Chapter 1
Passivity-Based Ensemble Control for Cell Cycle Synchronization

Karsten Kuritz, Wolfgang Halter and Frank Allgöwer

Abstract   We investigate the problem of synchronizing a population of cellular oscillators in their cell cycle. Restrictions on the observability and controllability of the population imposed by the nature of cell biology give rise to an ensemble control problem specified by finding a broadcast input based on the distribution of the population. We solve the problem by a passivity-based control law, which we derive from the reduced phase model representation of the population and the aim of sending the norm of the first circular moment to one. Furthermore, we present conditions on the phase response curve and circular moments of the population which are sufficient for synchronizing a population of cellular oscillators.

1.1   Introduction

The cell cycle is central to life. Every living organism relies on the cell division cycle for reproduction, tissue growth, and renewal. Malfunction in this highly controlled cell cycle machinery is linked to various diseases, including Alzheimer's disease and cancer [10, 26]. Cause and cure of these diseases are two sides of the same coin, and thus understanding of the cell cycle machinery and approaches to control it are subjects of ongoing research [20]. Mathematically, the cell cycle machinery can be described as dynamical system which obeys limit cycle behavior [3, 7] with dynamics of the general form

$$\dot{x} = f(x, u) . \tag{1.1}$$

Therein, the states x represent different molecular species in the cell which can be indirectly affected by external inputs u such as growth conditions, drugs, and other

environmental factors. Another control approach can be realized by directly regulating the expression levels of specific proteins, e.g., by optogenetics [14]. Besides the agent-based description, with each agent beeing a cellular oscillator with dynamics (1.1), proliferating cell populations are often represented by structured population models [2, 9]. The resulting dynamics are governed by partial differential equations, belonging to the *Liouville equations* [1] of the general form

$$\partial_t \rho(x, t) = -\langle \partial_x, f(x, u)\rho(x, t)\rangle \ . \tag{1.2}$$

The concept of reduced phase models connects the nonlinear dynamics in (1.1) with age-structured population models, thereby facilitating control approaches based on the phase distribution of nonlinear oscillators [12, 18]. Control of these oscillators is studied intensively, e.g., by the authors of [19, 22, 23].

   In this article, we address the following control problem: Find a control input *u* for a population of identical cellular oscillators such that the agents are synchronized in their cell cycle. Several constraints imposed by the nature of cell biology complicate the task. (1) Experimental observation of the cell cycle state 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 cells in the cell cycle must be reconstructed [13, 25]. (2) Two new agents arise by division at the end of the cell cycle, resulting in exponential growth of the number of controlled agents and non-smooth boundary conditions of the PDE. (3) Only broadcast input signals can be realized, giving rise to an ensemble control problem.

   Our approach to solve the above stated control problem is organized as follows. Section 1.2 introduces the theoretic foundation of our control approach, compromising the classical input-output framework for passivity-based controller design and reduced phase models for the representation of weakly coupled oscillators. The control methodology is developed in Sect. 1.3. Section 1.4 examines the control methodology applied to a nonlinear ODE model of the mammalian cell cycle. Section 1.5 contains concluding comments.

1.2 Theoretical Foundation

As mentioned above, we are interested in controlling a population of many identical uncoupled dynamical systems (1.1). The dynamics of the population follows the aforementioned Liouville equation (1.2), so for a given input $u(t)$ and initial distribution $\rho(x, 0) = \rho_0(x)$ we may find the solution of the PDE

$$\rho(\cdot, t) = \Upsilon(u, \rho_0, t) \ , \quad t > 0 \ . \tag{1.3}$$

An observable feature may for instance be the moments of (1.3), and the output of the system may be any function of these moments. More general, we consider any function which maps the solution of the PDE to a scalar value as a possible output

function

$$y(t) = h(\rho(\cdot, t)), \quad y(t) \in \mathbb{R}. \tag{1.4}$$

We will develop our control methodology on the fundamentals of classical input-output frameworks and the concept of reduced phase models, reviewed below.

1.2.1 Input/Output Mapping and Control Approach

With output (1.4) given, we note that the system can now be recast as an input-output mapping of an input signal u to an output signal y. Following the formal framework treated in [4], let $x : \mathbb{R}^+ \to \mathbb{R}$ be a scalar function of time and

$$x_T = \begin{cases} x(t), & t \leq T \\ 0, & t > T \end{cases} \tag{1.5}$$

the T-truncated signal. Given the L^2 inner product

$$\langle x, y \rangle = \int_0^\infty x(t)y(t)\mathrm{d}t, \tag{1.6}$$

we let

$$\mathscr{L}_e \triangleq \left\{ x : \forall T \in \mathbb{R}^+, \ \langle x_T, x_T \rangle < \infty \right\} \tag{1.7}$$

be the space of signals x with the property that all truncations have finite L^2-norm and

$$\mathscr{L} \triangleq \{ x : \langle x, x \rangle < \infty \} \tag{1.8}$$

the space of signals for which this holds for the complete signal.

We now define the mapping

$$\begin{aligned} H_1 : \quad & \mathscr{L}_e \to \mathscr{L}_e, \\ & u \mapsto y \end{aligned} \tag{1.9}$$

which takes an arbitrary input signal $u \in \mathscr{L}_e$ and returns the output signal $y \in \mathscr{L}_e$, depending on the initial distribution $\rho_0(x)$ and its evolution dynamics (1.2).

Given this approach, the passivity of such a system can be studied using the classical input-output framework treated in [4], avoiding the difficulties of formulating a proper state space for defining a storage function. Such a state space may for instance be found by taking the circular moments as state variables, however, moment closure might not be given. With the mapping H_1 defined, we want to apply an output feedback approach as depicted in Fig. 1.1.
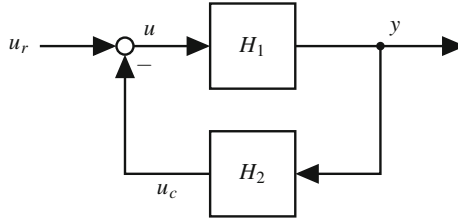
Fig. 1.1 The output is chosen such that it is connected to our goal of synchronizing (or balancing) the population of agents. If the mapping H_1 is passive and the controller H_2 is strictly passive one concludes that $y \in \mathscr{L}$

1.2.2 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 excellent book [11] 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

$$\dot{\xi}(t) = f(\xi(t)) , \quad \xi(t) \in \mathbb{R}^n \tag{1.10}$$

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

$$\dot{\theta}(t) = \omega , \quad \theta(t) \in S^1 \tag{1.11}$$

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 [24] and its basic idea, illustrated in Fig. 1.2, 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 (1.11). 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 $\xi(0)$

$$M_{\xi(0)} = \{z(0) \in W \colon \|\xi(t) - z(t)\| \to 0 \text{ as } t \to \infty\} . \tag{1.12}$$

Furthermore, Guckenheimer [8] showed, that there always exists a neighborhood W of a limit cycle that is invariantly foliated by the isochrons $M_\xi, \xi \in \gamma$ 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 (1.11). 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. 1.2).
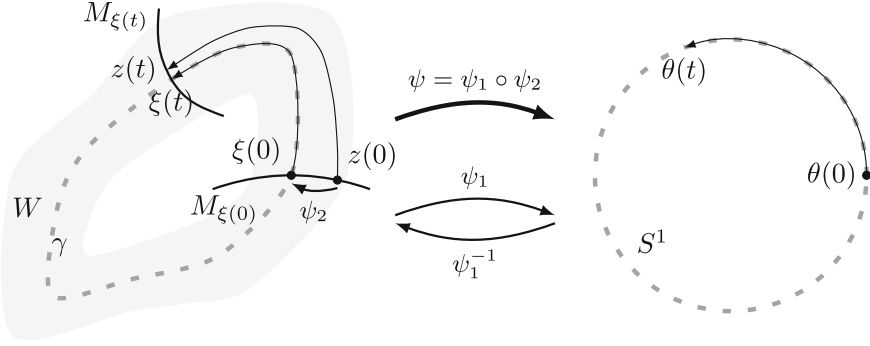
Fig. 1.2 A neighborhood W of the limit cycle γ of an oscillator is invariantly foliated by isochrons M_ξ. The flow maps isochrons to isochrons. The function $\psi = \psi_1 \circ \psi_2$ maps an oscillator $\xi(t) \in W$ uniquely to its phase on the unit circle $\theta(t) = \psi(\xi(t))$

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

$$\dot{\xi}(t) = f(\xi(t)) + u(t) , \quad \xi(0) = \xi_0 \in W \tag{1.13}$$

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

$$\dot{\theta}(t) = \omega + Z(\theta(t)) u(t) . \tag{1.14}$$

Here, weakly forced is in the sense that ε is sufficiently small such that $\xi(t)$ stays inside the neighborhood W for all $t > 0$. The function Z is called phase response curve (PRC) and describes the magnitude of phase changes after perturbing an oscillatory system. Based on *Malkins Theorem* [15, 16], the PRC is the solution of the adjoint problem $dZ(t)/dt = -(Df(\xi(t)))^\top Z(t)$, with the normalization condition $Z(t)f(\xi(t)) = 1$ for any t, where Df is the Jacobian matrix which is evaluated along the periodic orbit, $\xi(t) \in \gamma$.

1.2.3 From Reduced Phase Model to Age-Structured Population Models

To simplify the notation, we replace the phase variable θ in the remainder by the variable $x \in S^1$. Given a family of weakly coupled identical oscillators in its reduced phase representation (1.14), the corresponding Liouville equation for the time evolution of the number density $n(x, t)$ of oscillators on the unit circle reads

$$\partial_t n(x, t) + \partial_x (\kappa(x, u)n(x, t)) = 0 . \tag{1.15}$$

The vector field equals the reduced phase model $\kappa(x, u) = \omega + Z(x)u$. In case of a cell population, a division of a mother cell into two daughter cells results in the boundary condition

$$n(0, t) = 2\,n(2\pi, t) \ . \tag{1.16}$$

The model (1.15) and (1.16), with $u(t) = 0$, belongs to the model class of age-structured population models, based on the well-known von Foerster–McKendrick models [6, 17], which are widely used to study cell cycle-related processes. The distribution of cells $q(x, t) = n(x, t)/N(t)$, obtained by normalizing the number density with the total cell number $N(t) = \int_0^{2\pi} n(x, t)\mathrm{d}x$ admits a time-invariant distribution

$$\bar{q}(x) = 2\gamma e^{-\gamma x} \ , \tag{1.17}$$

where $\gamma = \frac{\log 2}{T_d}$ is the growth rate of the population [21].

We further define the k-th circular moment of some distribution ρ as

$$m_k(\rho(\cdot, t)) = \int_0^{2\pi} e^{ikx} \rho(x, t)\mathrm{d}x \ . \tag{1.18}$$

By omitting the argument in (1.18), we refer to the complex number $m_k = re^{ik\phi}, r \in [0, 1], \phi \in S^1$, obtained by evaluating $m_k(\rho(\cdot, t))$ with some specified distribution. In a synchronized population corresponding to a Dirac delta distribution, the length of the first circular moment $|m_1| = r$ is equal to one. The control problem to synchronize (or balance) the agents in the population can now be stated as:

Problem 1.1 Given the system defined by (1.15) and (1.16), find a control input u, such that $|m_1(q(\cdot, t))| \to 1$ (or 0).

1.3 Results

We will first elaborate how to choose an output function h such that it is connected to our goal of synchronizing (or balancing) the population of agents. At the same time, the mapping H_1 is passive under this choice of output and by applying a strictly passive controller H_2 in the control approach of Fig. 1.1, we conclude that $y \in \mathcal{L}$. We will then study invariance properties and conditions of our system under the proposed control law. An interpretation of this result along with some further considerations indicate that the control law indeed synchronizes (or balances) the population of agents, thereby solving Problem 1.1.

1.3.1 Enabling Passivity-Based Controller Design

The controller design based on the theory of passive systems benefits from a system model for which the control objective remains constant whenever $u = 0$. This property is not met by the model (1.15). In the following section, we propose state transformations $n(x, t) \rightarrow p(x, t)$ such that $|m_1(p(\cdot, t))|$ remains constant whenever $u = 0$. The first transformation employing (1.17) eliminates the discontinuity at the boundary by defining $\tilde{n}(x, t) = n(x, t)/\bar{q}(x)$, resulting in

$$\partial_t \tilde{n}(x, t) + \partial_x \left(\kappa(x, u)\tilde{n}(x, t) \right) = \gamma \kappa(x, u)\tilde{n}(x, t) , \qquad \tilde{n}(0, t) = \tilde{n}(2\pi, t) . \quad (1.19)$$

Next, we define $p(x, t) = \tilde{n}(x, t)/\int_0^{2\pi} \tilde{n}(x, t)\mathrm{d}x$ which is a proper probability distribution with PDE

$$\partial_t p(x, t) + \partial_x \left(\kappa(x, u)p(x, t) \right) = u\gamma p(x, t) \left(Z(x) - \int_0^{2\pi} Z(x)p(x, t)\mathrm{d}x \right) , \quad (1.20)$$

$$p(0, t) = p(2\pi, t) .$$

The system (1.20) has now the favorable properties that facilitate the feedback approach for synchronization of the population: (1) $p(x, t)$ is a proper probability distribution, (2) $p(x, t)$ is smooth over the boundary, and (3) the length of the first circular moment $|m_1(p(\cdot, t))|$ remains constant whenever $u = 0$. Furthermore, if $|m_1| = 1$, then the agents are synchronized.

1.3.2 Synchronization of the Population

With the model (1.20) given, it remains to define an appropriate output and a suitable output feedback control law which synchronizes the population. This will be achieved by choosing the output $y = h(p(\cdot, t))$ such that: (1) $y = 0$ whenever the population is synchronized, and (2) the map $H_1 : u \mapsto y$ is passive. As synchrony is equivalent to $|m_1| = 1$, we first study the time derivative of $|m_1(p(\cdot, t))|$ evolving under (1.20), viz.

$$\frac{\mathrm{d}}{\mathrm{d}t}|m_1(p(\cdot, t))| = \left((\gamma + \mathrm{i})m_{-1} \int_0^{2\pi} \mathrm{e}^{\mathrm{i}x} Z(x)p(x, t)\mathrm{d}x \right.$$

$$\left. - 2\gamma m_1 m_{-1} \int_0^{2\pi} Z(x)p(x, t)\mathrm{d}x + (\gamma - \mathrm{i})m_1 \int_0^{2\pi} \mathrm{e}^{-\mathrm{i}x} Z(x)p(x, t)\mathrm{d}x \right) u . \quad (1.21)$$

In the following, we define $d^p(x) = d(p(\cdot, t), x)$ with

$$d(p(\cdot, t), x) = \sum_{l=-1}^{1} d_l \, e^{ilx} , \tag{1.22}$$

$$d_{-1} = (\gamma - i)m_1 , \quad d_0 = -2\gamma m_1 m_{-1} , \quad d_1 = (\gamma + i)m_{-1} .$$

This leads to a more practical representation of (1.21) in terms of the inner product

$$\frac{d}{dt} |m_1(p(\cdot, t))| = \langle Z, d^p p(\cdot, t) \rangle u , \tag{1.23}$$

which is zero whenever $u = 0$. Thus, by choosing the output as

$$h(p(\cdot, t)) = \langle Z, d^p p(\cdot, t) \rangle , \tag{1.24}$$

we arrive at the following observations.

Lemma 1.1 *The system H_1 given by* (1.9) *with output* (1.24) *and internal dynamics* (1.20) *is passive.*

Proof Following the definition of [4], the system is passive if $\langle y, u \rangle_T \geq \beta, \forall u \in \mathcal{L}_e$, $\forall T \in \mathbb{R}^+$. We constructed y such that

$$\langle y, u \rangle_T = \int_0^T y(t)u(t)dt = \int_0^T \frac{d}{dt} |m_1(p(\cdot, t))| \, dt = |m_1(p(\cdot, T))| - |m_1(p(\cdot, 0))|$$

and as the norm of the first circular moment of a probability distribution is upper bounded by 1, we can choose $\beta = -1$.   □

Theorem 1.1 *If the output feedback $u(t) = -y(t)$ is chosen for system H_1 and the output $y(t)$ is given by* (1.24), *$y(t)$ converges to zero.*

Proof The result follows directly from the basic passivity theorem given in [4], namely that the output of a passive system H_1 lies in $\mathcal{L}$ if the output is fed back through a strictly passive system H_2. By Lemma 1.1, H_1 is a passive system. Further, we chose H_2 as the identity function $H_2 x = x$, which indeed is strictly passive, and $y \in \mathcal{L}$. With y being uniform continuous we know from Barbalat's Lemma, that $y(t) \rightarrow 0$, thereby concluding the proof.   □

Next, we study the invariance properties of our system having zero output. Our study is based on the properties of Fourier series and the Fourier coefficients of Z, d^p, and $p(\cdot, t)$ in (1.24). The Fourier series of a function $F : x \mapsto F(x)$ in any 2π-interval is $F(x) = \sum_{k=-\infty}^{\infty} a_k e^{ikx}$ with Fourier coefficients $a_k = \frac{1}{2\pi} \int_0^{2\pi} e^{-ikx} F(x) \, dx$. To keep the notation in accordance with the definition of the circular moments in (1.18), we introduce a modified series representation with $F(x) = \sum_{k=-\infty}^{\infty} \frac{b_k}{2\pi} e^{-ikx}$ and altered coefficients $b_k = \int_0^{2\pi} e^{ikx} F(x) dx$. A distribution $p(\cdot, t)$ is contained in a forward invariant set in $E = \{p : h(p) = 0\}$ if and only if $h(p(\cdot, t + \tau)) = 0, \ \forall \tau \geq 0$. The modified series representation leads to the following lemma:

Lemma 1.2 *Let c_k, d_k, and m_k be the coefficients of Z, d^p and $p(\cdot, t)$, respectively. Then E is invariant if and only if*

$$k c_k v_k = 0 , \quad \forall k \in \mathbb{Z} , \tag{1.25}$$

with $v_k = \sum_{l=-1}^{1} d_l m_{k-l}$.

Proof Due to the periodicity of the cell cycle we know that E is in an invariant set if and only if $h(p(\cdot, t + \tau)) = 0, \forall \tau \in [0, T]$, which is due to the constant propagation ($u = 0$) of $p(x, t)$ with $\frac{dx}{dt} = \omega$ equal to $h(p_{\omega\tau}(\cdot, t)) = h(p_\sigma(\cdot, t)) = 0, \ \forall \sigma \in [0, 2\pi]$, where we define $p_\sigma(x, t) = p(x - \sigma, t)$. We will use this notation to denote a shift in x also for Z later on. If $h(p_\sigma(\cdot, t)) = 0$, then this is also true for its derivative $\frac{d}{dt} h(p_\sigma(\cdot, t))$ resulting in the following condition for invariance

$$\frac{d}{dt} \langle Z, d^{p_\sigma} \, p_\sigma(\cdot, t) \rangle = 0, \quad \forall \sigma \in [0, 2\pi] . \tag{1.26}$$

The derivative is obtained by employing the identity from the PDE (1.20) with $u = 0$: $\partial_t p(x, t) = -\omega \partial_x p(x, t)$ and subsequently integrating by parts. Furthermore, the shift in x is transferred to the PRC by a change of variables $x = \xi + \sigma$, changing (1.26) to

$$\langle \frac{d}{dx} Z_{-\sigma}, d^p \, p(\cdot, t) \rangle = 0, \quad \forall \sigma \in [0, 2\pi] . \tag{1.27}$$

The last steps of the proof are: (1) substituting $p(\cdot, t)$ and $Z_{-\sigma}$ with its modified Fourier series and (2) employing Parseval's theorem. With $(c_k)_k$ being the coefficients of Z, the coefficients of the argument shifted derivative $dZ_{-\sigma}/dx$ in (1.27) are $\left(-ik e^{-ik\sigma} c_k \right)_k$. The function d^p has Fourier coefficients d_{-1}, d_0, d_1, and all other coefficients equal zero. The product $d^p p(\cdot, t)$ has modified coefficients $(v_k)_k$. By Parseval's theorem, the inner product in (1.27) equals the sum of its coefficients

$$\langle \frac{d}{dx} Z_{-\sigma}, d^p \, p(\cdot, t) \rangle = \frac{-i}{(2\pi)^2} \sum_{k=-\infty}^{\infty} e^{-ik\sigma} k c_k v_k \tag{1.28}$$

which can be written as inner product, and therefore the condition for invariance is

$$\langle (e^{-ik\sigma})_k, (k c_k v_k)_k \rangle = 0 , \quad \sigma \in [0, 2\pi] , \ k \in \mathbb{Z} . \tag{1.29}$$

The series $\left(e^{-ik\sigma} \right)_k$ are basis functions of a complete orthogonal basis, hence the inner product (1.29) is zero if and only if $k c_k v_k = 0, \forall k \in \mathbb{Z}$. This equals (1.25), thereby concluding the proof of Lemma 1.2. $\qquad\square$

With Lemma 1.2 at hand, we can identify conditions on the phase response curve Z, such that the synchronized and balanced population are the only invariant ones.

Theorem 1.2 *If the the output feedback $u(t) = -y(t)$ is chosen for system H_1 and the output $y(t)$ is given by (1.24), then*

$$\mathscr{M}_0 = \{p \colon |m_1(p)| = 0\} \ ,$$
$$\mathscr{M}_1 = \{p \colon |m_1(p)| = 1\}$$

are invariant sets in E. Furthermore, if the first moment of Z is not equal to zero, i.e., $c_1 \neq 0$, then no other invariant set exists.

Proof By Lemma 1.2, invariance of E requires Eq. (1.25) to be fulfilled. Invariance of $\mathscr{M}_0$ and $\mathscr{M}_1$ is then verified by showing that $v_k = 0$, $\forall k \in \mathbb{Z}$. As $|m_1| = 0$ implies $m_1 = m_{-1} = 0$, (1.25) is trivially met, and $\mathscr{M}_0$ is invariant. If $|m_1| = 1$, then all moments have length one and $m_k = e^{ik\phi}$. All terms in v_k cancel out, hence $\mathscr{M}_1$ is invariant. To conclude the proof of Theorem 1.2 we verify that $c_1 = 0$ is a necessary condition for (1.25) by showing that $v_1 \neq 0$ whenever $|m_1| \notin \{0, 1\}$. m_1 and m_{-1} are again represented as complex numbers. Furthermore $p(\cdot, t)$ is a probability distribution with $m_0 = 1$ by definition and we get

$$v_1 = r \left(e^{-i\phi} (\gamma + i) + e^{i\phi} ((\gamma - i)m_2 - 2\gamma r) \right) \ . \tag{1.30}$$

From $|m_1| = r \neq 0$, $e^{-i\phi}$ and $e^{i\phi}$ are orthogonal and $\gamma > 0$ by definition, it follows that $v_1 \neq 0$. Hence, $\mathscr{M}_0$ and $\mathscr{M}_1$ are the only invariant sets in E if $c_1 \neq 0$. $\qquad \square$

We will now discuss some aspects regarding the convergence to a synchronized (or balanced) population, given that the first moment of the phase response is not equal to zero. If the output is given by (1.24) and the output feedback $u(t) = -\varepsilon \, y(t)$, $\varepsilon > 0$, is chosen for system H_1, then

$$\frac{\mathrm{d}}{\mathrm{d}t} |m_1(p(\cdot, t))| = -\varepsilon \, h(p(\cdot, t))^2 \leq 0 \ , \qquad \forall t \geq 0 \ , \tag{1.31}$$

and $|m_1(p(\cdot, t))|$ decreases monotonically. Furthermore, the average of (1.31) over one period is strictly monotonically decreasing whenever $|m_1| \notin \{0, 1\}$. These observations suggest that $|m_1(p(\cdot, t))|$ approaches $\mathscr{M}_0$ from almost all initial conditions and the population is balanced. Synchronization of the population is achieved by sign reversal of the output function $y(t) = -h(p(\cdot, t))$ and the same output feedback. Sign reversal of the output preserves passivity of the system and by $\frac{\mathrm{d}}{\mathrm{d}t}|m_1(p(\cdot, t))| \geq 0$, p approaches $\mathscr{M}_1$ and a synchronized distribution is achieved.

Remark 1.1 Theorems 1.1 and 1.2 and the fact that an attractive set becomes a repelling set by sign reversal, strongly suggest that the population with output (1.24) and control input $u(t) = \varepsilon \, y(t)$ converges to a Dirac delta distribution. However, due to topological reasons, analysis of convergence of $p(\cdot, t)$ is difficult and beyond the scope of the present study.

1.4 Example

We conclude by demonstrating the developed control methodology on the reduced phase model (1.20). The underlying ODE model is a 5-state skeleton model of a mammalian cell cycle [7]. We extended the model by an additive input to the dynamics of Cyclin A

$$\dot{x}_{CycA} = f_{CycA}(x) + \frac{1.6\,(\alpha - x_{CycA})}{0.1 + \alpha - x_{CycA}}\,u(t)\,. \tag{1.32}$$

The input can be thought of, for e.g., an optogenetic signal causing a direct induction of Cyclin A expression with the total amount of Cyclin A being upper bounded by α. The phase response curve Z was obtained by solving the appropriate adjoint equation using the dynamic modeling program XPPAUT [5]. We take u according to Theorem 1.1 and simulated both the synchronizing and balancing scenario with h as defined in (1.24). The results are depicted in Fig. 1.3. In the synchronizing scenario, one observes how the first moment approaches the unit circle, indicating that the distribution of cells indeed converges to the Dirac distribution. This can also be observed in the simulation snapshots. By sign reversal of the output and starting with an imbalanced cell density, we further see that this process is reversed and the population approaches a uniform distribution.
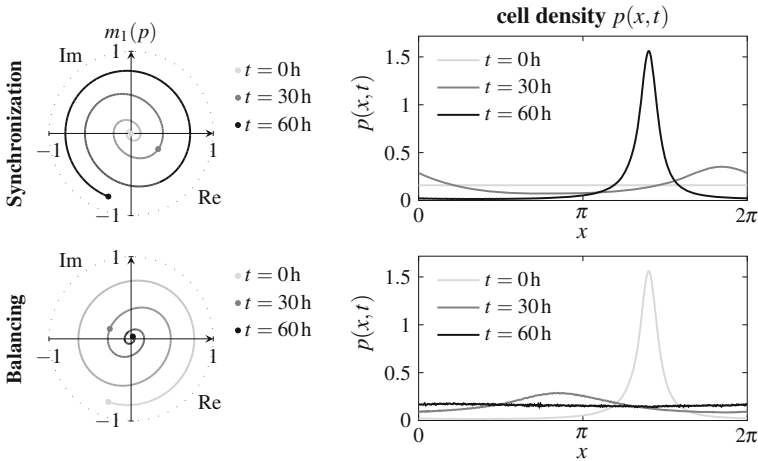

Fig. 1.3 Simulation of (1.20) derived from a 5-state cell cycle model with both a synchronizing (top) and a balancing (bottom) controller. On the left: temporal evolution of the first circular moment m_1 in the complex plane. On the right: snapshots of the cell density over the cell cycle position

1.5   Conclusion and Outlook

We studied the ensemble control problem of synchronizing a cell population in their cell cycle with restriction of the observation to representative samples of the population. Starting with a single cell as oscillator on a limit cycle, we developed a reduced phase model of the population with a broadcast input acting via the phase response curve. We then proposed state transformations for the age-structured population type model which enable controller design in the input-output framework for passive systems. Formulating the control problem in terms of the first circular moment of the population led to the desired output feedback which synchronizes the population. Finally, we derived sufficient conditions on the phase response curve for the synchronization of the population. We concluded by illustrating the controller action on a model of the mammalian cell cycle.

The present study solves the ensemble control problem of cell cycle synchronization by sending the first circular moment to one. However, we believe, that the here presented approach might be suitable to achieve any desired moment-determinate distribution by steering the circular moments of the population to the corresponding values of the target distribution.

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