



Spatial exposure-hazard and landscape models for assessing the impact of GM crops on non-target organisms



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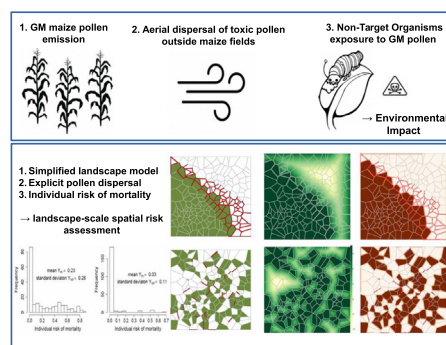
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HIGHLIGHTS

- GM crops may impact non-target organisms in agricultural landscapes.
- Spatial determinants of GM risk are assessed using generic spatial exposure-hazard and landscape models.
- A Global Sensitivity Analysis is performed for spatial worst-case scenarii.
- It confirms the importance of space and GM pollen emission.
- It shows that the optimal spatial distribution of GM depends on our knowledge of NTO habitats.

GRAPHICAL ABSTRACT



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ABSTRACT

The cultivation of Genetically Modified (GM) crops may have substantial impacts on populations of non-target organisms (NTOs) in agroecosystems. These impacts should be assessed at larger spatial scales than the cultivated field, and, as landscape-scale experiments are difficult, if not impossible, modelling approaches are needed to address landscape risk management.

We present an original stochastic and spatially explicit modelling framework for assessing the risk at the landscape level. We use techniques from spatial statistics for simulating simplified landscapes made up of (aggregated or non-aggregated) GM fields, neutral fields and NTO's habitat areas. The dispersal of toxic pollen grains is obtained by convolving the emission of GM plants and validated dispersal kernel functions while the locations of exposed individuals are drawn from a point process. By taking into account the adherence of the ambient pollen on plants, the loss of pollen due to climatic events, and, an experimentally-validated mortality-dose function we predict risk maps and provide a distribution giving how the risk varies within exposed individuals in the landscape.

Then, we consider the impact of the Bt maize on *Inachis io* in worst-case scenarii where exposed individuals are located in the vicinity of GM fields and pollen shedding overlaps with larval emergence. We perform a Global Sensitivity Analysis (GSA) to explore numerically how our input parameters influence the risk. Our results confirm the important effects of pollen emission and loss. Most interestingly they highlight that the optimal spatial distribution of GM fields that mitigates the risk depends on our knowledge of the habitats of NTOs, and finally, moderate the influence of the dispersal kernel function.

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1. Introduction

Nowadays, one of the most successful bio-pesticides for insect control is the bacterium *Bacillus thuringiensis* (Bt) which, upon

sporulation, produces insecticidal proteins that belong to the Cry and Cyt families and are mostly active against larval stages of different insect orders (Bravo et al., 2011). This biocontrol agent or its insecticidal products can be sprayed and used in conventional and organic crop systems and, Cry expressing genes from the bacterium have been introduced into transgenic commercial crops to create genetically modified (GM) insect tolerant varieties (Mendelsohn et al., 2003). Among them, GM maize varieties producing Bt Cry proteins (e.g. Monsanto's MON810, Syngenta's Bt11 and Pioneer's 1507 Bt maize (Romeis and Meissle, 2011)) introduced for controlling the European Corn Borer, a pest that causes substantial losses, have been some of the most examined GM crops. Each of these Bt maize produces a specific insecticidal Cry protein (i.e. Cry1Ab for MON810 and Bt11 and Cry1F for 1507) whose impact on insect may depend on both the protein and the targeted species (Bravo et al., 2011). Moreover, whereas all these GM plants produce the toxic proteins in most of their plant tissues the concentrations can vary significantly between tissues within a plant, and also, between varieties (Mendelsohn et al., 2003).

Although the Bt maize primarily targets pests that are detrimental to the crop, the Bt toxin is also active against some non-target beneficial, neutral or patrimonial species that should be protected. As the Bt toxin is also expressed in pollen (Felke et al., 2010), which is dispersed by wind outside maize fields (Angevin et al., 2008) and can reach habitats of non-target organisms (NTOs) that may be exposed to the xenobiotics (EFSA, 2015; Hofmann et al., 2014), the cultivation of GM maize represents a risk toward non-target populations living in agroecosystems. While the controversial example of the impact of Bt maize on the monarch butterfly (*Danaus plexippus*) has led to several studies (Losey et al., 1999; Pleasants et al., 2001; Sears et al., 2001), the conservation of NTOs exposed to GM crops is still a debated subject (Holst et al., 2013; Kruse-Plass et al., 2017; Lang and Otto, 2010; Perry et al., 2013, 2017, 2012, 2010).

Risk assessment, which is the determination of quantitative or qualitative estimate of risk related to a recognised hazard, is a key component of public policy making for the authorization of new biological or chemical compounds used in human activities (e.g. industrial chemicals, pesticides or biotechnology-based plants) (Suter II, 2016). Regarding environmental or ecological risk assessment (ERA) several components should be considered, i) the identification and characterization of the hazard, ii) the locations of the xenobiotics sources, iii) the dispersal mode, iv) the exposed populations and v) the mode of exposure (Andow and Zwahlen, 2006). Albeit the risk assessment process requires expert advice, the use of statistical tools and mathematical models is generally fundamental for quantifying risk and testing management strategies. As xenobiotics emitted by anthropic activities generally have the potential to spread over mid or long distances, it is now recognised that efficient ERAs should be carried out at the landscape scale (Angevin et al., 2008; Focks, 2014; Gilligan et al., 2007; Graham et al., 1991; Topping et al., 2015).

Several models have been developed for assessing the risk of Bt maize on non-target *Lepidoptera* (Holst et al., 2013; Lang et al., 2015; Perry et al., 2010; Sears et al., 2001) and their outputs have been often considered for scientific advice, for instance by the Panel on Genetically Modified Organisms of the European Food Safety Authority (EFSA) (EFSA, 2010, 2012, 2015, 2016). Nevertheless, none of them considered a spatial modelling framework, such as those developed for coexistence studies with explicit models for the dispersal process and the spatial structure of the landscape (Klein et al., 2003; Lavigne et al., 2008). The importance of considering explicitly space to understand and predict the behaviour of ecological systems driven by dispersal mechanisms and spatial interactions has been demonstrated by numerous works (Bolker et al., 2000; Durrett and Levin, 1994; Filipe and Maule, 2004) and spatial models are thus recognised to be central for improving ERA at the landscape level (Focks, 2014; Graham et al., 1991; Papaix et al., 2014b; Topping et al., 2016).

Therefore, the management of GM crops at the landscape level for protecting NTOs is still at an early stage of development and the improvement of models is still needed to support it (Lang et al., 2015).

In this study we concentrate on the spatial determinants of the risk for worst-case scenarios where exposed individuals are located in the vicinity of GM fields and when pollen shedding and larval emergence overlap. We first present an original spatial and stochastic modelling framework for assessing the risk of GM crops on spatially distributed NTOs in agricultural landscapes. The framework combines i) tools of spatial statistics and stochastic geometry for structuring simplified agricultural landscapes and simulating the locations of exposed individuals, ii) a method based on a convolution product and dispersal kernels for predicting the spread of toxic Bt pollen grains in the landscape, and iii) a dose-mortality relationship for assessing the risk of mortality. Then, we consider the impact of the Bt maize MON810 on the peacock butterfly *Inachis io*, a typical European NTO. We perform a Global Sensitivity Analysis (GSA) to assess numerically the influence of the spatial structure of the landscape, pollen emission, dispersal, adherence and loss on the mean and the standard deviation of the individual risk of mortality. We finish the paper by discussing our work and its interest for ERA and the management of GM crops at the landscape level.

2. Material and methods

2.1. Typical biological system

Following previous studies (Holst et al., 2013; Lang et al., 2015; Perry et al., 2012, 2010) we considered the example of the impact of the GM maize (*Zea mays*) MON810, which expresses the Cry1Ab insecticidal protein, on the peacock butterfly (*Inachis io*) for which an empirical dose-mortality relationship was established (Felke et al., 2010). *I. io* is an important European patrimonial colourful butterfly which feeds on a wide variety of flowering plants (nectariferous plants) and lay eggs on the leaves of the host plant *Urtica dioica* (i.e. nettle) (Pullin, 1986). In intensive agricultural systems nettle is essentially distributed on non-cultivated field margins. Given that the pollen of GM maize spread beyond cultivated fields and reach the habitat of patrimonial butterfly (e.g. field margins), *I. io* larva feeding on nettle can ingest toxic pollen grains and exhibit lethal or sublethal physiological damages.

2.2. Spatial exposure-hazard and landscape models

2.2.1. Overall presentation

The modelling framework consists of four stochastic and deterministic steps that are illustrated in Fig. 1 and detailed below. First, a landscape made up of GM fields, neutral fields and larvae habitat areas, where host plants are located, is drawn from a stochastic spatial process (Fig. 1A). Second, the spatial distribution of the amount of pollen, after pollen shedding and aerial dispersal, is obtained through a deterministic process that aggregates the temporal dynamic of pollen shedding in one step and integrates the contribution of all emitting sources (i.e. GM maize fields) in the landscape (Fig. 1B). Third, a map of the risk is calculated using a dose-mortality relationship (Fig. 1C). Fourth, the spatial distribution of exposed larvae is drawn from a stochastic *spatial point process* on habitat areas (Fig. 1C). Finally, the mean and the standard deviation of the risk are both extracted from the resulting distribution describing the probability of mortality (i.e. the risk) of exposed individuals in the landscape (Fig. 1D).

2.2.2. Simulation of landscapes

A stochastic landscape simulator was developed assuming that i) the landscape is made of convex plots, ii) fields can be either

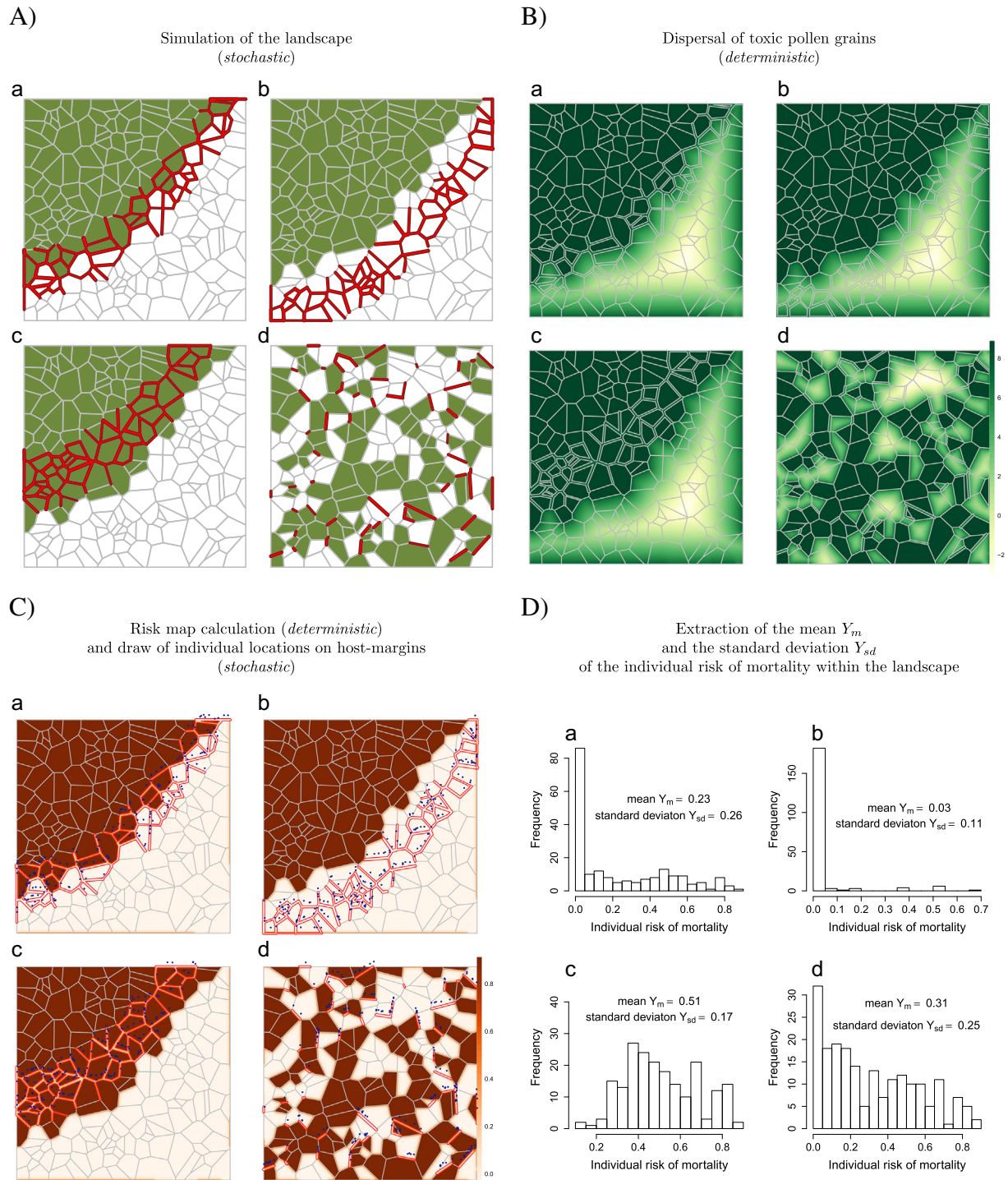


Fig. 1. Illustration of the steps of the spatially-explicit exposure-hazard model. A) Structuration of the landscape made of GM fields (green polygons), neutral zones (white polygons), and habitat areas (red polygons). B) Simulation of pollen dispersal using Eqs. (1) and (2) (maps show the amount of pollen deposited on host-plants in the log-scale). C) Risk map and draw of the spatial distribution of individuals on host-margins (blue points). D) Output distributions describing the between-individuals risk of mortality and extraction of the mean Y_m and the standard deviation Y_{sd} . a), b), c) and d) represent four contrasted situations regarding the spatial aggregation of GM fields and the location of host-margins in relation to GM fields. Landscapes were simulated with $\rho = \{2500, 2500, 2500, 30\}$ and $\tau = \{0, 0.18, -0.18, 0.1\}$ respectively.

cultivated with GM maize, and thus emit toxic pollen grains, or non-emitting neutral ones and iii) the host plants of exposed larvae are only located on field margins thereafter called host-margins. Furthermore the landscape model was tuned to allow the control of i) the spatial aggregation of emitting fields, ii) the proportion of GM fields, iii) the location of host-margins in relation to GM fields, and, iv) the width of host-margins.

The landscape is first structured by partitioning a $5000 \times 5000m^2$ domain with a *Voronoi tessellation* on 1 seed points drawn from a *binomial homogeneous spatial point process* (Chiu et al., 2013; Illian et al., 2008). More realistic tessellations could be used for drawing the geometry of agricultural fields (Kiêu et al., 2013), but it has been shown that *Voronoi tessellations* based on *binomial point processes* are relevant for assessing the interaction between the spatial arrangement

of the landscape and the dispersal of pollen grains (Lavigne et al., 2008; Le Ber et al., 2009). Then, for a given proportion of GM fields p we draw both the spatial distribution of GM fields and host-margins on the set of polygons and segments defined by the tessellation using *marked polygonal and point processes*, and a thresholded *stationary spatial Gaussian process* with a *Matérn covariance function* whose range parameter ρ controls the spatial aggregation of emitting fields. After having set a first threshold of the *Gaussian process* that appropriately allocates the GM fields, the host-margins are defined by using another threshold which is dependent on the first one and controlled by the parameter τ . Finally, we add thickness to host-margins by dilating the segments with thicknesses drawn from a Gamma distribution parametrised with its mean u (i.e. the mean width of host-margins) and a variance empirically fixed to 4. A full mathematical description of the landscape model which enables the simulation of a continuum of situations illustrated in Fig. 1A and an illustration of the effects of the parameters on the spatial structure of landscapes are given in Appendix A1.

2.2.3. Simulation of pollen dispersal

The accumulated number of Bt pollen grains in the ambient air and located at position (x, y) is defined by the convolution product:

$$R_a(x, y) = \int \int E(x', y') K(x - x', y - y') dx' dy' = E \otimes K(x, y), \quad (1)$$

where K is a dispersal kernel function (Filipe and Maule, 2004; Kot et al., 1996; Nathan et al., 2012) modelling the density probability function of the deposit locations of particles released from a point source, and E is the total number of pollen grains emitted by square metre during flowering.

In the example of *Lepidoptera* larvae, as susceptible individuals ingest transgenic pollen grains that are present on the leaves of host-plants (Lang and Otto, 2015), an individual on a host plant located at position (x, y) is not exposed to the amount of pollen $R_a(x, y)$ of the ambient air. Indeed, only a fraction of the total amount of pollen adheres on leaves and climatic events (e.g. rain or strong wind) can cause significant loss (Hofmann et al., 2016; Holst et al., 2013; Pleasants et al., 2001). Thus, we assume that the amount of toxic pollen $R(x, y)$ at position (x, y) is obtained from:

$$R(x, y) = R_a(x, y) \omega (1 - \psi) \quad (2)$$

where ω and ψ are respectively the percentage of pollen that adheres to leaves and the total loss of pollen. While one could consider that ω and ψ could be aggregated into one single parameter, they represent distinct processes with different parameter range (Pleasants et al., 2001) and might have contrasted influences on the risk.

Albeit some dispersal kernels have already been fitted to experimental field data (Klein et al., 2003; Lavigne et al., 2008), pollen dispersal is still a discussed topic when evaluating the risk of Bt maize on NTOs (EFSA, 2015; Hofmann et al., 2014) and none of the proposed models integrates explicitly the dispersal process. Therefore, to assess the influence of the kernel on the risk we tested four contrasted kernel functions that mainly differ at short and long distances: i) an isotropic Normal Inverse Gaussian (NIG) kernel (Klein et al., 2003), ii) an anisotropic NIG that considers wind, iii) a Bivariate Student (2Dt) kernel (Lavigne et al., 2008) and iv) a Geometric kernel (Devaux et al., 2005). A full mathematical description is given in Appendix A2.

2.2.4. Risk of mortality

A risk map providing the probability of mortality P_{death} (i.e. the risk) at every location is calculated from $R(x, y)$ and an empirical

dose-mortality relationship fitted for *I. io* and considered by previous modelling works (Perry et al., 2010):

$$P_{death} = \frac{e^{-9.304+2.473\log_{10}(D)}}{1 + e^{-9.304+2.473\log_{10}(D)}} \quad (3)$$

where D is the concentration of maize MON810 pollen grains on the location of the larva (cm^{-2}).

A distribution describing how the risk of mortality varies among exposed individuals is obtained by simulating their locations with a *binomial homogeneous point process* of 500 points on host-margins, and assessing the risk of mortality (i.e. P_{death}) for each individual-point (Fig. 1C). To limit border effects induced by the periodic boundary conditions used in the numerical method for calculating pollen dispersal (see Appendix A2), the locations of individuals are restricted to the habitat zones located only in a $4750 \times 4750m^2$ box (none of the exposed larvae is close to the borders of the landscape).

2.3. Numerical simulations and Global Sensitivity Analysis (GSA)

We assessed the influence of our input parameters on the risk using numerical simulations and a GSA. Sensitivity analysis (SA) methods allow to study how the uncertainty in the output of a model can be apportioned to different sources of uncertainty in the model input (Saltelli et al., 2008). These methods are generally used to determine the most influencing input variables, detect some interaction effects within the model, or, verify and understand complex models (Favre et al., 2013).

Our input parameters of interest consisted of eight continuous input parameters related to pollen emission, adherence, loss, to the spatial arrangement of the landscape and, one categorical variable (i.e. the dispersal kernel K) (Table 1). As our model is stochastic it gives a distribution of the risk in output. For this study we summarised this distribution by its mean Y_m and standard deviation Y_{sd} (Fig. 1D). To perform a GSA on these two outputs we first designed a numerical experiment, based on an optimal low-discrepancy Latin Hypercube Sample of 1000 points with 10 replicates of each point (Favre et al., 2013), which was repeated for each of the four dispersal kernel functions. Prior distributions were defined for each continuous input parameters of the model before running the simulations (Table 1 & Appendix A3). For the parameters related to pollen, the input distributions were chosen according to the literature. The intensity of pollen emission E was obtained by fixing plant density to $7plant.m^{-2}$ and considering only the number of pollen grains produced per plant E_p ($E = 7E_p grains.m^{-2}$). For E_p the available knowledge allowed the construction of a realistic Gamma distribution (Angevin et al., 2008; Ricci et al., 2012) (Table 1). For the percentage of pollen lost ψ and the percentage of pollen adhering on leaves ω , that are both still difficult to estimate, we tuned two uniform distributions based on orders of magnitude given by Pleasants et al. (2001) (Table 1). The input distributions of parameters that control the structure of the landscape were empirically chosen. For the proportion of GM fields p , the number of fields l and the mean width of host-margins u we tuned uniform distributions that allowed us to investigate a continuum of situations between i) low and high proportion of fields cultivated with Bt maize, ii) small and large plots and iii) narrow field margins and larger habitat that could represent refuges for NTOs. The use of a U-shaped distribution for the range parameter ρ made possible the continuous exploration of the effect of the spatial aggregation of GM fields while promoting extreme disaggregated and aggregated cases. Finally, as we chose to focus on NTOs that are the most at risk, i.e. lying in the vicinity of GM fields, we tuned a uniform distribution for τ that allowed us to investigate a range of landscapes structure between situations where host-margins are inside or contiguous GM fields, and ones where host-margins are located at mid-distances (Fig. 1 & Appendix A1).

Table 1
Input parameters considered for the Global Sensitivity Analysis.

Parameter		Units	Input values	Source
E_p	Total amount of pollen produced per plant	pollen grains.plant ⁻¹	$\Gamma(\text{mean} = 8.10^6, \text{sd} = 4.10^6)$	(Angevin et al., 2008; Ricci et al., 2012)
ψ	Percentage of pollen lost	%	$U(0.2, 0.8)$	(Pleasant et al., 2001)
ω	Percentage of pollen adhering on leaves	%	$U(0.3, 0.6)$	(Pleasant et al., 2001)
p	Proportion of GM fields	%	$U(0.3, 0.8)$	Empirically tuned
l	Number of fields		$U(50, 500)$	Empirically tuned
u	Margin width	m	$U(1, 30)$	Empirically tuned
τ	Location of host-margins related to GM fields		$U(-0.18, 0.18)$	Empirically tuned
ρ	Range parameter	m	$1 + 2999.Beta(0.3, 0.3)$	Empirically tuned
K	Dispersal kernel function		isotropic and anisotropic NIG, 2Dt, Geometric	(Devaux et al., 2005; Hofmann et al., 2014; Klein et al., 2003; Lavigne et al., 2008)

Although the two parameters of the sigmoid function (i.e. eq(3)) used to predict the individual risk of mortality could have also been introduced in the GSA, in this study we kept them fixed. This choice is justified by our main interest on the spatial determinants of the risk rather than providing accurate risk predictions. Furthermore, considering the specific case of the impact of maize MON810 on *I. io* and the fitted dose-response function makes the comparison with previous works easier. While fixing a few parameters is not unusual when applying SA methods, one could argue that it is not a true GSA but rather a quasi-GSA.

The Sensitivity Indices (SIs) (Sobol, 2001) for the mean risk Y_m and the variability of the risk Y_{sd} were estimated using separate meta-models with second-order interactions (Faivre et al., 2013). We used Generalized Linear Models (Gamma distribution and log link function) and considered $\{\rho, p, l, \omega, \psi, E_p, \tau, u\}$ as continuous predictors and the effect of the dispersal kernel K as a categorical variable with four levels (see Appendix A3). SIs were obtained by calculating the

deviance explained by the parameters and their interactions. All the simulations and analyses were performed using the R free software (R Core Team, 2015).

3. Results

The output of the simulations provided distributions of the mean Y_m and the standard deviation Y_{sd} of the individual risk of mortality in the landscape (Figs. 2 & 3). Their means were $\bar{Y}_m = \{0.056, 0.064, 0.037, 0.054\}$ and $\bar{Y}_{sd} = \{0.036, 0.041, 0.030, 0.032\}$ for respectively the isotropic NIG, anisotropic NIG, 2Dt and the Geometric kernel. The output distributions of Y_m and Y_{sd} all exhibited a positive skewness and the Leptokurtic behaviour of some distributions suggests that the occurrence of situations with substantial higher mortality and uncertainty is likely. Our simulations, that mainly aimed at exploring some spatial components of the risk rather than providing accurate risk predictions, suggested a mean

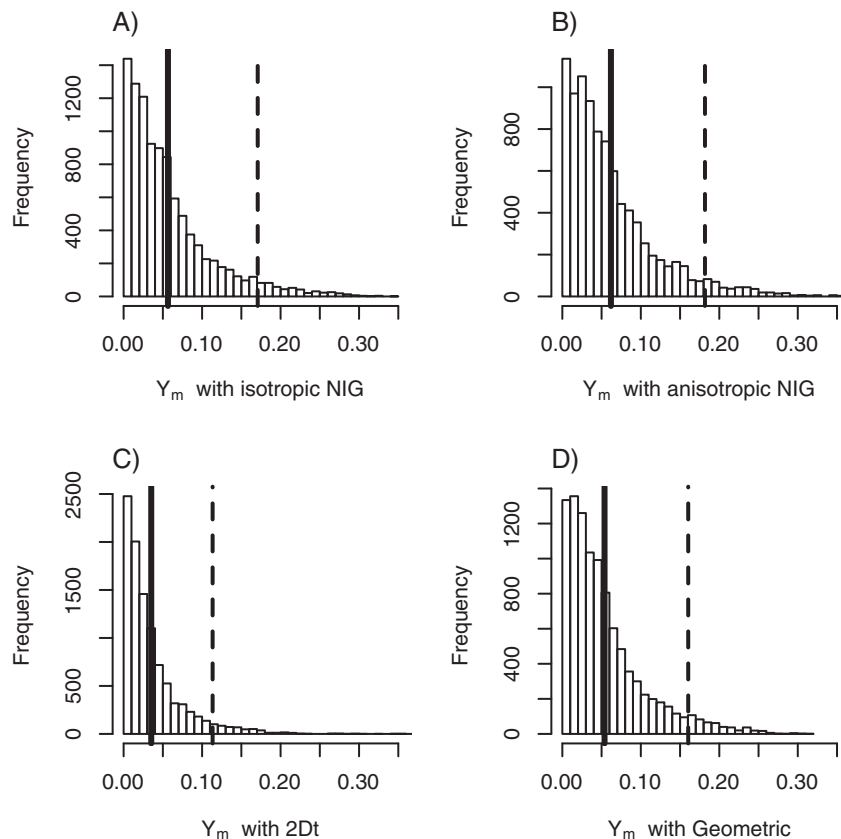


Fig. 2. Histograms representing the distributions of the mean individual mortality Y_m for the four dispersal kernels considered in the GSA : A) NIG, B) NIG with wind, C) 2Dt and D) Geometric. For each distribution the vertical black line shows the mean of the distribution whereas the vertical dotted line displays the 0.95-Quantile. The values of the mean, the Kurtosis and the 0.95-Quantile of the distributions are $\bar{Y}_m = \{0.056, 0.064, 0.037, 0.054\}$, $Kurt[Y_m] = \{3.10, 2.50, 4.11, 2.71\}$, and $Q_{95}[Y_m] = \{0.17, 0.18, 0.11, 0.16\}$ respectively for A), B), C) and D).

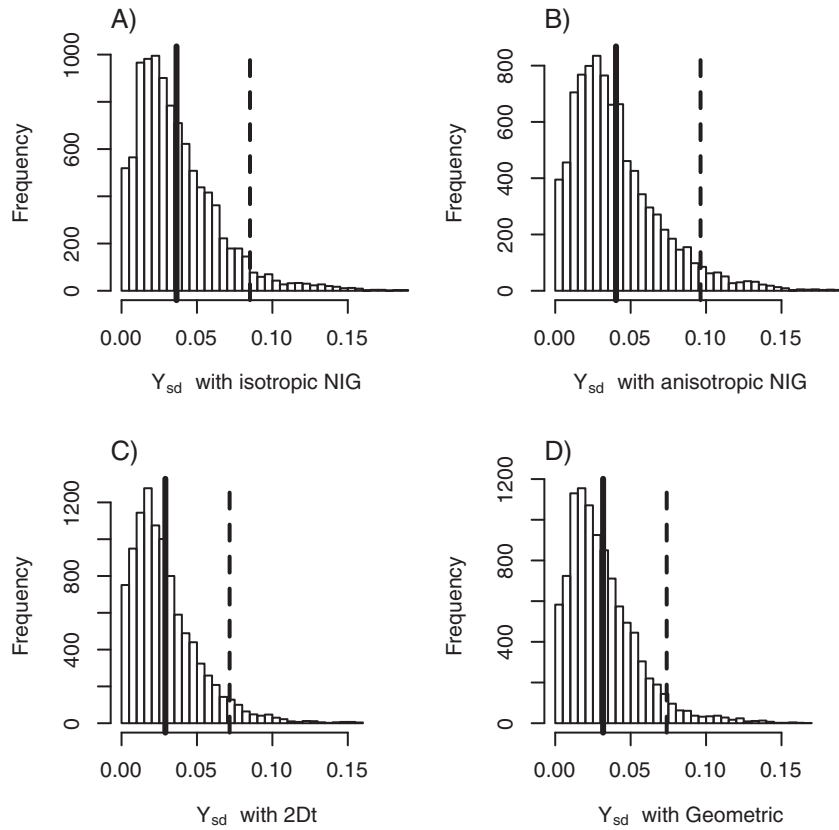


Fig. 3. Histograms representing the distributions of the standard deviation of the individual mortality Y_{sd} for the four dispersal kernels considered in the GSA : A) NIG, B) NIG with wind, C) 2Dt and D) Geometric. For each distribution the vertical black line shows the mean of the distribution whereas the vertical dotted line displays the 0.95-Quantile. The values of the mean, the Kurtosis and the 0.95-Quantile of the distributions are $Y_{sd} = \{0.036, 0.041, 0.030, 0.032\}$, $Kurt[Y_{sd}] = \{3.17, 2.27, 3.21, 3.30\}$, and $Q_{95}[Y_{sd}] = \{0.085, 0.096, 0.072, 0.074\}$ respectively for A), B), C) and D).

risk that is a little higher than those obtained by Perry et al. (2010) with a semi-spatial empirical model for pollen spread in simpler landscapes.

The metamodelling approach allowed us to quantify the SIs for Y_m and Y_{sd} (Table 2 & Fig. 4A). While for the mean risk Y_m our meta-model was able to explain 71% of the deviance, it only explained 56% of the deviance for the standard deviation of the risk Y_{sd} (Table 2). The introduction of higher order interactions and quadratic terms did not substantially reduce the residual deviances. Not surprisingly, the GSA pointed out the importance of parameters directly related to the level of pollen lying on the leaves of host plants on both the mean risk and its variability (Table 2 & Fig. 4A). Indeed, the total amount of pollen produced per maize plant E_p , the losses ψ , and to a lesser extent, the adherence of pollen ω had a strong influence on Y_m (1st order SI of 15.8, 9.7 and 2.4 respectively) and were the most influential parameters for Y_{sd} (1st order SI of 25.4, 13.9 and 3.8 respectively) (Table 2).

Nevertheless, these parameters showed no substantial interactions with other parameters (Fig. 4A). The difference in the SIs of ω and ψ , that have a similar influence in Eq. (2), is explained by their distinct input distributions (Table 1).

The dispersal kernel K had a significant effect on both Y_m and Y_{sd} (1st order SI of 3.8 and 2.3 respectively) but, i) no substantial interactions with other parameters were detected and, ii) it appeared to be only the sixth and fifth most influential input parameter on Y_m and Y_{sd} (Table 2) respectively. The two most visible effects were i) the little decrease in Y_m induced by the 2Dt which may be explained by its behaviour at very short distances (more dense before 2 m (Lavigne et al., 2008) where only a small fraction of exposed individuals were located among the simulated cases (Fig. S1)), and, ii) the effect of the anisotropic NIG which boosted Y_{sd} .

The GSA also highlighted a strong influence of three parameters involved in the spatial structure of the landscape. Indeed, whereas

Table 2
Sensitivity Indices for the mean Y_m and the standard deviation Y_{sd} of the landscape-scale risk (SI higher than 5 are in bold).

Parameter	$Y_m (R^2=0.71)$			$Y_{sd} (R^2 = 0.56)$		
	Deviance	1st order SI	2nd order SI	Deviance	1st order SI	2nd order SI
E_p	7531	15.8	0.3	7148	25.4	0.3
ψ	4637	9.7	0.2	3927	13.9	0.3
ω	1144	2.4	0.3	1059	3.8	0.3
p	137	0.3	0.4	<0.1	<0.1	0.1
l	69	0.1	0.5	26	0.1	0.3
u	3217	6.8	0.5	1459	5.2	0.4
τ	9686	20.3	11.1	387	1.4	1.7
ρ	4	<0.1	10.8	317	1.1	1.2
K	1791	3.8	0.4	635	2.3	0.5

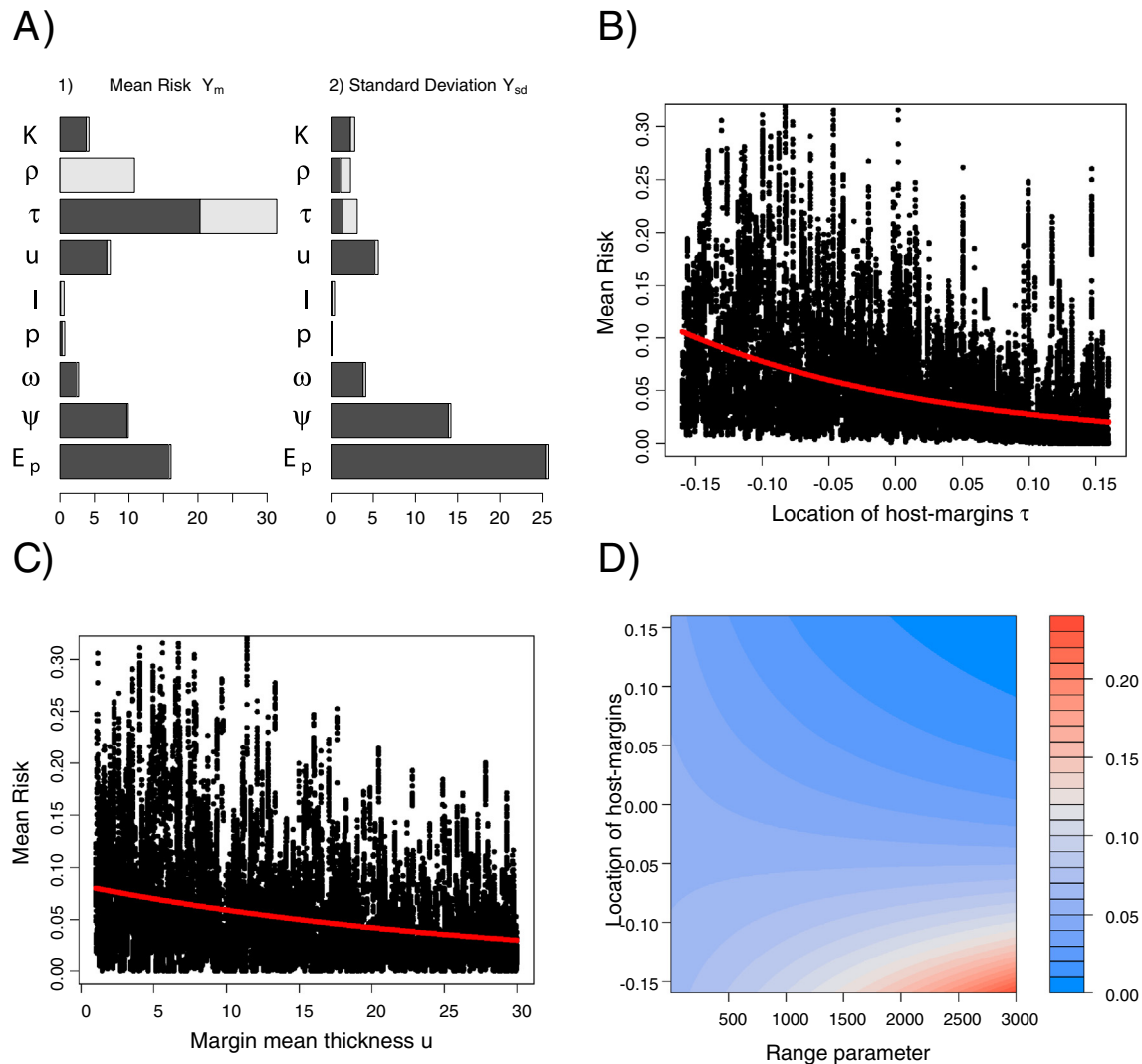


Fig. 4. Display of (A) Sensitivity Indices of our model, (B) the changes in Y_m with the location of host-margins τ , (C) the changes in Y_m with the mean width of host margins u , and (D) the interaction between the location of host-margins and the range parameter $\tau * \rho$. A.1) represents SIs for the mean individual mortality Y_m while (A.2) shows those for the standard deviation Y_{sd} . The SIs are obtained by dividing the deviance of parameters by the total deviance of the metamodel. First order SI are represented in dark-grey while second-order indices are in light-grey. In (B & C) the data (model outputs) are represented with black dots and predictions of the metamodel in red. D) shows how the mean risk changes with the location of host-margins and the range parameter as predicted by the metamodel. Dark blue indicates low risk whereas red corresponds to higher mean risk.

the number of fields l and the proportion of GM fields p poorly influenced Y_m ($SI_{tot} = 0.6$ & 0.07 respectively) and Y_{sd} ($SI_{tot} = 0.4$ & 0.01 respectively) (Fig. 4A & Table 2), the location of host-margins in relation to GM fields τ , the spatial aggregation of GM fields ρ , and the width of host-margins u influenced significantly Y_m ($SI_{tot} = 31.4$, 10.8 & 7.3 respectively), and in a lesser extent, Y_{sd} ($SI_{tot} = 3.1$, 2.3 & 5.6 respectively) (Table 2). Despite the fact we concentrated on exposed NTOs the most at risk and did not consider long distances, a limited positive repulsiveness ($\tau > 0$) already reduced the risk (Fig. 4B). The range parameter ρ that controls the spatial aggregation of emitting fields had an important effect on Y_m through its interaction with τ (2nd order $SI = 10.8$). Logically, landscapes with aggregated GM fields and habitat areas located away from them mitigated the risk (Fig. 4D). However, this interaction also suggested that if the location of habitat areas cannot be managed or is unknown (no control of τ) it might be, on average, relevant to disaggregate Bt fields in the landscape to prevent the occurrence of hazardous situations (Fig. 4D). Finally, in line with previous findings and suggestions (Perry et al., 2010; Pleasants et al., 2001) the observed effect of host-margins width u shows that even a small increase in the size

of habitat areas (e.g. 5 m) may help to reduce significantly the risk (Fig. 4C).

4. Discussion

In this study we focused on the role of space in landscape ERA by considering spatial exposure-hazard and landscape models in worst-case scenarios where individuals are temporally and spatially exposed to toxic particles. In a context where the protection of NTOs exposed to GM crops is still discussed among the scientific community (EFSA, 2016; Hofmann et al., 2016; Holst et al., 2013; Kruse-Plass et al., 2017; Perry et al., 2013, 2017, 2012), this work provides a methodological contribution to model-based ERA, gives insight into the spatial determinants of the risk which might be considered for the design of mitigation strategies at the landscape level and, points out the components that would require strong attention in further modelling studies and data collection. Albeit this study was carried out for the specific case of Bt maize on the typical NTO *I. io*, our models may apply to other instances that involve several sources of spreading toxic particles and immobile exposed individuals in a

landscape (e.g. the risk of pesticides on NTOs (Topping et al., 2015, 2016)). For the ecological impact of GM crops, known variations in the susceptibility of species and in the toxicity of Cry proteins produced by Bt crops (e.g. the maize 1507 expressing the Cry1F protein versus the maize MON810 that produces the Cry1Ab) may modulate the highlighted effects (EFSA, 2012; Perry et al., 2012), but, we believe that our results may be qualitatively generic for various NTOs exposed to Bt pollen in agroecosystems.

Regarding previous studies on the impact of GM Bt maize on non-target *Lepidoptera* our modelling framework exhibits some original components. First, it expands previous models of exposure (Holst et al., 2013; Lang et al., 2015; Perry et al., 2012, 2010) to a spatial version with an explicit model for the wind-borne dispersal of pollen grains. Albeit several models have been developed and validated against experimental data for maize pollen dispersal (Arritt et al., 2007; Klein et al., 2003), the models used for assessing the impact of GM crops on NTOs either ignore this spatial process (Holst et al., 2013), or, only consider an empirical function that describes a dispersal gradient (i.e. how the amount of pollen change with the distance to the closest emitting field) (Hofmann et al., 2016; Perry et al., 2012; Pleasants et al., 2001). As it assumes a perfect mixing between interacting individuals (here emitting Bt maize plants and exposed larvae) the mean-field approximation of non-spatial models might lead to overestimations of the risk when NTOs are not located in emitting fields (see Section 3 in Appendix A2). Semi-spatial approaches based on empirical dispersal gradients give a robust description of pollen deposition patterns recorded during specific experiments but, as they do not integrate the contribution of every sources with the dispersal process, can fail to predict the effects of both the landscape and the intensity of pollen emission on the spatial distribution of pollen (Klein et al., 2006; Lavigne et al., 2008). Thus, we believe that our explicit dispersal model, which was inspired by theoretical works (Bolker et al., 2000; Coville, 2015; Durrett and Levin, 1994; Filipe and Maule, 2004) and models developed for investigating the coexistence of GM and non-GM crops (Angevin et al., 2008; Klein et al., 2003, 2006; Lavigne et al., 2008), is likely to improve landscape-scale predictions and feed the discussion on dispersal mechanisms for risk assessment (EFSA, 2015; Hofmann et al., 2014). Second, in order to investigate the effect of the spatial arrangement of landscapes we have used tools from spatial statistics to build an original stochastic landscape generator. While such methodology only provides a simplified representation of real agricultural landscapes, it captures key components of their spatial arrangement and is relevant to study the interaction between landscape structure and spatial population dynamics (Lavigne et al., 2008; Le Ber et al., 2009; Papaix et al., 2014a). In this work we designed a model that concentrates on worst-case scenarios with exposed individuals located at short or mid-distances to the closest GM field and, we controlled and varied only a few characteristics of the landscapes. However, existing methods of stochastic geometry (Chiu et al., 2013) and optimisation algorithms can be used to create more complex landscape models and assess *in silico* the influence of other descriptors on the risk (e.g. insecticide treated fields, host plant density, non-Bt maize fields) (Parisey et al., 2016). Third, in our model the exposed individuals are discrete (individual-based model (Durrett and Levin, 1994)) and two sources of spatial stochasticity are introduced when simulating landscapes and individual locations. Thus, it provides information at the individual level and gives a distribution of the between-individuals risk variability which is recognised to be important in quantitative ERA, for instance to design and evaluate management strategies (Suter II, 2016).

After having presented our model we considered the typical example of the impact of the maize MON810 on *I. io* and performed a GSA to assess the influence of our input parameters on the mean and the standard deviation of the risk at the landscape level. Although we did not mean to provide accurate risk predictions, our results

suggested a mean risk in the same order of magnitude of previous works (Perry et al., 2012, 2010). However, the output distributions of our *in silico* analysis pointed out the likely occurrence of situations with significant higher mortality and variability which illustrates the difficulty of managing the risk at the landscape level. Then, as suggested by numerous empirical and theoretical studies (Coville, 2015; EFSA, 2010; Perry et al., 2010; Thomas and Jones, 1993) the GSA showed the substantial effect (without interactions with other parameters) of the size of the habitat zones, where individuals may ingest the toxic pollen (Fig. 4A&C). While it is known that large refuge areas (e.g. meadows) promote the conservation of butterfly populations, a limited increase in the size of field margins with host plants also seems to support the protection of NTOs (see the decrease of the risk for small distances in Fig. 4C). Unsurprisingly, the GSA highlighted the main role of the location of host-margins in relation to emitting fields. Furthermore, the results also pointed out the substantial interaction between the spatial aggregation of GM fields and the location of host-margins. Landscapes with aggregated GM fields and habitat areas located away from GM crops would logically promote a decrease in the risk. However, if the spatial distribution of host plants is unknown, disaggregating GM fields may support risk mitigation. In practice, to overcome the lack of knowledge about the location of host plants or exposed individuals it would be interesting to manage the distribution of habitat zones (field margins or refuges) by sowing host plant species in suitable locations in the landscape. The GSA also exhibited the expected substantial effects of pollen emission, adherence and loss on both the mean and the variability of the risk (Table 2). Nevertheless, these parameters are generally highly variable and unfortunately almost impossible to control. Despite that, a better quantification of these processes would be important to improve quantitative predictions and decrease the uncertainty due to the lack of knowledge in modelling approaches (Suter II, 2016). Perhaps non-intuitively regarding the current debate about pollen dispersal for evaluating the risk of Bt maize (Hofmann et al., 2016; Kruse-Plass et al., 2017; Perry et al., 2017), our study moderates the expected influence of the dispersal kernel which came out relatively low in the hierarchy of the most influential parameters. This result is explained by location of exposed individuals in the vicinity of GM fields (Fig. S1), for which range of distances (i.e. closest GM field-exposed individual distances mainly between 4 and 500 m) the considered dispersal kernels have similar behaviours (Lavigne et al., 2008). It is recognised that dispersal mechanisms can interact strongly with the landscape structure at large spatial scales (Keitt et al., 1997). Typically, at short and mid-distances the amount of received particles depends mostly on the production of the closest source while at long distances (over 1 km here) it is mainly influenced by the total production in the landscape (i.e. pollen background level) and its spatial structure (Klein et al., 2006; Lavigne et al., 2008). Then, we suggest that new model-based landscape risk assessment could compare several experimentally-tested dispersal kernel functions to quantify the risk, and its variability, and identify critical situations when focusing on populations living about the toxic sources (short and mid-distances). However, if particular attention is paid to long distance issues, e.g. to define isolation distances that would prevent any hazard, it would be crucial to consider several validated kernels with contrasted long distance behaviours and, it is likely that the influence of parameters related to the toxic background level (i.e. the proportion of GM fields) would increase.

In this study we have confirmed the importance of treating explicitly space for landscape ERA. However, as the temporal dimension is known to be central in the specific case of the environmental impact of GM crops (Holst et al., 2013), focusing only on space is not enough to provide accurate risk predictions. Then, further quantitative approach should include the temporal dynamics of pollen emission (Angevin et al., 2008), pollen loss due to temporally distributed rain events (Allard and Bourotte, 2015; Walker et al., 2017) and, the phenology of

exposed individuals (Holst et al., 2013). As shown by numerous studies spatio-temporal models are central to the design of appropriate prevention policies (Angevin et al., 2008; Coville, 2015; Gilligan et al., 2007; Papaix et al., 2014b; Parisey et al., 2016) and would be useful for supporting the management of GM crops in agroecosystems (Walker et al., 2017). In addition, it would be relevant to consider recent empirical works to relax our assumptions regarding the feeding behaviour of exposed individuals and the variability in the spatial distribution of pollen grains within host-plant leaves and between host-plants (Hofmann et al., 2016; Lang and Otto, 2015). Furthermore, as *I. io* are generally clumped in real conditions it would be insightful to take into account more realistic spatial distributions of exposed individuals, as well as variability in the susceptibility of individuals located on the same host-plant, using existing methods for modelling spatial point processes (e.g. marked point processes, clustered point processes) (Illian et al., 2008). While such refinement could improve risk prediction, our main conclusions may still be valid. In fact, at the landscape level a group of individuals feeding on the same plant would be considered to be in the same location in the landscape. Then if individuals have equal susceptibility, clumps can be obtained by replicating the point process draw and the output distribution at the landscape level is similar. Nevertheless, the introduction of more realistic experimentally-validated toxicokinetic-toxicodynamics models (Derendorf and Meibohm, 1999) appears to be the major challenge in current ERAs and will be crucial for quantifying long-term impacts with sublethal effects, still seldom considered (Ashauer et al., 2011). Whereas these advanced ecotoxicological quantitative methods are common in ERA, e.g. for the impacts of chemical products on aquatic organisms, their use is still lacking in the case of GM crops for which only debated empirical dose-mortality relationships are available (Holst et al., 2013; Perry et al., 2013). Finally, another difficulty for the quantitative risk assessment of the impacts of GM crops on NTOs is the lack of empirical data which could enable the accurate quantification of key biological processes. While a strong experimental effort to improve the estimation of the related parameters (and their uncertainties) is critical, recent methods developed for the GSA of stochastic and spatio-temporal models (Marrel et al., 2012, 2016) would help to improve the estimation of SIs and thereby, gain insight into the most influential parameters and processes on which we should concentrate.

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