Modeling abnormal TNF Levels and Immunosuppressant Drugs
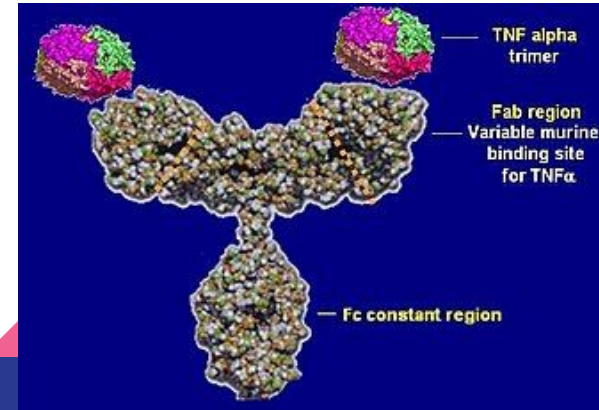
By: Brian Donovan

Background

Mainly utilized to treat Crohn's, Ulcerative Colitis, and Arthritis - autoimmune disorders

Reduce the amount of Tumor Necrosis Factor via suppression

Prevents symptoms, varying from acute pain to abcesses and further complications

TNF alpha trimer

Fab region
Variable murine binding site for TNFα

Fc constant region

Goals

Model and Create a control system which includes three main factors: Remicade Levels, Remicade Antibodies, abnormally unhealthy TNF levels (above a normal amount, TNF level of zero equivalent to maximum level of TNF level)

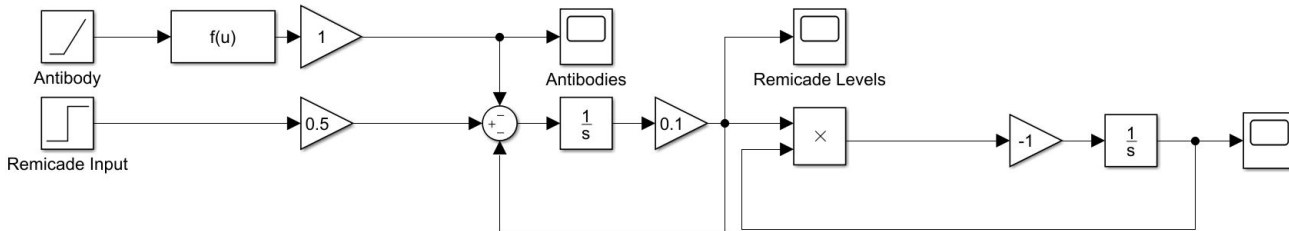Utilize a Model which utilize various presence of antibodies, and TNF levels
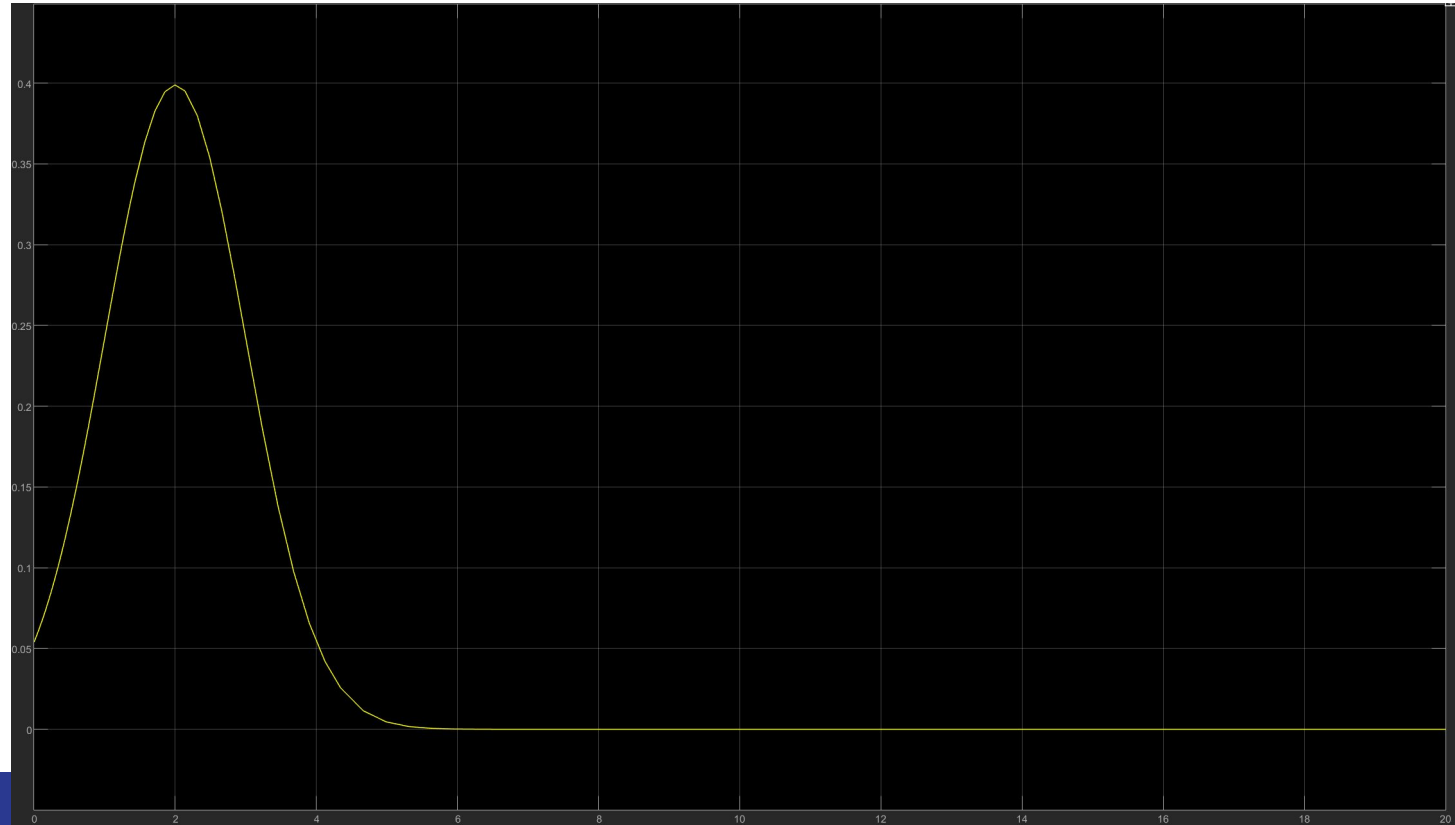
Assumptions and Model

Antibodies begin at zero, peak around two weeks, and decays eventually towards zero - utilized gaussian function to model presence of antibodies

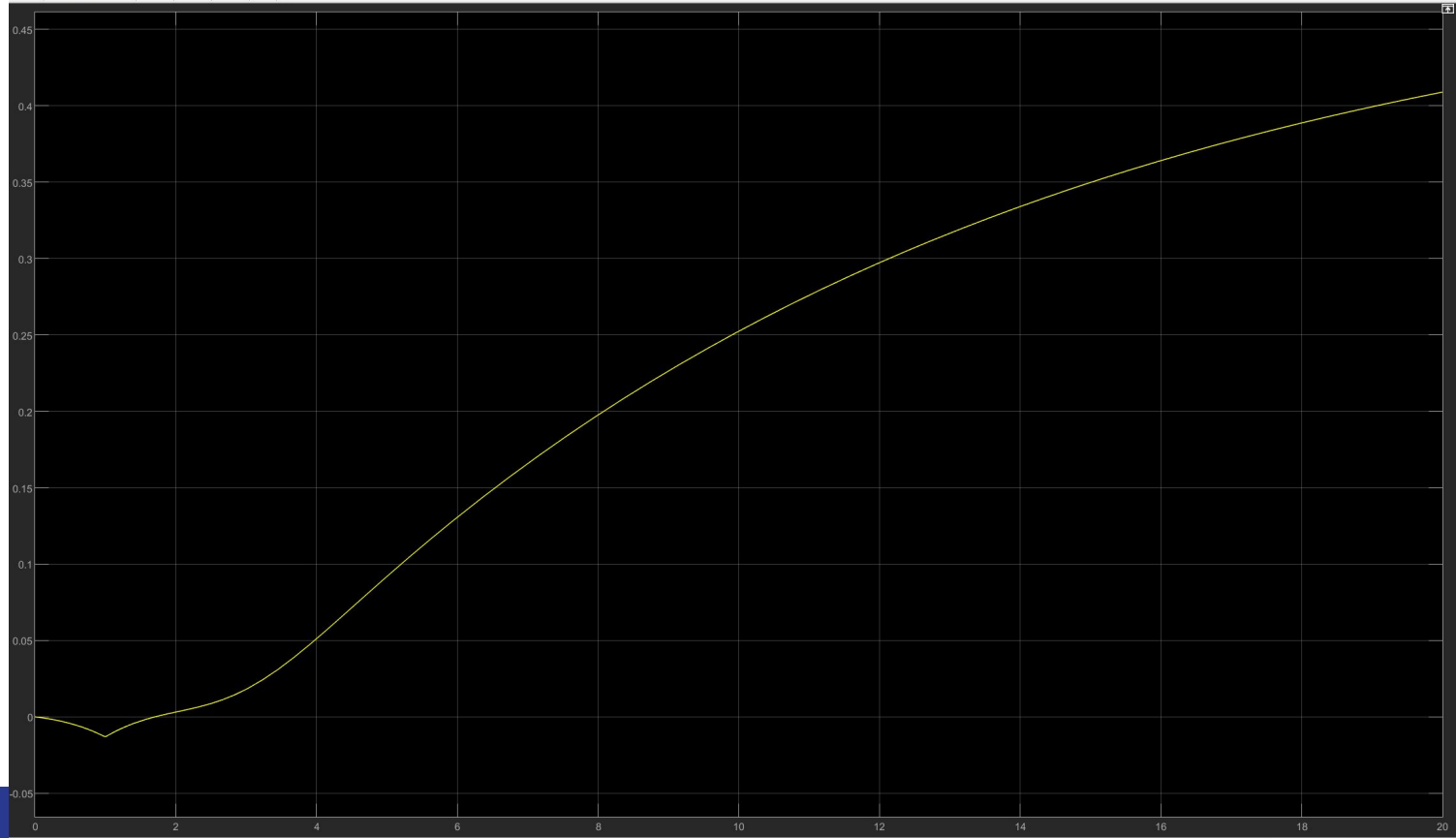Continuous Remicade Injection - studying the TNF output for a continuous input of Remicade
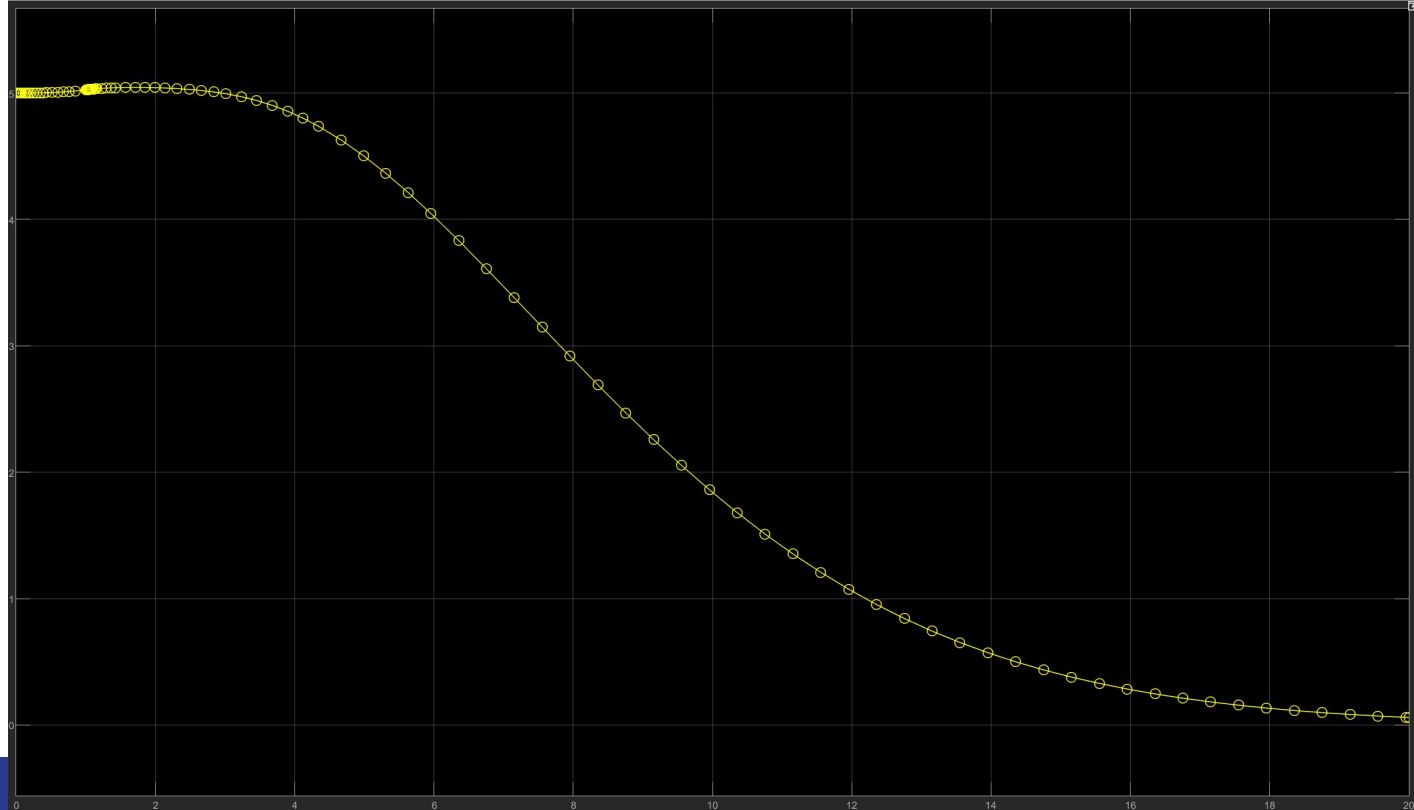
Remicade does not suppress any healthy levels of TNF

Model - Antibodies

Model - Remicade Levels

Model - TNF Levels

Transfer Function

average value of $\frac{1}{10-0}\int_0^{10} \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}\frac{(x-2)^2}{1}} \approx \frac{1}{10}$

$\mathcal{L}^{-1}\left\{\frac{dR}{dt} = -A(t) + \alpha r(t) - cN(t)\right\}$

$\mathcal{L}^{-1}\left\{\frac{dN}{dt} = -\gamma N(t) \cdot r(t)\right\}$

$\mathcal{L}^{-1}\left\{\frac{dA}{dt} = \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{(x-2)^2}{1}\right)}\right\}$

$r(0)=0$

$s R(s) - r(0) = -\beta A(s) + \alpha R(s) - cN(s)$

$s N(s) - n(0) = -\gamma N(s) \cdot R(s)$

$n(0) = s$

$\frac{1}{10}$ = average value or the linearized term

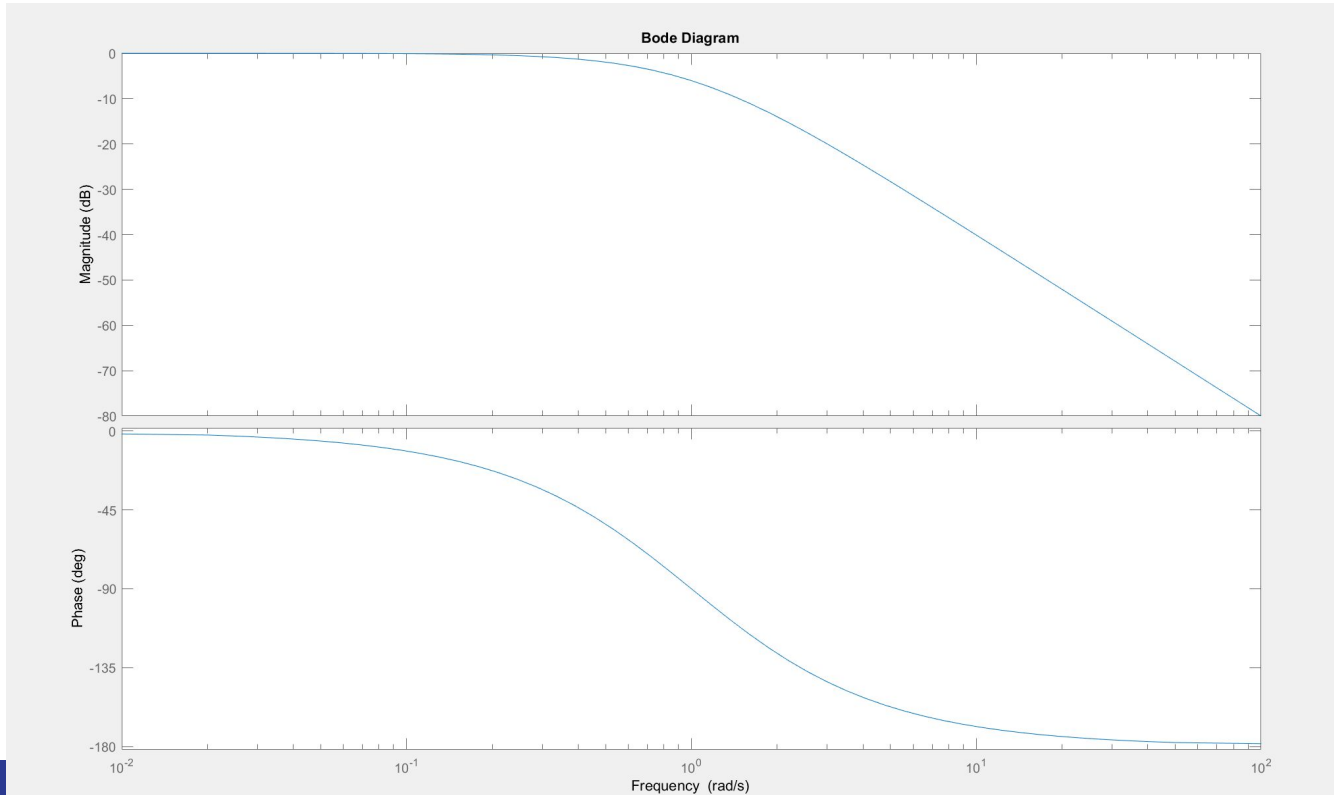$s R(s) = -\beta A(s) + \alpha R(s) - cN(s)$

$s N(s) + \gamma N(s) - S = R(s)$

$s^2 N(s) + \gamma s N(s) - Ss = -\beta \frac{1}{10} + \alpha R(s) - cN(s)$

$s^2 N(s) + \gamma s N(s) - Ss - \beta/10 + c N(s) = \alpha R(s)$

$s^2 N(s) + \gamma s N(s) + c N(s) = \alpha R(s) \implies H(s)$

$$\boxed{\frac{\alpha}{s^2 + \gamma s + c} = H(s)}$$

Bode Plot - Stability Analysis

Advantages

Allows for a variety of inputs, allowing one to model a variety of scenarios for a patient

Create a model for unhealthy levels of TNF relating to Remicade and Remicade Antibodies

Errors

TNF Protein levels are rarely measured specifically - costly both monterally and time wise, general protein levels measured typically via blood

Infusions are periodic, one is not constantly infused with Remicade or similar drugs constantly

Assuming antibodies reduce over time, antibodies could increase over time => rejection of the drug

Remicade still decreases amount of TNF (below normal levels)

Simplifications within Sensitivity Analysis

Sources

Melsheimer, Richard. "Remicade® (Infliximab): 20 Years of Contributions to Science and Medicine." *NCBI*, 2019, www.ncbi.nlm.nih.gov/pmc/articles/PMC6679695/.

Hendler, Steven A. "High-Dose Infliximab Therapy in Crohn's Disease: Clinical Experience, Safety, and Efficacy." *Journal of Crohn's and Colitis*, 13 Feb. 2015, academic.oup.com/ecco-jcc/article/9/3/266/361857.