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SENSITIVITY ANALYSIS FOR OSCILLATING DYNAMICAL SYSTEMS*

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Abstract. Boundary value formulations are presented for exact and efficient sensitivity analysis, with respect to model parameters and initial conditions, of different classes of oscillating systems. Methods for the computation of sensitivities of derived quantities of oscillations such as period, amplitude, and different types of phases are first developed for limit-cycle oscillators. In particular, a novel decomposition of the state sensitivities into three parts is proposed to provide an intuitive classification of the influence of parameter changes on period, amplitude, and relative phase. The importance of the choice of time reference, i.e., the phase locking condition, is demonstrated and discussed, and its influence on the sensitivity solution is quantified. The methods are then extended to other classes of oscillatory systems in a general formulation. Numerical techniques are presented to facilitate the solution of the boundary value problem and the computation of different types of sensitivities. Numerical results are verified by demonstrating consistency with finite difference approximations and are superior both in computational efficiency and in numerical precision to existing partial methods.

Key words. periodic system, limit cycle, nonlinear ODEs, boundary value problem, amplitude sensitivity, period sensitivity, phase sensitivity, phase locking condition

AMS subject classifications. 65L10, 49N20, 65P99

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1. Introduction. Sensitivity analysis is a useful tool for the analysis of dynamic systems. It can be used to give local information on the impact of an infinitesimal parameter change on the behavior of the system, including derived functions of its output. As such, sensitivity analysis can be applied in model reduction, in stability analysis, or in the analysis of biochemical pathways, to name a few [29]. While there are higher-order sensitivities and different methods to compute “global” sensitivities, the sensitivities discussed in this article are local, first-order sensitivities, defined as

$$s_{ij}(t, \phi) \equiv \frac{\partial y_i}{\partial \phi_j}(t, \phi) = \lim_{\epsilon \rightarrow 0} \frac{y_i(t, \phi + \epsilon \mathbf{e}_j) - y_i(t, \phi)}{\epsilon},$$

where \mathbf{e}_j is the j th unit vector and y_i is the i th component of $\mathbf{y}(t, \phi)$, a scalar or vector state variable that changes in time according to a dynamic system

$$\frac{d}{dt} \mathbf{y}(t, \phi) = \mathbf{f}(\mathbf{y}(t, \phi), t, \phi).$$

The vector or scalar valued quantity ϕ can be either a model parameter, an initial condition of the dynamic system, or a combination of both.

The efficient and accurate calculation of sensitivity information in dynamic systems is well understood [8, 19] and can be performed easily using a variety of numerical software packages, e.g., Jacobian [33].

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This paper reports on methods that were specifically developed to enable the calculation of sensitivity information for oscillating dynamic systems. Different classes of such systems are distinguished, and their respective treatment is detailed. Where applicable, previous work is built upon in order to present a comprehensive guide to sensitivity analysis of oscillating systems. Due to the exact and intuitive nature of the equations and methods in this work, the quantities that are computed relate to well-defined derived functions of the dynamic systems, in particular, period, amplitude, and different kinds of phases.

1.1. Limit-cycle oscillators and nonlimit-cycle oscillators. This manuscript covers the sensitivity analysis of different classes of oscillating dynamical systems, all of which are described by systems of ordinary differential equations (ODEs). Before beginning the discussion, a general distinction needs to be made between the different classes: nonlimit-cycle oscillators, limit-cycle oscillators, and intermediate-type oscillators.

In this work, the term *nonlimit-cycle oscillator* (NLCO) is used to describe any autonomous oscillating system in which any initial condition repeats periodically. In other words, their periodic orbits are not isolated, and they do not exhibit transient behavior. The initial conditions and parameters both determine the trajectory of oscillation. Prominent examples of such systems are most predator-prey models such as the Lotka–Volterra system [18].

In *limit-cycle oscillators* (LCOs), on the other hand, the periodic orbit is isolated and closed [25], meaning it is determined solely by the parameters of the system, and the shape and position of the limit cycle in phase space is independent of the initial conditions as long as the initial conditions lie within the region of attraction of the periodic orbit. Stable limit cycles, which are the focus of the present work, are approached in an asymptotic fashion from any initial condition within this region of attraction, unless the initial conditions lie exactly on the limit-cycle trajectory. If an LCO is described by ODEs, then there must be a nonlinearity in the equations [25]. Many oscillatory biological systems have been modeled as LCOs, such as the circadian clock [9, 23] which will be examined in detail later. An intrinsic property of LCOs is the capability to return to the original oscillation (albeit phase shifted) after a perturbation in one or several state variables. This property makes LCOs an intuitive choice for the modeling of the biological oscillators in the circadian clock mechanism that show robustness to such perturbations with respect to amplitude and period, yet are entrainable to a specific phase of oscillation by outside signals [7].

Because these two classes of oscillators show different parameter and initial condition dependencies, their sensitivity analysis was formulated separately and is discussed in the following sections. Due to their more interesting and challenging nature, the majority of the present work focuses on LCOs, and the theory necessary for their treatment is developed first. The extension to NLCOs is then easily shown.

Intermediate-type oscillators are systems that can show behaviors previously attributed to both other types, in that their periodic orbits are not isolated, but transients can still be found at least in some manifold. It is shown how these intermediate-type oscillators relate mathematically to both other classes, and a general formulation is presented in this paper which covers all classes of oscillators.

2. Sensitivity analysis of limit-cycle oscillators. In the context of this manuscript, an LCO is defined as a dynamic system with periodic orbit of period T whose monodromy matrix \mathbf{M} (section 2.2.1) has exactly one eigenvalue equal to one, and as a consequence the matrix $[(\mathbf{M} - \mathbf{I}) \quad \dot{\mathbf{y}}(T)]$ has rank n_y (see Corollary 4.2).

2.1. The boundary value problem. Sensitivity analysis of stable LCO systems is challenging due to several of their characteristics. First, the system asymptotically approaches the limit-cycle trajectory but never exactly reaches it, unless the initial conditions lie on the limit cycle. Consequently, if the aim is to analyze the limit-cycle trajectory, initial conditions on the periodic orbit must be identified. Clearly, those initial conditions are not independent of the parameter values, which determine the shape and location of the limit-cycle trajectory. Therefore, the initial conditions for the parametric sensitivities cannot be set to zero, as is usually done for dynamic systems when the initial conditions are independent of the parameters.

A boundary value problem (BVP) is formulated for $\mathbf{y}_0(\mathbf{p})$ and $T(\mathbf{p})$ subject to

$$(2.1) \quad \mathbf{y}(T(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) - \mathbf{y}_0(\mathbf{p}) = \mathbf{0},$$

$$(2.2) \quad \dot{y}_i(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = 0,$$

where $\dot{y}_i(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p}))$ is an arbitrary component of $\frac{d}{dt}\mathbf{y}(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p}))$ with $i \in \{1, \dots, n_y\}$, and $\mathbf{y}(t, \mathbf{p}; \mathbf{y}_0(\mathbf{p}))$ is given by the solution of

$$(2.3) \quad \frac{d}{dt}\mathbf{y}(t, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = \mathbf{f}(\mathbf{y}(t, \mathbf{p}; \mathbf{y}_0(\mathbf{p})), \mathbf{p}),$$

$$(2.4) \quad \mathbf{y}(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = \mathbf{y}_0(\mathbf{p}),$$

where $\mathbf{y}(t, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) \in \mathbb{R}^{n_y}$ are the state variables and $\mathbf{p} \in \mathbb{R}^{n_p}$ are the parameters. By solving this BVP for given values for \mathbf{p} , initial conditions for the state variables that lie on the limit cycle are obtained as well as the period of oscillation $T(\mathbf{p})$.

If only (2.1) were used, this BVP would have infinitely many solutions. The (n_y+1) st condition in (2.2) is one possible example of a *phase locking condition* (PLC), which fixes the solution to an isolated point on the limit cycle. In this example, this is where $\dot{y}_i(0) = 0$. From the fact that (2.3) describes an oscillating system, at least one such point exists. Any arbitrary state variable can be chosen for this constraint, as long as a valid PLC is formulated. A PLC is valid if it defines an isolated point on the periodic orbit (this restriction excludes, e.g., stationary points in flat regions of the trajectory of y_i from being used in (2.2)) and it yields a solution that is unique and smooth in a neighborhood of \mathbf{p} (this restriction excludes, for example, points where both $\dot{y}_i(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = 0$ and $\ddot{y}_i(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = 0$, as will be discussed in sections 2.7.1 and 2.7.2). The choice of PLC presented here is useful for computing derived quantities, such as the peak-to-peak sensitivities presented in section 2.7.2, and will be used for all examples unless otherwise mentioned.

Note that $\mathbf{y}_0(\mathbf{p})$ and $T(\mathbf{p})$ calculated in this manner are functions of \mathbf{p} .

2.2. Floquet theory.

2.2.1. The monodromy matrix. Given a $\mathbf{y}(t)$ that satisfies (2.1) and (2.3), then $\mathbf{A} \equiv \frac{\partial \mathbf{f}}{\partial \mathbf{y}}$ will be a matrix with periodic coefficients. Let $\mathbf{H}(t)$ be the solution to the linear system with periodically time-varying coefficients

$$(2.5) \quad \dot{\mathbf{H}}(t) = \mathbf{A}(t)\mathbf{H}(t)$$

with $\mathbf{H}(0) = \mathbf{I}$. The matrix \mathbf{H} can be interpreted as the partial derivatives of the state variables \mathbf{y} of the LCO with respect to the initial conditions $h_{ij} \equiv \frac{\partial y_i}{\partial y_{0j}}$.

The monodromy matrix \mathbf{M} of this system is defined as $\mathbf{M} \equiv \mathbf{H}(T)$ and has the property

$$(2.6) \quad \mathbf{H}(t + T) = \mathbf{H}(t)\mathbf{M}.$$

The eigenvalues ρ of \mathbf{M} are called multipliers [22] (or characteristic roots [11]) of (2.5). The characteristic exponents of (2.5) are then $\lambda_i = \frac{1}{T} \ln \rho_i$. The multipliers or exponents can be used to determine whether a solution of (2.1) and (2.3) is stable. A solution to (2.1) and (2.3) is orbitally stable if one multiplier is equal to 1 and all others lie inside the unit circle [1]. The eigenvalues and eigenvectors of \mathbf{M} provide information on bifurcation behavior [6] and phase noise [14, 5, 3]. Throughout this section of the paper, it is assumed that the solution of (2.3) is orbitally stable, that one multiplier is equal to 1, and that all others lie inside the unit circle.

2.2.2. General properties of the matrix \mathbf{H} . Given a general periodically time-varying linear system

$$(2.7) \quad \dot{\mathbf{X}}(t) = \mathbf{A}(t)\mathbf{X}(t),$$

the state transition matrix relates $\mathbf{X}(s)$ to $\mathbf{X}(t)$, as in

$$(2.8) \quad \mathbf{X}(t) = \mathbf{H}(t, s)\mathbf{X}(s).$$

It is assumed that the state transition matrix $\mathbf{H}(t, s)$ of the linear system in (2.5) can be factored so that it takes the form [4]

$$\mathbf{H}(t, s) = \mathbf{U}(t)\mathbf{D}(t - s)\mathbf{V}(s).$$

If $\mathbf{H}(t, s)$ is diagonalizable, then $\mathbf{D}(t)$ is of the form

$$\mathbf{D}(t) = \begin{bmatrix} 1 & 0 & 0 & \cdots \\ 0 & e^{t\lambda_2} & 0 & \cdots \\ 0 & 0 & \cdots & \cdots \\ 0 & \cdots & & e^{t\lambda_{n_y}} \end{bmatrix},$$

where λ_i are the characteristic exponents of system (2.3) and where $\mathbf{U}(t) \in \mathbb{R}^{n_y \times n_y}$ and $\mathbf{V}(t) \in \mathbb{R}^{n_y \times n_y}$ are both T -periodic and nonsingular for all t and satisfy

$$\mathbf{U}(t) = \mathbf{V}^{-1}(t).$$

If $\mathbf{H}(t, s)$ is not diagonalizable, then $\mathbf{D}(t)$ takes a block-diagonal form [24], with as many blocks \mathbf{D}_i as there are linearly independent eigenvectors, with each block of size $n_i \times n_i$ taking the form

$$(2.9) \quad \mathbf{D}_i(t) = \begin{bmatrix} e^{\lambda_i t} & te^{t\lambda_i} & \cdots & \frac{1}{(n_i-1)!}t^{(n_i-1)}e^{t\lambda_i} \\ 0 & e^{t\lambda_i} & \cdots & \frac{1}{(n_i-2)!}t^{(n_i-2)}e^{t\lambda_i} \\ 0 & 0 & \ddots & \vdots \\ 0 & 0 & \cdots & e^{t\lambda_i} \end{bmatrix}.$$

The first row and column of $\mathbf{D}(t)$ is the same in both cases, as by definition the system has exactly one multiplier equal to one. For $s = 0$, $\mathbf{H}(t, s)$ becomes $\mathbf{H}(t)$ in (2.5), and it follows that $\mathbf{H}(t)$ can be written as $\mathbf{H}(t) = \mathbf{H}_1(t) + \mathbf{H}_2(t)$, where $\mathbf{H}_1(t)$ and $\mathbf{H}_2(t)$ are both solutions to (2.5) given by

$$(2.10) \quad \begin{aligned} \mathbf{H}_1(t) &= [\dot{\mathbf{y}}(t) \quad \mathbf{O}_{n_y, n_y-1}] \mathbf{V}(0), \\ \mathbf{H}_2(t) &= [\mathbf{O}_{n_y, 1} \quad \mathbf{G}(t)] \mathbf{V}(0) \end{aligned}$$

with $\mathbf{O}_{i,k}$ being the zero matrix with i rows and k columns [22, 2]. Furthermore, because all characteristic exponents λ_i have negative real parts for $i > 1$, the matrix $\mathbf{H}_2(t)$ decays for large times t so that $\mathbf{H}(t) \rightarrow \mathbf{H}_1(t)$, and $\mathbf{H}_1(t)$ is T -periodic.

2.3. Parametric sensitivity analysis. Suppose a dynamic system is described by (2.3). Then, the matrix of parametric sensitivities $s_{ij} \equiv \frac{\partial y_i}{\partial p_j}$ satisfy the following differential equation:

$$(2.11) \quad \frac{d}{dt} \mathbf{S}(t, \mathbf{p}) = \mathbf{A}(t, \mathbf{p}) \mathbf{S}(t, \mathbf{p}) + \mathbf{B}(t, \mathbf{p}),$$

where $\mathbf{A}(t, \mathbf{p}) = \frac{\partial \mathbf{f}}{\partial \mathbf{y}}(\mathbf{y}(t, \mathbf{p}), \mathbf{p})$, $\mathbf{B}(t, \mathbf{p}) = \frac{\partial \mathbf{f}}{\partial \mathbf{p}}(\mathbf{y}(t, \mathbf{p}), \mathbf{p})$, and $\mathbf{S}(t, \mathbf{p}) \in \mathbb{R}^{n_y \times n_p}$.

In the analysis of oscillatory systems, the family of periodic solutions $\mathbf{y}(t, \mathbf{p})$ of (2.3) is of interest. These solutions describe an oscillation with period $T(\mathbf{p})$, and therefore satisfy (2.1). As a consequence, $\mathbf{f}(\mathbf{y}(t, \mathbf{p}), \mathbf{p})$, $\mathbf{A}(t, \mathbf{p})$, and $\mathbf{B}(t, \mathbf{p})$ are periodic in time as well (for the remainder of this section, only the periodic solution is analyzed, unless otherwise stated). It was previously shown [22] that the general solution of (2.11) is

$$(2.12) \quad \mathbf{S}(t, \mathbf{p}) = t\mathbf{R}(t, \mathbf{p}) + \mathbf{Z}(t, \mathbf{p}) + \mathbf{H}(t, \mathbf{p})(\mathbf{S}(0, \mathbf{p}) - \mathbf{Z}(0, \mathbf{p})),$$

where $\mathbf{R}(t, \mathbf{p})$ is $T(\mathbf{p})$ -periodic in time and contains the influence of the period on the sensitivity solution.

$$(2.13) \quad \mathbf{R}(t, \mathbf{p}) = -\frac{\dot{\mathbf{y}}(t, \mathbf{p}; \mathbf{y}_0(\mathbf{p}))}{T(\mathbf{p})} \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}),$$

where $\dot{\mathbf{y}}(t, \mathbf{p}; \mathbf{y}_0(\mathbf{p}))$ is a column vector of length n_y and $\frac{\partial T}{\partial \mathbf{p}}$ is a row vector of length n_p . The matrix $\mathbf{Z}(t, \mathbf{p})$ is also periodic in time with period $T(\mathbf{p})$ and corresponds to the partial derivative of the state variables with respect to the parameters, with the period kept constant.

$$\mathbf{Z} = \left(\frac{\partial \mathbf{y}}{\partial \mathbf{p}} \right)_{T(\mathbf{p})=\text{const}}.$$

The third term of (2.12) takes into account the influence of the initial conditions for the sensitivities $\mathbf{S}(0, \mathbf{p})$. As shown in the previous section, $\mathbf{H}(t, \mathbf{p})$ does not decay, and therefore if the initial conditions $\mathbf{S}(0, \mathbf{p})$ are not equal to $\mathbf{Z}(0, \mathbf{p})$, this term does not decay. The underlying cause is that, in fact, the \mathbf{y}_0 that satisfies (2.1)–(2.3) does depend on the parameters \mathbf{p} , and thus $\mathbf{S}(0, \mathbf{p})$ is not the zero matrix (as it would be in other dynamical systems in which the initial conditions are not influenced by the parameters). If this influence of the initial conditions is to be captured in the total sensitivity, one effectively wants to compute the quantity

$$\mathbf{S} \left(t, \mathbf{p}; \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}} \right) \equiv \frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(t, \mathbf{p}, \mathbf{y}_0) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}} + \frac{\partial \mathbf{y}}{\partial \mathbf{p}}(t, \mathbf{p}, \mathbf{y}_0),$$

where $\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(t, \mathbf{p}, \mathbf{y}_0) = \mathbf{S}(t, \mathbf{p}; \mathbf{0})$ are the sensitivities at constant initial conditions. In other words, the nonzero sensitivity initial conditions $\mathbf{S}_0(\mathbf{p}) \equiv \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p})$ need to be determined. It was previously shown [22] that the solution of (2.11) then takes the form

$$(2.14) \quad \mathbf{S}(t, \mathbf{p}; \mathbf{S}_0(\mathbf{p})) = t\mathbf{R}(t, \mathbf{p}) + \mathbf{Z}(t, \mathbf{p}; \mathbf{S}_0(\mathbf{p})),$$

where $\mathbf{Z}(0, \mathbf{p}; \mathbf{S}_0(\mathbf{p})) = \mathbf{S}_0(\mathbf{p})$.

Several characteristics of the sensitivity trajectories become apparent. As (2.14) shows, the parametric sensitivities of a periodic system are composed of two parts. The periodic part $\mathbf{Z}(t, \mathbf{p}; \mathbf{S}_0(\mathbf{p}))$ is sometimes referred to as the “cleaned out” sensitivity coefficients in previous publications [27] and was reported to contain the influence of the parameters on the “shape” of the oscillation [17]. This quantity can be further decomposed to distinguish amplitude from phase contributions, which will be discussed in more detail in section 2.5.1.

The unbounded part $t\mathbf{R}(t, \mathbf{p})$ contains information on the influence of the parameters on the period of the oscillation. The unboundedness of this part caused concern in some previous work, and it was proposed to scale the time t to obtain a “cyclic time” to avoid the problem [27]. However, it is crucial to notice that even if the unboundedness of this part is eliminated, another source of error and transients in the general solution remains. This is the error caused by inappropriate initial conditions for \mathbf{S} , which leads both to a transient of unknown magnitude as well as a persistent, periodic contribution as time goes to infinity, as can be seen in (2.12) and section 2.2.2. In order to calculate meaningful sensitivities $\mathbf{S}(t, \mathbf{p}; \mathbf{S}_0(\mathbf{p}))$ as well as $\mathbf{Z}(t, \mathbf{p})$ and $\mathbf{R}(t, \mathbf{p})$ for any given time t , correct initial conditions $\mathbf{S}_0(\mathbf{p})$ need to be determined. Methods to compute the exact initial conditions and the various parts of the sensitivity for both LCOs and NLCOs are detailed next.

2.4. Boundary value formulation for the period sensitivities. Equations (2.1)–(2.2) can be differentiated with respect to the parameters \mathbf{p} , yielding the following expressions:

$$(2.15) \quad \frac{d\mathbf{y}}{dt}(T, \mathbf{p}, \mathbf{y}_0) \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}) + \left(\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(T, \mathbf{p}, \mathbf{y}_0) \right)_{\mathbf{y}(0)=const.} + \frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(T, \mathbf{p}, \mathbf{y}_0) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}) - \frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(0, \mathbf{p}, \mathbf{y}_0) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}) = \mathbf{0},$$

$$(2.16) \quad \frac{\partial f_i}{\partial \mathbf{y}}(\mathbf{y}_0, \mathbf{p}) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}) + \frac{\partial f_i}{\partial \mathbf{p}}(\mathbf{y}_0, \mathbf{p}) = \mathbf{0}.$$

This set of equations can then be rewritten in matrix form as

$$(2.17) \quad \begin{bmatrix} (\mathbf{M}(\mathbf{p}) - \mathbf{I}) & \dot{\mathbf{y}}(T, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) \\ \frac{\partial f_i}{\partial \mathbf{y}}(\mathbf{y}_0, \mathbf{p}) & 0 \end{bmatrix} \begin{bmatrix} \mathbf{S}_0(\mathbf{p}) \\ \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}) \end{bmatrix} = \begin{bmatrix} -\mathbf{S}(T, \mathbf{p}; \mathbf{0}) \\ -\frac{\partial f_i}{\partial \mathbf{p}}(\mathbf{y}_0, \mathbf{p}) \end{bmatrix},$$

where \mathbf{I} is the $n_y \times n_y$ identity matrix, $\mathbf{M}(\mathbf{p})$ is the monodromy matrix of the sensitivity system $\frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(T, \mathbf{p}, \mathbf{y}_0)$, and $\mathbf{S}(T, \mathbf{p}; \mathbf{0})$ is the solution of sensitivity equation (2.11) for zero initial conditions at time T , $(\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(T, \mathbf{p}, \mathbf{y}_0))_{\mathbf{y}(0)=const.}$. This equation can be solved for the matrix of unknowns

$$\begin{bmatrix} \mathbf{S}_0(\mathbf{p}) \\ \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}) \end{bmatrix},$$

obtaining a set of initial conditions for the sensitivities $\mathbf{S}_0(\mathbf{p})$ and the period sensitivities.

Using these quantities, it will be shown that all the various parts of the sensitivities can be computed exactly, without using iterative processes or approximations.

There have been several previous approaches to calculate the period sensitivities in LCOs. Typically, the fact that the unbounded term will dominate at large times

is used to estimate the period sensitivity in an iterative procedure [2, 15, 17, 13]. Another approach uses a method based on singular value decomposition [32]. A third method involves the computation of relative phase sensitivities [15, 10]. All these methods have in common that at some point during the numerical procedure, estimations are made, typically where the exact mathematical quantity involves a limit that is estimated by truncating the sequence finitely.

Rosenwasser and Yusupov [22] describe a very similar BVP-based method for LCOs that allows the calculation of the period sensitivities in the same way as presented here and that is exact (i.e., the only source of error is the numerical tolerance to which the BVP is solved). Because a different type of PLC is used, the solution for the sensitivity initial conditions is different. A recent publication by Vytyaz et al. [30] reaches similar conclusions to [22] via a different line of reasoning and presents a BVP-based strategy to solve for $\mathbf{Z}(t)$. The work presented here shows how the choice of PLC influences the solution of the sensitivity trajectories (section 2.5) and the fact that the choice of PLC matters in performing relative phase sensitivity (section 2.7.1). While reference [22] shows a decomposition of the sensitivity solution into two parts that separate out the influence of the period (section 2.3), this work introduces a meaningful decomposition into three parts, where the influence of relative phase is separated from that of the amplitudes (section 2.5.1). Furthermore, this work extends all theory to oscillator types other than LCOs in section 4.2.

2.5. Many sensitivity systems for limit-cycle oscillators. Instead of (2.2), other PLCs can be used, as long as the resulting system is well-posed [16]. An example [22] is to choose a suitable value a for one of the state variables y_j such that $y_j(0, \mathbf{p}) = a$ forms the $(n_y + 1)$ st equation of the BVP. This change will only affect the last row of the matrix equation (2.17) and yields the same period sensitivities $\frac{\partial T}{\partial \mathbf{p}}$, as will become evident after the following analysis.

The matrix $(\mathbf{M}(\mathbf{p}) - \mathbf{I})$ is singular with a rank of $(n_y - 1)$, because it has been assumed that \mathbf{M} has exactly one eigenvalue equal to one, and therefore $(\mathbf{M}(\mathbf{p}) - \mathbf{I})$ has exactly one eigenvalue equal to zero. The partial system

$$(2.18) \quad \begin{bmatrix} (\mathbf{M}(\mathbf{p}) - \mathbf{I}) & \dot{\mathbf{y}}(T, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) \end{bmatrix} \begin{bmatrix} \mathbf{S}_0(\mathbf{p}) \\ \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}) \end{bmatrix} = \begin{bmatrix} -\mathbf{S}(T, \mathbf{p}; \mathbf{0}) \end{bmatrix}$$

of (2.17) does not have a unique solution, but $\frac{\partial T}{\partial \mathbf{p}}$ is still uniquely determined by this system.

What follows is that if \mathbf{S}_0^* is a solution of (2.18), then $\hat{\mathbf{S}}_0 = \mathbf{S}_0^* + \dot{\mathbf{y}}(0)\delta(0)$ is also a solution; $\delta(0)$ is any row vector of size n_p . The vector $\dot{\mathbf{y}}(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = \dot{\mathbf{y}}(T, \mathbf{p}; \mathbf{y}_0(\mathbf{p}))$ is a right eigenvector of $(\mathbf{M} - \mathbf{I})$ associated with the zero eigenvalue because it is a right eigenvector of the monodromy matrix \mathbf{M} , associated with the multiplier equal to one [5].

THEOREM 2.1. *Suppose that at a solution of (2.1)–(2.2), the Jacobian matrix on the left-hand side of (2.17) with respect to $\mathbf{y}_0(\mathbf{p})$ and $T(\mathbf{p})$ is nonsingular. Then*

1. $\frac{\partial T}{\partial \mathbf{p}}(\mathbf{p})$ is determined uniquely by (2.18), i.e., independent of the choice of PLC.
2. any solution of (2.11) for T -periodic \mathbf{A} and \mathbf{B} has the form

$$(2.19) \quad \mathbf{S}(t) = -\frac{t}{T}\dot{\mathbf{y}}(t)\frac{\partial T}{\partial \mathbf{p}} + \mathbf{Q}(t).$$

3. if \mathbf{S} is a solution of (2.11), then

$$\hat{\mathbf{S}}(t) = -\frac{t}{T}\dot{\mathbf{y}}(t)\frac{\partial T}{\partial \mathbf{p}} + \mathbf{Q}(t) + \dot{\mathbf{y}}(t)\boldsymbol{\gamma}$$

is also a solution of (2.11) (e.g., for another PLC), where $\boldsymbol{\gamma} \equiv [\gamma_1, \gamma_2, \dots, \gamma_{n_p}]$ is any time invariant row vector.

4. any initial condition \mathbf{S}_0 for (2.11) that satisfies (2.18) yields a solution \mathbf{S} with a T -periodic \mathbf{Q} in (2.19).

Proof.

1. By hypothesis, (2.17) has a unique solution. In other words, the square matrix is of rank $(n_y + 1)$, and therefore the partial system in (2.18) must be of full rank (n_y) (because one extra row can only increase the rank by one). Because $[\mathbf{M}(\mathbf{p}) - \mathbf{I}]$ is of rank $n_y - 1$, the partial system equation (2.18) can be put in the following row echelon form:

$$\left[\begin{array}{ccccc|c} * & * & \cdots & * & * & * \\ 0 & * & \cdots & * & * & * \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & * & * & * \\ 0 & 0 & \cdots & 0 & 0 & * \end{array} \right] \left[\begin{array}{c} \mathbf{S}_0(\mathbf{p}) \\ \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}) \end{array} \right] = \left[\begin{array}{c} -\boldsymbol{\Psi}\mathbf{S}(T, \mathbf{p}; \mathbf{0}) \end{array} \right],$$

where $\boldsymbol{\Psi}$ is a matrix representing the elementary row operations performed to obtain row-echelon form. Because the $(n_y + 1)$ st column must contribute a pivot to the system, $\frac{\partial T}{\partial \mathbf{p}}$ is uniquely determined.

2. The general solution of (2.11) is given by (2.12) and shows it can always be decomposed as (2.19) such that $\mathbf{Q}(t)$ is not necessarily periodic but contains the influence of the initial conditions and the periodic part $\mathbf{Z}(t)$.
3. Take a solution \mathbf{S} to (2.11) of the form (2.19). Then, if $\dot{\mathbf{y}}\boldsymbol{\gamma}$ is added to \mathbf{S} ,

$$(2.20) \quad \dot{\hat{\mathbf{S}}} + \ddot{\mathbf{y}}\boldsymbol{\gamma} = \mathbf{A}(\mathbf{S} + \dot{\mathbf{y}}\boldsymbol{\gamma}) + \mathbf{B},$$

which solves (2.11) because

$$\ddot{\mathbf{y}} = \mathbf{A}\dot{\mathbf{y}}.$$

Furthermore, all solutions $\hat{\mathbf{S}}(t)$ can be decomposed as in (2.19) because

$$\mathbf{S} + \dot{\mathbf{y}}\boldsymbol{\gamma} = t\mathbf{R} + \mathbf{Q} + \dot{\mathbf{y}}\boldsymbol{\gamma},$$

where $\mathbf{R} = -\frac{\dot{\mathbf{y}}}{T}\frac{\partial T}{\partial \mathbf{p}}$, and $\frac{\partial T}{\partial \mathbf{p}}$ is uniquely determined by (2.18) so that $\hat{\mathbf{R}} = \mathbf{R}$. Then

$$\hat{\mathbf{S}} = t\mathbf{R} + \mathbf{Q}(t) + \dot{\mathbf{y}}(t)\boldsymbol{\gamma}.$$

4. Substitute (2.12) into (2.18) to obtain

$$(\mathbf{M} - \mathbf{I})(\mathbf{S}_0 - \mathbf{Z}(0)) = \mathbf{0}.$$

$\mathbf{Q}(t+T) - \mathbf{Q}(t) = \mathbf{S}(t+T) - \mathbf{S}(t) + \dot{\mathbf{y}}(t)\frac{\partial T}{\partial \mathbf{p}}$, so by using (2.12) together with (2.6) to obtain

$$\mathbf{Q}(t+T) - \mathbf{Q}(t) = \mathbf{H}(t)(\mathbf{M} - \mathbf{I})(\mathbf{S}_0 - \mathbf{Z}(0)) = \mathbf{0},$$

and therefore \mathbf{Q} is T -periodic. \square

It is important to note that once a solution for the BVP in (2.1) is found (using any PLC), it is irrelevant which PLC is used to compute the sensitivity matrices (as long as it is consistent with the initial conditions found from the solution of the BVP). This is due to the fact that the influence of the initial conditions is only implicit in the matrices \mathbf{A} and \mathbf{B} , and it was shown that all solutions are consistent with those.

2.5.1. Decomposition of the periodic $\mathbf{Z}(t)$ matrix. It was suggested in reference [17] that the periodic matrix $\mathbf{Z}(t)$ contains information on how the shape of the limit cycle depends on the parameters of the system, where the influence of the period change is eliminated. Furthermore, this matrix is thought to contain information on phase behavior of the limit cycle [15]. Presumably, if any information on the shape of the limit cycle is to be found, one would like to eliminate all components that encode phase information or, in other words, that are in the $\dot{\mathbf{y}}(t)$ direction. The matrix $\mathbf{Z}(t)$ can then be written as a sum of two contributions:

$$\mathbf{Z}(t) = \mathbf{W}(t) + \dot{\mathbf{y}}(t)\delta(t).$$

The initial condition from a solution of (2.18) that is orthogonal to the null space of $(\mathbf{M} - \mathbf{I})$ will be termed $\mathbf{W}(0)$.

Because $\dot{\mathbf{y}}(T)$ spans the null space of $(\mathbf{M}(\mathbf{p}) - \mathbf{I})$, $\mathbf{W}(0)$ can be computed by augmenting (2.18) with this eigenvector (corresponding to the zero eigenvalue) as the $(n_y + 1)$ st row. The resulting system of equations is

$$(2.21) \quad \begin{bmatrix} (\mathbf{M}(\mathbf{p}) - \mathbf{I}) & \dot{\mathbf{y}}(T, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) \\ \dot{\mathbf{y}}^T(T, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) & 0 \end{bmatrix} \begin{bmatrix} \mathbf{W}(0) \\ \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}) \end{bmatrix} = \begin{bmatrix} -\mathbf{S}(T, \mathbf{p}; \mathbf{0}) \\ \mathbf{0} \end{bmatrix}.$$

The $(n_y + 1)$ st row in this situation does not represent a PLC and can thus be added for any solution of the BVP in (2.1).

However, this method provides only an initial condition. The matrix $\mathbf{W}(t)$ is constructed from any matrix $\mathbf{Z}(t)$ (or from $\mathbf{S}(t)$, in the exact same manner) using the projection

$$(2.22) \quad \mathbf{W}(t) = \left(\mathbf{I} - \frac{\dot{\mathbf{y}}(t) \dot{\mathbf{y}}(t)^T}{\|\dot{\mathbf{y}}(t)\|^2} \right) \mathbf{Z}(t).$$

It is known that $\mathbf{Z}(t + T) = \mathbf{Z}(t)$ as well as $\dot{\mathbf{y}}(t + T) = \dot{\mathbf{y}}(t)$, so it is clear that $\mathbf{W}(t + T) = \mathbf{W}(t)$ is periodic also. Using the same argument, the contribution in the $\dot{\mathbf{y}}(t)$ direction

$$\delta(t) = \frac{1}{\|\dot{\mathbf{y}}(t)\|^2} [\dot{\mathbf{y}}(t)^T \mathbf{Z}(t)]$$

is also T -periodic.

In summary, this decomposition of the matrix $\mathbf{Z}(t)$ leads to a three-part decomposition of the overall sensitivities, yielding

$$\mathbf{S}(t) = -\frac{t}{T} \dot{\mathbf{y}}(t) \frac{\partial T}{\partial \mathbf{p}} + \mathbf{W}(t) + \dot{\mathbf{y}}(t)\delta(t).$$

The interpretation of the latter two parts as containing shape and phase information, respectively, is justified in the following text.

2.6. Amplitude sensitivities. Define the amplitude of y_i as

$$\Omega_i(\mathbf{p}) \equiv y_i(t_{i,\max}(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) - y_i(t_{i,\min}(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})),$$

where $t_{i,\max}$ and $t_{i,\min}$ are times at which y_i attains its maximum and minimum value, respectively, and differentiate with respect to \mathbf{p} to obtain

$$\begin{aligned} \frac{\partial \Omega_i}{\partial \mathbf{p}}(\mathbf{p}) &= \mathbf{s}_i(t_{i,\max}(\mathbf{p}), \mathbf{p}; \mathbf{S}_0(\mathbf{p})) + \dot{y}_i(t_{i,\max}(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) \frac{\partial t_{i,\max}}{\partial \mathbf{p}}(\mathbf{p}) \\ &\quad - \mathbf{s}_i(t_{i,\min}(\mathbf{p}), \mathbf{p}; \mathbf{S}_0(\mathbf{p})) - \dot{y}_i(t_{i,\min}(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) \frac{\partial t_{i,\min}}{\partial \mathbf{p}}(\mathbf{p}), \end{aligned}$$

where \mathbf{s}_i represents the i th row of the full sensitivity matrix. The amplitude of oscillation is thus a derived quantity specific to each state variable, and because $\mathbf{y}(t)$ is a smooth function, the terms multiplied by $\dot{y}_i(t_{i,\max}(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}))$ and by $\dot{y}_i(t_{i,\min}(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}))$ vanish; the amplitude sensitivity is the difference between the sensitivities at the maximum and the minimum of this state variable, as shown in references [2, 15]. Furthermore, the sensitivity of the amplitude of y_i can be calculated directly from any of the sensitivities \mathbf{S} , \mathbf{Z} , or \mathbf{W} . From the fact that $\dot{y}_i(t_{i,\max}) = 0$, it follows that $\mathbf{s}_i(t_{i,\max}) = \mathbf{z}_i(t_{i,\max}) = \mathbf{w}_i(t_{i,\max})$. This illustrates the fact that \mathbf{W} contains information on the shape of the limit cycle.

THEOREM 2.2. *For an LCO, the matrix $\mathbf{W}(t)$ is uniquely defined by $\mathbf{y}(t)$ for each point on the limit cycle.*

Proof. Take two sensitivity solutions $\mathbf{S}_1(t, \mathbf{p}; \mathbf{S}_{0,1}(\mathbf{p}))$ and $\mathbf{S}_2(s, \mathbf{p}; \mathbf{S}_{0,2}(\mathbf{p}))$, constructed using PLC₁ and PLC₂, respectively. The two PLCs define time references such that at some point on the limit cycle, $\mathbf{y}(t = \alpha) = \mathbf{y}(s = \beta)$. Differentiate with respect to the parameters to obtain

$$\mathbf{S}_1(t = \alpha) + \dot{\mathbf{y}}(t = \alpha) \frac{\partial \alpha}{\partial \mathbf{p}} = \mathbf{S}_2(s = \beta) + \dot{\mathbf{y}}(s = \beta) \frac{\partial \beta}{\partial \mathbf{p}},$$

showing that solutions satisfying (2.18) differ only in their contributions in the direction $\dot{\mathbf{y}}(t)$, and this difference is eliminated by using the projection described in (2.22) to construct $\mathbf{W}(t)$. \square

COROLLARY 2.3. *The only difference between any two sensitivity solutions for the same $\mathbf{y}_0(\mathbf{p})$ is $\delta(t)$.*

2.7. Phase sensitivities.

2.7.1. The relative phase sensitivities $\delta(t)$. This section will show that there is an intuitive interpretation of $\delta(t)$ as a quantification of how the timing of an event defined by a PLC depends on the parameters of the system. In other words, the quantity $\delta(t)$ is a relative phase sensitivity, where “relative phase” is defined as a time difference $(\beta - \alpha)$ between two events, described by two different PLCs.

Take $\mathbf{y}^*(t, \mathbf{p}; \mathbf{y}_0^*(\mathbf{p}))$ to be the solution of the BVP using PLC₁, leading to a sensitivity solution

$$(2.23) \quad \mathbf{S}^*(t) = -\frac{t}{T} \dot{\mathbf{y}}^*(t) \frac{\partial T}{\partial \mathbf{p}} + \mathbf{W}^*(t) + \dot{\mathbf{y}}^*(t) \delta^*(t),$$

and $\mathbf{y}^{**}(s, \mathbf{p}; \mathbf{y}_0^{**}(\mathbf{p}))$ to be the solution of the BVP using PLC₂, leading to a sensitivity solution

$$(2.24) \quad \mathbf{S}^{**}(s) = -\frac{s}{T} \dot{\mathbf{y}}^{**}(s) \frac{\partial T}{\partial \mathbf{p}} + \mathbf{W}^{**}(s) + \dot{\mathbf{y}}^{**}(s) \delta^{**}(s).$$

Define a pair (α, β) by

$$(2.25) \quad \mathbf{y}^*(t = \beta, \mathbf{p}; \mathbf{y}_0^*(\mathbf{p})) = \mathbf{y}^{**}(s = \alpha, \mathbf{p}; \mathbf{y}_0^{**}(\mathbf{p}))$$

and thus also $\dot{\mathbf{y}}^*(\beta, \mathbf{p}; \mathbf{y}_0^*(\mathbf{p})) = \dot{\mathbf{y}}^{**}(\alpha, \mathbf{p}; \mathbf{y}_0^{**}(\mathbf{p}))$. Differentiate (2.25) with respect to \mathbf{p} to obtain

$$\mathbf{S}^*(\beta) + \dot{\mathbf{y}}^*(\beta) \frac{\partial \beta}{\partial \mathbf{p}} = \mathbf{S}^{**}(\alpha) + \dot{\mathbf{y}}^{**}(\alpha) \frac{\partial \alpha}{\partial \mathbf{p}}.$$

Equations (2.23)–(2.24) can be used to cancel identical terms:

$$\mathbf{W}^*(\beta) + \dot{\mathbf{y}}^*(\beta) \left(-\frac{\beta}{T} \frac{\partial T}{\partial \mathbf{p}} + \frac{\alpha}{T} \frac{\partial T}{\partial \mathbf{p}} + \delta^*(\beta) + \frac{\partial \beta}{\partial \mathbf{p}} - \frac{\partial \alpha}{\partial \mathbf{p}} - \delta^{**}(\alpha) \right) = \mathbf{W}^{**}(\alpha).$$

By Theorem 2.2, $\mathbf{W}^*(\beta) = \mathbf{W}^{**}(\alpha)$ and because the system is not stationary, $\dot{\mathbf{y}}^*(\beta) \neq \mathbf{0}$, so that

$$(2.26) \quad \frac{\partial(\alpha - \beta)}{\partial \mathbf{p}} = \frac{(\alpha - \beta)}{T} \frac{\partial T}{\partial \mathbf{p}} + \delta^*(\beta) - \delta^{**}(\alpha).$$

This result is interesting because it enables two effects to be distinguished. The first term is the overall contribution of the period sensitivity to the sensitivity of the phase, whereas the following two terms describe the flexibility of the limit cycle in the sense that phase variation can occur independently of period variation.

Note that if PLC_1 and PLC_2 had been chosen in such a way that they locked the phase at the same point but using different PLCs, then $\beta = \alpha$, and the influence of different PLCs on the sensitivity solution is entirely quantified by the different δ s. This effect is illustrated in Figure 2.1, and it makes clear the need for a precise definition of “phase” when analyzing oscillatory dynamical systems. Care must be taken to use only PLCs that are valid. An example of an invalid PLC would be to use $y_i(0) = \xi$ at an extremum of y_i , because in this scenario the point $y_i(0) = \xi$ might no longer exist after an infinitesimal parameter change, i.e., the phase sensitivity is not defined.

Note, furthermore, that if $\alpha = 0$, the measure $-\frac{\partial(\alpha - \beta)}{\partial \mathbf{p}}$ describes the sensitivity of the timing of the event $\mathbf{y}^*(t = \beta)$ with reference to the time scale defined by PLC_1 .

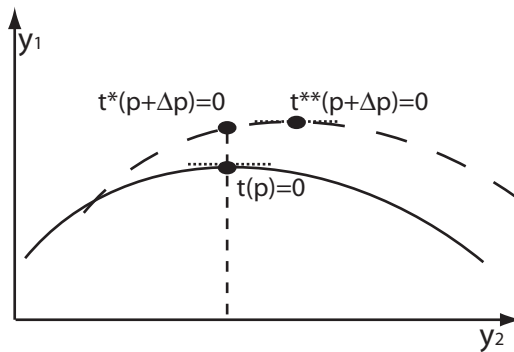


FIG. 2.1. Illustration of the effect of the PLC on the sensitivity solution. A finite perturbation of the parameters from \mathbf{p} to $(\mathbf{p} + \Delta \mathbf{p})$ causes a shift of the limit cycle from the solid line to the dashed line. The PLC $y_1(0) = 0$ results in a new time reference shown as t^* ; the PLC $y_2(0) = \xi$ results in the time t^* .

2.7.2. Peak-to-peak phase sensitivities. The peak-to-peak sensitivities defined here are one particular kind of relative phase sensitivities, where the relative phase of interest is the time difference between extrema in different state variables. While the formulation presented above can be used, the structure of the problem lends itself to a shortcut which will be described briefly.

Suppose the time scale is defined using the PLC

$$(2.27) \quad \dot{y}_1(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = 0.$$

Then define $\beta(\mathbf{p})$ from the equation

$$(2.28) \quad \dot{y}_j(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = 0,$$

i.e., β is the time of the extremum in y_j relative to the extremum in y_1 . This can also be written as

$$(2.29) \quad f_j(\mathbf{y}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})), \mathbf{p}) = 0$$

and differentiated with respect to \mathbf{p} to yield

$$(2.30) \quad \frac{\partial f_j}{\partial \mathbf{y}}(\mathbf{y}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})), \mathbf{p}) \left(\dot{\mathbf{y}}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) \frac{\partial \beta}{\partial \mathbf{p}}(\mathbf{p}) + \mathbf{S} \left(\beta(\mathbf{p}), \mathbf{p}; \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}) \right) \right) + \frac{\partial f_j}{\partial \mathbf{p}}(\mathbf{y}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})), \mathbf{p}) = \mathbf{0},$$

which can be solved directly for $\frac{\partial \beta}{\partial \mathbf{p}}(\mathbf{p})$, providing the peak-to-peak sensitivity without the calculation of $\delta \mathbf{s}$. Again, close attention should be paid to the validity of the PLC for the point chosen. If in this case, $\frac{\partial f_j}{\partial \mathbf{y}}(\mathbf{y}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})), \mathbf{p}) \dot{\mathbf{y}}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = 0$ in (2.30), or in other words $\ddot{\mathbf{y}}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) = 0$, the PLC is not valid, and this equation cannot be used to determine a unique $\frac{\partial \beta}{\partial \mathbf{p}}$ (an intuitive example here is the case of a saddle point in y_j , where an infinitesimal parameter change might remove the stationary point and turn the saddle point into an inflexion point instead). In this case, it may be possible to use higher-order derivatives of the PLC with respect to the parameters to determine a unique $\frac{\partial \beta}{\partial \mathbf{p}}$. However, this analysis is not detailed here.

This simplified method yields the same result as the more general method from the previous section, as evident after the following exercise. Take (2.27) as PLC₁, yielding the time reference $\mathbf{y}(t)$. Use (2.28) as the second PLC, with the time reference $\mathbf{y}^{**}(s)$ and $\alpha = 0$, so that $\mathbf{y}(\beta) = \mathbf{y}^{**}(0)$. Then (2.30) can be written as

$$(2.31) \quad \frac{\partial f_j}{\partial \mathbf{y}}(\mathbf{y}(\beta, \mathbf{p}), \mathbf{p}) \left(\dot{\mathbf{y}}(\beta, \mathbf{p}) \left(\frac{\partial \beta}{\partial \mathbf{p}}(\mathbf{p}) - \frac{\beta}{T} \frac{\partial T}{\partial \mathbf{p}} + \delta(\beta) \right) + \mathbf{W}(\beta, \mathbf{p}) \right) + \frac{\partial f_j}{\partial \mathbf{p}}(\mathbf{y}(\beta, \mathbf{p}), \mathbf{p}) = \mathbf{0}.$$

From the second PLC it is known that

$$(2.32) \quad \frac{\partial f_j}{\partial \mathbf{y}}(\mathbf{y}^{**}(0, \mathbf{p}), \mathbf{p}) (\mathbf{W}^{**}(0) + \dot{\mathbf{y}}^{**}(0, \mathbf{p}) \delta^{**}(0)) + \frac{\partial f_j}{\partial \mathbf{p}}(\mathbf{y}^{**}(0, \mathbf{p}), \mathbf{p}) = \mathbf{0},$$

where, as shown in Theorem 2.2, $\mathbf{W}^{**}(0) = \mathbf{W}(\beta)$, and thus (2.32) can be substituted into (2.31) to obtain

$$(2.33) \quad \frac{\partial f_j}{\partial \mathbf{y}}(\mathbf{y}(\beta, \mathbf{p}), \mathbf{p}) \dot{\mathbf{y}}(\beta, \mathbf{p}) \left(\frac{\partial \beta}{\partial \mathbf{p}}(\mathbf{p}) - \frac{\beta}{T} \frac{\partial T}{\partial \mathbf{p}} + \delta(\beta) - \delta^{**}(0) \right) = \mathbf{0},$$

which is consistent with (2.26). In fact, this simpler method can be used for any type of PLC for the zero time reference, as long as the time β is defined by an extremum in $y_j(t)$.

Notice that this type of sensitivity again reduces to (2.18) if one considers the special case of

$$f_1(\mathbf{y}(T(\mathbf{p}); \mathbf{p}, \mathbf{y}_0(\mathbf{p})), \mathbf{p}) = 0.$$

After differentiation, this leads to

$$\begin{aligned} \frac{\partial f_1}{\partial \mathbf{y}}(\mathbf{y}(T(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})), \mathbf{p}) \left(\dot{\mathbf{y}}(T(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})) \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}) + \mathbf{S} \left(T(\mathbf{p}), \mathbf{p}; \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}) \right) \right) \\ + \frac{\partial f_1}{\partial \mathbf{p}}(\mathbf{y}(T(\mathbf{p}), \mathbf{p}; \mathbf{y}_0(\mathbf{p})), \mathbf{p}) = \mathbf{0}. \end{aligned}$$

From rearranging (2.15) using $\mathbf{S}(T(\mathbf{p}), \mathbf{p}; \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p})) = (\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(T, \mathbf{p}, \mathbf{y}_0))_{\mathbf{y}(0)=const.} + \frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(T, \mathbf{p}, \mathbf{y}_0) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p})$ and $\frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(0, \mathbf{p}, \mathbf{y}_0) = \mathbf{I}$, it is known that

$$\frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}) = \dot{\mathbf{y}}(T(\mathbf{p}); \mathbf{p}, \mathbf{y}_0(\mathbf{p})) \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}) + \mathbf{S} \left(T(\mathbf{p}), \mathbf{p}; \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}) \right).$$

Because the partial derivatives of f_1 are T -periodic, it is shown that this equation reduces to the PLC used in (2.16), making this peak-to-peak sensitivity consistent with the computation of the period sensitivities earlier. The period sensitivities can therefore be considered a special case of the peak-to-peak sensitivities, namely, the time difference of a peak of one state variable to the next peak in the same state variable.

3. Sensitivity analysis for nonlimit-cycle oscillators. We define an NLCO as a dynamic system with periodic orbits in which the rank of the matrix (3.2) is equal to one. This implies that the monodromy matrices \mathbf{M} have exactly n_y eigenvalues equal to one (see Corollary 4.3).

3.1. Sensitivity analysis. For NLCOs, the initialization of the parametric sensitivities is straightforward. The parametric sensitivities at time $t = 0$ are zero, because the initial conditions do not depend on the parameter values. As a consequence, the sensitivities \mathbf{S} can easily be determined by integration of (2.11) with $\mathbf{S}_0 = \mathbf{0}$. The full sensitivities can be decomposed, as in the case of a LCO [18]:

$$\mathbf{S}(t) = -\frac{t}{T} \dot{\mathbf{y}}(t) \frac{\partial T}{\partial \mathbf{p}} + \mathbf{Z}(t).$$

3.2. The BVP. Since for NLCOs the initial conditions determine the periodic behavior together with the parameters and there is no asymptotic behavior, the BVP solution is reduced to a single unknown. The period $T(\mathbf{p}, \mathbf{y}_0)$ of the system is not known a priori, but is easily determined, for example, by the solution of a BVP for $T(\mathbf{p}, \mathbf{y}_0)$ subject to

$$(3.1) \quad \mathbf{y}(T(\mathbf{p}, \mathbf{y}_0), \mathbf{p}, \mathbf{y}_0) - \mathbf{y}_0 = \mathbf{0}.$$

When the BVP is differentiated with respect to the parameters, a matrix equation similar to (2.18) is obtained, where the matrix

$$(3.2) \quad \begin{bmatrix} (\mathbf{M} - \mathbf{I}) & \dot{\mathbf{y}}(T, \mathbf{p}, \mathbf{y}_0) \end{bmatrix}$$

has rank one, due to two possible scenarios. The rank of $(\mathbf{M} - \mathbf{I})$ can either be zero or one, depending on the nature of the dynamic system. In either case, (3.2) has rank one, and n_y PLCs are needed to pose a BVP of full rank. A natural choice is to set all n_y initial conditions.

3.2.1. Period and amplitude sensitivities. The derivatives of the boundary condition in (3.1) with respect to parameters \mathbf{p} and initial conditions \mathbf{y}_0 yield

$$(3.3) \quad \dot{\mathbf{y}}(0, \mathbf{p}, \mathbf{y}_0) \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{y}_0) = -\mathbf{S}(T, \mathbf{p}; \mathbf{0})$$

and

$$(3.4) \quad \dot{\mathbf{y}}(0, \mathbf{p}, \mathbf{y}_0) \frac{\partial T}{\partial \mathbf{y}_0}(\mathbf{p}, \mathbf{y}_0) = (\mathbf{I} - \mathbf{M}).$$

Equation (3.3) can be solved for $\frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{y}_0)$. The rank of $(\mathbf{M} - \mathbf{I})$ determines the solution of (3.4). It is clear that in the case of $(\mathbf{I} - \mathbf{M})$ having rank zero, the initial conditions have no influence on the period of the oscillation. This is the case, for example, in the linear harmonic oscillator. The example presented in section 6.3 is nonlinear and has a nondiagonalizable matrix $(\mathbf{I} - \mathbf{M})$ of rank one, still with all zero eigenvalues. In this case, because (3.2) has rank one, $(\mathbf{M} - \mathbf{I}) = \dot{\mathbf{y}}(T)\boldsymbol{\psi}$, where $\boldsymbol{\psi}$ is a row vector of length n_y . It follows that period sensitivities with respect to the initial conditions can be calculated, and $\frac{\partial T}{\partial \mathbf{y}_0}(\mathbf{p}, \mathbf{y}_0) \equiv -\boldsymbol{\psi}$.

The amplitude sensitivities can be calculated in the same manner as described for LCOs.

3.2.2. Relative phase sensitivities. It is known that

$$\mathbf{S}(0, \mathbf{p}, \mathbf{y}_0) = \mathbf{Z}(0, \mathbf{p}, \mathbf{y}_0) = \mathbf{W}(0, \mathbf{p}, \mathbf{y}_0) + \dot{\mathbf{y}}(0, \mathbf{p})\boldsymbol{\delta}(0, \mathbf{p}, \mathbf{y}_0) = \mathbf{0}$$

and because, by construction the columns of $\mathbf{W}(0, \mathbf{p}, \mathbf{y}_0)$ are orthogonal to $\dot{\mathbf{y}}(0, \mathbf{p})$,

$$\mathbf{W}(0, \mathbf{p}, \mathbf{y}_0) = \mathbf{0}$$

and

$$\boldsymbol{\delta}(0, \mathbf{p}, \mathbf{y}_0) = \mathbf{0}.$$

However, neither $\mathbf{W}(t)$ nor $\boldsymbol{\delta}(t)$ are identically zero, as the example in Figure 6.3 shows. It follows that, for any given point on the periodic orbit, the matrix \mathbf{W} is not uniquely defined by the state variables, because the choice of PLC in the form of all initial conditions is arbitrary and any point on the cycle could have been chosen.

A relative phase sensitivity analysis can still be performed, and two examples will be shown here. To avoid repetition, the general case is discussed later in section 4.3. Let the “relative phase” be defined here as a time difference β between the time zero, as defined by the set of initial conditions \mathbf{y}_0 , and one differentiable PLC that locks one degree of freedom, e.g.,

$$(3.5) \quad y_i(t = \beta, \mathbf{p}, \mathbf{y}_0) = \psi.$$

This PLC can be differentiated with respect to the parameters, resulting, for this example, in

$$-\frac{\beta}{T}\dot{y}_i(\beta)\frac{\partial T}{\partial \mathbf{p}} + \mathbf{w}_i(\beta) + \dot{y}_i(\beta)\boldsymbol{\delta}(\beta) + \dot{y}_i(\beta)\frac{\partial \beta}{\partial \mathbf{p}} = \mathbf{0},$$

where $\mathbf{w}_i(\beta)$ is the i th row of the matrix $\mathbf{W}(t)$. If $\dot{y}_i(\beta) \neq 0$, this equation can be solved to yield

$$\frac{\partial \beta}{\partial \mathbf{p}} = \frac{\beta}{T} \frac{\partial T}{\partial \mathbf{p}} - \frac{\mathbf{w}_i(\beta)}{\dot{y}_i(\beta)} - \delta(\beta).$$

Again, it is important to note that (3.5) is not a valid PLC at a point where $\dot{y}_i(\beta) = 0$, as discussed for the case of LCOs in section 2.7.1.

Similarly, the method for peak-to-peak sensitivity calculation in section 2.7.2 needs only to be modified slightly to be applicable to NLCOs. Instead of a first PLC, the time reference is defined by the initial condition, but the relative phase β is still defined by a PLC that locks the phase at a stationary point of a state variable y_j (and as discussed in section 2.7.2, a point where $\ddot{y}_j(\beta(\mathbf{p}), \mathbf{p}, \mathbf{y}_0) = 0$ cannot be analyzed in this manner):

$$(3.6) \quad \dot{y}_j(\beta(\mathbf{p}), \mathbf{p}, \mathbf{y}_0) = 0.$$

Again, this PLC is differentiated with respect to \mathbf{p} to yield

$$(3.7) \quad \begin{aligned} & \frac{\partial f_j}{\partial \mathbf{y}}(\mathbf{y}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0), \mathbf{p}) \left(\dot{\mathbf{y}}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0) \frac{\partial \beta}{\partial \mathbf{p}}(\mathbf{p}) + \mathbf{S}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{0}) \right) \\ & + \frac{\partial f_j}{\partial \mathbf{p}}(\mathbf{y}(\beta(\mathbf{p}), \mathbf{p}; \mathbf{y}_0), \mathbf{p}) = \mathbf{0}, \end{aligned}$$

which can be solved directly for $\frac{\partial \beta}{\partial \mathbf{p}}(\mathbf{p})$. Relative phases between two events defining a time β and a time α , respectively, on the periodic orbit can now be calculated simply by performing separate analyses with reference to the common time zero defined by the initial conditions and then taking the difference, i.e., $\frac{\partial(\beta-\alpha)}{\partial \mathbf{p}} = \frac{\partial \beta}{\partial \mathbf{p}} - \frac{\partial \alpha}{\partial \mathbf{p}}$.

4. General formulation for the sensitivity analysis of all types of oscillators.

4.1. Intermediate-type oscillators. An intermediate-type oscillator in the context of this manuscript is a dynamic system with periodic orbits that is not described by the definitions for either the LCO or the NLCO. The monodromy matrix \mathbf{M} can have k eigenvalues equal to 1, where $1 < k \leq n_y$. Then, the matrix (3.2) has rank m , where $1 < m \leq n_y$ and $(n_y + 1 - m)$ PLCs are needed.

THEOREM 4.1. *Let n_u equal the number of linearly independent eigenvectors of \mathbf{M} corresponding to eigenvalues equal to unity, and let d be the degeneracy of the Jordan block corresponding to the eigenvector $\dot{\mathbf{y}}(T)$. Then the rank m of the matrix*

$$[(\mathbf{M} - \mathbf{I}) \quad \dot{\mathbf{y}}(T)]$$

is given by

$$m = \begin{cases} 1 + n_y - n_u & \text{if } d = 0, \\ n_y - n_u & \text{otherwise.} \end{cases}$$

Proof. Let \mathbf{T} be a matrix with $\dot{\mathbf{y}}(T)$ as its first column that takes \mathbf{M} to its Jordan form. Applying the row and column operations

$$\mathbf{T}^{-1} [(\mathbf{M} - \mathbf{I}) \quad \dot{\mathbf{y}}(T)] \begin{bmatrix} \mathbf{T} \\ 1 \end{bmatrix}$$

yields

$$\begin{bmatrix} \mathbf{N}_1 & & & & \mathbf{e}_1 \\ & \mathbf{N}_2 & & & \mathbf{0} \\ & & \ddots & & \vdots \\ & & & \mathbf{N}_{n_u} & \mathbf{0} \\ & & & & \mathbf{J} & \mathbf{0} \end{bmatrix},$$

where $\mathbf{N}_1, \dots, \mathbf{N}_{n_u}$ are nilpotent Jordan blocks, \mathbf{J} is a Jordan matrix corresponding to all the eigenvalues not equal to unity, and \mathbf{e}_1 is the first unit vector of appropriate dimension. If $d = 0$, this matrix becomes

$$\begin{bmatrix} 0 & & & & 1 \\ & \mathbf{N}_2 & & & \mathbf{0} \\ & & \ddots & & \vdots \\ & & & \mathbf{N}_{n_u} & \mathbf{0} \\ & & & & \mathbf{J} & \mathbf{0} \end{bmatrix},$$

and it is clear that each nilpotent Jordan block reduces the rank by one, but the final column also contributes one pivot. If $d > 0$, then each nilpotent Jordan block reduces the rank by one, and the final column does not contribute a pivot. \square

COROLLARY 4.2. *For an oscillator, $m = n_y$ iff $n_u = 1$ and $d = 0$ (LCO).*

Proof. If $n_u = 1$ and $d = 0$ (LCO), then $m = n_y$. If $m = n_y$, then

1. if $d = 0$, then $n_u = 1$;
2. if $d > 0$, then $n_u = 0$, contradicting $d > 0$. \square

COROLLARY 4.3. *If $m = 1$, then \mathbf{M} has n_y eigenvalues equal to unity (NLCO).*

Proof. If $m = 1$, then $d \leq 1$, because otherwise the first nilpotent block contributes a second pivot. If $d = 0$, then $n_u = n_y$. If $d = 1$, then $n_u = n_y - 1$, and the additional eigenvalue equals unity. \square

4.2. General formulation of the BVP. The general BVP formulation is to solve the following equations for $T(\mathbf{p}, \mathbf{q})$ and $\mathbf{y}_0(\mathbf{p}, \mathbf{q})$:

$$(4.1) \quad \mathbf{y}(T(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})) = \mathbf{y}_0(\mathbf{p}, \mathbf{q}),$$

$$(4.2) \quad \mathbf{g}(\mathbf{y}_0(\mathbf{p}, \mathbf{q}), \mathbf{p}, \mathbf{q}) = \mathbf{0},$$

where $\mathbf{y}(T(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q}))$ is given by the solution of (2.3) from the initial condition

$$\mathbf{y}(0, \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})) = \mathbf{y}_0(\mathbf{p}, \mathbf{q}).$$

A distinction is made between the parameters \mathbf{p} that appear in the right-hand sides of the ODEs and the additional parameters \mathbf{q} introduced by the PLC equations (4.2). In general the choice of the number and interpretation of the parameters \mathbf{q} is arbitrary when formulating the PLC equations.

The number of PLC equations (4.2) introduced is dictated by the rank deficiency of the condition for a closed orbit (4.1). In addition, the Jacobian of the full system of (4.1)–(4.2) must be full rank.

4.2.1. Period sensitivities. Equations (4.1)–(4.2) can be formally differentiated with respect to \mathbf{p} and \mathbf{q} , yielding period and initial condition sensitivities with

respect to both

$$\begin{aligned}
& \dot{\mathbf{y}}(T, \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}) + \frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(T, \mathbf{y}_0, \mathbf{p}, \mathbf{q}) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}) \\
& + \left(\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(T, \mathbf{y}_0, \mathbf{p}, \mathbf{q}) \right)_{\mathbf{y}(0)=const.} = \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}), \\
& \frac{\partial \mathbf{g}}{\partial \mathbf{y}_0}(\mathbf{y}_0, \mathbf{p}, \mathbf{q}) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}) + \frac{\partial \mathbf{g}}{\partial \mathbf{p}}(\mathbf{y}_0, \mathbf{p}, \mathbf{q}) = \mathbf{0}, \\
& \dot{\mathbf{y}}(T, \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \frac{\partial T}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}) + \frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(T, \mathbf{y}_0, \mathbf{p}, \mathbf{q}) \frac{\partial \mathbf{y}_0}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}) = \frac{\partial \mathbf{y}_0}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}), \\
& \frac{\partial \mathbf{g}}{\partial \mathbf{y}_0}(\mathbf{y}_0, \mathbf{p}, \mathbf{q}) \frac{\partial \mathbf{y}_0}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}) + \frac{\partial \mathbf{g}}{\partial \mathbf{q}}(\mathbf{y}_0, \mathbf{p}, \mathbf{q}) = \mathbf{0}.
\end{aligned}$$

Both systems can then be solved for the unknowns $(\frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}), \frac{\partial T}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}))$ and $(\frac{\partial \mathbf{y}_0}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}), \frac{\partial T}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}))$, respectively.

4.2.2. Amplitude sensitivities. When the sensitivity equations are integrated from the initial conditions $\frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q})$ and $\frac{\partial \mathbf{y}_0}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q})$, amplitude sensitivities with respect to both \mathbf{p} and \mathbf{q} can be computed as described in section 2.6.

4.3. Relative phase sensitivities. Any type of phase β in reference to the time zero, which is implicitly defined by (4.2), can be analyzed if a valid, differentiable PLC is formulated. In general, a valid PLC is one that defines an isolated point which is guaranteed to exist for any parameter value in a neighborhood of the current value \mathbf{p} . Let this PLC be

$$(4.3) \quad h(\mathbf{y}(\beta(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})), \mathbf{p}, \mathbf{y}_0(\mathbf{p}, \mathbf{q})) = 0,$$

which can be differentiated with respect to the parameters to yield

$$\begin{aligned}
& \frac{\partial h}{\partial \mathbf{y}}(\mathbf{y}(\beta(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})), \mathbf{p}, \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \left(\dot{\mathbf{y}}(\beta, \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \frac{\partial \beta}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}) \right. \\
& + \left. \frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(\beta, \mathbf{p}, \mathbf{q}, \mathbf{y}_0) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}) \left(\frac{\partial \mathbf{y}}{\partial \mathbf{p}}(\beta, \mathbf{p}, \mathbf{q}, \mathbf{y}_0) \right)_{\mathbf{y}_0=const.} \right) \\
& + \frac{\partial h}{\partial \mathbf{p}}(\mathbf{y}(\beta(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})), \mathbf{p}, \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \\
& + \frac{\partial h}{\partial \mathbf{y}_0}(\mathbf{y}(\beta(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})), \mathbf{p}, \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q}) = \mathbf{0}.
\end{aligned}$$

All parts of this equation are known except the relative phase sensitivities $\frac{\partial \beta}{\partial \mathbf{p}}(\mathbf{p}, \mathbf{q})$, which can now be computed easily and exactly. Similarly, the differentiation of (4.3) can be performed with respect to the PLC parameters \mathbf{q} to yield

$$\begin{aligned}
& \frac{\partial h}{\partial \mathbf{y}}(\mathbf{y}(\beta(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})), \mathbf{p}, \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \left(\dot{\mathbf{y}}(\beta, \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \frac{\partial \beta}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}) \right. \\
& + \left. \frac{\partial \mathbf{y}}{\partial \mathbf{y}_0}(\beta, \mathbf{p}, \mathbf{q}, \mathbf{y}_0) \frac{\partial \mathbf{y}_0}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}) \right) + \frac{\partial h}{\partial \mathbf{q}}(\mathbf{y}(\beta(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})), \mathbf{p}, \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \\
& + \frac{\partial h}{\partial \mathbf{y}_0}(\mathbf{y}(\beta(\mathbf{p}, \mathbf{q}), \mathbf{p}; \mathbf{y}_0(\mathbf{p}, \mathbf{q})), \mathbf{p}, \mathbf{y}_0(\mathbf{p}, \mathbf{q})) \frac{\partial \mathbf{y}_0}{\partial \mathbf{q}}(\mathbf{p}, \mathbf{q}) = \mathbf{0}.
\end{aligned}$$

5. Numerical methods. The computationally most demanding part of performing the sensitivity analysis as described in this article is the solution of the BVP. Therefore, an efficient technique was developed to reduce the computational effort involved in this step.

5.1. Transformation of the BVP. In order to simplify the BVP shown in (2.1) and (2.2), the problem was transformed to yield

$$(5.1) \quad \hat{\mathbf{y}}(1, \mathbf{p}; \hat{\mathbf{y}}_0) - \hat{\mathbf{y}}_0 = \mathbf{0},$$

$$(5.2) \quad f_i(\hat{\mathbf{y}}(0, \mathbf{p}; \hat{\mathbf{y}}_0), \mathbf{p}) = 0,$$

where

$$\frac{d}{dt} \hat{\mathbf{y}}(\hat{t}, \mathbf{p}; \hat{\mathbf{y}}_0) = T \cdot \mathbf{f}(\hat{\mathbf{y}}(\hat{t}, \mathbf{p}; \hat{\mathbf{y}}_0), \mathbf{p}),$$

thus allowing for integration to time 1 for all iterations of the BVP solution. For simplicity, the transformed state variables $\hat{\mathbf{y}}$ are taken to be \mathbf{y} , and the transformed time \hat{t} will be called t for the remainder of this discussion.

5.2. Solution of the BVP. For the efficient solution of large-scale BVPs, an inexact Newton solver (NITSOL) [21] was used. The algorithm is an implementation of Newton's method where an approximate solution to the Newton equation is found using a linear, iterative solver. The Newton equation is relaxed to an inexact Newton condition, which allows for more global convergence properties and for efficient solution of large-scale problems. This algorithm requires only a vector of directional sensitivities in the direction of the current step as gradient information, rather than a sensitivity matrix. The directional sensitivities with respect to the variables of the BVP (\mathbf{y}_0, T) were integrated, along with the original ODE system using CVODES [12]. CVODES is a stiff ODE initial value problem solver with sensitivity analysis capabilities. As an option within CVODES, the staggered-corrector method for forward sensitivity analysis [8] was chosen for its numerical efficiency.

By avoiding the calculation of the full matrix of sensitivities, the total number of differential equations during integration is reduced by $n_y \times (n_y - 1)$ [20]. The directional sensitivities $\mathbf{r} \equiv \mathbf{P}\mathbf{d}$, where $\mathbf{d} \equiv (\mathbf{d}_{\mathbf{y}_0} \ d_T)$ is the current step of the Newton iterative solver, were integrated from time zero to time one, according to

$$\begin{aligned} \dot{\mathbf{y}} &= T\mathbf{f}(\mathbf{y}, \mathbf{p}), \\ \dot{\mathbf{r}} &= T \frac{\partial \mathbf{f}}{\partial \mathbf{y}} \mathbf{r} + \mathbf{f} d_T, \end{aligned}$$

where \mathbf{P} are the sensitivities of the state variables \mathbf{y} with respect to the variables of the BVP (\mathbf{y}_0, T) and d_T is the T -coordinate of the current step. The initial conditions for this system are $\mathbf{r}_0 = \mathbf{P}_0\mathbf{d}$, with

$$\mathbf{P}_0 = \begin{bmatrix} \mathbf{I}_{n_y} & \mathbf{0}_{1, n_y} \end{bmatrix}.$$

The Jacobian matrix of the BVP is the matrix obtained by partial differentiation of (5.1)–(5.2) with respect to (\mathbf{y}_0, T) . However, it is not necessary to compute the entire matrix, because only the Jacobian-vector product of the BVP is required by the inexact Newton solver, which can be calculated directly from the chain rule and

the directional sensitivities obtained after integration. The Jacobian-vector product is then

$$\mathbf{J}\mathbf{d} = \begin{bmatrix} \mathbf{r} - \mathbf{d}_{\mathbf{y}_0} \\ \frac{\partial f_t}{\partial \mathbf{y}} \mathbf{d}_{\mathbf{y}_0} \end{bmatrix},$$

where $\mathbf{d}_{\mathbf{y}_0}$ is the column vector containing the current step in the \mathbf{y}_0 -coordinates, which is computed by NITSOL at each iteration.

Integration was performed in CVODES [12] with absolute and relative tolerances of 10^{-10} and 10^{-8} , respectively. The BVP was solved to a relative tolerance of 10^{-6} and absolute tolerance of 10^{-8} . No preconditioning was used.

Table 6.6 shows the effective system size for integration in comparison to the full sensitivity system. The method affords especially large savings of CPU time when the system has a large number of state variables.

It should be mentioned that, for small systems or for such LCOs that have a known short transient time (i.e., that approach the periodic orbit rapidly from any initial condition), it can be effective to solve the BVP simply by integrating over a sufficiently large time span and using an event detection algorithm to assert sufficient convergence and to detect the period of oscillation. For the case of the NLCO, the solution of the BVP has only one independent variable T , making this method preferable. It was used for the very small example systems discussed in sections 6.1 and 6.3. However, it is usually not known if a limit-cycle system has short transient times, and as system size increases, this method becomes inefficient.

5.3. Solution of the sensitivity equations. Once the BVP was solved, \mathbf{M} and $\mathbf{S}(T, \mathbf{p}; \mathbf{0})$ were calculated from a sensitivity analysis over one period using the staggered-corrector sensitivity analysis functionality of CVODES [12] with full error control. The absolute and relative tolerances were set to 10^{-10} and 10^{-8} , respectively. The matrix operations to solve (2.17) were performed in MATLAB.

6. Applications and comparison to existing methods.

6.1. The Goodwin oscillator—an LCO. The Goodwin oscillator is a small system comprising 3 states and 6 parameters. It has been used in the biological literature to model a very basic circadian clock [23]. It is governed by the set of nonlinear ODEs in (6.1), which can be interpreted as a messenger ribonucleic acid (mRNA) concentration X , a clock protein concentration Y , and a transcription inhibition factor Z . Since the processes of transcription and translation are not chemical reactions, the system does not obey mass conservation; a fact that is closely related to the limit-cycle properties of the oscillator

$$(6.1) \quad \begin{aligned} \frac{dX}{dt} &= p_1 \frac{1}{1 + Z^9} - p_4 X, \\ \frac{dY}{dt} &= p_2 X - p_5 Y, \\ \frac{dZ}{dt} &= p_3 Y - p_6 Z. \end{aligned}$$

The parameters used throughout this example are $\mathbf{p} = (2.6574, 1.5749, 1.2985, 0.1357, 0.1362, 0.1360)$. The BVP formulation described in section 2.1 using the PLC $\dot{Z}(t = 0) = 0$ was solved yielding the results given in Table 6.1.

TABLE 6.1

Results of the sensitivity analysis for the Goodwin oscillator. The resulting initial conditions were $X(0) = 0.0315$, $Y(0) = 0.1946$, and $Z(0) = 1.8582$, with a period of $T = 27.9613$.

Parameter	p_1	p_2	p_3	p_4	p_5	p_6
$\frac{\partial T}{\partial \mathbf{p}}$	0.0063	0.0106	0.0129	-68.6251	-68.7215	-68.6746
$\frac{\partial X_0}{\partial \mathbf{p}}$	0.0012	-0.0179	-0.0218	0.0489	0.1708	0.1718
$\frac{\partial Y_0}{\partial \mathbf{p}}$	0.0073	0.0123	-0.1349	-0.1438	-0.1412	1.2885
$\frac{\partial Z_0}{\partial \mathbf{p}}$	0.0696	0.1175	0.1425	-1.3735	-1.3488	-1.3608

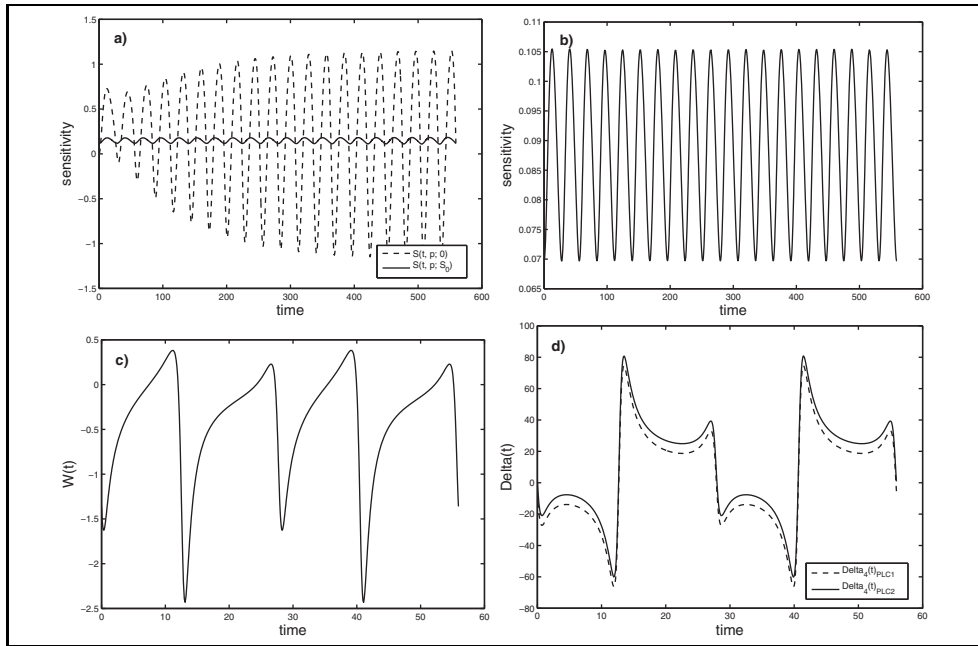


FIG. 6.1. Sensitivity trajectories for the Goodwin oscillator, all with respect to parameter p_4 : (a) full sensitivity of Z , as a function of initialization; $\mathbf{S}(t, \mathbf{p}; \mathbf{S}_0)$ (solid) vs. $\mathbf{S}(t, \mathbf{p}; \mathbf{0})$ (dashed) (both are unbounded, as verified over a longer integration period); (b) period independent, periodic part $\mathbf{Z}(t, \mathbf{p}; \mathbf{S}_0)$; (c) period and phase independent part $\mathbf{W}(t, \mathbf{p})$; (d) relative phase sensitivity with respect to p_4 , $\delta_{p_4}(t, \mathbf{p})$, for two different PLCs (PLC_1 : $\dot{Z}(0) = 0$, PLC_2 : $Y(0) = 0.19457$).

Sensitivity trajectories. The trajectories for some of the state sensitivities as well as for $\mathbf{Z}(t)$, $\mathbf{W}(t)$, and $\delta(t)$ are shown in Figure 6.1. As discussed earlier in this manuscript, it is difficult to compare sensitivity trajectories obtained by different methods. First, if the initial conditions \mathbf{S}_0 in (2.12) are set to zero, a nondecaying error is introduced. Second, since the computation of exact sensitivity trajectories relies on the use of a PLC and since multiple PLCs are possible for any given point on the cycle, one cannot compare a solution obtained using a given PLC to any other solution using zero initial conditions due to the lack of a common reference point. If one attempted to calculate the bounded (purely periodic) part of the solution only, as has been done previously [15, 17], both of these sources of discrepancy remain. While one reference [27] mentions the need to define a time reference in order to obtain a unique sensitivity function, the influence of the initial condition—in particular as a function of the PLC—was neglected, and the influence of the PLC was assumed to be time invariant.

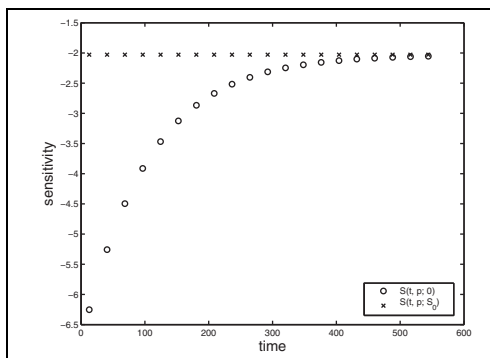


FIG. 6.2. Results for the sensitivity of the extrema of Z with respect to parameter p_4 computed as described here (x) and as described in reference [15] (o).

The results presented here emphasize the importance of a time reference for the calculation of sensitivity information and introduce the notion of a PLC used for that purpose, thus allowing us to isolate the shape and location sensitivities contained in \mathbf{W} that are independent of the PLC.

Amplitude sensitivities. Previous sensitivity methods often relied on extracting partial sensitivity information for oscillating systems. What facilitated the computation of sensitivities at the extrema of a state variable y_i (as needed for the computation of the amplitude sensitivities) is the fact that at those times, all contributions but those of $\mathbf{w}_i(t_{\text{extremum}})$ drop because $\dot{y}_i(t_{\text{extremum}})$ is zero. Therefore, these quantities could previously be estimated by waiting for the transient of the first term of (2.12) to decay, even in the absence of correct initial conditions for the sensitivities \mathbf{S} [22, 15]. A graphical comparison to the method proposed in this work is shown in Figure 6.2. The iterative method can take many periods of oscillation to converge to a close approximation of the exact value, which is obtained immediately using the boundary value method.

6.2. Relative phase sensitivities in the *Drosophila* circadian clock. A method for the calculation of peak-to-peak sensitivities was suggested by Gunawan and Doyle [10] based largely on previous work by Kramer, Rabitz, and Calo [15]. A very simple model of the *Drosophila* circadian clock [28] was analyzed. The method described in section 2.7.2 of this work was applied to the same model using the same parameter values to allow for direct comparison. Numerical results are presented in Table 6.2. The peak-to-peak sensitivities as computed in this work agree very well with the finite difference approximation, with the maximum deviation being 0.06%. In comparison, previous results appear to compute the “period stretch” sensitivity of the peak-to-peak distance as result of the period sensitivity $\frac{\beta}{T} \frac{\partial T}{\partial \mathbf{p}}$, judged by the close match of the respective numerical results (maximum deviation 1.7%).

6.3. Application to the Lotka–Volterra model—a small NLCO. An example of a nonlimit-cycle oscillator is the Lotka–Volterra oscillator [18], which can be associated with a chemical reaction scheme such as

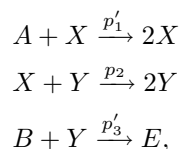


TABLE 6.2

Results of the peak-to-peak sensitivity analysis for the *Drosophila* circadian oscillator [28]. The initial conditions of the state variables M and P at the maximum of M were $M(0) = 2.6444$ and $P(0) = 0.36244$, with a period of $T = 24.204$. $\frac{\partial \beta}{\partial \mathbf{p}}$ = peak-to-peak sensitivities, FD = finite difference approximation of $\frac{\partial \beta}{\partial \mathbf{p}}$ (with a finite difference of $\epsilon = 0.01$), $\frac{\beta}{T} \frac{\partial T}{\partial \mathbf{p}}$ = overall phase shift induced by period sensitivity, $\frac{\partial \Phi}{\partial \mathbf{p}}$ = peak-to-peak phase sensitivities from [10], and FD = finite difference approximation of $\frac{\partial \Phi}{\partial \mathbf{p}}$ from [10].

Parameter	$\frac{\partial \beta}{\partial \mathbf{p}}$	FD	$\frac{\beta}{T} \frac{\partial T}{\partial \mathbf{p}}$	$\frac{\partial \Phi}{\partial \mathbf{p}}$ [10]	FD [10]
ν_m	0.4938	0.4938	0.8653	0.8543	0.4923
k_m	-56.525	-56.490	-64.308	-63.457	-56.512
ν_p	0.9876	0.9876	1.7306	1.7014	0.9846
k_{p1}	0.0221	0.0221	-0.0138	-0.0135	0.0223
k_{p2}	-7.591	-7.5908	-10.878	-10.724	-7.6604
k_{p3}	-36.011	-35.991	-31.080	-30.635	-35.982
K_{eq}	-0.0001	-0.0001	0.0010	0.0010	-0.0001
P_{crit}	3.6138	3.6119	16.455	16.241	3.6333
J_p	-17.481	-17.473	-37.042	-36.517	-17.517

TABLE 6.3

Results of the period sensitivity analysis with respect to the parameters of the Lotka–Volterra oscillator described in section 6.3. The parameterization of the system was $p_1 = p_2 = p_3 = 1.0$ with initial conditions $Y_0 = X_0 = 0.5$, resulting in a period of $T = 6.6939$. FD stands for finite difference approximation using $\epsilon = 0.001$.

Parameter	p_1	p_2	p_3	X_0	Y_0
$\frac{\partial T}{\partial \mathbf{p}}$	-2.8077	-1.0786	-2.8077	-1.0786	-1.0786
$\frac{\partial T}{\partial \mathbf{p}}$ [18]	-2.793	-1.120	-2.780	-1.1	-1.1
FD	-2.8092	-1.0804	-2.8092	-1.0766	-1.0766

where the concentrations A and B are constant and can be lumped with the rate parameters so that $p_1 = Ap'_1$ and $p_3 = Bp'_3$. Then the system can be written as

$$(6.2) \quad \begin{aligned} \frac{dX}{dt} &= p_1 X - p_2 XY, \\ \frac{dY}{dt} &= p_2 XY - p_3 Y. \end{aligned}$$

As the oscillator is based on a set of chemical reactions, it obeys mass conservation, and it is clear that the initial conditions of X and Y will have an influence on the amplitude of the oscillation. Sensitivity analysis with respect to initial values and parameters was performed for the parameterization given in reference [18]. Table 6.3 summarizes the results of the sensitivity analysis and compares them to a finite difference approximation. The methods presented in this work result in better agreement.

Some of the sensitivity trajectories for the Lotka–Volterra oscillators are shown in Figure 6.3.

6.3.1. Relative phase and peak-to-peak sensitivities. Two different kinds of relative phase sensitivities were computed, and both results compared favorably to a finite difference approximation, as shown in Table 6.4.

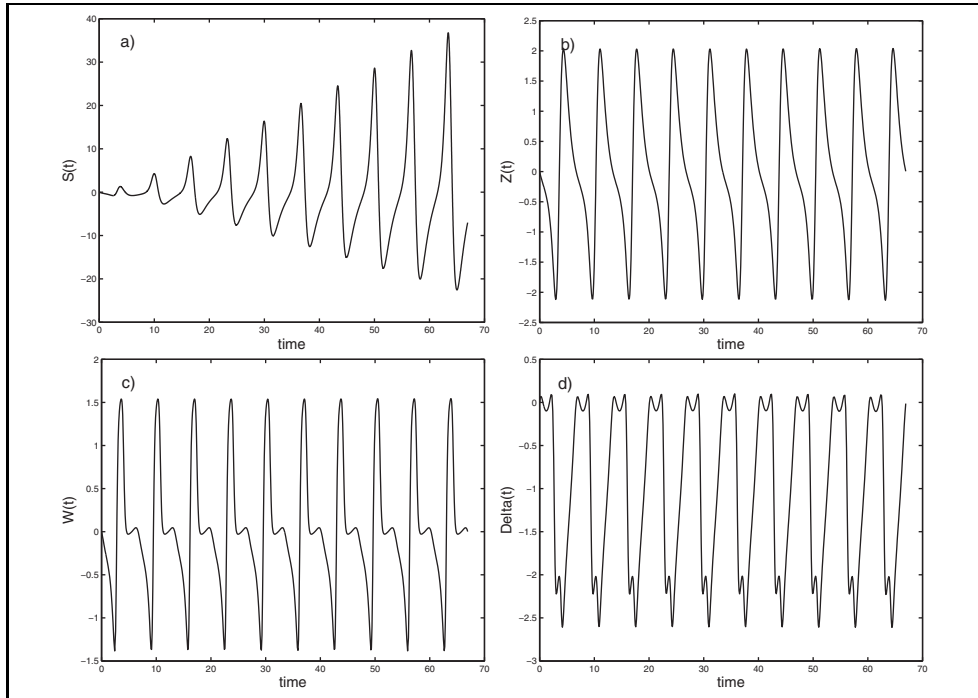


FIG. 6.3. Sensitivity trajectories for the Lotka-Volterra oscillator of state variable Y with respect to parameter p_3 over 10 periods of integration: (a) unbounded, full sensitivity, $\mathbf{S}(t, \mathbf{p}; \mathbf{0})$; (b) period independent, periodic part $\mathbf{Z}(t, \mathbf{p}; \mathbf{0})$; (c) period and phase independent part $\mathbf{W}(t, \mathbf{p})$; (d) relative phase sensitivity $\delta(t, \mathbf{p})$ where the initial conditions chosen provide the PLC.

TABLE 6.4

Results of the relative phase sensitivity analysis with respect to the parameters of the Lotka-Volterra oscillator described in section 3.2.2. β_1 describes the peak-to-peak time distance between the time zero and the maximum of X , and β_2 is the time to $X(\beta_2) = 0.7$. FD indicates the result of a finite difference approximation using $\epsilon = 0.001$.

Parameter	p_1	p_2	p_3
$\frac{\partial \beta_1}{\partial \mathbf{p}}$	-3.9746	-0.4547	-1.0997
$\frac{\partial \beta_2}{\partial \mathbf{p}}$	-0.9711	0.4948	-0.1234
FD (β_1)	-3.9706	-0.4540	-1.0993
FD (β_2)	-0.9696	0.4951	-0.1234

6.4. Application to a small intermediate-type oscillator. An example on an intermediate-type oscillator is the following linear system

$$\dot{\mathbf{y}} = \begin{bmatrix} 0 & p_1 & 0 \\ p_2 & 0 & 0 \\ p_2 & 0 & p_3 \end{bmatrix} \mathbf{y},$$

where $\mathbf{p} = (1, -1, -3)$. This system is a harmonic, two-dimensional oscillator coupled with a third variable which exponentially decays onto the the periodic orbit. Consequently, the monodromy matrix \mathbf{M} has two eigenvalues equal to one, and (3.2) has rank one, indicating the need for two PLCs. A natural choice is to select $y_{1,0}(\mathbf{p}, \mathbf{q}) = q_1$

TABLE 6.5

Results of the relative phase sensitivity analysis with respect to the parameters \mathbf{p} and \mathbf{q} of the intermediate-type oscillator as described in section 4.3. FD indicates the result of a finite difference approximation using $\epsilon = 0.001$. The relative phase was $\beta = 0.5247$.

Parameter	p_1	p_2	p_3	q_1	q_2
$\frac{\partial \beta}{\partial \phi_i}$	0.0271	0.5525	0	-0.2898	0.5
FD	0.0274	0.5527	0.0005	-0.2885	0.4996

and $y_{2,0}(\mathbf{p}, \mathbf{q}) = q_2$, where $\mathbf{q} = (2, 0)$. Differentiation with respect to \mathbf{p} and \mathbf{q} , respectively, then yields

$$\begin{bmatrix} (\mathbf{M} & - & \mathbf{I}) & \dot{\mathbf{y}}(T) \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{\partial \mathbf{y}_0}{\partial \mathbf{p}} \\ \frac{\partial T}{\partial \mathbf{p}} \end{bmatrix} = \begin{bmatrix} -\mathbf{S}(T, \mathbf{p}; \mathbf{0}) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

and

$$\begin{bmatrix} (\mathbf{M} & - & \mathbf{I}) & \dot{\mathbf{y}}(T) \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{\partial \mathbf{y}_0}{\partial \mathbf{q}} \\ \frac{\partial T}{\partial \mathbf{q}} \end{bmatrix} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ 1 & 0 \\ 0 & 1 \end{bmatrix}.$$

The resulting sensitivities are $\frac{\partial T}{\partial \mathbf{p}} = \begin{bmatrix} -3.1416 & 3.1416 & 0 \end{bmatrix}$, $\frac{\partial T}{\partial \mathbf{q}} = \begin{bmatrix} 0 & 0 \end{bmatrix}$,

$$\frac{\partial \mathbf{y}_0}{\partial \mathbf{p}} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0.06 & 0.54 & -0.16 \end{bmatrix},$$

and

$$\frac{\partial \mathbf{y}_0}{\partial \mathbf{q}} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ -0.3 & 0.1 \end{bmatrix}.$$

All results are in excellent agreement with the respective finite difference approximations (not shown) and are intuitive if one considers that the first two state variables form in fact a harmonic oscillator that behaves in pure NLCO fashion.

6.4.1. Relative phase sensitivities. The relative phase sensitivity of the phase β defined by the PLC $y_2(\beta) = -1$ was computed with respect to both the parameters \mathbf{p} and \mathbf{q} . The results are shown in Table 6.5 in comparison to a finite difference approximation. Good agreement is found between both numerical results.

6.5. Application to a large LCO. The currently most detailed model of the mammalian circadian clock mechanism was published recently [9] and consists of 73 state variables and 231 parameters (after separating some of the repeatedly used 38 original model parameters). It describes five feedback loops, four of which are negative, and the remaining one is a positive feedback loop. Using mass action kinetics, the interactions between protein, mRNA, and deoxyribonucleic acid (DNA) species is modeled. In addition, transport processes are also included to distinguish species

TABLE 6.6

CPU times for the integration of the 73 state mammalian circadian clock oscillator, with or without different sensitivity systems, on a Pentium IV processor (2.2GHz, 1.0 GB of RAM). Full sensitivity system refers to the computation of the full sensitivity matrix with full error control for the entire integration. Direction sensitivity system refers to the computation of only a sensitivity matrix-vector product. "Analytical Jacobian" indicates that an analytical expression for the Jacobian matrix was provided, "Jacobian-vector-product by automatic differentiation" indicates that a subroutine was created using DAEPACK [26], which allows the efficient evaluation of the Jacobian-vector-product directly. The integration of the system without sensitivity evaluation was included as a control for the comparison.

Sensitivity method	Sensitivities evaluated?	CPU time [sec.]	Factor rel. to ODE system	Number of ODEs
Full sensitivity system, analytical Jacobian	No	0.201	1	73
	Yes	6.820	34	73 + (74 * 73)
Directional sensitivities, analytical Jacobian	Yes	0.589	2.9	2*73
Directional sensitivities, Jacobian-vector product, automatic differentiation	No	0.194	0.97	73
	Yes	0.439	2.2	2*73

with different intracellular localization. A detailed discussion of the results of the period sensitivity analysis of this model is given in a forthcoming publication [31]. In short, the period sensitivity analysis revealed that most high sensitivity parameters are located in the Per2 loop, and, conversely, that most parameters in the Per2 loop have high period sensitivity. Therefore, the Per2 loop can be identified as the negative feedback loop which sets the period of oscillation. Sensitivity analysis allowed the discovery of a link between network structure and functionality encoded within it.

The computationally most expensive part of the method was the solution of the BVP, whose CPU time depended mainly on the quality of the initial guess, i.e., on the number of iterations needed in NITSOL. A reasonable initial guess was generated by integrating the state variables only for a short period of time (1-2 estimated periods) to the point specified in the PLC. A typical run resulted then in approximately 10 iterations. Consequently, the use of directional sensitivities in the iterative Newton algorithm became a significant time saver. The CPU time necessary for integration of one period for the system on a Pentium IV processor (2.2GHz, 1.0 GB of RAM) is shown in Table 6.6. It should be mentioned that, for the previous sensitivity analysis methods, the full sensitivity system must be integrated over at least tens of periods in order to obtain appropriate estimates for period and amplitude sensitivities, thereby making the solution of the BVP more than worthwhile in comparison.

The computation of the monodromy matrix and $\mathbf{S}(T, \mathbf{p}; \mathbf{0})$ required 5.71 and 19.7 seconds, respectively, and the matrix manipulations took approximately 0.15 seconds.

7. Conclusion. This work provides a unified treatment of the sensitivity analysis of oscillating systems and their implicit derived properties such as period, phase, and amplitude. A BVP is solved once, yielding the period sensitivities and the initial conditions for the sensitivity trajectories. The full sensitivity trajectories can then be computed and decomposed into three parts, containing the influence of the period sensitivity, phase sensitivity, and amplitude sensitivity. All parts can be computed without approximations beyond the numerical error implicit in solving the BVP and in numerically efficient ways. The focus of this work is to provide a well-defined time

reference by introducing the concept of PLCs, to identify the influence of the PLC on the sensitivity solution, and also to isolate the shape and location sensitivities that are independent of the PLC. This provides a useful and intuitive framework for the computation of relevant quantities such as peak-to-peak sensitivities.

The methods are computationally competitive, because the computational cost of solving the BVP is outweighed by the advantages of a comprehensive method for sensitivity analysis of oscillators. Each of the quantities previously computed using iterative methods required an a priori unknown amount of integration time to achieve close approximation of the exact solution. Conversely, once the BVP is solved, any subsequent calculation requires only a minimum of computational effort, usually associated with integration times of under one period, which is a large improvement over previously suggested methods for those cases where appropriate methods existed.

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