

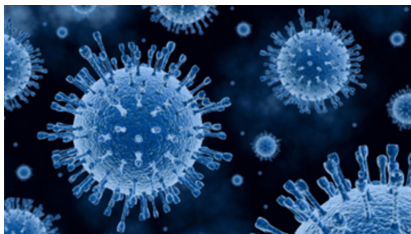
# Modeling the Spreading of Diseases

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# We shall model a very complex phenomenon by simple math....

## Assumptions:

- We consider a perfectly mixed population in a confined area
- No spatial transport, just temporal evolution
- We do not consider individuals, just a grand mix of them (cf. statistical mechanics vs thermodynamics)

We consider very simple models, but these can be extended to full models that are used world-wide by health authorities. Typical diseases modeled are flu, measles, swine flu, HIV, ...

All these slides and associated programs are available from  
<https://github.com/hplgit/disease-modeling>.

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# We keep track of 3 categories in the SIR model

- **S**: susceptibles - who can get the disease
- **I**: infected - who have developed the disease and infect susceptibles
- **R**: recovered - who have recovered and become immune

Mathematical quantities:

$S(t)$ ,  $I(t)$ ,  $R(t)$ : no of people in each category

Goal:

Find and solve equations for  $S(t)$ ,  $I(t)$ ,  $R(t)$



The traditional modeling approach is very mathematical -  
our idea is to model, program and experiment

- Numerous books on mathematical biology treat the SIR model
- Quick modeling step (max 2 pages)
- Nonlinear differential equation model
- Cannot solve the equations, so focus is on discussing stability (eigenvalues), qualitative properties, etc.
- Very few extensions of the model to real-life situations

Dynamics in a time interval  $\Delta t$ :  $\Delta t \beta SI$  people move from S to I

### S-I interaction:

- In a mix of S and I people, there are  $SI$  possible pairs
- A certain fraction  $\Delta t \beta$  of  $SI$  meet in a (small) time interval  $\Delta t$ , with the result that the infected “successfully” infects the susceptible
- The loss  $\Delta t \beta SI$  in the S category is a corresponding gain in the I category

### Remark

It is reasonable that the fraction depends on  $\Delta t$  (twice as many infected in  $2\Delta t$  as in  $\Delta t$ ).  $\beta$  is some unknown parameter we must measure, supposed to not depend on  $\Delta t$ , but maybe time  $t$ .  $\beta$  lumps a lot of biological and sociological effects into one number.

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For practical calculations, we must express the S-I interaction with symbols

Loss in  $S(t)$  from time  $t$  to  $t + \Delta t$ :

$$S(t + \Delta t) = S(t) - \Delta t \beta S(t) I(t)$$

Gain in  $I(t)$ :

$$I(t + \Delta t) = I(t) + \Delta t \beta S(t) I(t)$$

# Modeling the interaction between R and I

## R-I interaction:

- After some days, the infected has recovered and moves to the R category
- A simple model: in a small time  $\Delta t$  (say 1 day), a fraction  $\Delta t \nu$  of the infected are removed ( $\nu$  must be measured)

We must subtract this fraction in the balance equation for  $I$ :

$$I(t + \Delta t) = I(t) + \Delta t \beta S(t) I(t) - \Delta t \nu I(t)$$

The loss  $\Delta t \nu I$  is a gain in  $R$ :

$$R(t + \Delta t) = R(t) + \Delta t \nu I(t)$$

## We have three equations for $S$ , $I$ , and $R$

$$S(t + \Delta t) = S(t) - \Delta t \beta S(t) I(t) \quad (1)$$

$$I(t + \Delta t) = I(t) + \Delta t \beta S(t) I(t) - \Delta t \nu I(t) \quad (2)$$

$$R(t + \Delta t) = R(t) + \Delta t \nu I(t) \quad (3)$$



Before we can compute with these, we must

- know  $\beta$  and  $\nu$
- know  $S(0)$  (many),  $I(0)$  (few),  $R(0)$  (0?)
- choose  $\Delta t$

# The computation involves just simple arithmetics

- Set  $\Delta t = 6$  minutes
- Set  $\beta = 0.0013$ ,  $\nu = 0.8333$
- Set  $S(0) = 50$ ,  $I(0) = 1$ ,  $R(0) = 0$

$$S(\Delta t) = S(0) - \Delta t \beta S(0) I(0) \approx 49.99$$

$$I(\Delta t) = I(0) + \Delta t \beta S(0) I(0) - \Delta t \nu I(0) \approx 1.002$$

$$R(\Delta t) = R(0) + \Delta t \nu I(0) \approx 0.0008333$$

- In reality,  $S$ ,  $I$ ,  $R$  are integers and events are discrete (meet, get sick)
- In the model, we work with real numbers and continuous events
- Reasonable approximation in a not too small population

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And we can continue...

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$$R(2\Delta t) = R(\Delta t) + \Delta t \nu I(\Delta t) \approx 0.00167$$

Repeat...

$$S(3\Delta t) = S(2\Delta t) - \Delta t \beta S(2\Delta t) I(2\Delta t) \approx 49.98$$

$$I(3\Delta t) = I(2\Delta t) + \Delta t \beta S(2\Delta t) I(2\Delta t) - \Delta t \nu I(2\Delta t) \approx 1.017$$

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But this is getting boring! Let's ask a computer to do the work!



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But this is getting boring! Let's ask a computer to do the work!

## First, some handy notation

$$S^n = S(n\Delta t), \quad I^n = I(n\Delta t), \quad R^n = R(n\Delta t)$$

$$S^{n+1} = S((n+1)\Delta t), \quad I^{n+1} = I((n+1)\Delta t), \quad R^{n+1} = R((n+1)\Delta t)$$

The equations can now be written more compactly (and computer friendly):

$$S^{n+1} = S^n - \Delta t \beta S^n I^n \tag{4}$$

$$I^{n+1} = I^n + \Delta t \beta S^n I^n - \Delta t \nu I^n \tag{5}$$

$$R^{n+1} = R^n + \Delta t \nu I^n \tag{6}$$

## With variables, arrays, and a loop we can program

Suppose we want to compute until  $t = N\Delta t$ , i.e., for  $n = 0, 1, \dots, N - 1$ . We can store  $S^0, S^1, S^2, \dots, S^N$  in an array (or list).

Python (Matlab):

```
t = linspace(0, N*dt, N+1)  # all time points
S = zeros(N+1)
I = zeros(N+1)
R = zeros(N+1)

for n in range(N):
    S[n+1] = S[n] - dt*beta*S[n]*I[n]
    I[n+1] = I[n] + dt*beta*S[n]*I[n] - dt*nu*I[n]
    R[n+1] = R[n] + dt*nu*I[n]
```

## Here is the complete program

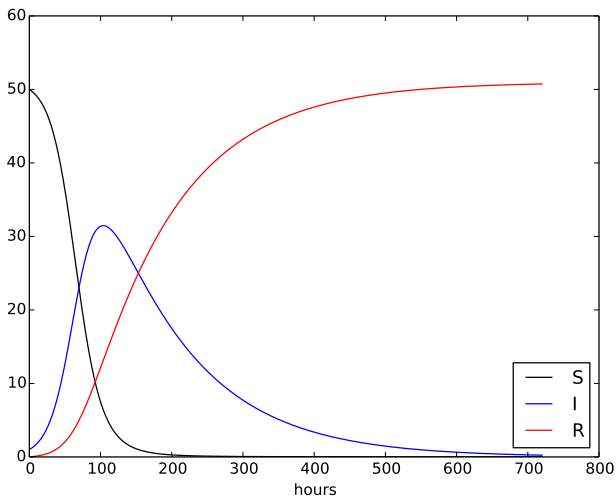
```
beta = 0.0013
nu = 0.8333
dt = 0.1          # 6 min (time measured in hours)
D = 30            # simulate for D days
N = int(D*24/dt)  # corresponding no of hours

from numpy import zeros, linspace
t = linspace(0, N*dt, N+1)
S = zeros(N+1)
I = zeros(N+1)
R = zeros(N+1)

for n in range(N):
    S[n+1] = S[n] - dt*beta*S[n]*I[n]
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# Plot the graphs
from matplotlib.pyplot import *
plot(t, S, 'k-', t, I, 'b-', t, R, 'r-')
legend(['S', 'I', 'R'], loc='lower right')
xlabel('hours')
show()
```

# We have predicted a disease!



# How much math and programming did we use?

## Math:

- Plain arithmetics
- The concept of a graph (i.e., discrete function in time)
- Units
- Greek letters

## Programming:

- Variable
- Array
- Loop
- Plotting

## Detour: The standard mathematical approach

We had from intuition established

$$S(t + \Delta t) = S(t) - \Delta t \beta S(t) I(t)$$

$$I(t + \Delta t) = I(t) + \Delta t \beta S(t) I(t) - \Delta t \nu I(t)$$

$$R(t + \Delta t) = R(t) + \Delta t \nu R(t)$$

The mathematician will now make *differential equations*. Divide by  $\Delta t$  and rearrange:

$$\frac{S(t + \Delta t) - S(t)}{\Delta t} = -\beta S(t) I(t)$$

$$\frac{I(t + \Delta t) - I(t)}{\Delta t} = \beta S(t) I(t) - \nu I(t)$$

$$\frac{R(t + \Delta t) - R(t)}{\Delta t} = \nu R(t)$$

## A derivative arises as $\Delta t \rightarrow 0$

In any calculus book, the derivative of  $S$  at  $t$  is defined as

$$S'(t) = \lim_{\Delta t \rightarrow 0} \frac{S(t + \Delta t) - S(t)}{\Delta t}$$

If we let  $\Delta t \rightarrow 0$ , we get derivatives on the left-hand side:

$$S'(t) = -\beta S(t)I(t)$$

$$I'(t) = \beta S(t)I(t) - \nu I(t)$$

$$R'(t) = \nu R(t)$$

This is a 3x3 system of differential equations for the functions  $S(t)$ ,  $I(t)$ ,  $R(t)$ . For a unique solution, we need  $S(0)$ ,  $I(0)$ ,  $R(0)$ .



# Bad news: we cannot solve these equations!

Time to ask a numerical methods expert:

Replace the derivative with a *finite difference*, e.g.,

$$S'(t) \approx \frac{S(t + \Delta t) - S(t)}{\Delta t}$$

which is accurate for small  $\Delta t$ .

This brings us back to the first model, which we can solve on a computer!

# Parameter estimation is needed for predictive modeling

- Any small  $\Delta t$  will do
- One can reason about  $\nu$  and say that  $1/\nu$  is the mean recovery time for the disease (e.g., 1 week for a flu)
- $\beta$  must in some way be measured, but we don't know what it means...

## So, what if we don't know $\beta$ ?

- Can still learn about the *dynamics* of diseases
- Can find the sensitivity to and influence of  $\beta$
- Can apply *parameter estimation* procedures to fit  $\beta$  to data

## Let us extend the model: no life-long immunity

### Assumption

After some time, people in the R category lose the immunity. In a small time  $\Delta t$  this gives a leakage  $\Delta t \gamma R$  to the S category. ( $1/\gamma$  is the mean time for immunity.)



$$S^{n+1} = S^n - \Delta t \beta S^n I^n + \Delta t \gamma R^n \quad (7)$$

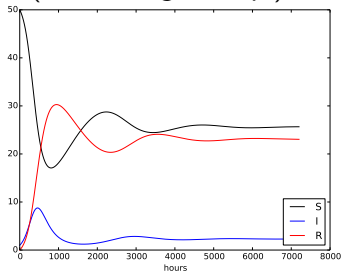
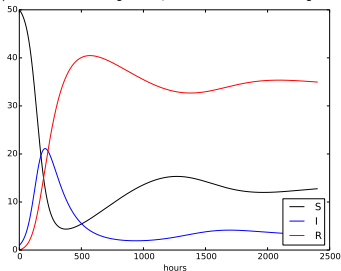
$$I^{n+1} = I^n + \Delta t \beta S^n I^n - \Delta t \nu I^n \quad (8)$$

$$R^{n+1} = R^n + \Delta t \nu R^n - \Delta t \gamma R^n \quad (9)$$

No complications in the computational model!

# The effect of loss of immunity

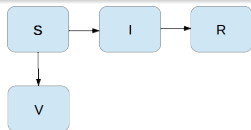
$1/\gamma = 50$  days.  $\beta$  reduced by 2 and 4 (left and right, resp.):



# What is the effect of vaccination?

## Assumptions

A fraction  $p$  of the  $S$  category, per time unit, is vaccinated with success. Then in time  $\Delta t$ ,  $p\Delta t S$  will move to a vaccinated category,  $V$ . This does not affect the  $I$  and  $R$  categories.



$$S^{n+1} = S^n - \Delta t \beta S^n I^n + \Delta t \gamma R^n - p\Delta t S^n \quad (10)$$

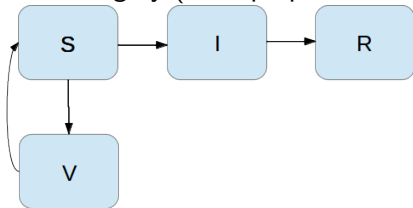
$$V^{n+1} = V^n + p\Delta t S^n \quad (11)$$

$$I^{n+1} = I^n + \Delta t \beta S^n I^n - \Delta t \nu I^n \quad (12)$$

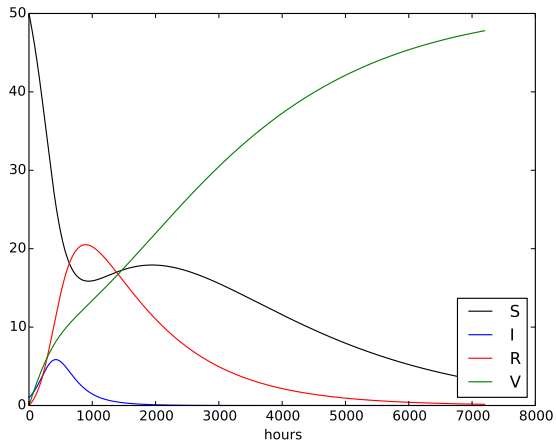
$$R^{n+1} = R^n + \Delta t \nu R^n - \Delta t \gamma R^n \quad (13)$$

# Many possibilities for adjusting the model...

The effect of vaccination decreases over time, so we may move people back to the S category (term proportional to  $\Delta t V$ ).



# Effect of adding vaccination



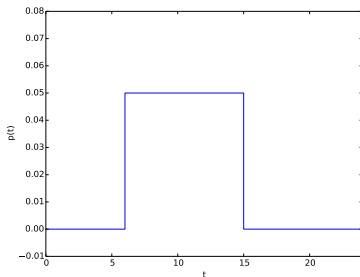
$(p = 0.0005)$

# What is the effect of an intensive vaccination campaign?

10 times more intense vaccination for 10 days, 6 days after outbreak:

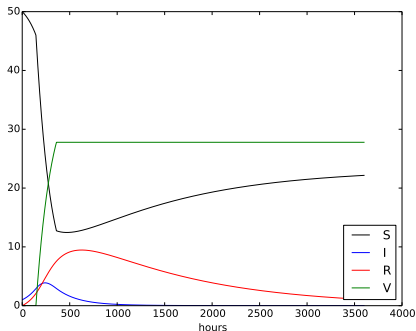
$$p(t) = \begin{cases} 0.005, & 6 \leq t \leq 15, \\ 0, & \text{otherwise} \end{cases}$$

Implementation: Let  $p^n$  be an array as  $V^n$ . Set  $p^n = 0.05$  for  $n = 6 \cdot 24/0.1, \dots, 15 \cdot 24/0.1$  (days  $\cdot 24/\Delta t$ , 24 is hours per day).





# Effect of vaccination campaign



Note:

- Mathematicians would be scared by the cusps on the curves...
- Could now let the computer run a lot of cases and find the optimal vaccination period

# We can experiment with other campaigns



Wearing masks lowers  $\beta$ :

$$\beta(t) = \begin{cases} \beta_1, & 0 \leq t < 5, \\ \beta_2 < \beta_1, & t \geq 5 \end{cases}$$

Very easy to implement. (Used to be complicated in differential equation models...)

And now for something similar: zombification!



**Zombification:** The disease that turns you into a zombie.

# Zombie modeling is almost the same as SIR modeling

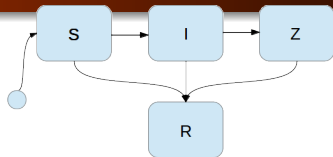
## Categories

- 1 S: susceptible humans who can become zombies
- 2 I: infected humans, being bitten by zombies
- 3 Z: zombies
- 4 R: removed individuals, either conquered zombies or dead humans

Mathematical quantities:  $S(t)$ ,  $I(t)$ ,  $Z(t)$ ,  $R(t)$

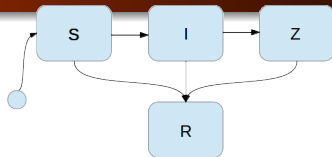
Zombie movie: *The Night of the Living Dead*, George A. Romero, 1968

# Dynamics of the zombie SIZR model



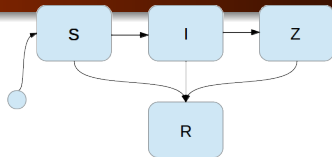
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- 2 Susceptibles die naturally or get killed and then enter the removed category. The no of deaths in time  $\Delta t$  is  $\Delta t \delta_S S$ .
- 3 We also allow new humans to enter the area with zombies (necessary in a war on zombies):  $\Delta t \Sigma$  during a time  $\Delta t$ .
- 4 Some infected turn into zombies (Z):  $\Delta t \rho I$ , while others die (R):  $\delta_I \Delta t I$ .
- 5 Nobody from R can turn into Z (important - otherwise zombies win).
- 6 Killed zombies go to R:  $\Delta t \alpha SZ$ .

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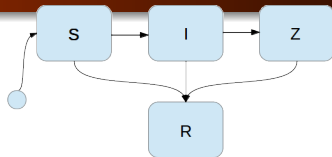
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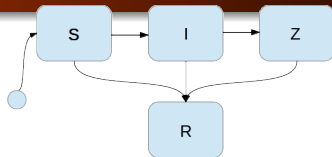
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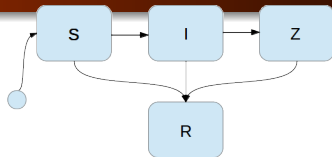


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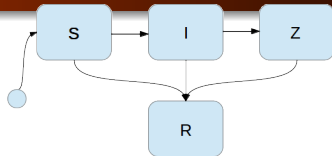
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- 6 Killed zombies go to R:  $\Delta t \alpha SZ$ .

# Dynamics of the zombie SIZR model



- 1 Susceptibles are infected by zombies:  $-\Delta t \beta SZ$  in time  $\Delta t$  (cf. the  $\Delta t \beta SI$  term in the SIR model).
- 2 Susceptibles die naturally or get killed and then enter the removed category. The no of deaths in time  $\Delta t$  is  $\Delta t \delta_S S$ .
- 3 We also allow new humans to enter the area with zombies (necessary in a war on zombies):  $\Delta t \Sigma$  during a time  $\Delta t$ .
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# The four equations in the SIZR model for zombification

$$S^{n+1} = S^n + \Delta t \Sigma - \Delta t \beta S^n Z - \Delta t \delta_S S^n$$

$$I^{n+1} = I^n + \Delta t \beta S^n Z^n - \Delta t \rho I^n - \Delta t \delta_I I^n$$

$$Z^{n+1} = Z^n + \Delta t \rho I^n - \Delta t \alpha S^n Z^n$$

$$R^{n+1} = R^n + \Delta t \delta_S S^n + \Delta t \delta_I I^n + \Delta t \alpha S^n Z^n$$

## Interpretation of parameters:

- $\Sigma$ : no of new humans brought into the zombified area per unit time.
- $\beta$ : the probability that a theoretically possible human-zombie pair actually meets physically, during a unit time interval, with the result that the human is infected.
- $\delta_S$ : the probability that a susceptible human is killed or dies, in a unit time interval.
- $\delta_I$ : the probability that an infected human is killed or dies, in a unit time interval.
- $\rho$ : the probability that an infected human is turned into a zombie, during a unit time interval.
- $\alpha$ : the probability that, during a unit time interval, a theoretically

# Simulate a zombie movie!

## Three fundamental phases

- 1 The initial phase (4 h)
- 2 The hysteric phase (24 h)
- 3 The counter attack phase (5 h)



How do we do this? As  $p$  in the vaccination campaign - the parameters take on different constant values in different time intervals.

H. P. Langtangen, K.-A. Mardal and P. Røtnes: Escaping the Zombie Threat by Mathematics, in A. Whelan et al.: *Zombies in the Academy - Living Death in Higher Education*, University of Chicago Press, 2013

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# Effective war on zombies

Introduce attacks on zombies at selected times  $T_0, T_1, \dots, T_m$ .

Model: Replace  $\alpha$  by

$$\alpha_0 + \omega(t),$$

where  $\alpha_0$  is constant and  $\omega(t)$  is a series of Gaussian functions (peaks) in time:

$$\omega(t) = a \sum_{i=0}^m \exp \left( -\frac{1}{2} \left( \frac{t - T_i}{\sigma} \right)^2 \right)$$

Must experiment with values of  $a$  (strength),  $\sigma$  (duration is  $6\sigma$ ), point of attacks ( $T_i$ ) - with proper values humans beat the zombies!



# Summary

- A complex spreading of diseases can be modeled by intuitive, simple accounting of movement between categories
- Such models are known as *compartment models*
- Result: difference equations that are easy to simulate on a computer
- (Can let  $\Delta t \rightarrow 0$  and get differential equations)
- Easy to add new effects (vaccination, campaigns, zombification)

All these slides and associated programs are available

Site: <https://github.com/hplgit/disease-modeling>. Just do

```
git clone https://github.com/hplgit/disease-modeling.git
```