

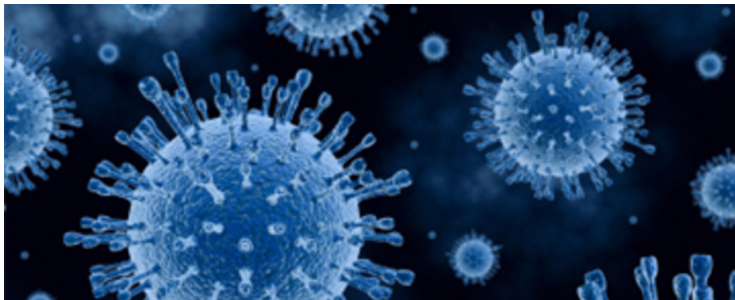
Mathematical Modeling of the Spreading of Diseases

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A very complex phenomenon is modeled by simple math....

Assumptions:

- We have a perfectly mixed population in a confined area
- We do not consider spatial movements, just how the disease evolves in time
- 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: flu, measles, swine flu, HIV, ...

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We keep track of 3 categories

Categories (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).

Goal:

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

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

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 Δt , 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 Δt , and β is some unknown parameter we must measure, supposed to not depend on Δt , but maybe time t .

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

Loss in $S(t)$:

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

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 Δt (say 1 day), a fraction $\Delta t \nu$ of the infected are removed (ν 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 :

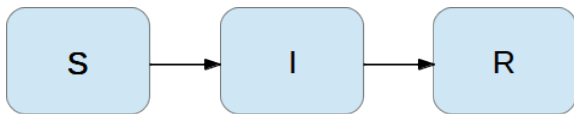
$$R(t + \Delta t) = R(t) + \Delta t \nu I(t)$$

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 β and ν
- know $S(0)$ (many), $I(0)$ (few), $R(0)$ (0?)
- choose Δt

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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- Reasonable approximation in a not too small population

And we can continue...

$$S(2\Delta t) = S(\Delta t) - \Delta t \beta S(\Delta t) I(\Delta t) \approx 49.87$$

$$I(2\Delta t) = I(\Delta t) + \Delta t \beta S(\Delta t) I(\Delta t) - \Delta t \nu I(\Delta t) \approx 1.011$$

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

Repeat...

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

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

$$R(3\Delta t) = R(2\Delta t) + \Delta t \nu R(2\Delta t) \approx 0.0025$$

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

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

The equations can now be written as

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

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

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

We 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

Let time be measured in hours.

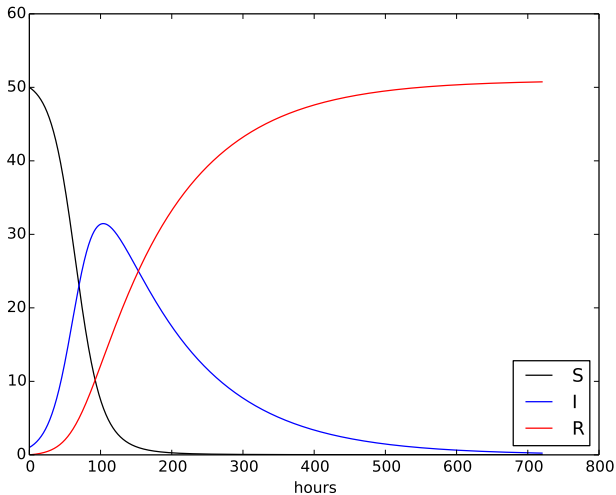
```
beta = 0.0013
nu = 0.8333
dt = 0.1          # 6 min
D = 30            # simulate for D days
N = int(D*24/dt)  # corresponding no of hours

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]
    I[n+1] = I[n] + dt*beta*S[n]*I[n] - dt*nu*I[n]
    R[n+1] = R[n] + dt*nu*I[n]

# 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?

- Plain arithmetics
- The concept of a graph (i.e., discrete function in time)
- Units
- 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 a *differential equations*. First, divide by Δt and move S , I , and R to the left-hand side:

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

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

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

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:

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

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

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

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 Δt .

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

Parameter estimation is needed for predictive modeling

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

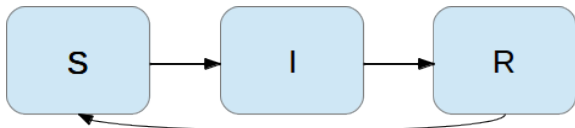
So what if we don't know β ?

- Can still learn about the *dynamics* of diseases
- Can find the sensitivity to and influence of β
- Can apply *parameter estimation* procedures to fit β 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 Δt this gives a leakage $\Delta t \gamma R$ to the S category. ($1/\gamma$ is the mean time for immunity.)



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

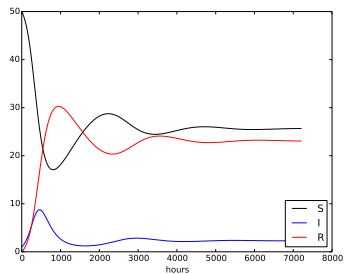
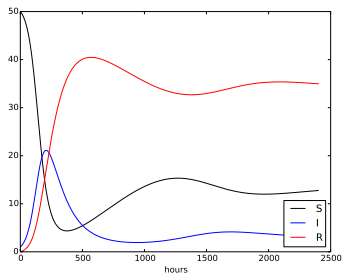
$$I^{n+1} = I^n + \Delta t \beta S^n I^n - \Delta t \nu I^n \quad (8)$$

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

No complications in the computational model!

The effect of loss of immunity

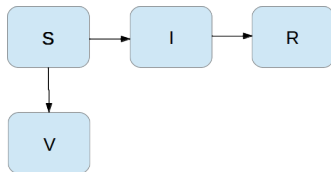
$1/\gamma = 50$ days. β reduced by 2 and 4:



What is the effect of vaccination?

Assumptions.

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



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

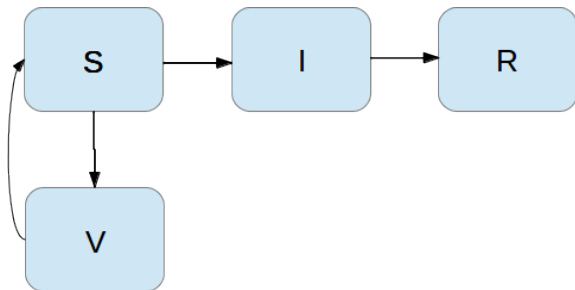
$$V^{n+1} = V^n + p\Delta t S^n \quad (11)$$

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

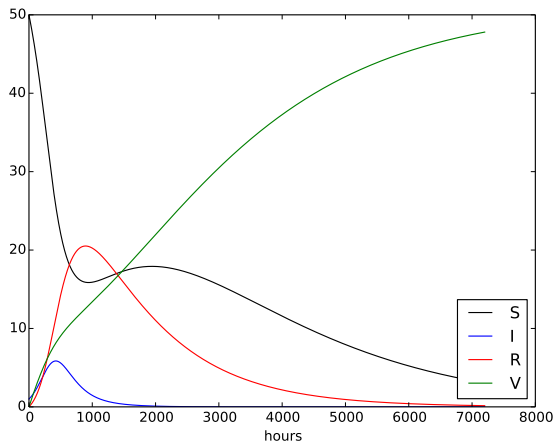
$$R^{n+1} = R^n + \Delta t \nu R^n - \Delta t \gamma R^n \quad (13)$$

Many possibilities for adjusting the model...

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



Effect of adding vaccination



$(p = 0.005)$

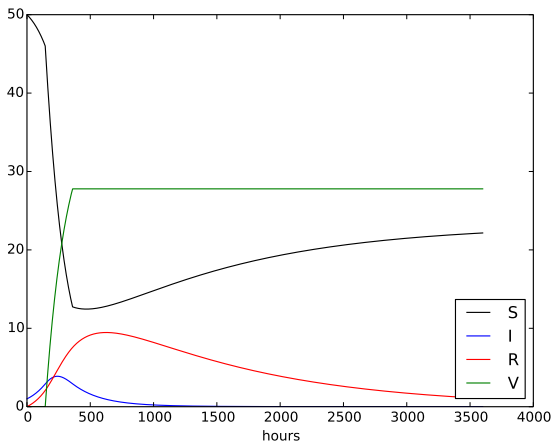
What is the effect of an intensive vaccination campaign?

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

$$p(t) = \begin{cases} 0.05, & 6 \leq t \leq 15, \\ 0, & \text{otherwise} \end{cases}$$

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 24h per day Δt).

Effect of vaccination campaign



Could now let the computer run a lot of cases and find the optimal vaccination period.

We can experiment with other campaigns



Masks lower β :

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

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

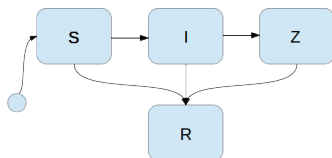
Categories.

- 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: $S(t)$, $I(t)$, $Z(t)$, $R(t)$

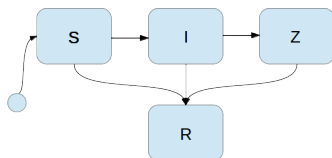
Zombie movie: *The Night of the Living Dead*, George A. Romero, 1968

Dynamics of the zombie SIZR model



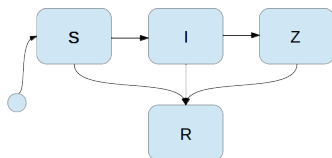
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- 2 Susceptibles die naturally or get killed and then enter the removed category. The no of deaths in time Δt is $\Delta t \delta_S S$.
- 3 We also allow new humans to enter the area with zombies (necessary in a war on zombies): $\Delta t \Sigma$ during a time Δt .
- 4 Some infected turn into zombies (Z): $\Delta t p I$, 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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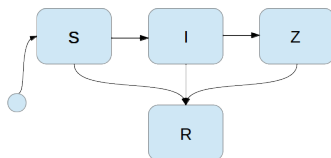
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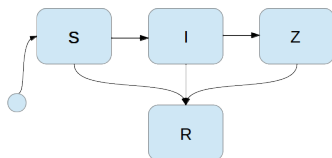
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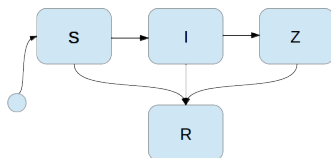
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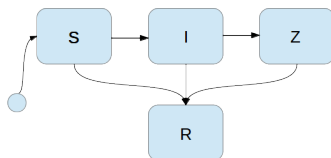
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The four equations in the SIZR model for zombification

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

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

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

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

Interpretation of parameters:

- Σ : no of new humans brought into the zombified area per unit time.
- β : 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.
- δ_S : the probability that a susceptible human is killed or dies, in a unit time interval.
- δ_I : the probability that an infected human is killed or dies, in a unit time interval.
- ρ : the probability that an infected human is turned into a zombie, during a unit time interval.
- α : 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 and K.-A. Mardal and P. Rønnes: 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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H. P. Langtangen and 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

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.

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Effective war on zombies

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

Model: Replace α by

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

where α_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), σ (duration is 6σ), point of attacks (T_i)

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

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