Nonlinear control studies for circadian models in system biology

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Notations

1. Biology and Biochemical Systems

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid created after transcription</td>
</tr>
<tr>
<td>rRNA</td>
<td>ribosomal ribonucleic acid providing a mechanism for decoding mRNA</td>
</tr>
<tr>
<td>tRNA</td>
<td>transfer ribonucleic acid corresponding to the appropriate mRNA codon</td>
</tr>
<tr>
<td>A</td>
<td>adenine, a chemical base</td>
</tr>
<tr>
<td>G</td>
<td>guanine, a chemical base</td>
</tr>
<tr>
<td>C</td>
<td>cytosine, a chemical base</td>
</tr>
<tr>
<td>T</td>
<td>thymine, a chemical base</td>
</tr>
<tr>
<td>U</td>
<td>uracil, a chemical base</td>
</tr>
<tr>
<td>Hb</td>
<td>haemoglobin, a chemical formula for blood</td>
</tr>
<tr>
<td>$O_2$</td>
<td>oxygen, a chemical formula for oxygen</td>
</tr>
<tr>
<td>n</td>
<td>number of molecules</td>
</tr>
<tr>
<td>x</td>
<td>concentration of ligand (atom, ion, or molecule)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>the concentration rate of main elements in the chemical reaction</td>
</tr>
<tr>
<td>frq</td>
<td>frequency, a gene in mechanism of Neurospora circadian rhythms</td>
</tr>
<tr>
<td>FRQ</td>
<td>protein of frq gene</td>
</tr>
<tr>
<td>Bmal1</td>
<td>PAS protein or MOP3, a gene in mechanism of mammalian rhythms</td>
</tr>
<tr>
<td>CKI$\epsilon$</td>
<td>casein kinase , a gene in mechanism of mammalian rhythms</td>
</tr>
</tbody>
</table>
\( Rev - Erb \alpha \) orphan nuclear receptor, a gene in mechanism of mammalian rhythms

\( Per_{2} \) period, a gene in mechanism of mammalian rhythms

\( Cry \) cryptochrome, a gene in mechanism of mammalian rhythms

\( BMAL1 \) protein of Bmal1 gene

\( PER_{2} \) protein of Per2 gene

\( CRY \) protein of Cry gene

2. Mathematics

\( \eta \) periodic orbit or limit cycle

\( \gamma \) lipschitz constant

\( \nu_{p} \) one-sided Lipschitz constant

\( k \) constant number

\( \theta \) Constant number

Vector of unknown parameters

\( t \) time index

\( f(\cdot) \) a function

\( \phi \) vector of input parameters

\( CT \) transpose of constant matrix \( C \)

\( P \) positive definite matrix

\( \hat{x} \) estimate of state variable \( x \)

\( u \) system input

\( y \) system state variables

system outputs

\( \Gamma^{*} \) adjoint Green’s function

\( s(\cdot) \) classical coefficient sensitivity

\( \rho \) vector of parameters

\( \mathbb{R}^{n} \) the n-dimensional Euclidean space
Notations

\( \subset \) \hspace{1cm} \text{subset of} \\
\( \| x \| \) \hspace{1cm} \text{the norm of a vector } x \\
\( \| \| \) \hspace{1cm} \text{the absolute value} \\
\( < \) \hspace{1cm} \text{less than} \\
\( \leq \) \hspace{1cm} \text{less than or equal to} \\
\( \forall \) \hspace{1cm} \text{for all} \\
\( < , , > \) \hspace{1cm} \text{euclidean product on } \mathbb{R}^n \\
\( \sum \) \hspace{1cm} \text{summation} \\
\( \in \) \hspace{1cm} \text{belongs to} \\
\( \rightarrow \) \hspace{1cm} \text{tends to}
Publications

Journal papers

1. L. TonThat and Z. Ding, Circadian Phase Resetting Using Nonlinear Output-Feedback Control, accepted for publication in *Journal of Biological Systems (JBS)*.

2. L. TonThat and Z. Ding, Reduced-order observer design for a class of nonlinear systems and its application to a circadian model, prepared to submit to *Transactions of the Institute of Measurement and Control*.

3. L. TonThat and Z. Ding, Recovery of circadian phases with adaptive back-stepping, preparing for submission to *BMC Systems Biology*.

Conference papers

1. L. TonThat and Z. Ding, One-sided Lipschitz observer design for circadian models, accepted for presentation at the *50th Conference on Decision and Control*, Orlando, USA, 2011

2. L. TonThat and Z. Ding, Circadian Phase Control By Using Observer-based Back-stepping Design, accepted for presentation at the *9th IEEE International Conference on Control & Automation (IEEE ICCA’11)*, Santiago, Chile, 2011
Abstract

Circadian rhythms exist in almost all living species, and they occupy an important role in daily biological activities of these species. This thesis deals with reduction of measurements in circadian models, and recovery of circadian phases. Two mathematical models of circadian rhythms are considered: a 3rd order model for Neurospora and a 7th order model for Mammals.

The reduction of measurements in circadian models is demonstrated in this thesis by the proposals for an observer design for the two mathematical models of circadian rhythms. Both mathematical models contain strong nonlinearities, which make the observer design challenging. Two observer designs, reduced-order and one-sided Lipschitz, are applied to the circadian models to tackle the nonlinearities. Reduced-order observer design is based on a state transformation to make certain nonlinearities have no impact on the observer errors, and the design of one-sided Lipschitz observer is based on systems with one-sided Lipschitz nonlinearities. Both observer designs are based on the existing methods in literature. The existing method of reduced-order observer has been applied to a class of multi-output nonlinear systems. A new reduced-order observer design which extends the existing one in literature is presented in this thesis. In this new reduced-order observer method, the observer error dynamics can be designed by choosing the observer gain, unlike the existing one, where the observer error dynamics depend on the invariant zeros under certain input-output map.

The recovery of circadian phases is undertaken to provide a solution to phase shifts which occur in circadian disorders. The restoration of circadian phases is performed by the synchronizations of trajectories of a controlled model with trajectories of a reference model. The reference model and the controlled model have phase differences, and both these models are based on a given 3rd order model of Neurospora circadian rhythms. The phase differences are reflected by different initial conditions, and by parameter uncertainty. The synchronizations of the two models are performed by using back-stepping method for the case of different initial conditions, and by using adaptive back-stepping method for the remaining case.
Several simulation studies of the proposed observer designs and the proposed schemes of synchronizations are carried out with the results shown in this thesis.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Finally, i would like to thank all of my friends who helped and supported me during three years of my PhD course.
Chapter 1

Introduction

1.1. Introduction

The rotation of the Earth around the Sun gives the concepts of daytime and night-time. A complete cycle of the Earth around the Sun is about 24 hours. Therefore, the total period of daytime and night-time is 24 hours. 24 hours is also the average period for biological activities of all living organisms on the Earth. For almost every living organisms, their daily biological activities are governed by rhythms. These rhythms are known as circadian rhythms.

Circadian rhythms exist in most living species, and they are self-sustained and periodic oscillations [9]. Besides self-sustained and periodic oscillations, entrainment of light/dark cycles from environment is another property of circadian rhythms. Circadian rhythms are known to scientists because of their important roles in living species. In plants, the circadian rhythms affect their biological activities such as movements of leaf, tissue growth and differentiation, and enzyme activities [84]. In humans, circadian rhythms can affect normal life under the symptoms such as jet lag and sleep deprivation. These symptoms are caused by disruption of circadian rhythms. Disruption of circadian rhythms can lead to more serious diseases. The result obtained in [55] suggests that disruption of circadian rhythms can increase the risk of cancer. In order to avoid mischievousness of circadian disruptions, a deep understanding of circadian rhythms is required.

The nature of circadian oscillations is shown through its mechanism. Mechanism of circadian rhythms is based on dynamics of some certain genes and proteins. Different species have different genes and proteins contributed to their mechanisms of circadian rhythms. Along with the discovery of DNA and the advancements in technologies, the corresponding genes and
proteins taking part in the mechanisms of circadian rhythms in living species are identified. The remarkable discovery of the genetic basis for mammalian circadian rhythms in 1994 [82] has led to more results of key genes in mammals. Period genes [4], Cry genes [80], Clock gene, Bmal1 gene [12], and orphan nuclear reactor REV − ERBα [60] have been reported in later years. In other species, Neurospora and Drosophila, the key genes contributed to mechanisms of circadian rhythms are also identified. The results of these key genes are summarized in [69]. With the identified key genes, mathematical models of circadian rhythms can be developed.

Mathematical modelling is an important tool created to test and to develop further analysis of a mechanism or a process. Construction of mathematical model is originated by the desire of transformation of conceptual models into mathematical formulations which can allow critical testing [8]. Conceptual models are models of reality which can describe basic features of a process or mechanism in practice [8]. Based on dynamics of identified genes and their productions (proteins), mathematical models of circadian rhythms have been developed. The results presented in [30] and [85] have shown a mathematical model of Neurospora circadian rhythms and a mathematical model of mammalian circadian rhythms. These mathematical models are two typical examples of mathematical models proposed for circadian rhythms of Neurospora and mammals. These models are created based on the mechanism of the Goodwin model [31], and they are used throughout this thesis. With the existence of mathematical models of circadian rhythms, research studies of various aspects of circadian rhythms have been carried out, e.g. amplitude of circadian oscillations entrained by 24h light/dark cycles [48], entrainment in a model of the mammalian circadian oscillator [28], robustness of circadian models to noise ([29], [50], [76]), and sensitivity analysis [34], [35]. The existence of circadian models have also attracted the attention of control researchers. Some inspired research areas have been introduced in [75]. These research areas include four topics for application of control theory: adaptive control of bifurcation parameters, robust stability from structure, system identification and reverse engineering, and disturbance rejection with signal detection [75]. We shall focus on reduction of measurements in circadian models and phase recovery of circadian rhythms.
Reduction of measurements of a circadian model has not been much considered in theory. This may be due to the advancements of technologies, and the developments of many methods used in experiments which make measurements of circadian rhythms become easier and faster in practice. This may also be due to the complexities of the circadian models with strong non-linearities, and lack of appropriate methods in theory. Nevertheless, whatever the reasons given, the reduction of measurements is still important to circadian models, especially to circadian models having high order and strong nonlinearities. For circadian models having high order and strong nonlinearities, the measurements of the internal state variables of these models are not always easy for direct calculation. They are sometimes either difficult for direct calculation or time-consuming. With reduction of measurements, the internal state variables which are difficult to measure can be avoided. With these state variables avoided, the time-consuming for measurements is also decreased. In control theory, there is a tool which can show the reduction of measurements. This tool is known as observer. In this thesis, we propose observer designs for circadian models.

Opposite to reducing measurements of circadian models, the recovery of circadian phases is an important topic in the research studies of circadian rhythms. This topic originated from the desire of finding medical treatment for disorders of circadian rhythms in practice. Circadian disorders are the disruptions of internal clock system. Circadian disorder usually occurs when the internal rhythms cannot keep up with changes in external environment rhythms. The mismatches occurred between internal rhythms and external environment rhythms result in the phase shifts between them. Removal of these phase shifts is the task of medical treatment. With phase shifts removed, the altered circadian rhythms restore to their normal status. Besides medicine, in reality, the usual medical treatment of circadian disorder is based on the entrainment of circadian rhythms to light/dark cycles. In theory, several results have been reported on circadian phase resetting in literature (for example, [5], [49], [74]). Continuing with the phase recovery of circadian rhythms as an objective, we propose back-stepping and adaptive back-stepping control design methods to deal with this problem.
1.2. Aims and Objectives of the thesis

This thesis concentrates in two aspects of circadian rhythms and circadian models. They are:

- reduction of measurements for circadian models
- removal of the phase shifts caused by the disruption of circadian rhythms

In order to fulfill these two tasks, we provide

- recent results of Lipschitz and reduced-order observer designs to two circadian models which are: a 3rd order model for Neurospora and a 7th order model for Mammals.
- a new design method which extends performance of the reduced-order observer used in this thesis
- the back-stepping and adaptive back-stepping methods to recover the phases shifts in Neurospora circadian model.

1.3. Outlines of the thesis

Besides chapter 1, the rest of the thesis is arranged as following:

Chapter 2 presents biological studies, sensitivity analysis, mathematical models of circadian rhythms, and Lyapunov stability theorem & observer designs. Biological studies include the reviews of suprachiasmatic nucleus, DNA, genes, proteins, and the biological processes involved in the creation of proteins from genes. Sensitivity analysis is the important process of investigate the behaviour of circadian phases. With limit cycles, isochrones, local sensitivity analysis, application of sensitivity analysis to circadian models summarized in this chapter, the sensitivity analysis which has been carried out in literature is briefly described. In the next part of this chapter, mechanisms and equations of two mathematical models of Neurospora and mammalian circadian rhythms are described. These two mathematical models are the most important results in this chapter because they will be used throughout the thesis. The final part of this chapter reviews Lyapunov theorem and some basic observer designs which are important tools in linear
and nonlinear control theories. The high gain observer recently used for circadian model of Neurospora rhythms is also covered in this part.

Chapter 3 deals with the observer designs to circadian models. Three observer designs are proposed in this chapter. These three observer designs are different to the high gain observer design discussed in chapter 2. Detailed design of one-sided Lipschitz observer is firstly described. The proposed one-sided Lipschitz observer design is based on the recent result in literature. The reduced-order observer design is considered next. Similar to the proposed one-sided Lipschitz observer method, this reduced-order observer has been also presented in literature. Extended design of this reduced-order observer is the final observer design considered. The three proposed observer designs are then applied to two mathematical models of circadian rhythms given in chapter 2. The performances of these observer designs are shown by simulation studies with the results presented in this chapter. With the results obtained, the comparisons of these performances are carried out. The discussions of performances of the proposed observer designs are also included in this chapter.

Chapter 4 deals with circadian phase resetting using nonlinear output feedback control. The circadian phase resetting is shown by the synchronizations of altered trajectories with reference trajectories via back-stepping method. Altered trajectories are generated from a controlled model while reference trajectories are generated from a reference model. Detailed control design, back-stepping method, and stability analysis are presented in this chapter. In this chapter, both reference model and controlled model are based on the mathematical model of Neurospora circadian rhythm presented in chapter 2. Furthermore, the phase differences between these two models are caused by choosing different initial conditions. The controlled model generating the altered rhythms is assumed to have unknown state variables. An observer design is required to estimate the unknown states. One-sided Lipschitz observer design described in chapter 3 is chosen to estimate these unknown states. Its design procedure is presented in this chapter. After both the control and observer methods have been applied, discussions of their performances are carried out. Details of these discussions are included in this chapter.
Chapter 5 also deals with circadian phase resetting. Unlike previous chapter, the phase differences between reference and controlled models caused by a change in amplitude of an unknown parameter. The change in amplitude of an unknown parameter can cause unexpected oscillations. If controlled model is assumed to have unknown state variables, these unexpected oscillations make observer design of this model, and the control design based on it become more difficult. In order to prevent this difficulty, we consider a simple case for controlled model where all measurements of this model are assumed to be available. As a result, observer design is not required in this chapter. Without observer involved, the synchronizations are carried out using adaptive back-stepping method. Design procedure of adaptive back-stepping and the stability analysis are presented in this chapter. Similar to chapter 4, discussion of performances of control design is also carried out. This discussion is included in this chapter.

Chapter 6 summarizes the results achieved in chapters 3,4, and 5. In addition, a brief discussion of future direction of research is included in this chapter.
Chapter 2

Background studies

2.1. Biological studies

2.1.1. Suprachiasmatic nucleus

Suprachiasmatic nucleus or SCN plays an important role in mammalian circadian rhythms. The ability to readjust its own oscillations with the rhythms of the external world, and the ability to organize the internal rhythms of peripheral tissues (e.g., liver, kidney) are two characteristics of SCN. SCN is a small region of anterior hypothalamus which is located above optic chiasm. Because of this strategic position, SCN is able to directly receive the information regarding environmental lighting conditions via retina-to-SCN pathways [67]. Research studies of SCN have found that SCN consists of two tiny structures, and each of them contains approximately 8000 to 10,000 neurons [79]. For SCN, all of its activities are carried out via these neurons.

Because the neurons contained in SCN have independent rhythms [86], SCN is cell autonomous. Experimental results reported in [41] have shown that even when SCN is isolated from receiving the environmental light cycles, it still oscillates with its own period. The independent oscillations of SCN are affected by the light input which is sent from the external rhythms. After the visual input which carries the information of environmental light-dark entrainment has been captured, since SCN is autonomous, it adjusts itself to maintain synchronization with external rhythms. Then, with new phases of oscillations, SCN coordinates the timing of other oscillators located in peripheral tissues [68]. Since SCN allows the internal rhythms to receive entrainment of lightning cycles from environment, its destruction can lead to the elimination of this ability. The result achieved in [71] shows the total loss of entrainment to LD (light/dark) cycle of hamsters when their brains have been removed. The hamsters with the removal of SCN
became arrhythmic, and they maintained their daily activities by free-running rhythms. The arrhythmic animals can recover their circadian rhythms through transplantation of SCN, and these restored circadian rhythms have the properties of the donors [64].

2.1.2. DNA

The discovery of DNA has marked an important advancement in bioscience. Throughout the years, it becomes a very important tool which has been applied to many fields of technologies such as genetic engineering, bioinformatics, DNA nanotechnology and so on. Deoxyribonucleic acid or known as DNA exists in the nucleus of every living cell. DNA was firstly discovered by a young Swiss physician named Frederick Miescher in 1869 [15]. However, the significance of this discovery was not fully recognized by Frederick Miescher at that time because he only thought DNA as ‘nuclein’ which has only some important roles in cells [15]. One significant breakthrough of DNA is the result obtained in [3] where DNA is suspected to carry the genetic information. This is later confirmed in [36] that DNA has its role in heredity. The structure of DNA was firstly revealed in 1953 [83].

DNA is a genetic material which carries the genetic information of most living organisms. The information of DNA is contained in the association of four chemical bases: adenine, guanine, cytosine, and thymine which are abbreviated as $A$, $G$, $C$ and $T$. $A$ always pairs with $T$, and $G$ always with $C$. The pairs $A-T$ and $G-C$ are called the base pairs in molecular biology and genetics. The bond which creates the connection in base pairs is hydrogen bond. These base pairs are also attached with other chemical elements sugar and phosphate. The combination of sugar and base is called a ‘nucleoside’, while the attachment of base pair, sugar, and phosphate is called a ‘nucleotide’ [66]. Chemistry formulas of adenine, guanine, cytosine, and thymine are shown in Figure 2.1.

The arrangement of nucleotides forms a shape which is called double helix from scientists. This double helix is the representation of molecule model of DNA which is suggested in [83]. The firstly suggested form of DNA, double helix, is then proved correctly afterwards. The double helix has an image of a twisted ladder. Each of this ladder’s rungs is formed by base pairs while
the vertical sidepieces of the ladder are formed by the sugar and phosphate molecules. These two vertical sidepieces of the ladder, the two long strands, are anti-parallel to each other. They run in two opposite directions in which one runs in the 5’ to 3’ and the remaining one runs in the 3’ to 5’ direction. 5’ and 3’ are the nomenclature derived from the system of sugar ring [66]. A segment of DNA is given in Figure 2.2.

One of the important characteristics of DNA is the ability to replicate. DNA replication process is the basis for heredity of DNA. The purpose of this process is to create two identical DNA from an original DNA. According to [66], in general, this process has three stages which are initiation, elongation and termination. DNA polymerases have important role in DNA replication. They help to synthesize the old strands with the new created strands after the cells are divided.

2.1.3. Genes and Proteins

Gene is an instruction manual showing how to create and operate for all parts of a living organism. It is considered as a unit of heredity which composes of DNA. One strand of DNA can contain a lot of genes. Variety of nucleotides of DNA molecule leads to variety of genes
in a body. Genes are represented by sequences. A gene is a sequence of DNA. One of the known methods to examine the DNA for protein-coding regions is the open reading frame (or ORF) [17]. By using ORF to “read” DNA, sequences of genes are identified. Although ORF has a start codon, it does not have stop codons [17]. The ORF normally starts with a triplet of DNA bases (ATG), and possibly ends at stop signal which is also a triplet of DNA bases (either TGA, TTA or TAG) [66].

Production of a gene is a protein. Proteins are synthesized after the translation process of (mRNA) genes. If genes are instructions manuals, proteins are the machines executing the commands as instructed. Proteins are essential to living organisms. A living body requires proteins to be functional. Proteins are normally spread out in every part of a body in order to keep this body operating.

Since proteins are produced by genes, proteins have indirect relationship with DNA. In other words, a gene is the intermediary point between a DNA and its encoded protein. The gene which is used to communicate between DNA and protein is ribonucleic acid (RNA). There are many types of RNA such as ribosomal RNA (rRNA) or transfer RNA (tRNA), messenger RNA (mRNA). Based on the type of encryption of a gene, the corresponding RNA is produced. For
instance, if a protein is produced from a gene, the RNA must be the mRNA.

2.1.4. Transcription and Translation processes

Proteins are produced from genes via transcription and translation processes. Transcription process is the process by which an RNA copy of one of the strands in the DNA double helix is created. This process occurs in a nucleus or in cytoplasm based on the type of cell of a living organism. There are two types of cells which are prokaryotic cell and eukaryotic cell. Eukaryotic cell contains complex structures, and it has a clear division between nucleus and cytoplasm. A representative of living species having such kind of cell is mammal. For eukaryotic cell, transcription process takes place in nucleus. The prokaryotic cell is different to eukaryotic cell. This cell contains simple structure, and does not have a nucleus. Prokaryotic cell is found in bacteria. For prokaryotic cell, transcription and translation processes take place in cytoplasm.

The transcription process starts with the break of the hydrogen bonds between complementary nucleotides of DNA. During the transcription of mRNA, the DNA is read from ‘5’ to ‘3’ direction. This is opposite to DNA replication where DNA is read in ‘3’ to ‘5’ direction. After the break of two strands of DNA, only one strand of DNA is selected as a template strand for transcription. The remaining strand of DNA is called coding strand. RNA polymerase is then used to synthesize the four chemical bases $A$, $T$, $G$, and $C$ on the template strand with $U$, $A$, $C$, and $G$ respectively on the mRNA. Note that instead of the usual chemical base Thymine (abbreviated $T$), $T$ is replaced by Uracil (abbreviated $U$) on mRNA. The transcription process is stopped when it encounters a stop signal (a codon). Codon is a sequence of chemical bases. Stop signal or stop codon is usually a sequence of three nucleotides (three chemical bases). For transcription process, the stop codons of prokaryotes and eukaryotes are different. After the synthesis, a full mRNA strand is completed. The sequence of mRNA is the same as coding strand’s sequence except the replacement of $U$ to $T$.

The final step to produce protein is the translation process. Translation is the process which is used to decode the created mRNA after transcription process. The production of translation process is linear chain of amino acids which are called polypeptides or proteins. The translation
process is performed by ribosomes which are the complexes of RNA and protein. Ribosomes ‘read’ mRNA and translate it into sequence of protein. The translation is implemented by following the rule of genetic code. Different to transcription process, translation process has initial point or start codon. The initial point for reading ribosomes is normally used with the sequence \textit{AUG}. Subsequently, the reading continues with three nucleotides at a time. The ‘reading’ process only stops when one of three codons (\textit{UAA, UGA, UAG}) is met. After this process finishes, a protein is produced.

2.2. Sensitivity analysis

2.2.1. Limit cycles

Oscillation is an important phenomenon which occurs in dynamic systems. A typical image of oscillation is the swing of pendulum. Another example of oscillation is the variation in dynamic of a spring in mass-spring system. The dynamics of a pendulum and dynamics of a spring are periodic. Therefore, an oscillation is also known as a periodic motion. In a phase plane or phase portrait, periodic motion is represented by a closed trajectory. For nonlinear systems, this closed trajectory is called a ‘limit cycle’.

Limit cycle is a typical phenomenon of nonlinear systems. Linear systems do not have limit cycle. Limit cycles take the form of isolated closed curves corresponding to periodic motion in the phase plane [18]. More precisely, in limit cycles, all neighboring trajectories spiral toward to neighbored region of a particular point (equilibrium point) or away from it. An example of limit cycle is Van der Pol limit cycle. This limit cycle plays an important role in the development of nonlinear dynamics.

The direction of neighbouring trajectories (spiral toward or away) leads to the concepts of stability of limit cycles. There are three cases of stability properties of limit cycles: stability, half-stability and instability. If all neighbouring trajectories approach limit cycles, the limit cycles are stable. On the contrary, if these trajectories move away from limit cycles, the limit cycles are unstable. Being neither stable nor unstable is called half-stable or semi-stable. Poincare-
Bendixson Criterion theorem can be used to predict the existence of limit cycles or the existence of periodic orbits [43].

### 2.2.2. Isochron

Phase tracking is an important research area of circadian rhythms. Besides identification of periods of every living organism, phase tracking can help to observe the changes of circadian oscillations against with varied types of the inputs, e.g. the light. Based on the effect of considered inputs to the changes of circadian oscillations, medical treatments may be developed to solve the problems occurring in circadian rhythms, e.g. jet lag, sleeping disorders. In theory, one of the methods is developed to deal with the phase tracking is the concept of ‘isochron’.

The concept of ‘isochron’ was firstly developed by Winfree in his research of the patterns of phase in biological cycles [87]. Further analysis of this concept is carried out in [32], and it is later summarized again in [88]. Consider a dynamic system which has a known periodic orbit \( \eta \) with certain period \( T \), and it has an initial condition \( x^n(0) \). Another initial condition \( x_{test}(0) \neq x^n(0) \) which is in the basin attraction of periodic orbit \( \eta \) is chosen. This initial condition \( x_{test}(0) \) does not belong to limit cycle or periodic orbit \( \eta \) as \( x^n(0) \), and it has asymptotic (or latent phase) with \( x^n(0) \). A definition of isochron is given by

**Definition 2.1** ([35]) With \( x^n(0) \) as an initial condition of periodic orbit \( \eta \), the isochron associated with \( x^n(0) \) is the set of all initial conditions \( x_{test}(0) \) such that

\[
\lim_{t \to \infty} \| x^n(t) - x_{test}(t) \| = 0,
\]

where \( x_{test}(t) = \eta(t + \phi(x)) \). \( \phi(x) \) is the latent phase of \( x \), and \( \phi(x) \) takes the values in \([0, T]\) (\( \phi(x) = kT \) where \( k \) is an integer).

Visualization of isochrones is depicted in Figure 2.3. In Figure 2.3, small black circle represents the initial condition \( x^n(0) \) while small yellow circle represents the initial condition \( x_{test}(0) \). The dotted lines \( \phi \) which cut limit cycle \( \eta \) are isochrones. Besides, in Figure 2.3, \( x^n(0) \) and \( x_{test}(0) \) are placed on the same isochron, in other words, \( x_{test} \) is in the basin attraction of limit cycle \( \eta \).
and it has phase equivalent with $x^n$. As the time increases, $x_{test}(0)$ will synchronize with $x^n(0)$.

Through the years, isochron has become an important concept which has been used to investigate the dynamics of biological oscillators [11], [34], [35]. Phase response curve (PRC), an important tool for investigation of circadian phase behaviour, is based on this concept.

### 2.2.3. Local sensitivity

Consider a dynamic system which is presented by

$$\dot{y} = f(y, \phi, t),$$  \hspace{1cm} (2.1)

where $\phi$ is vector of input parameters, $t$ is time, and $y$ is state variable which is assumed to be continuous in $t$ and $\phi$. The differential equation (2.1) has initial condition $y(0) = c$, and it is assumed to have one solution $y(\phi, t)$. Besides, for system (2.1), state variable $y$ is sensitive to parameter $\phi$ if a small change of $\phi$ produces a large change of $y$, and if the small change of $\phi$ does not cause any change of $y$, $y$ is not sensitive to $\phi$. The local sensitivity for the system (2.1)
is defined in [81], and it is described by

$$s (y, \phi_j) = \frac{\partial y (t, \phi_j)}{\partial \phi_j} = \lim_{\Delta \phi_j \to 0} \frac{y (t, \phi_j + \Delta \phi_j) - y (t, \phi_j)}{\Delta \phi_j},$$  

(2.2)

where $s (y, \phi_j)$ is local sensitivity of $y$, $\phi_j$ is the varied parameter, and $\Delta \phi_j$ is the small change of $\phi_j$ parameter.

2.2.4. Application of sensitivity analysis to circadian models

Light can cause changes to phases of circadian rhythms. Understanding of the mechanism of light entrainment of circadian rhythms requires an understanding of circadian phase behaviour under perturbation. Sensitivity analysis is used for this purpose. Research studies of sensitivity analysis have been given in [34] and [35]. In [34] and [35], sensitivity analysis is carried out for circadian phases under several cases of perturbations. Two typical perturbations considered are state and parametric perturbations.

State perturbation is a situation in which the nominal system is perturbed at a state value at time $t$. The perturbation causes the corresponding state to jump off the limit cycle resulting in the possibility of movement of the perturbed state from its current isochron to another isochron. This change of position incurs a phase shift [11], [35]. The perturbed state will finally approach the limit cycle as the time increases. However, because of the phase shift, the perturbed state is not able to recover to its formal status on the limit cycle as it would have been if the state perturbation had not been occurred [35]. If the state perturbation is an infinitesimal perturbation, the phase shift caused by this perturbation can be measured by using the state impulse phase response curve (or sIPRC). A general formula of sIPRC is given in [35], and it is described by

$$s_{IPRC} (x^n (t)) = s_{IPRC_k} (x^n (t)) = \frac{\partial \phi}{\partial x_k} (x^n (t)),$$

(2.3)

where $x$ is state variable of a dynamic system, $\eta$ is the periodic orbit or limit cycle of the considered dynamic system, and $\phi$ is a function of position.
Similar to state perturbation, parametric perturbation also causes the phase shift. Consider a dynamic system which is described by

\[ \dot{x} = f(x(t), \rho), \]

where \( x \in \mathbb{R}^n \) denotes the state variables, \( \rho \in \mathbb{R}^m \) denotes the parameters, \( t \) is the time, and \( f \) is the function of states \( x \) and parameters \( \rho \). For the parametric perturbation, a formula is developed in [34]. According to [34], the formula of parametric sensitivity analysis is given by

\[ \left( \frac{\partial \phi(t)}{\partial \rho_j} \right)_\eta = \sum_{i=1}^{n} Q_i(t) \frac{\partial x_i(t)}{\partial \rho_j}, \]

where \( x \) is the state variable of system (2.4), \( \rho \) denotes the parameters of system (2.4), the subscript \( \eta \) signifies the limit cycle created by system (2.4), and \( \phi \) is the phase of limit cycle \( \eta \) which refers to the relative position on the orbit. Besides, in equation (2.5), \( Q_i \) represents IC (initial condition) phase sensitivity which can be computed using Green’s function. Green’s function is one of the methods used to solve the inhomogeneous equations. This method is named after the name of British mathematician George Green who developed the theory in 19th century. Relevant information and examples of Green’s function have been mentioned in [25]. According to [34], the computation of \( Q_i \) is described by

\[ Q_j = - \lim_{t' \to \infty} \Gamma^*_{i,j}(t, t') \left/ \frac{dx_i(t')}{dt} \right., \]

where \( \Gamma^*_{i,j}(t, t') \) is an adjoint Green’s function of \( \Gamma(\Gamma_{i,j}(t, t')) \).

2.3. Mathematical models of circadian rhythms

2.3.1. Hill equation

One of the mathematical equations which is used in the construction of a mathematical model of circadian rhythms is the Hill equation. The Hill equation is frequently used in biochemical
studies. It was firstly used by Hill in his test for molecules of the haemoglobin [37]. Consider the chemical reactions which are given by

\[ Hb + O_2 \rightleftharpoons HBO_2, \]  
\[ Hb_n + nO_2 \rightleftharpoons HB_nO_{2n} \]

where \( Hb \) represents haemoglobin which is a protein for transporting oxygen in the body by blood cell, and \( O_2 \) is chemical formula of oxygen. For the reactions given in system (2.7), an equation is offered to describe the observations made from these reactions. This equation is later known as Hill equation. The Hill equation is described by

\[ y = \beta \frac{Kx^n}{1 + Kx^n}, \]  

where \( K \) is the equilibrium constant of each chemical reaction, \( n \) shows number of molecules of a chemical element (e.g. \( Hb_n \) represents the cooperation of \( n \) molecules of \( Hb \)), and \( \beta \) is constant number representing the rate or the percentage of the concentration of main elements joined in the reaction. Besides, in equation (2.8), \( x \) represents concentration of ligand (atom, ion, or molecule), and \( y \) is the output.

### 2.3.2. Mathematical model of circadian rhythms in Neurospora

The model given in [30] is considered. This model describes molecular mechanism of circadian rhythms in Neurospora. Its molecular mechanism is based on the negative feedback exerted by FRQ proteins on the expression of \( frq \) gene. Transcription of \( frq \) gene yields messenger RNA (mRNA), and the translation of which synthesizes FRQ protein. Since cell of Neurospora is eukaryotic cell, the transcription process occurs in nucleus. After the translation process which takes place in cytoplasm, these synthesized FRQ proteins are then transferred into nucleus where they inhibit the transcription of \( frq \) gene. A new activation of \( frq \) gene transcription will restart the cycle.
From the given mechanism of Neurospora circadian rhythms, dynamics of these variables, \(frq\) mRNA, FRQ protein, and nuclear FRQ protein, are described by the following set of differential equations:

\[
\begin{align*}
\dot{x}_1 &= v_s \frac{K_i^n}{K_i^n + x_3^n} - v_m \frac{x_1}{K_M + x_1} \\
\dot{x}_2 &= k_s x_1 - v_d \frac{x_2}{K_d + x_2} - k_1 x_2 + k_2 x_3, \\
\dot{x}_3 &= k_1 x_2 - k_2 x_3
\end{align*}
\]  

where \(x_1, x_2,\) and \(x_3\) denote the concentration of \(frq\) mRNA, the concentration of FRQ protein outside nucleus, and the concentration of nucleus FRQ protein respectively. Values of three state variables \(x_1, x_2,\) and \(x_3\) are assumed to only have positive values. According to the mechanism given in [30], parameter \(v_s\) denotes the rate of transcription of \(frq\) gene. The other parameters involved in system (2.9) are \(K_i, n, v_m, K_M\) which represent the threshold constant beyond which nuclear FRQ protein inhibits the transcription of \(frq\), the Hill coefficient showing the degree of co-operativity of the inhibition process, the maximum rate of \(frq\) mRNA degradation, and the Michaelis constant related to the latter process respectively. The parameters \(k_s, k_1, k_2\) denote the rate constant measuring the rate of FRQ synthesis, the rate constants of the transport of FRQ into and out of the nucleus respectively. The parameter \(v_d\) denotes maximum rate of FRQ degradation, and \(K_d\) is the Michaelis constant related to this process. According to the design of 3rd order Neurospora model given in [30], the parameters which are appeared in (2.9) have their default values set as: \(v_s = 1.6nM.h^{-1}, K_i = 1nM, n = 4, v_m = 0.7nM.h^{-1}, K_M = 0.4nM, k_s = 1h^{-1}, v_d = 4nM.h^{-1}, K_d = 1.4nM, k_1 = 0.3h^{-1}, k_2 = 0.15h^{-1}\).

Circadian rhythms of Neurospora are periodic oscillations. Furthermore, these rhythms have a standard period of 21.5 hours [26]. With set of parameters as above, dynamics of state variables of (2.9) sustain periodic oscillations, and the period of these periodic oscillations is guaranteed to be 21.5 hours. Simulation studies have been carried out in MATLAB. The initial condition is chosen as \(x(0) = \begin{bmatrix} 5 & 1 & 1 \end{bmatrix}^T\). The dynamics of the state variables are shown in Figure 2.4.
2.3.3. Circadian model of Mammals

2.3.3.1 Mathematical model of circadian rhythms in Mammals

In this section, a model of mammalian circadian rhythms is briefly introduced. Mammals are high-level species compared with Neurospora. This leads to a more complicated mechanism of mammalian circadian rhythms than the mechanism of Neurospora circadian rhythms. A 7th order model of mammalian circadian rhythms presented in [85] is considered. Mechanism of this model is based on the mechanism which has been presented in [68]. This mechanism consists of negative and positive feedback loops. Each of these feedback loops describes three main processes of transcription, translation, and inhibition of key genes. For mammalian circadian rhythms, the key genes have been identified as Clock, Bmal1, casein kinase (CKIε), orphan nuclear receptor (REV – ERβα), group of Per, and group of Cry genes [45]. However, for the mechanism given in [85], only Per2 gene, Cry gene, and Bmal1 gene are used as parts of mammalian circadian oscillators. Besides these genes, there exists BMAL1* in this mechanism. BMAL1* is considered as a phosphorylated form of BMAL1 [22], or as a complex with CLOCK protein [58], and it activates the transcriptions of Per2 and Cry genes. BMAL1* is used to
replace the heterodimer BMAL1/CLOCK since CLOCK protein is expressed at a constant level [56].

The mechanism of mammalian model starts with the activation of BMAL1* resulting in activation of the transcriptions of Per2 gene and Cry gene to produce Per2 mRNA and Cry mRNA separately. However, in this mechanism, the expressions of Per2 gene and Cry gene, mRNAs of Per2 and Cry, and their proteins, are represented by the same variables [85]. Therefore, instead of independent Per2 mRNA and Cry mRNA, Per2/Cry mRNA is yielded with the activation of BMAL1*. Similar to Neurospora, cell of mammal is eukaryotic cell. Therefore, the transcription processes of all involved genes occur in cytoplasm. A complex of PER2/CRY (heterodimer PER2/CRY) is then synthesized after the translation of Per2/Cry mRNA. This complex is transferred back to the nucleus, and it inhibits the Per2/Cry transcription afterwards. This complex simultaneously activates the transcription of Bmal1 gene. The activation of transcription of Bmal1 gene yields Bmal1 mRNA, and the translation of which synthesize BMAL1 protein. Similar to PER2/CRY protein, BMAL1 protein is synthesized in cytoplasm. This protein is then transported back to nucleus. In nucleus, nuclear BMAL1 in its active form BMAL1* restarts a new circadian cycle.

Based on the mechanism just described, dynamics of involved mRNAs and proteins are governed by the following set of differential equations:

\[
\begin{align*}
\dot{x}_1 &= \frac{v_{1b}(x_7 + c)}{k_{1b}(1 + (\frac{x_7}{k_{1i}})^p) + x_7 + c} - k_{1d}x_1 \\
\dot{x}_2 &= k_{2b}x_1^4 - (k_{2d} + k_{2t})x_2 + k_{2t}x_3 \\
\dot{x}_3 &= k_{2t}x_2 - (k_{2t} + k_{3d})x_3 \\
\dot{x}_4 &= \frac{v_{4b}x_3^m}{k_{4b}^m + x_3^m} - k_{4d}x_4, \\
\dot{x}_5 &= k_{5b}x_4 - (k_{5d} + k_{5t})x_5 + k_{6t}x_6 \\
\dot{x}_6 &= k_{5t}x_5 - (k_{6t} + k_{6d} - k_{6a})x_6 + k_{7a}x_7 \\
\dot{x}_7 &= k_{6a}x_6 - (k_{7} + k_{7d})x_7
\end{align*}
\] (2.10)
where in this case, states \( x_1, x_2, \) and \( x_3 \) represent the concentrations of \( \text{Per2/Cry} \) mRNA, PER2/CRY complex protein in cytoplasm, and PER2/CRY complex in nucleus respectively. States \( x_4, x_5, x_6 \) denote the concentration of \( \text{Bmal1} \) mRNA, the concentration of BMAL1 protein in cytoplasm, and nuclear BMAL1 protein respectively. The remaining state, \( x_7 \), represents the concentration of BMAL1*. All of state variables are assumed to have positive values. The meaning of all parameters involved in system (2.10) are established in [85].

Parameters involved in system (2.10) are chosen such that system (2.10) is able to show its entrainment to light/dark cycle, and its sustainability of periodic oscillations which are dynamic features of circadian rhythms. A global parameter search scheme perhaps could have been used to find such parameters. This scheme is presented in [51] and [52]. Based on the search scheme and the analysis which are carried out in [53], in addition, the experimental observations, values of parameters appeared in system (2.10) are given in [85] with their default values chosen as:

\[
\begin{align*}
v_{1b} &= 9 \text{nM.h}^{-1}, \quad k_{1b} = 1 \text{nM}, \quad k_{1i} = 0.56 \text{nM}, \quad c = 0.01 \text{nM}, \quad p = 8, \quad k_{1d} = 0.12 \text{h}^{-1}, \\
k_{2b} &= 0.3 \text{nM}^{-1}.\text{h}^{-1}, \quad s = 2, \quad k_{2d} = 0.05 \text{h}^{-1}, \quad k_{2t} = 0.24 \text{h}^{-1}, \quad k_{3t} = 0.02 \text{h}^{-1}, \quad k_{3d} = 0.12 \text{h}^{-1}, \\
v_{4b} &= 3.6 \text{nM}.\text{h}^{-1}, \quad k_{4b} = 2.16 \text{nM}, \quad m = 3, \quad k_{4d} = 0.75 \text{h}^{-1}, \quad k_{5b} = 0.24 \text{h}^{-1}, \quad k_{5d} = 0.06 \text{h}^{-1}, \\
k_{5t} &= 0.45 \text{h}^{-1}, \quad k_{6t} = 0.06 \text{h}^{-1}, \quad k_{6d} = 0.12 \text{h}^{-1}, \quad k_{6a} = 0.09 \text{h}^{-1}, \quad k_{7a} = 0.003 \text{h}^{-1}, \quad k_{7d} = 0.09 \text{h}^{-1}.
\end{align*}
\]

**Remark 2.1** Similar to Neurospora model, with the values of parameters set as above, dynamics of state variables of model (2.10) sustain periodic oscillations with period of 24.18h. This period is also the standard period of human circadian rhythms [14].

Simulation studies also have been carried out in MATLAB. The initial condition of (2.10) is chosen with \( x(0) = \begin{bmatrix} 0.25 & 0.28 & 0.85 & 0.3 & 0.25 & 0.6 & 0.855 \end{bmatrix}^T \). The dynamics of the state variables are shown in Figure 2.5.

**2.3.3.2 Analysis of mammalian model**

Along with mathematical model (2.10), analysis has been presented in [85]. This analysis concentrates in investigating the essential of positive feedback loop for the occurrence of oscillations, and the interaction of positive and negative feedback loops.
The essential of positive feedback loop for the occurrence of oscillations of system (2.10) is firstly investigated. The investigation is carried out by comparing the dynamics of mathematical model (2.10) with and without positive feedback at a given strength of negative feedback [85]. In order to do this, parameter $v_{4b}$ showing the rate of transcription of $Bmal1$ mRNA, and $c$ having the role of a constant of activator for transcription of $Per2/Cry$ mRNA are varied [85].

The default value of $c$ has been set as $c = 0.01$ in previous section. With this value of $c$, the threshold value of $v_{4b}$ is found to be $v_{4b} = 0.36$ [85]. We test whether $v_{4b} = 0.36$ is the actual threshold value of $v_{4b}$ or not. Instead of default value $v_{4b} = 3.6$ in the previous section, value of $v_{4b}$ is reset to four values $v_{4b} = 1, v_{4b} = 0.5, v_{4b} = 0.36,$ and $v_{4b} = 0.1$. Except $v_{4b}$, values of the remaining parameters of system (2.10) are unchanged. Dynamics of state variables of system (2.10) are shown from Figure 2.6 to Figure 2.9 for four values of $v_{4b}$.

Results obtained in Figure 2.6 and Figure 2.7 have shown that above $v_{4b} = 0.36$, system (2.10) sustains oscillations. At $v_{4b} = 0.36$, although the oscillations still occur for dynamics of state $x_1, x_2$ and $x_3$, dynamics of $x_4, x_5, x_6$ and $x_7$ are no longer oscillations. As seen in Figure 2.8, dynamics of $x_4, x_5, x_6$ and $x_7$ converge to their steady states. For $v_{4b}$ below
Figure 2.6. Dynamics of state variables of mammalian model with $v_{4b} = 1$

Figure 2.7. Dynamics of state variables of mammalian model with $v_{4b} = 0.5$
Figure 2.8. Dynamics of state variables of mammalian model with $v_{4b} = 0.36$

Figure 2.9. Dynamics of state variables of mammalian model with $v_{4b} = 0.1$
0.36 (\(v_{4b} < 0.36\)), the oscillations are removed. This is shown in Figure 2.9 where at \(v_{4b} = 0.1\), system (2.10) reaches its steady state indicated by a stable concentration of \(Per2/Cry\) mRNA [85]. Based on the results shown for four cases of \(v_{4b}\), \(v_{4b} = 0.36\) is really the actual threshold value of \(v_{4b}\).

Continuing with the investigation of the essential of positive feedback loop for the occurrence of oscillations, we consider system (2.10) without positive feedback loop. In other words, value of \(v_{4b}\) is set to zero. With \(v_{4b} = 0\), dynamics of state variables \(x_4, x_5, x_6,\) and \(x_7\) in positive feedback loop corresponding with this parameter converge to zero steady state. The existence of oscillations of this system now depends on the variation in value of parameter \(c\). Value of \(c\) is adjusted to \(c = 1, c = 0.1, c = 0.02,\) and \(c = 0.01\). Dynamics of state variables of system (2.10) corresponding to these values are shown from Figure 2.10 to Figure 2.13.

![Figure 2.10. Dynamics of state variables of mammalian model at \(c = 1\) and \(v_{4b} = 0\)](image)

As shown in Figure 2.10 and Figure 2.11, at high values of \(c\) (\(c = 0.1\) and \(c = 1\)), without the existence of positive feedback, system (2.10) still sustains oscillations in negative feedback loop. As shown in Figure 2.12, at \(c = 0.02\), the oscillations still occur though the amplitudes of these oscillations are decreased as time increases. At value of \(c\) below 0.02, \(c = 0.01 < 0.02\), system (2.10) does not oscillate. This is shown in Figure 2.13 where dynamics of states \(x_1, x_2\) and \(x_3\) of
Figure 2.11. Dynamics of state variables of mammalian model at $c = 0.1$ and $v_{4b} = 0$

Figure 2.12. Dynamics of state variables of mammalian model at $c = 0.02$ and $v_{4b} = 0$
system (2.10) converge to their steady states. Since the oscillations do not occur below this value of $c$ ($c = 0.02$), then this is considered to be the threshold value of $c$. This threshold value of $c$ obtained is also the threshold value of $c$ which has been given in [85]. Without positive feedback, the existence of oscillations is controlled by variation in value of $c$, and these oscillations occur at above threshold value of $c$. Therefore, it is possible to say that the constant activator $c$ may replace positive feedback for generating oscillations [85].

The second analysis is carried out to investigate the interaction of positive and negative feedback loops. In the mechanism of mammalian circadian model presented in section 2.3.3.1, dynamics of $Per2/Cry$ mRNA and PER2/CRY proteins create negative feedback loop. Positive feedback loop is formed by the dynamics of $Bmal1$ mRNA and BMAL1 proteins. Since the nuclear PER2/CRY protein regulates both negative and positive feedback loops, there is interaction occurring in these two loops. The analysis of interaction of two feedback loops is carried out by varying parameters $k_{1i}$ and $v_{4b}$ at fixed values of constant activator $c$. Parameter $k_{1i}$ is inhibitory constant which affects the strength of negative feedback while $v_{4b}$ affects the strength of positive feedback. The results showing the interplay of positive and negative feedback are summarized in Figure 2.14 where parameters $k_{1i}$ and $v_{4b}$ are varied at four values of constant.
activator \( c, c = 0.025, c = 0.01, c = 0.008, c = 0 \).

In Figure 2.14, colored area shows region of oscillations while the black coloured area represents the region of steady state. The behaviours of the dynamics of the system (with or without oscillations) can be found based on Figure 2.14. Small black circle in Figure 2.14B represents the behaviours of dynamics of system (2.10) at the default values set in the previous section. As shown in Figure 2.14B, small black circle is in the colored area. Thus, with the set of default values, the system (2.10) oscillates.

2.4. Lyapunov stability theorem & Observer designs

2.4.1. Lyapunov stability

Stability theory is an important tool in control theory. It is used to analyze the stability of a dynamical system. For dynamic systems, there are various types of stability problems. One
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of them is the stability of equilibrium points. In nonlinear control theory, the stability of equilibrium points can be expressed in the sense of Lyapunov stability. Since the Lyapunov stability will be considered in nonlinear control methods presented in later chapters, a brief description of it is presented in this section.

The Lyapunov stability is applied to autonomous and non-autonomous systems. The autonomous system is described by

\[ \dot{x} = f(x), \]  

where \( f : D \to \mathbb{R}^n \) is a locally Lipschitz map from a domain \( D \subset \mathbb{R}^n \) into \( \mathbb{R}^n \). Since the circadian models used in this thesis are mainly considered as autonomous systems, we briefly review notions and theorems related with the Lyapunov stability of autonomous systems. Without loss of generality, system (2.11) can be always assumed to have equilibrium point at the origin. In other words, \( f(x) \) of system (2.11) can be assumed to satisfy \( f(0) = 0 \). The equilibrium point \( x = 0 \) of system (2.11) can have three types of dynamics: stability, instability, and asymptotic stability. These three types of dynamics are defined as following

**Definition 2.2 ([43])** The equilibrium point \( x = 0 \) of (2.11) is

- **stable if, for each \( \epsilon > 0 \), there is \( \delta = \delta(\epsilon) > 0 \) such that**

  \[ \|x(0)\| < \delta \Rightarrow \|x(t)\| < \epsilon, \forall t \geq 0 \]

- **unstable if it is not stable**

- **asymptotically stable if it is stable and \( \delta \) can be chosen such that**

  \[ \|x(0)\| < \delta \Rightarrow \lim_{t \to \infty} x(t) = 0 \]

Based on definition 2.2, we state the Lyapunov’s stability theorem as
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**Theorem 2.1** ([43]) Let \( x = 0 \) be an equilibrium point for system (2.11) and \( D \subset \mathbb{R}^n \) be a domain containing \( x = 0 \). Let \( V : D \rightarrow \mathbb{R} \) be a continuously differentiable function such that

\[
V(0) = 0 \quad \text{and} \quad V(x) > 0 \quad \text{in} \; D - \{0\} \\
\dot{V}(x) \leq 0 \quad \text{in} \; D
\]  

(2.12) \hspace{1cm} (2.13)

Then, \( x = 0 \) is stable. Moreover, if

\[
\dot{V}(x) < 0 \quad \text{in} \; D - \{0\}
\]  

(2.14)

then \( x = 0 \) is asymptotically stable.

Function \( V \) stated in above theorem is usually called as Lyapunov function [43]. If function \( V \) satisfies the condition (2.12) stated in theorem 2.1, it is called as positive definite. If \( V \geq 0 \) for \( x \neq 0 \), it is said to be positive semidefinite. Negative sign of positive definite and semi-positive definite (\( -V(x) \)) are called negative definite and negative semi-definite respectively.

One dynamical system does not have a unique solution of Lyapunov function. It can have many Lyapunov function candidates. There is no fixed method to find Lyapunov functions [43]. A chosen Lyapunov function sometimes can not reflect actual stability of a dynamical system. Consider an example given below

**Example 2.1** ([43]) Consider the pendulum equation with friction. This system is described by

\[
\dot{x}_1 = x_2 \\
\dot{x}_2 = -a \sin(x_1) - bx_2
\]  

(2.15)

The Lyapunov function \( V(x) = a (1 - \cos x_1) + (1/2)x_2^2 \) is considered for the system (2.15) in the example above. With this chosen Lyapunov function candidate, the derivative \( \dot{V}(x) \) is negative semidefinite. According to theorem 2.1, the considered system is stable. However, in the phase portrait, the origin of system (2.15) is asymptotically stable for \( b > 0 \) [43]. In this
situation, another Lyapunov function candidate is chosen such that $\dot{V}(x)$ is negative definite. Instead of introduction of a new Lyapunov function candidate, we can use LaSalle’s theorem to support the chosen Lyapunov function. This theorem is described as

**Theorem 2.2** ([43]) Let $\Omega \subset D$ be a compact set that is positively invariant with respect to (2.11). Let $V : D \to \mathbb{R}$ be a continuously differentiable function such that $\dot{V}(x) \leq 0$ in $\Omega$. Let $E$ be the set of all points in $\Omega$ where $\dot{V}(x) = 0$. Let $M$ be the largest invariant set in $E$. Then every solution starting in $\Omega$ approaches $M$ as $t \to \infty$.

Besides LaSalle’s theorem 2.2, there are two corollaries which can also support the Lyapunov stability. These two corollaries are known as the theorems of Barbashin and Krasovskii [43]. They are described as

**Corollary 2.1** ([43]) Let $x = 0$ be an equilibrium point for system (2.11). Let $V : D \to \mathbb{R}$ be a continuously differentiable positive definite function on a domain $D$ containing the origin $x = 0$, such that $\dot{V}(x) \leq 0$ in $D$. Let $S = \left\{ x \in D | \dot{V}(x) = 0 \right\}$ and suppose that no solution can stay identically in $S$, other than the trivial solution $x(t) \equiv 0$. Then, the origin is asymptotically stable.

**Corollary 2.2** ([43]) Let $x = 0$ be an equilibrium point for system (2.11). Let $V : \mathbb{R}^n \to \mathbb{R}$ be a continuously differentiable, radically unbounded, positive definite function such that $\dot{V}(x) \leq 0$ for all $x \in \mathbb{R}^n$. Let $S = \left\{ x \in \mathbb{R}^n | \dot{V}(x) = 0 \right\}$ and suppose that no solution can stay identically in $S$, other than the trivial solution $x(t) \equiv 0$. Then, the origin is asymptotically stable.

**2.4.2. Linear observer design**

Consider a linear system described by

$$
\dot{x}(t) = Ax(t) + Bu(t) \quad (2.16)
$$

$$
y(t) = Cx(t)
$$
where \( x \in \mathbb{R}^n \) is the state variable, \( u \in \mathbb{R}^p \) is the input, \( A, B, C \) are constant matrices with appropriate dimensions, and \( y \in \mathbb{R}^m \) is the output.

For system (2.16), the observer can take the form as

\[
\dot{\hat{x}}(t) = A\hat{x}(t) + Bu(t) + L(y - C\hat{x}(t)),
\]

where \( L \in \mathbb{R}^{n \times m} \) is an observer gain. If error \( \tilde{x} = x - \hat{x} \), error dynamics are described by

\[
\dot{\tilde{x}}(t) = (A - LC)\tilde{x}(t)
\]

The system (2.18) is asymptotically stable if resultant matrix of \( A - LC \) has real parts of its eigenvalues on the left hand plane. The eigenvalues of resultant matrix of \( A - LC \) depends on the choice of observer gain \( L \). Linear observer design (2.17) is known as Luenberger’s observer or identity observer. Result of this observer design has been presented in [54]. One of the conditions for the existence of observer design (2.17) is the complete observability of linear system (2.16). The observability of system (2.16) is described by the following theorem

**Theorem 2.3** ([54]) If observability matrix

\[
O = \begin{bmatrix} C \\ CA \\ CA^2 \\ \vdots \\ CA^{n-1} \end{bmatrix},
\]

has rank \( n \), system (2.16) is completely observable.

### 2.4.3. Reduced-order observer design

Another observer design called reduced-order observer design has also been presented in [54]. An observer is called reduced-order observer if its order is lower than the original system after
a state transformation. Moreover, when dealing with nonlinear systems, reduced-order observer
design allows the nonlinearities in some directions to be avoided. Because of this advantage,
reduced-order observer design is applied to estimate the unknown states of nonlinear systems.
A reduced-order observer design for nonlinear system will be presented in chapter 3. A similar
design procedure of reduced-order observer is applied to both linear and nonlinear systems.
Thus, in order to have better understanding of the reduced-order observer design which will be
presented in the next chapter, a brief description of its design procedure for linear systems is
presented in this section.

Consider again linear system (2.16). This system is assumed to be able to transform to a new
system which has simpler structure than the original system. Let a non-singular matrix \( V \) be the
state transformation of linear system (2.16). This nonsingular matrix is described by

\[
P = \begin{bmatrix} V \\ C \end{bmatrix}, \quad V \in \mathbb{R}^{(n-m)\times n},
\]  
(2.19)

where \( C \in \mathbb{R}^{m \times n} \) is matrix of output of linear system (2.16). Let

\[
\bar{x}(t) = Px(t),
\]  
(2.20)

and let \( \bar{x} \) be partitioned as

\[
\bar{x}(t) = \begin{bmatrix} w(t) \\ y(t) \end{bmatrix},
\]  
(2.21)

where \( w(t) \) are unknown state variables of linear system (2.16), and \( y \in \mathbb{R}^m \) are the outputs
or the known state variables of linear system (2.16). Let matrix \( PAP^{-1} \) and matrix \( PB \) be
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Partitioned as

\[ PAP^{-1} = \begin{bmatrix} A_{1,1} & A_{1,2} \\ A_{2,1} & A_{2,2} \end{bmatrix}, \quad PB = \begin{bmatrix} B_1 \\ B_2 \end{bmatrix} \] (2.22)

Multiplying both sides of system (2.16) by matrix \( P \) and using (2.20), (2.21), and (2.22), we obtain dynamics of transformed system as:

\[
\begin{aligned}
\dot{x}(t) &= \begin{bmatrix} \dot{w}(t) \\ \dot{y}(t) \end{bmatrix} = \begin{bmatrix} A_{1,1} & A_{1,2} \\ A_{2,1} & A_{2,2} \end{bmatrix} \begin{bmatrix} w(t) \\ y(t) \end{bmatrix} + \begin{bmatrix} B_1 \\ B_2 \end{bmatrix} u(t) \\
\end{aligned}
\] (2.23)

From (2.23), dynamics of \( w(t) \) and \( y(t) \) are obtained as

\[
\begin{aligned}
\dot{w}(t) &= A_{1,1}w(t) + A_{1,2}y(t) + B_1 u(t) \\
\dot{y}(t) &= A_{2,1}w(t) + A_{2,2}y(t) + B_2 u(t)
\end{aligned}
\] (2.24, 2.25)

Define

\[ v(t) = w(t) - Ey(t), \] (2.26)

where \( E \in \mathbb{R}^{(n-m) \times m} \). The dynamics of \( v \) are obtained as

\[
\begin{aligned}
\dot{v}(t) &= \dot{w}(t) - E\dot{y}(t) = (A_{1,1} - EA_{2,1})w(t) + (A_{1,2} - EA_{2,2})y(t) \\
&\quad + (B_1 - EB_2) u(t)
\end{aligned}
\] (2.27)

Substituting (2.26) to (2.27), we have

\[
\begin{aligned}
\dot{v}(t) &= (A_{1,1} - EA_{2,1})v(t) + (A_{1,2}E - EA_{2,1}E + A_{1,2} - EA_{2,2})y(t) \\
&\quad + (B_1 - EB_2) u(t)
\end{aligned}
\] (2.28)
The reduced-order observer design of system (2.28) is described by

$$\dot{\hat{v}}(t) = (A_{1,1} - EA_{2,1}) \dot{v}(t) + (A_{1,2}E - EA_{2,1}E + A_{1,2} - EA_{2,2}) \dot{y}(t) + (B_1 - EB_2) u(t) \quad (2.29)$$

The estimates of unknown states $w(t)$ are given by

$$\dot{\hat{w}}(t) = \dot{\hat{v}}(t) + Ey(t) \quad (2.30)$$

**Remark 2.2** The reduced-order observer design of linear system (2.16) is obtained in equation (2.29). The definition (2.26) has been made in order to find the dynamics of unknown states in original system (2.29). In research studies of reduced-order observer design for nonlinear systems, with proper matrix $E$ chosen, the nonlinearities involved in the considered dynamical systems can be removed.

### 2.4.4. High gain observer

Since reduction of measurements in circadian models using observers has not been considered in literature, there are not any results of observer designs to circadian models over past few years. Recently, a result of high gain observer design has been reported in [24] for parameter estimations of biochemistry models. Consider a class of nonlinear system which is described by

$$\begin{align*}
\dot{x} &= Ax + \Phi(x, u), \\
y &= Cx \quad (2.31)
\end{align*}$$

where $x \in \mathbb{R}^n$ is the system state, $u \in \mathbb{R}^p$ is the input, $A, B, C$ are constant matrices with appropriate dimensions, $\Phi(x, u) \in \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ is nonlinear function, and $y \in \mathbb{R}^m$ is the output.
For such systems as (2.31), high gain observer can be designed as

\[ \dot{\hat{x}} = A\hat{x} + \Phi(\hat{x}, u) + S_\infty^{-1}C' (y - C\hat{x}), \]  

(2.32)

where \( C = \begin{bmatrix} 1 & 0 & \ldots & 0 \end{bmatrix} \). The observer design (2.32) is the high gain observer design which has been presented in [27]. It is also the observer design which is applied to a mathematical model of Neurospora circadian rhythm in [24]. In observer design (2.32), resultant matrix \( S_\infty^{-1}C' \) is the observer gain where \( C' \) is the transpose matrix of constant matrix \( C \) of system (2.31), and \( S_\infty^{-1} \), a symmetric matrix, is the solution of equation

\[ \theta S_\infty + A'S_\infty + S_\infty A - C'C = 0 \]  

(2.33)

for \( \theta \) large enough. In equation (2.33), \( A' \) is the transpose matrix of constant matrix \( A \) of system (2.31) and \( \theta \) is a varied constant. In this section, we describe the application of the high gain observer design (2.32) to Neurospora model (2.9).

In order to use high gain observer design (2.32), system (2.16) must have triangular form. Therefore, in the application of high gain observer design (2.32) to Neurospora model (2.9) in [24], Neurospora model (2.9) has to be able to transform to a new system which has triangular structure.

Let

\[ g = Gx, \]  

(2.34)

where \( g \in \mathbb{R}^n \) is the state variable of the new system, and \( G \) is a chosen state transformation matrix for Neurospora model (2.9) which has its value described by

\[ G = \begin{bmatrix} 0 & 0 & 1 \\ 0 & k_1 & 0 \\ k_1k_s & 0 & 0 \end{bmatrix}, \]  

(2.35)
New parameters for the transformed system are obtained as

$$ A_1 = GAG^{-1} = \begin{bmatrix} -0.6 & 1 & 0 \\ 0.3 & -0.5 & 1 \\ 0 & 0 & 0 \end{bmatrix}, G\Phi(x, u) = \begin{bmatrix} 0 \\ -v_d \frac{k_1g_2}{k_1K_A+g_2} \\ v_k \frac{k_1k_s K_h^a}{K_h^a+g_1} - v_m \frac{k_1k_s g_3}{K_M K_h^a+g_1} \end{bmatrix} $$ (2.36)

With output chosen for original system (2.9) as

$$ C = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}, $$ (2.37)

after the state transformation (2.34), output of the new system is obtained as

$$ C_1 = CG^{-1} = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, $$ (2.38)

The output value $C_1$ satisfies the condition of value $C$ of high gain observer design (2.32). The observer gain of system (2.32) is calculated next. In order to do this, value of $S_\infty$ has to be found because in the high gain observer design (2.32), the observer gain is calculated as $L_1 = S_\infty^{-1} C'_1$ where $S_\infty$ is the solution of equation (2.33). Let $\theta = 0.5$. Substituting values of $A_1$ and $C_1$ obtained in (2.36) and (2.37) respectively to the equation (2.33), and using function ARE in MATLAB, we obtain

$$ S_\infty = \begin{bmatrix} 1 & 0.85 & 0.275 \\ 0.85 & 0.785 & 0.3025 \\ 0.275 & 0.3025 & 0.1512 \end{bmatrix}, L_1 = S_\infty^{-1} C'_1 = \begin{bmatrix} 1 & 0.85 & 0.275 \end{bmatrix}^T $$

Although $L_1$ is the high gain of observer of the transformed system, value of $L_1$ is also the observer gain of the observer for original system (2.9). Dynamics of the unknown state variables $x_1$ (the concentration of $frq$ mRNA), $x_2$ (the concentration of FRQ protein outside nucleus), and their estimates are depicted in Figure 2.15 and Figure 2.16.

Results obtained in Figure 2.15 and Figure 2.16 have shown that the high gain observer
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Figure 2.15. Dynamics of unknown state $x_1$ and its estimate for application of high gain observer at $\theta = 0.5$

Figure 2.16. Dynamics of unknown state $x_2$ and its estimate for application of high gain observer at $\theta = 0.5$
design (2.32) successfully estimate the unknown states $x_1$, $x_2$. We increase $\theta = 0.5$ to $\theta = 1$. For $\theta = 1$, the following parameters are obtained as

$$S_\infty = \begin{bmatrix} 2 & 2.2 & 1.1 \\ 2.2 & 2.92 & 1.76 \\ 1.1 & 1.76 & 1.21 \end{bmatrix}, \quad L_1 = S_\infty^{-1}C_1' = \begin{bmatrix} 2 & 2.2 & 1.1 \end{bmatrix}^T$$

The dynamics of unknown states $x_1$, $x_2$, and their estimates in Neurospora model are depicted in Figure 2.17 and Figure 2.18 for $\theta = 1$.

![Figure 2.17. Dynamics of unknown state $x_1$ and its estimate for application of high gain observer at $\theta = 1$](image)

As seen in Figure 2.17 and Figure 2.18, the successful estimations occur at approximately $t = 10h$ for $\theta = 1$. For $\theta = 0.5$, the time required for estimations is at approximately $t = 15h$. Since $10h < 15h$, the performance of high gain observer design (2.32) at $\theta = 1$ is better than the one at $\theta = 1$. In theoretical design of high gain observer design (2.32), the performance can be improved by increasing the parameter $\theta$. This has been shown in the better performance of high gain observer (2.32) at $\theta = 1$ than at $\theta = 0.5$. In order to find the best performance of high gain observer design (2.32), value of parameter $\theta$ is increased again.
Let’s increase value of $\theta = 1$ to $\theta = 1.5$. For $\theta = 1.5$, the following parameters are obtained as

$$S_\infty = \begin{bmatrix} 3.0000 & 4.0500 & 2.4750 \\ 4.0500 & 7.1550 & 5.1975 \\ 2.4750 & 5.1975 & 4.0837 \end{bmatrix}, \quad L_1 = \begin{bmatrix} 3 \quad 4.05 \quad 2.475 \end{bmatrix}^T$$

The dynamics of unknown states $x_1, x_2$, and their estimates are depicted in Figure 2.19 and Figure 2.20 for $\theta = 1.5$.

Results obtained in Figure 2.19 and Figure 2.20 have shown that the high gain observer successfully estimates the unknown states at approximately $t = 10h$. $t = 10h$ is also the time required to estimate the unknown states in case of $\theta = 1$. Since there is no improvement of performance of high gain observer at value of parameter $\theta$ above 1, we choose $\theta = 1$ as the standard value of $\theta$ which gives the best performance of high gain observer (2.32) to Neurospora model (2.9).
Figure 2.19. Dynamics of unknown state $x_1$ and its estimate for application of high gain observer at $\theta = 1.5$

Figure 2.20. Dynamics of unknown state $x_2$ and its estimate for application of high gain observer at $\theta = 1.5$
2.5. Conclusions

Some essential background studies have been covered in this chapter. In these studies, mathematical models of circadian rhythms of Neurospora and mammals are the most important results because they are the control objectives which will be presented in later chapters. Along with the results of circadian models, sensitivity analysis applied to these models plays an important role in research studies of circadian rhythms in this thesis. Besides behaviors of circadian systems under perturbations investigated, based on the results achieved through sensitivity analysis of mathematical models of Neurospora and mammalian circadian rhythms, the parameters which are sensitive to light input can also be identified.

Besides sensitivity analysis, the review of the high gain observer design which has been successfully applied to Neurospora model in literature is also an essential knowledge in this thesis. The application of this observer to Neurospora model, and the analysis of its performance can provide a piece of detailed study of application of observer design to circadian models.
Chapter 3

Observer Designs and their applications to circadian models

3.1. Introduction

In control theory, observer is designed to estimate the unknown states of a system. Along with advancements in control theory, the last decades have witnessed a significant development of nonlinear observer design. Many results of observer designs have been presented in literature [19, 46, 77, 90, 93]. Among the observer designs presented in literature, there are two notable results of reduced-order and one-sided Lipschitz observers for non-linear dynamic systems. These two results have been reported in [20] for reduced-order observer and in [39] for one-sided Lipschitz observer. The nonlinearities involved in circadian models (2.9) and (2.10) are recognized as one-sided Lipschitz nonlinearities. In addition, systems (2.9) and (2.10) satisfy the specified conditions in [20] for multi-output nonlinear systems. Therefore, the results achieved in [20] and [39] are found to be appropriate observer designs which can be applied to circadian systems (2.9) and (2.10).

There are two broad design approaches for nonlinear observer designs. The first one is based on a non-linear state transformation by which the error dynamics of state is linear. The state observer design can then be performed by using linear techniques. One of the examples of this design approach is given in [91]. In this approach, necessary and sufficient conditions for the existence of the state transformation have been established. The recent result of reduced-order observer design reported in [20] belongs to this approach. An observer is called reduced-order observer if its order is lower than the original system. In addition, a suitable design of reduced-order observer can allow the nonlinearities included in the applied nonlinear systems
to be removed after a state transformation. The observer design presented in [20] is based on a key concept called differential stability, which generalizes the concept of zero dynamics of nonlinear control design for nonlinear observer design. The reduced-order observer is exploited to estimate the unknown states if dynamics of these states are differentially stable under a state transformation.

One of the applied nonlinear systems that has been considered for this new reduced-order observer design is a class of multi-output (MO) nonlinear systems. Due to the specified conditions, the application of this observer is limited. More particular, for nonlinear systems which may have many outputs such as model of mammalian circadian rhythms (2.10), such reduced-order observer design is not able to fully utilize the available output measurements. To solve this problem, a new reduced-order observer design is developed in this chapter. This new developed observer design improves the performance of observer errors beyond the inherent zero dynamics of the original systems. Furthermore, it is capable of dealing with nonlinear systems of which the reduced order dynamics may not be differential stable. In this chapter, the reduced-order observer design [20], and the new design of it are applied to circadian models.

The second approach of nonlinear observer design does not require state transformation. The observer design is directly based on the original systems. One of the examples of this design approach is given in [78]. The one-sided Lipschitz observer design belongs to this approach. An observer is called one-sided Lipschitz observer if its design is based on one-sided Lipschitz condition. The one-sided Lipschitz observer is another type of Lipschitz observer which is based on Lipschitz condition. Besides result reported in [39], several results of Lipschitz observer design have been presented in literature (for example, [1], [62], [63]). In some cases, due to technical difficulties, the Lipschitz observer can not be applied. In those cases, Lipschitz observer can be replaced by one-sided Lipschitz observer. Similar to [62] and [63], one-sided Lipschitz observer design given in [39] does not show clearly how to obtain the observer gain value. This problem is resolved in the new result which is presented in [92]. In this chapter, following the design procedure obtained in [92], one-sided Lipschitz observer is applied to
circadian models.

Through the applications of observer designs to the mathematical models (2.9) and (2.10) which have been given in chapter 2, we can illustrate the procedures of the proposed design methods. In addition, through the applications of observer designs, we are also able to show the possibility of reducing measurements in system biological research on circadian rhythms.

3.2. Lipschitz observers

3.2.1. Lipschitz and one-sided Lipschitz conditions

If a nonlinear function \( \Phi(x, u) \) satisfies Lipschitz condition described by

\[
\| \Phi(x, u) - \Phi(\hat{x}, u) \| \leq \gamma \| x - \hat{x} \|, \forall x, \hat{x} \in \mathbb{R}^n,
\]

(3.1)

it is called Lipschitz nonlinearity. In (3.1), \( \Phi(x, u) \in \mathbb{R}^n \times \mathbb{R}^m \rightarrow \mathbb{R}^n \) is nonlinear function with respect to a state variable \( x \) of a system, and \( \gamma \) is the Lipschitz constant. Value of \( \gamma \) is positive. Any systems containing Lipschitz nonlinearities are known as Lipschitz systems.

Besides Lipschitz condition, there is another condition which is so-called one-sided Lipschitz condition. One-sided Lipschitz condition has been introduced in [16] which is described by

\[
\langle f(x, u) - f(\hat{x}, u), x - \hat{x} \rangle \leq \upsilon_p \| x - \hat{x} \|, \forall x, \hat{x} \in \mathbb{R}^n,
\]

(3.2)

where \( \upsilon_p \) is one-sided Lipschitz constant, \( f(x, u) = P\Phi(x, u) \) with \( P \) as positive definite matrix, and \( \langle \cdot, \cdot \rangle \) is an Euclidean product on \( \mathbb{R}^n \). Value of \( \upsilon_p \) may be negative value, and in some cases, this value may be found smaller than Lipschitz constant \( \gamma \) [16], [39], [92]. If a nonlinear function satisfies (3.2), it is called one-sided Lipschitz nonlinearity.

3.2.2. Mean value theorem

For Lipschitz nonlinearities, values of \( \gamma \) are not always straightforward to obtain by using (3.1). When Lipschitz constant \( \gamma \) can not be found by using (3.1), a method introduced in [89] is used
instead. This method is also known as the mean value theorem which is described by

\[ f'(\zeta) = \frac{f(x) - f(\hat{x})}{x - \hat{x}}, \]  

(3.3)

where \( \zeta \in [x, \hat{x}] \). Value of Lipschitz constant is equivalent to the maximum value of function \(|f'(\zeta)|\).

### 3.2.3. Observer designs

Consider a class of nonlinear system which is described by

\[ \dot{x} = Ax + \varphi(x, u) + Bu, \]  

(3.4)

\[ y = Cx \]

where \( x \in \mathbb{R}^n \) is the state, \( u \in \mathbb{R}^p \) is the input, \( A, B, C \) are constant matrices with appropriate dimensions, \( y \in \mathbb{R}^m \) is the output, and \( \varphi(x, u) \in \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n \) is a nonlinear function.

Consider an observer of (3.4) which has its form described by

\[ \dot{\hat{x}} = A\hat{x} + \varphi(\hat{x}, u) + Bu + L(y - C\hat{x}), \]  

(3.5)

where \( L \) is observer gain with \( L \in \mathbb{R}^{n \times m} \). If \( \varphi(x, u) \) are Lipschitz nonlinearities, the observer design (3.5) can be applied to nonlinear system (3.4) if the next theorem is satisfied.

**Theorem 3.1** ([63]) *If a value of \( L \) is chosen such that \( (A - LC) \) is stable and the following inequality

\[(A - LC)^T P + P(A - LC) + 2\gamma^2 PP + I < 0 \]  

(3.6)*

is satisfied, where \( P \) is a positive definite matrix, and \( \gamma \) is Lipschitz constant of \( \varphi(x, u) \), the observer (3.5) yields asymptotically convergence estimate for system (3.4).*

The observer design based on Theorem 3.1 can be easily applied to low order nonlinear systems. For high order nonlinear systems, the application of this proposed observer design becomes inconveniently due to the difficulty in selection of value of observer gain \( L \) such that...
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$A - LC$ is stable, and the linear matrix inequality (3.6) is satisfied. One-sided Lipschitz observer is considered instead. Design procedure of one-sided Lipschitz observer is firstly presented in [39]. This design is shown in theorem 3.2.

**Theorem 3.2** ([39]) If observer gain $L$ is chosen such that $(A - LC)$ is stable and

$$(A - LC)^T P + P (A - LC) + 2\nu_p I < 0 \quad (3.7)$$

is satisfied, where $P$ is a positive definite matrix, $\nu_p$ is one-sided Lipschitz constant of $f(x, u) = P\varphi(x, u)$ such that (3.2) holds, the observer (3.5) yields asymptotically convergence estimate for system (3.4).

Similar to Theorem 3.1, Theorem 3.2 does not clearly show how to calculate the observer gain value $L$. Result presented in [92] overcomes this problem. The new developed one-sided Lipschitz observer design is based on the following theorem

**Theorem 3.3** ([92]) Consider nonlinear system (3.1) with condition (3.2) satisfied. If there exists a positive value $\sigma$ such that the inequality

$$A^T P + PA - \sigma C^T C + 2\nu_p I < 0 \quad (3.8)$$

is satisfied, where $P$ is a positive definite matrix, and $\nu_p$ is one-sided Lipschitz constant of $P\varphi(x, u)$ with respect to $x$, the observer (3.5) having $L = \frac{\sigma}{2} P^{-1} C^T$ as observer gain yields asymptotically convergence estimate for system (3.4).

Instead of dependence on observer gain value $L$, the condition for existence of one-sided Lipschitz observer depends on a positive constant $\sigma$, where its value is easier to compute than value of observer gain $L$. Theorem 3.3 is particularly applied to systems having nonlinearities satisfied (3.2). However, this theorem can also be applied to the case of Lipschitz nonlinearities. Consider $\varphi(x, u)$ as Lipschitz nonlinearities, and $P$ as a positive definite matrix which has
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general form described by

\[
P = \begin{bmatrix}
  p_{1,1} & p_{1,2} & \cdots & p_{1,n} \\
p_{2,1} & p_{2,2} & \cdots & p_{2,n} \\
  \vdots & \vdots & \ddots & \vdots \\
p_{n,1} & p_{n,2} & \cdots & p_{n,n}
\end{bmatrix} \in \mathbb{P}_n(i, \lambda),
\]

where \(|p_{ik}| \leq \lambda, i = 1, 2, \ldots, n\), \(\lambda\) is a small positive real constant, and \(n\) denotes number of state variables of the system. Instead of (3.8), according to [92], linear matrix inequality (LMI) is modified with the form described by

\[
A^T P + PA - \sigma C^T C + 2n \sum_{i=1}^{n} \gamma_i \lambda_i I < 0, \tag{3.9}
\]

where \(\gamma_i\) indicates Lipschitz constants for each of Lipschitz nonlinear functions, and \(\lambda_i\) denotes small positive real constants. In LMI (3.9), \(n \sum_{i=1}^{n} \gamma_i \lambda_i\) represents values of the one-sided Lipschitz constant \(v_p\). Values of \(\lambda_i\) can be chosen such that \(n \sum_{i=1}^{n} \gamma_i \lambda_i < (\sum_{i=1}^{n} \gamma_i^2)^{\frac{1}{2}}\). After a positive value of \(\sigma\) is obtained by solving (3.9), based on Theorem 3.3, value of observer gain is then found by using equation \(L = \frac{\sigma}{2} P^{-1} C^T\).

3.2.4. Application of one-sided Lipschitz observers to circadian models

3.2.4.1 Arrangements of Lipschitz nonlinearities

From structure of (3.1), nonlinear function \(\varphi(x, u)\) may be taken as

\[
\varphi(x, u) = \begin{bmatrix}
  \varphi_{1a}(x_1) \\
  \varphi_{1b}(x_3) \\
  \varphi_2(x_2)
\end{bmatrix} = \begin{bmatrix}
  -v_m \frac{x_1}{K_{M} + x_1} \\
  v_s \frac{K_{n}}{K_{n} + x_3} \\
  v_d \frac{x_2}{K_{d} + x_2}
\end{bmatrix} \tag{3.10}
\]
for Neurospora model (2.9), and

\[
\varphi(x, u) = \begin{bmatrix}
\varphi_1(x_3, x_7) \\
\varphi_2(x_1) \\
\varphi_4(x_3)
\end{bmatrix} = \begin{bmatrix}
\frac{v_{1b}(x_7+c)}{k_{1b}(1+x_1^{p_1})+x_7+c} \\
x_1^p \\
\frac{v_{4b}x_3^{m_1}}{k_{4b}^{m_1}+x_3^{m_1}}
\end{bmatrix}
\] (3.11)

for mammalian model (2.10).

### 3.2.4.2 Choices of state outputs

In literature, outputs of the mathematical models of Neurospora and Mammals are not clearly specified. Therefore, we may choose the outputs for these models. Value of $C$ is chosen such that the observability of matrix $(C, A)$ is guaranteed. Furthermore, since observers are designed to circadian models in order to show the possibility of reducing measurements, value of $C$ is kept as simple as possible. Based on the given requirements, value of $C$ may be chosen as:

\[
C = \begin{bmatrix}
0 & 0 & 1
\end{bmatrix}
\] (3.12)

for Neurospora model, and

\[
C = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0
\end{bmatrix}
\] (3.13)

for mammalian model.

**Remark 3.1** The values of $C$ given in (3.12) and (3.12) have been chosen among the sets of values of $C$ which satisfy the observability of matrix $(C, A)$. In addition, these two values of $C$ are also chosen such that there are the least involvements of parameters in dynamics of state variables in system (2.9) and (2.10).
3.2.4.3 Application to Neurospora model

Using Lipschitz condition (3.1), we have

\[
\left\| -v_m \frac{x_1}{K_M + x_1} + v_m \frac{\hat{x}_1}{K_M + \hat{x}_1} \right\| \leq \frac{v_m}{K_M} \| x_1 - \hat{x}_1 \|
\]

\[
\left\| -v_d \frac{x_2}{K_d + x_2} + v_d \frac{\hat{x}_2}{K_d + \hat{x}_2} \right\| \leq \frac{v_d}{K_d} \| x_2 - \hat{x}_2 \|
\]

Values of Lipschitz constants are obtained with \( \gamma_{1a} = \frac{v_m}{K_M} = 1.01 \) for \( \varphi_{1a}(x_1) \), and with \( \gamma_2 = \frac{v_d}{K_d} = 10.7962 \) for \( \varphi_2(x_2) \). For nonlinear function \( \varphi_{1b}(x_3) \), its Lipschitz constant \( \gamma_{1b} \) is obtained by using mean value theorem given in equation (3.3). From Lipschitz condition (3.1),

\[
| \varphi_{1b}(x_3) - \varphi_{1b}(\hat{x}_3) | \leq \gamma_{1b} | x_3 - \hat{x}_3 |
\]

By using (3.3),

\[
| \varphi_{1b}(x_3) - \varphi_{1b}(\hat{x}_3) | = | f'(\zeta) (x_3 - \hat{x}_3) | = \left| -\frac{n\zeta^{n-1}}{(K_1^n + \zeta^n)^2} \right| | x_3 - \hat{x}_3 |,
\]

(3.14)

where \( \zeta \in [\min(x_3, \hat{x}_3), \max(x_3, \hat{x}_3)] \). Maximum value of \( | f'(\zeta) | \) is equivalent to Lipschitz constant \( \gamma_{1b} \). This value of \( | f'(\zeta) | \) by solving equation \( | f''(\zeta) | = 0 \). The result is obtained as \( \gamma_{1b} = 1.7043 \) for \( \varphi_{1b}(x_3) \). After values of all required Lipschitz constants are found, we solve (3.9) to obtain

\[
\sigma = 197.1422, \quad L = \begin{bmatrix} 1.4721 \\ 1.6396 \\ 4.4247 \end{bmatrix}.
\]

For Neurospora model, the observer has its form described by

\[
\dot{\hat{x}} = A\hat{x} + \varphi(\hat{x}, u) + L(y - C\hat{x}).
\]

(3.15)
Let initial condition of the observer design (3.15) be \( \hat{x}(0) = \begin{bmatrix} 0 & 0 & 0 \end{bmatrix}^T \). Figure 3.1 and Figure 3.2 show the dynamics of unknown state variables \( x_1, x_2 \) and their estimates.

![Figure 3.1. Unknown state \( x_1 \) and its estimate for \( C = [0, 0, 1] \) in Neurospora model](image)

### 3.2.4.4 Application to mammalian model

Lipschitz constant \( \gamma_2 \) of \( \varphi_2(x_1) \) is firstly calculated. Value of \( \gamma_2 \) is computed by using (3.3) rather than using (3.1). From Lipschitz condition (3.1),

\[
|\varphi_2(x_1) - \varphi_2(\hat{x}_1)| \leq \gamma_2 |x_1 - \hat{x}_1|
\]

From (3.3), we have

\[
|f'(\zeta_1)| = |s\zeta_1^{s-1}| = \left| \frac{\varphi_2(x_1) - \varphi_2(\hat{x}_1)}{x_1 - \hat{x}_1} \right|,
\]

where \( \zeta_1 \in [\min(x_1, \hat{x}_1), \max(x_1, \hat{x}_1)] \). Since state \( x_1 \) is known, and amplitude of \( x_1 \in [0.2627, 1.518] \), therefore, \( \zeta_1 \in [0.2627, 1.518] \). With \( s = 2 \), Lipschitz constant of \( \varphi_2(x_1) \) is obtained as \( \gamma_2 = 2*|\zeta_1| = 3.038 \). Value of Lipschitz constant \( \gamma_4 \) of \( \varphi_4(x_3) \) is calculated by using the same method which has been applied to find Lipschitz constant of \( \varphi_{16}(x_3) \) in Neurospora.
model. This result is obtained as $\gamma_4 = 0.864$. For $\varphi_1(x_3, x_7)$, from Lipschitz condition (3.1),

$$
\| \varphi_1(x_3, x_7) - \varphi_1(\hat{x}_3, \hat{x}_7) \| \leq \gamma_1 \frac{\| x_3 - \hat{x}_3 \|}{\| x_7 - \hat{x}_7 \|},
$$

(3.17)

where $\gamma_1$ is Lipschitz constant of $\varphi_1(x_3, x_7)$. On the other hand,

$$
| \varphi_1(x_3, x_7) - \varphi_1(\hat{x}_3, x_7) + \varphi_1(x_3, x_7) - \varphi_1(x_3, \hat{x}_7) |
\leq | \varphi_1(x_3, x_7) - \varphi_1(\hat{x}_3, x_7) | + | \varphi_1(x_3, x_7) - \varphi_1(x_3, \hat{x}_7) |
$$

(3.18)

From (3.3), we have

$$
| \varphi_1(x_3, x_7) - \varphi_1(\hat{x}_3, x_7) | = | f'(\zeta_2)(x_3 - \hat{x}_3) |
$$

(3.19)

$$
| \varphi_1(x_3, x_7) - \varphi_1(x_3, \hat{x}_7) | = | f'(\zeta_3)(x_7 - \hat{x}_7) |
$$

(3.20)

for any non zeros $\zeta_2 \in [\min(x_3, \hat{x}_3), \max(x_3, \hat{x}_3)]$, and $\zeta_3 \in [\min(x_7, \hat{x}_7), \max(x_7, \hat{x}_7)]$. Function $f'(\zeta_2)$ is differentiated function of $\varphi_1(x_3, x_7)$ with respect to $x_3$ while function $f'(\zeta_3)$ is
differentiated function of $\varphi_1(x_3, x_7)$ with respect to $x_7$. By substituting (3.19), (3.20) to (3.18), we obtain

$$|\varphi_1(x_3, x_7) - \varphi_1(\hat{x}_3, x_7) + \varphi_1(x_3, x_7) - \varphi_1(x_3, \hat{x}_7)|$$

$$\leq |f'(\zeta_2) (x_3 - \hat{x}_3)| + |f'(\zeta_3) (x_7 - \hat{x}_7)|$$

(3.21)

Besides, according to Cauchy-Schwarz inequality, we have

$$(3.21) \leq \| f'(\zeta_2) \|_{x_3 - \hat{x}_3} \| x_3 - \hat{x}_3 \| = \| f'(\zeta_3) \|_{x_7 - \hat{x}_7} \| x_7 - \hat{x}_7 \|$$

(3.22)

**Remark 3.2** The inequalities (3.18) and (3.22) are true $\forall x, \zeta \in \mathbb{R}^n$. Therefore, even if the state variables of mammalian system (2.10) are negative, the inequalities (3.18) and (3.22) still hold.

From (3.22), value $\gamma_1$ can be obtained as $\gamma_1 = \sqrt{(\max(f'(\zeta_2)))^2 + (\max(f'(\zeta_3)))^2}$. Maximum values of $f'(\zeta_2)$ and $f'(\zeta_3)$ are obtained by solving equations $|f''(\zeta_2)| = 0$ and $|f''(\zeta_3)| = 0$. Nevertheless, in order to solve $|f''(\zeta_2)| = 0$ and $|f''(\zeta_3)| = 0$, boundaries of state variables $x_3$ and $x_7$ are required. These boundaries can be defined by ranges of amplitudes of dynamics of $x_3$ and $x_7$. From chosen value of $C$ in (3.13), dynamics of states $x_3$ and $x_7$ are known outputs. From Figure 2.5, we estimate $x_3 \in [0.8, 1.861]$, $x_7 \in [0.85, 1.11]$. The maximum values and minimum values of state variables $x_3, x_7$ are then substituted to solve $|f''(\zeta_2)| = 0$, and $|f''(\zeta_3)| = 0$. The results are obtained with $\max(f'(\zeta_2)) = 2.9909 \times 10^{-17}$ and $\max(f'(\zeta_3)) = 0.4906$. Lipschitz constant of nonlinear function $\varphi_1(x_3, x_7)$ has its value as $\gamma_1 = \sqrt{(2.9909 \times 10^{-17})^2 + (0.4906)^2} = 0.4906$. We then solve LMI (3.8) to obtain
σ = 181.0579, L = 
\[
\begin{bmatrix}
0.3323 & 0 & 0 \\
0 & -0.0402 & 0 \\
0 & 0.4278 & 0 \\
0 & 0 & -0.0022 \\
0 & 0 & 0.0045 \\
0 & 0 & 0.0155 \\
0 & 0 & 0.3247 \\
\end{bmatrix}
\]

The dynamics of unknown and their estimates $x_2$, $x_4$, $x_5$, $x_6$ are shown from Figure 3.3 to Figure 3.6.

![Figure 3.3. Dynamics of unknown state $x_2$ and its estimate in mammalian model](image)
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Figure 3.4. Dynamics of unknown state $x_4$ and its estimate in mammalian model

Figure 3.5. Dynamics of unknown state $x_5$ and its estimate in mammalian model
3.2.4.5 Discussion

Application of observer designs to circadian models has not been much consideration in literature. This leads to the deficiency of results which can be used to judge the performances of proposed one-sided Lipschitz observers shown above. Since there are no standard data for performances of observers of circadian models, in order to evaluate the performances of proposed one-sided Lipschitz observers, result obtained for phase tracking is used instead. With proposed control inputs, rhythms of 10th order Drosophila model are tracked, and restored at approximate time $t_1 = 40$ h by using model-based optimal control [74]. Another result which is recently presented in [21] has shown that instead of using phase response curve (PRC), rhythms of 3rd order Neurospora model can be tracked using PID control. The time required for phase tracking is at approximately $t_2 = 150$ h. Since $t_1 < t_2$, $(0 \leq t \leq 40$ h) is chosen as the desired range of time for performances of the one-sided Lipschitz observers of circadian models (2.9) and (2.10).

The results depicted from Figure 3.1 to Figure 3.6 have shown that the proposed one-sided Lipschitz observers of both circadian models give asymptotic estimates of unmeasured state
variables within desired range of time. Furthermore, the one-sided Lipschitz observer designed to Neurospora model has better performance than the one designed to mammalian model. This may be mainly due to the complexities in the mammalian model compared with a 3rd order one for Neurospora. Besides, computation of Lipschitz constants may also be responsible for slower performance of observer designed for mammalian model than the one for Neurospora model.

Consider Neurospora model (2.9). Instead of (3.12), value of $C$ is chosen as

$$C = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

(3.23)

for Neurospora model. With chosen value of $C$ as (3.23), the values of $\sigma$ and observer gain $L$ are obtained as

$$\sigma = 50.0883, L = \begin{bmatrix} 0.8667 & 0.2354 \\ 2.0833 & -0.0152 \\ -0.0152 & 0.9276 \end{bmatrix}$$

The unknown state variable $x_1$ and its estimate are depicted in Figure. 3.7. Different values of $C$ may affect the performance of the observer. This is shown with slightly faster convergence of dynamic of $x_1$ in Figure. 3.7 than dynamic of $x_1$ in Figure. 3.1. The reason for faster convergence may be due to fewer unmeasured state variables in value of $C$ given in (3.23) (1 unknown state variable) than in value of $C$ given in (3.12) (2 unknown state variables), which affects the speed of estimation.

### 3.3. Reduced-order observers

#### 3.3.1. Existing result in literature

In this section, the procedure of reduced-order observer design of multi-output (MO) non-linear systems which has been presented in [20] is summarized. Consider a class of MO nonlinear
system which is described by

\[
\begin{align*}
\dot{x} &= Ax + \phi(y, u) + F\varphi(x, u), \\
y &= Cx
\end{align*}
\]  

(3.24)

where \( x \in \mathbb{R}^n \) is the state vector, \( u \in \mathbb{R}^p \) is the control input, \( y \in \mathbb{R}^m \) is the output, \( \phi \) is a known non-linear smooth vector field, \( \varphi(x, u) \in \mathbb{R}^n \times \mathbb{R}^s \rightarrow \mathbb{R}^m \) is a smooth nonlinear function, and \( A \in \mathbb{R}^{n \times n}, C \in \mathbb{R}^{m \times n}, \) and \( F \in \mathbb{R}^{n \times m} \) are constant matrices.

For systems with structures as (3.24), certain conditions are specified in the next assumption.

**Assumption 1**

1. \( \{C, A\} \) is observable.

2. \( C \) has full row rank, \( \text{span}\{F\} \) is a complement subspace of \( \ker\{C\} \) in \( \mathbb{R}^n \)

3. All the invariant zeros of \( \{A, F, C\} \) are with negative real parts.

From Assumption 1(1) and 1(2), a non-singular state transformation matrix \( M \) can be obtained...
such that

\[
CM^{-1} = \begin{bmatrix} I_m & 0_{m \times (n-m)} \end{bmatrix}
\]  

(3.25)

Matrices of \( Mx, MF \) are partitioned as

\[
Mx = \begin{bmatrix} \chi_1 \\ \chi_2 \end{bmatrix}, \chi_1 = y \in \mathbb{R}^m, \quad (3.26)
\]

\[
MF = \begin{bmatrix} F_1 \\ F_2 \end{bmatrix}, \quad (3.27)
\]

and matrices \( MAM^{-1}, M\phi \) are partitioned as

\[
MAM^{-1} = \begin{bmatrix} A_{1,1} & A_{1,2} \\ A_{2,1} & A_{2,2} \end{bmatrix} \quad (3.28)
\]

\[
M\phi = \begin{bmatrix} \phi_1 \\ \phi_2 \end{bmatrix} \quad (3.29)
\]

From Assumption 1(2), \( CF \) is invertible, and if \( F_1 \in \mathbb{R}^{m \times m} \), then \( CF = F_1 \). After the state transformation, with

\[
z = g(x) = \chi_2 - F_2F_1^{-1}\chi_1, \quad (3.30)
\]

the linear dynamics of \( z \) are described by

\[
\dot{z} = \left( A_{2,2} - F_2F_1^{-1}A_{1,2} \right) z + q(y, u), \quad (3.31)
\]
where

\[
q(y, u) = (A_{2,2} - F_2F_1^{-1}A_{1,2}) F_2F_1^{-1}\chi_1 + (A_{2,1} - F_2F_1^{-1}A_{1,1}) \chi_1 + \phi_2(y, u) - F_2F_1^{-1}\phi_1(y, u)
\]  
(3.32)

If matrix \((A_{2,2} - F_2F_1^{-1}A_{1,2})\) is Hurwitz, in other words, Assumption 1(3) is satisfied, the reduced-order observer can be designed as

\[
\dot{\hat{z}} = (A_{2,2} - F_2F_1^{-1}A_{1,2}) \hat{z} + q(y, u)  
\]  
(3.33)

\[
\hat{x} = M^{-1}\begin{bmatrix} y \\ \hat{z} + F_2F_1^{-1}y \end{bmatrix}
\]

Let \(e = z - \hat{z}\). The error dynamics are given by

\[
\dot{e} = (A_{2,2} - F_2F_1^{-1}A_{1,2}) e  
\]  
(3.34)

**Remark 3.3** The nonlinear function \(\varphi(x, u)\) is removed in (3.31) due to particular choice of (3.30)

**Remark 3.4** From (3.34), \(\lim_{t \to \infty} e \to 0\) if resultant matrix \((A_{2,2} - F_2F_1^{-1}A_{1,2})\) is Hurwitz. Thus, the convergence of reduced-order observer design shown above for MO nonlinear systems depends on invariant zeros of resultant matrix \((A_{2,2} - F_2F_1^{-1}A_{1,2})\).

### 3.3.2. Extension of existing reduced-order observer design

Due to the conditions specified in Assumption 1, the reduced-order observer design in section 3.3.1 can only be applied to system (3.24) if this system satisfies the condition \(\text{rank}(C) = \text{rank}(F)\). For nonlinear systems with many outputs where \(\text{rank}(C)\) can be greater than \(\text{rank}(F)\), such reduced-order observer design is not good enough. In this section, a new reduced-order observer design for the case \(\text{rank}(C) > \text{rank}(F)\) is proposed.
Since the input and output involved in $\phi(y, u)$ are all available, therefore, without loss of generality, $\phi = 0$ can be assumed. Consider MO system (3.24) with $\phi = 0$

$$
\dot{x} = Ax + F\varphi(x, u), \quad \text{ (3.35)}
$$

$$
y = Cx
$$

where $x \in \mathbb{R}^n$ is the state, $u \in \mathbb{R}^p$ is the control input, $y \in \mathbb{R}^m$ is the output, $\varphi(x, u) \in \mathbb{R}^{n \times m} \rightarrow \mathbb{R}^n$ is a smooth nonlinear function, and $A \in \mathbb{R}^{n \times n}$ is constant matrix. Different from system (3.24), in system (3.35), constant matrix $F \in \mathbb{R}^{n \times q}$, where rank $F = q$, and $C' = \begin{bmatrix} C_1 \\ C_2 \end{bmatrix}$, where $C_1 \in \mathbb{R}^{q \times n}, C_2 \in \mathbb{R}^{(m-q) \times n}$, and rank$(C) = m$. rank$(C) >$rank$(F)(m > q)$ is assumed.

The following conditions are specified in Assumption 2 below.

**Assumption 2**

1. $\{C, A\}$ is observable.

2. $C_1$ has full row rank, span$\{F\}$ is a complement subspace of ker$\{C_1\}$ in $\mathbb{R}^n$

From Assumption 2(2), one can choose a non-singular transformation matrix

$$
M = \begin{bmatrix} C_1 \\ Q \end{bmatrix}, \quad \text{ (3.36)}
$$

where $M \in \mathbb{R}^{n \times n}$, such that

$$
C_1M^{-1} = \begin{bmatrix} I_q & 0_{q \times (n-q)} \end{bmatrix} \quad \text{ (3.37)}
$$

By letting

$$
M^{-1} = \begin{bmatrix} M_1 & M_2 \end{bmatrix}, \quad \text{ (3.38)}
$$
where $M_1 \in \mathbb{R}^{n \times q}$, we have

$$
\begin{bmatrix}
C_1 \\
Q
\end{bmatrix}
\begin{bmatrix}
M_1 & M_2
\end{bmatrix}
= 
\begin{bmatrix}
I & 0 \\
0 & I
\end{bmatrix}
$$

(3.39)

Consider partitions of matrices $Mx, MF,$ and $MAM^{-1}$ as (3.26), (3.27) and (3.28) respectively. By using (3.26), (3.38), the output of system (3.35) is then obtained as

$$
y = Cx = CM^{-1} \chi = 
\begin{bmatrix}
C_1 \\
C_2
\end{bmatrix}
\begin{bmatrix}
M_1 & M_2
\end{bmatrix} \chi
$$

(3.40)

More specific,

$$
y_1 = \chi_1
$$

(3.41)

$$
y_2 = C_2 M_1 \chi_1 + C_2 M_2 \chi_2
$$

(3.42)

Similar to design in section 3.3.1, from Assumption 2(2), $(C_1 M^{-1}) (M F) = C_1 F$ invertible. If $F_1 \in \mathbb{R}^{q \times q}, C_1 F = F_1$. From (3.26), (3.27), (3.28), the dynamics of $\chi_1$ and $\chi_2$ are obtained as

$$
\dot{\chi}_1 = A_{1,1} \chi_1 + A_{1,2} \chi_2 + F_1 \varphi(x, u)
$$

$$
\dot{\chi}_2 = A_{2,1} \chi_1 + A_{2,2} \chi_2 + F_2 \varphi(x, u)
$$

With the same definition as (3.30), linear dynamics of $z$ are obtained as

$$
\dot{z} = (A_{2,2} - F_2 F_1^{-1} A_{1,2}) z + (A_{2,2} - F_2 F_1^{-1} A_{1,2}) F_2 F_1^{-1} \chi_1
$$

$$
+ (A_{2,1} - F_2 F_1^{-1} A_{1,1}) \chi_1
$$

(3.43)

Equation (3.43) is in the same format as (3.31) where

$$
q(y, u) = (A_{2,2} - F_2 F_1^{-1} A_{1,2}) F_2 F_1^{-1} \chi_1 + (A_{2,1} - F_2 F_1^{-1} A_{1,1}) \chi_1.
$$
Remark 3.5 Similar to previous design in section 3.3.1, the nonlinear function \( \varphi(x,u) \) are removed in system (3.43) because of the particular choice of (3.30).

Substituting (3.41) to (3.43), and then combining with (3.42), we have

\[
\dot{z} = (A_{2,2} - F_2^{-1} A_{1,2}) z + (A_{2,2} - F_2^{-1} A_{1,2}) F_2 F_1^{-1} y_1 \\
+ (A_{2,1} - F_2^{-1} A_{1,1}) y_1 \\
y_2 = C_2 M_1 \chi_1 + C_2 M_2 \chi_2
\] (3.44)

By applying (3.30) and (3.41) to (3.45),

\[
\dot{z} = (A_{2,2} - F_2^{-1} A_{1,2}) z + (A_{2,2} - F_2^{-1} A_{1,2}) F_2 F_1^{-1} y_1 \\
+ (A_{2,1} - F_2^{-1} A_{1,1}) y_1 \\
y_2 = C_2 M_2 z + (C_2 M_1 + C_2 M_2 F_2 F_1^{-1}) y_1
\] (3.45)

Let

\[
\tilde{A} = (A_{2,2} - F_2^{-1} A_{1,2}) \\
\tilde{C}_2 = C_2 M_2
\]

Equations (3.46) and (3.47) can be rewritten as

\[
\dot{z} = \tilde{A} z + (A_{2,2} - F_2^{-1} A_{1,2}) F_2 F_1^{-1} y_1 + (A_{2,1} - F_2^{-1} A_{1,1}) y_1 \\
y_2 = \tilde{C}_2 z + (C_2 M_1 + C_2 M_2 F_2 F_1^{-1}) y_1
\] (3.48)

For system (3.48), another condition is specified. This condition is specified in the below assumption.

**Assumption 3** \((\tilde{A}, \tilde{C}_2)\) is detectable or observable.
If Assumption 3 is satisfied, in other words, \((\tilde{A}, \tilde{C})\) is detectable or observable, the reduced-order observer can be designed as

\[
\dot{\hat{z}} = \tilde{A}\hat{z} + (A_{2,2} - F_2F_1^{-1}A_{1,2})F_2F_1^{-1}y_1 + (A_{2,1} - F_2F_1^{-1}A_{1,1})y_1 \\
+ L(\tilde{C}z - \tilde{C}\hat{z})
\]

(3.49)

The estimate of \(x\) is given by

\[
\hat{x} = M^{-1}\begin{bmatrix}
y_1 \\
\hat{z} + F_2F_1^{-1}y_1
\end{bmatrix}
\]

(3.50)

With \(e = z - \hat{z}\), the error dynamics are given by

\[
\dot{e} = (\tilde{A} - L\tilde{C})e \\
= (A_{2,2} - F_2F_1^{-1}A_{1,2} - L\tilde{C})e
\]

(3.51)

**Remark 3.6** Assumption 3 guarantees the existence of the reduced-order observer design (3.49) for system (3.48) which is in a similar form as the well-known Luenberger observer design discussed in chapter 2. A similar assumption as Assumption 3 was used in [38] for linear systems

**Remark 3.7** As shown in (3.51), the observer error dynamics are dominated by zero dynamics with involvement of observer gain \(L\) which is different to (3.34). For (3.34), if resultant matrix of \((A_{2,2} - F_2F_1^{-1}A_{1,2} - L\tilde{C})\) is Hurwitz, \(\lim_{t \to \infty} e \to 0\). With the involvement of observer gain \(L\), the convergence of reduced-order observer (3.51) is based on invariant zeros of matrix \((A_{2,2} - F_2F_1^{-1}A_{1,2} - L\tilde{C})\) with the choice of value \(L\) rather than sole stability of invariant zeros \(\{A, F, C\}\) as previous design in section 3.3.1.
3.3.3. Application of reduced-order observer designs to circadian model

In this section, two examples are presented. The first example shows the application of reduced-order observer design which is based on the method presented in section 3.3.1. Meanwhile, the second example shows the application of new reduced-order observer design developed in section 3.3.2. Both original and developed reduced-order observer designs are then applied to mammalian model (2.10).

From the structure shown in (3.24), for system (2.10), we may take

\[
\varphi(x, u) = \begin{bmatrix}
\frac{v_{1b}(x_7+c)}{k_{1b}(1+x^p_{1i})^4+x_7+c} \\
\frac{v_{4b}x^p_{7}}{k_{1b}^2(1+x^p_{3i})^2+x_3+c}
\end{bmatrix}, 
F = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0
\end{bmatrix}^T.
\]

Example 3.1 Consider system (2.10) with

\[
C = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 1
\end{bmatrix}
\]

The chosen value of \( C \) satisfies Assumption 1(1) and 1(2). The unknown state variables are identified as \( x_3, x_4, x_5, x_6, x_7 \). One can choose a non-singular state transformation matrix \( M \).
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with

\[
M = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
\]

This value of \( M \) satisfies (3.25). Using (3.27) and (3.28), values of parameters of new system after state transformation are obtained as

\[
F_1 = \begin{bmatrix}
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{bmatrix},
F_2 = \begin{bmatrix}
0 & 0 & 0 \\
0 & 0 & 1 \\
0 & 0 & 0
\end{bmatrix},
\]

and

\[
A_{1,1} = \begin{bmatrix}
-0.12 & 0 & 0 \\
0 & -0.29 & 0 \\
0 & 0 & -0.093
\end{bmatrix},
A_{1,2} = \begin{bmatrix}
0 & 0 & 0 & 0 \\
0.02 & 0 & 0 & 0 \\
0 & -0.657 & 0 & 0.09
\end{bmatrix},
\]

\[
A_{2,1} = \begin{bmatrix}
0 & 0.24 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0.003
\end{bmatrix},
A_{2,2} = \begin{bmatrix}
-0.14 & 0 & 0 & 0 \\
0 & -0.75 & 0 & 0 \\
0 & 0.24 & -0.51 & 0.06 \\
0 & -0.003 & 0.45 & -0.27
\end{bmatrix}
\]
In addition, from (3.26) and chosen value of $M$,

$$\chi_1 = \begin{bmatrix} x_1 \\ x_2 \\ x_4 + x_7 \end{bmatrix}, \chi_2 = \begin{bmatrix} x_3 \\ x_4 \\ x_5 \\ x_6 \end{bmatrix}$$

From calculated values of $A_{1,1}, A_{1,2}, A_{2,1}, A_{2,2}, F_1$ and $F_2$, linear dynamics of $z$ is obtained as

$$\dot{z} = \begin{bmatrix} -0.14 & 0 & 0 & 0 \\ 0 & -0.093 & 0 & -0.09 \\ 0 & 0.24 & -0.51 & 0.06 \\ 0 & -0.003 & 0.45 & -0.27 \end{bmatrix} z + \begin{bmatrix} 0 & 0.24 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0.24 \\ 0 & 0 & 0 \end{bmatrix} y$$

(3.52)

The eigenvalues or the invariant zeros of $\{A, F, C\}$ of system (3.52) are calculated as

$$\left\{ \begin{array}{c} -0.6338 \\ -0.1196 + 0.1306i \\ -0.1196 - 0.1306i \\ -0.1400 \end{array} \right\}$$

(3.53)

Since eigenvalues (3.53) have negative real parts, system (3.52) has Assumption 1(3) satisfied.
Therefore, a reduced-order observer can be designed as

\[
\dot{\hat{z}} = \begin{bmatrix}
-0.14 & 0 & 0 & 0 \\
0 & -0.093 & 0 & -0.09 \\
0 & 0.24 & -0.51 & 0.06 \\
0 & -0.003 & 0.45 & -0.27 \\
\end{bmatrix} \hat{z} + \begin{bmatrix}
0 & 0.24 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0.24 \\
0 & 0 & 0 \\
\end{bmatrix} y
\]

\[
\hat{x} = \begin{bmatrix}
1 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1 \\
\end{bmatrix} \hat{z} + \begin{bmatrix}
0 & 0 & 0 \\
0 & 0 & 1 \\
0 & 0 & 0 \\
0 & 0 & 0 \\
\end{bmatrix} y
\]

With \(e = z - \hat{z}\), the error dynamics are obtained as

\[
\dot{e} = \begin{bmatrix}
-0.14 & 0 & 0 & 0 \\
0 & -0.093 & 0 & -0.09 \\
0 & 0.24 & -0.51 & 0.06 \\
0 & -0.003 & 0.45 & -0.27 \\
\end{bmatrix} e
\]  (3.54)

Notice that eigenvalues calculated in (3.53) are also the eigenvalues of system (3.54). The dynamics of unknown state variables \(x_3, x_4, x_5, x_6, x_7\) and their estimates are shown from Figure. 3.8 to Figure. 3.12.

As shown from Figure. 3.8 to Figure. 3.12, the reduced-order observer design gives asymptotic estimates of the unmeasured state variables. However, this observer design is only applicable in case of \(\text{rank}(C) = \text{rank}(F)\). This is implied in Assumption 1(2). In case of \(\text{rank}(C) > \text{rank}(F)\), \(CF\) is not invertible, therefore, \(F_1\) is not invertible. As a result, (3.28) can not be proceeded. However, this problem can be solved by using the proposed method in section 3.3.2. This is shown by the next example.
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Figure 3.8. Dynamics of $x_3$ and its estimates

Figure 3.9. Dynamics of $x_4$ and its estimates
Figure 3.10. Dynamics of $x_5$ and its estimates

Figure 3.11. Dynamics of $x_6$ and its estimates
Example 3.2 Consider system (2.10) with

\[
C = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
\]

Values of \( C_1, C_2 \) are identified as

\[
C_1 = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0
\end{bmatrix},
C_2 = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
\]

Following the procedure introduced in section 3.3.2, we have
$M = M^{-1} = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}$

$M_1 = \begin{bmatrix}
1 & 0 \\
0 & 1 \\
0 & 0 \\
0 & 1 \\
0 & 0 \\
0 & 0
\end{bmatrix}$

$M_2 = \begin{bmatrix}
0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}$

and

$F_1 = \begin{bmatrix}
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{bmatrix}$

$F_2 = \begin{bmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}$

$\chi_1 = \begin{bmatrix}
x_1 \\
x_2 \\
x_3
\end{bmatrix}$

$\chi_2 = \begin{bmatrix}
x_4 \\
x_5 \\
x_6 \\
x_7
\end{bmatrix}$

With

$A_{1,1} = \begin{bmatrix}
-0.12 & 0 & 0 \\
0 & -0.29 & 0 \\
0 & 0 & -0.75
\end{bmatrix}$

$A_{1,2} = \begin{bmatrix}
0 & 0 & 0 & 0 \\
0.02 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}$

$A_{2,1} = \begin{bmatrix}
0 & 0.24 & 0 \\
0 & 0 & 0.24 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}$

$A_{2,2} = \begin{bmatrix}
-0.14 & 0 & 0 & 0 \\
0 & -0.51 & 0.06 & 0 \\
0 & 0.45 & -0.27 & 0.003 \\
0 & 0 & 0.09 & -0.093
\end{bmatrix}$
system (3.46) is obtained as
\[
\dot{z} = \begin{bmatrix}
-0.14 & 0 & 0 & 0 \\
0 & -0.51 & 0.06 & 0 \\
0 & 0.45 & -0.27 & 0.003 \\
0 & 0 & 0.09 & -0.093
\end{bmatrix}
z + \begin{bmatrix}
0 & 0.24 & 0 \\
0 & 0 & 0.24 \\
0 & 0 & 0
\end{bmatrix} y_1
\] (3.55)
\[
y_2 = \begin{bmatrix}
0 & 0 & 0 & 1
\end{bmatrix} z
\]

For system (3.55), without involvement of observer gain \( L \), eigenvalues or invariant zeros of \( \{A, F, C\} \) are calculated as
\[
\begin{bmatrix}
-0.0907 \\
-0.1888 \\
-0.5936 \\
-0.1400
\end{bmatrix}
\] (3.56)

System (3.55) has \( (\hat{A}, \hat{C}) \) detectable, therefore, Assumption 3 is satisfied. Observer gain value \( L \) is chosen such that \( (\hat{A} - L\hat{C}) \) of system (3.55) is stable. This also means that the eigenvalues have their negative real parts placed on the left hand plane. By choosing value of \( L = \begin{bmatrix}
0.2 & 0.1 & 0.8 & 1
\end{bmatrix}^T \), the reduced-order observer design can be proposed as
\[
\dot{\hat{z}} = \begin{bmatrix}
-0.14 & 0 & 0 & 0 \\
0 & -0.51 & 0.06 & 0 \\
0 & 0.45 & -0.27 & 0.003 \\
0 & 0 & 0.09 & -0.093
\end{bmatrix}\hat{z} + \begin{bmatrix}
0 & 0.24 & 0 \\
0 & 0 & 0.24 \\
0 & 0 & 0
\end{bmatrix} y_1 + L (\hat{C}z - \hat{C}\hat{z})
\]

The estimate of \( \hat{x} \) is given by
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\[
\hat{x} = \begin{bmatrix}
1 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{bmatrix} \hat{z}
\]

The error dynamics are given by

\[
\dot{e} = \begin{bmatrix}
-0.14 & 0 & 0 & -0.2 \\
0 & -0.51 & 0.06 & -0.1 \\
0 & 0.45 & -0.27 & -0.797 \\
0 & 0 & 0.09 & -1.093
\end{bmatrix} e
\]

For error dynamics (3.57), eigenvalues are calculated as

\[
\{-0.1400, -0.2661, -0.6081, -0.9988\}
\]

Notice that the eigenvalues (3.57) are obtained with the involvement of observer gain \(L\). The dynamics of unmeasured states \(x_3, x_5, x_6\) and their estimates are depicted from Figure. 3.13 to Figure. 3.15.

With the chosen value for \(L\), the eigenvalues obtained in (3.58) have negative real parts on the left half plane further than the eigenvalues calculated in (3.56). This is also true with the comparison between (3.58) and (3.53). As a result, reduced-order observer design with the existence of \(L\) has faster convergence rate than the one without it. In other words, the reduced-order observer design in Example 2 has better performance than the one in Example 1. This is clearly shown in Figure. 3.14 and Figure. 3.15 where the estimates of \(x_5, x_6\) converge to their
exact values faster than the results shown in the previous example.

![Figure 3.13. Dynamics of $x_3$ and its estimate](image)

3.4. Evaluation of performances of one-sided Lipschitz and new reduced-order observer designs

Consider state output values which has been given in Example 2 for one-sided Lipschitz observer design. This value is described by

$$C = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$  \hspace{1cm} (3.59)

The unknown state variables are $x_3$, $x_5$, and $x_6$. The Lipschitz constant values of mammalian model have been calculated in section 3.2.4.4. Using these Lipschitz constant values and solving
Figure 3.14. Dynamics of $x_5$ and its estimate

Figure 3.15. Dynamics of $x_6$ and its estimate
(3.9), values of $\sigma$ and observer gain $L$ are obtained as

$$
\sigma = 14.7701, \quad L = \begin{bmatrix}
0.2753 & 0 & 0 & 0 \\
0 & 0.3399 & 0 & 0 \\
0 & -0.1057 & 0 & 0 \\
0 & 0 & 0.4137 & -0.0022 \\
0 & 0 & -0.0454 & 0.0011 \\
0 & 0 & -0.0350 & 0.0197 \\
0 & 0 & -0.0022 & 0.2872
\end{bmatrix}.
$$

With new values of $\sigma$ and observer gain $L$ just calculated, the responses of these unknown state variables are depicted in Figure. 3.16, Figure. 3.17, and Figure. 3.18.

Figure 3.16. Dynamics of $x_3$ and its estimates using one-sided Lipschitz observer with value of $C$ as (3.59)

The improved reduced-observer design given in section 3.3.2 has better performances than the one summarized in section 3.3.1. Its performances have been shown from Figure. 3.13 to Figure. 3.15. These performances are compared with the performances of one-sided Lipschitz observer presented from Figure. 3.16 to Figure. 3.18. The results obtained show that one-sided
Figure 3.17. Dynamics of $x_5$ and its estimates using one-sided Lipschitz observer with value of $C$ as (3.59)

Figure 3.18. Dynamics of $x_6$ and its estimates using one-sided Lipschitz observer with value of $C$ as (3.59)
Lipschitz observer has slower convergence than the improved reduced order observer design. The reason may be due to nature of reduced-order observer design where a lower order system than the original system is obtained after a state transformation. Since this new system is simpler than the original system with nonlinear functions avoided, the observer applied to this system has better performance than the observer applied to original system. In other words, reduced-order observer applied to the new and lower order system after state transformation has better performance than one-sided Lipschitz observer applied to original system.

The desired range of time has been chosen to be 40h in section 3.2.4.5. For new value of $C$ chosen in (3.59), the results obtained from Figure 3.16 to Figure 3.18 have shown that the one-sided Lipschitz observer design does not converge the estimated states to their actual states within the desired range of time. The computation of Lipschitz constants of nonlinearities may be again the reason which affects the convergent rate of one-sided Lipschitz observer.

### 3.5. Conclusions

We have proposed designs of reduced-order and one-sided Lipschitz observers to circadian models of Neurospora and Mammals. For reduced-order observer, a new design is proposed for a class of MO nonlinear systems. One significant development of the new proposed reduced-observer design is the condition given in Assumption 3 which allows the involvement of observer gain $L$ in its design and also in its error dynamics. With the existence of $L$, the convergent rate of this new design method is no longer limited by the dynamics of invariant zeros. Furthermore, the observer error dynamics can be improved by the choice of value $L$. With this improvement, the new proposed reduced-observer design can apply to wide range of MO nonlinear systems with more choice of output values $C$.

Due to strict conditions for output value $C$, the new design of reduced-order observer which extends the existing one in literature has limit in its application to nonlinear systems if compared with one-sided Lipschitz observer. However, like one-sided Lipschitz observer, this new reduced-order observer design has been successfully applied to the mammalian model in this chapter. Although the proposed one-side Lipschitz observer design has more flexibility in
its application to nonlinear systems than the new reduced-order observer design, it can only
deal with bounded nonlinearities. The new reduced-order observer design allows not only
bounded nonlinearities but also with non-sector bounded nonlinearities. Through the achieved
results from simulation studies, we have also shown the possibility of reducing measurements
in biological study of circadian rhythms by using observers. The proposed observer designs can
be considered to apply to the next chapter.
Chapter 4

Circadian phase resetting using nonlinear output-feedback control

4.1. Introduction

For mammals, the circadian clock gene, also known as the circadian pacemaker, is placed in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus [57]. The circadian pacemaker captures information sent from an external environment cue such as light, and then coordinates the timing of other slave clocks or slave oscillators in other parts of the body [68]. Any changes of environment cues which cause the mismatches between external and internal rhythms can lead to the disruption of circadian rhythms. The existence of these mismatches in longer term has a negative impact to health. This phenomenon is known as circadian disorders. Jet lag due to trans-continent flight, and sleeping disorder due to irregular sleep-wake cycles are two typical examples of circadian disorders [72], [73]. In practice, one of the known medical treatments for circadian disorders is the application of light [10]. Light is major external environmental cue, and with light input, the circadian phase can be adjusted to the light/dark rhythms at destination.

The effect of light to circadian rhythms has been investigated in literature. Many results have been presented [28], [48], where the light input whose shape is usually considered as “ON/OFF” function (continuous pulses) is applied to proposed circadian models. Based on the fact that light can be used to adjust the circadian phase in practice, there are also research studies of circadian phase resetting in theory. The results presented in recent years [5], [6] have shown the circadian rhythms are successfully restored using model predictive control (MPC) through the application of continuous light input to a developed circadian model. Besides MPC, there are also reports on circadian rhythm restoration by using flatness-based control to a Drosophila
In this chapter, we aim for the restoration of circadian phases. In order to achieve this objective, we propose an alternative control design method which synchronizes trajectories generated from a controlled model with the trajectories generated from a reference model via back-stepping approach. The control input is designed by using back-stepping method. Then, this input is applied to controlled system to control its trajectories. Both reference system and controlled system are based on a 3rd order mathematical model of Neurospora circadian rhythms presented in section 2.3.2 of chapter 2. The trajectories generated by controlled system represent the altered rhythms. Meanwhile, the reference trajectories represent the desired rhythms which the trajectories of controlled system are adjusted to match. For nonlinear systems which may have some of their internal state variables which are difficult for direct measurement such as circadian model, a tool is needed to estimate these states. In control theory, state estimations are carried out by using observers. Therefore, a suitable observer design is required. The proposed one-sided Lipschitz observer design in chapter 3 is exploited to estimate the unknown state variables of the circadian model.

4.2. Back-stepping design

Back-stepping is a known control design method in nonlinear control systems theory. Design of back-stepping method can be found in [47]. In this section, a brief description of back-stepping design is presented. In order to use back-stepping design, the considered systems have to be in ‘triangular’ structure or in strict feedback form.
The strict feedback form is described by

\[
\begin{align*}
\dot{\zeta}_1 &= \zeta_2 + \psi_1 (\zeta_1) \\
\dot{\zeta}_2 &= \zeta_3 + \psi_2 (\zeta_1, \zeta_2) \\
& \vdots \\
\dot{\zeta}_{n-1} &= \zeta_n + \psi_{n-1} (\zeta_1, \zeta_2, \ldots, \zeta_{n-1}) \\
\dot{\zeta}_n &= u + \psi_n (\zeta_1, \zeta_2, \ldots, \zeta_n)
\end{align*}
\] (4.1)

where \( \zeta \in \mathbb{R}^n \) are state variables, and \( \psi(x, u) \in \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n \) are nonlinear functions. Define

\[
\begin{align*}
\xi_1 &= \zeta_1 \\
\xi_n &= \zeta_n - \alpha_{n-1} (\zeta_1, \zeta_2, \ldots, \zeta_n)
\end{align*}
\] (4.2, 4.3)

where \( \alpha_{n-1} \) are stabilizing functions. For new system including dynamics of \( \xi_1, \ldots, \xi_n \), the control input can be designed as

\[
u = -\xi_{n-1} - c_n \xi_n - \psi_n (\zeta_1, \zeta_2, \ldots, \zeta_{n-1}) + \sum_{i=1}^{n-1} \frac{\partial \alpha_{n-1}}{\partial \zeta_i} (\zeta_{i+1} + \psi_i (\zeta_1, \zeta_2, \ldots, \zeta_i))
\] (4.4)

where \( c_n \) are positive constants. Stability of system created by (4.2) and (4.2) is considered. Its stability is guaranteed by the concept of Lyapunov stability. For this system, a Lyapunov function candidate is defined, and this function is described by

\[
V = \frac{1}{2} \sum_{i=1}^{n} \xi_i^2
\] (4.5)
4.3. Phase control

4.3.1. System transformation

In order to apply back-stepping control design method, the applied system (2.9) has to be in 'triangular' structure. System (2.9) is not in the considered structure. Therefore, this system requires state transformation. The state transformation is carried out by following procedure shown in equations (2.34) and (2.35) which are given in section 2.4.4 for high gain observer design. Let

\[ q = Tx, \]

(4.6)

where \( T \) is non-singular state transformation matrix. Value of \( T \) has the same value of \( G \) given in (2.35) where

\[ T = \begin{bmatrix} 0 & 0 & 1 \\ 0 & k_1 & 0 \\ k_1k_s & 0 & 0 \end{bmatrix}, \]

(4.7)

Neurospora model, system (2.9), is transformed to a new system which is described by

\[ \begin{align*}
\dot{q}_1 &= q_2 - k_2 q_1 \\
\dot{q}_2 &= q_3 - k_1 q_2 + k_1 k_2 q_1 - v_d \frac{k_1 q_2}{k_1 K_d + q_2}, \\
\dot{q}_3 &= v_s \frac{k_1 k_s K_i^n}{K_i^n + q_1^n} - v_m \frac{k_1 k_s q_3}{K_M k_1 k_s + q_3}
\end{align*} \]

(4.8)

After the state transformation, the initial condition of transformed system (4.8) is found to be

\[ q(0) = \begin{bmatrix} 1 & 0.5 & 1.25 \end{bmatrix}^T. \]

Dynamics of the state variables of transformed system (4.8) are shown in Figure. 4.1.
4.3.2. Reference model and Controlled model

We choose system (4.8) and its set initial conditions as the reference model and chosen initial values of this model. As a result, the trajectories which are shown in Figure 4.1 for system (4.8) are also the dynamics of state variables of the reference model. These trajectories are considered as the desired controlled behaviors for circadian rhythms at destination.

The controlled model takes the same form of (4.8). This model is described by

\[
\begin{align*}
\dot{z}_1 &= z_2 - k_2 z_1 \\
\dot{z}_2 &= z_3 - k_1 z_2 + k_1 k_2 z_1 - v_d \frac{k_1 z_2}{k_1 K_d + z_2} \\
\dot{z}_3 &= v_s k_1 k_s K_i^n + z_1^n - v_m \frac{k_1 k_s z_3}{K_m k_1 k_s + z_3}
\end{align*}
\] (4.9)

The outputs of controlled model are altered trajectories which have their phases shifted compared with the reference trajectories of system (4.9). The phase shifts are reflected by choosing different initial conditions. Consider initial conditions of controlled system (4.9) be

\[
z(0) = \begin{bmatrix} 1.5 & 1 & 1.75 \end{bmatrix}^T.
\]
in Figure 4.2, Figure 4.3, and Figure 4.4. As seen from these figures, the controlled model has its phases delayed with the phases of reference model, and value of the phase difference is approximately +6.5h.

**Remark 4.1** The reference and controlled models describe the circadian rhythms of a certain living species (Neurospora) in two places having different time zones in practice. Since these two models describe the circadian rhythms in the same living species, they have identical structures. However, because of different time zones, the reference and controlled models have phase differences. For circadian models, the different time zones is theoretically represented by different settings of initial conditions or by different values of parameters. A case of phase differences caused by different values of parameters is considered in chapter 5. In this chapter, chapter 4, the phase differences are reflected by the different settings of initial conditions. In theory, the phase differences caused by different settings of initial conditions can be solved by providing a state transformation which can do phase shifts. However, this can not be easily applied in practice. Instead of providing a state transformation, a form of control input is designed. Based on this control input, the phase differences caused by different settings of initial conditions may be easier to solve in practice. The procedure of control design is described in later sections.

### 4.3.3. Control objective and control input target

Our control objective is to synchronize the trajectories of controlled model with the trajectories of reference model. A control input is applied to the controlled system. Consider again the original system (2.9). Among the parameters appeared in (2.9), parameter $v_s$, which denotes the rate of $frq$ mRNA transcription, is sensitive to light input [42]. Therefore, for Neurospora circadian rhythms, this parameter is usually used as control target in several results which have
Figure 4.2. Dynamics of reference and controlled state variables $q_1$ and $z_1$

Figure 4.3. Dynamics of reference and controlled state variables $q_2$ and $z_2$
been presented in literature [6], [21]. If \( v_s \) is the control target, system (2.9) is rewritten as:

\[
\begin{align*}
\dot{x}_1 &= (v_s + u) \frac{K^n}{K^n + x_3^n} - v_m \frac{x_1}{K_M + x_1} \\
\dot{x}_2 &= k_s x_1 - v_d \frac{x_2}{K_d + x_2} - k_1 x_1 + k_2 x_3, \\
\dot{x}_3 &= k_1 x_2 - k_2 x_3
\end{align*}
\] (4.10)

After the transformation by using (4.6), (4.7), instead of (4.9), we obtain the new controlled model with the involvement of control input as

\[
\begin{align*}
\dot{z}_1 &= z_2 - k_2 z_1 \\
\dot{z}_2 &= z_3 - k_1 z_2 + k_1 k_2 q_1 - v_d \frac{k_1 z_2}{k_1 K_d + z_2} \\
\dot{z}_3 &= v_s k_1 k_s K^n - v_m \frac{k_1 k_s z_3}{K_M k_1 k_s + z_3} + u_z \frac{k_1 k_s K^n}{K^n + q^n_1}
\end{align*}
\] (4.11)

\textbf{Remark 4.2} The control input \( u_z \) may be the light input or the other input signals (e.g. the electricity)
4.3.4. Application of one-sided Lipschitz observer design

Both reference and controlled models have the same structure as system (3.4). Based on the structure of (3.4), for system (4.11), nonlinear functions \( \varphi(x, u) \) may be taken as

\[
\varphi(x, u) = \begin{bmatrix}
\varphi_1(z_2) \\
\varphi_2(a(z_1)) \\
\varphi_2(b(z_3)) \\
\end{bmatrix} = \begin{bmatrix}
-k_1 z_2 \\
\frac{k_1 k_s K_m}{K_d} z_1 \\
-k_1 k_s z_3 \\
\end{bmatrix}
\]

Since system (4.8) is the reference model, without loss of generality, we can assume that all state variables are measurable. For controlled model (4.11), this model may be assumed to have unmeasured state variables. Value of \( C \) given in equation (2.37), \( C = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \), is assumed to be outputs of original system (4.10). After state transformation using (4.6) and (4.7), new value of \( C \) of system (4.11) is calculated as

\[
C_2 = CT^{-1} = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}
\]  \tag{4.12}

\( C_2 \) has the same value of \( C_1 \) given in equation (2.38) in chapter 2. As shown in \( C_2 \), state variables \( z_2 \) and \( z_3 \) are unknown. The proposed one-sided Lipschitz observer design is applied to find these two unknown states.

The nonlinearities of system (4.11) are Lipschitz nonlinearities. Therefore, we apply Theorem 3.3 with modified LMI (3.9). In order to use linear matrix inequality (LMI) (3.9), values of Lipschitz constants \( \gamma_i \) in LMI (3.9) are needed to be calculated.

Using Lipschitz condition (3.1), we have

\[
\begin{align*}
\left\| -\frac{v_d k_1 z_2}{k_1 K_d + z_2} + \frac{v_d k_1 \hat{z}_2}{k_1 K_d + \hat{z}_2} \right\| & \leq \frac{v_d}{K_d} \| z_2 - \hat{z}_2 \| \\
\left\| -\frac{v_m k_1 k_s z_3}{K_M k_1 k_s + z_3} + \frac{v_m k_1 k_s \hat{z}_3}{K_M k_1 k_s + \hat{z}_3} \right\| & \leq \frac{v_m}{K_M} \| z_3 - \hat{z}_3 \|
\end{align*}
\]

Values of Lipschitz constants are obtained with \( \gamma_1 = \frac{v_d K_d}{K_d} = 10.7962 \) for \( \varphi_1(z_2) \), and \( \gamma_{2b} = \frac{v_m K_M}{K_M} = 10.7962 \) for \( \varphi_2(z_3) \).
\( \frac{v_m}{K_m} = 1.01 \) for \( \varphi_{2b}(z_3) \). For nonlinear function \( \varphi_{2a}(z_1) \) which has Lipschitz constant \( \gamma_{2a} \), the Lipschitz constant value can be computed by using (3.3). Using the same procedure which has been applied to find Lipschitz constant of \( \varphi_{1b}(x_3) \) in section 3.2.4.3, Lipschitz constant \( \gamma_{2a} \) of \( \varphi_{2a}(z_1) \) is found to be \( \gamma_{2a} = 0.325 \).

The observer (3.5) is applied to controlled model (4.11). Its design is described by

\[
\dot{\hat{z}} = A_2 \hat{z} + \varphi(\hat{z}, u) + B_2 u + L(C_2 z - C_2 \hat{z}),
\]  

(4.13)

where \( A_2 = TAT^{-1} \) and \( B_2 = TB \). \( A \) and \( B \) are matrices of original Neurospora circadian system represented in equation (4.10).

After the Lipschitz constants are found, we solve LMI (3.9) to obtain

\[
\sigma = 113.6063, L = \begin{bmatrix} 3.9887 \\ 2.6067 \\ 1.3469 \end{bmatrix},
\]

(4.14)

Let initial condition of observer (4.13) be \( \hat{z} = \begin{bmatrix} 0 & 0 & 0 \end{bmatrix}^T \). The dynamics of unknown state variables \( z_2, z_3 \) and their estimates are shown in Figure. 4.5 and Figure. 4.6.

4.3.5. Procedure of control design

Define

\[
e_1 = \hat{z}_1 - q_1
\]

\[
e_2 = \hat{z}_2 - q_2
\]

(4.15)

\[
e_3 = \hat{z}_3 - q_3
\]
Figure 4.5. Dynamics of unknown controlled state variable $z_2$ and its estimate

Figure 4.6. Dynamics of unknown controlled state variable $z_3$ and its estimate
Based on equations (4.2) and (4.3), let

\[ \omega_1 = e_1 \]
\[ \omega_2 = e_2 - \alpha_1 \]
\[ \omega_3 = e_3 - \alpha_2 \]  

(4.16)

The error dynamics are then obtained as

\[ \dot{e}_1 = e_2 - k_2 e_1 \]  
\[ \dot{e}_2 = e_3 - k_1 e_2 + k_1 k_2 e_1 - \frac{v_d k_d^2 K_d e_2}{(k_1 K_d + \hat{z}_2) (k_1 K_d + q_2)} \]  
\[ \dot{e}_3 = v_i k_i k_s K_i^n + \hat{z}_1^n - v_s k_1 k_s K_s^n + u_s \frac{k_1 k_s K_i^n}{K_i^n + \hat{z}_1^n} + \frac{k_1 k_s K_i^n}{K_i^n + \hat{z}_1^n} \]  
\[ - \frac{v_m K_M (k_1 k_s)^2 e_3}{(K_M k_1 k_s + \hat{z}_3) (K_M k_1 k_s + q_3)} \]  

(4.17)

(4.18)

(4.19)

From (4.17), dynamic of \( \omega_1 \) is obtained as

\[ \dot{\omega}_1 = e_2 - k_2 e_1 \]
\[ = \omega_2 + \alpha_1 - k_2 e_1 \]  

(4.20)

The stabilizing function \( \alpha_1 \) is designed as:

\[ \alpha_1 = -c_1 \omega_1 + k_2 e_1 \]  

(4.21)

The resultant dynamic of \( \omega_1 \) is:

\[ \dot{\omega}_1 = -c_1 \omega_1 + \omega_2 \]  

(4.22)
We continue to find dynamics of $\omega_2$ and $\omega_3$. The dynamic of $\omega_2$ is obtained as

$$
\dot{\omega}_2 = e_3 - k_1 e_2 + k_1 k_2 e_1 - \frac{v_d k_1^2 K_d e_2}{(k_1 K_d + \dot{z}_2) (k_1 K_d + q_2)} - \frac{\partial \alpha_1}{\partial e_1} \dot{e}_1
$$

$$
= \omega_3 + \alpha_2 - k_1 e_2 + k_1 k_2 e_1 - \frac{v_d k_1^2 K_d e_2}{(k_1 K_d + \dot{z}_2) (k_1 K_d + q_2)} - \frac{\partial \alpha_1}{\partial e_1} \dot{e}_1, \quad (4.23)
$$

where the stabilizing function $\alpha_2$ is described by

$$
\alpha_2 = -\omega_1 - c_2 \omega_2 + k_1 e_2 - k_1 k_2 e_1 + v_d k_1 \frac{k_1 K_d e_2}{(k_1 K_d + \dot{z}_2) (k_1 K_d + q_2)} + \frac{\partial \alpha_1}{\partial e_1} \dot{e}_1
$$

$$
= -\omega_1 - c_2 \omega_2 + \frac{k_1 K_d e_2}{(k_1 K_d + \dot{z}_2) (k_1 K_d + q_2)} + \frac{\partial \alpha_1}{\partial e_1} \dot{e}_1 \quad (4.24)
$$

Substituting (4.24) to (4.23) to obtain the resultant dynamic of $\omega_2$ as

$$
\dot{\omega}_2 = -\omega_1 - c_2 \omega_2 + \omega_3 \quad (4.25)
$$

The final dynamic of $\omega_3$ is described by

$$
\dot{\omega}_3 = \frac{k_1 k_s K_i^n}{K_i^n + \dot{z}_1^n} - \frac{k_1 k_s K_i^n}{K_i^n + q_1^n} + u_z k_1 k_s K_i^n - \frac{v_m K_M (k_1 k_s)^2 e_3}{(K_M k_1 k_s + z_3) (K_M k_1 k_s + q_3)}
$$

$$
- \frac{\partial \alpha_2}{\partial e_1} \dot{e}_1 - \frac{\partial \alpha_2}{\partial e_2} \dot{e}_2 \quad (4.26)
$$

**Remark 4.3** $\dot{e}_1, \dot{e}_2$ appeared in (4.23), (4.24), (4.26) are dynamics of state variables which are given in (4.17), (4.18), and (4.19).

Based on (4.4), the control input is designed as

$$
u_z = \frac{K_i^n + \dot{z}_1^n}{k_1 k_s K_i^n} \left[ -\omega_2 - c_3 \omega_3 - \frac{k_1 k_s K_i^n}{K_i^n + \dot{z}_1^n} + \frac{k_1 k_s K_i^n}{K_i^n + q_1^n} + \frac{\partial \alpha_2}{\partial e_1} (e_2 - k_2 e_1) \right]
$$

$$
+ \frac{\partial \alpha_2}{\partial e_2} \left( e_3 - k_1 e_2 + k_1 k_2 e_1 - \frac{v_d k_1^2 K_d e_2}{(k_1 K_d + \dot{z}_2) (k_1 K_d + q_2)} \right) \quad (4.27)
$$
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Substituting (4.27) to (4.26) to get the final resultant dynamic of $\omega_3$ as

$$\dot{\omega}_3 = -\omega_2 - c_3 \omega_3$$  \hspace{1cm} (4.28)

**Stability analysis:** Based on (4.5), Lyapunov function is defined as

$$V = \frac{1}{2} (\omega_1^2 + \omega_2^2 + \omega_3^2)$$  \hspace{1cm} (4.29)

Substituting (4.22), (4.25) and (4.28) to $V$ in (4.29) to obtain $\dot{V}$ as

$$\dot{V} = \omega_1 \dot{\omega}_1 + \omega_2 \dot{\omega}_2 + \omega_3 \dot{\omega}_3$$

$$= \omega_1 (-c_1 \omega_1 + \omega_2) + \omega_2 (-\omega_1 - c_2 \omega_2 + \omega_3)$$

$$+ \omega_3 (-\omega_2 - c_3 \omega_3)$$

$$= -c_1 \omega_1^2 - c_2 \omega_2^2 - c_3 \omega_3^2$$

With $c_1, c_2, c_3$ are positive constants, $\dot{V} < 0$. As a result, the system which contains error dynamics (4.17), (4.18), and (4.19) is asymptotically stable.

According to Figure. 4.2, Figure. 4.3, and Figure. 4.4, dynamics of state variables of controlled system (4.11), $z_1, z_2, z_3$, are stabilized at $t \geq 50h$. Therefore, the controller is applied at $t = 50h$. Parameters $c_1, c_2$, and $c_3$ can have different positive values. However, for simplicity, $c_1, c_2$, and $c_3$ are chosen to have the same values. Positive values of $c$ are chosen as $c_1 = c_2 = c_3 = 0.1$. Notice that dynamics of state variables $z_2, z_3$ of controlled model are unknown (according to the chosen output value $C_2$ in (4.12)). With the applied control input at $t \geq 50h$, the dynamics of unknown state variables $z_2, z_3$ of controlled model and their estimates are synchronized with the dynamics of state variables $q_2, q_3$ of reference model respectively. The results are shown in Figure. 4.7, Figure. 4.8. The dynamic of control input which forces the synchronization is depicted in Figure 4.9.
Figure 4.7. Synchronized dynamics of $z_2$, its estimate, and $q_2$ in case of $c_1 = c_2 = c_3 = 0.1$

Figure 4.8. Synchronized dynamics of $z_3$, its estimate, and $q_3$ in case of $c_1 = c_2 = c_3 = 0.1$
Remark 4.4 The form of control input achieved in Figure 4.9 may present the displacements of movements of molecules obtained by the effect of medicine in practice. This input may also be the electricity waveform produced by the sources embedded into the body.

4.4. Discussions

Data collected for phase restoration are used as desired performances to compare with the results obtained by using back-stepping method. By applying optimal control with 1-minute light pulse as continuous control input, the range of time required to recover the circadian phase is about $\Delta t = 38h$ for range of initial phase difference from +6h to +7h [40]. Let this range of time $(0 \leq t \leq 38h)$ be the expected range for phase restoration. Figure. 4.7 and Figure. 4.8 have shown that the reference trajectories are tracked and restored at approximately $t = 80h$. Since the controller is applied at $t = 50h$, therefore, the time required for phase synchronizations is about $\Delta t_1 = 80 - 50 = 30h$. Since $\Delta t_1 = 30h < \Delta t = 38h$, this result of $\Delta t_1$ is within the desired range of time, and it is also better than the expectation. As a result, the performances of proposed control design satisfy the desired performances.
Values of $c_1, c_2, c_3$ are altered. Values of $c_1, c_2, c_3$ are reset as $c_1 = c_2 = c_3 = 1$. Similar to the previous case, with the applied control input at $t \geq 50h$, the dynamics of unknown state variables $z_2, z_3$ of controlled model and their estimates are also synchronized with the dynamics of state variables $q_2, q_3$ of reference model respectively. In this case, the results are shown in Figure. 4.10 and Figure. 4.11. The dynamic of applied control input is depicted in Figure. 4.12.

![Graph showing synchronized dynamics of $z_2$, its estimate, and $q_2$ in case of $c_1 = c_2 = c_3 = 1$.](image)

Figure 4.10. Synchronized dynamics of $z_2$, its estimate, and $q_2$ in case of $c_1 = c_2 = c_3 = 1$

As shown in Figure. 4.10 and Figure. 4.11, the trajectories of controlled model track the reference trajectories at approximately $t = 85h$. The time required to reset the phases of controlled model is then calculated approximately at $\Delta t_2 = 85 - 50 = 35h$. We then compare the achieved range of time in this case with the range of time calculated in previous case. Since $\Delta t_1 = 30h < \Delta t_2 = 35h$, therefore, the performances of proposed control design for phase synchronizations in case of $c_1 = c_2 = c_3 = 0.1$ are better than the performances shown in the case of $c_1 = c_2 = c_3 = 1$. Although the performances of the case $c_1 = c_2 = c_3 = 1$ are not as good as the results shown in previous case, these performances still satisfy the desired performances because $\Delta t_2$ is still within the chosen range of time ($\Delta t_2 < \Delta t$).

Values of $c$ are then increased to $c_1 = c_2 = c_3 = 1.5$, $c_1 = c_2 = c_3 = 2$, and $c_1 = c_2 = c_3 = 3$. The dynamics of unknown states $z_2, z_3$, and their estimates for three new values of $c$
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Figure 4.11. Synchronized dynamics of $z_3$, its estimate, and $q_3$ in case of $c_1 = c_2 = c_3 = 1$

Figure 4.12. Dynamics of control input in case of $c_1 = c_2 = c_3 = 1$
are depicted from Figure. 4.13 to Figure. 4.18. As shown in Figure. 4.13 and Figure. 4.14, the dynamics of unknown states and their estimates successfully track the reference trajectories at approximately $t_3 = 100h$. The time required for phase synchronizations at $c_1 = c_2 = c_3 = 1.5$ is approximately at $\Delta t_3 = 100 - 50 = 50h$ which is longer than the time required or phase synchronizations at the previous values of $c$ ($c_1 = c_2 = c_3 = 0.1$ and $c_1 = c_2 = c_3 = 1$). Moreover, this range of time does not satisfy the desired range of time chosen.

Consider the remaining two new values of $c$, $c_1 = c_2 = c_3 = 2$ and $c_1 = c_2 = c_3 = 3$. For $c_1 = c_2 = c_3 = 2$, Figure. 4.15 and Figure. 4.16 have shown that the synchronizations are carried out successfully. In this case, the time required for phase synchronizations is at approximately $\Delta t_4 = 110 - 50 = 60h$. With value of $\Delta t_4$ just calculated, obviously, the speed of synchronization process is not improved if compared with the results shown for the previous cases of $c$. It tends to decrease as values of $c$ are increased. Besides unimproved speed, there are small transient oscillations appeared in the synchronized dynamics of $z_2$, $z_3$, and their estimates. Increase of values of $c$ causes more transient oscillations to appear in the dynamics of state variables. This is clearly shown in Figure. 4.17 and Figure. 4.18 where the synchronizations are carried out at value of $c_1 = c_2 = c_3 = 3$.

Figure 4.13. Synchronized dynamics of $z_2$, its estimate, and $q_2$ in case of $c_1 = c_2 = c_3 = 1.5$
Figure 4.14. Synchronized dynamics of $z_3$, its estimate, and $q_3$ in case of $c_1 = c_2 = c_3 = 1.5$

Figure 4.15. Synchronized dynamics of $z_2$, its estimate, and $q_2$ in case of $c_1 = c_2 = c_3 = 2$
Figure 4.16. Synchronized dynamics of $z_3$, its estimate, and $q_3$ in case of $c_1 = c_2 = c_3 = 2$

Figure 4.17. Synchronized dynamics of $z_2$, its estimate, and $q_2$ in case of $c_1 = c_2 = c_3 = 3$
From the performances for the five considered cases of values of $c$, we may conclude that the control design has best performances for small values of $c$, in particular, for values of $c \leq 1$. Between the two considered small values of $c$, $c_1 = c_2 = c_3 = 0.1$ and $c_1 = c_2 = c_3 = 1$, $c_1 = c_2 = c_3 = 0.1$ is considered as ideal values of $c$ which give the better results for phase recovery.

**Remark 4.5** In general, according to the stability analysis carried out in section 4.3.5, if values of $c$ are large positive real constants, the speed of synchronizations is very fast. Several cases of values of $c$ have been tested in section 4.4, and the ideal values of $c$ are found based on the observations from simulation studies. Evaluation of performance of a control design based on the observations from simulation studies is a method which is usually used in nonlinear control theory.

**4.5. Conclusions**

We have proposed observer-based back-stepping for circadian phase resetting of a Neurospora model. The performances of proposed control design and the observer design have been evaluated by simulation studies. For control design, the achieved results have shown that the trajecto-
ries of a controlled model having unmeasured state variables are successfully synchronized with trajectories of a reference model. The performances of synchronization scheme are within the desired range of time. Furthermore, these performances can be improved by varying positive values of constants $c_1, c_2, c_3$. Among the values of $c$ considered, $c_1 = c_2 = c_3 = 0.1$ gives the best performance for restoration of circadian phases. For observer design, detailed evaluation also shows that the proposed one-sided Lipschitz observer give asymptotically estimates of unmeasured state variables of controlled model.

In analyses of mathematical models of circadian rhythms, phase differences are caused not only by different initial conditions but also by parameter uncertainties. The proposed scheme for control design in this chapter is not capable of dealing with the case of phase differences caused by parameter uncertainties. This problem can be solved in the next chapter with the application of adaptive back-stepping.
Chapter 5

Circadian phase resetting using adaptive back-stepping control

5.1. Introduction

Besides light, temperature has also an effect to phase shifts of circadian rhythms [23, 59, 70]. Thus, instead of light treatment, circadian disorder, especially sleep disorder, can be alternatively healed using temperature treatment. Nevertheless, since controlling temperature is more difficult than controlling light, in addition, light is major environmental cue, light treatment for circadian disorder is more favorable than temperature treatment. With light considered as the control input, this chapter focuses on circadian phase recovery for circadian disorders.

The two reference and controlled models of Neurospora circadian rhythms which have been used in chapter 4 are continued to be considered in this chapter. These two models have phase differences. Unlike chapter 4 where the phase differences have been reflected by choosing different initial conditions, in this chapter, parameter uncertainty is the reason to cause the changes of phases between these two models.

In Neurospora model, there are four parameters of which their changes in amplitudes can cause the phase shifts. They are $v_s$, transcription rate of frq gene, $v_m$, the degradation rate of frq mRNA, $k_s$, the FRQ protein translation rate, and $v_d$, the maximum phosphorylated FRQ protein degradation rate. These four parameters are considered to be the most prominent individual control targets [6] because of their sensitivities to the light input. Among these four parameters, $v_s$ is considered to be the most sensitive parameter [6]. This is proved in research studies of circadian models given in [2], [7], where the results obtained have shown that mRNA transcription rates are among the most sensitivity with respect to phase changes.
Furthermore, the use of $v_s$ for phase analysis and phase control has been presented in several results in literature (e.g. [6], [30], [42]). Therefore, the parameter whose changes in amplitude can cause the phase differences between the reference and controlled model is chosen to be $v_s$.

In theory, scientists use developed hypotheses to create the mathematical models of circadian rhythms [44]. Values of parameters involved in these mathematical models are chosen, and then adjusted to satisfy the given hypotheses. Therefore, these values can be considered as uncertainties. Taking into account that the mathematical models of circadian rhythms have uncertainty parameters, the chosen parameter $v_s$ which causes the phase differences between the two models may be treated as unknown parameter.

Similar to chapter 4, our control objective is to synchronize the altered trajectories of controlled model with the trajectories of reference model in this chapter. However, instead of proposed control design in chapter 4, the phase synchronizations are carried out via adaptive back-stepping method. Without loss of generality, all state variables of the reference model are assumed to be measurable. The controlled model can have unknown state variables. The changes in amplitude of unknown parameter can cause unexpected oscillations, and this can make the observer design for controlled model difficult. The observer designs presented in chapter 3 are not capable of dealing with the case of parameter uncertainty. Before finding appropriate observer design, we consider a simple case where all measurements of state variables of controlled model are assumed to be known. Thus, unlike chapter 4, this chapter does not require observer design.

### 5.2. Adaptive back-stepping design

Consider a third order nonlinear system which is described by

\[
\begin{align*}
\dot{\varpi}_1 &= \varpi_2 + \psi_1 (\varpi_1) \\
\dot{\varpi}_2 &= \varpi_3 + \psi_2 (\varpi_1, \varpi_2) , \\
\dot{\varpi}_3 &= u + \psi_3 (\varpi_1, \varpi_2, \varpi_3) \theta
\end{align*}
\]
where \( \varpi_1, \varpi_2, \varpi_3 \) are state variables, \( \psi_1, \psi_2, \psi_3 \) are smooth nonlinear functions, and \( \theta \) is an unknown constant parameter. The adaptive back-stepping design of (5.1) are started with the following definitions:

\[
\varsigma_1 = \varpi_1 \quad (5.2) \\
\varsigma_2 = \varpi_2 - \alpha_1, \quad (5.3) \\
\varsigma_3 = \varpi_3 - \alpha_2 \quad (5.4) \\
\hat{\theta} = \theta - \hat{\theta} \quad (5.5)
\]

where \( \hat{\theta} \) in (5.5) is estimation of unknown constant parameter \( \theta \). The first dynamic of \( \varsigma_1 \) is obtained as

\[
\dot{\varsigma}_1 = \varpi_2 + \psi_1 (\varpi_1) \\
= \varpi_2 - \alpha_1 + \alpha_1 + \psi_1 (\varpi_1) \\
= \varsigma_2 + \alpha_1 + \psi_1 (\varpi_1) \quad (5.6)
\]

The stabilizing function \( \alpha_1 \) in (5.6) is designed as:

\[
\alpha_1 = -c_1 \varsigma_1 - \psi_1 (\varpi_1) \quad (5.7)
\]

Substituting (5.7) to (5.6) to obtain the resultant dynamic of \( \varsigma_1 \) as

\[
\dot{\varsigma}_1 = -c_1 \varsigma_1 + \varsigma_2 \quad (5.8)
\]
Consider the dynamic of $\varsigma_2$ which is described by

$$
\dot{\varsigma}_2 = \dot{\omega}_2 - \dot{\alpha}_1
$$

$$
= \omega_3 + \psi_2 (\omega_1, \omega_2) - \frac{\partial \alpha_1}{\partial \omega_1} \dot{\omega}_1 \\
= \varsigma_3 + \alpha_2 + \psi_2 (\omega_1, \omega_2) - \frac{\partial \alpha_1}{\partial \omega_1} \dot{\omega}_1
$$

(5.9)

With stabilizing function $\alpha_2$ of (5.9) designed as

$$
\alpha_2 = -\varsigma_1 - c_2 \varsigma_2 - \psi_2 (\omega_1, \omega_2) + \frac{\partial \alpha_1}{\partial \omega_1} \dot{\omega}_1
$$

(5.10)

we substitute (5.10) to (5.9) to obtain the resultant dynamic of $\varsigma_2$ as

$$
\dot{\varsigma}_2 = -\varsigma_1 - c_2 \varsigma_2 + \varsigma_3
$$

(5.11)

The final dynamic of $\varsigma_3$ is described by

$$
\dot{\varsigma}_3 = \dot{\omega}_3 - \dot{\alpha}_2
$$

$$
= u + \psi_3 (\omega_1, \omega_2, \omega_3) \theta - \frac{\partial \alpha_2}{\partial \omega_1} \dot{\omega}_1 - \frac{\partial \alpha_2}{\partial \omega_2} \dot{\omega}_2
$$

(5.12)

The control input $u$ of (5.12) can be designed as

$$
u = -\varsigma_2 - c_3 \varsigma_3 - \psi_3 (\omega_1, \omega_2, \omega_3) \theta + \frac{\partial \alpha_2}{\partial \omega_1} \dot{\omega}_1 + \frac{\partial \alpha_2}{\partial \omega_2} \dot{\omega}_2
$$

(5.13)

Substituting (5.13) to (5.12), and then using (5.5) to obtain the final resultant dynamic of $\varsigma_3$ as

$$
\dot{\varsigma}_3 = -\varsigma_2 - c_3 \varsigma_3 + \psi_3 (\omega_1, \omega_2, \omega_3) \theta
$$

(5.14)
In order to guarantee the stability of system (5.1), consider a Lyapunov function candidate

\[ V = \frac{1}{2} \left( \varsigma_1^2 + \varsigma_2^2 + \varsigma_3^2 + \tilde{\theta}^T \tau^{-1} \tilde{\theta} \right) \]  

(5.15)

where \( \tau \) is adaptive gain, and it is a positive definite matrix.

### 5.3. Design procedures

#### 5.3.1. Control input target

In chapter 4, the phase differences were caused by different initial conditions, and the chosen control input target was \( v_s \). The control input target was chosen to be \( v_s \) because \( v_s \) is the most sensitive parameter to light if compared with the other parameters \( v_m \) (the degradation rate of \( frq \) mRNA), \( k_s \) (the FRQ protein translation rate), and \( v_d \) (the maximum phosphorylated FRQ protein degradation rate). Besides this reason, since manipulation of \( v_s \) can provide more immediate phase recovery [6], we again choose \( v_s \) as the control input target.

#### 5.3.2. Reference model and Controlled model

System (4.8) is chosen as reference model in this chapter. This system is described by

\[
\begin{align*}
\dot{r}_1 & = r_2 - k_2 r_1 \\
\dot{r}_2 & = r_3 - k_1 r_2 + k_1 k_2 r_1 - v_d \frac{k_1 r_2}{k_1 K_d + r_2} \\
\dot{r}_3 & = v_s k_1 k_s K_i^n \frac{k_1 k_s r_3}{K_i^n + r_1^n} - v_m \frac{k_1 k_s r_3}{K_M k_1 k_s + r_3}
\end{align*}
\]  

(5.16)

As described in section 2.3.2, circadian system of Neurospora (2.9) has default value of \( v_s = 1.6 \). This value of \( v_s \) is also chosen as the value of \( v_s \) for the reference model (5.16). The trajectories generated from the reference model at \( v_s = 1.6 \) are considered as the desired controlled behaviors for circadian rhythms of controlled model.

Consider Neurospora model (2.9) with \( v_s \) as unknown parameter and as control input target.
This system is described by

\[
\begin{align*}
\dot{x}_1 &= (\theta + u) \frac{K_1^n}{K_1^n + x_3^n} - v_m \frac{x_1}{K_M + x_1} \\
\dot{x}_2 &= k_s x_1 - v_d \frac{x_2}{K_d + x_2} - k_1 x_2 + k_2 x_3, \\
\dot{x}_3 &= k_1 x_2 - k_2 x_3,
\end{align*}
\] (5.17)

where \(\theta\) is the unknown value of parameter \(v_s\). With

\[ h = Tx \]

where \(T\) is the state transformation matrix having the same value as equation (4.7), system (5.17) is transformed to a new system described by

\[
\begin{align*}
\dot{h}_1 &= h_2 - k_2 h_1 \\
\dot{h}_2 &= h_3 - k_1 h_2 + k_1 k_2 h_1 - v_d \frac{k_1 h_2}{k_1 K_d + h_2} \\
\dot{h}_3 &= \theta \frac{k_1 k_s K_1^n}{K_1^n + h_1^n} - v_m \frac{k_1 k_s h_3}{K_M k_1 k_s + h_3} + u \frac{k_1 k_s K_1^n}{K_1^n + h_1^n}
\end{align*}
\] (5.18)

**Remark 5.1** \(\theta\) represents the unknown parameter \(v_s\) which is the transcription rate of \(frq\) mRNA. Taking into account that the transcription rate is enhanced when light is considered as input signal in practice, the control input \(u\) is applied to this parameter as shown in system (5.18). The input \(u\) is then obtained by the proposed control design which is shown in later section.

System (5.18) is chosen as the controlled model. Since the phase differences are reflected by varying parameter values of circadian models, value of \(v_s\) of controlled model (5.18) is set differently with \(v_s\) of reference model, in other words, \(\theta \neq 1.6\). Value of \(v_s = 2\) or \(\theta = 2\) is chosen as the actual value of mRNA transcription rate for system (5.18). If the phase differences between reference and controlled models reflect the symptom caused by jet lag in practice,
trajectories generated from the reference model represent the rhythms at the destination while trajectories of controlled model (5.18) are the rhythms at the departure position.

In this chapter, initial conditions of both reference and controlled models are assumed to take the same values. Let initial condition of reference model be \( r(0) = \begin{bmatrix} 1 & 0.5 & 1.25 \end{bmatrix}^T \) as chapter 4. Values of \( r(0) \) are also the values for \( h(0) \) of controlled model. The responses of controlled model and reference model are shown in Figure. 5.1, Figure. 5.2, and Figure. 5.3. As shown in Figure. 5.1, Figure. 5.2, and Figure. 5.3, with the new value of amplitude of \( v_s \), the periods of reference oscillations are changed. Trajectories of controlled model now oscillate with longer period than the trajectories of reference model.

According to the simulated results shown in Figure. 5.1, Figure. 5.2, and Figure. 5.3, dynamics of state variables of controlled system (5.18), \( h_1, h_2, h_3 \), are stabilized at \( t \geq 50h \). Therefore, if a control input is designed, it is considered to apply at \( t = 50h \).

![Figure 5.1. Dynamics of reference and uncontrolled state variables \( r_1 \) and \( h_1 \)](image-url)
Figure 5.2. Dynamics of reference and uncontrolled state variables $r_2$ and $h_2$

Figure 5.3. Dynamics of reference and uncontrolled state variables $r_3$ and $h_3$
5.3.3. Control design

All dynamics of state variables of controlled model (5.18) are assumed to be measurable. Define

\[ e_1 = h_1 - r_1 \]
\[ e_2 = h_2 - r_2 \]
\[ e_3 = h_3 - r_3 \]

Using (5.16), (5.18), the error dynamics of \( e_1, e_2, e_3 \) are obtained as

\[ \dot{e}_1 = e_2 - k_2 e_1 \]  
\[ \dot{e}_2 = e_3 - k_1 e_2 + k_1 k_2 e_1 - v_d k_1 \frac{k_1 K_d e_2}{(k_1 K_d + h_2) (k_1 K_d + r_2)} \]  
\[ \dot{e}_3 = \theta k_1 k_s K_n - v s k_1 k_s K_n - v_m k_1 k_s \frac{K_M k_1 k_s e_3}{(K_M k_1 k_s + h_3) (K_M k_1 k_s + r_3)} + u k_1 k_s K_n \frac{K_n}{K_n + h_1} \]  

Following the procedure given in section 5.2 (from (5.1) to (5.14)), the control input \( u \) can be found such that dynamics of \( e_1, e_2, \) and \( e_3 \) are bounded. Based on the definitions given in (5.2), (5.3), (5.4), (5.5), define

\[ \varsigma_1 = e_1 \]  
\[ \varsigma_2 = e_2 - \alpha_1 \]  
\[ \varsigma_3 = e_3 - \alpha_2 \]  
\[ \tilde{\theta} = \theta - \hat{\theta} \]

Consider the first dynamic of \( \varsigma_1 \). Dynamic of \( \varsigma_1 \) is described by

\[ \dot{\varsigma}_1 = e_2 - k_2 e_1 = \varsigma_2 + \alpha_1 - k_2 e_1 \]
With $\alpha_1$ designed as

$$\alpha_1 = -c_1 \varsigma_1 + k_2 e_1,$$

the resultant dynamic of $\varsigma_1$ is

$$\dot{\varsigma}_1 = -c_1 \varsigma_1 + \varsigma_2 \quad (5.27)$$

We continue finding the two dynamics of $\varsigma_2$, and $\varsigma_3$. Dynamic of $\varsigma_2$ is described by

$$\dot{\varsigma}_2 = \dot{e}_2 - \dot{\alpha}_1$$

$$= e_3 - k_1 e_2 + k_1 k_2 e_1 - v_d k_1 \frac{k_1 K_d e_2}{(k_1 K_d + h_2) (k_1 K_d + r_2)} - \frac{\partial \alpha_1}{\partial e_1} \dot{e}_1$$

$$= \varsigma_3 + \alpha_2 - k_1 e_2 + k_1 k_2 e_1 - v_d k_1 \frac{k_1 K_d e_2}{(k_1 K_d + h_2) (k_1 K_d + r_2)} - \frac{\partial \alpha_1}{\partial e_1} \dot{e}_1 \quad (5.28)$$

Substituting

$$\alpha_2 = -\varsigma_1 - c_2 \varsigma_2 + k_1 e_2 - k_1 k_2 e_1 + v_d k_1 \frac{k_1 K_d e_2}{(k_1 K_d + z_2) (k_1 K_d + r_2)} + \frac{\partial \alpha_1}{\partial e_1} \dot{e}_1$$

to (5.28) to obtain

$$\dot{\varsigma}_2 = -\varsigma_1 - c_2 \varsigma_2 + \varsigma_3 \quad (5.29)$$

The third dynamic of $\varsigma_3$ is described by

$$\dot{\varsigma}_3 = \dot{e}_3 - \dot{\alpha}_2$$

$$= u \frac{k_1 k_s K_i^n}{K_i^n + h_i^n} + \theta \frac{k_1 k_s K_i^n}{K_i^n + z_1^n} - v_s \frac{k_1 k_s K_i^n}{K_i^n + r_1^n} - \frac{\partial \alpha_2}{\partial e_1} \dot{e}_1 - \frac{\partial \alpha_2}{\partial e_2} \dot{e}_2 \quad (5.30)$$
The control input $u$ can be designed as

$$
 u = \frac{K^n_i + h^n_1}{k_1 k_s K^n_i} \left[ -\varsigma_2 - c_3 \varsigma_3 - \left( \hat{\theta} k_1 k_s K^n_i - v_s k_1 k_s K^n_i + r^n_1 \right) + \frac{\partial \alpha_2}{\partial e_1} \dot{e}_1 + \frac{\partial \alpha_2}{\partial e_2} \dot{e}_2 \right] 
$$

(5.31)

With the substitution of (5.31) to (5.30) and the definition given in (5.25), final resultant dynamic of $\varsigma_3$ is obtained as

$$
 \dot{\varsigma}_3 = -\varsigma_2 - c_3 \varsigma_3 + \hat{\theta} k_1 k_s K^n_i 
$$

(5.32)

Stability analysis: Consider Lyapunov function (5.15). Substituting (5.27), (5.29) and (5.32) to $V$ in (5.15) to obtain $\dot{V}$ as

$$
 V = \frac{1}{2} \left( \varsigma_1^2 + \varsigma_2^2 + \varsigma_3^2 + \hat{\theta}^T \tau^{-1} \hat{\theta} \right) 
$$

\Rightarrow

$$
 \dot{V} = \dot{\varsigma}_1 \varsigma_1 + \dot{\varsigma}_2 \varsigma_2 + \dot{\varsigma}_3 \varsigma_3 - \hat{\theta}^T \tau^{-1} \hat{\theta} 
$$

$$
 = -c_1 \dot{\varsigma}_1^2 - c_2 \dot{\varsigma}_2^2 - c_3 \dot{\varsigma}_3^2 + \left( \varsigma_3 \frac{k_1 k_s K^n_i}{K^n_i + h^n_1} - \hat{\theta}^T \tau^{-1} \right) \hat{\theta} 
$$

(5.33)

From (5.33), an adaptive law is chosen as

$$
 \dot{\hat{\theta}} = \tau \varsigma_3 \frac{k_1 k_s K^n_i}{K^n_i + h^n_1} 
$$

(5.34)

where $\tau$ is an adaptive gain, and it is a positive constant in this case. Substituting (5.34) to (5.33), equation (5.33) is obtained as

$$
 \dot{V} = -c_1 \dot{\varsigma}_1^2 - c_2 \dot{\varsigma}_2^2 - c_3 \dot{\varsigma}_3^2 
$$

(5.35)

With positive values of $c_1, c_2, c_3$, $\dot{V} < 0$. This ensures the boundedness of $\varsigma_1, \varsigma_2, \varsigma_3$ and $\dot{\theta}$. Therefore, with the proposed control $u$ obtained in (5.31), error dynamics (5.19), (5.20) and (5.21) are asymptotically stable.
5.3.4. Results and Discussions

Positive values of $c$ are chosen as $c_1 = c_2 = c_3 = 1$. With the applied control input at $t \geq 50h$ and adaptive gain value $\tau = 1$, the dynamics of state variables $h_1, h_2, h_3$ of controlled model are synchronized with the dynamics of state variables $r_1, r_2, r_3$ of reference model respectively. The results are shown in Figure. 5.4, Figure. 5.5, and Figure. 5.6. The dynamic of control input which forces the synchronizations is depicted in Figure 5.7. The synchronizations occur at approximately $t = 150h$ respectively. Although the synchronizations are successful, the results are not good because of the existences of some small mismatches in Figure 5.4 and Figure 5.5 at $t = 150h$ and $t = 170h$.

Values of $c_1, c_2, c_3$ are altered. $c_1, c_2, c_3$ are changed from $c_1 = c_2 = c_3 = 1$ to $c_1 = c_2 = c_3 = 3$. The adaptive gain constant $\tau$ remains the same value ($\tau = 1$). The responses of controlled and reference models are depicted in Figure 5.8, Figure 5.9, and Figure 5.10. The control input of this case is shown in Figure 5.11. These new results are compared with the previous results shown from Figure 5.4 to Figure 5.6. Dynamics of controlled state variables $h_1, h_2, \text{ and } h_3$ synchronize with the reference trajectories $r_1, r_2, \text{ and } r_3$ at $t = 60h$ respectively.

Figure 5.4. Synchronized dynamics of $h_1$ and $r_1$ in case of $c_1 = c_2 = c_3 = \tau = 1$
Figure 5.5. Synchronized dynamics of $h_2$ and $r_2$ in case of $c_1 = c_2 = c_3 = \tau = 1$

Figure 5.6. Synchronized dynamics of $h_3$ and $r_3$ in case of $c_1 = c_2 = c_3 = \tau = 1$
Figure 5.7. Dynamics of control input in case of $c_1 = c_2 = c_3 = \tau = 1$

The synchronizations are carried out faster in case of $c_1 = c_2 = c_3 = 3$ than in case of $c_1 = c_2 = c_3 = 1$. Furthermore, the mismatches existed in the previous results are removed in the new results.

Let $0 \leq t \leq 38h$ be the time required for phase restoration. This range of time has been used as the desired performances for recovery of circadian phases in chapter 4. The time required to reset the circadian phases in case of $c_1 = c_2 = c_3 = 1$ and $c_1 = c_2 = c_3 = 3$ are calculated. The results are obtained as $\Delta t_1 = 150 - 50 = 100h$ for $c_1 = c_2 = c_3 = 1$, and $\Delta t_2 = 60 - 50 = 10h$ for $c_1 = c_2 = c_3 = 3$. Since $\Delta t_2 < 38h < \Delta t_1$, the performances of the case of $c_1 = c_2 = c_3 = 3$ satisfy the desired performances while the performances of the case of $c_1 = c_2 = c_3 = 1$ do not.
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Figure 5.8. Synchronized dynamics of $h_1$ and $r_1$ in case of $c_1 = c_2 = c_3 = 3, \tau = 1$

Figure 5.9. Synchronized dynamics of $h_2$ and $r_2$ in case of $c_1 = c_2 = c_3 = 3, \tau = 1$
Figure 5.10. Synchronized dynamics of $h_3$ and $r_3$ in case of $c_1 = c_2 = c_3 = 3, \tau = 1$

Figure 5.11. Dynamics of control input in case of $c_1 = c_2 = c_3 = 3, \tau = 1$
Remark 5.2  Similar to Figure 4.9, the form of control input obtained in Figure 5.11 may present the displacements of movements of molecules obtained by the effect of medicine. This control input may also be the signals (e.g. bio-electricity) produced by the sources embedded in the body to control the movements of molecules in practice.

In case of $c_1 = c_2 = c_3 = \tau = 1$, the dynamic of estimated parameter is shown in Figure 5.12. As seen in Figure 5.12, this dynamic finally converges to the true value of parameter of $\nu_s$ chosen for controlled model ($\theta = 2$). Value of $\tau = 1$ is changed to $\tau = 10$ and $c_1, c_2, c_3$ are still kept at $c_1 = c_2 = c_3 = 1$. The synchronized dynamics of controlled trajectories and reference trajectories are depicted in Figure 5.13, Figure 5.14, and Figure 5.15. As shown in Figure 5.13, Figure 5.14, and Figure 5.15, for $c_1 = c_2 = c_3 = 1, \tau = 10$, the synchronizations occur at approximately $t = 130h$. The time required for circadian phase resetting is calculated as $\Delta t_3 = 130 - 50 = 80h$. Although this range of time is not as good as the achieved range of time in case of $c_1 = c_2 = c_3 = 3, \tau = 1$, it is much better than the result obtained in case of $c_1 = c_2 = c_3 = \tau = 1$.

![Figure 5.12. Dynamic of estimated parameter $\hat{\theta}$ in case of $c_1 = c_2 = c_3 = \tau = 1$](image-url)
Figure 5.13. Synchronized dynamics of $h_1$ and $r_1$ in case of $c_1 = c_2 = c_3 = 1, \tau = 10$

Figure 5.14. Synchronized dynamics of $h_2$ and $r_2$ in case of $c_1 = c_2 = c_3 = 1, \tau = 10$
Figure 5.15. Synchronized dynamics of $h_3$ and $r_3$ in case of $c_1 = c_2 = c_3 = 1, \tau = 10$

Figure 5.16. Dynamic of estimated parameter $\hat{\theta}$ in case of $c_1 = c_2 = c_3 = 1, \tau = 10$
Chapter 5. Circadian phase resetting using adaptive back-stepping control

Increase of adaptive gain value may lead to the faster convergence of estimated parameter $\hat{\theta}$ to its true parameter $\theta$. New dynamic of estimated parameter $\hat{\theta}$ is depicted in Figure 5.16. Compared with Figure 5.12, Figure 5.16 actually shows the faster convergence of estimated parameter in case of $\tau = 10$ than in case of $\tau = 1$. We have shown in Figure 5.8, Figure 5.9, and Figure 5.10 that by increasing values of $c$, $c_1 = c_2 = c_3 = 1$ to $c_1 = c_2 = c_3 = 3$ while value of $\tau$ is kept at $\tau = 1$, the speed of phase recovery is improved. Through the results which have just been shown from Figure 5.13 to Figure 5.15 with $\tau = 10$, another way to improve this speed is to increase the adaptive gain $\tau$.

Depending on problems, values of $c$ and $\tau$ are adjusted to be suitable. According to the shown results in three cases, variation in adaptive gain value $\tau$ gives less effect to the performances of control input than alteration of positive constants $c_1, c_2, c_3$. Therefore, $c_1 = c_2 = c_3 = 3, \tau = 1$ are chosen as ideal values of $c$ and adaptive gain $\tau$.

5.4. Conclusions

We have proposed adaptive back-stepping to recover the altered rhythms of Neurospora model in this chapter. The altered rhythms are generated by a controlled model, and they have phase differences with the reference rhythms. The phase differences are caused by the uncertainty in parameter $\nu_s$ which is considered as the most sensitive parameter to light input. The observer is not required since the controlled model is assumed to have all available measurements of state variables in this chapter. The performance of proposed control design has been evaluated by simulation studies. Detailed evaluation have shown that the trajectories of a controlled model having unmeasured state variables are successfully synchronized with trajectories of a reference model. For some values of positive constants $c$ and adaptive gain value $\tau$, the performances of synchronization scheme are not within the desired range of time. However, these performances can be improved by varying positive values of constants $c_1, c_2, c_3$ and $\tau$. 
Chapter 6

Conclusions

6.1. Conclusions

We have proposed observer designs, back-stepping, and adaptive back-stepping control designs to circadian models in this thesis. Detailed designs of proposed observers and their applications to circadian models have been given in chapter 3. Chapter 4 and Chapter 5 have presented the detailed procedures of applications of back-stepping and adaptive back-stepping to circadian models.

In chapter 3, the observer designs have been proposed to deal with reduction of measurements in mathematical models of circadian rhythms. Two types of observer designs, one-sided and reduced-order, have been applied to two mathematical models of circadian rhythms of Neurospora and mammals. Both types of observers have given asymptotic estimates of unmeasured state variables of both Neurospora model and mammalian model. Furthermore, their performances are within the chosen desired range of time. With the dependence on dynamics of invariant zeros, the existing method of reduced-order observer in literature which is also presented in this chapter has shown its limitation in its application to mammalian model. This limitation has been removed by the improved reduced-order observer design presented in this chapter. In the new developed reduced-order observer design, the dependence on dynamics of invariant zeros is replaced by the dependence on an observer gain $L$ which is involved in this new developed design, and also in its error dynamics. The achieved results in this chapter have shown that the new improved reduced-order observer design also gives asymptotic estimates of unmeasured state variables of mammalian model.

In chapter 4, the control design, back-stepping method, has been proposed to deal with the restoration of circadian phases. The restoration of circadian phases has been carried out
by synchronizations of trajectories of a controlled model with the trajectories of a reference model. The synchronizations have been performed via back-stepping method. Both reference and controlled models are based on the 3rd order mathematical model of Neurospora circadian rhythms given in chapter 2. These two models have phase differences which are reflected by choosing different initial conditions. The controlled model presented in this chapter has unknown state variables. These unknown states are estimated by using one-sided Lipschitz observer design which has been presented in the previous chapter. The achieved results obtained in chapter 3 have shown that the proposed one-sided Lipschitz observer gives asymptotic estimates of unmeasured state variables of controlled model. These achieved results have also shown the successful synchronizations of trajectories of the controlled model with the reference trajectories. In literature, light is manually designed as continuous pulses which has been used as the control input to achieve phase restorations. Through the application of the proposed control design method in this chapter, we have shown the different form of control input for light which would also achieve the same objective.

In chapter 5, the adaptive back-stepping has been proposed to deal with the restoration of circadian phases. The reference and controlled models used in chapter 4 are considered again in this chapter. Unlike chapter 4 where phase differences are caused by choosing different initial conditions, the altered trajectories are caused by the change in amplitude of an unknown parameter in this chapter. The unknown parameter which has been chosen is $v_s$ of Neurospora model because of its most sensitivity to the light input. The control input target is again $v_s$ because it can provide immediate phase recovery. In order to avoid complexities of observer design, the controlled model has been assumed to have all available measurements of state variables. In other words, the observer design is not required in this chapter. The achieved results have shown that the proposed control design has successfully synchronized the altered trajectories with the reference trajectories. In chapter 4, the performances of control design scheme are improved by varying positive constant values $c_1, c_2,$ and $c_3$. Besides variation in values of $c$, the performances can also improved by alteration of value of adaptive gain $\tau$ in this
6.2. Direction of future research

With proposed observer and control designs performed in chapters 3, 4, and 5, two aspects of circadian rhythms, reduction of measurements of circadian models and restoration of circadian phases, have been dealt with. Another aspect of circadian rhythm is the effect of internal noises to the mechanism of circadian rhythms. Molecular noises have direct effects to dynamics of genes and proteins. In practice, the molecular noise is identified generally as stochastic noise which exists normally in the biochemical events (e.g. gene expression). Such kind of noise can help to improve the control balance in human [61] or to cause the generation of errors in DNA replication leading to mutation and evolution [65]. The performances of observer and control designs presented in this thesis have not been tested with the involvement of molecular noises in the circadian models. Therefore, we recommend three points for future research studies of this thesis:

- A new observer design which has capability to deal with circadian models having the involvement of stochastic noise. In particular, the Lipschitz observer design shown in this thesis is combined with noise filter (e.g. Kalman filter) in order to eliminate the stochastic noise involved.

- Examination of the performances of control designs shown in this thesis with the circadian models having stochastic noise for circadian phase re-settings

- Investigation of new mathematical models for circadian rhythms. The available methods of system identification are very helpful to achieve this task.
References


[59] B.L. Parry, B. LeVeau, N. Mostofi, H.C Naham, R. Loving, P. Clopton, and J.C.
Gillin. Temperature circadian rhythms during the menstrual cycle and sleep deprivation in
premenstrual dysphoric disorder and normal comparison subjects. *J Biol Rhythms*, 12:34–

The orphan nuclear receptor *rev – erv α* controls circadian transcription within the positive

[61] A.A. Priplata, B.L. Patritti, J.B. Niemi, R. Hughes, D.C. Gravelle, L.A. Lipsitz, A. Veves,


[63] R. Rajamani and Y.M Cho. Existence and design of observers for nonlinear systems:

[64] M.R. Ralph, R.G. Foster, F.C. Davis, and M. Menaker. Transplanted suprachiasmatic


