Ensemble Controllability of Cellular Oscillators

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***Abstract*—Many diseases including cancer, Parkinson's disease and heart diseases are caused by loss or malfunction of regulatory mechanism of an oscillatory system. Successful treatment of these diseases might involve recovering the healthy behavior of the oscillators in the system, i.e., achieving synchrony or a desired distribution of the oscillators on their periodic orbit. In this paper, we consider the problem of controlling the distribution of a population of cellular oscillators described in terms of phase models. Different practical limitations on the observability and controllability of cellular states naturally lead to an ensemble control formulation in which a population-level feedback law for achieving a desired distribution is sought. A systems theoretic approach to this problem leads to Lyapunov- and LaSalle-like arguments, from which we develop our main contribution, novel necessary and sufficient conditions for the controllability of phase distributions in terms of the Fourier coefficients of the phase response curve. Since our treatment is based on a rather universal formulation of phase models, the results and methods proposed in this paper are readily applicable to the control of a wide range of other types of oscillating populations, such as circadian clocks, and spiking neurons.**

***Index Terms*—Systems biology, Emerging control applications, Distributed parameter systems, Cellular dynamics, Biological systems**

I. Introduction

PERIODIC fluctuations in biological processes are found at all levels of life and are often the result of changes in gene expression. These rhythms play key roles in a variety of important processes, including the cell cycle, circadian regulation, metabolism, embryo development, neuron firing and cardiac rhythms [1], [2]. Biological oscillators function as finely tuned dynamic systems in which time-delayed negative feedback gives rise to sustained rhythms. The rhythms are robust to noise while remaining acutely sensitive to various environmental and intracellular cues. Malfunction in these highly controlled oscillators is linked to various diseases, including Parkinson's and Alzheimer's disease, sleep disorder, cardiovascular diseases and cancer [3]–[5]. Cause and cure of these diseases are two sides of the same coin, and thus understanding oscillatory mechanisms and approaches to control it are subjects of ongoing research.

Mathematically, these oscillatory systems can be described as dynamical system with dynamics of the general form

$$\dot{x} = f(x, u) \ , \tag{1}$$

exhibiting a stable limit cycle [6], [7]. Therein, the states x represent different molecular species in the cell which can be affected by external inputs u such as media, drugs, optogenetic approaches or environmental factors. Besides the agent-based description, with each agent being a cellular oscillator with dynamics (1), oscillating cell populations are modeled in terms of the distribution of cells in state space [8]. The resulting dynamics are governed by partial differential equations, belonging to the class of *Liouville equations* [9] of the general form

$$\partial_t \varrho(t, x) = -\langle \partial_x, f(x, u)\varrho(t, x)\rangle \ . \tag{2}$$

Nonlinear oscillating systems are often studied by transforming the complex dynamic equations that describe their behavior into a phase coordinate representation [10], [11]. This approach yields simplified yet accurate reduced phase models that capture essential properties of an oscillating system with a stable periodic orbit and is especially compelling from a control-theoretic perspective [12], [13]. Control design can be achieved for systems where the phase, but not the state, can be observed, and where the input response can be approximated experimentally when the dynamics are unknown [14]–[16].

Control of cellular oscillators is significant in biology, with a particular relevance in neuroscience [17], [18]. Applications in clinical medicine include protocols for coping with jet lag [5], [19]–[21], clinical treatments for neurological disorders including epilepsy [22] and Parkinson's disease [23]–[26]. Furthermore, control of cellular oscillators takes place in cardiac pacemakers and during cancer treatment [27]. A common goal is to recover the healthy behavior of the oscillators, e.g., by achieving synchrony or a desired distribution of the oscillators on their periodic orbit. The above mentioned applications are based on various theoretical results. For instance, optimal control approaches are widely studied with different focus based on the field of application [25], [28]. Furthermore, controllability of oscillators is studied within the framework of Lie algebra [29], [30] where Lie brackets of drift and control vector fields are used to, e.g., compute reachable sets for a population of non-identical oscillators [28]. Recently, [26] proposed a common control law for synchronizing and desynchronizing neural populations which is equivalent to the formulation from which we develop our controllability conditions.

In this paper we address the problem of finding a control input u such that a population of identical oscillators converges to a desired distribution on their limit cycle. Several constraints imposed by the nature of cell biology complicate the task: First, experimental observation of the phase of individual agents over time is barely possible. A more realistic experimental observation is composed of representative samples drawn from the population from which the distribution of oscillators on their limit cycle must be reconstructed [16], [31].

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Secondly, only broadcast input signals can be realized, giving rise to an ensemble control problem [21], [32]. We address this task by relating the control problem to the Fourier series of the phase response curve, thereby providing necessary conditions for control of the population to a desired distribution.

Our approach to solve the above stated control problem is organized as follows. Section II first introduces the theoretic foundation of our control approach, comprising the concept of reduced phase models for weakly coupled oscillators and the representation of circular distributions by Fourier series. The control methodology including conditions for controllability of the population is developed in Section III. Furthermore, the special case of synchronization is discussed. Section IV examines the control methodology in different scenarios, illustrating the derived controllability conditions in simulation examples. Section V contains concluding comments.

II. Background and Problem Formulation

As motivated in the introduction, we seek to find a broadcast input signal which steers the population of oscillators to a desired distribution on their limit cycle. We will develop the control methodology on the concept of reduced phase models, reviewed below. At the end of this section we state the density control problem (see also [26]) and relate it to a control problem for the moments of the population, cf. [33], [34].

A. Reduced phase models

In the following we review the basic concept of reduced phase models and phase response curves briefly and refer the interested reader to the book [2] and references therein. The notion of reduced phase models greatly simplifies the system to be controlled. The main statement of the concept of reduced phase models is the following: Consider a family of dynamical systems of the form

$$\dot{\xi}(t) = \hat{f}(\xi(t)) \,, \quad \xi(t) \in \mathbb{R}^n \,, \tag{3}$$

with an exponentially stable limit cycle $\gamma \subset \mathbb{R}^n$ with period T_d. Then

$$\dot{\theta}(t) = \omega \,, \quad \theta(t) \in S^1 \,, \tag{4}$$

is a local canonical model for such oscillators, where $\theta(t)$ is called the phase of the oscillator with frequency $\omega = \frac{2\pi}{T_d}$. This statement is based on the notion of *isochrons* introduced by Winfree [35] and its basic idea, illustrated in Fig. 1, is to find a neighborhood W of γ and a function $\psi \colon W \to S^1$, such that $\theta(t) = \psi(\xi(t))$ is a solution of (4). Winfree called the set of all initial conditions $z(0) \in \mathbb{R}^n$ of which the solution $z(t)$ approaches the solution $\xi(t)$, with $\xi(0) \in \gamma$, an *isochron* of $\xi(0)$ defined as

$$M_{\xi(0)} = \{ z(0) \in W \colon \|\xi(t) - z(t)\| \to 0 \text{ as } t \to \infty \} \,. \tag{5}$$

Furthermore, Guckenheimer [36] showed that there always exists a neighborhood W of a limit cycle that is invariantly foliated by the isochrons M_ξ, $\xi \in \gamma$, in the sense that the flow maps isochrons to isochrons. Consider the function $\psi_2 \colon W \to \gamma$, sending a point in the neighborhood $z \in M_\xi \subset W$ to the generator of its isochron $\xi \in \gamma$. Additionally, the periodic orbit of an oscillator is homeomorphic to the unit circle. One can therefore define the function $\psi_1 \colon \gamma \to S^1$ which maps the solution $\xi(t)$ with $\xi(0) \in \gamma$ to the solution of (4). The function $\psi \colon W \to S^1$ is a composition of ψ_1 and ψ_2, $\psi = \psi_1 \circ \psi_2$, mapping $\xi(t) \in W$ uniquely to its corresponding phase $\theta(t)$ of the reduced phase model (Fig. 1).

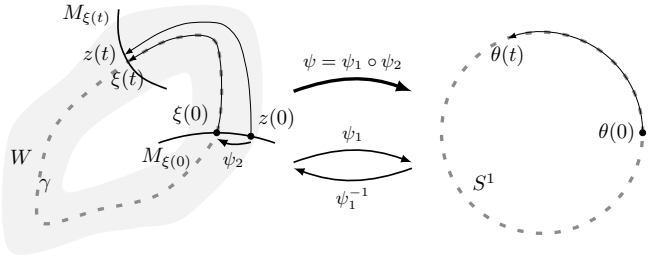

Figure 1. A neighborhood W of the limit cycle γ of an oscillator is invariantly foliated by isochrons M_ξ. The flow maps isochrons to isochrons. The function $\psi = \psi_1 \circ \psi_2$ maps an oscillator $\xi(t) \in W$ uniquely to its phase on the unit circle $\theta(t) = \psi(\xi(t))$.

Applying the theory of reduced phase models to a weakly forced oscillator

$$\dot{\xi}(t) = f(\xi(t), u(t)) \,, \quad \xi(0) = \xi_0 \in W \,, \quad u(t) \in \mathbb{R} \tag{6}$$

where the term $u(t) = \varepsilon v(t)$ denotes an exogeneous input, one obtains the reduced phase model of the form

$$\dot{\theta}(t) = \omega + Z(\theta(t))\, u(t) \,. \tag{7}$$

Here, weakly forced refers to the situation where ε is sufficiently small such that $\xi(t)$ stays inside the neighborhood W for all $t > 0$. The function Z is called the *phase response curve* (PRC) and describes the magnitude of phase changes after perturbing an oscillatory system. Based on *Malkin's Theorem* [37], [38] the PRC is the solution of the adjoint problem $\mathrm{d}\, Z(t)/\mathrm{d}\, t \;=\; -\left(\mathrm{D} f(\xi(t))\right)^\top Z(t)$, with the normalization condition $Z(t) f(\xi(t)) = 1$ for any t, where $\mathrm{D}f$ is the Jacobian matrix which is evaluated along the periodic orbit, $\xi(t) \in \gamma$.

B. Problem statement

Given a family of weakly coupled identical oscillators in its reduced phase representation (7), the corresponding Liouville equation for the time evolution of the density, $p : \mathbb{R}_+ \times S^1 \to \mathbb{R}_+$, of oscillators on the unit circle reads

$$\partial_t p(t,\theta) + \partial_\theta \left(\kappa(\theta, u) p(t,\theta)\right) = 0 \tag{8}$$

with the boundary condition $p(t,0) = p(t,2\pi)$ and the initial condition $p(0,\theta) = p_0(\theta)$. Here, the (controlled) vector field is obtained from the reduced phase model, i.e., $\kappa(\theta, u) = \omega + Z(\theta)u$. The target distribution, $q : \mathbb{R}_+ \times S^1 \to \mathbb{R}_+$, is supposed to be 2π-periodic with angular velocity ω and can thus be described by the PDE

$$\partial_t q(t,\theta) + \omega\, \partial_\theta q(t,\theta) = 0 \tag{9}$$

with the boundary condition $q(t,0) = q(t,2\pi)$ and the initial condition $q(0,\theta) = q_0(\theta)$. This PDE has the explicit solution $q(t,\theta) = q_0\left((\theta - \omega t) \mod 2\pi\right)$ which can be thought of as rotating initial density. We assume that p_0 and q_0 are (strictly)

positive on $[0, 2\pi]$, which results in the positivity of p_t and q_t for all $t \geq 0$. These definitions lead to the control problem as described similarly in [26]:

Problem 1: Given the system defined by (8) and (9), find a control input u depending on population-level data, such that the density $p(t, \theta)$ converges towards a desired periodic distribution $q(t, \theta)$.

As will become apparent in our subsequent analysis, Fourier coefficients of the densities and of the phase response curve will play a crucial role in both the formulation and the solution of the problem. This is not too surprising since all the functions involved in our problem setup can be viewed as 2π-periodic functions. We define the Fourier coefficients of a distribution $p(t, \cdot) \sim m_k := \int_0^{2\pi} p(t, \theta)\, \mathrm{e}^{-\mathrm{i}\, k\theta}\, \mathrm{d}\,\theta$, similarly for the desired distribution we have $q(t, \cdot) \sim \alpha_k$ and for the phase response curve we have $Z(\cdot) \sim c_k$. For better readability we will define a shorthand notation for frequently used expressions. Let $p(t, \theta)$ be a distribution function on the unit circle at time t. We will use $p_t(\theta) = p(t, \theta)$ especially when referring to the function in a L_2 inner product $\langle \cdot, \cdot \rangle$, i.e., we denote the L_2-norm of $p(t, \theta)$ by

$$\langle p_t, p_t \rangle = \int_0^{2\pi} p(t, \theta) p(t, \theta)\, \mathrm{d}\,\theta\,.$$

III. Ensemble Control for Oscillator Moments

The starting point will be the introduction of a natural cost functional V by which the control problem can be formulated as the minimization of V. In investigating the dynamics of V, we eventually arrive at the very favorable dynamic structure $\frac{\mathrm{d}}{\mathrm{d}\,t} V(t) = \phi(t) u(t)$, where ϕ incorporates population-level data. Thus, we are immediately led to the simple (population-level) feedback law $u(t) = -\phi(t)$, resulting in $\frac{\mathrm{d}}{\mathrm{d}\,t} V(t) = -\phi(t)^2 \leq 0$. A LaSalle-like argument then establishes the convergence $V(t) \to 0$ rigorously.

A. Controller design for arbitrary distributions

Given the model (8) and (9), we introduce a cost functional that measures the distance between the actual density $p(t, \theta)$ and the reference density $q(t, \theta)$. It is natural to choose this cost functional as the L_2-norm of the difference between both distributions

$$V(t) = \frac{1}{2} \langle \Delta_t, \Delta_t \rangle \tag{10}$$

where $\Delta_t = p_t - q_t$. The time derivative of the storage function (10) under the dynamics given by (8) and (9) can be obtained from a straightforward but somewhat involved computation as

$$\frac{\mathrm{d}}{\mathrm{d}\,t} V(t) = \left(\int_0^{2\pi} (\partial_\theta \Delta_t) Z p_t\, \mathrm{d}\,\theta \right) u(t)\,. \tag{11}$$

This result was independently obtained in [26] where also a detailed derivation can be found. Given this result, it is immediate to apply the *population-level feedback law*

$$u(t) = -\left(\int_0^{2\pi} (\partial_\theta \Delta_t) Z p_t\, \mathrm{d}\,\theta \right), \tag{12}$$

which clearly results in $\frac{\mathrm{d}}{\mathrm{d}\,t} V(t) \leq 0$. To guarantee that $V(t) \to 0$, as $t \to \infty$, we need to study the set of solutions under which $\frac{\mathrm{d}}{\mathrm{d}\,t} V(t) \equiv 0$ similarly to the idea of LaSalle's invariance principle for the classical finite-dimensional case. Our main result on the convergence properties reads as follows.

Theorem 1: Consider (8) and (9) in closed loop with the control (12). Suppose all Fourier coefficients of Z are non-zero, then, for all choices of p_0 and q_0, $p_t \to q_t$ as $t \to \infty$.

Proof: It is clear that, with the given feedback law, we have $\dot{V} \leq 0$. To conclude the result, we need to additionally show that under the stated assumptions for the PRC Z, we can rule out the existence of solutions p_t and q_t for which $\Delta_t \neq 0$ but $\dot{V} \equiv 0 \Leftrightarrow u \equiv 0$. This would correspond to the system p_t evolving without external input, i.e., $\partial_t p_t = -\partial_\theta(\omega p_t)$, the solution of which is of the form $p_t(\theta) = p_0(\theta - \omega t)$. Similarly, we have $\Delta_t(\theta) = \Delta_0(\theta - \omega t)$, and thus $(\partial_\theta \Delta_t)(\theta) = (\partial_\theta \Delta_0)(\theta - \omega t)$. Under this assumption, we have

$$\int_0^{2\pi} (\partial_\theta \Delta_t) Z p_t\, \mathrm{d}\,\theta = \int_0^{2\pi} Z \Psi_t\, \mathrm{d}\,\theta = \langle Z, \Psi_t \rangle$$

with $\Psi_t : \theta \mapsto (\partial_\theta \Delta_0)(\theta - \omega t) p_0(\theta - \omega t)$. Suppose for the sake of contradiction that $\Delta_0 \neq 0$. As Δ_0 is a difference of two probability densities, it furthermore cannot be a constant function, so that we can conclude $\partial_\theta \Delta_0 \neq 0$. As the product of two non-zero functions, of which one is positive, we can conclude that Ψ_0 is non-zero and thus has a non-vanishing sequence of Fourier coefficients (ψ_k). Now, by Parseval's theorem, we have

$$u(t) = -\int_0^{2\pi} Z \Psi_t\, \mathrm{d}\,\theta = -\langle Z, \Psi_t \rangle = -\sum_{k=-\infty}^{\infty} c_k \psi_k\, \mathrm{e}^{-\mathrm{i}\, k\omega t},$$

where $\psi_k\, \mathrm{e}^{-\mathrm{i}\, k\omega t}$ is the kth Fourier coefficient of Ψ_t. We can view the sequence $(c_{-k}\psi_{-k})$ as the Fourier coefficients of the function $u_\omega : t \mapsto u(t/\omega)$. Since this sequence is non-zero by the assumption that $c_k \neq 0$, $\forall k \in \mathbb{Z}$ and the non-vanishing of the sequence (ψ_k), we can conclude that u_ω and thus u is not identically zero, yielding the contradiction. ∎

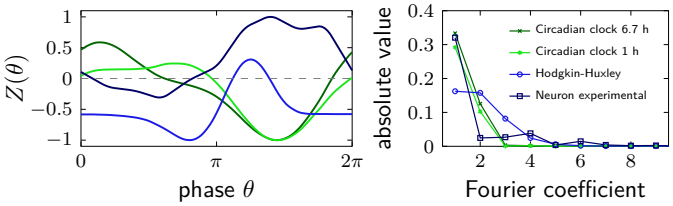

Figure 2. Left: PRCs of the circadian clock in response to a $6.7h$ and $1h$ light impulse (green). Curve obtained experimentally and reported in [39]. PRCs of neurons from Hodgkin-Huxley model [40] and from experiments [41] (blue). Right: Absolute values of the Fourier coefficients of the PRCs.

Theorem 1 relies on a PRC with non-vanishing Fourier coefficients. This condition is rarely met in a biological context where the shape of the PRC is determined by rather smooth dynamics in the biological system. Examples of PRCs from circadian clock and neuron activity are shown in Fig. 2. The absolute value of the Fourier coefficients decreases rapidly with the 5th coefficient being practically zero in all cases. Based on Theorem 1 the feedback (12) would not result in convergence of p_t to q_t in these examples. Thus, we considered variants of the cost functional (10) in which we

are not interested in the L_2-norm of the difference Δ_t but rather some projection $P(\Delta_t)$, where $P : L_2 \to L_2$ is an orthogonal projection onto a finite-dimensional subspace of L_2. A particularly important special case is given by setting $P = P_N : p_t \mapsto \frac{1}{2\pi}\sum_{k=-N}^{N} \mathrm{e}^{\mathrm{i}\,k(\cdot)}\langle \mathrm{e}^{-\mathrm{i}\,k(\cdot)}, p_t\rangle$, which would yield a case where we are only interested in the tracking for the first N Fourier coefficients of p_t and q_t as $t \to \infty$. Thus, in the following we will consider the more general cost functional

$$V(t) = \frac{1}{2}\langle P\Delta_t, P\Delta_t\rangle. \tag{13}$$

For this modified case, we have the following main result.

Theorem 2: Let $\nu_Z \in \mathbb{N}$ be such that $c_k \neq 0$ for $|k| \leq \nu_Z$. Then, (8) and (9) in closed loop with the feedback law

$$u(t) = -\left(\int_0^{2\pi} P_{\nu_Z}(\partial_\theta \Delta_t) Z p_t \,\mathrm{d}\,\theta\right)$$

will result in the convergence of the first ν_Z moments of p to the first ν_Z moments of the target distribution q.

Proof: A direct computation along the lines of the previous case shows that

$$\frac{\mathrm{d}}{\mathrm{d}\,t}V(t) = \left(\int_0^{2\pi} P(\partial_\theta \Delta_t) Z p_t \,\mathrm{d}\,\theta\right) u(t)\ .$$

With $P = P_{\nu_Z}$ and the above feedback law, we clearly have $\frac{\mathrm{d}}{\mathrm{d}\,t}V(t) \leq 0$. It is left to show that under the assumption on Z, there can be no non-trivial configuration of p and q resulting in $\frac{\mathrm{d}}{\mathrm{d}\,t}V \equiv 0 \Leftrightarrow u \equiv 0$. Again, this would correspond to the system p_t evolving without external input, i.e., $\partial_t p_t = -\partial_\theta(\omega p_t)$, the solution of which is of the form $p_t(\theta) = p_0(\theta - \omega t)$, and similarly, $\Delta_t(\theta) = \Delta_0(\theta - \omega t)$. Let d_k denote the Fourier coefficients of Δ_0. Then $(\partial_\theta \Delta_t)(\theta) = \frac{1}{2\pi}\sum_{k=-\infty}^{\infty}(\mathrm{i}\,k d_k\,\mathrm{e}^{-\mathrm{i}\,k\omega t})\,\mathrm{e}^{\mathrm{i}\,k\theta}$ and thus

$$(P_{\nu_Z}(\partial_\theta \Delta_t))(\theta) = \frac{1}{2\pi}\sum_{k=-\nu_Z}^{\nu_Z}(\mathrm{i}\,k d_k)\,\mathrm{e}^{\mathrm{i}\,k(\theta-\omega t)}\ .$$

Thus, the integral under consideration can again be written as $u(t) = -\int_0^{2\pi} Z\Psi_t \,\mathrm{d}\,\theta$, where $\Psi_t : \theta \mapsto (P_{\nu_Z}(\partial_\theta \Delta_0))(\theta - \omega t)p_0(\theta - \omega t)$. Ψ_0 is given by $\psi_k = \sum_{\ell=-\nu_Z}^{\nu_Z}\mathrm{i}\,\ell d_\ell m_{k-\ell}$, and the kth Fourier coefficient of Ψ_t is given by $\psi_k\,\mathrm{e}^{-\mathrm{i}\,k\omega t}$. Now the mapping $(d_k)_{|k|\leq\nu_Z} \mapsto (\psi_k)_{|k|\leq\nu_Z}$ is a linear mapping involving a Toeplitz matrix generated by the Fourier coefficients m_k of p_0 [42]. Since p_0 is positive, this Toeplitz matrix is positive definite so that we can conclude that $(\psi_k)_{|k|\leq\nu_Z}$ is non-zero. By the same line of argument as before, the claim follows. ∎

A commonly observed phenomenon is that smoothness of a function correlates with the rate of decay of its Fourier coefficients. The dependence of the statement in Theorem 2 on the coefficients in the phase response curve can be interpreted in light of the smoothness of the functions. The degree of controllability of the distribution of agents on the unit circle is determined by the ruggedness of the PRC. The distribution of agents can be controlled to the same ruggedness as the ruggedness of the PRC by which the input affects the system. Given the well-known relation on rate of decay of Fourier coefficients for continuous periodic functions and their smoothness, our results practically restrict the controllability of oscillators in an ensemble control framework to only few circular moments [43]. However, a fast rate of decay of Fourier coefficients correlates with the rate of convergence of the Fourier transform to the actual function, such that smooth target distribution might be achieved with high precision.

B. Synchronization of the population

Synchronizing a population of agents on their limit cycle is a common fundamental control goal which is naturally included in the above described setup. A synchronized population is commonly achieved by sending the length of the first moment to one, $|m_1| \to 1$, cf. [34]. Based on Theorem 2 we arrive at the following result: Suppose $\nu_Z \geq 1$ and a target distribution characterized by $|\alpha_1| = 1$, then the feedback law

$$u(t) = -\left(\int_0^{2\pi} P_1(\partial_\theta \Delta_t) Z p_t \,\mathrm{d}\,\theta\right)$$

will result in synchronization of the population with $|m_1| \to 1$. Thus, in this special case where one tries to achieve a synchronized population, it is sufficient to control only the first moment which is possible if the first moment of the PRC is non-zero.

IV. Numerical Examples

We illustrate the performance and also limitations of our controller in three different scenarios. To this end artificial phase response curves, as well as target distributions were generated and the number of moments under control was varied. We denote the index of the largest non-zero Fourier coefficient of q and Z by ν_q and ν_Z, respectively. Furthermore, let ν_u be the number of Fourier coefficients used in the projection P to calculate the input u as in Theorem 2. The scenarios comprise the following combinations:

1) ν_Z, ν_u and ν_q are identically equal to one (Figure 3 a);
2) ν_Z is smaller than ν_u and ν_q (Figure 3 b);
3) ν_Z and ν_u are larger than ν_q (Figure 3 c);

The PRCs were constructed to have identical Fourier coefficients for all moments such that $Z(\theta) = \sum_{k=-\nu_Z}^{\nu_Z} 1\,\mathrm{e}^{\mathrm{i}\,k\theta}$. The circular moments of the target distributions were chosen to be evenly distributed at equal distance from the origin $q_0(\theta) = \frac{1}{2\pi}\sum_{k=-\nu_q}^{\nu_q}\alpha_k^0\,\mathrm{e}^{\mathrm{i}\,k\theta}$ with $\alpha_0^0 = 1$, $\alpha_n^0 = \frac{1}{8}\,\mathrm{e}^{\mathrm{i}(\pi/8 + \frac{n}{2\pi\nu_q})}$ for $n = 1, \ldots, \nu_q$, and $\alpha_n^0 = 0$ for $n > \nu_q$. The system in scenario 1 is initialized with a distribution with all moments equal to zero except $m_3 = 0.05$. In all other scenarios, the system is initialized with a uniform distribution $p_0(\theta) = (2\pi)^{-1}$.

We will briefly summarize the most important observations in general and individually for the three scenarios. In any case, moments larger than ν_Z cannot be controlled and might evolve as side effect of the control of the moments smaller or equal ν_Z. This effect can be seen in Scenario 1 where the second moment deviates significantly from zero and the third moment stays close to the value where it was initialized (Fig. 3 a). The effect can be reduced by controlling more moments than present in the target distribution as shown in Scenario 3, where ν_Z is much larger than ν_q (Fig. 3 c). Finally, implications of Theorem 2 are clearly demonstrated

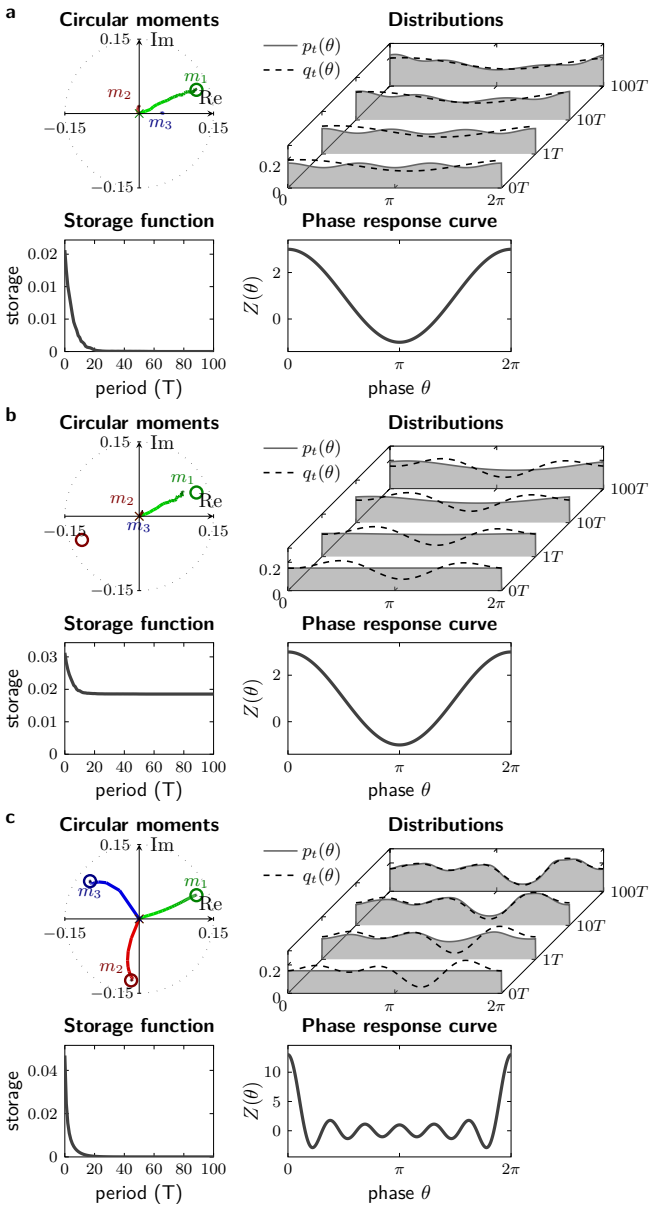

Figure 3. Simulation results for the different scenarios. Initial conditions of circular moments and desired value are indicated by the symbols 'x' and 'o', respectively. a) Scenario 1 with $\nu_Z = 1$, $\nu_u = 1$ and $\nu_q = 1$. b) Scenario 2 with $\nu_Z = 1$, $\nu_u = 2$ and $\nu_q = 2$. c) Scenario 3 with $\nu_Z = 6$, $\nu_u = 6$ and $\nu_q = 3$.

in Scenario 2. Only the first moment of the PRC is non-zero and both non-zero moments of the target distribution were used in the controller. The input converges to zero, however, as a consequence of Theorem 2, invariant distributions other than those with $P(\Delta_t) = 0$ exist, leading to oscillations with a distribution far off the desired one and neither of the moments converges to the corresponding one of the target distribution (Fig. 3 b).

Finally, we study the special case of synchronizing a population of oscillators by tracking a target distribution with $|\alpha_1| = 1$. The first moment of p tends towards the unit circle as the cells approaches a synchronized population (Fig. 4). A synchronized population corresponds to a Dirac delta distribution which by definition has the length of all moments equal to one. As a consequence of synchronizing the population by controlling the first moment, all moments approach the unit circle. A sufficient condition to achieve synchrony is that only the first moment of the PRC is non-zero. This result is in line with previous works on cell cycle synchronization where only the length of the first moment was considered in the controller design [34].

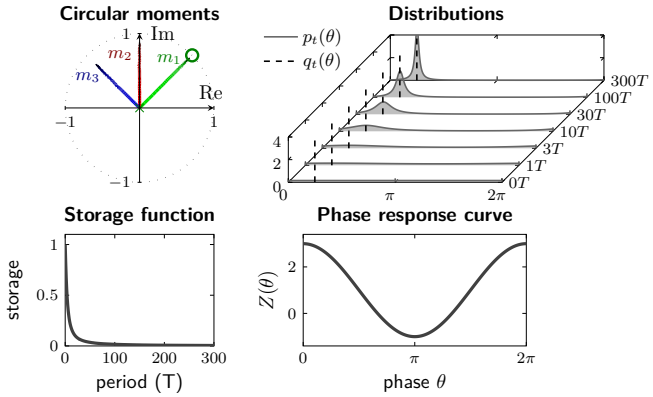

Figure 4. Synchronization scenario with $\nu_Z = 1$, $\nu_q = \infty$ and $\nu_u = 1$.

V. Conclusions

In the present paper, we investigated the control problem of achieving a desired distribution of cellular oscillators on the periodic orbit of their limit cycle. Using the reduced phase model representation of oscillatory systems a cost functional was formulated that promoted a population-level feedback law as the solution. A LaSalle-like argument was used to derive novel analytical conditions for the ability to control phase distributions in terms of the Fourier coefficients of the phase response curve. Our main result states that full control to any desired distribution is only possible if all moments of the PRC are non-zero. Moreover, we derived a condition for convergence of the first N moments of the population to those of the target distribution, which requires that only the first N moments of the phase response curve are non-zero. In this light, we also discussed how the task of achieving synchrony is a special case where it is sufficient that the first moment of the PRC is non-zero as a synchronized population is specified already by its first moment (or any other) having length equal to one. The feedback control is applicable to many systems given the input response occurs rapidly and the communication between individual oscillators is weak, i.e., the circadian clock and spiking neurons. The symptoms in Parkinson's disease, for example, are associated with elevated synchrony of neurons, and the reduction of this synchrony by deep brain stimulation is correlated to the alleviation of the symptoms. A compelling extension of this work is to consider networks of coupled oscillators, whose interactions are characterized by a coupling function acting between each pair of oscillators. In the future, it might be interesting to extend the theory to noisy systems which present more realistic models with regard to real applications. The noise might even

have a positive effect on the control problem as it pushes the moments to the origin so that higher moments in the population which cannot be controlled, due to zero moments of a realistic PRC, might thereby vanish.

REFERENCES

[1] A. T. Winfree, *Timing of Biological Clocks*. Henry Holt and Company, 1986.

[2] F. C. Hoppensteadt and E. M. Izhikevich, *Weakly Connected Neural Networks*, ser. Applied Mathematical Sciences. Springer New York, 1997, vol. 126.

[3] D. Hanahan and R. A. Weinberg, "Hallmarks of cancer: the next generation." *Cell*, vol. 144, no. 5, pp. 646–74, 2011.

[4] B. Zhivotovsky and S. Orrenius, "Cell cycle and cell death in disease: past, present and future," *J. Intern. Med.*, vol. 268, no. 5, pp. 395–409, 2010.

[5] H. P. Mirsky, A. C. Liu, D. K. Welsh, S. A. Kay, and F. J. Doyle, "A model of the cell-autonomous mammalian circadian clock," *Proc. Natl. Acad. Sci.*, vol. 106, no. 27, pp. 11 107–11 112, 2009.

[6] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *J. Physiol.*, vol. 117, no. 4, pp. 500–544, 1952.

[7] A. T. Winfree, *The Geometry of Biological Time*, ser. Interdisciplinary Applied Mathematics. New York, NY: Springer New York, 2001, vol. 12.

[8] M. Gyllenberg and G. F. Webb, "A nonlinear structured population model of tumor growth with quiescence," *J. Math. Biol.*, vol. 28, no. 6, pp. 671–694, 1990.

[9] R. Brockett, "Notes on the Control of the Liouville Equation," in *Lect. Notes Math.*, ser. Lecture Notes in Mathematics. Springer Berlin Heidelberg, 2012, vol. 2048, pp. 101–129.

[10] Y. Kuramoto, "Self-entrainment of a population of coupled non-linear oscillators," in *Int. Symp. Math. Probl. Theor. Phys.* Berlin/Heidelberg: Springer-Verlag, 1975, vol. 39, pp. 420–422.

[11] A. T. Winfree, "Biological rhythms and the behavior of populations of coupled oscillators," *J. Theor. Biol.*, vol. 16, no. 1, pp. 15–42, 1967.

[12] Y. Kuramoto, *Chemical Oscillations, Waves, and Turbulence*, ser. Springer Series in Synergetics. Springer Berlin Heidelberg, 1984, vol. 19.

[13] R. E. Mirollo and S. H. Strogatz, "Synchronization of Pulse-Coupled Biological Oscillators," *SIAM J. Appl. Math.*, vol. 50, no. 6, pp. 1645–1662, 1990.

[14] D. Wilson and J. Moehlis, "Determining individual phase response curves from aggregate population data," *Phys. Rev. E*, vol. 92, no. 2, p. 022902, 2015.

[15] ——, "Isostable reduction with applications to time-dependent partial differential equations," *Phys. Rev. E*, vol. 94, no. 1, pp. 1–14, 2016.

[16] K. Kuritz, D. Stöhr, N. Pollak, and F. Allgöwer, "On the relationship between cell cycle analysis with ergodic principles and age-structured cell population models," *J. Theor. Biol.*, vol. 414, pp. 91–102, 2017.

[17] E. M. Izhikevich, *Dynamical systems in neuroscience*. MIT press, 2007.

[18] L. Glass, "Synchronization and rhythmic processes in physiology," *Nature*, vol. 410, no. 6825, pp. 277–284, 2001.

[19] A. M. Vosko, A. Avidan, and C. Colwell, "Jet lag syndrome: circadian organization, pathophysiology, and management strategies," *Nature and Science of Sleep*, vol. 2, p. 187, 2010.

[20] V. Carmona-Alcocer, J. H. Abel, T. C. Sun, L. R. Petzold, F. J. Doyle, C. L. Simms, and E. D. Herzog, "Ontogeny of Circadian Rhythms and Synchrony in the Suprachiasmatic Nucleus," *The Journal of Neuroscience*, vol. 38, no. 6, pp. 1326–1334, 2018.

[21] J.-S. Li, I. Dasanayake, and J. Ruths, "Control and synchronization of neuron ensembles," *IEEE Transactions on Automatic Control*, vol. 58, no. 8, pp. 1919–1930, 2013.

[22] I. Z. Kiss, M. Quigg, S.-H. C. Chun, H. Kori, and J. L. Hudson, "Characterization of Synchronization in Interacting Groups of Oscillators: Application to Seizures," *Biophysical Journal*, vol. 94, no. 3, pp. 1121–1130, 2008.

[23] L. Hofmann, M. Ebert, P. A. Tass, and C. Hauptmann, "Modified Pulse Shapes for Effective Neural Stimulation," *Frontiers in Neuroengineering*, vol. 4, no. 9, pp. 1–10, 2011.

[24] D. Wilson and J. Moehlis, "Optimal Chaotic Desynchronization for Neural Populations," *SIAM J. Appl. Dyn. Syst.*, vol. 13, no. 1, pp. 276–305, 2014.

[25] T. Matchen and J. Moehlis, "Real-time stabilization of neurons into clusters," in *2017 American Control Conference (ACC)*, 2017, pp. 2805–2810.

[26] B. Monga, G. Froyland, and J. Moehlis, "Synchronizing and desynchronizing neural populations through phase distribution control," in *2018 Annual American Control Conference (ACC)*, 2018, pp. 2808–2813.

[27] C. Feillet, G. T. J. van der Horst, F. Levi, D. A. Rand, and F. Delaunay, "Coupling between the Circadian Clock and Cell Cycle Oscillators: Implication for Healthy Cells and Malignant Growth," *Frontiers in Neurology*, vol. 6, no. 5, pp. 1–7, 2015.

[28] A. Zlotnik and J.-S. Li, "Optimal Subharmonic Entrainment of Weakly Forced Nonlinear Oscillators," *SIAM Journal on Applied Dynamical Systems*, vol. 13, no. 4, pp. 1654–1693, 2014.

[29] R. Brockett, "On the control of a flock by a leader," *Proceedings of the Steklov Institute of Mathematics*, vol. 268, no. 1, pp. 49–57, 2010.

[30] ——, "Nonlinear systems and differential geometry," *Proceedings of the IEEE*, vol. 64, no. 1, pp. 61–72, 1976.

[31] S. Zeng, S. Waldherr, C. Ebenbauer, and F. Allgower, "Ensemble Observability of Linear Systems," *IEEE Trans. Automat. Contr.*, vol. 61, no. 6, pp. 1452–1465, 2016.

[32] J.-S. Li, "Ensemble control of finite-dimensional time-varying linear systems," *IEEE Transactions on Automatic Control*, vol. 56, no. 2, pp. 345–357, 2011.

[33] S. Zeng and F. Allgöwer, "A moment-based approach to ensemble controllability of linear systems," *Systems & Control Letters*, vol. 98, pp. 49–56, 2016.

[34] K. Kuritz, W. Halter, and F. Allgöwer, "Passivity-Based Ensemble Control for Cell Cycle Synchronization," in *Emerg. Appl. Control Syst. Theorys*, 1st ed., R. Tempo, S. Yurkovich, and P. Misra, Eds. Springer International Publishing, 2018, pp. 1–13.

[35] A. T. Winfree, "Patterns of phase compromise in biological cycles," *J. Math. Biol.*, vol. 1, no. 1, pp. 73–93, 1974.

[36] J. Guckenheimer, "Isochrons and phaseless sets," *J. Math. Biol.*, vol. 1, no. 3, pp. 259–273, 1975.

[37] I. G. Malkin, *Methods of Poincare and Liapunov in theory of non-linear oscillations*. Moscow: Gostexizdat, 1949.

[38] ——, *Some Problems in Nonlinear Oscillation Theory*. Moscow: Gostexizdat, 1956.

[39] M. A. St Hilaire, J. J. Gooley, S. B. S. Khalsa, R. E. Kronauer, C. A. Czeisler, and S. W. Lockley, "Human phase response curve to a 1 h pulse of bright white light," *The Journal of Physiology*, vol. 590, no. 13, pp. 3035–3045, 2012.

[40] P. Ashwin, S. Coombes, and R. Nicks, "Mathematical frameworks for oscillatory network dynamics in neuroscience," *The Journal of Mathematical Neuroscience*, vol. 6, no. 1, p. 2, 2016.

[41] K. M. Stiefel, B. S. Gutkin, and T. J. Sejnowski, "Cholinergic neuromodulation changes phase response curve shape and type in cortical pyramidal neurons," *PLOS ONE*, vol. 3, no. 12, pp. 1–7, 12 2008.

[42] U. Grenander and G. Szegő, *Toeplitz forms and their applications*. Univ of California Press, 1958.

[43] G. Polya and N. Wiener, "On the Oscillation of the Derivatives of A Periodic Function," *Trans. Am. Math. Soc.*, vol. 52, no. 2, pp. 249–256, 1942.