Epidemiology and evolution of infectious diseases in a periodic environment

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This dissertation is dedicated to the fathers and mothers
who have educated and nurtured me to adulthood!

Xin dành tặng cho những người mẹ, người cha
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CHAPTER 1

INTRODUCTION

1.1 Introduction

Les fluctuations périodiques de l'environnement associées aux saisons affectent le développement et la dynamique des populations de nombreux organismes vivants. La transmission des maladies infectieuses est elle aussi soumise aux effets de la saisonnalité [Alt+06; GF06]. Pour mieux appréhender ces effets il est nécessaire de s'appuyer sur des modèles mathématiques. Le lien entre épidémiologie des maladies infectieuses et mathématiques est très ancien. Par exemple, c'est en 1760 que le mathématicien Daniel Bernoulli a utilisé un modèle pour démontrer l'intérêt de la "variolisation" pour augmenter l'espérance de vie en protégeant contre les ravages de la variole [Ber82; Ber60]. Mais c'est après l'essor de "la théorie des germes" développée par Pasteur au XIXème siècle que la formalisation mathématique de l'épidémiologe a pu prendre de l'ampleur. En effet, avec la théorie des germes, l'étiologie des maladies infectieuses est reliée à des agents microbiens invisibles à l'oeil nu mais qui peuvent se transmettre d'un hôte à un autre. Pour comprendre les épidémies il devient donc indispensable de comprendre la dynamique de ces microbes.

C'est à la fin du XIXème siècle que le médecin britannique Ronald Ross démontre que la malaria est transmise par des moustiques. Ce même Ross développera les premiers modèles mathématiques permettant de décrire cette transmission vectorielle. Il utilisera ces modèles pour démontrer qu'il existe un seuil de densité de la population de vecteur en dessous duquel le parasite ne peut plus persister dans la population [Cox10].. Ce type de résultats a permis d'imaginer rapidement des méthodes de contrôle basées sur la lutte anti-vectorielle. Les applications pratiques de ces travaux ont contribué au développement de l'épidémiologie mathématique. On peut citer en particulier les travaux fondateurs de Kermack et McKendrick (1927) et le développement des modèles compartimentaux qui permettent de résumer simplement les grandes étapes du cycle de vie d'une infection.

Au cours des années 1950-1960, des modèles deterministes des maladies infectieuses ont été développés, comme le modèle SIR (susceptible-contaminé-récupéré). Ensuite, vers 1970-1980, des modèles aléatoires de propagation de la maladie sont introduits permettant l'incorporation du caractère aléatoire et de la variabilité dans la transmission de la maladie. Dans les années 1980, les modèles mathématiques ont commencé à prendre en compte la dynamique évolutive des pathogènes. En effet, les microbes ont un temps de génération court, de grandes tailles de population et des taux de mutation élevés. Ils ont donc un potentiel évolutif important leur permettant de contourner l'immunité de leur hôte et les médicaments comme les antibiotiques. Il existe plusieurs ouvrages de référence qui font le point sur le développement de l'épidémiologie mathématique (Anderson & May 1991, Heesterbeek, Diekmann & Britton , Nowak & May 2000) [AAM92; Hee+15; HR95a; HR95b; DHB13; DH00].

Au cours des quatre dernières décennies, l'impact des maladies infectieuses sur la société s'est accru. Parallèlement, de nombreux outils nouveaux sont appliqués dans la recherche épidémiologique. Spécifiquement, les années 1990-2000 ont vu l'émergence de modèles informatiques et de simulations, fournissant de nouveaux outils pour étudier la propagation des maladies dans des populations complexes. En complément, à partir des années 2000, l'intégration de données provenant de diverses sources, telles que les dossiers de santé électroniques, les médias sociaux et les appareils portables, a permis de valider et d'améliorer les modéles épidémiologiques. Ces modèles ont été utilisés pour éclairer la prise de décision en matière de santé publique et pour guider les réponses aux épidémies : citons l'épidémie de SRAS de 2003, la pandémie de H1N1 de 2009 et la pandémie de COVID-19 en cours.

Cette thèse se place dans la continuité de ces travaux et se concentre sur les effets de la saisonnalité. Nous distinguerons trois types d'effets de la saisonnalité. Premièrement, nous étudierons comment la saisonnalité affecte la persistence des maladies vectorielles. Nous analyserons ici des modèles déterministes qui nous permettront d'identifier les conditions favorables à la circulation d'un pathogène. Deuxièmement, nous étudierons les conséquences de la stochasticité démographique sur les risques d'émergence d'une maladie infectieuse. En particulier nous quantifierons les risques d'émergence en fonction des variations temporelles de la transmission au fil des saisons. Enfin, dans une troisième partie nous étudierons les conséquences évolutives de la saisonnalité sur les stratégies de dormance des pathogènes. Nous utiliserons ici des modèles de dynamique adaptative pour analyser l'évolution de la dormance des maladies à transmission vectorielle.

1.2 Influence de la saisonnalité sur la persistence des maladies à transmission vectorielle

La capacité d'un pathogène à se développer dans une population est souvent mesurée par le nombre de reproduction R_0 : dans un modèle déterministe, le pathogène produit une épidémie si et seulement si $R_0 > 1$. On peut calculer R_0 dans le cadre d'un environnement fluctuant, disons périodique, pour des modèles simples (voir e.g. [BG06]). Malheureusement, c'est plus compliqué pour les modèles à transmission vectorielle. On a montré ([Bac07]) qu'une fluctuation périodique de la densité des vecteurs peut diminuer R_0 alors ([WZ08]) qu'une fluctuation périodique des taux de transmission peut augmenter R_0.

Il existe deux autres indicateurs de la capacité de croissance d'une population : $\lambda = \rho(\phi_A(T))$ le rayon spectral de la matrice de monodromie, et l'indicateur P de [HR95a; HR95b]. Les signes de $R_0 - 1$, $\lambda - 1$ et $P - 1$ sont les mêmes. Nous avons établi, pour des perturbations périodiques d'ordre ϵ des coefficients du modèle, à l'aide de la théorie des perturbations des opérateurs linéaires (voir [Kat66]) l'existence de développements de Taylor:

$$\lambda = \lambda_0 + \epsilon\lambda_1 + \epsilon^2\lambda_2 + o(\epsilon^2)\,,$$
$$P = P_0 + \epsilon P_1 + \epsilon^2 P_2 + o(\epsilon^2)\,.$$

L'étude de la nullité et du signe de λ_1 et λ_2 permet de retrouver les résultats de [Bac07; WZ08] et de les généraliser. L'utilisateur de l'indicateur P permet de développer une intuition plus biologique des signes des P_i, et donc de l'influence de l'environnement sur le taux de croissance du pathogène, en identifiant les décalages entre les fluctuations de l'environnement et les fluctuations des populations de vecteurs et des hôtes infectés.

1.3 Risque d'émergence dans un modèle stochastique logistique

Nous étudions plus en profondeur les interactions entre stochasticité et saisonnalité. Nous choisissons d'étudier le modèle logistique stochastique en environnement périodique. C'est une chaîne de Markov $X^{(K,T)}$ inhomogène à valeurs dans $\{0, \dots, K\}$ avec K la *capacité de charge*, la taille maximale de la population. Le taux de mort est une constante μ et le taux de naissance est $\beta(\frac{t}{T})(1 - \frac{x}{K})$ pour une population de taille x, avec $T > 0$ la période, β une

fonction borélienne positive 1-périodique.

Le but de notre étude est de bien comprendre le comportement du processus stochastique $X^{(K,T)}$. Cela permettra de développer une intuition biologique, appuyée par des heuristiques probabilistes et des simulations, pour traiter le problème de la détermination du timing optimal d'une intervention visant à minimiser le risque d'émergence dans un environnement périodique.

Le nombre de reproduction est donné par $R_0 = \frac{\langle\beta\rangle}{\mu}$ avec $\langle\beta\rangle = \int_0^1 \beta(u)\,du$ la moyenne du taux de transmission. L'approximation déterministe de la dynamique de l'épidémie est la solution de l'EDO

$$\frac{dx}{dt} = x\beta\left(\frac{t}{T}\right)x(1-x) - \mu x\,,$$

dont le comportement est bien connu : si $R_0 < 1$ il y a convergence rapide vers 0, alors que si $R_0 > 1$, il existe un attracteur périodique non trivial.

Pour le processus stochastique, on sait que si $R_0 < 1$ alors, comme dans le cas déterministe, il y a extinction rapide et on suppose donc désormais que $R_0 > 1$. Les effets de la stochasticité sur la dynamique épidémiologique sont multiples.

Quand la période des fluctuations est petite (i.e., $T \to 0$) on note qu'un phénomène de *moyennisation* se produit: la stochasticité ne disparaît pas, mais on peut remplacer le processus $X^{(K,T)}$ par le processus $\bar{X}^{(K)}$ obtenu en remplaçant le taux de transmission $\beta(t/T)$ par la moyenne $\langle\beta\rangle$. On peut alors utiliser les résultats classiques sur l'évaluation du temps d'extinction ([AD98; KL89]) et la quasi stationnarité ([DS67]).

Quand la période des fluctuations est importante il n'est plus possible de moyenner le taux de transmission. Il faut alors distinguer plusieurs phases dans l'épidémie avant d'arriver à une émergence.

Premièrement, il existe une *probabilité de take off*, c'est à dire la probabilité que la population atteigne une taille macroscopique (de l'ordre de K). Cette probabilité est la même que pour le processus de branchement associé, et dépend de l'instant d'introduction du pathogène.

Deuxièmement, rappelons que comme la population est finie, il y a presque sûrement extinction. On désire alors comprendre quand ce temps d'extinction τ_0 est petit ou grand. On suppose pour cela qu'il existe au moins une période défavorable pour le pathogène pendant laquelle on a $\beta(t) < \mu$ (un "hiver" si l'on veut se référer à la saisonnalité). On montre alors l'existence d'une *capacité critique* K_C telle que si $K \ll K_C$ l'extinction est rapide et si $K \gg K_C$ le temps d'extinction est très grand et la dynamique du système stochastique tend vers un *équilibre quasi stationnaire périodique*.

Par ailleurs, lorsque la capacité $K \to +\infty$, alors le processus est bien approché par le processus de naissance et de mort en environnement périodique, précédemment étudié par [CG20].

Nous utilisons notre compréhension des effets de la saisonnalité sur la dynamique épidémiologique pour étudier la façon optimale d'intervenir dans le but de limiter le risque d'émergence. Nous considérons un scénario avec taux de transmission en créneau $\beta(t) = \beta_G \mathbf{1}_{(0\leq t\leq 1-\gamma)}$, avec $\beta_G < \mu$. L'intervention consiste à remplacer β_G par $\beta_C < \beta_G$ sur une période de temps (sur laquelle la capacité de reproduction du pathogène est diminuée). On montre, en construisant des heuristiques qui sont validées par des simulations numériques, que la période optimale d'intervention se situe juste avant l'hiver du pathogène. La comparaison avec les résultats pour les processus de naissance et de mort montre l'importance de l'existence de la densité dépendance (ici liée à la présence d'une capacité K) sur les décisions concernant l'intervention.

1.4 Évolution de la dormance

Le phénomène de dormance consiste, pour un organisme vivant, à faire face à une période défavorable de son environnement en modifiant ses caractéristiques physiologiques. Pendant cette période l'organisme peut "décider" de limiter son développement, ses activités de recherche de nourriture et/ou de reproduction, et les reprendre pendant une période favorable. Ce phénomène de dormance est observé chez de nombreuses plantes (dormance des graines ou de l'appareil végétatif) pendant l'hiver ou lors de période de sécheresse. Mais ce phénomène existe également chez certains animaux (e.g., hibernation de certains mammifaires, diapause de nombreux insectes). Le phénomène de dormance est également assez répandu parmi les microbes. Certains virus de l'Herpes peuvent se maintenir à l'état dormant et se réactiver bien des années après la première infection. Certaines bactéries sont capables de former des spores qui peuvent résister à la dessication ou aux traitements antibiotiques. Enfin, certaines espèces de malaria comme le *Plasmodium vivax* mais aussi de nombreux *Plasmodium* aviaires peuvent également se maintenir à l'état dormant dans leur hôte. Le parasite peut même disparaitre de la circulation sanguine pendant plusieurs années avant de se réactiver. Dans quelles conditions ces stratégies de dormance évoluent et quelles sont les composants de l'environnement qui signalent aux parasites qu'il est temps de rentrer en dormance ou, au contraire, de reprendre un cycle de vie actif?

Nous tenterons de répondre à ces questions en reprenant l'analyse d'un modèle de maladie à transmission vectorielle. Dans le scénario considéré, la saisonnalité affecte la densité de la population de vecteurs. Le pathogène peut infecter son hôte vertébré sous deux formes : (i) une forme *active* dans laquelle l'hôte peut infecter des vecteurs (si un vecteur pique un hôte infecté) ou guérir, (ii) une forme *passive* (ou dormante) dans laquelle le parasite ne peut se transmettre

au vecteur mais l'hôte ne peut pas guérir. Les mécanismes permettant de faire passer un parasite de l'état actif à l'état passif peuvent être indépendants de l'environnement. Dans ce cas, les taux de transition entre ces deux états sont constants et on parle alors de *traits constitutifs*. Mais ils peuvent également être variables et dépendre de certaines variables environnementales. On parle alors de *traits plastiques*. Par exemple, certains *Plasmodium* aviaire ont la capacité de réagir à la présence de piqures de moustiques [Cor+14]. Nous avons donc modifié un peu le modèle analysé dans le premier chapitre de cette thèse pour étudier l'évolution de la dormance et de la réactivation.

Tout d'abord, nous avons rajouté un compartiment "dormant" dans le cycle de vie de l'infection. La transition vers ce stade est contrôlée par le taux de dormance d. Le retour vers le statut "actif" de l'infection est contrôlée par le taux de réactivation r. Une *analyse de l'invasion* d'un mutant dans une population résidente stabilisée est effectuée à l'aide du *gradient de sélection* en environnement périodique, outil mathématique développé par [LG22]. Sous l'hypothèse que l'invasion entraîne la fixation, une étude évolutive permet alors de déterminer les paramètres optimaux vers lesquels les mutations vont faire évoluer le pathogène : taux de dormance et réactivation, périodes de dormance et de réactivation. Les implications biologiques des différentes stratégies d'adaptation sont discutées et étayées par des simulations numériques.

1.5 Quelques Perspectives

Cette thèse montre les conséquences que peuvent avoir les fluctuations périodiques de l'environnement sur la dynamique des maladies infectieuses. Nous illustrons ces conséquences dans le cadre d'un pathogène à transmission vectorielle car les fluctuations saisonnières de la température et de l'humidité se traduisent par des fluctuations saisonnières de la population de vecteurs, et du nombre de piqûres journalières.

Chaque chapitre aborde un aspect différent de la saisonnalité. Le premier chapitre analyse la persistence d'un pathogène et montre comment la saisonnalité peut augmenter ou, au contraire, diminuer la persistence du pathogène. Ce premier chapitre est basé sur l'analyse d'un modèle déterministe. Nous mettons en évidence les effets contrastés de la saisonnalité dans l'abondance et/ou dans le taux de piqûre du vecteur sur la persistence du pathogène. Cependant, seuls la densité vectorielle et le taux de piqure sont analysés. Il est naturel de prévoir dans le futur d'étudier l'influence de la saisonnalité à travers les variations conjointes de tout un ensemble de paramètres associés à d'autres étapes du cycle de vie: le taux de transmission de la maladie de l'hôte vertébré au vecteur, le taux de mortalité du vecteur, le taux de guérison de l'infection

dans l'hôte vertébré mais aussi les stratégies de dormance et de réactivation (chapitre 3).

Dans le deuxième chapitre nous étudions les effets de la saisonnalité sur les risques d'émergence. Le modèle stochastique utilisé repose sur un scénario épidémiologique assez simple, le modèle logistique. Nous montrons ici comment le choix de la période de contrôle de l'épidémie, période pendant laquelle une politique sanitaire diminue le potentiel de transmission du pathogène, influence le risque d'émergence de l'épidémie. Nous aimerions généraliser ces résultats à des modèles avec transmission vectorielle et explorer plus avant le lien avec les modèles de branchement (en particulier le phénomène *winter is coming* se produit-il toujours ?). Il serait également intéressant d'essayer de faire le lien avec le chapitre sur la dormance en autorisant d'autres stratégies d'exploitation de l'hôte vertébré. Est-ce que les prédictions sur les risques d'émergence sont affectés par la présence de dormance?

Le troisième chapitre utilise un troisième formalisme, la dynamique adaptative, pour étudier l'évolution de la dormance et de la réactivation. Dans un environnement constant, si μ_H est le taux de mort de l'hôte, si d, r (resp. d_m, r_m) sont les taux de dormance et de réactivation du résident (resp. du mutant), le mutant envahit le résident si et seulement si

$$\frac{d}{r+\mu_H} > \frac{d^m}{r^m+\mu_H}.$$

Nous aimerions mieux comprendre l'effet des fluctuations périodiques sur l'évolution de la dormance constitutive (il est un peu surprenant que plus de fluctuations favorise moins de dormance dans le modèle actuel). Il serait également intéressant de s'inspirer du chapitre 1 pour modéliser la dynamique de population de vecteurs avec un modèle de croissance logistique. Ce modèle démographique serait plus réaliste et pourrait peut-être permettre de faire des prédictions testables sur l'évolution de la plasticité. Sur la plasticité il serait intéressant de considérer que cette capacité à changer de phénotype est coûteuse. Dans ce cas, il serait intéressant de déterminer les environnements dans lesquels on peut s'attendre à trouver cette plasticité.

D'une manière générale il serait intéressant d'essayer de faire se rejoindre ces différents chapitres en mélangeant épidémiologie, stochasticité et évolution dans des environnements fluctuants. Par exemple, l'étude de l'effet d'une fluctuation environnementale stochastique sur l'évolution de la dormance serait particulièrement intéressante d'un point de vue biologique. Cette question a déjà été abordée dans le contexte de l'évolution de la dormance des graines chez les plantes mais pas dans un contexte épidémiologique.

CHAPTER 2

SEASONALITY AND THE PERSISTENCE OF VECTOR-BORNE PATHOGENS

Many vector-borne diseases are affected by the seasonality of the environment. Yet, seasonality can act on distinct steps of the life-cycle of the pathogen and it is often difficult to predict the influence of the periodic fluctuations of the environment on the persistence of vector-borne pathogens. Here we analyze a general vector-borne disease model and we account for periodic fluctuations of different components of the pathogen's life-cycle. We develop a perturbation analysis framework to obtain useful approximations to evaluate the overall consequences of seasonality on the persistence of pathogens. This analysis reveals when seasonality is expected to increase or to decrease pathogen persistence. We show that seasonality in vector density or in the biting rate of the vector can have opposite effects on persistence and we provide a useful biological explanation for this result based on the covariance between key compartments of the epidemiological model. This framework could be readily extended to explore the influence of seasonality on other components of the life cycle of vector-borne pathogens.

2.1 Introduction

The ability of a pathogen to spread in a fully susceptible host population is governed by its basic reproduction ratio R_0 which measures the number of secondary cases produced by a typical infected case. The pathogen will spread and induce an epidemic if and only if $R_0 > 1$ (and it will rapidly go extinct if $R_0 < 1$). Hence the basic reproduction ratio provides a way to evaluate the epidemic potential of different pathogens and constitutes a key epidemiological quantity to control infectious diseases. The basic reproduction ratio of the simplest epidemiological model with a single compartment of infected hosts takes a very simple and intuitive form: $R_0 = \beta/\gamma$ (i.e., the transmission rate β times the duration of infection $1/\gamma$). The next generation matrix (a per-generation way to compute population dynamics) can be used to compute R_0 when multiple compartments (e.g., different infectious stages, different hosts) are required to describe the

life cycle of the pathogen in a constant environment where transitions rates are fixed [DHR10]. Indeed, in a constant environment, a per-generation way of measuring population growth is appropriate because the timing of the new infection does not matter.

But things become more complicated in fluctuating environments where the timing of new infections matters. For instance, many studies have shown that periodically changing environments may affect the R_0 [HR95a; HR95b; Bac07; WZ08]. The analysis of these models is more challenging and does not always yield consistent results regarding the qualitative effects of seasonality on R_0. For instance, periodic fluctuations in the density of mosquito vectors can reduce R_0 [Bac07] while a fluctuation in the transmission rate yields higher R_0 in another vector-borne model [WZ08]. Why do these different models yield opposite conclusions? Can we build up an intuitive and biological understanding of the behavior of these complex time-varying models? We try to answer these questions in the following with the analysis of simple periodic models of vector-borne pathogens. We derive different threshold quantities for the persistence of the pathogen that allows us to discuss the combined effects of periodic fluctuations of various components of the pathogen's life cycle.

2.2 The model

Let us consider the spread of a vector-borne pathogen which requires an explicit description of the dynamics of the infection among human hosts and mosquito vectors. We use a classical model of vector-borne transmission [AAM92] that tracks the densities of four types of hosts (uninfected and infected humans, uninfected and infected vectors) which yields the following system of ordinary differential equations (the parameters of the model are described in Table 2.1):

$$\begin{aligned}
\frac{\mathrm{d}S_H}{\mathrm{d}t} &= \theta - a\beta_{VH}\frac{I_V S_H}{N_H} - \mu_H S_H,\\
\frac{\mathrm{d}I_H}{\mathrm{d}t} &= a\beta_{VH}\frac{I_V S_H}{N_H} - (\mu_H + \gamma_H) I_H,\\
\frac{\mathrm{d}R_H}{\mathrm{d}t} &= \gamma_H I_H - \mu_H R_H,\\
\frac{\mathrm{d}S_V}{\mathrm{d}t} &= \rho_V N_V - a\beta_{HV} I_H S_V - \mu_V S_V,\\
\frac{\mathrm{d}I_V}{\mathrm{d}t} &= a\beta_{HV} I_H S_V - \mu_V I_V.
\end{aligned} \tag{2.1}$$

For the sake of simplicity, we assume that the total density of the human population $S_H + I_H + R_H = N_H$ remains constant which implies that $\theta = \mu_H (S_H + I_H + R_H)$.

In a constant environment, we assume that the parameters that govern the life cycle of the vector do not vary with time and if the fecundity of the vector compensates exactly its mortality (i.e., $\rho_V = \mu_V$) the total density of the vector population $S_V + I_V = N_V$ is also constant. In this scenario, the basic reproduction ratio is readily derived from the linearisation of the above system at the disease free equilibrium ($I_V = I_H = R_H = 0, S_H = N_H, S_V = N_V$) which yields ([HR95a]):

$$R_0 = \frac{a\beta_{VH}}{\mu_V} \frac{a\beta_{HV} N_V}{\mu_H + \gamma_H}. \tag{2.2}$$

In other words, the R_0 can be interpreted as the expected number of human hosts infected by an infected vector during its lifetime (the first ratio in (2.2)) times the expected number of vectors infected by an infected host throughout the duration of its infection (the second ratio in (2.2)).

In a fluctuating environment, several parameters of the pathogen may vary with time [Mor+13; Tes+18] and these variations are likely to affect R_0. Several previous studies have developed ways to compute R_0 in periodic environments [HR95a; HR95b; Bac07; WZ08]. Seasonality is usually modelled through the use the T-periodic function $f(t) = \cos(2\pi t/T)$ which may affect different biological processes and thus different parameters in the dynamical system (2.1). Bacaer analyzed a model of malaria transmission when the density of the mosquito population fluctuates periodically with $N_V(t) = N_V(1 + \epsilon f(t))$ [Bac07]. This analysis combines a Fourier decomposition of $N_V(t)$ with a perturbation analysis for small ϵ to compute an approximation of R_0 as a function of ϵ. This approach yields a particularly useful approximation for the effect of seasonality:

$$R_0 = \frac{a\beta_{VH}}{\mu_V} \frac{a\beta_{HV} N_V}{\mu_H + \gamma_H} \left(1 - \epsilon^2 Q\right) + o(\epsilon^2), \tag{2.3}$$

where $Q = \frac{1}{2} \frac{\left(\frac{T}{2\pi}\right)^2 (\mu_H + \gamma_H)\mu_V}{1 + \left(\frac{T}{2\pi}\right)^2 (\mu_V + \mu_H + \gamma_H)^2}$. This expression shows that, since $Q > 0$, the periodic fluctuations of the densities of mosquitoes tend to decrease R_0 and thus to limit the persistence of malaria. Yet, it is difficult to understand *why* this is the case.

An alternative approach to handle the analysis of the periodic system is to use Floquet theory

which is based on the analysis of the linearization of (2.1) which yields:

$$\frac{d\boldsymbol{X}}{dt} = \boldsymbol{A}(t)\,\boldsymbol{X}(t)\,, \quad \text{with } \boldsymbol{X}(t) = (I_H(t), I_V(t))^\top \tag{2.4}$$

and $\boldsymbol{A} : \mathbb{R} \to \mathcal{M}_{2\times 2}$ a continuous matrix valued T periodic function and $\lambda = \rho(\mathbf{\Phi_A}(T))$ the spectral radius of the monodromy matrix of system (2.4), that is

$$\frac{d\mathbf{\Phi_A}}{dt} = \boldsymbol{A}(t)\mathbf{\Phi_A}(t) \quad \text{with} \quad \mathbf{\Phi_A}(0) = I. \tag{2.5}$$

In other words, λ is the asymptotic growth rate of the epidemic in the initial phase of the epidemic and if $\lambda > 1$ the pathogen density grows exponentially and $\boldsymbol{X}^*(t) = (I_H^*(t), I_V^*(t))^\top$ is the (unique up to a constant) positive vector solution of (2.4) such that $\lambda^{-t}\boldsymbol{X}^*(t)$ has period T. It is obtained by letting $\boldsymbol{X}^*(0)$ be the positive eigenvector associated to the monodromy matrix and its spectral radius: $\mathbf{\Phi_A}(T)\boldsymbol{X}^*(0) = \lambda\boldsymbol{X}^*(0)$. The vector $\lambda^{-t}\boldsymbol{X}^*$ may be thought as the stable composition of the pathogen population in the periodic environment, for the linearized model (2.5).

Crucially, as pointed out by Heesterbeek and Roberts [HR95a; HR95b], this formalism yields another interesting quantity which is akin to the original definition of R_0 as it provides the expected number of secondary cases :

$$P = \frac{\int_0^T I_V^*(s)a(s)\beta_{VH}\,ds}{\mu_V \int_0^T I_V^*(s)\,ds} \frac{\int_0^T I_H^*(s)a(s)\beta_{HV}N_V(s)\,ds}{(\mu_H+\gamma_H)\int_0^T I_H^*(s)\,ds}. \tag{2.6}$$

As in (2.2) the first ratio of (2.6) refers to the expected number of human hosts infected by an infected vector during its lifetime, while the second ratio of (2.6) refers to the expected number of vectors infected by an infected human throughout the duration of its infection. The integral over one period of the fluctuation accounts for the fluctuations of the different parameters of the pathogen's life-cycle. This quantity can also be expressed in terms of the covariances between different key epidemiological variables:

$$P = \underbrace{\frac{\beta_{VH}\beta_{HV}\langle a\rangle^2\langle N_V\rangle}{\mu_V\,(\mu_H + r_H)}}_{P_0} \left(1 + \frac{\mathrm{Cov}\,(a, N_V)}{\langle a\rangle\langle N_V\rangle}\right)\left(1 + \frac{\mathrm{Cov}\,(I_V^*, a)}{\langle I_V^*\rangle\langle a\rangle}\right)\left(1 + \frac{\mathrm{Cov}\,(I_H^*, aN_V)}{\langle I_H^*\rangle\langle aN_V\rangle}\right). \tag{2.7}$$

Where $\langle f \rangle = \frac{1}{T}\int_0^T f(s)ds$, and $\mathrm{Cov}(f,g) = \frac{1}{T}\left(\int_0^T f(s)g(s)ds - \int_0^T f(s)ds \int_0^T g(s)ds\right)$. As expected, in the absence of temporal fluctuations all the covariances vanish and P_0 is equal to R_0 given in (2.2). We will see in the following that this expression of P can be particularly useful to understand the effects of seasonality.

Thanks to the works of Heesterbeek and Roberts [HR95a; HR95b] (see also [WZ08]) we thus have three threshold parameters R_0, λ and P that can be used to determine the ability of the pathogen to invade the population. Indeed, even if these three quantities are not equivalent, they are all equal when the pathogen reaches the threshold value $R_0 = 1$. Since the signs of $R_0 - 1$, $\lambda - 1$ and $P - 1$ are the same we can analyze the effect of seasonality on the persistence of the pathogen population using these three quantities around $R_0 = \lambda = P = 1$. Note, however, that the effect of seasonality we discuss in this limit remains qualitatively robust for other values of R_0.

In the following, we study the effect of seasonality on the stability of the disease-free equilibrium through the effect of ϵ which captures the magnitude of the influence of seasonality of distinct parameters of the model. We use a perturbation analysis of λ for small values of ϵ at $\lambda = 1$. First, we contrast the effect of seasonality on various quantities that affect the vector population and the transmission of the disease. We show that the effect of seasonality on λ depends on which trait is affected by the fluctuations of the environment. Second, we use the quantity P to provide a biological interpretation of these effects of seasonality in terms of covariance between different dynamical variables.

2.3 Results

Seasonality is known to affect various components of the life-cycle of vector-borne pathogens [Mor+13]. In the following, we assume that seasonal variations may act directly on the density of the vector population and/or on the biting rate of mosquitoes. More specifically we use the following T-periodic functions with $f(t) = \cos(2\pi t/T)$:

$$N_V(t) = N_V(0)(1 + \epsilon\, C_I f(t))\,, \quad a(t) = a_0(1 + \epsilon\, C_{II} f(t))\,, \tag{2.8}$$

where $C_I \geq 0$ and $C_{II} \geq 0$ control the magnitude of the effect of seasonality on $N_V(t)$ and $a(t)$, respectively. This model allows to account for the effects of seasonality on multiple traits

of the pathogen. In the following, we contrast two extreme scenarios: (i) model I when $C_I = 1$ and $C_{II} = 0$ and (ii) model II when $C_I = 0$ and $C_{II} = 1$.

We derive an approximation for λ for small values of ϵ (see Supplementary Information section (2.6)):

$$\lambda = \lambda_0 + \epsilon\,\lambda_1 + \epsilon^2\lambda_2 + o(\epsilon^2), \tag{2.9}$$

with $\lambda_0 = 1$ because we focus on the persistence of the pathogen population and where λ_1 and λ_2 refer to the first and second-order effects of seasonality with:

$$\lambda_1 = < f > T\,(C_I + 2C_{II})\,\frac{(\mu_H + \gamma_H)\mu_V}{\gamma_H + \mu_H + \mu_V}, \tag{2.10}$$

$$\lambda_2 = \frac{(\mu_H + \gamma_H)\mu_V T\kappa}{2(\gamma_H + \mu_H + \mu_V)}, \tag{2.11}$$

with

$$\kappa = C_I C_{II} - \frac{T^2((C_I + C_{II})\mu_V - C_{II}(\mu_H + \gamma_H))((C_I + C_{II})(\mu_H + \gamma_H) - C_{II}\mu_V)}{4\,\pi^2 + T^2(\gamma_H + \mu_H + \mu_V)^2}.$$

2.3.1 First order effect

Seasonality has a first-order effect on the stability of the disease-free equilibrium as soon as $< f > \neq 0$. For instance, consider a simple square function where $f(t) = 1$ for $t \in [0, (1-W)T]$ and $f(t) = -1$ for $t \in [(1-W)T, T]$ (with $0 < W < 1$) as illustrated in **Figure 2.1**. The parameter W governs the duration of the "winter". Higher values of W yield longer winter seasons where the total density of vectors is reduced (model I) or when the biting rate of the vector is reduced (model II). **Figure 2.1** shows that longer winters (i.e., $W > 0.5$) yield $< f >< 0$ and, in this case, more seasonality (i.e., higher values of ϵ) reduces pathogen persistence in both models I and II. In contrast, shorter winters (i.e., $W < 0.5$) yield $< f >> 0$ and, in this case, more seasonality increases pathogen persistence in both models I and II. Note that the slope of λ at $\epsilon = 0$ is λ_1, which is twice larger for model II than for model I, in agreement with equation (2.10).

However, this first-order effect of seasonality vanishes when $< f >= 0$. In particular, $< f >= 0$ for the classical scenarios we considered where $f(t) = \cos(2\pi t/T)$. In this case, we thus need to examine the second-order effect of seasonality in (2.11).

2.3.2 Second order effect

Next, we analyze the second-order effect of seasonality on λ and, in contrast with the previous section, we show that seasonality has different qualitative effects on λ in models I and II (Figure (2.2), (2.3)).

Fluctuations in vector density

In model I we have $C_I = 1$ and $C_{II} = 0$ and equation (2.9) reduces to

$$\lambda = 1 \; - \; \epsilon^2 \frac{(\mu_H + \gamma_H)\mu_V T}{2(\mu_V + \mu_H + \gamma_H)} \left(\frac{T^2(\mu_H + \gamma_H)\mu_V}{4\,\pi^2 + T^2(\mu_H + \mu_V + \gamma_H)^2} \right) + o(\epsilon^2) < 1. \tag{2.12}$$

We thus recover the effect of seasonality discussed by Bacaer [Bac07] where fluctuations of vector densities reduce the persistence of the pathogen. However, we can use the threshold quantity P to gain some insight in the understanding of the qualitative effect of the fluctuations of vector densities. In particular, we can use (2.6) to show that the stability of the disease-free equilibrium is governed by the covariance between I_H^* and N_V. In the Supplementary Information section (2.6) we derive an approximation of this covariance which shows that this covariance is always negative, which implies that $P < 1$ and thus that $\lambda < 1$ (2.13):

$$P = 1 + \frac{\mathrm{Cov}(I_H^*, N_V)}{\langle I_H^* \rangle \langle N_V \rangle} = 1 - \epsilon^2 \frac{T^2\,(\mu_H + \gamma_H)\,\mu_V}{2\left(4\pi^2 + T^2\,(\mu_V + \mu_H + \gamma_H)^2\right)} + o(\epsilon^2) < 1. \tag{2.13}$$

Since the effect of seasonality is governed by the sign of the covariance between I_H^* and N_V it is important to understand why this covariance is negative. We expect this covariance to be negative whenever the lag between the fluctuations of N_V and the fluctuations of I_H^* are larger than $T/4$ (the covariance is nil when the lag is exactly equal to $T/4$ which corresponds to a phase lag of $\pi/2$). Fluctuations in N_V first drive fluctuation in I_V with a lag approximately equal to $T/4$ (**Figure** (2.4)). Second, these fluctuations in the density of infected vectors drive the fluctuations in the dynamics in I_H. This two-step process yields a lag $> T/4$ between N_V and I_H^*, which results in a negative covariance between I_H^* and N_V (see **Figure** (2.4)).

At this stage, it is tempting to conclude that any fluctuation in the total density of the vector population always results in the same qualitative effect. But, as we will see in the following, some fluctuation in vector density may have the opposite effect on pathogen persistence. Note that the fluctuations of $N_V(t)$ assumed in model I (see equation (2.8)) re-

sults from specific assumptions regarding the per-capita growth rate of the vector population: $\rho_V(t) = \mu_V + \epsilon\frac{2\pi}{T}\frac{\sin(2\pi t/T)}{1+\epsilon\cos(2\pi t/T)}$. In the following, we study another model (model I') where we use a different periodic function to model the fluctuation of the per-capita growth rate of the vector population $\rho_V(t) = \mu_V(1 + \epsilon\cos(2\pi t/T))$ as in [Lor+96; HR95b]. This yields the following vector dynamics (see **Figure 2.5** and Supplementary Information section 2.6.4):

$$N_V(t) = N_V(0)\exp\left(\epsilon C_{I'} f(t)\right) = N_V(0)(1 + \epsilon C_{I'} f(t) + \epsilon^2\frac{C_{I'}^2 f^2(t)}{2} + o(\epsilon^2)). \tag{2.14}$$

Again the examination of P helps us understand what is going on. The average value of N_V is affected by seasonality and fluctuations increase the mean density of vectors which feed back on transmission. Indeed, unlike model I where $< N_V >= N_V(0)$, in model I' $< N_V >= N_V(0)(1 + \epsilon^2 C_{I'}^2/4)$. This yields the following expression for P:

$$\begin{aligned} P &= \left(1 + \frac{\epsilon^2 C_{I'}^2}{4}\right)\left(1 + \frac{\mathrm{Cov}\left(I_H^*, N_V\right)}{\langle I_H^*\rangle\langle N_V\rangle}\right) \\ &= 1 + \epsilon^2 C_{I'}^2\left(\frac{1}{4} - \frac{\left(\mu_H + \gamma_H\right)\mu_V}{2 + \frac{T^2}{2\pi^2}(\mu_V + \mu_H + \gamma_H)^2}\right) + o(\epsilon^2) > 1, \end{aligned} \tag{2.15}$$

which also yields:

$$\lambda = 1 + \epsilon^2 C_{I'}^2\frac{\left(\mu_H + \gamma_H\right)\mu_V T}{(\mu_V + \mu_H + \gamma_H)}\left(\frac{1}{4} - \frac{\left(\mu_H + \gamma_H\right)\mu_V}{2 + \frac{T^2}{2\pi^2}(\mu_V + \mu_H + \gamma_H)^2}\right) + o(\epsilon^2) > 1. \tag{2.16}$$

Interestingly the covariance between the fluctuations of the density of infected hosts and the density of the vector population in (2.15) remains negative (as in model I, see **Figure** (2.7)). Yet, the effect of seasonality on the average density of the vector population is positive and overwhelms its effect on the covariance. This explains why seasonality has a positive effect on pathogen persistence in model I' (**Figure 2.2**).

Fluctuations in biting rates

In model II we have $C_I = 0$ and $C_{II} = 1$ and equation (2.9) reduces to

$$\lambda = 1 + \epsilon^2\frac{\left(\mu_H + \gamma_H\right)\mu_V T}{2(\mu_H + \gamma_H + \mu_V)}\left(\frac{T^2(\mu_H + \gamma_H - \mu_V)^2}{4\,\pi^2 + T^2(\mu_H + \gamma_H\mu_V)}\right) + o(\epsilon^2) > 1. \tag{2.17}$$

In other words, seasonality is increasing disease persistence in this model (**Figure 2.2**).

Again, we can use equation (2.6) for P to get a better understanding of this result. Since seasonality affects only the biting rate a the density of the vector population N_V is constant and we get

$$P = \left(1 + \frac{\mathrm{Cov}(I_V^*, a)}{\langle I_V^* \rangle \langle a \rangle}\right)\left(1 + \frac{\mathrm{Cov}(I_H^*, a)}{\langle I_H^* \rangle \langle a \rangle}\right) \tag{2.18}$$

$$= 1 + \frac{\mathrm{Cov}(I_V^*, a)}{\langle I_V^* \rangle \langle a \rangle} + \frac{\mathrm{Cov}(I_H^*, a)}{\langle I_H^* \rangle \langle a \rangle} + o(\epsilon^2) = 1 + \epsilon^2 \left(\frac{T}{2\pi}\right)^2 (\mu_H + \gamma_H - \mu_V)^2 + o(\epsilon^2) > 1 \tag{2.19}$$

To understand the sign of $P - 1$ we need to understand the sign of the covariances that appear in (2.19). Crucially, we obtained approximations for these covariances in the Supplementary Information section (2.6), and we show that the sign of $\mathrm{Cov}(I_V^*, a)$ is the sign of $(\mu_H + \gamma_H) - \mu_V$ and is the opposite sign of $\mathrm{Cov}(I_H^*, a)$. Indeed, the duration of infection in the host, $1/(\mu_H + \gamma_H)$, and in the vector, $1/\mu_V$, govern the speed at which the dynamics of the infections reacts to a fluctuation of the biting rate. A shorter duration of infection in one host relative to the other leads to a positive covariance with the biting rate as well as a larger amplitude of fluctuations because the epidemic spreads faster with shorter generation time (see **Figure 2.6**). Interestingly, the sum of these two covariances is always positive, unless the duration of infection in both hosts is equal (i.e., $\mu_H + \gamma_H = \mu_V$). **Figure** 2.6 illustrates the influence of the relative duration of infection in the two hosts on the sign of the covariances and on the amplitude of the oscillations.

2.4 Discussion

Periodic fluctuations of the environment due to seasonality can affect dramatically the dynamics of infectious diseases [Alt+06; Mar18]. In vector-borne diseases, understanding the overall influence of seasonality is difficult because fluctuations in temperature alter multiple life-history traits of the vector and the pathogen [Mor+19; Mor+13; SWT17; Tes+18; Mor+17]. Hence multiple steps of the life-cycle of the pathogen may be affected simultaneously by seasonality. Previous theoretical analysis of the influence of seasonality focused mainly on the influence of fluctuations in vector density [Hee+15; Lor+96; Bac07] and showed how these fluctuations could either increase or decrease the persistence of vector-borne pathogens. Fluctuations in transmission rates have also been shown to affect the persistence of vector-borne pathogens [WZ08]. Yet, we currently lack a good understanding of the influence of seasonality when the periodic fluctuations of the environment can affect multiple components of the

pathogen life-cycle. Here we expand earlier studies of the effect of seasonality to provide a deeper understanding of the influence of periodic fluctuations of the environment on the basic reproduction ratio (and thus on the persistence) of vector-borne pathogens. Pathogen persistence varies with the speed, the amplitude and the shape of the fluctuations as well as on the specific life-history traits modified by seasonality.

The speed and the amplitude of seasonal fluctuations. Our analysis shows that lower speed of fluctuations (i.e., higher T) and higher amplitudes (i.e., higher ϵ) always magnify the effects of seasonality. Indeed, faster fluctuations (e.g., daily) or fluctuations with small amplitudes tend to average out and they tend to have a negligible effect on epidemiological dynamics.

The shape of seasonal fluctuations. If the periodic functions $f(t)$ used to model the effect of seasonality are such that $< f > \neq 0$ we expect a first order effect of seasonality. This effect simply results from the effect of seasonality on transmission opportunities. For instance, if the influence of seasonality is only to increase the duration of a winter season in which the density of vectors is very low, seasonality will always result in lower disease persistence because it will decrease the average density of vectors. We illustrated this scenario in **Figure 2.1**. In contrast, if we use periodic functions where $< f >= 0$ this first-order effect of seasonality vanishes. Yet, seasonality can still have a second-order effect on pathogen persistence. This second-order effect can be qualitatively different from the first-order effect (compare **Figures 2.1** and **2.2**). It is interesting to note that this second-order effect can also be affected by the shape of the fluctuations. This is illustrated by the difference between model I and model I' (see **Figures 2.2**). Both models assume that seasonality affects the fluctuation of vector density but the shape of the fluctuation varies between the two models (**2.5**) and affects qualitatively the influence of seasonality on pathogen persistence.

The life-history traits altered by seasonal fluctuations. As pointed out before, the influence of seasonality varies with the life-history traits affected by seasonality [HR95a; HR95b; Bac07; WZ08]. In the present paper, we focused on the influence of seasonality on two quantities: the vector density (model I) and the biting rate of the vector (model II). In the first order, fluctuations in both quantities had similar effects on pathogen persistence because both quantities are linked to pathogen transmission. Yet, it is interesting to note that fluctuations in the biting rate where twice more impactful. This factor 2 stems from the fact that biting rates act at two different stages of the pathogen life-cycle, while vector density acts only once. This

is clear from the expression of R_0 in equation (2.2) where a appears twice and N_V only once.

At the second order, the influence of seasonality varies between models I and II and when seasonality acts on both the biting rate and the vector density, the overall influence of seasonality depends on the magnitude of the influence of seasonality on these two traits (i.e., the parameters C_I and C_{II} in equation (2.11)). A better understanding of these effects can be obtained from the examination of P and the covariance between different dynamical variables of the system. In a fluctuating environment, several dynamical variables change through time and the phase shift between these quantities determines if the average transmission is increased or decreased by seasonality. Indeed, if X and Y refer to dynamical quantities involved in transmission, the average transmission will given by $< XY >=< X >< Y > + \mathrm{Cov}(X, Y)$ and hence by the covariance between these quantities. The analysis of models I and II illustrates how one can gain an intuitive understanding of the effect of seasonality via the examination of these covariance terms. Our examination of the covariance is akin to the interpretation of the effect of seasonality mediated by the relative timing between the peaks in prevalence in the vector and in the host populations [Hee+15; Lor+96].

To conclude, we present a general theoretical framework that allows us to extend previous analyses of the influence of seasonal fluctuations of the environment on the R_0 of vector-borne pathogens. Our analysis highlights the complexity of the influence of seasonality and the necessity to take into account the details of the biology of the pathogen and the vector to understand the effect of seasonality because very similar models can yield qualitatively different conclusions on the influence of seasonality. We hope the present theoretical framework will be used to explore the influence of seasonality in a broader range of epidemiological scenarios tailored to the biology of different infectious diseases. This will help improve the accuracy of risk maps aiming to identify geographic regions that are most likely to be subject to the emergence or the re-emergence of some pathogens [Kra+16; Jon+08; Kit00]. In addition, our analysis could also help identify more effective time-varying control measures against pathogens [GF06; CG20].

2.5 Tables and Figures

Table 2.1 – Parameters and variables of the models

Symbol	Description
Parameters	
a	biting rate of vectors
β_{VH}	rate of transmission from an infected vector to a susceptible host
β_{HV}	rate of transmission from an infected host to a susceptible vector
ρ_V	growth rate of the vector
μ_V	death rate of the vector
μ_H	death rate of the host
γ_H	recovery rate of the infected host
Variables	
θ	the periodic influx of susceptible hosts
S_H	density of susceptible hosts
I_H	density of infected hosts
R_H	density of recovered hosts
N_H	density of the total host population: $N_H = R_H + I_H + S_H$
S_V	density of susceptible vectors
I_V	density of infected vectors
N_V	total vector population density: $N_V = S_V + I_V$

2.6 Supplementary information

2.6.1 The vector-borne disease model

We consider the following dynamical system

$$\begin{aligned}
\frac{\mathrm{d}S_H}{\mathrm{d}t} &= \theta - a\beta_{VH}\frac{I_V S_H}{N_H} - \mu_H S_H,\\
\frac{\mathrm{d}I_H}{\mathrm{d}t} &= a\beta_{VH}\frac{I_V S_H}{N_H} - (\mu_H + \gamma_H) I_H,\\
\frac{\mathrm{d}R_H}{\mathrm{d}t} &= \gamma_H I_H - \mu_H R_H,\\
\frac{\mathrm{d}S_V}{\mathrm{d}t} &= \rho_V N_V - a\beta_{HV} I_H S_V - \mu_V S_V,\\
\frac{\mathrm{d}I_V}{\mathrm{d}t} &= a\beta_{HV} I_H S_V - \mu_V I_V.
\end{aligned} \tag{2.20}$$

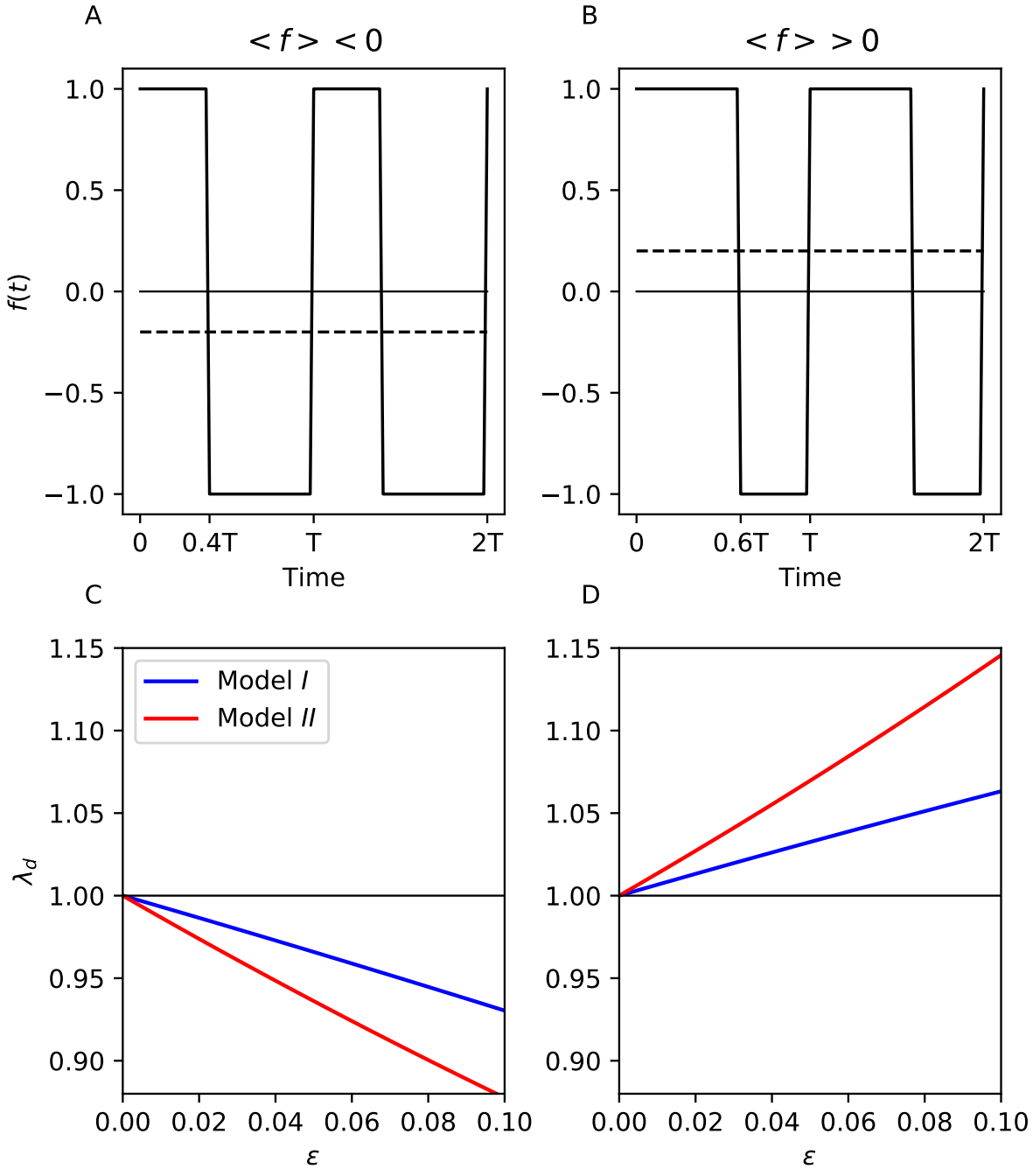

Figure 2.1 – **The first order effect of seasonality drives the stability of the disease-free equilibrium when** $< f > \neq 0$**.** In **(A)** We assume $x = 0.4$ and thus $f(t) = \mathbb{1}_{(0 \leq \lfloor t/T \rfloor < 0.4T)} - \mathbb{1}_{(0.4T \leq \lfloor t/T \rfloor < T)}$. In **(B)** we assume $x = 0.6$ and thus $f(t) = \mathbb{1}_{(0 \leq \lfloor t/T \rfloor < 0.6T)} - \mathbb{1}_{(0.6T \leq \lfloor t/T \rfloor < T)}$. In **(C)** and **(D)** we plot the effect of seasonality (i.e., ϵ) on λ_ϵ for the two scenarios **(A)** and **(B)**. In model I, $C_I = 1, C_{II} = 0$ so that $N_V = 1 + \epsilon f(t)$, $a(t) = 1$. In model II, $C_I = 0, C_{II} = 1$, so that $N_V(t) = 1, a(t) = 1 + \epsilon f(t)$. Parameters values: $T = 5, \beta_{HV} = 1, \beta_{VH} = 2, \mu_H = 0.5, \mu_V = 1, \gamma_H = 1.5$.

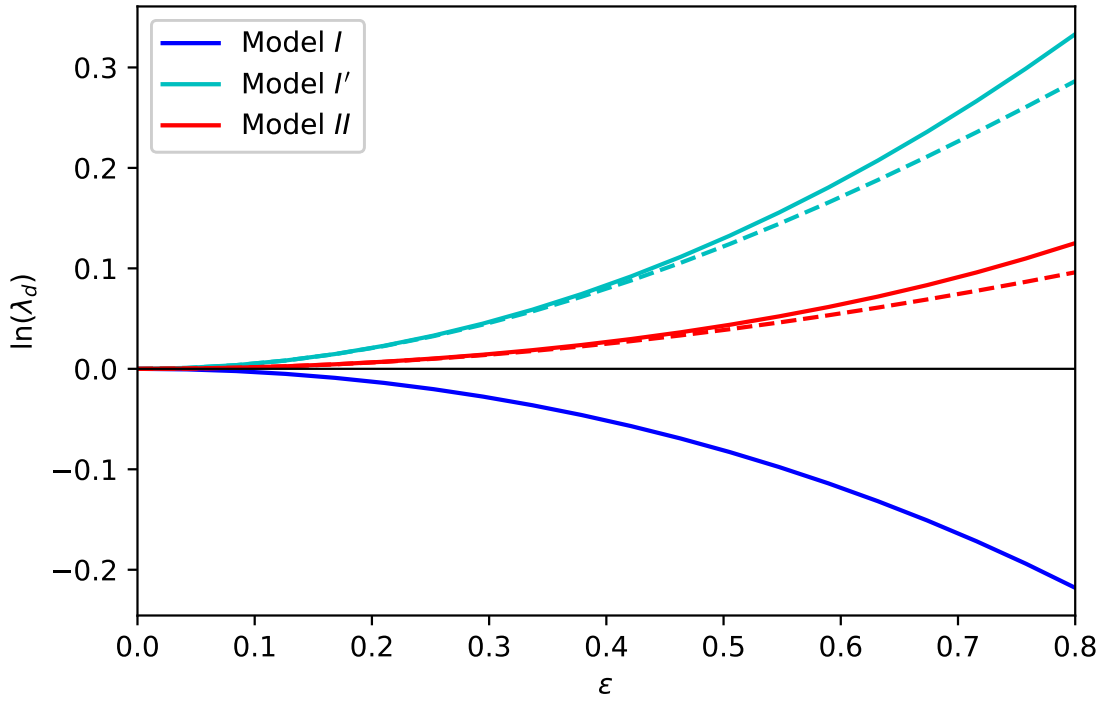

Figure 2.2 – **The second order effect of seasonality on λ_ϵ for three different models**. The blue, cyan and red curves represent the value of $\log \lambda_\epsilon$ in models I, I' and II, respectively. The solid line indicates the exact numerical result while the dashed lines indicate the second order approximation given in equations (2.12), (2.17) and (2.16). In models I and I': $C_I = 1, C_{II} = 0$. In model II: $C_I = 0, C_{II} = 1$. Parameter values: $T = 5, f(t) = \cos(2\pi t/T), \mu_H = 0.5, \mu_V = 1, \gamma_H = 1.5, \beta_{HV} = 1, \beta_{VH} = 2$.

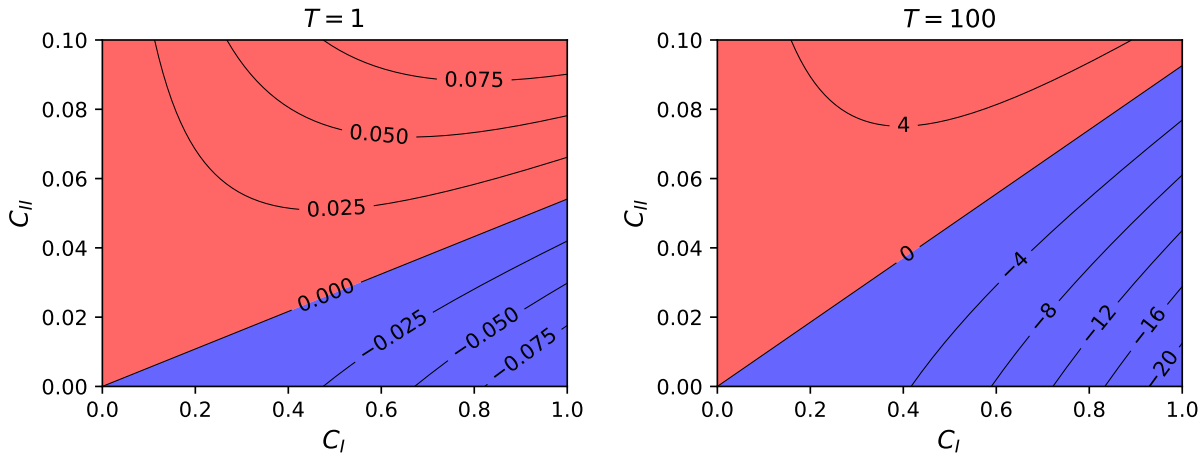

Figure 2.3 – **Joint effects of C_I and C_{II} on λ_2 in equation** (2.11). We plot the second order effect of seasonality on λ where $f(t) = \cos(2\pi t/T)$. We use red shading when $\lambda_2 > 0$, and blue shading when $\lambda_2 < 0$. On the left panel, we use $T = 1$ and the difference in λ_2 between each isocline is 0.025, and on the right panel we use $T = 100$ and the difference in λ_2 between each isocline is 4. Parameter values: $\mu_H = 0.05, \mu_V = 1, \gamma_H = 5$.

For the sake of simplicity we assume that the total density of the human population $S_H + I_H + R_H = N_H$ remains constant which implies that $\theta = \mu_H (S_H + I_H + R_H)$.

2.6.2 The constant case

In a constant environment, we assume that the parameters that govern the life cycle of the vector do not vary with time and if the fecundity of the vector compensates exactly its mortality (i.e., $\rho_V = \mu_V$) the total density of the vector population $S_V + I_V = N_V$ is also constant. In this scenario, the basic reproduction ratio is readily derived from the linearisation of the above system at the disease free equilibrium ($I_V = I_H = R_H = 0, S_H = N_H, S_V = N_V$) which yields (see [DHR10]):

$$\frac{d\mathbf{X}}{dt} = \boldsymbol{A}\,\boldsymbol{X}(t)\,, \quad \text{with } \boldsymbol{X}(t) = (I_H(t), I_V(t))^\top\,, \tag{2.21}$$

with

$$\boldsymbol{A} = \begin{pmatrix} -(\mu_H + \gamma_H) & a\beta_{VH} \\ a\beta_{HV} N_V & -\mu_V \end{pmatrix} \tag{2.22}$$

To determine the ability of the pathogen to invade the population. We use one of the three thresholds P, λ and R_0 was introduced by [HR95b; HR95a] and [WZ08].

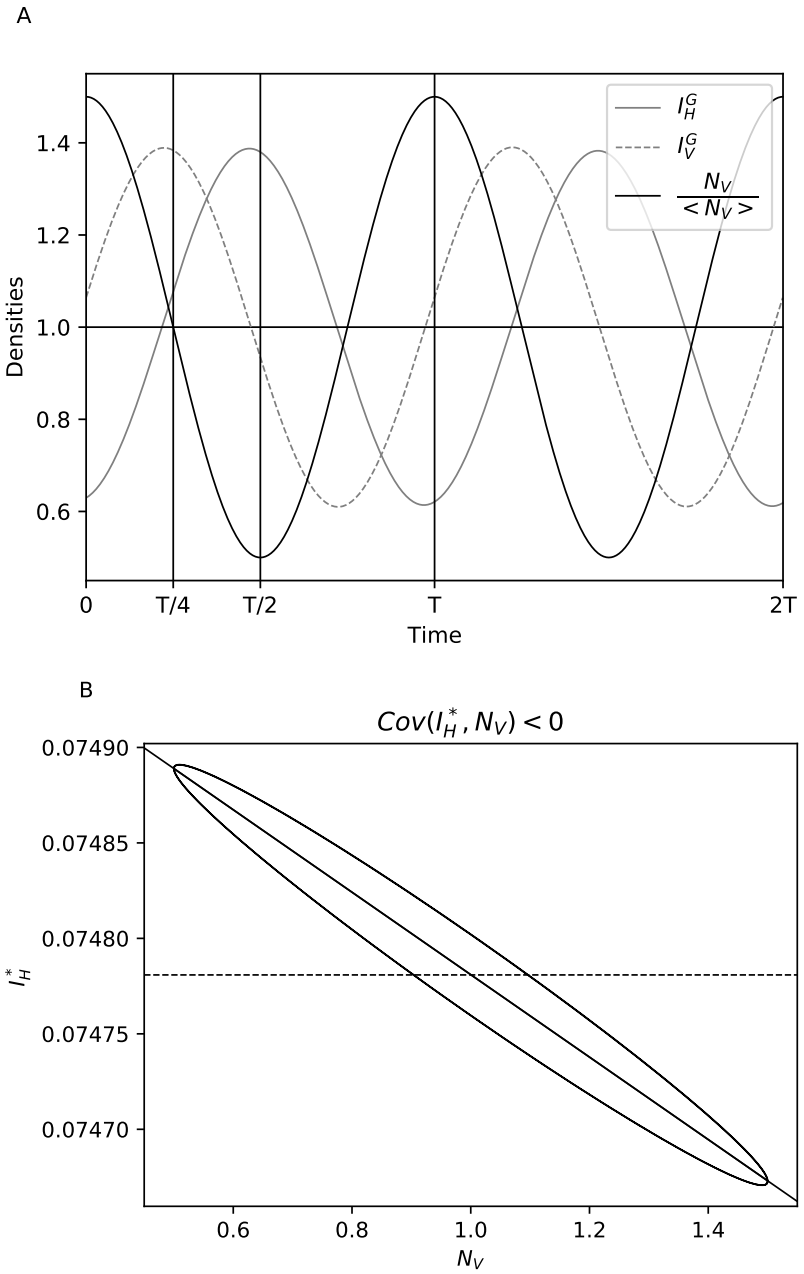

Figure 2.4 – **Understanding the covariance between N_V and I_H^* in model I.** In **(A)**, we plot the density of the vector population N_V (full black line), the density of infected vectors I_V (dashed gray line with scale $I_V^G = 1 + 100\left(\frac{I_V^*(t)}{\langle I_V \rangle} - 1\right)$), the density of infected hosts I_H (full gray line with scale $I_H^G = 1 + 3500\left(\frac{I_H^*(t)}{\langle I_H \rangle} - 1\right)$. Note that the densities I_V^* and I_H^* are rescaled using I_V^G and I_H^G to better visualize the lag with the fluctuations of N_V. The density of the infected vector population I_V^* follows the fluctuations of N_V with a lag approximately equal to $T/4$. The density of infected hosts I_H^* is driven by the fluctuations of infected vectors which yields a larger lag behind the fluctuations of N_V (this lag is close to $T/2$). In **(B)** we present the dynamics of N_V and I_H^* for the same parameter values to show how a lag $> T/4$ results in a negative $\mathrm{Cov}\,(N_V, I_H^*)$. The sign of $\mathrm{Cov}(I_H^*, N_V)$ is given by the slope of the regression line (full black line). Parameter values: $a_0 = N_V(0) = \beta_{HV} = 1$, $1 = \beta_{VH}, \epsilon = 0.5, T = 1$, $\mu_V = 1, \mu_H = 0.01, \gamma_H = 0.1$.

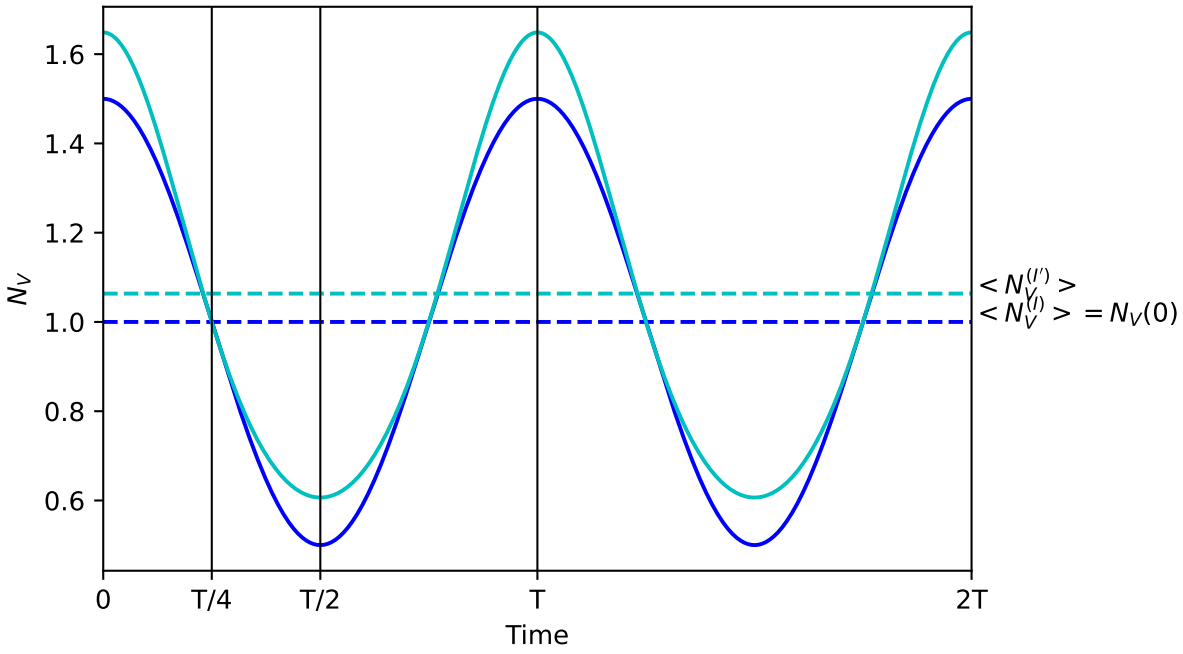

Figure 2.5 – **Fluctuations of the density of vectors in models I and I'.** In model I (blue curve) we assume $N_V(t) = 1 + \epsilon f(t)$. In model I' (cyan curve) we assume $N_V(t) = e^{\epsilon f(t)}$. The dashed lines indicate the average value of the density of the vector population and we see that this average value is higher in model I'. This effect on the average density of vectors drives the first-order effect of seasonality in model I' we illustrate in Figure (2.2). Parameter values: $\epsilon = 0.5$ and $T = 10$, $f(t) = \cos(2\pi t/T)$.

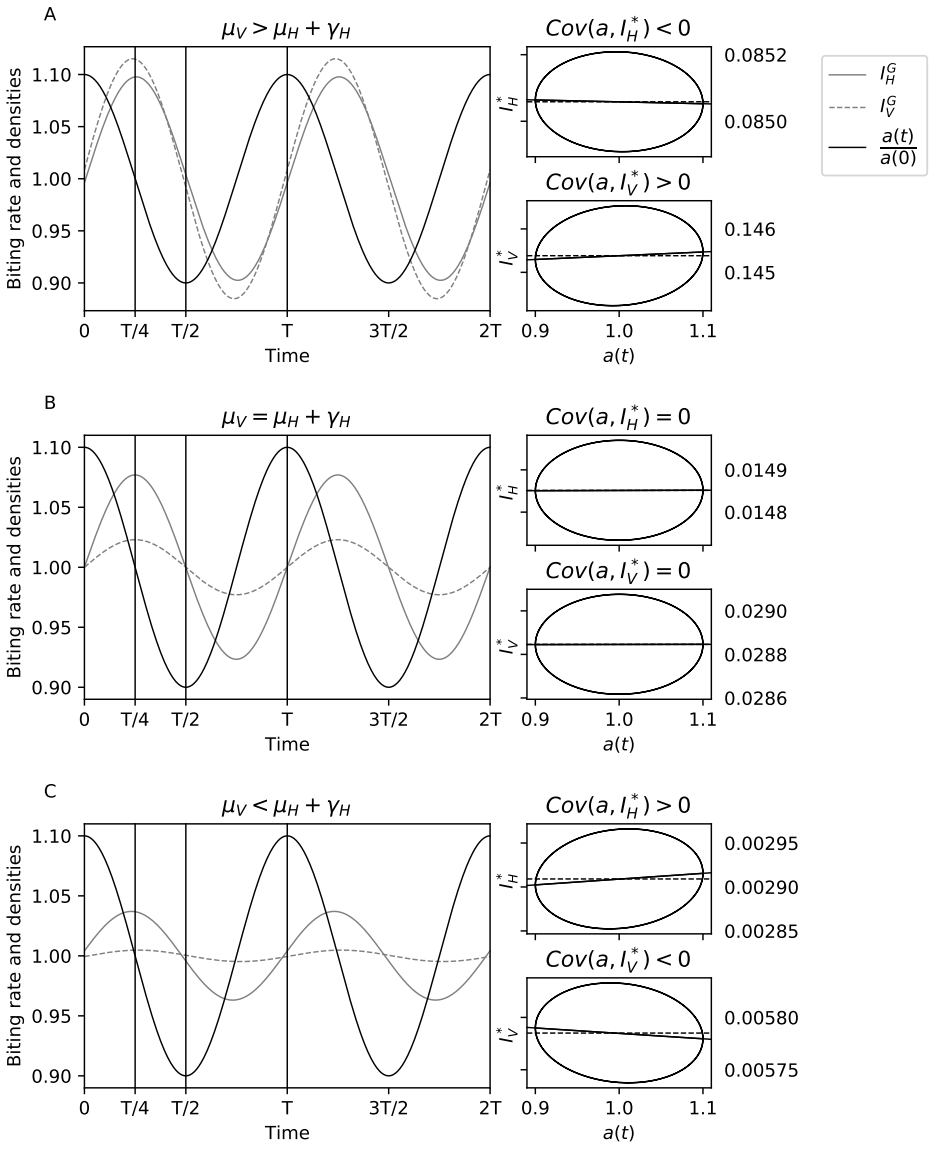

Figure 2.6 – **Understanding the covariance between a, I_V^* and I_H^* in model II.** We plot the joint dynamics of the biting rate (solid black line), the density of infected vectors (dashed gray line with $I_V^G = 1 + 100\left(\frac{I_V^*(t)}{\langle I_V \rangle} - 1\right)$) and the density of infected hosts (full gray line with $I_H^G = 1 + 650\left(\frac{I_H^*(t)}{\langle I_H \rangle} - 1\right)$) in different scenarios. In **(A)** we assume $\gamma_H = 0.01$ and thus $\mu_V > \mu_H + \gamma_H$. In this case the lag between the fluctuation of $a(t)$ and $I_V(t)^*$ is lower than $T/4$ which leads to $\mathrm{Cov}(a, I_V^*) > 0$ as indicated on the phase diagram on the right panel. In contrast, the lag between the fluctuation of $a(t)$ and $I_H(t)^*$ is higher than $T/4$ which leads to $\mathrm{Cov}(a, I_V^*) < 0$. As in Figure (2.2) the sign of the covariance is given by the slope of the regression line indicated on the phase plane with a black line. In **(B)** we assume $\gamma_H = 0.49$ and thus $\mu_V = \mu_H + \gamma_H$. In this case the lag between the fluctuation of $a(t)$ and both $I_V(t)^*$ and $I_H(t)^*$ is equal to $T/4$ which implies that $\mathrm{Cov}(a, I_V^*) = \mathrm{Cov}(a, I_H^*) = 0$. In case **(C)** we assume $\gamma_H = 1.25$ which implies that $\mu_V < \mu_H + \gamma_H$. Compare with **(A)** and note how the modification of a single parameter affects the sign of both $\mathrm{Cov}(a, I_V^*)$ and $\mathrm{Cov}(a, I_H^*)$. Other parameter values: $\epsilon = 0.5, a_0 = N_V(0) = \beta_{HV} = \beta_{VH} = 1$, $\mu_V = 0.5, \mu_H = 0.01, T = 1$.

We rewrite the constant matrix $\boldsymbol{A} = \boldsymbol{F} - \boldsymbol{V}$ such that $\boldsymbol{F}$ and $\boldsymbol{V}$ satisfies the Next Generation Theorem [DHR10] and yields

$$\boldsymbol{F} = \begin{pmatrix} 0 & a\beta_{VH} \\ a\beta_{HV}N_V & 0 \end{pmatrix} \quad \boldsymbol{V} = \begin{pmatrix} \mu_H + \gamma_H & 0 \\ 0 & \mu_V \end{pmatrix}.$$

Therefore

$$\boldsymbol{F}\boldsymbol{V}^{-1} = \begin{pmatrix} 0 & \dfrac{a\beta_{VH}}{\mu_V} \\ \dfrac{a\beta_{HV}N_V}{\mu_H + \gamma_H} & 0 \end{pmatrix},$$

and

$$R_0 = \rho\left(\boldsymbol{F}\boldsymbol{V}^{-1}\right) = \frac{a\beta_{VH}}{\mu_V}\frac{a\beta_{HV}N_V}{\mu_H + \gamma_H}. \tag{2.23}$$

2.6.3 The periodic case

We assume that the vector population and the biting rate oscillate using the following periodic functions

$$N_V(t) = N_V(0)(1 + \epsilon C_I\, f(t)), \tag{2.24}$$
$$a(t) = a_0(1 + \epsilon\, C_{II} f(t)), \tag{2.25}$$

where $f(t)$ is a periodic function with period T and ϵ measures the amplitude of the effects of seasonal fluctuations. Taylor expansion of the transition matrix $\boldsymbol{A}(t)$ for small ϵ yields:

$$\boldsymbol{A}(t) = \boldsymbol{A}_0 + \epsilon f(t)\boldsymbol{A}_1 + \epsilon^2 f(t)^2 \boldsymbol{A}_2 + o(\epsilon^2), \tag{2.26}$$

with $o(\epsilon^2)$ uniform in time and

$$\boldsymbol{A}_0 = \begin{pmatrix} -(\mu_H + \gamma_H) & a_0\beta_{VH} \\ a_0\beta_{HV}N_V(0) & -\mu_V \end{pmatrix}, \tag{2.27}$$

$$\boldsymbol{A}_1 = \begin{pmatrix} 0 & a_0\beta_{VH}C_{II} \\ a_0\beta_{HV}N_V(0)(C_I + C_{II}) & 0 \end{pmatrix}, \tag{2.28}$$

$$\boldsymbol{A}_2 = \begin{pmatrix} 0 & 0 \\ a_0\beta_{HV}N_V(0)C_IC_{II} & 0 \end{pmatrix}. \tag{2.29}$$

We let $\boldsymbol{L} = \mathbf{\Phi}_{\mathbf{A}}(T)$ be the monodromy matrix associated with $\boldsymbol{A}(t)$. We first observe that thanks to Duhamel's formula (see subsection 2.6.5) for perturbation of linear operators, we have the Taylor expansion

$$\mathbf{L} = \mathbf{L}_0 + \epsilon \mathbf{L}_1 + \epsilon^2 \mathbf{L}_2 + o(\epsilon^2), \tag{2.30}$$

where

$$\begin{aligned}
\mathbf{L}_0 &= e^{T\boldsymbol{A}_0} \\
\mathbf{L}_1 &= \int_0^T e^{(T-s)\boldsymbol{A}_0} f(s) \boldsymbol{A}_1 e^{s\boldsymbol{A}_0}\, ds \\
\mathbf{L}_2 &= \int_0^T e^{(T-s)\boldsymbol{A}_0} f(s)^2 \boldsymbol{A}_2 e^{s\boldsymbol{A}_0}\, ds + \int_0^T e^{(T-s)\boldsymbol{A}_0} f(s) \boldsymbol{A}_1 \int_0^s e^{(s-\tau)\boldsymbol{A}_0} f(\tau) \boldsymbol{A}_1 e^{\tau \boldsymbol{A}_0}\, d\tau\, e^{s\boldsymbol{A}_0}\, ds\,.
\end{aligned}$$

Since $\boldsymbol{A}_0$ is cooperative (with non negative off-diagonal entries) and irreducible, the matrix $\mathbf{L}_0$ has positive entries, and by Perron Frobenius theorem, the spectral radius $\lambda_0 = \rho(\mathbf{L}_0)$ is an isolated eigenvalue with positive left and right eigenvectors $\mathbf{v}_0, \mathbf{u}_0$. Therefore, see e.g. [Kat66] or [Klo17], for small ϵ there exists positive left and right eigenvectors of $\mathbf{L}$ with eigenvalue $\lambda = \rho(\mathbf{L})$: we have

$$\mathbf{L}\mathbf{u} = \lambda \mathbf{u}\,, \quad \mathbf{v}\mathbf{L} = \lambda \mathbf{v}\,, \quad \mathbf{v}\mathbf{u} = 1 = (1,1)^T \mathbf{u}\,, \tag{2.31}$$

and we have Taylor expansions for $\lambda, \mathbf{u}, \mathbf{v}$ and therefore for P:

$$\mathbf{u} = \mathbf{u}_0 + \epsilon \mathbf{u}_1 + \epsilon^2 \mathbf{u}_2 + o(\epsilon^2), \tag{2.32}$$

$$\lambda = \lambda_0 + \epsilon \lambda_1 + \epsilon^2 \lambda_2 + o(\epsilon^2), \tag{2.33}$$

$$P = P_0 + \epsilon P_1 + \epsilon^2 P_2 + o(\epsilon^2)\,. \tag{2.34}$$

Assumption Without loss in generality, and to simplify statements, we shall assume that $R_0 = P_0 = \lambda_0 = 1$. Indeed the transformation $\boldsymbol{A}_0 \to \boldsymbol{A}_0 + \kappa I$ translates to $\lambda_0 \to \lambda_0 e^{\kappa T}$.

First order results

We shall assume that $\langle f \rangle = \int_0^1 f(s)\, ds \neq 0$.

Proposition 1. *The first order approximations of λ and P are given by:*

$$\lambda = 1 + \epsilon\langle f\rangle T(C_I + 2C_{II})\frac{\mu_V(\mu_H+\gamma_H)}{\mu_V+\mu_H+\gamma_H} + o(\epsilon)\,, \tag{2.35}$$

$$P = 1 + \epsilon\langle f\rangle T(C_I + 2C_{II}) + o(\epsilon)\,. \tag{2.36}$$

Proof. Identifying the coefficient of ϵ in $\mathbf{Lu} = \lambda\mathbf{u}$ yields:

$$\mathbf{L}_1\mathbf{u}_0 + \mathbf{L}_0\mathbf{u}_1 = \lambda_1\mathbf{u}_0 + \lambda_0\mathbf{u}_1\,. \tag{2.37}$$

Multiplying on the left by $\mathbf{v}_0$, we get since $\mathbf{v}_0\mathbf{L}_0 = \lambda_0\mathbf{v}_0$ and $\mathbf{v}_0\mathbf{u}_0 = 1$,

$$\lambda_1 = \mathbf{v}_0\mathbf{L}_1\mathbf{u}_0 = \int_0^T \mathbf{v}_0 e^{(T-s)\boldsymbol{A}_0} f(s)\boldsymbol{A}_1 e^{s\boldsymbol{A}_0}\mathbf{u}_0\, ds\,. \tag{2.38}$$

Since $\boldsymbol{A}_0\mathbf{L}_0 = \boldsymbol{A}_0 e^{T\boldsymbol{A}_0} = e^{T\boldsymbol{A}_0}\boldsymbol{A}_0 = \mathbf{L}_0\mathbf{u}_0$ and $\mathbb{R}\mathbf{u}_0$ is the eigenspace of $\mathbf{L}_0$ with eigenvalue $\mathbf{u}_0$, we infer that $\mathbf{u}_0$ is an eigenvector of $\boldsymbol{A}_0$ and since $e^{T\boldsymbol{A}_0}\mathbf{u}_0 = \lambda_0\mathbf{u}_0 = \mathbf{u}_0$ we get that $\boldsymbol{A}_0\mathbf{u}_0 = 0$. Similarly $\mathbf{v}_0\boldsymbol{A}_0 = 0$ and thus $e^{s\boldsymbol{A}_0}\mathbf{u}_0 = \mathbf{u}_0$ and $\mathbf{v}_0 e^{s\boldsymbol{A}_0} = \mathbf{v}_0$. Eventually, we get

$$\lambda_1 = T\langle f\rangle\mathbf{v}_0\boldsymbol{A}_1\mathbf{u}_0 = T(C_I + 2C_{II})\frac{\mu_V(\mu_H+\gamma_H)}{\mu_V+\mu_H+\gamma_H}. \tag{2.39}$$

We have used explicit formulas for $\mathbf{u}_0$ and $\mathbf{v}_0$. Let $\alpha = a_0\beta_{VH}$ and $\gamma = a_0\beta_{HV}N_V(0) = \frac{\mu_V(\mu_H+\gamma_H)}{\alpha}$. Then

$$\mathbf{u}_0 = \frac{1}{\alpha+\mu_H+\gamma_H}(\alpha, \mu_H+\gamma_H)^T\,, \qquad \mathbf{v}_0 = \frac{\alpha+\mu_H+\gamma_H}{\alpha(\mu_H+\gamma_H+\mu_V)}(\mu_V, \alpha)^T. \tag{2.40}$$

To obtain the first order expansion of P, we recall P formula (see (2.7)): since for $\epsilon = 0$, we have $P_0 = R_0 = 1$, we have

$$P = P_0\frac{\langle a\rangle\langle aN_V\rangle}{a_0^2 N_V(0)}\left(1+\frac{\mathrm{Cov}(a,N_V)}{\langle a\rangle\langle N_V\rangle}\right)\left(1+\frac{\mathrm{Cov}(a,I_V^*)}{\langle a\rangle\langle I_V^*\rangle}\right)\left(1+\frac{\mathrm{Cov}(aN_V,I_H^*)}{\langle aN_V\rangle\langle I_H^*\rangle}\right). \tag{2.41}$$

Recall that we have

$$\mathbf{X}^*(t) = \mathbf{\Phi}_{\mathbf{A}}(t)\mathbf{u} = e^{t\boldsymbol{A}_0}\mathbf{u}_0 + o(1) = \mathbf{u}_0 + o(1)\,. \tag{2.42}$$

Therefore, since $I_V^* = e_2^T\mathbf{X}^*$ is the second coordinate of $\mathbf{X}^*$, and the covariance with a constant

is 0,

$$\mathrm{Cov}(a, I_V^*) = \mathrm{Cov}(a_0(1 + C_{II}\epsilon f(s)), e_2^T \mathbf{X}^*(s)) = a_0 C_{II}\epsilon \,\mathrm{Cov}(f(s), e_2^T \mathbf{u}_0) + o(\epsilon) = o(\epsilon)\,. \tag{2.43}$$

Similarly $\mathrm{Cov}(aN_V, I_H^*) = o(\epsilon)$ and $\mathrm{Cov}(a, N_V) = C_I C_{II}\epsilon^2 \,\mathrm{Var}(f) = o(\epsilon)$. Hence

$$\begin{aligned} P &= \frac{\langle a\rangle\langle aN_V\rangle}{a_0^2 N_V} + o(\epsilon) \\ &= \langle 1 + \epsilon C_{II} f(s)\rangle \,\langle (1 + \epsilon C_I f(s) + o(\epsilon))(1 + \epsilon C_{II} f(s))\rangle + o(\epsilon) \\ &= 1 + \epsilon(C_I + 2C_{II}) + o(\epsilon)\,. \end{aligned}$$

□

Second order results

Expansion for λ

Proposition 2. *With $w = \mu_H + \gamma_H + \mu_V$, $f(t) = \cos(2\pi t/T)$ and $c = 1 + w^2\left(\frac{T}{2\pi}\right)^2$ we have the second order Taylor expansion*

$$\lambda = 1 + \epsilon^2 \lambda_2 + o(\epsilon^2)\,, \tag{2.44}$$

where

$$\begin{aligned} \lambda_2 &= \boldsymbol{v}_0 \mathbf{L}_2 \boldsymbol{u}_0 + (1 - e^{-Tw})^{-1}\, \boldsymbol{v}_0 (\mathbf{L}_1)^2 \boldsymbol{u}_0 \\ &= \frac{(\mu_H + \gamma_H)\mu_V T}{2(\gamma_H + \mu_H + \mu_V)} \left(C_I C_{II} - \frac{T^2((C_I + C_{II})\mu_V - C_{II}(\mu_H + \gamma_H))((C_I + C_{II})(\mu_H + \gamma_H) - C_{II}\mu_V)}{4\,\pi^2 + T^2(\gamma_H + \mu_H + \mu_V)^2} \right). \end{aligned}$$

Proof. Without loss in generality we can assume $\gamma_H = 0$ and then replace in the final formulas μ_H by $\mu_H + \gamma_H$. Since $\lambda_1 = const.T\langle f\rangle = 0$, we obtain from (2.37)

$$\mathbf{L}_1 \mathbf{u}_0 = \left(I - e^{T\boldsymbol{A}_0}\right) \mathbf{u}_1. \tag{2.45}$$

Observe that the spectrum of $\boldsymbol{A}_0$ is $\sigma(\boldsymbol{A}_0) = \{0, -w\}$ where $w = -\mathrm{trace}(\boldsymbol{A}_0)$ Let $\pi(x) = x - \langle x, \mathbf{v}_0\rangle \mathbf{u}_0$ be the projection on $\mathbf{v}_0^\perp$ of the decomposition $\mathbb{R}^2 = \mathbf{v}_0^\perp \oplus \mathbb{R}\mathbf{u}_0$. Since $\mathbf{v}_0 \mathbf{L}_1 \mathbf{u}_0 = \lambda_1 = 0$ we have

$$\mathbf{u}_1 = \left(I - e^{T\boldsymbol{A}_0}\right)^{-1} |_{G_0} \mathbf{L}_1 \mathbf{u}_0\,, \tag{2.46}$$

where $G_0 = \mathbf{v}_0{}^{\perp} = Ker(\boldsymbol{A}_0 + wI)$, $\mathbf{u}_1 \in G_0$. Since if $\mathbf{v}_0 x = 0$ then $\boldsymbol{A}_0 x = -wx$ we obtain

$$\mathbf{u}_1 = \left(1 - e^{-Tw}\right)^{-1} \mathbf{L}_1 \mathbf{u}_0. \tag{2.47}$$

Identifying the coefficients of ϵ^2 in $\mathbf{L}_\epsilon = \lambda_\epsilon \mathbf{u}_\epsilon$ one gets

$$\mathbf{L}_2\mathbf{u}_0 + \mathbf{L}_1\mathbf{u}_1 + \mathbf{L}_0\mathbf{u}_2 = \lambda_0\mathbf{u}_2 + \lambda_2\mathbf{u}_0.$$

Multiplying on the left by $\mathbf{v}_0$, we get, since $\lambda_0 = 1$,$\lambda_1 = 0$, $\mathbf{v}_0\mathbf{u}_0 = 1$, $\mathbf{v}_0\mathbf{L}_0 = \mathbf{v}_0$,

$$\lambda_2 = \mathbf{v}_0\mathbf{L}_2\mathbf{u}_0 + \left(1 - e^{-Tw}\right)^{-1} \mathbf{v}_0 \left(\mathbf{L}_1\right)^2 \mathbf{u}_0. \tag{2.48}$$

From lemma (6)

$$\left(1 - e^{-wT}\right)^{-1} \left(\mathbf{L}_1\right)^2 \mathbf{u}_0 = \frac{T}{2\pi c} N(T, -w) \left(\boldsymbol{A}_0\boldsymbol{A}_1 - \boldsymbol{A}_1\boldsymbol{A}_0\right) \frac{\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0}{w^2}.$$

Combing with the result of lemma (7) hence,

$$\begin{aligned}
\lambda_2 &= \mathbf{v}_0\mathbf{L}_2\mathbf{u}_0 + \left(1 - e^{-wT}\right)^{-1} \mathbf{v}_0 \left(\mathbf{L}_1\right)^2 \mathbf{u}_0 \\
&= -\frac{1}{c}\left(w\left(\frac{T}{2\pi}\right)^2 \frac{T}{2} + \frac{T}{2\pi} N(T, -w)\right) \mathbf{v}_0\boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1\mathbf{u}_0 - \frac{T}{2\pi c} N(T, -w) \mathbf{v}_0\boldsymbol{A}_1\boldsymbol{A}_0 \frac{\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0}{w^2} \\
&\quad + \frac{T}{2}\mathbf{v}_0\left(I + \frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_2\mathbf{u}_0 - \frac{1 - e^{-Tw}}{2c'w^2}\mathbf{v}_0\boldsymbol{A}_0\boldsymbol{A}_2\mathbf{u}_0. \\
&= -\frac{T}{2c}\left(\frac{T}{2\pi}\right)^2 \mathbf{v}_0\boldsymbol{A}_1\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0 + \frac{T}{2}\mathbf{v}_0\left(I + \frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_2\mathbf{u}_0.
\end{aligned}$$

By the definition of $\boldsymbol{A}_0, \boldsymbol{A}_1$ and $\boldsymbol{A}_2$, one gets

$$\begin{aligned}
\lambda_2 &= -\frac{T}{2c}\left(\frac{T}{2\pi}\right)^2 \mathbf{v}_0\boldsymbol{A}_1\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0 + \frac{T}{2}\mathbf{v}_0\left(I + \frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_2\mathbf{u}_0. \\
&= -\frac{T}{2c}\left(\frac{T}{2\pi}\right)^2 \frac{\mu_V\mu_H}{w}\left(\left(\left(C_I + C_{II}\right)\mu_H - \mu_V C_{II}\right)\left(\left(C_I + C_{II}\right)\mu_V - \mu_H C_{II}\right)\right) + \frac{T}{2}\frac{C_{II}C_I\mu_H\mu_V}{w} \\
&= \frac{T\mu_V\mu_H}{w}\left(\frac{C_{II}C_I}{2} - \frac{1}{2c}\left(\frac{T}{2\pi}\right)^2 \left(\left(C_I + C_{II}\right)\mu_H - \mu_V C_{II}\right)\left(\left(C_I + C_{II}\right)\mu_V - \mu_H C_{II}\right)\right).
\end{aligned}$$

□

Expansion for P:

Let us remember that we assume that $R_0 = \dfrac{a_0^2 \beta_{VH} \beta_{HV} N_V(0)}{\mu_V(\mu_H + \gamma_H)} = 1$. Therefore, since $\langle a \rangle = a_0$, $\langle N_V \rangle = N_V(0)$ we get

$$P = \left(1 + \frac{\mathrm{Cov}\,(a, N_V)}{\langle a \rangle \langle N_V \rangle}\right)\left(1 + \frac{\mathrm{Cov}\,(I_V^\star, a)}{\langle I_V^\star \rangle \langle a \rangle}\right)\left(1 + \frac{\mathrm{Cov}\,(I_H^\star, aN_V)}{\langle I_H^\star \rangle \langle aN_V \rangle}\right). \tag{2.49}$$

For $f(t) = \cos(2\pi t/T)$ we have $\langle f^2 \rangle = 1/2$. Therefore, the first factor of (2.49) is

$$\frac{\mathrm{Cov}\,(a, N_V)}{\langle a \rangle \langle N_V \rangle} = \mathrm{Cov}(1 + \epsilon C_{II} f, 1 + \epsilon C_I f) = \epsilon^2 C_I C_{II} \left\langle f^2 \right\rangle = \frac{\epsilon^2}{2} C_I C_{II}\,. \tag{2.50}$$

The second factor is computed with the help of formula (2.61) of Lemma 3 below:

$$\frac{\mathrm{Cov}(I_V^*, a)}{\langle I_V^* \rangle \langle a \rangle} = \frac{\mathrm{Cov}(I_V^*, 1 + \epsilon C_{II} f)}{\langle I_V^* \rangle} \tag{2.51}$$

$$= -\epsilon^2 \frac{C_{II}}{2c} \left(\frac{T}{2\pi}\right)^2 \mu_V \left(-C_{II}\mu_V - C_I \mu_V + C_{II}\mu_H\right) + o(\epsilon). \tag{2.52}$$

Similarly, for the third factor, we get

$$\frac{\mathrm{Cov}\,(I_H^\star, aN_V)}{\langle I_H^\star \rangle \langle aN_V \rangle} = \frac{\mathrm{Cov}(I_H^*, (1 + \epsilon C_{II} f)(1 + \epsilon C_I f))}{\langle I_H^* \rangle \langle (1 + \epsilon C_{II} f)(1 + \epsilon C_I f) \rangle} \tag{2.53}$$

$$= \epsilon \left((C_I + C_{II}) \frac{\langle I_H^*, f \rangle}{\langle I_H^* \rangle (1 + \frac{1}{2}\epsilon^2 C_I C_{II})} + \epsilon C_I C_{II} \frac{\langle I_H^*, f^2 \rangle}{\langle I_H^* \rangle (1 + \frac{1}{2}\epsilon^2 C_I C_{II})} \right) \tag{2.54}$$

$$= -(C_I + C_{II}) \frac{\epsilon^2}{2c} \left(\frac{T}{2\pi}\right)^2 \mu_H (-C_{II}\mu_H + C_I \mu_V + C_{II}\mu_V) + \frac{1}{2}\epsilon^2 C_I C_{II} + o(\epsilon^2)\,. \tag{2.55}$$

Combining all these yields, since $c = 1 + w^2 \left(\dfrac{T}{2\pi}\right)^2$,

$$\boxed{P = 1 + \epsilon^2 \left[\frac{C_{II} C_I}{2} - \frac{1}{2c} \left(\frac{T}{2\pi}\right)^2 \left((C_I + C_{II})\,\mu_V - C_{II}\mu_H \right) \left((C_I + C_{II})\,\mu_H - C_{II}\mu_V \right) \right] + o(\epsilon^2)}. \tag{2.56}$$

We derive equation ((2.13)) by letting $C_{II} = 0$ and $C_I = 1$ (and μ_H is replaced by $\mu_H + \gamma_H$). Similarly, we derive equation ((2.15)) by letting $C_I = 0$ and $C_{II} = 1$.

Lemma 3. *We have,*

$$\langle \boldsymbol{X}^* \rangle = \boldsymbol{u}_0 + \epsilon \frac{T}{2\pi}(I + \frac{\boldsymbol{A}_0}{w})\boldsymbol{A}_1\boldsymbol{u}_0 + o(\epsilon)\,. \tag{2.57}$$

$$\langle \boldsymbol{X}^* f \rangle = -\epsilon \frac{1}{2c}\left(\frac{T}{2\pi}\right)^2 \boldsymbol{A}_0\boldsymbol{A}_1\boldsymbol{u}_0 + o(\epsilon)\,. \tag{2.58}$$

$$\left\langle \boldsymbol{X}^* f^2 \right\rangle = \frac{1}{2}\boldsymbol{u}_0 + o(\epsilon)\,. \tag{2.59}$$

Therefore,

$$\frac{\langle I_H^* f\rangle}{\langle I_H^*\rangle} = -\frac{\epsilon}{2c}\left(\frac{T}{2\pi}\right)^2 \mu_H(-C_{II}\mu_H + C_I\mu_V + C_{II}\mu_V) + o(\epsilon)\,. \tag{2.60}$$

$$\frac{\langle I_V^* f\rangle}{\langle I_V^*\rangle} = -\epsilon \frac{1}{2c}\left(\frac{T}{2\pi}\right)^2 \mu_V\left(-C_{II}\mu_V - C_I\mu_V + C_{II}\mu_H\right) + o(\epsilon)\,. \tag{2.61}$$

Proof. We first give an expansion of $\mathbf{X}^*(t)$ itself in terms of powers of ϵ.

$$\begin{aligned}
\mathbf{X}^*(t) &= \mathbf{\Phi}_{\mathbf{A}}(t)\mathbf{u}_\epsilon \\
&= \Big[e^{\boldsymbol{A}_0 t} + \epsilon\int_0^t e^{(t-s)\boldsymbol{A}_0}\boldsymbol{A}_1 f(s) e^{s\boldsymbol{A}_0} ds + \epsilon^2\left(\int_0^t e^{(t-s)\boldsymbol{A}_0}\boldsymbol{A}_1 f(s)\int_0^s e^{(s-\tau)\boldsymbol{A}_0}\boldsymbol{A}_1 f\,(\tau)\, e^{\tau\boldsymbol{A}_0} d\tau ds\right. \\
&\quad \left. + \int_0^t e^{(t-s)\boldsymbol{A}_0}\boldsymbol{A}_2 f^2(s) e^{s\boldsymbol{A}_0} ds\right) + O(\epsilon^2)\Big] \times \left(\mathbf{u}_0 + \epsilon\mathbf{u}_1 + \epsilon^2\mathbf{u}_2 + O(\epsilon^3)\right) \\
&= e^{\boldsymbol{A}_0 t}\mathbf{u}_0 + \epsilon\left(\int_0^t e^{(t-s)\boldsymbol{A}_0}\boldsymbol{A}_1 f(s) e^{s\boldsymbol{A}_0} ds\mathbf{u}_0 + e^{\boldsymbol{A}_0 t}\mathbf{u}_1\right) + \epsilon^2\left(e^{\boldsymbol{A}_0 t}\mathbf{u}_2 + \int_0^t e^{(t-s)\boldsymbol{A}_0}\boldsymbol{A}_1 f(s) e^{s\boldsymbol{A}_0} ds\mathbf{u}_1\right. \\
&\quad \left. + \int_0^t e^{(t-s)\boldsymbol{A}_0}\boldsymbol{A}_1 f(s)\int_0^s e^{(s-\tau)\boldsymbol{A}_0}\boldsymbol{A}_1 f\,(\tau)\, e^{\tau\boldsymbol{A}_0} d\tau ds\mathbf{u}_0 + \int_0^t e^{(t-s)\boldsymbol{A}_0}\boldsymbol{A}_2 f^2(s) e^{s\boldsymbol{A}_0} ds\mathbf{u}_0\right) + o(\epsilon).
\end{aligned}$$

Computation of $\langle \mathbf{X}^*, f\rangle$

$$\begin{aligned}
&\int_0^T f(t)\,\mathbf{X}^*(t) dt \\
&= \int_0^T f(t) e^{\boldsymbol{A}_0 t}\mathbf{u}_0 dt + \epsilon\left(\int_0^T f(t)\int_0^t e^{(t-s)\boldsymbol{A}_0} f\,(s)\,\boldsymbol{A}_1 e^{s\boldsymbol{A}_0}\mathbf{u}_0 ds dt + \int_0^T f(t) e^{\boldsymbol{A}_0 t}\mathbf{u}_1 dt\right) + o(\epsilon)\,.
\end{aligned}$$

The first term is easily computed

$$\int_0^T f(t) e^{\boldsymbol{A}_0 t}\mathbf{u}_0 dt = \int_0^T f(t)\mathbf{u}_0 dt = T\langle f\rangle\mathbf{u}_0 = 0\,.$$

The first term of the ϵ factor is:

$$\begin{aligned}
&\int_0^T f(t) \int_0^t e^{(t-s)\boldsymbol{A}_0} f\,(s)\, \boldsymbol{A}_1 e^{s\boldsymbol{A}_0} \mathbf{u}_0 ds dt \\
&\quad = \int_0^T f\,(t) \int_0^t f\,(s) \left(I + \frac{\boldsymbol{A}_0}{w} - \frac{e^{-w(t-s)}\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \mathbf{u}_0 ds dt \\
&\quad = -\int_0^T f(t) \int_0^t f(s) e^{-w(t-s)} ds dt \frac{\boldsymbol{A}_0 \boldsymbol{A}_1 \mathbf{u}_0}{w} \\
&\quad = -\frac{1}{c} \left(\frac{wT}{2} \left(\frac{T}{2\pi} \right)^2 + \frac{T}{2\pi} N(T, -w) \right) \frac{\boldsymbol{A}_0 \boldsymbol{A}_1 \mathbf{u}_0}{w}.
\end{aligned}$$

The second term of the ϵ factor is:

$$\begin{aligned}
&\int_0^T f(t) e^{\boldsymbol{A}_0 t} \mathbf{u}_1 dt \\
&\quad = \int_0^T f(t) \left(I + \frac{\boldsymbol{A}_0}{w} - \frac{e^{-wt}\boldsymbol{A}_0}{w} \right) dt \frac{T}{2\pi c} \frac{\boldsymbol{A}_0 \boldsymbol{A}_1 \mathbf{u}_0}{w} \\
&\quad = -N(T, -w) \frac{T}{2\pi c w^2} \boldsymbol{A}_0^2 \boldsymbol{A}_1 \mathbf{u}_0 \\
&\quad = N(T, -w) \frac{T}{2\pi c w} \boldsymbol{A}_0 \boldsymbol{A}_1 \mathbf{u}_0 \text{ since } \boldsymbol{A}_0^2 = -w\boldsymbol{A}_0.
\end{aligned}$$

Hence, the ϵ factor is

$$\begin{aligned}
&-\frac{1}{c} \left(\frac{wT}{2} \left(\frac{T}{2\pi} \right)^2 + \frac{T}{2\pi} N(T, -w) \right) \frac{\boldsymbol{A}_0 \boldsymbol{A}_1 \mathbf{u}_0}{w} + \left(\frac{T}{2\pi} \right)^2 \left(\frac{3N(T, -w)}{4cc'} + \frac{wT^2}{4\pi c} \right) \frac{\boldsymbol{A}_1 \boldsymbol{A}_0}{w} \boldsymbol{A}_1 \mathbf{u}_0 \\
&\quad = -\frac{T}{2c} \left(\frac{T}{2\pi} \right)^2 \boldsymbol{A}_0 \boldsymbol{A}_1 \mathbf{u}_0,
\end{aligned}$$

from which we deduce (2.58).

Computation of $\langle \mathbf{X}^* \rangle$

$$\int_0^T \mathbf{X}^*(t) dt = \int_0^T e^{\boldsymbol{A}_0 t} \mathbf{u}_0 dt + \epsilon \left(\int_0^T \int_0^t e^{(t-s)\boldsymbol{A}_0} \boldsymbol{A}_1 f(s) e^{s\boldsymbol{A}_0} \mathbf{u}_0 ds dt + \int_0^T e^{\boldsymbol{A}_0 t} \mathbf{u}_1 dt \right) + o(\epsilon)\,.$$

From expression (2.97), the first term is

$$\int_0^T e^{\boldsymbol{A}_0 t} \mathbf{u}_0 dt = \int_0^T \mathbf{u}_0 dt = T\mathbf{u}_0$$

From expression (2.97) we get:

$$\begin{aligned}\int_0^T e^{\boldsymbol{A}_0 t}\mathbf{u}_1 dt &= (1-e^{-Tw})^{-1}\frac{N(T,-w)}{w}\left(\int_0^T e^{t\boldsymbol{A}_0}\boldsymbol{A}_0\,dt\right)\boldsymbol{A}_1\mathbf{u}_0\\ &= (1-e^{-Tw})^{-1}\frac{N(T,-w)}{w}(e^{T\boldsymbol{A}_0}-I)\boldsymbol{A}_1\mathbf{u}_0\\ &= N(T,-w)\frac{\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0}{w^2}\,.\end{aligned}$$

Eventually,

$$\begin{aligned}&\int_0^T\int_0^t e^{(t-s)\boldsymbol{A}_0}\boldsymbol{A}_1 f(s)e^{s\boldsymbol{A}_0}dsdt\mathbf{u}_0\\ &= \frac{T^2}{2\pi}\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\left(I+\frac{\boldsymbol{A}_0}{w}\right)\mathbf{u}_0-\frac{1}{c}\left(-2w\left(\frac{T}{2\pi}\right)^2 N(T,-w)+\frac{T^2}{2\pi}\right)\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\frac{\boldsymbol{A}_0\mathbf{u}_0}{w}\\ &\quad-\frac{N(T,-w)}{w}\frac{\boldsymbol{A}_0}{w}\boldsymbol{A}_1\left(I+\frac{\boldsymbol{A}_0}{w}\right)\mathbf{u}_0+\frac{N(T,-w)}{w}\frac{\boldsymbol{A}_0\boldsymbol{A}_1\boldsymbol{A}_0\mathbf{u}_0}{w^2}.\end{aligned}$$

Combining the preceding we get (2.57).

Computation of $\langle \mathbf{X}^* f^2\rangle$ Since $e^{t\boldsymbol{A}_0}\mathbf{u}_0=\mathbf{u}_0$, we get

$$\int_0^T f^2(t)\mathbf{X}^*(t)dt=\int_0^T \sin\left(\frac{2\pi t}{T}\right)^2 e^{\boldsymbol{A}_0 t}\mathbf{u}_0 dt+o(\epsilon)=\frac{T}{2}\mathbf{u}_0+o(\epsilon)\,. \tag{2.62}$$

Computation of $\dfrac{\langle I_H^* f\rangle}{\langle I_H^*\rangle}$ if $e_1=(1,0), e_2=(0,1)$ are the coordinate vectors, then $I_H^*=e_1^T\mathbf{X}^*$. Therefore, $\langle I_H^* f\rangle = e_1^T\langle \mathbf{X}^* f\rangle$ and thanks to the matrix computations

$$\begin{aligned}e_1^T\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0 &= \frac{\alpha\mu_H\left(-C_{II}\mu_H+C_I\mu_V+C_{II}\mu_V\right)}{\alpha+\mu_H}\\ e_2^T\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0 &= \frac{\mu_H\mu_V\left(-C_{II}\mu_V-C_I\mu_V+C_{II}\mu_H\right)}{\alpha+\mu_H}\,,\end{aligned} \tag{2.63}$$

we get

$$\begin{aligned}\frac{\langle I_H^* f\rangle}{\langle I_H^*\rangle} &= \frac{\int_0^T f(t)e_1^T\mathbf{X}^*(t)dt}{\int_0^T e_1^T\mathbf{X}^*(t)dt}\\ &= \left(-\epsilon\frac{T}{2c}\left(\frac{T}{2\pi}\right)^2 e_1^T\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0+o(\epsilon)\right)\frac{1}{Te_1^T\mathbf{u}_0}\left(1-\epsilon\frac{T^2}{2\pi}e_1^T\left(I+\frac{\boldsymbol{A}_0}{w}\right)\frac{\boldsymbol{A}_1\mathbf{u}_0}{Te_1\mathbf{u}_0}+o(\epsilon)\right)\\ &= \frac{1}{Te_1^T\mathbf{u}_0}\left(-\epsilon\frac{T}{2c}\left(\frac{T}{2\pi}\right)^2 e_1^T\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0+o(\epsilon)\right)\end{aligned}$$

$$= \frac{1}{T\dfrac{\alpha}{\alpha+\mu_H}} \frac{-\epsilon T}{2c}\left(\frac{T}{2\pi}\right)^2 \frac{\alpha\mu_H\left(-C_{II}\mu_H + C_I\mu_V + C_{II}\mu_V\right)}{\alpha+\mu_H} + o(\epsilon)$$
$$= -\epsilon\frac{1}{2c}\left(\frac{T}{2\pi}\right)^2 \mu_H\left(-C_{II}\mu_H + C_I\mu_V + C_{II}\mu_V\right) + o(\epsilon) \tag{2.64}$$

Similarly,

$$\begin{aligned}
\frac{\langle I_V^* f\rangle}{\langle I_V^*\rangle} &= \frac{\int_0^T f(t)e_2^T x(t)dt}{\int_0^T e_2^T x(t)dt} \\
&= \left(-\epsilon\frac{T}{2c}\left(\frac{T}{2\pi}\right)^2 e_2^T \boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0 + o(\epsilon)\right)\frac{1}{Te_2^T\mathbf{u}_0}\left(1 - \epsilon\frac{T^2}{2\pi}e_2^T\left(I + \frac{\boldsymbol{A}_0}{w}\right)\frac{\boldsymbol{A}_1\mathbf{u}_0}{Te_2^T\mathbf{u}_0} + O(\epsilon)\right) \\
&= \frac{1}{Te_2^T\mathbf{u}_0}\left(\frac{-\epsilon T}{2c}\left(\frac{T}{2\pi}\right)^2 e_2^T\boldsymbol{A}_0\boldsymbol{A}_1\mathbf{u}_0\right) + o(\epsilon) \\
&= \frac{1}{T\dfrac{\mu_H}{\alpha+\mu_H}}\left[\frac{-\epsilon T}{2c}\left(\frac{T}{2\pi}\right)^2 \frac{\mu_V\mu_H\left(-C_{II}\mu_V - C_I\mu_V + C_{II}\mu_H\right)}{\alpha+\mu_H}\right] + o(\epsilon) \\
&= -\epsilon\frac{1}{2c}\left(\frac{T}{2\pi}\right)^2 \mu_V\left(-C_{II}\mu_V - C_I\mu_V + C_{II}\mu_H\right) + o(\epsilon).
\end{aligned} \tag{2.65}$$

□

2.6.4 An alternative model for the fluctuation of vector density: Model $I^{'}$

In model I' we assume that $N_V(t) = N_V(0)e^{\epsilon C_{I'} f(t)}$. This results from an alternative model of vector reproduction used in [HR95a; HR95b]. We assume that the per capita growth rate varies around its mean following

$$\rho_V(t) = \mu_V(1 - \epsilon\kappa\sin(2\pi t/T))\,. \tag{2.66}$$

Then the total vector population N_V satisfies the ODE

$$\frac{dN_V}{dt} = (\rho_V - \mu_V)N_V, \tag{2.67}$$

and is therefore given by

$$N_V(t) = N_V(0)\exp(\epsilon\kappa\frac{T}{2\pi}\cos(2\pi t/T))\,, \tag{2.68}$$

that is we take $C_I' = \kappa \frac{T}{2\pi}$. This yields

$$\boldsymbol{A}_1 = \begin{pmatrix} 0 & 0 \\ a_0 \beta_{HV} N_V(0) C_{I'} & 0 \end{pmatrix}, \qquad \boldsymbol{A}_2 = \begin{pmatrix} 0 & 0 \\ a_0 \beta_{HV} N_V(0) \frac{1}{2} C_{I'}^2 & 0 \end{pmatrix}. \tag{2.69}$$

There is no fluctuation in the biting rate so $\langle a \rangle = a_0$. On the other hand we have $\langle N_V \rangle = N_V(0)(1 + \epsilon^2 \frac{C_{I'}}{4} + o(\epsilon^2))$. The expression of P is thus:

$$P = \frac{\langle N_V \rangle}{N_V(0)} \left(1 + \frac{\mathrm{Cov}\,(a, N_V)}{\langle a \rangle \langle N_V \rangle}\right) \left(1 + \frac{\mathrm{Cov}\,(I_V^\star, a)}{\langle I_V^\star \rangle \langle a \rangle}\right) \left(1 + \frac{\mathrm{Cov}\,(I_H^\star, aN_V)}{\langle I_H^\star \rangle \langle aN_V \rangle}\right). \tag{2.70}$$

$$= (1 + \epsilon^2 \frac{C_{I'}}{4} + o(\epsilon^2)) \left(1 + \frac{\mathrm{Cov}\,(I_H^\star, N_V)}{\langle I_H^\star \rangle \langle N_V \rangle}\right). \tag{2.71}$$

We observe that the second order term, in ϵ^2, of $N_V(t)$ may only give a term in ϵ^3 in the covariance. In a nutshell, we can keep the same expansion as in the preceding section, the one given by Lemma 3, replacing $C_{I'}$ by C_I and C_{II} by 0. Therefore:

$$P = (1 + \epsilon^2 \frac{C_{I'}}{4} + o(\epsilon^2)) \left(1 - C_{I'} \frac{\epsilon^2}{2c} \left(\frac{T}{2\pi}\right)^2 \mu_V \mu_H + o(\epsilon^2)\right). \tag{2.72}$$

This leads easily to the expression (2.15) (if we substitute at the end $\mu_H + \gamma_H$ to μ_H). The fact that $P_\epsilon > 1$ comes from the following sequence of inequalities

$$\begin{aligned} P &= 1 + \frac{\epsilon^2 C_{I'}^2}{2} \left(\frac{1}{2} - \frac{\left(\frac{T}{2\pi}\right)^2 \mu_H \mu_V}{1 + (\mu_H + \mu_V)^2 \left(\frac{T}{2\pi}\right)^2}\right) + o(\epsilon^2) \\ &\geq 1 + \frac{\epsilon^2 C_{I'}^2}{2} \left(\frac{1}{2} - \frac{1}{4} \frac{\left(\frac{T}{2\pi}\right)^2 (\mu_H + \mu_V)^2}{1 + (\mu_H + \mu_V)^2 \left(\frac{T}{2\pi}\right)^2}\right) + o(\epsilon^2) \\ &\geq 1 + \frac{\epsilon^2 C_{I'}^2}{8} \frac{\left(\frac{T}{2\pi}\right)^2 (\mu_H + \mu_V)^2}{1 + (\mu_H + \mu_V)^2 \left(\frac{T}{2\pi}\right)^2} + o(\epsilon^2) > 1\,. \end{aligned}$$

To compute the influence on λ of the model I', we only need to modify the Taylor expansion(2.26) of $\mathbf{A}(t)$: we still have no first-order term $\lambda = 1 + \epsilon^2 \lambda_2$, and we just plug in the new expressions of $\boldsymbol{A}_1$ and $\boldsymbol{A}_2$ into the formula

$$\lambda_2 = -\frac{T}{2c} \left(\frac{T}{2\pi}\right)^2 \mathbf{v}_0 \boldsymbol{A}_1 \boldsymbol{A}_0 \boldsymbol{A}_1 \mathbf{u}_0 + \frac{T}{2} \mathbf{v}_0 \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_2 \mathbf{u}_0\,,$$

to obtain formula ((2.16)).

2.6.5 Auxiliary results

Bounding the flow of an ODE

First, we show that control on the coefficients of an ODE gives control on the flow of the ODE.

Lemma 4. *Let* $\mathbf{A} : [0, a] \to \mathcal{M}_{d\times d}$ *be a continuous matrix function, and* $\mathbf{\Phi_A}(t)$ *be its fundamental matrix*

$$\frac{d\mathbf{\Phi_A}(t)}{dt} = \mathbf{A}(t)\,\mathbf{\Phi_A}(t)\,, \qquad \mathbf{\Phi_A}(0) = \mathbf{I}_d\,. \tag{2.73}$$

Then,

$$\|\mathbf{\Phi_A}(t)\| \leq \exp\left(t \sup_{s\leq t} \|\mathbf{A}(s)\|\right). \tag{2.74}$$

Proof. Let $x \in \mathbb{R}^d$. Then $x(t) = \mathbf{\Phi_A}(t)x(t)$ is the solution of

$$\frac{dx}{dt} = \mathbf{A}(t)\,x(t)\,, \quad x(0) = x\,. \tag{2.75}$$

Hence,

$$x(t) = x + \int_0^t \mathbf{A}(s)x(s)\,ds, \tag{2.76}$$

and taking norms yield

$$\|x(t)\| \leq \|x\| + \int_0^t \|\mathbf{A}(s)\|\|x(s)\|\,ds \leq \|x\| + \sup_{s\leq t}\|\mathbf{A}(s)\| \int_0^t \|x(s)\|\,ds\,. \tag{2.77}$$

We conclude by Gronwall's Lemma. □

Duhamel's formula and Taylor expansions

Let us denote by $\mathbf{\Phi_A}$ the fundamental matrix of the differential flow generated by the continuous matrix function $t \to \mathbf{A}(t)$. It is the solution of the differential equation

$$\frac{d\mathbf{\Phi_A}}{dt} = \mathbf{A}\mathbf{\Phi_A}(t) \tag{2.78}$$

with initial condition $\mathbf{\Phi_A}(0) = \mathbf{I}$ (the identity matrix).

If $\mathbf{B}(t)$ is another continuous matrix function, then we have

$$\mathbf{\Phi_{A+B}}(t) = \mathbf{\Phi_A}(t)\Big(\mathbf{I} + \int_0^t \mathbf{\Phi_A}(s)^{-1}\mathbf{B}(s)\,\mathbf{\Phi_{A+B}}(s)ds\Big) \tag{2.79}$$

Let us see how it allows to determine Taylor's expansion. Let us start from

$$\mathbf{A}(t) = \mathbf{A}_0 + \epsilon f(t)\mathbf{A}_1 + o(\epsilon) \tag{2.80}$$

with $o(\epsilon)$ uniform in time. Then since $\mathbf{\Phi}_{\mathbf{A}_0}(t) = e^{t\mathbf{A}_0}$, by Duhamel's formula

$$\mathbf{\Phi_A}(t) = e^{t\mathbf{A}_0}\Big(\mathbf{I} + \int_0^t e^{-s\mathbf{A}_0}(\epsilon f(s)\mathbf{A}_1 + o(\epsilon))\,\mathbf{\Phi_A}(s)\,ds\Big) \tag{2.81}$$

Since, by Lemma 4, $\sup_{s\leq T}\|\mathbf{\Phi_A}(s)\| \leq C < +\infty$, we have

$$\mathbf{\Phi_A}(t) = e^{t\mathbf{A}_0} + \epsilon\, e^{t\mathbf{A}_0}\int_0^t e^{-s\mathbf{A}_0} f(s)\mathbf{A}_1\,\mathbf{\Phi_A}(s)\,ds + o(\epsilon) \tag{2.82}$$

This implies that $\mathbf{\Phi_A}(t) = e^{t\mathbf{A}_0} + o(1)$ which we reinject in the integral term of (2.82) to get

$$\mathbf{\Phi_A}(t) = e^{t\mathbf{A}_0} + \epsilon\, e^{t\mathbf{A}_0}\int_0^t e^{-s\mathbf{A}_0} f(s)\mathbf{A}_1\, e^{s\mathbf{A}_0}\,ds + o(\epsilon) \tag{2.83}$$

Similarly, we obtain the Taylor expansion (2.30).

Some results of integral calculations.

Recall that $c := 1 + w^2\left(\frac{T}{2\pi}\right)^2$. Let $c' := 1 + w^2\left(\frac{T}{4\pi}\right)^2 = \frac{c+3}{4}$

Lemma 5. *Let $N(t,x) = \int_0^t f(s)e^{xs}ds$, where x is a real number. Then, for $T, w > 0$,*

$$N(T,w) = \frac{-\frac{T}{2\pi}(e^{wT}-1)}{1 + w^2(\frac{T}{2\pi})^2} < 0, \quad N(T,-w) = \frac{-\frac{T}{2\pi}(e^{-wT}-1)}{1 + w^2(\frac{T}{2\pi})^2} = -N(T,w)e^{-wT} > 0. \tag{2.84}$$

Proof.

$$\begin{aligned} N(t,k) &= \int_0^t f(s)e^{ks}ds \\ &= \int_0^t \sin(2\pi s/T)e^{ks}ds \end{aligned}$$

$$
\begin{aligned}
&= -\frac{T}{2\pi}\int_0^t e^{ks}d\cos(2\pi s/T) \\
&= -\frac{T}{2\pi}\left((e^{kt}\cos(2\pi t/T+)-1)-k\int_0^t e^{ks}\cos(2\pi s/T+)ds\right) \\
&= -\frac{T}{2\pi}(e^{kt}\cos(2\pi t/T)-1)+k\left(\frac{T}{2\pi}\right)^2\int_0^t e^{ks}d\sin(2\pi s/T) \\
&= -\frac{T}{2\pi}(e^{kt}\cos(2\pi t/T)-1)+k\left(\frac{T}{2\pi}\right)^2 e^{kt}\sin(2\pi t/T)-\left(k^2\frac{T}{2\pi}^2\right)N(t,k)
\end{aligned}
$$

Therefore,

$$
N(t,k)=\frac{-\frac{T}{2\pi}(e^{kt}\cos(2\pi t/T)-1)+k\left(\frac{T}{2\pi}\right)^2(e^{kt}\sin(2\pi t/T))}{1+k^2(\frac{T}{2\pi})^2} \tag{2.85}
$$

□

Let us list now some computations that can be established in the same way.

$$
\begin{aligned}
\int_0^T f(2s)e^{ws}ds &= \frac{-\frac{T}{4\pi}\left(e^{wT}-1\right)}{c'}=\frac{c}{2c'}N(T,w), \\
\int_0^T f(2s)e^{-ws}ds &= \frac{c}{2c'}N(T,-w).
\end{aligned}
$$

By using integration by parts, one also gets

$$
N_3(h,t,k)=\int_0^t\cos(h2\pi s/T)e^{ks}ds=\frac{\frac{T}{2\pi h}e^{kt}\sin\left(2\pi th/T\right)+k\left(\frac{T}{2\pi h}\right)^2\left(e^{kt}\cos\left(2\pi ht/T\right)-1\right)}{1+k^2\left(\frac{T}{2\pi h}\right)^2}.
$$

We also list some results in the calculation of the integral.

$$
\begin{aligned}
&\int_0^T\sin\left(2\pi t/T\right)\int_0^t\sin\left(2\pi s/T\right)\int_0^s\sin\left(2\pi\tau/T\right)d\tau dsdt=0 \\
&\int_0^T e^{-wt}\sin\left(2\pi t/T\right)\int_0^t\sin\left(2\pi s/T\right)e^{ws}\int_0^s\sin\left(2\pi\tau/T\right)d\tau dsdt=\left(\frac{T}{2\pi}\right)^2\left(\frac{3N(T,-w)}{4cc'}+\frac{wT^2}{4\pi c}\right) \\
&\int_0^T f(t)\int_0^t f(s)\int_0^s f(\tau)e^{-w(s-\tau)}d\tau dsdt=-\frac{1}{c}\left(\frac{T}{4\pi}\right)^2\left(\frac{3N_2(1,T,-w)}{c'}+\frac{wT^2}{\pi}\right) \\
&\int_0^T f(t)e^{-wt}\int_0^t f(s)\int_0^s f(\tau)e^{w\tau}d\tau ds=0
\end{aligned}
$$

$$\int_0^t f(s)\int_0^s f(\tau)e^{-w\tau}d\tau ds=\frac{5}{3}\frac{N(T,-w)}{c'c''}\left(\frac{T}{4\pi}\right)^2$$

$$\int_0^T f(t)e^{-wt}\int_0^t f(s)e^{ws}\int_0^s f(\tau)e^{-w\tau}d\tau dsdt \tag{2.86}$$

$$=\frac{1}{c^2}\left(\frac{T}{4\pi}\right)^2\left(\frac{-8\,(5c-8)}{9c''}N(T,-w)+4wT\frac{T}{4\pi}\left(1+e^{-wT}\right)\right) \tag{2.87}$$

$$\int_0^T f(t)\int_0^t f(s)e^{-ws}\int_0^s f(\tau)d\tau dsdt=\left(\frac{T}{2\pi}\right)^2\frac{5N(T,-w)}{6c'c''} \tag{2.88}$$

$$\int_0^T e^{-wt}\sin\left(2\pi t/T\right)\int_0^t \sin\left(2\pi s/T\right)\int_0^s \sin\left(2\pi\tau/T\right)d\tau dsdt=\left(\frac{T}{2\pi}\right)^2\frac{5N(T,-w)}{12c'c''} \tag{2.89}$$

$$\int_0^t \sin(2\pi s/T)e^{ws}\int_0^s \sin(2\pi\tau/T)d\tau ds=-\left(\frac{T}{2\pi}\right)\left(\frac{N_2(2,w,t)}{2}-N_2(1,w,t)\right) \tag{2.90}$$

$$\int_0^t \sin\left(2\pi s/T\right)e^{ws}\int_0^s \sin\left(2\pi\tau/T\right)e^{-w\tau}d\tau ds \tag{2.91}$$

$$=\frac{1}{c}\left(\left(\frac{T}{4\pi}\right)^2\left(\cos\left(4\pi\frac{t}{T}\right)-1\right)+\frac{T}{2\pi}N(t,w)\right)-\frac{w}{2c}\left(\frac{T}{2\pi}\right)^2\left(t-\frac{T}{4\pi}\sin\left(4\pi\frac{t}{T}\right)\right) \tag{2.92}$$

$$\int_0^T\int_0^t \sin 2\pi\frac{s}{T}dsdt=\frac{T^2}{2\pi} \tag{2.93}$$

$$\int_0^T\int_0^t \sin 2\pi\frac{s}{T}e^{-ws}dsdt=\frac{1}{c}\left(-2w\left(\frac{T}{2\pi}\right)^2N(T,-w)+\frac{T^2}{2\pi}\right) \tag{2.94}$$

$$\int_0^T\int_0^t sin2\pi\frac{s}{T}e^{-w(t-s)}dsdt=\frac{N(T,-w)}{w} \tag{2.95}$$

$$\int_0^T e^{-wt}\int_0^t sin2\pi\frac{s}{T}dsdt=\frac{N(T,-w)}{w} \tag{2.96}$$

Computation of $\mathbf{L}_1$ and $\mathbf{L}_2$

Since $\boldsymbol{A}_0$ has two different eigenvalues, 0 and $-w=tr(\mathbf{A}_0)$ we have the formula

$$e^{s\mathbf{A}_0}=I-\frac{1}{w}\left(e^{-ws}-1\right)\boldsymbol{A}_0\qquad(s\in\mathbb{R})\,. \tag{2.97}$$

Lemma 6. *We have*

$$\mathbf{L}_1=N(T,-w)\frac{(\boldsymbol{A}_0\boldsymbol{A}_1-\boldsymbol{A}_1\boldsymbol{A}_0)}{w}\,. \tag{2.98}$$

Since $\boldsymbol{A}_0\boldsymbol{u}_0 = 0$ *this yields*

$$\mathbf{L}_1\boldsymbol{u}_0 = N(T,-w)\frac{\boldsymbol{A}_0\boldsymbol{A}_1\boldsymbol{u}_0}{w}. \tag{2.99}$$

And thus,

$$\boldsymbol{u}_1 = (1-e^{-Tw})^{-1}\mathbf{L}_1\boldsymbol{u}_0 = (1-e^{-Tw})^{-1}N(T,-w)\frac{\boldsymbol{A}_0\boldsymbol{A}_1\boldsymbol{u}_0}{w}\,. \tag{2.100}$$

Proof.

$$\mathbf{L}_1 = \int_0^t e^{(t-s)\boldsymbol{A}_0} f(s)\boldsymbol{A}_1 e^{s\boldsymbol{A}_0} ds \tag{2.101}$$

$$= \int_0^t f(s)\left(\left(I+\frac{\boldsymbol{A}_0}{w}\right) - e^{-w(t-s)}\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\left(\left(I+\frac{\boldsymbol{A}_0}{w}\right) - e^{-ws}\frac{\boldsymbol{A}_0}{w}\right) ds \tag{2.102}$$

$$= \int_0^t f(s)\left[\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\left(I+\frac{\boldsymbol{A}_0}{w}\right) - e^{ws}e^{-wt}\frac{\boldsymbol{A}_0}{w}\boldsymbol{A}_1\left(I+\frac{\boldsymbol{A}_0}{w}\right)\right. \tag{2.103}$$

$$\left. -e^{-ws}\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\frac{\boldsymbol{A}_0}{w} + e^{-wt}\frac{\boldsymbol{A}_0\boldsymbol{A}_1\boldsymbol{A}_0}{w^2}\right] ds \tag{2.104}$$

$$\Rightarrow \mathbf{L}_1 = \int_0^T f(s)\left[-e^{ws}e^{-wT}\frac{\boldsymbol{A}_0}{w}\boldsymbol{A}_1\left(I+\frac{\boldsymbol{A}_0}{w}\right) - e^{-ws}\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\frac{\boldsymbol{A}_0}{w}\right] ds \tag{2.105}$$

$$\mathbf{L}_1 = -N(T,-w)\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\frac{\boldsymbol{A}_0}{w} - N(T,w)e^{-wT}\frac{\boldsymbol{A}_0}{w}\boldsymbol{A}_1\left(I+\frac{\boldsymbol{A}_0}{w}\right)$$

$$= N(T,-w)\frac{(\boldsymbol{A}_0\boldsymbol{A}_1 - \boldsymbol{A}_1\boldsymbol{A}_0)}{w}. \tag{2.106}$$

□

Lemma 7. *We have*

$$\mathbf{L}_2\boldsymbol{u}_0 = \frac{3T}{8\pi c'}N(T,-w)\frac{\boldsymbol{A}_0\boldsymbol{A}_1}{w}\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\boldsymbol{u}_0 + \frac{T}{2}\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_2\boldsymbol{u}_0 - \frac{1-e^{-Tw}}{2c'w^2}\boldsymbol{A}_0\boldsymbol{A}_2\boldsymbol{u}_0$$
$$+ \frac{3T}{8\pi c'}N(T,-w)\frac{\boldsymbol{A}_0}{w}\boldsymbol{A}_1\frac{\boldsymbol{A}_0}{w}\boldsymbol{A}_1\boldsymbol{u}_0 - \frac{1}{c}\left(w\left(\frac{T}{2\pi}\right)^2\frac{T}{2} + \frac{T}{2\pi}N(T,-w)\right)\left(I+\frac{\boldsymbol{A}_0}{w}\right)\boldsymbol{A}_1\frac{\boldsymbol{A}_0}{w}\boldsymbol{A}_1\boldsymbol{u}_0.$$

Proof. We have $\mathbf{L}_2 := \mathbf{L}_2^1 + \mathbf{L}_2^2$, with

$$\mathbf{L}_2^1 = \int_0^T e^{(T-s)\boldsymbol{A}_0} f(s)\boldsymbol{A}_1 \int_0^s e^{(s-\tau)\boldsymbol{A}_0} f(\tau)\boldsymbol{A}_1 e^{\tau\boldsymbol{A}_0} d\tau ds \tag{2.107}$$

$$\mathbf{L}_2^2 = \int_0^T e^{(T-s)\boldsymbol{A}_0} f(s)\boldsymbol{A}_2 e^{s\boldsymbol{A}_0} ds. \tag{2.108}$$

One has

$$
\begin{aligned}
&\int_0^t e^{(t-s)\boldsymbol{A}_0} f(s)\boldsymbol{A}_1 \int_0^s e^{(s-\tau)\boldsymbol{A}_0} f(\tau)\boldsymbol{A}_1 e^{\tau \boldsymbol{A}_0} d\tau ds \\
&= \int_0^t f(s) \left(\left(I + \frac{\boldsymbol{A}_0}{w} \right) - e^{ws} e^{-wt} \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \int_0^s f(\tau) \left[\left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \right. \\
&\qquad \left. - e^{w\tau} e^{-ws} \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) - e^{-w\tau} \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} + e^{-ws} \frac{\boldsymbol{A}_0 \boldsymbol{A}_1 \boldsymbol{A}_0}{w^2} \right] d\tau ds \\
&= \int_0^t f(s) \int_0^s f(\tau) d\tau ds \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \\
&\quad - \int_0^t f(s) e^{ws} \int_0^s f(\tau) d\tau ds \frac{e^{-wt} \boldsymbol{A}_0 \boldsymbol{A}_1}{w} \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \\
&\quad - \int_0^t f(s) \int_0^s f(\tau) e^{-w(s-\tau)} d\tau ds \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \\
&\quad + \int_0^t f(s) \int_0^s f(\tau) e^{w\tau} d\tau ds e^{-wt} \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \\
&\quad - \int_0^t f(s) \int_0^s f(\tau) e^{-w\tau} d\tau ds \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \\
&\quad + \int_0^t f(s) \int_0^s f(\tau) e^{-w(\tau-s)} d\tau ds e^{-wt} \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \\
&\quad + \int_0^t f(s) e^{-ws} \int_0^s f(\tau) d\tau ds \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \\
&\quad - \int_0^t f(s) \int_0^s f(\tau) d\tau ds e^{-wt} \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w^2} \boldsymbol{A}_1 \boldsymbol{A}_0 .
\end{aligned}
$$

As a result, we can compute $\mathbf{L}_2$ and use equalities (2.86)-(2.92):

$$
\begin{aligned}
\mathbf{L}_2^1 &= \int_0^T f(s) \left(\left(I + \frac{\boldsymbol{A}_0}{w} \right) - e^{ws} e^{-wT} \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \int_0^s f(\tau) \left[\left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \right. \\
&\qquad \left. - e^{w\tau} e^{-ws} \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) - e^{-w\tau} \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} + e^{-ws} \frac{\boldsymbol{A}_0 \boldsymbol{A}_1 \boldsymbol{A}_0}{w^2} \right] d\tau \\
&= - \int_0^T f(s) e^{ws} \int_0^s f(\tau) d\tau ds \frac{e^{-wT} \boldsymbol{A}_0 \boldsymbol{A}_1}{w} \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \\
&\quad - \int_0^T f(s) \int_0^s f(\tau) e^{-w(s-\tau)} d\tau ds \left(I + \frac{\boldsymbol{A}_0}{w} \right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right) \\
&\quad + \int_0^T f(s) \int_0^s f(\tau) e^{w\tau} d\tau ds e^{-wT} \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w} \right)
\end{aligned}
$$

$$
\begin{aligned}
&- \int_0^T f(s) \int_0^s f(\tau) e^{-w\tau} d\tau ds \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \\
&+ \int_0^T f(s) \int_0^s f(\tau) e^{-w(\tau - s)} d\tau ds e^{-wT} \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \\
&+ \int_0^T f(s) e^{-ws} \int_0^s f(\tau) d\tau ds \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \\
= &\frac{3T}{8\pi c'} N(T, -w) \frac{\boldsymbol{A}_0 \boldsymbol{A}_1}{w} \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w}\right) \\
&- \frac{1}{c} \left(w \left(\frac{T}{2\pi}\right)^2 \frac{T}{2} + \frac{T}{2\pi} N(T, -w)\right) \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w}\right) \\
&\frac{3T}{8\pi c'} N(T, -w) \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w}\right) \\
&+ \frac{3T}{8\pi c'} N(T, -w) \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \\
&+ \frac{1}{c} \left(-w \left(\frac{T}{2\pi}\right)^2 \frac{T}{2} + \frac{T}{2\pi} N(T, w)\right) e^{-wT} \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \\
&+ \frac{3T}{8\pi c'} N(T, -w) \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w}.
\end{aligned}
$$

Therefore

$$
\begin{aligned}
\mathbf{L}_2^1 \mathbf{u}_0 = &\frac{3T}{8\pi c'} N(T, -w) \frac{\boldsymbol{A}_0 \boldsymbol{A}_1}{w} \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \mathbf{u}_0 + \frac{3T}{8\pi c'} N(T, -w) \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \mathbf{u}_0 \\
&- \frac{1}{c} \left(w \left(\frac{T}{2\pi}\right)^2 \frac{T}{2} + \frac{T}{2\pi} N(T, -w)\right) \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_1 \frac{\boldsymbol{A}_0}{w} \boldsymbol{A}_1 \mathbf{u}_0.
\end{aligned}
$$

and

$$
\begin{aligned}
\mathbf{L}_2^2 \mathbf{u}_0 &= \int_0^T e^{(T-s)\boldsymbol{A}_0} \boldsymbol{A}_2 f^2(s) e^{s\boldsymbol{A}_0} ds \mathbf{u}_0 \\
&= \frac{1}{2} \int_0^T \left(I + \frac{\boldsymbol{A}_0}{w} - e^{-Tw} e^{sw} \frac{\boldsymbol{A}_0}{w}\right) \left(1 - \cos \frac{4\pi s}{T}\right) ds \boldsymbol{A}_2 \mathbf{u}_0 \\
&= \frac{1}{2} \left[T \left(I + \frac{\boldsymbol{A}_0}{w}\right) - \frac{1 - e^{-Tw}}{c' w^2} \boldsymbol{A}_0\right] \boldsymbol{A}_2 \mathbf{u}_0 \\
&= \frac{T}{2} \left(I + \frac{\boldsymbol{A}_0}{w}\right) \boldsymbol{A}_2 \mathbf{u}_0 - \frac{1 - e^{-Tw}}{2c' w^2} \boldsymbol{A}_0 \boldsymbol{A}_2 \mathbf{u}_0.
\end{aligned}
$$

□

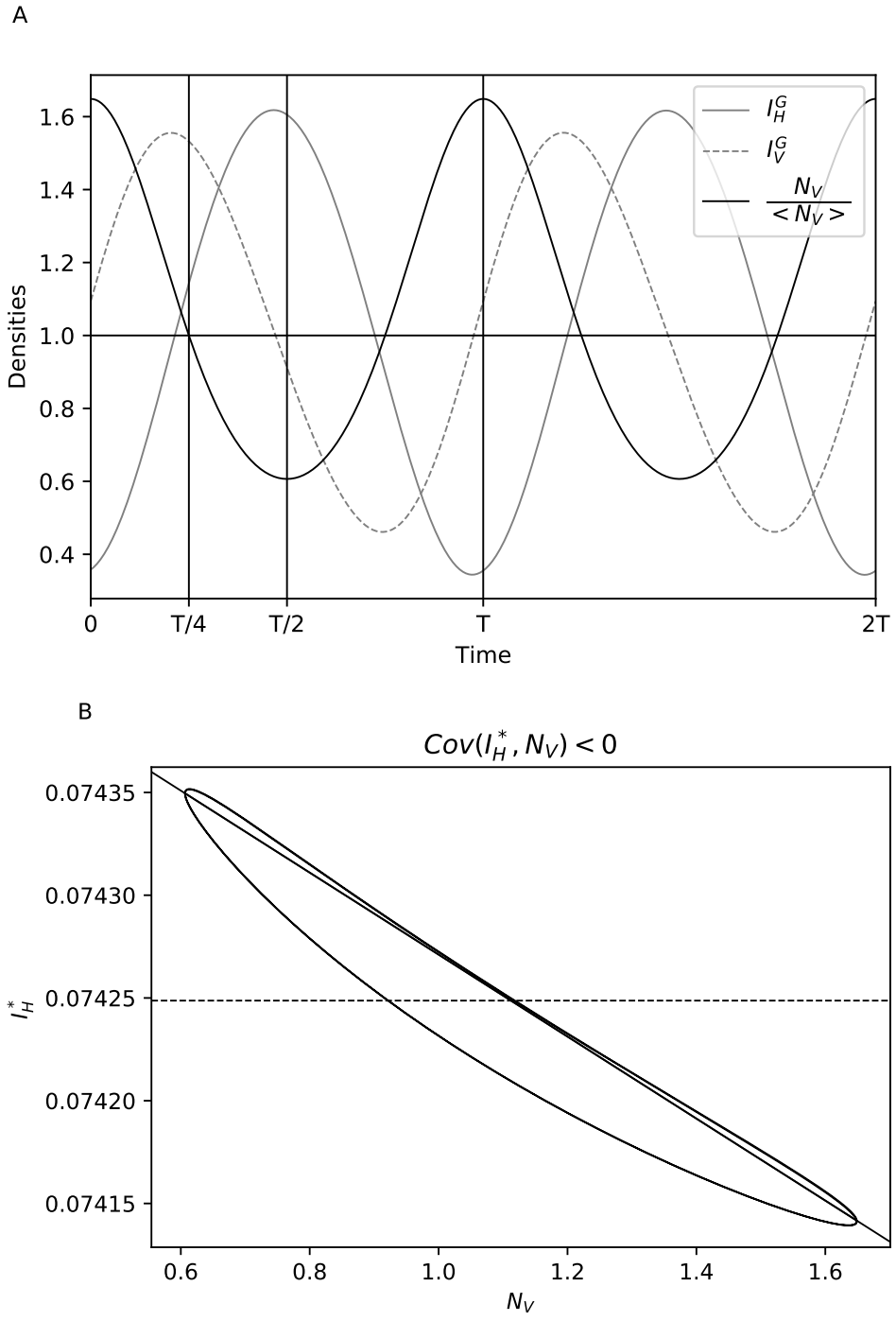

Figure 2.7 – **Understanding the covariance between N_V and I_H in model I'.** The same information as in figure (2.6) with the infected vector $I_V^G = 1 + 150\left(\frac{I_V(t)}{\langle I_V \rangle} - 1\right)$ and infected host $I_H^G = 1 + 6000\left(\frac{I_H(t)}{\langle I_H \rangle} - 1\right)$. Parameters values: $a_0 = N_V(0) = \beta_{HV} = 1, 1 = \beta_{VH}, \epsilon = 0.5, T = 1, \mu_V = 1, \mu_H = 0.01, \gamma_H = 0.1$.

CHAPTER 3

TIMING INFECTIOUS DISEASE CONTROL TO MINIMIZE THE RISK OF PATHOGEN EMERGENCE

The seasonality of the environment can have a dramatic impact on the ability of a pathogen to emerge and to induce a major epidemic. In finite host populations, we identify a critical population size of the host population below which the probability of pathogen emergence is very small. This critical population size is very sensitive to the period and to the amplitude of the fluctuations of the environment. These results have practical implications for the design of more effective control strategies aiming to limit the risk of pathogen emergence. In particular, we show that the deployment of pathogen control at the end of a favorable period for pathogen transmission often yields a lower probability of pathogen emergence.

3.1 Introduction

The ability of a pathogen to spread in a fully susceptible population is governed by its reproduction number R_0 [AM79; AM86]. In a simple logistic model with direct pathogen transmission R_0 measures the number of secondary cases produced by an infected case and takes the simple form $R_0 = \beta/\mu$ where β is the transmission rate and $\frac{1}{\mu}$ the duration of the infection. When $R_0 < 1$, a pathogen rapidly goes to extinction after its introduction in the host population. When $R_0 > 1$, in the deterministic approximation (i.e., when the host population is assumed to be infinitely large) the pathogen will spread and will ultimately reach an endemic equilibrium, with a positive density of infected and susceptible hosts.

In a finite host population, however, the pathogen is doomed to go extinct after some time. Yet, the distribution of the time to go extinct after pathogen introduction is often bimodal: extinction may either take place very fast or much longer after the introduction of the pathogen

[WHI55; Bai64]. To account for this bimodality it is useful to define the probability $p_{ext} = 1/R_0$ that the pathogen population goes extinct very fast. In contrast, with probability $p_e = 1 - p_{ext}$, the pathogen takes off and results in a major epidemic. After this *emergence*, the density of infected hosts is expected to fluctuate stochastically around an endemic equilibrium [DHB13; AJ12; AD13] and the extinction time of such pathogen populations may be very long, even when the size of the population is modest.

Periodic fluctuations of the environment can have dramatic effects on the epidemiological dynamics of infectious diseases [Bac07; Hee+15; Mor+13; KCG22]. Yet, in a simple epidemiological scenario with direct transmission and a single host type, the basic reproduction number is simply $R_0 = \frac{\langle\beta\rangle}{\langle\mu\rangle}$, a ratio of the average value of β and μ over one period of the fluctuation. Second, seasonality can also affect the probability of emergence. As pointed out by Carmona & Gandon [CG20] the timing of the introduction relative to the fluctuations of the environment has a massive impact on the probability to take off $p_e(t_0)$. In particular, this probability of emergence is reduced just before the "bad" transmission season from the perspective of the pathogen. Under the assumption that the introduction time of the pathogen is uniformly distributed throughout the year it is possible to compute $< p_e >$ the average probability of emergence. Carmona & Gandon [CG20] studied the influence of periodic fluctuations of the environment on $< p_e >$ in an infinite host population size and showed that $< p_e >$ may be minimized for some periodic functions.

In the following, we extend this analysis to analyze the dynamics of pathogen epidemics in finite host populations. First, we identify a threshold host population size below which the risk of pathogen emergence $< p_e >$ becomes vanishingly small. Second, we explore alternative control strategies that modify pathogen transmission and we identify the best time to implement a control to limit the risk of pathogen emergence.

3.2 The model

We denote by K the capacity, i.e. the maximal host population, and $X^{(K)}(t)$ the number of infected host at time t, so that the number of susceptible hosts is $S^{(K)}(t) = K - X^{(K)}(t)$. The

stochastic dynamics is described by the transitions :

$$X^{(K)} \to X^{(K)} + 1 \text{ with rate} \qquad \beta(t)X^{(K)}(t)\left(1 - \frac{X^{(K)}(t)}{K}\right), \tag{3.1}$$

$$X^{(K)} \to X^{(K)} - 1 \text{ with rate} \qquad \mu X^{(K)}(t). \tag{3.2}$$

Note that the pathogen transmission rate is density dependent because the availability of susceptible hosts drops when the epidemic spreads in the host population. Besides, we assume that $\beta(t)$ is a T-periodic, piecewise continuous function, modeling the seasonality of the environment. In contrast, we assume that the death rate is constant and equal to $\mu > 0$.

The deterministic approximation says that for large values of K, starting the epidemic with a proportion x_0 of infected hosts, the stochastic process $\frac{X^{(K)}(t)}{K}$ is well approximated on finite time intervals by the solution of the logistic ODE

$$\frac{dx(t)}{dt} = \beta(t)x(t)(1 - x(t)) - \mu x(t)\,, \qquad x(0) = x_0. \tag{3.3}$$

Observe that in case $\langle\beta\rangle > \mu$, all trajectories are attracted to the unique periodic solution of the ODE (3.3) given by :

$$x^\star(t) = \frac{1}{e^{-\varphi(t)}\left(\int_0^t \beta(s)e^{\varphi(s)}ds + \frac{1}{e^{\varphi(T)}-1}\int_0^T \beta(s)e^{\varphi(s)}ds\right)}\,, \quad \text{with} \quad \varphi(t) = \int_0^t (\beta(s) - \mu)\,ds\,. \tag{3.4}$$

However, observe that since $X^{(K)}$ is a Markov process on the finite state space $\{0, \ldots, K\}$ with 0 as the only absorbing state and all the other states communicating, we know that almost surely it is absorbed at 0, that is *extinction is almost sure*.

3.3 Results

3.3.1 The constant case

The stochastic dynamics of the pathogen depend on the value of its reproduction number $R_0 = \frac{\beta}{\mu}$. Let $\tau_0^{(K)}$ be the time to extinction of the pathogen population after introducing some infected hosts in the host population:

$$\tau_0^{(K)} = \inf\left\{t > 0 : X^{(K)}(t) = 0\right\}. \tag{3.5}$$

If $R_0 < 1$ then $\tau_0^{(K)}$ is stochastically dominated by an exponential random variable of parameter $\mu - \beta$ (see section (3.7.1)). Consequently, whatever the value of the carrying capacity K, the expected time to extinction is at most equal to $\frac{1}{\mu-\beta}$.

If $R_0 > 1$, then we consider the *take off probability* : the probability that for large capacity K, the pathogen reaches a fixed proportion $x_0 K$, with $0 < x_0 < 1$. From section (3.7.2) of Supplementary Information we get

$$\mathbb{P}\left(\exists t > 0, X^{(K)}(t) \geq x_0 K \mid X^{(K)}(0) = 1\right) \geq 1 - \frac{\mu}{\beta(1-x_0)}, \tag{3.6}$$

and

$$\limsup_{K\to+\infty} \mathbb{P}\left(\exists t > 0, X^{(K)}(t) \geq x_0 K \mid X^{(K)}(0) = 1\right) \leq 1 - \frac{\mu}{\beta}. \tag{3.7}$$

Hence we infer that

$$\mathbb{P}\left(X^{(K)} \text{ takes off }\right) = 1 - \frac{\mu}{\beta}. \tag{3.8}$$

If we work conditionally on the take off, and thanks to the Markov property, this means that we assume that $\frac{X^{(K)}(0)}{K} \to x_0 \in (0,1)$. [AD98] proved that the mean extinction time of this process is *exponential in the capacity* K:

$$\mathbb{E}\left[\tau_0^{(K)}\right] \sim \sqrt{\frac{2\pi}{K}} \frac{R_0}{(R_0-1)^2} e^{KV_0}, \quad \text{with} \quad V_0 = \ln R_0 - 1 + \frac{1}{R_0} > 0. \tag{3.9}$$

We obtain the same asymptotic when starting with a single pathogen. Indeed, upper and lower bound obtained in formulas (2.5-2.8) of [KL89] combine to give the approximation

$$\mathbb{E}\left[\tau_0^{(K)} \mid X^{(K)}(0) = 1\right] = \frac{1}{\mu(R_0-1)} \sqrt{\frac{2\pi}{K}} \left(e^{KV_0} + O(1)\right), \tag{3.10}$$

with $O(1)$ bounded. In particular, the speed of the convergence to the quasi-stationary distribution (QSD) has to be faster than of the speed of extinction (see (3.7.3)). According to [CCM16], for all $K > 1$ with

$$\alpha_1(K) = 1 - \frac{\mu}{\beta} + O\left(\frac{1}{K}\right). \tag{3.11}$$

The process goes to extinction with probability close to $1 - \alpha_1(K)$ and with probability close to $\alpha_1(K)$ the process obeys the QSD ν^K on an interval exponentially large in K. More precisely,

see Remark 3.6, 3.8 of [CCM16] if $K \log^2 K \ll t \ll \frac{1}{\sqrt{K}} e^{V_0 K}$ then

$$d_{TV}\left(\mathbb{P}_1\left(X_t^K \in (.), \alpha_1(K)\nu^K + (1-\alpha_1(K))\,\delta_0\right)\right) \ll 1, \tag{3.12}$$

where $d_{TV}(\mu,\nu)$ is the total variation distance between two probability measures μ and ν which is given by:

$$d_{TV}(\mu,\nu) := \sup_{A\in\mathcal{P}(\mathbb{N})} |\mu(A) - \nu(A)|$$

Furthermore, we shall assume that we can prove as in Theorem 3.7 [CCM16] that the QSD ν^K is close to a Gaussian distribution G^K centered at $K\tilde{x}_{eq}$,with $\tilde{x}_{eq} = 1 - \frac{\mu}{\beta}$, $\exists \sigma > 0$, $G^K \sim \mathcal{N}\left(K\tilde{x}_{eq}, \frac{\sigma}{\sqrt{K}}\right)$ and

$$d_{TV}\left(G^K, \nu^K\right) = \frac{O(1)}{\sqrt{K}}. \tag{3.13}$$

In the general case, by a coupling argument that the probability of surviving the first period is increasing in K, if $t_0 < 1 - \gamma + \frac{\log K}{T(\beta-\mu)}$. It follows from Theorem 3.3 [CCM19] there exits $C_1, C_2, C_3, C_4, C_5 > 0$ and for all $t > 0$

$$d_{TV}\left(\mathbb{P}_1\left(X_t^K \in .\right), \alpha_1(K)\nu^K + (1-\alpha_1(K))\,\delta_0\right) \leq C_1 e^{-C_2 K - C_3 t e^{-C_4 K}} + C_5 e^{-\frac{C_6 t}{\log K}}, \tag{3.14}$$

3.3.2 The periodic case

Given a 1-periodic locally bounded function β we consider $X^{(K,T)}$ a stochastic logistic process with carrying capacity K and T-periodic birth rate $t \to \beta(t/T)$. We shall observe a very different behavior for small and large periods.

The reproduction number can be computed from the branching process approximation [CG20; Bac07; Hee+15]:

$$R_0 = \frac{\langle\beta\rangle}{\mu}, \qquad \text{with} \quad \langle\beta\rangle = \frac{1}{T}\int_0^T \beta(s/T)\,ds = \int_0^1 \beta(u)\,du\,. \tag{3.15}$$

If $R_0 < 1$, then $\tau_0^{(K)}$ is stochastically dominated by the absorption time $\tau_0(Z^{(T,+)})$ of a linear

birth death process with birth rate $t \to \beta(t/T)$ and death rate μ, which has a finite expectation that depends on T but not on K (see section (3.7.1)).

If $R_0 > 1$ the behavior depends strongly on the length of period T as we shall see in the next sections.

3.3.3 Short period approximations

We establish in section (3.7.4) a homogenization result. The whole process $(X^{(K,T)}(t), t \geq 0)$ converges in distribution to the process $(\bar{X}^{(K)}(t), t \geq 0)$, a stochastic logistic process with carrying capacity K, death rate μ and *constant birth rate* $\langle\beta\rangle$. Observe that this convergence in distribution holds on the whole time interval $[0, +\infty[$, that is for the whole duration of the epidemic, and whatever the initial number of infections (in particular it implies the convergence in distribution of the extinction times). In contrast, the deterministic approximation only holds on finite time intervals, and for a large initial population. In other words, the whole behavior of $X^{(K,T)}$ is well approximated by the whole behavior of $\bar{X}^{(K)}$ (see Figure 3.1) which is described at the end of section (3.3.1)

3.3.4 Long period approximations

We are unable to handle the general situation and shall restrict ourselves to the following step transmission functions

$$t \to \beta(t/T) = \beta_0 \, \mathbf{1}_{(0 \leq \frac{t}{T} \leq 1-\gamma)} \qquad (t \in [0, T]) \,, \tag{3.16}$$

with $\gamma \in (0, 1)$ and $\beta_0 > \mu$. Hence the time interval $(0, (1-\gamma)T)$ is "Good" for the pathogen (e.g. summer season) and the time interval $((1-\gamma)T, T)$ is "Bad" for the pathogen (e.g. a winter season).

The take off probability

In contrast to the constant coefficients case, this stochastic process depends strongly on the introduction time of the pathogen.

Let us first look at the deterministic approximation (3.3). The unique solution with $x(t_0 T) =$

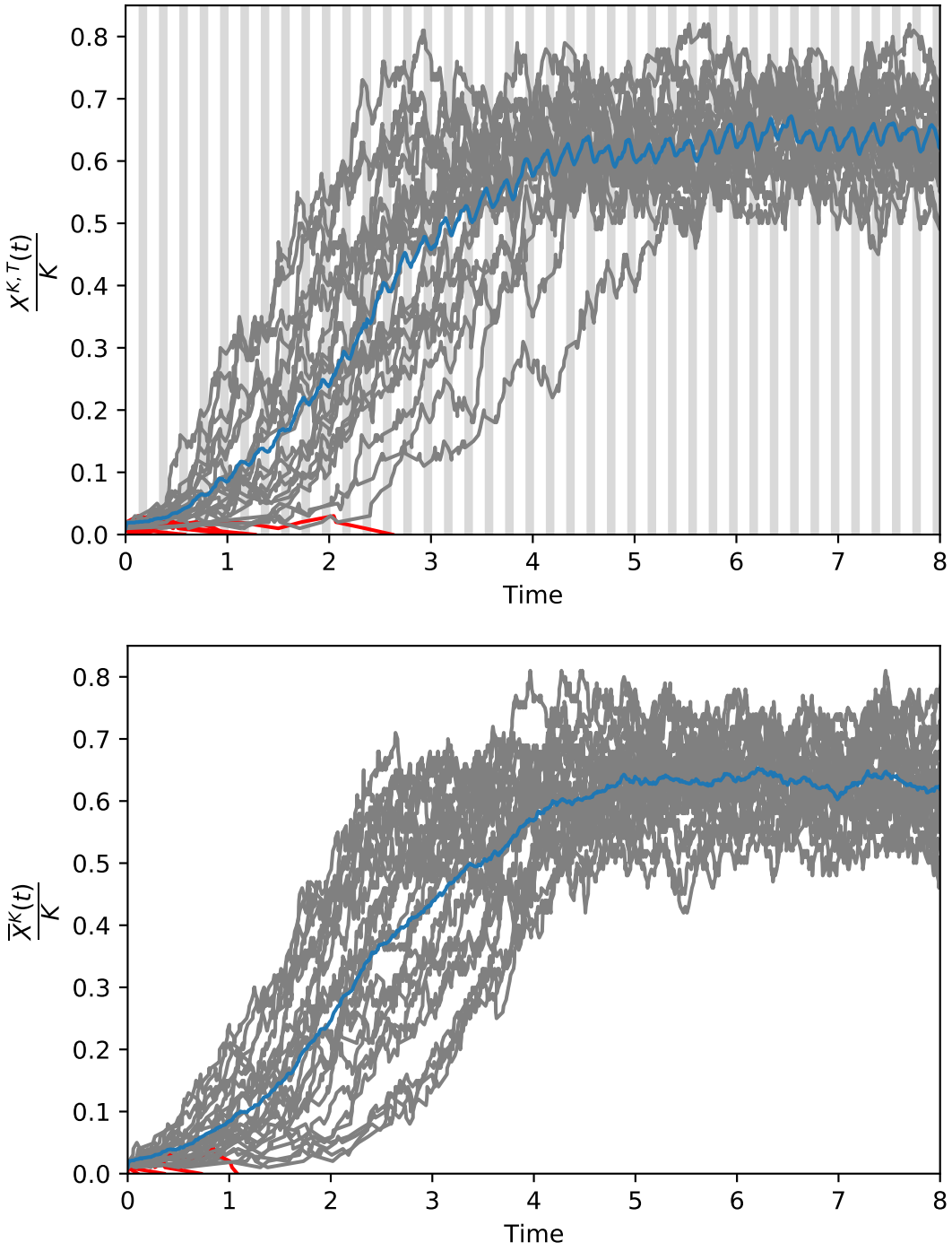

Figure 3.1 – **Periodic quasi stationary distribution and Homogenization.**. The gray lines represent the trajectories of the stochastic process $\frac{1}{K}X^{(K,T)}(t)$(top panel) and $\frac{\bar{X}^{(K)}(t)}{K}$ (bottom panel- the process with birth rate $\beta_0\,(1-\gamma)\,T$). The blue curve represents the average of 30 simulated trajectories and the red curve represents the trajectories of the process that result in extinction. The time interval is 40 periods. Parameters: There is 1 infected individual introduced for all processes, carrying capacity $K = 100$, period $T = 0.2$. step birth rate $\beta(t/T) = \beta_0\,\mathbf{1}_{(0\leq t/T\leq 1-\gamma)}$, $\beta_0 = 4.0$, $\gamma = 0.3$, constant death rate $\mu = 1$. In the top panel, the simulation with β varies with time. The bottom panel is the full stochastic with the average β. In both figures, there are 5 trajectories that vanished.

x_0, i.e. the proportion x_0 of pathogen introduced at time t_0T, satisfies (see lemma (17).)

$$\frac{1}{x((1-\gamma)T)} - \frac{1}{x_{eq}} = e^{-T(\beta_0-\mu)(1-\gamma)} \left(\frac{e^{\varphi(t_0T)}}{x_0} - \int_0^{t_0T} \beta_0 e^{\varphi(s)} ds - \frac{e^{\gamma\mu T}}{x_{eq}} \right), \tag{3.17}$$

where

$$x_{eq} = \left(1 - \frac{\mu}{\beta_0}\right) e^{\gamma\mu T} \frac{e^{(1-\gamma)T\beta_0 - T\mu} - 1}{e^{(1-\gamma)T(\beta_0-\mu)} - 1}.$$

With this explicit formula, we can define a critical time t_c such that $|x_{eq} - x((1-\gamma)T)| \leq \epsilon$ iff $t_0 < t_c$ for K large (see (3.80)) with

$$t_c = 1 - \gamma + \frac{1}{T(\beta_0 - \mu)} \log \left(\frac{\frac{\epsilon\beta_0}{\beta_0-\mu} + \frac{e^{\gamma\mu T}-1}{e^{T(1-\gamma)(\beta_0-\mu)}-1}}{\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right)(x_{eq} - \epsilon)} \right). \tag{3.18}$$

Therefore, see Figure 3.2, if $0 < t_0 < t_c$ the pathogen introduced at time t_0T has at time $(1-\gamma)T$ a density close to its equilibrium density. On the other hand, if $t > t_c$ the pathogen has not enough time to grow and the density at time $(1-\gamma)T$ is intermediary (it can be quite small).

Let us now consider the stochastic process and the following heuristic. $X^{(K,T)}(t)$ is well approximated for small times by a linear birth death process with birth rate β_0 and death rate μ, so with probability μ/β_0 it will go extinct and with probability $1 - \frac{\mu}{\beta_0}$ it will grow like $t \to e^{(\beta_0-\mu)t}$. Therefore it shall need a time of order $\frac{\log K}{\beta_0-\mu}$ to reach a density of order the capacity K. Therefore, if $t_0 \in (t_c^K, 1-\gamma)$ where

$$t_c^K = 1 - \gamma - \frac{\log K}{T(\beta_0 - \mu)}, \tag{3.19}$$

the pathogen introduced at time t_0T has not enough time to reach its endemic equilibrium before the bad season. In contrast, if $t_0 < t_c^K$ then the pathogen shall with probability $1 - \frac{\mu}{\beta_0}$ reach at time $(1-\gamma)T$ its quasi stationary distribution with is concentrated on the value Kx_{eq}. The take off probability is the probability of reaching a population of order K before the bad season: for large enough K,

$$\mathbb{P}\left(\text{take off} \mid X(t_0T) = 1\right) \simeq \begin{cases} 1 - \frac{\mu}{\beta_0} & \text{if} \quad 0 < t_0 < t_c^K. \\ 0 & \text{if } t_0 > t_c^K. \end{cases} \tag{3.20}$$

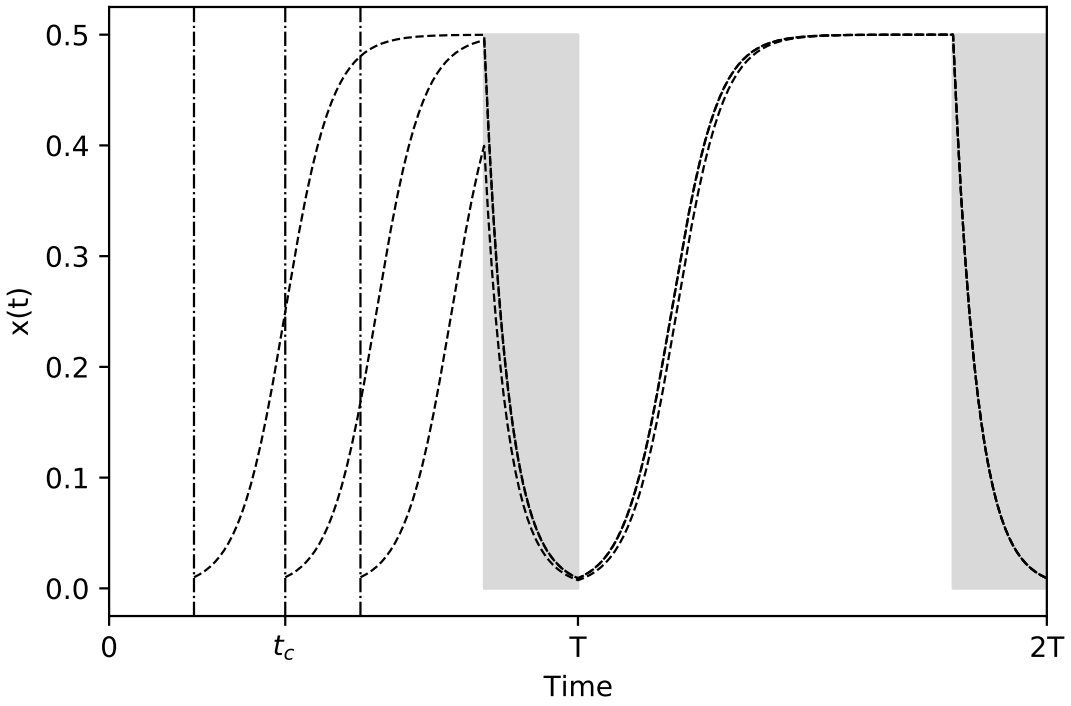

Figure 3.2 – **Reaching the equilibrium density depends on the starting time** : We start three different trajectories: t_c is the critical time for which the trajectory has just enough time to be close to the equilibrium value before the bad season. Parameters values: $\beta(t) = \beta_0 \, \mathbf{1}_{(0 \leq t/T \leq 1-\gamma)}$, $\beta_0 = 1$, $\mu = 1$,$\gamma = 0.3$, $T = 20$,$\epsilon = 0.005$,$x_0 = 0.01$, $t_c = 0.4362$.

Mean extinction time and critical capacity

According to the description of the end of section (3.3.1), conditionally on take off, the pathogen introduced at time $t_0 T$, with $t_0 < 1 - \gamma - \dfrac{C \log K}{T(\beta_0 - \mu)}$, with C a constant, yields a population of size $X^{(K,T)}((1-\gamma)T) \simeq K x_{eq}$. Observe that on the time interval $((1-\gamma)T, T)$ the process $X^{(K,T)}$ is a death process with death rate μ, hence an individual survives this time interval with probability $e^{-\gamma\mu T}$. Consequently, the probability of surviving the first period, conditionally on take off is:

$$\begin{aligned} p_{per} &= \mathbb{P}\left(X^{(K,T)}(T) > 0 \mid X^{(K,T)}(t_0 T) = 1, \text{take off}\right) && (3.21)\\ &\simeq \mathbb{P}\left(X^{(K,T)}(T) > 0 \mid X^{(K,T)}((1-\gamma)T) = K x_{eq}\right) && (3.22)\\ &= \mathbb{E}\left[1 - (1 - e^{-\gamma\mu T})^{X^{(K,T)}((1-\gamma)T)}\right] && (3.23)\\ &\simeq 1 - (1 - e^{-\gamma\mu T})^{K x_{eq}}\,. && (3.24) \end{aligned}$$

Following [CG20] we can define a critical capacity, for large periods, as

$$K_C = \frac{e^{\gamma\mu T}}{x_{eq}}\,. \tag{3.25}$$

If $K \ll K_C$ then $p_{per} \simeq 0$ and thus, even if there is a take off, with a high probability, that the pathogen will not survive the first period.

If $K \gg K_C$ then conditionally on take off, thanks to the Markov property, the number of periods that the pathogen survives is a geometric random variable of parameter $1 - p_{per}$ and therefore

$$\mathbb{E}\left[\tau_0^{(K,T)} \mid \text{take off}\right] \simeq T\frac{1}{1 - p_{per}} \simeq T(1 - e^{-\gamma\mu T})^{-K x_{eq}}\,. \tag{3.26}$$

The mean extinction time is thus exponential in the carrying capacity.

Large time behavior

We establish in section (3.7.3) the existence of a quasi periodic stationary distribution. Therefore, when there is a take off, we have for large t, but not too large (because the pathogen population is doomed to go extinct in a finite host population), a good approximation in the distribution of $\frac{X^{(K,T)}(t)}{K}$ by $\alpha^{(K)}(t)$ a periodic distribution on $\{1, \ldots, K\}$ (see Figure 3.3).

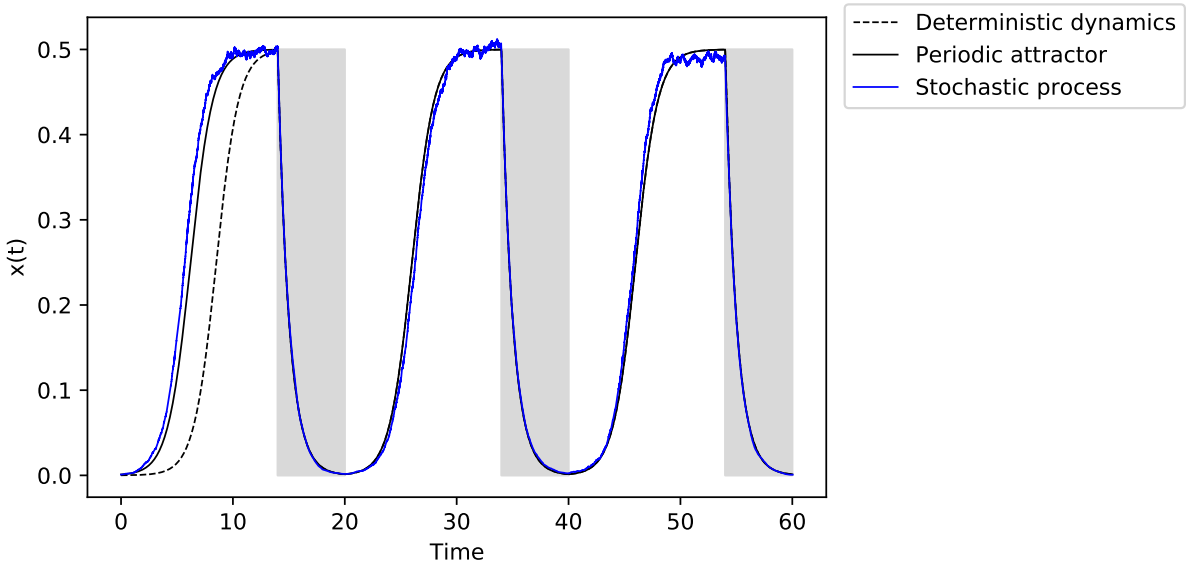

Figure 3.3 – **The periodic attractor in deterministic and stochastic model**. In solid black line, the periodic attractor $x^*(t)$, in dashed black line the deterministic dynamics $x(t)$ and in solid blue line the stochastic process $X^{(K,T)}(t)/K$. The winter season is shaded in gray. Parameter values : $\mu = 1, \gamma = 0.3, \beta_0 = 2, T = 20, \beta(t) = \beta_0 \mathbb{1}_{(0 \leq \lfloor t/T \rfloor < 1-\gamma)}$,, $X^{(K,T)}(0) = 10$ (to avoid early extinction), $x_0 = 1/K$, $K = 10^4$, $T = 20$.

3.4 The optimal timing of disease control strategies

In the following section, we are going to explore the effectiveness of different control strategies. We assume, as in the above sections that the transmission rate of the pathogen is alternating between two values. In the "Good" season the birth rate is $\beta_G > \mu$. In the "Bad" season, the birth rate is $\beta_B < \mu$. To control the epidemic we can deploy control strategies to decrease the transmission during the Good season. In other words, control reduces β from β_G to $\beta_C < \beta_G$. If the intensity of control is small (*weak control*) we have $\beta_C > \mu$, but if the intensity of control is large (*strong control*) we have $\beta_C < \mu$. If we cannot apply the control throughout the Good season, should we apply the control just before or just after the Bad season?

To answer this question we will compare two strategies: **GCB**, where control is used just before the Bad season, and **CGB** where control is used just after the Bad season. In the following the duration of the Good, Controlled and Bad periods are respectively $\pi_G T, \pi_C T$ and $\pi_B T$ with

$\pi_G + \pi_C + \pi_B = 1$ and the transition rate in the Bad period of both strategies is $\beta_B = 0$:

$$\beta_{GCB}(t) = \begin{cases} \beta_G & 0 \le t/T < \pi_G \\ \beta_C & \pi_G \le t/T < \pi_G + \pi_C \\ 0 & \pi_G + \pi_C \le t/T < 1 \end{cases}, \qquad \beta_{CGB}(t) = \begin{cases} \beta_C & 0 \le t/T < \pi_C \\ \beta_G & \pi_C \le t/T < \pi_G + \pi_C \\ 0 & \pi_G + \pi_C \le t/T < 1 \end{cases} \tag{3.27}$$

The best strategy is the less risky one, where the risk is defined as the probability that a pathogen is introduced randomly in the first period $[0, T]$ manages to survive the first period :

$$r = \frac{1}{T}\int_0^T p_1(t_0)\, dt_0 = \int_0^1 p_1(t_0 T) dt_0\,, \text{ with } p_1(t_0 T) = \mathbb{P}\left(X^{(K,T)}(T) > 0 \mid X^{(K,T)}(t_0 T) = 1\right). \tag{3.28}$$

For small periods, the strategies are equivalent, since the process is well approximated by a stochastic logistic process with constant rates. Yet, when the period is large it is unclear which strategy should be used to reduce the risk.

3.4.1 Heuristics for large periods

We shall denote by winter the time interval where $\beta(t) < \mu$: when the control is weak, i.e. $\beta_C > \mu$ the winter is the Bad time interval; when the control is strong, the winter is the union of the controlled time interval and of the bad time interval.

As for the simple step transmission function (see Figure 3.3), there is a time interval just before winter where the pathogen has not enough time to reach a size of order K. Fortunately, since the growth rate is either exponential at the beginning, the length of this time interval is of order $\dfrac{\ln(K)}{T(\beta - \mu)}$, and we shall neglect its impact in the computation of the risk.

The heuristic we develop is suited for intermediate values of K with respect to T.

When the pathogen is introduced just before the Bad period, that is $\beta(t_0 T) > \mu$ but if t_W is the start of the next unfavorable region, the expected size attained at t_W, which is of the order $e^{(\beta(t_0)-\mu)(t_W - t_0)}$ is not of the order of the magnitude of the capacity, we shall say that we have no approximation for the probability of surviving the first period. Fortunately, this region is of size $\dfrac{\log K}{T\,(\beta - \mu)}$, in both GCB and CGB cases, so we can ignore its contribution to the risk (for large T).

Eventually, when $t_0 T$ is in a favorable region, where β is constant, and it has time to expand, then with probability $1 - \mu/\beta(t_0)$ it will reach a size of order the capacity K. It is easy to prove by a coupling argument that the probability of surviving the first period is increasing in K. The

heuristic we develop is suitable for intermediate values of K : we shall assume that $\log K = aT$ with $a \in \mathbb{R}_+^*$. According to the description of the behaviour in the constant case, we shall assume that the population just before winter will get close to the quasi stationary distribution, which is itself close to $N = e^{aT} x_{eq} = e^{aT}(1 - \mu/\beta(t_0))$. Then, the probability of surviving the first period will be the probability that N independent individuals survive the unfavorable region. We know that the difference between the risks will be very small.

First case : weak control : $\beta_C > \mu$. Let p_B be the probability that a pathogen introduced at the beginning of the Bad period survives this bad period. We have $p_B = e^{-\mu T \pi_B}$. Since the number of pathogens we can expect to have at the beginning of the bad period, that is the end of the controlled region, when there is a take off, is $N_{GCB} \simeq e^{aT}(1 - \mu/\beta_C)$ Therefore, for large periods T we make the approximation for the GCB

$$\begin{aligned} r_{GCB} &\simeq (\pi_G(1 - \mu/\beta_G) + \pi_C(1 - \mu/\beta_C))(1 - (1 - p_B)^{N_{GCB}}) \simeq C_{GC}\Big(1 - (1 - e^{-\pi_B \mu T})^{e^{aT}(1-\mu/\beta_C)}\Big) \\ &\simeq C_{GC}\left(1 - e^{-\left(e^{aT}(1-\mu/\beta_C) - e^{\mu \pi_B T}\right)}\right), \end{aligned} \tag{3.29}$$

where the first factor is

$$\begin{aligned} C_{GC} &:= \frac{1}{T}\int_0^{T(\pi_G+\pi_C)} \mathbb{P}\left(\text{take off} \mid X(t_0) = 1\right) dt_0 \\ &= \frac{1}{T}\int_0^{T\pi_G} \mathbb{P}\left(\text{take off} \mid X(t_0) = 1\right) dt_0 + \frac{1}{T}\int_{T\pi_G}^{T(\pi_G+\pi_C)} \mathbb{P}\left(\text{take off} \mid X(t_0) = 1\right) dt_0 \\ &= \frac{1}{T}\int_0^{T\pi_C} \mathbb{P}\left(\text{take off} \mid X(t_0) = 1\right) dt_0 + \frac{1}{T}\int_{T\pi_C}^{T(\pi_G+\pi_C)} \mathbb{P}\left(\text{take off} \mid X(t_0) = 1\right) dt_0 =: C_{CG} \end{aligned}$$

and the second factor is the probability that N individuals alive at the beginning of the winter period will survive this winter period.

Similarly, we make the approximation, for the CGB case: with the same constant $C_{GC} = C_{CG}$ since $\beta_C > \mu$,

$$\begin{aligned} r_{CGB} &\simeq C_{CG}(1 - (1 - p_B)^{N_{CGB}}) \simeq C_{CG}\Big(1 - (1 - e^{-\pi_B \mu T})^{e^{aT}(1-\mu/\beta_G)}\Big) \\ &\simeq C_{CG}\left(1 - e^{-\left(e^{aT}(1-\mu/\beta_G) - e^{\mu \pi_B T}\right)}\right). \end{aligned} \tag{3.30}$$

Therefore, since $\beta_C < \beta_G$, we have for the approximations $r_{CGB} > r_{GCB}$, that is the strategy GCB is better than the strategy CGB. This is confirmed by the simulations, see Figure 3.4.

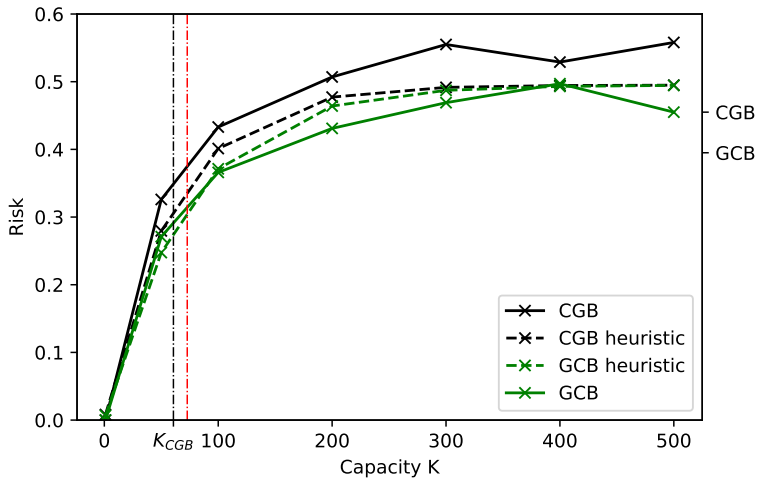

Figure 3.4 – **Weak Control: The risk as a function of the capacity K of the environment** The strategy GCB is better. For each capacity K, we introduced a single infected host randomly in $[0, T]$ and we computed the risk as the mean number of times the pathogen survives the first period from 1000 replicate simulations. The solid curves indicate the numerical results and the dotted curves indicate the heuristic approximations (3.29),(3.30). The values $GCB = 0.495$ and $CGB = 0.395$ on the right vertical line indicate the branching process approximation values given by formula (3.39): the risk is much lower because it is computed for the branching process, which is stochastically larger, and it is computed over a very long time, not just one period. $K_{CGB} = \frac{e^{\pi_B \mu T}}{1-\frac{\mu}{\pi_G}} \approx 60, K_{GCB} = \frac{e^{\pi_B \mu T}}{1-\frac{\mu}{\pi_C}} \approx 73$. Parameters : $\beta_G = 5$, $\beta_C = 2$, $\mu = 0.5$, $T = 20$, $\pi_G = \pi_C = 0.3$, $\pi_B = 0.4$.

Second case : strong control: $\beta_C < \mu$.

There the unfavorable region, where $\beta(t) < \mu$, has two parts: the Controlled region and the Bad region. We assume that when introduced in the Good region, the pathogen has time to reach an equilibrium density that is close to $N = e^{aT}(1 - \mu/\beta_G)$. When the pathogen is introduced at time t_0, with t_0 in an unfavorable region, that is when $\beta(t_0) < \mu$, with a probability close to 1, it will go extinct before the first period. As in the first case, the autumn region has a length bounded by a.

The probability that a pathogen at the beginning of the winter region escapes this winter region, and thus survives one period, depending on the structure of the winter region : p_{CB} for Controlled then Bad, or p_{BC} for Bad then Controlled. Therefore our approximation is now, with $N = e^{aT}(1 - \mu/\beta_G)$,

$$r_{GCB} \simeq \pi_G(1 - \mu/\beta_G)\Big(1 - (1 - p_{CB})^N\Big), \tag{3.31}$$

$$r_{CGB} \simeq \pi_G(1-\mu/\beta_G)\Big(1-(1-p_{BC})^N\Big). \tag{3.32}$$

Therefore, we only need to compare p_{GCB} and p_{CGB}. To this end, we shall assume that there is no density dependence on this time interval :

Let us recall the probability of survival at time t for a birth-death process with birth rate $\lambda(s)$ and death rate $\mu(s)$ is given by

$$\mathbb{P}\left(X(t)>0|X(0)=1\right) = \left(1+\int_0^t \mu(s)e^{-\varphi(s)}\,ds\right)^{-1} \tag{3.33}$$

with $\varphi(t)=\int_0^t(\lambda(s)-\mu(s))\,ds$. Hence,

$$p_{CB} = 1/(1+T\mu\kappa_{CB})\,, \qquad p_{CGB} = 1/(1+T\mu\kappa_{BC})\,, \tag{3.34}$$

with

$$\kappa_{CB} = \frac{1-e^{-T\pi_C(\beta_C-\mu)}}{T(\beta_C-\mu)} + e^{-T\pi_C(\beta_C-\mu)}\frac{e^{T\mu\pi_B}-1}{T\mu}\,, \tag{3.35}$$

$$\kappa_{BC} = \frac{e^{T\mu\pi_B}-1}{T\mu} + e^{T\mu\pi_B}\frac{1-e^{-T\pi_C(\beta_C-\mu)}}{T(\beta_C-\mu)}\,. \tag{3.36}$$

We have for $\pi_B=0$, $\kappa_{CB}=\kappa_{BC}$ and

$$\frac{\partial\kappa_{BC}}{\partial\pi_B} = e^{T\mu\pi_B}\left(1+\frac{\mu}{\beta_C-\mu}\left(1-e^{-T\pi_C(\beta_C-\mu)}\right)\right) > \frac{\partial\kappa_{CB}}{\partial\pi_B} = e^{-T(\beta_C-\mu)\pi_C}e^{T\mu\pi_B}\,. \tag{3.37}$$

Therefore, $\kappa_{BC} > \kappa_{CB}$, $r_{GCB} < r_{GBC}$ and GCB is better than CGB (see Figure 3.5). From the two preceding cases, we always get that the risk with GCB strategy yields lower than CGB strategy. Put simply, we should assume control of preventive measures right before winter arrives.

3.4.2 Comparison with the branching process (no density dependence)

It is interesting to compare the recommendation we make regarding the timing of the control to the results obtained by [CG20] with a branching process approximation (section (3.7.7) for detailed computations). The branching process approximation provides an accurate evaluation of the risk of pathogen emergence when there is no density dependence. Hence, this comparison allows us to study the effect of density dependence on the influence of the timing of control.

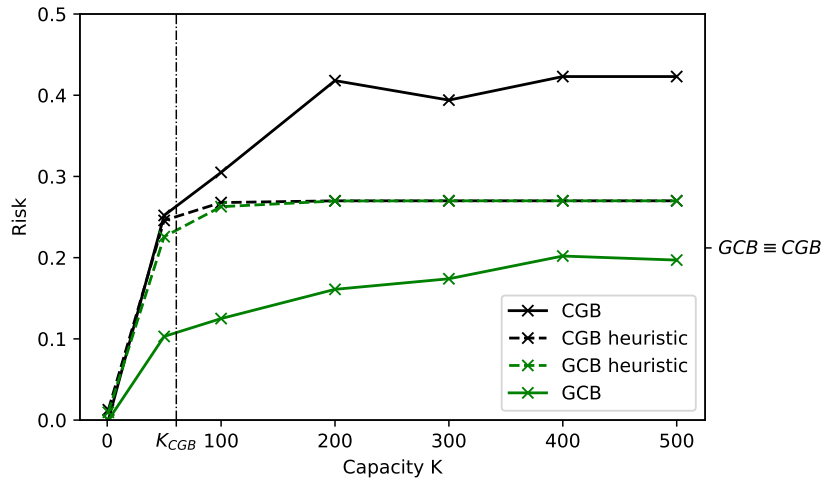

Figure 3.5 – **Strong control: The risk as a function of the capacity K of the environment** The strategy GCB is better. For each capacity K, we introduced a single infected host randomly in $[0, T]$ and we computed the risk as the mean number of times the pathogen survives the first period from 1000 replicate simulations. The right-hand side indicates the risk by using the branching process approximation. $GCB = CGB = 0.212$, $K_{CGB} = K_{GCB} = \frac{e^{\pi_B \mu T}}{1-\frac{\mu}{\pi_G}} \approx 60$. Its values are less than heuristic results $p_1(t_0 T) = \mathbb{P}\left(X^{(K,T)}(T) > 0 \mid X^{(K,T)}(t_0 T) = 1\right) \geq \mathbb{P}\left(\forall t > t_0 T, X^{(K,T)}(t) > 0 \mid X^{(K,T)}(t_0 T) = 1\right)$. Parameters : $\beta_G = 4$, $\beta_C = 0.2$, $\mu = 0.5$, $T = 20$,$\pi_G = \pi_C = 0.3$, $\pi_B = 0.4$.

In the absence of density dependence, the risk of pathogen emergence is well approximated by (see equation 2.6 [CG20])

$$\tilde{r}_i = \lim_{T\to\infty} \frac{1}{T} \int_0^T \left(1 - \frac{\mu}{\beta_i(t/T)}\right) \mathbf{1}_{(t/T \notin \mathrm{WIC}_i)} dt \approx \int_0^1 \left(1 - \frac{\mu}{\beta_i(t)}\right) \mathbf{1}_{(t \notin \mathrm{WIC}_i)} dt, \tag{3.38}$$

where $\mathrm{WIC}_i = \{t_0 \in [0,1), \beta_i(t_0) < \mu \text{ or } \exists s > t_0, \varphi_i(s) \leq \varphi_i(t_0)\}$. and $\varphi_i(t) = \int_0^t \beta_i(s) - \mu(s) ds$ with $i \in \mathcal{D} := \{\mathrm{GCB}, \mathrm{CGB}\}$. If nothing further is mentioned about the subindex, we will implicitly understand that we are considering both strategies.

Under the assumption that $\beta_G > \beta_C > \mu$, then the computation detailed in the Supplementary Information of [CG20], for all cases yields that

$$\tilde{r}_{GCB} < \tilde{r}_{CGB} \tag{3.39}$$

Therefore, as in the density dependent case, it is better to act just before the winter (Figure 3.4).

Next, under the assumption that $\beta_G > \mu > \beta_C$. Then, again from the Supplementary Information of [CG20] we get that

$$\tilde{r}_{GCB} = \tilde{r}_{CGB} = \frac{\varphi_{GCB}(1)}{\beta_G} = \frac{\varphi_{CGB}(1)}{\beta_G} \tag{3.40}$$

Therefore in this case, the strategies are equivalent for the branching process approximation, whereas we see that the strategy GCB, acting before the winter, is better for the density dependent stochastic logistic process (Figure 3.5).

3.5 Discussion

Seasonal fluctuations of the environment can affect pathogen dynamics [Alt+06; GF06]. However the implications of these fluctuations for the risk of pathogen emergence are often difficult to analyze. We have previously explored the influence of seasonality in a scenario where the host population size was assumed to be very large [CG20]. The assumption of a large host population implies that the transmission rate is not limited by the availability of susceptible hosts and we can use a birth-death branching model to study the influence of seasonality. We showed that the risk of emergence depends a lot on the time of the introduction of the pathogen during the year.

Here we study the more realistic scenario where the host population is finite. After pathogen emergence, the pathogen population can not grow without bound but settles around an endemic equilibrium. When the period of the fluctuations is small the effect of seasonality can be captured by simply taking the average transmission and death rates. When the period of the fluctuation is large relative to the lifespan of an infection, it is important to distinguish different steps in pathogen emergence.

We show that the risk of pathogen emergence depends both on the time of introduction (which drives the "take off" probability) as well as the pathogen density before the winter when transmission is limited. Indeed, the larger the pathogen population size before the winter, the higher the risk of emergence. This effect yields a critical host population size below which the pathogen is unlikely to survive the winter period.

In the second step of the analysis of this model, we study the influence of a control strategy that aims at reducing the pathogen transmission rate. We explore when it is best to limit pathogen transmission to limit the risk of emergence: just before the winter season, or just after? Interestingly, we derive different heuristic results that indicate that it is better to act just before the winter. The magnitude of this effect depends on the intensity of the control that is applied but the qualitative effect holds.

This result has practical implications for pathogen and pest control. Indeed, under a limited amount of resources, it is always better to act at the end of a favorable transmission season. Different effects combine to maximize the risk of pathogen extinction. For instance, if we want to limit the emergence of malaria it is best to apply vector control just before the summer (or the dry) season when the density of vectors is expected to be lower. In contrast, for viruses of the winter viruses that tend to spread with colder temperatures a control strategy that acts at the end of the winter is likely to be more effective in reducing the risk of emergence. of course, these recommendations should not be relevant for highly transmitted diseases where emergence is almost certain. However our results could be particularly relevant to limit the re-emergence of seasonal diseases with lower R_0.

3.6 Tables and Figures

Table 3.1 – Parameters and variables of the models

Symbol	Description
Parameters	
β	rate of transmission from an infected host to a susceptible host
μ	death rate of the host
K	carrying capacity
T	period of the seasonal fluctuations
π_G, π_C, π_B	durations of Good, Controlled and Bad periods, $\pi_G+\pi_C+\pi_B = 1$
Variables	
$X^{(K,T)}$	stochastic density of infected hosts (carrying capacity K and period T).
$\tau_0^{(K)}$	extinction time
K_C	critical capacity

3.7 Supplementary Information

3.7.1 A bound on the mean extinction time

By comparing the birth and death rates, we can construct a coupling, that is on the same space the process $X^{(K,T)}$ and a linear birth death process $Z^{+,T}$ with birth rate $t \to \beta(t/T)$ and death rate μ, such that

$$\forall t\,, \quad X^{(K,T)}(t) \leq Z^{+,T}(t) \qquad a.s. \tag{3.41}$$

Hence the mean time to extinction of $X^{(K,T)}$ is bounded by the mean time to extinction of $Z^{+,T}$, which does not depends on K :

$$\begin{aligned}
\mathbb{E}\left[\tau_0^{(K,T)}\right] &\leq \mathbb{E}\left[\tau_0^{(+,T)}\right] \\
&= \int_0^\infty \mathbb{P}\left(\tau_0^{(+,T)} > t\right) dt \\
&= \int_0^\infty \mathbb{P}\left(Z^{+,T}(t) > 0\right) dt \\
&= \int_0^\infty \left(1 + \mu \int_0^t e^{-\varphi_T(s)}\, ds\right)^{-1} dt\,,
\end{aligned}$$

with

$$\varphi_T(t) = \int_0^t (\beta(s/T) - \mu) ds = T\varphi(t/T) \tag{3.42}$$

which has asymptotic

$$\lim_{t\to+\infty} \frac{1}{t}\varphi_T(t) = \frac{1}{T}\varphi_T(T) = \langle\beta\rangle - \mu\,, \quad \text{with } \langle\beta\rangle = \int_0^1 \beta(u)\, du\,. \tag{3.43}$$

Therefore, when $R_0 < 1$, that is $\langle\beta\rangle < \mu$, the expectation of $\tau_0^{(+,T)}$ is finite. Moreover, in the constant case, we have

$$\mathbb{E}\left[\tau_0^{(K)}\right] \leq \mathbb{E}\left[\tau_0^{(+)}\right] = \int_0^\infty \left(1 + \mu \int_0^t e^{-(\beta-\mu)s}\, ds\right)^{-1} dt \leq \int_0^\infty e^{-(\mu-\beta)t}\, dt = \frac{1}{\mu - \beta}\,. \tag{3.44}$$

We have used in the last equation the inequality, satisfied for $x \geq 1$ and $a > 0$:

$$\frac{1}{1 + a(x-1)} \leq \frac{1}{x} \max(1, 1/a)\,.$$

In the general periodic case, we can combine this inequality with Lemma 11 to obtain an upper bound. Indeed, we obtain that

$$\sup_t |\varphi_T(t) - (\langle\beta\rangle - \mu)t| \leq CT \quad \text{with } C = 2\sup_{s\leq 1}|\beta(s) - \mu|$$

Hence,

$$\begin{aligned}\mathbb{E}\left[\tau_0^{(K)}\right] &\leq \int_0^\infty \left(1 + \mu e^{-CT}\int_0^t e^{-(\langle\beta\rangle-\mu)s}\,ds\right)^{-1} dt \\ &\leq \max\left(1, e^{CT}\left(1 - \frac{\langle\beta\rangle}{\mu}\right)\right)\int_0^\infty e^{(\langle\beta\rangle-\mu)t}\,dt \\ &\leq \frac{1}{\mu - \langle\beta\rangle}\max\left(1, e^{CT}\left(1 - \frac{\langle\beta\rangle}{\mu}\right)\right)\end{aligned}$$

3.7.2 Take off probability in the constant case

This is a classical result for the constant case, see e.g. [BD95]. We first look at the coupling (3.41) in the constant case: Z^+ is a linear birth and death process with birth rate β and death rate μ such that a.s.

$$\forall t \geq 0, X^{(K)}(t) \leq Z^+(t). \tag{3.45}$$

For $x_0 \in (0,1)$ we have

$$\mathbb{P}\left(\exists t > 0, X^{(K)}(t) \geq x_0 K\right) \leq \mathbb{P}\left(\exists t > 0, Z^+(t) \geq x_0 K\right) \tag{3.46}$$

Therefore, since either $Z^+(t) = 0$ for $t \geq t_0$ or $\lim_{t\to+\infty} Z^+(t) = +\infty$, we have

$$\limsup_{K\to+\infty} \mathbb{P}\left(\exists t > 0, X^{(K)}(t) \geq x_0 K\right) \leq \mathbb{P}\left(\lim_{t\to+\infty} Z^+(t) = +\infty\right) = 1 - \frac{\mu}{\beta}\,. \tag{3.47}$$

Given $x_0 \in (0,1)$, we can enhance the coupling by constructing another linear birth death process Z^- with birth rate $\beta(1-x_0)$ and death rate μ :

$$Z^-(t) \leq X^{(K)}(t) \quad \text{if } t < S(\omega) \tag{3.48}$$

with

$$S(\omega) = \inf\left\{t > 0 : X^{(K)}(t) \geq x_0 K\right\}. \tag{3.49}$$

Therefore, since either $Z^-(t) = 0$ for $t \geq t_0$ or $\lim_{t\to+\infty} Z^-(t) = +\infty$, we have

$$\mathbb{P}\left(\exists t>0, X^{(K)}(t)\geq x_0K\right) \geq \mathbb{P}\left(\exists t>0, Z^{-}(t)\geq x_0K\right) \tag{3.50}$$

$$\geq \mathbb{P}\left(\lim_{t\to+\infty} Z^{-}(t)=+\infty\right) = 1-\frac{\mu}{\beta(1-x_0)}\,. \tag{3.51}$$

3.7.3 Quasi stationary distribution in the constant case

Since the Markov chain $X^{(K)}$ has a finite state space and is irreducible before being absorbed at 0, [DS65; DS67] established the existence of a quasi stationary distribution , a probability α on $\{1,\dots,K\}$, which is a Yaglom limit : for every starting point $x=1,\dots,K$,

$$\lim_{t\to+\infty} \mathbb{P}_x\Big(X^{(K)}(t)\in A \mid \tau_0>t\Big) = \alpha(A)\,. \tag{3.52}$$

Moreover, there exists another probability π on $\{1,\dots,K\}$, and a number $\theta>0$, such that for any $x,y\in\{1,\dots,K\}$:

$$\lim_{t\to+\infty} e^{-\theta t}\mathbb{P}_x\Big(X^{(K)}(t)=y\Big) = \pi_x\alpha_y\,,$$
$$\lim_{t\to+\infty} e^{-\theta t}\mathbb{P}_x\Big(\tau_0^{(K)}>t\Big) = \pi_x\,.$$

3.7.4 Homogenization for small periods

We prove that when the period T is small, one can replace the periodic stochastic logistic process by a stochastic logistic process whose constant coefficients are the average of the preceding.

More precisely, given two locally bounded positive measurable functions β,μ and a positive integer K, *the stochastic logistic process with birth rate β, death rate μ and capacity K*, is the inhomogeneous pure jump Markov process $(X(t), t\geq 0)$, in fact an inhomogeneous continuous-time Markov chain, with values in $\{0,\dots,K\}$ and generator

$$Lf(x) = \beta(t)x\left(1-\frac{x}{K}\right)(f(x+1)-f(x)) + \mu(t)x\,(f(x-1)-f(x)) \qquad (x=0,1,\dots,K\,.). \tag{3.53}$$

We say that X is a $SLP(\beta,\mu,K)$.

Given a 1-periodic positive measurable locally bounded function β, a constant $\mu>0$, a positive integer K and a period $T>0$, we consider $X^{(K,T)}$ a stochastic logistic process with birth rate $t\to\beta(t/T)$, constant death rate μ and capacity K. The average process $\bar{X}^{(K)}$ is

a $SLP(\langle\beta\rangle, \mu, K)$ where $\langle\beta\rangle = \int_0^1 \beta(s)\, ds = \frac{1}{T}\int_0^T \beta(u/T)\, du$ is the average birth rate. We assume that the two processes start from the same integer x_0.

Theorem 8. *When $T \to 0$, the process $X^{(K,T)}$ converges in distribution to the process $\bar{X}^{(K)}$, for Skorokhod topology on the space $D([0,\infty[)$ of cadlag processes defined on $[0,\infty[$.*

Corollary 9. *When $T \to 0$ the extinction time of the process $X^{(K,T)}$ converges to the extinction time of the process $\bar{X}^{(K)}$. In consequence, when $\bar{R}_0 = \frac{\langle\beta\rangle}{\mu} > 1$, this time is exponential in the carrying capacity K.*

Proof. Since the Markov chain $X^{(K,T)}$ (resp. $\bar{X}^{(K)}$) has 0 for absorbing state, and $\{1,\dots,K\}$ is an open communicating class, we have, if $\tau_0^{(K,T)} = \inf\left\{t > 0 : X^{(K,T)}(t) = 0\right\}$ and $\bar{\tau}_0 = \inf\left\{t > 0 : \bar{X}(t) = 0\right\}$, we have as $T \to 0$,

$$\mathbb{P}\left(\tau_0^{(K,T)} > t\right) = \mathbb{P}\left(X^{(K,T)}(t) > 0\right) \to \mathbb{P}\left(\bar{X}^{(K)}(t) > 0\right) = \mathbb{P}\left(\bar{\tau}_0^{(K)} > t\right). \tag{3.54}$$

□

Remark 10. *Therefore if the period T is small enough, and $\bar{R}_0 = \langle\beta\rangle/\mu > 1$, the time to absorption of $X^{(K,T)}$ is very long, we still have a periodic Yaglom limit, but the process $X^{(K,T)}$ is close to $\bar{X}^{(K)}$, hence the periodic Yaglom limit is close to a fixed distribution, the Yaglom limit of $\bar{X}^{(K)}$, a distribution concentrated around the value $K(1-\mu/\langle\beta\rangle)$ (the equilibrium value of the deterministic approximation of $\bar{X}^{(K)}$). In Figure 3.6 we see that for a small period $T = 0.2$ and capacity $K = 50$, the deterministic process is indistinguishable from the periodic attractor after 20 periods. We observe that after this warming up of 20 periods, the stochastic processes $\bar{X}^{(K)}$ and $X^{(K,T)}$ fluctuate around this periodic solution. We do have observed simulations with no take off, for $X^{(K,T)}$ or $\bar{X}^{(K)}$, this happens with the probability $\mu/\beta(0)$, but given the take off, the time of extinction is so large that we do not observe it.*

Proof of Theorem 8. Usually, this kind of result is proved by establishing the convergence of generators, and applying a generalization of Trotter-Kato's theorem (see e.g. [Kur69]). Unfortunately, we do not have pointwise convergence of the function $\beta(t/T)$ to the constant function $\langle\beta\rangle$: only a Cesaro limit exists, thanks to periodicity.

Therefore, we are going to use a very general theorem dealing with convergence of semi martingales, [JS03, Theorem 2.21, page 80], which states that it is enough to prove the convergence of the triplet of characteristics.

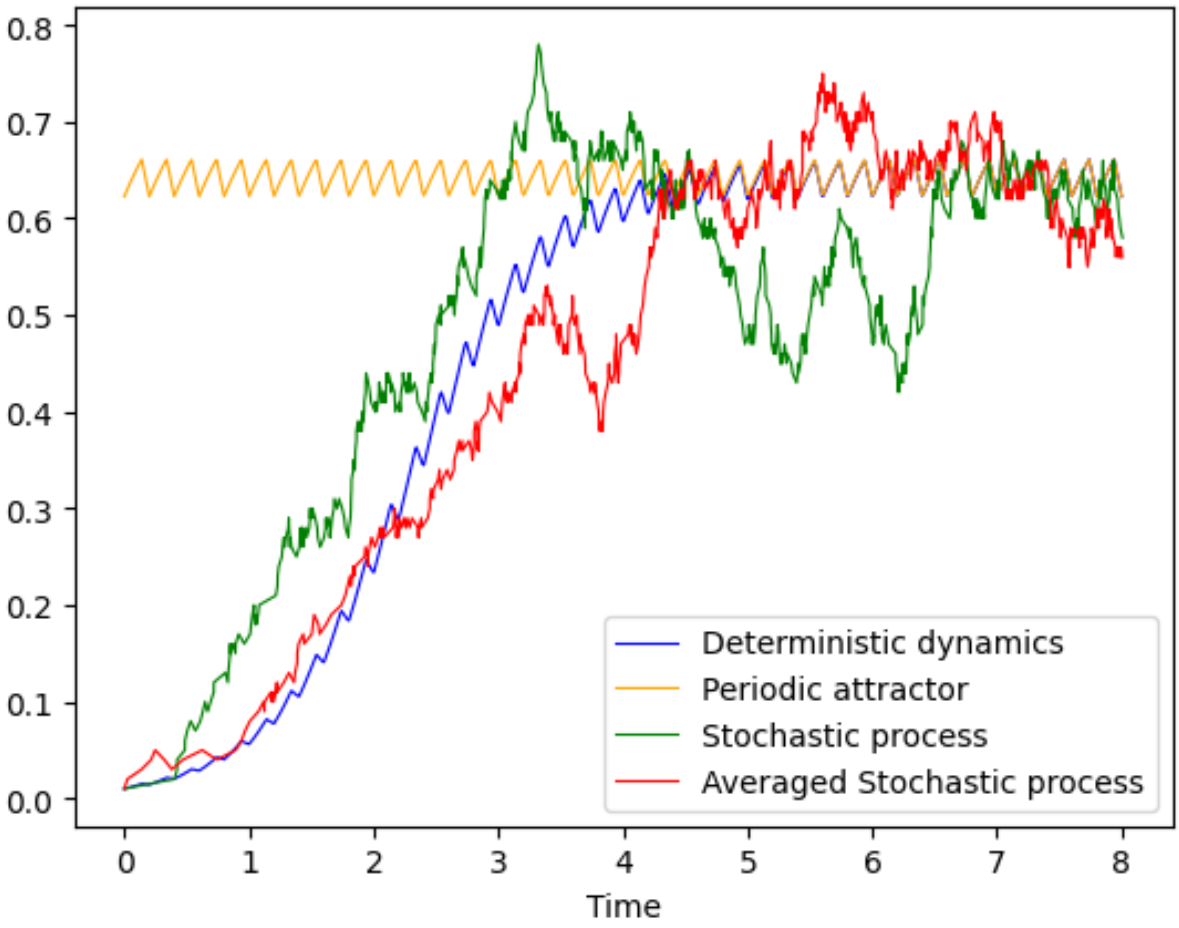

Figure 3.6 – **Periodic quasistationary Yaglom distribution for small periods.** In blue the deterministic approximation $x(t)$, in orange the periodic attractor $x^*(t)$ (they are indistinguishable after twenty periods). In green the stochastic logistic process $\frac{1}{K}X^{(K,T)}(t)$. Parameters: capacity $K = 50$, period $T = 0.2$ step birth rate $\beta(t/T) = \beta_0 \, \mathbf{1}_{(0 \leq t/T \leq 1-\gamma)}$, $\beta_0 = 2.0$, $\gamma = 0.3$, constant death rate $\mu = 1$.

In order to simplify the notation, I will omit K with the implication that K is fixed. Here the jumps are bounded, and the characteristic triple of $X^{(T)}$ (resp. $\bar{X}$) is $(0, 0, \nu^{(T)})$ (resp. $(0, 0, \bar{\nu})$). There only remains to verify the assumption: for every bounded nonnegative measurable function g, $\left(g * \nu_t^{(T)} - g * \bar{\nu}_t\right)(X^{(T)})$ converges in probability to 0 when $T \to 0$.

In fact since $\nu^{(T)}$ is the compensator of the jumps of $X^{(T)}$, we have

$$g * \nu^{(T)}(t,x) = \int_0^t [\beta(s/T)x(1-x/K)(g(x+1)-g(x)) + \mu x(g(x-1)-g(x))]\, ds$$
$$g * \bar{\nu}(t,x) = \int_0^t [\langle\beta\rangle x(1-x/K)(g(x+1)-g(x)) + \mu x(g(x-1)-g(x))]\, ds\,.$$

Consequently, applying Lemma 12 to the step function $s \to X^{(T)}(s)(1-X^{(T)}(s)/K)(g(X^{(T)}(s)+1) - g(X^{(T)}(s)))$, we get

$$\begin{aligned}
&\left|g * \nu_t^{(T)}(X^{(T)}) - g * \bar{\nu}_t(X^{(T)})\right| \\
&\quad = \left|\int_0^t (\beta(s/T) - \langle\beta\rangle) X^{(T)}(s)(1 - X^{(T)}(s)/K)(g(X^{(T)}(s)+1) - g(X^{(T)}(s)))\, ds\right| \\
&\quad \leq 4T\|\beta\|_\infty \times 2K\|g\|_\infty.
\end{aligned}$$

Hence, this random variable converges almost surely to 0 as $T \to 0$.

□

Integration tools

We think these results are well known. Since we have been unable to find references, we state them along with their proofs.

Lemma 11. *Let f be a measurable locally bounded 1-periodic function, and $\langle f\rangle = \int_0^1 f(s)\, ds$ be its average. Then, for any $T > 0$,*

$$C_f(T) := \sup_{t\geq 0}\left|\int_0^t f(s/T)\, ds - t\langle f\rangle\right| \leq 2\|f\|_\infty T\,. \tag{3.55}$$

Proof. With $n = \lfloor t\rfloor$, since f is of period 1:

$$\frac{1}{t}\int_0^t f(s)\, ds = \frac{1}{t}\left(n\langle f\rangle + \int_0^{t-n} f(s)\, ds\right). \tag{3.56}$$

Consequently, since $\left|\frac{n}{t} - 1\right| \leq \frac{1}{t}$

$$\left|\frac{1}{t}\int_0^t f(s)\,ds - \langle f\rangle\right| \leq |\langle f\rangle|\left|\frac{n}{t} - 1\right| + \frac{1}{t}\|f\|_\infty \leq 2\|f\|_\infty \frac{1}{t}\,. \tag{3.57}$$

And thus,

$$\left|\int_0^t f(s/T)\,ds - t\langle f\rangle\right| = T\left|\int_0^{t/T} f(u)\,du - \frac{t}{T}\langle f\rangle\right| \leq 2T\|f\|_\infty. \tag{3.58}$$

□

Lemma 12. *Let f be a measurable locally bounded 1-periodic function, and $\langle f\rangle = \int_0^1 f(s)\,ds$ be its average. Then, for any $T > 0$, for any continuous or step function g defined on $[0, t]$,*

$$\left|\int_0^t f(s/T)g(s)\,ds - \langle f\rangle\int_0^t g(s)\,ds\right| \leq 4T\|f\|_\infty \sup_{s\leq t}|g(s)|\,. \tag{3.59}$$

Proof. Assume first that g is a step function

$$g(s) = \sum_{i=1}^n \alpha_k\,\mathbf{1}_{(t_i\leq s<t_{i+1})}\,. \tag{3.60}$$

Let $F(t) = \int_0^t f(s/T)\,ds$ and $G(t) = F(t) - t\langle f\rangle$. Then, thanks to Lemma 11

$$\begin{aligned}\left|\int_0^t f(s/T)g(s)\,ds - \langle f\rangle\int_0^t g(s)\,ds\right| &= \left|\sum_{i=1}^n \alpha_i(G(t_{i+1}\wedge t) - G(t_i\wedge t))\right| \\ &\leq \sup_{i\leq n}|\alpha_i| 2 \sup_{s\geq 0}|G(s)| \text{(the sum has only one non zero term)} \\ &\leq \sup_{s\leq t}|g(s)| \times 2 \times 2\|f\|_\infty T\,.\end{aligned}$$

If g is a continuous function, for any $\epsilon > 0$, there exists a step function g_ϵ such that $\sup_{s\leq t}|g(s) - g_\epsilon(s)| \leq \epsilon$. □

3.7.5 Proof of the periodic Yaglom limit for the stochastic periodic logistic process

We give a direct proof since the continuous Markov chain has a finite state space. A simulation is given in Figure 3.7.

We consider a continuous time inhomogeneous Markov chain $(Z_t, t \geq 0)$ with values in $E = \{0, \ldots, N\}$, and 0 as unique absorbing point. Let L_t be the time dependent infinitesimal

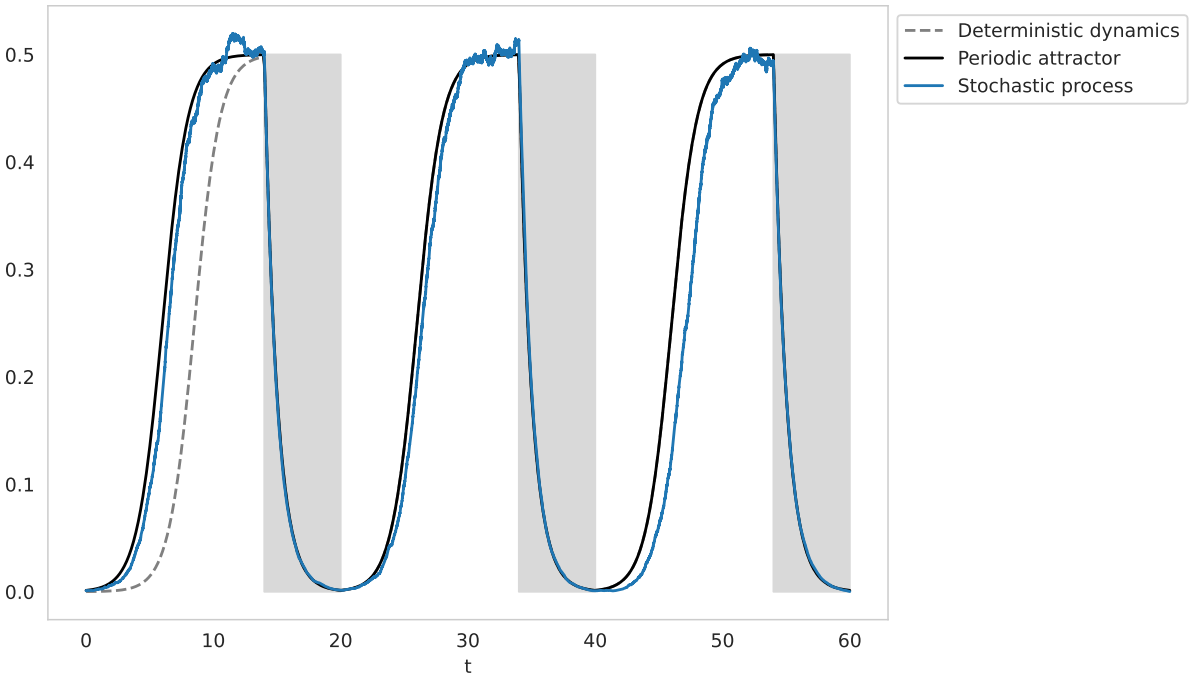

Figure 3.7 – **Periodic quasistationnary Yaglom distribution for large periods.** In dashed gray the deterministic approximation $x(t)$, in solid black the periodic attractor $x^*(t)$ (they are indistinguishable after one period). In blue the stochastic logistic process $\frac{1}{K}X^{(K,T)}(t)$. Parameters : capacity $K = 4000$, period $T = 20$ step birth rate $\beta(t/T) = \beta_0 \, \mathbf{1}_{(0 \leq t/T \leq 1-\gamma)}$, $\beta_0 = 2.0$, $\gamma = 0.3$, constant death rate $\mu = 1$.

generator and let $(T_{s,t})_{0\leq s\leq t}$ be the family of Markovian transition operators

$$T_{s,t}f(x) = \mathbb{E}\left[f(Z_t) \mid Z_s = x\right] \qquad (x \in E). \tag{3.61}$$

The first hitting time of 0 is

$$T_0 = \inf\left\{t > 0 : Z_t = 0\right\} \tag{3.62}$$

and $(P_{s,t}, 0 \leq s \leq t)$ is the family of sub markovian kernels associated to the process killed when it reaches 0:

$$P_{s,t}f(x) = \mathbb{E}\left[f(Z_t)\,\mathbf{1}_{(t<T_0)} \mid Z_s = x\right] = \mathbb{E}\left[f(Z_t)\,\mathbf{1}_{(Z_t\neq 0)} \mid Z_s = x\right] \qquad (x \in E^* = \{1,\ldots,N\})\,. \tag{3.63}$$

We assume the process to be strongly irreducible, a notion we explain below : there exists a kernel $\Lambda(x,y)$ such that for any $t \geq 0, x, y$: $Q_t(x,y) = L_t\mathbb{1}_{\{y\}}(x) \geq \Lambda(x,y)$, $\Lambda^* = \Lambda_{E^*}$ is irreducible and the exists $x_0 \neq 0$ such that $\Lambda(x_0, 0) > 0$.

We assume furthermore that the jump rates appearing in L_t are 1-periodic, and write $L_{t+1} = L_t$.

Proposition 13. *Under the preceding assumptions, there exists a probability α on E^*, a real number $\theta > 0$ and a positive vector $(\pi(x) > 0, x \in E^*)$ such that for any function f:*

$$\lim_{n\to+\infty} e^{\theta(n+t)}\mathbb{E}_x\left[f(Z_{n+t})\,\mathbf{1}_{(Z_{n+t}\neq 0)}\right] = e^{\theta t}\alpha(P_{0,t}f)\pi(x)\,. \tag{3.64}$$

Hence, we have the Yaglom limit

$$\lim_{n\to+\infty} \mathbb{E}_x\left[f(Z_{n+t}) \mid Z_{n+t} \neq 0\right] = \frac{\alpha(P_{0,t}f)}{\alpha(P_{0,t}1)}\,. \tag{3.65}$$

Proof. The *first step* is to show that the matrix $P = P_{0,1}$ is irreducible. Let $x \neq y$.

Indeed, since E^* is finite and Λ^* irreducible, there exists an integer $m \geq 1$ such that $\forall x, y \in E^*, \Lambda^m(x,y) > 0$. Consequently, there exists a path $x_0 = x, x_1, \ldots, x_m = y$ such that $\Lambda(x_i, x_{i+1}) > 0$ for $1 \leq i \leq m-1$.

Let $q_t(x)$ be the total jump intensity at x at time t. Then, if $\tau_1, \ldots, \tau_n$ are the jump times,

$$\begin{aligned} P_{s,t}(x,y) &\geq \mathbb{P}\left(Z(\tau_i) = x_i, 1 \leq i \leq m, \tau_m \leq t < \tau_{m+1} \mid Z_s = x_0\right) \\ &= \int \prod_{0\leq i\leq m} e^{-s_{i+1}q_{s_i}(x_i)} Q_{s_i}(x_i, x_{i+1})\,\mathbf{1}_{(s_0=s<s_1<\ldots<s_m<t<s_{m+1})} \prod ds_i dx_{m+1} > 0\,. \end{aligned}$$

Hence for any $s < t$ the matrix $P_{s,t}$ has positive coefficients and therefore is primitive.

The *second step* is to apply Perron Frobenius theorem to the matrix P. Since $\Lambda(x_0, 0) > 0$, we can show as in the preceding step that $T_{0,1}(x, 0) > 0$ for any $x \in E^*$. Hence the spectral radius of P is $\rho = e^{-\theta} < 1$ with $\theta > 0$. There exist a positive vector $\pi >> 0$ and a positive (line) vector $\alpha >> 0$ such that $1 = \sum_i \alpha_i = 1$ (α is a probability on E^*) such that

$$\alpha P = \rho\alpha\,, \quad P\pi = \rho\pi \qquad \lim_{n\to+\infty} \rho^{-n} P^n = A\,. \tag{3.66}$$

with $A = \pi\alpha$ the projection matrix $A_{i,j} = \pi_i \alpha_j$.

The *last step* makes use of the periodicity of the coefficients. Since $L_{t+1} = L_t$ we have $P_{s+1,t+1} = P_{s,t}$ and thus $P_{0,t+n} = P^n \circ P_{0,t}$. Hence,

$$\lim_{n\to+\infty} e^{\theta n} P_{0,n+t} f(x) = \alpha(P_{0,t} f)\pi(x)\,. \tag{3.67}$$

Applying this relation to $f = 1$, we obtain

$$\lim_{n\to+\infty} e^{n\theta} P_{0,n+t} 1(x) = \lim_{n\to+\infty} e^{n\theta} \mathbb{P}_x(T_0 > n + t) = \alpha(P_{0,t}1)\pi(x). \tag{3.68}$$

The Yaglom limit is obtained by taking the ratio of the two preceeding limits since

$$\mathbb{E}_x\left[f(Z_{n+t}) \mid Z_{n+t} \neq 0\right] = \frac{P_{0,n+t} f(x)}{P_{0,n+t} 1(x)}\,. \tag{3.69}$$

□

3.7.6 The deterministic model

Lemma 14. *Consider the following ODE:*

$$\begin{cases} \dfrac{dx(t)}{dt} & = \beta(t)x(t)\left(1 - x(t)\right) - \mu(t)x(t) \\ x(t_0) & = x_0\,. \end{cases} \tag{3.70}$$

with $\beta(t), \mu(t)$ are positive functions for all $t \geq t_0$. Then equation (4.61) *has an unique solution:*

$$x(t) = \frac{e^{\varphi(t)}}{C_{t_0} + \int_0^t \beta(s) e^{\varphi(s)} ds}, \tag{3.71}$$

where

$$\varphi(t) = \int_0^t (\beta(s) - \mu(s))\, ds, \quad C_{t_0} = \frac{e^{\varphi(t_0)}}{x(t_0)} - \int_0^{t_0} \beta(s) e^{\varphi(s)} ds.$$

Proof. Since the first equation of (4.61)

$$\begin{aligned}
\frac{dx(t)}{dt} &= \beta(t)x(t)\left(1 - x(t)\right) - \mu(t)x(t) \\
\Rightarrow \frac{dx(t)}{dt} &= \left(\beta(t) - \mu(t)\right)x(t) - \beta(t)x^2(t) \\
\Rightarrow \frac{dx(t)}{x^2(t)dt} - \frac{\left(\beta(t) - \mu(t)\right)}{x(t)} &= -\beta(t) \text{ if } x(t) \neq 0 \\
\Rightarrow \frac{dy}{dt}(t) + \left(\beta(t) - \mu(t)\right)y(t) &= \beta(t) \text{ where } y(t) = \frac{1}{x(t)} \\
\Rightarrow \frac{d\left(y(t)\exp\left(\int_{t_0}^t \left(\beta(s) - \mu(s)\right) ds\right)\right)}{dt} &= \beta(t)\exp\left(\int_{t_0}^t \left(\beta(s) - \mu(s)\right)\right) ds.
\end{aligned}$$

We integrate both sides over $[t_0, t]$ yields

$$\begin{aligned}
y(t) &= \exp\left(-\int_{t_0}^t \left(\beta(s) - \mu(s)\right) ds\right)\left(y(t_0) + \int_{t_0}^t \beta(s)\exp\left(\int_{t_0}^s \left(\beta(u) - \mu(u)\right) du\right)\right) \\
\Rightarrow x(t) &= \frac{1}{\exp(-\left(\varphi(t) - \varphi(t_0)\right))\left(y(t_0) + \int_{t_0}^t \beta(s)\exp\left(\varphi(s) - \varphi(t_0)\right)\right)} \\
&= \frac{e^{\varphi(t)}}{\frac{e^{\varphi(t_0)}}{x(t_0)} + \int_{t_0}^t \beta(s)e^{\varphi(s)}ds} \\
&= \frac{e^{\varphi(t)}}{C_{t_0} + \int_0^t \beta(s)e^{\varphi(s)}ds},
\end{aligned}$$

□

Lemma 15. *The solution of ODE* (4.61) *with periodic coefficients having a period of* T *such that* $\frac{1}{T}\int_0^T \beta_T(s)ds =: \langle\beta_T\rangle > \langle\mu_T\rangle := \frac{1}{T}\int_0^T \mu_T(s)ds$ *converges to the periodic attactor :*

$$x^\star(t) = \frac{e^{\varphi_T(t)}}{\int_0^t \beta_T(s)e^{\varphi_T(s)}ds + \frac{1}{e^{\varphi_T(T)}-1}\int_0^T \beta_T(s)e^{\varphi_T(s)}ds}. \tag{3.72}$$

Proof. Assume that $\beta_T(t)$ and $\mu_T(t)$ are $T-$ periodic functions, we have

$$\varphi_T(t) = \int_0^t \beta_T(s) - \mu_T(s)ds = \int_0^t \left(\beta\left(\frac{s}{T}\right) - \mu\left(\frac{s}{T}\right)\right) ds = T\varphi\left(\frac{t}{T}\right).$$

Therefore $\beta(t) := \beta_T(tT)$, $\mu(t) := \mu_T(tT)$ are periodic functions with period 1 and $\varphi(t) = \frac{\varphi_T(tT)}{T}$. We have

$$\begin{aligned}
&\varphi_T(t+nT) = \sum_{k=0}^{n-1} \int_{kT}^{(k+1)T} (\beta_T(s) - \mu_T(s))\, ds + \int_{nT}^{t+nT} (\beta_T(s) - \mu_T(s))\, ds \\
\Leftrightarrow\ &\varphi_T(t+nT) = \varphi_T(t) + \sum_{k=0}^{n-1} \int_0^T (\beta_T(s) - \mu_T(s))\, ds \\
\Leftrightarrow\ &\varphi_T(t+nT) = \varphi_T(t) + n\varphi_T(T).
\end{aligned}$$

We also have

$$\begin{aligned}
&\frac{1}{x(t)} = e^{-\varphi_T(t)} \left(\frac{e^{\varphi_T(t_0T)}}{x(t_0T)} - \int_0^{t_0T} \beta_T(s)e^{\varphi_T(s)}ds + \int_0^t \beta_T(s)e^{\varphi_T(s)}ds\right) \quad \forall t > 0 \\
\Rightarrow\ &\frac{1}{x(t)} = e^{-\varphi_T(t)} \left(C_{t_0T} + \int_0^t \beta_T(s)e^{\varphi_T(s)}ds\right) \quad \forall t \geq 0
\end{aligned}$$

$$\begin{aligned}
\Rightarrow\ &\frac{1}{x(t+nT)} = e^{-\varphi_T(t+nT)} \left(C_{t_0T} + \int_0^{t+nT} \beta_T(s)e^{\varphi_T(s)}ds\right) \quad \forall 0 \leq t < T \\
\Leftrightarrow\ &\frac{1}{x(t+nT)} = e^{-\varphi_T(t)-n\varphi_T(T)} \left(C_{t_0T} + \sum_{k=0}^{n-1} \int_{kT}^{(k+1)T} \beta_T(s)e^{\varphi_T(s)}ds + \int_{nT}^{nT+t} \beta_T(s)e^{\varphi_T(s)}ds\right) \\
\Leftrightarrow\ &\frac{1}{x(t+nT)} = e^{-\varphi_T(t)-n\varphi_T(T)} \left(C_{t_0T} + \sum_{k=0}^{n-1} \int_0^T \beta_T(s)e^{\varphi_T(s)+k\varphi_T(T)}ds + \int_0^t \beta_T(s)e^{\varphi_T(s)+n\varphi_T(T)}ds\right) \\
\Leftrightarrow\ &\frac{1}{x(t+nT)} = e^{-\varphi_T(t)} \left(C_{t_0T}e^{-n\varphi_T(T)} + \frac{1-e^{-n\varphi_T(T)}}{e^{\varphi_T(T)}-1} \int_0^T \beta_T(s)e^{\varphi_T(s)}ds + \int_0^t \beta_T(s)e^{\varphi_T(s)}ds\right)
\end{aligned}$$

Therefore,

$$x(t+nT) = \frac{e^{\varphi_T(t)}}{C_{t_0T}e^{-n\varphi_T(T)} + \frac{1-e^{-n\varphi_T(T)}}{e^{\varphi_T(T)}-1} \int_0^T \beta_T(s)e^{\varphi_T(s)}ds + \int_0^t \beta_T(s)e^{\varphi_T(s)}ds}, \tag{3.73}$$

Assume that $\varphi_T(T) > 0$, the solution of ODE (4.61) with coefficients periodic with period T converges to the following periodic attractor is given by (3.72). □

Remark 16. *$x^*(t)$ is given by* (3.72) *is also the solution of ODE* (4.61) *with initial value*

$$x^*(0) = \frac{e^{\varphi_T(T)} - 1}{\int_0^T \beta_T(s) e^{\varphi_T(s)} ds} = \left(1 - \frac{\mu}{\beta_0}\right) \frac{e^{(1-\gamma)T\beta_0 - T\mu} - 1}{e^{(1-\gamma)T(\beta_0-\mu)} - 1}.$$

Lemma 17. *In particular case with $\beta_T(t) = \beta_0 \mathbb{1}_{0 \leq \{t/T\} < 1-\gamma}$, $\mu_T(s) = \mu$ such that $(1-\gamma)\beta_0 > \mu$,. Let $x(t)$ be the solution of equation* (4.61) *with periodic coefficients and $x^*(t)$ is its periodic attractor, we can control the distance between the solution and its periodic attractor through the following expression*

$$x_{eq} - x\left((1-\gamma)T\right) < \epsilon \Leftrightarrow t_0 < (1-\gamma) + \frac{1}{T(\beta_0 - \mu)} \log\left(\frac{\frac{\epsilon\beta_0}{\beta_0-\mu} + \frac{e^{\gamma\mu T}-1}{e^{T(1-\gamma)(\beta_0-\mu)}-1}}{\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right)(x_{eq} - \epsilon)}\right) \tag{3.74}$$

Proof. We have

$$x_{eq} := \sup_{t\in[0,T]} x^*(t) = x^*((1-\gamma)T) \tag{3.75}$$

$$= \frac{e^{\varphi_T((1-\gamma)T) - \varphi_T(T)}\left(e^{\varphi_T(T)} - 1\right)}{\int_0^T \beta_T(s) e^{\varphi_T(s)} ds} \tag{3.76}$$

$$= e^{\gamma\mu T} x^*(0), \tag{3.77}$$

and

$$x\left((1-\gamma)T\right) = \frac{e^{(1-\gamma)T(\beta_0-\mu)}}{C_{t_0T} + \int_0^{(1-\gamma)T} \beta_T(s) e^{\varphi_T(s)} ds}.$$

We have

$$\varphi_T(T) = \int_0^T \left(\beta_T(s) - \mu_T\right) ds = \beta_0 \left(1-\gamma\right) T - T\mu = T\left(\beta_0(1-\gamma) - \mu\right). \tag{3.78}$$

Furthermore,

$$\int_0^T \beta_T(s) e^{\varphi_T(s)} ds = \int_0^{(1-\gamma)T} \beta_0 e^{\varphi_T(s)} ds = \frac{\beta_0}{\beta_0 - \mu}\left(e^{(1-\gamma)T(\beta_0-\mu)} - 1\right). \tag{3.79}$$

From the previous computations, yields

$$\frac{1}{x(t)} - \frac{1}{x^*(t)} = e^{-\varphi_T(t)}\left(C_{t_0T} - \frac{1}{e^{\varphi_T(T)} - 1}\int_0^T \beta_T(s) e^{\varphi_T(s)} ds\right).$$

Therefore

$$\begin{aligned}\frac{1}{x((1-\gamma)T)} - \frac{1}{x_{eq}} &= e^{-T(\beta_0-\mu)(1-\gamma)}\left(C_{t_0T} - \frac{1}{e^{\varphi_T(T)}-1}\int_0^T \beta_T(s)e^{\varphi_T(s)}ds\right)\\ &= e^{-T(\beta_0-\mu)(1-\gamma)}\left(C_{t_0T} - \frac{e^{\gamma\mu T}}{x_{eq}}\right).\end{aligned}$$

Hence

$$\begin{aligned}x_{eq} - x\left((1-\gamma)T\right) &= x_{eq}x\left((1-\gamma)T\right)e^{-T(\beta_0-\mu)(1-\gamma)}\left(C_{t_0T} - \frac{e^{\gamma\mu T}}{x_{eq}}\right)\\ &= x_{eq}\frac{e^{(1-\gamma)T(\beta_0-\mu)}}{C_{t_0T}+\int_0^{(1-\gamma)T}\beta_T(s)e^{\varphi_T(s)}ds}e^{-T(\beta_0-\mu)(1-\gamma)}\left(C_{t_0T} - \frac{e^{\gamma\mu T}}{x_{eq}}\right)\\ &= \frac{x_{eq}C_{t_0T} - e^{\gamma\mu T}}{C_{t_0T}+\int_0^{(1-\gamma)T}\beta_T(s)e^{\varphi_T(s)}ds}.\end{aligned}$$

That implies

$$\begin{aligned}&x_{eq} - x\left((1-\gamma)T\right) < \epsilon\\ \Leftrightarrow&\frac{x_{eq}C_{t_0T} - e^{\gamma\mu T}}{C_{t_0T}+\int_0^{(1-\gamma)T}\beta_T(s)e^{\varphi_T(s)}ds} < \epsilon\\ \Leftrightarrow&x_{eq}C_{t_0T} - C_{t_0T}\epsilon < e^{\gamma\mu T} + \frac{\epsilon\beta_0}{\beta_0-\mu}\left(e^{(1-\gamma)T(\beta_0-\mu)}-1\right)\\ \Leftrightarrow&e^{t_0T(\beta_0-\mu)}\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right) + \frac{\beta_0}{\beta_0-\mu} < \frac{e^{\gamma\mu T} + \frac{\epsilon\beta_0}{\beta_0-\mu}\left(e^{(1-\gamma)T(\beta_0-\mu)}-1\right)}{x_{eq}-\epsilon}\\ \Leftrightarrow&e^{t_0T(\beta_0-\mu)}\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right) < \frac{e^{\gamma\mu T} + \frac{\epsilon\beta_0}{\beta_0-\mu}e^{(1-\gamma)T(\beta_0-\mu)} - x_{eq}\frac{\beta_0}{\beta_0-\mu}}{x_{eq}-\epsilon}\\ \Leftrightarrow&e^{t_0T(\beta_0-\mu)} < \frac{\frac{\epsilon\beta_0}{\beta_0-\mu}e^{(1-\gamma)T(\beta_0-\mu)} + \left(e^{\gamma\mu T}-1\right)\frac{e^{T(1-\gamma)(\beta_0-\mu)}}{e^{T(1-\gamma)(\beta_0-\mu)}-1}}{\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right)(x_{eq}-\epsilon)}\\ \Leftrightarrow&t_0T(\beta_0-\mu) < \log\left(\frac{\epsilon\beta_0}{\beta_0-\mu}e^{(1-\gamma)T(\beta_0-\mu)} + \left(e^{\gamma\mu T}-1\right)\frac{e^{T(1-\gamma)(\beta_0-\mu)}}{e^{T(1-\gamma)(\beta_0-\mu)}-1}\right)\\ &\qquad - \log\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right) - \log\left(x_{eq}-\epsilon\right)\end{aligned}$$

$$\Leftrightarrow t_0 T(\beta_0-\mu) < (1-\gamma)T(\beta_0-\mu) + \log\left(\frac{\epsilon\beta_0}{\beta_0-\mu} + \frac{e^{\gamma\mu T}-1}{e^{T(1-\gamma)(\beta_0-\mu)}-1}\right) - \log\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right)(x_{eq}-\epsilon)$$

$$\Leftrightarrow t_0 < (1-\gamma) + \frac{1}{T(\beta_0-\mu)} \log\left(\frac{\frac{\epsilon\beta_0}{\beta_0-\mu} + \frac{e^{\gamma\mu T}-1}{e^{T(1-\gamma)(\beta_0-\mu)}-1}}{\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right)(x_{eq}-\epsilon)}\right)$$

So with $x_{eq} = e^{\gamma\mu T}\left(1-\frac{\mu}{\beta_0}\right)\frac{e^{T((1-\gamma)\beta_0-\mu)}-1}{e^{(1-\gamma)T(\beta_0-\mu)}-1}$,

$$x_{eq} - x\left((1-\gamma)T\right) < \epsilon \Leftrightarrow t_0 < (1-\gamma) + \frac{1}{T(\beta_0-\mu)} \log\left(\frac{\frac{\epsilon\beta_0}{\beta_0-\mu} + \frac{e^{\gamma\mu T}-1}{e^{T(1-\gamma)(\beta_0-\mu)}-1}}{\left(\frac{1}{x_0} - \frac{\beta_0}{\beta_0-\mu}\right)(x_{eq}-\epsilon)}\right). \quad (3.80)$$

□

Remark 18. *If* $\gamma = 0, x_{eq} = 1 - \frac{\mu}{\beta_0}$,

$$x_{eq} - x\left((1-\gamma)T\right) < \epsilon \Leftrightarrow t_0 < 1 + \frac{1}{T(\beta_0-\mu)} \log\left(\frac{\epsilon x_0}{(x_{eq}-x_0)(x_{eq}-\epsilon)}\right). \quad (3.81)$$

3.7.7 Optimal disease control strategies for the branching process approximation

First of all, recall that $\beta(t)$ is the transition rate with two strategies is given by expression (3.27) and the death rate is fixed with value μ. We shall compute the asymptotic risk given by expression (3.38) We have

$$\varphi_{GCB}(1) = \pi_G(\beta_G-\mu) + \pi_C(\beta_C-\mu) - \mu(1-\pi_G-\pi_C) = \varphi_{CGB}(1) := \varphi(1) \text{ for short}$$

First case, weak control : $\beta_G > \beta_C > \mu$.

Setting $c_j = \pi_j(\beta_j-\mu)$ for $j \in \{G, C, B\}$. There are 4 situations that probably happen,
Case 1 $c_G > \varphi(1) > c_C$
There exits $t_0^* \in [\pi_G, 1)$ such that $t_0^*(\beta_G-\mu) = \varphi_{GCB}(t_0^*) = \varphi(1)$. The integrated rate $\varphi_i(t), \forall i \in \mathcal{D}$ is given in Figure 3.8 A.

$$\tilde{r}_{GCB} = \int_0^{t_0^*} \left(1 - \frac{\mu}{\beta_G(t)}\right) \mathbb{1}_{t\notin \mathrm{WIC}_{GCB}} dt = \frac{\varphi(1)}{\beta_G}. \quad (3.82)$$

Similarly, there exits $t_1^* \in [\pi_C, 1)$ such that $\varphi(1) = \varphi_{CGB}(t_1^*) = \pi_C(\beta_C - \mu) + (t_1^* - \pi_C)(\beta_G - \mu)$,

$$\tilde{r}_{CGB} = \int_0^{t_1^*} \left(1 - \frac{\mu}{\beta_{CGB}(t)}\right) \mathbb{1}_{t \notin \text{WIC}_{CGB}} dt = (1 - \mu/\beta_C)\pi_C + (1 - \mu/\beta_G)(t_1^* - \pi_C) \quad (3.83)$$

$$= \frac{1}{\beta_G}\varphi(1) + \pi_C(\beta_C - \mu)(\frac{1}{\beta_C} - \frac{1}{\beta_G}) > \frac{\varphi(1)}{\beta_G}. \quad (3.84)$$

Case 2: $c_G + c_C > \varphi(1) > \max(c_G, c_C)$

There exits $t_0^* \in [\pi_G, \pi_G + \pi_C)$ such that $\pi_G(\beta_G - \mu) + (t_0^* - \pi_G)(\beta_C - \mu) = \varphi_{GCB}(t_0^*) = \varphi(1)$.
Furthermore, there exists $t_1^* \in [\pi_C, \pi_G + \pi_C)$ and $\varphi(1) = \varphi_{CGB}(t_1^*) = \pi_C(\beta_C - \mu) + (t_1^* - \pi_C)(\beta_G - \mu)$.
The integrated rate $\varphi(t)$ is given in Figure 3.8 B. We obtain,

$$\tilde{r}_{GCB} = \int_0^{t_0^*} \left(1 - \frac{\mu}{\beta_{GCB}(t)}\right) \mathbb{1}_{t \notin \text{WIC}_{GCB}} dt = \left(1 - \frac{\mu}{\beta_G}\right)\pi_G + (t_0^* - \pi_G)\left(1 - \frac{\mu}{\beta_C}\right). \quad (3.85)$$

$$= \frac{\varphi(1)}{\beta_C} + \pi_G(\beta_G - \mu)\left(\frac{1}{\beta_G} - \frac{1}{\beta_C}\right) \quad (3.86)$$

$$\tilde{r}_{CGB} = \int_0^{t_1^*} \left(1 - \frac{\mu}{\beta_{CGB}(t)}\right) \mathbb{1}_{t \notin \text{WIC}_{CGB}} dt = \left(1 - \frac{\mu}{\beta_C}\right)\pi_C + (t_1^* - \pi_C)\left(1 - \frac{\mu}{\beta_G}\right) \quad (3.87)$$

$$= \frac{\varphi(1)}{\beta_G} + \pi_C(\beta_C - \mu)\left(\frac{1}{\beta_C} - \frac{1}{\beta_G}\right) = \tilde{r}_{GCB} + \left(\frac{1}{\beta_C} - \frac{1}{\beta_G}\right)(1 - \pi_G - \pi_C)\mu \quad (3.88)$$

Case 3: $c_C > \varphi(1) > c_G$ We obtain $\pi_G(\beta_G - \mu) + (t_0^* - \pi_G)(\beta_C - \mu) = \varphi_{GCB}(t_0^*) = \varphi(1) = \varphi_{CGB}(t_1^*) = t_1^*(\beta_C - \mu)$.
The integrated rate $\varphi(t)$ is given in Figure 3.8C. We obtain,

$$\tilde{r}_{GCB} = \int_0^{t_0^*} \left(1 - \frac{\mu}{\beta_{GCB}(t)}\right) \mathbb{1}_{t \notin \text{WIC}_{GCB}} dt = \left(1 - \frac{\mu}{\beta_G}\right)\pi_G + (t_0^* - \pi_G)\left(1 - \frac{\mu}{\beta_C}\right). \quad (3.89)$$

$$= \frac{\varphi(1)}{\beta_C} + \pi_G(\beta_G - \mu)\left(\frac{1}{\beta_G} - \frac{1}{\beta_C}\right) \quad (3.90)$$

$$\tilde{r}_{CGB} = \int_0^{t_1^*} \left(1 - \frac{\mu}{\beta_{CGB}(t)}\right) \mathbb{1}_{t \notin \text{WIC}_{CGB}} dt = t_1^*\left(1 - \frac{\mu}{\beta_C}\right) \quad (3.91)$$

$$= \frac{\varphi(1)}{\beta_C} > \tilde{r}_{GCB} \quad (3.92)$$

Case 4: $\min(c_G, c_C) > \varphi(1) > 0$ We obtain $t_0^*(\beta_G - \mu) = \varphi_{GCB}(t_0^*) = \varphi(1) = \varphi_{CGB}(t_1^*) = t_1^*(\beta_C - \mu)$.

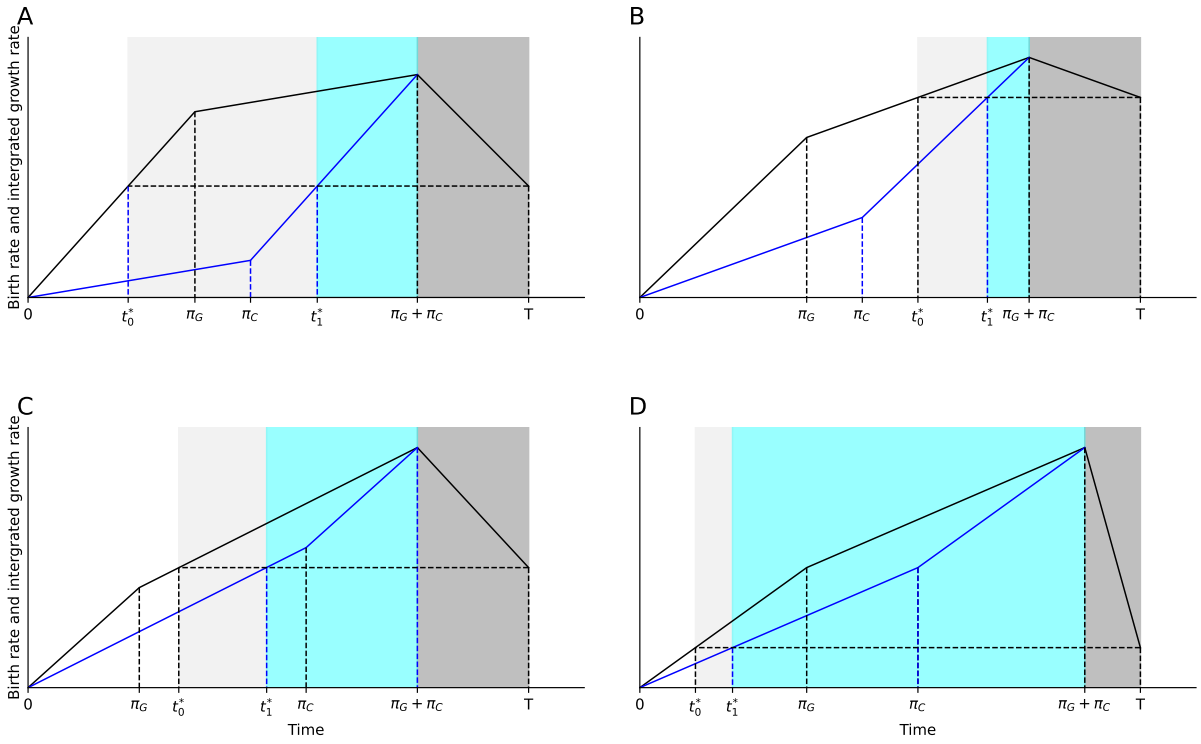

Figure 3.8 – **Risk for branching process with weak control: GCB vs CGB.** The integrated rate is drawn in black for strategy GCB and in blue for strategy CGB. The grey areas indicate the WIC for strategy GCB. The blue areas indicate the WIC for strategy CGB.

The integrated rate $\varphi(t)$ is given in Figure 3.8D. We obtain,

$$\tilde{r}_{GCB} = \int_0^{t_0^*} \left(1 - \frac{\mu}{\beta_{GCB}(t)}\right) \mathbb{1}_{t \notin \text{WIC}_{GCB}} dt = t_0^* \left(1 - \frac{\mu}{\beta_G}\right) = \frac{\varphi(1)}{\beta_G} \tag{3.93}$$

$$\tilde{r}_{CGB} = \int_0^{t_1^*} \left(1 - \frac{\mu}{\beta_{CGB}(t)}\right) \mathbb{1}_{t \notin \text{WIC}_{CGB}} dt = t_1^* \left(1 - \frac{\mu}{\beta_C}\right) = \frac{\varphi(1)}{\beta_C} > \tilde{r}_{GCB} \tag{3.94}$$

Hence in all cases, GCB has a lower risk than CGB.

Second case, strong control : $\beta_G > \mu > \beta_C$. In this case, we see in Figure 3.9 that

$$\tilde{r}_{GCB} = \tilde{r}_{CGB} = \int_0^{t_0^*} (1 - \frac{\mu}{\beta_G}) dt = \frac{\varphi(1)}{\beta_G}. \tag{3.95}$$

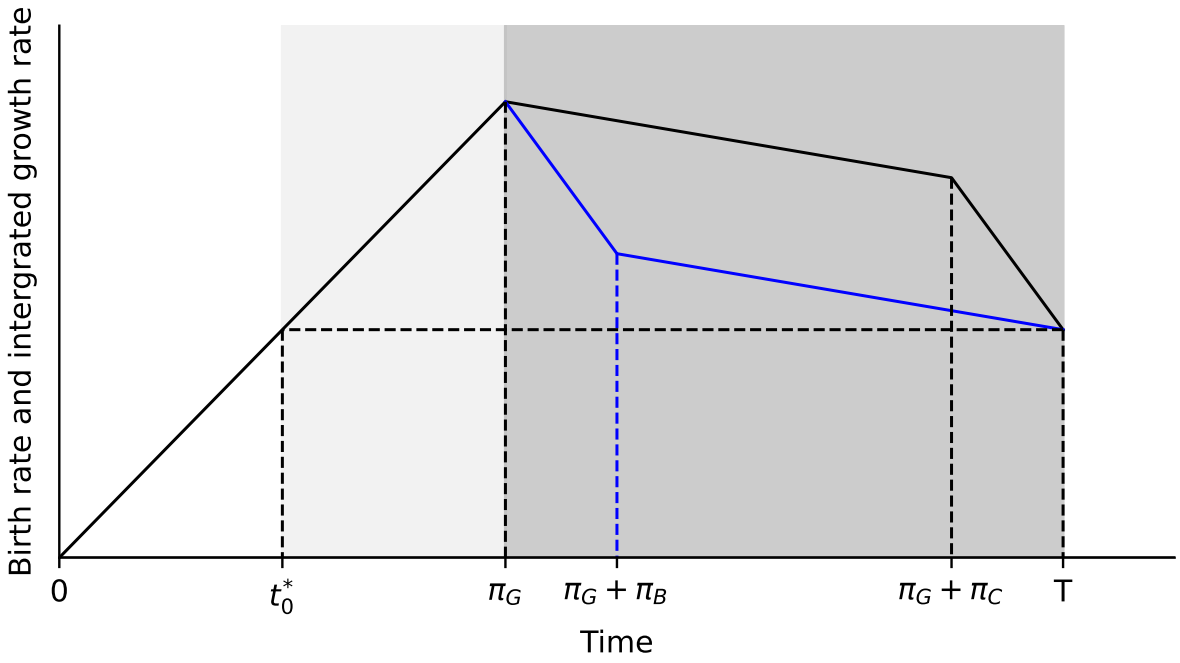

Figure 3.9 – **Risk for branching process with strong control: GCB vs CGB.**
The integrated rate is drawn in black for strategy GCB and in blue for strategy CGB $\equiv$ GBC. The grey areas indicate the WIC for strategy GCB.

3.7.8 The generalized stochastic logistic process : A stochastic epidemic model with a non constant total population

The discrete numbers of Susceptible and Infected are denoted by $S^{(n)}$ and $I^{(n)}$. The susceptible hosts immigrate at rate λn where n is *system size* that indicates the order of magnitude of the total population (the scaling parameter).

The process $X^{(n)} = (S^{(n)}, I^{(n)})$ is a continuous Markov chain on $\mathbb{N}^2$ with rates given by

$$\begin{aligned}
(s,i) \to (s+1,i) \text{ rate } \lambda n & \qquad \text{recruitment of a susceptible} \\
(s,i) \to (s-1,i) \text{ rate } \mu s & \qquad \text{death of a susceptible} \\
(s,i) \to (s,i-1) \text{ rate } \mu i & \qquad \text{death of an infected} \\
(s,i) \to (s-1,i+1) \text{ rate } \beta \frac{si}{n} & \qquad \text{infection of a susceptible}
\end{aligned}$$

The total population $N^{(n)}(t) = S^{(n)}(t) + I^{(n)}(t)$ is not constant anymore but is a continuous time Markov chain on $\mathbb{N}$ with rates

$$\begin{aligned}
z \to z+1 \text{ rate } \lambda n \\
z \to z-1 \text{ rate } \mu z \, .
\end{aligned}$$

Therefore $N^{(n)}(t)$ converge in distribution to $\mathcal{P}(\lambda n/\mu)$ a Poisson distribution with mean $n' = n\lambda/\mu$. Indeed, without loss in generality, we assume that $n = 1$(fixed), $\lambda n = \lambda$, the total population $N^{(n)}(t) = S^{(n)}(t) + I^{(n)}(t)$ has generator

$$L^N g(k) = \lambda \left(g(k+1) - g(k)\right) + \mu k \left(g(k-1) - g(k)\right)$$

If $g(k) = k$, $L^N g(k) = \lambda - \mu g(k)$. So if $f(x) = g(s+i) = s+i$, $x = (s,i)$ then

$$L^N f(x) = \lambda - \mu f(x)$$

Since $\left(N^{(n)}(t)\right)_{t \geq 0}$ is a continuous time Markov chain on $\mathbb{N}$, irreducible and it has a unique invariant probability $\Pi \left(\Pi \mathrm{Q}^N = 0\right)$ with Q is a infinitesimal matrix, which is reversible:

$$\begin{aligned}
& \Pi(x) L(x, x+1) && = \Pi(x+1) L(x+1, x) \\
\Leftrightarrow \quad & \Pi(x)\lambda && = \Pi(x+1)\mu(x+1) \\
\Rightarrow \quad & \Pi(x) && = \frac{e^{-\frac{\lambda}{\mu}}}{x!} \left(\frac{\lambda}{\mu}\right)^x
\end{aligned}$$

This means that $\Pi = \mathcal{P}(\lambda/\mu)$. So $\exists \gamma > 0, \forall x \in \mathcal{R}_+^* \; \exists \, C(x) > 0$ such that :

$$\sup_A \parallel \mathbb{P}_x \left(N^{(n)}(t) \in A \right) - \Pi(A) \parallel \leq C(x) e^{-\gamma t}.$$

The first intuition is that this process $I^{(n)}$ behaves as the stochastic logistic process $X(n')$ that is as if the total population is constant and equal to n'.

It is easy to apply Kurtz's theorem again and see that the deterministic approximation, the limit of $X^{(n)}/n$, is the solution of

$$\frac{dS}{dt} = \lambda - \beta(t)\frac{SI}{S+I} - \mu S \tag{3.96}$$

$$\frac{dI}{dt} = \beta(t)\frac{SI}{S+I} - \mu I \,. \tag{3.97}$$

and therefore the total population is $N = S + I$ solution of

$$\frac{dN}{dt} = \lambda - \mu N \,. \tag{3.98}$$

Therefore, even when $\beta(t)$ is T-periodic, the total population converges exponentially fast to n' :

$$\lim_{t \to +\infty} N(t) = n' = n\lambda/\mu \,. \tag{3.99}$$

We are going to show that when $R_0 = \frac{\langle \beta \rangle}{\mu} > 1$, then the deterministic process $(S(t), I(t))$ has a periodic attractor $(S^*(t), I^*(t))$ which is the only periodic solution of (3.96). We can even show the existence of a Yaglom limit, a periodic quasi stationary distribution, for the process $X^{(n)}(t)/n$ see Figure 3.7.

Furthermore, we obtain, for the step function $\beta(t/T) = \beta_0 \, \mathbf{1}_{(0 \leq t/T \leq 1-\gamma)}$ by using the same heuristics as in the section (3.7.6) , the same critical size n_c given by

$$n_C = \frac{e^{\gamma \mu T}}{n_{eq}} = \frac{e^{\gamma \mu T}}{\lambda/\mu}$$

Proof of the periodic Yaglom limit

We shall make an heavy use of [CV23].

The constant coefficients case

The generalized SI process $X^{(n)}$ his a continuous time Markov chain with values in $\mathbb{N}^2$ and generator given by

$$L^{(n)}f(x) = \lambda n(f(s+1,i) - f(s,i)) + \mu s(f(s-1,i) - f(s,i)) \tag{3.100}$$

$$+ \mu i(f(s,i-1) - f(s,i)) + \beta \frac{si}{s+i}((f(s-1,i+1) - f(s,i))\,. \tag{3.101}$$

To apply the general results of [CV23], we consider the process X that is $X^{(n)}$ absorbed in the set $\{(s,0) : s \in \mathbb{N}\}$. We let L be its generator and $(P_t)_{t\geq 0}$ is semigroup. Its state space is $E \cup \{\partial\}$ with $E = \{(s,i) : s \in \mathbb{N}, i \neq 0\}$. In order to apply Theorem 5.1 of [CV23], we consider a specific point $x^0 = (1,1) \in E$ and set

$$\lambda_0 = \inf\left\{\lambda > 0 : \liminf_{t\to+\infty} e^{\lambda t}\mathbb{P}_{x^0}\Big(X_t = x^0\Big) > 0\right\}. \tag{3.102}$$

We have, for a function $f(x) = \phi(|x|)$ with $|x| = s + i$,

$$Lf(x) \leq \lambda n(\phi(|x|+1) - \phi(|x|)) + \mu|x|(\phi(|x|-1) - \phi(|x|))\,. \tag{3.103}$$

Let $z = |x|$ to simplify notations. Then, for $\phi(z) = e^z$,

$$Lf(x) \leq f(x)\Big(\lambda n(e-1) - \mu z(1-e^{-1})\Big) \leq -\lambda_1 f(x) + C\,\mathbf{1}_{(x\in D_0)} \tag{3.104}$$

with $D_0 = \{x : |x| \leq M_0\}$ and $\lambda_1 = \mu M_0(1-e^{-1}) - \lambda n(e-1)$. We see that by taking M_0 large enough, we can ensure $\lambda_1 > \lambda_0$. We can even ensure that $\lambda_1 > \sup_{x\in E} q(x,\partial) = d$, and therefore obtain, following Remark 11, section 5 of [CV23], that there exists $\alpha \in (0,1)$ and a quasi stationary probability measure ν such that for $f(x) = e^{|x|}\int f(x)\,d\nu(x) < +\infty$: for every probability measure μ

$$\|\mathbb{P}_\mu(X_t \in .\mid t < \tau_\partial) - \nu\|_{TV} \leq C\alpha^t \mu(f)\,. \tag{3.105}$$

The periodic case

We consider the same model. Instead of a constant transmission rate β, we consider a T-periodic transmission rate $\beta(t)$. We cannot apply as easily the results of [CV23] since now the process $X^{(n)}$ is an inhomogeneous Markov process. However, since the time inhomogeneity

happens only in the transmission rate β, we still have for a function $f(x) = \phi(|x|)$ with $|x| = s + i$,

$$L_t f(x) \leq \lambda K(\phi(|x|+1) - \phi(|x|)) + \mu|x|(\phi(|x|-1) - \phi(|x|))\,. \tag{3.106}$$

We need to look closely at the proof of Theorem 5.1 of [CV23]. We see that the first step is to check **Assumption (F)**.The strong Markov property ensures $(F0)$, the irreducibility ensures $(F3)$ and $(F1)$ if we take $L = D_0$ finite, and $(F2)$ is derived from the Foster-Lyapunov inequality (3.106). We can then obtain that **Assumption (E)** is satisfied by the sub-Markovian semigroup $(P_n)_{n\geq 0}$ of $(X_{nt_2}, n \geq 0)$. The proof is exactly the same as the proof of Theorem 3.5 in section 11.5. Since $(X_{nT}, t \geq 0)$ is a temporally homogeneous Markov process we can conclude on the existence of constants $C > 0$, $\alpha \in (0,1)$, and of a Quasi Stationary Distribution ν such that for every probability measure μ,

$$\|\mathbb{P}_\mu(X_{nT} \in . \mid nT < \tau_\partial) - \nu\|_{TV} \leq C\alpha^{nT}\mu(f)\,. \tag{3.107}$$

It should be clear that to deal with the process $(X_{t+t_0}, t \geq 0)$ with $t_0 > 0$ an arbitrary time, we only need to consider the shifted function $\beta(t + t_0)$, and all the proofs above can be adapted so that for every probability measure μ s.t. $\mu(f) < +\infty$, that we have the existence of constants $C(t_0) > 0$, $\alpha(t_0) \in (0,1)$, and of a probability measure ν_{t_0} s.t.

$$\|\mathbb{P}_\mu(X_{nT+t_0} \in . \mid nT < \tau_\partial) - \nu_{t_0}\|_{TV} \leq C(t_0)\alpha(t_0)^{nT}\mu(f)\,. \tag{3.108}$$

Consequently, we have proved the existence of a periodic Yaglom Limit.

CHAPTER 4

EVOLUTION OF PATHOGEN DORMANCY IN FLUCTUATING ENVIRONMENTS

Dormancy is a strategy that evolved in many different species to cope with the variability of the environment. Here we explore the evolution of dormancy in a vector-borne pathogen in response to periodic fluctuations of the abundance of vectors due to seasonality. We consider different scenarios where the investment into dormancy is constrained to be constant or is allowed to vary plastically with some component of the environment. We show that a constant investment in dormancy is generally not adaptive. Yet, plastic dormancy strategies can readily evolve in a seasonal environment. We study how the pathogen can use different cues to identify the best time the switch its investment into dormancy. This model may help understand the diversity of life-history strategies of a broad range of vector-borne pathogens and in particular malaria parasites.

Many parasites can produce dormant stages that can reactivate a long time after the infection of the host. For instance, some malaria parasites like *Plasmodium vivax* can induce relapse many months after the clearance of first infection. Did dormancy evolve in vector-borne pathogens to cope with the fluctuations of the environment? Here we show how seasonality can drive periodic fluctuations of the abundance of vectors and select for dormancy. In particular, we show that plastic investment in dormancy is particularly adaptive to track the fluctuations of vector densities.

4.1 Introduction

Many different species produce offspring that stop their development and stay in a dormant stage, sometimes for a very long time [ED05]. This ability to produce dormant stages is thought to be an adaptation to the temporal variability of the environment [KBH02; SD73]. For instance, many microbes have the ability to delay growth to cope with periods where growth conditions become unfavorable [Bal+04; Bue+12]. Here we want to examine the evolution of dormancy in

a vector-borne pathogen under the influence of seasonal variations of the abundance of vectors. We consider a scenario where the pathogen can decide between two host-exploitation strategies. First, the pathogen can replicate actively in the host in the hope to be picked up by a vector and transmitted to a new host. Second, the pathogen can lay dormant in the host tissue and avoid the risk of being targeted by the host immune system but give up the possibility to infect a new host. For instance, this decision has to be made by *Plasmodium vivax* which is a species of human malaria that can replicate asexually in the bloodstream of an infected host or lay dormant as a hypnozoite in the leaver. Hypnozoites can remain dormant for several months before relapsing. It is interesting to note that different isolates of *P. vivax* relapse at different rates which suggests the possibility there is a heritable variation on this trait. Besides, some malaria species (e.g. *P. falciparum*) have lost the ability to produce hypnozoites which may also suggest that dormancy may not always be adaptive. Finally, we also want to note that some malaria parasites have the ability to adopt plastic strategies in response to a change of the environment. For instance, mosquito bites can trigger a higher investment into pathogen transmission in the avian malaria parasite *P. relictum* [Cor+14]. Is it possible to select for plastic dormancy strategies in vector-borne pathogens?

To answer this question we extend a general vector-borne pathogen model subject to periodic fluctuations of the abundance of vectors [KCG22] to account for the possibility of entering a dormant stage in the life-cycle of the infection. First, we study the epidemiological dynamics of this model and study the influence of dormancy and seasonality on pathogen persistence. Second, we derive a general selection gradient on the rate of dormancy and on the reactivation rate. Third, we use this selection gradient can be used to study the evolution of dormancy in a constant or in a temporally variable environment. We contrast different scenarios where (i) dormancy and reactivation are fixed traits or (ii) the investment in dormancy and reactivation is conditional on different environmental cues.

4.2 The model

We consider the epidemiological of a population with susceptible, infectious and recovered hosts S_H, I_H, R_H, and susceptible and infected vectors S_V, I_V as in [KCG22]. We also add an additional compartment D_H which refers to host infected with a dormant stage of the pathogen. In this stage, the parasite cannot transmit to the vector but it is invisible from the immune system of the host and consequently, the infection cannot be cleared in this stage. The epidemiological

dynamics of the system is driven by the following set of ordinary differential equations:

$$\dot{S}_H = \theta - \beta_V I_V \frac{S_H}{N_H} - \mu_H S_H \tag{4.1}$$

$$\dot{I}_H = \beta_V I_V \frac{S_H}{N_H} - (\gamma + \mu_H + d) I_H + r D_H \tag{4.2}$$

$$\dot{D}_H = d I_H - (r + \mu_H) D_H \tag{4.3}$$

$$\dot{R}_H = \gamma I_H - \mu_H R_H \tag{4.4}$$

$$\dot{S}_V = \rho_V(t) \left(1 - \frac{N_V(t)}{K}\right) N_V - \beta_H (I_H + \alpha D_H) S_V - \mu_V S_V \tag{4.5}$$

$$\dot{I}_V = \beta_H (I_H + \alpha D_H) S_V - \mu_V I_V. \tag{4.6}$$

The parameter θ describes the influx of new host and this flux is assumed to compensate exactly the mortality so that $\theta = \mu_H N_H$ where $N_H = I_H + S_H + D_H + R_H$. As a result, the host population is a constant. Without loss of generality, from now on, we will always implicitly understand $N_H = 1$. Other parameters of the model are described in table (4.1). In particular, the parameter α measures the ability of dormant infections to transmit the pathogen. If $\alpha = 0$, the compartment D_H is not infectious and the pathogen has to reactivate and go back to the compartment I_H to transmit to new hosts. In contrast, when $\alpha = 1$, the compartment D_H is as infectious as the compartment I_H .

We assume that the dynamics of the density $N_V = S_V + I_V$ of the vector population is driven by the balance between the fluctuations of $\rho_V(t)$ and the constant per-capita death rate μ_V which yields:

$$\dot{N}_V = \rho_V(t) \left(1 - \frac{N_V(t)}{K}\right) N_V - \mu_V N_V(t). \tag{4.7}$$

4.3 Results

4.3.1 Effect of dormancy, relapse and seasonality on pathogen persistence

In the event of the absence of seasonal patterns, the total vector population size N_V attains $\frac{K(\rho_V - \mu_V)}{\rho_V}$. Consequently, within this stable environment, the basic reproductive ratio can be derived either through the next-generation technique or by means of a perturbation analysis approach (see (4.6)), though an explicit formulation for R_0 is unavailable. To address this

limitation, we introduce a novel parameter.

$$R_0^{'} = \frac{rd}{(r+\mu_H)(\gamma+\mu_H+d)} + \frac{\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)} + \frac{d\alpha\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)(r+\mu_H)}.$$

We show in section (4.6.1) that

— $R_0 > 1$ if and only if $R_0^{'} > 1$

— $R_0 < 1$ if and only if $R_0^{'} < 1$

Next, we assume that seasonality acts on the per-capita growth rate of the vector and is driven by the following step function:

$$\rho_V(t) = \begin{cases} \rho & \text{if } 0 \leq \left\{\frac{t}{T}\right\} < 1-\sigma \\ 0 & \text{otherwise} \end{cases} \tag{4.8}$$

where $\{x\} = x - \lfloor x \rfloor$ is the fractional (decimal) part of x, $0 \leq \{x\} < 1$. The periodic attractor of $\hat{N}_V(t)$ (see proposition (19)) is :

$$\hat{N}_V(t) = \frac{Ke^{\varphi(t)}}{\int_0^t \rho_V(s)e^{\varphi(s)}ds + \frac{1}{e^{\varphi(T)}-1}\int_0^T \rho_V(s)e^{\varphi(s)}ds}$$

where $\varphi(t) = \int_0^t(\rho_V(s) - \mu(s))ds$. We extend the perturbation analysis used by [KCG22] to derive an approximation for λ with $\lambda = \rho(\Phi_{\mathbf{A}}(T))$ the spectral radius of the monodromy matrix of system (4.42).

$$\frac{d\Phi_{\mathbf{A}}}{dt} = \boldsymbol{A}(t)\Phi_{\mathbf{A}}(t) \quad \text{with} \quad \Phi_{\mathbf{A}}(0) = I \tag{4.9}$$

The asymptotic growth rate of the epidemic in the initial phase of the epidemic for small values of σ

$$\lambda = \lambda_0 + \sigma\lambda_1 + o(\sigma) \tag{4.10}$$

In the constant case (without seasonality $\sigma = 0$), we assume that $\lambda_0 = 1$ and λ_1 refer to the first-order effects of seasonality on pathogen persistence. The perturbation analysis yields:

$$\lambda_1 = -\frac{T\beta_H\beta_V\frac{K}{\rho}\left(1+\frac{\alpha d}{r+\mu_H}\right)}{1 + \frac{d\left(r+\alpha\beta_H\frac{K(\rho-\mu_V)}{\rho}\frac{\beta_V}{\mu_V}\right)}{(r+\mu_H)^2} + \frac{\beta_V\beta_H K(\rho-\mu_V)\left(1+\frac{\alpha d}{r+\mu_H}\right)}{\rho\mu_V^2}} < 0 \tag{4.11}$$

In other words, our model shows that an increase of σ leads to a reduction in the duration of the vector population's growth rate. As a result, a negative effect on pathogen persistence (Figure (4.1)) because the average number of vectors is decreasing (see proposition (22)). It's important to note that the intensity of seasonality, denoted as ρ, remains constant and the length of the seasonality period is controlled by the parameter $1 - \sigma$.

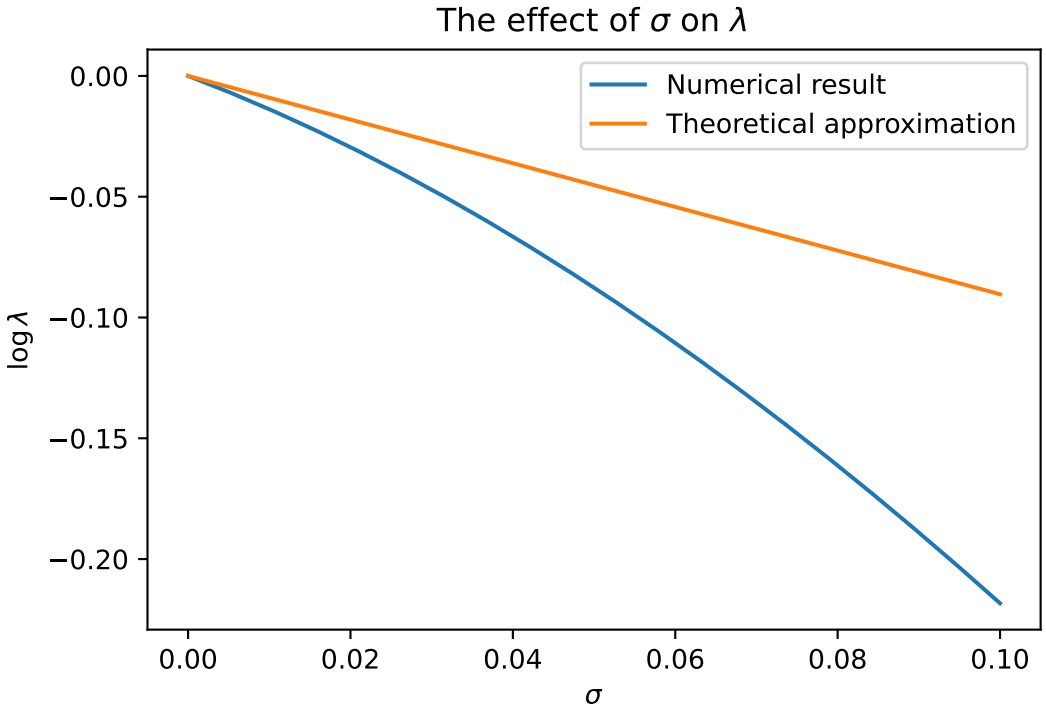

Figure 4.1 – **The effect of seasonality on λ.** An increase of σ leads to a negative effect on pathogen persistence. Parameters: $T = 3, \alpha = 1, \sigma = 0.5, \beta_V = 1, \beta_H = 1, \gamma = 0.5, \mu_V = 1, \mu_H = \frac{1}{4}\left(\sqrt{17} - 3\right), d = 1, r = 1$.

4.3.2 The selection gradient

In the following text, we apply the method utilized by [LG22] to derive the selection coefficient associated with a mutant in a periodically fluctuating environment under the assumption that selection is weak. This selection coefficient can be applied to determine the fate of the mutant (invasion or extinction) and thus to identify evolutionary stable strategies. We assume the mutant phenotype z_m (dormant intensity, reactivation intensity, timing to relapse,...) to be close to the resident phenotype z_w (i.e $z_m = z_w + \epsilon$ with ϵ small).

To follow the dynamics of the mutant we track the dynamics of the vector $\mathbf{X}_m(t) = (I_H^m, D_H^m, I_V^m)^\top$, with:

$$\frac{d\mathbf{X}_m}{dt} = \mathbf{A}_m \mathbf{X}_m \tag{4.12}$$

with

$$\mathbf{A}_m = \begin{pmatrix} -(\gamma + d_m + \mu_H) & r_m & \beta_V \hat{S}_H \\ d_m & -(r_m + \mu_H) & 0 \\ \beta_H \hat{S}_V & \alpha\beta_H \hat{S}_V & -\mu_V \end{pmatrix}$$

The coefficient a_{jk} of matrix $\mathbf{A}_m$ are the transition rates from an infection in state k to a new infection in state j. $\hat{S}_H$ and $\hat{S}_V$ are the host and vector population at the periodic attractor state. Note that we dropped the dependence to time to simplify the notation. However, these transition rates are allowed to vary with time because of fluctuations of host densities but also because allocation to dormancy and reactivation may fluctuate over time.

Fluctuating environment involves variations in the quantity and quality within different classes. Class frequencies and reproductive values are the means through which these variations are manifested, and they hold a crucial significance within the realm of evolutionary theory The coefficient of selection on the mutant at time t is determined by the instantaneous selection gradient (see [LG22]):

$$S(t) = \sum_{j,k} \hat{v}_j(t) \left.\frac{\partial a_{jk}(t)}{\partial z_m}\right|_{z_m = z_w} \hat{f}_k(t), \tag{4.13}$$

where f_k is the frequency of the infections in state k and v_j is the individual reproductive value of infections in state j, where $j, k \in \{I_H, D_H, I_V\}$.
It follows the dynamic

$$\frac{d\mathbf{v}^\top}{dt} = -\mathbf{v}^\top \mathbf{A}_w + r_w \mathbf{v}^\top \tag{4.14}$$

and

$$\frac{d\mathbf{f}}{dt} = \mathbf{A}_w \mathbf{f} - r_m \mathbf{f} \tag{4.15}$$

where $\mathbf{f} = (f_{I_H}, f_{D_H}, f_{I_V})$, $\mathbf{v}^\top = (v_{I_H}, v_{D_H}, v_{I_V})$, $r_w = \sum_k \sum_j a_w^{kj} f_j$ is the per-capital growth rate of the monomorphic resident population. Note that these quantities have been normalized so that $\sum_k f_k = 1$ and $\sum_j f_j v_j = 1$. The $\hat{}$ notation indicates that reproductive values and class

frequencies are calculated when the system sits in its periodic attractor.

The selection gradient on dormancy and reactivation can thus be obtained from averaging the selection coefficient over one period of the fluctuation of the resident attractor which yields:

$$S_d = -\left\langle \hat{f}_{I_H}(t)\left(\hat{v}_{I_H}(t) - \hat{v}_{D_H}(t)\right)\right\rangle \left.\frac{\partial d}{\partial z_m}\right|_{z_m=z_w}, \tag{4.16}$$

$$S_r = \left\langle \hat{f}_{D_H}(t)\left(\hat{v}_{I_H}(t) - \hat{v}_{D_H}(t)\right)\right\rangle \left.\frac{\partial r}{\partial z_m}\right|_{z_m=z_w}. \tag{4.17}$$

where we use the notation $\langle g\rangle = \frac{1}{T}\int_0^T g(s)ds$ to indicate the average over one period of the fluctuation. In order to compute the above selection coefficients we need to compute the class frequencies and the reproductive values of the different infection states.

Class frequencies:
The dynamics of class frequencies is given by:

$$\begin{aligned}
\frac{df_{I_H}(t)}{dt} &= -\left(\gamma + \mu_H + d\right) f_{I_H}(t) + r f_{D_H}(t) + \beta_V \hat{S}_H f_{I_V}(t) - r_w f_{I_H}(t)\\
\frac{df_{D_H}(t)}{dt} &= df_{I_H}(t) - \left(r + \mu_H\right) f_{D_H}(t) - r_w f_{D_H}(t)\\
\frac{df_{I_V}(t)}{dt} &= \beta_H \hat{S}_V f_{I_H}(t) + \alpha\beta_H \hat{S}_V f_{D_H}(t) - \mu_V f_{I_V}(t) - r_w f_{I_V}(t).
\end{aligned} \tag{4.18}$$

Where $r_w = \sum_{j,k} a_w^{jk}(t) f^k(t)$ is the per-capital growth rate of resident population. When the system sits at its periodic attractor $\langle r_w\rangle = 0$ and $\left\langle \frac{d}{dt}\left(\ln f_i\right)\right\rangle = 0$ so if we divide both side by f_i and average over one period we can show that

$$\left\langle \frac{f_{I_H}(t)}{f_{D_H}(t)}\right\rangle = \frac{r + \mu_H}{d}. \tag{4.19}$$

Reproductive values:
The dynamics of reproductive values are given by:

$$\frac{dv_{I_H}(t)}{dt} = \left(\gamma + d + \mu_H\right) v_{I_H}(t) - d v_{D_H}(t) - \beta_H \hat{S}_V v_{I_V} + r_w v_{I_H}(t) \tag{4.20}$$

$$\frac{dv_{D_H}(t)}{dt} = -r v_{I_H}(t) + \left(r + \mu_H\right) v_{D_H}(t) - \alpha\beta_H \hat{S}_V(t) v_{I_V}(t) + r_w v_{D_H}(t) \tag{4.21}$$

$$\frac{dv_{I_V}(t)}{dt} = -\beta_V \hat{S}_H v_{I_H}(t) + \mu_V v_{I_V} + r_w v_{I_V} \tag{4.22}$$

4.3.3 Evolution without seasonality

Let us first focus on the scenario where the environment does not fluctuate with time. In other words, we assume there is no seasonality and $\sigma = 0$. In this case we can use (4.16) and (4.17) with the trait $z = d$ and $z = r$ to show that:

$$S_d = -S_r \frac{\hat{f}_{I_H}}{\hat{f}_{D_H}}. \tag{4.23}$$

Moreover, there exists a *critical value*

$$\alpha_c = \frac{\mu_H}{\mu_H + \gamma}. \tag{4.24}$$

which plays a significant role in dictating the evolutionary path. When $\alpha > \alpha_c$, $S_d > 0 > S_r$ pathogen evolves in a way that increases the dormancy or decreases the reactivation rate. On the contrary, when $\alpha < \alpha_c$, the pathogen moves towards decreasing the reactivation rate or increasing dormancy with $S_d < 0 < S_r$ (see section (4.6.3)).

If $\alpha = 0$, we can use (4.19) to show that a mutant with a strategy d_m and r_m will invade a resident with strategy d_w and r_w if and only if

$$\frac{r_m + \mu_H}{d_m} > \frac{r_w + \mu_H}{d_w} \tag{4.25}$$

This means that if dormancy and reactivation evolve independently, dormancy evolves towards minimal values, while reactivation evolves towards maximal values. In the general case, the mutant will invade if and only if (see section (4.6.4))

$$\frac{(r + \mu_H)(\gamma + \mu_H) + d\mu_H}{r + \mu_H + \alpha d} \geq \frac{(r_m + \mu_H)(\gamma + \mu_H) + d_m \mu_H}{r_m + \mu_H + \alpha_m d_m} \tag{4.26}$$

4.3.4 Evolution with seasonality: no plasticity

First, we are going to analyze a case where dormancy and reactivation rates are constant. To be more specific, our objective is to understand how seasonality impacts the existence of a critical value under the condition of constant dormant and reactivation rates: unfortunately, we have no analytical formula. However, we have successfully obtained its existence through

numerical methods and observed that it coincides with the critical value α_c of the constant case. When $\alpha > \alpha_c$, the selection gradient with respect to the dormancy rate is denoted as $S_d = \left\langle -\hat{f}_{I_H} \left(\hat{v}_{I_H} - \hat{v}_{D_H} \right) \right\rangle$ and is found to be positive. In other words, on this interval of α, dormancy is always selected regardless of the alpha intensity value. Conversely, when $\alpha < \alpha_c$, the selection gradient S_d can take positive and negative values (see figure (4.2)).

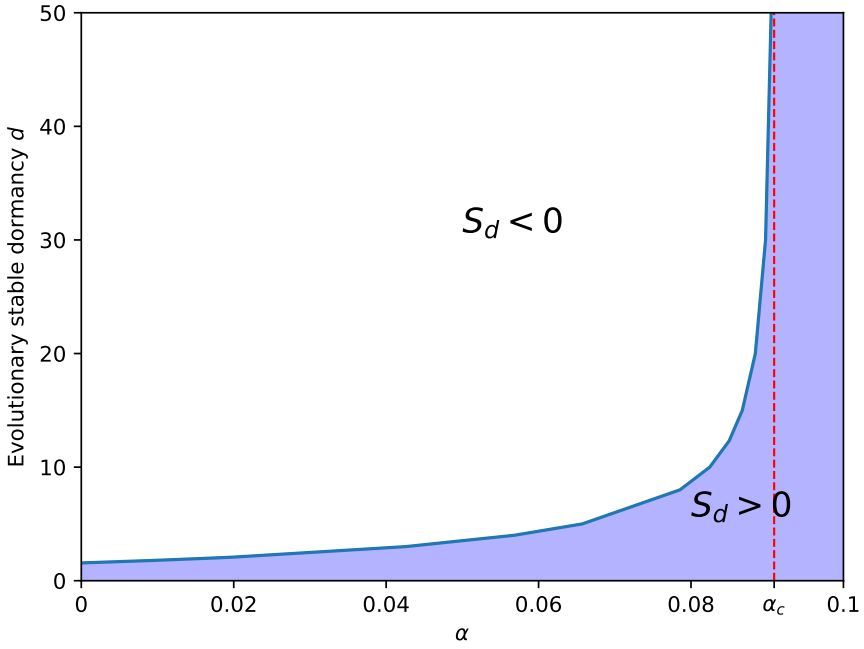

Figure 4.2 – **Evolutionary stable dormancy strategy in a periodic environment.** In the case take account for the seasonality ($\sigma > 0$), the blue curve indicates the evolutionary stable dormancy. The blue area shows the positive selection gradient with respect to dormant intensity. Parameters: $T = 6, \sigma = 0.4, \rho = 50, \beta_V = \gamma_H = 1, \beta_H = 3, \mu_V = 4, \mu_H = 0.1, r = 4$.

4.3.5 Evolution with seasonality: with plasticity

In the following, we use the selection gradient on dormancy and reactivation to study the evolution of plastic investment in these two traits. Specifically, we explore scenarios where the investment in dormancy and reactivation fluctuate with time-varying quantities. First, we examine a situation where the strategy varies with time t. Through numerical analysis, with $\alpha > \alpha_c$, pathogens switch into dormant duration at the favorable period. Second, we investigate a situation where the strategy varies with the density of vectors $N_V(t)$. Pathogens proactively switch to dormant duration before the occurrence of the unfavorable period remaining dormant

until the next favorable season comes. As a result, the length of dormant duration exceeds the duration of the unfavorable period.

Plasticity with time

We assume (i) that the pathogen invests into dormancy at rate d_0 during the time interval $[t_s^d, t_e^d]$ (outside this interval we assume $d = 0$), (ii) that the pathogen invests into reactivation at rate r_0 during the time interval $[t_s^r, t_e^r]$ (outside this interval we assume $r = 0$). In other words, we assume $d(t) = d_0 \mathbb{1}_{\left[t_s^d, t_e^d\right)}(t)$ and $r(t) = r_0 \mathbb{1}_{[t_s^r, t_e^r)}$. In the following we are going to look for the evolutionary stable values of $t_s^d, t_e^d, t_s^r, t_e^r$.

Selection for plastic dormancy:

We have

$$\frac{\partial \mathbf{A}_m}{\partial d_0} = \frac{\partial \mathbf{A}_m}{\partial d} \frac{\partial d(t)}{\partial d_0} = \begin{pmatrix} -1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \mathbb{1}_{\left[t_s^d, t_e^d\right)}(t) \tag{4.27}$$

and $\dfrac{\partial d(t)}{\partial t_s^d} = -d_0 \delta_{t_s^d}(dt)$ indeed since, $d_\epsilon(t) = d_0 \mathbb{1}_{\left[t_s^d + \epsilon, t_e^d\right)}(t) = d(t) - d_0 \mathbb{1}_{\left[t_s^d, t_s^d + \epsilon\right)}(t)$ and $d^\epsilon(t) = d_0 \mathbb{1}_{\left[t_s^d, t_e^d + \epsilon\right)}(t) = d(t) + d_0 \mathbb{1}_{\left[t_e^d, t_e^d + \epsilon\right)}(t)$ hence

$$\frac{\partial d(t)}{\partial t_s^d} = \lim_{\epsilon \to 0} \frac{d_\epsilon(t) - d(t)}{\epsilon} = -\lim_{\epsilon \to 0} \frac{d_0}{\epsilon} \mathbb{1}_{\left[t_s^d, t_s^d + \epsilon\right)}(t) = -d_0 \delta_{t_s^d}(dt) \tag{4.28}$$

$$\frac{\partial d(t)}{\partial t_e^d} = \lim_{\epsilon \to 0} \frac{d^\epsilon(t) - d(t)}{\epsilon} = \lim_{\epsilon \to 0} \frac{d_0}{\epsilon} \mathbb{1}_{\left[t_e^d, t_e^d + \epsilon\right)}(t) = d_0 \delta_{t_e^d}(dt). \tag{4.29}$$

The selection gradient on t_s^d is

$$\mathcal{S}_{t_s^d} = \frac{1}{T} \int_0^T -d_0 \left(-\hat{v}_{I_H} + \hat{v}_{D_H}\right) \hat{f}_{I_H}(t) \delta_{t_s^d}(dt)\, dt = \frac{d_0}{T} \left(\hat{v}_{I_H}(t_s^d) - \hat{v}_{D_H}(t_s^d)\right) \hat{f}_{I_H}(t_s^d). \tag{4.30}$$

The selection gradient on t_e^d is

$$\mathcal{S}_{t_e^d} = \frac{1}{T} \int_0^T d_0 \left(-\hat{v}_{I_H} + \hat{v}_{D_H}\right) \hat{f}_{I_H}(t) \delta_{t_e^d}(dt)\, dt = -\frac{d_0}{T} \left(\hat{v}_{I_H}(t_e^d) - \hat{v}_{D_H}(t_e^d)\right) \hat{f}_{I_H}(t_e^d). \tag{4.31}$$

Selection for plastic reactivation:

As in the previous section, we have

$$\frac{\partial \mathbf{A}_m}{\partial r_0} = \frac{\partial \mathbf{A}_m}{\partial r}\frac{\partial r(t)}{\partial r_0} = \begin{pmatrix} 0 & 1 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 0 \end{pmatrix} \mathbb{1}_{[t_s^r, t_e^r)}(t). \tag{4.32}$$

Similarly $\dfrac{\partial r(t)}{\partial t_s^r} = -r_0\delta_{t_s^r}(dt)$, $\dfrac{\partial r(t)}{\partial t_e^r} = r_0\delta_{t_e^r}(dt)$.

The selection on t_s^r is

$$\mathcal{S}_{t_s^r} = -\frac{1}{T}\int_0^T r_0\left(\hat{v}_{I_H} - \hat{v}_{D_H}\right)\hat{f}_{D_H}(t)\delta_{t_s^r}(dt)\,dt = -\frac{r_0}{T}\left(\hat{v}_{I_H}(t_s^r) - \hat{v}_{D_H}(t_s^r)\right)\hat{f}_{D_H}(t_s^r). \tag{4.33}$$

The selection on t_e^r is

$$\mathcal{S}_{t_e^r} = \frac{1}{T}\int_0^T r_0\left(\hat{v}_{I_H} - \hat{v}_{D_H}\right)\hat{f}_{D_H}(t)\delta_{t_e^r}(dt)\,dt = \frac{r_0}{T}\left(\hat{v}_{I_H}(t_e^r) - \hat{v}_{D_H}(t_e^r)\right)\hat{f}_{D_H}(t_e^r). \tag{4.34}$$

Let us assume that there is an ESS with respect to t_s^d, t_e^d, t_s^r and t_e^r. Then, from the relation of expressions (4.30) (4.31) , (4.33) and (4.34) $S_{t_s^d} = S_{t_e^d} = S_{t_s^r} = S_{t_e^r} = 0$. Since $\alpha < \alpha_c$ there are only two timings t in a period such that $\hat{v}_{I_H}(t) = \hat{v}_{D_H}(t)$ we find that [1] $t_s^d \equiv t_e^r, t_e^d \equiv t_s^r$. Hence we can write $d(t) = d_0\mathbb{1}_{[t_s^d, t_e^d)}(t), r(t) = r_0\mathbb{1}_{[t_e^d, t_s^d)}(t)$. When the pathogens encounter an unfavorable environment, they will switch into a dormant state until the next favorable period where they will relapse (see Figure (4.3)).

Plasticity with vector density

Understanding the relationship between the timing of dormancy and the state of relapse has provided us with valuable insights into the physiological mechanism of the population. In the following, we will assume the transition point of the species will depend on the size of the population, which means there will be a threshold N_V^*. When $\hat{N}_V(t) \geq N_V^*$ we reactivate the dormant hosts at rate r_0. When $\hat{N}_V(t) < N_V^*$ we put host in a dormant state at rate d_0. Given $N_V^* \in \left(\hat{N}_V(0), \hat{N}_V(0)e^{\sigma\mu T}\right)$ from the argument in the preceding section, we assume that $d(t) = d_0\mathbb{1}_{[t_s^d, t_e^d)}$ and $r(t) = r_0\mathbb{1}_{[t_e^d - T, t_s^d)}$, we have two values $(1-\sigma)\,T < t_s^d < T < t_e^d < t_s^d + T$ such that $\hat{N}_V(t_s^d) = \hat{N}_V(t_e^d) = N_V^*$. Therefore $t_e^d = t_0 \in [0, (1-\sigma)T)$ where t_0 is given in proposition (20). We shall compute the selection gradient on the period $\left[t_e^d - T, t_e^d\right]$ with

1. Here we use the notation $m \equiv n$ with the implication that there exists $k \in \mathbb{Z}$, such that $m = n + kT$,

$z = N_V^*$,

$$\mathcal{S} = \left\langle v \frac{\partial \mathbf{A}}{\partial z}(t) f \right\rangle, \text{ with } \frac{\partial \mathbf{A}}{\partial z}(t) = \frac{\partial \mathbf{A}}{\partial d}(t)\frac{\partial d}{\partial z}(t) + \frac{\partial \mathbf{A}}{\partial r}(t)\frac{\partial r}{\partial z}(t). \tag{4.35}$$

Since $d(t) = d_0 \mathbb{1}_{\left[t_s^d \leq t < t_e^d\right)}$ and $r(t) = r_0 \mathbb{1}_{t_e^d - T \leq t < t_s^d}$ we have

$$\frac{\partial d}{\partial z}(t) = -d_0 \frac{\partial t_s^d}{\partial z}(t)\delta_{t_s^d}(dt) + d_0 \frac{\partial t_e^d}{\partial z}(t)\delta_{t_e^d}(dt), \tag{4.36}$$

$$\frac{\partial r}{\partial z}(t) = r_0 \frac{\partial t_s^d}{\partial z}(t)\delta_{t_s^d}(dt) - r_0 \frac{\partial t_e^d}{\partial z}(t)\delta_{t_e^d - T}(dt). \tag{4.37}$$

We compute $\dfrac{\partial t_s^d}{\partial z}(t)$ from the equation $\hat{N}_V(t_s^d) = N_V^*$ that we differentiate

$$1 = \frac{\partial N_V^*}{\partial z} = N_V^{'}(t_s^d)\frac{\partial t_s^d}{\partial z}(t)$$

and since $N_V^{'}(t) = \left(\rho_V(t)\left(1 - \dfrac{\hat{N}_V(t)}{K}\right) - \mu_V\right)\hat{N}_V(t)$, we get

$$\frac{\partial t_s^d}{\partial z}(t) = \frac{1}{N_V^{'}(t_s^d)} = -\frac{1}{\mu_V N_V^*}, \quad \frac{\partial t_e^d}{\partial z}(t) = \frac{1}{N_V^{'}(t_e^d)} = \frac{1}{\left(\rho\left(1 - \frac{N_V^*}{K}\right) - \mu_V\right)N_V^*}. \tag{4.38}$$

Putting everything together gives the gradient

$$\begin{aligned}
\mathcal{S}(t) &= (-\hat{v}_{I_H} + \hat{v}_{D_H})\left(\frac{\partial d}{\partial z}(t)\hat{f}_{I_H} - \frac{\partial r}{\partial z}(t)\hat{f}_{D_H}\right) \\
&= (-\hat{v}_{I_H} + \hat{v}_{D_H})\left(\hat{f}_{I_H}\left(-d_0\frac{\partial t_s^d}{\partial z}(t)\delta_{t_s^d}(dt) + d_0\frac{\partial t_e^d}{\partial z}(t)\delta_{t_e^d}(dt)\right)\right. \\
&\qquad \left. -\hat{f}_{D_H}\left(r_0\frac{\partial t_s^d}{\partial z}(t)\delta_{t_s^d}(dt) - r_0\frac{\partial t_e^d}{\partial z}(t)\delta_{t_e^d - T}(dt)\right)\right) \\
&= (-\hat{v}_{I_H} + \hat{v}_{D_H})\left(-\left(\hat{f}_{I_H}d_0 + \hat{f}_{D_H}r_0\right)\frac{\partial t_s^d}{\partial z}(t)\delta_{t_s^d}(dt) + \hat{f}_{I_H}d_0\frac{\partial t_e^d}{\partial z}(t)\delta_{t_e^d}(dt) + \hat{f}_{D_H}r_0\frac{\partial t_e^d}{\partial z}(t)\delta_{t_e^d - T}(dt)\right).
\end{aligned}$$

Therefore

$$\mathcal{S} = \left(-\hat{v}_{I_H}(t_s^d) + \hat{v}_{D_H}(t_s^d)\right)\left(\hat{f}_{I_H}(t_s^d)d_0 + \hat{f}_{D_H}(t_s^d)r_0\right)\frac{1}{\mu_V N_V^*} \tag{4.39}$$

$$+\left(-\hat{v}_{I_H}(t_e^d)+\hat{v}_{D_H}(t_e^d)\right)\left(\hat{f}_{I_H}(t_e^d)d_0+\hat{f}_{D_H}(t_e^d)r_0\right)\frac{1}{\left(\rho\left(1-\frac{N_V^*}{K}\right)-\mu_V\right)N_V^*}.$$

In the particular case, if $r(t)$ is fixed, then the expression (4.39) reduces

$$\mathcal{S}=\left(\left(-\hat{v}_{I_H}(t_s^d)+\hat{v}_{D_H}(t_s^d)\right)\hat{f}_{I_H}(t_s^d)\frac{1}{\mu_V}+\frac{1}{\rho\left(1-\frac{N_V^*}{K}\right)-\mu_V}\left(-\hat{v}_1(t_e^d)+\hat{v}_{D_H}(t_e^d)\right)\hat{f}_{I_H}(t_e^d)\right)\frac{d_0}{N_V^*}. \tag{4.40}$$

The relation between t_s^d and t_e^d be shown preceding, and the numerical optimization procedure (see figure (4.3)). Pathogens enter a state of dormancy in response to an unfavorable period, guided by cues from the density of the number vector. Consequently, this dormancy period occurs later in winter and extends until the beginning of summer. It differs from the selective direction of time, where pathogens always proactively switch whenever they detect unfavorable cues.

Plasticity with infectivity of the dormant infections

From equation (4.13) we have the selection gradient on infectivity of the dormant infectious given by

$$\mathcal{S}_\alpha=\beta_H\hat{V}_{I_V}\hat{f}_{D_H}\hat{S}_V>0 \tag{4.41}$$

Hosts with higher α have higher fitness. When $\alpha=1$ the compartment D_H is considered as compartment I_H. Combined with the two preceding sections, with $\alpha=1$, the selection on time $S_{t_s^d}<0, S_{t_e^d}>0$, an decrease t_s^d or an increase t_e^d get higher fitness. In other words, pathogens prefer dormancy the whole period.

4.4 Discussion

We have extended a classical model of vector-borne transmission to account for the ability of some pathogens to enter a dormant state. This dormant state protects the pathogen during the bad season because the host immune system cannot clear the infection. However dormancy is very costly in this model because it prevents pathogen transmission from the D_H hosts.

Our analysis first shows that seasonality has a positive effect on pathogen persistence in this model. This effect is due to the influence of seasonality on the average density of vectors. Note, however, that we know from [KCG22] that this effect of seasonality is very sensitive to the assumptions regarding the influence of seasonality on different components of the life-cycle.

However the main objective of the present study was to explore the evolution of the pathogen investment in dormancy and reactivation. We found that when dormancy and reactivation are assumed to be constant in time, selection tends to favor lower values of dormancy and higher values of reactivation. Yet, if we allow dormancy to vary with time or with other time varying quantities (e.g. the density of vectors) plastic strategies of dormancy and reactivation can evolve. This plastic investment allows the pathogen to track the fluctuations of the densities of vectors and invest more into transmission (lower dormancy and more reactivation) when many vectors are around.

It would be interesting to analyze modified versions of the life-cycle. First, it would be interesting to study the robustness of our results when we vary the growth function of the vector. In the current model, the vector density grows exponentially during the "good" period and it drops exponentially during the "bad" period for the vector. In natural conditions, the density of the vector population may follow a more logistic growth curve where the density stabilizes around some carrying capacity during the "good" period and drops rapidly to zero in the "bad" season. Would these square-wave dynamics alter the outcome of the evolution of dormancy?

We would also like to analyze a slightly more complex version of the model where investment in dormancy could be costly but would not lead the host to be unable to transmit the pathogen. In this case, the hosts of type D_H would still be able to transmit to the vector. The benefit of dormancy would come from the fact that if immunity clears infection from these D_H hosts they would enter a compartment R_D where the parasite could eventually reactivate and enter again the infectious class D_H. We expect that this model would induce a lower cost in dormancy and could lead to fixed investment in dormancy in seasonal environments.

4.5 Tables and Figures

Table 4.1 – Parameters and variables of the models

Symbol	Description
Parameters	
d	rate of dormancy
r	rate of reactivation
β_V	rate of transmission from an infected vector to a susceptible host
β_H	rate of transmission from an infected host to a susceptible vector
ρ_V	growth rate of the vector
μ_V	death rate of the vector
μ_H	death rate of the host
γ	recovery rate of the infected host
T	period of the seasonal fluctuations
σ	intensity of the seasonal fluctuations
ϵ	phenotypic effect of the mutation (assumed to be small)
t_s^d	starting time of dormant period
t_e^d	ending time of dormant period
t_s^d	starting time of reactivation
t_s^d	ending time of reactivation
α	infectivity of the dormant infections
Variables	
θ	influx of susceptible hosts
S_H	density of susceptible hosts
I_H	density of infected hosts
D_H	density of dormant hosts
R_H	density of recovered hosts
N_H	total host population density: $N_H = S_H + I_H + D_H + R_H$
S_V	density of susceptible vectors
I_V	density of infected vectors
N_V	total vector population density: $N_V = S_V + I_V$

4.6 Supplementary information

In the following, we will complete the unproven results from the main text. Specifically, in Section (4.6.1), we will calculate an alternative quantitative value for the reproductive values R_0 and integrate it with the next-generation theorem. Section (4.6.2) uses a perturbation analysis approach in order to find the threshold where the pathogen develops in case the environment is not fluctuating. Section (4.6.3) finds the threshold of infectivity of the dormant infections in without seasonality case. Section (4.6.4) gives a condition mutant will invade the population. Section (4.6.5) solved some problems related to the logistic equation and section (4.6.6) study model under the influence of seasonality which was used in section (4.3.1)

4.6.1 The reproductive value

The next generation approach

We can compute the reproductive value R_0 by linearising the system at the disease free equilibrium (**DFE**) $I_V = I_H = D_H = R_H = 0, N_V = S_V, N_H = S_H$ with $\mathbf{X}(t) = (I_H, D_H, I_V)^\top$ satisfies the system.

$$\frac{d\mathbf{X}(t)}{dt} = \mathbf{A}\mathbf{X}(t), \tag{4.42}$$

where

$$\mathbf{A} = \begin{pmatrix} -(\gamma + d + \mu_H) & r & \beta_V \\ d & -(r + \mu_H) & 0 \\ \beta_H N_V & \alpha\beta_H N_V & -\mu_V \end{pmatrix}. \tag{4.43}$$

By the representation $\mathbf{A}$ as $\mathbf{A} = \mathbf{F} - \mathbf{V}$ with

$$\mathbf{F} = \begin{bmatrix} 0 & r & \beta_V \\ d & 0 & 0 \\ \beta_H N_V & \alpha\beta_H N_V & 0 \end{bmatrix}, \quad \mathbf{V} = \begin{bmatrix} (\gamma + \mu_H + d) & 0 & 0 \\ 0 & (r + \mu_H) & 0 \\ 0 & 0 & \mu_V \end{bmatrix},$$

which satisfy the next-generation theorem [HCD09] then the basic reproductive value R_0 is given by

$$R_0 = \rho\left(\mathbf{F}\mathbf{V}^{-1}\right) \text{ where } \mathbf{F}\mathbf{V}^{-1} = \begin{bmatrix} 0 & \frac{r}{r+\mu_H} & \frac{\beta_V}{\mu_V} \\ \frac{d}{\gamma+\mu_H+d} & 0 & 0 \\ \frac{\beta_H N_V}{\gamma+\mu_H+d} & \frac{\alpha\beta_H N_V}{r+\mu_H} & 0 \end{bmatrix}. \tag{4.44}$$

We have

$$\begin{aligned} &\det\left(\mathbf{F}\mathbf{V}^{-1} - tI\right) \\ &= -t^3 - \frac{r}{r+\mu_H}\left(-t\frac{d}{\gamma+\mu_H+d}\right) + \frac{\beta_V}{\mu_V}\left(\frac{d\alpha\beta_H N_V}{(\gamma+\mu_H+d)(r+\mu_H)} + \frac{t\beta_H N_V}{\gamma+\mu_H+d}\right) \\ &= -t^3 + t\left[\frac{dr}{(r+\mu_H)(\gamma+\mu_H+d)} + \frac{\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)}\right] + \frac{d\alpha\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)(r+\mu_H)}. \end{aligned} \tag{4.45}$$

Look at the equation

$$\begin{aligned} &\det\left(\mathbf{F}\mathbf{V}^{-1} - tI\right) = 0 \\ \Leftrightarrow\ &-t^3 + t\left[\frac{dr}{(r+\mu_H)(\gamma+\mu_H+d)} + \frac{\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)}\right] + \frac{d\alpha\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)(r+\mu_H)} = 0. \end{aligned}$$

Apply Vieta's theorem to the cubic equation (4.45), which has three distinct solutions t_1, t_2, and t_3 that satisfy:

$$\begin{aligned} t_1 + t_2 + t_3 &= 0 \\ t_1t_2 + t_1t_3 + t_2t_3 &= -\left(\frac{rd}{(r+\mu_H)(\gamma+\mu_H+d)} + \frac{\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)}\right) \\ t_1t_2t_3 &= \frac{d\alpha\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)(r+\mu_H)}. \end{aligned}$$

It is easy to show that there are two negative solutions and one positive solution $t_1 < t_2 < 0 < t_3$. We set $f(t) = -t^3 + t\left[\frac{dr}{(r+\mu_H)(\gamma+\mu_H+d)} + \frac{\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)}\right] + \frac{d\alpha\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)(r+\mu_H)}$. Since $f(0) > 0$, hence

— If $f(1) > 0$ then $t_3 > 1$.

— If $f(1) < 0$ then $t_3 < 1$.

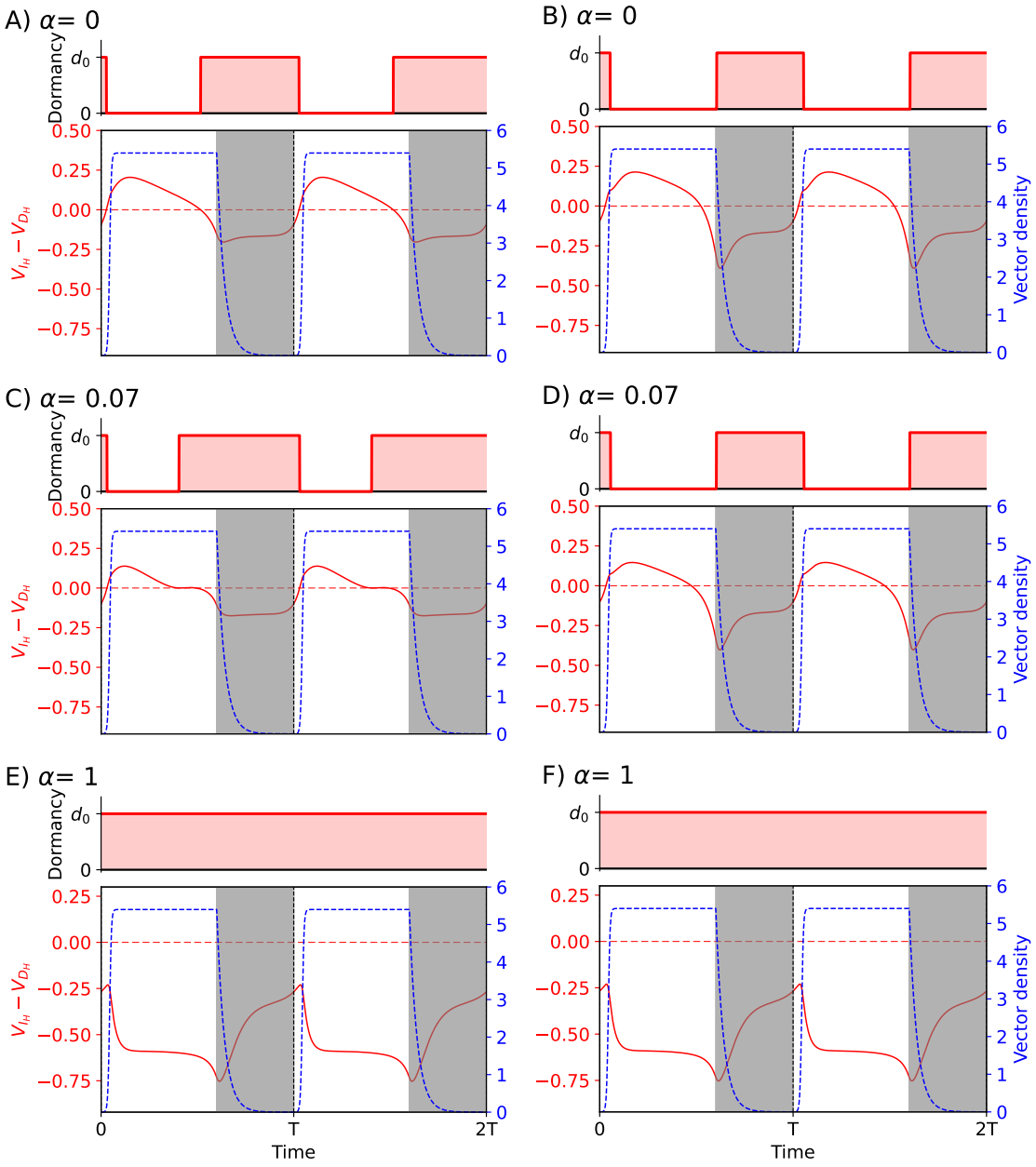

Figure 4.3 – **Plasticity** . For $\alpha = 0$, figure A, $t_s^d = 0.51648T, t_e^d = 1.02736T$. figure B, $t_s^d = 0.60445T$, $\hat{N}_V(t_s^d) = \hat{N}_V(t_e^d) = 4.83143$. For $\alpha = 0.07$, figure C, $t_s^d = 0.0.4041415T, t_e^d = 1.03048T$, figure D, $t_s^d = 0.602997T$, $\hat{N}_V(t_s^d) = \hat{N}_V(t_e^d) = 4.9858$ and $\alpha = 1$, there is no $t_s^d, t_e^d \in [0, T)$ such that $S_{t_s^d} = S_{t_e^d} = 0$. More precisely, we always have $S_{t_s^d} < 0$ and $S_{t_e^d} > 0$. Pathogens prefer decreasing t_s^d and increasing t_e^d in other words, pathogens prefer dormancy. The gray areas indicate unfavorable reason $[(1-\sigma)T + kT, T + kT)$, the orange areas depict dormant period. It lays on time interval $\left[t_s^d + kT, t_e^d + kT\right)$. The red line indicates $V_{I_H} - V_{D_H}$ and the blue curve indicates vector population oscillates around its equilibrium value. Common parameter values: $T = 5, \sigma = 0.4, \beta_V = 1, \beta_H = 3, \alpha = 0.2, \gamma = 1, d_0 = 5, r_0 = 4, \rho = 50, \mu_V = 5, \mu_H = 0.1, r(t) = r_0 \mathbb{1}_{[t_e^d, t_s^d + T)}(t)$ .114

In the general case, we can not compute directly the reproductive value R_0 , but we can compare $\rho\left(\mathbf{FV}^{-1}\right)$ with 1 by comparing the value of $f(1) = -1 + \dfrac{rd}{(r+\mu_H)(\gamma+\mu_H+d)} + \dfrac{\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)} + \dfrac{d\alpha\beta_V\beta_H N_V}{\mu_V(\gamma+\mu_H+d)(r+\mu_H)}$ with 0.

4.6.2 Perturbation analysis approach

In the constant case, without seasonality, matrix $\mathbf{A}$ become $\mathbf{A}_0$ with the implication $\sigma = 0$. The characteristic equation $\det|\mathbf{A}_0 - t\mathbf{I}| = 0$ is given by

$$-(\mu_V+t)(\gamma+d+\mu_H+t)(r+\mu_H+t) + dr(\mu_V+t) + \beta_V(\alpha d\beta_H N_V + \beta_H N_V(r+\mu_H+t)) = 0. \tag{4.46}$$

We have

$$\begin{aligned}
&-(\mu_V+t)(\gamma+d+\mu_H+t)(r+\mu_H+t) + dr(\mu_V+t) + \beta_V(\alpha d\beta_H N_V + \beta_H N_V(r+\mu_H+t)) \\
&\quad = -(\mu_V+t)\left[[t^2 + t(\gamma+d+\mu_H+r+\mu_H) + (\gamma+d+\mu_H)(r+\mu_H) - dr\right] \\
&\qquad + \beta_V\beta_H N_V(d\alpha + r + \mu_H + t) \\
&\quad = -t^3 - t^2C_2 - tC_1 + C_0,
\end{aligned}$$

with

$$C_2 = \gamma + d + \mu_H + r + \mu_H + \mu_V \tag{4.47}$$

$$C_1 = (\gamma+d+\mu_H)(r+\mu_H) + \mu_V(\gamma+d+\mu_H+r+\mu_H) - dr - \beta_V\beta_H N_V \tag{4.48}$$

$$C_0 = -\mu_V(r+\mu_H)(\gamma+d+\mu_H) + rd\mu_V + \beta_V\beta_H N_V(r+\mu_H+d\alpha). \tag{4.49}$$

Without loss of generality by change the matrix $\mathbf{A}_0$ by $\mathbf{A}_0 - s(\mathbf{A}_0)I$ [2], we assume that $s(\mathbf{A}_0) = 0$. It is equivalent $t = 0$ is one solution of the characteristic equation. So, we get

$$-\mu_V(r+\mu_H)(\gamma+d+\mu_H) + rd\mu_V + \beta_V\beta_H N_V(r+\mu_H+d\alpha) = 0. \tag{4.50}$$

We divide both sides with $\mu_V(r+\mu_H)(\gamma+d+\mu_H)$ and yields

$$\boxed{\frac{\beta_V\beta_H N_V(r+\mu_H+d\alpha)}{\mu_V(\gamma+d+\mu_H)(r+\mu_H)} + \frac{rd}{(\gamma+d+\mu_H)(r+\mu_H)} = 1.} \tag{4.51}$$

2. $s(\mathbf{A}) = \max\{\Re(z) : z \in \text{ Set of eigenvalues of matrix } \mathbf{A}\}$

In order to show that 0 is the spectral abscissa of matrix $\mathbf{A}_0$. It is sufficient to establish that 0 is the highest real part among all the eigenvalues of $\mathbf{A}_0$. It is equivalent to showing that the following equation has two solutions with a negative real part.

$$t^2 + C_2 t + C_1 = 0. \tag{4.52}$$

Indeed, $C_2 > 0$ and

$$\begin{aligned}
C_1 &= (\gamma + d + \mu_H)(r + \mu_H) + \mu_V(\gamma + d + \mu_H + r + \mu_H) - dr - \beta_V \beta_H N_V \\
&= (\gamma + d + \mu_H)(r + \mu_H) + \mu_V(\gamma + d + \mu_H + r + \mu_H) - dr - \frac{\mu_V(\gamma + d + \mu_H)(r + \mu_H) - rd\mu_V}{r + \mu_H + d\alpha} \\
&\geq (\gamma + d + \mu_H)(r + \mu_H) + \mu_V(\gamma + d + \mu_H + r + \mu_H) - dr - \frac{\mu_V(\gamma + d + \mu_H)(r + \mu_H) - rd\mu_V}{r + \mu_H} \\
&= (\gamma + d + \mu_H + \mu_V)(r + \mu_H) - dr + \frac{dr\mu_V}{r + \mu_H} > 0.
\end{aligned}$$

The last inequality from the sum of the two first terms is positive and the last term is positive. Therefore, all other solutions of (4.46) with real part negative. In other words, 0 is the spectral abscissa of matrix A. In the constant case, $\lambda_0 = \rho\left(e^{T\mathbf{A}_0}\right) = 1$ if and only if the condition (4.51) holds and it is also the condition we find with the next-generation approach (formula (4.44).

4.6.3 Evolution without seasonality

In this case we consider $\sigma = 0$, therefore, at DFE we have:

$$\begin{aligned}
\mu_H(I_H + R_H + D_H) - \beta_V I_V S_H &= 0, \\
\beta_V I_V S_H - (\gamma + \mu_H + d) I_H + r D_H &= 0, \\
dI_H - (r + \mu_H) D_H &= 0, \\
\gamma I_H - \mu_H R_H &= 0.
\end{aligned}$$

Hence,

$$R_H = \frac{\gamma I_H}{\mu_H}, \qquad D_H = \frac{dI_H}{r + \mu_H}.$$

Therefore,

$$\begin{aligned} 0 &= \beta_V I_V S_H - (\gamma + \mu_H + d) I_H + r D_H \\ &= \beta_V I_V S_H - (\gamma + \mu_H + d) I_H + \frac{dr}{r + \mu_H} I_H \\ &= \beta_V I_V S_H - \left(\gamma + \mu_H + d + \frac{dr}{r + \mu_H}\right) I_H \qquad (4.53) \\ \Leftrightarrow \beta_V I_V S_H &= \left(\gamma + \mu_H + d + \frac{dr}{r + \mu_H}\right) I_H \qquad (4.54) \end{aligned}$$

Furthermore, since

$$\dot{S}_V = \rho_V(t) \left(1 - \frac{N_V(t)}{K}\right) N_V(t) - \beta_H \left(I_H + \alpha D_H\right) S_V - \mu_V S_V, \qquad (4.55)$$

$$\dot{I}_V = \beta_H \left(I_H + \alpha D_H\right) S_V - \mu_V I_V. \qquad (4.56)$$

Therefore

$$\dot{N}_V = \rho_V(t) \left(1 - \frac{N_V(t)}{K}\right) N_V(t) - \mu_V N_V.$$

In the constant case, when $\sigma = 0$ one gets $\hat{N}_V = K\left(1 - \frac{\mu_V}{\rho}\right)$, and $\beta_H \left(I_H + \alpha D_H\right) S_V - \mu_V I_V = 0$

$$\begin{aligned} \Leftrightarrow \mu_V I_V &= \beta_H \left(I_H + \alpha D_H\right) S_V \qquad (4.57) \\ &= \beta_H \left(1 + \frac{\alpha d}{r + \mu_H}\right) I_H S_V. \end{aligned}$$

From (4.54) and (4.57) yields,

$$\hat{S}_H \hat{S}_V \frac{\beta_V \beta_H}{\mu_V} = \frac{\mu_H + \gamma + \frac{\mu_H d}{r + \mu_H}}{1 + \frac{\alpha d}{r + \mu_H}}.$$

Since $\mathbf{v}_0 A = 0$ with $\mathbf{v}_0 \gg 0$.[3] We get $0 = (\mathbf{v}_0 A)_3 = 0 \Rightarrow \beta_V \hat{S}_H \mathbf{v}_0(1) - \mu_V \mathbf{v}_0(3) = 0$

3. $x = (x_1, \cdots, x_n) \gg 0 : x_i > 0 \, \forall \, i \in [1, n]$

$\Rightarrow \mathbf{v}_0(3) = \dfrac{\beta_V \hat{S}_H \mathbf{v}_0(1)}{\mu_V}$, and $(\mathbf{v}_0 A)_2 = 0$ hence $r\mathbf{v}_0(1) - (r+\mu_H)\,\mathbf{v}_0(2) + \alpha\beta_H \hat{S}_V \mathbf{v}_0(3) = 0$.

We have

$$\begin{aligned}
& r\mathbf{v}_0(1) - (r+\mu_H)\,\mathbf{v}_0(2) + \alpha\beta_H \hat{S}_V \mathbf{v}_0(3) && = 0 \\
\Leftrightarrow \quad & r\mathbf{v}_0(1) - (r+\mu_H)\,\mathbf{v}_0(2) + \alpha\beta_H \hat{S}_V \frac{\beta_V \hat{S}_H \mathbf{v}_0(1)}{\mu_V} && = 0 \\
\Leftrightarrow \quad & \left(r + \alpha\beta_H \hat{S}_V \frac{\beta_V \hat{S}_H}{\mu_V}\right) \mathbf{v}_0(1) && = (r+\mu_H)\,\mathbf{v}_0(2) \\
\Leftrightarrow \quad & \left(r + \alpha \frac{\mu_H + \gamma + \dfrac{\mu_H d}{r+\mu_H}}{1 + \dfrac{\alpha d}{r+\mu_H}}\right) \mathbf{v}_0(1) && = (r+\mu_H)\,\mathbf{v}_0(2).
\end{aligned}$$

If $d(t) = d, r(t) = r$, $S_d = -S_r \dfrac{f_{I_H}(t)}{f_{D_H}(t)}$ with $S_d = \hat{f}_{I_H}(\hat{v}_{S_H} - \hat{v}_{I_H})$.

$$\begin{aligned}
& S_d && \geq 0 \\
\Leftrightarrow \quad & \mathbf{v}_0(2) && \geq \mathbf{v}_0(1) \\
\Leftrightarrow \quad & r + \alpha \frac{\mu_H + \gamma + \dfrac{\mu_H d}{r+\mu_H}}{1 + \dfrac{\alpha d}{r+\mu_H}} && \geq r + \mu_H \\
\Leftrightarrow \quad & \alpha\left(\mu_H + \gamma + \frac{\mu_H d}{r+\mu_H}\right) && \geq \mu_H\left(1 + \frac{\alpha d}{r+\mu_H}\right)
\end{aligned}$$

$$\begin{aligned}
\Leftrightarrow \quad & \alpha(\mu_H + \gamma) && \geq \mu_H \\
\Leftrightarrow \quad & \alpha && \geq \frac{\mu_H}{\mu_H + \gamma}.
\end{aligned}$$

4.6.4 Evolutionary invasion analysis

To study whether the mutant invades and could become an epidemic, we use adaptive system methodology . If the mutant invades the population, we have a dynamic system

$$\begin{aligned}
\dot{S}_H &= -\beta_V (I_V + I_V^m) S_H + \mu_H (I_H + I_H^m + D_H + D_H^m + R_H) \\
\dot{I}_H &= \beta_V I_V S_H - (\gamma + \mu_H + d) I_H + r D_H \\
\dot{D}_H &= d I_H - (r + \mu_H) D_H
\end{aligned}$$

$$
\begin{aligned}
\dot{R}_H &= \gamma\left(I_H + I_H^m\right) - \mu_H R_H \\
\dot{S}_V &= \rho_V(t)\left(1 - \frac{N_V(t)}{K}\right) N_V - \beta_H\left(I_H + I_H^m + \alpha D_H + \alpha^m D_H^m\right) S_V - \mu_V S_V \\
\dot{I}_V &= \beta_H\left(I_H + \alpha D_H\right) S_V - \mu_V I_V \\
\dot{I}_H^m &= \beta_V I_V^m S_H - \left(\gamma + \mu_H + d_m\right) I_H^m + r^m D_H^m \\
\dot{D}_H^m &= d^m I_H^m - \left(r_m + \mu_H\right) D_H^m \\
\dot{I}_V^m &= \beta_H\left(I_H^m + \alpha^m D_H^m\right) S_V - \mu_V I_V^m
\end{aligned}
\tag{4.58}
$$

NB: $N_V = I_V + S_V + I_V^m$.

To study the stability of the mutant system, we compute the Jacobian matrix at the DFE

$$
\mathbf{R}_m = \begin{pmatrix}
-\left(\gamma + d_m + \mu_H\right) & r_m & \beta_V \\
d_m & -\left(r_m + \mu_H\right) & 0 \\
\beta_H S_V & \alpha_m \beta_H S_V & -\mu_V
\end{pmatrix}
$$

Applying the result of the previous section (4.6.1), the mutant invades if and only if

$$
\begin{aligned}
& \frac{d_m}{\gamma + \mu_H + d_m}\frac{r_m}{r_m + \mu_H} + \frac{\beta_V \beta_H S_V\left(r_m + \mu_H + \alpha_m d_m\right)}{\left(\gamma + \mu_H + d_m\right)\left(r_m + \mu_H\right)\mu_V} && \geq 1 \\
\Leftrightarrow \quad & \frac{\beta_V \beta_H S_V\left(r_m + \mu_H + \alpha_m d_m\right)}{\left(r_m + \mu_H\right)\mu_V} && \geq \gamma + \mu_H + \frac{d_m \mu_H}{r_m + \mu_H} \\
\Leftrightarrow \quad & \frac{\beta_V \beta_H S_V}{\mu_V} && \geq \frac{\left(r_m + \mu_H\right)\left(\gamma + \mu_H\right) + d_m \mu_H}{r_m + \mu_H + \alpha_m d_m} \\
\Leftrightarrow \quad & \frac{\left(r + \mu_H\right)\left(\gamma + \mu_H\right) + d\mu_H}{r + \mu_H + \alpha d} && \geq \frac{\left(r_m + \mu_H\right)\left(\gamma + \mu_H\right) + d_m \mu_H}{r_m + \mu_H + \alpha_m d_m}
\end{aligned}
\tag{4.59}
$$

Hence, the mutant invades if and only

$$
\frac{\left(r + \mu_H\right)\left(\gamma + \mu_H\right) + d\mu_H}{r + \mu_H + \alpha d} \geq \frac{\left(r_m + \mu_H\right)\left(\gamma + \mu_H\right) + d_m \mu_H}{r_m + \mu_H + \alpha_m d_m} \tag{4.60}
$$

4.6.5 The deterministic model

Proposition 19. *We consider the following ODE:*

$$
\begin{cases}
\dfrac{dx(t)}{dt} & = \rho_V(t) x(t)\left(1 - \dfrac{x(t)}{K}\right) - \mu_V(t) x(t), \\
x(t_0 T) & = x_0\,.
\end{cases}
\tag{4.61}
$$

Where $\rho_V(t), \mu_V(t)$ are positive function for all $t \geq t_0T$. There is a unique periodic attractor is given by:

$$x^\star(t) = \frac{e^{\varphi(t)}}{\int_0^t \frac{\rho_V(s)}{K} e^{\varphi(s)} ds + \frac{1}{e^{\varphi(T)}-1} \int_0^T \frac{\rho_V(s)}{K} e^{\varphi(s)} ds}. \tag{4.62}$$

where $\varphi(t) = \int_0^t \rho_V(s) - \mu_V(s) ds$.

Proof. Since the first equation of (4.61)

$$\begin{aligned}
\frac{dx(t)}{dt} &= \rho_V(t)x(t)\left(1 - \frac{x(t)}{K}\right) - \mu_V(t)x(t) \\
\Rightarrow \frac{dx(t)}{dt} &= \left(\rho_V(t) - \mu_V(t)\right)x(t) - \frac{\beta(t)}{K}x^2(t) \\
\Rightarrow \frac{dx(t)}{x^2(t)dt} - \frac{\left(\rho_V(t) - \mu_V(t)\right)}{x(t)} &= -\frac{\rho_V(t)}{K} \text{ if } x(t) \neq 0 \\
\Rightarrow \frac{dy}{dt}(t) + \left(\rho_V(t) - \mu_V(t)\right)y(t) &= \frac{\rho_V(t)}{K} \text{ where } y(t) = \frac{1}{x(t)} \\
\Rightarrow \frac{d\left(y(t)\exp\left(\int_{t_0T}^t \left(\rho_V(s) - \mu_V(s)\right) ds\right)\right)}{dt} &= \frac{\rho_V(t)}{K}\exp\left(\int_{t_0T}^t \left(\rho_V(s) - \mu_V(s)\right)\right) ds.
\end{aligned}$$

Integrating both sides over the interval $[t_0T, t]$ results in:

$$\begin{aligned}
y(t) &= \exp\left(-\int_{t_0T}^t \left(\rho_V(s) - \mu_V(s)\right) ds\right)\left(y(t_0T) + \int_{t_0T}^t \frac{\rho_V(s)}{K}\exp\left(\int_{t_0T}^s \left(\rho_V(u) - \mu_V(u)\right) du\right)\right) \\
\Rightarrow x(t) &= \frac{1}{\exp(-\left(\varphi(t) - \varphi(t_0T)\right))\left(y(t_0T) + \int_{t_0T}^t \frac{\rho_V(s)}{K}\exp\left(\varphi(s) - \varphi(t_0T)\right)\right)} \\
&= \frac{e^{\varphi(t)}}{\frac{e^{\varphi(t_0T)}}{x(t_0T)} + \int_{t_0T}^t \frac{\rho_V(s)}{K} e^{\varphi(s)} ds} \\
&= \frac{e^{\varphi(t)}}{C_{t_0T} + \int_0^t \frac{\rho_V(s)}{K} e^{\varphi(s)} ds},
\end{aligned}$$

where

$$\varphi(t) = \int_0^t \left(\rho_V(s) - \mu_V(s)\right) ds, \quad C_{t_0T} = \frac{e^{\varphi(t_0T)}}{x(t_0T)} - \int_0^{t_0T} \frac{\rho_V(s)}{K} e^{\varphi(s)} ds.$$

If $t_0T < (1-\gamma)T$, $C = e^{t_0T(\rho-\mu_V)}\left(\frac{1}{x_0} - \frac{\rho}{T(\rho-\mu_V)}\right) + \frac{\rho}{T(\rho-\mu_V)}$. Assume that $\rho_V(t) =$

$\rho_V(t)$ and $\mu_V(t) = \mu_V(t)$ are T - periodic functions, we have

$$\varphi(t) = \int_0^t \rho_V(s) - \mu_V(s)ds = \int_0^t \left(\beta_1\left(\frac{s}{T}\right) - \mu_1\left(\frac{s}{T}\right)\right) ds = T\varphi_1\left(\frac{t}{T}\right).$$

Therefore $\beta_1(t) = \rho_V(tT)$, $\mu_1(t) = \mu_V(tT)$ and $\varphi_1(t) = \frac{\varphi(tT)}{T}$ are periodic functions with period 1. Without say anything, we keep in mind $\beta_1(t) = \rho_V(t), \mu_1(s) = \mu_V(s), \varphi_1(t) = \varphi(t)$ are $1-$ periodic function. We have

$$\begin{aligned}
&\varphi(t+nT) = \sum_{k=0}^{n-1} \int_{kT}^{(k+1)T} (\rho_V(s) - \mu_V(s))\, ds + \int_{nT}^{t+nT} (\rho_V(s) - \mu_V(s))\, ds \\
\Leftrightarrow\ &\varphi(t+nT) = \varphi(t) + \sum_{k=0}^{n-1} \int_0^T (\rho_V(s) - \mu_V(s))\, ds \\
\Leftrightarrow\ &\varphi(t+nT) = \varphi(t) + n\varphi(T).
\end{aligned}$$

We also have

$$\begin{aligned}
&\frac{1}{x(t)} = e^{-\varphi(t)}\left(\frac{e^{\varphi(t_0T)}}{x(t_0T)} - \int_0^{t_0T} \frac{\rho_V(s)}{K} e^{\varphi(s)} ds + \int_0^t \frac{\rho_V(s)}{K} e^{\varphi(s)} ds\right) \quad \forall t > 0 \\
\Rightarrow\ &\frac{1}{x(t)} = e^{-\varphi(t)}\left(C + \int_0^t \frac{\rho_V(s)}{K} e^{\varphi(s)} ds\right) \quad \forall t \geq 0,
\end{aligned}$$

where with $C = \dfrac{e^{\varphi(t_0T)}}{x(t_0T)} - \int_0^{t_0T} \rho_V(s) e^{\varphi(s)} ds = e^{t_0T(\rho-\mu_V)}\left(\dfrac{1}{x_0} - \dfrac{\rho}{\rho-\mu_V}\right) + \dfrac{\rho}{\rho-\mu_V}$.

$$\begin{aligned}
\Rightarrow\ &\frac{1}{x(t+nT)} = e^{-\varphi(t+nT)}\left(C + \int_0^{t+nT} \frac{\rho_V(s)}{K} e^{\varphi(s)} ds\right) \quad \forall 0 \leq t < T \\
\Leftrightarrow\ &\frac{1}{x(t+nT)} = e^{-\varphi(t)-n\varphi(T)}\left(C + \sum_{k=0}^{n-1} \int_{kT}^{(k+1)T} \frac{\rho_V(s)}{K} e^{\varphi(s)} ds + \int_{nT}^{nT+t} \frac{\rho_V(s)}{K} e^{\varphi(s)} ds\right) \\
\Leftrightarrow\ &\frac{1}{x(t+nT)} = e^{-\varphi(t)-n\varphi(T)}\left(C + \sum_{k=0}^{n-1} \int_0^T \frac{\rho_V(s)}{K} e^{\varphi(s)+k\varphi(T)} ds + \int_0^t \frac{\rho_V(s)}{K} e^{\varphi(s)+n\varphi(T)} ds\right) \\
\Leftrightarrow\ &\frac{1}{x(t+nT)} = e^{-\varphi(t)}\left(Ce^{-n\varphi(T)} + \frac{1-e^{-n\varphi(T)}}{e^{\varphi(T)}-1} \int_0^T \frac{\rho_V(s)}{K} e^{\varphi(s)} ds + \int_0^t \frac{\rho_V(s)}{K} e^{\varphi(s)} ds\right).
\end{aligned}$$

Therefore,

$$x(t+nT) = \frac{e^{\varphi(t)}}{Ce^{-n\varphi(T)} + \frac{1-e^{-n\varphi(T)}}{e^{\varphi(T)}-1} \int_0^T \frac{\rho_V(s)}{K} e^{\varphi(s)} ds + \int_0^t \frac{\rho_V(s)}{K} e^{\varphi(s)} ds}, \tag{4.63}$$

where

$$C = e^{t_0 T(\rho-\mu_V)}\left(\frac{1}{x_0} - \frac{\rho}{K(\rho-\mu_V)}\right) + \frac{\rho}{K(\rho-\mu_V)}.$$

Assume that $\varphi(T) > 0$, the solution of ODE (4.61) converges to the following periodic attractor:

$$x^\star(t) = \frac{e^{\varphi(t)}}{\int_0^t \frac{\rho_V(s)}{K} e^{\varphi(s)} ds + \frac{1}{e^{\varphi(T)}-1}\int_0^T \frac{\rho_V(s)}{K} e^{\varphi(s)} ds}. \tag{4.64}$$

□

Proposition 20. *Let $t_1 \in [(1-\sigma)T, T)$, with $\hat{N}_V$ is given by* (4.62)*, there exist $t_0 \in [0, (1-\sigma)T)$ satisfies $\hat{N}_V(t_1) = \hat{N}_V(t_0)$ and*

$$t_0 = \frac{1}{\rho-\mu_V}\left(T(1-\sigma)\rho - t_1\mu_V + \log\left(1 - D\frac{\rho-\mu_V}{\rho}\right)\right. \tag{4.65}$$
$$\left. - \log\left(1 - D\frac{\rho-\mu_V}{\rho} + e^{T(1-\sigma)\rho - t_1\mu_V} - e^{T(1-\sigma)(\rho-\mu_V)}\right)\right)$$

with

$$D = \frac{1}{e^{\varphi(T)}-1}\int_0^T \rho_V(s) e^{\varphi(s)} ds. \tag{4.66}$$

Proof. Since $\hat{N}_V(t)$ is a periodic function on $[0, T)$ therefore, with given $t_1 \in [T(1-\sigma), T)$ there exists $t_0 \in [0, (1-\sigma)T)$ such that $\hat{N}_V(t_1) = \hat{N}_V(t_0)$. We have

$$\frac{e^{t_0(\rho-\mu_V)}}{e^{t_0(\rho-\mu_V)} - 1 + D\frac{\rho-\mu_V}{\rho}} = \frac{e^{T(1-\sigma)\rho - t_1\mu_V}}{e^{T(1-\sigma)(\rho-\mu_V)} - 1 + D\frac{\rho-\mu_V}{\rho}}$$
$$\Leftrightarrow e^{t_0(\rho-\mu_V)}\left(e^{T(1-\sigma)(\rho-\mu_V)} - e^{T(1-\sigma)\rho - t_1\mu_V} - 1 + D\frac{\rho-\mu_V}{\rho}\right) = e^{T(1-\sigma)\rho - t_1\mu_V}\left(-1 + D\frac{\rho-\mu_V}{\rho}\right),$$

therefore

$$t_0 = \frac{1}{\rho-\mu_V}\left(T(1-\sigma)\rho - t_1\mu_V + \log\left(D\frac{\rho-\mu_V}{\rho} - 1\right)\right.$$
$$\left. - \log\left(D\frac{\rho-\mu_V}{\rho} - 1 + e^{T(1-\sigma)(\rho-\mu_V)} - e^{T(1-\sigma)\rho - t_1\mu_V}\right)\right)$$

□

4.6.6 The periodic case

In this section, we assume that the dormancy and recovery rate are fixed meanwhile the growth rate of the vector fluctuates seasonally. We can assume that in one period the growth rate has the following step form:

$$\rho_V(t) = \begin{cases} \rho & \text{if } 0 \leq \left\{\frac{t}{T}\right\} < 1-\sigma \\ 0 & \text{otherwise} \end{cases} \tag{4.67}$$

4.6.7 Influence of seasonality on the growth rate λ

We linearise the system (4.42) near the disease free equilibrium ($S_H = 1, S_V = N_V$, $D_H = R_H = I_H = I_V = 0$).

$$\frac{d\mathbf{X}}{dt}(t) = \mathbf{A}(t)\mathbf{X} \tag{4.68}$$

where,

$$\mathbf{A}(t) = \begin{pmatrix} -(\gamma + d + \mu_H) & r & \beta_V \\ d & -(r + \mu_H) & 0 \\ \beta_H \hat{N}_V(t) & \alpha\beta_H \hat{N}_V(t) & -\mu_V \end{pmatrix} \tag{4.69}$$

Since $\rho_V(t)$ is a periodic function with period T, and σ measures the duration of the effects of seasonality. Let $\mathbf{L} = \Phi_{\mathbf{A}}(T)$ be the monodromy matrix associated to matrix $\mathbf{A}(t)$ and $\lambda = \rho(\mathbf{L})$ the spectral radius of its monodromy matrix.

The Taylor expansion of the transition matrix $\mathbf{A}(t)$ for small σ give

$$\mathbf{A}(t) = \mathbf{A}_0 + \mathbf{A}_1\sigma + o(\sigma), \tag{4.70}$$

with $o(\sigma)$ uniform in time.

Assumption: By the transformation $\mathbf{A}_0 \to \mathbf{A}_0 + \kappa\mathbf{I}$ translate λ_0 to $\lambda_0 \to \lambda_0 \exp(\kappa T)$. Without loss in generality and to simplify statements, we assume that $R_0 = \lambda_0 = 1$.

Proposition 21. *For $\lambda = \rho(\Phi_{\boldsymbol{A}}(T))$ the spectral radius of the monodromy matrix we have*

$$\lambda = 1 + \sigma\lambda_1 + o(\sigma) \tag{4.71}$$

with $\lambda_1 < 0$ therefore the decrease in the favorable time period leads to a decrease in the growth rate of the population.

Proof. If $0 \leq t < (1-\sigma)T$ we can rewrite $\hat{N}_V(t)$ as the form:

$$\begin{aligned}
\hat{N}_V(t) &= \frac{Ke^{\varphi(t)}}{\int_0^t \rho_V(s)e^{\varphi(s)}ds + \dfrac{K}{\hat{N}_V(0)}} \\
&= \hat{N}_V(0)\frac{Ke^{\varphi(t)}}{\hat{N}_V(0)\int_0^t \rho_V(s)e^{\varphi(s)}ds + K} \\
&= \hat{N}_V(0)\left(1 + \frac{Ke^{t(\rho-\mu_V)} - \hat{N}_V(0)\frac{\rho}{\rho-\mu_V}\left(e^{t(\rho-\mu_V)}-1\right) - K}{\hat{N}_V(0)\dfrac{\rho}{\rho-\mu_V}\left(e^{t(\rho-\mu_V)}-1\right) + K}\right) \\
&= \hat{N}_V(0)\left(1 + \frac{\left(K - \hat{N}_V\frac{\rho}{\rho-\mu_V}\right)\left(e^{t(\rho-\mu_V)}-1\right)}{\hat{N}_V(0)\dfrac{\rho}{\rho-\mu_V}\left(e^{t(\rho-\mu_V)}-1\right) + K}\right).
\end{aligned}$$

We have

$$\begin{aligned}
\hat{N}_V(0) &= \frac{K\left(e^{\varphi(T)}-1\right)}{\int_0^T \rho_V(s)e^{\varphi(s)}ds} \\
&= \frac{K\left(e^{T((1-\sigma)\rho-\mu_V)}-1\right)}{\dfrac{\rho}{\rho-\mu_V}\left(e^{T(1-\sigma)(\rho-\mu_V)}-1\right)} \\
&= \frac{K(\rho-\mu_V)}{\rho}\left(1 + \frac{e^{T((1-\sigma)\rho-\mu_V)} - e^{T(1-\sigma)(\rho-\mu_V)}}{e^{T(1-\sigma)(\rho-\mu_V)}-1}\right) \\
&= \frac{K(\rho-\mu_V)}{\rho}\left(1 + \frac{e^{T(1-\sigma)(\rho-\mu_V)}\left(e^{-\sigma T\mu_V}-1\right)}{e^{T(1-\sigma)(\rho-\mu_V)}-1}\right) \\
&= \frac{K(\rho-\mu_V)}{\rho}\left(1 - \frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}\right) + O(\sigma).
\end{aligned}$$

Furthermore,

$$\begin{aligned}
\frac{K}{\hat{N}_V(0)}\frac{\rho-\mu_V}{\rho} &= \frac{\int_0^T \rho_V(s)e^{\varphi(s)}ds}{e^{\varphi(T)}-1}\frac{\rho-\mu_V}{\rho} \\
&= \frac{e^{T(\rho-\mu_V)(1-\sigma)}-1}{e^{T(\rho(1-\sigma)-\mu_V)}-1} \\
&= \frac{e^{T(\rho(1-\sigma)-\mu_V)}e^{\sigma T\mu_V}-1}{e^{T(\rho(1-\sigma)-\mu_V)}-1} \\
&= \frac{e^{T(\rho(1-\sigma)-\mu_V)}e^{\sigma T\mu_V} - e^{\sigma T\mu_V} + e^{\sigma T\mu_V} - 1}{e^{T(\rho(1-\sigma)-\mu_V)}-1}
\end{aligned}$$

$$
\begin{aligned}
&= e^{\sigma T \mu_V} + \frac{e^{\sigma T \mu_V} - 1}{e^{T(\rho(1-\sigma)-\mu_V)} - 1} \\
&= 1 + \frac{\sigma T \mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)} - 1} + O(\sigma) \text{ when } \sigma \sim 0.
\end{aligned}
$$

The preceding argument yields, for $t \in [0, (1-\sigma)T)$

$$
\begin{aligned}
\hat{N}_V(t) &= \hat{N}_V(0) \left(1 + \frac{\left(K - \hat{N}_V \frac{\rho}{\rho-\mu_V}\right)\left(e^{t(\rho-\mu_V)} - 1\right)}{\hat{N}_V(0)\frac{\rho}{\rho-\mu_V}\left(e^{t(\rho-\mu_V)} - 1\right) + K} \right) \\
&= \hat{N}_V(0) \left(1 + \frac{\left(\frac{K}{\hat{N}_V(0)\frac{\rho}{\rho-\mu_V}} - 1\right)\left(e^{t(\rho-\mu_V)} - 1\right)}{e^{t(\rho-\mu_V)} - 1 + \frac{K}{\hat{N}_V(0)\frac{\rho}{\rho-\mu_V}}} \right) \\
&= \hat{N}_V(0) \left(1 + \frac{\frac{\sigma T \mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)} - 1}\left(e^{t(\rho-\mu_V)} - 1\right)}{e^{t(\rho-\mu_V)} + \frac{\sigma T \mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)} - 1}} \right) + O(\sigma) \\
&= \hat{N}_V(0) \left(1 + \frac{\sigma T \mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)} - 1} \frac{e^{t(\rho-\mu_V)} - 1}{e^{t(\rho-\mu_V)}} \right) + O(\sigma) \\
&= \frac{K(\rho-\mu_V)}{\rho} \left(1 - \frac{\sigma T \mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)} - 1} \right) \left(1 + \frac{\sigma T \mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)} - 1} \frac{e^{t(\rho-\mu_V)} - 1}{e^{t(\rho-\mu_V)}} \right) + O(\sigma) \\
&= \frac{K(\rho-\mu_V)}{\rho} \left(1 - \frac{\sigma T \mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)} - 1} e^{-t(\rho-\mu_V)} \right) + O(\sigma).
\end{aligned}
$$

If $(1-\sigma)\,T \leq t < T$ we have,

$$
\begin{aligned}
\hat{N}_V(t) &= \frac{K e^{\varphi(t)}}{\int_0^t \rho_V(s) e^{\varphi(s)} ds + \frac{K}{\hat{N}_V(0)}} \\
&= \frac{K e^{\varphi(t)}}{\frac{K(e^{\varphi(T)} - 1)}{\hat{N}_V(0)} + \frac{K}{\hat{N}_V(0)}} \\
&= \hat{N}_V(0) \frac{e^{\varphi(t)}}{e^{\varphi(T)}} = \hat{N}_V(0) e^{(T-t)\mu_V} \\
&= \frac{K(\rho-\mu_V)}{\rho} \left(1 - \frac{\sigma T \mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)} - 1} \right) e^{\mu_V (T-t)} + O(\sigma).
\end{aligned}
$$

Since

$$\begin{aligned}\mathbb{1}_{0\leq\left\{\frac{t}{T}\right\}<1-\sigma} &= 1+\sigma\lim_{\epsilon\to 0}\frac{\mathbb{1}_{0\leq\left\{\frac{t}{T}\right\}<1-\sigma-\epsilon}-\mathbb{1}_{0\leq\left\{\frac{t}{T}\right\}<1-\sigma}}{\epsilon}+O(\sigma)\\ &= 1-\sigma\lim_{\epsilon\to 0}\frac{\mathbb{1}_{1-\sigma-\epsilon\leq\left\{\frac{t}{T}\right\}<1-\sigma}}{\epsilon}+O(\sigma)\\ &= 1-\sigma\delta_{1-\sigma}\left(\left\{\frac{t}{T}\right\}\right)+O(\sigma)\end{aligned}$$

We have

$$\begin{aligned}A(t) &= \left[\frac{K(\rho-\mu_V)}{\rho}\left(1-\frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}e^{-T(\rho-\mu_V)\left\{\frac{t}{T}\right\}}\right)\right]\mathbb{1}_{0\leq\left\{\frac{t}{T}\right\}<(1-\sigma)}\\ &\quad+\left[\frac{K(\rho-\mu_V)}{\rho}\left(1-\frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}\right)e^{\mu_V T\left(1-\left\{\frac{t}{T}\right\}\right)}\right]\mathbb{1}_{(1-\sigma)\leq\left\{\frac{t}{T}\right\}<1}+O(\sigma)\\ &= \frac{K(\rho-\mu_V)}{\rho}\left[1-\frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}e^{-T(\rho-\mu_V)\left\{\frac{t}{T}\right\}}\right.\\ &\quad\left.+\left(\left(1-\frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}\right)e^{\mu_V T\left(1-\left\{\frac{t}{T}\right\}\right)}-1+\frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}e^{-T(\rho-\mu_V)\left\{\frac{t}{T}\right\}}\right)\mathbb{1}_{(1-\sigma)\leq\left\{\frac{t}{T}\right\}<1}\right]+O(\sigma)\\ &= \frac{K(\rho-\mu_V)}{\rho}\left(1-\frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}e^{-T(\rho-\mu_V)\left\{\frac{t}{T}\right\}}+\left(e^{\mu_V T\left(1-\left\{\frac{t}{T}\right\}\right)}-1\right)\sigma\delta_{1-\sigma}\left(\left\{\frac{t}{T}\right\}\right)\right)+O(\sigma)\\ &= \frac{K(\rho-\mu_V)}{\rho}\left(1-\frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}e^{-T(\rho-\mu_V)\left\{\frac{t}{T}\right\}}+\left(e^{\mu_V T\sigma}-1\right)\sigma\delta_{1-\sigma}\left(\left\{\frac{t}{T}\right\}\right)\right)+O(\sigma)\\ &= \frac{K(\rho-\mu_V)}{\rho}\left(1-\frac{\sigma T\mu_V e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}e^{-T(\rho-\mu_V)\left\{\frac{t}{T}\right\}}\right)+O(\sigma).\end{aligned}$$

When σ is closed to 0, we can rewrite $\mathbf{A}(t)$ as the following form $\mathbf{A}(t)=\mathbf{A}_0+\mathbf{A}_1 e^{-T\left\{\frac{t}{T}\right\}(\rho-\mu_V)}\sigma+O(\sigma)$ where

$$\mathbf{A}_0=\begin{pmatrix}-(\gamma+d+\mu_H) & r & \beta_V\\ d & -(r+\mu_H) & 0\\ \beta_H\dfrac{K(\rho-\mu_V)}{\rho} & \alpha\beta_H\dfrac{K(\rho-\mu_V)}{\rho} & -\mu_V\end{pmatrix}, \tag{4.72}$$

and

$$\mathbf{A}_1=-T\mu_V\beta_H\frac{K(\rho-\mu_V)}{\rho}\frac{e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1}\begin{pmatrix}0&0&0\\0&0&0\\1&\alpha&0\end{pmatrix}. \tag{4.73}$$

Since matrix $\mathbf{A}_0$ is cooperative and irreducible, there exists $\mathbf{v}_0, \mathbf{u}_0$ are the positive left(right) eigenvector associated to matrix $\mathbf{A}_0$ correspond eigenvalue 0. We use the Duhamel's formula with $\mathbf{L} = \mathbf{L}_0 + \epsilon \mathbf{L}_1 + o(\epsilon)$ where

$$\mathbf{L}_0 = e^{T\mathbf{A}_0}, \tag{4.74}$$

$$\mathbf{L}_1 = \int_0^T \mathbf{v}_0 e^{(T-s)\mathbf{A}_0} \mathbf{A}_1 e^{s\mathbf{A}_0} \mathbf{u}_0 e^{-s(\rho-\mu_V)} ds. \tag{4.75}$$

Let $\mathbf{u}_0 = (a_0, a_1, a_2)$, $\mathbf{v}_0 = (b_0, b_1, b_2)$, since $\mathbf{A}_0\mathbf{u}_0 = 0 = \mathbf{v}_0\mathbf{A}_0$ implies the following relationship:

$$\begin{aligned} a_1 &= \frac{d}{r+\mu_H} a_0, \\ a_2 &= \frac{\beta_H K(\rho-\mu_V)\left(1+\frac{d}{r+\mu_H}\alpha\right) a_0}{\rho\mu_V}. \end{aligned}$$

Explanation

$$\begin{aligned} & \beta_H \frac{K(\rho-\mu_V)}{\rho}(a_0 + a_1\alpha) - \mu_V a_2 = 0 \\ \Leftrightarrow \quad & \beta_H \frac{K(\rho-\mu_V)}{\rho}\left(1+\frac{d}{r+\mu_H}\alpha\right) a_0 - \mu_V a_2 = 0 \\ \Leftrightarrow \quad & a_2 = \frac{\beta_H K(\rho-\mu_V)\left(1+\frac{d}{r+\mu_H}\alpha\right) a_0}{\rho\mu_V}, \end{aligned}$$

and

$$b_1 = \frac{r + \alpha\beta_H\beta_V \frac{K(\rho-\mu_V)}{\rho} \frac{}{\mu_V}}{r+\mu_H} b_0, \tag{4.76}$$

$$b_2 = \frac{\beta_V}{\mu_V} b_0. \tag{4.77}$$

We have

$$\begin{aligned} & rb_0 - (r+\mu_H)\, b_1 + \alpha\beta_H \frac{K\,(\rho-\mu_V)}{\rho} b_2 \quad = 0 \\ \Leftrightarrow \quad & rb_0 - (r+\mu_H)\, b_1 + \alpha\beta_H \frac{K\,(\rho-\mu_V)}{\rho} \frac{\beta_V}{\mu_V} b_0 \quad = 0 \\ \Leftrightarrow \quad & b_1 = \frac{r + \alpha\beta_H \dfrac{K\,(\rho-\mu_V)}{\rho} \dfrac{\beta_V}{\mu_V}}{r+\mu_H} b_0 \quad . \end{aligned}$$

Furthermore, with $\langle \mathbf{v}_0, \mathbf{u}_0 \rangle = 1$ we have

$$\sum_{i=0}^{2} a_i b_i = 1 \Rightarrow a_0 b_0 \left(1 + \frac{d\left(r + \alpha\beta_H \frac{K(\rho-\mu_V)}{\rho}\frac{\beta_V}{\mu_V}\right)}{(r+\mu_H)^2} + \frac{\beta_V \beta_H K\,(\rho-\mu_V)\left(1+\frac{\alpha d}{r+\mu_H}\right)}{\rho\mu_V^2} \right) = 1$$

This implies $a_0 b_0 = \dfrac{1}{\left(1 + \dfrac{d\left(r + \alpha\beta_H \dfrac{K\,(\rho-\mu_V)}{\rho}\dfrac{\beta_V}{\mu_V}\right)}{(r+\mu_H)^2} + \dfrac{\beta_V \beta_H K\,(\rho-\mu_V)\left(1+\dfrac{\alpha d}{r+\mu_H}\right)}{\rho\mu_V^2} \right)}$.

Assume that $\mathbf{v}$ and $\mathbf{u}$ are the left and right eigenvectors associated to matrix $\mathbf{L}$. The Taylor expansion give

$$\mathbf{u} = \mathbf{u}_0 + \mathbf{u}_1\sigma + o(\sigma) \tag{4.78}$$

$$\mathbf{v} = \mathbf{v}_0 + \mathbf{v}_1\sigma + o(\sigma) \tag{4.79}$$

therefore, by using the Taylor expansion again for $\mathbf{L}$ yields

$$\mathbf{L}_1\mathbf{u}_0 + \mathbf{L}_0\mathbf{u}_1 = \lambda_1\mathbf{u}_0 + \lambda_0\mathbf{u}_1. \tag{4.80}$$

Multiply both sides on the left by $\mathbf{v}_0$, combined with $\mathbf{v}_0\mathbf{L}_0 = \mathbf{v}_0, \mathbf{v}_0\mathbf{u}_0 = 1$.

$$\begin{aligned} \lambda_1 = \mathbf{v}_0\mathbf{L}_1\mathbf{u}_0 &= \int_0^T \mathbf{v}_0 e^{(T-s)\mathbf{A}_0}\mathbf{A}_1 e^{s\mathbf{A}_0}\mathbf{u}_0 e^{-s(\rho-\mu_V)} ds \\ &= \int_0^T \mathbf{v}_0\mathbf{A}_1\mathbf{u}_0 e^{-s(\rho-\mu_V)} ds \\ &= \mathbf{v}_0\mathbf{A}_1\mathbf{u}_0 \frac{1-e^{-T(\rho-\mu_V)}}{\rho-\mu_V} \\ &= -T\mu_V\beta_H \frac{K(\rho-\mu_V)}{\rho} \frac{e^{T(\rho-\mu_V)}}{e^{T(\rho-\mu_V)}-1} b_2\,(a_0+\alpha a_1)\, \frac{1-e^{-T(\rho-\mu_V)}}{\rho-\mu_V} \end{aligned}$$

$$= -T\mu_V\beta_H\frac{\beta_V}{\mu_V}\frac{K}{\rho}a_0b_0\left(1+\frac{\alpha d}{r+\mu_H}\right)$$

$$= -\frac{T\beta_H\beta_V\dfrac{K}{\rho}\left(1+\dfrac{\alpha d}{r+\mu_H}\right)}{1+\dfrac{d\left(r+\alpha\beta_H\dfrac{K(\rho-\mu_V)}{\rho}\dfrac{\beta_V}{\mu_V}\right)}{(r+\mu_H)^2}+\dfrac{\beta_V\beta_H K(\rho-\mu_V)\left(1+\dfrac{\alpha d}{r+\mu_H}\right)}{\rho\mu_V^2}} < 0.$$

□

Proposition 22. *The mean of the vector population is given by:*

$$\left\langle \hat{N}_V \right\rangle = \frac{1}{T}\left(\frac{K(\rho-\mu)}{\rho}(1-\sigma)T - \frac{K\sigma T\mu}{\rho} + \frac{K(\rho-\mu)}{\rho}\frac{\tau_1-1}{\tau_2-1}\frac{\left(e^{\sigma T\mu}-1\right)}{\mu}\right), \tag{4.81}$$

with $\tau_1 = e^{T((1-\sigma)\rho-\mu)}$ *and* $\tau_2 = e^{T(1-\sigma)(\rho-\mu)}$ *and it decreases with increasing seasonality.*

Proof. If $0 \leq \left\{\frac{t}{T}\right\} < 1-\sigma$, we have

$$\hat{N}_V(t) = \hat{N}_V(0)\left[1+\frac{\left(K-\hat{N}_V(0)\dfrac{\rho}{\rho-\mu}\right)\left(e^{t(\rho-\mu)}-1\right)}{\hat{N}_V(0)\dfrac{\rho}{\rho-\mu}\left(e^{t(\rho-\mu)}-1\right)+K}\right]$$

$$= \hat{N}_V(0)\left[1+\frac{\left(K-\hat{N}_V(0)\dfrac{\rho}{\rho-\mu}\right)\left(e^{t(\rho-\mu)}-1\right)}{\hat{N}_V(0)\dfrac{\rho}{\rho-\mu}\left(e^{t(\rho-\mu)}-1+\dfrac{K(\rho-\mu)}{\hat{N}_V(0)\rho}\right)}\right]$$

$$= \hat{N}_V(0)\left[1+\left(\frac{K(\rho-\mu)}{\hat{N}_V(0)\rho}-1\right)\left(1-\frac{\dfrac{K(\rho-\mu)}{\hat{N}_V(0)\rho}}{e^{t(\rho-\mu)}-1+\dfrac{K(\rho-\mu)}{\hat{N}_V(0)\rho}}\right)\right]$$

$$= \hat{N}_V(0)\left[\frac{K(\rho-\mu)}{\hat{N}_V(0)\rho}-\frac{\left(\dfrac{K(\rho-\mu)}{\hat{N}_V(0)\rho}-1\right)\dfrac{K(\rho-\mu)}{\hat{N}_V(0)\rho}}{e^{t(\rho-\mu)}-1+\dfrac{K(\rho-\mu)}{\hat{N}_V(0)\rho}}\right].$$

From definition of τ_1 and τ_2 implies $\tau_2 = \tau_1 e^{\sigma T\mu}$, and

$$\frac{\partial\tau_1}{\partial\sigma} = -T\rho\tau_1, \qquad \frac{\partial\tau_2}{\partial\sigma} = -T(\rho-\mu)\tau_2.$$

We have

$$\begin{aligned}
&\int_0^{(1-\sigma)T} \frac{dt}{e^{t(\rho-\mu)} + \frac{K(\rho-\mu)}{\hat{N}_V(0)\rho} - 1} \\
&= \frac{1}{\rho-\mu} \int_0^{(1-\sigma)T} \frac{de^{t(\rho-\mu)}}{e^{t(\rho-\mu)}\left(e^{t(\rho-\mu)} + \kappa\right)} \text{ with } \kappa = \frac{K(\rho-\mu)}{\hat{N}_V(0)\rho} - 1 \\
&= \frac{1}{\kappa(\rho-\mu)} \ln\left(\frac{e^{t(\rho-\mu)}}{e^{t(\rho-\mu)} + \kappa}\right)\Bigg|_0^{(1-\sigma)T} \\
&= \frac{1}{(\rho-\mu)\kappa} \ln \frac{\tau_2(\kappa+1)}{\tau_2+\kappa}.
\end{aligned}$$

Since $\hat{N}_V(0) = \frac{K(\rho-\mu)}{\rho}\frac{\tau_1-1}{\tau_2-1}$ lead to

$$\begin{aligned}
\kappa &= \frac{K(\rho-\mu)}{\hat{N}_V(0)\rho} - 1 = \frac{\tau_2-1}{\tau_1-1} - 1 \\
\Rightarrow \frac{e^{(1-\sigma)T(\rho-\mu)}(\kappa+1)}{e^{(1-\sigma)T(\rho-\mu)}+\kappa} &= \frac{\tau_2(\tau_2-1)}{(\tau_1-1)\left(\tau_2 + \frac{\tau_2-\tau_1}{\tau_1-1}\right)} \\
&= \frac{\tau_2(\tau_2-1)}{(\tau_1-1)\tau_2 + \tau_2 - \tau_1} \\
&= \frac{\tau_2(\tau_2-1)}{\tau_1(\tau_2-1)} = \frac{\tau_2}{\tau_1} = e^{\sigma T\mu} \\
\Rightarrow \int_0^{(1-\sigma)T} \frac{dt}{e^{t(\rho-\mu)} + \frac{K(\rho-\mu)}{\hat{N}_V(0)\rho} - 1} &= \frac{1}{(\rho-\mu)\kappa} \ln \frac{e^{(1-\sigma)T(\rho-\mu)}(\kappa+1)}{e^{(1-\sigma)T(\rho-\mu)}+\kappa} = \frac{\sigma T\mu}{\kappa(\rho-\mu)} \\
&= \frac{\sigma T\mu(\tau_1-1)}{(\tau_2-\tau_1)(\rho-\mu)},
\end{aligned}$$

and

$$\begin{aligned}
&\hat{N}_V(0)\left(1 - \frac{\hat{N}_V(0)\rho}{K(\rho-\mu)}\right)\left(\frac{K(\rho-\mu)}{\hat{N}_V(0)\rho}\right)^2 \frac{\sigma T\mu}{\kappa(\rho-\mu)} \\
&= \frac{K(\rho-\mu)}{\rho}\frac{\tau_1-1}{\tau_2-1}\left(1 - \frac{\tau_1-1}{\tau_2-1}\right)\left(\frac{\tau_1-1}{\tau_2-1}\right)^2 \frac{\sigma T\mu(\tau_1-1)}{(\tau_2-\tau_1)(\rho-\mu)} \\
&= \frac{K\sigma T\mu}{\rho}.
\end{aligned}$$

Therefore

$$\int_0^{(1-\sigma)T} \hat{N}_V(s)ds = \frac{K(\rho-\mu)}{\rho}(1-\sigma)T - \hat{N}_V(0)\left(1-\frac{\hat{N}_V(0)\rho}{K(\rho-\mu)}\right)\left(\frac{K(\rho-\mu)}{\hat{N}_V(0)\rho}\right)^2 \frac{\sigma T\mu}{\kappa(\rho-\mu)}$$
$$= \frac{K(\rho-\mu)}{\rho}(1-\sigma)T - \frac{K\sigma T\mu}{\rho}. \tag{4.82}$$

On the other hand, if $1-\sigma \leq \left\{\frac{t}{T}\right\} < 1$, $\hat{N}_V(t) = \hat{N}_V(0)e^{(T-t)\mu_V}$,

$$\begin{aligned}\int_{(1-\sigma)T}^{T} \hat{N}_V(s)ds &= \hat{N}_V(0)\int_{(1-\sigma)T}^{T} e^{(T-t)\mu}dt \\ &= \frac{\hat{N}_V(0)\left(e^{\sigma T\mu}-1\right)}{\mu} \\ &= \frac{K(\rho-\mu)}{\rho}\frac{\tau_1-1}{\tau_2-1}\frac{\left(e^{\sigma T\mu}-1\right)}{\mu}.\end{aligned} \tag{4.83}$$

Summing up the expressions from (4.82) and (4.83) gives:

$$\left\langle \hat{N}_V \right\rangle = \frac{1}{T}\left(\frac{K(\rho-\mu)}{\rho}(1-\sigma)T - \frac{K\sigma T\mu}{\rho} + \frac{K(\rho-\mu)}{\rho}\frac{\tau_1-1}{\tau_2-1}\frac{\left(e^{\sigma T\mu}-1\right)}{\mu}\right). \tag{4.84}$$

We pose

$$\mathbf{A}_1 = \frac{1}{T}\left(\frac{K(\rho-\mu)}{\rho}(1-\sigma)T - \frac{K\sigma T\mu}{\rho}\right)$$
$$A_2 = \frac{K(\rho-\mu)}{T\rho\mu}\frac{\tau_1-1}{\tau_2-1}\left(e^{\sigma T\mu}-1\right).$$

First of all, we will compute the derivative for each term.

$$\frac{\partial \mathbf{A}_1}{\partial \sigma} = -\frac{K(\rho-\mu)}{\rho} - K\mu = -K. \tag{4.85}$$

We have

$$\frac{\tau_1-1}{\tau_2-1}\left(e^{\sigma T\mu}-1\right) = 1 + \frac{2-e^{\sigma T\mu}-\tau_1}{\tau_2-1}$$
$$\Rightarrow \frac{\partial}{\partial\sigma}\frac{\tau_1-1}{\tau_2-1}\left(e^{\sigma T\mu}-1\right) = \frac{\left(-T\mu e^{\sigma T\mu}+T\rho\tau_1\right)(\tau_2-1)+\left(2-e^{\sigma T\mu}-\tau_1\right)T(\rho-\mu)\tau_2}{(\tau_2-1)^2}$$

$$
\begin{aligned}
&= \frac{-T\rho e^{\sigma T\mu}\tau_2 + T\mu\tau_1\tau_2 + T\mu e^{\sigma T\mu} - T\rho\tau_1 + 2T\left(\rho-\mu\right)\tau_2}{\left(\tau_2-1\right)^2} \\
&\leq \frac{-T\rho\tau_1\left(\left(e^{\sigma T\mu}\right)^2+1\right) + T\mu e^{\sigma T\mu}\left(1+\left(\tau_1\right)^2\right) + 2T\left(\rho-\mu\right)\tau_2}{\left(\tau_2-1\right)^2} \\
&\leq \frac{-2T\rho\tau_1 e^{\sigma T\mu} + T\mu e^{\sigma T\mu}\left(1+\left(\tau_1\right)^2\right) + 2T\left(\rho-\mu\right)\tau_1 e^{\sigma T\mu}}{\left(\tau_2-1\right)^2} \\
&= \frac{-2T\mu\tau_1 e^{\sigma T\mu} + T\mu e^{\sigma T\mu}\left(1+\left(\tau_1\right)^2\right)}{\left(\tau_2-1\right)^2} \\
&= \frac{T\mu e^{\sigma T\mu}\left(\tau_1-1\right)^2}{\left(\tau_2-1\right)^2} \leq T\mu.
\end{aligned}
$$

Indeed,

$$
\begin{aligned}
&\frac{e^{\sigma T\mu}\left(\tau_1-1\right)^2}{\left(\tau_2-1\right)^2} \leq 1 \\
&\Leftrightarrow e^{\sigma T\mu}\left(\tau_1-1\right)^2 \leq \left(e^{\sigma T\mu}\right)^2\tau_1^2 - 2e^{\sigma T\mu}\tau_1 + 1 \\
\Leftrightarrow \left(e^{\sigma T\mu}\right)^2\tau_1^2 - e^{\sigma T\mu}\tau_1^2 + 1 - e^{\sigma T\mu} &\geq 0 \\
\Leftrightarrow \left(e^{\sigma T\mu}\tau_1^2 - 1\right)\left(e^{\sigma T\mu}-1\right) &\geq 0 \text{ since } \tau_1 \geq 1, e^{\sigma T\mu} \geq 1.
\end{aligned}
$$

Hence

$$
\frac{\partial}{\partial\sigma}\frac{K\left(\rho-\mu\right)}{T\rho\mu}\frac{\tau_1-1}{\tau_2-1}\left(e^{\sigma T\mu}-1\right) \leq K. \tag{4.86}
$$

From (4.84) , (4.85) and (4.86) yields $\langle N_V\rangle$ is a decreasing function with respect to σ.

□

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COLLEGE ED MATHEMATIQUES
DOCTORAL STIC
PAYS DE LA LOIRE

Nantes Université

Titre : Epidémiologie et évolution des maladies infectieuses en environnement périodique

Mot clés : Environnement périodique, Model maladies, Dormance, Gradient de sélection.

Résumé : Cette thèse montre une partie des conséquences que peuvent avoir les fluctuations périodiques de l'environnement sur la dynamique des maladies infectieuses. Nous illustrons ces conséquences dans le cadre d'un pathogènes à transmission vectorielle car les insectes vecteurs sont très sensibles aux fluctuations de la température et de l'humidité. Chaque chapitre aborde un aspect différents de la saisonnaité. Le premier chapitre analyse la persistence d'un pathogène et montre comment la saisonnalité peut augmenter, ou, contraire, diminuer la persistence du pathogène. Ce premier chapitre est basée sur l'analyse d'un modèle déterministe. Dans le deuxième chapitre nous étudions les effets de la saisonnalité sur les risques d'émergences. Le modèle stochastique utilisé repose sur un scénario épidémiologique assez simple mais ils peut se généraliser à des modèles avec transmission vectorielle . Nous montrons ici comment le moment du traitement peut avoir un impact sur le risque d'émergence (ou d'éradiaction) de l'épidémie. Le troisième chapitre utilise un troisième formalisme, la dynamique adaptative, pour étudier l'évolution de la dormance et de la réactivation.

Title: Epidemiology and evolution of infectious diseases in a periodic environment

Keywords: Periodic environment, Disease models, Dormancy, Selection gradient.

Abstract: This thesis shows some of the consequences that periodic fluctuations in the environment can have on the dynamics of infectious diseases. We illustrate these consequences in the context of a vector-borne pathogen. Each chapter addresses a different aspect of seasonality. The first chapter analyzes the persistence of a pathogen and shows how seasonality can increase or decrease the persistence of the pathogen. This first chapter is based on the analysis of a deterministic model. In the second chapter, we study the effects of seasonality on the risks of emergence. The stochastic model used is based on a relatively simple epidemiological scenario but can be generalized to models with vector transmission. We show here how the timing of treatment can have an impact on the risk of emergence (or eradication) of the epidemic. The third chapter uses a third formalism, adaptive dynamics, to study the evolution of dormancy and reactivation.