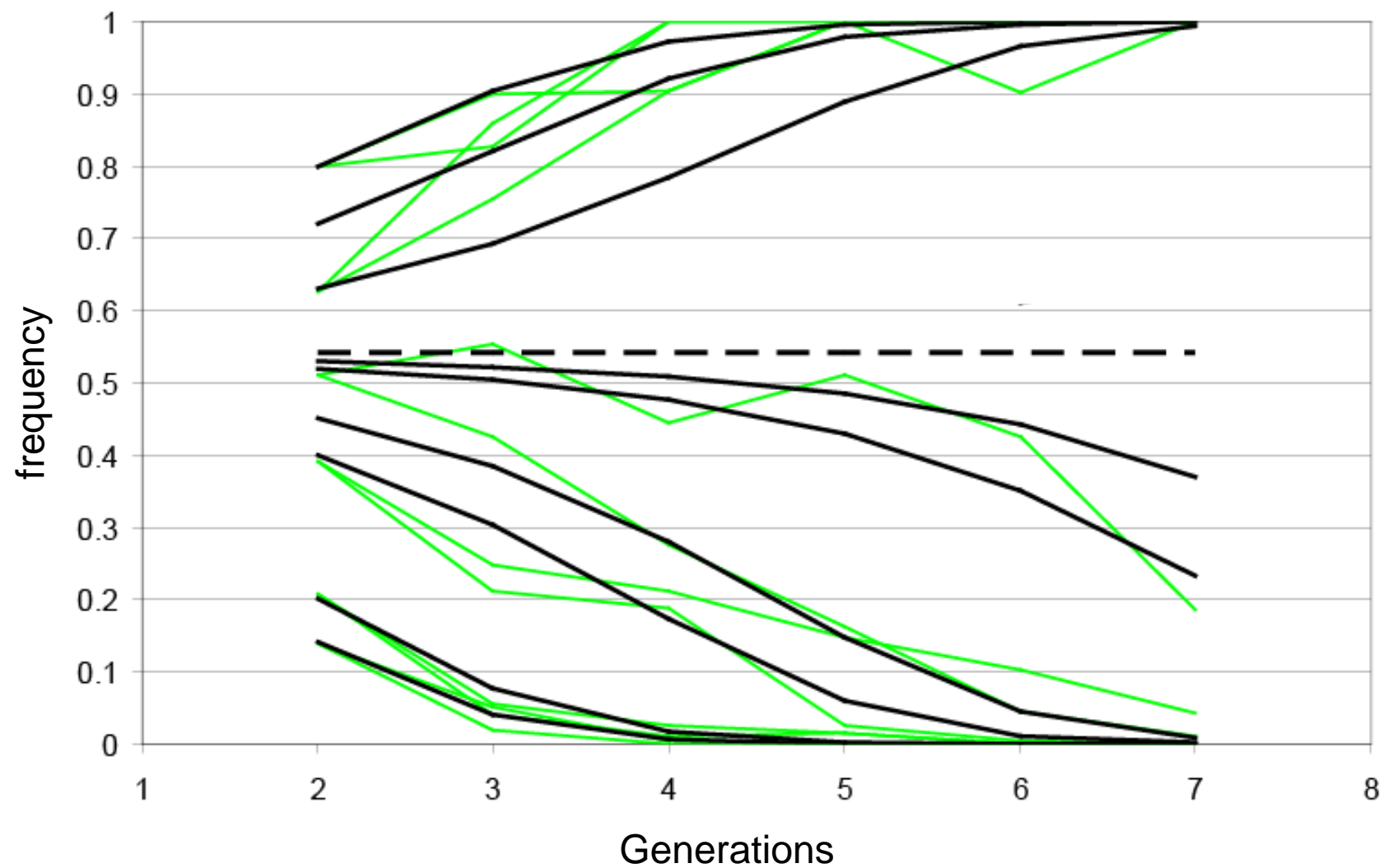
Figure 3 | An example of an engineered underdominant system that is based on mutual suppression of lethal constructs.

Davis 2001; Sinkins and Gould 2006





Theory and Data



A black and white electron micrograph showing numerous Sigma virus particles. The particles are elongated, rod-shaped structures with a distinct outer shell and a darker, more electron-dense core. They are scattered across the field of view, some appearing in small clusters and others isolated. The background is a grainy, light gray texture.

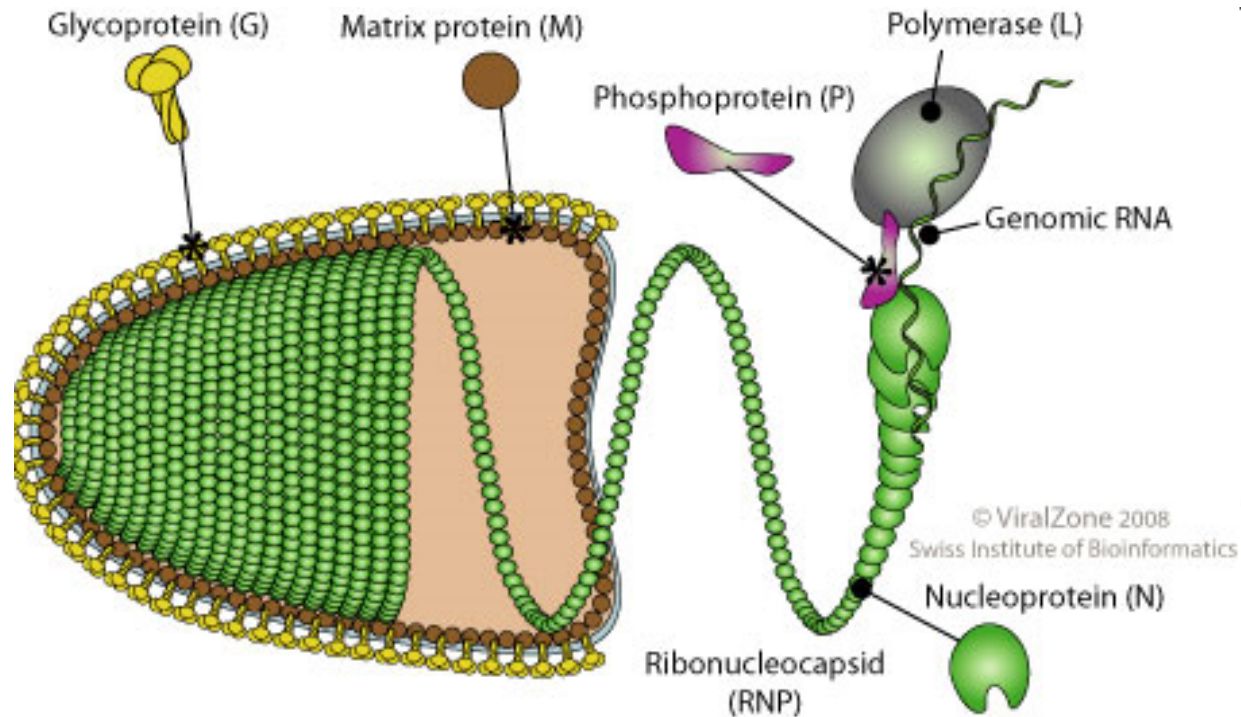
A model disease -- Sigma virus

Sigma virus is a Rhabdovirus that infects *D. melanogaster* and is vertically transmitted via the gametes.

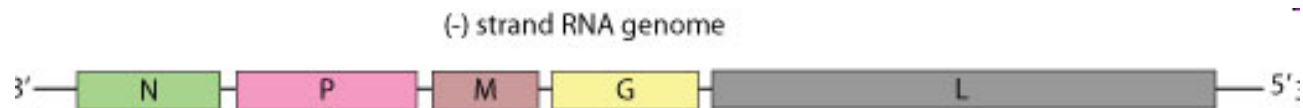
Negative sense (3'-5') single strand genome RNA virus.

Rhabdoviruses infect many plants (include crop diseases, some spread by insects), food animals (cattle, trout, salmon, again some spread by insects), and the most well known is rabies.

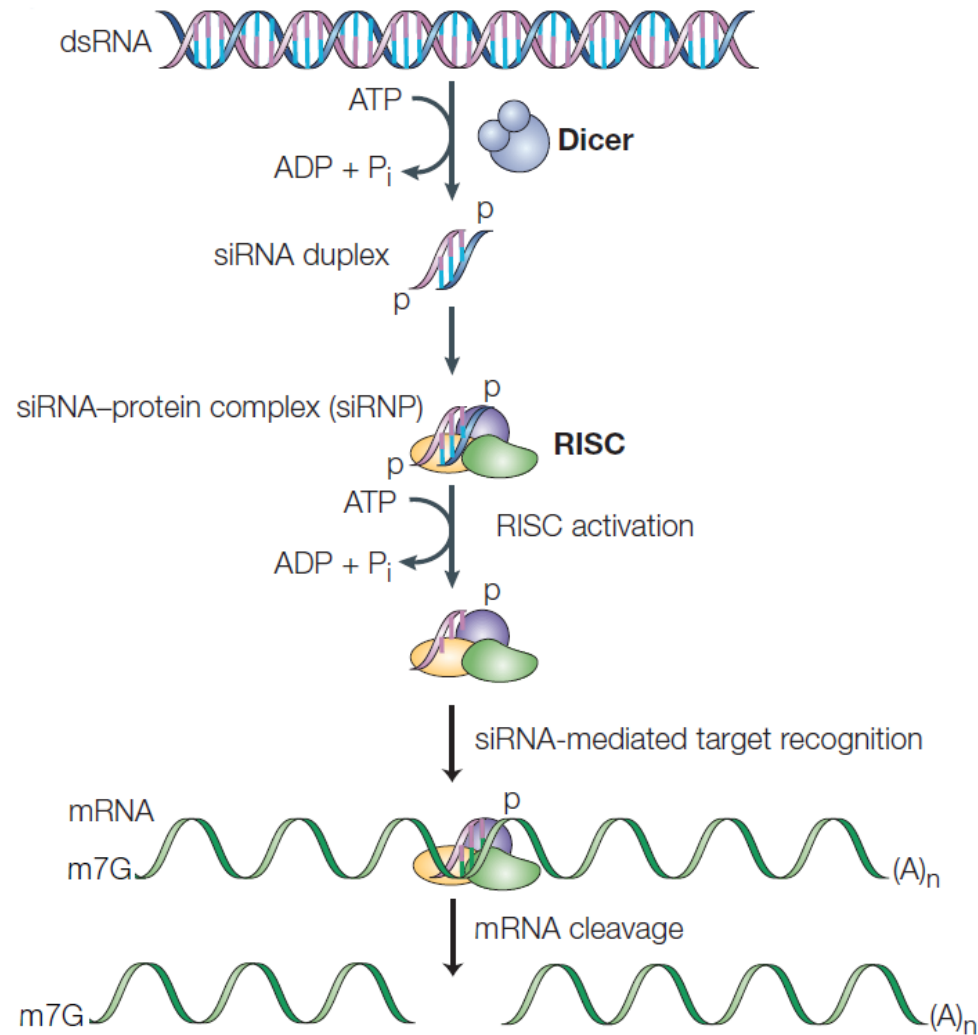
Rhabdovirus Structure



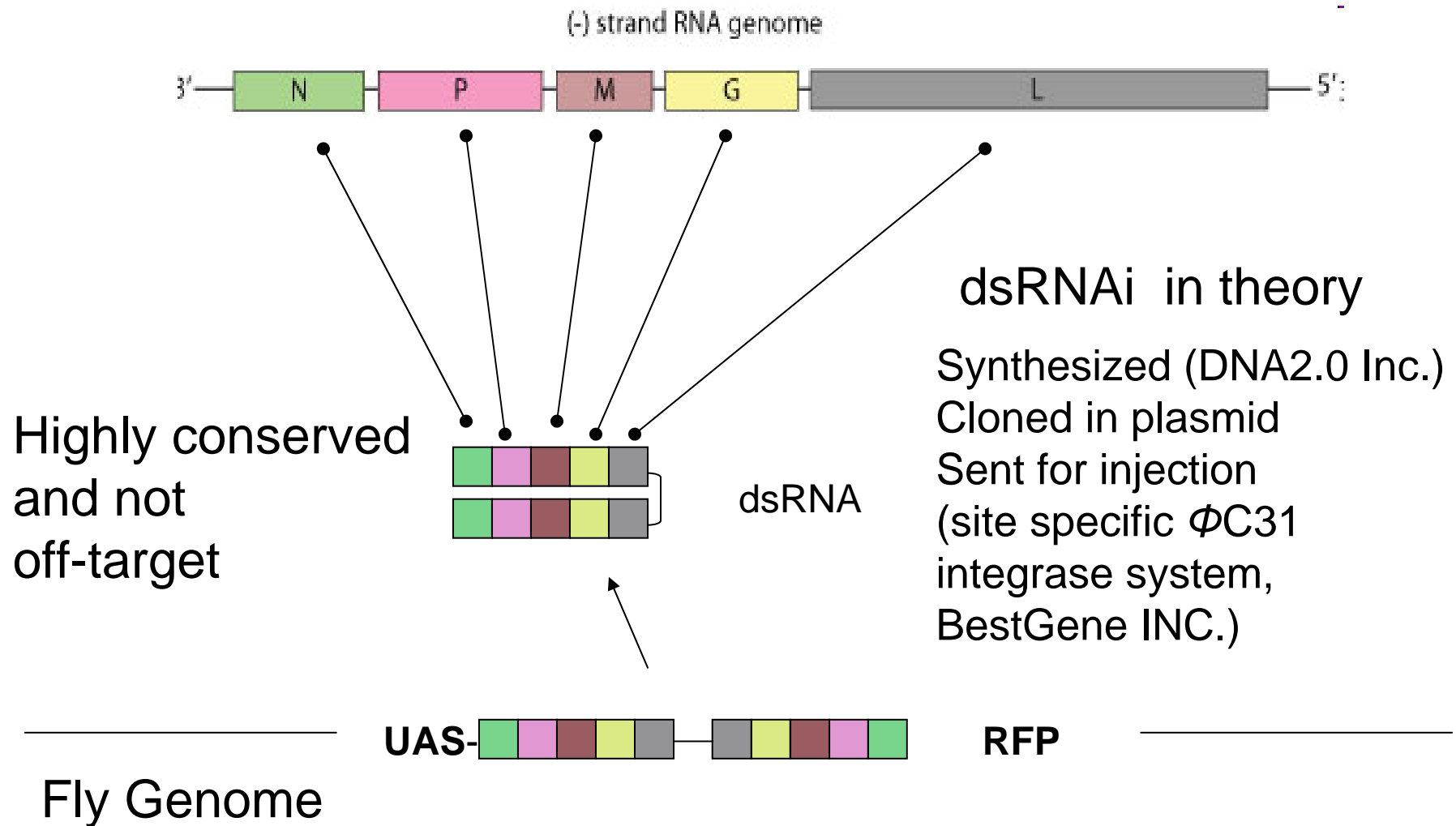
Enveloped, bullet shaped. 180 nm long and 75 nm wide.



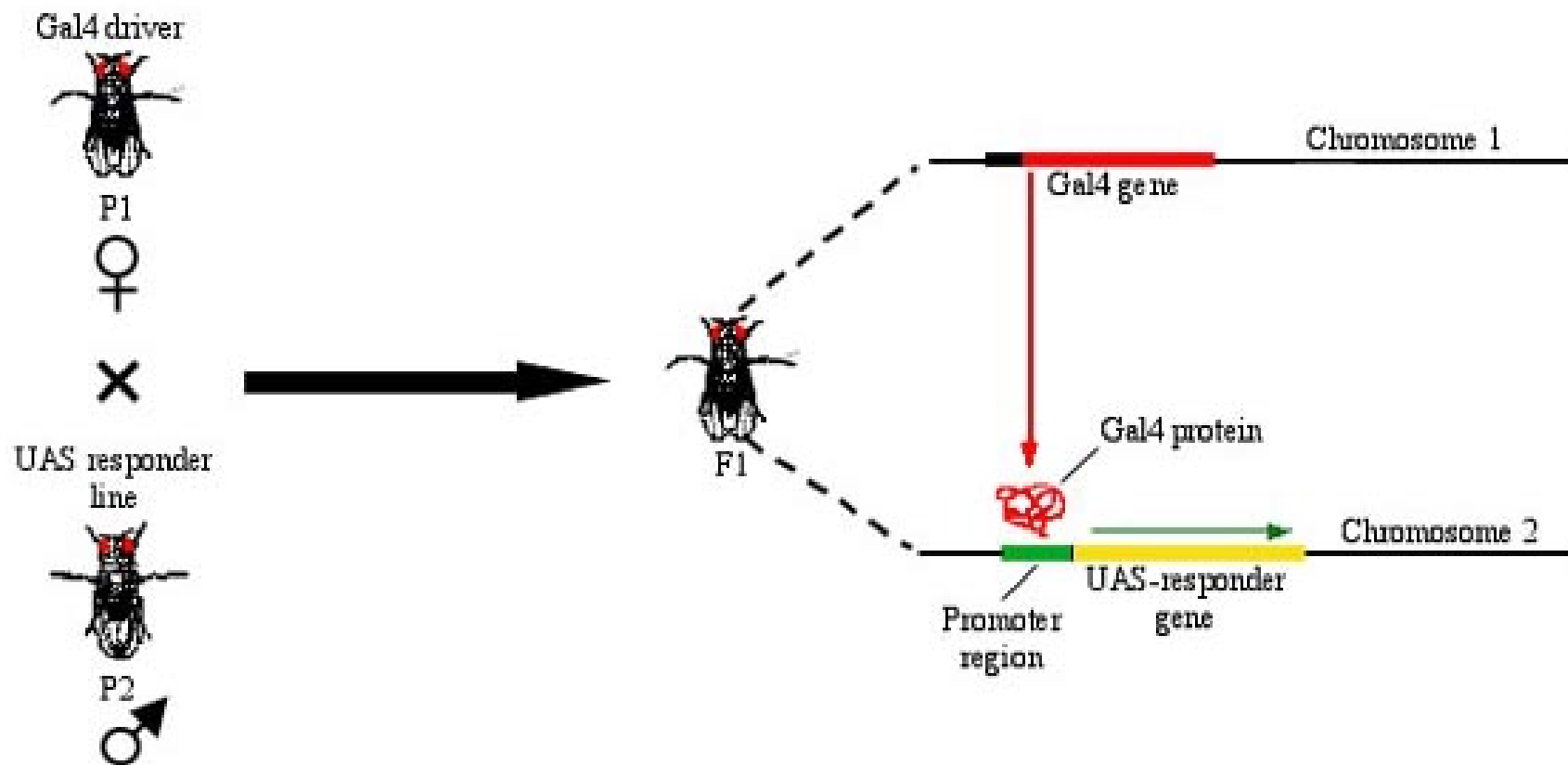
Gene expression knockdown by dsRNAi



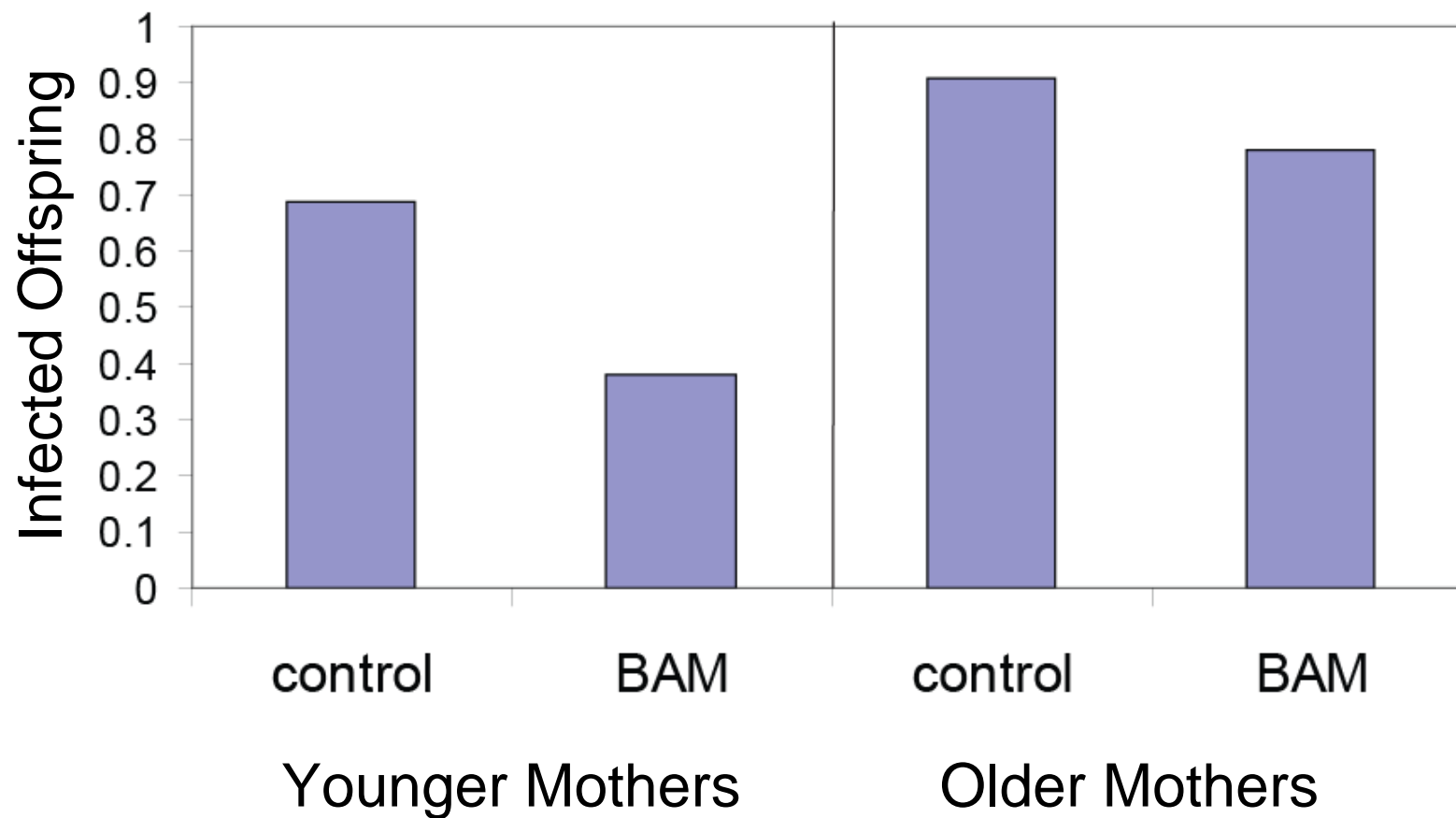
Dykxhoorn *et al.* 2003



GAL4 -> UAS Expression

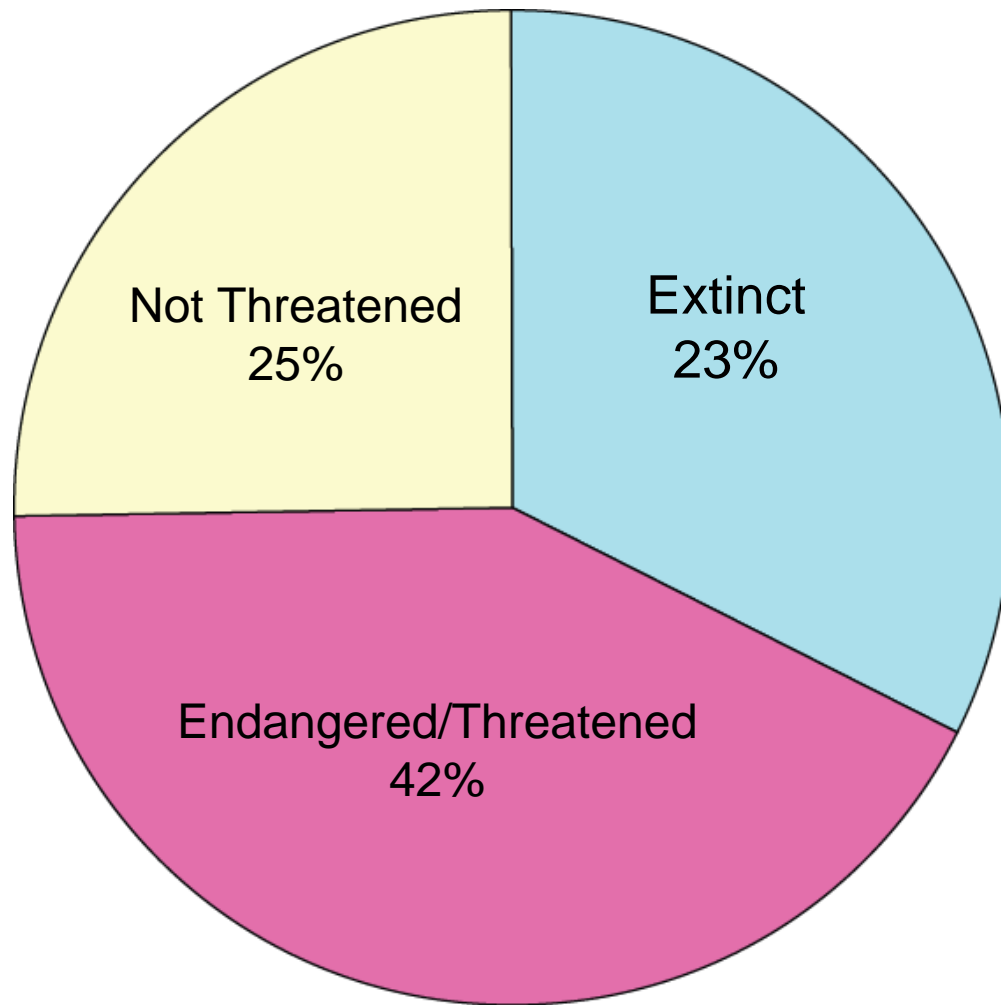


bag-of-marbles expression



A possible conservation application with
endemic Hawaiian birds and avian malaria

Status of Endemic Hawaiian Birds



Contributors include
Habitat loss
Predation
Avian diseases

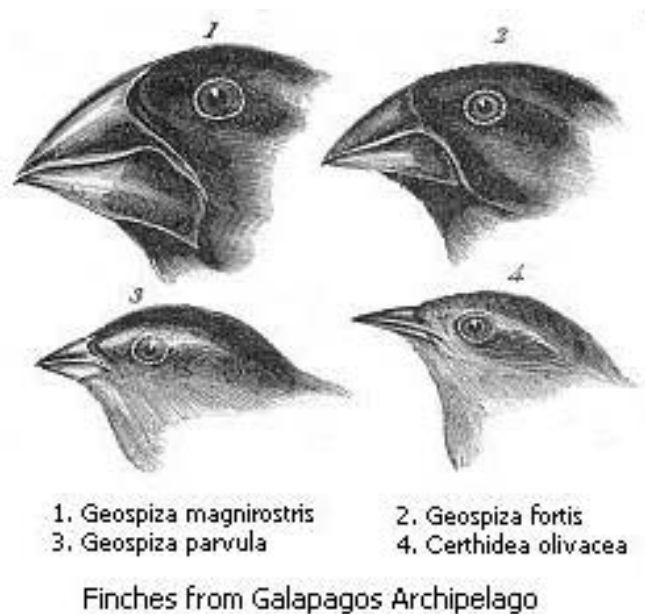


Culex mosquitoes were accidentally introduced in the early 19th century and are infected with avian malaria.



One bite by an infected *Culex* is likely to kill a juvenile L'iwi (Atkinson *et al.* 1993)

Culex mosquitoes are also now established on the Galapagos islands, and avian malaria has recently been reported there (<http://whc.unesco.org/en/news/445>, July 1, 2008).



<http://www.kiwifoto.com/>



Genetic transformation of *Culex* has been possible since 2001.

Transforming *Culex* Populations

- If an engineered genetic construct gave resistance to avian malaria (*cf.* Jasinskiene *et al.* 2007; Kokoza *et al.* 2010) and could be linked to an underdominant system...
- Releases of transgenic *Culex* that result in a frequency above \hat{p} could transform an island population to be resistant to avian malaria.
- Parts of the islands could be left untransformed to allow natural resistance in the birds to evolve.
- Underdominance should also prevent the genetic modification from becoming established in the native home range of *Culex* mosquitoes.

Other interests

Human evolution/prehistory

Gene-Culture coevolution

Adaptation, selfish genes and selective
sweep detection (ABC approaches)

Evolutionary game theory

Hybrid speciation and invasive lineages

Ethics and regulation of GM insects

Genetic sterile insect technique

Acknowledgements

Philipp Altrock – Theory

Chip Aquadro (Cornell U) – Global Fly Lines

Kevin Cook (Indiana U) – Drosophila Genetics

Kent Golic (U of Utah) – FLP-FRT translocations

Fred Gould (NC State U) – Gene Drive Systems

Francis Jiggins (U of Edinburgh) – Sigma Virus

Kata Langer – Internship

The Max Planck Society – Support

Anita Möller – Technician

Hagen Müller – Student

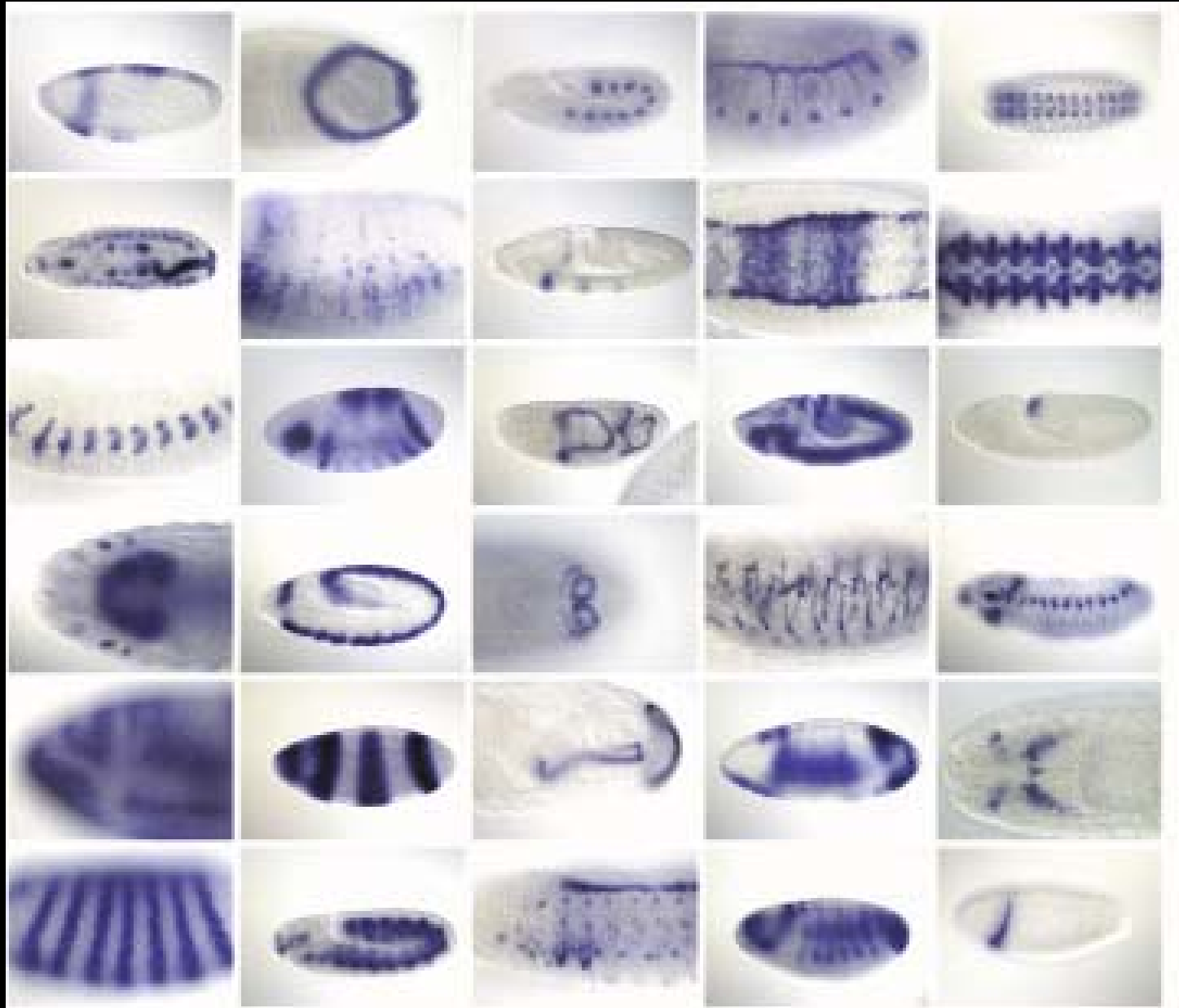
The Monday Theory Chalk Talk Group (MPI Plön)

Guy Reeves – Engineering

Diethard Tautz – Support

Arne Traulsen – Theory

Kata Weiß – Internship



Tomancak et al. 2002

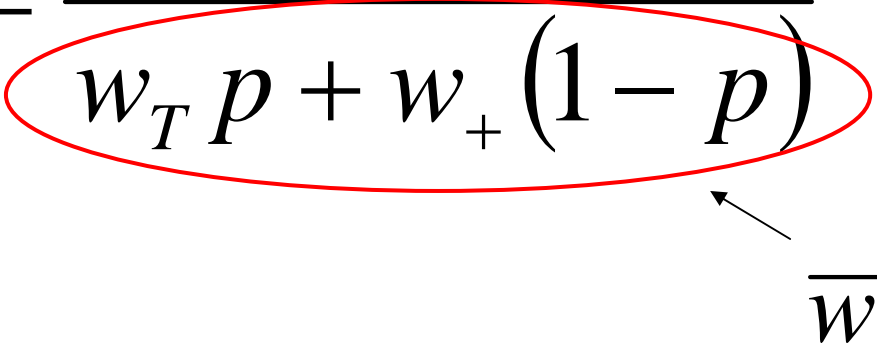


<http://www.tolweb.org/Plasmodium>

The contribution to the next generation is normalized by the total contribution from both alleles to give an allele frequency in the population.

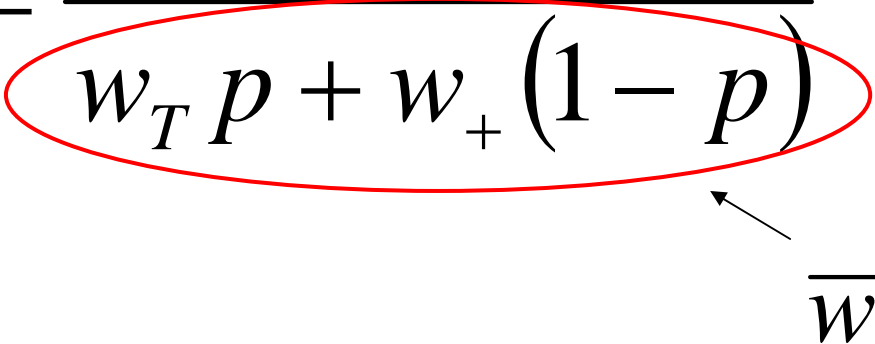
$$p' = \frac{w_T p}{w_T p + w_+ (1 - p)}$$

The contribution to the next generation is normalized by the total contribution from both alleles to give an allele frequency in the population.

$$p' = \frac{w_T p}{w_T p + w_+ (1 - p)}$$


\overline{w}

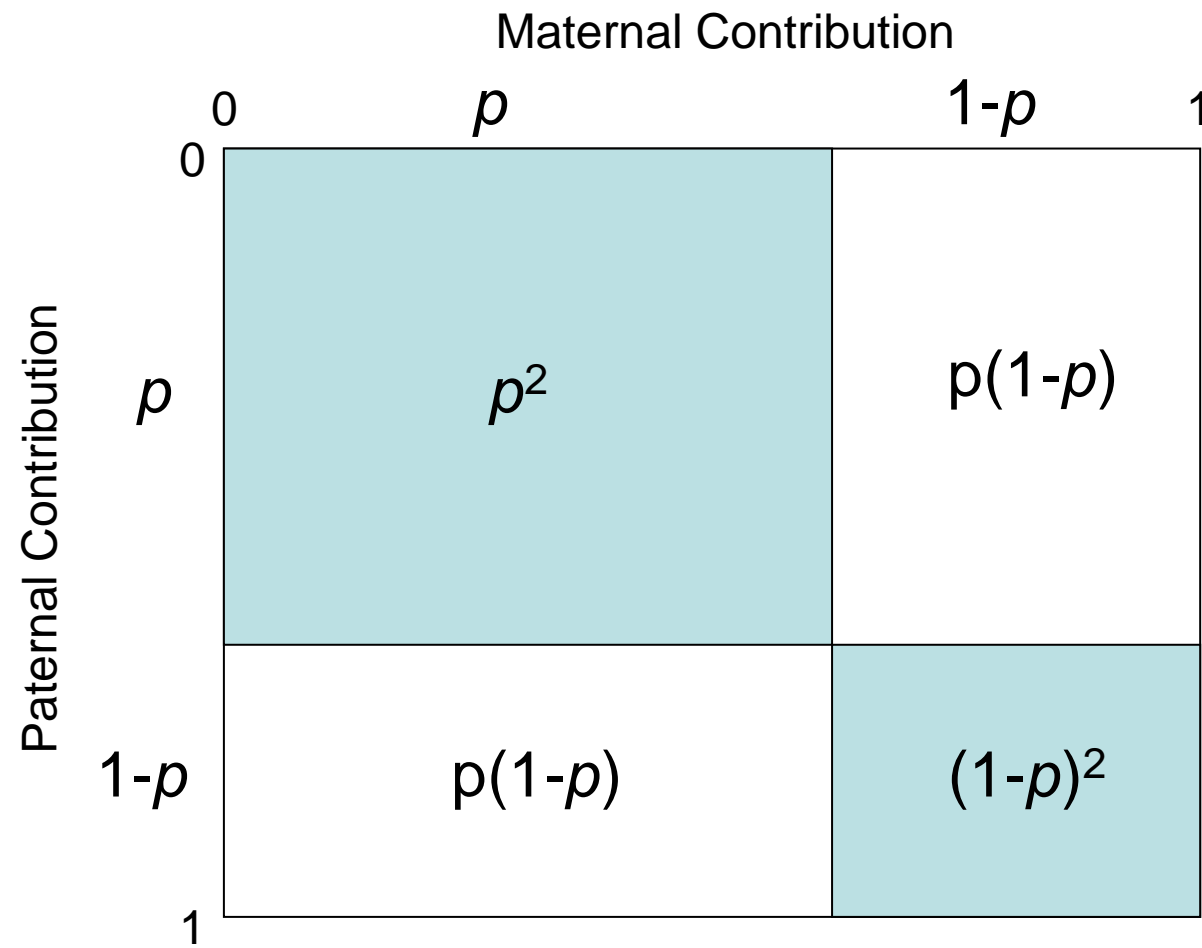
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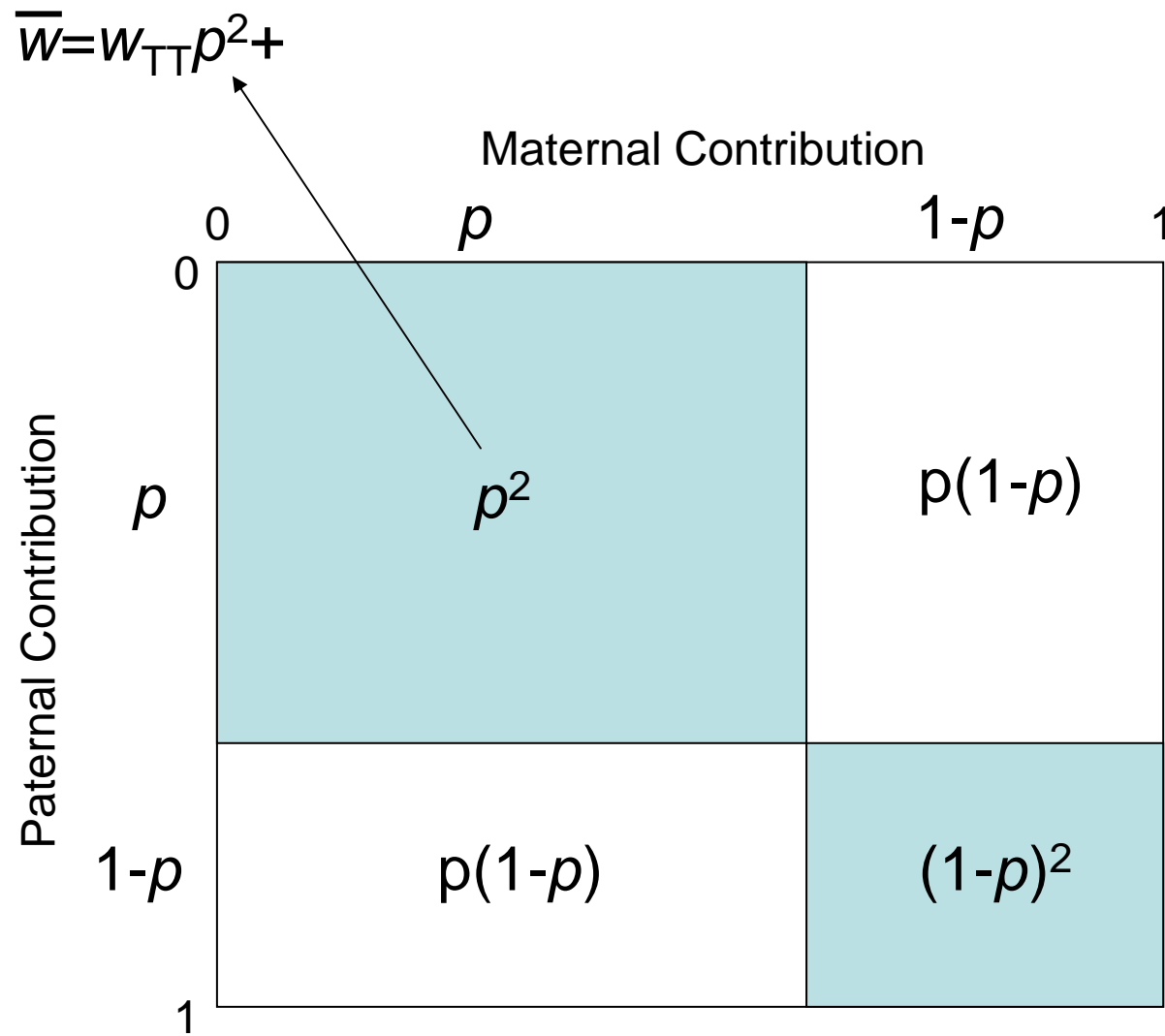
\overline{w}

$$p' = \frac{w_T p}{\overline{w}}$$

Building the model:

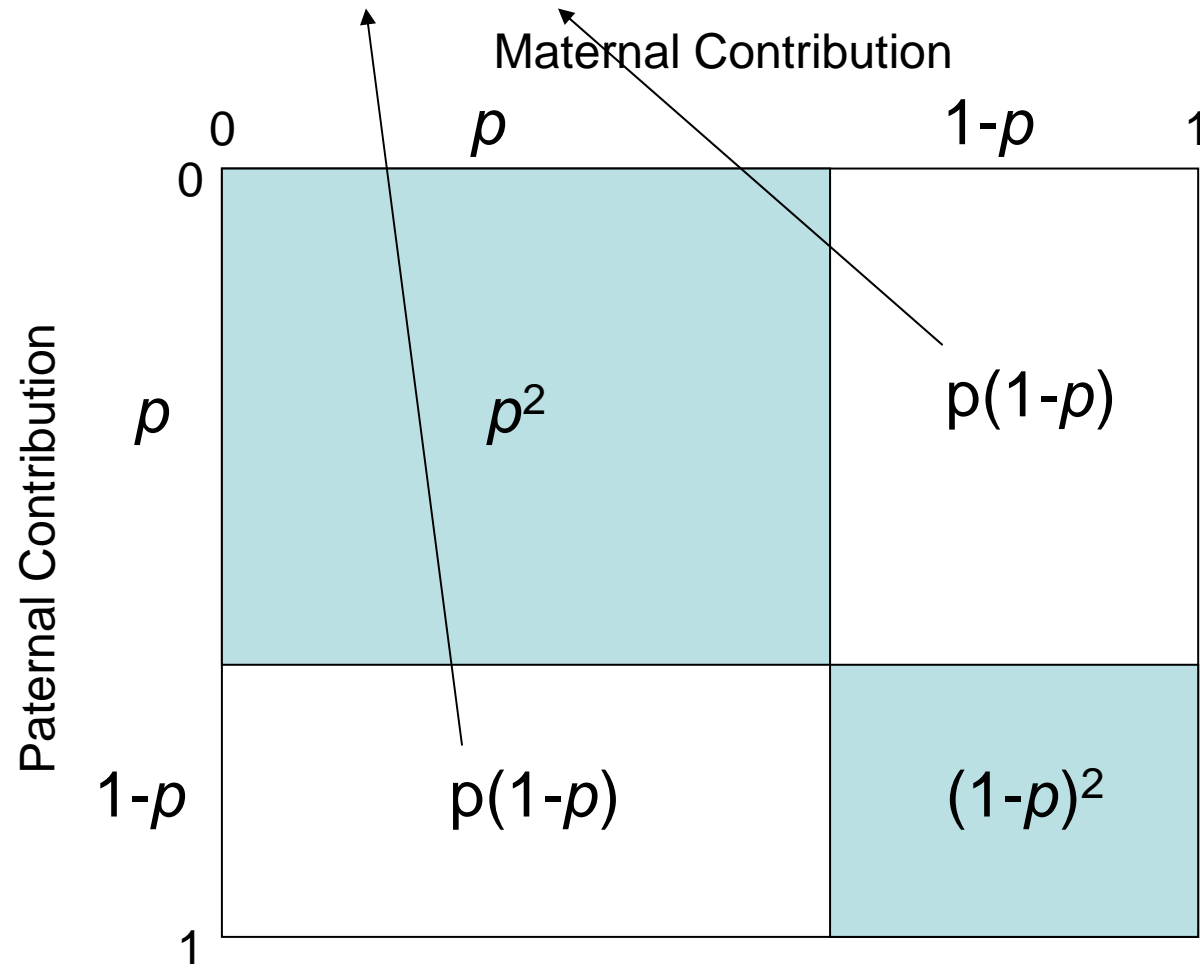


Building the model:



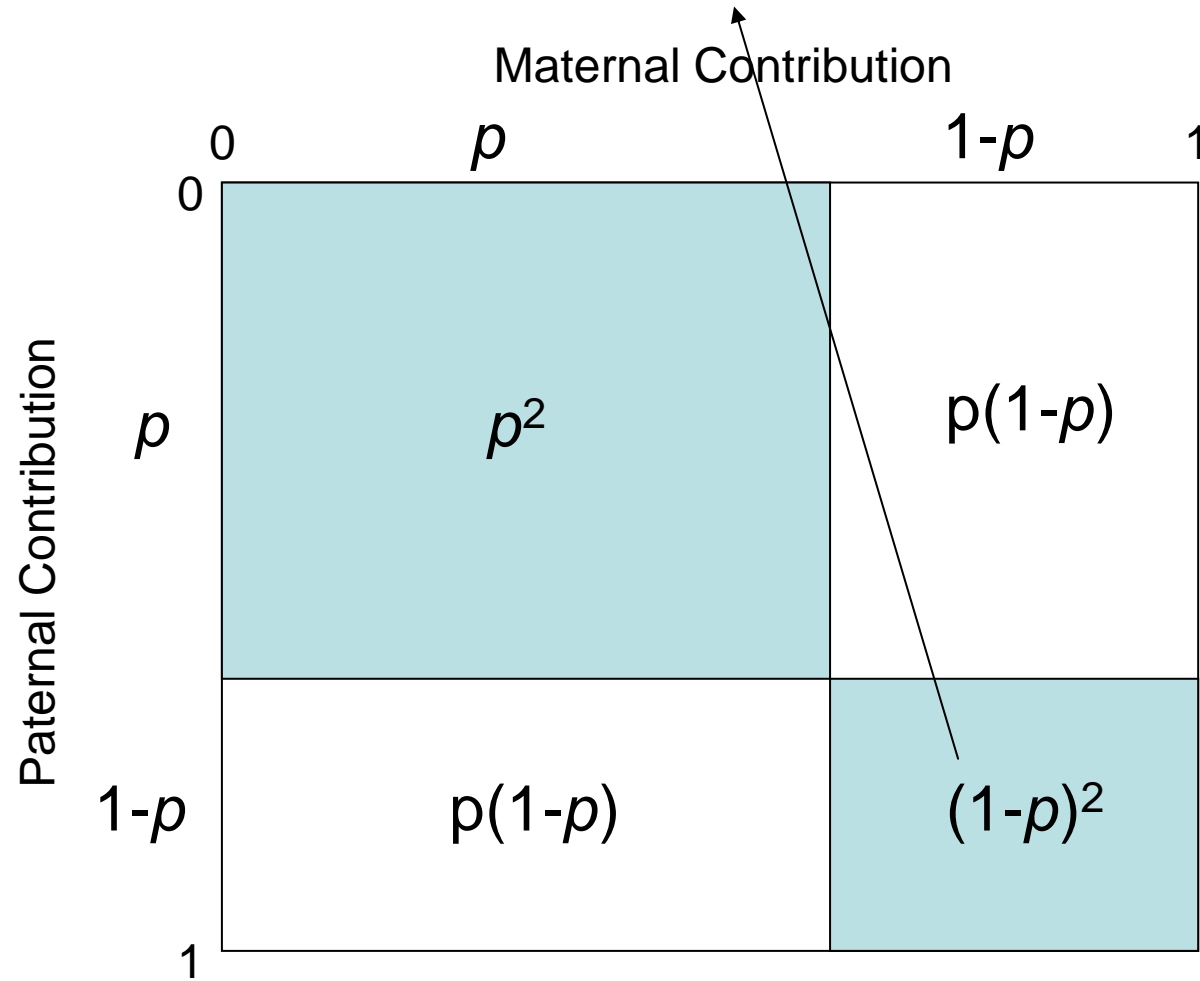
Building the model:

$$\bar{w} = w_{TT}p^2 + 2w_{T+}p(1-p) +$$



Building the model:

$$\bar{w} = w_{TT}p^2 + 2w_{T+}p(1-p) + (1-p)^2$$



Building the model:

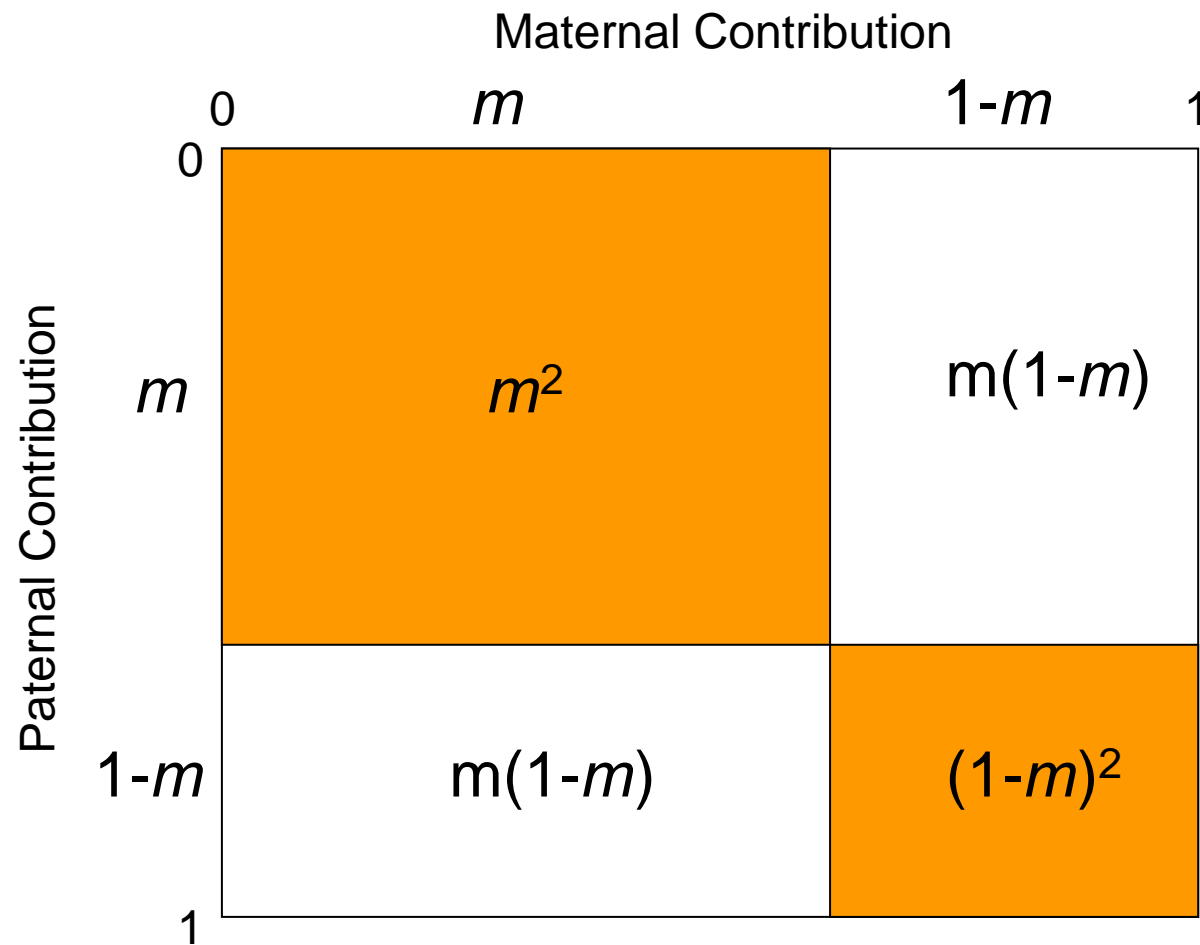
$$\bar{w} = w_{TT}p^2 + 2w_{T+}p(1-p) + (1-p)^2$$

$$p' = w_{TT}p^2 + \cancel{2}w_{T+}p(1-p) + (\cancel{1-p})^2$$

$$p' = (w_{TT}p^2 + w_{T+}p(1-p)) / \bar{w}$$

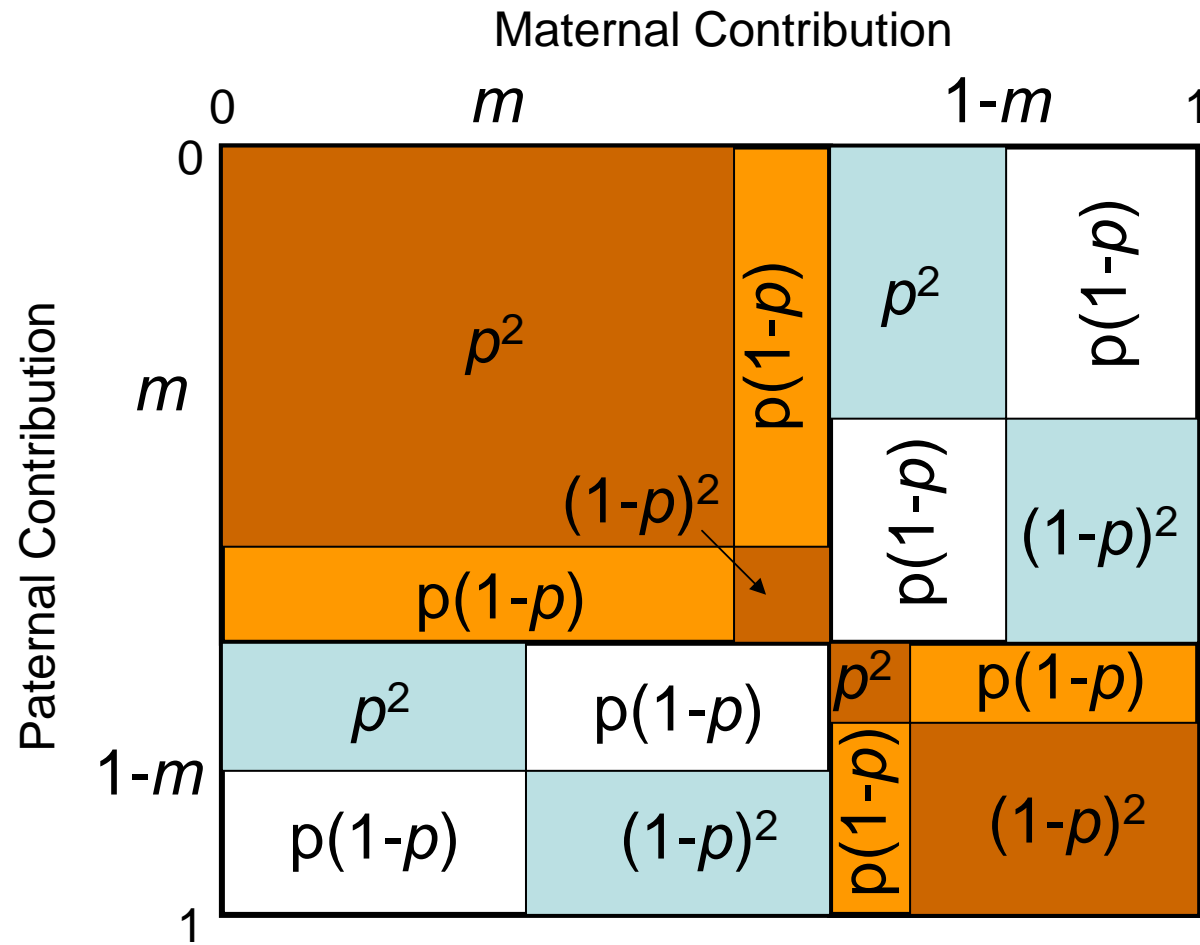
Building the model (on a higher level):

Migrants and non-migrants



Building the model (on a higher level):

Migrants and non-migrants



Building the model (on a higher level):

$$\begin{aligned}\bar{w}_1 = & (1-m)^2(w_{TT}p_1^2 + 2w_{T+}p_1(1-p_1) + (1-p_1)^2) + \\ & 2m(1-m)(\dots\dots\dots) + \\ & m^2(\dots\dots\dots)\end{aligned}$$

The expected change in frequency of the underdominant allele each generation can be written in a Wright-Fisher manner.

$$p'_1 = \frac{\left((1-m)^2 (p_1^2 + wp_1(1-p_1)) + 2m(1-m) \left(p_1 p_2 + \frac{w(p_1(1-p_2) + p_2(1-p_1))}{2} \right) + m^2 (p_2^2 + wp_2(1-p_2)) \right)}{\bar{w}_1}$$

Where

$$\begin{aligned} \bar{w}_1 = & (1-m)^2 (p_1^2 + 2wp_1(1-p_1) + (1-p_1)^2) + \\ & 2m(1-m) (p_1 p_2 + wp_1(1-p_2) + wp_2(1-p_1) + (1-p_1)(1-p_2)) + \\ & m^2 (p_2^2 + 2wp_2(1-p_2) + (1-p_2)^2) \end{aligned}$$