Modeling Levels of Abnormally Heightened Tumor Necrosis Factor to Predict Recovery Times Among Patients

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***Abstract*— Remicade levels, Tumor Necrosis Factor levels, and Remicade antibody levels were modeled with SIMULINK and MATLAB to produce an estimation for when a patient enters a state of remission. The model was found to be a useful beginning to model immunosuppressant drugs and further understand the mathematical side to the patient, the biosystem.**

***Clinical Relevance*— This establishes a model, allowing medical professionals caring for patients with autoimmune disorder to predict recovery times and levels of antibodies, Remicade, and abnormal values of TNF**

I. Introduction

Remicade in 1998 was the first FDA approved drug to inhibit the production of TNF (tumor necrosis factor) proteins. One of the main distinctions of Crohn's disease is the over production of TNF, causing the patient to overreact to various stimulus and overproduce TNF causing mass inflammation. Remicade, or Infliximab, originally called anti-TNF-α antibody cA2 was designed to administer anti-TNF antibodies to a patient to reduce the production of TNF and thus reduce over inflammation. A patient with Crohn's or other autoimmune disorders such as Arthritis and Ulcerative Colitis overproduces TNF proteins. For Crohn's the TNF proteins concentrate around the small or/and large intestine where the concentration causes unhealthy leaves of inflammation which leads to a variety of symptoms including malnutrition, pain, unhealthy stool patterns, fatigue, and also lead to more urgent symptoms such as abscess (primarily perianal) which when not treated right away can lead to sepsis or necrotizing fasciitis which can lead to death.

Remicade infusions can easily prevent these symptoms and help patients guide their Crohn into remission. However, the introduction of the drug can cause the body to react and produce antibodies to the Remicade (referred to as antibodies) as the body sees the foreign substance as something harmful and thus consume the drug as well. The creation of a new medical device which measures the current concentration of the drug within the bloodstream (currently cycled around the body) and the amount of antibodies as well as administering Remicade can be the first step from reducing the amount of infusions visits and further prevent hospitals when the patient reacts to a stimulus causing an abnormally high production of TNF.

Within the research conduct, a model utilizing control system topics is designed to model the abnormally unhealthy TNF levels within the blood stream. The TNF levels are modeled based on a certain abnormally unhealthy TNF level initial condition and Remicade Antibodies, as well as Remicade Drug levels. Further the model is designed to be easily altered to better model for different patients, ones which have a much greater level of abnormal TNF or a greater level of Remicade Antibodies.

II. Procedure

Apparatus:

For the modeling of the control system, Simulink, a service provided by MATLAB is utilized to create the models. The model was based on a
control system modeled initially through differential equation shown within figure 1. The block diagram of the differential equations is shown within figure 2.

Figure 1:

$$\frac{dR}{dt} = -\beta A(t) + \alpha R(t) - \mu N(t)$$

$$\frac{dN}{dt} = -\gamma N(t) \cdot R(t)$$

$$\frac{dA}{dt} = \begin{cases} \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{(x-2)^2}{1}\right)} & \text{if } x \geq 0 \\ 0 & \text{if } x < 0 \end{cases}$$

Figure 1: The general differential equation system for the biosystem. A(t) describes the current level of antibodies within a patient in millions of antibodies. N(t) describes the level of abnormal TNF within a patient's system in millions of abnormally high protiens. R(t) describes the amount of Remicade inputted into a patient's system in milligrams. The variety of constants are representative of a variety of factors which can be modeled for. The alpha coefficient describes how efficiently the body can process the input of Remicade, since the coefficient is a measure of efficiency values from zero to one are the most logical to utilize. The beta coefficient describes a factor of how prevalent the antibodies are for the respective patient and allow for patients which produce more antibodies to be better described by the variety of outputs shown. The coefficient mu describes how efficiently abnormal TNF levels consume Remicade, and values between zero and one are most logical to utilize as the coefficient is a measure of efficiency. Finally, the gamma coefficient

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describes how effective the Remicade is at reducing abnormal levels of TNF within a patients system, again most logically taking values from zero to one.

Figure 2:

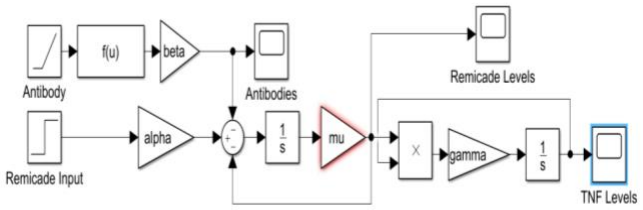

Figure 2 is a block diagram representation of the differential equation model.

III. Model Assumptions

The patient is assumed to begin with the absence of any Remicade antibodies and begins producing the antibodies after the initial injection of Remicade. The particular assumption stems from current scientific understandings about antibodies and the complexity of the Remicade drug which would suggest all patients start out with no antibodies. Furthermore, the patient is assumed to produce antibodies, due to the complexity of the molecule and the presence of an overactive immune system which will immediately react to the foreign substance entering the patient's blood stream, leading the immune system to classify the drug as a threat to the body leading to antibody production. Additionally, the patient is assumed to slow down their production of Remicade antibodies over time, as patients who successfully respond to the drug must have a decrease in antibodies over time and a reduction of abnormal TNF levels.

The Remicade drug typically is infused every four to eight weeks, and instead of utilizing spikes of Remicade drugs which decay until the next infusion, the average amount of Remicade was utilized and was assumed to be inputted into the body over time within the control system. Choosing to utilize an average allows the model of abnormal TNF levels to have a more understandable prediction and leads to the overall clarity of the model. Discrete inputs every four weeks simply leads to possible misinterpretations of the abnormal TNF levels due to the absence of clarity within the model.

Another assumption about the model is how the Remicade fails to suppress exceeding levels of TNF. The assumption stems from the drug's overall purpose, to suppress unhealthy levels of TNF, and how due to an over presence of TNF levels within. When TNF levels are within the range for typical person (the levels of abnormal TNF are zero), any additional suppression of TNF is negligible as no significant downsides to blocking additional TNF levels and the Remicade drug's effectiveness at suppressing TNF decreases when the TNF levels continue to decrease as the chance of the drug finding TNF and then suppressing it decreases as there are lower amounts of TNF within the blood stream.

IV. Results

Figures for a typical amount of Remicade injected (averaged for a constant injection), antibodies for a patient, and abnormal TNF levels, and are figure 3,4, and 5 respectively. The input dose was assumed to be once every four weeks and a typical dose of 5 mg/kg or 400 mg every four weeks for a 80 kg person.

Figure 3:

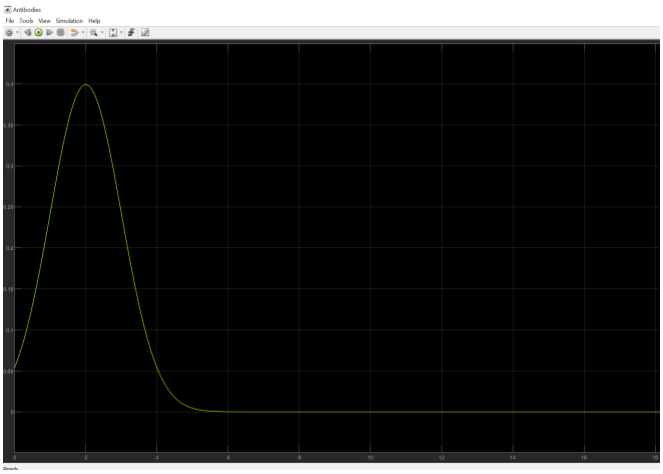

Figure 3 describes the levels of Remicade antibodies within a patient. The x axis describes time, and its units are in weeks. The y axis is the number of antibodies in millions.

Figure 4:

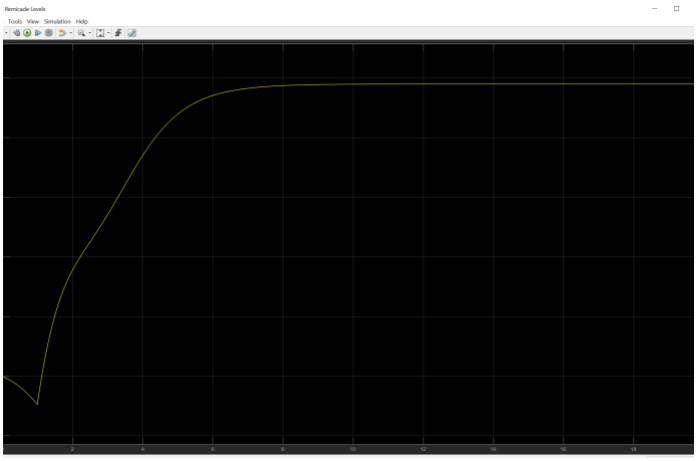

Figure 4 describes the levels of Remicade within a patient. The x axis describes time, and its units are in weeks. The y axis is the level of Remicade in milligrams. Any negative values in the amount of Remicade describe times where there are more antibodies than Remicade within the patient and blocks any Remicade from suppressing abnormal TNF levels.

Figure 5:

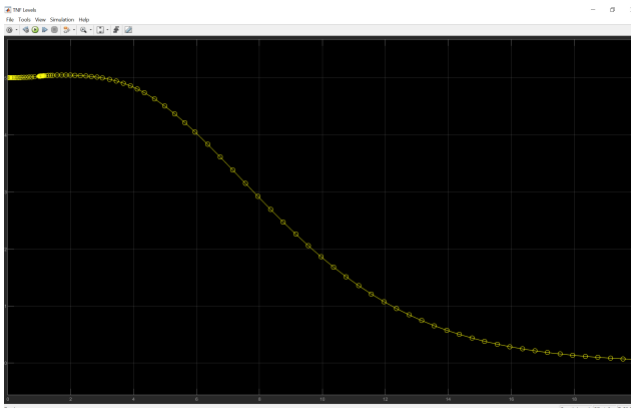

Figure 5 describes the levels of abnormal TNF within the patient. The x axis describes time, and its units are in weeks. The y axis is the level of abnormally high TNF levels in millions. Initially the amount of TNF increases as none of the drug is suppressing the production of TNF, leading to more inflammation and a higher level of abnormal TNF levels, but then quickly begins to settle as the patient approaches remission.

To further learn more about the stability of the model, a transfer function and bode plot was utilized for a typical Remicade patient. Within figure 6, the derivation for a transfer function is shown and a corresponding bode plot is shown. To simplify the transfer function, the value of antibodies was ignored as well as the initial conditions for abnormal TNF levels and Remicade levels. The antibody levels were ignored due to the minute value of the antibodies averaged for a 10-week period. The initial conditions for both the Remicade levels and abnormal TNF levels were ignored in the production of the transfer function as the transfer function is primarily utilized to find if the model is stable for all initial conditions.

Figure 6:

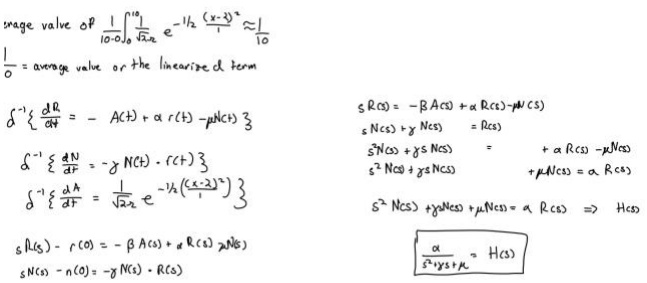

Figure 6 describes how the transfer function was derived for the function was derived and the overall transfer function.

To analyze the stability of the transfer function and draw implications of the original system, a Bode plot was created.

Figure 7 & 8 show the Bode plot for the transfer function utilizing simple constants to better understand the stability of the overall system for a typical patient responding to the drug.

Figure 7:

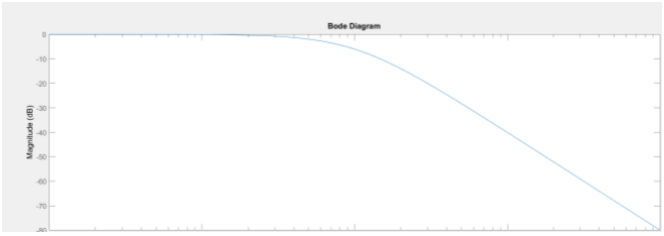

Figure 7 describes the magnitude plot for the transfer function.

Figure 8:

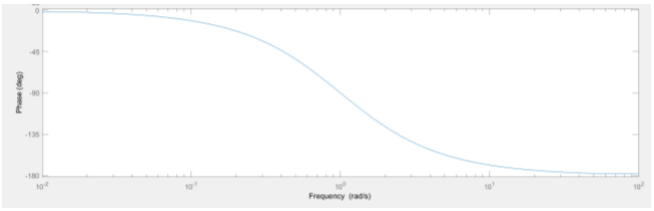

Figure 8 describes the frequency plot for the transfer function. From the transfer function it can be easily seen that the system is stable due to a phase margin of zero degrees and is thus larger than the amplitude margin which is negative producing a stable system. The stable system ensures the patient recovers, as the Bode Plot refers to the transfer function of the abnormal levels of TNF and Remicade levels, meaning as the system becomes stable, the abnormal TNF levels approach a constant number and within patients who reach a state of remission, the value is zero.

V. Conclusion

Throughout modeling an approximate system for abnormal TNF levels, one can utilize the model to predict times at which patients of a variety of autoimmune disorders are beginning a state of remission or when the abnormal TNF levels reach zero, or when the stability of the biological system is reached.

The model does provide the possibility for one to provide a variety of estimates for a variety of patients by utilizing coefficients to better predict how long until the beginning of remission. Accounting for a variety of variables, such as the peak of antibody production, or the efficiency of the Remicade when within the patient's system (which is affected by a variety of factors including the muscle percentage among others). Such coefficients allow for the model to provide estimates for patients who respond quickly when beginning the new drug, who have utilized the drug for years and are currently struggling with a flare, and even patients from differing background (height, age, weight, gender, etc.). The

manipulation of variables allows for the model to be applied to a variety of patients to better predict their recovery process.

Although the system has been proved to be a useful model which can be designed to model the levels of abnormal TNF within recovering patients, and the model can be adjusted to better model a variety of patients, the model does not universally apply the most accurate prediction possible for all patients. One of the model's error stems within the assumption regarding the patient's response to the drug. Assuming the patient always responds in a positive manner to the drug prevents the possibility for the model to be an accurate prediction to a patient who fails to positively respond to the drug. Failing to respond to the drug in a positive manner can happen from the patient producing more antibodies over time, which completely suppresses the Remicade, not allowing the drug to then suppress abnormal TNF levels.

Another error rises from the lack of medical knowledge surrounding TNF. Extensive research on measuring the levels of TNF within patients has not been conducted due to the cost, both timely and finical, of testing patients. Within the system of differential equations which laid the foundation of the model, it was assumed the levels of abnormal TNF decreased proportionate to the Remicade levels and the TNF levels and a constant coefficient. If further research reveals this relationship does not fully hold or fails to include a vital piece, the model's prediction regarding the abnormal TNF levels could greatly vary from the true patient's levels.

Another possible source of error could stem from how the Remicade is administered to patients. The model utilizes a constant stream of Remicade rather than periodic infusions. Thus, the levels of Remicade will not stabilize to a singular value but rather rise after initial infusion and then slowly fall prior to the next infusion. This would then affect the levels of abnormal TNF as it would decay similarly to the model for a short period after the infusion, but then tapper off as the level of Remicade within the patient lowers. Although possibly leading to a longer period of recovery for the patient, the prediction time from the current model should simply be a slightly underestimate for the time to the beginning of remission for a patient. The slight under estimation stems from the periods of lower Remicade levels within the patient's blood stream leading to a smaller reduction in abnormal TNF levels, thus requiring the patient to take longer to recover. However, the error is typically mitigated as there is typically more Remicade within the blood stream than there is consumed.

Although there exist possible errors within the model, the present errors provide possible areas of improvements. Two possible areas to improve the model and then reduce the error within the model are from utilizing a more accurate representation of how Remicade is infused into the bloodstream and expanding on other factors which impact Remicade levels. Utilizing repeating spikes of Remicade input into the system, modeling a typical infusion of Remicade can lead to a more accurate prediction for time until remission for a patient and reveal a better predictor for the levels of abnormal TNF within a patient as well as Remicade levels. Additionally, coefficients could be utilized as a beginning estimate for influences from a patient's background could affect certain levels of one of the measured substances within the biosystem. With more research on possible relationships between the descriptors of a patient (such as weight and muscle composition, two factors known to affect Remicade levels within the blood stream), possible mathematical models could then be utilized within the model to provide a more realistic prediction for certain levels over time and ultimately time until remission.

With improvements to the model, the model can be utilized for other drugs which are injected or infused into a patient; thus, the model can be applied to other illnesses as well. Better predicting recovery times can lead to more adequate medication levels for patients and to better comprehend the overall process the patient's bodies endures while on an immunosuppressant drug.

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