A SLOW-FAST MODEL FOR COINFECTION BY OPPORTUNISTIC DISEASES

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Abstract Traditional biomedical approaches treated each disease in isolation. Nowadays, it is increasingly recognized that synergistic disease interactions are of great importance [2]. We consider a host population affected by an infectious disease, *primary disease*, which facilitates individuals acquiring a *secondary (opportunistic) disease*. The primary disease is a rather long-term infection while the secondary disease is a short-term infection affecting only the infected individuals of the primary disease. To distinguish between short and long-term infection the model is written in the form of a two time scales system. This feature allows a dimension reduction of the system what makes its mathematical analysis more tractable [1].

The model We consider three epidemiological stages: *susceptible* S, *primary infected* U and *coinfected* V. There are slow and fast processes

- **Slow time scale**: The primary disease transmission is density dependent with recovery rate γ and transmission rates β_u, β_v.
  The model includes demography with death rate m, disease extra mortality rates m_u, m_v, reproduction rate r (and the disease reductions $0 < a_v \leq a_u \leq 1$).
  The effect on individuals in class q of competition with individuals in class p is denoted by c_{pq}, for $p, q \in \{s, u, v\}$.
- **Fast time scale**: The opportunistic disease transmission is frequency dependent with recovery rate δ and transmission rate λ.

Considering together the slow and the fast dynamics yields the slow-fast system

Fast process — Slow processes; $\varepsilon \sim 0_+$

$$\begin{cases} \dfrac{dS}{d\tau} = \varepsilon\left[r(S+a_uU+a_vV) - mS - (c_{ss}S+c_{su}U+c_{sv}V)S - (\beta_uU+\beta_vV)S + \gamma U\right] \\ \dfrac{dU}{d\tau} = \dfrac{-\lambda UV}{U+V} + \delta V + \varepsilon\left[-(m+m_u)U - (c_{us}S+c_{uu}U+c_{uv}V)U + \beta_uSU + \beta_vSV - \gamma U\right] \\ \dfrac{dV}{d\tau} = \dfrac{\lambda UV}{U+V} - \delta V + \varepsilon\left[-(m+m_v)V - (c_{vs}S+c_{vu}U+c_{vv}V)V\right] \end{cases}$$

Opp. disease — Demography — Competition — Primary disease

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

$$dn/d\tau = f(n) + \varepsilon s(n) \quad (1)$$

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 y^* is a hyperbolic equilibrium of the reduced system

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

we can describe the behavior of system (1) in terms of $(x^*(y^*), y^*)$.

Results Using the reduction technique, the original slow-fast system is analyzed by means of the reduced system (2) in terms of the slow variables S and $I = U + V$, the total amount of infected individuals,

$$\begin{cases} dS/dt = (r-m)S - c_{ss}S^2 + AI - BSI, \\ dI/dt = -CI + DSI - EI^2, \end{cases}$$

where A, B, C, D, E depend on δ/λ, the secondary disease parameters. The following quantities depend also on δ/λ and help in describing the outcomes of the aggregated system

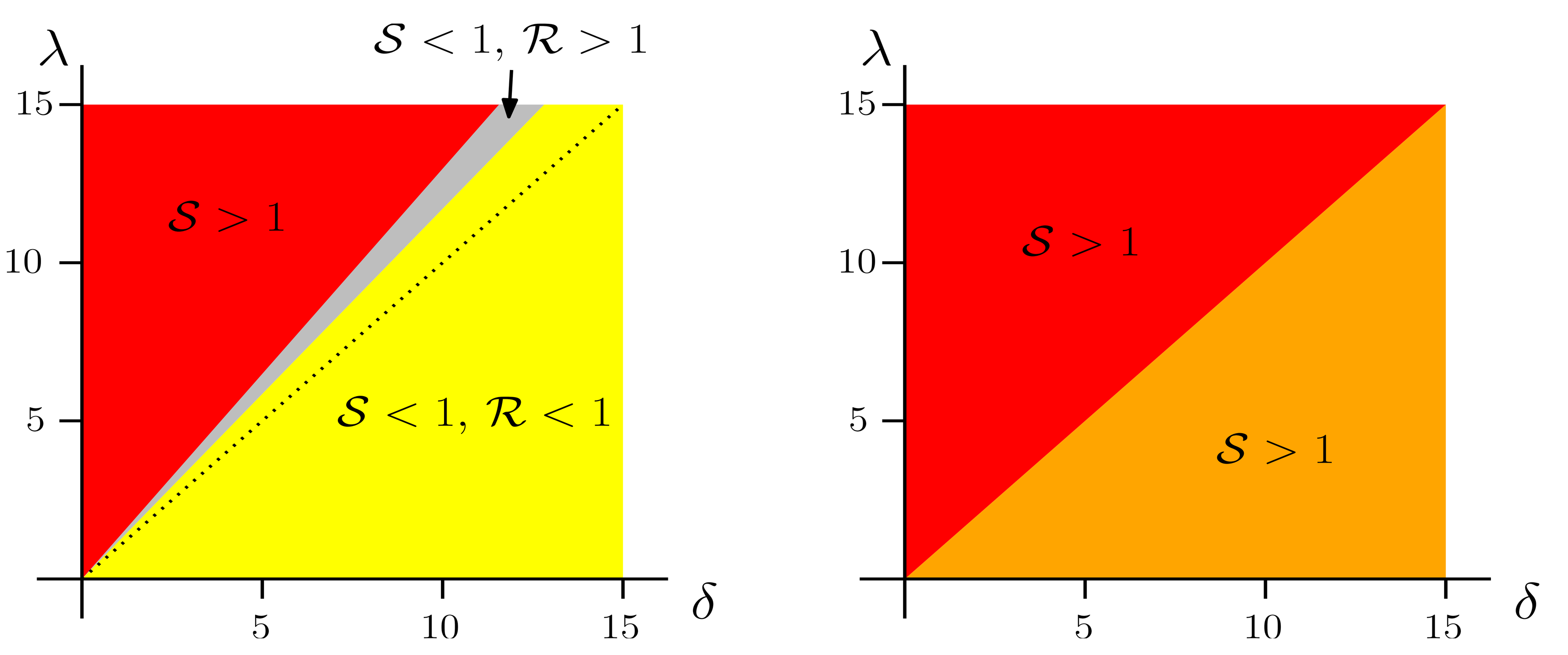
$$\mathcal{R} = \frac{E(r-m) + AD + BC}{2\sqrt{(c_{ss}E + BD)AC}} \qquad \mathcal{S} = \frac{(r-m)D}{c_{ss}C}$$

The opportunistic disease can change the primary disease outcome since

- $\mathcal{S} > 1 \Rightarrow$ Disease endemic: coinfection if $\delta < \lambda$
- $\mathcal{S} < 1 \Rightarrow \begin{cases} \mathcal{R} < 1 \Rightarrow \text{Disease free.} \\ \mathcal{R} > 1 \Rightarrow \text{Depending on initial values, disease free or endemic scenario (coinfection if } \delta < \lambda). \end{cases}$

Note that the opportunistic disease can not invade if $\delta \geq \lambda$.

Epidemiological outcomes as function of δ and λ for two different sets of parameter values



Yellow: disease free. **Orange**: endemic primary infection. **Gray**: disease free or endemic coinfection, depends on initial values. **Red**: endemic coinfection.

APPLICATIONS: If there are procedures to modify the recovery and transmission rates (δ, λ) of the opportunistic disease:

- Knowing the actual values of δ and λ allows to design measures to change the epidemiological scenario.
- If each procedure has associated different economical cost, the shorter distance between regions may not be feasible or optimal.

References

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

[2] E.C. Griffiths, A.B.P. Pedersen, A. Fenton, O.P. Petchey (2011). *The nature and consequences of coinfection in humans*. Journal of Infection 63 (3): 200–206

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