A slow-fast dynamic decomposition links neutral and non-neutral coexistence in interacting multi-strain pathogens

Erida Gjini, Sten Madec

A slow-fast dynamic decomposition links neutral and non-neutral coexistence in interacting multi-strain pathogens

Erida Gjini[1*] and Sten Madec[2**]

[1]Instituto Gulbenkian de Ciência, Oeiras, Portugal
[2]University of Tours, France
[*]egjini@igc.gulbenkian.pt
[**]Sten.Madec@lmpt.univ-tours.fr

July 6, 2016

Article information

- **Short running title** Slow-fast dynamics in interacting multi-strain pathogens
- **Keywords**
  neutrality — coexistence — diversity — slow manifold— epidemiological model— coinfection
- **Article type** Research article
- **Number of words in main text** 3500
- **Number of references** 66
- **Number of figures** 4
- **Corresponding** Erida Gjini
  Instituto Gulbenkian de Ciência
  Rua da Quinta Grande 6,
  2780-156
  Oeiras
  Portugal
  Phone: +351 214 407 968
  Email: egjini@igc.gulbenkian.pt; gjini.erida@gmail.com

Abstract (126 words)

Understanding the dynamics of multi-type microbial ecosystems remains a challenge, despite advancing molecular technologies for diversity resolution within and between hosts. Analytical progress becomes difficult when modelling realistic levels of community richness, relying on computationally-intensive simulations and detailed parametrisation. Simplification of dynamics in polymorphic pathogen systems is possible using aggregation methods and the slow-fast dynamics approach. Here we develop one new such framework, tailored to the epidemiology of an endemic multi-strain pathogen. We apply Goldstone's idea of slow dynamics resulting from spontaneously broken symmetries, to study direct interactions in co-colonization, ranging from competition to facilitation between strains. The slow-fast dynamics approach interpolates between a neutral and non-neutral model for multi-strain coexistence, and quantifies the exact asymmetries that are important for the maintenance and stabilisation of diversity.

Introduction

Interacting systems of structured populations are typically hard to describe. The challenges of representing hierarchical dynamics apply in multi-species ecological ensembles (Auger, 1983; Coyte et al., 2015), multi-strain microbial pathogens (Ferguson et al., 2003; Gomes and Medley, 2002; Gupta et al., 1996), and more generally across ecosystems (Levin et al., 1997). To address these challenges, models have to rely on simplification, such as aggregation methods, separation of time scales and suitable approximation (Auger and Poggiale, 1998; De Roos et al., 2008; Kryazhimskiy et al., 2007; Levin, 1992; Levins, 1966; Rossberg and Farnsworth, 2011). The study of multi-strain pathogens is growing rapidly thanks to molecular advances, quantifying microbial diversity and host immunological history to unprecedented resolution (Biek et al., 2015; Gog and Grenfell, 2002; Grenfell et al., 2004). Yet, the principles that govern strain composition, interactions, and dynamics at the within- and between- host levels remain largely undefined.

Here we report a new analytical framework for endemic multi-strain pathogens, characterized by direct interactions among strains upon co-infection. A resident microbial strain can decrease or increase the rate of a secondary strain acquisition for the host, and different strains might exhibit different interaction types and magnitudes (Faust and Raes, 2012). How does this variation affect global epidemiological dynamics? We address this question focusing on a parsimoniuous epidemiological model that describes colonization and co-colonization dynamics by circulating subtypes of such a pathogen. We start by analyzing multi-type coexistence under symmetric type interactions, and derive the explicit links with the non-symmetric system using a slow-fast dynamics approach, from singular perturbation theory (Fenichel, 1979; Tychonoff, 1935).

Complex systems, such as multi-strain pathogen systems, typically require a high dimensional description with many degrees of freedom, especially under stochasticity. Yet, their long-term behavior is often of a low dimensional nature. The main challenge lies in the identification of the dynamically meaningful slow variables and projection of the effective dynamics in this low dimensional representation (Coifman et al., 2008; Singer et al., 2009).

Our approach is inspired by Goldstone's idea of symmetry breaking yielding slow dynamics (Goldstone et al., 1962), with applications in physics (Golubitsky and Stewart, 2002; Sethna, 2006), and Hubell's neutral hypothesis for community assembly processes (Hubbell, 2001). A long-standing debate in ecology is whether coexistence of different species results from niche adaptation (Gause, 1934), or because of a balance of neutral processes such as immigration, speciation and extinction (MacArthur, 1967). This question also applies when studying genetic or antigenic polymorphisms in pathogens (Grenfell et al., 2004; Gupta and Maiden, 2001; Lipsitch et al., 2009; Lipsitch and O'Hagan, 2007). Most likely, neutral and niche mechanisms combine to generate coexistence patterns within and between species (Leibold et al., 2004), and one or the other may dominate depending on the scale of consideration (Adler et al., 2007; Wiegand et al., 2012). The difficulty lies in disentangling the two.

Here we follow the recent efforts to link these two macroecological theories (Chisholm and Pacala, 2010; Tilman, 2004). With our study on endemic multi-strain pathogens, we contribute to novel conceptual unification in this field. We show that neutral dynamics between strains occurs on a fast time-scale, whereas the non-neutral stabilizing forces act on a slow time-scale, dependent on strain interaction asymmetries. We quantify exactly which asymmetries matter for multi-strain coexistence, and how overall transmission intensity affects stabilization of diversity. Together, our results define a new analytical approach to better understand microbial ecosystems.

Materials and Methods

Slow-fast systems

Separation of dynamics into fast and slow components are ubiquitous in studies of ecological and eco-evolutionary dynamics (Auger and Poggiale, 1998; Cortez, 2011; Hastings, 2004; Rinaldi and Muratori, 1992; Rinaldi and Scheffer, 2000), and more generally in the evolution of dynamical systems. The approach relies on a canonical system of equations where the variables change in two (or more) time scales, as follows:

$$\frac{dx}{dt} = f(x, y)$$
$$\frac{dy}{dt} = \varepsilon g(x, y)$$

with the small parameter $0 < \varepsilon \ll 1$, where $f(x, y)$ and $g(x, y)$ are bounded. In this example, y is the slow variable and x is the fast one. By taking $\varepsilon = 0$ in this system, we obtain the critical fast system, where the slow variable may be treated as a constant: $y = const.$ Therefore, one first characterizes $x(t) \to \Phi(y)$ as $t \to +\infty$ for some smooth function Φ verifying $f(\Phi(y), y) = 0$. The set $(\Phi(y), y)$ is called the slow manifold.

When making the change of time scale $\tau = \varepsilon t$, one obtains an equivalent slow system:

$$\begin{aligned} \varepsilon \frac{dx}{d\tau} &= f(x, y) \\ \frac{dy}{d\tau} &= g(x, y) \end{aligned}$$

where by taking $\varepsilon = 0$, we obtain the critical slow dynamics. When reducing to the slow manifold $x = \Phi(y)$, this slow dynamics is defined by:

$$\frac{d}{d\tau} z(\tau) = g(\Phi(z), z). \tag{1}$$

Thus for small ε, in a first time $x \to \Phi(y) + O(\varepsilon)$, while y remains constant, and in a second time, y follows the slow dynamics. The precise statement is given by Tychonoff's theorem (Hoppensteadts, 1966; Lobry and Sari, 1998, 2005; Tychonoff, 1935). A more geometrical point of view was obtained by Fenichel (Fenichel, 1979) (see also Verhulst (2007) and the references therein for a most recent overview of these methods). Projection onto the slow manifold is nontrivial, the slow and fast time scales being coupled. Knowledge of a good parametrisation of such a slow manifold is key to equation-free modelling and computation of complex multi-scale systems.

Multi-strain model with direct interactions at co-infection

We consider a multi-type pathogen, transmitted via direct contact, following susceptible-infected-susceptible (SIS) epidemiological dynamics. Examples could include *Streptococcus pneumoniae* and *Haemophilus Influenzae*. For generality and analytical convenience, we group the pathogen types in two groups, denoted by V and N. With a set of ordinary differential equations, we track the proportion of hosts in 6 compartments: susceptibles, S, hosts colonized by one V type I_V, hosts colonized by one N type I_N, and co-colonized hosts I_{VV}, I_{NN}, and I_{VN} with two types of each combination, independently of their order of acquisition. We have:

$$\left\{ \begin{array}{ll} \frac{d}{dt} S & = \mu(1 - S) - S(\lambda_V + \lambda_N) + \gamma I \\ \frac{d}{dt} I_V & = \lambda_V S - I_V(k_{VV}\lambda_V + k_{VN}\lambda_N) - (\mu + \gamma) I_V \\ \frac{d}{dt} I_N & = \lambda_N S - I_N(k_{NV}\lambda_V + k_{NN}\lambda_N) - (\mu + \gamma) I_N \\ \frac{d}{dt} I_{VV} & = k_{VV}\lambda_V I_V - (\mu + \gamma) I_{VV} \\ \frac{d}{dt} I_{NN} & = k_{NN}\lambda_N I_N - (\mu + \gamma) I_{NN} \\ \frac{d}{dt} I_{VN} & = k_{VN}\lambda_N I_V + k_{NV}\lambda_V I_N - (\mu + \gamma) I_{VN}, \end{array} \right. \tag{2}$$

where $I = I_V + I_N + I_{VV} + I_{NN} + I_{VN}$, and the forces of infection for each sub-group of strains are: $\lambda_V = \beta(I_V + I_{VV} + \frac{1}{2} I_{VN})$ and $\lambda_N = \beta(I_N + I_{NN} + \frac{1}{2} I_{VN})$.

Because all variables refer to proportions in different classes, the last equation can be omitted using $S + I = 1$. Susceptibles are recruited at constant rate μ, equal to the per-capita departure rate. Upon exposure, a host can become colonized by one V or N type. Single and dual carriers contribute equally to the force of infection for each group of types, and hosts carrying two pathogen clones transmit either with equal probability. β denotes the per-capita transmission coefficient, while γ denotes the clearance rate back to the susceptible class, assuming no immune memory. Single carriers can acquire an additional pathogen clone at a rate, modified by a relative factor k_{ij}, describing the interaction between the resident and the challenge type upon encounter. Values of k_{ij} below 1 correspond to antagonism/competition between types from group i and j, while $k_{ij} \geq 1$ correspond to facilitation. All carriage episodes are cleared with equal efficiency, assuming type-transcending clearance mechanisms.

In this formulation, pathogen diversity is modeled only with a reduced number of - in this case two, - groupings, assuming equivalence with respect to transmission and clearance rate. Realistic variations between pathogen types in direct interaction abilities will be studied as dynamic symmetry-breaking perturbations to the system (Golubitsky and Stewart, 2002) at the level of groups. A schematic diagram of the model is given in Figure 1. The model has been recently applied to the context of pneumococcal bacteria Gjini et al. (2016), focusing on direct serotype competition (Dawid et al., 2007; Riley and Gordon, 1999). Here we generalize to any interaction between strains, including facilitation (Xavier et al., 2011).

In the following, we apply the slow-fast dynamics perspective to better understand the time evolution of such an endemic multi-strain pathogen system. We find a subtle connection between interaction coefficients among strains in a single host upon co-infection, and useful low-dimensional representations for their transmission dynamics at the population level. By uncovering a slow-fast dynamic decomposition, directly related to asymmetric strain interactions, we provide new avenues for theoretical exploration of microbial competition and facilitation networks.

Results

Neutral model

The simple version of the epidemiological model uses the equivalence assumption for strain interaction at co-colonization:

$$k_{VV} = k_{NN} = k_{VN} = k_{NV} = k. \tag{3}$$

As detailed in Appendices, the neutral system always admits the trivial disease-free equilibrium, stable for $R_0 = \frac{\beta}{\mu+\gamma} < 1$, which corresponds to the basic reproduction number of the pathogen (Diekmann et al., 1990). If $R_0 > 1$ instead, the system has a full curve S_0 of neutrally-stable equilibria (see (8)), which is given by

$$S_0 = \{(S, I_V(z), I_N(z), I_{VV}(z), I_{NN}(z), I_{VN}(z)),\ z \in [-1, 1]\},$$

and satisfies

$$\begin{aligned} S &= 1/R_0, \\ I_V(z) + I_N(z) &= I_1^* \\ I_{VV}(z) + I_{NN}(z) + I_{NV}(z) &= I_2^* = 1 - S - I_1^*. \end{aligned} \tag{4}$$

More specifically,

$$I_1^* = \frac{R_0 - 1}{R_0(k(R_0-1)+1)} \text{ and } I_2^* = \frac{k(R_0-1)^2}{R_0(k(R_0-1)+1)},$$

defining a conservation law for single and dual colonization prevalence. Free variation of $z \in [-1, 1]$ modulates the relative sub-division into type prevalences, and enables hierarchies at the group level. If $R_0 > 1$ then S_0 attracts all trajectories of the dynamical system. Depending on the exact values of R_0 and k, single or dual colonization may dominate in the population. Clearly, the neutral model is simple analytically, but somewhat degenerate: depending on the initial conditions, any point of S_0 may be a final attractor.

Such result stems from the symmetry constraints, related to the population-dynamic neutrality principle postulated by Hubbell (2001), in which populations can achieve equilibria at arbitrary population sizes, the requirement being a conservation law for total population size summed over all species. Here, we show analogously that in an epidemiological system, a conservation law applies to the overall prevalence of single and dual colonization in the population, which can be freely partitioned among permutable constituent strains.

The slow-fast dynamics decomposition

Our approach is to take neutrality as a first approximation, to study the effects of deviations from it. Thus, we consider next the system (2), without the neutral assumption (3), which is biologically more realistic, but still remains hard to analyze. We investigate the effect of differential interaction coefficients at dual colonization by two different pathogen types, thus the dynamics of (2) for

$$k_{VV} \approx k_{NN} \approx k_{VN} \approx k_{NV}. \tag{5}$$

We denote by k the average within-group interaction coefficient:

$$k = \frac{1}{2}(k_{VV} + k_{NN}). \tag{6}$$

Defining ε, in a unique manner, as the Euclidean distance of $[k_{VV}, k_{VN}, k_{NV}, k_{NN}]$ from $[k, k, k, k]$ in $\mathbb{R}^4$:

$$\epsilon = \sqrt{(k_{VV}-k)^2 + (k_{NN}-k)^2 + (k_{VN}-k)^2 + (k_{NV}-k)^2},$$

we can rewrite each interaction coefficient of the original system as:

$$k_{ij}^{\varepsilon} = k + \varepsilon\alpha_{ij}, \text{ for } i,j \in \{V,N\} \text{ and } 0 < \varepsilon \ll 1. \tag{7}$$

In a first approximation ($\varepsilon = 0$), one obtains the neutral model, which we characterized above. If $\varepsilon > 0$ is sufficiently small, in a first time, the dynamics follow the neutral system tending *quickly* to some point of S_0, and in a second time, the dynamics move *slowly* on S_0. Therefore there are two timescales which are nontrivially mixed in the system.

Next, we disentagle these two timescales by explicitly finding the fast and the slow variables. Thus, we are able to compute the *slow* dynamics, which are described by a single equation, fully determined by the coefficients α_{ij}. By virtue of the Tychonoff theorem (Tychonoff, 1935), we obtain that the long time behavior of solutions of (2) is asymptotically close to the behavior of solutions of the slow dynamics on S_0.

Broken symmetry of interactions: slow manifold

The mathematical derivations for the dynamics for $\varepsilon \neq 0$, are detailed in Supporting Appendices. Here we report only the main result. We find that two hyper-parameters:

$$\Theta = \alpha_{VV} - \alpha_{NN} + \left(1 + \frac{2}{k(R_0 - 1)}\right)(\alpha_{NV} - \alpha_{VN})$$

and

$$\Gamma = \alpha_{NV} + \alpha_{VN},$$

govern the asymptotic dynamics of the system for small ε. The epidemiological variables are given by

$$I_V = \frac{1}{2}I_1^*(1+z), \quad I_N = \frac{1}{2}I_1^*(1-z), \quad I_{VN} = \frac{kR_0 I_1^* I^*}{2}(1-z^2) \tag{8}$$

$$I_{VV} = \frac{1+z}{2}I_2^* - \frac{kR_0 I_1^*(I_1^* + I_2^*)}{4}(1-z^2),$$

$$I_{NN} = \frac{1-z}{2}I_2^* - \frac{kR_0 I_1^*(I_1^* + I_2^*)}{4}(1-z^2),$$

where z follows the (slow) dynamics

$$\frac{d}{d\tau}z = A(\Theta - \Gamma z)(1-z^2), \; z(0) \in [-1,1], \tag{9}$$

over the time scale $\tau = \varepsilon t$. In the above expressions, I_2^*, I_1^* and their sum I^* are derived from the neutral system, and A is a positive constant.

The possible equilibrium states of (9) are described in Figure 2, depicting stability of the V-N coexistence, single stability of either competitive exclusion equilibrium V-only/N-only, or bistability of both exclusion equilibria separated by an unstable coexistence fixed point. All these asymptotic scenarios are determined by the magnitudes of the broken symmetries in the group-wise direct interaction coefficients, as summarized by Θ and Γ. In contrast to the neutral model, the slow dynamics for $\varepsilon \neq 0$ do not display a global conservation law for single and dual colonization; these may change with z.

Interpretation of Θ and Γ

Our analysis shows that the V-N coexistence steady state, corresponds to the solution $z^* = \frac{\Theta}{\Gamma}$, which is positive when $|\Theta| < |\Gamma|$, and is stable whenever $\Gamma > 0$ (represented by the dark grey region in Figure 2). Upon substitution of this solution into the original variables, this steady state can be obtained in terms of the original model parameters. Intuitively, $\Gamma > 0$ means a strong exchange between groups while $\Gamma < 0$ means a weak exchange between the two groups. This shows that V-N that coexistence is stable if pathogen subtypes from each group allow co-colonization by the other group easily, and unstable otherwise.

Similarly, the N-only steady state corresponds to the $z = -1$ solution, while the V-only steady steady corresponds to the $z = 1$ solution. These two solutions may be stable or unstable. A scenario of bistability of the exclusion equilibria ($z = \pm 1$) arises for $\Gamma < 0$, and $|\Theta| < |\Gamma|$, where the coexistence solution $z^* = \frac{\Theta}{\Gamma}$ is unstable.

Notice that the slow dynamics depend nontrivially on the basic reproduction number R_0, the mean value of within-group interaction k, and the relative asymmetries in group-wise directed coefficients, given by the α_{ij}. While Γ depends only on the total sum of between-group interaction, Θ is a nonlinear function of more parameters, including R_0 and k, and subtle differences in the α's.

More specifically, Θ comprises a first term that represents $\Delta_{self} = \alpha_{VV} - \alpha_{NN}$, a measure of how different the two groups of pathogen types are in relation to *self*-interaction, plus a term $\Delta_{non-self} = \alpha_{NV} - \alpha_{VN}$, a measure of how different the two groups of pathogen types are in relation to interaction with $non-self$, i.e. the other group. The latter term is weighted by a k- and R_0- dependent factor.

As shown in Appendices, the latter factor represents exactly the ratio between dual and single colonization (I_2^*/I_1^*) in the symmetric system (Eqs.(2), (3)), namely how predominant carriage of two pathogen clones versus just one, is in the population. It is this general dominance of strain co-occurrence that scales the relative importance of cross-group interaction differences in the slow dynamics of the complete system.

Approximation error

Since our approximation is derived from a singular perturbation expansion for small deviation from neutrality, we expect that convergence of the approximation to the exact solution improves as the perturbation becomes smaller and is uniform over all time, as our system does not have chaotic or periodic attractors. Thus, we measure accuracy through the maximum error over all times when approximating 5-dimensional trajectories (S equation omitted), similar to the approach by Rossberg and Farnsworth (2011), evaluating aggregation methods for multi-species dynamics. The overall error of our slow-fast approximation is given by:

$$E = \sqrt{\sum_{i=1}^{5} \max_t \left(var_i^{approx}(t) - var_i(t) \right)^2}, \tag{10}$$

where variable var is indexed to represent $I_V(t)$, $I_N(t)$, $I_{VV}(t)$, $I_{NN}(t)$ and $I_{VN}(t)$. We ran trajectories of the original and approximated systems starting from the slow manifold at the point $z(0) = 0$ for a period of time equal to $T = 10^8$. As expected, we find that the error tends to zero as ε tends to zero, i.e. as the asymmetry in interaction coefficients decreases. Furthermore, the speed of convergence is independent of R_0 or k (Figure 3). This confirms the validity of our approximation, and its robustness to variation in overall intensity of transmission or interaction strength between types.

Temporal description

The slow-fast decomposition of the epidemiological dynamics of interacting strains allows us to be precise about the temporal course of system trajectories. Our analysis reveals that first, during a time scale of the order $O(\varepsilon \ln(1/\varepsilon))$, the system follows the neutral dynamics from any initial condition and approaches the line of neutrally-stable equilibria. Subsequently, in a time-scale of the order $O(\varepsilon)$ the dynamics follow the slow manifold, where the stabilizing forces act. Figure 4 illustrates these two time-scales.

Although in our model, we have assumed a constant R_0, this does not exclude the possibility that R_0 may change or fluctuate over time, for example due to weather conditions or antibiotic use. Indeed, from the definition of Θ and the equilibria on the slow manifold (Figure 2), we can see that under fixed strain interaction parameters, changes in R_0 alone can be sufficient to alter the pattern of dominance among groups of strains at the stable coexistence equilibrium, or even shift the system from stable coexistence to an exclusion state. For such changes in R_0 to effectively impact the slow dynamics, a necessary requirement is that they must occur over a time scale slower than $O(\varepsilon)$.

Discussion

Microbial pathogens display diversity on many levels, including genetic and antigenic polymorphisms, and thus are bound to be resilient in nature. Understanding the ecology underpinning this diversity is crucial to explain how these systems might respond to human interventions, such as vaccines and drugs (Colijn and Cohen, 2015; Lipsitch, 1997; Martcheva et al., 2008), and how they might spontaneously evolve (Dercole et al., 2002). We therefore must seek for comprehensive models that can provide mathematical and ecological insight into the short- and long- term dynamics of such systems. On one hand, computer simulations may offer quick illustrations of hypotheses and investigation of scenarios. Yet, they cannot

provide a deep understanding, required for successful control. Given the complexity and nonlinearity of such multi-strain systems, approximations are key to maximimize insight and explanatory power at minimal complexity.

In this paper we have presented a new analytical approach, based on a slow-fast decomposition for the dynamics of interacting subtypes at the epidemiological level. While the neutral model, based on symmetric interactions at co-colonization, provides the template of neutrally-stable equilibria for coexistence reachable on a fast time scale, the non-neutral model, allowing for asymmetric interactions, captures the slow-stabilizing dynamics. Proponents of the neutral theory have recognized that trophically similar species in communities might be ecologically equivalent, at least to a first approximation (Chave, 2004; Hubbell, 2006). Although the notion that species differences promote coexistence, - by inducing stabilizing effects at the community level - is generally accepted, it is still unclear which differences matter for coexistence, or whether differences are necessarily needed for coexistence. This debate is ongoing for almost all pathogen systems, most-prominently multi-strain pathogens such as the bacteria pneumococci (Lipsitch et al., 2009), dengue viruses (Mier-y Teran-Romero et al., 2013) or Human papillomaviruses (Murall et al., 2014).

Here, focusing on direct interaction at co-colonization between strains as our trait of interest, we have addressed exactly the question of which differences matter at the group level, summarizing the slow stabilizing forces with only two hyper-parameters Γ and Θ. In these hyper-parameters, the asymmetries in intra-group and inter-group interactions at co-colonization combine with type-transcending basic reproduction number R_0 and average interaction coefficient k. The net result is that effective multi-strain coexistence at the level of groups occurs only within certain regions of parameter space, depending on the corresponding Γ and Θ.

This slow-fast dynamics approach can be applied to study various perturbations of the system and its relaxation time back to equilibrium, or to consider the effects of globally-changing trends such as a time-varying R_0. For instance, if seasonality drives a different transmission intensity in winter and in summer, depending on the amplitude of the difference in R_0, we may expect not only overall endemic prevalence to fluctuate, but also different dominance patterns between pathogen types to arise in the two periods, despite their underlying interaction parameters remaining constant. This influence of R_0 on the slow component of the dynamics that we have characterized here, highlights that knowledge of the asymmetry in strain interactions is critical to understand how type-specific prevalences may change purely due to the effect of changes in global transmission. Time-varying R_0 may occur alone or in conjunction with type-specific interventions such as multivalent vaccines. Thus, it is possible that parallel changes in overall transmission of a multi-strain pathogen, during a targeted vaccination programme, might boost the reduction of vaccine subtypes, or counteract it, depending on the underlying interaction strengths between vaccine and non-vaccine strains.

In theoretical ecology, much attention has been paid to the shape of competition kernels as a major determinant of the equilibrium distributions of species along the phenotype space and their demographic stability (Leimar et al., 2013; Scheffer and van Nes, 2006). The role of transient dynamics for persistence on ecological time scales has also been increasingly appreciated, especially in cyclic systems (Hastings, 2001). As the study of community ecology is gaining momentum in the microbiome era (Bucci and Xavier, 2014; Pepper and Rosenfeld, 2012), elucidating the dynamical components and consequences of inter- and intra-species interactions is becoming increasingly important. Interactions within microbial communities occur in a range of habitats as diverse as the gut (Flint et al., 2007), nasopharynx (Bosch et al., 2013) and the skin (Grice and Segre, 2011). Although some studies have addressed the magnitude of interaction strengths (McCann et al., 1998) and the diversity of interaction types (Mougi and Kondoh, 2012) for ecological community stability, theoretical advances in this field are still much needed. In this context, approaches similar to the one adopted here, based on a slow-fast dynamics decomposition, can prove useful to better understand within-host processes in health and disease, also mediated by interactions between micro-organisms.

In this study, extending and generalizing previous work (Gjini et al., 2016), we have detailed how asymmetric direct interaction (competition/facilitation) between clones at the epidemiological level acts as an alternative route to stabilization of polymorphism in endemic pathogen systems, with the neutral model as a first-order approximation. When pathogen sub-types are grouped in two sets, interaction parameters that describe each group can vary with type composition. While the symmetric system accommodates a family of neutrally-stable steady states, realistic small perturbations drive slow stabilizing dynamics nearby, that we have fully characterized.

Although we have considered groups of pathogen subtypes equivalent in all other life-history traits, e.g. transmission rates, in the future, a more realistic scenario could allow for some variation. This would introduce another layer of varibility between the two groups, namely in their ability to colonize susceptible hosts,

besides simply their ability to co-colonize. Such transmission rate differential would alter the landscape of steady-states, potentially allowing for multistability of alternative coexistence equilibria. Furthermore, the magnitude of such differential (R_0^V/R_0^N), would reshape the slow-fast dynamics decomposition that we obtained here, possibly enabling a third relevant time-scale to emerge. Such theoretical scenario could be relevant in studies of antibiotic resistance dynamics, where strains may vary in their direct competitive abilities, as well as in their fitness cost of resistance (e.g. lower transmission rate).

Our study delineates the path for further inquiry into co-variation between group-specific R_0 and interaction strengths k_{ij}, likely to drive new coexistence patterns and eco-evolutionary dynamics. Feedbacks arising from asymmetrical competition have been shown to lead to evolutionary reversals in regimes of ecological bistability (Dercole et al., 2002), where the evolution of traits modifying competitive performance follows selection forces that switch direction whenever the population alternates between a high and low density equilibrium. Extending our model to group-specific R_0 could allow for multiple coexistence equilibria, such that the multi-strain system could rest in a state of high prevalence or in a state of low prevalence under the exact same conditions. The slow-fast epidemiological and evolutionary dynamics pertinent to these cases remain to be addressed in future studies.

Finally, our model considers an ecological scenario with only two sets of pathogen subtypes, ($n = 2$) characterized by *net* pairwise interactions. The next obvious challenge is to extend the slow-fast dynamic decomposition to a higher n. Will multiple nested slow-fast dynamics emerge? In practice, we might always want to restrict analysis to a relatively small set of functionally relevant groups of types, defined by taxonomic or antigenic properties, or practical purposes such as types targeted by a vaccine vs. non-target ones. Thus, an explicit resolution at the level of individual types may not strictly be needed. Yet, generalising our framework to a larger number of competing groups of pathogen subtypes is an exciting avenue for the future, and the basic setup for slow-fast dynamic decomposition that we develop here will provide a useful foundation.

References

Adler, P. B., HilleRisLambers, J., and Levine, J. M. (2007). A niche for neutrality. *Ecology letters*, 10(2):95–104.

Auger, P. (1983). Hierarchically organized populations: interactions between individual, population, and ecosystem levels. *Mathematical biosciences*, 65(2):269–289.

Auger, P. and Poggiale, J.-C. (1998). Aggregation and emergence in systems of ordinary differential equations. *Mathematical and computer modelling*, 27(4):1–21.

Biek, R., Pybus, O. G., Lloyd-Smith, J. O., and Didelot, X. (2015). Measurably evolving pathogens in the genomic era. *Trends in ecology & evolution*, 30(6):306–313.

Bosch, A. A. T. M., Biesbroek, G., Trzcinski, K., Sanders, E. A. M., and Bogaert, D. (2013). Viral and bacterial interactions in the upper respiratory tract. *PLoS Pathog*, 9(1):e1003057.

Bucci, V. and Xavier, J. B. (2014). Towards predictive models of the human gut microbiome. *Journal of molecular biology*.

Chave, J. (2004). Neutral theory and community ecology. *Ecology Letters*, 7(3):241–253.

Chisholm, R. A. and Pacala, S. W. (2010). Niche and neutral models predict asymptotically equivalent species abundance distributions in high-diversity ecological communities. *Proceedings of the National Academy of Sciences USA*, 107(36):15821–15825.

Coifman, R. R., Kevrekidis, I. G., Lafon, S., Maggioni, M., and Nadler, B. (2008). Diffusion maps, reduction coordinates, and low dimensional representation of stochastic systems. *Multiscale Modeling & Simulation*, 7(2):842–864.

Colijn, C. and Cohen, T. (2015). How competition governs whether moderate or aggressive treatment minimizes antibiotic resistance. *eLife*, 4:e10559.

Cortez, M. H. (2011). Comparing the qualitatively different effects rapidly evolving and rapidly induced defences have on predator–prey interactions. *Ecology letters*, 14(2):202–209.

Coyte, K. Z., Schluter, J., and Foster, K. R. (2015). The ecology of the microbiome: Networks, competition, and stability. *Science*, 350(6261):663–666.

Dawid, S., Roche, A. M., and Weiser, J. N. (2007). The blp bacteriocins of streptococcus pneumoniae mediate intraspecies competition both in vitro and in vivo. *Infection and Immunity*, 75(1):443–451.

De Roos, A. M., Schellekens, T., Van Kooten, T., Van De Wolfshaar, K., Claessen, D., and Persson, L. (2008). Simplifying a physiologically structured population model to a stage-structured biomass model. *Theoretical population biology*, 73(1):47–62.

Dercole, F., Ferrière, R., and Rinaldi, S. (2002). Ecological bistability and evolutionary reversals under asymmetrical competition. *Evolution*, 56(6):1081–1090.

Diekmann, O., Heesterbeek, J., and Metz, J. A. (1990). On the definition and the computation of the basic reproduction ratio r 0 in models for infectious diseases in heterogeneous populations. *Journal of mathematical biology*, 28(4):365–382.

Faust, K. and Raes, J. (2012). Microbial interactions: from networks to models. *Nature Reviews Microbiology*, 10(8):538–550.

Fenichel, N. (1979). Geometric singular perturbation theory for ordinary differential equations. *Journal of Differential Equations*, 31(1):53–98.

Ferguson, N. M., Galvani, A. P., and Bush, R. M. (2003). Ecological and immunological determinants of influenza evolution. *Nature*, 422(6930):428–433.

Flint, H. J., Duncan, S. H., Scott, K. P., and Louis, P. (2007). Interactions and competition within the microbial community of the human colon: links between diet and health. *Environmental microbiology*, 9(5):1101–1111.

Gause, G. F. (1934). *The struggle for existence*. Williams and Wilkins, Baltimore, MD.

Gjini, E., Valente, C., Sá-Leão, R., and Gomes, M. G. M. (2016). How direct competition shapes coexistence and vaccine effects in multi-strain pathogen systems. *Journal of Theoretical Biology*, 388:50–60.

Gog, J. R. and Grenfell, B. T. (2002). Dynamics and selection of many-strain pathogens. *PNAS*, 99(26):17209–17214.

Goldstone, J., Salam, A., and Weinberg, S. (1962). Broken symmetries. *Physical Review*, 127(3):965.

Golubitsky, M. and Stewart, I. (2002). *The Symmetry Perspective: From equilibrium to chaos in Phase Space and Physical Space*. Birkhauser Verlag.

Gomes, M. G. M. and Medley, G. F. (2002). Dynamics of multiple strains of infectious agents coupled by cross-immunity: a comparison of models. In *Mathematical approaches for emerging and reemerging infectious diseases: models, methods, and theory*, pages 171–191. Springer.

Grenfell, B. T., Pybus, O. G., Gog, J. R., Wood, J. L., Daly, J. M., Mumford, J. A., and Holmes, E. C. (2004). Unifying the epidemiological and evolutionary dynamics of pathogens. *science*, 303(5656):327–332.

Grice, E. A. and Segre, J. A. (2011). The skin microbiome. *Nature Reviews Microbiology*, 9(4):244–253.

Gupta, S. and Maiden, M. C. (2001). Exploring the evolution of diversity in pathogen populations. *Trends in microbiology*, 9(4):181–185.

Gupta, S., Maiden, M. C., Feavers, I. M., Nee, S., May, R. M., and Anderson, R. M. (1996). The maintenance of strain structure in populations of recombining infectious agents. *Nature medicine*, 2(4):437–442.

Hastings, A. (2001). Transient dynamics and persistence of ecological systems. *Ecology Letters*, 4(3):215–220.

Hastings, A. (2004). Transients: the key to long-term ecological understanding? *Trends in Ecology & Evolution*, 19(1):39–45.

Hoppensteadts, F. (1966). Singular perturbations on the infinite interval. *Transaction of the American Mathematical Society*, 123:521–535.

Hubbell, S. P. (2001). *The unified neutral theory of biodiversity and biogeography (MPB-32)*, volume 32. Princeton University Press.

Hubbell, S. P. (2006). Neutral theory and the evolution of ecological equivalence. *Ecology*, 87(6):1387–1398.

Kryazhimskiy, S., Dieckmann, U., Levin, S. A., and Dushoff, J. (2007). On state-space reduction in multi-strain pathogen models, with an application to antigenic drift in influenza a. *PLoS Comput Biol*, 3(8):e159.

Leibold, M. A., Holyoak, M., Mouquet, N., Amarasekare, P., Chase, J., Hoopes, M., Holt, R., Shurin, J., Law, R., Tilman, D., et al. (2004). The metacommunity concept: a framework for multi-scale community ecology. *Ecology letters*, 7(7):601–613.

Leimar, O., Sasaki, A., Doebeli, M., and Dieckmann, U. (2013). Limiting similarity, species packing, and the shape of competition kernels. *Journal of Theoretical Biology*, 339:3–13.

Levin, S. A. (1992). The problem of pattern and scale in ecology: the robert h. macarthur award lecture. *Ecology*, 73(6):1943–1967.

Levin, S. A., Grenfell, B., Hastings, A., and Perelson, A. S. (1997). Mathematical and computational challenges in population biology and ecosystems science. *Science*, 275(5298):334–343.

Levins, R. (1966). The strategy of model building in population biology. *American scientist*, 54(4):421–431.

Lipsitch, M. (1997). Vaccination against colonizing bacteria with multiple serotypes. *PNAS*, 94(12):6571–6576.

Lipsitch, M., Colijn, C., Cohen, T., Hanage, W. P., and Fraser, C. (2009). No coexistence for free: neutral null models for multistrain pathogens. *Epidemics*, 1(1):2–13.

Lipsitch, M. and O'Hagan, J. J. (2007). Patterns of antigenic diversity and the mechanisms that maintain them. *Journal of the Royal Society Interface*, 4(16):787–802.

Lobry, C. and Sari, T. (1998). On tykhonov's theorem for convergence ofsolutions of slow and fast systems. *Electronic Journal of Differential Equations*, 19:1–22.

Lobry, C. and Sari, T. (2005). Singular perturbation methods in control theory. *Contrôle non linéaire et Applications*, 64:155–182.

MacArthur, R. H. (1967). *The theory of island biogeography*, volume 1. Princeton University Press.

Martcheva, M., Bolker, B. M., and Holt, R. D. (2008). Vaccine-induced pathogen strain replacement: what are the mechanisms? *Journal of The Royal Society Interface*, 5(18):3–13.

McCann, K., Hastings, A., and Huxel, G. R. (1998). Weak trophic interactions and the balance of nature. *Nature*, 395(6704):794–798.

Mier-y Teran-Romero, L., Schwartz, I. B., and Cummings, D. A. (2013). Breaking the symmetry: Immune enhancement increases persistence of dengue viruses in the presence of asymmetric transmission rates. *Journal of Theoretical Biology*, 332:203–210.

Mougi, A. and Kondoh, M. (2012). Diversity of interaction types and ecological community stability. *Science*, 337(6092):349–351.

Murall, C. L., McCann, K. S., and Bauch, C. T. (2014). Revising ecological assumptions about Human papillomavirus interactions and type replacement. *Journal of Theoretical Biology*, 350:98–109.

Pepper, J. W. and Rosenfeld, S. (2012). The emerging medical ecology of the human gut microbiome. *Trends in Ecology & Evolution*, 27(7):381–384.

Riley, M. A. and Gordon, D. M. (1999). The ecological role of bacteriocins in bacterial competition. *Trends in microbiology*, 7(3):129–133.

Rinaldi, S. and Muratori, S. (1992). Slow-fast limit cycles in predator-prey models. *Ecological Modelling*, 61(3):287–308.

Rinaldi, S. and Scheffer, M. (2000). Geometric analysis of ecological models with slow and fast processes. *Ecosystems*, 3(6):507–521.

Rossberg, A. G. and Farnsworth, K. D. (2011). Simplification of structured population dynamics in complex ecological communities. *Theoretical ecology*, 4(4):449–465.

Scheffer, M. and van Nes, E. H. (2006). Self-organized similarity, the evolutionary emergence of groups of similar species. *Proceedings of the National Academy of Sciences USA*, 103(16):6230–6235.

Sethna, J. (2006). *Statistical mechanics: entropy, order parameters, and complexity*, volume 14. Oxford University Press.

Singer, A., Erban, R., Kevrekidis, I. G., and Coifman, R. R. (2009). Detecting intrinsic slow variables in stochastic dynamical systems by anisotropic diffusion maps. *Proceedings of the National Academy of Sciences*, 106(38):16090–16095.

Tilman, D. (2004). Niche tradeoffs, neutrality, and community structure: a stochastic theory of resource competition, invasion, and community assembly. *Proceedings of the National Academy of Sciences USA*, 101(30):10854–10861.

Tychonoff, A. (1935). Ein fixpunktsatz. *Mathematische Annalen*, 111(1):767–776.

Verhulst, F. (2007). Singular perturbation methods for slow–fast dynamics. *Nonlinear Dynamics*, 50(4):747–753.

Wiegand, T., Huth, A., Getzin, S., Wang, X., Hao, Z., Gunatilleke, C. S., and Gunatilleke, I. N. (2012). Testing the independent species' arrangement assertion made by theories of stochastic geometry of biodiversity. *Proceedings of the Royal Society B: Biological Sciences*, 279(1741):3312–3320.

Xavier, J. B., Kim, W., and Foster, K. R. (2011). A molecular mechanism that stabilizes cooperative secretions in pseudomonas aeruginosa. *Molecular microbiology*, 79(1):166–179.

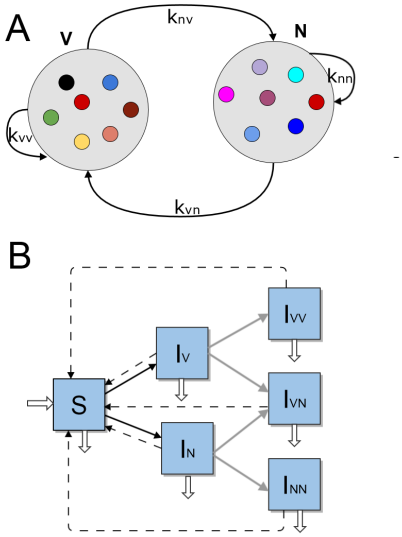

Figure 1: Model diagram. A) Pathogen strains grouped in two sets, V and N, characterized by within-group and between-group interaction. B) SIS structure with single and dual colonization. The black arrows refer to λ_V, λ_N. The gray arrows refer to altered acquisition of a secondary clone $k_{ij}\lambda_i$. The dashed arrows depict clearance.

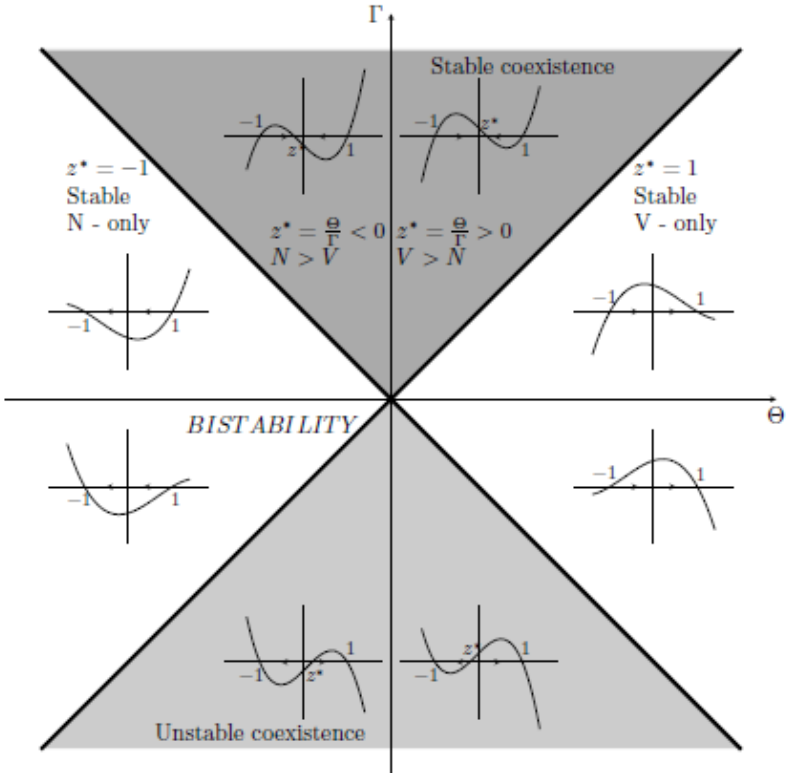

Figure 2: Graphical summary of the system equilibria for multi-strain dynamics on the slow manifold described by Eq.(9), as a function of the hyper-parameters $\Theta = \alpha_{VV} - \alpha_{NN} + \left(1 + \frac{2}{k(R_0 - 1)}\right)(\alpha_{NV} - \alpha_{VN})$ and $\Gamma = \alpha_{NV} + \alpha_{VN}$.

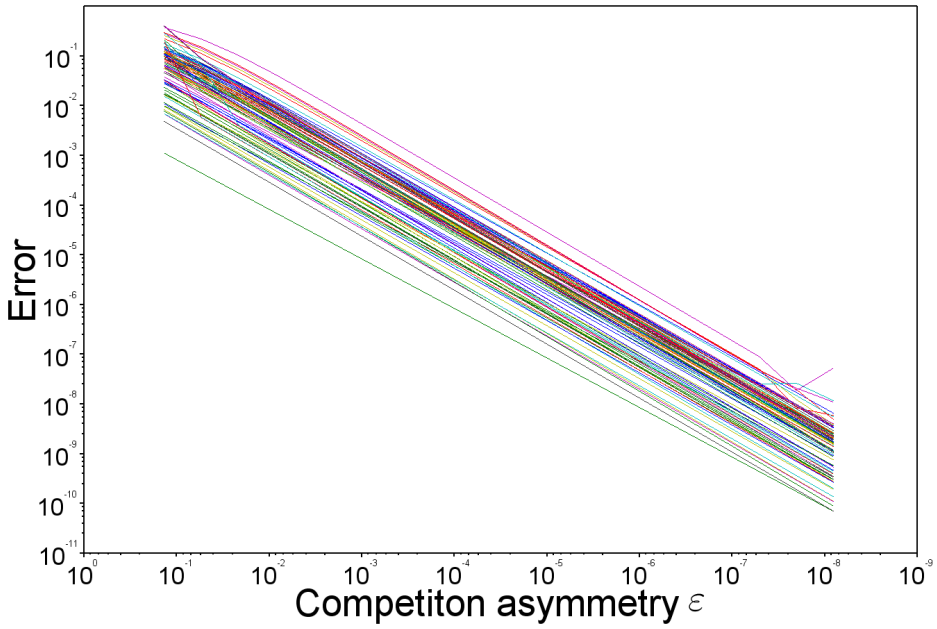

Figure 3: As the asymmetries among interaction coefficients vanish $\epsilon \to 0$, the error of the slow-fast approximation tends to zero. The different lines depict different random combinations of R_0 and k, in the range $R_0 \in (1, 8]$ and $k \in (0, 1]$, and random choice of $\alpha_{ij} \in (-1, 1)$.

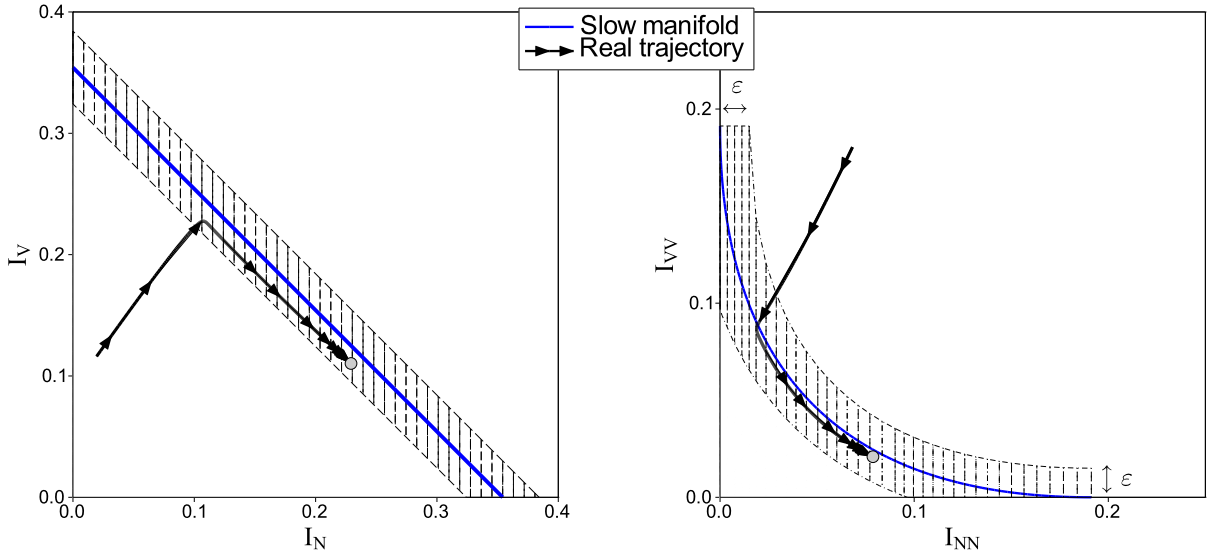

Figure 4: Convergence to the equilibrium in two timescales. The system trajectories (black arrows) reach an ε neighborhood of the slow manifold (in blue) in a time of the order $O(\varepsilon \ln(1/\varepsilon))$. Once in this neighborhood, the trajectories stay ε-close to the slow manifold and follow the slow dynamics, taking a time of order $O(\varepsilon)$ to reach (more precisely, to go exponentially close to) the equilibria. Left panel: single colonization variables. Right panel: dual colonization variables.

Online Supporting Appendices

for *A slow-fast dynamic decomposition links neutral and non-neutral coexistence in interacting multi-strain pathogens*, by Erida Gjini and Sten Madec

A An equivalent representation by change of variables

The first step is to write the original system in an equivalent slow-fast form allowing the use of singular perturbation theory. For this, it is convenient to adopt the following change of variables:

$$I_1 := I_V + I_N, \quad I := I_1 + I_{VV} + I_{NN} + I_{VN}$$

and

$$J_1 := I_V - I_N, \quad J = I_V - I_N + I_{VV} - I_{NN}.$$

With these notations, one gets $\lambda_V = \frac{\beta}{2}(I+J)$ and $\lambda_N = \frac{\beta}{2}(I-J)$. With these variables and $k_{ij} = k + \varepsilon\alpha_{ij}$ for $i, j \in \{N, V\}$, the system reads:

$$\left\{\begin{array}{ll} \frac{d}{dt}S & = m(1-S) - \beta SI \\ \frac{d}{dt}I & = \beta SI - mI \\ \frac{d}{dt}I_1 & = \beta SI - mI_1 - \beta k I I_1 + \varepsilon\frac{\beta}{4}g_1(I, I_1, J, J_1) \\ \frac{d}{dt}J & = \beta SJ - mJ + \frac{k\beta}{2}(I_1 J - J_1 I) + \varepsilon\frac{\beta}{4}g_2(I, I_1, J, J_1) \\ \frac{d}{dt}J_1 & = \beta SJ - mJ_1 - k\beta J_1 I + \varepsilon\frac{\beta}{4}g_3(I, I_1, J, J_1) \\ \frac{d}{dt}I_{VN} & = -mI_{VN} + \frac{k\beta}{2}(I_1 I - J_1 J) + \varepsilon\frac{\beta}{4}g_4(I, I_1, J, J_1) \end{array}\right. \tag{11}$$

Where $m = \gamma + \mu$ and the functions g_k are explicit quadratic functions of the variables I, I_1, J and J_1 and of the parameters α_{ij} (see Appendix E).
The main aim for this change of variables arises from the following two facts about the system (11): i) The system is triangular by (three) blocks : the dynamics of (S, I) depend only on (S, I), the dynamics of (I_1, J, J_1) do not depend on I_{VN}. ii) The dynamics of the first block (S, I) do not depend on ε.

B The explicit slow-fast system

The point *ii*) above ensures that (S, I) tends to

$$(S^*, I^*) = \left(\frac{1}{R_0}, 1 - \frac{1}{R_0}\right)$$

as $t \to +\infty$ and uniformly in ε. Hence, without loss of generality, one may suppose that $S = S^*$ and $I = I^*$ and we note

$$g_i^*(J, J_1) = g_i(I^*, I_1^*, J, J_1).$$

Moreover, since the dynamics of I_{VN} does not have any effect on the dynamics of the variables (I_1, J, J_1), we may reduce our analysis to the system of the block (I_1, J, J_1). Finally, since we are interested only on the approximation of the order 1 in ε, we write $I_1(t) = I_1^* + \varepsilon x(t)$ where I_1^* is the stationary solution of the equation of I_1 for $\varepsilon = 0$, that is

$$I_1^* = \frac{\beta S^* I^*}{m + \beta k I^*} = \frac{(R_0 - 1)}{R_0\,(1 + k(R_0 - 1))}.$$

We will also denote the stationary solution of $I_2 = I - I_1$ for $\varepsilon = 0$ by

$$I_2^* = I^* - I_1^* = \frac{k\beta(I^*)^2}{m + k\beta I^*} = \frac{k(R_0-1)^2}{R_0(1 + k(R_0 - 1))}.$$

Using these notations, we focus on the system

$$\left\{\begin{array}{ll} \frac{d}{dt}x & = -(m + \beta k I^*)x + \frac{\beta}{4}g_0^*(J, J_1) + O(\varepsilon) \\ \frac{d}{dt}\begin{pmatrix} J \\ J_1 \end{pmatrix} & = A\begin{pmatrix} J \\ J_1 \end{pmatrix} + \frac{\varepsilon}{2}k\beta x \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}\begin{pmatrix} J \\ J_1 \end{pmatrix} \\ & \qquad + \varepsilon\frac{\beta}{4}\begin{pmatrix} g_1^*(J, J_1) \\ g_2^*(J, J_1) \end{pmatrix} + O(\varepsilon^2) \end{array}\right. \tag{12}$$

where the linear part of the dynamic of (J, J_1) is given by the matrix

$$A = \begin{pmatrix} \frac{1}{2}k\beta I_1^* & -\frac{1}{2}k\beta I^* \\ m & -(k\beta I^* + m) \end{pmatrix}.$$

The system (12) is not yet written on a slow-fast form. However, the order 0 terms of the dynamics of $(J, J_1)^t$ are linear, and independent of x. This implies that the slow and fast directions can be computed by a simple spectral analysis of the matrix A. The matrix A has two real eigenvalues : 0 and $-\mu = tr(A) = \frac{1}{2}k\beta I_1^* - (k\beta I^* + m) < 0$. Denoting $V_\mu = (I_2^*, 2I^*)^t$ and $V_0 = (I^*, I_1^*)^t$ the two corresponding eingenvectors, we see that the component $y(t)$ of $(J(t), J_1(t))^t$ in the direction of V_μ goes exponentially fast to zero, while the component $z(t)$ of $(J(t), J_1(t))^t$ in the direction of V_0 varies very slowly. Hence, V_μ and V_0 give respectively the fast and the slow directions. The new variables $y(t)$ and $z(t)$ are obtained explicitly from $J(t) = I_2^* y(t) + I^* z(t)$ and $J_1(t) = 2I^* y(t) + I_1^* z(t)$. This leads to

$$z = a\frac{J}{I} + (1-a)\frac{J_1}{I_1}$$

with $a = \frac{2I^2}{2I^2 - I_2 I_1} \in [0, 1]$. Since J/I and J_1/I_1 both belong to $(-1, 1)$, we get $z \in (-1, 1)$. With these new variables, one obtains the explicit slow-fast system:

$$\left\{ \begin{array}{ll} \frac{d}{dt}x & = -(m + \beta k I^*)x + \frac{\beta}{4} f_0(y, z) + O(\varepsilon) \\ \frac{d}{dt}y & = -\mu y + O(\varepsilon) \\ \frac{d}{dt}z & = \varepsilon\big(f_2(x, y, z) + O(\varepsilon)\big) \end{array} \right. \tag{13}$$

where $f_0(y, z) = g_0^*\big(I_2^* y + I^* z, 2I^* y + I_1^* z\big)$ and f_2 may be computed explicitly. Now, we can apply the Tychonov's Theorem. This is done in two steps: i) First we show that the fast dynamics of the fast variables x and y goes exponentially fast in time to a (slow) manifold parametrized by the slow variable z. ii) Second, we describe the slow dynamics of z while (x, y) belong to this slow manifold.

C Fast dynamics: the Neutral system

Taking $\varepsilon = 0$ in (13), we obtain the system describing the *fast* dynamics

$$\left\{ \begin{array}{ll} \frac{d}{dt}x & = -(m + \beta k I^*)x + \frac{\beta}{4} f_0(y, z) \\ \frac{d}{dt}y & = -\mu y \\ \frac{d}{dt}z & = 0 \end{array} \right. \tag{14}$$

It is clear that any solution x, y, z tends to $\Phi(z) = (x^*(z), 0, z)$ where $z = z(0)$ and $x^*(z) = \frac{\beta f_0(0,z)}{4(m+\beta k I^*)}$. Remark that, returning to the original variables, the system (14) describes the dynamics of the system (12) for $\varepsilon = 0$. This system matches exactly the neutral dynamics: that is the system (2) with $k_{VV} = k_{NN} = k_{NV} = k_{VN} = k$ (Eq. (5)). More precisely, if $\varepsilon = 0$ in (12), it is clear that when $R_0 > 1$,

$$(S(t), I(t), I_1(t)) \underset{t\to+\infty}{\longrightarrow} (S^*, I^*, I_1^*)$$

Moreover, from $y \to 0$ in (14) we deduce $J \to I_1^* z$ which implies

$$I_V(t) = \frac{1}{2}(I_1(t) + J_1(t)) \underset{t\to+\infty}{\longrightarrow} \frac{1}{2} I_1^*(1 + z)$$

and

$$I_N(t) = \frac{1}{2}(I_1(t) - J_1(t)) \underset{t\to+\infty}{\longrightarrow} \frac{1}{2} I_1^*(1 - z).$$

Besides, we have $J(t) \to I^* z$, so from the last equation of (12), we get

$$I_{VN}(t) \to \frac{k\beta I_1^* I^*}{2m}(1 - z^2).$$

Finally, since $I_{VV} = I_2(t) + J(t) - J_1(t) - I_{VN}(t)$, we obtain

$$I_{VV}(t) \underset{t\to+\infty}{\longrightarrow} \frac{I_2^*}{2}(1 + z) - \frac{k\beta I_1^* I^*}{2m}(1 - z^2)$$

and similarly

$$I_{NN}(t) \underset{t\to+\infty}{\longrightarrow} \frac{I_2^*}{2}(1 - z) - \frac{k\beta I_1^* I^*}{2m}(1 - z^2).$$

D Slow dynamics: the Non-neutral system

If $0 < \varepsilon \ll 1$, the parameter z is not free, but varies deterministically very slowly. Thus, what remains to compute are the slow dynamics of z. To do so, we define the slow time-scale $\tau = \varepsilon t$. Plugging this in (13), we obtain

$$\begin{cases} \varepsilon \frac{d}{d\tau} x &= -(m + \beta k I^*)x + \frac{\beta}{4} f_0(y,z) + O(\varepsilon) \\ \varepsilon \frac{d}{d\tau} y &= -\mu y + O(\varepsilon) \\ \frac{d}{d\tau} z &= f_2(x,y,z) + O(\varepsilon) \end{cases} \tag{15}$$

Taking $\varepsilon = 0$ in (15) yields

$$\begin{cases} 0 &= -(m + \beta k I_1^*)x + \frac{\beta}{4} f_0(y,z) \\ 0 &= -\mu y \\ \frac{d}{d\tau} z &= f_2(x,y,z) \end{cases} \tag{16}$$

The manifold $\Phi(z) = (x^*(z), 0, z)$ is invariant for (16). The dynamics of z along this manifold are given by the slow equation

$$\frac{d}{d\tau} z = f_2(x^*(z), 0, z)$$

Replacing f_2 and x^* by their expressions, we obtain:

$$\frac{d}{d\tau} z = A(\Theta - \Gamma z)(1 - z^2), \tag{17}$$

where we have

$$A = \frac{\beta I^* I_1^* I_2^*}{8(I^*)^2 - 4 I_1^* I_2^*},$$
$$\Gamma = \alpha_{VN} + \alpha_{NV}$$

and

$$\Theta = \alpha_{VV} - \alpha_{NN} + \left(1 + 2\frac{I_1^*}{I_2^*}\right)(\alpha_{NV} - \alpha_{VN}).$$

E Details of the mathematical derivations

E.1 Explicit functions in system (11)

In the system (11), using the fact that $\alpha_{VV} + \alpha_{NN} = 0$, the functions g_k are given explicitly by :

$$\begin{aligned} g_0(I, I_1, J, J_1) = &- I_1 I(\alpha_{NV} + \alpha_{VN}) \\ &- I_1 J(\alpha_{VV} - \alpha_{NN} + \alpha_{NV} - \alpha_{VN}) \\ &- J_1 I(\alpha_{VV} - \alpha_{NN} - \alpha_{NV} + \alpha_{VN}) \\ &+ J_1 J(\alpha_{NV} + \alpha_{VN}) \end{aligned}$$

$$\begin{aligned} g_1(I, I_1, J, J_1) = &+ I_1 I(\alpha_{NV} - \alpha_{VN}) \\ &+ I_1 J(\alpha_{NV} + \alpha_{VN}) \\ &- J_1 I(\alpha_{NV} + \alpha_{VN}) \\ &- J_1 J(\alpha_{NV} - \alpha_{VN}) \end{aligned}$$

$$\begin{aligned} g_2(I, I_1, J, J_1) = &+ I_1 I(\alpha_{NN} - \alpha_{VV} + \alpha_{NV} - \alpha_{VN}) \\ &+ I_1 J(\alpha_{VN} + \alpha_{NV}) \\ &- J_1 I(\alpha_{VN} + \alpha_{NV}) \\ &- J_1 J(\alpha_{VV} - \alpha_{NN} + \alpha_{NV} - \alpha_{VN}) \end{aligned}$$

$$
\begin{aligned}
g_3(I, I_1, J, J_1) = &- I_1 I(\alpha_{NV} + \alpha_{VN}) \\
&+ I_1 J(\alpha_{NV} - \alpha_{VN}) \\
&- J_1 I(\alpha_{NV} - \alpha_{VN}) \\
&- J_1 J(\alpha_{VN} + \alpha_{NV})
\end{aligned}
$$

E.2 Details of the computation of the slow-fast form (13)

The explicit slow-fast form is given by making the following linear change of variables in the system (11):

$$
\begin{pmatrix} J(t) \\ J_1(t) \end{pmatrix} = P \begin{pmatrix} y(t) \\ z(t) \end{pmatrix} \text{ where } P = \begin{pmatrix} I_2^* & I^* \\ 2I^* & I_1^* \end{pmatrix}.
$$

Thus, we obtain

$$
\begin{aligned}
\frac{d}{dt}\begin{pmatrix} y \\ z \end{pmatrix} &= P^{-1}\frac{d}{dt}\begin{pmatrix} J \\ J_1 \end{pmatrix} \\
&= P^{-1}AP\begin{pmatrix} y \\ z \end{pmatrix} + \frac{\varepsilon}{2}k\beta x P^{-1}\begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} P\begin{pmatrix} y \\ z \end{pmatrix} \\
&\quad + \frac{\varepsilon}{4}\beta P^{-1}\begin{pmatrix} g_1^*(I_2^* y + I^* z, I^* y + I_1^* z) \\ g_2^*(I_2^* y + I^* z, I^* y + I_1^* z) \end{pmatrix} + O(\varepsilon^2).
\end{aligned}
$$

From the very definition of P, we get the following:

$$
P^{-1}AP = \begin{pmatrix} -\mu & 0 \\ 0 & 0 \end{pmatrix}.
$$

Straightforward calculations give:

$$
P^{-1}\begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} P = \frac{1}{\det(P)}\begin{pmatrix} I_1^* I_2^* & I^* I_1^* \\ -2I^* I_2^* & -2(I^*)^2 \end{pmatrix}
$$

$$
P^{-1}\begin{pmatrix} g_1^*(I_2^* y + I^* z, I^* y + I_1^* z) \\ g_2^*(I_2^* y + I^* z, I^* y + I_1^* z) \end{pmatrix} = \frac{1}{\det(P)}\begin{pmatrix} \upsilon(y,z) \\ \gamma(y,z) \end{pmatrix},
$$

where υ and γ are two polynomials of y and z of degree 2, and may easily be computed using the definitions of the functions g_i^* and of the matrix P. Thus, denoting

$$
f_2(x,y,z) = -\frac{k\beta x}{\det(P)}\left[I^* I_2^* y + (I^*)^2 z\right] + \frac{\beta}{4}\gamma(y,z), \tag{18}
$$

we obtain the system (13).

E.3 Explicit computation of the slow dynamics equation

Denote $A = \alpha_{VV} - \alpha_{NN}$, $B = \alpha_{NV} - \alpha_{VN}$ and $\Gamma = \alpha_{VN} + \alpha_{NV}$. From $y = 0$, we deduce $J = I^* z$ and $J_1 = I_1^* z$ which provides

$$
\gamma(0,z) = \frac{I^* I_1^* I_2^*}{\det(P)}\left((B-A) - z^2(B+A) - 2\frac{I^*}{I_2^*}B(1-z^2)\right).
$$

and

$$
x^*(z) = \frac{I_1^* I_2^*}{4kI^*}\left(\gamma(1-z^2) + 2Az\right).
$$

Plugging these two expressions into (18) and remarking that $\det(P) < 0$, yields the final expression

$$
\begin{aligned}
f_2(x^*(z),0,z) &= \frac{\beta I^* I_1^* I_2^*}{4\det(P)}\left(\Gamma z + (B-A) - 2\frac{I^*}{I_2^*}B\right)(1-z^2) \\
&= \frac{\beta I^* I_1^* I_2^*}{4|\det(P)|}\left(A + B(1+\frac{I_1^*}{I_2^*}) - \Gamma z\right)(1-z^2).
\end{aligned}
$$