Stochastic approaches to within-host viral dynamics

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Topics for today

1. Background on HIV epidemiology and biology
2. Within-host mathematical models of HIV infection
3. **Introduction to branching process models**

Why use a stochastic model?

- **Differential equation models describe the *averaged* behaviour of the system :**
  - Apply to *many* players (cells, viruses in a human)
  - Apply to *frequent* events among the players
- **Stochastic effects are very important when numbers are small.**
  - Apply when there are few players
  - Apply when *rare events* are important
    - Panda reproduction

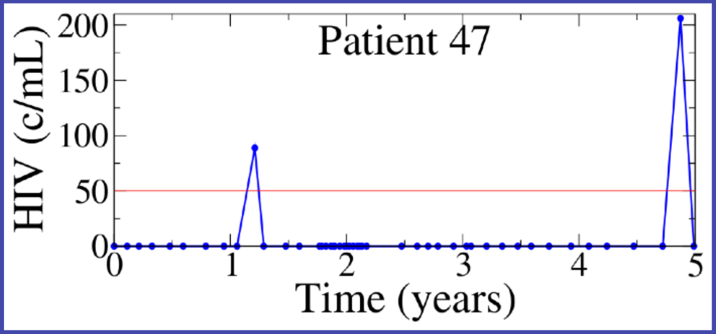
Stochastic events in HIV infection

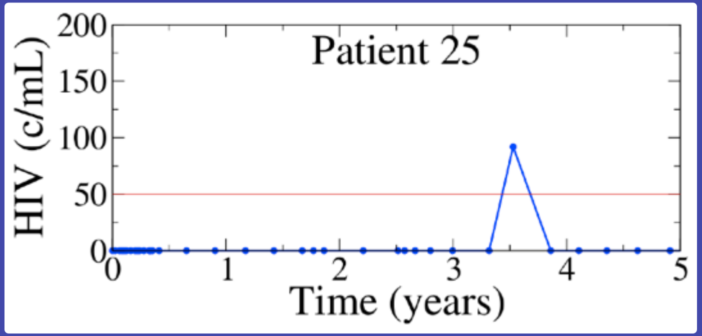
INITIAL INFECTION:

- Even *riskiest* sex or blood contact infects <5% of the time
  - Blood transfusion ~80%
- Most developed infections show a *single founder*
- Suggests that the events of infection are intrinsically random and rare

TREATED INFECTION:

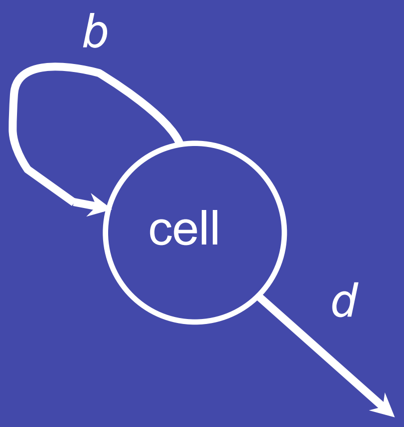
- On successful treatment, viral load is very low (5-50 copies/ml of blood)
- Viral *blips* are observed:
  - infrequent episodes of detectable but low viral load





Understanding a simple birth-death process

- A population *N(t)* of infected cells that reproduce at rate *b* and die at rate *d*:
- ODE: $$\frac{dN}{dt} = bN - dN$$
- Soln: $$N(t) = N_0 e^{(b-d)t}$$

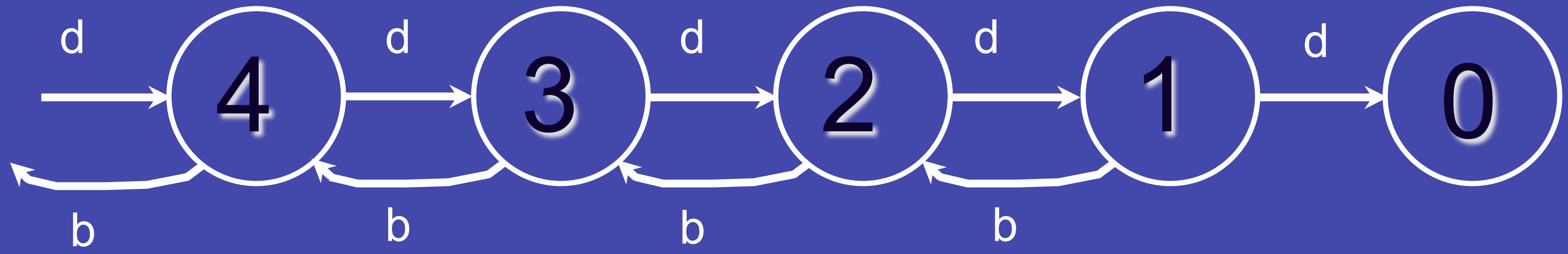


- Population becomes infinite if b > d
- Population goes extinct (in infinite time) if b < d
- How do we say “98% chance of extinction”?

Probabilistic interpretation

- Interpret d and b as the *rates* at which events happen

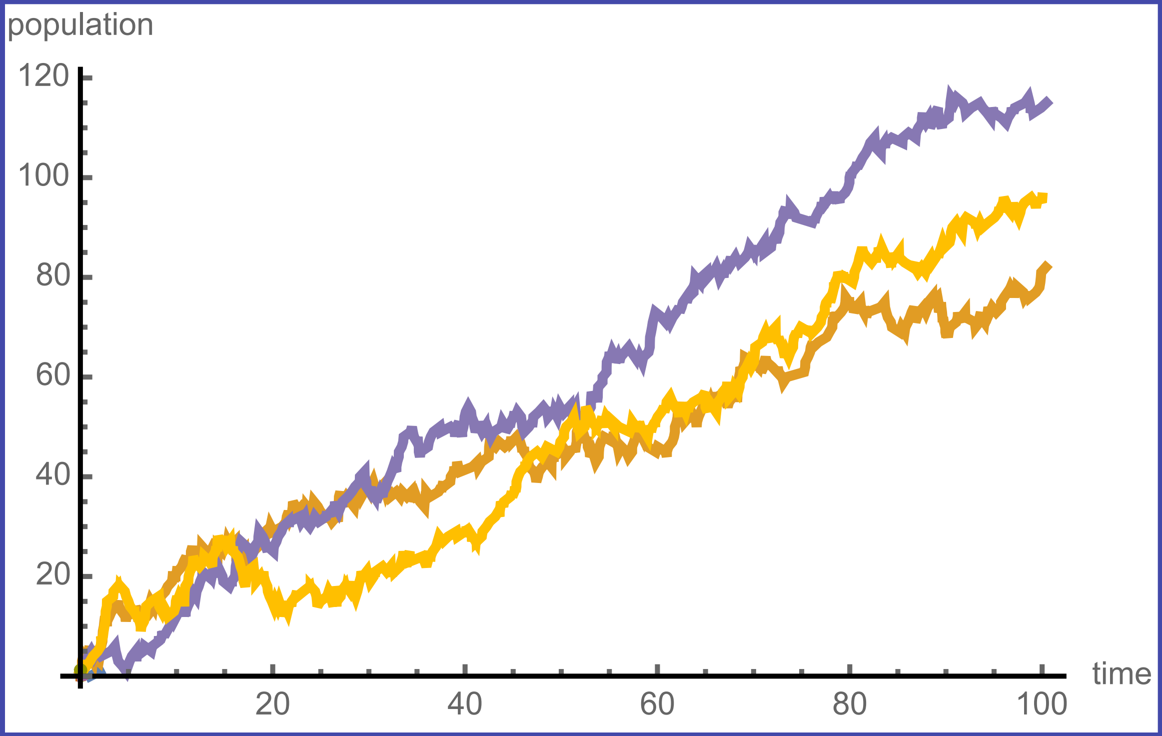
individual is born in interval Δt	$n \xrightarrow{bn\Delta t} n+1$
individual dies in interval Δt	$n \xrightarrow{dn\Delta t} n-1$



- We say that birth and death events are "exponentially distributed" or "are drawn from a Poisson process"
- Birth and death events are independent

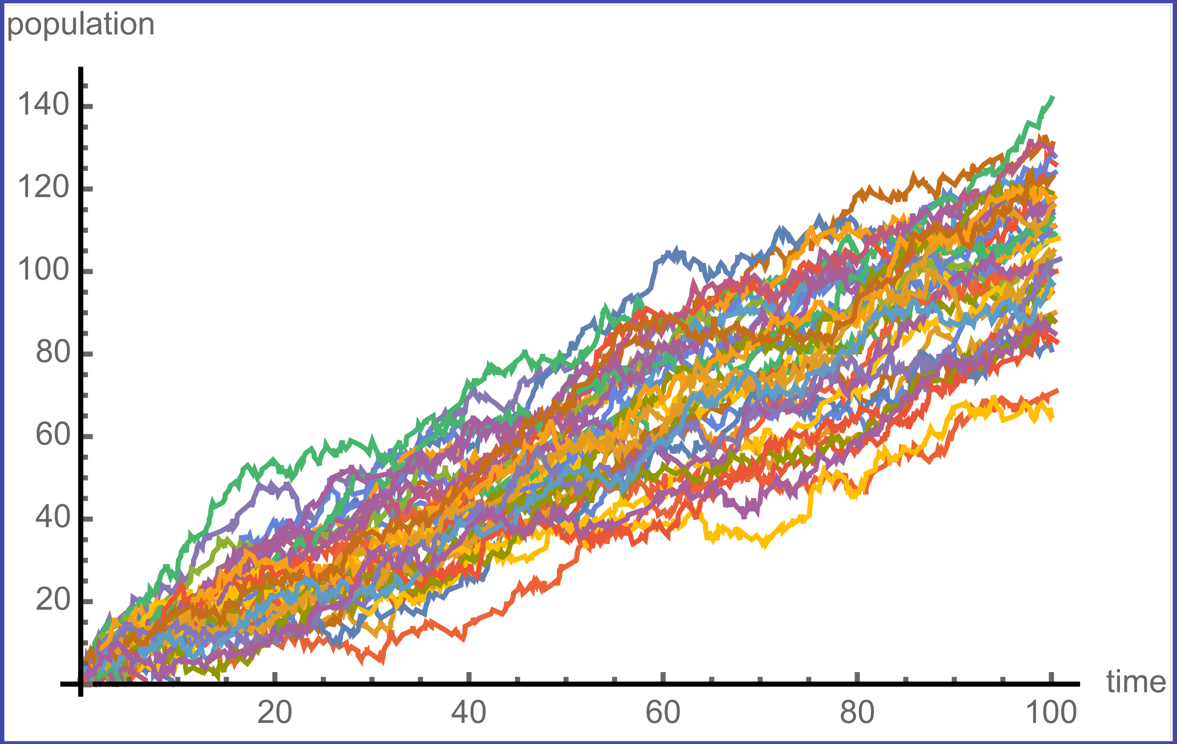
Simulations of the birth-death process

Set birth rate b=3/day; death rate d=2/day; make 10 simulations



Simulations of the birth-death process

Set birth rate b=3/day; death rate d=2/day; make 100 simulations



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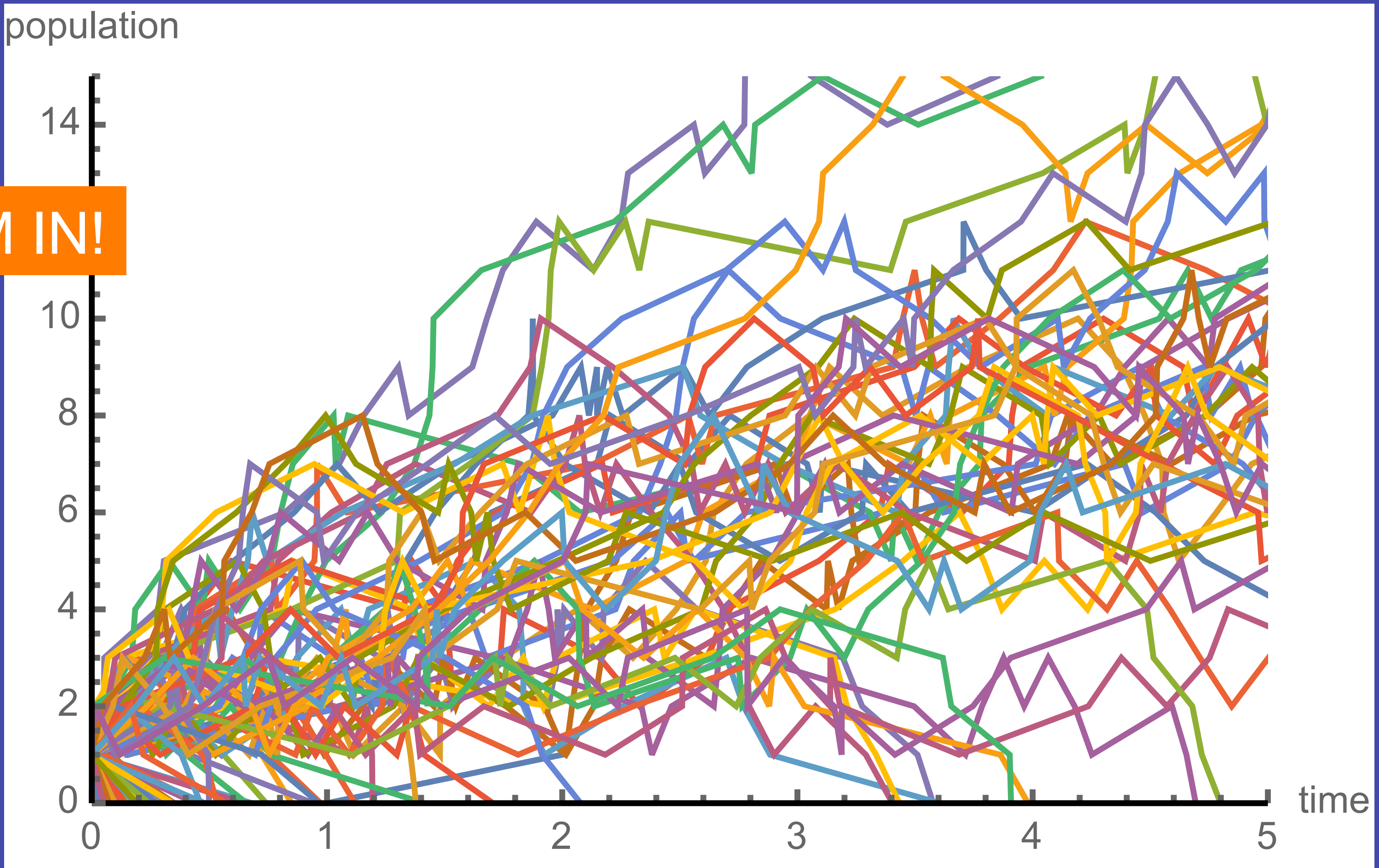
ZOOM IN!



Simulations of the birth-death process

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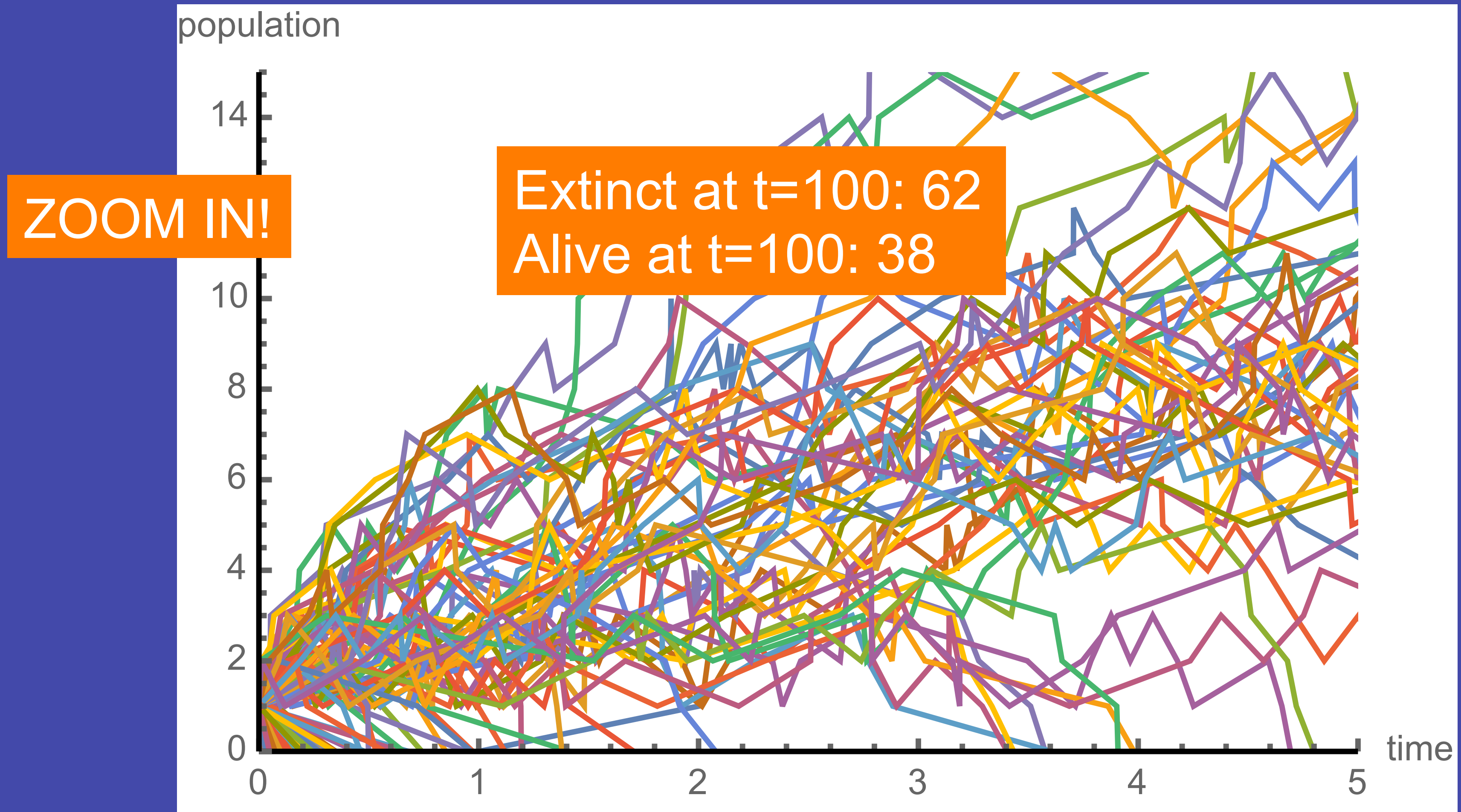
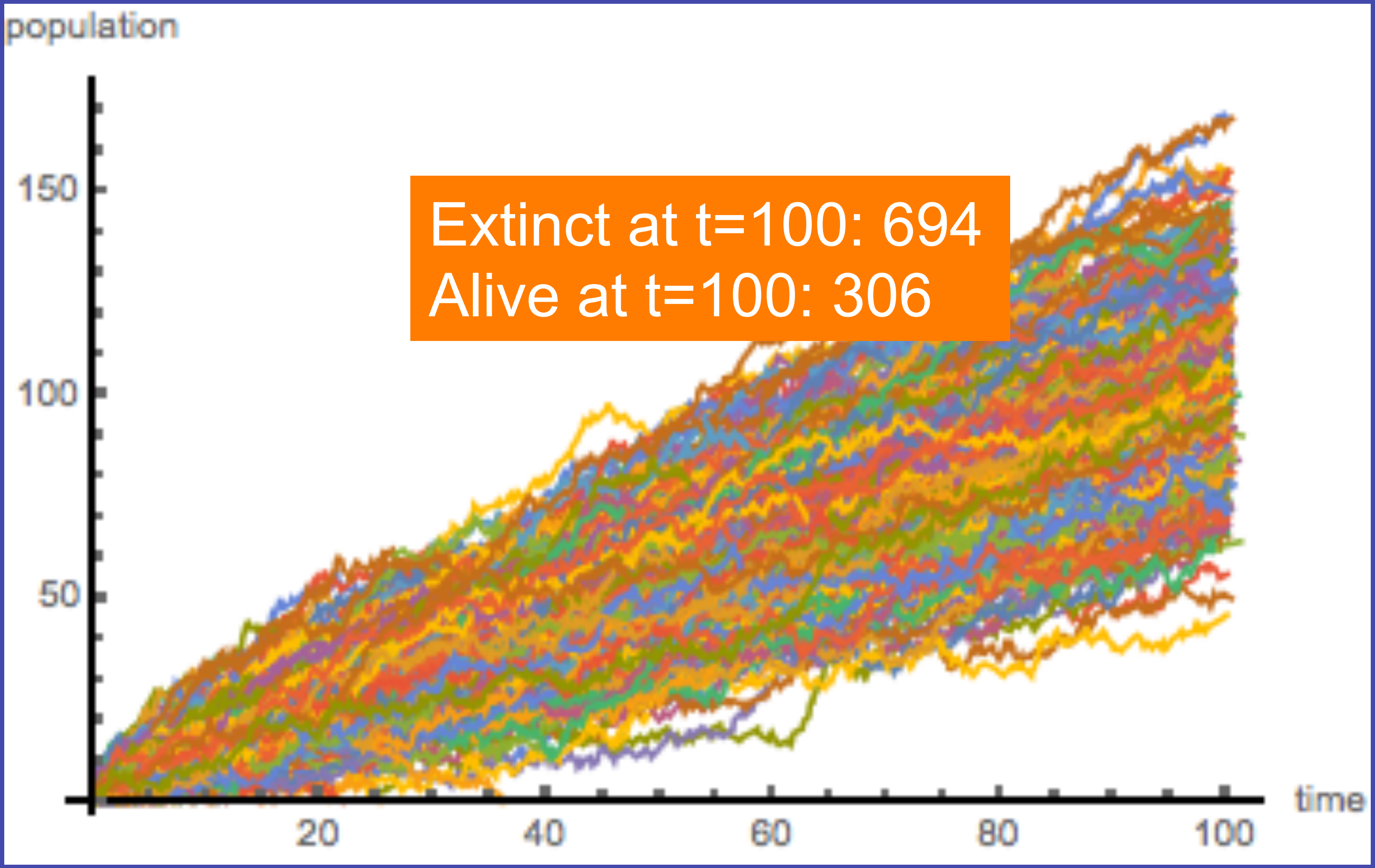


Simulations of the birth-death process

Set birth rate b=3/day; death rate d=2/day; make **1000** simulations



Simulations of the birth-death process

Set birth rate b=3/day; death rate d=2/day; make **10000** simulations

10000 simulations:
Extinct at t=100: 6677
Alive at t=100: 3323

Probabilistic interpretation

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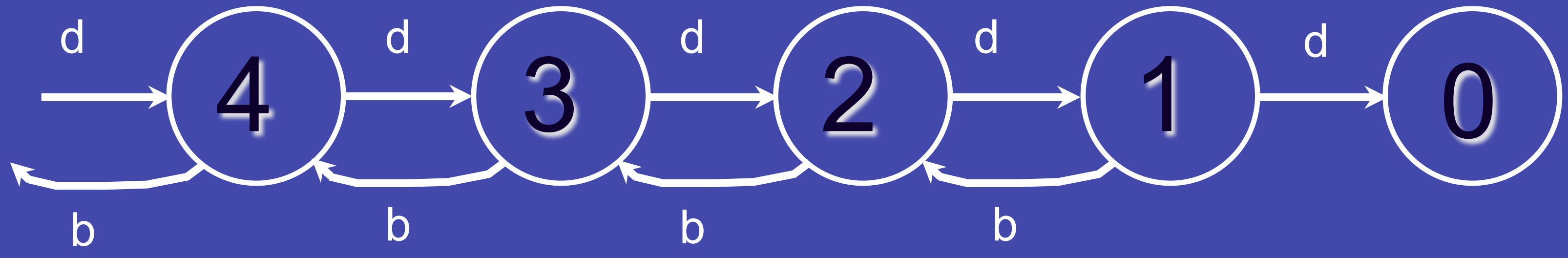
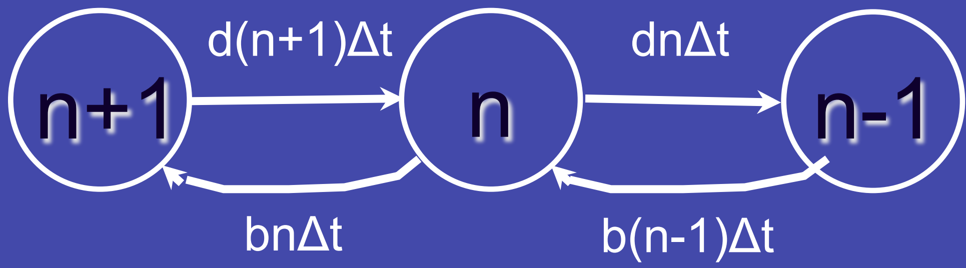


- Define

$$P_{n,n_0}(t) = \text{prob}(N(t) = n \text{ given } N(0) = n_0)$$

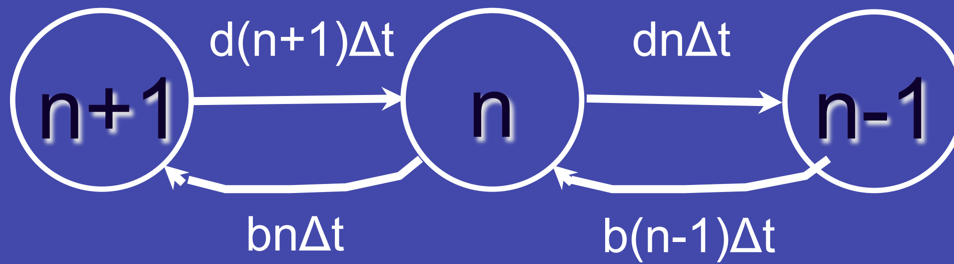
$$p_{ext}(t) \equiv P_{0,n_0}(t) = \text{prob}(\text{extinct by time } t)$$

How do the probabilities change in time?



$$
\begin{aligned}
P_{n,n_0}(t+\Delta t) &= d(n+1)\Delta t P_{n+1,n_0}(t) \\
&+ b(n-1)\Delta t P_{n-1,n_0}(t) \\
&+ (1 - dn\Delta t - bn\Delta t P_{n,n_0}(t))
\end{aligned}
$$

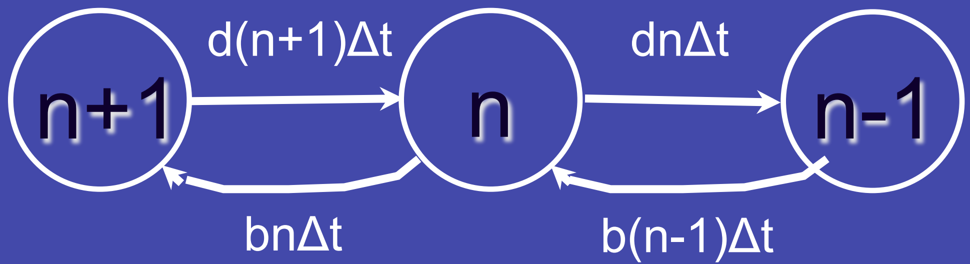
How do the probabilities change in time?



$$\frac{P_{n,n_0}(t+\Delta t) - P_{n,n_0}(t)}{\Delta t} = d(n+1)P_{n+1,n_0}(t) + b(n-1)P_{n-1,n_0}(t) - (dn + bn)\,P_{n,n_0}(t)$$

Take the limit: infinite system of differential equations

How do the probabilities change in time?



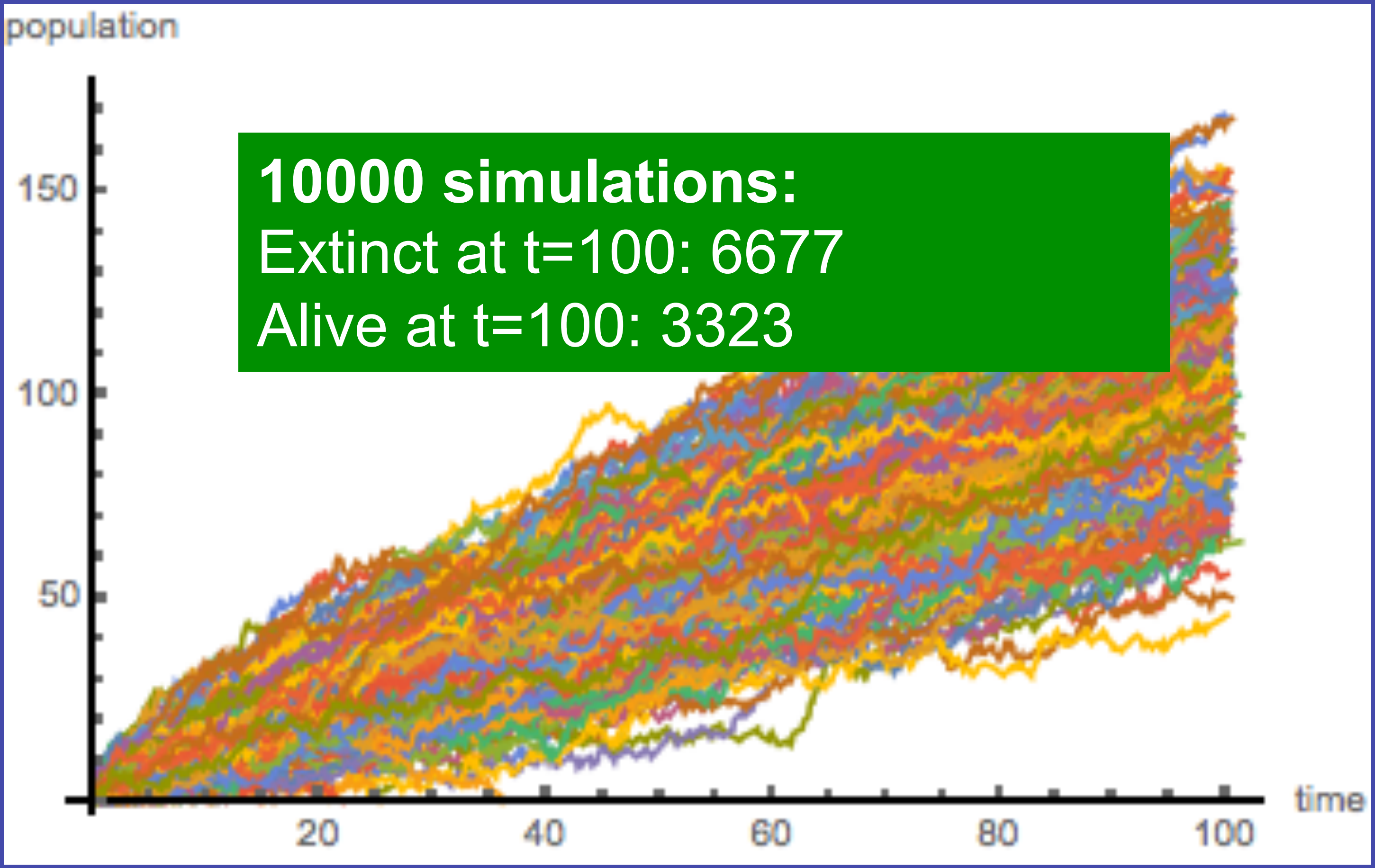
$$\frac{dP_{n,n_0}}{dt} = d(n+1)P_{n+1,n_0}(t) + b(n-1)P_{n-1,n_0}(t) - (d+b)\,nP_{n,n_0}(t)$$

This is called the Forward Kolmogorov (Master) equation

(problem sheet 2)

Simulations of the birth-death process

Set birth rate b=3; death rate d=2; make **1000** simulations



How to simulate (Gillespie's algorithm)

(For the birth-death process with rates b and d)

Initialize $t=0$, $N=N_0$, $i=1$.

1. Calculate the *next event time* t_i
2. Choose *which event* (birth or death) happens at t_i
3. Update:
   i++, $t=t_i$ and either N++ or N--.
4. Go to step 1 (or stop if $N=0$)

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Next event time: distribution of simultaneous exponential processes is exponential

$$t_i \sim \mathrm{Exp}[b+d]$$

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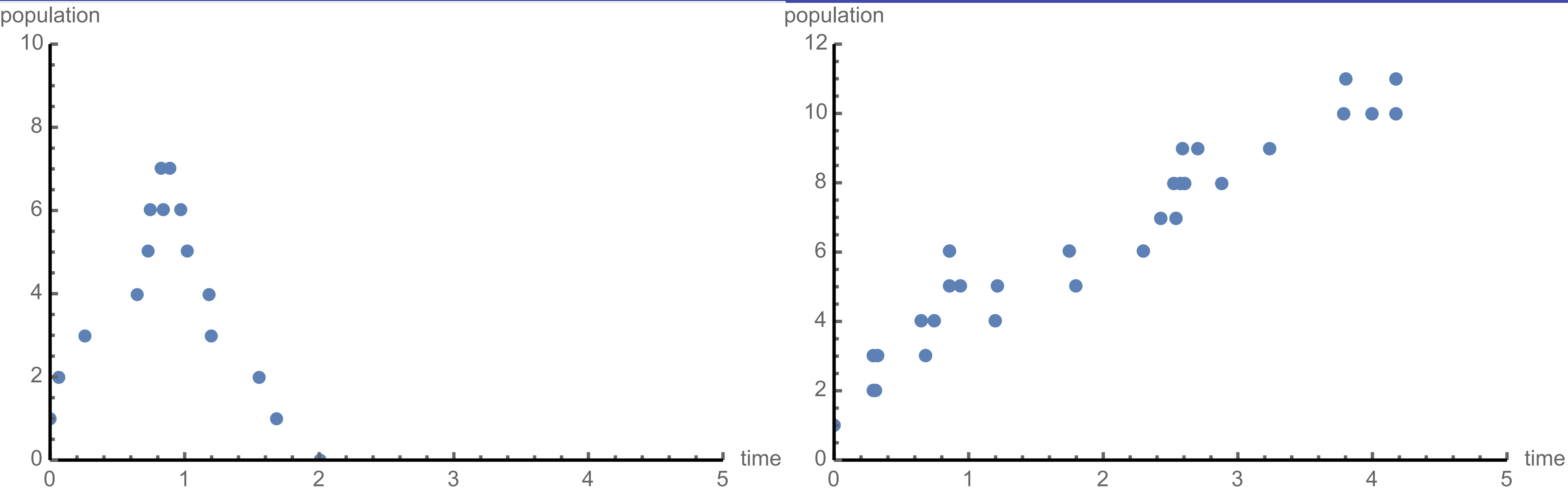
Which event? Choose according to the event rates (propensities)!
Pick a random number x uniformly on [0,1] and choose:

$$\text{Birth if } x < \frac{b}{b+d} \qquad \text{Death if } x > \frac{b}{b+d}$$



Very efficient algorithm for simulation
(two random numbers per step)
Easily expandable to more complicated cases

But not an efficient way to sample *rare events*.

This afternoon:

Birth-death process
Gillespie simulations

Tomorrow: multitype processes – application to HIV infection