Mathematical Analysis of a Biological Clock Model

Examensarbete utfört i Reglerteknik
vid Tekniska högskolan i Linköping
av

Henrik Ohlsson

LITH-ISY-EX-06/3663-SE
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Linköping, 13 June, 2006
Have you thought of why you get tired or why you get hungry? Something in your body keeps track of time. It is almost like you have a clock that tells you all those things.

And indeed, in the suprachiasmatic region of our hypothalamus reside cells which each act like an oscillator, and together form a coherent circadian rhythm to help our body keep track of time. In fact, such circadian clocks are not limited to mammals but can be found in many organisms including single-cell, reptiles and birds. The study of such rhythms constitutes a field of biology, chronobiology, and forms the background for my research and this thesis.

Pioneers of chronobiology, Pittendrigh and Aschoff, studied biological clocks from an input-output view, across a range of organisms by observing and analyzing their overt activity in response to stimulus such as light. Their study was made without recourse to knowledge of the biological underpinnings of the circadian pacemaker. The advent of the new biology has now made it possible to "break open the box" and identify biological feedback systems comprised of gene transcription and protein translation as the core mechanism of a biological clock.

My research has focused on a simple transcription-translation clock model which nevertheless possesses many of the features of a circadian pacemaker including its entrainability by light. This model consists of two nonlinear coupled and delayed differential equations. Light pulses can reset the phase of this clock, whereas constant light of different intensity can speed it up or slow it down. This latter property is a signature property of circadian clocks and is referred to in chronobiology as "Aschoff's rule". The discussion in this thesis focus on develop a connection and also a understanding of how constant light effect this clock model.
Abstract

Have you thought of why you get tired or why you get hungry? Something in your body keeps track of time. It is almost like you have a clock that tells you all those things.

And indeed, in the suprachiasmatic region of our hypothalamus reside cells which each act like an oscillator, and together form a coherent circadian rhythm to help our body keep track of time. In fact, such circadian clocks are not limited to mammals but can be found in many organisms including single-cell, reptiles and birds. The study of such rhythms constitutes a field of biology, chronobiology, and forms the background for my research and this thesis.

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My research has focused on a simple transcription-translation clock model which nevertheless possesses many of the features of a circadian pacemaker including its entrainability by light. This model consists of two nonlinear coupled and delayed differential equations. Light pulses can reset the phase of this clock, whereas constant light of different intensity can speed it up or slow it down. This latter property is a signature property of circadian clocks and is referred to in chronobiology as "Aschoff’s rule". The discussion in this thesis focus on develop a connection and also a understanding of how constant light effect this clock model.
Acknowledgements

I would like to say thank you to everyone that has supported me during the time I have been writing on my thesis. People to be mentioned are my family, Erica, Fiona, Lena, Sophie, David, Linus, Lauren and Guly. My advisors, Professor C.V. Hollot, Professor Tamás Kalmár-Nagy and Markus Gerdin and to my examiner Professor Torkel Glad. Finally i would like to acknowledge the National Science Foundation for their financial support.
Contents

I  Introduction  3
  1  Introduction . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 5
  2  Model of the Transcriptional-Translational Process . . . . . . . . 6
  3  Analysis Ideas . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 8
  4  Motivation . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 10
  5  Previous Work . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 10
  6  Future Research . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 10
  7  Explanation of Frequently Used Expressions . . . . . . . . . . . . . 10

References  13

II  Papers  17

A  Describing Function Analysis  19
  1  Introduction . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 21
  2  Background . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 21
  3  A Dual-Input Describing Function Analysis - Considering the Bias
     and the First Harmonic . . . . . . . . . . . . . . . . . . . . . . . . . 24
     3.1  Discussion . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 27
  4  Multiple-Input Describing Function Analysis - Considering the Bias,
     the First and the Second Harmonic . . . . . . . . . . . . . . . . . . . 30
     4.1  Discussion . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 34
  A  Derivation of the Dual-Input Describing Function for a General
     Case - Considering the Bias and the First Harmonic . . . . . . . . . 34
  B  Derivation of the Multiple-Input Describing Function for a General
     Case - Considering the Bias, First and the Second Harmonic . . . . 36

References  40

B  Multiple Scales Analysis  43
  1  Introduction . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 45
  2  Model of the Transcriptional-Translational Process . . . . . . . . 47
  3  Dimensional Analysis and Scaling . . . . . . . . . . . . . . . . . . . . 49
  4  The Equilibrium Solution . . . . . . . . . . . . . . . . . . . . . . . . . 50
  5  Simplifications . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 51

ix
Preface

In Malaysia thousands of fire flies flashes unisonly every night, girls living together synchronize their menstrual cycle, atoms pulsing together form a laser beam; synchronization is a mystical property of nature and is in some sense beauty. I have for long been fascinated by synchronization [30] and oscillations and I do not think that it can be for nothing that this kind of mathematical order is preferred.

In this thesis I discuss the analysis of a biological clock model. The clock, with which means, an organisms manage to synchronize to the environmental cycle is actually itself built up of synchronized oscillations in thousands of cells and is a robust machinery necessary for the organism’s organs to work together.

The main part of the research preceding this thesis was done at University of Massachusetts and started as an independent study in control. My advisor, Professor C.V. Hollot, made me interested in biological clocks and the use of control in the same area. After having finished my independent study I got the opportunity to continue my work as a research assistant. My job continued for a little more then a year and was sponsored by the National Science Foundation (NSF). The work resulted in several speeches and research papers, some which I have chosen to include in this thesis.
Part I

Introduction
1 Introduction

While delay is ubiquitous in physical, chemical and biological processes, its influence on many of these phenomena are still not well understood. Frequent flyers often suffer from what is known as "jet lag" [3] which is the slow synchronization of the body’s biological clock to a different timezone. As this biological clock is responsible for establishing rhythms for sleep, body temperature, hormonal concentrations, etc. it has profound importance on our lives. These rhythms have an approximately 24-hour period\(^1\), and this is why they are also called circadian rhythms (the Latin term "circadian" literally means "around a day").

To synchronize its time to that of the environment, the biological clock primarily uses light [27],[28]. The ability is crucial for the survival of the organism and circadian rhythms has been observed in even the simple unicellular cyanobacteria [7], [19], [33], [10].

For more complex organisms, such as mammals, a special part of the brain, called the Supra Chiasmatic Nucleus (SCN) is responsible for synchronization. Biochemical processes in the cells of the SCN are synchronized and together act as the biological clock to provide signals for the liver, kidney, etc. to work together in harmony [25]. Inside a single cell interlocking biological/chemical feedback loops (see Figure 1) result in oscillations in the concentrations of protein and mRNA. In short, mRNA gets transcribed and translated, protein is created and inhibits new transcription of mRNA. The process is called a transcriptional-translational process and can be seen as a negative feedback loop, where protein inhibits, indirectly, itself.

The transcriptional-translational process leads to fluctuations in mRNA and protein concentrations [19], [33],[35],[10] which mainly gets affected by light but also for example temperature, even though the overall rhythm expressed is robust to temperature changes. The oscillations are said to be circadian [39], [15] meaning that they are approximately 24 hours under constant conditions, temperature compensated and gets affected by light [18].

As already mentioned, light is probably the most important input to the clock. Light pulses can shift the clock and different light intensity levels regulates the speed. For nocturnal organisms an increase in light intensity level lengthens the period of the circadian cycle (or equivalently, decreases its frequency) and the revers for diurnal organisms. The effect of constant light has long been known and is stated in "Aschoff’s Rule" [16].

There are many models of biological clocks, generally described by nonlinear, delayed dynamics. Because concentrations are usually seen as variables models, are of a typical form of systems called positive systems. Even though, because of the the high number of states and complexity caused by the nonlinearities and delays any form of analysis are usually very tedious.

Interested in how light effects the clock maybe we do not need to understand the most complex models [8]? A fairly simple one that catch the effect of light is a model by Scheper et al. [37]. It is a transcriptional-translational model i.e., it

\(^1\) Quite interesting is that the human biological clock has a free running period, i.e., no external excitement, of approximately 25 hours.
describes the circadian rhythmic behavior of a single cell and does not take into account any sort of coupling or interaction between cells. Two coupled differential equations are needed but nonlinear and with a delay. Seeing the structure of Scheper et al.’s model as the important thing, we choose the parameters in such a way so that the most important feature for us, the way light effects the model, is kept but also in order to get a so easy model to analyze as possible.

To show that our clock model, which is a model for a nocturnal, behave according to Aschoff’s rule the period of our clock model need to increase with light intensity. A common way is to see a light change as a change in mRNA production rate [32], [34], [40], [24] and we therefore aim to show that our, structurally equal to Scheper et al.’s model, behave accordingly.

2 Model of the Transcriptional-Translational Process

In the transcriptional-translational process in a biological cell the physical transportation of mRNA and protein can be described using delays. A model using such a description is a model by Scheper et al. The coupled equations describing this model are

$$\frac{dM(t)}{dt} = \frac{r_M}{1 + (\frac{P(t)}{k})^n} - q_M M(t),$$

$$\frac{dP(t)}{dt} = r_P M(t - \tau)^m - q_P P(t)$$

Figure 1. The transcriptional-translational process.
Table 1. Parameters used by Scheper et al.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value of parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r_M )</td>
<td>mRNA production rate constant</td>
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<tr>
<td>( r_P )</td>
<td>protein production rate constant</td>
</tr>
<tr>
<td>( q_M )</td>
<td>mRNA degradation rate constant</td>
</tr>
<tr>
<td>( q_P )</td>
<td>protein degradation rate constant</td>
</tr>
<tr>
<td>( n )</td>
<td>Hill coefficient</td>
</tr>
<tr>
<td>( m )</td>
<td>nonlinearity in protein synthesis cascade</td>
</tr>
<tr>
<td>( \tau )</td>
<td>duration of protein synthesis cascade</td>
</tr>
<tr>
<td>( k )</td>
<td>scaling constant</td>
</tr>
</tbody>
</table>

where \( M \) and \( P \) are the relative concentrations of mRNA and protein respectively. \( r_P, r_M \) are production rate constants and \( q_P \) and \( q_M \) are degradation rate constants for mRNA respectively protein. \( \tau \) is a delay and \( m \) is the nonlinearity in the protein cascade. \( n \) is the Hill coefficient and \( k \) a scaling constant. The parameter values used by Scheper et al. are shown in Table 1.

The equations describes how concentrations of mRNA and protein change during the transcriptional-translational process in a single cell of a nocturnal mammalian. The oscillations are circadian, i.e., periodic of approximately 24 hours and the model is a description of a biological clock.

One of the most important inputs to a biological clock is light. Different light intensity levels contributes to different clock periods according to Aschoff’s rule, that is, for a nocturnal animal the period increase with increasing light intensity. Commonly, light is seen as something that effects the mRNA production rate.

Using \( m = 1, q_M = q_P = q, k = 1, n = 3 \) the system (1, 2) now has the form

\[
\dot{M}(t) = \frac{r_M}{1 + P(t)^3} - qM(t), \quad (3)
\]

\[
\dot{P}(t) = r_P M(t - \tau) - qP(t) \quad (4)
\]

where the dot denotes differentiation with respect to time. This is not the same set of parameter values that Scheper et al. used even though the structure is the same. But the two behaves similar to light (see Figure 2), which is what matters for us. Secondly, not much is said about the reason of Scheper et al.’s specific choice of parameter values and an open question is how much measurements/biology that is behind. There should also be pointed out that there are many models structurally equal to Sheper’s, see for example [22]. Motivated by this we aim to show Aschoff’s rule for the the model with the modified parameter set, that is, that the period is increasing with increasing light intensity (nocturnal).
If we express \( M(t) \) from the second equation as
\[
M(t) = \frac{\dot{P}(t + \tau) + qP(t + \tau)}{r_P}
\]
and substitute it into (3) to yield
\[
\frac{\dot{P}(t + \tau) + q\dot{P}(t + \tau)}{r_P} = \frac{r_M}{1 + P(t)^3} - q \frac{\dot{P}(t + \tau) + qP(t + \tau)}{r_P}
\]
we get by shifting the time variable by \( \tau \)
\[
\ddot{P} + 2q\dot{P} + q^2P = \frac{r_M r_P}{1 + P(t - \tau)}.
\]
With \( q_M = q_P = 0.21, \tau = 5 \), and \( r_M = 1 \) we get a period close to 24 hours and with that a circadian model. We will therefore in the following study the general system (above) with particular interest in the behavior at \( q_M = q_P = 0.21, \tau = 5 \), and \( r_M = 1 \).

### 3 Analysis Ideas

A straightforward way to analyze oscillations occurring in nonlinear systems is by applying a **describing function analysis**. The idea of this method is to approximate oscillations by truncation of their Fourier expansion. If the system
can be separated into a linear and a nonlinear part in a closed loop the analysis is particularly suitable. Further, to be able to truncate the Fourier expansions and get a good result the linear part need to be of a good lowpass nature.

A describing function analysis is given in part II, Paper A, of this thesis. Because the oscillations are biased at least two terms have to be included in the truncated Fourier expansion. It turns out that a two term approximation will not be enough though and to get a better approximation and hopefully see a dependency of light in the period also a third term was included. The equation system needed to be solved was in this case too complicated and the result was just obtained numerically. The two term approximation caught the dependency of $q_M$, $q_P$ and $\tau$ and were obtained as a side result in the attempt to examine the dependency of $r_M$.

Perturbation methods are good tools for examine how a perturbation of a parameter effects a system. Because the method suits systems for which the unperturbed dynamics are fully known, for example almost linear systems, the perturbation theory was not directly applicable. A short introduction to perturbation theory is given in Strogatz [29]. Extensions like poicaré-lindstedt’s method, see [26], were also applied but without success.

The Hopf bifurcation theorem, which name not properly reflect its statement, can be used to show periodic behavior of a nonlinear system. It is further possible, after having shown the existence of periodic solutions, to extract how the period is dependent of the bifurcation parameter with center manifold theory [14], [21]. The theory of center manifolds is mathematically very tedious and often replaced by a Methods of Multiple Scales approach [9]. Even though the reliability of the result of a Method of Multiple Scales approach can be discussed this is seldom mentioned.

A method of multiple scales approach, which also can be seen as a perturbation approach, is given in part II, Paper B. After a standard analysis of the nonlinear system the existence of bifurcation point could be established by the Hopf bifurcation theorem [14]. To examine how the period was effected by small perturbations of this bifurcation point the methods of multiple scales was then used.

The methods of multiple scales is reduces to a basic perturbation approach if the number of time scales are set to one. The method can therefore be seen as a more general perturbation method. As mentioned a perturbation approach is suitable if the unperturbed system is known, which is not our case. To get around this a variable substitution or scaling can be done and this is shown in more detailed in part II, Paper B. A good introduction to the methods of multiple scales is given in Steven Strogatz book Nonlinear Dynamics and Chaos [29] and in [9].

Even the method of multiple scales failed to express the periods dependency of $r_M$ and a possible reason is presented in part II, Paper C
4 Motivation

An important question to ask before putting too much time into a research subject is if there is any need for it. Therefore before reading further, some motivating applications that support a better knowledge of the biological clock are here stated.

Experiments have shown that for hamsters and mice a 15 minutes light pulse at a well chosen time can phase shift their clock 4 hours. Knowing more of how the clock works maybe we would be able to shift our clock, in the same way as for hamsters and mice, to avoid for example jet lag [3]. A big group of people suffer of sleeping disorders, knowing more of what effects the clock we would probably be able to treat this in a more effective way than we do today. Also, medical treatment works differently well depending on when they are applied, understanding more and we may get a better idea of when to apply a certain drug. There are many more reasons for a better knowing of the biological clock but probably these are motivating enough.

5 Previous Work

Similar types of nonlinearity are commonly seen in equations describing concentration equilibriums in biology and also chemistry, see the Michaelis-Menten [1] and compare to the Glass-Mackey equation. Notice also the delayed negative feedback in the system. Negative feedback of this form occurs frequently in nature and has previously been discussed by Campbell et al. [4], [5].

The need to describe vibrations and oscillations also occurs frequently in other fields, for example, machine tool vibrations [36] and congestion control [11].

6 Future Research

Concerning analysis of this special clock model, a center manifold analysis would be interesting to see.

More general, more work is needed to fully understand the method of multiple scales. As Steven Strogatz wrote in [29], "It’s hard to justify this idea rigourously, but it works!", where "this idea" refers back to the main idea of multiple scales (to work with two or more independent time scales).

Center Manifold theory applied to delayed system is not that commonly seen either and there is very hard to find software that even can handle the most basic analysis such as drawing bifurcation diagrams.

7 Explanation of Frequently Used Expressions

In the attached papers some expressions and abbreviations are frequently used. For the reader not used to the subject a gathering of expressions with explanations here follows.
Almost Linear A system of the form
\[
\dot{x} = Ax + \epsilon f(x)
\]
where \(f\) is a nonlinear function and \(\epsilon\) is small.

Center manifold analysis By looking at the eigenvalues of the A-matrix in a linearization around an equilibrium the stability properties of the equilibrium can be established with the exception of the eigenvalues being purely imaginary. Center manifold theory treats this kind of problems by a reduction of the system to a less complex. The analysis is then carried out on the new system which share many interesting properties with the full system.

Chronobiology Field in biology concerned with timing and rhythmic phenomenon.

Circadian The Latin term "circadian" literally means "around a day". For a rhythm to classify as circadian it is needed to have the following properties:
- A periodicity of approximately 24 hours without external excitation.
- Temperature compensated, meaning that it proceeds the same period independent of temperature. Notice that this does not say that the chemical reactions are temperature compensated.
- The rhythm period can be reset by a light or dark pulse.

Degradation The reduction of a chemical compound to another less complex.

DF Describing Function

DIDF Dual Input Describing Function

Diurnal Organism active during the day; opposite of nocturnal.

Hopf bifurcation A bifurcation is a sudden change in the characteristics of a nonlinear system obtained when a parameter is changed, commonly called the bifurcation parameter. To have a Hopf bifurcation the change is needed to be from an equilibrium point into a limit cycle.

MIDF Multiple Input Describing Function

MMS Methods of Multiple Scales

mRNA messenger RNA

Perturbation Theory Theory treating the change of the dynamics caused by the perturbation of a parameter.

PRC "A Phase Response Curve (PRC) is a plot of the magnitude of phase shifting due to a pulse versus the time at which the pulse was applied. Experimenters have determined phase response curves for many organisms, many oscillating types of physiology, and using many forms of perturbation." [13].
SCN  Suprachiasmatic nucleus

Secular terms  Terms that would make the system to resonance and the oscillations to grow unlimited.

Transcription  The process by which a gene is copied into messenger RNA.

Translation  The process by which messenger RNA (mRNA) specifies the sequence of a protein.
References


Part II

Papers
Paper A

Describing Function Analysis

Author: Henrik Ohlsson
A Describing Function Approach to Examine the Period’s Dependency of a Parameter Change

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Abstract

With the goal to explain how parameters symbolizing light, humidity, etc. effect the period of a model of a biological clock we derive a dual-input describing function. We discuss its failure to describe the relationship for a parameter, commonly thought of as the way light effects a clock, and we present a successful extension of the dual-input describing function, the multiple-input describing function.

Keywords: multiple-input describing function, circadian, Aschoff’s rule, transcriptional-translational model.

1 Introduction

An important feature of living organisms are their ability to entrain to the environmental cycle. The ability is crucial for the organism’s survival and the most important environmental phenomenon to entrain to is probably the night-day-cycle.

Many studies have been carried out during the years and many models for the mechanism that keeps track of time, commonly called the biological clock, has been presented. One of the most important features for models have been the ability to describe the effect light causes [13], [14], which is quite natural with the importance to entrain to the day-night cycle in mind, and as early as 1960 Aschoff presented results for how different intensities of constant light effected the clock. His result has been commonly called Aschoff’s rule [7], [3].

To verify Aschoff’s rule and get a better picture of how light effect the clock a describing function analysis of a clock model similar to a model by Scheper et al. [18] is here presented. How changes, possible caused by temperature, humidity, etc., in other parameters effect the clock is also examined.

2 Background

Organisms keep track of time. Something tells them, and also us, when it is time to eat and to sleep. Jet lag [2] is also a sign that we have a robust mechanism
for timing, a clock. The clock keep oscillating without any need of external excitation, it is a self-sustained oscillation. The rhythm expressed is unsensitive for temperature changes but get effected by, for example, light and humidity. The clock express a circadian$^1$ rhythm [20], [6].

Circadian rhythms are biological process that oscillate with an approximate 24 hour periodicity when there are no external timing cues [9].

Light is probably the most important input signal to the biological clock and the way constant light effects the clock is described by Aschoff’s rule and the way light pulses do by a phase response curve. Aschoff’s rule states:

Brighter light results in a shorter period length in day-active animals, whereas in night-active animal the reverse is true [9].

A phase response curve or PRC is a graph that describes the phase shift caused by a 15 minutes (sometimes one hour) light pulse hitting the clock at a certain time modulo the period time, see [9]. The PRC is closely related to what a engineer would call an impulse response. What is missing is something that connects the effect by constant light and light pulses. There is no theory for how an arbitrary light signal affects the clock, there is no convolution integral.

The clock has been studied from an input-output view for years. It being a black box with light, temperature, etc. as inputs and activity as an output. Just recently though, technology made it possible to look inside the cells and identify the different pieces of the clock. It was then shown that a special part of the mammalian brain, called the Supra chiasmatic nucleus (the SCN), provides a necessary and sufficient signal for the liver, kidney etc. to synchronize and to work together [12]. It was further observed that each cell in the SCN express a circadian rhythm and that they are all synchronized, oscillating with the same period but not necessarily the same phase.

Interests in how the clock works has resulted in many models during the years. For the intracellular circadian rhythm generator, i.e., the clock in a single SCN cell one of the most famous models is a model by Leloup J-C and Goldbeter A. [8] which describes the clock of a mammalian. Leloup and Goldbeter’s model is pretty complex and uses 19 nonlinear equations. This model size is common for clock models and make analysis very hard. Interested in how light effects the clock, maybe we do not need to understand the most complex models? Infact, it has been shown that another of Goldbeter’s models [5], described by 5 nonlinear equations can actually be reduced to a van Der Pol oscillator, see [4].

A fairly simple model that catch the effect of light is a model by Scheper et al. [18]. It is a transcriptional-translational model i.e., it describes the transcription and translation of mRNA and the inhibitory effect caused by protein on new

---

$^1$The word "circadian" comes from Latin and means "about a day" (about, "circa ", and a day, "dia ").
transcription of mRNA. Just two coupled differential equations are needed but nonlinear and with a delay. The two equations are given in (1) and (2).

\[
\frac{dM}{dt} = \frac{r_M}{1 + (\frac{P}{k})^n} - q_M M
\]  

(1)

\[
\frac{dP}{dt} = r_P M (t - \tau)^m - q_P P
\]  

(2)

In above equations \( M \) and \( P \) are the relative concentrations of mRNA and protein respectively and will be periodic for a certain parameter set. \( r_P, r_M \) are production rate coefficients and \( q_P \) and \( q_M \) are degradation rate constants for mRNA respective protein. \( \tau \) is a delay and \( m \) is the nonlinearity in the protein cascade. \( n \) is the Hill coefficient and \( k \) a scaling constant. The parameter values used by Scheper et al. are shown in Table 1.

To understand how arbitrary light signals and also other phenomena that change the production or degradation rate effects the clock period it is necessary to have a good understanding of how the most simple signals affect the period, i.e., affects caused by different intensities of constant light, levels of humidity and so on. A light change is commonly seen as a change in the mRNA production rate constant [16], [17], [21], [11]. However, there is research showing a more complex result where fast light changes effect the production rate constant and slow changes in light effects the degradation constant for protein [10]. We here look at how different values of either the production or degradation rates contribute to the period and try to establish some understanding and relationship between different parameter values and the period. A good understanding is not seen as a numerically derived relationship between different intensities of constant light and the period, it is something more.
Table 2. The choice of parameter values

<table>
<thead>
<tr>
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<tbody>
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<td>$r_M$</td>
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</tr>
<tr>
<td>$r_P$</td>
<td>protein production rate constant</td>
</tr>
<tr>
<td>$q_M$</td>
<td>degradation rate constant</td>
</tr>
<tr>
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<td>duration of protein synthesis cascade</td>
</tr>
<tr>
<td>$k$</td>
<td>scaling constant</td>
</tr>
</tbody>
</table>

This paper present a describing function analysis aimed to gain a better understanding of how a change of a single parameter value effect the period expressed by the model by Scheper et al. The choice of reference parameter values are not the same as the parameter set used by Scheper et al. and are given in Table 2. The model with the choice of parameters is shown in (3) and (4).

\[
\frac{dM}{dt} = \frac{r_M}{1 + P^3} - q_M M = r_M (1 - \frac{P^3}{1 + P^3}) - q_M M \quad (3)
\]

\[
\frac{dP}{dt} = M(t - \tau) - q_P P \quad (4)
\]

Notice that very importantly the system still have the desired reaction to changes in protein production rate, i.e., light changes, as for Scheper et al.’s parameter set even though with this special choice the model has just one nonlinearity compared to Scheper et al.’s that has two. Further, with a $r_M \approx 1$ a period close to 24 hours is obtained.

3 A Dual-Input Describing Function Analysis - Considering the Bias and the First Harmonic

For an oscillating system not close to a bifurcation point bifurcation theory and/or center manifold theory can usually not be used to examine properties of the system. Two theories that can handle systems not close to the bifurcation point are perturbation theory and describing function analysis. A describing function analysis is a good way to examine changes in the dynamics caused by parameter changes, not having to know the unperturbed system in advance as in perturbation theory, and will be presented here. Because the oscillations in relative concentrations are biased our first approach is a dual-input describing function (DIDF), dual because
3 A Dual-Input Describing Function Analysis - Considering the Bias and the First Harmonic

we assume that a good approximation of $P$ can be given by a bias and a first harmonic.

For the mathematically interested the theory for a general case is discussed in Appendix A. In this section we just briefly discuss the expressions obtained in our case. Further, a short introduction to describing function analysis is given in Reglerteori by T. Glad and L. Ljung [19] and a more detailed discussion in Multiple-Input Describing Function and Nonlinear System Design by Gelb and Vander Velde [1].

Our system, (3) and (4), can be separated into a linear and a nonlinear part as follows. Take the Laplace transform of (3) and (4):

$$sM = r_M f(P) - q_M M,$$

$$sP = r_P M e^{-\tau s} - q_P P$$

where $f(P)$ is now seen as the Laplace transform of the signal coming from the nonlinear part, $f(P) = \frac{1}{1+P^3}$, with $P$ as an input. By combining (5) and (6) we get:

$$sP = r_P r_M \frac{f(P)}{s+q_M} e^{-\tau s} - q_P P$$

$$\Leftrightarrow P = r_P r_M \frac{f(P)}{(s+q_M)(s+q_P)} e^{-\tau s}$$

$$\Leftrightarrow P = F(P) G(s).$$

Our system has been transformed into a nonlinear and a linear part which is exactly what the general theory presented in Appendix A discuss. Before applying the general theory we should stress that to be able to use describing function analysis it is important that the linear part is a good enough low pass filter so that the assumption to consider only the bias and first harmonic in the system is enough. In hope that this is the case we continue to derive the dual-input describing function and check the validity of result after the derivation.

To summarize what is better described in Appendix A, if assuming that our system oscillate, the nonlinear part can be approximated with a describing function. By further invoking harmonic balance we could obtain a set of equations which can be use to give an approximation for $P$ of the form $P = C_0 + C_1 \sin \omega t$ and hopefully a expression for how $\omega$ depends on $r_M$.

If we first assume that $P = C_0 + C_1 \sin \omega t$, where $\omega > 0$, $C_0 \geq C_1 \geq 0$ are to be decided, the dual-input describing function

$$Y_f(C_0, C_1)$$

has to satisfy

$$Y_f(C_0, C_1) G(\omega) = 1$$

\footnote{this is motivated if we see $P$ as the amount of protein that is of course greater that zero}
to get harmonic balance in the system. Because this is a complex equation we obtain two expressions for the three unknowns. A third expression is obtained by considering the bias in the system,

\[ C_0 = \frac{1}{2\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha))d\alpha \mid G(0) \mid. \quad (8) \]

Expressing (7) explicitly we get

\[ \frac{1}{\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha)) \cos(\alpha)d\alpha = 0. \quad (9) \]

where we used

\[ G(s) = \frac{r_{PM}}{(s + q_M)(s + q_P)} e^{-\tau s} \]

as the linear part and

\[ f(P) = \frac{1}{1 + P^3} \quad (10) \]

as the nonlinear part. Notice that (9) is actually true for all memoryless nonlinearities and is motivated in [1], pp 306. Also

\begin{align*}
\frac{1}{\pi} \int_0^{2\pi} \frac{1}{1 + (C_0 + C_1 \sin(\alpha))^3} \sin(\alpha)d\alpha &= \\
\frac{1}{\pi} \int_0^\pi \frac{1}{1 + (C_0 + C_1 \sin(\alpha))^3} \sin(\alpha)d\alpha &+ \frac{1}{\pi} \int_\pi^{2\pi} \frac{1}{1 + (C_0 + C_1 \sin(\alpha))^3} \sin(\alpha)d\alpha \\
&\leq \frac{1}{\pi} \int_0^\pi \frac{1}{1 + C_0^3} \sin(\alpha)d\alpha &+ \frac{1}{\pi} \int_\pi^{2\pi} \frac{1}{1 + C_0^3} \sin(\alpha)d\alpha = 0
\end{align*}

because

\[ 0 \leq C_0 + C_1 \sin(\alpha) \mid_{\pi \leq 0 \leq 2\pi} \leq C_0 \leq C_0 + C_1 \sin(\alpha) \mid_{0 \leq \alpha \leq \pi}. \]

This gives a describing function

\[ Y_f(C_0, C_1) = -\frac{1}{C_1} \mid \frac{1}{\pi} \int_0^{2\pi} \frac{1}{1 + (C_0 + C_1 \sin(\alpha))^3} \sin(\alpha)d\alpha \mid. \quad (11) \]

In our search for \( \omega, C_0 \) and \( C_1 \) we have now three explicitly given equations by combining (7), (10), (8), (9) and (11):

\[ -\pi + 2\pi \gamma = \arg G(\omega), \quad (12) \]
3 A Dual-Input Describing Function Analysis - Considering the Bias and the First Harmonic

Figure 1. Nyquist plot of $G(\omega)$ with $r_M = r_P = 1$, $q_M = q_P = 0.21$ and $\tau = 5$.

$$\frac{1}{|G(0)|} = \frac{1}{C_1} \frac{1}{2\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha)) d\alpha = \frac{1}{C_0} \frac{1}{2\pi} \int_0^{2\pi} \frac{1}{1 + (C_0 + C_1 \sin(\alpha))^3} d\alpha,$$

(13)

$$\frac{1}{|G(\omega)|} = \frac{1}{C_1} \left| \frac{1}{\pi} \int_0^{2\pi} \frac{\sin(\alpha)}{1 + (C_0 + C_1 \sin(\alpha))^3} d\alpha \right|.$$

(14)

Discussion

From the dual-input describing function we are able to extract some information about how the frequency of the oscillations depends on the different parameters.

The frequency’s dependency of $r_M$. A change in $r_M$ is a pure gain change in $G(\omega)$ and because the dual-input describing function is real it is easy to see...
that $\omega$ and also the period $\frac{2\pi}{\omega}$ is not affected by a change in $r_M$. That is, because $\arg G(\omega,r_M) = -\pi$ always occurs for the same $\omega$ independent of $r_M$. $\omega$ is constant and approximately 0.267 rad/sec for the parameter values given in Table 2.

We just saw that by just considering the bias and the first harmonic in the system we will get a constant period independent of $r_M$. Inconsistent, simulations shows a $r_M$ dependence in the period of the clock model by Scheper et al. which is consistent with Aschoff’s rule. Would a better approximation, $P = C_0 + C_1 \sin \omega t + C_2 \sin(2\omega t + \psi)$ instead of as in our previous analysis $P = C_0 + C_1 \sin \omega t$, get the dependency of $r_M$ in the period that we are looking for? A spectral analysis of the signal $P$ from simulations of (3) and (4) could give us a hint of how important the second harmonic is in the system. Figure 2 shows an approximation of the spectrum (FFT) of $P$ from simulations for a range of $r_M$ values, all other parameter values as in Table 2. The plot was normalized such that the magnitude of the first harmonic was always one for every $r_M$.

![Figure 2. FFT of $P$ with $r_M$ varying between 1.65 and 2.](image)

Figure 3 show the FFT for $r_m = 1$ to give a better visualization of the
importance of the second harmonic.

![Graph](image.png)

**Figure 3.** FFT of $P$, $r_M = 1$.

From above analysis, basically by using (9), the following can be said:

In general, for a closed loop consisting of a linear and a nonlinear part with the argument of the linear part $\angle G(a, b) \neq \pi$ and with a memoryless nonlinearity it is necessary to include higher harmonics to see a change in the period of the oscillations due to a pure gain change of the linear part. This holds for our system and therefore make it impossible to see a dependency in $\omega$ of $r_M$.

**The frequency’s dependency of $\tau$.** A change in $\tau$ is a pure phase change of $G(\omega)$. Increasing $\tau$ will decrease the frequency for which $\angle G(\omega) = -\pi$ and therefore increase the period of the oscillations in the system.

**The frequency’s dependency of $q_M$ and $q_P$.** A change in $q_M$ or $q_P$ is a phase and gain change in $G(\omega)$ and increasing any of them would give a higher frequency for the oscillations in the system.
4 Multiple-Input Describing Function Analysis - Considering the Bias, the First and the Second Harmonic

Motivated by above discussion we now look into including the second harmonic component in the system to be able to describe the frequency’s dependency of $r_M$. To do so we assume that $P$ can be described by a bias, first and a second harmonic and then get a multiple-input describing function (MIDF). We, again, as in the dual-input describing function analysis direct the mathematically interested to Appendix B for the general theory and here just present the application of the theory to our system.

The general theory discuss a closed system consisting of a linear and a nonlinear part. We showed earlier that our system can be separated into a linear and a nonlinear part,

$$f(P) = \frac{1}{1 + P^3},$$

$$G(s) = \frac{r_P r_M}{(s + q_M)(s + q_P)} e^{-\tau s}$$

and the general theory is therefore directly applicable.

Before even make an attempt to solve the equations necessary, the harmonic equations, analytically the system was solved numerically. This to see if this multiple-input describing function would be able to catch the $r_M$ dependency in the period before looking in to more tedious analytical approach. With the use of the parameter values given in Table 2 an approximation to the first terms in the Fourier expansion of $P$, i.e., $C_0, C_1, C_2, \psi$ and $\omega$ in $P = C_0 + C_1 \sin \omega t + C_2 \sin(2\omega t + \psi) + \ldots$ were therefore numerically searched for. A measure of how good our parameter set, $C_0, C_1, C_2, \psi$ and $\omega$, was obtained by computing the error in the numerical attempt to solve the equation system. To minimize the error over all parameter sets was quite time consuming and to get a hint of where to search a spectral analysis of $P$ was done. Table 3, 4 and 5 shows the results from the spectral analysis and also values for $C_0, C_1, C_2, \psi$ and $\omega$ computed numerically, by solving the harmonic balance equations, in Matlab. $V$ was used as some sort of cost function and denote therefore in some sense how good the numerical approximations are. With the approximation from the multiple-input describing function analysis for $P$ we can now by using the equation

$$\frac{dP}{dt} = r_P M(t - \tau) - qP$$

get

$$M = C_0 \frac{q}{r_P} + C_1 \frac{i\omega + q}{r_P} |\sin(\omega(t + \tau) + \arctan \frac{\omega}{q})|$$

$$+ C_2 \frac{2i\omega + q}{r_P} |\sin(2\omega(t + \tau) + \psi + \arctan \frac{2\omega}{q})|.$$
Table 3. For $r_m = 1$, approximation to the multiple-input describing function (MIDF), the dual-input describing function (DIDF) and values from a spectral analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MIDF</th>
<th>DIDF</th>
<th>Simulink</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_0$</td>
<td>2.252</td>
<td>2.257</td>
<td>2.2418</td>
</tr>
<tr>
<td>$C_1$</td>
<td>0.677</td>
<td>0.679</td>
<td>0.64</td>
</tr>
<tr>
<td>$C_2$</td>
<td>0.053</td>
<td>0</td>
<td>0.0474</td>
</tr>
<tr>
<td>$\psi$</td>
<td>$-0.64$</td>
<td>$0$</td>
<td></td>
</tr>
<tr>
<td>$\omega$</td>
<td>0.2629</td>
<td>0.26676</td>
<td>0.2634</td>
</tr>
<tr>
<td>$V$</td>
<td>0.0021</td>
<td>0.000051</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. For $r_m = 1.2$, approximation to the multiple-input describing function (MIDF), the dual-input describing function (DIDF) and values from a spectral analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MIDF</th>
<th>DIDF</th>
<th>Simulink</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_0$</td>
<td>2.42</td>
<td>2.44</td>
<td>2.401</td>
</tr>
<tr>
<td>$C_1$</td>
<td>0.85</td>
<td>0.89</td>
<td>0.795</td>
</tr>
<tr>
<td>$C_2$</td>
<td>0.08</td>
<td>0</td>
<td>0.069</td>
</tr>
<tr>
<td>$\psi$</td>
<td>$-0.63$</td>
<td>$0$</td>
<td></td>
</tr>
<tr>
<td>$\omega$</td>
<td>0.2611</td>
<td>0.26676</td>
<td>0.2622</td>
</tr>
<tr>
<td>$V$</td>
<td>0.0672</td>
<td>0.0004</td>
<td></td>
</tr>
</tbody>
</table>

A plot of the approximation of the limit cycle given by multiple-input describing function analysis, dual-input describing function analysis and also from simulations of (1) and (2) are shown in Figure 4, 5 and 6. The first plot for $r_M = 1$, the second for $r_M = 1.2$ and the third $r_M = 2$.

Seeing that the multiple-input describing function was able to catch the dependency in the period of $r_M$ a long and tedious attempt to solve the equations analytically or at least after a minor simplification solve it was done. Unfortunately without success.
Table 5. For $r_m = 2$, approximation to the multiple-input describing function (MIDF), the dual-input describing function (DIDF) and values from a spectral analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MIDF</th>
<th>DIDF</th>
<th>Simulink</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_0$</td>
<td>2.855</td>
<td>2.89</td>
<td>2.875</td>
</tr>
<tr>
<td>$C_1$</td>
<td>1.132</td>
<td>1.185</td>
<td>1.195</td>
</tr>
<tr>
<td>$C_2$</td>
<td>0.126</td>
<td>0</td>
<td>0.135</td>
</tr>
<tr>
<td>$\psi$</td>
<td>-0.65</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>$\omega$</td>
<td>0.2590</td>
<td>0.26676</td>
<td>0.2586</td>
</tr>
<tr>
<td>$V$</td>
<td>0.006</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. For $r_M = 1$, approximation of limit cycle coming from multiple-input describing function analysis (MIDF), dual-input describing functions analysis (DIDF) and as a reference the limit cycle from simulations in Simulink of (1) and (2). Parameter values used are given in table 2.
Figure 5. For $r_M = 1.2$, approximation of limit cycle coming from multiple-input describing function analysis (MIDF), dual-input describing functions analysis (DIDF) and as a reference the limit cycle from simulations in Simulink of (1) and (2). Parameter values used are given in table 2.

Figure 6. For $r_M = 2$, approximation of limit cycle coming from multiple-input describing function analysis (MIDF), dual-input describing functions analysis (DIDF) and as a reference the limit cycle from simulations in Simulink of (1) and (2). Parameter values used are given in table 2.
4.1 Discussion

The failure to get a dependence of $r_M$ in the period with the dual-input describing function analysis and the success using a multiple-input describing function analysis shows the importance of a second harmonic in the system. The existence of the second harmonic in the system was also confirmed by a spectral analysis. Further, the failure to find an analytic expression for the multiple-input describing function led us to just numerically derived results which showed the dependency of $r_M$ but gave no further insight or understanding.

A Derivation of the Dual-Input Describing Function for a General Case - Considering the Bias and the First Harmonic

Consider a system defined by Figure 7, where $G(s)$ is a linear part and $f(P)$ a nonlinear (observe that the Laplace transform of $f(P)$ is undefined because it is nonlinear and therefore the need to use mix notation in Figure 7). Let $P = C_0 + C_1 \sin(\omega t)$\(^3\) and look for $\omega$, $C_0$ and $C_1$ that give a periodic oscillating system. The idea is to let our $P$ go through, be modified by the system and when it returns, it is a closed loop system, set the modified signal equal to the original $P$ and identify the unknowns, $\omega$, $C_0$ and $C_1$.

The nonlinearity transforms $P$ to $F(P) = \text{/Fourie/} = A_0 + A_1 \sin(\omega t + \phi_1) + A_2 \sin(2\omega t + \phi_2) + \ldots$. If we use the trigonometric formula $\sin(\omega t + \phi_1) = \sin(\omega t) \cos(\phi_1) + \cos(\omega t) \sin(\phi_1)$ and skip terms with a angle frequency higher than $\omega$ we get that

$$f(C_0 + C_1 \sin(\omega t)) = A_0 + A_1 (\sin(\omega t) \cos(\phi_1) + \sin(\phi_1) \cos(\omega t)) = A_0 + b \sin(\alpha) + a \cos(\alpha)$$

\(^3\)C_0, C_1 and $\omega \geq 0$

Figure 7. Block diagram.
where the notation

\[ a = A_1 \sin(\phi_1), \quad b = A_1 \cos(\phi_1), \quad \alpha = \omega t \]

was introduced. Skipping the high frequency terms is motivated if for example the linear part can be seen as a lowpass filter. We will not care so much about that now and continue as if it would be a good approximation to skip high frequency terms and then check the final result. It follows that

\[ A_1 = \sqrt{a^2 + b^2}, \quad \phi_1 = \arctan(a/b). \quad (16) \]

To identify the Fourier coefficient, \( b \), multiply (15) by \( \sin(\alpha) \) and integrate \( \alpha \) over a whole period,

\[ b = \frac{1}{\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha)) \sin(\alpha) d\alpha = \frac{1}{\pi} \int_0^{2\pi} (A_0 + b \sin(\alpha) + a \cos(\alpha)) \sin(\alpha) d\alpha = b \pi \]

\[ \Leftrightarrow \quad b = \frac{1}{\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha)) \sin(\alpha) d\alpha. \quad (17) \]

Analogously, we identify \( a \) by multiplying (15) by \( \cos(\alpha) \) and integrate,

\[ a = \frac{1}{\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha)) \cos(\alpha) d\alpha. \quad (18) \]

Finally just integrate (15) to get \( A_0 \),

\[ A_0 = \frac{1}{2\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha)) d\alpha. \quad (19) \]

We continue to walk around the loop, let now \( f(C_0 + C_1 \sin(\omega t)) \) be linear transformed by \( G \),

\[ G(f(C_0 + C_1 \sin(\omega t))) = A_0 \mid G(0) \mid + A_1 \mid G(\omega) \mid (\sin(\omega t + \phi_1 + \angle G(\omega)). \]

With the goal to find periodic oscillations and harmonic balance in our system, search \( C_0 \) and \( C_1 \) such that \( G(f(C_0 + C_1 \sin(\omega t))) = C_0 + C_1 \sin(\omega t) \), which implies, using the expressions (16), (17), (18) and (19):

\[ C_0 = A_0 \mid G(0) \mid \Rightarrow \quad \frac{1}{\mid G(0) \mid} = \frac{1}{C_0} \frac{1}{2\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha)) d\alpha, \quad (20) \]

\[ C_1 = A_1 \mid G(\omega) \mid = \sqrt{a^2 + b^2} \mid G(\omega) \mid \Rightarrow \quad \frac{1}{\mid G(\omega) \mid} = \frac{1}{C_1} \sqrt{a^2 + b^2}, \quad (21) \]
\[ \phi_1 + \angle G(\omega) = 2\pi \nu \quad , \nu \text{ integer.} \]  

(22)

Define the complex valued function \( Y_f(C_0, C_1) \), the dual-input describing function, as follows:

\[ Y_f(C_0, C_1) = \frac{1}{C_1} \sqrt{a^2 + b^2} e^{i\phi_1}. \]

The dual-input describing function will satisfy

\[ Y_f(C_0, C_1) G(\omega) = 1 \]

(23)

according to (21) and (22). Equation (23) give us an equation in the three unknowns \( C_0, C_1 \) and \( \omega \). A second equation is given by (20). Since (23) is complex, (20) and (23) are hopefully enough to find the three unknowns, \( C_0, C_1 \) and \( \omega \).

B Derivation of the Multiple-Input Describing Function for a General Case - Considering the Bias, First and the Second Harmonic

Consider a system shown in Figure 7 and assume that a good approximation of \( P \) is the first three terms in its Fourier expansion, that is, choose

\[ P = C_0 + C_1 \sin \omega t + C_2 \sin(2\omega t + \psi). \]

Continue by taking the Fourier expansion of \( f(P) \),

\[ f(P) = f(C_0 + C_1 \sin \omega t + C_2 \sin(2\omega t + \psi)) = A_0 + A_1 \sin(\omega t + \phi_1) + A_2 \sin(2\omega t + \phi_2) + ... \]

Use the trigonometric formula \( \sin(x + y) = \sin(x) \cos(y) + \sin(y) \cos(x) \) and skip terms with an angle frequency greater than \( 2\omega \). Here again, just as in the dual-input case, we assume that the linear part is a low pass filter and that we can approximate the signals in the system with the three first terms in their Fourier expansion. We get

\[ f(C_0 + C_1 \sin(\omega t) + C_2 \sin(2\omega t + \psi)) = A_0 + a_1 \cos(\alpha) + b_1 \sin(\alpha) + a_2 \cos(2\alpha) + b_2 \sin(2\alpha) \]

(24)

where the notation

\[ a_1 = A_1 \sin(\phi_1), \quad b_1 = A_1 \cos(\phi_1), \quad a_2 = A_2 \sin(\phi_2), \quad b_2 = A_2 \cos(\phi_2), \quad \alpha = \omega t \]

was introduced. It follows that

\[ A_1 = \sqrt{a_1^2 + b_1^2}, \quad \phi_1 = \arctan(a_1/b_1), \quad A_2 = \sqrt{a_2^2 + b_2^2}, \quad \phi_2 = \arctan(a_2/b_2). \]
To obtain an expression for $b_1$ multiply (24) by $\sin(\alpha)$ and integrate $\alpha$ over a whole period.

\[
\int_0^{2\pi} f(C_0 + C_1 \sin(\alpha) + C_2 \sin(2\alpha + \psi)) \sin(\alpha) d\alpha
\]

\[
= \int_0^{2\pi} (A_0 + a_1 \cos(\alpha) + b_1 \sin(\alpha) + a_2 \cos(2\alpha) + b_2 \sin(2\alpha)) \sin(\alpha) d\alpha = b_1 \pi
\]

\[
\Rightarrow b_1 = \frac{1}{\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha) + C_2 \sin(2\alpha + \psi)) \sin(\alpha) d\alpha.
\]

Similarly we obtain $a_1$, multiply (24) by $\cos(\alpha)$ and integrate.

\[
a_1 = \frac{1}{\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha) + C_2 \sin(2\alpha + \psi)) \cos(\alpha) d\alpha.
\]

To obtain $b_2$, multiply (24) by $\sin(2\alpha)$ and integrate.

\[
b_2 = \frac{1}{\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha) + C_2 \sin(2\alpha + \psi)) \sin(2\alpha) d\alpha.
\]

To obtain $a_2$, multiply (24) by $\cos(2\alpha)$ and integrate.

\[
a_2 = \frac{1}{\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha) + C_2 \sin(2\alpha + \psi)) \cos(2\alpha) d\alpha.
\]

Finally just integrate (24) to obtain $A_0$.

\[
A_0 = \frac{1}{2\pi} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha) + C_2 \sin(2\alpha + \psi)) d\alpha.
\]

Let now $f(C_0 + C_1 \sin(\alpha) + C_2 \sin(2\alpha + \psi))$ be linear transformed by $G$

\[
G(f(C_0 + C_1 \sin(\omega t) + C_2 \sin(2\omega t + \psi)))
\]

\[
= A_0 \mid G(0) \mid + A_1 \mid G(\omega) \mid (\sin(\omega t + \phi_1 + \arg G(\omega)))
\]

\[
+ A_2 \mid G(2\omega) \mid (\sin(2\omega t + \phi_2 + \arg G(2\omega))). \quad (25)
\]

With the goal to find periodic oscillations and obtain harmonic balance in our system search $C_0$, $C_1$, $C_2$ and $\psi$ such that $G(f(C_0+C_1 \sin(\omega t)+C_2 \sin(2\omega t+\psi))) = C_0 + C_1 \sin(\omega t) + C_2 \sin(2\omega t + \psi)$, which gives, using (25), that
\[ C_0 = A_0 \mid G(0) \mid \Rightarrow \frac{1}{|G(0)|} = \frac{1}{C_0} \int_0^{2\pi} f(C_0 + C_1 \sin(\alpha) + C_2 \sin(2\alpha + \psi)) d\alpha, \]

\[ C_1 = A_1 \mid G(\omega) \mid = \sqrt{a_1^2 + b_1^2} \mid G(\omega) \mid \Rightarrow \frac{1}{|G(\omega)|} = \frac{1}{C_1} \sqrt{a_1^2 + b_1^2}, \]

\[ \phi_1 + \arg G(\omega) = 2\pi \nu_1, \quad \nu_1 \text{ integer}, \]

\[ C_2 = A_2 \mid G(2\omega) \mid = \sqrt{a_2^2 + b_2^2} \mid G(2\omega) \mid \Rightarrow \frac{1}{|G(2\omega)|} = \frac{1}{C_2} \sqrt{a_2^2 + b_2^2} \]

and

\[ \phi_2 + \arg G(2\omega) = 2\pi \nu_2 + \psi, \quad \nu_2 \text{ integer}. \]

Define the complex valued function \( Y_{f1}(C_0, C_1, C_2, \psi) \) as

\[ Y_{f1}(C_0, C_1, C_2, \psi) = \frac{1}{C_1} \sqrt{a_1^2 + b_1^2} e^{i\phi_1} = \frac{1}{C_1} (ia_1 + b_1). \]  

(26)

Define analogously the complex valued function \( Y_{f2}(C_0, C_1, C_2, \psi) \) as

\[ Y_{f2}(C_0, C_1, C_2, \psi) = \frac{1}{C_2} \sqrt{a_2^2 + b_2^2} e^{i\phi_2} = \frac{1}{C_2} (ia_2 + b_2). \]  

(27)

Then \( Y_{f1}(C_0, C_1, C_2, \psi) \) will satisfy

\[ Y_{f1}(C_0, C_1, C_2, \psi) G(\omega) = 1 \]

and \( Y_{f2}(C_0, C_1, C_2, \psi) \)

\[ Y_{f2}(C_0, C_1, C_2, \psi) G(2\omega) e^{-i\psi} = 1. \]

We now have three equations that have to be satisfied:

\[ C_0 = A_0 \mid G(0) \mid, \]  

(28)

\[ Y_{f1}(C_0, C_1, C_2, \psi) G(\omega) = 1, \]  

(29)

\[ Y_{f2}(C_0, C_1, C_2, \psi) G(2\omega) e^{-i\psi} = 1. \]  

(30)

Unknown are \( C_0, C_1, C_2, \psi \) and \( \omega \). How do we solve this? Pick a value for \( C_1, C_2 \) and \( \psi \), say \( C_1^*, C_2^* \) resp. \( \psi^* \). (28) gives \( C_0^* \). Thereafter (26) gives \( Y_{f1}(C_0^*, C_1^*, C_2^*, \psi^*) \) and (27) \( Y_{f2}(C_0^*, C_1^*, C_2^*, \psi^*) \) (two points in the complex plane). Let \( V \) be a measure of how good our values of \( C_0, C_1, C_2 \) and \( \psi \) can approximate (29) and (30). Define \( V \) as

\[ V(C_0, C_1, C_2, \psi) \]

\[ = \min_{\nu, \phi} \mid Y_{f1}(C_0, C_1, C_2, \psi) - \frac{1}{G(\omega)} \mid + \mid Y_{f2}(C_0, C_1, C_2, \psi) - \frac{e^{i\psi}}{G(2\omega)} \mid \]
Search the value of $C_0$, $C_1$, $C_2$ and $\psi$ that minimize $V$.

A Matlab/Simulink program that minimize $V$ for arbitrarily chosen $G(s)$ and $f(P)$ was created to find the minimal $V$ and the associated $C_0$, $C_1$, $C_2$, $\psi$ and $\omega$ values. A good reference that discuss the computation of describing functions in Matlab and Simulink is an article in Matlab’s Newsletter -MATLAB digest, see [15].
References


References


Paper B

Multiple Scales Analysis

Authors: Henrik Ohlsson, Tamás Kalmár-Nagy
Confirmation of Aschoff’s Rule in a Delay Equation Model for Circadian Rhythm

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Abstract

To properly use the Hopf bifurcation theorem to prove the existent of periodic orbits and to predict how the period depends on the bifurcation parameter one need to prove asymptotic stability at an eventual bifurcation point. This is properly done by an often so tedious center manifold analysis and therefore commonly replaced by a not so tedious method of multiple scales. The following present an example from biology, showing that the method of multiple scales is not always reliable and enough.

1 Introduction

While delay is ubiquitous in physical, chemical and biological processes, its influence on many of these phenomena are still not well understood. Frequent flyers often suffer from what is known as “jet lag” [1] which is the slow synchronization of the body’s biological clock to a different timezone. As this biological clock is responsible for establishing rhythms for sleep, body temperature, hormonal concentrations, etc. it has profound importance on our lives. These rhythms have an approximately 24-hour period, and this is why they are also called circadian rhythms (the Latin term “circadian” literally means “around a day”).

To synchronize its time to that of the environment, the biological clock primarily uses light [19], [20]. This ability is crucial for the survival of the organism and circadian rhythms has been observed in even the simple unicellular cyanobacteria [4], [13], [22], [7].

For more complex organisms, such as mammals, a special part of the brain, called the Supra Chiasmatic Nucleus (SCN) is responsible for synchronization. Biochemical processes in the cells of the SCN are synchronized and together act as the biological clock to provide signals for the liver, kidney, etc. to work together in harmony [18]. Inside a single cell, interlocking biological/chemical feedback loops (see Figure 1) result in oscillations in the concentrations of protein and mRNA. In short, mRNA get transcribed and translated, protein is created and inhibits new transcription of mRNA. The process is called a transcriptional-translational process and can be seen as a delayed negative feedback loop, where protein inhibits, indirectly, itself.

The transcriptional-translational process leads to fluctuations in mRNA and protein concentrations [13], [22], [24], [7] which mainly get affected by light but also
for example temperature, even though the overall rhythm expressed is robust to temperature changes. The oscillations are said to be circadian [27], [10] meaning that they are approximately 24 hours under constant conditions, temperature compensated and gets affected by light [12].

As already mentioned, light is probably the most important input to the clock. Light pulses can shift the clock and different light intensity levels regulates the speed. For nocturnal organisms an increase in light intensity level lengthens the period of the circadian cycle (or equivalently, decreases its frequency) and the otherwise for diurnal organisms. How constant light effects organisms has long been known and is stated in “Aschoff’s Rule” [11].

There are many models for biological clocks, generally described by nonlinear, delayed dynamics. Because concentrations are usually seen as variables models are of a typical form of systems called positive systems. Even though, because of the the high number of states and complexity caused by the nonlinearities and delays any form of analysis are usually very tedious.

Interested in how light effects the clock maybe we do not need to understand the most complex models [5]? A fairly simple one that catch the effect of light is a model by Scheper et al. [26]. It is a transcriptional-translational model i.e., it describes the circadian rhythm behavior of a single cell and thus not take into account any sort of coupling or interaction between cells. Two coupled differential equations are needed but nonlinear and with a delay. Seeing the structure of Scheper et al.’s model as the important thing we choose the parameters in such a
way so that the most important feature for us, the way light effects the model, is kept but also in order to get a so easy model to analyze as possible.

To show that our clock model, which is a model for a nocturnal, behave according to Aschoff’s rule the period of our clock model need to increase with light intensity. A common way is to see a light change as a change in mRNA production rate [21], [23], [28], [17] and we therefore aim to show that our model, structurally equal to Scheper et al.’s model, behave accordingly.

To further motivate, there should be pointed out that there are many models structurally equal to Scheper’s, see for example [16].

Section 2, Model of the Transcriptional-Translational Process, presents the model and in section 3, Dimensional Analysis and Scaling, the model description is rewritten in the purpose to simplify further treatment. The equilibrium is computed in section 4 and for future purposes the nonlinearity is expanded and simplified in section 5. The stability properties of the equilibrium is examined in section 6, Stability of the Equilibrium Solution. This to get a better picture of what kind of nonlinear system we are working with and to get ideas of how to continue the analysis and obtain information for the clock period. The section following, section 7, discuss periodic behavior. To test our results obtained a numerical analysis is presented in section 8. With the interesting values of $r_M$ (the ones for which the clock model has a period of approximately 24 hours) not too far away from the bifurcation value a center manifold approach would be suitable, see [15]. Then the center manifold together with the Hopf bifurcation theorem, see [9], could be used to prove the existence of periodic solutions and to give an expansion of the period in the bifurcation parameter, which will be a scaled version of light in our case. A center manifold approach is pretty heavy mathematically though and is commonly replaced by a method of multiple scales approach which also suites the analysis close to the bifurcation point. With the simplifications used in section 5 a multiple scales approach is presented in section 9.

## 2 Model of the Transcriptional-Translational Process

In the transcriptional-translational process in a biological cell the physical transportation of mRNA and protein can be described using delays. A model using such a description is a model by Scheper et al. (1999). The coupled equations describing this model are

\[
\frac{dM(t)}{dt} = \frac{r_M}{1 + (\frac{P(t)}{k})^n} - q_M M(t)
\]

\[
\frac{dP(t)}{dt} = r_P (t - \tau)^m - q_P P(t)
\]

where $M$ and $P$ are the relative concentrations of mRNA and protein respectively. $r_P$, $r_M$ are production rate constants and $q_P$ and $q_M$ are degradation rate constants for mRNA respectively protein. $\tau$ is a delay and $m$ is the nonlinearity in the protein
Table 1. Parameters used by Scheper’s model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value of parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_M$</td>
<td>mRNA production rate constant $hr^{-1}$</td>
</tr>
<tr>
<td>$r_P$</td>
<td>protein production rate constant $1hr^{-1}$</td>
</tr>
<tr>
<td>$q_M$</td>
<td>degradation rate constant $0.21hr^{-1}$</td>
</tr>
<tr>
<td>$q_P$</td>
<td>protein degradation rate constant $0.21hr^{-1}$</td>
</tr>
<tr>
<td>$n$</td>
<td>Hill coefficient $2.0$</td>
</tr>
<tr>
<td>$m$</td>
<td>nonlinearity in protein synthesis cascade $3.0$</td>
</tr>
<tr>
<td>$\tau$</td>
<td>duration of protein synthesis cascade $4.0hr$</td>
</tr>
<tr>
<td>$k$</td>
<td>scaling constant $1$</td>
</tr>
</tbody>
</table>

cascade. $n$ is the Hill coefficient and $k$ a scaling constant. The parameter values used by Scheper et al. are shown in Table 1.

The equations describes how concentrations of mRNA and protein change during the transcriptional-translational process in a single cell of a nocturnal mammalian. The oscillations are circadian, i.e., periodic of approximately $24$ hours and the model is a description of a biological clock.

One of the most important inputs to a biological clock is light. Different light intensity levels contributes to different clock periods according to Aschoff’s rule, i.e., for a nocturnal animal the period increase with increasing light intensity. Commonly light is seen as something that effects the mRNA production rate.

Using $m = 1$, $q_M = q_P = q$, $k = 1$, $n = 3$ the system (1, 2) now has the form

$$\dot{M}(t) = \frac{r_M}{1 + P(t)^3} - qM(t)$$

$$\dot{P}(t) = r_P M(t - \tau) - qP(t),$$

where the dot now denotes differentiation with respect to time. This is not the same set of parameter values that Scheper et al. used even thought the structure is the same. But the two behaves similar to light (see Figure 2), which is our interest.

Secondly, not much is said about the reason of Scheper et al.’s specific choice of parameter values and an open question is how much measurements/biology that is behind. We therefore aim to show Aschoff’s rule for the the model with the modified parameter set, that is, the period is increasing with increasing light intensity (nocturnal).

We express $M(t)$ from the second equation as

$$M(t) = \frac{\dot{P}(t + \tau) + qP(t + \tau)}{r_P}$$
and substitute it into (3) to yield

\[ \frac{\dot{P}(t + \tau) + q \dot{P}(t + \tau)}{r P} = \frac{r_M}{1 + P(t)^3} - \frac{q \dot{P}(t + \tau) + q P(t + \tau)}{r P}. \]

Shifting the time variable by \( \tau \) gives

\[ \ddot{P} + 2q \dot{P} + q^2 P = \frac{r_M r_P}{1 + P^3(t - \tau)}. \]  \hspace{1cm} (4)

While in the following we will study the general system (above) we will be particularly interested in the behavior at \( q_M = q_P = 0.21, \tau = 5 \), the reason being that at these parameter values we get a period close to 24 hours.

Similar types of nonlinearity are commonly seen in biology, compare Glass-Mackey equation. Notice also the delayed negative feedback in the system. Negative feedback of this form occurs frequently in nature and has previously been discussed by Campbell et al. [2], [3]. Other areas where similar systems occurs are for example studies of machine tool vibrations [25] and congestion control [8].

### 3 Dimensional Analysis and Scaling

In order to simplify our system and understand the role of physical quantities we start by nondimensionalizing our system. Define a dimensionless time by \( \xi = t/T \) where \( T \) is a characteristic time scale specified later. Using \( x(\xi) = P(\xi T) \)
we can express the derivatives and the delay as follows

\[
\frac{dP}{dt} = \frac{1}{T} \frac{dx}{d\xi}, \quad \frac{d^2P}{dt^2} = \frac{1}{T^2} \frac{d^2x}{d\xi^2} \quad \text{and} \quad P(t - \tau) = x(\xi - \frac{\tau}{T}).
\]

Further, by substitute \(\xi T\) for \(t\) in (4) and using above expressions for the derivatives and the delay we obtain

\[
\frac{1}{T^2} \frac{d^2x}{d\xi^2} + \frac{2q}{T} \frac{dx}{d\xi} + q^2 x = \frac{r_M r_P}{1 + x^3(\xi - \frac{\tau}{T})}.
\]

If we multiply by \(T^2\) we get

\[
\frac{d^2x}{d\xi^2} + [2qT] \frac{dx}{d\xi} + [q^2T^2] x = \frac{[r_M r_P T^2]}{1 + x^3(\xi - \frac{\tau}{T})}
\]

where the terms in parentheses are dimensionless groups. We have the freedom to choose the time scale \(T\), so we choose \(T = 1/q\). Introducing \(\bar{\tau}\) as \(\tau q\) to simplify the notation (5) becomes

\[
\frac{d^2x}{d\xi^2} + 2 \frac{dx}{d\xi} + x = \frac{\gamma}{1 + x^3(\xi - \frac{\bar{\tau}}{T})},
\]

with \(\gamma = \frac{r_M r_P}{q^2}\) serving as a bifurcation parameter.

4 The Equilibrium Solution

The system is in equilibrium, when the state \(x\) is not changing (this also implies \(x(\xi) = x(\xi - \bar{\tau})\)) i.e., its derivatives are zero. So for the equilibrium solution

\[
x(\xi) \equiv \bar{x} = \frac{\gamma}{1 + \bar{x}^3}
\]

should hold, or equivalently

\[
\bar{x}^4 + \bar{x} - \gamma = 0.
\]

It is easy to see that there is a unique equilibrium point \(\bar{x}\) satisfying (7). Indeed, \(\bar{x}^4 + \bar{x}\) is a strictly monotone function of \(\bar{x}\) (with a value of 0 at \(\bar{x} = 0\)) and therefore for a positive \(\gamma\), there is only one \(\bar{x}\) satisfying

\[
\gamma = \bar{x}^4 + \bar{x}
\]

Figure 3 shows a plot of the equilibrium point for \(\gamma \in [0, 25]\).

Introducing a new variable \(y = x - \bar{x}\) (the difference between the solution and the equilibrium) we transform the equation into

\[
y'' + 2y' + y + \bar{x} = \frac{\bar{x}^4 + \bar{x}}{1 + (y(\xi - \bar{\tau}) + \bar{x})^3}
\]

where \(\prime\) now means differentiation with respect to the nondimensional time \(\xi\).
5 Simplifications

In order to prepare for further analysis we will in this section first expand around the equilibrium point $\bar{x}$. Assuming small oscillations it is motivated to disregard high order terms. Another simplification can be made if we assume that the bifurcation parameter will always be close to some nominal value. Therefore, a linearization with respect to the bifurcation parameter around some nominal value is done. Last, a scaling is done. This type of scaling is pretty common in literature and make the equation suitable for a perturbation method approach, see for example [6].

Expanding around $\bar{x}$ or equivalently $y = 0$ and keeping terms of up to third order yields

$$y'' + 2y' + y = -\mu y(\xi - \bar{\tau}) + \mu_2 y^2(\xi - \bar{\tau}) + \mu_3 y^3(\xi - \bar{\tau})$$

(8)

with

$$\mu = \frac{3\bar{x}^3}{1 + \bar{x}^3} = \frac{3\bar{x}^4}{\gamma} \geq 0,$$

$$\mu_2 = \frac{3\bar{x}^2(2\bar{x}^3 - 1)}{(1 + \bar{x}^3)^2},$$

$$\mu_3 = -\frac{\bar{x}(10\bar{x}^6 - 16\bar{x}^3 + 1)}{(1 + \bar{x}^3)^3}.$$
If we express $\bar{x}$ as a function of $\mu$ ($\mu < 3$)

$$\bar{x} = \left(\frac{\mu}{3 - \mu}\right)^{\frac{1}{3}}$$

then

$$\mu_2 = \mu^2 (\mu - 1) (3 - \mu)^{\frac{2}{3}},$$

$$\mu_3 = -\frac{1}{3} (3\mu^2 - 6\mu + 1) \mu^{\frac{1}{3}} (3 - \mu)^{\frac{2}{3}}.$$

We can also express $\gamma$ as a function of $\mu$

$$\gamma = 3 \left(\frac{\mu}{(3 - \mu)^{\frac{1}{3}}}\right)^{\frac{1}{3}}.$$

Further, we can linearize, with respect to $\mu$, around a critical value $\mu_{cr}$ (later we will let the critical value be $\mu$ at the bifurcation point). This yields

$$y'' + 2y' + y = - (\mu_{cr} + \varepsilon) y(\xi - \bar{\tau}) + (\alpha + \beta \varepsilon) y^2(\xi - \bar{\tau}) + (\gamma + \delta \varepsilon) y^3(\xi - \bar{\tau})$$

where

$$\mu = \mu_{cr} + \varepsilon,$$

$$\alpha = \frac{\mu_{cr}^{2/3} (-2 \mu_{cr} + \mu_{cr}^2 - 1)}{(3 - \mu_{cr})^{2/3}},$$

$$\beta = \frac{-2 \mu_{cr}^2 - 3 \mu_{cr} + 1}{(3 - \mu_{cr})^{2/3} \sqrt[3]{\mu_{cr}}},$$

$$\gamma = -\frac{2}{3} \sqrt[3]{\mu_{cr}} \left(-9 \mu_{cr}^2 + 3 \mu_{cr}^3 + 1 + 3 \mu_{cr}\right),$$

$$\delta = \frac{1/3 \left(9 \mu_{cr}^3 + 25 \mu_{cr} - 33 \mu_{cr}^2 - 1\right)}{\mu_{cr}^{2/3} \sqrt[3]{3 - \mu_{cr}}}. $$

Instead of the time variable, we will rescale the length

$$y = \varepsilon X$$

to yield

$$X'' + 2X' + X = -\mu_{cr} X_{\tau} + \varepsilon \left(-X_{\tau} + \alpha X_{\tau}^2\right) + \varepsilon^2 \left(\beta X_{\tau}^2 + \gamma X_{\tau}^3\right).$$

### 6 Stability of the Equilibrium Solution

To investigate the stability properties of the equilibrium solution we consider the linearized equation (equation (8) without the nonlinear terms)

$$y'' + 2y' + y = -\mu y(\xi - \bar{\tau}).$$
Using the assumption \( y(\xi) = e^{\lambda \xi} \) we obtain the characteristic equation

\[
(\lambda + 1)^2 = -\mu e^{-\lambda \bar{\tau}} \iff D(\lambda) = e^{\lambda \bar{\tau}}(\lambda + 1)^2 + \mu = 0. \tag{10}
\]

Observe that (10) has infinitely many solutions for \( \lambda \) because of the transcendental term \( e^{\lambda \bar{\tau}} \) (induced by the delay). To be able to tell if the equilibrium solution is unstable we need to find out whether any of the infinitely many eigenvalues \( \lambda \) have a positive real part. As a first step we describe the curves in the \((\bar{\tau}, \mu)\) parameter space where there is a pair of pure imaginary eigenvalues \( \lambda = \pm i\omega \).

\[
e^{i\omega \bar{\tau}}(i\omega + 1)^2 = -\mu.
\]

This complex equation can be separated into a real and imaginary part

\[
\omega^2 - 1 = \mu \cos \omega \bar{\tau}, \tag{11}
\]
\[
2\omega = \mu \sin \omega \bar{\tau}, \tag{12}
\]

which have to hold at the same time. The trigonometric part can be eliminated by squaring and adding (11) and (12). We get

\[
\mu^2 = (\omega^2 + 1)^2
\]

which simplifies to

\[
\mu(\omega) = \omega^2 + 1 \tag{13}
\]

because \( \mu \) is positive.

Dividing (12) by (11), excluding singular cases, we can get an expression for \( \bar{\tau} \)

\[
\bar{\tau}(\omega) = \frac{1}{\omega} \left( j\pi + \arctan \frac{2\omega}{\omega^2 - 1} \right), \quad j = 0, 1, \ldots
\]

The expression for \( \mu \) and \( \bar{\tau} \) are both parameterized by \( \omega \). Figure 4(a) shows a plot of \((\bar{\tau}(\omega), \mu(\omega))\) while 4(b) of \((\bar{\tau}(\omega), \gamma(\omega))\). The curves in a stability lobe diagram tell us when purely imaginary values occurs and can therefore help us separate stable and unstable regions. Because of the delay an infinite number of eigenvalues exist and more information is therefore needed to tell when the first, real or complex conjugate pair, pass from the left half to the right half of the complex plane.

To get to that information and to be able to characterize the stability of the regions bounded by the curves we will next compute the velocity with which the imaginary roots cross the imaginary axis

\[
\Gamma = \Re \frac{d\lambda(\mu)}{d\mu} \bigg|_{\mu = \mu_{cr}}
\]

where \( \mu_{cr} \) denote the critical value of the bifurcation parameter \( \mu \) at which the characteristic equation (10) has pure imaginary roots.

We obtain \( \Gamma \) through implicit differentiation of the characteristic equation as

\[
\frac{dD(\lambda(\mu), \mu)}{d\mu} = \frac{\partial D(\lambda(\mu), \mu)}{\partial \mu} + \frac{\partial D(\lambda(\mu), \mu)}{\partial \lambda} \frac{d\lambda(\mu)}{d\mu} = 0
\]
Confirmation of Aschoff’s Rule in a Delay Equation Model for Circadian Rhythm

\[ \Gamma = -\Re \left\{ \frac{\partial D(\lambda(\mu), \mu)}{\partial \mu} \right\} \bigg|_{\lambda = i\omega, \mu = \mu_{cr}} \]

Next

\[ \frac{\partial D(\lambda(\mu), \mu)}{\partial \mu} \bigg|_{\lambda = i\omega, \mu = \mu_{cr}} = 1 \]  \hspace{1cm} (14)

\[ \frac{\partial D(\lambda(\mu), \mu)}{\partial \lambda} \bigg|_{\lambda = i\omega, \mu = \mu_{cr}} = -e^{i\omega \bar{\tau}} (\bar{\tau} \omega^2 - 2 i\omega \bar{\tau} - 2 i\omega - 2) \]  \hspace{1cm} (15)

and

\[ \frac{d\lambda(\mu)}{d\mu} \bigg|_{\mu = \mu_{cr}} = \frac{e^{-i\omega \bar{\tau}}}{\bar{\tau} \omega^2 - 2 i\omega \bar{\tau} - 2 i\omega - 2} \]  \hspace{1cm} (16)

Therefore

\[ \Gamma = \Re \left\{ \frac{e^{-i\omega \bar{\tau}}}{\bar{\tau} \omega^2 - 2 i\omega \bar{\tau} - 2 i\omega - 2} \right\} \]  \hspace{1cm} (17)

\[ = \frac{(\bar{\tau} \omega^2 - \bar{\tau} - 2) \cos(\omega \bar{\tau}) + \omega (2 \bar{\tau} + 2) \sin(\omega \bar{\tau})}{\bar{\tau}^2 \omega^4 + 2 \bar{\tau}^2 \omega^2 + 4 \bar{\tau} \omega^2 + \bar{\tau}^2 + 4 \bar{\tau} + 4 + 4 \omega^2} \]  \hspace{1cm} (18)

\[ = \frac{(\bar{\tau} \omega^2 - \bar{\tau} - 2) \frac{\omega^2}{\mu_{cr}} + \omega (2 \bar{\tau} + 2) \frac{2\omega}{\mu_{cr}}}{\bar{\tau}^2 \omega^4 + 2 \bar{\tau}^2 \omega^2 + 4 \bar{\tau} \omega^2 + \bar{\tau}^2 + 4 \bar{\tau} + 4 + 4 \omega^2} \]  \hspace{1cm} (19)

\[ = \frac{\bar{\tau} \omega^4 + (2 \bar{\tau} + 2) \omega^2 + \bar{\tau} + 2}{\bar{\tau}^2 \omega^4 + 2 \bar{\tau}^2 \omega^2 + 4 \bar{\tau} \omega^2 + \bar{\tau}^2 + 4 \bar{\tau} + 4 + 4 \omega^2} > 0 \]  \hspace{1cm} (20)

We conclude that the roots to the characteristic equation always cross the imaginary axis with a positive velocity which implies that the lower bounding curve is the stability boundary (show that at \( \mu = 0 \) the system is stable and invoke continuity). The linear system is stable below this, unstable above.
7 Periodic Orbits

The necessary condition for the existence of periodic orbits (The Hopf bifurcation theorem [9]) is that the rightmost characteristic roots cross the imaginary axis with a non-zero velocity when changing the bifurcation parameter $\mu$. We can from derived results then conclude that there exist periodic orbits.

To finally show the existence of a Hopf bifurcation we would also need to show that the nonlinear system's equilibrium is asymptotically stable at the bifurcation point, see [9]. To conclude this center manifold theory could be used. Such an analysis would also provide expressions for how the period of the oscillations depend on the bifurcation parameter but would be pretty tiresome, see center manifold for delays in e.g. [9]. We chose instead to examine some alternative ways, but first, a numerical analysis to check the validity of our result.

8 Numerical Analysis

A variety of packages/programs exist for bifurcation analysis of systems of ordinary differential equations, e.g., AUTO, CONTENT and LocBif. For delayed ordinary differential equations, on the other side, there are a limited number of packages. We chose to explore the possibilities of a package for Matlab, DDE-biftool. [14]. This use the concept of continuation or path following and can given a set of periodic solutions compute their continuation.

8.1 Analysis Using DDE-biftool

Choosing $\gamma = 0$ to be the smallest $\gamma$-value of interest an stable equilibrium point is found at this very leftmost $\gamma$-value. The system is analyzed for a second $\gamma$-value, just a little bigger than the first, to find a stable equilibrium point. Having the equilibrium points for two $\gamma$-values the branch of equilibriums can now be continued using DDE-biftool. A stability change is recognized suggesting a bifurcation point for a certain $\gamma$-value. Given an approximation of this bifurcation point DDE-biftool is able to correct it and continue the branches of periodic solutions evolving from the bifurcation point. The plots produced are shown in Figure 5(a) and 5(b). Information of how the period of the periodic solutions change with $\gamma$ is also given and is depicted in Figure 5(c).

Looking back at the stability lobe diagram we see that for $\tau = 5$ or $\bar{\tau} = 5 \times 0.21 = 1.05$ we are supposed to have a bifurcation point at a $\gamma$-value close to 15. This is supported by the numerical analysis and can be seen in Figure 5.

9 Two-Scales Expansion

The method of multiple scales is commonly used to exam systems having more than one time scale. Worth mentioning is that the method reduces to ordinary perturbation analysis if just one timescale is used. The method have shown to be very effective and is very frequently seen in literature [6]. What is not that
commonly seen is that it can fail and even less, any sort of discussion of when and why the methods fail. What is important to stress though is its possibility to fail and that the result given by the method always have to been checked.

The analysis is closely following the analysis by Das and Chatterjee in Multiple Scales Without Center Manifold Reductions for Delay Differential Equations Near Hopf Bifurcations [6].

Define $T_0 = \epsilon t$ and assume that $X(t)$ can be seen as depending on the slow time $T_0$ and time $t$, which will be treated as independent times,

$$x(t) = X(t, T_0)$$
and expanded in $\varepsilon$

$$X(t,T_0) = X_0(t,T_0) + \varepsilon X_1(t,T_0) + \varepsilon^2 X_2(t,T_0) + \ldots$$

Substitute the expansion into (9) to obtain

$$X_{0tt} + 2X_{0t} + X_0 + \mu_{cr} X_0(t-\bar{\tau},T_0)$$
$$+ \varepsilon[\mu_{cr} X_1(t-\bar{\tau},T_0) + 2 X_{1t} + X_1 + 2 X_0 \tau_0 + X_1 + 2 X_0 \tau T_0$$
$$+ X_0 (t-\bar{\tau},T_0) - \alpha X_0 (t-\bar{\tau},T_0)^2] + O(\varepsilon^2) = 0. \quad (21)$$

(21) must hold for all $\varepsilon$ and we can therefore separate into one for every power. The $\varepsilon^0$-equation is the linearization of our original system, (4), at the bifurcation point if $\mu_{cr}$ is chosen to be the $\mu$-value at the bifurcation point (see the stability lobe diagram, Figure 4(a)). This simplifies the analysis in the way that the approximations derived in section 5 will be suitable. We further know from previous analysis that all eigenvalues except two are in the open left plane and that those will result in a sum of infinitely many decaying oscillations. The two that are not in the open left half plane are two purely imaginary eigenvalues, say at $\pm i\omega_0$. The final oscillations, after all transients have died out, will be the one associated with the two purely imaginary eigenvalues and we therefore assume that it is sufficient to work with $X_0$ of the form

$$X_0 = A \sin \omega_0 t + B \cos \omega_0 t$$

with $A$ and $B$ dependent on the slowly varying time $T_0$. Notice that we have in some way got around that the unperturbed solutions should be know by this assumption.

The $\varepsilon^1$-equation has the form

$$X_{1tt} + 2X_{1t} + X_1 + \mu_{cr} X_1 (t-\bar{\tau},T_0)$$
$$+ 2 X_0 \tau_0 + 2 X_0 \tau T_0 + X_0 (t-\bar{\tau},T_0) - \alpha X_0 (t-\bar{\tau},T_0)^2 = 0. \quad (22)$$

Using our assumed $X_0$ in (22) and set the secular terms equal to zero we end up with two coupled first order differential equations,

$$2A T_0 - 2\omega_0 B T_0 + B \sin \omega_0 \bar{\tau} + A \cos \omega_0 \bar{\tau} = 0,$$
$$2B T_0 - 2\omega_0 A T_0 - A \sin \omega_0 \bar{\tau} + B \cos \omega_0 \bar{\tau} = 0.$$ 

Which we solve for $A T_0$ and $B T_0$,

$$A T_0 = - \left( B \sin \omega_0 \bar{\tau} + A \cos \omega_0 \bar{\tau} + \omega_0 \left( - A \sin \omega_0 \bar{\tau} + B \cos \omega_0 \bar{\tau} \right) \right) \frac{1}{2 \left( 1 + \omega_0^2 \right)}, \quad (23)$$

$$B T_0 = \left( \omega_0 \left( B \sin \omega_0 \bar{\tau} + A \cos \omega_0 \bar{\tau} \right) - ( - A \sin \omega_0 \bar{\tau} + B \cos \omega_0 \bar{\tau} ) \right) \frac{1}{2 \left( 1 + \omega_0^2 \right)}. \quad (24)$$
Before going on with (23) and (24) we will derive some expressions by making a change to polar coordinates,

\[ A = R \cos \varphi, \]  
\[ B = R \sin \varphi. \]  

Taking the absolute time derivative,

\[ A = R \cos \varphi, \]  
\[ B = R \sin \varphi. \]  

and using

\[ \frac{dA}{dt} = \varepsilon A T_0, \]  
\[ \frac{dB}{dt} = \varepsilon B T_0. \]  

we obtain

\[ \varepsilon A = \dot{R} \cos \varphi + R \dot{\varphi} \sin \varphi, \]  
\[ \varepsilon B = \dot{R} \sin \varphi + R \dot{\varphi} \cos \varphi. \]

Multiplying by \( \sin \varphi \) and \( \cos \varphi \) we can after combining obtain

\[ \dot{R} = \varepsilon (B T_0 \sin \varphi + A T_0 \cos \varphi), \]  
\[ \dot{\varphi} = \frac{\varepsilon}{R} (A T_0 \sin \varphi - B T_0 \cos \varphi). \]

Substituting the expressions for \( A T_0 \) and \( B T_0 \) giving by (23) resp. (24) the \( \dot{\varphi} \)-equation become independent of \( R \) and can be solved separate. We obtain

\[ \dot{\varphi} = \varepsilon \frac{\sin \omega_0 \bar{t} + \omega_0 \cos \omega_0 \bar{t}}{1 + \omega_0^2} \approx 0.114 \varepsilon \]  

using that \( \bar{t} = 5 \cdot 0.21 \) and \( \omega_0 = 0.2665/0.21 \). What does this mean? We have that

\[ X_0 = A \sin \omega_0 t + B \cos \omega_0 t \]

and with \( A = R \cos \varphi \) and \( B = R \sin \varphi \),

\[ X_0 = R \cos \varphi \sin \omega_0 t + R \sin \varphi \cos \omega_0 t. \]

Therefore

\[ X_0 = R \sin (\varphi + \omega_0 t) \]

or

\[ X_0 = R \sin ((\dot{\varphi} + \omega_0) t). \]

We get that the frequency is increasing with \( \mu \) which is opposite to what we wanted to see. Figure 6 shows the frequency measured in simulations of (9) and also the approximation obtained by the two scales method.

By studying the expressions for \( \varepsilon \) of higher orders one realize that \( X_1, X_2 \) and so on will all be faster varying terms and that \( X_0 \) will decide the period for \( X \). There is then no reason to continue and examine the \( \varepsilon^2 \)-equation, \( X_0 \) will decide the period of the oscillations.
Adding a third time scale will not change change the result significantly, we would still get an incorrect result saying that the period is decreasing with $\mu$. A reason could be that we are not working in the right coordinate base. The methods of multiple scales is not invariant under coordinate transformations and a change of coordinates would maybe turn the result into a correct one. This brings up the question of how reliable the method actually is and emphasis the importance of checking the results given by the method of multiple scales.
References


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Paper C

Multiple Scales’s Dependency of Linear Coordinate Transformations

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Multiple Scales’s Dependency of Linear Coordinate Transformations

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Abstract
The effect of a rotation of the coordinate frame on the method of multiple scales (MMS) is examined through an example. Basically, a linear coordinate transformation of an almost linear system is performed. Thereafter the method of multiple scales is used to approximate a solution in the transformed coordinates and finally the computed approximation is transformed back to the original coordinate frame. A comparison to simulation result show a dependency of the coordinate frame in which the multiple scale analysis is carried out.

Keywords: method of multiple scales, coordinate transformation.

1 Introduction
To properly examine nonlinear oscillations a center manifold analysis can be used, see [2]. Commonly this tedious analysis is replaced and that often with a method of multiple scales analysis [1].

Many example of magical results can be found but not so much showing the failure of the method and even more seldom a discussion of why it fails or succeeds. In the following the theory of multiple scales is applied to the van Der Pol oscillator. We show that the result of the analysis will be depended of the coordinate frame and thereby propose the question of what is the optimal coordinate frame.

2 The Method of Multiple Scales Applied to the van Der Pol Oscillator
Consider the system (the van Der Pol Oscillator alike):
\[ \ddot{y} + y - \epsilon(1 - \epsilon y^2)\dot{y} = 0. \] (1)
To examine the oscillations expressed by the system a we employ the methods of multiple scales. Before applying though, a coordinate transformation is done, basically a rotation. After an analysis of the transformed system the result is taken back to the original coordinate frame and the dependency of different coordinate transformations is considered.
We start by looking over the details of the coordinate transformation, then proceed by applying the method of multiple scales to the transformed system and finally transform the result back to the original coordinate frame. With

\[
Y = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \dot{y} \\ y \end{pmatrix}
\]

we get

\[
\dot{Y} = \bar{A}Y + f(Y), \quad \bar{A} = \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix}, \quad f(Y) = \begin{pmatrix} \epsilon(1 + \epsilon y_2^2)y_1 \\ 0 \end{pmatrix}.
\]

Introduce the coordinate transformation

\[
Y = R(\theta)X, \quad R(\theta) = \begin{pmatrix} \cos \theta & -\sin \theta \\ \sin \theta & \cos \theta \end{pmatrix}, \quad X = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}
\]

with the inverse transformation

\[
R^{-1}(\theta) = R(-\theta).
\]

In the x-coordinate frame the system get the form

\[
R(\theta) \dot{X} = \bar{A}R(\theta)X + f(R(\theta)X)
\]

\[
\Leftrightarrow \dot{X} = R(-\theta)\bar{A}R(\theta)X + R(-\theta)f(R(\theta)X)
\]

\[
\Leftrightarrow \dot{X} = \bar{A}X + R(-\theta)f(R(\theta)X)
\]

where

\[
f(R(\theta)X) = \begin{pmatrix} \epsilon(1 + \epsilon(\sin \theta x_1 + \cos \theta x_2)^2)(\cos \theta x_1 - \sin \theta x_2) \\ 0 \end{pmatrix}.
\]

The system takes the form

\[
\dot{X} = \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} X
\]

\[
+ \begin{pmatrix} \cos \theta & \sin \theta \\ -\sin \theta & \cos \theta \end{pmatrix} \begin{pmatrix} \epsilon(1 + \epsilon(\sin \theta x_1 + \cos \theta x_2)^2)(\cos \theta x_1 - \sin \theta x_2) \\ 0 \end{pmatrix}
\]

\[
\Leftrightarrow \dot{X} = \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} X
\]

\[
+ \begin{pmatrix} \cos \theta(\epsilon(1 + \epsilon(\sin \theta x_1 + \cos \theta x_2)^2)(\cos \theta x_1 - \sin \theta x_2)) \\ -\sin \theta(\epsilon(1 + \epsilon(\sin \theta x_1 + \cos \theta x_2)^2)(\cos \theta x_1 - \sin \theta x_2)) \end{pmatrix}.
\]

Assume that \(X\) can be seen as dependent on \(t\) and \(T = \epsilon t\) being a slow time. Make a power expansion of \(X\),

\[
x_1(t, T) = x_{10} + \epsilon x_{11} + \epsilon^2 x_{12} + ..., \]

\[
x_2(t, T) = x_{20} + \epsilon x_{21} + \epsilon^2 x_{22} + ..., \]
Both the coefficient in front of cosine and sine need to be zero to avoid secular
Collecting cosine and sine terms

\[
\begin{align*}
&\epsilon \cos \theta (1 + \epsilon (\sin \theta (x_{10} + ..) + \cos \theta (x_{20} + ..))^2) (\cos \theta (x_{10} + ..) - \sin \theta (x_{20} + ..)) \\
&- \epsilon \sin \theta (1 + \epsilon (\sin \theta (x_{10} + ..) + \cos \theta (x_{20} + ..))^2) (\cos \theta (x_{10} + ..) - \sin \theta (x_{20} + ..)) 
\end{align*}
\]

Notice that the dot denotes derivative wrt to the absolute time. The 0th order
equation becomes:

\[
\begin{pmatrix}
x_{10,tt} \\
x_{20,tt}
\end{pmatrix} = \begin{pmatrix}
0 & -1 \\
1 & 0
\end{pmatrix}
\begin{pmatrix}
x_{10} \\
x_{20}
\end{pmatrix}
\]

where subscript \(t\) denotes partial derivatives with respect to \(t\). Which has a solution:

\[
\begin{align*}
x_{10} &= -A(T, \theta) \sin t + B(T, \theta) \cos t \\
x_{20} &= A(T, \theta) \cos t + B(T, \theta) \sin t
\end{align*}
\]

\(A\) and \(B\) are here seen as 'constants' with respect to \(t\) but functions of \(T\), the slow
time. \(t\) and \(T\) are here seen as independent, see \([3]\).

Further the first order equation becomes

\[
\begin{pmatrix}
x_{10,tt} + x_{11,tt} \\
x_{20,tt} + x_{21,tt}
\end{pmatrix} = \begin{pmatrix}
0 & -1 \\
1 & 0
\end{pmatrix}
\begin{pmatrix}
x_{11} \\
x_{21}
\end{pmatrix} + \begin{pmatrix}
\cos \theta \\
-\sin \theta
\end{pmatrix} (\cos \theta x_{10} - \sin \theta x_{20})
\]

\[
\Leftrightarrow \begin{pmatrix}
x_{11,tt} \\
x_{21,tt}
\end{pmatrix} = \begin{pmatrix}
-x_{21} - x_{10,tt} + \cos \theta (\cos \theta x_{10} - \sin \theta x_{20}) \\
x_{11} - x_{20,tt} - \sin \theta (\cos \theta x_{10} - \sin \theta x_{20})
\end{pmatrix}
\]

Taking the partial derivative wrt \(t\) of the second row and then substitute the first
for \(x_{11,tt}\) gives

\[
x_{21,tt} = -x_{21} - x_{10,tt} + \cos \theta (\cos \theta x_{10} - \sin \theta x_{20}) - x_{20,tt} - \sin \theta (\cos \theta x_{10} - \sin \theta x_{20})
\]

with the solution from the 0th order equation we get:

\[
x_{21,tt} = -x_{21} - (A_T(T, \theta) \sin t + B_T(T, \theta) \cos t) \\
+ \cos \theta (A_T(T, \theta) \sin t + B(T, \theta) \cos t) - \sin \theta (A(T, \theta) \cos t + B(T, \theta) \sin t)) \\
- (A_T(T, \theta) \sin t + B(T, \theta) \cos t) - \sin \theta (A(T, \theta) \cos t - B(T, \theta) \sin t) \\
- \sin \theta (-A(T, \theta) \sin t + B(T, \theta) \cos t). 
\]

Collecting cosine and sine terms

\[
x_{21,tt} = -x_{21} + [2A_T(T, \theta) - \cos^2 \theta A(T, \theta) + \sin \theta A(T, \theta)] \sin t \\
+ [-2B_T(T, \theta) + \cos^2 \theta B(T, \theta) - \sin \theta B(T, \theta)] \cos t.
\]

Both the coefficient in front of cosine and sine need to be zero to avoid secular
terms,

\[
\Xi_T(T, \theta) + (\sin \theta - \cos^2 \theta) \Xi(T, \theta) = 0,
\]

(3)
where \( \Xi \) can be replaced by \( A \) or \( B \). (3) has a solution

\[
\Xi(T, \theta) = C(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)T}}.
\]

Inserted in the 0th order equation we get

\[
x_{10} = -C_1(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)T}} \sin t + C_2(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)T}} \cos t,
\]

\[
x_{20} = C_1(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)T}} \cos t + C_2(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)T}} \sin t.
\]

With \( T = \epsilon t \)

\[
x_1 \approx x_{10} = -C_1(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)\epsilon t}} \sin t + C_2(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)\epsilon t}} \cos t \quad (4)
\]

\[
x_2 \approx x_{20} = C_1(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)\epsilon t}} \cos t + C_2(\theta) \sqrt{e^{(-\sin \theta + \cos^2 \theta)\epsilon t}} \sin t \quad (5)
\]

Further can \( C \) be decided from initial conditions. For the plots shown in Figure 2 \( Y(0) = [0 \ 1]^T \) which gets transformed to \( X(0) = [\sin \theta \ \cos \theta]^T \). Using (4) results in \( C_1(\theta) = \cos \theta \) and \( C_2(\theta) = \sin \theta \).

To get back to \( y \) we need to make a transformation using \( R \),

\[
Y = R(\theta)X.
\]

We get

\[
y = \sin \theta \ x_1 + \cos \theta \ x_2 \approx \sin \theta \ x_{10} + \cos \theta \ x_{20}
\]

A comparison between simulations of (1) and the result from multiple scales is shown in Figure 2. The dependency of \( \theta \) in the approximation produced by the method of multiple scales is clear. \( \theta = 0 \) give a much better fit with the simulations then \( \theta = \pi/2 \).

![Figure 1](image)

**Figure 1.** The method of multiple scales approximation \((x_{20}, \text{solid line})\) plotted together with simulation result \((y, \text{dashed line})\). (a) \( \theta = 0 \) and (b) \( \theta = \pi/2 \).

The approximation is good for small \( t \)s but as time grows the solution for \( \epsilon = 0.1 \) will converge to a limit cycle while the approximation will not. To get a
approximation that does not grow off to infinity or goes to zero, which now is the case, the first order equation need to be solved to give the second order partial derivatives with respect to $T$. Having the solution to the second order equation we can get a better approximation of $A(T,\theta)$ and $B(T,\theta)$ using

\[
\frac{A(T,\theta)}{d\theta} = \epsilon A_T(T,\theta) + \epsilon^2 A_{TT} + \ldots,
\]

\[
\frac{B(T,\theta)}{d\theta} = \epsilon B_T(T,\theta) + \epsilon^2 B_{TT} + \ldots
\]

At this point we just computed the first term in these expansions and used that as an approximation.

## 3 A System With a Hopf Bifurcation

Now consider the system

\[
\ddot{u} + u - (\epsilon - u^2) \dot{u} = 0
\]

which has a Hopf bifurcation when $\epsilon = 0$ and is not very suitable for a perturbation approach. The reason being that the unperturbed system is unknown. After a rescaling,

\[
u = \epsilon y
\]

we obtain

\[
\ddot{y} + y - \epsilon(1 - \epsilon y^2) \dot{y} = 0
\]

Note that the Hopf theorem does not hold for this rescaled system! The new system, which is the same as we discussed in the previous section, has a pleasant structure for a multiple scales analysis, it is almost linear and the unperturbed system is therefore a linear system with a known solution.

The application is identical to that above and won’t be repeated here. After arriving at $y$ a scaling of $\epsilon$ take us back to our original system

\[
u = \epsilon y.
\]

One realize that the method of multiple scales can be used to study the behavior close to the bifurcation point even for a not almost linear system as an alternative to for example a center manifold analysis. One also realize that it is dependent on the coordinate frame and the question of what the optimal choice of coordinate frame arise.

## 4 Conclusion

A dependency of coordinate system for the result produced by a multiple scales analysis has been shown for a nonlinear example. This can explain the total failure of the methods of multiple scales at some applications and also emphasis the importance of checking the results obtained by the method. An open question is what the optimal coordinate frame is.
References


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