A systematic approach to evaluate sustained stochastic oscillations

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Abstract

Although the populations of biological systems are inherently discrete and their dynamics are strongly stochastic, it is usual to consider their limiting behaviour for large environments in order to study some of their features. Such limiting behaviour is described as the solution of a set of ordinary differential equations, i.e., a continuous and deterministic trajectory. It will be shown that this trajectory does not always average correctly the system behaviour, such as sustained oscillations, in the neighbourhood of deterministic equilibrium points. In order to overcome this mismatch, an alternative set of differential equations based on polar coordinates is proposed. This set of equations can be used to easily compute the average amplitude and frequency of stochastic oscillations.

1 Introduction

The population dynamics of many biochemical systems can be naturally described in terms of continuous-time Markov chains (CTMCs). In these processes, the population of each species is given by an integer number and the occurrence of a reaction is represented by an event (or jump). The time to the next event follows an exponential distribution whose mean depends on the rate associated to the reaction and the population of each species that takes part in the reaction. The resulting dynamics are therefore stochastic.

Alternatively, the dynamics of such systems can be described by considering population densities instead of absolute populations. When the size (or volume) of the system is significantly large, limit theorems [10, 6, 9] offer an appealing mathematical tool to compute the average behaviour of the system densities. In particular, limit theorems provide a system of ordinary differential equations (ODE) whose solution is the limiting behavior of the densities when the system size tends to infinity. It must be noted that, in contrast to the CTMC dynamics, the trajectory described by an ODE is continuous and deterministic.

Although the use of ODEs is straightforward and they represent a mathematically proved average behaviour (continuous and deterministic), they might also provide a somewhat myopic view of the original discrete and stochastic system since only the average behaviour is being considered. This can lead to conclusions about the dynamics in which important properties such as commutations, stochastic resonance, etc. are passed over [7, 2, 4, 1].

This paper focuses on evaluating stochastic oscillations that are frequently seen as equilibrium points by the limiting ODE. Identifying oscillatory behaviour and estimating quantitative properties like amplitude and frequency, is crucial to correctly analyse real biological systems where such behaviour is essential [5, 8], e.g., reactions associated to circadian rhythm.

The method proposed here to evaluate stochastic oscillations is based on the design of an ODE that expresses the system behaviour in polar coordinates. The method is also applicable to other application domains in which similar stochastic models are considered, e.g., population dynamics, ecological models, etc.

As a running example a simple population dynamics system described in [2, 12] is considered. The system is similar to those arising when modeling biochemical reactions [11] and predator-prey systems [14]. The state of the system is given by two populations (integer variables) S and I representing the number of susceptible and infected individuals. There are three events, *Birth*, *Contagion*, *Death*, that modify the state of the system. Table 1 shows the effect and rates of each event, e.g., event *Contagion* decreases the number of susceptible individuals by one, increases the

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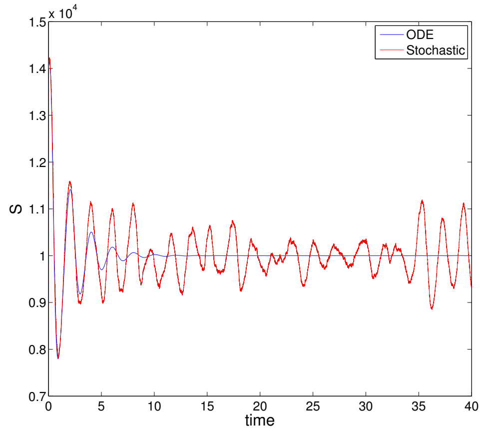

Figure 1: Time evolution of variable S according to the ODE (1) and the CTMC.

number of infected individuals by one and has rate $w_c = (\beta{\cdot}S{\cdot}I)/V$. Parameters a, b and β are related to the rates of *Birth*, *Death* and *Contagion* respectively, and V represents the size (or volume) of the system.

Event	Effect	Transition rate
Birth	$\{S, I\} \to \{S{+}1, I\}$	$w_b = a{\cdot}V$
Contagion	$\{S, I\} \to \{S{-}1, I{+}1\}$	$w_c = (\beta{\cdot}S{\cdot}I)/V$
Death	$\{S, I\} \to \{S, I{-}1\}$	$w_d = b{\cdot}I$

Table 1: Events and rates of the running example.

The described system dynamics can be expressed by means of the following chemical reactions:

$$\emptyset \xrightarrow{w_b} S \qquad S + I \xrightarrow{w_c} 2I \qquad I \xrightarrow{w_d} \emptyset$$

Let us focus on the concentrations $x_1{=}\frac{S}{V}$ and $x_2{=}\frac{I}{V}$ of the populations of susceptible and infected individuals. When the parameters of the CTMC satisfy some convergence conditions, its limiting behaviour as V tends to infinity can be expressed as an ODE [10, 3]. Assuming the example satisfies such conditions, its limiting behaviour can be expressed by the following ODE:

$$\frac{dx_1}{dt} = -\beta{\cdot}x_1{\cdot}x_2 \quad \frac{dx_2}{dt} = \beta{\cdot}x_1{\cdot}x_2 - b{\cdot}x_2 \qquad (1)$$

Figure 1 shows the time evolution of $S = V{\cdot}x_1$ given by both the solution of ODE (1) and just one stochastic simulation run of the CTMC. The parameters used in Figure 1 are $a{=}1$, $b{=}10$, $\beta{=}10$ and $V{=}10^4$. For these parameters the ODE dynamics has only one equilibrium point at $x_1^{eq}{=}1$, $x_2^{eq}{=}0.1$, thus in terms of populations the equilibrium point is $S^{eq}{=}10^4$, $I^{eq}{=}10^3$.

Notice that, whereas the ODE shows damped oscillations tending toward its equilibrium point ($S^{eq}{=}10^4, I^{eq}{=}10^3$), the CTMC dynamics exhibits sustained oscillations [2, 13]. Thus, for this example, the ODE representing the limiting behaviour does not capture the sustained oscillations of the CTMC.

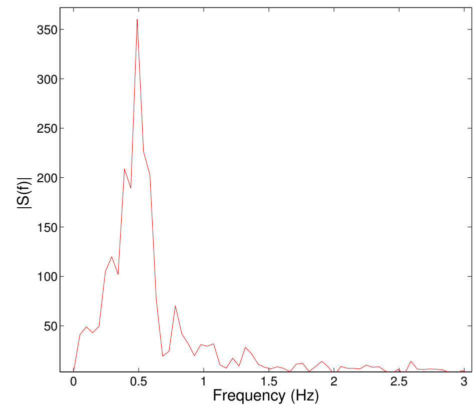

Figure 2: Frequency spectrum of the stochastic trajectory of variable S.

Figure 2 shows the frequency spectrum of the stochastic trajectory of Figure 1, i.e., it represents the signal in the frequency domain. A clear peak appears around the frequency 0.5. This phenomenon cannot be observed if the results of several runs of the CTMC are then averaged. In other words, the averaged populations converge to the solution of the ODE, but the ODE does not imitate the oscillations present in the CTMC dynamics around the equilibrium.

The goal of the paper is to develop an ODE that provides a complementary view of the dynamics of the CTMC that correctly averages sustained oscillations. Sections 2 and 3 describe the stochastic and deterministic models for the systems under consideration. The behaviour of both models around equilibrium points is analysed in Section 4. Section 5 proposes an ODE based on polar coordinates to average stochastic oscillations. Section 6 concludes the paper.

2 Stochastic models

The dynamics of many biological systems with discrete populations can be naturally expressed in terms of CTMCs. The following parameters allow us to describe the dynamics of the concentrations of the populations over time.

Definition 1 (System parameters)

- $V \in \mathbb{R}_{>0}$ *is the size (or volume);*
- $q \in \mathbb{N}$ *is the number of species;*
- $n_0 \in \mathbb{Z}^q_{\geq 0}$ *is the initial population of the q species;*
- $\boldsymbol{\alpha} = \{\alpha_1, \ldots, \alpha_E\}$ *is a set of* $E \in \mathbb{N}$ *events;*
- $\boldsymbol{\delta} = \{\delta_1, \ldots, \delta_E\}$ *defines the system change after the occurrence of events, i.e.,* $\delta_j \in \mathbb{R}^q$ *determines the population density change produced by* α_j*;*
- $\mathbf{w} = \{w_1, \ldots, w_E\}$ *is a set of functions such that* $w_j : \mathbb{R}^q_{\geq 0} \to \mathbb{R}_{\geq 0}$ *defines the transition rate of event* α_j*, i.e.,* $w_j(x)$ *is the transition rate of* α_j *when the population density is* x*.*

For a population $n \in \mathbb{Z}^q_{\geq 0}$, its density (or concentration) is $x{=}n/V$. Although some variables, such as x, depend on time, for readability we will use x rather than $x(t)$. E.g., the parameters for the event *Death* of the running example are: $\delta_d = (0, -1/V)$ and $w_d(x_1, x_2) = b{\cdot}V{\cdot}x_2$. The system evolution follows the usual dynamics of a CTMC: when an event α_j takes place, the population density is updated from x to $x{+}\delta_j$. The time to the next event is exponentially distributed. For a given density x, the mean of the exponential distribution associated to event α_j is $1/w_j(x)$. We will restrict our attention to CTMCs that satisfy the mass-action law, i.e., those processes whose reaction rates are proportional to the product of the concentrations of the participating species.

3 Deterministic models

The vector field for species $i \in \{1 \ldots q\}$ is given by [13]:

$$F_i(x^c) = \textstyle\sum_{j=1}^{E} \delta_j{\cdot}w_j(x^c) \qquad (2)$$

where $x^c \in \mathbb{R}^q_{\geq 0}$ denotes the state of the process. In the deterministic model the state x^c represents the average behaviour of the stochastic model, that is the reason why the different notations x and x^c are used for the Markovian and the deterministic models respectively.

When the parameters of the CTMC satisfy certain conditions [10, 3], its limiting behaviour is given by the following set of differential equations:

$$\frac{dx^c}{dt} = \textstyle\sum_{j=1}^{E} \delta_j{\cdot}w_j(x^c) \qquad (3)$$

A state x^{eq} is said to be a deterministic equilibrium point if it holds that $\sum_{j=1}^{E} \delta_j \cdot w_j(x^{eq}) = 0$. This paper focuses on systems having only one deterministic equilibrium. The ODE given in (3) is a deterministic approximation for the densities of the species in the system. For the particular system parameters of the running example ODE (3) corresponds to ODE (1) .

Figure 3 shows the evolution of the ODE (1) in the phase space over 20 time units. Each dot in the figure corresponds to the state of a simulation run of the CTMC after 20 time units. Conversely, as Figure 1 demonstrates, at time 20 the deterministic trajectory has already reached its equilibrium point. It can be observed that the *center of mass* of the black dots lays on the equilibrium point towards which the ODE converges. This is an expected result since the system satisfies the conditions of the limit theorems [10].

The static picture of Figure 3 does not show that each particular run is not tending to the deterministic equilibrium point. This at first glance surprising phenomenon can be intuitively explained. Figure 4 shows the potential evolutions, i.e., changes produced by the events, of the state of the CTMC together with the rates associated to them. If (s^{eq}, i^{eq}) is a deterministic equilibrium point, all the components of the vector field cancel out, i.e., (2) becomes null, and therefore the solution ODE remains at (s^{eq}, i^{eq}). However, the CTMC does not remain at the deterministic equilibrium indefinitely since the rates of the events at that point are positive. Moreover at the deterministic equilibrium all three rates are equal, hence the CTMC will evolve similarly to a random walk in a neighborhood close to the equilibrium. In fact, as pointed out in [13], non-extinction deterministic equilibria have associated a region of stochastic instability. This intuitive explanation is developed mathematically in the next section.

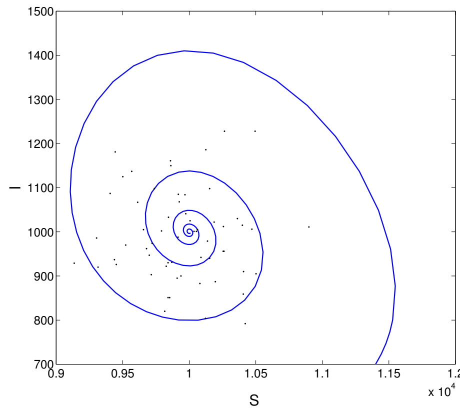

Figure 3: Evolution of the ODE (1) in the phase space and final states of several simulation runs.

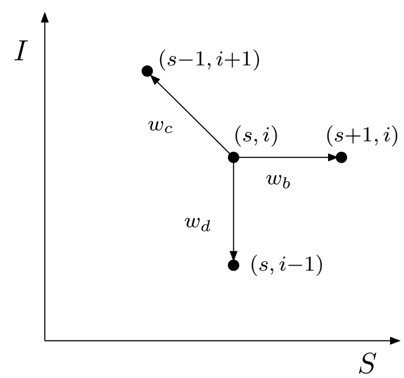

Figure 4: Phase space evolution of the CTMC.

4 System behaviour around equilibrium points

We now compare the evolution, with respect to a deterministic equilibrium point, of ODE (3) and the CTMC. We focus on the evolution of the euclidian distance squared from the system state to the equilibrium point.

Let $x^{eq} \in \mathbb{R}^q$ be a deterministic equilibrium point, i.e., $\sum_{j=1}^{E} \delta_j \cdot w_j(x^{eq}) = 0$. Let us define the distance of a point $x \in \mathbb{R}^q$ to x^{eq} as:

$$D(x, x^{eq}) = \sum_{i=1}^{q} (x_i - x_i^{eq})^2 \tag{4}$$

The variation of $D(x^c, x^{eq})$ per time unit, where x^c is the continuous trajectory provided by (3), is given by:

$$\frac{dD(x^c, x^{eq})}{dt} = \sum_{i=1}^{q} \frac{d(x_i^c - x_i^{eq})^2}{dt} \tag{5a}$$

$$= \sum_{i=1}^{q} 2\cdot(x_i^c - x_i^{eq}) \cdot \frac{dx_i^c}{dt} \tag{5b}$$

$$= \sum_{i=1}^{q} \Big(2\cdot(x_i^c - x_i^{eq}) \cdot \sum_{i=1}^{E} \delta_{ji} \cdot w_j(x^c)\Big) \tag{5c}$$

where δ_{ji} is the density change of the i^{th} species due to the occurrence of event α_j. The expression in (5b) is obtained by applying the chain rule, and (5c) is obtained by using Equation (3).

In order to compute the time evolution of (4) on the CTMC, we will first obtain an expression for the expected change of $D(x, x^{eq})$ after the occurrence of an event. To obtain such an expression, the embedded Markov chain is used. In the following, all the expressions related to expected values depend on the current state x, i.e., they are conditional expectations. For brevity, the current state will be omitted in the expressions, e.g., $\mathbb{E}[\Delta D(x, x^{eq})|x]$ will be shortened to $\mathbb{E}[\Delta D(x, x^{eq})]$. Let us define $R(x)$ as the average number of events per time unit:

$$R(x) = \sum_{j=1}^{E} w_j(x)$$

By the product rule of the difference operator we have:

$$\Delta(x_i - x_i^{eq})^2 = 2\cdot(x_i - x_i^{eq}) \cdot \Delta x_i + (\Delta x_i)^2$$

and hence the expected increment of $D(x, x^{eq})$ after an event is:

$$\mathbb{E}[\Delta D(x, x^{eq})] = \mathbb{E}\left[\sum_{i=1}^{q} \Delta(x_i - x_i^{eq})^2\right]$$
$$= \mathbb{E}\left[\sum_{i=1}^{q} \big(2\cdot(x_i - x_i^{eq}) \cdot \Delta x_i + (\Delta x_i)^2\big)\right]$$
$$= \sum_{i=1}^{q} \mathbb{E}[(\Delta x_i)^2] + \sum_{i=1}^{q} 2\cdot(x_i - x_i^{eq}) \cdot \mathbb{E}[\Delta x_i]$$
$$= \sum_{i=1}^{q} \mathbb{E}[(\Delta x_i)^2] + \sum_{i=1}^{q} \left(2\cdot(x_i - x_i^{eq}) \cdot \frac{\sum_{j=1}^{E} \delta_{ji} \cdot w_j(x)}{R(x)}\right)$$

Since at state x, the average number of events per time unit is $R(x)$, the average change of the distance squared per time unit is given by:

$$\frac{d\mathbb{E}[\Delta D(x, x^{eq})]}{dt} = R(x) \cdot \mathbb{E}[\Delta D(x, x^{eq})] \tag{7a}$$

$$= R(x)\cdot \sum_{i=1}^{n} \mathbb{E}[(\Delta x_i)^2] + \sum_{i=1}^{q} \Big(2\cdot(x_i - x_i^{eq})\cdot \sum_{j=1}^{E} \delta_{ji}\cdot w_j(x)\Big) \tag{7b}$$

By making use of Equations (5c) and (7b), the following equality for the same concentrations of the continuous and discrete trajectories, $x^c = x$, is obtained:

$$\frac{d\mathbb{E}[\Delta D(x, x^{eq})]}{dt} = R(x)\cdot \sum_{i=1}^{n} \mathbb{E}[(\Delta x_i)^2] + \frac{dD(x^c, x^{eq})}{dt}$$

More precisely, if x is not a deadlock point, i.e., there is at least one event α_j with strictly positive $w_j(x)$, then $R(x)\cdot\sum_{i=1}^{n} \mathbb{E}[(\Delta x_i)^2] > 0$ and it holds that:

$$\frac{d\mathbb{E}[\Delta D(x, x^{eq})]}{dt} > \frac{dD(x^c, x^{eq})}{dt} \tag{8}$$

Equation (8) implies that ODE (3) is not averaging correctly the distance to the equilibrium point of the CTMC dynamics.

Due to the mass-action law, $R(x)$ is proportional to V for a given concentration x, i.e., $R(x)=O(V)$ where $O(V)$ is the Landau notation to describe limiting behaviours. On the other hand, the changes in the concentration x produced by events are $O(1/V)$, hence $\sum_{i=1}^{q} \mathbb{E}[(\Delta x_i)^2] = O(1/V^2)$ implying that:

$$R(x) \cdot \big(\sum_{i=1}^{q} \mathbb{E}[(\Delta x_i)^2]\big) = O(1/V)$$

Therefore as V tends to infinity, $R(x) \cdot \sum_{i=1}^{q} \mathbb{E}[(\Delta x_i)^2]$ vanishes and the ODE (3) improves its quality with respect to the average distance to equilibrium. Nevertheless, in many practical cases V is finite, and the term $R(x) \cdot \sum_{i=1}^{q} \mathbb{E}[(\Delta x_i)^2]$ cannot be ignored.

5 Stochastic oscillations

5.1 Polar ODE

To study the behaviour of the CTMC around the deterministic equilibrium, we propose to average the distance to the deterministic equilibrium for the different potential evolutions, i.e., events, of the CTMC. To achieve this goal, an ODE based on polar coordinates is designed. The origin of such coordinates is the deterministic equilibrium x^{eq} around which the system dynamics is to be studied. Notice deterministic equilibrium points can be easily computed by solving the system of equations $\sum_{j=1}^{E} \delta_j \cdot w_j(x^{eq}) = 0$ (see Equation (3)). In contrast to the classical approach that focuses on the cartesian coordinates, polar coordinates explicitly refer to the distance to an equilibrium state. After some mathematical considerations, an ODE that averages the distance and angle to the deterministic equilibrium is obtained. We will constrain our attention to systems with two species, i.e., $q = 2$.

Figure 5 shows the system evolution after the event *Contagion* for the cartesian (S, I) and polar (r, ϕ) coordinates. For the polar coordinates the deterministic equilibrium (s^{eq}, i^{eq}) is taken as the origin.

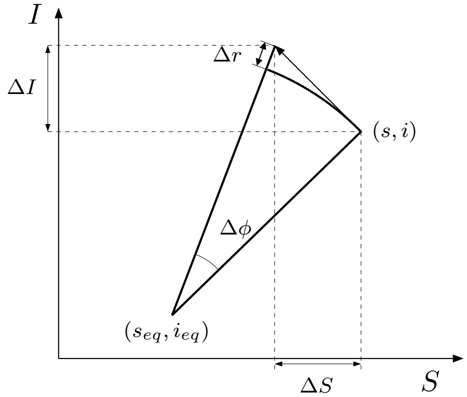

Figure 5: System evolution from event *Contagion*.

To define the state of the process in polar coordinates, radial and angular coordinates are required. The distance, or radial coordinate, of a point x to the equilibrium point x^{eq} is given by the function $rad(x)$:

$$r = rad(x) = \sqrt{(x_1 - x_1^{eq})^2 + (x_2 - x_2^{eq})^2} \qquad (9)$$

For a given x, the angular coordinate of ϕ is given by:

$$\phi = atan(x_2 - x_2^{eq}, x_1 - x_1^{eq}) \qquad (10)$$

where $atan(y, x) : \mathbb{R}\times\mathbb{R} \rightarrow \mathbb{R}$ is the arctangent of a point with cartesian coordinates (x, y). The range of $atan(y, x)$ is $(-\pi, \pi]$.

For the running example, the expected increment at state x of the radial coordinate is given by:

$$\mathbb{E}[\Delta r] = \frac{\sum_{j=1}^{E} w_j(x) \cdot rad(x + \delta_j)}{R(x)} - rad(x) \qquad (11)$$

and the expected increment of the angle ϕ is:

$$\mathbb{E}[\Delta\phi] = \frac{\sum_{j=1}^{E} w_j(x) \cdot atan(x + \delta_j)}{R(x)} - atan(x) \qquad (12)$$

where $atan$ is as in (10) but now has one bidimensional argument instead of two unidimensional ones.

There are two problems associated with equation (12). First, when the state is close to angle $\phi = \pi$, the function $atan$ might yield values close to π for the angle after a given event, and close to $-\pi$ for the angle after another event if the abscissa is crossed. The average of those angles will be close to 0, which is not meaningful. Second, the angular coordinate ϕ might be used not only to localize the state of the system but also to evaluate the overall number of degrees traveled by the system around the equilibrium. To cope with these two issues $\mathbb{E}[\Delta\phi]$ is redefined as follows:

$$\mathbb{E}[\Delta\phi] = \frac{\sum_{j=1}^{E} w_j(x) \cdot \big(atan(x + \delta_j) + g(x, \delta_j)\big)}{R(x)} - atan(x) \qquad (13)$$

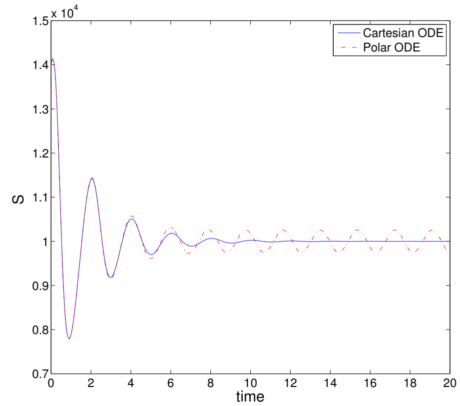

Figure 6: Time evolution of ODEs (3) and (15).

where $g(x, \delta_j)$ is defined as:

$$g(x, \delta_j) = \begin{cases} -2\cdot\pi & \text{if } atan(x) < -\frac{\pi}{2} \text{ and } atan(x + \delta_j) > \frac{\pi}{2} \\ +2\cdot\pi & \text{if } atan(x) > \frac{\pi}{2} \text{ and } atan(x + \delta_j) < -\frac{\pi}{2} \\ 0 & \text{otherwise} \end{cases} \qquad (14)$$

The term $g(x, \delta_j)$ is used to check whether ϕ has crossed the value π. If the crossing is clockwise, then $g(x, x + \delta_j) = -2\cdot\pi$, while if it is counterclockwise, then $g(x, x + \delta_j) = 2\cdot\pi$. Thus, $g(x, x + \delta_j)$ allows the increments of $\mathbb{E}[\Delta\phi]$ to be smooth.

The inclusion of $g(x, x + \delta_j)$ in the computation of $\mathbb{E}[\Delta\phi]$ solves the two mentioned problems: a) the average of angles close to π is now ensured to be close to π; b) if ϕ is updated according to its increments computed with $g(x, x + \delta_j)$ it will record the number of degrees traveled by the system around the equilibirum.

At a given state x, the average number of events per time unit is $R(x)$. Hence, the term $R(x) \cdot \mathbb{E}[\Delta r]$ is the average speed of change of r. Given that the same reasoning applies to ϕ, the following ODE can be used to describe the behaviour over time of r and ϕ:

$$\frac{dr}{dt} = R(x) \cdot \mathbb{E}[\Delta r] \quad \frac{d\phi}{dt} = R(x) \cdot \mathbb{E}[\Delta\phi] \qquad (15)$$

Given that x is just the cartesian coordinate of (r, ϕ), ODE (15) is composed of 2 equations and 2 variables.

5.2 Average amplitude and frequency

Consider again the running example. Figures 6 and 7 show the evolution of both ODEs, (3) (labelled cartesian ODE) and (15) (labelled polar ODE), over time and in the phase space. It can be observed that, while (3) exhibits damped oscillations, (15) tends to a limit cycle with clear sustained oscillations.

The ODEs present complementary views both useful for analysing the CTMC dynamics. While (3) focuses on the limiting behaviour of the concentrations

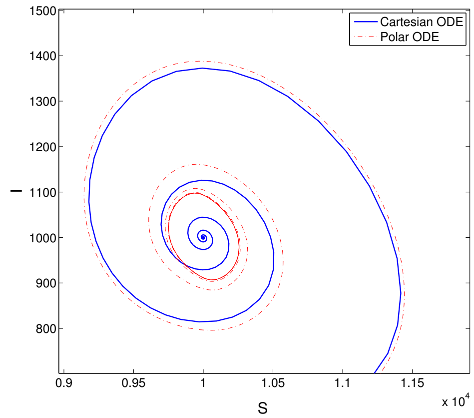

Figure 7: Phase space evolution of ODEs (3) and (15).

as V goes to infinity, (15) describes the dynamics in terms of polar coordinates for a given V which uncovers the oscillating behaviour around the equilibrium.

The ODE (15) can be used to evaluate the average oscillations of the CTMC. To compute the average distance to the equilibrium, $\overline{r}$, of the oscillation in the steady state, the following formula can be used:

$$\overline{r} = \lim_{\tau \to \infty} \frac{1}{\tau} \cdot \int_0^\tau r dt \tag{16}$$

For the running example $\overline{r} = 1.801 \cdot 10^{-2}$, thus the average distance in terms of populations (not densities) to the deterministic equilibrium is $\overline{r} \cdot V = 180.1$. This value is in good agreement with the average distance to the equilibrium of the dots shown in Figure 3.

In (15) the term $d\phi/dt$ is the angular speed ω of the system for angle ϕ. Thus the average angular speed of the system in steady state is given by:

$$\overline{\omega} = \lim_{\tau \to \infty} \frac{1}{\tau} \cdot \int_0^\tau \omega dt = \lim_{\tau \to \infty} \frac{\phi}{\tau} \tag{17}$$

For the example $f = \omega/(2 \cdot \pi) = 0.535$ which matches the peak exhibited in Figure 2. This can be interpreted as if the dots in Figure 3 where orbiting around the equilibrium point at an average frequency of 0.535.

6 Conclusions

Limit theorems constitute a useful mathematical tool for computing the limiting behaviour of large systems appearing in biology, chemistry and ecology. When applied to CTMCs such theorems can be used to obtain a set of ordinary differential equations (ODE) whose solution is the limiting behavior of the system when the size tends to infinity. Although important conclusions can be drawn from the limiting behaviour, it must be taken into account that it can also mask interesting features of the system dynamics as oscillations.

It has been shown that the ODE associated to the limiting behaviour does not average correctly the variations of the distance to a deterministic equilibrium point. More precisely, while the solution of the ODE is stable at such a point, the original CTMC is unstable in a neighbourhood of this point.

To average the evolution of the distance to the equilibrium, an ODE based on polar coordinates has been developed. Such an ODE can be used to compute the average amplitude and frequency of oscillation of the system in the steady state. The developed ODE must be understood as a complementary tool to understand the behaviour of the CTMC: while the initial ODE describes the overall *cartesian* tendency of populations, the proposed ODE describes the oscillating behaviour of the populations. A limitation is that the ODE must have a unique equilibrium point; a possible direction of future work is to extend this work to systems where the ODE has multiple equilibria.

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