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A MINIMAL MODEL COUPLING COMMUNICABLE AND NON-COMMUNICABLE DISEASES

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Abstract. This work presents a model combining the simplest communicable and non-communicable disease models. The latter is, by far, the leading cause of sickness and death in the World, and introduces basal heterogeneity in populations where communicable diseases evolve. The model can be interpreted as a risk-structured model, another way of accounting for population heterogeneity. Our results show that considering the non-communicable disease (in the end, a dynamic heterogeneous population) allows the communicable disease to become endemic even if the basic reproduction number is less than 1. This feature is known as subcritical bifurcation. Furthermore, ignoring the non-communicable disease dynamics results in overestimating the basic reproduction number and, thus, giving wrong information about the actual number of infected individuals. We calculate sensitivity indices and derive interesting epidemic-control information.

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1. Introduction

It is a fact that non-communicable diseases (NCDs), that include cardiovascular disease, cancer, chronic respiratory disease, or diabetes, are the main cause of sickness and death worldwide [37]. Just in 2000 NCDs were responsible for 35 million deaths (about 60% of all deaths around the world). These figures raised to 41 million death in 2020 (*i.e.* about 71% of deaths worldwide) [37]. NCDs are the result of a combination of non-reversible genetic and physiological factors, but also of environmental and behavioral factors that may be reverted. The use of, or exposure to tobacco, alcohol abuse, unhealthy diets, or physical inactivity [12] are among these revertible factors, as well as air pollution and environmental contamination [29]. NDCs are very common and, therefore, play a key role in the epidemiology of communicable or infectious diseases (CD) [9], [38], that have its own broad interest [6]. These synergistic interactions of a disease with pre-existing social, structural, political, or health conditions are known as syndemics [32]. Whenever some communities suffer from a higher impact of a disease than others, syndemics scientists explain that many factors work together in a synergistic way, and populations with the highest morbidity and mortality are those that experience the greatest impact

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of these interactions. For instance, the interplay between coinfection and pregnancy in Sub-Saharan Africa [33] or, more recently COVID19 [27].

A shared feature of both NCDs and the above mentioned pre-existing conditions is that induce an structure into the population which, in the end, define different risk-classes in front of CDs. These risk classes do not need to be static (we care of reversible NCDs), and its synergistic interaction with epidemic dynamics needs to be understood as a whole, allowing policy makers and managers implement effective, optimal actions [27].

The reproduction number, R_0, is a key quantity in the dynamics of a communicable disease. R_0 stands for the average number of secondary infections produced by an infected individual in a population made just of susceptible individuals [3]. It is well known that $R_0 > 1$ enables communicable diseases to become endemic. However $R_0 < 1$ does not always lead to the eradication of the communicable disease. This somewhat counter-intuitive fact is known as *subcritical bifurcation* [14] (also often less properly named *backward bifurcation* [17]). Mechanisms leading to subcritical bifurcations in epidemiological models are proposed in [15], while general necessary and sufficient conditions for an epidemiological model to display a subcritical bifurcation are obtained in [7]. This phenomenon has important consequences from the viewpoint of epidemics control, since reducing R_0 below 1 may not be sufficient to avoid the disease endemic scenario [34]. An instance of this unfortunate behavior is shown in the case of TB in India, [36].

This work is aimed to analyze the interplay between NCDs and CDs. For this purpose, in Section 2 we set up a minimal model using one of the simplest transmission laws [3] for CDs and the minimal number of epidemiological stages. The structure of the model presented herein can be seen as a simplified variant of risk-structured SIS models [22], [15], [23]. In doing so, we isolate the *net effect* of the NCD/risk-structure on the behavior of the CD. Thus, we disentangle the role of dynamic heterogeneity (a structured population such that individuals can move from class to class) in the screened population from other processes (see the discussion in Sect. 4). In Section 3, we analyze the model and derive sufficient and necessary conditions enabling a subcritical bifurcation. We discuss the results and its implications on the control of the CD in Section 4. Section 5 gathers the main conclusions of the manuscript.

2. Model formulation

We focus on the interplay CD-NCD under minimal settings avoiding further processes as, for instance, demography. This approach yields a *laboratory model* that can be further expanded to face more general, realistic settings. The model is built upon ordinary differential equations.

We assume that individuals affected by the NCD are somehow weaker to face the CD. At time t the population is partitioned into susceptible individuals $S(t)$, *i.e.* those that are affected neither by the CD nor the NCD, weakened individuals $W(t)$, *i.e.* those that suffer from the NCD but are not infected by the transmissible disease, and individuals infected by the CD, $I(t)$, regardless of whether they are weakened or not.

In the absence of infected individuals, the NCD dynamics is nothing but a two-compartment linear model

$$\begin{cases} S' = -aS + bW, \\ W' = aS - bW, \end{cases} \tag{2.1}$$

the simplest closed two-compartment model, meaning that nothing enters from or leaves to the outside. The transition rates are constant; mode sophisticated transitions are possible [30], [28], but we disregard this approach here to keep the model formulation minimal as mentioned. For instance addiction to substances (tobacco, alcohol,...) can be modelled at the first attempt by this linear model, also social class mobility [30], or the dynamics of being pregnant/not pregnant as underlaying risk factor [33].

As for the CD, we consider roughly a SIS model [22] that affects a population of susceptible individuals that is heterogenous and dynamic. SIS models are appropriate for sexually transmitted diseases and bacterial infections such that infected individuals become infective within a sort amount of time and do not gain immunity to the disease once the infection is overcame [34]. Thus, we do not consider further epidemiological stages as

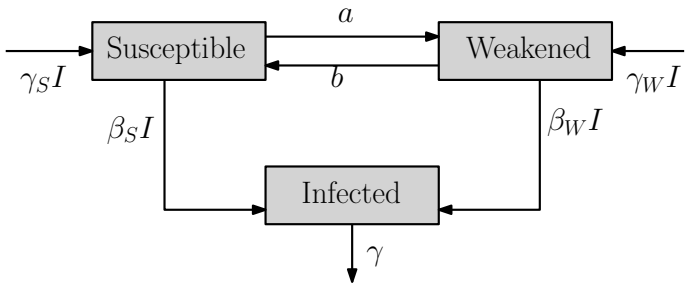

FIGURE 1. Flow diagram associated to system (2.2).

asymptomatic or recovered individuals. In the other extreme recovered individuals may acquire immunity to the disease and be removed from the model as, for instance, in [20].

Next, we define the rates at which individuals move from one compartment to each other, see Figure 1. We assume that susceptible individuals become weakened at a constant rate a and get out of the weakened class also at a constant rate b. The dynamics of the transmissible disease is somehow similar to (but not exactly) the classical SIS model [3] with density-dependent transmission. Susceptible and weakened individuals are assumed to behave differently concerning the CD so that the transmission rates $\beta_S I$ and $\beta_W I$ differ from each other. We assume that infected individuals recover and become immune at rate γ. Note that we do not know whether an infected individual suffers or not from the NCD. Thus, we do not care about recovered individuals (that leave the model). We further consider that susceptible (in front of the CD) individuals are introduced at rates $\gamma_S I$ and $\gamma_W I$ in the corresponding compartment S and W, so that the population size is kept constant. The construction and further analysis can be done *mutatis mutandi* by considering frequency-dependent transmission (see [3] for a discussion on density-dependent vs frequency-dependent transmission).

The ordinary differential equations system produced by the above-stated hypotheses consists of two coupled submodels: one describing the communicable disease and another one that describes the non-communicable disease. The combined model reads as follows

$$\begin{cases} S' = -aS + bW - \beta_S SI + \gamma_S I, \\ W' = aS - bW - \beta_W WI + \gamma_W I, \\ I' = \beta_S SI + \beta_W WI - \gamma I, \end{cases} \tag{2.2}$$

where $\gamma_S + \gamma_W = \gamma$. Note that the total population size $N(t) := S(t) + W(t) + I(t) = N$ remains constant, as $N'(t) = 0$.

For sake of completeness, let us revisit these two well known (sub)models: the SIS model and the model for non-communicable diseases.

The CD SIS submodel. If susceptible individuals are all of the class, system (2.2) simplifies into

$$\begin{cases} S' = -\beta_S SI + \gamma_S I, \\ I' = \beta_S SI - \gamma_S I, \end{cases} \tag{2.3}$$

where $S(t) + I(t) = N$ remains constant over time. It is nothing but the classical SIS model with density-dependent transmission [3]. A straightforward analysis reveals that system (2.3) possesses two equilibrium

points: the trivial equilibrium $(S^*, I^*) = (N, 0)$ (no infected individuals) and a the endemic-disease equilibrium

$$(S^*, I^*) = \left(\frac{\gamma_S}{\beta_S},\, N - \frac{\gamma_S}{\beta_S}\right) \tag{2.4}$$

The well known *basic reproduction number*

$$R_{0,S} = \frac{\beta_S}{\gamma_S} N \tag{2.5}$$

determines whether the disease-free equilibrium ($R_{0,S} < 1$) or the endemic-disease equilibrium ($R_{0,S} > 1$) is globally asymptotically stable (GAS) for system (2.3).

The NCD compartment submodel. In the absence of the infectious disease ($I(t) = 0$), system (2.2) reduces to system (2.1) where $S(t) + W(t) = N$ remains constant over time. We will discuss in Section 4 further extensions of this submodel. We assume $N > 0$ (there are individuals) so that there exists a non trivial equilibrium point

$$(S^*, W^*) = \left(\frac{b}{a+b} N,\, \frac{a}{a+b} N\right) \tag{2.6}$$

where $b/(a+b)$ and $a/(a+b)$ are the fraction of susceptible and weakened individuals within the entire population N. It is straightforward that the nontrivial equilibrium (2.6) is a global attractor. This feature can be interpreted as the non-communicable disease being structural to the population.

3. Results

In this section, we analyze the long term behavior of the solutions of system (2.2), that is, the so-called equilibrium points and their stability.

A first step consists of showing that the model is well behaved, that is,

Proposition 3.1. *The solutions of system (2.2) are bounded from above and the non negative cone is forward invariant.*

Proof. All the solutions of system (2.2) are bounded since the total population size is kept constant because $S'(t) + W'(t) + I'(t) = 0$. Thus, any solution of system (2.2) evolves in the plane $S(t_0) + W(t_0) + I(t_0) = N$ (valid for all $t \geq t_0$) where N stands for the total population size.

The invariance of the non negative cone

$$\bar{\mathbb{R}}^3_+ := \left\{(S, W, I) \in \mathbb{R}^3;\, S \geq 0,\, W \geq 0,\, I \geq 0\right\}$$

is equivalent to prove that any solution with initial values on the boundary can not become negative as the time growths. For instance, assume that $W(t_0) = 0$ and $S(t_0), I(t_0) \neq 0$. It follows that $W(t_0)' = aS(t_0) + \gamma_W I(t_0) \geq 0$, so that $W(t)$ can not become negative. The same holds assuming $S(t_0) = 0$ but $W(t_0), I(t_0) \neq 0$. Assume now that $I(t_0) = 0$ and $S(t_0), W(t_0) \neq 0$. Then $I'(t_0) = 0$ regardless of the value of $S(t_0)$ and $W(t_0)$. There are no infected individuals and there will be none. The solution of the system evolves constrained by $S(t_0) + W(t_0) = N = cte$, that is to say that system (2.2) is reduced to system (2.1) and its solution converge to (2.6). □

As we have already said, the non-communicable disease is supposed to be inherent to that population. The first result consists of determining conditions so that an outbreak of the communicable disease lead to an

endemic disease scenario. In other words, we seek conditions enabling the semitrivial equilibrium point

$$E_0^* = (S_0^*, W_0^*, I_0^*) = \left(\frac{b}{a+b} N,\ \frac{a}{a+b} N,\ 0 \right) \tag{3.1}$$

to be asymptotically stable (communicable-disease-free state) or unstable (endemic communicable disease scenario). Note that semitrivial equilibrium point E_0^* consists of the components of the nontrivial equilibrium (2.6) of system (2.1) along with 0 infected individuals in the third entry.

Proposition 3.2. *Consider system (2.2), the disease free equilibrium E_0^* given by (3.1) and the reproductive number R_0 defined by*

$$R_0 = \frac{b\beta_S + a\beta_W}{(a+b)(\gamma_S + \gamma_W)} N. \tag{3.2}$$

Then E_0^* is locally asymptotically stable (LocAS) if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof. It follows from a standard analysis of the sign of the eigenvalues of the Jacobian matrix of the flow of system (2.2). This result follows the same using the next generation method [35]. □

Thus the CD free equilibrium (3.1) is unstable if $R_0 > 1$, which leads to a CD endemic scenario. On the other hand, $R_0 < 1$ implies that the CD free equilibrium (3.1) is locally asymptotically stable, meaning that any CD outbreak will fade out (at least if the number of infected individuals is small enough). These results provide us with valuable but incomplete information. Namely:

1. What are the conditions leading the CD free scenario to be globally asymptotically stable? *i.e.*, what are the conditions ensuring that CD free scenario will be achieved regardless of the strength of a potential outbreak?
2. What role does the NCD play in the dynamics of communicable disease?

In other words, we are interested in the structure of the set of the positive equilibrium points of system (2.2) and its stability. The positive equilibrium points are the component-wise positive solutions to system

$$\begin{cases} 0 = -aS + bW - \beta_S SI + \gamma_S I, \\ 0 = aS - bW - \beta_W WI + \gamma_W I, \\ 0 = \beta_S SI + \beta_W WI - \gamma I, \end{cases} \tag{3.3}$$

where $\gamma = \gamma_S + \gamma_W$. Weakened individuals behave differently from susceptible individuals in front of the CD, being plausible $\beta_W \geq \beta_S$ and $\gamma_W \leq \gamma_S$ with at least one of the inequalities being strict. We assume $\beta_W > \beta_S$ through the manuscript while no assumption is made on γ_S and γ_W since these coefficients are not proper recovery rates.

Let us assume that $I(t_0) \neq 0$ since otherwise system (3.3) reduces to system (2.1). Thus, the third equation can be simplified and solved, say, in W:

$$W = \frac{\gamma_S + \gamma_W - \beta_S S}{\beta_W}. \tag{3.4}$$

Note that $S'(t)+W'(t)+I'(t)=0$ so that one equation, say, the first one in (3.3) can be neglected. Using that the total population $S+W+I=N$ yields

$$S=\frac{\beta_W}{\beta_W-\beta_S}\left(N-\frac{\gamma_S+\gamma_W}{\beta_W}-I\right). \tag{3.5}$$

Finally, we get from the second equation in (3.3) that the number of infected individuals at equilibrium is the solution of the quadratic polynomial equation

$$\Psi(I)=\alpha_2 I^2+\alpha_1 I+\alpha_0=0 \tag{3.6}$$

where

$$\begin{aligned}\alpha_2&=-\frac{\beta_S\beta_W}{\beta_W-\beta_S}<0,\\ \alpha_1&=-\frac{\beta_S(b+\gamma_W)+\beta_W(a+\gamma_S)-\beta_S\beta_W N}{\beta_W-\beta_S},\\ \alpha_0&=-\frac{(\gamma_S+\gamma_W)(a+b)-(b\beta_S+a\beta_W)N}{\beta_W-\beta_S},\end{aligned} \tag{3.7}$$

and, indeed, $I(t)$ is the solution of the differential equation

$$I'=\Psi(I)=\alpha_2 I^2+\alpha_1 I+\alpha_0. \tag{3.8}$$

The following Proposition 3.3 describes the posible outcomes of system (2.2) by analyzing equation (3.8).

Proposition 3.3. *Consider system (2.2) along with the basic reproduction number R_0 as defined in (3.2) and*

$$\Delta=\left(\frac{a+\gamma_S}{\beta_S}+\frac{b+\gamma_W}{\beta_W}\right)\frac{1}{N} \tag{3.9}$$

Then:

1. *Condition $\alpha_1^2-4\alpha_0\alpha_2<0$ implies that the trivial solution $E_0^*=(S^*,W^*,0)$ as defined in (3.1) is GAS.*
2. *Assume $\alpha_1^2-4\alpha_0\alpha_2=0$. Then:*
   (a) *If, in addition, $\Delta\geq 1$, it follows that E_0^* is GAS.*
   (b) *Otherwise, $\Delta<1$ implies that E_0^* is LocAS and*

$$I^*=\frac{-\alpha_1}{2\alpha_2} \tag{3.10}$$

   is a semi-stable equilibrium point from the right, meaning that $I(t_0)>I^*$ implies $I(t)\to I^*$ while $I(t_0)<I^*$ implies $I(t)\to 0$, as E_0^* is LocAS.
3. *Assume $\alpha_1^2-4\alpha_0\alpha_2>0$. Then,*
   (a) *$R_0>1$ implies that E_0^* is unstable and there exists a GAS endemic disease equilibrium $E_+^*=(S_+^*,W_+^*,I_+^*)$, where $I_+^*>0$.*
   (b) *$R_0<1$ and $\Delta\geq 1$ entail the disease free equilibrium E_0^* to be GAS.*
   (c) *$R_0<1$ and $\Delta<1$ imply the existence of two endemic disease equilibrium $E_\pm^*$ such that $E_0^*<E_-^*<E_+^*$, being E_0^* and E_+^* LocAS while E_-^* is unstable.*

Proof. Note that $\beta_W > \beta_S$, since weakened individuals are weaker in front of the CD. It is immediate to calculate the number of infected individuals I^* (if any) at equilibrium by solving equation (3.6), so that

$$I^*_{\pm} = \frac{-\alpha_1 \pm \sqrt{\alpha_1^2 - 4\alpha_0\alpha_2}}{2\alpha_2} \tag{3.11}$$

then, S^* and W^*, the number of susceptible and weakened individuals at equilibrium can be calculated from I^* using (3.5) and (3.4).

For statement 1, note that condition $\alpha_1^2 - 4\alpha_0\alpha_2 < 0$ yields no infected individuals at equilibrium, so that $I(t) \to 0$ as $t \to \infty$. Therefore, system (2.2) asymptotically approaches system (2.1). Note that substituting $I^* = 0$ in (3.4) and (3.5) does not leads to E_0^* as defined in (2.6) because (3.40) and (3.5) have been derived assuming $I^* \neq 0$.

Thus, we assume from now on that $\alpha_1^2 - 4\alpha_0\alpha_2 \geq 0$. Direct calculations yield

$$\alpha_0 = 0 \Leftrightarrow R_0 = 1, \quad \alpha_0 < 0 \Leftrightarrow R_0 < 1, \quad \alpha_0 > 0 \Leftrightarrow R_0 > 1$$

along with

$$\alpha_1 = 0 \Leftrightarrow \Delta = 1, \quad \alpha_1 < 0 \Leftrightarrow \Delta > 1, \quad \alpha_1 > 0 \Leftrightarrow \Delta < 1,$$

where Δ is given by (3.9).

We focus now in statement 2. It is clear then that $\alpha_1^2 - 4\alpha_0\alpha_2 = 0$ implies that I^* as defined in (3.10) is the unique solution to equation (3.6). In addition, $\Delta \geq 1$ implies $I^* \leq 0$ and arguing as before yields 2(a). On the contrary, $\Delta < 1$ implies $I^* > 0$. Then, $\Psi(I) < 0\ \forall I \neq I^*$ and $\Psi(I^*) = 0$ so that 2(b) holds to be true.

As for statement 3 we assume now $\alpha_1^2 - 4\alpha_0\alpha_2 > 0$. Note that $R_0 > 1$ is equivalent to $\alpha_0 > 0$. Besides, $\alpha_2 < 0$ so that it follows from (3.11) that $I^*_- < 0$ and $I^*_+ > 0$. Basic qualitative theory for scalar autonomous differential equations yield that I^*_+ is GAS, since $\Psi(0) = \alpha_0 > 0$, $\Psi(I) > 0\, \forall I \in (0, I^*)$, and $\Psi(I) < 0\, \forall I > I^*$ which proves 3(a). Statements 3(b) and 3(c) hold from similar reasoning. □

Remark 3.4. Proposition (3.3) does not cover all the possible combinations of the values of R_0 and Δ, that we include next. We claim that $I^* = 0$ is GAS if either

1. $\Delta = 1$ and $R_0 = 1$,
2. $\Delta = 1$ and $R_0 < 1$,
3. or $\Delta < 1$ and $R_0 > 1$.

The proof follows from direct calculations with expression (3.11).

Therefore, it is not difficult to classify all the possible qualitatively different outcomes in terms of sign of α_0 and α_1 (given that $\alpha_2 < 0$) or, equivalently, depending on whether R_0 and Δ are smaller or larger that the threshold value 1. Figure 2 sketches the qualitatively different cases.

Panels in Figure 2 display $I' = \Psi(I)$; that is to say, the intercept with the horizontal axis is the amount of infected individuals at equilibrium (since $I' = 0$). Note that the sign of $I'(t)$ determines whether the number of infected individuals $I(t)$ increases ($I' > 0$) or decreases ($I' < 0$), which yields the stability of the equilibrium points.

Essentially, three scenarios are possible: the global CD free scenario (left and central panels in the first row of Fig. 2), the global endemic CD scenario (right panel in the first row and left and central panels at the second row of Fig. 2), and a third intermediate one that predicts either endemic disease or disease free scenarios depending on the initial amount of infected individuals (right panel of the second row of Fig. 2). These features are better shown with a bifurcation diagram, being R_0 the bifurcation parameter, see Figure 3. In this context, Δ is the

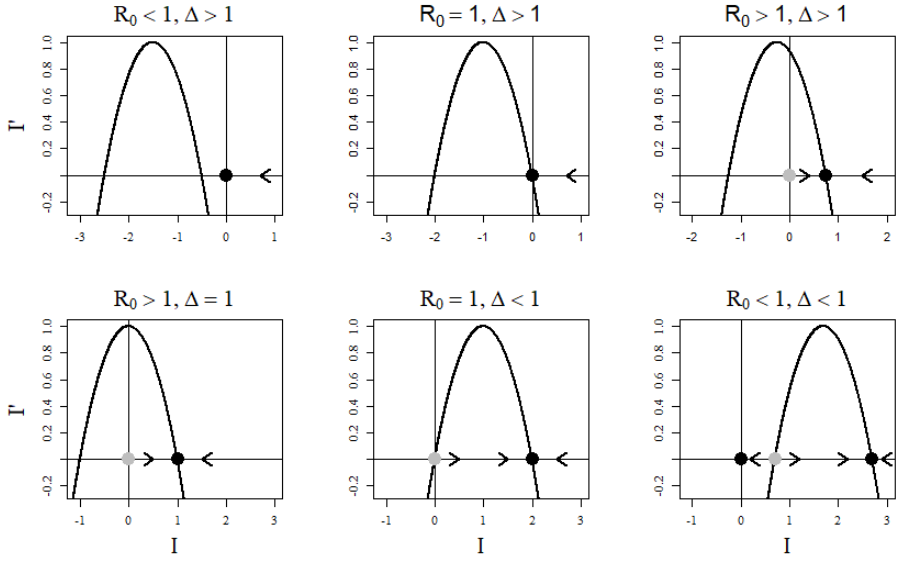

FIGURE 2. Each panel displays the parabola defined by equation (3.6) in the I-I' plane for different combinations of R_0 and Δ. Solid dots are the feasible equilibrium points that are asymptotically stable (black) and unstable (gray).

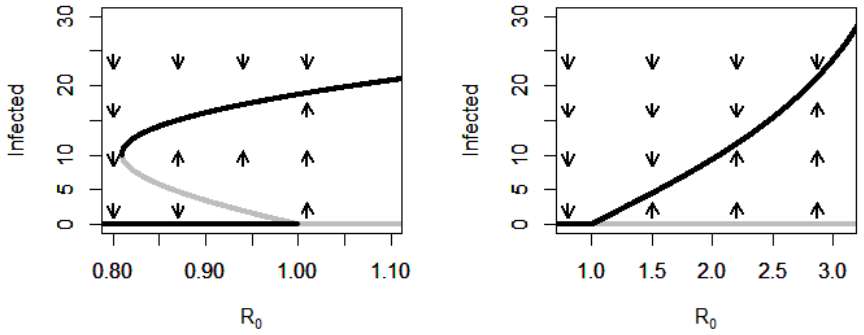

FIGURE 3. Bifurcation diagrams plotting the total number of infected individuals at equilibrium for different values of R_0. The left panel displays a subcritical bifurcation and the right panel a supercritical bifurcation. In gray unstable equilibrium points and in black LocAS equilibrium points. Parameter values (guessed): left panel $\beta_W = 1$; $\beta_S = 0.2$; $\gamma_S = 11.8$; $\gamma_W = 16.6$, $a \in [0.01, 8]$, $b = 3.6$; right panel $\beta_W = 1.1$; $\beta_S = 0.1$; $\gamma_S = 11.8$; $\gamma_W = 16.6$, $a \in [0.01, 8]$, $b = 1$.

so-called direction of bifurcation, so that $\Delta < 1$ leads to a subcritical (or backward) bifurcation (left panel in Fig. 3) and $\Delta > 1$ yields a supercritical (or forward) bifurcation (right panel in Fig. 3).

For $R_0 < 1$ the solution $I^* = 0$ is locally asymptotically stable, *i.e.* the presence of a small number of infected individuals is not enough to trigger an epidemic disease state, and the infected population will fade away regardless of the value of Δ. However, due to management decisions or natural causes, the values of the parameters involved in the expression of R_0 may change and increase R_0 so that it crosses the threshold value $R_0 = 1$. In such a case, the solution $I^* = 0$ is destabilized, which means that the communicable disease becomes endemic even if there is a little initial amount of infected individuals.

The quantity Δ plays a key role when $I^* = 0$ is stable ($R_0 < 1$): namely if $\Delta > 1$ then $I^* = 0$ is globally asymptotically stable, which means that any epidemic outbreak will fade away regardless of the initial number

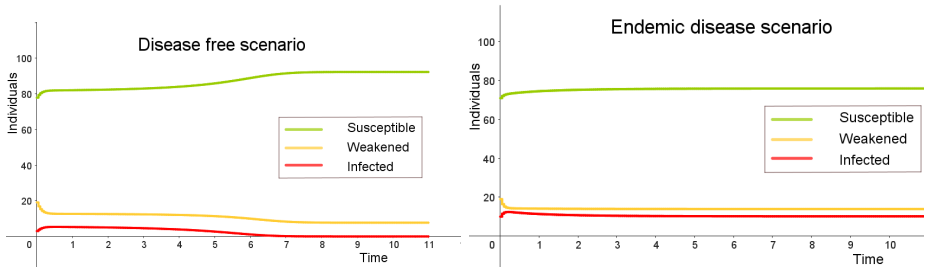

FIGURE 4. Solutions to system (2.2) with parameter values $\beta_W = 1$; $\beta_S = 0.2$; $\gamma_S = 12.5$; $\gamma_W = 16.6$, $N = 100$, $a = 0.3$, and $b = 3.6$. Initial values $(S_0, W_0, I_0) = (78, 19, 3)$ (left) and $(S_0, W_0, I_0) = (71, 19, 10)$ (right). The parameter values are such that $R_0 = 0.9$ and $\Delta = 0.64$, so that a subcritical bifurcation occurs as in the left panel of Figure 3. Thus, the initial number of infected individuals determines whether the infectious disease becomes endemic (right panel) or not (left panel).

of infected individuals. On the contrary, $\Delta < 1$ implies that there exists $R_0^* < 1$ such that for each $R_0^* < R_0 < 1$ there exist a threshold number of infected individuals given by I_-^* (see Eq. (3.11)) such that beyond it the disease becomes endemic and stabilize at I_+^* (see Eq. (3.11)). For $\Delta < 1$ and $R_0 < R_0^*$ the disease disapperars as $I^* = 0$ becomes globally asymptotically stable.

The stability of all the other equilibrium points in Figure 2 follows reasoning as before.

4. Discussion

We next discuss our finding on system (2.2). Its apparent simplicity allows, instead, to emerge relevant features. First of all, we account for the possibility of subcritical bifurcation under minimal settings, see Section 4.1. We also analyze the consequences of not considering explicitly the NCD in Section 4.2. Then, in Section 4.3, we focus on the effect of control strategies (*via* modifying the coefficients of the system). In particular, we calculate the sensitivity indices, we derive bounds for these indices, we focus on the effect of modifying several coefficients at once, and we reveal possible unexpected consequences when trying to handle disease outbreaks.

4.1. Subcritical bifurcation

Regardless of the approach (CD vs NCD or CD risk structure) system (2.2) may undergo a subcritical bifurcation, which is against the R_0-dogma [31] that states that $R_0 > 1$ leads to disease endemicity while $R_0 < 1$ induces disease eradication. Usual causes of subcritical bifurcation are the use of imperfect vaccine [5], [16], structured immunity [31] or exogenous re-infection in TB disease [11]. In [34] subcritical bifurcation was also reported for a simple SIS model; this model is simplest that ours in the sense of having only two compartments, but it is more sophisticated since the transmission rate nonlinear, which makes a huge difference.

In [15] several other biological or epidemiological mechanisms are proposed such as vaccine-induced immunity waning at a slower rate than natural immunity, disease-induced mortality in vector-borne diseases, and differential susceptibility in risk-structured models (related to the latter, see [22] and [23]).

Subcritical bifurcations can be found also in co-infection by an opportunistic disease model [26], where two communicable diseases were considered (one of them with saturating treatment rate [24]).

A salient feature of the model proposed and analyzed here lies in its ability to undergo a subcritical bifurcation while not incorporating any of the above-mentioned mechanisms. Thus, we show that subcritical bifurcations in epidemiology are not such a rare occurrence. On the contrary, plain heterogeneity in the CD susceptible class is enough to make a subcritical bifurcation possible.

Thus, system (2.2) shows that subcritical bifurcations may occur in epidemic models simply by considering the dynamics associated with a heterogeneous population, which can be seen as a common factor in the above-mentioned models.

4.2. What if the non-communicable disease is not explicitly considered?

Thus, let us assume that there is no weakened individuals compartment so that the CD follows the simplest model (2.3). Even if we do not consider an explicit compartment, the NCD is present in the population, and the coefficients of system (2.3) must reflect in some way this fact. It is reasonable assuming that the NCD-induced population heterogeneity will be captured by any reasonable sampling procedure performed to estimate the coefficients of the model by weighting the corresponding transmission (β_S and β_W) and recovery (γ_S and γ_W) coefficients. This hypothesis is equivalent to assuming that the dynamics associated with the NCD has already achieved an equilibrium, which is the usual assumption when dealing with time-scale systems [1] (also known as *quasi-steady-state approximation* [13]) that has been used in co-infection by an opportunistic disease models [25], [26], where both diseases are transmissible. Thus a fraction $b/(a+b)$ of the total population is free of the NCD and the remaining fraction $a/(a+b)$ is not. Then, to obtain a fair comparison, transmission and the recovery rates are set to

$$\beta_S \frac{b}{a+b} + \beta_W \frac{a}{a+b}, \qquad \gamma_S \frac{b}{a+b} + \gamma_W \frac{a}{a+b}, \tag{4.1}$$

respectively, which yield the corresponding basic reproductive number:

$$\widehat{R}_0 = \frac{b\beta_S + a\beta_W}{b\gamma_S + a\gamma_W} N, \qquad (\widehat{S}^*, \widehat{I}^*) = N\left(\frac{1}{\widehat{R}_0}, N - \frac{1}{\widehat{R}_0}\right) \tag{4.2}$$

Direct calculations yield

$$\frac{\widehat{R}_0}{R_0} = 1 + \frac{a\gamma_S + b\gamma_W}{b\gamma_S + a\gamma_W}. \tag{4.3}$$

That is, the ratio (4.3) is always larger than 1, implying that explicit consideration of the NCD dynamics in the model does matter. Neglecting its effect leads to overestimating the basic reproductive number and, thus, i) thinking of an endemic disease scenario that may be not real and ii) overestimating the number of infected individuals at equilibrium.

Figure 5 displays the bifurcation diagram of the total amount of infected individuals at equilibrium I^* (in black, bottom line) and $\widehat{I}^*$ (in blue, upper line) versus $\widehat{R}_0$ and R_0, that both appear in the horizontal axis.

4.3. Sensitivity analysis, sensitivity indices and epidemic control

Finally, we accomplish a sensitivity analysis of the outcome of the model to the parameters of the model.

In Section 3 we have shown that the long term behavior of the model can fully be described in terms of R_0 and Δ. We first examine the expressions of R_0 and Δ. Next, we calculate the corresponding sensitivity indices [8]. Then we have drawn concussion useful for control purposes.

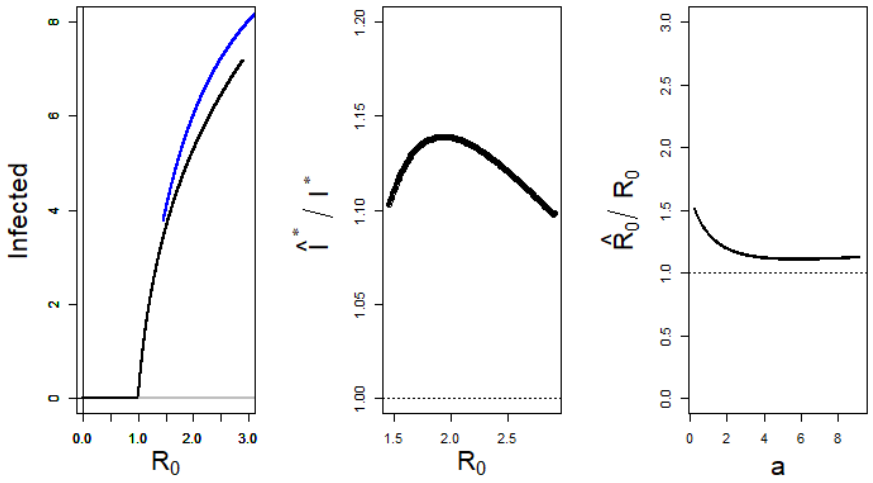

FIGURE 5. Left panel: bifurcation diagram of the number of infected individuals at equilibrium of the classical SIS model (2.3, in blue, top curve) with transmission rate $\beta = b\beta_S/(a+b) + a\beta_W/(a+b)$ and recovery rate $\gamma = b\gamma_S/(a+b) + a\gamma_W/(a+b)$ and system (2.2) in black, bottom curve. The bifurcation parameter is $\hat{R}_0$ and R_0, respectively, for $N = 12, b = 35.4, \beta_S = 1, \beta_W = 9.1, \gamma_S = 8.4, \gamma_W = 15.3$ and $a \in [0.1, 10]$ (guessed parameter values). Note that expression (4.3) and the parameters values explain the aparent gap in $\widehat{I}^*$. Central panel, the ratio $\widehat{I}^*/I^*$. Right panel: the ratio $\widehat{R}_0/R_0$.

Grouping terms in the expression of Δ (see Eq. (3.9)) yields

$$\begin{aligned} \Delta &= \left(\frac{\gamma_S}{\beta_S} + \frac{\gamma_W}{\beta_W}\right)\frac{1}{N} + \left(\frac{a}{\beta_S} + \frac{b}{\beta_W}\right)\frac{1}{N} \\ &= \underbrace{\frac{1}{R_{0,S}} + \frac{1}{R_{0,W}}}_{\text{Block 1}} + \underbrace{\left(\frac{a}{\beta_S} + \frac{b}{\beta_W}\right)\frac{1}{N}}_{\text{Block 2}} \end{aligned} \tag{4.4}$$

Interestingly, the first block includes the basic reproduction numbers corresponding to either no weakened class (all individuals are susceptible) or no susceptible class (all individuals are weakened, *i.e.*, the analogous case with other values for γ and β). In contrast, the second block includes the ratio of the rates at which individuals leave the susceptible class (a/β_S) or the weakened class (b/β_W). Two conclusions can be drawn from (4.4): on the one hand, Δ depends linearly on a and b (see the top right panel of Fig. 6). Therefore, Δ changes linearly with these parameters. On the other hand, Δ depends non-linearly on the corresponding basic reproduction numbers or, ultimately, on the transmission rates (see the bottom right panel of Fig. 6).

Concerning R_0, it depends linearly on β_S and β_W (see expression (3.2) and the bottom left panel of Fig. 6). On the contrary, R_0 depends non-linearly on a and b, although the effect is quasi-linear (see expression (3.2) and the top left panel of Fig. 6).

4.3.1. Sensitivity indices

In avoiding the communicable disease becoming endemic (or promoting endemicity) we must control the values of R_0 and Δ (see Fig. 3). It is useful to know the relative importance of the parameters involved in the expressions of R_0 and Δ, so we can choose which of them must be changed when developing intervention strategies.

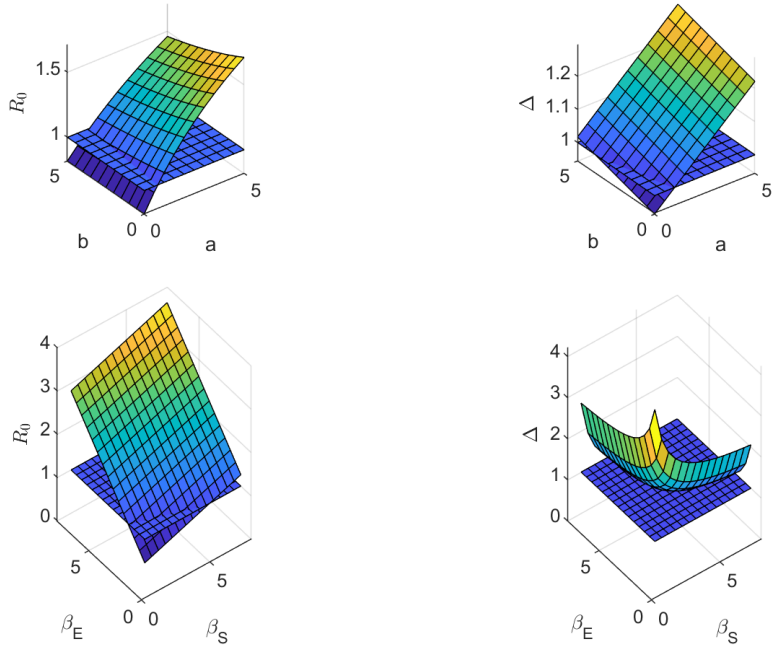

FIGURE 6. Left (right, respt.) column, R_0 (Δ, respt.) as function of coefficients a, b (top) and β_W, β_S (bottom). All the panels display also the threshold plane $R_0 = 1$ (left column) and $\Delta = 1$ (right column).

The normalized forward sensitivity index of a variable, u, that depends differentiably on a parameter p is defined in [8] as:

$$\gamma_p^u := \frac{\partial u}{\partial p} \times \frac{p}{u} = \frac{\frac{\partial u}{\partial p}}{\frac{u}{p}} \tag{4.5}$$

For the convenience of the reader we sketch the derivation of the sensitivity index (4.5) in Appendix A. Its interpretation is as follows. When increasing (or decreasing) p_0 by ϵ (meaning increasing p_0 to $p_0 + \epsilon p_0 = (1+\epsilon)p_0$) u increases (or decreases) by $\epsilon\, \gamma_p^u\big|_{p=p_0}$ times $u(p_0)$. Let us underline that this interpretation is *local* and *approximated* in the same sense the Taylor's expansion is so (see Appendix A).

We have used (4.5) to derive the analytical expression for the sensitivity index of R_0 and Δ, defined by (8) and (13) respectively, to each of the six parameters considered in our model. We show the corresponding expressions in Table 1.

Assume now that u depends on parameters $p_1, \cdots, p_n$. Without lost of generality, we assume that all the parameters vary simultaneously by ϵ. A direct application of the generalized Taylor's expansion yields that the corresponding sensitivity index is

$$\sum_{i=1}^{n} \gamma_{p_i}^u \tag{4.6}$$

That is to say that the sensitivity indices are additive, but (or and) the sign of each sensitivity index matters. Note that when the sum of the different indices is 1 (or -1) the variation caused in the variable u is the same variation introduced in the parameters times the corresponding sensitivity index.

TABLE 1. Sensitivity indices of R_0 (8) and Δ (13) to recovery and transmission rates of the NCD and the transmissible disease considered in our model.

	R_0	Δ
a	$\frac{ab}{a+b}\frac{\beta_w-\beta_s}{b\beta_s+a\beta_w}$	$\frac{a\beta_w}{(a+\gamma_s)\beta_w+(b+\gamma_w)\beta_s}$
b	$\frac{ab}{a+b}\frac{\beta_s-\beta_w}{b\beta_s+a\beta_w}$	$\frac{b\beta_s}{(a+\gamma_s)\beta_w+(b+\gamma_w)\beta_s}$
β_s	$\frac{b\beta_s}{b\beta_s+a\beta_w}$	$-\frac{(a+\gamma_s)\beta_w}{(a+\gamma_s)\beta_w+(b+\gamma_w)\beta_s}$
β_w	$\frac{a\beta_w}{b\beta_s+a\beta_w}$	$-\frac{(b+\gamma_w)\beta_s}{(a+\gamma_s)\beta_w+(b+\gamma_w)\beta_s}$
γ_s	$-\frac{\gamma_s}{\gamma_s+\gamma_w}$	$\frac{\gamma_s\beta_w}{(a+\gamma_s)\beta_w+(b+\gamma_w)\beta_s}$
γ_w	$-\frac{\gamma_w}{\gamma_s+\gamma_w}$	$\frac{\gamma_w\beta_s}{(a+\gamma_s)\beta_w+(b+\gamma_w)\beta_s}$

TABLE 2. Infimum and supremum values of sensitivity index of R_0 and Δ. The cells are empty when no meaningful bounds can be provided.

	Sensitivity indices of R_0		Sensitivity indices of Δ	
	Infimum value	Supremum value	Infimum value	Supremum Value
a	–	–	0	1
b	–	–	0	1
β_s	0	1	–1	0
β_w	0	1	–1	0
γ_s	–1	0	0	1
γ_s	–1	0	0	1

Most of the expressions of these sensitivity indices are complex so it is not possible to set an order from most sensitive to least sensitive without evaluating them at some baseline parameter values. However, some general conclusions can be drawn.

When real data is available the above analysis is made of precise figures, we invite the interested reader the work [2], were a complete sensibility analysis is carried out for a SIARD model on COVID19.

4.3.2. Implications for managing disease outbreaks

Epidemiologists look at R_0 at the beginning of epidemic outbreaks [4], [22] (but see also [10] for a less theoretical approach). R_0 depends on the parameters of the model and a key question is that of ascertaining which coefficients modify to get the larger change in R_0 with minimum effort.

We next derive information from the expression of the sensitivity indices useful for disease managers (see Tab. 1). All the mathematical relations follow straightforward from the expressions gathered in Table 1. We assume that a, b, β_s, β_w, γ_s, $\gamma_w > 0$.

Bounds for the sensitivity indices. On the one hand, most of the expressions for the sensitivity indices are fractions in which the numerator is one of the summands of the denominator. As all the parameters are positive quantities, the absolute value of these indices is less than one. More specifically, Table 2 shows infimum and supremum values of sensitivity indices of R_0 and Δ.

As shown in Table 2, the supremum value of the sensitivity indices is 1. So, it is not possible to change R_0 (or Δ) by an amount bigger than the change ϵ introduced in the parameter times R_0 (or Δ).The interpretation of the infimum value -1 is the same, but in that case, the modification introduced in the parameters and the change in R_0 (or Δ) have the opposite direction. In addition, note that we are considering a Taylor expansion to first order, so no big changes can be targeted.

TABLE 3. Expressions of sums of indices when different combinations of parameters are simultaneously modified producing minimal, none or maximal response on R_0 and Δ.

R_0	Δ
$\gamma_{\beta_s}^{R_0} + \gamma_{\beta_w}^{R_0} = 1$	$\gamma_{\beta_s}^{\Delta} + \gamma_{\beta_w}^{\Delta} = -1$
$\gamma_{\gamma_s}^{R_0} + \gamma_{\gamma_w}^{R_0} = -1$	–
$\gamma_{\gamma_s}^{R_0} + \gamma_{\gamma_w}^{R_0} + \gamma_a^{R_0} + \gamma_b^{R_0} = -1$	$\gamma_{\gamma_s}^{\Delta} + \gamma_{\gamma_w}^{\Delta} + \gamma_a^{\Delta} + \gamma_b^{\Delta} = 1$
$\gamma_a^{R_0} + \gamma_b^{R_0} = 0$	–
$\gamma_{\beta_s}^{R_0} + \gamma_{\beta_w}^{R_0} + \gamma_{\gamma_s}^{R_0} + \gamma_{\gamma_w}^{R_0} + \gamma_a^{R_0} + \gamma_b^{R_0} = 0$	$\gamma_{\beta_s}^{\Delta} + \gamma_{\beta_w}^{\Delta} + \gamma_{\gamma_s}^{\Delta} + \gamma_{\gamma_w}^{\Delta} + \gamma_a^{\Delta} + \gamma_b^{\Delta} = 0$

Comparing communicable disease management strategies. Tables 1 and 2 allow us to compute how much modifying a *single* coefficient of the model makes R_0 or Δ vary. However, it is possible to act on *more than one* coefficient of the model at once. Table 3 gathers combinations of parameters to be modified simultaneously and equally that produce minimal, none, or maximal responses on R_0 and Δ.

We next examine how the expressions gathered in Table 3 can be used to decide on epidemics management strategies.

A key question from the point of view of managing a CD that of deciding to act either on a target population (for instance, weakened individuals) or equally on all the susceptible individuals regardless of their status. More specifically, the question is: What will produce a larger change in R_0, an effect ϵ_1 applied only on (say) β_w, or a weaker effect $\epsilon_2 < \epsilon_1$ applied on both β_s and β_w? This question is equivalent to compare $\gamma_{\beta_w}^{R_0}\epsilon_1 R_0$ to $(\gamma_{\beta_w}^{R_0} + \gamma_{\beta_s}^{R_0})\epsilon_2 R_0$. Note that

$$\gamma_{\beta_s}^{R_0} + \gamma_{\beta_w}^{R_0} = 1. \tag{4.7}$$

Direct calculations yield that

$$\gamma_{\beta_w}^{R_0}\epsilon_1 R_0 < (\gamma_{\beta_w}^{R_0} + \gamma_{\beta_s}^{R_0})\epsilon_2 R_0 \qquad \Leftrightarrow \qquad \frac{\epsilon_1}{\epsilon_2} < \frac{1}{\gamma_{\beta_w}^{R_0}} \tag{4.8}$$

provided (4.7). Note that ϵ must be negative in order to reduce transmission.

Analogous questions can be addressed related to those expressions summing up to -1 or 0.

Are unexpected management effects possible? We already know that the endemic states bifurcate from the disease-free scenario as R_0 crosses the threshold value 1. The bifurcation can be either subcritical ($R_0 < 1$ and $\Delta < 1$) or supercritical ($R_0 \geq 1$ and $\Delta \geq 1$). The bifurcation direction would make a huge difference, as in the subcritical case $R_0 < 1$ does not lead necessarily to a disease-free scenario. Changing any parameter of the model will make vary simultaneously R_0 and Δ which would result in an unexpected outcome.

For instance, let us assume that the conditions are such that $R_0 > 1$ and $\Delta > 1$, that is, the system is in the endemic disease scenario. Assume also that efforts are put into modifying the value of some coefficients to push R_0 below 1. Then, as a result, can Δ also go below 1, undergoing a subcritical bifurcation? It would happen if reducing R_0 (by any means) would entail a simultaneous reduction in Δ. A necessary condition is that the corresponding sensitivity indices have the same sing. It is apparent that it is not possible if the efforts are put in modifying coefficients β_s, β_w, γ_s or γ_w (see Tab. 1).

However, it is also apparent that the sign of the sensitivity indices of R_0 and Δ with respect to a (respectively b) is the same provided $\beta_w > \beta_s$ (respectively, if $\beta_w < \beta_s$). Indeed direct calculations show that $R_0 > 1$ and

$\Delta > 1$ for $N = 70$, $a = 0.27$, $b = 15$, $\beta_S = 3.02$, $\beta_W = 7.2$, $\gamma_S = 20$, $\gamma_W = 6.9$ but $R_0 < 1$ and $\Delta < 1$ keeping all the previous parameter values but $a = 0.17$.

5. Conclusions

The minimal model presented herein shows that R_0 subcritical (backward) bifurcation can be much more usual than expected by the literature. The underlying mechanism can be though of *dynamic heterogeneity* in the non infected compartment, which NCDs is a particular case. That is to say, not only the epidemiological state (susceptible – infected) of a given individual may change on time, also its propensity to be infected may evolve on time along its life-cycle.

This feature strongly supports the idea that acting on target sub-populations can be key when managing/controlling epidemics. One may act on the transmission rate affecting that class, or either on removing individuals from one risk-class to the other one.

We hope the results presented herein would promote further research. On the one hand, we hope experimental scientists find this research interesting and would test the model at their laboratory. On the other hand, more complex extensions of system (2.2) should be of interest, as considering asymptomatic, recovered, immune, vaccinated,..., compartments. Also, it is of great interest approaching the problem here addressed with other modelling tools as difference equations [21] or fractional differential equations [18] or [19].

Declarations

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Conflicts of interest/Competing interests. The authors of this work certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Appendix A.

A first approach to the idea of the sensitivity of u to p is using the derivative of u with respect to p. However, doing so does not allow to fairly compare the sensitivity of u to two different parameters if those parameters are expressed in different units. Defining the sensitivity index as in (4.5) fixes this problem (see the most right hand side expression). Furthermore, consider that u depends on the parameters $p_1, \cdots, p_n$. We may assume without loss of generality that $p_2, \cdots, p_n$ are held constant, that is equivalent to assume that u depends only on $p = p_1$. The Taylor's expansion approximation of $u(p)$ to the first order at $p = p_0$, is given by:

$$u(p) \approx u(p_0) + \left.\frac{\partial u(p)}{\partial p}\right|_{p_0} (p - p_0) \tag{A.1}$$

When varying the parameter p by an amount of $\epsilon = (p - p_0)/p_0$, that is to say, from p_0 to $p_0 + \epsilon p_0$ (A.1) becomes

$$u(p_0 + \epsilon p_0) - u(p_0) \approx \left.\frac{\partial u(p)}{\partial p}\right|_{p_0} \epsilon p_0. \tag{A.2}$$

Taking into account the definition of the sensitivity index (4.5), multiplying and dividing the right hand side of (A.2) by $u(p_0)$ yields:

$$u(p_0 + \epsilon p_0) - u(p_0) \approx \gamma_p^u\big|_{p_0} \epsilon u(p_0) \tag{A.3}$$

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