EEEN30150: Modeling the Effects of Deep Brain Stimulation on Parkinsonian Tremor

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Dr Paul Curran

Conor Igoe

13360786

Contents

Declaration

I declare that the work described in this report was done by the person named above, and that the description and comments in this report are my own work, except where otherwise acknowledged. I understand the definition of plagiarism. I have read and understand the consequences of plagiarism as discussed in the School Policy on Plagiarism, the UCD Plagiarism Policy and the UCD Briefing Document on Academic Integrity and Plagiarism.

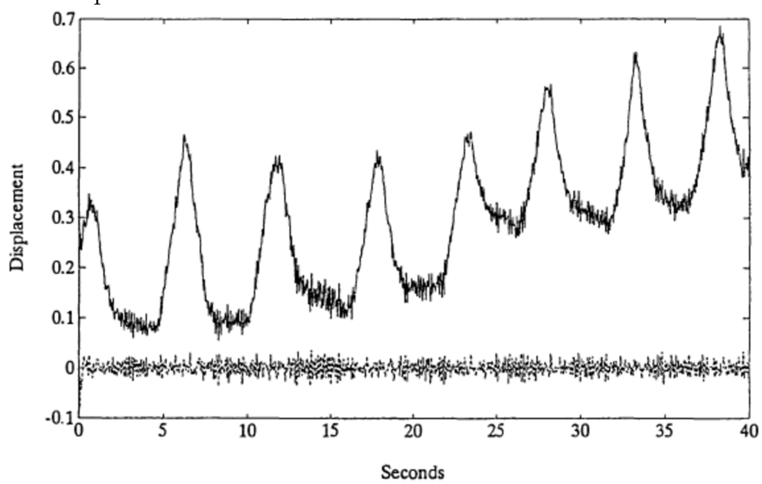
Signed: . . . .

Date: . . . . . . 15 / 4 / 2017 . . . .

Introduction

Motivation

Figure 1: Real patient Parkinsonian Tremor measurements from Davidson et al.[1]



Parkinsonian Tremor is symptomatic of the neurogenerative disorder Parkinson's Disease. Along with pharmaceutical drugs, Deep Brain Stimulation (D.B.S.) is a clinical intervention that is successful in treating such tremor for a minority of patients. Though first introduced in a clinical setting in 1987, the exact mechanics of D.B.S. is poorly understood and remains an active area of research. The goal of this project is to use a control theory model of Parkinsonian Tremor proposed by Davidson et al.[1] to investigate the effects of various forms of D.B.S.

For a more in depth coverage of recent work related to phenomenological control theory modeling of Parkinsonian tremor, refer to Sageanne Serriff's report.

Distribution of Responsibilities

CONOR IGOE: nullcline analysis in Phase Space; animation of results

SAGEANNE SENNEFF: derivation of system of equations; mathematical analysis; supplementary analysis; discussion of related and future work

LIONEL FABIANI: system implementation in MATLAB & Simulink; code explanation

Mathematical Model of Tremor

The 2nd order Ordinary Differential Equation (ODE) system under consideration for this project is shown in Equation (1) below. For a derivation and mathematical analysis of Equation (1), as well as a high level model interpretation and explanation of notation, refer to Sageanne Senneff's report.

$$\frac{d^2y}{dt^2} + \left(2b - k\left(\frac{2/\pi}{1 + y^2/h^2}\right)\right)\frac{dy}{dt} + b^2 y = f_{\mathrm{DBS}}(t) \tag{1}$$

Equation 1 takes the form of a family of oscillators known as Liénard Oscillators[2]. Furthermore, Equation 1 can be decomposed into a system of two 1st order ODEs using the Liénard Transformation, yielding the system of equations in Equation (2). For an in depth treatment of the Liénard Transformation, refer to Sageanne Senneffe's report.

$$\begin{aligned}\dot{x} &= y - \left(2bx - \frac{2}{\pi}k\arctan\left(\frac{x}{h}\right)\right)\\ \dot{y} &= -b^2x + f_{\mathrm{DBS}}(t)\end{aligned} \tag{2}$$

Using the system of equations in Equation (2), this report investigates the qualitative effects of various forms of $f_{\mathrm{DBS}}(t)$ on the ODE system for a given set of initial conditions.

Note that y in Equation (2) is **not** the same y as in Equation (1).

Autonomous System Phase Space Analysis: $f_{\mathbf{DBS}}(t) = 0$

When analyzing the dynamics of a system of ODEs as in Equation (1), it is convenient to plot the system in phase space. In this 2nd order system, the phase space corresponds to a phase plane, where the dependent variable (y) is plotted against its derivative (dy/dt). Under the Liénard Transformation, the dynamics of the system in Equation (2) can similarly be understood through a plot of y against x. Informally, in such a plot, a point on the phase plane follows a *trajectory* around the plane over time in response to a field of vectors governing the point's *velocity* at each point on the plane. For the system in Equation (2), a unique isolated closed trajectory, or *limit cycle*, can be shown to exist in phase space. In this project, it is of interest to investigate the nature of this limit cycle in phase space. This section considers the qualitative impact of the values of parameters h, k and b on the shape of the limit cycle in the autonomous case where $f_{\text{DBS}} = 0$. Note that all analyses in this section use the initial conditions $x(0) = 0.01$, $y(0) = 0.01$, satisfying the Liénard Oscillator conditions necessary to ensure the existence of a unique limit cycle. Refer to Sageanne Serreff's report for a more in-depth outline of the Liénard Oscillator conditions and their implications on the analysis of the system in Equation (2). Note that the analysis covered in this section is best illustrated in the accompanying video to this section: `https://youtu.be/odOiEEPt2cI`

Effects of h

For a given set of initial conditions, plotting the resulting trajectory of a point in phase space for various values of h shows the relationship between h and the shape of the resulting limit cycle of the system. The blue line plot in Figure 2 shows the trajectory of a point in phase space for $h = 0.01$; the red line plot shows the trajectory for $h = 0.99$.

It is evident from inspection of Figure 2 that a relationship exists between the shape and size of the limit cycle and the value of h. To gain an intuition behind the nature of this relationship, it is instructive to inspect the *nullclines* of the system, the curves for which the "flow" on the phase plane is purely vertical or purely horizontal. Setting both $\dot{x}$ and $\dot{y}$ to zero in Equation (2), we obtain the following two nullcline equations

$$\begin{aligned} &\dot{x} = y - \left(2bx - \frac{2}{\pi}k\arctan\left(\frac{x}{h}\right)\right) = 0 \\ \implies &y = 2bx - \frac{2}{\pi}k\arctan\left(\frac{x}{h}\right) \end{aligned} \tag{3}$$

$$\begin{aligned} &\dot{y} = -b^2x + f_{\text{DBS}}(t) = -b^2x + 0 = 0 \\ \implies &x = 0 \end{aligned} \tag{4}$$

Equation (4) shows that, in the autonomous case, the $\dot{y}$ nullcline lies on the y axis. Equation (3) shows that the $\dot{x}$ nullcline, expressed as a function of x, is described by a combination of two terms: a linear dependence on x, with slope $2b$, and a non-linear sigmoidal dependence on x. For a given value of k, the value of h controls the *scaling* of the non-linear term along the x axis. Qualitatively speaking, this scaling determines the *steepness* of the non-linear transition between the sigmoidal asymptotic values. When combined with the linear term, for a given non-linear amplitude, values of h over the region of interest[1] $0 < h <= 1$ correspond to qualitatively small differences in the $\dot{x}$ nullcline. Figure 3 reveals these qualitative differences, showing the two plots of Figure 2 with the $\dot{x}$ and $\dot{y}$ nullclines plotted in red and yellow, respectively. Note the non-linear steepness for $h = 0.99$ compared to the steepness for $h = 0.01$. Also note the limit cycle peaks, $x = 970$ for $h = 0.99$ compared to $x = 1180$ for $h = 0.01$.

[1]Refer to Sageanne Senneff's report for a discussion on the region of interest for all parameters in Equation (2)

Figure 2: Phase Plane Trajectory $f_{\mathrm{DBS}}(t) = 0$

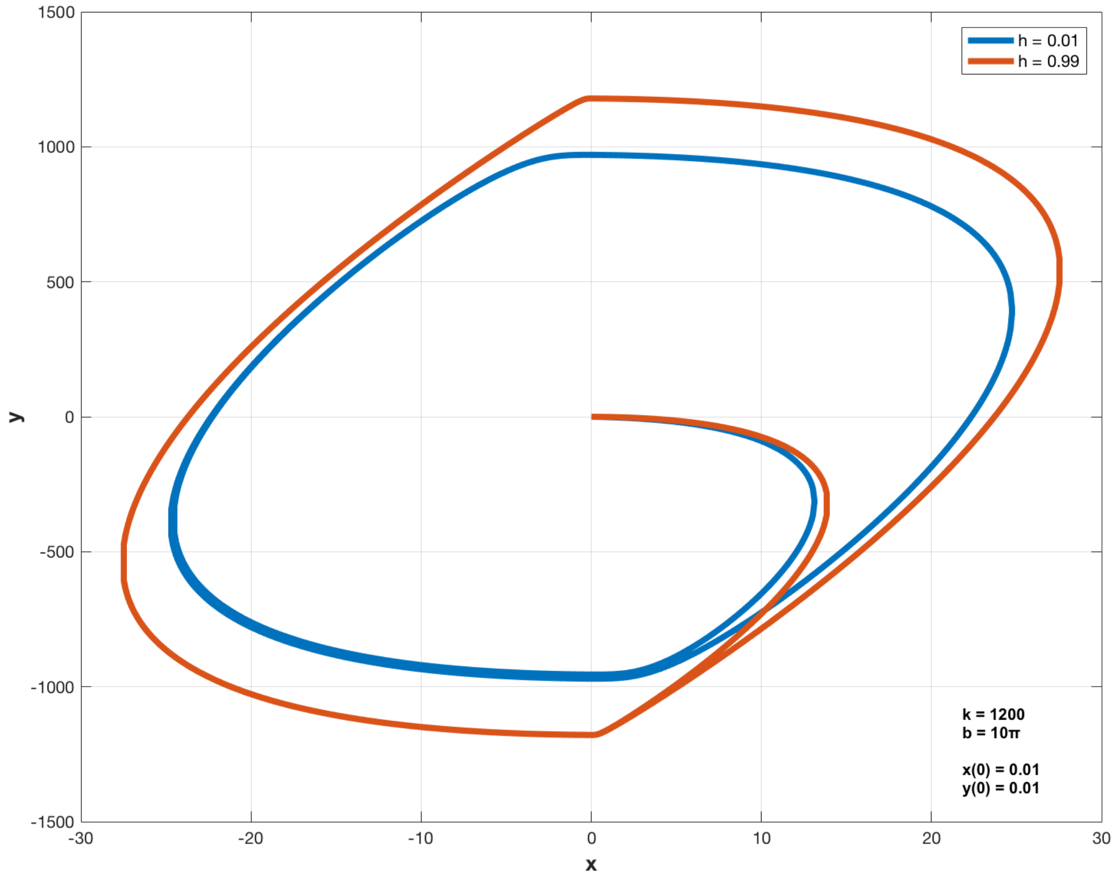
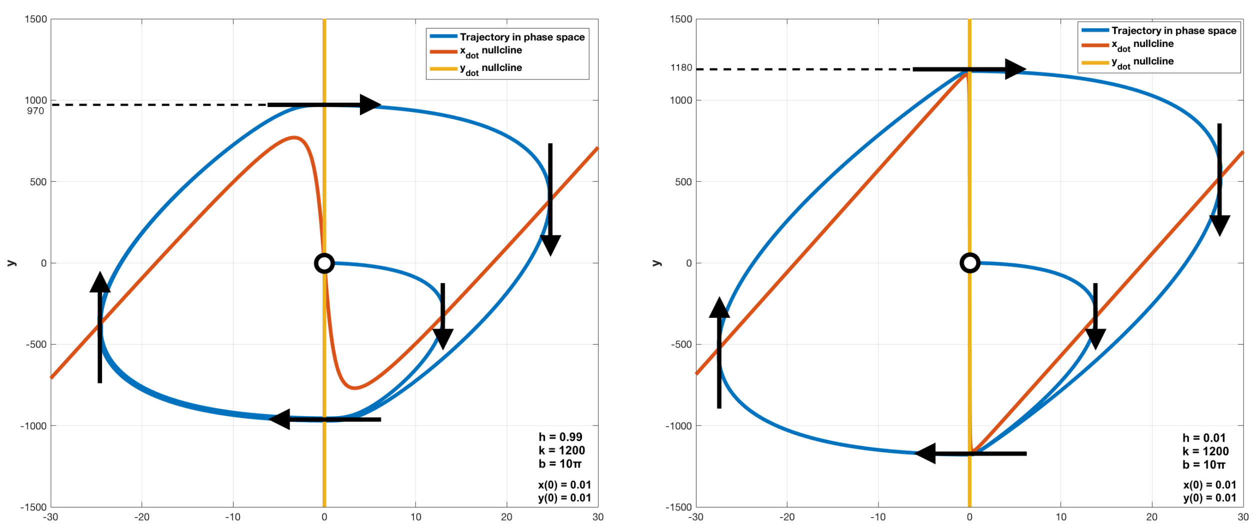


Figure 3: Phase Plane Trajectory with Nullclines for $f_{\mathrm{DBS}}(t) = 0$; $h = 0.99$ (left) and $h = 0.01$ (right). Black arrows indicated the flow direction where the limit cycle crosses a nullcline. The open circle indicates the unstable equilibrium point of the system in phase space.



Effects of k

A similar analysis is used in understanding the effects of values of k on the limit cycle of the system. The blue line plot in Figure 4 shows the trajectory of a point in phase space for $k = 800$; the red line plot shows the trajectory for $k = 1200$.

Inspecting the $\dot{x}$ nullcline from Equation (3) again, we observe that, informally, k controls the *size of the non-linear "gap"* from the otherwise linear dependency on x (the $-b^2x$ term in Equation (3)). Figure 5 illustrates this relationship between k and the $\dot{x}$ nullcline. Note the size of the "gap" for $k = 800$ compared to $k = 1200$.

Figure 4: Phase Plane Trajectory $f_{\text{DBS}}(t) = 0$

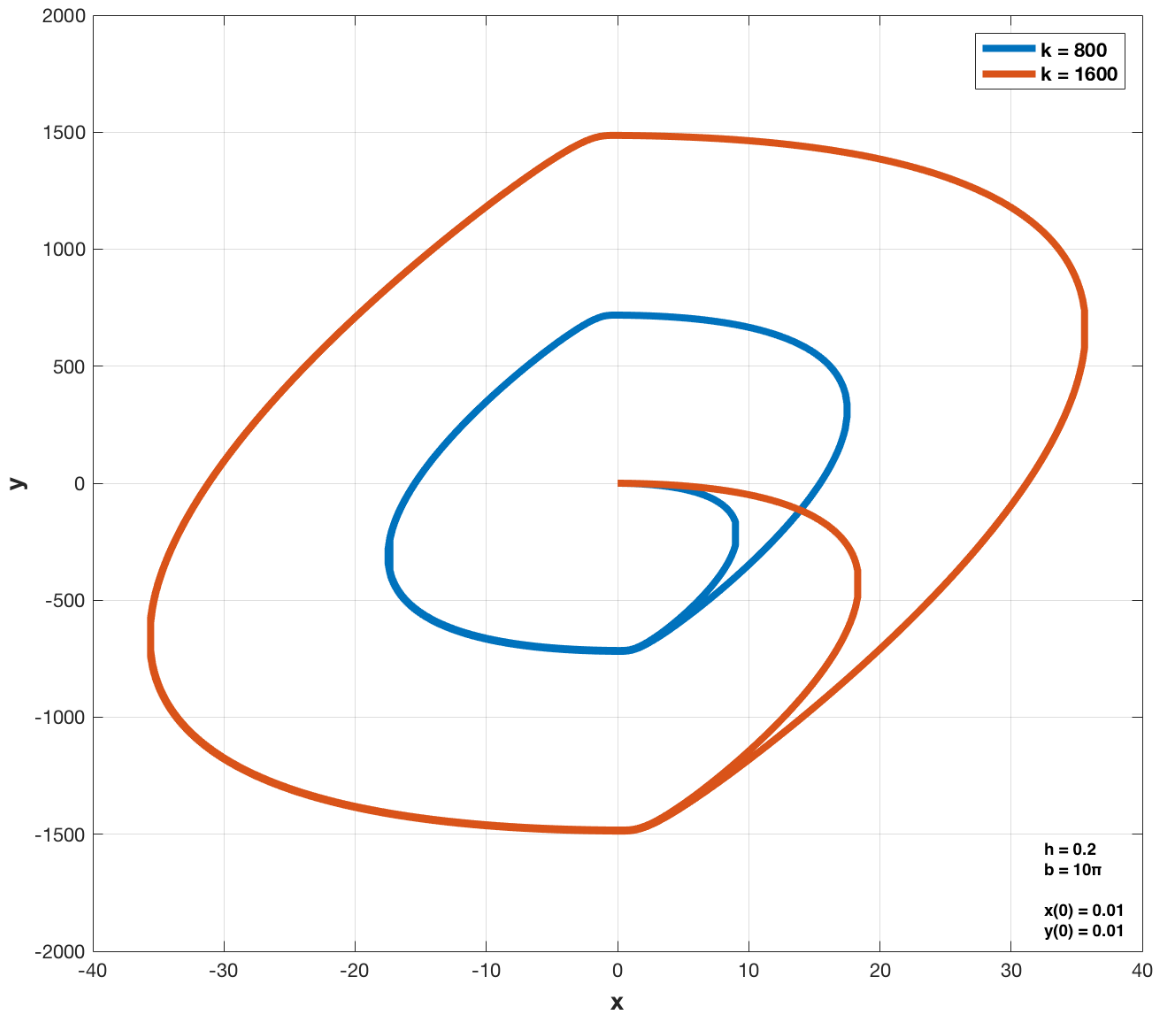
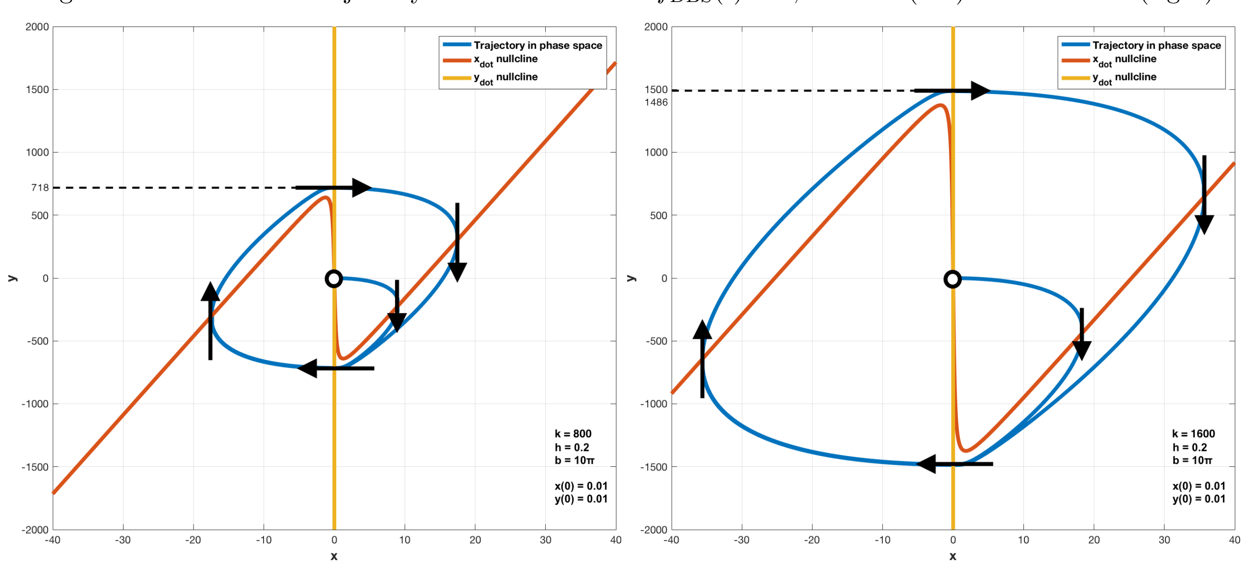


Figure 5: Phase Plane Trajectory with Nullclines for $f_{\text{DBS}}(t) = 0$; $k = 800$ (left) and $k = 1600$ (right)



Effects of b

It is evident from Figure 6 that a relationship exists between the value of b and the shape of the limit cycle. Following a similar analysis to that of parameters h and k, inspecting Equation (3) reveals that the value of b determines the *slope* of the linear term in the $\dot{x}$ nullcline. Figure 7 illustrates this relation, showing the resulting nullclines for $b = 8\pi$ and $b = 12\pi$. Informally, the value of b can be seen to determine the "width" of the limit cycle. Note the increase in the slope of the linear region of the $\dot{x}$ nullcline for $b = 12\pi$ compared to $b = 8\pi$ in Figure 7, and the corresponding decrease in the peak of $|x|$.

Figure 6: Phase Plane Trajectory $f_{\mathrm{DBS}}(t) = 0$

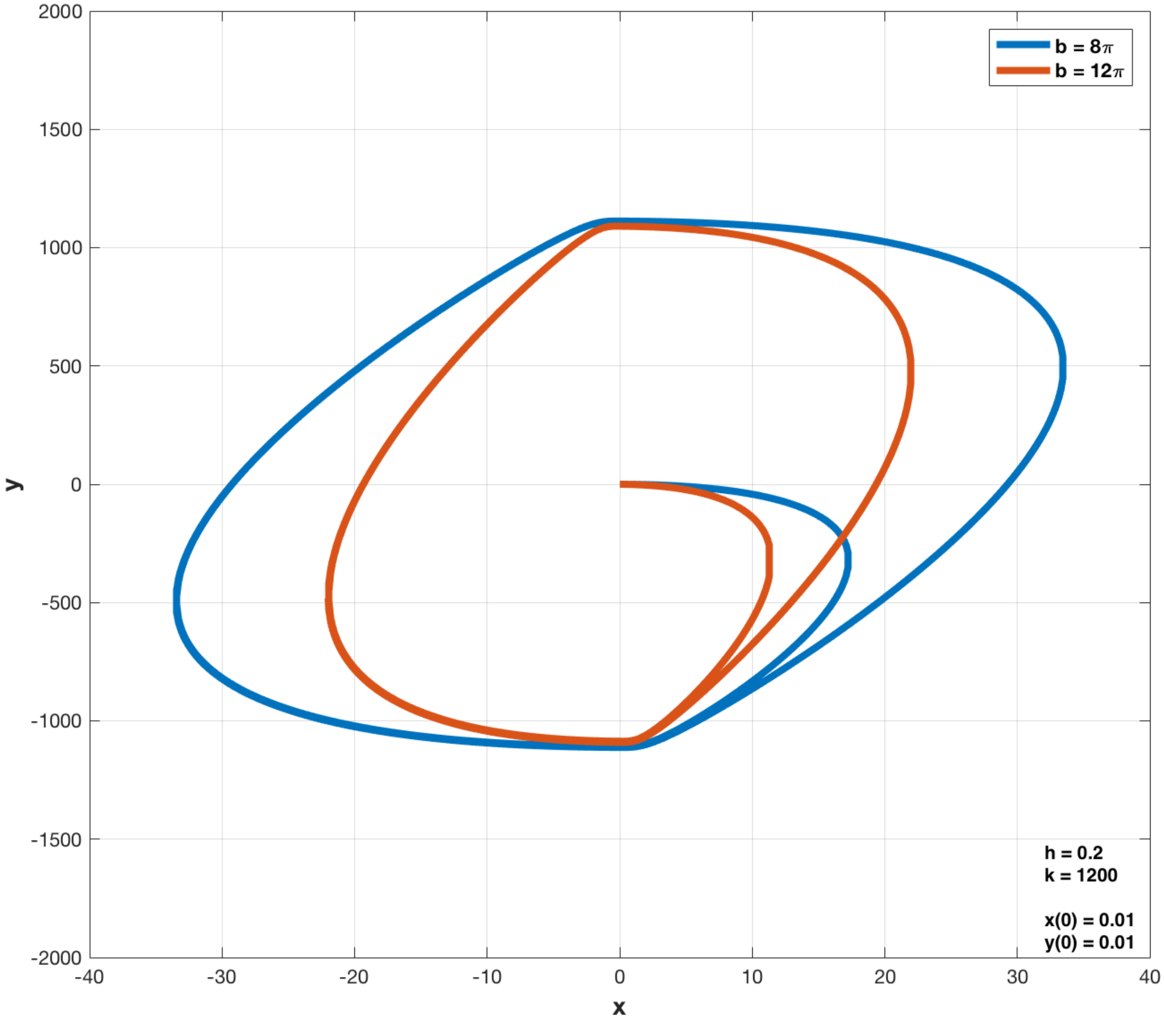
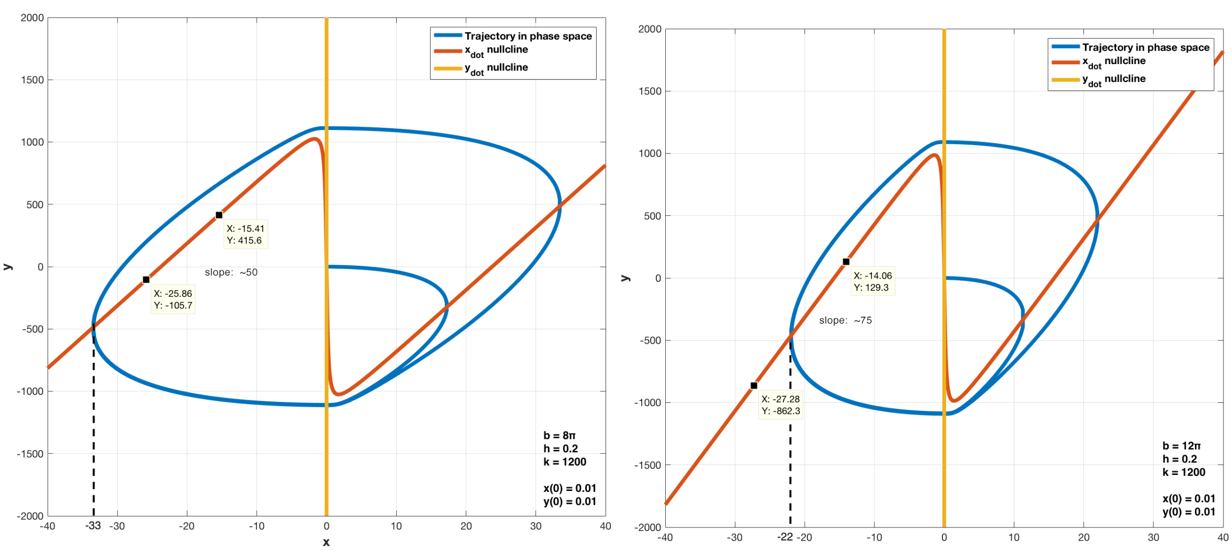


Figure 7: Phase Plane Trajectory with Nullclines for $f_{\mathrm{DBS}}(t) = 0$; $b = 8\pi$ (left) and $b = 12\pi$ (right)



Non-Autonomous System Phase Space Analysis

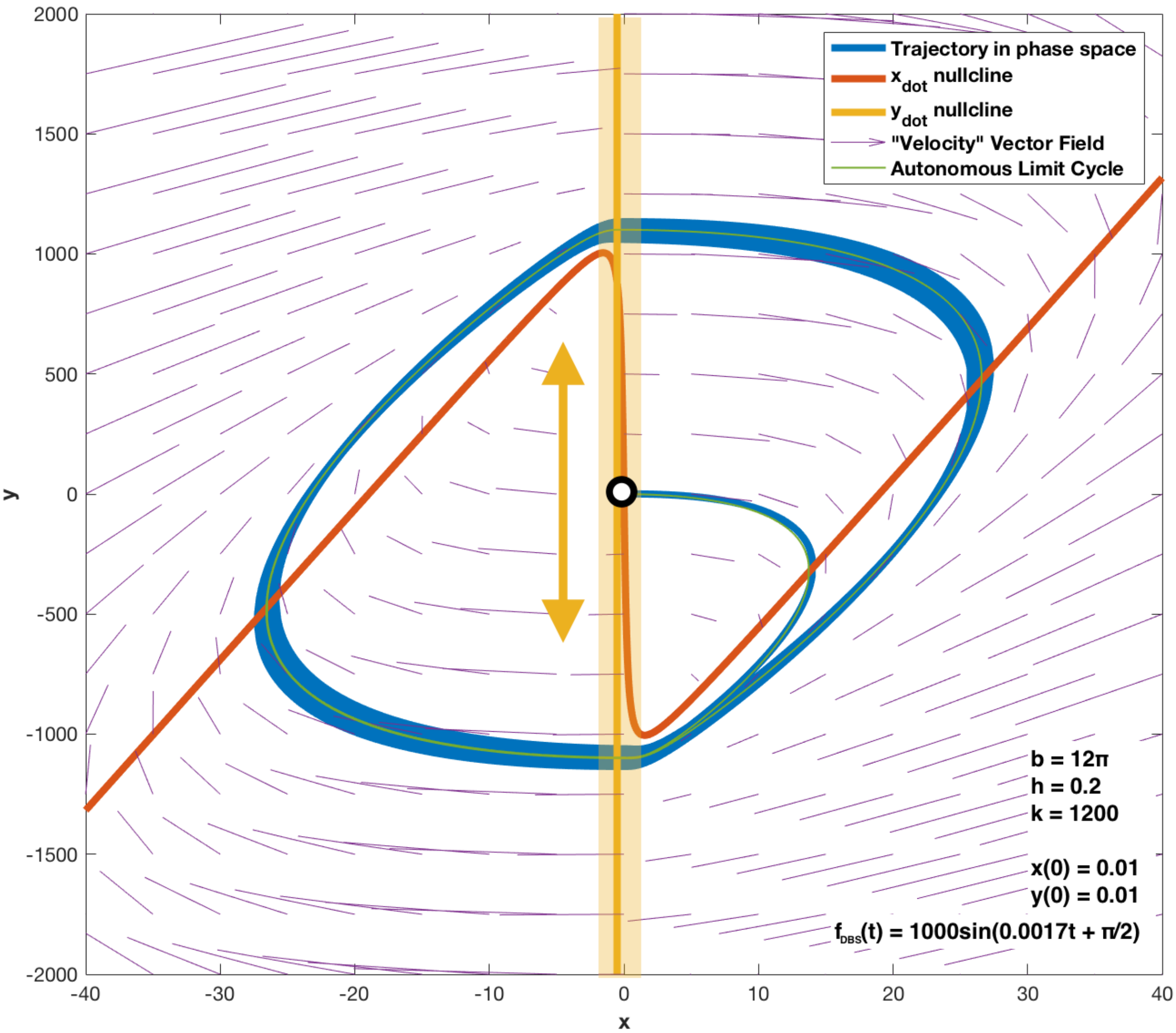
It is of interest to investigate the effects of various forms of $f_{\mathrm{DBS}}(t)$ on the trajectory in phase space and to determine if it is possible to achieve a trajectory that lies inside the limit cycle of the autonomous case.

Sinusoidal $f_{\mathbf{DBS}}(t)$

Using a sinusoidal term in Equation (5) and experimenting with parameter values, the following results were obtained for the resulting trajectories in phase space, shown in figures 8 and 9. Note that ω is in rad/s and ϕ is in rad.

$$f_{\mathrm{DBS}}(t) = A\sin(\omega t + \phi) \tag{5}$$

Figure 8: Phase Plane Trajectory with Nullclines for $f_{\mathrm{DBS}}(t) = 1000\sin(0.0017t + \pi/2)$. Note that, as the system is non-autonomous, the Vector Field (indicated at sample points in purple) is non-static. The yellow band indicates the region inside which the $\dot{y}$ nullcline shifts; the yellow double-ended arrow indicates that the stable equilibrium point moves up and down the $\dot{x}$ nullcline.



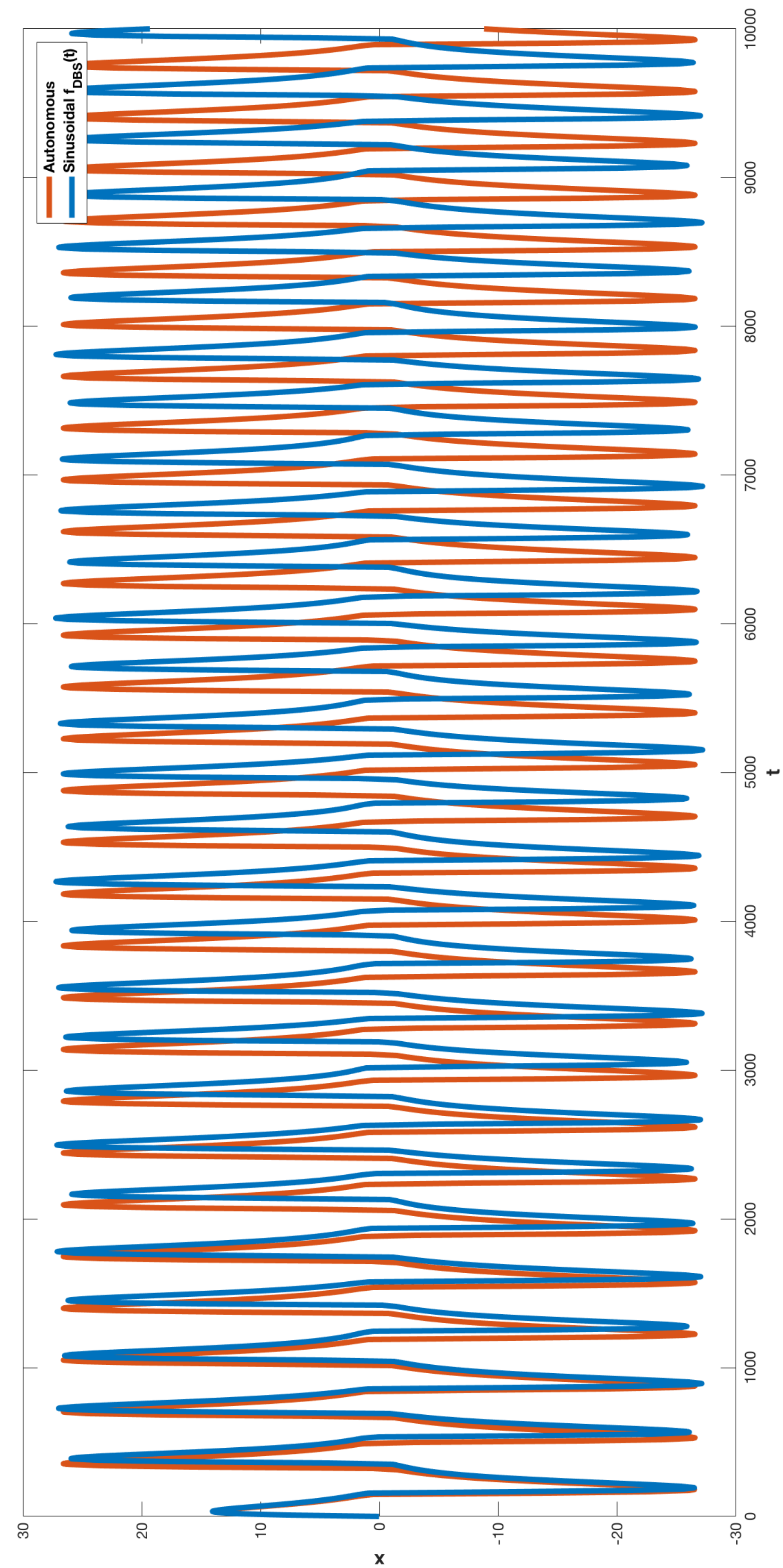


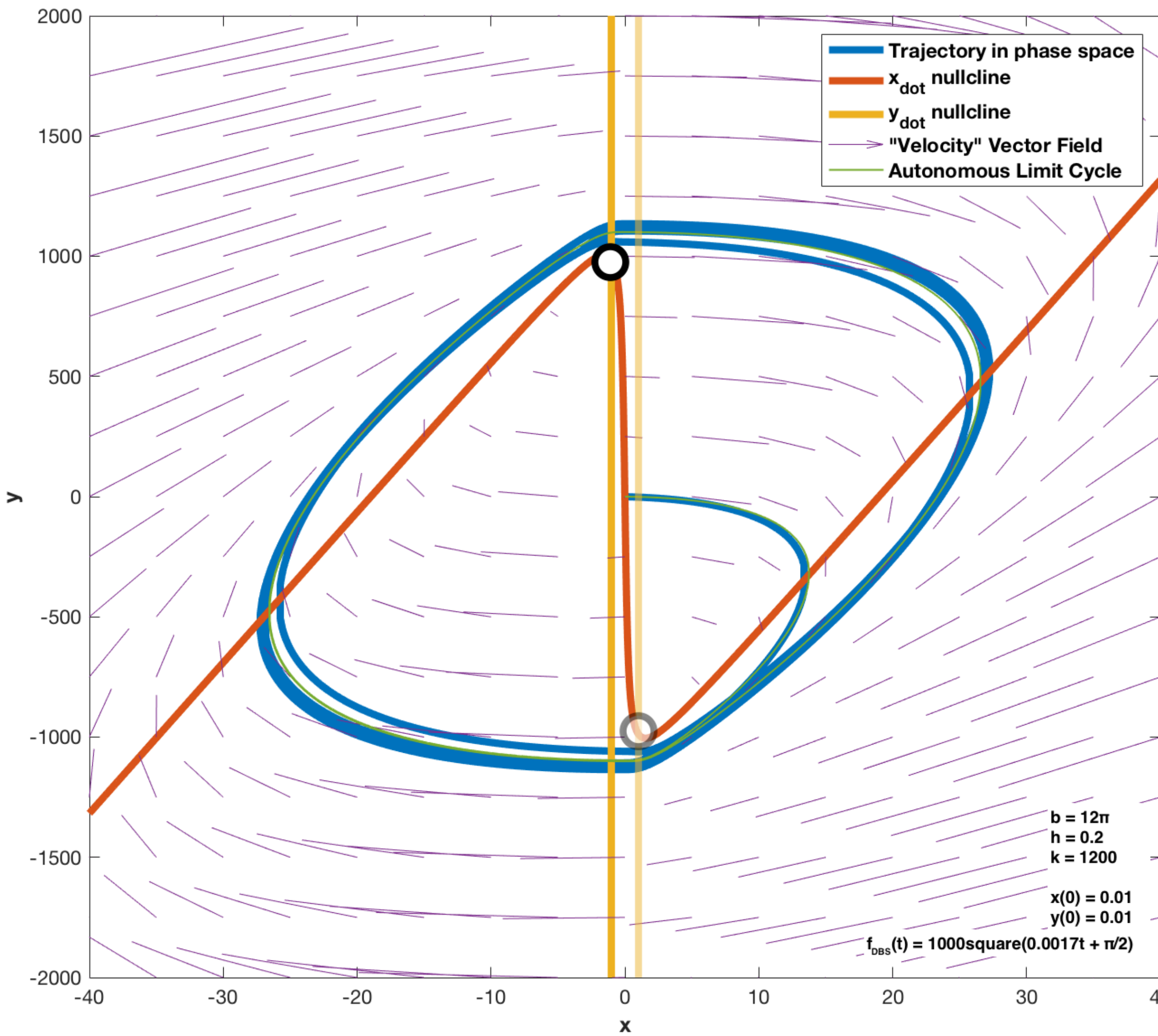
Figure 9: Plot of x against t for $f_{\mathrm{DBS}}(t) = 1000\sin(0.0017t + \pi/2)$ with comparison against autonomous system.

Uniform Square Wave $f_{\mathbf{DBS}}(t)$

Using a square wave with 50% duty cycle term in Equation (6) and experimenting with parameter values, the following results were obtained for the resulting trajectories in phase space, shown in figures 10 through 11. Note again that ω is in rad/s and ϕ is in rad.

$$f_{\mathrm{DBS}}(t) = A\mathrm{square}(\omega t + \phi) \tag{6}$$

Figure 10: Phase Plane Trajectory with Nullclines for $f_{\mathrm{DBS}}(t) = 1000\mathrm{square}(0.0017t + \pi/2)$. Note that, as the system is non-autonomous, the Vector Field (indicated at sample points in purple) is non-static. The faded yellow line and faded open circle indicates the alternative position of the $\dot{y}$ nullcline during the other half of the squarewave period.



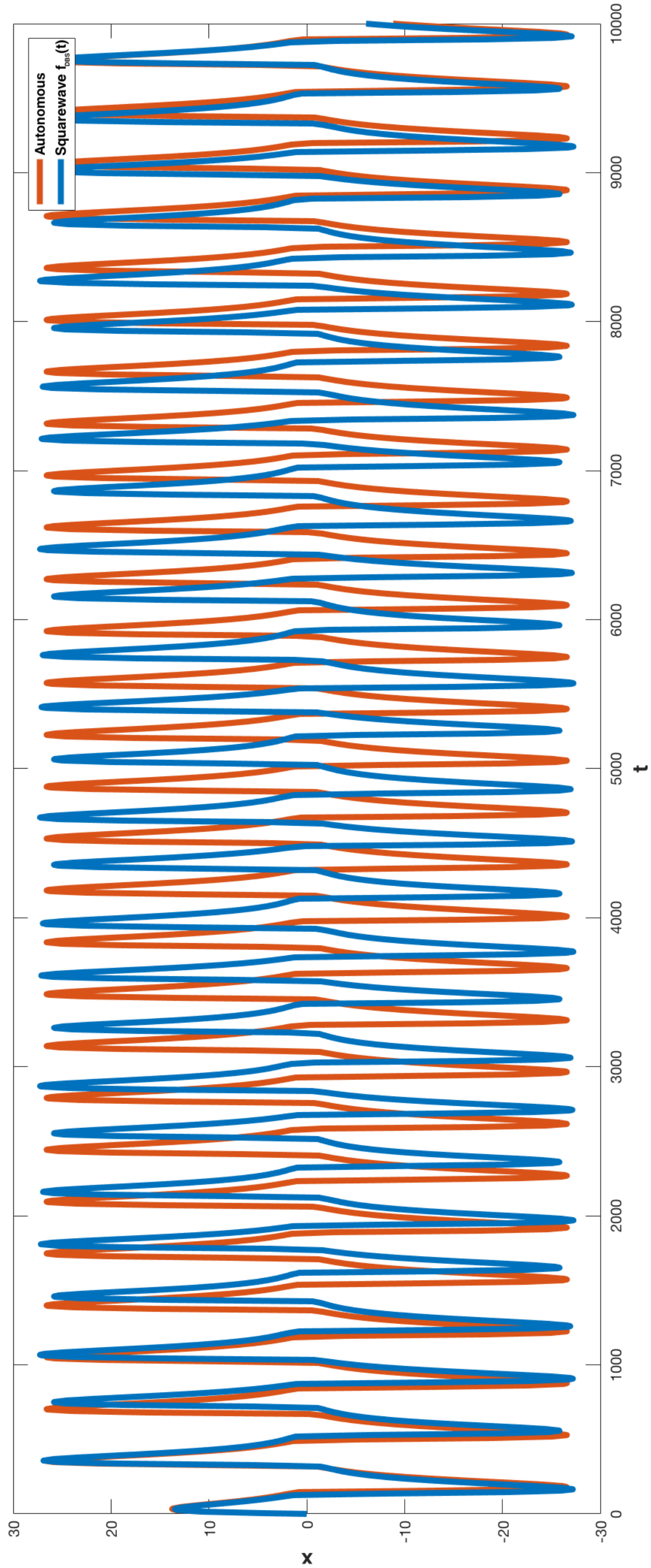


Figure 11: Plot of x against t for $f_{\mathrm{DBS}}(t) = 1000\sin(0.0017t + \pi/2)$ with comparison against autonomous system.

Analysis

A rough analysis is presented here. Further study is required in order to determine mathematical relationships between parameter values and phase space trajectory.

For all cases of $f_{\text{DBS}}(t)$ considered in this report, the effect is to shift the $\dot{y}$ nullcline left and right in the phase plane about its position in the autonomous system, the $x = 0$ line. The surrounding vector field of "velocities" is influenced by this shifting, introducing a new trajectory for the non-autonomous system in the phase plane.

When the effect of $f_{\text{DBS}}(t)$ results in a shifting of the $\dot{y}$ nullcline past the position on the x axis of either the local maximum or local minimum of the s-shaped $\dot{x}$ nullcline, the Liénard conditions for the existence of a unique limit cycle are no longer satisfied, and the equilibrium point on the intersection of the two nullclines becomes a *stable* equilibrium point. The resulting trajectory is illustrated in figure 12. Refer to Sageanne's report for a detailed analysis of the Liénard conditions.

Figure 12: Phase Plane trajectory with nullclines for $f_{\text{DBS}}(t) = -10000$ with comparison against autonomous system. Note the equilibrium point marked as a solid black circle, indicating a stable equilibrium point.

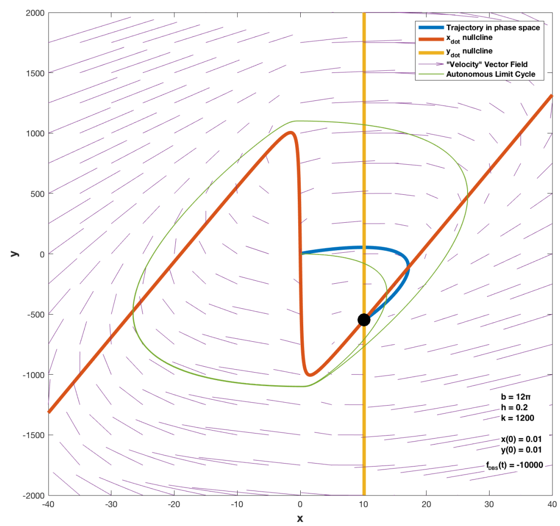
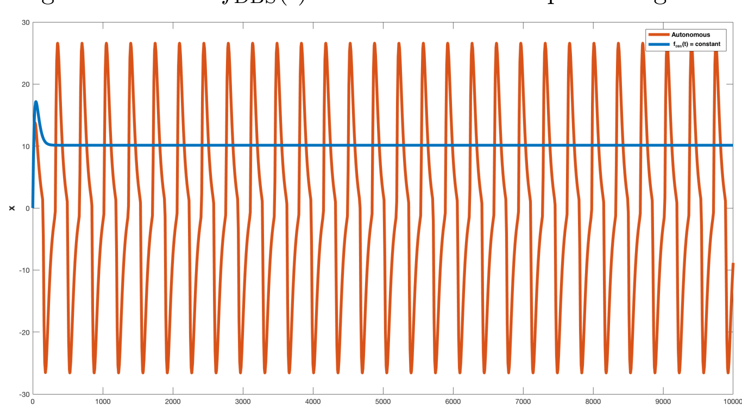


Figure 13: Plot of x against time for $f_{\text{DBS}}(t) = -10000$ with comparison against autonomous system.



The change of stability of the equilibrium point implies a trivial solution to the ultimate goal of Parkinsonian Tremor modeling research: use a constant $f_{\mathrm{DBS}}(t)$ term of large enough amplitude to change the stability of the equilibrium point of the system. Unfortunately, it is unlikely that such a "solution" will have desirable effects on a patient with Parkinsonian Tremor, as it is quite likely that the model used in this project does not accurately reflect the physiological reaction to such high amplitudes.

It is evident that trajectory in phase space can indeed be effected by use of non-zero, time varying f_{DBS}. However, it is also evident that it is not generally possible to obtain a trajectory significantly far inside the limit cycle of the autonomous system with the cases considered; nor is it possible to achieve such a trajectory without also incurring a trajectory that diverges outside the autonomous limit cycle. In this sense, the models of Parkinsonian Tremor and Deep Brain Stimulation considered in this project do not lend themselves to meaningful analysis.

Animation of Results

A video illustrating the non-autonomous simulation is available on YouTube at:

`https://youtu.be/39Eik9vLsNY`

Note that the axes of the phase plane in the video are inverted for illustrative purposes.

The Matlab code used to generate the animation is available on the accompanying GitHub repository for this report at:

`https://github.com/cvigoe/DBS`

A high level overview for what is largely a trivial case of graph plotting in Matlab is included below for the `animation.m` file.

- The relevant simulation file is called once to simulate the autonomous system (for comparison purposes) and once using the required parameter values (refer to Lionel Fabiani's report for documentation for the code in each of the simulation files). Each call returns a five column matrix, with a number of rows equal to the number of time steps of the simulation. The columns of the matrix are $[t;\ x;\ y;\ \dot{x};\ \dot{y}]$
- Animation of the simulated results is achieved by plotting successively more rows from the second returned matrix (successive number of rows are not necessary for the autonomous system as the limit cycle does not change with time) using a loop that loops over all of the rows in the non-autonomous simulation matrix
- Matlab's `quiver` function is used to plot the "velocity" vectors at sample points on the phase plane at each iteration of the loop
- Legends, titles and annotations are added
- The resulting plot is saved as a frame of a Matlab movie
- After looping through the entire matrix, the movie is written to an output file

References

[1] IEEE transactions on bio-medical engineering 61(3):957-65 *Application of Describing Function Analysis to a Model of Deep Brain Stimulation.* Davidson et. al. March 2014

[2] Non-Linear Dynamics and Chaos *Phase Plane, Limit Cycles*. Steven H. Strogatz. December 2000