SUSTAINABLE AGRO-PASTORAL SYSTEMS: CONCEPTS, APPROACHES AND TOOLS

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Mathematical approaches to infectious diseases control

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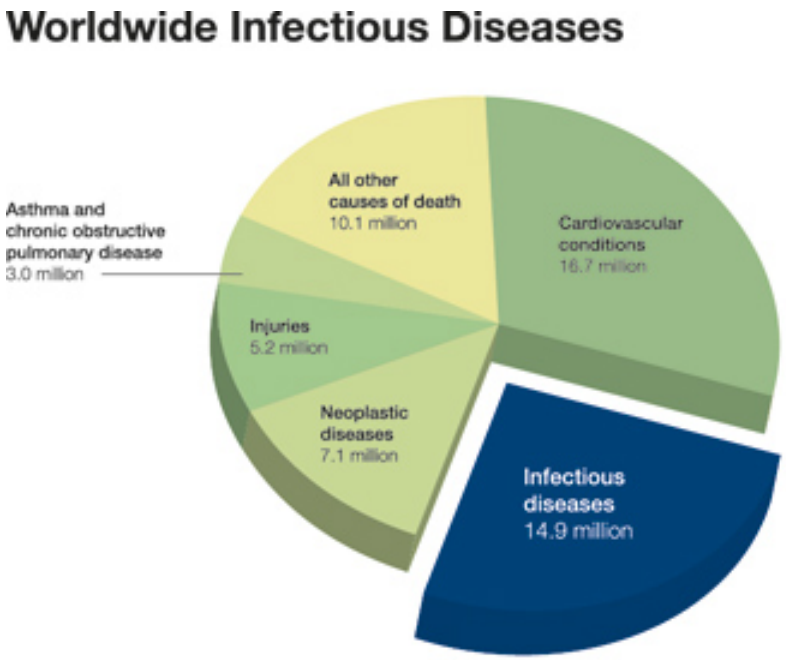
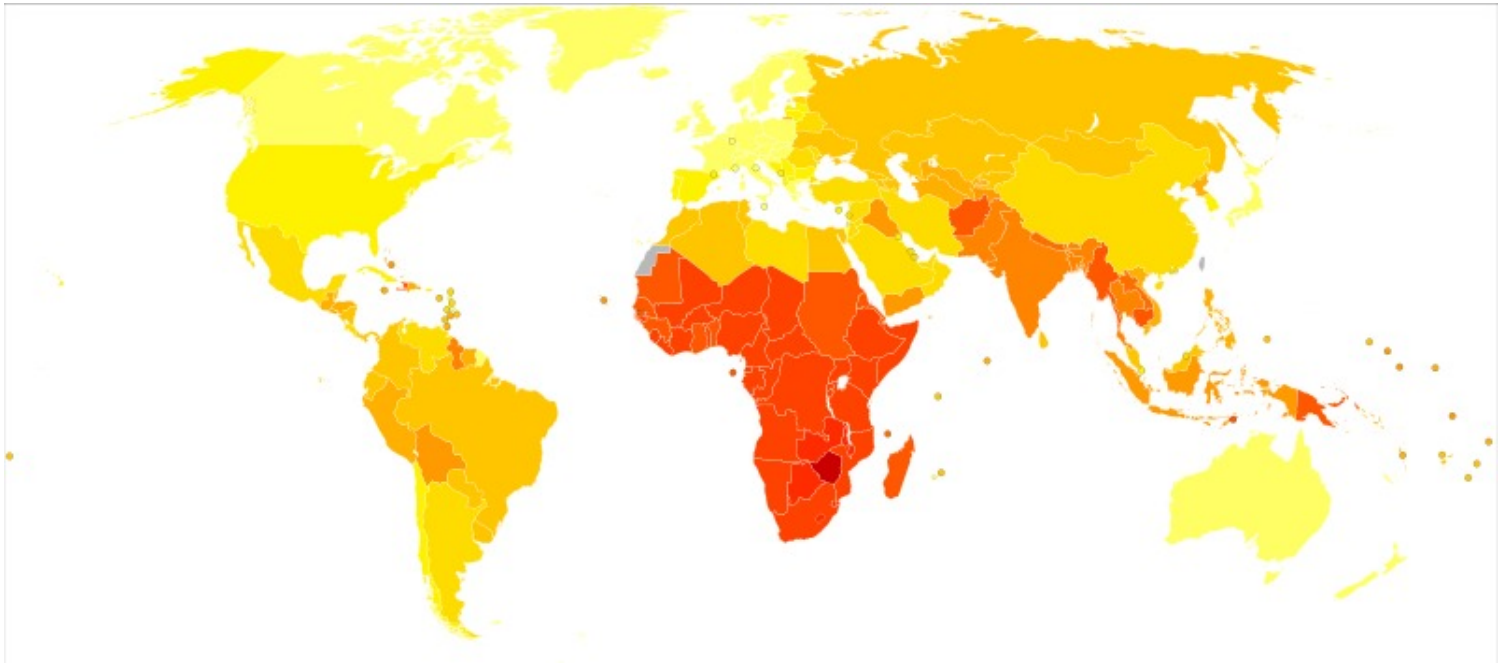
Leading causes of death



Infectious Diseases	Annual deaths (millions)
Respiratory infections	3.96
HIV/AIDS	2.77
Diarrhoeal diseases	1.80
Tuberculosis	1.56
Vaccine-preventable childhood diseases	1.12
Malaria	1.27
STDs (other than HIV)	0.18
Meningitis	0.17
Hepatitis B and C	0.16
Tropical parasitic diseases	0.13
Dengue	0.02
Other infectious diseases	1.76

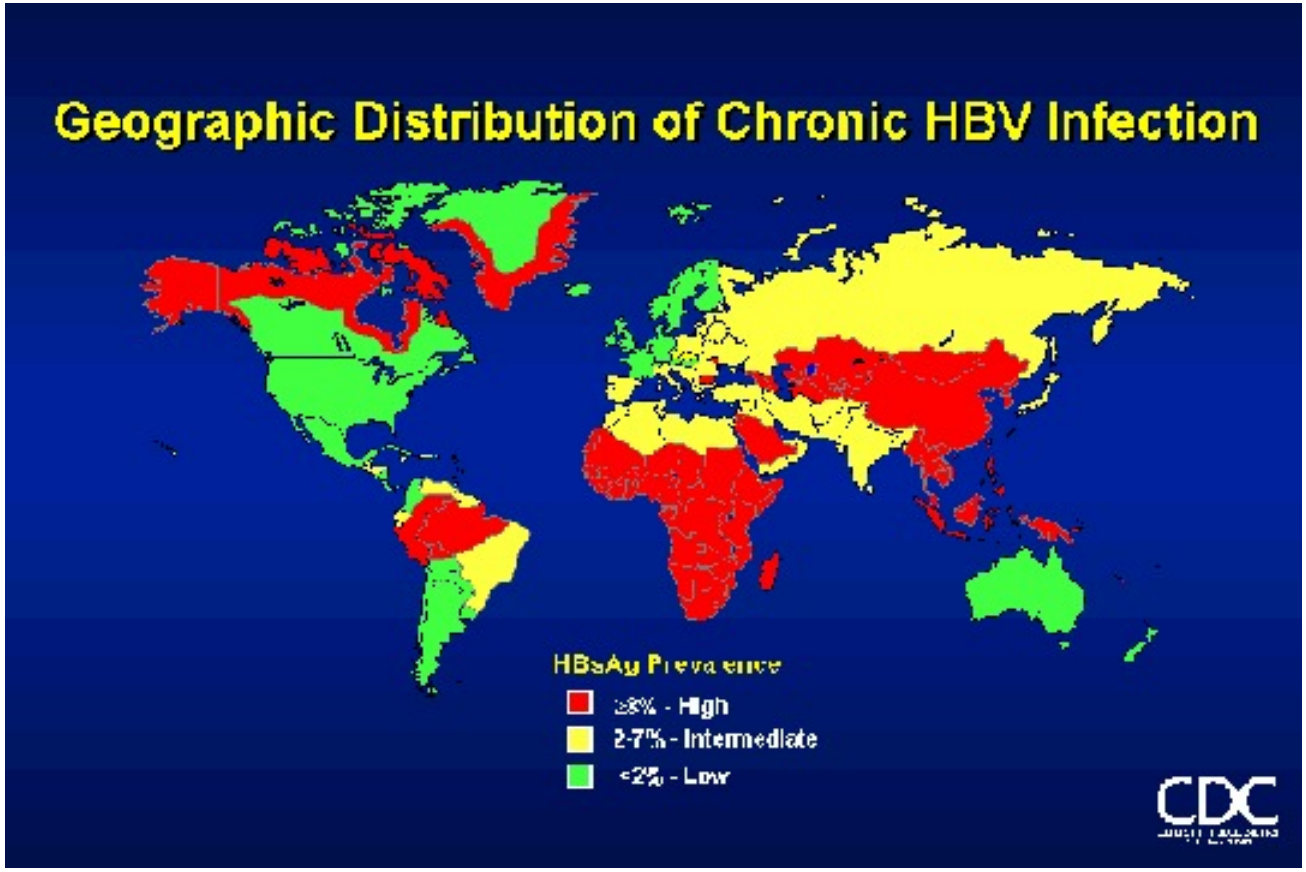
Year 2002. Data from University of Melbourne, http://www.doherty.unimelb.edu.au/study.html

Infectious diseases: north–south gap



Disability-adjusted life year (DALY), a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. World Health Organization, Department of Measurement and Health Information. February 2009.

Vertically transmitted diseases, HBV



Centers for Disease Control's (CDC) presentation entitled: Epidemiology and Prevention of Viral Hepatitis A to E: An Overview.

Taken from: Texas Department of State Health http://www.dshs.state.tx.us

OUTLINE

- Horizontally and Vertically transmitted diseases
- Mathematical disease control
- Applications to real scenarios
- Periodically varying contact rate

Disease transmission

Horizontally transmitted diseases: contacts with infectious hosts, which may be a direct physical contact or an indirect one, through e.g. biting insects.

Vertically transmitted diseases: transfer from parent to offspring. For example, an infectious mother may transmit the disease to her fetus by means of bodily fluid or breast milk. Some diseases that can be vertically transmitted include hepatitis B, herpes simplex, syphilis, rubella (german measles), Chagas disease (american trypanosomiasis) and HIV-AIDS.

Some mathematical literature:

Busenberg, Cooke. Biomath., 23. Springer (1993)

Li, Smith, Wang. SIAM J. Math. Anal., 62 (2001)

d'Onofrio. Appl. Math. Comput., 18 (2005)

Li, Zhou. Chaos Sol. Frac., 40 (2009)

Mathematical disease control: two possible approaches

1. Qualitative analysis of models:
Existence of equilibria and/or periodic orbits; local and global stability analysis; Forward and backward bifurcations.

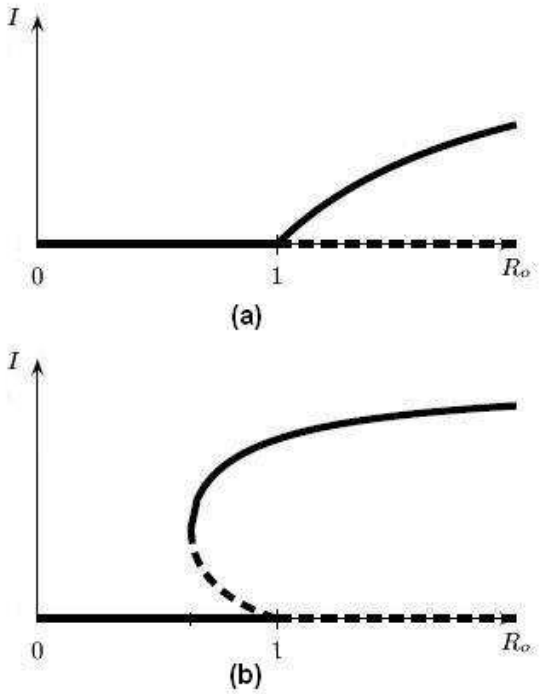
Goal: Find the individual role of the parameters. Act on parameters (when possible) in order to control the disease (when possible, try to eradicate it). Typical example: Basic reproduction number R_0.

Literature:

Anderson, May. Oxford Uni. Press (1991)

Capasso. Lect. Notes Biomathematics (1993)

Brauer, van den Driessche, Wu. Lect. Notes Math. (2008)



Qualitative bifurcation diagrams for the forward (a) and backward (b) bifurcations respectively. The bifurcation parameter is the basic reproductive number R_0. The solid lines (-) denotes stability; the dashed line (–) denotes instability.

Mathematical disease control: two possible approaches

2. Optimal control:
Define a strategy and control the system to produce the *best* outcome.

Goal: Make decisions involving complex biological situations.

Literature:

Morton, Wickwire. Adv. Appl. Prob., 6 (1974)

Behncke. Optim. Control Appl. Meth., 21 (2000)

Lenhart, Workman. Chapman & Hall/CRC (2007)

Anita, Arnautu, Capasso. Birkaüser (2010)

Blayneh, Lenhart et al., Bull. Math. Biol., 72 (2010)

Hansen, Day. J. Math. Biol, 62 (2011)

OUR AIM TODAY

Use both qualitative analysis and optimal control theory to assess the control of a large class of diseases, i. e. the deseases which transmit both horizontally and vertically.

Literature on the mathematical model:

Li, Smith, Wang. SIAM J. Math. Anal., 62 (2001): Original model. Bilinear incidence rate.

Li, Wang. IMA Math. Appl., 126 (2002): Add vaccination as control measure

d'Onofrio. Appl. Math. Comput., 140 (2003): Periodic contact rates

THE MODEL

$$\begin{aligned}
\dot{S} &= bS + bR + b(1-p)E + b(1-q)I - bS - \beta(t)SI - rS \\
\dot{E} &= b(pE + q\phi_1 I) + \beta(t)SI - (e+b)E \\
\dot{I} &= bq\phi_2 I + eE - (g+b)I \\
\dot{R} &= rS + gI - bR.
\end{aligned}$$

Main assumptions:

- The general form of the contact rate (CR) is time-dependent, $\beta(t)$;
- The natural birth rate and death rate are assumed to be equal, and denoted by b;
- It is assumed that a fraction of the offsprings of latent and infectious individuals are latent at birth. There is also the possibility that an offspring of a infectious individual may born straight infectious. p is the probability that an offspring of a latent individual has to be born latent, $(q\phi_1)$ and $(q\phi_2)$ are the probabilities that an offspring of a infectious individual has to be born latent or infectious, respectively, where $\phi_1 + \phi_2 = 1$, $\phi_1, \phi_2 \geq 0$, $p, q \in [0, 1]$.

Vertical transmission: $pE \to E; \quad q\phi_1 I \to E; \quad q\phi_2 I \to I.$

Dynamical behaviour results

Suppose β is a periodic function of period ω: $\beta(t+\omega) = \beta(t)$. The model admits the disease free equilibrium

$$E_0 = (b_0, 0, 0)\,, \qquad b_0 = b/(b+r)$$

Theorem 1 *E_0 is LAS if the maximum modulus of the Floquet's eigenvalues of the following periodically varying linear system:*

$$\begin{pmatrix} y_1' \\ y_2' \end{pmatrix} = \begin{pmatrix} -(a+b(1-p)) & bq\phi_1 + b_0\beta(t) \\ a & -(b(1-q\phi_2)+g) \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$

is strictly less than one. This condition guarantees also that E_0 is GAS in the region:

$$\Gamma = \left\{(S,E,I) \in \mathbf{R}^3_+ : 0 \le S \le b_0; \quad S+E+I \le 1\right\}$$

Proof: Linearize and use the properties of cooperative dynamical system (d'Onofrio, Appl. Math. Comput., 2003).

Dynamical behaviour for constant CR

Assume $\beta(t) = k$, $r = 0$, $\phi_1 = 1$, $\phi_2 = 0$. Introduce the *basic reproductive number*:

$$R_0 = \frac{k\,e}{(b+e)(b+g) - bp(b+g) - bqe}. \tag{1}$$

The model admits the *disease-free* equilibrium $P_0 \equiv (1, 0, 0)$ on the boundary of Γ, and an *endemic* equilibrium $\overline{P} \equiv (\overline{S}, \overline{E}, \overline{I})$ in the interior of Γ, where:

$$\overline{S} = \frac{1}{R_0}; \quad \overline{I} = \frac{e\,b\,(R_0 - 1)}{(b+e)(b+g)R_0}; \quad \overline{E} = \frac{b(R_0 - 1)}{(b+e)R_0}. \tag{2}$$

Dynamical behaviour for constant CR

Theorem 2 *If $R_0 \leq 1$, then P_0 is the only equilibrium and it is globally stable in Γ. If $R_0 > 1$, then P_0 is unstable and there exists a unique endemic equilibrium $\overline{P}$, and it is globally stable in the interior of Γ.*

Proof: The global stability result may be obtained using the *geometric approach to stability* due to M. Li and J. Muldowney (SIAM J. Math. Anal., 1996). See:
Li, Smith, Wang, SIAM J. Math. Anal., 62 (2001)
Buonomo, Lacitignola, J. Math. Anal. Appl., 348 (2008).

Conclusion: The system undergoes a transcritical (forward) bifurcation at $R_0 = 1$ (the R_0-*dogma*, Reluga, Medlock, Perelson, J. Theor. Biol., 2008)

Vaccination strategies

Goal. Minimize the total number of infectious individuals and the cost associated with vaccination during the vaccination campaign on $[0, t_f]$.

Objective functional:

$$J(r) = \int_0^{t_f} \left(A\, I + r^2(t) \right) dt,$$

where $r(t)$ is a measurable function such that: $0 \leq r(t) \leq 0.9$, for $t \in [0, t_f]$.

Remarks

- A is a *weight* parameter describing the comparative importance of the two terms in the functional.
- We consider a quadratic cost on the control, which is the simplest and widest used nonlinear representation of vaccination cost

See e.g. Asano et al., Math. Biosci. Engin., 5 (2008) Jung et al., Disc. Cont. Dyn. Sys. B, 2 (2002) Jung et al., J. Theor. Biol., 260 (2009)

Optimal control problem

Find $0 \leq r(t) \leq 0.9$, for $t \in [0, t_f]$, to minimize

$$J(r) = \int_0^{t_f} \left(A\, I + r^2(t) \right) dt,$$

subject to

$$\begin{aligned}
\dot{S} &= b - b(pE + qI) - bS - \beta(t)SI - rS \\
\dot{E} &= b(pE + q\phi_1 I) + \beta(t)SI - (e + b)E \\
\dot{I} &= bq\phi_2 I + eE - (g + b)I \\
\dot{N} &= b - bN,
\end{aligned}$$

and

$$S(0) \geq 0, \quad E(0) \geq 0, \quad I(0) \geq 0, \quad N(0) = 1.$$

Pontryagin's maximum principle

It is a constrained control problem. Apply the Pontryagin's maximum principle (Pontryagin et al., 1962) and minimize pointwise the Hamiltonian:

$$H(S, E, I, N) = A\, I + r^2 + \sum_{i=1}^{4} \lambda_i\, f_i$$

The adjoint equations are:

$$\dot{\lambda}_i = -\frac{\partial H}{\partial x_i}; \qquad i = 1, \ldots, 4$$

Here x_i, $i = 1, 2, 3, 4$ are the state variables S, E, I and N, and f_i are the right hand sides of the system.

Optimality system

Adjoint equations:

$$\begin{aligned}
\dot{\lambda}_1 &= [b + r + \beta(t)I]\ \lambda_1 - \beta(t)I\,\lambda_2;\\
\dot{\lambda}_2 &= bp\,\lambda_1 + (e + b - pb)\ \lambda_2 - e\,\lambda_3;\\
\dot{\lambda}_3 &= -A + [bq + \beta(t)S]\ \lambda_1 - [bq\phi_1 + \beta(t)S]\ \lambda_2 + (g + b - bq\phi_2)\ \lambda_3;\\
\dot{\lambda}_4 &= b\,\lambda_4.
\end{aligned}$$

Transversality equations:

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = 0. \tag{3}$$

Characterization of the optimal control r^*:

$\frac{\partial H}{\partial r} = 0$, at $r = r^*$, on the set $\{t \in [0, t_f] : 0 \leq r \leq 0.9\}$. That is:

$$r^* = \begin{cases} 0 & \text{if } S^*\lambda_1 < 0 \\ \frac{S^*\lambda_1}{2} & \text{if } 0 \leq S^*\lambda_1 \leq 1.8 \\ 0.9 & \text{if } S^*\lambda_1 > 1.8. \end{cases}$$

Existence of the optimal control profile

Theorem 3 *There exists an optimal control $r^*(t)$ and the corresponding solution, $S^*(t)$, $E^*(t)$, $I^*(t)$, $N^*(t)$, and H^*, that solves the optimal control problem. Furthermore, there exist adjoint functions $\lambda_i(t)$, $i = 1, 2, 3, 4$, that are solutions of the adjoint equations and transversality conditions.*

The existence and the uniqueness of the optimal control, for small t_f, is standard because the model is linear in the control variable and is bounded by a linear system in the state variables (see, e.g., Fleming and Rishel, 1975). The convexity of the objective functional in r on the closed, convex, control set Γ ensures that it is a minimizing problem.

Numerical settings

We use the so called forward - backward sweep method. The eight ordinary differential equations consisting the optimality system are numerically solved together with the control characterization.
The process begin with an initial guess on the control variable. Then, the state equations are solved simultaneously forward in time, and next the adjoint equations are simultaneously solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs.
The solver used for the state and adjoint systems is a Runge-Kutta fourth order procedure.

Literature:

Jung, Lenhart, Feng. DCDS-B, 4 (2002)

Lenhart, Workman. Chapman & Hall/CRC (2007)

Asano, Gross, Lenhart, Real. Math. Biosci. Eng., 5 (2008)

Blayneh, Lenhart et al., Bull. Math. Biol., 72 (2010)

Epidemiological parameters: dynamics of rubella in China

In a recent paper, Gao and Hethcote (Math. Biosci., 2006) considered an age structured model to evaluate the dynamics of rubella over time in China, under various scenarios of vaccination or non-vaccination. We will estimate our epidemiological parameters by using data from their paper (unless otherwise stated). In this way we test our theoretical findings on the same case study in China.

- *Natural birth rate, b*: 0.012
- *Rate at which the exposed individuals become infectious, e*: 36.5 per year.
- *Rate at which the infectious individuals recover, g*: 30.417 per year.
- *Fractions p and q of the offspring from the exposed and infectious class that are born into the exposed class*: 0.65.

Epidemiological parameters: dynamics of rubella in China

• *Contact rate*, β_0: The average force of infection of rubella for people between 0 and 50 years is 0.196 per year, according to Gao and Hetchote's data. Assume $d = 0$, then the force of infection is modelled as a linear term $\beta_0 I$, where β_0 is the contact rate. Hence, at the endemic state it is:

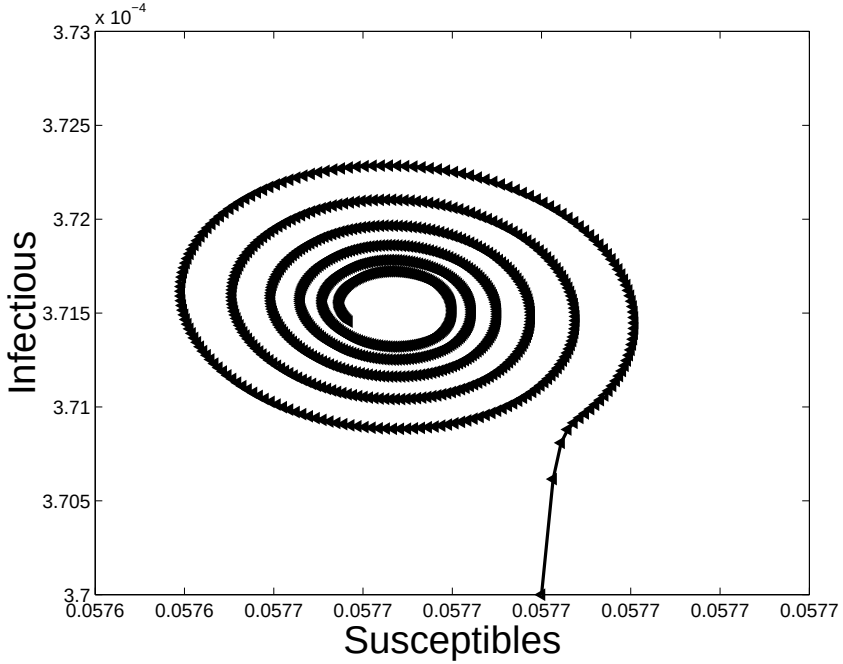
$$\beta_0 \frac{e\, b\, (R_0 - 1)}{(b+e)(b+\sigma)R_0} = 0.196,$$

i.e.,

$$\beta_0 = 0.196 \frac{(b+e)(b+g)}{eb} + \frac{[(b+e)(b+g) - bp(b+g) - bqe]}{e}.$$

The values above for b, e, g, p, q, drive to $\beta_0 = 527.59$ per individual per year (and, consequently, $R_0 = 17.34$).

Convergence to endemic equilibrium



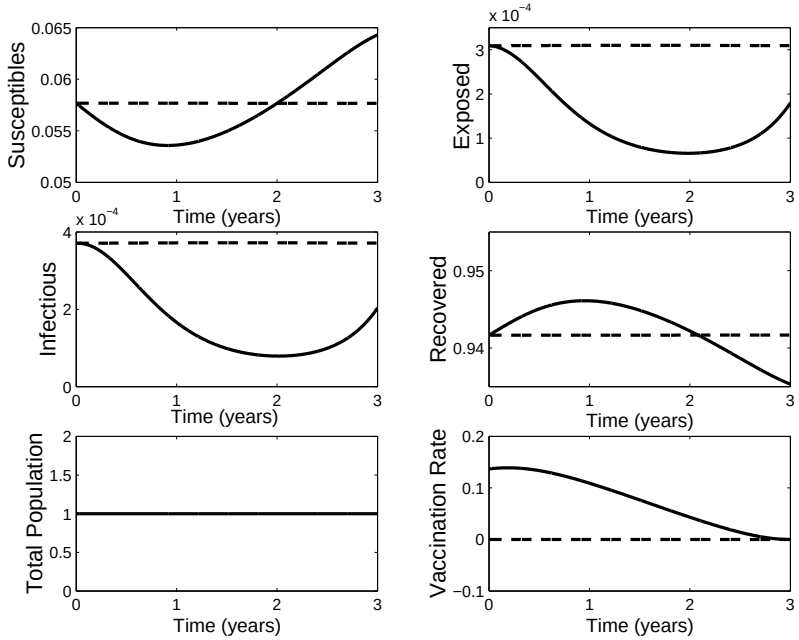
Assuming no vaccination ($r = 0$) and constant contact rate ($d = 0$), the solutions converge to the endemic state indipendently of initial data, in agreement with Theorem 1. Here the convergence is depicted in the $S - I$ plane. The equilibrium is a stable focus. The simulation is performed with $\phi_1 = 1$, $\phi_2 = 0$.

Prediction of endemic state

According to WHO data statistics, the reported cases of rubella in China are increasing in the last years. There were 24,015 reported cases in 2004, that jumped to 74,746 in 2007 and 120,354 in 2008. According to our model, the cases will increase until the endemic state will be reached, which corresponds to $I^* \approx 3.70 \cdot 10^{-4}$, that is to say, taking into account of a total population of $1.3 \cdot 10^9$ individuals, that 481,000 infected individuals are expected at the endemic state.

In other words, in absence of vaccination the model predicts a strong increase of total rubella cases in China, up to 225%.

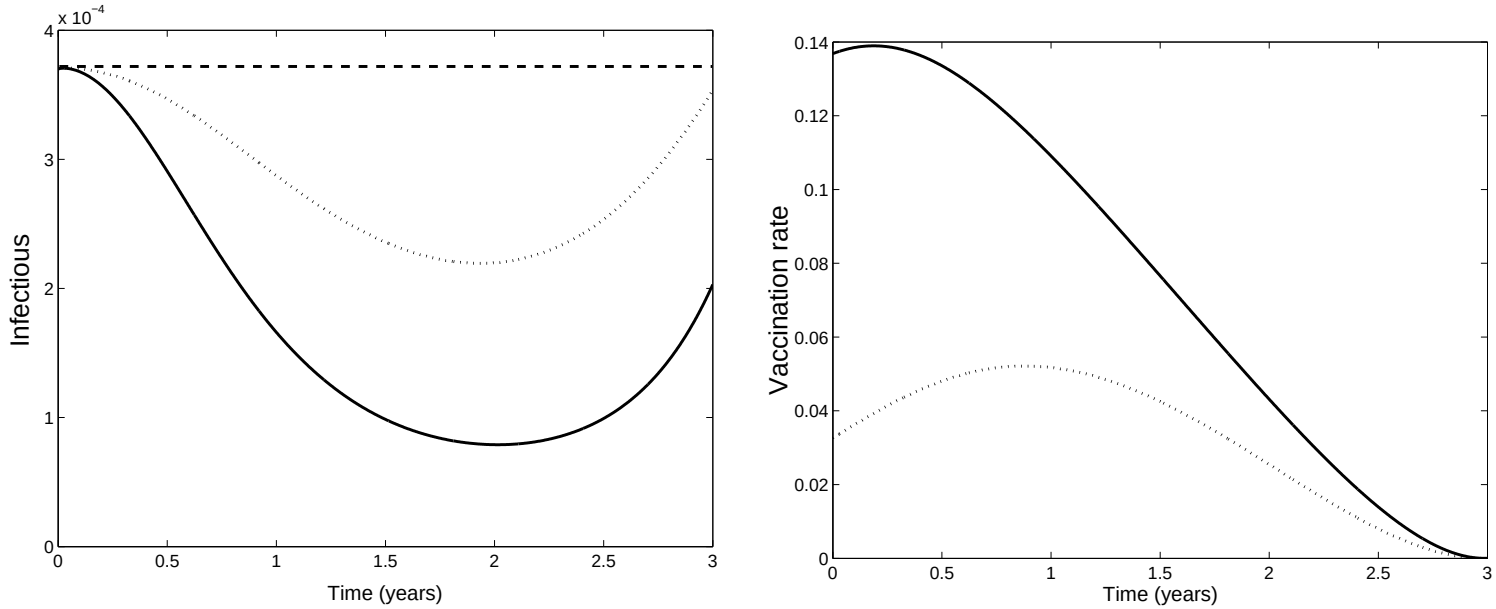
Controlling rubella in China



The vaccination rate is at the highest possible value in the first stage of vaccination campaign. Gaff and Schaefer (Math. Biosci. Eng., 2009) find a similar optimal vaccination policy for several different epidemic model with SIR and SEIR structure. Vaccinate at the highest possible rate as early as possible is essential for controlling an epidemic.

According to the optimal strategy, the infectious can be reduced up to 75% around the second year of campaign. At the end of campaign, infectious and exposed both show an increasing trend, due to the immission of new susceptibles. However they are more or less the half of those who were at the beginning. **This result can be helpful to plan periodic vaccination campaigns**.

The role of the weight parameter A



Infectious (on the left) and Vaccination rate (on the right) versus time. The solid lines correspond to the case $A = 100$, the dotted line to the case $A = 30$. The straight line in the left picture is the equilibrium solution. By reducing the parameter A, we observe that **the maximum vaccination rate shifts on the right in the optimal control profile** (right). Hence, if the vaccination cost is relatively high, a gradual increase of the vaccination rate is suggested. Of course, higher is the priority of cost reduction, lower is the efficacy of the campaign on disease burden (left).

Seasonally varying contact rate

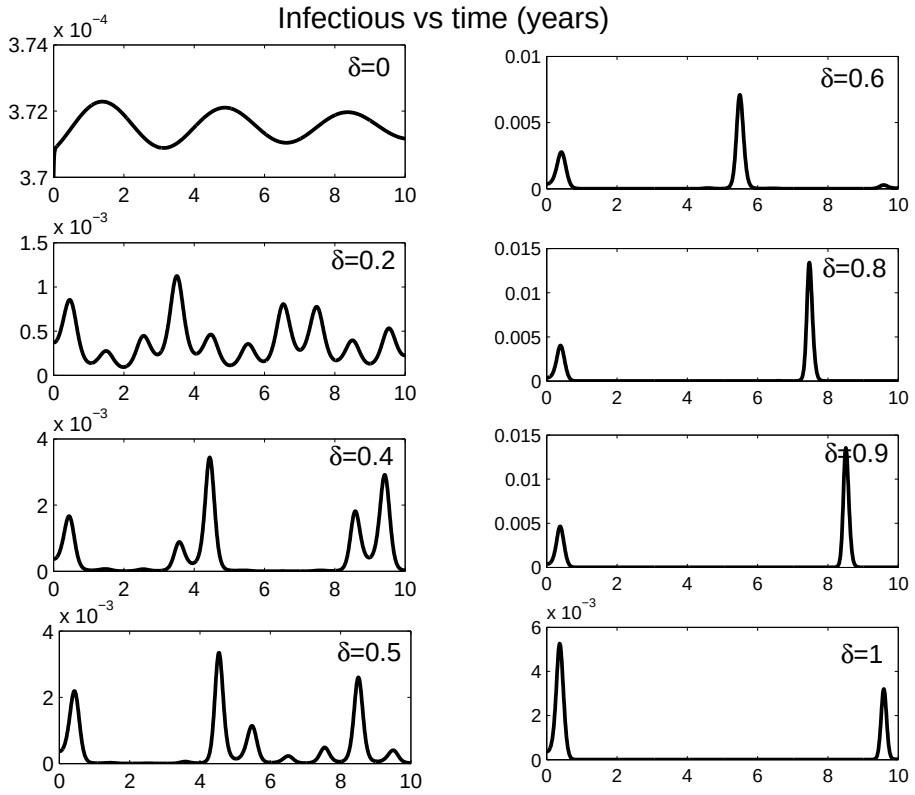
One-year period sinusoidal function:

$$\beta(t) = \beta_0 \, (1 + d \, \sin(2\pi \, t))$$

where β_0 gives the mean contact rate, $0 \leq d \leq 1$ represents the strenght of the seasonal forcing, and t has units of years.

Epidemiological motivation: Several childhood diseases are driven by the seasonally changing CR between children which increases sharply at the beginning of each school year, and strongly controls the ensuing disease transmission (Stone, Olinky, Huppert. Nature, 2007).

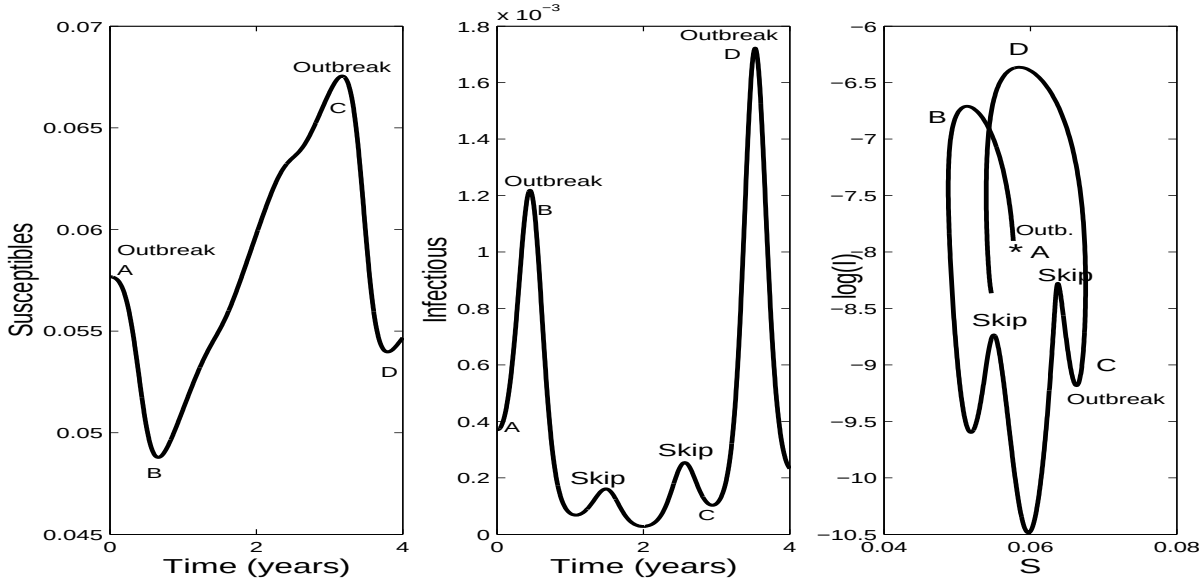
Effect of the strenght of seasonal forcing, d



The simulation runs for 10 time units with $r = 0$, $\phi_1 = 1$, $\phi_2 = 0$. The initial data are near to the endemic equilibrium state that system admits for $d = 0$.

Skip and peaks (Stone, Olinky, Huppert. Nature, 2007)

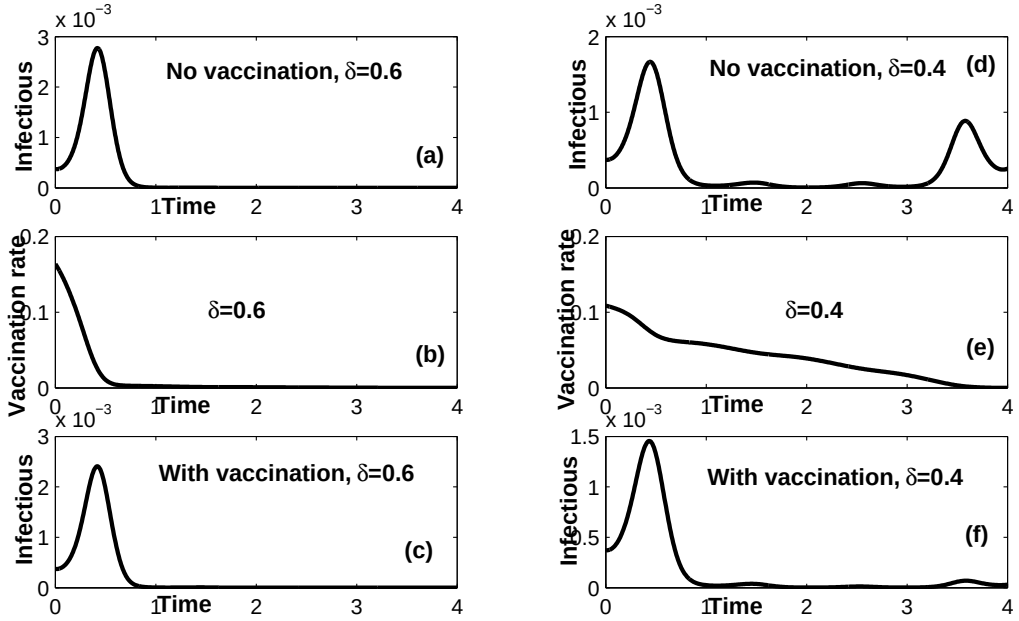
Skip: Susceptibles always continues to increase despite the fact that the infections pass through a maximum.



There are two major epidemic outbreaks, from point A to B, and from point C to D, respectively. The two infectious peaks between $t = 1$ and $t = 3$ do not produce a decrease of susceptibles, so that large - scale outbreaks do not take place (i.e. there are two *skips*). The simulation runs for 4.5 time units with $r = 0$, $\phi_1 = 1$, $\phi_2 = 0$, $d = 0.3$.

Forecast about future outbreaks or skips may depend critically on the size of S after a major outbreak.

Controlling peaks



On the left, $d = 0.6$. There is only one major epidemic outbreak, (a). The maximum vaccination effort is concentrated at the beginning of the epidemic outbreak, (b), and this reduces the fraction of infectious, (c). On the right, $d = 0.4$ and two large scale epidemics occur, (d). **In this case the optimal policy is to distribute the vaccination effort over time**, (e). This allows to sensibly reduce the second infectious peak (the outbreak is virtually avoided), (f).

Conclusions

• We assess the effect of control strategies on a community affected by a disease that transmits both horizontally and vertically.

• We apply the SEIR epidemic model with vertical transmission introduced by Li, Smith, Wang (SIAM J. Math. Anal., 2001) to epidemic spread of rubella. This system undergoes a forward bifurcation at $R_0 = 1$. We perform an optimal control approach and test our theoretical findings to simulate simple scenarios for rubella vaccination strategies in China.

Conclusions

• Gao and Hethcote (Math. Biosci., 2006) observed that an unsufficient vaccination campaign may drive the total congenital rubella syndrome (CRS) incidence in China to be more than twice the current level. Furthermore, they find that routine vaccination coverage of over 80% of 1-year old children may sensibly reduce the CRS cases and eliminating rubella in fifty years. Moreover, a mass vaccinations combined with routine vaccinations may help to accelerate the eradication of rubella.
Taking into account that the percentage of 1-years old children in 2000 was 0.01, we can estimate that at least $10.4 \cdot 10^6$ vaccinations are needed to obtain the eradication predicted by Gao and Hethcote.

Here, in the case $A = 100$, we get a maximum initial vaccination rate of 0.137 with a suceptibles endemic level of 0.05767, so that at least $10.27 \cdot 10^6$ vaccinations are estimated. These results are comparable with the ones obtained by Gao and Hethcote.

Conclusions

• In the case of periodically varying CR it is stressed the importance to predict epidemic peaks. Maximum vaccination effort is concentrated at the beginning of singular epidemic outbreak whereas the optimal policy is to distribute the vaccination effort over time in case of predicted multiple outbreaks. This will stop future major outbreaks.

Some further directions

- Real data validation for the periodic CR;
- Age structure;
- Treatment (multiple controls);

References

B. Buonomo, *A simple analysis of vaccination strategies for rubella*, Math. Biosci. Eng., 8, 677–687 (2011)

B. Buonomo, *On the optimal vaccination strategies for horizontally and vertically transmitted infectious diseases*, J. Biol. Systems, 19, 263–279 (2011)

Thank you!