Dynamics of two feline retroviruses (FIV and FeLV) within one population of cats

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SUMMARY

We present a deterministic model of the dynamics of two microparasites simultaneously infecting a single host population. Both microparasites are feline retroviruses, namely Feline Immunodeficiency Virus (FIV) and Feline Leukaemia Virus (FeLV). The host is the domestic cat *Felis catus*. The model has been tested with data generated by a long-term study of several natural cat populations. Stability analysis and simulations show that, once introduced in a population, FIV spreads and is maintained, while FeLV can either disappear or persist. Moreover, introduction of both viruses into the population induces an equilibrium state for individuals of each different pathological class. The viruses never induce the extinction of the population. Furthermore, whatever the outcome for the host population (persistence of FIV only, or of both viruses), the global population size at the equilibrium state is only slightly lower than it would have been in the absence of the infections (i.e. at the carrying capacity), indicating a low impact of the viruses on the population. Finally, the impact of the diseases examined simultaneously is higher than the sum of the impact of the two diseases examined separately. This seems to be due to a higher mortality rate when both viruses infect a single individual.

1. INTRODUCTION

In the past, a wide range of epidemiological models have been developed for the spread of pathogens within host populations. These theoretical models deal mainly with simple systems involving a parasite (a microparasite or a macroparasite, as defined in Anderson & May (1979)) infecting one host species. Few models deal with three species interactions, such as a parasite infecting two competitors, one predator and one prey, or other similar complex systems (May & Hassell 1981; Holt & Pickering 1985; Hochberg & Holt 1990; Hochberg *et al.* 1990; Begon *et al.* 1992). However, host species, or even individuals, are usually not infected by just a single parasite species, but rather by a whole parasite community (review in Combes 1995). Relatively unexpected dynamic behaviours, not predicted from pairwise species interactions, may arise from multi-species studies (Hochberg *et al.* 1990). For example, when natural competitors, a generalist and a specialist, attack a common prey, steady equilibrium states may exist that were not predicted by the pairwise study of the species (Hassell & May 1986). In addition, little emphasis has generally been devoted to biological aspects of such models. For example, biological hypotheses have often been unrealistic or far from reality, and epidemiological surveys have rarely been conducted to complete theoretical work.

Here, we present a biologically realistic epidemiologic model of such a complex system: the dymanics of two pathogens within a single host population. The host is the domestic cat (*Felis catus*) and the two pathogens are two feline retroviruses of major importance: Feline Immunodeficiency Virus (FIV) and Feline Leukaemia Virus (FeLV). Interest in these two viruses is enhanced because both are lethal, they are found worldwide and they infect several wild felid species, most of which are endangered (Carpenter & O'Brien 1995, for FIV; Jessup *et al.* 1993, for FeLV). Epidemiological surveys conducted on natural domestic cat populations with FIV and FeLV over a five year period (Courchamp *et al.* 1997; Fromont *et al.* 1997*a*) provided the data used in this model.

The model combined two previous models: one describing the dynamics of FIV in cat populations (Courchamp *et al.* 1995*a*), the second describing FeLV dynamics in cat populations (Fromont *et al.* 1997*b*). These models were based on the work of Anderson & May (e.g. 1991). Despite different transmission modes, these two models showed comparable results on each pathogen–cat pair. Namely, persistence of each disease in the population occurred, inducing a stable host population equilibrium, close

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to the uninfected population size. Moreover, parameter estimation revealed low transmission rates for both diseases. The aim of these two previous models was mainly to understand the dynamics of disease spread within a susceptible host population. The aim of the present model is to study the two viruses simultaneously, and to evaluate their respective roles in the disease-induced changes in dynamics of the host population. In particular, we will focus on the viruses' impact within the population, in terms of reduction of the population size. Of major importance is whether considering both virus dynamics simultaneously induces a qualitative change in the model behaviour when compared to modelling the viruses alone, and why this change might occur.

2. MATERIAL AND METHODS

The material and methods used in this paper have been more fully described in previous works (Courchamp *et al.* 1995*a*; Fromont *et al.* 1997*b*). We will thus be concise concerning the description of the viruses, the host and the construction of the model. Here, we will only describe biological properties important for the model. Mathematical developments are similar to those presented in the previous models (Courchamp *et al.* 1995*a*; Fromont *et al.* 1997*b*). We do, however, provide details of the stability analysis of this model in the Appendix.

(*a*) *Host population*

Populations of domestic cats are known to vary greatly in their social structures (Liberg & Sandell 1988). A wide range of amicable interactions occur between many cats in most populations, mainly within limited social groups. In addition, in many populations, fights occur among males, depending on the mating system and territorial behaviour (Macdonald *et al.* 1987; Liberg & Sandell 1988; Pontier 1993), and also between males and females, for example in defence of offspring against potential infanticides (Macdonald *et al.* 1987). Both amicable and aggressive interactions may allow virus transmission (Courchamp *et al.* 1995*b*). Throughout this work, the term 'population' always refers to the host population.

(*b*) *Viruses*

(i) *FIV*

FIV is a lentivirus inducing AIDS in cats and is thought to be transmitted by bites during fights. There is no vertical transmission (from mother to offspring). FIV infection leads to lifelong antibody (and virus) carriers. The clinical staging of FIV infection is very similar to that of the Human Immunodeficiency Virus infection, with a short acute stage, a long asymptomatic period (lasting up to several years, and in which the cat is healthy, and may reproduce), a persistent generalized lymphadenopathy, an AIDS-related complex associated with chronic infections, and finally AIDS. As in humans infected by HIV, feline AIDS is characterized by a loss of immunological defences and subsequent opportunistic infections. The cat is infectious during all these five stages of infection, which have been estimated to last an average of five years (Pedersen & Barlough 1991). We will use this estimate in the model (the mortality rate due to FIV infection will thus be 0.2). There is no recovery from nor immunity to FIV, either natural or artificial. For further details on FIV, see the complete reviews published on various aspects (molecular: Elder & Phillips 1994; genetic: Miyazawa *et al.* 1994; immunological: Lin 1992; clinical: Pedersen & Barlough 1991; epidemiological: Courchamp & Pontier 1994; general: Bendinelli *et al.* 1995).

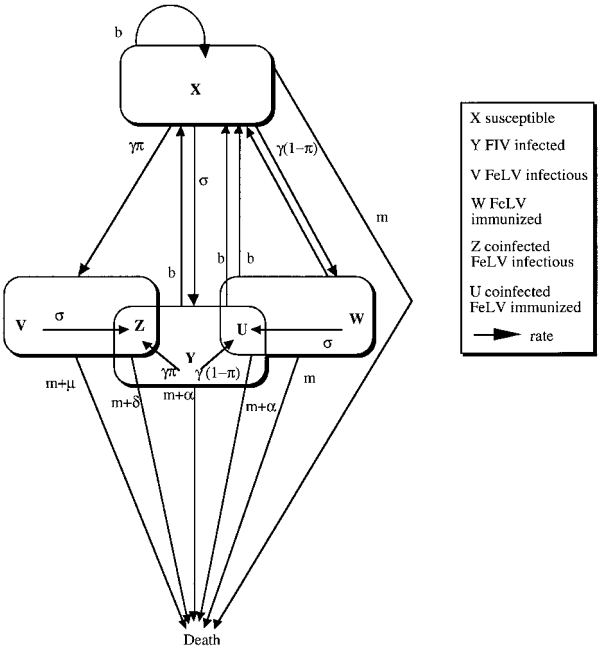

Figure 1. Flow chart of the population infected by both FIV and FeLV. Variable names are given in the text.

(ii) *FeLV*

FeLV is a retrovirus which leads to immunosuppression in infected cats, with clinical features comparable to those of FIV infection. This oncovirus is transmitted via 'amicable' contact (by saliva, through licking, maternal grooming, food sharing) and also through mating or biting. FeLV can also be transmitted vertically. Infection is followed by a temporary viraemic stage, which is generally asymptomatic, and then by two possible outcomes. Approximately two thirds of the infected individuals develop natural immunity and recover from infection. These naturally immunized cats are not infectious, have a normal life expectancy and are believed to be immunized for life. Individuals that do not become naturally immunized become persistently viraemic and die within an average of two years from various proliferative or immunosuppressive disorders. This mortality rate (0.5) will be used in this model (Fromont *et al.* 1997*b*). Almost 80% of infected pregnant females abort or give birth to viraemic kittens that die within weeks to months. A more complete description of this virus and its properties is given by Hardy (1993).

FIV and FeLV are independently transmitted, but coinfection is followed by an acceleration and an enhancement of FIV induced symptoms (Pedersen *et al.* 1990). Indeed, FeLV is a potent activator of FIV replication both qualitatively and quantitatively (Torten *et al.* 1990). This interaction will be taken into account in the model in the form of a higher mortality rate for coinfected individuals (the assumption is made that this higher mortality rate is equal to the sum of the two individual virus induced mortality rates).

(*c*) *The model*

Let N be the total number of cats at time t, and K the carrying capacity of the population at equilibrium. Natality rate b is constant, whereas the mortality rate, m, is linearly related to N, and has the form $(m + rN/K)$, with the population intrinsic rate of increase $r = b - m$. The population dynamics when there is no pathogen follows the logistic equation

$$\frac{\mathrm{d}N}{\mathrm{d}t} = rN\left(1 - \frac{N}{K}\right). \tag{1}$$

The FIV transmission coefficient is σ and all infected cats die from FIV infection at a rate α. FIV infected individuals do participate in reproduction, and give birth to susceptible kittens. We consider only one pathological stage, the asymptomatic period, assuming AIDS developing cats will die within a time too short to be considered in the model. FeLV is transmitted to cats at a rate γ, a proportion $(1-\pi)$ of which become naturally immunized after a short time (1–4 months), which is not taken into account, and are not infectious. A proportion π of cats will become infectious and die at a rate μ. We consider that, as FeLV infectious pregnant females abort or give birth to infected kittens that die within a very short time, FeLV infectious cats do not participate in reproduction. Cats can be infected by both viruses simultaneously, and thus die at a rate $\delta = \alpha + \mu$. For biological reasons, and as previously discussed (Courchamp *et al.* 1995*a*, 1997; Fromont *et al.* 1997*b*), the transmission rates will be characteristic of proportionate mixing models for both FIV and FeLV.

Cats not infected by either of the two considered viruses are denoted X and will be termed susceptible throughout this work. FIV infected cats are denoted Y, FeLV infected cats are V and FeLV naturally immunized cats are W. Coinfected cats are Z if they are FeLV infectious and U if they are FeLV naturally immunized. The compartmental representation is shown in figure 1.

A set of first order equations describes the dynamics of the FIV and FeLV infected cat population as given by the above hypothesis:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = b(X+Y+W+U) - mX - \frac{rNX}{K} - \frac{\sigma X(Y+U+Z)}{N} - \frac{\gamma X(V+Z)}{N}, \tag{2}$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \frac{\sigma X(Y+U+Z)}{N} - mY - \frac{rNY}{K} - \alpha Y - \frac{\gamma Y(V+Z)}{N}, \tag{3}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{\gamma X(V+Z)}{N}\pi - mV - \frac{rNV}{K} - \mu V - \frac{\sigma(Y+U+Z)V}{N}, \tag{4}$$

$$\frac{\mathrm{d}W}{\mathrm{d}t} = \frac{\gamma X(V+Z)}{N}(1-\pi) - mW - \frac{rNW}{K} - \frac{\sigma(Y+U+Z)W}{N}, \tag{5}$$

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \frac{\gamma Y(V+Z)}{N}\pi - mZ - \frac{rNZ}{K} - (\alpha+\mu)Z + \frac{\sigma(Y+U+Z)V}{N}, \tag{6}$$

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \frac{\gamma Y(V+Z)}{N}(1-\pi) - mU - \frac{rNU}{K} - \alpha U + \frac{\sigma(Y+U+Z)W}{N}. \tag{7}$$

The equation for the total population is obtained by adding the six equations (2)–(7):

$$\frac{\mathrm{d}N}{\mathrm{d}t} = rN\left(1 - \frac{N}{K}\right) - \alpha Y - (b+\mu)V - (b+\alpha+\mu)Z - \alpha U. \tag{8}$$

Simulations have been carried out, in order to confirm and visualize the behaviour predicted by the model analysis, with the computer program Dynamac (Rousseau 1988).

3. RESULTS

(*a*) *Stability analysis*

(i) *Equilibrium points*

As a first step, equilibrium points of this system are calculated. For this, we introduce the proportions

$$x = \frac{X}{N},\ y = \frac{Y}{N},\ v = \frac{V}{N},\ w = \frac{W}{N},\ z = \frac{Z}{N},\ u = \frac{U}{N},$$

such that $0 \leqslant x, y, v, w, z, u \leqslant 1$ and $x + y + v + z + w + u = 1$. The following system is obtained:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \sigma(1-p)(u+z) + y[\sigma(1-p) - \alpha - \gamma(v+z) - b + (b+\mu)v + (b+\alpha+\mu)z + \alpha y + \alpha u], \tag{9}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \gamma\pi(1-p)z + v[\gamma\pi(1-p) - \mu - \sigma(y+u+z) - b + (b+\mu)v + (b+\alpha+\mu)z + \alpha y + \alpha u], \tag{10}$$

$$\frac{\mathrm{d}w}{\mathrm{d}t} = \gamma(1-p)(1-\pi)(v+z) + w[-\sigma(y+u+z) - b + (b+\mu)v + (b+\alpha+\mu)z + \alpha y + \alpha u], \tag{11}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \gamma\pi yv + \sigma v(y+u) + z[\gamma\pi y - \alpha - \mu + \sigma v - b + (b+\mu)v + (b+\alpha+\mu)z + \alpha y + \alpha u], \tag{12}$$

$$\frac{\mathrm{d}u}{\mathrm{d}t} = \gamma y(v+z)(1-\pi) + \sigma w(y+z) + u[\sigma w - \alpha - b + (b+\mu)v + (b+\alpha+\mu)z + \alpha y + \alpha u], \tag{13}$$

where, $p = 1 - x = y + v + w + z + u$, i.e. we removed the proportion of susceptible individuals from the ODE (ordinary differential equation) system.

To calculate the equilibrium points, we solve the following system:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{\mathrm{d}v}{\mathrm{d}t} = \frac{\mathrm{d}w}{\mathrm{d}t} = \frac{\mathrm{d}z}{\mathrm{d}t} = \frac{\mathrm{d}u}{\mathrm{d}t} = 0.$$

In order to be admissible, an equilibrium point should satisfy

$$0 \leqslant x^*, y^*, v^*, w^*, z^*, u^*, p^* \leqslant 1.$$

The set of equations (9)–(13) reveals the presence of five equilibrium points in the (y, v, w, z, u) phase plane:

$$e1 = (0,0,0,0,0),$$

$$e2 = (0,0,0,1,0),$$

$$e3 = \left(1 + \frac{b}{(\alpha-\sigma)}, 0, 0, 0, 0\right),$$

$$e4 = \left(0, \frac{b(b+\mu-\gamma\pi)}{(b+\mu)(b+\mu-\gamma)}, \frac{(b+\mu-\gamma\pi)[b\gamma(1-\pi)-\mu(b+\mu-\gamma)]}{\gamma\pi(b+\mu)(b+\mu-\gamma)}, 0, 0\right),$$

$$e5 = (y_5^*, v_5^*, w_5^*, z_5^*, u_5^*).$$

These points correspond to the vanishing of both diseases ($e1$), of FeLV ($e3$), of FIV ($e4$), or to the existence of only one pathological class (FIV and FeLV infectious coinfected cats ($e2$)). The last equilibrium point, $e5$, is the most interesting as it corresponds to the situation where all pathological classes are present.

(ii) *Conditions for existence*

Note that R_0 and R_0' are the basic reproduction rate of FIV and of FeLV, respectively (Jacquez *et al.* 1991), and that R_1 and R_1' are the net reproductive rate of the host population when FIV and FeLV are endemic, respectively (Busenberg & Cooke 1993). Similarly, R_1'' is the net reproductive rate of the host population when both diseases are endemic.

Equilibrium point existence conditions are the following.

(i) $e1$ and $e2$ are always admissible.

(ii) $e3$ is admissible if and only if $(b/(\sigma-\alpha)) \leqslant 1$, that is if $(\sigma/(b+\alpha)) \geqslant 1$. Note that (Courchamp *et al.* 1995)

$$R_0 = \frac{\sigma}{b+\alpha}. \tag{14}$$

Thus, $e3$ is admissible if and only if $R_0 \geqslant 1$.

(iii) $e4$ is admissible if and only if $b+\mu-\gamma\pi < 0$, that is if $(\gamma\pi/(b+\mu)) \geqslant 1$. Note that (Fromont *et al.* 1997*b*)

$$R_0' = \frac{\gamma\pi}{b+\mu}. \tag{15}$$

Thus, $e4$ is admissible if and only if $R_0' \geqslant 1$.

(iv) $e5$ is numerically admissible as soon as $R_0 \geqslant 1$ and $R_0' \geqslant 1$.

One has (Courchamp *et al.* 1995; Fromont *et al.* 1997*b*)

$$R_1 = \frac{b}{(m+\alpha y_3^*)}, \tag{16}$$

$$R_1' = \frac{b}{(m+(b+\mu)v_4^*)}. \tag{17}$$

Similarly, we find that

$$R_1'' = \frac{b}{(m+(b+\mu)v_5^*+(b+\alpha+\mu)z_5^*+\alpha y_5^*+\alpha u_5^*)}, \tag{18}$$

where y_3^*, v_4^*, v_5^*, z_5^*, y_5^* and u_5^* correspond to coordinates of the equilibrium points, as defined below.

(iii) *Stability analysis*

For each stable equilibrium point $ek = (y^*, v^*, w^*, z^*, u^*)$, we calculate the corresponding $Pk = (X^*, Y^*, V^*, W^*, Z^*, U^*)$. The total population, $N^* = X^*+Y^*+V^*+W^*+Z^*+U^*$, satisfies the differential equation (8), which is asymptotically equivalent to

$$\frac{\mathrm{d}N}{\mathrm{d}t} = N\left(-r\frac{N}{K}+A\right),$$

with

$$A = r-\alpha y^*-(b+\mu)v^*-(b+\alpha+\mu)z^*-\alpha u^*.$$

When $A<0$, then the total population decreases and goes extinct. The population converges to the stable state $P0$. When $A>0$ the population converges to one of the states Pk (defined below). This condition on the sign of A gives the rates R_1, R_1' and R_1''.

The Jacobian matrix, calculated for each point ek, indicates that (see Appendix for details):

(i) $e1$ is locally stable if and only if $(\sigma/(\alpha+b)) < 1$ and $(\gamma\pi/(b+\mu)) < 1$ (equivalent to $R_0 < 1$ and $R_0' < 1$) and gives $P1$. We can note that stability of $e1$ implies non-existence of $e3$ and $e4$;

(ii) $e2$ cannot be locally stable;

(iii) $e3$ is stable if

$$\begin{cases} R_0 \geqslant 1, \\ R_0' < 1, \end{cases}$$

this equilibrium gives

$$\begin{cases} P0 & \text{if } R_1 < 1, \\ P3 & \text{if } R_1 \geqslant 1; \end{cases}$$

(iv) $e4$ is stable if

$$\begin{cases} R_0 < 1, \\ R_0' \geqslant 1, \end{cases}$$

this equilibrium gives

$$\begin{cases} P0 & \text{if } R_1' < 1, \\ P4 & \text{if } R_1' \geqslant 1; \end{cases}$$

(v) $e5$ is stable if

$$\begin{cases} R_0 \geqslant 1, \\ R_0' \geqslant 1, \end{cases}$$

this equilibrium gives

$$\begin{cases} P0 & \text{if } R_1'' < 1, \\ P5 & \text{if } R_1'' \geqslant 1. \end{cases}$$

Note that for $e3$ stability, the condition $R_0' < 1$ is sufficient, but not necessary (see the Appendix). A necessary and sufficient condition (NSC) is that $R_0' < 1+B$, with

$$B = \frac{\alpha x_3^*(b+\alpha-\sigma)}{(\alpha y_3^*-\mu-\sigma)(b+\mu)}. \tag{19}$$

For $e4$ stability, the condition $R_0 < 1$ is necessary, but not sufficient (see the Appendix). An NSC is that $R_0 < 1-C$ with

$$C = \frac{b+\mu}{b+\alpha}v_4^*. \tag{20}$$

With (from equations (9)–(14))

$$P0 : \begin{cases} X_0^* = 0, \\ Y_0^* = 0, \\ V_0^* = 0, \\ W_0^* = 0, \\ Z_0^* = 0, \\ U_0^* = 0, \end{cases}$$

which corresponds to the extinction of the population, $P0$ is locally stable if either one of the following set of conditions holds

$$\begin{cases} R_0 > 1, & R_0' < 1, & R_1 < 1, \\ R_0 < 1, & R_0' > 1, & R_1' < 1, \\ R_0 > 1, & R_0' > 1, & R_1'' < 1. \end{cases}$$

As for $e3$ and $e4$ stability, the conditions $R_0' < 1$ (first line) and $R_0 < 1$ (second line) are not the strict NSC. The corresponding NSC are $R_0' < B$ and $R_0 < 1-C$, as given in (19) and (20).

$$P1 : \begin{cases} X_1^* = K, \\ Y_1^* = 0, \\ V_1^* = 0, \\ W_1^* = 0, \\ Z_1^* = 0, \\ U_1^* = 0, \end{cases}$$

which corresponds to the vanishing of both viruses, $P1$ is locally stable if and only if $R_0 < 1$ and $R_0' < 1$.

$P2$ does not exist, as $e2$ is never stable:

$$P3 : \begin{cases} X_3^* = \dfrac{b}{(\sigma-\alpha)} N_3^*, \\ Y_3^* = 1 - \dfrac{b}{(\sigma-\alpha)} N_3^*, \\ V_3^* = 0, \\ W_3^* = 0, \\ Z_3^* = 0, \\ U_3^* = 0, \end{cases}$$

which corresponds to the vanishing of FeLV, with $N_3^* = K - I_{\mathrm{FIV}}$ (see equations (21)–(22)); $P3$ is locally stable if $R_0 > 1$, $R_0' < 1$ and $R_1 > 1$, with $R_0' < 1$ again being a sufficient but not necessary condition. The corresponding NSC is $R_0' < B$.

$$P4 : \begin{cases} X_4^* = \dfrac{\mu(b+\mu-\gamma) - b\gamma(1-\pi)}{\gamma\pi(b+\mu-\gamma)} N_4^*, \\ Y_4^* = 0, \\ V_4^* = \dfrac{b(b+\mu-\gamma\pi)}{(b+\mu)(b+\mu-\gamma)} N_4^*, \\ W_4^* \\ = \dfrac{(b+\mu-\gamma\pi)[b\gamma(1-\pi) - \mu(b+\mu-\gamma)]}{\gamma\pi(b+\mu)(b+\mu-\gamma)} N_4^*, \\ Z_4^* = 0, \\ U_4^* = 0, \end{cases}$$

which corresponds to the vanishing of FIV, with $N_4^* = K - I_{\mathrm{FeLV}}$ (see equations (21)–(22)); $P4$ is locally stable if and only if $R_0 < 1$, $R_0' > 1$ and $R_1' > 1$, with $R_0 < 1$ again being a necessary but not sufficient condition. The corresponding NSC is $R_0 < 1 - C$.

$$P5 : \begin{cases} X_5^* = x^* N_5^*, \\ Y_5^* = y^* N_5^*, \\ V_5^* = v^* N_5^*, \\ W_5^* = w^* N_5^*, \\ Z_5^* = z^* N_5^*, \\ U_5^* = u^* N_5^*, \end{cases}$$

which corresponds to the presence of both viruses in equilibrium in the population, with $N_5^* = K - I_{\mathrm{FeLV+FIV}}$; numerical simulations suggest that $P5$ is locally stable as soon as it exists, i.e. when $R_0 > 1$, $R_0' > 1$ and $R_1'' > 1$.

These results are summarized in figure 2. The presented simulations represent the evolution in time of the different pathological classes of the population.

The parameter denoted I_{disease} represents the impact of the disease on the population. By impact, we mean the difference between the population size at the disease-free equilibrium (K) and the population size at equilibrium when the disease is endemic (N^*).

We have

$$I_{\mathrm{FIV}} = \frac{K}{r}\alpha\left(1 - \frac{b}{\sigma-\alpha}\right), \tag{21}$$

$$I_{\mathrm{FeLV}} = \frac{K}{r}\frac{b(b+\mu-\gamma\pi)}{b+\mu-\gamma}. \tag{22}$$

Due to the mathematical complexity of the system, we could not express $I_{\mathrm{FeLV+FIV}}$. However, as this model is deterministic, $I_{\mathrm{FeLV+FIV}}$ has been studied through simulations. We can note that I_{FeLV} and I_{FIV} are constants in a given population. Similarly, simulations show that $I_{\mathrm{FeLV+FIV}}$ is also a constant.

(*b*) *Application to biological data*

To choose which conditions are biologically realistic, we used the data obtained from several feline populations monitored yearly, since 1982 for dynamic parameters (Pontier 1993) and since 1991 for epidemiological parameters (Courchamp *et al.* 1995*b*, 1997). From these studies, we know the values of b, m and N. From literature data, we have estimates of π, α and μ. As α and μ are not always precisely estimated, we studied the sensitivity of the model to α and μ (mortality rates of FIV and FeLV, respectively) through simulations. The non-sensitivity of the model to these parameters has been observed, and was also previously demonstrated in the models of viruses taken separately (Courchamp *et al.* 1995*a*; Fromont *et al.* 1997*b*). We will thus use values commonly accepted in the literature, that is 0.2 for α and 0.5 for μ (see Courchamp *et al.* 1995*a*; Fromont *et al.* 1997*b*). The transmission coefficients σ and γ (for FIV and FeLV respectively) are two parameters that may strongly depend on the population under consideration, and for which no estimate is available. We can thus study the existence of the different possible cases with different conditions for σ and γ. Using previously named values for b, m, π, α and μ, this gives the results shown in table 1. The value of σ estimated from the FIV model (see Courchamp *et al.* 1995*a*) indicates that only states in the right-hand column of table 1 are likely, i.e. only the presence of FIV alone or of both viruses in the population is possible.

The impact of the diseases on the population size has also been considered in this model. Although we strongly suspect that they differ according to population spatial and social structure, we have no way

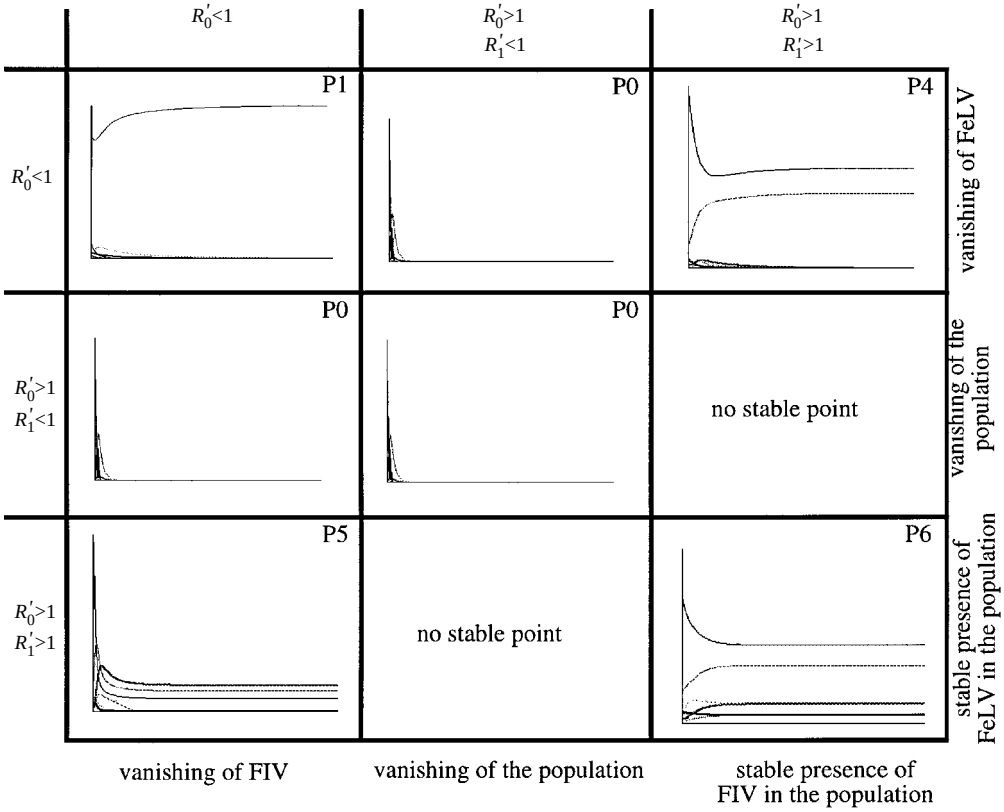

Figure 2. Summary of possible outcomes for the model behaviour, in function of R_0, and R_1 in the columns and of R_0', and R_1' in the rows. Simulations illustrate each of the cases. The expression of the equilibrium points Pk are given in the text.

Table 1. *Domain of biological values for the model dynamics*

	$\sigma < 2.6$	$\sigma > 2.6$
$\gamma < 8.88$	P1	P3
$\gamma > 8.88$	P4	P5

to estimate the value of the disease transmission coefficients in natural conditions. From equations (21) and (22), we evaluated the influence of the diseases' transmission coefficients (σ and γ) on the impact of the viruses. Figure 3*a* shows that the FIV transmission coefficient (σ) has a low effect on FIV impact on the population, whereas the influence of the FeLV transmission coefficient (γ) on FeLV impact is higher. In both cases, the disease impact remains low (even when extremely high transmission rates values are used). FeLV alone has a higher impact than FIV alone, but this case is not predicted by the model. Figure 3*b* represents the impact of both diseases when taken into account simultaneously, with variation of both transmission rates. It is interesting to note that the impact of both diseases taken simultaneously is higher than the sum of individual impacts. For example, with biological parameters previously estimated from one of our monitored populations, one finds an impact of 1.5% for FIV alone, 3.0% for FeLV alone, but 7.5% for both diseases.

4. DISCUSSION

We have presented a model of the dynamics of a domestic cat population within which two viruses spread simultaneously. Theoretically, the model shows that all classically expected epidemiological situations are possible: extinction of the host population, of one or both diseases, and simultaneous presence of both diseases. In each case, the pathological classes present reached an equilibrium state.

The output of the model using available biological data shows that only two solutions are biologically realistic. Extinction of the population does not occur, nor does the simultaneous extinction of both diseases: at least one virus always remains. The case in which only FeLV is maintained in the population is not possible with the biological values used as parameters in the model. The two remaining possibilities imply that FIV maintains itself in a stable equilibrium in the population, independently of the behaviour of the other virus.

Results obtained with the model are in agreement with epidemiological observations (in the literature and by our team). FIV has been found in all populations, while some were free from FeLV. Some of these FeLV-free populations, such as the one we study, are regularly in contact with this virus, and it thus seems possible that this virus does not persist in all populations (Courchamp *et al.* 1995*b*; Fromont *et al.* 1997*a*). In this context, the long term monitoring of natural populations is particularly interesting: one popula-

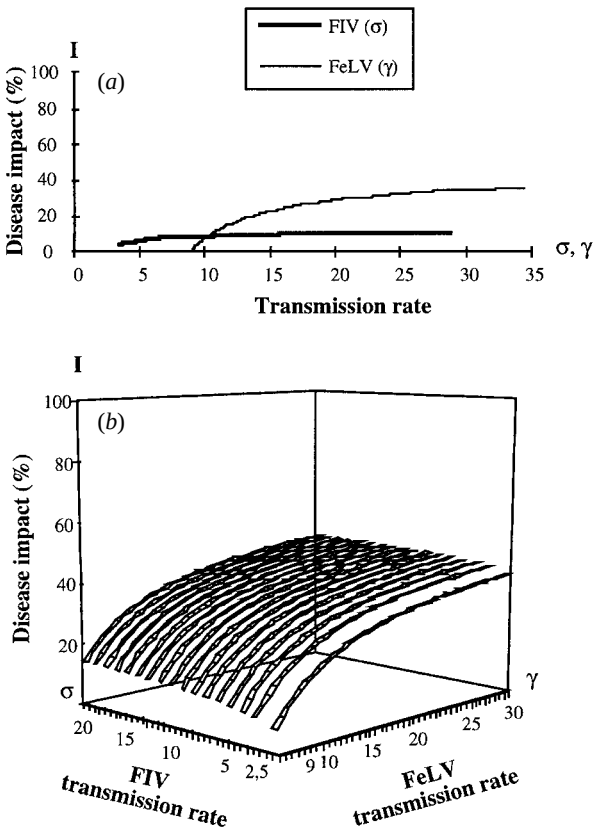

Figure 3. Impact of the viruses on the population size, in function of the transmission rate of the viruses. (*a*) for FeLV and FIV alone, and (*b*) for FeLV and FIV simultaneously. The impact (I) is the difference between the disease-free population size at equilibrium (K) and the population size when the disease is endemic (N^*). I_{FIV} and I_{FeLV} are obtained from analytical study of the model, $I_{\mathrm{FeLV/FIV}}$ is obtained through simulations of the model (each point of the curves repesents the result of a different simulation).

tion of cats monitored by our team ($N \approx 60$) was free of FeLV on the first four samplings (two samplings each year). One infected cat appeared at the fifth sampling, two others at the sixth sampling and three others six months later. The low FeLV transmission rate predicted by our model seems to be realistic. Only long term epidemiological surveys will show if the virus will persist in this population, or if, as predicted by our model, it will disappear.

In addition, the model shows that whatever the fate of the host population (persistence of FIV only or of both viruses), the population size at the equilibrium state is only slightly lower than it would have been in the absence of the viruses, indicating a low viral impact on the host populations. Furthermore, we have demonstrated that the impact of both diseases considered simultaneously is higher than the sum of the disease impacts evaluated separately. However, for a given prevalence of two different viruses, the higher the number of coinfected individuals in a population, the lower the number of total infected individuals (either by one virus or the other). Thus, such a higher impact should be due to a higher mortality rate in coinfected individuals compared to individuals infected by a single virus. Indeed, in our case, coinfection induces an increase in and acceleration of symptoms induced by each virus, leading more rapidly to death (Pedersen *et al.* 1990). This has been taken into account in the model. *In natura*, this pathological association should thus induce a higher impact when both viruses simultaneously infect a single population.

There are few mathematical models dealing with three species systems. Some theoretical studies have considered most possible interactions such as competition, predation and parasitism, or several of these categories at the same time (see, for example, Anderson & May 1986). Nevertheless, models applied to concrete cases, with biological data, are even scarcer. There are some epidemiological models that describe systems with macroparasites. This type of model takes species population dynamics into account through one equation only. Thus, a system with one host and two macroparasites can be modelled by a set of three equations only. Unfortunately, microparasite associated models are more complex to manipulate when taking two parasites and a host species into account, because these models describe host population dynamics, with the many different possible pathological states (and as many equations). Our model is, to our knowledge, the first to describe the dynamics of a system involving one host and two viruses infecting the same species (and possibly the same individual), which is based upon a concrete biological example. Progress towards a better understanding of impact of pathogen communities on their host populations requires this kind of cross-disciplinary study.

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APPENDIX 1.

Some details are given concerning the stability analysis of the equilibrium points.

To show the stability of an equilibrium point $(y^*, v^*, w^*, z^*, u^*)$, we must demonstrate that the eigenvalues of the Jacobian matrix are negative or have some negative real parts.

(1) For $e1$, the eigenvalues of the Jacobian matrix are $-b < 0$, $-\alpha-\mu-b < 0$, $-b-\alpha < 0$, $\sigma-\alpha-b$ and $\gamma\pi-\mu-b$, so that $e1$ is locally stable if and only if $\sigma-\alpha-b < 0$ and $\gamma\pi-\mu-b < 0$, which is equivalent to

$$R_0 = \frac{\sigma}{b+\alpha} < 1 \quad \text{and} \quad R_0' = \frac{\gamma\pi}{b+\mu} < 1.$$

(2) If $e2$ were locally stable, then the ODE for z_2^*

$$JJ_3 = \begin{pmatrix} \dfrac{-b\gamma\pi}{\alpha-\sigma} - \sigma - \mu + \alpha & \dfrac{-b\gamma\pi}{\alpha-\sigma} \\ \gamma\pi\left(1+\dfrac{b}{\alpha-\sigma}\right) + \sigma + \dfrac{b\sigma}{\alpha-\sigma} & \gamma\pi\left(1+\dfrac{b}{\alpha-\sigma}\right) - \mu - b + \dfrac{b\alpha}{\alpha-\sigma} \end{pmatrix}, \tag{23}$$

$$JJ_4 = \begin{pmatrix} \gamma\pi(1-p_4^*) + 2(b+\mu)v_4^* - \mu - b - \gamma\pi v_4^* & -\gamma\pi v_4^* \\ -\gamma(1-\pi)v_4^* + \gamma(1-\pi)(1-p_4^*) + w_4^*(b+\mu) & -\gamma(1-\pi)v_4^* - b + (b+\mu)v_4^* \end{pmatrix}, \tag{24}$$

$$JJ_4' = \begin{pmatrix} \sigma(1-p_4^*) - \alpha - b + (b+\mu-\gamma)v_4^* & \sigma(1-p_4^*) & \sigma(1-p_4^*) \\ \gamma\pi v_4^* + \sigma v_4^* & -\alpha - \mu + \sigma v_4^* - b + (b+\mu)v_4^* & \sigma v_4^* \\ \gamma(1-\pi)v_4^* + \sigma w_4^* & \sigma w_4^* & \sigma w_4^* - \alpha - b + (b+\mu)v_4^* \end{pmatrix}. \tag{25}$$

$$\begin{pmatrix} \begin{array}{l} -\sigma(u+z) \\ +\sigma(1-p) \\ -\alpha+\alpha(y+u) \\ +(b+\alpha+\mu-\gamma)z \\ -b+(b+\mu-\gamma)\nu \\ +(\alpha-\sigma)y \end{array} & \begin{array}{l} +y(-\sigma-\gamma+b+\mu) \\ -\sigma(u+z) \end{array} & -\sigma(y+u+z) & \begin{array}{l} -\sigma(u+z) \\ +\sigma(1-p) \\ +(\alpha-\sigma-\gamma+\mu+b)y \end{array} & \begin{array}{l} -\sigma(u+z) \\ +\sigma(1-p) \\ +(\alpha-\sigma)y \end{array} \\ \begin{array}{l} -\gamma\pi z \\ +\nu(-\gamma\pi-\sigma+\alpha) \end{array} & \begin{array}{l} -\gamma\pi z+\gamma\pi(1-p) \\ -\mu-b \\ +(b+\alpha+\mu-\sigma)z \\ -\gamma\pi\nu+2(b+\mu)\nu \\ +(\alpha-\sigma)(y+u) \end{array} & -\gamma\pi(z+\nu) & \begin{array}{l} -\gamma\pi z+\gamma\pi(1-p) \\ +(-\gamma\pi-\sigma+b+\alpha+\mu)\nu \end{array} & \begin{array}{l} -\gamma\pi z \\ +\nu(-\gamma\pi-\sigma+\alpha) \end{array} \\ \begin{array}{l} -\gamma(1-\pi)(\nu+z) \\ +w(\alpha-\sigma) \end{array} & \begin{array}{l} -\gamma(1-\pi)(\nu+z) \\ +\gamma(1-\pi)(1-p) \\ +w(\mu+b) \end{array} & \begin{array}{l} -\gamma(1-\pi)(\nu+z) \\ -b+(b+\mu)\nu \\ +(\alpha-\sigma)(y+u) \\ +(b+\alpha+\mu-\sigma)z \end{array} & \begin{array}{l} -\gamma(1-\pi)(\nu+z) \\ +\gamma(1-\pi)(1-p) \\ +w(\alpha-\sigma+\mu+b) \end{array} & \begin{array}{l} -\gamma(1-\pi)(\nu+z) \\ +w(\alpha-\sigma) \end{array} \\ \begin{array}{l} (\gamma\pi+\sigma)\nu \\ +(\gamma\pi+\sigma)z \end{array} & \begin{array}{l} \gamma\pi y+\sigma(y+u) \\ +z(\sigma+b+\mu) \end{array} & 0 & \begin{array}{l} \gamma\pi y-\alpha-\mu+\sigma\nu \\ +(b+\mu)\nu+\alpha(u+y) \\ -b+2(b+\alpha+\mu)z \end{array} & \sigma\nu+\alpha z \\ \begin{array}{l} \gamma(1-\pi)(\nu+z) \\ +\sigma w+\alpha u \end{array} & \begin{array}{l} \gamma(1-\pi)y \\ +(b+\mu)u \end{array} & \sigma(y+z+u) & \begin{array}{l} \gamma(1-\pi)y+\sigma w \\ +(b+\alpha+\mu)u \end{array} & \begin{array}{l} \sigma w-\alpha+(b+\mu)\nu \\ +\alpha y+(b+\alpha+\mu)z \\ -b+2\alpha u \end{array} \end{pmatrix} \tag{26}$$

would be equivalent to

$$\begin{aligned} \frac{\mathrm{d}z}{\mathrm{d}t} &= z[-\alpha-b-\mu+(\alpha+b+\mu)z] \\ &= z(z-1)(\alpha+b+\mu) \\ &= f(z). \end{aligned}$$

But $f'(0) = -\alpha-b-\mu < 0$ and $f'(1) = \alpha+b+\mu > 0$ so that $z_2^* = 1$ is unstable. Thus $e2$ cannot be locally stable.

(3) $e3$ is admissible if and only if $R_0 > 1$. Next the eigenvalues of the Jacobian matrix evaluated at $e3$ are first: $b+\alpha-\sigma < 0$, $b\sigma/(\alpha-\sigma) < 0$, and $-\sigma+\alpha < 0$, and the next eigenvalues of a 2×2 matrix JJ_3 (equation (23)).

One has

$$\mathrm{Tr}(JJ_3) = \gamma\pi - \mu - b - \frac{b\alpha}{\sigma-\alpha} + \alpha - \mu - \sigma,$$

$$\begin{aligned} \det(JJ_3) &= (\alpha-\mu-\sigma)\left[\gamma\pi-\mu-b-\frac{b\alpha}{\sigma-\alpha}\right] \\ &\quad - \frac{b\gamma\pi\alpha}{\sigma-\alpha} \\ &= \underset{<0}{(\alpha-\sigma-\mu)}\underset{<0}{[(\gamma\pi-\mu-b)}\underset{<0}{(\sigma-\alpha)}\underset{>0}{]} \\ &\quad \underset{<0}{-b\alpha}\underset{<0}{(\gamma\pi-b-\mu+b+\alpha-\sigma)}, \end{aligned}$$

$\mathrm{Tr}(JJ_k)$ and $\det(JJ_k)$ being the trace and the determinant of the JJ_k Jacobian matrix, respectively.

When $R_0 > 1$ and $R_0' < 1$, $\mathrm{Tr}(JJ_3) < 0$ and $\det(JJ_3) > 0$, so the last two eigenvalues are negative or have negative real parts. The condition $R_0' < 1$ is sufficient to have the stability of the equilibrium point $e3$, but is not necessary. Indeed, one has

$$x_3^* = \frac{b}{\sigma-\alpha},$$

so that

$$\begin{cases} \mathrm{Tr}(JJ_3) = \gamma\pi - \mu - \sigma x_3^* + \alpha - \mu - \sigma, \\ \det(JJ_3) = (\alpha - \mu - \sigma)[\gamma\pi - \mu - \sigma x_3^*] \\ \qquad\qquad -\gamma\pi\alpha x_3^*. \end{cases}$$

Thus, a necessary and sufficient condition to have both $\det(JJ_3) > 0$ and $\mathrm{Tr}(JJ_3) < 0$ is

$$\gamma\pi - \mu - \sigma x_3^* < \frac{\gamma\pi\alpha x_3^*}{\alpha - \mu - \sigma},$$

that is

$$R_0' < \frac{\alpha - \mu - \sigma}{\alpha y_3^* - \mu - \sigma} \frac{\alpha(1 - y_3^*) + b + \mu}{b + \mu}.$$

(4) $e4$ is admissible if and only if $R_0' > 1$. We must calculate the eigenvalues of the Jacobian matrix, which are those of a 2×2 matrix (JJ_4) (equation (24)) and those of a 3×3 matrix (JJ_4') (equation (25)).

At this point using suitable software for symbolic computation can be useful. We have demonstrated (Suppo 1996) that if $R_0 < 1$ and $R_0' > 1$, then $\det(JJ_4) > 0$ and $\mathrm{Tr}(JJ_4) < 0$, so that the eigenvalues of JJ_4 are negative or have negative real parts.

We have demonstrated (Suppo 1996) that if $R_0 < 1$ and $R_0' > 1$, then $\mathrm{Tr}(JJ_4') > 0$. Next, we use the Routh–Hurwitz criterion (Murray 1989): the eigenvalues of $JJ_4' = (a_{ij})_{1 \leqslant i,j \leqslant 3}$ are negative or have negative real part if and only if

$$\begin{cases} \mathrm{Tr}(JJ_4') < 0, \\ \det(JJ_4') < 0, \\ \det(JJ_4') - D^* \mathrm{Tr}(JJ_4') > 0, \end{cases}$$

where

$$D = a_{11}a_{33} + a_{11}a_{22} + a_{22}a_{33} - a_{12}a_{21} - a_{13}a_{31} - a_{23}a_{32}.$$

After some calculus, we find that $e4$ is locally stable if and only if

$$R_0 < 1 - \frac{b + \mu}{b + \alpha} v_4^* \quad \text{and} \quad R_0' > 1$$

(Suppo 1996).

(5) $e5$ is numerically stable if $R_0 \geqslant 1$ and $R_0' \geqslant 1$.

The Jacobian matrix in the general case is shown as equation (26).

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