Zoonotic Spillover – Part 2

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A simple problem

- We have looked at simple models for large populations
- What if instead we have a population size of 10?
- What would be the most likely size of an outbreak?

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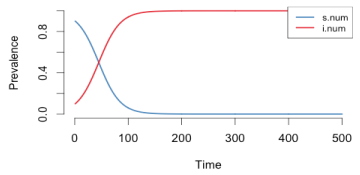

- Why are predictions from this model not very meaningful?

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1. **Individual based models** – track what happens to each individual and allows chance to determine whether or not they become infected at each time step.
2. **Discrete-time compartment models** – treat S population as a single compartment but allow chance to determine the total number of individuals infected by the infectious persons from the previous generations.
3. **Continuous time (time to next event) compartment models –** susceptible population as a single compartment and allow chance to determine when the next event happens.

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Individual based models (IBM)

- This method is the most intuitive but most computationally intensive
  1. Calculate risk (λ_t) that each S individual will become infected in the next time interval
  2. Draw a random number from 0-1 for each S individual
  3. If the random number is < λ_t, the individuals becomes infected
  4. Count up the number of I individuals at t+1
  5. If $I_{t+1} = 0$, outbreak is over, otherwise go back to step 1.

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λ_t – the Reed-Frost equation

- In our deterministic models: $\lambda_t = \beta I_t$
- This doesn't hold for a small population (e.g. N=10)

$$\lambda_t = 1-(1-p)^I$$

p = probability of effective contact between 2 individuals in a time step. Analogous to β except, p is a probability per time step and β is a continuous time rate.

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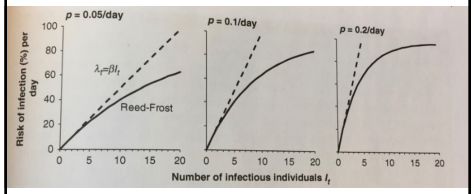

Vynnycky and White, 2010

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A Worked Example of an IBM

- Time step = 1 serial interval (e.g. infectious in 1 time step and recovered in next)
- N = 10, I = 1, R_0 = 2, individual mix randomly so risk between t and t+1 = (λ)

$$p = R_0 / N$$

p= 0.2 per time step

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Iteration 1 (λ =0.2 per time step)

Individual Number	Random Number
1	0.7646
2	0.0067
3	0.3043
4	0.4629
5	0.7621
6	0.3313
7	0.6141
8	0.9751
9	0.3124
10	0.8564

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Iteration 2 (λ= 0.2 per time step)

Individual Number	Random Number
1	0.2397
2	
3	0.8675
4	0.4123
5	0.7376
6	0.039
7	0.0948
8	0.0207
9	0.5342
10	0.3459

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Iteration 3 (λ= 0.488 per time step)

Individual Number	Random Number
1	0.2153
2	-
3	0.2704
4	0.8621
5	0.6967
6	-
7	-
8	-
9	0.0985
10	0.0123

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Iteration 4 (λ= 0.590 per time step)

Individual Number	Random Number
1	-
2	-
3	-
4	0.7511
5	0.6023
6	-
7	-
8	-
9	-
10	-

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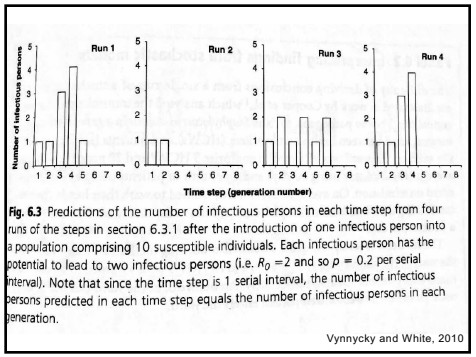

Fig. 6.3 Predictions of the number of infectious persons in each time step from four runs of the steps in section 6.3.1 after the introduction of one infectious person into a population comprising 10 susceptible individuals. Each infectious person has the potential to lead to two infectious persons (i.e. $R_0 = 2$ and so $p = 0.2$ per serial interval). Note that since the time step is 1 serial interval, the number of infectious persons predicted in each time step equals the number of infectious persons in each generation.

Vynnycky and White, 2010

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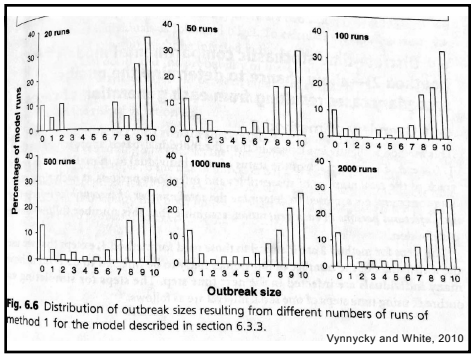

Fig. 6.6 Distribution of outbreak sizes resulting from different numbers of runs of method 1 for the model described in section 6.3.3.

Vynnycky and White, 2010

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Outcome of Interest = Outbreak Size

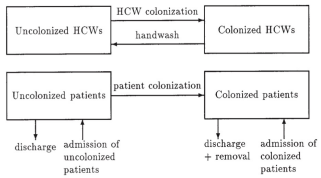

Figure 1 Flow diagram of the model illustrating the rates of transitions between the four compartments. See table I for an explanation of the parameters, and table II for details of the events represented by the arrows. Note that in the stochastic version of the model, the transition rates are interpreted as probabilities of the transitions occurring in a given interval of time.

Cooper et al., 1999

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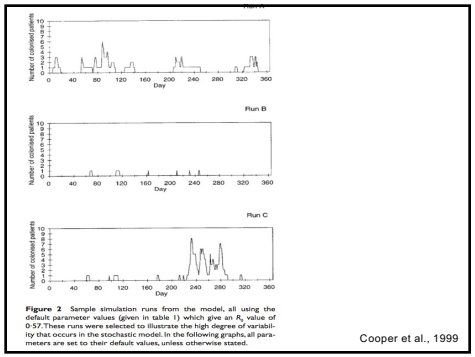

Figure 2 Sample simulation runs from the model, all using the default parameter values (given in table 1) which give an R_0 value of 0·57. These runs were selected to illustrate the high degree of variability that occurs in the stochastic model. In the following graphs, all parameters are set to their default values, unless otherwise stated.

Cooper et al., 1999

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Discrete-time compartment models

- Allowing chance to determine the number of secondary cases resulting from each generation of cases.
- Less labour intensive than IBM
- Random numbers used to determine the total number of S individuals infected by the I individuals in each generation assuming this number follows some distribution.

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Discrete-time compartment models

- Steps are essentially the same but use the distribution of the number of individuals likely to be infected to determine how many individuals are infected in the next time step (e.g. serial interval).
- How do we calculate the distribution of the number of susceptible individuals infected during a given time step?

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$\lambda_t = 0.8$

1. Both remain S
2. One remains S (One becomes I)
3. Both become I

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$\lambda_t = 0.8$

Both remain S

- Each has a probability of $(1- \lambda_t)$ of remaining S
- Probability that both remain S is $(1- \lambda_t)^2$

What is the probability that they both remain Susceptible?

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$\lambda_t = 0.8$

One remains S (One becomes I)

What is the probability of this?

$2\lambda_t (1- \lambda_t) = 2*0.8*0.2=0.32$

What is the logic behind this?

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$\lambda_t = 0.8$

Both become I

- Each has a probability of (λ_t) of becoming I
- Probability that both become I is $(\lambda_t)^2$ = 0.8*0.8=0.64

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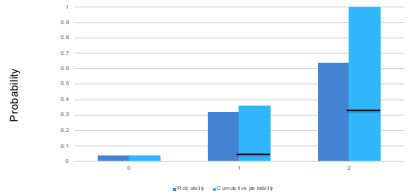
Sampling from a Distribution



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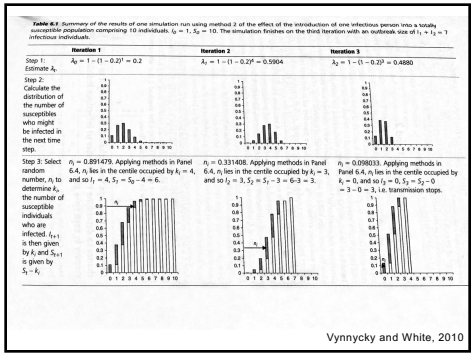

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Continuous-time ('time to next event') compartment models

- This approach uses chance to determine when the next event occurs (size of dt), and the type of transition that occurs (e.g. infection or recovery)
- Stochastic implementation of differential equations

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Continuous-time ('time to next event') compartment models

1. Calculate the rate M_t (rate at which individuals can change their status)
   - M_t is the hazard rate, chance of event over a small time period
   - For a simple SIR model, the hazard rate is the sum of the rate at which individuals become infected + the rate at which individuals recover.

$$M_t = \beta S(t) I(t) + r I(t)$$

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Continuous-time ('time to next event') compartment models

2. Draw a random number, n_1 between 0 and 1 and calculate the time after which the next transition occurs, given by:

$$T = -\ln(n_1)/M_t$$

Probability that there has been no event by time T (p_T) = $e^{-Mt,T}$

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Continuous-time ('time to next event') compartment models

3. Rearrange the equations to calculate the probability that each type of transition will occur. Calculate the range in which a random number must lie for a given transition to occur.

Probability that an individual becomes I in each dt = β S(t) I(t)/M_t

Probability that an individual recovers in each dt = $r(t)$ I(t)/M_t

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Continuous-time ('time to next event') compartment models

Probability that an individual becomes I in each dt = β S(t) I(t)/M_t

Probability that an individual recovers in each dt = $r(t)$ I(t)/M_t

If random # is in the interval (0, β S(t) I(t)/M_t), then an individual becomes infected otherwise an individual recovers.

4. Draw a random # to determine the transition event that occurs next then update # of individuals in compartments and go back to 1.

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An example of the Continuous time approach

- S(0) = 10, I(0) = 1, β = 0.1/day, D = 2 days = 0.5/day. These parameters give us R0 = 2
- What is M(0)? M(0) = 1.5 per day
- Draw a random number, n_1 = 0.46
- T = -ln(n_1)/M_0, so next transition occurs when? T = 0.518 days

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An example of the Continuous time approach

- Probability that S →I, β S(0) I(0)/M_t = 0.667
- Probability that I →R, *r(0)* I(0)/M_t = 0.337
- So if random # lies within (0, 0.667) you will have an infection event, otherwise you will have a recovery event
- Draw a random number, n_2 = 0.56
- What event is going to occur? infection
- So at time T = 0.518 days,

S = 9, I = 2, R = 0

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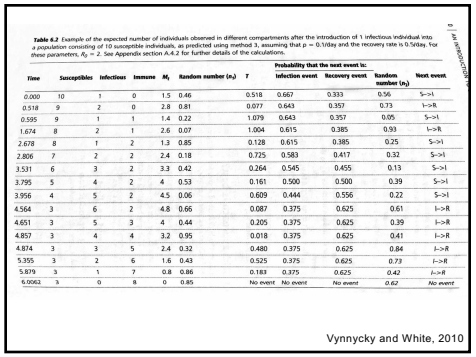

Table 6.2 Example of the expected number of individuals observed in different compartments after the introduction of 1 infectious individual into a population consisting of 10 susceptible individuals, as predicted using method 3, assuming that $p = 0.1$/day and the recovery rate is 0.5/day. For these parameters, $R_0 = 2$. See Appendix section A.4.2 for further details of the calculations.

Time	Susceptibles	Infectious	Immune	M_t	Random number (n_1)	T	Probability that the next event is: Infection event	Recovery event	Random number (n_2)	Next event
0.000	10	1	0	1.5	0.46	0.518	0.667	0.333	0.56	S-->I
0.518	9	2	0	2.8	0.81	0.077	0.643	0.357	0.73	I-->R
0.595	9	1	1	1.4	0.22	1.079	0.643	0.357	0.05	S-->I
1.674	8	2	1	2.6	0.07	1.004	0.615	0.385	0.93	I-->R
2.678	8	1	2	1.3	0.85	0.128	0.615	0.385	0.25	S-->I
2.806	7	2	2	2.4	0.18	0.725	0.583	0.417	0.32	S-->I
3.531	6	3	2	3.3	0.42	0.264	0.545	0.455	0.13	S-->I
3.795	5	4	2	4	0.53	0.161	0.500	0.500	0.39	S-->I
3.956	4	5	2	4.5	0.06	0.609	0.444	0.556	0.22	S-->I
4.564	3	6	2	4.8	0.66	0.087	0.375	0.625	0.61	I-->R
4.651	3	5	3	4	0.44	0.205	0.375	0.625	0.39	I-->R
4.857	3	4	4	3.2	0.95	0.018	0.375	0.625	0.41	I-->R
4.874	3	3	5	2.4	0.32	0.480	0.375	0.625	0.84	I-->R
5.355	3	2	6	1.6	0.43	0.525	0.375	0.625	0.73	I-->R
5.879	3	1	7	0.8	0.86	0.183	0.375	0.625	0.42	I-->R
6.0062	3	0	8	0	0.85	No event	No event	No event	0.62	No event

Vynnycky and White, 2010

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Which Method to Use?

- Mostly depends on:
  - Computational resources and power available
  - Population size
  - Number of events

- Spillover is an inherently stochastic event so this needs to be considered in the modelling approach.

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