

## Catálogo

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## Supplementary Material 1

### 1 Probability of activation of a gene

If  $c(t)$  is the concentration of a Transcription Factor (TF) in the nucleus, the probability that the TF successfully binds to the promoter site of a gene at time  $t + \Delta t$  and active it (state *on*) is:

$$p^{on}(t + \Delta t) = p^{on}(t) + k_1 c(t) \cdot p^{off}(t) \Delta t - k_{-1} p^{on}(t) \Delta t + o(\Delta t) \quad (1)$$

where  $p^{off}(t)$  is the probability that the gene is inactive (state *off*) at time  $t$ ,  $k_1$  is the rate constant of transition from state *off* to state *on*,  $k_{-1}$  is the rate constant of transition from state *on* to state *off*, and  $o(\Delta t)$  is a random function of  $\Delta t$  such that  $\frac{o(\Delta t)}{\Delta t} \rightarrow 0$  when  $\Delta t \rightarrow 0$ .

Eq. (1) is the master equation for the process of transition from state 0 to state 1 for a single gene due to the binding of a TF to its promoter.

Dividing Eq. (1) by  $\Delta t$  and calculating the limit when  $\Delta t \rightarrow 0$  we obtain:

$$\lim_{\Delta t \rightarrow 0} \frac{p^{on}(t + \Delta t) - p^{on}(t)}{\Delta t} = k_1 c(t) \cdot p^{off}(t) - k_{-1} p^{on}(t) + \lim_{\Delta t \rightarrow 0} \frac{o(\Delta t)}{\Delta t} \quad (2)$$

which leads to:

$$\frac{dp^{on}(t)}{dt} = k_1 c(t) \cdot p^{off}(t) - k_{-1} p^{on}(t) \quad (3)$$

Assuming that the binding of the TF to the promoter site is a Bernoulli process:  $p^{on}(t) + p^{off}(t) = 1$ , and we finally obtain:

$$\frac{dp^{on}(t)}{dt} = k_1 c(t) \cdot (1 - p^{on}(t)) - k_{-1} p^{on}(t) \quad (4)$$

### 2 Probability of inhibition of a gene

The presence of a competitive inhibitor of the TF activity, which not necessarily acts on the same promoter site, can be modeled as:

$$\frac{dp^{on}(t)}{dt} = \frac{k_1 c(t)}{inh(t) + \gamma} \cdot (1 - p^{on}(t)) - k_{-1} p^{on}(t) \quad (5)$$

where  $inh(t)$  is the concentration of the inhibitor in the nucleus, and  $\gamma$  is a constant. Expression (5) corresponds to Eqs. 5-8 of the main text.



## *Supplementary Material 2*

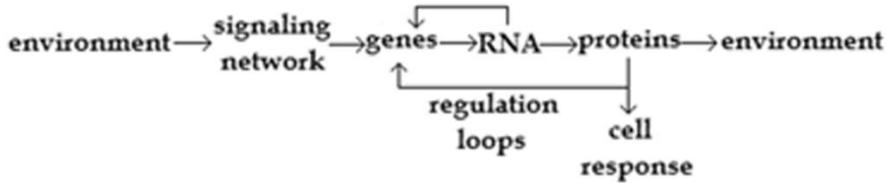
### 1 Stability analysis of nonlinear systems

Cells are complex networks of physicochemical processes that support their highly organized structure and function. Thus, each cellular process sustained by a cell involves different levels of cellular organization. Each level of organization can be represented as a cell's subsystem (subnetwork) that functions in a modular mode. In this form, cells can be modeled as formed by a set of subsystems like the gene regulatory network (GRN), the network of synthesis and distribution of proteins, the network of signaling pathways, and the metabolic network, among others.

The information flow through the set of cellular subsystems that controls the cell response to environmental signals occurs according to the canonical schema of SM 2 Figure 1. Tumor-inducing DNA or RNA viruses can drastically modify this flow of information.

An important remark from SM 2 Figure 1 is that the flow of information through cellular subsystems is due to a continuous flow of matter and energy, according to the respective laws of conservation. Taking into account the flow of matter at each point of the cell, the respective mass balance equation is:

$$\frac{\partial c_k(\mathbf{x}, t)}{\partial t} = \sum_r \nu_{rk} \cdot \omega_r(c_1(\mathbf{x}, t), c_2(\mathbf{x}, t), \dots, c_k(\mathbf{x}, t), \dots, c_s(\mathbf{x}, t)) + D_k \nabla^2 c_k(\mathbf{x}, t) \quad (1)$$



**SM 2 Figure 1.- Flow of information between cell subsystems.** Changes in environmental conditions are sensed by cell signaling networks, which code and transmit this information to the nucleus. Coded information is decoded by the transcription machinery that, in response to this information, activates and inactivates a set of specific genes, giving rise to a specific distribution of effectors proteins. These proteins are responsible for the cell specific response to the environmental conditions. Some of these proteins can be used to regulate gene expression, acting as specific transcription factors that form complex regulatory loops inside the nucleus. Proteins can also be secreted to modify the cell environment. Tumor-inducing viral RNA and DNA can modify this flow of information by acting directly on the cell genome, drastically modifying the population of effectors proteins and their function.

Equation (1) means that the local rate of variation of the concentration of the substance  $k$  (denoted by  $c_k$ ) at point  $\mathbf{x}$  at time  $t$  is equal to the net rate of diffusion of  $k$  inside the cell volume  $V$  (denoted by  $D_k \nabla^2 c_k(\mathbf{x}, t)$ ) plus the rate of formation/degradation of  $k$  due to the local chemical reactions inside  $V$ . In Eq. (1),  $\omega_r$  represents the local rate of the chemical reaction  $r$ , which is a functional of the concentration of the reactive substances at point  $\mathbf{x}$  at time  $t$ , and  $\nu_{rk}$  is the stoichiometric coefficient of  $k$  in reaction  $r$ .

The reaction term of Eq. (1) can be rewritten as:

$$\sum_r \nu_{rk} \cdot \omega_r (c_1(\mathbf{x}, t) c_2(\mathbf{x}, t) \dots c_k(\mathbf{x}, t) \dots c_s(\mathbf{x}, t)) = f_k(c_1(\mathbf{x}, t), c_2(\mathbf{x}, t), \dots, c_k(\mathbf{x}, t), \dots, c_s(\mathbf{x}, t)) \quad (2)$$

$k = 1, 2, \dots, s$

leading to:

$$\frac{\partial c_k(\mathbf{x}, t)}{\partial t} = f_k(c_1(\mathbf{x}, t), c_2(\mathbf{x}, t), \dots, c_k(\mathbf{x}, t), \dots, c_s(\mathbf{x}, t)) + D_k \nabla^2 c_k(\mathbf{x}, t) \quad k = 1, 2, \dots, s \quad (3)$$

which is the well known form of the reaction-diffusion equation for the substance  $k$ . It indicates that the temporal variation of the concentration of  $k$  at point  $\mathbf{x}$  at time  $t$  depends on the balance between the chemical processes in which this substance takes part, represented by the function  $f_k$ , and its diffusion rate in the cellular medium. Function  $f_k$  is generally a nonlinear function of the concentration of the reactive substances, and Eq. (3) usually has not an analytical solution. In a homogeneous medium, the diffusive term in Eq. (3) is null, and  $f_k$  completely defines the entire system dynamics in the  $s$ -dimensional phase space, which is defined by the set of concentration values of the  $s$  reactive substances. The systems dynamics is represented by a trajectory in this space or **phase space**, defined by the column vector  $\mathbf{c}(t) = \langle c_1(t) c_2(t) \dots c_s(t) \rangle^T$ . In nonlinear systems this trajectory can have peculiar characteristics like high sensitivity to initial conditions, bifurcations and complex loops that represent a great variety of dynamical behaviors observed in biological systems like limit cycles, hysteresis, bistability, ultra sensitivity, among others. In a no homogeneous medium, the diffusive term of Eq. (3) produces a more complex dynamical behavior of the system, giving rise to phenomena like traveling waves, spirals and spatially located bursting of second messengers and proteins, among others.

The first problem concerning the dynamics of nonlinear systems is the determination the steady points of the system in the phase space.

A steady point is a column vector  $\mathbf{c}^o = \langle c_1^o(t) c_2^o(t) \dots c_s^o(t) \rangle^T$  for which equation:

$$\dot{\mathbf{c}}(t) = \mathbf{f}(\mathbf{c}(t)), \text{ where } \mathbf{f}(\mathbf{c}(t)) = \begin{bmatrix} f_1(c_1(t), c_2(t), \dots, c_k(t), \dots, c_s(t)) \\ \vdots \\ f_s(c_1(t), c_2(t), \dots, c_k(t), \dots, c_s(t)) \end{bmatrix} \quad (4)$$

becomes zero. Once the set of steady points of the system is settled on, is necessary to determine their stability. Eq. (4) subject to the initial condition  $\mathbf{c}(0) = \mathbf{c}_0$  defines a **nonlinear dynamical system**.

The steady point  $\mathbf{c}^o$  of a dynamical system is **Liapunov stable** if for each  $\varepsilon > 0$  exists a  $\delta > 0$  such that  $\|\mathbf{c}(t) - \mathbf{c}^o\| < \varepsilon$  whenever  $\|\mathbf{c}(0) - \mathbf{c}^o\| < \delta$ , i.e., any trajectory that initiates at a distance  $\delta$  of the steady point  $\mathbf{c}^o$  remains at a distance  $\varepsilon$  of it all time.

The steady point  $\mathbf{c}^o$  of a dynamical system is attracting if exists a  $\delta > 0$  such that  $\lim_{t \rightarrow \infty} \mathbf{c}(t) = \mathbf{c}^o$  for any trajectory  $\mathbf{c} = \mathbf{c}(t)$  whenever  $\|\mathbf{c}(0) - \mathbf{c}^o\| < \delta$ , i.e., any trajectory that initiates at a distance  $\delta$  of the steady point  $\mathbf{c}^o$  will converge to it eventually. In this case, the point  $\mathbf{c}^o$  is an **attractor** of the dynamical system in the phase space. A steady point  $\mathbf{c}^o$  Liapunov stable and attractor is asymptotically stable. A steady point  $\mathbf{c}^o$  that is neither stable nor attractor is unstable, and is a **repulsor** in the phase space.

Generally, the nonlinear systems trajectories cannot be determined in an analytical form. However, it is possible to perform a qualitative analysis to find out the global behavior of the dynamical system in the corresponding phase space. As a vector can be assigned to each point of this space, according to Eq. (4), the vector field associated to the phase space can be drawn. By flowing this vector field, a phase point traces a solution  $\mathbf{c}(t)$  of the dynamical system, corresponding to a trajectory winding through the phase space.

It is of importance to point out the fact that if the function  $\mathbf{f}$  of Eq. (4) is continuous and all its partial derivatives  $\frac{\partial f_i}{\partial c_j}$   $i, j = 1, 2, \dots, s$  are also continuous in  $\mathbf{c}$  for a given subset  $D \subset \mathfrak{R}^n$ , then for every  $\mathbf{c}_0 \in D$  the initial value problem of Eq. (4), has solution  $\mathbf{c}(t)$  in some time interval  $(-t, t)$  around  $t = 0$  and this solution is unique. A topological implication of this theorem is that two trajectories cannot intersect and, as consequence, chaos is ruled out of any 2-dimensional phase space but arises as a possible behavior of every  $s$ -dimensional dynamical system with  $s > 2$  (Strogatz, 1994).

The phase space analysis of the dynamics of a nonlinear system takes into account the following aspects: 1) the number, position and stability of the steady points; 2) the arrangement of the trajectories near the steady points; and 3) the existence and stability of closed orbits.

The arrangement of the trajectories around steady points is determined by linearization of the original nonlinear system, and analysis of the behavior of the eigenvalues of the Jacobian matrix of the linearized system around each steady point. For example, considering a 2-dimensional phase space and a steady point  $\mathbf{c}^o = \langle c_1^o, c_2^o \rangle^T$ , a small perturbation from this steady state drives the nonlinear

dynamical system  $\begin{bmatrix} \dot{c}_1(t) \\ \dot{c}_2(t) \end{bmatrix} = \begin{bmatrix} f_1(c_1(t), c_2(t)) \\ f_2(c_1(t), c_2(t)) \end{bmatrix}$  into a new trajectory  $\delta \mathbf{c}(t) = \langle \delta c_1(t), \delta c_2(t) \rangle^T$ , where  $\delta c_1(t) = c_1(t) - c_1^o$ , and  $\delta c_2(t) = c_2(t) - c_2^o$ . In this form:

$$\begin{aligned} \delta \dot{c}_1 = \dot{c}_1 &= f_1(c_1^o, c_2^o) + \left. \frac{\partial f_1}{\partial c_1} \right|_{(c_1^o, c_2^o)} \delta c_1 + \left. \frac{\partial f_1}{\partial c_2} \right|_{(c_1^o, c_2^o)} \delta c_2 + O(\delta^2 c_1, \delta^2 c_2, \delta c_1 \delta c_2) \\ &= \left. \frac{\partial f_1}{\partial c_1} \right|_{(c_1^o, c_2^o)} \delta c_1 + \left. \frac{\partial f_1}{\partial c_2} \right|_{(c_1^o, c_2^o)} \delta c_2 + O(\delta^2 c_1, \delta^2 c_2, \delta c_1 \delta c_2) \text{ because } f_1(c_1^o, c_2^o) = 0 \end{aligned} \quad (5)$$

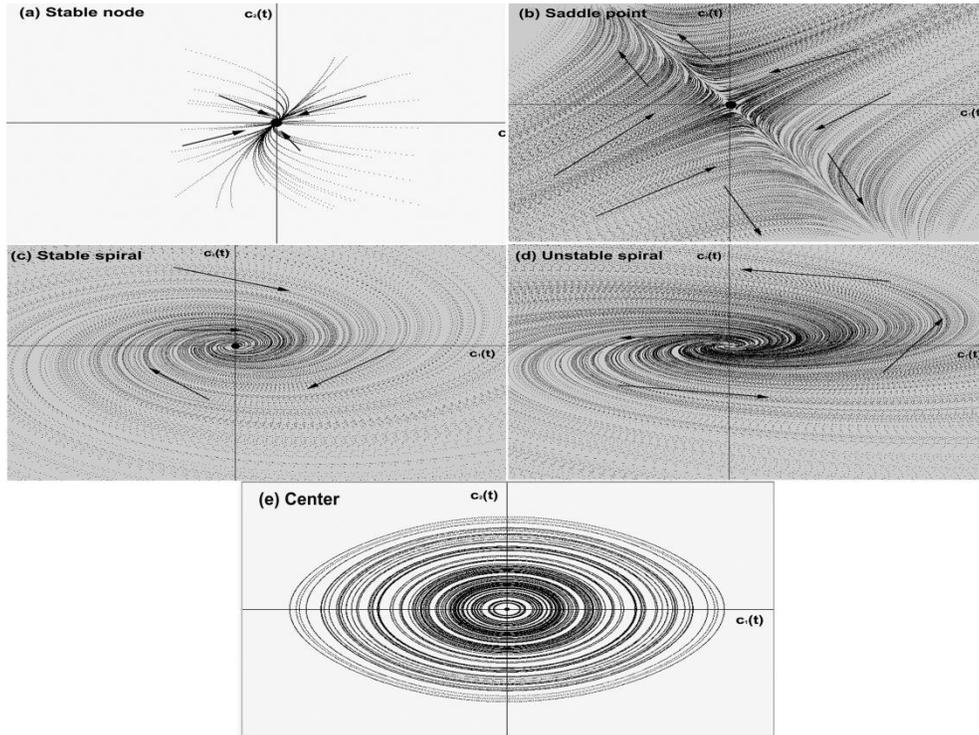
in a similar form:

$$\delta \dot{c}_2 = \dot{c}_2 = \left. \frac{\partial f_2}{\partial c_1} \right|_{(c_1^o, c_2^o)} \delta c_1 + \left. \frac{\partial f_2}{\partial c_2} \right|_{(c_1^o, c_2^o)} \delta c_2 + O(\delta^2 c_1, \delta^2 c_2, \delta c_1 \delta c_2) \quad (6)$$

which leads to the linearized dynamical system:

$$\begin{bmatrix} \delta \dot{c}_1(t) \\ \delta \dot{c}_2(t) \end{bmatrix} = \begin{bmatrix} \left. \frac{\partial f_1}{\partial c_1} \right|_{(c_1^o, c_2^o)} & \left. \frac{\partial f_1}{\partial c_2} \right|_{(c_1^o, c_2^o)} \\ \left. \frac{\partial f_2}{\partial c_1} \right|_{(c_1^o, c_2^o)} & \left. \frac{\partial f_2}{\partial c_2} \right|_{(c_1^o, c_2^o)} \end{bmatrix} \begin{bmatrix} c_1(t) \\ c_2(t) \end{bmatrix} = \mathbf{J}[c_1, c_2] \begin{bmatrix} c_1(t) \\ c_2(t) \end{bmatrix} \quad (7)$$

$J_{[c_1, c_2]}$  represents the Jacobian matrix of the linearized dynamical system in Eq. (6). The eigenvalues  $\lambda_1, \lambda_2$  of  $J_{[c_1, c_2]}$  can be calculated from the characteristic equation:  $|J_{[c_1, c_2]} - \lambda I| = 0$ . Depending on the nature of the eigenvalues, it is possible to know the arrangement of the trajectories near each steady point of the nonlinear system (SM 2 Figure 2). This linearization process can be extended to perform the phase space analysis of higher dimensional nonlinear dynamical systems (Edelstein-Keshner, 2005).



**SM 2 Figure 2.- Classification of the steady points of a 2-dimensional linearized dynamical system.** (a) There is a stable node or attractor in the phase space when both eigenvalues  $\lambda_1$  and  $\lambda_2$  are real and negative (when both eigenvalues are positive, the steady point is an unstable node or repulsor); (b) There is a saddle point in the phase space when both eigenvalues  $\lambda_1$  and  $\lambda_2$  are real, but one of them is positive and the other is negative. The stable manifold is spanned by the eigenvector associated to the negative eigenvalue. The unstable manifold is spanned by the eigenvector associated to the positive eigenvalue. (c) There is a stable spiral in the phase space when both eigenvalues  $\lambda_1$  and  $\lambda_2$  are complex conjugated with negative real part. (d) On the contrary, if both eigenvalues  $\lambda_1$  and  $\lambda_2$  are complex conjugated with positive real part the spiral is unstable. (e) When  $\lambda_1$  and  $\lambda_2$  are pure imaginary the steady point is a center surrounded by a series of stable closed orbits. All figures show the flow of the dynamical system in the phase space spanned by the basis conformed by the variables  $c_1(t)$  and  $c_2(t)$ . The black point represents the steady point of the dynamical system, and the arrows mark out the direction of the flow of the vector field.

An important question that arises at this point is whether the behavior of the trajectories obtained from Eq. (7) accurately reflects the real behavior of the trajectories of the original nonlinear system. If the linearized system has a saddle, a node or a spiral at a given steady point, then the original nonlinear system also has a saddle, a node or a spiral at that steady point. Furthermore, if a steady point is a stable saddle or node of the linearized dynamical system, then it is also a stable saddle or node of the nonlinear system. In this case, the neglected nonlinear terms of Eq. (5) and Eq. (6) practically have no effect on the stability of these points when  $\text{Re}(\lambda) \neq 0$ , for both eigenvalues. This kind of steady points is known as **hyperbolic points**, and they are not affected by the small nonlinear

perturbations. The topological implication of this fact is that the vector field corresponding to a saddle or a node is not altered by small nonlinear perturbations and, as consequence, has **structural stability**.

When the eigenvalues of the Jacobian matrix are pure imaginary  $\lambda = \pm i$ , the steady point is a center. The trajectories around this point are closed orbits that are stable. However, the neglected nonlinear terms in Eq. (5) and Eq. (6) can produce an imperfect closure of the orbit, giving rise to a spiral. In this form, the vector field corresponding to a center is altered by small nonlinear perturbations that transform the center into a spiral and, as consequence, has not structural stability.

According to their stability, steady points of 2-dimensional dynamical systems can be classified into a: 1) **Robust case**, which includes repellers or sources, for which both eigenvalues have  $\text{Re}(\lambda) > 0$ ; attractors or sinks, for which both eigenvalues have  $\text{Re}(\lambda) < 0$  and saddles, for which one eigenvalues has  $\text{Re}(\lambda) > 0$  and the other one has  $\text{Re}(\lambda) < 0$ ; 2) **Marginal case**, which includes centers for which both eigenvalues are pure imaginary, and non-isolated steady points for which one eigenvalue has  $\text{Re}(\lambda) = 0$ .

However, the phase space of a nonlinear system can exhibit another kind of closed orbits called **limit cycles**, which cannot be observed in linear systems. A limit cycle is an isolated trajectory for which neighbor trajectories can be only spirals that converge to it or diverge from it. If all the spirals converge into the limit cycle, this closed orbit is stable, otherwise is unstable. The existence of this kind of closed trajectories in the plane is settled down by the Poincaré-Bendixson theorem. According to this theorem, exists a trajectory  $C$ , which is either a closed orbit or a spiral that converges to a closed orbit as  $t \rightarrow \infty$ , confined inside a certain closed bounded region  $R$  of the plane. This theorem assumes 1) the existence of a vector field  $\dot{c} = f(c)$  that is continuously differentiable on an open set of the plane containing  $R$ , and 2)  $R$  does not contain any fixed point (Edelstein-Keshner, 2005). A consequence of this theorem is that in a 2-dimensional phase space any trajectory trapped into a closed bounded region  $R$  must converge to a limit cycle.

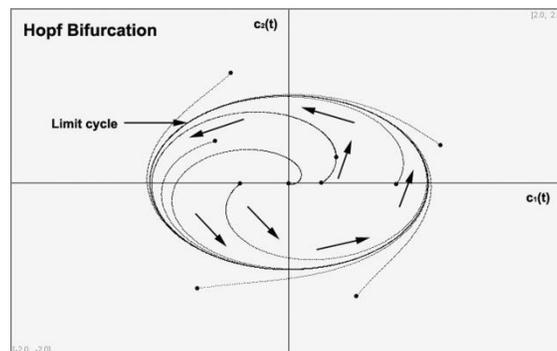
However, in higher dimensional systems the Poincaré-Bendixson theorem does not longer apply and trajectories can be trapped into a closed region of the phase space without converge into a limit cycle or settle down to a fixed point, and they could be attracted by a complex geometric object called strange attractor, which is a fractal set on which the motion is no periodic and sensitive to very small changes in initial conditions. This sensitivity makes the motion unpredictable as  $t$  increases, giving rise to a **chaotic dynamics**.

The qualitative features of the vector field of a biochemical dynamical system are strongly dependent on the set of parameters of its corresponding set of differential equations. As the value of one of these parameters changes, the qualitative features of the vector field undergo local variations around the steady points. This parameter-dependent change in the local topological structure of a vector field is known as bifurcation. They generally occur in a one-dimensional subspace, and the rest of the dimensions of the phase space are affected as consequence of the flow that can be attracted or repelled from this subspace (Strogatz, 1994; Edelstein-Keshner, 2005). Taking into consideration the imaginary plane, we can roughly classify bifurcations into two cases: 1) the eigenvalues of the Jacobian matrix are both real and bifurcations occur along the real axis as certain parameter  $\alpha$  changes. This kind of bifurcation comprises the saddle-node bifurcation; the transcritical bifurcation, and the subcritical and supercritical pitchfork bifurcation. 2) The eigenvalues of the Jacobian matrix

are complex conjugated. Bifurcations occur crossing the imaginary axis as certain parameter  $\alpha$  changes. This kind of bifurcation comprises the supercritical and subcritical Hopf bifurcation.

In the first case, a) the saddle-node bifurcation causes local variations in the vector field around two points: a saddle and a node, as a bifurcation parameter  $\alpha$  changes. These points become closer as parameter  $\alpha$  varies until they collide and annihilate each other. This type of bifurcation has interesting applications in some models of biological processes that imply the presence of chemical switches; b) a transcritical bifurcation occurs when two steady points interchange their stability as the bifurcation parameter  $\alpha$  varies; c) the normal form of an ordinary differential equation (ODE) that exhibits a subcritical pitchfork bifurcation is:  $\dot{c} = \alpha c + c^3$ . When  $\alpha < 0$ , there are one stable steady point at  $c_1^o = 0$ , and there are two unstable points at  $c_{2,3}^o = \pm\sqrt{-\alpha}$ . When  $\alpha > 0$  the only real steady point  $c^o = 0$  becomes unstable. The normal form of an ODE that exhibits a supercritical pitchfork bifurcation is  $\dot{c} = \alpha c - c^3$ . When  $\alpha < 0$  the only real steady point  $c^o = 0$  is stable. For  $\alpha > 0$  there is an unstable steady point at  $c_1^o = 0$ , and two stable steady points at  $c_{2,3}^o = \pm\sqrt{\alpha}$ .

In the second case, the presence of a Hopf bifurcation leads the system to a limit cycle. As the bifurcation parameter  $\alpha$  varies, when a certain critical value  $\alpha_c$  is reached the supercritical Hopf bifurcation drives the transformation of a stable spiral into an unstable spiral that converges to a stable limit cycle (SM 2 Figure 2). The case of a subcritical Hopf bifurcation is more complicated. A typical example is when an unstable limit cycle shrinks to zero amplitude as the bifurcation parameter  $\alpha$  reaches its critical value  $\alpha_c$ , at which the cycle engulfs the node rendering it unstable and making the system to jump to a distant attractor when  $\alpha > \alpha_c$ . This new attractor could be a steady point, another limit cycle, infinity or a chaotic attractor (for higher dimensional systems).



**SM 2 Figure 2.- Supercritical Hopf bifurcation.** This kind of bifurcation transforms a stable spiral into an unstable spiral that converges to a stable limit cycle when the value of the bifurcation parameter  $\alpha$  reaches some critical value  $\alpha_c$ . The black points in the figure are different initial conditions of the dynamical system. The arrows mark out the direction of the flow of the vector field. The phase space is spanned by  $c_1(t)$  and  $c_2(t)$ .