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by

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# Epidemiological study of Feline Immunodeficiency Virus in domestic cat populations (*Felis catus*)

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# Epidemiological study of Feline Immunodeficiency Virus in populations of domestic cat (*Felis catus*)

## ABSTRACT

Feline Immunodeficiency Virus (FIV) is a lentivirus that induces lethal immunosuppression in domestic cats (*Felis catus*). It is thought that FIV is transmitted through bites during fights.

We studied the dynamics of FIV within cat population through a mathematical model that we built. This compartimental deterministic model shows the following. Once introduced in a population, FIV is always maintained. Infection leads neither to the extinction of susceptible individuals nor of the whole population, but to a stable equilibrium stage of susceptible and sensible cats. The proportions of these pathological classes are dependent upon parameters specific to the population. The model also shows that when the population has reached an equilibrium, the reduction of the population size is low. In addition, the transmission rate, estimated throught the model, is always low and differs according to the population. When FIV dynamics is modeled simultaneously with the dynamics of Feline Leukemia Virus, it can be maintained alone, or together with the other virus (which also presents a stable equilibrium of individuals numbers). Theses two possibilities are the only ones encountered in the litterature or on the field.

We also conducted, over a span of three years, epidemiological studies of four natural populations of domestic cats living in contrasting environments: three rural populations of approximately 60, 250 and 300 cats and one urban population of 35 to 75 cats. Blood samples were taken from trapped cats at least once each year in each population, and statistical analyses (simple t, chi-square and trend statistic tests, non-parametric tests, Multiple Correspondence Analysis, Logistic Regressions, ...) were applied to serological results, to analyze the dynamics and circulation of FIV infections within these populations. These studies permitted us to validate the theoretical results obtained by the mathematical model, and show that FIV is present in all populations, with stable prevalence rates, of approximatively 10%. The main infection risk factors are sex, weight, age, and roaming habits: heavy roaming male adults are more likely than others to be infected. This is mainly due to the fact that FIV is transmitted by bites. Thus FIV infection probability depends on individual fight probability, and of the social status of the cat. Consequently, the prevalence rates depend upon the social characteristics of the population. The results of our mathematical model agree with field epidemiological studies and the literature. All seem to suggest that currently FIV have a low impact on domestic cat populations.

# INTRODUCTION

Parasitism is the driving force for great biological phenomenons. Even though it is not the only one, from the genom to the ecosystem level, *via* the immune system, the organism or the population, there is no place where life goes on without a virus, a nematode or a parasite DNA. Superficially, parasitism may seem to exist only through exceptional issues, such as spectacular epidemics. However, those manifestations usually result from the deregulation of the fine biological machinery, and their effects are probably less dramatic in the long run than those that parasitism exerts slowly with time. For example, parasitism influences the becoming of individuals, arbitrates intra or interspecific conflicts, and shapes species. Unfortunately, most ecological studies still do not account for parasitism, as if its discretion was synonymous of insignificance. Similarly, most epidemiological studies (and especially those concerning microparasites) deal with epidemics, which are exceptional episodes during which a parasite species overcomes the limits of its usual frontiers.

This work presents a study of a microparasite, which has been chosen not for the importance of the harm it may have caused before the study was undertaken, but rather for the numerous interesting characteristics of both the microparisite and the host species. The study tries to elucidate the mechanisms regulating the interactions of this

host/parasite system, and to evaluate the importance of the virus influence on the host at the population level.

This work is based on the **study of the spread of Feline Immunodeficiency Virus (FIV) and the interactions of its dynamics with that of its host population, the domestic cat, *Felis catus*.** This study was undertaken in two ways. We first developed of a mathematical model describing the virus species dynamics in theoretical cat populations. We then verified this model with from epidemiological studies on natural cat populations.

This work therefore contains three distinct and complementary parts.

The first part is a review of the published material necessary for this work and comprises four chapters with different objectives. Chapters I and IV deal with the particularly broad subjects parasitism and modeling, respectively. These chapters therefore aim at emphasizing one particular aspect of each domain and underlining its importance in our context, rather than presenting a state of the art in both these domains. In this respect, the first chapter only deals with the **influence of parasitism** on the infected host and the significance of epidemiological studies. Similarly, the fourth chapter deals only with the usefulness of **modeling in these epidemiological studies**. On the other hand, Chapters II and III discuss more defined subjects: **domestic cat and Feline Immunodeficiency Virus**. These two chapters not only discuss the particular aspects directly related to this work, but also summarize the whole scientific literature of interest.

The second part contains two chapters and studies FIV dynamics in domestic cat populations through mathematicals models. The first model deals with **FIV spread dynamics** in a population of domestic cats. The second model, derived from the first one, deals with the **simultaneous spread dynamics of FIV and of a related feline retrovirus** (the Feline Leukemia Virus, FeLV), whose transmission modes are different from that of FIV. This model describes an original and complex dynamic system: two parasites and one host. Chapters V and VI present the models, results and discussion. This modeling work has been carried out at a time when little was known about FIV epidemiology, so that the general information (epidemiological processes trends) obtained from this theoretical study gave us a better understanding of the system. Nevertheless, since modeling, which is a more and more indispensable step in epidemiology, should be coupled with field epidemiological studies, we carried epidemiological studies in a third part.

The third part of this work, containing three chapters, deals with the FIV/cat populations interactions from an epidemiological point of view. We carried two epidemiological studies on natural populations of domestic cats with contrasted characteristics. Chapter VII analyzes the published serological studies, in an attempt to highlight potential bias or lacks, and to fill them up in our own studies. This **critical analysis of the literature** is followed by an eighth chapter dealing with the **epidemiological study of a population of domestic cats living in a rural environment**, and monitored during four years for FIV epidemiology. Chapter IX presents the **epidemiological study of a second population, situated in an urban environment**,

which I monitored during the three years of my Ph.D. work. This study is followed by a short comparative study of these two populations, and of two other rural populations also monitored by our team. During these studies, we tried to describe the epidemological patterns of these populations by analyzing the role that parameters such as sex, age, genotype or body weight of individual may have on FIV infection. We have also extended our investigations to the spatial aspect, since the spatial structure of a population may highly govern pathogen spread patterns within itself. From there, we tried to investigate the mechanism of virus spread within the population, as well as the factors influencing it.

Even though the results of each of the studies of the second and the third parts are carefully discussed at the end of each chapter, they are summarized in a **general discussion**, in the light of broader scientific subjects that we have not dealt with during this work, such has evolutive biology and conservation biology. The various perspectives and contributions of this work will also be discussed in the final part.

The English version of this manuscript being shorter than the original one, the first part (bibliography) is only summarized in a few pages. Both chapters of the second part are presented through publications resulting from this work: one published manuscript, one manuscript in revision and one manuscript in preparation. The three chapters of the third part are also presented through manuscripts: one published manuscript, one submitted manuscript, and one manuscript in preparation. A fourth published manuscript is also included as it deals with many discussed points of this part. Only the general discussion will be identical to the original.

"Hear and attend and listen; for this befell and behapened and became and was, O my Best Beloved, when the Tame animals were wild. The Dog was wild, and the Horse was wild, and the Cow was wild, and the Sheep was wild, and the Pig was wild-as wild as wild could be-and they walked in the Wet Wild Woods by their wild lones. But the wildest of all the wild animals was the Cat. He walked by himself and all the places were alike to him".

Rudyard Kipling, Just So Stories.

# PART ONE: SCIENTIFIC CONTEXT: FROM PARASITISM TO MATHEMATICAL MODELS

# CHAPTER I:

# INFLUENCE OF PARASITISM

## (SHORT REVIEW)

Ecological literature has long neglected the potential role of parasitism in determining the state and future of individuals, population dynamics, community structures and even species evolution.

Parasites are often defined as potentially harmful species that partly depend upon one or several host species for their habitat and their food. This harm can be observed for an individual or for the entire population level through the decrease of the individual fitness or of the intrinsic population growth rate, respectively (Keymer *et al*., 1991).

Parasites are usually categorized either as macroparasites (mainly arthropods and helminths) or microparasites (bacteria, viruses and protozoans, Anderson & May, 1979). However, this distinction is based on their population characteristics rather than on a taxonomic basis (Dobson & Hudson, 1986). The generation time of macroparasites is much longer than that of microparasites, and their direct multiplication within the host is absent or weak. Their distribution is often heterogeneous, since only a few individuals carry many parasites, while most individuals are barely infected (Bradley & May, 1978;

Dobson & May, 1986a). Microparasites are characterized by their small size, their short generation time, their high reproduction rate within the host and their tendency to confer immunity to the host after the first infection. The length of infection is usually much shorter than the host life time (except for some species, such as lentiviruses, Narayan & Clements, 1989; Dawson, 1988). It is thus of a transient nature (Anderson & May, 1979). Microparasites are characterized by sporadic outbreaks.

Parasitism influence is mostly observed in infected individuals. Although hardly demonstrable in practice, parasites can reduce the host fitness, which implies that selection tends to favourize adaptations of the host that minimize the impact of infection. Such a fitness decrease in the host may be caused by weakened reproduction or survival. The decrease of survival may be due either to directly induced death or to morbidity inducing weakness towards competitors, predators and other parasites (Scott 1988, Hudson *et al.*, 1992).

Parasitism is strongly linked to the host physiological conditions. A weakened individual is more prone to infection by parasites and induced symptoms. Studies demonstrating the relationship between the transmission of parasites and the host behaviour (Keymer & Read, 1991; Combes, 1991) show that the host behaviours that are necessary to its survival, such as feeding and reproduction, are those mainly used for the transmission of parasites (Apanius & Schad, 1994). Parasites are able not only to exploit the behaviours of the host for infection, but also to induce changes, leading to three phenomena (Brodeur & McNeil, 1989; Smith-Trail, 1980). The first phenomenon is the release of parasitic propagules outside the original host to infect new individuals, as observed in the case of rabies. Parasites are also able to redirect the metabolic pathways of the host to favourize their own growth. Finally, parasites manage to keep their host alive until they are fully developed. Similarly, infected hosts can adapt to parasites in three major ways (Holmes, 1983): behaviour (Hart, 1990), genetics and immune response (Mitchison, 1990). The immune response is particular interesting in the case of viruses, and especially those that, such as FIV, induce immunodepression.

Parasites affect also the populations of infected hosts. Sporadic outbreaks, despite their dramatic manifestations, may affect population growth to a lesser extend than the continuous presence of subclinical endemic infections (Gregory & Keymer, 1989). Since parasites weaken the survival and reproduction of infected individuals, their global effect on populations is a reduction of population growth rate and size (Keymer *et al.*, 1991). However, many mathematical models show that microparasites affecting host survival do not induce depression of the host population far below the equilibrium state in the absence of the disease (*e.g.* MacCallum & Dobson, 1995). This suggests that parasites might act as host growth population regulators (Anderson & May, 1979; Mena-Lorca & Hethcote, 1992; Smith, 1994b). Despite the highly devastating effects of sporadic outbreaks, it is difficult to determine whether parasites act on the population size as a density dependent regulator or as an occasional density-independent mortality source. Nevertheless, like competition and predation, parasitism is often regarded as acting in a density-dependent way, thereby being a regulator of populations density (Dobson &

Hudson, 1986; Dietz, 1988). It is generally agreed that there is a population density (or size) threshold below which a given disease cannot establish and persist (Anderson & May, 1985). In small sized populations, host/parasite relationships dynamics is particularly fragile, and outbreaks do not tend to last (Dobson & May, 1986a; Lyles & Dobson, 1993).

Parasitism may affect the social organization of a population (Price *et al*., 1986; Møller *et al.*, 1993). In the context of parasitism, the disadvantages of living in a society (mainly infection risk, Poulin, 1991) may be balanced by advantages such as allogrooming (Hart, 1990), antibody sharing (Brambell, 1970), and lower vector-borne infection probability in some cases (Davies *et al*., 1991; Apanius & Schad, 1994). From a population point of view, infection may influence host age structure, such as in the case of a pathogen specific to individuals belonging to a particular age category (Anderson & Crombie, 1985), or a pathogen affecting differently individuals of different ages (Gulland & Fox, 1992). Similarly, both sex do not respond equally to pathogens (Alexander & Stimson, 1988), so that parasites may modify the population sex-ratio (Weatherhead & Bennett, 1991; Gulland & Fox, 1992; Rousset *et al.*, 1992; Rigaud & Juchault, 1993). Parasitism also influences the spatial distribution of host populations (Gregory, 1990). Daily movements sequences may be altered in presence of parasites (Rubenstein & Hohmann, 1989), and that parasites may induce nest or pasture site desertion (Feare, 1976; King *et al.*, 1977; Folstad *et al.*, 1991; Bouliner, 1992), or influence young dispersal (Brown & Bromberger-Brown, 1992). It is noteworthy that these movements may favour parasite spread.

Parasitism influences communities through the infected host species. Most studies only refer only to one host/one parasite systems, although several pathogens may infect a single species, or even a single individual (Hawkins, 1990; Hochberg & Hawkins, 1992; 1993), with complex interactions. Similarly several host species may share a common parasite species. It is important to consider parasites as potential competitive mediators, since they may favourize one species to the detriment of another. The introduction as well as the eradication of a species in an ecosystem may affect interactions of many species in this ecosystem, such as in the case of the introduction of myxomatosis in Australia (Fenner, 1994), of avian malaria in Hawaii (Van Riper *et al*., 1986), or of rinderpest in Serengeti (Spinage, 1962).

Parasitism is also a major selective factor for species evolution (Hochberg *et al*., 1992; Anderson, 1994). Because of their influence on host survival, reproduction or dispersal, parasites can influence the genetics of the population (O'Brien & Evermann, 1988; Scott, 1988, Gulland *et al*., 1993). The importance of fitness cost due to parasite resistance suggests that an evolution towards an increased resistance will be at the expense of other fitness compounds (Bowers *et al*., 1994). Nevertheless, optimal fitness for a host does not necessarily require total eradication of the parasites (Wakelin, 1994; Combes, 1995). Coevolution means that two species simultaneously undergo a genetic change in response to a durable interaction (Toft & Karter, 1990). Very simply, best adapted hosts either behaviourally or physiologically have a better fitness and their

characteristics, if inheritable, are selected. Parasites thereby contribute to the continuous shaping of their host species. Similarly, hosts are the main evolutive strength of parasites, in that parasites with the best transmissibility and virulence are favoured at the evolutive scale (provided their great virulence is not prejudicial to their transmissibility).

Epidemiology studies the frequency and distribution in space and time of diseases in a defined population, as well as the role of determining factors, and their eventual control. Epidemiology can also be defined as the ecology of diseases (Ewald, 1988). There are in fact four types of epidemiology. Descriptive epidemiology consists in collecting and describing data that may be relevant *a priori*, and basically consists in establishing rates by rationing the number of individuals presenting one particular pathological condition to the population size. Analytical epidemiology investigates the relationships between causes and effects, and an evaluates risk factors. Experimental epidemiology tests hypothesis by developing experimental models to handle one or several factors: for example a prophylactic try. Finally, ecological epidemiology, also called mathematical epidemiology (Anderson & May, 1991), identifies the factors and processes affecting the transmission and persistence of pathogens (Smith, 1994a) and uses mainly mathematical models. This work reports on epidemiological studies belonging to the second and fourth categories.

During this work, we will attemp to determine the influence of VIF on domestic cat at the individual level, on its populations, on the ecosystems it lives in, and on the history and becoming of its species.

# CHAPTER II:

# DOMESTIC CAT

## (SHORT REVIEW)

We are going to review the main characteristics of domestic cats and its populations, in order to highlight the more interesting elements on an epidemiological point of view.

The name domestic employed for cat defines a species: *Felis catus*. In this case, domestic cat is not opposed to wild concerning the degree of human influence, but to the wild cat species, *Felis silvestris*. This distinction can be ambiguous since domestic cats present various dependence degree towards humans. In general, three categories are distinguished. First the indoor domestic cats, depending upon humans for food, and sometimes for movements. Then, feral domestic cats, depending upon human only through food, with feeding people or garbage, and which are free for their movements and reproduction. These are the roaming cats of our cities and villages. Finally, domestic cats that returned to wildness, not depending upon humans, and the proximity of whom they do not tolerate, found for example in open country or in some islands. These cats are sometime uneasy to distinguish from wild cats, with which they can reproduce.

In this work, where it will be question of natural population of domestic cats, most of the time feral, domestic cats will design the species *Felis catus*, whatever its degree of dependence upon humans.

Having followed humans in their conquest of the world (Todd, 1977), the domestic cats have a cosmopolite distribution, under every latitude, from equator to polar circle. The domestic cat has a high adaptation capacity. Cat is an opportunist predator, and occasionally a scavenger, and the predation level on each prey species partially depends of its relative availability and is thus variable according to regions or seasons (Hubbs, 1951; Marshall, 1961; Coman & Brunner 1972; Bayly, 1978; Fitzgerald, 1986). The fact that cat is at the top of food chains in ecosystems where it lives reminds the potential ecological importance of its parasites.

The population structure is important for pathogen spread characteristics within these populations. Domestic cats present a high degree of their population spatial and social structure variability (Kerby & Macdonald, 1988; Liberg & Sandell, 1988). The domestic cat has a complex social life, from solitary to living in high social groups, with many intermediate states (Leyhausen, 1986). Domestic cats live in groups when allowed by ecological conditions, that is, mainly when feeding resources are sufficiently concentrated and stable to allow the requirements of more than one individual (Macdonald, 1983; Natoli, 1985a; Macdonald *et al.* 1987; Liberg & Sandell, 1988). The relationships between adult females are most of the time amicable, but tend to be aggressive towards strangers of both sexes, especially when they rear kitten (Leyhausen, 1965). Aggressive relationships between males may be frequent, especially towards lower hierarchically ranked males (Natoli, 1991). Despite reproduction is the main cause of fights, territorial defense is also important.

This variability of social and spatial organization of cat populations seems to be linked to the variability of their mating system. However, a promicuist reproduction behaviour is described in urban environment (Natoli & De Vito 1991). In this environment, males and females both have several sexual mates (Natoli & DeVito, 1986). Observations in rural environment suggest a more pologynous mating system, with female monopolization by males, which can lead to fights (Liberg 1981; Pontier 1984; Macdonald *et al.*, 1987; Liberg & Sandell 1988; Pontier *et al*., 1995). Density and social environment seem to modify apparition of such mating behaviour (Pontier, 1993).

This social structure variability is closely linked to the one of their spatial population structure. Indeed, cat population density is highly variable, from less than one to more than 2000 cats per $km^2$ (Liberg & Sandell, 1988). In fact populations where cats live in large social groups, such as in urban environment, with high density can be distinguished from those with smaller groups.

Cat home ranges may vary from 0,1 to 200 ha for females to nearly 1000 ha for males (Liberg & Sandell, 1988; Tabor, 1983; Fitzgerald & Veitch, 1985; Natoli & DeVito, 1988; 1991; Haspel & Calhoon, 1989; Page *et al*., 1993). Home range overlapping degree is important (Fitzgerald & Karl, 1986), especially in cats of a common social group (Izawa *et al.* 1982). Because they rear altricial young, abundance

and distribution of food and shelters (for young rearing) determine home range size for females (Van Aarde, 1979; Macdonald, 1983; Natoli, 1985a). Male home ranges size, in average three time larger, is determined by receptive females density and distribution (Liberg, 1981). It increases during the reproduction period, and vary with the male social status. Thus, spatial structure of cat populations is mainly determined by human habitat structure (Pontier, 1993).

At birth, sex-ratio is equilibrated (Nelson *et al*., 1969; Robinson & Cox, 1970). In populations in rural environment, adult sex-ratio is in general not equilibrated in favour of females (Liberg 1980; Pontier, 1984), and this desequilibrium increases with age (Pontier, 1993). This desequilibrium might be due to a trend of males to disperse, and simply to roam (Liberg, 1981). Observations in urban populations suggest an equilibrium of sex-ratio.

The age structure depends on the considered population. As it is uneasy to determine precisely age of feral cats (especially if only observations are carried), age classes are often determined, such as those defined according to the social or the reproductive status (van Aarde 1978; Liberg (1980). Observations on most populations indicate that populations are mainly constituted of adults (Derenne, 1976; Jones, 1977; van Aarde, 1978; Konecny, 1983). The total number of cats decreases exponentially with age (Legay & Pontier, 1983).

At a maximum of eight weeks, young are weaned. Dispersal may be induce by aggressivity of resident adult males (Liberg, 1980; Warner, 1985; Fitzgerald & Karl, 1986), but arise only after weaning and, in rural environment, concern only males. Dispersal is the more important density regulation mechanism (Natoli, 1985). This phenomenon also has a major importance concerning pathogen spread within groups and populations. Group structure and cat dispersal processes highly depend on territorial behaviour and dominance relationships. Our first results in urban environments suggest an equilibrium of the sex-linked dispersal.

In the absence of limiting resources, such as food, there are two mainly cited mortality causes: vehicles and hunters (Pontier, 1984). Pathogens must be added, as they can have and important impact on some groups or populations (Warner, 1985). The impact of these different mortality causes vary however in intensity. They can be very strong in rural populations with high road traffic and hunt activity, giving an average of 3 to 4 years of survival (Legay & Pontier, 1983; Pontier, 1984; Warner, 1985). They can also be much lower, such as in sub-Antarctic islands, where there are no competition, parasite, predator or hunter, and in which the average survival is closer to 8 years (Derenne, 1976; Konecny, 1983).

Genetic of domestic cats is particular by the fact they bear a number of coat color polymorphism (Robinson, 1977, Todd, 1977). In this context, an interesting link can be done between epidemiology and genetics through the Orange gene (Pontier *et al*., 1995) and FIV infection.

Parasites infecting domestic cats are well known, when compared to other animal host species. For example, the viruses are the best known (after the human one), with 14 viruses well studied (Artois, pers. comm.). Concerning ecological studies, we have seen than cats were present in most parts of the world and are often tame and can be easily observed. The domestic status of the cat also provides the possibility of quasi-exhaustive censuses of the individuals of a population (Pontier, 1984), and thus of rarely available ecological parameters. Moreover, due to high variability, domestic cat populations are comparable to some other species populations, allowing thus a comparison with populations that are less available to observation, such as other carnivorous. Finally, and it will be developed in the next chapter, domestic cats constitute an increasing center of interest for scientist involved in HIV research, due to the homologous virus infecting this animal.

# CHAPTER III:

# FELINE IMMUNODEFICIENCY VIRUS

**(SHORT REVIEW)**

In 1986, Pedersen and coll. isolated the Feline Immunodeficiency Virus (FIV, Pedersen *et al.*, 1987). Morphological, biochemical and genetic research on this virus have led to its classification in the lentivirus (Yamamoto, 1988; Olmsted *et al*., 1989a; Talbott *et al*., 1989; Sparger, 1993). The genomic organization of FIV has a similar complexity compared to other lentiviruses. Its genetic diversity is similar to that of primate lentiviruses. Indeed, more than 20 different strains have already been isolated, with up to 20% of variability between strains infecting several individuals (Miyazawa *et al.*, 1989b; Maki *et al*., 1992). In the same way, there is a high variability degree within viruses of a single individual (Sodora *et al.*, 1994). Despite being the closest lentivirus to primate lentivirus, FIV is genetically closer to non-primate lentiviruses (Olmsted *et al*., 1989a; Talbott *et al*., 1989; Egberink *et al*., 1990a; Phillips *et al*., 1990; Maki *et al*., 1992; Matsuo *et al*., 1992).

Following infection, either natural or experimental, cats produce antibodies against the virus envelop proteins, the p24 antibodies being the first produced (Hosie & Jarrett, 1990). Detection of FIV is indirect, based on the research of these antibodies,

which are, as is FIV, lifelong in infected cats. Anti-FIV antibody research need at least to use two distinct methods, in general ELISA test and confirmation by Western Blot. Moreover, it is important to retest negative cats at least two months after the first test, in order to take into account cats that would have been in the first stage of infection, and thus bearing not enough antibodies to be detected.

Five stages are usually described in FIV infection: acute stage, asymptomatic seropositivity period, persistent lymphadenopathy, Arc (for AIDS Related Complex) and AIDS (Pedersen *et al*., 1989; Ishida & Tomoda, 1990; Msika 1991). The first stage corresponds to a seroconversion phase, and last 2 to 4 weeks. The second one is a months to years long seropositivity period. During this long stage, typical to the lentivirus family, the cat is in good health conditions, but is infectious. The persistent generalized lymphadenopathy (PGL) last around one year and may be linked to anorexia (Ishida *et al*., 1992). The ARC stage consist in PGL linked symptom apparition. Cats in this stage generally present chronic infections, in particular of the mouth cavity, of the upper respiratory tract and other body locations but no opportunistic infection. AIDS is characterized by lost of immune defense, rapidly inducing death (in a few months, Ishida & Tomoda, 1990; Ishida *et al*., 1992; Shelton *et al.*, 1990b). As for humans, AIDS development mechanisms are not known, and it is even not sure that all infected cats will develop one. A great number of clinical studies has been carried, highlighting a wide range of clinical signs in FIV infected cats (Hosie *et al*., 1989; Ishida & Tomoda, 1990; Lutz, 1990; Pedersen *et al*., 1989; Yamamoto *et al*., 1989; Pedersen et Barlough, 1991). There is nor natural immunization, neither natural recovering. As for HIV, only palliative treatment may be applied, and thus only experimentally.

Several experimental vaccines allow now a protection to cats against infection by homologous or heterologous strains (Lehmann *et al.*, 1991; Yamamoto *et al*., 1991; Yamamoto *et al*., 1993; Hodatsu *et al*., 1993; Hosie *et al*., 1993; Verschoor *et al*., 1995). However, their efficiency is limited to particular experimental conditions.

FIV transmission mode has not yet been determined with certitude. It is though that FIV is not sexually transmitted, but that is rather transmitted by bites (Sparger, 1993). Infections would thus occur during fights for females monopolization or for territory defense. The virus has been found everywhere in the world it has been looked for. Seventeen other felid species also bear anti-FIv antibodies. FIV infection in human do not seem to be possible (Lutz, 1990; Yamamoto *et al*., 1993).

FIV studies can bring major informations in several domains. The most evident interest is in veterinary science. In addition to cat sanitary aspect, FIV could be an interesting model of epidemiological studies. Moreover, presence of antibodies to apparently specific FIV strains in non-domestic species implies another interest of lentiviruses studies, for biodiversity conservation. In addition, FIV strains and their feline host could be a good model to study host/parasite coevolution, especially concerning virulence evolution (Ewald, 1994). Finally, FIV is a particularly well fitted study model of its human homologous, the Human Immunodeficiency Virus, on many domains (Courchamp *et al.*, 1994).

# CHAPTER IV:

# USE OF MATHEMATICAL MODELS IN EPIDEMIOLOGY

## (SHORT REVIEW)

In order to study FIV epidemiology within domestic cat populations, we chose to use modeling. This method provides advantages that are not given by experimentation. A model is a simplified constructing aiming to mimic a (biological here) process, in order, for example, to highlight informations that were hardly available (either by observation or experimentation) in reality. Indeed, epidemiology is a science dealing with complex phenomenons, with the study of interactions of at least two populations dynamics (the one of the host and the one of the parasite), situated in different spatial and temporal scales, with specific parameters. Modeling of the spatial and temporal spread of a microparasite with a mammal host population requires not only knowledge on parameters of the populations of the host and of the parasite, but also of parameters concerning the interactions between the two species. The aim of mathematical models in epidemiology is to describe, understand, predict and/or control pathogen dynamics.

Modeling, especially in epidemiology, may allow to work with parameters that are not available by experimentation and to have a rapid access to very long period over which dynamic data begin to have an interesting epidemiological meaning. Modeling

allows in this context, not only to simulate experimentations (for example the introduction of a lethal virus in a susceptible population), but also to do it a sufficiently high number of times to have a statistical meaning. However, modeling should not be substituted to experimentation: it is a complementary tool, often necessary, but never sufficient by itself.

While many biologists do not use modeling, many model producing scientists produce tools that are not directed or accessible (and thus not useful) to biologists. Despite this kind of problem, common in interface sciences (such as here mathematics and biology), modeling is more and more often used in human and animal epidemiology.

We are going to briefly present the choices that have been made in this work. Hypothesis simplification is unavoidable in epidemiological models, just as it is essential to use a minimum or parameters in order to be able to analyze the respective role of each of them in the model behaviour (Mollison, 1987). One of main characteristics of this model will thus be simplicity. An eventual complexification of the model will be held step by step, in order to distinguish the contribution of each new hypotheses. This process has been followed for the realization of the model, with a first model with FIV dynamics within cat populations, then of FeLV dynamics, a feline retrovirus that is, due to higher possible pathological states, a little more complex to model, in these populations, and finally of both viruses simultaneously in the population.

In addition, the model is constructed in such a way for each hypothesis to be associated to mathematical parameter, in order to easily change some of them to modify the entire model. Thus, this simplicity will allow comparisons and adaptations to other viruses or host population, a point that was asked for in the modeling prospects. For example, the FIV model has been easily modifiable to describe FeLV dynamics.

Concerning the more technical aspects, it seems that an analytical model would be more adapted to our case than a simulation. This first choice is moreover imposed mainly by the scarcity of data at the beginning of the model, and thus a need of a more explanatory model rather than a quantitative one. Deterministic models give results presented by a unique value, while stochastic models use statistics and probability, and thus provide informations on parameter variability. This kind of model could be more adapted to small sized populations (Jacquez 1990, Longini 1986), or two first stages of epidemics, where infected individuals are still few (Mollison 1987). Nevertheless, stochastic models require precise data that were not available at the beginning of the study (and still are not). Thus, the presented models will be of a deterministic nature. In addition, these models will be compartimental (Bailey, 1975). Compartimental models are different for micro and macroparasites (Scott & Smith, 1994). While host/macroparasite association modeling require to take into account the distribution of macroparasites among the hosts (Anderson, 1982b), host/microparasite systems will be studied through the dynamics of the number of infected host, by the modeling of the flux between a number of host pathological states (Dobson & May, 1986).

"Comprendre signifie simplifier". D. Strogov.

Courchamp F., Pontier P., Langlais M. & Artois M. 1995. Population dynamics of Feline Immunodeficiency Virus within cat populations. *Journal of Theoretical Biology*. 175/4: 553-560.

# CHAPTER V

## POPULATION DYNAMICS OF FELINE IMMUNODEFICIENCY VIRUS WITHIN CAT POPULATIONS

## 1 Introduction

Despite the large number of existing models describing the influence of microparasites on host populations, no model is available, to our knowledge, of the circulation of retroviruses within populations of mammals (except the special case of humans). Nevertheless, the retroviruses are very interesting because of their particular circulation pattern. Indeed, the very long seropositivity period, as well as the succession of different clinical stages, induce the need for specific models. Moreover, the functionning of host populations may be very specific, hence their modelling requires a good understanding of the patterns of the hosts' spatial and social structures. We present here a simple model of the circulation of the Feline Immunodeficiency Virus (FIV), a feline retrovirus, within a population of domestic cats (*Felis catus*). Because they live in a variety of ecological conditions, domestic cat populations show a high degree of variability in their spatial and social structures which can be compared to other populations of FIV-infected non-domestic felids that are more difficult to study in natural habitats. The wide prevalence of FIV infection in natural populations of cats provides an opportunity to analyze the consequences of population structures on the circulation of the virus. Although the nature of this model is rather qualitative, the values of parameters like transmission rate and carrying capacity may inform on impact (in terms of reduction of number of cats due to the disease) of the lentivirus within cat populations, and on the influence of cat population functioning on the spread of the virus.

## 2 Materials and methods

### 2 1 Hosts population

The domestic cat is present in large numbers on all continents and on numerous islands (Todd, 1977; Legay, 1986). The spatial organization of female cats, like other carnivorous species, is determined by both abundance and dispersion of feeding resources (Macdonald, 1983; Liberg & Sandell, 1988). The spatial distribution of female cats is principally determined by the spatial organization of human habitats in rural areas, as females are associted with to human shelters (for kitten rearing, Liberg, 1981; Pontier, 1984). The spatial distribution of males, at least during the reproductive season, seems to be governed instead by the distribution of receptive females (Liberg, 1980, 1981; Liberg & Sandell, 1988). Stray cats in urban areas are organized in large social groups around shelter and feeding resources (Dards, 1979; Calhoon & Haspel, 1989). Density is high in these groups (up to 2000 cats per $km^2$, Natoli & De Vito, 1988, 1991) in contrast with rural areas where the density is much lower (from less than 1 cat per $km^2$ to 30 cats per $km^2$, Corbett, 1979 in McDonald *et al.*, 1987; Liberg & Sandell 1988). Also, different mating systems have been observed in relation to spatial and social organization of populations: from promiscuity in high-density urban areas (Natoli & De Vito, 1988), to polygyny with monopolization of females in low-density rural areas (Macdonald *et al.*, 1987; Liberg & Sandell, 1988). Thus the pattern of human habita is the main factor which determines the social and reproductive patterns of the domestic cat populations.

We monitored each year three rural cat populations in France: Barisey-la-Côte (since 1990), Aimargues (since 1982), Saint-Just Chaleyssin (since 1982), and one urban stray cat population in Lyon (since 1991). These cat populations are characterized by different densities, survival parameters, and mating systems (Pontier, 1993, Table I). We observed a promiscuous mating system in the urban stray cats, while a polygynous mating system was observed in the three rural cat populations (Pontier, 1993). From these studies, fecundity, averaged over females of all ages, has been estimated in rural areas at 4.8 offsprings per year (*i.e.* 2.4 per cat), and the mortality rate, per cat, at 0.6 year. In urban areas, preliminary observations lead us to a value of 1.85 for fecundity and between 0.6 and 0.8 for mortality (unpublished data). An epidemiological study has been carried out each year since 1991 in the four cat populations on a representative sample of cats. Partial results of the epidemiological survey are given Table I.

| **Population** | **Habitat** | **FIV rate** ($y$) | **N** (cats) | **Sampling** (cats) | **Mating system** | **Density** (cats/km$^2$) |
|---|---|---|---|---|---|---|
| Barisey-La-Côte (BC) | rural | 9,1 | 60 | 33 | Polygynous | 200 |
| Aimargues (AI) | rural | 9,5 | 203 | 42 | Polygynous | 120 |
| St-Just-Chaleyssin (SJ) | rural | 24,4 | 299 | 45 | Polygynous | 250 |
| Lyon (LY) | urban | 33,33 | 40 | 18 | Promiscuous | 1100 |

**Table I**: Main characteristics of the four studied populations.

### 2 2 Microparasite

FIV is a recently identified virus inducing AIDS in cats (Pedersen *et al.*, 1987; Pedersen *et al.*, 1993). It belongs to the lentiviruses subfamily of retroviruses (Olmsted *et al.*, 1989), which also includes Human and Simian Immunodeficiency Viruses (HIV and SIV). However, the transmission mode of FIV seems to be through by bites inflicted during fights (Yamamoto *et al.*, 1989) instead of sexual contact, in contrast to HIV. Indeed, the major parameters influencing FIV infection seem to be behaviour (roaming or not), sex and age (Lutz, 1989; Sparger *et al.*, 1993). In addition to providing a relevant model for HIV studies, FIV is of particular interest in veterinary science, as infection with FIV gives rise to a wide range of clinical signs (Brown *et al.*, 1991; O'Neil *et al.*, 1991), with a clinical staging very similar to human AIDS (Ishida & Tomoda, 1990). An attempt has been made to delineate the clinical course of FIV infection in a series of five stages analogous to those of HIV infection in humans (Pedersen & Barlough, 1991; Sparger, 1993). First, the infected cat suffers from an acute stage occuring several weeks after infection and lasting 4-16 weeks. Despite recovering from the primary stage of illness, virtually all cats infected with FIV become lifelong carriers of the virus. The first stage is followed by an asymptomatic carrier phase lasting months to years, during which the behaviour of the cat does not seem to be affected. There follows persistent generalized lymphadenopathy (PGL), AIDS-related complex (ARC) and AIDS,

charaterized by miscellaneous disorders and opportunistic infections. Because of the very long period separating infection from death due to AIDS, and the low survival rate of roaming cats (Legay & Pontier, 1983; Pontier, 1993), the majority of infected cats would be expected to die from "natural causes" (road accidents, hunting, poisoning, Hamilton *et al.*, 1969) before reaching the terminal stages of FIV infection. Thus, they should have time to transmit the virus, but not to die from it, hence an expected low impact of the virus within natural populations of domestic cats. The impact of FIV is one aspect of the virus which we attempt to study with the model, the other being the viral transmission rate.

### 2 3 The model

The model we present here is based on Anderson and May's work (e.g. Anderson & May, 1991). The dynamics of a cat population are represented by a set of differential equations. Let *N* be the total number of cats at time t, and K be the carrying capacity of the habitat at equilibrium. Concerning the demographic parameters, we assume that the density dependence acts primarily on mortality. Hence the birth rate is constant (Pontier, 1984; 1993). Next the death rate is linearly related to *N*, and has the form (m+r*N*/K), where m is the natural death rate and r=b-m≥0 is the population growth rate in the absence of resource limits. When the population is free from FIV, the dynamics of the population is given by the familiar logistic equation (Verlhust 1838):

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) \qquad (1)$$

Next, in order to describe the spread of FIV through the population, we introduce susceptible cats denoted by X(t) = *X*, and infected ones denoted by Y(t) = *Y*, so that *X*+*Y* = *N*.

For the sake of simplicity, we assume here that there is only one stage of illness combining acute, seropositivity, PGL, ARC and AIDS stages. Indeed, we can assume that infected sick individuals no longer participate in social life as they are too weak in the last stages to compete for territories or mates. We can also assume that the time they remain at these three last stages is too short, and their roaming habits become too restricted, to die from "natural causes". Thus, as they do not contribute to the reproductive effort of the population, or the transmission of FIV, the infected/sick class can be ignored.

We call ρ the encounters rate within the population, β the frenquency of an aggressive contacts resulting in a bite (when an encounter occurs), and c the efficiency of the FIV transmission by biting. It is feasible to estimate c through experimental bites, but it is not feasible to estimate either the encounters rate or the probability of being bitten, when an encounter occurs. This would requires intense behavioural observations, as the rate would depend heavily on the respective hierarchical positions of the two

protagonists. Moreover, the results would certainly not be generalizable to populations other than the one studied. Thus, as it is yet not possible to estimate separately ρ, β and c, and to reduce the complexity of the model, we decided to consider ρβc as a composite parameter, σ, which may be defined as the rate of effective bites (for transmission of FIV). The death rate due to AIDS is α (1/α is the length of the infectious period), and is independent of population density.

For the following biological reasons, the transmission rate will not be characteristic of mass action models but rather of proportionate mixing models (Busenberg & Cooke, 1993). We assume that an individual's infection status does not affect the probability of having direct contacts with others, and that the rate at which an individual comes into contact with others in the population is a constant ρ. Then, of all the contacts had by a single susceptible individual, a proportion equal to Y/(X+Y) is with infected individuals. Thus the rate at which contacts between susceptible and infected individuals occur is equal to ρXY/(X+Y). Then the force of horizontal transmission is cρβXY/(X+Y), that is, σXY/N. Next we assume that there is no vertical transmission (Ueland & Nesse, 1992), and there is no recovery of infected cats, by either natural or artificial means.

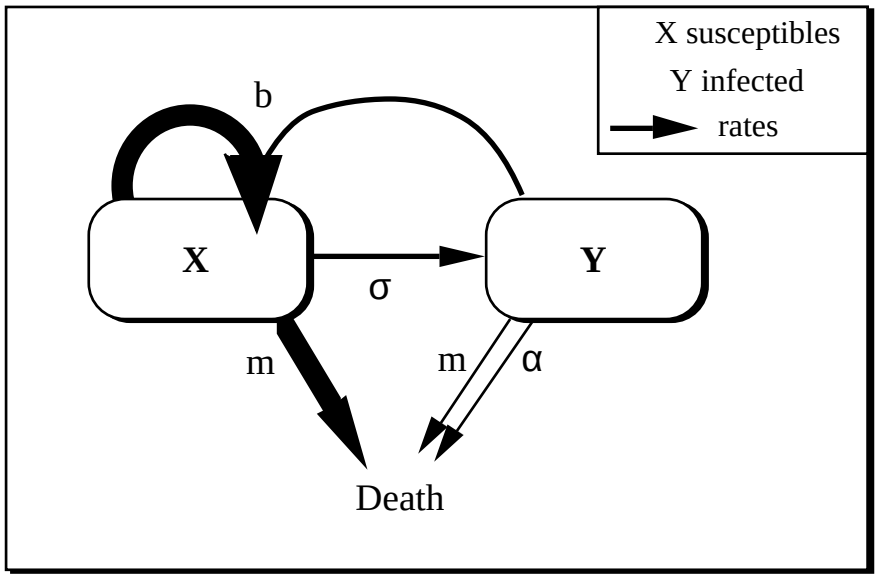


**Figure 1**: Flowchart of the FIV/cat model, with susceptible individuals noted (*X*) and infected individuals noted (*Y*). There is no possibility of recovery, and no vertical transmission. b is the birth rate, m the intrinsic death rate, σ the effective bite rate, α the mortality rate due to AIDS.

The compartmental representation is shown in Figure 1. A set of first order differential equations describing the dynamics of cat populations infected with FIV is thus given by the proportionate mixing model:

$$\frac{dX}{dt} = b(X+Y) - mX - \frac{rNX}{K} - \frac{\sigma XY}{N} \qquad (2)$$

$$\frac{dY}{dt} = \frac{\sigma XY}{N} - mY - \frac{rNY}{K} - \alpha Y \qquad (3)$$

The equation for the total population is obtained by adding the equations (2) and (3):

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) - \alpha Y \qquad (4)$$

Simulations have been carried out with the computer program Dynamac (Rousseau, 1988, see Figure 2).

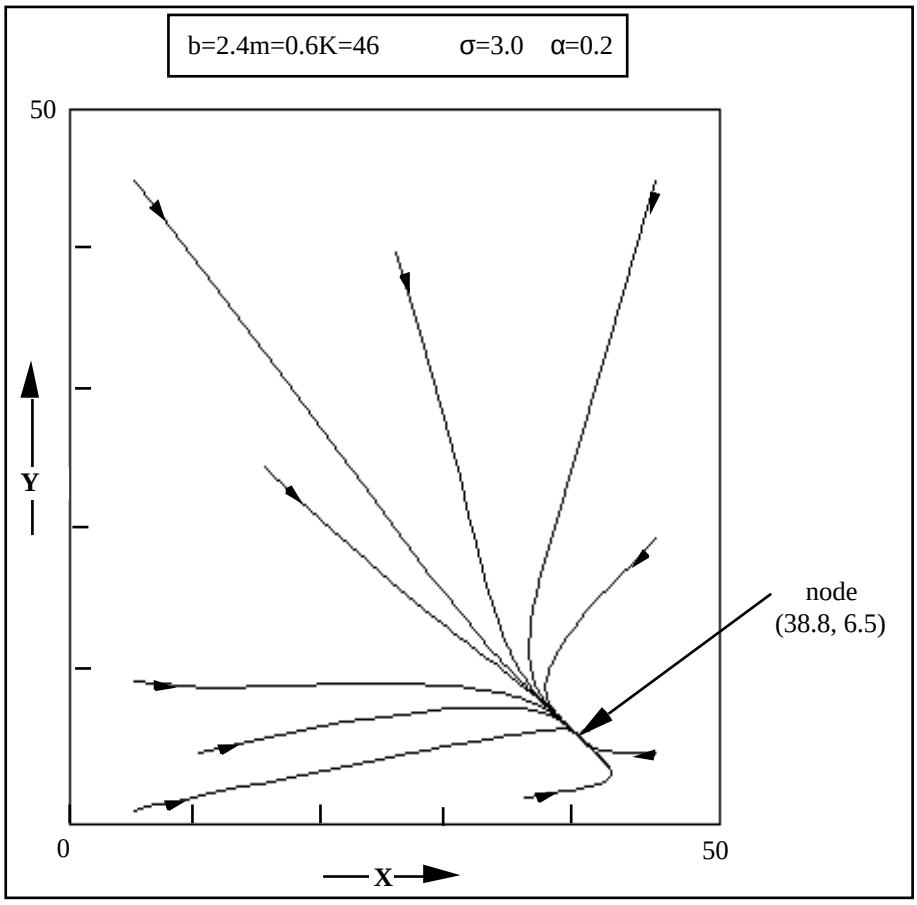


**Figure 2**: Phase portrait for different initial conditions of susceptible and infected individual numbers (*X* and *Y* individuals). Dynamics of FIV reach in any case an equilibrium point, or node, illustrating the stability of the model.

## 3 Results

### 3 1 Stability analysis

When the effective contact rate $\sigma$ is smaller or equal to the death rate $\alpha$ induced by the FIV, the ingoing flux of the infected class is lower than the outgoing flux, and the number of infected cats is decreasing: this is easily seen from equation (3). Hence

$0 < \sigma \leq \alpha$ implies $Y(t) \longrightarrow 0$ as $t \longrightarrow +\infty$

Thus, from now on, we assume $\sigma > \alpha$. This is a biologically realistic hypothesis, as the literature (Pedersen *et al.*, 1993) shows the length of FIV infection to be between 2 and 8 years ($0.5>\alpha>0.125$), and, as we will see, $\sigma$ is always larger).

Setting the time derivatives to zero in equations (2) and (3), we deduce that the following equilibrium solutions are possible:

$$X_1^* = 0 \text{ and } Y_1^* = 0$$

$$X_2^* = K \text{ and } Y_2^* = 0$$

$$X_3^* = \frac{bK\,(\alpha^2-\alpha\sigma+b\sigma+\alpha m-\sigma m)}{(\sigma-\alpha)^2\,(b-m)} \text{ and } Y_3^* = \frac{K\,(\sigma-\alpha-b)\,(\alpha^2-\alpha\sigma+b\sigma+\alpha m-\sigma m)}{(\sigma-\alpha)^2\,(b-m)}$$

provided the latter is positive. The first two equilibrium points correspond to trivial and uninteresting solutions: disappearance of either the disease or the population. The third one is non-trivial and interesting, and has also been obtained directly from computer program analyses (Mathematica Wolfram Research, Inc.). A detailed stability analysis which we summarize here is found in the Appendix.

To study the conditions of stability of those equilibria, we introduce two threshold parameters, both of them having a biological significance. According to the value of these parameters, one or the other equilibrium states will operate at a given time. According to Jacquez and coll. (1991), in a population at the equilibrium stage, the reproductive number, $R_o$, is "the number of infected individuals generated by one infective when all contacts of the infective are susceptibles". The disease will spread if and only if this number is greater than one. $R_o$ is defined as the average number of effective infectious contacts per cat per unit time multiplied by the mean duration of life of an infected cat when the population is at equilibrium stage. Hence, from equations (2) and (3), we obtain:

$$R_o = \frac{\sigma}{\alpha+b} \qquad (5)$$

In fact, at equilibrium N=K; thus $\alpha+r(N/K)+m = \alpha+b$ is the death rate induced by both disease and demography, $1/(\alpha+b)$ being the life expectancy of an infected cat. When

Ro ≤ 1, one has $Y(t) \longrightarrow 0$ and $X(t) \longrightarrow K$ over time: the epidemic disappears and the population will settle at its disease-free equilibrium number K (Anderson *et al.*, 1981; Bentil & Murray, 1993).

When Ro > 1, then the prevalence $y(t) = \frac{Y(t)}{N(t)}$ of infected individuals stabilizes to

$$y^* = 1 - \frac{b}{\sigma - \alpha} \qquad (6)$$

A second threshold parameters arises (see Appendix). Set

$$R_1 = \frac{b}{m + \alpha y^*} \qquad (7)$$

This is the "net reproductive cœfficient of the population when the disease is endemic" (Busenberg & Cooke, 1993). Still assuming $R_o > 1$, when $R_1 \leq 1$ the population becomes extinct ($N(t) \longrightarrow 0$), while when $R_1 > 1$, the disease remains endemic and approaches a unique equilibrium ($X(t) \longrightarrow X_3^*$ and $Y(t) \longrightarrow Y_3^*$).

### 3 2 Parameter estimations

Equilibria have been observed *in natura*, from a long-term study of three domestic cat populations in rural areas (12 years for Saint-Just-Chaleyssin (SJ) and Aimargues (AI), and three years for Barisey-La-Côte (BC), Pontier, 1984; 1993). Thus, we assume that $dN/dt=0$. As the serological state of individuals is only followed for two years, there is no indication whether we also have $dY/dt=0$. Nevertheless, as we know that an equilibrium state is dictated, only the three equilibrium points are possible solutions. Serological data indicate that $Y \neq 0$, hence we deduce that the only possible equilibrium state is when the disease is present within the population: $X = X_3^*$ and $Y = Y_3^*$. Thus, we have $dX/dt = dY/dt = 0$

At equilibrium, $dN/dt = 0$, hence, from equation (4): $rN(1-N/K) - \alpha Y = 0$.

Thus, $K = \frac{rN^2}{(rN - \alpha Y)}$

And from equation (3), we have $\sigma = \frac{N}{X}(\alpha + m + \frac{rN}{K})$

We thus have five parameters to consider (b, m, K, σ and α), two being deduced from biological data (b and m). Indeed, as mentioned above, the values of b and m are 2.4 and 0.6 respectively for rural populations, and 1.85 and 0.7 for the urban one. From the three remaining parameters, α is the "less unkown". The total length of infection (1/α) is still not known with precision, and may be highly variable: however, it is thought to be on average between three and six years (Moraillon, 1990; Pedersen & Barlough, 1991;

Sparger, 1993). Thus, we can express K and σ as functions of α, with values of α falling within a narrow range. Figure 3 shows values of σ and K, for the four studied populations and for values of 1/α varying more than expected in reality (from two to ten years). The variation of K and σ with values of α is not large, showing that α is not a major parameter of the model, after it reaches one year. This figure also shows the variation of $R_o$ and $R_1$ for different values of α: $R_o$ and $R_1$ are always greater than 1, leading to the third equilibrium point: ($X_3$*, $Y_3$*). The transmission rate, (λ), may be defined as the rate of effective bites received by a cat per unit of time (σ), multiplied to the proportion of infected cats in the population (λ=σy*). Thus 1/λ is the average time between two infections. Figure 3 also shows that the variation of values of 1/λ, according to the variation of α, is not important and that there is a great difference in values of transmission rates for the four populations, from an average time between infections of around one year, to one of around four years (LY and SJ on the one hand, and AC and BC on the other). We can also see that values of *N* are always less than but very close to K.

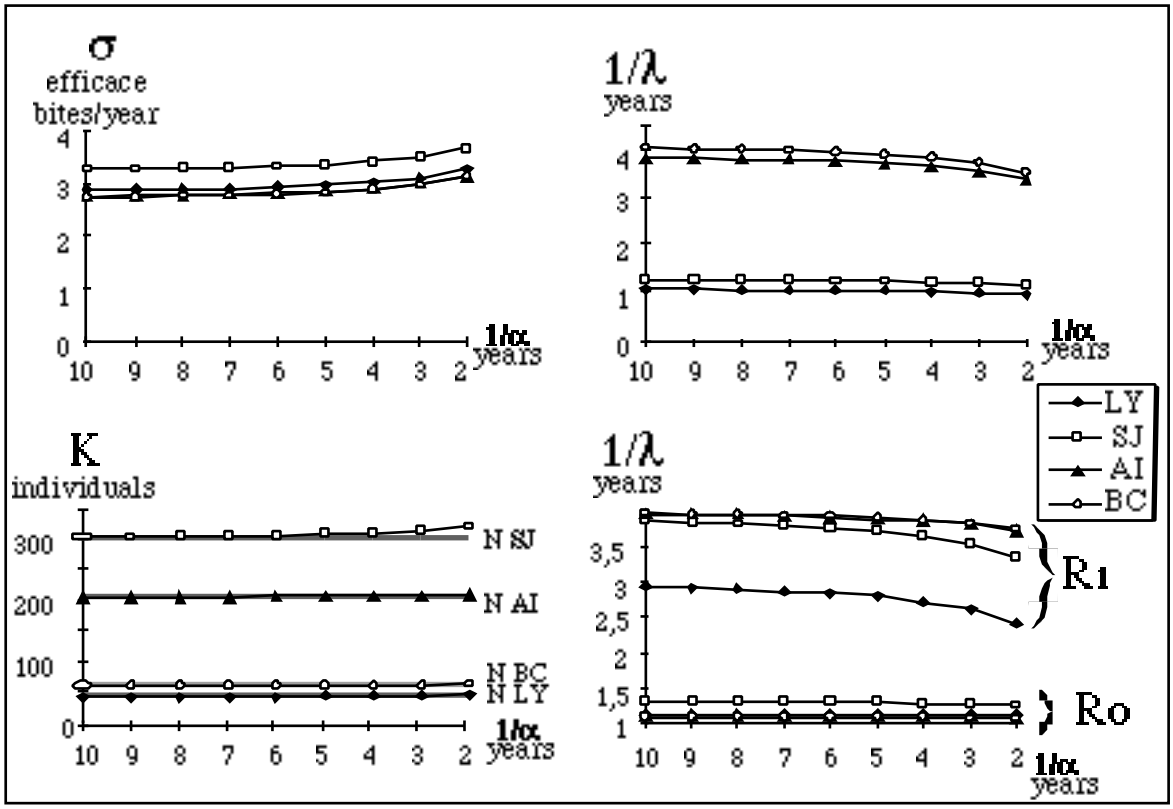


**Figure 3**: Influence of α on different parameters of the model for the four studied populations (Lyon (LY), Saint-Just-Chaleyssin (SJ), Barisey-La-Côte (BC) and Aimargues-Le-Cailar (AC)). 1/α is the infectious period length, σ the effective bite rate, 1/λ the average time between two infections, K the carrying capacity of the habitat in the absence of virus, and Ro the reproductive number. These parameters do not seem to be affected by variations in the death rate due to AIDS.

## 4 Discussion

The main results of the model are given below.

A-When FIV is introduced in a population of cats, infection inevitably develops and is maintained ($R_o$>1 and $R_1$>1). We have no means of verifying this experimentally (*i.e.* by introducing viruses within a natural population). However, FIV has been found everywhere in the world, even on some islands, and at relatively high rates (11.04% on average, on 59 FIV serosurveys (for a review, see Courchamp & Pontier, 1994). Moreover, we have serological proof of its presence in different parts of the world as far back as stored sera are available, which is 1974, 1972 or 1968, according to continents (Gruffydd-Jones *et al.*, 1988; Sabine *et al.*, 1988; Furuya *et al.*, 1990; Moraillon *et al.*, 1990; Shelton *et al.*, 1990).

B-The introduction of FIV does not lead to the extinction of susceptible or infected cats, but to a stable equilibrium stage of both categories, in proportions dependent upon parameters specific to the population ($dX/dt=dY/dt=0$). The stable equilibrium stage of the total population dynamics is observed *in natura* in several natural populations of cats, over more than twelve years (Pontier, 1993).

C-The impact of the virus, in terms of reduction of the population size at equilibrium, is not significant ($K \approx N$). We have no means of verifying this result, but it seems at least intuitively sensible, if we consider the life expextancy and infection duration ratio.

D-The transmission rate is always low ($1/\lambda$>1 year), confirming field observations that FIV is not very contagious (Shelton *et al.*, 1990). With the long duration of infection, this again is consistent with a low-impact virus.

In addition with to general properties of FIV dynamics within domestic cat populations, we also have determined that the transmission rate ($\lambda$) differs clearly according to the population. Thus the dynamics of FIV circulation within cat populations appears to be influenced by the characteristics of the host population. This result is not surprising as the spatial distribution of the cats in the local population, and more generally the population's biological properties (survival pattern, social structures, mating system and dispersal pattern) largely differ according to the fragmentation of human habitat (Pontier, 1993). This may in turn largely influence the pattern of diffusion of cat diseases. The highest transmission rates of FIV are obtained both in one of the rural cat populations (Saint-Just Chaleyssin) and in the urban cat population (Lyon). The former is characterized by a low cat density and a high degree of polygyny, and the latter by the highest density and a promiscuous mating system. The lowest rates of transmission are observed in the rural cat populations characterized by intermediate densities, and maybe by a lower degree of polygyny. Even if we cannot rule out the possibility that differences

in FIV prevalence rates between cat populations are partially linked to geographical position of these populations (LY and SJ populations are geographically close to each other), these differences should result mainly from the differences in behavioural mechanisms of the individuals. Thus it is crucial to investigate the behavioural mechanisms involved in the transmission of FIV.

In conclusion, it should be noted that, by design, the purpose of this model is more conceptualisation of the mechanisms of FIV transmission than predictions or precise parameter estimations. Nevertheless, the four points highlighted by the model, as well as obtained values for the estimated parameters, are in agreement with field observations and the literature. It is also interesting to note that these points support the hypothesis that the virus originally arose in the distant past. Considering both the worldwide repartition of FIV strains, and that many non-domestic felid species are infected by specific but very similar strains of FIV (Courchamp & Pontier, 1994), it can be hypothesized (Olmsted *et al.*, 1992) that FIV might have been present even before the speciation of felids, giving an interesting example of host-parasite coevolution.

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**Appendix**

**Mathematical Analysis**

When $\sigma \leq \alpha$, one gets $\frac{\sigma XY}{N} \leq \alpha Y$ because $X \geq 0$, $Y \geq 0$ and $X+Y=N$. Hence,

$$\frac{dY}{dt} \leq -[m + \frac{(b-m)}{K}) N ] Y(t) < 0 \text{ if } Y(t)>0$$

So that $Y(t) \longrightarrow 0$ as $t \longrightarrow +\infty$ when $\sigma \leq \alpha$

Assuming $\sigma > \alpha$ to hold, let us introduce the prevalence $y(t)$ and $x(t)=1-y(t)$:

$$y(t) = \frac{Y(t)}{N(t)} , \qquad x(t) = \frac{X(t)}{N(t)} .$$

One finds after some calculations two logistic equations:

$$\frac{dy}{dt} = [(\sigma-\alpha-b) - (\sigma-\alpha) y] y$$

$$\frac{dx}{dt} = [b-(\sigma-\alpha) x] (1-x).$$

Let us look at the dynamics of the prevalence; one has two equilibria:

$$y=0 \quad \text{and} \quad y^*=1-\frac{b}{(\sigma-\alpha)}.$$

Now $0 \leq y(t) \leq 1$ so that the latter is pertinent if and only if $\frac{b}{(\sigma-\alpha)}$ lies in [0,1]; from $\sigma > \alpha$ this is possible if and only if $Ro \geq 1$. As a first conclusion, it follows that,

- if $R_o \leq 1$ then $y(t) \longrightarrow 0$ and $x(t) \longrightarrow 1$ as $t \longrightarrow +\infty$,

- if $R_o > 1$ then $y(t) \longrightarrow y^*$ and $0 < y^* < 1$ as $t \longrightarrow +\infty$,

Let us now look at the dynamics of the total population $N$, given by (4).

When $R_o \leq 1$ the equation for N is asymptotically equivalent to (1); thus $N(t) \longrightarrow K$, $Y(t) = y(t)N(t) \longrightarrow 0$ and $X(t) \longrightarrow K$ as $t \longrightarrow +\infty$.

If $R_o > 1$ the equation for $N$ is asymptotically equivalent to

$$\frac{dN}{dt} = [(b-m-\alpha y^*) - \frac{(b-m)}{K} N] N.$$

Reintroducing the threshold parameter $R_1$, one gets

- if $R_1 \leq 1$ then $N(t)$ -> 0 and the population gets extinct: $X(t)$ —>0 and $Y(t)$ —>0 as

$t$ —> +∞,

- if $R_1 > 1$ then $N(t)$ —> $\frac{K(b-m-\alpha y^*)}{(b-m)}$ and an endemic state emerges: $X(t)$ —>$X^*$ and

$Y(t)$ —>$Y^*$ as $t$ —> +∞

with $X^* = \frac{bK\,(\alpha^2-\alpha\sigma+b\sigma+\alpha m-\sigma m)}{(\sigma-\alpha)^2\,(b-m)}$ and $Y^* = \frac{K\,(\sigma-\alpha-b)\,(\alpha^2-\alpha\sigma+b\sigma+\alpha m-\sigma m)}{(\sigma-\alpha)^2\,(b-m)}$

.

These results may be summarized in the following table:

| | | $y(t)$ | $N(t)$ | $X(t)$ | $Y(t)$ |
|---|---|---|---|---|---|
| $R_o \leq 1$ | | 0 | K | K | 0 |
| $R_o > 1$ | $R_1 \leq 1$ | $y^*$ | 0 | 0 | 0 |
| $R_o > 1$ | $R_1 > 1$ | $y^*$ | N* | X* | Y* |

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# CHAPTER VI

## MODELING THE FELINE LEUKEMIA VIRUS (FELV) IN NATURAL POPULATIONS OF CATS (*FELIS CATUS*)

## 1 Introduction

During recent years, knowledge and prevision for the epidemiology of parasitic diseases have greatly been improved with modelling techniques. Special interest is devoted to the Retroviridae family, due to the importance of Human Immunodeficiency Virus (HIV) infection. Numerous models have been proposed for this infection (Bailey, 1994), whereas the circulation of animal retroviruses had not been modelled until recently (Courchamp *et al.*, 1995).

Our interest is focused here on Feline Leukemia Virus (FeLV), a feline retrovirus (Jarrett *et al.*, 1973), and on its impact in natural populations of domestic cats (*Felis catus*). For this purpose, we build a deterministic model of FeLV circulation.

The first aim of this model is to study the importance of transmission parameters (which were previously estimated from experimental studies) on disease persistence and stability. We also evaluate the impact of the virus on cat populations growth.

Our second aim concerns the practical problem of eradication of infections. Mass vaccination or removal (culling) of infected individuals are the two main ways that are usually proposed to control parasitic or infectious diseases. For most diseases, both methods can be used, but the question remains which is better, both for economic and efficiency reasons. A classical example is that of fox rabies control in Europe, where a controversy remains between theoretical results (Anderson *et al.*, 1981, Smith and Harris, 1991, Aubert, 1994).

In the case of FeLV infection, vaccination of susceptible cats and removal of infected ones are possible and practised (Hardy *et al.*, 1976a, Hardy, 1993). The removal, the first possible method, was applied as soon as the first detection tests were available (Hardy *et al.*, 1976a). A large removal programme was applied in catteries in the Netherlands, which reduced the prevalence of cats positive for FeLV from 9% in 1974 to 3% in 1985 (Weijer *et al.*, 1986). The first vaccine was commercialized in 1985 (Pedersen *et al.*, 1985). All commercial vaccines were proved to protect cats from subsequent infection (Panel Report on the Colloquium on Feline Leukemia Virus/Feline Immunodeficiency Virus: tests and vaccination, 1991), but they require to keep on with the vaccination lifelong. No longitudinal survey has yet compared the prevalence of FeLV infection before and after a vaccination program, thus the efficiency of vaccination is not known at the population level. We investigate the question by studying the stability of models including either vaccination or removal measures. Then we discuss the interest of both measures taking into account their cost and benefit, and comparing FeLV and the control of other diseases.

## 2 Material and methods

### 2 1 Host populations

The spatial and social organization of populations of domestic cats, *Felis catus*, depends on their habitat (Pontier *et al.*, 1995). In rural as in urban areas, growth of cat populations is limited by environmental resources, such as food and shelters from human origin (Calhoon and Haspell, 1989).

Three rural cat populations have been monitored, since 1982 for Aimargues and Saint-Just Chaleyssin, and since 1990 for Barisey-la-côte. One urban cat population, Lyon-Croix-Rousse, has been monitored since 1992 (Pontier, unpublished). The main characteristics of the studied populations are given Table I. Annual birth and death rates per cat have been estimated from the Saint-Just Chaleyssin population (Legay and Pontier, 1985, Pontier, 1993). As the population size, sex ratio and age structure remain stable, mean fecundity and mortality rates were averaged on individuals of all ages, and were estimated as 2.4 and 0.6 per year, respectively (Pontier, unpublished).

We undertook an epidemiological study of the four cat populations since 1991. Serological status of a sample of cats is determined yearly to assay occurence of FeLV p27 antigen. A summary of the results obtained is given Table I. Few cats from these populations are medicalized (less than 5%, Pontier and Artois, unpublished), and nearly none have been vaccinated or tested for FeLV, thus we consider there is no direct human intervention on the virus circulation.

| **Population** | **Habitat** | **Density** (cats/km2) | **Population size** (cats) | **Sampling size** (cats) | **FeLV rate** (%) |
|---|---|---|---|---|---|
| St-Just-Chaleyssin | rural | 250 | 299 | 108 | 12.12 |
| Aimargues | rural | 120 | 203 | 124 | 3.80 |
| Barisey la-Côte | rural | 200 | 60 | 74 | 0 |
| Lyon | urban | 1100 | 40 | 42 | 0 |

**Table I:** The sampling size is given considering all four samplings per population. The sampling size may be higher than the population size, as the sampling size includes all cats sampled during the four years of study. FeLV antigen-positive cats were detected with the ELISA test. Data from Pontier and Artois unpublished.

### 2 2 Virus

The Feline Leukemia Virus (FeLV) is an oncogenic and immunosuppressive virus of the domestic cat (for a review see Hardy, 1993). FeLV belongs to the Retroviridae family and the Oncovirinae subfamily, like Human T-Lymphotropic Viruses (Jarrett *et al.*, 1973, Wong-Staal and Gallo, 1985). Its transmission mode may be epigenic, from queen to foetus during pregnancy (Hoover *et al.*, 1983), or horizontal, mainly by saliva

(by biting, liking or sharing the same feeding plates, Rojko and Olsen, 1984). The force of infection depends on the transmission rate, i.e. the number of effective contacts per unit of time when one infectious host is present (Capasso 1993). The transmission rate was calculated by evaluating experimentally its inverse, *i.e.* the time between the first contact with a contagious individual and the onset of infection, detected by the apparition of viremia. In this purpose, the development of infection was studied among susceptible cats exposed to a contaminated environment (Pedersen *et al.*, 1977, Grant *et al.*, 1980). The mean duration before infection was between 3.4 and 13 months according to the age of cats, which means a transmission rate between 0.96 and 3.48 per year.

The clinical course of FeLV infection begins with a phase of transient infection lasting up to four months (Hardy *et al.*, 1973, Rojko *et al.*, 1979). Transiently infected cats are considered as a minor source of infection, as the virus excretion is very low (Francis *et al.*, 1979). This stage may lead to two possible outcomes.

First, a large proportion of the infected cats (65%, Hoover and Mullins, 1991) stops the virus replication, and becomes immune to reinfection (Rojko *et al.*, 1979). These cats may be considered as clinically recovered, and seem to stay immunized for life, although this question is still discussed (Hardy *et al.*, 1976b, Pacitti, 1985, Charreyre and Pedersen, 1991). The immune cats are no longer contagious, and have a normal life expectancy (McClelland *et al.*, 1980, Francis and Essex, 1980, Rojko *et al.* 1982). Immunized females give birth to kittens which are passively protected by maternal antibodies during a few weeks, and then become susceptible (Hoover *et al.*, 1983).

Thirty to 40% of the infected cats fails to develop the appropriate immune response and becomes persistently viremic (Hardy *et al.*, 1976b). The viremia remains lifelong and causes various proliferative or immunosuppressive disorders which lead to death within a few weeks to several years. Francis and Essex (1980) estimated the mean duration between infection and death of viremic cats to 20.9 months, which means a mortality rate of 0.57 per year. Data from three others authors bring to annual mortality rates of 0.51, 0.53 and 0.51 (Weijer and Daams, 1976, Hardy, 1980, Ishida *et al.*, 1981), calculated on 20, 36 and 14 months respectively, and assuming a constant mortality rate. Moreover, the fertility of viremic queens is strongly reduced, as 80% of pregnancies lead to abortion, and the few live kittens are viremic at birth and die early (Hoover *et al.*, 1983).

The following model will take into account population parameters (birth and death rates, evaluated to 2.4 and 0.6 per year in the Saint-Just Chaleyssin population) and parameters characterizing the dynamics of the infection: the transmission rate (here we will use the value of 2 per year), the proportion of infected cats that become persistently viremic (0.33), and the specific mortality rate of persistently viremic cats (0.53 per year, which is the value estimated with the largest sample size).

## 2 3 Model of FeLV circulation

The model developped and analysed here is based on Anderson and May's work (e.g. Anderson and May, 1991). The total number of cats at time *t* is denoted *N*. Let *b* be the natural birth-rate and let *m* be the natural death-rate so that *r* = *b* - *m* is the intrinsic growth-rate of the cat population in absence of ressource limitations and epidemic. The former acts through density-dependence on the death rate which takes the form $(m + r\frac{N}{K})$ where *K* is the carrying capacity of the habitat, while the birth-rate remains constant, given by *b*.

When the population is free from FeLV infection, the dynamics of the total population is governed by the logistic model (Verhulst, 1838):

$$\frac{dN}{dt} = rN(1 - \frac{N}{K}) \qquad (1)$$

When the virus is present, we assume that cats may be divided into three categories, according to the clinical stage: susceptible (denoted *X)*, persistently viremic (*Y*) and immune (*Z*) cats. For sake of simplicity, we do not consider transient viremic cats as a category, as we assume that this stage (lasting two to four months) is short enough to be neglected regarding to the duration of life or infection of cats (several years). The compartmental representation is presented Figure 1.

We call $\sigma$ the transmission rate of the infection, per year. Like for other retroviruses, we considered that infectious contacts, depending on the social behaviour of individuals, do not increase with population size (Capasso, 1993, Courchamp *et al.*, 1995). The force of infection was formulated according to the proportionate mixing model, which considers that the incidence of infection is a function of the proportion, rather than the number, of infected individuals (Hethcote and Yorke, 1984, in Capasso, 1993, Hethcote and Van Ark, 1987).

When cats are infected, they become either persistently viremic (in proportion $\pi$), or immune (1-$\pi$). Immune and susceptible cats have a normal life expectancy and reproduction. We considered that kittens born from immune females are as susceptible as adult cats. We also assume that infected queens do not participate anymore in reproduction, as their progeny die as foetus or kittens (Hoover *et al.*, 1983). The persistently viremic cats have a specific mortality rate $\alpha$ due to FeLV infection.

We first consider that there is no vaccination nor removal of any cat, which is close to what is observed in our studied cat populations (Pontier and Artois, unpublished).

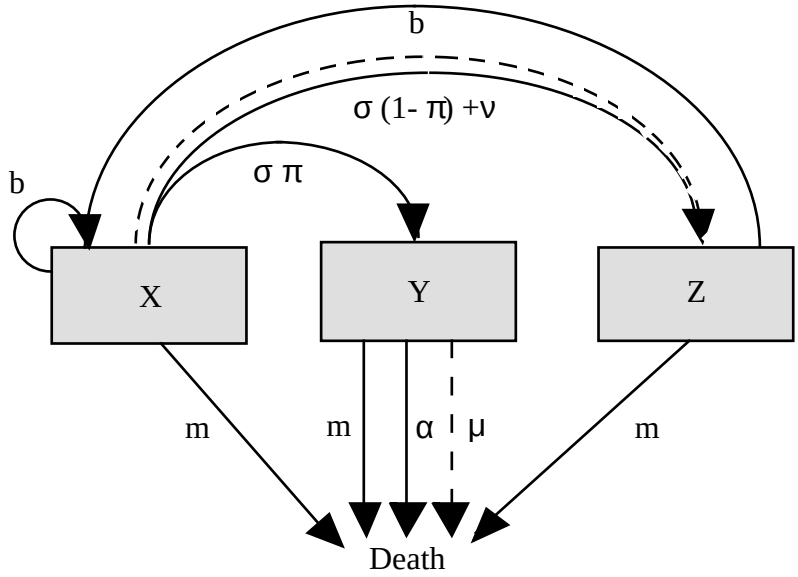


**Figure 1:** Susceptible individuals are denoted *X*, persistently viremic ones are *Y*, and immune cats are *Z*. Transient infected cats are not considered as a category, and only susceptible and immune cats take part in the reproduction. Viremia or immunity stages are not reversible and immune cats have the same life expectancy than susceptible ones. b is the birth rate, m the intrinsic death rate, σ the transmission rate, π the proportion of infected cats that become persistently viremic, and α the mortality rate due to FeLV infection. Dotted lines show the prophylaxis measures, with ν=vaccination rate of susceptible cats and μ=removal rate of infected cats.

Finally, the dynamics of cat population may be described by the following set of differential equations:

$$\frac{dX}{dt} = b(X+Z) - mX - r\frac{N}{K}X - \sigma\frac{XY}{N} \qquad (2)$$

$$\frac{dY}{dt} = \sigma\frac{XY}{N}\pi - mY - r\frac{N}{K}Y - \alpha Y \qquad (3)$$

$$\frac{dZ}{dt} = \sigma\frac{XY}{N}(1-\pi) - mZ - r\frac{N}{K}Z \qquad (4)$$

The equation for the total population *N* is obtained by adding the three previous ones:

$$\frac{dN}{dt} = rN(1-\frac{N}{K}) - (b+\alpha)Y \qquad (5)$$

Simulations of the models have been carried out with the computer program Dynamac (Rousseau, 1988), using the parameters values previously estimated in the literature.

**Modelling FeLV prophylaxis**

Our aim is to compare the efficiency of control programmes, as two types of measures have been recommended to control FeLV infection, removal of infected cats and vaccination of susceptible ones.

The previous model was modified to take into account the two prophylaxis means. First, let $\nu$ be the instantaneous vaccination rate of susceptible cats. We considered that only susceptible cats are vaccinated, and that the vaccine is completely efficient lifelong, which is consistent with what is known about vaccination. Equations (2) and (4) are respectively modified as follows:

$$\frac{dX}{dt} = b(X+Z) - mX - r\frac{N}{K}X - \sigma\frac{XY}{N} - \nu X \qquad (2')$$

$$\frac{dZ}{dt} = \sigma\frac{XY}{N}(1-\pi) + \nu X - mZ - r\frac{N}{K}Z \qquad (4')$$

Equations (3) and (5) are not modified.

For the second control measure, we considered that the persistently viremic cats are removed at a per capita rate $\mu$. Only equations (3) and (5) are changed from the first model, and become:

$$\frac{dY}{dt} = \sigma\frac{XY}{N}\pi - mY - r\frac{N}{K}Y - \alpha Y - \mu Y \qquad (3')$$

$$\frac{dN}{dt} = rN(1-\frac{N}{K}) - (b+\alpha+\mu)Y \qquad (5')$$

The model with both possible measures is presented Figure 1. In order to compare the two measures, we consider that they are not applied together. A stability analysis of the model with both vaccination and elimination is performed in the Appendix.

## 3 Results

### 3 1 Stability analysis

Setting the time derivatives to zero in equations (2), (3), (4) and (5), we find after some calculations three stationary points:

$$X_1^* = Y_1^* = Z_1^* = 0$$

$$X_2^* = K, Y_2^* = Z_2^* = 0$$

$$X_3^* = x^* N^*, Y_3^* = y^* N^*, Z_3^* = N^* - X_3^* - Y_3^*$$

wherein

$$x^* = \frac{(\sigma - \alpha)(b + \alpha) - \sigma\pi b}{\sigma\pi\ (\sigma - b - \alpha)}, \quad y^* = \frac{b(\sigma\pi - b - \alpha)}{(b + \alpha)(\sigma - b - \alpha)}, \quad N^* = K\left[1 - \frac{b(\sigma\pi - b - \alpha)}{r(\sigma - b - \alpha)}\right]$$

provided 0<x*, y*<1.

The first two possibilities correspond to trivial solutions: eradication of either the cat population or the disease. The third one is the most interesting equilibrium point where the disease persists within the population. As expected, the total size of the population $N^*$ is less than the carrying capacity K. The depression of the population size is $\frac{b(\sigma\pi - b - \alpha)}{r(\sigma - b - \alpha)}$.

We show (Appendix) that there is a first threshold parameter, the reproductive number

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

The trivial state $(X_2^*, Y_2^*, Z_2^*)$ is stable if and only if $R_0 < 1$; furthermore introducing a secondary threshold parameter

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

one shows that when $R_0 > 1$,

$R_1 \leq 1$ implies N(t)–0 as t goes to +∞ and so do *X(t), Y(t), Z(t)*

while

$R_1 > 1$ implies $X(t)–X^*$, $Y(t)–Y^*$ and $N(t)–N^*$.

### 3 2 Parameter estimation

With the above condition for the existence of a non-trivial solution, it is possible to re-estimate the value of σ, from the other parameters value estimated in the literature. We assume that birth and death rates (b=2.4, m=0.6), proportion of infected cats becoming persistently viremic (π=0.33), and specific mortality rate (α=0.53) are the "less unknown" parameters, as they have been estimated from large samples, and by several authors for α.. The condition $1 < \frac{\sigma\pi}{(b+\alpha)}$ implies σ>8.9, whereas the experimentally estimated value for σ is 0.96 to 3.48 according to age of cats. This discrepancy will be discussed below.

### 3 3 Simulations

Simulations of this model are presented Figure 2. For birth rate, death rate, proportion of infected cats that become persistently viremic and specific mortality rate for persistently viremic cats, we used the parameter values estimated in the literature (*i.e.* respectively b=2.4, m=0.6, π=0.33 and α=0.53). As expected with the parameter estimation, a simulation using the literature-estimated value for the transmission rate σ (0.96 to 3.48) led to the second trivial solution, *i.e.* extinction of the disease from the population (simulation not shown). Then we arbitrarily chose for σ a value higher than 8.9, (σ=10 in Figure 2), in order to fill the condition for a non-trivial solution. In this case, the FeLV prevalence y* is 4.28% and the depression of host population size is 6.98%. If we use the extreme values estimated for π and α (*i.e.* 0.3 to 0.4 for π and 0.51 to 0.57 for α), the estimated prevalence is ranging from 0.8 to 12.4%, and the depresssion of host population size from 1.34 to 20.18%.

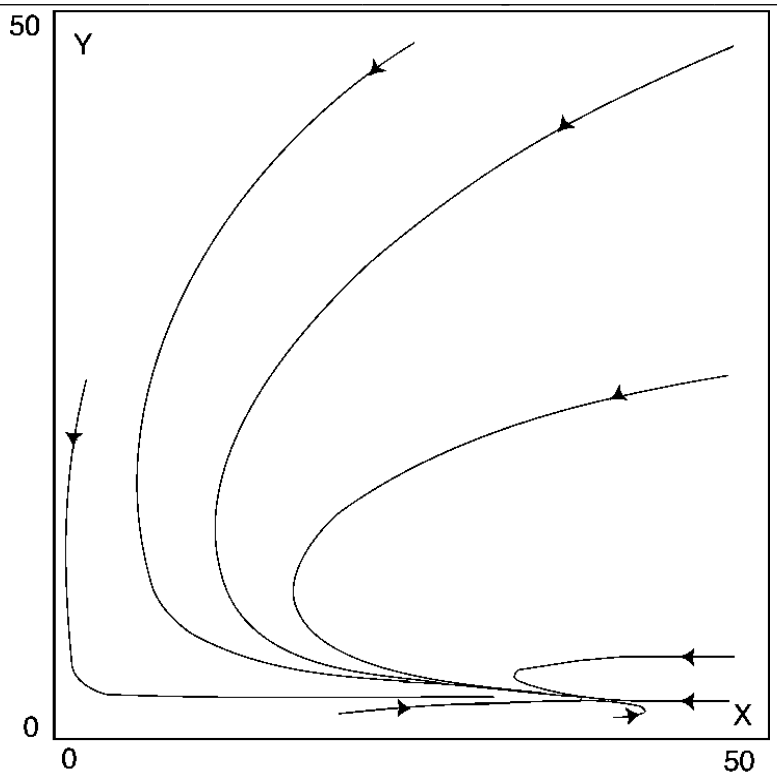


**Figure 2:** Phase portrait for different initial conditions of susceptible (*X*) and persistently viremic individuals (*Y*). Dynamics of the population reaches an equilibrium point for *X*, *Y* and *Z*. Here, b=2.4, m=0.6, σ=10, π=0.33, α=0.53, K=50. At the equilibrium, *X**=39.53, *Y**=1.99, *Z**=4.99, *Y**/*N**=4.28%.

### 3 4 Prophylaxis

#### 3 4 1 Impact of prophylaxis

In the first prophylaxis program, *i.e.* vaccination, the stability analysis performed in Appendix yields modified threshold parameters

$$R_0^V(\nu) = R_0(0,\nu) = \frac{\sigma\pi b}{(b+\alpha)(b+\nu)},$$

$$R_1^V(\nu) = R_1(0,\nu) = \frac{b}{m+(b+\alpha)y_3}.$$

The dynamics are similar to the one without any prophylaxis program with modified values $x_3^*, y_3^*$ and $N_3^*$ given in (A8), (A9) and (A10).

In the second prophylaxis program, *i.e.* removal of infected cats, the modified threshold parameters now are

$$R_0^R(\mu) = R_0(\mu, 0) = \frac{\sigma\pi}{b+\alpha+\mu},$$

$$R_1^R(\mu) = R_1(\mu,0) = \frac{b}{m+(b+\alpha+\mu)y_3}.$$

The dynamics is modified accordingly: see Appendix.

### 3 4 2 Comparing prophylaxis programs

Assume that $R_0 = \frac{\sigma\pi}{(b+\alpha)} > 1$ so that the disease free trivial equilibrium is unstable. For large enough $\nu$ or $\mu$ this equilibrium becomes stable again.

More specifically, in the vaccination program, the minimal value for the vaccination rate $\nu$ is $\nu_0$ so that $R_0(0,\nu_0) = 1$ say

$$\nu_0 = \frac{b}{b+\alpha}\sigma\pi - b = b\left[\frac{\sigma\pi}{b+\alpha} - 1\right]$$

In the elimination program, the minimal value for $\mu$ is $\mu_0$ so that $R_0(\mu_0,0) = 1$ say

$$\mu_0 = \sigma\pi - (b+\alpha) = (b+\alpha)\left[\frac{\sigma\pi}{b+\alpha} - 1\right]$$

Clearly one has $0<\nu_0<\mu_0$ as long as $\alpha>0$. Hence if one is only interested in the respective magnitude of the effort parameters $\nu$ and $\mu$, the vaccination program is more efficient than the removal of infected cats.

One may also check that when $R_0 = \frac{\sigma\pi}{(b+a)} > 1$ then

$$R_0^V(x) < R_0^R(x), \quad 0 < x < \nu_0.$$

## 4 Discussion

### 4 1 Circulation of the FeLV virus

The prevalence rate calculated with the model, using the extreme parameter values proposed in the literature, ranges from 0.8 to 12.4%. The observed rates in the studied populations (for which FeLV is present) are in this same range of values (4.84±1.93% for Aimargues and 11,11±3.02% for Saint-Just Chaleyssin), which

suggests that those parameter values are realistic ones. However, such a comparison must be only qualitative, as the parameter evaluation is not accurate.

When introduced in an homogeneous cat population, with the condition that $1 < R_0$, the infection is maintained, leading to a stable equilibrium, where the host population size is less than the carrying capacity K. The host population depression (6.98%) is weak but detectable. This result suggests stable behaviour for the disease, which actually occurs as an endemic infection all over the world. For example, authors found prevalence rates such as 13.6% in U.S.A. (Ehrlund and Adams, 1984), 2.6% in Australia (Wilkinson and Thompson, 1987), 23.1% in Chile (Correa *et al.,* 1989), 4.5% in United Kingdom (Hosie *et al.,* 1989), 3.2% in Japan (Ishida *et al.,* 1981), or 12.5% in Senegal (Alogninouwa *et al.,* 1992).

### 4 2 Parameter estimation

Among the three parameters describing the disease transmission, two (proportion of infected cats becoming persistently viremic $\pi$ and specific death rate for persistently viremic cats $\alpha$) are measurable directly. Such measures were made experimentally (Hardy *et al.,* 1976b, Weijer and Daams, 1976, Francis and Essex, 1980, Hardy, 1980, Ishida *et al.,* 1981), and, although only a few studies are available, we assume those results are accurate.

The estimation of the transmission rate $\sigma$ is one of the most interesting results of the model. Although our model does not allow us to study this parameter extensively, the first estimation shows that $\sigma$ should be much higher (at least 8.9 contacts per year) than observed before (0.96 to 3.48, Grant *et al.,* 1980). But the observed value may have been largely underestimated: the time between the first contact with a viremic cat and the detection of viremia varies from 3.3 to 13 months (Grant *et al.,* 1980), but the test used does not detect early infection (Hardy *et al.,* 1973).

### 4 3 Impact of the prophylaxis

In term of quantitative results, the analysis of the model including prophylaxis permits to conclude that vaccination of susceptible individuals is more efficient than removal of infected ones. Using the same kind of model, divergent results have been obtained, according to disease. Vaccination has been found to be the best way to control rabies in red foxes (*Vulpes vulpes*), particularly in low and medium density fox populations (Anderson *et al.,* 1981), while Barlow (1991) showed that bovine tuberculosis in New Zealand possum (*Trichosurus vulpecula*) populations is better controlled by culling. The differences in the pathogenesis of the diseases may explain this discrepancy. The type of model used to represent the virus circulation also explained the different results obtained. Using a spatial stochastic model and taking into account the role of fox population heterogeneity on the transmission of rabies, Smith

and Harris (1991) found that vaccination may increase the total fox density, and subsequently rabies incidence. Field results showed that vaccination is much more efficient than culling alone (Aubert *et al.*, 1994), although it may suffer a relative failure in some places (Aubert, 1995). Thus characteristics of both population and disease are important parameters to take into account to model the impact of prophylaxis measures.

Moreover, the quantitative results concerning FeLV infection are not comparable to rabies or tuberculosis. The FeLV tests reveal whether a cat is contagious or not, so that it is possible to eliminate only seropositive cats and to immunize only negative cats, while vaccinating or culling programs for fox rabies involve healthy as well as rabid animals, so that the proportion of individuals to be treated is not comparable.

Finally, a good measure of efficiency must take into account the cost and benefit of each proposal. The cost of FeLV prophylaxis must take into account several aspects. First, the cost of both FeLV tests and vaccines is supported by volunteer cat owners. Secondly, FeLV infection is not considered as dangerous for public health. Consequently, there is no obligatory prophylaxis for FeLV control, contrary to fox rabies or bovine tuberculosis (but we can imagine that a prophylaxis plan could start in order to protect wild felids like the European wild cat *Felis silvestris,* which may be threatened by FeLV infection, Artois and Remond, 1994). Lastly, the psychological cost of a removal programme for FeLV control is heavy, because of the affective importance of cats. In conclusion, for all of these reasons, and for its higher efficiency, vaccination seems to be the best way to eradicate FeLV infection. A prophylaxis programme using both vaccination and elimination would be necessarily more efficient (Annex), but, as discussed above, in the field, both measures have not the same cost, and elimination may only be considered as a complementary measure of a vaccination plan.

### 4 4 Model used

Compartmental models are particularly interesting for their simplicity and for they have been extensively studied (see for example Capasso, 1993), but they also include some constraints which may invalid the conclusions concerning the disease studied. First, the chosen model assumes that the rates of crossing between the compartments are constant, which means that the characteristics of the population, environment and disease do not evolve with time. However, this is a good hypothesis if we consider a short-term period so that the environment is stable, and we may consider that the population characteristics are stable too, as this stability has been observed in our more than ten year study period (Pontier, unpublished). Moreover, our epidemiological study is in accordance with the results of the model: the prevalence rates for the five years of study ranging from 1.92 to 5.45% for Aimargues, and from 8.70 to 17.07% for Saint-Just Chaleyssin, with no significant tendency between years, which suggest that prevalence is at equilibrium (Fromont *et al.*, in prep.).

A particular constraint is linked to the choice of the logistic model, relating to the choice of density dependent parameters. The fact that birth rate is constant at the population level is actually established in rural populations (Pontier, unpublished), but the density-dependence of mortality rate is more difficult to observe. This density-dependence can lead to an excessive stability which may not exist in reality. However, the model results, *i.e.* a global stability of the population size around the carrying capacity of the habitat K, seems convincing compared to our long-term study (Pontier, unpublished), and to our epidemiological results (Fromont *et al.*, in prep.).

The third implicit hypothesis of the model is to consider both population and environment as homogeneous. Actually, this is not true either for the individuals, or for the environment. Differences exist in individual behaviour between cats according to their age and sex (Liberg, 1981, Turner and Bateson, 1988), and also according to population (Liberg and Sandell, 1988, Pontier *et al.,* 1995). Moreover, the spatial structure of cat populations is highly variable (Pontier, 1993), from dispersed cat groups in rural areas where human habitat in scattered, to clustered and isolated populations where the resources are heterogeneously distributed as in urban areas (Natoli and de Vito, 1988). Such variability may influence the transmission of infection, as it was found theoretically for fox rabies (Smith and Harris, 1991). Actually, prevalence of FeLV infection differs with their sex and age. Males are more often infected than females (Hosie *et al.*, 1989), and, although kittens are more susceptible to the virus, cats aged 3-5 years are more often infected, due to their higher exposure (Weijer and Daams, 1976, Grant *et al.,* 1980, Hosie *et al.*, 1989). Moreover, our epidemiological results show that two out of the four studied populations are free from FeLV infection (Table I), and a more detailed study suggests that the spatial structure of cat populations, and in particular its total size, may influence FeLV circulation (Fromont *et al.*, in prep.). To analyze FeLV persistence within populations according to populations characteristics, it thus seems necessary to take into account a fair amount of spatial structuring. Our future work will use another type of model which takes into account explicitely the spatial structure of cat populations.

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## Appendix

## Mathematical Analysis

Let *X(t)*, *Y(t)* and *Z(t)* be the respective numbers of susceptible, persistently viremic and immune cats at time *t*. Thus *X(t) + Y(t) + Z(t) = N(t)* represents the total population at time *t*. We consider the set of differential equations describing the dynamics of the cat population with both removal of infected cats and vaccination of susceptible ones, namely

$$\frac{dX}{dt} = b(X+Z) - mX - r\frac{N}{K}X - \sigma\frac{XY}{N} - vX, \tag{A1}$$

$$\frac{dY}{dt} = \sigma\frac{XY}{N}\pi - mY - r\frac{N}{K}Y - \alpha Y - \mu Y, \tag{A2}$$

$$\frac{dZ}{dt} = \sigma\frac{XY}{N}(1-\pi) - mZ - r\frac{N}{K}Z + vX. \tag{A3}$$

The differential equation for the total population $N$ is derived upon adding (A1)-(A3), say

$$\frac{dN}{dt} = rN(1-\frac{N}{K}) - (b+\alpha+\mu)Y; \tag{A4}$$

recall $r = b - m$. Let us introduce the proportions $x = X/N$, the prevalence $y = Y/N$ and $z = Z/N$ so that $0 \le x,y,z \le 1$ and $x + y + z = 1$. One may express the time derivative of $x = X\frac{1}{N}$ as

$$\frac{dx}{dt} = \frac{1}{N}\frac{dX}{dt} - \frac{X}{N^2}\frac{dN}{dt};$$

substituting in this relation the explicit expressions of *dX/dt* and *dN/dt* given by the right hand sides of (A1) and (A4) and using the simplification $z = 1 - x - y$, one gets after cautious algebraic manipulations

$$\frac{dx}{dt} = b - (b+v)x - by - (\sigma - b - \alpha - \mu)xy. \qquad \text{(A5)}$$

Along the same lines one finds

$$\frac{dy}{dt} = \left[\sigma\pi x - (b+\alpha+\mu) + (b+\alpha+\mu)y\right]y. \qquad \text{(A6)}$$

Lastly, the identity $Y = yN$ allows to rewrite the differential equation (A4) as

$$\frac{dN}{dt} = N\left[r(1-N/K) - (b+\alpha+\mu)y\right]. \qquad \text{(A7)}$$

*Stability analysis of the prevalence*

Looking for the stationary states of Equations (A5) and (A6) one gets two semitrivial states

$$y_1^* = 0, \quad x_1^* = \frac{b}{b+v};$$
$$y_2^* = 1, \quad x_2^* = 0$$

and after some new algebraic manipulations or using a suitable software system for symbolic computation

$$y_3^* = \frac{\sigma\pi b - (b+\alpha+\mu)(v+b)}{(b+\alpha+\mu)(\sigma - b - \alpha - \mu)} = \frac{(\sigma\pi - b - \alpha - \mu)b - (b+\alpha+\mu)v}{(b+\alpha+\mu)(\sigma - b - \alpha - \mu)}, \qquad \text{(A8)}$$

$$x_3^* = \frac{(\sigma - \alpha - \mu + v)(b+\alpha+\mu) - \sigma\pi b}{\sigma\pi(\sigma - b - \alpha - \mu)}; \qquad \text{(A9)}$$

this latter is feasible provided $0 < x_3^*, y_3^* < 1$ and $0 \le x_3^* + y_3^* \le 1$.

The jacobian matrix of (A5)-(A6) reads

$$J(x,y) = \begin{pmatrix} -(b+\nu)-(\sigma-b-\alpha-\mu)y & -b-(\sigma-b-\alpha-\mu)x \\ \sigma\pi y & \sigma\pi x-(b+\alpha+\mu)+2(b+\alpha+\mu)y \end{pmatrix}$$

The first stationary state supplies the threshold parameter $R_0$. One has

$$J(x_1^*, y_1^*) = \begin{pmatrix} -(b+\nu) & -b-(\sigma-b-\alpha-\mu)\frac{b}{b+\nu} \\ 0 & \sigma\pi\frac{b}{b+\nu}-(b+\alpha+\mu) \end{pmatrix};$$

hence $(x_1^*, y_1^*)$ is (locally) stable if and only if

$$R_0(\mu,\nu) = \frac{\sigma\pi b}{(b+\nu)(b+\alpha+\mu)} < 1.$$

The second stationary state is always unstable. Actually the determinant and the trace of the jacobian matrix at $(x_2^*, y_2^*)$ are given by

$$\det J(x_2^*, y_2^*) = \sigma\pi b-(b+\alpha+\mu)(\sigma+\nu)+(b+\alpha+\mu)(\alpha+\mu),$$
$$\mathrm{Tr}J(x_2^*, y_2^*) = b+\alpha+\mu-(\sigma-\alpha-\mu+\nu).$$

Assuming first $R_0(\mu,\nu) \geq 1$ it follows $b+\alpha+\mu < \sigma$ using this inequality in the last term on the right hand side of the equation for the determinant one finds

$$\det J(x_2^*, y_2^*) \leq (\sigma\pi-\sigma-\nu)(b+\alpha+\mu) < 0,$$

because $0 \leq \pi < 1$, yielding instability.

Next when $R_0(\mu,\nu)<1$ one gets $\sigma\pi b<(b+\nu)(b+\alpha+\mu)$ and thus from the equation for the determinant

$$\det J(x_2^*,y_2^*)<(b+\alpha+\mu)(b-\sigma+\alpha+\mu);$$

if $TrJ(x_2^*,y_2^*)>0$ the stationary state is unstable while $TrJ(x_2^*,y_2^*)\le 0$ implies

$b-\sigma+\alpha+\mu\le\nu-\alpha-\mu$ so that

$$\det J(x_2^*,y_2^*)<(b+\alpha+\mu)(\nu-\alpha-\mu)$$

and $(x_2^*,y_2^*)$ is unstable as soon as $\nu\le\alpha+\mu$.

Lastly, irrespectively of $R_0(\mu,\nu)$ if $\alpha+\mu<\nu$ then

$$\det J(x_2^*,y_2^*)<\sigma\pi b-(b+\alpha+\mu)\sigma=\sigma(\pi b-b-\alpha-\mu)\le 0.$$

Hence (0,1) cannot be stable.

As far as the non trivial stationary state is concerned one first shows that it is feasible if and only if $R_0(\mu,\nu)>1$. Actually when this holds $y_3^*>0$: the numerator of the first fraction in (A8) is positive and so does its denominator because $b+\alpha+\mu<\sigma$, as noted earlier in this case; next, removing the negative term at the numerator of the second fraction in (A8) one gets $y_3^*<1$. From (A6), any positive stationary state is a solution of

$$0=\sigma\pi x^*-(b+\alpha+\mu)(1-y^*); \qquad \text{(A10)}$$

thus $R_0(\mu,\nu)>1$ implies

$$0<x_3^*\le\frac{b+\nu}{b}\frac{b+\alpha+\mu}{\sigma\pi}(1-y_3^*)<1$$

and $(x_3^*, y_3^*)$ is feasible provided one shows $0 \le x_3^* + y_3^* \le 1$ which is left to the reader. Now assuming $R_0(\mu, v) \le 1$. and $b + \alpha + \mu < \sigma$ one has $y_3^* \le 0$. The remaining case is $R_0(\mu, v) \le 1$ and $b + \alpha + \mu > \sigma$; if $(x_3^*, y_3^*)$ is feasible then $0 \le x_3^* \le 1 - y_3^*$ and it follows from Equation (A10) that

$$0 \le (\sigma\pi - b - \alpha - \mu)(1 - y_3^*) < 0$$

a contradiction.

Going back to the stability of $(x_3^*, y_3^*)$ one has

$$TrJ(x_3^*, y_3^*) = -v\frac{b + \alpha + \mu}{\sigma - b - \alpha - \mu} - \frac{\sigma\pi b}{b + \alpha + \mu} + \frac{\sigma\pi - b - \alpha - \mu}{\sigma - b - \alpha - \mu} b.$$

Now $R_0(\mu, v) > 1$ implies $\sigma > \sigma\pi > b + \alpha + \mu$ so that

$$0 < \frac{\sigma\pi - b - \alpha - \mu}{\sigma - b - \alpha - \mu} < 1$$

while

$$\frac{\sigma\pi}{b + \alpha + \mu} > \frac{\sigma\pi b}{(b + \alpha + \mu)(b + \nu)} = R_0(\mu, \nu) > 1.$$

Thus $\mathrm{TrJ}(x_3^*, y_3^*) < 0$. Lastly from (A5) and (A6) $(x_3^*, y_3^*)$ is a solution of

$$(b + \nu) + (\sigma - b - \alpha - \mu) y_3^* = b\frac{1 - y_3^*}{x_3^*} = b\frac{\sigma\pi}{b + \alpha + \mu};$$

using these relations the determinant can be written

$$\det J(x_3^*, y_3^*) = \sigma\pi(\sigma - b - \alpha - \mu) x_3^* y_3^* > 0.$$

Hence $(x_3^*, y_3^*)$ is (locally) stable as long as it exists.

*Stability with prophylaxis*

In this setting when $R_0(\mu,\nu) < 1$ the prevalence *y(t)* goes to 0 as *t* goes to $+\infty$; Equation (A7) for *N* is asymptotically equivalent to the logistic equation (1) so that as *t* goes to $+\infty$

$$N(t) \to K, X(t) \to \frac{b}{b+\nu} K, \quad \text{Y(t)} \to 0 \text{ and } Z(t) \to \frac{\nu}{b+\nu} K.$$

Next if $R_0(\mu,\nu) > 1$, Equation (A7) is asymptotically equivalent to the differential equation of the logistic type

$$\frac{dP}{dt} = P\left[b - m - (b+\alpha+\mu)y_3^* - \frac{r}{K}P\right];$$

introducing the second threshold parameter $R_1(\mu,\nu)$

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

one obtains as *t* goes to $+\infty$

$R_1(\lambda,\mu) \le 1$ implies N(t) $\to$ 0, as well as X(t),Y(t) and Z(t) $\to$ 0

while

$R_1(\lambda,\mu) > 1$ implies $N(t) \to N_3^*(\mu,\nu)$

with

$$N_3^*(\mu,\nu) = \frac{K}{r}\left[b - m - (b+\alpha+\mu)y_3^*\right] \qquad \text{(A11)}$$

and $X(t) \to x_3^* N_3^*, Y(t) \to y_3^* N_3^*$.

*Stability without prophylaxis*

The conclusion follows from the previous case upon setting $\mu = \nu = 0$.

Bouloux C., Courchamp F., Fromont E. & Suppo C. Modelling the spread of two feline viruses within a population of domestic cats. In preparation.

# CHAPTER VII

## POPULATION DYNAMICS OF TWO FELINE RETROVIRUSES (FIV AND FELV) WITHIN ONE POPULATION OF CATS

## 1- INTRODUCTION

In the past years, a wide range of epidemiological models have been produced on spread of pathogens within host populations. These theoretical models dealt with simple systems including a parasite (a microparasite or a macroparasite, as defined in Anderson & May, 1979) infecting an host species. Few models dealt with three species host interactions, such as a parasite infecting a single host, 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 not infected by a single parasite species, but rather by a whole parasite community (Hochberg & Hawkins, 1992; 1993; Combes, 1995). In addition, little emphasis was generally devoted to biological aspects in such models. For example, biological hypothesis were often not taken into account, unrealistic or far from reality, and epidemiological surveys were rarely conducted to complete theoretical work.

Here, we present such a complex system, with the study of the circulation of two pathogens within a single host population, through an epidemiological model in which the biological aspects have been taken into account. The host is the domestic cats (*Felis catus*), who lives in populations of highly variable dynamics and social structures. The two pathogens are two feline retroviruses of major importance (Zenger, 1992; Hardy, 1993; Bendinelli *et al.*, 1995): Feline Immunodeficiency Virus (FIV) and Feline Leukemia Virus (FeLV). Interest of these two viruses is provided by several aspects among which the fact that both virus are lethal, that they are found worldwide and that they can infect several wild felid species (Courchamp & Pontier, 1994 for FIV, and Meric, 1984; Briggs & Ott, 1986, Citino 1986; Boid *et al.* ,1991; Jessup *et al.*, 1993, for FeLV), most of which are already endangered. An epidemiological survey has been conducted on natural populations on FIV and FeLV during a five years period (Courchamp *et al*., submitted), providing data used in the model. Finally these two viruses seem to have different transmission modes: by bites during fights for FIV and by direct contact through liking for FeLV. Even if multispecies system dynamics are often not very different from what is expected with a good understanding of species interactions two by two, relatively unexpected dynamic behaviours may arise from such a study (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 study of the separated species two by two (Hassell & May, 1986). In this context, we are going to study simultaneous dynamics of two major domestic cat pathogens.

The model has been built from a first model describing the spread of FIV in cat populations (Courchamp *et al*., 1995a) and a second one describing FeLV circulation in similar populations (Fromont *et al*., *submitted* a). These models were based on Anderson & May's work (e.g. Anderson & May, 1991). The interesting point of these two models is that, despite different transmission modes, the two models showed relatively similar results. Namely, persistence of disease in the population, through a stable equilibrium stage, which is reached inducing a low reduction of the population size. Moreover, parameter estimation revealed low transmission rates for both diseases. The aim of these

two previous models was mainly to understand the dynamic mechanisms of the diseases through their spread within a susceptible host population, and thus to evaluate their respective impact within the population, in terms of reduction of the population size. In contrast, the aim of the present model is rather to study the behaviour of the two virus dynamics when taken into account together, and to evaluate their respective role in the disease-induced changes of the host population dynamics. It will be evaluated whether to take into account both virus dynamics simultaneously induce a qualitative change in the model behaviour when compared to modeling of viruses alone, and why.

## 2- MATERIALS & METHODS

As we mainly re-used the materials and methods fully described in previous works (Courchamp *et al*., 1995a; Fromont *et al*., *submitted* a), we will here be very concise concerning the description of the viruses, the host and the construction of the model. Indeed, we will here describe biological properties only with regards to hypothesis for the model.

### *(a) Host population*

Populations of cats are known to vary greatly in their social structures (Liberg & Sandell 1988). However, a wide range of amicable interactions occur between many cats in most populations, mainly within limited social groups. In addition, in many populations (for example, in rural environment), fights occur between males, due to the mating system and territorial behaviour (Macdonald *et al*., 1987; Liberg & Sandell 1988; Pontier, 1993), and between males and females, for example for defense of offspring against potential infanticides (Macdonald *et al*., 1987; Feldman, 1993).

### *(b) Viruses*

#### *(i) FIV*

FIV is a lentivirus inducing AIDS in cats (Pedersen *et al*., 1987), and is thought to be transmitted by bites during fights (Yamamoto *et al*., 1989). FIV infection leads to lifelong antibodies (and virus) carriers. The clinical staging of FIV infection is very similar to the one of Human Immunodeficiency Virus infection (Ishida & Tomoda, 1990), with a short acute stage, a long asymptomatic period (lasting up to several years, and in which the cat is healthy), a Persistent Generalized Lymphadenopathy, AIDS-Related Complex, associated with chronic infections, and finally AIDS. As in humans infected by HIV, feline AIDS is caracterized by opportunistic infections, allowed by a loss of immunological defenses. The cat is infectious during all these five stages of infection. There is no recovery nor immunization to FIV, either natural or artificial. For further details on this virus, one should refer to the complete reviews published on its

various aspects (molecular: Elder & Phillips, 1994; Bendinelli *et al*., 1995; genetic: Miyazawa *et al*., 1994; immunologic: Lin, 1992; epidemiological: Courchamp & Pontier, 1994; clinical: Pedersen & Barlough, 1991; Ishida & Tomoda, 1990).

*(ii) FeLV*

FeLV is a retrovirus which leads to immunosuppression in infected cats, with a clinical feature comparable to the one of FIV infection (Yamamoto *et al*., 1988). It is an oncovirus (Jarrett *et al.*, 1973), as is Human T-Lymphotropic Virus (HT-LV 1 et 2, Wong-Stall & Gallo, 1985). FeLV is transmitted by amicable contact (saliva, through licking, maternal grooming, food sharing, ...) but also by mating or biting (Rojko and Olsen, 1984). FeLV can also be transmitted from mother to kitten (Hoover *et al.*, 1983). Infection is followed by a temporary viremic stage (Rojko *et al.*, 1979) lasting two to four months (Hardy *et al.*, 1973). This period is generally asymptomatic and may lead to two different issues. Approximately two thirds of the infected individuals (Hoover & Mullins, 1991) develop lifelong immunization and recover from infection (Pacitti, 1985). These immunized cats are no more infectious and have a normal life expectancy (Francis & Essex, 1980; McClelland *et al.*, 1980). These cats are recovered (Pacitti, 1985) and should be immunized for life (Hardy *et al.*, 1976). Individuals that do not become naturally immunized become persistently viremic and will die within two years in average (Weijer & Daams, 1976; Hardy, 1980; Francis & Essex, 1980) from various proliferative or immunosuppressive disorders. Almost 80% of infected queens abort or give birth to viremic kittens that will die within weeks to months (Hoover *et al*., 1983). A more complete description of this virus and its properties is given by Hardy (1993). An epidemiological review is given by Fromont *et al*. (*submitted* b). Infectious period length has been estimated by several authors giving mortality rates (the inverse) around 0.5 (Weijer & Daams, 1976; Francis & Essex, 1980; Hardy, 1980). Transmission rate has been estimated by evaluating its inverse, the time between the first contact with an infected cat and apparition of symptoms (Grant *et al.*, 1980): between 1.0 and 3.5 infections by year and by cat. (voir si c'est utile pour le 8,88, sinon le virer)

FIV and FeLV are independently transmitted, but coinfection is followed by an acceleration and an enhancement of FIV induced symptoms (Martinon & Lévy, 1993). Indeed, FeLV is a potent activator of FIV replication both qualitatively and quantitatively (Torten *et al.*, 1990; Pedersen *et al.*, 1990). For sake of simplicity, this will not be taken into account in he model.

*(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 growth rate r=b-m. The population dynamics when there is no pathogen, thus follows the equation:

$$dN/dt = rN\,(1-N/K) \qquad (1)$$

FIV is transmitted at a rate $\sigma$ and cats die from FIV infection, with no possible recovery, at a rate $\alpha$. FIV infected individuals do participate to reproduction, and give birth to susceptible kittens (FIV can not be transmitted from queen to kitten). We consider only one pathological stage, the seropositive 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 $\gamma$, a proportion $\pi$ of which becoming naturally immunized after a non significant time and being no more infectious. A proportion of $(1-\pi)$ cats will become infectious and will die at a rate $\mu$. There is no vertical transmission and, as infected queen abort or give birth to infected kitten that will die within a neglectible time, non immunized cats do not participate to reproduction. Cats can be infected by both virus simultaneously, and thus die at a rate $\delta$. For sake of simplicity, we will assume in a first time that $\delta=\alpha+\mu$. For biological reasons, and as previously discussed (Courchamp *et al*., 1995a; Fromont *et al*., *submitted* a), the transmission rates will be characteristics of proportionate mixing models for both FIV and FeLV.

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

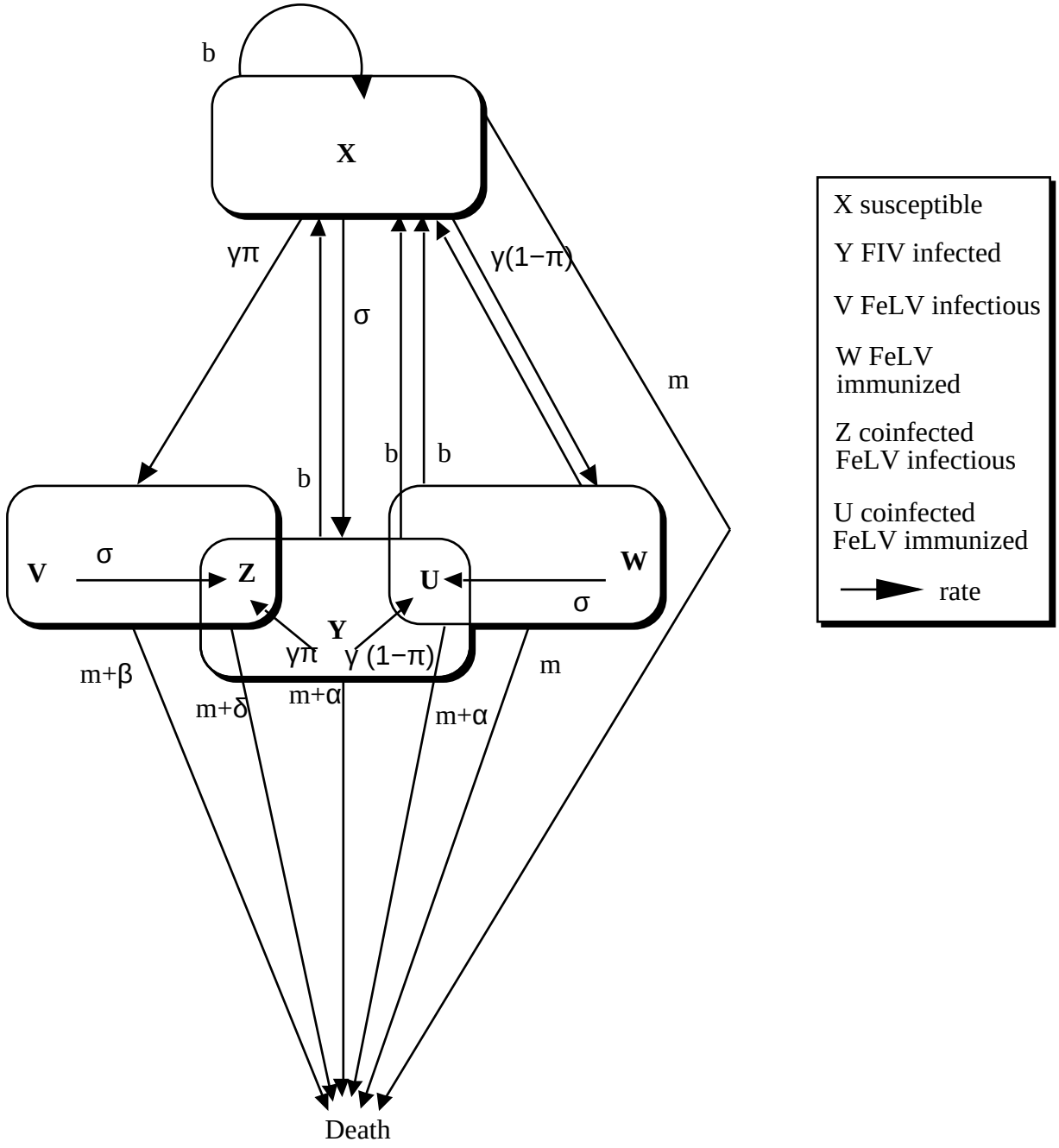


**Figure 1**: Flow chart of the population infected by both FIV and FeLV. Variable name are given in the text. A set of first order equations describes the dynamics of the FIV and FeLV infected population as given by the above hypothesis.

$$\frac{dX}{dt} = b(X+Y+W+U)-mX - \frac{rNX}{K} - \frac{\sigma X(Y+U+Z)}{N} - \frac{\gamma X(V+Z)}{N} \quad (2)$$

$$\frac{dY}{dt} = \frac{\sigma X(Y+U+Z)}{N} - mY - \frac{rNY}{K} - \alpha Y - \frac{\gamma Y(V+Z)}{N} \quad (3)$$

$$\frac{dV}{dt} = \frac{\gamma X(V+Z)}{N}\pi - mV - \frac{rNV}{K} - \beta V - \frac{\sigma(Y+U+Z)V}{N} \quad (4)$$

$$\frac{dW}{dt} = \frac{\gamma X(V+Z)}{N}(1-\pi) - mW - \frac{rNW}{K} - \frac{\sigma(Y+U+Z)W}{N} \quad (5)$$

$$\frac{dZ}{dt} = \frac{\gamma Y(V+Z)}{N}\pi - mZ - \frac{rNZ}{K} - (\alpha+\beta)Z + \frac{\sigma(Y+U+Z)V}{N} \quad (6)$$

$$\frac{dU}{dt} = \frac{\gamma Y(V+Z)}{N}(1-\pi) - mU - \frac{rNU}{K} - \alpha U + \frac{\sigma(Y+U+Z)W}{N} \quad (7)$$

The equation for the total model is obtained by adding these six above equations:

$$dN/dt = rN(1-N/K) - \alpha Y - (b+\mu)V - (b+\alpha+\mu)Z - \alpha U \quad (8)$$

Simulations have been carried out with the computer program Dynamac (Rousseau, 1988).

## 3- RESULTS

### *(a) Stability analysis*

#### *(i) Equilibrium points existence analysis*

In a first step, equilibrium points of this system are calculated. In order to do it more simply, we introduce the proportions $x=\frac{X}{N}$, $y=\frac{Y}{N}$, $v=\frac{V}{N}$, $w=\frac{W}{N}$, $z=\frac{Z}{N}$ and $u=\frac{U}{N}$, such as $0 \le x, y, v, w, z, u \le 1$ and $x+y+v+z+w+u=1$. The following system is obtained:

$$(dx/dt) = b(y+w+u)+x[-\sigma(y+u+z)-\gamma(v+z)+(b+\mu)v+(b+\alpha+\mu)z+\alpha y+\alpha u] \quad (9)$$

$$(dy/dt) = \sigma x(u+z)+y[\sigma x-\alpha-\gamma(v+z)-b+(b+\mu)v+(b+\alpha+\mu)z+\alpha y+\alpha u] \quad (10)$$

$$(dv/dt) = \gamma\pi xz+v[\gamma\pi x-m-\sigma(y+u+z)-b+(b+\mu)v+(b+\alpha+\mu)z+\alpha y+\alpha u] \quad (11)$$

$$(dw/dt) = \gamma x(1-\pi)(v+z)+w(-\sigma(y+u+z)-b+(b+\mu)v+(b+\alpha+\mu)z+\alpha y+\alpha u] \quad (12)$$

$$(dz/dt) = \gamma\pi yv+\sigma v(y+u)+z[\gamma\pi y-\alpha-\mu+\sigma v-b+(b+\mu)v+(b+\alpha+\mu)z+\alpha y+\alpha u] \quad (13)$$

$$(du/dt) = \gamma y(v+z)(1-\pi)+\sigma w(y+z)+u[\sigma w-\alpha-b+(b+\mu)v+(b+\alpha+\mu)z+\alpha y+\alpha u] \quad (14)$$

This set of equations reveals the presence of six equilibrium points:

- E1 = (1, 0, 0, 0, 0, 0)
- E2 = (0, 0, 1, 0, 0, 0)
- E3 = (0, 0, 0, 0, 1, 0)
- E4 = $\left(\frac{b}{(\sigma-\alpha)}, 1+\frac{b}{(\alpha-\sigma)}, 0, 0, 0, 0\right)$
- E5 = $\left(\frac{\mu(b+\mu-\gamma)-b\gamma(1-\pi)}{\gamma\pi(b+\mu\gamma)}, 0, \frac{b(b+\mu-\gamma\pi)}{(b+\mu)(b+\mu-\gamma)}, 1-x^*-v^*, 0, 0\right)$
- E6 = ($x^*$, $y^*$, $v^*$, $w^*$, $z^*$, $u^*$)

These points correspond to the vanishing of both diseases (E1), of FeLV (E4), of FIV (E5), or of the existence of only one pathological class (FeLV infected ill cats (E2) and FIV and FeLV ill coinfected cats (E3)). The last equilibrium point, E6, is the most interesting as it corresponds to the situation where both infections are present, with all pathological classes, and in equilibrium.

*(ii) Equilibrium point existence conditions*

Let us remind that $R_o$, $R_o$' and $R_o$" are the basic reproduction rate of FIV, of FeLV and of both diseases respectively (Jacquez *et al*., 1991), and that $R_1$, $R_1$' and $R_1$" are the net reproductive rate of the population when FIV, FeLV and both diseases are endemic, respectively (Busenberg & Cooke, 1993).

Equilibrium point existence conditions are the following:

There is no problem of existence for E1, E2 and E3.

E4 exists if and only if $\frac{b}{(\sigma-\alpha)} \leq 1$, that is if $\frac{\sigma}{b+\alpha} \geq 1$. Note that we find the relation:

$$R_o = \frac{\sigma}{b+\alpha} \geq 1 \qquad (15).$$

E5 exists if and only if $b+\mu - \gamma\pi < 0$, that is if $\frac{\gamma\pi}{b+\mu} \geq 1$. Note that we also find the relation:

$$R'_o = \frac{\gamma\pi}{b+\mu} \geq 1 \qquad (16).$$

E6 exists if and only if $R_o \geq 1$ et $R'_o \geq 1$. This condition is equivalent to $R''_o \geq 1$, with

$$R''_o = \frac{\sigma\gamma\pi}{b+\alpha+\mu} \qquad (17).$$

Indeed, one have $R_o R'_o = \frac{\sigma\gamma\pi}{(b+\mu)(b+\alpha)} \leq \frac{\sigma\gamma\pi}{b+\alpha+\mu}$ (because b>0).

Thus if $R_o R'_o \geq 1 \Rightarrow R''_o > 1$

*(iii) Equilibrium points stability analysis*

The Jacobian matrix, calculated for each point, indicates that:

E1 is stable if and only if $\frac{\sigma}{\alpha+b} < 1$ and $\frac{\gamma\pi}{(b+\mu)} < 1$ (equivalent to $R_o<1$ et $R'_o<1$) and gives P1. We can note that equilibrium of E1 implies inexistence of E4 and E5.

E2 and E3 can not be stable.

E4 is stable if $\begin{cases} R_o \geq 1 \\ R'_o < 1 \end{cases}$.

This equilibrium gives $\begin{cases} P0, \text{ if } R_1 = \frac{b}{(m+\alpha y4^*)} < 1 \\ P4, \text{ if } R_1 \geq 1 \end{cases}$.

E5 is stable if $\begin{cases} R_o < 1 \\ R'_o \geq 1 \end{cases}$.

This equilibrium gives $\begin{cases} P0, \text{ if } R'_1 = \frac{b}{(m+(b+\mu)v5^*)} < 1 \\ P5, \text{ if } R'_1 \geq 1 \end{cases}$.

E6 is stable if $\begin{cases} R_o \geq 1 \\ R'_o \geq 1 \end{cases}$.

This equilibrium gives $\begin{cases} P0, \text{ if } R''_1 = \frac{b}{(m+(b+\mu)v6^*+(b+\alpha+\mu)z6+\alpha y6^*+\alpha u6^*)} < 1 \\ P6, \text{ if } R''_1 \geq 1 \end{cases}$.

With, from equations (9) to (14):

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,

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 vanishing of the population,

P4: $\begin{cases} X_4^* = \dfrac{b}{(\sigma-\alpha)} N^* \\ Y_4^* = (1-\dfrac{b}{(\sigma-\alpha)})\, N^* \\ V_4^* = 0 \\ W_4^* = 0 \\ Z_4^* = 0 \\ U_4^* = 0 \end{cases}$ , which corresponds to the vanishing of FeLV,

P5: $\begin{cases} X_5^* = \dfrac{\mu\,(b+\mu-\gamma) - b\gamma\,(1-\pi)}{\gamma\pi(b+\mu-\gamma)}\, N^* \\ Y_5^* = 0 \\ V_5^* = \dfrac{b\,(b+\mu+\gamma\pi)}{(b+\mu)\,(b+\mu+\gamma)}\, N^* \\ W_5^* = \dfrac{(b+\mu-\gamma\pi)\,[b\gamma\,(1-\pi) - \mu\,(b+\mu-\gamma)]}{\gamma\pi(b+\mu)\,(b+\mu+\gamma)}\, N^* \\ Z_5^* = 0 \\ U_5^* = 0 \end{cases}$

, with $N^* = \dfrac{K}{N}\left( r - \dfrac{b\,(b+\mu-\gamma\pi)}{b+\mu-\gamma} \right)$, which corresponds to the vanishing of FIV,

P6: $\begin{cases} X_6^* = x^*N^* \\ Y_6^* = y^*N^* \\ V_6^* = v^*N^* \\ W_6^* = w^*N^* \\ Z_6^* = z^*N^* \\ U_6^* = u^*N^* \end{cases}$ , which corresponds to the presence of both viruses in equilibrium in the population

These results are summarized in Figure 2. The presented simulations represent evolution with time of the different pathological classes of the population. Each simulation has been carried with parameters values chosen as explained in the next section.

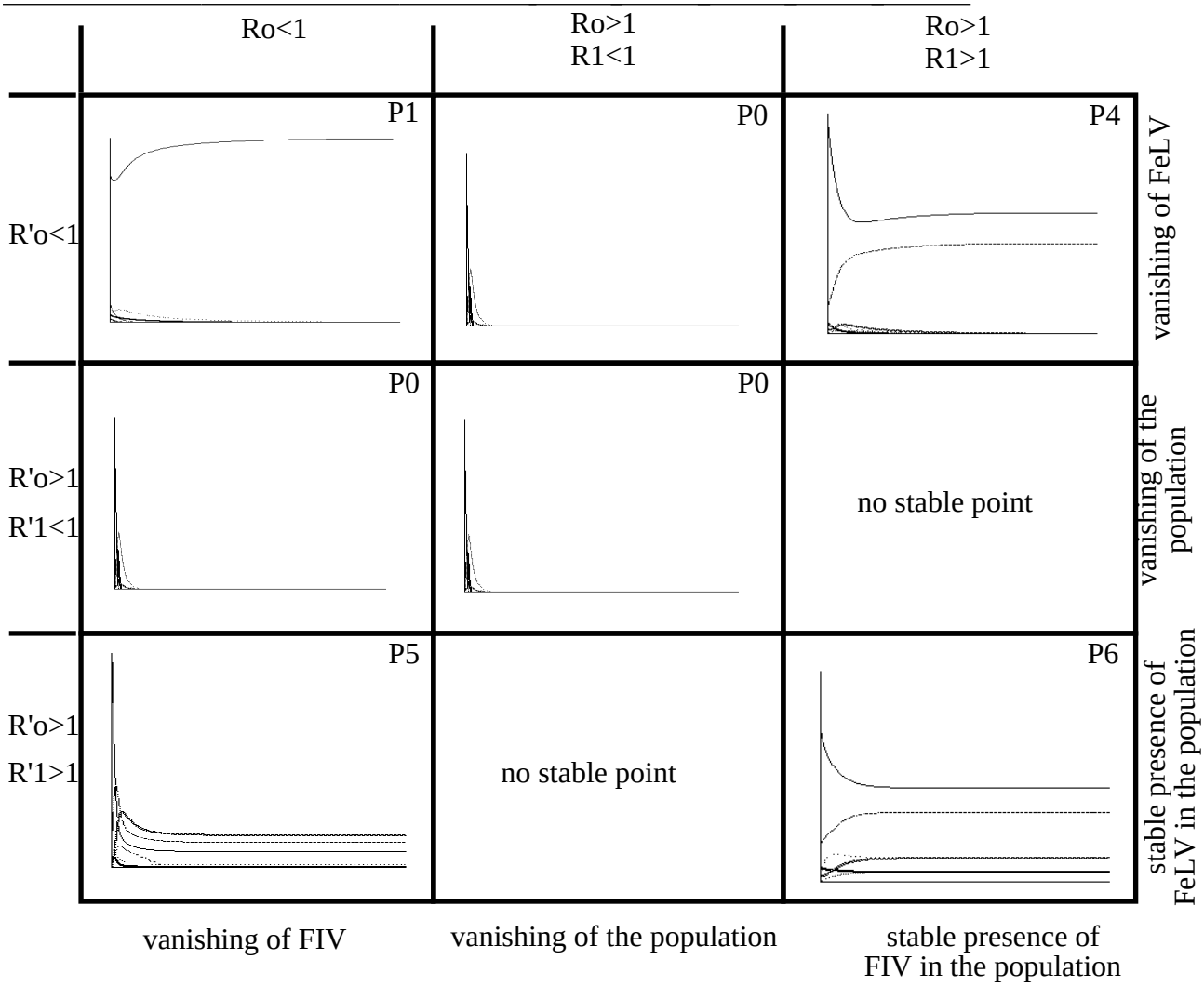


**Figure 2**: recapitulative of different possible cases for the model behaviour, in function of $R_o$, and $R'_o$ on one hand, et $R_1$, and $R'_1$ on the other hand. Simulations illustrate each of the cases.

*(b) Application to the biological data*

We can now search, among the predicted ones, in which conditions we are concerning the biological values available on domestic cat populations, VIF and FeLV epidemiology. We know the values of b, m and π. We studied the sensitivity of α and μ (mortality rates of FIV and FeLV respectively). This study shows that variability of these parameters values do not modify quantitatively the model results (and very slightly modify quantitative results). We will thus take values commonly admitted in literature, that is 0.20 for α and 0.53 for μ. We can now study the existence of the different possible cases with different conditions for σ and γ (transmissions rates for FIV and FeLV respectively). With previously named values for b, m, π, α and μ, one find:

| γ \ σ | σ<2,6 | σ>2,6 |
|---|---|---|
| γ<8,88 | P1 | P4 |
| γ>8,88 | P5 | P6 |

**Table I**: Domain of biological values for the model dynamics.

The value of σ estimated from the FIV model (Courchamp *et al*., 1995a) indicates that we can only be in the last column of Table I: presence of FIV alone or of both viruses in the population. Pas clair

## 4. DISCUSSION

We presented here the modeling of the dynamics of a domestic cat population within which spread not only one virus, as do classical models, but two viruses simultaneously. These two viruses are sufficiently close from an epidemiological point of view to be easily associated in common mathematical model: both are feline retroviruses currently infecting domestic cats. After a relatively long period, they induce death in infected individuals they have previously immunodepressed. Nevertheless, there are important differences between these viruses. They have different transmission rates (FIV is less efficiently transmitted), as well as different mortality rates (FIV kills less rapidly its host). For FeLV, a high proportion of infected individuals escape symptoms (and associated death), due to an immune response against the virus.

Theoretically, the model shows that all classically expected epidemiological situations are possible: vanishing of the population, of both disease, or only one, and simultaneous presence of both diseases. In each case, one can note that the present pathological classes (susceptible individuals , FIV infected but FeLV immunized ones, ..) reach a steady equilibrium state. Whatever the epidemiological becoming of the population, it will be stable.

A confrontation of theoretical results of the model with available biological data implies the existence of only two solutions among the seven described ones. These situations are stable presence of FIV in the population, and presence, also in a stable way, of both viruses in the population. It can be noted that vanishing of the population is not possible: the viruses, when they are together, do not have a sufficiently important impact on populations to make them disappear. When modeled alone, both viruses do not either make the population disappear. The simultaneous vanishing of both disease is not possible, there remains always at least one virus. The two initial models also predicted no disease vanishing. Results are even more interesting if we consider that the case in which only FeLV is maintained in the population is not possible with used biological values for the parameters of the model. The only two possibilities implies the presence of FIV which maintain itself in the population independently of the behaviour of the other virus. Three main results can be summarized in the following way:

i) once introduced in a population, FIV develops and is maintained, while FeLV may disappear or persist, ii) introduction of both viruses in the population induces steady equilibrium stages of individuals from different pathological classes, iii) whatever the becoming of the population (persistence of FIV only or of both viruses), the global population size at the equilibrium state is only weakly lower than it would have been in the absence of the infections (carrying capacity), indicating a low impact of the viruses on the populations. In addition, the viruses never induce the vanishing of the population.

We can highlight that results obtained with the model are in agreement with epidemiologically studied populations. Whether in the literature or the populations studied by our team, FIV has been found in all studied populations, while some were free from FeLV. Some of these FeLV-free populations, such as one we studied in rural environment, are however certainly in close contact with this virus, and it seems thus possible that this virus can not persist in the population (Courchamp *et al*., 1995b; Fromont *et al*., *in press*). In this context, the long term monitoring of natural populations is particularly interesting: a urban population of cats monitored by our team was free of FeLV the first two years of study. The last year, there has been two infected cats. Only long term epidemiological surveys will teach us if the virus can persist in the population, or if, as predicted by our model, it will disappear.

It has been suggested (Fromont *et al.*, submitted a) that FeLV absence in some natural populations (natural is here opposed to theoretical ones) was due to a low population size that would not allow disease to persist. Indeed, it has been several times demonstrated that there is a threshold below which a given infection can not persist (Anderson & May, 1985). This parameter has not yet been estimated in our model. However, it is noteworthy that, population size being here taken into account, through a

proportionate mixing transmission rate, that small sized populations may not allow FeLV to persist durably. A second hypothesis is linked to spatial structure of domestic populations. Populations in which FeLV is not encountered have small numbers of individuals, and are isolated by habitat fragmentation (Fromont *et al., in press.*). These two hypothesis are not exclusive, and an interaction between them is possible. A spatial aspect in the FeLV model will be necessary to validate this hypothesis. It is especially important in the case of these FeLV viruses, as it is transmitted by direct contact (mainly during amicable contacts such as licking or feeding places sharing), and thus between socially close individuals. Indeed FeLV spread may be strongly linked to spatial structure of populations, especially spatial distribution and group size. Eventual integration of spatial aspects would be done in this two parasites/one host model only if it provides interesting results in the FeLV model.

There are few mathematical models dealing with three species systems. Some theoretical studies have overlooked most of the possible systems, implying competition, predation, parasitism (or several of these categories at the same time) linked-interactions (see for example Anderson & May, 1986). Nevertheless, such models applied to concrete cases, with biological data, are even scarcer. There are some, but the epidemiological models then always describe systems with macroparasites. Indeed, this type of model can take a species population dynamics into account only through one equation. Thus, a system with one host and two macroparasites can be modeled by a set of three equations. In revenge, microparasite associated models are more complex to manipulate when taking two parasites and a host species into account, because those models describe the host population dynamics, with the many different possible pathological states (and as many equations). It is, to our knowledge, the first model describing 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 case.

This type of multispecies epidemiological models, even if more complex than more classical systems, is however necessary. Indeed, a single host individual, and moreover a single host population, is not infected by a unique parasite, but rather by a community of interacting species.

This highlights the importance of taking into account several virus simultaneously within a population in field ecological and epidemiological studies. If this kind of studies remains scarce, it should only be due to difficulties typical to this type of studies. These are mainly of two types: on one hand they require an investment in two different (but complementary) scientific fields, mathematics and biology, and on the other hand, they need the biological study of one host species and two parasites species within a single host population. Indeed, domestic cats present many aspects making this species an ideal candidate for this kind of studies. First, they present populations of highly variable dynamics, social and spatial structures (Liberg & Sandell, 1986), allowing thus comparisons with contrasted situation. Secondly, these populations are numerous, and easier to observe and capture than most of similar species (such as carnivorous). Their domestic status allow the collecting of quasi-exhaustive data in some populations (for example the population size and sex and age structures, Pontier, 1984). Finally, the

domestic cat's health is especially well studied, with one of the best known viral fauna: 14 carefully studied viruses. Our team monitors since 1991 epidemiology of several cat populations, through five feline viruses of major importance: FIV, FeLV, feline herpes virus, feline calici virus and feline parvovirus (FPV). This kind of study allows to realize the model we presented here.

The presented model requires however to be improved. This is a first step, and next improvements of this model will imply further biological hypothesis that induced too much complexity in analytical study to be at once taken into account. Among these may be the higher mortality rate of coinfected individuals. The absence of this hypothesis in this model might explain that to take into account both viruses dynamics simultaneously does not change basically the results obtained from the first two models of virus dynamics alone. Indeed, the main interaction between both viruses is the higher induced mortality that we have considered additive here, while it is not in reality. Coinfecion indeed induces an increasing and acceleration of symptoms induced by each virus, leading very rapidly to death (Torten *et al.*, 1990; Pedersen *et al.*, 1990; Martinon & Lévy, 1993). However, if this pathological class may theoretically change qualitatively the model behaviour, the low number of coinfected individual diminishes its importance. Indeed, only one coinfected individual has been found among a total of around 400 individuals, on all the individuals of four natural populations monitored by our team during a five years study. This extremely low coinfection rate may be partly explained by the low infection rates for both viruses. However, and this is the most important, if viruses were acting independantly, a coinfection rate equal to the product of both infection rates would be expected. The coinfection rate is however much lower. In fact, these two viruses have opposed transmission modes: FIV is transmitted during fights (by bites) and FeLV during amicable contacts (such as liking and food sharing). It has been shown that all individuals do not have the same behaviour, in particular concerning transmission in these two viruses (Courchamp *et al*., 1995b). Thus, dominant and aggressive individuals play a major role in FIV spread. Similarly, socially amicable cats will favour FeLV transmission. At-risk categories are opposed for both diseases (Courchamp *et al*., 1995). This explains why interactions are low for these two viruses.

It could thus be interesting to study, in a similar way, simultaneous dynamics of two feline viruses which at-risk categories are at least partially overlapping. Similarly, one of these viruses at least should have a prevalence rate high enough for the coinfection number to be important. In this context, simultaneous modeling of FIV and Feline Parvo Virus (FPV) could provide major informations concerning the importance to take several viruses into account in theoretical as well as empirical studies. Such a model could provide informations concerning the potential influence of a virus dynamics on the dynamics of another virus infecting the same host. Indeed, FPV induced mortality is very high, and its transmission is epidemics, inducing very high prevalence rates (up to 100% in some infected populations, Drapier, 1992). It could be thus possible to study if presence of one of the viruses precludes or limits the presence of the other virus (competition), or even if it fourizes it, as found in some complex models (*e.g.* Hochberg & Holt, 1990). It could even be interesting to study, provided that analytical complexity allows us, simultaneous dynamics of more than two viruses. The field epidemiological

studies conducted by our team indicate indeed that all looked viruses (5 feline viruses) are present in most populations we study.

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"Infectious disease is one of the few genuine adventures left in the world. The dragons are all dead and the lance grows rusty in the chimney corner... About the only sporting proposition that remains unimpaired by the relentless domestication of a once free-living human species is the war against those ferocious little fellows creatures, which lurk in the dark corners and stalk us in the bodies of rats, mice and all kinds of domestic animals; which fly and crawl with the insects, and waylay us in our food and drink and even in our love." Hans Zinsser.

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## CHAPTER VIII

# FELINE IMMUNODEFICIENCY VIRUS: AN EPIDEMIOLOGICAL REVIEW

## 1 Introduction

Feline Immunodeficiency Virus (FIV) is a newly identified virus [1] inducing AIDS in cats (*Felis catus*). FIV is of particular interest for domestic cats' health, as infection with FIV gives rise to a wide range of clinical signs, secondary infections being common [2, 3, 4, 5]. FIV belongs to the family of retroviruses, and has the characteristics of the non-oncogenic retroviruses that are associated with chronic progressive infections: the lentiviruses. FIV is specific both towards species (only feline species can be infected [2]), and towards target cells (FIV infects lymphocytes, macrophages, astrocytes and microglia cells, [6, 7, 8]). Nevertheless, genetical studies have shown that FIV is closely related to HIV [9, 10]. FIV has been found worldwide in pet cats, feral cats and non-domestic felids. Except for the transmission modes (that seems to be mostly by bites [2] and not reproduction) and the fact that it is antigenically distinct, FIV is very similar to HIV: genetically, morphologically, biochemically and pathologically [11]. Both lentiviruses have similar biological properties, namely magnesium dependent Reverse Transcriptase activity, prolonged latency, and persistence of infection despite humoral responses [12, 13, 14, 15]. The clinical staging of feline AIDS also is very similar to human AIDS [16, 17]. Hence, FIV could be a good model of HIV studies on numerous fields [18].

This paper reviews the results from 59 epidemiological studies from all over the world, including 85,529 cats. As many syntheses on FIV molecular or pathological properties are published, we only consider here epidemiological aspects, which have been neglected. Published results being sometimes inconsistent or statistically not significant because of insufficient numbers of cats, and being sometimes contradictory according to studies, our approach allowed much more reliable results. This synthesis permits us to exploit the statistical possibilities offered by such a large number of individuals in a way that is not allowed by individual studies. Several interesting conclusions may be drawn from this synthesis. One of the main points is that FIV transmission is mostly influenced by behavioral parameters, hence the need to study the dynamics of cat populations and their social structures, in relation to ecological parameters, to further investigate virus circulation within cat populations. The other point is the many arguments that are in good agreement with the hypothesis of appearance of FIV at an early date.

## 2 Material and methods

Fifty nine serological surveys from all over the world have been taken into account, providing serological results for 85,529 cats. Due to their origin (veterinary hospitals), cats are mostly considered according to two categories; sick and apparently healthy cats (see annex). A few survey also consider a few feral cats or cats suspected to be infected with FIV. These suspected cats are individuals in close contact with known FIV infected cats, or are immunodeficient cats that are Feline Leukemia Virus (FeLV) seronegative (FeLV causes the same symptoms that FIV, 14). In most of the 59 surveys, FIV infection was diagnosed by detection of antibodies by Enzyme Linked ImmunoSorbent Assay and positive test results confirmed by Western Blot. A few studies used ImmunoFluorescence

Assay instead. As there was no populational reference in any of the available samples, data were pooled for all subsequent analyses, and FIV prevalence (percentage of infected cat) has been estimated for the overall sample. We investigated potential effects on FIV infection of health status (sick or apparently healthy), sex (and neutering), age, breed (European, mixed breed or purebred cats), roaming habits (indoor, feral or freely roaming indoor cats) and group size (number of cats living in the same house). As available data in the literature were restricted to classical contingency tables, analyses have been conducted for each factor taken separately. Moreover, not all data could be fully used, because variables were not recorded in the same way for all available studies, or because published data were not precise enough. In particular, as class limits were heterogeneous according to studies, age classes have been arranged according to four limit types (A, B, C and D, in Figure 1). Also, new classes according to group size have been established to regroup dissimilar classes.

Differences of FIV prevalence between categories of cats, according to the above described factors, were tested using the Chi-square test. The $\chi^2$, $\rho$ and confidence intervals values were calculated using the computer program StatView IV (© Abacus Concepts Inc.). As the possible relationship between FIV prevalence and average national densities was not expected to be linear, we used the Spearman rank correlation test.

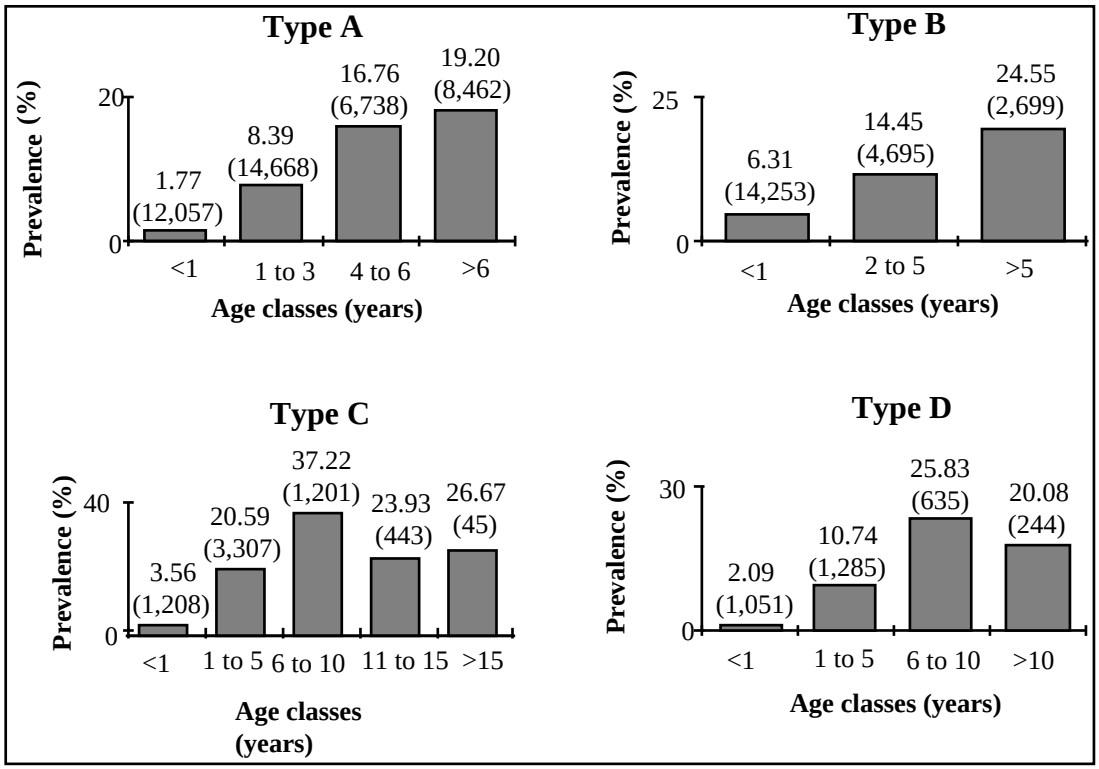


**Figure 1**: FIV prevalence and number of individuals screened (into brackets) for the four main types of encountered age class distribution: A, B, C and D. Types A and B show an increase of FIV prevalence with age classes. These distribution types concern a higher sample than C and D types, allowing statistically more reliable conclusions , but are less precise than C and D types. C and D types show the increase of FIV prevalence with age classes up to the 6-10 years old class, and a decrease after.

## 3 Results and discussion

### 3 1 Worldwide distribution:

FIV has been isolated in all states of the U.S.A., Canada, Argentina [19], Japan, China [20, in 21], India, Taiwan, Australia, New-Zealand, South Africa (Spencer, Spencer & Flamand, unpublished data), Botswana (Spencer & Osofsky, unpublished data), Tanzania [22], Kenya [22], U.K., France, Italy, Spain (Altimira, *pers. com*.), Netherlands, Finland, Norway, Switzerland, Germany, Hungary, Greece, Russia [23] and Austria (see Annex). No report of FIV serosurvey of felids, to our knowledge, has been published for other countries, except non-domestic felids tested in Namibia, and for which results were negative [79].

Serological evidence of FIV has been found since 1968 both in the U.S.A. and Japan [14, 55], 1972 in Australia [27], 1974 in France [80] and 1975 in the U.K. [81].

### 3 2 Worldwide prevalence:

The overall infection rate, calculated from the 85,529 domestic cats is 11.04%. If we consider the approximate number of 400 million cats over the world [82], around 44 million cats actually are FIV infected (much more if we consider that 10% to 15% of FIV infected individuals are seronegative, [60, 83]). But there is a bias in considering cats in veterinary hospitals representative of worldwide cats, as only a very weak proportion of animals visit veterinaries (less than 10% in the rural cat populations followed by our team). Moreover, cats on routine visit at veterinary hospitals are at low risk, their owner take care of them, and thus rarely allow them to roam. On the other hand, sick cats are at high risk of being infected because they are already ill. Thus not only are samples of this kind of survey biased, but furthermore the bias cannot be evaluated. Nevertheless, the number of individuals taken in this synthesis is statistically sufficient to provide a suitable worldwide prevalence rate estimate.

It has been suggested [57] that differences in FIV prevalence rates between countries may reflect differences in cat density (which may affect the spread of the virus within the population) and in behavior of animal caretakers towards their cats (with regards to roaming permission and number of cats per household). There actually is a significant difference in FIV prevalence between countries and even continents (Figure 2), but it is not possible to assess here if it is due to differences in virus strains, cat behavior, other factors or unrepresentativity of the samples. However, no correlation has been found between national cat densities from 16 countries [82] and average prevalence by country ($\rho_a$=0.224, P=0.385 and $\rho_b$=-0.244, P=0.344, Figure 2). It is clear here that such prevalence rate differences are not interpretable because of heterogeneous origins of the cat samples and possible bias affecting records.

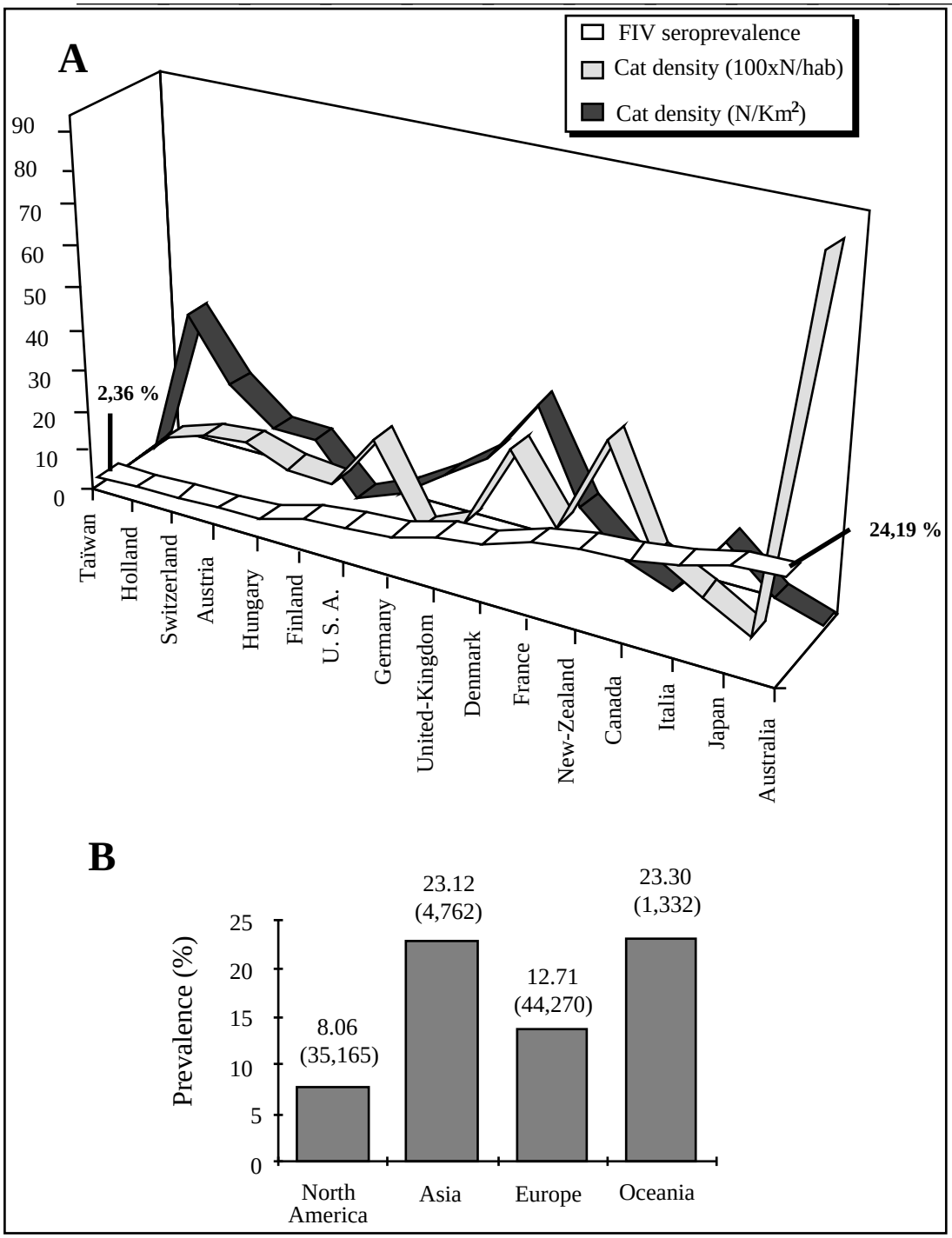


**Figure 2**: A: Potential correlation between national prevalence and cat density. Countries are ranked according to increasing FIV prevalence. Associated cat densities are in number of cats per human inhabitant (x100, for scale convenience) and in number of cats per $km^2$. Values are not given, as only a tendency was desired. Spearman rank test shows no correlation between the density and FIV prevalence at the country scale. However, a $\chi^2$ test shows that there are significant differences of FIV prevalence between countries. The second part of the figure, B, shows that there are also significant differences in FIV prevalence between continents. FIV prevalence and number of individuals screened (into brackets) are given.

### 3 3 Virus specificity:

Different strains of FIV infecting domestic cats have been reported throughout the world [1, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93]. FIV has also been shown to infect North American, Indian, Russian, Southern and Eastern African non-domestic felids (in the wild as well as in African, American, Australian and European zoos). It has now been isolated in lions (*Panthera leo*), cheetahs (*Acinonyx jubatus*), tigers (*Panthera tigris*), bobcats (*Lynx rufus*), pumas (*Felis concolor*), leopards (*Panthera pardus*), snow leopards (*Panthera uncia*), jaguars (*Panthera onca*), Pallas cats (*Felis manul*) and flat-headed cats (*Ictailurus planiceps*) [22, 23, 93, 94, 95, 96, 97, 98]. The absence of FIV infection for some other tested felid species may result from the very low number of individuals screened [1 to 10: 90, 99 or 1 to 23: 94, 100]. There are high differences in seroprevalence according to continents. For example the tested Asian, West African and Namibian lion populations seem free of infection, whereas East African ones show high rates of prevalence (up to 90% [92]).

Genetic studies have shown that the overall genetic differences between Feline Immunodeficiency Viruses infecting felids are at least as large as those within primate lentiviruses [95, 97]. These Feline Immunodeficiency Viruses seem to be specific, for example a strain isolated from an infected lion could not infect a domestic cat [96]. However, only one such experiment have been published. Further research needs to be done concerning the real status of the species not already known to be infected, as well as virus specificity and evolutionary relationship between the Feline Immunodeficiency Viruses.

### 3 4 Factor effects:

*Health status*: A significant higher FIV prevalence was found in the category of sick cats compared to the two other categories ($\chi^2$=1,891.38, P<$10^{-4}$, Table I). It is clear that having three times more infected cats among the ill cats than in the apparently healthy ones results from the fact that cats recorded in these surveys came mostly from veterinary hospital. Thus the healthy cats are here rarely seropositive, whereas the tested ill cats are often high risk individuals. In fact, with a populational point of view, an epidemiological study would find the opposite: the longer the seropositivity period, the higher the ratio [healthy/ill] among infected cats. Moreover, if we consider the low survival rates of free-roaming cats in natural populations [101], few of these infected individuals should reach the age of developing AIDS, increasing this ratio.

*Sex*: This synthesis clearly highlights that males are between two and three times (2.45) more likely to be infected than females. But females are still relatively often infected, compared to the frequency of fights they have. Females sometimes fight but it is quite rare [102]. We hypothesize that another possible mean of transmission from males to females is likely to occur. Females are bitten at the neck by males during mating, and these bites can cause severe wounds (Natoli, *pers. com.*). Moreover, females can mate with

several males during a single œstrus (up to seven, [103]). This particular bite might be a specific infection mode for females.

*Neutering*: Reported results for neutered cats differ according to studies, for males as well as for females. Concerning the 45,507 cats for which neutering status was given, there was a higher degree of infection in neutered males and females than in their intact counterparts ($\chi^2$=724.75, P<$10^{-4}$, Table I). Castrated males do not anymore participate in courtship which is the main source of fights [104], but they strongly preserve their territorial behavior. Moreover, many castrated cats may have been infected before being neutered (for cats coming from veterinary hospitals and pounds). Furthermore, it has been shown that mean age and median age at death were higher for castrated than for intact males, even for those known not to have died from trauma or poisoning (evidence that the long lives of castrated males were not only due to less exposure to violence [105]). One report [72] where neutered cats are more often positive than their intact counterparts shows that the average age of neutered cats is 3.2 years older than that of intact cats. The higher degree of prevalence found in neutered males may be a consequence of their longer life.

*Age*: The four distribution types showed significant differences in FIV infection with age ($\chi^2$=1700.97, P<$10^{-4}$ for A type and $\chi^2$=701.15, P<$10^{-4}$ for B, C and D types put together at the B type). There is a progressive increase of prevalence, followed by a decrease, the inflection point being within the class of 6 to 10 years of age (see figure 1, types C and D). Adults are more likely to be infected than kittens, probably because they fight and are bitten more often than kittens. Furthermore, the long period of positivity causes an accumulation of the number of positive cats with age. The decrease may be due to the fact that the oldest individuals are lower risk individuals (e.g. indoor cats).

*Roaming habits*: Indoor cats were less often infected than outdoor cats ($\chi^2$=609.56, P<$10^{-4}$, Table I) which obviously fight more often than indoor cats. The way of life of cats living indoors but allowed to roam was associated to an intermediate risk factor: they thus showed an intermediate rate of infection. The relatively important rate of prevalence for indoor cats (4.52%) may be explained by the fact that these cats were in veterinary hospitals for diverse illnesses, and thus represent the higher risk class of indoor cats.

*Breed*: On the 55,051 cats for which breed was given, domestic (European) cats had the highest prevalence rate, nearly double that of purebred cats ($\chi^2$=34.46, P<$10^{-4}$, Table I). Siamese cats were as often FIV infected as European cats, and also double that of purebred cats ($\chi^2$=0.402, P=.500). Purebred and mixed breed cats have the same prevalence rate ($\chi^2$=8.90, P=0,065). The observed breed effect has to be taken with caution, as purebred cats are mostly indoor cats whereas domestic cats are more often allowed to roam. Siamese cats are very common in natural domestic cat populations (e.g. up to 32% in some French and 34% in some American cat populations, [106, 107]) and most of them are not bought by owners (contrary to purebred cats), and thus are allowed to roam. Even if this hypothesis should be considered, no genetic predisposition has ever been shown.

*Group size*: A significant difference was found between groups of different sizes, with the lowest percentage of seropositive cats in groups of two to five individuals

($\chi^2$=14.78, P=.0006, Table I). This may be explained by the fact that FIV does not seem to be very contagious [11] and because those cats are often related, e.g. with matrilinear groups [101], and are mainly pacific and socially stable [108]. Households with a larger number of cats are often animal shelter-type homes frequently introducing free-roaming cats and thus representing higher risk groups. As interactions between individuals may differ according to their age, sex, and kinship [109], the group structure is probably a more important parameter than its size and has to be considered when explaining FIV prevalence variability among groups.

| vital statistic | Total number of cats | Number of FIV positive | % of FIV positive |
|---|---|---|---|
| **Health statut distribution** | | | |
| Healthy | 35,474 | 1,847 | 5.21 |
| Sick | 43,941 | 7,026 | 15.99 |
| Other | 5,964 | 562 | 9.43 |
| **Sex distribution** | | | |
| intact males | 13,455 | 1,739 | 12.92 |
| castrated males | 12,577 | 1,954 | 15.54 |
| intact females | 10,931 | 559 | 5.12 |
| spayed females | 8,544 | 568 | 6.65 |
| **Age distribution** | See Figure 2 | | |
| **Roaming habits** | | | |
| indoor | 12,166 | 550 | 4.52 |
| indoor/outdoor | 27,166 | 3,346 | 12.32 |
| feral | 6,818 | 1,071 | 15.71 |
| **Breed distribution** | | | |
| domestic | 40,477 | 5,240 | 12.95 |
| misc. purebred | 6,953 | 482 | 6.93 |
| siamese | 309 | 43 | 13.92 |
| persian | 444 | 22 | 4.95 |
| himalayan | 282 | 13 | 4.61 |
| abyssinian | 47 | 4 | 8.51 |
| others | 120 | 2 | 1.67 |
| mixed breeds | 8,319 | 683 | 8.21 |
| All pure and mixed breeds | 16,294 | 1,249 | 7.67 |
| **Group size distribution** | | | |
| 1 | 23,498 | 2,423 | 10.31 |
| 2 to 5 | 18,286 | 1,708 | 9.34 |
| >5 | 4,177 | 468 | 11.20 |
| **Total study** | 85,529 | 9,441 | 11.04 |

**Table I:** Prevalence of FIV infection, according to several vital statistics, for the totality of the serosurveys studied here. All tests are significant, but only roaming habits, sex and age directly affect risk of FIV infection.

*Potential cofactors*: Since FIV infection affects processing of many pathogens, we looked for potential pathological cofactors. First, FeLV is a potent activator of FIV replication both quantitatively and qualitatively: co-infection of cats with FIV and FeLV enhances the severity of FIV infection and affects the distribution of FIV DNA in various tissues [110, 111]. Second, it has been shown that FeSFV (Feline Syncitia Forming Virus) is isolated more often in cats infected by FIV than in cats free from FIV [76, 112]. However this seems to be due to a similar infection mode (through bites). Last, it has also been shown that FHV-1 (Feline Herpes Virus type 1) might act as a cofactor which contributes to acceleration of clinical disease in cat AIDS (FHV-1 transactivates the FIV Long Terminal Repeat, [113, 114]), but these results are still debated [115]. In brief, FIV infection enhances severity and accelerates the clinical signs of many pathogens, and some viruses also affect FIV infection processes, but there is still no evidence that transmission of FIV may be facilitated by any pathogen.

In conclusion, FIV infection is mostly characterized by parameters linked to behavior: sex, age and roaming habits. The fact that not all individuals have the same infection risk is a major information to be taken into account for epidemiological studies.

The pitfall in all these serological surveys is that factors supposed to affect the spread of the virus were never taken into account simultaneously, thus it was not possible to avoid confounding effects. Moreover, as they had a specific (veterinary) aim, these surveys had no populational reference. A population of cats is primarily defined by the ability of individuals to meet at anytime [116]. Cats are known to develop different types of social and spatial structures, and mating systems according to habitat [117]. This may affect the spread of the virus and the rate of prevalence of FIV within cat populations. There is, to our knowledge, no epidemiological study for which a sample is representative of a natural population except that started by our team (Courchamp *et al.*, in prep.). This kind of study is strongly warranted.

Evidence of FIV infection throughout the world, as far back as stored sera are available (25 years ago), the fact that it is rather endemic [108], and does not seem to be very contagious [14, 17], all this is in agreement with the hypothesis that FIV is not recent. It could in fact be as old as the age of spread of domestic cats throughout the world, that is, several thousand years. The existence of very close but probably specific Feline Immunodeficiency Viruses for numerous non-domestic felid species [92, 95, 96] even suggests the possibility of the existence of an ancestor of FIV before felid species divergence [96], estimated at 3 million to 6 million years ago. Moreover, a long-term study of three domestic cat populations (since 1982; [101, 117, 118]) showed that, although FIV is highly present (Courchamp *et al.*, in prep.), the number of individuals in all three populations has reached an equilibrium state. Another result showed by this long term study is that survival of free roaming cats is very low, at least in rural habitats [117, 118]. With an age of infection around one to two years old [79] and a total of five to seven years from infection to death due to AIDS [21, 17], very few outdoor infected cats will reach the age of dying from AIDS. Furthermore, our first results obtained through the modeling of the circulation of FIV within domestic cat populations [119] showed that FIV has a low

impact. According to our model, introduction of FIV does not lead to extinction of susceptible or infected cats, but to a stable equilibrium stage of both categories, the virus reduces the size of the host population, even when equilibrium is reached, but weakly (less than 5%), and the transmission rate also is low [119]. All of these findings are in agreement with the hypothesis of a long coevolution between retroviruses and felids.

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**Annex:** Synthesis of data published on epidemiologic surveys throughout the world, according to the health status of the cats. As it is the most used differenciation between individuals in these surveys, the first, second and third columns show the FIV rate and number of tested individuals (in brackets) for respectively healthy cats, sick cats and cats of other categories (feral cats, cats suspected to be infected, cats in contact with FIV-positive cats, or cats for which none is precised).

**ANNEX**

| Country | Reference | % FIV infected in healthy (n) | % FIV infected in sick (n) | % FIV infected in other (n) |
|---|---|---|---|---|
| Australia | 24 | | | 32 (65) suspect |
| | 25 | | 26 (467) | |
| | 26 | 29 (72) | 28 (211) | |
| | 27 | 6.7 (30) | 10.8 (37) | 3.5 (111) suspect |
| | 28 | 30 (141) | | |
| Austria | 29 | | | 3.2 (2,180) unknown |
| | 30 | | 3.5 (1,905) | |
| Denmark | 31 | 5.3 (513) | 19.4 (489) | |
| | 32 | | | 18.4 (499) feral |
| | 33 | 4.1 (367) | 19.1 (105) | |
| Finland | 34 | | | 6.6 (196) feral |
| France | 35 | 5.6 (4,456) | 23.7 (5,574) | |
| | 36 | | | 32 (66) feral |
| | 37 | 22.1 (208) | | |
| | 38 | 4.1 (146) | 22.1 (398) | |
| | 39 | 15.2 (354) | 27 (1,084) | |
| Germany | 40 | 3.2(2,613) | 12.3(3,488) | |
| | 41 | | | 9.5 (674) unknown |
| | 42 | 4.5 (138) | | |
| Greece | 43 | 1.4 (143) | 8.5 (59) | |
| Hungary | 44 | 0 (90) | 30.7 (13) | |
| Italia | 45 | | 24 (277) | |
| | 46 | | 17.14 (35) | |
| | 47 | | | 64.3 (56) in contact |
| | 48 | 2.1 (142) | 12 (151) | |
| | 49 | 9.25 (54) | 13.9 (144) | |
| | 50 | 8.2 (134) | | 10 (20) feral |
| | 51 | 12.0 (740) | 30.6 (1,123) | |
| | 52 | 9.3 (209) | | 15.3 (230) suspect |
| | 53 | 2.4 (42) | 15.79 (323) | |
| | 54 | 7 (648) | 22 (891) | |
| Japan | 55 | 9.17 (338) | 13.9 (101) | |
| | 56 | 3.6 (55) | 22.7 (260) | |
| | 57 | 12.4 (1,584) | 43.9 (1,739) | |
| | 16 | 5.2 (326) | 6.46 (232) | |
| Netherlands | 37 | 3 (198) | 1 (123) | |
| | 42 | 0 (78) | 7 (256) | |
| New-Zealand | 58 | 6.82 (88) | 27.27 (110) | |
| Norway | 59 | 5.9 (85) | 10.1 (139) | |
| Switzerland | 37 | 2.8 (178) | 3.7 (775) | |
| | 60 | 0.7 (561) | 3.4 (860) | |
| Taïwan | 61 | 1.42 (70) | 0 (41) | 12.5 (16) feral |
| U. K. | 62 | 0 (28) | 22.34 (94) | 27 (90) feral |
| | 63 | 5.8 (1,007) | 18.6 (1,204) | |
| | 64 | 4.8 (667) | 13.2 (4211) | |
| | 65 | 16 (19) | 79 (43) | |
| | 37 | 12.8 (431) | 0 (98) | |
| U.S.A. | 66 | 11.8 (51) | 12.3 (423) | |
| | 67 | | | 8.4 (95) unknown |
| | 68 | | | 5.1 (506) feral |
| | 69 | 3.6 (83) | 15 (40) | |
| | 70 | | 15 (54) | |
| | 71 | 4 (15,374) | 11.6 (12,602) | |
| | 72 | | | 6 (432) suspects |
| | 73 | 5.2 (957) | 15.2 (599) | |
| | 5 | 12.5 (40) | | |
| | 74 | | | 4.2 (119) feral |
| | 75 | 8 (194) | 13 (166) | 26 (258) unknown |
| | 76 | 1.1 (361) | 8.9 (226) | |
| | 14 | | | 14.4 (351) suspect |
| | 77 | 2.4 (585) | | |
| U.S.A. + Canada | 78 | 1.2 (511) | 14 (2,254) | |
| TOTAL | | 5.21 (35,474) | 15.99 (43,941) | 9.43 (5,964) |

Courchamp F., Artois M. & Pontier P. Epidemiology of Feline Immunodeficiency Virus in a rural domestic cat population. *Submitted*.

# CHAPTER IX

# EPIDEMIOLOGY OF FELINE IMMUNODEFICIENCY VIRUS IN A RURAL DOMESTIC CAT POPULATION

## 1 Introduction

Feline Immunodeficiency Virus (FIV) is a worldwide feline lentivirus similar to HIV (which causes AIDS in humans); its irreversible infection leads to fatal disease in cats [1]. Due to strong similarities between these viruses, the pair cat-FIV is considered as a suitable biological model for HIV studies in many fields [2-4].

FIV antibodies have been found in ten non-domestic felid species (reviewed in [5]), with very high prevalence rates in some populations: more than 70% in a captive population of Asian lion (*Panthera leo persica*, [6]), and more than 80% in some natural East African lion populations (*Panthera leo*, [7]). Even if it has not yet been proven that the strains infecting the different species are pathogenic, FIV may be a real threat, given that all of the 37 species in the Felidae, except the domestic cat, are considered threatened or endangered [8, 9]. For example, one third of an endangered population of less than 50 Florida Panthers, *Felis concolor coryi*, is infected [10] and some threatened populations of wild felids are in close contact with infected domestic cats (e.g. *Felis silvestris* in Europe, [11], [12] and *Felis iriomotensis* in Japan, Ono, 1985, *in* [13]). Unfortunately, epidemiological data on FIV within natural populations of felids are very scarce. This is mainly due to the difficulty of studying wild felid species. Domestic cats are a much more suitable animal model to study, in laboratories as well as in natural conditions. Domestic cat populations are known to vary widely, from solitary cats to large social groups (reviewed in 14). Such population differences in social organisation can affect spread patterns of viruses. Moreover, some domestic cat populations may be compared, for given aspects, with non-domestic felid populations. In this context, as well as for domestic cat health considerations, and as a relevant biological model for HIV studies, FIV epidemiological studies of domestic cat populations are of major interest.

A large number of FIV serological surveys has now been published for domestic cats, indicating relatively high prevalence rates all over the world (reviewed in [5]). Unfortunately, all of these studies were based on unrelated cats from veterinary facilities, without any population references. Moreover, the factors analyzed were never taken into account simultaneously, precluding the highlighting of potential links between them on FIV infection. To our knowledge, no epidemiological study of representative samples of FIV in natural populations of domestic cats has been published. Avoiding the above shortcomings, we present here an epidemiological study of a natural population of domestic cats living in a rural habitat in France. The temporal variation of FIV prevalence during the four years of epidemiological study allows us to analyze whether FIV infection is endemic or epidemic in this population. We discuss the role of factors suspected to affect disease transmission, such as sex, age or origin of the cats. Finally, the spatial distribution of infected cats is also analyzed in order to explore its potential role in the dissemination of FIV in the population.

## 2 Materials and Methods

### 2 1 Population

The cat population of Saint-Just-Chaleyssin has been monitored yearly since 1982 by one of us [15]. This population is located in France, in a rural village (1500 inhabitants) at approximately 30 km from Lyon. Around 340 cats belong to the population, two thirds of which are females (Fig. 1).

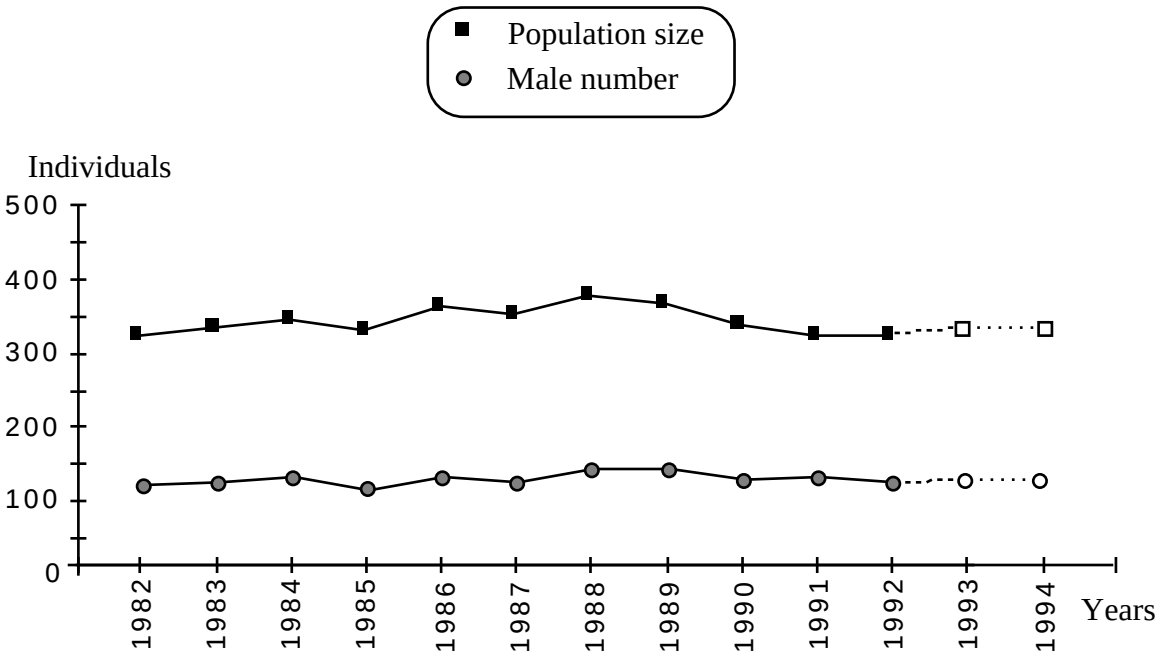


**Figure 1**: Population size (number of individuals) and sex ratio (number of males) in the population from 1982 to 1994. Total number of individuals in the population is not yet available for 1993 and 1994.

### 2 2 Sampling

Cats were first quasi-exhaustively censused yearly (since 1982) by interviewing the village inhabitants. Since 1991, a sample of cats was randomly selected each year from owners who allowed a blood sample on their cats. Cats were caught directly in their house. A few cats, known to be untamed, were trapped in lured cages. Some individuals were caught several times on different years. The cats were anaesthetized with a mixture of ketamin chlorhydrate (Imalgène 1000, Rhône Mérieux, 15 mg/kg) and acepromazin (Vétranquil 5.5%, Sanofi, 0.5 mg/kg) by intramuscular injection. For each cat, we recorded six individual parameters as potential risk factors: sex, age, weight, roaming habits, origin and group size. We divided individuals into four sex

classes: males, females, castrated males and neutered females. Age classes were based on Liberg's classification [16]: cats of one year old or less, cats 2 to 3 years old, 3 to 4 years old and cats 5 years old or more (mean life expectancy of cats in this population is from 3 to 5 years, according to sex, [15]). The three weight classes, which generally divide individuals into three groups of approximately equal size, were less than 3 kg, 3 to 4 kg and more than 4 kg. Roaming habits were: roams freely, not always allowed to roam, roams rarely. Origin was: cats born in the village, cats brought from elsewhere and cats that "appeared one day", from an unknown origin. Finally, group size (number of conspecifics living in the same household) was divided into three classes: cats living alone, groups of two cats, groups of more than two cats. In addition, by blood sample, we recorded the presence of antibodies to FIV (kittens under 6 months were not taken into account as they were not sampled for blood).

### 2 3 Serological tests

A large range of methods is available for the detection of either this virus or associated antibodies (reviewed in [3]). Despite some false seropositives and false seronegatives, the ELISA method (Cite-combo; Idexx) we used is considered "the most sensitive and desirable" for screening tests [3, 17]. To avoid false positives, all positive sera were confirmed by Western Blot [18].

### 2 4 Statistical analysis

*Samples*

Sample representativeness was tested each year by comparing sex and age distributions with those of the whole population for that year.

In order to study factor effect on a larger sample, we composed an artificial sample by pooling the four yearly samples. This has been possible since the population size and sex structures are in equilibrium (Fig. 1), no year effect on prevalence was found (see results), and no difference in age structure was found between the four samples ($\chi^2$=7.938, ddl = 9, p=0.5404). Multiply recorded individuals were removed from the pooled sample, only one (randomly chosen) record being kept. The pooled sample includes 124 cats.

*Multiple Correspondence Analysis:*

Multivariate analysis was done in order to study the role of the six potential risk factors taken simultaneously, on FIV infection. As the potential linear models of a logistic regression were too numerous with six risk factors, the analysis was done in two steps: first, we eliminated risk factors that are not linked to FIV by an exploratory analysis of the data set, and secondly, we calculated a logistic regression with the remaining risk factors.

We thus first used an exploratory multivariate analysis of the pooled sample. The appropriate tool is a Multiple Correspondence Analysis (MCA, [19]). The diagram of correlation ratios between the factorial axes of the MCA and the factors was generated. We retained only the factorial axes with which the FIV correlation coefficient was the highest (Fig. 2A). Next we selected, for each of the six risk factors and among the retained factorial axes, the factorial axis on which the correlation coefficient of the risk factor was the highest. Then, for each of the six risk factors, we calculated the Gaussian distribution of its categories on the selected factorial axis of the MCA (Fig. 2B), and we compared them with the distribution of the two categories of FIV (infected or not) on the same factorial axis. Such a procedure allows us to distinguish risk factors whose category distributions are completely overlapping, and thus, that may not (or little) influence FIV infection, from those with non-overlapping categories.

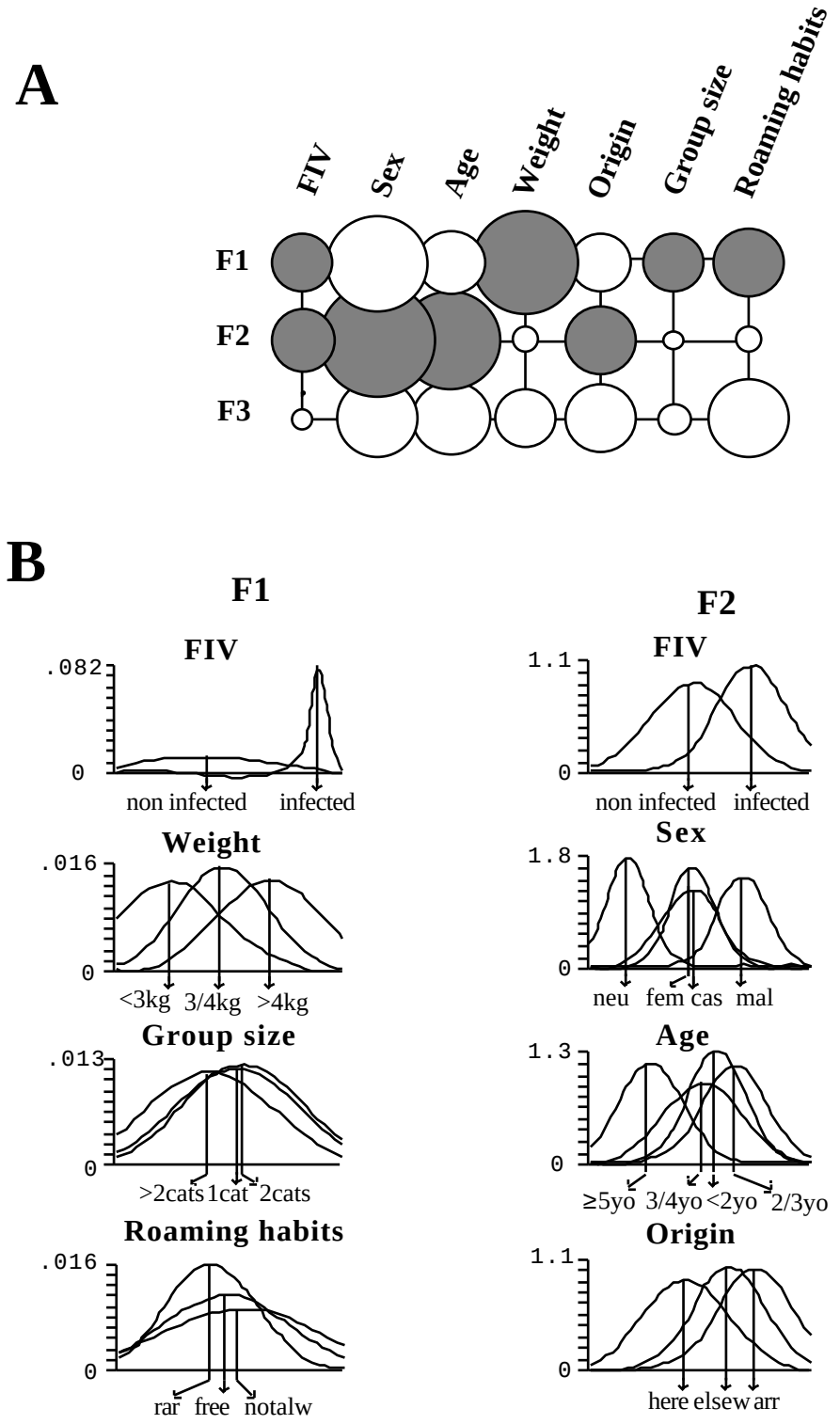


**Figure 2: A:** Correlation ratio diagram of the 3 first factorial axes (F1, F2, F3) and the variables (FIV and the six risk factors). The larger the circle, the higher the representation of the risk factor on the factorial axis. For each risk factor, the correlation coefficient of the selected factorial axis is in grey, the others are in white. **B**: Gaussian distributions of each of the variable (FIV and the six risk factors) categories on the factorial axis for which the risk factor representation is the best (F1 and F2: first and second factorial axes, respectively). The categories are: males (mal), females (fem), castrated males (cmal), neutered females (nfem), less than 2 years (<2yo), 2 to 3 years (2/3yo), 3 to 4 years (3/4yo), 5 years or more (≥5yo), less than 3kg (<3kg), 3 to 4 kg (3/4kg), more than 4 kg (>4kg), born in this village (here), brought from elsewhere (elsew), arrived one day (arr), free to roam (free), not always allowed to roam (notalw), rarely allowed to roam (rar), one single cat (1cat), two cats (2cats), more than two cats (>2cats)

*Generalized Linear Models*

Logistic regressions were used to estimate quantitatively the influence of several factors taken simultaneously, as well as their possible interactions on FIV infection [20]. For these regressions, we used risk factors selected through the MCA. We tested various effects of all possible models with a backward approach. Each of these models was noted with its number of parameters (K) and a measure of its goodness-of-fit, the scaled deviance (SD). Instead of the classical Akaike Information Criterion (AIC, [21]), we calculated for each candidate model, the $AIC_C$ for small-sample bias correction [22]:

$$AIC_C = SD + 2K + \frac{2\,(K+1)\,(K+2)}{n-K-2}$$ , where n is the total number of individuals.

We selected the model with the lowest $AIC_C$ value as the best statistical choice for describing our data set.

*Spatial analysis*

Since the spatial distribution of cats may influence FIV dissemination, each cat's home position was recorded on the village map, with its serological status: seropositive or seronegative (Fig. 3 A). In order to highlight potential clustering of infected cats, we analyzed, on the pooled sample, spatial distribution of seropositive cats compared to seronegative ones, through a matrix of distances (with classes of distances). From this matrix, we compared the distance distributions between seropositive cats and between seropositive and seronegative cats, by a Wilcoxon test for discrete distributions [23].

*Software*

The $\chi^2$ values and confidence intervals were calculated with StatView IV software (© Abacus Concepts Inc., 1992). MCA was performed with ADE software [24]. Logistic regressions were performed with GLIM software [25].

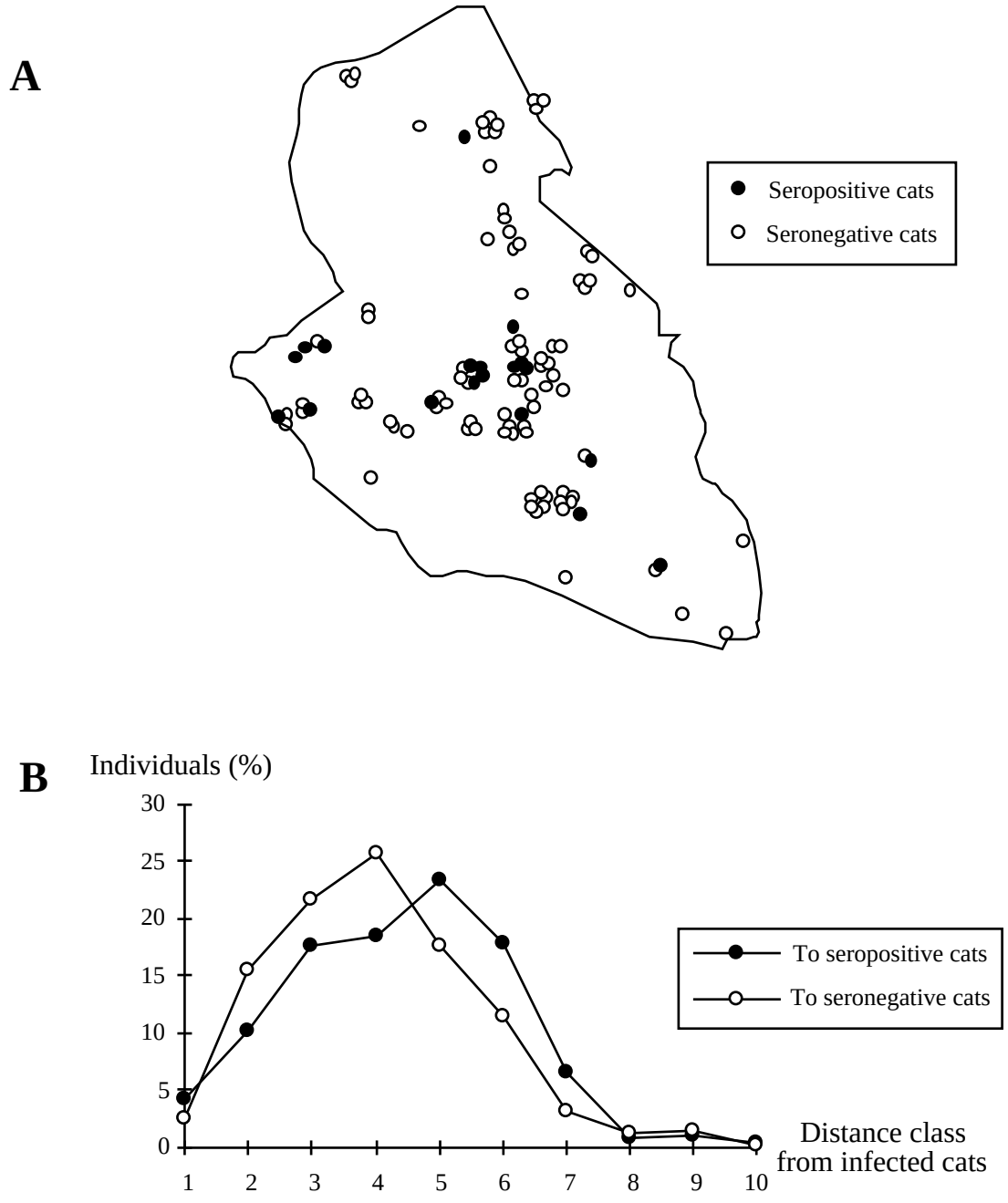


**Figure 3**: **A**: Spatial distribution of the sampled cats on the map of the study area, Saint-Just-Chaleyssin. The white circles represent the FIV negative cats, whereas the black circles represent the FIV positive ones. Overlapping circles mean that the cats live in the same group, *i.e.* in the same household. **B**: Distribution of relative distances from infected cats to seropositive cats (black circles) and to seronegative cats (white circles). Seropositive cats are significantly further from other seropositive cats than are seronegative ones.

## 3 Results

### 3 1 Population and sample representativeness

During the four years of the epidemiological study, as well as the ten preceeding years, the population size remained stable. Also, the population structure shows no significant differences between years (e.g. sex ratio: $\chi^2$=5.233, ddl = 12, p=0.9498, Fig. 1). Size of the samples were 46, 53, 48 and 44 individuals for respectively 1991, 1992, 1993 and 1994, which corresponds to approximately one-sixth of the population size. The four samples were significantly representative of population structures for both sex and age distributions ($0.404 \leq \chi^2 \leq 5.797$, ddl = 3, $0.9394 \leq p \leq 0.1219$ for sex; and $0.007 \leq \chi^2 \leq 1.298$, ddl = 3, $0.9323 \leq p \leq 0.2546$ for age).

### 3 2 FIV prevalence

The overall rate of FIV infection was 19.6 (± 5.8) %, 15.1 (± 4.9) %, 14.3 (± 5.1) % and 9.1 (± 4.3) % for 1991, 1992, 1993 and 1994 respectively, and 13.7 (± 3.1) % for the pooled sample. Despite a slight decrease, there was no significant difference in prevalence rates between years (LRT=2.186, p<0.077).

### 3 3 Risk factors

The Gaussian distributions of the categories of the six risk factors (Fig. 2), show that males, young adults, heaviest cats and immigrant cats are more likely to be FIV infected (this is confirmed by simple chi-square tests and Wilcoxon tests for discrete distributions, see Fig. 4). Similarly, roaming habits and group size have a low effect, if any, on FIV infection, and their distribution curves are too overlapping to be selected for further analysis. Thus, multivariate analysis led us to select sex, age, weight and origin for the logistic regression. The $AIC_C$ of the different models of the logistic regression with these four risk factors led us to select two very close models with very close $AIC_C$ value: 67.548 and 67.679. The first one takes into account the four principal factors: sex (factor S), weight (factor W), origin (factor O) and age (factor A), and the second these four principal factors and the sex and age interaction:

$$\text{Logit}\,(p_{ijkl}) = \text{Log}\left(\frac{p_{ijkl}}{(1-p_{ijkl})}\right) = C + S_i + W_j + O_k + A_l + S_i.A_l$$

where $p_{ijkl}$ is the probability of being FIV positive taken by cats of sex i, weight j, origin k and age l and C is a constant. The interaction of sex and age shows that females are more likely to be infected when they are young and males when they are older. Predicted values and residuals have been calculated according to the two selected models. Differences between observed and predicted values are low for each of the category arrangements (0.191 and 0.324 individuals on the average, for the first and the

second models respectively), indicating that information on the four factors provide a good estimate of the probability of being FIV infected.

### 3 4 Spatial analysis

Distances between seropositive cats were significantly higher than the distances between seropositive and seronegative cats (ST*= 4.01, p<0.047, Fig. 3B).

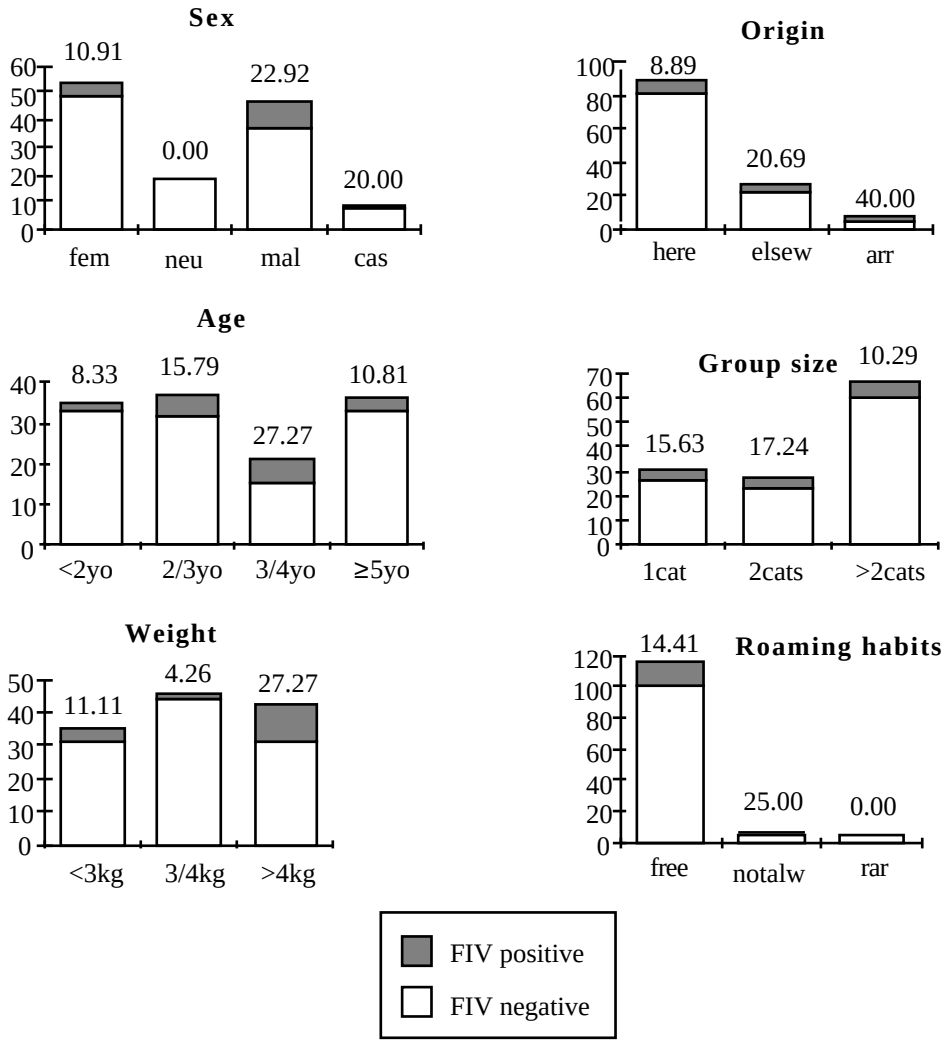


**Figure 4**: Number of FIV seropositive and seronegative individuals for the different categories of six studied risk factors in the pooled sample. The FIV prevalence rate is given for each category. The category legend is given figure 2.

## 4 Discussion

### 4 1 FIV prevalence rate

Since the cat samples are representative of the population, we can infer the real prevalence rates in the population: 13.7 ± 3.1%. Morevover, supposing that 15% of seronegative cats are infected [26, 27], the FIV population prevalence rate reaches 15.8 ± 3.3%. The slight decrease of FIV prevalence is not statistically significant, and may be due to the low number of infected individuals in this population, and thus in the samples. This suggests an endemic state of FIV infection in this population.

### 4 2 Risk factors

The main mode of FIV transmission is thought to be by bites [17, 28]. As it is known that males fight more often than females [14], the greater proportion of infected males is logical. The mating system of our cat population is suspected to be, at least partially, polygynous [15, 29]. Such a mating system seems to be based on fights between male competitors for monopolizing one or several females [16] and of females against males to prevent potential infanticides [30, 31]. Morevover, cats fight for territorial defense. Even if, as has been suggested, males have a higher immunological susceptibility to parasites [32], their more aggressive behaviour is sufficient to explain the male predisposition to FIV infection. Castrated males are no longer involved in reproduction-linked fights, but are however infected at the same level as non-castrated males. This may indicate that territorial-linked fights, which are still present in castrated male behaviour, are the main cause of FIV infection in males. In a previous study [5], we hypothesized that females were infected mainly by males through neck biting during the mount. Here, we show that none of the 19 neutered females was FIV infected, whereas 6 of the 49 reproductive females were FIV infected. This goes in the direction of our previous hypothesis.

The heavier cats are more likely to be infected, certainly because they are more aggressive and fight more often than lighter ones. This is in accordance with Liberg who showed in farm cats that the heaviest males were the most dominant and aggressive [16].

There is no natural vertical FIV transmission [28, 33] and maternal antibodies prevent or limit infection in neonates [34]. Moreover, kittens and juveniles do not fight before they become a threat for sexually mature cats (more than one year old). We thus hypothesize that a high infection rate arises when the young cats have reached sexual maturity, followed by a lower but quite constant rate. As FIV infection is very long, an accumulation of infected cases develops with age. This may explain why, although young adult males are more likely to be infected, oldest males are also often infected. On the contrary, females are more likely to be infected when they are young. The reason for this may be due to the small number of infected females (6).

Cats that "appeared one day" in a house are much more likely to be FIV infected than cats that have a known origin (born in the village, or brought in from elsewhere). Either the cats of unknown origin were infected during their dispersal, having crossed territories of infected individuals, or they were cats with strong roaming habits, classically considered to be high-risk individuals. Cats brought from a neighbouring village are more likely to become infected than cats born in the village. A possible explanation is that these cats are often brought (or bought) when kittens, and may be allowed to roam only when they become adults. Thus, when they are confronted with other cats, they are perceived as adult strangers and are more frequently aggressed. A higher prevalence rate in neighbouring populations is not a satisfying explanation, as they have the same characteristics.

Roaming habits is a classic risk factor discussed in the literature, outdoor cats being more exposed to bites than indoor cats. Here the roaming effect was not striking, which may be explained by the homogeneity of cats roaming habits in our population (more than 90% of cats roam freely or almost freely, [15]).

The absence of group size effect may be due to low FIV contagiousness [28] and to the fact that cats living in the same household are often related in this population (Pontier, *unpublished data*) and hence may be socially more stable than cats living alone [35].

### 4 3 Influence of spatial structure

The analysis shows that the distance between two seropositive cats was larger than that between one seropositive and one seronegative cat. This confirms that FIV is not very contagious. It also suggests that FIV is transmitted through roaming individuals, maybe during fights linked to territorial defense.

## 5 Conclusion

An important result of this study is the report of the FIV prevalence rate of a natural population of domestic cats, 13.7±3.1%, studied through representative samples, which has not been done before. A second important result is that FIV seems to be endemic in our population. The endemic state of the disease is also suggested by simulations performed with a deterministic model of FIV spread [36]. A third important result is that individuals do not have the same infection risk, and the factors influencing FIV infection are strongly linked to behaviour: sex, age, weight and origin. Finally, the spatial analysis confirms the importance of behaviour for FIV epidemiology: transmission of FIV within the population seems to be mainly due to roaming individuals, which infect spatially distant conspecifics, probably during fights for territorial defense. The high variability of social structures of cat populations [37] and their associated behaviours make these populations a relevant model for the study of virus spread in wild felid populations (which are more difficult to study and may be threatened by disease outbreaks, e.g. feline infectious peritonitis in the cheetah,

*Acinonyx jubatus*, in Oregon [8, 38], or more recently, canine distemper virus in Serengeti Park lions [39]).

The existence of at-risk behaviour (fights) for FIV infection may be compared to the HIV situation. Indeed, the two main particularities of HIV epidemiology are the lentivirus infection processes (infection, then, several years after an asymptomatic period, irreversible illness leading to death), and the existence of at-risk individuals, determined by their behaviour. Thus epidemiological studies of FIV infection, taking the population into consideration, could be a suitable model for understanding HIV spread. In particular, since FIV at-risk behaviours may depend on the social structure of the population [15, 40], we hypothesize that the evolution of host/virus interactions, and in particular evolution of virulence (which is of major interest in human lentiviruses studies [41, 42]), varies according to cat population characteristics. Furthermore, we hypothesize that FIV-like viruses should have evolved towards different degrees of virulence according to the social systems of non-domestic felid host species, which could explain why there is still no evidence of death caused by some of these strains. FIV epidemiological studies could be of major importance for threatened felid species, and provide a suitable biological model for HIV virulence evolution in human populations.

## Acknowledgments

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# CHAPTER X

## INFLUENCE OF BEHAVIOUR AND OF SOCIAL STATUS ON FELINE IMMUNODEFICIENCY VIRUS EPIDEMIOLOGY: EVIDENCE FROM AN URBAN POPULATION OF DOMESTIC CATS (*FELIS CATUS*)

## 1 Introduction

Feral domestic cats are abundant in most occidental towns and cities: their popultions are found in most graveyards and hospitals (*e.g.* Jackson, 1981; Rees, 1981; Young 1981). Domestic cat populations present highly variable structures (Liberg & Sandell, 1986), and populations living in rural or in urban environments seem to be situated on the two extrems of a gradient of population spatial and social structures. Characteristics of these two types of populations are very different. Particularly, dynamics, social and spatial characteristics may influence the dynamics and spread of viruses such as FIV.

The aim of this study is to describe such a population of domestic cats living in urban environment. Dynamics, social and spatial structure, and especially epidemiology of a domestic cat population living in an urban environment have been monitored since 1992. Epidemiological results are presented hereafter. Dynamical, social and spatial aspects are dealt with only in the epidemiological context.The epidemiological data concern the Feline Immunodeficiency Virus (FIV). FIV is a feline lentivirus homologous to HIV, and causing AIDS in cats (reviews in Courchamp & Pontier, 1994; Bendinelli *et al.*, 1995). In a second aprt, we will compare the results of this study with those obtained on three populations of domestic cats living in rural environment.

## 2 Material and methods

### 2 1 Study area:

The studied population lives in a hospital situated in the center of Lyon, France (Hôpital de la Croix-Rousse). This hospital is 7.5 ha large and is surrended by walls or fences leading to busy streets, except on one part to a garden leading to a more calm street. The hospital was founded in 1861, and is covered by a network of undergrounds, part of which are totaly unvisited by humans (no light, mud floor, rubbles,...). There is one passage leading to the sewers.

Abundant vegetation (grass and bushes), as well as numerous passages (basement windows) to the undergrounds provide resting sites and shelter to the cats. Water, dry cat food and food remnants of the hospital kitchen are dayly provided to cats by nurses. It seems that cat presence in this hospital is ancient, and was even encouraged (or tolerared) some decades ago. Indeed, cat doors have been found in some doors in the underground. It is probable that cats presence was a security againts rodents.

### 2 2 Census and data collection and processing:

The study has begun in December 1992 and currently goes on. Data presented here concern the period from the beginning to August 1995. During a three years period, observations have been realized by many observers. A folder of standardized identity pictures was always available on the field, in order to ensure the cats identifications. For each observation, we noted the date and time, the weather, the name of the cat, the precise location (on a map), the activity of the cat, the presence of other cats (and their identity) and the name of the observer. In addition, we regularly investigated the hidden parts of the hospital (bushes and undergrounds) in order to find kittens or dead individuals.

Six trapping periods (TP) were realized during the three years period, every 6 monthes approximatively. Cats were trapped with lured cages, baits being as appetizing and diverses as possible (fresh meat or fish -cooked or not-, dry cat food or mash).

Once captured, the cats were passed from the trap to a box with a movable inner side facing a grid. This systems allowed us to jam the cat against the grid, and to perform the anaesthesia without direct handling. The cats were tranquilized with a mixing of ketamin chlorhydrate (Imalgène 1000, Rhône Mérieux, 15 mg/kg) and acepromazin (Vétranquil 5.5%, Sanofi, 0.5 mg/kg) by intramuscular injection. For each cat, we recorded sex, age, weight, health conditions, coat color phenotype. Individual file were completed with pictures of the coat pattern, photographs and morphological datas (length, width and height of the head). Each trapping period required the presence of at least 6 people during several day.

Sex of individuals was estimated by secondary sexual characteristics when untrapped. Age was known with precision for cats born in the hospital during the study (58.3%), and was estimated for older cats, or cats immigrating from outside of the population. Estimation was based on teeth state, when cats where trapped. According to Natoli (Natoli, 1985), cats were considered as being part of one of the four following age groups: kittens (less than 6 months old), juveniles (less than one year old), subadults (less than 18 months), adults (more than 18 months). Cats were then marked by subcutaneous injection of a electronic flea and by a numbered coloured collar (one different colour for all cats each session). For each cats (exept kittens under three monthes of age), a blood sample was taken for serological analysis of anti-FIV antibodies presence. As stress induced by capture, captivity and handling is known to be a favouring factor for appearence of diseases (e.g. Burrows, 1992; Burrows *et al*., 1994), food was supplied in abundance during captivity, and a minimal treatment was provided to individuals presenting signs of bad health condition or weakness.

The ELISA method (Cite-combo; IDEXX) is considered as the most sensitive and desirable for screening tests (Sparger 1993), and was selected for this study. To avoid false positives, all positive sera were confirmed by Western Blot (Lutz *et al*. 1988).

From the data collected through observations and trapping, each cat was known individually. Data were recorded in a data base (4D for Macintosh). For each observation, several variables are associated with the name of the observed cat (date, wheather, activity,...), together with the position of the cat on a digitalized map. All positions can then be obtained by a request, allowing to view all the places where the cats had been

observed on a map (see Figure **1**). The calculus of the surface of an area arbitrarily selected was also possible for preliminary analysis of home range pattern. Data treatment was then carried by Statview IV.

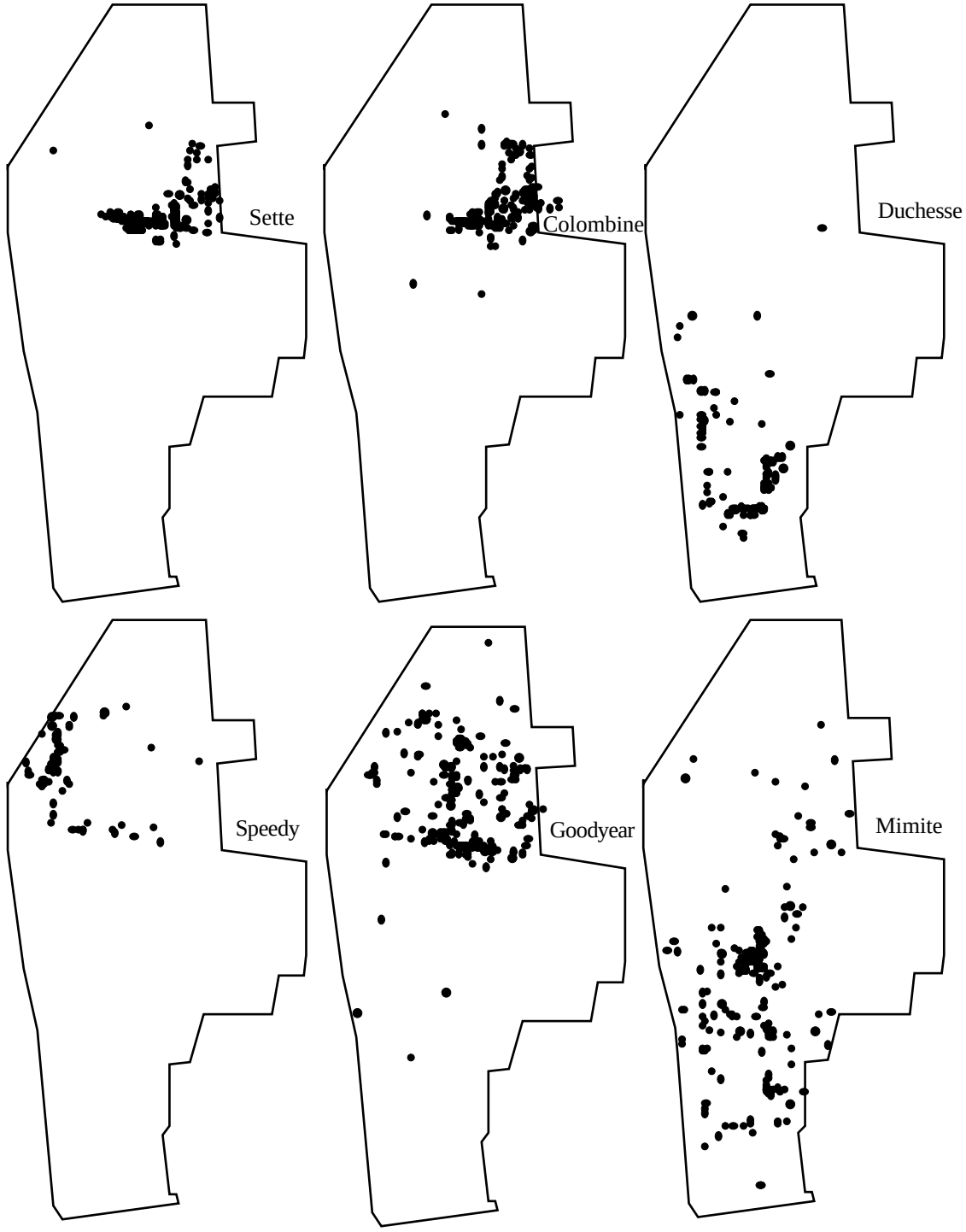


**Figure 1**: Examples of home ranges. This figure shows that frontiers may be marked, and overlapping may be important.

## 3 Results

### 3 1 Population characteristics:

Before analysing the epidemiological pattern of the population, we present hereafter the spatial, social and dynamics characteristics of the population.

#### 3 1 1 Population structure:

During the three years period, a total of 162 different individuals were identified in the hospital. The sex structure of the population is given for the six TP Figure **2**. Only 6 individuals were not sexed. Sex structure of samples is equilibrated ($\chi^2$>0.264; P=0.607). There are more males than females in the population (97 males, 65 females), but this trend is not significant ($\chi^2$=1.210; P=0.271). Age structure of the population is given for the six TP Figure **3**. There are more adults in the population, and also more kittens acoording to the period of the year. Coat color phenotype were known for each cat of the population during the three years, and the genetic structure of the population is given for the six TP Figure **4**. This figure shows the steady stability of genotypes and predominance of some alleles, such as non-agouti, suggesting strong kin relations between individuals.

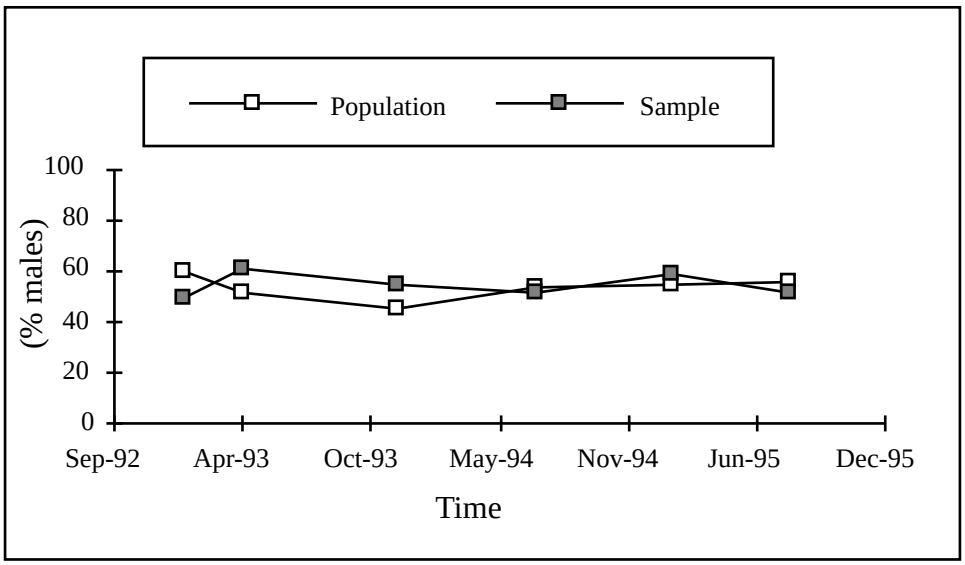


**Figure 2**: Sex structure of the population estimated at the six Trapping Periods

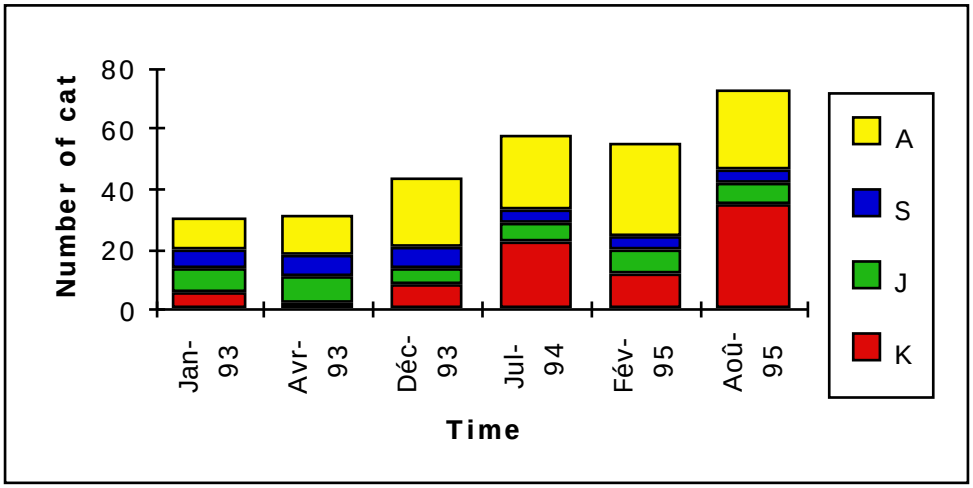


**Figure 3**: Age structure of the population estimated at the six Trapping Periods. A: Adults, S: Subadults, J: Juveniles, K: Kittens.

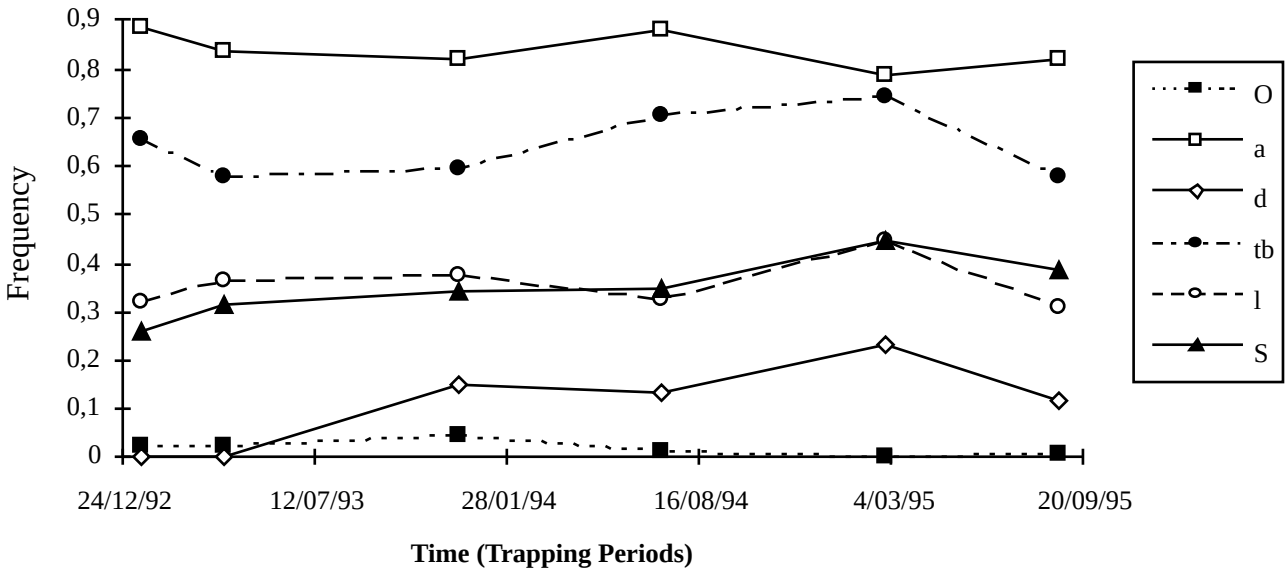


**Figure 4**: Genetic structure of the population estimated at the six Trapping Periods

### 3 1 2 Spatial and social structures

#### 3 1 2 1 Spatial structure

Cats were not homogeneously distributed in the hospital, large parts of which having null density, other being overcrowded. The total density of the cats varies from 3.33 to 7.47 cats/ha according to the date of the study.

The spatial structure of the population has been studied from December 1993 to May 1995. A total of 5868 individual sights have been recorded. An estimation of the home range has been calculated empirically for prelimirary analysis. Data are available for 64 cats, for wich we have at least 10 sights (10-317). Individual home range went from approximatively 0.508 ± 0.095 ha for males, to 0.508 ± 0.095 ha for females. There was also a difference in mean home range of adults (1.052 ± 0.150 ha), of subadults (0.243 ± 0.047 ha) and of juveniles (0.016 ± 0.007 ha), kittens staying in general within a few meters from their shelter. Even if not quantified in these preliminary analysis, overlapping of home range was large (see Figure 1), for males as well as for females, but degree of overlapping depended on social skills and hierarchical rank of individuals.

We tested the correlation of the size of the selected area (corresponding to an estimation of the home range) with sex, with weight and with an estimation of the head size (length*width*height) of individuals. This estimation of the head size is strongly correlated with the weigth of individuals (n=55; r=0.85; P<0.0001), giving an estimation of body size, and certainely of hierarchy status. Indeed it has been shown that heavier individuals are often the dominant ones (Liberg, 1981). We chose head size instead of body weight because this last measure could vary according to period of the year (and pregnancy of females). Results are shown Figure **5**. There is a good correlation between weight and home range size (n=48; r=0.54; P<0.0001), but mainly between head size and home range size (n=44; r=0.68; P<0.0001). It can be considered that individuals with larger home ranges are those with the heavier body, and thus the high ranking ones in social status.

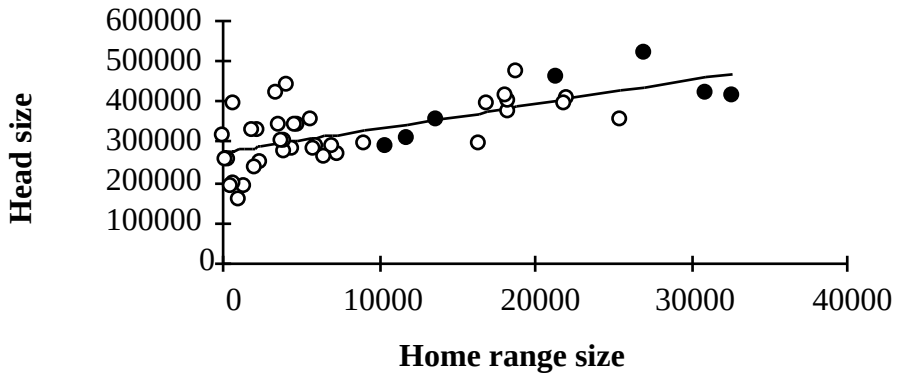


**Figure 5**: This figure illustrates the correlation between home range and head size (which is strongly correlated with body mass). Individuals with largest head size are considered as high ranked males. It shows also, as later discussed, a comparison of the home range size of FIV infected individuals (black circle) and of non infected individuals (white circles). In average, infected cats have a larger home range.

### 3 1 2 2 Social structure

Marking behaviour seems to be linked to cat social status: individuals with the larger home ranges have more often been observed marking ($\chi^2$=77.010; P<0.0001). Similarly, these cats were more often seen walking than other cats ($\chi^2$=72.744; P<0.0001). Preliminary observations of matings (Bernoud & Mion, 1995) suggest that mating system of this population is at least partially promicuist. By opposition, observations in rural environment suggested polygynous mating systems (Pontier, 1993). Communal nursing have not been observed in the population, although some females reared their kitten simultaneously (but separately).

A social hierarchy may be suggested for males, according to several criteria, among which proximity research by females or kitten (Natoli & DeVito, 1991), home range size, marking behaviour, body mass (and head size) or agonisitic, submissive or avoidance behaviours. According to field observations, it is thus possible to suggest that some males are high-ranked. These males are more often observed walking ($\chi^2$=299.102; P<0.0001), marking ($\chi^2$=299.102; P<0.0001) and observing ($\chi^2$=12.184; P=0.0005). These behaviours may be associated to a territorial defense or surveillance. These males were also seen more frequently mounting a female ($\chi^2$=6,752; P=0,0094), or attacking another cat ($\chi^2$=5.668; P=0.0173), which is also specific to high-ranked males.

### 3 1 3 Population dynamics:

#### 3 1 3 1 apparent survival:

On a three years period, 24 dead bodies were found in the hospital, whereas 40 cats disappeared. The cats that disappeared can also have dispersed, and as not all bodies were found, the survival rate can not be given with precision. However, we know that it is comprised between 73.38% (if all disappeared cats dispersed) and 62.74% (if they all died) per year (averaging (geometrically) the survival on a three years period).

Juvenile survival (kitten reaching 12 months old) rate can also be estimated. From the 97 cats that were seen kitten in the hospital , only 30 reached 12 monthes old, that is 31,93%. This is an overestimation of the real juvenile survival, as many litters were lately discovered.

#### 3 1 3 2 Fecundity

During the study, 97 kittens were found in the hospital, among which three were seen put in the hospital by owners after birth. During this period, the population counted 67 females, 28 of which being sexually mature. Thus, an estimation of the fecundity rate during the study period is between 1.12 and 2.61 kitten/female/year if we take into account all females or only females that were observed pregnant or lactating. Female gave

birth to one or two litters per year. As for mortality, fecundity is difficult to estimate with precision: the queens hide themselves to give birth and raise their kitten, and few were found sooner than a week after birth, especially at the beginning of the study, when the undergrounds were not totally investigated. This is thus an underestimated fecondity rate, as most early discovered litters had more kitten (up to 7). In literature, litter size is 4 to 5 kittens (Legay & Pontier, 1985). Our estimate is much lower. Natality rate is estimated between 83.41% and 86.55%.

#### 3 1 3 3 Migration:

During the study period, we saw 27 new cats not born in the population, only 13 of which succeeded to integer the population, *i.e.* regularly seen for more than one month. Among these 13 cats, 10 were females. One pregnant female was seen to investigate the hospital but did not seem to stay in the population. The immigration rate can be estimated to be 2.61% per year. Inversely, 22 cats born in the population disappeared from the hospital. As there were 13 males among these 22 individuals, it can be suggested that dispersal is not higher in males in this population. Cat that disappeared may have died and remain unfound, but, as many cats were seen going out of the hospital, some of them may have dispersed. Again, we can estimate that the maximum emigration rate is between 9.02 and 4.75, if all individuals are taken into account, or all individuals but those for which emigration is less problable (e.g. a more than three years old female that gave several litters in the hospital).

We can now calculate a growth rate of the population. We assume the growth rate is equal to the difference between (natality + emigration) and (mortality + immigration). We obtain thus 24.09% increase per year on three years (supposing increase is constant).

### 3 2 Epidemiology

#### 3 2 1 FIV prevalence rates:

The global prevalence rates obtained from the six TP are given Figure **6**. It is possible, as we know the number of individuals that were present during the TP, to estimate, in addition to the sample-based estimation, the maximum and minimum prevalence rate in the population (if all uncaptured cats are infected, or all infection free). These estimates are given Figure 7. There is no significant evolution of prevalence with time (LRT*=2.4, ddl=1, P=0.128)).

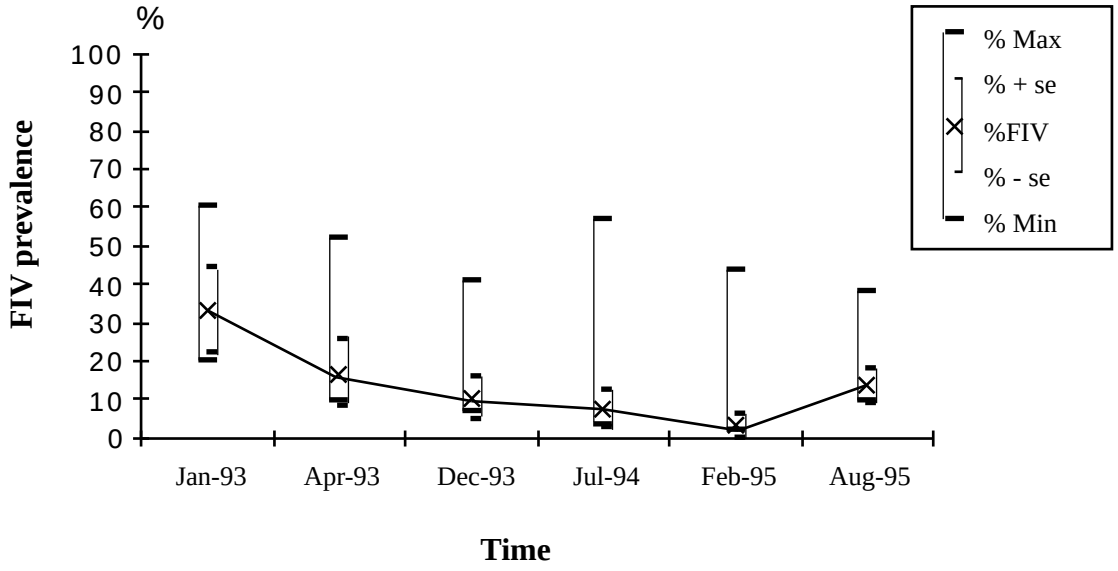


**Figure 6:** Prevalence rates estimated from the sample (%FIV), if all non tested individuals are not infected (%Min) or if they are all infected (%Max). Confidence limites are indicated (% - se; % + se).

### 3 2 2 Risk factors

As, despite considerable effort, each sample size was not very large, and as FIV prevalence rate is generally not very high (Courchamp & Pontier, 1994; Courchamp *et al*., submitted), few individuals were FIV-positive (6, 3, 3, 2, 1 and 7, for the six TP respectively, with a total of 12 different individuals). Thus, it was difficult to test, for each TP, potential risk factors such as sex, age or phenotype (Courchamp & Pontier, 1994; Courchamp *et al*., *submitted*). That is why we pooled individuals of the six TP together (see Courchamp *et al*., *submitted*). We tested effects of age, sex and weight on the probability of being seropositive. Statistical test suggest a significant difference between infected and non infected cats for weight (t=-2.578; P=0.0257), but not for age (t=-1.851; P=0.0911) or sex ($\chi^2$=0.668; P=0.4138). Nevertheless, these results have to be taken with caution, due to the small size of samples. Figure 7 shows that averaged values of mean age and male percentage are more important for infected cats that for other cats.

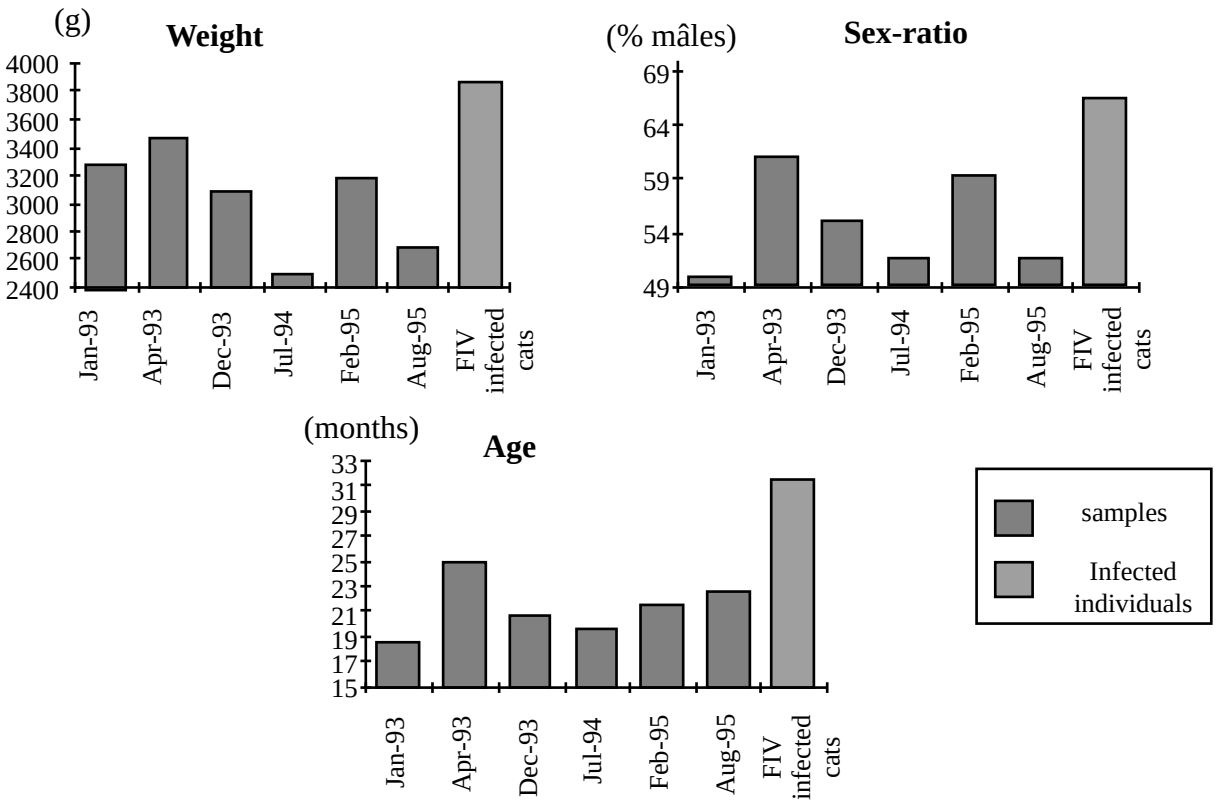


**Figure 7**: Comparason between mean values of infected cats and other cats of the samples for weight, sex-ratio and age.

We looked for a correlation between social status as previoulsy defined, and FIV serological status. Results show FIV that infected cats are significantly more often observed walking ($\chi^2$=6.850; P=0.0089), marking ($\chi^2$=14.975; P=0.0001) or observing ($\chi^2$=10.343; P=0.0013) that non infected cats. Home range size of positive cats is in average larger than the one of non infected cats, suggesting a higher social rank of infected cats (see Figure 5). Also, more mating by infected males have been observed ($\chi^2$=6.752; P=0.0094).

### 3 2 3 Trapping efficiency:

Among the 162 identified cats, 25 were absent at any TP (they were transient cats, or kitten born and died between two TP). On the 139 remaining cats, only 1 has never been captured. On the total study period, the trapping efficiency is 99.3% (Figure 8). Recapture has been more difficult. In order to verify a suspected bias in capture concerning FIV infection, we tested the distribution of recapture number of cats, and compared results for cats according to serological status. Results show that infected individuals escape recapture more often than other cats (t=2.601; ddl=10; P=0.026). For

this reason, as this result was suspected, we greatly improved the trapping effort for the sixth trapping session (see Figure 9).

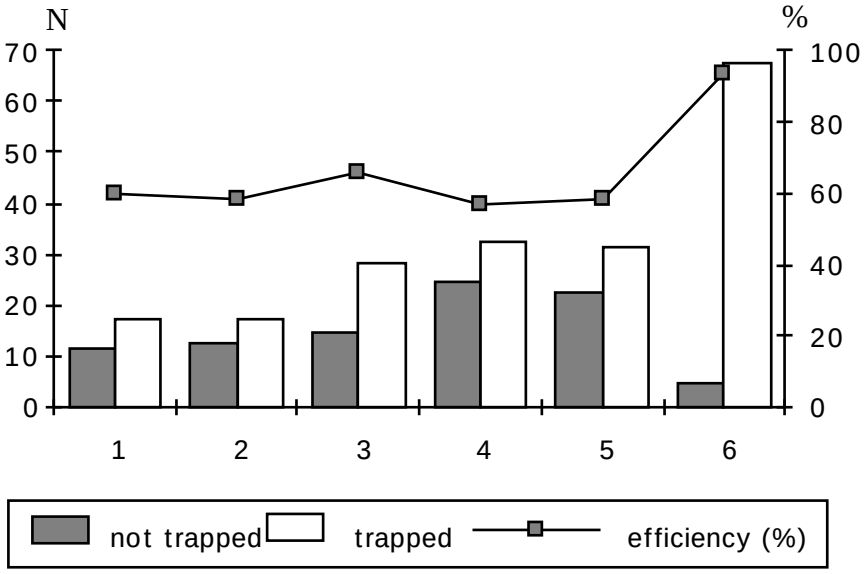


**Figure 8**: Evolution of trapping efficiency for the six trapping periods, according to the hours of trapping.

### 3 2 6 Comparison with other populations

Three other populations, Saint-Just-Chaleyssin (SJ, see Couchamp *et al.*, *submitted*), Aimargues (AI) and Barisey-La-Côte (BC, Pontier, 1993) have been monitored for FIV epidemiology by our team since 1991. Results will not be detailled here. Instead, we will briefly compare population characteristics. Saint-Just-Chaleyssin is a population of approximatively 300 cats, in a lowly fragmented human habitat, Barisey-La-Côte is an isolated village of approximatively 60 cats and Aimargues is a highly fragmented population of approximatively 250 cats. In these three populations, the density is low, the mating system is polygynous with female monopolization, sex-ratio is equilibrated in favour of females, due to disperal (and related mortality) which is more important in males (Pontier *et al.*, 1995).

FIV is present each year in these populations (Figure 9). Whatever the population, evolution of prevalence rate with time is not significant (BC: LRT=0.311; P=0.565; AI: LRT=3.794; P=0.084; SJ: LRT=2.186; P=0.078). Comparison between population for a given year show no significant differences (1991: $\chi^2$=0.985; P=0.6111; 1992: $\chi^2$=3.382; P=0.1844; 1993: $\chi^2$=2.286; P=0.3189; 1994: $\chi^2$=4.389; P=0.1114). Factors that have been shown to have an influence of FIV infection, such as age, sex, weight and phenotype for example, have the same influence on FIV in these population (see results for SJ in Courchamp *et al*., *submitted*).

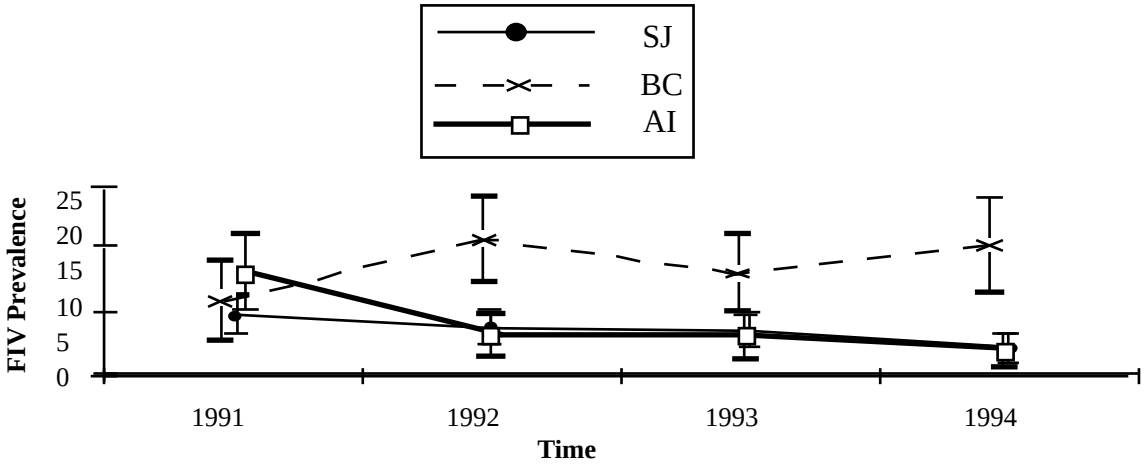


**Figure 9**: Evolution of FIV prevalence rates for Aimargues (AI), Barisey-La-Côte (BC) and Saint-Just-Chaleyssin (SJ). There is no significant difference bewteen years of a given population, or between population of a given year.

The Orange allele has also been studied in these populations, as a link between weight and this allele has already been shown (Pontier *et al*., 1995). Orange males are indeed in average heavier than non-Orange ones. It has been suggested that Orange males could be more agressive in rural environment, where the frequency of this allele is high, and thus manage to perform more mates (Pontier *et al*., 1995). Indeed, in rural environment, males fight for female monopolization, and heavier males could thus have an advantage. Orange cats are often dominant on other cats. Here, we looked for a link beween this allele and the FIV infectection probability. As each of the sample is relatively statistically small, and as there is no difference between these three populations or between years, individuals of all the three rural populations have been pooled. Several time sampled individuals have been considered only once, the year being chosen randomly. The population of Lyon Croix-Rousse has not been taken in this analysis, due to the very low frequency of Orange allele (see Figure 5). The global effect of phenotype is significant on this pooled sample ($\chi^2$=5.555; ddl=1; P=0.018).

A logistic regression, with sex, age and phenotype, lead to the model with 3 main factors (Sex, Age, Orange), in addition to the Age/Orange and Sex/Orange interactions (see Figure 10)

$$\text{Logit}\,(p_{ijk}) = \text{Log}\left(\frac{p_{ijk}}{(1-p_{ijk})}\right) = C + S_i + A_j + O_k + A_j.O_k + S_i.O_k$$

where C is a constant, and $P_{ijk}$ is the probability of being infected for cats of sex i, age j and phenotype k.

Analysis of results confirms that Orange cats, either males or females, are more often infected than other cats (Figure 11).

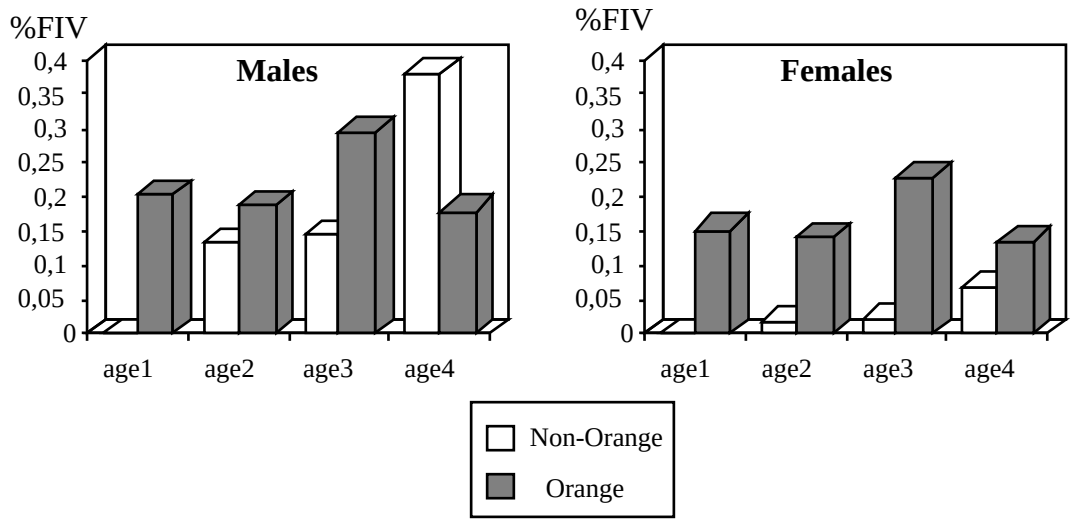


**Figure 10**: FIV infection rate, according to age classes, sex and phenotype. Age classes are: age1: 1 year old or less, age2: 2 and 3 years old, age3: 3 and 4 years old, et age4: 5 years old or more.

It is clear that Orange cats are more often infected than other cats, this trend being even higher in females. Males are more often infected than females (either Orange or not). FIV Prevalence increases with age, as expected (see Courchamp & Pontier, 1994; Courchamp *et al., submitted*). Indeed, adults are more likely to be infected than younger cats, and there is an accumulation of infected cats number with time (because induced mortality rate is low). However, in the last age class, the prevalence rate is lower than in the previous one in Orange males as well as in Orange females. It is **peu problable** that Orange cats have a physiology that confers them a lower survival, or that they die faster when they are FIV infected. In revenge, infected Orange cats may be more exposed to natural mortality (as the dominant cats have a higher mortality rate, Hamilton *et al.*, 1969), and it is possible that few of them reach the higher age class.

## 4 Discussion

### 4 1 Composition, structure and population dynamics in urban environment

Most of parameters, such as age and sex structure, mortality, natality and dispersal rates have not yet, to our knowledge, been described in urban domestic cat populations. The main reason might be the difficulty of estimating this rates.

First, we found an equilibrated and stable sex structure. Age structure changes with time, towards a younger population, but this could be due to the seasons at which the 4th and 6th captures have been done, immediatly after kitten birth. Natality is high. As cats have no owner, and carefully hide their kittens, litters are not eliminated by humans, as it

is the case in rural cat populations. Moreover, females are well fed in this population, and they give birth to one or two litters each year.

Mortality rate is low, compared to rural cat populations (Pontier, 1993). In fact cats of this population are not exposed to inclemencies, and habitat heterogeneity and instability, typical of this environment (Tabor, 1983) is absent in this population. Cats are overfed by nurses, and they seem to be in good health conditions, few of them bearing macroparasites. Moreover, usual cat mortality causes (vehicles, hunters, dogs) is weak in the hospital, even if several cats have been killed during the study (by cars or by illintentionned people). However, it is difficult to distinguish between mortality and dispersal when bodies are not found.

Density is high, heterogeneous and seem to be linked to resource (feeding) disponibility. Shelters are not limiting. Home range size and overlapping degree and sex and age-linked differences are similar as previouly published (Liberg & Sandell, 1986). Home ranges are highly overlapping, but behaviours of marking and temporal sharing of home range are observed. Mating system seems at least partially promicuist. Concerning dispersal, there is not a greater proportion of males dispersing after weaning than females. This may explain the equilibrated sex-ratio. Settling up of immigrant cats is possible.

### 4 2 Epidemiology

FIV, although lethal, is present in all populations we studied, at a sufficiently high prevalence rate to be detected.

Results suggest that sex, age and social status (estimated by weight, head size and home range size) have an influence on FIV infection probability. Heavy adult males, which are the dominant cats, are more likely to be infected by FIV than are other cats. Male dominance vary in time, and attemps to change social status lead to fights and thus to infections.

The evolution of FIV prevalence is not significant on the six capture sessions. However, it is significant if only the five first sessions are taken into account ($LRT=9.864$; $P<0.01$). The increase of prevalence rate might be due to a better trapping efficiency (Figure 8), where all the present cats, but 5 were trapped (that is, 73 individuals). A slight bias in previous capture has been suspected, highlighted, and corrected in the last capture session. Indeed, we have shown that individuals that are the more likely to escape recapture are also the more linkely to be FIV infected: they are the high ranked cats of the population. The result of the sixth capture session highlights the need of long term studies in epidemiology. With only five capture sessions, one could have concluded to prevalence decrease. Further monitoring provided both knowledge that some individual may escape recapture (and induce a bias in results) and additional data, leading to prevalence stability conclusion. Similarly, in a previous study of a rural cat population (Courchamp *et al., submitted*), the first four prevalence rates were continuously decreasing (although not significantly). A fifth capture session reveals a

higher prevalence rate, highlighting that stability has to be considered on a long term basis, and not only on few capture sessions.

### 4 3 Influence of population characteristics on epidemiology

#### 4 3 1 Comparaison of population charactéristics

We have seen that the studied populations greatly differ in most of their structural and functionnal characteristics, with on one hand the three rural populations and on the other hand the urban population.

Mainly, in the three rural populations, and at the opposite of the urban one, Aimargues (AI), Barisey-La-Côte (BC) and Saint-Just-Chaleyssin (SJ), the density is low and the population size is high. Mating system is polygynous (Pontier, 1993; Pontier & Natoli, sous presse), whereas it is, at least partially, promicuist in Lyon Croix-Rousse. As a result, there should be fewer fights between males, and maybe between males and females, in the urban population. Similarly, females should mate with more males in this population than in rural ones. In summary, it can be said that the rural cat population may have a greater proportion of agonistic interactions than in urban populations. At the opposite, the population of domestic cats of Lyon Croix-Rousse seems to have more interactions, but, among them less aggressive ones.

#### 4 3 1 2 Population Epidemiology

Prevalence evolution is not significant, whatever the considered population. The prevalence rate is not different between populations, which could be due to small size of samples, and low prevalence rates, that preclude to compare data with a strong statistical basis.

Concerning risk factors, bites being the cause of infection in both types of populations, cats that are the more likely to fight are the more likely to be FIV infected. These cats are heavy Orange male roaming adults in rural environment, and heavy (and large) male adults with large home ranges and strong marking habits in urban populations. In both cases, these individuals seem to be the dominant ones. It is likely that, as it is the case in human infection with HIV, a small proportion of cats with strong at-risk activity (sex in human, fight in cats) is involved in most of the lentivirus tranmissions.

### 4 5 Conclusion

FIV transmission is governed in all populations by a common process: bites. These bites are linked to fights, thus to social status. However, population structures (social, spatial and dynamics) induce different behavioural patterns. It is the case for the mating

system, which can induce, according to the populations, more or less fights between males, or more or less female mounts by males. Thus, there is a strong influence of dynamics, density, and social structure of domestic cat populations on parasites dynamics and spread within them. These behavioural patterns, typical of these populations, reflect their FIV epidemiologic pattern.

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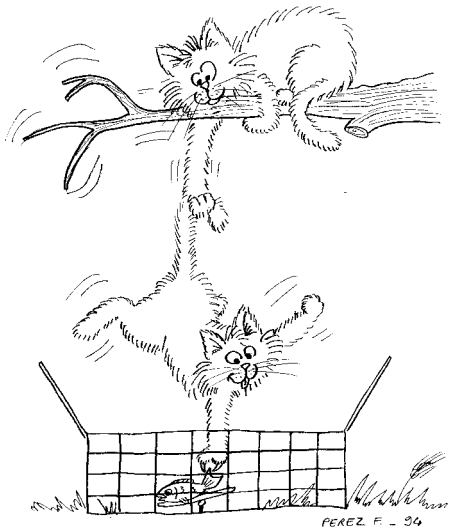


"D'après une théorie, le jour ou quelqu'un découvrira à quoi sert l'Univers et pourquoi il est là, le dit Univers disparaitra sur-le-champ pour se voir remplacer par quelque chose de considérablement plus inexplicable et plus bizarre.

Selon une autre théorie, la chose se serait en fait déjà produite". Douglas Adams, le guide du routar galactique.

## GENERAL DISCUSSION

## 1 Limitations and improvement of the study

We would like to discuss the limitations this type of study contains, before discussing the results perspectives of this works.

### 1 1 Evolution of the mathematical model

A first point which is not really a limit, and for which improvement is part of the nature of the method: modeling. A model can always be improved, and must therefore be considered as a modifiable entity. This is why models proposed here, like any model, do not provide all the responses of the FIV problem. They bring some responses, and mainly directions to follow in order to get closer to other responses. Once the model reaches the goal, or can obviously not reach the goal, it must be modified to improve its performances (not necessarily in the same direction). A model can therefore always be either improved in order to get more information about the biological studied phenomenon, or modified so that it prospects in different but complementary directions, thereby revealing gradually the overall image of the studied phenomenon. The models presented in this work are determinist. Even if the next versions of the FIV model are not entirely stochastic, to add some stochastics in the existing models would be beneficial. Stochastics greatly influences lentivirose epidemiology. Many groups studied HIV transmission probability in humans (Le Pont, 1991; De Vincenzi *et al*., 1992), and the asymptomatic length distribution in HIV seropositive individuals (Lui *et al*., 1988; Medley *et al*., 1987; 1988). Moreover, as will be discussed later, this kind of study often deals with too small numbers of individuals for neglecting stochastic events. An example is the study of the urban population, where a total of 12 infected individuals in three years can hardly reflect a general infection pattern.

As truly said Bachelard, "Whatever the starting point of scientific activity, this activity cannot convince unless by quitting its basic domain: if it is experience, there must be theorization, if it is theory, there must be experimentation (Bachelard, 1934, *in* Yoccoz, 1994). Modeling in ecology (or at least in epidemiology) should be part of a gradual improvement, alternating modeling and validation by field data. Validation is not only necessary to test the model robustness, but also essential to improve it, even if this means altering the initial model. We therefore highlighted the importance of behaviour for FIV dynamics and spread within domestic cat populations in field epidemiological studies (Chapter VIII and IX). These parameters can logically be accounted for in the next version of the model, together with sex and age (or social class, which is equivalent), through a Leslie matrix model. Such a model should allow to include the mortality rates and virus transmission rates, that are different between classes. Similarly, the spatial pattern of the disease is important enough to be modelized (Chapter VIII and IX).

### 1 2 Serological test sensitivity

Detection of the number of seropositive individuals in the tested samples was problematic. Serological tests that are used were not 100% reliable (Chapter II and third part). While false positives can be virtually eliminated after a second analysis (WB), tests concluding seronegativity are unreliable. Indeed, some individuals produce antibodies against proteins other than p24 (the protein detected by commonly used tests, Furuya *et al*., 1992a), or even no antibody at all (Brunner & Pedersen, 1989; Dandekar, 1992). This occurs for infected cats in the initial or final stage, when their antibody level in the blood is low or null. These false negatives occur for 10 to 15% of the infected cats (Hopper *et al*., 1989; Lutz *et al*., 1990). We minimized the risk of getting false negatives by testing the cats several times during the study (every couple of months).

### 1 3 Sample representativity

Individuals have different probabilities of being captured. In rural environment, cats were caught in their owner's house, or trapped. We have hypothesized that less tamed cats may be among the roaming ones, and thus be more at risk for FIV. However, even very untamed cats were studied: their owner locked them in their house before we came, or they were trapped when we knew we could not approach them. Some individuals are easier to trap in the urban environment: especially young cats. It is clear that, without a particular effort, individuals that are epidemiologically "important" may escape the trapping.

We obtained trapping rates ranging from 58 to 92% depending on the trapping session, with an overall global trapping efficiency of 99.3%. These rates, much higher than published ones (Jones, 1977; Hall & Pelton, 1979; Liberg, 1980; Konecny, 1983), can be explained by the higher density of cats we encountered. While cats are said to be naturally curious (we have confirmed this during our trapping), they rapidly become untrustfull with age or experience, and recapture is harder than first capture. The same authors also published very low recapture rates. Study areas are generally higher than are ours, but low trapping rates are more likely due to the unwilling of cats to get into the traps than to a low probability trap encountering by these cats.

### 1 4 Stochastics

A third limit inherent to this kind of study is the low number of infected individuals in the population, and therefore in the samples. The prevalence rate of FIV, which is fairly high for a lethal endemic infection, prevents the study of a many risk factors. It is indeed difficult to study the correlation between age of individuals and serological status (even with age classes) when dealing with only 1 to 12 infected cats. Multivariate analyses are therefore impossible. Moreover, particularly on small numbers of individuals, the results cannot be interpreted but when accounting for the stochastics

of processes concerning lentiviruses. This kind of limitation typical to epidemiological studies on "small" populations (a population of 50 cats is however fairly important) is accentuated by the low FIV transmission rate. The resulting low incidence rate (number of newly infected individuals by unit of time) increases the interest of long term studies of dynamic processes of this science.

### 1 5 Short length of the study

An issue related to the previous one is the dynamic nature of epidemiology, which require long-term studies. If short term biological and ecological studies often give poor results, this is even stronger in epidemiology when a yearly (in the best case) field campaign gives a mere estimation of the infection rate. Even with two yearly trapping sessions (which seemed to be a maximum, since some cats showed a response to trapping), a three-year study would give "only" 6 points on a curve. Moreover, due to our lack of experience in this kind of field study on domestic cat populations, estimation of some population parameters could be less precise at the beginning of the study than at the end. We have shown that results from a short period study (with few experimental sessions) might show a trend that was not found with a more longer study (and more experimental points).

### 1 6 Need for complementary studies

Finally, epidemiology is a science that implies pluridisciplinarity, as defined by Legay (1986b). Analytical epidemiology requires indeed a good knowledge of the studied population. When studying a population epidemiologicaly, or comparing the epidemiological patterns of two populations, it is necessary to know the population characteristics. This is even more critical when epidemiological patterns are assumed to depend on these population characteristics. Unfortunately, dynamics and spatial and social structures of domestic cat populations still suffer from an important lack of knowledge. For example, in the case of FIV, the need of knowing the behavioural pattern of studied population has soon emerged. But this scientific field is particularly wide, and even narrower subdivisions (for example an urban population mating system description), which could have led to considerable progress, is sufficiently important to constitute on its own a Ph. D. Thesis subject. This is an advantage of human epidemiology, that partly explains the great advance it has on epidemiology of less studied animal populations.

All these limitations are encountered in most epidemiological studies. However, as for sample representativity, they are not unresolvable obstacles, and improvement is sometimes just a matter of time. Keeping these limitations in mind (but also of their relative importance), the results of this work do not loose their intrinsic value.

## 2 Results summary

### 2 1 Theoretical models

The part dealing with FIV dynamics within population of domestic cats brought the following information:

1- Once introduced in a population, FIV develops and is always maintained.

2- Introduction of FIV in a population leads neither to elimination of susceptible individuals, nor of the whole population, but rather to a constant number (equilibrium) of infected individuals in the population.

3- The ratio of susceptible to infected individuals in the population at equilibrium depends on the population characteristics.

4- Once the equilibrium is reached, the population size is slightly smaller than at the initial equilibrium (around 5% of the initial population).

5- FIV transmission rate is low.

6- FIV is always present in the population, with equilibrium states of numbers of individuals of different epidemiological classes, even when its dynamics is modeled together with that of FeLV. FIV is then present alone, or together with FeLV, which also presents a constant number of individuals. These are the only two alternatives reported in the literature or on the field.

### 2 2 Field studies

Empirical studies of FIV epidemiology in natural populations gave the following results:

7- FIV is present in all the seven populations we studied (Figure I-1), but also in all places in the world it has been looked for.

8- FIV infection rates seem to be stable in natural populations, suggesting an endemic nature of the virus, and thereby confirms our theoretical results.

9- Infection rates seem relatively important for an endemic lethal virus in any studied population.

10- The prevalence rate depends on the considered population, especially its spatial and social structure.

11- there are risk factors, linked to the transmission mode, by bites, implying a strong link with individuals behaviour

12- Individuals participating to fights, that is mainly heavy, Orange-gene carrier, roaming adult males, are highly susceptible to FIV infection.

13- The hierarchy status, based on aggressive interactions, seems to determine the probability of being infected by FIV.

14- Because of its dependence upon behaviour, FIV transmission depends on the social system of populations. It is spatially non-homogeneous, and lower within social groups than between groups.

15- A specific transmission mode from male to female may exist, by bite at the neck during mount

16- Vertical transmission seems highly unlikely in natural conditions.

## 3 Discussion and suggestions for future work

### 3 1 Impact of FIV in domestic cat population

From an epidemiological point of view, the ubiquitous presence of FIV, in addition its high prevalence rate (Chapters VII, VIII and IX), indicates an endemic state of the virus worldwide. This was confirmed by serological evidence of FIV as far in time as looked for (Chapter VII), and was suggested by our model (Chapter V). Moreover the low transmission rate suggested by our model, which confirms literature data (Yamamoto et al., 1989), corroborates this assumption. At the individual level, the mean life time expectancy of cats in natural conditions is from three to five years depending on sex (Legay & Pontier, 1983). FIV is usually transmitted at one or two years of age, and seropositivity is developed within the next five years. This suggests that the probability a cat develops an AIDS and dies from it is low (Courchamp *et al*., 1995a). A long term study of two populations in rural environment (Pontier, 1993) indicates that cat populations present a stable equilibrium state of size (Figure VIII-1). Epidemiological studies showed that FIV has been present (with a stable equilibrium state) since at least 1991 (Chapter VIII). This virus has a low transmission rate and has been present in France since 1972 (Moraillon, 1990), or even much longer (3 to 6 million years, Olmsted *et al*., 1992, and see Chapter VII), and has therefore probably been present in these populations since at least the beginning of the long term study (1982). For this reason, the stability of the population, despite the virus at a high rate, is another indication of the endemic state of the disease. Moreover, the low population size decrease due to the infection, that our model predicted, is another indication of the low influence, at the population level, of this virus on domestic cats. Finally, the low pathogenicity at the population level, and the fact that domestic cat is not an endangered species, are supplementary evidences of the low threat of this virus on this species.

This suggests that, from a population point of view, FIV barely decreases the population size in natural conditions. Qualitatively (at the species level, thus at a long term scale), FIV is probably present at an evolutive scale. It therefore influences

selection, and thereby contributes to the evolution of the *Felis catus* species, and to the characteristics of the populations it generates (see § 3.3).

### 3 2 Influence of FIV on non-domestic felids species

At least sixteen non-domestic felid species were susceptible to FIV infection (Table X-I and Chapter VII). Other species, that have been tested, and revealed negative results for the presence of anti-FIV antibodies, had actually been tested only for a few individuals (see Table X-I), and it should not be concluded that these species are not infected by FIV. These species are actually most probably infected, if FIV antiquity and coevolution of the different strains with felid species are considered true (see after). However, it is quite useless to admit that all these species are infected. For all the 16 species testing positive for infection, the transmission mode remains unknown. Furthermore, FIV infection has not been shown to induce clinical signs in species other than domestic cats, except the lion for death has been observed (Poli *et al*., 1995). In the lack of kind of data, one should consider the worth alternative, namely that FIV may well be lethal to other felid species, which would greatly affect biodiversity conservation. All the 36 non-domestic felid species are considered as threatened or endangered (O'Brien *et al*., 1985, Wozencraft, 1993). Table X-I presents the felid species, precising those that are threatened according to the classification of two different international organisms. FIV serological status is also given.

As for biodiversity conservation, several points are to be considered:

-some populations are highly infected by FIV. More than 71% of 22 tested individuals from the Asian threatened species *Panthera leo persica* were infected (Letcher & O'Connor, 1991). Similarly, more than 80% of 98 tested individuals from a natural populations of East African lions were infected (Spencer *et al*., 1992). Finally, more than 90% of 44 tested individuals from South African populations of lions were infected (Brown *et al*., 1993),

-some populations are highly exposed to FIV. Some species live in close contact with infected domestic populations. It is the case of the European wild cat ,already threatened by habitat destruction, hybridization with domestic cat (French *et al*., 1988) and by infection by FeLV for which domestic cats constitute a reservoir (Artois & Remond, 1994). Similarly, the Iriomote cat (*Felis iriomotensis*), has only 80 to 100 individuals left, in a small Japanese island (Ono, 1985, *in* Mochizuki *et al*., 1990), and the Iberian lynx (*Lynx pardinus*) is almost extinct (Castro & Palma, 1994). Both species are in close contact with domestic cats.

-some infected populations are highly fragile. Many threatened species and sub-species are infected by FIV. It is the case of the flat-headed cat (*Ictailurus planiceps*), the snow leopard (*Panthera uncia*), and the cheetah, which show more than 25% infected individuals in some populations (Brown *et al*., 1993). Florida panthers (*Felis concolor coryi*) has one third of its 50 individuals infected by FIV (Barr *et al*., 1989).

The danger bearing on some of these species for which the FIV serological status remains unknown should not be less important.

-some species are barely known. In some species, such as the Andean cat (*Felis jacobita*, Figure X-1), or the Borneo cat (*Felis badia*), only a few individuals have been observed (see Table X-I). These species are barely known because scarcely represented, and therefore particularly fragile and susceptible to parasites (Thorne & Williams, 1988).

**Figure X-1**: Photograph of a young Andean cat (*Felis jacobita*)

Assuming long coevolution of FIV and felids (see next paragraph), the FIV influence on these felids may seem negligible. However, most of these populations are highly unbalanced, and long coevolution of a parasite and its host does not necessarily implies an evolution towards avirulence.

Data about non-domestic felids are still cruelly scarce, even about those which are the less badly known**.** There is a great need of increasing our knowledge not only of the dynamics and social and spatial structures of these populations, but also of the epidemiology and the pathology induced by their different parasites in general, among which FIV. These felids are all predators, and often super-predator of the ecosystem in which they live. Thus, they have few competitors, and their disparition could not be balanced by the remplacement by a similar species living in the same ecosystem. Therefore, this knowledge is critical for biodiversity conservation, not only for these species but also for all those that are ecologically linked to them.

| Species | Scientific name | US F&WS | IUCN | FIV Status |
|---|---|---|---|---|
| lion | *Panthera leo* | 1 sub-species threatened | 1 sub-species threatened | + |
| tiger | *Panthera tigris* | threatened | threatened | + |
| leopard | *Panthera pardus* | threatened | vulnerable (2 sub-species threatened) | + |
| jaguar | *Panthera onca* | threatened | vulnerable | + |
| snow leopard | *Panthera uncia* | threatened | threatened | + |
| clouded leopard | *Neofelis nebulosa* | threatened | vulnerable | - (7+21) |
| marbled cat | *Felis marmorata* | threatened | | - (3+2) |
| Canadian lynx | *Lynx canadensis* | | | nt |
| Eurasian lynx | *Lynx lynx* | | | nt |
| bobcat | *Lynx rufus* | 1 sub-species threatened | | + |
| spanish lynx | *Lynx pardinus* | threatened | vulnérable | nt |
| caracal | *Lynx caracal* | | | - (1) |
| cheetah | *Acinonyx jubatus* | threatened | vulnerable (1 sub-species threatened) | + |
| serval | *Felis serval* | 1 sub-species threatened | | - (16+10) |
| african golden cat | *Felis aurata* | | | nt |
| asiatic golden cat | *Felis temmincki* | threatened | | nt |
| leopard cat | *Felis bengalensis* | 1 sub-species threatened | | + |
| fishing cat | *Felis viverrina* | | | nt |
| flat-headed cat | *Felis planiceps* | threatened | | + |
| rusty-spotted cat | *Felis rubiginosa* | | | nt |
| Bornean cat | *Felis badia* | | rare | nt |
| Iriomote cat | *Felis iriomotensis* | threatened | threatened | nt |
| jaguarondi | *Felis* | 4 sub-species threatened | | + |
| puma | *Felis concolor* | 3 sub-species threatened | 2 sub-species threatened | + |
| ocelot | *Felis pardalis* | threatened | vulnerable | + |
| margay | *Felis wiedii* | threatened | vulnerable | + |
| little spotted cat | *Felis tigrina* | threatened | vulnerable | + |
| kodkod | *Felis guigna* | | | nt |
| Geoffroy's cat | *Felis geoffroyi* | | | + |
| Andean cat | *Felis jacobita* | threatened | rare | nt |
| Pampas cat | *Felis colocolo* | | | - (3) |
| European and African wildcats | *Felis silvestris et Felis libyca* | | vulnerable | (8+23+11) |
| Pallas's cat | *Felis manul* | | | + |
| jungle cat | *Felis chaus* | | | - (6) |
| black-footed cat | *Felis nigripes* | threatened | 1 sub-species threatened | - (4) |
| sand cat | *Felis margarita* | 1 sub-species threatened | | - (5) |
| chinese desert cat | *Felis bieti* | | | nt |

**Table X-I**: Actual felids species, their conservation status (F&WS: Fish & Wildlife Service), and their FIV serological status (+: antibody detection, - (*n*): no detection on n individuals tested, nt: not tested). After Barr *et al.*, 1989; Mochizuki *et al*., 1990; Letcher *et al.*, 1991; Lutz *et al.*, 1992; Olmsted *et al.*, 1992; Spencer *et al.*, 1992; Barr *et al.*, 1993; Brown *et al.*, 1993; Spencer & Morkel, 1993; Artois & Remond, 1994; Brown *et al*., 1994; Carpenter & O'Brien, 1995.

### 3 3 Evolution of virulence

Parasitic interactions are key factors for evolution of both host and parasite species. In the actual scientific context, where the renewal of evolutive concepts brings up enthusiastic perspectives, a reflection on an evolutive point of view on the FIV/cat system seems indispensable. The conventional wisdom, denounced by Ball more thna 50 years ago (Ball, 1943), and stating that parasitism evolves systematically towards mutualism, is now completely challenged (review in Ewald, 1994). The virulence of a pathogen may increase when correlates of increase virulence, such as increasing of pathogen multiplication, increase the transmission rate (Levin & Pimentel, 1981). Therefeore, the evolution of a pathogen might lead to an increased virulence as long as it does not prevent the transmission of this pathogen (Ewald, 1987; 1994). A host infected by a highly virulent strain may even enhance the pathogen transmission rate, such as in the case of vector borne diseases, where hosts confined to bed remain accessible, or in the case of gastric infections where transmissions are done by contaminated water (Ewald, 1991b).

In a relatively socially stable domestic cat population where fights are rare, to be transmitted, FIV must remain infectious until the cat fights with another cat. If such fights occur only every several years, the typical infectious length of a direct transmission pathogen (some days to some weeks) would lead to the extinction of the viral strain genotype. Only genotypes that are able to increase this period may exploit this transmission niche. One requirement is to avoid destruction of the parasite by the host immune system. This is achieved in three ways: hiding, becoming invisible, or becoming unreachable. For this, three solutions arise: to hide, to become invisible, or unreachable. For example, it may infect cells hardly reachable by immune defenses and increase the period during which few or no antigens are produced. Microparasites infecting cells of the immune system are not only getting unreachable, but also confuse the immune system cells (Combes, 1995). The virus may thus, by a combination of these three solutions, evolve towards an increased infectious period. When the fight rate increases, the benefit of increased infectious periods is expected to decrease, and virulence to increase. More virulent strains should then be selected in more aggressive populations. The potential of the rapid evolution of viruses is known (Brown & Holmes, 1994). When the strains become more virulent, each bite become more infectious and transmits more virulent strains, and increased virulence may be thus selected. One may think that, by a counter-selection mechanism of aggressive individuals, this type of process could have favourized, even slightly, socially more aggressive cat populations. Moreover, in domestic cats, infection is followed by many clinical signs, among which mouth infections (gingivitis, abscess, tongue ulceration, ...). This is accompanied by an important increase of viral particles, and even of free infected cells in saliva (Cadoré, pers. comm.), that may strongly increase the infection power of bites. Cats at this state of infection are not only more infectious than others, but also propagate more virulent strains (as in the case of the final HIV infection stages, Ewald, 1994). Cats reaching this clinical stage are weakened and may be the focus of attacks by challengers looking for dominance. In this case, more virulent strains, which are also the more debilitating, may

indirectly provoke such hierarchical modification attempts, thereby encouraging their own selection. This hypothesis leads to two further suppositions.

First, 16 felid species bear anti-FIV antibodies, and these strains seem relatively specific (Lutz *et al*., 1994). I think it highly probable that other species are also infected. Different felid social systems, from highly social lions prides (Paker, 1992) to more solitary behaviour exhibited by other felid species (Kleinman & Eisenberg, 1973), are then likely to select, by their specific biting rates, different degrees of virulence. For example, in a naturally scarce species, for which meetings generally lead to avoidance rather than fights, a virulent strain would have high probability to disappear by killing its host, while a less virulent strain would be selected. Felid species with highly structured social systems, such as domestic cats and lions, therefore would carry strains more virulent than other species do. Extensive study of strains infecting lions are thus very important. Indeed if lethal symptoms induced by FIV infection have already been documented in lions, among 16 infected species, it is the only species, with domestic cats, for which such pathogeny has been observed (Carpenter & O'Brien, 1995; Poli *et al*., 1995). This could suggest that this species is also associated to highly virulent strains. These are the only two species defined as social, with frequent physical conflicts in their social patterns. In some of these species, infection may not be followed by the same mechanism, from either a quantitative or a qualitative point of view, than in those documented for the domestic cat. First, while FIV transmission modes between cats are not totally elucidated, (the exact proportion of transmission by bites in the total possible modes is not known), those concerning other felid species have not been yet investigated: it is not established yet whether FIV transmission occurs by bites in other felid species. The selection of less virulent strains in less social species can also, theoreticaly, be explained with amicable associated transmission. In this context, the socio-ethological study of non-domestic felids takes on a new importance, especially for biodiversity considerations (for these felids as well as the many ecologically linked ones).

The second supposition that can be made is the following: selecting less virulent strains should be possible. This could be achieved, thanks to the high mutation rate of lentiviruses, by decreasing virus transmission, for example by modifying social structure of the host population (decreasing the fight rate). It should be interesting to test this hypothesis by testing virulence degree of FIV strains infecting populations of cats with different social structures. In case of positive results, this hypothesis could explained at least partly, the greater virulence of FIV strains infecting domestic cats, when compared to less social felids. Similarly, while the study of the evolution of virulence in populations of felids with different social structures is hardly thinkable experimentally, a mathematical model accounting for virulence and its evolution should provide major information. We are currently working on such a model.

### 3 4 Phylogeny

One of the most direct ways of lentiviruses evolution study is phylogenetic tree construction. Due to the high genetic diversity specific to lentiviruses, several studies have already been published on phylogeny of different FIV strains. The DNA of many FIV strains from different part of the world have already been sequenced (Chapter III), indicating a certain degree of typology. According to some of these studies, FIV could have been present in the distant past (3 to 6 million years according to Olmsted *et al*., 1992). Nevertheless, due to the complexity of the phylogenetic classification methods (*e.g.* Li, 1981; Li *et al*., 1985; Felsenstein, 1985; 1988; Hendy & Penny, 1989; Hendy, 1991; 1993; Baum, 1992; Penny *et al*., 1992; Ragan, 1992; Charleston *et al*., 1993; Hasegawa & Fujiwara, 1993; Purvis *et al*., 1994), some published results turned out to be biased, mainly due to inappropriate use of some phylogenetic models (Gouy, pers. comm.). Moreover, phylogenetic works are not particularly easy when the study model has exceptionally high mutation rates as have lentiviruses (Sonigo *et al.*, 1985; Wain-Hobson *et al.*, 1985; Li *et al*., 1988; Smith *et al.*, 1988; Gojobori *et al.*, 1990; Myers *et al.*, 1992). Studies in this direction would be interesting, since they have often been relatively descriptive so far. Indeed, FIV has been found on every continent, and it should be thinkable to look for its original focus, or at least to redesign its geographical and temporal dissemination, coupling a phylogenetic study of available FIV strains to history of world colonization by cats. Similarly, it would be interesting to attempt a comparison between a phylogenetic tree of the felid species evolution and an evolutive tree of felids infecting FIV strains. I have already done some exploratory analysis of FIV strains phylogeny. Unfortunately, if primate lentiviruse sequences are relatively numerous (*e.g.* Alizon *et al.*, 1986; Ratner *et al*., 1985; Yokoyama & Gojobori, 1987; Tristem *et al*., 1992; Louwagie *et al*., 1993; Müller *et al*., 1993; Chakrabarti *et al*., 1987; Sharp *et al*., 1994), actual data on felid lentiviruses are still too scarce (only sequences of strains infecting domestic cats, pumas and lions are available) to allow great success. It is for me evident that such a program of research and systematic sequencing of such strains would provide major information, about virus evolution (and origin and evolution of FIV has a particular importance due to its proximity with HIV), and about evolution of host/parasite systems in general. Such a research program is currently envisaged by our team, through a collaboration with the team of C. Gautier, from Lyon.

## 4 Contribution of this study

When I undertook this study, I emphasized the proximity of this virus to HIV, the induced pathogenicity in the domestic cat, the potential threat it represents for non-domestic felids conservation, the total absence of knowledge on epidemiological pattern, and the eventual contribution in the knowledge of domestic cat populations through epidemiology. Each of these aspects is discussed hereafter in order to highlight the eventual contribution**.**

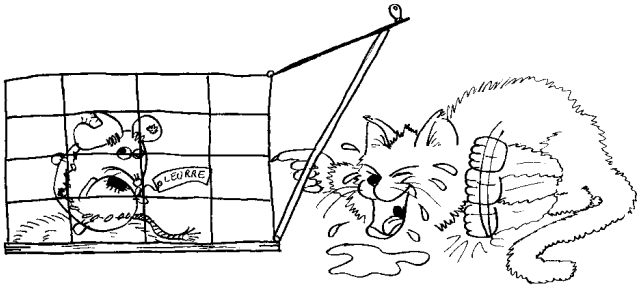
As far as using FIV as an HIV model study, only molecular aspects (and especially therapeutic or prophylactic ones) are in general studies (Chapter III). We suggested here two new similarity domains where FIV could be used as a model for HIV (Discussion in Chapter VIII). These are epidemiology (same specific succession of clinical and aclinical stages, and transmission risk linked to behavioural characteristic) and virus evolution (genetic, biological and biochemical similarities of both lentiviruses, and analogy to epidemiological processes). These statements are obviously risky, because there remains consistent differences between both viruses (for example the transmission mode), and it is easier to study epidemiology of humans than on animals in natural conditions. Nevertheless, at least theoreticaly, existing similarities justify comparisons, and new ways of research should not be ignored on the basis that they seem hazardous.

If the pathological aspect of FIV infected cats has been tackled during this work only to discuss already established results, we hope that we have highlighted the huge lack of scientific research in the study of threat of different virus strains on non-domestic felids, and the urgent need to complete them.

Domestic cat (or more broadly host) population typology by an epidemiological characterization has only slightly been discussed (Chapter IX). However, different parameters studies in this work may, to some extent, be used as a population marker, in the sense that different epidemiological patterns might arise from different population types, and if necessary, to characterize them.

FIV epidemiological contributions are more evident, since this work presents the only epidemiological study published to date, concerning this virus in domestic cat populations, and since knowledge in this domain was scarce at the beginning of the study.

Finally, the originality of this work is, to my mind, mainly du to the specificity of study types that are presented here. Indeed, it stands at the interface of several scientific fields, such as population dynamics and epidemiology, and theoretical work (modeling) and field epidemiological work. Based on the frequency of published studies at the intersection of several science, little effort is devoted to this type of pluridisciplinary thought process. Research of knowledge on all "important" aspects (concerning several scientific domains) of a phenomenon, is obviously conducted at the detriment of the sum and the specialization degree of the information that can be collected from each of them. Nevertheless, acquiring knowledge about several aspects of a process may appear to be more essential for its understanding than specializing in a more particular aspect. Even if it is sometimes perilous and often uncomfortable to walk durably in equilibrium at the frontier separating two different scientific fields (or two scientific processes in the same science), it is possible and certainly worth trying.


LEURRE

# ANNEX

IMPACT OF TWO FELINE RETROVIRUSES ON NATURAL POPULATIONS OF DOMESTIC CAT

## 1 Introduction

Among numerous viruses that infect domestic cats (*Felis catus*), two retroviruses are of major importance (Hardy 1993, Bendinelli *et al*. 1995): feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV). FIV and FeLV have been found in all places in the world where they have been investigated. A synthesis of available literature (Courchamp & Pontier 1994) highlights that antibodies to FIV have always been found at relatively high rates: considering 59 serosurveys (including more than 85,000 tested cats), the "average" FIV prevalence rate is around 11.0%. Similarly, a synthesis of 74 serosurveys indicates a global FeLV prevalence antigens of 14.21%, on more than 110,000 tested individuals (Fromont 1994).

Furthermore, FIV and FeLV are known to infect several non-domestic felids (for a FIV review: Courchamp & Pontier 1994, for FeLV: Meric 1984, Briggs & Ott 1986, Citino 1986, Boid *et al.* 1991, Jessup *et al.* 1993). The other feline species have not yet been (or only slightly) investigated. However, most of them are endangered (Wozencraft 1993). Thus, there is an urgent need, for biodiversity preservation, to complete the epidemiological knowledge on such viruses.

FIV is a recently identified lentivirus inducing an AIDS-like syndrome in cats (Pedersen *et al.* 1987). Transmission of FIV occurs through bites during fights (Yamamoto *et al.* 1989). FIV infection induces a long asymptomatic stage (lasting months to years, Sparger 1993) followed by AIDS, characterized by miscellaneous disorders and opportunistic infections (Sparger 1993). As there is no immunity nor recovery, either natural or artificial, infected cats die from this infection (Sparger 1993).

FeLV is probably the most common single, non-traumatic, cause of death in adult domestic cats (Jarrett 1985). This oncovirus is transmitted horizontally (mainly through licking, maternal grooming, mating, food sharing), and also vertically, from mother to kitten (Jarrett 1985). Most of FeLV infected cats seem to recover from infection, develop an immunity, and do not become excreting carriers (Fromont 1994), whereas the others become persistently viremic and, after a long asymptomatic stage, develop FeLV-related diseases and die (Hardy 1993). Clinical features of FeLV and FIV are very similar (Yamamoto *et al.* 1988). As interactions are not quantitatively important (Yamamoto *et al.* 1988), these two viruses will be here considered independently.

Populations of domestic cats are known to present a high degree of variability of their spatial and social structure (Liberg & Sandell 1988) and possibly of their mating behavior (Natoli & DeVito 1988, Pontier & Natoli in press). Populations structures are partly determined by resource availability (Macdonald 1983) and habitat fragmentation (Pontier *et al.* 1995). Such population structures can in return affect circulation of pathogens (Loehle 1995, Courchamp *et al., unpublished results*). Similarly, virus transmission mode is also a major parameter affecting the circulation pattern of viruses within populations. Despite strong similarities between FIV and FeLV (mainly due to similar pathological courses), we hypothesize that differences in their infection modes should induce strong dissimilarities in their respective spread patterns.

The aim of this paper is, through a synthesis of our already published data, to compare FIV and FeLV spread patterns and to study the respective impact of both retroviruses, in terms of reduction of the number of individuals, within natural populations of domestic cats. We used complementary approaches. First, from an epidemiological study of natural populations of domestic cats, we estimated, for both viruses, the infection risk of different categories of cats (Fromont 1994, Courchamp *et al. unpublished results*). Second, we built an epidemiological model of the circulation of these viruses within populations, in order to estimate their respective impact (Courchamp *et al.* 1995, Fromont *et al., unpublished results*). Finally, some results of a long term dynamical monitoring on two of these populations give indications of the impact of infection at both the individual and population level (Pontier 1993).

## 2 Epidemiological study

We have studied the epidemiology of FIV and FeLV in three populations of mostly freely roaming cats in rural habitats, located in France. These populations differ in size, density and fragmentation of habitat (*i.e.* clustering of cat houses). Two of them, Aimargues (AI) and Saint-Just-Chaleyssin (SJ) has been monitored annually since 1981 by one of us (Pontier 1993), and the other, Barisey-La-Côte (BC) has been investigated by our team since 1990. The epidemiological surveys of FIV and FeLV started in 1991 in the three populations.

A representative sample of cats, of a sixth to a half of the populations, was taken each year from the three populations. Cats were caught directly at their owner's house, or with lured cages when they were too untamed. Some cats were caught several times. Each year, for each cat, a blood sample was taken in order to determine the serological status of individuals for FIV and FeLV, and several individual factors were recorded. These factors are sex, neutering status, age, weight (which can determine the social status of cats), roaming habits (which is an indication of the exposure of cats to other cats), group size (a group being defined by the cats living in the same house), and group health (presence or not of the studied virus in another cat of the group).

### 2 1 Prevalence rates

FIV is present in the three populations (Table I) at relatively high prevalence rates, but the differences between years and between populations are not significant ($\chi^2 \leq 4{,}38$; $p \geq 0{,}05$, and $TRL \leq 3{,}79$; $p \geq 0{,}05$). One population, BC, is free of FeLV. The two other populations show no evolution of FeLV prevalence rate with time ($TRL \leq 0{,}47$; $p \geq 0{,}05$). The prevalence differences between SJ and AI are not significant ($\chi^2 \leq 3{,}15$; $p \geq 0{,}05$), but this may be due to the relatively small available samples. BC is a small population of cats (approximately 60 individuals, according to years), has a low cat density (120 cats/km$^2$) and is highly fragmented. As the presence of FeLV is established in BC neighboring domestic cat populations (as close as 5 kms, Rioux *pers. comm.*) and in wild cats (Felis silvestris, Artois & Remond 1994), several hypothesis

may explain this absence in BC itself. The potential (and possibly repetitive) extinction, could be a result of stochastic processes in a population with a low density (which should induces fewer amicable interactions), and a small population size (60 individuals), following the principle that, due to the low transmission rates, the smaller the population size, the higher the probability of virus extinction.

**Table I**: Prevalence rates of the three populations, Saint-Just-Chaleyssin (SJ), Barisey-La-Côte (BC) and Aimargues (AI), for three consecutive years (1991, 1992 and 1993), for **A**: FIV. **B**: FeLV. FeLV is always absent in one of the three populations (BC). Differences between populations or between years are not significant.

**A: FIV:**

| Pop. | SJ | | | BA | | | AI | | |
|---|---|---|---|---|---|---|---|---|---|
| Year | %-se | < % < | %+se | %-se | < % < | %+se | %-se | < % < | %+se |
| **1991** | 13,72 | **19,57** | 25,41 | 4,52 | **10,00** | 15,48 | 8,89 | **14,29** | 19,69 |
| **1992** | 10,18 | **15,09** | 20,01 | 12,67 | **18,60** | 24,54 | 2,39 | **5,45** | 8,52 |
| **1993** | 9,29 | **14,29** | 19,28 | 8,67 | **13,95** | 19,24 | 2,35 | **5,36** | 8,37 |
| **1994** | 4,76 | **9,09** | 13,42 | 11,11 | **17,65** | 24,18 | 1,05 | **3,45** | 5,84 |

**B: FeLV:**

| Pop. | SJ | | | BA | | | AI | | |
|---|---|---|---|---|---|---|---|---|---|
| Year | %-se | < % < | %+se | %-se | < % < | %+se | %-se | < % < | %+se |
| **1991** | 4,54 | **8,70** | 12,85 | 0,00 | **0,00** | 0,00 | 1,48 | **4,76** | 8,05 |
| **1992** | 6,97 | **11,32** | 15,67 | 0,00 | **0,00** | 0,00 | 2,39 | **5,45** | 8,52 |
| **1993** | 5,88 | **10,20** | 14,53 | 0,00 | **0,00** | 0,00 | 1,09 | **3,57** | 6,05 |
| **1994** | 8,46 | **13,64** | 18,81 | 0,00 | **0,00** | 0,00 | 1,05 | **3,45** | 5,84 |

### 2 2 Risk factors

With univariate statistical tests (Chi-square and non-parametric trend statistics tests), we tested the influence on infections of each factor taken separately. We also analyzed the influence of several factors simultaneously in order to highlight potential interactions. For this, we used Multiple Correspondence Analysis (MCA, Escoffier & Pagès 1990) and Generalized Linear Models through logistic regressions (Aitkin *et al.* 1989). The two infections do not affect the same categories of individuals. Indeed, FIV infection risk is characterized by sex, age, weight and roaming habits: immigrant, well built, sexually mature males (not too old) are more likely to become infected with FIV (Courchamp *et al., unpublished results*). In contrast, FeLV infection risk is characterized by neutering status, age, group size and group health: entire, young cats living in large groups with FeLV infected mates are more likely to be FeLV infected (Fromont 1994). A detailed analysis of these results shows that factors influencing FIV infection are mostly linked to aggressive behavior, whereas factors influencing FeLV

are characteristic of the cat group. This is consistent with the different modes of transmission of the two viruses: FIV is transmitted by bites through fights, whereas FeLV is transmitted through more friendly contacts. Heavy adult males are often the high ranking cats (Liberg, 1981), that is, cats that are likely to fight, which explains their propensity to FIV infection. It is also known that young cats living in large groups often have amicable contacts (Natoli, pers. comm.), which could explain why they are more often infected with FeLV than other individuals.

Thus, we can hypothesize that the two viruses will show different circulation patterns: in a given population, FIV transmission should occur between social groups mainly through aggressive contacts occurring between high-ranking males, whereas FeLV should spread, mostly within social groups through more friendly contacts, with a pattern similar to the direct contact diffusion ones (Figure 1).

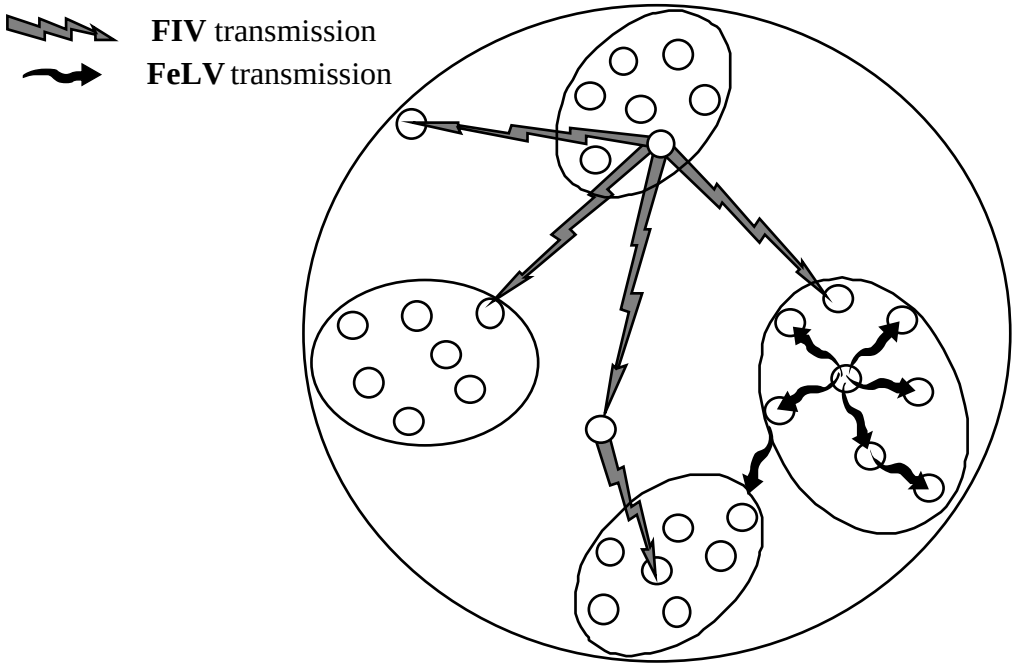



**Figure 1** : Representation of spread patterns of FIV ( ) and FeLV ( ) between and within the social groups of a theoretical population. The two viruses show totally different patterns of circulation : FIV infects at-risk individuals while FeLV spreads infecting close cats similar to the direct contact diffusion patterns.

## 3 Modeling of virus spread

Theoretical insight of the influence of both retroviruses is provided by a deterministic model which we constructed (Courchamp *et al.* 1995, Fromont *et al., unpublished results*). Despite some differences, the two retroviruses share strong similarities on a modeling point of view: they show comparable succession of asymptomatic and clinical stages (Yamamoto *et al*. 1988), leading to death (and they infect the same host, the domestic cat). For this reason, we chose to use the same type of model for both viruses, in order to compare their respective results. This is a SIR type compartmental model, based on Anderson & May's work (Anderson & May 1991), for which we used some parameters obtained from the epidemiological and the dynamical studies (e.g. prevalence rates, birth and mortality rates) or in litterature (e.g. death rates due to the diseases). Cat population dynamics are represented by a set of differential equations, each one representing a serological status (susceptible, infected, immunized, Figure 2). Values of parameters that were not directly accessible on the field (e.g. rate of effective transmission) were estimated with the model at the equilibrium. Detailled description of the model being available elsewhere (Courchamp *et al.* 1995), details will not be given here.

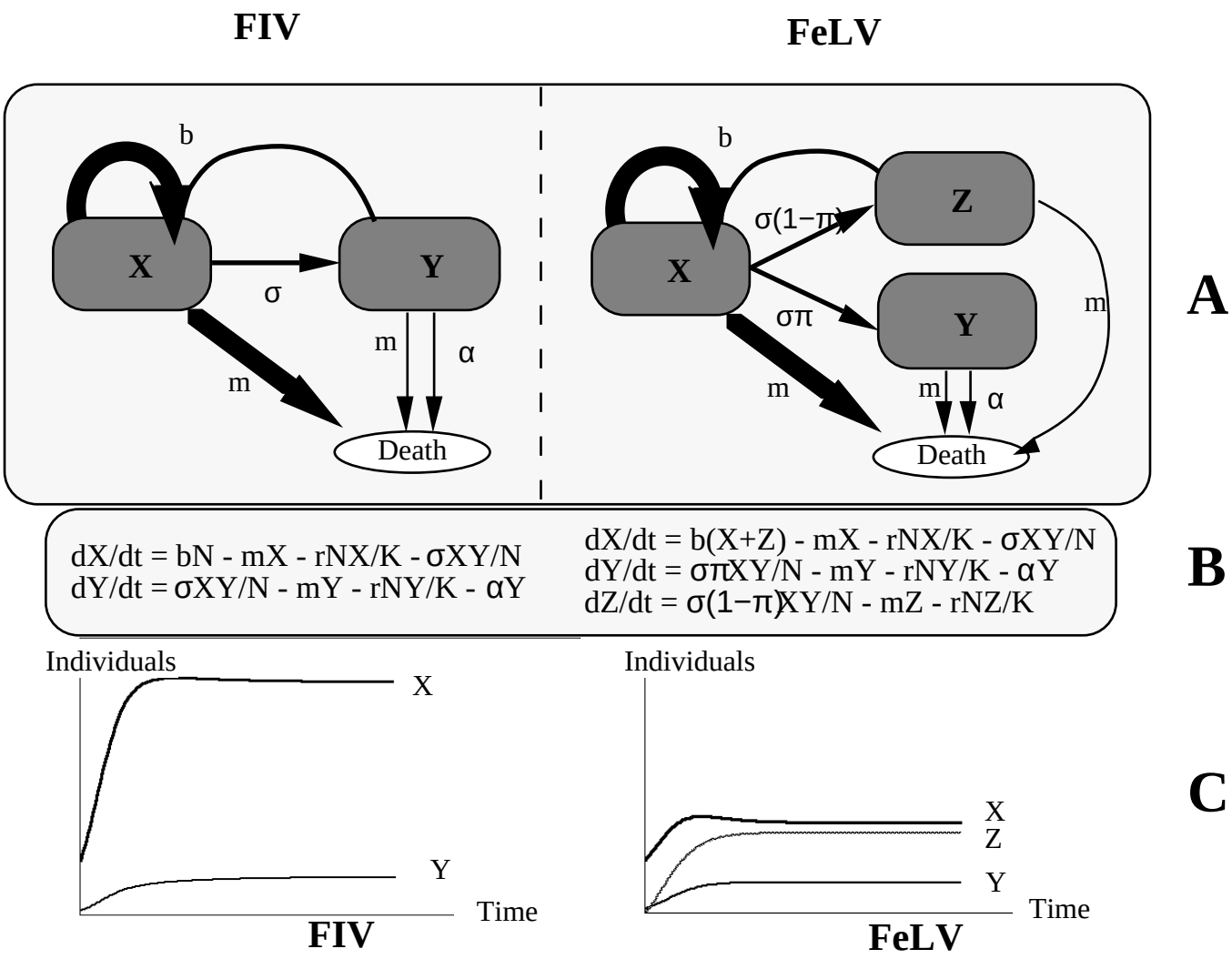



**Figure 2** : Compartmental representation (**A**), equations (**B**), and simulations (**C**) of FIV and FeLV models. **A** : compartments *X*, *Y* and *Z* represent different subpopulations : susceptible, infected or immunized, respectively. Arrows represent the rates between these subpopulations, or between them and death, and their width is a qualitative indication of the importance of the rates. **B** : set of simple differential equations corresponding to the compartmental representation. d*X*/dt, d*Y*/dt and d*Z*/dt give the dynamics of *X*, *Y* and *Z* individuals, respectively. The birth rate is b, and m is the natural mortality rate (r=b-m), K is the carrying capacity of the habitat at equilibrium and *N* is the total number of cats in the population at time t. The rate of effective transmissions is σ, α is the death rate due to the viruses, and π is the ratio of FeLV non immunized cats. **C** : simulation of the model : number of susceptible and infected individuals (FIV) or susceptible, infected and immunized individuals (FeLV), as a function of time, show that a stable equilibrium is reached. No scale is given for X neither for Y, as only qualitative results are important here.

The simulations we obtained for FIV and for FeLV are shown in Figure 2. For both viruses, analysis of the model stability, simulations and parameters estimations reveal that once introduced, the viruses are always maintained in the population. Two of the possible equilibrium solutions of the model, the elimination of the population due to the epidemics and extinction of viruses, are shown to be unrealistic regarding to biological parameters value. The third possible solution is a stable equilibrium state, reached by susceptible, infected and immunized cats. Furthermore, there is a low reduction of the population size (around 5%), once this equilibrium is reached and there is a low transmission rate. Findings of the model are consistent with field observations and literature. All these points suggest an endemic state of the diseases and a low impact on the populations.

## 4 Long term dynamical study

The long-term monitoring during 13 years (Pontier 1993) of two populations, Aimargues and Saint-Just-Chaleyssin, has provided several interesting results both at the individual and population levels.

First, at the individual level, the mean life expectancy of the studied cat is short in natural conditions, from 3 to 5 years on average, according to sex and to populations (Pontier 1993). This means that with a first exposure to infection occurring around 1-2 years old on average for FIV and infection lasting on average 5 years (Moraillon 1990), few infected cats should live long enough to die from FIV. On average, first FeLV exposure occurs earlier in life, and the infection period is shorter (but may last several years, Jarrett 1985). However, most of the cats seem to be naturally immunized (Fromont 1994) so that, here again, few cats should die from this virus. Thus, at the individual level, the probability of dying either from FIV or FeLV is low in natural conditions.

At the population level, sex and age structures, as well as the size of AI and SJ remained stable for more than 13 years (Pontier 1993). Our epidemiological study showed that both viruses were present in these populations at least since 1991. As the prevalence rates are stable, and the transmission rates low (Yamamoto *et al.* 1989, Courchamp *et al.,* 1995, Fromont 1994), the infections certainly date from before 1991 in these populations. In fact, we know that both viruses have been present in France for at least twenty years (Irgens *et al.* 1972, Moraillon 1990), and we suspect them to be much more ancient (Benveniste *et al.* 1975, Courchamp & Pontier 1994). Thus, the stability of the population despite the presence of both viruses suggests an endemic state of the diseases: at least during the last few years, both viruses seemed to have a low impact on cat populations. This is confirmed by already published surveys: FIV and FeLV are found worldwide since at least 25 years in different parts of the world (Jarrett *et al.* 1964, Courchamp & Pontier, 1994). Both viruses are found at relatively important prevalence rates, and no epidemic has ever been reported for either virus (in

natural conditions; multi-cats household FeLV outbreaks are different situations). The impact of a virus in a host population depends primarily on both the viral pathogenicity and the host species status (endangered or not). Even if these retroviruses kill domestic cats, the low pathogenicity at the population level, as well as the non-endangered status of this species, are evidence of their low impact in natural populations of domestic cats.

## 5 Conclusion

Despite differences of infection risk in categories of individuals, and the fact that virus circulation probably depends on social structures of populations, similar conclusions are reached from the different aspects of the study of these viruses. The mortality rates induced by both viruses are low in natural conditions, and both diseases seem to be endemic. In addition, the domestic cat being a non-endangered species, these three points together strongly suggest a low impact of FIV and FeLV upon natural populations of domestic cats.

Even if differences in FeLV prevalence rates between the three populations are not significant, we note that the higher the density, the higher the FeLV prevalence rate. Cat population density is known to be directly linked to the frequency of amicable behaviour (Natoli *pers. comm.*), and it may be hypothesized that this is the reason why the gradient of cat density between the three populations reflects the gradient of FeLV prevalence rate. Similarly, althoug the impact of both viruses is low, the impact of FIV seems slightly greater than the impact of FeLV in these three rural populations. These rural populations are characterized by polygynous mating systems, with female monopolization by males, that induce rather high levels of aggressive behavior (Pontier, 1993). As we also hypothesized that populations with high levels of amicable social interactions should have higher FeLV and lower FIV prevalence rates, the epidemiological study of a population in which social interactions are suspected to be more frequent, an urban population of domestic cats (Pontier, 1993), is currently being realized by our team.

## Acknowledgments

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**Chapter IX**

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**Chapter X**

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## 1 Introduction

Among numerous viruses that infect domestic cats (*Felis catus*), two retroviruses are of major importance (Hardy 1993, Bendinelli *et al*. 1995): feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV). FIV and FeLV have been found in all places in the world where they have been investigated. A synthesis of available literature (Courchamp & Pontier 1994) highlights that antibodies to FIV have always been found at relatively high rates: considering 59 serosurveys (including more than 85,000 tested cats), the "average" FIV prevalence rate is around 11.0%. Similarly, a synthesis of 74 serosurveys indicates a global FeLV prevalence antigens of 14.21%, on more than 110,000 tested individuals (Fromont 1994).

Furthermore, FIV and FeLV are known to infect several non-domestic felids (for a FIV review: Courchamp & Pontier 1994, for FeLV: Meric 1984, Briggs & Ott 1986, Citino 1986, Boid *et al.* 1991, Jessup *et al.* 1993). The other feline species have not yet been (or only slightly) investigated. However, most of them are endangered (Wozencraft 1993). Thus, there is an urgent need, for biodiversity preservation, to complete the epidemiological knowledge on such viruses.

FIV is a recently identified lentivirus inducing an AIDS-like syndrome in cats (Pedersen *et al.* 1987). Transmission of FIV occurs through bites during fights (Yamamoto *et al.* 1989). FIV infection induces a long asymptomatic stage (lasting months to years, Sparger 1993) followed by AIDS, characterized by miscellaneous disorders and opportunistic infections (Sparger 1993). As there is no immunity nor recovery, either natural or artificial, infected cats die from this infection (Sparger 1993).

FeLV is probably the most common single, non-traumatic, cause of death in adult domestic cats (Jarrett 1985). This oncovirus is transmitted horizontally (mainly through licking, maternal grooming, mating, food sharing), and also vertically, from mother to kitten (Jarrett 1985). Most of FeLV infected cats seem to recover from infection, develop an immunity, and do not become excreting carriers (Fromont 1994), whereas the others become persistently viremic and, after a long asymptomatic stage, develop FeLV-related diseases and die (Hardy 1993). Clinical features of FeLV and FIV are very similar (Yamamoto *et al.* 1988). As interactions are not quantitatively important (Yamamoto *et al.* 1988), these two viruses will be here considered independently.

Populations of domestic cats are known to present a high degree of variability of their spatial and social structure (Liberg & Sandell 1988) and possibly of their mating behavior (Natoli & DeVito 1988, Pontier & Natoli in press). Populations structures are partly determined by resource availability (Macdonald 1983) and habitat fragmentation (Pontier *et al.* 1995). Such population structures can in return affect circulation of pathogens (Loehle 1995, Courchamp *et al., unpublished results*). Similarly, virus transmission mode is also a major parameter affecting the circulation pattern of viruses within populations. Despite strong similarities between FIV and FeLV (mainly due to similar pathological courses), we hypothesize that differences in their infection modes should induce strong dissimilarities in their respective spread patterns.

The aim of this paper is, through a synthesis of our already published data, to compare FIV and FeLV spread patterns and to study the respective impact of both retroviruses, in terms of reduction of the number of individuals, within natural populations of domestic cats. We used complementary approaches. First, from an epidemiological study of natural populations of domestic cats, we estimated, for both viruses, the infection risk of different categories of cats (Fromont 1994, Courchamp *et al. unpublished results*). Second, we built an epidemiological model of the circulation of these viruses within populations, in order to estimate their respective impact (Courchamp *et al.* 1995, Fromont *et al., unpublished results*). Finally, some results of a long term dynamical monitoring on two of these populations give indications of the impact of infection at both the individual and population level (Pontier 1993).

## 2 Epidemiological study

We have studied the epidemiology of FIV and FeLV in three populations of mostly freely roaming cats in rural habitats, located in France. These populations differ in size, density and fragmentation of habitat (*i.e.* clustering of cat houses). Two of them, Aimargues (AI) and Saint-Just-Chaleyssin (SJ) has been monitored annually since 1981 by one of us (Pontier 1993), and the other, Barisey-La-Côte (BC) has been investigated by our team since 1990. The epidemiological surveys of FIV and FeLV started in 1991 in the three populations.

A representative sample of cats, of a sixth to a half of the populations, was taken each year from the three populations. Cats were caught directly at their owner's house, or with lured cages when they were too untamed. Some cats were caught several times. Each year, for each cat, a blood sample was taken in order to determine the serological status of individuals for FIV and FeLV, and several individual factors were recorded. These factors are sex, neutering status, age, weight (which can determine the social status of cats), roaming habits (which is an indication of the exposure of cats to other cats), group size (a group being defined by the cats living in the same house), and group health (presence or not of the studied virus in another cat of the group).

### 2 1 Prevalence rates

FIV is present in the three populations (Table I) at relatively high prevalence rates, but the differences between years and between populations are not significant ($\chi^2 \leq 4,38$; $p \geq 0,05$, and $TRL \leq 3,79$; $p \geq 0,05$). One population, BC, is free of FeLV. The two other populations show no evolution of FeLV prevalence rate with time ($TRL \leq 0,47$; $p \geq 0,05$). The prevalence differences between SJ and AI are not significant ($\chi^2 \leq 3,15$; $p \geq 0,05$), but this may be due to the relatively small available samples. BC is a small population of cats (approximately 60 individuals, according to years), has a low cat density (120 cats/km$^2$) and is highly fragmented. As the presence of FeLV is established in BC neighboring domestic cat populations (as close as 5 kms, Rioux *pers. comm.*) and in wild cats (Felis silvestris, Artois & Remond 1994), several hypothesis

may explain this absence in BC itself. The potential (and possibly repetitive) extinction, could be a result of stochastic processes in a population with a low density (which should induces fewer amicable interactions), and a small population size (60 individuals), following the principle that, due to the low transmission rates, the smaller the population size, the higher the probability of virus extinction.

**Table I**: Prevalence rates of the three populations, Saint-Just-Chaleyssin (SJ), Barisey-La-Côte (BC) and Aimargues (AI), for three consecutive years (1991, 1992 and 1993), for **A**: FIV. **B**: FeLV. FeLV is always absent in one of the three populations (BC). Differences between populations or between years are not significant.

**A: FIV:**

| Pop. | SJ | | | BA | | | AI | | |
|---|---|---|---|---|---|---|---|---|---|
| Year | %-se | < % < | %+se | %-se | < % < | %+se | %-se | < % < | %+se |
| **1991** | 13,72 | **19,57** | 25,41 | 4,52 | **10,00** | 15,48 | 8,89 | **14,29** | 19,69 |
| **1992** | 10,18 | **15,09** | 20,01 | 12,67 | **18,60** | 24,54 | 2,39 | **5,45** | 8,52 |
| **1993** | 9,29 | **14,29** | 19,28 | 8,67 | **13,95** | 19,24 | 2,35 | **5,36** | 8,37 |
| **1994** | 4,76 | **9,09** | 13,42 | 11,11 | **17,65** | 24,18 | 1,05 | **3,45** | 5,84 |

**B: FeLV:**

| Pop. | SJ | | | BA | | | AI | | |
|---|---|---|---|---|---|---|---|---|---|
| Year | %-se | < % < | %+se | %-se | < % < | %+se | %-se | < % < | %+se |
| **1991** | 4,54 | **8,70** | 12,85 | 0,00 | **0,00** | 0,00 | 1,48 | **4,76** | 8,05 |
| **1992** | 6,97 | **11,32** | 15,67 | 0,00 | **0,00** | 0,00 | 2,39 | **5,45** | 8,52 |
| **1993** | 5,88 | **10,20** | 14,53 | 0,00 | **0,00** | 0,00 | 1,09 | **3,57** | 6,05 |
| **1994** | 8,46 | **13,64** | 18,81 | 0,00 | **0,00** | 0,00 | 1,05 | **3,45** | 5,84 |

### 2 2 Risk factors

With univariate statistical tests (Chi-square and non-parametric trend statistics tests), we tested the influence on infections of each factor taken separately. We also analyzed the influence of several factors simultaneously in order to highlight potential interactions. For this, we used Multiple Correspondence Analysis (MCA, Escoffier & Pagès 1990) and Generalized Linear Models through logistic regressions (Aitkin *et al.* 1989). The two infections do not affect the same categories of individuals. Indeed, FIV infection risk is characterized by sex, age, weight and roaming habits: immigrant, well built, sexually mature males (not too old) are more likely to become infected with FIV (Courchamp *et al., unpublished results*). In contrast, FeLV infection risk is characterized by neutering status, age, group size and group health: entire, young cats living in large groups with FeLV infected mates are more likely to be FeLV infected (Fromont 1994). A detailed analysis of these results shows that factors influencing FIV infection are mostly linked to aggressive behavior, whereas factors influencing FeLV

are characteristic of the cat group. This is consistent with the different modes of transmission of the two viruses: FIV is transmitted by bites through fights, whereas FeLV is transmitted through more friendly contacts. Heavy adult males are often the high ranking cats (Liberg, 1981), that is, cats that are likely to fight, which explains their propensity to FIV infection. It is also known that young cats living in large groups often have amicable contacts (Natoli, pers. comm.), which could explain why they are more often infected with FeLV than other individuals.

Thus, we can hypothesize that the two viruses will show different circulation patterns: in a given population, FIV transmission should occur between social groups mainly through aggressive contacts occurring between high-ranking males, whereas FeLV should spread, mostly within social groups through more friendly contacts, with a pattern similar to the direct contact diffusion ones (Figure 1).

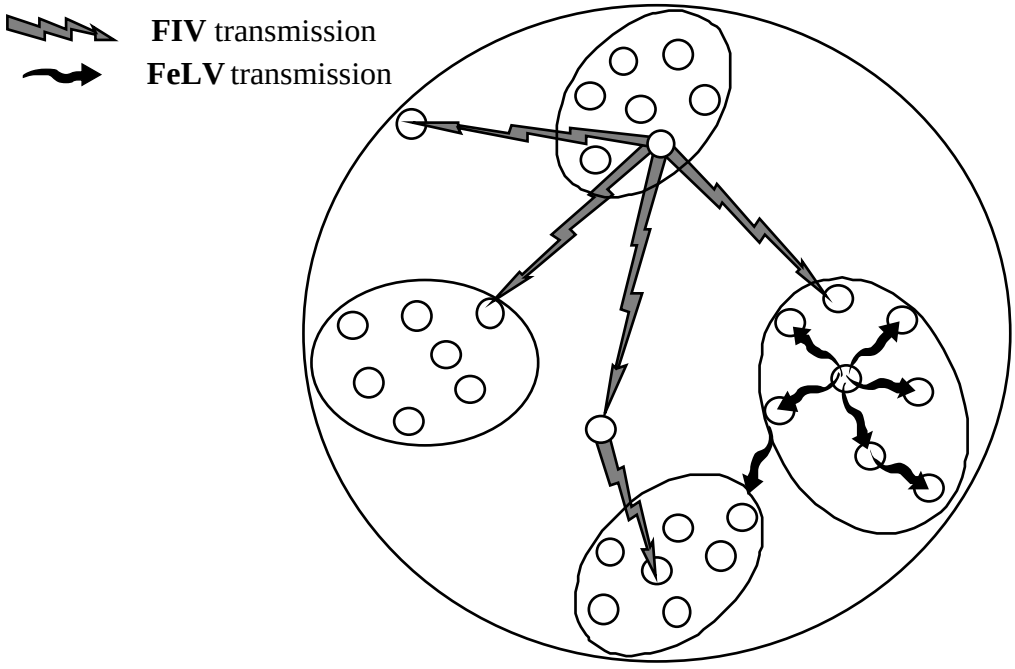


**Figure 1** : Representation of spread patterns of FIV ( ) and FeLV ( ) between and within the social groups of a theoretical population. The two viruses show totally different patterns of circulation : FIV infects at-risk individuals while FeLV spreads infecting close cats similar to the direct contact diffusion patterns.

## 3 Modeling of virus spread

Theoretical insight of the influence of both retroviruses is provided by a deterministic model which we constructed (Courchamp *et al.* 1995, Fromont *et al., unpublished results*). Despite some differences, the two retroviruses share strong similarities on a modeling point of view: they show comparable succession of asymptomatic and clinical stages (Yamamoto *et al*. 1988), leading to death (and they infect the same host, the domestic cat). For this reason, we chose to use the same type of model for both viruses, in order to compare their respective results. This is a SIR type compartmental model, based on Anderson & May's work (Anderson & May 1991), for which we used some parameters obtained from the epidemiological and the dynamical studies (e.g. prevalence rates, birth and mortality rates) or in litterature (e.g. death rates due to the diseases). Cat population dynamics are represented by a set of differential equations, each one representing a serological status (susceptible, infected, immunized, Figure 2). Values of parameters that were not directly accessible on the field (e.g. rate of effective transmission) were estimated with the model at the equilibrium. Detailled description of the model being available elsewhere (Courchamp *et al.* 1995), details will not be given here.

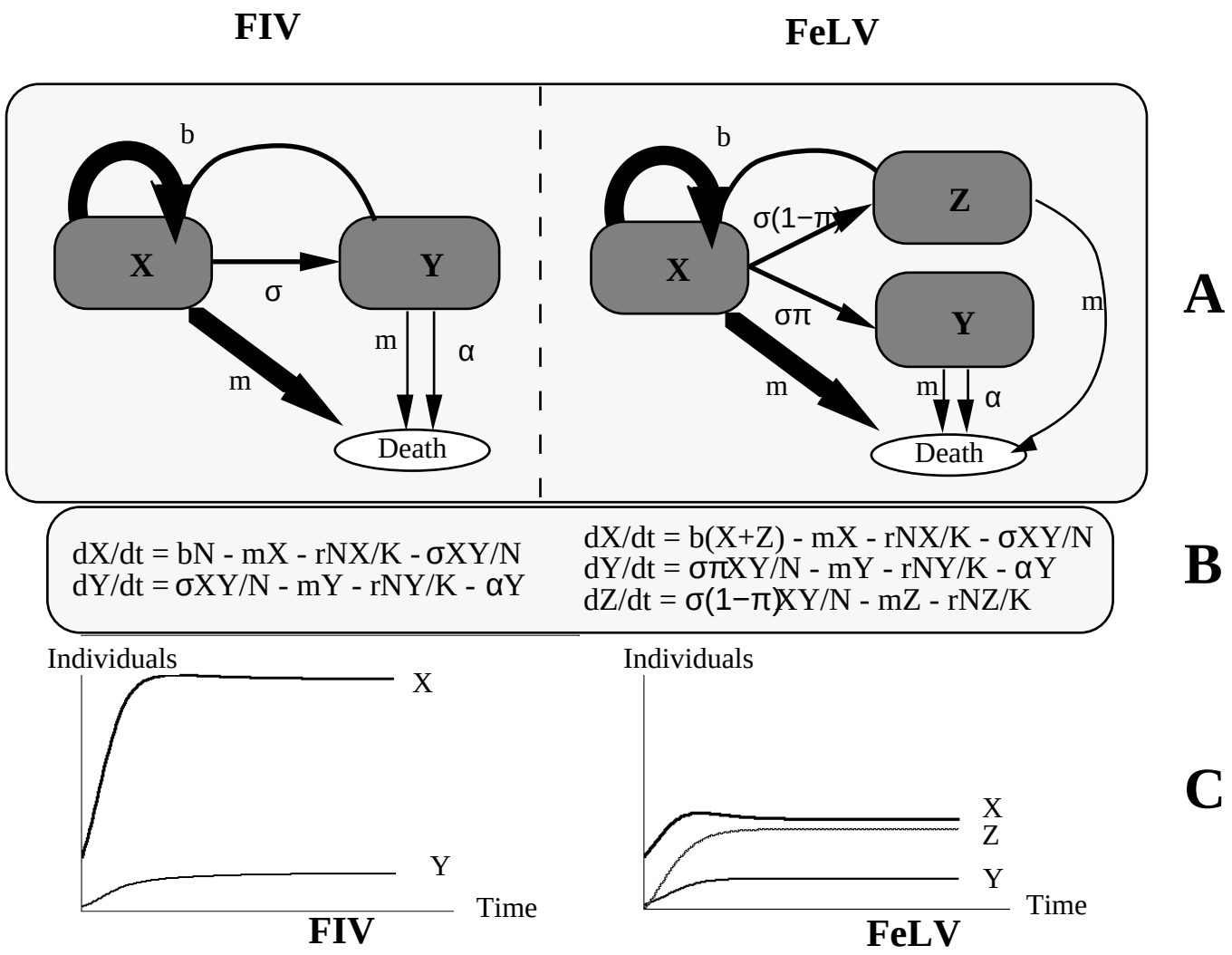


**Figure 2** : Compartmental representation (**A**), equations (**B**), and simulations (**C**) of FIV and FeLV models. **A** : compartments *X*, *Y* and *Z* represent different subpopulations : susceptible, infected or immunized, respectively. Arrows represent the rates between these subpopulations, or between them and death, and their width is a qualitative indication of the importance of the rates. **B** : set of simple differential equations corresponding to the compartmental representation. d*X*/dt, d*Y*/dt and d*Z*/dt give the dynamics of *X*, *Y* and *Z* individuals, respectively. The birth rate is b, and m is the natural mortality rate (r=b-m), K is the carrying capacity of the habitat at equilibrium and *N* is the total number of cats in the population at time t. The rate of effective transmissions is σ, α is the death rate due to the viruses, and π is the ratio of FeLV non immunized cats. **C** : simulation of the model : number of susceptible and infected individuals (FIV) or susceptible, infected and immunized individuals (FeLV), as a function of time, show that a stable equilibrium is reached. No scale is given for X neither for Y, as only qualitative results are important here.

The simulations we obtained for FIV and for FeLV are shown in Figure 2. For both viruses, analysis of the model stability, simulations and parameters estimations reveal that once introduced, the viruses are always maintained in the population. Two of the possible equilibrium solutions of the model, the elimination of the population due to the epidemics and extinction of viruses, are shown to be unrealistic regarding to biological parameters value. The third possible solution is a stable equilibrium state, reached by susceptible, infected and immunized cats. Furthermore, there is a low reduction of the population size (around 5%), once this equilibrium is reached and there is a low transmission rate. Findings of the model are consistent with field observations and literature. All these points suggest an endemic state of the diseases and a low impact on the populations.

## 4 Long term dynamical study

The long-term monitoring during 13 years (Pontier 1993) of two populations, Aimargues and Saint-Just-Chaleyssin, has provided several interesting results both at the individual and population levels.

First, at the individual level, the mean life expectancy of the studied cat is short in natural conditions, from 3 to 5 years on average, according to sex and to populations (Pontier 1993). This means that with a first exposure to infection occurring around 1-2 years old on average for FIV and infection lasting on average 5 years (Moraillon 1990), few infected cats should live long enough to die from FIV. On average, first FeLV exposure occurs earlier in life, and the infection period is shorter (but may last several years, Jarrett 1985). However, most of the cats seem to be naturally immunized (Fromont 1994) so that, here again, few cats should die from this virus. Thus, at the individual level, the probability of dying either from FIV or FeLV is low in natural conditions.

At the population level, sex and age structures, as well as the size of AI and SJ remained stable for more than 13 years (Pontier 1993). Our epidemiological study showed that both viruses were present in these populations at least since 1991. As the prevalence rates are stable, and the transmission rates low (Yamamoto *et al.* 1989, Courchamp *et al.,* 1995, Fromont 1994), the infections certainly date from before 1991 in these populations. In fact, we know that both viruses have been present in France for at least twenty years (Irgens *et al.* 1972, Moraillon 1990), and we suspect them to be much more ancient (Benveniste *et al.* 1975, Courchamp & Pontier 1994). Thus, the stability of the population despite the presence of both viruses suggests an endemic state of the diseases: at least during the last few years, both viruses seemed to have a low impact on cat populations. This is confirmed by already published surveys: FIV and FeLV are found worldwide since at least 25 years in different parts of the world (Jarrett *et al.* 1964, Courchamp & Pontier, 1994). Both viruses are found at relatively important prevalence rates, and no epidemic has ever been reported for either virus (in

natural conditions; multi-cats household FeLV outbreaks are different situations). The impact of a virus in a host population depends primarily on both the viral pathogenicity and the host species status (endangered or not). Even if these retroviruses kill domestic cats, the low pathogenicity at the population level, as well as the non-endangered status of this species, are evidence of their low impact in natural populations of domestic cats.

## 5 Conclusion

Despite differences of infection risk in categories of individuals, and the fact that virus circulation probably depends on social structures of populations, similar conclusions are reached from the different aspects of the study of these viruses. The mortality rates induced by both viruses are low in natural conditions, and both diseases seem to be endemic. In addition, the domestic cat being a non-endangered species, these three points together strongly suggest a low impact of FIV and FeLV upon natural populations of domestic cats.

Even if differences in FeLV prevalence rates between the three populations are not significant, we note that the higher the density, the higher the FeLV prevalence rate. Cat population density is known to be directly linked to the frequency of amicable behaviour (Natoli *pers. comm.*), and it may be hypothesized that this is the reason why the gradient of cat density between the three populations reflects the gradient of FeLV prevalence rate. Similarly, althoug the impact of both viruses is low, the impact of FIV seems slightly greater than the impact of FeLV in these three rural populations. These rural populations are characterized by polygynous mating systems, with female monopolization by males, that induce rather high levels of aggressive behavior (Pontier, 1993). As we also hypothesized that populations with high levels of amicable social interactions should have higher FeLV and lower FIV prevalence rates, the epidemiological study of a population in which social interactions are suspected to be more frequent, an urban population of domestic cats (Pontier, 1993), is currently being realized by our team.

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