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# Trophic transfer of pesticides: the fine line between predator-prey regulation and pesticide-pest regulation

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**Running Title** Sensitive line of predator/pesticide pest-regulation

## Abstract

1. Understanding pesticide impacts on populations of target/non-target species and communities is a challenge to applied ecology. When predators that otherwise regulate pest densities ingest prey contaminated with pesticides, this can suppress predator populations by secondary poisoning. It is, however, unknown how species relationships and protocols of treatments (e.g. anticoagulant rodenticide (AR)) interact to affect pest regulation.
2. To tackle this issue, we modelled a heuristic non-spatialized system including montane water voles, specialist vole predators (stoats, weasels), and a generalist predator (red fox) which consume voles, mustelids and other prey. By carrying out a broad-range sensitivity analysis on poorly known toxicological parameters, we explored the impact of 5 farmer functional responses (defined by both AR quantity and threshold vole density above which AR spreading is prohibited) on predator-prey interactions, AR transfer across the trophic chain and population effects.
3. Spreading AR to maintain low vole densities suppressed mustelid and fox populations, leading to vole population dynamics being entirely regulated by AR use. Such vole-suppression treatment regimes inhibited predation ecosystem services and promoted pesticide dependence.

34 4. Keeping vole density below acceptable bounds by spreading AR while maintaining suffi-  
35 cient voles as prey resources led to less AR being applied and extended periods without AR  
36 in the environment, benefiting predators while avoiding episodes with high vole density.  
37 This may meet farm production interests while minimizing the impact on mustelid and  
38 fox populations and associated ecosystem processes. These alternating phases of mustelids  
39 and farmer regulation highlight the consequence of intraguild relationship where mustelids  
40 may rescue foxes from poisoning. Both global and wide-range sensitivity analysis illustrate  
41 the tightrope between predator-prey regulation and pesticide-pest regulation.

42 5. *Synthesis and applications* Different pesticide protocols lead to a rich variety of predator-  
43 prey dynamics in agro-ecosystems. Our model reveals the need to maintain refuges with  
44 sufficient non-poisoned voles for sustaining specialist mustelids, to conserve the predator  
45 community given the potential of secondary poisoning with rodenticides. We suggest that  
46 long periods without pesticide treatment are essential to maintain predator populations,  
47 and that practices of pesticides use that attempt to permanently suppress a pest over a  
48 large scale are counterproductive.

49 **Keywords** biodiversity conservation; secondary poisoning; cyclic fluctuations; pesticides; cascade  
50 effects; ecosystem service; sensitivity analysis ; ecological control

## 51 1 Introduction

52 Since the “green revolution” following the 1950s, pesticides use has increased to control pests  
53 damaging properties, public health or crops (Tilman et al., 2002). Pesticides usage is varyingly  
54 triggered by the perception/estimation of pest densities. Natural enemies (e.g., predators, para-  
55 sites, competitors) also reduce pest densities and hence may preclude the need for using pesticides  
56 (Michalko and Pekár, 2017). Natural enemies are, however, also affected by pesticides, either  
57 by direct exposure, through ingestion of contaminated prey (Berny, 2007) or indirectly through  
58 cascading consequences of effects of resource depletion (Halstead et al., 2014). Thus, under some  
59 regimes of pesticides use, pest populations only become regulated by pesticides once predators have  
60 collapsed. To preserve ecosystem health and the services that predators provide through regulation  
61 of pest densities, we need to assess the feasibility and benefit of pesticide treatment regimes in their  
62 ability to control pest species with minimal damage to predators (Halstead et al., 2014). It is how-  
63 ever empirically challenging to assess the overall impact of pesticide treatments on the dynamics of  
64 species linked by trophic interactions. In this context, process-based models describing simplified  
65 scenarios are powerful tools to reveal hidden patterns by disentangling processes emerging from  
66 pesticide impacts on predator-prey systems (e.g., Baudrot et al. (2018)).

67 Voles and other grassland rodent species undergo multi-annual population cycles (e.g., Krebs  
68 (2013)). At their peaks, they may attain extremely high densities, causing substantial damage  
69 to grass/cultivated crops and forestry and conflicts with humans (Delattre and Giraudoux, 2009).  
70 Farmers worldwide expand financial resources to purchase and spread anticoagulant rodenticides

71 (hereafter AR), hoping to reduce vole populations and damages, and increase profits despite the  
72 investment required (Stenseth et al., 2003). They do so according to protocols, equivalent to farmer  
73 functional responses (hereafter FFR), that involve varying amounts of AR spread in response to  
74 different thresholds in vole densities.

75 Voles and many small rodents are perceived as pests, but they are also keystone species, crucial  
76 to the functioning of grassland and forest ecosystems, as well as being the prey of numerous preda-  
77 tors, including species of conservation concern (Delibes-Mateos et al., 2011; Coeurdassier et al.,  
78 2014). Their population cycles create pulses of resources crucial to the viability of a wide range of  
79 resident predators and the aggregation of mobile avian vole predators (Korpimaki and Norrdahl,  
80 1991). The smallest mustelids (e.g. weasels *Mustela nivalis*) are specialist vole predators. Their  
81 numerical response has been shown theoretically to be necessary for generating predator-prey cy-  
82 cles (Hanski et al., 1991). They are said to be responsible for driving 3-to-5-year vole cycles in  
83 Fennoscandia (the specialist predation hypothesis) (Hanski et al., 1991). Generalist resident preda-  
84 tors like foxes (*Vulpes vulpes*) are expected to have regulatory and limiting effects on voles, owing  
85 to dietary plasticity that slows down vole population increase at low density (Hanski et al., 1991).  
86 Foxes do not show numerical responses to vole abundance (Weber et al., 2002) but they influence  
87 the food chain through occasional killing and consumption of bite-sized mustelids. Mustelids form  
88 a small proportion of fox diet (0-10%) but their offtake could represent a significant portion of the  
89 population (reviewed in Lambin (2018)).

90 Anticoagulant rodenticides are non-selective toxicants with deleterious effects on non-target  
91 fauna (e.g. Coeurdassier et al. (2014)). Despite AR being exclusively licensed for rodent control,  
92 a large number of predator species are secondarily exposed to AR (Sánchez-Barbudo et al., 2012).  
93 Consumption of dead and sub-lethally intoxicated voles reduced fox abundance in farmland in east-  
94 ern France (Jacquot et al., 2013) and ARs caused short-term declines in stoats in New Zealand  
95 (Alterio, 1996). Rodent-eating mustelid populations are affected by ARs given the pervasive levels  
96 of contamination reported (McDonald et al., 1998). Thus, there is little doubt ARs use inadvertently  
97 depresses predator populations. As predators likely limit vole populations, it is essential to under-  
98 stand when AR use becomes counterproductive by altering the pest population dynamics, producing  
99 more frequent outbreaks and high residual vole abundance.

100 With the aim of understanding the potentially complex interactions between prey that are per-  
101 ceived as pest, predators and farmers spreading rodenticide in response to vole abundance and their  
102 functional responses, we studied a simplified system inspired by cyclically fluctuating montane wa-  
103 ter voles (*Arvicola scherman*), small mustelids (stoats, weasels) that mostly eat voles (specialists),  
104 and foxes (generalists), with voles and mustelids as food items. We used a process-based model  
105 using differential equations to explore 5 FFR types of AR spread, combining population dynamics,  
106 predator-prey interactions and rodenticide transfer across the trophic chain. Model parameters and  
107 FFR were inspired by farming systems in the Jura Mountains, Franche-Comté (France), the region  
108 of Comté cheese production. In Franche-Comté, farmers shifted from polyculture to almost exclu-

109 sively grass production for milk used to produce cheese from the early 1970s (Giraudoux et al.,  
 110 1997). Due to recurrent vole outbreaks and damages to grasslands, massive rodenticide treatments  
 111 were implemented from the early 80s with consequences on non-target wildlife. Practices were de-  
 112 veloped technically under pressure from public opinion, farmer unions and farmer technical orga-  
 113 nizations collaborating with researchers to find treatment regimes with less harmful consequences  
 114 for biodiversity (Delattre and Giraudoux, 2009).

115 Hence, our main objective was to explore the properties of FFR in relation to varying population  
 116 sensitivity to AR on the global tri-trophic population dynamics made of vole outbreak frequencies  
 117 and guild of interacting predators.

## 118 2 Materials and Methods

119 We specified and parameterized the tri-trophic system of voles-mustelids-foxes with use of AR by  
 120 farmers in response to vole density. We considered several FFR depending on the AR amount and  
 121 vole threshold triggering AR spreading to assess AR upward transfer through the trophic web. In  
 122 all cases, parameterization units are on hectare<sup>-1</sup> and day<sup>-1</sup>.

### 123 2.1 Model for the tri-trophic dynamic

124 We considered a tri-trophic system described by Figure 1 and equations (1-5); parameterization is  
 125 provided in Table 1. Voles, denoted  $V$ , were the primary prey, Mustelids,  $M$ , intermediate preda-  
 126 tors, and Foxes,  $F$ , were top predators, consuming voles and mustelids. For each species, the  
 127 instantaneous variation of population size over time is:

$$\begin{cases} \frac{dV}{dt} &= Vr_V \left(1 - \frac{V}{K_V}\right) - \Phi_{V,M}(V)M - \Phi_{V,F}(V, M)F \\ \frac{dM}{dt} &= \varepsilon_M \Phi_{V,M}(V)M - m_M M - \Phi_{M,F}(V, M)F \\ \frac{dF}{dt} &= Fr_F \left(1 - \frac{F}{K_F}\right) \end{cases} \quad (1)$$

128 The vole population followed a logistic growth rate, with  $r_V$  the maximal reproduction rate,  
 129 fixed at  $r_V = \ln(2 \times 600)/365$  per day, since montane water vole populations can increase from 0 to  
 130 600 individuals ha<sup>-1</sup> or more (Giraudoux et al., 1997), resulting in the equilibrium density being  
 131 fixed at  $K_V = 600$  individuals. The vole population was preyed upon by mustelid and fox popula-  
 132 tions. The vole consumption rate at different vole densities was described by functional responses  
 133 ( $\Phi_{V,M}$  for mustelids,  $\Phi_{V,F}$  for foxes), see equation (2). We assumed small mustelids behave as spe-  
 134 cialist predators (King and Powell, 2006), we considered a numerical response linearly dependent  
 135 on the functional response with parameter  $\varepsilon_M$  (dimensionless) as conversion efficiency of prey into  
 136 newborn predator (see Supporting Information - Appendix S1). The mustelid background mortality  
 137 rate (i.e. all other reasons of death: ageing, disease, etc.) was  $m_M$  parameterized has the inverse

138 of life expectancy (Table 1). We assumed foxes had a logistic growth rate function, parameterized  
 139 with maximal growth rate  $r_F = \ln(3)/365$  and equilibrium density  $K_F = 0.03$  individuals  $\text{ha}^{-1}$   
 140 (Ruelle et al., 2003) without numerical response (Weber et al., 2002).

141 Since we treated small mustelids as vole specialist predators, we assumed a Holling Type II  
 142 functional response with attack rate  $a_M$  and handling time  $h_M$  (equation (2)). We then represented  
 143 foxes feeding on voles and mustelids by a multi-species functional response derived from Holling  
 144 Type III, referring to generalist feeding behaviour (Baudrot et al., 2016). For that, we denoted  
 145  $a_{VF}$  and  $a_{MF}$  the fox attack rate on voles and mustelids respectively. The parameter  $h_F$  was the  
 146 handling time for foxes.

$$\begin{aligned}\Phi_{V,M}(V)M &= \frac{a_M V}{1 + h_M a_M V} \\ \Phi_{V,F} &= \frac{a_{VF} V}{a_{VF} V + a_{MF} M} \times \frac{(a_{VF} V + a_{MF} M)^2}{1 + h_F (a_{VF} V + a_{MF} M)^2} \\ \Phi_{M,F}(V, M)F &= \frac{a_{MF} V}{a_{VF} V + a_{MF} M} \times \frac{(a_{VF} V + a_{MF} M)^2}{1 + h_F (a_{VF} V + a_{MF} M)^2}\end{aligned}\quad (2)$$

147 Parameterization of functional responses was estimated to fit the daily satiation level of preda-  
 148 tors for handling times, and the observed 5-6 year vole cycles for attack rates (Table 1). We assumed  
 149 foxes spent longer searching for voles than mustelids, based on each species diet and daily number  
 150 of individuals captured. Therefore,  $a_{VF}$  was considered larger than  $a_{MF}$  and selected to produce  
 151 6-year vole cycles without AR.

## 152 2.2 Model with rodenticide

153 Figure 1 represents the whole study system. Rodenticide is spread in grasslands during treatments,  
 154 denoted  $T_{Broma}(V)$ , triggered by vole density  $V$ . Firstly, baits (50 mg  $\text{kg}^{-1}$  of bromadiolone, here-  
 155 after AR) were spread in grasslands at quantity 7.5 to 20  $\text{kg ha}^{-1} \text{day}^{-1}$ . Notation  $\text{day}^{-1}$  stands  
 156 because of the daily time resolution. Such quantity,  $C$ , was available for voles, and a proportion  
 157 disappeared in the environment at rate  $k_0$  (set at  $k_0 = 0.0815$ ) (Sage et al., 2008). The proportion  
 158 consumed per vole, with rate  $\kappa(C)$ , was assumed to be an increasing function. The function  $\kappa(C)$   
 159 was characterized by a maximum ingestion  $M_{in}$ , and a half-saturation constant for ingestion  $D_{in}$  in  
 160 [ $\text{mg kg}^{-1}$ ]:

$$\kappa(C) = \frac{M_{in} \times C}{D_{in} + C} \quad (3)$$

161 For the toxicokinetics of AR (i.e. internal compound dynamics) leading to AR concentrations  
 162 in animal body (voles, mustelids and foxes), we considered an uptake without biotransformation  
 163 and time-regulated distribution, (i.e. AR concentration in the body of animals was instantly ho-  
 164 mogeneous) and that the whole body was consumed or scavenged without selection/rejection of  
 165 tissues-organs. We also assumed disappearance including excretion of the parent compound and  
 166 metabolisation, and that metabolites were non-toxic and/or excreted in the scats. For the toxi-

167 cokinetics of AR ingested by voles, a fraction  $C_V$  was assumed to remain active and available to  
 168 predators ingesting voles. The absorption rate of ARs ( $\eta$ ) exceeds 50% in less than 24h (Jacquot  
 169 et al., 2013). The excretion rate from voles,  $k_{out,V}$  was  $0.4 \text{ day}^{-1}$  (Sage et al., 2008). The mortality  
 170 rate through ARs was  $\mu(D_V)$ . Death through poisoning created a dead vole population ( $V_d$ ) with AR  
 171 concentration  $C_V$ . Dead voles could either be scavenged by mustelids/foxes or decompose at rate  
 172  $d$ . We assumed AR in dead voles disappeared from the system when voles decomposed (assumed  
 173 in one week:  $d = 1/7 \text{ day}^{-1}$ ). Mustelids could feed on live voles  $V$ , or non-decomposed dead voles  
 174  $V_d$  and we assumed a Type II functional response adapted for a multi-species functional response  
 175 (Baudrot et al., 2016). Mustelids ingested AR with absorption rate  $\eta_M$  (ratio between biomasses of  
 176 voles,  $B_V$ , and mustelids,  $B_M$ ) and the total of ingested voles (alive  $V$  and dead  $V_d$ ) was defined  
 177 by function  $\Theta_M(V, V_d)$  (Table 1).

178 A fraction of AR ingested was accumulated in weasels while the rest was excreted with rate  
 179  $k_{out,M}$ . AR contaminating weasel through vole poisoning, is denoted  $D_M$ , induces lethal effect at  
 180 rate  $\mu_M(D_M)$ , additive to natural mortality rate  $m_M$ . Parameter definitions are further detailed  
 181 in Supporting Information (Appendix S1). AR was ingested by foxes with a rate proportional to  
 182 the functional response of foxes to voles, dead voles and mustelids. Foxes also accumulated AR  
 183 available in their prey, resulting in upward AR transfer in the trophic chain. Foxes accumulated AR  
 184 in concentration  $C_F$ . A fraction of AR was excreted by foxes at rate  $k_{out,F}$  at a rate between 0.38  
 185 and  $0.72 \text{ day}^{-1}$  (Sage et al., 2010), and AR caused fox mortality at rate  $\mu_F(D_F)$ .

186 We used log-logistic equations for describing dose-dependent mortality of animals exposed to  
 187 AR. Vole and predator mortality rates due to AR  $\mu_X(D_X)$  ( $X$  referring to the considered species)  
 188 were expressed by equation (5):

$$\mu_X(\zeta_X) = 1 - \frac{1}{1 + (LD_{50}/\zeta_X)^H} \quad (4)$$

189 The parameter  $LD_{50}$  is the daily median lethal dose (50% of population dying), parameter  $H$   
 190 is the Hill's coefficient modulating the curve steepness (see Table 1). Parameterization of  $LD_{50}$  is  
 191 important since it defines the inflexion point of the ecotoxicological effect. While it is a classical  
 192 parameter targeted in experiments, empirical estimates of its value are highly uncertain and indeed  
 193 span different order of magnitude for the same species and under the same experimental design  
 194 (Grolleau et al., 1989; Erickson and Urban, 2004; Sage et al., 2010; Karmaus et al., 2018). We  
 195 therefore carefully explored this parameterization through a wide-range sensitivity analysis detailed  
 196 here-after (see also Figure 2).

### 197 2.3 The farmer functional responses (FFRs) explored through simulation

198 We considered a range of realistic FFRs spanning treatments during vole outbreaks only and a  
 199 precautionary approach in which treatments only takes place at intermediate or low vole density  
 200 threshold. These scenarios are inspired by historic and contemporary protocols of bromadiolone

201 use to control montane water voles in Franche-Comté, but also representative of practice globally  
202 (Delattre and Giraudoux, 2009): (A) a scenario without AR treatment, (B) a scenario with high  
203 vole density threshold triggering treatment ( $500 \text{ ind ha}^{-1}$ ) and high AR amount per treatment ( $20$   
204  $\text{kg ha}^{-1}$ ), (C) a third scenario with intermediate triggering threshold ( $250 \text{ ind ha}^{-1}$ ) and high AR  
205 per treatment ( $20 \text{ kg ha}^{-1}$ ), (D) scenario with intermediate threshold ( $250 \text{ ind ha}^{-1}$ ) and low AR  
206 amount ( $7.5 \text{ kg ha}^{-1}$ ) and (E) scenario with low threshold ( $50 \text{ ind ha}^{-1}$ ) and low treatment ( $7.5$   
207  $\text{kg ha}^{-1}$ ). To check the influence of predators such as foxes and intraguild predation on the system  
208 dynamics, we also simulated scenarios with and without foxes. Our simulations tracked the linked  
209 vole-mustelid-fox dynamics for 40 years, after a “burn-in” period of 10 years to reduce dependency  
210 of results upon initial conditions, to observe several vole cycles and to characterise AR effects on  
211 these species population dynamics. This burn-in period also had AR treatment triggered at specific  
212 vole densities and with a given rodenticide quantity for each FFR. The burn-in phase was selected  
213 according to a set of simulations with different initial conditions. Those simulations showed that in  
214 a given FFR (i.e., same threshold of vole density and amount of AR spread), the dynamics of the  
215 population were converging toward a similar pattern.

## 216 2.4 Numerical Simulation and Sensitivity Analysis

217 All numerical analysis have been done using the open language R and particularly the ODE solver  
218 package *deSolve* (Soetaert et al., 2010). Model implementation and code to run analysis are avail-  
219 able on a Github repository (Baudrot et al., 2020).

220 We applied a wide-range sensitivity analysis on lethal dose parameters (i.e.  $LD_{50}$ ) for voles,  
221 mustelids and foxes, to explore changes in dynamical patterns. While wide-range variations of each  
222 parameter is likely to impact the global pattern, the lethal dose parameter is a direct characteristic  
223 of the toxicological part of the model. The variability of  $LD_{50}$  from *in vivo* acute systemic toxicity  
224 studies under same experimental design spans 2 to 3 order of magnitude (see rat oral acute toxicity  
225 in Karmaus et al. (2018)), which makes it challenging to assess risk with exposure models. Since  
226 the  $LD_{50}$  parameter of fox appears to have low impact on dynamical pattern in our model, we  
227 evaluated only 4 different values (i.e. 0.5, 1.5, 2 and 7 ppm) which are consistent with a large  
228 range covering such a parameter (Erickson and Urban, 2004; Sage et al., 2010). For the prey and  
229 the specialist predator, this parameter was much more sensitive, so we explored 10 values for both,  
230 respectively in the range  $[0.7 - 7]$  ppm and  $[1 - 25]$  ppm following consistent ranges (Grolleau  
231 et al., 1989; Erickson and Urban, 2004). We classified the subsequent 1600 simulations according  
232 to the dynamical pattern of mustelids population: either "periodic regulation by mustelid" or "AR  
233 permanent regulation" where mustelids collapse.

234 Then, we performed a local sensitivity analysis to study changes in model outputs apportioned  
235 to small variation around model parameters input (Saltelli et al., 2019). We applied a first-order  
236 Sobol’s sensitivity index  $S_i$  defined as  $S_i = \mathbb{V}(\mathbb{E}_{-i}(y|x_i))/\mathbb{V}(y)$ , where  $\mathbb{V}(y)$  is the variance of  $y$  when  
237 all factors are allowed to vary,  $\mathbb{E}_{x \sim i}(y|x_i)$  the mean of  $y$  when one factor is fixed (Sobol and Saltelli,



238 1993). We defined the domain of variation with a beta distribution within an hyperspace of plus  
239 or minus 10% from the original value for all parameters. For output variable of local sensitivity  
240 analysis, we estimated the following cost functions: (i) Number of treatment events per FFR; (ii)  
241 Cumulative amount of AR (kg); (iii) Proportion of time when the AR-induced mortality of mustelids  
242 higher than 50% (i.e. lethal exposure profile killing 50% of mustelid population); (iv) Proportion of  
243 time when the mortality of mustelids was higher than 50% due to natural mortality (see Supporting  
244 Information - DATA available); (v) Proportion of time when the vole density was below 50 voles  
245  $\text{ha}^{-1}$ , as a proxy for time when forage grass grows with low herbivore influence; (vi) Mean vole,  
246 mustelid and fox densities.

## 247 **3 Results**

248 Allowing for mortality by predators ingesting AR-poisoned voles changed the outcome of predator-  
249 prey dynamics involving vole, mustelid and fox populations. Secondary poisoning led to a rich  
250 spectrum of emergent dynamics according to the FFR to vole abundance. Without AR (scenario  
251 A), vole dynamics were regulated by mustelid predation that gave rise to a 6-year cycles (Figure 3)  
252 typical of prey-specialist dynamics, while the generalist fox population remained at its carrying  
253 capacity (i.e.,  $0.03 \text{ ind ha}^{-1}$ , see Table 1). Based on this null model, we explored 4 scenarios of  
254 treatment described earlier and denoted respectively B, C, D and E, defined by the vole density  
255 threshold triggering treatment (respectively: 500, 250, 250 and  $50 \text{ ind ha}^{-1}$ ) and the AR amount  
256 per treatment (respectively: 20, 20, 7.5 and  $7.5 \text{ kg ha}^{-1}$ ).

### 257 **3.1 Sensitivity analysis of model parameters**

258 The exploration of ecotoxicological uncertainties on population dynamics was performed for the  
259 lethal dose parameters  $LD_{50}$  for voles, mustelids and foxes (see Figure 2). From the 1600 pat-  
260 terns explored two typical patterns emerged. On the one hand (i) vole dynamics were sequentially  
261 regulated by either AR treatments, which we refer to as farmer-regulated phase, or by mustelids,  
262 mustelids-regulated phase (see in Figure 3 panel c. B-2). This succession of farmer-regulated and  
263 mustelids-regulated phases are denoted "Mustelid periodic regulation" in Figure 2 (black pixels).  
264 On the other hand, (ii) vole dynamics were permanently regulated by AR treatments, because of  
265 crashes of the mustelid population we refer to as "Permanent AR regulation" in Figure 2 (grey pix-  
266 els). We see that  $LD_{50}$  for foxes does not change the general pattern of dynamics. Both scenario B  
267 and D exhibited the highest fractions of "Mustelid periodic regulation" compared to scenarios C and  
268 E. This illustrates the tight line that exists between resource and AR impact to benefit from predator  
269 regulation periods.

270 For other parameters, we performed a local sensitivity analysis where we computed a first order  
271 sensitivity index (Sobol and Saltelli, 1993; Saltelli et al., 2019) given the contribution of each  
272 parameter to the variance (in Figure 5 for scenario D - intermediate amount of  $7.5 \text{ kg AR}$  at threshold

273 density of 250 voles). Parameter values were moved within +/- 10% interval around the fixed  
274 value as defined in scenario D (see Table 1). Crossing all cost functions to test the sensitivity of  
275 model parameters (Figure 5), the influence of each parameter was quite homogeneous. There was  
276 no redundant or conversely any parameters with a dominant influence on model behaviour. The  
277 homogeneity of the sensitivity to parameters was particularly true for densities of predators to which  
278 we focused our attention.

### 279 3.2 Population dynamics

280 While both "Mustelid periodic regulation" and "Permanent AR regulation" pattern occurred under  
281 the 4 scenarios with AR (B, C, D and E) (see Figure 2), we illustrate in Figure 3 the most contrasting  
282 population dynamics for each of scenario in order to better describe their underlying mechanism.  
283 The boundary between contrasting dynamics lies for vole  $LD_{50}$  around 1.5 to 2 ppm and in the  
284 range 2 to 2.25 ppm for mustelid  $LD_{50}$ .

285 From Figure 3, we see that scenario B (high vole density threshold triggering treatment and  
286 high AR amount per treatment) and scenario D (intermediate threshold and low AR amount) ac-  
287 counts for the most of dynamics with sequential farmer-regulated phase and mustelids-regulated  
288 phase. Farmer-regulated periods started when densities of living voles triggered treatments. This  
289 produced sudden declines of live voles followed by increases of dead voles. However, the vole pop-  
290 ulation recovered quickly which triggered repeated further treatments and pulses of availability of  
291 contaminated (both live and dead) voles. Also, in scenario D, vole declines were not as deep as  
292 when pulses of AR amount were high like in scenario B (see Supporting Information), owing to the  
293 reduced AR amount per treatment. Mustelids and sometimes foxes also experienced AR-induced  
294 declines during this period (Figure 3-c,f,g,h and Figure 4). For the predators, mustelid-regulated  
295 periods started when mustelid numbers grew slowly to a peak, which depressed vole density, pre-  
296 cluding AR treatments and releasing the fox population from secondary poisoning, such that its  
297 abundance rebounded. Vole depletion by mustelids and subsequent mustelid declines allowed the  
298 vole population to grow again up to threshold densities that initiated a new period of regulation by  
299 farmers.

300 For scenario C (intermediate threshold and high AR), vole dynamics were mostly regulated by  
301 AR treatment only (e.g. Figure 3-e). Populations of live and dead voles experienced high frequency  
302 fluctuations driven by AR. As AR treatments were frequent, being triggered by vole peaks, contami-  
303 nated dead voles were always abundant (see Supporting Information: peaks at  $90 \text{ ind ha}^{-1}$ ). With  
304 scenario E (low threshold, low AR) vole populations were maintained by farmers at around 50 voles  
305  $\text{ha}^{-1}$  (See Figure 3 and Supporting Information). The population of live voles was regulated by  
306 treatments. For most of simulations (except when vole  $LD_{50}$  with high, Figure 2), whenever voles  
307 reached densities triggering treatment, predator populations experienced strong declines. However,  
308 fox densities were higher compared to scenario C (intermediate threshold, high AR) (see Support-  
309 ing Information), reflecting the reduced amount of AR used (7.5 kg) and transferred to foxes as

310 there were lower vole densities. The maximum numbers of dead voles under this scenario E was  
311 relatively low (highest around 15 ind ha<sup>-1</sup>) but, due to frequent treatments, there was a steady  
312 replenishment of contaminated dead voles. This, in turn, induced mustelid and fox mortality and  
313 population declines (Supporting Information). Additionally, low availability of live voles triggered  
314 small mustelids mortality through starvation, down to abundances similar to those resulting from  
315 AR use (Supporting Information).

### 316 **3.3 Influence of intra-guild predation**

317 Figure 4 shows the system dynamics under a scenario D, where successive farmer-regulated and  
318 mustelids-regulated phases occurred. This simulation shows that the removal of foxes did not elim-  
319 inate the successions of mustelids-regulated and farmer-regulated phases. However, the mustelid  
320 regulated period allowed short-term peaks of voles, suggesting the emergence of a classical one-  
321 predator - one-prey cycles interrupted by a farmer-regulated period. Without foxes, population  
322 dynamics of mustelids presented a more chaotic behaviour, while it presented regular cyclic pattern  
323 with fox occurrence. Therefore, this simple model suggests a stabilizing role of a generalist predator  
324 (foxes in this system) during the mustelid-regulated period. At the end of the mustelid-regulated  
325 period, foxes strongly contributed to vole mortality and, to a lesser degree, mustelid mortality. Con-  
326 sequently, the removal of foxes implied less predation on voles during the mustelid regulated period,  
327 and short-term vole releases from mustelid predation. The 2-year rolling mean of vole density (blue  
328 lines in Figure 4) illustrates the change of regime from farmer-regulated to mustelids-regulated  
329 alternating phases. Indeed, the amplitude of averaged vole densities (i.e., the amplitude of vole cy-  
330 cles for the 2-year rolling mean) was relatively stable at the beginning of farmer regulation periods  
331 and then suddenly decreased to become minimal before sharply increasing, announcing a regime  
332 change. These changes in density amplitude may be used as an early-warning signal of the regime  
333 transition.

## 334 **4 Discussion**

335 Considering that rodenticide kills not only voles but also their predators through secondary poison-  
336 ing, our models show that AR profoundly changes the modeled outcome of predator-prey dynamics  
337 involving vole, mustelid and fox populations beyond what mere intuition could elucidate. Our study  
338 reveals how the dual influences of the amount of pesticide spread and the vole density threshold  
339 triggering AR spread drive (i) pesticide spreading frequency, (ii) predation ecosystem service, and  
340 subsequently (iii) the control of pest outbreaks. Two types of a rich spectrum of emergent dynam-  
341 ics, including farmer or mustelid regulation changing from classical predator prey dynamics arose  
342 because poisoned voles acted as global stressor on the food chain.

## 343 **4.1 Modelling farmer regulation into a classical predator-prey system**

344 The threshold functional response of farmers deciding when to apply varying amounts of rodenti-  
345 cides according to prevailing vole density was crucial in selecting the emergent ecosystem dynamics,  
346 resulting in much variability in ecosystem and conservation and farming production interests. In  
347 the idealised ecosystem our models depict, farmers spreading rodenticide not only depleted vole  
348 prey exploited by specialist and generalist predators but also created pulses of lethally or sub-  
349 lethally poisoned voles that subsequently poison their predators. Arguably this set of ecological  
350 interactions has similarities with circumstances where a pathogen affecting prey species also in-  
351 fects predators, as in the case with the flea vectored plague (*Yersinia pestis*) infecting prairie dogs  
352 (*Cynomys* spp.) and black footed ferrets (*Mustela nigripes*) in central US (Matchett et al., 2010).  
353 However, to our knowledge, the behaviour of such tri-trophic model with multiple reciprocal in-  
354 teractions has not been explored. This is despite the obvious relevance to the management of the  
355 globally widespread circumstances where keystone small mammals are poisoned and may second-  
356 darily poison their predators (Delibes-Mateos et al., 2011).

357 Under the "reference" scenario without AR spreading (A), we assumed a predator-prey cycle  
358 which is a plausible pattern thoroughly explored theoretically (Hanski et al., 2001), though with  
359 debated empirical support (Lambin, 2018). There is no controversy on the role of small mustelids  
360 tracking vole dynamics, though it is not yet well understood whether there is sufficient lag between  
361 predators and prey for predation to drive steep declines (King and Powell, 2006). Parameters of  
362 the reference scenario for our predator-prey model were biologically realistic and tuned to generate  
363 population fluctuations similar to those observed in the studied cyclic system (Delattre and Girau-  
364 doux, 2009). The addition of pulses of rodenticide and their toxicokinetics in vole and predators  
365 are based on previous experiments with bromadiolone, a widely used AR, ensuring biologically  
366 realistic functional forms and their parameterization. Irrespective of the FFR considered, the fre-  
367 quency of vole cycles dramatically increased compared to the reference scenario, except during  
368 mustelid-regulated phases emerging under some FFR scenarios.

## 369 **4.2 How specialist predators may protect generalists from poisoning**

370 An interesting model behaviour with farmer- and mustelid-regulated phases alternating with low  
371 frequency was seen with scenarios B (high vole threshold, high AR) and D (intermediate vole thresh-  
372 old, intermediate AR), and to a lesser extent scenario C (intermediate vole threshold, high AR) and  
373 rarely with scenario E (lowest vole density threshold). Such flipping between alternative states in  
374 population dynamics has been previously described in predator-prey model where weasels rely on  
375 a primary prey and entrain the dynamics of secondary prey (Hanski and Henttonen, 1996) but not  
376 for the kind of indirect interaction we explore here. It further demonstrates that adding biologically  
377 realistic complexity to simple models may drastically change the emergent properties of trophic  
378 interactions. From these scenarios, we understand that the emergence of successive farmer- and  
379 mustelid-regulated phases is neither driven by vole density threshold alone nor by AR amount, but

380 instead by a subtle combination of both. Also, under scenarios with low  $LD_{50}$  for fox, the mod-  
381 elling description of these patterns uncovered the dual key roles of mustelids on fox dynamics, as  
382 intraguild competitors and as a vector for poisoning. This led to a surprising form of facilitation  
383 for foxes: mustelids protect foxes from collapses. The establishment of such a response can be  
384 described in 3 steps. Firstly, low mustelid densities inhibit their regulation of voles and contribute  
385 to farmer AR use. In line with empirical evidence, the latter directly impacts foxes by poisoning  
386 (Jacquot et al., 2013). Secondly, fox predation on mustelids is reduced, and with an intermediate  
387 AR amount, this allows mustelids to slowly recover. Vole outbreaks and subsequently farmer AR  
388 treatments are then gradually delayed, benefitting mustelids recovery. This is the point of transi-  
389 tion from farmer to mustelids regulation regimes, starting the third step: mustelids increase faster,  
390 suppressing vole densities and precluding the need for AR treatments, and eventually indirectly  
391 allowing the fox population growth.

392 Our findings that complexities in trophic interaction, induced by the poisoning of predator by  
393 poisoned prey, may cause the system to flip between alternative states is novel and robust. However,  
394 given we only explored deterministic and spatially homogeneous versions of our model, any infer-  
395 ence on the frequency of flipping between states should be cautious given the inherent stochastic  
396 nature of natural and farmland environments. If such dynamics occur within real farming sys-  
397 tems, flipping between states is unlikely to emerge with regularity where many other factors impact  
398 population dynamics. While generalists are known to have stabilising effect (Hanski et al., 1991),  
399 the benefit of specialist predators imparted to generalist predator and resulting increase in the  
400 prevalence of intraguild predation would be difficult to detect in empirical studies. Nevertheless,  
401 other generalist predators such as the endangered red kite (*Milvus milvus*) which feed on voles op-  
402 portunistically, occupy areas with bromadiolone treatments and are also affected by rodenticides  
403 (Coourdassier et al., 2014) and may therefore also benefit from the presence of mustelids in the  
404 ecosystem.

### 405 **4.3 How region-wide vole suppression may inhibit ecosystem services**

406 In many situations, notably scenario E and C and when vole and mustelids are highly sensitive  
407 to AR, the whole system was solely driven by farmer regulation, whereby the chronic use of AR  
408 completely suppressed the pest-regulation ecosystem service of predators. It has previously been  
409 shown empirically that repeated rodenticide treatments are highly detrimental to the populations of  
410 predators and reduce their densities (Jacquot et al., 2013). Secondary poisoning of predators is an  
411 established reality (Berny, 2007). Through modelling, we formalised the insight that some poison  
412 deployment protocols, including those presently used in the empirical system which motivated our  
413 study, are counterproductive if employed on a large scale, suppressing natural predator regulation  
414 of pest rodents. It has been long known that poisoning rodents with AR permeates the food chain  
415 at peak abundance, achieves little in terms of protecting crops and may have strong deleterious  
416 impact (Olea et al., 2009). In Franche-Comté, a change in treatment protocols, from controlling

417 voles at high densities to low-intermediate densities, has reduced the mortality of non-target species  
418 (including foxes) (Jacquot et al., 2013). Nevertheless, deployment regimes of pesticides that can  
419 contaminate the food chain should also include periods of time which permit predator populations  
420 to rebound and avoid extirpation from the ecosystem. We have shown that, over time, farmers who  
421 strictly maintain voles at low density thresholds would likely suppress predation services provided  
422 by vole predators and, in so doing, instigate pesticide dependence. In addition, small mammals  
423 like voles certainly have ecosystem functions. Our results also suggest that the presence of small  
424 mustelids in ecosystems is beneficial for biodiversity conservation (see above) and agriculture inter-  
425 ests. Given the importance of vole cycles and their trophic interactions, it is desirable to maintain  
426 vole population fluctuations of sufficient amplitude to maintain ecosystem processes.

#### 427 **4.4 Managing rodents and ecosystems**

428 Presently, in Franche-Comté, farmers relying on bromadiolone alone can only treat pre-emptively  
429 when voles are at low densities (scenario E) whereas those also using alternative methods (i.e.,  
430 mechanical, not pesticide-based) are allowed to spread AR in low quantity up to intermediate vole  
431 densities (scenario D). Spreading AR in low quantity seems superficially desirable, but our heuris-  
432 tic model, assuming an idealised homogenous landscape, shows this is associated with frequent  
433 treatments. Consequently, it would induce a near permanent availability of a small number of in-  
434 toxicated voles which, combined with low availability of non-contaminated voles, would reduce  
435 predator populations. Therefore, the extreme situation of using a low vole density threshold (sce-  
436 nario E) at a large scale is undesirable because it depletes the prey resources of foxes and mustelids  
437 and their populations. Triggering treatment at intermediate vole density with a low amount of AR  
438 (scenario D) allows for temporal refuges, i.e. longer periods free of rodenticide necessary for preda-  
439 tor densities to rebound while simultaneously avoiding episodes with high vole density, as required  
440 by farm production interests. Under a landscape management approach, such temporal refuges  
441 could arguably be substituted for by spatial refuges, with parts of the landscape free of pesticides  
442 and fuel the recolonisation of the farming landscape by predator populations.

443 Our key result and the basis for management prescriptions is that allowing for refuges where  
444 voles are not poisoned and allowed to persist at medium-high densities such that they can be  
445 exploited by mustelids is crucial for predator population recovery and preserving the ecosystem  
446 services mustelids deliver. Treatment regimes allowing temporal and/or spatial refuges seems com-  
447 patible with both conservation and farming interests. A critical insight is to avoid potential side  
448 effects of chronic low-dose AR prescription (e.g., depletion of community services, stimulation of  
449 resistances), as is well known with antibiotics, by demanding regularly long-term period without  
450 treatment. However, combining chronic treatments and long periods free of AR may be difficult  
451 to achieve in real systems. Our model only considers temporal refuges, and the conceptualization  
452 of untreated areas as equivalent to triggering treatment at intermediate vole density cannot pro-  
453 vide guidance on the size of these spatial refuges. Nevertheless, while management of voles is

454 implemented at the scale of fields, mustelids and foxes roams over much larger areas (King and  
455 Powell, 2006), such that large refuges with medium-high vole densities voles would be required  
456 while maintaining low vole density at local scale.

## 457 **4.5 Conclusion and perspectives**

458 Our process-based model revealed pesticides that permeate the food chain upward can lead to di-  
459 verse population dynamics with alternative states regulated by predators and farmers. It also shows  
460 that the practice currently promoted to use low-dose AR treatments at low vole density could have  
461 the undesirable side-effects of leading to chronic application of AR on a large scale, in the absence  
462 of refuges, and the depletion of the vole predator community. This emerging question would benefit  
463 from a landscape modelling approach to characterize spatial refuges. An other prerequisite for this  
464 work becoming applied and guiding management practice would be to further explore toxicologi-  
465 cal lethal and sublethal (e.g. growth, reproduction, behaviour) effects of pesticides on population  
466 dynamics. We have also uncovered a counterintuitive mechanism whereby, owing to intraguild  
467 predation, mustelids could rescue foxes from poisoning. This suggest that contemporary Environ-  
468 mental Risk Assessment of pesticides that mostly consider one-species - one-compound experiments  
469 fail to capture the impact of pesticides on trophic links. Assessing risk at the ecosystem level is  
470 empirically challenging such that process-based modelling can play a critical role.

## 471 **Authors' contributions**

472 XL conceived the initial idea; all authors developed the concept; VB and JF developed the models  
473 and led manuscript writing; VB implemented the model and ran simulations. GC contributed treat-  
474 ment protocols; MC, JF and VB explored model parameters; XL, PG and MC contributed critically  
475 to drafts; all authors gave final approval for publication.

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## 482 **DATA availability statement**

483 All code and data used for this manuscript are available on Github [https://zenodo.org/badge/](https://zenodo.org/badge/latestdoi/233555669)  
484 [latestdoi/233555669](https://zenodo.org/badge/latestdoi/233555669) (Baudrot et al., 2020).

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Table 1 – Populations dynamics and toxicological parameters used in the model simulations. Notation ppm stands for parts-per-million [ $\text{mg kg}^{-1}$ ] and n.d. denotes a dimensionless parameter. See description in Methods.

Parameters	Definitions	Units	Value
<b>Population dynamics parameters</b>			
$r_V$	Maximal growth rate of voles	$\text{day}^{-1}$	$\ln(2 \times 600)/365$
$K_V$	Carrying capacity of voles	$\text{ind ha}^{-1}$	600
$a_M$	Attack rate of mustelids on voles	$\text{day}^{-1}$	1/30
$h_M$	Handling time of mustelids on voles	day	1/3.5
$a_{VF}$	Attack rate of foxes on voles	$\text{day}^{-1}$	1/10
$a_{MF}$	Attack rate of foxes on mustelids	$\text{day}^{-1}$	$1/10 \times 80/300$
$h_F$	Handling time of foxes on voles	day	1/6
$\varepsilon_M$	Conversion efficiency of ingested food	n.d.	0.0025
$m_M$	Natural mortality rate of mustelids	$\text{day}^{-1}$	$1/(0.8 \times 365)$
$r_F$	Maximal growth rate of foxes	$\text{day}^{-1}$	$\ln(3)/365$
$K_F$	Carrying capacity of foxes	$\text{ind ha}^{-1}$	0.03
$B_V$	Mean biomass of a vole individual	g	80
$B_M$	Mean biomass of a mustelid individual	g	300
$B_F$	Mean biomass of a fox individual	g	5800
$d$	Degradation rate of dead vole	$\text{ind.day}^{-1}$	1/7
<b>Toxicological parameters</b>			
$T_{broma}(V)$	Farmer input AR function of vole density	$\text{mg ha}^{-1} \text{day}^{-1}$	Scenarios
$k_0$	Disappearance of AR in the field	$\text{day}^{-1}$	$(0.106 + 0.057)/2$
$M_{in}$	Maximal intake rate of vole	$\text{ppm day}^{-1}$	$6 \times 1/5$
$D_{in}$	Half saturation intake rate of vole	ppm	100
$H_V, H_M, H_F$	Hill's coefficient dose-response curve	n.d.	4
$LD_{50,X}$	Lethal Dose for 50% of individuals of X	ppm	see Text
$\eta_M$	AR uptake rate in mustelids	n.d.	0.5
$\eta_F$	AR uptake rate in foxes	n.d.	0.5
$k_{out,V}$	Excretion rate of AR by voles	$\text{day}^{-1}$	0.4
$k_{out,M}$	Excretion rate of AR by mutelids	$\text{day}^{-1}$	0.6
$k_{out,F}$	Excretion rate of AR by foxes	$\text{day}^{-1}$	0.6

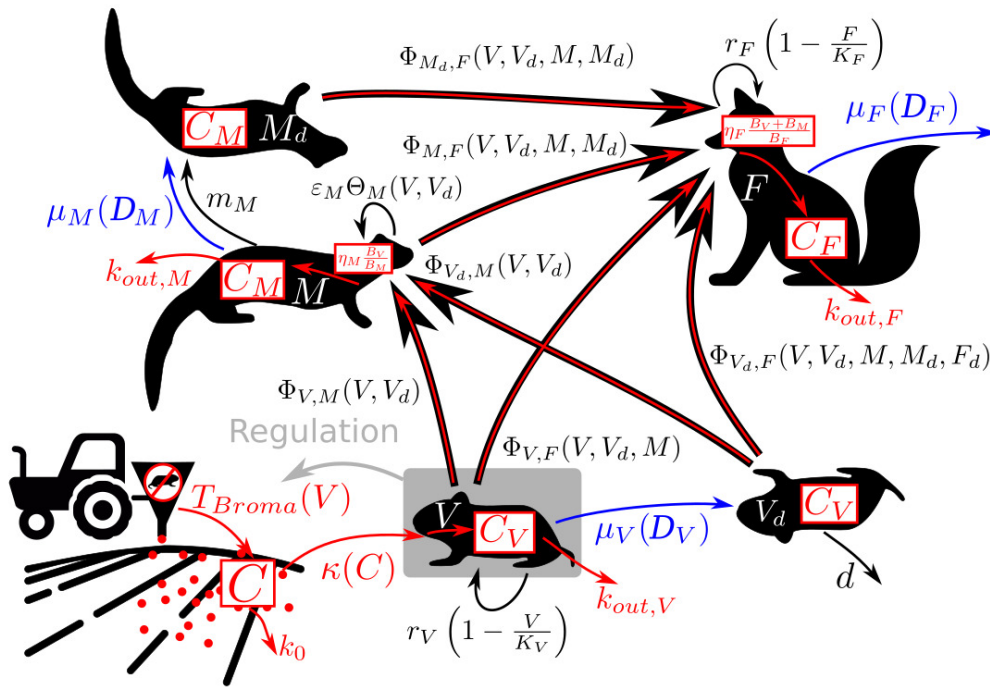


Figure 1 – Flow diagram of the fate and impacts of anticoagulant rodenticide (AR, bromadiolone) in a tri-trophic food web. Black arrows and equations correspond to natural dynamics with trophic interactions, red arrows and equations represent the transfer of AR through the system and its accumulation into the different compartments. The arrows and equations in blue correspond to its impact (i.e., death of individuals) on the three species populations.

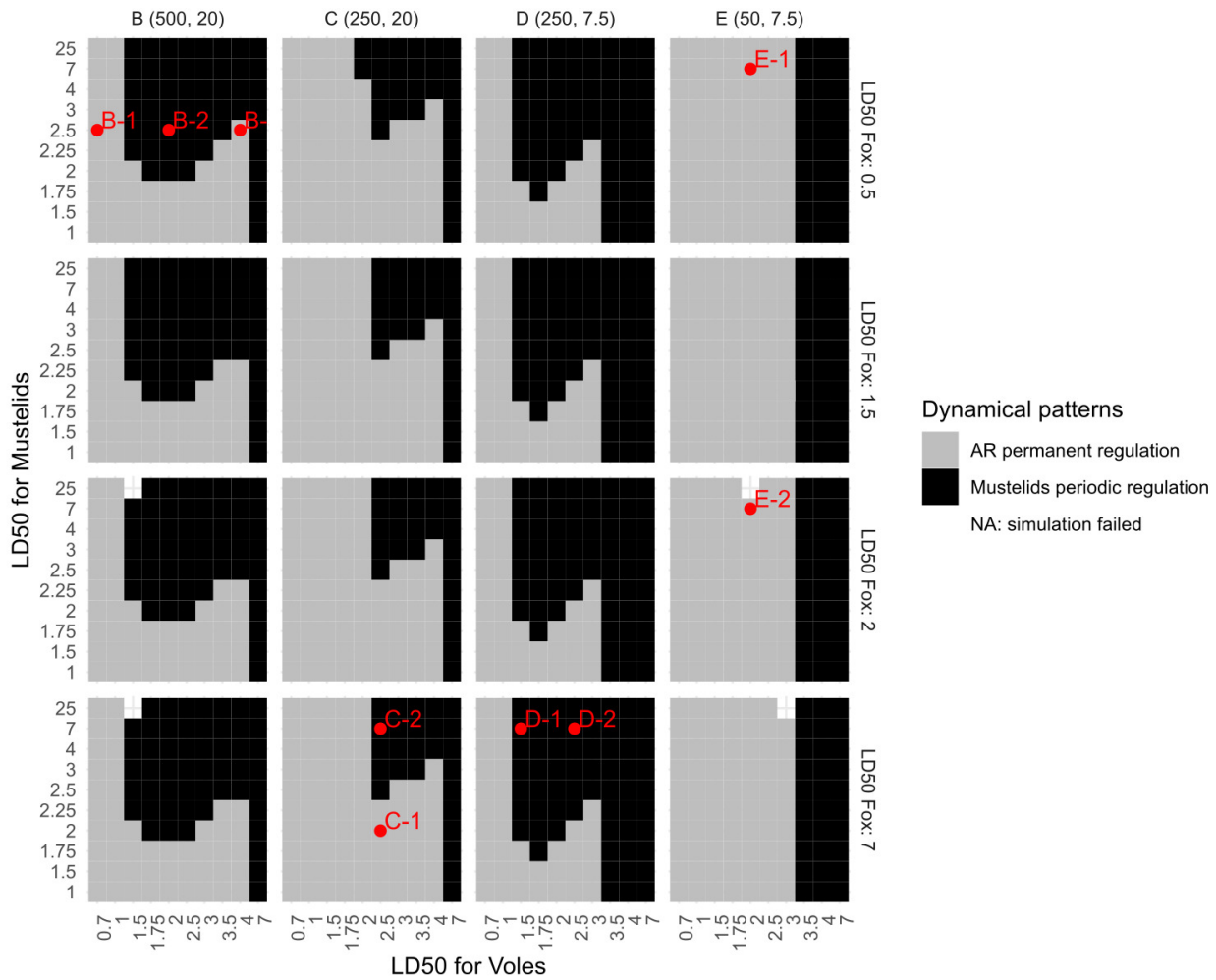


Figure 2 – Global sensitivity analysis of Lethal Dose for voles, mustelids and predators on the population dynamics of mustelids: "Mustelids periodic regulation" (see Figure 3-c,f,g,h) or "Permanent AR regulation" (see Figure 3-b,d,e,i,j). Points are simulations in Figure 3.

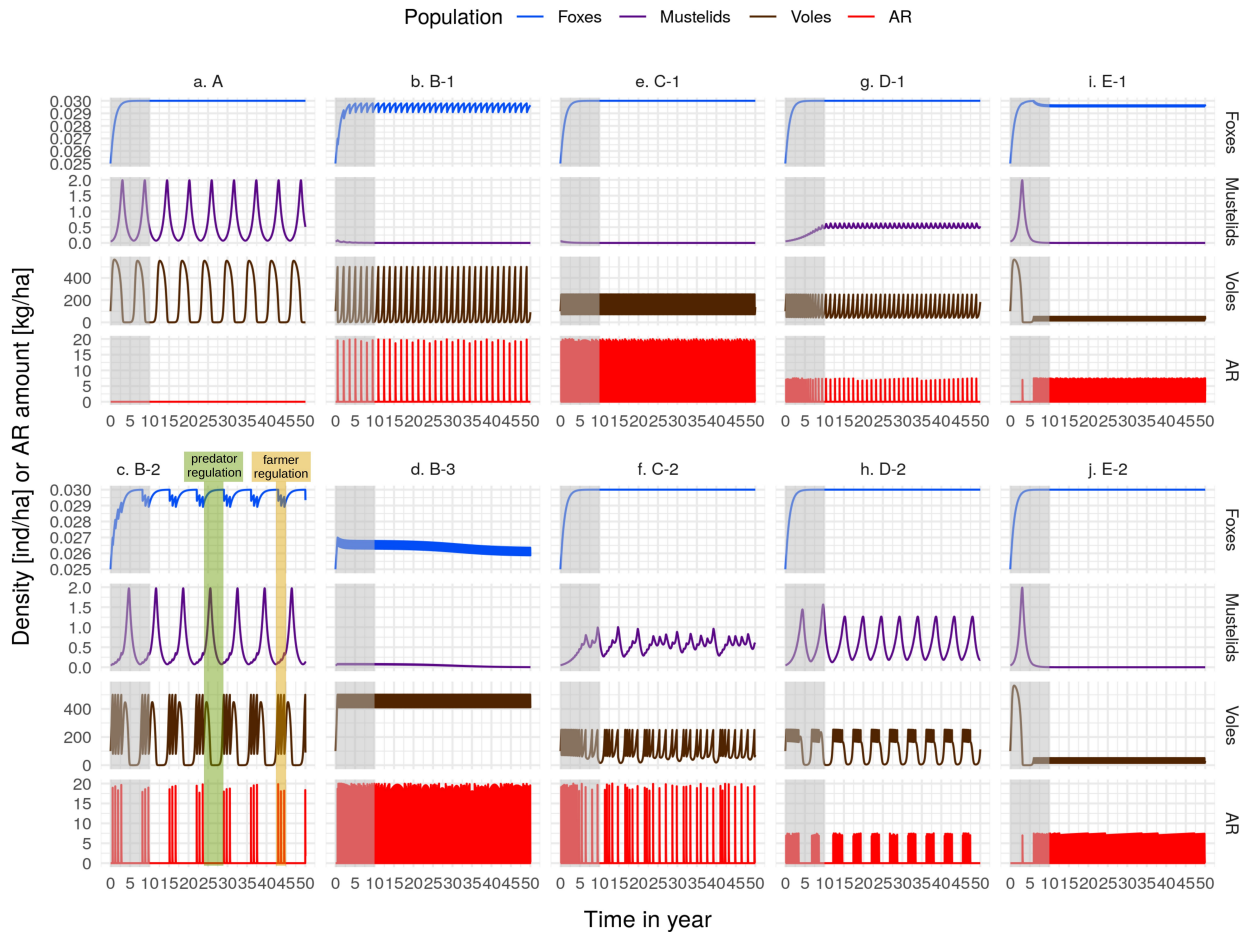


Figure 3 – Variation of population densities simulated over 50 years (10 years of burn-in period in grey area). Capital letter corresponds to farmer functional response: A the null model (no AR), B (vole threshold: 500in/ha, AR 20kg/ha), C(250,20), D(250, 7.5) and E(50,7.5). Numbers correspond to points in Figure 2. Panel c (B-2) illustrates predator-regulation and farmer-regulation phases, that can also be found in other graphics (C-2, D-1, D-2).

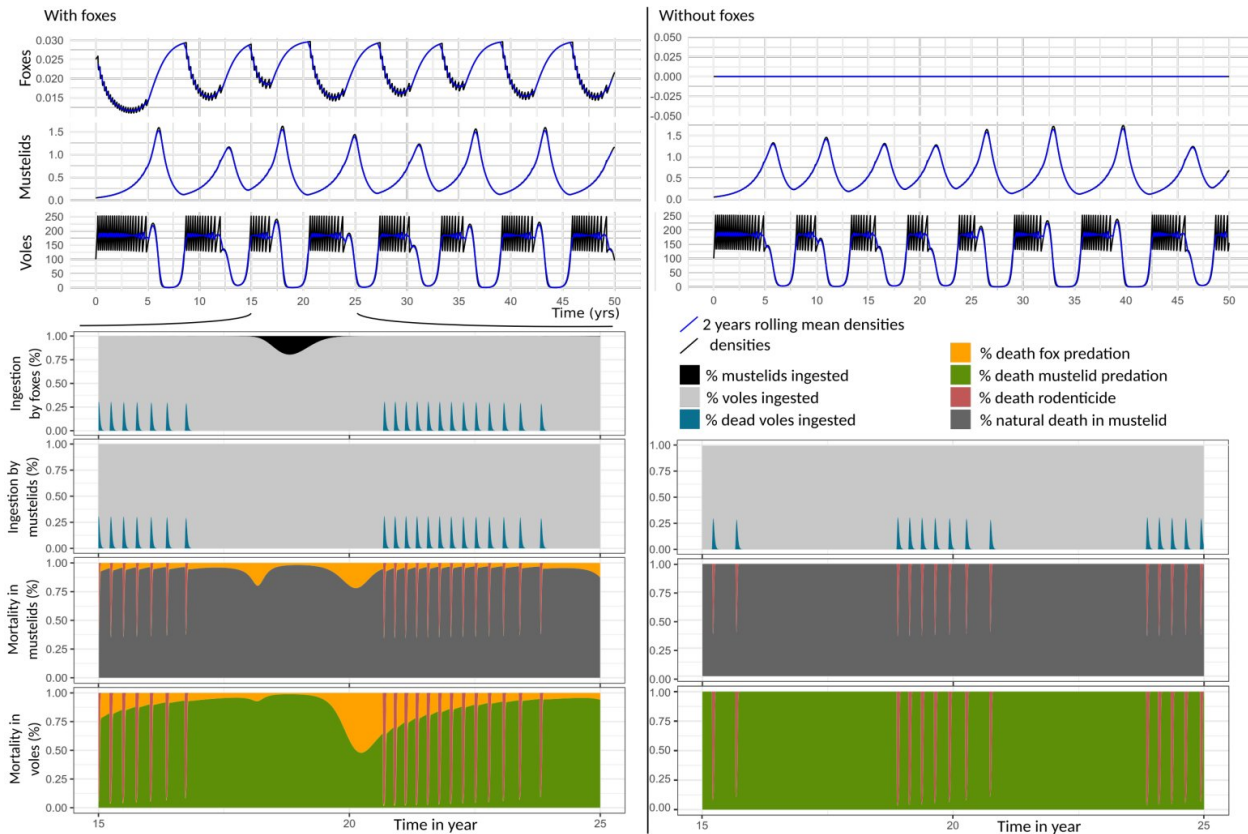


Figure 4 – Effects of intraguild predation. Top panels: daily densities of voles (in black) and 2-years rolling means of densities (in blue) for the farmer functional response  $d$  (i.e., 7.5kg of rodenticide at threshold density of 250 voles) with and without foxes (left and right respectively). Bottom graphics: stacked charts of ingestion and mortality proportion.

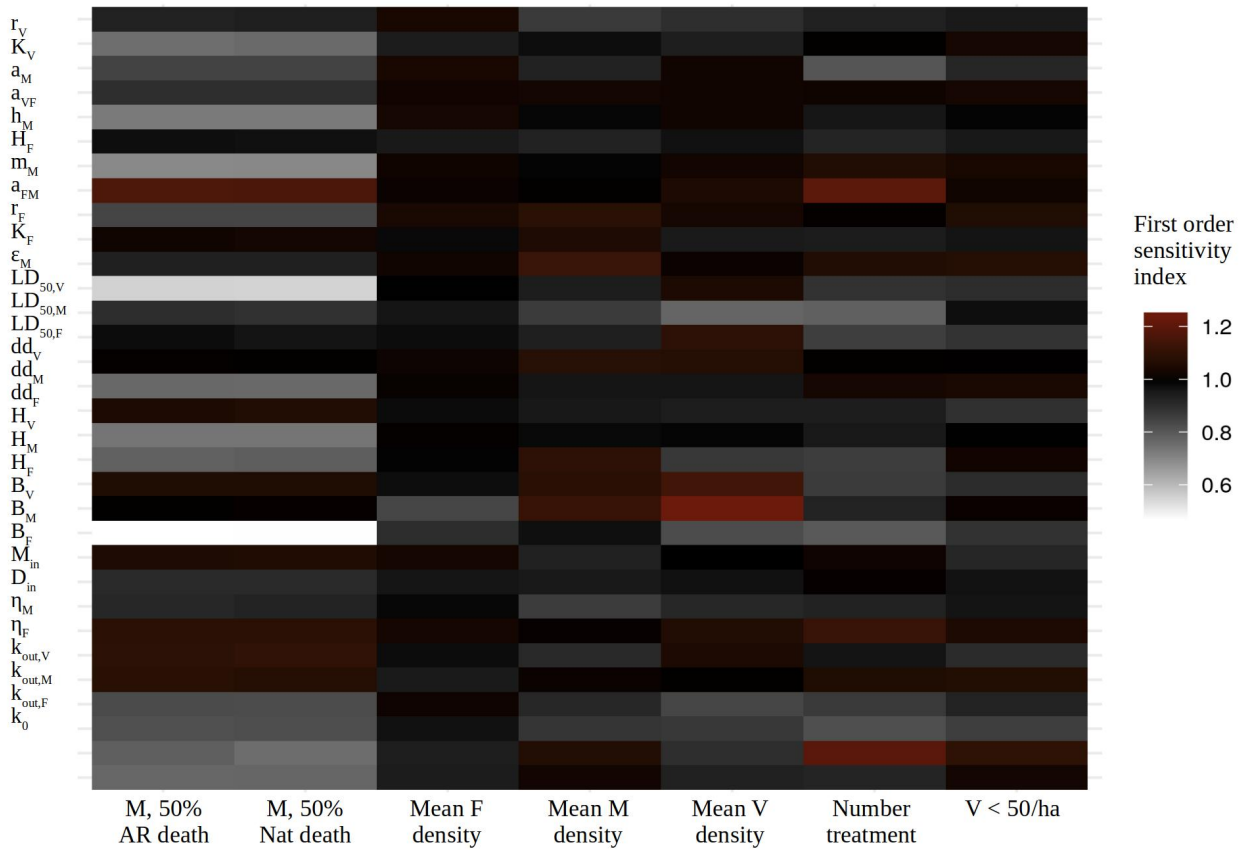


Figure 5 – Local sensitivity analysis: First-order Sobol's sensitivity index (denoted  $S_p$  for parameter  $p$ ) providing the global sensitivity of cost functions to parameters of the model (Sobol and Saltelli, 1993) for the model d (i.e., 7.5kg of AR at threshold density of 250 voles). Analysis is based on 4200 simulations. Values reflect the expected fractional reduction in the variance for each cost functions that would be achieved if a specific parameter is fixed. Values of  $S_p$  may be greater than one due to the potential correlation between variables.