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A SINGULARLY PERTURBED SIS MODEL WITH AGE STRUCTURE

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Abstract. We present a preliminary study of an SIS model with a basic age structure and we focus on a disease with quick turnover, such as influenza or common cold. In such a case the difference between the characteristic demographic and epidemiological times naturally introduces two time scales in the model which makes it singularly perturbed. Using the Tikhonov theorem we prove that for certain classes of initial conditions the nonlinear structured SIS model can be approximated with very good accuracy by lower dimensional linear models.

1. **Introduction.**

The evolution of most real systems is a result of an interplay of many driving forces, often of widely different magnitude and duration. Such multiple scale systems, depending on needs and resources, can be modelled at various levels of resolution by focusing on the effects specific to a particular scale. Typically we distinguish three basic scales: *individual* or *microscopic*, *mesoscopic* and *macroscopic*, see e.g. [1, 4, 13, 14]. We note that this division is not cast in stone and may vary from application to application. For instance, in gas dynamics, the microscopic scale refers to the description of the matter as an ensemble of individual particles interacting within the framework of the Newtonian dynamics, at the mesoscopic level we look at the gas by means of the one-particle distribution function which averages over the energies of particles and is subject to the Boltzmann equation

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and, finally, at the macroscopic level we treat the gas as a continuum and describe it using the Navier-Stokes or the Euler equations. On the other hand, in the population dynamics the microscopic scale provides the description of the population through mechanisms occurring at an individuals' time scale, the mesoscopic scale refers to the evolution of the population as a whole, at the generation's time scale, and the macroscopic level could mean the time scale of the species or the geological time scale. However, there could be many intermediate phenomena which could be included in one or the other level.

It is clear that the microscopic description provides the most detailed information but at a considerable, if not insurmountable, computational cost. Also, in many cases such a detailed information is redundant. On the other hand, the macroscopic description typically involves measurable quantities, so that the analysis and computations immediately can be verified by experiment, and it is computationally less involved. However, for some applications, it may be too crude.

In any case, when we decide to model a multiscale system at a particular level, apart from the most detailed, microscopic, one (if such does exist), we are faced with the question of how to collect the variables from the lower levels to create an aggregated system which, on the one hand, is robust and easy to handle and, on the other, preserves all relevant features of the original one. In particular, with multiple time scales in the problem, intuitively it is expected that, in a long run, the evolution will be determined by the slowest processes and only slightly influenced by the fast ones.

In most cases questions of this type lead to the so-called singularly perturbed problems. If the models are described by systems of ordinary differential equations, these can be handled by techniques based on the Tikhonov theorem, described below, or offered by the geometric singular perturbation theory, see e.g. [8, 9, 11].

Problems of this type occur in numerous biological applications. In particular, they allowed to validate many phenomenological models such as Michaelis-Menten theory of the enzyme kinetics, see [2, 6, 9, 16, 20], or the Allee models, [2, 23]. However, so far it seems not to have been realized that multiscale phenomena may naturally occur in epidemiological problems and that a systematic application of the singular perturbation theory can result in a significant simplification of the original models. This paper is intended to present a preliminary study of such an application using a simple compartmental age-structured SIS model as an example. As we shall see, here a nonlinear model can be replaced, with a very good accuracy, by a linear one. On the other hand, a more detailed study reveals that even such a relatively simple model offers a number of mathematical challenges.

Before we move to the description and analysis of this particular model, let us give a brief description of how multiple time scales naturally occur in epidemiological applications. If we describe, say, a human population, then the basic demographic, or vital, parameters are the birth rate β and the death rate μ. A natural unit of time in a human population is 1 year and, if we assume the average lifespan to be, say, 70 years, then $\mu = 1/70 \approx 0.014$ per person per year. For the birth rate we can use a typical value $\beta = 0.02$, also per person per year, see e.g. [5]. In any case, we see that the demographic parameters are $O(10^{-2})$. Now, let us introduce a common disease, such as flu or common cold, into this population. Basic modelling is done by SIS or SIR model with key parameters being the, per capita, recovery rate γ and the transmission rate λ. The recovery rate is the inverse of the average duration of the disease which, in the above mentioned cases, is $5-10$ days, so $\gamma \in (0.1, 0.2)$ per person per day. For the transmission rate λ we can use the data reported for the flu outbreak in a dormitory, reported in [16] to be $\lambda = 0.00213$, or $\lambda \in (0.0259, 0.0296)$ for the common cold in Chinese dormitories, [22]. If we use both demographic and epidemiological mechanisms in the model, then we have to use the same units of time and, if we are interested in the population level dynamics, we use 1 year as the time unit. This means that all disease related rates must be multiplied by 365. Thus, the order of the ratio of the typical demographic parameter in the equation to the typical epidemiological parameter ranges between $O(10^{-2})$ and $O(10^{-3})$ which makes it reasonable to consider this ratio as a small parameter and use an appropriate singular perturbation method to provide a simplified aggregated model.

We must emphasize, however, that these considerations are highly model specific. There are diseases, such as HIV/AIDS, whose duration is several years and which thus act at the same time scale as the demographic processes. Also, there are diseases in which the transmission rate is small in comparison with the recovery rate. For instance, for the measles outbreak in New York in 1962, λ is estimated to be of the order of 10^{-6} per person per day (the basic reproduction number $R_0 = N\lambda/\gamma \approx 18, \gamma \approx 5$ days, the population $N \approx 8 \times 10^6$, see [7, p. 9]) and thus, in principle, could be included into the 'small' terms.

The paper is organized as follows. In Section 2 we shall briefly discuss the main analytical tool, that is, the Tikhonov theorem, employed in this paper. A more detailed explanation of its background is referred to the appendix. In Section 3 we introduce the model and present its basic features. As our main aim is to discuss certain untypical features of the application of the Tikhonov theorem, we have chosen a simplified SIS model with basic age structure so as to avoid additional technical difficulties. Similar analysis of a more realistic case can be found in [21]. Section 4 is devoted to the proofs of applicability of the Tikhonov theorem, in Section 5 we discuss the long time dynamics of the model and in the final Sections 6 and 7 we present a numerical illustration, summarize the main results and discuss some open problems.

2. Tikhonov theorem.

We are concerned with the models in which the existence of two characteristic time scales leads to singularly perturbed systems of the form

$$\begin{aligned} \mathbf{x}' &= \mathbf{f}(t,\mathbf{x},\mathbf{y},\epsilon)\,, \qquad \mathbf{x}(0) = \overset{\circ}{\mathbf{x}}\,, \\ \varepsilon\mathbf{y}' &= \mathbf{g}(t,\mathbf{x},\mathbf{y},\epsilon)\,, \qquad \mathbf{y}(0) = \overset{\circ}{\mathbf{y}}\,, \end{aligned} \tag{1}$$

where $'$ denotes differentiation with respect to t and $\mathbf{f}$ and $\mathbf{g}$ are sufficiently regular functions from open subsets of $\mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}_+$ to, respectively, $\mathbb{R}^n$ and $\mathbb{R}^m$, for some $n, m \in \mathbb{N}$. The Tikhonov theorem, originally formulated for (1) with ϵ independent right hand side, see e.g. [24, 28], but easily seen, [2], to be valid for the general case, gives conditions ensuring that the solutions $(\mathbf{x}_\epsilon(t), \mathbf{y}_\epsilon(t))$ of (1) converge to $(\bar{\mathbf{x}}(t), \bar{\mathbf{y}}(t,\bar{\mathbf{x}}))$, where $\bar{\mathbf{y}}(t,\mathbf{x})$ is the solution to the equation

$$0 = \mathbf{g}(t,\mathbf{x},\mathbf{y},0), \tag{2}$$

often called the quasi steady state, and $\bar{\mathbf{x}}(t)$ is the solution of the equation

$$\mathbf{x}' = \mathbf{f}(t,\mathbf{x},\bar{\mathbf{y}}(t,\mathbf{x}),0), \qquad \mathbf{x}(0) = \overset{\circ}{\mathbf{x}}, \tag{3}$$

obtained from the first equation of (1) by substituting the unknown $\mathbf{y}$ by the known quasi steady state $\bar{\mathbf{y}}$. The interest in such a reduction lies in the fact that (2), (3) form an algebraic-differential system and, since in many cases (2) can be explicitly solved, the complexity of the problem is greatly reduced at the cost, however, of only obtaining approximate solutions to (1). Nevertheless, for small ϵ the system (1) becomes very stiff and the solution to (2), (3) offers a much better approximation than that obtained directly from (1).

The validity of the Tikhonov theorem depends on a number of intertwined assumptions. Here we provide just a brief sketch of them, referring the reader to the appendix for a more detailed discussion of their meaning. The first main assumption is that the solutions to (2) are isolated in some set $[0,T]\times\bar{\mathcal{U}}$, where $T>0$ and $\bar{\mathcal{U}}$ is a compact subset of the $\mathbf{x}$-domain of (1) and that they have well defined basins of attractions. Crucial roles are played by the auxiliary equation

$$\frac{d\,\tilde{\mathbf{y}}}{d\,\tau} = g(t,\mathbf{x},\tilde{\mathbf{y}},0)\,, \tag{4}$$

obtained from the second equation in (1) by the change of variables $t\to\tau=t/\epsilon$ and setting $\epsilon=0$ in the resulting equation (here t and $\mathbf{x}$ play the role of parameters), and by the initial layer problem

$$\frac{d\hat{\mathbf{y}}}{d\tau} = \mathbf{g}(0,\overset{\circ}{\mathbf{x}},\hat{\mathbf{y}},0)\,, \qquad \hat{\mathbf{y}}(0)=\overset{\circ}{\mathbf{y}}, \tag{5}$$

obtained from (4) by setting $t=0$ and $\mathbf{x}=\overset{\circ}{\mathbf{x}}$, where $(\overset{\circ}{\mathbf{x}},\overset{\circ}{\mathbf{y}})$ are the initial conditions for (1). We note that for each fixed t and $\mathbf{x}$ the quasi steady state solution $\bar{\mathbf{y}}(t,\mathbf{x})$ of (2) is an equilibrium of (4). Then we require that $\bar{\mathbf{y}}(t,\mathbf{x})$ is an asymptotically stable equilibrium of (4) uniformly for $(t,\mathbf{x})\in[0,T]\times\bar{\mathcal{U}}$. Further, we assume that $\bar{\mathbf{x}}(t)\in\mathcal{U}$ for $t\in[0,T]$ provided $\overset{\circ}{\mathbf{x}}\in\bar{\mathcal{U}}$ and that $\overset{\circ}{\mathbf{y}}$ belongs to the basin of attraction of the stationary point $\bar{\mathbf{y}}(0,\overset{\circ}{\mathbf{x}})$ of (5). Then the following theorem is true.

Theorem 2.1. *Let the above assumptions (see also Assumptions 1 – 5 in the appendix for details) be satisfied. Then there exists $\varepsilon_0>0$ such that for any $\varepsilon\in\,]0,\varepsilon_0]$ there exists a unique solution $(\mathbf{x}_\varepsilon(t),\mathbf{y}_\varepsilon(t))$ of Problem (1) on $[0,T]$ and*

$$\begin{aligned}\lim_{\varepsilon\to0}\mathbf{x}_\varepsilon(t) &= \bar{\mathbf{x}}(t), \qquad t\in[0,T]\,,\\ \lim_{\varepsilon\to0}\mathbf{y}_\varepsilon(t) &= \bar{\mathbf{y}}(t), \qquad t\in\,]0,T]\,,\end{aligned} \tag{6}$$

where $\bar{\mathbf{x}}(t)$ is the solution of (3) and $\bar{\mathbf{y}}(t)=\bar{\mathbf{y}}(t,\bar{\mathbf{x}})$ is the solution of (2).

The convergence in Tikhonov's theorem in $(6)_1$ is uniform with respect to $t\in[0,T]$, but in $(6)_2$ it is not uniform on $[0,T]$. However, in the latter case the convergence is uniform on any interval $[\zeta,T]$, $\zeta>0$. This is the so-called initial layer effect and one can include the initial layer term to obtain the uniform convergence on $[0,T]$.

Proposition 1. *Under the assumption of Theorem 2.1 we have*

$$\lim_{\varepsilon\to0}\left(\mathbf{y}_\varepsilon(t)-\bar{\mathbf{y}}(t)-\hat{\mathbf{y}}\left(\frac{t}{\varepsilon}\right)+\bar{\mathbf{y}}(0,\overset{\circ}{\mathbf{x}})\right)=0, \tag{7}$$

uniformly for $t\in[0,T]$, where $\hat{\mathbf{y}}(\tau)-\bar{\mathbf{y}}(0,\overset{\circ}{\mathbf{x}})$ is the correction in initial layer (the initial layer term).

Actually, under suitable assumptions it can be proved, see [2, 24, 25], that

$$\begin{aligned}&\mathbf{x}_\varepsilon(t)-\bar{\mathbf{x}}(t)=O(\varepsilon)\,,\\ &\mathbf{y}_\varepsilon(t)-\bar{\mathbf{y}}(t)-\hat{\mathbf{y}}\big(\tfrac{t}{\varepsilon}\big)+\bar{\mathbf{y}}(0,\overset{\circ}{\mathbf{x}})=O(\varepsilon)\,,\end{aligned} \tag{8}$$

uniformly on $[0,T]$.

We shall apply the Tikhonov theorem to a model population divided into two age groups: juveniles and adults and with an SIS type disease. The disease is supposed to last significantly shorter than any demographic process in the population. To have realistic parameters in the model, we consider the common cold or influenza whose infection and recovery rates were discussed in the introduction. While it is clear that the common cold affects both juveniles and adults, the data from the National Center for Health Statistics, see e.g. [17], indicate that children have about six to ten colds a year and, in families with children in school, the number of colds per child can be as high as 12 a year. At the same time, adults average about two to four colds a year. Similarly, it is argued, [19], that children are the driving force for the spread of influenza which suggests that their infection rate is higher than that of adults. Having this in mind, we further simplify the model by assuming that the disease only affects the juveniles. We note that a similar analysis has been recently carried out for a more realistic model with an SIRS type disease in the population, yielding analogous results, [21].

As we shall see, in our model the quasi steady states intersect along an isolated lower dimensional manifold where the uniform hyperbolicity (attractiveness) of the quasi steady state is lost. Such a case seems not to be covered by [26] and though it is mentioned in [27], the author does not provide much elucidation. Some situations of this kind can be handled by a version of the exchange lemma, see e.g. [9, 11, 15, 18] or fall within the theory of canard points, see e.g. [12]. However, the emphasis of these theories is different than that intended in the Tikhonov theorem. Also the case encountered in the presented model directly fits into neither of them and thus seems to require an individual approach.

In this paper we focus on the analysis away from the intersection of the quasi steady states and, by a careful application of the Tikhonov theorem, we show that for appropriate classes of the initial data the convergence in (6) occurs on time intervals of an arbitrary length. In epidemiological terms, our result means that for small stable populations such a disease does not leave any trace in the demography of the population whilst for larger and expanding populations its influence persists on the demographic time scale. What also is important is that in both cases the nonlinear systems can be approximated with very good accuracy by lower dimensional linear systems. Next we give a numerical illustration of the results proved in the paper and also present some numerical evidence illustrating the behaviour of the solutions while they pass close to the intersection of the quasi steady states. The mathematical analysis of it is referred to the forthcoming paper, [3]. We conclude the paper by a comprehensive discussion of the assumptions of the Tikhonov theorem.

3. **The model and its properties.**

3.1. **The SIS model.**

One of the simplest epidemiological models is the SIS model describing the evolution of a nonlethal disease which does not induce immunity after recovery. Examples of such diseases are offered by the common cold or influenza. The model can be written as

$$\begin{aligned} S' &= -\lambda SI + \gamma I, \\ I' &= \lambda SI - \gamma I, \\ S(0) &= S_0, \quad I(0) = I_0, \end{aligned} \tag{9}$$

where S and I describe, respectively, the size of the susceptible and infective population, respectively. As discussed in Introduction, the parameter λ is the transmission rate of the disease while the parameter γ is the recovery rate. A typical infection we have in mind lasts several days, so it is natural to take 1 day as the unit of time in (9).

Derivation of the basic properties of (9) is immediate. The Picard theorem gives local solvability, semi-axes $I = 0, S > 0$ and $S = 0, I > 0$ consist of trajectories and $(0, 0)$ is an equilibrium so that the first quadrant is positively invariant. Adding together both equations of (9) we obtain $N' = 0$, where $N(t) = S(t)+I(t)$ is the total population at time t. Thus the total population is constant: $N(t) = N_0 = S_0+I_0$ for any t for which the solutions exists. Hence, no nonnegative solution can blow up at a finite time and consequently the nonnegative solutions are globally defined. The equilibria in the first quadrant are given by the lines $(S, 0), S \geq 0$, and $(\gamma/\lambda, I), I \geq 0$ and clearly are not isolated. We see that the equilibrium lines are also isoclines with $S' > 0, I' < 0$ for $S < \gamma/\lambda$ and $S' < 0, I' > 0$ for $S > \gamma/\lambda$. Moreover, from $I(t) + S(t) = N_0$ it follows that the trajectories are the lines:

$$\begin{aligned} \{(S, I) \in \mathbb{R}^2_+;\ I + S = N_0, 0 < S < \gamma/\lambda\} \quad &\text{if} \quad N_0 \geq \gamma/\lambda, 0 < S_0 < \gamma/\lambda,\\ \{(S, I) \in \mathbb{R}^2_+;\ I + S = N_0, 0 < S < N_0\} \quad &\text{if} \quad N_0 < \gamma/\lambda,\\ \{(S, I) \in \mathbb{R}^2_+;\ I + S = N_0, \gamma/\lambda < S < N_0\} \quad &\text{if} \quad N_0 > \gamma/\lambda, S_0 > \gamma/\lambda. \end{aligned}$$

Thus, by monotonicity, any solution $(S(t), I(t))$ with $N_0 \geq \gamma/\lambda, 0 < S_0 < \gamma/\lambda$ tends to $(\gamma/\lambda, N_0 - \gamma/\lambda)$, any solution $(S(t), I(t))$ with $N_0 < \gamma/\lambda, 0 < S_0 < \gamma/\lambda$ tends to $(N_0, 0)$ and any solution $(S(t), I(t))$ with $N_0 \geq \gamma/\lambda, S_0 > \gamma/\lambda$ tends to $(\gamma/\lambda, N_0 - \gamma/\lambda)$.

3.2. **An SIS model with an age structure and its basic properties.** Next, let us embed this disease into some population. For our model, let the disease affect only juvenile, prereproductive, part of the population. In the absence of the disease, the demographical equation takes the form

$$\begin{aligned} n_1' &= -\mu_1 n_1 - a_1 n_1 + b n_2,\\ n_2' &= -\mu_2 n_2 + a_1 n_1,\\ n_1(0) &= \mathring{n}_1, \quad n_2(0) = \mathring{n}_2, \end{aligned} \tag{10}$$

where n_1 and n_2 are the sizes of, respectively, juvenile and adult populations, μ_1, μ_2 are the death rates of juveniles and adults, a_1 is the rate of moving from the juvenile to the adult class and b is the birth rate. Clearly, only adults can reproduce and the offspring emerge in the juvenile class. The solutions to (10) are given by the matrix exponential $\{e^{t\mathcal{A}}\}_{t\geq 0}$, where $\mathcal{A}$ is the matrix of coefficients of (10). Since $\mathcal{A}$ is positive off-diagonal, $e^{t\mathcal{A}} \geq 0$, that is, the components of the solution $(n_1(t), n_2(t)) = e^{t\mathcal{A}}(\mathring{n}_1, \mathring{n}_2)$, originating from non-negative initial data, are also nonnegative.

As we said above, we introduce a disease only affecting the juveniles. Thus, we write $n_1 = s + i$, where s and i are the numbers of susceptibles and infectives in the juvenile population. However, as discussed in Introduction, we cannot simply combine (9) and (10). Indeed, for the demographical processes of (10) a proper unit of time would be 1 year, whereas for (9) with our type of disease, the unit of time is 1 day. So, combining (10) and (9) we have to rescale time in the latter to years which amounts to multiplying the coefficients of (9) by 365. In other words, if λs is the average number of infected susceptibles by one infective in a unit time of (9) (1 day), then the average number of infected susceptibles in the unit of time of (10), that is, in one year, is $365\lambda s$. Using a large number $1/\epsilon$ instead of 365, we can write the combined nondimensionalized system as

$$\begin{aligned} s'_\epsilon &= -(\mu_1+a_1)s_\epsilon + bn_{2,\epsilon} + \frac{1}{\epsilon}(-\lambda s_\epsilon i_\epsilon + \gamma i_\epsilon), \\ i'_\epsilon &= -(\mu_1^*+a_1)i_\epsilon + \frac{1}{\epsilon}(\lambda s_\epsilon i_\epsilon - \gamma i_\epsilon), \\ n'_{2,\epsilon} &= -\mu_2 n_{2,\epsilon} + a_1(s_\epsilon + i_\epsilon), \\ s_\epsilon(0) &= \overset{\circ}{s}, \quad i_\epsilon(0) = \overset{\circ}{i}, \quad n_{2,\epsilon}(0) = \overset{\circ}{n}_2 . \end{aligned} \tag{11}$$

We adjusted the population part of (10) by introducing a different death rate μ_1^* among infectives. It is natural to assume

$$\mu_1^* > \mu_1. \tag{12}$$

We assume that there is no vertical transmission of the disease, that is, the neonates are always susceptible and also that the disease does not persist to adulthood. To avoid dealing with subcases, we assume that all coefficients $\mu_1, \mu_2, \mu_1^*, b, a_1, \lambda, \gamma$ are strictly positive. Writing (11) in the form

$$\begin{aligned} s'_\epsilon &= -\left(\mu_1 + a_1 + \epsilon^{-1}\lambda i_\epsilon\right) s_\epsilon + \epsilon^{-1}\gamma i_\epsilon + bn_{2,\epsilon}, \\ i'_\epsilon &= -(\mu_1^* + a_1 - \epsilon^{-1}(\lambda s_\epsilon - \gamma))i_\epsilon, \\ n'_{2,\epsilon} &= a_1 s_\epsilon + a_1 i_\epsilon - \mu_2 n_{2,\epsilon}, \end{aligned} \tag{13}$$

we see that the solution $(s_\epsilon, i_\epsilon, n_{2,\epsilon})$, as long as it is bounded, solves a linear system whose matrix has nonnegative coefficients off the diagonal. Thus, the first octant $\mathbb{R}^3_+$ of $\mathbb{R}^3$ is invariant under the flow defined by (11). We observe that the SIS part is only mixing and thus, by aggregating the variables i_ϵ and s_ϵ according to $n_{1,\epsilon} = i_\epsilon + s_\epsilon$ and adding the first two equations in (11), we obtain

$$\begin{aligned} \epsilon s'_\epsilon &= -\epsilon(\mu_1+a_1)s_\epsilon + \epsilon b n_{2,\epsilon} + (n_{1,\epsilon} - s_\epsilon)(\gamma - \lambda s_\epsilon), \\ n'_{1,\epsilon} &= -(\mu_1^*+a_1)n_{1,\epsilon} + (\mu_1^* - \mu_1)s_\epsilon + bn_{2,\epsilon}, \\ n'_{2,\epsilon} &= -\mu_2 n_{2,\epsilon} + a_1 n_{1,\epsilon}. \end{aligned} \tag{14}$$

Let us rewrite the last two equations as

$$\begin{aligned} n'_{1,\epsilon} &= -(\mu_1+a_1)n_{1,\epsilon} + bn_{2,\epsilon} - (\mu_1^* - \mu_1)i_\epsilon, \\ n'_{2,\epsilon} &= -\mu_2 n_{2,\epsilon} + a_1 n_{1,\epsilon}. \end{aligned} \tag{15}$$

Since $(\mu_1^* - \mu_1)s_\epsilon \geq 0$ and $-(\mu_1^* - \mu_1)i_\epsilon \leq 0$, by e.g. considering Picard iterates, (14) and (15) with $\overset{\circ}{n}_1, \overset{\circ}{n}_2 \geq 0$ yield

$$e^{t\mathcal{A}^*}\begin{pmatrix} \overset{\circ}{n}_1 \\ \overset{\circ}{n}_2 \end{pmatrix} \leq \begin{pmatrix} n_{1,\epsilon}(t) \\ n_{2,\epsilon}(t) \end{pmatrix} \leq e^{t\mathcal{A}}\begin{pmatrix} \overset{\circ}{n}_1 \\ \overset{\circ}{n}_2 \end{pmatrix}, \tag{16}$$

where $\{e^{t\mathcal{A}^*}\}_{t\geq 0}$ is the matrix exponential generated by the right hand side of (10) with μ_1 replaced by μ_1^*. In other words, the population with the disease develops slower than the population without the disease but faster than the population with no disease but with the disease specific mortality rate.

Since $n_{1,\epsilon} = i_\epsilon + s_\epsilon$ and $i_\epsilon, s_\epsilon \geq 0$, (16) implies that neither i_ϵ nor s_ϵ can blow up in finite time and thus solutions $(s_\epsilon, i_\epsilon, n_{2,\epsilon})$ of (11), originating from nonnegative initial conditions $\overset{\circ}{s}, \overset{\circ}{i}, \overset{\circ}{n}_2 \geq 0$, (or $(s_\epsilon, n_{1,\epsilon}, n_{2,\epsilon})$ of (14) with initial conditions $\overset{\circ}{n}_1, \overset{\circ}{n}_2 \geq 0$, $0 \leq \overset{\circ}{s} \leq \overset{\circ}{n}_1$), exist globally in time. In particular, the set

$$\mathcal{V} = \{(s, n_1, n_2) \in \mathbb{R}^3_+;\ s \leq n_1\} \tag{17}$$

is invariant under the flow generated by (14).

4. **Application of the Tikhonov theorem.** The system (14) is in the form for which we can try to apply the Tikhonov theorem to find the limit equation satisfied by the solutions as $\epsilon \to 0$. The equation for the quasi steady states resulting from (2) is

$$0 = (n_1 - s)(\gamma - \lambda s) \tag{18}$$

and, denoting $\nu = \gamma/\lambda$, the quasi steady states are

$$\bar{s} = n_1, \qquad \bar{s} = \nu. \tag{19}$$

Immediately we see that they coincide when n_1 passes through the value ν and hence they are not isolated. Precisely speaking, while for the availability of the Picard theorem we can take any set $\bar{\mathcal{U}} = [m_1, M_1] \times [m_2, M_2]$, $0 < m_i < M_i < \infty, i = 1, 2$, the solutions (19) intersect at $n_1 = \nu$ and thus are not isolated if $\nu \in [m_1, M_1]$. The immediate answer is to take either $[m_1, M_1']$ with $M_1' < \nu$ or $[m_1', M_1]$ with $m_1' > \nu$. However, the situation is not so simple since $\overline{\mathcal{U}}$ is required to contain the whole solution of the reduced equation (3) (see also Assumption 4 in the appendix). In our model the reduced equation is given by

$$\begin{aligned} \bar{n}_1' &= -(\mu_1^* + a_1)\bar{n}_1 + (\mu_1^* - \mu_1)\bar{s} + b\bar{n}_2, \\ \bar{n}_2' &= -\mu_2\bar{n}_2 + a_1\bar{n}_1, \end{aligned} \tag{20}$$

for appropriate $\bar{s}$ and its solution must stay in an appropriate $Int\overline{\mathcal{U}}$ in which the quasi steady state is isolated. This suggests two possible methods of approach.

- **M1:** Since, by continuity of the flow with respect to the initial conditions, for any compact $K \subset \mathcal{U}$ there is T_K such that solutions with initial conditions in K will stay in $Int\overline{\mathcal{U}}$ for $t \in [0, T_K]$, we can restrict the asymptotic analysis only to this time interval. One of the problems here is that the range of ϵ for which the solutions $(n_{1,\epsilon}(t), n_{2,\epsilon}(t), s_\epsilon(t))$ are attracted to the solution of (20) depends on T_K and thus is not explicitly given. Alternatively, using the Verhulst's approach, [28, Theorem 8.1], the interval on which the solutions to (20) attract solutions to (14) may depend on ϵ. Further, for larger t the asymptotic behaviour of solutions may be dramatically different from that over $[0, T_K]$.
- **M2:** The other possibility is to look for positively invariant subsets of $Int\overline{\mathcal{U}}$. This will give asymptotics valid on each finite interval $[0, T]$, $T > 0$, at the cost of (possibly) getting the result for a restricted range of initial conditions.

Here we pursue the second option. In [3] we investigate under what conditions one can combine both approaches to get a more comprehensive picture of the full dynamics.

Let us return to our problem. The auxiliary equation (4) is

$$\frac{d\tilde{s}}{d\tau} = (n_1 - \tilde{s})(\gamma - \lambda\tilde{s}) \tag{21}$$

and we see that $\bar{s} = n_1$ is stable if $n_1 < \nu$ and $\bar{s} = \nu$ is stable if $n_1 > \nu$. Accordingly, let us define

$$\Pi_\pm := \{(n_1, n_2) \in \mathbb{R}^2_+;\ n_1 \gtrless \nu\}$$

Thus, if we select $\bar{s} = n_1$, then we must find a set $\overline{\mathcal{U}}$ contained in Π_- which is invariant for solutions of the reduced system (20) which, in this case, is just the original system (10)

$$\begin{pmatrix} \bar{n}_1' \\ \bar{n}_2' \end{pmatrix} = \mathcal{A} \begin{pmatrix} \bar{n}_1 \\ \bar{n}_2 \end{pmatrix}. \tag{22}$$

On the other hand, if we take $\bar{s} = \nu$, then we must find a set $\overline{\mathcal{U}}$ contained in Π_+ which is invariant for the flow defined by

$$\begin{pmatrix} \bar{n}_1' \\ \bar{n}_2' \end{pmatrix} = \mathcal{A}^* \begin{pmatrix} \bar{n}_1 \\ \bar{n}_2 \end{pmatrix} + \begin{pmatrix} \nu(\mu_1^* - \mu_1) \\ 0 \end{pmatrix}, \tag{23}$$

see the definition of $\mathcal{A}^*$ under (16).

First, let us consider stability of the stationary point $(0,0)$ of (22). It is asymptotically stable if and only if the trace of the matrix is negative and the determinant is positive. Further, it is stable (but not asymptotically) if and only if the trace is negative and the determinant is 0 (in which case the equilibria form a line). Since the trace of the coefficient matrix is $-\mu_1 - \mu_2 - a_1 < 0$, we have stability if and only if

$$\frac{\mu_2}{a_1} \geq \frac{b}{\mu_1 + a_1}, \tag{24}$$

with asymptotic stability if the inequality is sharp. Geometrically, (22) is asymptotically stable if and only if the isocline $\bar{n}_1' = 0$, that is $\bar{n}_2 = b^{-1}(\mu_1 + a_1)\bar{n}_1$ is above the isocline $\bar{n}_2' = 0$: $\bar{n}_2 = \mu_2^{-1} a_1 \bar{n}_1$ in the first quadrant and it is unstable otherwise. The case of neutral stability corresponds to the case when both isocline coincide, forming a line of equilibria.

To simplify further considerations, let us assume that $\mathcal{A}^*$ is invertible (this assumption only will be used in Section 5). Then (23) can be written as

$$\frac{d}{dt}\left(\begin{pmatrix} \bar{n}_1 \\ \bar{n}_2 \end{pmatrix} + (\mathcal{A}^*)^{-1} \begin{pmatrix} \nu(\mu_1^* - \mu_1) \\ 0 \end{pmatrix}\right) = \mathcal{A}^*\left(\begin{pmatrix} \bar{n}_1 \\ \bar{n}_2 \end{pmatrix} + (\mathcal{A}^*)^{-1} \begin{pmatrix} \nu(\mu_1^* - \mu_1) \\ 0 \end{pmatrix}\right) \tag{25}$$

from which we see that the stationary point is given by

$$\bar{\mathbf{n}}^* = \begin{pmatrix} \bar{n}_1^* \\ \bar{n}_2^* \end{pmatrix} = -(\mathcal{A}^*)^{-1} \begin{pmatrix} \nu(\mu_1^* - \mu_1) \\ 0 \end{pmatrix} = \begin{pmatrix} \frac{\nu\mu_2(\mu_1^* - \mu_1)}{\mu_2(\mu_1^* + a_1) - ba_1} \\ \frac{\nu a_1(\mu_1^* - \mu_1)}{\mu_2(\mu_1^* + a_1) - ba_1} \end{pmatrix}. \tag{26}$$

We see that $\bar{\mathbf{n}}^*$ is in the first octant if and only if $(0,0)$ is an asymptotically stable equilibrium for $\{e^{t\mathcal{A}^*}\}_{t\geq 0}$, that is, if and only if

$$\frac{\mu_2}{a_1} > \frac{b}{\mu_1^* + a_1}. \tag{27}$$

Furthermore, by (26), $\bar{\mathbf{n}}^* \in \Pi_+$ if and only if

$$\frac{\mu_2(\mu_1^* - \mu_1)}{\mu_2(\mu_1^* + a_1) - ba_1} > 1 \quad \Leftrightarrow \quad \frac{\mu_2}{a_1} < \frac{b}{\mu_1 + a_1},$$

that is, when $\{e^{t\mathcal{A}}\}_{t\geq 0}$ is unstable. Finally, $\bar{\mathbf{n}}^*$ is an asymptotically stable equilibrium if and only if $\{e^{t\mathcal{A}^*}\}_{t\geq 0}$ is asymptotically stable.

Let us further clarify the relation between the forward invariance of the sets $\Pi_\pm$ and the stability of $\{e^{t\mathcal{A}}\}_{t\geq 0}$. In general, there exist linear systems for which $(0,0)$ is unstable but trajectories starting in Π_- stay there for $t > 0$ (e.g. when $(0,0)$ is a saddle point and $n_1 = 0$ is an unstable manifold). However, as we shall see below, such a behaviour is impossible for solutions of (22).

For arbitrary $\overset{\circ}{\mathbf{x}} = (\overset{\circ}{x}_1, \overset{\circ}{x}_2) \in \mathbb{R}^2$, we introduce the notation

$$\begin{pmatrix} x_{\mathcal{A},1}(t, \overset{\circ}{\mathbf{x}}) \\ x_{\mathcal{A},2}(t, \overset{\circ}{\mathbf{x}}) \end{pmatrix} = e^{t\mathcal{A}} \begin{pmatrix} \overset{\circ}{x}_1 \\ \overset{\circ}{x}_2 \end{pmatrix},$$

where the subscript $\mathcal{A}$ or/and the dependence on the initial condition $\overset{\circ}{\mathbf{x}}$ will be dropped if no misunderstanding is possible.

Lemma 4.1. *Assume that* $(0,0)$ *is unstable for* $\{e^{t\mathcal{A}}\}_{t\geq 0}$*, that is,*

$$\frac{\mu_2}{a_1} < \frac{b}{\mu_1 + a_1} \tag{28}$$

and let $\overset{\circ}{\mathbf{x}} \geq 0$*. Then* $\lim_{t\to\infty} x_{\mathcal{A},i}(t, \overset{\circ}{\mathbf{x}}) = \infty$ *for* $i = 1, 2$*.*

Proof. To simplify notation we consider the matrix

$$\begin{pmatrix} -a & b \\ c & -d \end{pmatrix}$$

with $a, b, c, d > 0$ and $ad - bc < 0$, that is, having the same structure as (22) with (28). Such a matrix always has two distinct real eigenvalues

$$\lambda_{\pm} = \frac{-(a+d) \pm \sqrt{(a-d)^2 + 4bc}}{2}$$

of different signs in which case $(0,0)$ is a saddle. The eigenvectors satisfy

$$\begin{pmatrix} -a - \frac{-(a+d)\pm\sqrt{\Delta}}{2} & b \\ c & -d - \frac{-(a+d)\pm\sqrt{\Delta}}{2} \end{pmatrix} \begin{pmatrix} e_1^{\pm} \\ e_2^{\pm} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix},$$

where $\Delta = (a-d)^2 + 4bc$. In the 'plus' case we have

$$-a - \frac{-(a+d) + \sqrt{\Delta}}{2} < -\frac{a-d}{2} - \frac{|a-d|}{2} \leq 0$$

and similarly for the other entry containing λ_+, while in the 'minus' case

$$-a - \frac{-(a+d) - \sqrt{\Delta}}{2} > -\frac{a-d}{2} + \frac{|a-d|}{2} \geq 0$$

with analogous inequality for the other entry containing λ_-. This means that (e_1^+, e_2^+) has the entries of the same sign while (e_1^-, e_2^-) are of the opposite sign. Thus, the stable line passes through the open second and fourth quadrants and the unstable line through the first and third. Hence, there are no solutions which can stay in any strip parallel to one of the axes of the first quadrant. □

Now we are ready to formulate and prove the main result of the paper.

Theorem 4.2. *1. Assume that the equilibrium solution* $(0,0)$ *to (10) is stable, let* $0 \leq \overset{\circ}{s} \leq \overset{\circ}{n}_1, 0 \leq \overset{\circ}{n}_1 < \nu, \overset{\circ}{n}_2 < \nu(\mu_1 + a_1)/b$ *and let* $0 < T < \infty$ *be an arbitrary number. Then the solution* $(s_\epsilon(t), n_{1,\epsilon}(t), n_{2,\epsilon}(t))$ *to (14) satisfies*

$$\begin{aligned}
\lim_{\epsilon\to 0^+} s_\epsilon(t) &= \bar{n}_1(t), & t &\in]0, T], \\
\lim_{\epsilon\to 0^+} i_\epsilon(t) &= 0, & t &\in]0, T], \\
\lim_{\epsilon\to 0^+} n_{1,\epsilon}(t) &= \bar{n}_1(t), & t &\in [0, T], \\
\lim_{\epsilon\to 0^+} n_{2,\epsilon}(t) &= \bar{n}_2(t), & t &\in [0, T],
\end{aligned}$$

where $(\bar{n}_1(t), \bar{n}_2(t))$ *is the solution to (22) with the initial condition specified above. Furthermore*

$$\lim_{\epsilon\to 0^+}\left(s_\epsilon(t) - \bar{n}_1(t) - \frac{\nu(\overset{\circ}{s} - \overset{\circ}{n}_1) + \overset{\circ}{n}_1 (\nu - \overset{\circ}{s}) \exp\left(\frac{\lambda(\nu - \overset{\circ}{n}_1)t}{\epsilon}\right)}{\overset{\circ}{s} - \overset{\circ}{n}_1 + (\nu - \overset{\circ}{s}) \exp\left(\frac{\lambda(\nu - \overset{\circ}{n}_1)t}{\epsilon}\right)} + \overset{\circ}{n}_1\right) = 0$$

uniformly for $t \in [0, T]$.

2. *Assume that the equilibrium solution* $(0,0)$ *to (10) is unstable or stable (but not asymptotically stable), let* $0 \le \overset{\circ}{s} \le \overset{\circ}{n}_1, \overset{\circ}{n}_1 > \nu, \overset{\circ}{n}_2 > \nu(\mu_1 + a_1)/b$ *and let* $0 < T < \infty$ *be an arbitrary number. Then the solution* $(s_\epsilon(t), n_{1,\epsilon}(t), n_{2,\epsilon}(t))$ *to (14) satisfies*

$$\begin{aligned}
\lim_{\epsilon\to 0^+} s_\epsilon(t) &= \nu, & t &\in]0, T],\\
\lim_{\epsilon\to 0^+} i_\epsilon(t) &= \bar{n}_1(t) - \nu, & t &\in]0, T],\\
\lim_{\epsilon\to 0^+} n_{1,\epsilon}(t) &= \bar{n}_1(t), & t &\in [0, T],\\
\lim_{\epsilon\to 0^+} n_{2,\epsilon}(t) &= \bar{n}_2(t), & t &\in [0, T],
\end{aligned}$$

where $(\bar{n}_1(t), \bar{n}_2(t))$ *is the solution to (23) with the initial condition specified above. Furthermore*

$$\lim_{\epsilon\to 0^+}\left(s_\epsilon(t) - \frac{\nu(\overset{\circ}{s} - \overset{\circ}{n}_1) + \overset{\circ}{n}_1 (\nu - \overset{\circ}{s}) \exp\left(\frac{\lambda(\nu - \overset{\circ}{n}_1)t}{\epsilon}\right)}{\overset{\circ}{s} - \overset{\circ}{n}_1 + (\nu - \overset{\circ}{s}) \exp\left(\frac{\lambda(\nu - \overset{\circ}{n}_1)t}{\epsilon}\right)}\right) = 0, \qquad t \in [0, T].$$

Proof. **Case 1. quasi steady state** $\bar{s} = n_1$**.** From the considerations above, we see that if we are to have solutions to (22) staying in Π_-, then we must focus on the stable case (24). Clearly, this is not sufficient as $\bar{n}_1$ may initially grow crossing the line $n_1 = \nu$ before returning to the origin. Thus, we have to discuss the behaviour of solutions in more detail.

First, let us find the direction of the field along $n_1 = \breve{\nu} \le \nu$. We have

$$n_1' = bn_2 - \breve{\nu}(\mu_1 + a_1)$$

and thus the field is directed inward the set $\{(n_1, n_2) \in \mathbb{R}^2_+, n_1 \le \breve{\nu}\}$ for $n_2 < \breve{\nu}(\mu_1 + a_1)/b$. So, the solution cannot escape through $n_1 = \breve{\nu}$ as long as $n_2 < \breve{\nu}(\mu_1 + a_1)/b$. Consider now n_2' along $n_2 = \breve{\nu}(\mu_1 + a_1)/b$ with $0 \le n_1 \le \breve{\nu}$. We have

$$n_2' = -\frac{\mu_2 \breve{\nu}(\mu_1 + a_1)}{b} + a_1 n_1 \le a_1 \breve{\nu}\left(-\frac{\mu_2(\mu_1 + a_1)}{a_1 b} + 1\right) \le 0$$

by (24). The inequality is strict either if $n_1 < \breve{\nu}$ or if $(0,0)$ is an asymptotically stable equilibrium. Otherwise, in the considered case $\mu_2/a_1 = b/(\mu_1 + a_1)$, then the point $(\breve{\nu}, \breve{\nu}(\mu_1 + a_1)/b)$, where $n_2' = 0$, is actually a stationary point (the line $-\mu_2 n_1 + a_1 n_2 = -bn_1 + (\mu_1 + a_1)n_2 = 0$ consists of stationary points) and thus no trajectory can escape through it. Hence

$$K_{\breve{\nu}} = \{(n_1, n_2) \in \mathbb{R}^2_+;\ n_1 \le \breve{\nu}, n_2 \le \breve{\nu}(\mu_1 + a_1)/b\} \tag{29}$$

is positively invariant for $\{e^{t\mathcal{A}}\}_{t\ge 0}$ for any $\breve{\nu} \le \nu$.

Summarizing, if we take $\overline{\mathcal{U}} = K_{\breve{\nu}}$ for arbitrary $\breve{\nu} < \nu$, then the solution $\bar{s}(n_1, n_2) = n_1$ is isolated in $\overline{\mathcal{U}}$ and the solution of the reduced equation originating from $\overline{\mathcal{U}}$ stays there for all $t > 0$.

Let us consider the auxiliary equation (21). As we noted, $\tilde{s} = n_1$ is a stable equilibrium of this equation and, by monotonicity of solutions, this stability is uniform with respect to the parameter $(n_1, n_2) \in K_{\breve{\nu}}$ with any $\breve{\nu} < \nu$.

For uniform stability, if we denote by $\Psi(\tilde{s}, n_1)$ the right hand side of the auxiliary equation (21), then we find

$$\left.\frac{\partial \Psi}{\partial \tilde{s}}\right|_{\tilde{s}=n_1} = -\gamma + \lambda n_1$$

which is negative uniformly for $(n_1, n_2) \in K_{\bar{\nu}}$, which shows that the convergence is uniform in n_1. Finally, taking $\mathring{\mathbf{n}} = (\mathring{n}_1, \mathring{n}_2) \in K_{\breve{\nu}}$, we consider the initial layer equation (5)

$$\frac{d\hat{s}}{d\tau} = (\mathring{n}_1 - \hat{s})(\gamma - \lambda \hat{s}). \tag{30}$$

Then, for applicability of the Tikhonov theorem, we need to select the initial condition $\mathring{s}$ in the domain of attraction of $\mathring{n}_1$. Though in principle we could take any $\mathring{s} < \nu$, from the conditions of the problem we know that we must take $\mathring{s} < \mathring{n}_1$.

Case 2. quasi steady state $\bar{s}(n_1, n_2) = \nu$. Similarly to the case 1, we consider the field along the line $n_1 = \nu + \delta b/(\mu_1^* + a_1) > \nu$ for some $\delta > 0$. Along this line the field (n_1', n_2') points to the right, that is, towards increasing n_1, provided

$$n_2 \geq \frac{(\mu_1 + a_1)\nu}{b} + \delta.$$

Let us look at the direction of the field along $n_2 = \delta + (\mu_1 + a_1)\nu/b$. We find that n_2' is positive provided

$$n_1 > \frac{\mu_2}{a_1}\frac{\mu_1 + a_1}{b}\nu - \frac{\delta}{a_1}. \tag{31}$$

We see that to ensure that $n_1 \geq \nu$, we should take the unstable/stable case of the original population, that is, to assume

$$\frac{\mu_2}{a_1} \leq \frac{b}{\mu_1 + a_1}.$$

To make the notation simpler, we see that we always can take $\eta = \delta \max\{1, b/(\mu_1^* + a_1)\}$ as a common value and claim that for any $\eta \geq 0$ the set

$$\overline{\mathcal{U}}_\eta = \left\{(n_1, n_2) \in \mathbb{R}_+^2;\ n_1 \geq \nu + \eta, n_2 \geq \frac{(\mu_1 + a_1)\nu}{b} + \eta\right\}$$

is invariant under the flow generated by (23). The case $\delta = 0$ and $\mu_2 a_1/(\mu_1 + a_1)b = 1$ in (31) is dealt with by noting that then the point $(\nu, (\mu_1 + a_1)\nu/b)$ is an equilibrium of (23) and thus no trajectory can escape through it. Furthermore, for $(n_1, n_2) \in \overline{\mathcal{U}}_\eta$ with $\eta > 0$ the solutions (19) are isolated. As before,

$$\left.\frac{\partial \Psi}{\partial \tilde{s}}\right|_{\tilde{s}=\nu} = -\lambda n_1$$

which is negative uniformly for $(n_1, n_2) \in \overline{\mathcal{U}}_\eta$ so that the convergence is uniform in n_1. Finally, taking $\mathring{\mathbf{n}} = (\mathring{n}_1, \mathring{n}_2) \in \overline{\mathcal{U}}_\eta$ we consider the initial layer equation

$$\frac{d\hat{s}}{d\tau} = (\mathring{n}_1 - \hat{s})(\gamma - \lambda \hat{s}).$$

Then, for the applicability of the Tikhonov theorem we need to select the initial condition $\overset{\circ}{s}$ in the domain of attraction of $\hat{s} = \nu$. Clearly, the domain of attraction is $0 \leq \overset{\circ}{s} < \overset{\circ}{n}_1$.

Finally, we can solve the initial layer equation (30) to obtain the initial layer correction in the form

$$\hat{s}\left(\frac{t}{\epsilon}\right) = \frac{\nu(\overset{\circ}{s} - \overset{\circ}{n}_1) + \overset{\circ}{n}_1 (\nu - \overset{\circ}{s}) \exp\left(\frac{\lambda(\nu - \overset{\circ}{n}_1)t}{\epsilon}\right)}{\overset{\circ}{s} - \overset{\circ}{n}_1 + (\nu - \overset{\circ}{s}) \exp\left(\frac{\lambda(\nu - \overset{\circ}{n}_1)t}{\epsilon}\right)}. \tag{32}$$

□

5. **Comments on the 'stable-unstable' case.** An interesting dynamics develops when $\{e^{t\mathcal{A}^*}\}_{t\geq 0}$ is (asymptotically) stable and $\{e^{t\mathcal{A}}\}_{t\geq 0}$ is unstable, that is, if

$$\frac{\mu_2}{a_1} < \frac{b}{\mu_1 + a_1}, \qquad \frac{\mu_2}{a_1} > \frac{b}{\mu_1^* + a_1}. \tag{33}$$

In other words, we focus on the case when $(0, 0)$ is an asymptotically stable equilibrium for $\{e^{t\mathcal{A}^*}\}_{t\geq 0}$ and an unstable equilibrium for $\{e^{t\mathcal{A}}\}_{t\geq 0}$. Let us analyse the local dynamics of the problem (14). Clearly, we have an equilibrium at $(0, 0, 0)$. To find the other equilibrium $(\check{s}_\epsilon, \check{n}_{1,\epsilon}, \check{n}_{2,\epsilon})$, first we see from (13) that $\check{s}_\epsilon = \nu + \epsilon\lambda^{-1}(a_1 + \mu_1^*)$. Then, by $\check{n}_{2,\epsilon} = a_1\mu_2^{-1}\check{n}_{1,\epsilon}$, we find

$$\check{n}_{1,\epsilon} = \frac{\mu_2(\mu_1^* - \mu_1)}{\mu_1^*\mu_2 + a_1(\mu_2 - b)}\check{s}_\epsilon$$

and we see that $\check{n}_{1,\epsilon} > 0$ if and only if the second inequality in (33) is satisfied, that is, if $\{e^{t\mathcal{A}^*}\}_{t\geq 0}$ is stable. Similarly, it is easy to see that $\check{n}_{1,\epsilon} > \check{s}_\epsilon$ holds if and only if $\{e^{t\mathcal{A}}\}_{t\geq 0}$ is asymptotically stable. Summarizing, in the case (33) there exists a biologically relevant stationary point to (14). Moreover, we see that as $\epsilon \to 0^+$, then $\check{s}_\epsilon \to \nu$ and $(\check{n}_{1,\epsilon}, \check{n}_{2,\epsilon})$ converges to the stationary point of the equation (23), thus to the stationary point of the reduced system on the manifold $s = \nu$. Let us consider the stability of the equilibria. It turns out that it is easier to work with (13). Since (13) and (14) are related by a linear change of variables,

$$\begin{pmatrix} s \\ n_1 \\ n_2 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} s \\ i \\ n_2 \end{pmatrix},$$

the linearizations are given by similar matrices and thus eigenvalues are the same and the eigenvectors are related by the same linear change of variables. The Jacobian is given by

$$J(s, i, n_2) = \begin{pmatrix} -(\mu_1 + a_1) - \frac{\lambda i}{\epsilon} & -\frac{\lambda s}{\epsilon} + \frac{\gamma}{\epsilon} & b \\ \frac{\lambda i}{\epsilon} & -(\mu_1^* + a_1) + \frac{\lambda s - \gamma}{\epsilon} & 0 \\ a_1 & a_1 & -\mu_2 \end{pmatrix}.$$

It is easy to see that the characteristic equation at $(0, 0, 0)$ is given by

$$(\omega + \mu_1^* + a_1 + \gamma\epsilon^{-1})(\omega^2 + \omega((\mu_1 + a_1) + \mu_2) + (\mu_1 + a_1)\mu_2 - a_1 b) = 0$$

and $(0, 0, 0)$ is unstable if $\{e^{t\mathcal{A}}\}_{t\geq 0}$ is unstable. Let $\omega_1 := -(\mu_1^* + a_1 + \gamma\epsilon^{-1}) < 0$. Then the eigenvector corresponding to ω_1 is given by $\mathbf{e}_1 = (0, 1, 0)$, that is, it is parallel to the i-axis. Next we note that the matrix obtained by crossing out the row and column of $J(0, 0, 0)$, which contain $-(\mu_1^* + a_1 + \gamma\epsilon^{-1})$, is exactly $\mathcal{A}$ and thus it has eigenvectors $\mathbf{e}_2 = (e_1^+, 0, e_2^+)$, $e_i^+ > 0, i = 1, 2$, corresponding to $\omega_2 > 0$ and $\mathbf{e}_3 = (e_1^-, 0, e_2^-)$, $e_1^- < 0, e_2^- > 0$, corresponding to $\omega_3 < 0$, respectively, as described in Lemma 4.1. By similarity, the eigenvectors of the linearization of (14), that is, in the (s, n_1, n_2) variables, are given by $\mathbf{v}_1 = (0, 1, 0)$, $\mathbf{v}_2 = (e_1^+, e_1^+, e_2^+)$ and $\mathbf{v}_3 = (e_1^-, e_1^-, e_2^-)$. Thus, $\mathbf{v}_1$ and $\mathbf{v}_2$ are on the manifold $n_1 = s$. Note that the stable direction is outside the positive octant which suggests that $(0, 0, 0)$ is repelling in the positive octant. This, in fact, can also be proved directly.

Proposition 2. *Under assumptions of this section, let $(s_\epsilon(t), n_{1,\epsilon}(t), n_{2,\epsilon}(t))$ be the solution to (14) with initial data $(\overset{\circ}{s}, \overset{\circ}{n}_1, \overset{\circ}{n}_2) \in \mathcal{V}$ (see (17)) which satisfy $\overset{\circ}{s} \leq \nu$. Then there is t_0 such that $s_\epsilon(t_0) > \nu$ (and thus $n_{1,\epsilon}(t_0) > \nu$) and*

$$(n_{1,\epsilon}(t_0), n_{2,\epsilon}(t_0)) \in \overline{\mathcal{U}}_\eta = \left\{(n_1, n_2) \in \mathbb{R}^2_+;\ n_1 \geq \nu + \eta, n_2 \geq \frac{(\mu_1 + a_1)\nu}{b} + \eta\right\} \tag{34}$$

for some $\eta > 0$.

Proof. Assume that $s_\epsilon(t) \leq \nu$ for all $t \geq 0$. Then $i_\epsilon(t)(-\lambda s_\epsilon(t) + \gamma) \geq 0$ for $t \geq 0$ and thus

$$e^{t\mathcal{A}} \begin{pmatrix} \overset{\circ}{s} \\ \overset{\circ}{n}_2 \end{pmatrix} \leq \begin{pmatrix} s_\epsilon(t) \\ n_{2,\epsilon}(t) \end{pmatrix}. \tag{35}$$

By (33) and Lemma 4.1, any trajectory originating from the first quadrant has both components diverging to infinity. Thus we cannot have $s_\epsilon(t) \leq \nu$ for all t. Let $\hat{t}_0$ be the first time at which $s_\epsilon(\hat{t}_0) = \nu$. We claim that $s'_\epsilon(\hat{t}_0) > 0$. Indeed, s_ϵ must be nondecreasing on $(\hat{t}_0 - \delta, \hat{t}_0]$ for some $\delta > 0$ so $s'_\epsilon(\hat{t}_0) \geq 0$. Consider isoclines of (10) with n_1 replaced by s: $n_2 = (\mu_1 + a_1)s/b$ and $n_2 = a_1 s/\mu_2$. Assume $s'_\epsilon(\hat{t}_0) = 0$. Then $(\nu, n_{2,\epsilon}(\hat{t}_0)) = (\nu, \nu(\mu_1 + a_1)/b)$ is the intersection of the isocline $s' = 0$ and $s = \nu$. The other isocline intersects $s = \nu$ at $(\nu, \nu a_1/\mu_2)$ and $n_{2,\epsilon}(\hat{t}_0) < \nu a_1/\mu_2$ by (33). On the other hand

$$s''_\epsilon(\hat{t}_0) = -(\mu_1 + a_1)s'_\epsilon(\hat{t}_0) + bn'_{2,\epsilon}(\hat{t}_0) = b(-\mu_2 n_{2,\epsilon}(\hat{t}_0) + a_1\nu) > 0$$

which is a contradiction. Thus $n_{2,\epsilon}(\hat{t}_0) > -(\mu_1 + a_1)/b$ and, by continuity, we see $n_{2,\epsilon}(t) > -(\mu_1 + a_1)/b$ and $n_{1,\epsilon}(t) \geq s_\epsilon(t) > \nu$ for $t \in (\hat{t}_0, \hat{t}_0 + \delta')$ for some $\delta' > 0$. □

Let us look at the properties of the other equilibrium of (14). We have

$$J(\hat{s}_\epsilon, \hat{i}_\epsilon, \hat{n}_{2,\epsilon}) = \begin{pmatrix} -(\mu_1 + a_1) - \frac{\lambda \hat{i}}{\epsilon} & -(\mu_1^* + a_1) & b \\ \frac{\lambda \hat{i}}{\epsilon} & 0 & 0 \\ a_1 & a_1 & -\mu_2 \end{pmatrix},$$

where we used the formula for $\hat{s}_\epsilon$. The characteristic equation becomes

$$\begin{aligned} \omega^3 \quad &+ \quad \omega^2 \left(\mu_2 + \mu_1 + a_1 + \frac{\lambda \hat{i}_\epsilon}{\epsilon}\right) + \omega \left(\mu_2(\mu_1 + a_1) + \frac{\lambda \hat{i}_\epsilon}{\epsilon}(\mu_2 + \mu_1^* + a_1) - ba_1\right) \\ &+ \quad \frac{\lambda \hat{i}_\epsilon}{\epsilon}\left((\mu_1^* + a_1)\mu_2 - ba_1\right) \\ &= \quad \omega^3 + A\omega^2 + B\omega + C = 0. \end{aligned}$$

To use the Hurwitz criterion, we see that $A > 0$, $C > 0$, by (33). Since $\hat{i}_\epsilon = \hat{n}_{1,\epsilon} - \hat{s}_\epsilon$, we see that as $\hat{s}_\epsilon \to \nu$ and

$$n_{1,\epsilon} \to \frac{\mu_2(\mu_1^* - \mu_1)}{\mu_1^*\mu_2 + a_1(\mu_2 - b)}\nu > \nu$$

(again by (33)), AB is of the order of ϵ^{-2} while C is of the order of ϵ^{-1} and thus $AB - C > 0$ for small ϵ. Thus, by the Hurwitz criterion, $(\hat{s}_\epsilon, \hat{i}_\epsilon, \hat{n}_{2,\epsilon})$ (and hence $(\hat{s}_\epsilon, \hat{n}_{1,\epsilon}, \hat{n}_{2,\epsilon})$) is locally asymptotically stable for small $\epsilon > 0$.

In this way we see that when the conditions (33) hold and $0 \leq \overset{\circ}{s} \leq \overset{\circ}{n}_1, \overset{\circ}{n}_1 > \nu, \overset{\circ}{n}_2 > \nu(\mu_1 + a_1)/b$, then not only does $(s_\epsilon, n_{1,\epsilon}, n_{2,\epsilon}) \to (\nu, \bar{n}_1, \bar{n}_2)$ on any time interval $[0, T]$ as $\epsilon \to 0$ but also the respective equilibria converge.

6. **Numerical illustration.** In this section we present a numerical illustration of the results presented in the paper. The unit for the population is 100, for the demographical parameters we use the unit year^{-1}, the unit of γ is day^{-1} and for λ is (day $\times$ 100 people)$^{-1}$.

(1): For Theorem 4.2. 1. we use $\mu_1 = 0.043, \mu_2 = 0.029, a_1 = 0.05, b = 0.046, \mu_1^* = 0.075, \gamma = 0.14, \lambda = 0.18$ (so that $\nu \approx 7.78$) and $\epsilon = 0.1, 0.01$ with $\overset{\circ}{s} = 0.19, \overset{\circ}{n}_1 = 0.76, \overset{\circ}{n}_2 = 1.55$. See see Figs. 1 – 3.

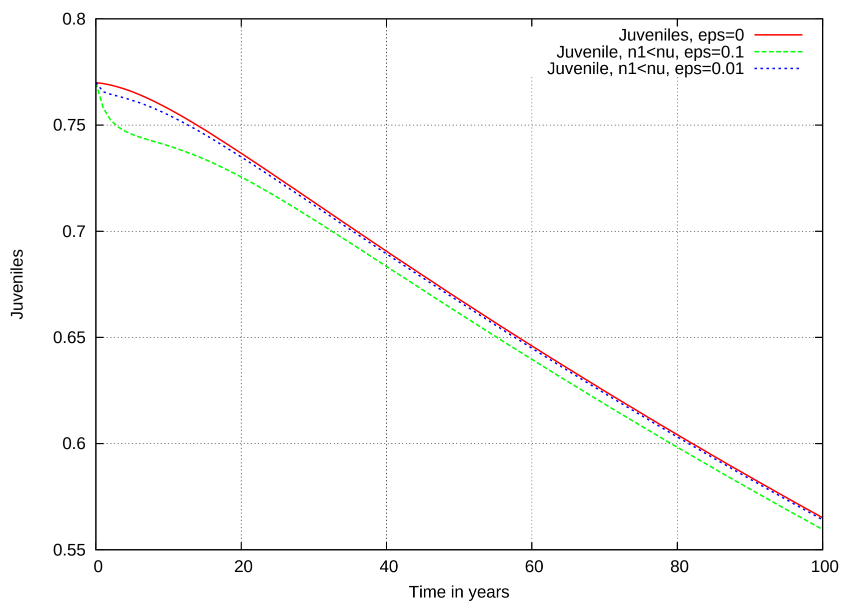

FIGURE 1. The quasi steady state for juveniles (solution to (22); eps $= 0$) attracting solutions $n_{1,\epsilon}$ of (14) under assumptions of Theorem 4.2. 1.

(2): For Theorem 4.2. 2. we use $\mu_1 = 0.043, \mu_2 = 0.029, a_1 = 0.05, b = 0.057, \mu_1^* = 0.046, \gamma = 0.14, \lambda = 0.18$ and $\epsilon = 0.1, 0.01, 0.001$. The initial conditions are $\overset{\circ}{s} = 0.7, \overset{\circ}{n}_1 = 0.8, \overset{\circ}{n}_2 = 1.3$. See Figs. 4 – 6.

(3): Illustration of the results of Section 5, see Fig. 7. Here we take $\mu_1 = 0.043, \mu_2 = 0.029, a_1 = 0.05, b = 0.057, \mu_1' = 0.075, \gamma = 0.14, \lambda = 0.18$ and $\epsilon = 0.1, 0.01, 0.001$ with $\overset{\circ}{s} = 0.7, \overset{\circ}{n}_1 = 0.79, \overset{\circ}{n}_2 = 1.95$.

The final two cases pertain to the situation when either $\{e^{t\mathcal{A}}\}_{t\geq 0}$ is asymptotically stable, that is, when (24) holds with the strict inequality, but the

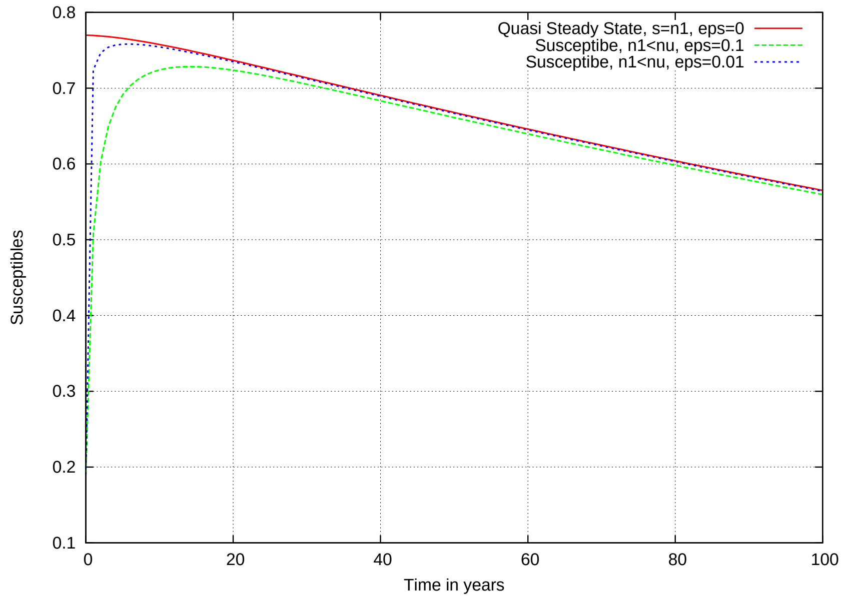

FIGURE 2. The quasi steady state for susceptibles ($s = n_1$) attracting solutions s_ϵ of (14) under assumptions of Theorem 4.2. 1. Notice the nonuniform approximation close to $t = 0$.

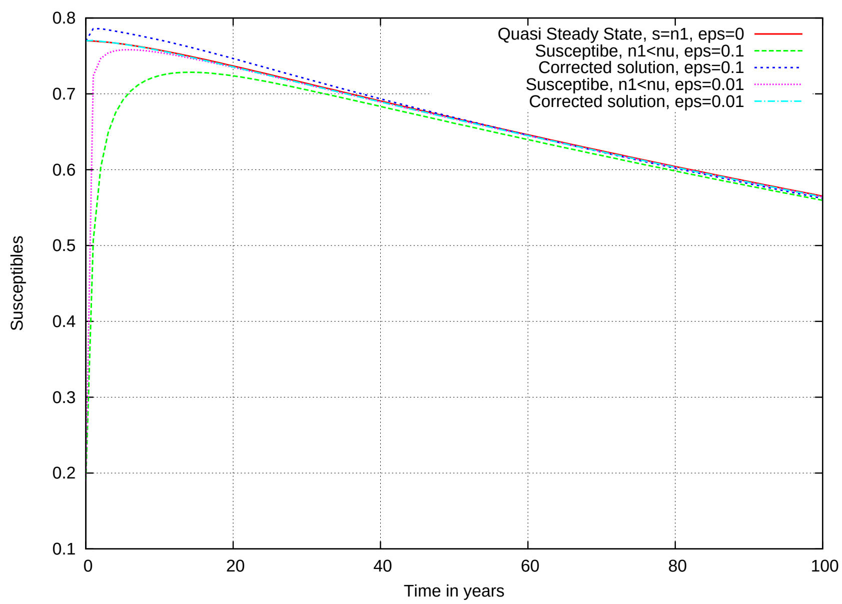

FIGURE 3. The quasi steady state for susceptibles ($s = n_1$) attracting solutions s_ϵ of (14), together with the initial layer correction (32). The case of Theorem 4.2. 1.

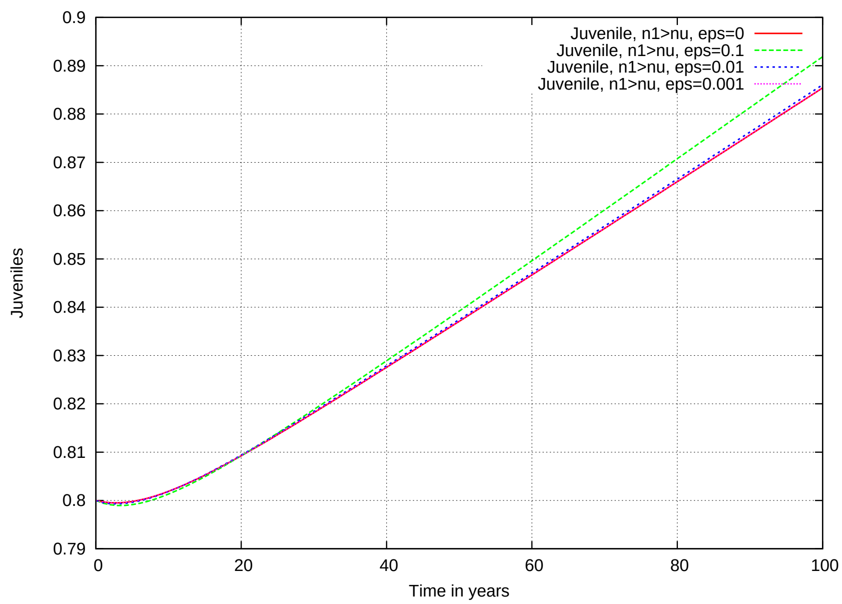

FIGURE 4. Quasi steady state juveniles (eps =0), solution to (23), attracting solutions $n_{1,\epsilon}$ to (14) under assumptions of Theorem 4.2. 2.

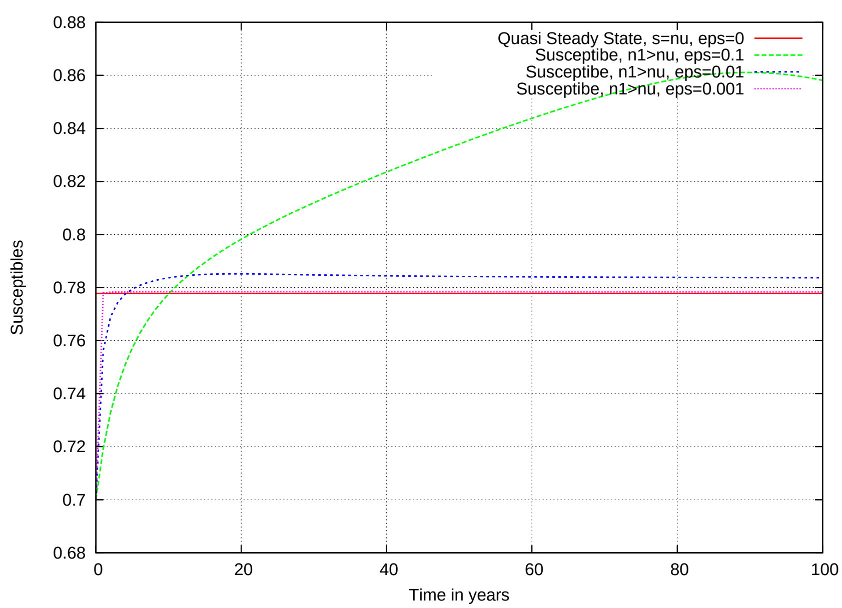

FIGURE 5. The quasi steady state for susceptibles ($s = \nu$) attracting solutions s_ϵ of (14) under assumptions of Theorem 4.2. 2. Notice the nonuniform approximation close to $t = 0$ (in particular for eps=0.1).

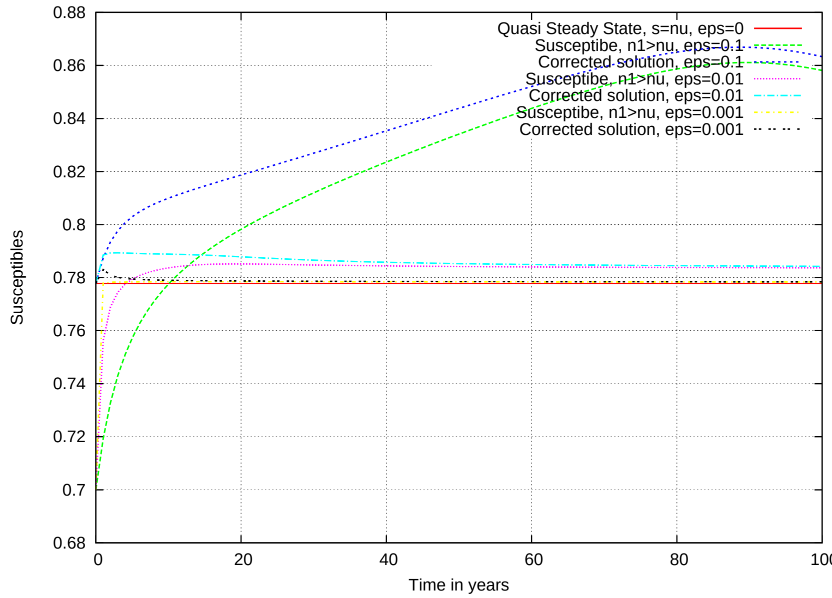

FIGURE 6. The quasi steady state for susceptibles ($s = \nu$) attracting solutions s_ϵ of (14), together with the initial layer correction (32). The case of Theorem 4.2. 2.

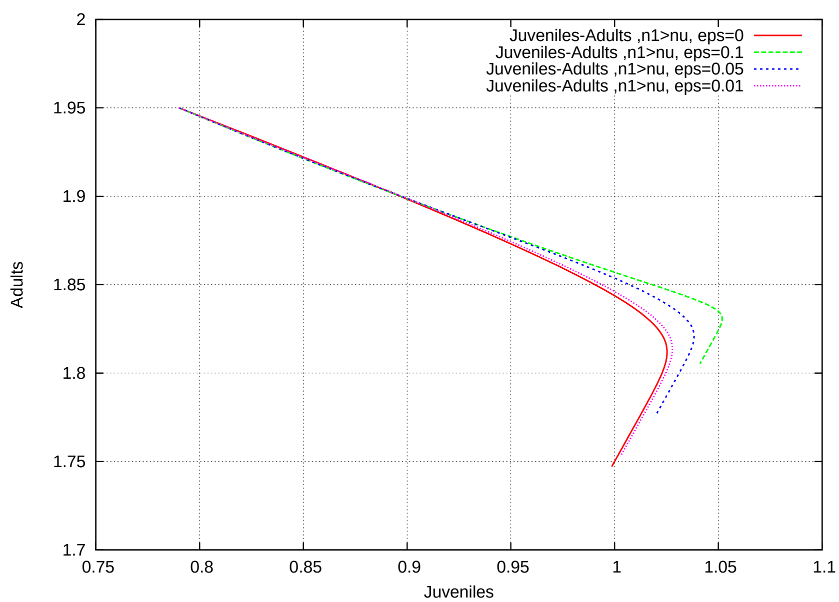

FIGURE 7. The orbit of (23) and orbits $(n_{1,\epsilon}, n_{2,\epsilon})$ of (23) attracted to their respective equilibrium states. Calculations for $0 \le t \le 100$.

initial conditions do not satisfy the assumptions of Theorem 4.2. 1. (item 4 below), or if $\{e^{t\mathcal{A}}\}_{t\geq 0}$ is unstable but the initial conditions do not satisfy the assumptions of Theorem 4.2. 2. (item 5 below). As intuitively expected, in the first case the solution $(s_\epsilon, n_{1,\epsilon}, n_{2,\epsilon})$ of (14) is first attracted to $(\nu, \bar{n}_1, \bar{n}_2)$, where $(\bar{n}_1, \bar{n}_2)$ solves (23) and, when $n_{1,\epsilon}$ passes below ν, s_ϵ starts being attracted to $\bar{n}_1$ and $(n_{1,\epsilon}, n_{2,\epsilon})$ to the solution $(\bar{n}_1, \bar{n}_2)$ of (22). The second case is the converse of the previous one with, however, an interesting phenomenon that, say, s_ϵ, having passed above ν, continues for some time along the now repelling quasi steady state $\bar{s} = \bar{n}_1$ and then moves quickly to the attracting quasi steady state $\bar{s} = \nu$. We note that such a behaviour was observed in e.g. [18] for a predator-prey model. An analytical proof that such a behaviour indeed occurs mathematically is more involved and therefore it is referred to [3].

(4): Here we consider an asymptotically stable $\{e^{t\mathcal{A}}\}_{t\geq 0}$ with large initial data. The calculations are performed for $\mu_1 = 0.043, \mu_2 = 0.029, a_1 = 0.05, b = 0.046$, $\mu_1^* = 0.075, \gamma = 0.14, \lambda = 0.18, \epsilon = 0.1, 0.01, 0.001$ and $\overset{\circ}{s} = 0.19, \overset{\circ}{n}_1 = 1.4, \overset{\circ}{n}_2 = 1.55$. See Fig. 8.

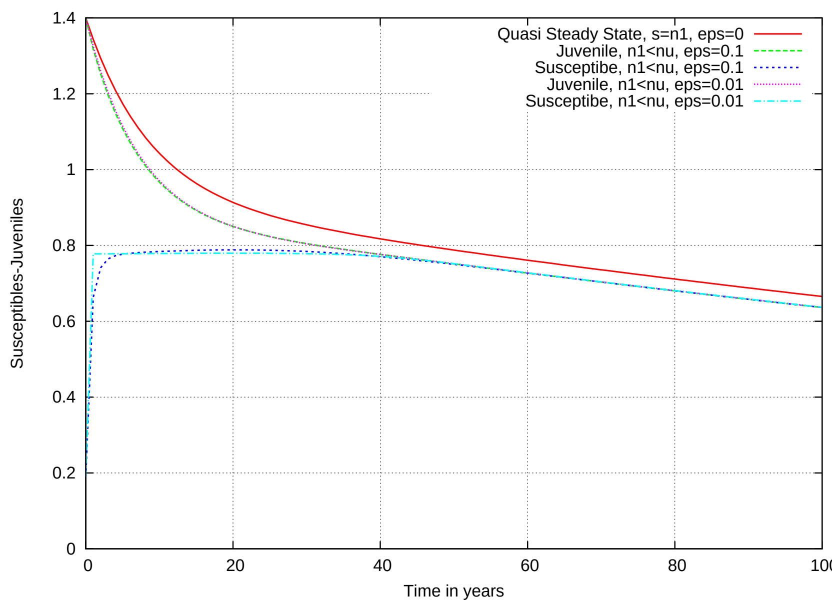

FIGURE 8. The susceptibles' curves s_ϵ first follow the quasi steady state $\bar{s} = \nu$ as long as it is attracting and then, having passed to the basin of attraction of $\bar{s} = \bar{n}_1$, follows the new attracting quasi steady state.

(5): Here we consider unstable $\{e^{t\mathcal{A}}\}_{t\geq 0}$ with small data. The calculations are performed for $\mu_1 = 0.043, \mu_2 = 0.029, a_1 = 0.05, b = 0.057$, $\mu_1^* = 0.046, \gamma = 0.14, \lambda = 0.18, \epsilon = 0.1, 0.01, 0.001$ and $\overset{\circ}{s} = 0.7, \overset{\circ}{n}_1 = 0.76, \overset{\circ}{n}_2 = 1.27$. See Fig. 9.

7. **Conclusions.** The main objective of the presented paper is to show how the Tikhonov theorem can be used to simplify some classes of epidemiological models

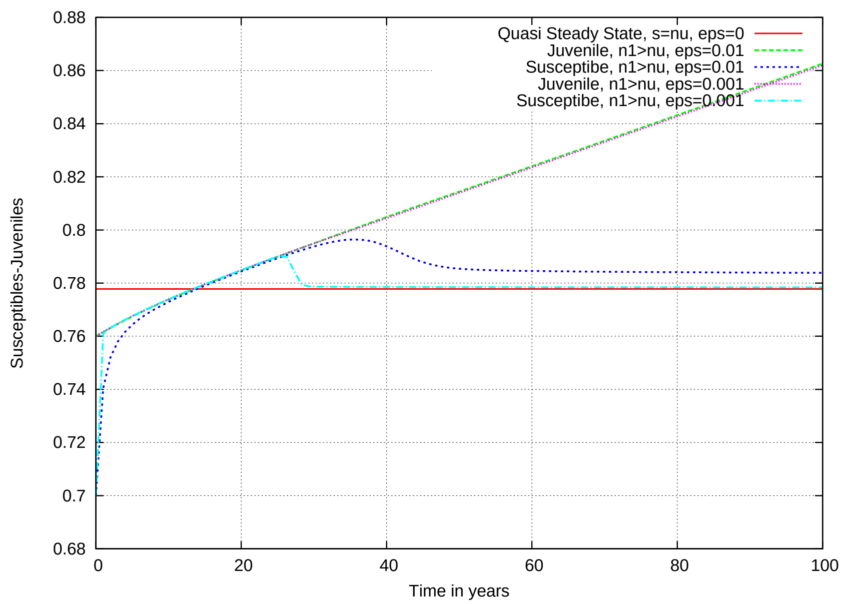

FIGURE 9. The susceptibles' curves s_ϵ first follow the quasi steady state $\bar{n}_1$ as long as it is attracting and then, having passed to the basin of attraction of the quasi steady state $\bar{s} = \nu$, eventually follows it. Note, however, that for some time s_ϵ follows the now repelling state $\bar{s} = \bar{n}_1$.

with age structure, by exploiting different time scales appearing in the model. The discussed model was simple enough so as to allow for explicit calculations but, at the same time, required some care in the analysis due to the fact that the quasi steady states were not isolated.

Let us summarize the analytical results. We have proved that if the original population is stable and both initial conditions are not too large then, for short lasting diseases, the total population behaves, on time intervals of an arbitrary length, as if there was no disease at all. On the other hand, if the population is expanding, then even if the disease has a very quick turnover, its trace is present in the long time dynamics of the population. In other words, in the latter case the juvenile population directly depends on the equilibrium value of the disease and the number of susceptibles stays close to this value over arbitrary long time intervals. While the model seems to be too simplified to allow for real epidemiological data supporting these observations, they are consistent with the properties of the classical SIS model. Indeed, as we observed in Subsection 3.1, the long time behaviour of its solutions is solely determined by the initial size N_0 of the population. Here we also must take into account that the adult population contributes to the juveniles so we must keep the former also small (resp. large) enough in the stable (resp. unstable) case so that it will not overshoot the threshold by moving the system into the other regime.

Even such a simplified model presents a number of analytical challenges. We do not have a complete theory of the cases demonstrated on Figures 8 and 9, that is, when the solution originates at a large populations in the stable case (24) or from a small population in the unstable case (28). In both cases the difficulty is that the solutions pass close to the intersection of the quasi steady states. These make them similar to the so-called canard solutions, see [12], but it is not clear whether the latter theory can be applied here, see the forthcoming paper [3]. Another subject of the current research is to make the models more realistic by, for instance, including the adults' infections with age specific infection rates and to approach the problem from the epidemiological point of view, that is, to apply the theory to a real well researched disease so that all theoretical results could be tested against the observational data.

8. **Appendix – the assumptions of the Tikhonov theorem.** Here we list and discuss the assumptions of the theory which play essential role in its applications. The first assumption is the standard requirement of the regularity of the right hand side of the system

$$\begin{aligned} \mathbf{x}' &= \mathbf{f}(t,\mathbf{x},\mathbf{y},\epsilon)\,, \qquad \mathbf{x}(0) = \mathring{\mathbf{x}}\,,\\ \varepsilon\mathbf{y}' &= \mathbf{g}(t,\mathbf{x},\mathbf{y},\epsilon)\,, \qquad \mathbf{y}(0) = \mathring{\mathbf{y}}\,, \end{aligned} \tag{36}$$

to ensure its unique solvability and continuous dependence of its solutions on the parameter ϵ. Precisely, assume that there are: a bounded open set $\mathcal{U} \subset \mathbb{R}^n$, an open set $\mathcal{V} \subset \mathbb{R}^m$ and scalars $T > 0, \epsilon_0 > 0$ such that the conditions listed in Assumptions $1 - 5$ are satisfied.

Assumption 1. *The functions* $\mathbf{f}$, $\mathbf{g}$*:*

$$\begin{aligned} \mathbf{f} &: \quad [0,T]\times\bar{\mathcal{U}}\times\mathcal{V}\times[0,\epsilon_0] \longmapsto \mathbb{R}^n\,,\\ \mathbf{g} &: \quad [0,T]\times\bar{\mathcal{U}}\times\mathcal{V}\times[0,\epsilon_0] \longmapsto \mathbb{R}^m\,, \end{aligned}$$

are continuous and satisfy the Lipschitz condition with respect to the variables $\mathbf{x}, \mathbf{y}, \epsilon$*, uniformly in* $t \in [0,T]$.

For the degenerate system, obtained from (36) by setting $\epsilon = 0$,

$$\begin{aligned} \mathbf{x}' &= \mathbf{f}(t,\mathbf{x},\mathbf{y},0), \qquad \mathbf{x}(0) = \mathring{\mathbf{x}}\,,\\ 0 &= \mathbf{g}(t,\mathbf{x},\mathbf{y},0), \end{aligned} \tag{37}$$

the following assumption is satisfied.

Assumption 2. *For any* $(t,x) \in [0,T]\times\bar{\mathcal{U}}$ *there exists a unique solution* $\mathbf{y}(t) = \phi(t,\mathbf{x}) \in \mathcal{V}$ *of the second equation of (37) which satisfies*

$$\phi \in C^0\big([0,T]\times\bar{\mathcal{U}}\,;\,\mathcal{V}\big)$$

and it is isolated in $[0,T]\times\bar{\mathcal{U}}$*, that is, there exists* $\delta > 0$ *such that*

$$\mathbf{g}(t,\mathbf{x},\mathbf{y},0) \neq 0\,, \qquad \text{for} \quad 0 < |\mathbf{y}-\phi(t,\mathbf{x})| < \delta\,, \qquad (t,\mathbf{x}) \in [0,T]\times\bar{\mathcal{U}}\,.$$

Consider the following auxiliary equation

$$\frac{d\,\tilde{\mathbf{y}}}{d\,\tau} = g(t,\mathbf{x},\tilde{\mathbf{y}},0)\,, \tag{38}$$

where t and $\mathbf{x}$ are treated as parameters.

Assumption 3. *Assume that the solution* $\tilde{\mathbf{y}}_0 := \phi(t,\mathbf{x})$ *of Eq. (38) is an asymptotically stable equilibrium, uniformly with respect to* $(t,\mathbf{x}) \in [0,T]\times\bar{\mathcal{U}}$*, that is, for any* $\eta > 0$ *there exists* $\delta > 0$ *such that for all* $(t,\mathbf{x}) \in [0,T]\times\bar{\mathcal{U}}$

$$|\tilde{\mathbf{y}}(0) - \phi(t,\mathbf{x})| < \delta \quad \Longrightarrow \quad \begin{cases} \forall\, \tau > 0 \ |\tilde{y}(\tau,t,\mathbf{x}) - \phi(t,\mathbf{x})| < \eta \quad \text{and} \\ \lim\limits_{\tau\to\infty} \tilde{\mathbf{y}}(\tau,t,\mathbf{x}) = \phi(t,\mathbf{x}), \end{cases} \tag{39}$$

where the convergence above is uniform for $(t,\mathbf{x}) \in [0,T]\times\bar{\mathcal{U}}$.

Remark 1. The original formulation by Tikhonov was incorrect as he assumed only asymptotic stability whereas his proof relied on the uniform (with respect to $(t,\mathbf{x})$) asymptotic stability. This point was clarified by Hoppensteadt [10]. Note, however, that the versions of the Tikhonov theory in [24, 25] are correct.

Remark 2. We observe that Assumption 3 is satisfied if the eigenvalues of the linearization of (38) at $\tilde{\mathbf{y}}_0 = \phi(t,\mathbf{x})$ all have real parts negative uniformly in $(t,\mathbf{x}) \in [0,T]\times\bar{\mathcal{U}}$.

Next, consider the following problem for the reduced equation

$$\dot{\bar{\mathbf{x}}} = f(t,\bar{\mathbf{x}},\phi(t,\bar{\mathbf{x}}),0)\,, \qquad \bar{\mathbf{x}}(0) = \mathring{\mathbf{x}}. \tag{40}$$

Assumption 4. *Assume that the function* $(t,\mathbf{x}) \mapsto f(t,\mathbf{x},\phi(t,\mathbf{x}),0)$ *satisfies the Lipschitz condition with respect to* $\mathbf{x}$ *in* $[0,T]\times\bar{\mathcal{U}}$ *and that the unique solution* $\bar{\mathbf{x}} = \bar{\mathbf{x}}(t)$ *of Eq. (40) on* $[0,T]$ *satisfies*

$$\bar{\mathbf{x}}(t) \in \operatorname{Int}\bar{\mathcal{U}} \qquad \forall\, t \in]0,T[\,.$$

Finally consider the Cauchy problem for the initial layer equation

$$\frac{d\hat{\mathbf{y}}}{d\tau} = \mathbf{g}(0,\mathring{\mathbf{x}},\hat{\mathbf{y}},0)\,, \qquad \hat{\mathbf{y}}(0) = \mathring{\mathbf{y}}. \tag{41}$$

Assumption 5. *Let* $\mathring{\mathbf{y}}$ *belong to the region of attraction of the solution* $\mathbf{y} = \phi(0,\mathring{\mathbf{x}})$ *of equation* $\mathbf{g}(0,\mathring{\mathbf{x}},\mathbf{y},0) = 0$*, that is, the solution* $\hat{\mathbf{y}} = \hat{\mathbf{y}}(\tau)$ *of Eq. (41) satisfies*

$$\lim_{\tau\to\infty} \hat{\mathbf{y}}(\tau) = \phi(0,\mathring{\mathbf{x}})\,,$$

and $\hat{\mathbf{y}}(\tau) \in \mathcal{V}$ *for all* $\tau \geq 0$.

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