Stochastic Multistrain Dengue Modeling

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Abstract

We proposed and analize a full multistrain Stochastic model for studying Dengue Dynamics. The model is presented both as a Continuous-time markov process and as a set of It stochastic differential equations. Sugestions of how to explore the dynamics numerically is also provided, along with source code examples.

Introduction

Dengue fever is a arthropod-borne viral disease which causes between 50 and 100 million cases annualy around the world.

Dengue is caused by a flavivirus of which 5 different strains have been identified so far. These strains are distinguished by their antigenicity and are thus referred to as serotypes. Most epidemics around the globe are caused by a combination of the first four serotypes, DENV-1, DENV-2, DENV-3 and DENV-4.

The dengue viruses provide long-lasting immunity which is restricted to the particular serotype the individual has been exposed to, with the display of a partial immunity to the other types (cross-immunity).

Multi-strain dynamics

In this paper we propose a stochastic 4-serotype SIR model with cross-immunity to describe multi-strain Dengue dynamics. The model allows for up to 4 dengue infections of the same individual with reduction of susceptibility, denoted by δ, after the first Dengue episode due to cross immunity. Immunity to each serotype is considered complete and permanent. Figure 1 depicts all 48 possible states and 64 state-transitions included in the model.

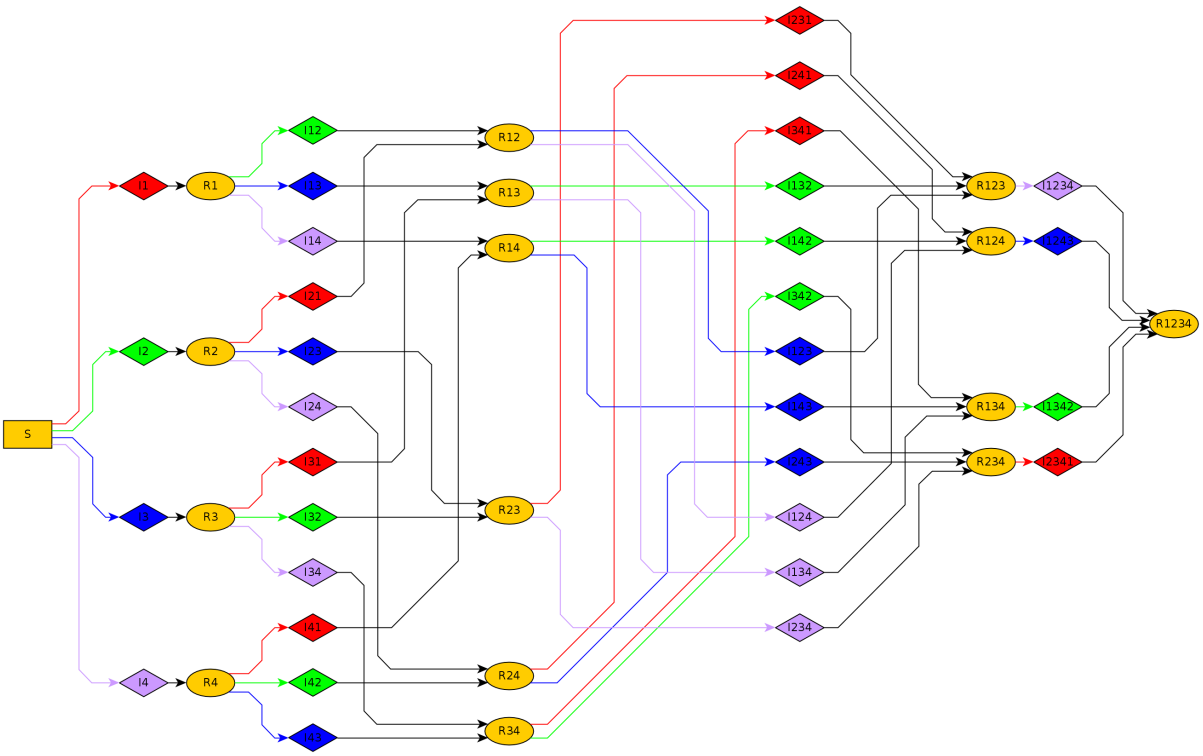

Figure 1: **Block diagram detailing the stochastic model.** Infected individuals with different Dengue viruses are represented by different colors. Infections are also represented by colored arrows matching the virus type.

Deterministic Model

The derivation of the stochastic model is based on the deterministic ordinary differential equations below

$$
\begin{cases}
\dfrac{dS}{dt} = -\beta S I_{*i} - \mu S + \mu N & \text{(1a)} \\
\dfrac{dI_i}{dt} = \beta S I_{*i} - (\sigma + \mu) I_i & \text{(1b)} \\
\dfrac{dI_{[i]j}}{dt} = \beta \delta R_i I_{*j} - (\sigma + \mu) I_{[i]j} & \text{(1c)} \\
\dfrac{dI_{[ij]k}}{dt} = \beta \delta R_i j I_{*k} - (\sigma + \mu) I_{[ij]k} & \text{(1d)} \\
\dfrac{dI_{[ijk]l}}{dt} = \beta \delta R_i j k I_{*l} - (\sigma + \mu) I_{[ijk]l} & \text{(1e)} \\
\dfrac{dR_i}{dt} = \sigma I_i - \delta R_i (I_{*j} + I_{*k} + I_{*l}) - \mu R_i & \text{(1f)} \\
\dfrac{dR_{ij}}{dt} = \sigma I_{ij} - \delta R_{ij} (I_{*k} + I_{*l}) - \mu R_{ij} & \text{(1g)} \\
\dfrac{dR_{ijk}}{dt} = \sigma I_{ijk} - \delta R_{ijk} I_{*l} - \mu R_{ijk} & \text{(1h)} \\
\dfrac{dR_{ijkl}}{dt} = \sigma I_{ijkl} - \mu R_{ijkl} & \text{(1i)}
\end{cases}
$$

Table 1: **State-transitions and probabilities:** $P(\Delta X(t)|X(t))$. The transitions are summarized below. Fully expanded, the system contemplates 64 possible state transitions, as can be verified in figure 1. †: Non-zero elements of $(\Delta X)_i$.

i	Transition	Probability, p_i	State Change†	Description
1..4	$S \to I_i$	$\beta S I_{*i} \Delta t$	$\Delta S(t) = -1,\ \Delta I_i(t) = 1$	Primary infection
5..8	$I_i \to R_i$	$\sigma I_i \Delta t$	$\Delta I_i(t) = -1,\ \Delta R_i(t) = 1$	Primary recovery
9..20	$R_i \to I_{[i]j}$	$\beta\delta R_i I_{*j} \Delta t$	$\Delta R_i(t) = -1,\ \Delta I_{[i]j}(t) = 1$	Secondary infection
21..32	$I_{[i]j} \to R_{ij}$	$\sigma I_{[i]j} \Delta t$	$\Delta I_{[i]j}(t) = -1,\ \Delta R_{ij}(t) = 1$	Secondary recovery
33..44	$R_{ij} \to I_{[ij]k}$	$\beta\delta R_{ij} I_{*k} \Delta t$	$\Delta R_{ij}(t) = -1,\ \Delta I_{[ij]k}(t) = 1$	Tertiary infection
45..56	$I_{[ij]k} \to R_{ijk}$	$\sigma I_{[ij]k} \Delta t$	$\Delta I_{[ij]k}(t) = -1,\ \Delta R_{ijk}(t) = 1$	Tertiary recovery
57..60	$R_{ijk} \to I_{[ijk]l}$	$\beta\delta R_{ijk} I_{*l} \Delta t$	$\Delta R_{ijk}(t) = -1,\ \Delta I_{[ijk]l}(t) = 1$	Quaternary infection
61..64	$I_{[ijk]l} \to R_{ijkl}$	$\sigma I_{[ijk]l} \Delta t$	$\Delta I_{[ijk]l}(t) = -1,\ \Delta R_{ijkl}(t) = 1$	Quaternary recovery
65	$\to S$	$\mu N \Delta t$	$\Delta S = 1$	Birth
66..113	$All \to$	$\mu N \Delta t$	$\Delta S = \Delta I_* = \Delta R_* = -1$	Death
114	No transition	$1 - \sum_i p_i$	No change	—

Where S are individuals susceptible to all 4 types of dengue, I_i infectious with Dengue type i, R_i individuals recovered from Dengue type i and $N(t) = S(t) + I_*(t) + R_*(t)$ is the total population size at time t. Infectious individuals already on their secondary and later Dengue infections are represented by indices $\{i, j, k, l\}$ which can take values in the close interval $(1, 4)$. For example, $I_{[23]1}$ is an individual which has had Dengues type 2 and 3 in the past – and therefore is immune to them – and is currently transmitting Dengue 1. The index outside the bracket denotes current infection. Recovered individuals indices denote their immunity, so for instance R_{123} is an individual which is immune to Dengue types 1, 2 and 3, but not to 4. Let $I_{*i} = \sum I_{[\ldots]i}$ with $[\ldots]$ representing exposure history of the infected individual which can vary from 0 to 3 in length. All individuals are born to the S state and birth and death rates are equal.

Stochastic Model

Let's now assume that $S(t)$, $I_*(t)$ and $R_*(t)$ are random variables representing the state of a stochastic process. The possible state-transitions and their probabilities are listed in table 1.

The stochastic model can be described as a continuous time Markov jump process. Let

$$\overrightarrow{X}(t) = [S(t), I_1(t), I_2(t), \ldots, R_{1234}(t)]$$

be the state of the system at the time t. $\sum X(t) = N, \forall t$ with N being the population size. The system is written as a forward Kolmogorov differential equation, which in matrix form looks like

$$\frac{dp_i(t)}{dt} = Q p_i(t) \tag{2}$$

Where $p_i(t)$ is the vector of transition probabilities (given in table 1) and Q is the generator matrix, whose values represent the transition rates between all possible states of the system. The full formula and matrices are ommited due to their large sizes.

The model can also represented as a system of It stochastic differential equations. To derive the equivalent system of It SDEs, we follow the procedure of Allen (2007).

The procedure starts with the identification of the all the possible transitions of the system's state and the probabilities associated with them, which we have already done (Table 1). The second step is to derive the expectation and covariance for these changes.

Expected Change and Covariance Matrix

It is useful to calculate the expected change and the covariance matrix for the changes

$$\begin{aligned}\Delta X = [&\Delta S, \Delta I_1, \Delta I_2, \Delta I_3, \Delta I_4, \Delta R_1, \Delta R_2, \Delta R_3, \Delta R_4, \Delta I_{12}, \Delta I_{13}, \Delta I_{14},\\ &\Delta I_{21}, \Delta I_{23}, \Delta I_{24}, \Delta I_{31}, \Delta I_{32}, \Delta I_{34}, \Delta I_{41}, \Delta I_{42}, \Delta I_{43},\\ &\Delta R_{12}, \Delta R_{13}, \Delta R_{14}, \Delta R_{23}, \Delta R_{24}, \Delta R_{34}, \Delta I_{231}, \Delta I_{241},\\ &\Delta I_{341}, \Delta I_{132}, \Delta I_{142}, \Delta I_{342}, \Delta I_{123}, \Delta I_{143}, \Delta I_{243}, \Delta I_{124},\\ &\Delta I_{134}, \Delta I_{234}, \Delta R_{123}, \Delta R_{124}, \Delta R_{134}, \Delta R_{234},\\ &\Delta I_{1234}, \Delta I_{1243}, \Delta I_{1342}, \Delta I_{2341}, \Delta R_{1234}]^T\end{aligned}$$

Thus from the probabilities of table 1,

$$E(\Delta X) = \sum_{i=1}^{114} p_i (\Delta X)_i = \begin{pmatrix} -\beta S \sum_{i=1}^{4} I_{*1} + \mu N - \mu S \\ \beta S I_{*1} - \sigma I_1 - \mu I_1 \\ \vdots \\ \beta S I_{*4} - \sigma I_4 - \mu I_4 \\ \sigma I_1 - \beta \delta R_1 \sum_{j \neq 1} I_{*j} - \mu R_1 \\ \vdots \\ \sigma I_4 - \beta \delta R_4 \sum_{j \neq 4} I_{*j} - \mu R_4 \\ \beta \delta R_i I_{*j} - \sigma I_{[i]j} - \mu I_{[i]j} \\ \sigma I_{[i]j} - \beta \delta R_{ij} I_{*k} - \mu R_{ij} \\ \beta \delta R_{ij} I_{*k} - \sigma I_{[ij]k} - \mu I_{[ij]k} \\ \sigma I_{[ij]k} - \beta \delta R_{ijk} I_{*l} - \mu R_{ijk} \\ \beta \delta R_{ijk} I_{*l} - \sigma I_{[ijk]l} - \mu I_{[ijk]l} \\ \sigma I_{[ijk]l} - \mu R_{1234} \end{pmatrix} \Delta t \tag{3}$$

The expected change, $E(\Delta X)$, is a 48×1 vector. The covariance matrix is a 48×48 matrix, $\Sigma(\Delta X) = E([\Delta X][\Delta X]^T) = \sum_{i=1}^{114} p_i (\Delta X)_i (\Delta X)_i^T = V \Delta t$ (see Allen (2007) for details).

It stochastic differential equations have the following general form:

$$dX(t) = \mu(X(t), t)dt + S(X(t), t)dW(t) \tag{4}$$

where $W(t)$ is a 48×1 vector of independent Wiener processes. It turns out that the diffusion matrix $S = \sqrt{V} = \sqrt{\Sigma / \Delta t}$. In order to avoid having to write down V to take its square root, we will use an equivalent formulation for 4

$$dX(t) = \mu(X(t), t)dt + B(X(t), t)dW^*(t) \tag{5}$$

To compute B, we must first denote each change in table 1, $(\Delta X)_i$ as $(\Delta_{1i}, \Delta_{2i}, \ldots, \Delta_{48i})$ which is equivalent to writing $(\Delta_{Si}, \Delta_{I_1 i}, \ldots, \Delta_{R_{1234} i})$, as each component represents the amount

Table 2: Parameters used for simulations

Parameter	Value	Description
β	500/(N*52)	Transmission rate: 500 casesyear
δ	0.2	
σ	1/1.5	
μ	$\frac{1}{70\times52}$	mortality rate
N	50000	Population size

and direction (sign) of the change in all state variables. The we can define each (i, j) element in matrix B as:

$$B_{ij} = \Delta_{ij}\sqrt{\frac{p_j}{\Delta t}} \tag{6}$$

B is then a 48×113 matrix, whereas S is a 48×48 matrix. Although B is a larger matrix, its easier to compute as it doesn't require taking the square root of a matrix. It can be shown that $B \times B^T = V = S^2$.

Numerical simulations

Deterministic model

To serve as background for the exploration of the stochastic dynamics we will first simulated the correpondent deterministic model of (1). Figure xx shows that with premanent partial cross immunity, along with separate Introduction of each virus, we get damped oscillations, as long as we have suffient demographical renewal of the population.

SDE model

There are different approaches to simulate the proposed stochastic models, the Kolmogorov version, can be simulated using Gillespie's algorithm which works well for small population sizes but becomes unwieldy for larger populations.

The SDE version however does not suffer from these scalability issues, with a number of solvers available for their simulation (Higham, 2001).

The parameter values used for the numerical simulations can be found on table 2. The simulations presented here were done with the Stochpy solver (Maarleveld et al., 2013).

On figure 3 we can see that the SDE dynamics converges on average to the same endemic equilibrium as the ODE model, but it sustains the oscillations a lot longer. Another interesting feature is that in the SDE model we can see alternating serotypes even though they are introduced simultaneously (see fig. 4).

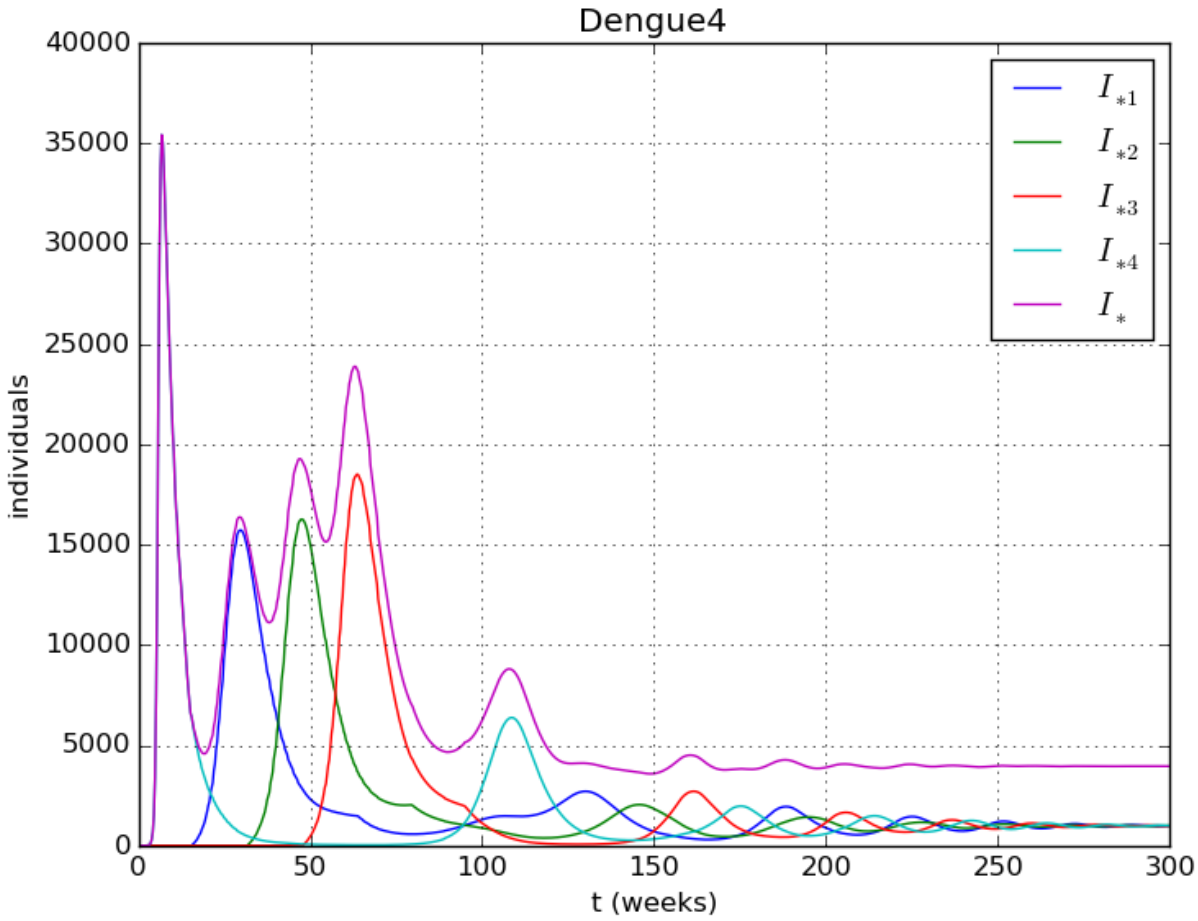

Figure 2: Simulation with parameters as given in table 2. Serotypes 4, 1, 2 and 3 were introduced separately a times 0, 5, 10 and 15, respectively.

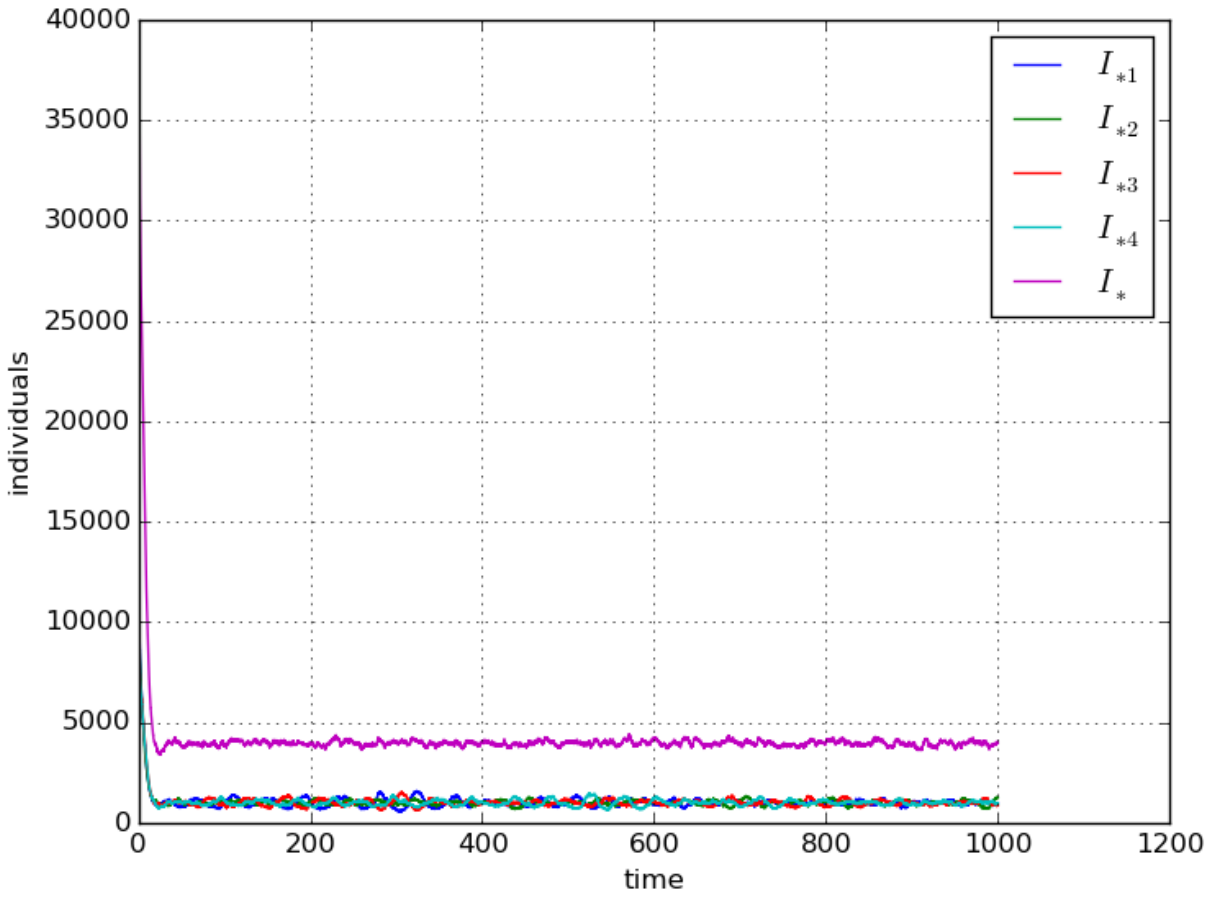

Figure 3: Total infected with each serotype.

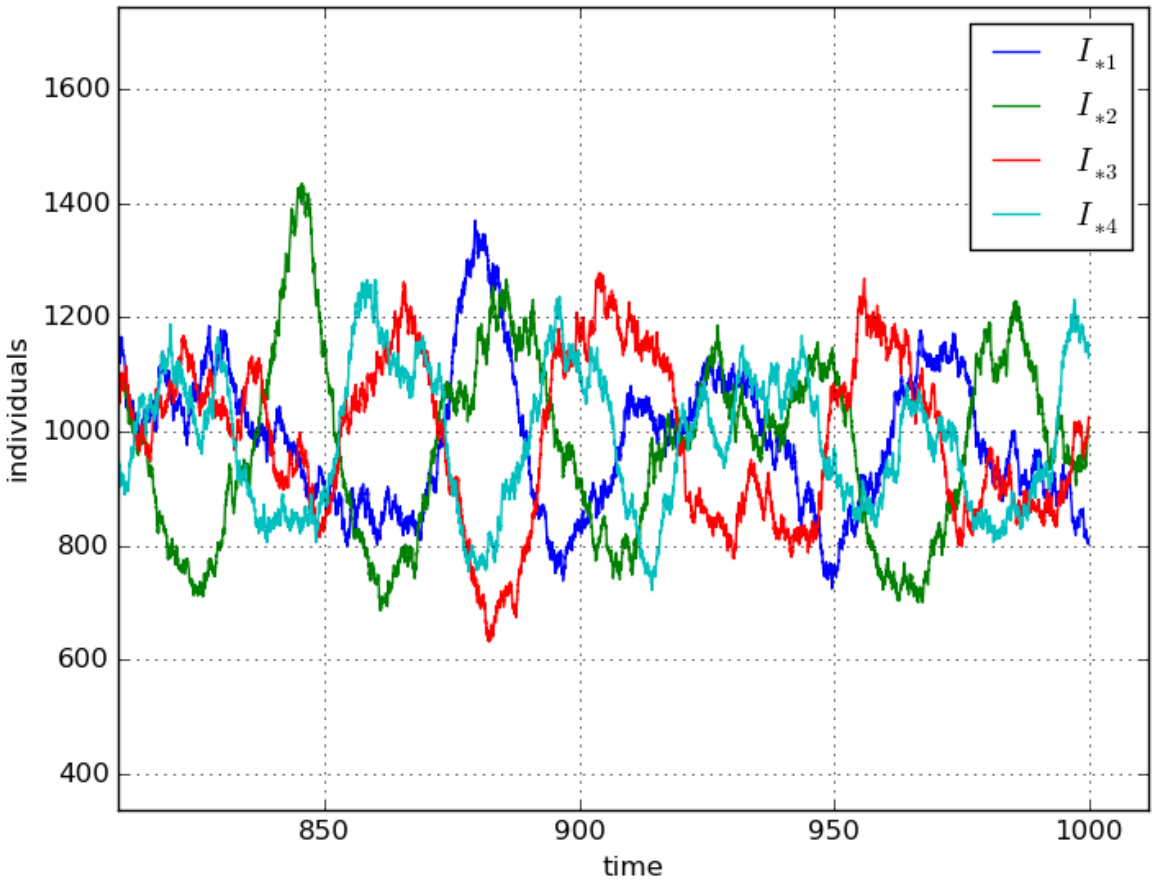

Figure 4: Detail of figure 3. Notice the sustained oscillations even after a 1000 weeks.

References

Allen, E. (2007). *Modeling with Itô stochastic differential equations*, volume 22. Springer Science & Business Media.

Higham, D. J. (2001). An algorithmic introduction to numerical simulation of stochastic differential equations. *SIAM review*, 43(3):525–546.

Maarleveld, T. R., Olivier, B. G., and Bruggeman, F. J. (2013). StochPy: A Comprehensive, User-Friendly Tool for Simulating Stochastic Biological Processes. *PLoS ONE*, 8(11):e79345.