Abstract

In this report a high dimensional model of glycolysis is described by the Stuart–Landau equation. Describing the glycolysis in this way reduces the number of dimensions considerably. However, it is also an approximation, and the main objective is to compare the Stuart–Landau approximation with the original model. This is possible because a way to transform the Stuart–Landau coordinates back to the physical space exists. In the last chapter a table lists the results when the amplitudes, the periods, and the mean values for the Stuart–Landau approximation and the original model are compared.

Contents

Chapter 1

Introduction

1.1 Identifying the problem

This report is the product of a combined masters thesis in chemistry and mathematics. An area where these two disciplines naturally meet is chemical kinetics. When doing chemical kinetics one may end up with a chemical model based upon a high–dimensional coupled differential equation system. However, the dynamics can qualitatively be described by normal forms, which are, if the right conditions are present, a lower dimensional problem. In this report normal forms will be used to describe such a high dimensional biochemical system – glycolysis.

In the late 1950's it was indicated that the concentration of NADH in the glycolysis of yeast cells oscillates in time. This has been confirmed many times since then, both in cell extract and *in vivo*. Also, it has been reported that when mixing two cell populations oscillating 180° out off phase, the NADH oscillations will disappear, but reappear after some time. This is being interpreted as the individual cell's ability to synchronize its oscillations to the bulk oscillation.

On the background of these findings Sune Danø, together with Finn Hynne and Preben Sørensen, did a series of experiments on glycolysis. Contrary to the earlier experiments that where made in closed systems, these experiments were done in an open vessel. Using fluorescence spectrophotometry, they showed that when solutions of glucose, cyanide, and yeast cells where pumped into a cuvette with a suspension of yeast cells, the cells could be kept in a well defined oscillatory state. If the rate of glucose inflow was lowered, the oscillations disappeared. The mechanism responsible for this characteristic behavior was of course modeled, resulting in a very detailed model which describes 18 different metabolites.

One purpose of this model is to enable an investigation of the coupling phenomena. However, if each cell is described by such a comprehensive model, coupling a large number together will make the numerical computations somewhat troublesome. In the model the flow of glucose is a parameter that can be varied. This results in qualitative new behavior, as in the experiments, i.e. oscillations emerge or disappear. At this point the theory of center manifolds and normal forms can be applied, which can reduce the model considerably [1]. Sørensen's group is interested in describing glycolysis within each cell via normal forms, because this will ease the computations significantly when studying the coupling phenomena.

However, describing the model via a normal form is an approximation. Therefore, Preben Sørensen suggested the following working hypothesis: How well does the normal form approximate the original model? In order to answer the question I will extend it by asking:

How well does the normal form approximation describe the amplitude, the period and the mean value of the oscillation given by the model proposed by Danø *et al*?

In order to answer the question the following approach is used:

- The first section is devoted to introducing some aspects of chemical kinetics, since this is the very basis of the model. My hope is then that mathematicians can benefit from reading this report as well as chemists.

- After this introduction the model is presented.

- In chapter 3 the theory of center manifolds and normal forms are discussed. This discussion is based on the approach suggested by Ipsen and Hynne.

- The results derived in chapter 3 is used to compute the normal form coefficients.

- The normal form approximation is then compared with the original model.

- In the final chapter the results will be listed, and a first approach on how to study the coupling is illustrated.

[1] This is will be explained in details later.

The approach given in Ipsen and Hynne differs slightly from the standard approach as it is seen in for example [14], [1], and [9]. At first sight this method seems tedious, however, it provides a way to transform the normal form coordinates back to the physical space, which enables the comparison. I had some difficulties understanding this method, and I hope that others will find chapter 3 helpful if they are to apply this approach. However, chapter 3 to be a complete description, but rather a supplement to the article. Also, in appendix B I give an example on how a normal form can be derived via Mathematica. It is my hope that the script file will catalyse the process for others when getting started.

1.2 Acknowledgement

Being a guest at chemistry laboratory 3 in these 10 months has been both interesting and enjoyable. I would like to thank Preben Sørensen and Finn Hynne for taking their time to help me whenever I needed it. Also, I must thank Sune Danø for making this such a pleasant stay, and for always helping and suggesting ideas on how to solve any kind of problem.

Finally, I thank Anders Bisgaard – "the second member" of the group. Anders' way off patiently listening and working around a problem suited me perfectly, and we had many very good and "in depth" discussions. I truly hope that Anders will assist others in the same way as he assisted me.

Chapter 2

The glycolysis model

In this chapter the glycolysis model proposed by Danø and Hynne is presented. First some general aspects of chemical kinetics and modelling will be discussed, which hopefully will give a little insight, especially for the mathematicians, in chemical kinetics.

2.1 Chemical kinetics: An overview

This section is based on [11], [10] and [12], unless otherwise stated.

In chemical kinetics one is often interested in proposing a model that can reproduce the experiments. The model is based on a chemical mechanism which can be more or less complicated, depending on the purpose of the model. If one is interested in a model that shows the qualitative behavior of the experiments, a simple mechanism, consisting of two or three reactions steps often suffice. If, on the other hand, one wishes a more quantitative description of the experimental data, the mechanism can be described by empirically determined reactions steps. [1] No matter what you are interested in doing, the mechanism proposed must, of course, be based on chemical intuition and already accepted mechanisms, as for example the Michaelis–Menten mechanism.

The next step is to suggest the differential equations describing the mechanism. These are often a set of coupled nonlinear differential equation,

[1] Scott [11] makes a distinction between the quantitative and qualitative description, in that he defines the later as a model and the quantitative description as a mechanism. I will not make use of this distinction, but simply explain the purpose of the mechanism. Also, I will define a model as the mechanism as well as the differential equations describing it.

ordinary or partial depending on the nature of the system, as it will be explained later. The dynamical system is then analysed (numerically and/or analytically), and compared to the experiments. If the model does not fit the experimental results well, the mechanism is changed and the process is repeated. (What the criterion is for the model to fit well, is often weakly defined, if defined at all.) The iterative process is illustrated in figure 2.1. This way of doing chemical kinetics can be seen in [6].

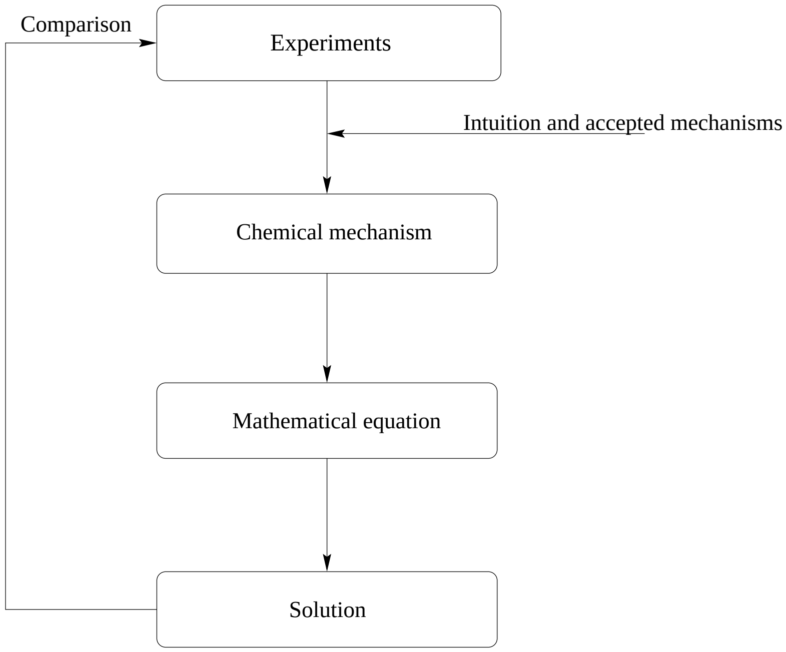

Figure 2.1: An illustration of the iterative process when doing chemical kinetics

2.1.1 Experiments

Closed reaction tanks and equilibrium. When doing the experiments, the physical settings are of extreme importance. If the experiments are done in a closed vessel the system will eventually settle and reach chemical equilibrium [2]. When chemical equilibrium is reached the principle of detailed balance is obtained. To explain this principle consider the following equilib-

[2]In a closed vessel only energy (often as heat) is exchanged with surroundings.

rium:

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{C} + \mathrm{D}$$

Assume that the concentrations of each chemical species are close to zero. Then the reaction rate for the forward reaction can be well approximated by the law of mass action: $v_+ = k_+[\mathrm{A}][\mathrm{B}]$, where k_+ is the reaction constant for the forward reaction, and is not a function of the concentrations. Also, the backward reaction rate can be written in terms of the law of mass action: $v_- = k_-[\mathrm{C}][\mathrm{D}]$. Since the chemical equilibrium is a dynamical state, in which the forward reaction rate is equal to the backward reaction rate, the following is true at equilibrium:

$$k_+[\mathrm{A}][\mathrm{B}] = k_-[\mathrm{C}][\mathrm{D}] \tag{2.1}$$

(Note: No concentration is zero.) This constrain is called the principle of detailed balance. Also, when a chemical system has reached chemical equilibrium, the concentration of each species is constant in time. These two restrictions leads to the fact that the equilibrium state is an unique state for the system, and all other states are transient. A very illustrative example is given in [12, p. 33]. This does not mean that no interesting behavior can be observed in closed systems. If initial conditions are far from equilibrium, complex transients can be observed, such as oscillations and chaos [13]. Actually these transients can last for several hours depending on the initial concentrations.

The law of mass action states that the probability for two species (A and B) to collide is proportional to the product of the two, that is, A and B are randomly distributed in the mixture. When A and B have reacted the local concentration of the two is locally altered, and A and B from the surrounding areas will migrate to this area due to the concentration gradient. This means that the position of the chemical species are no longer random. At large concentrations this is more pronounced, so when applying the law of mass action, the concentrations should be kept low. Also, the mixture can be stirred in order to approximate homogeneity.

The rate constant is temperature dependent. This temperature dependence is expressed in the Arrhenius equation as:

$$k_n = Ae^{-E/RT} \tag{2.2}$$

A is named the pre-exponential factor, E is the activations energy, and R the is the gas constant. If the initial reaction is exothermic, the reaction rate increases according to 2.2. This increases the reaction rate, and thereby increases the temperature, and so on. This means that the equilibrium will be reached more rapidly. This type of feedback is called thermal feedback, and is of great interest when operating in isolated vessels, i.e. vessels which do not exchange heat or matter with surroundings.

Let's return to the experimental settings. A closed tank reactor can be stirred or it can be unstirred. In the case where it is stirred the reaction mixture is homogeneous, and the concentrations only varies in time. However, if the tank is unstirred the concentration may also vary with respect to space. The following reaction can show this behavior. If a drop of iodide is added to a solution off iodate ions and a suitable reductant a travelling wave can be observed. [3] This is due to the positive feedback in the reaction mechanism, in which iodide enhances its one production. This means that iodide is produced in the area where the drop is added, and then diffuses to areas with no iodide (because of the concentration gradient). Here it will react with the iodate, and so forth. Thus, the reaction mixture is behind the wavefront and unreacted iodate solution is ahead of the front. The front is moving with a constant velocity through the mixture, which is characteristic for such reaction–diffusion systems.

Open reaction tanks. The steady state is a state where the concentrations does not change in time – but is not to be confused with chemical equilibrium: Even though the concentration of each chemical species is constant, the principle of detailed balance does not exist. The steady state is often studied in open vessels, or more precisely in Continuous–flow well–Stirred Tank Reactors, CSTRs. An open vessel is a reactor where matter and energy are exchanged with the surroundings. The inflow of reactants and outflow of reactions mixture (or products) keeps the system from reaching chemical equilibrium. In such tank reactors different types of exotic phenomena can be observed. This includes sustained oscillations, period doubling, hysteresis and chaos. Also, qualitative changes (bifurcations) of systems can be observed. For example, the steady state suddenly "disappears" and oscillations emerge, when varying an inflow of one of the reactants [4].

In CSTRs the reactions mixture is homogeneous (since it is stirred), and there exists no variants in the concentrations with respect to space. Open tank reactors can also be unstirred. In these systems even more complicated phenomena such as Turing structures can be observed: Here an initially

[3]This also known as the Landolt clock reaction, see also page 13.

[4]The term "bifucation" is somewhat ambiguous, but will become more clear in chapter 3

well–mixed solution, can, after some time, show an ordered structure.

When doing the experiments it may not be the actual concentration that is being measured, but, for example, the electromotive force as a function of time. This naturally makes the interpretation a bit more troublesome, and some effort to interpret the data is needed.

2.1.2 Mechanisms

The mechanism consists of a series of reaction steps, that is believed to actually happen in the reaction mixture. An ideal way of thinking is simply that two species collides, and with some probability they make a product. The probability that three molecules collides are normally considered to be infinite small. These types of steps, are called elementary steps, and can be described by the law of mass action. (An elementary step can also involve the spontaneous decomposition of a molecule). In real situations this idealistic way of interpreting the reaction mechanism is often not possible, and experimental overall steps are used. For example, one mechanism proposed for the Landolt clock reaction consists of two non-elementary steps:

$$\begin{array}{lllllllllllll} \mathrm{IO_3^-} & + & \mathrm{5I^-} & + & \mathrm{6H^+} & \rightarrow & \mathrm{3I_2} & + & \mathrm{3H_2O} & & & & \\ \mathrm{H_3As0_3} & + & \mathrm{I_2} & + & \mathrm{H_20} & \rightarrow & \mathrm{H_3As0_4} & + & \mathrm{2I^-} & + & \mathrm{2H^+} \end{array}$$

However, sometimes it is possible to propose a mechanism of elementary steps. The reaction between hydrogen and oxygen producing water is an example. (For a limited range of pressure and temperature.)

Another very important mechanism is the Michaelis–Menten mechanism. This mechanism is often used when simplifying enzyme–kinetics, and is used extensively in the model of glycolysis. An enzyme, E, binds a substrate, S, and a complex, ES, is formed. The interaction between the enzyme and the substrate favours the formation of product, P. The enzyme can then once again can react with a substrate:

$$E + S \rightleftharpoons ES \rightarrow E + P$$

(Please see [12] for further discussion.) The real fun starts when more complicated enzyme–mechanisms are considered. For example, the enzyme may form a complex with more than one substrate, there may be a competitive inhibition between two substrates, etc. Allosteric inhibition, where the enzyme structure and function is effected, is also of great importance in biochemistry, for example, many proteins in the cell membrane are allosterically controlled by ions and hormones. Here a series of Michaelis–Menten like steps are often used to describe the mechanism. This is also used extensively in the model of glycolysis.

Whether a reaction step is considered to be reversible or irreversible depends on the Gibbs free energy of the reaction. If ΔG is large and negative the reactants are thought to be fully converted to product, and if ΔG is close to zero a reversible step is assumed. The line between reversibility and irreversibility is normally not strictly defined.

2.1.3 Mathematical equations

The chemical mechanism results in a differential equation system, that describes the concentration of each species with respect to time and space. If the reaction is carried out in a well stirred reaction tank no spatial effect is present, and the differential equations are therefore ordinary:

$$\dot{\mathbf{c}} = f(\mathbf{c}) \tag{2.3}$$

where $\mathbf{c} \in \mathbf{R}_+^n$ and the components of this vector are the concentrations of the chemical species, $\dot{\mathbf{c}}$ denotes the derivative with respect to time and f is a vector function. If each step in the mechanism is an elementary step and is believed to follow the law of mass action, f is simply quadratic or linearly dependent of the concentrations. (This was illustrated in equation 2.1). In many applications f is determined by experiments, or a series of already known rate equations are lumped together, creating a set of very complex equations. Such equations will be shown later when the rate expressions for glycolysis are presented. Also, at the end of this section, it will be illustrated how a reaction mechanism can be put on the form of 2.3.

The number of elements in $\mathbf{c}$ need not to be the same as the number of species involved. There might be some conservation constrains in the system. For example, if a species A is either on the form $\overline{\mathrm{A}}$ or A, then the analytical concentration of A is: $c_{\mathrm{A}} = [\mathrm{A}] + [\overline{\mathrm{A}}]$. This means that if c_{A} is constant (typically in closed vessels), $\overline{\mathrm{A}}$ is determined if A is determined. The minimum number of species that is needed to describe the whole system is called the degrees of freedom.

If the tank is not stirred, the equations describing the system are far more complicated, because this involves a diffusion term as well as the reaction term described by equation 2.3. This means that the differential equations are no longer ordinary but partial. The normal way to treat this is to add a diffusion term to 2.3, and in the case where the spatial motion is one dimensional:

$$\dot{\mathbf{c}} = f(\mathbf{c}) + D\nabla^2\mathbf{c}$$

D is the diffusion matrix, and $\nabla^2 \mathbf{c} = (\partial^2[\mathrm{X}_1]/\partial x^2, \ldots, \partial^2[\mathrm{X}_n]/\partial x^2)^T$, where X_i represent the chemical species and x represent the spatial dimension.

If the system is open, terms describing the inflow and outflow must be included. The inflow term must describe how much of each reactant is added to the reaction tank per time unit. This inflow/outflow may be varied in the experiment, which can be written as

$$\dot{\mathbf{c}} = f(\mathbf{c}; \mathbf{p})$$

$\mathbf{p} \in \mathbf{R}^p$ where $\mathbf{p}$ represents the variable parameter.

Depending on the number of reactions steps, the equations describing the mechanism have a number of constants. It is possible to determine some of these by experiments where each reaction step is isolated. But in most cases some constants are not experimentally determinable. These constants are then determined by fitting them to the experimental data. In general, the more constants that have to be fitted, the less trustworthy is the mechanism.

2.1.4 Solutions

Once the differential equations are written down, there exist many different ways to solve them. The approach is of course dependent on what the main objective is. In many cases, the differential equations are integrated numerically, and compared with the experimental results. However, the numerical solutions are not well suited to obtain an exact qualitative analysis of the system – such as the nature of a steady state. If one wants to describe the model qualitative, many ways of simplifying the dynamical system are at hand. These are of both mathematical and chemical nature. Let me give an example of the later: If the concentration of one chemical species is relatively much larger than the others, it is often assumed that the concentration of this chemical species does not change significantly in time compared to the others. (For example, the concentration of the solvent is almost constant, even though it may react with the solutes.) Also, in a buffered mixture, the proton concentration is often thought of as constant.

Such simplifications often lead to a system of differential equations, with low dimension (one, two or three) and with a minimum number of coefficients. This allows a traditional mathematical analysis, where nullclines, phase space, Routh–Hurwitz criterion etc. can be applied in order to determine the nature of the system. Most textbooks treating chemical kinetics also focus on low dimensional cases. However, the mechanism of glycolysis consists of 24 almost all non-elementary steps and involves 18 different species. A low dimensional description of such systems is only obtainable in very special cases, and will be treated in the following chapter.

I will finish this section by giving an example on how a chemical mechanism can result in a differential equation system on the form 2.3. This mechanism is proposed by Wilhelm and Hänggi [15], and is not related to any experiments, but is of purely theoretical interest.

The WH model

The mechanism consists of the following elementary steps:

$$\mathrm{A} \rightarrow \mathrm{X} \tag{2.4}$$
$$2\,\mathrm{Y} \rightleftharpoons \mathrm{Z} \tag{2.5}$$
$$\mathrm{X}+\mathrm{Z} \rightarrow \mathrm{Y}+\mathrm{Z} \tag{2.6}$$
$$\mathrm{Y} \rightarrow \mathrm{B} \tag{2.7}$$

To simplify the problem, let [A] be very large compared to the concentration of all the other species. That is, assume that [A] is constant with respect to time [5]. B can be thought of as an inert product that does not influence any earlier steps, and is thus of no interest. Also, assume that the reaction mixture is homogeneous, which can be obtained if the tank reactor is well stirred. Since each reaction step is thought to be an elementary step, the reaction rate for 2.4 can be written as:

$$v^1 = k_1[\mathrm{A}]$$

where superscripts indicate that it is the reaction rate for the first reaction. The reaction rates for reactions 2.5–2.7 follows:

$$v_+^2 = k_2[\mathrm{Y}]^2 \quad , \quad v_-^2 = k_{-2}[\mathrm{Z}] \quad , \quad v^3 = k_3[\mathrm{X}][\mathrm{Z}] \quad , \quad v^4 = k_4[\mathrm{Y}]$$

Subscripts $+/-$ indicate forward and backward reaction, respectively. The unit for k_1, k_{-2} and k_4 is t^{-1}, and for k_2 and k_3 it is $M^{-1}t^{-1}$, M being mol per volume and t the time unit.

The dynamics of each chemical species can be expressed in the following way: Reaction 2.4 can be written as:

$$0 = \nu_{\mathrm{A}}\mathrm{A} + \nu_{\mathrm{X}}\mathrm{X}$$

[5] Another way to simplify the problem is to let A being pumped into vessel at the same rate that it is consumed.

where ν_A and ν_X are the stoichiometric coefficients for A and X. The coefficients are, by definition, negative for reactants and positive for products. For reaction 2.4 the rate of *formation* of X can be written as:

$$\frac{1}{\nu_X}\frac{d[X]}{dt} = v^1 \quad \Rightarrow \quad \frac{d[X]}{dt} = k_1[A]$$

because ν_X =1. In reaction 2.6 $\nu_X = -1$, so the rate of *consumption* of X in this reaction step is:

$$\frac{d[X]}{dt} = -k_3[X][Z]$$

The overall rate is then simply the sum of the formation and the consumption:

$$\frac{d[X]}{dt} = k_1[A] - k_3[X][Z]$$

In the same way the overall rates for Y and Z can be written down:

$$\begin{aligned}
\frac{d[Y]}{dt} &= -2k_2[Y]^2 + 2k_{-2}[Z] + k_3[X][Z] - k_4[Y] \\
\frac{d[Z]}{dt} &= k_2[Y]^2 - k_{-2}[Z]
\end{aligned}$$

This is the desired form. However, the differential system can be put into a dimensionless form. To do this set:

$$x = \frac{k_4}{k_1[A]}[X] \quad , \quad y = \frac{k_4}{k_1[A]}[Y] \quad , \quad z = \frac{k_4}{k_1[A]}[Z] \quad , \quad \tau = k_4 t \tag{2.8}$$

This means that:

$$\frac{d[X]}{dt} = k_1[A]\frac{dx}{d\tau} \quad , \quad \frac{d[Y]}{dt} = k_1[A]\frac{dy}{d\tau} \quad , \quad \frac{d[Z]}{dt} = k_1[A]\frac{dz}{d\tau} \tag{2.9}$$

(Recall [A] is constant.) Substituting [X], [Y] and [Z] (given indirectly by equation 2.8) and $d[X]/dt, d[Y]/dt$ and $d[Z]/dt$ (given by 2.9) in the rate expressions for each the chemical specie, one obtains:

$$\begin{aligned}
\frac{dx}{d\tau} &= 1 - \mu xz \\
\frac{dy}{d\tau} &= -2\beta y^2 + 2\gamma z + \mu xz - y \\
\frac{dz}{d\tau} &= \beta y^2 - \gamma z
\end{aligned} \tag{2.10}$$

where:

$$\mu = \frac{k_3 k_1 [\mathrm{A}]}{k_4^2} \quad , \quad \beta = \frac{k_2 k_1 [\mathrm{A}]}{k_4^2} \quad , \quad \gamma = \frac{k_2}{k_3}$$

I will return to this model in the next chapter, when discussing the Stuart–Landau equation. •

After this (of course, far from complete) review on chemical kinetics, the glycolysis model proposed by Danø and Hynne can be discussed.

2.2 The glycolysis mechanism

The experiments, primarily done by Danø, were carried out in a CSTR, with inflow of glucose and cyanide solutions, and a third inflow of starved yeast cells (*Saccharomyces cerevisiae*). The excess reaction mixture was simply the outflow. The bulk intra cellular NADH fluorescence was measured. Depending on the inflow of glucose, they observed either a steady state or sustained oscillations. The amplitude of these oscillations where growing as the square root of the deviation form the bifurcation point [6] as the rate of glucose inflow was increased. In the same experiment they also showed that if a small amount of a metabolite (for example acetaldehyde), is added to the oscillatory system, the system will return to the same oscillatory state after a transient. In figure 2.2 the squared amplitude of the fluorescence measurements is plotted as a function of inflow of glucose.

These experiments reflect the decomposition of glucose in the glycolysis [3], and if they are to be explained, a mechanism for glycolysis must be proposed. This is what Danø together with Hynne did. Their mechanism is very detailed and therefore very complicated, involving a substantial amount of biochemical consideration. I will not go through their mechanism in details (simply because I have another agenda), but only present the big picture in this model.

All the general theory of glycolysis is based on [18]. Glycolysis converts a six–carbon sugar into two molecules of pyruvate, thereby producing ATP from ADP. This decomposition takes place in the cytoplasm of the cell and is anaerobic. The fact that the process is not dependent on a specific organel, makes glycolysis rather easy to study, compared to other biochemical pathways. In both anaerobic and aerobic organisms, the product of glycolysis is 2 ATP molecules and two pyruvate molecule per glucose. The fate of the pyruvate is dependent on the oxygen available: If conditions are aerobic the

[6] The term bifurcation point will be discussed later

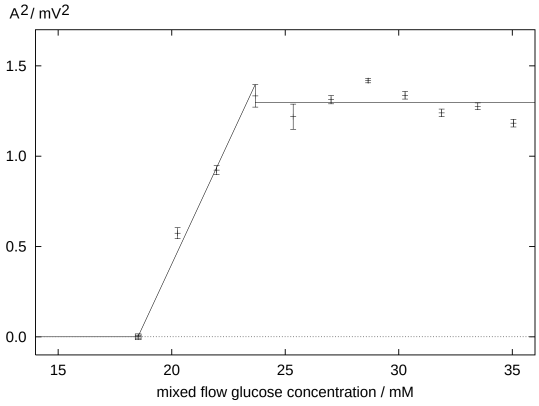

Figure 2.2: A plot of the square of the amplitude in the fluorescence measurements, as a function of the glucose inflow. By courtesy of Sune Danø.

pyruvate is channeled in to the aerobic part of the metabolism, which results in a complete oxidation of pyruvate to CO_2. In the absence of oxygen, a mechanism for anaerobic oxidation[7] of NADH to NAD^+ at the expense of pyruvate takes place. This contributes to maintain a constant concentration of NAD^+ inside the cell.(NAD^+ is used in an earlier step in glycolysis.) The products of this oxidation is ethanol and CO_2 in *Saccharomyces cerevisiae* (this is called alcoholic fermentation). The overall reaction mechanism for glycolysis and the following alcoholic fermentation is:

$$C_6H_{12}O_6 \ + \ 2ADP \ + \ 2P_i \rightarrow 2C_2H_5OH \ + \ 2CO_2 \ + \ 2ATP \ + \ 2H_2O$$

Many of the intermediates in glycolysis are used in the anabolism (the biosynthetic pathways). In the experiments the starved yeast cells where suspended in a phosphate buffer, with no nitrogen source available. This should halt the protein synthesis, and minimize the use of any intermediates of glycolysis. However, glycerol is still synthesized. The starved cells also have the ability to store glucose as glycogen. This is for future catabolic use. (The mechanisms providing the cell with energy.) This, of course, also influences the dynamics of glycolysis.

glycolysis itself consists of around 10 reaction steps. These steps have one thing in common – they are all controlled by enzymes. To make things even worse, some of the enzyme reactions are allosterically regulated. For example, phosphofructokinase (PFK) is inhibited by ATP, but allosterically

[7]This can be achieved when adding cyanide

activated by ADP and AMP. This means that the enzyme activity is dependent on the ATP–ADP status in the cell. In most simple glycolysis models (such as the Sel'kov model), this reaction step is thought to be the step responsible for the oscillations.

Figure 2.3 on page 24 illustrates the mechanism proposed by Danø and Hynne. The mechanism uses earlier work, primarily the work of Nielsen [8], as a skeleton. The experiments were done on living cells, which means that the transport of glucose from the extracellular environment to the cytoplasm must be considered in the mechanism. Also, ethanol, acetaldehyd (ACA) and glycerol are believed to flow out of the cell. The cytoplasm is assumed to be homogeneous, thus the cell itself is also assumed to be a CSTR (with rather complicated flows).

Some reactions steps are thought to be reversible and others to be irreversible. The only true irreversible step is the production of acetaldehyde from pyruvate [2]. As mentioned in the last section, the choice of reversibility is based on Gibbs free energy. ΔG for the reaction steps in the cytoplasm are estimated by considering the concentrations in the cell. However, not every concentration of each metabolite are determined, so whether the reactions steps in which these metabolites are reactants or products are assumed to be reversible or not, depends on intuition alone. To give an impression of the magnitude of ΔG, (at pH=7 and T=25$°C$) consider the PFK. The Gibbs free energy in this reaction step is about -9.3 kJ/mol [2], and is approximated to be irreversible. The reaction between dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate is on the other hand estimated to be reversible because $\Delta G \approx 0 kJ/mol$.

As mentioned above, some of the enzyme reaction steps are effected allosterically. Exactly how, and which ones, is not yet fully discovered. The active transport of glucose into the cell is known to be inhibited by glucose-6-phosphate (G6P); also hexokinase (HK) is inhibited by G6P. As mentioned earlier the PFK is thought to be inhibited by ATP, but activated by fructose-1,6-biphosphat (FBP), ADP and AMP. Pyruvatekinase (PK) is also allosteric affected, in that it is activated by FBP, and inhibited by ATP. Not all these allosteric effects are of equal importance, in the description of glycolysis. In the mechanism the inhibition of the active transport by G6P is included, as is the allosteric effect of ATP and AMP on PFK. Also, the production of glycogen is not explicitly included in the mechanism.

Finally, it should be mentioned that some known reaction steps are lumped together into one single step. For example the reaction step 7 actually consists of 3 reaction steps. (This is also why no name of the enzyme is given.)

Following the method discussed in the last section, a differential system can be made, describing the mechanism given in figure 2.3. The rate of each reaction step is given in appendix A. The rates 6, 10, 12, 13, 16, and 17 are reaction rates implemented by Danø and Hynne. The others are taken from the literature. It is worth noting that none of the concentrations and constants are zero or negative. This means that none of the denominators are zero at any time.

ATP, ADP, and AMP, NADH and NAD^+ cannot leave the cell, and neither are they pumped into the cell. The analytical concentrations of ATP and NADH is therefore:

$$
\begin{aligned}
c_{\mathrm{ATP}} &= [\mathrm{ATP}] + [\mathrm{ADP}] + [\mathrm{AMP}] \\
c_{\mathrm{NADH}} &= [\mathrm{NADH}] + [\mathrm{NAD}^+]
\end{aligned}
$$

So, if the concentrations of ATP and ADP is known, the concentration of AMP follows immediately . Also, if [NADH] is known $[\mathrm{NAD}^+]$ is simply given by $c_{\mathrm{NADH}} - [\mathrm{NADH}]$. The extracellular glucose concentration is held constant (by the inflow). This means that the mechanism has 15 degrees of freedom, hence there must be 15 coupled differential equations to describe the dynamics:

$$
\begin{aligned}
\frac{d[\mathrm{Glc}]}{dt} &= v_+^1 - v_-^1 - v_+^2 \\
\frac{d[\mathrm{G6P}]}{dt} &= v_+^2 - v_+^3 + v_-^3 \\
\frac{d[\mathrm{ATP}]}{dt} &= -v_+^2 - v_+^4 + v_+^7 - v_-^7 + v_-^8 - v_+^{11} + v_-^{11} - v_+^{17} \\
\frac{d[\mathrm{ADP}]}{dt} &= v_+^2 + v_+^4 - v_+^7 + v_-^7 - v_+^8 - 2v_+^{11} + 2v_-^{11} + v_+^{17} \\
\frac{d[\mathrm{F6P}]}{dt} &= v_+^3 - v_-^3 - v_+^4 \\
\frac{d[\mathrm{FBP}]}{dt} &= v_+^4 - v_+^5 + v_-^5 \\
\frac{d[\mathrm{GAP}]}{dt} &= v_+^5 - v_-^5 - v_+^6 + v_-^6 + v_+^{14} - v_-^{14} \\
\frac{d[\mathrm{DHAP}]}{dt} &= v_+^5 - v_-^5 - v_+^{14} + v_-^{14} - v_+^{15} \\
\frac{d[\mathrm{DPG}]}{dt} &= v_+^6 - v_-^6 - v_+^7 + v_-^7 \\
\frac{d[\mathrm{NADH}]}{dt} &= v_+^6 - v_-^6 - v_+^{10} - v_+^{15}
\end{aligned}
$$

$$
\begin{aligned}
\frac{d[\mathrm{PEP}]}{dt} &= v_+^7 - v_-^7 - v_+^8 \\
\frac{d[\mathrm{Pyr}]}{dt} &= v_+^8 - v_+^9 \\
\frac{d[\mathrm{ACA}]}{dt} &= v_+^9 - v_+^{10} - v_+^{12} \\
\frac{d[\mathrm{EtOH}]}{dt} &= v_+^{10} - v_+^{13} \\
\frac{d[\mathrm{Glyc}]}{dt} &= v_+^{15} - v_+^{16}
\end{aligned}
$$

v_+^1, for example, is the reaction rate of the forward reaction in step 1, which is the step that transport the extracellular glucose into the cell. Recall, that each reaction rate is listed in appendix A.

The worst is still to come. The number of constants in the differential equation system is no the less 56. Since glycolysis has been investigated intensively for many years, a lot of data are accessible. Still, around half of the parameters are undetermined. When scanning the parameter space (at the bifurcation point, that is, where the stable steady state becomes unstable), they discarded all parameter set that did not show a pair off eigenvalues with zero real part. They also fitted their parameters such that before the bifurcation point all eigenvalues of Jacobian had negative real part (the stable steady state), and after the bifurcation point a pair of complex conjugated eigenvalues with positive real part emerged (the unstable steady state). Finally, the parameters should reproduce the frequency of 9.12 rad/min that earlier experiments had showed. In this way they tested millions of parameter sets. According to [10] this makes the model somewhat instable with respect to the parameters.

The analysis is actually already done, since the parameters are fitted to show the qualitative behavior seen in the experiments. So what is left to do? Following the method described in the last section, a comparison should be made. This is of course not sensible, because (again) with these parameters the model fits well. This surfaces the real problem.

In the experiments, with a large number of cells it has been shown that the oscillations of intracellular NADH is due to synchronisation of the cells. This can be shown by mixing two cell suspensions oscillating 180° out of phase. Just after mixing, the bulk NADH oscillations disappear, but reappear after some time. This coupling has been theoretically investigated, however, only with a limit number of cells, and the cell models have been very simple (see [17] and [16]).

The group around Sørensen is interested in coupling a large number of cells. Also, they want to have a cell model that describes glycolysis well; like the one just described. These two demands may seem contradictory, but actually it need not to be so.

In the paper "Systematic derivation of amplitude equations and normal forms for dynamical systems" [5] Ipsen and Hynne presents a way to derive normal forms. Their approach is somewhat different from the standard approach, in that an algebraic equation transforming the normal form coordinate back to the physical space is given explicitly. One objective of this report is to describe each cell via its normal form, and then couple the normal forms together. Since the dynamics of a normal form typically is described by one or two dynamical variables, the numerical computations can be reduced significantly, when a large amount of cells are coupled.

However, since the normal form describes the dynamics in a neighborhood of the bifurcation point, a comparison of the normal form approximation and the original differential system is in place. This approach is possible since the transformation back to the physical space is at hand, and is the main objective of this report. In the next chapter I describe the derivation of the normal forms, taking the same approach as Ipsen and Hynne.

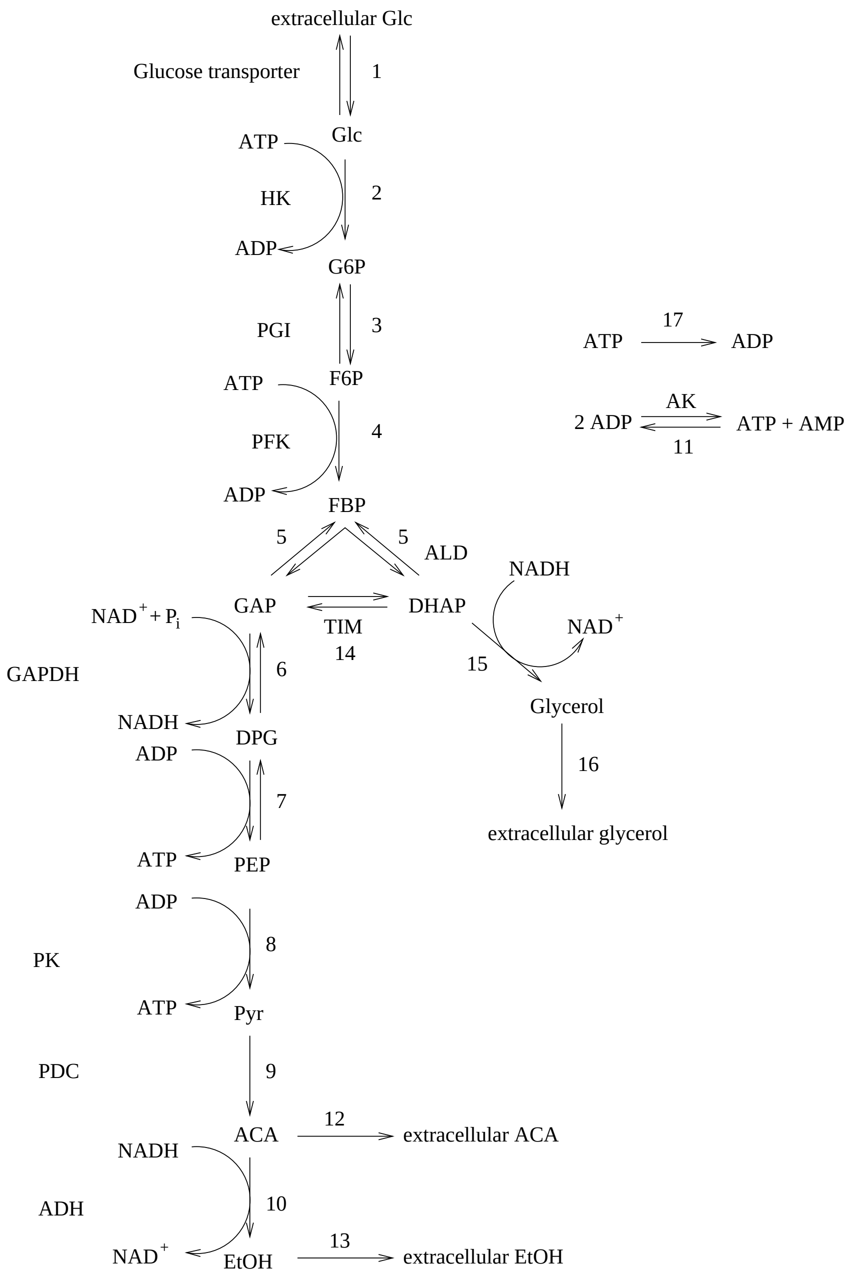

Figure 2.3: The mechanism proposed by Danø and Hynne.

Chapter 3

The Stuart–Landau equation

When working with dynamical systems one is often interested in evaluating the stability of steady states (the fixed points), since this provides much information about the limit behavior. The usual way to determine the stability of the fixed point is to evaluate the linear systems, i.e. evaluating the eigenvalues of the Jacobian at each single fixed point. If a fixed point is hyperbolic [1] the linear analysis is sufficient to determine the stability (the Hartman–Grobman theorem). However, if a fixed point is nonhyperbolic the linear analysis is inconclusive, and the nonlinear terms must be considered.

As mentioned in the previous chapter, a parameter p can be varied, and if at some point, p_0, the stability of the fixed point changes, heuristically, one can say that the system undergoes a bifurcation at p_0. At the point where the stability changes the fixed point is nonhyperbolic, and thus in order to describe the dynamics around the bifurcation point one needs to consider the nonlinear terms[2].

One way to approach the nonlinear analysis is: 1) reducing the dimensions, and 2) removing as many nonlinear terms as possible. Two mathematical tools deals with these problems: The theory of center manifolds and normal forms. Text books treating nonlinear dynamics consider these tools, for example [14] and [9]. Articles have also been published, and in [1] Crawford suggest how to approach a nonlinear problem, when applying the center manifold theory and normal forms:

- Reduction: Restrict the dynamical system to the appropriate center

[1] A hyperbolic fixed point is a fixed point for which the Jacobian has no eigenvalues with zero real part.

[2] The condition that the fixed point is nonhyperbolic, when the system to undergoes a bifurcation is not sufficient but a necessary condition.

manifold.

- Normalization: If possible put the reduced system into a simpler form.
- Describe the effects of varying a parameter, i.e. introduce small linear (and if possible nonlinear) terms into the normal form (unfolding)
- Study the dynamical system described by the unfolded normal form.

The standard literature deals primarily with the qualitative dynamics. However, if one wishes to describe the system quantitatively as well, the approach introduced by Ipsen, Hynne and Sørensen in [5] can be used. I will combine the approach given by Crawford and by Ipsen *et al.* However, to ease the discussion a bit, some modifications are done. Also, I hope to be more explicit when discussing the theory of manifolds, than Ipsen *et al* were allowed to be.

3.1 Linear settings

In order to discuss the nonlinear theory, the linear settings must be in place. To obtain this, consider the following autonomous differential equation system:

$$\dot{\mathbf{x}} = f(\mathbf{x})$$

where $\mathbf{x} \in \mathbf{R}^n$ and f has continuous partial derivatives to any desired degree. Let $\mathbf{x}_s$ be the fixed point of interest. Taylor expanding f about $\mathbf{x}_s$ yields:

$$\begin{aligned} \dot{\mathbf{x}} &= f(\mathbf{x}_s) + Df(\mathbf{x}_s)(\mathbf{x} - \mathbf{x}_s) + N(\mathbf{x}) \\ &= Df(\mathbf{x}_s)(\mathbf{x} - \mathbf{x}_s) + N(\mathbf{x}) \end{aligned} \tag{3.1}$$

Note by definition $f(\mathbf{x}_s) = \mathbf{0}$. $Df(\mathbf{x}_s)$ is the Jacobian evaluated at the fixed point, and N denotes the nonlinear part of f. To simplify the problem we can translate the fixed point to the origin via: $\mathbf{y} = \mathbf{x} - \mathbf{x}_s$. Since $\dot{\mathbf{y}} = \dot{\mathbf{x}}$, equation 3.1 becomes:

$$\dot{\mathbf{y}} = Df(\mathbf{x}_s)(\mathbf{y}) + \tilde{N}(\mathbf{y}) = J\mathbf{y} + \tilde{N}(\mathbf{y}) \tag{3.2}$$

The vector field can be represented in the eigenspace of J. Using the fact that every point $\mathbf{y}$ can be written as $U\mathbf{z}$, where U changes the coordinates from the eigenbasis to the original basis, the above equation can be written as:

$$U\dot{\mathbf{z}} = JU\mathbf{z} + \tilde{N}(U\mathbf{z})$$

which can be rewritten as:

$$\dot{\mathbf{z}} = \Lambda \mathbf{z} + \hat{N}(\mathbf{z}) \tag{3.3}$$

where $\Lambda = U^{-1}JU$ and $\hat{N}(\mathbf{z}) = U^{-1}(\tilde{N} \circ U)(\mathbf{z})$. Also, the columns in U span the basis of the eigenspace.

If some of the eigenvalues are complex, the corresponding complex eigenvectors will span a subspace in the eigenspace. However, it is possible to choose another basis spanned by the real and imaginary part of the eigenvectors because we to begin with wish to work in real vector spaces. Let, for example, J have 2 complex conjugated eigenvalues, $\lambda_{1,2} = a \pm ib$, with the corresponding eigenvectors $\mathbf{u}_1 = \overline{\mathbf{u}}_2 = \mathrm{Re}(\mathbf{u}_1) + i\mathrm{Im}(\mathbf{u}_1)$, and let J have a single real valued eigenvalue, λ_3, with the corresponding eigenvector $\mathbf{u}_3$. Then the matrix, P, can be defined as:

$$P = (\mathrm{Re}(\mathbf{u}_1)\ \mathrm{Im}(\mathbf{u}_1)\ \mathbf{u}_3)$$

where the columns in P span $\mathbf{R}^3$. If $\mathbf{z}$ represents the coordinates of $\mathbf{y}$ in this basis, that is $\mathbf{y} = P\mathbf{z}$, and since P is invertible, the vector field can be written as:

$$\dot{\mathbf{z}} = \Lambda \mathbf{z} + \hat{N}(\mathbf{z}) \tag{3.4}$$

In this case $\Lambda = P^{-1}JP$ and $\hat{N}(\mathbf{z}) = P^{-1}(\tilde{N} \circ P)(\mathbf{z})$. Choosing this basis Λ is a block diagonal matrix, where the two blocks are:

$$\begin{pmatrix} a & b \\ -b & a \end{pmatrix} \quad , \quad \lambda_3 \tag{3.5}$$

Of course, all this can be extended to any case where there exist k distinct complex conjugated eigenvalues (i.e. k is even), and l distinct real valued eigenvalues. [3]

This will be used to describe the features of the linearized system. However, we first need to organize the eigenspace. The eigenvectors corresponding to eigenvalues with zero real part span a subspace in $\mathbf{R}^n$. If there are c such distinct eigenvalues, E^c is defined as the subspace:

$$E^c = \mathrm{span}\{\mathbf{u}_1, \ldots, \mathbf{u}_c\}$$

If, for example, $\mathbf{u}_1 = \overline{\mathbf{u}}_2$ are complex then $\mathbf{u}_1$ and $\mathbf{u}_2$ may be substituted by $\mathrm{Re}(\mathbf{u}_1)$ and $\mathrm{Im}(\mathbf{u}_1)$, respectively, such that a real valued vector subpace is

[3] I will not discuss the case where the eigenvalues have algebraic multiplicity greater than one, but simply refer to [9].

obtained. (This follows the above). E^c is denoted the center subspace. In the same manner E^s and E^u are spanned by the eigenvectors corresponding to eigenvalues having negative and positive real part, respectively.

$$\begin{aligned} E^s &= \operatorname{span}\{\mathbf{u}_{c+1}, \ldots, \mathbf{u}_{c+s}\} \\ E^u &= \operatorname{span}\{\mathbf{u}_{c+s+1}, \ldots, \mathbf{u}_{c+s+u}\} \end{aligned}$$

These subspaces are denoted as the stable subspace and the unstable subspace. $\mathbf{R}^n$ can then be thought of as the direct sum:

$$\mathbf{R}^n = E^c \oplus E^s \oplus E^u$$

Now, E^c, E^s and E^u are invariant under the vector field $\dot{\mathbf{z}} = \Lambda \mathbf{z}$ in the sense that, if for example $\mathbf{z}(0) = \mathbf{z}_0 \in E^s$ but $\mathbf{z} \notin E^c \oplus E^u$ then $\mathbf{z}(t, \mathbf{z}_0) \in E^s$ for all t. Thus, the solution will decay exponentially towards the fixed point as $t \to \infty$ (even though the unstable subspace exists).

If the fixed point under consideration is hyperbolic the flow generated by 3.4, and the linearized system have the same qualitative features. More precisely: The two flows are conjugated in a neighborhood of the hyperbolic fixed point (the Hartman–Grobman theorem). Two flows are said to be conjugated if they are homeomorphic. That is, if there exists a map, h, that maps the flow generated by 3.4 onto the flow generated by the linear part, such that h and h^{-1} are continuous.

In this way the Hartman–Grobman theorem states that if the fixed point is hyperbolic, we only need to consider the linear part of the vector field, i.e. the eigenvalues given by Λ, in order to determine the nature of the fixed point. In this way the linear analysis describes the qualitative behavior well. However, in the case where the fixed point is nonhyperbolic, the linear analysis is inconclusive, and the nonlinear terms must be considered. Before doing this let's first apply this linear description to the WH model:

The WH model

In chapter 2 the model was presented, and transformed into a dimensionless form. In a more compact form it may be written as:

$$\dot{\mathbf{y}} = f(\mathbf{y})$$

where $\mathbf{y} = (x, y, z)^T$ and $\dot{\mathbf{y}}$ denotes the derivative of $\mathbf{y}$ with respect to τ. Since f simply consists of polynomials we need not to be concerned about the differentiability. The model has only one fixed point which is:

$$\mathbf{y}_s = \left(\frac{\gamma}{\mu\beta}, 1, \frac{\beta}{\gamma}\right)$$

Following the method described above, the linear part is being "split off", that is:

$$f(\mathbf{y}) = Df(\mathbf{y}_s)(\mathbf{y} - \mathbf{y}_s) + N(\mathbf{y}) \tag{3.6}$$

where:

$$Df(\mathbf{y}_s) = \begin{pmatrix} -\mu\beta/\gamma & 0 & \gamma/\beta \\ \mu\beta/\gamma & -4\beta - 1 & 2\gamma + \gamma/\beta \\ 0 & 2\beta & -\gamma \end{pmatrix} \tag{3.7}$$

In order to ease the problem, Wilhelm and Hänggi have chosen $\beta = \gamma = 1$. The eigenvalues can now be found as the roots of the characteristic polynomial $p(\lambda) = \det(J - \lambda I) = 0$. If $\mu = \mu_c = (\sqrt{325} - 17)/6$ the eigenvalues are:

$$\lambda_{1,2} = \pm i\omega_0 = \pm i\sqrt{-18 + 5\sqrt{13}} \quad , \quad \lambda_3 = \frac{1}{6}(-18 - 5\sqrt{13})$$

With this choice of μ there exist two eigenvalues with zero real part, that is, $\dim(E^c) = 2$, and one eigenvalue with negative real part, $\dim(E^s) = 1$. The eigenvectors can then be determined by choosing a nullspace to $(J - \lambda_i I)$, $i = 1, 2, 3$, and can be approximated to:

$$\begin{aligned} \mathbf{u}_1 &= \mathrm{Re}(\mathbf{u}_1) + \mathrm{Im}(\mathbf{u}_1) = \begin{pmatrix} -3.00 \\ 0.50 \\ 1.00 \end{pmatrix} - i \begin{pmatrix} 2.91 \\ 0.08 \\ 0 \end{pmatrix} = \overline{\mathbf{u}}_2 \\ \mathbf{u}_3 &= \begin{pmatrix} 0.16 \\ -2.59 \\ 1.00 \end{pmatrix} \end{aligned}$$

Setting $U = (\mathrm{Re}(\mathbf{u}_1)\ \mathrm{Im}(\mathbf{u}_1)\ \mathbf{u}_3)$, and

$$\begin{pmatrix} x \\ y \\ z \end{pmatrix} = U \begin{pmatrix} z_1 \\ z_2 \\ z_3 \end{pmatrix} = U\mathbf{z}$$

the system can be written as:

$$\frac{d}{d\tau} \begin{pmatrix} z_1 \\ z_2 \\ z_3 \end{pmatrix} = \begin{pmatrix} 0 & \omega_0 & 0 \\ -\omega_0 & 0 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} \begin{pmatrix} z_1 \\ z_2 \\ z_3 \end{pmatrix} + \hat{N}(\mathbf{z}) \tag{3.8}$$

where $\hat{N}(\mathbf{z}) = U^{-1}(N \circ U)(\mathbf{z})$. Notice, that $\mathbf{z}$ represent the coordinates of the vector $\mathbf{y}$ in the basis spanned by the columns in U.

The question to be asked, is whether the fixed point is (asymptotically) stable or if it is unstable. Since the fixed point is nonhyperbolic, the Hartman–Grobman theorem does not apply, and we cannot conclude anything about the stability of the fixed point based on the linear analysis alone, hence we need to consider the nonlinear terms.

As mentioned in the beginning of this chapter, a vector field may undergo a bifurcation at a nonhyperbolic fixed point. A sufficient condition for a vector field to undergo a Hopf bifurcation is:

1. The Jacobian has two complex conjugated eigenvalues with zero real part, $\mathrm{Re}(\lambda_{1,2}) = 0$ at $\mu = \mu_c$, but with imaginary part different from zero $\mathrm{Im}(\lambda_{1,2}) \neq 0$. All other eigenvalues have real parts different from zero.

2. $d\mathrm{Re}(\lambda_{1,2})/d\mu \neq 0$ for $\mu = \mu_c$.

The last condition is called the transversality condition and ensures that the real part of the (critical) eigenvalues actually crosses the real axis. As it is seen above, the WH model fulfil the first condition and since $d\mathrm{Re}(\lambda_{1,2})/d\mu = -0.01$ at $\mu = \mu_c$, the WH model undergoes a Hopf bifurcation at μ_c. Actually, this report will evolve around the Hopf bifurcation. •

3.2 Reduction on the center manifold

Manifolds can be thought of as the nonlinear equivalent to subspaces. One can think of an m–dimensional manifold, W, as a surface embedded in $\mathbf{R}^n$, and parametrized by a map $h : \mathbf{R}^m \to \mathbf{R}^n$. W is called a C^r manifold if h is a C^r function. For example, a regular surface in $\mathbf{R}^3$ is a 2–dimensional manifold, because it locally can be represented by a differentiable map h:

$$h : (x, y) \mapsto (h_1(x, y), h_2(x, y), h_3(x, y)) \in V \tag{3.9}$$

where $(x, y) \in U$ and U and V are open subsets in $\mathbf{R}^2$ and $\mathbf{R}^3$, respectively. Also, a regular surface is a surface where the two columns in the matrix representing the differential of h, that is:

$$\begin{pmatrix} \partial h_1/\partial x & \partial h_1/\partial y \\ \partial h_2/\partial x & \partial h_2/\partial y \\ \partial h_3/\partial x & \partial h_3/\partial y \end{pmatrix} \tag{3.10}$$

are linearly independent. If the two columns are not linearly independent at a point (x, y), this point is said to be singular.

For our purpose we need to represent the manifold in a slightly different manner than the one given in 3.9. If the manifold has no singular points, it can locally be represented as a graph, according to the implicit function theorem. To illustrate this, consider a surface as above. If the two columns in equation 3.10 are linearly independent, the implicit theorem applies, and we may write the surface as the subset: $(x, y, z) \in \mathbf{R}^3$, where z locally can be written as a function $\hat{h}(x, y)$ and $\hat{h}$ is differentiable. The variables x and y are said to be the independent variables, whereas, z is the dependent variable. This important fact will be used soon.

A manifold can be invariant under the vector field in 3.4 in the same sense, as a subspace is invariant under the linear part. That is, if $\mathbf{z}_0 \in W$, then $\mathbf{z}(t, \mathbf{z}_0) \in W$ for all t.

The following definition is adopted from [1]. If $\mathbf{z}_s = \mathbf{0}$ is the fixed point under consideration, then the stable manifold, W^s of $\mathbf{0}$, can be defined as an invariant manifold that contains $\mathbf{0}$, and is tangent to E^s at $\mathbf{z} = \mathbf{0}$. The trajectories on W^s have the dynamical property, that if $\mathbf{z}_0 \in W^s$, then $\mathbf{z}(t, \mathbf{z}_0) \to \mathbf{0}$ as $t \to \infty$. The unstable manifold, W^u, can be defined in a similar way: W^u is tangent to the unstable subspace at the origin, $\mathbf{0} \in W^u$ and if $\mathbf{z}_0 \in W^u$, then $\mathbf{z}(t, \mathbf{z}_0) \to \mathbf{0}$ as $t \to -\infty$.

The center manifold, W^c, differs a bit from W^s and W^u. W^c is tangent to E^c, also $\mathbf{0} \in W^c$, but there is no general asymptotic characterization as $|t| \to \infty$. Also, let U denote a neighborhood of $\mathbf{0}$, and assume that the forward trajectories remain in U, that is: $\mathbf{z}(t) \in U$ for $t \geq 0$, then the trajectories converges to W^c. [4] This implies that in some cases one can restrict the attention to the dynamics on the center manifold. The neighborhood U in which W^c is locally attracting is illustrated in figure 3.1.

But how is the dynamics on the center manifold given? Well, this is actually what the remaining part of this chapter is about. The following modification of a theorem by Wiggins [14, p. 21], will lead the way:

Theorem 1 *Suppose that $\mathbf{R}^n = E^c \oplus E^s$, and the vector field in 3.4 is C^r, $r \geq 2$. Then the fixed point posses a C^r, c-dimensional center manifold, which locally can be represented by a graph (according to the implicit function theorem):*

$$W^c_{loc}(\mathbf{0}) = \{(\mathbf{z}_c, \mathbf{z}_s) \in \mathbf{R}^c \times \mathbf{R}^s \mid \mathbf{z}_s = \hat{h}(\mathbf{z}_c)\} \tag{3.11}$$

[4] This means that W^c is attracting. For definition of an attracting set see [14, p. 43]

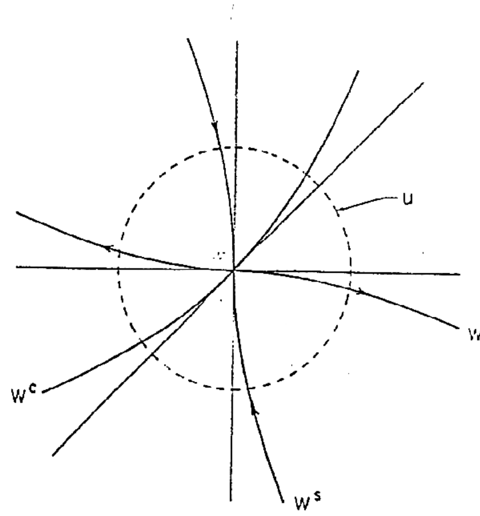

Figure 3.1: Illustration of the neighborhood, U, in which W^c is locally attracting. The straight lines represent the stable, unstable and center subspaces. From [1].

where $D\hat{h}(\mathbf{0}) = \mathbf{0}$, $\hat{h}(\mathbf{0}) = \mathbf{0}$, *and* $|\mathbf{z}_c| < \delta$ *for* δ *sufficient small. Also, the function* $\hat{h} : \mathbf{R}^c \to \mathbf{R}^s$ *is* C^r.

The conditions $D\hat{h}(\mathbf{0}) = \mathbf{0}$ and $\hat{h}(\mathbf{0}) = \mathbf{0}$ implies that W^c is tangent to the center subspace at the origin (fixed point).

To sum up: If the trajectories of a flow remains in U for $|t| \to \infty$, we can restrict the attention to the center manifold. The center manifold can in a neighborhood of the fixed point be represented by a graph $(\mathbf{z}_c, \mathbf{z}_s) \in \mathbf{R}^n$, where $\mathbf{z}_s$ is represented as a function of $\mathbf{z}_c$, that is, $\mathbf{z}_s$ and $\mathbf{z}_c$ is the dependent and independent variable respectively. To illustrate the results consider the WH model:

The WH model

Rewriting equation 3.8 a bit:

$$\dot{\mathbf{z}}_c = \Lambda_c \mathbf{z}_c + \hat{N}_c(\mathbf{z}_c, \mathbf{z}_s) \tag{3.12}$$
$$\dot{\mathbf{z}}_s = \Lambda_s \mathbf{z}_s + \hat{N}_s(\mathbf{z}_c, \mathbf{z}_s) \tag{3.13}$$

where $\mathbf{z}_c = (z_1, z_2)^T$, $\mathbf{z}_s = z_3$,

$$\Lambda_c = \begin{pmatrix} 0 & \omega_0 \\ -\omega_0 & 0 \end{pmatrix} \quad , \quad \Lambda_s = \lambda_3 \quad ,$$

and $(\hat{N}_c(\mathbf{z}_c, \mathbf{z}_s), \hat{N}_s(\mathbf{z}_c, \mathbf{z}_s))^T = \hat{N}(\mathbf{z})$. Now assume that the center manifold is an attracting set. Then we can restrict the attention to W^c, that is, $\mathbf{z}_s = \hat{h}(\mathbf{z}_c)$, which can be substituted into equations 3.12 and 3.13, hence:

$$\begin{aligned} \dot{\mathbf{z}}_c &= \Lambda_c \mathbf{z}_c + \hat{N}_c(\mathbf{z}_c, \hat{h}(\mathbf{z}_c)) \\ \dot{\mathbf{z}}_s &= D\hat{h}(\mathbf{z}_c)\dot{\mathbf{z}}_c \end{aligned} \tag{3.14}$$

These two differential equations are decoupled and we can simply consider equation 3.14. In figure 3.2 the parameterization of W^c is illustrated. •

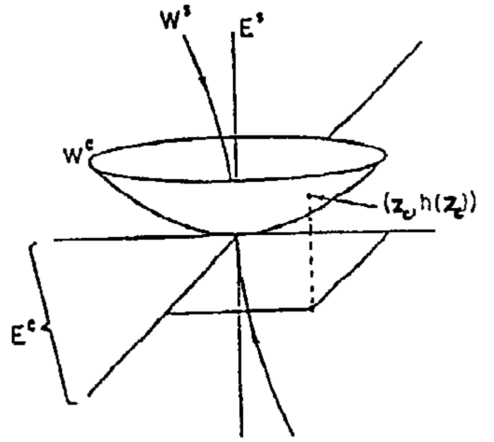

Figure 3.2: Illustration of the center manifold, in the case where $\dim(E^s) = 1$ and $\dim(E^c) = 2$, as is the case of the WH model. From [1].

All of the above is the traditional way of dealing with nonhyperbolic fixed points. Determine the dynamics restricted to W^c, that is, determine $\hat{h}$ is normally done via the invariant equation (see [14] or [9]).

As mentioned Ipsen *et al.* takes a different approach which I will follow. In their approach the center manifold is not parameterized as in theorem 1, but in the physical vector space. In this way it is possible to compare the dynamics restricted to the center manifold directly with the original model. (This will, hopefully, be more clear after reading this chapter.)

3.2.1 W^c parameterized in the original basis

Now, assume that $\dim(E^c) = c$ and $\dim(E^s) = s$ and $\mathbf{R}^n = E^c \oplus E^s$. Furthermore, assume that the eigenspace is spanned by the columns in the matrix:

$$U = (\mathbf{u}_1\ \mathbf{u}_2 \ldots\ \mathbf{u}_c\ \mathbf{u}_{c+1}\ \ldots\ \mathbf{u}_{c+s})$$

This follows the discussion from section 3.1. Finally, let $\mathbf{z}$ be the coordinates of a vector $\mathbf{y}$ in the eigenspace. If $\mathbf{y} \in W^c$, its coordinates can be written as $(\mathbf{z}_c, \hat{h}(\mathbf{z}_c))$ according to theorem 1. $\mathbf{y}$'s coordinates in the original basis is then:

$$\begin{aligned} \mathbf{y} &= U\mathbf{z} = U \begin{pmatrix} \mathbf{z}_c \\ \hat{h}(\mathbf{z}_c) \end{pmatrix} \\ &= (\mathbf{u}_1 \ldots \mathbf{u}_c)\mathbf{z}_c + (\mathbf{u}_{c+1} \ldots \mathbf{u}_{c+s})\hat{h}(\mathbf{z}_c) \end{aligned} \tag{3.15}$$

The question is now: How can $\mathbf{y}$ be parameterized by a vector $\mathbf{x} \in E^c \subset \mathbf{R}^n$ that has the following coordinates in the eigenspace:

$$\boldsymbol{\zeta}_c = (z_1, z_2, \ldots, z_c, 0, \ldots, 0)^T$$

and therefore the coordinates in the original basis:

$$\mathbf{x} = U\boldsymbol{\zeta}_c = (\mathbf{u}_1 \ldots \mathbf{u}_c)\mathbf{z}_c \ \ ?$$

It is possible to choose a function $\tilde{h} : \mathbf{R}^n \to \mathbf{R}^s$ so that:

$$\tilde{h}(\boldsymbol{\zeta}_c) = \hat{h}(\mathbf{z}_c) \tag{3.16}$$

Before continuing, let me give an illustration of equation 3.16. Let $\hat{h} : \mathbf{R}^2 \to \mathbf{R}^2$ by taking $(x, y) \to (x^2, y^2)$, and let $\tilde{h} : \mathbf{R}^3 \to \mathbf{R}^2$ by $(x, y, 0) \to (x^2, y^2)$. Then naturally $\hat{h}(x, y) = \tilde{h}(x, y, 0)$, for all $(x, y, 0)$ in the domain of $\tilde{h}$.

Realizing this, equation 3.15 can be written as:

$$\begin{aligned} \mathbf{y} &= \mathbf{x} + (\mathbf{u}_{c+1} \ldots \mathbf{u}_{c+s})\tilde{h}(\boldsymbol{\zeta}_c) \\ &= \mathbf{x} + (\mathbf{u}_{c+1} \ldots \mathbf{u}_{c+s})\tilde{h}(U^{-1}\mathbf{x}) \\ &= \mathbf{x} + \overline{h}(\mathbf{x}) \end{aligned}$$

where $\overline{h}(\mathbf{x}) = (\mathbf{u}_{c+1} \dots \mathbf{u}_{c+s})(\tilde{h} \circ U^{-1})(\mathbf{x})$. Since this can be done for all $\mathbf{y} \in W^c$, the center manifold can be written as:

$$W^c_{loc} = \{\mathbf{y} \in \mathbf{R}^n \mid \mathbf{y} = \mathbf{x} + \overline{h}(\mathbf{x})\} \tag{3.17}$$

where $\mathbf{x} \in E^c$ and $\overline{h} : \mathbf{R}^n \rightarrow \mathbf{R}^n$. In figure 3.3 the transformation is illustrated. The idea of this is to initialize the study of the dynamical system

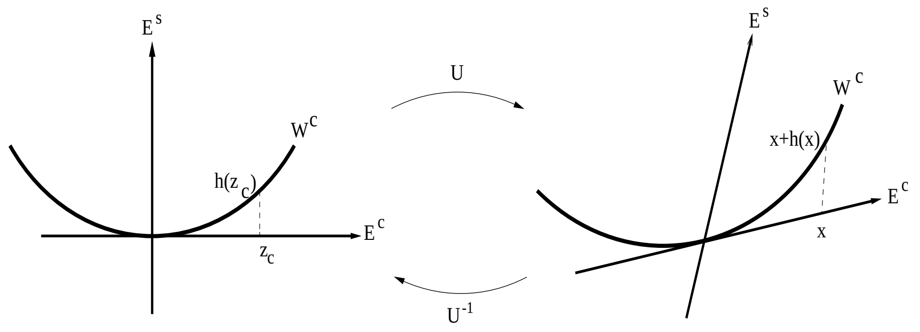

Figure 3.3: Illustration of the difference between the center manifold, parameterized in the eigenspace (left), and in the standard basis (right).

via 3.17, and then transform the problem to the eigenspace (being real or complex). The traditional approach differs a bit, in that the system is first transformed to eigenspace, and then the dynamics is investigated on the center manifold parameterized in the (real) eigenspace. The advantage of the method used here is, that it provides a straight forward way to transform the coordinates from the eigenspace to the physical space by an algebraic equation.

3.3 Normal forms

As discussed just above: The initial point is to find the dynamics restricted to the center manifold given in 3.17, that is, by the chain rule:

$$\dot{\mathbf{y}} = \dot{\mathbf{x}} + D\overline{h}(\mathbf{x})\dot{\mathbf{x}} = (I + D\overline{h}(\mathbf{x}))\dot{\mathbf{x}} \tag{3.18}$$

Substituting equation 3.18 and 3.17 in 3.2, one obtains:

$$(I + D\overline{h}(\mathbf{x}))\dot{\mathbf{x}} \quad = \quad J(\mathbf{x} + \overline{h}(\mathbf{x})) + N(\mathbf{x} + \overline{h}(\mathbf{x})) \tag{3.19}$$

For sufficient small $\mathbf{x}$ this can be written as:

$$\begin{aligned}\dot{\mathbf{x}} &= (I + D\overline{h}(\mathbf{x}))^{-1}(J\mathbf{x} + J\overline{h}(\mathbf{x}) + N(\mathbf{x} + \overline{h}(\mathbf{x}))\\ &= J\mathbf{x} + \overline{g}(\mathbf{x}) \end{aligned} \tag{3.20}$$

The idea is to find $\overline{g}$, because this function describes the flow restricted to the center manifold (in the original space).

Now, let the coordinates of $\mathbf{x}$ in the eigenspace be given by $\boldsymbol{\zeta}_c = U^{-1}\mathbf{x}$. Then equation 3.20 can be written in terms of coordinates in the eigenspace (complex or real):

$$\begin{aligned} U\dot{\boldsymbol{\zeta}}_c &= JU\boldsymbol{\zeta}_c + \overline{g}(U\boldsymbol{\zeta}_c)\\ \dot{\boldsymbol{\zeta}}_c &= \Lambda\boldsymbol{\zeta}_c + U^{-1}\overline{g}(U\boldsymbol{\zeta}_c)\\ &= U^{-1}(U\Lambda\boldsymbol{\zeta}_c + \overline{g}(U\boldsymbol{\zeta}_c)) \end{aligned} \tag{3.21}$$

Also, the term:

$$(I + D\overline{h}(\mathbf{x})) \tag{3.22}$$

in equation 3.19 can be expressed in terms of $\boldsymbol{\zeta}_c$. To do this set $\overline{h}(\mathbf{x}) = h(\boldsymbol{\zeta}_c)$, where $h = (\overline{h} \circ U)$, and $\boldsymbol{\zeta}_c = \boldsymbol{\zeta}_c(\mathbf{x})$. Now, by the chain rule this means:

$$D\overline{h}(\mathbf{x}) = Dh(\boldsymbol{\zeta}_c)\frac{\partial \boldsymbol{\zeta}_c}{\partial \mathbf{x}} = Dh(\boldsymbol{\zeta}_c)U^{-1}$$

so:

$$\begin{aligned} (I + D\overline{h}(\mathbf{x}))\dot{\mathbf{x}} &= (I + Dh(\boldsymbol{\zeta}_c)U^{-1})U\dot{\boldsymbol{\zeta}}_c\\ &= (U + Dh(\boldsymbol{\zeta}_c))\dot{\boldsymbol{\zeta}}_c \end{aligned} \tag{3.23}$$

Substituting equation 3.21 for $\dot{\boldsymbol{\zeta}}_c$ in equation 3.23:

$$(U + Dh(\boldsymbol{\zeta}_c))U^{-1}(U\Lambda\boldsymbol{\zeta}_c + \overline{g}(U\boldsymbol{\zeta}_c)) = (I + Dh(\boldsymbol{\zeta}_c)U^{-1})(U\Lambda\boldsymbol{\zeta}_c + \overline{g}(U\boldsymbol{\zeta}_c))$$

Also, the right hand side of 3.19 can be written in terms of $\boldsymbol{\zeta}_c$:

$$JU\boldsymbol{\zeta}_c + Jh(\boldsymbol{\zeta}_c) + N(U\boldsymbol{\zeta}_c + h(\boldsymbol{\zeta}_c))$$

Finally, equation 3.19 can be written as:

$$\begin{aligned} (I + Dh(\boldsymbol{\zeta}_c)U^{-1})(U\Lambda\boldsymbol{\zeta}_c + \overline{g}(U\boldsymbol{\zeta}_c)) &= JU\boldsymbol{\zeta}_c + Jh(\boldsymbol{\zeta}_c)\\ &\quad + N(U\boldsymbol{\zeta}_c + h(\boldsymbol{\zeta}_c)) \end{aligned} \tag{3.24}$$

Recall, the idea is to find an equation for $\overline{g}$. For simplicity, set $\overline{g}(U\boldsymbol{\zeta}_c) = g(\boldsymbol{\zeta}_c)$, and then isolate g in equation 3.24:

$$\begin{aligned} g(\boldsymbol{\zeta}_c) &= U\Lambda\boldsymbol{\zeta}_c - JU\boldsymbol{\zeta}_c + Jh(\boldsymbol{\zeta}_c) + N(U\boldsymbol{\zeta}_c + h(\boldsymbol{\zeta}_c)) \\ &\quad + Dh(\boldsymbol{\zeta}_c)(\Lambda\boldsymbol{\zeta}_c + U^{-1}g(\boldsymbol{\zeta}_c)) \\ &= Jh(\boldsymbol{\zeta}_c) + N(U\boldsymbol{\zeta}_c + h(\boldsymbol{\zeta_c})) + Dh(\boldsymbol{\zeta}_c)(\Lambda\boldsymbol{\zeta}_c + U^{-1}g(\boldsymbol{\zeta}_c)) \end{aligned} \tag{3.25}$$

because

$$U\Lambda\boldsymbol{\zeta}_c - JU\boldsymbol{\zeta}_c = (UU^{-1}JU - JU)\boldsymbol{\zeta}_c = (JU - JU)\boldsymbol{\zeta}_c = \mathbf{0}$$

Equation 3.25 is an implicit equation for g. If we can determine g, the solution can be substituted in 3.21, and thus the dynamics restricted to the center manifold is determined.

In the linear case one is interested in simplifying the linear part as much as possible by a linear transformation, that brings the Jacobian into the desired block form[5]. This is also the case in the nonlinear situation. By introducing a series of nonlinear transformations, we wish to bring the nonlinear part, that will be g, on the "simplest" possible form. By the simplest form it's meant the form where as many terms as possible in the Taylor expansion of g is zero.

In the standard approach the coordinate transformation is determined by the Lie bracket, L. L can be thought of as a linear function, acting on a space of vector valued monomials of degree k. In this way each term in h is determined such that g obtains the simplest form. Here a slightly different approach is used, but, of course, they are equivalent.

To illustrate this, consider a situation similar to that of the WH model. That is, $\dim(E^c) = 2$, $\dim(E^s) = 1$, where $\lambda_{1,2} = \pm i\omega_0$ and $\lambda_3 < 0$. This means that $\boldsymbol{\zeta}_c = (z_1, z_2, 0)^T$. Also assume that g, h and f are at least C^3 functions at every point in their domain. Taylor expanding h:

$$\begin{aligned} h(\boldsymbol{\zeta}_c) &= \sum_k h_k \boldsymbol{\zeta}_c^k \\ &= h_2\boldsymbol{\zeta}_c^2 + h_3\boldsymbol{\zeta}_c^3 + R(\boldsymbol{\zeta}_c) \end{aligned} \tag{3.26}$$

where $R(\boldsymbol{\zeta}_c)/||\boldsymbol{\zeta}_c||^3 \to \mathbf{0}$ as $\boldsymbol{\zeta}_c \to \mathbf{0}$. For our purpose it is sufficient to consider the second and third order terms. Therefore, equation 3.26 is truncated such that:

$$h(\boldsymbol{\zeta}_c) = h_2\boldsymbol{\zeta}_c^2 + h_3\boldsymbol{\zeta}_c^3 \tag{3.27}$$

[5]Not only is it the must simple form, it is also the must informative one.

where:

$$
\begin{aligned}
h_2\boldsymbol{\zeta}_c^2 &= \begin{pmatrix} h_{120} \\ h_{220} \\ h_{320} \end{pmatrix} z_1^2 + \begin{pmatrix} h_{111} \\ h_{211} \\ h_{311} \end{pmatrix} z_1 z_2 + \begin{pmatrix} h_{102} \\ h_{202} \\ h_{302} \end{pmatrix} z_2^2 \\
&= \mathbf{h}_{20} z_1^2 + \mathbf{h}_{11} z_1 z_2 + \mathbf{h}_{02} z_2^2
\end{aligned}
$$

and

$$
\begin{aligned}
h_3\boldsymbol{\zeta}_c^3 &= \begin{pmatrix} h_{130} \\ h_{230} \\ h_{330} \end{pmatrix} z_1^3 + \begin{pmatrix} h_{121} \\ h_{221} \\ h_{321} \end{pmatrix} z_1^2 z_2 + \begin{pmatrix} h_{112} \\ h_{212} \\ h_{312} \end{pmatrix} z_1 z_2^2 + \begin{pmatrix} h_{103} \\ h_{203} \\ h_{303} \end{pmatrix} z_2^3 \\
&= \mathbf{h}_{30} z_2^3 + \mathbf{h}_{21} z_1^2 z_2 + \mathbf{h}_{12} z_1 z_2^2 + \mathbf{h}_{03} z_2^3
\end{aligned}
$$

In the same way g and N are being Taylor expanded and truncated:

$$
\begin{aligned}
g(\boldsymbol{\zeta}_c) &= g_2\boldsymbol{\zeta}_c^2 + g_3\boldsymbol{\zeta}_c^3 \\
&= \mathbf{g}_{20} z_1^2 + \mathbf{g}_{11} z_1 z_2 + \ldots + \mathbf{g}_{03} z_2^3 \\
N(U\boldsymbol{\zeta}_c + h(\boldsymbol{\zeta}_c)) &= N_2\boldsymbol{\zeta}_c^2 + N_3\boldsymbol{\zeta}_c^3 \\
&= \mathbf{N}_{20} z_1^2 + \mathbf{N}_{11} z_1 z_2 + \ldots + \mathbf{N}_{03} z_2^3
\end{aligned}
$$

In equation 3.25 the term $Dh(\boldsymbol{\zeta}_c)$ appears. Assume that the Taylor expansion uniformly converges to its sum, $h(\boldsymbol{\zeta}_c)$, and the series is simply differentiated termwise.

Now, substituting all the Taylor expansions in the right hand side of equation 3.25, and the expansion for g in the left hand side one can isolate each term in g. This should not be done by hand! The coefficients for the second order terms are:

$$
\begin{aligned}
\mathbf{g}_{20} &= \mathbf{N}_{20} + (J - 2\lambda_1 I)\mathbf{h}_{20} && (3.28) \\
\mathbf{g}_{11} &= \mathbf{N}_{11} + (J - (\lambda_1 + \lambda_2) I)\mathbf{h}_{11} && (3.29) \\
\mathbf{g}_{02} &= \mathbf{N}_{02} + (J - 2\lambda_2 I)\mathbf{h}_{02} && (3.30)
\end{aligned}
$$

Let's recall the idea before continuing: In determining g, h can be chosen such that as many terms as possible can be removed (set to zero). This is equivalent to chose a nonlinear transformation (as in the traditional approach). Actually one may think of equation 3.28–3.30 as the action of the Lie bracket on the space of vector valued monomials of degree two. Now, setting g to zero means setting each term of g to zero, and therefore also

$\mathbf{g}_{20}, \mathbf{g}_{11}$ and $\mathbf{g}_{02}$. This again means setting:

$$-\mathbf{N}_{20} = (J - 2\lambda_1 I)\mathbf{h}_{20} \tag{3.31}$$
$$-\mathbf{N}_{11} = (J - (\lambda_1 + \lambda_2)I)\mathbf{h}_{11} \tag{3.32}$$
$$-\mathbf{N}_{02} = (J - 2\lambda_2 I)\mathbf{h}_{02} \tag{3.33}$$

As it is seen above determining h_2 is "simply" a matter of solving a set of linear equations. To be able to solve equations 3.31–3.33 the matrices must be regular (have full rank).This is fortunately the case most of the time, but not all the time. So two questions could be asked: 1) When is the problem solvable? 2) If it is not solvable what do one do?

The first question: J is always regular, but if an eigenvalue is substrated in the diagonal, the matrix is singular. For example the matrix: $(J - (\lambda_1 + 2\lambda_2 I))$ is singular because:

$$J - (\lambda_1 + 2\lambda_2)I = J - i(\omega_0 - 2\omega_0)I = J + i\omega_0 I$$

hence $-i\omega_0$ is substrated from the diagonal. In equations 3.31–3.33 this will not be the case, and h_2 can be determined so all coefficients in g_2 are simply zero. Stated differently: There exists a nonlinear transformation such that all terms in g_2 can be eliminated.

The second question: When a singular matrix arises, the corresponding coefficients in g cannot be eliminated by any transformation. This is called a resonant term. How the resonant term is determined, is simply a matter of evaluating each component in the resonant term at the time, which will be illustrated in the following. But first: A left eigenvector is defined as the row vector $\mathbf{v}_i$ where $\mathbf{v}_i J = \lambda_i \mathbf{v}_i$. Just as the columns in U can be interpreted as the right eigenvectors, $\mathbf{u}_i$, the rows in U^{-1} can be interpreted as the left eigenvectors.

Back to the original problem. As discussed above equations 3.31 – 3.33 could all be solved. Moving on to third degree, g_3:

$$\mathbf{g}_{30} = \mathbf{N}_{30} + (J - 3\lambda_1 I)\mathbf{h}_{30} + (2\mathbf{v}_1\mathbf{h}_{20} + \mathbf{v}_2\mathbf{h}_{11})\mathbf{g}_{20} \tag{3.34}$$
$$\begin{aligned}\mathbf{g}_{21} = {} & \mathbf{N}_{21} + (J - (2\lambda_1 + \lambda_2)I)\mathbf{h}_{21} - (\mathbf{v}_1\mathbf{h}_{11} - 2\mathbf{v}_2\mathbf{h}_{02})\mathbf{g}_{20} \\ & -(2\mathbf{v}_1\mathbf{h}_{20} + \mathbf{v}_2\mathbf{h}_{11})\mathbf{g}_{11}\end{aligned} \tag{3.35}$$
$$\begin{aligned}\mathbf{g}_{12} = {} & \mathbf{N}_{12} + (J - (\lambda_1 + 2\lambda_2)I)\mathbf{h}_{12} - (\mathbf{v}_1\mathbf{h}_{11} + 2\mathbf{v}_2\mathbf{h}_{02})\mathbf{g}_{11} \\ & -(2\mathbf{v}_1\mathbf{h}_{20} + \mathbf{v}_2\mathbf{h}_{11})\mathbf{g}_{20}\end{aligned} \tag{3.36}$$
$$\mathbf{g}_{03} = \mathbf{N}_{03} + (J - 3\lambda_2 I)\mathbf{h}_{03} - (2\mathbf{v}_1\mathbf{h}_{20} + \mathbf{v}_2\mathbf{h}_{11})\mathbf{g}_{02} \tag{3.37}$$

Equation 3.34 contains the coefficients $\mathbf{h}_{20}, \mathbf{h}_{11}$, and $\mathbf{g}_{20}$. These vectors have already been determined when looking at the second order terms.(This illustrates the iterative nature of this process.) Now, $\mathbf{g}_{20}$ was set to zero (because we could solve equation 3.31), so equation 3.34 becomes:

$$\mathbf{g}_{30} = \mathbf{N}_{30} + (J - 3\lambda_1 I)\mathbf{h}_{30}$$

Since, $\lambda_2 = \overline{\lambda}_1$ and the third eigenvalue is real, the matrix has full rank and the problem is solvable. This is also the case for $\mathbf{g}_{03}$ (see equation 3.37).

Looking at equation 3.35 and noting that $\mathbf{g}_{20} = \mathbf{g}_{11} = \mathbf{0}$, and $\lambda_1 = \overline{\lambda}_2$, it can be written as:

$$\mathbf{g}_{21} = \mathbf{N}_{21} + (J - \lambda_1 I)\mathbf{h}_{21} \tag{3.38}$$

which is a singular problem. This means that $\mathbf{g}_{21}$ is a resonant term, so it cannot be removed by any choice of $\mathbf{h}_{21}$. The same is true for $\mathbf{g}_{12}$:

$$\mathbf{g}_{12} = \mathbf{N}_{12} + (J - \lambda_2 I)\mathbf{h}_{12}$$

g can then be written as:

$$g(\boldsymbol{\zeta}_c) = \mathbf{g}_{21} z_1^2 z_2 + \mathbf{g}_{12} z_1 z_2^2 \tag{3.39}$$

Substituting 3.39 in the nonlinear part of equation 3.21 yields:

$$\dot{\boldsymbol{\zeta}}_c = \Lambda \boldsymbol{\zeta}_c + U^{-1}(\mathbf{g}_{21} z_1^2 z_2 + \mathbf{g}_{12} z_1 z_2^2) \tag{3.40}$$

This is actually a normal form. However, it can be reduced even more by considering each component in the $\mathbf{g}_{21}$ and $\mathbf{g}_{12}$. To do this the nonlinear part of equation 3.40 can be expressed as

$$U^{-1}(\mathbf{g}_{21} z_1^2 z_2 + \mathbf{g}_{12} z_1 z_2^2) = \begin{pmatrix} \mathbf{v}_1\mathbf{g}_{21} \\ \mathbf{v}_2\mathbf{g}_{21} \\ \mathbf{v}_3\mathbf{g}_{21} \end{pmatrix} z_1^2 z_2 + \begin{pmatrix} \mathbf{v}_1\mathbf{g}_{12} \\ \mathbf{v}_2\mathbf{g}_{12} \\ \mathbf{v}_3\mathbf{g}_{12} \end{pmatrix} z_1 z_2^2$$

Each component in the two vectors can be evaluated. Multiplying equation 3.38 by $\mathbf{v}_1$ from the left:

$$\begin{aligned} \mathbf{v}_1\mathbf{g}_{21} &= \mathbf{v}_1\mathbf{N}_{21} + \mathbf{v}_1(J - \lambda_1 I)\mathbf{h}_{21} \\ &= \mathbf{v}_1\mathbf{N}_{21} + (\mathbf{v}_1 J - \lambda_1 \mathbf{v}_1)\mathbf{h}_{21} \\ &= \mathbf{v}_1\mathbf{N}_{21} \end{aligned}$$

This means that $\mathbf{v}_1\mathbf{g}_{21}$ is nonzero, irrespective of the choice of $\mathbf{h}_{21}$. For simplicity the first component in $\mathbf{h}_{21}$ can be set to zero. Multiplying $\mathbf{g}_{21}$ by $\mathbf{v}_2$:

$$\begin{aligned} \mathbf{v}_2\mathbf{g}_{21} &= \mathbf{v}_2\mathbf{N}_{21} + \mathbf{v}_2(J - \lambda_1 I)\mathbf{h}_{21} \\ &= \mathbf{v}_2\mathbf{N}_{21} + (\mathbf{v}_2 J - \lambda_1 \mathbf{v}_2)\mathbf{h}_{21} \\ &= \mathbf{v}_2\mathbf{N}_{21} + (\lambda_2 - \lambda_1)\mathbf{v}_2\mathbf{h}_{21} \end{aligned} \tag{3.41}$$

This means that if $\mathbf{h}_{21}$ is chosen so that:

$$\mathbf{v}_2\mathbf{h}_{21} = -\frac{\mathbf{v}_2\mathbf{N}_{21}}{(\lambda_2 - \lambda_1)}$$

then $\mathbf{v}_2\mathbf{g}_{21} = 0$. The same argument can be used to determine the choice of $\mathbf{v}_3\mathbf{h}_{21}$, that is:

$$\mathbf{v}_3\mathbf{h}_{21} = -\frac{\mathbf{v}_3\mathbf{N}_{21}}{(\lambda_3 - \lambda_1)}$$

(It is actually not necessary to determine $\mathbf{v}_3\mathbf{g}_{21}$ since $z_3 = 0$). In the same way each component in the coefficient of $z_1 z_2^2$ can be considered. In this case $\mathbf{v}_2\mathbf{g}_{12}$ is the resonant component. This means that each coefficient can be written as:

$$\begin{pmatrix} \mathbf{v}_1\mathbf{g}_{21} \\ \mathbf{v}_2\mathbf{g}_{21} \\ \mathbf{v}_3\mathbf{g}_{21} \end{pmatrix} = \begin{pmatrix} \mathbf{v}_1\mathbf{g}_{21} \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \begin{pmatrix} \mathbf{v}_1\mathbf{g}_{12} \\ \mathbf{v}_2\mathbf{g}_{12} \\ \mathbf{v}_3\mathbf{g}_{12} \end{pmatrix} = \begin{pmatrix} 0 \\ \mathbf{v}_2\mathbf{g}_{12} \\ 0 \end{pmatrix}$$

by the right choice of $\mathbf{h}_{21}$ and $\mathbf{h}_{12}$. Then equation 3.40 can be written as:

$$\begin{aligned} \dot{z}_1 &= \lambda_1 z_1 + \mathbf{v}_1\mathbf{g}_{21} z_1^2 z_2 \\ \dot{z}_2 &= \lambda_2 z_2 + \mathbf{v}_2\mathbf{g}_{12} z_1 z_2^2 \end{aligned} \tag{3.42}$$

Because of the setup (defined earlier), the two eigenvalues are complex conjugated. So is z_1 and z_2, which means that the above equation can be decoupled. If we set $\lambda_1 = i\omega_0$ then 3.42 reaches the final form:

$$\dot{z}_1 = i\omega_0 z_1 + g_3 |z_1|^2 z_1 \tag{3.43}$$

with $g_3 = \mathbf{v}_1\mathbf{g}_{21}$ determined by 3.41.

The setup was defined to be a three dimensional dynamical system where $\dim(E^s) = 1$. This can be naturally expanded to n–dimensional systems, where $\dim(E^c) = 2$ and $\dim(E^s) = n - 2$. This, of course, makes things a bit more tedious. However, instead of the decomposition discussed above, a more practical way of determining the coefficients in the Taylor expansion exists. This approach is based on the Fredholm alternative, and can be implemented when calculating the normal form via software (see [5] for details).

Equation 3.43 describes the dynamical system restricted to the center manifold in coordinates of the eigenspace. Now, transforming the coordinates back to the original basis:

$$\mathbf{y} = \mathbf{x} + \overline{h}(\mathbf{x})$$

$$
\begin{aligned}
&= U\boldsymbol{\zeta}_c + h_2\boldsymbol{\zeta}_c^2 + h_3\boldsymbol{\zeta}_c^3 \\
&= \mathbf{u}_1 z_1 + \overline{\mathbf{u}}_1\overline{z}_1 + \mathbf{h}_{20}z_1^2 + \mathbf{h}_{11}z_1\overline{z}_1 + \mathbf{h}_{02}\overline{z}_1^2 + \mathbf{h}_{30}z_1^3 + \mathbf{h}_{21}z_1^2\overline{z}_1 \\
&\quad + \mathbf{h}_{12}z_1\overline{z}_1^2 + \mathbf{h}_{03}\overline{z}_1^3
\end{aligned}
$$

and voilá the coordinates in the original basis appears. Recall that $z_1 = \overline{z}_2$ and $\mathbf{u}_1 = \overline{\mathbf{u}}_2$. This transformation arises naturally from the determination of the normal form. The coefficients of the complex conjugated terms are also complex conjugated. (This is also intuitively reasonable since $\mathbf{y}$ must be real.) This means that:

$$\mathbf{h}_{20} = \overline{\mathbf{h}}_{02} \quad , \quad \mathbf{h}_{21} = \overline{\mathbf{h}}_{12} \quad \text{and} \quad \mathbf{h}_{03} = \overline{\mathbf{h}}_{03} \tag{3.44}$$

which ease the calculations a bit.

In this treatment, the Taylor expansions were truncated. If one wishes, the effect of higher order terms can also be considered, and there exists a condition that predicts when the resonant terms arise. A term is resonant whenever an eigenvalue is substrated in the diagonal of J. That is, whenever:

$$(J - (n\lambda_1 + m\lambda_2)I) \quad n = m + 1 \quad \text{or} \quad m = n + 1$$

where $n + m$ is the degree of the term under consideration. The resonant condition is fulfilled when $m + n$ is odd, that is, when $n + m = 3, 5, 7$ etc. This means that the next resonant term in g is $\mathbf{g}_{23}$ and $\mathbf{g}_{32}$. This resonant condition is equivalent to the condition seen in the standard literature (for example [14]).

Now, it would be naturally to exemplify all this with the WH model. However, I will postpone this a bit, because the truly interesting problem is to describe the dynamics just around the bifurcation point $\mu_c = (\sqrt{325} - 17)/6$. This will be done in the next section.

3.4 Suspended systems

One can be interested in describing the dynamics when a parameter, p, is varied. One way of handling such problems is to treat the parameter as a new independent variable, that is constant in time. First, consider the autonomous vector field:

$$\dot{\mathbf{y}} = f(\mathbf{y}; p) \tag{3.45}$$

$\mathbf{y} \in \mathbf{R}^n$, $p \in \mathbf{R}$, and f has continuous partial derivatives of any desired degree with respect to $\mathbf{y}$. Assume that $\mathbf{y}_s = \mathbf{0}$, and at $p = p_s$ the spectrum of the Jacobian has c eigenvalues with zero real part (the same setup as in section 3.3).

When treating the parameter as an independent variable we simply augment the original vector field by:

$$\begin{aligned}\dot{\mathbf{y}} &= Df(\mathbf{y}_s, p_s)(\mathbf{y}) + N(\mathbf{y}, p) \\ \dot{p} &= 0\end{aligned}$$

It is very important to note, that the eigenvalues of the matrix $Df(\mathbf{x}_s, p_s)$ are independent of p. Now, as it is seen the augmented system has, not c, but $c+1$ eigenvalues with zero real part. However, the center manifold theorem still applies, hence, W^c can be represented as the graph:

$$W^c = \{(\mathbf{y}, p) \in \mathbf{R}^n \times \mathbf{R} \mid \mathbf{y} = \mathbf{x} + \overline{h}(\mathbf{x}, p)\}$$

where $\mathbf{x} \in E^c$ and $\overline{h} : \mathbf{R}^n \times \mathbf{R} \to \mathbf{R}^n$. This is equivalent to equation 3.17. This means that if a point $\mathbf{y} \in W^c$, it can be written as:

$$\mathbf{y} = \mathbf{x} + \overline{h}(\mathbf{x}, p)$$

Treating the problem this way follows the method from above, and I will be brief. The derivative of $\mathbf{y}$ with respect to time:

$$\begin{aligned}\dot{\mathbf{y}} &= \dot{\mathbf{x}} + \frac{\partial \overline{h}(\mathbf{x}, p)}{\partial \mathbf{x}}\dot{\mathbf{x}} + \frac{\partial \overline{h}(\mathbf{x}, p)}{\partial p}\dot{p} \\ &= \left(I + \frac{\partial \overline{h}(\mathbf{x}, p)}{\partial \mathbf{x}}\right)\dot{\mathbf{x}} \qquad (3.46)\end{aligned}$$

because $\dot{p} = 0$. Now, in analogy to the situation with no variable parameter, we write:

$$\begin{aligned}\left(I + \frac{\partial \overline{h}(\mathbf{x}, p)}{\partial \mathbf{x}}\right)\dot{\mathbf{x}} &= J(\mathbf{x} + \overline{h}(\mathbf{x}, p)) + N(\mathbf{x} + \overline{h}(\mathbf{x}, p), p) \\ \dot{\mathbf{x}} &= J\mathbf{x} + \overline{g}(\mathbf{x}, p)\end{aligned}$$

Representing $\mathbf{x}$ and p in the eigenbasis via the coordinates $\boldsymbol{\zeta}_c$ and μ, respectively[6]:

$$\dot{\boldsymbol{\zeta}}_c = \Lambda \boldsymbol{\zeta}_c + U^{-1} g(\boldsymbol{\zeta}_c, \mu) \qquad (3.47)$$

[6] Choosing the eigenvectors properly $p = \mu$.

Also, the term $\partial \overline{h}(\mathbf{x},p)/\partial \mathbf{x}$ can be expressed in the eigenspace as:

$$\frac{\partial h(\boldsymbol{\zeta}_c,\mu)}{\partial \boldsymbol{\zeta}_c}U^{-1} = Dh(\boldsymbol{\zeta}_c,\mu)U^{-1} \tag{3.48}$$

where $h(\boldsymbol{\zeta}_c,\mu) = \overline{h}(\mathbf{x},p)$. This means that:

$$\begin{aligned}\left(I + \frac{\partial \overline{h}(\mathbf{x},p)}{\partial \mathbf{x}}\right)\dot{\mathbf{x}} &= (U + Dh(\boldsymbol{\zeta}_c,\mu))\dot{\boldsymbol{\zeta}}_c \\ &= (I + Dh(\boldsymbol{\zeta}_c,\mu)U^{-1})(U\Lambda\zeta_c + g(\boldsymbol{\zeta}_c,\mu))\end{aligned}$$

So $g(\boldsymbol{\zeta}_c,\mu)$, is implicitly given by:

$$\begin{aligned}g(\boldsymbol{\zeta}_c,\mu) &= Jh(\boldsymbol{\zeta}_c) + N(U\boldsymbol{\zeta}_c + h(\boldsymbol{\zeta}_c,\mu),\mu) \\ &\quad + Dh(\boldsymbol{\zeta}_c,\mu)(\Lambda\boldsymbol{\zeta}_c + U^{-1}g(\boldsymbol{\zeta}_c,\mu))\end{aligned} \tag{3.49}$$

To derive the normal form for the vector field 3.45, consider the same setup as in section 3.3, i.e. the spectrum of the Jacobian for the vector field given in 3.45 has two complex conjugated eigenvalues with zero real part. Now, by suspending the vector field as described above, p is being thought of as an independent variable and $\dim(E^c) = 3$ and $\dim(E^s) = 1$.

As in section 3.3, we are interested in transforming g into the simplest possible form, via a set of nonlinear transformations. In this case, the functions are dependent of μ, and they must also be expanded with respect to this variable (i.e. they are differentiable with respect to μ):

$$h(\boldsymbol{\zeta}_c,\mu) = \sum_{k,l} h_{k,l}\boldsymbol{\zeta}_c^k\mu^l \quad , \quad g(\boldsymbol{\zeta}_c,\mu) = \sum_{k,l} g_{k,l}\boldsymbol{\zeta}_c^k\mu^l,$$
$$N(U\boldsymbol{\zeta}_c + h(\boldsymbol{\zeta}_c,\mu),\mu) = \sum_{k,l} N_{k,l}\boldsymbol{\zeta}_c^k\mu^l$$

Here $\sum k + \sum l \geq 1$, with the case $k = 1$ and $l = 0$ excluded. I will content my self with the case $l = 1$, which means that the Taylor expansions only includes linear terms in μ. h can explicitly be written as:

$$h(\boldsymbol{\zeta}_c,\mu) = \mathbf{h}_{001}\mu + \mathbf{h}_{101}z_1\mu + \mathbf{h}_{011}z_2\mu + \mathbf{h}_{200}z_1^2 + \ldots + \mathbf{h}_{030}z_2^3$$

and:

$$\begin{aligned}N(U\boldsymbol{\zeta}_c + h(\boldsymbol{\zeta}_c,\mu),\mu) &= \mathbf{N}_{001}\mu + \mathbf{N}_{101}z_1\mu + \mathbf{N}_{011}z_2\mu \\ &\quad + \mathbf{N}_{200}z_1^2 + \ldots + \mathbf{N}_{030}z_2^3 \\ g(\boldsymbol{\zeta}_c,\mu) = \mathbf{g}_{001}\mu &+ \mathbf{g}_{101}z_1\mu + \mathbf{g}_{011}z_2\mu + \mathbf{g}_{200}z_1^2 + \ldots + \mathbf{g}_{030}z_2^3\end{aligned}$$

As in the case with no parameter, the Taylor expansion of h is assumed to converge uniformly to its sum $h(\boldsymbol{\zeta}_c, \mu)$, and the expansion is simply differentiated termwise.

Substituting the Taylor expansions in 3.49, each term can be isolated as in section 3.3. I will not do this explicitly, but simply note that two new resonant terms arise, namely $\mathbf{g}_{101}$ and $\mathbf{g}_{011}$ because:

$$\begin{aligned}\mathbf{g}_{101} &= \mathbf{N}_{101} + (J - \lambda_1 I)\mathbf{h}_{101} \\ \mathbf{g}_{011} &= \mathbf{N}_{011} + (J - \lambda_2 I)\mathbf{h}_{011}\end{aligned}$$

The components in $\mathbf{g}_{101}$ and $\mathbf{g}_{011}$ can be evaluated in the same way as in the case with $\mathbf{g}_{21}$ and $\mathbf{g}_{12}$, and the normal form for the suspended vector field becomes:

$$\dot{z}_1 \quad = \quad i\omega_0 z_1 + \mathbf{v}_1 \mathbf{g}_{101} \mu z_1 + \mathbf{v}_1 \mathbf{g}_{210} |z_1|^2 z_1$$

which will be written as:

$$\dot{z}_1 \quad = \quad (i\omega_0 + \sigma\mu) z_1 + g_3 |z_1|^2 z_1$$

This equation is referred to as the Stuart–Landau equation. (The sign of g_3 is usually set to be negative.) It is very important to note that the Stuart–Landau equation is the normal form for this specific setup (the case where the system undergoes a Hopf bifurcation).

The transformation back to the standard basis is given by:

$$\begin{aligned}\mathbf{y} &= \mathbf{x} + \overline{h}(\mathbf{x}, p) \\ &= \mathbf{u}_1 z_1 + \overline{\mathbf{u}_1 z}_1 + \mathbf{h}_{001}\mu + (\mathbf{h}_{101} z_1 + \mathbf{h}_{011}\overline{z}_1)\mu + \mathbf{h}_{200} z_1^2 + \mathbf{h}_{110} z_1 \overline{z}_1 \\ &\quad + \mathbf{h}_{020}\overline{z}_1^2 + \mathbf{h}_{300} z_1^3 + \mathbf{h}_{210} z_1^2 \overline{z}_1 + \mathbf{h}_{120} z_1 \overline{z}_1^2 + \mathbf{h}_{030}\overline{z}_1^3 \qquad (3.50)\end{aligned}$$

Still, we need a concrete example of the Stuart–Landau equation.

The WH model

In the WH model we choose μ as the variable parameter, [7] hence, we can write the vector field as:

$$\begin{aligned}\dot{\mathbf{y}} &= Df(\mathbf{y}_s, \mu_s)(\mathbf{y} - \mathbf{y}_s) + N(\mathbf{y}, \mu) \\ \dot{\mu} &= 0\end{aligned}$$

where $\mathbf{y} = (x, y, z)^T$. At $\mu_c = (\sqrt{325} - 17)/6$ we can apply the results discussed above.

[7] Actually, this is not sensible since μ cannot vary without variations in β and γ.

To determine the coefficients, we must determine each term in the Taylor expansion of N. This is done by Taylor expanding the vector field, and isolate the terms (once again), as it will be illustrated in the following. Since μ is thought of as a dynamical variable, the vector field is also expanded with respect to this variable. Following the notation by Ipsen *et al*, the nonlinear terms in the Taylor expansion can be written as:

$$f_\mu \mu + f_{\mathbf{y}\mu}(\mathbf{y}, \mu) + \frac{1}{2} f_{\mathbf{yy}}(\mathbf{y}, \mathbf{y}) + \frac{1}{3!} f_{\mathbf{yyy}}(\mathbf{y}, \mathbf{y}, \mathbf{y}) + \dots \tag{3.51}$$

where f_μ denotes the derivative of f with respect to μ etc. When using this notation it is worth noting that f_μ is a vector with 3 components, $f_{\mathbf{y}\mu}$ is a 3×3 matrix $f_{\mathbf{yy}}$ is a $3 \times 3 \times 3$ matrix and so on.

Now, since we are interested in describing the dynamics of $\mathbf{y} \in W^c$ we can substitute equation 3.50 into 3.51:

$$f_\mu \mu + f_{\mathbf{y}\mu}(\mathbf{u}_1 z_1 + \overline{\mathbf{u}}_1 \overline{z}_1 + \mathbf{h}_{001}\mu + \dots, \mu) + \dots \tag{3.52}$$

It can be shown that $f_{\mathbf{y}\mu}, f_{\mathbf{yy}}, \dots$ are linear in their arguments, which means that equation 3.52 can be written as:

$$f_\mu \mu + f_{\mathbf{y}\mu}(\mathbf{u}_1 z_1, \mu) + f_{\mathbf{y}\mu}(\overline{\mathbf{u}}_1 \overline{z}_1, \mu) + f_{\mathbf{y}\mu}(\mathbf{h}_{001}\mu, \mu) + \dots$$

Let's consider the coefficient N_{001}: The only coefficient for μ in the Taylor expansion of f is f_μ, so

$$\mathbf{N}_{001} = f_\mu = \frac{\partial f}{\partial \mu} = \begin{pmatrix} -5.8 \\ 5.8 \\ 0 \end{pmatrix}$$

evaluated at fixed point. Now, this means that $\mathbf{h}_{001}$ is determined by solving the linear equation:

$$\mathbf{N}_{001} = J\mathbf{h}_{001}$$

that is, $\mathbf{h}_{001} = (-34.0, 0, 0)^T$. This is, of course, the most simple coefficient to be determined. Nevertheless, determining the rest of the terms in N follows this method, and instead of deriving each term explicitly I will simply list the results:

$$\begin{aligned} N_{101} &= f_{\mu\mathbf{y}}(\mathbf{u}_1) + f_{\mathbf{yy}}(\mathbf{u}_1, \mathbf{h}_{001}) \\ N_{200} &= \frac{1}{2} f_{\mathbf{yy}}(\mathbf{u}_1, \mathbf{u}_1) \quad , \quad N_{110} = f_{\mathbf{yy}}(\mathbf{u}_1, \overline{\mathbf{u}}_1) \\ N_{300} &= f_{\mathbf{yy}}(\mathbf{u}_1, \mathbf{h}_{200}) + \frac{1}{6} f_{\mathbf{yyy}}(\mathbf{u}_1, \mathbf{u}_1, \mathbf{u}_1) \\ N_{210} &= f_{\mathbf{yy}}(\mathbf{u}_1, \mathbf{h}_{210}) + f_{\mathbf{yy}}(\overline{\mathbf{u}}_1, \mathbf{h}_{200}) + \frac{1}{2} f_{\mathbf{yyy}}(\mathbf{u}_1, \mathbf{u}_1, \overline{\mathbf{u}}_1) \end{aligned}$$

Notice, that we need to calculate $\mathbf{h}_{001}$ before we are able to calculate $\mathbf{h}_{101}$ etc. The coefficients in the Stuart–Landau equation can now be explicitly written as:

$$\begin{aligned}
\sigma &= \mathbf{v}_1 g_{101} = \mathbf{v}_1 \mathbf{N}_{101} = \mathbf{v}_1 (f_{\mu\mathbf{y}}(\mathbf{u}_1) + f_{\mathbf{yy}}(\mathbf{u}_1, \mathbf{h}_{001})) && (3.53)\\
g_3 &= \mathbf{v}_1 g_{210} = \mathbf{v}_1 \mathbf{N}_{210} \\
&= \mathbf{v}_1 (f_{\mathbf{yy}}(\mathbf{u}_1, \mathbf{h}_{210}) + f_{\mathbf{yy}}(\overline{\mathbf{u}}_1, \mathbf{h}_{200}) + \frac{1}{2} f_{\mathbf{yyy}}(\mathbf{u}_1, \mathbf{u}_1, \overline{\mathbf{u}}_1)) && (3.54)
\end{aligned}$$

As it can be seen it takes a substantial amount of computations in order to derive the normal form. However, using the proper software the computations can be dealt with quit easily. In appendix B a Mathematica script file shows how it can be done. Running this script file the following results comes about:

$$\begin{aligned}
\mathbf{h}_{001} &= (-34.00, 0, 0,)^T \\
\mathbf{h}_{101} &= (0.26 - 8.53i, 0.41 + 1.04i, 1.53 + 1.34i)^T \\
\mathbf{h}_{200} &= (-2.45 - 0.68i, 0.16 + 0.30i, 0.71 + 0.44i)^T \\
\mathbf{h}_{110} &= (3.00, 0, 0.51)^T \\
\mathbf{h}_{300} &= (-0.76 - 1.85i, -0.12 + 0.23i, 0.21 + 0.68i)^T \\
\mathbf{h}_{210} &= (0.26 - 8.54i, 0.42 + 1.04i, 1.53 + 1.34i)^T
\end{aligned}$$

and the coefficients in the Stuart–Landau equation:

$$\sigma = -0.01 - 0.06i \quad \text{and} \quad g_3 = -0.47 + 0.49i$$

Now , it remains to justify the purpose of the derivation of the Stuart–Landau equation. This will be done in the next chapter, especially in section 4.1, where the Stuart–Landau coefficients are computated for the glycolysis model.•

To sum up the approach by Crawford:

1. Reduction: Restrict the dynamics to the center manifold. This is done by representing W^c as a graph, where the dependent variables can be written as a function of the independent variables, and thereby is the number of variables reduced. In section 3.2.1 it was shown how W^c can be parameterized in the standard basis (or in any other relevant basis). This is to be used when applying the approach by Ipsen *et al.*

2. Normalization: By introducing a set of nonlinear transformations, the Taylor expansion of the nonlinear part of the vector field can be reduced significantly. In section 3.3 a specific normal form for the case $\dim(E^c) = 2$ and $\dim(E^s) = 1$ was derived, using the method described by Ipsen *et al.* This could be expanded to any case where $\dim(E^c) = 2$ and $\dim(E^s) = n - 2$.

3. Suspending the vector field: Using the setup discussed above and by treating the variable parameter (if such exists) as an independent dynamical variable the normal form resulted in the Stuart–Landau equation. The Stuart–Landau equation is equivalent to the unfolded normal form. This means that the Stuart–Landau equation describes all possible qualitative behavior of the system around the bifurcation point. For a rigours treatment of unfolding see [14] or [9]. This also explains the terminology used on page 26.

4. Study the unfolded normal form (Stuart–Landau equation): Vary the parameter, and study the dynamics of the Stuart–Landau equation.

This last item will be dealt with in the following chapter.

Chapter 4

Applying the Stuart–Landau equation to the glycolysis model

The main objective is to compare the original glycolysis model, proposed by Danø *et al*, with the normal form approximation. To be able to do this the coordinates from the normal form can be transformed back to the original space, which is done via a nonlinear transformation as discussed in chapter 3. In this chapter the amplitude, the period and the mean value are compared for the original model and the transformed normal form coordinates.

But first the results from the normal form will be discussed. This, of course, adds very little new to the understanding of the dynamics near the fixed point, since the parameters in the model are fitted to show a specific dynamical behavior. However, some important features will be pointed out and discussed, since they will be used when comparing the original model with the normal form approximation.

4.1 Results from the Stuart–Landau equation

In their experiments Danø, Hynne, and Sørensen varied the inflow of glucose in the reactor tank, which corresponds to varying the extra cellular glucose concentration. They found that when the flow of glucose is increased the stable fixed point becomes unstable, and oscillations emerge. The particular flow rate, where the fixed point changes stability, corresponds to an extra cellular glucose concentration of $13.62mM$ in the model.

In table 4.1 all the eigenvalues for the Jacobian, at [Glc$_{ex}$]=13.62 mM are listed.

λ_j		λ_j	
1	-179441.671	2	-7424.763
3	-1721.860	4	-792.471
5	-242.416	6	-133.138
7	-70.185	8	-24.662
9	-7.771	10	-3.819
11	-3.454	12	-0.224+0.022i
13	-0.224-0.022i	14	0.000+9.209i
15	0.000-9.209i		

Table 4.1: Eigenvalues for the model at the fixed point, and at the bifurcation point [Glc$_{ex}$]=13.62 mM.

At this point two complex conjugated eigenvalues have zero real part, and the rest of the eigenvalues have negative real part. This is analogue to the situation in chapter 3, since $\dim(E^c) = 2$ and $\dim(E^s) = 13$, thus we may describe the dynamics via the Stuart–Landau equation. Setting $z_1 = z$ in 3.50:

$$\dot{z} \quad = \quad (i\omega_0 + \sigma\mu)z + g_3|z|^2 z \tag{4.1}$$

To discuss the flow generated by 4.1 it is split into two equations, one describing the real part and the other describing the imaginary part. Set $z = z_1 + iz_2, \sigma = \sigma_1 + i\sigma_2$ and $g_3 = g_1 + ig_2$, then:

$$\begin{aligned} \dot{z}_1 &= g_1 z_1^3 - g_2 z_1^2 z_2 + g_1 z_1 z_2^2 - g_2 z_2^3 + z_1\sigma_1\mu - z_2\omega_0 - z_2\mu\sigma_2 \quad (4.2) \\ \dot{z}_2 &= g_2 z_1^3 + g_1 z_1^2 z_2 + g_2 z_1 z_2^2 + g_1 z_2^3 + z_2\sigma_1\mu + z_1\omega_0 + z_1\mu\sigma_2 \quad (4.3) \end{aligned}$$

Since the flow described by equation 4.2 and 4.3 have the same qualitative behavior in a neighborhood of the fixed point, as the flow generated by original dynamical system, the attention can be restricted to these two. Before calculating the coefficients in equation 4.1, some general features of the Stuart–Landau equation will be derived.

Evaluating the Jacobian at the fixed point $z_1 = z_2 = 0$:

$$J = \begin{pmatrix} \sigma_1\mu & -(\omega_0 + \sigma_2\mu) \\ \omega_0 + \sigma_2\mu & \sigma_1\mu \end{pmatrix} \tag{4.4}$$

which means that the eigenvalues for are: $\lambda_{1,2} = \sigma_1\mu \pm i(\omega_0 + \sigma_2\mu)$, so σ_1 can be written as:

$$\sigma_1 = \left.\frac{d\mathrm{Re}(\lambda_{1,2})}{d\mu}\right|_{\mu=0}$$

This means that if $\sigma_1 > 0$ for increasing μ then the real part of the eigenvalue goes from being negative to positive at the bifurcation point (since $\mathrm{Re}(\lambda_{1,2}) = 0$ at $\mu = 0$). It follows that the fixed point is asymptotically stable for $\mu < 0$ and unstable for $\mu > 0$. On the other hand, if σ_1 is negative the real part of λ_1 goes from being positive to negative. This means that the fixed point is unstable for $\mu < 0$ but stable for $\mu > 0$.

All this is a linear analysis. However, the linear analysis does not provide the information that can enable a conclusion concerning the stability of the limit cycle. To establish these informations equation 4.2 and 4.3, is expressed in polar coordinates: $z = re^{i\theta}$ (r and θ are function of time), where:

$$r^2 = z_1^2 + z_2^2 \quad \text{and} \quad \theta = \tan^{-1}\left(\frac{z_2}{z_1}\right)$$

for $z_1 \neq 0$. Differentiating both sides with respect to t:

$$\begin{aligned} 2r\dot{r} &= 2z_1\dot{z}_1 + 2z_2\dot{z}_2 \\ \dot{r} &= \frac{z_1\dot{z}_1 + z_2\dot{z}_2}{r} \end{aligned} \tag{4.5}$$

and

$$\begin{aligned} \dot{\theta} &= \frac{1}{1 + \left(\frac{z_2}{z_1}\right)} \frac{d}{dt}\left(\frac{z_2}{z_1}\right) \\ &= \frac{z_2\dot{z}_1 - \dot{z}_2 z_1}{r^2} \end{aligned} \tag{4.6}$$

Substituting equation 4.2 and 4.3 into 4.5 and 4.6 one obtains:

$$\dot{r} = \mu\sigma_1 r + g_1 r^3 \tag{4.7}$$

$$\dot{\theta} = \omega_0 + \mu\sigma_2 + g_2 r^2 \tag{4.8}$$

Equation 4.7 is very informative when evaluating the stability of the limit cycle: We are only interested in $r > 0$ since a negative radius is not physically meaningful. Figure 4.1 shows two plots of equation 4.7, one for $g_1 < 0$, $\mu\sigma_1 > 0$ and one for $g_1 > 0$, $\mu\sigma_1 < 0$. The curves crosses $\dot{r} = 0$ for:

$$r = \sqrt{-\frac{\mu\sigma_1}{g_1}} \quad \text{and} \quad r = 0 \tag{4.9}$$

where $\mu\sigma_1/g_1 < 0$, because the radius must be real. Now, for

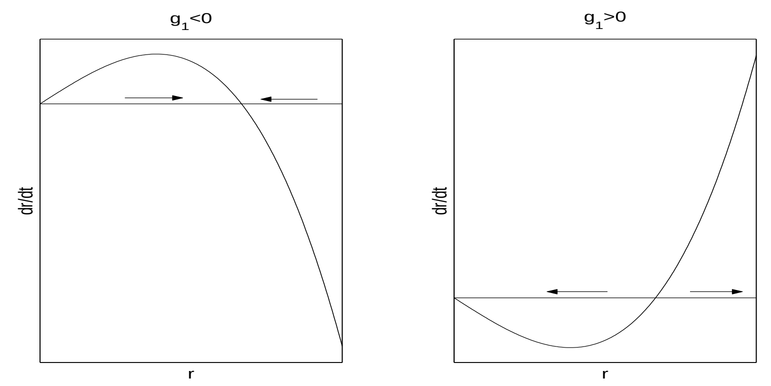

Figure 4.1: $\dot{r}$ vs. r for $r > 0$. In the left figure $\mu\sigma_1 > 0$ and in the right figure $\mu\sigma_1 < 0$.

$g_1 < 0$ In the interval $]0 : -(\mu\sigma_1/g_1)^{\frac{1}{2}}[$, $\dot{r} > 0$ which means that r increases with respect to time (illustrated by arrow). At $r > -(\mu\sigma_1/g_1)^{\frac{1}{2}}$, $\dot{r} < 0$ and r decreases. This means that for $g_1 < 0$ the limit cycle is stable and the radius is given by 4.9, and will be denoted r_{lim}.

$g_1 > 0$ In this case $\dot{r} < 0$ for $r \in \,]0 : -(\mu\sigma_1/g_1)^{\frac{1}{2}}[$, that is, r decreases in time. When $r > -(\mu g\sigma_1/g_1)^{\frac{1}{2}}$, r grows, hence the limit cycle is unstable.

$g_1 = 0$ If $g_1 = 0$ the stability of the limit cycle cannot be concluded, and higher order terms must be considered in the normal form. (This will be fifth order terms, due to the resonance conditions.)

Equation 4.9 predicts the radius of the limit cycle as being a function of the distance of the bifurcations parameter to the bifurcation point, that is, the radius of the limit cycle squared is proportional to μ. (This is also what Danø, Hynne and Sørensen observed in their experiments, see figure 2.2.)

Also equation 4.8 is useful, because it predicts the frequency of the limit cycle, ω_{lim}. On the limit cycle equation 4.8 can be written as:

$$\begin{aligned} \dot{\theta}_{lim} &= \omega_0 + \mu\sigma_2 + g_2 r_{lim}^2 \\ &= \omega_0 + \mu\left(\sigma_2 - \frac{g_2\sigma_1}{g_1}\right) \end{aligned}$$

so

$$\theta_{lim} = \left(\omega_0 + \mu\left(\sigma_2 + \frac{g_2\sigma 1}{g_1}\right)\right)t + \theta_0$$

which means that:

$$\omega_{lim} = \omega_0 + \mu \left(\sigma_2 - \frac{g_2 \sigma_1}{g_1} \right) \tag{4.10}$$

i.e, the frequency is proportional to the bifurcation parameter.

We are now able to discuss the stability of the fixed point around the bifurcation point, as well as to determine the stability of the emerging limit cycle of the glycolysis model. The only thing left to do is to determine the coefficients in the Stuart–Landau equation. To do this recall equations 3.53 and 3.54:

$$\begin{aligned}
\sigma &= \mathbf{v}_1 g_{101} = \mathbf{v}_1 (f_{\mu \mathbf{y}}(\mathbf{u}) + f_{\mathbf{yy}}(\mathbf{u}, \mathbf{h}_{001})) \\
g_3 &= \mathbf{v}_1 g_{210} = \mathbf{v}_1 (f_{\mathbf{yy}}(\mathbf{u}, \mathbf{h}_{210}) + f_{\mathbf{yy}}(\overline{\mathbf{u}}_1, \mathbf{h}_{200}) + \frac{1}{2} f_{\mathbf{yyy}}(\mathbf{u}, \mathbf{u}, \overline{\mathbf{u}}))
\end{aligned}$$

The Stuart–Landau coefficients can be calculated via the Mathematica script file given in B, by implementing the vector field described in section 2.2. The coefficients are listed in table 4.2. When varying μ around the bifurcation

ω_0	9.2082
σ	0.0261+0.0181i
g_3	-12.3223 - 22.0242i

Table 4.2: The coefficients in the Stuart–Landau equation for the glycolysis model.

point the following can be concluded:

$\mu < 0$ Because g_1 and σ_1 have opposite signs, no limit cycle is defined, and since $\sigma_1 > 0$ the fixed point is asymptotic stable. The trajectories spirals counter clock wise towards the fixed point due to the sign of ω_0.

$\mu = 0$ The trajectories still spirals towards the fixed point because $g_1 < 0$. The fixed point may be thought off as a stable limit cycle with $r_{lim} = 0$.

$\mu > 0$ Now the fixed point changes from being stable to unstable, and a stable limit cycle emerge, because $g_1 < 0$.

This is defined as a supercritical Hopf bifurcation. If $g_1 > 0$ (if the limit cycle is unstable) the system is said to undergo a subcritical Hopf bifurcation. Figure 4.2 is a phase plot of the Stuart–Landau equation for $\mu < 0, \mu = 0$

and $\mu > 0$. As it is illustrated, the fixed point, $(0, 0)$, is asymptotic stable for $\mu < 0$ and stable $\mu = 0$. But it is unstable for $\mu > 0$. This supports the results given above. The normal form hereby confirm the behavior of the

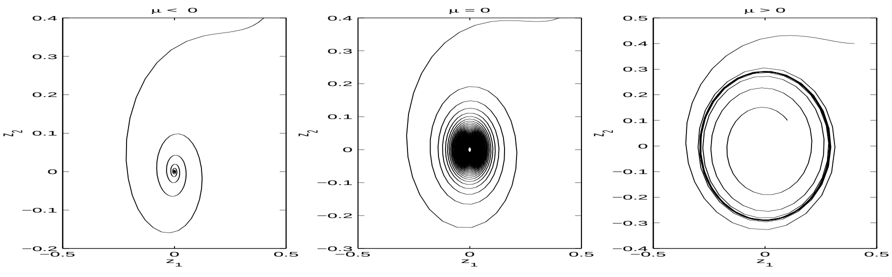

Figure 4.2: A phase plot of the dynamical vector field given in 4.2 and 4.3. The three figures are for $\mu < 0, \mu = 0$ and $\mu > 0$.The trajectories spirals counter clock wise. It is worth noting that the trajectories for $\mu = 0$, will eventually reach the origin.

original model. The normal form also predicts the radius of the limit cycle as well as the frequency (equations 4.9 and 4.10). The normal form description is a local description, and natural question is how well this description is, in a neighborhood of the fixed point. The next section is concerned with this question.

However, before doing this, I will finish this section of by side leap, since I still owe the reader the final treatment of the WH model:

The WH model

Recall from page 47 that $\mathrm{Re}(\lambda_{1,2}) = \sigma_1 < 0$, $\mathrm{Re}(g_3) = g_1 < 0$ and that $\omega_0 > 0$. Following the above:

$\mu < 0$ Since σ_1 and g_1 are both negative (as well as μ), a stable limit cycle exists. Since $\sigma_1 < 0$ the fixed pint is unstable for $\mu < 0$. The radius and frequency are given by 4.9 and 4.10. The trajectories spirals counter clock wise.

$\mu = 0$ The fixed point now becomes stable.

$\mu > 0$ No limit cycle are defined, and since $\sigma_1 < 0$ the fixed point is stable for $\mu > 0$.

As in case with the glycolysis model, this is also a supercritical Hopf bifurcation. That is, if μ is decreasing, the stable fixed point becomes unstable, and a stable limit cycle arises. This can be illustrated by replacing $<$ with $>$ and visa versa in figure 4.2. •

4.2 Comparison

As mentioned a few times: The comparison is done in the concentration space, that is, the coordinates from the normal form is transformed back to this space. This is done via equation 3.50:

$$\begin{aligned}\mathbf{y} &= \mathbf{u}z + \overline{\mathbf{u}z} + \mathbf{h}_{001}\mu + (\mathbf{h}_{101}z + \mathbf{h}_{011}\overline{z})\mu + \mathbf{h}_{200}z^2 + \mathbf{h}_{110}z\overline{z} \\ &\quad + \mathbf{h}_{020}\overline{z}^2 + \mathbf{h}_{300}z^3 + \mathbf{h}_{210}z^2\overline{z} + \mathbf{h}_{120}z\overline{z}^2 + \mathbf{h}_{030}\overline{z}^3 \end{aligned} \tag{4.11}$$

where $\mathbf{u} = \mathbf{u}_1$ and $z = z_1$. The vector $\mathbf{y}$ is a point in the 15 dimensional concentration space (i.e. $\mathbf{y}$ is a vector with 15 components). This means that the eigenvectors and all the coefficients in h are also vectors with 15 components. Listing all these vectors is therefore properly not very informative, so I simply refer to appendix B, once again, which shows how the calculations can be performed. The coordinates in $\mathbf{y}$ will be referred to as TNFC (Transformed Normal Form Coordinates). To compare the TNFC with the original model, the following approach was used:

- First the normal form was integrated using the lsode–integrator (in Octave). This integrator determines whether the differential equation system is stiff, and what kind of algorithm to use. To test the integrator a fourth and fifth order Runge–Kutta–Fehlberg and a stiff solver were applied, showing the same results. The integration was initialized close to the fixed point (origo)

- The data from the integration were transformed back to the concentration space using equation 4.11.

- The original system was integrated to be able to make the comparison. The initial condition was set to be the first dataset from the TNFC.

- This was done varying the extra cellular glucose concentration from 13.62 mM (the bifurcation point) to 17.12 mM with intervals of 0.1 mM. The intervals where then increased to 0.5mM for the glucose concentration 17.12 mM to 19.62 mM. This corresponds to $\mu =$ 13.62mM -[Glc$_{ex}$].

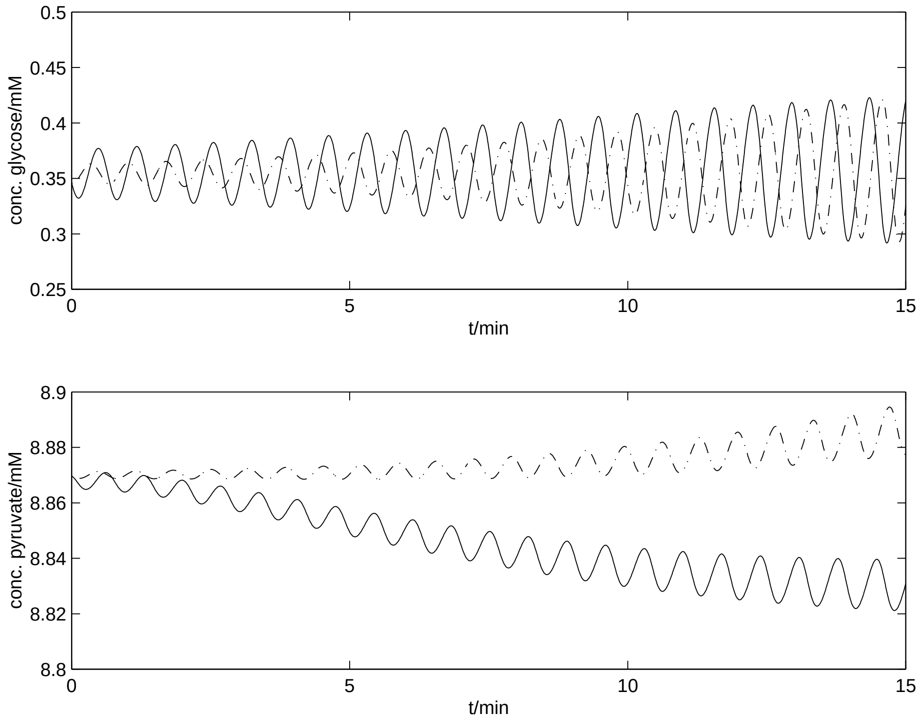

Figure 4.3: The figures show the concentration vs. time. The dotted lines are the TNFC. The extra cellular glucose concentration is 19.62 mM ($\mu = 6$).

In figure 4.3 the intra cellular glucose and pyruvate concentration vs. time for the original model and the TNFC are plotted. At first sight it seems that the TNFC do not approximate the different species equally well. This is, however, not the case. The absolute error is larger for the puryvate concentration than for glucose (since the mean value for pyruvate is around 8.82 mM, and 0.35 mM for glucose), but the relative error is the same for all species. This means that when comparing the TNFC with the original model, it is enough to compare the data from one single species. Thus, I have chosen to compare the TNFC and data form the original model via the intra cellular glucose concentration.

It is seen that the amplitude and the period is not in good agreement to begin with, but as time goes the amplitude and the period slowly synchronize. This is due to the transients in the original model, which is not included in the normal form approximation. Therefore the comparison of the data from the original model and the TNFC should be carried out when these stable transients have died out. By visual inspection this was the case when the integration had lasted for about 50–800 minutes, depending on the distance to the bifurcation point. To be sure the comparison of the original model and the TNFC was made for the time interval [300:400] min. for $6 \geq \mu \geq 0.4$, and [900:1000] min. for $0.4 > \mu > 0$. Also, to minimize the step length a cubic spline interpolation routine with a step size $1 \cdot 10^{-5}$ min. was applied on the data from the integration..

Using these data sets the amplitudes, the periods and the mean values where compared for the two descriptions.

4.2.1 Comparing the amplitudes

The amplitude was simply determined by finding the differences in the maximum and minimum of the oscillations, and divide it by two. This method do not provide a good error estimation. In figure 4.4 the amplitude is plotted as a function of the bifurcation parameter, μ. The amplitude has been forced to zero for $\mu = 0$. The qualitative behavior has already been pre-

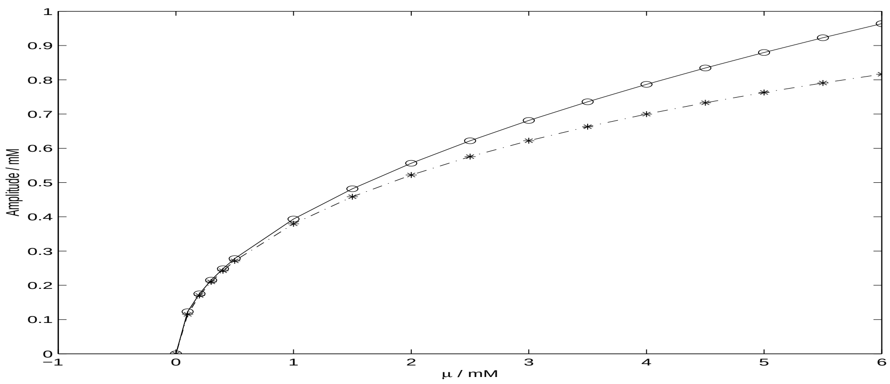

Figure 4.4: The amplitudes of the TNFC and the original model (dotted line) as functions of the bifurcation parameter. The extra cellular glucose concentration is 13.62 mM + μ.

dicted by the normal form, since the radius corresponds to the amplitudes of the oscillations. According to equation 4.9 is r_{lim} proportional to $\sqrt{\mu}$. This is also the case. (One can check this simply by plotting the amplitude squared vs. μ.)

Since $r \propto \sqrt{\mu}$, $dr/d\mu = k/2\sqrt{\mu}$ which means that at $\mu = 0$ the tangency is vertical. This might not be clear from the figure.

It is seen that the amplitude of the TNFC is larger than the amplitude of the original model. This is due to the higher order terms of the original model. At $\mu = 6$ the amplitude of the TNFC is around 18 % bigger than the amplitude of the original model. This linearly decreases as μ decreases, ending with a zero difference.

4.2.2 Comparing the periods

To determine the period the minima of the oscillations where determined (in the intervals described above). A new data set around this minima was constructed by adding data about two thirds of a period to each side. Then the time difference between the two maxima surrounding the minimum is simply the period. The maximum error for this method is the step length (i.e. $1 \cdot 10^{-5}$ min.).

It is actually possible to compare the results from the normal form directly with the original model because the period predicted by the normal form is the same as the period for the TNFC. This means that since the frequency of the oscillations is determined by equation 4.10, the period is also determined since $T_{lim} = 2\pi/\omega_{lim}$. That is:

$$T_{lim}^{-1} = \frac{\omega_0}{2\pi} + \left(\frac{\sigma_2}{2\pi} - \frac{g_2\sigma_1}{2\pi g_1} \right) \mu \tag{4.12}$$

If $1/T_{lim}$ (for the TNFC) is plotted against the bifurcation parameter a straight line with the slope $\sigma_2/2\pi - g_2\sigma_1/2\pi g_1$ crossing the y-axis at $\omega_0/2\pi$ should appear. In figure 4.5 this done showing the line predicted by the normal form. At $\mu = 0$ the curve for the TNFC is tangency to the curve of the original model. For $\mu = 6$ the period for the original model is only around 1% larger than the period for the TNFC.

4.2.3 Comparing the mean value

Finally the mean value was compared. Once the period is determined the mean value is given by:

$$m = \frac{1}{T} \int_0^T x(t) dt$$

where $x(t)$ is the dynamical variable. The integrator used was a simple Simpson integrator. Also in this case the error estimate is not readily obtainable.

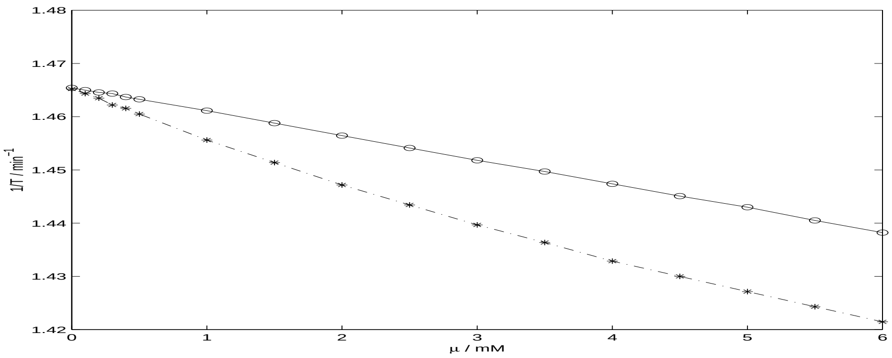

Figure 4.5: T_{lim}^{-1} vs. μ. The dotted line is the original model. As expected the linear dependence. The predicted slope is -0.045, which is the case for the full line. The lines crosses, as predicted by the normal form, at $\omega_0/2\pi$.

In figure 4.6 the mean value for the original model and for the TNFC is plotted. It is seen that the mean value for the TNFC is linear dependent on

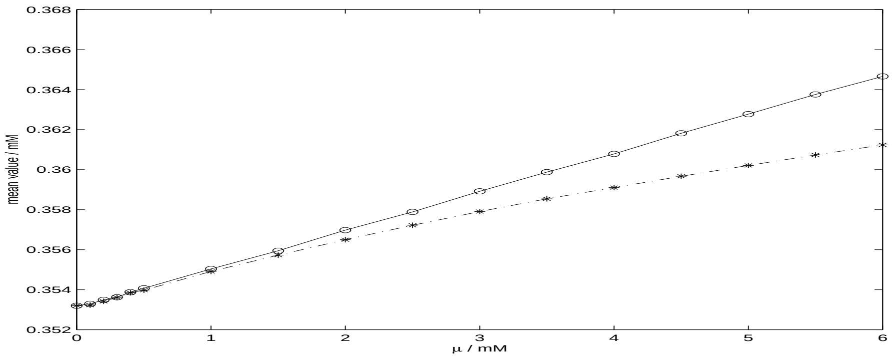

Figure 4.6: The mean value of original model, (dotted line), and of the TFNC.

the bifurcations parameter. The mean value predicted by the TNFC is only 0.4 % bigger than the actual mean value of the glycolysis model at $\mu = 6$.

Chapter 5

Discussion and applications

5.1 Discussion

Nonlinear studies of biological and chemical systems undergoing bifurcations is of great importance, since it may provide new information about the underlying mechanisms. The glycolysis model proposed by Danø and Hynne is an example of a model that is based on such nonlinear behavior found in their experiments. The foundation of the model is chemical kinetics, and it describes the variations of 18 different metabolites with respect to time. (This was discussed in chapter 2).

Around the bifurcation point the dynamics can be described in a lower dimensional space, in that the attention can be restricted to the center manifold. Not only the number of dimensions can be reduced, also the nonlinear part of the differential equation system can be reduced by introducing a set of nonlinear coordinates transformations. As in the linear case this brings about the simplest possible form – the normal form. However, it also twist out all the informative features about the system.

For a quantitative study and comparison (for example with experiments), one must also determine the transformation from the lower dimension space to the relevant physical space. (This is typically the concentration space for the chemist.) In [5] a systematic way of doing this is described, and in chapter 3 I have tried to exemplify this approach in the case where the system undergoes a Hopf bifurcation. It is my hope that this will aid other students to understand the method, however, it is not meant to be a fulfilling description.

Glycolysis is an example of a system that is believed to undergo a Hopf bifurcation. One purpose of this thesis has been to describe the glycolysis model via the Stuart–Landau equation. This is to be applied when coupling phenomena are to be investigated. Describing the glycolysis model via the Stuart–Landau equation, the local qualitative features are captured, but quantitatively the dynamics are approximated. Before coupling the cells, the natural question arises: How well is each cell approximated? To answer this question, the normal form coordinates can be transformed back to the physical space via the transformation described above.

In order to answer the question I have chosen to compare 1) the amplitudes, 2) the periods, and 3) the mean values generated by the original model and the Stuart-Landau equation. This was done by varying the bifurcation parameter μ, i.e. the extra cellular glucose concentration, in intervals. The results are given in figures 4.4, 4.5, and 4.6, and are summarized in table 5.1. A general feature is that the normal form (or rather its coordinates in

Dist. from bif.point (%)	Dif. in ampl. (%)	Dif. in period. (%)	Dif. in mean val. (%)
0.0	0.0	0.0	0.0
7.3	3.6	0.4	0.0
14.7	6.6	0.6	0.1
22.0	9.5	0.8	0.3
29.3	12.4	1.0	0.5
36.7	15.3	1.1	0.7
44.0	18.1	1.2	0.9

Table 5.1: Table showing the difference in amplitudes, periods and mean value.

the original basis) predicts larger values than the model for $\mu \neq 0$. This is due to the higher order terms in the model, which is not included in the Stuart–Landau description. The reason why the amplitude is described less accurately than the period and the mean value is properly also due to the nature of the higher order nonlinearities present in the model.

The error estimates in table 5.1 is for this particular system, and is not to be adopted to other systems. That is, the interval where the Stuart–Landau equation applies varies from system to system. For example, consider the result from [4] where the normal form approximation is discussed for the Oregonator model, which is yet another chemical model that undergoes a supercritical Hopf bifurcation. When the distance from the bifurcation point is 30 % the difference in amplitude is around 14.3 %. In the case with the glycolysis model, the difference is $\sim$ 12.5 %.

Also, it must be stressed that table 5.1 is the relative error for a single cell. That is, coupling a large number of cells together will result in a new system and the table is no longer valid.

Higher order terms in the normal form can be considered, which will be fifth order terms due to the resonant conditions. This may reveal new qualitative features of the system. One can be convinced about this fact, if the normal form is transformed into polar form like described on page 52:

$$\dot{r} = \mu\sigma_1 r + g_1 r^3 + g' r^5 \tag{5.1}$$

where g' is a real number. Equation 5.1 has one, two or three solutions for $r \geq 0$ depending on the coefficients. The case where $\mu\sigma_1 > 0$, $g_1 < -2\sqrt{\mu\sigma_1 g'}$, and $g' > 0$ is shown in figure 5.1. Here it is seen that the

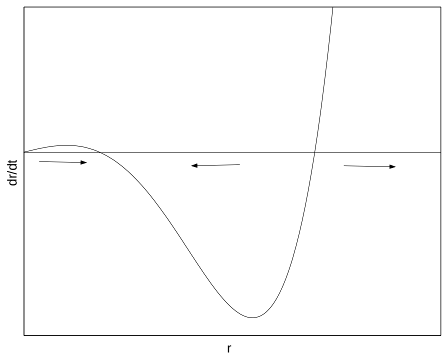

Figure 5.1: Figure showing equation 5.1 for $\mu\sigma_1 > 0$, $g_1 < -2\sqrt{\mu\sigma_1 g'}$ and $g' > 0$.

fixed point is unstable, and a stable limit cycle exists (supercritical Hopf bifurcation). This is also captured by the Stuart–Landau equation, but as it can be seen an unstable limit cycle also exists, which cannot be concluded by the Stuart–Landau approximation. In this way it is illustrated that by considering higher order terms, other features can be found[1]. It should also be noted that the higher order nonlinearities in the model may steam from nonlocal phenomena, and including higher order terms in the normal form will not reveal any new informations about the dynamics. (Since this is a local expansion.)

Also, if higher order terms the bifurcation parameter is included in the normal form, it would likely approximate the quantitative dynamics better.

[1] Computing g' , however, will take some effort.

I have not seen this discussed anywhere so it should only be thought of as a loose idea.

5.2 Application: Coupling

I will finish off by discussing how the Stuart–Landau equation can be used to study the coupling phenomena. I will only illustrate this numerically, and follow the method described by Matthews *et al.* in [7] closely.

In the previous chapters it has been shown how glycolysis can be described by Stuart–Landau equation. That is, the dynamics of the j´th cell can be described as:

$$\dot{z}_j = (i\omega_0 + \sigma\mu)z_j + g_3 z_j|z_j|^2$$

ω_0, σ, and g_3 are given in table 4.2. As a first approach it is assumed that the cells do not oscillate with equal frequency. To express this explicitly we can write:

$$\dot{z}_j = (i\omega_{0,j} + \sigma\mu)z_j + g_3 z_j|z_j|^2$$

where $\omega_{0,j}$ denotes the frequency of the j'th cell. (This is called the natural frequency of the j'th cell.) Now, defining the centroid as:

$$\overline{z} = \frac{1}{N}\sum_{i=1}^{N} z_i$$

where N is the number of cells in the population, we can make a linear all–to–all coupling by letting each cell couple to the centroid, that is:

$$\dot{z}_j = (i\omega_{0,j} + \sigma\mu)z_j + g_3 z_j|z_j|^2 + K(\overline{z} - z_j) \tag{5.2}$$

K denotes the coupling strength. This is straight forward, however, not very biochemically meaningful. Coupling the cells in this manner means that all metabolites are diffusing in and out of the cell equally well. This is of course not the case, since only EtOH, glucose, glycerol and acetaldehyd, is believed to do so.

Now, the frequencies are thought to be picked randomly from a normal distribution with the mean value $\omega_0 = 9.2\ rad/min$, and the standard derivation $\hat{\sigma}$. For convenience Matthews *et al.* introduce the parameter, Δ (see [7, p.295]) to represent the width of the normal distribution. In the case where the frequencies are normal distributed, $\Delta \propto \hat{\sigma}$. By varying the coupling strength, K, and the standard derivation, expressed by Δ, different coupling phenomena can be observed, as it will be described belove.

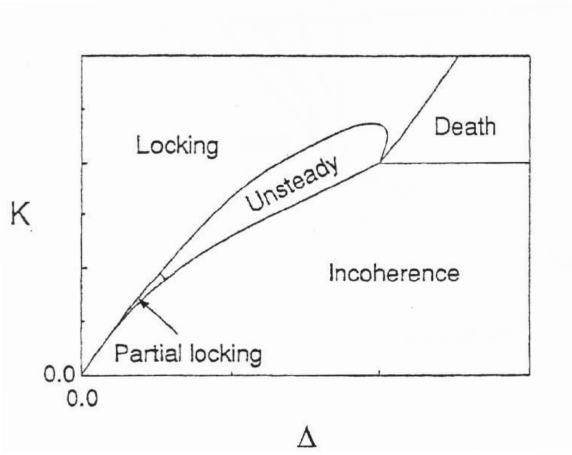

Figure 5.2: Phase diagram illustrating the regions in which the oscillators locks, are incoherent or where the amplitudes dies out. Also there exists a small region of unsteady phenomena (such as chaos), and a small region of partial locking. From [7].

Matthews *et al.* divide the Δ, K plan into three major areas, (see also figure 5.2):

- Incoherence: Incoherence is the state of the system where the oscillators (the cells) oscillate in their natural frequency, that is, the oscillations do not synchronize.
- Locking: If K is large compared to Δ locking occurs. In this state the oscillators couple, and their frequencies locks. (Synchronizes)
- Death: For K and Δ sufficiently large, the amplitudes of each oscillator dies out, and the system collapses to the fixed point (the origin).

In appendix C, figure C.1 – C.3 these three different states are illustrated by simulating 500 cells via Matlab – each cell is described by equation 5.2, and are represented as a point $(\mathrm{Re}(\overline{z}_j), \mathrm{Im}(\overline{z}_j))$ in the complex plane. For all the simulation $\mu = 6$.

Another way to illustrate the phenomena is to monitor the time course of the magnitude of the centroid: $r = (\mathrm{Re}(\overline{z})^2 + \mathrm{Im}(\overline{z})^2)^{\frac{1}{2}}$. This is done in figure 5.3. In figure 5.3 a) it can be seen that r fluctuates. One should suspect that r simply was zero. This is not the case because each cell has its

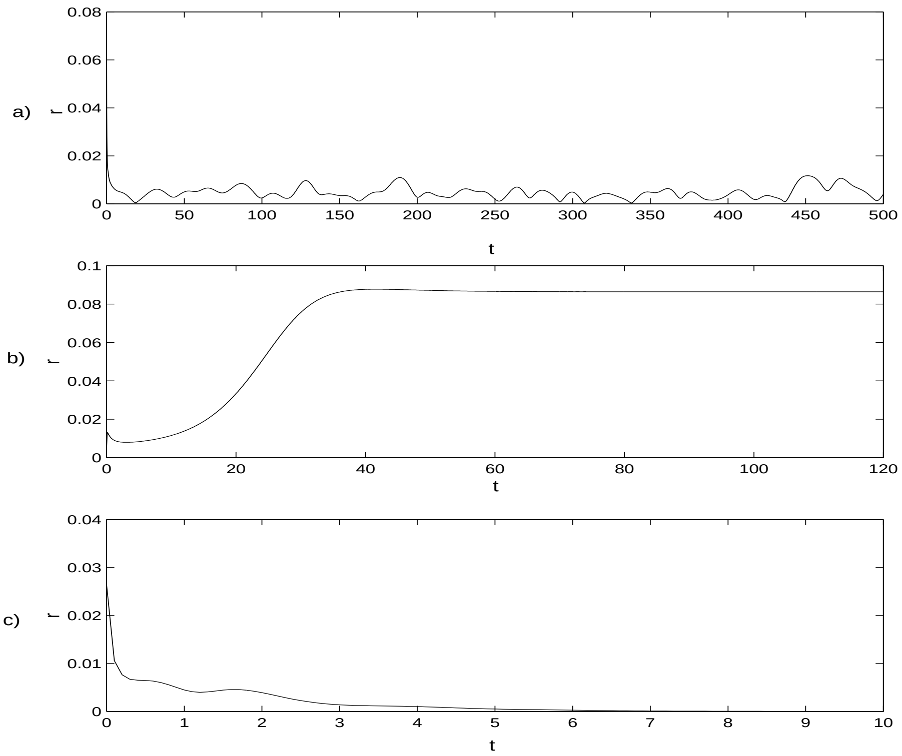

Figure 5.3: The time course of the magnitude of the centroid. a) Incoherence. b) Frequency locking. c) Amplitude death.

own natural frequency, and the cells are rarely uniformly distributed around the origin. Only for $N \to \infty$ one can expect the fluctuations to be zero. Figure 5.3 c) and b) shows the suspected: At frequency locking, the cells cluster (see figure C.2 in appendix C) and thereby "pulling" the centroid away from the origin. Also, it can be seen from figure b) that the distance to the origin is constant. Figure c) shows that for large K and Δ the system simply collapses into the stable fixed point (the origin).

I will finish off by showing the chaotic behavior that exists in the boundaries between the locked and incoherence state. Because of the statistical fluctuations discussed above, this state is not evident simply by looking at the time course of the magnitude of the centroid. However, if one also consider the cells represented in the complex plane, the chaotic state should be clear. In figure 5.4 r is plotted with respect to time. The dynamics of the cells are given in figure C.4 in appendix C. Here the chaotic behavior becomes apparent. In this chaotic state the frequencies of the cells do not

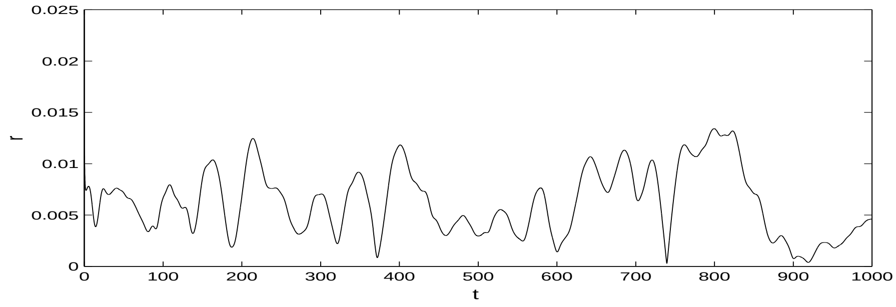

Figure 5.4: The time course of the the magnitude of the centroid in the chaotic state. Note that simply by considering this figure one cannot conclude whether this is a chaotic or a incoherent state.

lock, they do not fall into origin, or simply move around in plane with their natural frequencies, but rather move around in a random manner.

This, of course, do not describe the phase diagram in figure 5.2 very thoroughly, however, it illustrates the many different types of dynamical phenomena that can be examined. Also, one can vary the other parameters in the Stuart–Landau equation, or apply another type of coupling etc. In recent years analytical studies of these phenomena has been carried out in hope to get a deeper understanding of these coupling phenomena, that is believed to be responsible for the ordered structures seen in many places in biology.

Appendix A

Differential equations

The rate equations for the mechanism proposed by Danø and Hynne. By courtesy of Danø.

$$1: \quad v_+^1 = \frac{V_{1mf}\frac{[\mathrm{Glc}_{ex}]}{K_{1\mathrm{Glc}}}}{1+\frac{[\mathrm{Glc}_{ex}]}{K_{1\mathrm{Glc}}}+\frac{P_1\frac{[\mathrm{Glc}_{ex}]}{K_{1\mathrm{Glc}}}+1}{P_1\frac{[\mathrm{Glc}]}{K_{1\mathrm{Glc}}}+1}\left(1+\frac{[\mathrm{Glc}]}{K_{1\mathrm{Glc}}}+\frac{[\mathrm{G6P}]}{K_{1\mathrm{IG6P}}}+\frac{[\mathrm{Glc}][\mathrm{G6P}]}{K_{1\mathrm{Glc}}K_{1\mathrm{IIG6P}}}\right)}$$

$$v_-^1 = \frac{V_{1mr}\frac{[\mathrm{Glc}]}{K_{1\mathrm{Glc}}}}{1+\frac{[\mathrm{Glc}]}{K_{1\mathrm{Glc}}}+\frac{P_1\frac{[\mathrm{Glc}]}{K_{1\mathrm{Glc}}}+1}{P_1\frac{[\mathrm{Glc}_{ex}]}{K_{1\mathrm{Glc}}}+1}\left(1+\frac{[\mathrm{Glc}_{ex}]}{K_{1\mathrm{Glc}}}+\frac{[\mathrm{G6P}]}{K_{1\mathrm{IG6P}}}+\frac{[\mathrm{Glc}][\mathrm{G6P}]}{K_{1\mathrm{Glc}}K_{1\mathrm{IIG6P}}}\right)}$$

$$2: \quad v_+^2 = \frac{V_{2m}[\mathrm{ATP}][\mathrm{Glc}]}{K_{2\mathrm{DGlc}}K_{2\mathrm{ATP}}+K_{2\mathrm{Glc}}[\mathrm{ATP}]+K_{2\mathrm{ATP}}[\mathrm{Glc}]+[\mathrm{Glc}][\mathrm{ATP}]}$$

$$3: \quad v_+^3 = \frac{V_{3m}[\mathrm{G6P}]}{K_{3\mathrm{G6P}}\left(1+\frac{[\mathrm{F6P}]}{K_{3\mathrm{F6P}}}\right)+[\mathrm{G6P}]}$$

$$v_-^3 = \frac{V_{3m}\frac{[\mathrm{F6P}]}{K_{3\mathrm{eq}}}}{K_{3\mathrm{G6P}}\left(1+\frac{[\mathrm{F6P}]}{K_{3\mathrm{F6P}}}\right)+[\mathrm{G6P}]}$$

$$4: \quad v_+^4 = \frac{V_{4m}[\mathrm{F6P}]^2[\mathrm{ATP}]}{\left(K_4\left(1+\kappa_4\frac{[\mathrm{ATP}]^2}{[\mathrm{AMP}]^2}\right)+[\mathrm{F6P}]^2\right)(K_{4\mathrm{mATP}}+[\mathrm{ATP}])}$$

$$5: \quad v_+^5 = \frac{V_{5f}[\mathrm{FBP}]}{K_{5\mathrm{FBP}}+[\mathrm{FBP}]+\frac{[\mathrm{GAP}]K_{5\mathrm{DHAP}}V_{5f}}{K_{5eq}V_{5r}}+\frac{[\mathrm{DHAP}]K_{5\mathrm{GAP}}V_{5f}}{K_{5eq}V_{5r}}+\frac{[\mathrm{FBP}][\mathrm{GAP}]}{K_{5\mathrm{IGAP}}}+\frac{[\mathrm{GAP}][\mathrm{DHAP}]V_{5f}}{K_{5eq}V_{5r}}}$$

$$v_-^5 = \frac{V_{5f}\frac{[\mathrm{GAP}][\mathrm{DHAP}]}{K_{5eq}}}{K_{5\mathrm{FBP}}+[\mathrm{FBP}]+\frac{[\mathrm{GAP}]K_{5\mathrm{DHAP}}V_{5f}}{K_{5eq}V_{5r}}+\frac{[\mathrm{DHAP}]K_{5\mathrm{GAP}}V_{5f}}{K_{5eq}V_{5r}}+\frac{[\mathrm{FBP}][\mathrm{GAP}]}{K_{5\mathrm{IGAP}}}+\frac{[\mathrm{GAP}][\mathrm{DHAP}]V_{5f}}{K_{5eq}V_{5r}}}$$

$$
\begin{aligned}
6: \quad v_+^6 &= k_{6f}[\mathrm{GAP}][\mathrm{NAD}^+] \\
v_-^6 &= k_{6r}[\mathrm{DPG}][\mathrm{NADH}]
\end{aligned}
$$

$$
\begin{aligned}
7: \quad v_+^7 &= k_{7f}[\mathrm{DPG}][\mathrm{ADP}] \\
v_-^7 &= k_{7r}[\mathrm{PEP}][\mathrm{ATP}]
\end{aligned}
$$

$$
8: \quad v_+^8 = \frac{V_{8m}[\mathrm{ADP}][\mathrm{PEP}]}{(K_{8\mathrm{PEP}} + [\mathrm{PEP}])(K_{8\mathrm{ADP}} + [\mathrm{ADP}])}
$$

$$
9: \quad v_+^9 = \frac{V_{9m}[\mathrm{Pyr}]}{K_9 + [\mathrm{Pyr}]}
$$

$$
10: \quad v_+^{10} = \frac{V_{10m}[\mathrm{ACA}][\mathrm{NADH}]}{(K_{10\mathrm{NADH}} + [\mathrm{NADH}])(K_{10\mathrm{ACA}} + [\mathrm{ACA}])}
$$

$$
\begin{aligned}
11: \quad v_+^{11} &= k_{11f}[\mathrm{AMP}][\mathrm{ATP}] \\
v_-^{11} &= k_{11r}[\mathrm{ADP}][\mathrm{ADP}]
\end{aligned}
$$

$$
12: \quad v_+^{12} = k_{12}[\mathrm{ACA}]
$$

$$
13: \quad v_+^{13} = k_{13}[\mathrm{EtOH}]
$$

$$
\begin{aligned}
14: \quad v_+^{14} &= \frac{V_{14m}[\mathrm{DHAP}]}{K_{14\mathrm{DHAP}} + [\mathrm{DHAP}] + \frac{K_{14\mathrm{DHAP}}}{K_{14\mathrm{GAP}}}[\mathrm{GAP}]} \\
v_-^{14} &= \frac{V_{14m}\frac{[\mathrm{GAP}]}{K_{14eq}}}{K_{14\mathrm{DHAP}} + [\mathrm{DHAP}] + \frac{K_{14\mathrm{DHAP}}}{K_{14\mathrm{GAP}}}[\mathrm{GAP}]}
\end{aligned}
$$

$$
15: \quad v_+^{15} = \frac{V_{15m}[\mathrm{DHAP}]}{K_{15\mathrm{DHAP}}\left(1 + \frac{K_{15\mathrm{INADH}}}{[\mathrm{NADH}]}\right)\left(1 + \frac{[\mathrm{NAD+}]}{K_{15\mathrm{INAD}}}\right) + [\mathrm{DHAP}]\left(1 + \frac{K_{15\mathrm{NADH}}}{[\mathrm{NADH}]}\right)\left(1 + \frac{[\mathrm{NAD+}]}{K_{15\mathrm{INAD}}}\right)}
$$

$$
16: \quad v_+^{16} = k_{16}[\mathrm{glycerol}]
$$

$$
17: \quad v_+^{17} = k_{17}[\mathrm{ATP}]
$$

The stoichiometric constrains:

$$
\begin{aligned}
\mathrm{AMP} &= Atot - [\mathrm{ATP}] - [\mathrm{ADP}] = 3.93mM - [\mathrm{ATP}] - [\mathrm{ADP}] \\
\mathrm{NAD} &= Ntot - [\mathrm{NADH}] = 0.98mM - [\mathrm{NADH}]
\end{aligned}
$$

The coefficients (the units as been omitted):

$$
\begin{aligned}
V_{1mf} &= 223;\ V_{1mr} = 0.247031;\ K_{1Glc} = 1.1; \\
K_{1IG6P} &= 1.2;\ K_{1IIG6P} = 7.2;\ P_1 = 1.8; \\
V_{2m} &= 42.3946;\ K_{2ATP} = 0.063; K_{2Glc} = 0.1; K_{2DGlc} = 0.1; \\
V_{3m} &= 74.5569;\ K_{3G6P} = 0.03;\ K_{3F6P} = 0.01;\ K_{3eq} = 0.298; \\
V_{4m} &= 32.577;\ K_4 = 0.0016;\ \kappa_4 = 0.017;\ K_{4mATP} = 0.01; \\
V_{5f} &= 452.346;\ V_{5r} = 5.0V_{5f};\ K_{5eq} = 0.081;\ K_{5FBP} = 0.3; \\
K_{5GAP} &= 2.0;\ K_{5DHAP} = 2.0;\ K_{5IGAP} = 1.0; \\
k_{76f} &= 1529.78;\ k_{6r} = 180792; \\
k_{7f} &= 79548.5;\ k_{7r} = 710.254; \\
V_{8m} &= 429.562;\ K_{8ADP} = 0.3;\ K_{8PEP} = 0.2;\ K_{8DPEP} = 0.2; \\
V_{9m} &= 61.7186;\ K_9 = 0.3; \\
V_{10m} &= 690.231;\ K_{10NADH} = 0.01;\ K_{10ACA} = 0.78; \\
k_{f11} &= 1.443;\ k_{r11} = 0.444444; \\
k_{12} &= 64.152; \\
k_{13} &= 7.77052; \\
V_{15m} &= 932.385;\ K_{15DHAP} = 0.4;\ K_{15GAP} = 0.1; K_{15eq} = 0.04550; \\
V_{16m} &= 19.7556;\ K_{16NADH} = 0.13;\ K_{16DHAP} = 1.6; \\
K_{16INADH} &= 0.034;\ K_{16INAD} = 0.13; \\
k_{17} &= 3.45434; \\
k_{18} &= 26.2718;
\end{aligned}
$$

Appendix B

Mathematica script-file

Mathematica script file. This particular script file compute the coefficients in the WH–model, but can be used to derive the Stuart–Landau eqaution for any system.

```
(*The vector field.*)

f1=1-k2*x*z
f2=-y-2*k1*y^2+2*k3*z+k2*x*z
f3=k1*y^2-k3*z
f={f1,f2,f3}
c={x, y, z}

(*Linear settings, k2 = (Sqrt[325] -17)/6 *)

J=Outer[D,f,c]
J1=J /. {x->k3/(k1*k2), y->1, z->k1/k3}
J2=J1 /. {k1 -> 1,k2 -> (Sqrt[325] -17)/6, k3->1}
\[CapitalLambda]=Eigenvalues[J2]
\[Omega]=Im[\[CapitalLambda][[3]]]
u   = Eigenvectors[J2][[3]]
u   = u/u[[3]]
conju  = Conjugate[u]
v  = Eigenvectors[Transpose[J2]][[3]]
v  = v/v.u

(*Coefficients for the term z^2*)

fxx=Outer[D,J,c];
fxx1= fxx /. {x->k3/(k1*k2), y->1, z->k1/k3}
fxx2= fxx1 /. {k1 -> 1,k2 -> (Sqrt[325] -17)/6, k3->1}
fxxuu=fxx2.u.u
```

```
h200=LinearSolve[J2-2*I*\[Omega]*IdentityMatrix[3], -1/2*fxxuu]
h020=Conjugate[h200]

(*Coefficients for the term |z|^2 *)

fxxuconju=fxx2.u.conju
h110 = LinearSolve[J2, -fxxuconju]
h110=Simplify[h110]

(*Coefficients for z^3 *)

fxxx=Outer[D,fxx,c];
fxxx1= fxxx /. {x->k3/(k1*k2), y->1, z->k1/k3}
fxxx2= fxxx1 /. {k1 -> 1,k2 -> (Sqrt[325] -17)/6, k3->1}
fxxxuuu=fxxx2.u.u.u
fxxuh200=fxx2.u.h200
h300=LinearSolve[J2-3*\[Omega]*I*IdentityMatrix[3], -fxxuh200-1/6*fxxxuuu]
h030=Conjugate[h300]

(*Coefficients for the term z|z|^2 *)

fxxxuuconju=fxxx2.u.u.conju
fxxconjuh200=fxx2.conju.h200
fxxuh110=fxx2.u.h110
temp=fxxuh110+fxxconjuh200+1/2*fxxxuuconju
Qtemp=temp-(v.temp)*u
Qtemp2=Simplify[Qtemp1]
H210=LinearSolve[(J2-\[Omega]*I*IdentityMatrix[3]), -Qtemp2] (*Singul.prob.*)
h210=H210-(v.H210)*u
h120=Conjugate[h210]

(*Coefficients for \mu and z\mu*)

fmu=D[f,k2]
fmu1= fmu /. {x->k3/(k1*k2), y->1, z->k1/k3}
fmu2=fmu1 /. {k1 -> 1,k2 -> (Sqrt[325] -17)/6, k3->1}
h001=LinearSolve[J2, -fmu2]
fxmu=D[J,k2]
fxmu1=fxmu /. {x->k3/(k1*k2), y->1, z->k1/k3}
fxmu2=fxmu1 /. {k1 -> 1,k2 -> (Sqrt[325] -17)/6, k3->1}
fxxuh001=fxx2.u.h001
temp=fxmu2.u+fxxuh001
Qtemp1=temp-(v.temp)*u
Qtemp2=Simplify[Qtemp1]
H101=LinearSolve[(J2-\[Omega]*I*IdentityMatrix[3]), -Qtemp2] (*Singul.prob.*)
```

```
h101=H101-(v.H101)*u
h011=Conjugate[h101]

(*Coefficients in the Stuart-Landau equation.*)

g3=v.fxx2.u.h110 + v.fxx2.conju.h200+1/2*v.fxxxuuconju
\[Sigma]=v.fxmu2.u+v.fxxuh001

res= ColumnForm[{N[u], N[h200], N[h110], N[h020], N[h300], N[h210], \
      N[h120],N[h030],N[h001],N[h101],N[h011], N[g], N[\[Sigma]]}]

(*Save["~/Noauto/noautodat.m",res]*)
```

Appendix C

Oscillators in the complex plan

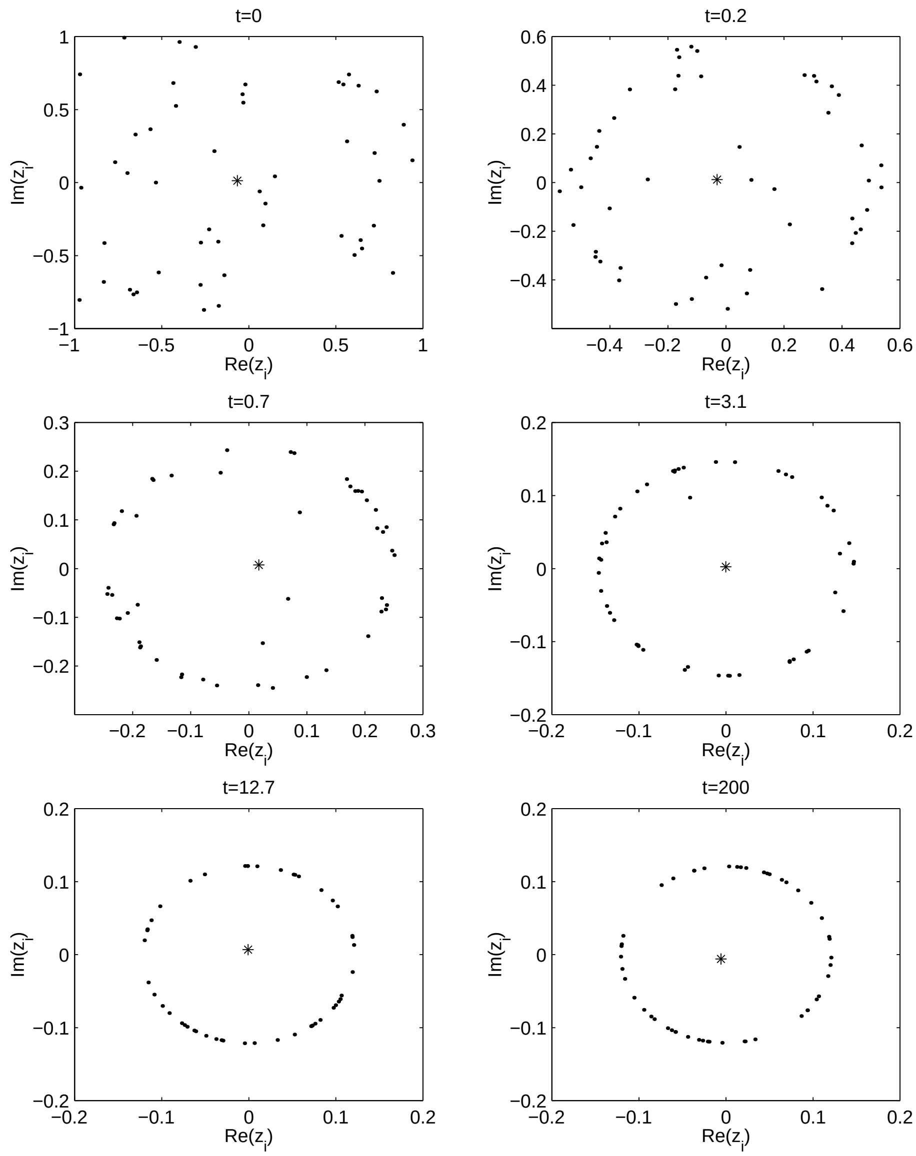

Figure C.1: Incoherence ($K = 0$ and $\Delta = 0.05$): The simulation is initialized such that all cells starts at random positions in the complex plane. After some time each cell simply moves at its own frequency, which means that the cells do not move around with the same speed. The asterisk represent the centroid. Only 50 of the 500 cells are shown.

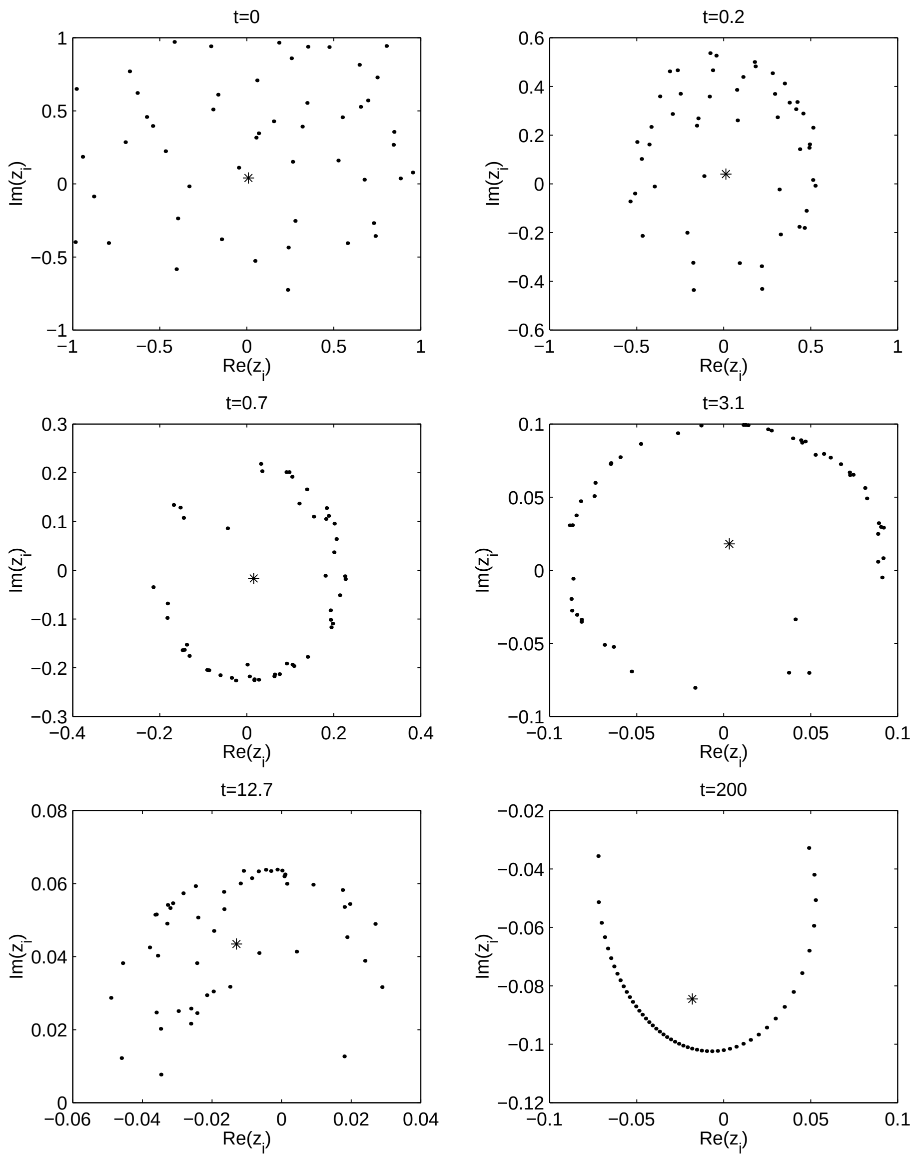

Figure C.2: Frequency locking ($K = 0.9$ and $\Delta = 0.05$): Starting at random positions, the cells clusters and locks their frequencies. The asterisk represent the centroid.

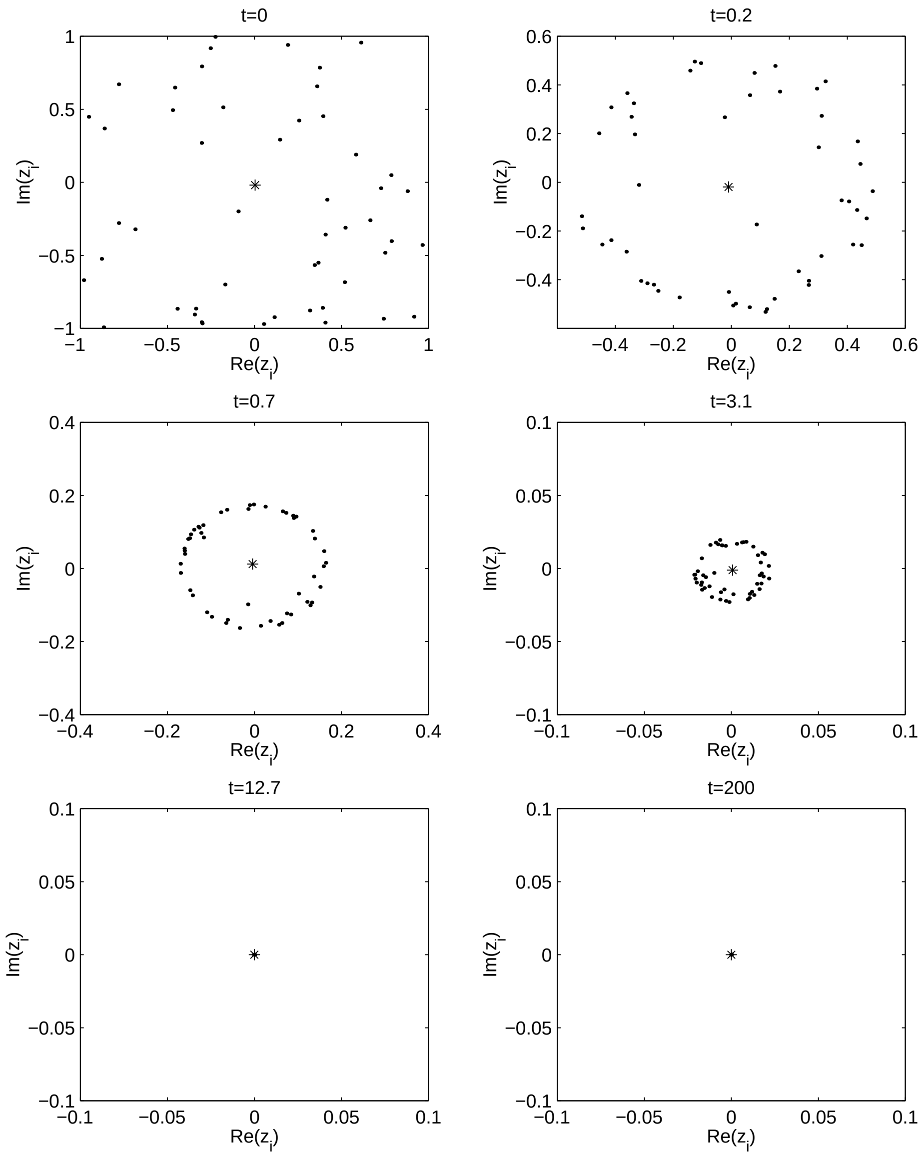

Figure C.3: Amplitude death ($K = 1.1$ and $\Delta = 1.1$): The cells simply falls into the stable fixed point, which means that the amplitudes dies out. The centroid is represented by the asterisk.

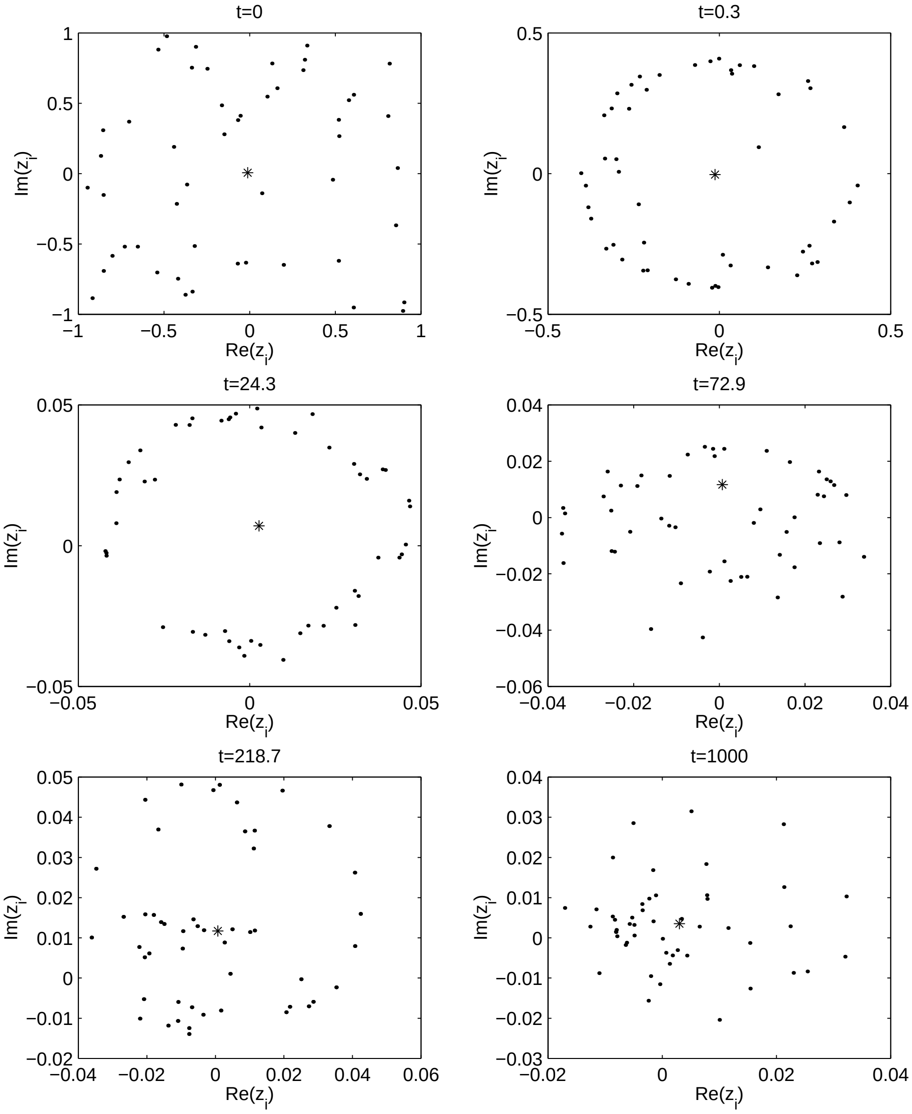

Figure C.4: Chaotic state ($K = 0.18$ and $\Delta = 0.16$): The cells seems to move around in an unordered fashion. The centroid is represented by the asterisk.

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