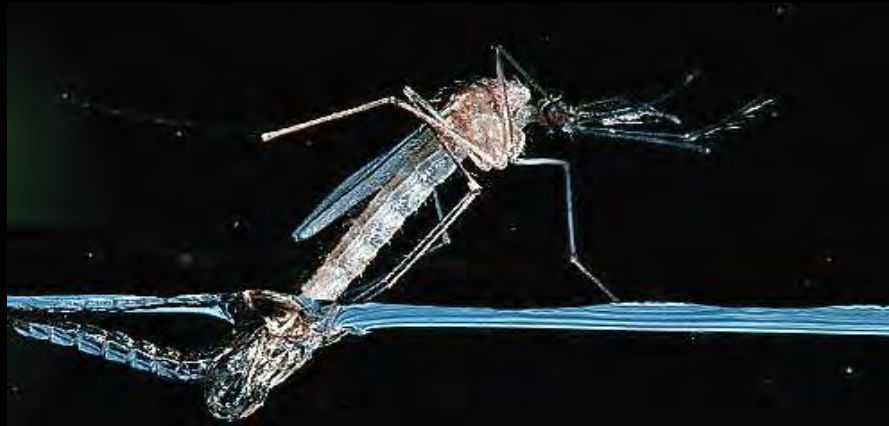


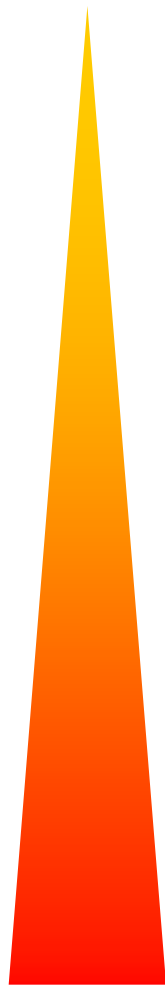
Evolutionary Systems Biology

Resistance gene replacement in the mosquito *Culex pipiens*



Pierrick LABBE, Nicolas SIDOS, Michel
RAYMOND, Thomas LENORMAND
and Mylène WEILL

Evolutionary Systems Biology



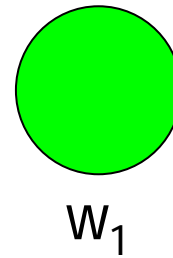
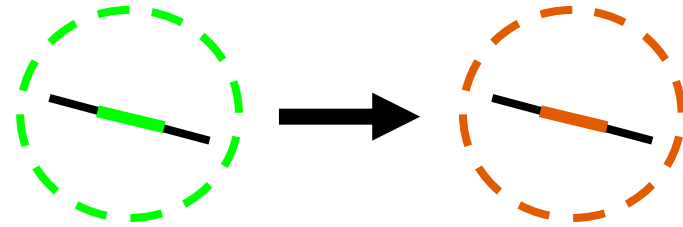
Molecule



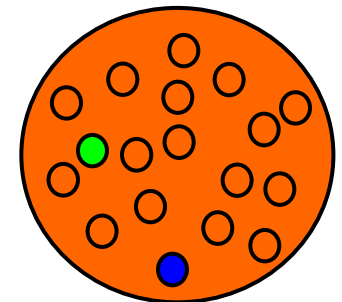
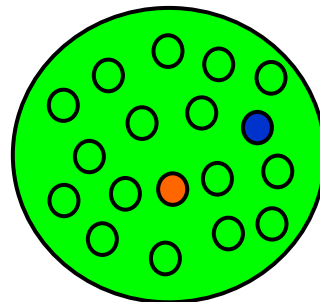
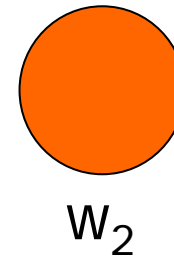
Individual



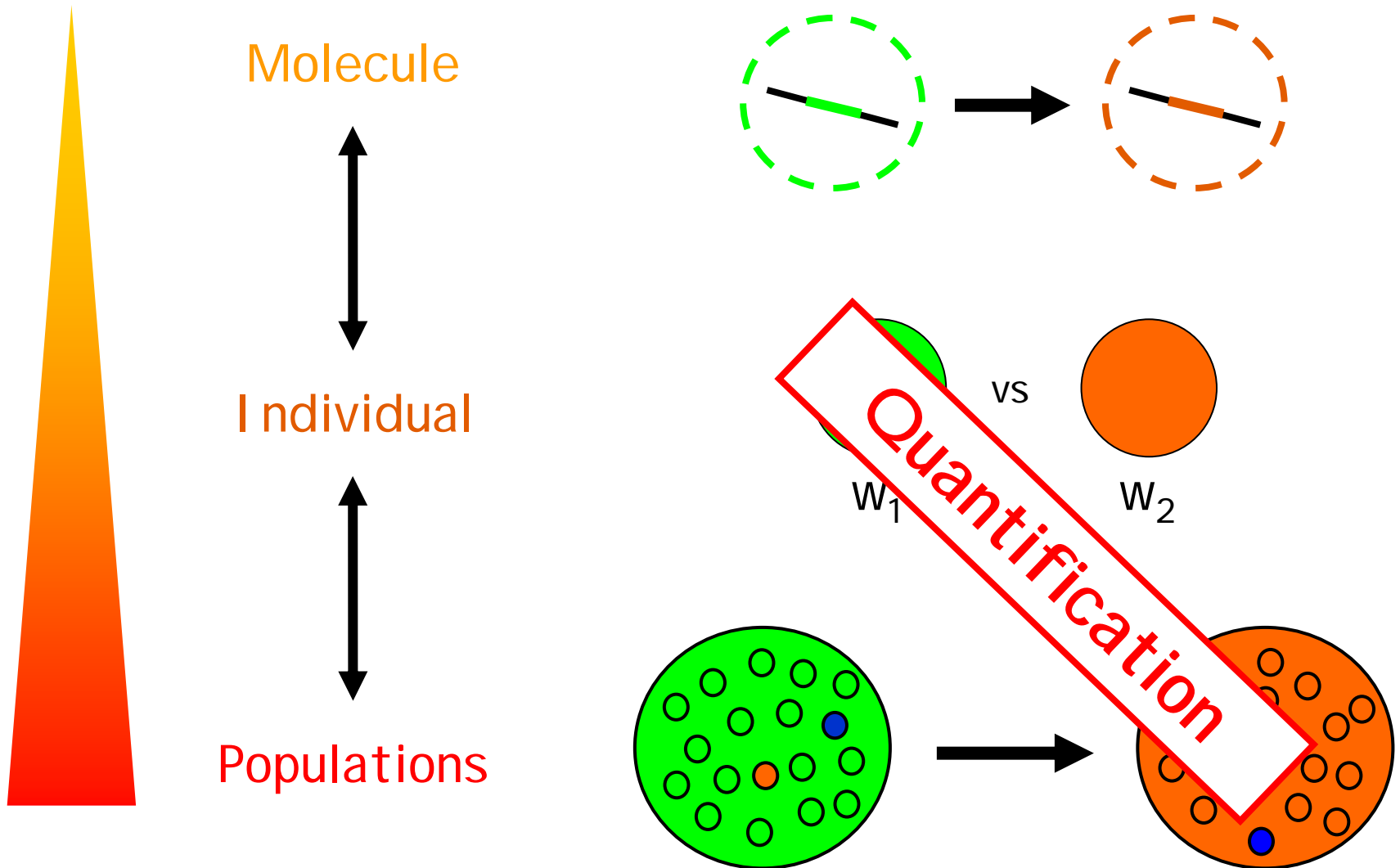
Populations



VS



Evolutionary Systems Biology

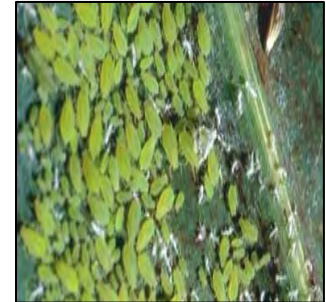


Insecticide resistance

→ Insecticides treatments against various pests

↳ Resistance

= Adaptation towards insecticides



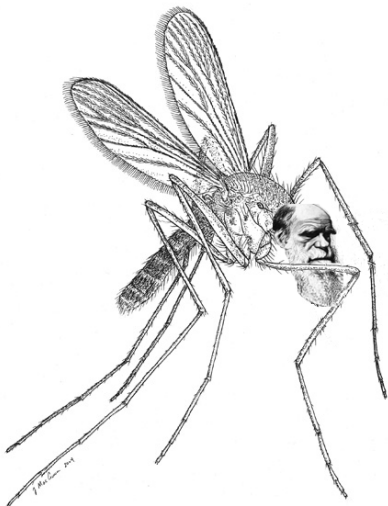
Insecticide resistance

→ Insecticides treatments against various pests

↳ Resistance

=Adaptation towards insecticides

→ Contemporary evolution under natural selection



→ Known selective agent

→ Known biochemical and molecular basis

→ Few genes with major effects

→ Fast evolution

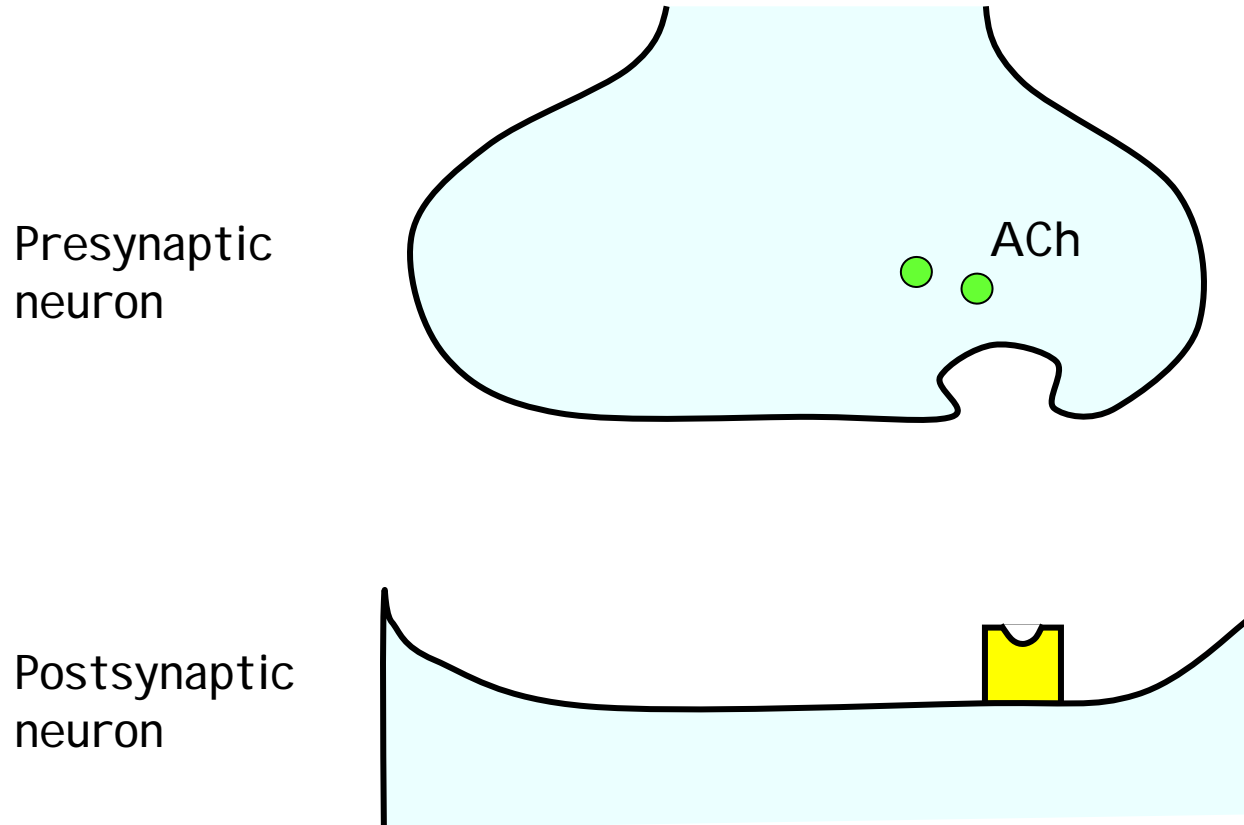
Culex pipiens resistance to OP

- Studied since ca. 40 years
 - Disease **vector**
(West Nile Virus, filariasis, etc.)
 - **Nuisance** (biting)

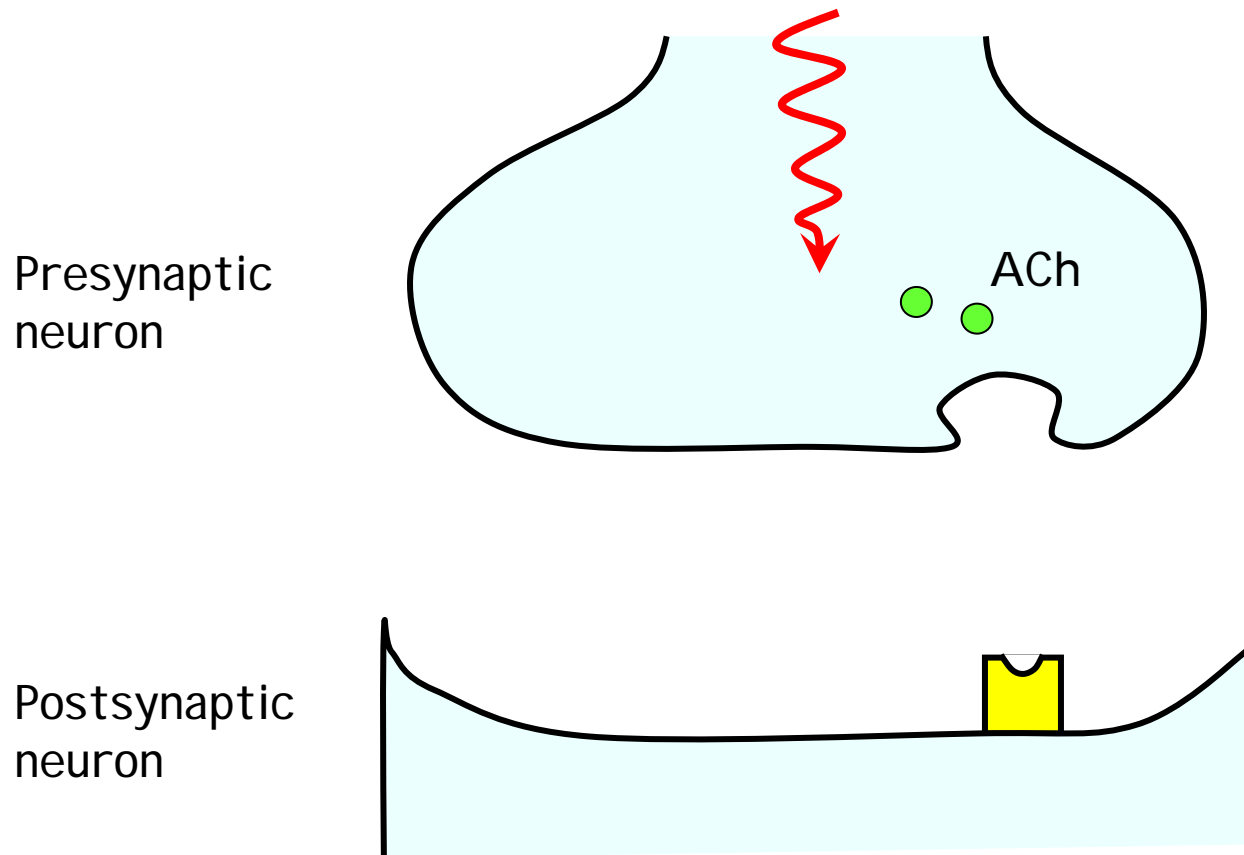
- 2 majors mechanisms of resistance
 - Target-site **mutation**
 - Insecticide **detoxification**



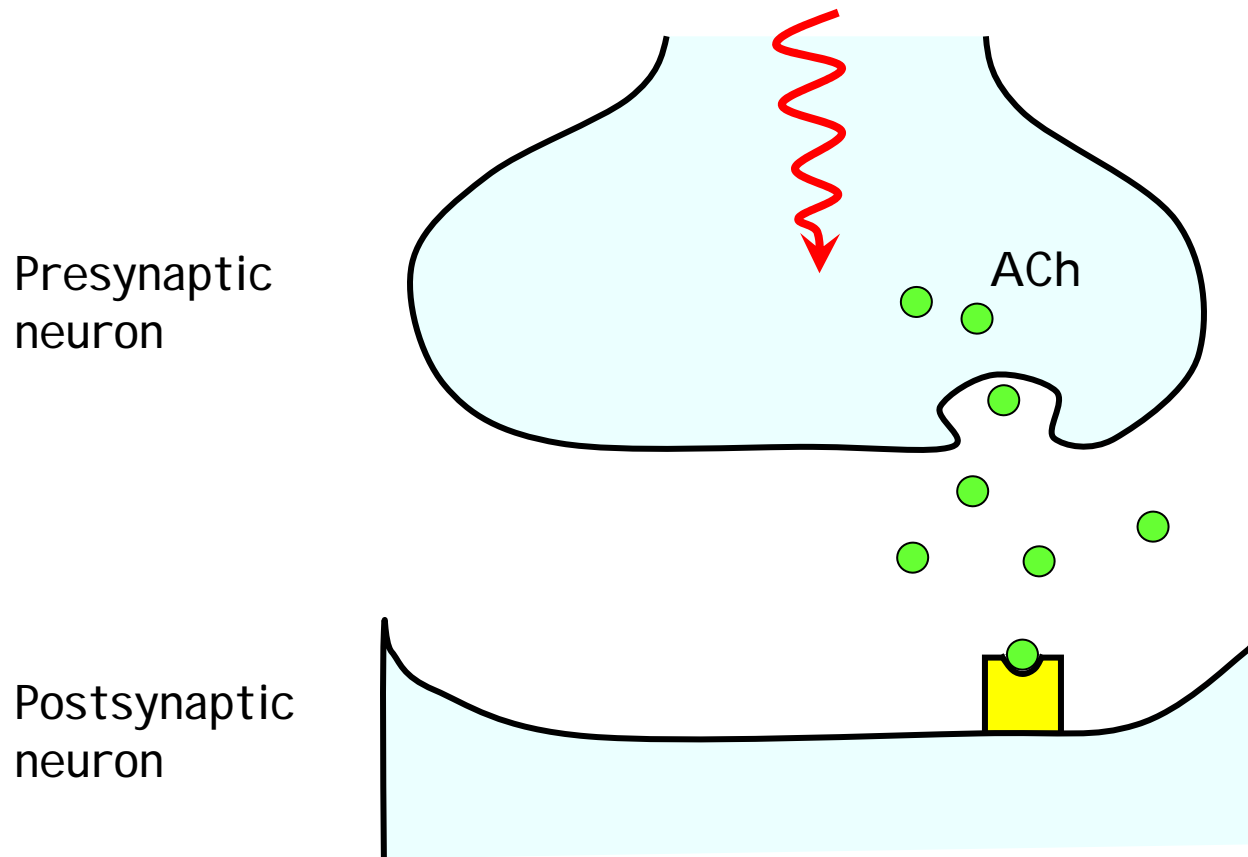
OP mode of action



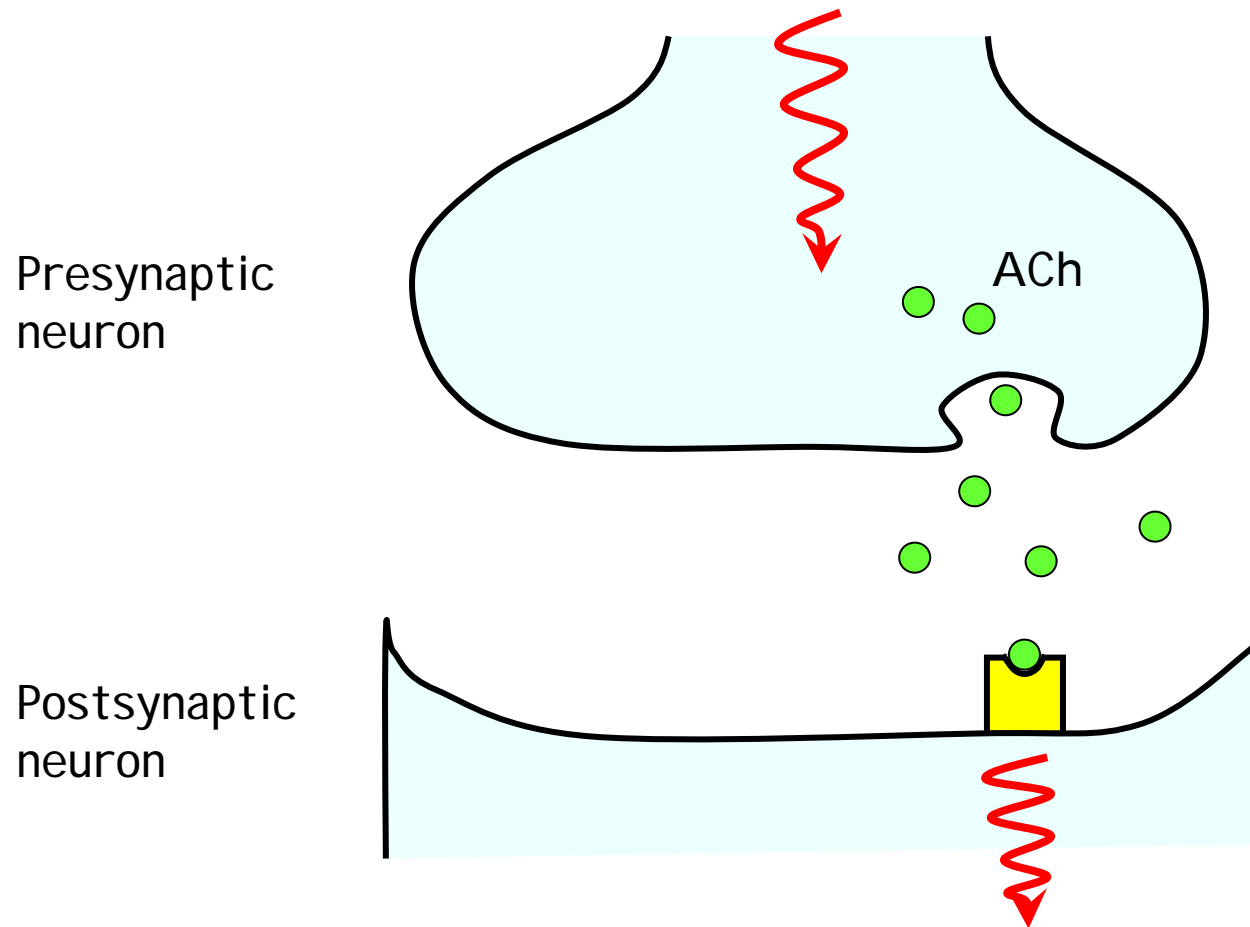
OP mode of action



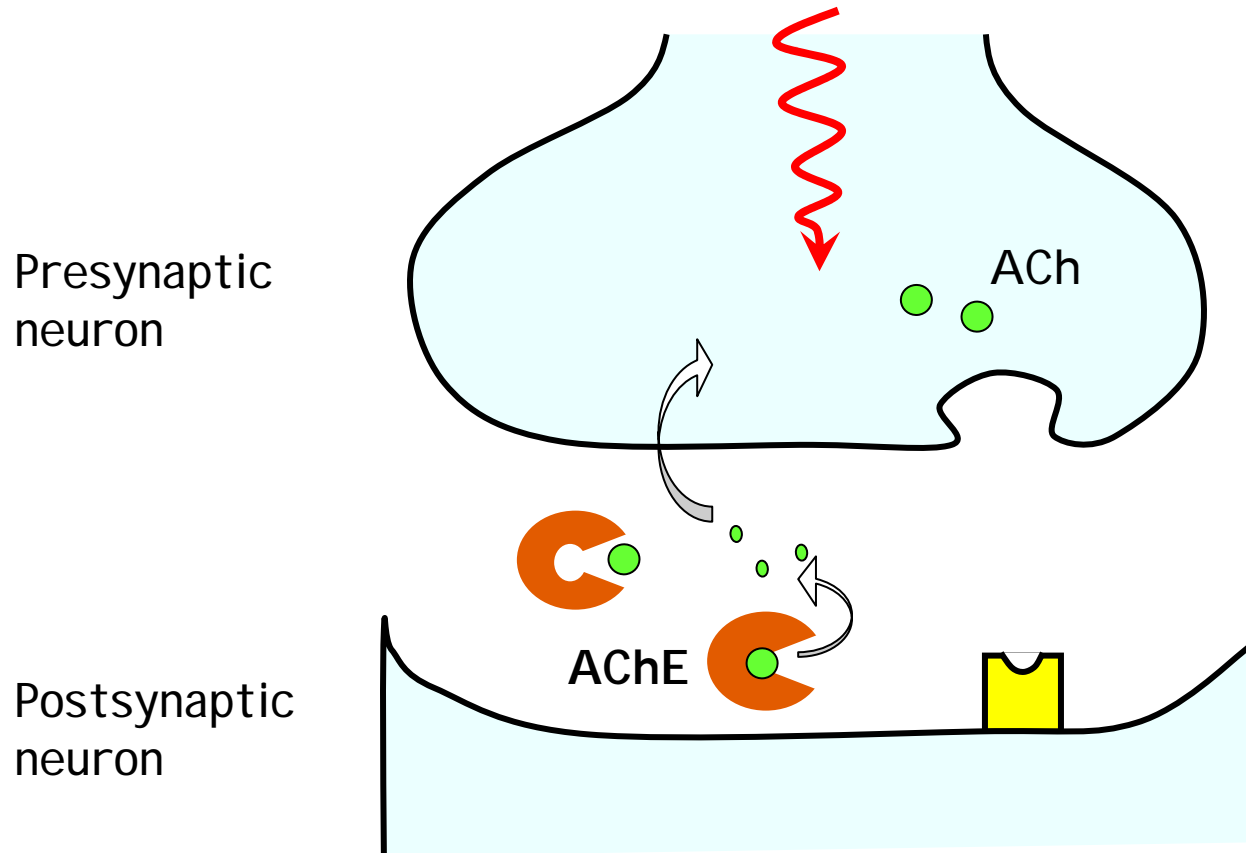
OP mode of action



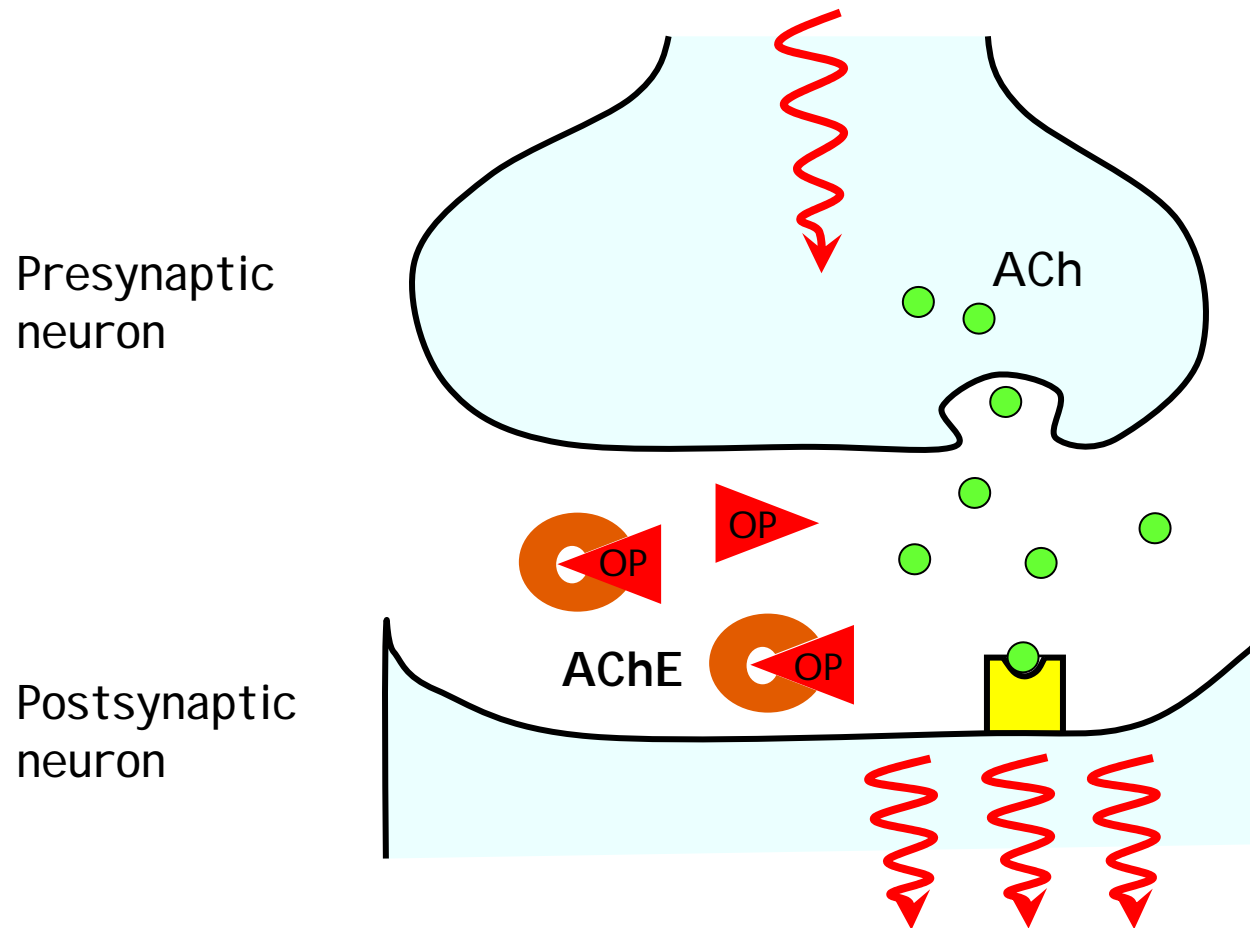
OP mode of action



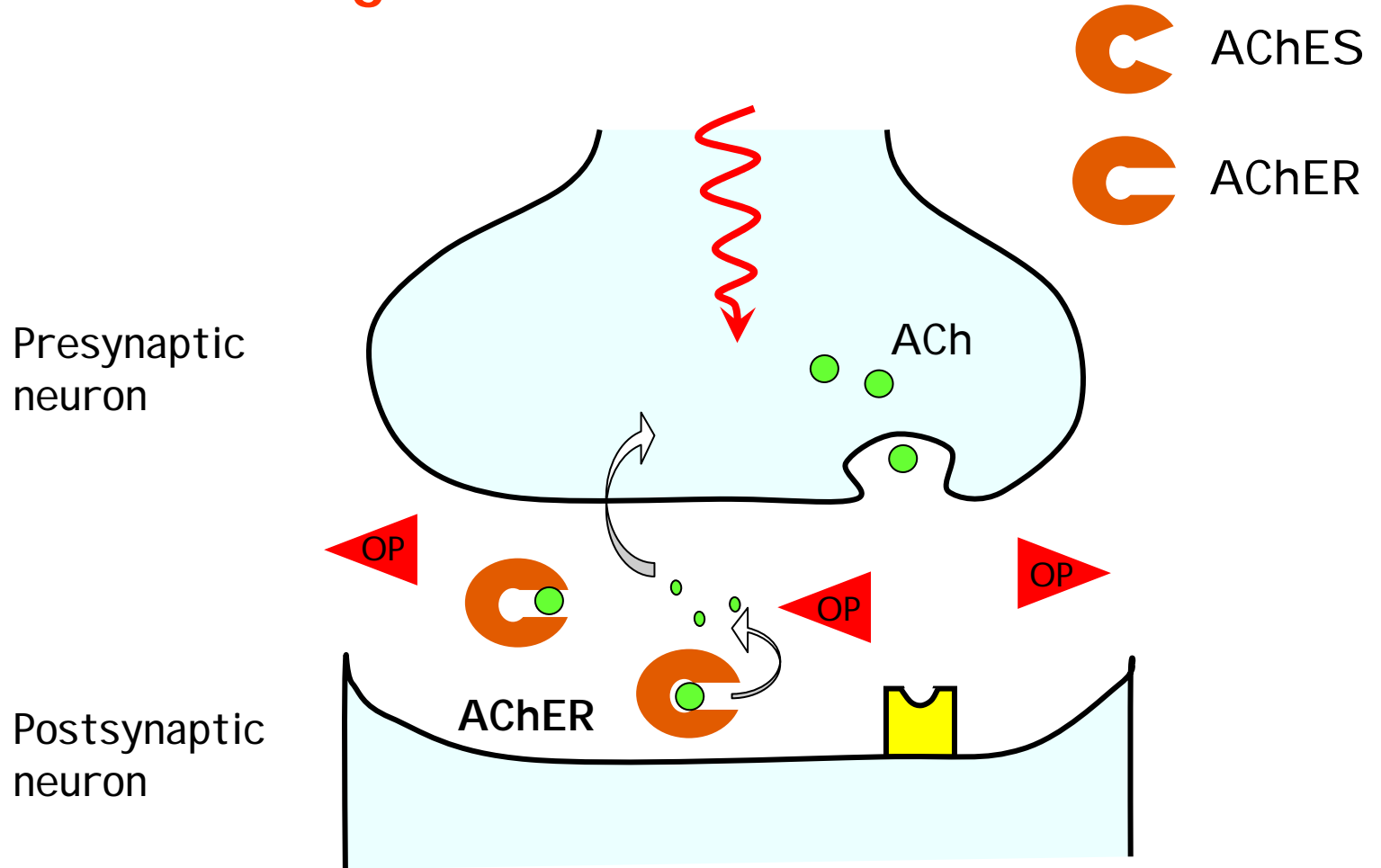
OP mode of action



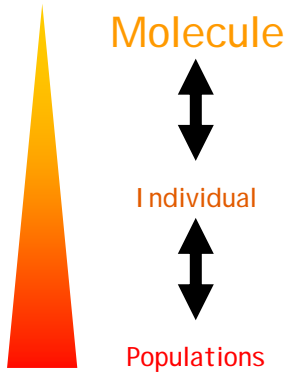
OP mode of action



Target-site resistance



A DNA mutation



Locus *ace-1* → a **unique mutation** (G119S)

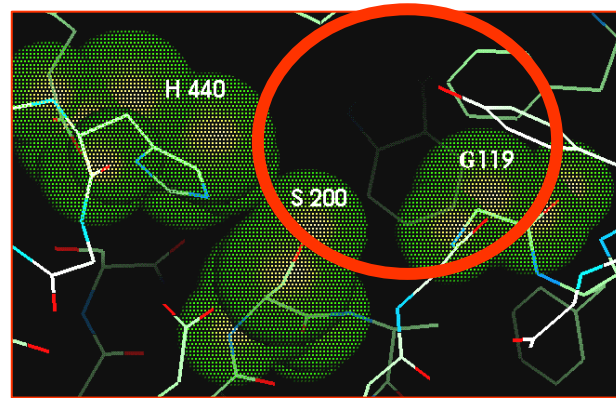
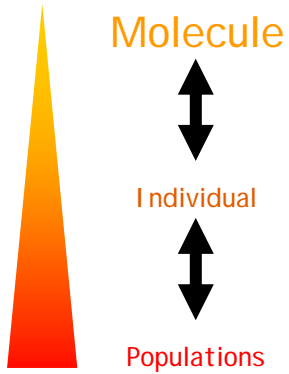
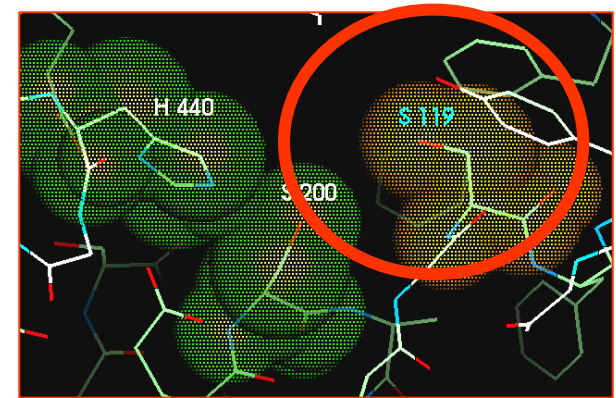


→ **5 independent** occurrences in *C. pipiens*

→ **Identical mutation** in
various insects

Weill et al. *Nature* 2003
Weill et al. *Current Biol* 2004
Alout et al. *JMedEntomol* 2007

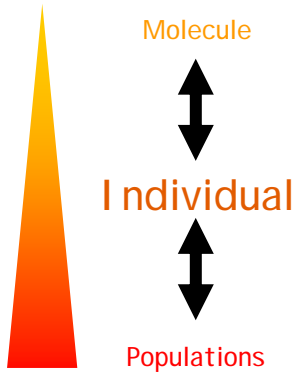
A protein modification

*ace-1^S**ace-1^R*

Steric hindrance → binding of insecticides

BUT → also binding of ACh

→ AChE1 activity reduction >60%



Resistant individual fitness

→ Resistance is an **advantage** in insecticide treated area

→ **BUT** there is a fitness **cost** of resistance

- **Mortality** > overwintering females (50% to 70%)
- **Developmental** time > (+8%)
- Mating **competition** < 3X
- Larval **predation** >2x
- **Wolbachia** density >

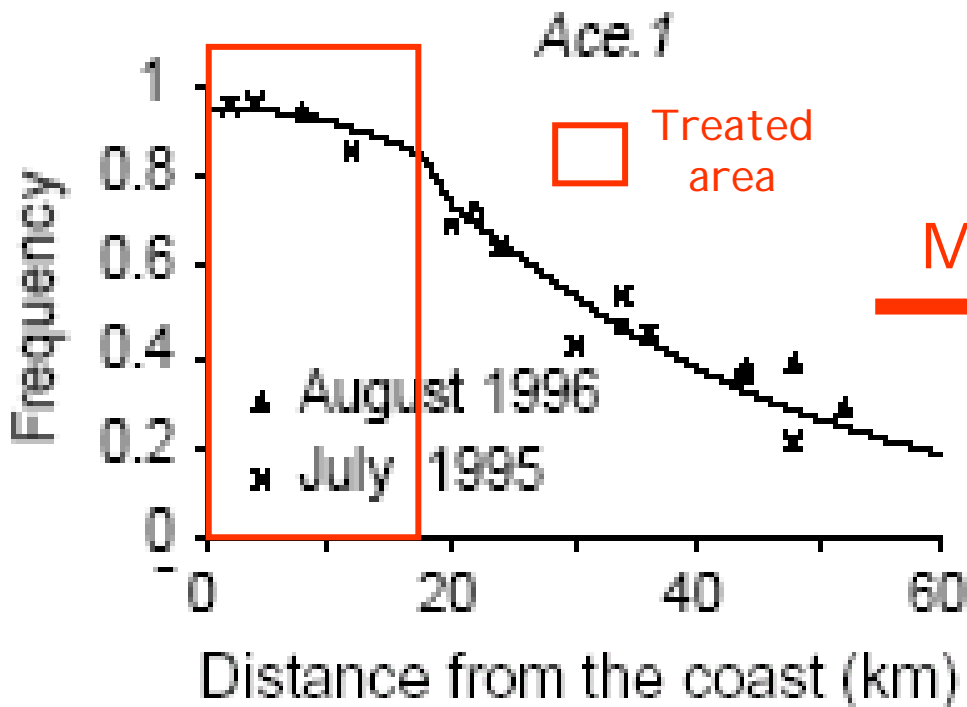
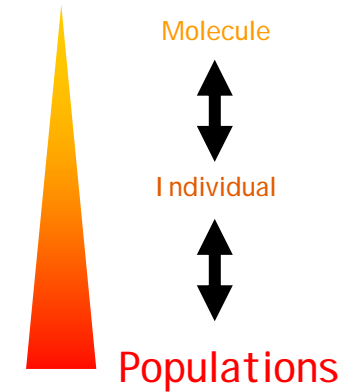
Berticat et al. *Genet Res* 2002

Berticat et al. *Proc R Soc Lond* 2002

Duron et al. *Evolution* 2006

Populations dynamics

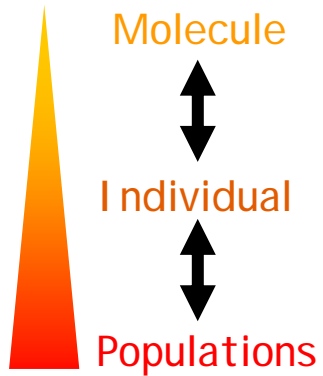
Fitnesses \rightarrow resistance allele frequency **cline**



| <i>W</i> | T | NT |
|----------|-------------------|-------------------|
| SS | 0.75 0.58-0.72 | 1 |
| RS | 0.75 0.66-0.83 | 1 0.99-1 |
| RR | 1 | 0.63 0.63-0.72 |

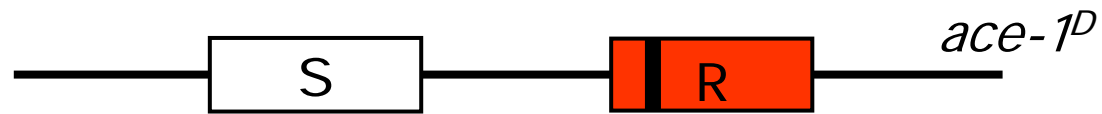
Lenormand et al. *Nature* 1999

Labbé et al. PLoS Genet 2007



New mutations: duplications

→ 12 different alleles in various places



→ Restore AChE1 activity → Spread in populations

→ Sometimes suffer from an additional cost
(probably inversions)

→ Similar duplication in *An. gambiae*

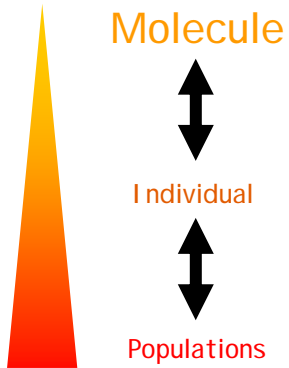
Djogbénou et al. *PLoS One* 2009

Labbé et al. *MBE* 2007

Labbé et al. *PLoS Genet* 2007

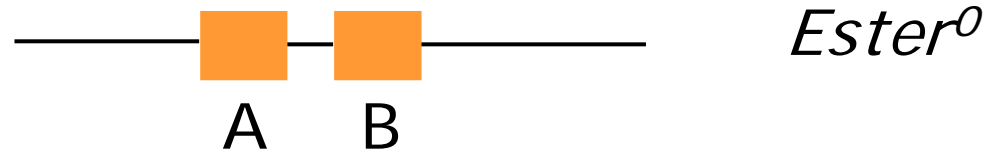
Lenormand et al. *Evolution* 1998

Bourguet et al. *Biochem Genet* 1996

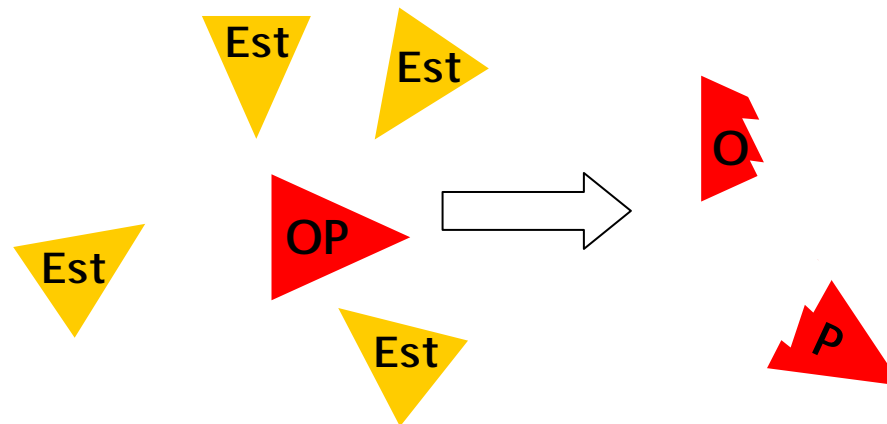


Insecticide detoxification

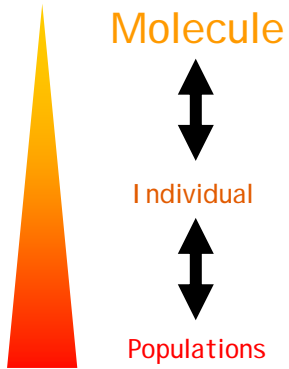
Second mechanism of resistance →
generalist carboxyl esterases



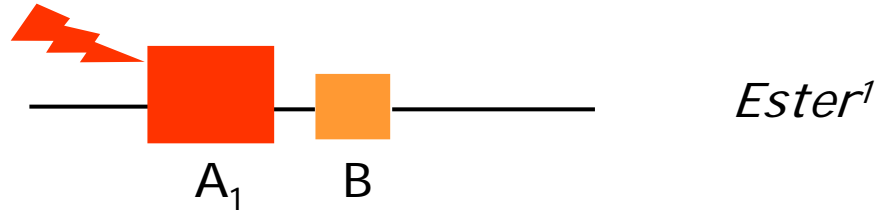
➔ Hydrolyse the ester bond within OP → inactivation



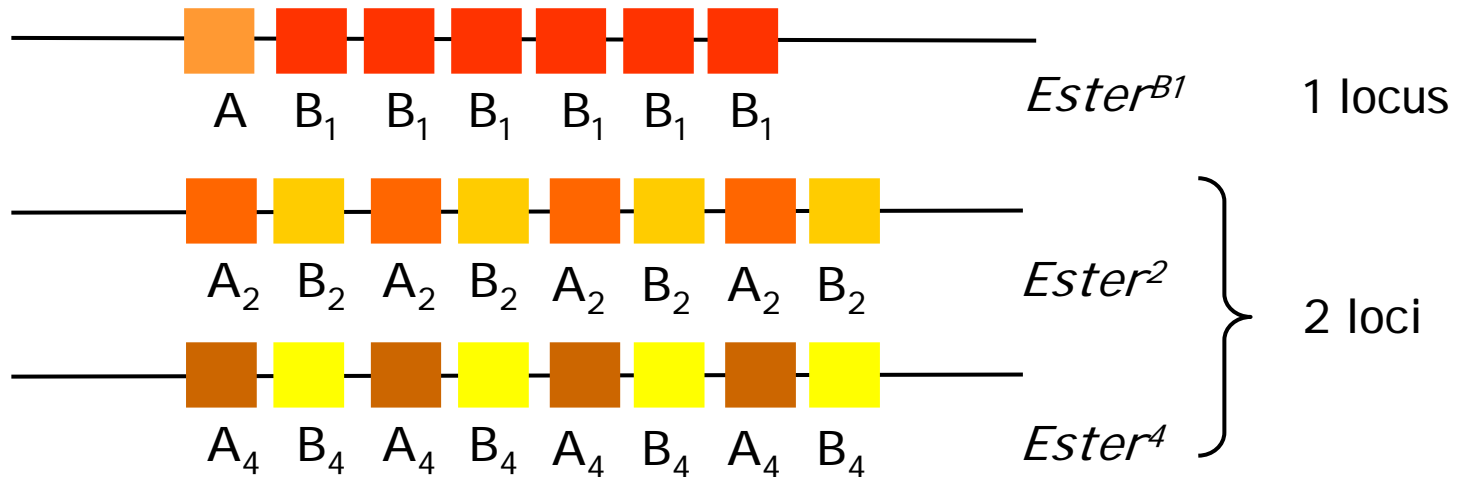
Esterases overproduction

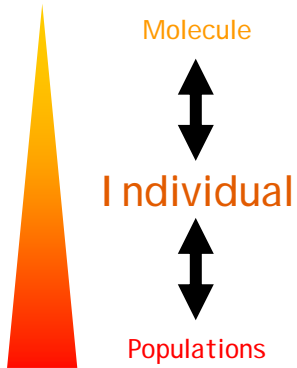


→ Up-regulation



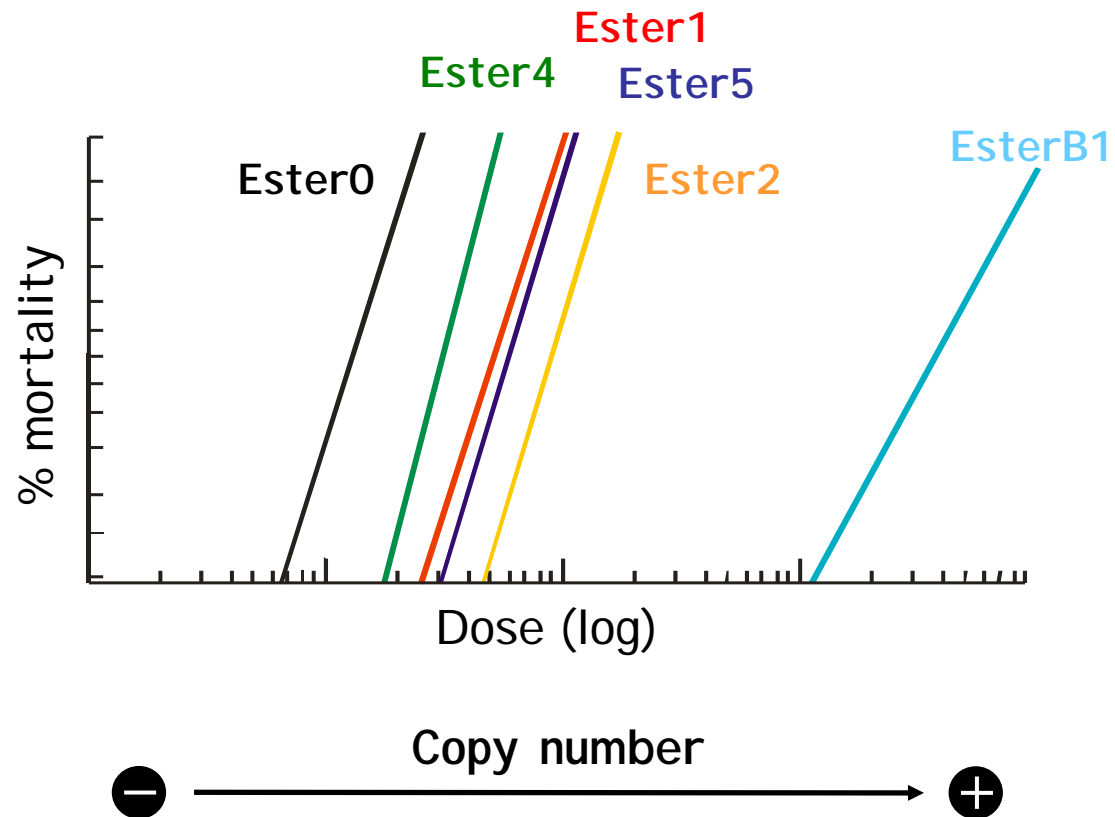
→ Gene amplification





Individual phenotypes

→ Different resistance levels conferred



Individual phenotypes



Molecule
 ↔
 Individual
 ↔
 Populations

→ Different **costs** of resistance

- Males mating **competition**
- **Development** time
- Fluctuating **asymmetry**
- Larval **mortality**
- **Fecundity**
- **Predation**
- *Wolbachia* density

Varies among
 resistance
alleles

Bourguet et al. *Evolution* 2004

Berticat et al. *Genet Res* 2002

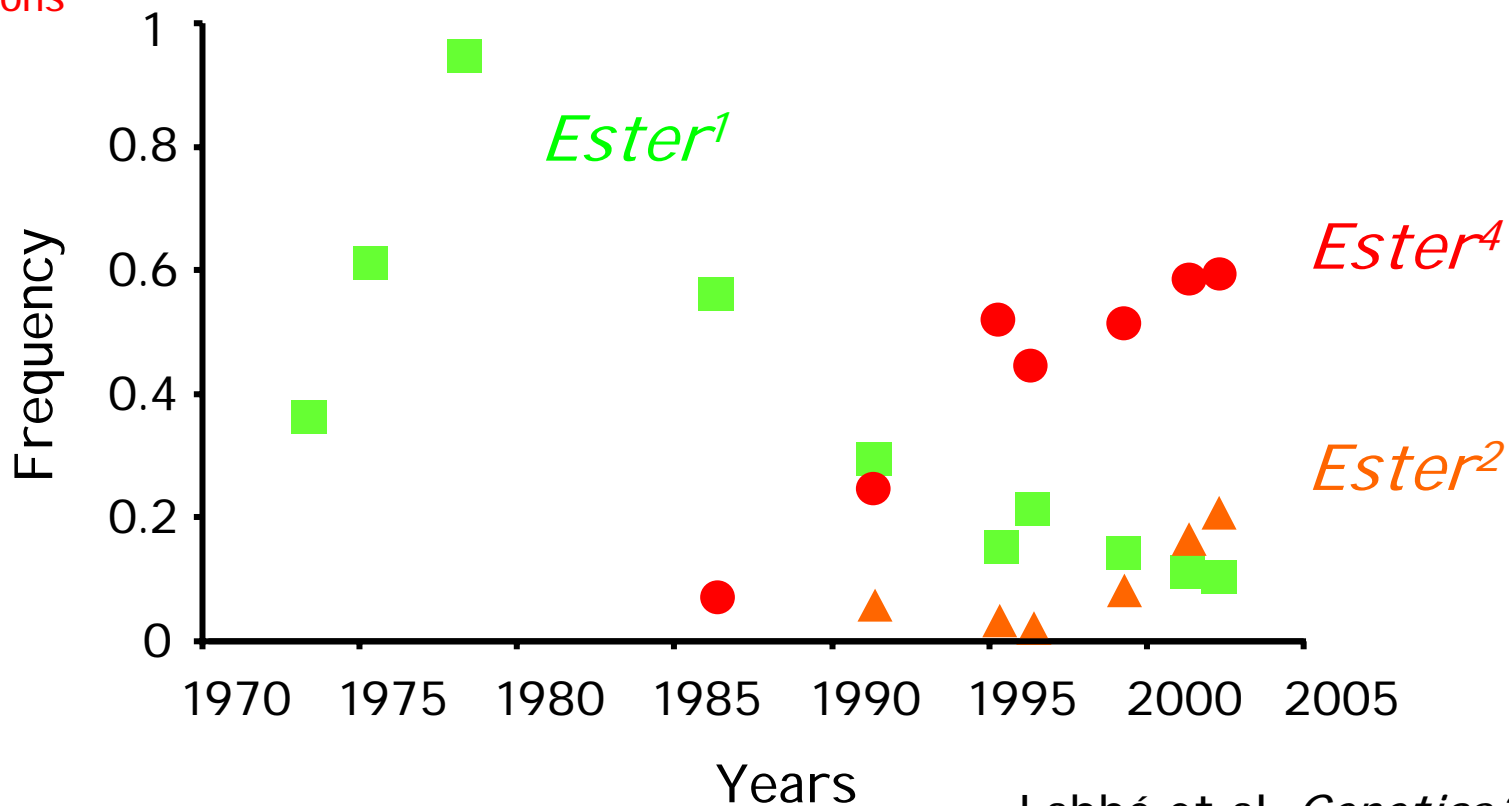
Berticat et al. *Proc R Soc Lond* 2002

Duron et al. *Evolution* 2006

Populations evolution

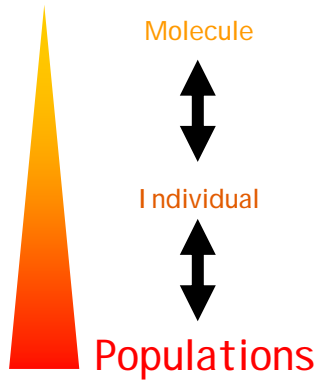
→ In Montpellier area → 3 alleles

↳ Allele replacement



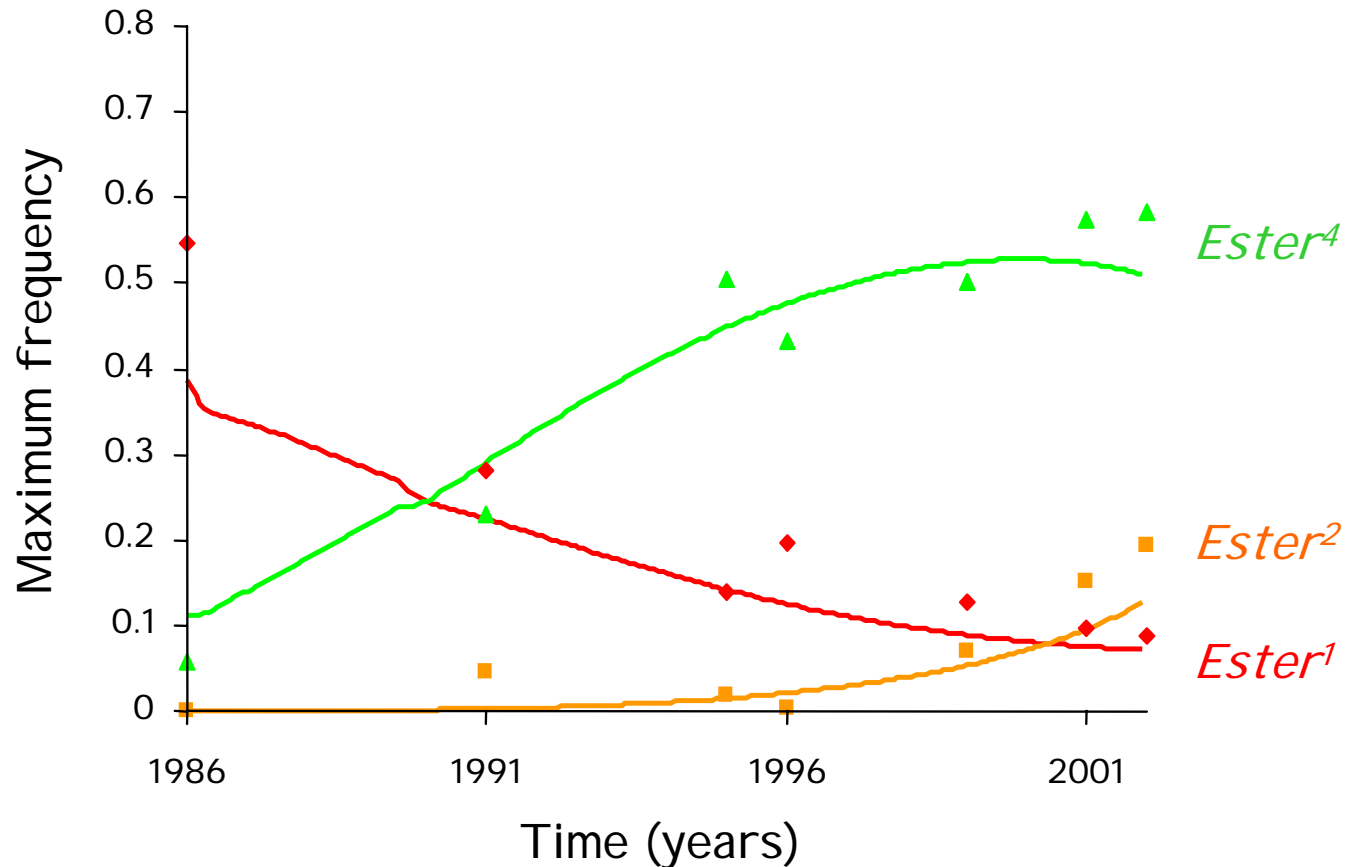
Labbé et al. *Genetics* 2009

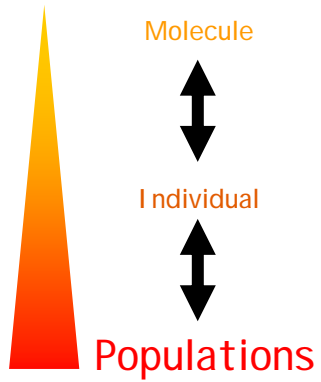
Guillemaud et al. *Evolution* 1998



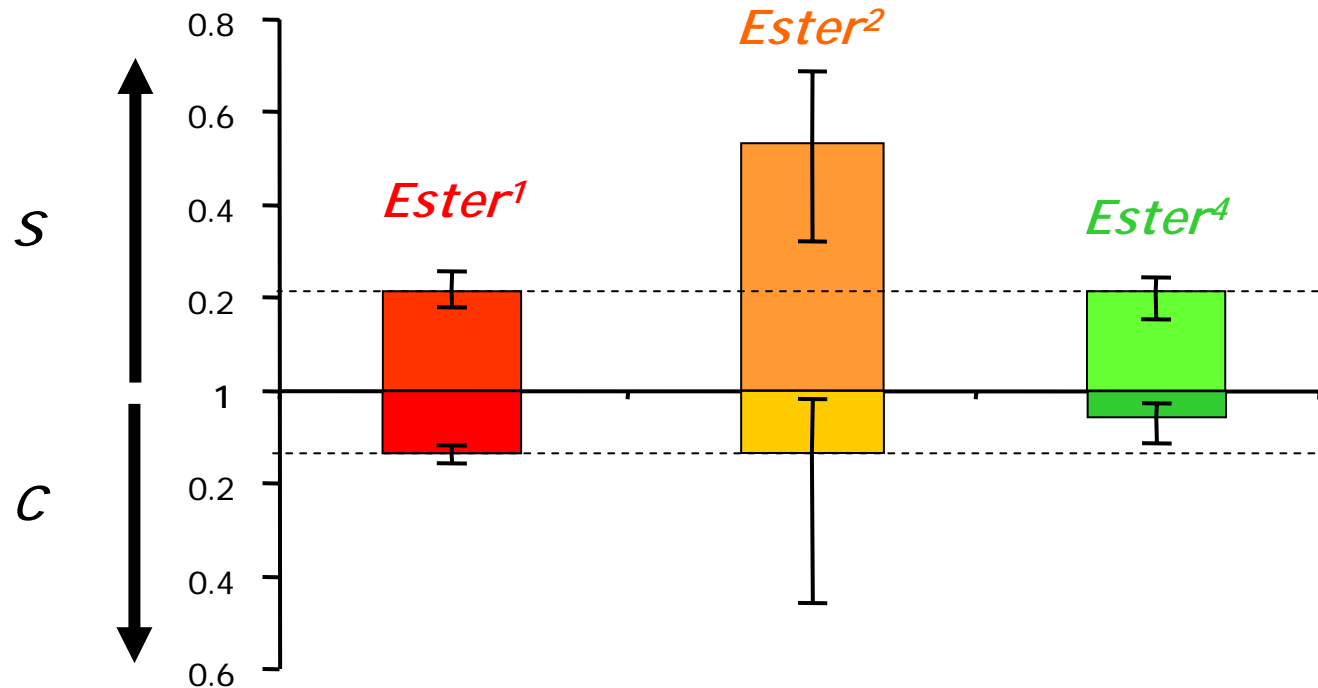
Quantitative model

→ Clines → model on data 1986-2002





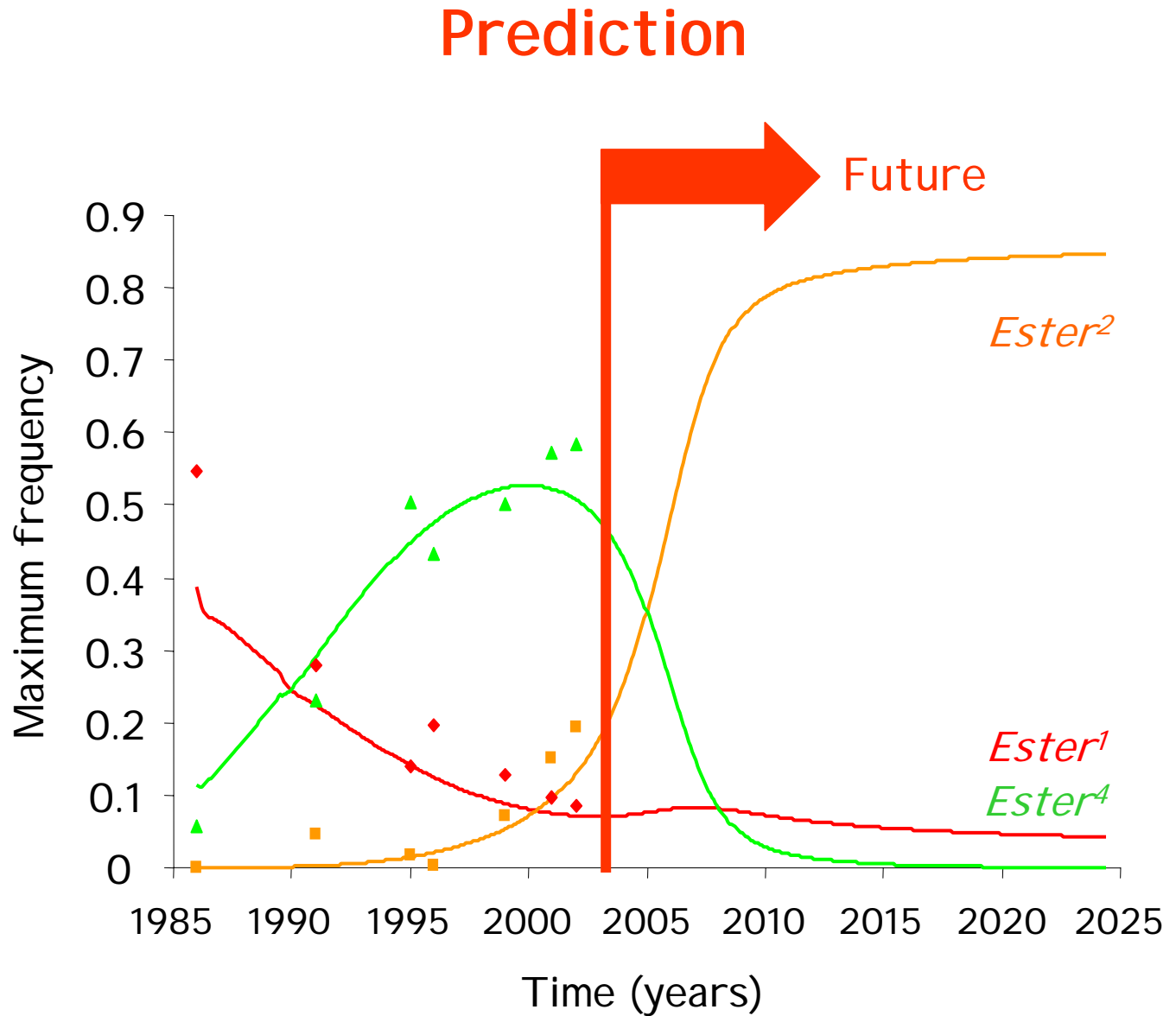
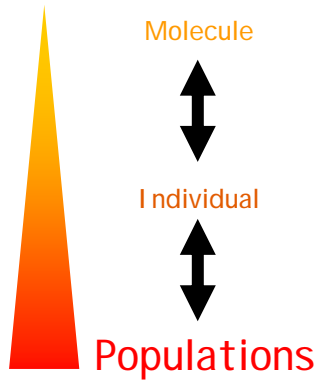
Quantitative fitness estimation



1972 → *Ester¹* → low res., high cost

1986 → *Ester⁴* → low res., low cost → generalist

1991 → *Ester²* → high res., high cost → specialist





→ Different approaches to understand mosquitoes adaptation to insecticides (test of theory)

ex: molecular biology, biochemistry, pop genetics, lab and field experiments, model, etc...

↳ ESB framework

→ Impact on human activities and development

ex: tourism development, disease dynamics and spread, public health, etc...

↳ Measure of the impact of treatment practices for vector resistance, predictions, new control strategies

Thanks to:

Nicole Pasteur
Olivier Duron
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Haoues Alout
Fabrice Chandre
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Alexandra Alvergne
Raja Ben Cheick
Maité Marquine
Valérie Durand
Sandra Unal
Clothilde Bernard
Patrick Makoundou

*And thank you for your
attention...*

