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
- A model for zoonotic transmission of waterborne disease
- The first schistosomiasis model of Woolhouse
- The third schistosomiasis model of Woolhouse – Heterogeneous contacts
- Spatial aspects – Cholera in Haiti

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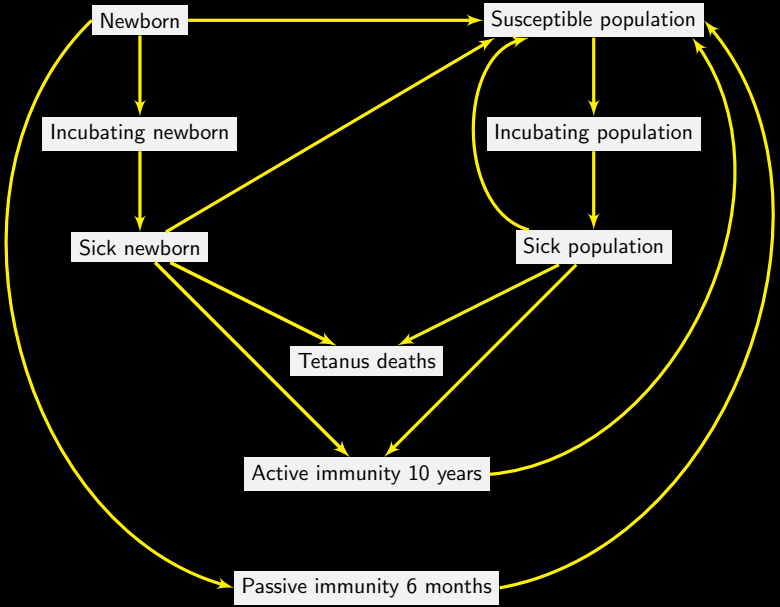
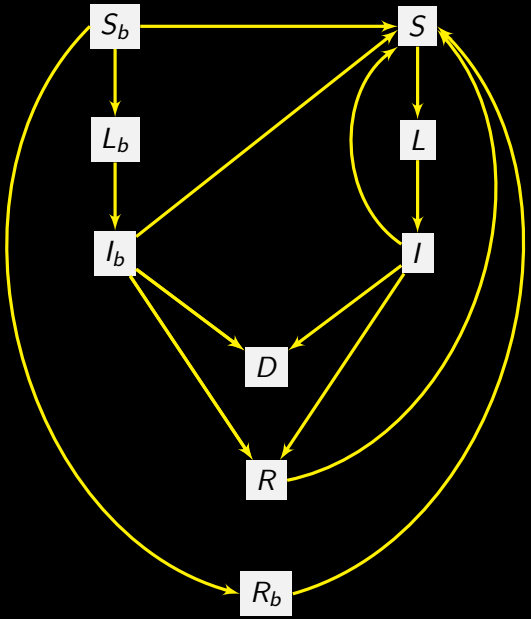

Newborn
Susceptible population
Incubating newborn
Incubating population
Sick newborn
Sick population
Tetanus deaths
Active immunity 10 years
Passive immunity 6 months


S_b
S
L_b
L
I_b
I
D
R
R_b

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

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

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

LAS EP $\Leftrightarrow s(Df(x^\star)) < 0$

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

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

LAS FP $\Leftrightarrow \rho(Df(x^\star)) < 1$

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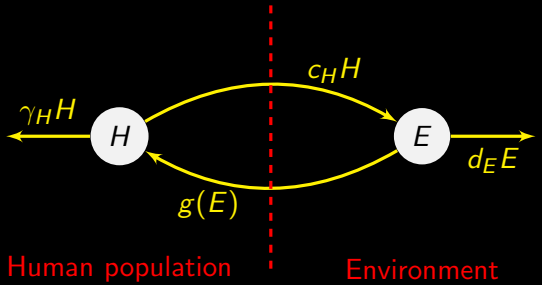
Recall the base model of Capasso

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



$1/\gamma_H$ 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

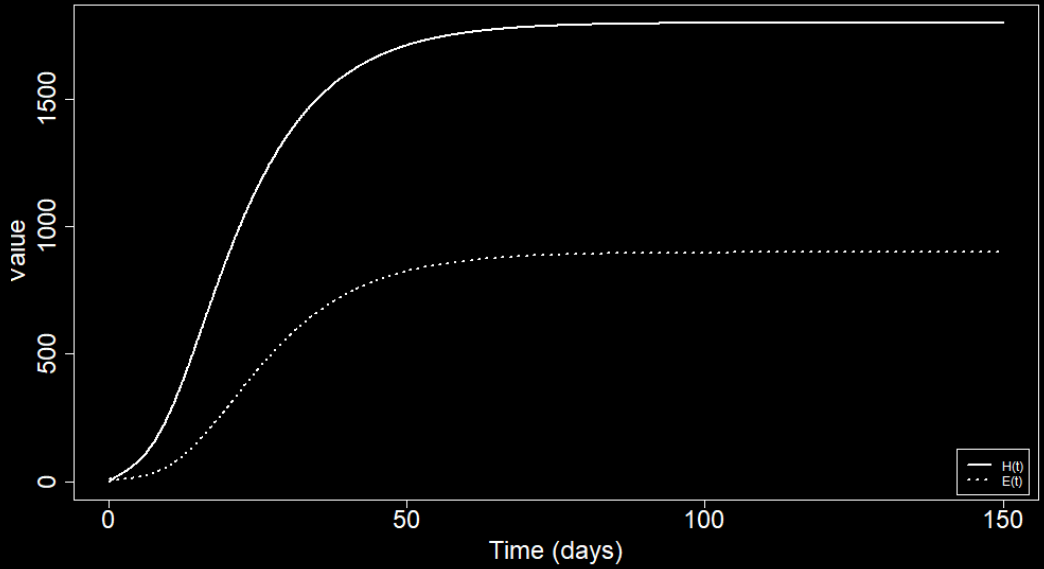
```r
# Put parameters in a list
params = list()
params$N = 1000       # Total population
params$gamma_H = 1/10 # Infectious period
params$d_E = 1/5      # Lifetime agent
params$c_H = 0.1      # Flow from humans
# Human characteristics and behaviour
params$beta = 0.2 # Fraction susceptible
params$p =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


Value
0
500
1000
1500
0
50
100
150
Time (days)
H(t)
E(t)

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)
  })
}
```

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

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

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)

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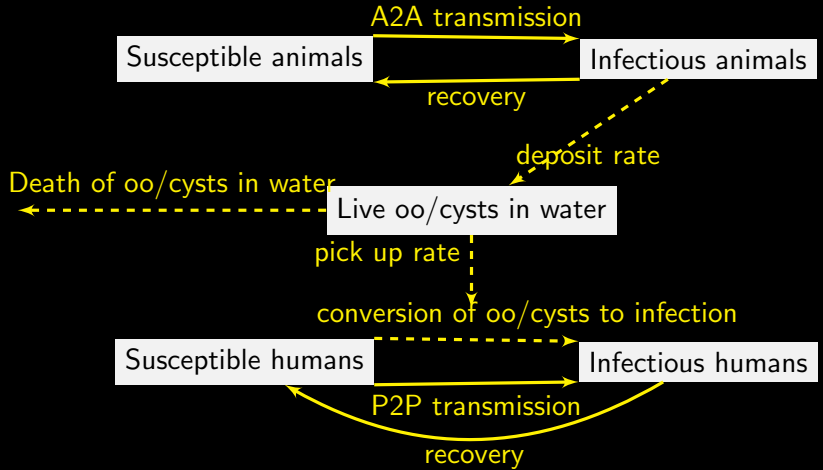
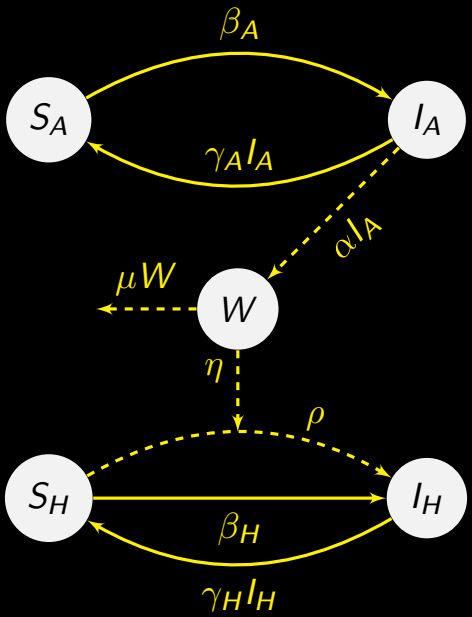
Zoonotic transmission of waterborne disease

Waters, Hamilton, Sidhu, Sidhu, Dunbar. Zoonotic transmission of waterborne disease: a mathematical model. *Bull Math Biol* (2016)
Used for instance to model Giardia transmission from possums to humans


A2A transmission
Susceptible animals
Infectious animals
recovery
deposit rate
Death of oo/cysts in water
Live oo/cysts in water
pick up rate
conversion of oo/cysts to infection
Susceptible humans
Infectious humans
P2P transmission
recovery


β_A
S_A
I_A
$\gamma_A I_A$
αI_A
μW
W
η
ρ
S_H
I_H
β_H
$\gamma_H I_H$

The full model

$$S_A' = -\beta_A S_A I_A + \gamma_A I_A \tag{14a}$$
$$I_A' = \beta_A S_A I_A - \gamma_A I_A \tag{14b}$$
$$W' = \alpha I_A - \eta W(S_H + I_H) - \mu W \tag{14c}$$
$$S_H' = -\rho\eta W S_H - \beta_H S_H I_H + \gamma_H I_H \tag{14d}$$
$$I_H' = \rho\eta W S_H + \beta_H S_H I_H - \gamma_H I_H \tag{14e}$$

Considered with $N_A = S_A + I_A$ and $N_H = S_H + I_H$ constant

Simplified model

Because N_A and N_H are constant, (14) can be simplified:

$$I_A' = \beta_A N_A I_A - \gamma_A I_A - \beta_A I_A^2 \tag{15a}$$
$$W' = \alpha I_A - \eta W N_H - \mu W \tag{15b}$$
$$I_H' = \rho\eta W(N_H - I_H) + \beta_H N_H I_H - \gamma_H I_H - \beta_H I_H^2 \tag{15c}$$

Three EP: DFE $(0, 0, 0)$; endemic disease in humans because of H2H transmission; endemic in both H and A because of W

Three EP: DFE $(0,0,0)$; endemic disease in humans because of H2H transmission; endemic in both H and A because of W

Let

$$\mathcal{R}_{0A} = \frac{\beta_A}{\gamma_A} N_A \quad \text{and} \quad \mathcal{R}_{0H} = \frac{\beta_H}{\gamma_H} N_H \tag{16}$$

- DFE LAS if $\mathcal{R}_{0A} < 1$ and $\mathcal{R}_{0H} < 1$, unstable if $\mathcal{R}_{0A} > 1$ or $\mathcal{R}_{0H} > 1$
- If $\mathcal{R}_{0H} > 1$ and $\mathcal{R}_{0A} < 1$, (15) goes to EP with endemicity only in humans
- Endemic EP with both A and H requires $\mathcal{R}_{0A} > 1$ and $\mathcal{R}_{0H} < 1$

Note that proof is **not** global

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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)

$$i'_H = \alpha N i_S - \gamma i_H \tag{17a}$$
$$i'_S = \beta H i_H (1 - i_S) - \mu_2 i_S \tag{17b}$$

- 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

$$\mathcal{R}_0 = \frac{\alpha N \beta H}{\gamma \mu_2} \tag{18}$$

(17) has two EP

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

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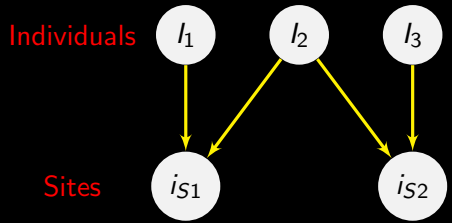
Heterogeneities in contact rates

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)



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$$I_i' = \alpha \left(\sum_j \eta_{ij} N i_{Sj} \right) - \gamma I_i \tag{19a}$$

$$i_{Sj}' = \beta \left(\sum_i \eta_{ij} I_i \right) (1 - i_{Sj}) - \mu_2 i_{Sj} \tag{19b}$$

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

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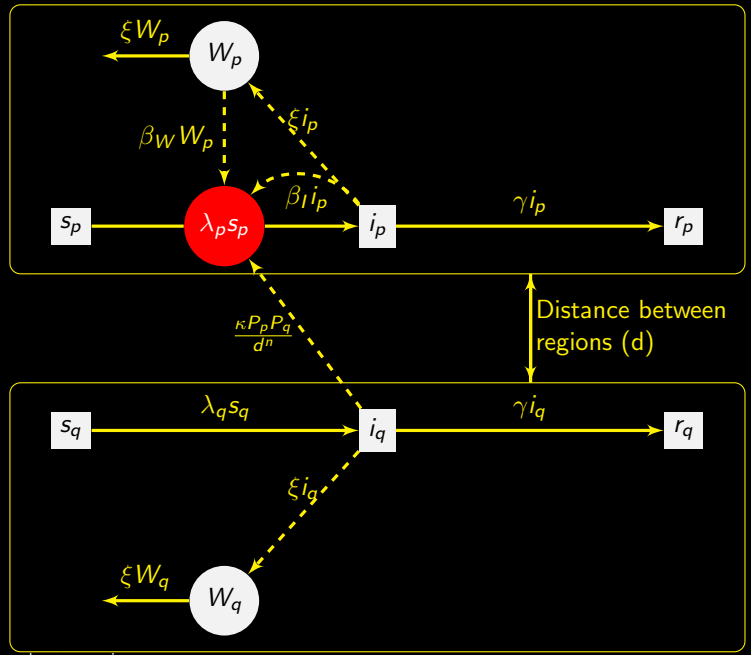
Spatial aspects – Cholera in Haiti

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)


ξW_p
W_p
ξi_p
$\beta_W W_p$
$\beta_I i_p$
s_p
$\lambda_p s_p$
i_p
γi_p
r_p
$\frac{\kappa P_p P_q}{d^n}$
Distance between regions (d)
s_q
$\lambda_q s_q$
i_q
γi_q
r_q
ξi_q
ξW_q
W_q

Metapopulation model with **implicit** movement

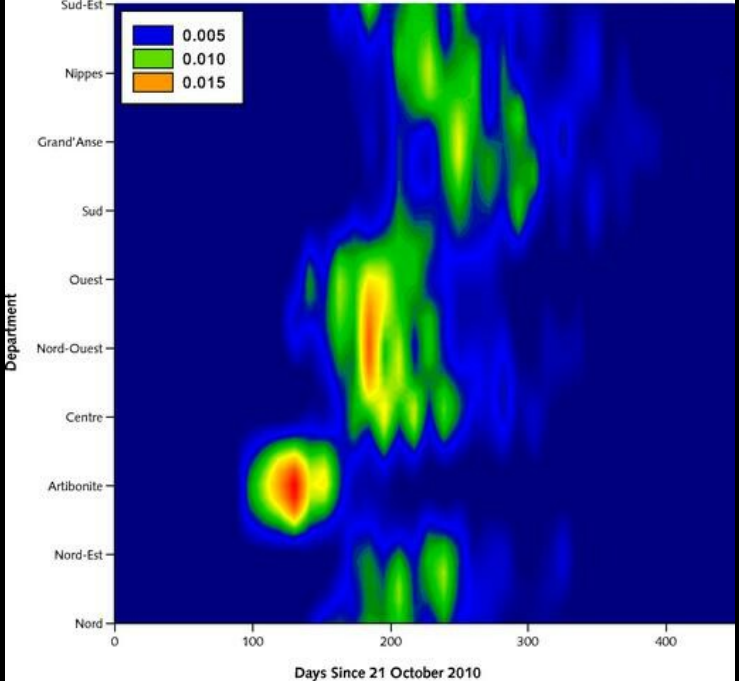
$$s_p' = \mu - \lambda_p s_p - \mu s_p \tag{20a}$$
$$i_p' = -\gamma i_p + \lambda_p s_p - \mu i_p \tag{20b}$$
$$r_p' = \gamma r_p - \mu r_p \tag{20c}$$
$$w_p' = \xi(i_p - w_p) \tag{20d}$$

with force of infection

$$\lambda_p = \beta_{i_p} i_p + \beta_{W_p} w_p + \sum_{q=1}^{10} \theta_{pq} i_q \tag{20e}$$

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

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


0.005
0.010
0.015
Sud-Est
Nippes
Grand'Anse
Sud
Ouest
Nord-Ouest
Centre
Artibonite
Nord-Est
Nord
Department
0
100
200
300
400
Days Since 21 October 2010