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Kedi Lösemi Virüsünde Endemik Denge

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ÖZ

Felin Lösemi Virüsü kedilerin bağışıklık sistemini zayıflatan bir virüstür ve virüsün bağışıklık sistemini baskılayan yapısı nedeniyle, virüsle enfekte olmuş kediler lenfoma, lösemi, ağır eritroid hipoplazi ve anemi gibi ciddi hastalıkların ortaya çıkması riskini daha fazla taşırlar. Duyarlı-Enfekte (SI) epidemik modeline dayalı SI_1I_2 kompartıman modeli, aşılama ve tedavinin olmadığı durumlarda, sokak kedileri için hastalığın endemik dengesini incelemek üzere kullanılmıştır. Hastalıklı kedi popülasyonunun duyarlı kedilerin final değerinden daha büyük olduğu parametre koşulları elde edilmiştir.

Endemic Equilibrium of Feline Leukemia Virus

Research Article

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ABSTRACT

Feline Leukemia Virus impairs the immune system of cats, and as a result of the immunosuppression characteristic of the virus, infected cats are under a greater risk for developing serious diseases like lymphomas, leukemia, severe erythroid hypoplasia and anemia. The compartmental model denoted by SI_1I_2 based on the epidemiological model Susceptible-Infected (SI) is used to investigate the endemic equilibrium of the disease for stray cats without vaccination and treatment. The conditions for parameters are obtained such that the final value of infected cats' population is higher than the final value of susceptible cats.

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1. Introduction

One of the most common infectious diseases in cats is caused by Feline Leukemia Virus (FeLV) which belongs to the genus Gammaretrovirus of the family Retroviridae in the subfamily Oncornavirinae (Neil, 2008; Hal, 2012; James, 2017). This feline-only virus impairs the immune system of the cat and can be the reason of severe and lethal diseases. In fact, the disease is the most common cause of cancer (Hartmann, 2011; Hartmann, 2012). The symptoms of infected cats include progressive weight loss caused by the loss of appetite, poor coat condition, anemia, persistent fever and diarrhea, skin, urinary, and upper respiratory tract infections, seizures, behavior changes, and other neurological disorders, inflammation of the nose, the cornea as well as inflammation of the gums and mouth, lymphoma which is the most common FeLV-associated cancer, fibrosarcomas which is the

cancer that develops from fibrous tissue, leukemia, infertility etc. (Ueland et al., 1992; Kipar et al., 2001; Dunham et al., 2008). FeLV is preventable by the use of an effective vaccine. However, the vaccine does not provide full protection. Cats whose immune system does not resist and eliminates the virus can live only few years after the FeLV diagnosis since treatment to clear the infection most often fails. The median survival time for cats with FeLV diagnosis is two and half years (Addie et al., 2000; Levy et al., 2008; Helfer-Hungerbuehler et al., 2015).

FeLV has initially four subgroups A, B and C as well as recombinations of these subgroups (Jarrett et al., 1973; Sarma et al., 1973; Jarrett, 1992). All naturally infected cats have subgroup A which is the dominant form, and is responsible for the immunosuppression characteristic of the disease. Once infected, additional mutated forms of FeLV-A may arise (Miyazawa, 2002; Sykes 2014; Mummoorthy et al., 2021). Cats with FeLV-B are under a greater risk for developing lymphomas whereas cats with FeLV-C have developed severe erythroid hypoplasia and anemia. 50 percent of FeLV-infected cats have a combination of subgroups A and B whereas 1 percent of them have a combination of subgroups C and A as AC, or of all subgroups as ABC. Subgroup A has a variety of strains ranging from non-pathogenic to very pathogenic (Vail, 2019). The pathogenecity increases dramatically if they are present with other subgroups (Macy et al., 2012), and these cats may manifest vastly different diseases. For example, the combination of subgroups A and B is more contagious and pathogenic than subgroup A alone. Cats infected with subgroups A and B often develop thymic lymphoma and myeloproliferative disease (Hoover, 1991; Lutz, 2009; Hartmann, 2012).

Cats can transfer the virus between themselves through prolonged contact with bodily fluids (Lee et al., 2002; Bande et al., 2012), mainly through saliva which may contain up to 100,000 virus particles per milliliter. Other sources of transmission are urine, faeces and nasal secretions as well as by licking, biting and mutual grooming, shared feeding bowls and litter pans (Richards, 2003; Sykes, 2014; Hartmann, 2020). The transmission of virus is also possible from an infected mother to the kittens in utero and via the milk (Hardy et al., 1976; Levy et al., 2008) since kittens are much more susceptible to the infection than adult cats, and therefore are at the greatest risk of infection if exposed. This type of transmission may occur transplacentally or during the nursing period (Hartmann, 2011; Sykes, 2014; Hartmann, 2020). The best way for preventing the spread of the disease is the elimination of the contact with the cats that are FeLV-positive since cats with persistent infection serve as sources of infection for other cats (Tartaglia, 1993; Levy, 2008; Lutz, 2009).

In this article, susceptible-infected model denoted by SI_1I_2 presented in (Ahmetolan et al., 2022) is used to describe FeLV for stray cats without vaccination and treatment. SI_1I_2 model has two infected stages I_1 and I_2 which have different clinical forms. The infected group I_2 has a higher mortality rate than the group I_1. The group I_1 represents cats infected with either of the subgroups. It should be noted that the subgroups are not distinguished and therefore they are all categorized under the group I_1. Cats in the group I_2 are experiencing serious health problems like cancer due to the presence of a

subgroup with other subgroups. Since the model is used for stray cats, it is assumed that the disease is transmitted either transplacentally or during the nursing period to the kittens from an infected mother.
The article is organised as follows. The mathematical model proposed in (Ahmetolan et al., 2022) is presented in Section 2. The positiveness of solution curves is proved for positive initial conditions. Equilibrium points are obtained, and endemic equilibrium point is investigated. For this equilibrium, the stability analysis is performed, and the conditions for parameters are derived for cases such that the final value of the susceptible population is smaller than the final value of each infected group. Theoretical results are demonstrated for suitable parameters for each case. Discussion of the results and concluding remarks are given in the final section.

2. Material and Methods

2.1. SI_1I_2 Model

The susceptible-infected model (Ahmetolan et al., 2022) considered in this work in its most general form is described by the following system of nonlinear ordinary differential equations

$$\begin{aligned} S' &= -\beta_1 S I_1 - \beta_2 S I_2 + (\delta_0 - \mu_0)S + (1-p)\delta_1 I_1 + (1-q)\delta_2 I_2, \\ I_1' &= \beta_1 S I_1 - \theta I_1 + (p\delta_1 - \mu_1)I_1, \\ I_2' &= \beta_2 S I_2 + \theta I_1 + (q\delta_2 - \mu_2)I_2. \end{aligned} \tag{1}$$

Here, S, I_1 and I_2 are the susceptible group and two infected groups, respectively. The contact rates of each infected group with the susceptibles are β_i for $i = 1,2$. Parameters δ_i and μ_i for $i = 0,1,2$ refer to the birth and death rates of groups S, I_1 and I_2, respectively. The parameter θ is the rate of population in the group I_1 who become a member of the group I_2. The parameters, $0 \le p \le 1$ and $0 \le q \le 1$ represent the proportion of infected newborn of the infected mother in groups I_1 and I_2, respectively. The non-constant total population size N is $N = S + I_1 + I_2$.
In this study for FeLV infection, I_1 represents the cats infected with either of the subgroups A, B or C. If one of these subgroups is present with other subgroups, then the infected cats in group I_1 become members of group I_2 with the rate of θ. Since the existence of a subgroup with other subgroups implies that the disease is more contagious and pathogenic, we assume $\beta_2 > \beta_1$. On the other hand, since the model is used for stray cats without any vaccination or treatment, it is also assumed that the disease is transmitted either transplacentally or during the nursing period to the kittens from an infected mother.
This corresponds to the fact that both parameters, p and q are equal to 1. For simplicity, we take $\beta_1 = 1$ and $\beta_2 = \beta$, and define

$$f_i = \delta_i - \mu_i \tag{2}$$

for $i = 0,1,2$. Since the death rate is higher than the birth rate in group I_2, the parameter f_2 is negative. Then, the equations given by (1) reduce to the following system of differential equations

$$\begin{aligned} S' &= -SI_1 - \beta SI_2 + f_0 S, \\ I_1{}' &= SI_1 - \theta I_1 + f_1 I_1, \\ I_2{}' &= \beta SI_2 + \theta I_1 + f_2 I_2 \end{aligned} \tag{3}$$

where

$$\beta > 1, \quad \theta - f_1 \neq 0, \quad f_2 < 0. \tag{4}$$

Note that $\beta_1 = 1$, $\beta_2 = \beta$ and $\beta_2 > \beta_1$. For the disease in consideration, the parameter θ is nonzero and the healthy population is not in equilibrium; that is, $f_0 \neq 0$.

The flow diagram of the model is illustrated in Figure 1 and the positiveness of solutions is given by the following proposition.

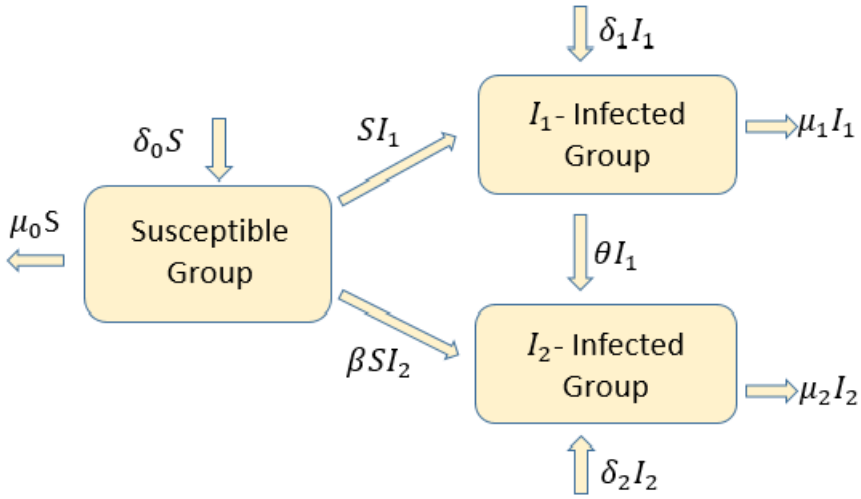

Figure 1. Diagram of SI_1I_2 model.

Proposition 1: The susceptible group S and the infected groups $I_1$and I_2 are positive if the initial conditions are chosen to be positive.

Proof: If S_0, $I_{1,0}$ and $I_{2,0}$ are the initial conditions for the susceptible and infected groups, S, $I_1$and I_2, respectively, then solving the equations in (3) yields the following at any time *t*

$$\begin{aligned} S(t) &= S_0 \exp\left(\int_0^t (-I_1 - \beta I_2 + f_0)\, d\tau\right), \\ I_1(t) &= I_{1,0} \exp\left(\int_0^t (S(\tau) - \theta + f_1)\, d\tau\right), \end{aligned} \tag{5}$$

$$I_2(t) = \exp\left(\int_0^t (\beta S(\tau) + f_2)\, d\tau\right) [I_{0,2} + \int_0^t \theta\, I_1 \exp(-\int_0^\tau (\beta S(\tau) + f_2)\, d\sigma)\, d\tau],$$

Solutions curves in (5) show that $S(t)$, $I_1(t)$ and $I_2(t)$ remain positive if the initial conditions S_0, $I_{1,0}$ and $I_{2,0}$ are chosen positive.

2.2. *Equilibrium Points*

To obtain the equilibrium points, each equation in (3) is set as zero. Then, the homogeneous system has the trivial solution, $S = I_1 = I_2 = 0$, which refers to the extinction of the specie. To find the nontrivial solution of this system, we consider the following cases.

1) $I_1 = 0$: The first equation in (3) yields that either $S = 0$ or $I_2 = f_0/\beta$. If $S = 0$, then from the last equation in (3), we obtain $I_2 = 0$. Since we search for a nontrivial solution of (3), then $I_2 = f_0/\beta$ and consequently $I_2 = -f_2/\beta$.

2) $I_1 \neq 0$: The second equation in (3) yields $S = \theta - f_1$. Substituting this value into the other equations gives $I_1 = f_0(\beta(f_1 - \theta) - f_2)/(\beta f_1 - f_2)$ and $I_2 = \theta f_0/(\beta f_1 - f_2)$.

The non-trivial critical equilibrium points and the conditions for positive solutions are summarized as follows for the ordered triple (S, I_1, I_2)

1) The point $P(-\frac{f_2}{\beta}, 0, \frac{f_0}{\beta})$ is I_1-free equilibrium. This equilibrium exists if f_0 is positive.

2) The point $Q(\theta - f_1, f_0 \frac{\beta(f_1-\theta)-f_2}{\beta f_1 - f_2}, \frac{f_0\theta}{\beta f_1 - f_2})$ is the endemic equilibrium. Existence of this equilibrium requires

$$f_0 > 0, \theta - f_1 > 0,\ \beta(f_1 - \theta) - f_2 > 0. \tag{6}$$

The shaded region in Figure 2 gives $(f_1, |f_2|)$ pairs for which the system admits an endemic equilibrium for $f_0 > 0$.

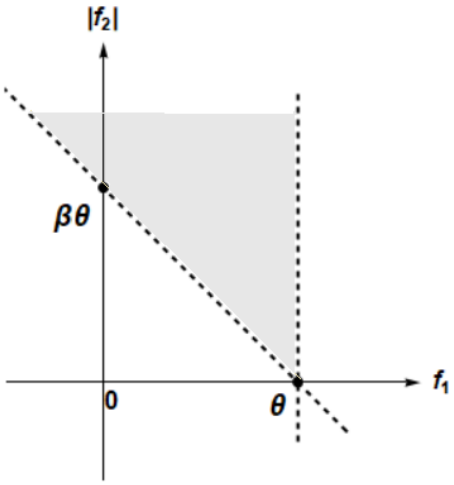

Figure 2. The shaded region for which the system admits an endemic equilibrium for $f_0 > 0$.

2.3. Endemic equilibrium

In this section, we consider the case where the system given by the equations in (3) admits an endemic equilibrium. The stability analysis is performed, and the conditions that the parameters satisfy are derived for the cases such that the final value of the susceptible population is smaller than the final value of each of the infected population.

2.3.1. Stability

In (Ahmetolan et al., 2022) , the stability of the system in (1) for $p = q = 1$ is investigated and the following proposition is given.

Proposition 2: Endemic equilibrium at the point $R(S_R^*, I_{1,R}^*, I_{2,R}^*)$ where

$$S_R^* = \frac{\theta - \delta_1 + \mu_1}{\beta_1},$$
$$I_{1,R}^* = \frac{\delta_0 - \mu_0}{\beta_1}\left(1 - \frac{\beta_2 \theta}{\beta_2(\delta_1 - \mu_1) - \beta_1(\delta_2 - \mu_2)}\right), \quad (7)$$
$$I_{2,R}^* = \frac{\theta(\delta_0 - \mu_0)}{\beta_2(\delta_1 - \mu_1) - \beta_1(\delta_2 - \mu_2)}$$

is locally asymptotically stable if the following conditions hold

$$\delta_0 - \mu_0 > 0, -\beta_1(\delta_2 - \mu_2) > \beta_2(\delta_1 - \mu_1), \ \beta_2 > \beta_1. \quad (8)$$

Since $\beta_1 = 1$ and $\beta_2 = \beta > 1$ for the FeLV model, the point R defined by (7) corresponds to the endemic equilibrium point Q for the system in (3). The conditions given in (6) for Q to exist satisfy the conditions in (8). Thus, the endemic equilibrium Q is locally asymptotically stable if it exists.

2.3.2. Endemic Equilibrium for $S_f < I_{1f} < I_{2f}$

Let S_f, I_{1f} and I_{2f} denote the final values of the susceptible group and two infected groups; that is, $\lim_{t\to\infty} S(t) = S_f$, $\lim_{t\to\infty} I_1(t) = I_{1f}$, $\lim_{t\to\infty} I_2(t) = I_{2f}$. If the components of the point Q is replaced in $S_f < I_{1f} < I_{2f}$, we find the following conditions

$$\beta f_1 - f_2 < (\beta + 1)\theta,$$
$$(\theta - f_1)(\beta f_1 - f_2) < \min\{\theta f_0, -f_0(f_2 + \beta(\theta - f_1))\}. \quad (9)$$

Theoretical results at the endemic equilibrium are demonstrated for suitable parameters satisfying (9) in Figure 3 such that the final value of the infected group I_2 is greater than the other two groups, and the final value of the susceptible group is smaller than the infected groups. As can be seen from the figure, such an equilibrium is locally asymptotically stable.

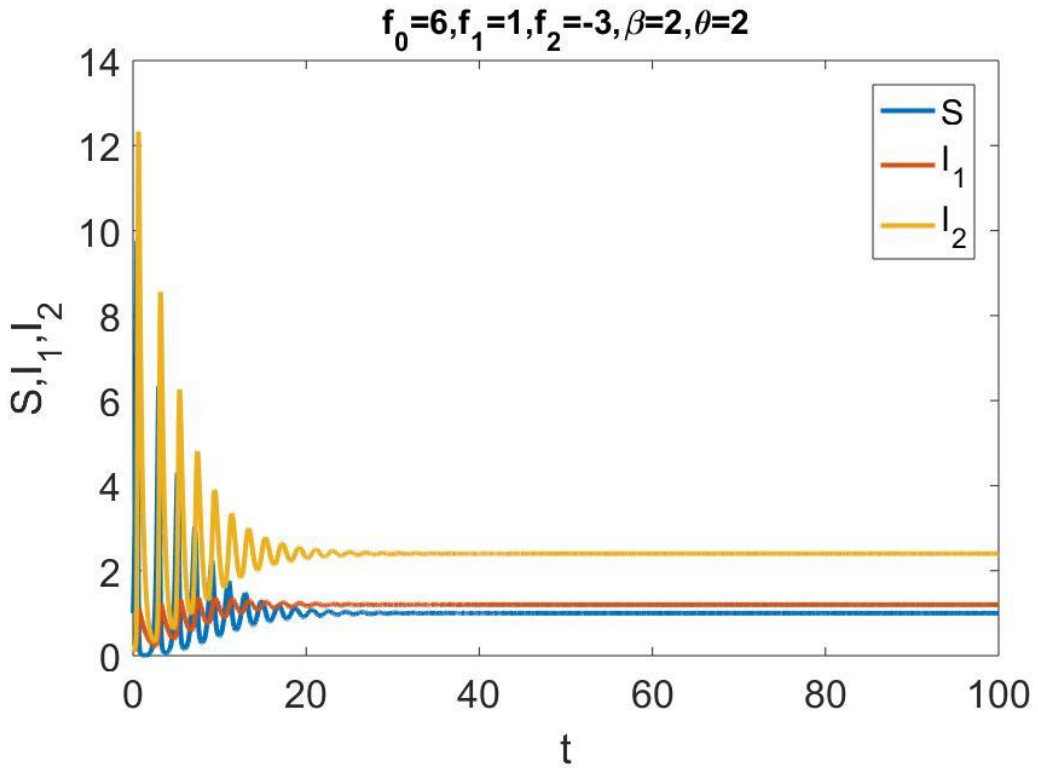

Figure 3. Numerical solutions of (3) with parameter values $f_0 = 6$, $f_1 = 1$, $f_2 = -3$, $\beta = 2$ and $\theta = 2$.

2.3.3. Endemic Equilibrium for $S_f < I_{2f} < I_{1f}$

Similar calculations for the case $S_f < I_{2f} < I_{1f}$ give the following conditions

$$\beta f_1 - f_2 > (\beta + 1)\theta,$$
$$(\theta - f_1)(\beta f_1 - f_2) < \min\{\theta f_0, -f_0(f_2 + \beta(\theta - f_1))\}. \quad (10)$$

Solution curves are demonstrated in Figure 4 for suitable parameters satisfying (10) such that the final value of the infected group I_1 is greater than the other two groups, and the final value of the susceptible group is smaller than the infected groups. As the figure shows, such an equilibrium is locally asymptotically stable.

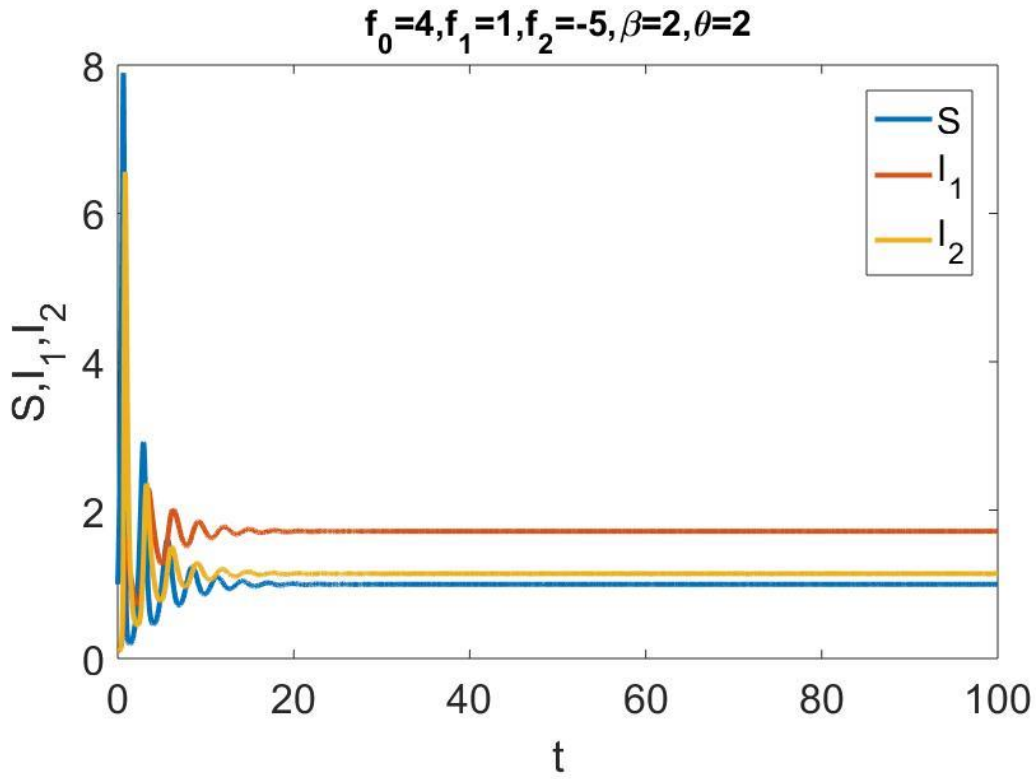

Figure 4. Numerical solutions of (3) with parameter values $f_0 = 4$, $f_1 = 1$, $f_2 = -5$, $\beta = 2$ and $\theta = 2$.

3. Results and Discussion

We study the endemic equilibrium of feline leukemia virus for stray cats without vaccination and treatment by using the epidemiological model Suscptible-Infected with two infected groups, I_1 and I_2. The group I_1 refers to the cats infected with any of the subgroups of FeLV, whereas the group I_2 represents the cats infected with multiple subgroups of FeLV. We assume that initially, the healthy population is not in equilibrium, and that all the newborns from infected mothers develop the disease

shortly after birth. We determine the region in terms of net population growth rates of the infected groups I_1 and I_2 for which the system admits an endemic equilibrium when the net susceptible-population growth rate is positive. We obtain conditions for parameters at this equilibrium such that the final value of susceptible cats is smaller than the final values of infected cats in each infected group. These cases for which each infection becomes an endemic disease can be seen in different scenarios for a variety of parameter combinations. Theoretical results and numerical solutions for suitable parameters show that such equilibria are locally asymptotically stable.

Conflict of Interest

The author declares no competing interests.

Authors' contributions

The author confirms sole responsibility for the article conception and design, analysis and interpretation of results, and manuscript preparation.

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