

A MODEL FOR COUPLED BELOUSOV-ZHABOTINSKY OSCILLATORS WITH DELAY

*Giovanni Pagano¹, Marcello Antonio Budroni², Raffaele D'Ambrosio³, Dajana Conte¹,
Ali Abou Hassan⁴, Sandra Ristori⁵, Federico Rossi⁶ and Beatrice Paternoster¹

¹ Department of Mathematics, University of Salerno
e-mail: {gpagano, dajconte, beapat}@unisa.it

² Department of Chemistry and Pharmacy, University of Sassari
e-mail: mabudroni@uniss.it

³ Department of Engineering and Computer Science and Mathematics, University of L'Aquila
e-mail: raffaele.dambrosio@univaq.it

⁴ Physico-Chemistry Laboratory of Electrolytes and Nanosystems Interfaciaux, Sorbonne University
e-mail: ali.abou_hassan@sorbonne-universite.fr

⁵ Department of Chemistry 'Ugo Schiff', University of Firenze
e-mail: sandra.ristori@unifi.it

⁶ Department of Physical Science, Earth and Environment, University of Siena
e-mail: federico.rossi2@unisi.it

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Abstract. The purpose of this work is to introduce time delays in an *Oregonator*-based model [11] to describe molecular communication in a system of coupled chemical oscillators [5]. With this approach we assume that the molecules responsible for communication (signal molecules) take a non-zero time τ to cross the barrier (phospholipid membrane) which physically separate the oscillators. In particular, here we present numerical results and we discuss and highlight the differences between delayed and non-delayed models.

1 INTRODUCTION

Networks of confined and relatively simple chemical oscillators are being used to model complex biological processes, such as cell-cell communication, neuronal signal transmission and passive diffusion across plasma membranes [26, 27]. From an experimental point of view, the confinement of the Belousov-Zhabotinsky (BZ) reaction [3, 28, 29] in various dispersed systems [10], revealed to be a valid tool to understand universal synchronisation behaviours, when the network communication is mediated by either activatory or inhibitory signals. The BZ reaction is one of the most famous example of self-organised chemical system, which can exhibit several dynamical regimes: periodic, aperiodic and chaotic oscillations [18, 20], autocatalysis and bistability [24], Turing structures and pattern formation [4, 19]. In

the last years, especially thanks to microfluidic techniques, it was possible to assess the impact of several factors on the global dynamics of BZ networks: arrangement geometry (arrays, squares, etc.), messenger molecules (inhibitors/activators) and type of confinement (surfactants, phospholipids, oils, etc.) [26].

In this context, to model the oscillations of the coupled BZ oscillators, several variants of the *Oregonator* system [11] were employed, either coupled through simple mass-transfer (ODE systems) or through molecular diffusion (PDE systems). Being the *Oregonator* stiff, several studies were also devoted to its numerical resolution. D’Ambrosio et al. [7, 8], for example, have recently used adapted numerical methods to follow the a priori known qualitative behavior of the solution. To solve efficiently stiff ODEs systems of which we know certain properties of the solution, one can use the Exponential Fitting (EF) technique, thus constructing methods adapted to the problem [16]. By proceeding in this way, it is also possible to construct semi-implicit Runge-Kutta methods whose coefficients depend on the Jacobian matrix of the system [9, 13, 14, 15].

In this paper we introduce a modelling strategy based on delayed coupled ordinary differential equations (DDE) to understand whether this approach could improve some quantitative aspects for the description of BZ networks. To this aim, we started from an ODEs system proposed by Budroni et al. to describe the communication in a network of diffusively coupled BZ oscillators, confined in phospholipid-separated micro-compartments [5]. In this example, communication between successive oscillators is controlled by the exchange of membrane-permeable molecules acting as activator (HBrO_2) or inhibitor (Br_2), thus some properties of the membrane (composition, permeability, lamellarity, etc.) influence the crossing time of the messenger molecules. By inserting a delay time in one of the two coupling terms (in this case related to Br_2) of the ODEs system, we can reproduce the effect of the membrane barriers and also explore the parameter space to predict and guide future experiments. Since the resulting DDEs system is also stiff, we used an ad hoc numerical algorithm (see [1] Supporting Information) for the numerical integration. Our results display a qualitative accordance with the experimental dynamics and with the previous ODE model (anti-phase synchronisation of adjacent oscillators), but a quantitative matching with experiments is yet to be attained. Interestingly, spanning the parameter space, we found an unexpected in-phase synchronisation scenario for large delay time. This observation is a starting point for further studies to guide future experiments.

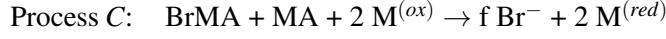
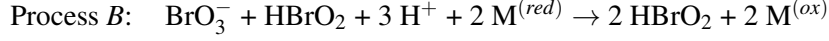
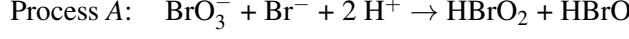
This work is structured as follows: we will first analyse, in Section 2, the ODEs model proposed by Budroni et al., discussing the reasons for the insertion of the delay time together with the formulation of the DDEs system. Next, in Section 3, we will show and analyse the numerical results of the DDEs system. Finally, in Section 4, some conclusions will be drawn and possible future implications will be discussed.

2 THE MODEL WITH DELAY

As aforementioned, arrays of phospholipid separated BZ micro-oscillators provide a relatively simple picture of the basic features responsible for the intercellular biological communication, when mediated by passive diffusion of activatory and/or inhibitory signal molecules. The mathematical description of such systems has been developed along the years starting from the classic scheme of the BZ reaction known as *Oregonator* [11, 25] and successively refined to include the effect of the membrane permeability [21], composition [27] and the simultaneous exchange of both activatory and inhibitory signals among micro-oscillators [5, 6].

In brief, the basic backbone of the kinetic scheme regulating the oscillatory regime of the BZ reaction

consists in three main stages: *inhibition* (Process A), *autocatalysis* (Process B) and *chemical clock reset* (Process C), described by the following chemical processes:



The original set of *Oregonator* ordinary differential equations was derived from Processes A–C, here we report the latest version of the equations modified to simulate the behaviour of an arbitrary long array of BZ micro-oscillators [5, 6]:

$$\begin{cases} \frac{dc_1^i}{dt} = -k_1 c_1^i c_2^i + k_2 a^i c_2^i - 2k_3 (c_1^i)^2 + k_4 a^i c_1^i \frac{(c_0 - c_4^i)}{(c_0 - c_4^i + c_{min})} \\ \quad - k_X (c_1^i - c_1^{i+1}) - k_X (c_1^i - c_1^{i-1}) \\ \frac{dc_2^i}{dt} = -3k_1 c_1^i c_2^i - 2k_2 a^i c_2^i - k_3 (c_1^i)^2 + k_6 c_3^i + k_9 c_4^i \\ \frac{dc_3^i}{dt} = 2k_1 c_1^i c_2^i + k_2 a^i c_2^i + k_3 (c_1^i)^2 - k_6 c_3^i - k_W (c_3^i - c_3^{i+1}) \\ \quad - k_W (c_3^i - c_3^{i-1}) \\ \frac{dc_4^i}{dt} = 2k_4 a^i c_1^i \frac{(c_0 - c_4^i)}{(c_0 - c_4^i + c_{min})} - k_9 c_4^i \end{cases} \quad (1)$$

where the index i represents the i -th micro-oscillator, the rate constants k_i are known and the functions $c_j^i(t)$ indicates the concentration of the substance j in the cell i at time t . In particular, the chemicals of the system are

$$c_1^i = [\text{HBrO}_2], \quad c_2^i = [\text{Br}^-], \quad c_3^i = [\text{Br}_2] \quad \text{and} \quad c_4^i = [\text{Fe}^{3+}].$$

Other fixed and constant parameters of the system (1) are c_0 , c_{min} and the coupling constants k_X and k_W . Finally, the vector a has dimension equal to the number of droplets considered, and each component is used to modulate the natural frequency of the corresponding oscillator. Coupling terms $k_X (c_1^i - c_1^j)$ and $k_W (c_3^i - c_3^j)$ accounts for the intercellular communication between subsequent droplets mediated by the activator HBrO_2 and the inhibitor Br_2 . The coupling intensity is given by the constants k_X and k_W , which depend on compartmentalisation constraints, such as permeability or lamellarity of the membrane, which also account for the droplets distance.

Starting from the set of ODEs (1), in this work we insert a delay time (τ), which affect the coupling term of adjacent micro-oscillators. The corresponding DDEs set is reported in (2). To understand whether the new model improves the matching with experimental results, we will compare our simulations with the experiments reported in [5] previously simulated with ODEs (1).

$$\begin{cases} \frac{dc_1^i}{dt} = -k_1 c_1^i c_2^i + k_2 a^i c_2^i - 2k_3 (c_1^i)^2 + k_4 a^i c_1^i \frac{(c_0 - c_4^i)}{(c_0 - c_4^i + c_{min})} \\ \quad -k_X (c_1^i - c_1^{i+1}(t)) - k_X (c_1^i - c_1^{i-1}(t)) \\ \frac{dc_2^i}{dt} = -3k_1 c_1^i c_2^i - 2k_2 a^i c_2^i - k_3 (c_1^i)^2 + k_6 c_3^i + k_9 c_4^i \\ \frac{dc_3^i}{dt} = 2k_1 c_1^i c_2^i + k_2 a^i c_2^i + k_3 (c_1^i)^2 - k_6 c_3^i - k_W (c_3^i - c_3^{i+1}(t - \tau)) \\ \quad -k_W (c_3^i - c_3^{i-1}(t - \tau)) \\ \frac{dc_4^i}{dt} = 2k_4 a^i c_1^i \frac{(c_0 - c_4^i)}{(c_0 - c_4^i + c_{min})} - k_9 c_4^i \end{cases} \quad (2)$$

3 NUMERICAL RESULTS

The general form of the DDEs system (2) is

$$\begin{cases} y'(t) = f(t, y(t), y(t - \tau)) & t \geq t_0 \\ y(t) = \phi(t) & t \leq t_0 \end{cases} \quad (3)$$

the history function $\phi(t)$ represents the value of the concentrations of substances involved in the DDEs system (2) before the initial instant $t_0 = 0$. In our case, we have fixed the history function equal to a constant vector y_0 . To compare our results with those reported in [5], we considered an array of eight coupled micro-oscillators ($i = 8$) and we analysed the simulated oscillation period (OP) for each oscillator and the phase difference among consecutive oscillators ($\Delta\Phi$).

We employed several Matlab routines to solve the DDEs system (3). The stiffness [17] of our DDEs created some problems with the *dde23* routine [2, 23] (high integration time and random crash of the code). For this reason we finally employed the *dde15s* code, written by Dr. Lawrence F. Shampine (Southern Methodist University, Dallas, TX) for the numerical resolution of the model proposed in [1]. This numerical algorithm is based on the Matlab *ode15s* [22] routine for solving stiff ODEs systems; *radar5* code [12] also yields similar results.

As preliminary results, we simply explored the influence of the delay time on the oscillation parameters by fixing the initial conditions and all the constants and by varying τ . Figures 1 and 2 show that, from an initial anti-phase synchronisation between consecutive oscillators, which occurs when there is no delay, an in-phase synchronisation when $\tau = 110$ s is achieved. Changes in the oscillation period of the system droplets and in the phase differences are shown in Figure 3. In this case, we can observe that, due to a very large delay, the oscillation period tends to lower by about 20/30 s compared to the case where there is no delay. Synchronization between consecutive oscillators is perfectly in-phase in the case with delay. With delays smaller than $\tau = 110$ s, the numerical results are quite similar to the case when there is no delay.

4 CONCLUSIONS

At present, our preliminary results do not allow to make a direct comparison between the ODEs-based modelling (1) and the introduction of the delay time in (2). However, our analysis showed a significant

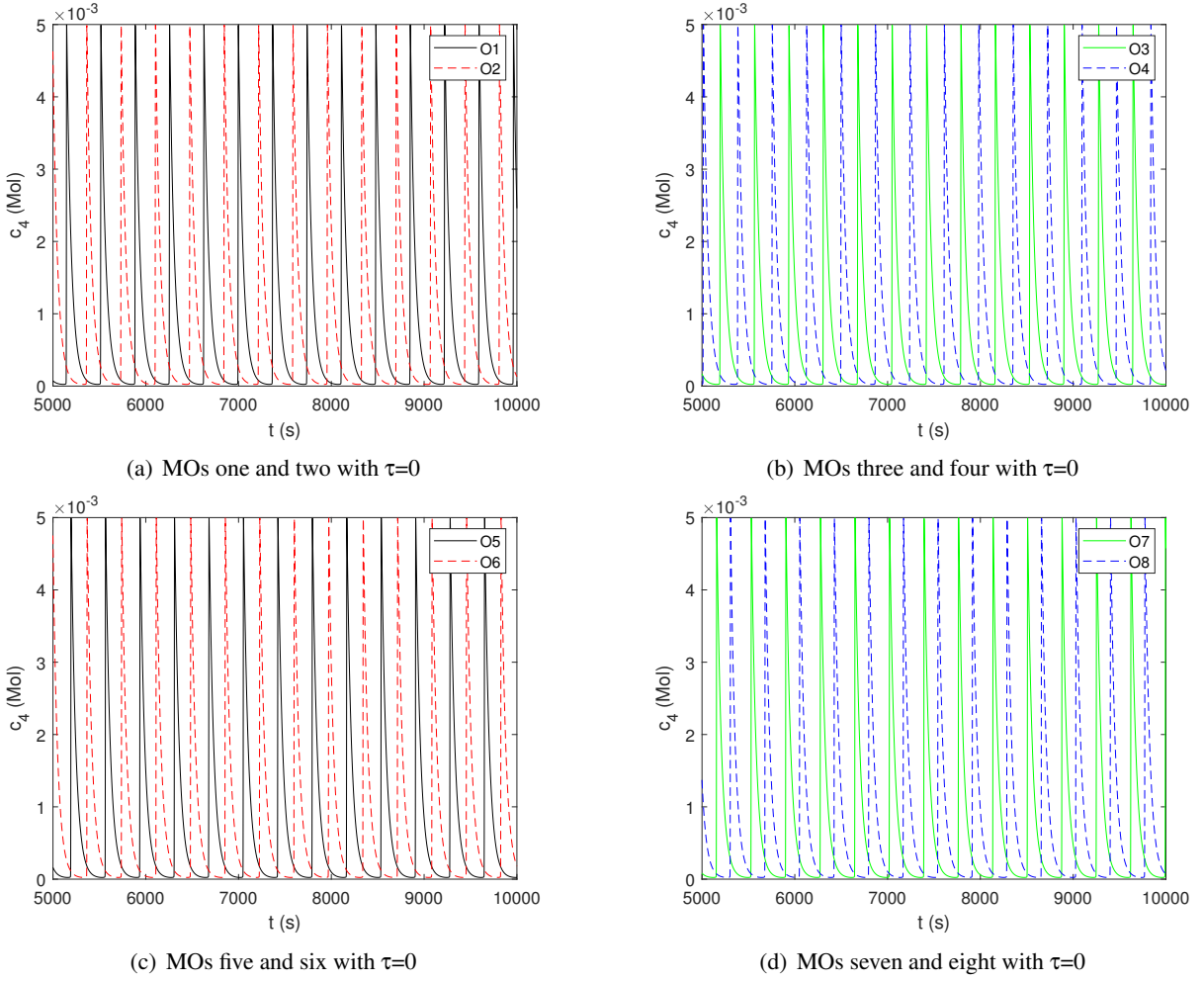


Figure 1: Trend of c_4 for all eight MicroOscillators (MOs) of the system, with $\tau=0$.

impact of τ on the global dynamics of the coupled micro-oscillators. In fact, by increasing the delay time, an initial anti-phase synchronisation scenario shifts to an in-phase configuration.

This observation is just a starting point for the ongoing investigation we are carrying out. A phase diagram of the system with respect to the modelling parameters is being mapped out. In addition, we are also assessing a more detailed parametrisation of the DDEs system with respect to the chemical properties of the molecules involved, this, for example, will suggest the insertion of a new different delay time for the activator species, now doesn't set.

Finally, we are also investigating in details the numerical resolution of the DDEs system (2) to overcome the stiffness issue. For example, we are adapting the works of D'Ambrosio et al. [7, 8], based on the EF technique, to consider the a priori known oscillating trend of the DDEs system solution.

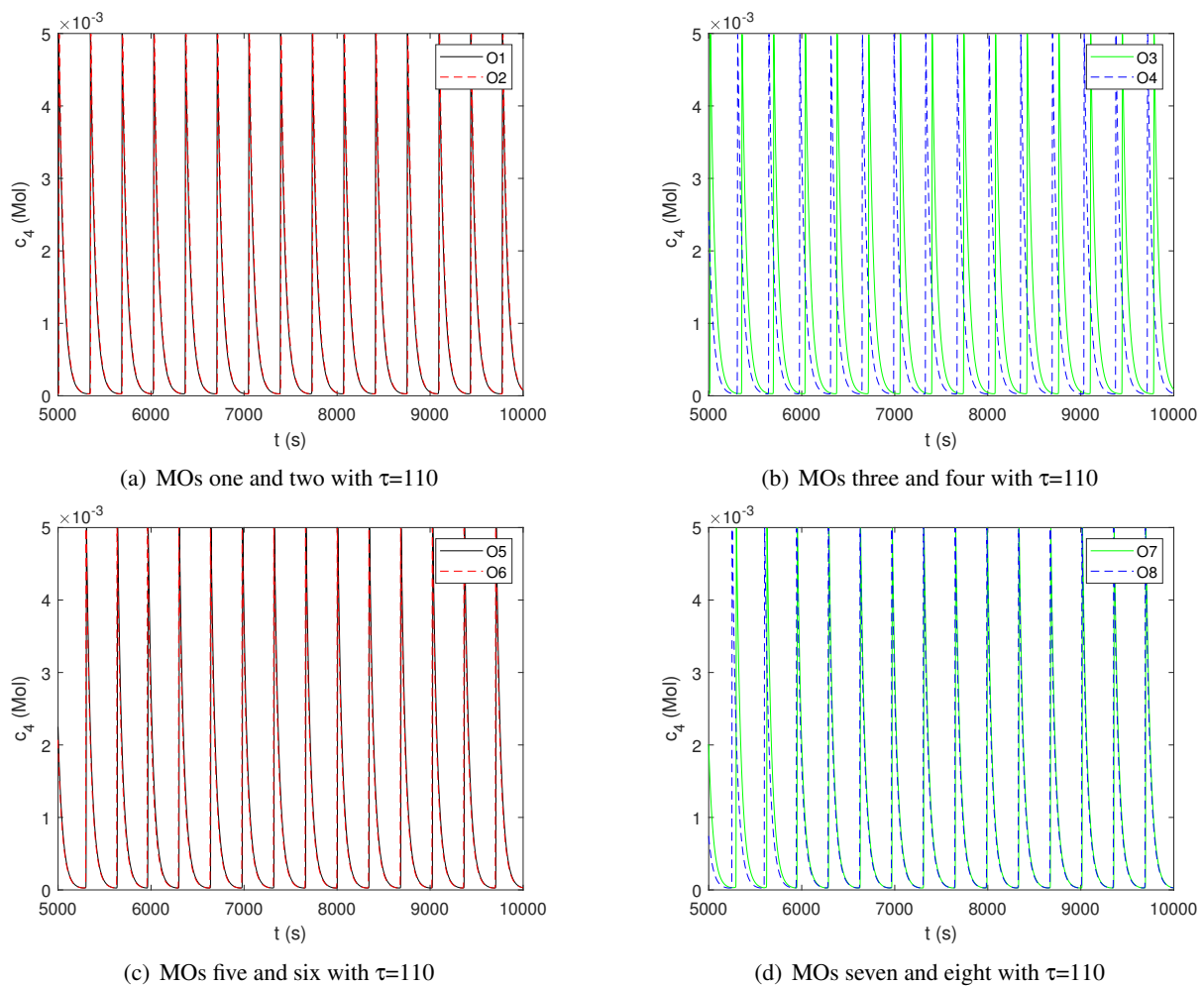


Figure 2: Trend of c_4 for all eight MicroOscillators (MOs) of the system, with $\tau=110$.

REFERENCES

- [1] Agrawal, V., Zhang, C., Shapiro, A.D., Dhurjati, P.S. (2004). *A dynamic mathematical model to clarify signaling circuitry underlying programmed cell death control in Arabidopsis disease resistance*. Biotechnol. Prog., 20, 426-42.
- [2] Bellen, A., Zerraro, M. (2003). *Numerical Methods for Delay Differential Equations*. Editor: Oxford University Press. Book necklace: Numerical Mathematics and Scientific.
- [3] Belousov, B. P. (1959). *An oscillating reaction and its mechanism*. Sborn. referat. radiat. med. (Collection of abstracts on radiation medicine), Medgiz.
- [4] Budroni, M.A., Rossi, F. (2015). *A novel mechanism for in situ nucleation of spirals controlled by the interplay between phase fronts and reaction-diffusion waves in an oscillatory medium*. J. Phys. Chem., C119(17), 9411-9417.

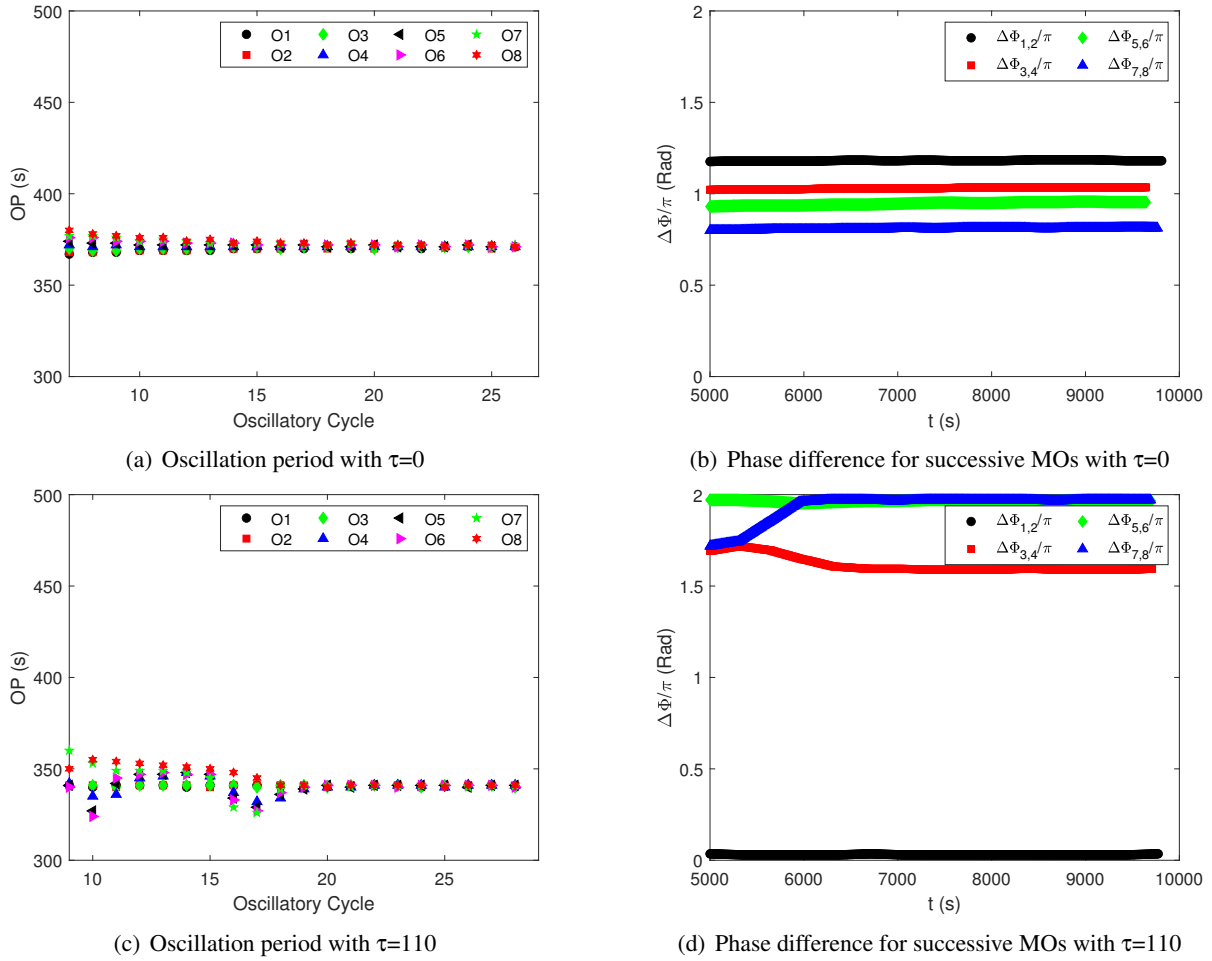


Figure 3: Period and Phase Difference of c_4 for the MicroOscillators (MOs) of the system, with $\tau=0$ and $\tau=110$.

- [5] Budroni, M.A., Torbensen, K., Ristori, S., Abou-Hassan, A., & Rossi, F. (2020). *Membrane Structure Drives Synchronization Patterns in Arrays of Diffusively Coupled Self-Oscillating Droplets*. J. Phys. Chem. Lett., 11, 2014-2020.
- [6] Budroni, M.A., Torbensen, K., Pantani O.L., Ristori, S., Rossi, F., & Abou-Hassan, A. (2020). *Microfluidic Compartmentalization of Diffusively Coupled Oscillators in Multisomes Induces a Novel Synchronization Scenario*. Chem. Commun., 58(79), 11771-11774.
- [7] D'Ambrosio, R., Moccaldi, M., Paternoster, B., Rossi, F. (2017). *On the Employ of Time Series in the Numerical Treatment of Differential Equations Modeling Oscillatory Phenomena*. Communications in Computer and Information Science, Vol. 708, 10.1007/978-3-319-57711-1-16.
- [8] D'Ambrosio, R., Moccaldi, M., Paternoster, B., & Rossi, F. (2018). *Adapted numerical modelling of the Belousov-Zhabotinsky reaction*. J. Math. Chem., 56, 2876-2897.
- [9] Conte, D., D'Ambrosio, R., Pagano, G., Paternoster, B. (2020). *Jacobian-dependent vs Jacobian-*

- free discretizations for nonlinear differential problems*. Computational and Applied Mathematics, 39. 10.1007/s40314-020-01200-z.
- [10] Epstein I. R. and Xu, B. (2016). *Reaction-diffusion processes at the nano- and microscales*. Nat. Nano., 11, 312-319.
- [11] Field, R. J. and Noyes, R. M. (1974). *Oscillations in chemical systems. IV. Limit cycle behavior in a model of a real chemical reaction*. J. Chem. Phys., 60, 1877-1884.
- [12] Guglielmi, N., Hairer, E. (2001). *Implementing Radau IIA Methods for Stiff Delay Differential Equations*. Computing 67, 1-12. <https://doi.org/10.1007/s006070170013>.
- [13] Ixaru, L. Gr. (2012). *Runge–Kutta method with equation dependent coefficients*. Comput. Phys. Commun., 183 (1):63-69.
- [14] Ixaru, L. Gr. (2013). *Runge–Kutta methods with equation dependent coefficients*. Lect. Notes Comput. Sci., 8236:327-336.
- [15] Ixaru, L. Gr. (2013). *Runge–Kutta methods of special form*. J. Phys. Conf. Ser., 413(1). Article number: 012033.
- [16] Ixaru, L. Gr. (2019). *Exponential and trigonometrical fittings: user-friendly expressions for the coefficients*. Numer. Algorithms, 82:1085-1096.
- [17] Lambert, D. J. (1991). *Numerical Methods for Ordinary Differential Systems: The Initial Value Problem*. Editor: John Wiley and Sons Inc.
- [18] Marchettini, N., Budroni, M. A., Rossi, F., Masia, M., Liveri, M. L. T., Rustici, M. (2010). *Role of the reagents consumption in the chaotic dynamics of the Belousov–Zhabotinsky oscillator in closed unstirred reactors*. Phys. Chem. Chem. Phys., 12(36), 11062-11069.
- [19] Rossi, F., Ristori, S., Rustici, M., Marchettini, N., Tiezzi, E. (2008). *Dynamics of pattern formation in biomimetic systems*. J. Theor. Biol., 255(4), 404-412.
- [20] Rossi, F., Budroni, M. A., Marchettini, N., Carballido-Landeira, J. (2012). *Segmented waves in a reaction–diffusion–convection system*. Chaos: an interdisciplinary. J. Nonlinear Sci. 22(3), 037109.
- [21] Rossi F., Zenati, A., Ristori, S., Noel, J.-M., Cabuil, V., Kanoufi, F., Abou-Hassan, A. (2015). *Activatory Coupling Among Oscillating Droplets Produced in Microfluidic Based Devices* Int. J. Unconven. Comp., 11(1), 23-36.
- [22] Shampine, L.F., Reichelt, M. (1997). *The Matlab ODE suite*. SIAM Journal on Scientific Computing, Vol. 18, No. 1, pp. 1-22, January 1997. 10.1137/S1064827594276424.
- [23] Shampine, L. F., Gladwell, I., Thompson, S. (2003). *Solving ODEs with MATLAB*. Editor: Cambridge University Press.
- [24] Taylor, A. F. (2002). *Mechanism and phenomenology of an oscillating chemical reaction*. Prog. React. Kinet. Mech. 27(4), 247-325.
- [25] Tomasi, R., Noel, J.-M., Zenati, A., Ristori, S., Rossi, F., Cabuil, V., Kanoufi, F., Abou-Hassan, A. (2014). *Chemical Communication between Liposomes Encapsulating a Chemical Oscillatory Reaction*. Chem. Sci. 5(5), 1854-1859.

- [26] Torbensen, K., Rossi, F., Ristori, S., Abou-Hassan, A. (2017). *Chemical communication and dynamics of droplet emulsions in networks of Belousov–Zhabotinsky micro-oscillators produced by microfluidics*. Lab. Chip., 17(7), 1179-1189.
- [27] Torbensen, K., Ristori, S., Rossi, F., Abou-Hassan, A. (2017). *Tuning the chemical communication of oscillating microdroplets by means of membrane composition*. J. Phys. Chem. C, 121(24), 13256-13264.
- [28] Zaikin, A.N., Zhabotinsky, A.M. (1970). *Concentration wave propagation in two-dimensional liquid-phase self-oscillating system*. Nature, 225(5232), 535-537.
- [29] Zhabotinsky, A.M., Rossi, F. (2006). *A brief tale on how chemical oscillations became popular: an interview with Anatol Zhabotinsky*. Int. J. Des. Nat. Ecodyn., 1(4), 323-326.