Environmentally Transmitted Pathogens
Models – Part deux :)

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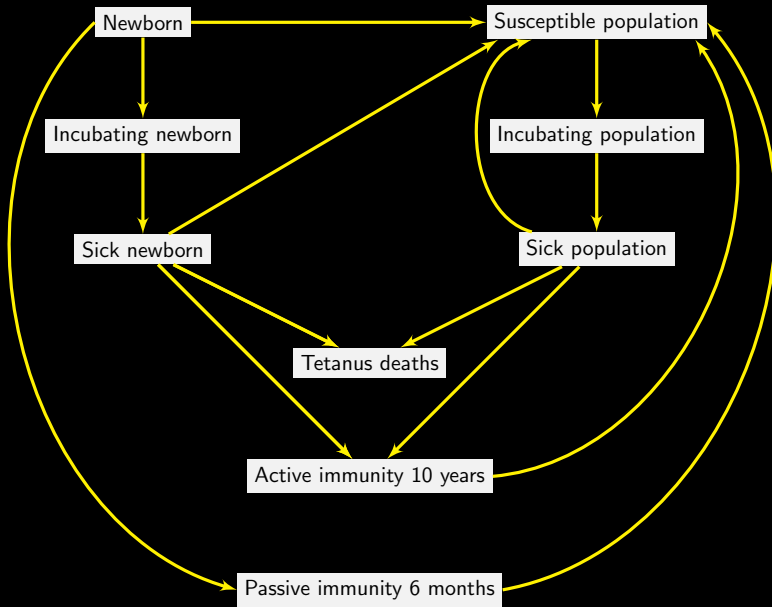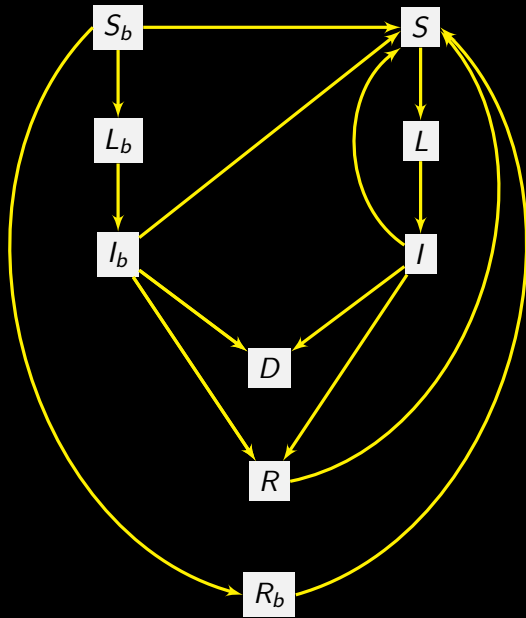
The discrete-time tetanus model (notation mine)

$$\Delta S_b = bT \tag{1a}$$

$$\Delta S = b(1 - \lambda_b)(T - R) + \nu R + \nu_b I + R_{5,2}\gamma_b I_b + R_{6,2}\gamma I - (\lambda + d - \delta_T)S \tag{1b}$$

$$\Delta L_b = \lambda_b b(T - R) - (\varepsilon_b + d - \delta_T)L_b \tag{1c}$$

$$\Delta L = \lambda S - (\varepsilon + d - \delta_T)L \tag{1d}$$

$$\Delta I_b = \varepsilon_b L_b - (\gamma_b + d - \delta_T)I \tag{1e}$$

$$\Delta I = \varepsilon L - (\gamma + d - \delta_T)I \tag{1f}$$

$$\Delta R = R_{5,7}\gamma_b I_b + R_{6,7}\gamma I - (\nu + d - \delta_T)R \tag{1g}$$

$$\Delta R_b = bR - (\nu_b + d - \delta_T)R_b \tag{1h}$$

$$\Delta D = R_{5,9}\gamma_b I_b + R_{6,9}\gamma I \tag{1i}$$

where

$$T = S + L_b + L + I_b + I + R + R_b \quad \text{and} \quad \delta_T = \frac{\Delta D}{T} \tag{1j}$$

Parameter assumptions – Tetanus

- **Incubation period** – Mean duration 6 days for newborn and 8 days for general population $\Rightarrow$ daily rate of exit $\varepsilon_b = 0.1667$ and $\varepsilon = 0.125$
- **Period of sickness** – Mean duration 3 days for newborn and 14 days for general population $\Rightarrow$ daily rate of exit $\gamma_b = 0.3333$ per sick newborn and $\gamma = 0.0714$ for sick general in general population
- **Mortality from tetanus** – Untreated tetanus cases, fatality rate 90% for newborn S_b and 40% for general population. Treated: 80% for newborn and 30% general population
- **Immunity** – Tetanus cases do not lead to immunity to reinfection. But as a general rule, recovered people are vaccinated. Convalescents and general population effectively immunised by complete course of vaccination go to R for average 10 years, daily rate of exit is $\nu = 0.000274$ per person.
- **Immunity of newborns** – Newborn to women vaccinated during pregnancy are temporarily protected by maternal antibodies and pass through R_b for a mean duration of 6 months. Daily rate of exit $\nu_b = 0.005479$ per immunised newborn

Parameter assumptions – Demography

Live birth rate 35 per 1,000 population and annual crude death rate 15 per 1,000 population (annual rate of growth 2%) $\Rightarrow$ daily birth and death rates $b = 0.00009889$ and $d = 0.0000411$ per person, respectively

Parameter assumptions – Force of infection

No H2H transmission $\Rightarrow$ incidence proportional to number of susceptible individuals and force of infection, which quantifies combined effect of all variables involved in infection process:

- ▶ degree of soil contamination with *Clostridium tetani*
- ▶ climate
- ▶ frequency of lesions
- ▶ proportion of rural population
- ▶ socioeconomic conditions
- ▶ level of medical care for the wounded and during deliveries

Force of infection acting on newborn (λ_b) and susceptible population (λ) fixed at 3 different levels adequate for reproducing the following stable annual incidence rates of tetanus cases in the community

- ▶ For newborn, 200 cases, 400 cases and 600 cases per 100,000 newborn
- ▶ For general population (without newborn), 9, 18 and 27 cases

A crash course on discrete-time systems

We have seen systems of ordinary differential equations (ODE) of the form

$$\frac{d}{dt}x(t) = f(x(t))$$

often written omitting dependence on t, i.e.,

$$x' = f(x) \tag{2}$$

where $x \in \mathbb{R}^n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$. The system is considered together with an initial condition $x(t_0) = x_0 \in \mathbb{R}^n$.

The **independent** variable $t \in \mathbb{R}$

A discrete-time system takes the form

$$x(t + \Delta t) = f(x(t)) \tag{3}$$

where $x(t) \in \mathbb{R}^n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$

In a discrete-time system, t is discrete and can be assumed to be in $\mathbb{Z}$ or $\mathbb{N}$ (in practice, before "recasting", it is in $\mathbb{Q}$), we often write $x(t + 1) = f(x(t))$, assuming $\Delta t = 1$..

Together with an initial condition $x(t_0) = x_0 \in \mathbb{R}^n$, this constitutes a sequence that describes the evolution of the state x

Similarities/differences

$$x' = f(x), x(t_0) = x_0, x \in \mathbb{R}^n \qquad x(t + \Delta t) = f(x(t)), x(t_0) = x_0, x \in \mathbb{R}^n$$

Equilibria (EP) $x^\star$ s.t. $f(x^\star) = 0_{\mathbb{R}^n}$ $\qquad$ Fixed points (FP) $x^\star$ s.t. $f(x^\star) = x^\star$

LAS EP $\Leftrightarrow s(Df(x^\star)) < 0$ $\qquad$ LAS FP $\Leftrightarrow \rho(Df(x^\star)) < 1$

Notation – if $A \in \mathcal{M}_n$ is a matrix, $\mathsf{Sp}(A) = \{\lambda \in \mathbb{C} : A\mathbf{v} = \lambda\mathbf{v}, \mathbf{v} \neq \mathbf{0}\}$ is its **spectrum**, i.e., the set of all its eigenvalues and

▶ $s(A) = \max\{\mathrm{Re}\,(\lambda), \lambda \in \mathsf{Sp}(A)\}$ is its **spectral abscissa**

▶ $\rho(A) = \max\{|\lambda|, \lambda \in \mathsf{Sp}(A)\}$ is its **spectral radius**

Some considerations about numerics

The tetanus model of Cvjetanović
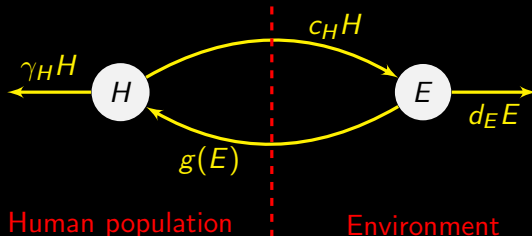The model of Capasso for ETP
The first schistosomiasis model of Woolhouse
The third schistosomiasis model of Woolhouse – Heterogeneous contacts
Spatial aspects – Cholera in Haiti

Recall the base model of Capasso

$$E' = c_H H - d_E E \tag{4a}$$
$$H' = g(E) - \gamma_H H \tag{4b}$$

$1/\gamma_H$ mean infectious period, $1/d_E$ mean lifetime of the agent in the environment, c_H growth rate of the agent due to the human population, $g(E)$ incidence of the agent on human population

Incidence function

$$g(E) = h(E)N\beta p \tag{5}$$

where

- ▶ $h(E)$ probability for an exposed susceptible to get the infection
- ▶ N total human population
- ▶ β fraction of susceptible individuals in N
- ▶ p fraction exposed to contaminated environment per unit time ("probability per unit time to have a "snack" of contaminated food")

Typically, we would assume p and β independent of E and H and h to be saturating. We take a Holling type II functional response

$$h(E) = h_{max}\frac{E}{h_{half} + E} \tag{6}$$

Simulating (in R) – Incidence function

```r
h = function(E, params) {
  # Use Michaelis Menten (Holling type II) growth
  OUT = params$g_max * E / (params$g_half+E)
  return(OUT)
}
g = function(E, params) {
  OUT = params$N * params$beta * params$p * h(E,params)
  return(OUT)
}
```

The right hand side

```
rhs_Capasso_ODE = function(t, x, params) {
  with(as.list(c(x, params)), {
    dE = c_H*H-d_E*E
    dH = g(E, params)-gamma_H*H
    list(c(dE, dH))
  })
}
```

Setting parameters

```
# Put parameters in a list
params = list()
params$N = 1000      # Total population
params$gamma_H = 1/10 # Infectious period
params$d_E = 1/5      # Lifetime agent
params$c_H = 0.1      # Flow from humans
# Human characteristics and behaviour
params$beta = 0.2 # Fraction susceptible
params$p = 0.1     # Probability of having "snack"
# Growth function
params$g_max = 10
params$g_half = 100
# Final time
params$t_f = 150
```

Running and plotting (base)

```r
IC <- c(E = 10, H = 0)
tspan = seq(from = 0, to = params$t_f, by = 0.1)

sol_ODE = ode(y = IC,
              func = rhs_Capasso_ODE,
              times = tspan,
              parms = params)

plot(sol_ODE[,"time"], sol_ODE[,"H"],
     type = "l", lwd = 2,
     xlab = "Time␣(days)", ylab = "Value")
lines(sol_ODE[,"time"], sol_ODE[,"E"],
      lwd = 2, lty = 3)
legend("bottomright", legend = c("H(t)", "E(t)"),
       lwd = c(2,2), lty = c(1,3), inset = 0.01)
```
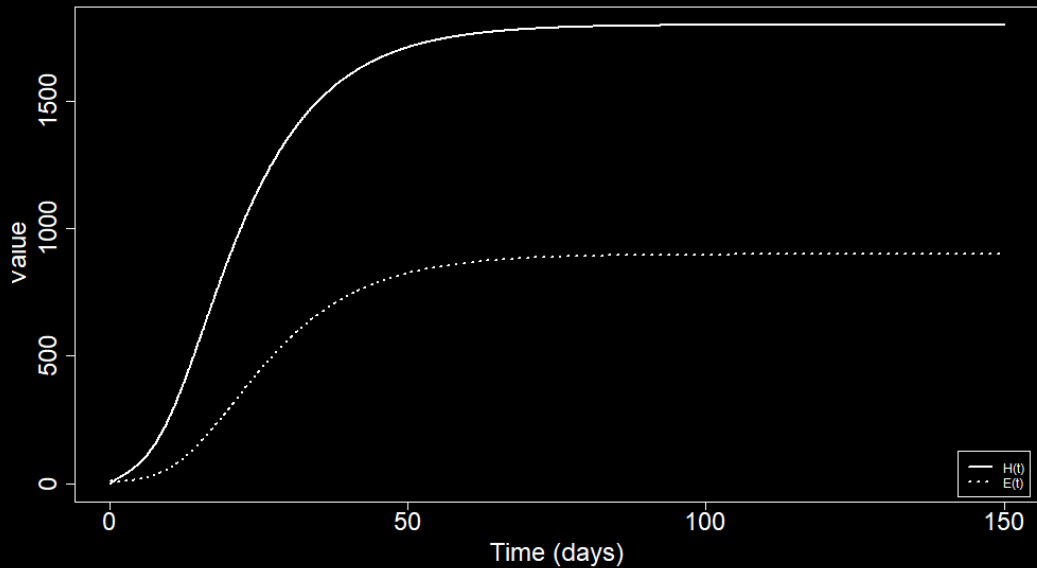
Let

$$\mathcal{R}_0 = \frac{g_+'(0)c_H}{d_E\gamma_H} \tag{7}$$

Theorem 1

▶ If $0 < \mathcal{R}_0 < 1$, then (4) admits only the trivial equilibrium in the positive orthant, which is GAS

▶ If $\mathcal{R}_0 > 1$, then two EP exist: $(0, 0)$, which is unstable, and $z^\star = (E^\star, H^\star)$ with $E^\star, H^\star > 0$, GAS in $\mathbb{R}_+^2 \setminus \{0, 0\}$

Computing $\mathcal{R}_0$

With the chosen g, we have

$$g'(E) = \frac{N\beta p g_{half} g_{max}}{(g_{half} + E)^2}$$

whence

$$g'_+(0) = \frac{N\beta p g_{max}}{g_{half}}$$

and thus

$$\mathcal{R}_0 = \frac{N\beta p g_{max}}{g_{half}} \frac{c_H}{d_E \gamma_H} \tag{8}$$

```
R0 = function(params) {
  with(as.list(params), {
    R0 = N*beta*p*g_max*c_H / (g_half*d_E*gamma_H)
    return(R0)
  })
}
```

Showing things dynamically using Shiny

Shiny is an R library (made by RStudio) to easily make interactive displays

See some documentation here

Some examples here and here

Create a subdirectory with the name of your app and a file called app.R in there

Structure of a Shiny app

Need to use library `shiny`

Define two elements
- ▶ `ui`, which sets up the user interface
- ▶ `server`, which handles the computations, generation of figures, etc.

I explain different elements as we progress. See the code in the `CODE` folder and `Capasso_simpleETP_shiny` subdirectory

The `ui` part

Here, we use `fluidPage` to create the UI. There are other functions: `fillPage`, `fixedPage`, `flowLayout`, `navbarPage`, `sidebarLayout`, `splitLayout` and `verticalLayout`

```r
# Define UI
ui <- fluidPage(
)
```

We now fill this function

A title and some sliders

```
# Application title
titlePanel("Simple ETP model of Capasso"),
# Sidebar with slider inputs for some parameters
sidebarLayout(
    sidebarPanel(
      sliderInput("inv_gamma_H",
                  "Average infectious period (days):",
                  min = 0,
                  max = 30,
                  value = 10),
      sliderInput("c_H",
                  "Flow from humans:",
                  min = 0,
                  max = 2,
                  value = 0.1),
```

Plus other sliders for all other parameters

Note the little trick...

```
sliderInput("inv_gamma_H",
"Average␣infectious␣period␣(days):",
min = 0,
max = 30,
value = 10),
```

I want to give a user friendly version of the parameter value, using the number of days rather than the inverse, whereas the model uses the latter. So I prefix the variable name by inv_ and then process as follows in the server part

```
params <- list()
for (param_name in names(input)) {
  if (grepl("inv_", param_name)) {
    new_param_name = gsubs("inv_", "", param_name)
    params[[new_param_name]] = 1/input[[param_name]]
  } else {
    params[[param_name]] = input[[param_name]]
  }
}
```

The simulation functions can be outside of `ui` or `server`, this makes the code neater

These functions are the same as before (right hand side, g, h, R0), so they are not shown here

The `server` **part**

```r
# Define server logic required to draw the result
server <- function(input, output) {
  ##
  ## Expression that generates the plot
  ##
  output$a_odePlot <- renderPlot({
    params <- list()
    params$N = 1000 # We could let this vary, we don't here..
    for (param_name in names(input)) {
      if (grepl("inv_", param_name)) {
        new_param_name = gsub("inv_", "", param_name)
        params[[new_param_name]] = 1/input[[param_name]]
      } else {
        params[[param_name]] = input[[param_name]]
      }
    }
    # Initial conditions and time span
    IC <- c(E = 10, H = 0)
    tspan <- seq(from = 0, to = params$tf, by = 0.1)
```

The `server` part (continued)

```r
    # Compute solution
    sol_ODE = ode(y = IC,
                    func = rhs_Capasso_ODE,
                    times = tspan,
                    parms = params)
    # Make the plot
    y_max = max(max(sol_ODE[,"H"]),sol_ODE[,"E"])
    plot(sol_ODE[,"time"], sol_ODE[,"H"],
            type = "l", lwd = 2,
            xlab = "Time (days)", ylab = "Value",
            ylim = c(0, y_max),
            main = sprintf("R_0=%1.2f", round(R0(params),2)))
    lines(sol_ODE[,"time"], sol_ODE[,"E"],
            lwd = 2, lty = 3)
    legend("topleft", legend = c("H(t)", "E(t)"),
              lwd = c(2,2), lty = c(1,3), inset = 0.01)
  })
}
```

Finally, run the code

```
# Run the application
shinyApp(ui = ui, server = server)
```

Adding a periodic component

Assume p in (5) takes the form

$$p(t) = p(t + \omega) > 0, \quad t \in \mathbb{R} \tag{9}$$

i.e., p has period ω. So we now consider the incidence

$$g(t, E) = p(t)h(E) \tag{10}$$

with h having the properties prescribed earlier. Letting

$$p_{min} := \min_{0 \leq t \leq \omega} p(t), \quad p_{max} := \max_{0 \leq t \leq \omega} p(t) \tag{11}$$

then we require that

$$\lim_{z \to \infty} \frac{g(z)}{z} < \frac{d_E \gamma_H}{c_H p_{max}} \tag{12}$$

Let

$$\mathcal{R}_0^{min} = \frac{c_H p_{min} h'_+(0)}{d_E \gamma_H}, \quad \mathcal{R}_0^{max} = \frac{c_H p_{max} h'_+(0)}{d_E \gamma_H} \tag{13}$$

Theorem 2

- ▶ *If* $0 < \mathcal{R}_0^{max} < 1$, *then* (4) *with incidence* (10) *always goes to extinction*
- ▶ *If* $\mathcal{R}_0^{min} > 1$, *then a unique nontrivial periodic endemic state exists for* (4) *with incidence* (10)

A model of Woolhouse

Woolhouse. On the application of mathematical models of schistosome transmission dynamics. I. Natural transmission. *Acta Tropica* **49**:241-270 (1991)

The model

Population of H individuals using a body of water containing N snails

i_H mean number of schistosomes per person and i_S the proportion of patent infections in snails (prevalence)

$$i'_H = \alpha N i_S - \gamma i_H \tag{14a}$$
$$i'_S = \beta H i_H (1 - i_S) - \mu_2 i_S \tag{14b}$$

- ▶ α number of schistosomes produced per person per infected snail per unit time
- ▶ $1/\gamma$ average life expectancy of a schistosome
- ▶ $1/\mu_2$ average life expectancy of an infected snail
- ▶ β transmission parameter

Let the basic reproductive rate for schistosomes be

$$\mathcal{R}_0 = \frac{\alpha N \beta H}{\gamma \mu_2} \tag{15}$$

(14) has two EP

- $(i_H^\star, i_S^\star) = (0, 0)$, LAS when $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 > 1$
- $(i_H^\star, i_S^\star) = \left(\dfrac{\alpha N}{\gamma} - \dfrac{\mu_2}{\beta H}, 1 - \dfrac{1}{\mathcal{R}_0} \right)$, which only "exists" when $\mathcal{R}_0 > 1$ (and is LAS then)

Heterogeneities in contact rates

I_i the number of schistosomes in person $i = 1, \ldots, H$ and i_{S_j} the proportion of patent infected snails in site $j = 1, \ldots, L$ (L sites each supporting N snails)
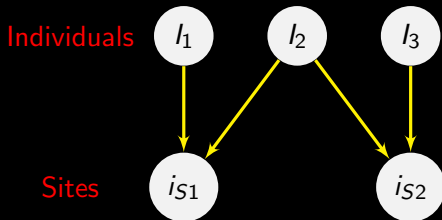
I_i the number of schistosomes in person $i = 1, \ldots, H$ and i_{Sj} the proportion of patent infected snails in site $j = 1, \ldots, L$ (L sites each supporting N snails)

$$I_i' = \alpha \left(\sum_j \eta_{ij} N i_{Sj} \right) - \gamma I_i \tag{16a}$$

$$i_{Sj}' = \beta \left(\sum_i \eta_{ij} I_i \right) (1 - i_{Sj}) - \mu_2 i_{Sj} \tag{16b}$$

η_{ij} rate of water contact by individual i at site j

Some considerations about numerics

- The tetanus model of Cvjetanović
- The model of Capasso for ETP
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- The third schistosomiasis model of Woolhouse – Heterogeneous contacts
- Spatial aspects – Cholera in Haiti

Spatial aspects – Cholera in Haiti

Tuite, Tien, Eisenberg, Earn, Ma & Fisman. Cholera Epidemic in Haiti, 2010: Using a Transmission Model to Explain Spatial Spread of Disease and Identify Optimal Control Interventions. *Annals of Internal Medicine* **154**(9) (2011)
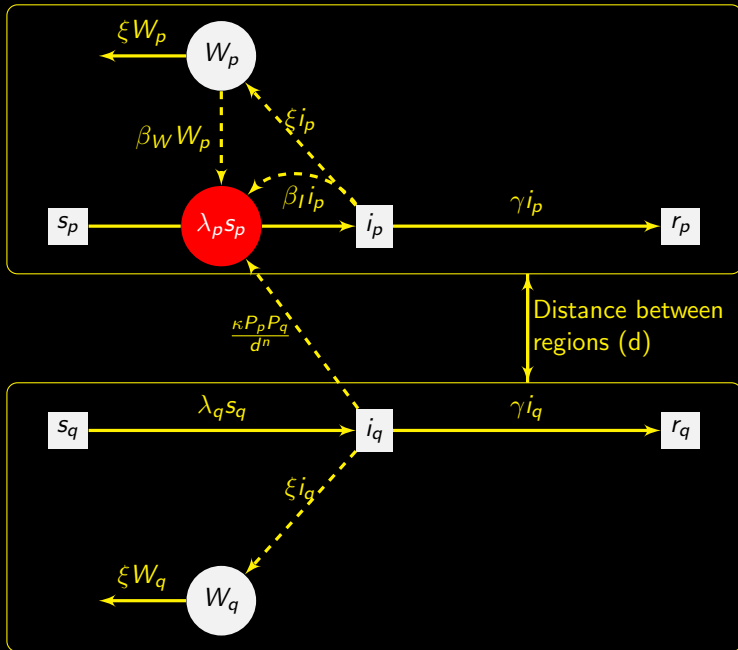
Metapopulation model with **implicit** movement

$$s_p' = \mu - \lambda_p s_p - \mu s_p \tag{17a}$$

$$i_p' = -\gamma i_p + \lambda_p s_p - \mu i_p \tag{17b}$$

$$r_p' = \gamma r_p - \mu r_p \tag{17c}$$

$$w_p' = \xi(i_p - w_p) \tag{17d}$$

with force of infection

$$\lambda_p = \beta_{i_p} i_p + \beta_{W_p} w_p + \sum_{q=1}^{10} \theta_{pq} i_q \tag{17e}$$

Influence of infection prevalence in q on incidence in p is gravity-type

$$\theta_{pq} = \kappa \frac{P_p P_q}{d^n}$$