A TIME SCALES APPROACH TO COINFECTION MODELS

M. Marvá, R. Bravo de la Parra
Dpto de Física y Matemáticas,
Universidad de Alcalá.
28871 Alcalá de Henares, Spain

E. Venturino
Dip. di Matematica "Giuseppe Peano",
Università di Torino
via Carlo Alberto 10, 10123 Torino, Italy

Abstract A coinfective disease (also known as opportunistic) is one that can invade an organism given the "opportunity" of a weakened immune system. Typically, a long illness period is needed to damage, and keep damaged, the immune system enabling the secondary invasion. Then, infected individuals by the primary (*slow*) *infection* can be also classified as susceptible or infected by the secondary (*fast*) *disease*.

It is of interest understanding the interrelation between the two infectious processes: possible feedback phenomenon, strengthening effect, effect of the secondary disease on persistence primary infection thresholds, etc. In spite of the impact of coinfection in public health [2], [3], there are few mathematical models devoted to understand this phenomenon. A major difficulty is that the resulting equations systems consist of a large number of coupled equations. We assume that the main infection and the secondary one evolve in different time scales. Then, approximate aggregation methods [1] apply to get a less dimensional system attaining asymptotic information of the complete model.

How does it work? The approach relies on *approximate aggregation* techniques for time scale systems [1]. Let $f, s : \mathbb{R}^N \to \mathbb{R}^N$ stand for the fast and the slow process. The prototype of *two time scale systems* reads as

$$dn/d\tau = f(n) + \varepsilon s(n) \tag{1}$$

where parameter $\varepsilon \sim 0^+$ stands for time scales ratio. Let us change variables $n \mapsto (x, y) \in \mathbb{R}^{N-k} \times \mathbb{R}^k$ in (1), which yields the slow fast form

$$\begin{cases} dx/d\tau = F(x,y) + \varepsilon G(x,y), \\ dy/d\tau = \varepsilon S(x,y). \end{cases}$$

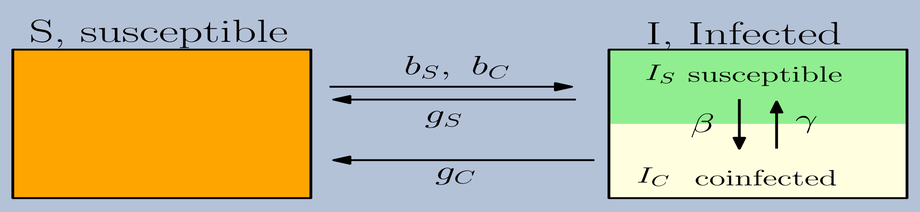
where x and y are the fast and the slow variables. Assume that for each $y \in \mathbb{R}^k$, $(x^*(y), y)$ is a hyperbolic asymptotically stable (fast) equilibrium of $dx/d\tau = F(x,y)$. If the reduced system

$$dy/dt = S(x^*(y), y) \qquad \text{where } t = \varepsilon\tau, \tag{2}$$

has a hyperbolic equilibrium y^*, we can describe the behavior of system (1) in terms of $(x^*(y^*), y^*)$ (see theorem 1). More general cases are allowed; see [1].

A toy model There is a slow disease; we note S and I the susceptible and infected individuals. Those infected by the slow disease are then susceptible, I_s, or coinfected, I_c, by the fast disease. Coinfected individuals are more infective and recover less than infected non-coinfected. Furthermore

- For the slow disease dynamics, individuals get infected at rate b_c (b_s) when they meet a coinfected (a non-coinfected). Coinfected (non-coinfected) individuals recover at rate g_c (g_s). Transmission follows true mass action law, as the process is slow, the population is homogeneously mixed.
- For the fast disease individuals get infected (recovered) at rate γ (β) according to the standard law.



Assuming the existence of time scales yields system

$$\begin{cases} \dfrac{dS}{d\tau} = & \varepsilon\left(-b_s S I_s - b_c S I_c + g_s I_s + g_c I_c\right), \\ \dfrac{dI_s}{d\tau} = -\beta\dfrac{I_s I_c}{I_s + I_c} + \gamma I_c + & \varepsilon\left(b_s S I_s + b_c S I_c - g_s I_s\right) \\ \dfrac{dI_c}{d\tau} = \beta\dfrac{I_s I_c}{I_s + I_c} - \gamma I_c + & \varepsilon\left(-g_c I_c\right) \end{cases} \tag{3}$$

Introducing the slow variable $I = I_s + I_c$, we get the fast equilibrium

$$(I_s^*, I_c^*) = (\mu_s, \mu_c) I, \text{ where } (\mu_s, \mu_c) = \begin{cases} (\gamma/\beta,\ 1 - \gamma/\beta) & \text{if } R_0 > 1 \\ (1,\ 0) & \text{if } R_0 < 1 \end{cases} \tag{4}$$

given $R_0 = \beta/\gamma$ the reproductive number of the fast disease. Then, we derive the reduced system in which (μ_s, μ_c) depend on whether $\gamma/\beta < 1$ as in (4)

$$\begin{cases} \dfrac{dS}{dt} = -(b_S\mu_S + b_C\mu_C) SI + (g_S\mu_S + g_C\mu_C) I, \\ \dfrac{dI}{dt} = (b_S\mu_S + b_C\mu_C) SI - (g_S\mu_S + g_C\mu_C) I, \end{cases} \tag{5}$$

Main results The aggregated system (5) looks like the classic SIS model following true mass action transmission law. Then, we can define the *global reproductive number*

$$\bar{R}_0 = \frac{b_S\mu_S + b_C\mu_C}{g_S\mu_S + g_C\mu_C} N, \tag{6}$$

which depends on the fast equilibrium and on N, the total population. Furthermore

Theorem 1. *The solution of the system* (3) *starting at* (S^0, I_s^0, I_c^0) *satisfies*

$$S(t) = S^* + o(1), \qquad I_s(t) = \mu_s I^* + o(1), \qquad I_c(t) = \mu_c I^* + o(1),$$

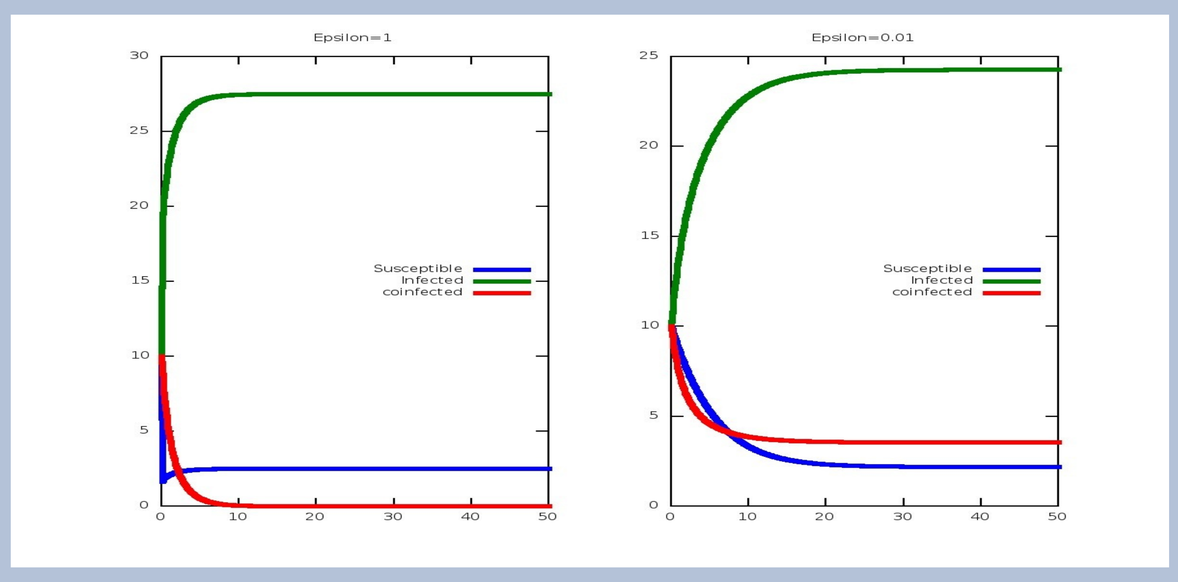
as $\varepsilon \to 0^+$ *uniformly on* $[t_1, \infty)$, *where* $t_0 < t_1$ *and*

$$(S^*, I^*) = \begin{cases} (\Lambda, N - \Lambda) & \text{if } \bar{R}_0 > 1 \\ (N,\ 0) & \text{if } \bar{R}_0 < 1 \end{cases} \qquad \text{and} \qquad \Lambda = \frac{g_s\mu_s + g_c\mu_c}{b_s\mu_s + b_c\mu_c}$$

N *is the population density and* (μ_s, μ_c) *depend on whether* $\gamma/\beta < 1$ *as in* (4).

The eradication of the fast disease has relevant influence on the system's outcome. Direct calculations show that $\bar{R}_0$ is larger when $R_0 > 1$ than when $R_0 < 1$, since coinfected individuals are more infective and recover less than infected non-coinfected. Indeed, expression (6) allows us to quantify the increase of $\bar{R}_0$ as R_0 crosses 1.

The decision of including or not time scales has consequences on the analysis Indeed, the Figures below display system (3) with the same initial values but $\varepsilon = 1$ (left, coinfected disappear) and $\varepsilon = 0.01$ (right, coinfected become endemic)



References

[1] P. Auger, J.-C. Poggiale, E. Sanchez. (2012). A review on spatial aggregation methods involving several time scales. Ecological Complexity Volume 10, pages 12–25.

[2] R.W. Cross et al. (2010). Impact of primary influenza infection on the immune response to secondary bacterial infection in aged mice . Conference: Conference on Options for the Control of Influenza VII Hong Kong, Influenza and other respiratory viruses. Vol: 5, num 1, 198–201.

[3] M. Zlamy et al. (2013) The impact of Rotavirus mass vaccination on hospitalization rates, nosocomial Rotavirus gastroenteritis and secondary blood stream infections BMC infectious diseases Vol: 13, 112

Address for correspondence: marcos.marva@uah.es