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Using singular perturbations to reduce an epidemiological model: application to Bovine Viral Diarrhoea Virus within-herd spread.

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Abstract

Studying the spread of a pathogen in a managed metapopulation such as cattle herds in a geographical region often requires to take into account both the within- and between-herd transmission dynamics. This can lead to high-dimensional metapopulation systems resulting from the coupling of several within-herd transmission models. To tackle this problem, we aim in this

paper at reducing the dimension of a tractable but realistic dynamical system reproducing the within-herd spread. The context chosen to illustrate our purpose is Bovine Viral Diarrhoea Virus (BVDV) transmission in a cattle herd structured in two age classes and several epidemiological states, including two infectious states (transiently and persistently infected). Different time scales, corresponding to the epidemiological and demographic processes, are identified which allow to build a reduced model. Singular perturbation technique is used to prove that, under some non-restrictive conditions on parameter values, the behaviour of the original system is quite accurately approximated by that of the reduced system. Simulations are also performed to corroborate the approximation quality. Our study illustrates the methodological interest of using singular perturbations to reduce model complexity. It also rigorously proves the biologically intuitive assumption that transiently infected individuals can be neglected in a homogeneous population, when capturing the global dynamics of BVDV spread.

Key words: perturbation methods, time scales, model reduction, dynamical system, BVDV

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1 Introduction

Theoretical studies on population dynamics most often involve relatively complex models, due to the intrinsic complexity of the phenomena that are captured (biological, demographic, etc.), to their interactions, and to the state dimension. Such is the case when studying the spread of a pathogen at a regional scale in a managed metapopulation such as cattle herds, which often requires to take into account the within-herd transmission dynamics, as well as the between-herd dynamics within the region of interest. Management induces an heterogeneous contact structure which needs to be taken into account for moderately propagating pathogens. This can lead to high-dimensional metapopulation systems resulting from the coupling of several similar local within-herd transmission models. An appropriate approach to tackle this problem is to reduce the dimension of an epidemiological model designed to study the spread of a disease in a managed herd.

A possible solution for reducing the complexity consists in taking advantage of the presence of several time scales in the system. Indeed, events can intrinsically occur at different velocities which allows, **under stability assumptions on the fast dynamics (see Khalil (1996) and appendix B)**, to neglect rapid events and therefore to build a lower-dimensional model, that can be handled analytically and that is governed by the dynamics of the slow events. Several mathematical methods allowing such system reduction, as aggregation of variables and singular perturbation, have been developed. These methods were used in biological fields, mainly in ecology (Lenbury, 1996; Lett et al., 2003), but also in epidemic modelling (González-Guzmán and Naulin, 1994; Song et al., 2002). From the methodological point of view, the aggregation

of variables, perfect or approximate (Iwasa et al., 1987, 1989) are by far the most frequently used. The method, revised in Auger and Bravo de la Parra (2000), was first applied in the frame of ordinary differential equations (Auger and Roussarie, 1994; Auger and Poggiale, 1998) and then derived for partial differential equations (Auger and Roussarie, 1994; Bravo de la Parra et al., 2000), discrete dynamical systems (Bravo de la Parra et al., 1995; Sanz and Bravo de la Parra, 1999) or for stochastic frameworks (Sanz et al., 2003; Sanz and Bravo de la Parra, 2007). Several papers, studying dynamics of structured population models, have used the singular perturbation method (Arino et al., 1999; Song et al., 2002).

In this paper, we are interested in reducing the order of an epidemiological model designed to study the spread of a disease in a managed herd. We aim at using the dimensionally reduced form of the model for further studies in a metapopulation context. A reduced-order model is easier to manipulate and control and can therefore be coupled with other similar local models for studying the propagation at the between-herd scale. In order to achieve a trade-off between complexity and tractability, we chose to adapt a generic epidemiological model to a concrete situation: Bovine Viral Diarrhoea Virus (BVDV) epizootic dynamics within a managed herd through a simplified but realistic model.

BVDV virus is a pestivirus which does not survive in the environment. Hence, horizontal transmission mainly occurs by direct contacts with infected animals. It leads to transiently infected animals excreting low amounts of virus during a couple of weeks (Baker, 1987) before becoming immune. No clear and specific clinical signs are usually observed. However, if infection occurs during early or

mid-pregnancy, it frequently generates embryonic and foetal deaths. For cows infected during mid-pregnancy that do not abort, vertical transmission is highly probable. These cows give birth to Persistently Infected (PI) calves (Hartley and Richards, 1988; Fray et al., 2000). PI animals excrete the virus during their whole life in a greater amount than transiently infected animals (Baker, 1987). PI dams always give birth to PI calves. PI animals have a higher lethality, with a half-life of one year (Houe, 1993). Consequently, the disease induces high economic losses, which is why several European countries are implementing control plans (Lindberg et al., 2006).

To model BVDV within-herd spread, a classical non structured SIR models (Susceptible / Infected / Recovered) is not adequate. Both vertical and horizontal transmissions should be considered as they lead to very different consequences. Transiently infected and PI animals cannot be regrouped in a single infectious status because their infectiousness and infection duration are drastically different. Hence, this herd structure should be considered when modelling BVDV spread. To date, several models have been developed to represent the spread of BVDV in a cattle herd; a review can be found in Viet et al. (2007). They generally aim at studying the effect of control measures and assessing efficiency. These models are usually complex models which integrate detailed herd dynamics and include most of current biological knowledge on BVDV transmission. Most often, this complexity renders their rigorous mathematical analysis impossible. Moreover, the metapopulation model generated by coupling several such models to study the between-herd transmission

at a regional scale could be difficult to simulate. The model that we propose here, whilst simpler than such complex high-dimensional models, still preserves the main characteristics of BVDV spread. It takes into account the heterogeneities in transmission that require the introduction of different disease statuses. It represents a compromise between realistic complexity and mathematical tractability.

The paper is organised as follows: in section 2, we first present the BVDV model, then we analyse its structural properties. Exploiting the different time scales in the system corresponding to different biological processes, reduced-order models are built using the singular perturbation approach (Khalil, 1996); we then check the accuracy of these time scale approximations by using appropriate theorems (section 3). In order to illustrate our analytical results, simulations are presented using realistic parameter values (section 4). Finally we discuss the methodology and the biological interpretation of our findings (section 5).

2 Epidemiological model

We present in this section a model describing BVDV dynamics in a cattle herd located in a region where the disease is endemic. Hence, neighbouring herds contribute to the herd contamination. Purchases however are considered to be safe, as we assume that tests are performed for each animal introduced in the herd.

The mathematical model is first presented. This model exhibits different time scales between the demographic and epidemiological

processes which are then outlined. Finally, we investigate the model equilibria.

2.1 Model description

The herd is structured in two age classes: **Class 1**, formed by juveniles (0–3 years), which are animals before breeding; and **Class 2** formed by adults (> 3 years of age). This population structure is motivated by herd management, outflows, reproduction and entries in the herd depending on age.

In age class i , animals are classified into mutually exclusive BVDV health statuses (Fig. 1): susceptible (S_i), transiently-infected (T_i), persistently-infected (P_i), recovered (i.e. immune; R_i). Recovered adults in age class 2 are actually divided into two statuses (M_2 and R_2), because an infection during pregnancy can lead to embryonic or foetal death or also to the birth of a PI calf. Hence, status M_2 has been added to enable representing such specific consequences that may occur in the year following the infection. Adults in status R_2 are recovered adults that have calved at least once since infection or animals that have been infected as juveniles (coming from R_1).

Since two infectious statuses are considered (transiently-infected, status T , and persistently-infected, status P), two specific infection rates (β_T and β_P respectively), independent of age are defined (Table 1). The force of infection in the herd – which drives the transition from the susceptible to the transiently-infected status – is assumed to be density-dependent. Animals from both age classes are assumed to be equally in contact (homogeneous mixing in the

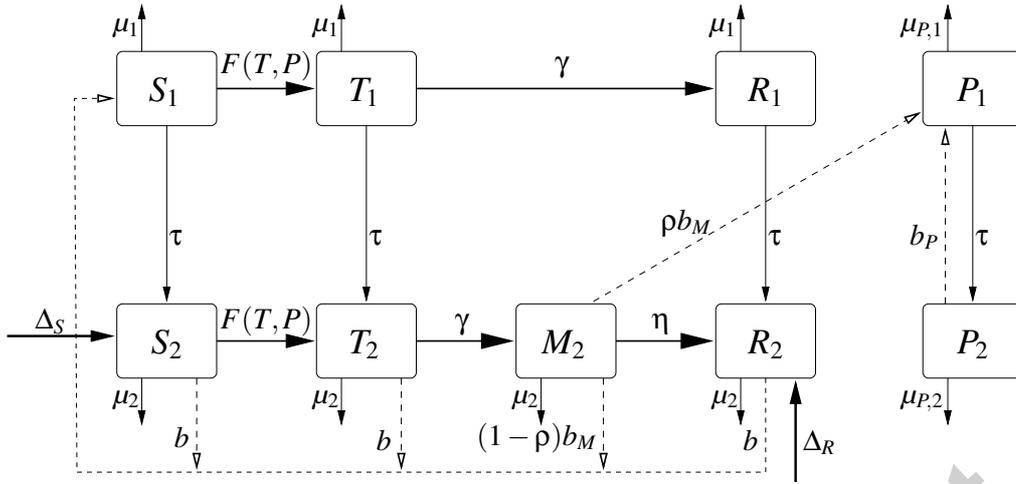


Fig. 1. Flow diagram of the epidemiological model representing BVDV health statuses per age classes and transitions between these states; in age class i , S_i : susceptible, T_i : transiently-infected, P_i : persistently-infected, R_i : recovered, M_2 : recovered but still pregnant since infection. Parameters are defined in Table 1 and the model equations are given by (1).

herd) and to have the same susceptibility to the disease. Hence, the force of infection will include $\beta_T T$ and $\beta_P P$ terms, with T the total number of transiently-infected animals ($T_1 + T_2$) and P the total number of persistently-infected animals ($P_1 + P_2$). We assume a constant additional infection rate β_v due to neighbouring contacts with infected animals of other herds. Thus, the force of infection is defined by $F(T, P) = \beta_T T + \beta_P P + \beta_v$.

After a transient infection, animals are assumed to recover with a recovery rate γ , independent of age. Recovered juveniles go to status R_1 . Recovered adults first go to status M_2 , and then to status R_2 with rate η (Table 1).

We assume that the infection has a strong impact on reproduction. Among adults in status M_2 , some have been infected during pregnancy and thus can

Table 1

Definition of the parameters used in the model.

Parameters	Interpretation	Dimension*
b	Natural birth rate	t^{-1}
b_P	Birth rate for PI infected individuals	t^{-1}
b_M	Birth rate for individuals infected during pregnancy	t^{-1}
μ_1, μ_2	Age-dependent mortality rate for non PI individuals	t^{-1}
μ_{P1}, μ_{P2}	Age-dependent mortality rate for PI individuals	t^{-1}
τ	Maturing rate	t^{-1}
Δ_S, Δ_R	Purchases of susceptible or resistant mature individuals	N/t
β_T	Infection rate due to transiently infected individuals	$(N.t)^{-1}$
β_P	Infection rate due to PI infected individuals	$(N.t)^{-1}$
β_v	External infection rate	t^{-1}
γ	Recovery rate	t^{-1}
ρ	Vertical transmission ratio	–
η	“ $M_2 \rightarrow R_2$ ” transfer rate	t^{-1}

* t =time, N =numbers

abort. Hence, the birth rate in status M_2 (b_M) is assumed to be reduced compared to the natural birth rate applied to other statuses ($b_S = b_T = b_R = b$). A specific birth rate is also considered for persistently-infected adults (status P_2 ; rate b_P) to account for a potential impact of the disease on the reproduction of PI animals. A systematic vertical transmission is considered for pregnant PI adults (status P_2). A partial vertical transmission is considered for pregnant adults in status M_2 , with rate ρ ; the remaining calves are born in status S_1 . Juveniles in all health statuses become adults with a maturing rate τ .

Outflows in such a managed population consist in natural mortality, culling and selling. The resulting global so-called mortality rate depends on age (μ_1 and μ_2 for juveniles and adults, respectively). These rates apply to all health statuses except status P . For status P , a disease-related mortality occurs in addition to these global mortality rates. Hence, a specific age-dependent mortality rate is defined (μ_{P_1} and μ_{P_2} for PI juveniles and PI adults, respectively).

Finally, adult animals can be purchased and introduced in the herd. Such inflows are assumed to be perfectly secure, considering automatic detection and rejection of animals able to spread the infection in the herd. As a result, no entry of infected animals (statuses T_2 or P_2) or of immune dams carrying a PI foetus (status M_2) is allowed. Hence, inflows only occur in statuses S_2 and R_2 , with constant entry flows Δ_S and Δ_R , respectively.

This leads to the following system of nine differential equations:

$$\left\{ \begin{array}{l} \dot{S}_1 = b(S_2 + T_2 + R_2) + (1 - \rho)b_M M_2 - (\tau + \mu_1)S_1 - F(T, P)S_1, \\ \dot{S}_2 = \Delta_S + \tau S_1 - \mu_2 S_2 - F(T, P)S_2, \\ \dot{T}_1 = -(\tau + \mu_1)T_1 - \gamma T_1 + F(T, P)S_1, \\ \dot{T}_2 = \tau T_1 - \mu_2 T_2 - \gamma T_2 + F(T, P)S_2, \\ \dot{P}_1 = b_P P_2 + \rho b_M M_2 - (\tau + \mu_{P_1})P_1, \\ \dot{P}_2 = \tau P_1 - \mu_{P_2} P_2, \\ \dot{R}_1 = -(\tau + \mu_1)R_1 + \gamma T_1, \\ \dot{M}_2 = \gamma T_2 - (\eta + \mu_2)M_2, \\ \dot{R}_2 = \Delta_R + \tau R_1 + \eta M_2 - \mu_2 R_2, \end{array} \right. \quad (1)$$

where: $T = T_1 + T_2$, $P = P_1 + P_2$, $F(T, P) = \beta_T T + \beta_P P + \beta_v$.

All parameters in this system are positive, as they represent positive quantities with biological meaning, and are summarised in Table 1.

We denote by $\mathbf{W} = (S_1, S_2, T_1, T_2, P_1, P_2, R_1, M_2, R_2)$ the state vector and by $\mathbf{W}(0)$ the initial condition. As these state variables represent population sizes, we set $\mathbf{W}(0) \geq 0$. The structure of the model then ensures that the state variables remain non negative in the course of time. Indeed, for system 1 the field is non negative along the boundaries of the non negative orthant. To prove this, let us consider that at time t , the i th element of the state vector $w_i(t) = 0$ and the other elements $w_{j \neq i} \geq 0$ ($i, j \in \{1, \dots, 9\}$). Straightforward computation shows that its derivative w_i , given by (1), is then also non negative. This ensures that w_i cannot become negative. So the non negative orthant is positively invariant.

2.2 Time scales

The transient infection and recovery processes occur at a time scale that is faster than the demography. In other words, the corresponding epidemiological parameters are greater than the demographic parameters. We hence introduce a scaling parameter ε such that:

$$\beta_T = \frac{\beta'_T}{\varepsilon}, \quad \beta_P = \frac{\beta'_P}{\varepsilon}, \quad \gamma = \frac{\gamma'}{\varepsilon}, \quad \text{with } 0 < \varepsilon \ll 1. \quad (2)$$

Considering some typical population size N_m , we assume that $N_m\beta'_T$, $N_m\beta'_P$ are parameters of the same order of magnitude as the remaining model parameters. The contamination by neighbouring herds or the local environment is assumed to be relatively small compared to the contamination generated by within-herd contacts with infected animals. Hence, β_v is smaller than the other epidemiological parameters and its order of magnitude is less than or equal to the order of magnitude of the demographic parameters. **We finally assume that γ' has at least the same order of magnitude as the demographic parameter. In this case, system 1 is a two time scale system.**

It is also reasonable to assume that individuals spend significantly more time in the susceptible state than in the transiently infected state, at least in moderately infected herds. It means that the recovery process runs faster than the infection process, in other words, that γ' has a greater order of magnitude than $N_m\beta'_T$, $N_m\beta'_P$, and the remaining model parameters. In that case, we introduce a second scaling parameter ε' such that:

$$\gamma = \frac{\gamma''}{\varepsilon'}, \quad \text{with } 0 < \varepsilon' < \varepsilon \ll 1. \quad (3)$$

We hence obtain a three time scale system.

All these assumptions on the order of magnitude of the parameters need to be verified on their numerical values to ensure relevant time scale separation in numerical simulations. This is done in section 4.

2.3 Equilibria

Epidemiological models usually exhibit at least two equilibria, the trivial equilibrium, which corresponds to an extinct population, and a disease-free equilibrium. There may also be an endemic steady point. As described below, our system has only one endemic steady state, provided that all parameters are positive.

In system (1), because of constant inflows corresponding to animal purchases, the population cannot become extinct and zero is not an equilibrium. Without these animal inflows (i.e. $\Delta_S = \Delta_R = 0$) though, zero would be an equilibrium.

Moreover, due to the external contamination term which acts like an infection reservoir, there is no disease-free equilibrium in system (1). In the absence of this infection source (i.e. $\beta_V = 0$), there would be such an equilibrium given by

$$\overline{W}^0 = (\overline{S}_1^0, \overline{S}_2^0, 0, 0, 0, 0, 0, 0, \overline{R}_2^0),$$

the non zero components of this vector being:

$$\overline{S}_1^0 = \frac{b(\Delta_R + \Delta_S)}{c_S}, \quad \overline{S}_2^0 = \frac{b\tau\Delta_R + \mu_2(\mu_1 + \tau)\Delta_S}{\mu_2 c_S}, \quad \overline{R}_2^0 = \frac{\Delta_R}{\mu_2},$$

provided that the following parameter condition holds:

$$c_S = (\mu_1 + \tau)\mu_2 - b\tau > 0. \quad (4)$$

This condition corresponds to the existence and the stability of the disease-free equilibrium and ensures that the population does not explode.

For a non trivial set of parameters, we show that system (1) admits a non negative endemic steady state given by:

$$\bar{W} = (\bar{S}_1, \bar{S}_2, \bar{T}_1, \bar{T}_2, \bar{P}_1, \bar{P}_2, \bar{R}_1, \bar{M}_2, \bar{R}_2), \quad \text{with } \bar{T} + \bar{P} > 0.$$

\bar{W} is a positive solution of $\dot{W} = 0$. After certain algebraic manipulations, we show that solving this non linear system amounts to finding a positive root of a third order polynomial in \bar{T}_1 (or \bar{T}_2 , both variables being quasi-symmetric), which has non analytically tractable formula. In order to circumvent this problem, we take advantage of the model time scales and use a second-order Taylor expansion of this polynomial around ε . For “small enough” values of ε and provided that (4) and the following condition **are** verified:

$$c_P = (\mu_{P_1} + \tau)\mu_{P_2} - b_P\tau > 0, \quad (5)$$

we can then deduce the existence of a positive equilibrium \bar{W} (see **appendix A**). Considering $\rho b_M M_2$ as an exogenous bounded input for the linear subsystem (P_1, P_2) , condition (5) can be interpreted as the stability requirement ensuring the non explosion of the permanently infected population.

This equilibrium is proved to be exponentially stable (Khalil, 1996) in section 3.1.

3 Model order reduction

Thanks to the different time scales that occur in system (1,2) and described in section 2.2, we can apply the singular perturbation theory to approximate this system by a lower-dimensional system. Theorems supporting our following analysis are given in appendix B.

3.1 Two time scales

With the following change of variables:

$$A_1 = S_1 + T_1 + R_1, \quad A_2 = S_2 + T_2 + M_2.$$

system (1,2) can be rewritten as:

$$\left\{ \begin{array}{l} \dot{A}_1 = b(A_2 - M_2 + R_2) + (1 - \rho)b_M M_2 - (\tau + \mu_1)A_1, \\ \dot{A}_2 = \Delta_S + \tau(A_1 - R_1) - \mu_2 A_2 - \eta M_2, \\ \dot{P}_1 = bP_2 + \rho b_M M_2 - (\tau + \mu_{P_1})P_1, \\ \dot{P}_2 = \tau P_1 - \mu_{P_2} P_2, \\ \dot{R}_2 = \Delta_R + \tau R_1 + \eta M_2 - \mu_2 R_2, \\ \varepsilon \dot{T}_1 = -\varepsilon(\tau + \mu_1)T_1 - \gamma' T_1 + \varepsilon F(T, P, \varepsilon)(A_1 - T_1 - R_1), \\ \varepsilon \dot{T}_2 = \varepsilon \tau T_1 - \varepsilon \mu_2 T_2 - \gamma' T_2 + \varepsilon F(T, P, \varepsilon)(A_2 - T_2 - M_2), \\ \varepsilon \dot{R}_1 = -\varepsilon(\tau + \mu_1)R_1 + \gamma' T_1, \\ \varepsilon \dot{M}_2 = \gamma' T_2 - \varepsilon(\eta + \mu_2)M_2, \end{array} \right. \quad (6)$$

where: $T = T_1 + T_2$, $P = P_1 + P_2$, $\varepsilon F(T, P, \varepsilon) = \beta'_T T + \beta'_P P + \varepsilon \beta_v$.

Setting $X = (A_1, A_2, P_1, P_2, R_2)$ and $Z = (T_1, T_2, R_1, M_2)$, this system takes the form of an autonomous singular perturbation model:

$$\dot{X} = f(X, Z, \varepsilon), \quad (7a)$$

$$\varepsilon \dot{Z} = g(X, Z, \varepsilon). \quad (7b)$$

Here X and Z are respectively called the slow and the fast variables.

The fast system (7b) has a unique non negative quasi steady state when $\varepsilon = 0$:

$$Z^* = (T_1^*, T_2^*, R_1^*, M_2^*) = h(X) = (0, 0, A_1, A_2). \quad (8)$$

By substituting this quasi steady state in the slow system (7a), we obtain the following linear reduced system:

$$\begin{cases} \dot{A}_1 = (1 - \rho)b_M A_2 + bR_2 - (\tau + \mu_1)A_1, \\ \dot{A}_2 = \Delta_S - (\eta + \mu_2)A_2, \\ \dot{P}_1 = \rho b_M A_2 + b_P P_2 - (\mu_{P_1} + \tau)P_1, \\ \dot{P}_2 = \tau P_1 - \mu_{P_2} P_2, \\ \dot{R}_2 = \Delta_R + \tau A_1 + \eta A_2 - \mu_2 R_2, \end{cases} \quad (9)$$

which is represented in Fig. 2.

If conditions (4-5) are verified, it allows a unique non negative steady state:

$$X^* = (A_1^*, A_2^*, P_1^*, P_2^*, R_2^*),$$

with:

$$\begin{cases} A_1^* = \frac{(1 - \rho)b_M}{\mu_1 + \tau} A_2^* + \frac{b}{\mu_1 + \tau} R_2^*, & P_1^* = \frac{\Delta_S \rho b_M \mu_{P_2}}{(\mu_2 + \eta)c_P}, \\ A_2^* = \frac{\Delta_S}{\mu_2 + \eta}, & P_2^* = \frac{\Delta_S \rho b_M \tau}{(\mu_2 + \eta)c_P}, \\ R_2^* = \frac{\mu_1 + \tau}{c_S} \left(\Delta_R + \frac{\Delta_S}{\mu_2 + \eta} \left(\eta + \frac{(1 - \rho)b_M \tau}{\mu_1 + \tau} \right) \right). \end{cases}$$

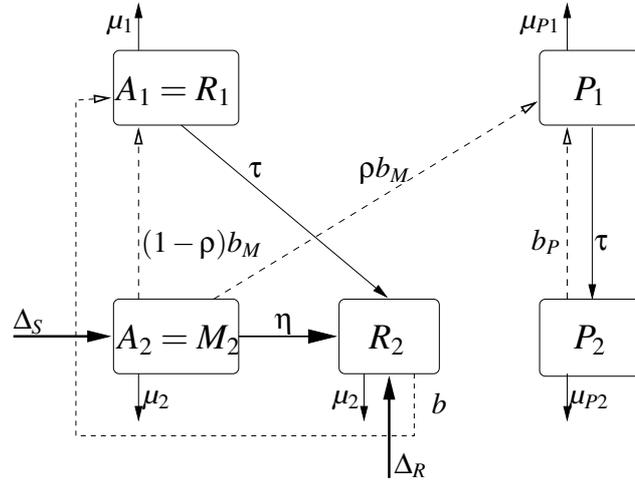


Fig. 2. Flow diagram of the reduced model given by equations (9), representing infection states per age classes and transitions between these states; recovered juveniles: $A_1 = S_1 + T_1 + R_1 = R_1$, recovered adults still in pregnancy since infection: $A_2 = S_2 + T_2 + M_2 = M_2$, recovered adults: R_2 , persistently-infected juveniles and adults R_1, R_2 . Parameters are defined in Table 1.

After certain algebraic manipulations, we obtain the characteristic polynomial of the Jacobian matrix of system (9) in X^* :

$$\chi(\lambda) = -(\lambda + \mu_1 + \tau) \left[\lambda^2 + (\mu_1 + \mu_2 + \tau)\lambda + c_S \right] \left[\lambda^2 + (\mu_{P1} + \mu_{P2} + \tau)\lambda + c_P \right].$$

Since c_S and c_P are positive, $-\chi$ is a product of first and second order polynomials, with real positive coefficients. According to the Routh–Hurwitz criterion, its roots, corresponding to the eigenvalues of system (9), are negative. As the reduced system is linear, X^* is hence globally exponentially stable.

The boundary layer system verified by

$$y = (t_1, t_2, r_1, r_2) = Z - h(X) = (T_1, T_2, R_1 - A_1, M_2 - A_2)$$

with $dt = \varepsilon d\nu$ is:

$$\begin{cases} \frac{dt_1}{d\nu} = -\gamma' t_1 - (\beta'_T(t_1 + t_2) + \beta'_P P)(t_1 + r_1), \\ \frac{dt_2}{d\nu} = -\gamma' t_2 - (\beta'_T(t_1 + t_2) + \beta'_P P)(t_2 + m_2), \\ \frac{dr_1}{d\nu} = \gamma' t_1, \\ \frac{dr_2}{d\nu} = \gamma' t_2. \end{cases} \quad (10)$$

From the model structure, we deduce that t_i ($i = 1, 2$) remain non negative and that $(t_i + r_i)$ ($i = 1, 2$) remain non positive. Hence, integrating and bounding $\frac{d(t_i+r_i)}{d\nu}$, we obtain:

$$|(t_i(\nu) + r_i(\nu))| \leq |(t_i(0) + r_i(0))| e^{-\beta_P P \nu}. \quad (11)$$

The last two equations of system (10) lead to:

$$\frac{dv_i}{d\nu} = e^{\gamma' \nu} \left(\frac{dr_i}{d\nu} + \gamma' r_i \right) = \gamma' e^{\gamma' \nu} (t_i + r_i), \quad \text{with } v_i = e^{\gamma' \nu} r_i.$$

Integrating and bounding this equation using (11), we obtain:

$$\begin{aligned} r_i(\nu) &= r_i(0) e^{-\gamma' \nu} + \gamma' e^{-\gamma' \nu} \int_0^\nu e^{\gamma' \xi} (t_i + r_i) d\xi, \\ |r_i(\nu)| &\leq |r_i(0)| e^{-\gamma' \nu} + |t_i(0) + r_i(0)| \frac{\gamma'}{\gamma' - \beta'_P P} (e^{-\beta'_P P \nu} - e^{-\gamma' \nu}). \end{aligned}$$

So the zero equilibrium of the boundary layer system (10) is globally exponentially stable.

Moreover f, g, h , the Jacobian of the reduced model (9) and $\partial g(X, Z, 0)/\partial Z$ are smooth functions. Hence, by applying theorems 1 and 2 given in appendix B, we conclude that when ε is ‘‘small enough’’:

- **(from theorem 1)** the reduced model is a good approximation of the original system (1), with $Z = Z^* = h(X)$ given by (8);

- (from theorem 2) the endemic steady state of system (1), obtained when conditions (4-5) are verified, is globally exponentially stable.

3.2 Three time scales

In order to reduce the three time scale system (1,3), we will proceed in two steps.

- (1) First, we choose the time scale of recovery as fast scale, and we pool demography and infection time scales into the slow time scale, applying the singular perturbation theory in the same way as in the previous section.
- (2) In a second step, we consider the reduced system obtained in step 1 as the new original system.

As in previous section, we need a change of variables to rewrite the original system in the singular perturbation form. Taking as new variables

$$A_1 = S_1 + T_1 + R_1, \quad A_2 = S_2 + T_2 + M_2, \quad G_1 = T_1 + R_1, \quad G_2 = T_2 + M_2.$$

system (1,3) becomes:

$$\left\{ \begin{array}{l} \dot{A}_1 = b(A_2 - M_2 + R_2) + (1 - \rho)b_M M_2 - (\tau + \mu_1)A_1, \\ \dot{A}_2 = \Delta_S + \tau(A_1 - R_1) - \mu_2 A_2 - \eta M_2, \\ \dot{P}_1 = bP_2 + \rho b_M M_2 - (\tau + \mu_{P_1})P_1, \\ \dot{P}_2 = \tau P_1 - \mu_{P_2} P_2, \\ \dot{R}_2 = \Delta_R + \tau R_1 + \eta M_2 - \mu_2 R_2, \\ \dot{G}_1 = -(\tau + \mu_1)G_1 + F(G, P, \varepsilon)(A_1 - G_1), \\ \dot{G}_2 = \tau(G_1 - R_1) - \mu_2 G_2 - \eta M_2 + \varepsilon F(G, P, \varepsilon)(A_2 - G_2), \\ \varepsilon' \dot{R}_1 = -\varepsilon'(\tau + \mu_1)R_1 + \gamma''(G_1 - R_1), \\ \varepsilon' \dot{M}_2 = \gamma''(G_2 - M_2) - \varepsilon'(\eta + \mu_2)M_2, \end{array} \right. \quad (12)$$

where: $G = G_1 + G_2$, $P = P_1 + P_2$,

$$\varepsilon F(G, P, \varepsilon) = \beta'_T(G - (R_1 + M_2)) + \beta'_P P + \varepsilon \beta_v.$$

We obtain respectively slow and fast variables:

$$X = (A_1, A_2, P_1, P_2, R_2, G_1, G_2) \text{ and } Z = (R_1, M_2).$$

The fast system of (12) has a unique non negative quasi steady state when

$\varepsilon' = 0$:

$$\tilde{Z} = (\tilde{R}_1, \tilde{M}_2) = h(X) = (G_1, G_2). \quad (13)$$

Substituting this quasi steady state in the slow system, we obtain the following semi-reduced system:

$$\left\{ \begin{array}{l} \dot{A}_1 = b(A_2 + R_2) + ((1 - \rho)b_M - b)G_2 - (\tau + \mu_1)A_1, \\ \dot{A}_2 = \Delta_S + \tau(A_1 - G_1) - \mu_2A_2 - \eta G_2, \\ \dot{P}_1 = bP_2 + \rho b_M G_2 - (\tau + \mu_{P_1})P_1, \\ \dot{P}_2 = \tau P_1 - \mu_{P_2}P_2, \\ \dot{R}_2 = \Delta_R + \tau G_1 + \eta G_2 - \mu_2 R_2, \\ \dot{G}_1 = -(\tau + \mu_1)G_1 + \left(\frac{\beta'_P}{\varepsilon} P + \beta_v \right) (A_1 - G_1), \\ \dot{G}_2 = -(\mu_2 + \eta)G_2 + \left(\frac{\beta'_P}{\varepsilon} P + \beta_v \right) (A_2 - G_2). \end{array} \right. \quad (14)$$

If conditions (4-5) are verified, and for ε sufficiently small, semi-reduced system (14) has a unique non negative steady state \tilde{X} (see appendix A for details).

$$\tilde{X} = (\tilde{A}_1, \tilde{A}_2, \tilde{P}_1, \tilde{P}_2, \tilde{R}_2, \tilde{G}_1, \tilde{G}_2).$$

Let us consider system (14) as our new original system, which is already in singular perturbation form with $\mathbf{X} = (A_1, A_2, P_1, P_2, R_2)$ and $\mathbf{Z} = (G_1, G_2)$ as fast and slow variables. The fast system of (14) has a unique non negative quasi steady state when $\varepsilon = 0$ given by

$$\mathbf{Z}^* = (G_1^*, G_2^*) = \mathbf{h}(\mathbf{X}) = (A_1, A_2).$$

Substituting this quasi steady state in the slow part of system (14), we obtain system (9) as reduced system. We saw in section 3.1 that the steady state of (9) is exponentially stable. Setting $\mathbf{y} = (\mathbf{y}_1, \mathbf{y}_2) = \mathbf{Z} - h(\mathbf{X}) = (G_1 - A_1, G_2 - A_2)$

and $dt = \varepsilon d\nu$, we write the boundary layer system as:

$$\begin{cases} \frac{d\mathbf{y}_1}{d\nu} = -\beta'_P P\mathbf{y}_1, \\ \frac{d\mathbf{y}_2}{d\nu} = -\beta'_P P\mathbf{y}_2. \end{cases} \quad (15)$$

As system (15) is linear **with negative eigenvalues, it is exponentially stable**, uniformly in (t, \mathbf{X}) . By applying theorem 1, we conclude that, for ε “small enough”, the reduced system (9) is a good approximation of semi-reduced system (14). In addition, with the appropriate shift of the origin, hypotheses of theorem 2 are also verified. So we obtain the exponential stability of \tilde{X} for the semi-reduced system (14).

Let us now consider system (12) and its approximation given by semi-reduced system (14). The corresponding boundary layer system verified by:

$$y = (y_1, y_2) = Z - h(X) = (R_1 - G_1, M_2 - G_2)$$

with $dt = \varepsilon' d\nu$ is:

$$\begin{cases} \frac{dy_1}{d\nu} = -\gamma'' y_1, \\ \frac{dy_2}{d\nu} = -\gamma'' y_2. \end{cases} \quad (16)$$

As (16) is linear and independent of (t, X) , the origin is trivially exponentially stable uniformly in (t, X) . Hence, theorem 1 allows to conclude that, for ε' “small enough”, the reduced model (14) is a good approximation of the complete system (1,3).

Finally, as in previous section, we conclude that, for well chosen ε and ε' , the reduced model (9) is a good approximation of the complete system (1,3).

4 Simulations

Simulations were performed using the Scilab² standard ODE integration procedure. We used realistic parameters values which are summarised in Table 2. Most parameter values were taken from the literature. When such referenced values were not available, we considered reasonable assumptions as follows: we assume that infection has no effect on the fertility of PI animals, so we set $b_P = b$; β_v was adjusted in order to obtain prevalences in the herd consistent with observations in BVDV endemic regions. Numerical values provided in published studies are not always errorless since biological data are often incomplete or scarce and sometimes missing. From this point of view, we have in our model two kinds of parameters: (i) well known parameters, namely demographic parameters (b , τ , μ_1 and μ_2) and parameters related to purchases (Δ_S and Δ_R), which are typical for cattle herds; (ii) parameters which are less well characterised, such as transmission parameters and those modelling the disease epidemiology (β_T , β_P , ρ , γ , η) or its direct impact on animal health (μ_{P1} and μ_{P2}). For the second group of parameters, sensible values corresponding to average patterns (when several different values were available in the literature) were derived from Ezanno et al. (2007), where these values are supported by a sensitivity analysis. Since time is measured in years in our simulations, the parameter units were set accordingly.

² Scilab, a free scientific software for numerical computation: <http://www.scilab.org>

Table 2

Realistic parameter values used for the numerical simulations (unit); parameter definitions are given in Table 1.

Demography	b, b_P	b_M^1	μ_1	μ_2	$\mu_{P_1}^2$	$\mu_{P_2}^2$	τ	η
(year ⁻¹)	0.6	0.5	0.7	0.25	1.4	1	0.3	1
Purchases	Δ_S^3	Δ_R^3						
(number.year ⁻¹)	4	4						
Epidemiology	β_T^4	β_P^5	β_v	γ^5	ρ^6			
	6×10^{-2}	1	4×10^{-2}	24	0.4			
	(number.year) ⁻¹		(year ⁻¹)		(no dimension)			

¹ in Hartley and Richards (1988); Fray et al. (2000).

² in Baker (1987); Houe (1993).

³ in Ezanno et al. (2006).

⁴ in Baker (1987); Brownlie et al. (1987); Houe (1999).

⁵ in Baker (1987); Houe (1999).

⁶ in Mc Clurkin et al. (1984); Fray et al. (2000)

For these parameter values, existence conditions (4,5) are fulfilled so there is an endemic steady state. Numerical computation of this equilibrium state for

the complete system leads to the following values:

$$\begin{aligned}\overline{S}_1 &= 25.5, & \overline{S}_2 &= 7, & \overline{P}_1 &= 1, & \overline{P}_2 &= 0.3, & \overline{R}_2 &= 96, \\ \overline{T}_1 &= 1.5, & \overline{T}_2 &= 0.5, & \overline{R}_1 &= 35, & \overline{M}_2 &= 8.5, \\ (\overline{A}_1 &= 62, & \overline{A}_2 &= 16, & \overline{G}_1 &= 36.5, & \overline{G}_2 &= 9).\end{aligned}\tag{17}$$

All simulations are performed using the following initial state expressed in numbers:

$$\mathbf{W}(0) = (65, 110, 1, 0, 0, 0, 0, 0, 0).\tag{18}$$

4.1 Two time scale simulations

4.1.1 Academic example

In this section, we aim at investigating the time scale separation properties of system (6), or equivalently of system (1,2). All parameters values are taken from Table 2 except for the infection and recovery rates, $\beta_P = \frac{\beta'_P}{\varepsilon}$, $\beta_T = \frac{\beta'_T}{\varepsilon}$, $\gamma = \frac{\gamma'}{\varepsilon}$. They are chosen such that $N_T\beta'_T$, $N_P\beta'_P$, and γ' have the same order of magnitude as the remaining parameters, where N_T and N_P are typical population sizes for the transiently and persistently infected animals respectively. Equilibrium state (17) gives an indication about these typical sizes. $\beta'_P = 0.5$, $\beta'_T = 0.1$, and $\gamma' = 1$ are adequate values.

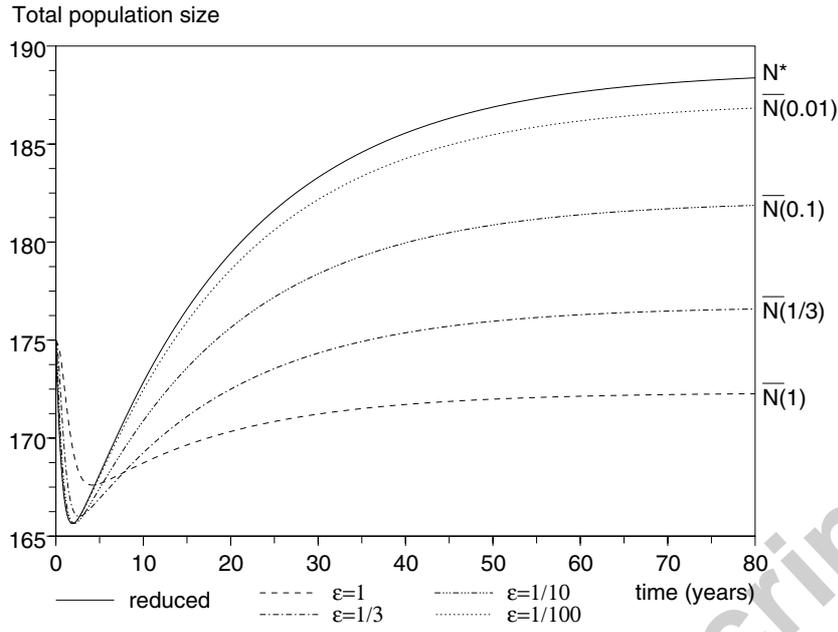
In order to illustrate the effect of time scale separation, we simulate and compare reduced system (9) with complete system (6) using different values of ε ($\varepsilon \in \{1, 1/3, 1/10, 1/100\}$). To compare those systems, subscript r is used for the variables corresponding to the reduced system plus the quasi steady state;

for example $W_r = (X_r, Z^*)$, where X_r is the solution of (9) and Z^* is given by (8). Let us also note $W^* = (X^*, Z^*)$. In the simulations, centred variables are represented. They are obtained by shifting the original variables of their equilibrium values, i.e. $W - \overline{W}(\varepsilon)$ for the complete model and $W_r - W^*$ for the reduced model.

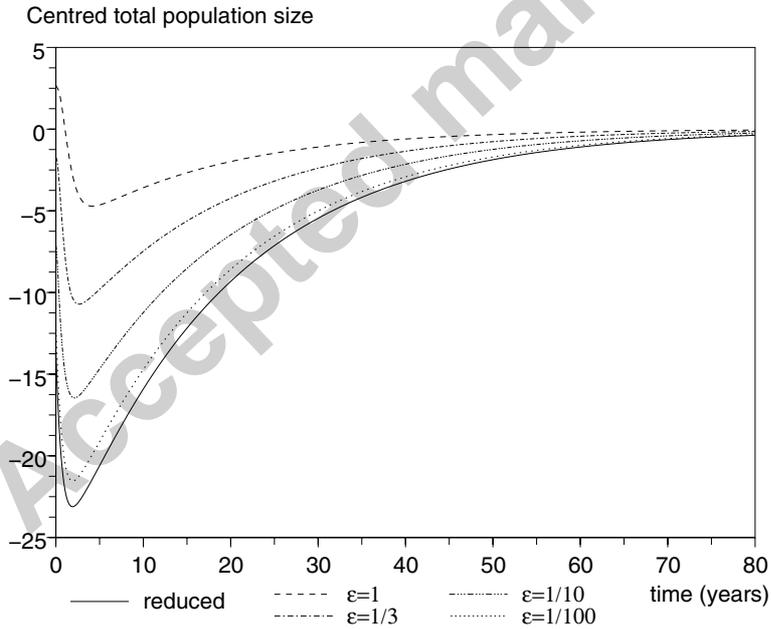
Fig. 3 represents the total population size obtained over a 80-year period. We note a static error between the complete and reduced systems in Fig. 3(a), which decreases as ε diminishes: from 16 individuals for $\varepsilon = 1$ to less than 2 individuals for $\varepsilon = 1/100$. This error is due to the ε -dependency of the complete system steady state $\overline{W}(\varepsilon)$. The equilibrium of the reduced model W^* corresponds to $\varepsilon = 0$. To bypass this static error effect we look at the centred variables in Fig. 3(b), which all tend towards zero. However, we notice that the transient dynamics approximation is then deteriorated.

Fig. 4 represents the centred infected population size, consisting of all transiently and persistently infected individuals, over a 4-year period. At the beginning of the simulations, a transient error appears between the complete and reduced systems, because of the neglected fast dynamics. It lasts longer for higher values of ε : up to 3 years for $\varepsilon = 1$, but less than 6 months for $\varepsilon = 1/10$ and barely noticeable for $\varepsilon = 1/100$. From these simulations, we deduce that with $\varepsilon = 1/10$, we obtain a decent approximation of the complete system by the reduced system in the transient phase.

Consequently, to approximate the original system (1), we use a “shifted” reduced system to compensate for the static error; “shifted” variables correspond to centred variables with an additional ε -dependent offset corresponding to the equilibrium of the original system: $W_r - W^* + \overline{W}(\varepsilon)$. With ε values lower



(a) Non centred



(b) Centred

Fig. 3. Total population size as a function of time for the complete system (6) for $\varepsilon \in \{1, 1/3, 1/10, 1/100\}$ and the reduced system (9). The centred graphs correspond to the total population size $N = A_1 + A_2 + P_1 + P_2 + R_2$ shifted of its equilibrium value, i.e. $N - \bar{N}(\varepsilon)$ for the complete system and $N_r - N^*$ for the reduced system. $\beta'_P = 0.5$, $\beta'_T = 0.1$, and $\gamma' = 1$; the remaining parameters are given in Table 2.

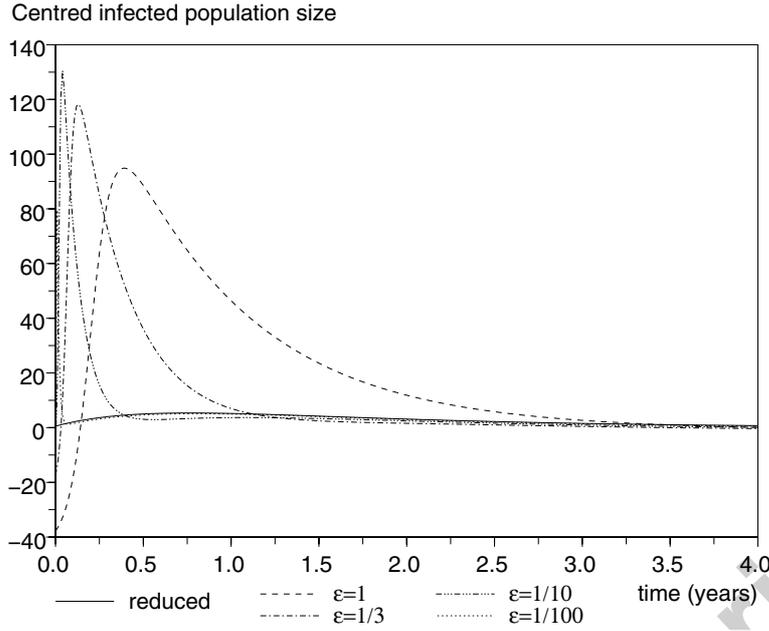


Fig. 4. Centred infected population size as a function of time for the complete system (6) for $\varepsilon \in \{1, 1/3, 1/10, 1/100\}$ and the reduced system (9). The graphs correspond to the infected population size $I = T_1 + T_2 + P_1 + P_2$ shifted of its equilibrium value, i.e. $I - \bar{I}(\varepsilon)$ for the complete system and $I_r - I^*$ for the reduced system. $\beta'_P = 0.5$, $\beta'_T = 0.1$, and $\gamma' = 1$; the remaining parameters are given in Table 2.

than $1/10$, we hence obtain a satisfying trade-off between the asymptotic and transient dynamics for the approximation.

4.1.2 Biological example

We use here the set of biologically relevant values given in Table 2. **According to the academic example shown above, with a time scale separation corresponding to $\varepsilon \leq 1/10$, the reduced model is a decent approximation of the complete system. We therefore set $\varepsilon = 1/10$ and check if the assumptions on the order of magnitude of the parameters are fulfilled (see section 2.2).**

From the endemic equilibrium values shown in (17), $N_P \simeq 1$ and $N_T \simeq 2$ are typical population sizes for the persistently and transiently infected animals respectively. Hence $\beta'_T N_T$, $\beta'_P N_P$ and γ' should at least have the same order of magnitude as the remaining parameters.

With $\varepsilon = 1/10$, we obtain the following values for the infection and recovery rates: $\beta'_T = 6 \times 10^{-3}$, $\beta'_P = 0.1$, and $\gamma' = 2.4$. γ' is higher than the remaining parameter, $N_P \beta'_P$ is a little lower, $N_T \beta'_T$ is much lower. This means that the time scale separation between demography and infection is poor, whereas it is relevant between recovery and the other phenomena involved in the model.

This result is shown on Fig. 5, when comparing the original and shifted reduced systems over a 20-year long period. The approximation is rather good on the long run for the infected population, but not as satisfying for the other variables.

4.2 Three time scale simulations

In this section, we present numerical simulations for system (12), or equivalently system (1,3). We still use the realistic parameter values in Table 2 and the initial condition (18) to perform these simulations. In order to separate the infection and recovery time scales, still assuming that $\varepsilon = 1/10$, we need to set $\varepsilon' < \varepsilon$ such that the recovery rate γ'' has the same order of magnitude as the remaining parameters; $\varepsilon' = 1/24$ leads to $\gamma'' = 1$, which is a suitable value, **since** $0 < 1/24 < 1/10$.

We use the previous notations for the reduced system and similarly denote

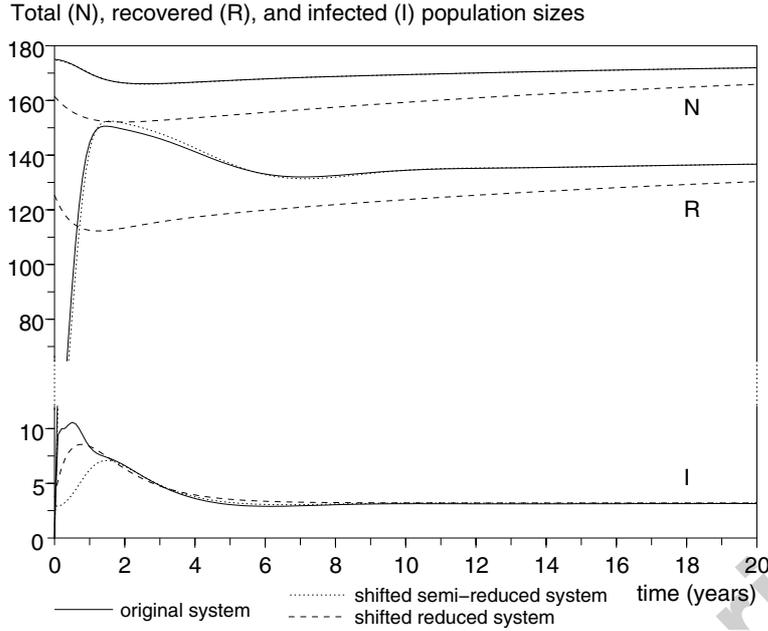


Fig. 5. Total ($N = S_1 + S_2 + T_1 + T_2 + P_1 + P_2 + R_1 + M_2 + R_2$), recovered ($R = R_1 + M_2 + R_2$), and infected ($I = T_1 + T_2 + P_1 + P_2$) population sizes as functions of time for: [solid lines] original system (1,3), $\overline{W}(\varepsilon, \varepsilon')$ being its steady state; [dotted lines] shifted semi-reduced system $W_s - \widetilde{W}(\varepsilon) + \overline{W}(\varepsilon, \varepsilon')$, where W_s and $\widetilde{W}(\varepsilon)$ are respectively the solution and steady state of (14) plus quasi steady state (13); [dashed lines] shifted reduced system $W_r - W^* + \overline{W}(\varepsilon, \varepsilon')$, where W_r and W^* are similarly defined for (9) plus (8). Parameter values are given in Table 2, \overline{W} in (17), $\varepsilon = 1/10$, $\varepsilon' = 1/24$.

with subscript s the variables corresponding to the semi-reduced system plus the quasi steady state; for example $W_s = (X_s, \widetilde{Z}(\varepsilon))$, where X_s is the solution of (14) and $\widetilde{Z}(\varepsilon)$ is given by (13). Let us also note $\widetilde{W} = (\widetilde{X}, \widetilde{Z})$.

In Fig. 5, we compare the original system (1) with the shifted semi-reduced and reduced systems over a 20-year long period. As previously, the (semi)-reduced variables are shifted to compensate for the static error. With two or three time scales, the reduced systems are similar, so we use the same shift for the reduced variables: $W_r - W^* + \overline{W}(\varepsilon, \varepsilon')$. The shifted semi-reduced variables

are similarly defined: $W_s = \widetilde{W}(\varepsilon) + \overline{W}(\varepsilon, \varepsilon')$. $\overline{W}(\varepsilon, \varepsilon')$ is the steady state of complete system (12); its numerical value is given in (17).

As expected, the semi-reduced system is a valid approximation of the complete system, in the transient phase and in the long time dynamics. As mentioned previously, the reduced system is not a satisfying approximation. However, it seems to fit the original system better than the semi-reduced system for the infected population. This is actually an artifact due to the representation of the aggregated infected population. If split up into transiently and persistently infected populations, as shown in Fig. 6, the semi-reduced system is a better approximation, especially for the persistently infected population. The transient infection dynamics is fast in both reduced systems, hence the transient error.

Fig. 7 compares the original system with the shifted semi-reduced and reduced systems for the juvenile and adult populations. Due to the fast recovery dynamics, there are almost no infected animals, especially in the adult population. BVDV is maintained in the flock because of the very few PI animals that are born and survive. Moreover, most adults are immunised: they were infected either during their juvenile years or as adults and recovered fast. For the biological parameter values given in Table 2, however, the infection dynamics is not really separated from the demographic dynamics. This explains why a relatively large fraction of juveniles remain in the susceptible state after their birth, which can also be seen in the steady state values given by (17).

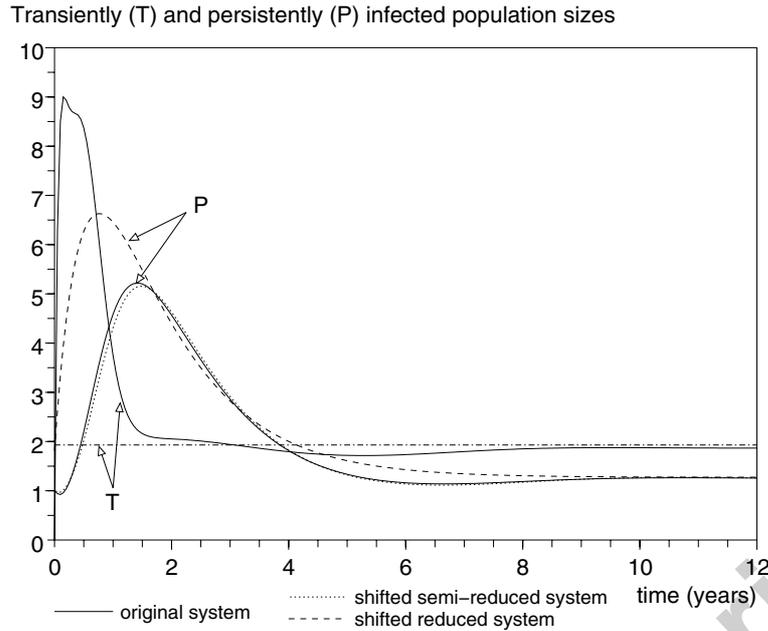


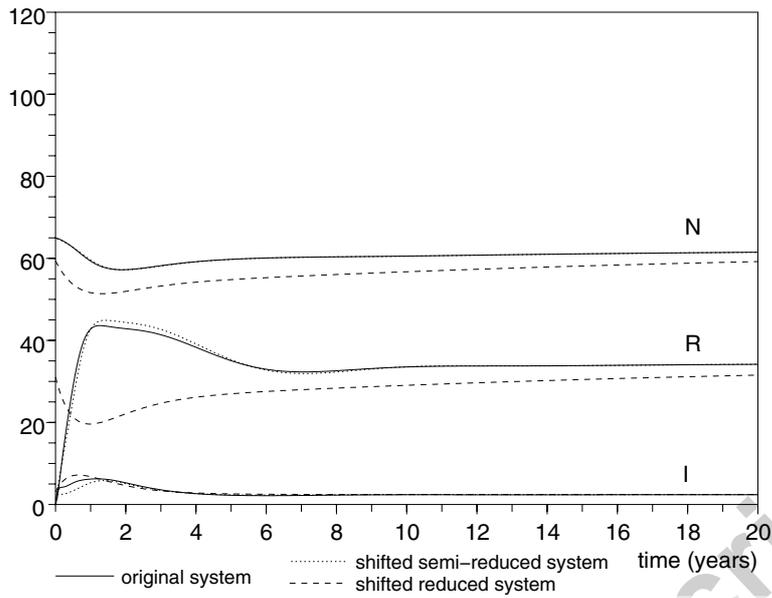
Fig. 6. Transiently (T) and persistently (P) infected population sizes as functions of time: [solid lines] T and P for original system (1,3); [dotted line] shifted P for semi-reduced system (14,13); [dashed line] shifted P for reduced system (9,8); [dash-dotted line] shifted T for the semi-reduced and reduced systems ($T = \bar{T}$). Variable definitions and parameter values are the same as in Fig. 5.

5 Discussion

Time scales can be used to reduce the dimension of epidemiological models. Singular perturbations are then valuable tools to corroborate the results of time scale approximations. Here, this method was applied to a model of BVDV spread in a cattle herd.

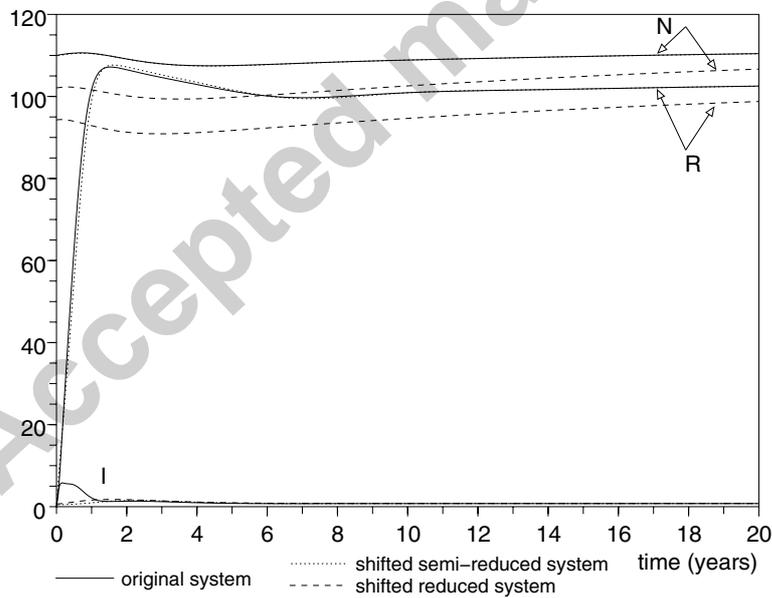
Even though singular perturbation theory is a well established technique which was already used in previous studies to reduce the dimension of biological systems, our work presents particularly interesting aspects when simultaneously considering theoretical and

Age class 1: total (N), recovered (R), and infected (I) population sizes



(a) Juveniles

Age class 2: total (N), recovered (R), and infected (I) population sizes



(b) Adults

Fig. 7. Age class specific total, recovered, and infected population sizes as functions of time for: [solid lines] original system (1,3); [dotted lines] shifted semi-reduced system (14,13); [dashed lines] shifted reduced system (9,8). Variable definitions and parameter values are the same as in Fig. 5.

applied perspectives: (i) contrary to the large majority of similar studies we introduce three time-scales (already used in Lenbury (1996) but in a less disease specific framework) related to biological processes of different speeds leading to satisfying asymptotic approximation of the initial system, obtained without forcing values of biological parameters; (ii) the dimension of our initial model is relatively high compared with other application-oriented studies using singular perturbation tools (such as Song et al. (2002)) and (iii) numerical values of parameters were chosen according to biological relevance, allowing further use of the reduced model in realistic context of BVDV spread in metapopulations.

We have developed a model representing BVDV spread in the herd which captures the main characteristics of the infection and of the host population. The population is structured into two age classes and takes into account the two types of infectious individuals. **Firstly**, transiently infected animals shed a low amount of virus during a few days (**transmission rate β_T**). **Secondly**, persistently infected animals may be born after the infection of their dam during mid-pregnancy, and they shed a large amount of virus for their entire life (**transmission rate β_P**). **Disease transmission mainly occurs via animal in the herd, but herds can also be contaminated in the field by contact with infected neighbouring herds, especially in endemic regions.** Therefore, a specific transmission rate (β_v) was considered to account for a **constant** risk of introducing the pathogen in the herd. As these three transmission rates, β_T , β_P **and** β_v , have different orders of magnitude, and moreover as infection processes go relatively faster than demography, several time scales were identified and used to propose a reduced system. Our model

of BVDV spread in a herd is still fairly simplified. Cattle herds usually have a finer structure and animals may have less contact with animals from other groups than from their own group (Ezanno et al., 2007). Furthermore, cattle herds are small populations and stochastic models may be more **appropriate** to represent the spread of a pathogen in such a population. However, the simplified model studied here has a dynamical infection behaviour which is consistent with the one obtained by simulating more detailed models. Therefore, it allows us to use the time scale separation to reduce the herd model and propose a tractable model for further work in a metapopulation context, through the coupling of several hence reduced local models.

In theory, singular perturbation order reduction requires a clear separation between the system time scales to obtain a valid approximation. In practical applications, it can be tested as soon as the separation factor ε is not more than $\frac{1}{10}$. In our model, a clear time scale separation is achieved for the recovery process. We hence rigorously proved a biological intuition: transiently infected individuals can be neglected when capturing the global dynamics of BVDV spread. However, time scale separation for the infection process is less obvious, at least with our realistic parameter values **which lead to very small typical infected population sizes (1-3 infected individuals)**. **In more contaminated herd, the time scale separation and hence the approximation would be better.** Simulations showed that even assuming a relatively good time scale separation between demography and infection, there was still a bias between the complete and reduced models. This is due to the ε -dependence of the steady state of the complete model, when the reduced system is computed assuming $\varepsilon = 0$ which makes it ε -independent. Using a shifted reduced system compensated for this static error, but it dete-

riorated the transient phase approximation. The singular perturbation theory allows this drawback **to be overcome** by the computation of an ε -dependent reduced model, as indicated in Khalil (1996). This should help making the complete reduction to five states more relevant even when the infection force is low. Our next efforts will be concentrated in this direction.

Our study has illustrated that singular perturbations are a very interesting tool to reduce model complexity. It allows to investigate rigorously intuitive simplifications that specialists in a field make on their systems, and to build reduced (though approximated) models that can be used, after coupling with other similar models, in a metapopulation framework.

A Existence of an endemic steady state

A.1 Original system

We want to prove the existence of a non negative equilibrium for the original model (1) denoted by vector:

$$\bar{W} = (\bar{S}_1, \bar{S}_2, \bar{T}_1, \bar{T}_2, \bar{P}_1, \bar{P}_2, \bar{R}_1, \bar{M}_2, \bar{R}_2),$$

with $\bar{T}_1 + \bar{T}_2 + \bar{P}_1 + \bar{P}_2 > 0$ so as to obtain an endemic steady state, for a non trivial set of parameters.

We first do some algebra and after successive substitutions and manipulations of different equations of system (1,2), we find that \bar{M}_2 , \bar{P}_1 and \bar{P}_2 are expressed as linear functions of \bar{T}_2 , \bar{R}_1 as a linear function of \bar{T}_1 and \bar{S}_1 , \bar{S}_2 and \bar{R}_2 depend

linearly on both \overline{T}_1 and \overline{T}_2 . More precisely, we have:

$$\begin{aligned}\overline{M}_2 &= \frac{\gamma'\overline{T}_2}{\varepsilon(\eta + \mu_2)}, & \overline{P}_1 &= \frac{\rho b_M \mu_{P_2} \gamma'\overline{T}_2}{\varepsilon c_P(\eta + \mu_2)}, & \overline{P}_2 &= \frac{\tau \rho b_M \gamma'\overline{T}_2}{\varepsilon c_P(\eta + \mu_2)}, \\ \overline{R}_1 &= \frac{\gamma'\overline{T}_1}{\varepsilon(\tau + \mu_1)}, & \overline{R}_2 &= \frac{\tau \gamma'\overline{T}_1}{\varepsilon(\tau + \mu_1)\mu_2} + \frac{\eta \gamma'\overline{T}_2}{\varepsilon(\eta + \mu_2)\mu_2} + \frac{\Delta_R}{\mu_2}, \\ \overline{S}_1 &= -(1 + \frac{s_{11}}{\varepsilon})\overline{T}_1 - \frac{s_{12}\overline{T}_2}{\varepsilon} + s_{10}, & \overline{S}_2 &= -\frac{s_{21}\overline{T}_1}{\varepsilon} - (1 + \frac{s_{22}}{\varepsilon})\overline{T}_2 + s_{20},\end{aligned}\tag{A.1}$$

where s_{11} , s_{12} , s_{10} , s_{21} , s_{22} and s_{20} are positive expressions of model parameters.

\overline{T}_1 (and \overline{T}_2 , their relationship being quasi-symmetric) can be calculated as a root of a third order polynomial $Q_{T_1}(x)$ (or $Q_{T_2}(x)$ respectively) and has non analytically tractable formula. In order to circumvent this problem, we use a second-order Taylor expansion of $Q_{T_1}(x)$ (and $Q_{T_2}(x)$ respectively) around ε and obtain that $\overline{T}_1 \sim \varepsilon \alpha_{T_1}$ (and $\overline{T}_2 \sim \varepsilon \alpha_{T_2}$ respectively), with $\alpha_{T_1} > 0$ (and $\alpha_{T_2} > 0$ respectively) under the assumptions $c_S > 0$ (4) and $c_P > 0$ (5).

Hence, with these assumptions and if ε is “small enough”, \overline{T}_1 and \overline{T}_2 are positive and we can easily see from (A.1) that the positivity is then also verified for \overline{P}_1 , \overline{P}_2 , \overline{R}_1 , \overline{R}_2 and \overline{M}_2 . Steady states \overline{S}_1 and \overline{S}_2 are also positive. Indeed, \overline{S}_1 can be directly computed from the equation describing the T_1 dynamic in the complete system (1) as a combination of positive quantities. \overline{S}_2 is linearly related to \overline{S}_1 , through a positive coefficient, from the equation describing the S_2 dynamic in system (1).

Consequently, parameter conditions (4-5) and a “small enough” ε ensure that system (1,2) has a positive endemic steady state.

A.2 Semi-reduced system

In the same way, one can prove existence of a unique endemic steady state $(\widetilde{A}_1, \widetilde{A}_2, \widetilde{P}_1, \widetilde{P}_2, \widetilde{R}_2, \widetilde{G}_1, \widetilde{G}_2)$ for the semi-reduced model (14) under similar assumptions. After successive substitutions and manipulations, we obtain the following relations:

$$\begin{aligned}\widetilde{R}_2 &= \frac{\tau\widetilde{G}_1}{\mu_2} + \frac{\eta\widetilde{G}_2}{\mu_2} + \frac{\Delta_R}{\mu_2}, & \widetilde{P}_1 &= \frac{\rho b_M \mu_{P_2} \widetilde{G}_2}{c_P}, & \widetilde{P}_2 &= \frac{\tau \rho b_M \widetilde{G}_2}{c_P}, \\ \widetilde{A}_1 &= -\frac{\mu_2((1-\rho)b_M - b)}{c_S} \widetilde{G}_2 + \frac{\Delta_S + \Delta_R}{c_S}, \\ \widetilde{A}_2 &= \frac{\mu_2 \tau((1-\rho)b_M - b) - \eta c_S}{\mu_2 c_S} \widetilde{G}_2 - \frac{\tau}{\mu_2} \widetilde{G}_1 + \frac{\tau \Delta_S \mu_2 + \tau b \Delta_R + \mu_1 \Delta_S \mu_2}{\mu_2 c_S},\end{aligned}\tag{A.2}$$

where all parameters are independent of ε .

Then, \widetilde{G}_1 (or \widetilde{G}_2) can be calculated as a root of a third order polynomial. Using the arguments given above, we obtain the existence of a unique positive solution $(\widetilde{G}_1, \widetilde{G}_2)$ under the assumptions $c_S > 0$ (4), $c_P > 0$ (5) and for ε “small enough”. Consequently, we obtain the positivity of $(\widetilde{P}_1, \widetilde{P}_2, \widetilde{R}_2)$ from (A.2); positivity of $(\widetilde{A}_1, \widetilde{A}_2)$ can be proved using the equation of system (14) at the equilibrium.

B Singular perturbation theory

Consider the standard singular perturbation model:

$$\dot{x} = f(t, x, z, \varepsilon), \quad x \in \mathbb{R}^n, \quad x(t_0) = \xi(\varepsilon), \tag{B.1a}$$

$$\varepsilon \dot{z} = g(t, x, z, \varepsilon), \quad z \in \mathbb{R}^m, \quad z(t_0) = \phi(\varepsilon). \tag{B.1b}$$

Call $z^* = h(t, x)$ the quasi steady state of equation B.1b with $\varepsilon = 0$, i.e. the solution of:

$$0 = g(t, x, z, 0)$$

The reduced model is:

$$\dot{x} = f(t, x, h(t, x), 0). \quad (\text{B.2})$$

Taking $y = z - h(t, x)$, we define the boundary-layer system as:

$$\frac{dy}{d\nu} = g(t, x, y + h(t, x), 0). \quad (\text{B.3})$$

The singular perturbation theory provides the following results (Khalil, 1996).

Theorem 1 *Assume that the following conditions are satisfied for all*

$$(t, x, z - h(t, x), \varepsilon) \in [0, \infty) \times B_r \times B_\rho \times [0, \varepsilon_0].$$

- *The functions f, g and their partial derivatives with respect to (x, z, ε) are continuous and bounded.*

The function $h(t, x)$ and the Jacobian $[\partial g(t, x, z, \varepsilon)/\partial z]$ have bounded first partial derivatives with respect to their arguments.

The Jacobian $[\partial f(t, x, h(t, x), 0)/\partial x]$ has bounded first partial derivatives with respect to x .

The initial data $\xi(\varepsilon)$ and $\phi(\varepsilon)$ are smooth functions of ε .

- *The origin of the reduced model (B.2) is exponentially stable.*
- *The origin of the boundary-layer system (B.3) is exponentially stable uniformly in (t, x) .*

Then, there exist positive constants μ_1, μ_2 and ε^ such that for all*

$$\|\xi(0)\| < \mu_1, \quad \|\eta(0) - h(t_0, \xi(0))\| < \mu_2, \quad \text{and} \quad 0 < \varepsilon < \varepsilon^*$$

the singular perturbation problem (B.1) has a unique solution $x(t, \varepsilon)$, $z(t, \varepsilon)$ defined for all $t \geq t_0 \geq 0$, and

$$\begin{aligned} x(t, \varepsilon) - x^*(t) &= O(\varepsilon) \\ z(t, \varepsilon) - h(t, x^*(t)) - \hat{y}(t/\varepsilon) &= O(\varepsilon) \end{aligned}$$

hold uniformly for $t \in [t_0, \infty)$, where $x^*(t)$ and $\hat{y}(t)$ are the solutions of the reduced (B.2) and boundary-layer problems (B.3).

Moreover, given any $t_b > t_0$, there is $\varepsilon^{**} \leq \varepsilon^*$ such that

$$z(t, \varepsilon) - h(t, x^*(t)) = O(\varepsilon)$$

holds uniformly for $t \in [t_b, \infty)$ whenever $\varepsilon < \varepsilon^{**}$.

Theorem 2 Assume that the following assumptions are satisfied for all

$$(t, x, \varepsilon) \in [0, \infty) \times B_r \times [0, \varepsilon_0].$$

- $f(t, 0, 0, \varepsilon) = g(t, 0, 0, \varepsilon) = 0$.
- The equation $0 = g(t, x, z, 0)$ has an isolated root $z = h(t, x)$ such that $h(t, 0) = 0$.
- The functions f , g and h and their partial derivatives up to order 2 are bounded for $z - h(t, x) \in B_\rho$.
- The origin of the reduced model (B.2) is exponentially stable.
- The origin of the boundary-layer system (B.3) is exponentially stable uniformly in (t, x) .

Then, there exists $\varepsilon^* > 0$ such that for all $\varepsilon < \varepsilon^*$, the origin of (B.1) is exponentially stable.

Note 1 Consider the alternative singular perturbation model:

$$\begin{aligned}\dot{X} &= F(t, X, Z, \varepsilon), & X \in \mathbb{R}^n, & & X(t_0) = \Xi(\varepsilon), \\ \varepsilon \dot{Z} &= G(t, X, Z, \varepsilon), & Z \in \mathbb{R}^m, & & Z(t_0) = \Phi(\varepsilon),\end{aligned}$$

where $(\bar{X}(\varepsilon), \bar{Z}(\varepsilon))$ is a non trivial equilibrium of this system.

Call $Z^* = H(t, X)$ the quasi steady state, solution of $G(t, X, Z, 0) = 0$. The reduced model is:

$$\dot{X} = f(t, X, H(t, X), 0).$$

Note $X = \bar{X}(\varepsilon) + x$, $Z = \bar{Z}(\varepsilon) + z$, and define:

$$\begin{aligned}f(t, x, z, \varepsilon) &= F(t, X, Z, \varepsilon), & \xi(\varepsilon) &= \Xi(\varepsilon) - \bar{X}(\varepsilon), \\ g(t, x, z, \varepsilon) &= G(t, X, Z, \varepsilon), & \phi(\varepsilon) &= \Phi(\varepsilon) - \bar{Z}(\varepsilon), \\ h(t, x) &= H(t, X) - Z^*,\end{aligned}$$

As long as $\bar{X}(0) = X^*$ and $\bar{Z}(0) = Z^*$ exist, with X^* the equilibrium of the reduced model, theorems 1 and 2 can be either applied to (f, g, h) or to (F, G, H) , using X^* for the reduced model and $(\bar{X}(\varepsilon), \bar{Z}(\varepsilon))$ for the system instead of the origin.

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