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Review

A tale of two rhythms: Locked clocks and chaos in biology

Mathias L. Heltberg,[1,4] Sandeep Krishna,[3] Leo P. Kadanoff,[2,5] and Mogens H. Jensen[1,2,*]
[1]Niels Bohr Institute, University of Copenhagen, 2100 Copenhagen, Denmark
[2]The James Franck Institute, The University of Chicago, Chicago, IL 60637, USA
[3]Simons Centre for the Study of Living Machines, National Centre for Biological Sciences TIFR, GKVK Campus, Bellary Road, Bangalore 560065, India
[4]Laboratoire de Physique Théorique, Ecole Normale Supérieure, 75 231 Paris Cedex 05, France
[5]Deceased
*Correspondence: mhjensen@nbi.ku.dk
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SUMMARY

The fundamental mechanisms that control and regulate biological organisms exhibit a surprising level of complexity. Oscillators are perhaps the simplest motifs that produce time-varying dynamics and are ubiquitous in biological systems. It is also known that such biological oscillators interact with each other—for instance, circadian oscillators affect the cell cycle, and somitogenesis clock proteins in adjacent cells affect each other in developing embryos. Therefore, it is vital to understand the effects that can emerge from nonlinear interaction between oscillations. Here, we show how oscillations typically arise in biology and take the reader on a tour through the great variety in dynamics that can emerge even from a single pair of coupled oscillators. We explain how chaotic dynamics can emerge and outline the methods of detecting this in experimental time traces. Finally, we discuss the potential role of such complex dynamical features in biological systems.

INTRODUCTION

Living species present us with a bewildering fauna of rhythms and oscillations: circadian rhythms (Nobel Prize 2017) (Zehring et al., 1984; Bargiello et al., 1984; Hardin et al., 1990; Thommen et al., 2010), cell cycles (Tsai et al., 2008), calcium oscillations (Goldbeter, 2002), pace maker cells (O'Rourke et al., 1994), transcription factor responses (Hoffmann et al., 2002; Lahav et al., 2004; Nelson et al., 2004; Krishna et al., 2006; Zhang et al, 2017), hormone secretion (Waite et al., 2009), and so on. Given the ubiquity of oscillators, a natural question is as follows: if two oscillators are each other's neighbors—as they might well be in tissues, organs, and cells—will they couple and generate complex dynamics? Two coupled rhythms are ubiquitous all over nature, not least in the biological world. Indeed, as described in physics, coupling two oscillators is one of the most general ways to produce diverse dynamics—from synchronization to chaos (Pikovsky et al., 2003). Therefore, it is important to consider the possibilities of how life might exploit the effects of complex dynamics arising from coupled oscillators, and whether these phenomena exhibit common properties even if one situation deals with cells and another with proteins.

Modern experimental tools now allow direct observation of the dynamical evolution of different proteins, molecules, and signals (Alon, 2006; Goldbeter, 2010; Sneppen, 2014). Thus, we can study the exact trajectory and take dynamical features such as responses and fluctuations into account and describe the existence of higher dimensional dynamics—with oscillations as the simplest example (Strogatz, 2018). This paves a way to new insights into biological systems, based on mathematical predictions and experimental tests.

In this review, we illustrate the effects that can arise from a set of two coupled oscillators (Nijhoff, 1893; Jensen et al., 1984; Bohr et al., 1984; Stavans et al., 1985; Gwinn and Westervelt, 1986; Pikovsky et al., 2003; Gupta et al., 2018). We work through simple, conceptual examples, starting with a small coupling constant existing between two oscillators where quasi periodicity and synchronization is found, and then discuss the concepts of multistable cycles, period doublings, and chaos that arise as the interaction strength increases (Strogatz, 2018). We define the characteristics of chaos and explain how chaotic dynamics might be identified from time traces in experimental biology. Finally, we describe the dynamical features that result from coupled oscillators in biology and speculate whether these functions and properties might be useful for biological systems. We argue that the importance of dynamics in maintaining the complexity found in life is one of the least investigated areas of modern science (Sneppen, 2014). We suggest that an interdisciplinary understanding of dynamical features in biological organisms can lead to great advances within systems biology.

Synchronization and entrainment between two oscillators

Oscillations are found in a vast number of biological systems (see Figure 1A for a schematic depicting the variety of the timescales of oscillations in biology), from the spikes in membrane potential to the circadian clock; and they typically arise in networks with

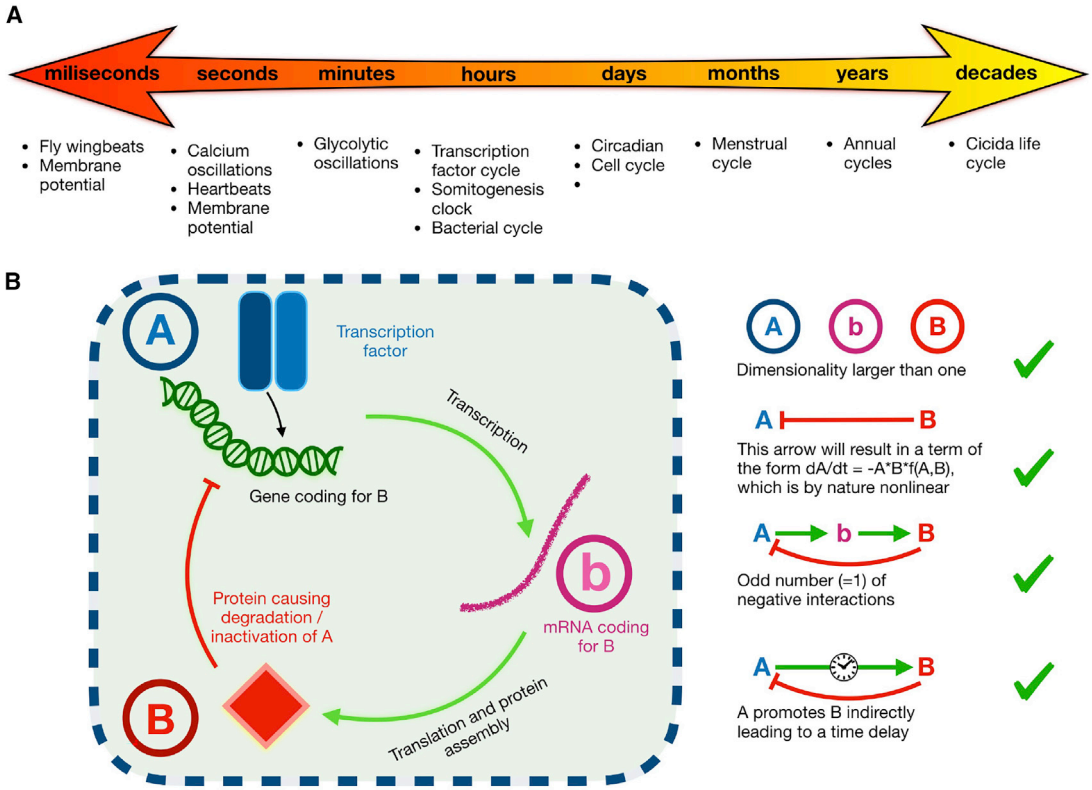


Figure 1. Diversity of oscillations in biology

(A) Schematic figure showing that oscillations in biology are a fundamental property which occur in a broad variety of different systems at many different timescales (Zehring et al., 1984; Bargiello et al., 1984; Hardin et al., 1990; Thommen et al., 2010; Tsai et al., 2008; Goldbeter, 2002; O'Rourke et al., 1994; Hoffmann et al., 2002; Lahav et al., 2004; Nelson et al., 2004; Waite et al., 2009; Zhang et al, 2017).

(B) Schematic version of a typical network with a transcription factor that stimulates production of its own inhibitor. Note that biological conditions (e.g., stresses, adaptive environmental stimuli, random fluctuations) may change the parameters that govern the interactions and therefore any oscillatory behavior the network exhibits (Mengel et al., 2010).

some fundamental ingredients (Figure 1B). When two oscillations interact, we term them as "coupled oscillators." This represents one of the oldest studies of a non-linear system and goes all the way back to the Dutch physicist and mathematician Christian Huygens (Nijhoff, 1893), who, in 1665, observed how pendulum clocks hanging on the same wall would synchronize with each other. Models of multiple interacting oscillators also show that interactions can lead to synchronization between the entire population of oscillators (Kuramoto, 1975; Garcia-Ojalvo et al., 2004). We will concentrate on the simplest form of coupled oscillators considering the situation where one oscillator (denoted as the external or *X*) is affecting another oscillator (denoted as the internal or *Y*) but is not affected back (Stavans et al., 1985) (i.e., this represents an oscillator driven by an external cycle. For a biological discussion, see Box 1). This is sufficient to give rise to a rich variety of dynamics in the internal oscillator. In such a case, where both the external and the internal systems show oscillations, the resulting dynamics depend on two fundamental properties: their frequency ratio and the interaction strength between the oscillators (Figure 2A).

(1) Frequency ratio: The "bare" ratio between the natural frequencies of the oscillators (i.e., in the absence of interaction between the oscillators).

(2) Interaction strength: The interaction strength describes how much the oscillator will be affected by the external cycle. Its definition depends on the particular system, but the amplitude of the forcing cycle is typically correlated with the interaction strength.

Depending on the frequency ratio, the oscillators can form a locked (or entrained) state, which is denoted by a rational number p/q, where they mathematically form a closed trajectory in phase space, which means that after p periods of the internal oscillator and q periods of the external oscillator the system returns to the same state. If there is no interaction, this will occur only if the frequency ratio is exactly a rational number (see the following section for a more detailed description). If they do not form a closed loop in phase space—typically for weak interactions—their motion will be quasi periodic, where their mutual trajectory will never repeat. In Figure 2B, this is indicated by the orange (external oscillator) and the blue (internal oscillator) trajectories, which have a phase difference that "drifts" over time. In other words, at one time *X* will have a low point right before the peak of *Y*, but after some time *X* will have a low point right after the peak of *Y*. Thereby, *Y* drifts in phase and is not locked with *X*.

If the interaction strength is non-zero, the two oscillations can synchronize even if the frequency ratio is not an exact rational

Box 1. The emergence of protein oscillations through negative feedback-loops with time delay

Oscillations are a fundamental ingredient of many systems in nature. They provide the simplest type of sustained dynamics, if the system is not in a steady state where there is no time variation. Here we focus on oscillations, known as limit cycles, that have a fixed amplitude, independent of the initial conditions of the system (i.e., a harmonic oscillator is not a limit cycle). From a biological perspective, such oscillations can arise through many different mechanisms, but oscillations of protein concentrations in particular are known to emerge from simple networks (Tiana et al 2007). In general, these networks should include:

(1) A dimensionality larger than one. By this we mean that the number of independent variables must be at least two (i.e., there should be interactions between two or more elements in the network).
(2) At least one non-linear term - these will naturally emerge from molecular interactions.
(3) A negative feedback-loop. Such loops can arise in multiple ways, for example in a circuit where one protein has a negative (i.e., inhibitory) impact on another, which in turn has a positive impact on the first. For a feedback-loop to be a negative, the number of negative interactions between components should be an odd number.
(4) There should be an effective time delay in the network. A typical example of this could be a transcription factor that enhances the production of its own inhibitor. Since several steps are involved in the formation of the inhibitor via transcription and translation, such systems exhibit a natural time delay.

These four ingredients are all present in many famous oscillatory protein networks for instance of p53 and NF-kB, as well as in biologically engineered oscillators (Elowitz and Leibler, 2000; Tsai et al., 2008; Jensen and Krishna 2012). From a theoretical point of view, fundamental insight into how these elements can lead to oscillatory dynamics has been mathematically derived (Anantha-subramaniam and Herzel 2014; Morant et al., 2009). One aspect that is not included in these four ingredients is the role of stochastic noise, which is always present in biological systems. Under the right circumstances, noise can drive a system which possesses a damped oscillator (that can be a linear system) into oscillations with well-defined amplitude statistics, and thereby make it look like a noisy limit cycle (Black and McKane 2010; Biancalani et al., 2017).

It is often found that oscillations are not observed at all times but may appear as a response to external stresses. This is schematized in Figure 1B, where a typical three-node network is shown. Here *A* represents a transcription factor, *b* represents the mRNA of *B*, and *B* is an inhibitor of A. Due to the generality of this mechanism, it is plausible that a large fraction of biological networks has the ability to exhibit oscillations triggered by different external stimuli.

number, which means that they will form a closed trajectory in phase space, where the external oscillator will pull the internal oscillator a bit, in order to achieve a rational observed frequency ratio for the system. When the interaction strength is less, the system tends not to synchronize unless the frequency ratio is close to a rational number.

As we increase the interaction strength, starting from a low value, regions of synchronization will be found for a larger span of the frequency ratio, and this structure is formally known as ''Arnold tongues'' (Arnol'd, 1965; Herman, 1979; Jensen et al., 1983, 1984), which are depicted as a diagram in Figure 2A. A ''region of synchronization'' means that the resulting dynamics of the two oscillators is locked to each other in a part of the parameter space, where the axes are the frequency of the external oscillator (or the frequency ratio) and the interaction strength (Heltberg and Jensen, 2019).

These regions can be identified by the observed number of rotations for the two oscillators. For instance, 1/2 would label a region of parameter space where the internal oscillator makes one rotation for every two rotations made by the external oscillator (the same logic goes for 1/3, see Figures 2A, 2C, and 2D). Here, we would like to stress a word of caution: in the literature, there is great mixture between defining 1/2 or 2/1 as the Arnold tongue, where the external oscillator makes two rotations every time the internal makes one. However, in the theory of Arnold tongues, there exist locked states, both where the external makes 2 and 1/2 rotations for each rotation of the internal. Therefore, one should not be confused by this notation but simply be careful writing out plainly whether the external or the internal has the longest period.

As the interaction strength between the two oscillators increases, highly complex phenomena start to emerge. The Arnold tongues are known to grow, meaning that the range of frequencies where the internal oscillator can be controlled widens. Therefore, it is intuitively not hard to imagine that the different tongues themselves start to overlap at some point. This means that for some interaction strengths, two or more Arnold tongues start sharing the same regions of parameter space (Jensen et al., 1984). This leads to the possibility that multiple stable limit cycles co-exist (Heltberg et al., 2016), which causes the internal oscillator to be able to exhibit different frequencies and amplitudes for identical parameters, depending on the initial conditions of the system (Figure 2E).

It is worth noting that the coexistence of two stable states of oscillations in the internal oscillator is defined as bistability (or multistability when there are more than two), which is observed in many biological systems. It is well known from physical studies of bistable systems that a particle, or even the entire system, can make transitions between the two solutions depending on the level of noise in the system. For the case of overlapping Arnold tongues, it is the system's trajectory that can jump between oscillatory states in the presence of noise and thereby change its amplitude and frequency dynamically. This phenomenon was discovered by Heltberg et al. in a study where the dynamical switching of oscillatory modes of NF-kB was found experimentally, and by means of mathematical modeling, the authors could explain the underlying mechanism for this behavior and how it could regulate the protein production (Heltberg et al, 2016). The switching between oscillatory states is named ''modehopping,'' and this phenomenon is believed to allow living organisms

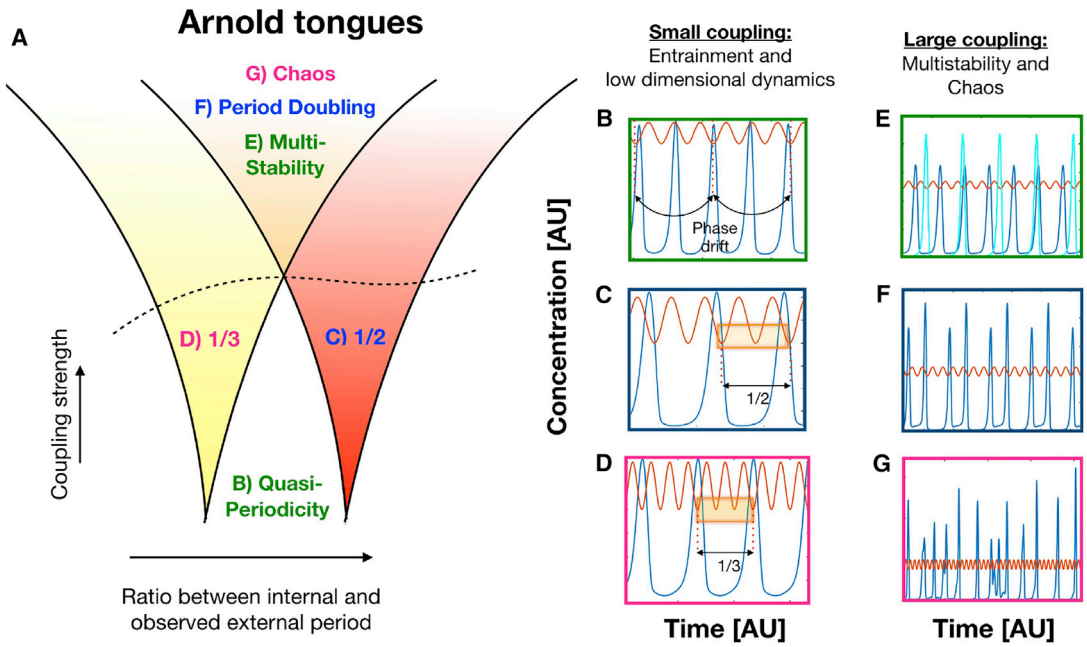


Figure 2. Complex dynamics with two coupled oscillators

(A) Schematic figure showing the growing regions of entrainment known as Arnold tongues (Arnold and Avez, 1968; Jensen et al., 1984). The horizontal axis represents a measure proportional to the external period (for instance its ratio to the unperturbed internal period) and the vertical axis represents the coupling (interaction) strength between the oscillators. The dotted line here represents the critical line where the tongues start to overlap. Arnold tongues are also shown in more details in Figure 3.

(B) Example of quasiperiodic dynamics where the two oscillators do not lock. Orange: external oscillator, blue: internal oscillator. Note that the scale of the internal oscillator is arbitrary in (B–E).

(C) Example of an entrained state (also called a locked or synchronized state), where the external frequency is two times the internal (colors as in B).

(D) Example of an entrained state, where the external frequency is three times the internal (colors as in B).

(E) Above the critical line (dashed line in A) multistability occurs, where two stable oscillations can be found for the same external frequency. Blue: 1/2 and cyan: 1/3.

(F) Example of period-doubling dynamics. Note that it is a locked state, but the internal oscillator exhibits two different peaks before returning to the initial point.

(G) Chaotic dynamics where the fixed frequency of the external oscillator leads to unpredictable dynamics with a spectrum of amplitudes and frequencies observed in the dynamics of the internal oscillator.

to use the existence of noise to exploit possibilities of oscillations with different amplitudes. We emphasize that coupling two oscillators gives a formal scheme to generate multistable cycles, both theoretically and experimentally, which is something that is otherwise completely tedious to achieve.

At this level of the interaction strength, a period-doubling sequence may also start to set in (Feigenbaum, 1978, 1979). Period doubling is a phenomenon where the internal oscillation starts to oscillate with two different amplitudes, for instance, one large and one small, before the pattern is repeated (Figure 2F). This phenomenon typically arises at the center of the Arnold tongues, which is explained further in the next section. Finally, if the interaction strength is increased even further, the system can become chaotic.

Chaos emerges from coupled oscillators

Chaos refers to a well-defined mathematical concept that can emerge in deterministic dynamical systems with at least three dimensions and at least one non-linear interaction. This should not be confused with the use of the word "chaos" in everyday language, which often refers to something that is without any underlying structure, whereas mathematical chaos is very well-defined (Strogatz, 2018).

Even though different definitions are currently being used in the field, the mathematical concept of chaos can be defined by the property that two trajectories, separated initially by an infinitely small amount, will exhibit exponentially diverging trajectories as time proceeds (Figure 3G). As initial conditions are never known with perfect precision, chaotic systems appear random since it is impossible to predict the outcome, even though the system is still deterministic. It should be mentioned that the recent advances of machine learning have enormously improved the predictability on both short term and long term (Lu et al., 2018; Pathak et al., 2018). The trace of a chaotic system is not closed, meaning that the trajectory never repeats itself, however, paradoxically it comes back, infinitely many times, arbitrarily close to states previously visited.

Note that a quasiperiodic behavior also produces an open trajectory, bounded within a sub volume in space, but unlike chaos, two quasi-periodic trajectories that are initiated close to each other will remain close as the system evolves. It can be shown that chaotic systems are confined in the sense that they do not "run off" to infinity, but they also are not "closed" in the sense that they do not repeat the same states as happens in an oscillating system. In some sense, this seems like a contradiction: a trajectory that is always moving within a bounded region but

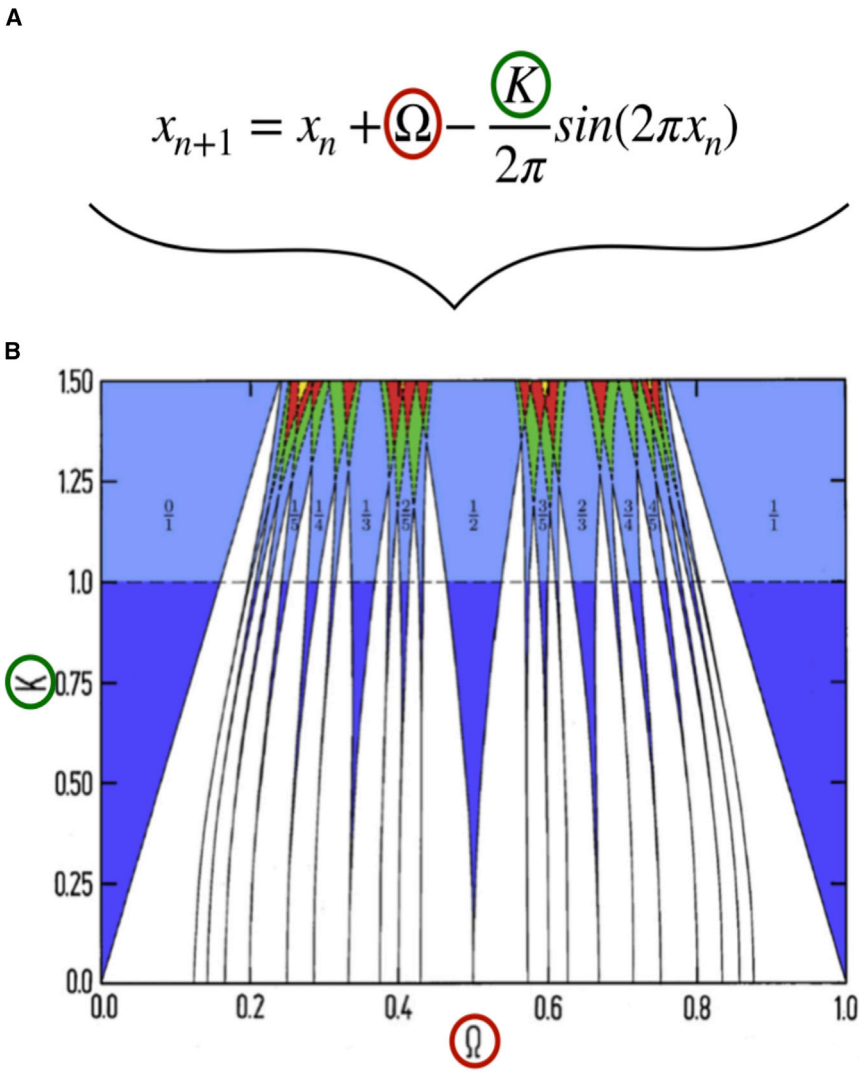


Figure 3. A simple model of coupled oscillators and Arnold tongues

(A) The sine circle map which is expressed in a continuous variable x_n depending on a discrete time step n. The map has two "external" parameters, Ω and K.

(B) The pattern of frequency locking and unlocking in this simplified mathematical model. The x axis on this graph is the basic period of the external oscillator, Ω. The y axis is the strength of the nonlinear interaction between the oscillators, K. The blue regions are ones in which the oscillators are locked; the numbers attached to each region describe the observed frequency ratio for the locking. The white regions show intermixed quasiperiodic and periodic behaviors, too finely intermingled to be separated by our plot. The green and red regions show similarly intermixed behavior, but now also including a chaotic element. The broken line at K = 1 indicates the onset of multistability and chaotic behavior. Above this line, chaos is possible (shown by a change in the blue color) and below it there is only quasiperiodic and locked behavior (Jensen et al., 1983, 1984).

nevertheless passes through new segments of the space that is not previously visited.

Thus, in order to have a trajectory that does not close in on itself, the chaotic trajectory needs to fill up a larger part of the phase space than for instance an oscillation. In mathematical terms, we observe that the chaotic trajectory generates a "strange attractor," and this attractor has a dimension that is larger than two, but not an integer, which is denoted a fractal dimension (Mandelbrot, 1983; Grassberger and Procaccia, 1983; Feder, 1988). Fractals are geometrical objects with the property that they repeat the same similar structures at arbitrary small scales, which come about because the motion on the attractor exhibits stretching and folding in the dynamics, often mimicked by how dough is mixed in a bakery, namely, also by means of stretching and folding (Strogatz, 2018). Many objects in nature exhibit this property (for instance, the ice crystals forming a snowflake), but when we need to define their dimensionality, the classical definition of integer dimensions is no longer valid. Therefore, fractal structures have a dimension that is a real number, and this definition has given rise to many important characterizations of shapes in nature.

These counterintuitive behaviors endow chaotic systems with the following unusual properties: (1) the evolution of the system is highly sensitive to initial conditions; (2) one point of the system is never revisited (i.e., no closed cycles); (3) the system "oscillates" with a spectrum of frequencies and amplitudes; and (4) the dimensionality of the phase space of the system is a noninteger number larger than two. It is tempting to explore whether these properties that, in some sense, are completely counterintuitive are present in biological systems. Below, we describe lessons learned from studying the universal behavior of coupled oscillators in physics, introduce the basic methods to determine chaotic traces in biological data, and discuss the potential advantages that complex dynamics may provide biological organisms.

Universal behavior of coupled oscillators

Historically, the study of two interacting oscillators saw a breakthrough in a simple mathematical model of coupled oscillators, known as the "sine circle map," constructed by A.A. Kolmogorov and later thoroughly investigated by Vladimir Arnold (Arnold and Avez, 1968; Arnol'd, 1965). The name "circle map" refers to the fact that it maps the motion on a torus into a one-dimensional discrete equation on a circle using a Poincare section, and the name "sine" refers to the fact that the interaction is described by a sine-function (Figure 3A). Basically, a Poincare section is a surface that records the point every time the trajectory passes through it (i.e., an N-1-dimensional surface for a trajectory in N dimensions). This model is constructed by considering the state of an oscillator as a phase. The oscillator is evolving cyclically on a closed orbit; and thus, we need only one variable to describe the behavior, and that has allowed great mathematical advances. Even though this model is completely

abstract, it can be used to describe the different kinds of trajectories, and the pattern of their mingling, produced by coupled oscillators (Herman, 1979; Feigenbaum et al., 1982; Jensen et al., 1983, 1984; Halsey et al., 1986).

This model includes two fundamental parameters: Ω, being the ratio between the two frequencies, in units of the external forcing cycle; and K being the interaction strength. As described above, the tendency of the two oscillators to synchronize depends on the strength of their interaction. Without any interaction (K = 0 in Figure 3), the oscillators are uncoupled and each oscillator proceeds with an unchanged frequency. For irrational values of Ω, the motion is quasiperiodic, and since there are infinitely more irrational numbers than rational ones, quasiperiodic behavior dominates the K=0 line (Feigenbaum et al., 1982; Strogatz, 2018).

As soon as the two oscillators interact just the slightest amount, i.e., $0 < K << 1$, the model displays frequency pulling, where the frequency of one oscillator is pulled or changed by the other, leading to a region of synchronization whenever Ω is in a small interval around each and every rational number, p/q. Figure 3 shows these regions of frequency locking as blue regions. For each value of the rational number p/q, there will be a region of synchronization called an Arnold tongue and, as K gets larger, the tongues widen. This part of the phase diagram is arranged in a very orderly fashion.

Some results from Henri Poincare's work can be used to show that for $K < 1$ only one solution exists at any point of parameter space (Arnold and Avez, 1968). Since each tongue represents a specific oscillation state it implies that no tongues can overlap, and every oscillating state represents a unique solution. The tongues 0/1 and 1/1 are special in the sense that their boundaries in the Ω-K plane are linear. At these boundaries, the value of the phase (θ_n) is either $\pi/2$ or $-\pi/2$, which is a measure of the phase difference between the internal and the external oscillator.

As K increases further the area covered by the tongues continues to grow until, at K = 1, there is only an infinitesimal area left for the irrational orbits. At this point, these quasiperiodic orbits occupy a fractal set (Mandelbrot, 1983; Feder, 1988) with a universal dimension measured to be 0.870 (Jensen et al., 1984) indicating that the irrational numbers only occupy a finite fraction of the x axis and are relegated to a set of zero length. Thus, the K = 1 line defines a complementary situation to that at K = 0 since the rational numbers now fill up the line while the irrationals fill nothing; however, they are still all there! Not only does this structure and dimension appear in the model, it has been experimentally verified in a number of physical systems, including the onset of turbulence (Stavans et al., 1985), Josephson junctions (Alstrøm et al., 1984; Yeh et al., 1984; He et al., 1985), one-dimensional conductors (Brown et al., 1984), semiconductors (Cumming and Linsay, 1987; Gwinn and Westervelt, 1986), and crystals (Martin and Martienssen, 1986). These observations tell us that universal knowledge about systems in nature can be extracted to a fascinating degree from a simple mathematical model.

At $K > 1$ there is a dramatic change in the behavior. The orderly progression of quasiperiodic orbits disappears, and the model begins to show a much richer behavior than heretofore. For some values of the model parameters, several different orbits, even orbits of different characters, are simultaneously possible. Which kind one sees depends upon the parameters and initial conditions of the motion, but it has been proven that the number of stable solutions can never exceed two. Here, cycles showing period doublings also exist (they typically arise around the center of each Arnold tongue), and these tend to increase their doubling number rapidly before turning into chaos. Therefore, chaotic orbits can also be found in this part of the diagram, where the long-term motion is completely unpredictable. The regions of locked motion still exist; and therefore, this model explains the completely massive degree of complex dynamics that can be found for large interaction strengths (Jensen et al., 1984; Bohr et al., 1984).

The reason for studying this abstract sine circle map in detail is that there is a lot to be learned about the qualitative features of all coupled oscillator systems based on such simple models. The point is that some features of models, particularly those involving how different kinds of motion arise and fit together, are "universal." That means that these features are to be found not only in simplified models but also in a wide variety of circumstances in which the same basic mechanisms are at work. The growth of the Arnold tongues has been proven to occur for all rational numbers in the simple model, and this has been observed in numerous experiments (for instance, Stavans et al., 1985). It can also easily be found by simulating dynamical systems of coupled oscillators for arbitrary choice of network sizes, parameters, etc.

One may include intrinsic noise in the sine circle map by adding a small normally distributed number to the equation. It turns out that the Arnold tongue diagram in Figure 3 is quite robust to the presence of intrinsic noise. Below the critical line, we know mathematically that there can only exist one stable solution; and therefore, the points will be smeared a bit, but the overall behavior is not affected. Above the critical line, the tongue structure is still robust and period doublings as well as chaotic dynamics can still be found for reasonably small levels of noise. Importantly, in the circle map with noise it is possible to observe mode hopping where the frequency performs transitions between two stable levels. Another universal feature of an Arnold tongue diagram is that the tongues will always appear in the same order, given by increasing rational numbers from the left to the right. In presence of noise and other non-linearities the tongues might bend (typically to the "right") and the tongue diagram will look less symmetric as compared with Figure 3. However, the overall structure and topology will remain the same.

Methods for inferring the existence of chaos from time-series data: Challenges for biology

A chaotic state exhibits unpredictability, as discussed above, and thus, one is tempted to ask whether it is possible to distinguish this from general stochastic dynamics. There are some fundamental differences, which are possible to detect in many cases that will be described below.

A chaotic strange attractor possesses a layered and detailed structure, which repeats itself on much finer scales (Strogatz, 2018). This type of fractal pattern can be characterized by means of a fractal dimension, which, as mentioned above, is a non-integer number (the first studied example of chaos, the Lorenz attractor, for instance, has a dimension of 2.05). A stochastic trajectory will not exhibit this fine detailed structure but will instead

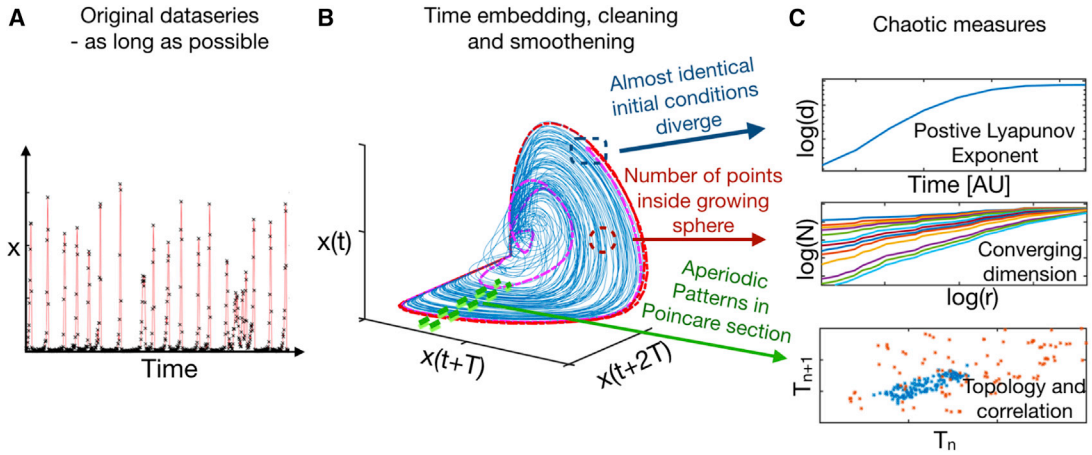


Figure 4. Schematized figure showing methods to detect chaotic dynamics in time traces

(A) Often one starts out with a complex one-dimensional pattern from experiments with recorded noise. We emphasize that the longer the trace is, the more probable it is that one can actually detect chaotic markers.

(B) Next it is customary to transform the data into a higher dimensional form, where one usually chooses an embedding dimension with a suitable value of a time delay. In this process it is also relevant to sort out as much noise as possible, by applying various de-noising algorithms along with relevant smoothening of data.

(C) Finally, one should use specific measures of chaos to see if it is possible to find the markers of chaos. The classical measure is to find two neighboring points and measure the divergence of their trajectories. Another method is to calculate the correlation dimension of the attractor, by increasing the embedding dimension and measuring the slope of log(N) versus log(R). Further, one can measure the discrete dynamics inside a Poincare section to compare the dynamics here with what is expected from a simple limit cycle with noise or another periodic cycle. Blue: example of points stochastically distributed around a limit cycle, red: example of points distributed due to chaotic dynamics.

appear as a smeared trajectory around the underlying deterministic trajectory. While time series from many physical experiments are quite stable and close to deterministic like the dynamical states found in convection, stochasticity and noise are ubiquitous in the biological world. This complicates detection of chaotic trajectories in real-world biological data (here, we use one-dimensional time-series data as an example). Three key elements are used to confront the challenge of showing the existence of chaos—(1) time-embedding, (2) de-noising algorithms, and (3) chaotic measures (See Figure 4).

Experimental time series are often measured in one dimension (meaning we measure, for instance, the concentration of one protein in time), whereas the underlying biological network can consist of numerous interacting components, giving a high dimensional space. Since chaotic dynamics can only exist in three dimensions or more, one needs to reconstruct the higher order attractor, but luckily, one can estimate the properties of the attractor by means of a time-embedding (Takens, 1981; Roux et al., 1983). In a time embedding of a time series we can at any time consider not just the present measurement (given by x(t)) but also observations made at times removed from the current time by multiples of a lag T (meaning x(t-n*T)). In this way, the time-embedded vectors x(t-n*T) generate a higher dimensional state space. It should be noted that there also exist methods that do not need the time embedding; for instance, a recent study (Toker et al., 2019) successfully relied on the 0-1 chaos test (Dawes and Freeland, 2008).

It is still difficult to investigate the detailed structure of the attractor due to the smearing from noise, which is always present in biological experiments. However, numerous de-noising algorithms exist (Hegger et al., 1999; Grassberger et al., 1993; Han and Chang 2013) and a great collection of these is found in the book by Kantz and Schreiber (Kantz and Schreiber, 2004). A very simple algorithm is suggested by T. Schreiber (Schreiber, 1993), which works well for many purposes, and is implemented in many software suites, for instance, MATLAB. The intuition behind it is to consider nearby points in the phase space generated by time embedding and then perturbing each point proportional to a weighted average of the nearby points. Using this method, one can recover the fine structure of the attractor in higher dimensions, especially if this is combined with smoothing methods. Here, de-noising algorithms present a way to remove a large fraction of the high-frequency noise, and a proper use will allow the detection of finer structures of the strange attractor. However, one should be careful since ''overuse'' of those methods will basically smear out everything and turn the fine layered structure into a broad distribution.

Finally, one should test whether the data, now cleaned and in higher dimensions, are actually chaotic. Here, major steps have been taken by Rodriguez and Laio, using clustering algorithms to compute the higher dimension of the attractor (Rodriguez and Laio 2014). One approach is to calculate the spectrum of ''Lyapunov exponents,'' by measuring the separation of two almost identical initial conditions (Wolf et al., 1985; Rosenstein et al., 1993). That is, from the time-embedded data one can identify two points that are very close in the phase space and subsequently measure the initial, exponential separation away from each other, which determines the Lyapunov exponent (Figure 4C, above). By repeating the procedure, one obtains a spectrum of exponents, which characterize the separation and if these are positive one defines the data to exhibit chaotic dynamics. This approach is the canonical way for classification of chaotic traces, but it relies on the noise level in the system being low. If the noise levels are very high, traces will diverge even though they are not chaotic simply due to phase drift.

Another way to distinguish chaos from lower dimensional dynamics, such as period doubled trajectories, is by estimating the fractal dimension of the attractor (Mandelbrot, 1983; Grassberger and Procaccia, 1983; Feder, 1988). Here, one constructs an n-dimensional space using time-embedding and considers the number of data points inside an arbitrary sphere of radius R. This results in estimates of the number of points inside a growing sphere and from the scaling as a function of the radius R one can extract the fractal dimension. As the number of dimensions increases, the gradient of the amount of points inside the growing sphere approaches a constant value, which is the attractor dimension (Figure 4C, middle).

Yet another way to distinguish chaos from lower dimensional dynamics, is to construct a Poincare section inside the embedded attractor and determine the correlations of the points in this section (Heltberg et al., 2017). Here, stochastic data will result in a cloud of points smeared by noise (if the noise level is not too high) and be correlated (blue in Figure 4C, below), whereas a strange attractor will show an underlying structure and topology (red in Figure 4C, below). More rigidly, by applying the Poincare section one can also use the topological signatures of chaos. This is neatly carried out by Amon and Lefranc, who use trajectories in the neighborhoods of periodic orbits, to estimate the knot type of these orbits and exploiting the fact that this knot type can be used to compute a lower bound on the degree of chaos (technically, the topological entropy, which if positive indicates the presence of chaos in a rigorous way) (Amon and Lefranc, 2004). A collection of such methods can be found in the book by Gilmore and Lefranc (Gilmore and Lefranc, 2003).

Examples of complex dynamics in biology

By now, a vast variety of different biological systems have been shown to possess interesting and complex dynamical features. We believe that it is still only the tip of the iceberg that has been observed, and in this section, we will review some classical examples in nature that have been proven to exhibit traits of complex dynamics.

A large number of biological studies from widely different areas, suggest that oscillations couple and form synchronized states. Famously, the synchronization of menstrual cycles in co-habiting women has been observed (McClintock, 1971), and conversely it has been said that locusts pick their 11-, 13-, or 17-year cycle so that other species will find it hard to period lock to them (Sota et al., 2013; Lloyd and Dybas, 1966). Examples of coupled oscillations and synchronized states also occur on smaller scales in biology, as discussed below.

Many groups have observed Arnold tongues in their investigations of biological systems. These include studies of circadian clocks (Abraham et al., 2010; Pfeuty et al., 2011; Schmal et al., 2015; Pittayakanchit et al., 2018), experimental studies of populations of synthetic oscillators in bacteria (Elowitz and Leibler, 2000; Mondragón-Palomino et al., 2011), mammalian cell cycles locked to the circadian clock (Gérard and Goldbeter, 2012; Bordyugov et al., 2015), protein oscillations perturbed by an external cytokine oscillation (Wang et al., 2011; Jensen and Krishna, 2012; Kellogg and Tay, 2015; Zambrano et al. 2016), and cell-cycle dynamics in Caulobacter (Lin et al., 2012) and yeast (Charvin et al., 2009). Deora and Sane (Deora et al., 2015) report the entrainment of wing and haltere oscillations in flies. Here, they cut the wings to manipulate the frequency and find that the halteres are phase locked up to a certain critical frequency.

At the scale of gene regulation, it has been found that many transcription factors show complex dynamical features, most famously p53 and NF-kB in response to external stresses. While the precise functional role of oscillations in these systems is still unclear, it is suggested that the dynamics might be an important response to external stresses (Tiana et al., 2002; Jensen et al., 2003; Nelson et al., 2004; Geva-Zatorsky et al., 2006; Purvis et al., 2012; Purvis and Lahav 2013; Zhang et al., 2017; Reyes et al., 2018; Hafner et al., 2019; Heltberg et al., 2019b). Since these proteins are a part of numerous upstream and downstream networks, it is intriguing that they might at specific times be part of coupled oscillator networks. In this case, the Arnold tongue diagram will tell which amplitudes and frequencies are capable of entraining the oscillations, and where the limits of such control lie. Entrainment of NF-kB has been observed, and it was shown how this entrainment affected the downstream genes affected by NF-kB (Kellogg and Tay, 2015) (See Box 2).

Following the theory outlined above, the complex dynamics of mode hopping was also found in this network and it was argued that this could induce multiplexity in gene regulation (Heltberg et al., 2016). Finally, computational studies might see the onset of chaos in biological systems, and such an onset has been argued to be helpful to biological function in order to enhance low-affinity genes and protein-complex diversity (Heltberg et al., 2019a).

At the scale of populations of cells, Hasty et al. (Mondragón-Palomino et al., 2011) inserted synthetic oscillatory gene circuits into bacteria and observed the entrainment of oscillations across the population. The coupling between cells here was hypothesized to be due to quorum sensing signals that these bacteria secrete. Gupta et al. (2016) showed that intrinsic biochemical noise can interact with dynamic non-linearities causing entrainment of the population mean of uncoupled intracellular oscillators, even though these oscillators may not be individually entrained. They called this effect stochastic population entrainment. In studies of cardiac dynamics, it has been found that high-risk cardiac patients exhibit low-dimensional chaos in their heartbeat intervals (Vybiral and Skinner, 1993).

At the scale of embryos, phase locking seems to play an important role in vertebrate somitogenesis. Cells in the presomitic mesoderm (PSM) show oscillations in various genes controlled by the Wnt morphogen, such as Axin or betacetenin (Mengel et al., 2010; Juul et al., 2018). Various theories exist to explain how such temporal periodicity is translated to the spatial periodicity required to form the somites, which eventually produce the vertebrae of the spine (Dequéant and Pourquié, 2008; Hubaud and Pourquié, 2014; Lauschke et al., 2013; Soroldoni et al., 2014). One suggestion is that the oscillations couple to a gradient of Wnt with cells effectively moving toward the lower end of this gradient as the PSM grows. This requires a tight phase locking between adjacent cells, and we may speculate that known inter-cellular couplings (such as Notch-Delta) between the oscillators of adjacent cells may be involved in entraining and phase locking these cells.

For the circadian clock (Thommen et al., 2010 and Pfeuty et al., 2011) propose that there are generic phase-locked loop mechanisms, which can ensure that the interaction strength goes to

Box 2. Observing coupled oscillators in biology

To investigate the effects and possibilities of coupled oscillations in biology, experimental data provide a crucial step. Here we describe how this can be studied in living single cells, by explaining some of the universal mechanisms leading to coupled oscillations.

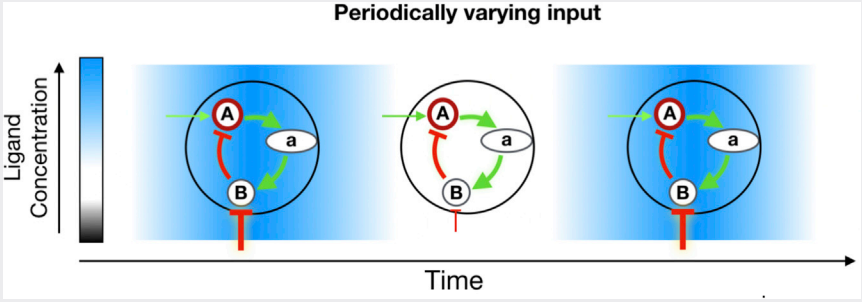
(1) Find a protein that can show oscillatory behavior. This could typically be a transcription factor since they usually form a negative feedback-loop with a large time delay. Through biological engineering, proteins could also be generated in a feedback-loop to produce oscillations (Elowitz and Leibler, 2000).

(2) Perturb by an external oscillation, which for instance could be a ligand delivered periodically. By using microfluidic chambers, one ensures that the feedback between the cell and the ligand is kept to a minimum.

(3) Consider if the minimum value of the external signal is sufficiently high to initiate oscillations on the internal system (in technical terms the internal oscillator should always be above the Hopf bifurcation, see Strogatz, 2018). If the external period is very long compared with the internal, the external signal should not oscillate between a high value and zero, because then the internal system would not oscillate independently and thus the system would not be of coupled oscillators (Zambrano et al., 2016; Heltberg et al., 2016).

(4) For the Arnold tongues to emerge, the amplitude and period of the external oscillator should be varied independently and in this way, synchronization will emerge by measuring the ratio between the external frequency and the observed internal frequency. The shape of the Arnold tongues can vary from system to system and will rarely look as regular as in Figure 3. Sometimes the tongues bend sharply most often to the right as the external frequency is increased.

For small amplitude oscillations of the external oscillator, the complex dynamics described in the main text should emerge. Theoretically, this should also be a way to induce chaotic dynamics in the concentration of the transcription factor. If such simple systems do produce the predicted effects of the non-linear coupling, it is encouraging to believe that given the many small networks found in living species, these effects would be ubiquitous in nature. Furthermore, it is worth stressing that in controlled conditions like this, one can study the downstream effects of dynamical features of proteins. Finally, we emphasize that in principle any experimental system that obeys the points 1–4 above should be able to entrain and lead to Arnold tongues. For instance, testing temperatures, mechanical forces, radiation, etc., in a time-varying dose delivered to organisms, could potentially give rise to the complex dynamical phenomena exhibited by coupled oscillators. A schematic picture of such a setup is shown in here.



Box figure: schematic figure showing an example of how coupled oscillations can occur *in vivo* and *in vitro*, by having an oscillating system in an environment of time-varying concentrations or other physical conditions. The colors indicate how the concentration shifts between a high and a low level, but never a level around zero (indicated by black color). As these concentrations vary, some of the interactions in the network are perturbed (here shown as a degradation of B).

zero when the phase difference between the external cycle and the oscillator vanishes. The same mechanisms shield the clock from variations in light because it does not see the light when entrained and prevents the appearance of chaos because the effective interaction strength goes to zero as entrainment sets in, thus avoiding the chaotic region, which always appears "higher" up in the Arnold tongue. As mentioned in the section on universal behavior of coupled oscillators the phase difference between the internal and external oscillator across the 1/1 tongue is shown to span from $-\pi/2$ to $\pi/2$. This has been investigated in several models (Bordyugov et al., 2015; Granada and Herzel, 2009) and it has been implied that the multiple stable phase lockings can have importance for a population where individuals synchronize to the circadian clock and in seasonal adaptation. For the NF-kB model (Jensen and Krishna, 2012; Heltberg et al., 2016) we have similarly also observed the phase span from $-\pi/2$ to $\pi/2$ across the 1/1 tongue.

It has been observed experimentally that somitogenesis involves repeated phase waves that travel from the posterior to the anterior within the PSM and mark the location of somite formation where they stop at the anterior end (Lauschke et al., 2013). Constraints have been derived to connect the size of somites, and the timing of their formation, to the growth of the PSM and the gradient of the somitogenesis clock period across the PSM (Juul et al., 2019).

In the field of neuroscience, neurons form a fantastically complex network, ranging from the subcellular networks that maintain the membrane potential on a single-cell level, to the most complex organizations of the nervous system (Korn and Faure, 2003; Power et al., 2012). On the single-cell level, chaotic

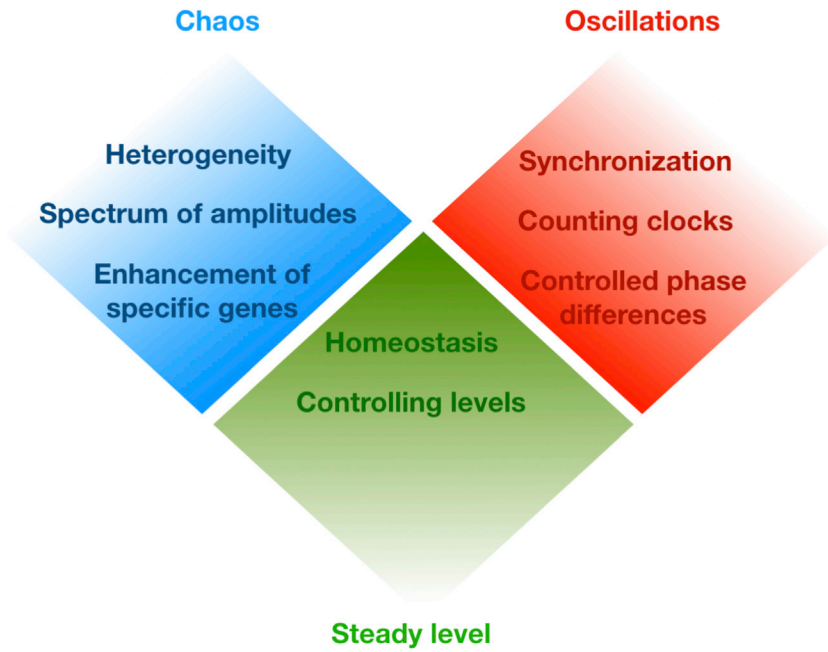


Figure 5. Schematic figure showing how fundamentally different types of dynamics may affect biological systems, with each playing different but important roles in maintaining the diverse functions and complexity of life

bursting has been found in several experiments (Hayashi and Ishizuka, 1992; Mpitsos et al., 1988), and on the network level, synchronization and chaos has been observed both *in vivo* studies (Babloyantz and Destexhe, 1986) as well as in numerous models (Abarbanel et al., 1996; Aihara et al., 1990; Rulkov, 2001; Rasmussen et al., 2017). A thorough understanding of the effects of complex dynamics is still absent, but it is well accepted that the various kinds of dynamics are necessary to obtain the high complexity found in the human brain (Avena-Koenigsberger et al., 2017). It has been argued that dynamical phenomena, such as chaotic dynamics and entrainment, might play an important role in the sleep-awake transition (Rasmussen et al., 2017), in acoustic stimulation (Will and Berg, 2007), and in information processing (Nicolis and Tsuda, 1985). Finally, complex dynamics has also played an important role in the mathematical investigation of ecology. Since the seminal work of May in the seventies (May, 1974), many studies have investigated the role especially of entrainment and chaotic dynamics in ecology (Ferrière and Gatto, 1993; May, 1987; Benincà et al., 2015; Schaffer and Kot, 1985). Even though this has been investigated for several decades now, the roles of the different kinds of dynamics and the transitions between these are still an open question to the field.

Concluding remarks

In this review, we have outlined the most important aspects of the fascinating fauna of dynamics that can arise from the coupling of two oscillators – from the control found in entrainment at low coupling strength, to the appearance of multi stable limit cycles and mode hopping at intermediate strength, to the intriguing aspects of chaotic dynamics at high interaction strength. As we have shown, these types of dynamics have been found in various biological systems, and as the technological methods of experimental biology are advancing quickly, there is good reason to believe that they will be observed in many more fundamental biological systems. However, in the investigation of complex dynamics, it has so far usually been detection of the dynamics and explanation of the dynamics through mathematical models that has governed the research. Very rarely have the effects of complex dynamics been thoroughly investigated. For instance, in the field of transcription factors, it is a fundamental question to figure out the detailed downstream effects that may be initiated when p53 and NF-kB start to oscillate in response to stress. One practical problem in such investigations lies in the difficulty of varying aspects of the oscillation, such as frequency, in a controlled manner *in vivo*.

Entrainment to an external oscillator that is under the control of the experimenter is one way to exert control over the internal biological oscillation and could be used to systematically explore how downstream effects vary as the oscillation is tuned by the external oscillator. We believe that there is a lot of regulation and control hidden in the dynamics of these biological systems, and that the understanding of the mechanisms and principles behind this can be one of the great steps forward in modern systems biology. As schematized in Figure 5, one can—from a pragmatic point of view—divide the observed dynamics into three qualitatively different types: steady state, oscillations, and chaos; each of which may be useful for different biological functions. While we have just started to appreciate the variety of oscillations in biology, the presence of chaos in biology is still embedded in controversy. Only the future will reveal how these different types of dynamics fit together in the complete puzzle of maintaining both complexity and regulation of living organisms, but at this stage it is tempting to believe that living organisms at some level take an advantage of the intriguing possibilities enabled by complex dynamics.

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