Modeling a population of switches via chaotic dynamics

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Abstract: This note investigates the behavior of a population of interconnected irreversible switches, whose switching mechanism is triggered by a chaotic map. Motivation comes from the fact that many emergent properties of biological systems are ruled by the activation of a population of biochemical switches, whose timing and fluctuations may lead to different cell fates. They have been usually investigated according to a stochastic approach, and in this work we show how some properties could be similarly explained in terms of the emergent properties of a chaotic system. With respect to noise, chaos comes out from a deterministic framework, thereby allowing the implementation of experimental procedures directed to investigate the behavior of the system according to different scenarios by means of a rigorous deterministic passage from mathematics to simulation, that cannot be honestly rendered for the stochastic framework, since pseudo-random sequences are usually invoked.

Keywords: Mathematical modeling, Chaotic Systems, Stochastic Systems, Synthetic Biology

1. INTRODUCTION

In this contribution we characterize a population of independent interconnected switches by means of chaotic maps and circuits. Inspiration stems from a recent paper [Manes et al. (2018)] where the same modeling problem was addressed according to a stochastic framework where the activation time of individual elementary switches was provided by a continuous-time Markov chain. Both works are motivated by the need to understand how timing and synchronization mechanisms emerge from a large variety of molecular and cellular activities in Systems Biology where, in many cases, switch-like regulators are involved in order to control complex molecular pathways and cellular functions. They may refer to an inherently discrete behavior, like for key biochemical regulators that can exist in two alternative biochemical conformations, often referred to as *on* and *off* states, thus obeying to an intrinsic binary dynamics. Typical examples include G proteins, molecular switches of pharmacological interest whose activation state depends on the bound nucleotide, [Kamato et al. (2015)], or proteins whose phosphorylation state controls enzyme activity - often within a kinase cascade - or the choice of interaction partner, [Salazar et al. (2010)]. On the other hand, there can be found biological phenomena that, though inherently continuous, can be usefully modeled by means of switches as well. This is the case of regulators that undergo a switch-like behavior, for instance when they are almost insensitive to small input stimuli until a threshold value, after which the response curve becomes very steep ("ultrasensitive" response). Ultrasensitivity can be generated in many different biochemical ways (for instance, nearly 40 years ago, a pioneering theoretical paper, [Goldbeter & Koshland (1981)], proposed that phosphorylation/dephosphorylation cycles can act as molecular switches in metabolism, cell cycle regulation and development), and it is known to enable more complicated systems, such as cascade amplifiers, bistable switches, and oscillators, to operate effectively. More details on ultrasensitivity can be found in [Ferrel & Ha (2014a,b,c)].

In [Manes et al. (2018)] a framework of stochastic mathematical models associated to populations of such kind of biological devices has been presented, individually modeled by irreversible switches. By showing different series and parallel combinations of elementary modules, a measure of the coherence in the activity of such switch populations was proposed, whose proper tuning allows to reduce the stochastic variability. The choice of a stochastic framework to model the basic switching biological device was motivated by the importance of the noise role in biological processes [Mettetal & van Oudenaarden (2007)]. Random fluctuations, provided by a wide set of concurring factors including, for instance, thermal noise or asynchronous occurrence of synthesis and degradation events, need to be considered when modeling most of the molecular processes involved in cellular regulation, as well as in gene expression, see e.g. [Bahar et al. (2006); Bruggeman et al. (2009)]. All these random factors can be thought of, for instance, as underlining the accumulation of an enzyme eventually stimulating the switch-like response.

In this work we investigate the possibility to model switching mechanisms beyond the classic Markov chain framework. In particular, we focus on the introduction of a deterministic, yet erratic, switching law based on chaotic systems [Buscarino et al. (2017)]. Chaos and chaotic flows are characterized by highly uncorrelated broadband oscillations with a strong sensitivity to initial conditions. Chaotic sequences will be then linked to switching mechanisms, determining in a fundamentally different way the time at which the switch occurs. It is worth to mention that chaotic sequences find application also in capturing the key features of signals reducing the number of measurements, a technique known as compressive sensing [Yu et al. (2010)]. The use of chaos is there adopted to the define the pseudo-random matrix in spite of the Gaussian or Bernoulli matrix considered in standard compressive sensing. The main advantage is the ease of physical implementation of chaos generators [Buscarino et al. (2017)].

Moreover, from a modeling perspective, chaos is the outcome of a deterministic nonlinear system and it has been proven valuable in controlling complex dynamical process. In [Bucolo et al. (2019)], chaotic vibrations are adopted to control the collective behavior of electromechanical switching devices.

These considerations led us to explore whether chaos can be a relevant model for those biological processes regulating the activation processes in cells. Moreover, chaos is controllable [Chen & Yu (2003)] and different chaotic systems can be coupled in order to include possible dependencies in concurrent switching.

The paper is organized as follows: in Section 2 the concept of chaotic irreversible switch will be presented considering the logistic map as a chaotic process driving the switching process; in Section 3 the analysis of a series of chaotic switches and their synchronization properties will be explored, while in Section 4 some preliminary results on the adoption of a continuous-time flow to drive the switching process are given. Finally, a comparative analysis between the proposed scenarios and the stochastic approach is given in Section 5.

2. CHAOTIC IRREVERSIBLE SWITCHES

In order to explore the effects of considering a chaotic dynamics to determine the switching time of irreversible switches, we will focus on two different dynamical systems to generate the chaotic sequences. In particular, we will consider switching times driven by a discrete-time flow regulated by a logistic map [Peitgen et al. (2006)] and the case of a continuous-time flow generated by the so-called Chua's circuit [Matsumoto et al. (1985); Fortuna et al. (2009)]. These two dynamical systems represent paradigmatic cases of discrete-time and continuous-time chaotic flows whose physical implementation are well standardized. In the view of the realization of a hybrid electronic apparatus able to mimic complex switching behavior, either using digital microcontrollers and/or analog components [Buscarino et al. (2017)].

The logistic map represents a paradigmatic example of a simple, first order discrete-time nonlinear system able to show a complex behavior, including deterministic chaos. Originally introduced in the XIX century by P. Verhulst [Strogatz et al. (2009); Peitgen et al. (2006)] to model the dynamics of the size of populations of living beings, the logistic map is described by the following equation:

$$x_{i+1} = rx_i\left(1 - x_i\right) \qquad (1)$$

where r is a system parameter. Notably, the system encompasses a unique quadratic nonlinearity. The value of the system parameter r allows to obtain a plethora of dynamical behavior, ranging from equilibria, periodic oscillations, intermittency and chaos. The idea is to adopt the logistic equation (1) to draw the switching time of an irreversible switch. We will choose the system parameter r, so that a chaotic behavior can be obtained. The logistical map (1), in fact, undergoes a cascade of period-doubling bifurcation by letting the parameter r increase [Buscarino et al. (2017)] which leads to a chaotic behavior spanning the entire interval $[0; 1]$ when $r = 4$. In the definition of the switching time for elementary chaotic switches, we exploit one of the peculiarities of chaotic systems, namely their strong sensitivity to initial conditions, i.e. the property for which choosing two arbitrarily close initial conditions, the evolution of the map strongly differs. The switching time τ_{ON} is, in fact, selected iterating T steps Eq. (1) starting from an initial condition x_0 selected as a random value drawn from a uniform distribution in the interval $[0; 1]$. The switching time is, hence, selected as $\tau_{ON} = x_T$, thus introducing the concept of elementary chaotic switch. We note here that, due to the intrinsic peculiarities of chaotic systems, the statistical properties of the distribution of initial condition does not influence the distribution of τ_{ON} as T increases.

To evaluate the distribution of switching times for the chaotic irreversible switch, the Cumulative Distribution Function (CDF) of τ_{ON}, i.e.

$$F(t) = P\left\{\tau_{ON} \leq t\right\}, \qquad t \geq 0 \qquad (2)$$

can be computed for (1) with $r = 4$ as

$$F(t) = \frac{2\sin^{-1}\sqrt{t}}{\pi}, \qquad 0 \leq t \leq 1, \qquad (3)$$

see [Peitgen et al. (2006)]. Note that the logistic map (1) for $r = 4$ assumes values in the interval $[0; 1]$, therefore switching times can be considered as normalized up to the largest time allowed with respect to the specifically modeled process.

3. SERIES OF IRREVERSIBLE CHAOTIC SWITCHES BASED ON THE LOGISTIC MAP

Let us consider a series of N_s irreversible switches, as schematically reported in Fig. 1.

Each switch is associated to a logistic map as in Eq. (1):

$$x^j_{i+1} = rx^j_i\left(1 - x^j_i\right) \qquad (4)$$

with $j = 1 \ldots N_s$ and $r = 4$, thus ensuring the emergence of a chaotic behavior [Buscarino et al. (2017)]. Let

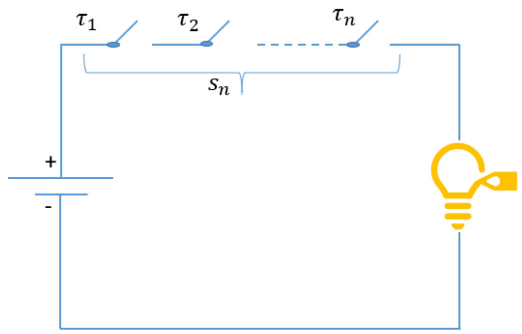

Fig. 1. Schematic representation of a series of N_s irreversible switches.

$\{\tau_1, \tau_2, \ldots \tau_{N_s}\}$ be the switching times for each switch in the series, with $\tau_j = x_T^j$ where $T = 1000$. Therefore, the series will be active with a $\tau_{ON} = \sup\{\tau_1, \tau_2, \ldots \tau_{N_s}\}$.

It is worth to note that the selection of T large enough is important to guarantee that the value assumed by the logistic map is uncorrelated with respect to the initial condition, thus ensuring that the stochastic selection of initial condition provides a limited influence on the statistical properties of $\{\tau_1, \tau_2, \ldots \tau_{N_s}\}$. We fixed $T = 1000$ to stress this point, however similar results can be found with values of T sensibly lower, due to the nature of the chaotic flow.

The CDF for the series of chaotic switches can be computed as

$$F_{N_s}(t) = P\{\tau_{ON} \le t\} = \prod_{i=1}^{N_s} P\{\tau_i \le t\} = \prod_{i=1}^{N_s} F_i(t) = \left(\frac{2\sin^{-1}\sqrt{t}}{\pi}\right)^{N_s} \quad (5)$$

with $0 \le t \le 1$. The CDF for $r = 4$ in (4) for different values of N_s is reported in Fig. 2.

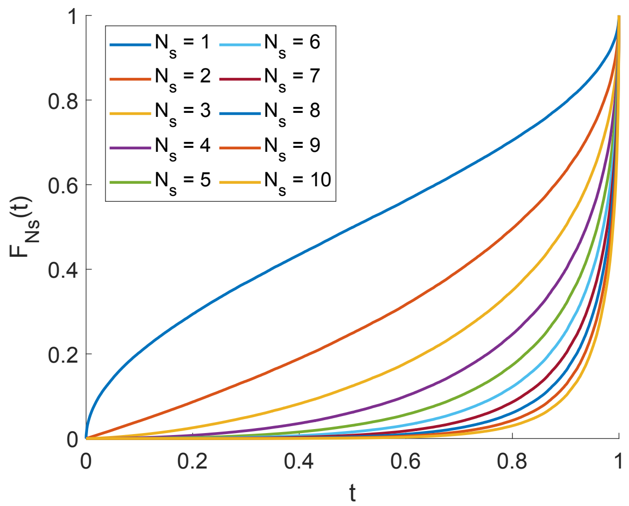

Fig. 2. CDF for series of N_s irreversible switches.

In order to determine the performance of the adoption of irreversible chaotic switches in terms of timing and synchronization of the switching processes, we calculated τ_{ON} for a series of N_s chaotic switches, over $N = 10^5$ realizations, fixing $r = 4$ in Eq. 1. The coefficient of variation [Manes et al. (2018)] defined as

$$CV_{N_s} = \frac{\sigma_{ON}}{\bar{\tau}_{ON}}$$

where σ_{ON} and $\bar{\tau}_{ON}$ are the standard deviation and mean value, respectively, of the switching times τ_s over the N realizations, is evaluated for different values of N_s, i.e. varying the number of switches in the series. In Fig. 3, the value of CV is reported for different values of N_s.

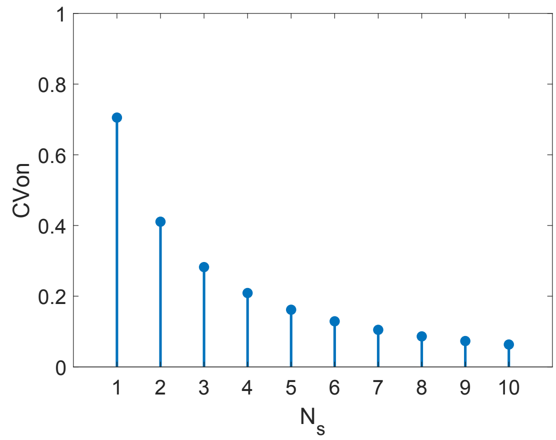

Fig. 3. Coefficient of variation calculated for N_s chaotic irreversible switches, each associated to a logistic map with $r = 4$.

The decreasing trend of CV reported in Fig. 3 allows to assess that the degree of switching synchronization for the population of chaotic switches in series increases when N_s is increased.

Moreover, CV approaches zeros with a decrease rate sensibly higher than that reported for stochastic switches [Manes et al. (2018)]. For the sake of comparison we report in Fig. 4, the CVs calculated for stochastic switches regulated by an exponential distribution of switching times as in [Manes et al. (2018)], thus enhancing the capability of the model to catch the ultrasensitive response observed in biochemical regulators [Ferrel & Ha (2014a)].

4. SERIES OF IRREVERSIBLE CHAOTIC SWITCHES BASED ON THE CHUA'S CIRCUIT

When considering a continuous-time chaotic dynamical system to govern switching mechanisms, a different strategy to select τ_{ON} is needed. Let us focus on the Chua's circuit, the first example of nonlinear circuit intentionally designed to observe chaos [Fortuna et al. (2009)]. The circuit dynamics is governed by the following dimensionless equations:

$$\begin{aligned} \dot{x} &= \alpha\,[y - h(x)] \\ \dot{y} &= x - y + z \\ \dot{z} &= -\beta y \end{aligned} \quad (6)$$

where

$$h(x) = m_1 x + \frac{1}{2}(m_0 - m_1)\,[|x+1| - |x-1|]$$

is a piece-wise linear (PWL) function, being α, β, m_0, and m_1 system parameters. The Chua's circuit chaotic

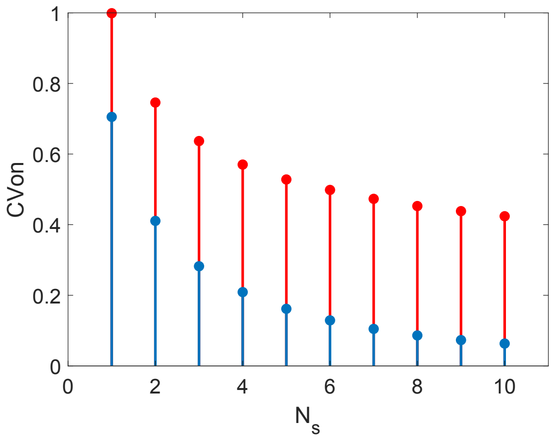

Fig. 4. Coefficient of variation calculated for N_s irreversible switches: stochastic switches (red), chaotic switches (blue: logistic map).

attractor is the well-known double-scroll when $\alpha = 9$, $\beta = 14.286$, $m_0 = -\frac{1}{7}$, and $m_1 = \frac{2}{7}$.

The selection of the switching time τ_{ON} is performed by defining the recurrence time t_R according to [Buscarino et al. (2013)], where it is defined as the time needed to the system trajectory to revisit a previously visited region of the phase-space. More specifically, given a trajectory $\mathrm{x}(t)$ solution of (6) with initial conditions $\mathrm{x}(t_0)$, let us take a general point $\bar{\mathrm{x}} = \mathrm{x}(\bar{t})$. We start from this point and determine when the trajectory comes close to $\bar{\mathrm{x}}$. More rigorously, when

$$||\mathrm{x}(t_1) - \bar{\mathrm{x}}|| \leq \rho$$

where ρ is a given threshold, then $t_R = t_1$.

In [Buscarino et al. (2013)], an extensive analysis of the recurrence time for different values of the system parameters has been performed. On the basis of this analysis, we select, without lack of generality, the region of the phase-space reported in Fig. 5, with $\rho = 0.02$. Therefore, given an initial condition selected as a random value drawn from a gaussian distribution with zero mean and unit standard deviation, the switching time of the chaotic irreversible switch associated to the Chua's circuit is $\tau_{ON} = t_R$. In this case, the CDF cannot be computed analytically, but must be derived numerical.

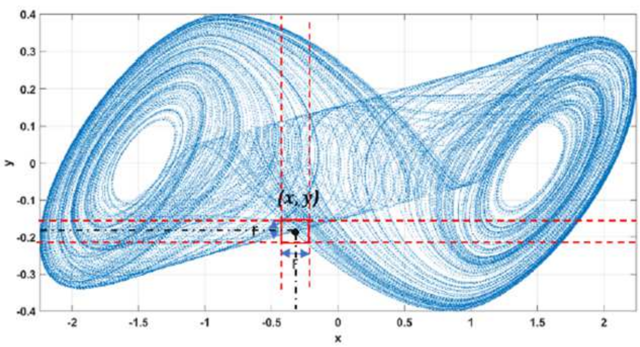

Fig. 5. Region of the Chua's circuit attractor for the definition of the recurrence time t_R. The region is centered on the point $(-0.32, -0.18)$ and the amplitude of the windows is $F = 2\rho = 0.04$ along both directions.

The preliminary results in terms of CV calculated for a series of N_s chaotic switches based on the Chua's circuit attractor is reported in Fig. 6, thus confirming the validity of the approach.

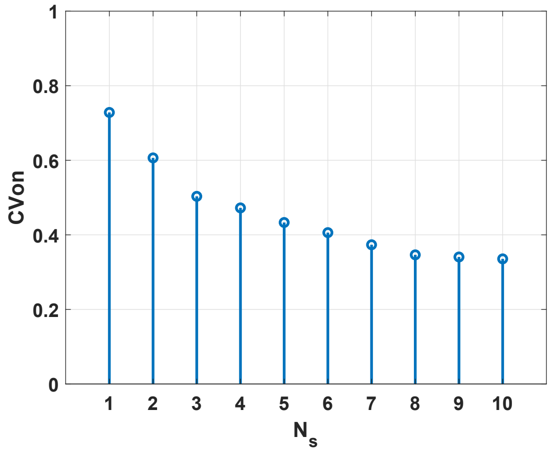

Fig. 6. Coefficient of variation calculated for N_s irreversible chaotic switches based on the Chua's circuit.

5. DISCUSSION AND CONCLUSIONS

The main result presented in this paper is the possibility to move beyond a stochastic approach for modeling timing and synchronization in populations of biologically inspired irreversible switches. The key feature observed in the context of a Markov approach, i.e. the enhancement of synchronizability in series of irreversible switching processes, is maintained also when considering a deterministic, yet erratic, dynamical process regulating the switching times. In this contribution, we focused on a comparative analysis with respect to the stochastic approach to model switching behavior. As it appears clearly from a direct comparison of the CV trends for the different strategies to select switching times (see Fig. 7), the descent rates with respect to N_s is significantly different among the three cases considered here. This represents a further key result, since it would allow, in a modeling perspective, a proper selection of the best switching mechanisms with respect to an observed physical process.

Moreover, the adoption of a deterministic rule based on the chaotic logistic map opens the way to novel scenarios, accounting also for ultrasensitivity in biological switching mechanism. In fact, the reduction of the coefficient of variation in a series of chaotic irreversible switches occurs at a lower number of switches in the series, with respect to the stochastic approach.

The contribution paves the way also towards the characterization of the process with respect to different chaotic dynamics, either discrete-time or continuous-time, regulating the switching times. Especially in the view of a circuit implementation of a programmable device exploiting real chaotic switches, we explored the possibility of adopting a continuous-time chaotic system to regulate switching mechanisms.

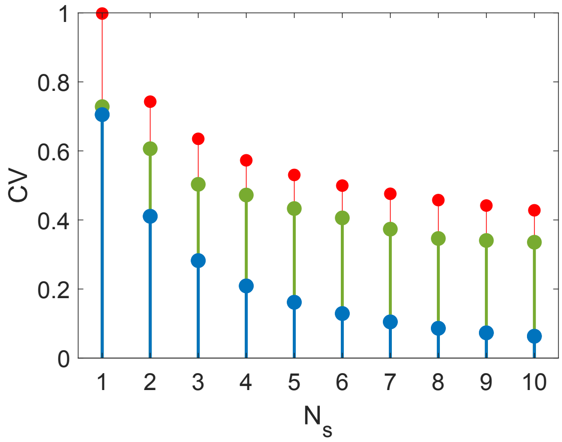

Fig. 7. Comparison of the coefficients of variation calculated for N_s irreversible: stochastic switches (red), chaotic switches (blue: logistic map; green: Chua's circuit).

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REFERENCES

Bahar, R., Hartmann, C.H., Rodriguez, K.A., Denny, A.D., Busuttil, R.A., Dollé, M.E., Calder, R.B., Chisholm, G.B., Pollock, B.H., Klein, C.A., Vijg, J., Increased cell-to-cell variation in gene expression in ageing mouse heart. *Nature*, 441, 10111014, 2006.

Bruggeman, F.J., Bluthgen, N., Westerhoff, H.V., Noise management by molecular networks. *PLoS Comput. Biol.* 5(9), 2009.

Bucolo, M., Buscarino, A., Famoso, C., Fortuna, L., Frasca, M. (2019). Control of imperfect dynamical systems. Nonlinear Dynamics, 98(4), 2989-2999.

Buscarino, A., Fortuna, L., Frasca, M., Chua's time, in Adamatzky, A., Chaos, CNN, memristors and beyond: A festschrift for Leon Chua. World Scientific, 2013.

Buscarino, A., Fortuna, L., Frasca, M., Essentials of Nonlinear Circuit Dynamics with MATLAB and Laboratory Experiments. CRC Press, 2017.

Chen, G., Yu, X. (Eds.), Chaos control: theory and applications. Springer Science & Business Media, 2003.

Ferrell, Jr,, J.E, Ha, S.H., Ultrasensitivity part I: Michaelian responses and zero-order ultrasensitivity. *Trends Biochem Sci*, 39(10), 496–503, 2014a.

Ferrell, Jr, J.E, Ha, S.H., Ultrasensitivity part II: multisite phosphorylation, stochiometric inhibitors, and positive feedback. *Trends Biochem Sci*, 39(11), 556–569, 2014b.

Ferrell, Jr, J.E, Ha, S.H., Ultrasensitivity part III: cascades, bistable switches, and oscillators. *Trends Biochem Sci*, 39(12), 612–618, 2014c.

Fortuna, L., Frasca, M., Xibilia, M. G., Chua's Circuit Implementations: Yesterday, Today And Tomorrow (Vol. 65). World Scientific, 2009.

Goldbeter, A., Koshland, Jr, D.E., An amplified sensitivity arising from covalent modification in biological systems. *Proc Natl Acad Sci*, 78, 6840–6844, 1981.

Kamato, D., Thach, L., Bernard, R., Chan, V., Zheng, W., Kaur, H., Brimble, M., Osman, N., Little, P.J., Structure, function, pharmacology, and therapeutic potential of the G protein, $G_{\alpha/q,11}$. *Front. Cardiovasc. Med.*, 2:14., 2015.

Manes, C., Palumbo, P., Cusimano, V., Vanoni, M., Alberghina, L., Modeling biological timing and synchronization mechanisms by means of interconnections of stochastic switches. *IEEE Control Systems Letters* 2(1), 19–24, 2009.

Matsumoto, T., Chua, L. O., Komuro, M., The Double Scroll, *IEEE Transactions on Circuits and Systems*, **32**, pp., 797–818, 1985.

Mettetal, J., van Oudenaarden, A., Necessary noise, *Science*, 317, 2007.

Peitgen, H. O., Jürgens, H., Saupe, D., Chaos and fractals: new frontiers of science. Springer Science & Business Media, 2006.

Salazar, C., Brummer, A., Alberghina, L., Hofer, T., Timing control in regulatory networks by multisite protein modifications. *Trends in Cell Biology*, 20(11), 634–641, 2010.

Strogatz, S., Nonlinear Dynamics and Chaos (2nd Ed.). Westview Press, 2014.

Yu, L., Barbot, J. P., Zheng, G., Sun, H. (2010). Compressive sensing with chaotic sequence. IEEE Signal Processing Letters, 17(8), 731-734.