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FELLOWSHIP FINAL REPORT

Coexistence near neutrality

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ABSTRACT

Co-infection is an important aspect of many infectious diseases, with substantial modeling efforts in the last decades. Yet, simple and sufficiently general mathematical frameworks to analyze and unify the full spectrum of hierarchical patterns emerging from co-infection interactions and variation in other fitness dimensions between two or more strains are missing. Here, we contribute to fill this gap, thanks to a model reduction obtained after assuming strain similarity. We model simultaneously 5 fitness dimensions where strains can differ close to neutrality, and decompose dynamics in two timescales: neutral dynamics between types on a fast *timescale, and non-neutral selective processes on a* slow *timescale, driven explicitly by trait variation and a replicator equation. We bridge adaptive dynamics and epidemiological multi-strain models, generalizing and advancing analytically these two perspectives on co-infection and coexistence.*

1- Introduction

Understanding competitive dynamics among many strains at the epidemiological level is key to explain and predict polymorphisms in virulence, transmissibility, antibiotic resistance and other biological traits of infectious agents. Typically, mathematical co-infection models have focused on the criteria leading to stable coexistence or competitive exclusion in specific systems, however, due to their complexity and nonlinearity, analytical solutions in co-infection models with many strains remain rare. In this study we advance our previous work on an SIS compartmental model with N strains (Madec and Gjini, 2020) under co-infection (co-colonization), to incorporate multiple fitness dimensions under the same framework: variation in transmissibility, duration of carriage, pairwise susceptibilities to co-infection, co-infection duration, and transmission priority effects from mixed co-infection. Taking advantage of singular perturbation techniques, under the assumption of strain similarity, we expose how strain dynamics on a slow timescale are explicitly governed by a replicator equation which encapsulates all traits and their interplay. This simplifies both analysis, and computation of such systems.

2- Methodological details

Co-infection models in epidemiology have a long history of study (Levin and Pimentel, 1981; Adler and Brunet, 1991; Nowak and May, 1994; May and Nowak, 1995; van Baalen and Sabelis, 1995; Alizon, 2013). Examples of multi-strain infectious agents where co-infection processes appear and shape epidemiology include Streptococcus pneumoniae bacteria, Bordetella pertussis, sMycobacterium tuberculosis, Staphylococcus Aureus, and many others, comprising plants and also inter-species co-colonization such as

between Haemophilus influenzae and pneumococcus serotypes, or co-infection with different viruses. Typically the strain-defining parameters are less variable within than between species. However, until now, models have not fully harnessed the conceptual and analytic advantages of strain similarity, except for comparisons between strain-specific basic reproduction numbers. In our approach, we take advantage of the assumption of strain similarity, and use singular perturbation theory to simplify the multi-strain co-infection dynamics.

While in the model analyzed earlier (Madec and Gjini, 2020), only co-colonization interactions were allowed to vary between strains, in the new work developed later, we extend the analysis to more trait variation between strains. We consider 5 traits that can vary between strains: transmission rate clearance rate, co-infection duration, pairwise vulnerabilitites to co-infection and transmission priority effects from co-infection. Net competition dynamics between *N* players can be complex because all traits interact nonlinearly to determine final strain fitness at the epidemiological level, but thanks to a derived replicator equation, we make such selective process entirely explicit.

Moreover, we show how the strain-transcending parameters, defining the neutral model at the center, feed back on the strain dynamics on the slow timescale, while tuning the net importance of each phenotypic axis.

3- Results and discussion

$$\begin{cases} \frac{dS}{dt} &= r(1-S) + \sum_{i=1}^{N} \gamma_i I_i + \sum_{i,j=1}^{N} \gamma_{ij} I_{ij} - S \sum_{i=1}^{N} F_i, \\ \frac{dI_i}{dt} &= F_i S - (r+\gamma_i) I_i - I_i \sum_{j=1}^{N} k_{ij} F_j, \qquad 1 \le i \le N, \\ \frac{dI_{ij}}{dt} &= k_{ij} I_i F_j - (r+\gamma_{ij}) I_{ij}, \qquad 1 \le i,j \le N, \end{cases}$$

The model follows the structure in (Madec and Gjini, 2020) but here two strains can differ in: transmission rate (*N*-dimensional vector), clearance rate (*N*-dimensional vector), co-colonization clearance rate (*NxN* matrix), altered susceptibilities to co-colonization (*NxN* matrix) and transmission biases from co-infection (*NxN* matrix). See Figure 1.

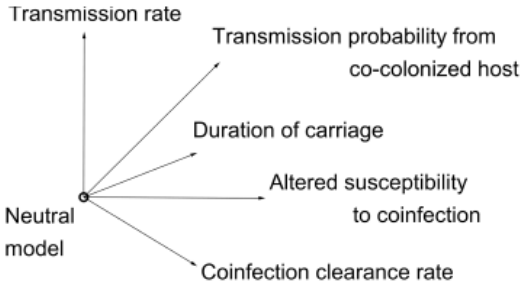

Figure 1*: Five traits where N strains may vary in our SIS model with co-infection (Le et al. 2021).*

Thus, any combination of relative fitness costs and advantages can be encapsulated, provided that their variation is not too big, as expected for similar conspecific strains, or similar infectious co-circulating `species'. Non-carriers (S) become carriers of either strain (singly-infected) with strain-specific force of infection:

$$F_i = \beta_i \left(I_i + \sum_{j=1}^{N} \left(p_{ij}^{i} I_{ij} + p_{ji}^{i} I_{ji} \right) \right)$$

where the mixed carriage compartment may transmit either strain with a slightly biased probability away from 1/2 depending on the order of arrival within-host (see Le et al. 2021).

The co-colonization interaction coefficients capture the altered relative susceptibilities to co-colonization between strains, when a host is already colonized, and transitions from primary colonization to co-colonization. Assuming strain similarity, the epidemiological dynamics in such an SIS model with co-infection, can be decomposed into a fast (neutral) component and slow (non-neutral) component.

The slow dynamics are shown to follow an explicit replicator equation, which includes in the net payoff matrix variation across 5 dimensions of fitness for each strain (Le et al. 2021). This equation allows to predict analytically the entire temporal dynamics of any two strains as a function of their epidemiological phenotypes.

The system evolves in two timescales. On the fast time-scale strains follow neutral dynamics, driven by mean-field parameters, where total

prevalence of susceptibles S, single infection, I and co-infection D, stabilize.

$$S^* = \frac{1}{R_0}, \qquad T^* = 1 - S^*, \qquad I^* = \frac{T^*}{1 + k(R_0 - 1)}, \qquad D^* = T^* - I^*.$$

On a slow time-scale, within conserved global epidemiological prevalences, complex non-neutral dynamics between strains takes place, where hierarchical frequency-dependent relationships between strains unfold.

Each system for *N=2* can be in one of four scenarios between 2 strains, depending on the signs of mutual invasion fitnesses: coexistence, exclusion, and bistability.

This defines the "edges" of a bigger N-strain network. We find that frequency dynamics are explicitly governed by the mutual invasion fitnesses.

In our model, invasion fitnesses (Geritz et al. 1998) are direct functions of strain variability along different traits and global mean-field parameters. As derived by Le et al. (PhD thesis 2021), we have:

$$\lambda_i^j = \theta_1 (b_i - b_j) + \theta_2 (-\nu_i + \nu_j) + \theta_3 (-u_{ij} - u_{ji} + 2u_{jj}) + \theta_4 \left(\omega_{ij}^i - \omega_{ji}^j\right) + \theta_5 (\mu (\alpha_{ji} - \alpha_{ij}) + \alpha_{ji} - \alpha_{jj})$$

where

$$\theta_1 = \left(\frac{T^*}{D^*}\right)^2, \quad \theta_2 = \frac{\gamma I^* (I^* + T^*)}{2mD^{*2}}, \quad \theta_3 = \frac{\gamma T^*}{2mD^*}, \quad \theta_4 = \frac{T^*}{D^*}, \quad \theta_5 = \frac{\beta I^* T^*}{2mD^*}.$$

Slow dynamics follow a replicator equation in terms of these pairwise invasion fitnesses (λ_{ij}):

$$\begin{cases} \dfrac{dz}{d\tau} = \Theta z \left(\Lambda z - z^T \Lambda z\right) \\ z_1 + z_2 + \cdots + z_N = 1 \end{cases}$$

This replicator equation allows direct analytical insights on the role of co-infection for ecological outcome between two strains (Le at al, 2021) as illustrated in the Figure 2.

Moreover it allows predicting any N-strain epidemiological dynamics for similar strains in co-infection systems, including limit cycles and complex attractors.

4 Conclusion

We linked population dynamics of N-strain endemic transmission in an SIS model with co-infection to slow selective dynamics in strain frequency space, and showed that such dynamics are given by a replicator equation involving the mutual invasion fitness matrix between strains.

Our framework generalizes single trait evolution to multiple trait evolution, exploring phenotypic differentiation along 5 different epidemiological dimensions, all of which contribute to mutual invasion fitness.

We highlight the utility of an analytical expression for explicit frequency dynamics between 2 or N strains, under an endemic global equilibrium, which allows to use the well-known replicator equation to make predictions for exclusion vs. coexistence, stability and complexity, as well as for the evolution of biodiversity, namely how the means of different traits act to shape their slow evolution dynamics.

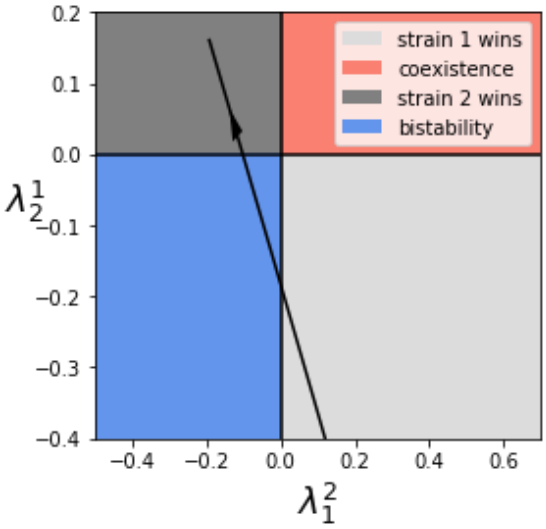

***Figure 2**: Studying system shifts as a function of co-infection prevalence in the system (μ=I*/D*=1/[(R_0-1)k] ratio of single to co-infection is varied, while trait relative variations are held fixed, here N=2 – see Le et al 2021).*

4- Perspectives of future collaborations with the host laboratory

We will submit projects in collaboration between the two groups, to French and

Portuguese Research funding agencies. Besides theoretical advances toward stochasticity and spatial dimensions of the dynamics, what remains is connecting our models with data, and we need more people, collaborators, and resources for this research.

5- Articles published in the framework of the fellowship

- Le, T. M. T., Madec, S., & **Gjini, E**. (2021). Disentangling how multiple traits drive 2 strain frequencies in SIS dynamics with co-infection. bioRxiv. submitted – (preprint) in review at JTB

- Le T.M.T., **Gjini E.** and Madec S. (2021) Quasi-neutral Dynamics in a Co-infection System with N Strains and Asymmetries along Multiple Traits submitted – arXiv (preprint) in review at JOMB

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7- References

1. Adler, F.R. and Brunet, R.C., 1991. The dynamics of simultaneous infections with altered susceptibilities. *Theoretical population biology*, *40*(3), pp.369-410.

2. Alizon, S., 2013. Co-infection and super-infection models in evolutionary epidemiology. *Interface focus*, *3*(6), p.20130031.

3. Gjini, E. and Madec, S., 2021. The ratio of single to co- colonization is key to complexity in interacting systems with multiple strains. *Ecology and Evolution*.

4. Geritz, S.A., Meszena, G. and Metz, J.A., 1998. Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evolutionary ecology*, *12*(1), pp.35-57.

5. Levin, S. and Pimentel, D., 1981. Selection of intermediate rates of increase in parasite-host systems. *The American Naturalist*, *117*(3), pp.308-315.

6. Le, T.M.T., Gjini, E. and Madec, S., 2021. Quasi-neutral Dynamics in a Coinfection System with N Strains and Asymmetries along Multiple Traits. *arXiv preprint arXiv:2104.07289***.**

7. Le, T.M.T., Madec, S. and Gjini, E., 2021. Disentangling how multiple traits drive 2 strain frequencies in SIS dynamics with coinfection. *bioRxiv*.

8. May, R.M. and Nowak, M.A., 1995. Coinfection and the evolution of parasite virulence. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, *261*(1361), pp.209-215.

9. May, R.M. and Nowak, M.A., 1994. Superinfection, metapopulation dynamics, and the evolution of diversity. *Journal of Theoretical Biology*, *170*(1), pp.95-114.

10. Madec, S. and Gjini, E., 2020. Predicting n-strain coexistence from co-colonization interactions: epidemiology meets ecology and the replicator equation. *Bulletin of mathematical biology*, *82*(11), pp.1-26.

11. van Baalen, M. and Sabelis, M.W., 1995. The dynamics of multiple infection and the evolution of virulence. *The American Naturalist*, *146*(6), pp.881-910.