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THE RATIO OF HIDDEN HIV INFECTION IN CUBA

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Abstract. In this work we propose the definition of the ratio of hidden infection of HIV/AIDS epidemics, as the division of the unknown infected population by the known one. The merit of the definition lies in allowing for an indirect estimation of the whole of the infected population. A dynamical model for the ratio is derived from a previous HIV/AIDS model, which was proposed for the Cuban case, where active search for infected individuals is carried out through a contact tracing program. The stability analysis proves that the model for the ratio possesses a single positive equilibrium, which turns out to be globally asymptotically stable. The sensitivity analysis provides an insight into the relative performance of various methods for detection of infected individuals. An exponential regression has been performed to fit the known infected population, owing to actual epidemiological data of HIV/AIDS epidemics in Cuba. The goodness of the obtained fit provides additional support to the proposed model.

1. **Introduction.** The main objective of this work is to study the proportion of infected individuals who are undetected over the detected infected population in a contagious disease, as an indirect methodology to provide an insight on the asymptomatic population. These individuals are often unaware of their own infection, thus they do not take prophylactic measures to avoid contagion to susceptible individuals. Information about undetected infected people is especially interesting for the HIV/AIDS epidemics since this asymptomatic stage can extend over time, avoiding early assistance and allowing for a greater spread of the disease. Indeed, the incubation period of AIDS is rather variable and, in contrast to other viral infections, the seropositive individual never ceases to be contagious, which further complicates the control of the epidemic spread. Consequently, a major topic for health systems is developing new strategies for early detection, that is to say minimizing the size of the undetected infected population. These strategies are expensive both in human and economic resources, thus the study of their efficiency is a key point.

Mathematical modelling of infectious diseases as dynamical systems has received considerable scientific interest along history (see e.g. [6, 2, 22]). Epidemiological models are often constructed upon systems of Ordinary Differential Equations

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(ODEs), by considering distinct populations as state variables. The success of mathematical models is partly due to their ability to provide valuable information about a number of issues: present incidence, future evolution, efficiency and effectiveness of health authorities strategies or simulated evolution in different conditions. In this context, the HIV/AIDS disease is not an exception, and since its beginning it awakened the interest of the experts. Many recent papers concentrate in rather specific countries or aspects of HIV/AIDS epidemiology, whereas a general framework can be found in [13].

The analysis of HIV/AIDS in Cuba is particularly interesting due to its low prevalence, especially when compared to other Caribbean countries. A model consisting of a system of ODEs has been proposed [8], focusing on modelling different means for detection of the infection that are implemented in Cuba. A detailed theoretical analysis of a rather similar model [23] and a comparison to real data [24] have also recently been proposed. All these models suffer from the lack of data for the unknown infected population, thus no regression or identification method can be directly used to estimate parameters, hindering the ability of modelling as a prediction tool. This is the key motivation for this work: provide qualitative information on the dynamical behaviour of the epidemic, even though the undetected infected population is unknown.

The starting point for this paper is the model of HIV/AIDS in Cuba [8], which is described in Section 2, defining the system of ODEs that model both detection and infection, and setting the value of the parameters that appear in the model.

After the model definition, the ratio of hidden infection is defined as the proportion between undetected and detected seropositive populations, thus avoiding the explicit use of the undetected infected population. The formal analysis of the ratio in Section 3 is the main contribution of this paper. The mathematical analysis proceeds with the standard techniques of dynamical systems theory (see e.g. [7] and references therein), focusing on stability, resulting that all trajectories tend to a stable equilibrium. The expression of this fixed point is given as a function of the system parameters, so the undetected infected population could be estimated when convergence has taken place, although the need for an accurate parameter estimation method is also realized.

The relative influence of the model parameters on the dynamics of the ratio of hidden infection is brought to light by the sensitivity analysis, presented in Section 4. Focusing on detection of the infection, it turns out that the effect of the contact tracing program could be less decisive than previously reckoned, which encourages the development of alternative methods for detection, such as the support to family doctors.

In contrast to many published papers, a substantial effort has been made to assess the proposed model by comparing theoretical results to actual epidemiological data. Hence in Section 5, an exponential regression has been performed in order to fit a curve to the evolution of the known seropositive population. The rationale is that the dynamics of the size of the infected population can be rewritten as a linear ODE, as long as the stable fixed point of the hidden infection ratio has been reached. The goodness of the obtained fit and the match to the empirical values of the parameters provide an independent support to the proposed methodology.

Some concluding remarks and directions for further research put an end to the paper in Section 6.

2. **Epidemic models and HIV/AIDS in Cuba.** As mentioned above, mathematical modelling of epidemiological diseases has acquired a great importance, as it allows for predicting the epidemic evolution and estimating the parameters of the disease spread, so allowing the design and assessment of strategies for control and prevention. Thus the design and analysis of novel proposals for enhancing mathematical models contribute to improve the efficiency of these health strategies.

The conventional approach to epidemiological modelling usually starts from a population model, which represents the flow of individuals from each population to another. This is also the case in this work, despite the fact that the whole of the infected population is not directly measurable. In particular, this model for the population dynamics of the HIV/AIDS epidemic in Cuba takes into account the contact tracing program carried out by the Cuban authorities: those individuals whose infection is detected are requested to disclose their sexual contacts in the last two years, who are in turn notified their situation and tested for HIV. The model of HIV/AIDS [4] is described by the system of nonlinear ODEs in Equation (1):

$$\begin{aligned}
\frac{dx}{dt} &= (\lambda - k_1 - \beta - \mu)\, x + \lambda' (y_1 + y_2) - k_2 \frac{x(y_1 + y_2)}{x + y_1 + y_2} \\
\frac{dy_1}{dt} &= -(\mu + \beta')\, y_1 + k_1\, x \\
\frac{dy_2}{dt} &= -(\mu + \beta')\, y_2 + k_2 \frac{x(y_1 + y_2)}{x + y_1 + y_2} \\
\frac{dz}{dt} &= \beta\, x + \beta' (y_1 + y_2) - \mu'\, z
\end{aligned} \tag{1}$$

Within the model there exist a number of variables that represent the populations of the epidemic, and a set of parameters that represent the transitions between the populations. The rest of this section is dedicated to provide a brief explanation of these equations and the variables and parameters that appear, in order to make the paper self-contained.

Three populations take part in the model of Equation (1), namely the variable x is the population of undetected seropositive individuals, the variable y is the population of detected seropositive individuals and the variable z is the population of patients that have developed AIDS. Incidentally, note that all variables x, y, z are positive for any reasonable interpretation of the model given by Equation (1). This observation will be useful to support the correctness of the definition of the hidden infection ratio in the next section. The set of individuals whose infection has been detected, comprising population y, has been divided into two subpopulations according to the method by which the detection took place: individuals in the population y_2 were detected by means of the contact tracing program and population y_1 comprises those individuals detected by some other method of the Cuban health program, which are called "random" methods[1]. The consideration of two different groups of detected infected individuals allows for evaluating the efficiency of the contact tracing program. This is particularly interesting since this program, on the one hand, has been considered to be one of the main reasons for the low prevalence of the disease in the country, and on the other hand, the program entails a great economic and human effort for the state.

[1]This is admittedly a misleading term, since no random search is involved: fortuitous detection of infections are included, but also reports of family doctors, analysis performed on pregnant women, etc.

TABLE 1. Values and meaning of the parameters in the model.

Parameter	Meaning	Value
λ	Rate of new infections due to undetected infected individuals (contact between x and susceptibles)	0.5750
λ'	Rate of new infections due to detected infected individuals (contact between y and susceptibles)	0.0403
μ	General mortality rate (x and y decrease)	0.0110
μ'	AIDS mortality rate (z decreases)	0.7740
β	Rate of transition of undetected HIV-infected population to AIDS (x progresses to z)	0.1300
β'	Rate of transition of detected HIV-infected population to AIDS (y progresses to z)	0.1660
k_2	Rate of detection related to the contact tracing program (x progresses to y_2)	0.1850
k_1	Rate of detection unrelated to the program (x progresses to y_1)	0.2190

The parameters that appear in the model of Equation (1) are summarized in Table 1, which gathers the meaning of each parameter, together with the values they are given in the experiments of this work. These values were obtained by similar statistical techniques to those used in [8] for a related model.

Next we consider the eventual transitions between populations that are represented in the model. The population of undetected seropositive individuals grows due to the infection of new individuals, due to contact with either undetected ($\lambda' y$) or detected (λx) infected ones; and it decreases because of the detection of individuals by means of the two considered methods ($k_1 x$ and $k_2 \dfrac{x y}{x+y}$), their transition to AIDS (βx) and the general population mortality (μx). The populations of known seropositive individuals (y_1 and y_2) grow due to the detection of new infections ($k_1 x$ and $k_2 \dfrac{x y}{x+y}$ respectively); and they decrease due to the transition to AIDS of seropositive patients ($\beta' y_1$ and $\beta' y_2$) and due to the general population mortality (μy_1 and μy_2). Finally, the population of individuals who have developed AIDS grows due to transition from both unknown (βx) and known ($\beta' y$) infected patients; and it decreases due to the mortality associated to AIDS sufferers ($\mu' Z$).

This paper does not put much emphasis on the model on its own, and the reader is referred to previous work [4] and references therein. However, it is worth commenting on the nonlinear term $k_2 \dfrac{x y}{x+y}$ that models the detection of infected individuals due to the contact tracing program. For the sake of comparison, consider the linear term $k_1 x$ in Equation (1), which represents random detection of infected individuals. The constant k_1 may be thought of as the inverse of the average time from infection to detection by random methods. Hence, k_1 is the average portion of the undetected population that becomes detected per time unit. In contrast, modelling the detection of the infection by active search has proved to be challenging, since linear models did not take into account the population y, which comprises the individuals who participated in the contact tracing program. Thus a nonlinear model was proposed [8], where the detection by contact tracing was defined by the term $k_2 y x$. Arguing by analogy to the linear rate k_1, the product $k_2 y$ might be

considered as a variable rate of detection, which would take into account the size of the detected infected population y. However, this assumption was too simplistic; for instance, consider the limiting case where $y \gg x$ that would represent the immediate detection of a substantial portion of the unknown infected population, which is obviously not the case. Consequently, different forms of this nonlinear term were analysed [16], proposing the term $k_2 \dfrac{y\,x}{x+y}$. In this case, the *proportionality rate* $k_2 \dfrac{y}{x+y}$ can be considered as a compromise between a constant rate k_2 and a variable rate $k_2\,y$ directly related to population y. This novel expression avoids that the detection rate may grow without bound: when the number of detected infected individuals is large, the rate amounts to the maximum attainable performance of the contact tracing program, represented by the value of k_2.

There is an increasing awareness that the size of the undetected infected population is a key aspect of AIDS modelling. Indeed, both the populations y and z that are included in the model of Equation (1) are recorded in statistical databases, whereas the population x is unknown. In the case of HIV infection, the influence of this hidden population on the epidemic is deepened by the long and variable incubation period of AIDS. Also, the size of this population must be somehow brought to light in order to validate epidemic models, so it is extremely important to have information on the infected population that does not know their situation. This information gives an idea of the efficiency of the detection policies and, consequently, of the control strategies which try to avoid the propagation of the disease. The fact that this undetected infection cannot be directly measured provides the motivation for this work. The main aim of this paper is to study indirectly the undetected VIH infected population in Cuba, by defining and analysing the ratio of the unknown infection to the population of seropositive individuals that have actually been recorded.

3. **The hidden infection ratio.**

The main objective of this work is to study the proportion of HIV individuals who are unknown to the health system. With this aim, the ratio of the hidden infection with respect to the detected population is defined, i.e. the quotient between the infected population that is not yet detected and the number of seropositive individuals that have been detected by the medical system. The study of this proportion allows to not use the undetected infected population in an explicit way, which is unknown by definition. It turns out that the obtained ratio is modelled by an ODE that can be explicitly expressed in terms of the ratio itself, with no reference to the original population. Then, this transformed model is studied on its own to analyse its stability and discuss its significance with respect to the epidemic evolution.

3.1. **Model definition.**

The ratio of hidden infection is defined as a quotient between undetected and detected HIV-infected populations. With the notation of the model given by Equation (1), the ratio of hidden infection r is given by:

$$r = \frac{x}{y} \tag{2}$$

Note that this definition is sensible because the populations are always strictly positive, as mentioned above. Since the populations change with time, so the ratio r does, hence we can regard the value of r as a dynamical system itself. Next we

are going to write the dynamical model of such ratio, basing upon the model of HIV/AIDS in Cuba, defined in Equation (1).

Firstly, the original model is reorganized by adding the two equations of the detected seropositive populations y_1 and y_2, which results:

$$\begin{aligned} \frac{d\,x}{d\,t} &= (\lambda - k_1 - \beta - \mu)\,x + \lambda'\,y - k_2\frac{x\,y}{x+y} \\ \frac{d\,y}{d\,t} &= -(\mu + \beta')\,y + k_1\,x + k_2\frac{x\,y}{x+y} \end{aligned} \tag{3}$$

where $y = y_1 + y_2$ has been substituted.

The model for the ratio r results from a straightforward application of the chain rule to the differentiation of Equation (2):

$$\frac{d\,r}{d\,t} = \frac{\partial\,r}{\partial\,x}\frac{d\,x}{d\,t} + \frac{\partial\,r}{\partial\,y}\frac{d\,y}{d\,t} = \frac{1}{y}\frac{d\,x}{d\,t} - \frac{x}{y^2}\frac{d\,y}{d\,t} = \frac{1}{y}\frac{d\,x}{d\,t} - r\,\frac{1}{y}\frac{d\,y}{d\,t} \tag{4}$$

Substituting into this expression the population dynamics, given by Equation (3), yields:

$$\frac{d\,r}{d\,t} = (\lambda - k_1 - \beta - \mu)\,r + \lambda' - k_2\frac{x}{x+y} - r\left(-(\mu+\beta') + k_1\,r + k_2\frac{x}{x+y}\right) \tag{5}$$

which, by grouping terms, results:

$$\frac{d\,r}{d\,t} = -k_1\,r^2 + (\lambda - k_1 - \beta + \beta')\,r + \lambda' - (1+r)\,k_2\frac{x}{x+y} \tag{6}$$

Note that, since $y > 0 \;\Rightarrow\; r > 0 \;\Rightarrow\; r + 1 > 0$, the nonlinear term $\dfrac{x}{x+y}$ can be further simplified through division of the numerator and denominator by y, thus $\dfrac{x}{x+y} = \dfrac{r}{r+1}$, leading to the final model:

$$\frac{d\,r}{d\,t} = -k_1\,r^2 + (\lambda - k_1 - k_2 - \beta + \beta')\,r + \lambda' \tag{7}$$

In the sake of simplicity, the parameter a is defined as $a = \lambda - k_1 - k_2 - \beta + \beta'$, so the ODE $\dfrac{d\,r}{d\,t} = \mathrm{f}(r)$ can be written as:

$$\frac{d\,r}{d\,t} = -k_1\,r^2 + a\,r + \lambda' \triangleq \mathrm{f}(r) \tag{8}$$

In this way, an expression has been obtained to model the dynamics of the ratio of the hidden infection, defined by a single ODE which only depends on the ratio r itself.

It turns out that Equation (8) has en explicit solution, which will now be computed. Firstly the quadratic equation $\mathrm{f}(r) = 0$, i.e. $k_1 r^2 - ar - \lambda' = 0$ is solved. Observe that the discriminant $a^2 + 4\,k_1\,\lambda'$ is strictly positive, since the values of all the parameters are always greater than zero, as long as a realistic model is intended. Then, the quadratic equation has two distinct real roots:

$$\begin{aligned} r_+ &= \frac{a + \sqrt{a^2 + 4\,k_1\,\lambda'}}{2\,k_1} \\ r_- &= \frac{a - \sqrt{a^2 + 4\,k_1\,\lambda'}}{2\,k_1} \end{aligned} \tag{9}$$

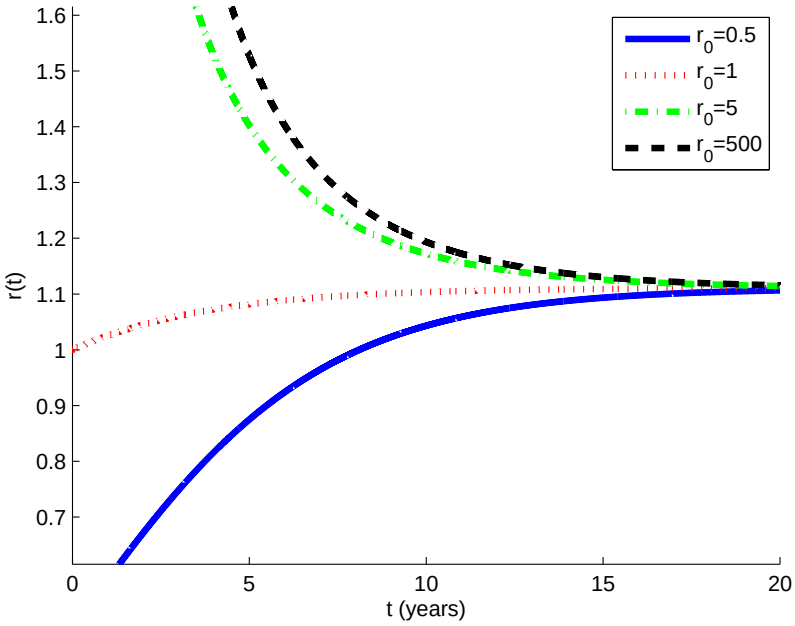

FIGURE 1. Dynamics of the ratio of the hidden infection.

The solution r_+ is positive and, since the square root of the discriminant is greater than a, the solution r_- is negative. Then, we can write $\mathrm{f}(r) = -k_1\,(r - r_+)\,(r - r_-)$ and Equation (8) is integrated to yield:

$$r(t) = \frac{r_+ - C\,r_-\,e^{-k_1(r_+ - r_-)\,t}}{1 - C\,e^{-k_1(r_+ - r_-)\,t}} \tag{10}$$

where $C > 0$ is the constant of integration. Given the initial value $r(0)$, the constant C can be computed and a particular trajectory is obtained.

Several instances of the curve family given by Equation (10), i.e. the solutions of the model (8), are presented in Figure 1. The parameters of the model are set to the values defined in Table 1, and different initial values of r are represented. Although a wide range of initial values has been considered, it is worth noting that a realistic initial value would be rather large, since at the early stage of the epidemic outbreak all infections are undetected, i.e. $x \gg y$. It is then an appealing feature that the qualitative behaviour of the trajectory of the ratio r remains similar even when the initial value is unboundedly increased, since this allows for discussing the epidemic behaviour despite errors in the initial value are assumed. The figure strongly suggests that the trajectory of $r(t)$ tends to a fixed point, which is the same regardless of the initial value $r(0)$. This behaviour, which is nonetheless obvious from the explicit solution in Equation (10), will be further discussed in the stability analysis of the system, performed in Section 3.2. Let us observe again that such convergence is more obvious for large, realistic values of the initial value and qualitatively robust to the increase of $r(0)$.

3.2. **Stability analysis.** In this section, we carry out the qualitative analysis of the model for the hidden infection ratio r, described by means of the ODE given by Equation (1). The usual steps of the analysis [15, 20] comprise three concepts:

1. Fixed points, i.e. equilibria, of the dynamical model, which are candidates to be attractors of the long-term trajectories of the system.
2. Asymptotic stability of the fixed points, by observing the sign of the jacobian of the model at such points.
3. Basin of attraction of the stable fixed point, in order to establish a global view of the dynamics of the trajectories.

Since the explicit solution of the ODE that defines the model is available, the long-term analysis of the trajectories is straightforward by considering $t \to \infty$ in Equation (10), which yields:

$$\lim_{t\to\infty} r(t) = r_+ \tag{11}$$

regardless of the initial value. Further, r_+ is a root of the right-hand side of the model defined by Equation (8), so it is a fixed point that fulfills $\mathrm{f}(r_+) = 0$. We conclude that the stable fixed point r_+ is globally asymptotically stable, if we restrict the phase space to the positive half-line $r > 0$, so the other fixed point r_- is dismissed. Since $r > 0$ holds for any initial point r, the value of the ratio r always converges to r_+ for physically meaningful values. This fact reconfirms the suggestion of Figure 1, which showed that the trajectories of the system approach the equilibrium r_+ regardless the chosen (positive) initial value. This theoretical results will be put in the light of real epidemiological data in the discussion in Section 5.2.

Since an explicit solution is available, there is no need to perform a conventional stability analysis. However we briefly recall the main steps of such analysis. The motivation for this apparent redundancy is twofold. On one hand, we suggest that qualitative analysis of stability often yields a more elegant and appealing way to grasp the interesting features of the trajectories of a dynamical system than the computation of the explicit solution, even if the latter is possible. On the other hand, even a slight modification of the model would lead to an unsolvable ODE, whereas the qualitative analysis would still be valid. This latter comment is particularly relevant, since the form of the nonlinear term $\dfrac{x\,y}{x+y}$ is subject to discussion. Some suggestions for model refinement will be pursued in Section 6. The stability of the model is analysed by evaluating the system Jacobian at the considered fixed point r_+:

$$\mathrm{f}'(r_+) = -2\,k_1 \left(\frac{-a - \sqrt{a^2 + 4\,k_1\,\lambda'}}{-2\,k_1} \right) + a = -\sqrt{a^2 + 4\,k_1\,\lambda'} < 0 \tag{12}$$

This expression is always negative, which proves that the fixed point r_+ is asymptotically stable.

The set of initial values that lead to trajectories that approach a stable fixed point, i.e. the *basin of attraction*, can be computed by means of Lyapunov's direct method [26]. With this aim, a Lyapunov function $V(r(t))$ is defined:

$$V(r) = -\int \left(-k_1 r^2 + a r + \lambda'\right)\, dr = \frac{k_1}{3} r^3 - \frac{a}{2} r^2 - \lambda'\, r + D \tag{13}$$

where the constant of integration D is chosen to meet the requirement $V(r_+) = 0$. It is straightforward to prove that all conditions for V being a Lyapunov function

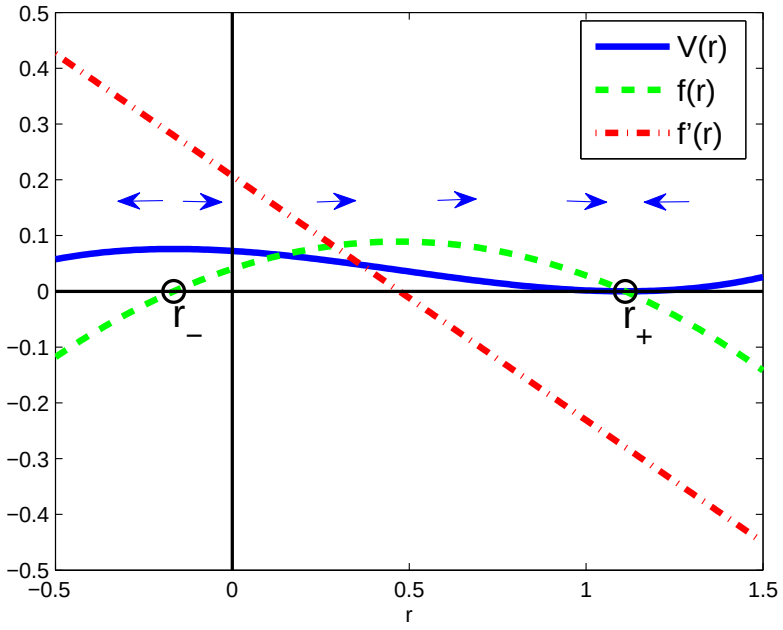

FIGURE 2. The Lyapunov function $V(r)$. System trajectories are represented by arrows that follow a downhill direction on the graph of V, towards the stable fixed point r_+. Note that the Jacobian $\mathrm{f}'(r)$ is positive at the unstable fixed point r_- and negative at the stable one r_+. The basin of attraction of r_+ includes all positive values $r > 0$.

are met in the interval (r_-, ∞): $V(r)$ is positive (at least) for every $r \geq r_-$, $r \neq r_+$, and $\dfrac{dV}{dt} < 0$ for every $r(t) \neq r_-, r_+$. In particular, since $r_- < 0$, the function V is a Lyapunov function for every r in the set of feasible states, which, as mentioned above, is restricted to the positive values. This fact proves again the *global* asymptotic stability of the fixed point r_+. Using the values of the parameters defined in Table 1, the form of the Lyapunov function is sketched in Figure 2, where the trajectory of the system variable r can be thought of as a downhill descent on the graph of $V(r)$.

4. **Sensitivity analysis of the system.** In order to gain further insight into the behaviour of the dynamical model of the ratio of hidden infection, in this section we analyse the relative influence of the parameters on the state variable r, i.e. the sensitivity analysis [14, 10] is performed. For each parameter $\theta \in \{\lambda, \lambda', \beta, \beta', k_1, k_2\}$ appearing in the dynamical model given by Equation (8), the sensitivity ψ_θ of the state variable r with respect to the parameter θ is defined as:

$$\psi_\theta = \frac{\partial r}{\partial \theta} \tag{14}$$

In the sensitivity analysis, since the interest is focused on the partial derivatives, each parameter can be dealt with individually, keeping the rest of the parameters

constant. Under sufficient smoothness conditions, the sensitivity can be computed by means of an ODE:

$$\frac{d\,\psi_\theta}{d\,t} = \frac{d}{d\,t}\frac{\partial\,r}{\partial\,\theta} = \frac{\partial}{\partial\,\theta}\frac{d\,r}{\partial\,t} = \frac{\partial\,\mathrm{f}}{\partial\,r}\frac{\partial\,r}{\partial\,\theta} + \frac{\partial\,\mathrm{f}}{\partial\,\theta} = \frac{\partial\,\mathrm{f}}{\partial\,r}\psi_\theta + \frac{\partial\,\mathrm{f}}{\partial\,\theta} \tag{15}$$

where f is the function that defines the dynamical model of the variable r

Consider the system of the ratio of the hidden infection, given by Equation (8). We recall that the Jacobian was computed in Equation (12):

$$\frac{\partial\,\mathrm{f}}{\partial\,r} = -2\,k_1\,r + a \tag{16}$$

and the partial derivatives with respect to the parameters are:

$$\begin{aligned} \frac{\partial\,\mathrm{f}}{\partial\,\lambda} = \frac{\partial\,\mathrm{f}}{\partial\,\beta'} &= r \\ \frac{\partial\,\mathrm{f}}{\partial\,\lambda'} &= 1 \\ \frac{\partial\,\mathrm{f}}{\partial\,\beta} = \frac{\partial\,\mathrm{f}}{\partial\,k_2} &= -r \\ \frac{\partial\,\mathrm{f}}{\partial\,k_1} &= -r\,(r+1) \end{aligned} \tag{17}$$

Then, for each parameter θ, the sensitivity ψ_θ results from substituting these values in Equation (15), yielding the following system of two coupled ODEs:

$$\begin{aligned} \frac{d\,r}{d\,t} &= -k_1\,r^2 + a\,r + \lambda' \\ \frac{d\,\psi_\theta}{d\,t} &= (-2\,k_1\,r + a)\;\psi_\theta + \frac{\partial\,\mathrm{f}}{\partial\,\theta} \end{aligned} \qquad \theta \in \{\lambda, \lambda', \beta, \beta', k_1, k_2\} \tag{18}$$

Interestingly, the first equation is uncoupled to the second, whereas the sensitivity does depend on the system states. Thus, there is no need to repeat the numerical solution of the equation of the variable r for each parameter sensitivity: the trajectories that were obtained in Section 3 can be substituted in the sensitivity ODE, and only this latter, linear equation must be integrated.

Before attempting the numerical solution of the sensitivity ODEs given by Equation (18), let us perform a brief qualitative analysis of this dynamical system. Note firstly that for each fixed point of the original model, a corresponding fixed point of the coupled system exists. Further, the Jacobian of the system of ODEs is:

$$\mathbf{J} = \begin{pmatrix} \mathrm{f}'(r) & 0 \\ D & \mathrm{f}'(r) \end{pmatrix} \tag{19}$$

where D is the derivative of the second equation with respect to the state r. Then, the Jacobian has a single eigenvalue with multiplicity two, which turns out to be the Jacobian of the original model. Therefore, each fixed point of the sensitivity system inherits the stability of the corresponding fixed point of the main dynamical model. In the particular system under study, consider the stable fixed point r_+ given by Equation (9). Then, the sensitivity ψ_θ with respect to each parameter θ will converge to a stable equilibrium given by equating to zero the right-hand side

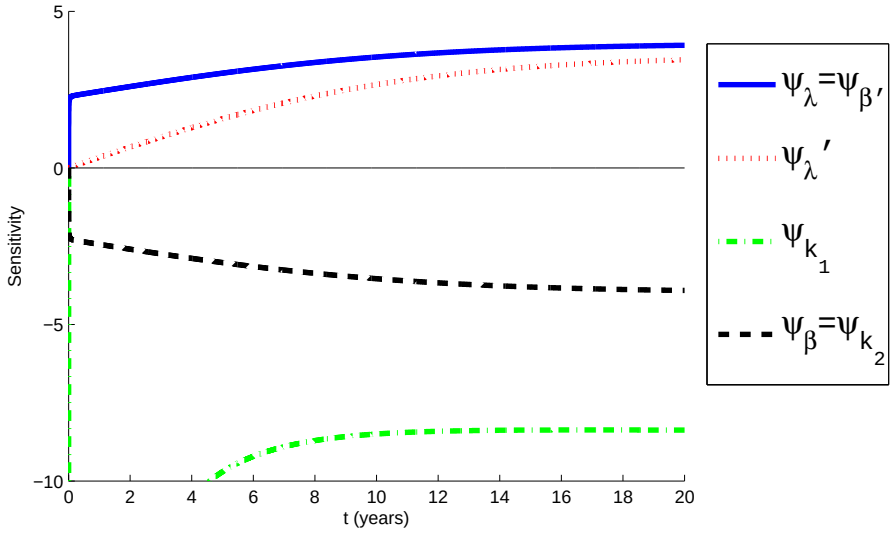

FIGURE 3. Sensitivity equations of the model of hidden infection ratio with respect to the parameters.

of Equation (15), i.e.:

$$\lim_{t\to\infty} \psi_\theta = -\left.\frac{\frac{\partial\, \mathrm{f}}{\partial\, \theta}}{\frac{\partial\, \mathrm{f}}{\partial\, r}}\right|_{r=r_+} = -\frac{\left.\frac{\partial\, \mathrm{f}}{\partial\, \theta}\right|_{r=r_+}}{-\sqrt{a^2+4\,k_1\,\lambda'}} \tag{20}$$

where the value of the Jacobian at the fixed point has been substituted according to Equation (12). A look at the partial derivatives computed in Equation (17) hints that, in the long term, the sensitivities to the parameters $\lambda, \beta, \beta', k_2$ will be all equal in absolute value, whereas the (absolute) sensitivity to the parameter k_1 will be relatively larger. We will further pursue this issue in the discussion in Section 5.2.

As mentioned above, sensitivity equations can be dealt with individually for each parameter, hence the process of obtaining a numerical solution of the sensitivity equations proceeds in three stages:

- Integrate the system equation to obtain the state trajectory r.
- Evaluate at each time instant the Jacobian and partial derivatives with respect to the parameters of the right-hand side f of the model equation.
- Numerically solve each uncoupled equation of the sensitivities.

This numerical procedure has been implemented using the values of the parameters in Table 1, and the results are shown in Figure 3. The initial value for the state variable r has been set as $r(0) = 500$, but results are quite similar for a wide range of initial values. As expected by the qualitative analysis, the trajectories of the sensitivities converge to a fixed point, which is roughly twice as large for parameter k_1, in absolute value. A large (negative) peak occurs in the transient regime of the sensitivity with respect to k_1, before convergence to the fixed point is apparent. Values up to $|\psi_{k_1}| > 600$ are reached for $t < 0.04$ (15 days), which have been left out of the range of the figure to avoid blurring the other graphs. We interpret this

phenomenon by realizing that, at early stages of the epidemic outbreak, the value of the ratio $r = \dfrac{x}{y}$ is large (theoretically infinite) because the detected infected population y is close to zero. Then, even a small number of randomly detected infected individuals is prone to force a large decrease in the value of the ratio r. However, the effect of the contact tracing program, measured by k_2, is negligible because a critical volume of detected infection y has not yet been unveiled in order to significatively affect the detection (i.e. the transition $x \to y$) through the term $k_2 \dfrac{x\,y}{x+y}$.

5. **Model fitting to statistical data of HIV-infected population.** In this section we aim to validate the proposed model for the ratio of hidden infection by comparison to the real data, which is available for the Cuban HIV epidemics. Firstly, a fit of the model to data is studied. However, since the undetected infected population is unknown, the model is indirectly assessed by fitting the detected infection to recorded data. Then, the results of the paper are discussed, focusing on the real-world interpretation. The objective is to put the theoretical results in a realistic context, in order to gain further insight on the evolution of the epidemic and provide some hints on the most suitable health policies.

5.1. **The dynamics of detected infection.** In this section, the proposed model for the ratio of hidden infection is put in the light of actual epidemiological data. The aim is to provide an assessment both of the model itself and the values of the parameters, in line with the methods of system identification [21, 25]. In particular, the parameters k_1, k_2 related to detection of infected individuals are especially interesting, since their value provides an indirect measure of the efficiency of health policies. In previous work, a novel method for parameter estimation for dynamical systems has been applied to similar epidemiological models [3, 12]. However, no estimation method can be directly applied to the proposed model given by Equation (8): on the one hand, the states r are not measurable, since data for the undetected infected population x are not available; on the other hand, a single equation would not provide enough information to estimate all the parameters in Table 1, e.g. because the effect of λ and k_2 are mixed into a. Both pitfalls can be traced to the concepts of observability [18] and identifiability [19] in control theory, respectively.

Since a direct identification of the system of hidden infection is not feasible, we adopt an indirect approach based upon the available data, which is the recorded infected population, given by variable y in the model of Equation (3). In this equation, let us substitute the unknown infected population as $x = r\,y$, according to the definition of the hidden ratio given by Equation (2). The substitution yields a linear ODE for y:

$$\frac{d\,y}{d\,t} = \left(-(\mu+\beta') + k_1\,r + k_2\frac{r}{r+1}\right) y \tag{21}$$

Of course this latter equation is not directly solvable because r has its own nonlinear dynamics. However, as mentioned in Section 3.2, where the dynamics and stability of $r(t)$ were analysed, the trajectories of the ratio tends in all its domain to the fixed point r_+. Thus assume that the convergence has already approximately been reached, so the value of the hidden infection ratio r can be considered to be constant for practical purposes. This simplification will be valid as long as we consider a time

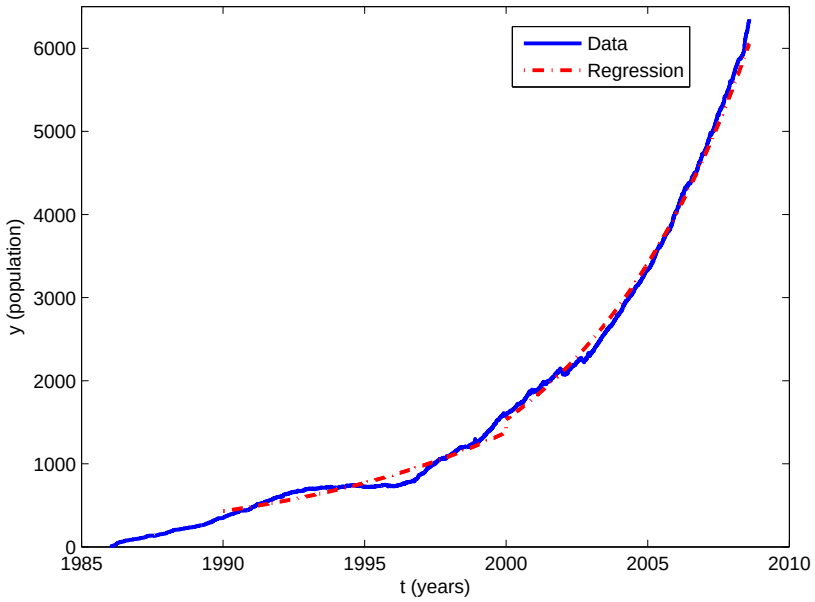

FIGURE 4. Exponential regression of population y for both periods $[1990, 2000]$ and $[2000, 2008]$.

window where the system has approximately reached a stationary regime. Then, the solution of Equation (21) is trivially given by:

$$y = y_0\, e^{b\,(t-t_0)} \tag{22}$$

where $b = -(\mu+\beta')+k_1\, r_+ + k_2 \dfrac{r_+}{r_+ + 1}$. Inspired by this equation, we conjecture that the size of the population y grows exponentially, and we will perform an exponential regression in order to estimate the values of y_0 and b.

The data that will be used to adjust the exponential model of Equation (22) contains information about all the HIV infections that have been recorded in Cuba[2] since the start of the epidemic outbreak, in 1986, up to 2008. Therefore, a daily series of the size of population y can be constructed, and used to perform an exponential fit of y with respect to t. Some preprocessing has been applied to data, in order to obtain meaningful results. Firstly, the first four years of epidemic data have been removed, so the hidden infection ratio can be assumed to have achieved an equilibrium. Besides, both the definition of the disease and the circumstances of infection detection are regarded to have considerably changed after 2000. This was observable in preliminary experiments, where it was impossible to satisfactorily fit both the initial point y_0 and the slope b of the curve. Consequently, two distinct periods have been considered—$[1990, 2000]$ and $[2000, 2008]$—and the coefficients y_0, b of the exponential model have been separately adjusted to data from each period.

The results of the exponential regression are graphically shown in Figure 4. For the first period $[1990, 2000]$, the obtained values of the estimates of the coefficients

[2]Needless to say, only anonymous data have been used in this paper.

TABLE 2. Error measures for both periods of the exponential regression to data of recorded HIV-infected population y: Mean Absolute Error (MAE), Mean Relative Error (MRE) and coefficient of determination (R^2).

Measure	Period 1	Period 2	Complete data base
t_0	1990	2000	
y_0	346	1598	
$\hat{y_0}$	430	1533	
b	0.1636	0.1636	0.1636
$\hat{b}$	0.1165	0.1600	
MAE	65.9584	81.3807	73.0843
MRE	0.0846	0.0278	0.0584
R^2	0.9234	0.9954	0.9969

are $\hat{y_0} = 423$, $\hat{b} = 0.1169$, whereas the regression for the second period $[2000, 2008]$ leads to the estimates $\hat{y_0} = 1514$, $\hat{b} = 0.1597$. Both the results for $\hat{y_0}$ and $\hat{b}$ seem to be coherent with actual data: on the one hand, $y(1990) = 344$ and $y(2000) = 1577$, so the obtained $\hat{y_0}$ are a good approximation, especially at the beginning of the second period in 2000, when any transient effects should have vanished and the hidden infection ratio is assumed to have practically converged to the equilibrium; on the other hand, if the fixed point r_+ is substituted according to Equation (9) in the expression $b = -(\mu + \beta') + k_1\, r_+ + k_2 \dfrac{r_+}{r_+ + 1}$ and the numerical values of the parameters are set to those assumed in Table 1, we obtain $b = 0.1636$, which also shows a striking approximation to the estimates $\hat{b}$ obtained for the first and second periods. We emphasize that the estimates $\hat{y_0}, \hat{b}$ have been obtained by regression from actual data, with neither resort to the model nor to the values of the parameters. Certainly, the rationale at the beginning of this section has inspired the choice of exponential, rather than linear, regression; but the obtained coincidence, with a completely independent procedure, provides an appealing support to both the model and the claim that the hidden infection ratio tends to an equilibrium.

In order to provide a quantitative assessment of the results of the exponential adjustment to the data of HIV epidemics, we have computed some goodness-of-fit measures, such as the Mean Absolute Error (MAE) and the Mean Relative Error (MRE):

$$\begin{aligned} MAE &= \frac{1}{N} \sum_{i=1}^{N} |y(i) - \hat{y}(i)| \\ MRE &= \frac{1}{N} \sum_{i=1}^{N} \left| \frac{y(i) - \hat{y}(i)}{y(i)} \right| \end{aligned} \tag{23}$$

where N is the dimension of the data vector y and the prediction $\hat{y}$ is computed from the estimates as $\hat{y} = \hat{y_0}\, e^{\hat{b}\,(t - t_0)}$. The computed errors are shown for each period and for the whole adjusted time range in Table 2. Although the absolute errors may seem considerable at first sight, observe that the relative errors are limited. In particular, the measure for the second period states that the error is below 3 %, which amounts to a satisfactory fit. Finally, the coefficient of determination R^2 has been computed and the results, shown in the last line of Table 2, produce a

value well above the 0.85 threshold, which is often considered the minimum for a satisfactory fit. The contrast between the different goodness of fit of both periods will be further discussed in the next section.

5.2. **Discussion.** In this section we aim to qualitatively assess the model of the hidden infection by comparison to epidemiological results. Admittedly one cannot expect an exact assessment of a biological process in the quantitative sense that a physical model can be validated. Indeed, we conjecture that some discrepancies suggest conclusions that "are not already obvious to the biologists" [22], thus contributing to shed light to, and enhance the prediction of, the epidemic evolution.

First of all, we can consider whether it is epidemiologically sensible the convergence of the hidden infection ratio towards a fixed value. Indeed, this fact has already been pointed out by combining epidemiological arguments and a linear model [9]. A related work [17] provided further support by linearizing a nonlinear model, which was quite similar to the one defined in Equation (1). With regard to the value of the hidden infection ratio r, the former of these works propose that more than 75 % of the HIV-infected persons are known, which would lead to a value $r = \frac{1}{3}$; whereas the latter obtains the value 0.29 for the ratio of underreporting, which has a similar meaning to the hidden infection ratio defined here. By substituting the numerical values of the parameters from Table 1 in the fixed point r_+ given by Equation (9), a ratio of hidden infection of $r^* = 1.11$ is obtained, that is to say that the size of the HIV-infected population that has not been detected by the Cuban health system is slightly greater than the detected one. Thus we obtain a hidden infection significantly larger than those reported so far. Certainly the methodologies cannot be exactly comparable because previous studies, among other disparities, resort to linear systems. Observe that the nonlinear term $k_2 \frac{x\,y}{x+y}$ that governs the detection due to the contact tracing program can be considered as a linear term multiplied by a sort of *variable rate* $\frac{y}{x+y}$ which is less than one. Therefore, a linear model is prone to overestimate the detection, leading to an increased ratio r that, in turn, further decreases the rate $\frac{y}{x+y} = \frac{1}{r+1}$, entering a self-limiting loop. Indeed, it is noteworthy that a significantly larger hidden infection ratio has been computed for a country with low detection rates [17]. The mathematical reason for the large value for r that provides the nonlinear model is thus clear. The question remains as to which is the *correct* value. Certainly this cannot be definitely answered, but the good fit to data that we have obtained in Section 5 suggests that the hidden infection could be larger than claimed, whereas large figures of detection should be taken rather cautiously.

Another source of information that could guide health policy decisions stem from the sensitivity analysis in Section 4. Let us concentrate on the effect of the parameters k_1, k_2 related to the detection of infected individuals. As mentioned above, sensitivities approach in the long term a fixed value. It was also explained that, in absolute values, the effect of the random detection k_1 decreases, whereas the contact tracing performance measured by k_2 grows as the number of detected individuals swell the ranks of participants in the program. Obviously, the sign of both sensitivities with respect to the detection rates is negative, because detection contributes to decrease the hidden infection. The crux of the matter is the relative strength of the effect of both parameters. The obtained results show that the system is more

sensitive to k_1 by a factor of $r+1$, that is to say that an increase in the value of k_1 leads to a decrease of the ratio r that approximately doubles the one resulting from a similar increase of k_2. Extrapolating this result to the epidemiological analysis of the HIV/AIDS epidemic, it can be concluded that increasing the detection of infected individuals by the so called random methods influences almost twice as much as by the contact tracing method. In order to obtain a valid policy rule, certainly the cost of each method should be taken into consideration, yet a cost analysis is out of the scope of this paper. Instead, the morale is that a significant investment in the contact tracing program, with the hope that the detection is drastically enhanced, may have a cost that is beyond the available resources, whereas methods directed to the general population are worth being considered. Certain awareness of this hint could be deduced from the growing support to the action of family doctors.

Although results are far from definitive, the goodness of the fit computed in Section 5 considerably endorses the proposed model. However, it is intriguing the different quality of the regression obtained in both time periods, which is apparent e.g. from the coefficients of determination shown in Table 2. One could argue that the adjustment is poor at the first period because the ratio r has not yet reached the equilibrium, but the fact is that the regression error is not concentrated at the beginning of the period. We point at three—possibly simultaneous—effects that could eventually explain the different behaviour:

- Due to harsh socioeconomic conditions during the nineties, HIV infections were often incorrectly recorded, that is to say that the data series for y is *noisy*.
- Parameters are assumed to be constant, but this is certainly a rough approximation. In particular,the parameters k_1, k_2 related to detection are heavily dependant on the resources that are allotted to health policies, which in turn depend on varying socioeconomic conditions, so the parameters should be regarded as *time-varying*.
- Although throughout this paper the HIV *model* given by Equation (1) has been taken for granted, as provided by renowned experts, it is indeed subject to discussion.

The first two items suggest using a method for parameter estimation that is both robust with respect to noise and able to deal with time-varying parameters. Although preliminary steps have been taken in this direction [5], there is considerable margin for improvement. The third point encourages in the search of refined models of HIV epidemics. Note that an ODE that models the hidden infection ratio can be obtained from any original HIV system, as long as the nonlinear term of detection due to contact tracing is expressed by an arbitrary function $g\left(\dfrac{x}{y}\right)$.

6. **Conclusions.** In this work the ratio of hidden infection has been defined as the proportion between the sizes of known and unknown HIV-infected populations. We aim at formalizing a notion that has been, more or less implicitly, assumed by epidemiologists, that is to say, the fundamental role of detection of infected individuals as a measure for epidemic control of HIV/AIDS. From the mathematical point of view, the contribution lies in the observation that the dynamics of the ratio can be derived from the original HIV model, leading to an uncoupled ordinary differential equation, which is then analysed within the framework of dynamical systems theory. The fixed points of the system are computed and the stability analysis reveals that

the positive equilibrium is globally asymptotically stable, if we restrict the phase space to the—physically meaningful—positive values. In other words, every trajectory of the system, regardless the initial point, approaches the fixed point. The particular value of the equilibrium depends on the values of the parameters, but it is noteworthy that the qualitative analysis is rather robust in this regard, since both the existence and the stability of the fixed point are proved for all—positive—parameter values. It is an appealing result that the theoretical analysis provides an independent support to the intuition of the epidemiology experts, who state that the proportion of undetected infected individuals with respect to the detected infected ones remains approximately constant for a given set of fixed parameters.

The sensitivity analysis of the model with respect to the parameters has also been carried out, confirming that both parameters k_1, k_2 related to detection of infected individuals have a negative effect on the hidden infection ratio. Far more interesting is the fact that the ratio is more sensitive to the random method detection parameterized by k_1 than to the contact tracing programmed measured by k_2. This somewhat unexpected find, and the usefulness that it could have for fixing health policies, have already been discussed in Section 5.2.

Owing to the records of HIV/AIDS epidemics in Cuba, an exponential regression has been performed on real data from the known HIV-infected population. The goodness-of-fit measures strongly support the exponential form for the infected population y. It turns out that, if the model for the hidden infection ratio is taken for granted and the equilibrium is assumed to have been reached, the dynamics of y can be rewritten as a linear ODE, thus the exponential dependance of y with respect to time. Also, the corresponding parameters approximately match those obtained from the regression. The significant fit of the exponential form obtained by two independent procedures provides an additional endorsement to the proposed model.

The presented work can be further expanded in several, complementary directions. It has already been mentioned in Section 5.2 the need for both robust methods for parameter estimation and refinement of the model of HIV/AIDS epidemics. With regard to estimation, we are currently engaged in the development of parametric identification techniques, studying their theoretical features and implementing their application to real-world problems. It is noteworthy that advances in parameter estimation can be put into connection with the analysis of the hidden infection ratio. For instance, one of the aims of parameter estimation is to obtain an estimate of the basic reproduction number R_0 [11], since the condition $R_0 < 1$ determines that the epidemic will eventually vanish. Then, in view of the results of the exponential regression presented above for the infected population, we conjecture that an adequate definition of the basic reproduction number could be $R_0 = (1 + r_+)\, e^b$, since it corresponds to the first-year growth of the infected population if an exponential form is assumed. As a general suggestion, we claim that the development of estimation methods for dynamical systems that deal with time-varying parameters should go hand in hand with model definition.

Another promising direction of ongoing research is the refinement of the model of HIV/AIDS epidemics. In particular, in connection with epidemiology experts, we aim at providing a more accurate representation of the detection due to the contact tracing program, i.e. the nonlinear term whose coefficient is k_2 in Equation (1). We suggest that the sort of *variable rate* of detection given by fraction $\dfrac{y}{x\,y} = \dfrac{1}{r+1}$

could be replaced by an arbitrary function $g(r)$, keeping the sensible conditions $g(r) > 0$, $g(0) = 1$, $g'(r) < 0$. Although an explicit solution of the ODE could not be computed, the qualitative stability analysis of Section 3 would still be valid under such perturbation. Then, reproducing the sensitivity analysis of Section 4 a model could eventually be agreed upon, such that the relative influence of both detection methods is coherent with experts' appraisal. The model could also be expanded to make space for further subdivisions of the populations, e.g. considering an y_3 population that comprises those infected individuals whose infection has been detected by family doctors, which is a method that is considered to be substantially increasing its efficiency in the last years. The model should also take into account the shifting epidemiologic and socioeconomic circumstances, such as the changes in the definition of AIDS [1] and the decrease in the mortality due to the disease, after the appearance of successful antiretroviral drugs. Certainly the adjustment of the model in a variable setting should be related to the usage of estimation methods that deal with time-varying parameters. Finally, regarding the adjustment of the model to real data, the population z of AIDS sufferers will also be fitted by exponential regression, which in turn will be compared to appropriate estimates of the corresponding parameters. The need for a robust, accurate estimation method for time-varying parameters of dynamical systems is pervasive.

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