

# From stochasticity to determinism in the collective dynamics of diffusively coupled cells

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## Abstract

We report a novel mechanism for the transition from stochasticity to determinism in  $\text{Ca}^{2+}$  oscillations via diffusive coupling of individual cells that are modelled by stochastic simulations of the governing reaction-diffusion equations. In particular, we show that by physiologically relevant conditions the collective dynamics of coupled cells is, unlike by isolated cells, deterministic for large enough ensemble sizes. The presented results explain the discrepancy regarding stochastic vs. deterministic nature between real-life recordings of physiological functions at cellular and organic level.

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## 1. Introduction

Biochemical systems are commonly modelled by differential equations or simulated by stochastic algorithms. The deterministic approach can be justified only when the participating molecule numbers are high enough to be approximated by concentrations. For low particle numbers stochastic algorithms are more accurate, but also computationally more expensive. Modelling of cellular processes, like  $\text{Ca}^{2+}$  oscillations, for example, is a typical example where the question arises whether the deterministic or the stochastic approach should be used. Many deterministic models have been developed in order to explain the occurrence of  $\text{Ca}^{2+}$  oscillations in the cell [1,2]. However, the number of receptors and ion channels in the cell can be very low (in the range of  $10^3$ – $10^5$  per cell), thus leading also to stochastic modelling of  $\text{Ca}^{2+}$  oscillations [2].

In the past, several approaches were proposed and developed in order to take into account influences of stochastic effects due to the fluctuations in particle number or the uncertainty related with the execution of a particular

reaction. Very often, the behaviour of such chemical systems was investigated when the control parameters or system variables were perturbed by noise [3–9]. As an alternative, stochastic modelling approaches involving numerical Monte-Carlo simulations of the master equation [10–13] were used. Recently, these methods have been employed very successfully for stochastic modelling of cellular biochemical systems [14–18].

Comparisons of the results obtained by stochastic and deterministic modelling of cellular oscillators have shown that qualitative differences between the outputs are possible. For example, it has been shown that for a deterministic steady state the stochastic model can yield oscillatory solutions [15,16], whereby this is true only for an intermediate volume considered in the stochastic simulation; whereas for a very large volume, i.e., when the number of involved particles is very high, it is known that stochastic solutions converge to the deterministic limit [10,11,15].

In addition to the well-known convergence of a stochastic solution to its deterministic limit when the number of particles in the cell increases, we presently present a new mechanism for the transition from stochasticity to determinism via diffusive coupling of individual cells. We show that the collective dynamics of coupled cells becomes deterministic for large enough ensemble sizes, although the sin-

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gle cell dynamics is by physiological conditions still stochastic. Our simulations are in accordance with real-life recordings of physiological functions at the cellular and organic level, thus providing ample support for deterministic modelling on macro system scales.

## 2. Single cell dynamics

We start by studying  $\text{Ca}^{2+}$  oscillations outputted by a single stochastically simulated cell. Specifically, we focus on the stochastic vs. deterministic nature of obtained solutions for physiologically relevant conditions regarding the number of  $\text{Ca}^{2+}$  ions forming the solutions. To this purpose, we use the model proposed by Houart et al. [19], and the Gillespie's simulation method [10,11]. The mathematical model considers changes of free  $\text{Ca}^{2+}$  concentration in the cytosol ( $Z$ ) and in the intracellular  $\text{Ca}^{2+}$  store ( $Y$ ), as well as the dynamics of  $\text{IP}_3$  ( $A$ ). We simulate the behaviour of the model by using parameter values for which the differential equations yield simple spike-like oscillations when integrated by a deterministic Runge–Kutta procedure. The parameter values, with the same notation as introduced in [19], are listed in the caption of Fig. 1.

To evaluate the level of determinism in the system, we use the method originally proposed by Kaplan and Glass [20], which is based on measuring average directional vectors in a coarse-grained phase space. The idea is that, in case of a deterministic solution, neighbouring trajectories in a small portion of the phase space should all point in the same direction, i.e., not cross, thus assuring uniqueness of solutions, which is the hallmark of determinism. The determinism factor  $0 \leq \kappa \leq 1$  is obtained by calculating the average length of all resultant vectors pertaining to a particular phase space box, whereby the resultant vectors are obtained by assigning a unit vector to each pass of the trajectory through a particular phase space box and calculating their vector sum. Hence, if the dynamics of oscillations is deterministic, the average length of all directional vectors  $\kappa$  will be 1, while for a completely random system  $\kappa = 0$ .

When simulating an isolated system stochastically, the defining quantity determining whether the output will be stochastic or deterministic is the number of reactants  $N$  actively participating in forming the solution. In our case,  $N$  is the number of  $\text{Ca}^{2+}$  ions in the smallest compartment considered by the model. Since concentrations  $Z$ ,  $Y$ , and  $A$

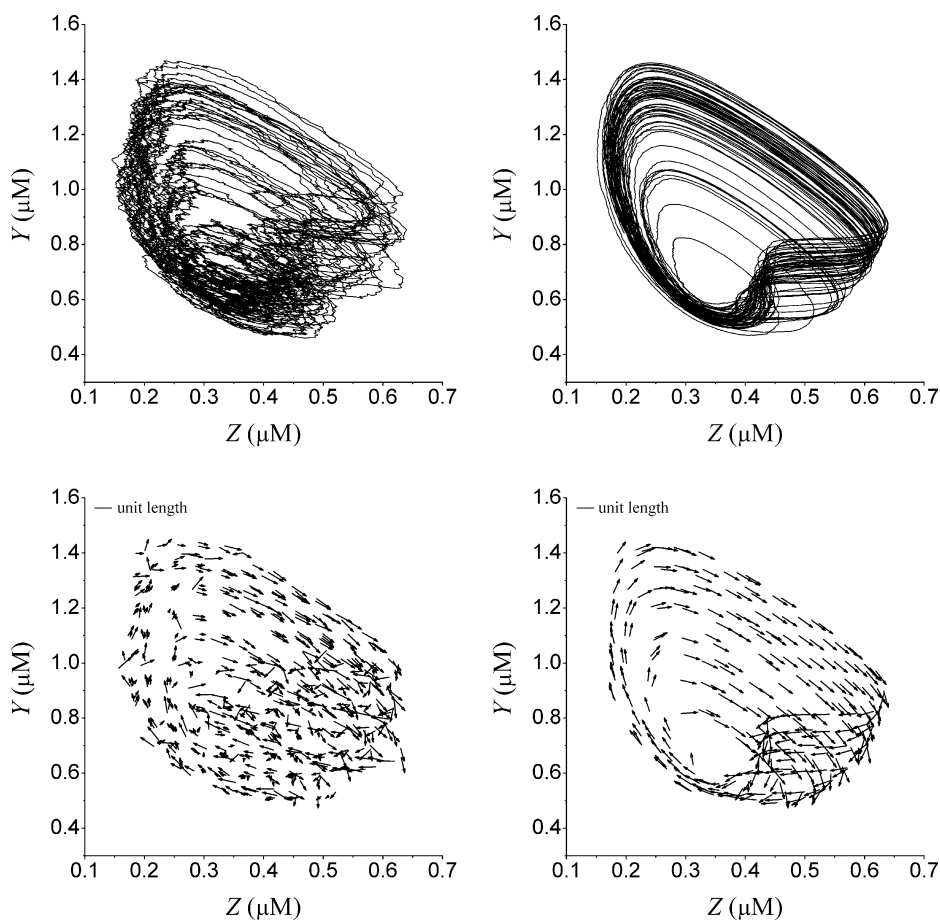


Fig. 1. Phase space plots (top row) and the pertaining average directional vector field approximations (bottom row) for one stochastically simulated cell. Left two panels:  $N = 6000$  ( $V = 10 \mu\text{m}^3$ ,  $\kappa \approx 0.4$ ); right two panels:  $N = 240000$  ( $V = 400 \mu\text{m}^3$ ,  $\kappa \approx 0.9$ ). Other system parameters:  $\beta = 0.64$ ,  $K_2 = 0.1 \mu\text{M}$ ,  $K_5 = 0.3194 \mu\text{M}$ ,  $K_A = 0.1 \mu\text{M}$ ,  $K_d = 1.0 \mu\text{M}$ ,  $K_Y = 0.3 \mu\text{M}$ ,  $K_Z = 0.6 \mu\text{M}$ ,  $k = 10.0 \text{ s}^{-1}$ ,  $k_f = 1.0 \text{ s}^{-1}$ ,  $\varepsilon = 11.0 \text{ s}^{-1}$ ,  $n = 4$ ,  $m = 2$ ,  $p = 1$ ,  $V_0 = 2.0 \mu\text{M s}^{-1}$ ,  $V_1 = 2.0 \mu\text{M s}^{-1}$ ,  $V_{M2} = 6.0 \mu\text{M s}^{-1}$ ,  $V_{M3} = 30.0 \mu\text{M s}^{-1}$ ,  $V_{M4} = 3.0 \mu\text{M s}^{-1}$  and  $V_{M5} = 50.0 \mu\text{M s}^{-1}$ .

are of the same order of magnitude, the number of particles depends directly on the volume of the corresponding compartment. Thus, the smallest  $N$  is given by the number of  $\text{Ca}^{2+}$  ions in the intracellular  $\text{Ca}^{2+}$  store  $Y$ . Fig. 1 shows two phase space portraits obtained for different  $N$  and the corresponding average directional vector field approximation obtained as outlined above. It is evident that stochastic effects are much more pronounced for small  $N$ , whilst for substantially larger  $N$  basically all resultant vectors are of unit length, which is a strong indicator for complete determinism. This is in agreement with the existing theory claiming that for large enough  $N$  the stochastic solution converges to the deterministic limit [10,11,15].

The question arises which of the two solutions presented in Fig. 1 better mimics a real-life experimental recording. In order to answer this question, we have to determine the number of particles  $N$  that corresponds to the free  $\text{Ca}^{2+}$  concentration in  $Y$ , which from Fig. 1 can be seen to equal approx.  $1 \mu\text{M}$  (on average). Considering a typical cell with a volume of about  $900 \mu\text{m}^3$ , the endoplasmic reticulum (ER), representing the main  $\text{Ca}^{2+}$  store, has a volume of about  $30 \mu\text{m}^3$ . Thus, by assuming that roughly the whole ER is available for  $\text{Ca}^{2+}$  storage, we consider  $30 \mu\text{m}^3$  being a good approximation for the volume of the smallest intracellular  $\text{Ca}^{2+}$  compartment considered by the studied model [19]. By calculating the particle number  $N$  for the average  $\text{Ca}^{2+}$  concentration  $1 \mu\text{M}$  and the volume  $30 \mu\text{m}^3$ , we obtain  $N \approx 18000$ , which indicates that the left panels in Fig. 1 better resemble the reality than the ones on the right.

To obtain a more accurate insight into the dynamics of a single stochastically simulated cell at physiological numbers of  $\text{Ca}^{2+}$  ions, we present  $\kappa$  in dependence on various  $N$  in Fig. 2. It is evident that for physiologically relevant conditions ( $N \approx 18000$ ,  $V \approx 30 \mu\text{m}^3$ )  $\kappa \approx 0.6$ , which suggests that real-life measurements of  $\text{Ca}^{2+}$  oscillations in a single cell can hardly be expected to be fully deterministic. Although a detailed study of such real-life recordings has not yet been made, our results can be qualitatively confirmed solely by visually inspecting the experimental traces available in literature [21–24], where a substantial base-line noise as well as quite heavily fluctuating peak heights can be inferred. Although these noisy features can (and should) at least to some extent be attributed to the measurement error, our theoretical results indicate that also the internal cell dynamics is to be held responsible. Indeed, Wolf et al. [25] report that mechanisms assuring intracellular  $\text{Ca}^{2+}$  oscillations are much more sensitive to fluctuations than, for example, circadian rhythms where deterministic oscillations can be obtained already at much smaller  $N$ . Interestingly, this is mainly due to the fact that  $\text{Ca}^{2+}$  oscillations rely on positive feedback loops, whilst circadian rhythms are driven by negative feedback loops. In the following section, we will show that diffusive coupling of individual cells eliminates the stochastic fingerprint of oscillations in a single cell, which explains the origin of determinism observed in experimental recordings obtained at the organic level [26,27].

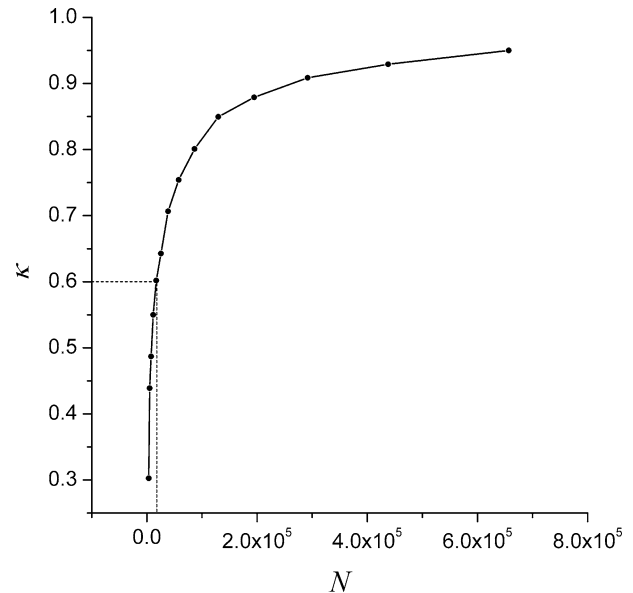


Fig. 2. Transition from stochasticity to determinism in a single stochastically simulated cell by increasing the value of  $N$ . The dashed line marks the physiologically relevant state given by  $N = 18000$  ( $V = 30 \mu\text{m}^3$ ).

### 3. Transition to determinism via cell coupling

The diffusive coupling of individual cells is modelled by a one-dimensional chain, whereby we introduce an additional flux of the form  $D\nabla^2 Z_i$  to the differential equation modelling changes of cytosolic  $\text{Ca}^{2+}$  concentration in each of the  $i = 1, 2, \dots, S$  coupled cells. The Laplacian is integrated into the numerical scheme via a first-order numerical approximation  $D(Z_{i-1} + Z_{i+1} - 2Z_i)$ , yielding nearest neighbour interactions, and periodic boundary conditions, whereby  $D = 70 \text{ s}^{-1}$  already incorporates the spacing between individual cells. Noteworthy, although several authors have emphasised also the importance of  $\text{IP}_3$  for intercellular communications [28,29], we find that below results do not differ considerably if we include also coupling via the variable  $A$ . Thus, for simplicity but without loss of generality, we presently do not consider diffusive coupling via  $\text{IP}_3$  in our calculations. Moreover, the collective dynamics of the ensemble is approximated via a simple mean-field approximation given by  $(\bar{Z}, \bar{Y}, \bar{A}) = (1/S) \sum_{i=1}^S (Z_i, Y_i, A_i)$ , where  $S$  is the number of coupled cells.

Fig. 3 shows time courses of  $\bar{Z}$  for two different  $S$ . It is evident that as  $S$  increases, the time traces become increasingly noise free and smooth, i.e., deterministic. Particularly, while the oscillations outputted by a single cell resemble experimentally obtained traces in that base-line and peak height fluctuations are well pronounced, the collective dynamics by  $S > 1$  is far more deterministic and has more the characteristics of an experimental recording obtained at the organic level, such is for example an ECG [27].

This visual assessment of the transition from stochasticity to determinism can be made quantitative by calculating  $\kappa$  for different  $S$ . The results in Fig. 4 show that the stochastic fingerprint of oscillations vanishes as  $S$  increases. Thereby, we

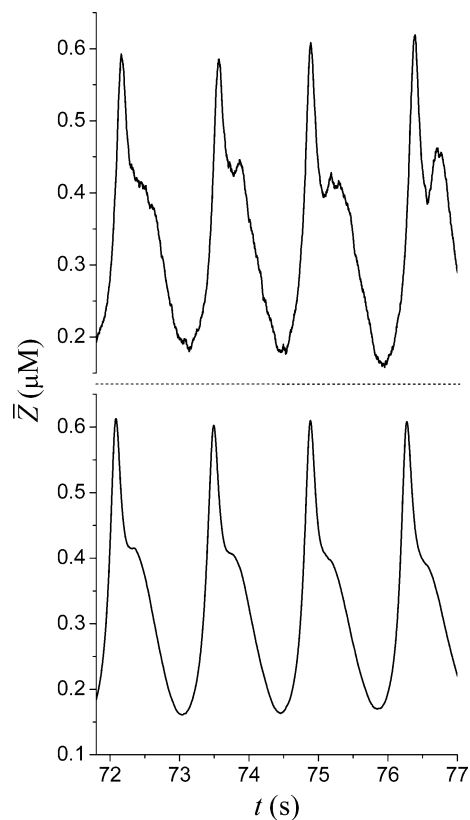


Fig. 3. Temporal plots of  $\bar{Z}$  for  $S=1$  (top panel) and  $S=100$  (bottom panel) obtained by setting  $N=18000$  for each individual cell.

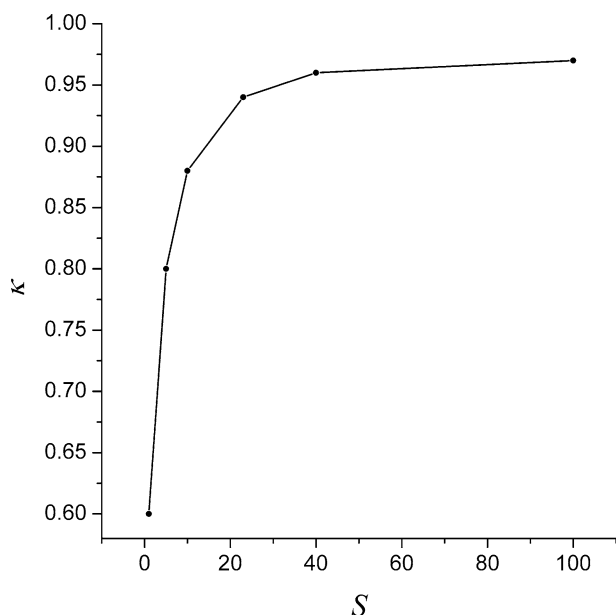


Fig. 4. Transition from stochasticity to determinism via diffusive coupling of several stochastically simulated cells by physiologically relevant conditions.

show that diffusive coupling of individual stochastically simulated cells can induce a transition from stochasticity to determinism in the limit of large enough system sizes. It should be noted, of course, that the minimal value of  $S$  nec-

essary for complete determinism ( $\kappa \approx 1$ ) increases if the number of active  $\text{Ca}^{2+}$  ions  $N$  pertaining to a single cell decreases. However, we find that for  $S \geq 100$  the system can be considered deterministic for all physiologically feasible settings.

Importantly, we note that the transition to determinism can be observed only at the collective level meaning that individual cells, even if coupled, still do not show fully deterministic behaviour. In particular, if one cell is simulated individually for a given  $N$ , its trace has the same  $\kappa$  as either of the traces pertaining to an individual cell forming the diffusively coupled ensemble. This implies that even under coupled conditions intracellular signalling still suffers from stochasticity. However, we emphasise that such signals, although somewhat burdened with noise ( $\kappa \approx 0.6$ ), can still have a well-defined frequency and peak heights, as shown in the top of Fig. 3, and are thus able to efficiently encode information either in their amplitude and/or in frequency. In this sense, it should not be assumed that stochasticity in a single-cell dynamics renders the whole behaviour physiologically irrelevant.

To explain these results, we argue that the reported transition from stochasticity to determinism is twofold. First, it should be noted that the mean-field approximation of the collective dynamics averages out at least some part of base-line fluctuations that can be observed by single cell oscillations. More importantly, however, the transition from stochasticity to determinism occurs due to the increase of the effective total system volume, which in the limit case  $D \rightarrow \infty$  would simply imply  $N \rightarrow SN$ . We emphasise also that the diffusive coupling induces self-organisation of the system dynamics. In particular, the coupled cells self-organise their dynamics with respect to  $D$  and  $S$ , which in turn leads to locally synchronous oscillations and an overall decrease in stochasticity in the collective dynamics of the system as presented in Figs. 3 and 4.

#### 4. Discussion

We show that diffusive coupling of individual stochastically simulated cells at physiologically relevant conditions can induce a transition from stochastic to deterministic behaviour in the collective dynamics of the system for large enough ensemble sizes. In particular, while a single cell at physiological conditions, whether uncoupled or coupled with its neighbour, exhibits a largely stochastic oscillatory behaviour with well-expressed base-line and peak height fluctuations, these stochastic markers vanish in the collective dynamics as the number of diffusively coupled cells increases. We argue that this transition occurs due to the mean-field effect and the increase of the effective total system volume, whereby a self-organizing effect on the system dynamics sets in, which leads to an overall decrease in stochasticity in the collective system dynamics. Importantly, the self-organisation manifests also as synchronisation of  $\text{Ca}^{2+}$  oscillation in neighbouring cells, which despite the fact that the determinism in each individual cell is not enhanced, still improves the overall reliability of the system in that vital information is

no longer encoded only by the dynamics in a single cell, but is effectively emitted by a whole cluster of nearby cells in which the concentration of  $\text{Ca}^{2+}$  oscillates with the same amplitude and/or frequency.

The presented results have important real-life implications. It is a well-established fact that virtually all real-life phenomena at small scales, i.e., cellular level, are heavily affected by the internal stochasticity given by the probability rather than a definite deterministic kinetic rate that some reaction will or will not occur [2,30]. Thus, it is not at all surprising that real-life experimental recordings of cellular functions often yield stochastically appearing traces, which we also confirmed presently by our theoretical calculations. On the other hand, recordings of physiological functions at organic level are often deterministic in appearance, which was confirmed mathematically numerous times for ECGs [27] and human locomotion [26], for example. Our theoretical results suggest that this discrepancy between experimental recordings obtained at cellular level and organic level can be attributed to the self-organisation of individual oscillators due to influences from neighbouring cells, which ultimately leads to the decrease in stochasticity in the collective dynamics of the whole organ. Noteworthy, synchronisation and phase synchronisation of coupled noisy oscillators has been the subject of several theoretical and experimental studies [31–34]. Although not directly linked to  $\text{Ca}^{2+}$  oscillations, phenomena described there appear to be generic and can thus be viewed as a source of inspiration for the present work.

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