ROSE-
HULMAN
UNDERGRADUATE
MATHEMATICS
JOURNAL

THE MATHEMATICAL MODELING BEHIND DUCHENNE MUSCULAR DYSTROPHY

William A Berrigan[a]

VOLUME 13, NO. 2, FALL 2012

Sponsored by

Rose-Hulman Institute of Technology
Mathematics Department
Terre Haute, IN 47803
Email: mathjournal@rose-hulman.edu
http://www.rose-hulman.edu/mathjournal

[a] Villanova University

ROSE-HULMAN UNDERGRADUATE MATHEMATICS JOURNAL
VOLUME 13, NO. 2, FALL 2012

THE MATHEMATICAL MODELING BEHIND DUCHENNE MUSCULAR DYSTROPHY

William A Berrigan

Abstract. We look at a mathematical model for the role of the immune system in Duchenne Muscular Dystrophy. A linear stability analysis is used on a set of differential equations to determine stable and unstable states. These states are a basis for investigation into possible therapeutic treatments.

Acknowledgements: I would like to thank Dr. Robert Styer for his encouragement and mentoring throughout the process. I would also like to thank Dr. Luis Sanchez for allowing me to shadow him and his team of doctors in the ICU. It is because of an encounter with a patient who had DMD that I decided to pursue further research on the disease.

1 Introduction

Muscular Dystrophy (MD) is an inherited disorder that leads to the weakening of the musculoskeletal system within the body. Duchenne Muscular Dystrophy is a subcategory of MD that was originally discovered by the French neurologist Guillaume-Benjamin-Amand Duchenne in 1861 via biopsy. It involves a more rapid decline in muscular stability. The disorder leads to an absence of the protein dystrophin, which plays an integral part in binding with other proteins in the muscular cell membrane. It is believed that this is not the only contributor to the development of the disease. Rather, the immune system infuses an overwhelming number of immune cells into the muscle cells. This causes increased muscle damage.

The mathematical modeling encompasses current and previous research that has been done using representative mouse models. In the next and main section, the mathematical model highlights the course of the immune system. We will be working with a series of differential equations that model a change in the macrophages, cytotoxic T cells, and helper T cells as well as their effects on normal, damaged, and regenerating cells. Specifically, the excess cytotoxic T cells will be seen to have the most destruction on the healthy muscle cells. In section 2 we perform a linear stability analysis on the equations in order to investigate possible therapeutic treatment based upon a derived bifurcation diagram. In the final section, we briefly review a model for lung development in DMD patients.

2 Mathematical Modeling of the DMD Patient Immune System

Dell'Acqua and Castiglione [DC] derive these basic differential equations, which will be referred to as (basic). They consist of the following:

$$N + D + R = 100$$

$$\frac{dM}{dt} = a_1 + b_1 MD - d_1 M$$

$$\frac{dH}{dt} = a_2 + b_2 MD - d_2 H$$

$$\frac{dC}{dt} = b_3 HD - d_3 C$$

$$\frac{dN}{dt} = a_4 R - b_4 CN - h\Delta N$$

$$\frac{dD}{dt} = b_4 CN - b_5 MD - d_4 D + h\Delta N$$

Each represents a given process either of the rate of change of the immune cell counts or the rate of change of the normal, damaged, or regenerating cells. The unit of time, t, is in weeks. The first equation is the conservation law. N represents the number of normal cells. D is the number of damaged cells. R is the number of regenerating cells. The first equation states that there only exist normal, damaged, and regenerating cells. In the second equation, dM/dt

represents the rate of change of the immune cell counts of macrophages over a given time in weeks. The body replenishes the macrophages at a constant rate a_1. d_1M, then, is the number of macrophages that die in the given time period. b_1MD is the local recruitment of cells given from the inflammatory response. The inflammatory response is a part of the adaptive immune system that reacts to injured tissue. Macrophage cells and damaged cells will constantly be interacting with each other. Naturally, if either the number of damaged cells, macrophage cells, or both were increased the interaction between both types of cells would increase as well. b_1 is the proportion of interactions that have significance in increasing dM/dt. The next two equations are very similar in structure. dH/dt is the rate of change of the helper t-cells. a_2 is the replenishment of the cells and d_2H is the loss of those cells through some damage greater than 0. b_2MD is once again an interaction term that corresponds to the local recruitment of cells. The fourth equation is the rate of change of the cytotoxic t-cells. This equation differs from the other two because there is no automatic replenishment of cells. Rather, it is simply an immune response. Therefore, there is no replenishment, but there remains a local recruitment (b_3HD) and cell death (d_3C).

The last two equations differ from the previous three. They reflect the rate of change of normal, damaged, and regenerating muscle cells. dN/dt is the rate of change of normal cells, also in weeks. a_4R is the rate at which muscle cells are replenished from the regenerating fibers. b_4CN is the interaction between the cytotoxic T cells and the normal muscle cells. This is the key term in relation to Duchenne Muscular Dystrophy. It is the proportion b_4 of cytotoxic T cells attacking the normal cells that causes the degradation of the muscle tissue. This degradation leads to the eventual loss of pulmonary and cardiac function. The hΔN inserted at the end of both equations is a one-time impulse damage that initiates the immune response, and therefore, the differential equations. This could be any mechanical stress of the muscle tissue that combined with the genetic predisposition causes the start of degradation of muscle tissue. The process could begin by an injury as small as a simple fall. The terms b_5MD and d_4D represent the damaged cells cleared out either by macrophages or other methods.

In order to decipher exactly what the differential equations are, it is important to have an understanding of the immune system. The body has two types of responses within the immune system. These include a normal response and an adaptive response.

The normal immune response is what the body does under ordinary healthy conditions. This includes the macrophages, mast cells and granulocytes, dendritic cells, and natural killer cells. Macrophages are immune defenders that engulf pathogens. Mast cells and Granulocytes are involved in the inflammatory response. The inflammatory response is the body's natural reaction to any sort of damaged tissue. A damaged cell will release chemicals such as histamine, bradykinin, and prostaglandins. These chemicals will then cause blood vessels to leak fluid into the tissues causing swelling. The swelling helps isolate foreign substances from spreading further into the body. Finally, natural killer cells destroy the body's own cells that have become infected with pathogens.

The adaptive immune response is different from the normal immune response of the body because it requires an acquired learning to an invasive pathogen. There are three main types of cells within this response. Two of these were included in the study. The two that were included were the Helper T Cells and the Cytotoxic T Cells. Helper T Cells coordinate the immune response. If helper T cells are destroyed the host immune system becomes more and more immobilized. This creates an easier pathway for the infection to infiltrate the body. The cytotoxic T cells, or killer T cells, destroy virally infected cells. Those cells were labeled to be destroyed by B-cells. B cells secrete antibodies within the body's fluids. The antibodies, then, will ambush foreign antigens. However, the antibodies will never make it into the cell to attack infected or distorted cells. Therefore, a B cell, at most, can neutralize an invader or tag them to be killed. The B cells are vital for the body because of its production of antibodies and its correlation with the "tagging" of invasive pathogens for T cells. However, since a muscle cell will never be penetrated by a B cell, it is not necessary to highlight them within the differential equations for Duchenne Muscular Dystrophy. The problems with DMD originate in the penetrating t-cells.

In Duchenne Muscular Dystrophy, the cytotoxic T cells destroy too many cells leading to a degrading of the tissue and loss of muscle utility. In the equations this is reflected in the fact that muscle damage rises in the presence of cytotoxic T cells. Those cells increase as helper T cells increase, which are boosted by high levels of macrophages.

The equations are firmly based on the anatomy and physiology of the body. However, they are not easily analyzed since they contain a total of 14 parameters. The next step, then, is to make the equations dimensionless. Making an equation dimensionless eliminates units allowing for the equations to be more easily analyzed.

Theorem 1: Let $t = t_c t$, $M = M_c M$, $H = H_c H$, $C = C_c C$, $N = N_c N$, and $\Delta = \Delta_c \Delta$ The equations listed below, to be referred to as (dimensionless), are the dimensionless equivalents of (basic) above.

$$\frac{dM}{dt} = d_1 t_c (M_0 - M) + b_1 D_c t_c M D$$

$$\frac{dH}{dt} = d_2 t_c (H_0 - H) + \frac{b_2 D_c t_c M_c M D}{H_c}$$

$$\frac{dC}{dt} = \frac{b_3 t_c H_c D_c}{C_c} H D - d_3 t_c C$$

$$\frac{dN}{dt} = \frac{a_4 t_c R_c}{N_c} R - b_4 t_c C_c C N - h t_c \Delta_c \Delta N$$

$$\frac{dD}{dt} = \frac{b_4 t_c C_c N_c}{D_c} C N - b_5 t_c M_c M D - d_4 t_c D + \frac{h t_c \Delta_c N_c \Delta N}{D_c}$$

$$N_c N + D_c D + R_c R = 100$$

$$M_0 = 429\ cells\ mm^{-3}\ and\ H_0 = 6.25 cells\ mm^{-3}$$

Proof: Making the equation $\frac{dD}{dt} = b_4CN - b_5MD - d_4D + h\Delta N$ dimensionless

$\frac{dD/D_c}{dt} = \frac{b_4CN}{D_c} - \frac{b_5MD}{D_c} - \frac{d_4D}{D_c} + \frac{h\Delta N}{D_c}$ (Division by D_c)

$\frac{dD}{dt/t_c} = t_c(\frac{b_4CN}{D_c} - b_5MD - d_4D + \frac{h\Delta N}{D_c})$ (Substitution of D and division of dt by t_c on left hand side)

$\frac{dD}{dt} = \frac{b_4t_cCN}{D_c} - b_5t_cMD - d_4t_cD + \frac{h\Delta Nt_c}{D_c}$ (Substitution of t)

$\frac{dD}{dt} = \frac{b_4t_cC_cN_cCN}{D_c} - b_5t_cM_cMD - d_4t_cD + \frac{h\Delta_cN_ct_c\Delta N}{D_c}$ (Substitution of C, N,M,Δ by similar methods as above)

The rest of the equations follow a similar proof pattern QED

The next theorem allows us to reduce the number of free parameters from 14 to 7.

Theorem 2: Assuming $N_c = D_c = R_c = 100$ and denoting:

$$t_c = \frac{1}{d_1}, M_c = \frac{d_1}{b_5}, H_c = \frac{10^2b_2}{b_5}, C_c = \frac{d_1}{b_4}, \Delta_c = d_1$$

$$\beta_1 = \frac{10^2b_1}{d_1}, \beta_2 = \frac{d_2}{d_1}, \beta_3 = \frac{10^{4b_2b_3b_4}}{b_5\,{d_1}^2}$$

$$\beta_4 = \frac{d_3}{d_1}, \beta_5 = \frac{a_4}{d_1}, \beta_6 = \frac{d_4}{d_1}$$

Then the equations listed below, to be referred to as (simplified), are the simplified version of (dimensionless) above.

$$\frac{dM}{dt} = M_0 - M + \beta_1MD$$

$$\frac{dH}{dt} = \beta_2(H_0 - H) + MD$$

$$\frac{dC}{dt} = \beta_3HD - \beta_4C$$

$$\frac{dN}{dt} = \beta_5R - CN - h\Delta N$$

$$\frac{dD}{Dt} = CN - MD - \beta_6D + h\Delta N$$

$$N + D + R = 1$$

Proof: Simplification of the equation $\frac{dD}{dt} = \frac{b_4t_cC_cN_cCN}{D_c} - b_5t_cM_cMD - d_4t_cD + \frac{h\Delta_cN_ct_c\Delta N}{D_c}$

$\frac{dD}{dt} = \frac{b_4\left(\frac{1}{d_1}\right)\left(\frac{d_1}{b_4}\right)100}{100}CN - b_5\left(\frac{1}{d_1}\right)\left(\frac{d_1}{b_5}\right)MD - d_4\left(\frac{1}{d_1}\right)D - \frac{h(d_1)(100)\left(\frac{1}{d_1}\right)\Delta N}{100}$ (By means of substitution)

$\frac{dD}{Dt} = CN - MD - \beta_6D + h\Delta N$ (arithmetic simplification; red changes to black for further study)

The rest of the equations follow a similar proof pattern. QED

Taking the newly formed equations, it is possible to develop a limiting system with h=0. When h=0 there is no mechanical stress that initiates the immune system's reaction. To find stationary solutions, set each derivative to zero on the left sides of the simplified equations above (so the first equation would become $0 = M_0 - M + \beta_1 MD$). Dell'Acqua and Castiglione [DC] claim the solution gives a homogenous polynomial of degree 4 that has, besides 0, one or three more real roots.

In our case, we plug in the values given by [DC] and find the stationary solutions using Maple. The stationary solutions are:

$$\{C = 0., Dm = 0., H = 0.0008586799090, M = 0.3121760906, N = 1.\},$$
$$\{C = 0.02699575726, Dm = 0.007813525996, H = 0.01282984593,$$
$$M = 1.679049945, N = 0.8666130966\}, \{C = 0.1814338976, Dm$$
$$= 0.009246910878, H = 0.07286093609, M = 8.533430500, N$$
$$= 0.5019375922\}, \{C = -0.2280988031, Dm = 0.4373487897, H$$
$$= -0.001936725477, M = -0.007004725019, N = -2.508098883\}$$

As predicted, there are a total of four stationary solutions. We can now apply a linear model to analyze the stability of the system of ODEs near each of these solutions. A linear stability analysis determines whether a steady state is stable or unstable. This is done by taking a small perturbation near the stationary state and analyzing whether or not the newly defined variable grows or decays.

Theorem 3: Let $M = Mstar + \varepsilon m$, $H = Hstar + \varepsilon h$, $N = Nstar + \varepsilon n$, $D = Dstar + \varepsilon d$, *and* $C = Cstar + \varepsilon c$

where the variables with star represent the value of the variables at a stationary solution and the epsilon term following the starred variable is a very small number representing the perturbation to the system. The following, then, are the linearized equations, referred to as (linearized), of (simplified).

$$\frac{dm}{dt} = (\beta_1 Dstar - 1)m + \beta_1 Mstar d$$
$$\frac{dh}{dt} = Dstar m - \beta_2 h + Mstar d$$
$$\frac{dc}{dt} = \beta_3 Dstar h - \beta_4 c + \beta_3 Hstar d$$
$$\frac{dn}{dt} = -Nstar c - (\beta_5 + Cstar)n - \beta_5 d$$
$$\frac{dd}{dt} = -Dstar m + Nstar c + Cstar n - (Mstar + \beta_6)d$$

Proof: Linearizing the equation $\frac{dM}{dt} = M_0 - M + \beta_1 MD$

Left Side of the equation:

Take the derivative of $M = Mstar + \varepsilon m$ (Mstar is a constant)

$$\frac{dM}{dt} = \varepsilon \frac{dm}{dt}$$

Right Side of the equation:

$M_0 - M + \beta_1 MD = M0 - Mstar - \varepsilon m + \beta_1 (Mstar + \varepsilon m)(Dstar + \varepsilon d)$ (substitution)

$= M0 - Mstar - \varepsilon m + \beta_1 MstarDstar + \beta_1 \varepsilon m Dstar + \beta_1 Mstar \varepsilon d + \beta_1 \varepsilon^2 md$ (expansion)

$= -\varepsilon m + \varepsilon \beta_1 m Dstar + \varepsilon \beta_1 d Mstar$ (Uses the fact that $M_0 - M + \beta_1 MD = 0$ by the definitions of the stationary stable state. Since ε is arbitrarily small we can ignore the term containing ε^2, which is even smaller.)

Solving :

$\frac{dm}{dt}\varepsilon = -\varepsilon m + \varepsilon \beta_1 m Dstar + \varepsilon \beta_1 d Mstar$ (sets left side equal to the right side)

$\frac{dm}{dt} = (\beta_1 Dstar - 1)m + \beta_1 Mstar d$ (eliminates the epsilon)

The rest of the equations follow a similar proof pattern. QED

We now write the linear system in matrix form.

$$d/dt \begin{bmatrix} m \\ h \\ c \\ n \\ d \end{bmatrix} = A \begin{bmatrix} m \\ h \\ c \\ n \\ d \end{bmatrix}$$ where the matrix A is

$$\begin{bmatrix} \beta_1 \cdot Dstar - 1 & 0 & 0 & 0 & \beta_1 \cdot Mstar \\ Dstar & -\beta_2 & 0 & 0 & Mstar \\ 0 & \beta_3 \cdot Dstar & -\beta_4 & 0 & \beta_3 \cdot Hstar \\ 0 & 0 & -Nstar & -Cstar - \beta_5 & -\beta_5 \\ -Dstar & 0 & Nstar & Cstar & -Mstar - \beta_6 \end{bmatrix}$$

Theorem 4 provides a method to compute the solution of the linear system using the eigenvalues and eigenvectors of matrix A.

Theorem 4: Let A have n distinct complex eigenvalues λ_i with associated eigenvectors $[v_i]$. The

$$\text{solution to d/dt} \begin{bmatrix} m \\ h \\ c \\ n \\ d \end{bmatrix} = A \begin{bmatrix} m \\ h \\ c \\ n \\ d \end{bmatrix} \text{ is}$$

$$\begin{bmatrix} m \\ h \\ c \\ n \\ d \end{bmatrix} = c_1 e^{\lambda_1 t}[v_1] + c_2 e^{\lambda_2 t}[v_2] + c_3 e^{\lambda_3 t}[v_3] + c_4 e^{\lambda_4 t}[v_4] + c_5 e^{\lambda_5 t}[v_5]$$

See Theorem 1 Section 7.3 with Theorem 3 Section 7.2 [EP] for a proof of this theorem. The solution contains exponential components that are dependent on the eigenvalues λ. To expand upon this we refer to Theorem 5.

Theorem 5: Let $\begin{bmatrix} m \\ h \\ c \\ n \\ d \end{bmatrix} = c_1 e^{\lambda_1 t}[v_1] + c_2 e^{\lambda_2 t}[v_2] + c_3 e^{\lambda_3 t}[v_3] + c_4 e^{\lambda_4 t}[v_4] + c_5 e^{\lambda_5 t}[v_5]$

If an eigenvalue has real part greater than 0, then the corresponding stationary solution is unstable.

Proof: Since the solution to the linear equations is:

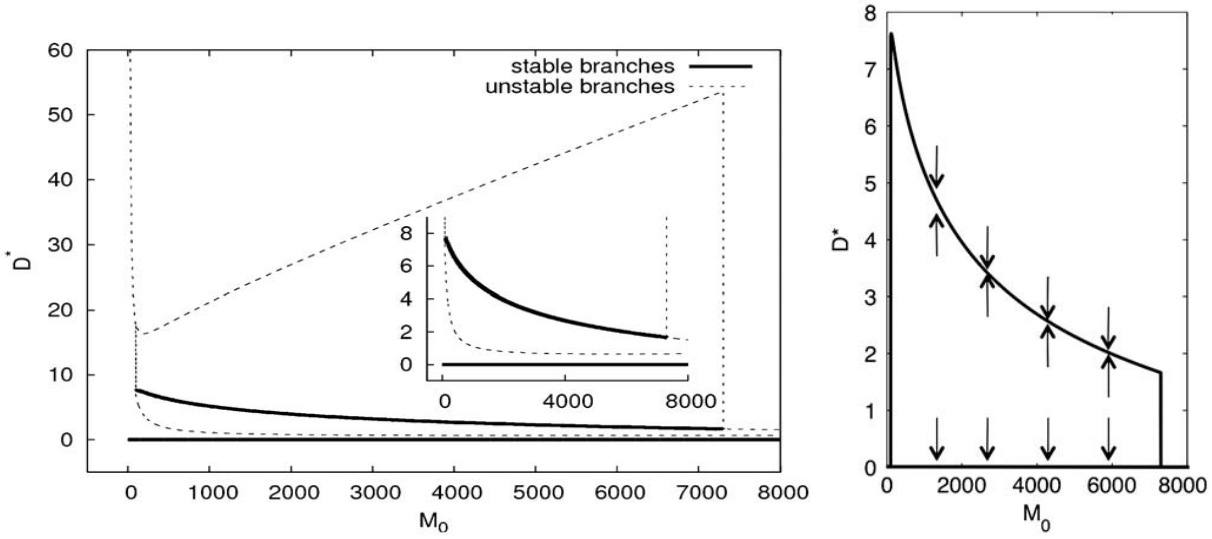
$$\begin{bmatrix} m \\ h \\ c \\ n \\ d \end{bmatrix} = c_1 e^{\lambda_1 t}[v_1] + c_2 e^{\lambda_2 t}[v_2] + c_3 e^{\lambda_3 t}[v_3] + c_4 e^{\lambda_4 t}[v_4] + c_5 e^{\lambda_5 t}[v_5]$$

if λ_i is greater than 0, then $e^{\lambda_i t}$ approaches infinity as t approaches an infinite value. QED

From Theorem 5 we see that if any λ is greater than 0 the solution grows exponentially to an infinite value. This will produce an infinite number of macrophages, helper T cells or cytotoxic T cells and establishes an unstable state. Therefore, when analyzing solutions, it is important to identify whether all eigenvalues have negative/positive real part. If there exists a positive real part of an eigenvalue, the solution found is unstable. To illustrate with concrete numbers, we use the solutions found earlier when setting the dimensionless equations to 0 and plug the values into the matrix, A. Maple programming solved for the eigenvalues and eigenvectors. The

eigenvalues corresponding to solutions 1 and 3 contain all negative real parts while at least one eigenvalue in solutions 2 and 4 contain a positive real part. This indicates that solutions 1 and 3 are stable, but 2 and 4 are not.

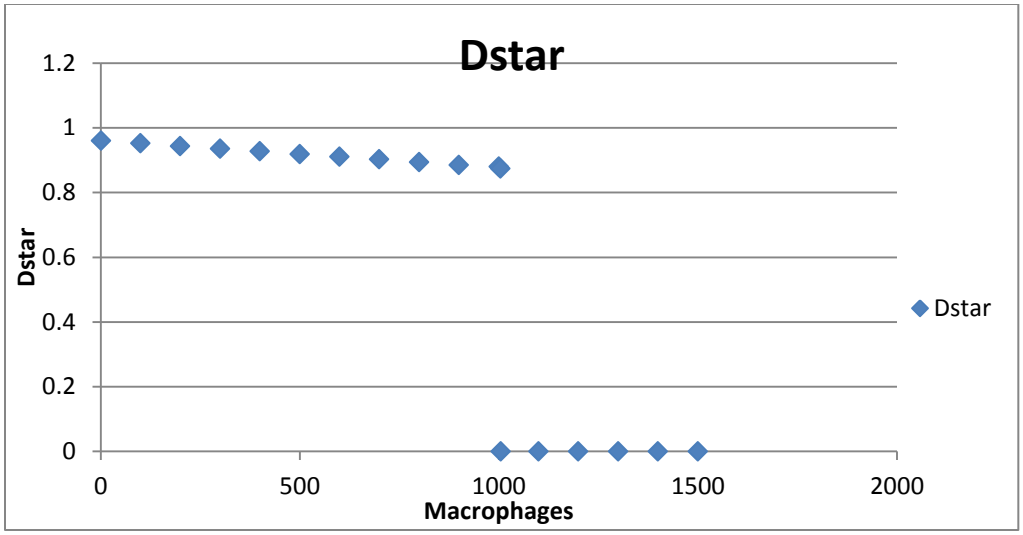
The mathematical model indicates, then, that there are regions of bistability. When the number of damaged cells (D) rises above a certain threshold represented by an unstable stationary point then the system is driven to the other stationary stable state. This is illustrated in the graphs below taken from [DC].



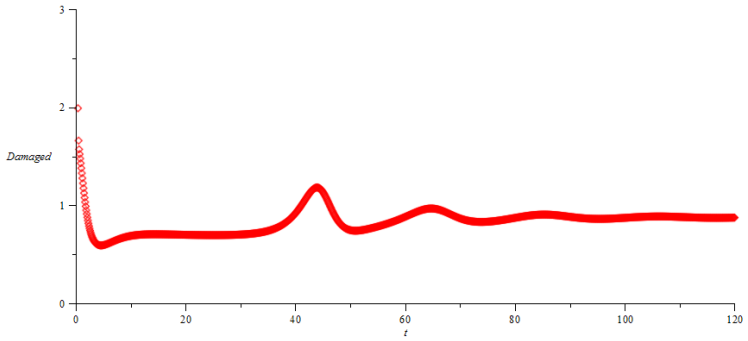
The arrows indicate the direction in which the system is driven. If it is in between a stable branch and an unstable branch it will be driven towards the stable branch. It can be noted that for values of M_0 less than 99 and greater than 7304 the branches drop off to include only one stable state, rather than a presence of a second one. Only the original stationary state is present, the healthy region of stability.

The graphs show D' as a function of M_0. The authors [DC] fix the β_1 value at 10.456. This is because β_1 is one of the only factors that can be controlled therapeutically. M_0 is the number of macrophages in a healthy muscle tissue. β_1 is the sensitivity of the immune system to the induced damage, normalized with respect to the death rate of those cells. The original β_1 from the given data in literature is 104.56. With medicine β_1 can be reduced by a power of 10 to be 10.456. This is important when looking at therapeutic solutions.

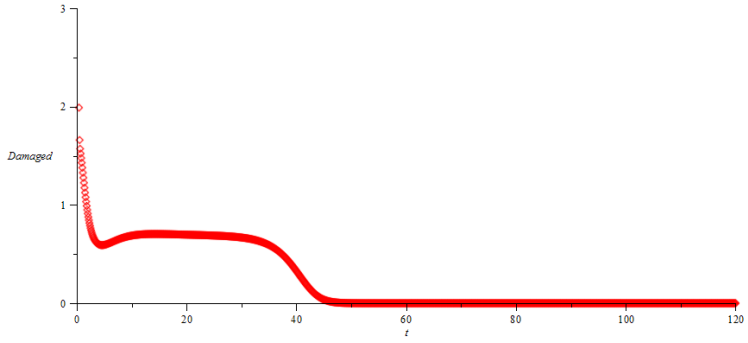
When β_1 is fixed at its original value of 104.56 we can produce the following graph of the stable branch solution of M_0 versus Dstar.



When $\beta_1$is fixed at 10.456 there are two regions (when $M_0 < 99$ and $M_o > 7304$) where there exists only the zero (healthy) stable state. When $\beta_1$is fixed at 104.56 a similar situation is observed. The regions, however, are drastically different (when $M_0 < .00164$ and $M_o > 1004.3$). The graphs below display the damaged cell pattern at (a) 1004 macrophages and (b)1005 macrophages as well as the regenerating cell pattern at (c) 1004 macrophages and (d) 1005 macrophages.

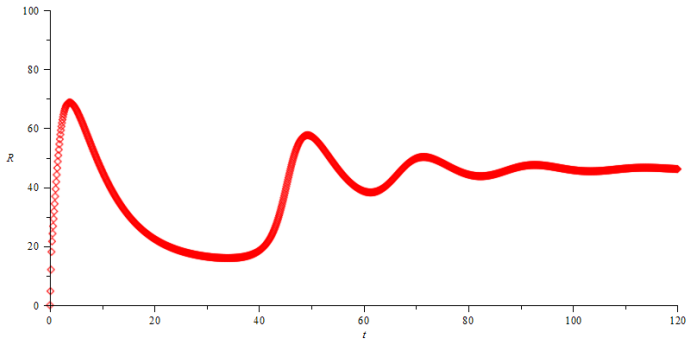


(a)

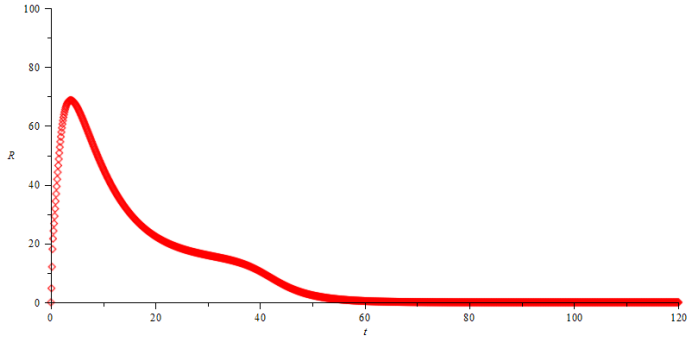


(b)

(c)



(d)



It is evident at 1004 macrophages that 1% of the cells remain damaged. While 1% are damaged, 46% of the cells are regenerating to reach the normal state. This, then, leaves a patient with only 53% normal cells. At 1005 macrophages, on the other hand, after the same time period has passed, there are no longer any observed damaged or regenerating cells. This is important clinically. It provides information for what level of macrophages is needed to drive a patient into the healthy region of stability at a given β_1.

When looking at the dimensionless equations, β_1 is the most important parameter because it has an effect on the entire system. If β_1 is reduced by a factor of 10 in the equation $\frac{dM}{dt} = M_0 - M + \beta_1 MD$, then the number of macrophages is reduced. If the number of macrophages is reduced, then so is the number of helper T cells. This is because of the presence of the interaction term MD within the dH/dt equation. Since the number of helper T cells is reduced, so is the number of cytotoxic T cells. Similarly, the dC/dt equation has the interaction term HD. In turn, since the number of cytotoxic T cells is less, the normal cells will not lose as much healthy tissue throughout time. As a result, damaged cells would be lessened as well. The excess of cytotoxic t-cells is the cause of the problem within Duchenne Muscular Dystrophy. It causes a degradation of normal cells. Recall that b_1 is the proportion of interactions of macrophages and damaged cells that increase the rate of change of macrophages and d_1 is the death rate of macrophages. Thus the sensitivity of the immune system to the induced damage, the parameter $\beta_1 = \frac{b_1}{d_1}$, has a direct impact on what could happen to the muscle tissue in the disease.

This study has shown that there are regions of bistability in the Duchenne Muscular Dystrophy model. One of the regions is associated with complete recovery and the other corresponds to a state with massive cell regeneration and degeneration. The immune response's strength can fluctuate based on the β_1 and M_0values, which were isolated within the analysis.

What this means for possible therapy in the future is that there are two regions in which to look. One can either search to drive the immune system into the mono-stability region of complete recovery or to a region where the basin of attraction of the other stable solution is too far to be reached with a physiological stress. If the latter were to happen the system would be driven back into the healthy region. There has been work done by Michelle Wehling [WST] that shows the effect of the depletion of macrophages on muscle fiber. In her study, it is shown that the macrophage depleted mdx mice showed a greater than 75% reduction in injured fiber concentration compared with non-depleted mice. This, then, is where further study is needed to investigate a relationship between the depletion of macrophages and whether or not the depletion can drive a patient to a state of recovery.

3 Mathematical Modeling of Lung Function

Another mathematical model that accompanies Duchenne Muscular Dystrophy focuses on the growth and decline of lung function with an augmented linear mixed effects model[SNB]. It involves an extension of linear mixed effects modeling where random changepoints are integrated as parameters and estimated using an algorithm.

An individual with normal lung function has a lung vital capacity that increases with age. The capacity reaches its maximum around age 20 and slowly declines throughout the rest of one's life. This is because of the normal aging process, not because of lung failure. Patients with Duchenne Muscular Dystrophy experience a rapid decline in lung function around age 14 and often die from cardiac problems associated with lung dysfunction.

The modeling done by Marc Scott took both single and variable tests for unconstrained and continuous versions of a switching regression model. The modeling was to effectively demonstrate the growth and decline of vital capacities in a patient with the disease. It primarily centered upon the age of change from growth to decline. What was found was that the unconstrained model better fit the data from his sample size. However, continuous models are more in correlation with the biological processes. His conclusions, then, could be skewed based on the fact that his tests did not include enough patients. Needless to say, both studies did find that the changepoint most frequently occurred at age 14. The unconstrained model, though, found that age 13 had close to the same frequency as age 14 while the continuous model displayed a much lower frequency.

More studies continue to be conducted using mice as test subjects. Mathematical modeling is often a part of these tests and studies. To further explain phenomena with Duchenne Muscular Dystrophy it will be necessary to investigate other methods of modeling.

4 Conclusions

The study we conducted has given insight into possible treatment of Duchenne Muscular Dystrophy. By focusing on the initial number of macrophages (M_0) and the sensitivity of the immune system to the induced damage (β_1) terms it has become apparent through bifurcation diagrams that there are possible solutions to the problem. By driving a system into a state of monostability a patient can enter full recovery. The state of monostability represents the healthy stationary state in which a patient is experiencing no damage to his muscle cells. In order to reach this state it is necessary to further investigate cytological and pharmacological treatments to control M_0 and β_1. It is also necessary to explore their overall effects on the human body.

References

[DC] Dell'Acqua, Guido; Castiglione, Filippo A mathematical model of Duchenne muscular dystrophy. *Applied and industrial mathematics in Italy III,* 311–322, Ser. Adv. Math. Appl. Sci., 82, *World Sci. Publ., Hackensack, NJ,* 2010

[EP] Edwards, Henry C; Penney, David E, *Differential Equations & Linear Algebra*, 412,419, *Prentice Hall, Upper Saddle River, NJ, 07458,* 2010

[SNB] Scott, Marc A.; Norman, Robert G.; Berger, Kenneth I. Modelling growth and decline in lung function in Duchenne's muscular dystrophy with an augmented linear mixed effects model. *J. Roy. Statist. Soc. Ser. C* 53 (2004), no. 3, 507–521

[WST] Wehling, Michelle; Spencer, Melissa J; Tidball, James G, A Nitric Oxide Synthase Transgene Ameliorates Muscular Dystrophy in Mdx Mice, *The Journal of Cell Biology,* Vol. 155, 123-131, *The Rockefeller University Press, New York, NY, 10065,* 2001