

# Structure of the Scientific Community Modelling the Evolution of Resistance

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Faced with the recurrent evolution of resistance to pesticides and drugs, the scientific community has developed theoretical models aimed at identifying the main factors of this evolution and predicting the efficiency of resistance management strategies. The evolutionary forces considered by these models are generally similar for viruses, bacteria, fungi, plants or arthropods facing drugs or pesticides, so interaction between scientists working on different biological organisms would be expected. We tested this by analysing co-authorship and co-citation networks using a database of 187 articles published from 1977 to 2006 concerning models of resistance evolution to all major classes of pesticides and drugs. These analyses identified two main groups. One group, led by ecologists or agronomists, is interested in agricultural crop or stock pests and diseases. It mainly uses a population genetics approach to model the evolution of resistance to insecticidal proteins, insecticides, herbicides, antihelminthic drugs and miticides. By contrast, the other group, led by medical scientists, is interested in human parasites and mostly uses epidemiological models to study the evolution of resistance to antibiotic and antiviral drugs. Our analyses suggested that there is also a small scientific group focusing on resistance to antimalaria drugs, and which is only poorly connected with the two larger groups. The analysis of cited references indicates that each of the two large communities publishes its research in a different set of literature and has its own keystone references: citations with a large impact in one group are almost never cited by the other. We fear the lack of exchange between the two communities might slow progress concerning resistance evolution which is currently a major issue for society.

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## INTRODUCTION

During the last century, the generalised and intensive use of human-made chemical pesticides and drugs (including antimicrobial and antimalarial drugs, insecticides, herbicides, fungicides, nematicides, and miticides) has allowed significant progress in controlling major threats to human health and agriculture [1–3]. However, the resistance to drugs and pesticides in pathogenic organisms, disease vectors and agricultural pests has generally developed shortly after the introduction of new molecules often resulting in significant control failures [1,4]. Antimicrobial drug resistance is an ever-increasing threat for public health. Since antibiotics came into general use in the 1950s, medical research has had to confront the recurrent evolution of resistance to most antibiotics used in hospitals against major microbial pathogens. For instance, a few years after the introduction of penicillin in 1943, strains of *Staphylococcus aureus* resistant to this antibiotic were detected in civilian hospitals [5]. Twenty years later, 80% of hospital *S. aureus* isolates were declared penicillin resistant [6]. More generally, the emergence of multidrug resistant bacterial strains has contributed to the continuous increase of hospital-acquired infections [7]. During the 20<sup>th</sup> century, insecticide resistance in disease vectors and agricultural pests has also emerged as a problem. In 1986, Georghiou [1] reported the existence of about 500 insect species resistant to at least one insecticide, 100 resistant plant-pathogens and more than 45 herbicide-resistant weed species. The evolution of insecticide resistance in mosquitoes is a remarkable instance of rapid human-induced changes in pest populations. Dichloro-diphenyl-trichloroethane (DDT) was first introduced to control mosquitoes in 1946, and one year later the first resistant mosquito species, *Aedes tritaeniorhynchus* and *A. sollicitans*, were detected. Currently, more than 100 mosquito species are known to be DDT resistant (cited by Hemingway et al. [8]).

This situation would not be necessarily problematic if pharmaceutical industries and agribusiness companies were able

to stay one step ahead of pathogenic organisms and agricultural pests, i.e. to develop and market new products before resistance causes significant control failures. However, the rate at which resistance evolves in target organisms makes the development of new pesticides and drugs increasingly costly and difficult [9–11]. In addition, cross resistance between chemicals belonging to the same family often results in molecules becoming ineffective before they are used. So, not only must the chemical product be novel but its target must also be novel. Because the number of molecules that can be developed is necessarily limited, the efficacy of existing products should be protected for the long-term. In view of these considerations, modelling the evolution of resistance became a keystone approach in agricultural and medical research with the aim of identifying the best strategies to avoid or at least delay the development of resistance [3].

Models of resistance evolution (either mathematical models or computer simulations) consider the evolutionary forces governing the temporal dynamics of adaptive genes in populations subjected to strong directional selection. These forces (selection, drift,

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mutation and migration, to point out the majors) have been clearly identified [12] and are logically identical for virus, bacteria, fungi, plants and arthropods facing drugs or pesticides. Therefore, scientists modelling the evolution of resistance in different biological organisms would be expected to work together and interact, publish in the same scientific journals, quote the same scientific references, use similar modelling approaches and, ultimately, share the same basic management strategies to avoid the development of resistance.

Our aim was to test whether this is the case. We analysed co-authorship and co-citation networks using a database of 187 models of resistance evolution published from 1977 to 2006 (Table S1). These network analyses describe the extent to which scientists modelling resistance evolution collaborate and share their knowledge (Figure 1). We used historical, methodological and geographical criteria to interpret the structure of the scientific community.

## RESULTS

### Database content

The bibliographic search in the CABs 1973–2006, Current Contents 1998–2006 and Medline 1950–2006 provided a dataset of 1,894 non redundant articles published in peer-reviewed scientific journals, dealing with resistance to pesticides or drugs. We removed all articles that did not deal with mathematical description or computer simulation of the temporal evolution of resistance. This resulted in a database containing 187 articles written by 321 different authors and citing a total of 4,154 bibliographic references. This database covered the range of all major drugs and pesticides: insecticidal proteins (39 articles), chemical insecticides (30), antibiotic drugs (29), herbicides (18), fungicides (15), antiviral drugs (14), antimalarial drugs (12), antihelminth drugs (10) and miticides (3); in addition there were

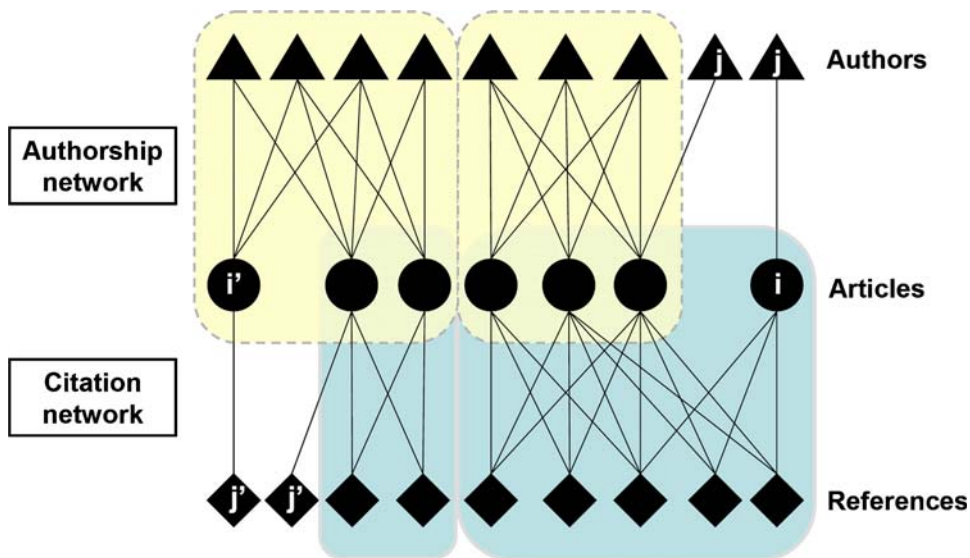
17 articles (hereafter referred to as ‘unspecific articles’) describing the evolution of resistance without reference to any specific class of pesticides or drugs.

The 187 articles were published between 1977 and 2006. More articles were published after than before 1995, mainly because of a larger number dealing with the evolution of drug resistance in bacteria and viruses. After 1995, publications concerning models of the evolution of resistance to chemical insecticides and to fungicides tended to be replaced by articles focusing on insecticidal proteins.

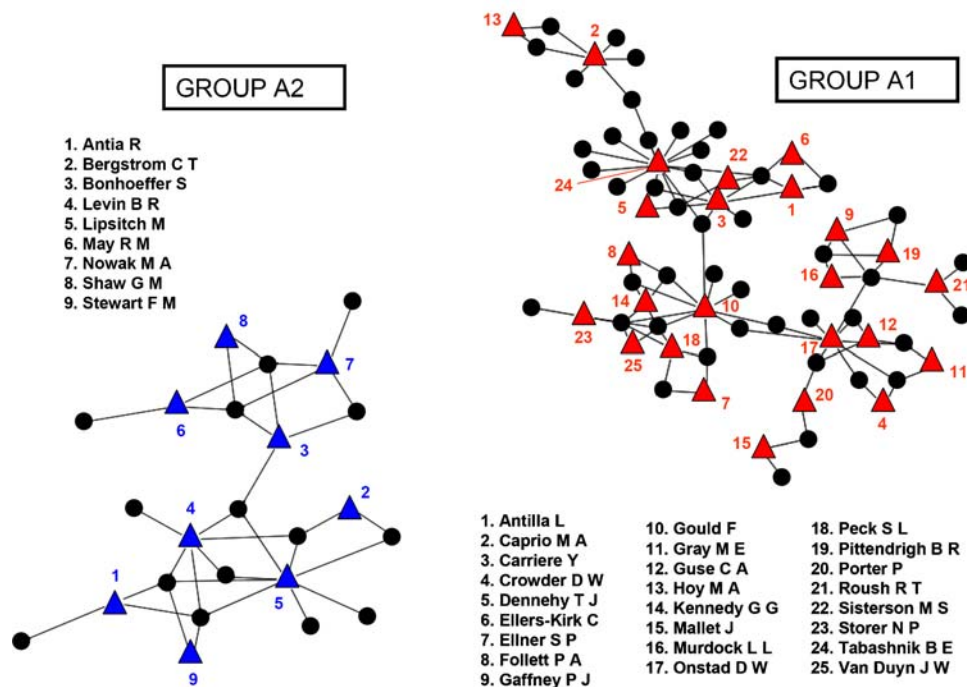
### Analysis of the authorship network

Forty-nine of the 187 articles were written by scientists who were not authors of any other article included in the database. These 49 articles were classified as ‘isolated’ articles and were not included in the authorship network analysis. This analysis was therefore based on 138 articles with 87 authors (necessarily authors of at least two articles). The authorship network was fragmented into 28 components of various sizes: a large component including 45 articles and 25 authors (named group A1; Figure 2), a medium component including 15 articles and 9 authors (group A2; Figure 2) and 26 small components each including fewer than 6 articles and 5 authors (‘small groups’).

We investigated possible causes of the fragmentation of the authorship network into collaborative groups by characterizing each article of the database according to: the type of drug or pesticide considered; the type of target organism considered; the modelling approach used; the first author’s geographical location; and the first author’s academic discipline (Table 1). We then tested for statistical associations between these descriptive categories and the observed collaborative grouping. The distributions of descriptors in each category were differently associated within the groups A1 and A2 (Fisher’s exact tests,  $p < 10^{-5}$  for each category). Articles belonging to group A1 were predominantly written by North-American biologists who only used a population genetics



**Figure 1. A schematic representation of the network analysis described in this study.** The middle layer represents the research articles (circles) selected for the study. Upper and lower layers represent authors of the articles (triangles) and bibliographic references cited in the articles (diamonds), respectively. Linking the three layers together gives rise to two bipartite networks. The architecture of the authorship network (upper network) was analysed to assess the extent to which the scientists collaborated. The architecture of the citation network (lower network) was analysed to quantify to which extent the knowledge circulates among them. In this example, two distinct collaborative groups (yellow, dotted lines) establish their research from different sets of cited literature (blue, continuous lines). Authors having published once ( $j$ ) and their corresponding articles ( $i$ ) were removed from the authorship network. Likewise references that were cited only once ( $j'$ ) and the corresponding citing articles ( $i'$ ) were removed from the citation network. Articles  $i$  and  $i'$  were considered to be articles “isolated” from the authorship and citation networks, respectively. doi:10.1371/journal.pone.0001275.g001



**Figure 2. Largest components of the authorship network.** Scientists (coloured triangles) are linked together through the articles (black circles) they have co-authored. The figure was obtained using the Tulip software [41] doi:10.1371/journal.pone.0001275.g002

approach to model resistance evolution to insecticides or insecticidal proteins in farm pests or farm diseases. One third of articles belonging to group A2 were written by European scientists and two thirds by North-American scientists; two thirds of these articles used epidemiological approaches to study the evolution of resistance in human parasites to antibiotic or antiviral drugs. Not surprisingly, more than two thirds of the authors were biologists, and a substantial proportion of the authors worked in medical institutes (Table 1). Both groups (A1 and A2) were too small for a clustering algorithm to be used.

‘Small groups’ included a large range of articles. They addressed all types of drugs and pesticides, and used both modelling approaches: population genetics (49%) and epidemiology (24%). More than 80% of the articles describing resistance to herbicides, fungicides, and antihelminthic drugs belonged to these small authorship networks (Table S2). The characteristics of isolated articles were diverse (Table S2), and they were mostly studies on insect farm pests and insect disease vectors; they used both epidemiological and population genetics models.

### Analysis of the citation network

A total of 4,154 references were cited by the 187 articles of the database; 3,297 were cited only once and were not included in the analysis. Five of the 187 articles of the database (further classified as ‘isolated articles’; see Figure 1) did not contain any list of references or did not share any reference with other articles of the database. These five articles were removed from the analysis. The citation network was hence composed of 182 articles and 857 citations. Unlike the authorship network, the citation network was fully connected. The clustering algorithm developed by Girvan and Newman [13] was used to investigate its structure: it organises the network in such a way that groups of densely connected nodes (here, articles and cited references) are separated from each other. The first split formed a group of 138 articles and 631 cited

references (called C1; Figure 3) and a group of 44 articles and 226 cited references (called C2; Figure 3). The clustering into the groups C1 and C2 was statistically validated by the multiresponse permutation procedure: the citation dissimilarity between articles of the database was lower within than between groups C1 and C2 ( $A = 0.010$ ,  $p < 0.001$ , Table S3). Conversely, the dissimilarity of source articles among citations was statistically lower within than between groups C1 and C2 ( $A = 0.013$ ,  $p < 0.001$ , Table S3).

When applied to the unipartite projection of the citation network on articles (see material and methods for details on this projection), the clustering algorithm produced two major groups named U1 and U2; Table S4) which were strongly correlated with the C1 and C2 groups, respectively. About 97% of the C1 articles belonged to the U1 group, and about 93% of the articles in group C2 belonged to the U2 group. Five articles of the C1 group were classified in the U2 group, and all but one of them addressed resistance to antimalarial drugs. This suggests that the antimalarial articles were loosely associated with group C1.

We had included all types of references in the bipartite citation network, so references shared by articles belonging to the same citation group, whether C1 or C2, could be either theoretical studies on the evolution of resistance or articles describing the biology of target organisms. To circumvent the bias of common grouping resulting from shared biological references, we applied the clustering algorithm to the unipartite network: this network links two articles of the database if one of them cited the other. Since our database included only theoretical models, common grouping could then only be due to shared theoretical references. We found that this unipartite co-citation network also displayed two major groups, named M1 and M2 (Table S5), which were, like U1 and U2, strongly correlated with the C1 and C2 groups, respectively. About 91% of the C1 articles belonged to the M1 group, and about 86% of the articles of the C2 group belonged to the M2 group. Eleven articles of the C1 group were classified in

**Table 1.** Within-group distribution of articles for the different descriptive categories.

Category	Descriptor	Percentage of Articles			
		A Groups		C Groups	
		A1	A2	C1	C2
Type of Drug or Pesticide	Antibiotic Drug	0.0	66.7	0.0	61.4
	Anthelmintic Drug	0.0	0.0	7.2	0.0
	Antimalarial Drug	0.0	6.7	8.7	0.0
	Antiviral Drug	0.0	20.0	0.0	31.8
	Fungicide	0.0	0.0	10.1	2.3
	Herbicide	0.0	0.0	13.0	0.0
	Insecticidal Protein	62.2	0.0	27.5	0.0
	Insecticide	26.7	0.0	21.0	0.0
	Miticide	2.2	0.0	1.4	0.0
	Unspecific	8.9	6.7	10.9	4.5
Type of Target Organism	Farm Pest or Disease	100.0	6.7	83.3	2.3
	Human Parasite	0.0	93.3	11.6	93.2
	Unspecific	0.0	0.0	5.1	4.5
Modelling Approach	Epidemiology	0.0	66.7	6.5	72.7
	Population Genetics	100.0	13.3	76.1	4.5
	Other	0.0	20.0	17.4	22.7
First Author's Location	Asia	0.0	0.0	8.7	2.3
	Europe	2.2	33.3	28.3	38.6
	North America	95.6	66.7	52.2	56.8
	Oceania	2.2	0.0	9.4	0.0
	South America	0.0	0.0	1.4	2.3
First Author's Discipline	Biology	95.6	73.3	86.2	36.4
	Economy	0.0	0.0	0.0	2.3
	Mathematics	4.4	6.7	7.2	13.6
	Medicine	0.0	20.0	6.5	47.7

For all categories, the distributions are significantly heterogeneous between groups A1 and A2, and between groups C1 and C2 (Fisher exact test,  $p < 10^{-5}$  in both cases).

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the M2 group; they included nine focusing on resistance to antimalarial drugs. This confirmed that the antimalaria articles were loosely associated with the C1 group.

The distributions of four of the five categories of descriptors were different within the groups C1 and C2 (Fisher's exact tests,  $p < 10^{-5}$ ). The location of the first author was the only category for which the distributions of the descriptors did not differ (at the 5% risk level) between the groups C1 and C2 (Fisher's exact test,  $p = 0.078$ ). Articles of group C2 were almost all devoted to the evolution of resistance in human parasites: they mainly focused on antibiotic and antiviral drugs (Table 1 and Figure 3). By contrast, articles of group C1 were generally devoted to models of resistance evolution in agricultural settings: they mainly focused on resistance to anthelmintic drugs, fungicides, herbicides, insecticides, or insecticidal proteins (Table 1 and Figure 3). The C1 cluster also included the articles devoted to resistance to antimalarial drugs, but, as indicated above, the association between these articles and the other articles belonging to the group C1 was weak. Groups C1 and C2 were also differentiated by the type of modelling approach: most of the articles of group C1 used population genetics models whereas epidemiological models were dominant in group C2 (Table 1). The first author's discipline also differed between the

two groups. Most first authors of C1 articles were biologists whereas there were similar numbers of biologist and medical first authors for C2 articles (Table 1). We confirmed that the 'isolated articles' were distributed across the different categories (Table S6).

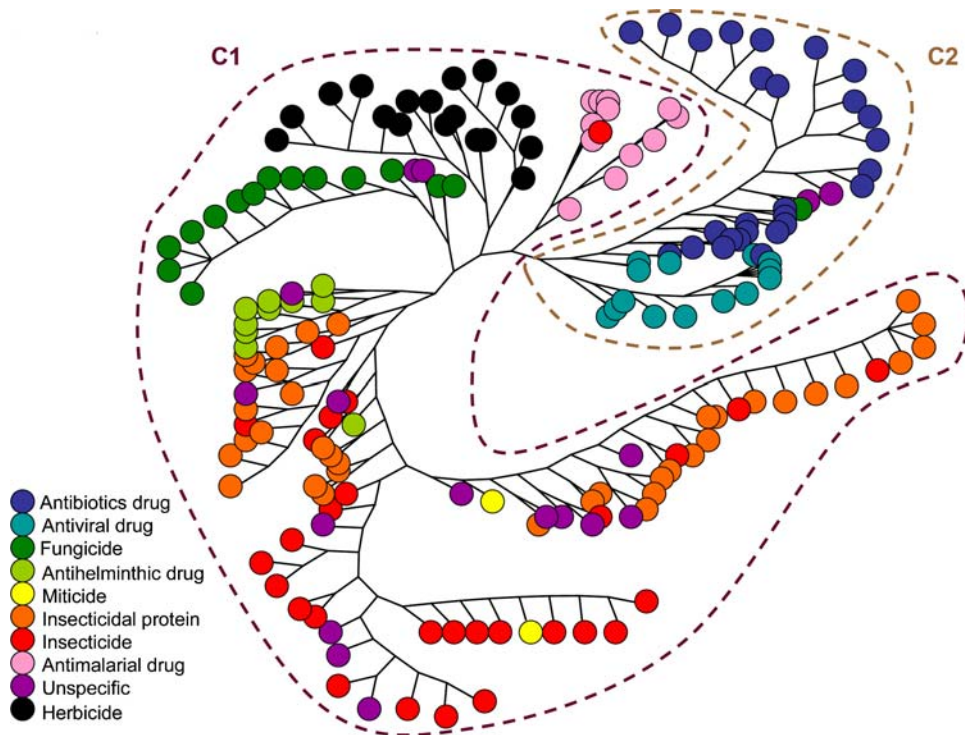
We further divided the whole network, by at each step splitting the largest remaining group. These additional splits distinguished seven groups within the C1 group. Consequently, the network then had eight groups in total (seven C1 subgroups plus the C2 group). This clustering was statistically validated by the multi-response permutation procedure (Table S7). The seven C1 subgroups were significantly different (Fisher's exact test,  $p < 10^{-5}$ ) with respect to the type of pesticide or drug they addressed (Table S8). As expected from the results obtained in our global analysis, the first group that split out from the C1 cluster consisted mostly of articles focusing on resistance to antimalarial drugs. The second group contained only articles focusing on resistance to herbicides. The third and fourth groups were mostly (87.5% and 90%) articles modelling resistance to fungicide and anthelmintic drugs, respectively. The fifth group included all the articles focusing on evolution of resistance in the western corn root worm, *Diabrotica virgifera virgifera*, to *Bt* corn. Finally, 80% of the articles belonging to the sixth and seventh subgroups were devoted to insecticides and insecticidal proteins also included most of the unspecific articles (Figure 3).

### Relationships between citation and authorship network groupings

Note that the A and C groupings described above were obtained independently from each other. Cross-classification of the 187 articles between the authorship and citation groups indicated that the two classifications were however not independent from each other (Table 2, Fisher's exact test,  $p < 10^{-5}$ ). All articles of the A1 authorship group were classified in the C1 citation group and all except two [14,15] of the articles of the A2 authorship group belonged to the C2 citation group. Moreover, five of the six 'isolated articles' of the citation network were also scored as isolated in the authorship classification (Table 2). The classification of the articles by May and Hassel [14] and Koella and Antia [15] in the C1 group is consistent with our characterization of this group (Table 1) as these articles dealt with pesticide resistance in agricultural settings and resistance to antimalaria drugs, respectively. They were attributed to the A2 authorship because R. M. May is also co-author of articles dealing with HIV resistance to antiviral drugs [16,17], and R. Antia is also co-author of articles dealing with antibiotic resistance [18,19]. Because the classifications based on the citation and the authorship networks were very similar and because author groups A1 and A2 were apparently unconnected, we analysed the information flow between groups using the citation network only.

### Information flow between citation groups

Overall, 48 of the 857 references were quoted both by articles belonging to the C1 group and articles belonging to the C2 group (Table S9). Thus, articles from group C1 and group C2 shared less than 5.6% of the references (after exclusion of all the references that were cited only once). The citation network analysis assigned 39.5% (19 articles) of the 48 shared references to group C1 and 60.5% (29 articles) to group C2; these shared references made up 3% of the total number of C1 citations and 12.8% of the total number of C2 citations, indicating that articles of the group C1 are more prone to quote C2 references than the reverse. The 48 article cited mostly reported models of the evolution of resistance to fungicides (30%), to antibiotics (27%) and general models of



**Figure 3. Hierarchical tree showing the structure of the citation network calculated using the 'edge betweenness' algorithm [13].** Due to space constraints, only the tree leaves corresponding to articles are depicted. Tree branches correspond to the splits of the network. The very first split produced two clusters called C1 and C2. Subsequent splits revealed divisions between seven subgroups within the C1 group. Tree leaf colours indicate the type of pesticide or drug considered by the articles.  
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theoretical population biology and genetics (16%). To assess the extent of information flow between C1 and C2 groups, we compared the five most frequently quoted references and journals of each group. The results were particularly striking: none of the five most cited references and journals of one group appeared in the top five of the other group (Table 3). Indeed, none of the most frequently quoted references of group C1 was quoted by group C2. Even the keystone article by Comins [20], which was quoted 35 times by group C1, did not appear among the references of the other group. By contrast, the most frequently quoted references of group C2 were in some cases quoted by group C1. For instance, the keystone book by Anderson and May [21], which was cited 18 times by group C2, was also cited four times by group C1 (Table 3). The five top journals cited by group C1 were mainly specialized in entomology. The only journal that was also cited by group C2 was *Phytopathology*. The five

top journals cited in the group C2 included two specialized medical journals, that were almost never cited by articles of the C1 group, and three generalist journals—*Science*, *Nature* and *PNAS*—that were frequently cited by articles of the C1 group (Table 3)

An alternative method for assessing the information flow between citation groups is to examine the articles of one group that cite references assigned to the other group. Only 28 of the articles of the database did so. The 28 articles included half of all articles in our database dealing with antimalarial drug resistance, 33% of the articles dealing with fungicide resistance evolution and 29% of the articles classified as 'unspecified' (Table S10). Among the 28 articles: (i) 21 articles, belonging to the group C1, cited at least one reference assigned to the group C2. One of these articles, that by Koella and Antia [15] cited the largest number of references belonging to the C2 group (6 citations). It is an epidemiological model describing the evolution of drug resistance in malaria parasite populations. Note that this article was one of the two C1 articles classified in the A2 authorship group because of R. Antia's interest in antibiotic resistance, which indicates that collaboration between scientists with different interests leads to research based on a wider literature, (ii) seven articles, belonging to the group C2, cited at least one reference assigned to the group C1. The article of Gubbins et al. [22] cited the largest number of references belonging to C1 group (9 citations); it presents a stochastic model of fungicide resistance evolution that quotes six models of antibiotic resistance and three general models from population biology.

## DISCUSSION

The absence of interconnection between scientists modelling the evolution of resistance has already been described [23,3]. Peck [23]

**Table 2. Contingency table crossing for the authorship and citation groups.**

Authorship Network	Citation Network			Total
	C1 Group	C2 Group	Isolated Articles	
A1 Group	45	0	0	45
A2 Group	2	13	0	15
Small Groups	58	19	1	78
Isolated Articles	33	12	4	49
Total	138	44	5	187

The independence of each network structure was significantly rejected (Fisher's exact test,  $p < 10^{-5}$ ).

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**Table 3.** The five most cited references and journals within the citation groups C1 and C2 and number of citations of these references/journals in each group.

Citation Group	Most Cited References	Quotation Number	
		C1	C2
C1	Comins <i>J. theor. Biol.</i> (1977) <b>64</b> , 177–197	35	0
	Tabashnik et al. <i>Env. Entomol.</i> (1982) <b>11</b> , 1137–1144	31	0
	Georghiou and Taylor <i>J. Econ. Entomol.</i> (1977) <b>70</b> , 319–323	26	0
	Roush and McKenzie <i>Annu. Rev. Entomol.</i> (1987) <b>32</b> , 361–380	23	0
	Gould. <i>Annu. Rev. Entomol.</i> (1998) <b>43</b> , 701–726	22	0
C2	Anderson and May (1991) <i>Oxford University Press</i>	4	18
	Bonhoeffer et al. <i>Proc. Natl. Acad. Sci. USA</i> (1997) <b>94</b> , 12106–12111	1	12
	Blower et al. <i>Science</i> (1996) <b>273</b> , 497–500	1	11
	Levin et al. <i>Clinic. Inf. Dis.</i> (1997) <b>24</b> , S9–S16	0	10
	Wei et al. <i>Nature</i> (1995) <b>373</b> , 117–122	0	10
<b>Most Cited Journals</b>			
C1	<i>Journal of Economic Entomology</i>	614	0
	<i>Environmental Entomology</i>	211	0
	<i>Annual Review of Entomology</i>	119	0
	<i>Phytopathology</i>	108	10
	<i>Pesticide Science/Pest Management Science</i>	99	0
C2	<i>Science</i>	84	97
	<i>Proceedings of the National Academy of Sciences of the USA</i>	74	92
	<i>Antimicrobial Agents Chemotherapy</i>	0	79
	<i>Nature</i>	53	65
	<i>New England Journal of Medicine</i>	2	62

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titled his article “*Antibiotic and insecticide resistance modeling—is it time to start talking?*”, illustrating the lack of interdisciplinary work in the field. It was indeed time to talk and there was much to be gained by cross-fertilization between the disciplines. Unfortunately, the article of Peck [23] was to a large extent ignored until 2004 and has not been cited more than six times. This illustrates surprisingly limited interest in this key article — note that other articles published in 2001 in the same journal have been cited (by July 2007 and according to the Web of Science) 17.2 times on average.

Although most people working on the evolution of resistance would agree that there is indeed some compartmentalization in the field, a thorough analysis of how the scientific community is structured had never been conducted, and the factors structuring it had never been identified. By contrasting the biology and genetics of insects and bacteria, Peck [23] restricted his analysis to antibiotics and insecticides ignoring models devoted to other pesticides or drugs. More importantly, the goal of Peck’s analysis was not to provide any quantitative measure of the isolation between groups of scientists but to alert the scientific community. He assumed that the community of scientists modelling resistance was significantly structured according to their interest in pesticides or drugs—in his case insecticides and antibiotics. By contrast, our aim was to test for the structure of the community using network analysis and including all major classes of drugs and pesticides. Using a database of 187 articles modelling the evolution of

resistance to all the various classes of pesticides and drugs, we performed network analyses with no *a priori* knowledge of view about the factors structuring the community.

Both authorship and citation networks identified two major scientific groups working in parallel in the field of resistance evolution modelling. One group is interested in resistance evolution in agricultural settings (i.e., crop or stock pests or causal agents of disease). It mainly uses a population genetics approach to model the evolution of resistance to insecticidal proteins, insecticides, herbicides, antihelminthic drugs or miticides. By contrast, the other group is interested in resistance evolution in human parasites and predominantly uses epidemiological models to study the evolution of resistance to antibiotic and antiviral drugs. Moreover, our analyses suggest that there is a small scientific group focusing on resistance to antimalarial drugs, and which is only weakly connected to the two major groups. Our analysis of cited references provides strong evidence that each of the two large communities establishes its research in a different set of literature and has its own keystone references. This is well illustrated by the very low percentage (less than 5.6%) of cited references shared by the two communities. The division is even clearer in the structure of collaborations between authors. We identified two large collaborative groups of scientists—one that explores resistance of human parasites and the other that works on insecticide resistance in insect crop pests—that have been coexisting without ever coming together to produce common publications.

Although robust and reliable, this result needs to be qualified. Indeed, there is information flow between the two citation groups although it is low volume. Some of the few references that are cross cited are general developments in the field of ecology and genetics, and this finding indicates that some theoretical literature is shared between citation groups. The articles of one group citing references of the other group, included 50% of all articles concerning antimalarial drug resistance models and 33% of the all those addressing fungicide resistance models. The two articles citing the largest number of references from the other group also focused on fungicide [22] and antimalarial drugs [15]. This is consistent with the type of modelling approach used for work on antimalarial drugs and fungicides. For antimalarial drugs resistance models, epidemiological approaches, typical of human parasite modelling, were used as frequently as population genetics approaches that are typical of agricultural pest modelling [24]. Fungicide models used epidemiological approaches leading the authors to cite literature of the C2 group. In these contexts, the modelling approach compartment might be preferred by the authors because the variable of interest is likely to be symptoms as perceived on the whole plant rather than the cryptic presence of individuals which are not countable. Indeed, the division of this scientific community into two major groups—one affiliated to agriculture and the other to medicine—is not perfectly correlated with the kind of modelling approach used: about 24% of models of C1 group are not population genetics models whereas 4.5% of the articles belonging to C2 group presented population genetics models. This would be expected to generate the need to cross cite references which is clearly not the case.

The compartmentalization between the two groups appears asymmetrical: modelling approaches, geographic origins and disciplines of the first authors are much more diverse for the community of researchers working in medicine than in agriculture (Table 1). In addition, the most cited journals quoted by the authorship group working on human parasite resistance are generalist journals and are also cited by the other group. The reverse is does not apply: the group working on agricultural pest resistance cites specialised (entomology or phytopathology) journals

that are not cited by the other group. For these reasons of ‘generalism’, ‘diversity’, and to a lesser degree ‘youth’, we believe that researchers working on the evolution of resistance in the medical sciences may be both more responsive to progress in other scientific fields and better disposed to multidisciplinary research.

The division of research on the evolution of resistance into two communities has, as stated above, already been reported [23,3]. Hastings [3] suggested that the modelling approach—epidemiology versus population genetics—and the reproduction mode of the organism under study structured the community: epidemiology models being used for asexual species (virus, bacteria, fungi) whereas population genetics models apply to sexually reproducing pathogens and pests. Peck [23] asserted that “*the lack of interdisciplinary work in resistance modelling seems to be that bacterial genetics differ substantially from the genetics of diploid organisms such as insects and mites*”. Our analysis of a large panel of articles suggests that the modelling approach is not the factor that best structured the community. This was clearly illustrated by the literature for antimalarial drugs and fungicides, and by the numerous population genetics models developed to analyse evolutionary outcomes in bacteria [18,25–27]. Moreover, explanations based on differences in reproductive modes or genetics are similarly not entirely satisfactory because large variations in recombination rates in insects (e.g. in aphids [28] as in bacteria [29]), and because the models of population genetics of haploid and diploid organisms are very similar. For instance, the Wright-Fisher and the coalescent models are nearly the same for both haploids and diploids [30].

Finally, contrary to previous suggestions by Hastings [3] and Peck [23], we think that the two separate groups have developed as a result of the more traditional division between research in agriculture (and related sciences) and medical sciences. The coexistence of two communities in the field of resistance evolution modelling—one specialized on agricultural pests or diseases, the other on human parasites—may not have initially arisen from the need to use different modelling approaches because of biological differences in target organisms. Moreover, even if this were the case, the methodology used for modelling should not, *per se*, preclude cross citation and scientific exchange. Given the almost complete absence of citation of the keystone articles of one community by the other community, we suggest that the division corresponds to the independent development of scientific groups around different leaders. Our view is that the article by Comins [20] may have given rise to a lineage of population genetics models on insect pests whereas the book by Anderson and May [21] may have initiated the proliferation of epidemiological models on human diseases. Merging of the two lineages may have been inhibited by the applied nature of research on the evolution of resistance: modelling the evolution of resistance evolution is driven by practical problems encountered by farmers or medical practitioners. Therefore, scientific exchanges may have occurred preferentially between scientists working with the same practical issues, and addressing the same audience. We also think that the current compartmentalization is due to the absence, when this scientific field first emerged, of major contributions by founders presenting general models of resistance evolution.

We fear that this historical, field-oriented division impedes the progress of research at a time when the development of new pesticides and drugs is a growing problem. Possibly, the subdivision into two communities has been beneficial by favouring the emergence of different models over mimicking those already developed in the other community. Hence, although the community is clearly divided into two groups, we now need to investigate whether or not they arrive at similar conclusions and management solutions. These issues will be addressed in a subsequent paper.

## MATERIALS AND METHODS

### Construction of the database

We established a database of articles presenting models (mathematical models or computer simulations) of the evolution of resistance to the most common classes of pesticides—insecticides, fungicides, herbicides, miticides and insecticidal proteins such as *Bacillus* toxins—and drugs—antibiotic, antiviral, antimalarial and antihelmintic drugs. We used a three-step process to select relevant articles without using any subjective *a priori* knowledge of the relevant literature. First, we selected in the Web of Science (1992–2006) database the four most cited articles concerning models (mathematical models or computer simulations) to study the evolution of resistance to each of the six following pesticides and drugs: insecticides, herbicides, fungicides, insecticidal proteins and antibiotic and antiviral drugs. We used the search formula  $TS = (\text{model} * \text{AND} \text{resistan} * \text{AND} X)$ , with X being one of the six pesticides or drugs under consideration. The most cited articles were then checked to verify their relevance. This resulted in a kernel of 24 ‘core articles’. The second step involved a search in the CABs 1973–2006, Current Contents 1998–2006 and Medline 1950–2006. The aim was to establish, using a trial and error method, a single search formula detecting the smallest set of articles that included at least all the 24 ‘core articles’. The final “formula” used—on September 1st 2006—for the search in the three bibliographic databases is given in Table S11. The third step was to reduce the dataset by removing all irrelevant articles: the summary and keywords of each article were carefully and independently read by two of us to verify that the article dealt with a mathematical model or a computer simulation of the temporal evolution of resistance in response to selective pressures induced by a pesticide or a drug. The final database consisted of a total of 187 articles (see the results section; the references of these articles are given in Table S1).

For each of the selected articles, a reading grid was completed with details of the type of drug or pesticide (insecticides, fungicides, herbicides, miticides, insecticidal proteins, and antibiotic, antiviral, antimalarial and antihelmintic drugs), the kind of target organism (farm pest and disease versus human parasite), the first author affiliations (geographical location of work and scientific discipline as indicated by the institution department). Each article was also classified according to the modelling approach used, according to Levin [27,31]: the population genetics approach considers the change in the frequencies of resistant and sensitive individuals as function of pesticide or drug use; whereas the epidemiological approach refers to the compartment model tradition of mathematical epidemiology of parasites as described by Anderson and May [21]. Models that could not be assigned to the “population genetics model” nor to the “epidemiological model” were classified as “other”.

### Network construction

All author names and all cited references in each article of the database were recorded. These data were used to build two bipartite undirected networks (R igraph package, *graph.adjacency* function [32,33]). The edges of the first network linked articles to their authors. This network, named the authorship network, had 508 nodes representing 187 articles connected with 321 authors. The edges of the second network linked articles to their bibliographic references. This network, named the citation network, had 4,387 nodes representing 187 articles connected with 4,154 cited references. The aim was to group articles according to their similarity in authorship or citations, so we removed all the authors who had published only once and all the references cited only once. Articles which were no longer linked to

any author or any reference were removed from the networks and were classified as “isolated articles”. This led to a simplified authorship network of 138 articles connected with 87 authors and a simplified citation network of 182 articles connected with 857 citations. These networks had 260 and 2,943 edges, respectively.

### Detection of connected components and clusters

We first identified the connected components of the two networks and measured their sizes using the *clusters* function of the R igraph package [32,33]. The citation network was found to be fully connected, so the clustering algorithm proposed by Girvan and Newman [13] was used to analyse its structure. This divisive algorithm selects the edges of the network to be cut based on their ‘edge betweenness’, a generalization of the centrality betweenness, originally defined for graph vertices [34,35]. Edge betweenness is (roughly) equal to the number of shortest paths linking all pairs of vertices going through an edge. It was calculated using the *edge.betweenness* function of the R igraph package [32,33]. As detailed by Girvan and Newman [13], if a network contains clusters that are loosely connected by few edges, the edges connecting these clusters have a high betweenness because all shortest paths between vertices of different clusters must pass through them. At a given stage, edges with the highest betweenness were therefore removed from the citation network and the betweenness for all the remaining edges was recalculated. This sequence was repeated until separation of clusters. Each cluster was then split in its turn, starting with the largest. The algorithm was run until no edge remained. The nested hierarchy of clusters was converted into a tree format using the *as.phylo.formula* function of the R ape package [33,36], and is represented as an unrooted radial tree with TreeView [37].

The clustering algorithm was originally designed for unipartite networks [13], so we also applied it to the unipartite projection of the citation network on articles. This projection yielded to a network having 182 nodes representing the 182 articles of the citation network. Two articles were connected with each other if they shared at least one reference. A total of 3,106 edges linked together the articles. We checked that the major divisions of this unipartite network were the same as those of the bipartite citation network.

Finally, we constructed the network with the 187 database articles as vertices and in which two articles were linked together if one cited the other. We found that sixteen articles were not cited by any other article of the database and did not cite any other article. Thus, they were not linked to any other article in the network. They were removed and classified as “isolated” articles. This led to a simplified, fully connected, unipartite network with 171 nodes and 590 edges, which was called the unipartite co-citation network. The information contained in this network was complementary to that of the bipartite citation network. Indeed, in the bipartite citation network, the common references through which the articles were linked were of various types: they were general reviews or books on resistance evolution, theoretical articles on resistance evolution, or specific studies on the biology of target organisms. By contrast, in the unipartite co-citation network, links corresponded to citations between theoretical studies only because our database was cleared to include only models of resistance evolution. The bipartite citation network therefore provides a general, exhaustive picture of knowledge flow between the 187 database articles, whereas the unipartite co-citation network gives an insight into the flow of theoretical knowledge only. We studied the architecture of the unipartite co-citation network with the clustering algorithm and compared it with that of the bipartite citation network.

### Statistical validation of clusters

The clusters obtained by clustering algorithm analysis with the bipartite citation network were statistically validated by testing whether element similarity—*i.e.* article similarity according to their cited references and reference similarity according to their source articles—was significantly higher within than among clusters. For this, we used the multiresponse permutation procedure (MRPP), a non-parametric method designed for testing differences among *a priori* defined groups [38]. The MRPP statistic  $\delta$  is the weighted within-group mean of the pairwise dissimilarities among their elements. Using the method of Prado et al. [39], dissimilarity was calculated here as a Jaccard distance and group size was taken for group weighting. The permutation algorithm included in the *mrpp* function of the R vegan package [33,40] calculates the expected statistics  $E(\delta)$  if groups were assembled at random. The within-group chance-corrected agreement ( $A$ ), defined as  $1-\delta/E(\delta)$ , has a maximum value of 1 when there is no dissimilarity among elements of any groups. The  $p$ -value is the probability of obtaining by chance a value of  $A$  equal or larger than the observed value.

## SUPPORTING INFORMATION

**Table S1** References of the 187 articles included in the database  
Found at: doi:10.1371/journal.pone.0001275.s001 (0.09 MB PDF)

**Table S2** Number of articles falling into the various descriptive categories for each group of the authorship network  
Found at: doi:10.1371/journal.pone.0001275.s002 (0.03 MB PDF)

**Table S3** Multiresponse permutation procedure (MRPP) analysis of group dissimilarities showing mean citation distance between articles and mean source articles distance between citations in each citation group  
Found at: doi:10.1371/journal.pone.0001275.s003 (0.02 MB PDF)

**Table S4** Contingency table crossing for citation groups obtained by applying the clustering algorithm to the bipartite citation and to the unipartite article networks  
Found at: doi:10.1371/journal.pone.0001275.s004 (0.01 MB PDF)

**Table S5** Contingency table crossing for citation groups obtained by applying the clustering algorithm to the bipartite citation and to the unipartite co-citation networks  
Found at: doi:10.1371/journal.pone.0001275.s005 (0.01 MB PDF)

**Table S6** Number of articles falling into the various descriptive categories for each group of the citation network  
Found at: doi:10.1371/journal.pone.0001275.s006 (0.03 MB PDF)

**Table S7** Multiresponse permutation procedure (MRPP) analysis of group dissimilarities showing mean citation distance between articles and mean source article distance between citations in each citation group  
Found at: doi:10.1371/journal.pone.0001275.s007 (0.02 MB PDF)

**Table S8** Number of articles focusing on the different types of drug or pesticide for each subgroup of the C1 cluster  
Found at: doi:10.1371/journal.pone.0001275.s008 (0.02 MB PDF)

**Table S9** List of the 48 references cited by articles belonging to the C1 group and articles belonging to the C2 group  
Found at: doi:10.1371/journal.pone.0001275.s009 (0.02 MB PDF)

**Table S10** Characteristics of the 28 articles of one group that cited references of the other group  
Found at: doi:10.1371/journal.pone.0001275.s010 (0.02 MB PDF)

**Table S11** Formulae used to search for relevant articles describing models of the evolution of resistance to pesticides and drugs within the CABs (1973–2006), Current Contents (1998–2006), and Medline (1950–2006) databases  
Found at: doi:10.1371/journal.pone.0001275.s011 (0.02 MB PDF)

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Conceived and designed the experiments: CV DB FD PF TG XR AW. Performed the experiments: CV DB FD PF TG XR AW. Analyzed the data: CV AW. Wrote the paper: CV DB FD PF TG XR AW.

## REFERENCES

- Georghiou GP (1986) The magnitude of the resistance problem. In: Glass E, ed. Pesticide Resistance: Strategies and Tactics for Management. Washington DC: Natl Acad Press. pp 14–43.
- Guillemot D (1999) Antibiotic use in humans and bacterial resistance. *Curr Opin Microbiol* 2: 494–498.
- Hastings IM (2004) The origins of antimalarial drug resistance. *Trends Parasitol* 20: 512–518.
- D'Alessandro U, Buttiens H (2001) History and importance of antimalarial drug resistance. *Trop Med Int Health* 6: 845–848.
- Levy SB, Marshall B (2004) Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med* 10: S122–S129.
- Chambers HF (2001) The changing epidemiology of *Staphylococcus aureus*? *Emerg Infect Dis* 7: 178–182.
- Finch R (2006) Gram-positive infections: lessons learnt and novel solutions. *Clin Microbiol Infect* 12: 3–8.
- Hemingway J, Ranson H (2000) Insecticide resistance in insect vectors of human disease. *Annu Rev Entomol* 45: 371–391.
- Marrone PG (1999) Microbial pesticides and natural products as alternatives. *Outlook Agri* 28: 149–154.
- Clarke T (2003) Drug companies snub antibiotics as pipeline threatens to run dry. *Nature* 425: 225–225.
- Norby SR, Nord CE, Finch R (2005) Lack of development of new antimicrobial drugs: a potential serious threat to public health. *Lancet Infect Dis* 5: 115–119.
- Maynard-Smith J (1998) *Evolutionary Genetics*. Oxford: Oxford University Press. 330 p.
- Girvan M, Newman MEJ (2002) Community structure in social and biological networks. *Proc Natl Acad Sci U S A* 99: 7821–7826.
- May RM, Hassell MP (1988) Population dynamics and biological control. *Philos Trans R Soc Lond B Biol Sci* 318: 129–169.
- Koella JC, Antia R (2003) Epidemiological models for the spread of antimalarial resistance. *Malaria Journal* 2.
- Bonhoeffer S, May RM, Shaw GM, Nowak MA (1997) Virus dynamics and drug therapy. *Proc Natl Acad Sci U S A* 94: 6971–6971.
- Nowak MA, Bonhoeffer S, Shaw GM, May RM (1997) Anti-viral drug treatment: dynamics of resistance in free virus and infected cell populations. *J Theor Biol* 184: 203–217.
- Levin BR, Lipsitch M, Perrot V, Schrag S, Antia R, et al. (1997) The population genetics of antibiotic resistance. *Clin Infect Dis* 24 Suppl 1: S9–16.
- Stewart FM, Antia R, Levin BR, Lipsitch M, Mittler JE (1998) The population genetics of antibiotic resistance. II: Analytic theory for sustained populations of bacteria in a community of hosts. *Theor Popul Biol* 53: 152–165.
- Comins HN (1977) The development of insecticide resistance in the presence of migration. *J Theor Biol* 64.
- Anderson RM, May RM (1991) *Infectious Diseases of Humans: Dynamics and Control*. Oxford: Oxford University Press. 761 p.
- Gubbins S, Gilligan CA (1999) Invasion thresholds for fungicide resistance: deterministic and stochastic analyses. *Proc Roy Soc Lond B Biol Sci* 266: 2539–2549.
- Peck SL (2001) Antibiotic and insecticide resistance modeling—is it time to start talking? *Trends Microbiol* 9: 286–292.
- Hastings IM (2001) Modelling parasite drug resistance: lessons for management and control strategies. *Trop Med Int Health* 6: 883–890.
- Bonhoeffer S, Lipsitch M, Levin BR (1997) Evaluating treatment protocols to prevent antibiotic resistance. *Proc Natl Acad Sci U S A* 94: 12106–12111.
- Austin DJ, Anderson RM (1999) Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models. *Philos Trans R Soc Lond B Biol Sci* 354: 721–738.
- Levin BR (2001) Minimizing potential resistance: a population dynamics view. *Clin Infect Dis* 33: S161–S169.
- Simon JC, Delmotte F, Rispe C, Crease T (2003) Phylogenetic relationships between parthenogens and their sexual relatives: the possible routes to parthenogenesis in animals. *Biol J Linn Soc* 79: 151–163.
- Maynard-Smith J, Smith NH, O'Rourke M, Spratt BG (1993) How clonal are bacteria? *Proc Natl Acad Sci U S A* 90: 4384–4388.
- Neuhauser C (2001) Mathematical models in population genetics. In: Balding D, Bishop M, Cannings C, eds. *Handbook of Statistical Genetics*. Chichester: John Wiley & Sons. pp 153–176.
- Levin BR (2002) Models for the spread of resistant pathogens. *Neth J Med* 60: 58–64; discussion 64–56.
- Csardi G (2006) igraph: IGraph class version 0.1.2. Available: <http://www.R-project.org>.
- R Development Core Team (2006) R: a language and environment for statistical computing. Available: <http://www.R-project.org>.
- Freeman LC (1979) Centrality in social networks I: conceptual clarification. *Soc Netw* 1: 215–239.
- Brandes U (2001) A faster algorithm for betweenness centrality. *J Math Sociol* 25: 163–177.
- Paradis E, Claude J, Strimmer K (2004) APE: analyses of phylogenetics and evolution in R language. *Bioinformatics* 20: 289–290.
- Page RDM (1996) TREEVIEW: an application to display phylogenetic trees on personal computers. *Comput Appl Biosci* 12: 357–358.
- Mielke PW, Berry KJ (2001) *Permutation Methods: A Distance Function Approach*. New-York: Springer-Verlag. 352 p.
- Prado PI, Lewinsohn TM (2004) Compartments in insect-plant associations and their consequences for community structure. *J Anim Ecol* 73: 1168–1178.
- Oksanen J, Kindt R, Legendre P, O'Hara RB (2006) *vegan: Community Ecology Package version 1.8.3*. Available: <http://cc.oulu.fi/~jarioksa/>.
- Auber D (2002) Tulip. In: Mutzel P, Jünger M, Leipert S, eds. *Graph Drawing: 9th International Symposium, GD 2001 Vienna, Austria, September 23–26, 2001*. New-York: Springer-Verlag. pp 488–491.

**Table S1.** References of the 187 articles included in the database.

1. Alstad, D. N. and D. A. Andow (1995). "Managing the Evolution of Insect Resistance to Transgenic Plants." Science **268**(5219): 1894-1896.
2. Argentine, J. A., J. M. Clark, et al. (1994). "Computer simulation of insecticide resistance management strategies for control of Colorado potato beetle (Coleoptera: Chrysomelidae)." Journal of Agricultural Entomology **11**(2): 137-155.
3. Arpaia, S., K. Chiriatti, et al. (1998). "Predicting the adaptation of Colorado potato beetle (Coleoptera: Chrysomelidae) to transgenic eggplants expressing CryIII toxin: The role of gene dominance, migration, and fitness costs." Journal of Economic Entomology **91**(1): 21-29.
4. Austin, D. J. and R. M. Anderson (1999). "Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models." Philos Trans R Soc Lond B Biol Sci **354**(1384): 721-38.
5. Austin, D. J., M. Kakehashi, et al. (1997). "The transmission dynamics of antibiotic-resistant bacteria: the relationship between resistance in commensal organisms and antibiotic consumption." Proc Biol Sci **264**(1388): 1629-38.
6. Austin, D. J., K. G. Kristinsson, et al. (1999). "The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance." Proc Natl Acad Sci U S A **96**(3): 1152-6.
7. Barnes, E. H. and R. J. Dobson (1990). "Population dynamics of *Trichostrongylus colubriformis* in sheep: computer model to simulate grazing systems and the evolution of anthelmintic resistance." International Journal for Parasitology **20**(7): 823-831.
8. Barnes, E. H., R. J. Dobson, et al. (1995). "Worm control and anthelmintic resistance: adventures with a model." Parasitology Today **11**(2): 56-63.
9. Benderly, M. and Y. Levy (1988). Modeling the buildup of multigenic resistance to systemic fungicides in a haploid fungal pathogen. Mededelingen van de Faculteit Landbouwwetenschappen, Rijksuniversiteit Gent. **53**: 589-595.
10. Bergstrom, C. T., M. Lo, et al. (2004). "Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals." Proceedings of the National Academy of Sciences of the United States of America **101**(36): 13285-13290.
11. Birch, C. P. D. and M. W. Shaw (1997). "When can reduced doses and pesticide mixtures delay the build-up of pesticide resistance? A mathematical model." Journal of Applied Ecology **34**(4): 1032-1042.
12. Blower, S. M., T. C. Porco, et al. (1998). "Predicting and preventing the emergence of antiviral drug resistance in HSV-2." Nat Med **4**(6): 673-8.
13. Bonhoeffer, S., M. Lipsitch, et al. (1997). "Evaluating treatment protocols to prevent antibiotic resistance." Proc Natl Acad Sci U S A **94**(22): 12106-11.
14. Bonhoeffer, S., R. M. May, et al. (1997). "Virus dynamics and drug therapy." Proc Natl Acad Sci U S A **94**(13): 6971-6.
15. Bonhoeffer, S. and M. A. Nowak (1997). "Pre-existence and emergence of drug resistance in HIV-1 infection." Proc Biol Sci **264**(1382): 631-7.
16. Boni, M. F. and M. W. Feldman (2005). "Evolution of antibiotic resistance by human and bacterial niche construction." Evolution Int J Org Evolution **59**(3): 477-91.
17. Caprio, M. A. (1998). "Evaluating resistance management strategies for multiple toxins in the presence of external refuges." Journal of Economic Entomology **91**(5): 1021-1031.
18. Caprio, M. A. (2001). "Source-sink dynamics between transgenic and non-transgenic habitats and their role in the evolution of resistance." J Econ Entomol **94**(3): 698-705.
19. Caprio, M. A. and M. A. Hoy (1994). "Metapopulation dynamics affect resistance development in the predatory mite, *Metaseiulus occidentalis* (Acari: Phytoseiidae)." Journal of Economic Entomology **87**(3): 525-534.

20. Caprio, M. A. and M. A. Hoy (1995). "Premating isolation in a simulation model generates frequency-dependent selection and alters establishment rates of resistant natural enemies." Journal of Economic Entomology **88**(2): 205-212.
21. Caprio, M. A. and D. M. Suckling (2000). "Simulating the impact of cross resistance between Bt toxins in transformed clover and apples in New Zealand." J Econ Entomol **93**(2): 173-9.
22. Caprio, M. A. and B. E. Tabashnik (1992). "Gene flow accelerates local adaptation among finite populations: simulating the evolution of insecticide resistance." Journal of Economic Entomology **85**(3): 611-620.
23. Carrière, Y. (2003). "Haplodiploidy, sex, and the evolution of pesticide resistance." Journal of Economic Entomology **96**(6): 1626-1640.
24. Carrière, Y., C. Eilers-Kirk, et al. (2001). "Predicting spring moth emergence in the pink bollworm (Lepidoptera: Gelechiidae): implications for managing resistance to transgenic cotton." J Econ Entomol **94**(5): 1012-21.
25. Carrière, Y. and B. E. Tabashnik (2001). "Reversing insect adaptation to transgenic insecticidal plants." Proc Biol Sci **268**(1475): 1475-80.
26. Castillo-Chavez, C. and Z. Feng (1997). "To treat or not to treat: the case of tuberculosis." J Math Biol **35**(6): 629-56.
27. Cavan, G., J. Cussans, et al. (2000). "Modelling different cultivation and herbicide strategies for their effect on herbicide resistance in *Alopecurus myosuroides*." Weed Research **40**(6): 561-568.
28. Cavan, G., J. Cussans, et al. (2001). "Managing the risks of herbicide resistance in wild oat." Weed Science **49**(2): 236-240.
29. Cerda, H. (2002). "A high-dose refugia management strategy for Bt transgenic crops: spraying the refugia." Antenna (London) **26**(2): 124-126.
30. Chilcutt, C. F. and B. E. Tabashnik (1999). "Simulation of integration of *Bacillus thuringiensis* and the parasitoid *Cotesia plutellae* (Hymenoptera: Braconidae) for control of susceptible and resistant diamondback moth (Lepidoptera: Plutellidae)." Environmental Entomology **28**(3): 505-512.
31. Chin, K. M. (1987). "A simple method of selection for fungicide resistance in plant pathogen populations." Phytopathology **77**(5): 666-669.
32. Cohen, T. and M. Murray (2004). "Modeling epidemics of multidrug-resistant *M. tuberculosis* of heterogeneous fitness." Nature Medicine **10**(10): 1117-1121.
33. Comins, H. N. (1977). "The development of insecticide resistance in the presence of migration." J Theor Biol **64**(1): 177-97.
34. Comins, H. N. (1979). "Analytic methods for the management of pesticide resistance." J Theor Biol **77**(2): 171-88.
35. Comins, H. N. (1986). "Tactics for resistance management using multiple pesticides." Agriculture, Ecosystems and Environment **16**(2): 129-148.
36. Coop, L. B., B. A. Croft, et al. (1994). Geographic information systems and simulation in regional orchard management: pesticide resistance in Hood River valley, Oregon. Acta Horticulturæ: 383-390.
37. Cornell, S. J., V. S. Isham, et al. (2003). "Spatial parasite transmission, drug resistance, and the spread of rare genes." Proceedings of the National Academy of Sciences of the United States of America **100**(12): 7401-7405.
38. Cross, A. P. and B. Singer (1991). "Modelling the development of resistance of *Plasmodium falciparum* to anti-malarial drugs." Transactions of the Royal Society of Tropical Medicine and Hygiene **85**(3): 349-355.
39. Crowder, D. W. and D. W. Onstad (2005). "Using a generational time-step model to simulate dynamics of adaptation to transgenic corn and crop rotation by western corn rootworm

- (Coleoptera: Chrysomelidae)." Journal of Economic Entomology **98**(2): 518-533.
40. Crowder, D. W., D. W. Onstad, et al. (2005). "Analysis of the dynamics of adaptation to transgenic corn and crop rotation by western corn rootworm (Coleoptera: Chrysomelidae) using a daily time-step model." Journal of Economic Entomology **98**(2): 534-551.
  41. Curtis, C. F., N. Hill, et al. (1993). "Are there effective resistance management strategies for vectors of human disease?" Biological Journal of the Linnean Society **48**(1): 3-18.
  42. Curtis, C. F. and L. N. Otoo (1986). "A simple model of the build-up of resistance to mixtures of anti-malarial drugs." Transactions of the Royal Society of Tropical Medicine and Hygiene **80**(6): 889-892.
  43. D'Agata, E. M. C., G. F. Webb, et al. (2005). "A mathematical model quantifying the impact of antibiotic exposure and other interventions on the endemic prevalence of vancomycin-resistant enterococci." J Infect Dis **192**(11): 2004-11.
  44. De Boer, R. J. and C. A. Boucher (1996). "Anti-CD4 therapy for AIDS suggested by mathematical models." Proc Biol Sci **263**(1372): 899-905.
  45. De Souza, K., J. Holt, et al. (1995). "Diapause, migration and pyrethroid-resistance dynamics in the cotton bollworm, *Helicoverpa armigera* (Lepidoptera: Noctuidae)." Ecological Entomology **20**(4): 333-342.
  46. Diggle, A. J., P. B. Neve, et al. (2003). "Herbicides used in combination can reduce the probability of herbicide resistance in finite weed populations." Weed Research **43**(5): 371-382.
  47. Dobson, R. J., D. A. Griffiths, et al. (1987). "A genetic model describing the evolution of levamisole resistance in *Trichostrongylus colubriformis*, a nematode parasite of sheep." IMA Journal of Mathematics Applied in Medicine and Biology **4**(4): 279-293.
  48. Doster, M. A., M. G. Milgroom, et al. (1990). "Quantification of factors influencing potato late blight suppression and selection for metalaxyl resistance in *Phytophthora infestans*: a simulation approach." Phytopathology **80**(11): 1190-1198.
  49. Dugatkin, L. A., M. Perlin, et al. (2005). "Antibiotic resistance and the evolution of group-beneficial traits. II: a metapopulation model." J Theor Biol **236**(4): 392-6.
  50. Dye, C. and M. A. Espinal (2001). "Will tuberculosis become resistant to all antibiotics?" Proceedings of the Royal Society of London Series B-Biological Sciences **268**(1462): 45-52.
  51. Dye, C. and B. G. Williams (2000). "Criteria for the control of drug-resistant tuberculosis." Proc Natl Acad Sci U S A **97**(14): 8180-5.
  52. Echevarria, F. A. M., G. Gettinby, et al. (1993). "Model predictions for anthelmintic resistance amongst *Haemonchus contortus* populations in southern Brazil." Veterinary Parasitology **47**(3-4): 315-325.
  53. Emery, V. C. and P. D. Griffiths (2000). "Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy." Proceedings of the National Academy of Sciences of the United States of America **97**(14): 8039-8044.
  54. Follett, P. A., F. Gould, et al. (1995). "High-realism model of Colorado potato beetle (Coleoptera: Chrysomelidae) adaptation to permethrin." Environmental Entomology **24**(2): 167-178.
  55. Follett, P. A., G. G. Kennedy, et al. (1993). "REPO: a stimulation model that explores Colorado potato beetle (Coleoptera: Chrysomelidae) adaptation to insecticides." Environmental Entomology **22**(2): 283-296.
  56. Garber, A. M. (1987). "Antibiotic exposure and resistance in mixed bacterial populations." Theor Popul Biol **32**(3): 326-46.
  57. Gardner, S. N., J. Gressel, et al. (1998). "A revolving dose strategy to delay the evolution of both quantitative vs major monogene resistances to pesticides and drugs." International Journal of Pest Management **44**(3): 161-180.
  58. Gatton, M. L., W. Hogarth, et al. (2001). "Time of treatment influences the appearance of

- drug-resistant parasites in Plasmodium falciparum infections." Parasitology **123**(6): 537-546.
59. Gazzoni, D. L. (1998). "Modeling insect resistance to insecticides using velvetbean caterpillar (*Anticarsia gemmatalis*) as an example." Pesticide Science **53**(2): 109-122.
  60. Georgioui, G. P. and C. E. Taylor (1977). "Genetic and biological influences in the evolution of insecticide resistance." J Econ Entomol **70**(3): 319-23.
  61. Gershengorn, H. B. and S. M. Blower (2000). "Impact of antivirals and emergence of drug resistance: HSV-2 epidemic control." AIDS Patient Care STDS **14**(3): 133-42.
  62. Gettinby, G., R. M. Newson, et al. (1988). "A simulation model for genetic resistance to acaricides in the African brown ear tick, *Rhipicephalus appendiculatus* (Acarina: Ixodidae)." Preventive Veterinary Medicine **6**(3): 183-197.
  63. Gettinby, G., A. Soutar, et al. (1989). "Anthelmintic resistance and the control of ovine ostertagiasis: a drug action model for genetic selection." International Journal for Parasitology **19**(4): 369-376.
  64. Gorddard, R. J., D. J. Pannell, et al. (1995). "An optimal control model for integrated weed management under herbicide resistance." Australian Journal of Agricultural Economics **39**(1): 71-87.
  65. Gorddard, R. J., D. J. Pannell, et al. (1996). "Economic evaluation of strategies for management of herbicide resistance." Agricultural Systems **51**(3): 281-298.
  66. Gould, F. (1986). "Simulation models for predicting durability of insect-resistant germ plasm: a deterministic diploid, two-locus model." Environmental Entomology **15**(1): 1-10.
  67. Gould, F. (1994). Potential and problems with high-dose strategies for pesticidal engineered crops. Biocontrol Science and Technology. **4**: 451-461.
  68. Gressel, J. and L. A. Segel (1990). "Modelling the effectiveness of herbicide resistance and mixtures as strategies to delay or preclude resistance." Weed Technology **4**(1): 186-198.
  69. Gressel, J., L. A. Segel, et al. (1996). "Managing the delay of evolution of herbicide resistance in parasitic weeds." International Journal of Pest Management **42**(2): 113-129.
  70. Groeters, F. R. and B. E. Tabashnik (2000). "Roles of selection intensity, major genes, and minor genes in evolution of insecticide resistance." J Econ Entomol **93**(6): 1580-7.
  71. Gubbins, S. and C. A. Gilligan (1999). "Invasion thresholds for fungicide resistance: deterministic and stochastic analyses." Proceedings of the Royal Society of London Series B-Biological Sciences **266**(1437): 2539-2549.
  72. Gutierrez, A. P., U. Regev, et al. (1979). "An economic optimization model of pesticide resistance: alfalfa and Egyptian alfalfa weevil - an example." Environmental Entomology **8**(1): 101-107.
  73. Hall, R. J., S. Gubbins, et al. (2004). "Invasion of drug and pesticide resistance is determined by a trade-off between treatment efficacy and relative fitness." Bull Math Biol **66**(4): 825-40.
  74. Hanson, D. E., D. A. Ball, et al. (2002). "Herbicide resistance in jointed goatgrass (*Aegilops cylindrica*): Simulated responses to agronomic practices." Weed Technology **16**(1): 156-163.
  75. Hastings, I. M. (1997). "A model for the origins and spread of drug-resistant malaria." Parasitology **115**(2): 133-141.
  76. Hastings, I. M. and M. J. Mackinnon (1998). "The emergence of drug-resistant malaria." Parasitology **117**(5): 411-417.
  77. Hastings, I. M., W. M. Watkins, et al. (2002). "The evolution of drug-resistant malaria: the role of drug elimination half-life." Philos Trans R Soc Lond B Biol Sci **357**(1420): 505-19.
  78. Heimpel, G. E., C. Neuhauser, et al. (2005). "Natural enemies and the evolution of resistance to transgenic insecticidal crops by pest insects: The role of egg mortality." Environmental Entomology **34**(3): 512-526.
  79. Hillier, J. G. and A. N. E. Birch (2002). "A bi-trophic mathematical model for pest adaptation to a resistant crop." Journal of Theoretical Biology **215**(3): 305-319.
  80. Hillier, J. G. and A. N. E. Birch (2002). "Travelling waves of resistance in a bi-trophic pest

- adaptation model." Journal of Theoretical Biology **219**(4): 507-519.
81. Hoshen, M. B., W. D. Stein, et al. (2002). "Mathematical modelling of malaria chemotherapy: combining artesunate and mefloquine." Parasitology **124**(1): 9-15.
  82. Howard, D. H. (2004). "Resistance-induced antibiotic substitution." Health Econ **13**(6): 585-95.
  83. Huang, Y., S. L. Rosenkranz, et al. (2003). "Modeling HIV dynamics and antiviral response with consideration of time-varying drug exposures, adherence and phenotypic sensitivity." Math Biosci **184**(2): 165-86.
  84. Ives, A. R. and D. A. Andow (2002). "Evolution of resistance to Bt crops: directional selection in structured environments." Ecology Letters **5**(6): 792-801.
  85. Jaffe, K., S. Issa, et al. (1997). "Dynamics of the emergence of genetic resistance to biocides among asexual and sexual organisms." J Theor Biol **188**(3): 289-99.
  86. Janssen, M. A. and W. J. Martens (1997). "Modeling malaria as a complex adaptive system." Artif Life **3**(3): 213-36.
  87. Jasieniuk, M., A. L. Brule-Babel, et al. (1996). "The evolution and genetics of herbicide resistance in weeds." Weed Science **44**(1): 176-193.
  88. Josepovits, G. (1989). "A model for evaluating factors affecting the development of insensitivity to fungicides." Crop Protection **8**(2): 106-113.
  89. Kawaguchi, I., A. Sasaki, et al. (2004). "Combining zooprophylaxis and insecticide spraying: a malaria-control strategy limiting the development of insecticide resistance in vector mosquitoes." Proc Biol Sci **271**(1536): 301-9.
  90. Kelman, E., R. S. Levy, et al. (2001). "Optimization of solutions for the one plant protection problem." Acta Biotheor **49**(1): 61-71.
  91. Kirschner, D. E. and G. F. Webb (1997). "Understanding drug resistance for monotherapy treatment of HIV infection." Bulletin of Mathematical Biology **59**(4): 763-785.
  92. Knipling, E. F. and W. Klassen (1984). "Influence of insecticide use patterns on the development of resistance to insecticides-a theoretical study." Southwestern Entomologist **9**(3): 351-368.
  93. Koella, J. C. and R. Antia (2003). "Epidemiological models for the spread of anti-malarial resistance." Malaria Journal **2**(3): (19 February 2003).
  94. Kranthi, K. R. and N. R. Kranthi (2004). "Modelling adaptability of cotton bollworm, *Helicoverpa armigera* (Hubner) to Bt-cotton in India." Current Science **87**(8): 1096-1107.
  95. Laxminarayan, R. (2004). "ACT now or later? Economics of malaria resistance." American Journal of Tropical Medicine and Hygiene **71**(2 supplement): 187-195.
  96. Leathwick, D. M., A. Vlassoff, et al. (1995). "A model for nematodiasis in New Zealand lambs: the effect of drenching regime and grazing management on the development of anthelmintic resistance." International Journal for Parasitology **25**(12): 1479-1490.
  97. Lenormand, T. and M. Raymond (1998). "Resistance management: the stable zone strategy." Proceedings of the Royal Society of London Series B-Biological Sciences **265**(1409): 1985-1990.
  98. Levin, B. R. (2001). "Minimizing potential resistance: A population dynamics view." Clinical Infectious Diseases **33**: S161-S169.
  99. Levin, B. R., M. Lipsitch, et al. (1997). "The population genetics of antibiotic resistance." Clin Infect Dis **24 Suppl 1**: S9-16.
  100. Levy, Y., Y. Cohen, et al. (1991). "Disease development and buildup of resistance to oxadixyl in potato crops inoculated with *Phytophthora infestans* as affected by oxadixyl and oxadixyl mixtures: experimental and simulation studies." Journal of Phytopathology **132**(3): 219-229.
  101. Levy, Y., R. Levi, et al. (1983). "Buildup of a pathogen subpopulation resistant to a systemic fungicide under various control strategies: a flexible simulation model." Phytopathology

- 73(11): 1475-1480.
102. Levy, Y. and R. S. Levy (1986). "Control strategies using systemic fungicides for limiting disease development and resistance buildup: practical implications of a simulation model." Phytoparasitica **14**(4): 303-312.
  103. Li, R. C., D. E. Nix, et al. (1994). "Pharmacodynamic modeling of bacterial kinetics: beta-lactam antibiotics against *Escherichia coli*." J Pharm Sci **83**(7): 970-5.
  104. Lipsitch, M. (2001). "Measuring and interpreting associations between antibiotic use and penicillin resistance in *Streptococcus pneumoniae*." Clinical Infectious Diseases **32**(7): 1044-1054.
  105. Lipsitch, M., C. T. Bergstrom, et al. (2000). "The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions." Proc Natl Acad Sci U S A **97**(4): 1938-43.
  106. Lipsitch, M. and B. R. Levin (1997). "The population dynamics of antimicrobial chemotherapy." Antimicrob Agents Chemother **41**(2): 363-73.
  107. Livingston, M. J., G. A. Carlson, et al. (2002). "Use of mathematical models to estimate characteristics of pyrethroid resistance in tobacco budworm and bollworm (Lepidoptera: Noctuidae) field populations." Journal of Economic Entomology **95**(5): 1008-1017.
  108. Longstaff, B. C. (1988). "Temperature manipulation and the management of insecticide resistance in stored grain pests: a stimulation study for the rice weevil, *Sitophilus oryzae*." Ecological Modelling **43**(3-4): 303-313.
  109. Mackinnon, M. J. and I. M. Hastings (1998). "The evolution of multiple drug resistance in malaria parasites." Transactions of the Royal Society of Tropical Medicine and Hygiene **92**(2): 188-195.
  110. Madden, A. D. (1995). "An assessment, using a modelling approach, of inbreeding as a possible cause of reduced competitiveness in triazine-resistant weeds." Weed Research (Oxford) **35**(4): 289-294.
  111. Madden, A. D., J. Holt, et al. (1995). "The role of uncultivated hosts in the spread of pyrethroid resistance in *Helicoverpa armigera* populations in Andhra Pradesh, India: a simulation approach." Ecological Modelling **82**(1): 61-74.
  112. Madsen, K. H., B. E. Valverde, et al. (2002). "Risk assessment of herbicide-resistant crops: A Latin American perspective using rice (*Oryza sativa*) as a model." Weed Technology **16**(1): 215-223.
  113. Magee, J. T. (2005). "The resistance ratchet: theoretical implications of cyclic selection pressure." J Antimicrob Chemother **56**(2): 427-30.
  114. Mallet, J. and R. Luttrell (1991). "A model of insecticidal control failure: the example of *Heliothis virescens* on cotton." Southwestern Entomologist(No. 15, Supplement): 201-212.
  115. Mallet, J. and P. Porter (1992). "Preventing Insect Adaptation to Insect-Resistant Crops - Are Seed Mixtures or Refugia the Best Strategy." Proceedings of the Royal Society of London Series B-Biological Sciences **250**(1328): 165-169.
  116. Mangel, M. and R. E. Plant (1983). "Multiseasonal management of an agricultural pest. I: development of the theory." Ecological Modelling **20**(1): 1-19.
  117. Mani, G. S. (1989). "Evolution of resistance with sequential application of insecticides in time and space." Proc R Soc Lond B Biol Sci **238**(1292): 245-76.
  118. Mason, G. A., B. E. Tabashnik, et al. (1989). "Effects of biological and operational factors on evolution of insecticide resistance in *Liriomyza* (Diptera: Agromyzidae)." Journal of Economic Entomology **82**(2): 369-373.
  119. Massad, E., S. Lundberg, et al. (1993). "Modeling and simulating the evolution of resistance against antibiotics." Int J Biomed Comput **33**(1): 65-81.
  120. Maxwell, B. D. (1992). Weed thresholds: the space component and considerations for herbicide resistance. Weed Technology. **6**: 205-212.
  121. Maxwell, B. D., M. L. Roush, et al. (1990). "Predicting the evolution and dynamics of

- herbicide resistance in weed populations." Weed Technology **4**(1): 2-13.
122. May, R. M. and M. P. Hassell (1988). "Population dynamics and biological control." Philosophical Transactions of the Royal Society of London, B **318**: 129-169.
123. Medvinsky, A. B., A. Y. Morozov, et al. (2004). "Modeling the invasion of recessive Bt-resistant insects: an impact on transgenic plants." J Theor Biol **231**(1): 121-7.
124. Michael, E., M. N. Malecela-Lazaro, et al. (2004). "Mathematical modelling and the control of lymphatic filariasis." Lancet Infectious Diseases **4**(4): 223-234.
125. Milgroom, M. G. (1990). "A stochastic model for the initial occurrence and development of fungicide resistance in plant pathogen populations." Phytopathology **80**(4): 410-416.
126. Milgroom, M. G. and W. E. Fry (1988). "A simulation analysis of the epidemiological principles for fungicide resistance management in pathogen populations." Phytopathology **78**(5): 565-570.
127. Mitchell, P. D. and D. W. Onstad (2005). "Effect of extended diapause on evolution of resistance to transgenic *Bacillus thuringiensis* corn by northern corn rootworm (Coleoptera: Chrysomelidae)." Journal of Economic Entomology **98**(6): 2220-2234.
128. Muggleton, J. (1986). "Selection for malathion resistance in *Oryzaephilus surinamensis* (L.) (Coleoptera: Silvanidae): fitness values of resistant and susceptible phenotypes and their inclusion in a general model describing the spread of resistance." Bulletin of Entomological Research **76**(3): 469-480.
129. Munro, A. (1997). "Economics and biological evolution." Environmental and Resource Economics **9**(4): 429-449.
130. Neve, P. B., A. J. Diggle, et al. (2003). "Simulating evolution of glyphosate resistance in *Lolium rigidum* I: population biology of a rare resistance trait." Weed Research **43**(6): 404-417.
131. Neve, P. B., A. J. Diggle, et al. (2003). "Simulating evolution of glyphosate resistance in *Lolium rigidum* II: past, present and future glyphosate use in Australian cropping." Weed Research **43**(6): 418-427.
132. Nibouche, S., P. Martin, et al. (2003). "A modelling approach of the sustainability of Bt Cotton grown by small farmers in West Africa." Resistant Pest Management Newsletter **13**(1): 55-58.
133. Nowak, M. A., S. Bonhoeffer, et al. (1997). "Anti-viral drug treatment: dynamics of resistance in free virus and infected cell populations." J Theor Biol **184**(2): 203-17.
134. Onstad, D. W. and F. Gould (1998). "Do dynamics of crop maturation and herbivorous insect life cycle influence the risk of adaptation to toxins in transgenic host plants?" Environmental Entomology **27**(3): 517-522.
135. Onstad, D. W. and F. Gould (1998). "Modeling the dynamics of adaptation to transgenic maize by European corn borer (Lepidoptera: Pyralidae)." Journal of Economic Entomology **91**(3): 585-593.
136. Onstad, D. W. and C. A. Guse (1999). "Economic analysis of transgenic maize and nontransgenic refuges for managing European corn borer (Lepidoptera: Pyralidae)." Journal of Economic Entomology **92**(6): 1256-1265.
137. Onstad, D. W., C. A. Guse, et al. (2002). "Modeling the development of resistance by stalk-boring lepidopteran insects (Crambidae) in areas with transgenic corn and frequent insecticide use." J Econ Entomol **95**(5): 1033-43.
138. Onstad, D. W., C. A. Guse, et al. (2001). "Modeling the dynamics of adaptation to transgenic corn by western corn rootworm (Coleoptera: Chrysomelidae)." Journal of Economic Entomology **94**(2): 529-540.
139. Parnell, S., C. A. Gilligan, et al. (2005). "Small-scale fungicide spray heterogeneity and the coexistence of resistant and sensitive pathogen strains." Phytopathology **95**(6): 632-639.
140. Peck, S. L. and S. P. Ellner (1997). "The effect of economic thresholds and life-history

- parameters on the evolution of pesticide resistance in a regional setting." American Naturalist **149**(1): 43-63.
141. Peck, S. L., F. Gould, et al. (1999). "Spread of resistance in spatially extended regions of transgenic cotton: Implications for management of *Heliothis virescens* (Lepidoptera: Noctuidae)." Journal of Economic Entomology **92**(1): 1-16.
142. Pittendrigh, B. R. and P. J. Gaffney (2001). "Pesticide resistance: can we make it a renewable resource?" J Theor Biol **211**(4): 365-75.
143. Pittendrigh, B. R., P. J. Gaffney, et al. (2004). "'Active' refuges can inhibit the evolution of resistance in insects towards transgenic insect-resistant plants." J Theor Biol **231**(4): 461-74.
144. Pittendrigh, B. R., P. J. Gaffney, et al. (2000). "Deterministic modeling of negative cross-resistance strategies for use in transgenic host-plant resistance." J Theor Biol **204**(1): 135-50.
145. Plapp, F. W., C. R. Browning, et al. (1979). "Analysis of rate of development of insecticide resistance based on simulation of a genetic model." Environmental Entomology **8**(3): 494-500.
146. Rainbolt, C. R., D. C. Thill, et al. (2004). "Herbicide-resistant grass weed development in imidazolinone-resistant wheat: Weed biology and herbicide rotation." Weed Technology **18**(3): 860-868.
147. Reluga, T. C. (2005). "Simple models of antibiotic cycling." Math Med Biol **22**(2): 187-208.
148. Richter, O., P. Zwerger, et al. (2002). "Modelling spatio-temporal dynamics of herbicide resistance." Weed Research **42**(1): 52-64.
149. Roberts, D. E. and R. M. Ribeiro (2001). "Comparison of different treatment regimens for the emergence of new resistance under therapy." JAIDS, Journal of Acquired Immune Deficiency Syndromes **27**(4): 331-335.
150. Rosenheim, J. A. and B. E. Tabashnik (1990). "Evolution of pesticide resistance: interactions between generation time and genetic, ecological, and operational factors." Journal of Economic Entomology **83**(4): 1184-1193.
151. Roush, R. T. (1994). Managing pests and their resistance to *Bacillus thuringiensis*: can transgenic crops be better than sprays? Biocontrol Science and Technology. **4**: 501-516.
152. Roush, R. T. (1998). "Two-toxin strategies for management of insecticidal transgenic crops: can pyramiding succeed where pesticide mixtures have not?" Philosophical Transactions of the Royal Society of London Series B-Biological Sciences **353**(1376): 1777-1786.
153. Ruppel, R. F. (1983). "Some observations on insecticide resistance." Great Lakes Entomologist **16**(4): 101-107.
154. Samore, M. H., M. Lipsitch, et al. (2006). "Mechanisms by which antibiotics promote dissemination of resistant pneumococci in human populations." American Journal of Epidemiology **163**(2): 160-170.
155. Seville, V., S. Chevret, et al. (1997). "Modeling the spread of resistant nosocomial pathogens in an intensive-care unit." Infect Control Hosp Epidemiol **18**(2): 84-92.
156. Shaw, M. W. (1989). "Independent action of fungicides and its consequences for strategies to retard the evolution of fungicide resistance." Crop Protection **8**(6): 405-411.
157. Shaw, M. W. (1989). "A model of the evolution of polygenically controlled fungicide resistance." Plant Pathology **38**(1): 44-55.
158. Shaw, M. W. (1993). "Theoretical analysis of the effect of interacting activities on the rate of selection for combined resistance to fungicide mixtures." Crop Protection **12**(2): 120-126.
159. Shaw, M. W. (2000). "Models of the effects of dose heterogeneity and escape on selection pressure for pesticide resistance." Phytopathology **90**(4): 333-339.
160. Sisterson, M. S., L. Antilla, et al. (2004). "Effects of insect population size on evolution of resistance to transgenic crops." J Econ Entomol **97**(4): 1413-24.
161. Sisterson, M. S., Y. Carrière, et al. (2005). "Evolution of resistance to transgenic crops: Interactions between insect movement and field distribution." Journal of Economic

- Entomology **98**(6): 1751-1762.
162. Smith, G. (1990). "A mathematical model for the evolution of anthelmintic resistance in a direct life cycle nematode parasite." International Journal for Parasitology **20**(7): 913-921.
  163. Smith, G., B. T. Grenfell, et al. (1999). Anthelmintic resistance revisited: under-dosing, chemoprophylactic strategies, and mating probabilities. International Journal for Parasitology. **29**: 77-91.
  164. Stewart, F. M., R. Antia, et al. (1998). "The population genetics of antibiotic resistance. II: Analytic theory for sustained populations of bacteria in a community of hosts." Theor Popul Biol **53**(2): 152-65.
  165. Stilianakis, N. I., C. A. Boucher, et al. (1997). "Clinical data sets to human immunodeficiency virus type 1 reverse transcriptase-resistant mutants explained by a mathematical model." Journal of Virology **71**(1): 161-168.
  166. Stilianakis, N. I., A. S. Perelson, et al. (1998). "Emergence of drug resistance during an influenza epidemic: insights from a mathematical model." J Infect Dis **177**(4): 863-73.
  167. Storer, N. P. (2003). "A spatially explicit model simulating western corn rootworm (Coleoptera: Chrysomelidae) adaptation to insect-resistant maize." J Econ Entomol **96**(5): 1530-47.
  168. Storer, N. P., S. L. Peck, et al. (2003). "Sensitivity analysis of a spatially-explicit stochastic simulation model of the evolution of resistance in *Helicoverpa zea* (Lepidoptera: Noctuidae) to Bt transgenic corn and cotton." Journal of Economic Entomology **96**(1): 173-187.
  169. Storer, N. P., S. L. Peck, et al. (2003). "Spatial processes in the evolution of resistance in *Helicoverpa zea* (Lepidoptera: Noctuidae) to Bt transgenic corn and cotton in a mixed agroecosystem: a biology-rich stochastic simulation model." Journal of Economic Entomology **96**(1): 156-172.
  170. Sutherst, R. W. and H. N. Comins (1979). "The management of acaricide resistance in the cattle tick, *Boophilus microplus* (Canestrini) (Acari: Ixodidae), in Australia." Bulletin of Entomological Research **69**(3): 519-540.
  171. Tabashnik, B. E. (1986). "Evolution of pesticide resistance in predator/prey systems." Bulletin of the Entomological Society of America **32**(3): 156-161.
  172. Tabashnik, B. E. (1986). "Model for managing resistance to fenvalerate in the diamondback moth (Lepidoptera: Plutellidae)." Journal of Economic Entomology **79**(6): 1447-1451.
  173. Tabashnik, B. E. (1990). "Implications of gene amplification for evolution and management of insecticide resistance." Journal of Economic Entomology **83**(4): 1170-1176.
  174. Tabashnik, B. E. (1994). "Delaying insect adaptation to transgenic plants - seed mixtures and refugia reconsidered." Proceedings of the Royal Society of London Series B-Biological Sciences **255**(1342): 7-12.
  175. Tabashnik, B. E., T. J. Dennehy, et al. (2005). "Delayed resistance to transgenic cotton in pink bollworm." Proc Natl Acad Sci U S A **102**(43): 15389-93.
  176. Tabashnik, B. E., F. Gould, et al. (2004). "Delaying evolution of insect resistance to transgenic crops by decreasing dominance and heritability." J Evol Biol **17**(4): 904-12; discussion 913-8.
  177. Tang, S., Y. Xiao, et al. (2005). "Integrated pest management models and their dynamical behaviour." Bull Math Biol **67**(1): 115-35.
  178. Tchetgen, E., E. H. Kaplan, et al. (2001). "Public health consequences of screening patients for adherence to highly active antiretroviral therapy." JAIDS, Journal of Acquired Immune Deficiency Syndromes **26**(2): 118-129.
  179. Temime, L., P. Y. Boelle, et al. (2005). "Penicillin-resistant pneumococcal meningitis: high antibiotic exposure impedes new vaccine protection." Epidemiology and Infection **133**(3): 493-501.
  180. Vacher, C., D. Bourguet, et al. (2003). "Modelling the spatial configuration of refuges for a

- sustainable control of pests: a case study of Bt cotton." J Evol Biol **16**(3): 378-87.
181. Wahl, L. M. and M. A. Nowak (2000). "Adherence and drug resistance: predictions for therapy outcome." Proceedings of the Royal Society of London Series B-Biological Sciences **267**(1445): 835-843.
182. Webb, G. F., E. M. C. D'Agata, et al. (2005). "A model of antibiotic-resistant bacterial epidemics in hospitals." Proc Natl Acad Sci U S A **102**(37): 13343-8.
183. Weersink, A., R. S. Llewellyn, et al. (2005). "Economics of pre-emptive management to avoid weed resistance to glyphosate in Australia." Crop Protection **24**(7): 659-665.
184. Wijngaarden, P. J., F. van den Bosch, et al. (2005). "Adaptation to the cost of resistance: a model of compensation, recombination, and selection in a haploid organism." Proceedings of the Royal Society of London. Series B, Biological Sciences **272**(1558): 85-89.
185. Wodarz, D. and A. L. Lloyd (2004). "Immune responses and the emergence of drug-resistant virus strains in vivo." Proceedings of the Royal Society of London Series B-Biological Sciences **271**(1544): 1101-1109.
186. Xu, D. S., J. Curtis, et al. (2005). "On the role of schistosome mating structure in the maintenance of drug resistant strains." Bulletin of Mathematical Biology **67**(6): 1207-1226.
187. Yeung, S. M., W. Pongtavornpinyo, et al. (2004). "Antimalarial drug resistance, artemisinin-based combination therapy, and the contribution of modeling to elucidating policy choices." American Journal of Tropical Medicine and Hygiene **71**(2 supplement): 179-186.

**Table S2.** Number of articles falling into the various descriptive categories for each group of the authorship network. For all categories, the distributions differ significantly between groups (Fisher exact test,  $p < 10^{-5}$ ).

Category	Descriptor	Number of Articles			
		A1 Group	A2 Group	Small Groups	Isolated Articles
Type of Drug or Pesticide	Antibiotic Drug	0	10	10	9
	Anthelmintic Drug	0	0	8	2
	Antimalarial Drug	0	1	6	5
	Antiviral Drug	0	3	6	5
	Fungicide	0	0	13	2
	Herbicide	0	0	15	3
	Insecticidal Protein	28	0	5	6
	Insecticide	12	0	4	14
	Miticide	1	0	2	0
	Unspecific	4	1	9	3
Type of Target Organism	Farm Pest or Disease	45	1	48	25
	Human Parasite	0	14	24	20
	Unspecific	0	0	6	4
Modelling Approach	Epidemiology	0	10	19	12
	Population Genetics	45	2	38	25
	Other	0	3	21	12
First Author's Location	Africa	0	0	1	0
	Asia	0	0	8	5
	Europe	1	5	35	17
	North America	43	10	25	21
	Oceania	1	0	9	3
	South America	0	0	0	3
First Author's Discipline	Biology	43	11	53	32
	Economy	0	0	0	1
	Mathematics	2	1	9	4
	Medicine	0	3	16	12

**Table S3.** Multiresponse permutation procedure (MRPP) analysis of group dissimilarities showing mean citation distance between articles and mean source articles distance between citations in each citation group. The chance-corrected agreement index (A) expresses the within-group homogeneity and has a maximum value of 1 when there is no dissimilarity among elements of any group. The *p*-value is the probability of obtaining by chance a value of A equal or larger than the observed value.

	Among Articles According to Their Citations					Among Citations According to Their Source Articles			
Citation Group	Group Size	Distance	A	<i>p</i> -value		Group Size	Distance	A	<i>p</i> -value
C1	138	0.98	0.010	$<10^{-3}$		631	0.98	0.013	$<10^{-3}$
C2	44	0.96				226	0.95		

**Table S4.** Contingency table crossing for citation groups obtained by applying the clustering algorithm to the bipartite citation and to the unipartite article networks. The six first splits of this unipartite network separated small groups of articles (composed of one or two articles) from a larger network. The seventh split highlighted two clusters of almost equal size called U1 and U2.

Number of Articles		Bipartite Citation Network	
		C1	C2
Unipartite Articles Network	U1	128	7
	U2	5	41
	Small Groups	5	3

**Table S5.** Contingency table crossing for citation groups obtained by applying the clustering algorithm to the bipartite citation and to the unipartite co-citation networks. The unipartite co-citation network was formed of 16 isolated articles and a large connected component containing 171 papers. The first split of this large component yielded two large groups of papers called M1 and M2.

Number of Articles		Bipartite Citation Network		
		C1	C2	Isolated
Unipartite	M1	122	0	0
Co-citation	M2	11	38	0
Network	Isolated Articles	5	6	5

**Table S6.** Number of articles falling into the various descriptive categories for each group of the citation network. For all categories, the distributions differ significantly between groups (Fisher exact test,  $p < 10^{-5}$ ).

Category	Descriptor	Number of Articles		
		C1 Group	C2 Group	Isolated Articles
Type of Drug or Pesticide	Antibiotic Drug	0	27	2
	Anthelmintic Drug	10	0	0
	Antimalarial Drug	12	0	0
	Antiviral Drug	0	14	0
	Fungicide	14	1	0
	Herbicide	18	0	0
	Insecticidal Protein	38	0	1
	Insecticide	29	0	1
	Miticide	2	0	1
	Unspecific	15	2	0
Type of Target Organism	Farm Pest or Disease	115	1	3
	Human Parasite	16	41	1
	Unspecific	7	2	1
Modelling Approach	Epidemiology	9	32	0
	Population Genetics	105	2	3
	Other	24	10	2
First Author's Location	Africa	0	0	1
	Asia	12	1	0
	Europe	39	17	2
	North America	72	25	2
	Oceania	13	0	0
	South America	2	1	0
First Author's Discipline	Biology	119	16	4
	Economy	0	1	0
	Mathematics	10	6	0
	Medicine	9	21	1

**Table S7.** Multiresponse permutation procedure (MRPP) analysis of group dissimilarities showing mean citation distance between articles and mean source article distance between citations in each citation group. The chance-corrected agreement index (A) expresses the within-group homogeneity and has a maximum value of 1 when there is no dissimilarity between elements of a group. The *p*-value is the probability of obtaining by chance a value of A equal or larger than the observed value. Here the C1 cluster was split into 7 subgroups and the whole network therefore had 8 groups.

Citation group	Among Articles According to Their Citations				Among Citations According to Their Source Articles			
	Group Size	Distance	A	<i>p</i> -value	Group Size	Distance	A	<i>p</i> -value
C1, subgroup 1	13	0.92	0.058	<10 <sup>-3</sup>	53	0.85	0.081	<10 <sup>-3</sup>
C1, subgroup 2	18	0.94			88	0.89		
C1, subgroup 3	16	0.82			51	0.89		
C1, subgroup 4	10	0.89			28	0.82		
C1, subgroup 5	5	0.77			46	0.64		
C1, subgroup 6	11	0.89			104	0.84		
C1, subgroup 7	65	0.95			261	0.96		
C2	44	0.96			226	0.95		

**Table S8.** Number of articles focusing on the different types of drug or pesticide for each subgroup of the C1 cluster. The distribution differs significantly between groups (Fisher exact test,  $p < 10^{-5}$ ).

Descriptor	Number of Articles						
	C1 sub1	C1 sub2	C1 sub3	C1 sub4	C1 sub5	C1 sub6	C1 sub7
Antibiotic Drug	0	0	0	0	0	0	0
Anthelmintic Drug	0	0	0	9	0	0	1
Antimalarial Drug	12	0	0	0	0	0	0
Antiviral Drug	0	0	0	0	0	0	0
Fungicide	0	0	14	0	0	0	0
Herbicide	0	18	0	0	0	0	0
Insecticidal Protein	0	0	0	0	5	8	25
Insecticide	1	0	0	0	0	2	26
Miticide	0	0	0	0	0	0	2
Unspecific	0	0	2	1	0	1	11

**Table S9.** List of the 48 references cited by articles belonging to the C1 group and articles belonging to the C2 group.

1. Anderson, R. M., and R. M. May. 1991. *Infectious Diseases of Humans: Transmission and Control*, 1 ed. Oxford University Press, Oxford, UK.
2. Anderson, R. M., and R. M. May. 1992. *Infectious Diseases of Humans: Transmission and Control*, 2 ed. Oxford University Press, Oxford, UK.
3. Austin, D. J., K. G. Kristinsson, and R. M. Anderson. 1999. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proceedings of the National Academy of Science USA* 96:1152-6.
4. Austin, D. J., N. J. White, and R. M. Anderson. 1998. The dynamics of drug action on the within-host population growth of infectious agents: Melding pharmacokinetics with pathogen population dynamics. *Journal of Theoretical Biology* 194:313-339.
5. Baquero, F., and J. Blazquez. 1997. Evolution of antibiotic resistance. *Trends in Ecology & Evolution* 12:482-487.
6. Barrett, J. A. 1983. Estimating relative fitness in plant parasites: some general problems. *Phytopathology* 73:510-512.
7. Birch, C. P. D., and M. W. Shaw. 1997. When can reduced doses and pesticide mixtures delay the build-up of pesticide resistance? A mathematical model. *Journal of Applied Ecology* 34:1032-1042.
8. Blower, S. M., P. M. Small, and P. C. Hopewell. 1996. Control strategies for tuberculosis epidemics: New models for old problems. *Science* 273:497-500.
9. Bonhoeffer, S., M. Lipsitch, and B. R. Levin. 1997. Evaluating treatment protocols to prevent antibiotic resistance. *Proceedings of the National Academy of Science USA* 94:12106-11.
10. Bonhoeffer, S., and M. A. Nowak. 1997. Pre-existence and emergence of drug resistance in HIV-1 infection. *Proceedings of the Royal Society of London B* 264:631-7.
11. Bremermann, H. J., and H. M. Thieme. 1989. A competitive-exclusion principle for pathogen virulence. *Journal of Mathematical Biology* 27:179-190.
12. Chin, K. M. 1987. A simple method of selection for fungicide resistance in plant pathogen populations. *Phytopathology* 77:666-669.
13. Crow, J. F., and M. Kimura. 1970. *An introduction to population genetics theory*. Harper & Row, New York, USA.
14. Dekker, J. 1976. Acquired resistance to fungicides. *Annual Review of Phytopathology* 14:511 pp.
15. Durrett, R., and S. Levin. 1993. The importance of being discrete (and spatial). *Theoretical Population Biology* 46:363-394.
16. Georghiou, G. P. 1986. *Pesticide resistance: strategies and tactics for management*. National Academy Press, Washington, DC USA.
17. Gubbins, S., and C. A. Gilligan. 1999. Invasion thresholds for fungicide resistance: deterministic and stochastic analyses. *Proceedings of the Royal Society of London B* 266:2539-2549.
18. Holt, R. D. 1977. Predation, apparent competition and the structure of the prey community. *Theoretical Population Biology* 12:197-229.
19. Kable, P. F., and H. Jeffery. 1980. Selection for tolerance in organisms exposed to sprays of biocide mixtures: a theoretical model. *Phytopathology* 70:8-12.
20. Karaoglanidis, G. S., C. C. Thanassoulopoulos, and P. M. Ioannidis. 2001. Fitness of *Cercospora beticola* field isolates - resistant and - sensitive to demethylation inhibitor fungicides. *European Journal of Plant Pathology* 107:337-347.

21. Kermack, W. O., and A. G. McKendrick. 1927. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London A* 115:700-721.
22. Leonard, K. J., and R. J. Czochoz. 1980. Theory of genetic interactions among populations of plants and their pathogens. *Annual Review of Phytopathology* 18:237-258.
23. Levin, B. R., and R. M. Anderson. 1999. The population biology of anti-infective chemotherapy and the evolution of drug resistance: more questions than answers, p. 125-137, *Evolution in Health and Disease*. Oxford University Press.
24. Levy, Y., R. Levi, and Y. Cohen. 1983. Build-up of a pathogen subpopulation resistant to a systemic fungicide under various control strategies: a flexible simulation model. *Phytopathology* 73:1475-1480.
25. Lipsitch, M., C. T. Bergstrom, and B. R. Levin. 2000. The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions. *Proceedings of the National Academy of Science USA* 97:1938-43.
26. Lipsitch, M., and B. R. Levin. 1997. The population dynamics of antimicrobial chemotherapy. *Antimicrob Agents Chemother* 41:363-73.
27. May, R. M., and R. M. Anderson. 1979. Population biology of infectious diseases: Part II. *Nature* 280:455-461.
28. May, R. M., and A. P. Dobson. 1986. Population dynamics and the rate of pesticide evolution, National Research Council, Pesticide resistance. National Academy of Science, Washington.
29. McPeck, M. A., and R. D. Holt. 1992. The evolution of dispersal in spatially and temporally varying environments. *American Naturalist* 140:1010-1027.
30. Milgroom, M. G. 1990. A stochastic model for the initial occurrence and development of fungicide resistance in plant pathogen populations. *Phytopathology* 80:410-416.
31. Milgroom, M. G., S. A. Levin, and W. E. Fry. 1989. Population genetics theory and fungicide resistance, p. xii + 377 pp. In K. J. Leonard and G. E. Fry (ed.), *Plant disease epidemiology Vol. 2: genetics, resistance, and management*. MacGraw-Hill Publishing Co., New York.
32. Nowak, M. A., and R. M. May. 1994. Superinfection and the evolution of parasite virulence. *Proceedings of the Royal Society of London B* 255:81-89.
33. Peck, S. L., and S. P. Ellner. 1997. The effect of economic thresholds and life-history parameters on the evolution of pesticide resistance in a regional setting. *American Naturalist* 149:43-63.
34. Phillips, M., and P. A. Phillips-Howard. 1996. Economic implication of resistance to antimalarial drugs. *Pharmacoeconomics* 10:225-238.
35. Press, W. H., B. P. Flannery, S. A. Teukolsky, and W. T. Vetterling. 1992. *Numerical Recipes in C*, 2 ed. Cambridge University Press, Cambridge, UK.
36. Rausher, M. D. 2001. Co-evolution and plant resistance to natural enemies. *Nature* 411:857-864.
37. Renshaw, E. 1991. *Modelling biological populations in space and time*. Cambridge University Press, Cambridge, UK.
38. Ribeiro, R. M., S. Bonhoeffer, and M. A. Nowak. 1998. The frequency of resistant mutant virus before antiviral therapy. *Aids* 12:461-465.
39. Rosenheim, J. A., and B. E. Tabashnik. 1991. Influence of generation time on the rate of response to selection. *American Naturalist* 137:527-541.
40. Shaw, M. W. 1989. Independent action of fungicides and its consequences for strategies to retard the evolution of fungicide resistance. *Crop Protection* 8:405-411.
41. Shaw, M. W. 1989. A model of the evolution of polygenically controlled fungicide resistance. *Plant Pathology* 38:44-55.

42. Shaw, M. W. 1993. Theoretical analysis of the effect of interacting activities on the rate of selection for combined resistance to fungicide mixtures. *Crop Protection* 12:120-126.
43. Shigesada, N., and K. Kawasaki. 1997. *Biological invasions: theory and practice*. Oxford University Press, Oxford UK.
44. Skylakakis, G. 1982. Epidemiological factors affecting the rate of selection of biocide-resistant genotypes of plant pathogenic fungi. *Phytopathology* 72:271-273.
45. Skylakakis, G. 1980. Estimating parasitic fitness of plant pathogenic fungi: a theoretical contribution. *Phytopathology* 70:696-698.
46. Warwick, S. I. 1991. Herbicide resistance in weedy plants: physiology and population biology. *Annual Review of Ecology and Systematics* 22:95-114.
47. Williamson, M. 1972. *The analysis of biological populations*. Edward Arnold, London, UK.
48. Wilson, E. O. 1971. *The insect societies*. Harvard University Press, Cambridge, Mass., USA.

**Table S10.** Characteristics of the 28 articles of one group that cited references of the other group.

Descriptor	Number of Articles		Percentage of Papers for Each Class in the Database	
	C1 Group	C2 Group	C1 Group	C2 Group
Antibiotic Drug	0	4	0	13.8
Anthelmintic Drug	0	0	0	0
Antimalarial Drug	6	0	50	0
Antiviral Drug	0	0	0	0
Fungicide	4	1	26.7	6.7
Herbicide	3	0	16.7	0
Insecticidal Protein	3	0	7.7	0
Insecticide	2	0	6.7	0
Miticide	0	0	0	0
Unspecific	3	2	17.6	11.8

**Table S11.** Formulae used to search for relevant articles describing models of the evolution of resistance to pesticides and drugs within the CABs (1973-2006), Current Contents (1998-2006), and Medline (1950-2006) databases. The ‘final formula’ for each database search consisted in the combination of the common and the database-specific formulae. Thus, the ‘Number of hits’ column presents the results of these combinations. This search provided a total dataset of 1,894 non redundant references (see Table S1).

Type of Formula	Database	Timespan	Type of Descriptors	Formula of Descriptors	Number of hits
Common	All	1973-2006	Topics	(insecticid* OR fungicid* OR herbicid* OR nematocid* OR acaricid* OR rodenticid* OR miticid* OR pesticid* OR antibio* OR antivir* OR bacillus) AND (resistan*) AND (model*)	-
Specific	CABs	1973-2006	Cabicodes	((HH000 or HH400 or HH405 or HH410 or FF500 or FF600) and DE=models)*	817
	Current Contents	1998-2006	Scientific area codes restriction	((Plant Sciences) OR (Multidisciplinary) OR (Experimental Biology) OR (Biology) OR (Molecular Biology Genetics) OR (Entomology Pest Control) OR (Research Laboratory Medicine Medical Technology) OR (Medical Research General Topics) OR (Immunology))	808
	Medline	1950-2006	MeSH	"Drug Resistance"[MAJR] OR "Drug Tolerance"[MAJR] OR "Models, Theoretical"[MAJR] OR "Computer Simulation"[MAJR] OR "Mathematical Computing"[MAJR] OR "Evolution"[MAJR] OR "Adaptation, Biological"[MAJR]	360

\* Codes used for the Cabicodes:

H000: Pathogen, Pest and Parasite and Weed Management (General)

HH400: Pesticides and Drugs (General)

HH405: Pesticides and Drugs: Control

HH410: Pesticide and Drug Resistance

FF500: Weeds and Noxious Plants

FF600: Pests, Pathogens and Biogenic Diseases of Plants.