Doctoral training school
Methods in Malaria Modeling
Simulation algorithms & numerics for epidemiological models

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Nov 13 - Dec 8, 2023

AIMS Center Senegal, Mbour

Outline

User manual to the course

Question block

Discuss in class!

Important block

This is important!

Search block

Search and think outside the box (and the classroom)!

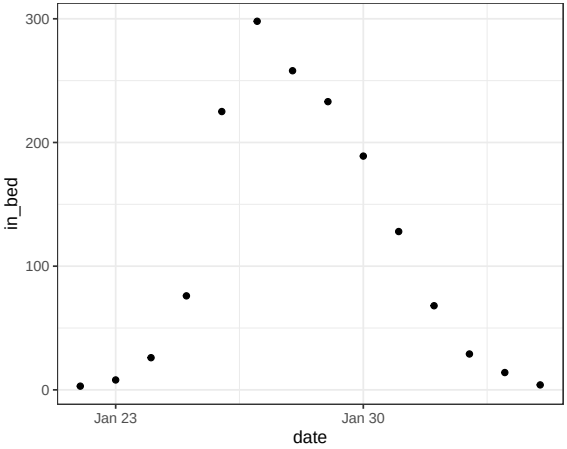
links to code in  and  , further reading 

Course web page

sites.google.com/aims.ac.rw/mamodafrica-trainingschool/week-3/ modsimul

Influenza outbreak in a boarding school: the data

date	in bed	convalescent	total
1978-01-22	3	0	763
1978-01-23	8	0	763
1978-01-24	26	0	763
1978-01-25	76	0	763
1978-01-26	225	9	763
1978-01-27	298	17	763
1978-01-28	258	105	763
1978-01-29	233	162	763



Influenza outbreak in a boarding school: model hypotheses

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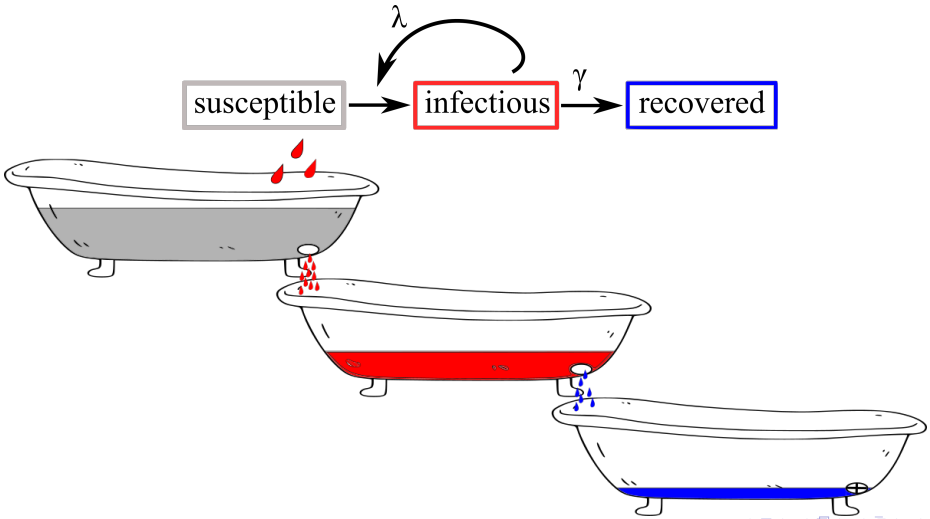
- **full immunity** upon recovery
  recovered individuals cannot become susceptible again

Influenza outbreak in a boarding school: bathtubs



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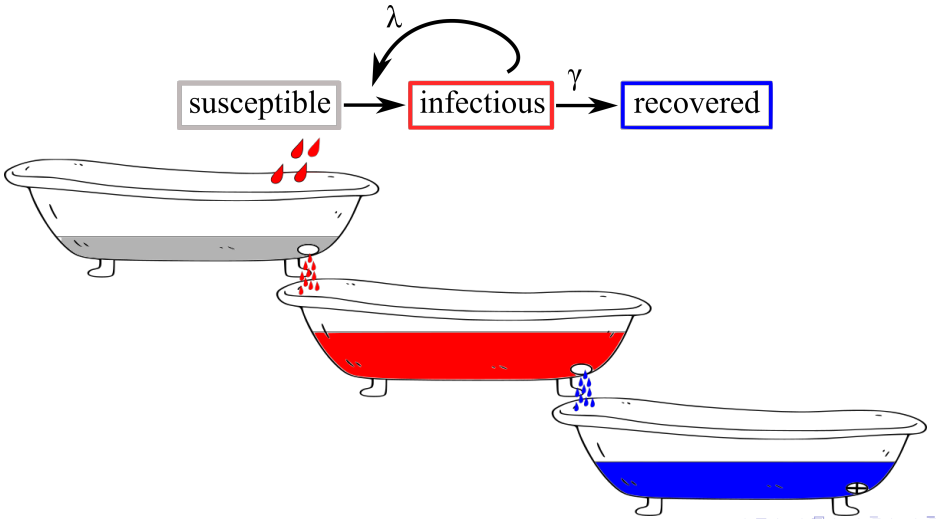

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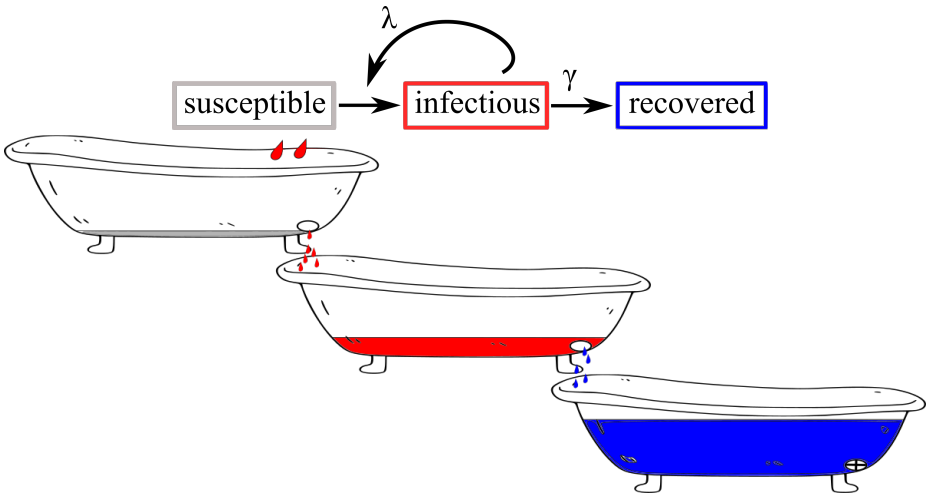
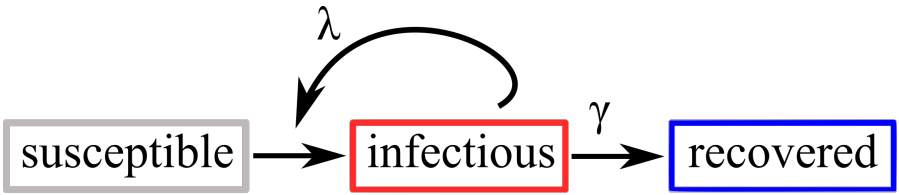


Influenza outbreak in a boarding school: compartments



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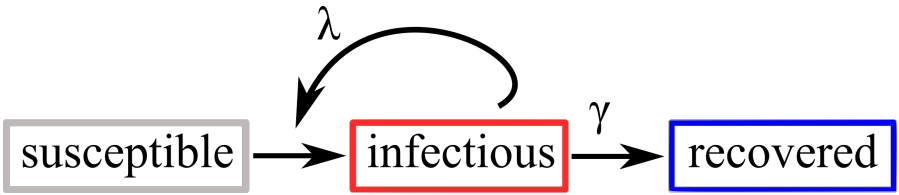

- **rate** = number of events happening within time step Δ

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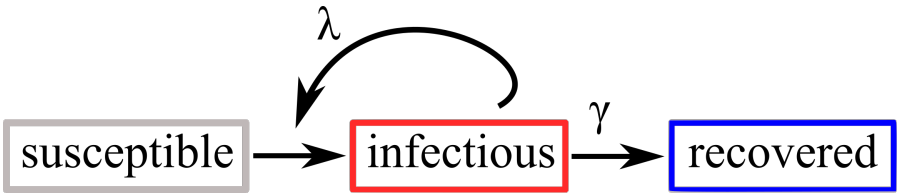

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- γ **recovery rate** from infection

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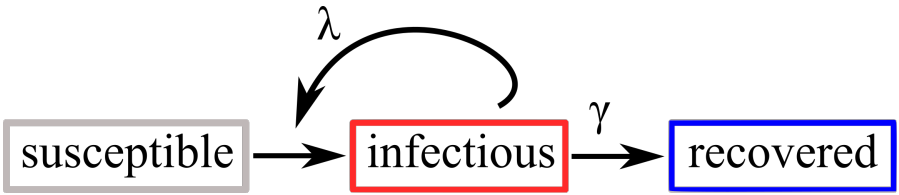

- **rate** = number of events happening within time step Δ
- γ **recovery rate** from infection
- $\lambda \equiv \lambda(I)$ **force of infection rate**

Influenza outbreak in a boarding school: compartments

Recurrence equation with update linear in time increment Δ

$$\begin{aligned} S(t+\Delta) &= S(t) + \Delta\{-\lambda(I(t))S(t)\} \\ I(t+\Delta) &= I(t) + \Delta\{\lambda(I(t))S(t) - \gamma I\} \\ R(t+\Delta) &= R(t) + \Delta\{\gamma I(t)\} \end{aligned}$$

Initial condition

$$\begin{aligned} S(0) &= S_0 < N \\ I(0) &= I_0 > 0 \\ R(0) &= 0 \end{aligned}$$

Influenza outbreak in a boarding school: force of infection

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Force of infection

$\lambda(I)$ rate at which new infectious created from susceptible

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Density-dependent transmission

Per capita contact rate between susceptible and infected depends on the **population density**. Transmission rates increase with density.

Influenza outbreak in a boarding school: force of infection

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Force of infection

$\lambda(I)$ rate at which new infectious created from susceptible

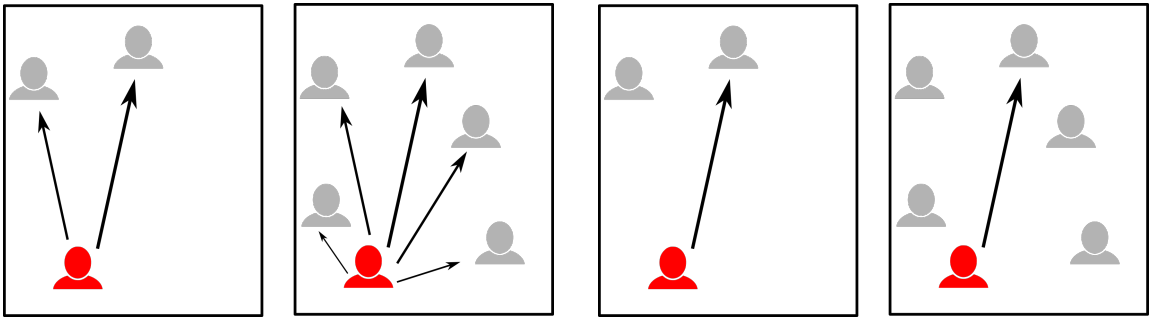
Density-dependent transmission

Per capita contact rate between susceptible and infected depends on the **population density**. Transmission rates increase with density.

Frequency-dependent transmission

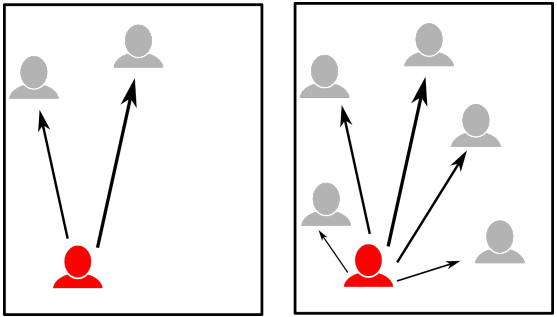
Per capita contact rate between susceptible and infected **does not depend** on the population density. Transmission rates do not change with density.

Density- vs frequency-dependent transmission

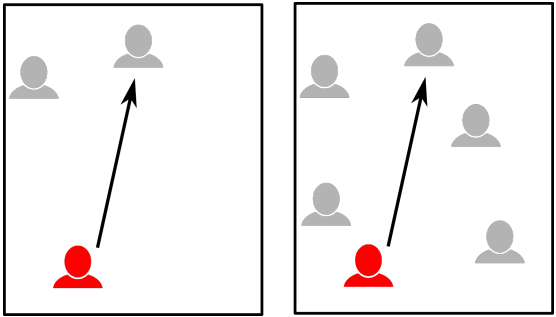


Density- vs frequency-dependent transmission

Density-dependent transmission
more individuals per area increases transmission



Frequency-dependent transmission
more individuals, no impact transmission



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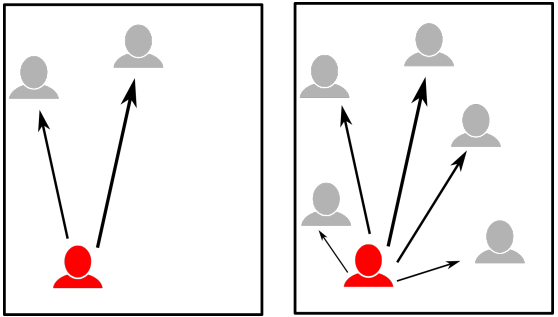
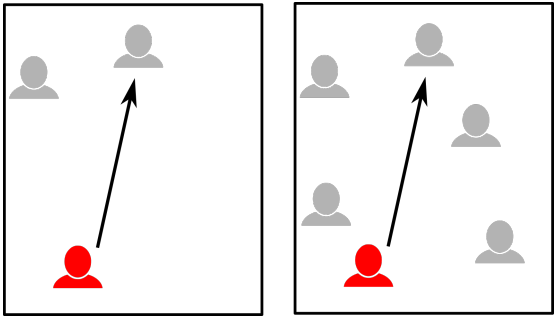


Influenza, Coronavirus, Malaria?, Polio

Frequency-dependent transmission
more individuals, no impact transmission



HIV, Malaria?

Density- vs frequency-dependent transmission

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Force of infection formula

$\lambda(I) = c\frac{I}{N}v$ with contact rate, probability of contact with infected individual, probability that contact S$\longleftrightarrow$ I leads to transmission

Two choices for contact rate:

1. $c = k\frac{N}{A}$: slope k of **density-dependent** contact rate per area A :

$$\lambda(I) = k\frac{N}{A}v\frac{I}{N} = \underbrace{\frac{k}{A}v}_{\beta} I = \beta I$$

2. $c = k'$ constant, **frequency-dependent** contact rate:

$$\lambda(I) = \underbrace{k'v}_{\beta'}\frac{I}{N} = \beta'\frac{I}{N}$$

Density- vs frequency-dependent transmission

Force of infection formula

$\lambda(I) = c\frac{I}{N}v$ with contact rate, probability of contact with infected individual, probability that contact S$\longleftrightarrow$ I leads to transmission

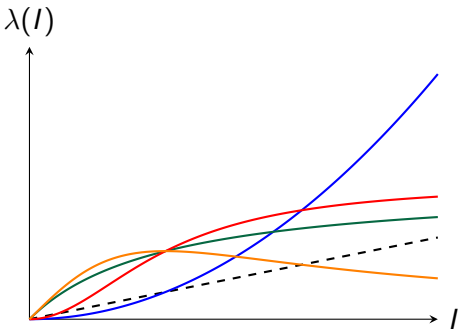
1. **density-dependent** $\lambda(I) = \beta I$
2. **frequency-dependent** $\lambda(I) = \beta' \frac{I}{N}$

   If N constant: mathematically equivalent but β, $\frac{\beta'}{N}$ different **biological meaning**

   Begon et al. 

Non-linear force of infection (foi)

- **linear** $\lambda(I) \sim I$: mass action



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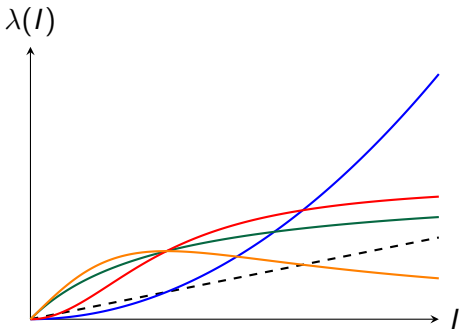
- **linear** $\lambda(I) \sim I$: mass action
- **quadratic** $\lambda(I) \sim I^2$: panic behavior



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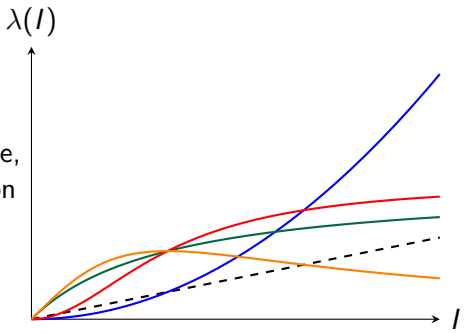

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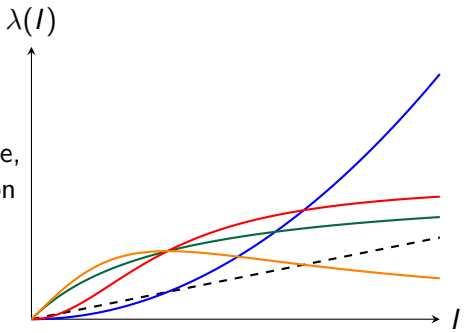

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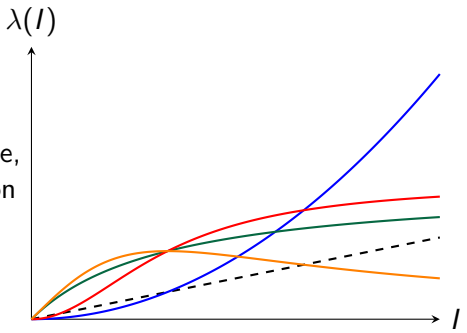
- **intervention** $\lambda \sim \frac{I}{f(I)}$, $f > 0$, $f' \geq 0$



Influenza outbreak in a boarding school: differential equation

- Recurrence equation with time increment Δ and $t_0 = 0$:

$$
\begin{aligned}
S(t+\Delta) &= S(t) + \Delta\{-\lambda(I(t))S(t)\} && (1)\\
I(t+\Delta) &= I(t) + \Delta\{\lambda(I(t))S(t) - \gamma I(t)\} && (2)\\
R(t+\Delta) &= R(t) + \Delta\gamma I(t) && (3)\\
& && (4)
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- First order differential equation, for all $t \geq 0$:

$$
\begin{aligned}
\lim_{\Delta\to 0} \frac{S(t+\Delta) - S(t)}{\Delta} = \frac{dS}{dt} &= -\lambda(I)S\\
\lim_{\Delta\to 0} \frac{I(t+\Delta) - I(t)}{\Delta} = \frac{dI}{dt} &= \lambda(I)S - \gamma I\\
\lim_{\Delta\to 0} \frac{R(t+\Delta) - R(t)}{\Delta} = \frac{dR}{dt} &= \gamma I
\end{aligned}
$$

Explicit first order Euler scheme for SIR model with linear foi

For equidistant time points $0 = t_0 < t_1 < \cdots < t_n$ write $\Delta \equiv \Delta t = t_{i+1} - t_i$, and $t_k = k\Delta t$:

$$S(t_{i+1}) = S(t_i) + \Delta \left\{ -\frac{\beta}{N} I(t_i) S(t_i) \right\} \tag{5}$$

$$I(t_{i+1}) = I(t_i) + \Delta \left\{ \frac{\beta}{N} I(t_i) S(t_i) - \gamma I \right\} \tag{6}$$

$$R(t_{i+1}) = R(t_i) + \Delta \gamma I(t_i) \tag{7}$$

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Group work: Solve the influenza SIR model numerically in R!

- Create a sequence of time steps t_i up to 15 days with step size $\Delta = 0.5$
- Create data frame, first row is initial condition $S = 762, I = 1, R = 0$
- $\beta = 1.1, \gamma = 0.5$, $N = 763$, try different β such that $\frac{\beta}{\gamma} < 1$ or $\frac{\beta}{\gamma} > 1$
- Write a loop over i and plot the graph $t_i \mapsto I(t_i)$ `01_ForwardEulerSIR.R`

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Numerical scheme for ordinary differential equation

Given an ODE $\frac{dx}{dt} = f(t,x)$ an (explicit one-step) scheme is given by continuous function $\Phi(t,x,h)$ with mesh $0 = t_0 < t_1 < \ldots t_n = T$ and $\Delta t = t_{i+1} - t_i$ s.th.

$$x^{k+1} = x^k + \Delta t \Phi(t_k, x^k, \Delta t)$$

Truncation error

The truncation error is $T_k(\Delta t) = \frac{x^{k+1} - x^k}{\Delta t} - \Phi(t_k, x(t_k), \Delta t)$

$$\lim_{\Delta t \to 0} T_k(\Delta t) = \frac{dx}{dt} - \Phi(t_k, x, 0)$$

Numerical schemes: Consistency, stability, convergence

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Consistency

The scheme is **consistent** with the ODE if $\Phi(t, x, 0) = f(t, x)$

Stability

The scheme is **stable** if $x \mapsto \Phi(t, x, h)$ is globally Lipschitz (i.e. almost differentiable)

Convergence

The scheme is converging if the global error $|x^k - x(t_k)| \to 0$ as $\Delta t \to 0$

Numerical schemes: Convergence = Consistency + Stability

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Dahlquist-Lax Theorem

Convergence $\Leftrightarrow$ Consistency + Stability

Explicit Euler is convergent

Set $\Phi(t_k, x^k, h) = f(t_k, x^k)$, for $h \in [0, H], t \in [0, T]$. Discuss why this scheme is convergent!

Remember from highschool: **Taylor** expansion
Any smooth function φ can be written locally around a point a:

$$\varphi(x) = \varphi(a) + \frac{(x-a)}{1!}\frac{d}{dx}\varphi(a) + \frac{(x-a)^2}{2!}\frac{d^2}{dx^2}\varphi(a) + \dots$$

- Apply Taylor to solution curve $t \mapsto x(t)$ at discretization points t_k:

$$x(t_{k+1}) = x(t_k + \Delta t) = x(t_k) + \frac{\Delta t}{1!}\frac{d}{dt}x(t_k) + \frac{(\Delta t)^2}{2!}\frac{d^2}{dt^2}x(t_k) + \dots$$

- since $\frac{d}{dt}x(t_k) = f(t, x(t_k))$, and $\frac{d^2}{dt^2}x(t_k) = \frac{\partial f}{\partial t}(t, x_k) + \frac{\partial f}{\partial x}(t, x_k)\frac{d}{dt}x(t, x_k)$
- numeric scheme

$$x(t_{k+1}) = x(t_k) + (\Delta t) f(t, x(t_k)) + \frac{1}{2}(\Delta t)^2 \left\{ \frac{\partial f}{\partial t}(t, x_k) + \frac{\partial f}{\partial x}(t, x_k) f(t, x(t_k)) \right\}$$

Second order for SIR model

Calculate the second order term of the scheme for each component of the SIR model and add it to the R code! Idem for the SIR model with quadratic force of infection function! Compare!

- Second order scheme: accurate, but f needs to be differentiable $\Rightarrow$ integral equation:

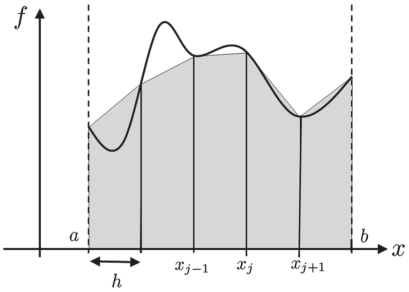
$$x(t_{k+1}) = x(t_k) + \int_{t_k}^{t_{k+1}} f(s)ds$$

- **Left endpoint** rule: $\int_{t_k}^{t_{k+1}} f(s)ds \approx (\Delta t) f(t_k)$ with (forward Euler) scheme:

$$x(t_{k+1}) = x(t_k) + (\Delta t) f(t_k, x^k)$$

- **Trapezoidal** rule: $\int_{t_k}^{t_{k+1}} f(s)ds \approx (\Delta t)\frac{1}{2}\left(f(t_k, x(t_k)) + f(t_{k+1}, x(t_{k+1}))\right)$ with **implicit** scheme

$$x(t_{k+1}) = x(t_k) + (\Delta t)\frac{1}{2}\left(f(t_k, x^k) + f(t_{k+1}, x^{k+1})\right)$$



Implicit numerical schemes: Trapezoidal rule

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Group A work: Solve influenza SIR model numerically in R!

- Solve the SIR model numerically using the function `ode` in the package `deSolve` (e.g. find syntax on stackoverflow or ChatGPT)
- look up in the help menu `?ode` different methods and their required parameters

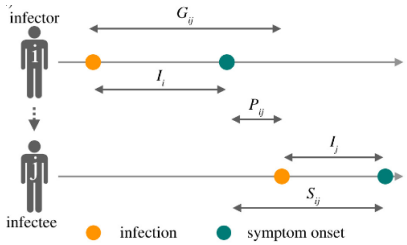
`02_deSolveSIR.R`

Group B work: Do-it-yourself trapezoidal scheme!

- Solve the SIR model numerically by implementing the trapezoidal scheme in R! ~~Don'use ChatGPT~~ you can use ChatGPT, but explain the result.

`03_SIR_trapezoidal.R`

The figure below from Lehtinen et al. shows between infector i and infectee j:



- G, **generation time**: **time between infection** of i and j
- S, **serial interval**: **time between symptom onset** of i and j
- I, **incubation time**: **time between infection** of i and **symptom onset** of j

Generation time and serial interval

Which of the three quantities G, S, I can be negative? What is the epidemiological meaning in this case? Can you give an example?

Influenza outbreak in a boarding school: difference equation

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$$\begin{aligned} S(i+1) &= S(i) - \lambda(I)(i)S(i) \\ I(i+1) &= I(i) + \lambda(I)(i)S(i) - \gamma I(i) \\ R(i+1) &= \gamma I(i) \end{aligned}$$

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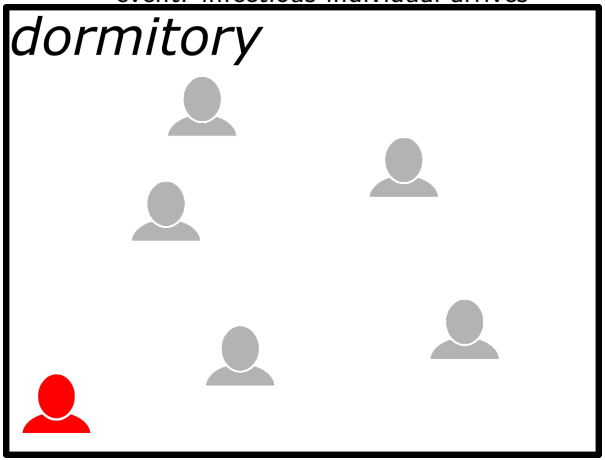
Update for next time step depends not only on now, but also past events!

Influenza outbreak in a boarding school: events

event: infectious individual arrives



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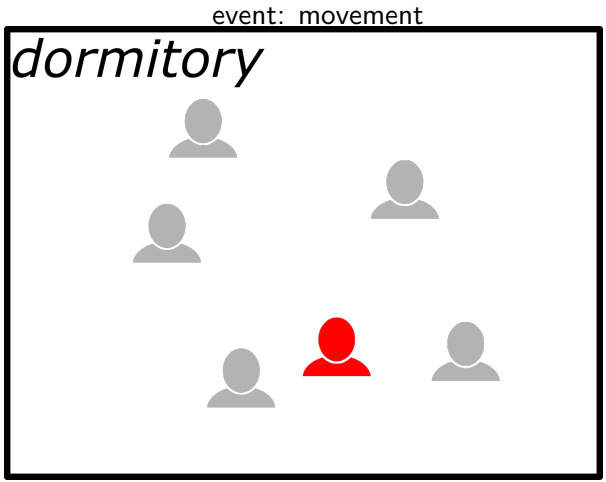
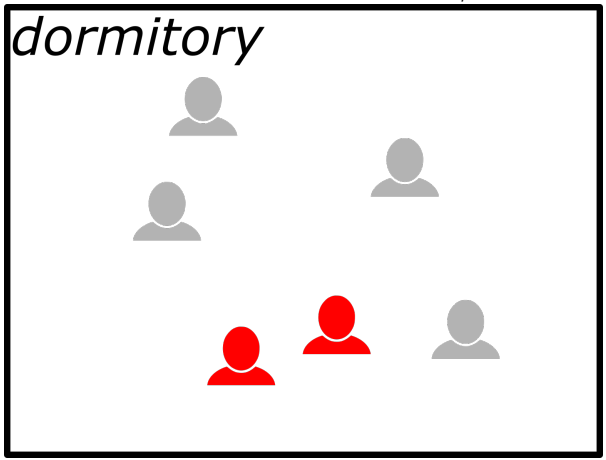


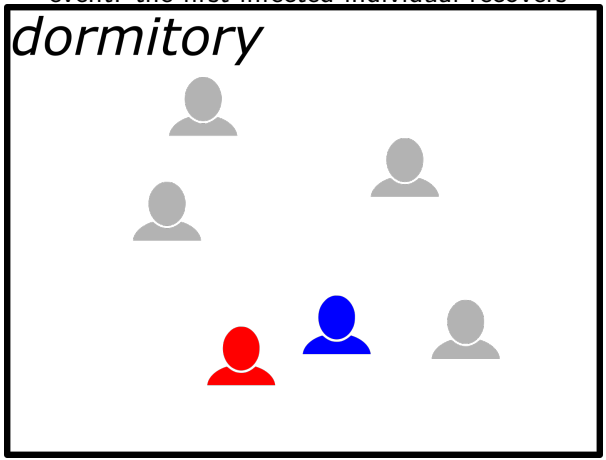
Influenza outbreak in a boarding school: events

event: infectious individuals transmits, two infected



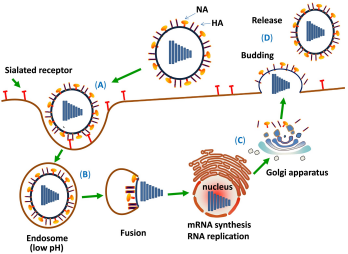
Influenza outbreak in a boarding school: events

event: the first infected individual recovers

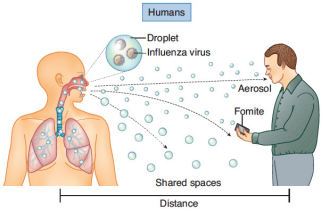


Why stochastic dynamics?

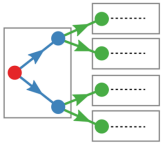
Many phenomena in biology are **intrinsically random** and **multi-scale**!



microbiology



biophysics



individual to population

- stochastic algorithms need **rules**, not explicit functions, **flexible!**
- stochastic algorithms explore **probabilistic** questions: extinction, criticality

"mean-field approximation" of deterministic equations by stochastic algorithm

Law of Large Numbers (LLN)

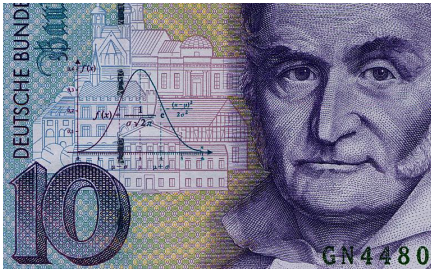
Mean of iid samples converges to expected value!
X_i iid r.v., then

$$\lim_{n\to\infty} \frac{1}{n}(X_1 + \ldots X_n) = \mathbb{E}(X_1)$$

strong LLN: a.s. convergence
weak LLN: convergence in probability

"mean-field approximation" of deterministic equations by stochastic algorithm

Central Limit Theorem (CLT)



Rescaled mean of iid samples with equal variance has Gaussian law as limit distribution!
X_i iid r.v. with $var(X_i) = \sigma^2$, and Y r.v. with law $\mathcal{N}(0, \sigma^2)$, then

$$\lim_{n\to\infty} \sqrt{n}\frac{1}{n}(X_1 + \dots X_n) = Y$$

CLT: convergence in probability

stochastic=random=aleatory=chance=?

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axioms of probability: universe+events+probability

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probability law of r.v. $f_X : (A, \mathcal{A}) \to [0, 1]$ with
$f(A) = \mathbb{P}(X^{-1}(A)) = \mathbb{P}(E \in \mathcal{F} : X(E) = A)$ for $A \in \mathcal{A}$

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Coin toss

Write down a **fair** coin toss as a r.v. using the definitions from above!

Discrete & continuous r.v.

discrete r.v. universe is countable or finite

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continuous r.v. universe is uncountable

$\Omega = \mathbb{R}_+$ and $f_X([0, a)) = \lambda \int_0^a e^{-\lambda y} dy$, but $f_X(\{b\}) = 0$!
"exponential distribution"

observable $\varphi : A \to \mathbb{R}$, then $\varphi(X)$ observable

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expectation : $\mathbb{E}(\varphi(X)) := \sum_z \varphi(y) f_X(y)$ resp. $\int_A \varphi(y) f_X(y) dy$

From random events to stochastic dynamics

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Warm-up

Calculate the expectation of Bernoulli and exponential r.v.!

From random events to stochastic dynamics

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convergence almost sure $\rightarrow$ in probability $\rightarrow$ in expectation

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Markov property $\mathbb{P}(X_{t+a} \in A | \mathcal{F}_t) = \mathbb{P}(X_{t+a} \in A | \sigma(X_t))$
"what happens in the future depends only on the present state"

Markov chain $\mathbb{P}(X_{n+1} = x_{n+1} | X_n = x_n, \ldots, X_1 = x_1) = \mathbb{P}(X_{n+1} = x_{n+1} | X_n = x_n)$
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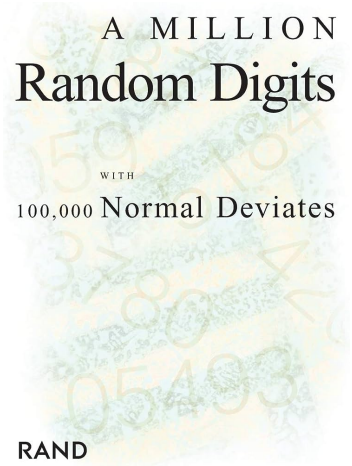
Memory-less r.v.

X r.v. **without memory** $\Longleftrightarrow$ X **exponentially** distr. with $\lambda = -\log(\mathbb{P}(X > 1))$

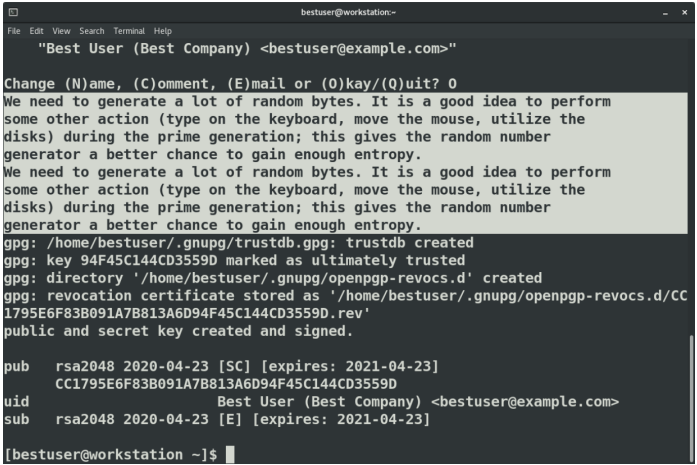
Random number generation: the physical way



buy the book...

Random number generation: the physical way

...or move your mouse: hardware random number generator



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inverse transform sampling

X real-valued r.v. and U uniformly distributed r.v. on $[0, 1]$, then r.v. $F_X^{-1}(U) \sim X$

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Sample from exponential distribution

random draws for r.v. $X \sim \text{Exp}(\lambda)$ by using uniformly distributed random numbers in the interval $[0, 1]$

cdf $F_X(t) = 1 - e^{-\lambda t} \Rightarrow$ **icdf** $F_X^{-1}(t) = -\log(-(t-1))/\lambda = \frac{\log(1-t)}{-\lambda}$

`04_inversesampling.R`

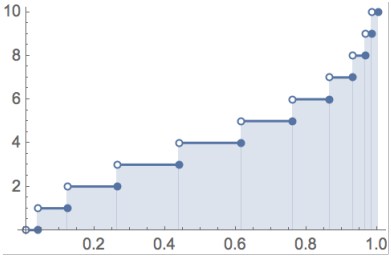
Sample from standard normal distribution

random draws for r.v. $X \sim \mathcal{N}(0, 1)$ by using uniformly distributed random numbers in the interval $[0, 1]$

Sample from discrete set

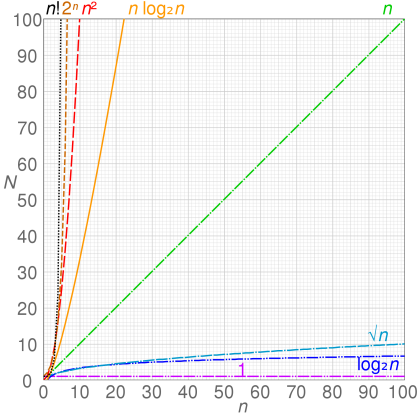
X is r.v. with values in discrete set $K = \{k_1, k_2, \dots\}$ with $\mathbb{P}(X = k_i) = p_i$ such that $\sum_i p_i = 1$.

Define $g : [0,1] \to K$ with
$g(x) = k_j \Leftrightarrow \sum_{i=1}^{j-1} p_i < x \leq \sum_{i=1}^{j} p_i$
If $U \sim$ uniform, then $X \sim g(U)$:
$\mathbb{P}(g(U) = k_j) = \mathbb{P}\left(\sum_{i=1}^{j-1} p_i < U \leq \sum_{i=1}^{j} p_i\right) = p_j$



- Landau notation: $f(n) = \mathcal{O}(g(n))$ for $n \to \infty$ if there are $M, n_0 > 0$ such that for all $n \geq n_0$:

$$|f(n)| \leq Mg(n)$$



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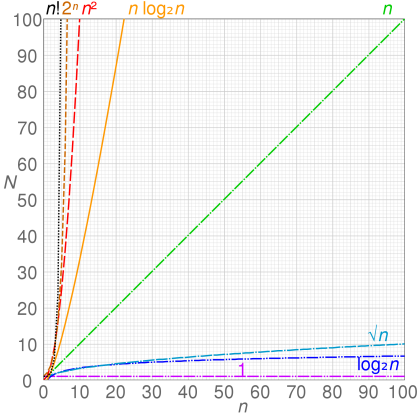

How to measure computational complexity

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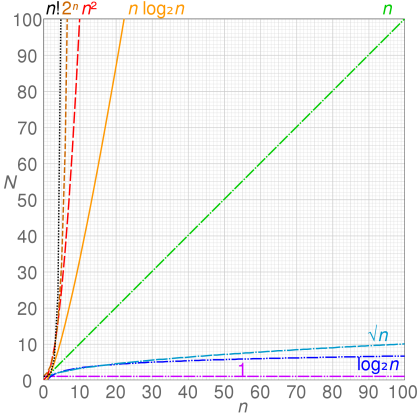
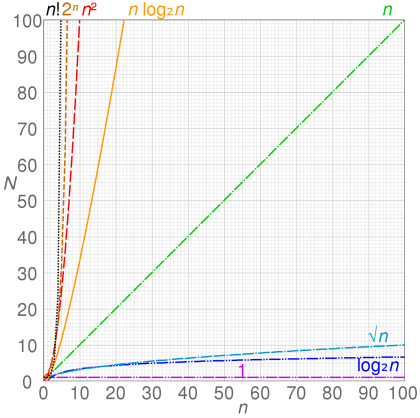
- e.g. $f(n) = 5n^3 + n + 5 \Rightarrow f(n) = \mathcal{O}(n^3)$
- **runtime** of algorithm: input size n, algorithm needs $\mathcal{O}(g(n))$ computation time for solution



- Landau notation: $f(n) = \mathcal{O}(g(n))$ for $n \to \infty$ if there are $M, n_0 > 0$ such that for all $n \geq n_0$:

$$|f(n)| \leq Mg(n)$$

- e.g. $f(n) = 5n^3 + n + 5 \Rightarrow f(n) = \mathcal{O}(n^3)$
- **runtime** of algorithm: input size n, algorithm needs $\mathcal{O}(g(n))$ computation time for solution
- e.g. **binary search** in list of size n has **logarithmic** run time, i.e. algorithm needs $\mathcal{O}(\log n)$ computation steps for solution



Benchmarking: compare the computing time of programs with same input/output

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Recursive vs dynamic programming

The Fibonacci numbers are defined by the recursion:

$$F_1 = 1, F_2 = 1, F_n = F_{n-1} + F_{n-2}$$

for $n > 2$. Calculate F_n by both recursive and dynamic programming (i.e. using already stored numbers). Use the R package `microbenchmark` to benchmark both functions and `system.time` to calculate the runtime as a function of n. What do you observe? `05_benchmarking.R`

Profiling: diagnosing required memory, frequency and duration of functional calls for each line of your computer code

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Profiling

Use the R function `Rprof` to profile both implementations of the Fibonacci number calculations. What do you observe? `06_profiling.R`

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Cyclomatic complexity: number of linearly independent paths through code

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Profiling

Use the R function `Rprof` to profile both implementations of the Fibonacci number calculations. What do you observe? `06_profiling.R`

Cyclomatic complexity: number of linearly independent paths through code

Cyclomatic complexity

Use the R package `cyclocomp` to profile both implementations of the Fibonacci number calculations. What do you observe? What are your conclusion? `07_cyclocomp.R`

Biochemical reaction networks

- species $\mathcal{S}$: chemical compounds whose dynamics we model
- reactions $\mathcal{R}$: how to convert one complex into another

Example

$$\mathcal{S} = \{A, B, C\}, \mathcal{C} = \{A + B, 2B, C, \emptyset\}, \mathcal{R} = \{A + B \to 2B, B \to C, C \to \emptyset\}$$

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- $A + B \to 2B$: A active, B inactive form of protein, B catalyzes A
- $B \to C$: B undergoes conformational change to become C
- $C \to \emptyset$: C is degraded

- $\mathcal{R} = \{y_k \to y'_k; y_k, y'_k \in \mathcal{C}\}$ with $y_k \equiv \sum_i y_{k,i} S_i$
- **stoichiometric** vectors of network: $\zeta_k := y'_k - y_k \in \mathbb{Z}^n$

Example

$$\mathcal{S} = \{A, B, C\}, \mathcal{C} = \{A + B, 2B, C, \emptyset\}, \mathcal{R} = \{A + B \to 2B, B \to C, C \to \emptyset\}$$

$\zeta_1 = [0, 2, 0] - [1, 1, 0] = [-1, 1, 0]$
$\zeta_2 = [0, 0, 1] - [0, 1, 0] = [0, -1, 1]$
$\zeta_3 = [0, 0, 0] - [0, 0, 1] = [0, 0, -1]$

$t \mapsto N(t) \in \mathbb{N}$ such that $N(0) = 0$, N constant except jumps of size $+1$.

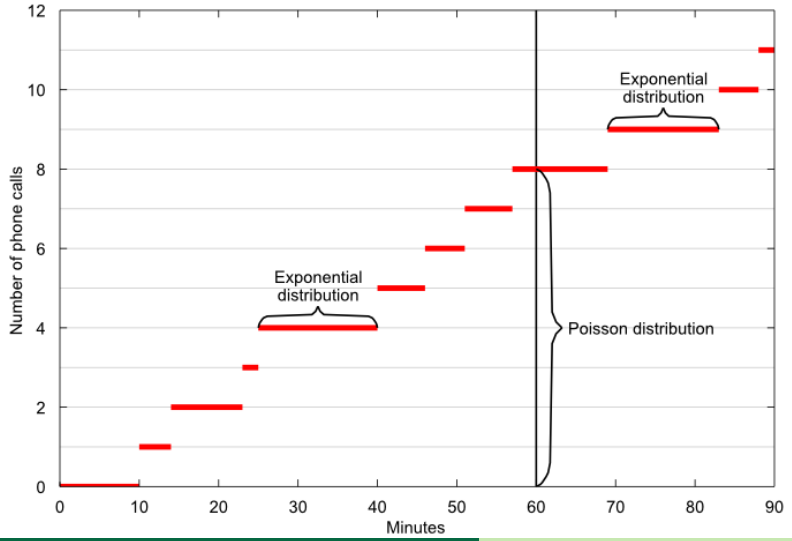
Poisson (point) process

Counting process such that

- $N(0) = 0$
- independent increments, i.e. $N(t_{k+1}) - N(t_k)$ are independent r.v. for $0 < t_1 < \cdots < t_{k+1}$
- distribution of $N(t + \Delta) - N(t)$ does not depend on t

  it follows: $\mathbb{P}(N(t) = k) = \frac{(\lambda t)^k}{k!} e^{-\lambda t}$ "number of arrivals until time t"
- jump time $S_k = \min\{t : N(t) \geq k\}$, then $S_k - S_{k-1} \sim Exp(\lambda)$

Poisson process



Counting processes and biochemical reactions

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Reaction dynamics as Markov jump processes

Let $\lambda_k : \mathbb{N}^{\mathcal{S}} \to \mathbb{R}_+$ be intensity function of reaction k for given molecular state. The counting processes R_k can we represented by iid Poisson processes Y_k with intensity 1 such that for **intensity function** $\lambda_k : \mathbb{N}^{\mathcal{S}} \to \mathbb{R}_+$:

$$R^k(t) = Y_k(\int_0^t \lambda_k(X(s))ds)$$

 Anderson& Kurtz, chapter 1, pp5

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Mass-action kinetics, seen by the chemist

At constant temperature, the rate of chemical reaction is directly proportional to the product of molar concentrations of reacting species.

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Mass-action kinetics, seen by the mathematician

$$\lambda_k(x) = \kappa_k \prod_i \frac{x_i!}{(x_i - y_{ki})!}$$

$x_i = \#$species i, $y_{ki} = \#$species i needed for reaction k, "falling factorial"

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Mass-action kinetics, seen by the mathematician

λ_k is proportional to the number of distinct subsets of the molecules present that can form the inputs for the reaction. E.g. for reaction $A+B \to 2B$, $\lambda_1(x) = \kappa_1 x_1 x_2$.

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Beyond mass-action kinetics

Think of physical or chemical reasons that could prevent the validity of the principle of mass-action!

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Beyond mass-action kinetics

Explain the concept of **cooperative binding** and how it would change the assumptions on biochemical reaction dynamics!

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Think of physical or chemical reasons that could prevent the validity of the principle of mass-action!

Beyond mass-action kinetics

Explain the concept of **cooperative binding** and how it would change the assumptions on biochemical reaction dynamics!

Beyond mass-action kinetics

Can you give an example for **non**-mass-action kinetics in epidemic processes?

stoichiometrically admissible: $\lambda_k(x) = 0$ if $x_i < y_{k,i}$ for all i (e.g. for $A + B \to 2B$ we need at least one A and one B for the reaction to happen)

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Reaction	Intensity function	Rate	molecular
$A + B \to 2B$	$\lambda_1(x) = \kappa_1 x_1 x_2$	κ_1	catalysis of protein inactivation
$B \to C$	$\lambda_2(x) = \kappa_2 x_2$	κ_2	conformational change
$C \to \emptyset$	$\lambda_3(x) = \kappa_3 x_3$	κ_3	degradation

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Reaction	Intensity function	Rate	~~molecular~~	epi
$S + I \to 2I$	$\lambda_1(S, I, R) = \beta SI$	β	~~catalysis of protein inactivation~~	new infections
$I \to R$	$\lambda_2(S, I, R) = \gamma I$	γ	~~conformational change~~	recovery
$R \to \emptyset$	$\lambda_3(S, I, R) = \delta R$	δ	~~degradation~~	death

Epidemics as biochemical reaction systems via Poisson processes

Reaction	Intensity function	Rate	Stoichiometry ζ	epi
$S + I \to 2I$	$\lambda_1(S, I, R) = \beta SI$	β	$[-1, 1, 0]$	new infections
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- time evolution of molecules per species is given by solution of the equation

$$X(t) = X(0) + Y^1(\int_0^t \lambda_1(X_s)ds)\zeta_1 + Y^2(\int_0^t \lambda_2(Y_s)ds)\zeta_2$$

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$$\begin{bmatrix} S(t) \\ I(t) \\ R(t) \end{bmatrix} = \begin{bmatrix} S(0) \\ I(0) \\ R(0) \end{bmatrix} + Y^1\left(\int_0^t \beta S(s)I(s)ds\right)\begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix} + Y^2\left(\int_0^t \gamma I(s)ds\right)\begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix}$$

Group work: simulate variations of the SIR models

For each of the examples draw the flow diagram for the disease dynamics, write the biochemical reaction network and stochiometric vectors!

Incubation period

From exposure to infectiousness, 5 days pass on average. Add a compartement for exposed but not yet infectious hosts!

Ebola-like dynamics

In addition to the basic model used for influenza, we consider also a fraction p of individuals to die from the disease. Contact of susceptibles with dead bodies before burial will lead to additional infections.

Group work: simulate variations of the SIR models

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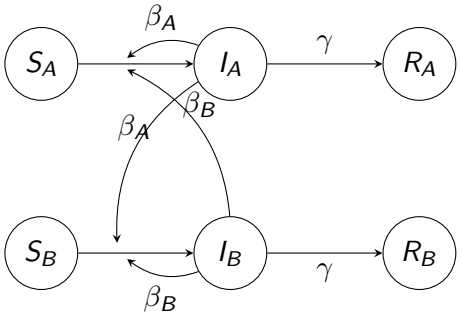
Two rooms in the dorm

In the boarding school there is a respiratory disease outbreak among the students. All of them live together in the same building, but there are two dormitories A and B. Students living in B prefer to visit those living in A, but not so much the other way around. We have seen the following contact rates:

$$A \xrightarrow{0.1} B \qquad B \xrightarrow{0.5} A \qquad A \xrightarrow{1} A \qquad B \xrightarrow{1} B$$

For infectivity $\beta_A > \beta_B$ and recovery rate γ, the flow diagram reads:



The **species** are $\{S_A, I_A, R_A, S_B, I_B, R_B\}$, the **complexes** are $\{S_A + I_A, 2I_A, R_A, S_B + I_B, 2I_B, R_B, S_A + I_B, I_A + I_B, S_B + I_A\}$, the **reactions** are $R_1 : S_A + I_A \to 2I_A$, $R_2 : I_A \to R_A$, $R_3 : S_B + I_B \to 2I_B$, $R_4 : I_B \to R_B$, $R_5 : S_A + I_B \to I_A + I_B$, $R_6 : S_B + I_A \to I_A + I_B$ and the stoichiometric matrix is

$$\begin{bmatrix} -1 & 0 & 0 & 0 & -1 & 0 \\ -1 & -1 & 0 & 0 & +1 & 0 \\ 0 & +1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & -1 \\ 0 & 0 & +1 & -1 & 0 & +1 \\ 0 & 0 & 0 & +1 & 0 & 0 \end{bmatrix}$$

- replace molecule numbers $X(t)$ by **concentration** $C(t) = \frac{1}{N}X(t)$

From Markov jump processes to differential equations

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- N total number of molecules at given volume (e.g. Avogadro's number $\times$ volume v, or total population)

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Concentration dynamics

$$C^N(t) = C^N(0) + \sum_{k=1} N^{-1} Y_k(N \int_0^t \lambda_k(C^N(s))ds)\zeta_k$$

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Concentration dynamics

$$C^{N_v}(t) := C^{N_v}(0) + \sum_{i=1}^{m} N_v^{-1} Y_k(N_v \int_0^t \lambda_k(C^{N_v}(s))ds)\zeta_k$$

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Convergence theorem

$$\lim_{N\to\infty} \mathbb{P}(\sup_{s\leq t} |C^N(s) - x(s)| \geq \epsilon) = 0$$

for each $\epsilon, t > 0$, weak law of large numbers

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- Proof built on Gronwall & Doob inequalities and martingale theory: Anderson & Kurtz, page 44f

Biochemical reaction systems: summary

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Biochemical reaction systems: summary

- **species** of molecules can form complexes, and changes between complexes define reactions
- **reactions** can be described by stoichiometric vectors
- under the **mass action assumption**, the rate of reaction is proportional to the number of molecules involved
- the evolution of molecules over time can be described mathematically as a Poisson process
- molecular **concentrations converge** towards deterministic limit as number of molecules goes to infinity

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Back to epidemic processes

For the simple SIR model, show that assumptions of the convergence theorem are satisfied.

Write explicitly the integral equation (8) and show how it relates to the ODE system.

Gillespie's algorithm: direct method

Simulate systems of biochemical **reactions** (e.g. susceptible meets infectious), assuming no more than two individuals at a time are involved in the reaction or events:

1. reminder:
$$X(t) = X(0) + Y^1(\int_0^t \lambda_1(X_s)ds)\zeta_1 + Y^2(\int_0^t \lambda_2(Y_s)ds)\zeta_2$$
2. suppose transition times between states t_i, define $X(t) = X(t_k)$ for $t \in [t_k, t_{k+1})$
3. initial condition $X(0) = x_0$

1. for $t = t_k$ calculate $\lambda_k(X_t)$ for all k
2. τ time to next event follows $\text{Exp}(\sum_k \lambda_k(X_t))$
3. next event K sampled with $\frac{\lambda_k(X_t)}{\sum_k \lambda_k(X_t)}$
4. update time: $t_{k+1} = t_k + \tau$
5. update state: $X(t_{k+1}) = X_{t_k} + \zeta_K$

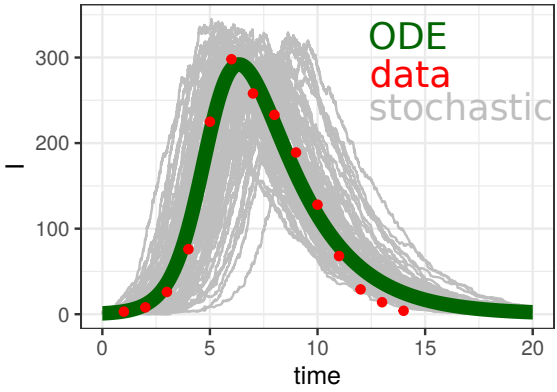
Gillespie's algorithm: direct method for SIR

Initial trajectory $\mathcal{T} = (t, S, I, R) = (0, 762, 1, 0)$
while $I > 0$ **do**
  Current state $\mathcal{S}$ last row of $\mathcal{T}$, $S = \mathcal{S}[2], I = \mathcal{S}[3], R = \mathcal{S}[4]$
  possible events vector: $\mathcal{E} = (\underbrace{\text{new infection}, \ldots, \text{new infection}}_{\text{S times}}, \underbrace{\text{clearance}, \ldots, \text{clearance}}_{\text{I times}})$
  rates vector: $\lambda = (\underbrace{\beta I/N, \ldots, \beta I/N}_{\text{S times}}, \underbrace{\gamma, \ldots, \gamma}_{\text{I times}})$
  time to next event: draw sample τ from Exp$(\sum_i \lambda_i)$
  choose next event: sample from $\mathcal{E}$ with probability $\frac{\lambda_i}{\sum_i \lambda_i}$
  if next event is "new infection" **then**
    $\mathcal{S} \leftarrow \mathcal{S} + (\tau, -1, 1, 0)$
  else if next event is "clearance" **then**
    $\mathcal{S} \leftarrow \mathcal{S} + (\tau, 0, -1, 1)$
  end if
  $\mathcal{T} \leftarrow [\mathcal{T}, \mathcal{S}]$
end while
return $\mathcal{T}$

Gillespie's direct method for influenza SIR model

- write the Gillespie direct method in R for an SIR model
- use the optimal parameters obtained for the ODE system: $\beta = 1.6692258, \gamma = 0.4434502$
- perform 100 realizations of the stochastic process and compare to the ODE solution
- does the law of large numbers hold?
- 08_GillespieDirect.R

Gillespie's direct method for influenza SIR model



What happens if you choose $\beta = 0.7$?

Gillespie's algorithm: first reaction method for SIR

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while $I > 0$ **do**
  Current state $\mathcal{S}$ last row of $\mathcal{T}$, $S = \mathcal{S}[2], I = \mathcal{S}[3], R = \mathcal{S}[4]$
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  rates vector: $\lambda = (\underbrace{\beta I/N, \ldots, \beta I/N}_{\text{S times}}, \underbrace{\gamma, \ldots, \gamma}_{\text{I times}})$
  time to event i: draw sample τ_i from $\text{Exp}(\lambda_i)$
  choose next event $E_\mu \in \mathcal{E}$: for $\mu = \arg\min_i \tau_i$
  if next event is "new infection" **then**
    $\mathcal{S} \leftarrow \mathcal{S} + (\tau_\mu, -1, 1, 0)$
  else if next event is "clearance" **then**
    $\mathcal{S} \leftarrow \mathcal{S} + (\tau_\mu, 0, -1, 1)$
  end if
  $\mathcal{T} \leftarrow [\mathcal{T}, \mathcal{S}]$
end while
return $\mathcal{T}$

Gillespie's algorithm: tau-leap

- direct method: sample time to next reaction, **only one reaction** per time step
- **tau-leap:** fix time to next reaction $\tau > 0$, sample **several reactions**
- **tau-leap assumption:** rates of reactions do not change within $[t, t + \tau)$
- tau-leap: $X(t + \tau) = X(t) + \sum_j P_j(\lambda_j \tau)$
- tau-leap: $P_j(x)$ are independent Poisson random variables with intensity x

1. for each event j, sample $K_j \sim \text{Poisson}(\lambda_j \tau)$ "number of times of event"
2. update: $S[t + \tau] = S[t] + \sum_j K_j v_{ij}$ for v_{ij} stoichiometric vector, state i, event j

- really fast, τ can be optimized, check assumptions!
- 09_GillespieTau.R

Group work: simulate variations of the SIR models

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Simulate SIR variations with Gillespie

For the three models from the group work (incubation period, Ebola-like and two rooms in dormitory) use the R package `GillespieSSA` to simulate trajectories! Play around with parameters!

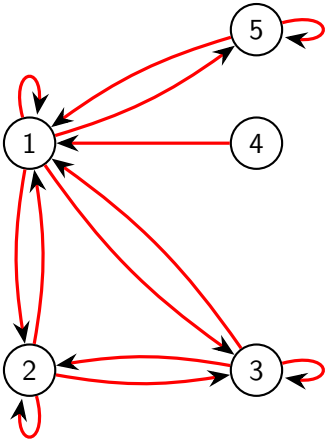
Gibson-Bruck method: speed up Gillespie with data structures

- **Problem:** model with **structure** for age, location, immunity, network, etc. has many different species and possible reactions $\Rightarrow$ Gillespie slow: two random number draw per iteration, event/rate updates
- **Solution:** Gibson-Bruck algorithm with **data structure**
- **dependency graph** between events $\Rightarrow$ event/rate update
- **indexed priority queue** of event times $\Rightarrow$ single random number draw needed

Gibson-Bruck method: dependency graph

node	reaction	propensity	affects	depends	event
1	$S + I \to I + I$	$\beta \mathbf{S}(t)\mathbf{I}(t)^a$	I, S	I, S	new infection
2	$I \to R$	$\gamma \mathbf{I}(t)$	I, R	I	clearance
3	$I \to \emptyset$	$\nu \mathbf{I}(t)$	I	I	virulence
4	$\emptyset \to S$	π	S	$\emptyset$	birth
5	$R \to S$	$\rho \mathbf{R}(t)$	R, S	R	immunity loss

[a] $\mathbf{I}(t)$ denotes sum of all I at time t etc.



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5	$R \to S$	$\rho \mathbf{R}(t)$	R, S	R	immunity loss

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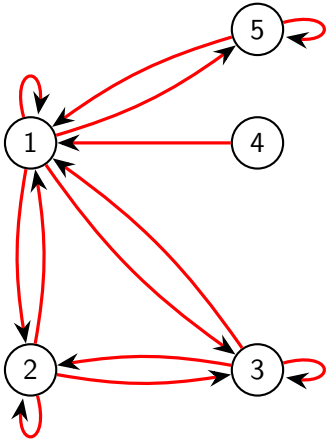

dependency graph: draw edge E_{ij} iff affects$(i) \cap$ depends$(j) \neq \emptyset$

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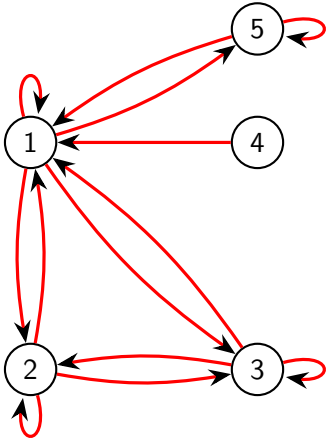
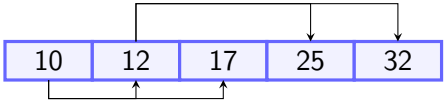


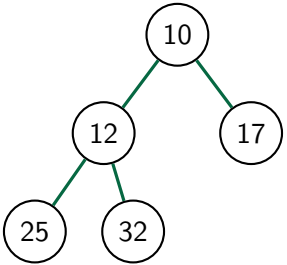
dependency graph: draw edge E_{ij} iff affects$(i) \cap$ depends$(j) \neq \emptyset$

update: reaction i happens $\to$ propensity update for $U_i = \{j : E_{ij} \neq 0\}$

Gibson-Bruck method: indexed priority queue

- priority queue: data structure such that elements with highest priority are served first
- binary heap: complete binary tree, key stored in each node is either less than or equal to the keys in the node's children
- $\mathcal{O}(logn)$ performance for inserts and removals, and $\mathcal{O}(logn)$ to build heap from n elements





Gibson-Bruck method: algorithm

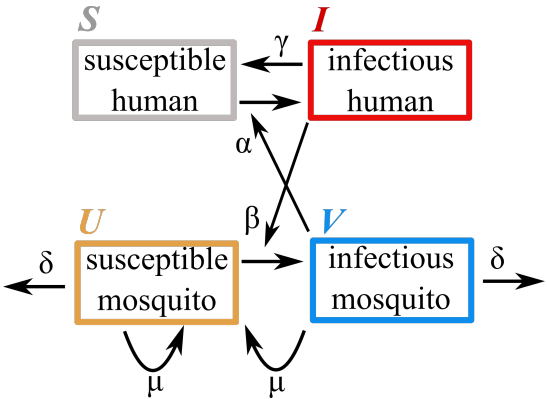
1: set t = 0; generate dependency graph $\mathcal{D}$ of reactions; calculate propensity function α_i for each reaction $i = 1, ..., M$; draw $\tau_i \sim \text{Exp}(\alpha_i)$; write absolute time $t_i = t + \tau_i$ in an indexed priority queue given by heap $\mathcal{Q}$.
2: **while** $t < t_{\text{max}}$ **do**
3: choose next reaction R_μ with μ root in $\mathcal{Q}$
4: update stoichiometry, i.e. copy number of molecules after reaction R_μ, set $t = t_\mu$
5: update reaction rates α_i for $i \in U_\mu$ using $\mathcal{D}$
6: update next reaction times in $\mathcal{Q}$ for updated α_i **without** new random number draw:

$$t_{i,\text{new}} = \frac{\alpha_{i,\text{old}}}{\underbrace{\alpha_{i,\text{new}}}_{\tau_{i,\text{new}}}}(t_{i,\text{old}} - t) + t$$

7: **end while**
8: **return** trajectory for each species and reaction times

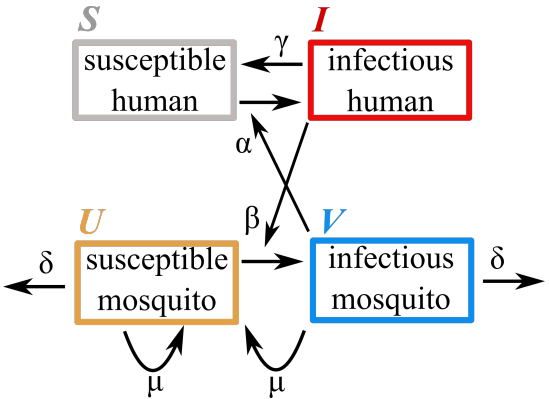
StochPy on

Malaria toy model: Gillespie-type simulation



- α host seeking and biting rate by (female) mosquito
- γ recovery rate from human infection
- β acquisition rate from infectious host to susceptible mosquito
- μ mosquito birth rate (from both susceptible and infected mosquitoes)
- δ death rate of adult mosquito

Malaria toy model: Gillespie-type simulation



$$
\begin{aligned}
\frac{dS}{dt} &= -\alpha S\frac{V}{H} + \gamma I \\
\frac{dI}{dt} &= \alpha S\frac{V}{H} - \gamma I \\
\frac{dU}{dt} &= -\beta U\frac{I}{H} + \mu(U+V) - \delta U \\
\frac{dV}{dt} &= \beta U\frac{I}{H} - \delta V
\end{aligned}
$$

Malaria toy model: Gillespie-type simulation

Where does the term $\frac{V}{H}$ come from?

- α host seeking and biting rate
- then, $\alpha(U+V)$ is expected number of bites
- $\frac{\alpha(U+V)}{H}$ are expected number of bites per human
- multiply with infectious mosquito density $\frac{V}{U+V}$ gives
- $\frac{V}{U+V}\frac{\alpha(U+V)}{H} = \frac{\alpha V}{H}$

$$
\begin{aligned}
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\frac{dU}{dt} &= -\beta U \frac{I}{H} + \mu(U+V) - \delta U \\
\frac{dV}{dt} &= \beta U \frac{I}{H} - \delta V
\end{aligned}$$

- 4 species: S, I, U, V
- 7 reactions: $S + V \to I + V$, $I \to S$, $U + I \to V + I$, $U \to \emptyset$, $V \to \emptyset$, $U \to 2U$, $V \to U + V$
- 7 intensities: $\alpha \frac{S}{H}$, γI, $\beta \frac{U}{H}$, δU,δV, μU, μV,
- stoichiometry 4×7 matrix:

$$\begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & -1 & 0 & 1 & 1 \\ 0 & 0 & +1 & 0 & -1 & 0 & 0 \end{bmatrix}$$

Malaria toy model: Gillespie-type simulation

For this model, the basic reproduction number is

$$\mathcal{R}_0 = \sqrt{\frac{\alpha\beta(U+V)/H}{\mu\gamma}}$$

Malaria toy model

Simulate with `GillespieSSA` and obtain an endemic equilibrium!
Choose $H = 1000$, $U + V = 5000$, $\mu = \delta = 1/10$, $\beta = \alpha = 0.03$ and search some values for γ in literature! Change the ratio of mosquito $M = U + V$ to human $H = S + I$!
Plot the curve of infected humans over two year!

`10_RossMcDonaldGillespie.R`

Malaria toy model: Gillespie-type simulation

$$
\begin{aligned}
\frac{dS}{dt} &= -\alpha V \frac{S}{H} + \gamma I \\
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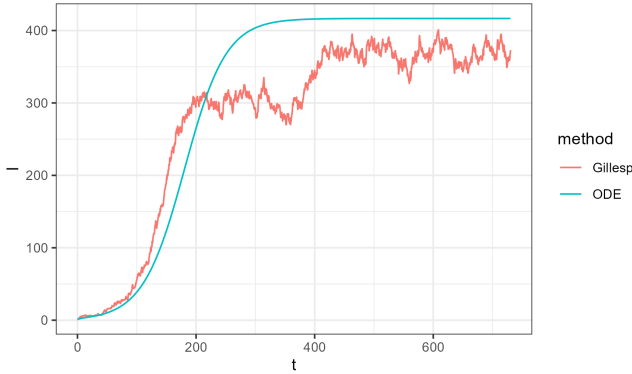
$$



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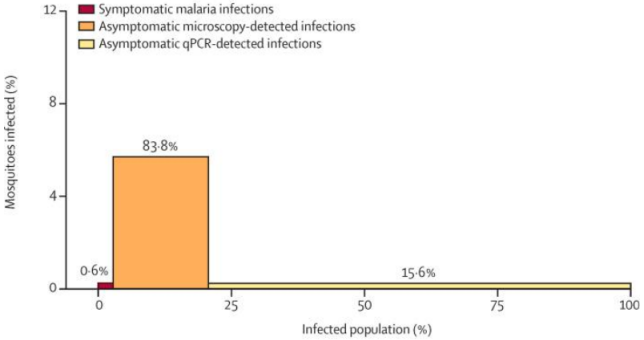
AIMS

Asymptomatic infections

Based on our Malaria toy model, we consider three classes of infected populations: confirmed cases I_c who are treated before gametocytemia, asymptomatic with high gametocytemia I_h and and asymptomatic with low gametocytemia I_l. We assume that hosts with high/low gametocytemia have a transmission rate β_h, β_l. The duration of infection with positive gametocytemia for I_c, I_h, I_l is $10, 45, 15$ days resp.

Asymptomatic Malaria toy model: Gillespie simulation



Andolina et al. 2021: The bar heights indicate the proportion of mosquitoes that became infected when feeding on this population. The bar widths indicate the proportion of the infected population.

Asymptomatic infections

Use the figure to discuss parameters for proportions of I_c, I_h, I_ℓ and the ratio of β_h over β_ℓ. Draw the flow diagram, use parameters from the toy model, write the reactions, rates and stoichiometric vectors. Simulate the dynamics of infection compartments with the Gillespie algorithm!

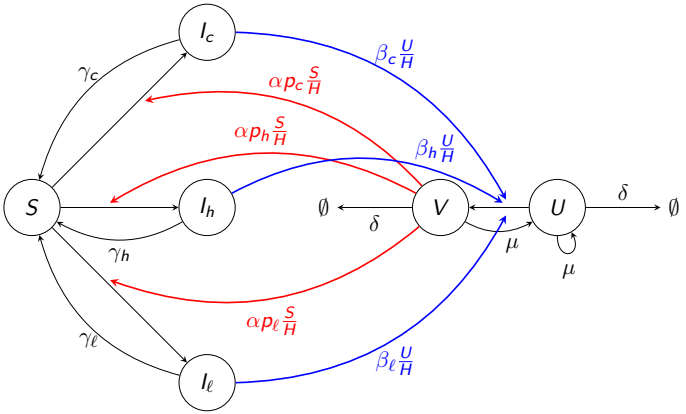
Asymptomatic Malaria toy model: Gillespie simulation

Proposed solution:

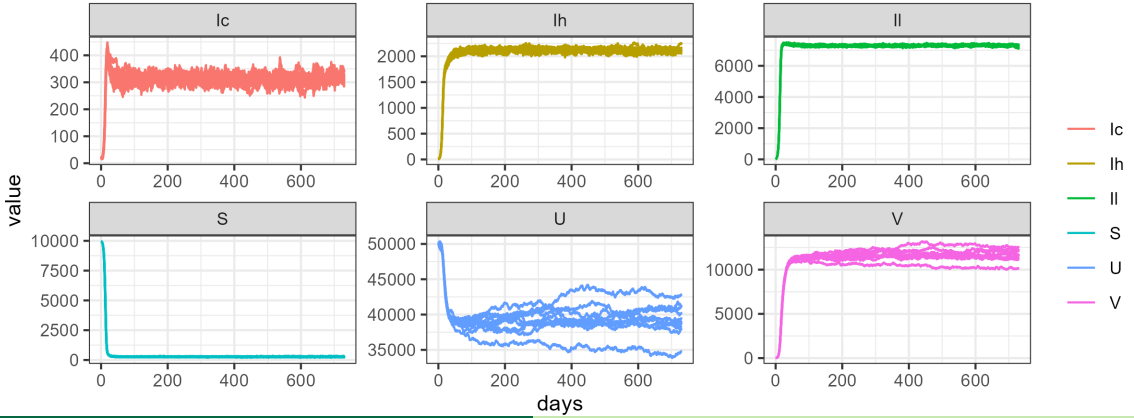
- New infections: Exposure to infectious mosquitoes V creates new infections in I_c, I_h, I_ℓ at rate $\alpha_c = p_c\alpha$, $\alpha_h = p_h\alpha$ and $\alpha_\ell = p_\ell\alpha$ where EIR $\alpha = 2$ and $[p_c, p_h, p_\ell] = [0.05, 0.17, 0.78]$ the relative proportion of confirmed/treated, high and low parasitemia infections after a mosquito bite.
- clearance rates for human infections are $\gamma_c = 1/10, \gamma_h = 1/45, \gamma_\ell = 1/15$.
- For transmission from humans to vectors, we assume that $\beta_c = 0.03$ and $\beta_h = 0.08$ and $\beta_\ell = K\beta_h$ for $K = 0.84/0.16$, i.e. the transmission ratio into I_h vs I_c infections.
- The life-cycle for the mosquitoes populations remains as in the toy-model before.
- `11_RossMcDonaldGillespieAsymptomatic.R`

Asymptomatic Malaria toy model: biochemical reaction system

1. $S + V \to I_c + V$ at rate $\alpha p_c \frac{S}{H}$
2. $S + V \to I_h + V$ at rate $\alpha p_h \frac{S}{H}$
3. $S + V \to I_\ell + V$ at rate $\alpha p_\ell \frac{S}{H}$
4. $I_c \to \emptyset$ at rate γ_c
5. $I_h \to \emptyset$ at rate γ_h
6. $I_\ell \to \emptyset$ at rate γ_ℓ
7. $U + I_c \to V + I_c$ at rate $\beta_c \frac{U}{H}$
8. $U + I_h \to V + I_h$ at rate $\beta_h \frac{U}{H}$
9. $U + I_\ell \to V + I_\ell$ at rate $\beta_\ell \frac{U}{H}$
10. $U \to \emptyset$ at rate δ
11. $V \to \emptyset$ at rate δ
12. $U \to U + U$ at rate μ
13. $V \to U + V$ at rate μ



With initial conditions $H = 10000$, $I_c(t) = 20, I_h(0) = 5, I_\ell(0) = 10$ and $V(0) = 8$ and $U(0) = 49992$, we obtain an endemic equilibrium of confirmed cases prevalence at roughly 3%, while a large part of the population is infected without symptoms at low-level parasitemia:



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AIMS

Test and treat vs. mass drug administration

For the asymptomatic model, we want to evaluate two different intervention strategies:

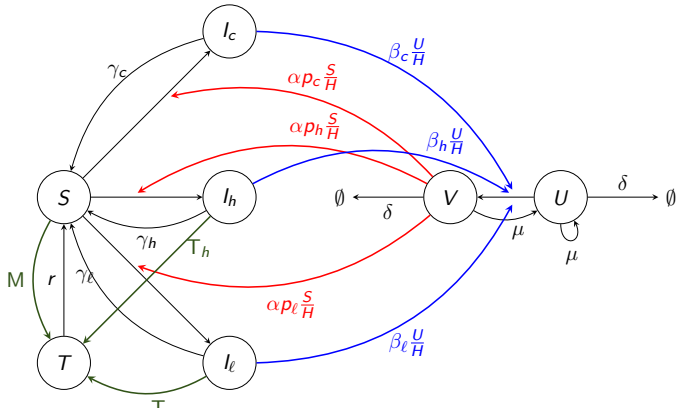
- test and treat: the antigen-based diagnostics has a sensitivity to detect 95% of asymptomatic cases with high gametocytemia and 15% with low gametocytemia, all positively tested are treated.
- mass drug administration: 95% of the entire population gets drug treatment, regardless of infection status

Simulate trajectories for the two strategies and the counterfactual starting from the endemic equilibrium obtained from the preceding exercise!
What is your metric of evaluation and which intervention would you recommend?

Asymptomatic Malaria intervention toy model: reaction system

For test and treat we assume that both I_h and I_ℓ move to treated compartment T. For mass drug administration, we also assume that S move into T.

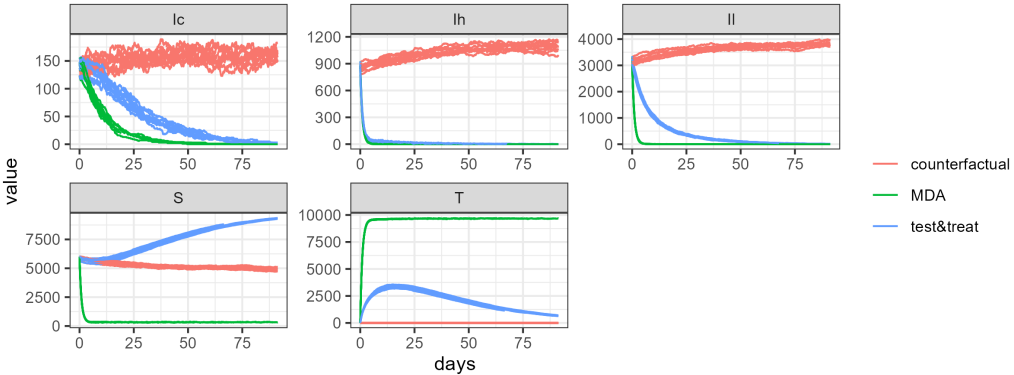
14. $I_h \to T$ at rate T_h
15. $I_\ell \to T$ at rate T_ℓ
16. $S \to T$ at rate M
17. $T \to S$ at rate $r = 1/30$



12_RossMcDonaldGillespieAsymptomatic_TTvsMDA.R

Asymptomatic Malaria intervention toy model: Gillespie simulation

- test and treat: $T_h = 0.95$, $T_\ell = 0.15$ and $M = 0$, $r = 1/30$
- MDA: $T_h = T_\ell = M = 0.98$, $r = 1/30$



Prevalence is close to 0 within 3 months, test sensitivity for I_ℓ is crucial to achieve elimination.

Stochastic differential equation heuristics

- consider SIR stochastic process $X(t) = [S(t), I(t)]$ s.th. for $\overline{X}(t) = \mathbb{E}(X(t))$

$$\frac{d\overline{S}}{dt} = -\beta \overline{S} \frac{\overline{I}}{\overline{N}} \qquad \frac{d\overline{I}}{dt} = \beta \overline{S} \frac{\overline{I}}{\overline{N}} - \gamma \overline{I}$$

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- divide time interval $[0, t]$ into subintervals of length Δt, with

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- further divide Δt s.th. for $\Delta t_i = t_i - t_{i-1} : \sum_i^n \Delta t_i = \Delta t$ and

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- if Δt_i small, assume $\Delta X(t_i)$ are iid on Δt

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$$\Delta X(t) = \sum_i \Delta X(t_i)$$

- if Δt_i small, assume $\Delta X(t_i)$ are iid on Δt
- for n large, CTL: $\frac{1}{\sqrt{n}} (\Delta X(t) - \mathbb{E}(\Delta X(t))) \sim \mathcal{N}(0, \mathbf{cov}(\Delta X(t)))$

At the order of Δt:

$$\mathbb{E}(\Delta X(t)) \approx \left[-\beta \overline{S}\frac{\overline{I}}{\overline{N}}, \beta \overline{S}\frac{\overline{I}}{\overline{N}} - \gamma \overline{I}\right] \Delta t = f \Delta t$$

At the order of Δt:

$$\mathbb{E}(\Delta X(t)) \approx \left[-\beta \overline{S}\frac{\overline{I}}{\overline{N}}, \beta \overline{S}\frac{\overline{I}}{\overline{N}} - \gamma \overline{I}\right] \Delta t = f \Delta t$$

At the order of Δt:

$$\mathbf{cov}(\Delta X) \approx \mathbb{E}((\Delta X)(\Delta X)^T) = \begin{pmatrix} \mathbf{cov}(\Delta S, \Delta S) & \mathbf{cov}(\Delta S, \Delta I) \\ \mathbf{cov}(\Delta S, \Delta I) & \mathbf{cov}(\Delta I, \Delta I) \end{pmatrix}$$

At the order of Δt:

$$\mathbb{E}(\Delta X(t)) \approx \left[-\beta\overline{S}\frac{\overline{I}}{\overline{N}}, \beta\overline{S}\frac{\overline{I}}{\overline{N}} - \gamma\overline{I}\right]\Delta t = f\Delta t$$

At the order of Δt:

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$$\mathbf{cov}(\Delta X) \approx \begin{pmatrix} \beta S\frac{I}{N} & -\beta S\frac{I}{N} \\ -\beta S\frac{I}{N} & \beta S\frac{I}{N} + \gamma I \end{pmatrix}\Delta t = C\Delta t$$

By assumption $\Delta X(t_i)$ are iid on Δt, and with $\Delta t = n\Delta t_i$ s.th.

$$\begin{aligned}
\mathbb{E}(\Delta X_1^2) &= \mathbb{E}(\Delta S^2) = \mathbb{E}(\sum_i \Delta S(t_i)^2) \\
&= \sum_i \mathbb{E}(\Delta S(t_i)^2) + 2\sum_{i<j} \mathbb{E}(\Delta S(t_i))\mathbb{E}(\Delta S(t_j)) \\
&= n\mathbb{E}(\Delta S(t_0)^2) + n(n-1)\mathbb{E}(\Delta S(t_0))^2 \\
&= n(-1)^2 \Delta t_1 \beta I(t_0)\tfrac{S(t_0)}{N} + n\, 0^2\, (1 - \Delta t_1 \beta I(t_1)\tfrac{S(t_1)}{N}) + (\Delta t)^2(1-\tfrac{1}{n})(\beta I(t_1)\tfrac{S(t_1)}{N})^2 \\
&\approx \Delta t \beta I(t_0)\tfrac{S(t_0)}{N}
\end{aligned}$$

at the order of Δt with $\mathbb{P}(\Delta S(t_i) = -1) = \Delta t_i \beta I(t_{i-1})\frac{S(t_{i-1})}{N}$

Stochastic differential equation heuristics

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AIMS

Stochastic differential equation

$$\Delta X(t) \approx f(X(t))\Delta t + G(X(t))\Delta W(t)$$

Stochastic differential equation

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- Here, the matrix G is such that $GG^T = C$ and

Stochastic differential equation heuristics

Stochastic differential equation

$$\Delta X(t) \approx f(X(t))\Delta t + G(X(t))\Delta W(t)$$

- Here, the matrix G is such that $GG^T = C$ and
- $\Delta W = [\Delta W_1, \Delta W_2]$ with $\Delta W_i \sim \mathcal{N}(0, \Delta t)$

Euler-Maruyama algorithm

We implement

$$\Delta X(t) \approx f(X(t))\Delta t + G(X(t))\Delta W(t)$$

by first order scheme

$$X[i+1] = X[i] + f(X[i])\Delta t + G(X[i])\eta\sqrt{\Delta t}$$

where $\eta \in \mathbb{R}^d$ with $\eta_k \sim \mathcal{N}(0,1)$ and d is the number of reactions.

In our SIR example:

$$f(S,I) = \begin{pmatrix} -\beta S \frac{I}{N} \\ \beta S \frac{I}{N} - \gamma I \end{pmatrix}$$

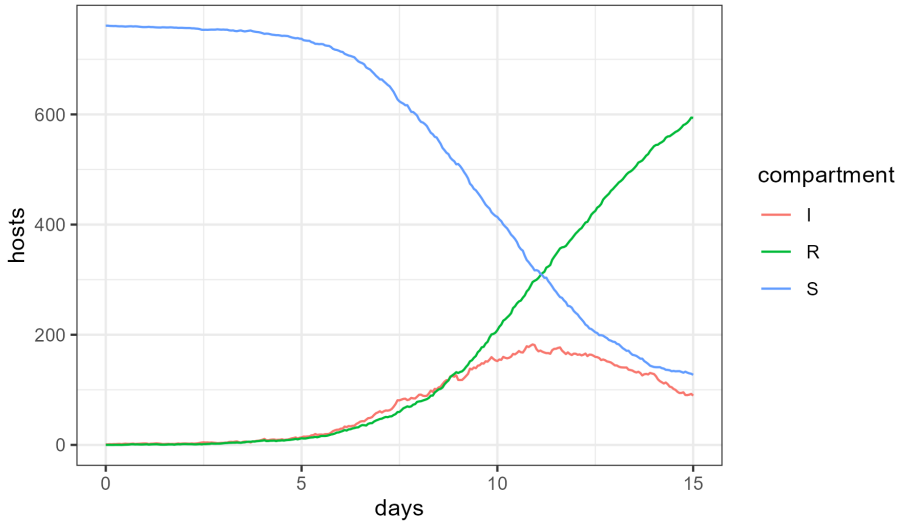
$$G(S,I) = \begin{pmatrix} -\sqrt{\beta S \frac{I}{N}} & 0 \\ \sqrt{\beta S \frac{I}{N}} & -\sqrt{\gamma I} \end{pmatrix}$$

Just take square roots of the rates from the ODE!

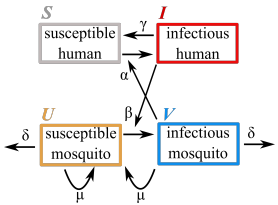
Implementation of Euler-Maruyama

Code the Euler-Maruyama scheme in R for the influenza boarding school SIR model! Simulate several trajectories! When choosing $\beta > \gamma$, do you have simulations where I get extinct early on? `13_ForwardEulerMaruyamaSIR.R`

Euler-Maruyama algorithm for SIR



Malaria toy model with stochastic differential equation



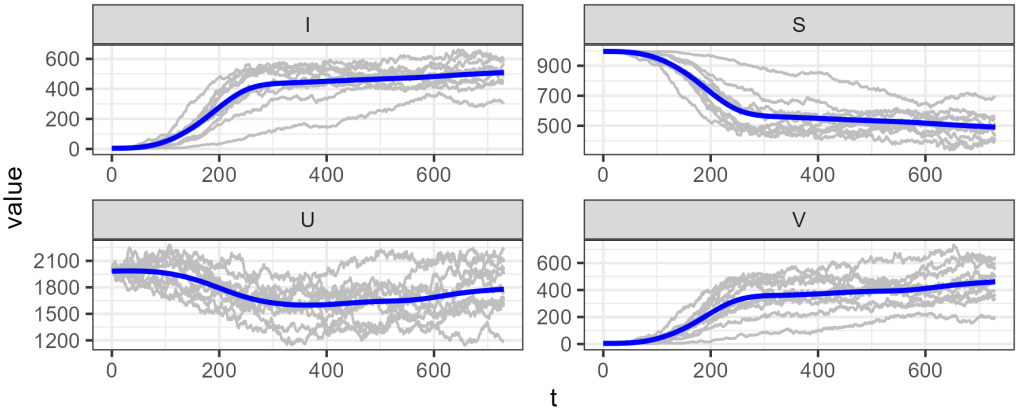
$$
\begin{aligned}
dS &= f_1\,dt - \sqrt{\alpha V \frac{S}{H}}\,dW^1 + \sqrt{\gamma I}\,dW^2 \\
dI &= f_2\,dt + \sqrt{\alpha V \frac{S}{H}}\,dW^1 - \sqrt{\gamma I}\,dW^2 \\
dU &= f_3\,dt - \sqrt{\beta U \frac{I}{H}}\,dW^3 + \sqrt{\mu U}\,dW^4 + \sqrt{\mu V}\,dW^5 - \sqrt{\delta U}\,dW^6 \\
dV &= f_4\,dt + \sqrt{\beta U \frac{I}{H}}\,dW^3 - \sqrt{\delta V}\,dW^7
\end{aligned}
$$

Euler-Maruyama for Malaria toy model

Implement the stochastic differential equation version of the Malaria toy model in R.

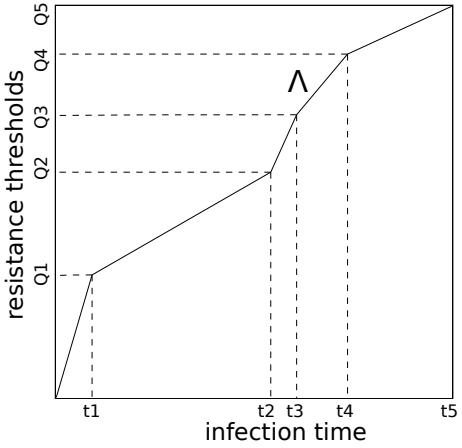
`14_RossMcDonaldForwardEulerMaruyama.R`

Euler-Maruyama for Malaria toy model



Sellke's method: infectious pressure

- **probabilistically equivalent** to SIR process
- iid $Q_1, \ldots, Q_n \sim \text{Exp}(1)$ for n susceptibles
- iid $T_{-(m-1)}, \ldots, T_n$ infection durations, **any distribution** on $\mathbb{R}_+$ (e.g. gamma, Weibull)
- m initially infected $T_{-(m-1)}, \ldots, T_0$
- $I(t)$ =number of infected at time t
- infectious "pressure" $\Lambda(t) = \int_0^t I(s)ds$



Sellke's method: infectious pressure

- susceptible i accumulates exposure to infection at rate equal to number of infected individuals
- ith susceptible becomes infected by time t_i if infectious pressure reached: $\Lambda(t_i) = Q_i$
- individual who was jth infected remains infected for time T_j and then clears
- infections happen at the right time:

$$\begin{aligned}
&\mathbb{P}(\text{susceptible } i \text{ infected by } t + dt | \text{not infected by } t) = \\
&= \mathbb{P}(Q_i < \Lambda(t + dt) | Q_i > \Lambda(t)) = \frac{\mathbb{P}(\Lambda(t) < Q_i < \Lambda(t + dt))}{\mathbb{P}(Q_i > \Lambda(t))} \\
&\approx \frac{(1 - e^{-\Lambda(t+dt)}) - (1 - e^{-\Lambda(t)})}{e^{-\Lambda(t)}} = 1 - e^{-[\Lambda(t+dt) - \Lambda(t)]} = 1 - e^{-\Lambda'(t)dt} \\
&= \Lambda'(t)dt = \beta I(t)dt
\end{aligned}$$

- **advantage**: generalize straight-forward to infection duration **with memory**

Stochastic simulation algorithms: summary table

algorithm	time	space	conv	non-Mark.	in practice
exact Gillespie	C	D	✓	✗	only for simple systems, slow
first reaction Gillespie	C	D	✗	✗	no need to sample next reaction
tau-leap Gillespie	D	D	✗	✗	fast for simple systems, step size tuning
Gillespie-Boguña	C	D	✗	✓	only for simple systems, slow
Gillespie-Gibson-Bruck	C	D	✗	✓	fast for system with many reactions
Sellke	C	D	✓	✓	only for simple systems
Euler-Maruyama	C	C	✓	✗	faster to simulate for large populations

Acknowledgements

Thanks for financial support to

BILL & MELINDA GATES foundation

Swiss TPH

Swiss Tropical and Public Health Institute

Lecture notes and resources

internet mathoverflow, stackoverflow, chatGPT, google colab

lecture notes Anderson, Kurtz: Stochastic Analysis of Biochemical Systems

lecture notes Allen: Stochastic Population and Epidemic Models

lecture notes Ammari, Wu, Yu: Numerical Methods for ODEs

history Ross: An Application of the Theory of Probabilities to the Study of a priori pathometry. -Part I

Articles

article Lehtinen et al. 

article Begon et al.