





Séminaire MIAT 22 octobre 2021

Étude de l'évolution des résistances aux fongicides chez *Zymoseptoria tritici,* quantification de ses déterminants à grande échelle

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Introduction – Agricultural systems need to be more sustainable

Widespread use of plant protection products (PPP) in agriculture

Fungicides



Herbicides



Insecticides



Increased **productivity** and potential **yield** of crops, harvest **quality** and **stability**

> BENEFICIAL EFFECTS

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Soil, water and air **pollution**, negative impact on **biodiversity**, **human health**, **resistance** build up

> UNINTENDED EFFECTS

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UNINTENDED

EFFECTS

Development of public policies towards a better use and a reduction of PPP



Resistance is defined as a **heritable and stable trait** in an organism, resulting in a **decrease** of the organism's **sensitivity to a biocidal** active substance

Population before selection





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Darwin, C. (1859). On the origin of species

The existence of a selection pressure will inevitably lead to the selection of adapted phenotypes in populations

Resistance is defined as a **heritable and stable trait** in an organism, resulting in a **decrease** of the organism's **sensitivity to a biocidal** active substance



May lead to resistance in practice and to an increase in PPP use

Alternative control methods: Cultivar tolerance, Prophylactic measures, Biocontrol, ...

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Changes in PPP use:



Rex Consortium. (2013). Trends in ecology & evolution

Alternative control methods: Cultivar tolerance, Prophylactic measures, Biocontrol, ...

Changes in PPP use:



Mixing fungicides: Most recommended and used in cereal crops

(FRAC, FAO, French & European guidelines)

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Alternative control methods: Cultivar tolerance, Prophylactic measures, Biocontrol, ...

Changes in PPP use:



Alternation

Temporal heterogeneity







Intensity heterogeneity

Heterogeneity within spray

How effective? At which scales? Which doses? Mixtures composition?

Lack of study concerning empirical approach at large spatiotemporal scales

• Ascomycete fungus responsible for septoria tritici blotch



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- Main disease on wheat: 18 q/ha (25%) (ARVALIS)



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- 70% of European fungicide uses

Fones & Gurr (2015). Fungal Genetics and Biology.



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Introduction – A great diversity of fungicides to control Z. tritici

• 5 fungicide modes of action (MoA)



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Introduction – A great diversity of resistance mechanisms in Z. tritici

- 5 fungicide modes of action (MoA)
- Resistance to all unisite fungicides

Benzimidazoles (BenR / BenS) Qols or Strobilurins (StrR / StrS) SDHIs or Carboxamides (CarR / CarS) DMIs or Triazoles (TriR / TriS)

Introduction – A great diversity of resistance mechanisms in Z. tritici

- 5 fungicide modes of action (MoA)
- Resistance to all unisite fungicides

Qualitative R Quantitative R

Benzimidazoles (BenR)

Qols or **Str**obilurins (StrR)

SDHIs or **Car**boxamids (CarR)

DMIs or Triazoles (TriR: LR \rightarrow MR \rightarrow HR)



TriR

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Benzimidazoles (BenR)
Qols or Strobilurins (StrR)
SDHIs or Carboxamids (CarR)
DMIs or Triazoles (TriR: LR → MR → HR)

Qualitative R

Quantitative R

Need for a reliable resistance monitoring





- Since 2004
- 70 locations monitored yearly
- Up to 10 different sprayed strategies + 1 unsprayed plot



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> A unique dataset: time and space scales, exhaustiveness of resistances

How resistance evolves on large time and space scales?

Section 1 - Historical review and quantification of resistance dynamics to fungicides in the French *Z. tritici* populations

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What are the determinants of resistance evolution at the regional scale?

Section 2 - Quantification of the effect of regional fungicides uses on resistance frequencies

How resistance evolves on large time and space scales?

Section 1 - Historical review and quantification of resistance dynamics to fungicides in the French *Z. tritici* populations

What are the determinants of resistance evolution at the regional scale?

Section 2 - Quantification of the effect of regional fungicides uses on resistance frequencies

How anti-resistance strategies modulate resistance evolution at the plot scale?

Section 3 - Quantification of the effect of mixing fungicides

Section 1 – Explored data

Variable to be explained

Resistance frequencies observed in unsprayed fields

"Biological spore traps": resistance frequency before any selection



Section 1 – Explored data

Variable to be **Resistance frequencies observed in unsprayed fields** explained

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Resistance frequencies observed in unsprayed fields

"Biological spore traps": resistance frequency before any selection



Explanatory variables

Year and Region

Garnault et al. (2019). Pest management science.

Section 1 – A spatial analysis highlighting contrasted dynamics

Mapping of the annual resistance status: Are spatial structures stable over time?

Spatial kriging (variogram estimation)



Garnault et al. (2019). Pest management science.

Section 1 – A spatial analysis highlighting contrasted dynamics

Mapping of the annual resistance status: Which are the geographical zones with higher frequencies?



Garnault et al. (2019). Pest management science.

Section 1 – A spatial analysis highlighting contrasted dynamics

Mapping of the annual resistance status: Which are the years/regions with higher/lower frequencies compared to the average?



Garnault et al. (2019). Pest management science.

Section 1 – Dynamic spatial structure for the StrR phenotype



Garnault et al. (2019). Pest management science.

Section 1 – Stable spatial structures for the TriR6 and TriR7-R8 phenotypes



Higher frequencies of TriR6 in Northern / North-Eastern regions
Section 1 – Stable spatial structures for the TriR6 and TriR7-R8 phenotypes



Higher frequencies of TriR6 in Northern / North-Eastern regions

Higher frequencies of TriR7-TriR8 in Southern / South-Western regions

Section 1 – Modelling resistance growth

Represents the counting protocol and the three main evolution stages of resistance

$$Y \begin{cases} = 0 & \text{with probability } \pi_0 \\ \sim \mathcal{B}(100, p) & \text{with probability } 1 - \pi_0 - \pi_{100} & \longrightarrow \text{ Selection} \\ = 100 & \text{with probability } \pi_{100} \end{cases}$$

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Observed resistance frequencies

Garnault et al. (2019). Pest management science.

Section 1 – Modelling resistance growth

Represents the counting protocol and the three main evolution stages of resistance





Garnault et al. (2019). Pest management science.

Section 1 – A dynamic approach to study relative fitness

Population dynamics approach: Hartl & Clark, 1997

Resistant phenotype

 $R(t) = R_0 \omega_R^t$ **Sensitive** phenotype (wild type) $S(t) = S_0 \omega_S^t$



individuals grow compared to others

Section 1 – A dynamic approach to study relative fitness

t

Population dynamics approach: Hartl & Clark, 1997

Resistant phenotype

Sensitive phenotype (wild type)

$$R(t) = R_0 \omega_R^t$$
$$S(t) = S_0 \omega_S^t$$

$$\omega = \frac{\omega_R}{\omega_S} \quad \text{the relative fitness}$$

How many times faster resistant individuals grow compared to others

$$p_{R(t)} = \frac{R(t)}{R(t) + S(t)}$$

$$logit(p_{R(t)}) = \ln\left(\frac{p_{R(t)}}{1 - p_{R(t)}}\right) = \ln\left(\frac{R(t)}{S(t)}\right) = \ln\left(\frac{R_0\omega_R^t}{S_0\omega_S^t}\right)$$

$$= \ln\left(\frac{R_0}{S_0}\right) + \ln\left(\frac{\omega_R^t}{\omega_S^t}\right) = \ln\left(\frac{R_0}{S_0}\right) + \ln\left(\frac{\omega_R}{\omega_S}\right)^t = \ln\left(\frac{R_0}{S_0}\right) + t * \ln(\frac{\omega_R}{\omega_S})$$

$$logit(p_{R(t)}) = \mu + \beta * t$$
 with $\mu = ln\left(\frac{R_0}{S_0}\right)$ and $\beta = ln(\omega)$

Section 1 – A model to estimate apparent relative fitness

 $Y \begin{cases} = 0 & \text{with probability } \pi_0 \\ \sim \mathcal{B}(100, p) & \text{with probability } 1 - \pi_0 - \pi_{100} \\ = 100 & \text{with probability } \pi_{100} \end{cases}$

$$logit(p_{ijln}) = (\mu + \alpha_i) + (\beta + \eta_i) * (l - 1)$$

Initial frequencies (*I*=1): global + regional

Growth rates: global + regional



Section 1 – A model to estimate apparent relative fitness

 $Y \begin{cases} = 0 & \text{with probability } \pi_0 \\ \sim \mathcal{B}(100, p) & \text{with probability } 1 - \pi_0 - \pi_{100} \\ = 100 & \text{with probability } \pi_{100} \end{cases}$

$logit(p_{ijln}) = (\mu + \alpha_i)$	Initial frequencies (I=1): global + regional
$+ (\beta + \eta_i) * (l-1)$	Growth rates: global + regional
$+ \delta_j$	Sampling date effect
+ ε_{ijkln}	Overdispersion
where $\varepsilon_{ijln} \underset{iid}{\sim} \mathcal{N}(0, \sigma^2)$	

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A model that can estimate relative fitness of resistance phenotypes from their frequency evolutions

$$logit(p_{i, j, l, \cdot}) = logit(p_{i, j, l-1, \cdot}) + (\beta + \eta_i)$$

Bayesian framework, MCMC algorithms, non-informative priors

$$logit(p_{i, j, l, \cdot}) = logit(p_{i, j, l-1, \cdot}) + (\beta + \eta_i)$$

We define for region parameters as $\eta_i \sim \mathcal{N}(0, \sigma_{\eta}^2)$, which is equivalent to the contrasts « sum = 0 » in frequentist models

How to test significance of variance parameters (variance hyperparameters or random effects) ?

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Pvalues are computed using credible intervals of parameters posterior densities



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How to test significance of variance parameters (variance hyperparameters or random effects) ?

$$\eta_i = \sigma_\eta * \eta'_i$$

avec $\eta'_i \sim \mathcal{N}(0, 1)$

$$logit(p_{i, j, l, \cdot}) = logit(p_{i, j, l-1, \cdot}) + (\beta + \eta_i)$$

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Evolution speeds differ among resistance phenotypes



Evolution speeds differ among resistance phenotypes

Evolution speeds differ among regions for a given resistance phenotype

- Progression front structure (QoI resistance, previously described on a West-to-East gradient by Torriani *et al.*, 2009)
- Stable and strong regionalization of resistance (DMI resistance)
- Constrated growth speeds among phenotypes
- Contrasted growth speeds among regions for a given phenotype
- Significant difference between spring and summer samples highlight intra-annual evolution

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Regional scale is interesting for resistance management

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- > Regional scale is interesting for resistance management
- Which factors modulate the selection at the regional scale?

• Section 2 - The regional drivers of resistance dynamics



> Can regional fungicides uses explain resistance frequencies?

Performanc

Variable to be explained

Resistance frequencies observed in unsprayed plots



Variable to be explained



Resistance frequencies observed in unsprayed plots

Explanatory variables

Selection pressure intensity: use of anti-septoria fungicides





Variable to be explained



Resistance frequencies observed in unsprayed plots

Explanatory variables

Selection pressure intensity: use of anti-septoria fungicides

Selection pressure heterogeneity: surfaces under organic wheat

> Population size proxy: Potential yield losses



 $logit(p_{i,j,l,\cdot}) = logit(p_{i,j,l-1,\cdot}) + (\beta + \eta_i)$ β + $\sum_{m=1}^{\infty} v_m * F_{m, i, j, l-1, \cdot}$ Selection pressure

Constant growth

- Associated MoA
- $v_m > 0$ (StrR, TriMR)

$$logit(p_{i, j, l, \cdot}) = logit(p_{i, j, l-1, \cdot}) + (\beta + \eta_i)$$

$$\beta$$

$$\beta$$
Constant growth

$$+ \sum_{m=1}^{M} v_m * F_{m, i, j, l-1, \cdot}$$
Selection pressure

$$+ \rho * P_{i, j, l-1, \cdot}$$
Population size

$$logit(p_{i, j, l, .}) = logit(p_{i, j, l-1, .}) + (\beta + \eta_i)$$

$$\beta$$
Constant growth

$$+ \sum_{m=1}^{M} \nu_m * F_{m, i, j, l-1, .}$$
Selection pressure

$$+ \rho * P_{i, j, l-1, .}$$
Population size

$$+ \kappa * R_{i, j, l-1, .}$$
Refuges





β is an integrative parameter: fitness cost (migration?, ...)

Section 2 – Regional fungicide use is the most important factor

The loss of explained variance induced by removing the factor from the model.



Yield losses effect was never selected

Regional fungicide use is the major factor in models: 42% to 88%

Garnault et al. (2020). New Phytologist.

Section 2 – Frequency change induced by active substances

Parameter		StrR	TriMR <2011
Constant growth (β)		- 3.71 *	- 4.12 •
Selection pressure (v_m)			
Qols	Kresoxym-methyl	4.23 ***	
	Pyraclostrobin	3.28 **	
DMIs	Cyproconazole		x
	Epoxiconazole		4.94 **
	Prochloraz		x
	Tebuconazole		x
Refuges (<i>k</i>)		3.26 ***	

Selected actives substances are pioneers and most used fungicides

Constant growth are negative → resistance cost ?

Garnault et al. (2020). New Phytologist.

Section 2 – Link between resistance factors and fungicide effects



	TriLR	TriMR		TriHR
		TriR6	TriR7- TriR8	
Pyrifenox				
Prochloraz				
Epoxiconazole				
Propiconazole				
Fluquinconazole				
Tebuconazole				
Metconazole				
Difenoconazole				
Prothioconazole				

Leroux & Walker (2011). Pest management science.

Sensitive Low

Resistance factor Medium High

Parameter		TriR6	TriR7-TriR8
Constant growth (β)		4.96 ***	1.52 ·
Selection pressure ($ u_m$)			
DMIs	Cyproconazole	х	2.46 **
	Epoxiconazole	х	x
	Prochloraz	3.7 ***	-3.95 ***
	Tebuconazole	-11.35 ***	2.6 *

Garnault et al. (2020). New Phytologist.
Section 2 – Prediction quality for the StrR phenotype

The model can estimate the average regional frequencies of resistances



Section 2 – Prediction quality for the StrR phenotype

The model can estimate the average regional frequencies of resistances



The model is able to recreate the North-South progression front

Section 2 – Prediction quality for the TriR6-7-8 phenotypes

The model is also able to represent the constant regionalization of TriR6 and TriR7-TriR8 phenotypes



- Regional fungicide use is the most important driver of resistance evolutions
- Estimated fungicide effects at the regional scale can in general be linked to resistance factors of phenotypes determined at the laboratory scale
- Model predictions are consistent with field observations
- Yield losses/Population size is not a constraining factor

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- Estimated fungicide effects at the regional scale can in general be linked to resistance factors of phenotypes determined at the laboratory scale
- Model predictions are consistent with field observations
- Yield losses/Population size is not a constraining factor
- The use of fungicides at the regional scale can be modulated to manage resistance evolution

Conclusions

- National monitoring data at large scales, a original approach:
 - Phenotype frequency
 - Time (>10 years)
 - Space (France)



Conclusions

- National monitoring data at large scales, a original approach:
 - Phenotype frequency
 - Time (>10 years)
 - Space (France)



- Large scale monitoring is an asset for:
 - The short-term recommandation
 - The long-term comprehension of resistance dynamics
 - The implementation of reliable and sustainable strategy of resistance management on large scales

Importati			Tableau	Cartographie Prédiction					
Importer	un CSV				Show 100	 entries 	5		
C:/Users/max 2004-2020 -	(im/Documents/BIOGE Corrige - Allege.csv	R&MalA	GE/CartoFreq/data/Frequences_CSV	//Septo	ligne 🔶	annee 🔶	code_essai	commune 👙	numero_depar
Donnée	es pluri-annuelles				2	2004	2004-VIMY	VIMY	62
Afficher	les statistiques annue	lles			3	2004	2004-VIMY	VIMY	62
Fréquence :					4	2004	2004-VIMY	VIMY	62
TriR7.R8				-	5	2004	2004-VIMY	VIMY	62
					6	2004	2004-VIMY	VIMY	62
Annee :				-	7	2004	2004-VIMY	VIMY	62
Modalité :				•	8	2004	2004-LURY SUR ARNON	LURY SUR ARNON	18
TNT				•	9	2004	2004-LURY SUR ARNON	LURY SUR ARNON	18
Région FRANCE	TriR7.R8.2013.TNT 33.60	n 120			10	2004	2004-BERRY BOUY	BERRY BOUY	18
AQU	77.50	2			11	2004	2004-BERRY BOUY	BERRY BOUY	18
BNO	21.25	4			12	2004	2004-STE SOLANGE	STE SOLANGE	18
BRE	69.62 37.78	8 9			13	2004	2004-STE SOLANGE	STE SOLANGE	18
CEN	44.09 30.00	11 8			14	2004	2004-STE SOLANGE	STE SOLANGE	18

Fréquence représentée :	
TriR7.R8	-
Année représentée :	
2013	-
Modalité représentée :	
TNT (n=120)	-
Evporter la légende au format PDE	
Le Exporter la légende au format PDF	•



Outil CartoFreq



Importation de variables explicatives :

Importer un Panel

Résultats du modèle :

pseudo-R² = 0.462

Paramètre	Estimation	Ecart.type	P.value	Signif.
FRANCE	0.438	0.029	0.000	***
AQU	-0.112	0.119	0.349	
BNO	-0.105	0.071	0.141	
BOU	0.093	0.127	0.467	
BRE	-0.066	0.059	0.265	
CEN	0.020	0.061	0.748	
CHA	0.009	0.065	0.895	
HNO	-0.028	0.060	0.642	







Thank you for your attention





Pression de sélection en fonction des traitements 33 essais 2013 - 2012 (11 + 22) avec Non MDR > 0 dans les témoins





Réunions Techniciens - Automne 2013

Késeau

Performance

Deployed hectares



Expected frequency change

$$EFC_{\theta} = 100 * (p^{e} - \bar{p})$$

$$\log it(p^{e}) = logit^{-1}(\bar{p}) + \hat{\theta} * \overline{X_{\theta}} \qquad \bar{p} = \frac{\bar{Y}}{100}$$



Tableaux rétrospectifs. GNIS & Unigrains.





Quantité de substances actives (Total et Total-(C+S) en tonnes)

Quantité de substances actives (C+S en tonnes)

En tonnes













Ecart Traité - Non Traité max q/ha





Leroux & Walker (2011). Pest management science.