The impact of dissociation on transposon-mediated disease control strategies

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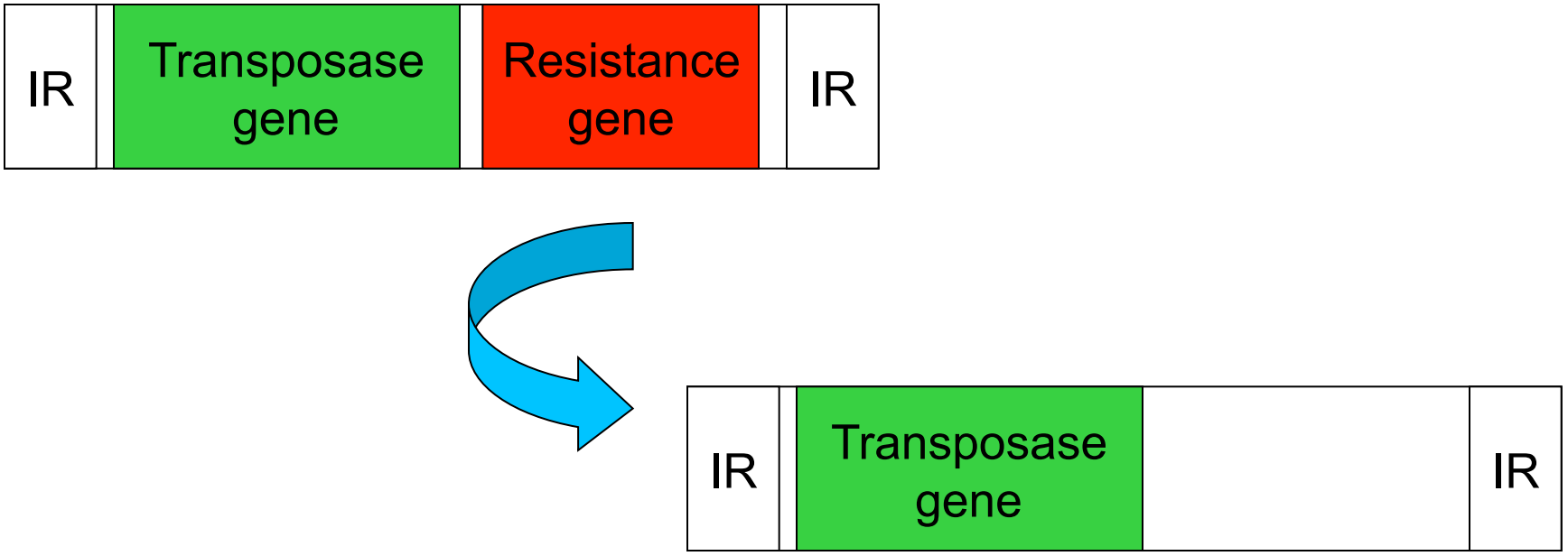
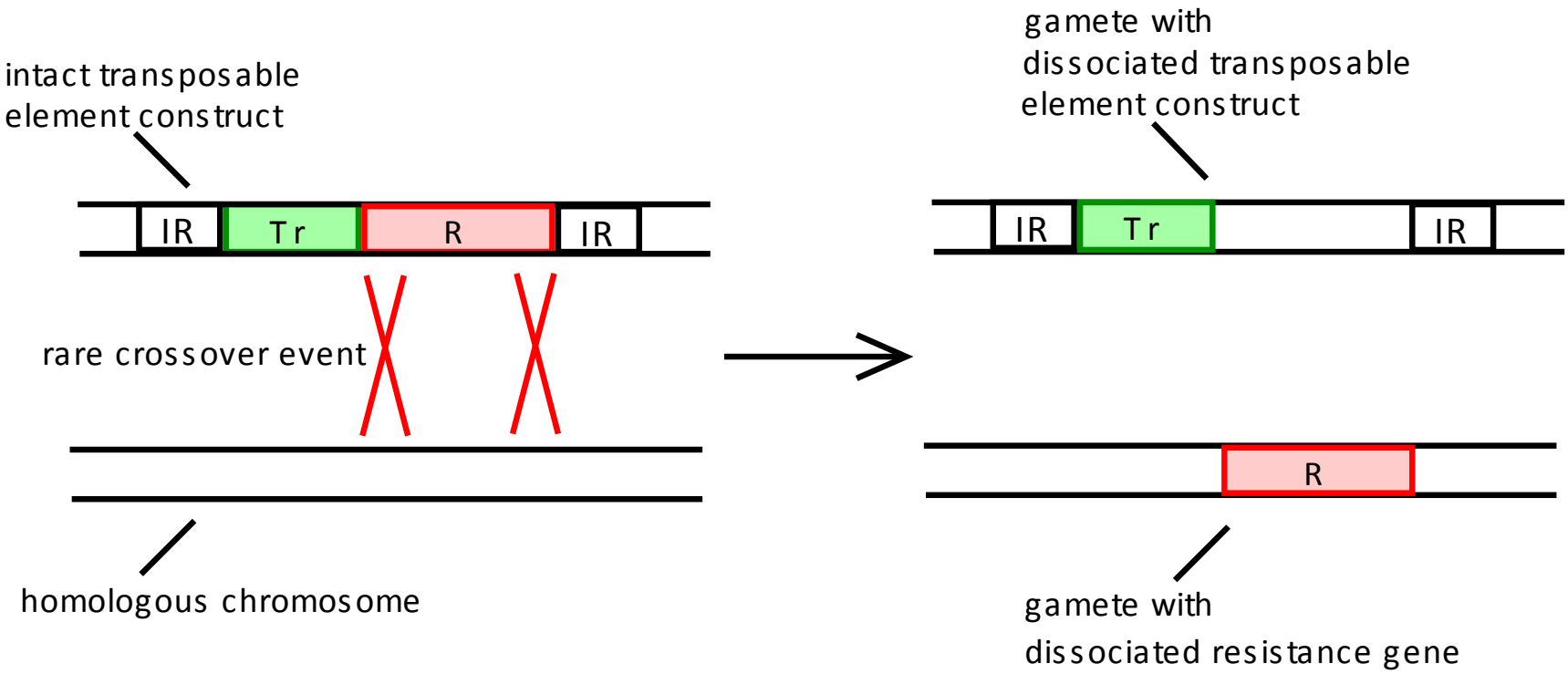


"It is misguided to continue to use scarce resources from the malaria-research budget for activities which could not control malaria but only produce NPS (Nature-paper synthetase)."

C. F. Curtis, ***Ecological aspects for application of genetically modified mosquitoes*** **(2003).**

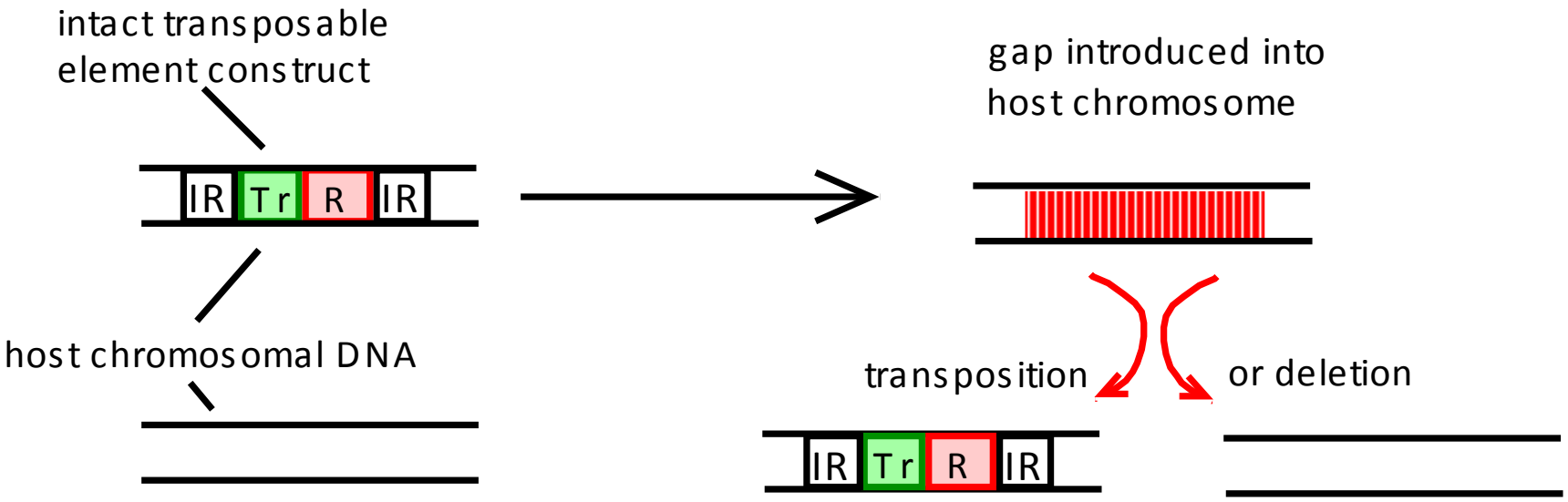
How is linkage lost between a TE and resistance gene?

1. Rare recombination events

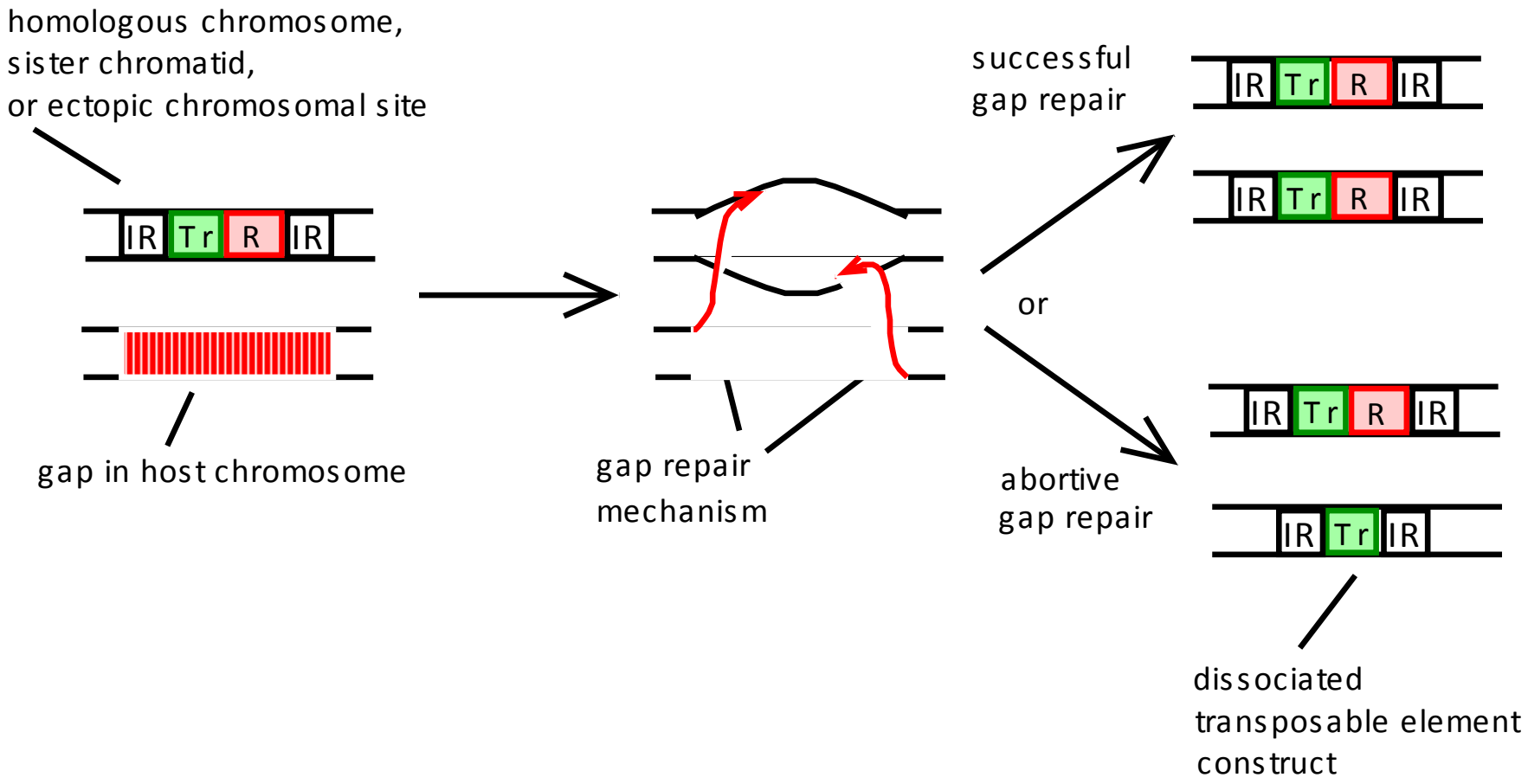


2. Internal deletion of DNA sequences within a TE

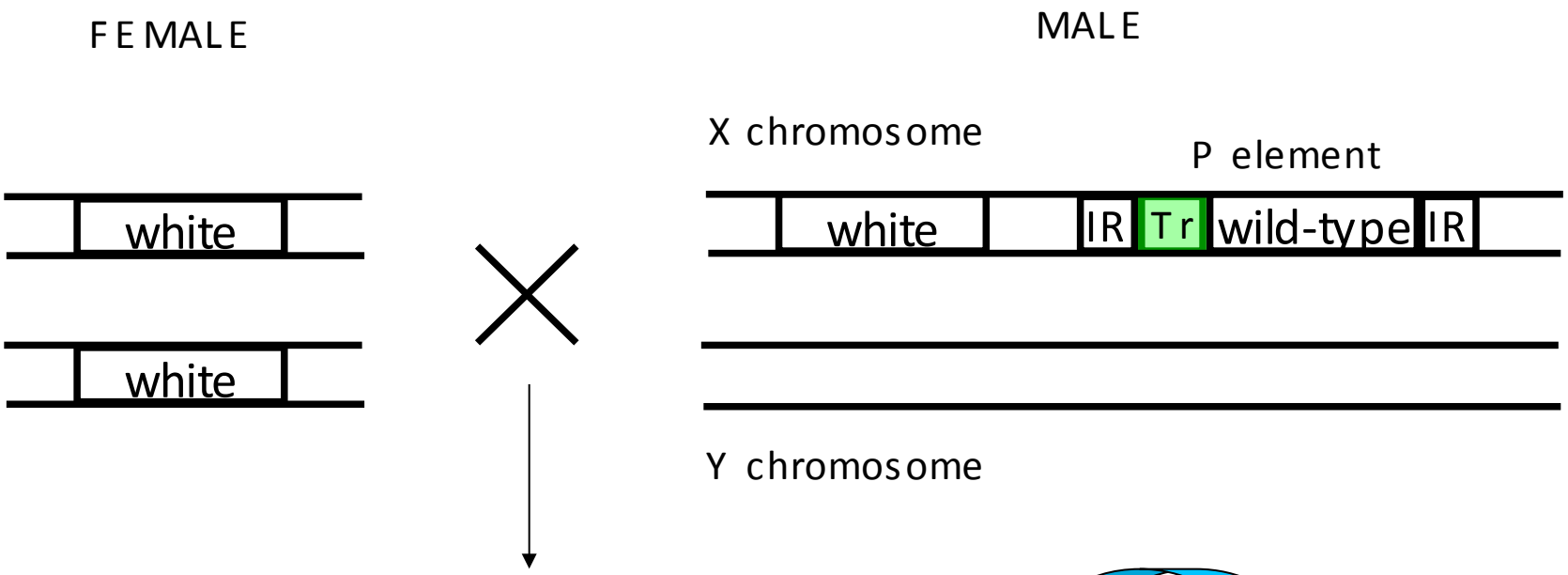
2. Abortive gap repair (Part 1)



2. Abortive gap repair (Part 2)



Measurement of dissociation rate for *P* elements in *D. melanogaster*



Phenotype:	**Interpretation:**
Wild-type female	Non-excision
White-eyed male	Non-insertion
White-eyed female	Excision
Wild-type male	Insertion

Dissociation rate
= 0.05 $TE^{-1}gen^{-1}$

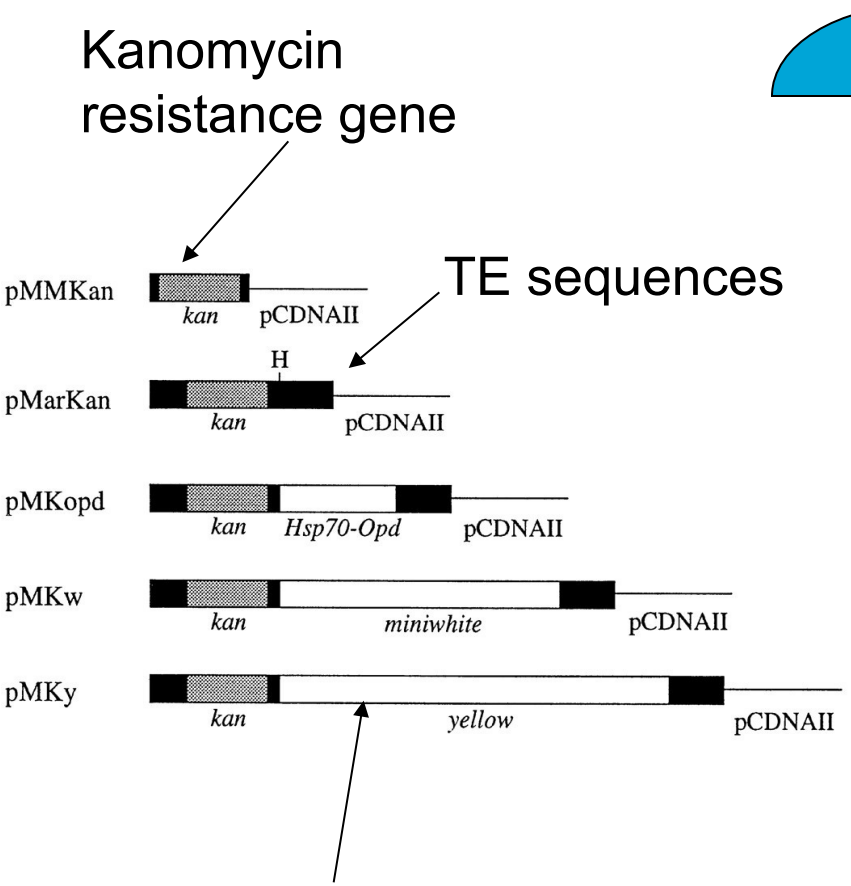
W. R. Engels, *Mobile DNA* (1989).

Internal deletion rates vary between TEs and host species:

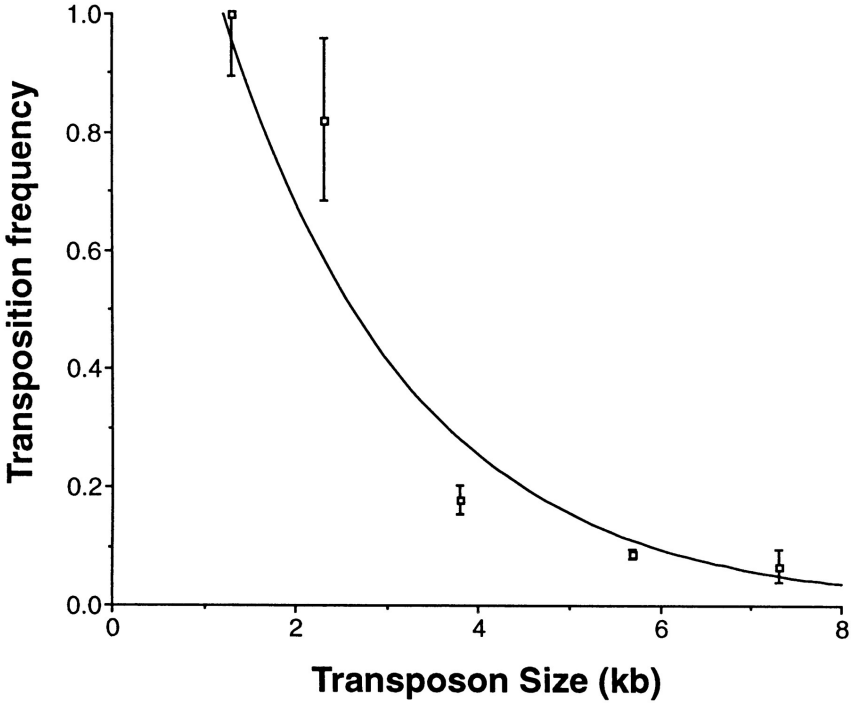
Fast:	**Slow:**
•*P* and *hobo* elements in *Drosophila melanogaster* •*Ds* elements in maize	•*Herves* element in *Anopholes gambiae* remains almost exclusively intact throughout evolutionary history

Question: What rate of dissociation can be tolerated by a TE-mediated disease control strategy?

Question: What if the resistance gene compromises the transposition rate?



Exogenous DNA used to increase transposon size



D. J. Lampe *et al.*, *Genetics* (1988).

Question: What if the resistance gene has an impact on the host fitness?

Fitness cost:	**Fitness benefit:**
•Mounting an immune response is generally associated with an evolutionary cost in insects	•Transgenic mosquitoes have been created that have no noticeable fitness cost when fed on *Plasmodium*-free blood •These mosquitoes are in fact more fit when fed on *Plasmodium*-infected blood

M. T. Marrelli *et al.*, *PNAS* (2007),
L. A. Moreira *et al.*, *Genetics* (2004),
A. R. Kraaijeveld & H. C. Godfray, *Nature* (1997).

Mathematical model:

$x_{(m,n)}(t)$

= proportion of disease vectors having:
m copies of the intact construct and
n copies of the dissociated construct
at time *t*

Total birth rate = Total death rate

Birth rate:

- All TE copies segregate independently

Death rate:

- Function of copy number
- Impact of resistance gene

Changes in host genotype:

Transposition:

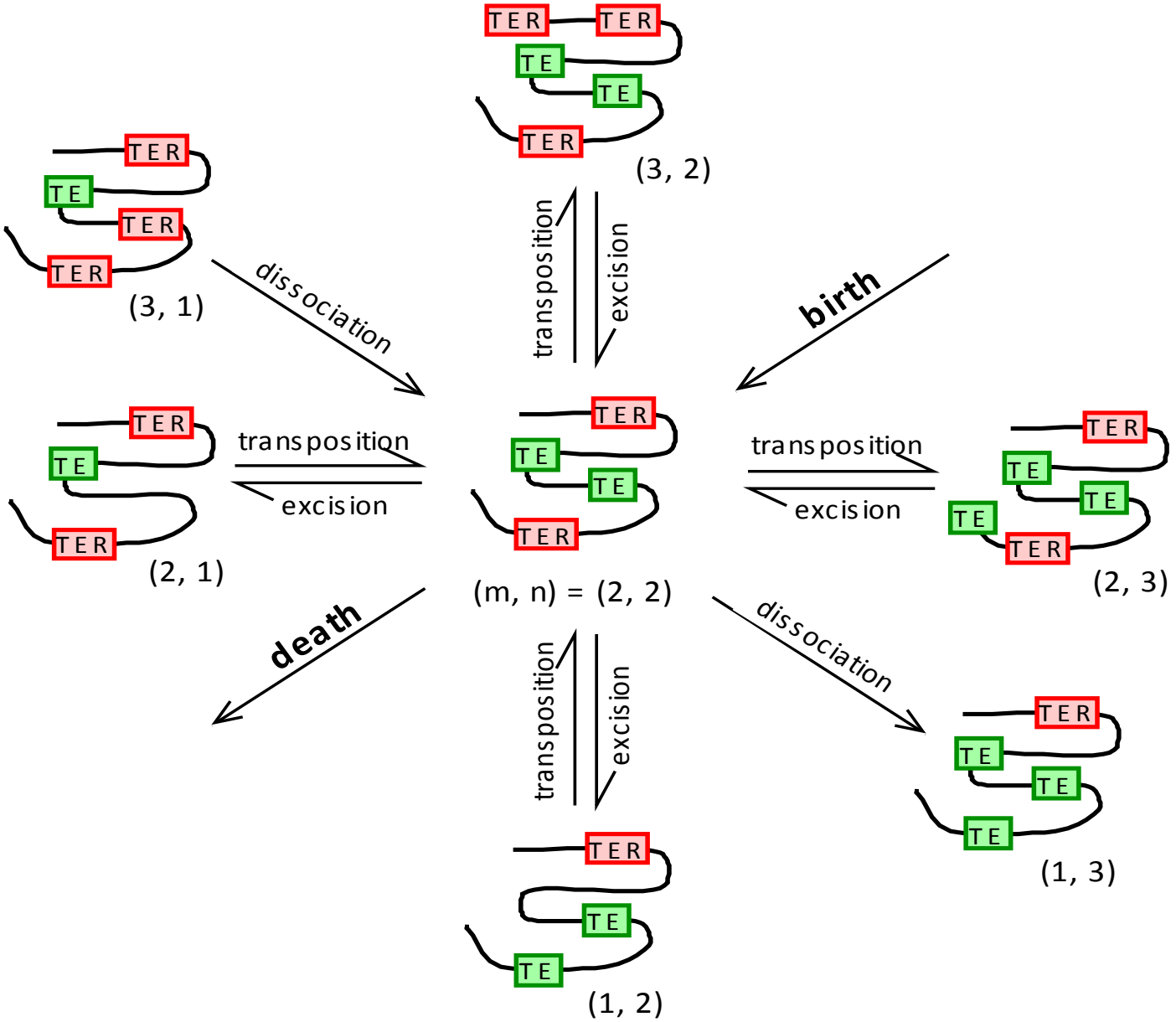
- Repression with increasing copy number
- Handicap of resistance gene

Deletion

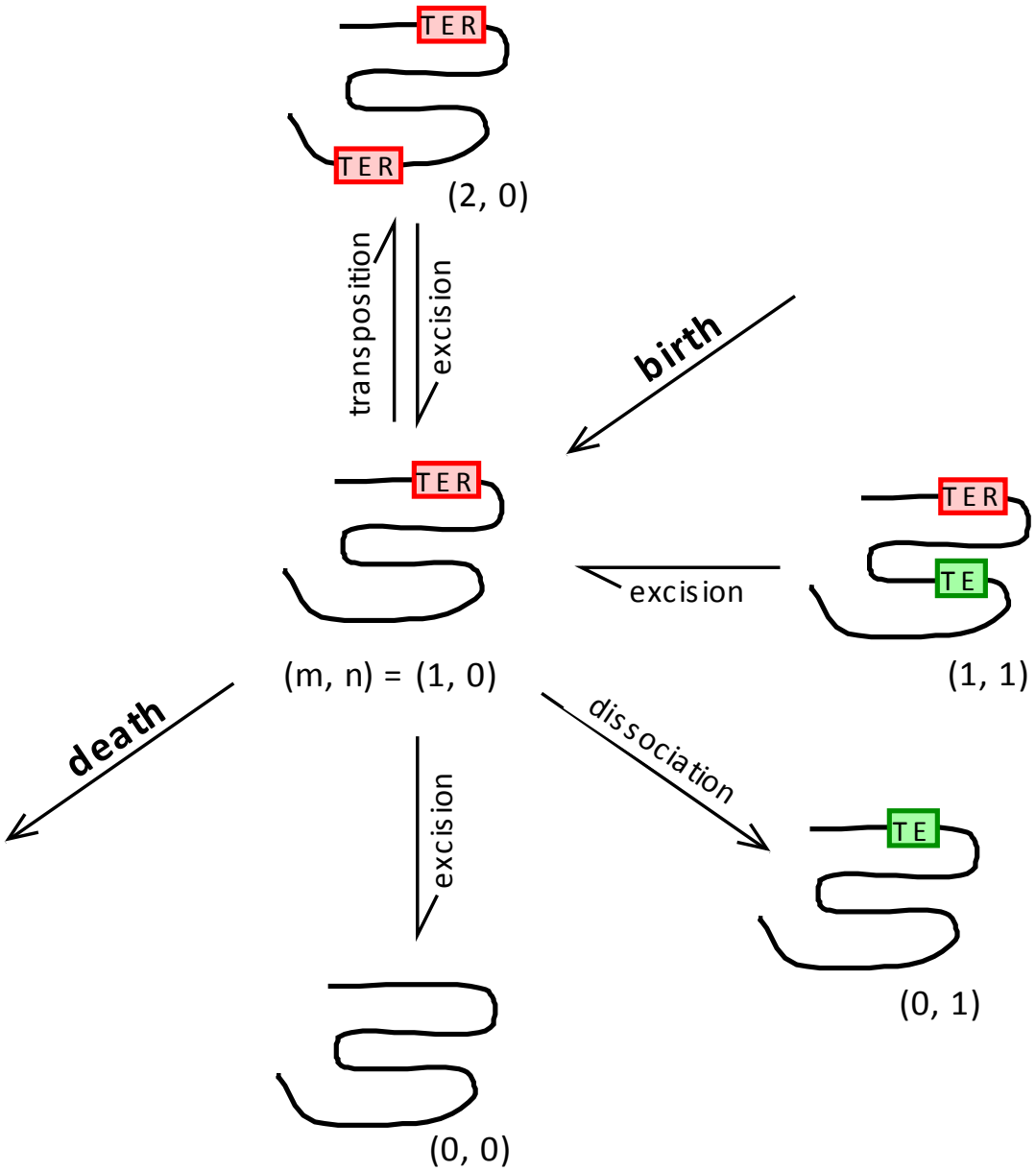
Dissociation:

- Proportional to transposition rate

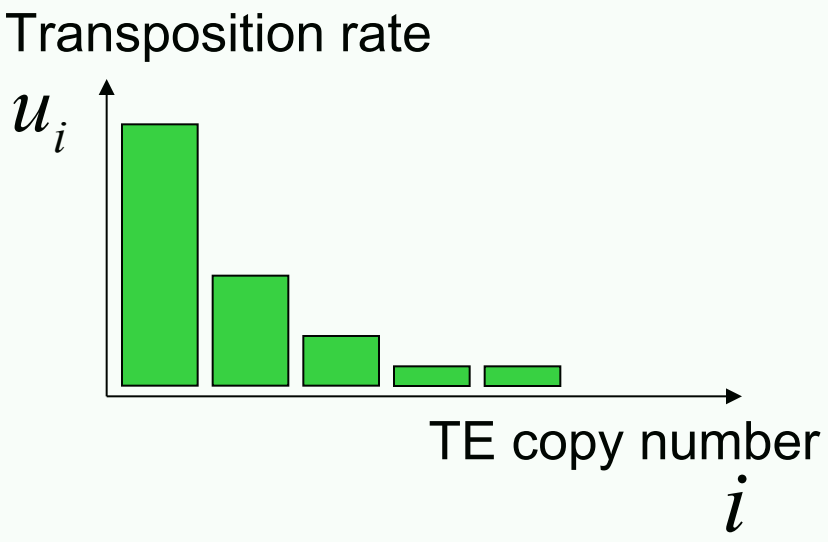
Mathematical model:



Mathematical model:



Repression of transposition

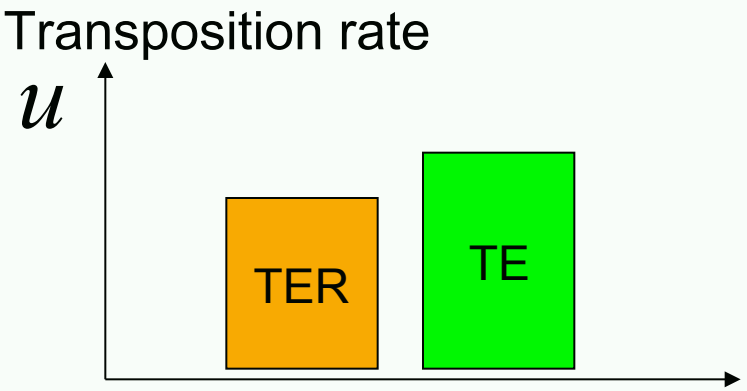


$$u_i = u_1 2^{-c(i-1)}$$

Sources:

- Self repression
- Host repression

Handicap of resistance gene

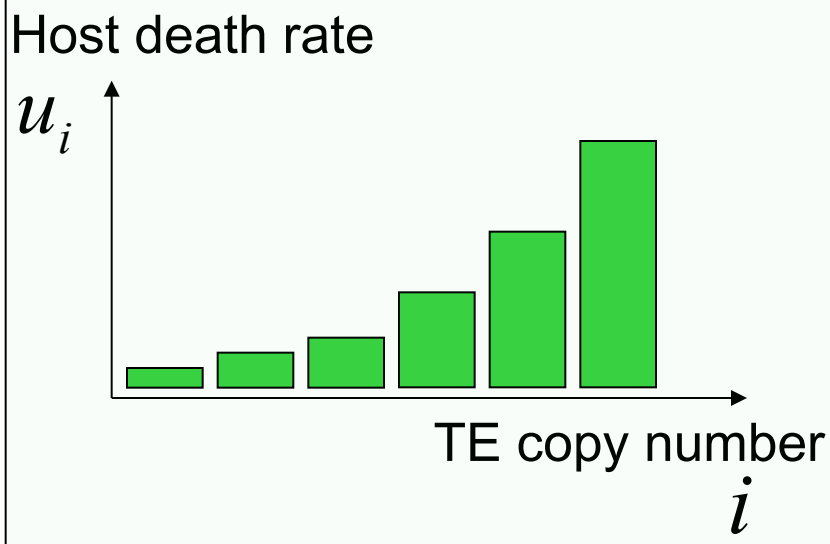


$$u_{TER} = (1-\delta)u_{TE}$$

Default parameter values:

- u_1 = 0.1 $TE^{-1}gen^{-1}$
- c = 3

Host fitness

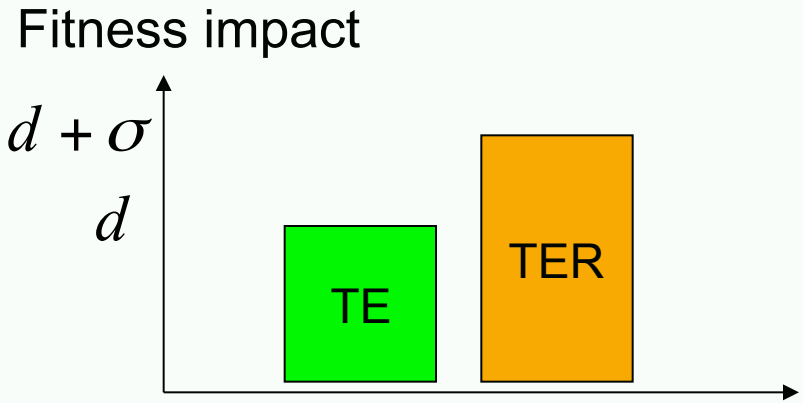


$$\mu_i = 1 + di^p$$

Sources:

- Insertional mutagenesis
- Ectopic recombination
- Act of transposition

Fitness impact of resistance gene

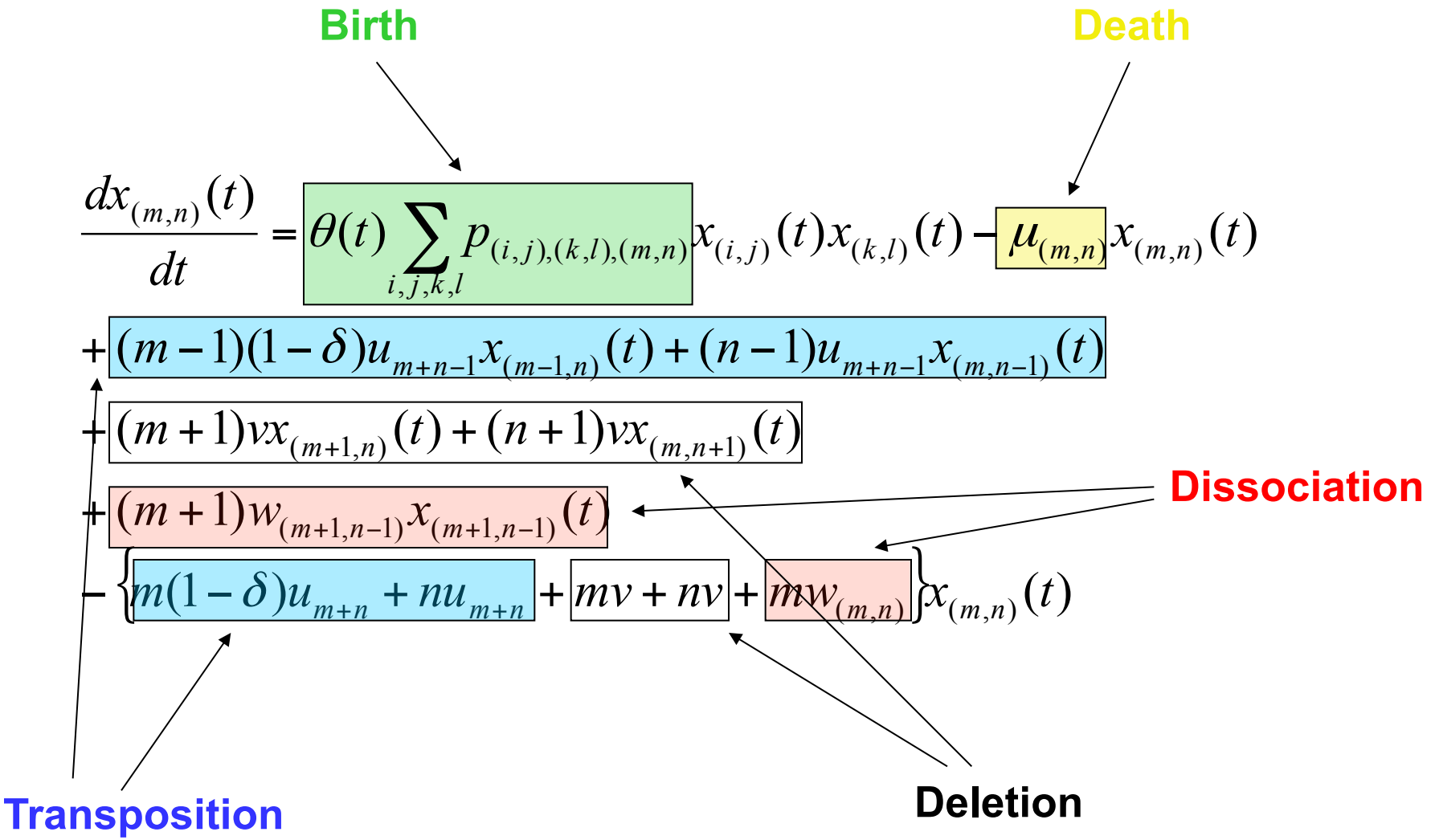


$$\mu_{(m,n)} = 1 + \left(d + \frac{m}{m+n}\sigma \right)(m+n)^p$$

Default parameter values:

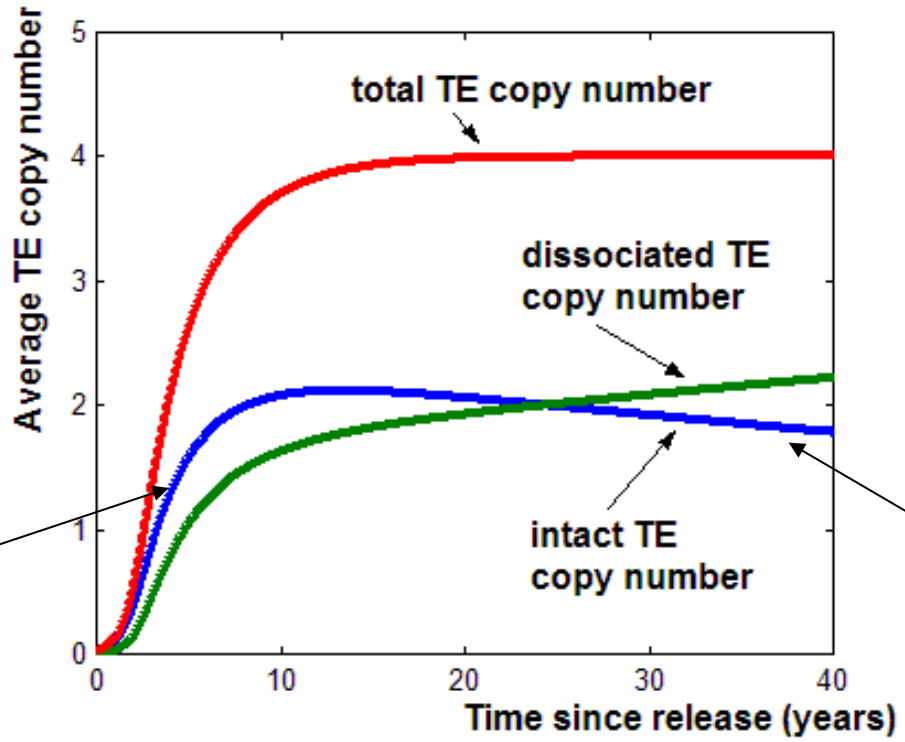
- μ_1 = 0.001 $TE^{-1}gen^{-1}$
- p = 1.5

What this all means mathematically



Loss of resistance gene is most rapid during the early stages of TE spread

Dissociation rate = 0.01 $TE^{-1}gen^{-1}$:

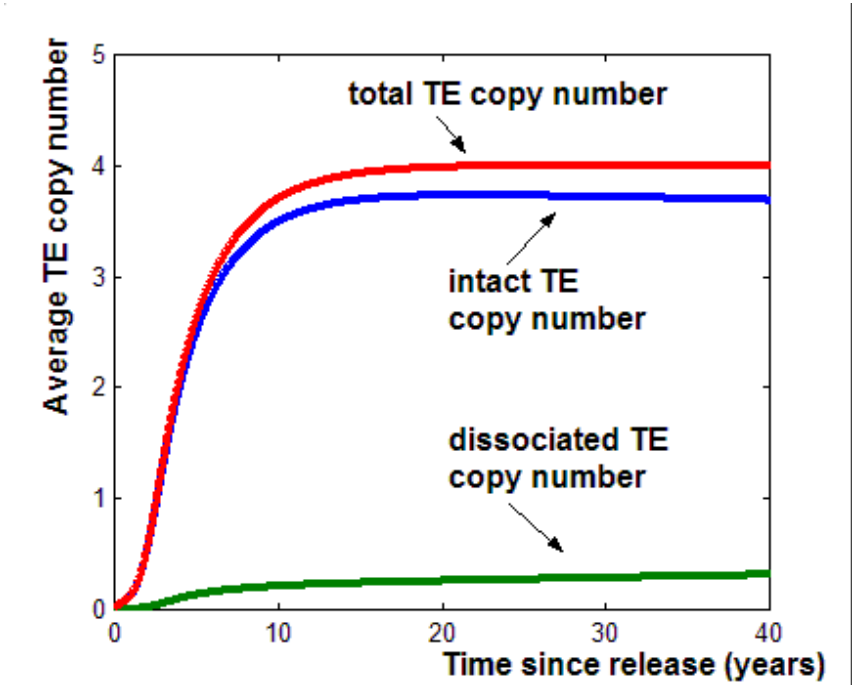


Dissociation often occurs during the act of transposition; hence the proportion of dissociated TEs increases rapidly early on.

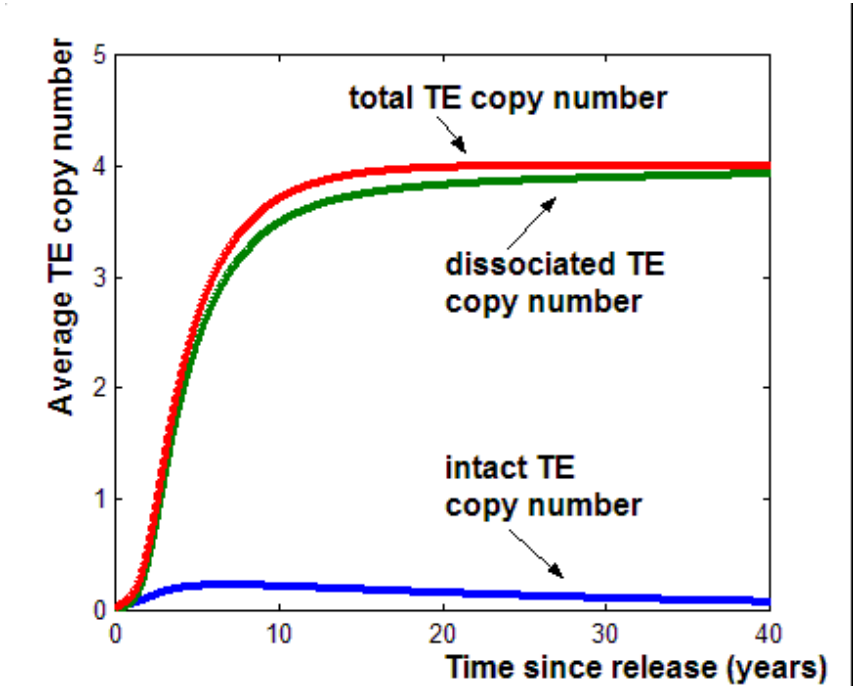
Following equilibrium, transposition still occurs to counteract selection and excision; hence the proportion of dissociated TEs continues to decrease slowly.

Loss of resistance gene depends strongly on dissociation rate

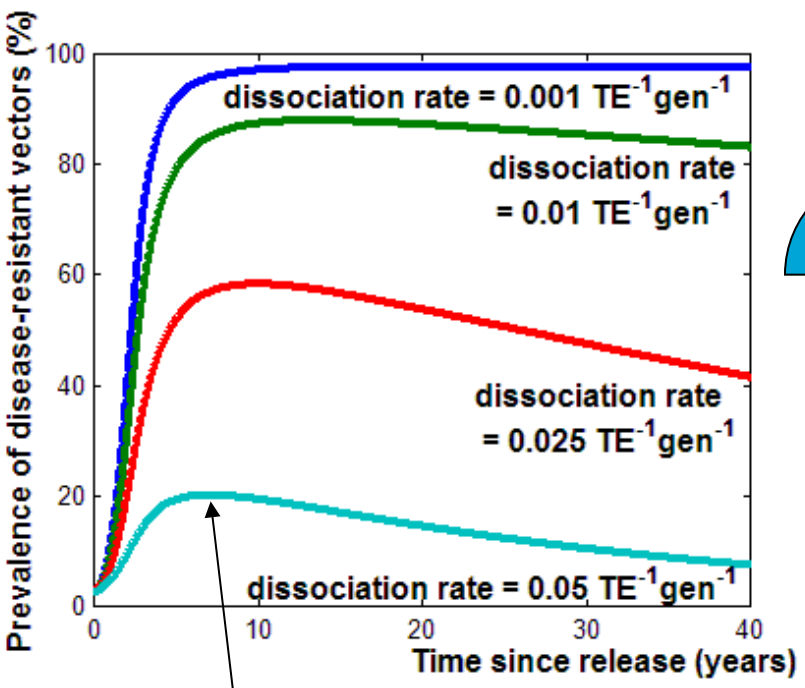
Dissociation rate = 0.001 $TE^{-1}gen^{-1}$:



Dissociation rate = 0.05 $TE^{-1}gen^{-1}$:

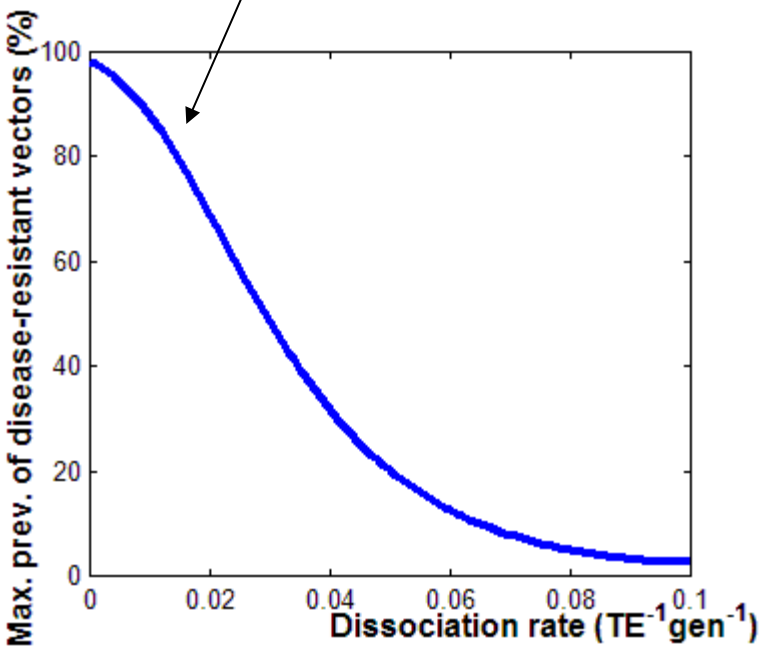


Prevalence of disease-resistant vectors strongly depends on dissociation rate



For *P* elements in *D. melanogaster*, the resistance gene would reach a maximum prevalence of ~20%

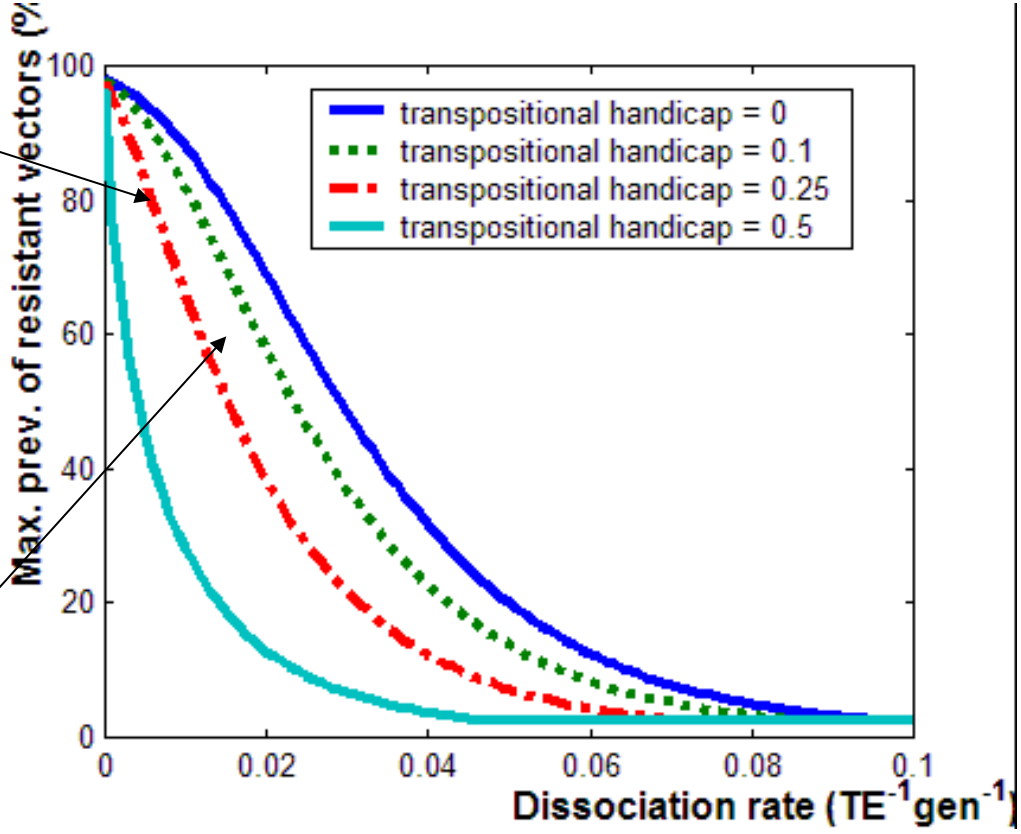
For dissociation rates < 0.013 $TE^{-1}gen^{-1}$, the disease resistance gene reaches a maximum prevalence of < 80%



Transpositional handicap reduces the prevalence of disease-resistance

For transpositional handicaps > 0.25, dissociation rate must be extremely small to achieve a high maximum prevalence

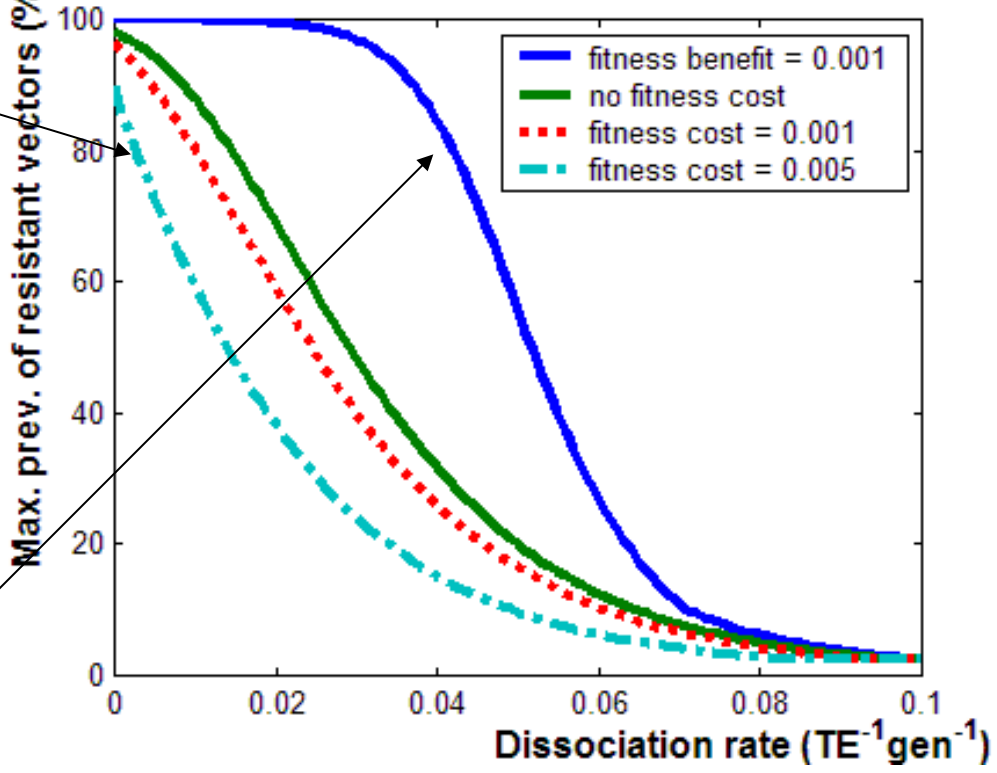
For a *Himar1* element increased in size by ~75%, the transpositional handicap is ~0.18



Fitness benefit greatly increases the prevalence of disease-resistance

For a fitness cost > 0.005 TE^{-1}, dissociation rate must be extremely small to achieve a high maximum prevalence

For a fitness benefit as small as 0.001 TE^{-1}, the dissociation rate required for disease control is greatly relaxed



Model conclusions

Dissociation rate:

- Critical parameter in determining the fate of the gene drive strategy
- Recommend dissociation rate < 0.01 $TE^{-1}gen^{-1}$
- If the dissociation rate is too large, then the introduction of resistance genes is reversible within a human time frame

Selective advantage of resistance gene:

- Not sufficient to drive resistance gene into population on its own
- When combined with gene drive strategy, greatly improves chances of success
- A fitness benefit ~ 0.001 TE^{-1} will make disease control realistic for moderate dissociation rates

Future research directions

- **Molecular biology:** Measure dissociation rates once transposition has been observed in host species, TEs of interest
- **Ecology:** Continue to seek accurate measurements of fitness consequences of disease-resistance genes
- **Epidemiology:** Imbed the spread of a resistance gene within a model of the epidemiology of malaria or Dengue fever

Acknowledgements

- **Molecular biology:** Prof. David O'Brochta
- **Vector biology:** Prof. Charles Taylor
- **Mathematical modeling:** Assoc. Prof. Tom Chou