

Environmentally Transmitted Pathogens

Models – Part deux :)

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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

Some considerations about numerics

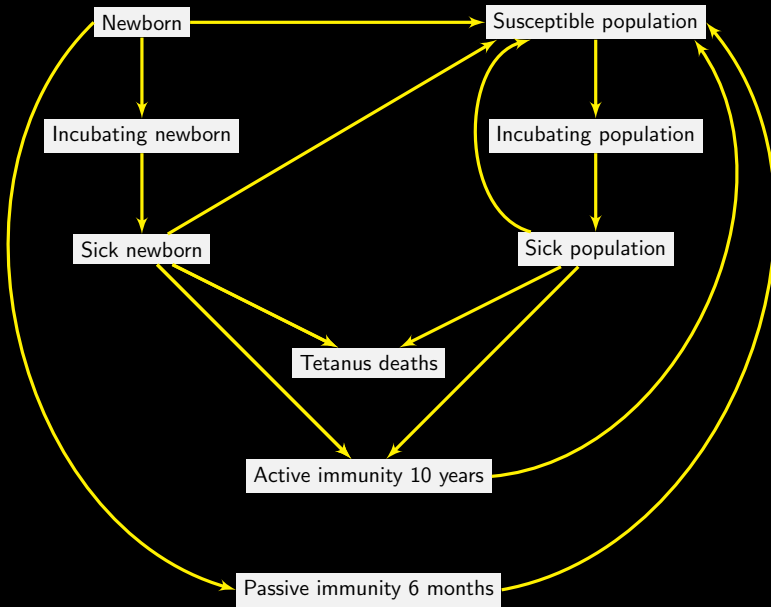
- The tetanus model of Cvjetanović

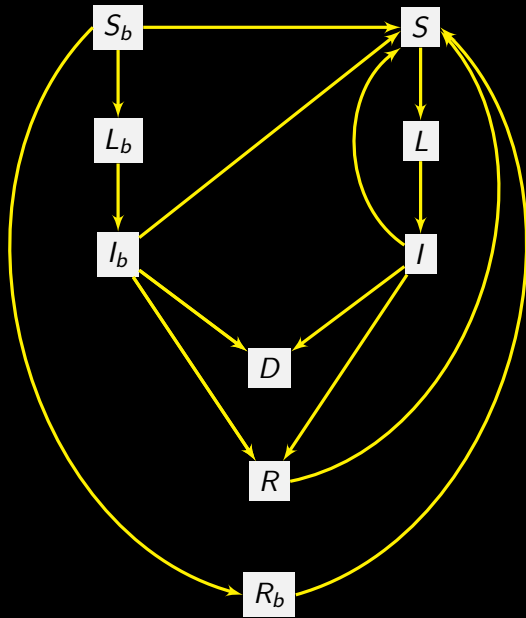
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The discrete-time tetanus model (notation mine)

$$\Delta S_b = bT \quad (1a)$$

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

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

$$\Delta L = \lambda S - (\varepsilon + d - \delta_T)L \quad (1d)$$

$$\Delta I_b = \varepsilon_b L_b - (\gamma_b + d - \delta_T)I_b \quad (1e)$$

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

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

$$\Delta R_b = bR - (\nu_b + d - \delta_T)R_b \quad (1h)$$

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

where

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

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 $f : \mathbb{R}^n \rightarrow \mathbb{R}^n$. 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

$$x(t + \Delta t) = f(x(t)) \quad (3)$$

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

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

$$x' = f(x), x(t_0) = x_0, x \in \mathbb{R}^n$$

Equilibria (EP) x^* s.t. $f(x^*) = 0_{\mathbb{R}^n}$

$$\text{LAS EP} \Leftrightarrow s(Df(x^*)) < 0$$

$$x(t + \Delta t) = f(x(t)), x(t_0) = x_0, x \in \mathbb{R}^n$$

Fixed points (FP) x^* s.t. $f(x^*) = x^*$

$$\text{LAS FP} \Leftrightarrow \rho(Df(x^*)) < 1$$

(s the **spectral abscissa** $= \max\{\text{Re}(\lambda), \lambda \in \text{Sp}(Df(x^*))\}$, ρ the **spectral radius** $= \max\{|\lambda|, \lambda \in \text{Sp}(Df(x^*))\}$)

Some considerations about numerics

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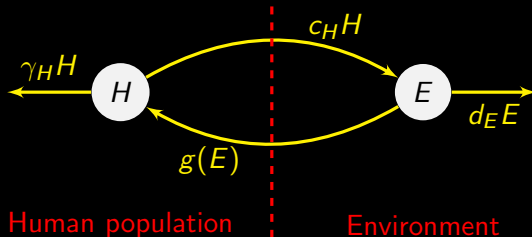
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Recall the base model of Capasso

$$E' = c_H H - d_E E \quad (4a)$$

$$H' = g(E) - \gamma_H H \quad (4b)$$



$1/\gamma_H$ 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

$$g(E) = h(E)N\beta p \quad (5)$$

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

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

Simulating (in R) – Incidence function

```
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

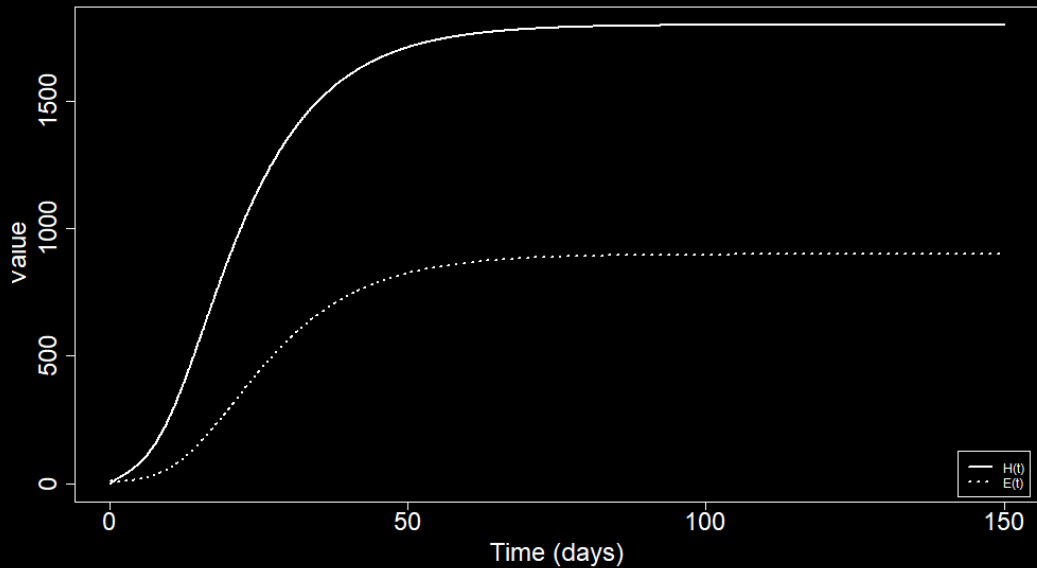
```
# Put parameters in a list
params = list()
params$N = 1000      # Total population
params$gamma_H = 1/10 # Infectious period
params$d_E = 1/5      # Lifetime agent
params$c_H = 0.1      # Flow from humans
# Human characteristics and behaviour
params$beta = 0.2     # Fraction susceptible
params$p = 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)

```
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

$$\mathcal{R}_0 = \frac{g'_+(0)c_H}{d_E\gamma_H} \quad (7)$$

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 $z^* = (E^*, H^*)$ with $E^*, H^* > 0$, 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

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

```
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`

```
# 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 server part

```
# 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)

```
# 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)
```

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

Adding a periodic component

Assume p in (5) takes the form

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

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

$$g(t, E) = p(t)h(E) \quad (10)$$

with h having the properties prescribed earlier. Letting

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

then we require that

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

Let

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

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)*

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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)

$$i'_H = \alpha N i_S - \gamma i_H \quad (14a)$$

$$i'_S = \beta H i_H (1 - i_S) - \mu_2 i_S \quad (14b)$$

- ▶ 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

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

(14) has two EP

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

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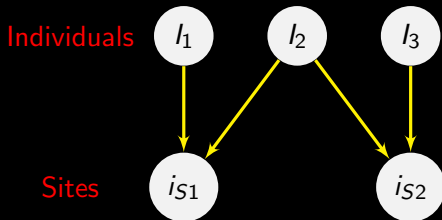
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Heterogeneities in contact rates

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



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

$$l'_i = \alpha \left(\sum_j \eta_{ij} N i_{Sj} \right) - \gamma l_i \quad (16a)$$

$$i'_{Sj} = \beta \left(\sum_i \eta_{ij} l_i \right) (1 - i_{Sj}) - \mu_2 i_{Sj} \quad (16b)$$

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

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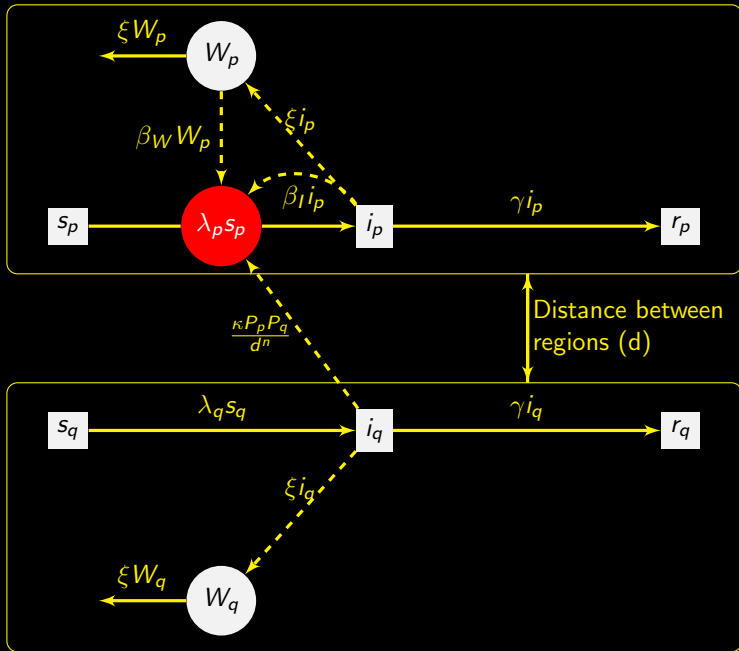
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Spatial aspects – Cholera in Haiti

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

$$s'_p = \mu - \lambda_p s_p - \mu s_p \quad (17a)$$

$$i'_p = -\gamma i_p + \lambda_p s_p - \mu i_p \quad (17b)$$

$$r'_p = \gamma r_p - \mu r_p \quad (17c)$$

$$w'_p = \xi(i_p - w_p) \quad (17d)$$

with force of infection

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

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

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