

# Modelling with SDEs in Biology

Formulation, Numerical Simulation and Analysis

## First day: Formulation of Models with SDEs

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UQ

*ODE + noise = Better Model*

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Population growth

$$\frac{dN}{dt} = a(t)N(t) \quad N_0 = N(0) = cte.$$

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$$a(t) = r(t) + \text{"noise"}$$

*ODE + noise = Better Model*

## Electric Circuits

$$L \cdot Q''(t) + R \cdot Q'(t) + \frac{1}{C} \cdot Q(t) = F(t)$$

$$Q(0) = Q_0$$

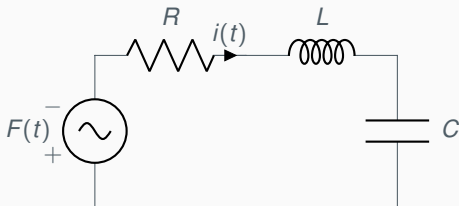
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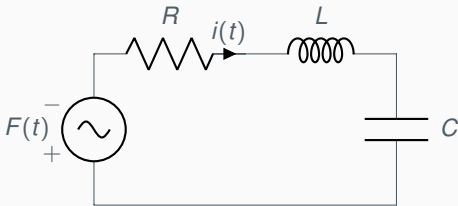
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## Electric Circuits

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$$F(t) = G(t) + \text{"noise"}$$

Example

$$dN(t) = aN(t)dt$$



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Get a SDE

$$dN(t) = aN(t)dt + \sigma N(t)dB(t)$$

# To fix ideas

## Example

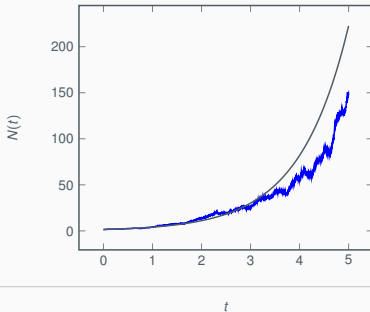
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# Some Important applications

- Finance
- Physics
- Chemistry
- Biology
- Epidemiology

Henston

$$dS_t = \mu S_t dt + \sqrt{V_t} S_t \left( \sqrt{1 - \rho^2} dW_t^{(1)} + \rho dW_t^{(2)} \right)$$

$$dV_t = \kappa(\lambda - V_t)dt + \theta \sqrt{V_t} dW_t^{(2)}$$



Hutzenthaler, M. and Jentzen, A. (2015).

**Numerical approximations of stochastic differential equations with non-globally lipschitz continuous coefficients.**

*Memoirs of the American Mathematical Society*, 236(1112).

# Some Important applications

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- **Physics**
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## Langevin

$$dX_t = -(\nabla U)(X_t)dt + \sqrt{2\varepsilon}dW_t$$



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## Brusselator

$$dX_t = \left[ \delta - (\alpha + 1)X_t + Y_t X_t^2 \right] dt + g_1(X_t) dW_t^{(1)}$$

$$dY_t = \left[ \alpha X_t + Y_t X_t^2 \right] dt + g_2(X_t) dW_t^{(2)}$$



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## Lotka Volterra

$$\begin{aligned}dX_t &= (\lambda X_t - kX_t Y_t)dt + \sigma X_t dW_t \\dY_t &= (kX_t Y_t - mY_t)dt\end{aligned}$$



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# Some Important applications

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## SIR

$$\begin{aligned}dS_t &= (-\alpha S_t I_t - \delta S_t + \delta)dt - \beta S_t I_t dW_t \\dl_t &= (\alpha S_t I_t - (\gamma + \delta)l_t)dt + \beta S_t I_t dW_t \\dR_t &= (\gamma l_t - \delta R_t)dt\end{aligned}$$

## Main objective

To present two of the common approaches in stochastic modeling with SDEs.

### Allen's approach

$DTMC \rightarrow CTMC \rightarrow SDE$

### Stochastic perturbation

$$dN(t)/dt = aN(t)$$

$$adt \rightsquigarrow adt + \sigma dB(t)$$

$$dN(t) = aN(t)dt + \sigma N(t)dB(t)$$

- 1 **Introduction** 

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- 2 **Discrete Time Markov Chains (DTMC)** 

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- 3 **Continuous Time Markov Chains (CTMC)** 

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- 4 **SDEs** 

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## Environmental effects

- Extinction
- Outbreaks

# Why noise?

## Environmental effects

- Extinction
- Outbreaks

## Environmental Brownian noise suppresses explosions.



Mao, X., Marion, G., and Renshaw, E. (2002).  
**Environmental brownian noise suppresses explosions in population dynamics.**

*Stochastic Processes and their Applications*,  
 97(1):95–110.

# Why noise?

## Environmental effects

- Extinction
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## Noise color induces extinction



Ripa, J. and Lundberg, P. (1996).

### **Noise Colour and the Risk of Population Extinctions.**

*Proceedings of the Royal Society B: Biological Sciences*, 263(1377):1751–1753.

# Why noise?

## Environmental effects

- Extinction
- Outbreaks

$\mathcal{R}_0$ : Endemic g.a.e.  $\rightarrow$  periodic oscillations



Allen, L. and van den Driessche, P. (2013).  
**Relations between deterministic and stochastic thresholds for disease extinction in continuous- and discrete-time infectious disease models.**  
*Mathematical Biosciences*, 243(1):99–108.

## In Biology

- **DTMC, CTMC**
- Stochastic perturbation of parameters
- Mean reverting processes

## DTMC + CTMC + ME $\rightarrow$ SDE



Allen, L. J. (2017).

**A primer on stochastic epidemic models: Formulation, numerical simulation, and analysis.**

*Infectious Disease Modelling*, 2(2):128–142.



## In Biology

- DTMC, CTMC
- **Stochastic perturbation of parameters**
- Mean reverting processes

$$\varphi dt \rightsquigarrow \varphi dt + \sigma dB_t$$



Gray, A., Greenhalgh, D., Hu, L., Mao, X., and Pan, J. (2011).

**A Stochastic Differential Equation SIS Epidemic Model.**

*SIAM Journal on Applied Mathematics*, 71(3):876–902.

## In Biology

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$$\varphi dt \rightsquigarrow \varphi dt + F(x)dB_t$$



Schurz, H. and Tosun, K. (2015).  
**Stochastic Asymptotic Stability of SIR Model with Variable Diffusion Rates.**  
*Journal of Dynamics and Differential Equations*, 27(1):69–82.

## In Biology

- DTMC, CTMC
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$$d\varphi_t = (\varphi_e - \varphi_t)dt + \sigma_\varphi dB_t$$



Allen, E. (2016).

**Environmental variability and mean-reverting processes.**

*Discrete and Continuous Dynamical Systems - Series B*, 21(7):2073–2089.

# Formulation of SDE: $DTMC \rightarrow CTMC + ME \rightarrow SDE$

To fix ideas, we recall the deterministic philosophy to formulate ODEs

- We study a process in an small interval of time  $\Delta t$
- Describe the resulting information in  $\Delta t$
- Letting  $\Delta t \rightarrow 0$  gives an ODE

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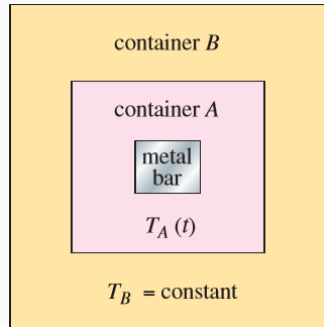
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## Newton's Cooling Law

$$\frac{T_A(t + \Delta t) - T_A(t)}{\Delta t} = \alpha(T_B - T_A(t))$$

Letting  $\Delta t \rightarrow 0$

$$\frac{dT_A(t)}{dt} = \alpha(T_B - T_A(t))$$





A stochastic analogy.

- i) Formulate a discrete stochastic model for the dynamical system under study, which describe changes in a small time interval  $\Delta t$
- ii) Compute the expected value and covariance for the difference in a short time  $\Delta t$
- iii) Letting  $\Delta t \rightarrow 0$ , the above information leads to the CTMC
- iv) Thus, we infer the SDE from the similarities in the forward-backward-Kolmogorov equation between the discrete and Continuous Markov Chain

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## Example: Formulation of a stochastic SIS model

Consider the deterministic SI model:

$$\frac{dS}{dt} = -\frac{\beta}{N}SI + (b + \gamma)I$$

$$\frac{dI}{dt} = \frac{\beta}{N}SI - (b + \gamma)I$$

$$N = S(t) + I(t)$$

Where  $N$  is constant and  $S(t) = N - I(t)$ .

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Where  $N$  is constant and  $S(t) = N - I(t)$ .

$$\mathcal{R}_0 = \frac{\beta}{b + \gamma}$$

$$\mathcal{R}_0 \leq 1$$

$$\Rightarrow \lim_{t \rightarrow \infty} (S(t), I(t)) = (N, 0)$$

$$\mathcal{R}_0 > 1$$

$$\Rightarrow \lim_{t \rightarrow \infty} (S(t), I(t)) = (S^*, I^*)$$

## Example: Formulation of a stochastic SIS model

Consider the process  $\{\mathcal{I}_t\}_{t=0}^{\infty}$  with time discrete and space of states  $\{0, 1, \dots, N\}$ .

(H-1)

$$\begin{aligned} p_i(t) &:= \mathbb{P}[\mathcal{I}(t) = i] \\ i &= 0, 1, 2, \dots, N \\ t &= 0, \Delta t, 2\Delta t, \dots, \end{aligned}$$

(H-2) Markov property

$$\mathbb{P}[I_{t+\Delta t} | I_0, I_{\Delta t}, \dots, I_t] = \mathbb{P}[I_{t+\Delta t} | I_t]$$

(H-3) The unique transitions with positive probability

$$p_{ji}(t + \Delta t) = \mathbb{P}[I_{t+\Delta t} = j | I_t = i]$$

are

$$i \rightarrow i+1, i \rightarrow i-1, i \rightarrow i$$



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$$p_{ji}(\Delta t) := \begin{cases} \frac{\beta i(N-i)}{N} \Delta t, & j = i+1 \\ (b + \gamma) i \Delta t, & j = i-1 \\ 1 - \left[ \frac{\beta i(N-i)}{N} + (b + \gamma) i \right] \Delta t, & j = i, \\ 0 & \text{otherwise} \end{cases}$$

where  $\Delta t$  is sufficiently small s.t.

$$\max_{i \in \{1, \dots, N\}} \{[b(i) + d(i)]\Delta t\} \leq 1$$

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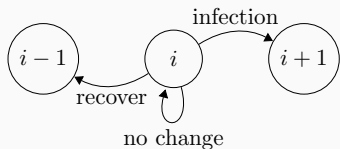
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FKE

$$\begin{aligned} p_i(t + \Delta t) = & p_{i-1}(t) b(i-1) \Delta t \\ & + p_{i+1}(t) d(i+1) \Delta t \\ & + p_i(t) (1 - [b(i) + d(i)] \Delta t) \end{aligned}$$



# Example: Formulation of a stochastic SIS model

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Thus  $P(\Delta t) =$

$$\begin{pmatrix} 1 & d(1)\Delta t & 0 & \dots & 0 & 0 \\ 0 & 1 - (b+d)(1)\Delta t & d(2)\Delta t & \dots & 0 & 0 \\ 0 & b(1)\Delta t & 1 - (b+d)(2)\Delta t & \dots & 0 & 0 \\ 0 & 0 & b(2)\Delta t & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & d(N-1)\Delta t & 0 \\ 0 & 0 & 0 & \dots & 1 - (b+d)(N-1)\Delta t & d(N)\Delta t \\ 0 & 0 & 0 & \dots & d(N-1)\Delta t & 1 - d(N)\Delta t \end{pmatrix}$$

$$p(t + \Delta t) = P(\Delta t)p(t) = P^{n+1}(\Delta t)p(0), \quad t = n\Delta t$$



# Expected Value of the SIS-DTMC

$$\mathbb{E}(I_{t+\Delta t}) = \sum_{i=0}^N i p_i(t + \Delta t)$$

$$\begin{aligned}\mathbb{E}(I_{t+\Delta t}) &= \sum_{i=0}^N ip_i(t + \Delta t) \\ &= \sum_{i=0}^N ip_{i-1}(t)b(i-1)\Delta t + \sum_{i=0}^{N-1} ip_{i+1}(t)d(i+1)\Delta t \\ &\quad + \sum_{i=0}^N ip_i(t)\Delta t - \sum_{i=0}^N ip_i(t)b(i)\Delta t - \sum_{i=0}^N ip_i(t)d(i)\Delta t\end{aligned}$$

$$\begin{aligned}
 \mathbb{E}(I_{t+\Delta t}) &= \sum_{i=0}^N ip_i(t + \Delta t) \\
 &= \sum_{i=0}^N ip_{i-1}(t)b(i-1)\Delta t + \sum_{i=0}^{N-1} ip_{i+1}(t)d(i+1)\Delta t \\
 &\quad + \sum_{i=0}^N ip_i(t)\Delta t - \sum_{i=0}^N ip_i(t)b(i)\Delta t - \sum_{i=0}^N ip_i(t)d(i)\Delta t \\
 \mathbb{E}(I_{t+\Delta t}) &= \mathbb{E}(I_t) + \sum_{i=1}^N p_{i-1}(t) \frac{\beta(i-1)(N-[i-1])}{N} \Delta t \\
 &\quad - \sum_{i=0}^{N-1} p_{i+1}(t)(b+\gamma)(i+1)\Delta t \\
 &= \mathbb{E}(I_t) + [\beta - (b+\gamma)]\Delta t \mathbb{E}(I_t) - \frac{\beta}{N} \Delta t \underbrace{\mathbb{E}(I_t^2)}_{\geq \mathbb{E}^2(I_t)}
 \end{aligned}$$

# Expected Value of the SIS-DTMC

$$\frac{\mathbb{E}(I_{t+\Delta t}) - \mathbb{E}(I_t)}{\Delta t} \leq [\beta - (b + \gamma)]\mathbb{E}(I_t) - \frac{\beta}{N}\mathbb{E}^2(I_t)$$

$$\frac{\mathbb{E}(I_{t+\Delta t}) - \mathbb{E}(I_t)}{\Delta t} \leq [\beta - (b + \gamma)]\mathbb{E}(I_t) - \frac{\beta}{N}\mathbb{E}^2(I_t)$$

$$\begin{aligned}\frac{d\mathbb{E}(I_t)}{dt} &\leq [\beta - (b + \gamma)]\mathbb{E}(I_t) - \frac{\beta}{N}\mathbb{E}^2(I_t) \\ &= \frac{\beta}{N}[N - \mathbb{E}(I_t)]\mathbb{E}(I_t) - (b + \gamma)\mathbb{E}(I_t)\end{aligned}$$

$$\frac{\mathbb{E}(I_{t+\Delta t}) - \mathbb{E}(I_t)}{\Delta t} \leq [\beta - (b + \gamma)]\mathbb{E}(I_t) - \frac{\beta}{N}\mathbb{E}^2(I_t)$$

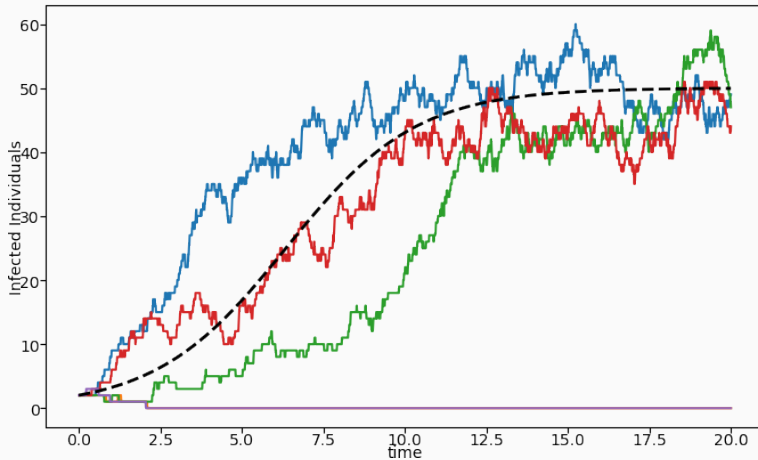
$$\begin{aligned}\frac{d\mathbb{E}(I_t)}{dt} &\leq [\beta - (b + \gamma)]\mathbb{E}(I_t) - \frac{\beta}{N}\mathbb{E}^2(I_t) \\ &= \frac{\beta}{N}[N - \mathbb{E}(I_t)]\mathbb{E}(I_t) - (b + \gamma)\mathbb{E}(I_t)\end{aligned}$$

$$\frac{d\mathbb{E}(I_t)}{dt} \leq \frac{\beta}{N}\mathbb{E}(S_t)\mathbb{E}(I_t) - (b + \gamma)\mathbb{E}(I_t)$$



# Example: Formulation of a stochastic SIS model

$N = 100$ ,  $\Delta t = 0.01$ ,  $\beta = 1$ ,  
 $b = 0.25$   $\gamma = 0.25$



$\mathcal{R}_0 = 2$ ,  
 $\bar{I} = 50$

Let  $\{I_t\}_{t \geq 0}, p_i(t) = \mathbb{P}[I_t = i]$ .

# Formulating a SIS-CTMC

Let  $\{I_t\}_{t \geq 0}, p_i(t) = \mathbb{P}[I_t = i]$ . Thus, the Markov property becomes in

$$\mathbb{P}[I_{t_{n+1}} | I_{t_0}, \dots, I_{t_n}] = \mathbb{P}[I_{t_{n+1}} | I_{t_n}]$$

for all  $t_0 < t_1 < \dots < t_n$

Let  $\{I_t\}_{t \geq 0}$ ,  $p_i(t) = \mathbb{P}[I_t = i]$ . Thus, the Markov property becomes in

$$\mathbb{P}[I_{t_{n+1}} | I_{t_0}, \dots, I_{t_n}] = \mathbb{P}[I_{t_{n+1}} | I_{t_n}]$$

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$$p_{ji}(\Delta t) := \begin{cases} \frac{\beta i(N-i)}{N} \Delta t + o(\Delta t), & j = i+1 \\ (b + \gamma)i \Delta t + o(\Delta t), & j = i-1 \\ 1 - \left[ \frac{\beta i(N-i)}{N} + (b + \gamma)i \right] \Delta t + o(\Delta t), & j = i \\ o(\Delta t) & \text{otherwise} \end{cases}$$

$$\lim_{t \rightarrow \infty} \frac{o(\Delta t)}{\Delta t} = 0$$

Using the notation for birth and death processes, we have

$$p_{ij}(\Delta t) := \begin{cases} b(i)\Delta t + o(\Delta t), & j = i + 1 \\ d(i)\Delta t + o(\Delta t), & j = i - 1 \\ 1 - [b(i) + d(i)]\Delta t + o(\Delta t), & j = i \\ 0 & \text{otherwise.} \end{cases}$$

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$$\mathbb{P}[I_0 = i_0] = 1,$$

$$\begin{aligned} p_i(t + \Delta t) = & p_{i-1}(t)b(i-1)\Delta t \\ & + p_{i+1}(t)d(i+1)\Delta t \\ & + p_i(t)[1 - (b(i) + d(i))]\Delta t + o(\Delta t) \\ & i = 1, 2, \dots, N \end{aligned}$$

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Thus

$$\begin{aligned} \frac{p_i(t + \Delta t) - p_i(t)}{\Delta t} = & p_{i-1}(t)b(i-1) + p_{i+1}(t)d(i+1) \\ & - p_i[t(b(i) + d(i))] + o(\Delta t) \\ & i = 1, 2, \dots, N. \end{aligned}$$

Hence, letting  $\Delta t \rightarrow 0$ , we obtain

$$\begin{aligned}\frac{dp_i(t)}{dt} &= p_{i-1}(t)b(i-1) + p_{i+1}(t)d(i+1) \\ &\quad - p_i[b(i) + d(i)] \\ i &= 1, 2, \dots, N.\end{aligned}$$



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$$Q = \begin{pmatrix} 0 & d(1) & 0 & \dots & 0 \\ 0 & -[b(1) + d(1)] & d(2) & \dots & 0 \\ 0 & b(1) & -[b(2) + d(2)] & \dots & 0 \\ 0 & 0 & b(2) & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & d(N) \\ 0 & 0 & 0 & \dots & -d(N) \end{pmatrix}$$

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Results that

$$\lim_{t \rightarrow \infty} p(t) = (1, 0, \dots, 0)^T$$

and

$$Q = \lim_{\Delta t \rightarrow 0} \frac{P(\Delta t) - I}{\Delta t}$$

# Expected value of the SIS-CTMC

Consider the m.g.f

$$\begin{aligned} M(\theta, t) &:= \mathbb{E}[\exp(\theta I_t)] \\ &= \sum_{i=0}^N p_i(t) \exp(i\theta) \end{aligned}$$

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Now we deduce a differential equation for the moments of our sis-CTMC.

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from r.h.s of FKE

$$\begin{aligned} &= \exp(\theta) \sum_{i=0}^N p_{i-1} \exp[(i-1)\theta] b(i-1) \\ &\quad + \exp(-\theta) \sum_{i=0}^N p_{i+1} \exp[(i+1)\theta] d(i+1) \\ &\quad - \sum_{i=0}^N p_i \exp(i\theta) (b(i) + d(i)) \end{aligned}$$



Substituting definition of  $b, d$  we obtain

$$\begin{aligned}\frac{\partial M}{\partial t} = & \beta(\exp(\theta) - 1) \sum_{i=1}^N ip_i \exp(i\theta) \\ & + (b + \gamma)(\exp(-\theta) - 1) \sum_{i=1}^N ip_i \exp(i\theta) \\ & - \frac{\beta}{N}(\exp(\theta) - 1) \sum_{i=1}^N i^2 p_i \exp(i\theta)\end{aligned}$$

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Following [Bailey, 1964] we can deduce from the above equation

$$\frac{d\mathbb{E}(I_t)}{dt} = [\beta - (b + \gamma)]\mathbb{E}(I_t) - \frac{\beta}{N}\mathbb{E}(I_t^2).$$

Then we conclude as in the SIS-DTMC.

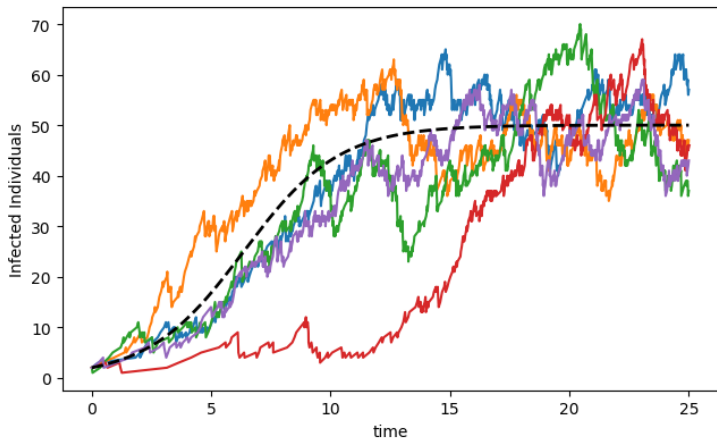


Bailey, N. T. J. (1964).

***The elements of stochastic processes with applications to the natural sciences.***

John Wiley & Sons, Inc., New York-London-Sydney.

## Using the Gillespie algorithm



Now, consider  $\{I_t\}_{t \geq 0}$ .

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# Formulating a SIS-SDE

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$$\mathbb{P}[I_{t_n} \leq y | I_{t_0}, \dots, I_{t_{n-1}}] = \mathbb{P}[I_{t_n} \leq y | I_{t_{n-1}}]$$

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Denote the transition p.d.f as

$$p(y, t + \Delta t; x, t)$$
$$y = I_{t+\Delta t}, \quad x = I_t$$

Set  $\Delta i = 1$ , then

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$$\begin{aligned}\frac{dp_i}{dt} &= p_{i-1}b(i-1) + p_{i+1}d(i+1) - p_i[b(i) + d(i)] \\ &= -\frac{p_{i+1}[d(i+1) - d(i+1)] - p_{i-1}[d(i-1) - d(i-1)]}{2\Delta i} \\ &\quad + \frac{1}{2} \frac{p_{i+1}[d(i+1) + d(i+1)] - 2p_i[b(i) + d(i)] + p_{i-1}[d(i-1) + d(i-1)]}{(\Delta i)^2}\end{aligned}$$

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$$\begin{aligned}\frac{\partial p(x, t)}{\partial t} &= \frac{\partial}{\partial x} \{ [b(x) - d(x)] p(x, t) \} + \frac{1}{2} \frac{\partial^2}{\partial t^2} \{ b(x) + d(x) p(x, t) \} \\ &= \frac{\partial}{\partial x} \left\{ \left[ \frac{\beta}{N} x(N-x) - (b + \gamma)x \right] p(x, t) \right\} \\ &\quad + \frac{1}{2} \frac{\partial^2}{\partial x^2} \left\{ \left[ \frac{\beta}{N} x(N-x) + (\beta + \gamma)x \right] p(x, t) \right\}\end{aligned}$$

## Using the SIS-CTMC probability transition kernel

$$p_{ji}(\Delta t) := \begin{cases} \frac{\beta i(N-i)}{N} \Delta t + o(\Delta t), & j = i + 1 \\ (b + \gamma) i \Delta t + o(\Delta t), & j = i - 1 \\ 1 - \left[ \frac{\beta i(N-i)}{N} + (b + \gamma) i \right] \Delta t + o(\Delta t), & j = i \\ o(\Delta t) & \text{otherwise.} \end{cases}$$



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Results that increment

$$\Delta I = I_{t+\Delta t} - I_t$$

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Fix time  $t$  s.t  $I_t = i$

$$\begin{aligned} \mathbb{E} \Delta I &= b(I_t) \Delta t - d(I_t) \Delta t + o(\Delta t) \\ &= \underbrace{[b(I)_t - d(I_t)]}_{:= \mu(I_t)} + o(\Delta t) \end{aligned}$$

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Thus

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$$\begin{aligned}l_{t+\Delta t} &= l_t + \Delta l_t \\ &\approx l_t + \mu(l_t)\Delta t + \sigma(l_t)\sqrt{\Delta t}\eta \\ \eta &\sim \mathcal{N}(0, 1)\end{aligned}$$

The Euler-Maruyama's recurrence equation.

Further, because under this setting, the Euler-Maruyama converge.

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Sustituting, the notation for birth and death processes

$$dl_t = \frac{\beta}{N} l_t (N - l_t) - (b + \gamma) l_t + \sqrt{\frac{\beta}{N} l_t (N - l_t) + (b + \gamma) l_t} dW_t.$$

