Dynamical Modelling of Autophagy in the Context of Alzheimer Disease

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Abstract

Autophagy is a biological process which occurs in all cells whereby peptides and proteins are broken down, or catabolised, into amino acids and simpler monosacharrides. The proper functioning of autophagy in neurons has been linked to several age related neurodgenrative dieseases, including Alzheimer's, Dementia, and Huntington's disease. In this report I create a dynamical model to simulate and further understand the kinetics of Autophagy in neurons.

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1 Introduction and Motivation

With the average life expectancy of human beings steadily growing in the western world, [1] age related neurodegenerative diseases represent a huge societal and economic challenge for the 21st century. In the United States alone, an estimated 5.4 million people have Alzheimer's disease, with this figure projected to grow to 13.8 million by the mid 21st century. There is however, no known cure for many of these diseases. [2]

Attempts to understand the root cause of this disease have historically been anatomical in nature, endeavouring to find a root cause of the disease by examining the interactions of various cellular components and processes from a biological perspective. One such process which has been linked to neurodegenrative disorders of aging (NDA's) is autophagy[6]. In this report, I examine the role of autophagy in neurons by modelling the kinetics of autophagosomes, organelles involved in the autophagic process, using the theory of dynamical systems. I construct a model for the sequestration of cellular material by these components. I furthermore interpret this model within the context of NDA's.

2 Autophagy: A Basic Description

Autophagy is an essential process that occurs in every cell in the body. It is an essential part of cell function, and is invoved in everything from maintaining cell homeostasis to disease prevention.[7]

While many different modes of autophagy have been observed, for the sake of this report I will focus on the analysis of the kinetics of macroautophagy. In macroautophagy, which I will now just refer to as autophagy, bubble like compartments in the cell fuse with the cytoplasm to form a double membrane structure known as an autophagosome, thus taking up any glycoproteins or other waste products contained therein. These autophagosomes are then transported to acidic compartments known as lysosomes.[5] In these lysosomes, glycoproteins and other waste products suspended in the cytoplasm are broken down by lysosomal enzymes, namely proteases and hydrolases.[4]

Neurons are made up of two compartments. They are the soma, inside which the nucleus and most organelles are contained, and the axon, which are used to send electrical impulses

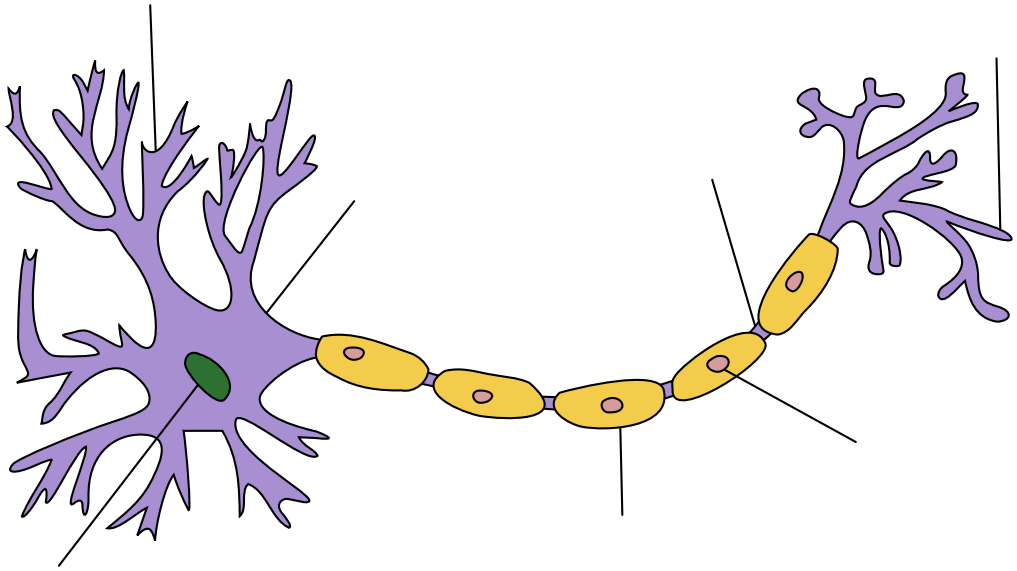

Figure 1: The structure of the neuron, with the axon and soma shown. Credit: By Quasar Jarosz at English Wikipedia, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=7616130

through the brain and to transport material. Autophagasomes are produced on the opposite end of the soma in neurons.[4][3] As such, they must undergo retrograde transport along the axon before fusing with lysosomes.[8] Autophagy is repsonsible for the sequstraion of many abberantly folded proteins associated with NDA's, including amyloid-beta, wild type alpha synuclein, and transactive response DNA binding protein 43 kDa.[8]

3 A Model for Autophagic Flux

The goal of this model is to find a way of mathematically formulating the buildup of autophagosomes along the axon, a contributor to neuronal cell death. As such, it is important to distinguish between somatic autophagosomes and synaptic autophagosomes. Two effects which to be considered in the concentration of synaptic autophagosomes are the rate at which they are produced distally in the axon, and the rate at which they flow to the cell soma. This is taken into account in the following equation.

$$\frac{dY}{dt} = P - k\frac{Y}{1+Y} \tag{1}$$

Here, Y is the concentration of synaptic autophagomes in the axon, P is the rate of production of autophagosomes in the cell, and k is the rate parameter controlling how quickly the autophagosomes travel along the axon to become somatic autophagosomes.

The concentration of somatic autophagosomes can be modelled as follows.

$$\frac{dS}{dt} = k\frac{Y}{1+Y} - SL \tag{2}$$

In this equation, we have that S is the concentration of somatic lysosomes in the cell, and L is the rate parameter controlling how fast the lysosomes eliminate the autophagosomes. These two equations give us a dynamical system governing how these two quantities change over time. All quantites S and Y are assumed to be positive.

The table below contains the dimensions of the quantities in question. S and Y are dimensionless quantities.

Model Parameters			
Parameter name	Symbol	Approximate Value	Units
Production rate of autophagosome	P	TBC	s^-1
Autophagasomal conversion rate	k	TBC	s^-1
Lysosomal rate of consumption	L	TBC	s^-1

A number of assumptions underlie this approach.

1. Firstly, it assumes that the rate at which the lysosomes consume the autophagosomes, L, is constant in time. This may well not be the case, considering the concentration of lysosomes in a neuron is itself dependent on a number of factors.

2. Secondly, it assumes that the rate at which the autophagosomes themselves is produced is constant.

3. Finally, it does not take into account the dependence of the transport of autophagosomes on other quantities, such as ATP or kinase.

In the following analysis, I hope to mitigate the effect of these assumptions by examining the dependence of the behaviour of the system as a function of the parameters k, L, and P.

4 Linear stability analysis

Letting the derivatives go to zero, we find that the one fixed point of the system is,

$$(Y^*, S^*) = \left(\frac{P}{k-P}, \frac{P}{L}\right) \tag{3}$$

We linearise the system by taking partial derivatives of the functions,

$$f(Y) = P - k\frac{Y}{1+Y} \tag{4}$$

and

$$g(S, Y) = k\frac{Y}{1+Y} - SL \tag{5}$$

with respect to the variables S and L. The linearised system will take the form,

$$\begin{pmatrix} \frac{dY}{dt} \\ \frac{dS}{dt} \end{pmatrix} = \begin{pmatrix} \frac{\partial f}{\partial Y} & \frac{\partial f}{\partial S} \\ \frac{\partial g}{\partial Y} & \frac{\partial g}{\partial S} \end{pmatrix} \tag{6}$$

The Jacobian matrix of our linearised system is therefore,

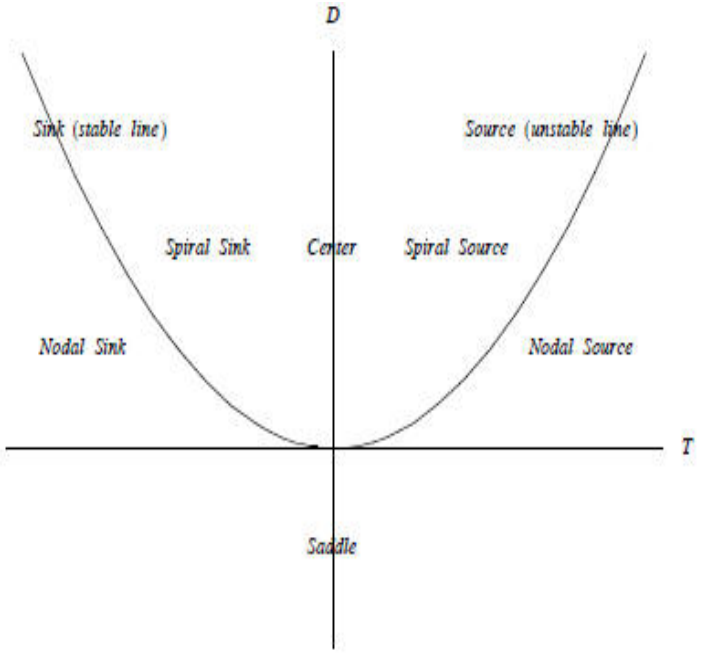

Figure 2: A graph demonstarting the dependence of the stability of fixed point on the trace and determinant of the Jacobian matrix evaluated at that point.

$$\mathscr{J}(Y,S) = \begin{pmatrix} 0 & \frac{k}{(y+1)^2} \\ -L & \frac{-k}{(y+1)^2} \end{pmatrix} \tag{7}$$

The value of the Jacobian matrix at the fixed point of the system is

$$\mathscr{J}(Y^*,S^*) = \begin{pmatrix} 0 & \frac{(k-P)^2}{k} \\ -L & -\frac{(k-P)^2}{k} \end{pmatrix} \tag{8}$$

Observe that, in order for the system to make physical sense, the fixed points must have positive coordinates. This implies

$$k > P \tag{9}$$

In terms of the underlying system, this makes sense. The rate at which the autophagosomes are being used up must be greater than the rate at which they are being produced. Otherwise, the concentration of synaptic lysosomes would increase exponentially.

The next step is to use the Jacobian to analyze the stability of the fixed point. The value of the determinant D of the Jacobian at the fixed point is

$$D = L\frac{(k-P)^2}{k} \tag{10}$$

Which we can observe is a strictly positive quantity. The trace of the Jacobian, T, can be found to be,

$$T = -\frac{(k-P)^2}{k} \tag{11}$$

which we can observe is a strictly negative quantity. There are now two possibilities for the nature of the fixed point in question. If we assume that the fixed point is a stable spiral, we have that $\frac{T^2}{4} < D$, which in this specific instance gives the expression,

$$k^2 - (4L + 2P)k + P^2 < 0 \tag{12}$$

If we assume that the point in question is a stable node, we reverse the direction of the above inequality.

$$k^2 - (4L + 2P)k + P^2 > 0 \tag{13}$$

We can see therefore that for certain critical parameter values, the behaviour of the system changes in a bifurcation.

4.1 The Stable Spiral Regime

We can gain a better feel for the dynamics of the autophagosomes by plotting their trajectories in a phase plane. In figure 3, we can see that all trajectories are drawn toward the fixed point. This suggests that for higher values of k the point is globally stable.

4.2 The Stable Node Regime

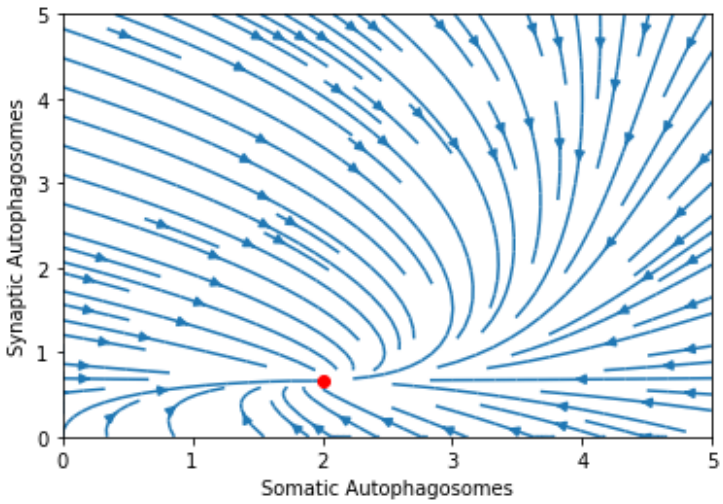

Figure 3: A phase diagram showing various trajectories. Here, $k = 5$, $P = 2$, and $L = 1$

5 Code Used

```
%pylab inline
import matplotlib.pyplot as plt
import numpy as np
svalues, yvalues = meshgrid(arange(0,5,0.001),arange(0,5,0.001))
k = 5
P = 2
L = 1
ydot = P - k*(yvalues/(1+yvalues))
sdot = k*(yvalues/(1+yvalues)) - svalues*L
streamplot(svalues,yvalues,sdot,ydot)
plt.xlabel("Somatic Autophagosomes")
plt.ylabel("Synaptic Autophagosomes")
plt.plot([P/L],[P/(k-P)],"ro")
plt.savefig(r'C:\Users\Ciaran\Pictures\Saved Pictures\spiral.png',bbox_inches
```

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