University of Nottingham
UK | CHINA | MALAYSIA

Stochastic Averaging for a Two-Strain Model of Infectious Disease Epidemiology

James Daniel Harborne

Supervisors: John R King, Wasiur R Khuda-Bukhsh

Presentation Overview

- Project Overview
- Preliminaries
- Two-Strain Epidemic Model
- Stochastic Averaging
- Future Work

Project Overview

Motivation

Mathematical modelling techniques allow us to build flexible representations of various physical and biological phenomena

Many real-world systems feature some element of randomness, so use of stochastic models can help to better represent this

Models may have a large number of dimensions; model reduction techniques allow us to significantly simplify complex systems.

Project Overview

Aims and objectives

- Build a model representing a disease with multiple strains (or multiple diseases in the same population)
- Apply the Stochastic Averaging Principle to obtain a reduced model
- Verify that the models agree in the large-number limit

Presentation Overview

Project Overview

Preliminaries

Two-Strain Epidemic Model

Stochastic Averaging

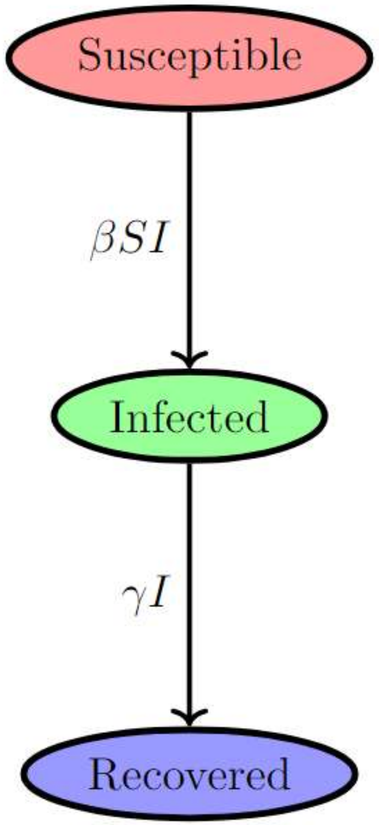
Future Work

Preliminaries

How to build a mathematical model

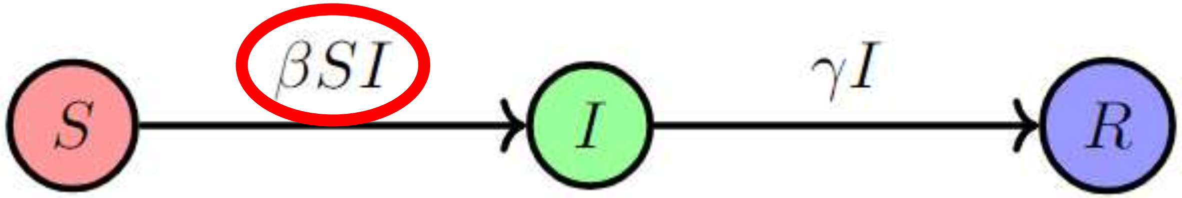
Kermack-McKendrick SIR Model:

- **S**usceptible individuals can become infected through interaction with an infected individual at rate β
- **I**nfected individuals have the disease and recover after a period of infection at rate γ
- **R**ecovered individuals can no longer be infected



Preliminaries

How to build a mathematical model



Ordinary Differential Equations (ODEs):

- ODEs are a key tool for mathematical modelling
- We use them to describe dynamical systems (evolving in time)
- ODEs are deterministic

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

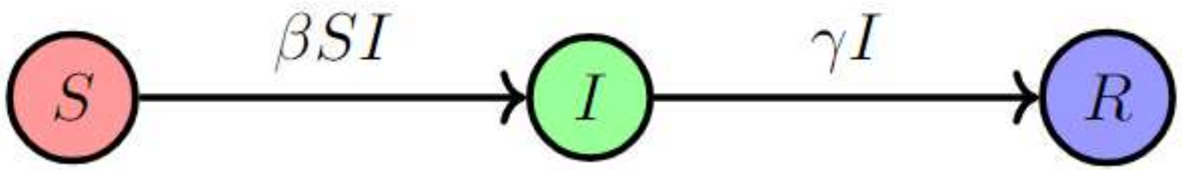
$$\frac{dR}{dt} = \gamma I$$

Preliminaries

How to build a mathematical model

Ordinary Differential Equations (ODEs):

- ODEs are a key tool for mathematical modelling
- We use them to describe dynamical systems (evolving in time)
- ODEs are deterministic



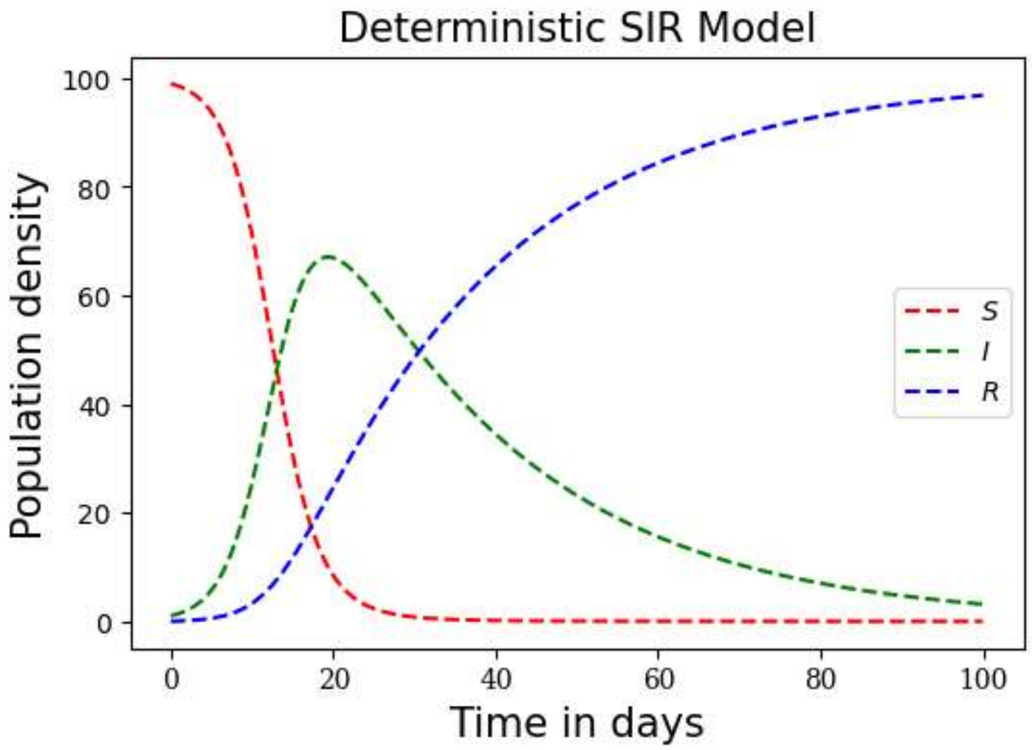
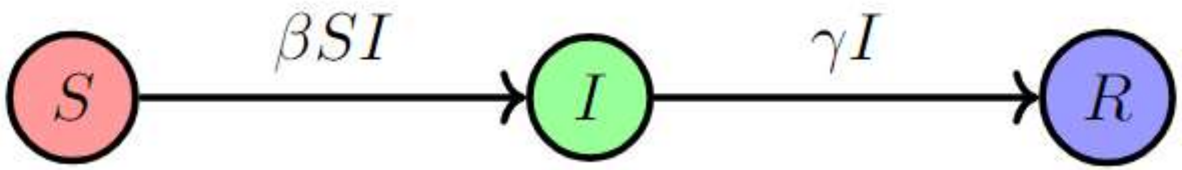


Figure 1: A plot of the solutions to the SIR ODE model. Parameter values used are β=0.4, γ=0.04, S(0)=97, I(0)=3, R(0)=0.

Preliminaries

How to build a mathematical model



Continuous Time Markov Chains (CTMC):

- CTMCs are one way of accounting for randomness
- They describe processes that change according to some probability
- CTMCs are stochastic

State Vector:

$$X = (S, I, R)$$

Intensity Functions:

$$\lambda_{(-1,1,0)}(X) = \frac{\beta SI}{N}$$

$$\lambda_{(0,-1,1)}(X) = \gamma I$$

Generator Equation:

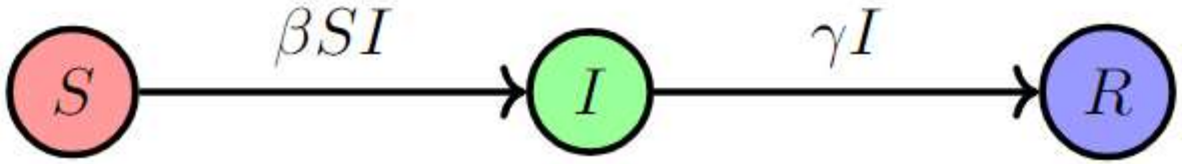
$$\mathcal{G}_n f(X) = \lambda_{(-1,1,0)}(X)\Big(f(X - e_1 + e_2)\Big) + \lambda_{(0,-1,1)}(X)\Big(f(X - e_2 + e_3)\Big)$$

Preliminaries

How to build a mathematical model

Continuous Time Markov Chains (CTMC):

- CTMCs are one way of accounting for randomness
- They describe processes that change according to some probability
- CTMCs are stochastic



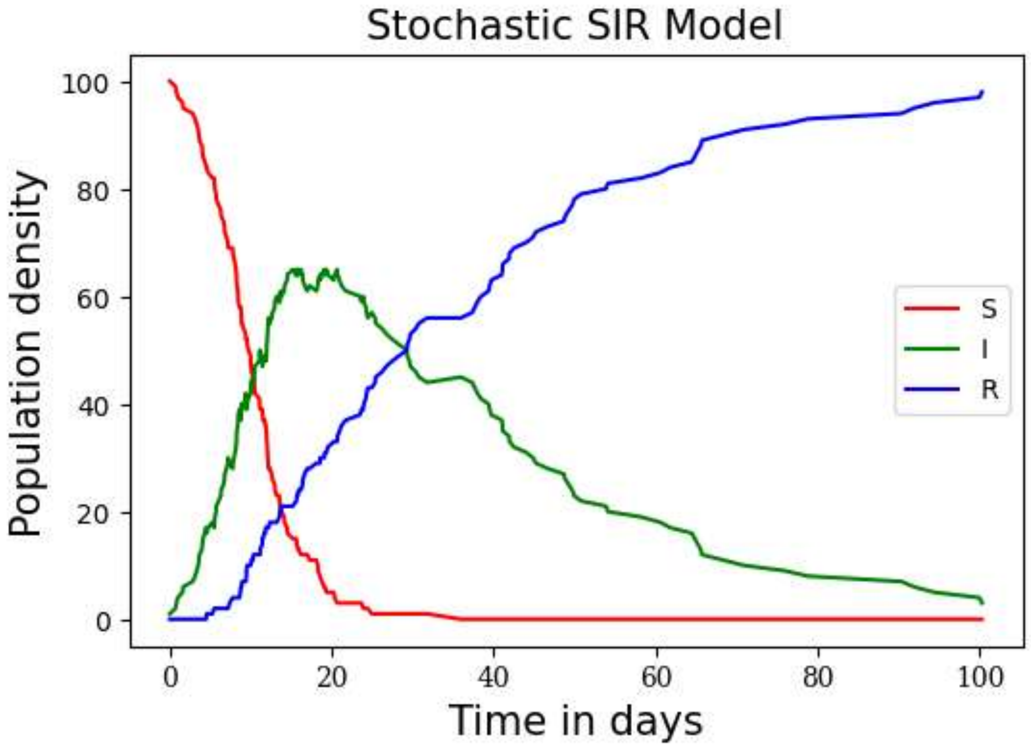


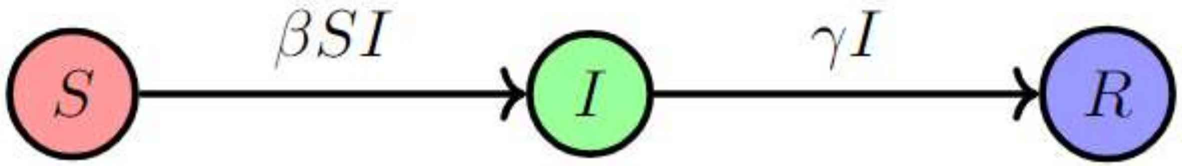
Figure 2: A plot of a single realisation of the SIR CTMC model. Parameter values used are $\beta=0.4$, $\gamma=0.04$, $S(0)=97$, $I(0)=3$, $R(0)=0$.

Preliminaries

How to build a mathematical model

Convergence:

- If our two models fulfil certain criteria, then we have that the stochastic model converges to the deterministic model as the system size becomes large



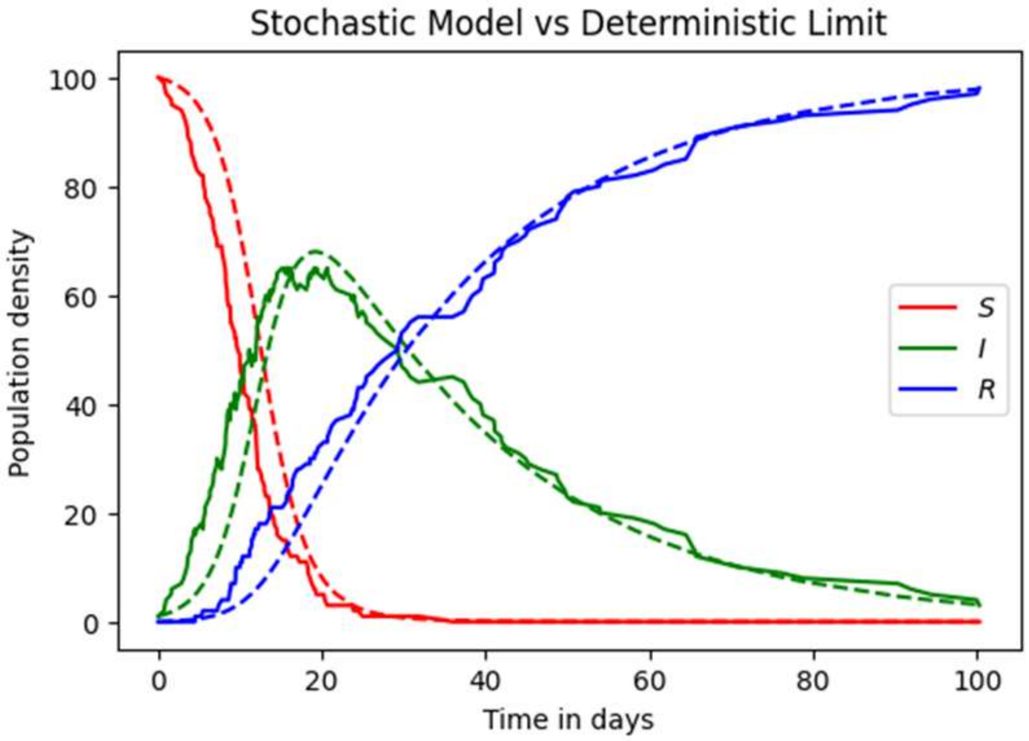
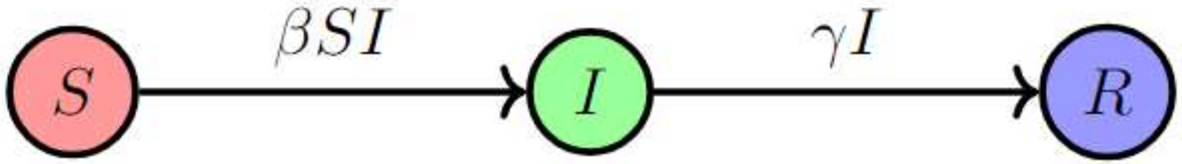


Figure 3: A plot comparing the solutions of the deterministic and stochastic SIR models. Parameter values used are N=100, β=0.4, γ=0.04, S(0)=97, I(0)=3, R(0)=0.

Preliminaries

How to build a mathematical model



Convergence:

- If our two models fulfil certain criteria, then we have that the stochastic model converges to the deterministic model as the system size becomes large

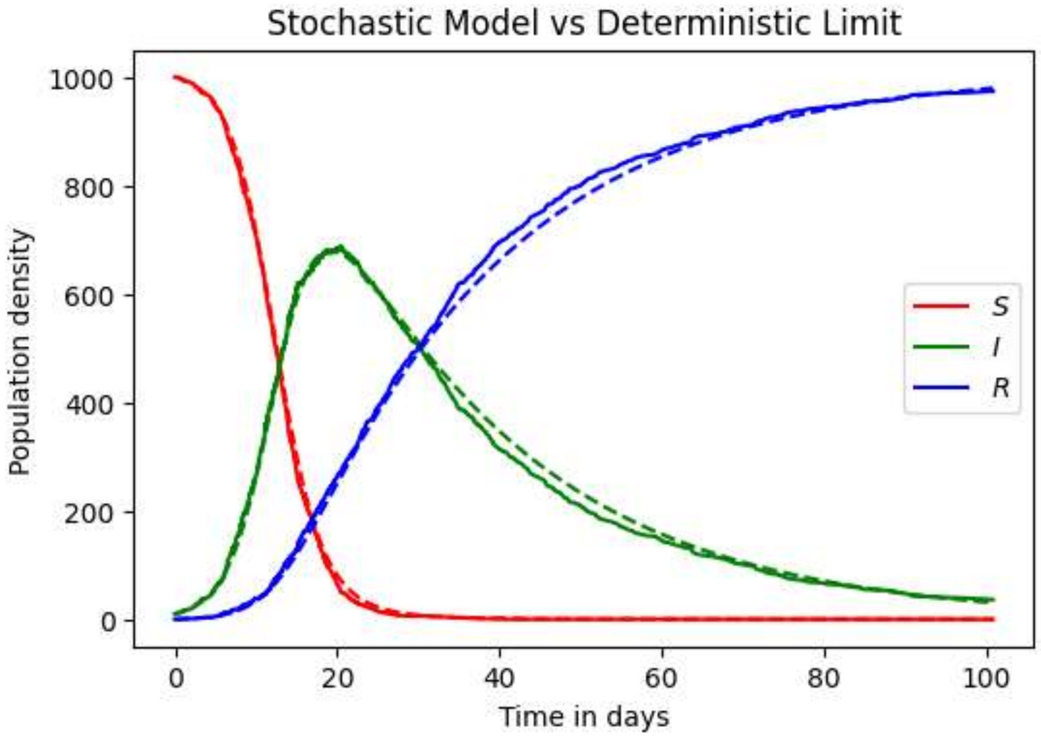


Figure 4: A plot comparing the solutions of the deterministic and stochastic SIR models. Parameter values used are N=1000, β=0.4, γ=0.04, S(0)=97, I(0)=3, R(0)=0.

Presentation Overview

Project Overview

Preliminaries

Two-Strain Epidemic Model

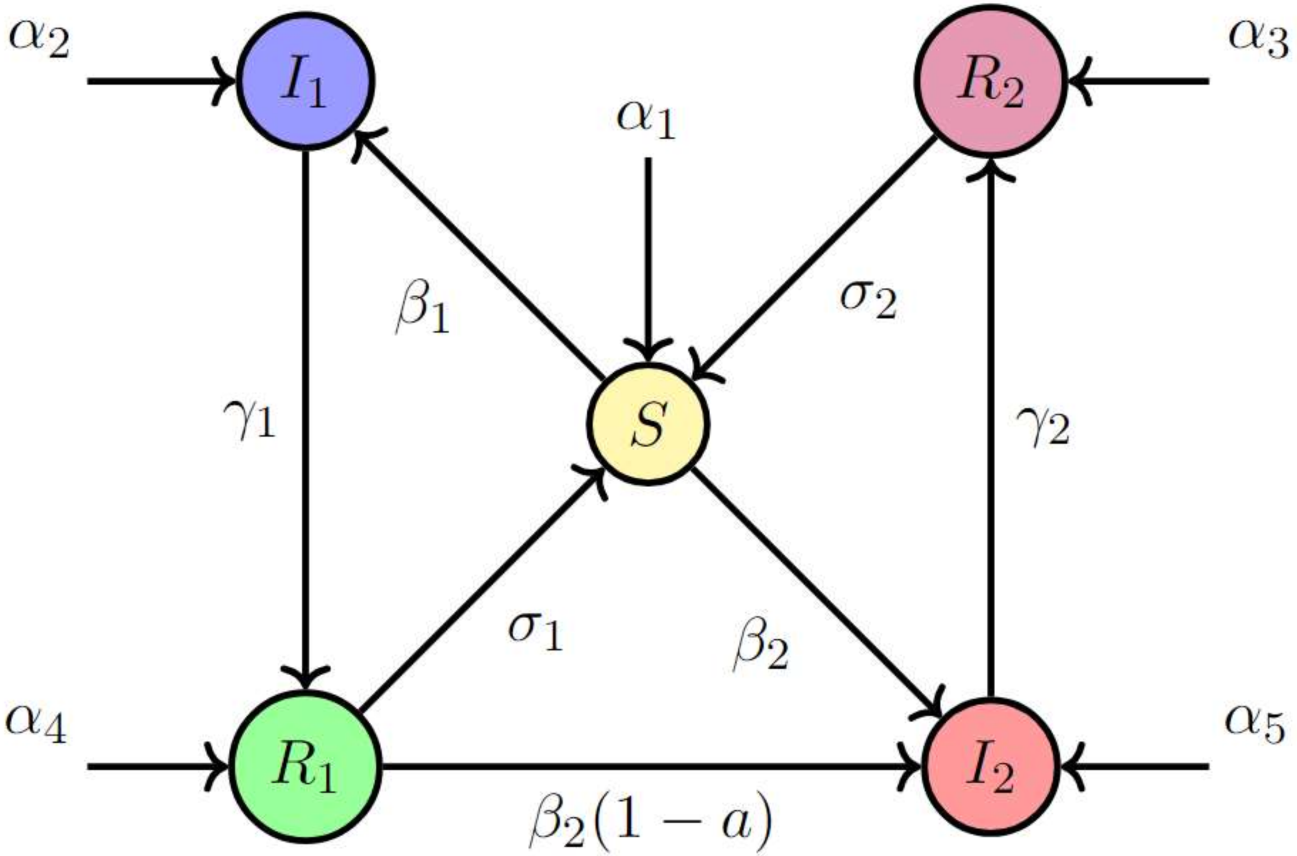
Stochastic Averaging

Future Work

Two-Strain Epidemic Model

Two-Strain Model

- We have two strains of a disease, 1 and 2
- There is a common pool of susceptible individuals
- We assume no co-infection
- We have partial cross-immunity

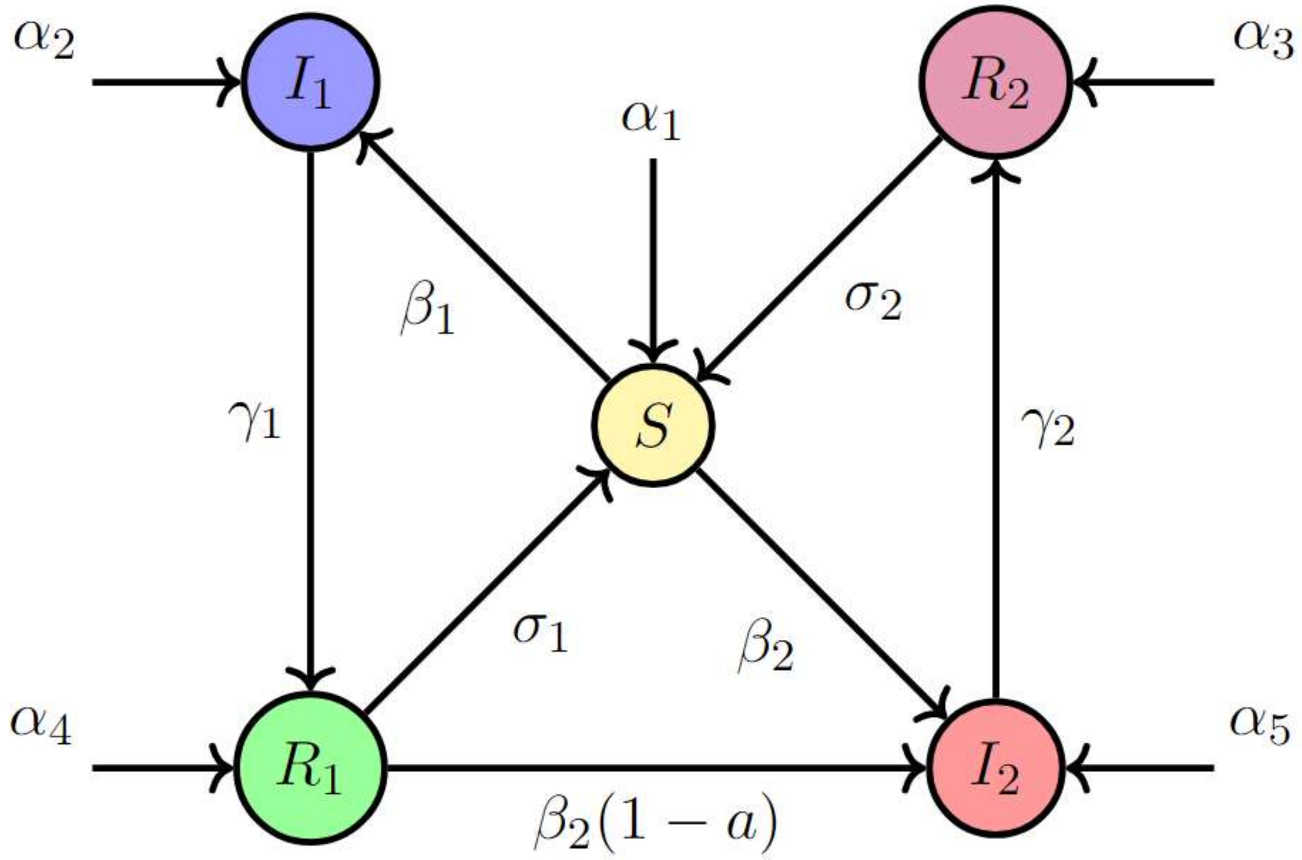


Two-Strain Epidemic Model

Possible Applications

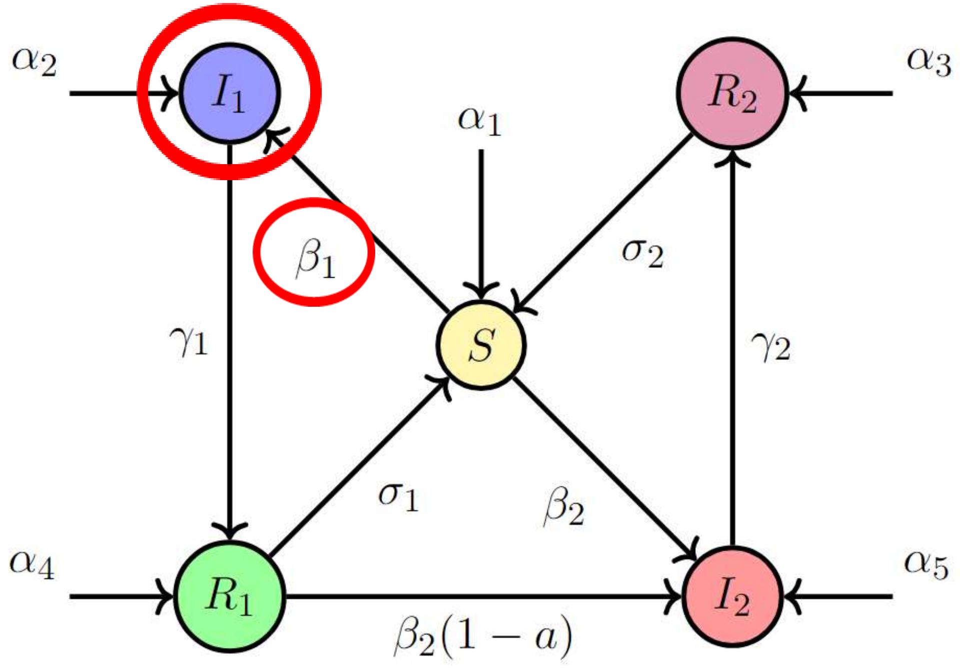
- Models of this type originated from the study of influenza, bacterial infections and parasites

- More recent examples include the emergence of disease variants, such as the Delta and Omicron strains of COVID-19



Two-Strain Epidemic Model

Two-Strain ODE Model



$$\frac{dS}{dt} = \alpha_1 - \beta_1 S I_1 - \beta_2 S I_2 + \sigma_1 R_1 + \sigma_2 R_2$$

$$\frac{dI_1}{dt} = \alpha_2 + \beta_1 S I_1 - \gamma_1 I_1$$

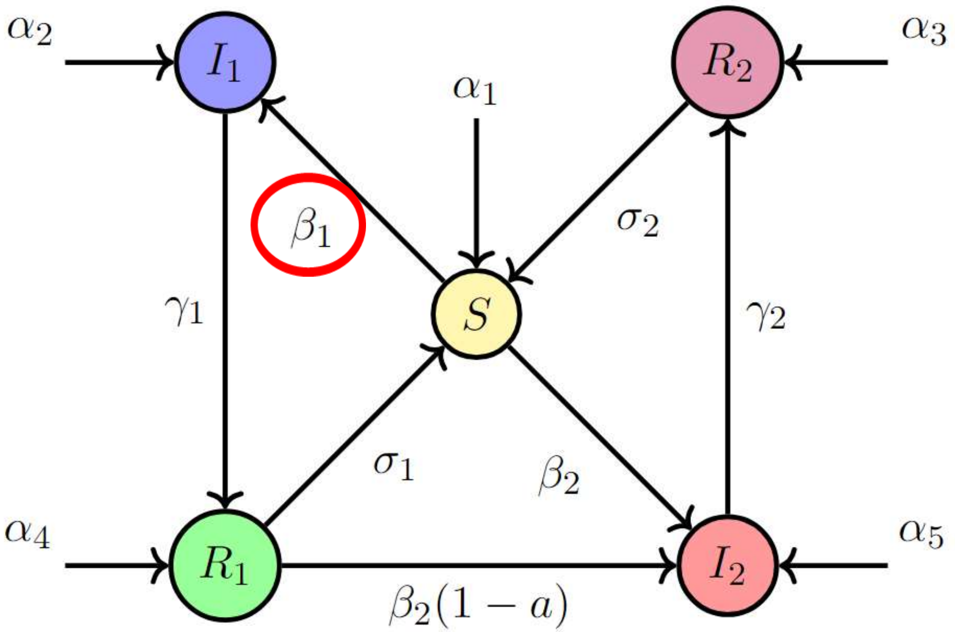
$$\frac{dR_1}{dt} = \alpha_3 + \gamma_1 I_1 - \sigma_1 R_1 - \beta_2 (1-a) R_1 I_2$$

$$\frac{dI_2}{dt} = \alpha_4 + \beta_2 S I_2 - \gamma_2 I_2 + \beta_2 (1-a) R_1 I_2$$

$$\frac{dR_2}{dt} = \alpha_5 + \gamma_2 I_2 - \sigma_2 R_2$$

Two-Strain Epidemic Model

Two-Strain CTMC Model



State Vector:

$$X^{(n)}(t) = \left(X_S^{(n)}(t), X_{I_1}^{(n)}(t), X_{R_1}^{(n)}(t), X_{I_2}^{(n)}(t), X_{R_2}^{(n)}(t)\right)$$

Intensity Functions:

$$\lambda_1^{(n)}(x) = \beta_1^{(n)} x_S x_{I_1}, \quad \lambda_2^{(n)}(x) = \gamma_1^{(n)} x_{I_1}, \quad \lambda_3^{(n)}(x) = \sigma_1^{(n)} x_{R_1},$$
$$\lambda_4^{(n)}(x) = \beta_2^{(n)} x_S x_{I_2}, \quad \lambda_5^{(n)}(x) = \gamma_2^{(n)} x_{I_2}, \quad \lambda_6^{(n)}(x) = \sigma_2^{(n)} x_{R_2},$$
$$\lambda_7^{(n)}(x) = \beta_2^{(n)}(1-a) x_{R_1} x_{I_2},$$

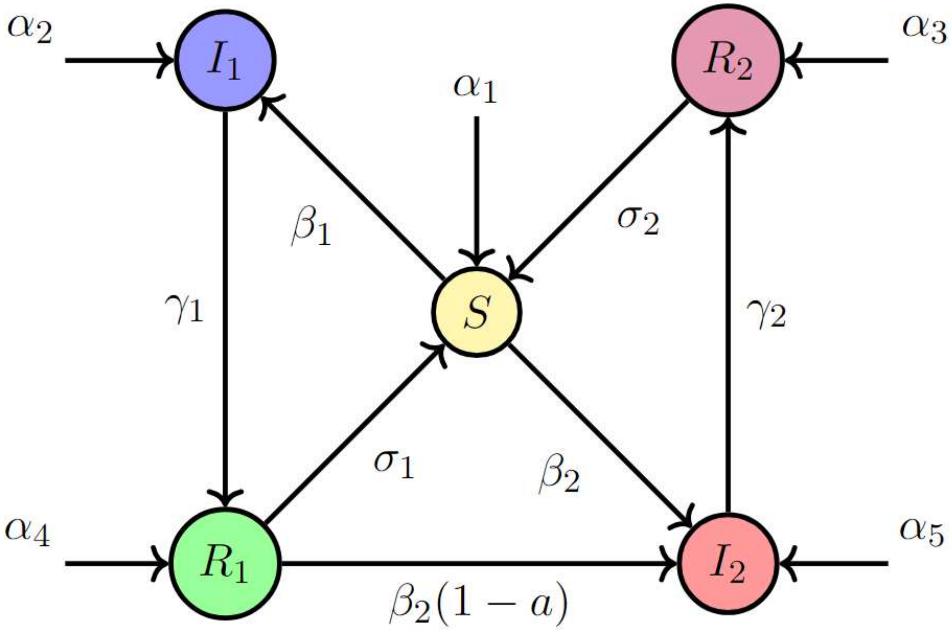
$$\lambda_8^{(n)}(x) = \alpha_1^{(n)}, \quad \lambda_9^{(n)}(x) = \alpha_2^{(n)}, \quad \lambda_{10}^{(n)}(x) = \alpha_3^{(n)}, \quad \lambda_{11}^{(n)}(x) = \alpha_4^{(n)}, \quad \lambda_{12}^{(n)}(x) = \alpha_5^{(n)},$$

Generator Equation:

$$\begin{aligned}\mathcal{G}_n f(x) = {} & \lambda_1^{(n)}(x)\Big(f(x-e_1+e_2) - f(x)\Big) + \lambda_2^{(n)}(x)\Big(f(x-e_2+e_3) - f(x)\Big) + \lambda_3^{(n)}(x)\Big(f(x-e_3+e_1) - f(x)\Big) \\ & + \lambda_4^{(n)}(x)\Big(f(x-e_1+e_4) - f(x)\Big) + \lambda_5^{(n)}(x)\Big(f(x-e_4+e_5) - f(x)\Big) + \lambda_6^{(n)}(x)\Big(f(x-e_5+e_1) - f(x)\Big) \\ & + \lambda_7^{(n)}(x)\Big(f(x-e_3+e_4) - f(x)\Big) + \lambda_8^{(n)}(x)\Big(f(x+e_1) - f(x)\Big) + \lambda_9^{(n)}(x)\Big(f(x+e_2) - f(x)\Big) \\ & + \lambda_{10}^{(n)}(x)\Big(f(x+e_3) - f(x)\Big) + \lambda_{11}^{(n)}(x)\Big(f(x+e_4) - f(x)\Big) + \lambda_{12}^{(n)}(x)\Big(f(x+e_5) - f(x)\Big)\end{aligned}$$

Two-Strain Epidemic Model

Convergence



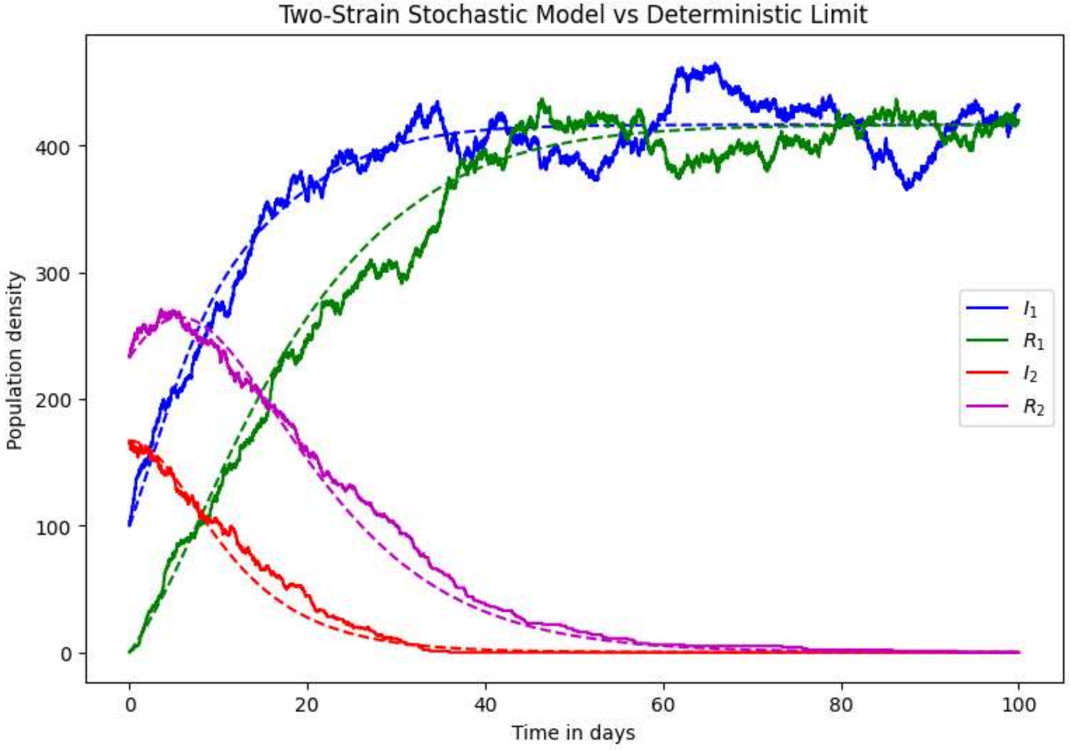
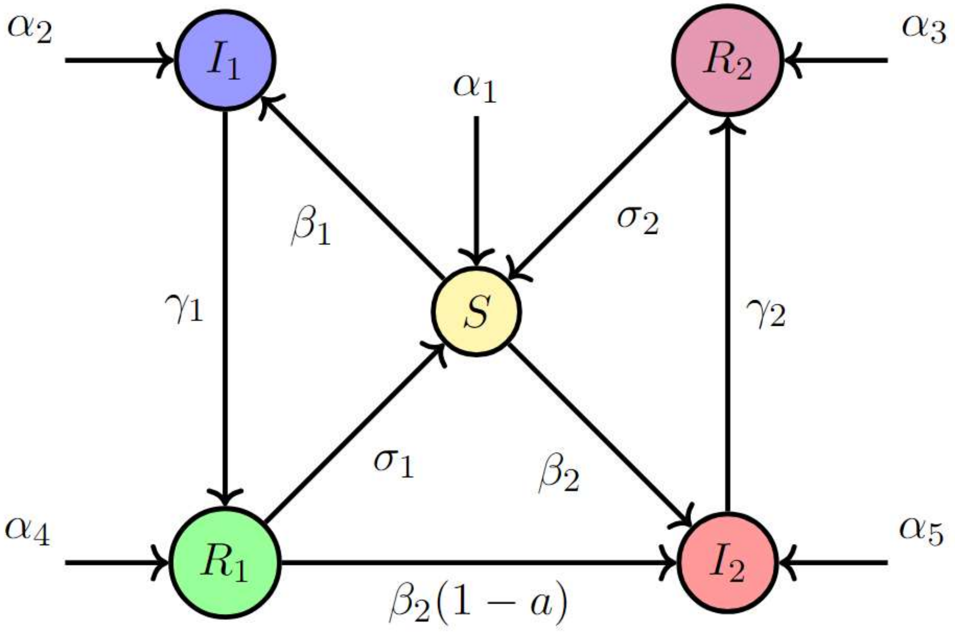


Figure 5: A plot comparing the solutions of the deterministic (dashed) and stochastic (solid) two-strain models. Parameter values used are $N = 1000,\ \beta_1 = 0.6,\ \beta_2 = 0.4,\ \gamma_1 = 0.1,\ \gamma_2 = 0.2,\ \sigma_1 = 0.1,\ \sigma_2 = 0.1$.

Two-Strain Epidemic Model

Convergence



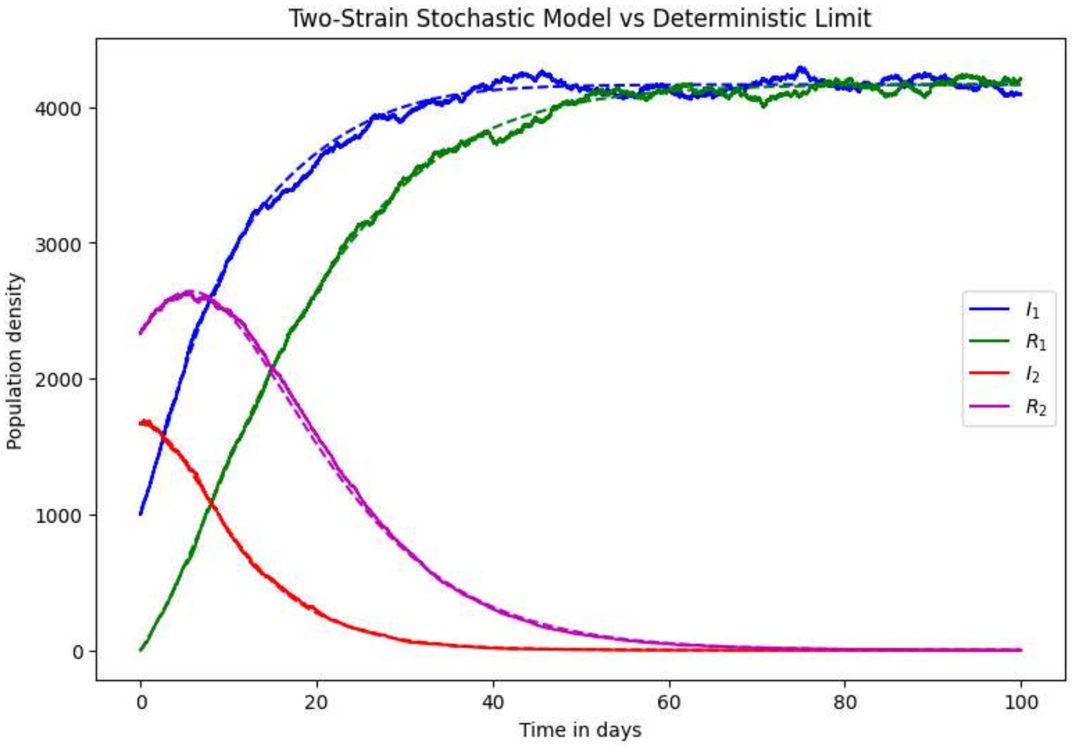


Figure 6: A plot comparing the solutions of the deterministic (dashed) and stochastic (solid) two-strain models. Parameter values used are $N = 10000,\ \beta_1 = 0.6,\ \beta_2 = 0.4,\ \gamma_1 = 0.1,\ \gamma_2 = 0.2,\ \sigma_1 = 0.1,\ \sigma_2 = 0.1$.

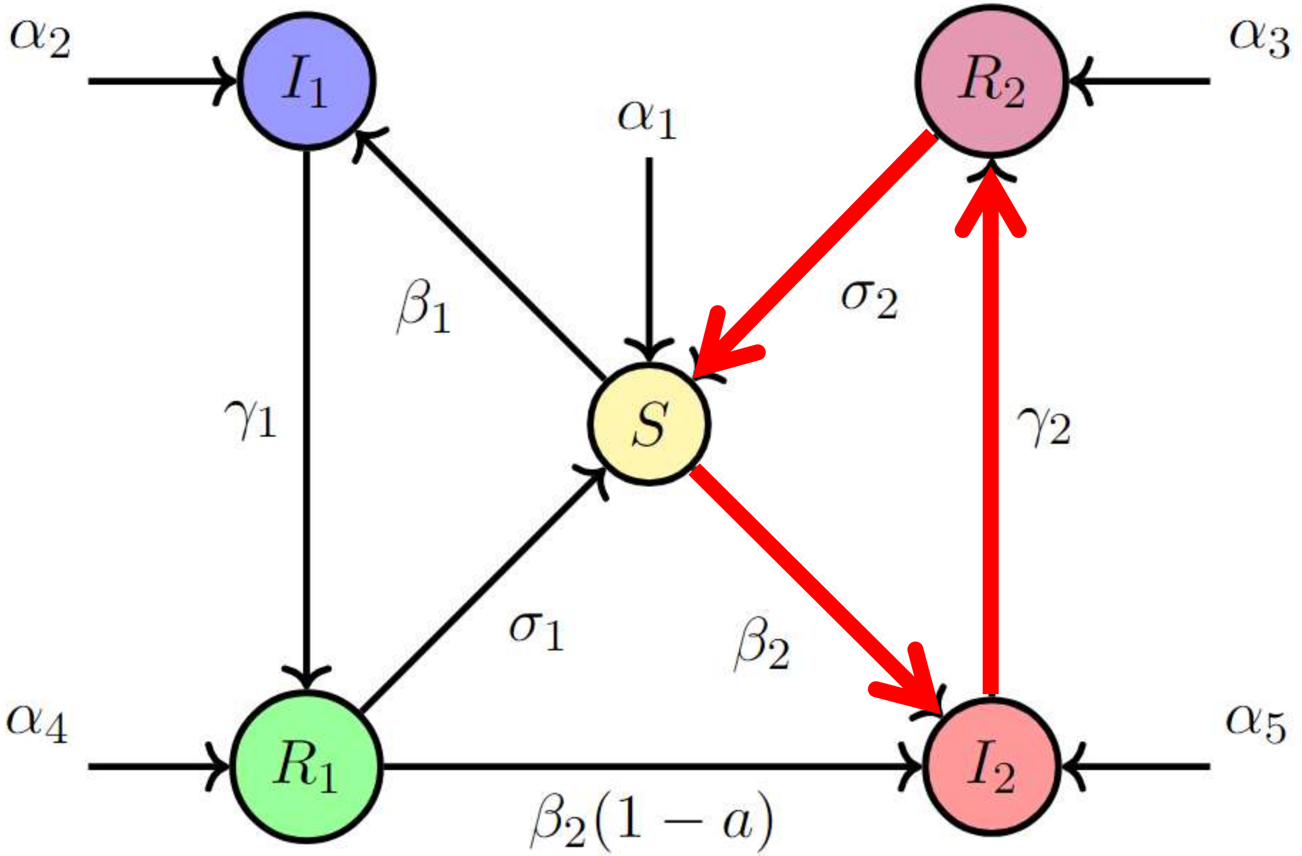
Presentation Overview

- Project Overview
- Preliminaries
- Two-Strain Epidemic Model
- Stochastic Averaging
- Future Work

Stochastic Averaging

Multiscale Problem

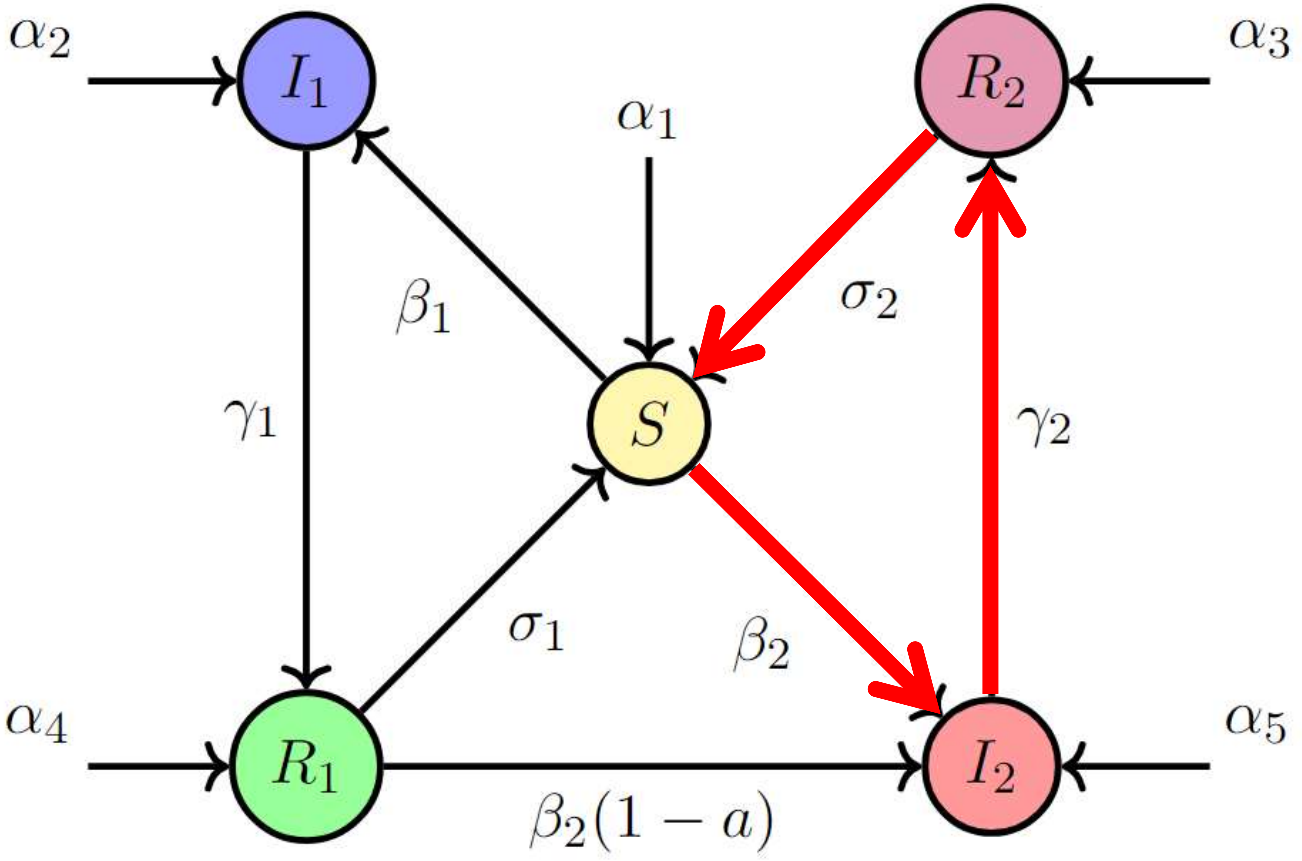
- We are interested in a scenario where the rates of infection and recovery of one strain are much faster than the other
- This assumption will allow us to apply the **stochastic averaging principle** to derive a reduced model



Stochastic Averaging

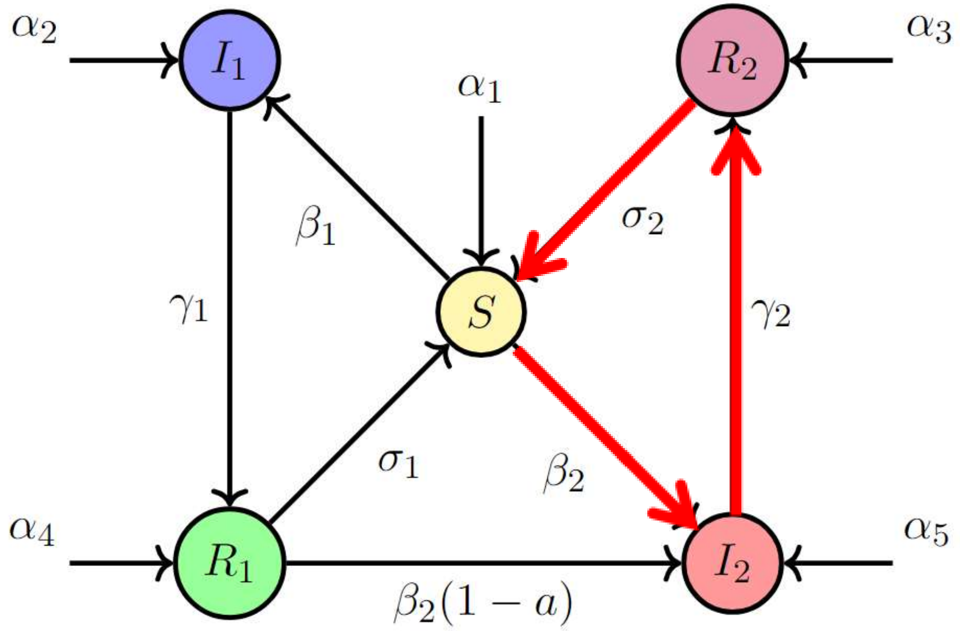
Possible Applications

- Two-strain model of tuberculosis
- Vector-borne illnesses and STDs
- Cancer therapy
- Strain-specific vaccination



Stochastic Averaging

Averaging Principle



Let T=[0,∞). We want to pick a parameter regime in which the rates of infection and recovery of the second strain are exponentially faster than those of the first strain. To achieve this, we pick the following parameter scalings

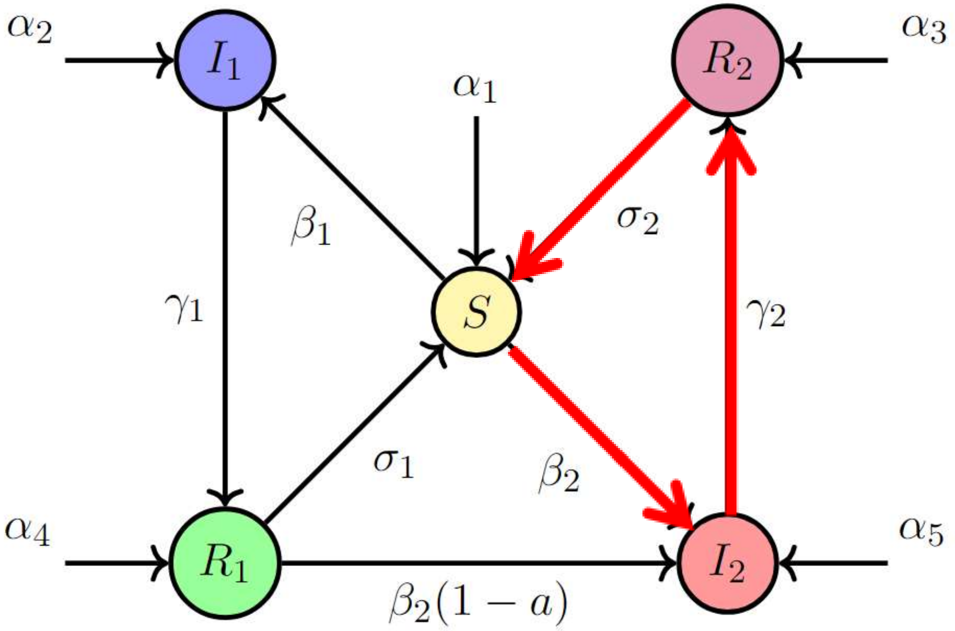
$$\beta_1^{(n)} = n^{-1}\beta_1, \quad \gamma_1^{(n)} = \gamma_1, \quad \sigma_1^{(n)} = \sigma_1,$$

$$\beta_2^{(n)} = \beta_2, \quad \gamma_2^{(n)} = n\gamma_1, \quad \sigma_2^{(n)} = n\sigma_2,$$

$$\alpha_i^n = n\alpha_i, \quad i \in \{1,2,3,4,5\}.$$

Stochastic Averaging

Averaging Principle



We then define the scaled process

$$Y^{(n)} = (Y_S^{(n)}, Y_{I_1}^{(n)}, Y_{R_2}^{(n)}, Y_{I_2}^{(n)}, Y_{R_2}^{(n)}) = (\frac{1}{n}X_S^{(n)}, \frac{1}{n}X_{I_1}^{(n)}, \frac{1}{n}X_{R_2}^{(n)}, X_{I_2}^{(n)}, X_{R_2}^{(n)}).$$

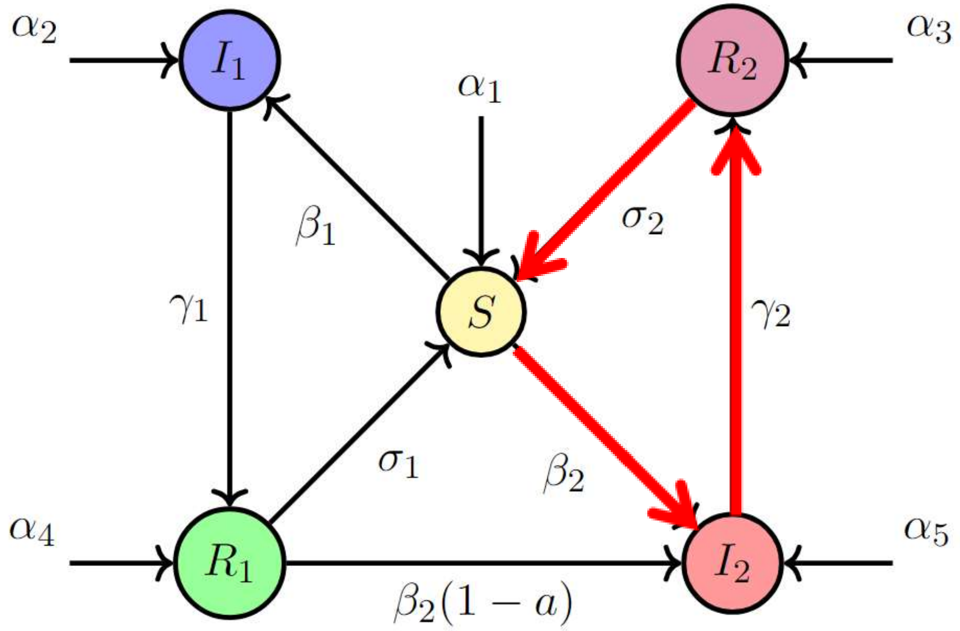
With intensity functions

$$\lambda_1(y) = \beta_1 y_S y_{I_1}, \quad \lambda_2(y) = \gamma_1 y_{I_1}, \quad \lambda_3(y) = \sigma_1 y_{R_1},$$
$$\lambda_4(y) = \beta_2 y_S y_{I_2}, \quad \lambda_5(y) = \gamma_2 y_{I_2}, \quad \lambda_6(y) = \sigma_2 y_{R_2},$$
$$\lambda_7(y) = \beta_2(1-a) y_{R_1} y_{I_2},$$

$$\lambda_8(y) = \alpha_1, \quad \lambda_9(y) = \alpha_2, \quad \lambda_{10}(y) = \alpha_3, \quad \lambda_{11}(y) = \alpha_4, \quad \lambda_{12}(y) = \alpha_5,$$

Stochastic Averaging

Averaging Principle



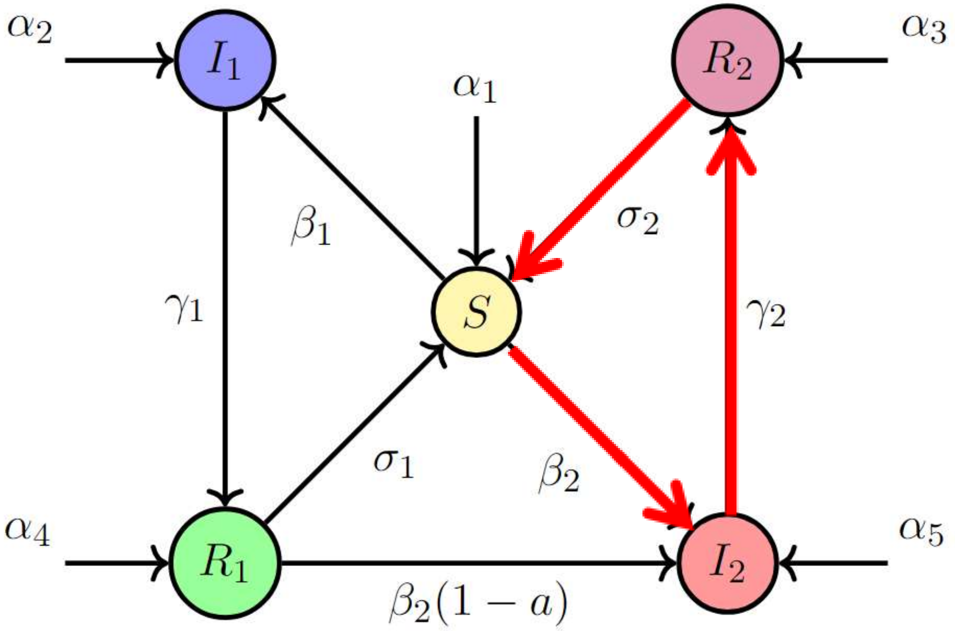
The process is then a CTMC with generator

$$\begin{aligned}\mathcal{L}_n f(y) = {} & n\lambda_1(y)\Big(f(y - \tfrac{1}{n}e_1 + \tfrac{1}{n}e_2) - f(y)\Big) + n\lambda_2(y)\Big(f(y - \tfrac{1}{n}e_2 + \tfrac{1}{n}e_3) - f(y)\Big) \\ & + n\lambda_3(y)\Big(f(y - \tfrac{1}{n}e_3 + \tfrac{1}{n}e_1) - f(y)\Big) + n\lambda_4(y)\Big(f(y - \tfrac{1}{n}e_1 + e_4) - f(y)\Big) \\ & + n\lambda_5(y)\Big(f(y - e_4 + e_5) - f(y)\Big) + n\lambda_6(y)\Big(f(y - e_5 + \tfrac{1}{n}e_1) - f(y)\Big) \\ & + n\lambda_7(y)\Big(f(y - \tfrac{1}{n}e_3 + e_4) - f(y)\Big) + n\lambda_8(y)\Big(f(y + \tfrac{1}{n}e_1) - f(y)\Big) \\ & + n\lambda_9(y)\Big(f(y + \tfrac{1}{n}e_2) - f(y)\Big) + n\lambda_{10}(y)\Big(f(y + \tfrac{1}{n}e_3) - f(y)\Big) \\ & + n\lambda_{11}(y)\Big(f(y + e_4) - f(y)\Big) + n\lambda_{12}(y)\Big(f(y + e_5) - f(y)\Big),\end{aligned}$$

for bounded, continuous functions $f\colon \mathbb{R}_+^3 \times \mathbb{N}^2 \to \mathbb{R}$ and $y = (y_S, y_{I_1}, y_{R_1}, y_{I_2}, y_{R_2}) \in \mathbb{R}_+^3 \times \mathbb{N}^2$

Stochastic Averaging

Averaging Principle



The form of the generator $\mathcal{L}_n$ shows that the infected and recovered variables for the second strain jump rapidly, while those of the first strain have approximately deterministic dynamics, according to the *average* dynamics of the second strain as $n \to \infty$.

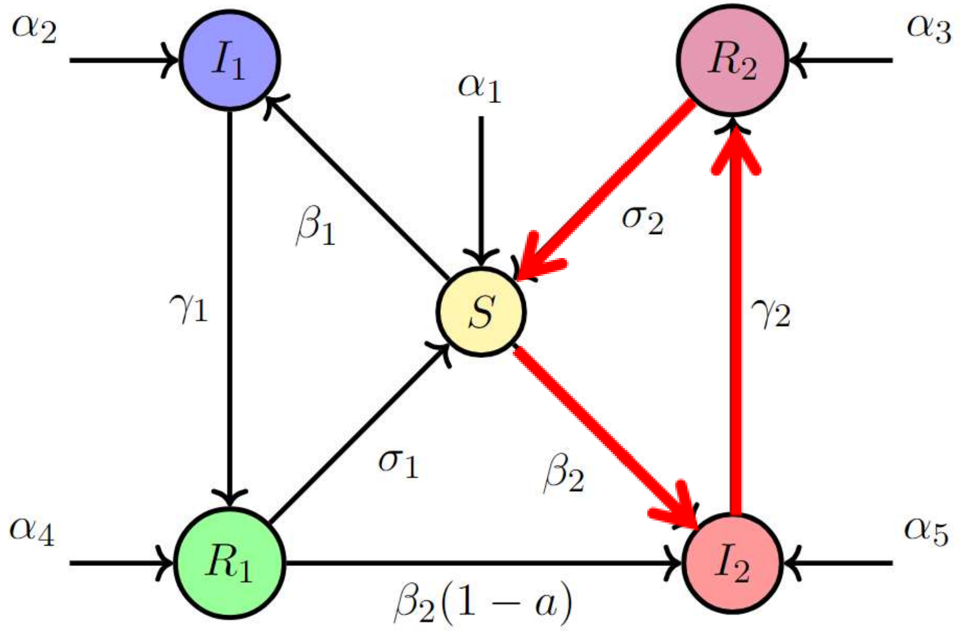
Therefore, we define a linear operator to describe the fast process

$$\begin{aligned} A_v g(z) = &(\beta_2 y_S) z_1 \big(g(z+e_1) - g(z)\big) + \gamma_2 z_1 \big(g(z-e_1+e_2) - g(z)\big) \\ &+ \sigma_2 z_2 \big(g(y-e_2) - g(z)\big) + (\beta_2(1-a) y_{R_1}) z_1 \big(g(z+e_2) - g(z)\big) \\ &+ \alpha_4 \big(g(z+e_1) - g(z)\big) + \alpha_5 \big(g(z+e_2) - g(z)\big) \end{aligned}$$

for fixed $v = (y_S, y_{I_1}, y_{R_1})$ and for bounded $g\colon \mathbb{N}^2 \to \mathbb{R}$.

Stochastic Averaging

Averaging Principle



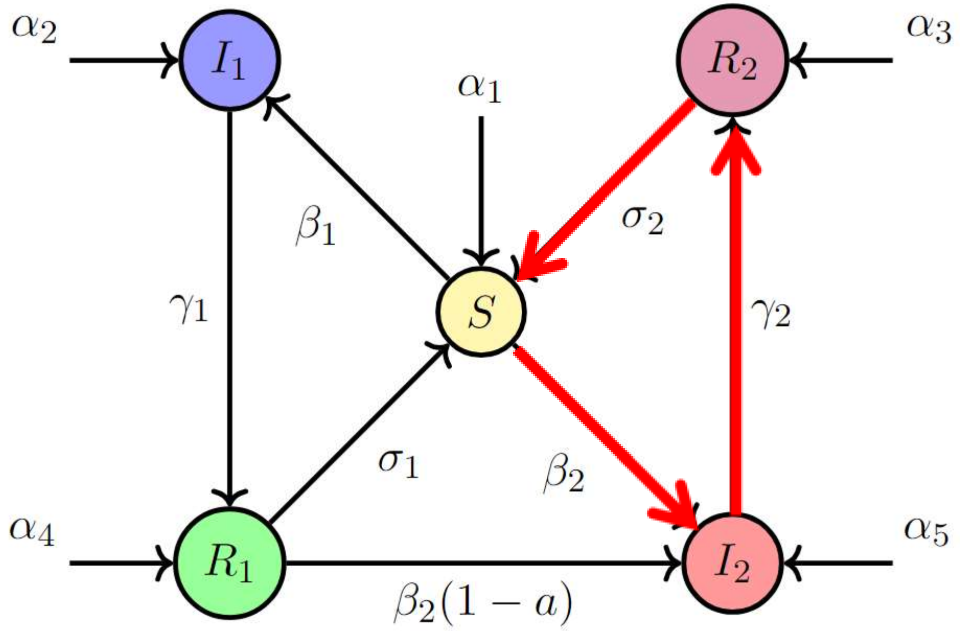
This operator generates an ergodic Markov process, particularly a birth-death process which, for any $v \in \mathbb{R}^3$, admits a unique stationary distribution $\pi_v(z)$.

Therefore, we expect the slower process $\left(Y_S^{(n)}, Y_{I_1}^{(n)}, Y_{R_1}^{(n)}\right)$ to converge to the deterministic $\left(y_S, y_{I_1}, y_{R_1}\right)$ as $n \to \infty$. That is

$$\left(\frac{1}{n}X_S, \frac{1}{n}X_{I_1}, \frac{1}{n}X_{R_1}\right) \Longrightarrow (y_S, y_{I_1}, y_{R_1})$$

Stochastic Averaging

Averaging Principle



Here, (y_S, y_{I_1}, y_{R_1}) is the solution to the following system of Ordinary Differential Equations (ODEs)

$$\frac{dy_S}{dt} = \alpha_1 - \beta_1 y_S y_{I_1} - \beta_2 \overline{y}_{I_2} y_S + \sigma_1 y_{R_1} + \sigma_2 \overline{y}_{R_2}$$

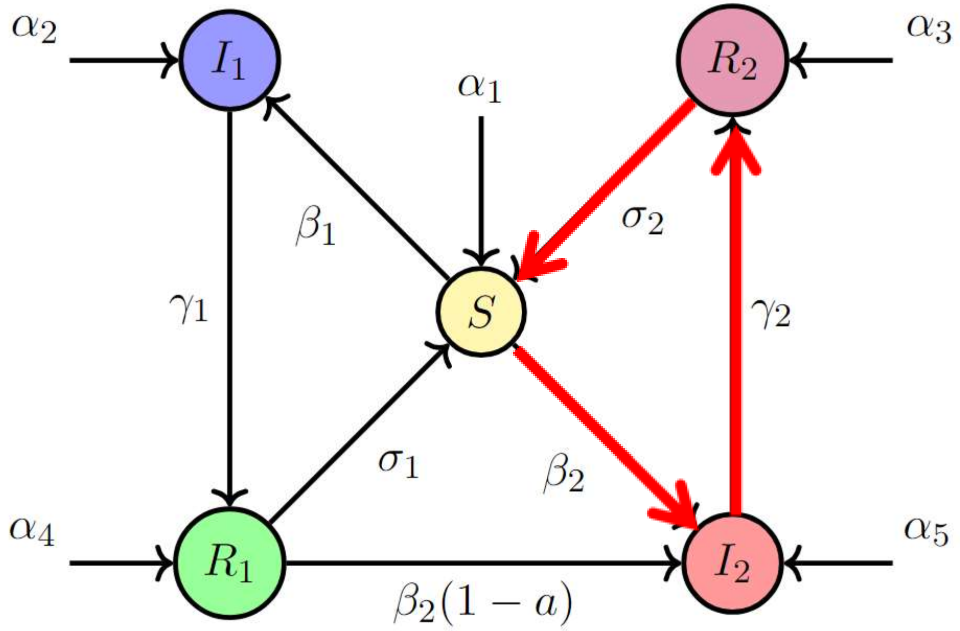
$$\frac{dy_{I_1}}{dt} = \alpha_2 + \beta_1 y_S y_{I_1} - \gamma_1 y_{I_1}$$

$$\frac{dy_{R_1}}{dt} = \alpha_3 + \gamma_1 y_{R_1} - \beta_2(1-a)\overline{y}_{I_2} y_{R_1}$$

Where the $\bar{y}_{I_2}$ and $\bar{y}_{R_2}$ are determined by the averaged values of the fast process.

Stochastic Averaging

Simulations



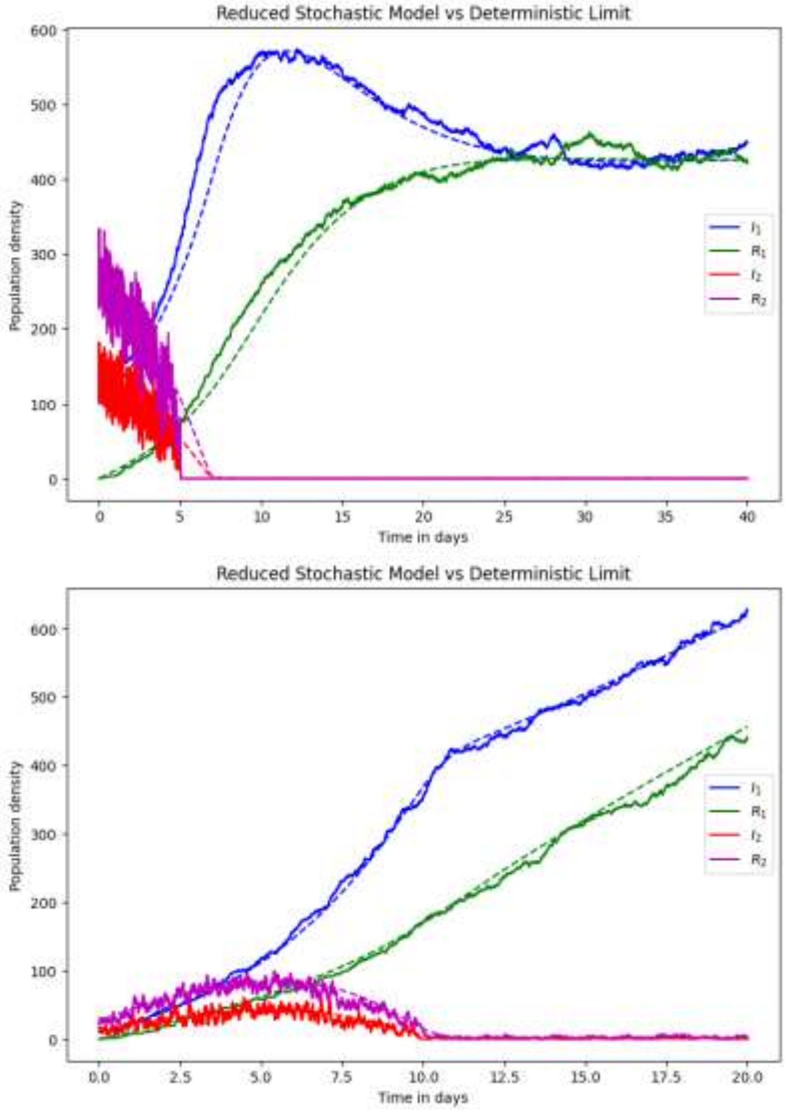
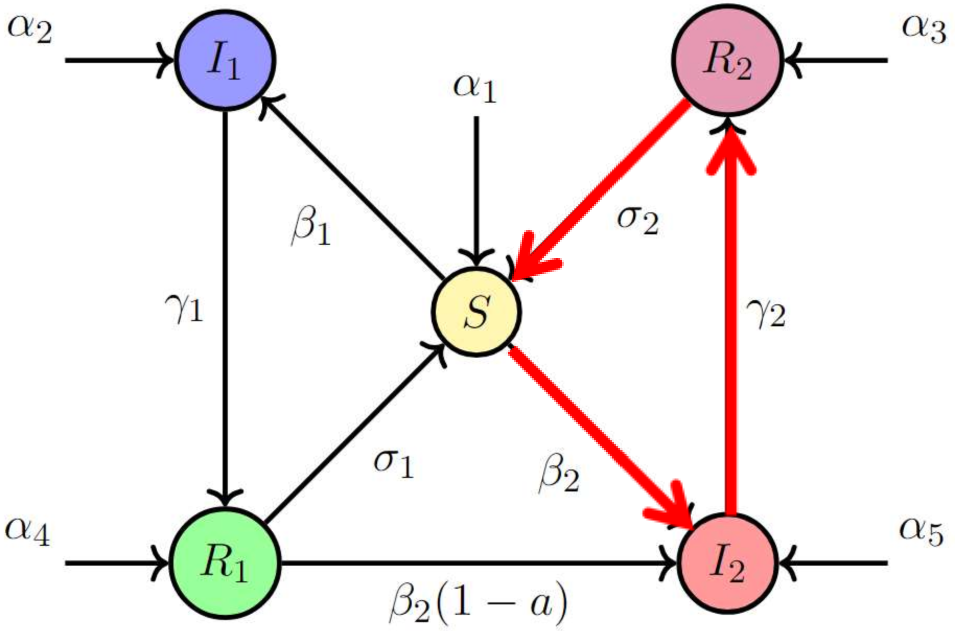


Figure 7: Comparisons of the solutions of the deterministic (dashed) and stochastic (solid) reduced two-strain models. Parameter values used are $N = 1000,\ \beta_1 = 0.6,\ \beta_2 = 0.4,\ \gamma_1 = 0.1,\ \gamma_2 = 0.2,\ \sigma_1 = 0.1,\ \sigma_2 = 0.1$, and $\alpha_i = 0$ for each $i = 1,2,3,4,5$ (upper plot), $\alpha_i = 0.1$ for each $i = 1,2,3,4,5$ (lower plot).

Simulations



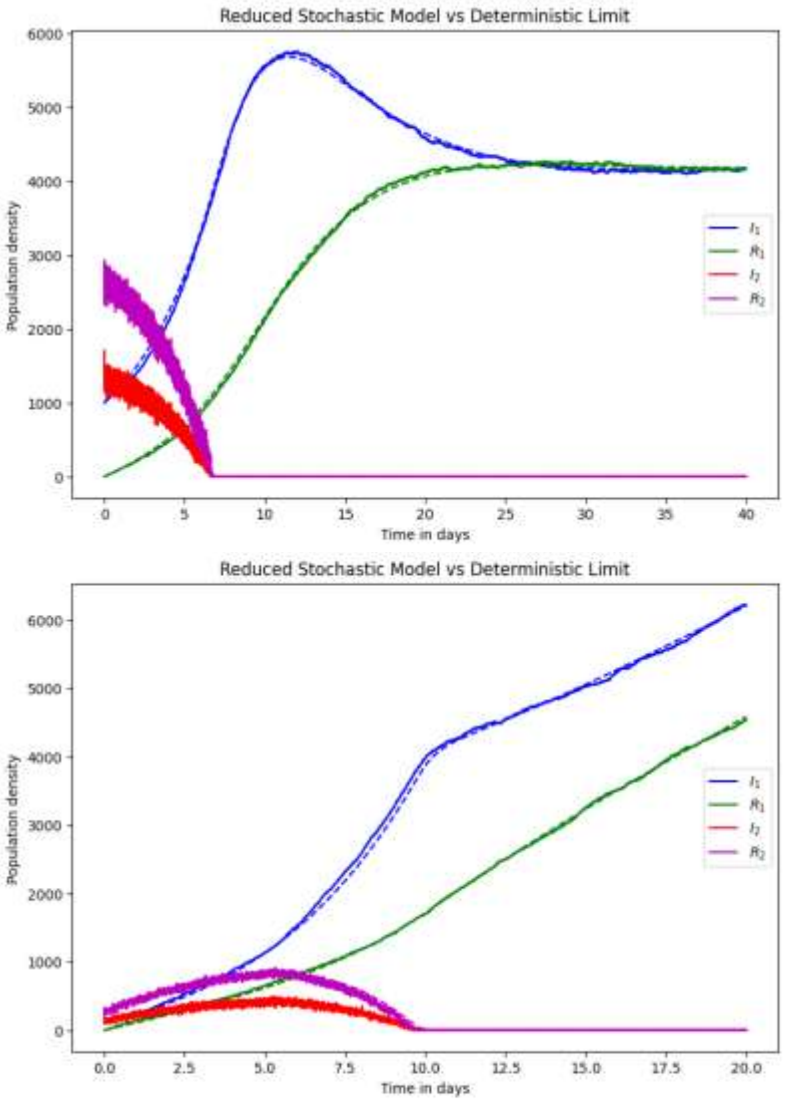


Figure 8: Comparisons of the solutions of the deterministic (dashed) and stochastic (solid) reduced two-strain models. Parameter values used are $N = 10000$, $\beta_1 = 0.6$, $\beta_2 = 0.4$, $\gamma_1 = 0.1$, $\gamma_2 = 0.2$, $\sigma_1 = 0.1$, $\sigma_2 = 0.1$, and $\alpha_i = 0$ for each $i = 1,2,3,4,5$ (upper plot), $\alpha_i = 0.1$ for each $i = 1,2,3,4,5$ (lower plot).

Presentation Overview

Project Overview

Preliminaries

Two-Strain Epidemic Model

Stochastic Averaging

Future Work

Future Plans

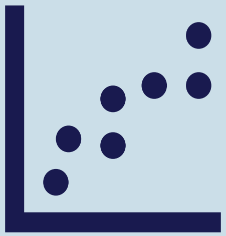
Short Term

Publish

Submit the work outlined in this presentation to an appropriate journal

Medium Term

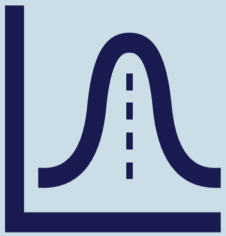
FCLN



We can quantify the fluctuations of the reduced model using a functional central limit theorem

Long Term

Large Deviations



We want to investigate the application of large deviations theory to our models

Final Notes

Acknowledgements

My Supervisors:

- John King
- Wasiur Khuda-Bukhsh

PowerPoint Consultant:

- Victoria Hann

References

- A Contribution to the Mathematical Theory of Epidemics | Proceedings of the Royal Society of London. Series A, Containing Papers of a Mathematical and Physical Character'. Accessed 29 September 2024. https://royalsocietypublishing.org/doi/10.1098/rspa.1927.0118.
- Anderson, David F., and Thomas G. Kurtz. 'Continuous Time Markov Chain Models for Chemical Reaction Networks'. In *Design and Analysis of Biomolecular Circuits*, edited by Heinz Koeppl, Gianluca Setti, Mario Di Bernardo, and Douglas Densmore, 3–42. New York, NY: Springer New York, 2011. https://doi.org/10.1007/978-1-4419-6766-4_1.
- Gillespie, Daniel T. 'Exact Stochastic Simulation of Coupled Chemical Reactions'. *The Journal of Physical Chemistry* 81, no. 25 (1 December 1977): 2340–61. https://doi.org/10.1021/j100540a008.
- Johnston, Matthew D., Bruce Pell, David A. Rubel, Matthew D. Johnston, Bruce Pell, and David A. Rubel. 'A Two-Strain Model of Infectious Disease Spread with Asymmetric Temporary Immunity Periods and Partial Cross-Immunity'. *Mathematical Biosciences and Engineering* 20, no. 9 (2023): 16083–113. https://doi.org/10.3934/mbe.2023718.
- Kang, Hye-Won, Wasiur R. KhudaBukhsh, Heinz Koeppl, and Grzegorz A. Rempała. 'Quasi-Steady-State Approximations Derived from the Stochastic Model of Enzyme Kinetics'. *Bulletin of Mathematical Biology* 81, no. 5 (1 May 2019): 1303–36. https://doi.org/10.1007/s11538-019-00574-4.
- Kurtz, Thomas. 'Averaging for Martingale Problems and Stochastic Approximation', 177:186–209, 2006. https://doi.org/10.1007/BFb0007058.

University of Nottingham
UK | CHINA | MALAYSIA

Thank you for listening

Questions?

Email: dan.harborne@nottingham.ac.uk