Optimizing Exogenous Testosterone Dosage for Male Hypogonadism

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***Abstract* - This study investigates the optimization of Testosterone Replacement Therapy (TRT) in the context of the hypothalamic-pituitary-gonadal (HPG) axis's regulation of testosterone production in men. Focusing on the equilibrium between maintaining the HPG axis's stability and maximizing TRT's therapeutic benefits, we explore short-acting testosterone therapies as an alternative to long-acting forms, which are known to cause significant HPG axis suppression. Using a simulated model of the HPG axis, we determined the optimal exogenous testosterone dosage that minimizes the inhibition of endogenous hormone production while still providing the therapeutic benefits of TRT. This approach could lead to more effective and physiologically more optimal treatment strategies for hypogonadism in aging men. We employed Simulink to mathematically determine safe TRT doses without risking harm to human subjects. We observed a steady 40% increase in testosterone levels at a dosage of 0.2ng/m, and identified 0.35ng/mL as the approximate safe upper limit for testosterone dosage in our model. These are just preliminary findings and should serve as a basis for more extensive research. Ideally, we would like our work to hopefully contribute to future TRT protocols, and also create a full closed loop transfer function under conditions of hypothalamic activation.**

I. BACKGROUND

Testosterone plays a critical role in men's health. It is essential for maintaining energy levels, physical strength, and overall quality of life[1]. Its production is regulated by the hypothalamic-pituitary-gonadal (HPG) axis, a complex hormonal system that involves the hypothalamus, pituitary gland, and the gonads[2]. The HPG axis operates through a finely-tuned mechanism of hormone secretion, which includes the pulsatile release of Gonadotropin-Releasing Hormone (GnRH) and Luteinizing Hormone (LH), ultimately stimulating testosterone synthesis.

As men age, a natural decline in testosterone levels occurs, leading to a condition known as hypogonadism. This

condition is characterized by symptoms like fatigue, depression, and muscle weakness, significantly impacting an individual's lifestyle[3]. Testosterone Replacement Therapy (TRT) has become a common method used to mitigate these effects [4] However, the administration of exogenous testosterone must be carefully managed to avoid disrupting the natural hormonal balance, especially the function of the HPG axis [5].

II. AIM

One of the aims of this study is to model the HPG axis as a simplified biosystem based on assumptions and parameters found in literature. The objective is to determine the optimal exogenous testosterone dosage that maintains the stability of the HPG system while maximizing the therapeutic benefits of testosterone replacement therapy. We aim to find the dosage levels that render equilibrium, ensuring the physiological integrity of the HPG axis while maintaining the therapeutic advantages associated with exogenous testosterone administration.

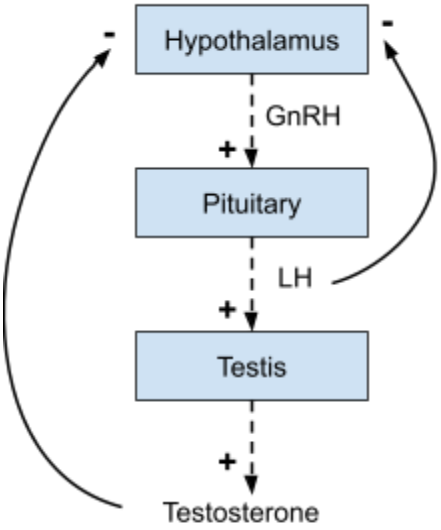

Figure 1. Simplified model of the male HPG axis used in this study

III. MODEL AND ASSUMPTIONS

We model testosterone regulation via the HPG axis using the following system of equations:

(1) $\dot{R}(t) = - d_R R(T) + r_R H(2 - L(t - \tau_{P\text{-}H}) / \hat{L} - T(t - \tau_{T\text{-}H}) / \hat{T})$

(2) $\dot{L}(t) = -d_L L(t) + r_L R(t - \tau_{H\text{-}P})$

(3) $\dot{T}(t) = - d_T T(t) + r_T L(t - \tau_{P\text{-}T} - \tau_0) + f(s)$

Here, we innovate on an existing model [6] of testosterone regulation. This model simplifies the complex interactions that modulate testosterone levels to 3 primary hormones: GnRH, LH, and Testosterone. **Figure 1.** The first equation models the factors that affect the rate of change of GnRH concentration in the blood. These are the decay of GnRH in the blood, as well as hypothalamic synthesis and secretion which is represented by a heaviside function that takes inputs from testosterone and LH levels to turn on and off release. Similarly, equations 2 and 3 which model the rate of change of LH and testosterone respectively, each include a decay term and a second term representing positive regulation from GnRH and LH respectively. To this system we add f(s) to model an exogenous step input of testosterone which we will vary for our tests.

This model does not account for interindividual or intra-individual variances in physiology that produce variations in time delays, decay rates, and response rates. Instead the model assumes linearity between

the relationships of hormones, their clearance rates, and receptor sensitivities, and utilized fixed values for these parameters obtained from experimental data[7-10] The parameter values used in the model are listed in **Table 1**.

IV. SENSITIVITY ANALYSIS

To evaluate the stability of our HPG axis model, we represent our equations in the frequency domain and visualize the closed loop system as a simplified block diagram in **Figure 2**. The transfer function H(s) in the diagram represents the relationship of testosterone as an input of GnRH. Here we simply represent the contribution of the heaviside function component of the system as a variable gain A. We perform a root locus analysis to determine the range of gain values for which the system is stable. The 33 minute time delay is the sum of all delays between GnRH release and testis stimulation. Since each time delay in the frequency domain is expressed as 1/e^(cs), where c represents the delay in minutes, the product of these expressions can be represented as a single delay. Upon root locus analysis, we confirmed that the closed loop system is stable for all gain values, since all real components of the system's poles were negative for all gain values. **Figure 3.**

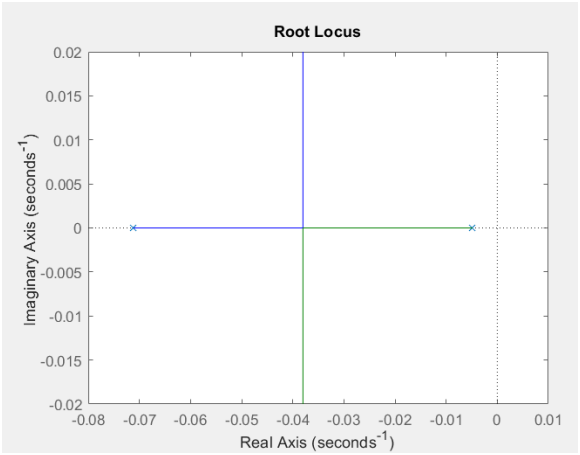

Figure 3: Root Locus of Closed Loop System

Next we modeled the system under the conditions where GnRH production stops and LH levels go to 0 due to excess levels of blood testosterone, the specific conditions we wish to simulate. The model simplifies to the following open loop transfer function H(s):

$$H(s) = \frac{1}{s + 0.023}$$

whose input is exogenous testosterone f(s) and output is T(s).

From the bode plot of H(s) in **Figure 4**, we observe a positive phase margin, indicating stability. However, with such a tight phase margin, in practical physiology, which is noisier than our model, instability may occur.

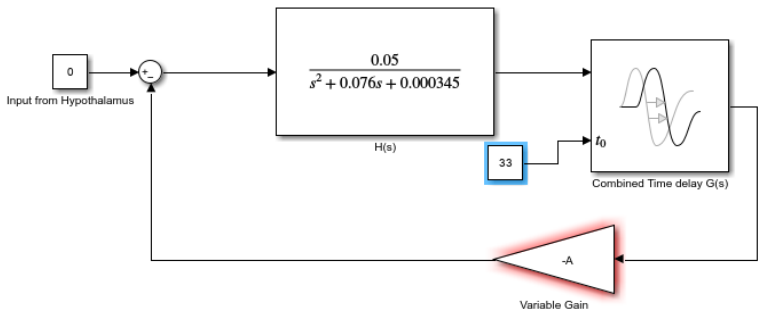

Figure 2

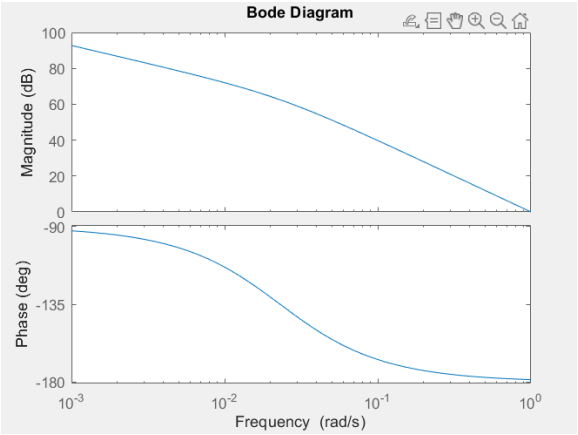

Figure 4: Bode Plot of Testosterone without feedback from LH

V. SIMULINK MODEL

A block model was then generated using Simulink, shown in **Figure 5**. The HPG axis regulation in our model starts when GnRH is released by the hypothalamus. GnRH then reaches the pituitary after a time delay of 3 minutes and stimulates the release of LH. This is simulated by multiplying the current concentration of GnRH by r_L, the response rate for LH. Then, LH reaches the testis after 5 minutes, but testosterone is not released until 25 minutes after the testis are stimulated. Therefore, the total delay time between the transport of LH and the release of testosterone is 30 minutes. The concentration of LH is then multiplied by $r_{T,}$ the response rate for testosterone. A steady dose of exogenous testosterone dosage is also injected into the system. This combined testosterone concentration is then multiplied by $d_{T,}$ the decay rate for testosterone. When the concentration of LH or testosterone increases above a certain threshold, the release of GnRH is turned off, which in turn causes the release of LH to decrease, subsequently decreasing the release of testosterone. The concentrations of LH and testosterone are measured, and when they fall below a certain threshold, the release of GnRH is turned on again. We simulated this by using a custom heaviside function block with the value comparing the concentrations of LH and testosterone. After GnRH is turned on, the cycle repeats.

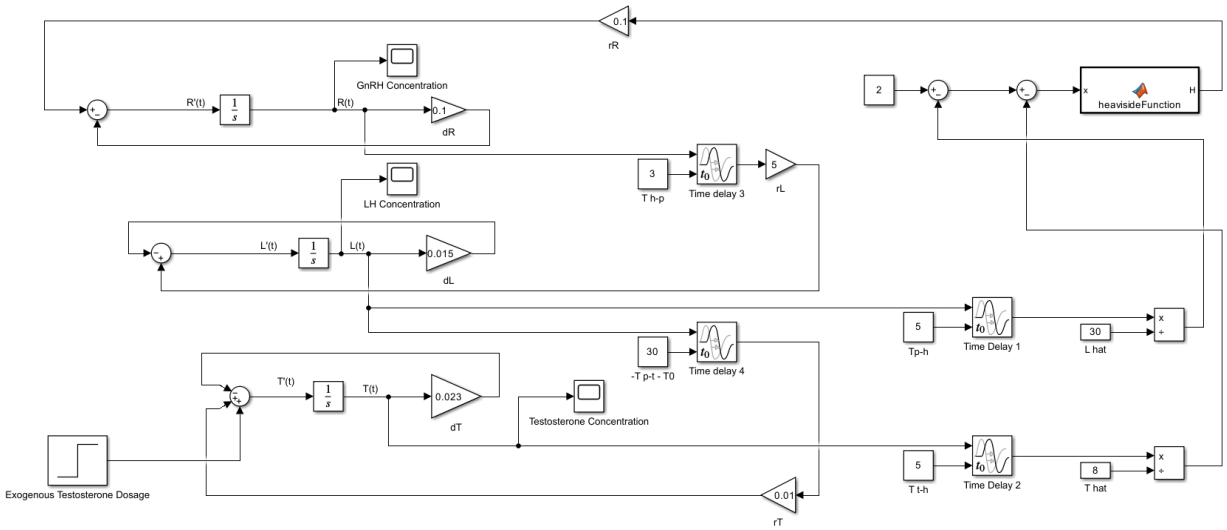

Figure 5. Simulink block model of the HPG male axis with a steady exogenous testosterone dosage.

VI. RESULTS

To model the natural system response, the exogenous dosage was omitted and the concentration of GnRH, LH and testosterone Vs. time were plotted as shown in **Figure 6.** Upon a step increase of 0.368ng/ml or more of exogenous testosterone, we observe as in **Figure 7**, that LH and GnRH levels go to 0 and do not return. Endogenous testosterone levels also go to 0 as the only some function of the steady step value of exogenous testosterone is maintained. However, upon administration of less than 0.368ng/mL of testosterone, hormone rhythmicity is maintained and hormone production does not cease permanently. Under a 0.2ng/mL dosage, we observed a 40% increase in the height of the regular testosterone peaks over no exogenous dosage. **Figure 8**.

To answer whether or not dose frequency impacts the system, we replaced the step input from the model with a pulse generator. As opposed to the step increase, where testosterone levels are maintained at elevated levels within the system, under pulsatile, rather than constant administration, rhythmicity of hormone levels was not abridged. However, these results do not suggest pulsatile administration is superior to a step increase, but are simply a natural consequence of the nature of our model. If testosterone levels exceed a certain threshold, GnRH production stops until testosterone levels drop. GnRH production and LH hormone production recommences once testosterone levels drop below the threshold again, which occurs only in a pulsatile input model. This occurs irrespective of dosage size or frequency, making it an insufficient input for studying dose-dependent HPG system failure. However, in a step input, since testosterone levels are maintained above the threshold, we can determine the maximum safe dosage effectively.

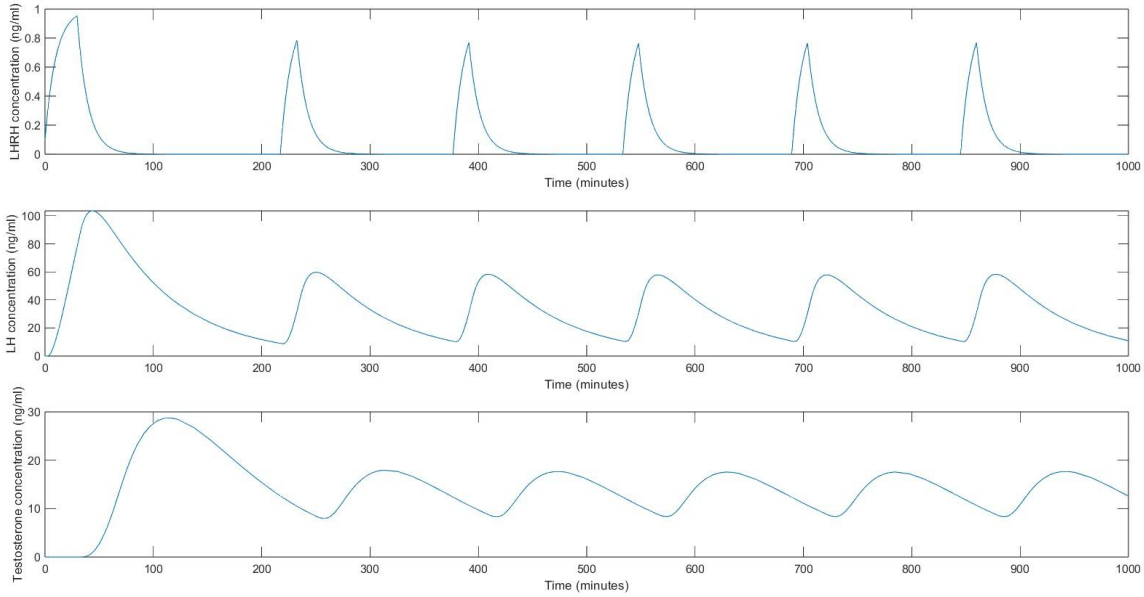

Figure 6. Natural Conditions. No dosage

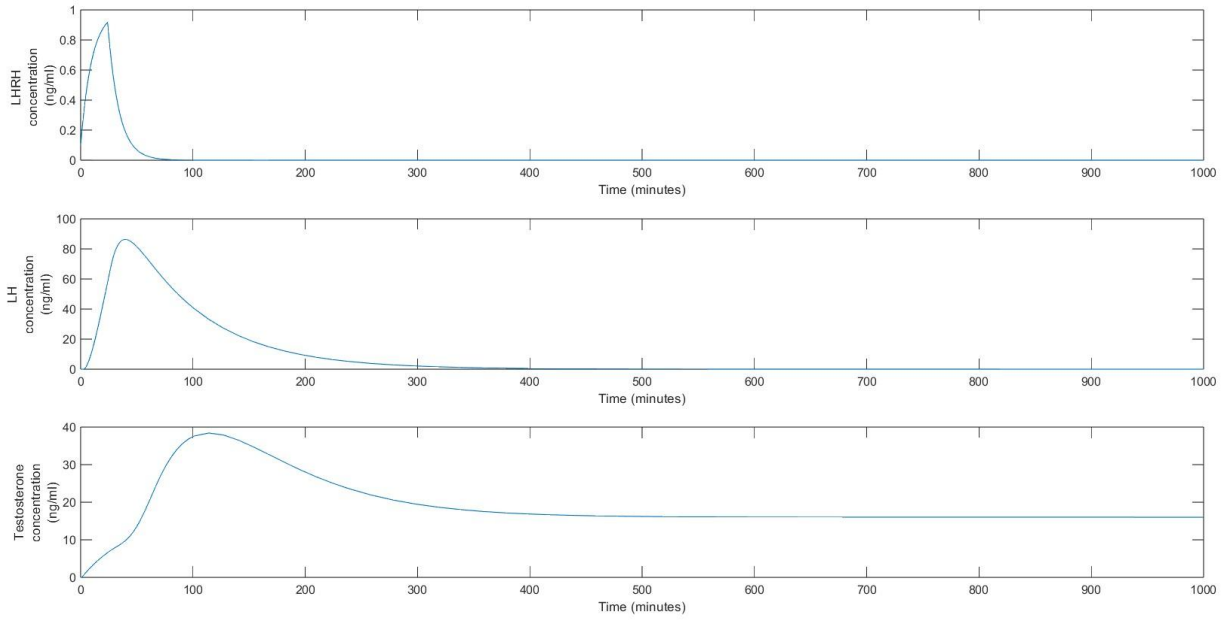

Figure 7. HPG axis regulation with a steady dosage of 0.368 ng/mL of testosterone.

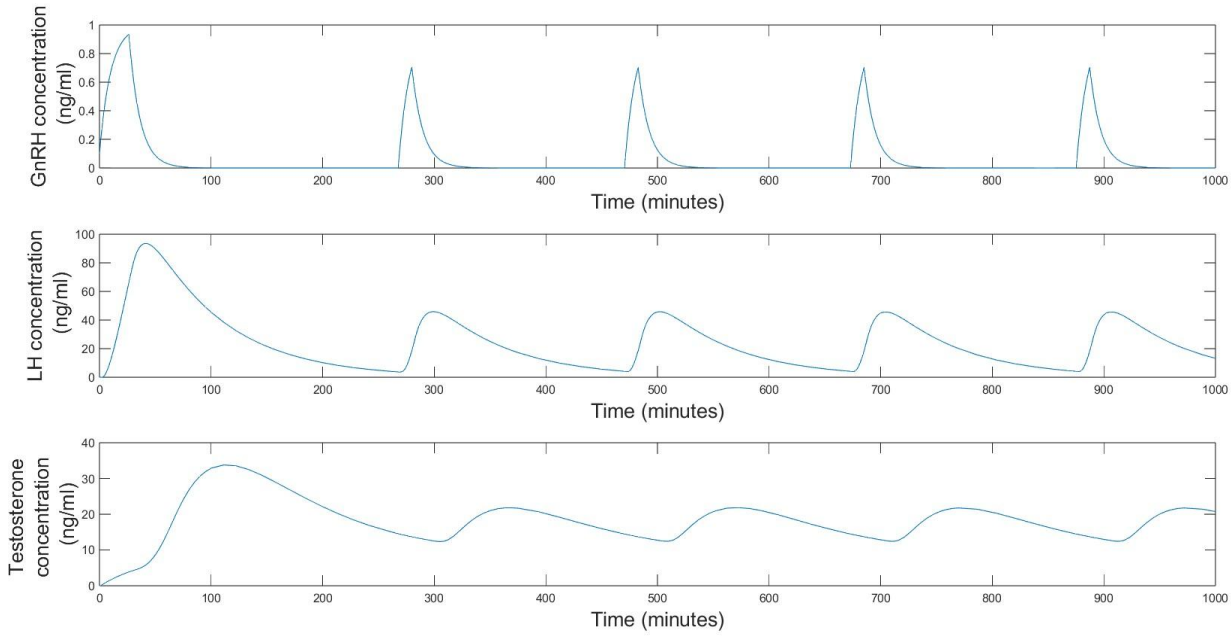

Figure 8. HPG axis regulation with a steady dosage of 0.2 ng/mL of testosterone.

VII. DISCUSSION

In regards to using short-acting testosterone therapies as modeled in the report we anticipate the max dose that is safe for patients for one time use would be 0.35 ng/mL. We anticipate the dose will have long term benefits as we observed that a

40% increase in the testosterone is associated with 0.2 ng/mL. The benefits we expect to notice from the increase are a rise in overall physical performance starting muscle mass growth, bone density, and greater energy levels. Simulations of dosages such as these are a safer alternative to experimentation on human subjects. However, the use of fixed parameters to model diverse and dynamic physiological elements limits the generalizability of our findings. Albeit, varying these parameters across the range of values observed experimentally in the literature resulted in only minimal changes in relative hormone levels observed within the simulation. The simplicity of our model, such as failure to account for diurnal variations in hormonal levels, among other temporal fluctuations hinders the immediate clinical value of our findings. Albeit, the patterns and levels of fluctuation observed in the simulations resembled experimental findings, suggesting our model may be of some clinical relevance[7-10].

VIII. ACKNOWLEDGEMENTS

We thank teaching assistant Benjamin Balster for his feedback on our preliminary findings which inspired several adjustments and new questions that went into our report.

APPENDIX

Table 1. Parameter values

Variable	**Value**	**Unit**	**Description**
r_R	0.1	ng/ml/min	Response rate for the production of LHRH
r_L	5	min^{-1}	Response rate for the production of LH
r_T	0.01	min^{-1}	Response rate for the production of testosterone
d_R	0.10	min^{-1}	Decay rate of LHRH in the bloodstream
d_L	0.015	min^{-1}	Decay rate of LH in the bloodstream
d_T	0.023	min^{-1}	Decay rate of testosterone in the bloodstream
T_{H-P}	3	min	Time delay of transport of LHRH between the hypothalamus and the pituitary
T_{P-T}	5	min	Time delay of transport of LH between the pituitary and the testis
T_{T-H}	5	min	Time delay of transport of testosterone between the testis and the hypothalamus
T_{P-H}	5	min	Time delay of transport of LH between the pituitary and the hypothalamus
T_0	25	min	Time delay between testis stimulation and testosterone release
$\hat{L}$	30	ng/nl	Concentration parameter of LH to turn on the hypothalamus
$\hat{T}$	8	ng/ml	Concentration parameter of testosterone to turn on the hypothalamus

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