Time-optimal Circadian Rhythm Entrainment is not Robust

Zidi Tao¹, Agung Julius¹ and John T. Wen¹

Abstract— This paper explores the continuity characteristics of value functions associated with optimal control in circadian rhythm entrainment problems. Our results demonstrate that when the optimal objective is to minimize the time required for entrainment, the corresponding value function is not Lipschitz continuous. This lack of Lipschitzianity suggests that the optimal cost and optimal trajectory are not robust under perturbation. As an alternative, we propose a new objective function that is based on the cumulative squared tracking error and show that the resulting value function is Lipschitz continuous. Through numerical simulations, we further establish that data-driven feedback control systems exhibit higher robustness to input perturbation when the data are collected from optimal control solutions that minimize the cumulative squared tracking error, as opposed to those that are time-optimal.

I. INTRODUCTION

Circadian rhythms are endogenous periodic oscillations that regulate the sleep-wake cycle, gene expression, metabolism, and many other biological activities [1]. They allow humans to adjust to predictable cyclic environmental changes, such as day and night. Disruption of circadian rhythms has adverse effects, such as fatigue and an increased risk of cardiovascular disease and cancer. Disrupted circadian rhythms also affect the level of cognition and productivity [2]. In this study, we use a widely accepted model proposed by Kronauer et al. [3] to represent circadian rhythm dynamics. The Kronauer model uses a Van der Pol oscillator to capture the oscillations of core body temperature and the effect of light on the amplitude and phase of this oscillation.

Circadian rhythm entrainment is the problem of using light as control input to synchronize a misaligned circadian phase with a reference circadian phase. Many studies focus on the time-optimal problem, which is to minimize the time taken to synchronize the circadian phases. As an example, timeoptimal entrainment eliminates the effect of jet lag as quickly as possible [4], [5], [6]. However, when we analyze the data of [5], [7] numerically, we observe that slight changes in the initial states can cause large changes in the value function in some regions. This leads to the problem that the timeoptimal control is not robust. An intuitive example showing that a value function is discontinuous is shown in Fig. 1. The example is a 1D harmonic oscillator (pendulum):

$$\frac{dx_1}{dt} = x_2, \frac{dx_2}{dt} = -x_1 + u,$$
(1)

where x_1 is the position and x_2 is the velocity. u is the force applied to the pendulum, and u is bounded: $u \in [0, 1]$. The target set is a circle centered on $x_1 = 1, x_2 = 0$ with radius 0.1. The red trajectory reaches the target set at 2.77 s, but the blue trajectory misses the target at first and reaches the target set at 6.41s. This illustrates that perturbing the initial states a little can change the final time significantly.



Fig. 1. An example showing the discontinuity in final time for time-optimal control in a harmonic oscillator (pendulum problem).

To address this problem, we propose an alternative optimization objective with minimum cumulative quadratic costs (MCQC) and demonstrate that its entrainment time is close to that for time-optimal entrainment. Some studies also minimize the difference between the current circadian phase and the reference circadian phase [8], [9], [10], but the authors do not consider the continuity properties of the value functions. This paper is the first paper to prove the Lipschitz continuity of value functions in circadian rhythm entrainment. We prove that MCQC entrainment has a value function that is Lipschitz continuous with respect to initial states. Continuity properties of value functions are essential for commonly used optimal control methods, such as dynamic programming and the Hamilton-Jacobi-Bellman equation [11]. Furthermore, deep reinforcement learning guarantees an improvement in performance in each iteration if the value function is smooth [12]. The stability of reinforcement learning is also related to the smoothness of the value function. In [13], Kobayashi applied a regularization method to make the value function smooth and demonstrated that the agent achieved better task performance with the smooth value function in a noisy environment. We also show through numerical simulations that when we use a data-driven method to control circadian rhythm entrainment, the data collected from the MCQC are more robust against input perturbation.

In this work, our main contributions are as follows:

- We prove that the time-optimal circadian entrainment problem has Lipschitz discontinuous value functions. We also prove that the MCQC entrainment has Lipschitz continuous value functions.
- We demonstrate that data-driven feedback using the MCQC control as data is more robust against input perturbation than using the time-optimal entrainment as data without sacrificing the entrainment time much.

II. THE KRONAUER MODEL FOR CIRCADIAN RHYTHM

We consider the widely accepted Kronauer model [3] to represent circadian rhythms. The dynamics of the model is:

$$\frac{dx}{dt} = \frac{\pi}{12} [x_c + \mu(\frac{1}{3}x + \frac{4}{3}x^3 - \frac{256}{105}x^7) + B], \quad (2)$$

$$\frac{dx_c}{dt} = \frac{\pi}{12} [qx_c B - (\frac{24}{0.99729\tau})^2 x - kxB], \qquad (3)$$

$$B = (1 - 0.4x)(1 - k_c x_c)u.$$
(4)

Here, $\mu = 0.13 \text{ h}^{-1}$, $k = 0.55 \text{ h}^{-1}$, $\tau = 24.2 \text{ h}$, $q = \frac{1}{3}$, $k_c = 0.4 \text{ h}$ are the model parameters. x is the normalized core body temperature and x_c is a fictional state that forms the Van der Pol oscillator with x. $X(t) \triangleq (x(t), x_c(t))$. $u \in [0, u_{max} \triangleq 0.2208]$ is the bounded light input. We denote the 16-h light and 8-h dark periodic light signals by $u_{ref}(t)$, and the resulting periodic state trajectories by $X_{ref}(t) \triangleq (x_{ref}(t), x_{c,ref}(t))$. The optimal entrainment problem is to find the input sequence u(t) that minimizes a cost function J under boundary constraints. We consider two cases: the time-optimal cost, $J \triangleq T, T$ being the time such that $|X(T) - X_{ref}(T)|$ is less than a tolerance ϵ , and the MCQC cost:

$$J \triangleq \int_0^{336} (x(t) - x_{ref}(t))^2 + (x_c(t) - x_{c,ref}(t))^2 dt.$$
 (5)

III. LIPSCHITZ CONTINUITY OF THE VALUE FUNCTION

A. General Theory

The necessary and sufficient conditions for the Lipschitz continuity of a value function have been studied in the previous literature [14], [15], [16], [17], [18], [19]. The conditions in [14], [15], [16], [17] are only applicable to time-optimal problem. In contrast, the conditions in [18] are not applicable to time-optimal problem. The most suitable theorem is in [19] which elaborated the necessary and sufficient conditions for the Lipschitz continuity of the value function for the Mayer problem with an arbitrary closed target set. Differential inclusions are used to represent the dynamics in [19]. Time-optimal entrainment and MCQC entrainment can both be represented as Mayer problems. We provide formal mathematical proofs of the value function Lipschitzianity in both circadian entrainment problems using conditions in [19].

If the system has the dynamics $\dot{X} = f(t, X(t), u(t))$, $X \in \mathbb{R}^n, t \in [t_0, T], u \in [0, u_{max}]$, the differential inclusion $\dot{X} \in F(X, t)$ represents the same dynamics if $F(X, t) \triangleq \{\dot{X} | \exists u(t) \in [0, u_{max}], \text{ s.t. } \dot{X} = f(t, X(t), u(t))\}$. Consider a system with differential inclusion dynamics:

$$X \in F(X,t), t \in [t_0,T], X \in \mathbb{R}^n, \tag{6}$$

subject to some initial constraint $X(t_0) = X_0$, and final constraint $X(T) \in M(T)$. $M(\cdot) : \mathbb{R} \to \mathbb{R}^n$ is a set-valued mapping representing the target set. We define $\Gamma \subset \mathbb{R}^n \times \mathbb{R}$ as the graph of $M(\cdot)$, $\mathcal{A}(X,t)$ as mapping a point $(X,t) \in \mathbb{R}^n \times \mathbb{R}$ to the set of any targets in Γ that can be reached from (X, t), and $D = \{(X_0, t_0) | \mathcal{A}(X_0, t_0) \neq \emptyset\}$ as the set of all initial states that can reach the targets in Γ .

Definition 1. A Mayer problem is an optimization problem:

$$\min g(X(T), T), \tag{7}$$

where $g : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}$ denotes a cost function, subject to the differential inclusion in Eq. (6) and boundary constraints $X(t_0) = X_0, X(T) \in M(T)$.

The value function of the Mayer problem, $V(X_0, t_0)$, is defined as the minimum of Eq. (7) under the initial constraint $X(t_0) = X_0$.

There are four assumptions about the system in [19].

Assumption 1. $F : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$ is nonempty, convex, and compact valued.

Assumption 2. Suppose H(P,Q) is the Hausdorff distance between two sets P,Q and F is measurable in t for every X, for every compact set $S \subset \mathbb{R}^n$, there is a locally integrable upper semicontinuous function $\lambda_S(\cdot)$ and a locally bounded function $m_S(\cdot)$ such that

$$H(F(X_1, t), F(X_2, t)) \le \lambda_S(t)|X_1 - X_2|,$$

 $|F(X,t)| \leq m_S(t)$, for every $t \in \mathbb{R}$ and $X, X_1, X_2 \in S$.

Assumption 3. For every compact set $K \subset \mathbb{R}^n \times \mathbb{R}$ and $\theta > 0$, there is a constant N such that, if $(X_0, t_0) \in K$ and $X(\cdot)$ is a solution of (6) in some interval $[t_0, t_0 + \tau], \tau \leq \theta$, then $||X(\cdot)||_C \leq N$, where $||X(\cdot)||_C \triangleq \sup\{|X(t)| : t \in [t_0, t_0 + \tau]\}$.

Assumption 4. If any $(X_k, t_k) \in \mathcal{A}(X_0, t_0)$ is reachable from an initial condition (X_0, t_0) and $t_k \to \infty$, then $g(X_k, t_k) \to \infty$.

Definition 2. [19] A closed valued mapping \mathcal{B} around a point $z \in \mathbb{R}^n \times \mathbb{R}$ is locally Lipschitz continuous if for every compact set $K \subset \mathbb{R}^n \times \mathbb{R}$, there are a constant L and a neighborhood V of $z \in \mathbb{R}^n \times \mathbb{R}$ such that

$$H(\mathcal{B}(z'), \mathcal{B}(z'')) \leq L|z'-z''|$$
, for every $z', z'' \in V \cap K$.

Then the necessary and sufficient condition for Lipschitz continuity of the value functions is as follows [19]:

Lemma 1. If Assumption 1-4 are satisfied and the mapping $(X,t) \rightarrow F(X,t)$ is continuous, the necessary and sufficient condition for the value function $V(X_0,t_0)$ to be locally Lipschitz continuous for $(X_0,t_0) \in D$ is as follows:

For every compact set $G \subset \mathbb{R}^n \times \mathbb{R}$, there is $\rho > 0$ such that, for every $(X,t) \in \partial \Gamma \cap G$ where t is a Lebesgue point (see Theorem 5.6.2 in [20]) of the mapping F(X,t), and $\partial \Gamma$ is the boundary of Γ :

$$\sup_{(l,l^0)\in N_{\Gamma}^{\perp}} \min_{\xi\in F(X,t)} \langle (l,l^0), (\xi,1) \rangle \le -\rho, \tag{8}$$

where $l \in \mathbb{R}^n$, $l^0 \in \mathbb{R}$, $N_{\Gamma}^{\perp}(z)$ is the set of all unit vectors orthogonal to Γ at $z \in \partial \Gamma$.

B. Lipschitz Continuity of the Value Function in the Timeoptimal Circadian Entrainment

We first convert the systems in Eqn. (2)-(4) to differential inclusion as in [19]. The differential inclusion F maps $(x(t), x_c(t), t)$ to the set

$$\left\{ \begin{bmatrix} \dot{x} \\ \dot{x}_c \end{bmatrix} \in \mathbb{R}^2 | \exists u \in [0, u_{max}] \text{ s.t. } \begin{bmatrix} \dot{x} \\ \dot{x}_c \end{bmatrix} = \vec{a} + \vec{b}u \right\}, \quad (9)$$

where

$$\vec{a} = \begin{bmatrix} \frac{\pi}{12} (x_c + \mu (\frac{1}{3}x + \frac{4}{3}x^3 - \frac{256}{105}x^7)) \\ \frac{\pi}{12} (-(\frac{24}{0.99729\tau})^2 x) \end{bmatrix},$$
(10)

$$\vec{b} = \begin{bmatrix} \frac{\pi}{12}(1 - 0.4x)(1 - k_c x_c) \\ \frac{\pi}{12}(q x_c - k x)(1 - 0.4x)(1 - k_c x_c) \end{bmatrix}.$$
 (11)

Suppose the entrainment process starts initially at $T_0 \in [0, 24)$ and the jet lag is $T_{lag} \in [0, 24)$, the initial condition $X(0) \triangleq [x(0), x_c(0)]$ as a function of T_0 and T_{lag} is:

$$X(0) = G(T_0, T_{lag}) \triangleq [x_{ref}(T_0 + T_{lag}), x_{c,ref}(T_0 + T_{lag})].$$

Definition 3. The time-optimal entrainment problem is to find optimal controls $\bar{u}_{TO}(t, X(0))$ that minimize the final time T subject to the differential inclusion in Eq. (9) with initial conditions $X(0) = G(T_0, T_{lag})$ and target set:

$$\{X(T) \in \mathbb{R}^2 | (x(T) - x_{ref}(T))^2 + (x_c(T) - x_{c,ref}(T))^2 \le \epsilon\}.$$

This $\epsilon \triangleq 0.01$ is the tolerance for reference tracking error and it corresponds to around 30 minutes of phase difference.

Lemma 2. The value function of the time-optimal entrainment is not Lipschitz continuous.

Proof: We first verify the assumptions for Lemma 1. The set in Eq. (9) is a line segment in \mathbb{R}^2 so Assumption 1 is satisfied. In our paper, the system dynamics is time-invariant. Thus, λ_S can be time-independent. Because F(X) is a polynomial function of x, x_c , it is locally Lipschitz. Therefore, for any compact set $S \in \mathbb{R}^2$, and for any $X, X_1, X_2 \in S$, there exists a λ_S for this S such that

$$H(F(X_1,t),F(X_2,t)) \le \lambda_S |X_1 - X_2|.$$

Because X is in a compact set S and \vec{a} and \vec{b} are polynomial functions of x, x_c , the images of x, x_c through \vec{a} and \vec{b} are compact. In addition, because $u \in [0, u_{max}]$ is compact, F(X,t) as the image of $\vec{a} + \vec{b}u$ is also compact. Thus, there exists a locally bounded function $m_S = \max(|\vec{a} + \vec{b}u|)$ such that $|F(X,t)| \leq m_S(t)$. Assumption 2 is also satisfied. The Kronauer model has regions of attraction and regions of repulsion at the same time. To prove Assumption 3, we prove that any initial states will converge to a compact set with bounded inputs. We can represent the circadian dynamics model as a differential equation

$$f(X, u, t) = \vec{a} + \vec{b}u$$

with $X \triangleq (x, x_c)$, \vec{a}, \vec{b} in Eq. (10),(11) and $u \in [0, u_{max}]$. For the set $S : \{X \in \mathbb{R}^2 | X^T X \ge 4\}$, we can find a positive definite Lyapunov function for all $X \in S$ such that

$$V(X) \ge 0.0001(x^4 + x_c^4), \ \dot{V} = \frac{dV}{dX} \cdot f(X, u, t) \le 0.$$
 (12)

A candidate of V(X) is found using SOSTOOLS [21]. This V(X) can be found at https://github.com/KiraTau/Value-Function-Continuity.git. Because $V(X) \ge 0.0001(x^4 + x_c^4)$,

$$|X| \le 10\sqrt{2}V^{\frac{1}{4}}(X). \tag{13}$$

Suppose the $\sup_{X \in S^{\complement}} V(X) = V_1$ where S^{\complement} represents the complement of S, the compact set $\Omega : \{X \in \mathbb{R}^2 | V(X) \le V_1 + 1\}$ is a positively invariant set because the boundary of Ω , $\partial\Omega$ has to be in S and $\dot{V}(X) \le 0$.

For an arbitrary compact set $K \subset \mathbb{R}^n \times \mathbb{R}$ and the initial condition $(X_0, t_0) \in K$, let $\theta > 0$ and $X(\cdot)$ be the solutions of (6) on some interval $[t_0, t_0 + \tau], \tau < \theta$. There are two possibilities for X_0 : $X_0 \in \Omega$ or $X_0 \in \Omega^{\complement}$.

First, we consider $X_0 \in \Omega$. Because Ω is a positively invariant set, the solutions $X(\cdot)$ of X_0 cannot leave Ω in the interval $[t_0, t_0 + \tau]$. The upper bound N of $||X(\cdot)||_C$ is $N = 10\sqrt{2}(V_1 + 1)^{\frac{1}{4}}$.

Next, we consider $X_0 \in \Omega^{\complement}$. Because $\Omega^{\complement} \subset S$, for all $X \in \Omega^{\complement}, \dot{V}(X) \leq 0.$ Consider the set $\Lambda : \{X \in \mathbb{R}^2 | V(X) \leq 0\}$ $V(X_0)$. For any X on the boundary of Λ , $\dot{V} \leq 0$, so Λ is also a positively invariant set. $X(\cdot)$ starting from X_0 will remain in the set Λ in interval $[t_0, t_0 + \tau]$. From Eq. (13), we acquire an upper bound N for $||X(\cdot)||_C \triangleq \sup\{|X(t)| : t \in$ $[t_0, t_0 + \tau]$: $N = 10\sqrt{2}V^{\frac{1}{4}}(X_0)$. Assumption 3 is satisfied. Lastly, g(X(T), T) = T, so Assumption 4 is also satisfied by definition. Now we can use the necessary and sufficient condition in Lemma 1 to prove that the value function is Lipschitz discontinuous. The lemma 1 is related to the dynamics pointing inward to the target boundary and to small-time local controllability in the neighborhood of the target boundary. If any points on the boundary $\partial \Gamma$ violate Eq. (8), it indicates that the states cannot reach the target in an arbitrarily small time and makes the value function Lipschitz discontinuous. We use counterexamples to show that the value function of time-optimal entrainment is Lipschitz discontinuous.

If we denote $\vec{V}_0 = X - X_{ref}(t)$, where

$$X_{ref}(t) = \begin{bmatrix} x_{ref}(t) \\ x_{c,ref}(t) \end{bmatrix}, X = \begin{bmatrix} x \\ x_c \end{bmatrix},$$

then a point $X \in \partial \Gamma$ at t is in the set $\{X : Z(X,t) = V_0^T V_0 - \epsilon = 0, \epsilon = 0.01\}$. The gradient of Z(X,t) = 0 is:

$$\begin{bmatrix} \frac{dZ}{dX} \\ \frac{dZ}{dt} \end{bmatrix} = \begin{bmatrix} 2\vec{V_0} \\ -2\dot{X}_{ref}^T\vec{V_0} \end{bmatrix} = 2\begin{bmatrix} \mathbb{1} \\ -\dot{X}_{ref}^T(t) \end{bmatrix} \cdot \vec{V_0}, \qquad (14)$$

where 1 is a 2 by 2 identity matrix. Because $\left(\frac{dZ}{dX}, \frac{dZ}{dt}\right)$ is orthogonal to Γ , the unit vectors (l, l_0) orthogonal to $\partial\Gamma$ are calculated by

$$(l, l_0) = \left(\frac{dZ}{dX}, \frac{dZ}{dt}\right) / \left| \left(\frac{dZ}{dX}, \frac{dZ}{dt}\right) \right|.$$
(15)

We can find multiple examples of $\langle (l, l_0), (\xi, 1) \rangle \geq 0$ by

numerically computing the signs. An example is shown in Fig. 2. For a reference point R on the periodic solution where $X_{ref}(58.16) = (0.4930, 0.9257)$, the boundary set will be the set $\partial\Gamma = \{\mathbb{R}^2 \times t | (x - 0.4930)^2 + (x_c - 0.9257)^2 = 0.01, t = 58.16\}$. We can find a point of interest $P = (0.4804, 0.8265, 58.16) \in \partial\Gamma$ such that

$$\sup_{\substack{(l,l^0)\in N_{\Gamma}^{\perp} \xi\in F(x(t),t)}} \min_{\langle (l,l_0), (\xi,1) \rangle} \\ = (\langle [-0.1251, -0.9880, -0.0903], [0.2576, -0.124, 1] \rangle) \\ = 5.483 \cdot 10^{-4},$$

which contradicts Eq. (8) in Lemma 1. The value function of time-optimal entrainment is not Lipschitz continuous. ■



Fig. 2. An example of a point P in the boundary set $\partial \Gamma$. The green arrow points in the direction of (l, l_0) and blue arrow points in the direction of ξ that satisfy $\sup_{(l,l^0) \in N_{\Gamma}^+} \min_{\xi \in F(x(t),t)} \langle (l, l_0), (\xi, 1) \rangle > 0$.

We can verify that for any $\epsilon \geq 0$, the value function will not be Lipschitz continuous using similar techniques as in the proof of Lemma 2. To visualize sharp changes in the entrainment time, we solve the time-optimal entrainment problem using gradient descent methods from [5] for initial conditions of T_0 uniformly sampled from 1 to 24, combined with T_{lag} uniformly sampled from 1 to 23. We define these initial conditions as the set:

$$\chi \triangleq \{X(0) = G(T_0, T_{lag}) | T_0 \in \{1, 2, \cdots, 24\},$$

$$T_{lag} \in \{1, 2, \cdots, 23\}\}.$$
(16)

The optimal entrainment times are plotted in Fig. 3.a. In Fig. 4, we plot the reference tracking errors for two cases: Case 1: $(T_0 = 19.2, T_{lag} = 19)$ and Case 2: $(T_0 =$ $19.3, T_{lag} = 19)$. In Case 2, the tracking error reaches the error threshold ϵ at t = 52.91 h, but in Case 1, the tracking error reaches ϵ at t = 60.04 h, which is 7.13 h longer. We can see that a small difference in the initial condition causes a large jump in the entrainment time. Therefore, we should not use the entrainment time as the most important metric to evaluate the performance of entrainment, especially in regions where the value function is not Lipschitz continuous.

C. Lipschitz Continuity of the Value Function in the MCQC Entrainment

We change the optimization objective to MCQC cost in Eqn. (5). We choose the optimization horizon to be T = 336 h which is much longer than the longest entrainment



Fig. 3. (a) Entrainment times T (in hours) for time-optimal entrainment. The red dots mark five regions where we observe jumps in T. (b) The cumulative quadratic costs (unitless) for MCQC entrainment.

time in time-optimal entrainment (see Fig. 3.a) so that any $X(0) \in \chi$ can reach entrainment. To convert this to a Mayer problem, we introduce a cumulative error variable e, where

$$\dot{e} = (x(t) - x_{ref}(t))^2 + (x_c(t) - x_{c,ref}(t))^2$$
 (17)

and $e(0) \triangleq 0$, so the states of the system are $\overline{X}(t) \triangleq (x(t), x_c(t), e(t))$. The differential inclusion $F(\overline{X}, t)$ is:

$$\left\{ \begin{bmatrix} \dot{x} \\ \dot{x}_c \\ \dot{e} \end{bmatrix} \in \mathbb{R}^3 | \exists u \in [0, u_{max}] \text{ s.t. } \begin{bmatrix} \dot{x} \\ \dot{x}_c \\ \dot{e} \end{bmatrix} = \vec{a} + \vec{b}u \right\}, \quad (18)$$

where

$$\vec{a} = \begin{bmatrix} \frac{\pi}{12} (x_c + \mu (\frac{1}{3}x + \frac{4}{3}x^3 - \frac{256}{105}x^7)) \\ \frac{\pi}{12} (-(\frac{24}{0.99729\tau})^2 x) \\ (x - x_{ref})^2 + (x_c - x_{c,ref})^2 \end{bmatrix},$$
$$\vec{b} = \begin{bmatrix} \frac{\pi}{12} (1 - 0.4x)(1 - k_c x_c) \\ \frac{\pi}{12} (q x_c - k x)(1 - 0.4x)(1 - k_c x_c) \\ 0 \end{bmatrix}.$$

Because J is only defined up to T, and Assumption 4 requires the value function to be a continuously increasing function. The performance index in this case is defined as

$$g(\overline{X}, t) \triangleq \begin{cases} e, t < T, \\ e + (t - T), t \ge T. \end{cases}$$
(19)

Definition 4. The MCQC entrainment problem is to find the optimal controls $\bar{u}_{QC}(t, \overline{X}(0))$ that minimize $g(\overline{X}(T), T)$ in Eq. (19) subject to the differential inclusion in Eq. (18) with initial conditions $\overline{X}(0) = (G(T_0, T_{lag}), 0)$ and target set:

$$\Gamma \triangleq \{\mathbb{R}^3 \times \mathbb{R} | (x, x_c, e) \in \mathbb{R}^3, t \ge T\}.$$
 (20)

Lemma 3. The value function of the MCQC entrainment is Lipschitz continuous.

Proof: Assumption 1-3 can be verified similarly as in the proof of Lemma 2. Assumption 4 is also satisfied in Eq. (19) by definition. The vectors orthogonal to the target boundary for any $(\overline{X}, t) \in \partial\Gamma$ are $N_{\Gamma}^{\perp} = (0, 0, 0, -1)$. For



Fig. 4. Comparisons of the reference errors $(x(t) - x_{ref}(t))^2 + (x_c(t) - x_{c,ref}(t))^2$ for two initial conditions that are close, Case 1: $(T_0 = 19.2, T_{lag} = 19)$ and Case 2: $(T_0 = 19.3, T_{lag} = 19)$ from the beginning of entrainment to the end, (top panel) for the entire time horizon, (bottom panel) zoomed in from t = 48 h.

any
$$(X,t) \in \partial \Gamma$$
,

$$\sup_{(l,l^0)\in N_{\Gamma}^{\perp}} \min_{\xi\in F(\overline{X},t)} \left(\langle (l,l^0), (\xi,1) \rangle \right)$$
(21)

$$= (\langle (0, 0, 0, -1), (\vec{a} + \vec{b}u, 1) \rangle) = -1.$$
(22)

The necessary and sufficient condition in Lemma 1 is satisfied and for any initial conditions (\overline{X}_0, t_0) , the value function $V(\overline{X}_0, t_0)$ is Lipscitz continuous.

The MCQC entrainment problems for all initial conditions $X(0) \in \chi$ in Eq. (16) are solved by CasADi nonlinear programming solver [22]. We can see that the cumulative costs do not show any significant changes with respect to the changes in the initial conditions in Fig. 3.b.

Key observation: On average, the time taken to reach the error threshold $\epsilon = 0.01$, denoted as T_{ϵ} , such that

$$(x(T_{\epsilon}) - x_{ref}(T_{\epsilon}))^2 + (x_c(T_{\epsilon}) - x_{c,ref}(T_{\epsilon}))^2 \le \epsilon,$$

for the MCQC is 0.94 h longer than time-optimal entrainment and the maximum difference is 9.42 h. The differences are plotted in Fig. 5. In 552 cases, 75% cases have a time difference of less than 1 h and only 3.44% have a time difference of greater than 6 h. The MCQC entrainment speed to drive $(x(t), x_c(t))$ to $(x_{ref}(t), x_{c,ref}(t))$ is still close to that of time-optimal entrainment.

IV. FEEDBACK ROBUSTNESS TO INPUT UNCERTAINTY

The time-optimal entrainment and the MCQC entrainment that we solved numerically in discrete time in Section III are open-loop controls. All controls are bang-bang solutions. In practice, the subject does not always strictly follow the light schedule. We apply a feedback controller based on Nearest Neighbor Search. After solving the optimal control for each initial condition $X_i(0) \in \chi, i \in \{1, 2, ..., 552\}$ in Eq. (16), we have the *i*-th trajectories of controls $\overline{u}_{TO}(t, X_i(0))$ or $\overline{u}_{QC}(t, X_i(0))$, states $(x_i(t), x_{c,i}(t))$ and reference $(x_{ref,i}(t), x_{c,ref,i}(t))$ respectively. Let T_i , N_i be the final time, and the number of time steps in the *i*-th case. At the *j*-th time step $t_j \in [0, T_i]$, the control is $\overline{u}_{TO}(t_j, X_i(0))$ or $\overline{u}_{QC}(t_j, X_i(0))$, the states are $(x_i(t_j), x_{c,i}(t_j))$ and the



Fig. 5. This plot shows the difference in T_{ϵ} between the MCQC entrainment and the time-optimal entrainment $T_{\epsilon,MCQC} - T_{\epsilon,TO}$ for all initial conditions (top pannel) and the distribution of the differences in percentage (bottom panel).

reference states are $(x_{ref,i}(t_j), x_{c,ref,i}(t_j))$. i, j are positive integer indices. The reference phase is:

$$\theta_{ref,i}(t_j) \triangleq -\tan^{-1}\left(\frac{x_{c,ref,j}(t_j)}{x_{ref,j}(t_j)}\right), \theta_{ref,i}(t_j) \in [0, 2\pi).$$

We denote $(\overline{u}_{TO}(t_j, X_i(0)), x_i(t_j), x_{c,i}(t_j), \theta_{ref,i}(t_j))$ as a data point $(\overline{u}_{TO,i,j}, x_{i,j}, x_{c,i,j}, \theta_{ref,i,j})$. Then

$$\overline{U}_{TO} \triangleq \{ (\overline{u}_{TO,i,j}, x_{i,j}, x_{c,i,j}, \theta_{ref,i,j}) \\
|i \in \{1, ..., 552\}, j \in \{1, \cdots, N_i\} \}$$
(23)

represents the set of all data points in the time-optimal entrainment. Similarly, with $\bar{u}_{QC,i,j}$ being the MCQC control, the set represents all data in the MCQC entrainment is

$$\overline{U}_{QC} \triangleq \{ (\bar{u}_{QC,i,j}, x_{i,j}, x_{c,i,j}, \theta_{ref,i,j}) \\ |i \in \{1, \dots, 552\}, j \in \{1, \cdots, N_i\} \}.$$
(24)

The feedback law for states (x, x_c, θ_{ref}) is defined as

$$B(x, x_c, \theta_{ref}) = \bar{u}_{k,\ell}, \text{ where}$$

$$(\overline{u}_{k,\ell}, x_{k,\ell}, x_{c,k,\ell}, \theta_{ref,k,\ell}) \in \overline{U}_{data}, data \in \{TO, QC\},$$

$$k, \ell = \underset{i \in [1,552], j \in [1,N_i]}{\arg \min} |(x, x_c, \theta_{ref}) - (x_{i,j}, x_{c,i,j}, \theta_{ref,i,j})|.$$

$$(25)$$

We tested both feedback with perturbed light schedules for cases that have initial states that show big jumps in the entrainment time with the initial states perturbation, marked in red in Fig. 3.a, because we expect that the input perturbation will have some major impacts on the entrainment process. The simulation steps can be summarized as follows:

- Randomly pick 5 times $\{t_1, \dots, t_5\}$ in [0, 96] h.
- Start with an initial condition $X(0) \in \chi$ in Eq. (16). We denote the control and the states at t as \overline{u} and $X(t,\overline{u})$. While $||X_{ref}(t) - X(t,\overline{u})||^2 > 0.01$, drive the system with control \overline{u} using the feedback law in Eq. (25). If the current time $t \in \{[t_i - 0.5, t_i + 0.5] | i \in \{1, \cdots, 5\}\}$, then the value \overline{u} changes from u_{max} to 0 or 0 to u_{max} .
- Drive the system with $\bar{u} = u_{ref}$ until t = 336 h.

• Compute the cumulative quadratic cost

$$J = \int_0^{350} \left(X_{ref}(t) - X(t, \bar{u}) \right)^2 dt.$$
 (26)

We tested the feedback using time-optimal data and MCQC data for 5 initial conditions $X(0) \in \chi$ in Eq. (16). For each case, we performed the simulations 50 times and $\{t_1, \dots, t_5\}$ were kept the same for the time-optimal feedback and the MCQC feedback. The statistics of time taken to reach the error threshold $\epsilon = 0.01$, T_{ϵ} and the cumulative quadratic costs J for 5 cases are summarized in a spreadsheet that can be found at https://github.com/KiraTau/Value-Function-Continuity.git. We plotted the normalized costs Jand entrainment time T_{ϵ} in Fig. 6. The costs J and entrainment time T_{ϵ} are normalized by dividing the unperturbed J and T_{ϵ} for the same initial conditions in Fig. 3. Using a paired t-test, we also find that the mean of J and T_{ϵ} are both significantly lower in the MCOC feedback control than in the time-optimal feedback control. Input perturbation causes smaller variations in J and T_{ϵ} in the MCQC feedback than in the time-optimal feedback. These results show that the MCQC feedback control is more robust to input perturbation than the time-optimal feedback.



Fig. 6. Box plots of the normalized quadratic costs J (top panel) and entrainment time T_{ϵ} (bottom panel) for MCQC and time-optimal feedback. Blue bars represent the time-optimal feedback and white bars represent the MCQC feedback. Red crosses represent outliers.

V. CONCLUSION

In this paper, we study the continuity properties of the value function in circadian rhythm entrainment problems. Time-optimal entrainment is not robust for circadian rhythm entrainment because the value functions are not Lipschitz continuous and the entrainment time is sensitive to state perturbation. Using entrainment time as a metric does not always represent how close the circadian states are to the reference states. We propose the MCQC entrainment and prove that its value function is Lipschitz continuous and observe that this objective does not sacrifice entrainment speed too much. We also find that if we use a feedback policy method to control circadian rhythm entrainment, the

MCQC feedback is more robust against input perturbation than the time-optimal feedback.

REFERENCES

- R. Foster and L. Kreitzman, Circadian rhythms: a very short introduction. Oxford University Press, 2017.
- [2] M. Figueiro and R. White, "Health consequences of shift work and implications for structural design," *Journal of Perinatology*, vol. 33, no. 1, pp. S17–S23, 2013.
- [3] M. E. Jewett, D. B. Forger, and R. E. Kronauer, "Revised limit cycle oscillator model of human circadian pacemaker," *Journal of biological rhythms*, vol. 14, no. 6, pp. 493–500, 1999.
- [4] K. Serkh and D. B. Forger, "Optimal schedules of light exposure for rapidly correcting circadian misalignment," *PLoS computational biology*, vol. 10, no. 4, p. e1003523, 2014.
- [5] A. A. Julius, J. Yin, and J. T. Wen, "Time optimal entrainment control for circadian rhythm," *PloS one*, vol. 14, no. 12, p. e0225988, 2019.
- [6] D. Wilson, "Optimal control of oscillation timing and entrainment using large magnitude inputs: An adaptive phase-amplitude-coordinatebased approach," *SIAM Journal on Applied Dynamical Systems*, vol. 20, no. 4, pp. 1814–1843, 2021.
- [7] Z. Tao, A. Julius, and J. T. Wen, "Robustness of optimal circadian rhythm entrainment under model perturbation," in 2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), pp. 1–4, IEEE, 2023.
- [8] C. Mott, D. Mollicone, M. Van Wollen, and M. Huzmezan, "Modifying the human circadian pacemaker using model based predictive control," in *Proceedings of the American Control Conference*, vol. 1, pp. 453– 458, 2003.
- [9] N. Bagheri, J. Stelling, and F. J. Doyle III, "Circadian phase resetting via single and multiple control targets," *PLoS computational biology*, vol. 4, no. 7, p. e1000104, 2008.
- [10] J. H. Abel and F. J. Doyle III, "A systems theoretic approach to analysis and control of mammalian circadian dynamics," *Chemical Engineering Research and Design*, vol. 116, pp. 48–60, 2016.
- [11] L. D. Berkovitz, "Optimal feedback controls," SIAM journal on control and optimization, vol. 27, no. 5, pp. 991–1006, 1989.
- [12] M. Pirotta, M. Restelli, and L. Bascetta, "Policy gradient in lipschitz markov decision processes," *Machine Learning*, vol. 100, pp. 255–283, 2015.
- [13] T. Kobayashi, "L2c2: Locally lipschitz continuous constraint towards stable and smooth reinforcement learning," in 2022 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS), pp. 4032– 4039, IEEE, 2022.
- [14] N. Petrov, "On the bellman function for the time-optimal process problem: Pmm vol. 34, n 5, 1970, pp. 820–826," *Journal of Applied Mathematics and Mechanics*, vol. 34, no. 5, pp. 785–791, 1970.
- [15] R. Yue, "Properties of the bellman function in time-optimal control problems," *Journal of optimization theory and applications*, vol. 94, pp. 155–168, 1997.
- [16] M. Maghenem and R. G. Sanfelice, "Lipschitzness of minimal-time functions in constrained continuous-time systems with applications to reachability analysis," in 2020 American Control Conference (ACC), pp. 937–942, IEEE, 2020.
- [17] P.-C. Aubin-Frankowski, "Lipschitz regularity of the minimum time function of differential inclusions with state constraints," *Systems & Control Letters*, vol. 139, p. 104677, 2020.
- [18] A. Davini, "Bolza problems with discontinuous lagrangians and lipschitz-continuity of the value function," *SIAM journal on control* and optimization, vol. 46, no. 5, pp. 1897–1921, 2007.
- [19] V. Veliov, "Lipschitz continuity of the value function in optimal control," *Journal of optimization theory and applications*, vol. 94, no. 2, pp. 335–363, 1997.
- [20] V. I. Bogachev and M. A. S. Ruas, *Measure theory*, vol. 1. Springer, 2007.
- [21] A. Papachristodoulou, J. Anderson, G. Valmorbida, S. Prajna, P. Seiler, P. A. Parrilo, M. M. Peet, and D. Jagt, SOS-TOOLS: Sum of squares optimization toolbox for MATLAB. http://arxiv.org/abs/1310.4716, 2021.
- [22] J. A. Andersson, J. Gillis, G. Horn, J. B. Rawlings, and M. Diehl, "Casadi: a software framework for nonlinear optimization and optimal control," *Mathematical Programming Computation*, vol. 11, pp. 1–36, 2019.